Amide Directed C(sp^3)-H Functionalisation of Saturated Amines

Charlotte E. Coomber

Supervisors: Tom D. Sheppard and Michael J. Porter

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Department of Chemistry
University College London
20 Gordon Street
London
WC1H 0AJ

Declaration

I, Charlotte E. Coomber confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm this has been acknowledged in the thesis.

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Abstract

This thesis describes research towards the development of C-H activation reactions of saturated amines.

Chapter 1 describes current approaches towards directed C-H activation.

Chapter 2 covers approaches towards the amide directed C-H functionalisation of saturated amines. Methodology for the arylation of bicyclic amines is developed, which gives high yields of arylated products with a variety of aryl iodides and bromides. The methodology is applied to mono-, bi- and tricyclic amines with excellent yields. The reaction is improved by the introduction of a novel solvent for C-H activation, and allows for the arylation of more challenging amine substrates. It is also shown that a simple methyl substitution on the directing group can improve the yield of arylated products.

Chapter 3 investigates how the directing group employed can influence both the selectivity and yields of C-H functionalisation. Different directing groups are investigated on a range of amines to establish if they can improve yield and selectivity.

Chapter 4 describes efforts towards elucidating the mechanism for C-H activation. Plausible reaction intermediates are isolated. Reaction progress kinetic analysis is performed to further probe the reaction and to establish the rate dependence on the different reaction components. Same excess experiments are employed to establish the effect of the product on catalyst activity and also to determine if there is any catalyst degradation over the course of the reaction.

Chapter 5 describes efforts towards sustainable amide synthesis. Direct condensation of a carboxylic acid with an amine using a borate catalyst is employed. Existing methods developed within the group are expanded to improve yields for more polar substrates, and poorly nucleophilic amines. A new ester solvent is introduced to improve solubility of these substrates and improve the sustainability and reduce cost of the process.

Impact statement

The work described in this thesis is efforts towards the development of C-H functionalisation reactions for application within the pharmaceutical industry and academic laboratories. The functionalisation of saturated amines using C-H activation is important for the synthesis of potential new drug scaffolds and fragments. Saturated compounds are incredibly important in medicinal chemistry as they are an underexplored area of chemical space in drug discovery. The functionalisation reactions developed were demonstrated on a range of saturated amines and were achieved without using toxic solvents of silver additives. The results of this work have been published in the Journal of Organic Chemistry, detailing a silver free arylation method for bicyclic amines.

Further work has also been carried out in the development of sustainable amide synthesis for use in both industrial and academic laboratories. It was show that ester solvents can be used as an alternative to hydrocarbon and ether solvents for borate catalysed amidation. The impact of this work was demonstrated through publication in the journal 'Organic and Biomolecular Chemistry'.

Overall this work contributes towards new methods for C-H activation as well as the further development of 'green' chemical processes for the synthesis of amides.

Acknowledgements

Firstly, I would like to thank Tom for giving me the opportunity to be part of his group and to work on this project. Tom's endless ideas, enthusiasm and patience have been an inspiration throughout my studies. I have learned a lot through his seemingly endless knowledge of chemistry.

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Finally, I would like to thank François for all his help and support throughout my studies. Without your love and guidance, the completion of this thesis would never have been possible.

Table of Contents

Abbreviations

Ac	Acetyl
AcOH	Acetic acid
aq.	Aqueous
Ar	Generic aryl group
MeCN	Acetonitrile
Bz	Benzoyl
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
Bp	Boiling point
Bu	Butyl
Cbz	Carboxybenzyl
CI	Chemical ionisation
CMD	Concerted metalation deprotonation
Cy	Cyclohexyl
CPME	Cyclopentyl methyl ether
DCE	1,2-dichloroethane
DCM	Dichloromethane
DIPEA	*N,N*-Diisoproylethylamine
DMC	Dimethyl carbonate
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsuphoxide
d.r	Diastereomeric ratio
ES	Electrospray ionisation
Et	Ethyl

Eq.	Equivalents
h	Hour(s)
HFIP	Hexafluoro-2-propanol
Hz	Hertz
IR	Infrared spectroscopy
m	Meta
Me	Methyl
Mg	Milligram
ml	Millilitre
mmol	Millimole
Mp	Melting point
NMR	Nuclear magnetic resonance spectroscopy
NEt_3	Triethylamine
o	Ortho
p	Para
Ph	Phenyl
PMI	Process mass intensity
PMP	Para methoxy phenyl
ppm	Parts per million
Pr	Propyl
Py	Pyridine
RDS	Rate determining step
t	Tertiary
Boc	*tert*-butoxycarbonyl
TAME	*tert*-amyl methyl ether

***t*AmOH**	*tert*-amyl alcohol/ 2-methyl butan-2-ol
***t*HxOH**	*tert*-hexanol/3-methyl-3-pentanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
TosMIC	Tosylmethyl isocyanide
TS	Transition state
UV	Ultraviolet
XRD	X-ray diffraction

“Science is not a boy's game, it's not a girl's game. It's everyone's game.

It's about where we are and where we're going.”

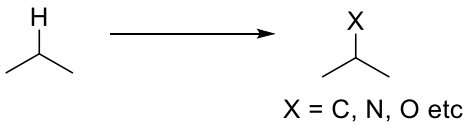
Nichelle Nichols

Chapter 1

Introduction to C-H Functionalisation

1.1 Introduction to C-H activation

The ability to treat an unactivated C-H bond as a functional group in synthetic chemistry has long proved a challenge for chemists. To be able to construct C-C, C-O, C-N or C-X bonds directly from C-H bonds without the need for pre-functionalisation can greatly cut down lengthy synthetic sequences to complex molecular targets, **Scheme 1.1**. Direct functionalisation of C-H bonds has the potential to save on reagents, solvents and labour by providing a more direct pathway towards the desired product.

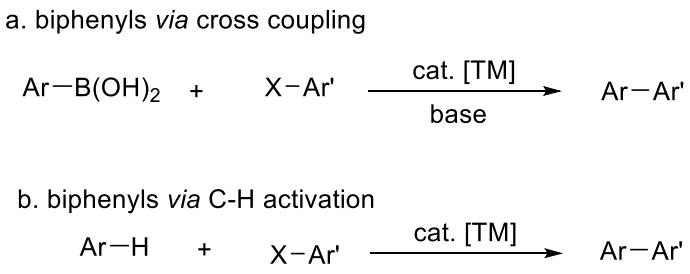


Scheme 1.1 C-H functionalisation

According to Shul'pin and Shilov C-H activation results in the replacement of a strong C-H bond with a weaker and easier to functionalise bond.[1] As nearly all organic molecules contain a C-H bond, the ability to selectively react just one of these is a powerful synthetic tool, but currently methodology is limited to certain types of C-H bonds. The direct activation of C-H bonds, particularly C(sp^3)-H bonds is a challenge due to the high bond dissociation energy, regioselectivity difficulties and the lack of an active LUMO or HOMO which can interact with metal catalysts. One of the greatest problems in C-H activation chemistry is the regioselectivity issues, due to the ubiquity of C-H bonds within organic compounds.

C-H activation reactions typically involve the cleavage of the C-H bond using a transition metal, to give a M-C intermediate which can go on to be functionalised in a subsequent reaction. Palladium complexes are attractive catalysts for these transformations; they can tolerate a wide range of oxidants and the cyclopalladated intermediates generated can be selectively functionalised. Most of these palladium catalysed transformations can take place in the presence of air and water which makes them practical for use in organic synthesis.

Palladium catalysed cross couplings have long been employed in synthesis. In an analysis of the reactions carried out in the drug discovery process by AstraZeneca, it was found that 4.6% of reactions were Suzuki cross couplings.[2] The issue with these cross couplings is they often require prefunctionalised starting materials,[3] which may require lengthy synthesis and generate undesired waste. In contrast, the direct activation of C-H bonds can allow for the use of unfunctionalised feedstocks, **Scheme 1.2.**[4]



Scheme 1.2 Cross coupling compared to C-H activation in biphenyl synthesis

The development of palladium catalysed C-H functionalisation can provide a route to a wide variety of compounds, as it can promote activation at both sp^2 and sp^3 centers.[5,6] A large body of research has focussed on the activation of C(sp^2)-H bonds, but this section will only focus on advances made in C(sp^3)-H bond activation of nitrogen containing scaffolds, as this is to be the focus of the project due to the importance of saturated rings in drug molecules.[7–10]

1.2 Saturated nitrogen containing compounds

Saturated nitrogen ring systems are important for medicinal chemistry and are found in many biologically active compounds. The drug molecules amantadine **1** and tromantadine **3** contain a saturated amino substituted ring as part of their core structure.

Nitrogen heterocycles also feature heavily in the core structure of numerous natural products (**Figure 1.1**) such as solifenacin **2** (a treatment for overactive bladder), ibogamine **4,** cocaine **5** and epibatidine **6**, an alkaloid isolated from *Epipedobates anthonyi* which is a potent analgesic.[11]

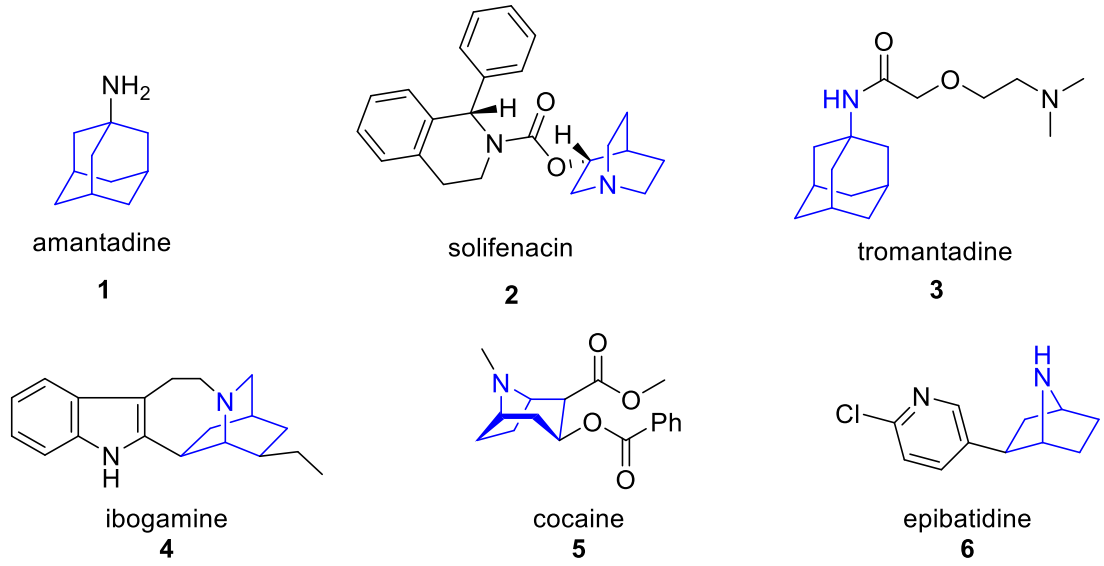
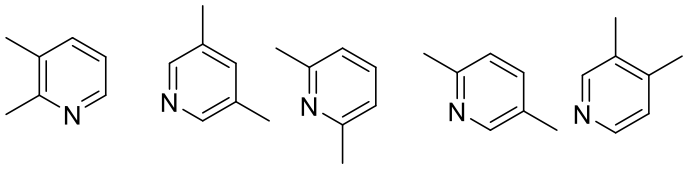


Figure 1.1 Examples of drug molecules and natural products with a saturated nitrogen containing framework

Access to functionalised ring systems is important for the development of more diverse and structurally complex molecules for use in pharmaceuticals.[12,13]

Lovering *et al.* have noted that on average, molecules with a higher proportion of sp^3 carbons in their structure were more likely to be successful drug molecules than those with a lower proportion of sp^3 carbons. This analysis has been questioned[14] but there are clear advantages to increasing saturation. For instance, increasing the degree of saturation within a potential drug candidate can give access to more architecturally diverse scaffolds with the capacity to access greater chemical space and three-dimensionality without significantly increasing the molecular mass. This can give rise to chirality and thus greater selectivity within a chiral environment such as the body. In oral drug candidates, too many aromatic rings can also have a negative effect on the properties required for a successful drug.[15] For example, the aromatic compound dimethyl pyridine has 5 possible isomers, but its fully saturated equivalent dimethyl piperidine has 34 possible isomers, **Figure 1.2**. This increases the amount of chemical space which can be explored, for only a small increase in molecular weight.[13]

a. Isomers of dimethylpyridine



b. Isomers of dimethylpiperidine

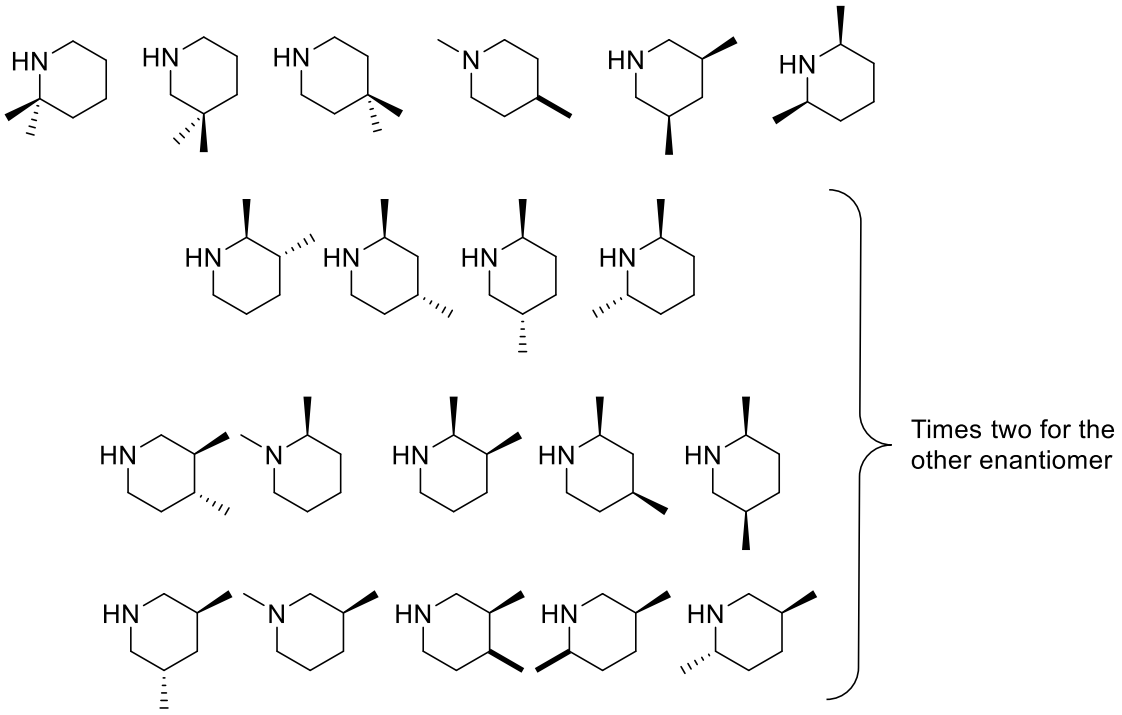


Figure 1.2 Isomers of dimethyl piperidine

In this context, the ability to rapidly synthesise a range of different analogues of sp^3 rich compounds will allow for the exploration of a less well used area of chemical space for potential drug candidates.

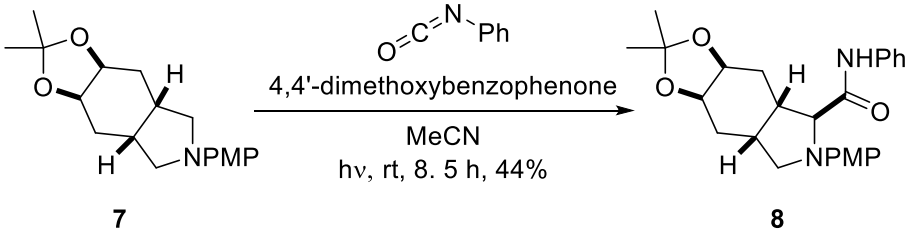
A direct method to functionalise these ring systems would cut down the lengthy synthetic routes previously required and so improve access to functionalised ring systems broadening the range of structures available for medicinal uses. Late stage functionalisation of drug-like molecules using C-H activation is a powerful technique to access new analogues for use in structure activity relationship (SAR) studies.[16]

1.3 C-H activation in late stage functionalisation

The ability to functionalise a drug molecule at a late stage in the synthesis can be an effective way to generate analogues of the structure, or for making small changes to the structure to increase potency without restarting the synthesis.

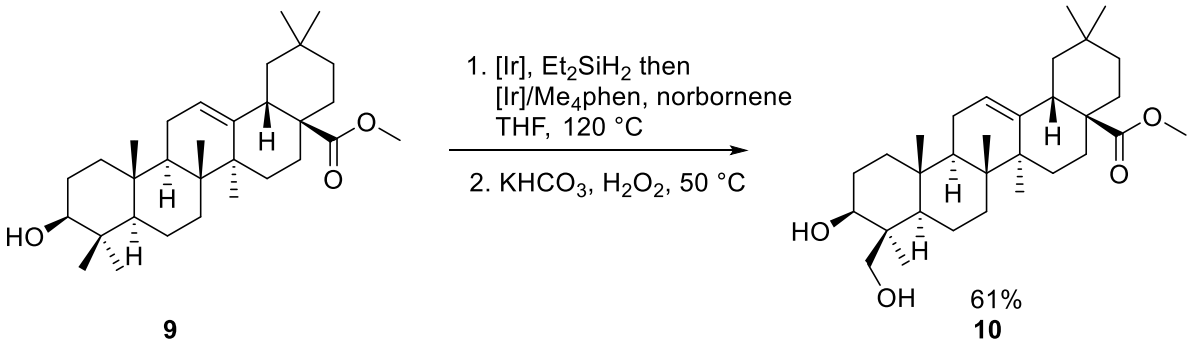
C-H activation reactions can be a powerful technique for late stage functionalisation. Nearly all drug compounds contain a C-H bond, and so it is the ideal handle for functionalisation. However, C-H bonds are chemically unreactive, and so methodology has been developed to use C-H bonds as functional groups capable of undergoing further chemical transformations. Selectivity limits the use of these reactions in drug discovery.

There are many examples of C-H bond activation at sp^3 centers that are innately reactive. Hydrogen abstraction at the most electron rich centre can be used to generate new C-C, C-N[17] and C-halogen bonds.[18] Yoshimitsu and coworkers employed a late stage C-H activation reaction to generate a new C-C bond in their total synthesis of kainic acid, **Scheme 1.3**. The reaction is selective for a C-H bond α to the nitrogen and goes *via* a radical pathway.[19]



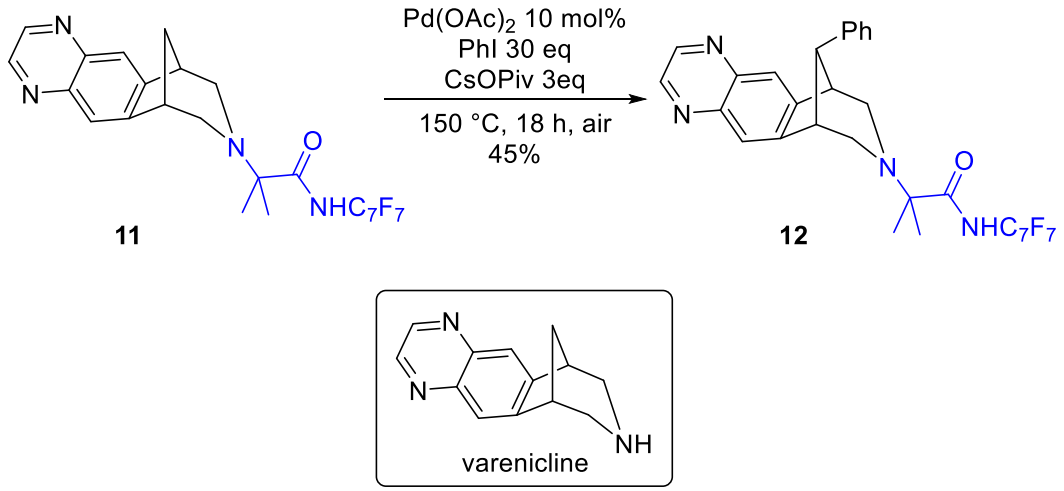
Scheme 1.3 C-H activation employed in the synthesis of kainic acid

C-H activation in late stage functionalisation can be guided by nearby ethers or alcohols. The silylation followed by oxidation of methyl oleanate can be achieved using an iridium catalyst followed by hydrogen peroxide, which is guided by the nearby alcohol, **Scheme 1.4**. This method can provide a route to C23 functionalised triterpenoids.[20]



Scheme 1.4 Alcohol guided C-H silylation/hydroxylation

Directed late stage functionalisation using palladium catalysis has been achieved on valerenicline (a treatment for smoking cessation), **Scheme 1.5**. A directing group had been installed on the piperidine nitrogen of compound **11** which can bind to the palladium catalyst to guide the C-H activation towards the bridgehead CH_2. The transformation proceeds with a moderate yield but requires a large excess of the iodobenzene coupling partner. It is possible to cleave this directing group using samarium (II) iodide to give the free amine.[21] It is only possible to functionalise one position



Scheme 1.5 C-H functionalisation of varenicline

1.4 Directed C-H activation and functionalisation of C(sp^3)-H bonds

General methods for the catalytic functionalisation of unactivated sp^3 C-H bonds in nitrogen containing scaffolds remains a significant challenge in synthetic chemistry. Advances in methodology for the halogenation, oxidation, arylation and alkylation of sp^3 C-H bonds are rapidly being made.[22]

As most molecules to be functionalised contain many different C-H bonds, the selectivity of guided C-H activation reactions may be achieved by sterics,[23–25] molecular recognition[26–28] or by directing groups.[29,30] The introduction of mono and bidentate directing groups to the scaffold to be functionalised has allowed for the control of the position of activation when sterics or molecular recognition cannot provide the required selectivity. In recent years there have been significant breakthroughs in the activation of C-H bonds by incorporating a removable auxiliary into the molecule to orientate and stabilise palladacyle intermediates.[31]

1.4.1 Monodentate Directing groups

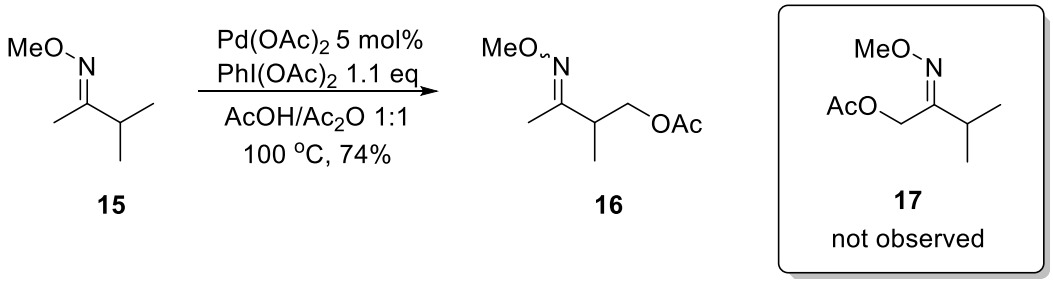
Monodentate directing groups have one atom that can coordinate to the metal catalyst to influence the position of activation.

Yu *et al.* employed pyridine as a monodentate directing group for the alkylation of primary C-H bonds with boronic acids, **Scheme 1.6**. The pyridine coordinates to the palladium catalyst to direct it towards the methyl group which is activated.

Scheme 1.6 pyridine as a directing group for alkylation

Although this gave good yields for the alkylation of C(sp^2)-H bonds (up to 75%), results were poor for activating C(sp^3)-H bonds with yields ranging from 40 – 56%.[32]

Methodology for the oxidative functionalisation of more reactive arene and alkene sp^2 C-H bonds has been developed using coordinating functional groups within the molecule that can chelate to the palladium catalyst and so direct the position of activation to one C-H bond.[2] Monodentate directing groups may be used to overcome some of the issues previously encountered with these types of reactions, such as over oxidation of products.[33] In 2004 Sanford *et al.* reported an oxime directed palladium catalysed oxygenation of unactivated sp^3 C-H bonds employing $PhI(OAc)_2$ as a stoichiometric oxidant, **Scheme 1.7**.



Scheme 1.7 Oxygenation of a sp^3 C-H bond

The high level of selectivity for the β-position to the oxime is due to the formation of a favourable 5-membered palladacycle **18** with no reactivity at the more acidic *α*-hydrogen (**Figure 1.3**). Substrates not possessing a methyl group at the *β*-position did not react, suggesting a selectivity for primary C-H bonds over secondary C-H bonds.[34]

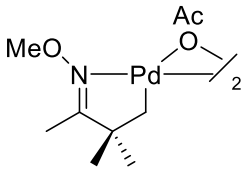


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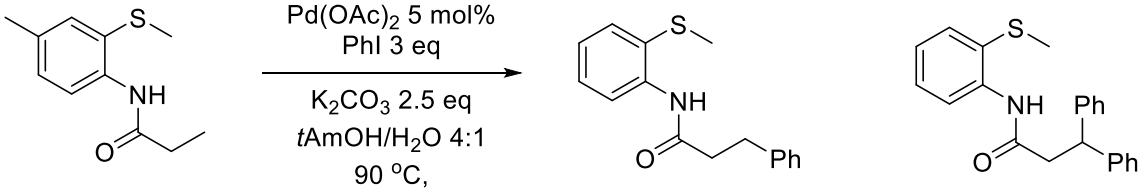
Figure 1.3 Proposed palladacycle intermediate of an oxime directed C-H activation

1.4.2 Sulphur containing directing groups

Thioaniline directing groups had been previously reported for the arylation and alkylation of both sp^2 and sp^3 C-H bonds, and provide good selectivity for the monoarylation of primary C-H bonds. In **Scheme 1.8** a 2-methylthioaniline directing group is used for the arylation of 2-methylthio-*N*-propionylaniline **19** leading to product **20** with 84% yield. Despite high selectivity for the primary C-H bond, these conditions do however result in the formation of 13% of diarylated product **21**.[35] This directing group has been applied to the functionalisation both of cyclopropanes[36] and cyclobutanes.[37]



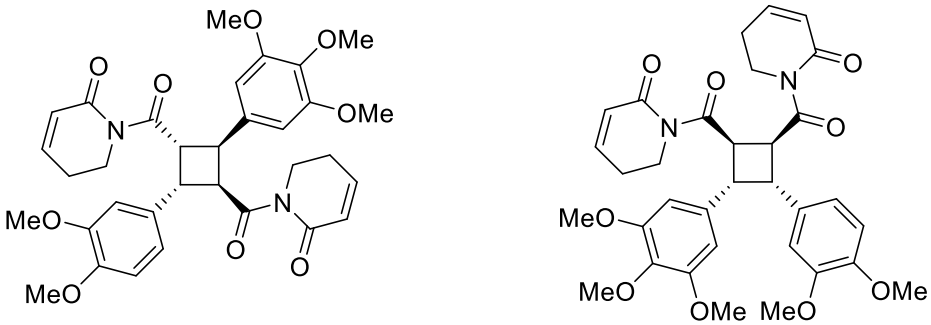
19

20
84%

21
13%

Scheme 1.8 Arylation directed by a 2-methylthioaniline group

An sp^3 arylation strategy using an *o*-thioanisidine directing group was successfully used in the total synthesis of piperarborenines B and D (**Figure 1.4**) for the addition of the aryl groups to the cyclobutane ring.[37]

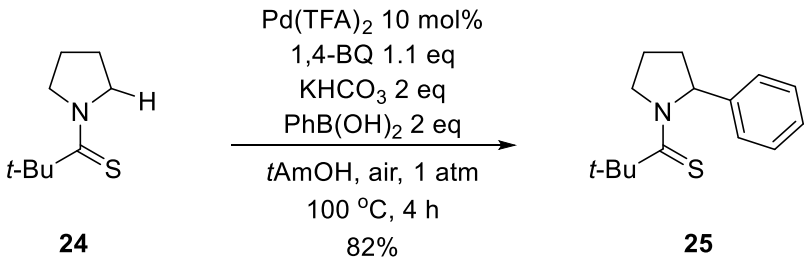


22
Piperarborenine B

23
Piperarborenine D

Figure 1.4 Piperarborenines B and D

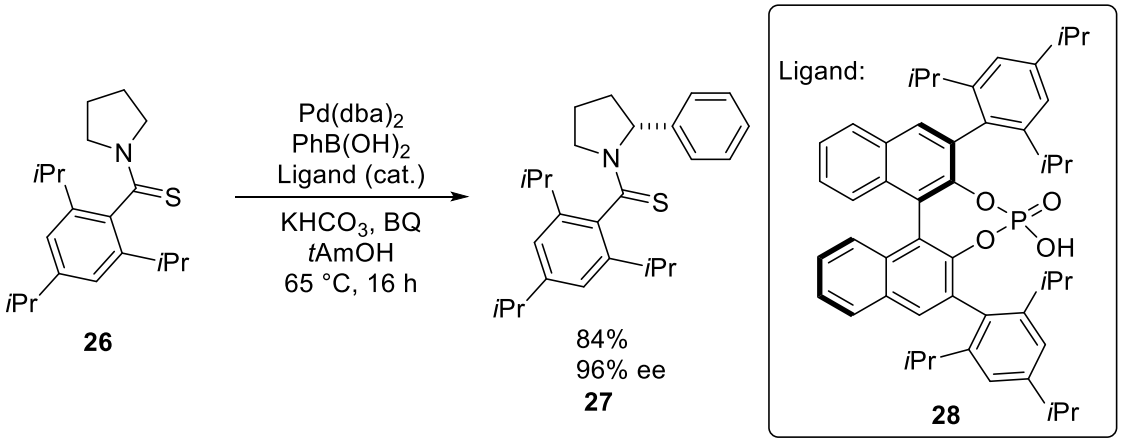
Thioamides such as **24** have been used as directing groups for the *α*-arylation of saturated azacycles using an aryl boronic acid; the sulphur can coordinate to the palladium catalyst to stabilise the palladium intermediate (**Scheme 1.9**). This reaction requires an equivalent of 1,4-benzoquinone and uses a boronic acid as the coupling partner.



Scheme 1.9 Arylation using a thioamide directing group

Surprisingly, no arylation of the terminal methyl groups in **24** was observed under the conditions shown in **Scheme 1.9** despite the usual preference for the activation of primary over secondary C-H bonds.[38]

This thioamide directing group can also be used in an enantioselective C-H arylation, by employing a chiral phosphoric acid ligand **28**, **Scheme 1.10**.

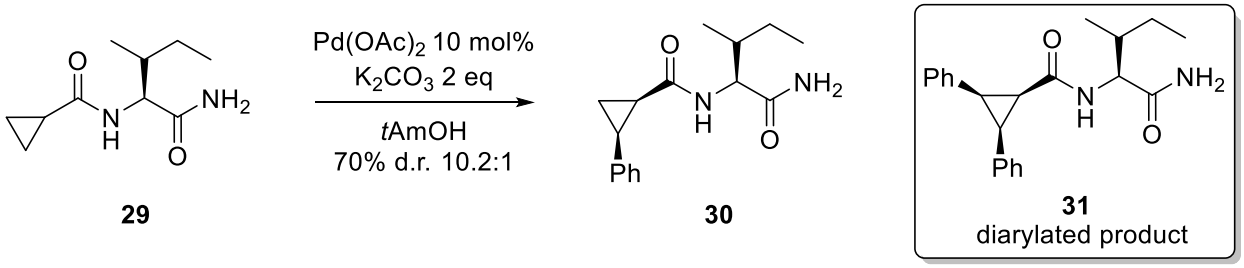


Scheme 1.10 Enantioselective arylation using a chiral ligand

1.4.3 Amino acids as directing groups

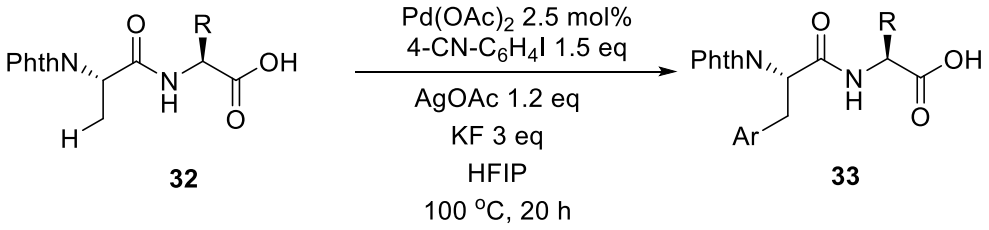
Amino acids have been used as bidentate directing groups for asymmetric functionalisation of C-H bonds to construct new stereogenic centres. They have the advantage of being both a directing group and potentially part of the final molecule due to the high number of peptide drugs available. There is a considerable advantage in using a directing group that is also part of the final target molecule; it reduces the number of synthetic steps required and increases the atom economy of the process.

The use of substrate bound isoleucine as both a bidentate directing group and a chiral auxiliary for the asymmetric arylation of cyclopropanes has been investigated (**Scheme 1.11**). Arylation of the cyclopropane moiety in **29** using isoleucine as a directing group led to **30** in good yield however some of the diarylated product **31** was observed. Other chiral auxiliaries were tested, such as valine, but isoleucine gave a superior yield and diastereoselectivity. Replacing the isobutyl group of *iso*-Leu with *tert*-butyl gives superior diastereoselectivity (13.7:1) but much lower yield (49%).[39]



Scheme 1.11 Example of an amino acid mediated arylation of a cyclopropane

Selective functionalisation of di, tri and tetrapeptides has also been achieved using amino acids as bidentate directing groups. **Scheme 1.12** shows an example of the C terminus of dipeptide **32** being arylated. These conditions were applied to a wide range of dipeptides with good yields (74 – 92%), and similar conditions can be applied to tri- and tetrapeptides.[40]

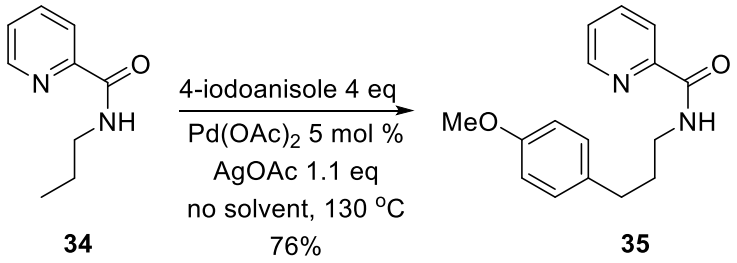


Scheme 1.12 Arylation of a dipeptide

1.4.4 Amide linked directing groups

Amide linked directing groups have proven useful for the C-H activation of amines. They are easy to install on the amine scaffold and are robust enough to withstand the forcing reaction conditions often required for C-H activation.

In seminal research by Daugulis it was shown that an amide linked pyridine containing auxiliary attached to the molecule can lead to selective C-H activation and subsequent arylation. The pyridine functionality can chelate to the palladium catalyst and facilitate the C-H activation and oxidative addition steps. **Scheme 1.13** shows a picolinamide group being used to direct C-H activation of aliphatic amine **34**, resulting in *γ*-activation. This method allows for the monoarylation of methyl groups, in preference to the activation of methylene C-H bonds.[41,42]



34 **35**

Scheme 1.13 Arylation of an aliphatic amine directed by a removable picolinamide auxiliary

A possible palladacyle intermediate **36** for this reaction is shown in **Figure 1.5**. These transformations require a free NH suggesting that palladium amides are involved in the catalytic cycle; corresponding *N*-methyl substituted amides were unreactive. Although steric hindrance around the amide nitrogen in the methylated substrates may also contribute to them not being reactive, crystal structures of palladacycle intermediates showing a deprotonated amide have been obtained.

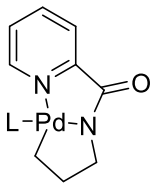


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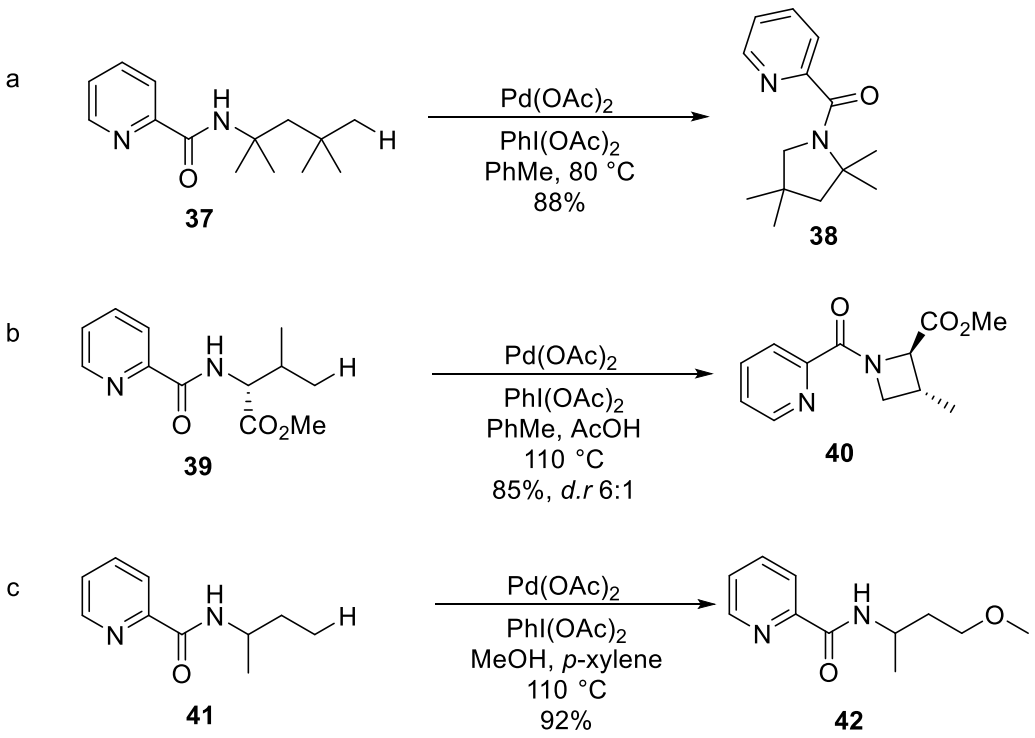
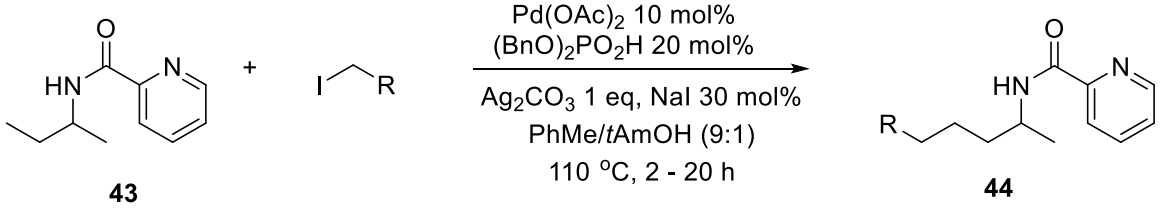
Figure 1.5 Palladacyle intermediate using a bidentate directing group

This picolinamide directing group can be used in the formation of carbon heteroatom bonds using a variety of conditions. The intramolecular amination to form pyrrolidines[43] and azetidines[44] can be achieved using $PhI(OAc)_2$ as the oxidant and palladium acetate as the catalyst. Alkoxylation can be achieved under similar conditions but in the presence of an alcohol, **Scheme 1.14**.[45]



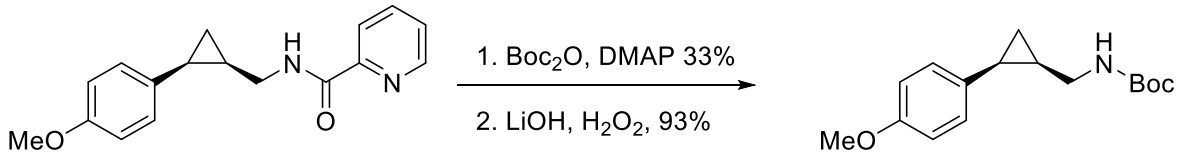
Scheme 1.14 Reactions using the picolinamide directing group

Chen *et al.* showed that the alkylation of unactivated sp^3 C(sp^3)-H bonds can be achieved using alkyl iodides and dibenzyl phosphate as an additive, **Scheme 1.15**. The reaction tolerated a range of alkyl iodides, giving products in 23 - 87% yield.[46]



Scheme 1.15 Picolinamide directed arylation of a C(sp^3)-H bond

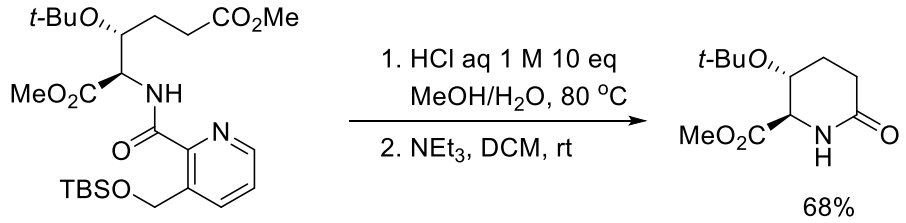
An important factor in the selection of a directing group is its ease of removal under conditions that can be tolerated by other functional groups present on the molecule. For example the picolinamide auxiliary of **45** has been removed to give the Boc-protected amine **46** in moderate yield over two steps, **Scheme 1.16**.[47] The need to derivatise the free amine products for purification also reduces the efficiency of the process.



45 **46**

Scheme 1.16 Removal of a picolinamide directing group to yield the Boc-protected amine

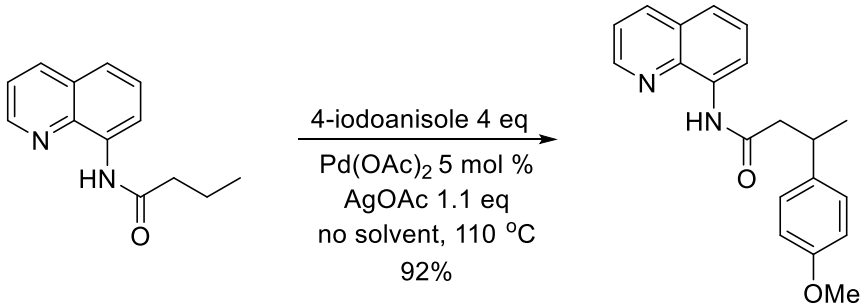
However, the picolinamide auxiliary can prove difficult to remove under conditions suitable for other functional groups on the molecule. A more easily removable auxiliary can be used in its place, such as the one shown in **Scheme 1.17**. The directing group is removed to give the free amine, followed by intramolecular cyclisation to furnish the disubstituted piperidinone **48**.[46] This substituted picolinamide directing group is installed using the corresponding carboxylic acid, which requires a lengthy synthesis unlike the unsubstituted 2-picolinic acid which is commercially available.



47 **48**

Scheme 1.17 Removal of an amide linked directing group and subsequent cyclisation

8-Aminoquinoline amides can also be used as a removable auxiliary for the arylation of sp^3 C-H bonds and are another example of a bidentate directing group. Reactions generally proceed faster than those using a picolinamide group but unlike the picolinamide auxiliary, secondary C-H bonds react faster than primary. **Scheme 1.18** shows the methylene group on compound **49** being arylated instead of the methyl;[35] a similar approach using nickel catalysis has been reported.[48] The aminoquinoline group has also been utilised for the functionalisation of amino acids, proving to be more effective than a pyridine directing group.[49]

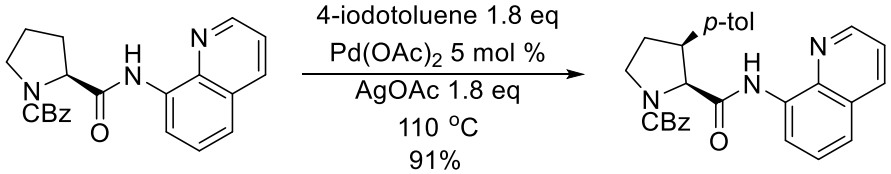


49 **50**

Scheme 1.18 Arylation directed by an aminoquinoline group

The alkylation of substrates bearing either a picolinamide or aminoquinoline directing group has been reported. Good results could be obtained for the alkylation of aromatic picolinamides however it was not possible to alkylate sp^3 C-H bonds in the same way.[50]

Functionalisation at the C2 position of pyrrolidines has attracted considerable research interest[51–53] and has been achieved using thioamide[38] and amidine directing groups.[54] Activation of the C3 position with stereocontrol has also been reported using palladium catalysis and an aminoquinoline directing group which will orientate towards the *cis*-C(3)-H, **Scheme 1.19**.

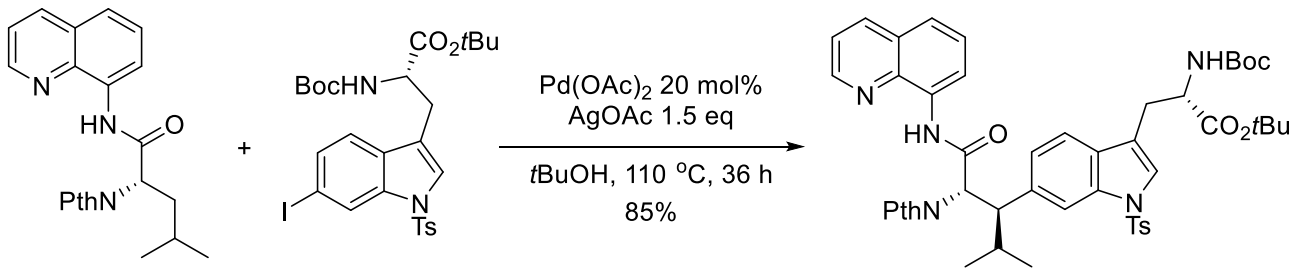


51 **52**

Scheme 1.19 Functionalisation of the C3 position of pyrrolidine

The reaction conditions shown in **Scheme 1.19** could be used with a good scope of *para* and *meta* substituted aryl iodides, however those with *ortho* substituents show lower yields due to increased steric congestion.[55]

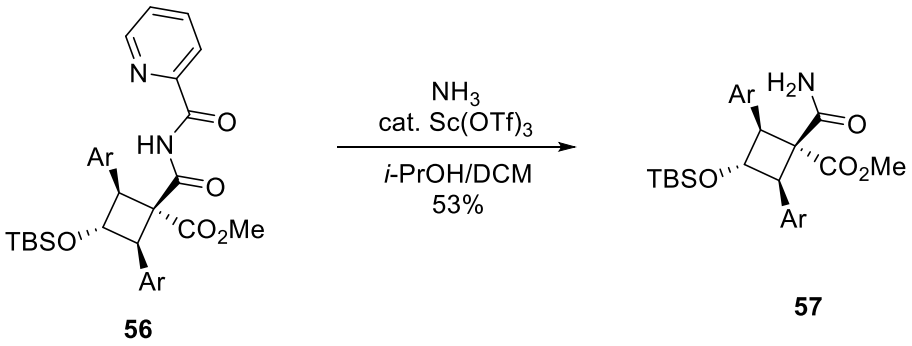
In 2010 directed C-H functionalisation was employed by Chen in the stereoselective indolylation of *N*-phthaloyl leucine **53** to form the Trp C6 to Leu Cβ linkage present in the natural product celogentin C, **Scheme 1.20**.[56] Previously this arylation method had only been applied to more simple aryl iodides.[41] As a drawback, this method uses a relatively high catalyst loading of 20 mol% and relies on stoichiometric amounts of silver acetate.



Scheme 1.20 Example of C-H activation applied in total synthesis

Despite extensive research into the use of these amide linked directing groups, difficulty in removing them limits their potential in late stage functionalisation unless the amide is also part of the desired final compound.

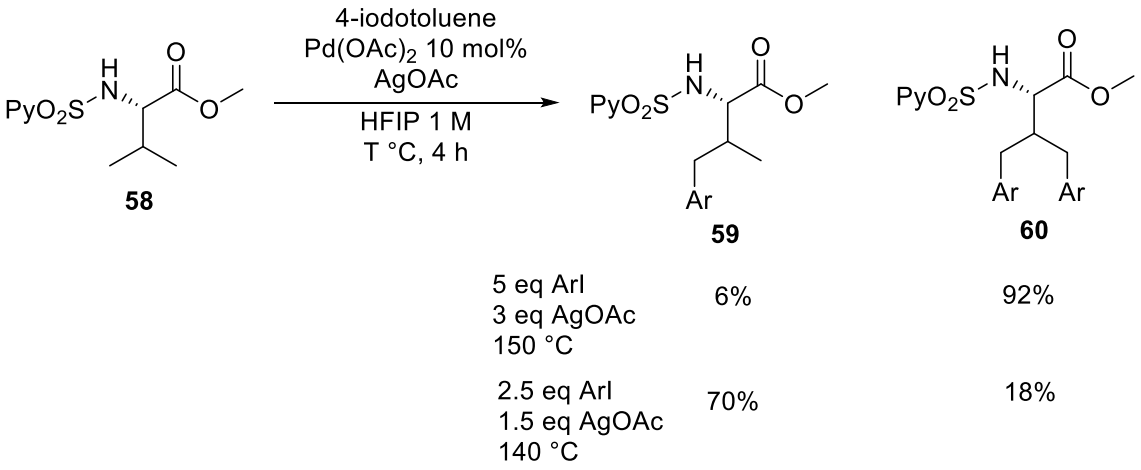
In the synthesis of dictazole A the amide linked directing group was replaced with the imide linked picolinamide based directing group (in compound **56**); this proved much easier to remove, **Scheme 1.21**.[57]



Scheme 1.21 Imide linked directing group removal

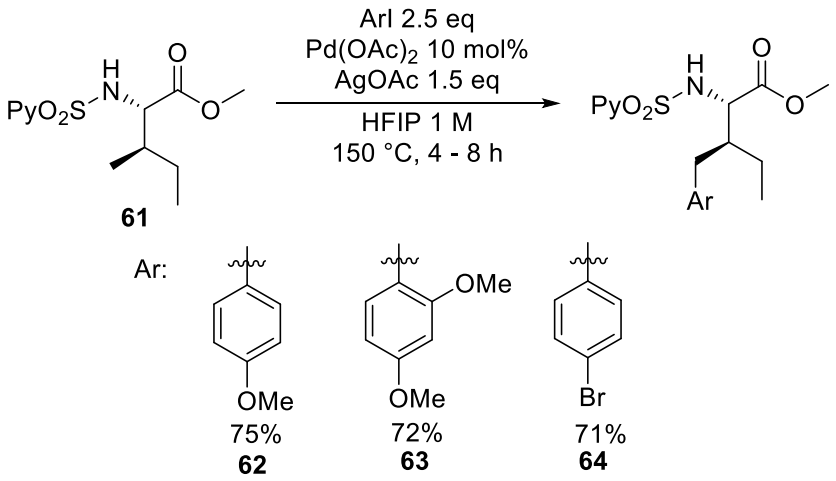
1.4.5 Sulphonamide linked directing groups

Sulphonamides provide an alternative linkage to amides for the tethering of a directing group to amine substrates. Carretero and coworkers introduced the *N*-(2-pyridyl) sulphonyl group as a directing group for the C(sp^3)-H functionalisation of amino acid derivatives. In the C-H functionalisation of the methyl ester of valine both the mono **59** and diarylated **60** products were observed due to the functionalisation of both equivalent methyl groups. Reducing the equivalents of aryl iodide and silver acetate could reduce the extent to which diarylation occurs, or increasing the equivalents of aryl iodide can give excellent yields of the diarylated product, **Scheme 1.22**. Presumably due to steric congestion no gem diarylation was observed.



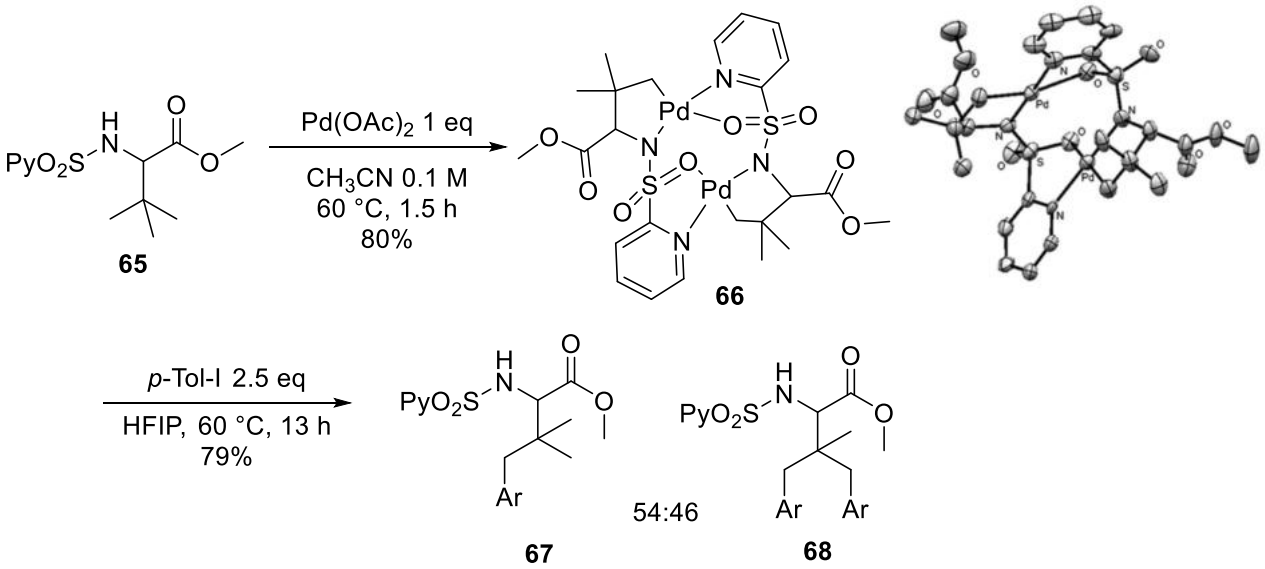
Scheme 1.22 Arylation of a valine derivative

The reaction could be applied to a range of amino acid derivatives, showing selectivity for C-H functionalisation at methyl groups. The reaction was tolerant of a small range of aryl iodides, including those with ortho substitution giving moderate yields of the products, **Scheme 1.23**.



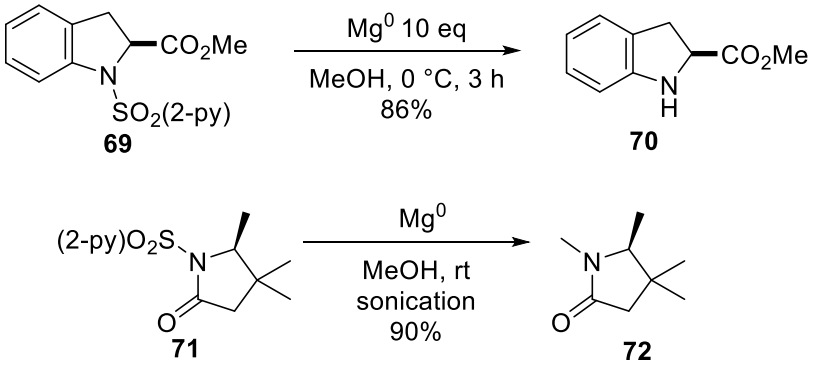
Scheme 1.23 Functionalisation of an allo-isoleucine derivative

A palladium (II) complex **X** was also isolated to show the role of the directing group in C-H activation. The stoichiometric reaction with $Pd(OAc)_2$ and compound **65** in acetonitrile gave bimetallic complex **66**, which was characterised by XRD. This complex could be reacted with an aryl iodide under the original reaction conditions to give the arylated products **67** and **68** in 79% yield, **Scheme 1.24**.[58]



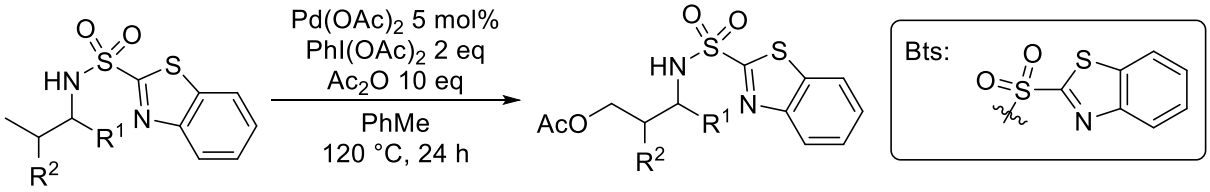
Scheme 1.24 Isolation of a bimetallic species and X-ray crystal structure of bimetallic complex **X**. H atoms omitted for simplicity

The 2-pyridylsulphonyl group has been shown to be easily removable under milder conditions than those used to remove picolinamide groups, and can act as an effective directing group.[59] Magnesium metal in methanol, or zinc and ammonium chloride in THF, can be used to cleave this directing group in good to excellent yield, **Scheme 1.25**.[60,61] This directing group has also been used for the carbonylative cyclisation of amines in amino acids and peptides.[62]



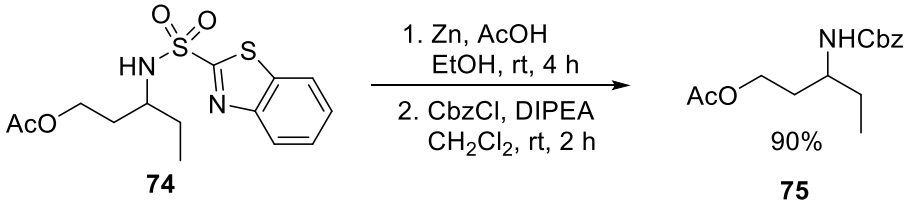
Scheme 1.25 Sulphonamide directing group cleavage

The Bts group was introduced by Xuan and co-workers for the acetoxylation of C(sp^3)-H bonds, **Scheme 1.26**, as a method to give *γ*-hydroxy amine derivatives. The reaction tolerated a range of aliphatic amines including those with methyl esters and protected alcohol groups, to give the acetoxylated products in good to excellent yields (52 – 85%).



Scheme 1.26 Bts directed acetoxylation

This group can be removed under mild conditions, something that was not possible with previous directing groups used for acetoxylation. Removal of the Bts group can be achieved using zinc and acetic acid in ethanol, which is followed by Cbz protection, **Scheme 1.27**.[63]

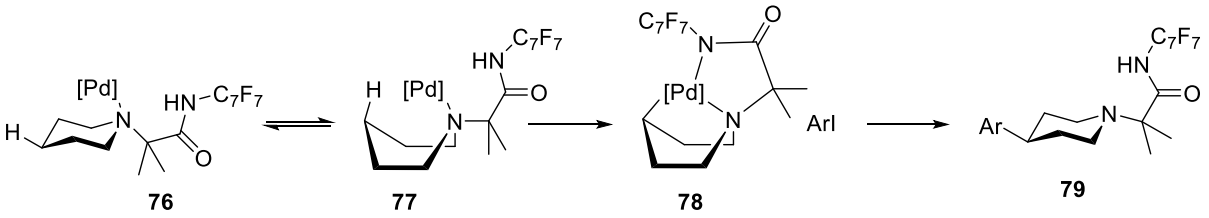


74 **75**

Scheme 1.27 Removal of Bts group

1.4.6 Arylation of nitrogen heterocycles

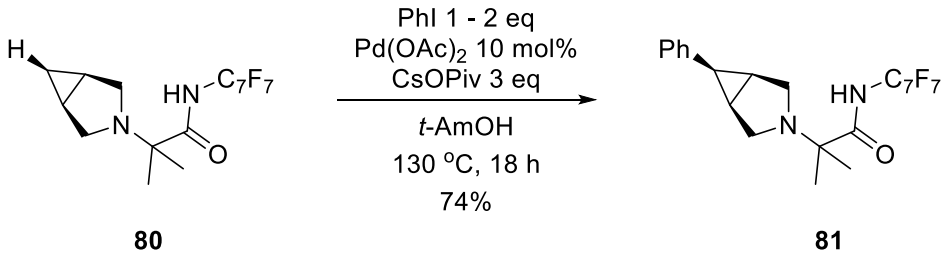
Methods to use directing groups that do not link to the nitrogen of the scaffold by an amide bond are being developed. The remote activation of nitrogen heterocycles has been reported *via* the generation of a [2.2.1] bicyclic palladacycle, **Scheme 1.28**, using a directing group that does not link to the substrate via an amide bond.



76 **77** **78** **79**

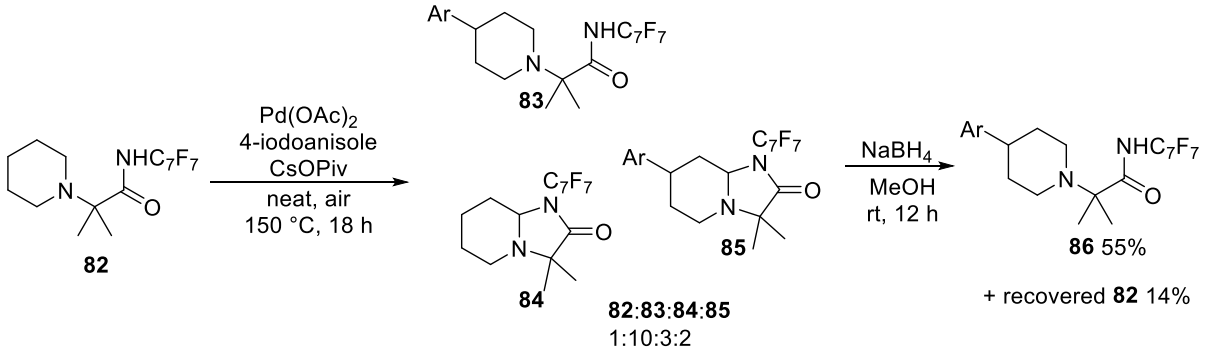
Scheme 1.28 General scheme for the activation of piperidine

A test substrate **80** was developed, featuring a fluoroamide directing group, and the reaction was optimised for transannular C-H arylation, **Scheme 1.29**. This directing group also features a free amide NH. The aryl group is installed on the concave face of azabicycle **81** and the reaction conditions performed well with a large scope of coupling partners including aryl iodides and bromides to give the arylated products in moderate to excellent yields. This method can be used to give functionalised nitrogen heterocycles, and the directing group can be removed using samarium (II) iodide, to give the amine product.[21]



Scheme 1.29 Optimised conditions for the arylation of a saturated nitrogen heterocycle

For the majority of substrates prepared using this method, an additional sodium borohydride reduction was required to remove the aminal side products **84** and **85**, **Scheme 1.30**.

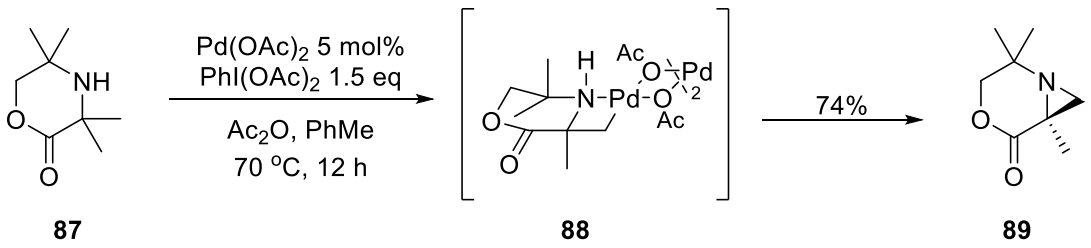


Scheme 1.30 Additional purification step in the isolation of arylated amines

1.4.7 Activation of free amines

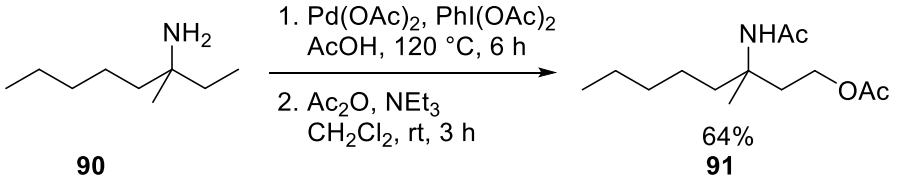
Functionalisation of the free amine can be a more efficient method for use in late stage functionalisation but does suffer from limitations and a narrow substrate scope.

The activation of free secondary amines has been reported, to generate strained nitrogen heterocycles, by the generation of the strained 4-membered palladacycle **88**. The first examples of free amine directed catalytic activation of primary C-H bonds by *Gaunt* required bulky disubstituted amine substrates, **Scheme 1.32** which limits their synthetic use. The method is also not applicable to primary amines due to the formation of unreactive *bis*(amine)-palladium complexes.[64,65] These 4-membered palladacycles have also been used in the arylation of hindered secondary amines using arylboronic esters.[66]



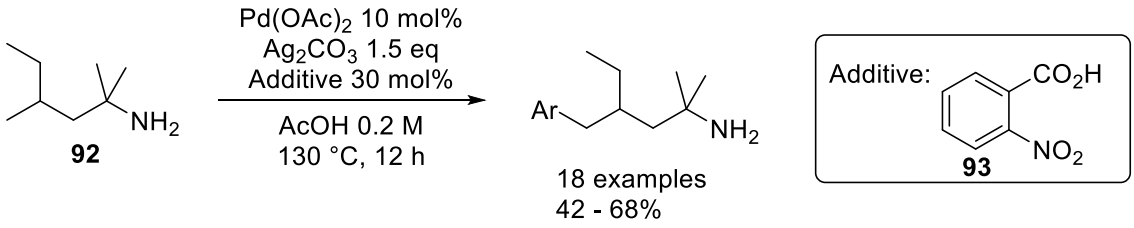
Scheme 1.31 *β*-Activation *via* a four membered palladacycle intermediate

Similar conditions were employed for the acetoxylation of primary amines with an α quaternary centre, **Scheme 1.32**. The conditions employed also result in the acylation of the amine. Previously this was not possible due to the formation of unreactive palladium complexes, but weak acids can aid the dissociation of the complex. Amines with an α tertiary centre gave poor yields giving the reaction a limited substrate scope.[67]



Scheme 1.32 Acetoxylation of a primary amine

With the knowledge that the addition of a weak acid aids the C-H functionalisation of free primary amines, the δ arylation of a free primary amine substrate **92** could be achieved by the addition of compound **93** in 30 mol%, **Scheme 1.33**. This method gave better yields when the amine was sterically crowded. Without the ligand and acetic acid solvent, the primary amine substrate would form a stable *bis* amine palladium complex leading to no C-H activation taking place.[68]

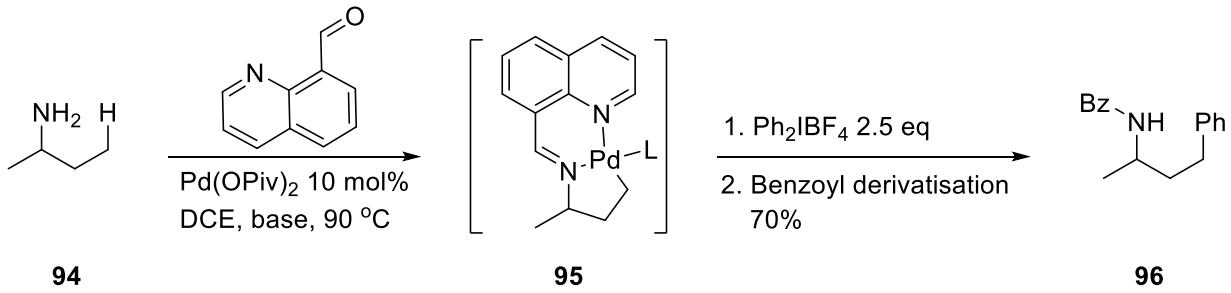


Scheme 1.33 δ-arylation of a free amine

1.4.8 Imine linked directing groups

The arylation of free amines can be achieved using an *in situ* generated imine linked directing group. With the advantage of not having two extra synthetic steps, moreover, the easy removal of the directing group improves the efficiency of the C-H functionalisation route. 8-Aminoquioline carboxaldehyde can be used to form an imine *in situ* with the amine

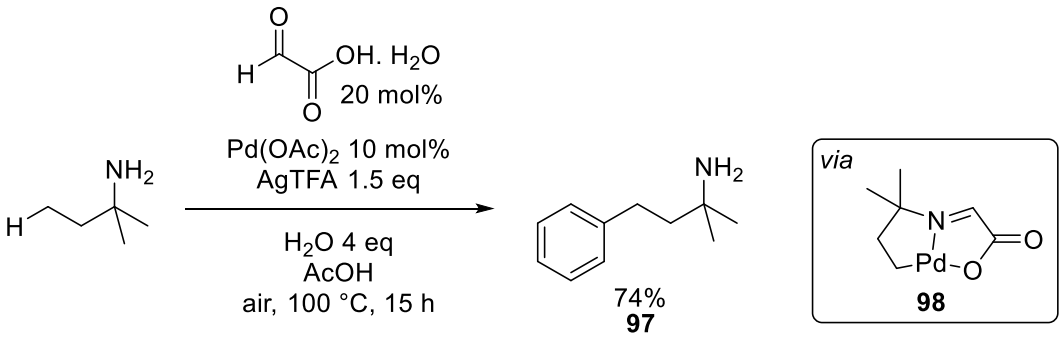
substrate. The palladium catalysed C-H activation can then take place, followed by the hydrolysis of the imine to give the amine product, **Scheme 1.34**.[69]



Scheme 1.34 Example of an *in situ* generated directing group

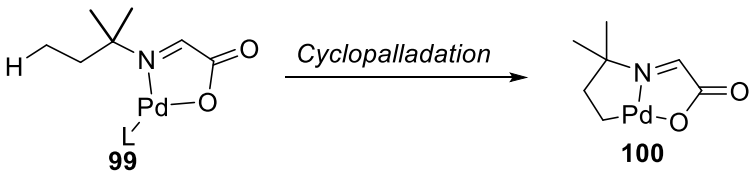
This example is limited in its utility, as it requires DCE as the solvent, which is toxic. The reaction also requires strict anhydrous conditions to prevent the hydrolysis of the *in situ* generated imine.

The use of *in situ* generated imines has gathered a significant research interest, as they have the potential to be catalytic. For the arylation of *tert*-amyl amine, glyoxylic acid was used as a transient directing group and could be used catalytically to give 74% of the product **97**, **Scheme 1.35**.[70]



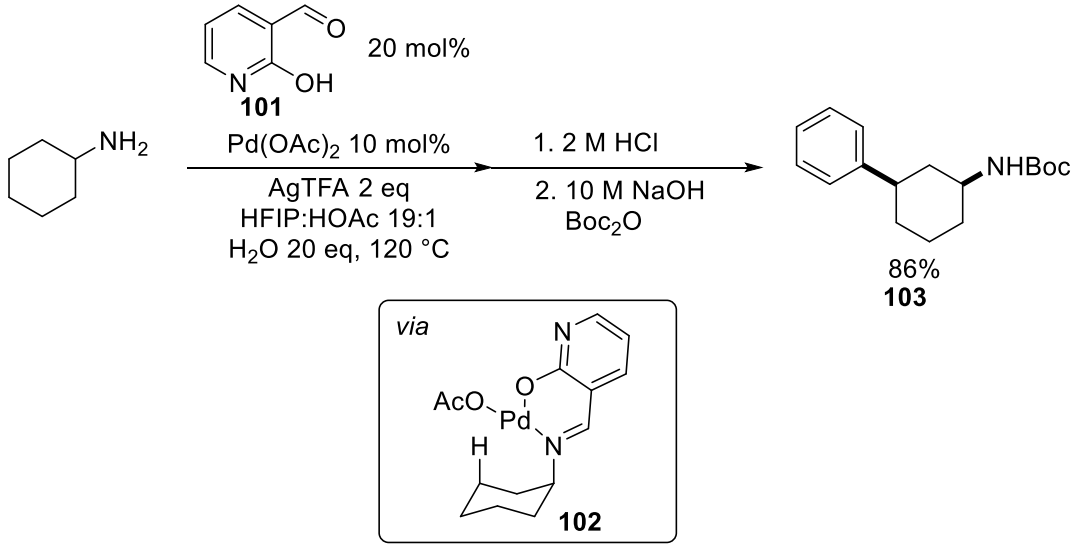
Scheme 1.35 Arylation of *tert*-amyl amine using a transient directing group

This reaction shows significantly reduced yields when applied to amines without an α-quaternary centre. This is due to the Thorpe-Ingold effect,[71] where angle compression favours ring closing reactions, which are needed for the C-H activation to occur. The gem dimethyl group in compound **99** moves the C-H bond to be activated closer to the palladium, and so accelerating the cyclopalladation.



Scheme 1.36 Cyclopalladation with a gem dimethyl group

In 2016 *Yu* and coworkers reported the C(sp^3)-H arylation of primary amines using a catalytic transient directing group, **Scheme 1.37**. Aldehyde **101** condenses with the primary amine to be functionalised to form the imine. The weakly acidic hydroxyl group of aldehyde **101** is deprotonated under the reaction conditions allowing the oxygen to coordinate to the palladium catalyst, to give complex **102**. The presence of water in the reaction allows for the hydrolysis of the *in situ* generated imine after C-H functionalisation to release the aldehyde, and Boc protection of the free amine is needed to ease purification. A wide variety of aryl iodides were tolerated in the reaction giving 40 – 91% yield of arylated product, and the scope included electron rich, electron poor and heterocyclic ring systems. This reaction does require the use of a stoichiometric silver salt, as well as HFIP as the solvent.[72]

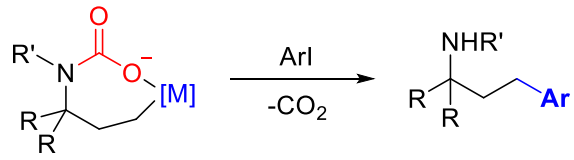


Scheme 1.37 *In situ* imine formation for directing C-H activation

1.4.9 Traceless directing groups

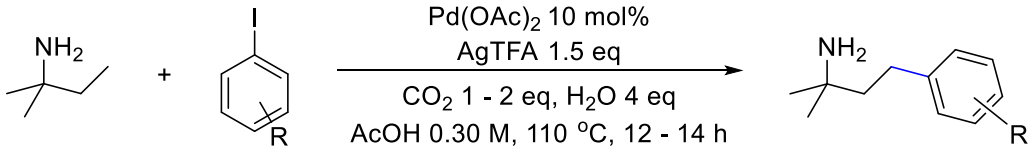
The use of carbon dioxide as a traceless directing group was demonstrated by Larrosa for the *meta* C(sp^2)-H functionalisation of phenols[73] and fluoroarenes[74] and can circumvent the difficulties associated with the addition and removal of a directing group. Carbon dioxide can also be used to direct C(sp^3)-H activation. It can react with amines, resulting in a transient carbamate which is able to coordinate to a palladium catalyst with the benefit of being more

chemically robust than an imine. **Scheme 1.38** shows the proposed metallocycle intermediate and product of this reaction.



Scheme 1.38 Approach using a hybrid CO_2 directing group

The reaction showed a wide substrate scope for the arylation of *tert*-amyl amine, with moderate to good yields (31 – 79%), **Scheme 1.39**.



Scheme 1.39 Conditions for the CO_2 directed C-H arylation

The methodology can also be applied to a range of primary and secondary amine substrates, **Figure 1.6**. While the reaction worked in moderate yields with primary amines, reduced yields were seen when employing secondary amine substrates. Amines with benzylic positions were not oxidised under the reaction conditions.[75]

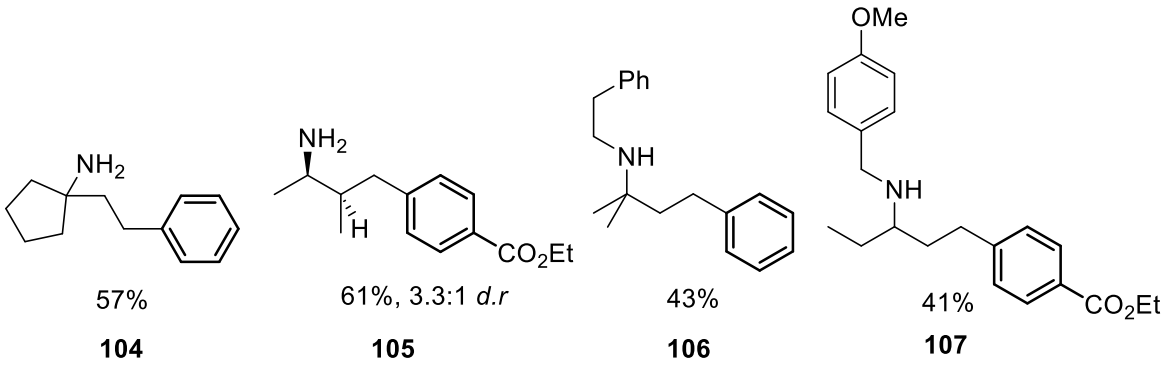
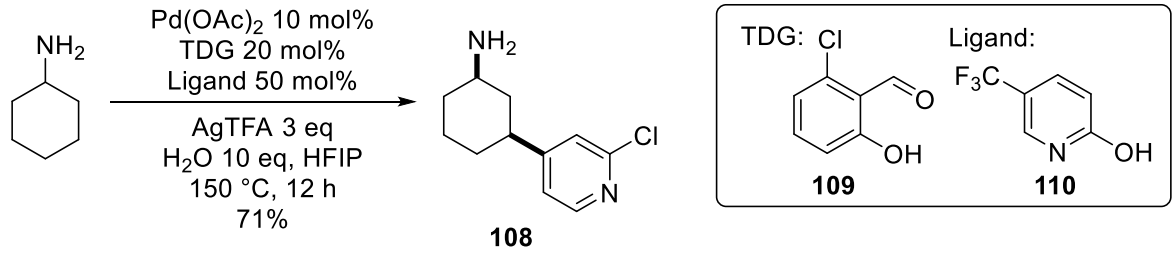


Figure 1.6 CO_2 directed C-H arylation

1.5 Ligand assisted C-H activation

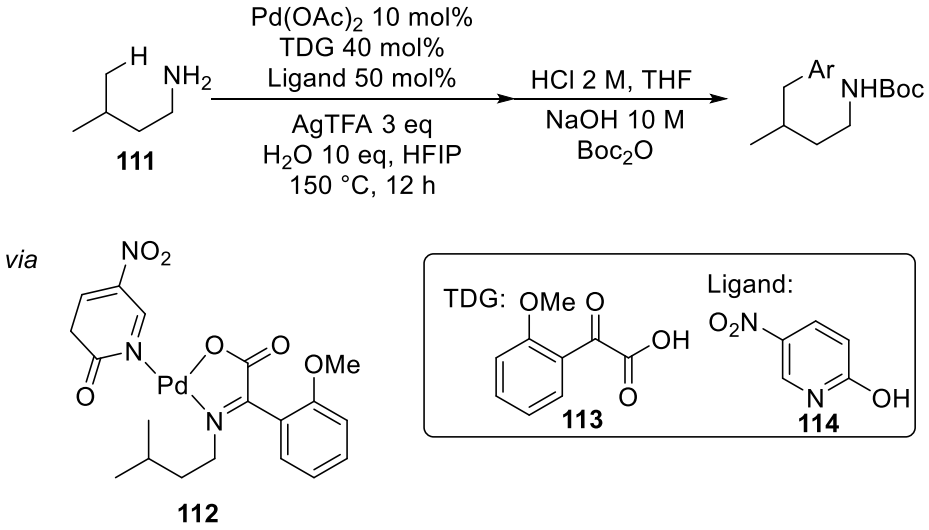
In palladium catalysed C-H activation reactions, unfavourable binding interactions of the reaction components with the catalyst can form unreactive complexes and prevent the desired reaction from proceeding.[76] The development of ligands for use in these reactions can help prevent these unwanted interactions.[77] The use of a chiral ligand can also lead to enantioenriched products.[78]

When using a transient directing group for the C-H functionalisation of aliphatic amines, low reactivity with heteroaryl iodide partners was seen due to the coordination of the aryl iodide to the palladium catalyst.[72] Introducing 2-pyridone ligand **110** prevented this unwanted coordination to the catalyst to give good yields of the heteroarylated products, **Scheme 1.40**. The reaction was also compatible with aryl bromides.



Scheme 1.40 Ligand assisted heteroarylation

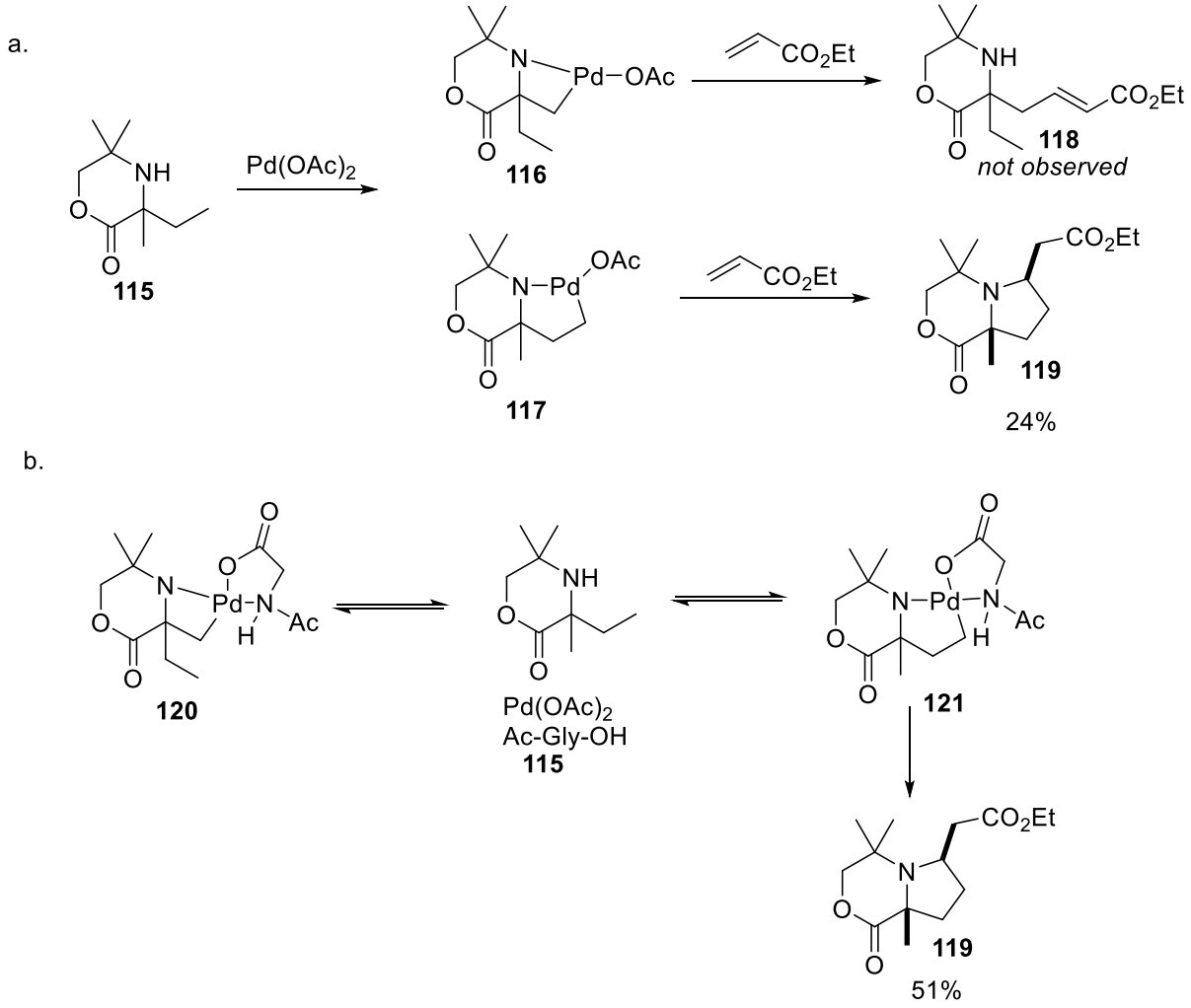
Ligand assisted C-H activation can also be used as a means to differentiate between the C-H bonds within a molecule, with a different directing group/ligand combination leading to γ or δ activation. Changing to transient directing group **113** to form a 5-membered chelate with the palladium, **112**, leads to δ activation, **Scheme 1.41**.[79]



Scheme 1.41 Ligand assisted δ arylation of aliphatic amines

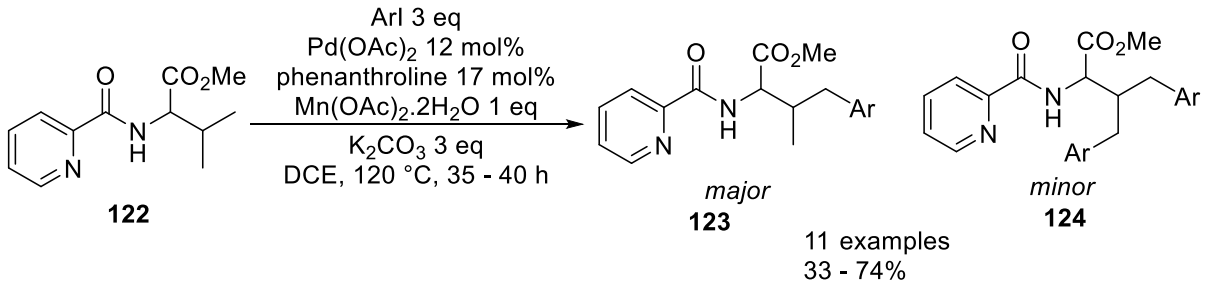
Ac-Gly-OH can be used as a ligand for the alkenylation of secondary amines to give complex pyrrolidines. Without the ligand both the 4 and 5 membered palladacycles **116** and **117** of amine **115** can be formed when treated with 1.5 equivalents of palladium acetate. When these complexes were reacted with an acrylate the pyrrolidine **119** was formed in 24% yield, **Scheme 1.42a**. The alkenylation product **118** from the 4-membered palladacycle **116** was not observed. The addition of the ligand increased this yield to 51% due to the ligand's ability to render the palladation reversible, and so driving the reaction towards the product

formed *via* the 5-membered palladacycle, **Scheme 1.42b**.[80] These amino acid ligands were first introduced by *Yu* and have been used for a number of applications in C-H functionalisation chemistry.[81–84]



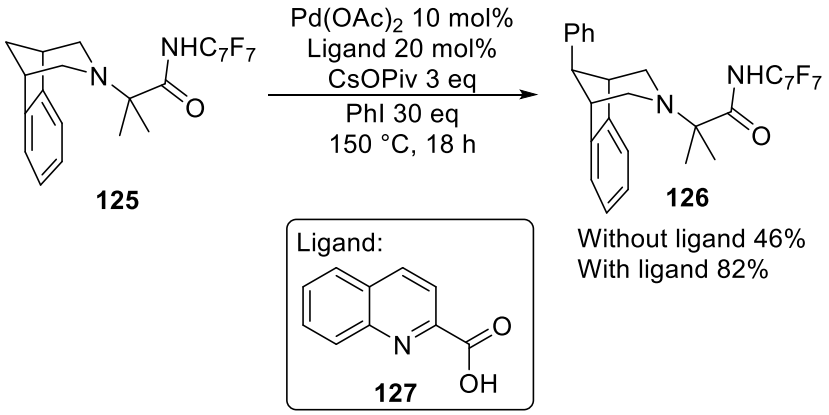
Scheme 1.42 Ligand assisted alkynylation

Picolinamide directed arylation of unnatural amino acids like **122** can be promoted by an inexpensive phenanthroline ligand, **Scheme 1.43**, which leads to a mixute of monoarylated **123** and diarylated **124** products. Unlike other picolinamide directed arylations which are proposed to go *via* a Pd^{II}/Pd^{IV} catalytic cycle, the mechanism for this Pd^{II}/Mn^{III} is unclear. As the addition of TEMPO suppresses the reaction the oxidative addition of the aryl iodide may occur *via* a single electron transfer pathway.[85]



Scheme 1.43 Phenanthroline promoted arylation.

Carboxylic acids can be used as ligands to enhance reactivity in palladium catalysed C-H functionalisation. Low yields were commonly encountered in the transannular arylation of nitrogen heterocycles such as **125** developed by Sanford. To improve upon this, a 2-picolinic acid ligand **127** was added to aid the turnover of the palladium catalyst. It was shown that the addition of this ligand played a role in the recovery of active catalyst from the precipitate which forms over the course of the reaction.[86]



Scheme 1.44 Ligand assisted transannular C-H arylation

1.6 Silver in C-H activation

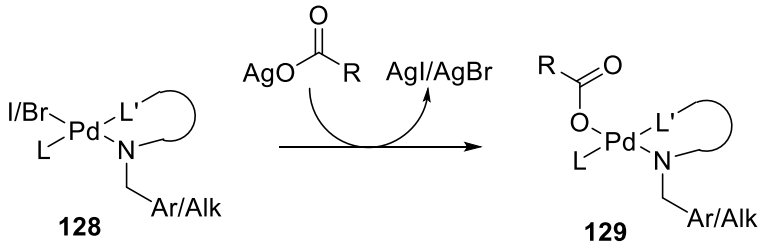
In directed C-H arylation and alkylation of amines a base is often included to promote the reaction. Silver salts such as silver acetate have been popular for use in these reactions, but there are drawbacks to their use. As the base is needed in stoichiometric quantities (typically 2 – 4 equivalents) the use of silver can be very expensive. Silver has also been identified by the ACS as an endangered element and is at a serious risk of supplies running out in the next 100 years.[87] Using a stoichiometric silver additive can also cause difficulties in the work-up and purification of products, due to the silver salts being difficult to remove during an aqueous work-up.

There are several potential roles which silver can play in a C-H functionalisation reaction. The most common to be proposed are:

1. Serving as a carboxylate source for the palladium (usually by abstracting a halide);
2. Acting as a terminal oxidant to regenerate the active Pd^{II} catalyst.

Other potential uses are for promoting the C-C bond coupling, reacting with the palladium to form bimetallic Pd-Ag intermediates which can facilitate C-H bond cleavage or the silver salt directly promoting C-H bond cleavage.[88]

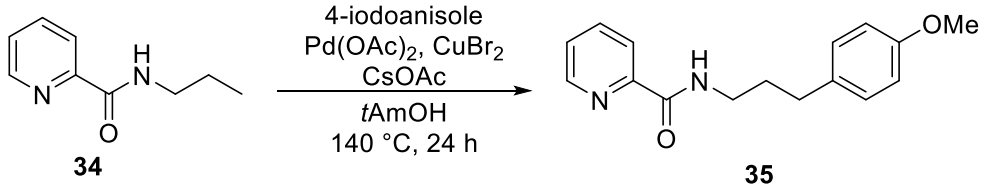
In the functionalisation of C(sp^3)-H bonds it is likely that the silver salt helps by abstracting a halide from the palladium catalyst, **Scheme 1.45**.[42,8] After the oxidative addition and reductive elimination of an aryl or alkyl halide from the palladium catalyst to generate the new carbon-carbon bond has taken place, complex **128**, the silver carboxylate salt can abstract the halide from the catalyst and replace it with a carboxylate ligand to regenerate the active palladium species **129**.



Scheme 1.45 Potential role of silver carboxylate salts

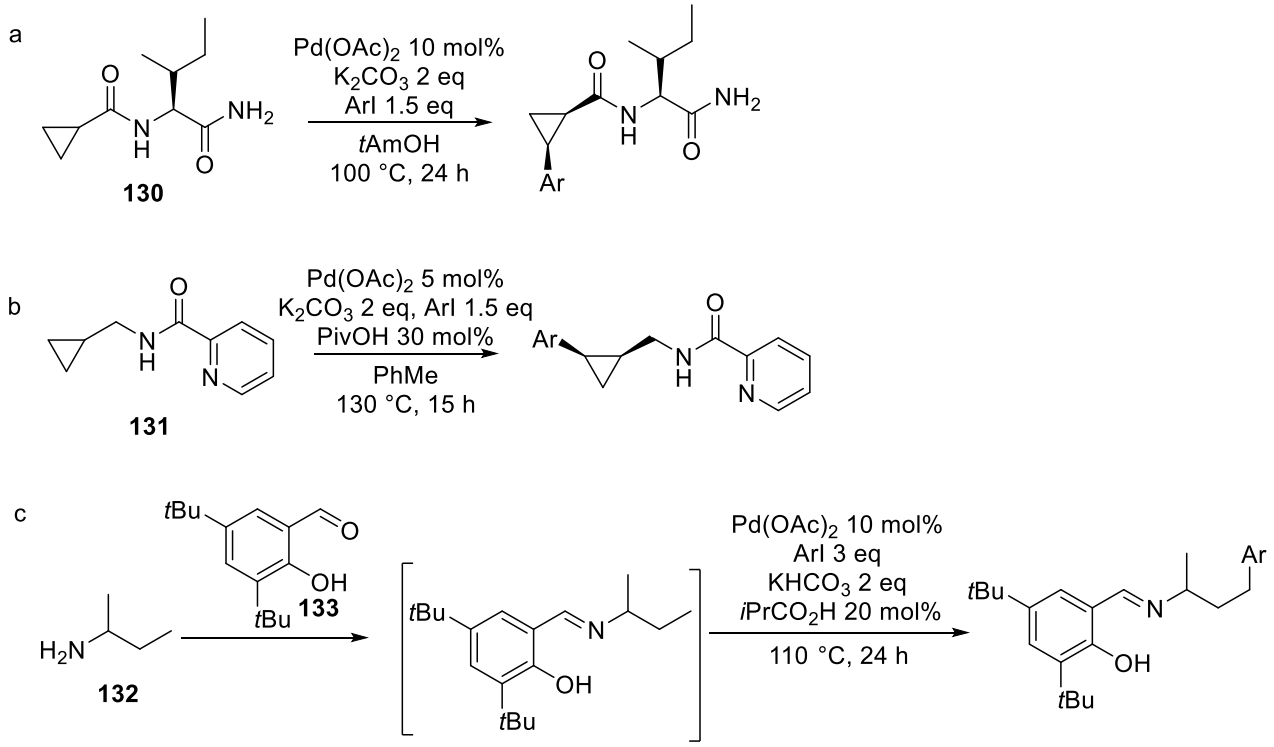
If this is the case it is possible to use an alternative base for the removal of halide from the palladium, and so remove the need for expensive silver additives. Other carboxylate salts and simple inorganic bases such as CsOAc and K_2CO_3 can be used to replace silver.

Cesium carboxylate salts can be used as alternatives to silver. For the arylation of amines directed by the picolinamide group, CsOAc can be used as the base to give good yields of the products, **Scheme 1.46**.[50] *Sanford* and co-workers used CsOPiv in their arylation of nitrogen heterocycles.[21]



Scheme 1.46 CsOAc as an alternative to silver

Potassium salts can also be used as bases in C-H functionalisation. They are often used with a carboxylic acid as a sub-stoichiometric additive. In the isoleucine directed arylation of a cyclopropane, potassium carbonate could be used as the base to give the arylated product, **Scheme 1.47a**.[39] The picolinamide directed arylation of cyclopropanes could also be achieved using the same base, but the presence of pivalic acid in 30 mol% was required to obtain high yields of the product, **Scheme 1.47b**.[47] When using a salicyl aldehyde **133** as a transient directing group, potassium hydrogen carbonate could be combined with 20 mol% of isobutyric acid to give the arylated free amines, **Scheme 1.47c**.[89]



Scheme 1.47 Potassium salts used in C-H functionalisation

1.7 Summary and project aims

The use of C-H activation as a method to functionalise otherwise inert C-H bonds has attracted a significant research effort, but has mostly focused on C(sp^2)-H functionalisation.[90–92] It has the potential to allow for the late stage functionalisation of drug candidates, as well as to provide a method for the synthesis of saturated compounds which could not previously be accessed in short synthetic sequences. These compounds increase the area of chemical space which can be explored in drug discovery.

A range of different methods for the C(sp^3)-H activation of amines have been developed. These include directed C-H activation using pre-installed or *in situ* generated directing groups. The activation of free amines is also possible, but this is limited to a small scope of amines and possible transformations. Many of these methods employ stoichiometric silver additives and toxic solvents, and there are few methods for the arylation of saturated bicyclic systems and heterocycles.

The aims of this project were:

- Develop C-H functionalisation methodology which can be applied to a range of mono, bi and tricyclic amine scaffolds using a nitrogen linked directing group.
- Find alternatives to stoichiometric silver salts and toxic solvents in C-H functionalisation reactions
- Investigate how electronics and structure of the directing group can control the position of functionalisation
- Study the mechanism for C-H functionalisation

Chapter 2

Arylation of saturated amines

2.1 Project aims and background

Many methods for the activation of C(sp^2)-H activation and some for C(sp^3)-H activation have been developed over the past 20 years (*vide supra,* introduction). A lot of these methods have failed to move away from the use of stoichiometric silver salts, and undesirable solvents (*vide supra*, Introduction).

Saturated amines feature in many pharmaceutical building blocks and APIs. Being able to make changes to their structure at a late-stage in synthesis by treating a C-H bond as a point to diversify the structure and synthesise analogues can be a powerful tool in drug discovery.

A key aim of this section of the project was to develop the arylation of saturated amines, with a focus on bridged bicyclic and tricyclic amines and amino substituted rings. There are several drugs on the market which feature these ring types, **Figure 2.1**, and so being able to perform C-H activation reactions on them can open up a larger amount of chemical space for drug discovery. It was important to perform these reactions without the use of stoichiometric silver salts, or toxic solvents such as DCE which are commonly used in C-H functionalisation reactions.

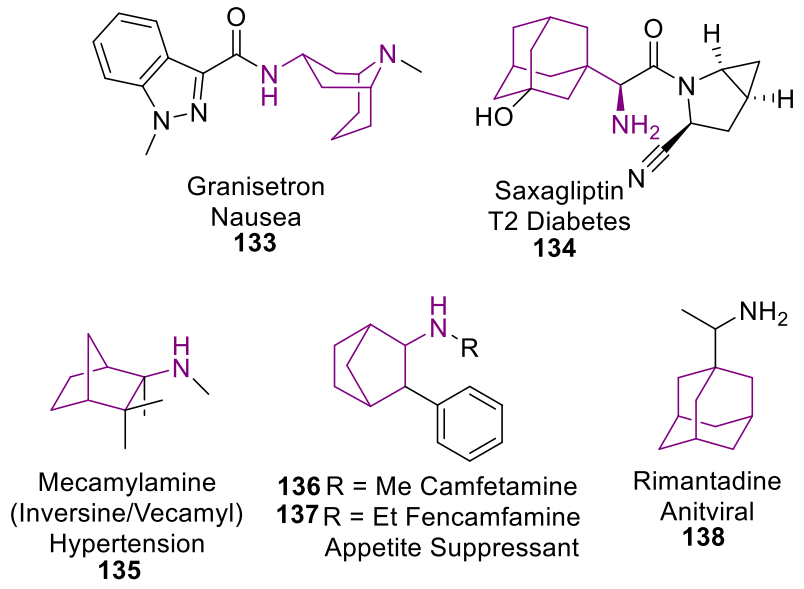


Figure 2.1 Drugs containing bicyclic and tricyclic amines

2.2 Synthesis of Starting Materials

Initial efforts were focussed on the synthesis of scaffolds on which to test C-H activation reactions. Amino substituted bicyclics provided a good starting point for these reactions as they are less likely to give the problem of *β*-hydride elimination. Amino substituted rings are

easily accessible and so were also used for initial screening of known reactions. Some simple commercially available amines were also used, **Figure 2.2**.

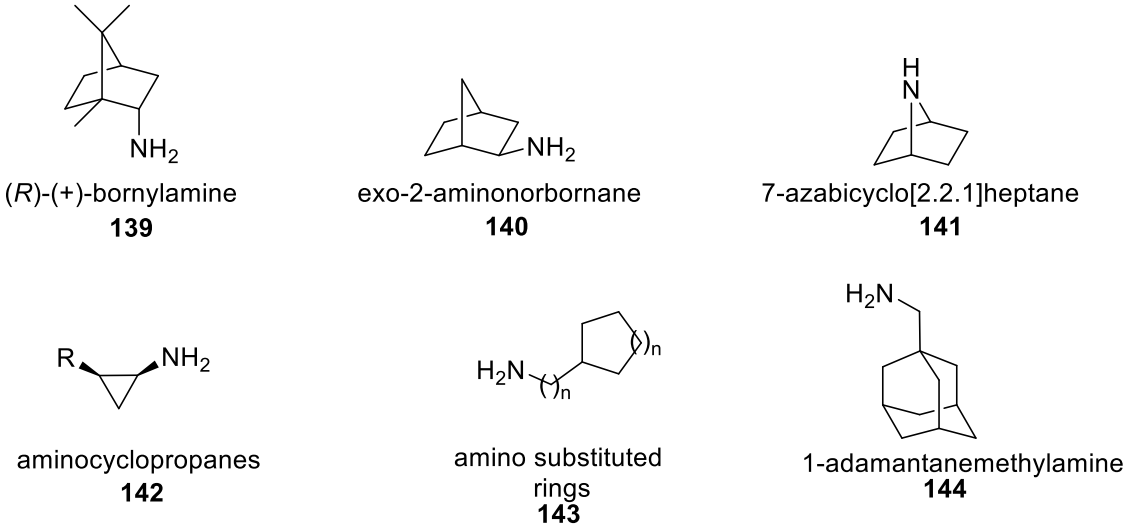


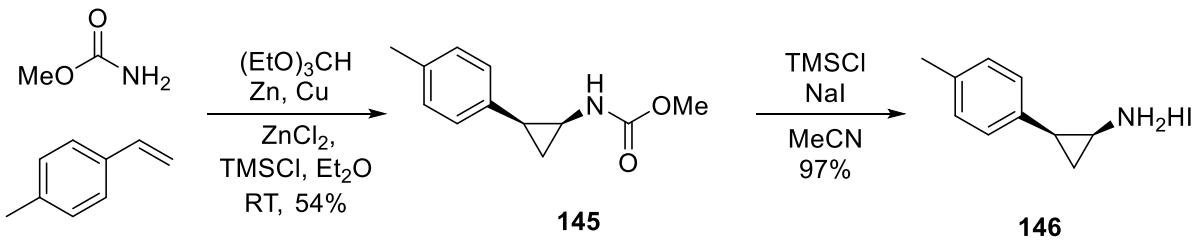
Figure 2.2 Examples of nitrogen containing scaffolds used

While many of these amines are commercially available, some had to be synthesised from nitrile, alkene or ketone starting materials.

2.2.1 Aminocyclopropane scaffold synthesis

Aminocyclopropanes are common in medicinal chemistry[93] and provide an interesting scaffold for C-H activation reactions. There are several methods available for their synthesis, and the addition of a protected aminocarbenoid to an alkene is the most simple.[94]

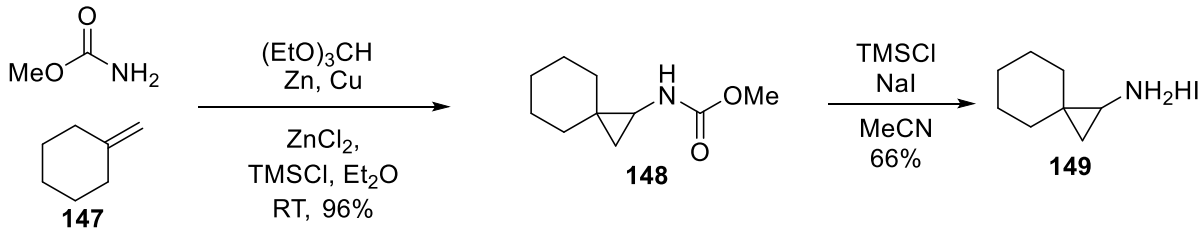
An amino cyclopropane was synthesised, using a one pot process which generates *in situ* a carbamatoorganozinc carbenoid. First, a novel carbamate protected aminocyclopropane was synthesised, giving compound **145** in moderate yield.[95] The *in situ* generation of TMS iodide was then used to cleave the carbamate, to furnish the desired aminocyclopropane as the iodide salt **146** in excellent yield, **Scheme 2.1**.[96, 97]



Scheme 2.1 Synthetic route for an aminocyclopropane scaffold

The same method can be applied to the synthesis of spirocyclic amines. When using exocyclic alkene **147**, the spirocyclic carbamate **148** is synthesised in excellent yield, **Scheme 2.2**. Deprotection of the carbamate using TMSI gives spirocyclic amine hydroiodide

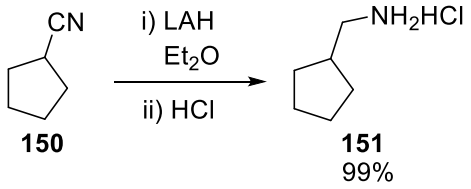
salt **149**. This spirocyclic amine has only previously been reported once in 1968, and required a lengthy synthesis.[98]



Scheme 2.2 Synthesis of a spirocyclic amine

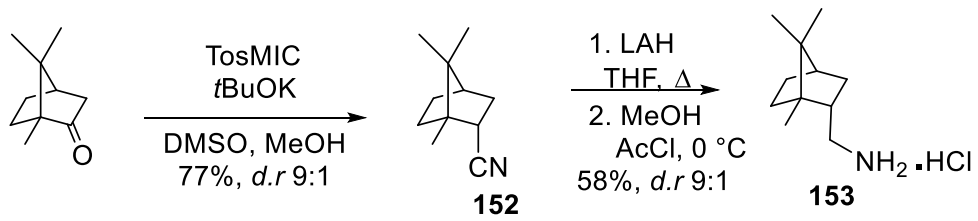
2.2.2 Synthesis of amines from nitriles

The reduction of nitriles using lithium aluminium hydride (LAH) provides an easy route for access to amines. Nitrile **150** was reduced to give amine hydrochloride salt **151** in high yield, **Scheme 2.3**.



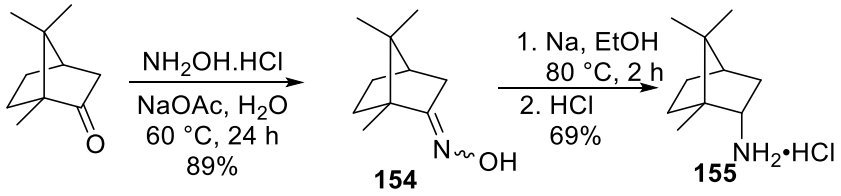
Scheme 2.3 Reduction of a nitrile using LAH

Tosylmethylisocyanide (TosMIC) may be used to convert a ketone into a nitrile *via* the Van Leusen reaction, which was first reported in 1977.[99] The nitrile then can be reduced using lithium aluminium hydride to give the corresponding amine. This method has been used to install a C1 fragment onto camphor to give **152**, **Scheme 2.4**. An extended reaction time of 72 h was required due to the steric bulk of the camphor substrate. Nitrile **152** was isolated as a 9:1 mixture of the *endo* and *exo* isomers.[100] Camphor provides an interesting target for activation and it is a privileged structure within medicinal chemistry; both camphor and its derivatives show potent biological activity such as use as a decongestant and in topical skin ointments.[101,102] Moreover, it is readily available as a racemic mixture or enantiomerically pure, and amines based on it are also commercially available.



Scheme 1.4 Reaction of camphor with TosMIC to install an additional CH_2 and subsequent reduction of the nitrile to give the amine

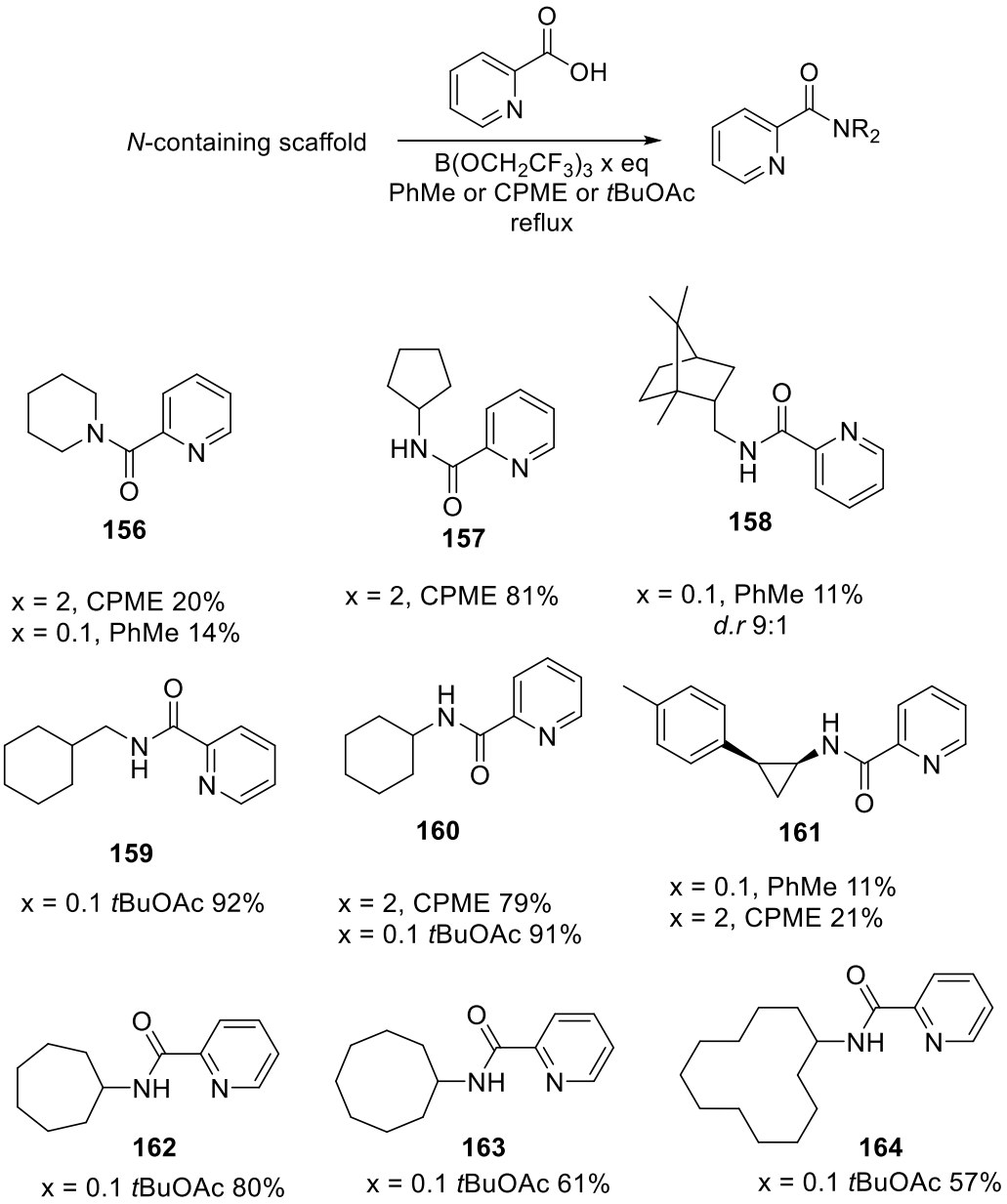
Endo-bornylamine **155** could be synthesised according to a known procedure starting from (+/-) camphor, *via* the oxime **154** followed by a reduction using sodium metal, **Scheme 2.5**. *R*-(+)-bornylamine **139** is also commercially available.



Scheme 2.5 Synthesis of (+/-)-bornylamine from camphor

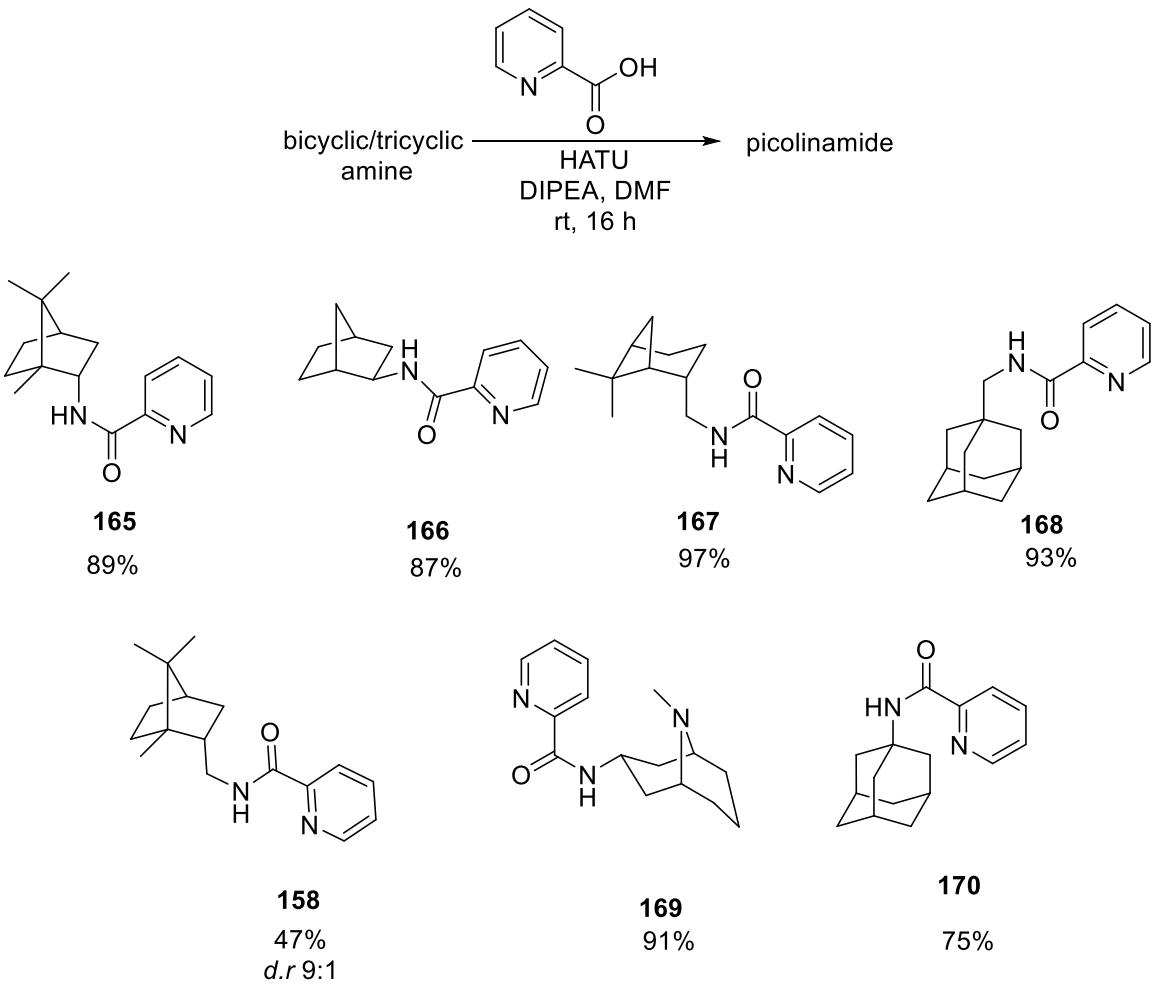
2.3 Addition of directing groups

Amide linked directing groups can be easily added on to the amine scaffolds through a simple amide coupling using $B(OCH_2CF_3)_3$ and 2-picolinic acid, using methodology previously developed within the group.[103–105] It has also been shown that $B(OCH_2CF_3)_3$ in catalytic quantities can be used to form amide bonds.[106,107] Both stoichiometric and catalytic amounts of $B(OCH_2CF_3)_3$ were used to add the directing group to the scaffold, and a range of picolinamides were synthesised, **Scheme 2.6**. This method can allow rapid access to the picolinamide substrates required for C-H functionalisation as it uses a solid phase resin work up and avoids the need for an aqueous work up. In some cases flash column chromatography can also be avoided. Reactions using catalytic $B(OCH_2CF_3)_3$ typically needed to be performed on >5 mmol scale which limits its use for synthesising amides from amines which are only available in small quantities.



Scheme 2.6 Picolinamide synthesis using $B(OCH_2CF_3)_3$

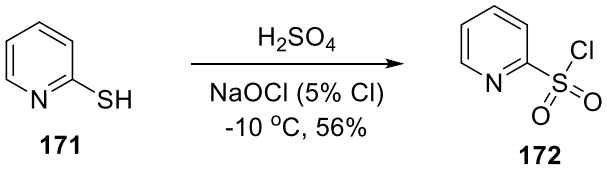
Since poor yields were obtained using the borate reagent for synthesis of some picolinamides, mostly due to the insolubility of the amine carboxylate salt in ether or hydrocarbon solvents, HATU was used to install directing groups on these substrates, **Scheme 2.7**. HATU couplings are also easier to perform on a smaller scale.



Scheme 2.7 Amides synthesised using HATU

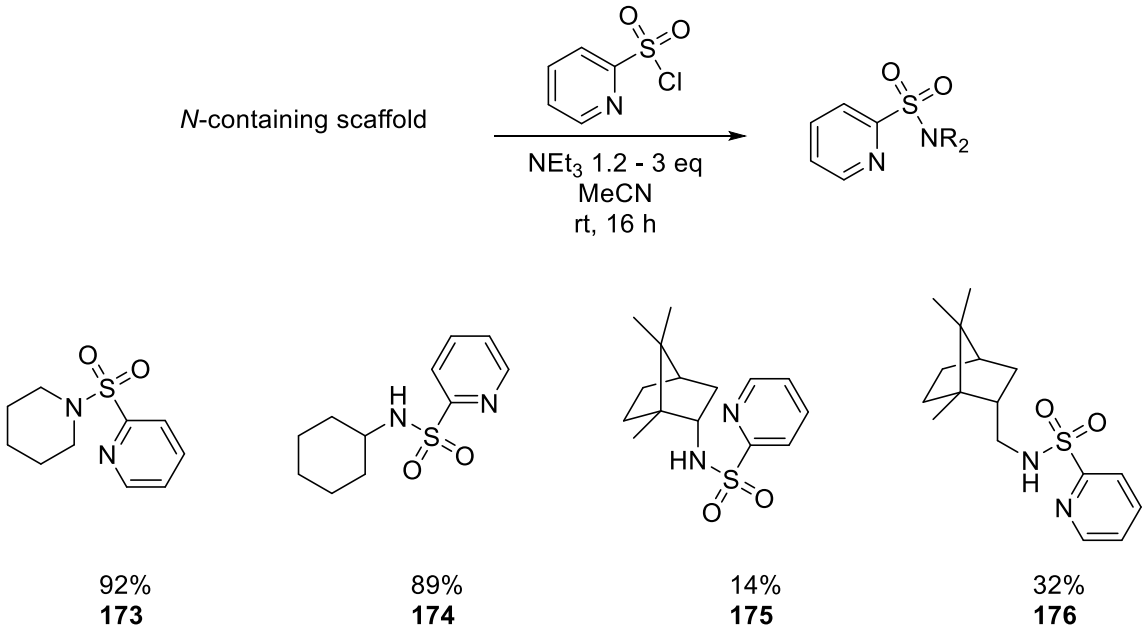
The HATU coupling gave good yields of amide substrates, including those synthesised from bicyclic and tricyclic amines. This method does require an aqueous work up and column chromatography for the isolation of pure picolinamides and so is a less efficient way of synthesising them compared to using $B(OCH_2CF_3)_3$. Amide **158** was later purified by our collaborators at AstraZeneca using preparatory HPLC to separate the *endo* and *exo* isomers.

As an alternative to amide linked directing groups, a 2-pyridylsulphonyl group was added to nitrogen containing scaffolds. This group has the advantage of being easier to remove under mild conditions than the picolinamide. The sulphonyl chloride **172** was first synthesised by a known procedure starting from **171**, **Scheme 2.8**.[108]



Scheme 2.8 Synthesis of 2-pyridylsulphonyl chloride

The general procedure for the addition of sulphonyl chloride **172** is shown in **Scheme 2.9**. For scaffolds that were used as their hydrochloride salts, 3 equivalents of triethylamine were used, compared to the 1.2 equivalents used for reactions involving free amines.[58]



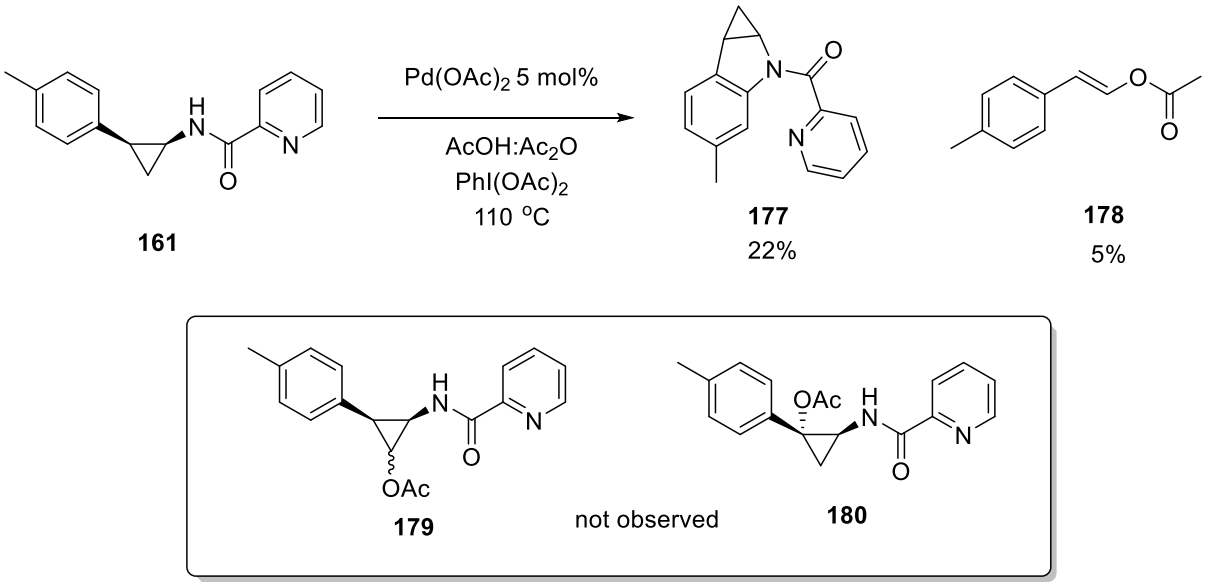
Scheme 2.9 Sulphonamide synthesis

2.4 C-H activation reactions

Once a set of nitrogen heterocycles and amino substituted rings with directing groups installed had been synthesised, several types of reactions were screened to establish a reliable test reaction with which to explore the reactivity of the different scaffolds. Known reactions for sp^3 and sp^2 C-H activation from the literature were adapted and explored using the picolinamides synthesised.

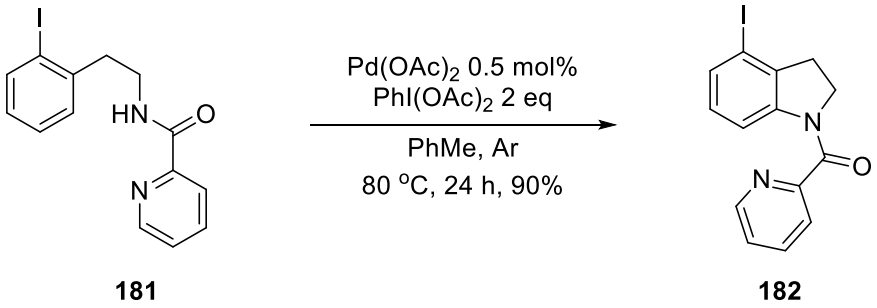
2.4.1 Acetylation reactions

The oxidation of the cyclopropane scaffold **161** was attempted using known conditions, **Scheme 2.10**.[34] Instead of giving the expected products **179** and **180**, cyclisation of the picolinamide occurred to give indoline **177**. A small amount of alkene **178** was observed.



Scheme 2.10 Attempted oxidation of a cyclopropane

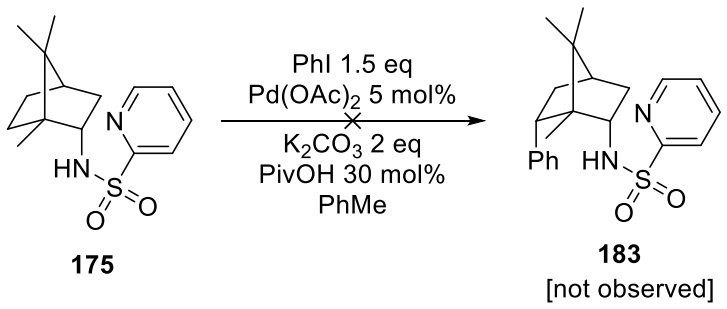
It has been shown that under similar conditions reaction the synthesis of indolines can be achieved through intramolecular amination directed by a picolinamide group[109] (**Scheme 2.11**) or a sulphonamide linked pyridine auxiliary.[61]



Scheme 2.11 Intramolecular amination to give an indoline product

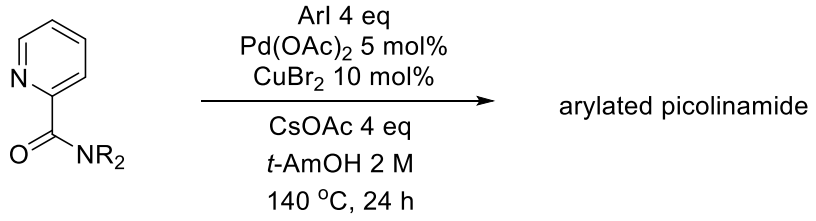
2.4.2 Arylation reactions

Auxiliary assisted arylation of sp^3 C-H bonds are usually mediated by the use of silver salts, such as silver acetate and silver phosphate, which are both expensive and unsustainable.[110–112] However, developments have been made using pivalic acid in the place of silver in these cross coupling reactions. An arylation of the bicyclic scaffold **175** using previously described conditions[47] failed to produce any of the arylated product **183**, **Scheme 2.12**.



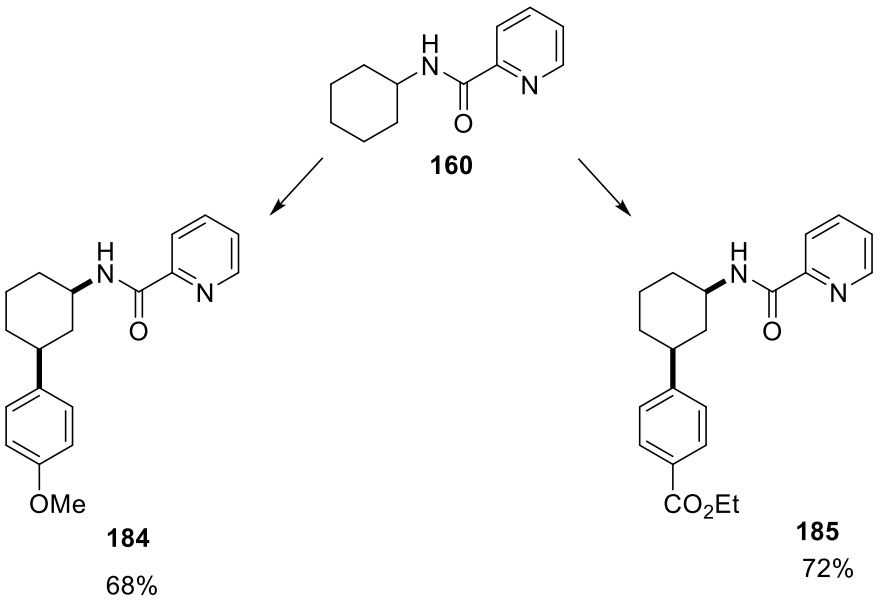
Scheme 2.12 Attempt at arylation of a bicyclic scaffold

Cesium salts have also been successfully used as an alternative to silver and reactions using them benefit from a simplified work up and lower cost than that associated with the use of silver salts.[50] A general method for these arylation reactions is shown in **Scheme 2.13**.



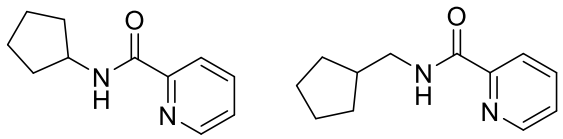
Scheme 2.13 General scheme for the arylation of picolinamides

Compound **160** was successfully arylated by two different aryl iodides with electron donating and electron withdrawing substituents under these conditions to give the products **184** and **185** shown in **Scheme 2.14**.[50] The reaction is completely selective for the *cis* configuration.



Scheme 2.14 Arylation of a monocyclic scaffold

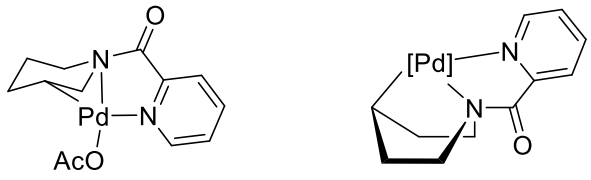
Disappointingly, no arylation was observed when the reaction was repeated using the cyclopentane scaffolds **157** and **186**, **Figure 2.3**.



157 **186**

Figure 2.3 Unreactive amides

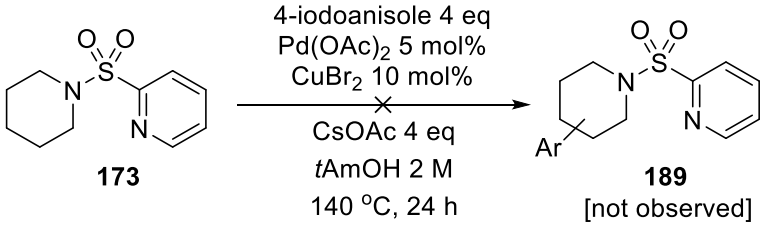
The same conditions were applied to piperidine scaffold **156**, but no reaction took place. A possible reason for this may be that the system was too strained to form the palladacycle required for activation, **Figure 2.4**. Previous activation of saturated nitrogen heterocycles required a linker between the nitrogen of the heterocycle and the carbonyl of the directing group amide.[21]



187 **188**

Figure 2.4 Possible palladacycle intermediates may be too strained

Replacement of the amide linked directing group with a sulphonamide linked directing group in **173** also did not result in the arylation reaction taking place, **Scheme 2.15**.



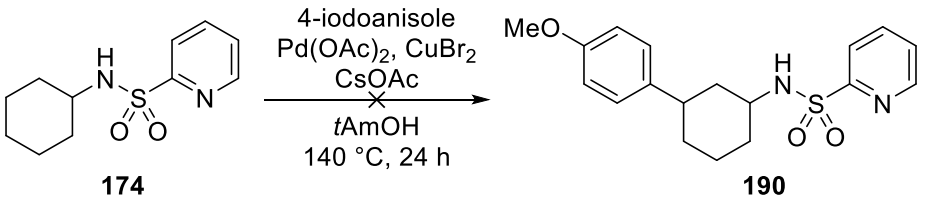
173 **189** [not observed]

Scheme 2.15 Arylation attempt using a sulphonamide linked directing group

Another potential reason for no arylation taking place on the heterocycle substrates could be the lack of a free NH on the directing group. These conditions previously were only used on substrates bearing this functionality, as it may be crucial for the catalytic pathway to take place.

Arylation of the sulphonamide of cyclohexylamine **174** was attempted. The pKa of the sulphonamide NH proton should be lower than in the picolinamide, and so should be easier to deprotonate which is required for the formation of the intermediate palladacycle. However,

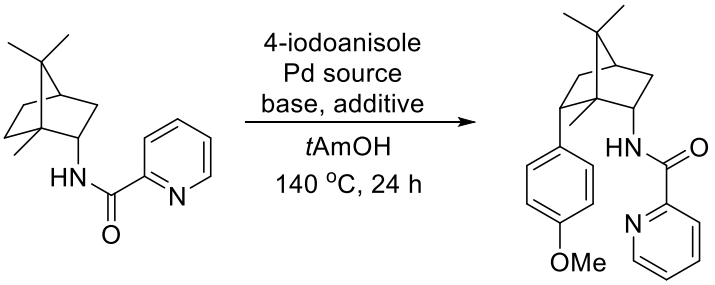
this reaction failed to produce any arylated product, instead just returning the starting material, **Scheme 2.16**.



Scheme 2.16 Attempted arylation using a sulphonamide linked directing group

The 2-pyridyl amide of bornylamine was selected as an interesting substrate for C-H activation; its bridged bicyclic system reduces the likelihood of β-hydride elimination. Previous arylation of the structure required the use of stoichiometric silver carbonate.[113] Silver free conditions developed by Daugulis *et al*[50] were applied to amide substrate **165**, **entry 4**, to give the arylated product in excellent yield. A 1 M concentration of the amide substrate in *t*AmOH was used, more dilute than the 2 M reported by Daugulis. Cesium acetate was used as an alternative base and iodide scavenger, and *t*AmOH as the solvent. Drying of the solvent was not required, neither was the strict exclusion of air and moisture. Other bases were evaluated for their efficiency in the process, with cesium pivalate giving an 81% yield of the product, **entry 3**. Potassium carbonate was also effective, giving **191** in 77% isolated yield, **entry 2**, and is an inexpensive and less hygroscopic alternative to cesium carboxylate bases. Sodium acetate gave a poor yield of the product, most likely due to insolubility in the reaction, **entry 1**.

Reducing the number of equivalents of the aryl iodide to three led to a reduced yield of 72%, **entry 7**. The concentration of the amide in *t*AmOH was important, and when the reaction was run at a more dilute 0.5 M concentration the yield dropped to 58%, **entry 8**. When copper (II) bromide was excluded from the reaction it was found that the yield dropped dramatically, **entry 6**. There was no reaction in the absence of palladium, **entry 5**, and $Pd_2(dba)_2$ was slightly less efficient as a catalyst, **entries 9** and **10**. Degassing the solvent had little effect on yield, **entry 11**, and there was a slight drop when the reaction was run in an air atmosphere, **entry 12**.



165 **191**

Scheme 2.17 Arylation of a bornylamine scaffold

Entry	Catalyst	Additive	Base	Yield
1	$Pd(OAc)_2$	$CuBr_2$	NaOAc	7
2	$Pd(OAc)_2$	$CuBr_2$	K_2CO_3	81 (77[b])
3	$Pd(OAc)_2$	$CuBr_2$	CsOPiv	81
4	**$Pd(OAc)_2$**	**$CuBr_2$**	**CsOAc**	**91[b]**
5	None	$CuBr_2$	CsOAc	0
6	$Pd(OAc)_2$	none	CsOAc	36
7[c]	$Pd(OAc)_2$	$CuBr_2$	CsOAc	72
8[d]	$Pd(OAc)_2$	$CuBr_2$	CsOAc	58
9	$Pd_2(dba)_2$	$CuBr_2$	CsOAc	72
10	$Pd_2(dba)_2$	none	CsOAc	45
11[e]	$Pd(OAc)_2$	$CuBr_2$	CsOAc	88
12[f]	$Pd(OAc)_2$	$CuBr_2$	CsOAc	80

[a] NMR yield calculated using 1,3,5-trimethoxybenzene as the internal standard. [b] Isolated yield. [c] 3 eq. ArI. [d] 0.5 M concentration. [e] Degassed solvent. [f] Reaction performed in an air atmosphere.

Table 2.1 Reaction optimisation for the arylation of amide **165**.

The orientation of the aryl group introduced was confirmed by single crystal X-ray diffraction, **Figure 2.5**, which shows the aryl group is in the *endo* position.

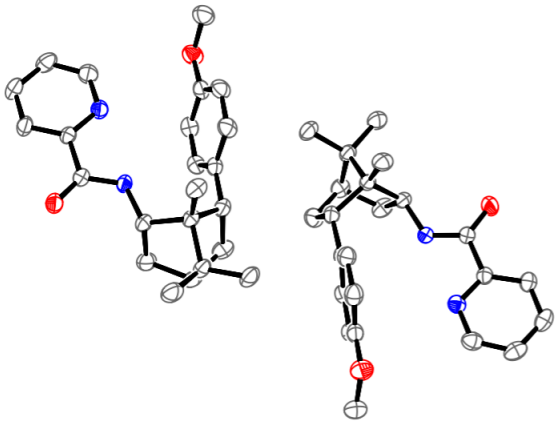
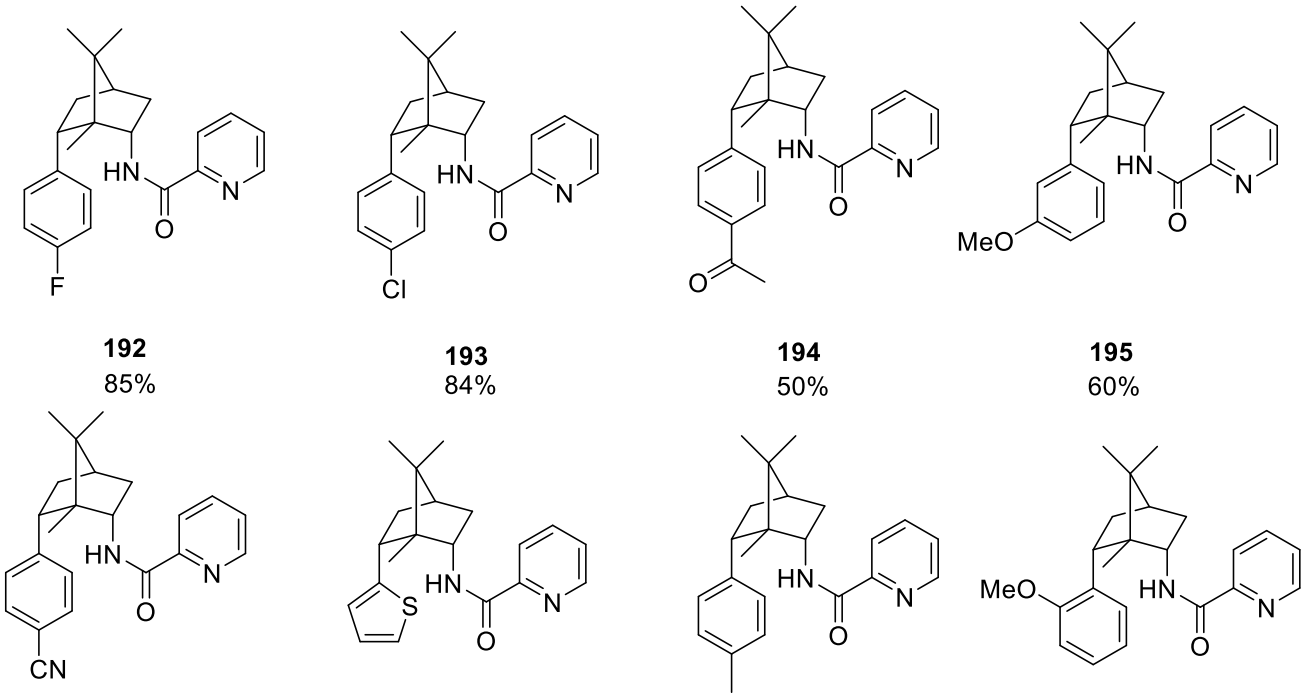


Figure 2.5 X-Ray crystal structure of compound **191.** Ellipsoids drawn to the 50% probability level

The reaction was compatible with a range of different substituted aryl iodides, and a scope for the reaction is shown in **Figure 2.6**. A lower yield of 44% was obtained for the *ortho* methoxy substituted aryl iodide, presumably due to increased steric congestion. The reaction could tolerate halogens in the *para* position, compounds **192** and **193.** Ketones and thiophenes were also used to give good yields of the arylated products **194** and **197**. The reaction could also tolerate the aryl iodides containing a cyano group to give product **196**.



192 85%

193 84%

194 50%

195 60%

196 72%

197 82%

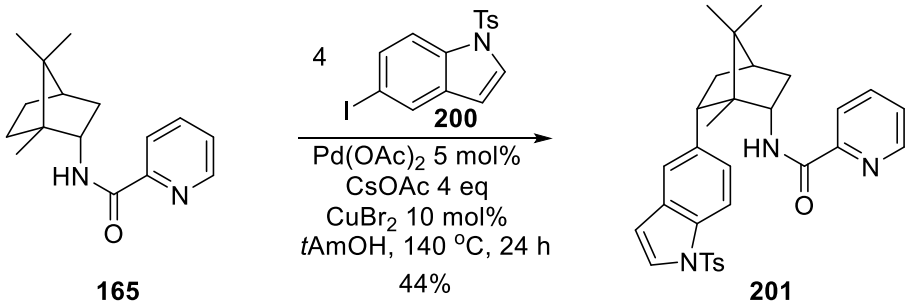
198 80%

199 44%

Figure 2.6 Aryl iodide scope

5-Iodoindole proved to be an unsuccessful coupling partner (not shown), possibly due to coordination of the deprotonated nitrogen of the heterocycle onto to the palladium catalyst,

poisoning the catalyst and so leading to no conversion for the reaction. After protection of the indole with a tosyl group a moderate yield could be obtained for the arylation reaction, **Scheme 2.18**.



Scheme 2.18 Arylation with a tosyl protected indole

Figure 2.7 shows two unsuccessful coupling partners: 2-iodotoluene and 3-iodopyridine. Having a pyridine ring on the aryl iodide may suppress the reaction by coordinating to the palladium acetate catalyst preventing the coordination of the directing group and subsequent C-H activation. Having bulky groups on the pyridine ring may block coordination and so allow activation to take place. Unlike 2-iodoanisole, 2-iodotoluene did not result in any arylated product due to the methyl group being less flexible than the methoxy and so sterically hindering oxidative addition to the palladium.

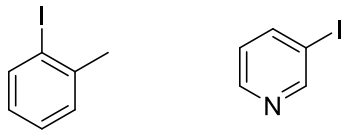
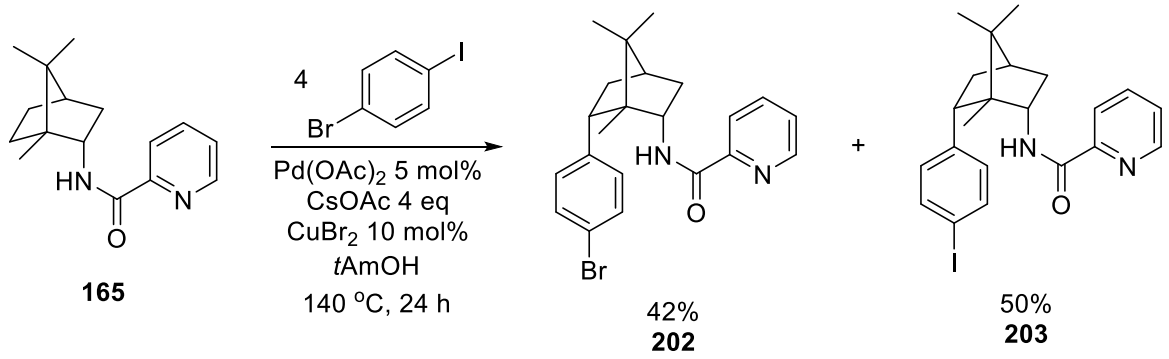


Figure 2.7 Unsuccessful coupling partners

Reaction with 4-bromoiodobenzene led to an inseparable 1:1.2 mixture of products **202** to **203**, **Scheme 2.19**, demonstrating that both aryl iodides and bromides are compatible with the reaction. The aryl bromide appeared to be more reactive in the reaction, giving a slightly higher yield of the corresponding arylated product **203**.



Scheme 2.19 Arylation using 4-bromoiodobenzene resulting in two products

On the discovery that aryl bromides may also act as coupling partners in the reaction, the scope of aryl bromides was investigated, with products formed in good to excellent yield, **Figure 2.8**. Aryl bromides are less common than aryl iodides as coupling partners in C-H activation, however they are cheaper and more readily available.[114,112,115,116] The use of aryl bromides allowed the substrate scope to be further expanded to include aldehydes, phenols and nitriles. A small *ortho* substituent on the aryl bromide gave a good yield of product **205**. Lower yields were seen when using aldehyde containing aryl bromides, **209** and **210**.

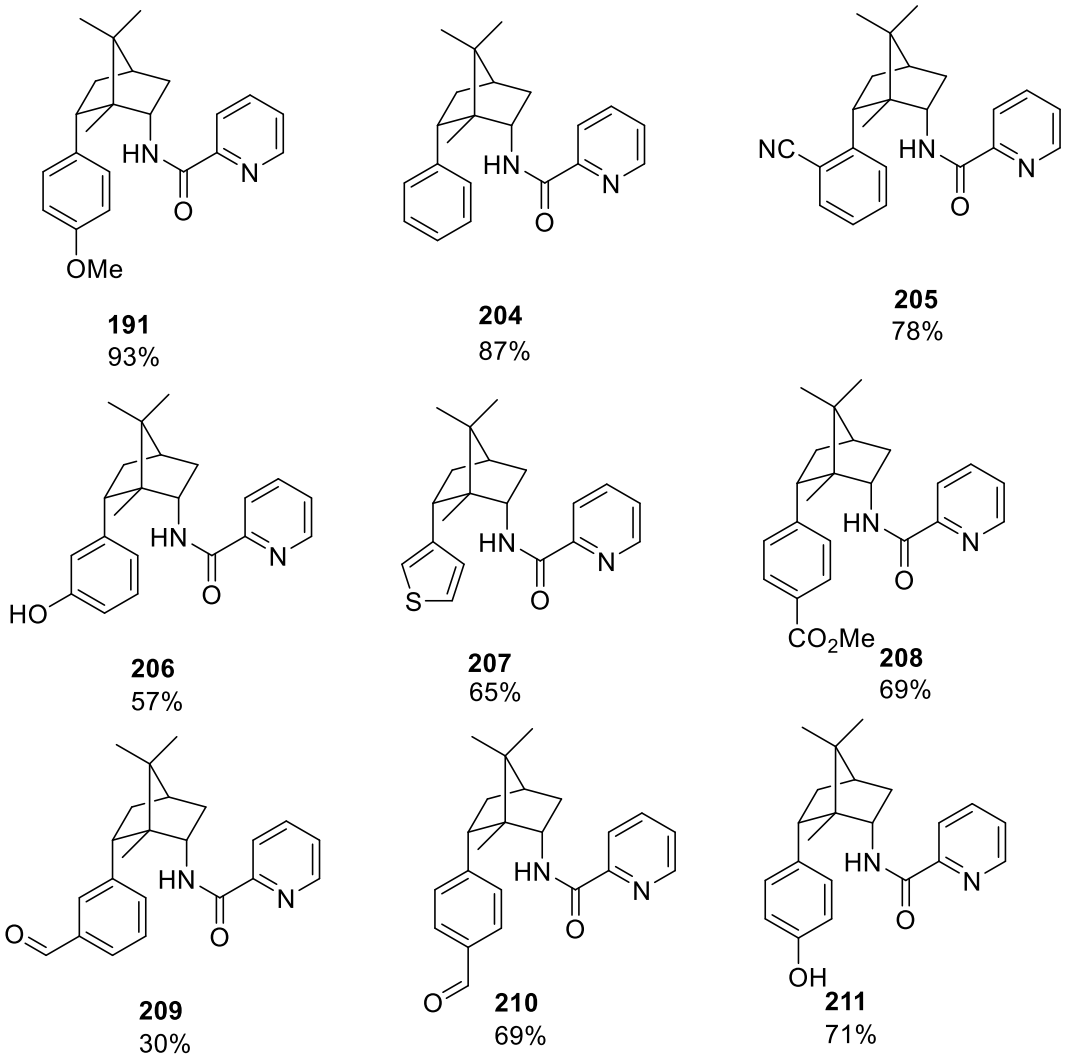
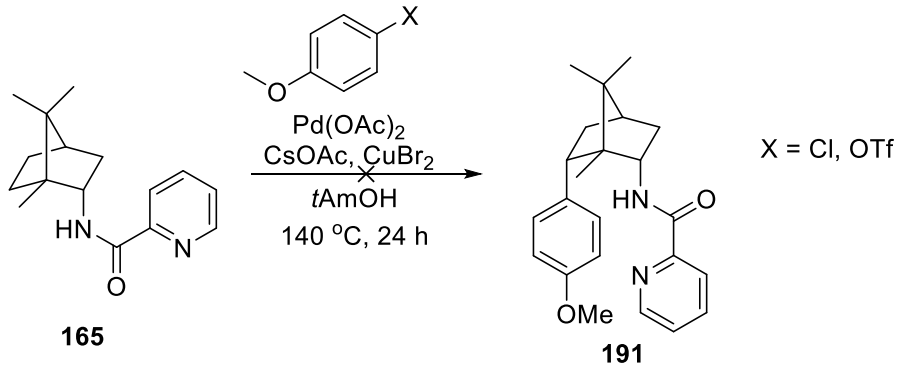


Figure 2.8 Aryl bromide scope

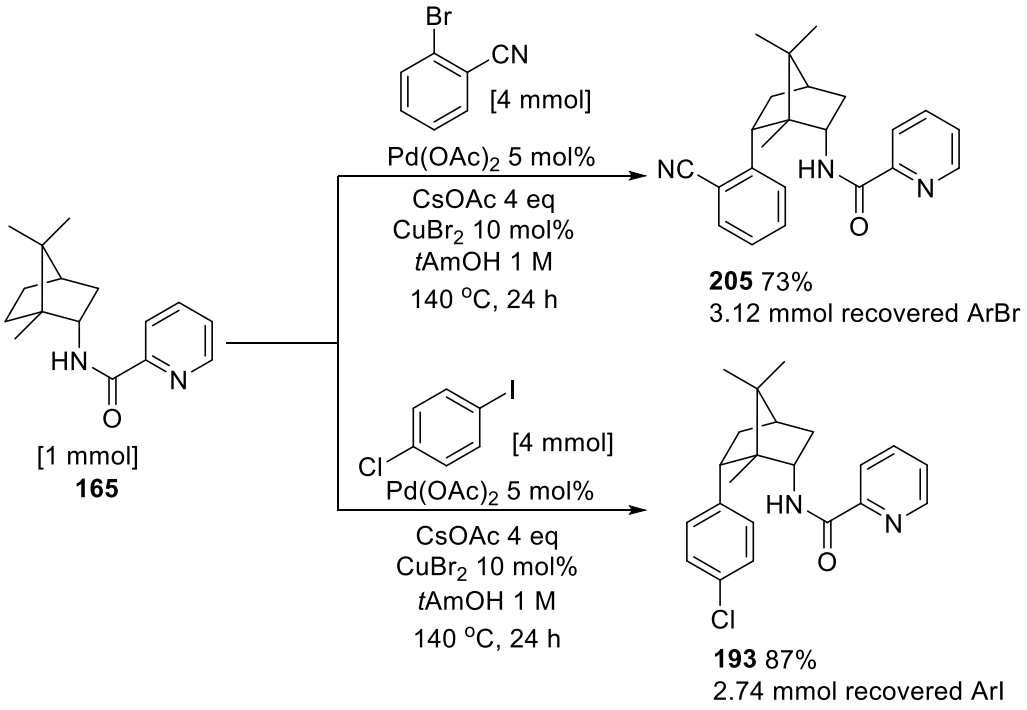
The reaction is limited to aryl bromides or aryl iodides. Using an aryl chloride or triflate does not result in any arylated product, **Scheme 2.20**.



Scheme 2.20 Attempted arylation using an aryl chloride or triflate

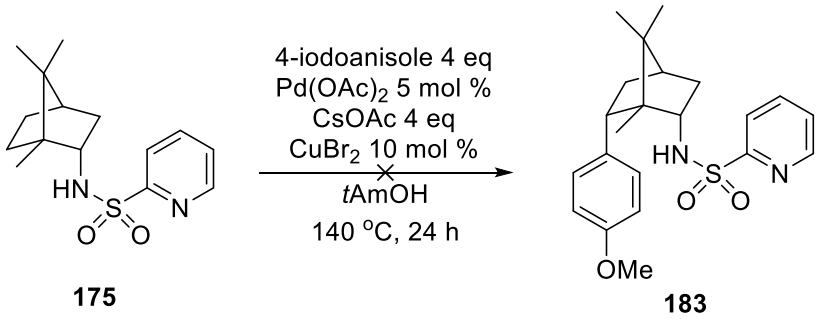
As the substrate scope was performed using small scale (0.1 mmol) reactions a scale up reaction to 1 mmol using 4-iodoanisole as the aryl iodide was performed to ensure the yield for the reaction was consistent on a larger scale. Gratifyingly the scale up gave an 86% yield of compound **191 (**91% on a 0.1 mmol scale).

One of the drawbacks of this method is the excess of aryl iodide or bromide needed to get a high yield. However, it was demonstrated that at the end of the reaction the excess could be recovered during the purification stage, **Scheme 2.21**. The yields on scale up are comparable to those obtained at a smaller scale. When recovering the aryl bromide, 3.12 mmol out of a possible 3.27 mmol (95%) was obtained. For the aryl iodide the recovery was not as efficient, with 2.74 mmol out of a possible 3.13. mmol (88%) recovered.



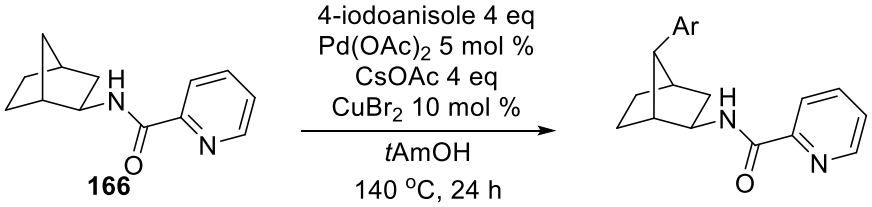
Scheme 2.21 Scale up reaction and recovery of excess aryl halides

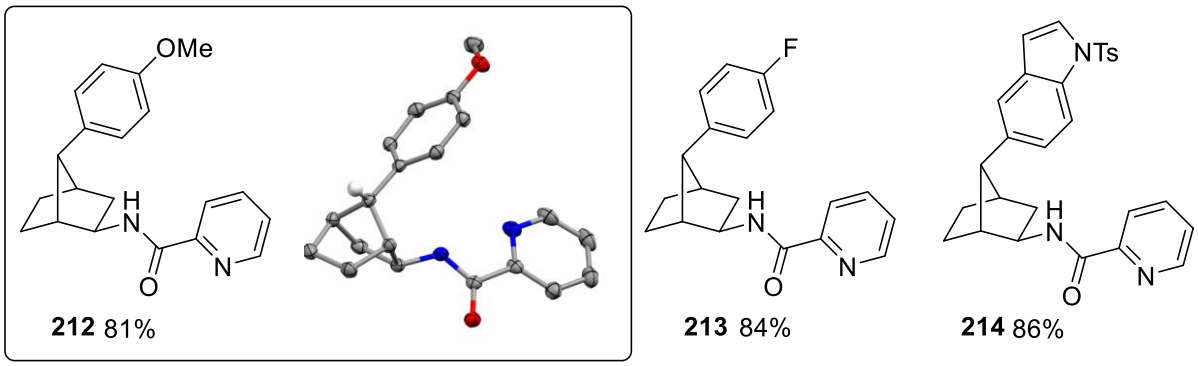
Replacing the amide link in the directing group of **165** with a sulphonamide leads to no arylation taking place, **Scheme 2.22**. As the NH of a sulphonamide is more acidic than in the amide, it would be expected that deprotonation of the NH by the palladium catalyst would be easier. But as no reaction took place the size or orientation of this directing group must be preventing the reaction.[117]



Scheme 2.22 Attempted arylation of a sulphonamide

The arylation of the bridgehead methylene of *exo*-2-aminonorbornane **166** was successful under identical conditions to bornylamine, **Scheme 2.23**. Again, the position of the C-H activation and arylation was confirmed by XRD.

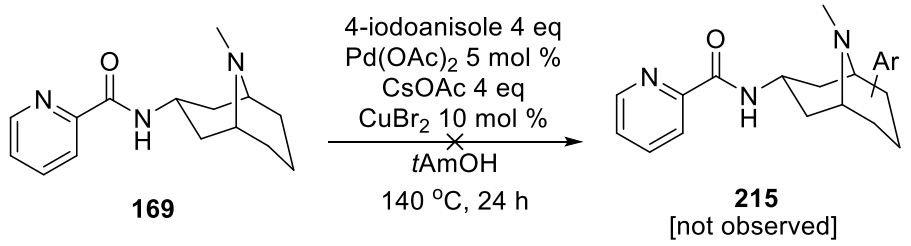




Scheme 2.23 Arylation of *exo*-aminonorborane and XRD crystal structure of **212**. Ellipsoids drawn to the 50% probability level

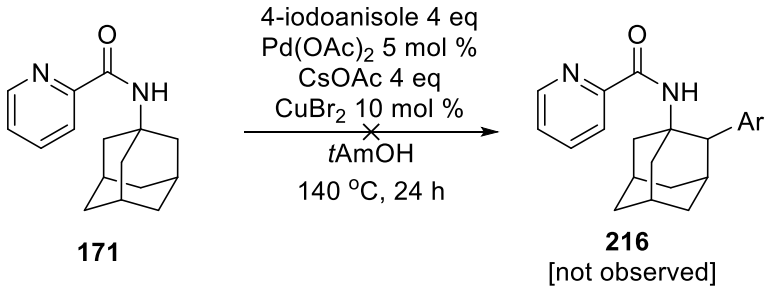
The incorrect orientation of a directing group can lead to unsuccessful C-H activation reactions. In amide **169** the directing group is pointing away from the molecule and so no reaction takes place, as only an unfavoured 4-membered palladacycle may be formed,

Scheme 2.24. The presence of a basic nitrogen within the bicyclic scaffold may also coordinate to the palladium catalyst and prevent C-H activation from taking place.



Scheme 2.24 Attempted activation of a nitrogen heterocycle

When adamantane scaffold **171** was treated under the same conditions as previous substrates no reaction was observed, **Scheme 2.25**.



Scheme 2.25 Attempted activation of an adamantane scaffold

For arylation of compound **171** to take place, palladacycle **217** is required to form. Compound **217** contains a more unusual four-membered palladacycle which is less favoured than a five-membered ring and in this case does not form to give the desired arylated product, **Figure 2.8**.

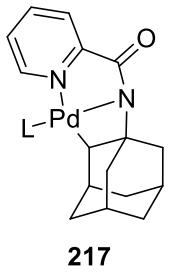
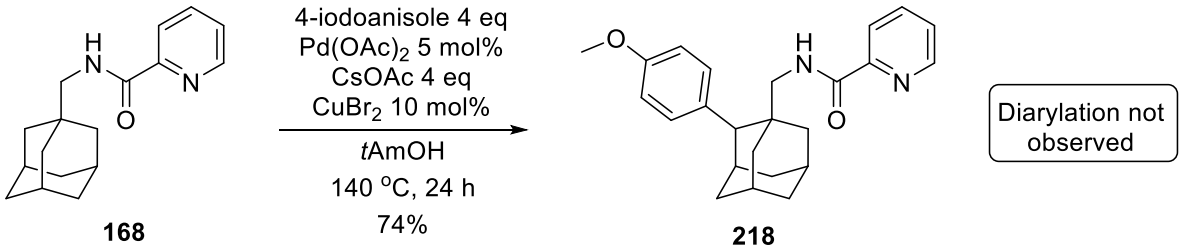


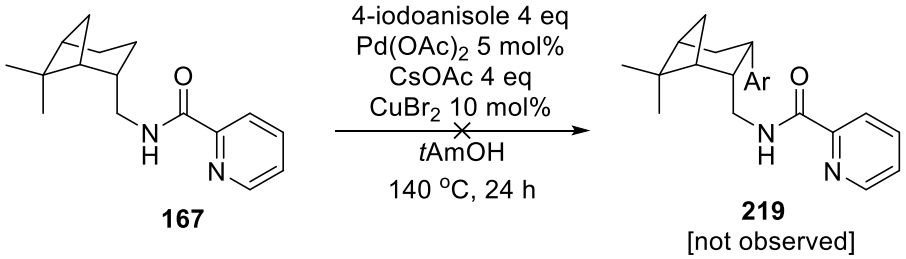
Figure 2.8 Proposed palladacycle required for activation of an adamantane scaffold

When a methylene unit is in between the nitrogen and the adamantane, C-H activation can take place *via* a 5-membered palladacycle and give a good yield of the monoarylated product **218**, **Scheme 2.26**. Although there are three identical CH_2 positions available for C-H functionalisation on compound **168**, none of the diarylated or triarylated products were observed, instead the reaction stopping after the installation of one aryl group. Steric crowding may be preventing the addition of another group.



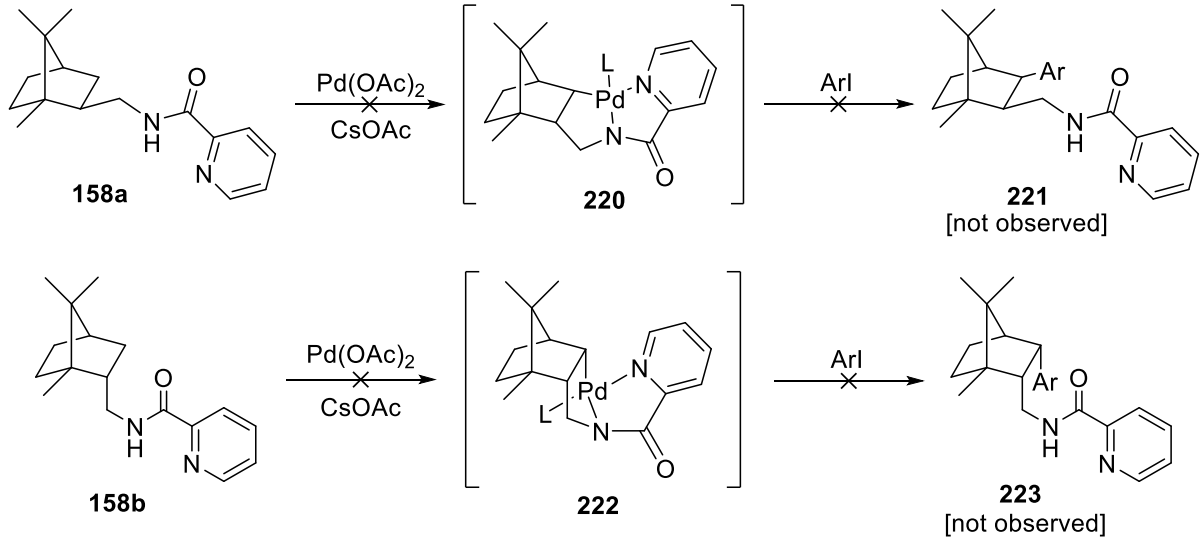
Scheme 2.26 Arylation of an adamantane derivative

When the directing group was more flexible, such as in **167**, no reaction was seen, **Scheme 2.27**. It would be expected that C-H activation would take place on the CH_2 which is γ to the amide to give **219**.



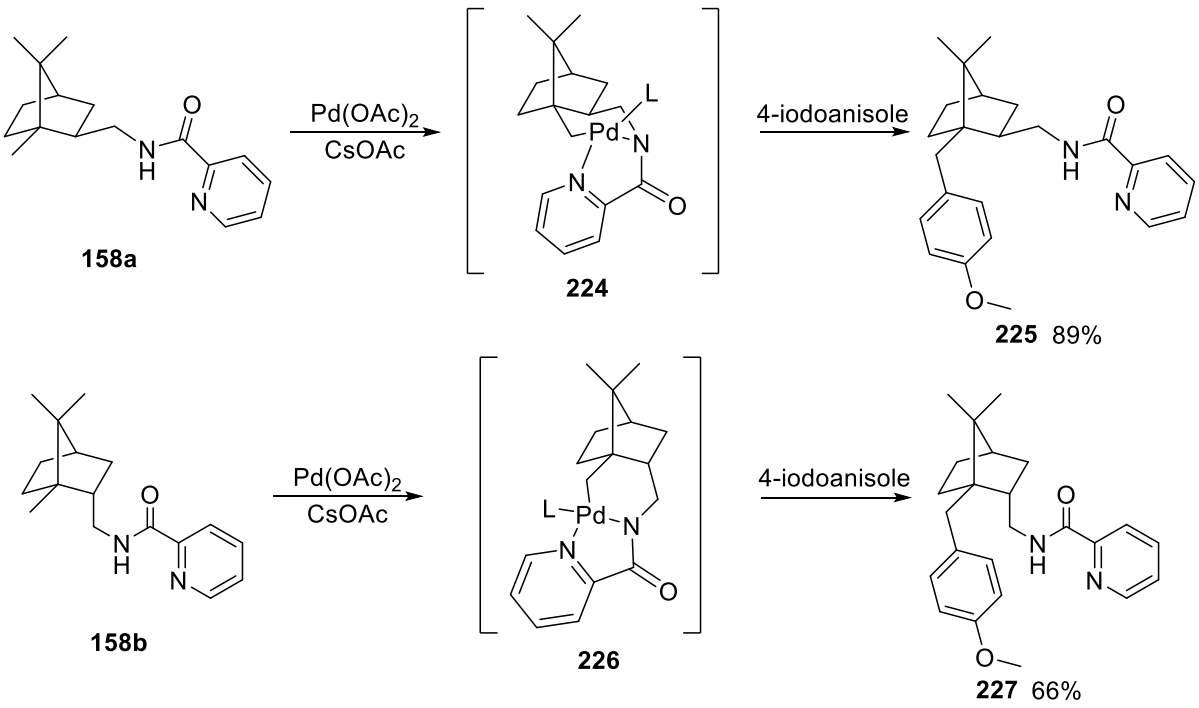
Scheme 2.27 Unsuccessful arylation of a *cis*-myrtanylamine scaffold

Not all C-H activation reactions proceed *via* the 5-membered palladacyle pathway that is usually the most favourable. Bicyclic amides **158a** and **158b** do not form the 5-membered palladacycles shown in **Scheme 2.28**, which would lead to the arylation of a CH_2 position.



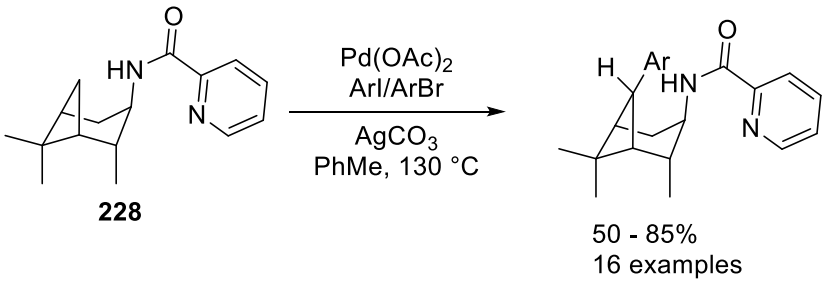
Scheme 2.28 Expected reactivity of two bicyclic compounds

Instead, these compounds prefer to form the more unusual 6-membered palladacycles **224** and **226** to give the arylated products, **Scheme 2.29**. A higher yield was seen when using *exo* amide **158a**, potentially due to the higher stability of palladacycle **224**.



Scheme 2.29 Arylation of bicyclic scaffolds *via* a 6-membered palladacycle

The formation of 6-membered palladacyles was previously observed in the C-H arylation of pinanamine. It was hypothesised that this unusual *δ*-activation was due to the conformation characteristics of amide **228**, which puts the directing group in close proximity to the bridgehead CH_2.[115]



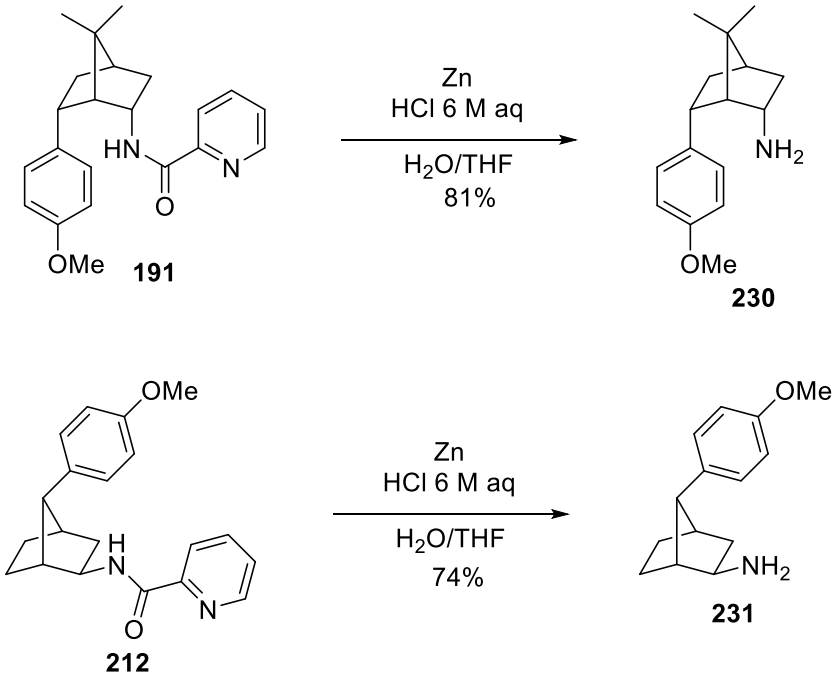
Scheme 2.30 Unusual remote *δ* C-H activation

Conformational restraint may also be the reason the *δ*-activation of amide **228**, as the directing group is in close proximity to the CH_3 group which is arylated, although the directing group is more flexible than that shown in **Scheme 2.30**. This is one of the few examples of remote *δ* C(sp^3)-H functionalisation.

2.5 Removal of the picolinamide auxiliary

The removal of the directing group is required to yield the free amines. In some cases this had been achieved using hydrolysis of the amide bond using a sodium hydroxide in ethanol or isopropanol.[118,119] Hydrolysis of the amide linkage using sodium hydroxide was not

successful returning only the starting material, even at elevated temperatures. The cleavage of picolinamides can also be achieved using zinc metal in HCl and water or water/THF.[120] This method proved effective for the deprotection of the bicyclic amides, **Scheme 2.31**. This method did not require protection of the amine from purification, instead an acid-base work up could be used to give the free amines in good yield.

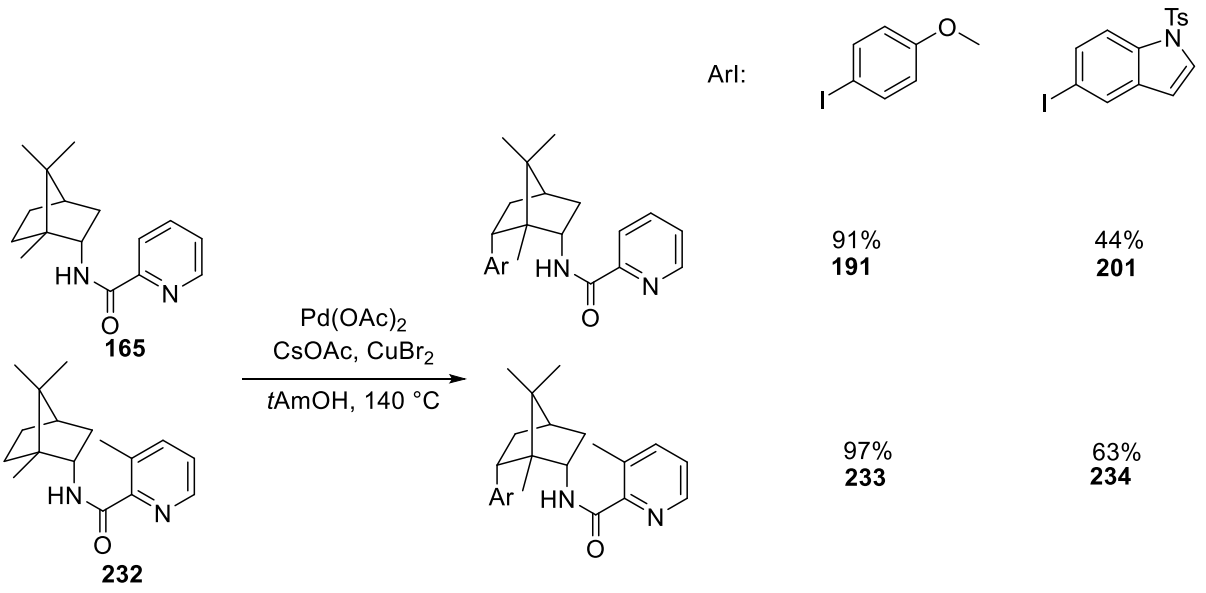


Scheme 2.31 Removal of the picolinamide auxiliary

2.6 Improvements to the reaction conditions

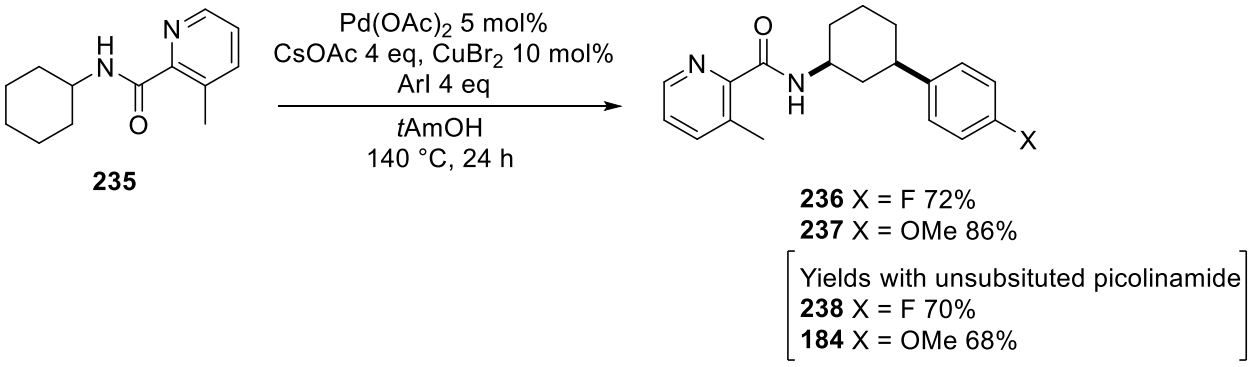
2.6.1 Directing group effects

Changing the electronics and sterics of the pyridine ring in the directing group can have an effect on the efficiency of the arylation reactions. It was first seen that changing from the picolinamide to 3-methylpicolinamide directing group could improve the yields of products in the arylation of bornylamine. This can be useful for those aryl halides that give poor yields, such as 5-iodoindole, **Scheme 2.32**.



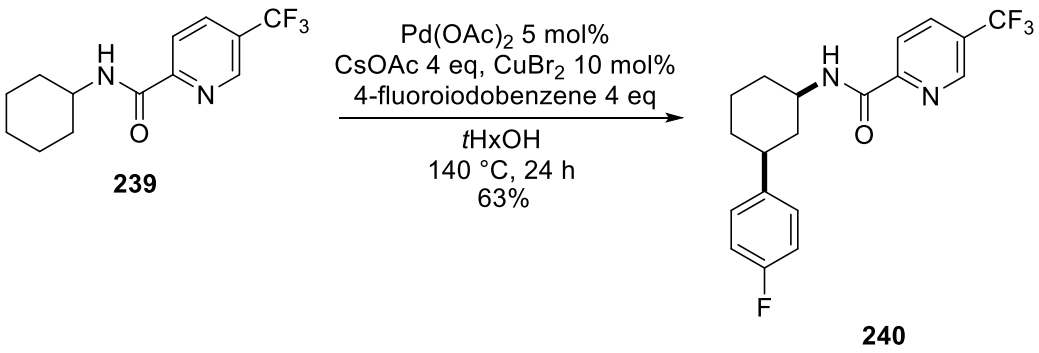
Scheme 2.32 Arylation of bornylamine using the 3-methylpicolinamide directing group

This group has a similar effect on the arylation of a simple cyclohexylamine substrate **235** and increases in yield can be seen for two different aryl iodides, **Scheme 2.33**.



Scheme 2.33 Arylation of cyclohexylamine using the 3-methylpicolinamide group

When using the 5-trifluoromethyl picolinamide directing group for the arylation of cyclohexylamine **239**, a lower yield of arylated product **240** is obtained, **Scheme 2.34**. The strongly electron withdrawing nature of the trifluoromethyl group may affect how well the pyridine nitrogen coordinates to the palladium catalyst, and so reduce its ability to direct C-H activation.

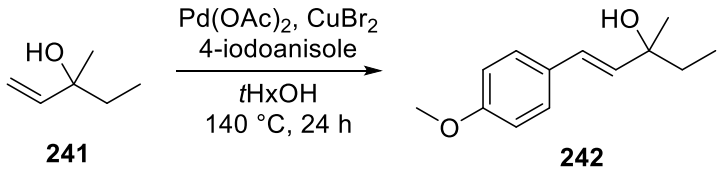


Scheme 2.34 Arylation using the 5-CF_3 picolinamide directing group

A similar effect was seen when a CF_3 group was introduced to the transient directing group used by Yu in the arylation of aliphatic amines. The yield with the unsubstituted directing group was 94%, but the addition of the CF_3 caused it to drop to 67%.[72]

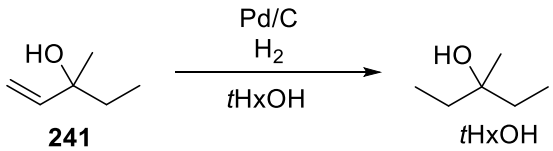
2.6.2 Solvent effects

For reactions with more challenging substrates low yields of arylated products were obtained in *t*AmOH, and so a solvent with a higher boiling point was needed so the temperature of the reaction could be increased. 3-Methyl-3-pentanol (*t*HxOH, b.p 123 °C at 1 atm) has not previously been reported as a solvent for use in any chemical reactions, instead being used in the synthesis of the tranquiliser emylcamate.[121] The use of this solvent allows for the reaction to be carried out at higher temperatures as when reaction temperature was set to 140 °C, the mixture reached 138 °C in *t*HxOH whereas in *t*AmOH the reaction mixture was measured to be only 122 °C. The commercially available *t*HxOH was contaminated with alkene **241**, which when used in C-H activation reactions underwent a Heck-type coupling to give compound **242**, **Scheme 2.35**.



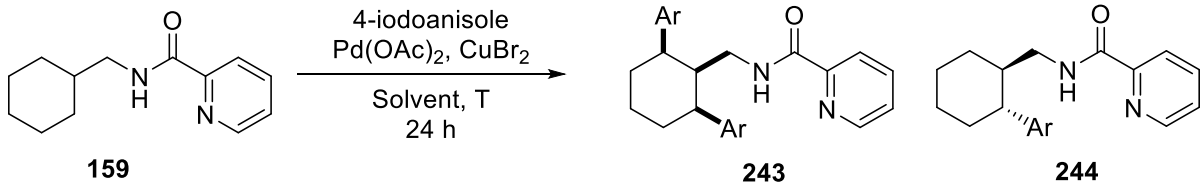
Scheme 2.35 Heck coupling of *t*HxOH impurity

To avoid this issue, hydrogenation of the solvent was carried out to remove the alkene prior to use, **Scheme 2.36**.



Scheme 2.36 Hydrogenation of alkene impurity

For the amide **159**, the arylation reaction produced a mixture of mono and diarylated products, with the diarylated product being the major product, **Scheme 2.37**. Under the reaction conditions previously optimised using *t*AmOH a poor yield of just 7% of the diarylated product **243** was obtained, **entry 1**. On changing to *t*HxOH the yield was increased to 25%, **entry 2**. Due to the higher boiling point of *t*HxOH compared to *t*AmOH it was possible to increase the reaction temperature to 150 °C which led to a higher yield, **entry 3**, but an increase to 160 °C led to a decrease in yield possibly due to decomposition of the catalyst. Increasing the number of equivalents of aryl iodide to six further increased the yield, **entry 5**, and a change from cesium acetate to cesium pivalate gave the highest yield of diarylated product, **entry 8**.



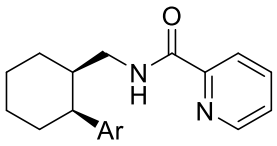
159 **243** **244**

Scheme 2.37 Arylation of cyclohexylmethylamine

Entry	Solvent	Temperature/ °C	Time/ hours	Diarylation 243	Monoarylation 244	ArI eq	Base
1	*t*AmOH	140	24	7%	<5%	4	CsOAc
2	*t*HxOH	140	24	25	7	4	CsOAc
3	*t*HxOH	150	24	65%	6%	4	CsOAc
4	*t*HxOH	150	48	63%	5%	4	CsOAc
5	*t*HxOH	150	24	70%	25%	6	CsOAc
6	*t*HxOH	150	24	68%	23%	8	CsOAc
7	*t*HxOH	160	24	57%	14%	4	CsOAc
8	***t*HxOH**	**150**	**24**	**77%**	**16%**	**6**	**CsOPiv**

Table 2.2 Optimisation of arylation conditions in *t*HxOH

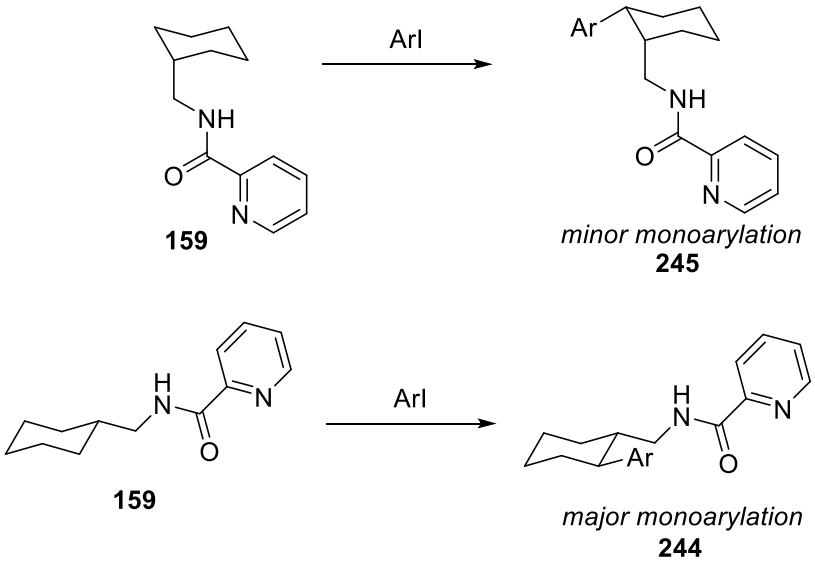
The diarylation product **243** from **Scheme 2.37** has an all *cis* stereochemistry, while the monoarylation product **244** is *trans*. The *cis* monoarylation product is only observed in trace quantities, as it goes straight on to react with another equivalent of aryl iodide, whereas the *trans* monoarylation product is unreactive.



245

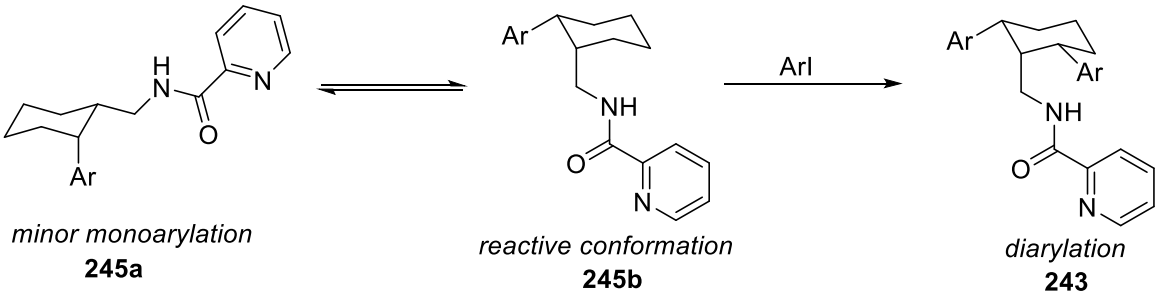
Figure 2.9 *Cis* monoarylation product

The two different monoarylation products are the result of C-H activation taking place when the directing group is in either the axial or equatorial position, **Scheme 2.38**. When the directing group is axial it leads to the minor monoarylated product **245**, as this is the isomer which lead to the diarylated product. However, when the directing group is in the equatorial position, major monoarylated product **244** is observed.



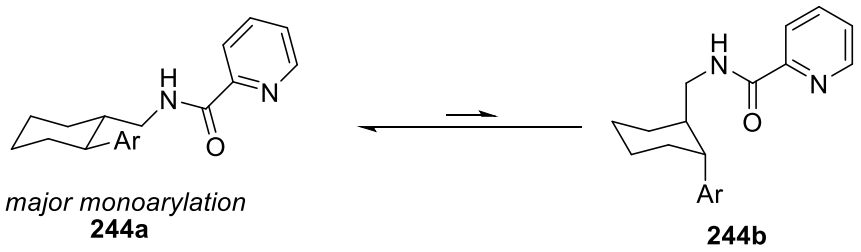
Scheme 2.38 Formation of monoarylation products

The minor monoarylation product has two possible chair conformations, **245a** and **245b**. The second conformation which puts the bulky aryl group in the equatorial position is likely the lowest in energy. For the second arylation to occur the amide directing group must be in the axial position, which it is in compound **245b**, and so the second arylation takes place when the monoarylation product has a *cis* configuration.



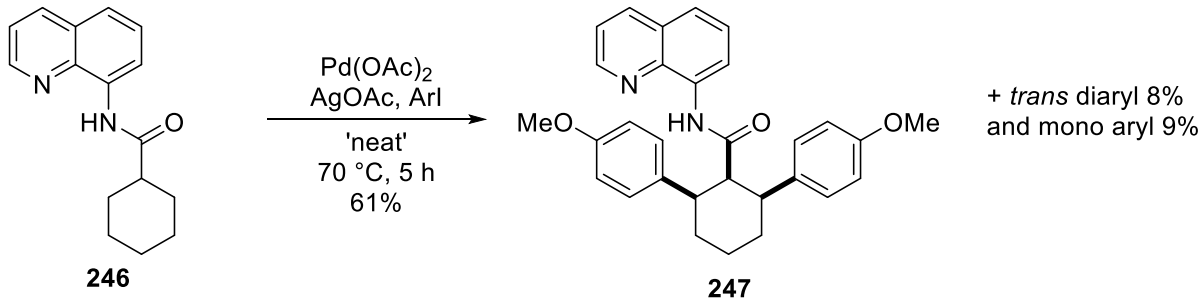
Scheme 2.39 Formation of the diarylated product from the monoarylated

The trans monoarylation product's lowest energy conformation has both substituents in the equatorial positions **244a**, and the ring flip to conformer **244b** having a high energy barrier. Due to this the directing group in monoarylation product **244a** will not go on to react to give any diarylation product.



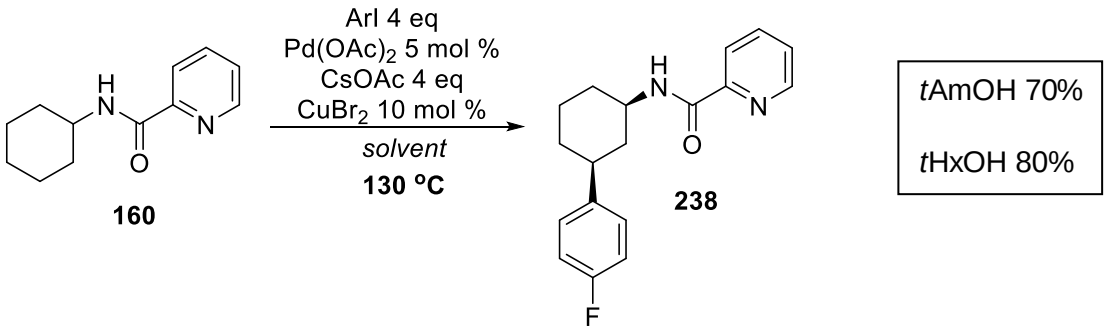
Scheme 2.40 Chair conformations of the minor arylation product

This selectivity of this reaction is the same as that which is observed in the arylation of a similar substrate, in which the 8-aminoquinoline directed C-H functionalisation of **246** gives the all *cis* diarylation product **247**, **Scheme 2.41**.[122]



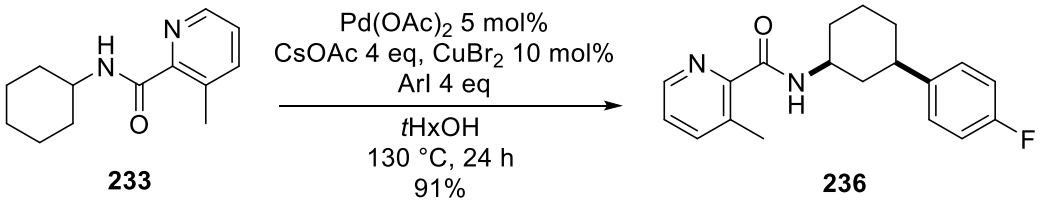
Scheme 2.41 All *cis* arylation of a cyclohexane ring

Improvements for other substrates can also be achieved using 3-methyl-3-pentanol, even without an increase in reaction temperature. In the arylation of cyclohexylamine **160**, **Scheme 2.42**, it can give an improvement in yield even at lower reaction temperatures to those needed with *t*AmOH.



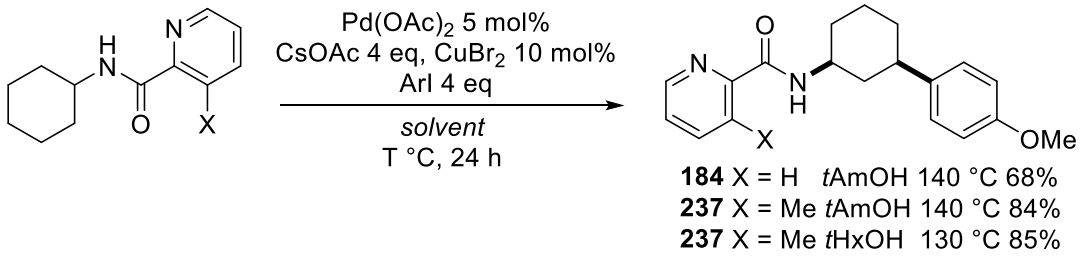
Scheme 2.42 Arylation of cyclohexylamine in 3-methyl-3-pentanol

This solvent effect can be combined with the improved 3-methyl picolinamide directing group to further increase the yield of arylated product **248**, **Scheme 2.43**.



Scheme 2.43 Arylation using the improved solvent and directing group

Similar results were seen when using the more electron rich 4-iodoanisole as the aryl iodide in the reaction. Under the original arylation conditions in *t*AmOH at 140 °C and employing the unsubstituted picolinamide directing group a 68% yield of arylated product was obtained. Changing to the 3-methyl picolinamide group gave an increase to 85%, and using the improved directing group and *t*HxOH as the solvent gave an 85% yield of product **249** at a reduced temperature of 130 °C, **Scheme 2.44**.

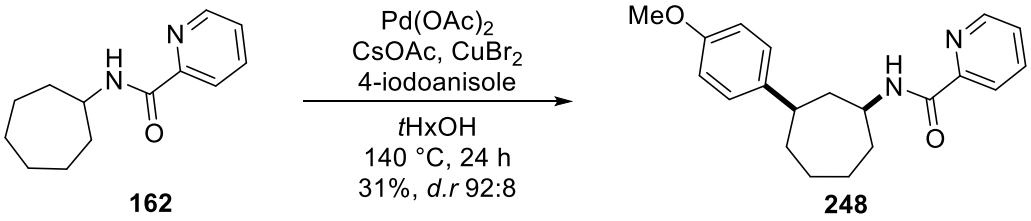


Scheme 2.44 Arylation of cyclohexylamine using 4-iodoanisole

2.6.3 Improving the substrate scope

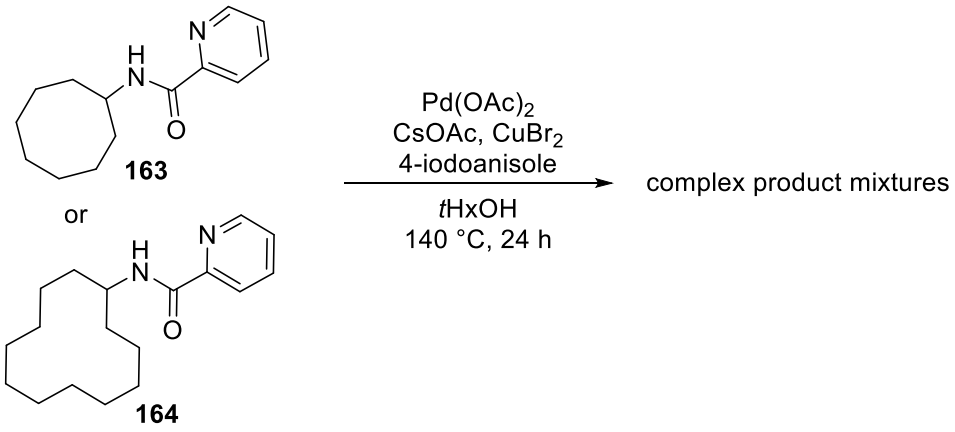
Using this improved solvent system, the arylation of larger cyclic amines were investigated. Firstly, the arylation of picolinamide substrates derived from 7, 8 and 12 membered amines were attempted. Unlike cyclohexane, these ring sizes do not have a single low energy conformation.[123] Medium sized rings also have the potential to undergo transannular C-H

functionalisation.[124] The arylation of the cycloheptane ring **162** proceeded cleanly, to give the arylated product **248** in a moderate yield and good diastereoselectivity, **Scheme 2.45**. The cycloheptane ring underwent a similar reaction to the cyclohexane, resulting in C-H functionalisation γ to the amide. The stereochemistry of product **248** is tentatively assigned as *cis*.



Scheme 2.45 Arylation of a 7-membered ring

When the cyclooctyl picolinamide **163** and cyclododecyl picolinamide **164** were reacted under the same conditions a complex mixture of arylated products were obtained.



Scheme 2.46 Attempted arylation of medium ring sizes

Potential products identified from the complex NMR are shown in **Figure 2.10**. It was not possible to separate these products from the mixture for full characterisation.

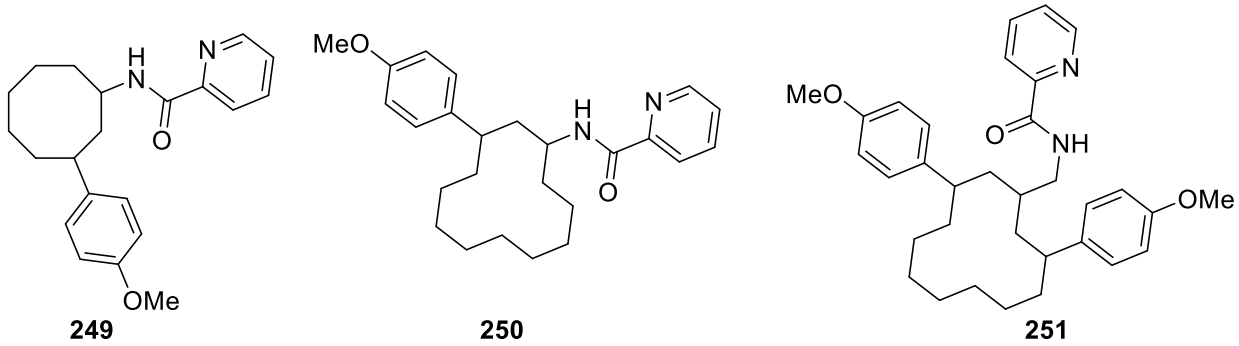
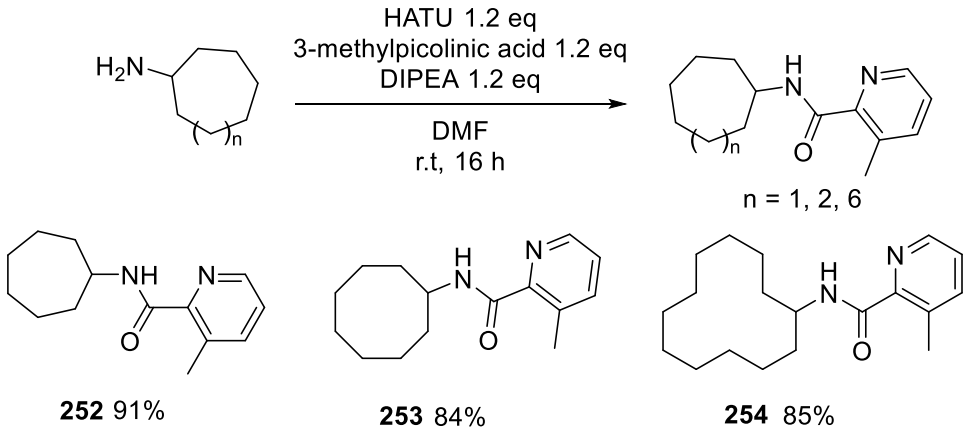


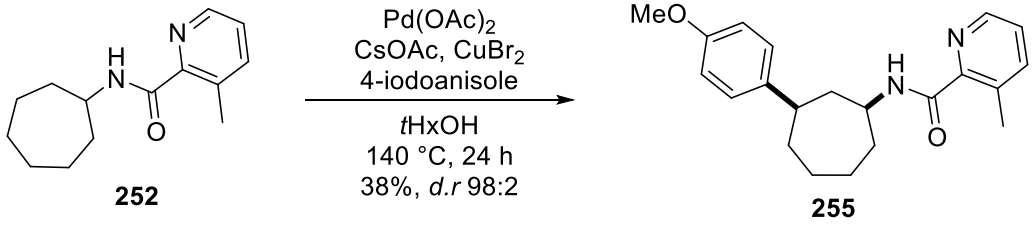
Figure 2.10 Potential arylation products

The 3-methylpicolinamide substrates were also synthesised, **Scheme 2.47**, to explore the effect changing the directing group would have on the outcome of the C-H activation.



Scheme 2.47 Synthesis of 3-methylpicolinamides

The addition of the 3-methyl directing group gave a modest increase in yield for the arylation of the cycloheptane ring, as well as an increase in diastereoselectivity, **Scheme 2.48**.



Scheme 2.48 3-Methyl picolinamide directed arylation

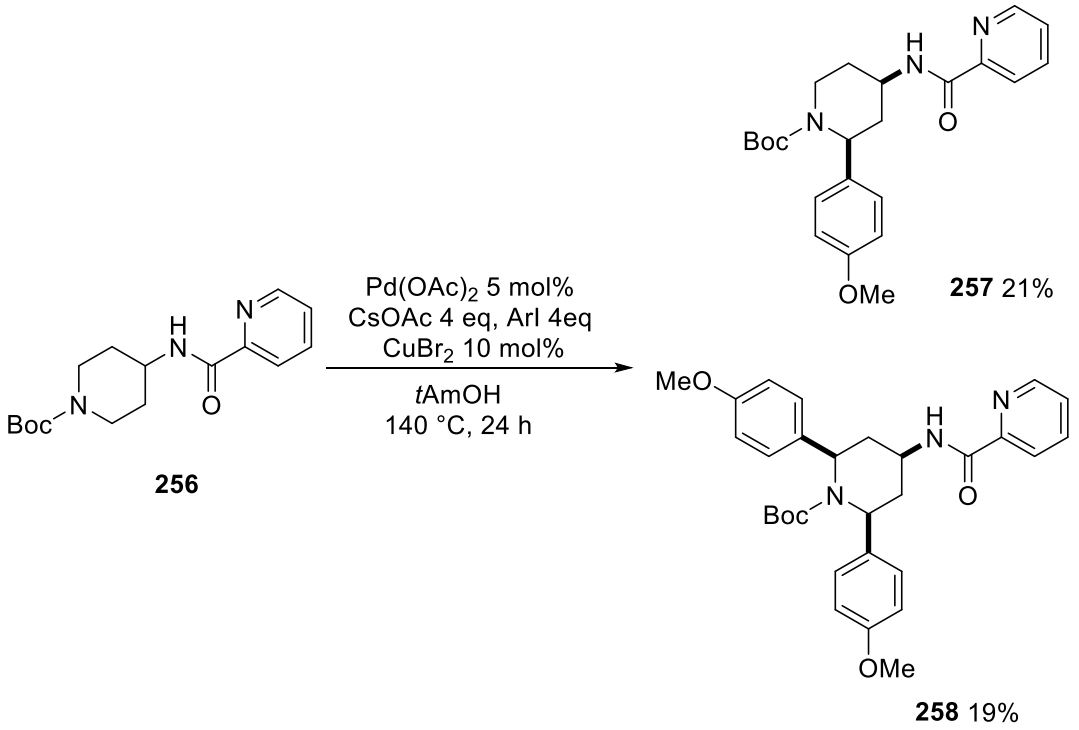
A change in directing group to the 3-methylpicolinamide for the 8- and 12-membered rings did not prevent the formation of a mixture of arylated products.

2.7 C-H functionalisation of heterocycles

2.7.1 Arylation of nitrogen heterocycles

The arylation of nitrogen heterocycles is more challenging, due to the presence of a basic nitrogen which can poison the palladium catalyst. Arylation of piperidine α to the nitrogen has been achieved using a ruthenium catalysed, pyridine directed method[125], or *via* a Negishi coupling.[126] For arylation β to the piperidine nitrogen, a carboxylic acid linked quinoline directing group has been used[112] or a ligand assisted approach can be taken.[127,128] Arylation of a 4-aminopiperidine using an amine linked directing group has not yet been reported.

Amide **256** was arylated in *t*AmOH, using a Boc protecting group to prevent the basic piperidine nitrogen coordinating to the palladium catalyst. This led to the formation of both the monoarylated product **257** as well as diarylated product **258**, **Scheme 2.49**.

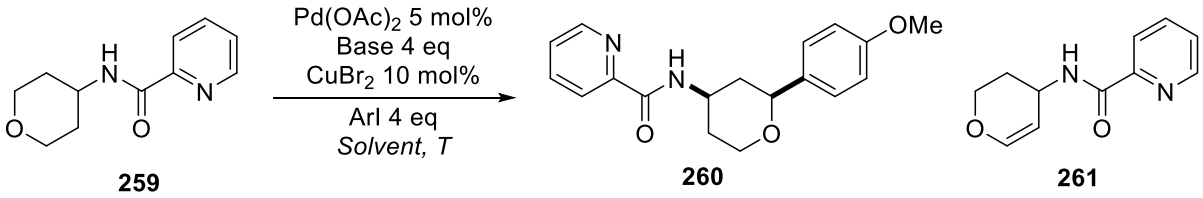


Scheme 2.49 Arylation of piperidine

Encouraged by this result, other protecting groups were investigated, to attempt to improve the yield. As the reaction is carried out at elevated temperatures, Boc protection of the piperidine was not ideal due its potential instability under the reaction conditions. The piperidine was synthesised with tosyl, Cbz and benzoyl protecting groups. Both the tosyl and Cbz protected piperidines were not compatible with the reaction and did not undergo arylation. The arylation reaction also failed when the solvent was changed to *t*HxOH. When using the benzoyl protecting group, trace quantities of both arylated products were observed.

2.7.2 Arylation of oxygen heterocycles

Oxygen heterocycles could also be effectively arylated under the improved reaction conditions, using 3-methyl-3-pentanol as the optimal solvent, **Scheme 2.50**. Unlike the arylation of cyclohexylamine, the arylation of compound **259** did result in the formation of the *β*-hydride elimination product **261** as well as the desired arylation product **260**. The effect of solvent and temperature of the reaction can be seen in **Table 2.3**. C-H activation of a tetrahydropyran scaffold has previously been achieved β to the cyclic oxygen using a ligand enabled protocol, directed by a carboxylic acid linked directing group.[129]



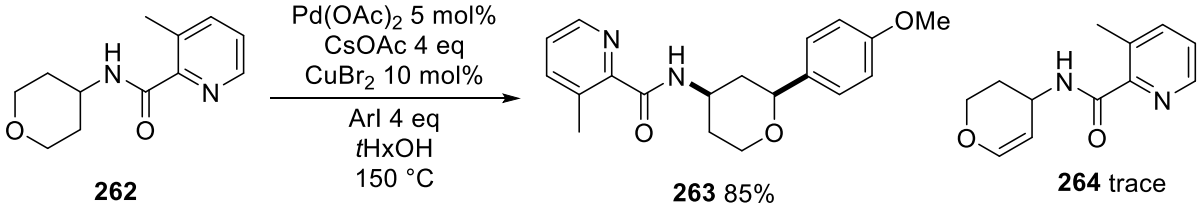
259 **260** **261**

Scheme 2.50 Arylation of an oxygen heterocycle

Entry	Solvent	Temperature	Base	Yield of 260	Yield of 261
1	*t*AmOH	140	CsOAc	24	Trace
2	*t*HxOH	140	CsOAc	15	Trace
3	*t*HxOH	140	CsOPiv	42	Trace
4	*t*HxOH	150	CsOAc	75	5
5	*t*HxOH	150	CsOPiv	55	3

Table 2.3 Optimisation of conditions for arylation of **259**

In order to improve the yield for the arylation, the 3-methylpicolinamide directing group was installed, to give compound **262** which was arylated under the optimum conditions from **Table 2.3**. This led to a 10% increase in yield, and a slight reduction of the formation of the β-hydride elimination product **264**.



262 **263** 85% **264** trace

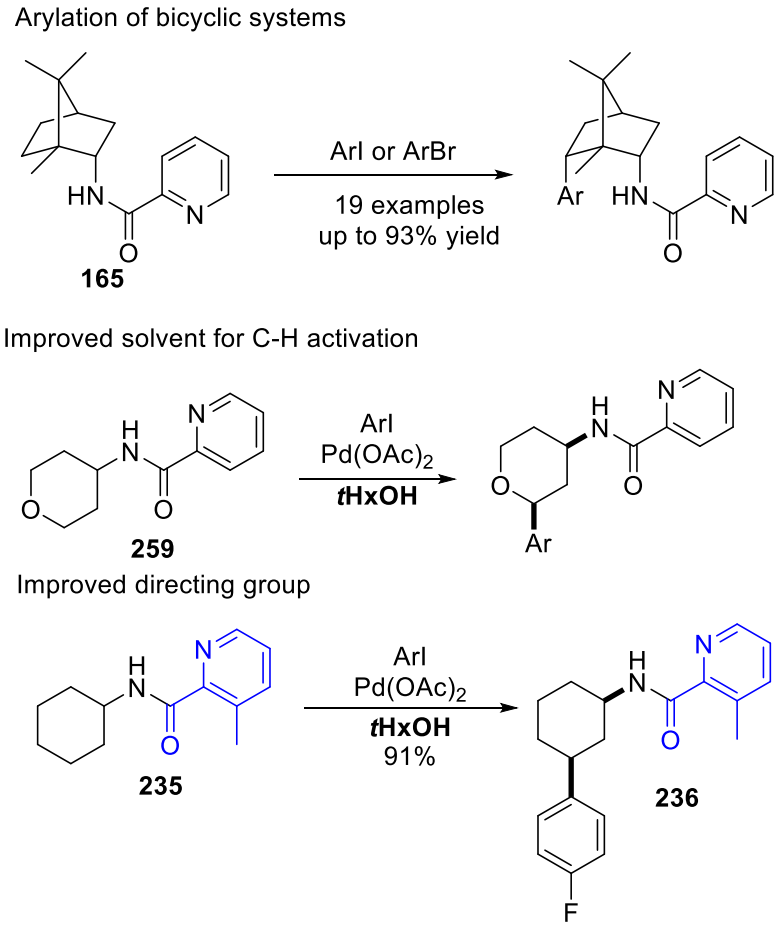
Scheme 2.51 Arylation using an improved directing group

2.8 Conclusions

A method for silver-free arylation of *R*-bornylamine was optimised, using cesium acetate as an alternative to silver. The reaction was compatible with both aryl iodides and aryl bromides and showed a wide range of tolerance for different functional groups including phenols, aldehydes and a protected indole. The methodology could be applied to a variety of amine scaffolds, with the majority showing selective *γ*-activation. An unusual *δ*-activation was also observed on a [2.2.1] bicyclic amine, which took place *via* a 6-membered palladacycle.

It was then demonstrated that a new solvent (*t*HxOH) for C-H activation could be used to improve the yields of arylated products when using more challenging amide substrates. When combined with the 3-methyl picolinamide group could increase the yields for the arylation of cyclohexylamine.

The arylation of oxygen and nitrogen heterocycles was also achieved by making use of the improvements to the reaction conditions. For the arylation of 4-aminotetrahydropyran, combing the improved solvent and directing group was used to give a high yield of arylated product.



Chapter 3

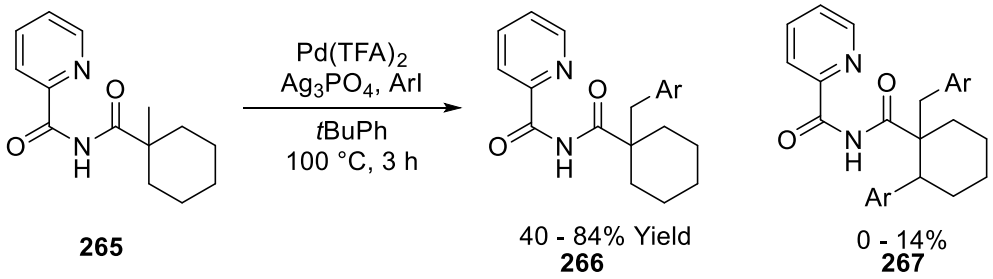
Directing group effects

3.1 Project aims and background

Many different directing groups have been developed for use in C-H activation, but little work has been done on studying how small differences in their structure can affect both the yield and selectivity of reactions.

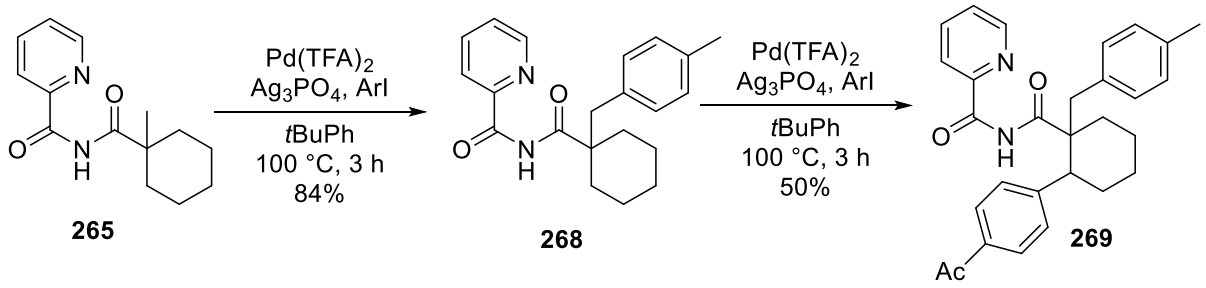
Most directing groups give arylation in the γ position relative to the amine to selectively give one product, but there are relatively few examples of C-H functionalisation of substrates that process two chemically distinct γ positions. When the molecule has both a CH_2 and CH_3 group that can potentially undergo C-H activation, the directing group can influence the selectivity of the reaction. In this chapter different directing groups are employed in the arylation of amines with two sites available for C-H functionalisation to investigate their effects on the selectivity of the C-H activation.

In a system employing an imide linked directing group by Shi, C-H activation preferentially took place on the methyl group of **265**, **Scheme 3.1**.[130] While most aryl iodides used only gave the monoarylated products **266**, aryl iodides with electron withdrawing groups such as *p*-fluoro and *p*-chloro gave small amounts of diarylated product **267**. It may be easier for these electron withdrawing aryl iodides to undergo oxidative addition, leading to diarylation of the substrate.



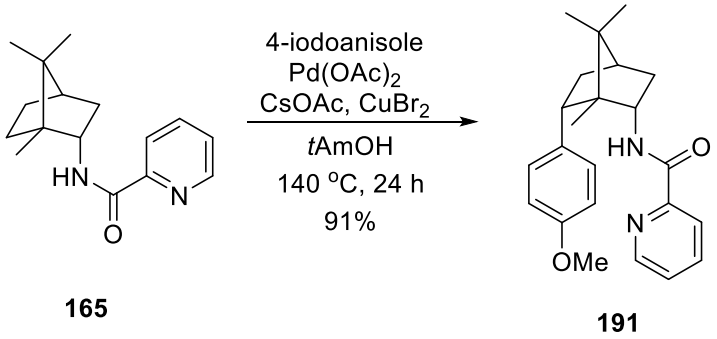
Scheme 3.1 Arylation using an imide linked directing group

However, it was possible using this directing group to perform sequential C-H functionalisation by first arylating on the methyl group and then adding in another aryl iodide, silver salt and palladium source, **Scheme 3.2**. The diastereoselectivity of the reaction is not discussed and no *d.r.* given for product **269**, but the ^{1}H NMR spectrum given in this account does suggest that the product is formed as a mixture of diastereoisomers.



Scheme 3.2 Sequential C-H functionalisation

We previously reported that for the arylation of bornylamine **165** (*vide supra*, Chapter 2), a different selectivity was observed, with the C-H activation taking place selectively on the CH_2 position, **Scheme 3.3**.[117]



Scheme 3.3 Arylation of bornylamine

Different directing groups have been evaluated to investigate their effect on the position of C-H activation on substrates which have more than one available site. Substituted picolinamides had previously been observed to influence the yield of C-H activations (*vide supra*, Chapter 2), and their effects have been further explored.

3.2 Substituted picolinamide directed arylation

After observing the effects that changing the electronics of the picolinamide directing group had on the yield of both cyclohexylamine and bornylamine substrates (*vide supra*, Chapter 2) a range of different directing groups were to be explored.

For discussion about substituted picolinamides, the numbering system shown in **Figure 3.1** is used.

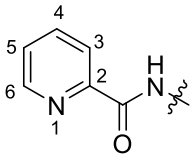
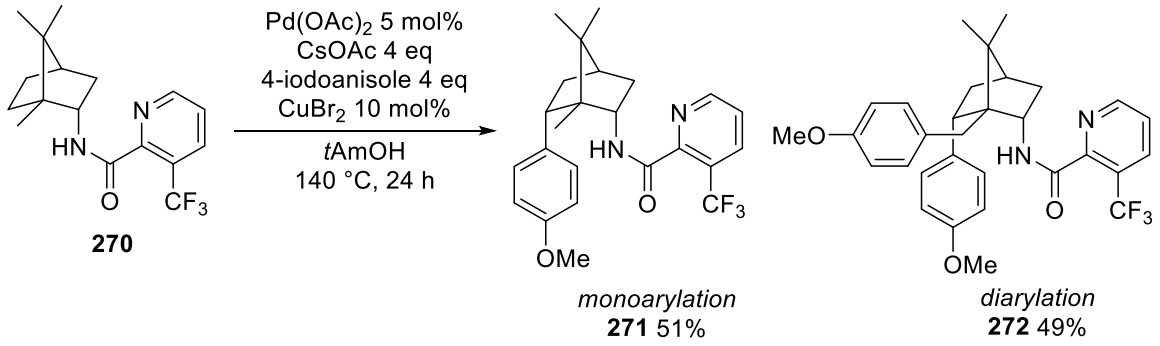


Figure 3.1 Numbering system for substituted picolinamides

The 3-methyl picolinamide group was seen to improve the yield of arylated products, particularly with challenging aryl iodides. On changing from this slightly electron donating group to the strongly withdrawing 3-CF_3 group, a dramatic change in both conversion of the starting amide to arylated product, and the selectivity of the C-H activation was observed, **Scheme 3.4**.



Scheme 3.4 Arylation using the 3-CF_3 picolinamide directing group

Bornylamine **139** contains two chemically distinct C-H bonds which are in the γ position relative to the amine and therefore are both able to undergo C-H activation *via* a 5-membered palladacyle, **Figure 3.2**. Previously only functionalisation of the CH_2 group was seen, despite CH_3 groups typically being more reactive. This suggests that the electronics or conformation of the substituted picolinamide may facilitate a second C-H activation on the methyl group.

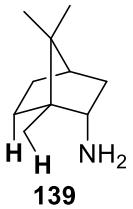
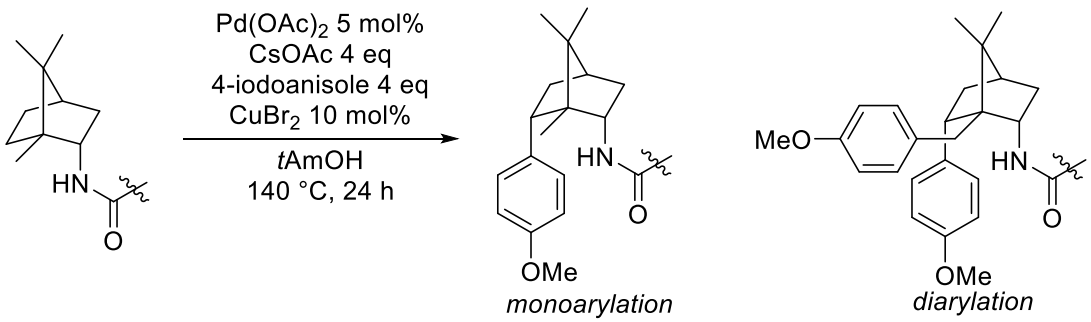


Figure 3.2 Structure of bornylamine, highlighting the two C-H positions that may be functionalised

To further investigate this effect a range of bornylamine derived picolinamides substituted with electron donating (methyl, methoxy) or electron withdrawing (trifluoromethyl) groups were synthesised and reacted under the arylation conditions, **Scheme 3.5**.



Scheme 3.5 General scheme for the arylation of substituted picolinamides

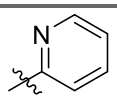
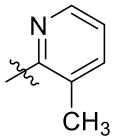
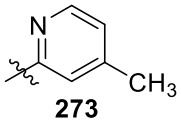
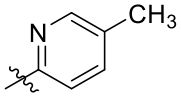
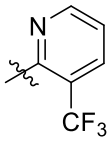
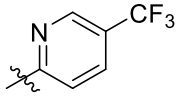
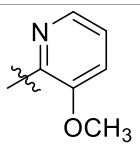
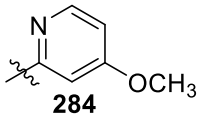
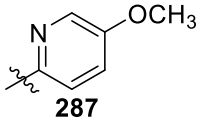
Entry	Directing group	Combined yield / % (isolated)	Ratio of *mono:di*
1	 **165**	91	**191** >98:2
2	 **232**	97	**233** >98:2
3	 **273**	97	**274:275** 88:12
4	 **276**	99	**277:278** 89:11
5	 **270**	100	**271:272** 51:49
6	 **279**	73	**280:281** 73:27
7	 **282**	100[a]	**283** >98:2
8	 **284**	99	**285:286** 79:21
9	 **287**	100	**288:289** 88:12

Table 3.1 Effects of substituted picolinamides on bornylamine arylation. [a] Yield by NMR

Previously, the unsubstituted and 3-methyl picolinamides proceeded under the reaction conditions to give the monoarylation product in excellent yield (**entries 1** and **2**). Having the electron donating methoxy group in the 3-position also only yields the monoarylation product, again in high yield. Moving the methyl group from the 3 position to the 4 and 5 positions results in an increase in the formation of the diarylated product, **entries 3** and **4**. Changing to a more electron donating methoxy group in the 4 and 5 positions increased further the amount of diarylated product, **entries 8** and **9**, resulting in a high overall conversion to the arylated products. Using the 3-trifluoromethyl substituted picolinamide results in the largest quantity of the diarylated product out of all the directing groups tested, followed by the 5-trifluoromethyl, **entry 6**. The 5-trifluoromethyl group also has a negative impact on the level of conversion of starting amide to arylated product, similar to the effect it had on the arylation of cyclohexylamine which also resulted in a lower yield of arylated product when compared to the unsubstituted picolinamide (*vide supra*, Chapter 2). It may be that the strongly electron withdrawing effect of the 5-trufluoromethyl group has a negative effect on how effectively the picolinamide group can coordinate to the palladium catalyst.

Overall, to obtain the highest yield and selectivity, the 3-methyl picolinamide was the superior directing group resulting in complete selectivity for arylation on the CH_2 as well as a high isolated yield of 97%.

In the case of the bornylamine scaffold, C-H activation took place preferentially at the CH_2 position suggesting that this is the lowest energy pathway. To further investigate this directing group effect, two amines with both CH_2 and CH_3 in the γ position relative to the amine, **Figure 3.3**, were used in C-H functionalisation reactions. Both of these positions can undergo C-H activation *via* a 5-membered palladacycle, **Figure 3.4**.

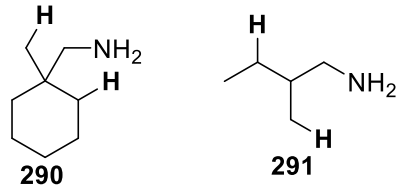


Figure 3.3 Amines for the investigation of directing group effects

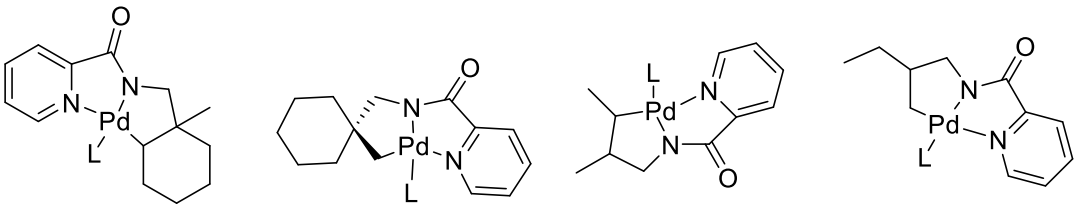
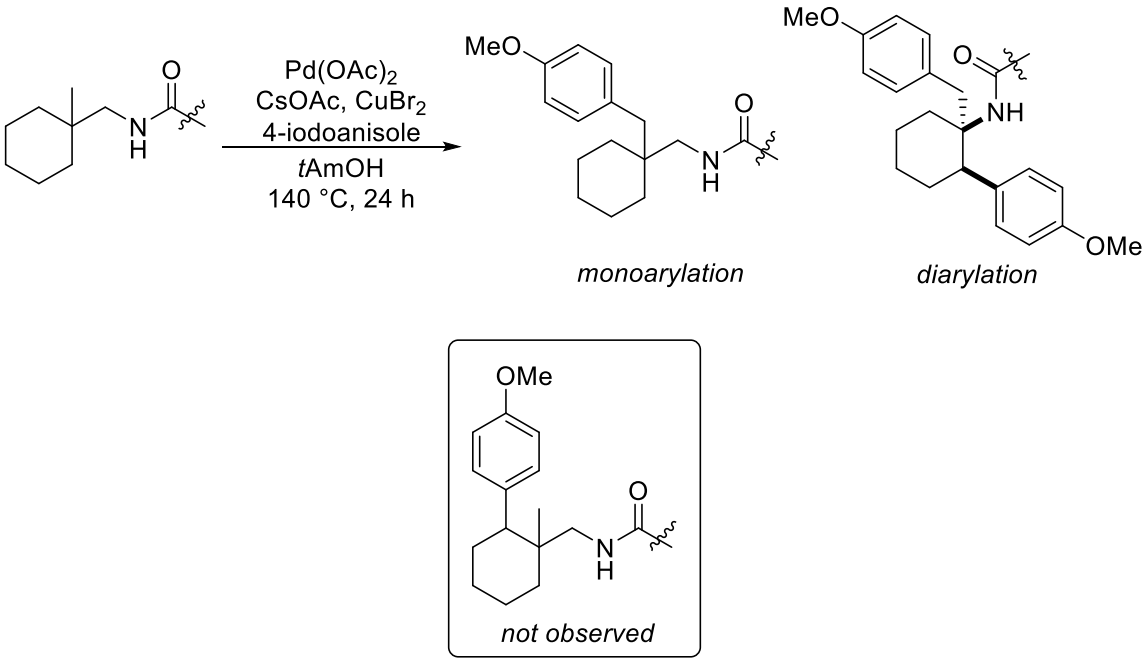


Figure 3.4 Potential palladacycles which may be formed by C-H activation

The cyclohexane scaffold was reacted under the same conditions as bornylamine, **Scheme 3.6**, using the different substituted picolinamide directing group. Arylation was preferentially seen on the CH_3 group. The monoarylation product where functionalisation of the methylene position has occurred was not observed.



Scheme 3.6 Monoarylation of a cyclohexane scaffold at the CH_2 position

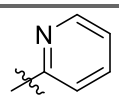
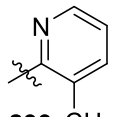
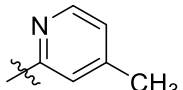
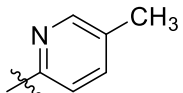
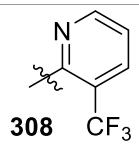
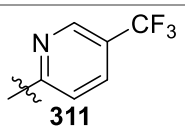
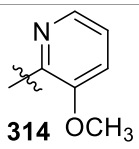
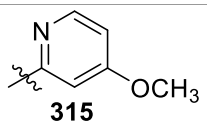
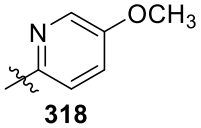
Entry	Directing group	Combined yield / % (isolated)	Ratio of *mono:di*	Yield *mono* / % (isolated)	Yield *di* / % (isolated)
1	 **296**	88	**297:298** 76:24	45	43
2	 **299**	62	**300:301** 83:17	57	5
3	 **302**	86	**303:304** 78:22	77	9
4	 **305**	54	**306:307** 78:22	43	11
5	 **308**	35	**309:310** 82:18	30	5
6	 **311**	57	**312:313** 77:23	39	18
7	 **314**	N/A	N/A	N/A	N/A
8	 **315**	77	**316:317** 79:21	54	23
9	 **318**	38	**319:320** 62:38	19	19

Table 3.2 Arylation of a cyclohexane scaffold using different picolinamides

The diarylated products were isolated as a mixture of diastereoisomers, **Figure 3.5**. Assignment of the stereochemistry was achieved by comparing the ^{1}H NMR spectra of **307a** and **307b** to computational predictions performed by Dr M. J. Porter, using the DP4 method of Goodman.[131]

In the DP4 method, ^{1}H and ^{13}C chemical shifts are calculated for each possible stereoisomer using a combination of molecular mechanics and density functional theory; these shifts are compared with the experimental values to provide a measure of the likelihood of each structure being correct. Use of this method with stereoisomers **307a** and **307b** assigned a probability of >99.9% that the major diastereomer has the structure **307a**, with the two anisyl groups on opposite faces of the cyclohexane ring.

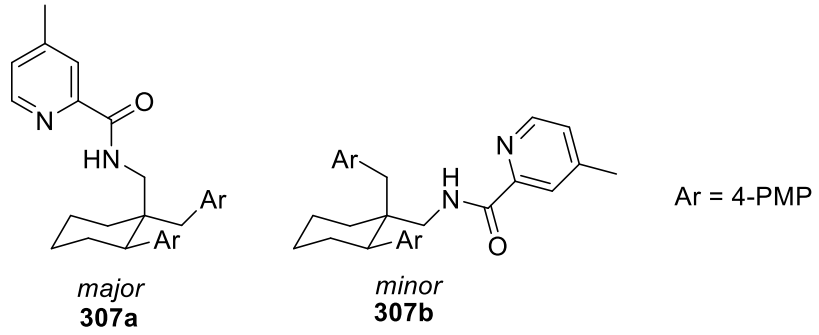
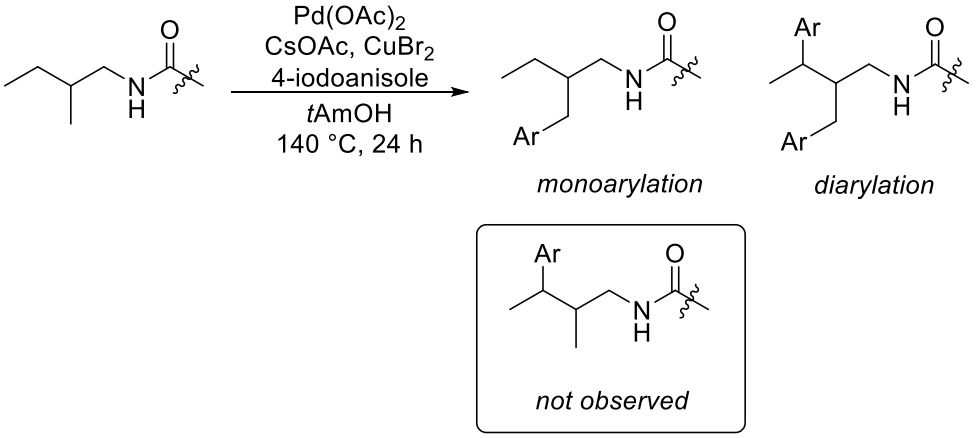


Figure 3.5 Stereochemical assignment of diarylated product **307**

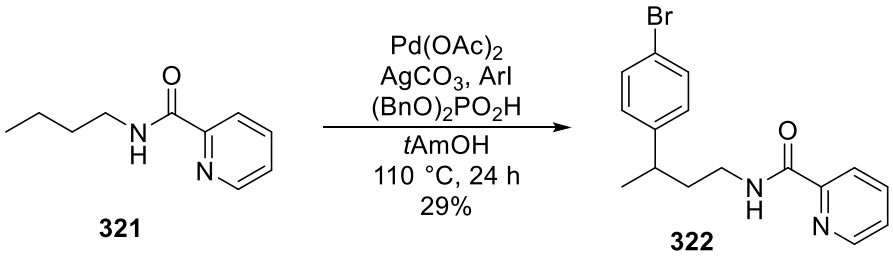
In this case, having a strongly electron rich methoxy directing group on the pyridine resulted in more diarylation when compared to the other directing groups. When the picolinamide has a substituent in the 3-position this reduces the extent of the diarylation, with the 3-trifluoromethyl and the 3-methyl resulting in similar ratios between mono and diarylated products being observed (**entries 2** and **5**). The electron withdrawing 3-trifluoromethyl does result in a lower conversion to arylated product, as does the 5-trifluoromethyl (**entry 6**). The 4-methyl and the unsubstituted picolinamides led to the highest conversion to the product (**entries 1** and **3**), and moderate selectivity for the monoarylated product. Having the methyl group in the 5- rather than 4-position makes little difference to the selectivity of the arylation but does reduce the overall conversion of the reaction (**entry 4**). It was not possible to obtain results for the 3-methoxy picolinamide due to difficulties in the purification of both the amide and the resulting arylated products (**entry 7**). The electron donating methoxy group in the 4- or 5- position (**entries 8** and **9**) resulted in very different overall yields of 77% and 38% respectively, and moderate selectivity. Unlike the bornylamine, using the 3-methyl picolinamide directing group was not the most effective for the arylation of this cyclohexane scaffold. Instead using the 4-methyl picolinamide as the directing group gave the highest yield of arylated product and moderate selectivity for the monoarylated product.

A similar selectivity was observed on the acyclic amine scaffold, which showed preference for mono arylation of the methyl group, with some diarylation taking place. Monoarylation product showing arylation of the methylene, was not observed in the reaction, **Scheme 3.7**.



Scheme 3.7 Arylation of an acyclic amine

When there is no methyl group available, as in the picolinamide directed arylation of butylamine **321**, *Chen* and co-workers showed that it reacted only on the methylene position in low yield, **Scheme 3.8**. The aryl bromide was not reactive.[132]



Scheme 3.8 Arylation of butylamine

The same set of substituted picolinamides were prepared from 2-methyl-butan-1-amine, and the effect of these directing groups on the yield and selectivity of the arylation was investigated, **Table 3.3**.

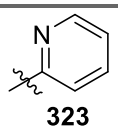
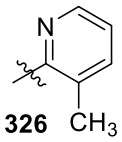
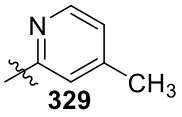
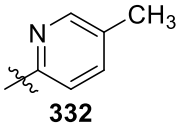
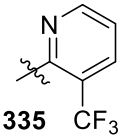
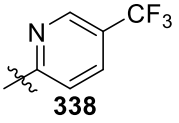
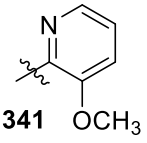
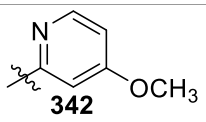
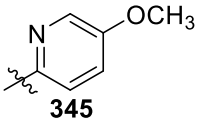
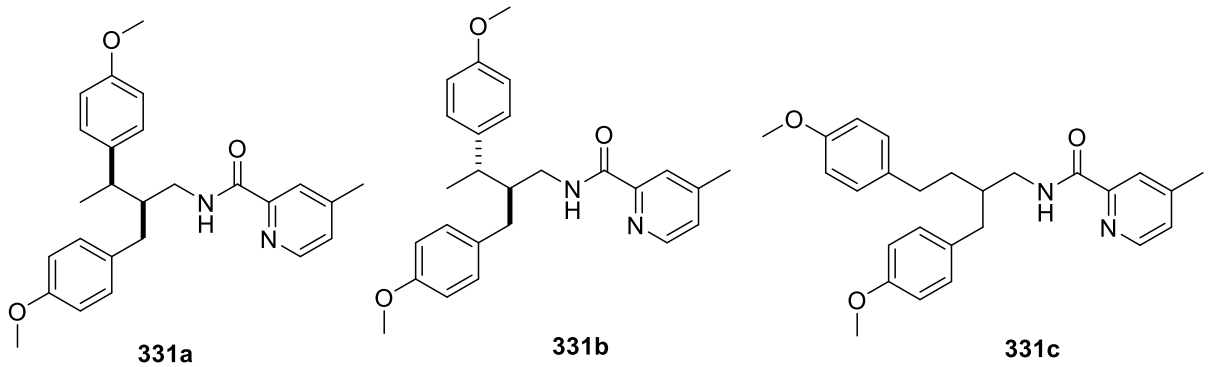
Entry	Directing group	Combined yield / % (isolated)	Yield *mono* / % (isolated)	Yield *di* / % (isolated)
1	 **323**	93	**324** 72	**325** 21
2	 **326**	78	**327** 73	**328** 5
3	 **329**	52	**330** 26	**331** 26
4	 **332**	98	**333** 87	**334** 11
5	 **335**	57	**336** 52	**337** 5
6	 **338**	45	**339** 41	**340** 4
7	 **341**	N/A	N/A	N/A
8	 **342**	55	**343** 55	**344** trace
9	 **345**	91	**346** 82	**347** 9

Table 3.3 Arylation of 2-methylbutan-1-amine

When reacted under the arylation conditions, the monoarylation product was the major product for all the different substituted picolinamides. Due to the complexity of the crude ^{1}H NMR spectra from these reactions it was not possible to establish the crude ratio between the two products. Instead the quantity of each product in the isolated material was measured to establish the selectivity of the reaction. Using the unsubstituted picolinamide (**entry 1**) resulted in poor selectivity for the monoarylated product, giving 72% of the monoarylation and 21% of the diarylation. 4-Methyl (**entry 3**) also showed poor selectivity, giving equal quantities of mono and diarylation, as well as a poor overall conversion. Having a more strongly electron donating methoxy group in the 4 position also gave a low overall conversion (**entry 8**), but improved selectivity. The other directing groups employed resulted in low quantities of the diarylated product. Having either the electron withdrawing 3-trifluoromethyl (**entry 5**) or 5-trifluoromethyl (**entry 6**) gave low overall conversion, but good selectivity for the monoarylation product. Having a mild (4-methyl, **entry 4**) or strongly (5-methoxy, **entry 9**) electron donating groups in the 5 position gave the highest overall conversions to arylated products, as well as moderate selectivity for the monoarylated product. The 3-methyl group (**entry 2**) was the superior directing group for achieving a high conversion as well as good selectivity for the monoarylation, with only 5% of the diarylation product being observed. The 3-methoxy group presented similar difficulties in the purification of the starting picolinamide and arylated products.

In the case of the 4-methyl substituted directing group, **entry 4**, the diarylated product was isolated as a mixture, **Figure 3.6**. The diarylated product **331c** is formed as a result of a 6-membered palladacycle to give arylation at the δ position. This product was identified using TOCSY NMR experiments, since the three compounds were isolated as an inseparable mixture.



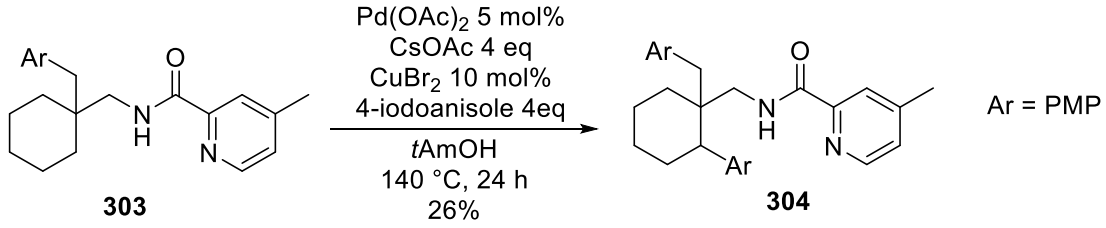
331a **331b** **331c**

2.22:1:1.15

Figure 3.6 Diarylated products

When the monoarylated compound **303** was resubmitted to the reaction conditions the diarylated product **304** was formed, **Scheme 3.9**. Previously the reaction employing the 4-

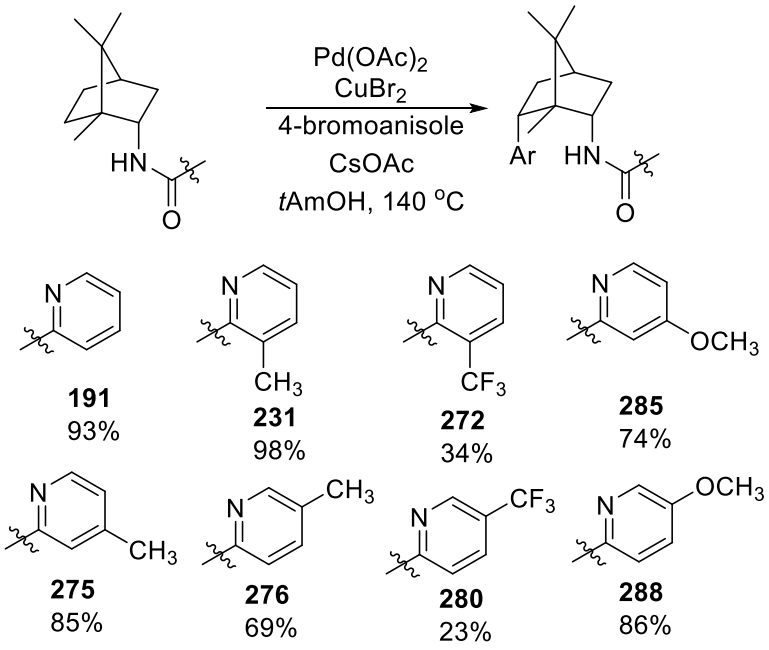
methyl picolinamide resulted in a 9% yield of the diarylated product. When synthesising this diarylated product from the monoarylated product **303** a higher yield of 26% is achieved, potentially due to the higher concentration of aryl iodide in this reaction as none of it is consumed to produce monoarylated product **303**. This indicated that there is the potential for a sequential C-H activation using two different aryl iodides.



Scheme 3.9 Sequential arylation of a cyclohexane scaffold

3.3 Reactions with aryl bromides

The picolinamide of bornylamine had been previously seen to react under the same conditions with aryl bromides to give arylated products.[117] The effect of yield and selectivity of substituted picolinamides was also studied when using aryl bromides as coupling partners. Interestingly only the monoaryl product was observed in all cases, **Scheme 3.10**.

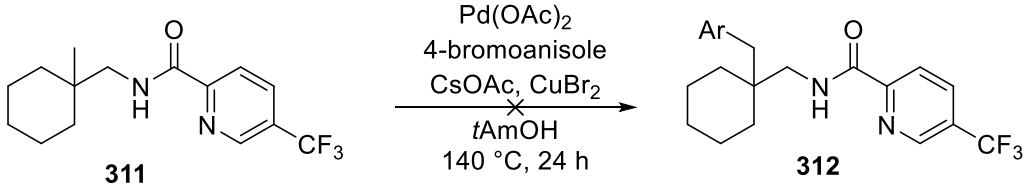


Scheme 3.10 Arylation of bornylamine using 4-bromoanisole

The electron withdrawing trifluoromethyl group in both the 3- and 5-positions had a negative effect on the yield of arylated product. Weakly and strongly electron donating groups in the 4- or 5-positions of the pyridine resulted in moderate to good yields of the arylated product. As with using aryl iodides, having the 3-methyl substituted picolinamide gave the highest

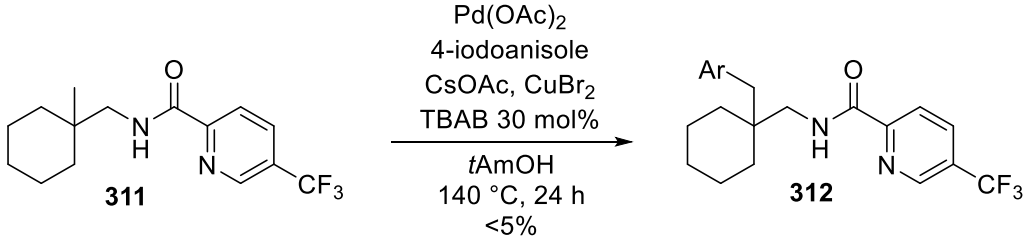
yield of 98%, and therefore was the most effective directing group for arylation using an aryl bromide.

Interestingly the same effect was not observed on the other amine scaffolds when employing an aryl bromide as a coupling partner. In the case of cyclohexane scaffold **311**, arylation was not evident when an aryl bromide was used, **Scheme 3.11**.



Scheme 3.11 Reaction of a cyclohexane with an aryl bromide

To establish why the reaction was not compatible with the aryl bromide a reaction using aryl iodide in the presence of TBAB was conducted, **Scheme 3.12**.

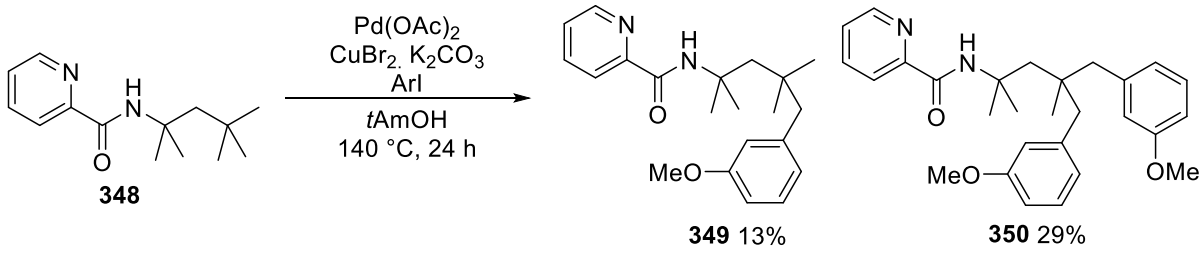


Scheme 3.12 Arylation with an aryl iodide in the presence of TBAB

The addition of 30 mol% of TBAB prevented the arylation proceeding as expected with the aryl iodide as the coupling partner, instead only a trace quantity of the arylated product **312** was observed. This suggests that the presence of bromide within the reaction prevents the C-H functionalisation from taking place.

3.4 Reactions with other amines

The effect of different directing groups would have on the arylation of compounds with two chemically identical positions available for C-H activation. *Daugulis* and co-workers showed that the picolinamide directed arylation of compound **348** resulted in a mixture of mono and diarylated compounds, **Scheme 3.13**. This compound has two equivalent methyl groups which can undergo C-H functionalisation. The major product for this reaction was the diarylated product which was produced in 29% yield. The minor monoarylation product was also observed in 13% yield. Overall conversion for this transformation was poor.[50]



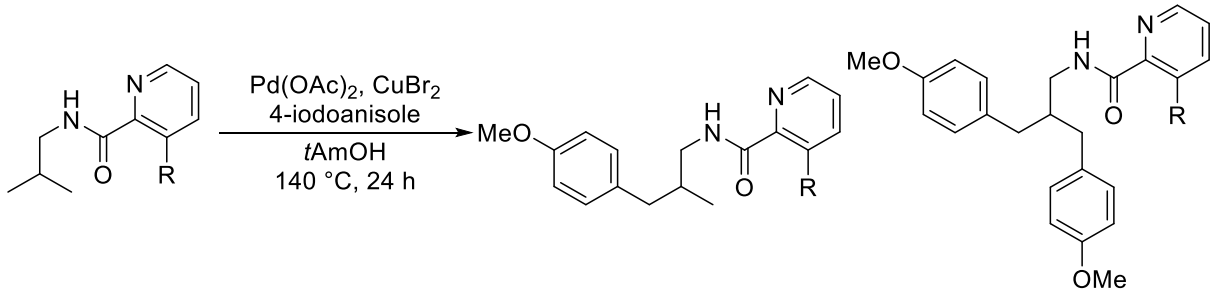
348

349 13%

350 29%

Scheme 3.13 Mono and diarylated products

Isobutylamine has two equivalent CH_3 positions γ to the amine which can be accessed in a picolinamide directed C-H activation. When the reaction is carried out using the unsubstituted picolinamide group, amide **351**, a mixture of mono **353** and di **355** arylated products are observed. On changing to the 3-methylpicolinamide group, a reduction in the diarylation product is seen, as well as an overall increase in conversion from starting amide **352** to arylated products **354** and **356**, **Scheme 3.14**.



351 R = H
352 R = Me

353 R = H 12%
354 R = Me 23%

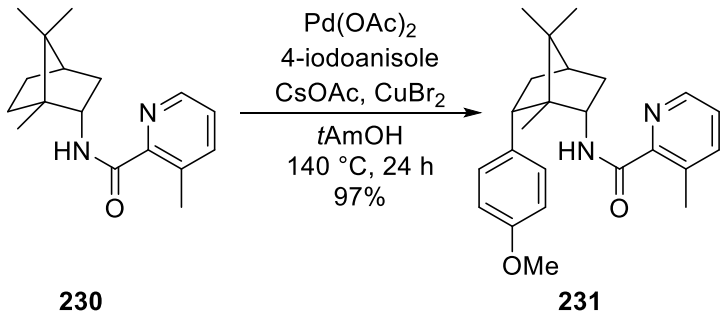
355 R = H 68%
356 R = Me 62%

Scheme 3.14 Arylation of isobutylamine

3.5 Conclusions

The effects of substituting the picolinamide directing group on selectivity and conversion of C-H functionalisation has been studied. Nine different directing groups were investigated for the influence on 3 different amines which had two chemically distinct γ-positions relative to the amine which are all accessible for C-H activation. The picolinamides studied included a range of electron rich and electron poor substituents, such as trifluoromethyl, methyl and methoxy.

It was shown that for achieving selective monoarylation in most cases the 3-methyl picolinamide directing group was superior. Higher yields in most cases were also observed in reactions using the 3-methyl picolinamide starting materials. Using more electron poor trifluoromethyl substituted picolinamides often resulted in lower conversion to C-H functionalised product potentially due to them not being able to coordinate to the palladium catalyst as effectively as the more electron rich picolinamides.



230 **231**

Scheme 3.15 Arylation using the 3-methyl picolinamide directing group

The coupling partner employed in C-H functionalisation was also seen to have an effect. For the arylation of the bicyclic bornylamine scaffold using an aryl bromide, all the directing groups used for the transformation gave the same selectivity giving only the monoarylated products. Which directing group was used did have an effect on the yields of arylated product obtained. Aryl iodides resulted in a mixture of mono and diarylation for most picolinamides.

Chapter 4

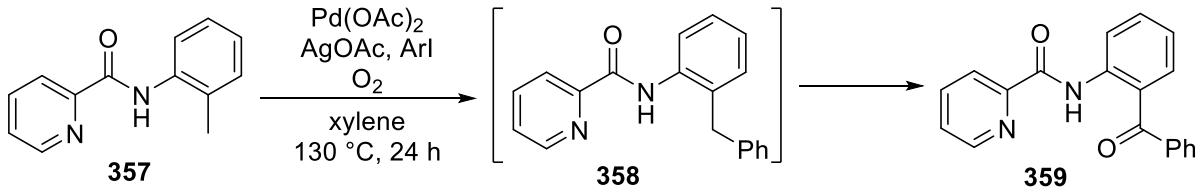
Mechanistic and kinetic studies

4.1 Project aims and background

In order to gain a deeper understanding of the C-H activation, the mechanism for the arylation was investigated. The isolation of potential intermediates can give an insight into the mechanism.

Palladium catalysed reactions, such as Suzuki and Stille couplings usually proceed *via* a Pd^{0}/Pd^{II} catalytic cycle.[133] C-H functionalisation reactions have been proposed to go *via* Pd^{0}/Pd^{II}, Pd^{III}/Pd^{III} or Pd^{II}/Pd^{IV} cycles, depending on the substrates and reaction conditions.[134]

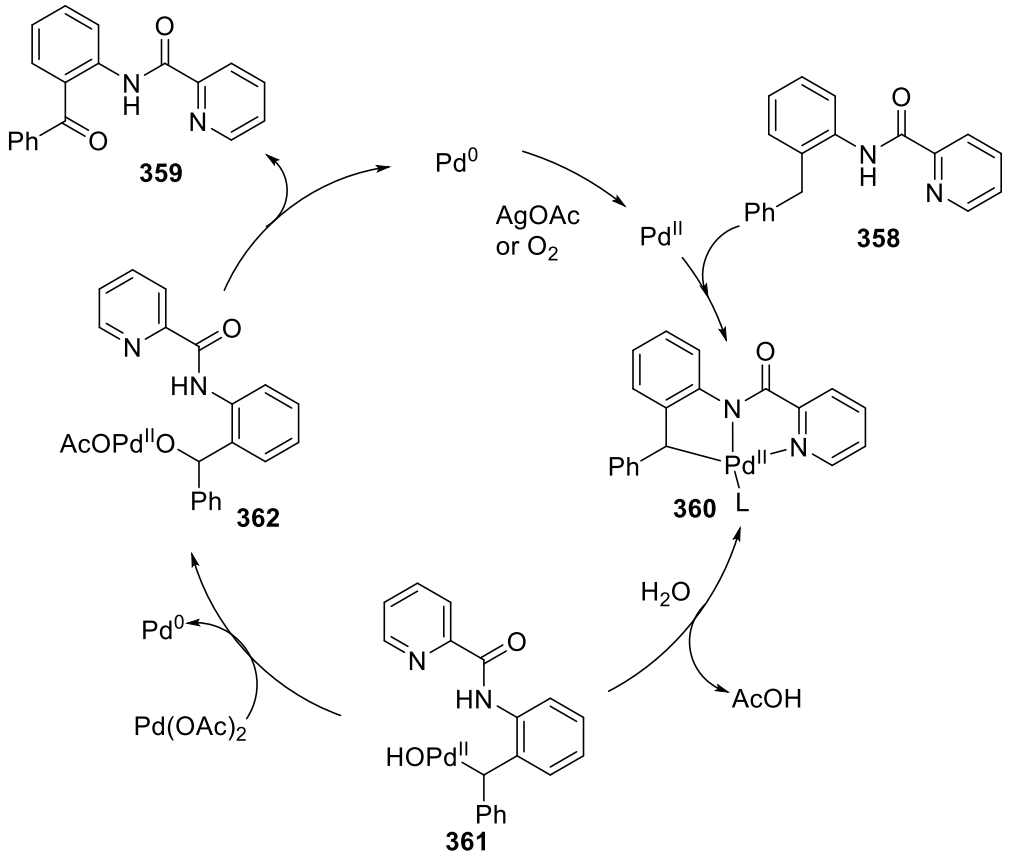
Zhang *et al*. reported a picolinamide directed, palladium catalysed sequential benzylic C-H arylation/oxidation. Firstly, arylation of the benzylic methyl group takes place to give **358**, followed by oxidation to **359**, **Scheme 4.1**.



357 358 359

Scheme 4.1 Arylation and subsequent oxidation of a benzylic methyl group

While the arylation is proposed to go *via* a Pd^{II}/Pd^{IV} cycle, the oxidation is proposed to go *via* a Pd^{0}/Pd^{II} cycle, which is more unusual in picolinamide directed C-H activations. The proposed catalytic cycle for this oxidation is shown in **Scheme 4.2**.

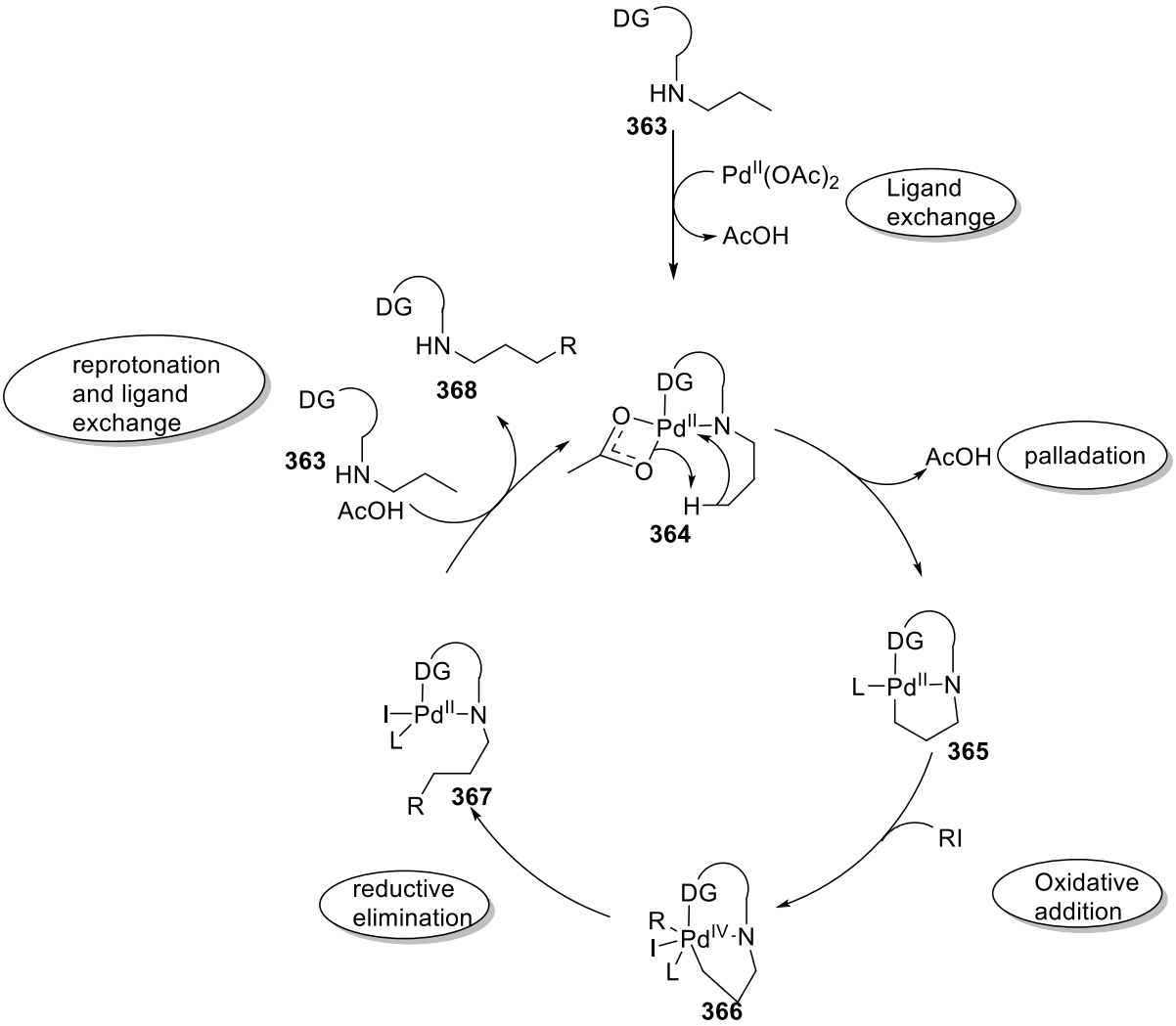


Scheme 4.2 An example of a Pd^0/Pd^{II} catalytic cycle

Oxidation involves a Pd^0 species which is reoxidised by silver acetate or molecular oxygen (**Scheme 4**). Firstly, substrate **358** coordinated to the palladium acetate, deprotonating the amide. Cleavage of the C-H bond *via* a CMD follows, to give complex **360**. A ligand exchange with water to gives intermediate **361**. Reductive elimination then ligand exchange with palladium acetate gives **362**, which then undergoes *β*-hydride elimination to furnish product **359**. The Pd^0 generated in the cycle is reoxidised by silver acetate or molecular oxygen. When the reaction was carried out using an $^{18}O_2$ atmosphere the ^{18}O labelled product was produced, indicating that the oxygen in the product originated from molecular oxygen. However, when the reaction was performed in the presence of $H_2{}^{18}O$ the ^{18}O labelled product was generated, suggesting the oxygen can also come from water. A possible explanation for these results is that the $^{18}O_2$ may act as the oxidant for Pd^0 to Pd^{II} and generate $H_2{}^{18}O$ which can participate in the catalytic cycle.[135] The ligand assisted C(sp^3)-H functionalisation of alkyl amines is also proposed to go *via* a Pd^0/Pd^{II} cycle.[78]

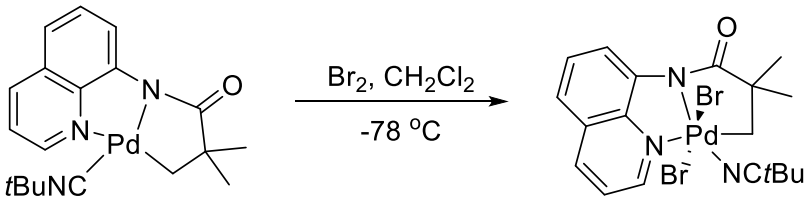
The majority of amide directed C-H arylation reactions are thought to proceed *via* a Pd^{II}/Pd^{IV} catalytic cycle, **Scheme 4.3**. To generate the active catalyst **364**, the amide nitrogen must be deprotonated either by the base present in the reaction or one of the ligands of the palladium species used in the reaction. C-H insertion then takes place *via* a concerted cyclometallation

deprotonation mechanism (CMD) to give complex **365**. Oxidative addition of the aryl halide give the octahedral Pd^{IV} species **366**. Reductive elimination to form the new C-C bond follows, to give complex **367**. Reprotonation of the amide, abstraction of the halide from the palladium and a ligand exchange regenerates the active palladium species **364** and releases the functionalised product **368**.



Scheme 4.3 General mechanism for C-H activation *via* a Pd^{II}/Pd^{IV} cycle

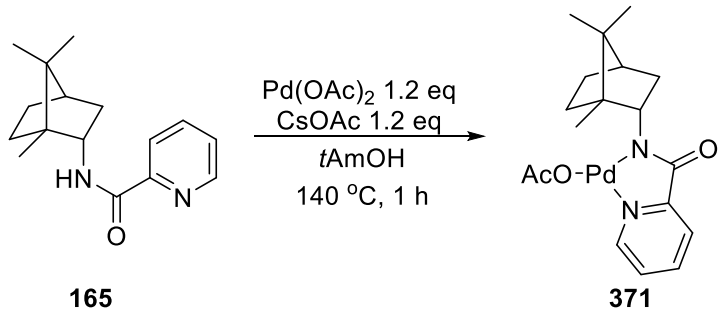
The high valent palladium (IV) intermediates are difficult to isolate and characterise.[136] The Pd^{IV} dibromide complex **370** was isolated on reaction of complex **369** with bromine (**Scheme 4.4**). Attempts to replace the bromine ligands with an alkyl or aryl group failed.[35]



Scheme 4.4 Isolation of a Pd^{IV} species

4.2 Isolation of reaction intermediates

Conditions to isolate intermediates in our arylation reactions were initially chosen to stay as close as possible to the original reaction conditions. **Scheme 4.5** shows the isolation of palladium complex **371**, with the N**H** deprotonated and the palladium catalyst coordinated to the directing group. A slight excess of palladium acetate was required to enable the reaction to go to completion and complex **371** was isolated in quantitative yield.



Scheme 4.5 Isolation of a palladium complex showing deprotonation of the NH

The ^{1}H NMR spectra for **371** shows a disappearance of the NH proton and a change in the chemical shift of the other protons on the molecule. The formation of complex **371** led to a dramatic upfield shift of the methine proton adjacent to the nitrogen atom, from 4.4 ppm in the starting amide **165** to 2.6 ppm in complex **371**, **Figure 4.1**. The absence of the NH proton can also be clearly seen, showing that the amide has been deprotonated. The complex was not water stable, so it was not possible to wash out the residual acetate present.

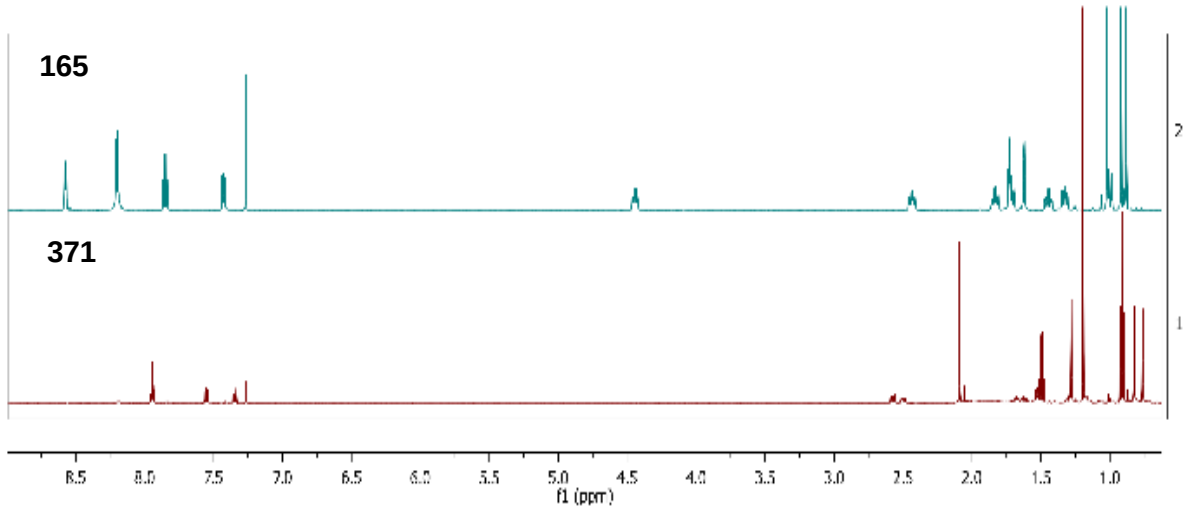
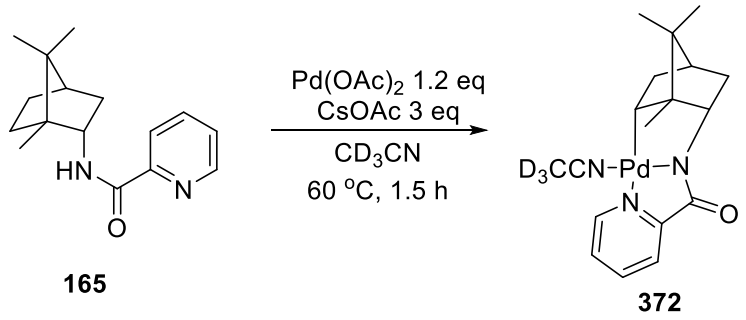


Figure 4.1 ^{1}H NMR spectra of **165** and **371** in $CDCl_3$

Under these conditions the activation of the C-H bond was not seen. In order to stabilise the palladacycle with a ligand once it had formed, the reaction was performed in deuterated acetonitrile, **Scheme 4.6**, giving the desired palladacycle **372**. No reaction was observed in the absence of the cesium acetate base. As in complex **371**, the amide of the directing group has been deprotonated. The isolation of this complex shows that C-H activation can take place in the absence of the aryl halide.



165 **372**

Scheme 4.6 Isolation of a palladacycle with palladation of a C-H bond

Formation of the cyclopalladated intermediate likely proceeds *via* a concerted metalation deprotonation (CMD) mechanism, **Figure 4.2**. This mechanism goes *via* a 6 membered transition state, leading to the 5-membered palladacycle which rationalises why the reaction is selective for the position γ to the amine. The picolinamide directing group brings the acetate ligand of the palladium close the C-H bond to be activated.[137]

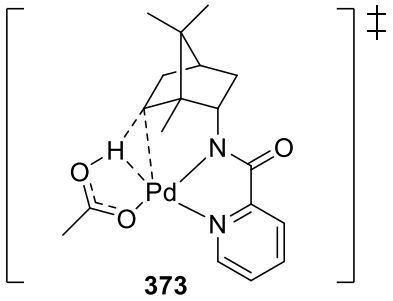


Figure 4.2 Potential transition state for the CMD step

The palladation product can be seen in the ^{1}H NMR. When comparing the starting amide **165** with palladacycle **372** it can be seen that the NH of the amide has been deprotonated in **372**. The presence of a new CH can be seen in the ^{1}H NMR of **X** at 2.63 ppm which corresponds to the proton on the carbon bonded to the palladium, **Figure 4.3**. It was not possible to obtain mass spectrometry data for palladacycle **372**.

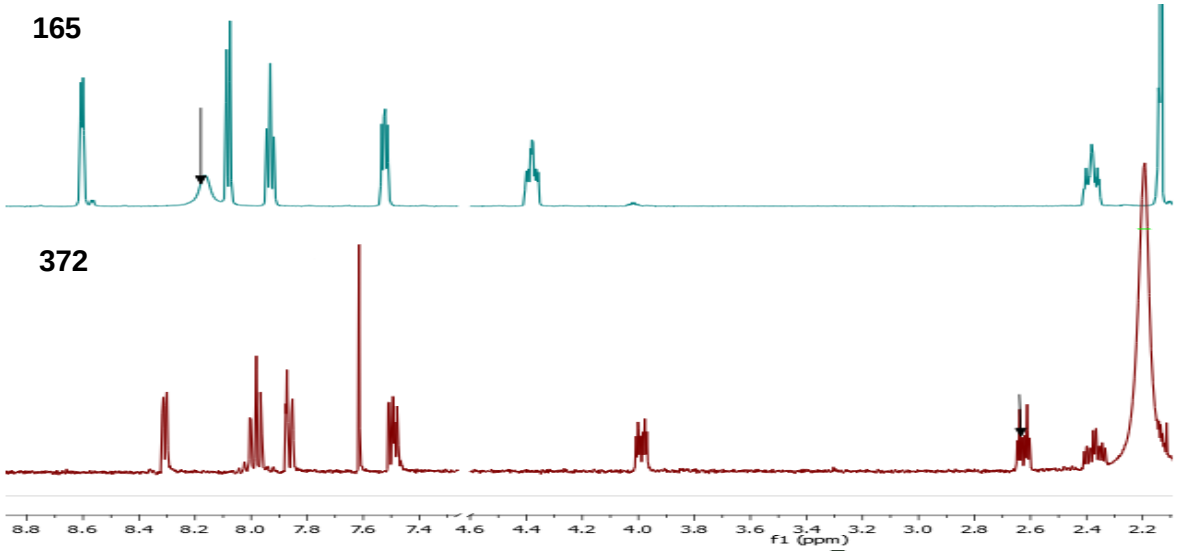
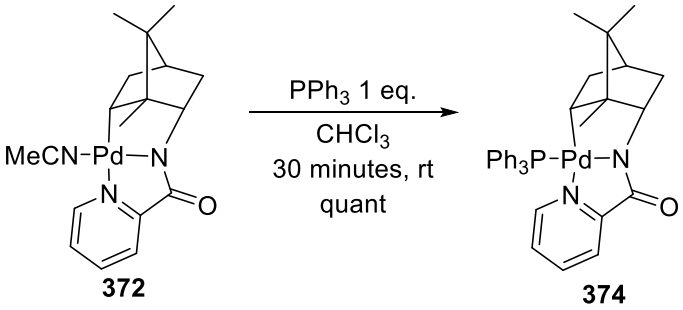


Figure 4.3 ^{1}H NMR of **165** and **372** in CD_3CN

It did not prove possible to grow crystals of palladacycle **372** for XRD to unambiguously assign the structure, and so a ligand exchange was carried out replacing the acetonitrile with a triphenylphosphine in quantitative yield, **Scheme 4.7**. Single crystals of **374** were grown, **Figure 4.4**. The crystal structure obtained clearly shows the palladium-carbon bond, as well as coordination of the pyridine to the palladium.



Scheme 4.7 Ligand exchange reaction

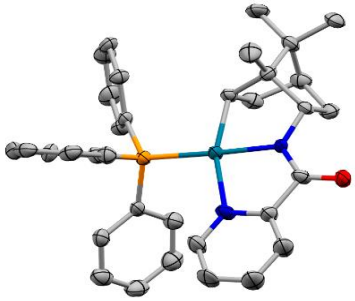
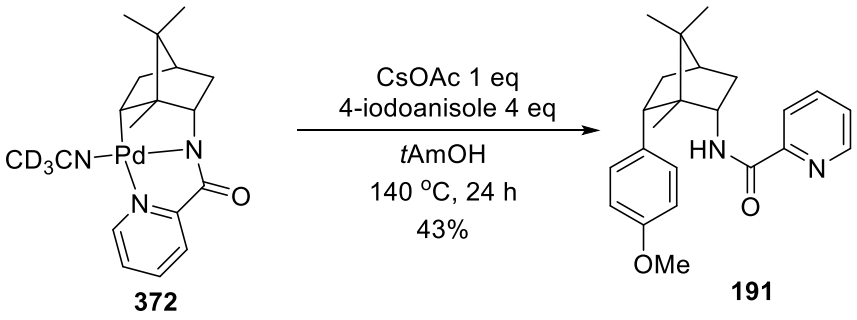


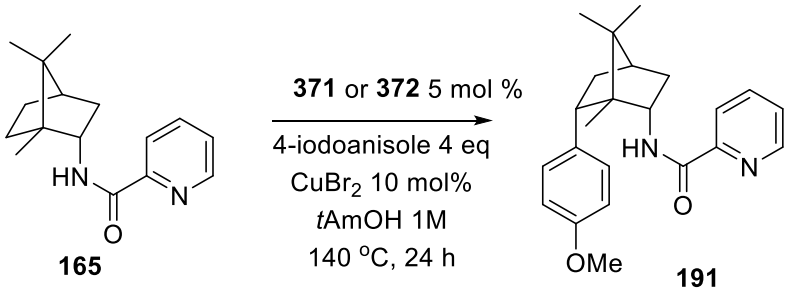
Figure 4.4 Crystal structure of palladacycle **374** – ellipsoids drawn to the 50% probability level

The isolated palladium complex **372** was returned to the reaction conditions with 4-iodoanisole to investigate if it would undergo the arylation reaction. When used in stoichiometric quantities, a disappointing yield of the arylated product was recovered, **Scheme 4.8**. Significant decomposition of the complex was seen, resulting in a black insoluble solid. This experiment is consistent with the C-H activation step occurring first followed by the oxidative addition of the aryl halide. This has previously been observed in aminoquinoline directed C-H arylation of aliphatic amines using aryl bromides where DFT studies showed that C-H activation followed by oxidative addition was the lower energy pathway.[138]



Scheme 4.8 Arylation of the palladium complex

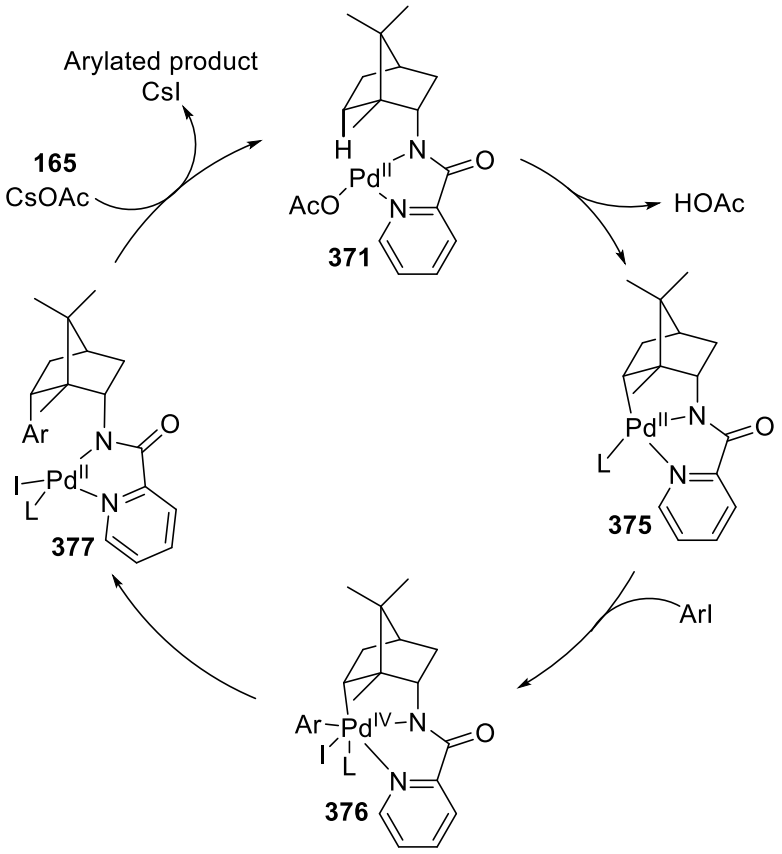
Using the complexes **371** and **372** as catalysts in the reaction in place of $Pd(OAc)_2$ gave good yields of 87% and 80% respectively, **Scheme 4.9**.



Scheme 4.9 Using the isolated palladium complexes as catalysts for the arylation reaction

4.3 Monoarylation pathway

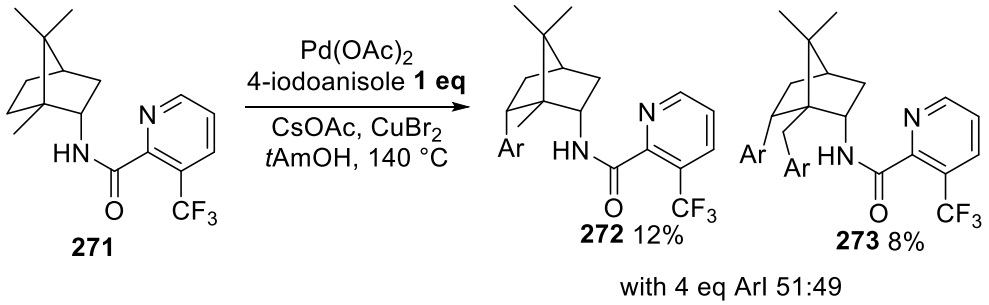
A catalytic cycle can now be proposed for the arylation reaction, **Scheme 4.10**. Firstly the amide NH is deprotonated, and the pyridine ring coordinates to the palladium, with loss of one molecule of acetic acid, to give intermediate **371**. C-H activation then occurs, most likely via a cyclometallation deprotonation mechanism, with loss of another molecule of acetic acid, to give palladacycle **375**. Oxidative addition of the aryl halide to give the palladium (IV) complex **376** follows, which is followed by a reductive elimination to form the new C-C bond. Ligand exchange and reprotonation of the amide furnishes the arylated product and regenerates the active catalyst **371**.



Scheme 4.10 Proposed mechanistic cycle

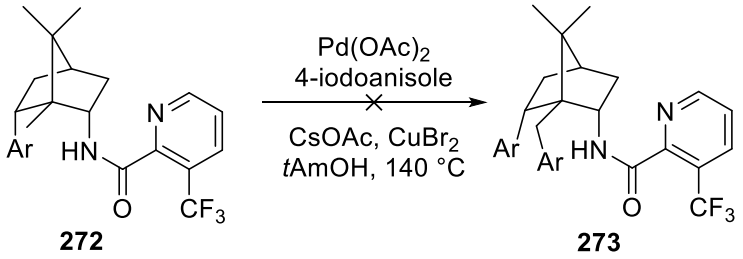
4.4 Diarylation pathway

In the case of some of the substituted picolinamides, some diarylation was observed. When the 3-trifluoromethyl picolinamide **271** was reacted with one equivalent of aryl iodide, diarylation was still occurring in a similar proportion to when 4 equivalents were used, but with a lower overall conversion, **Scheme 4.11**.



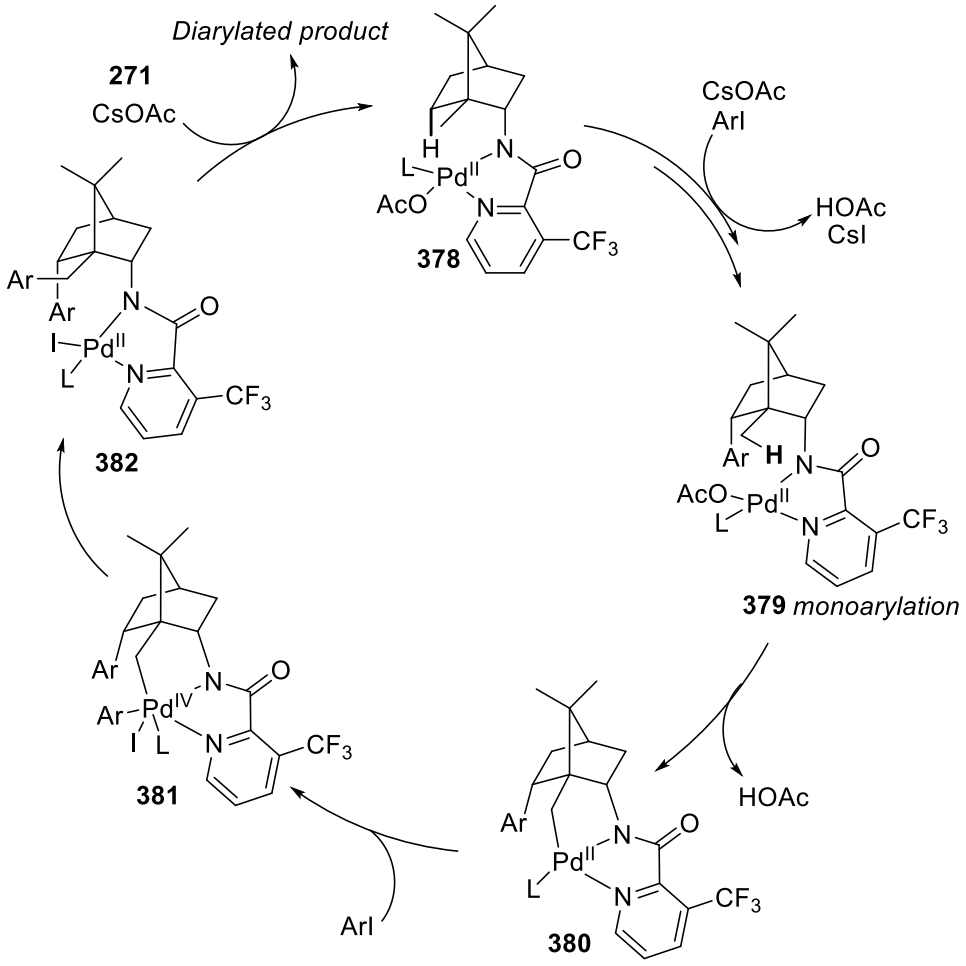
Scheme 4.11 Arylation using 1 equivalent of aryl iodide

When the monoaryl product **272** was resubmitted to the arylation conditions, only a trace quantity of the diarylation product **273** was observed, **Scheme 4.12**. These two experiments suggest that the second arylation occurs directly after the first, without the dissociation of the palladium catalyst. It appears that the palladium catalyst cannot re-coordinate to the monoaryl product, presumably due to steric crowding.



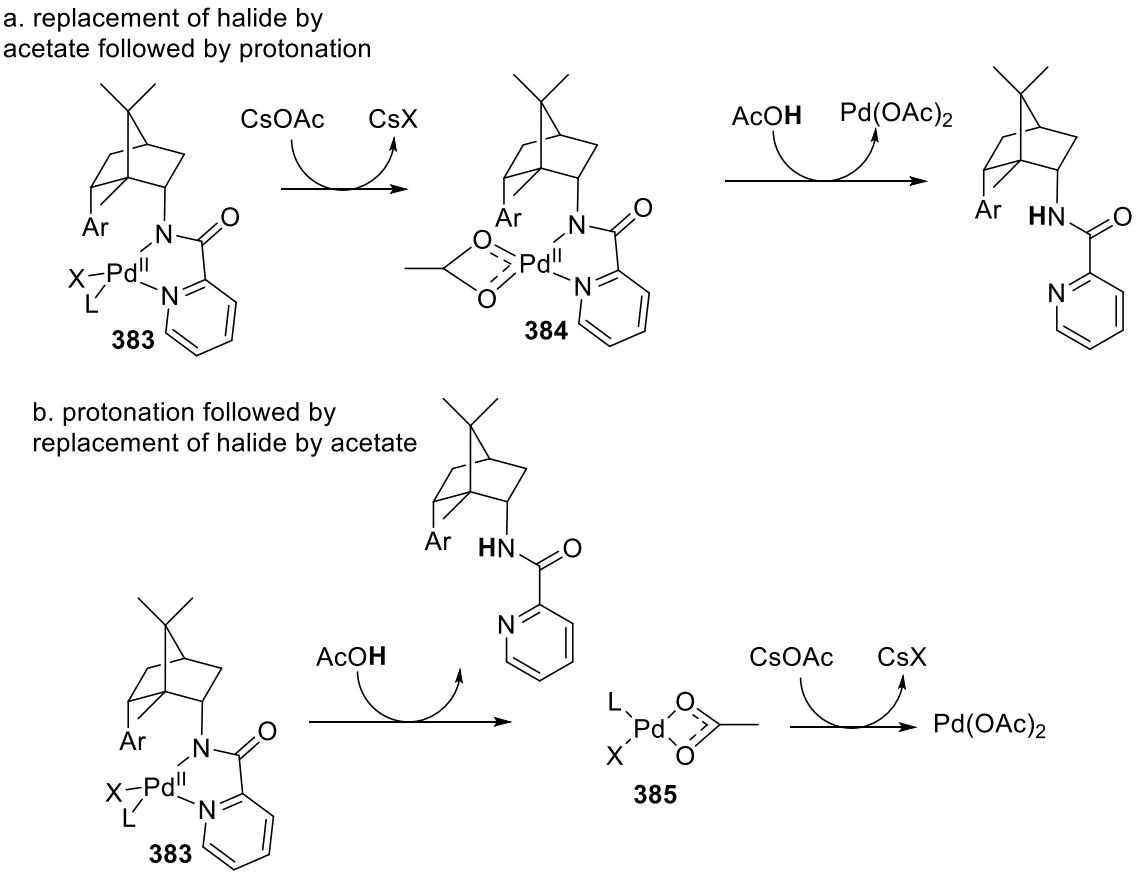
Scheme 4.12 Attempted arylation of the monoaryl product

The proposed catalytic cycle for the diarylation pathway is shown in **Scheme 4.13**. The first steps are analogous to the monoarylation pathway, with the palladium insertion *via* a CMD, followed by oxidative addition then reductive elimination to form the monoaryl compound. The pathway then differs from the monoarylation. Removal of the iodide from the palladium by the cesium acetate generates complex **379**. This is then able to undergo a second CMD, to give palladacycle **380**. Oxidative addition of another aryl iodide molecule gives complex **381**, which then undergoes reductive elimination to form the second C-C bond in complex **382**. The diarylation pathway then follows the same as the monoarylation; CsOAc removes the iodide from the palladium, and a ligand exchange furnishes the diarylated product and regenerates catalyst **378**.



Scheme 4.13 Catalytic cycle for the diarylation of bornylamine

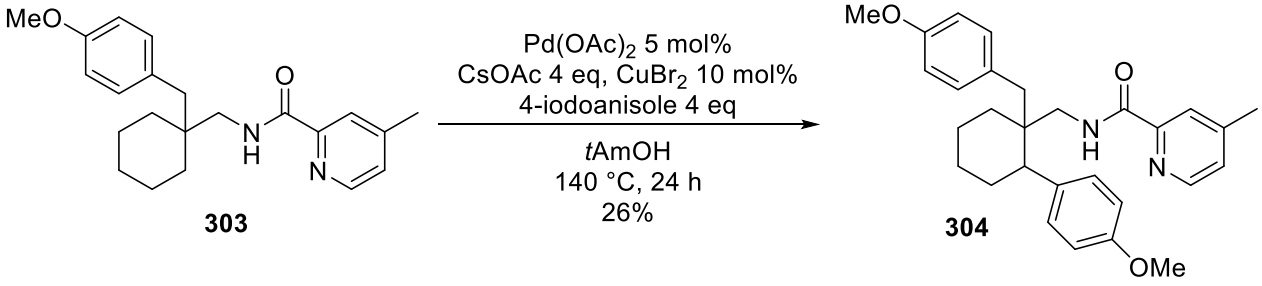
This diarylation pathway did not take place when arylating bornylamine using an aryl bromide with any of the substituted picolinamide groups. After the reductive elimination step of the mechanism, there is a series of ligand exchanges which take place to liberate the product and regenerate the active palladium species. The cesium acetate removes the halide from the palladium and replaces it with the acetate, releasing CsX. At this point complex **384** may undergo another C-H activation as in the case of the diarylation pathway, or the amide nitrogen can be protonated by the acetic acid in solution and regenerate palladium acetate to recoordinate to another molecule of the starting amide to continue the monoarylation pathway. It is not clear in which order these steps take place, and the protonation of then amide followed by abstraction of the halide by cesium acetate is also possible, **Scheme 4.14**.



Scheme 4.14 Potential pathways for ligand exchange. X = I or Br

The abstraction of the halide from the palladium is essential for the turnover of the catalyst. If this happens first (**Scheme 4.14**, pathway a) the complex **384** is set up to take part in another C-H activation *via* a CMD mechanism which leads to the diarylated product. However, should the protonation of the amide occur first (**Scheme 4.14**, pathway b) the arylation product is released and so does not undergo a second C-H activation, giving the monoarylation product. As seen previously, this product cannot recoordinate to the palladium acetate presumably due to steric bulk and so the reaction stops at the monoarylation product. The halide used may have an effect these on processes. In the case of the aryl iodide, with most of the directing groups used a second arylation takes place without dissociation of the palladium from the amide, and must go *via* pathway a, **Scheme 4.14**. As diarylation is not observed when using an aryl bromide, one reason for this may be the ease at which the halide is abstracted or the order in which the ligand exchanges occur, potentially going *via* pathway b, **Scheme 4.14**, preventing diarylation. It is also possible that the both of these pathways can operate in the same reaction, due to the fact that when using an aryl iodide, the monoarylation product is still observed.

For less sterically hindered systems, it is possible for the palladium to recoordinate to the monoarylated product. When monoarylated product **303** was resubmitted to the reaction conditions the diarylated product was obtained in 26% yield, **Scheme 4.15**.

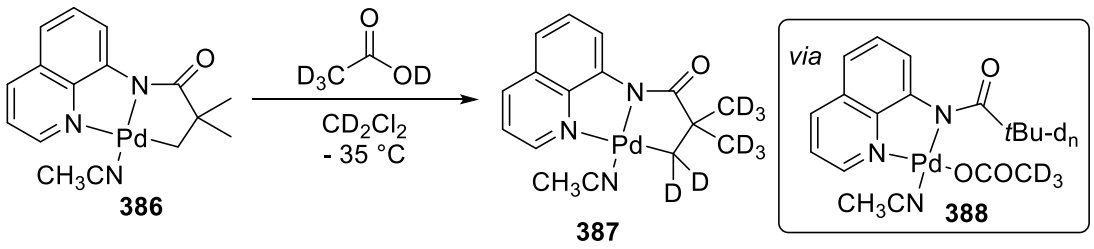


Scheme 4.15 Diarylation of a cyclohexane scaffold

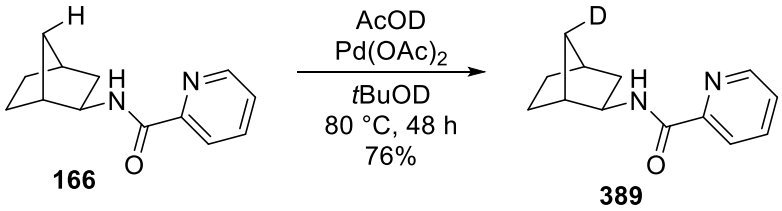
4.5 Reactions of palladium complexes

It has been previously suggested that the cyclometallation step of the mechanism is reversible. Complex **386** which was isolated in the aminoquinoline directed C-H activation could be deuterated by reaction with 40 equivalents of AcOH-d4 at -35 °C, **Scheme 4.16**.[35] Reacting picolinamide **166** with 10 equivalents of AcOD gave deuterated product **389**.[113] These two experiments show that in these cases the C-H activation step is reversible, and that the C-H activation step may take place in the absence of the aryl iodide coupling partner.

A. Deuteration of palladacycle



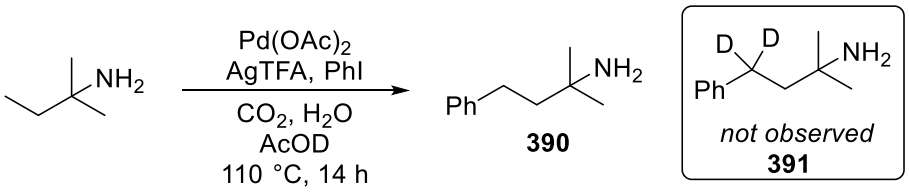
B. Deuteration of picolinamide



Scheme 4.16 Deuteration studies for C-H activation

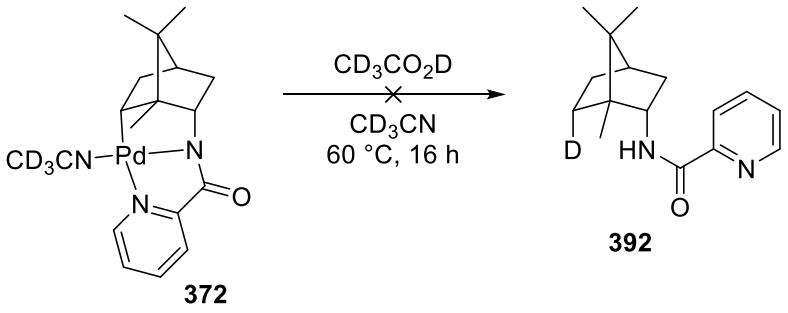
Not all cyclopalladation steps appear to be reversible. In Young and co-workers carbon dioxide mediated arylation of amines, **Scheme 4.17**, the addition of AcOD into the reaction

did not result in the formation of deuterated product **391**. This suggests in this case the palladation was not reversible or that the oxidative addition of iodobenzene was faster.[75]



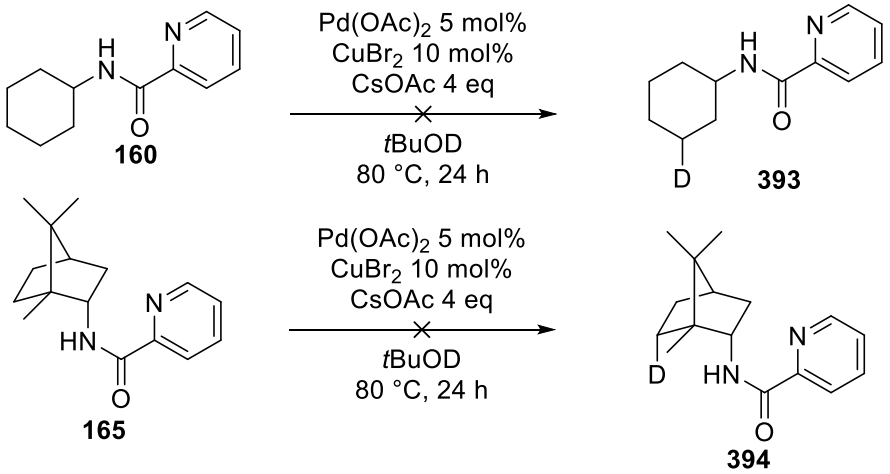
Scheme 4.17 C-H arylation with an irreversible C-H insertion

To see if the CMD step could be reversed in the arylation of bornylamine, palladacycle **372** was reacted with AcOH-d4, **Scheme 4.18**. No deuteration of the picolinamide to give compound **392** took place, instead just the starting palladacycle was seen. Increasing the temperature to reflux still did not result in the deuterated product. This suggests that the palladation step is irreversible.



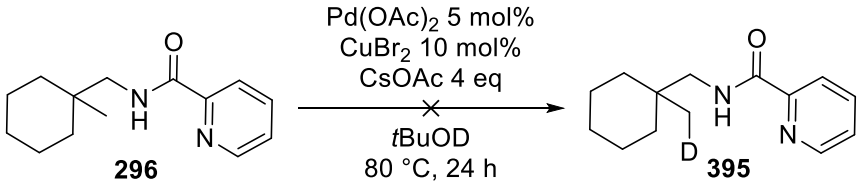
Scheme 4.18 Attempted deuteration of a palladacycle

Similarly, amide **165** was subjected to the arylation reaction conditions in the absence of the aryl iodide and in *t*BuOD instead of *t*AmOH. If the C-H palladation were reversible under the reaction conditions, it would be expected that some deuteration of the CH_2 group where C-H activation takes place would be observed. The same experiment was repeated using the cyclohexylamine scaffold **160**. It was not possible to isolate the palladacycle intermediate for this amide, **Scheme 4.19**.



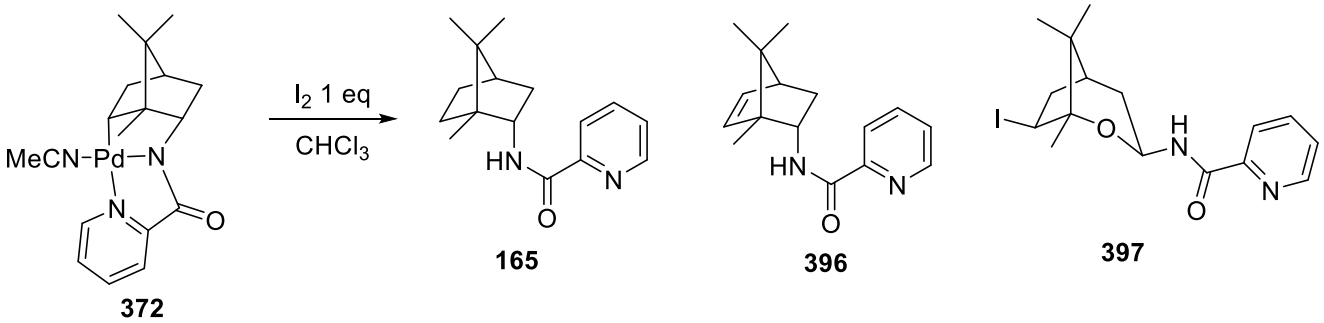
Scheme 4.19 Attempted deuteration of picolinamides

As no deuteration of the substrates took place in the reactions in **Scheme 4.19** it would appear that the palladation step of the catalytic cycle was irreversible under the reaction conditions. The same experiment was performed on amide **295** which undergoes C-H activation on the methyl group instead of the methylene but this was also irreversible, **Scheme 4.20**.



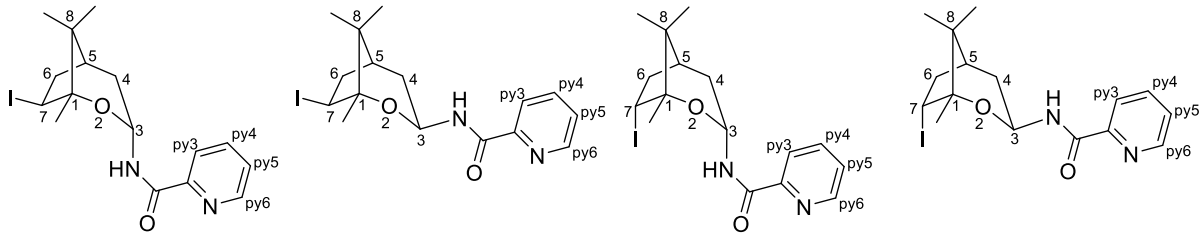
Scheme 4.20 Attempted deuteration

Further transformations of the isolated palladacycle were attempted. In an attempt to replace the C-Pd bond with a C-I, palladacycle **372** was stirred with iodine in chloroform at room temperature overnight. Three products were isolated: 1) the starting amide **165** 2) alkene **396** 3) [3.2.1] bicyclic ether **397** (**Scheme 4.21**).



Scheme 4.21 Reaction of a palladacycle with iodine

The stereochemistry of compound **397** was elucidated using NMR predictions performed by Dr M. J. Porter. For structures 1 – 4 a conformation search was carried out using the MMFF force field.[139] Each conformer was then subjected to geometry optimisation and chemical shift calculation using DFT, with the shifts for the individual conformers being combined by Boltzmann weighting. The resulting chemical shifts were then compared with the experimental values, **Table 4.1**.



1 2 3 4

Proton	**Observed data**	**Predicted structure 1**	**Predicted structure 2**	**Predicted structure 3**	**Predicted structure 4**
H3	5.70	5.77	5.79	5.73	6.21
H4a	2.05	2.50	1.94	2.53	2.08
H4b	1.69	1.45	1.57	2.26	1.82
H5	2.05	1.96	2.05	1.87	2.06
H6a	2.50	2.49	2.59	2.44	2.27
H6b	2.62	2.66	2.70	2.61	2.84
H7	4.92	4.70	4.79	4.20	4.14
1-Me	1.42	1.32	1.39	1.26	1.31
8-Me-a	1.16	1.27	1.35	1.31	1.54
8-Me-b	1.28	1.29	1.36	1.08	1.23
NH	8.37	7.81	7.51	8.07	7.31
py3	8.20	8.26	8.49	8.31	8.29
py4	7.85	7.79	8.02	7.91	7.81
py5	7.44	7.31	7.43	7.39	7.24
py6	8.56	8.65	8.84	8.84	8.59
RMS deviation		**0.21**	**0.26**	**0.31**	**0.39**

Table 4.1 ^{1}H NMR predictions

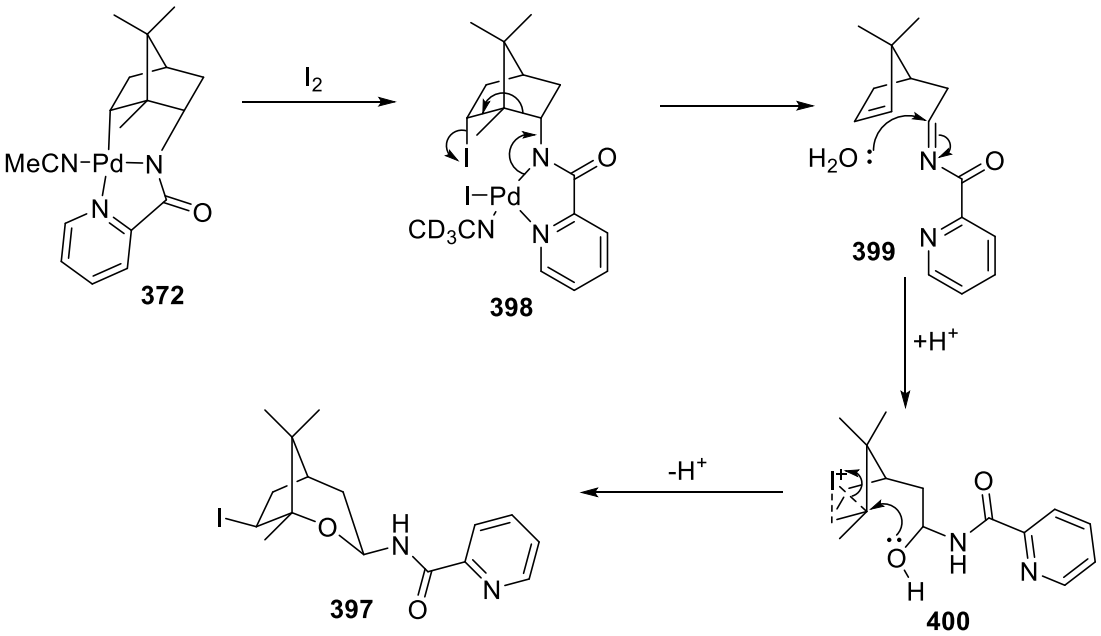
Good agreement with observed data <0.1 ppm

Moderate agreement with observed data 0.1 – 0.2 ppm

Poor agreement with observed data > 0.2 ppm

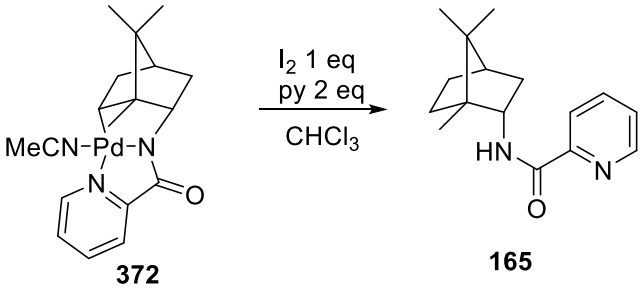
The predictions in **Table 4.1** allow for isomers **3** and **4** to be discounted. When the coupling constants are taken into account, the structure can be assigned as isomer **2**. The coupling constants for H3 – H4a and H3 – H4b were measured as 10 Hz and 4.7 Hz respectively in the experimental spectra. In isomer **1** the predicted coupling constants were 9.0 Hz and 0.8 Hz, and isomer **2** they were 11.1 Hz and 4.8 Hz.[131]

The proposed mechanism for this transformation is shown in **Scheme 4.22**. First, the iodine undergoes oxidative addition to the palladium followed by reductive elimination to give alkyl iodide **398**. This is followed by the formation of imine **399** by elimination of the iodide. Nucleophilic attack of the imine by water forms one of the new carbon-oxygen bond. The alkene is activated by iodine to give the iodonium cation which is opened by the oxygen to give the product **397**.



Scheme 4.22 Proposed mechanism for the reaction of a palladacycle with iodine

The reaction was then repeated in the presence of pyridine as a base to investigate if this would change the products of the reaction, **Scheme 4.23**.



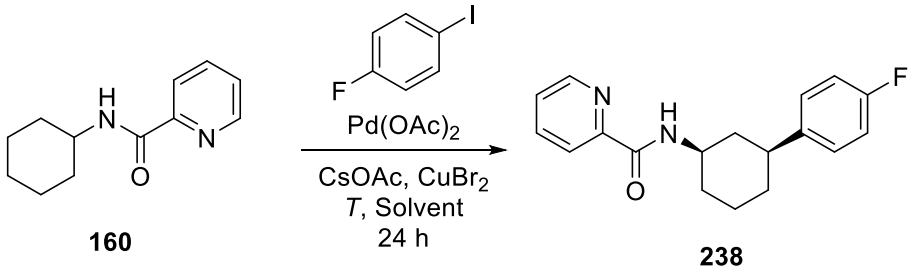
Scheme 4.23 Reaction of a palladacycle with iodine in the presence of a base

Under the conditions shown in **Scheme 4.23** none of the previous two products were observed, instead there was just recovery of the amide **165**. The palladacycle may be unstable in pyridine which can coordinate to the palladium more strongly than the acetonitrile ligand and so destabilise the complex.

4.6 Reaction Progress Kinetic Analysis

In order to gain a deeper understanding of the mechanism for C-H functionalisation the kinetics of the reaction were studied. Studies into kinetics can give the rate dependencies on the concentration of the components of the reaction, and determine the turnover limiting step of a catalytic cycle. Reaction progress kinetic analysis was formalised by Blackmond and can probe reactions at synthetically relevant conditions as well as allowing analysis of reactions from a minimal number of experiments.[140]

The kinetics of the reaction were studied using compound **160** as a model substrate. The reaction was optimised using 4 equivalents of aryl iodide, 5 mol% $Pd(OAc)_2$, 10 mol% $CuBr_2$, and the effect of changing the solvent and temperature is shown in **Table 4.2**.



Scheme 4.24 Arylation of cyclohexylamine

Entry	Solvent 1 M	Temperature	Yield – isolated
1	*t*HxOH	130	81
2	*t*AmOH	130	70
3	*t*AmOH	110	22
4	*t*HxOH	110	25

Table 4.2 Solvent and temperature

The rate dependence of the different reaction components for the reaction in **Scheme 4.24** was studied. The yield at different time points was determined by sampling of the reaction (which included an internal standard) at intervals and analysing the ^1H NMR spectra. Approximately 20 µl of the reaction mixture was removed and diluted with $CDCl_3$.

4.6.1 Order in catalyst

The order in catalyst was determined utilising Bures' method for the graphical determination of reaction order.[141] This method can determine the order in any reaction component by direct visual comparison of reaction concentration profiles. The reaction profiles at different concentrations of the catalyst will only overlay when the time axis is replaced by the time integral of the concentration of the reactant being studied raised to the correct order in the catalyst. This variable time normalised analysis allows for the whole reaction profile to be studied rather than just the initial rate and does not require a large number of data points.

However, as the orders are determined using visual analysis it not possible to obtain the precise values of kinetic constants.

The reaction was run using 2.5, 5 and 10 mol% of $Pd(OAc)_2$, on a 3 mmol scale. Included in the reaction mixture was 10 mol% of 1,3,5-trimethoxybenzene as the internal standard, which was used to determine the yield of the reaction by ^1H NMR. The overly of the time[cat]^{order} against [product] is shown in **Figure 4.5**. It is assumed that the concentration of the catalyst remains the same over the course of the reaction.[142]

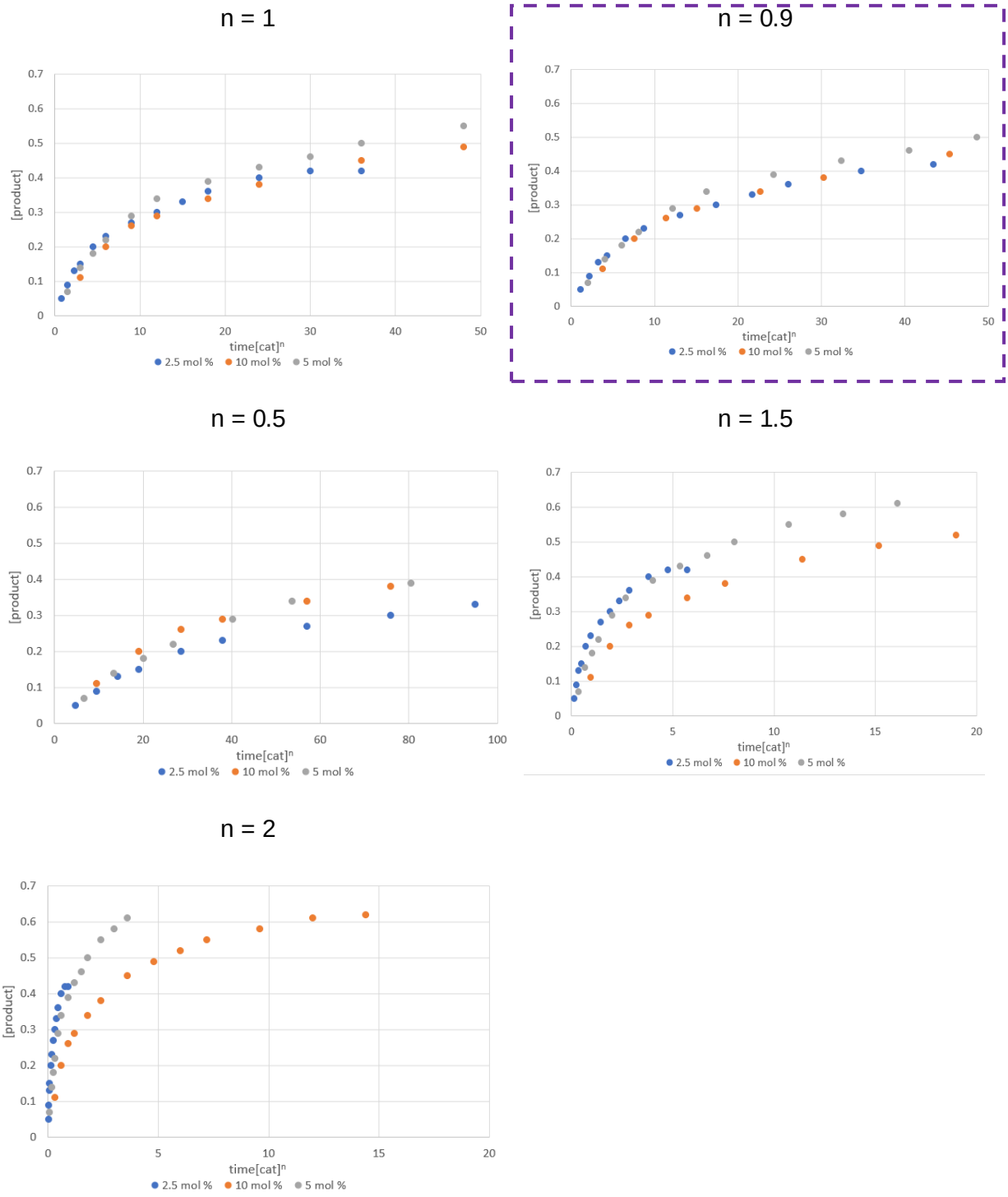


Figure 4.5 Determination of order in catalyst

The best overlay of all three traces is seen when n = 0.9, indicating a positive rate dependence on the catalyst. A reasonable overlay is seen at n = 1. It is important to note that this method cannot give a perfect answer for the order in catalyst as the reaction profile overlay is being judged by eye.

4.6.2 Order in aryl iodide

Next, the rate dependence on the concentration of aryl iodide was studied. Unlike when determining the order in catalyst, it cannot be assumed that the concentration of aryl iodide stays constant throughout the reaction. The trapezoid rule can be used to normalise the time ($t_i - t_{i-1}$) between each pair of data points by the average concentration of these points $\frac{[A]_i + [A]_{i-1}}{2}$ **Equation 4.1**. The reaction profiles for the different concentrations of aryl iodide will overlay when the time integral of the concentration of aryl iodide is raised to the correct order in aryl iodide.[143]

$$\int_{i=1}^{t=n} [\mathrm{A}]^{\alpha} \mathrm{d}t = \sum_{i=1}^{n} \left(\frac{[A]_i + [A]_{i-1}}{2} \right)^{\alpha} (t_i - t_{i-1})$$

Equation 4.1 Variable time normalisation

Reactions were run using 1, 2, 3 and 4 equivalents of aryl iodide, on a 3 mmol scale. As the reaction is run at a high (1 M) concentration in the *t*HxOH solvent, reducing the stoichiometry of the aryl iodide would reduce the overall solvent volume (*t*HxOH plus the aryl iodide). To make up for this, the amount of *t*HxOH was adjusted in the reactions with 1, 2 and 3 equivalents of aryl iodide, **Table 4.3**.

Entry	Equivalents ArI	Solvent volume (ml)	Concentration ArI (M)
1	4	3	4
2	3	3.34	2.69
3	2	3.69	1.49
4	1	4.04	0.74

Table 4.3 Equivalents and concentration of ArI used for determining order in ArI

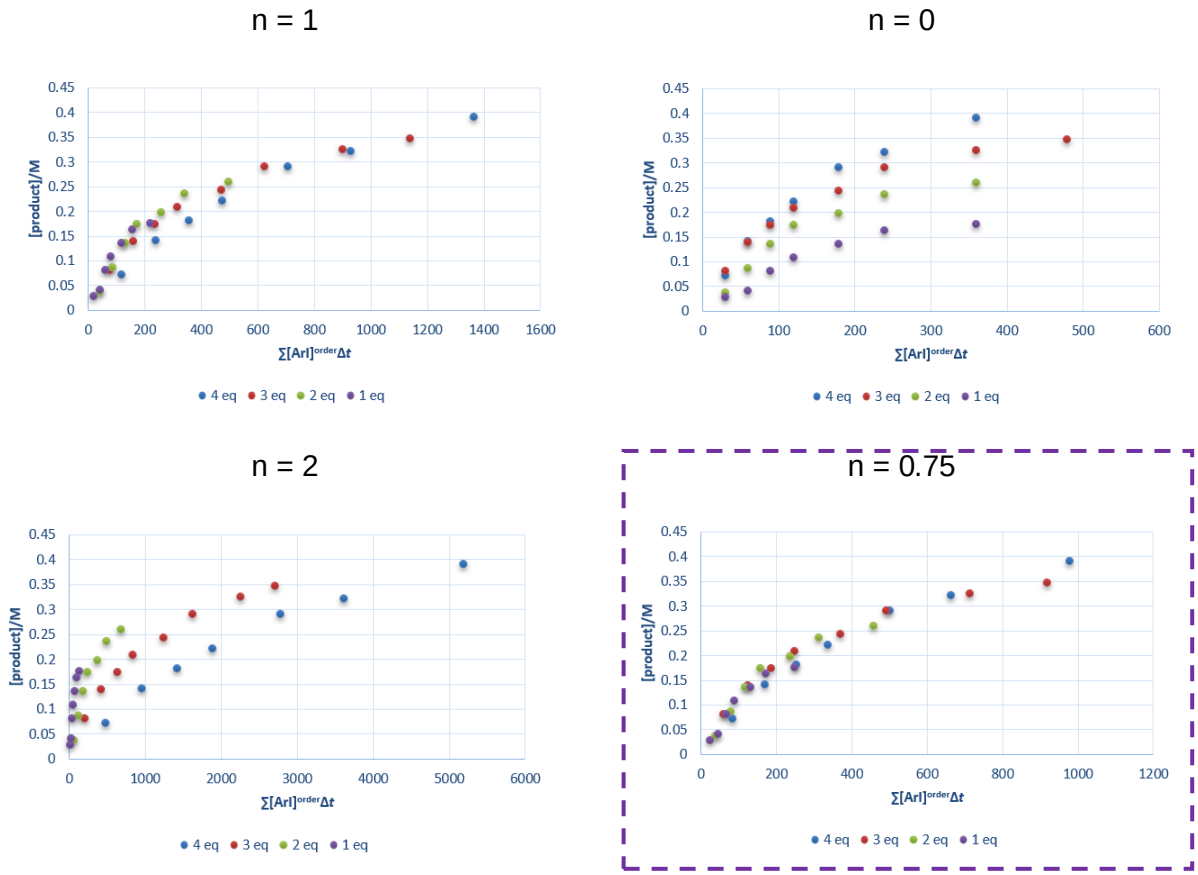


Figure 4.6 Determination of the order in aryl iodide

Although none of the graphs have a perfect overlay of the reaction profiles, the best overlay of the four traces is seen when n = 0.75. This shows there is a positive rate dependence on the aryl iodide.

4.6.3 'Same excess' experiments

The 'same excess' experiments designed by Blackmond can be used to determine if over the course of the reaction the palladium catalyst degrades, or if the arylated product inhibits the catalyst. It provides a rapid way to determine whether the catalyst maintains its activity after a number of turnovers.[144]

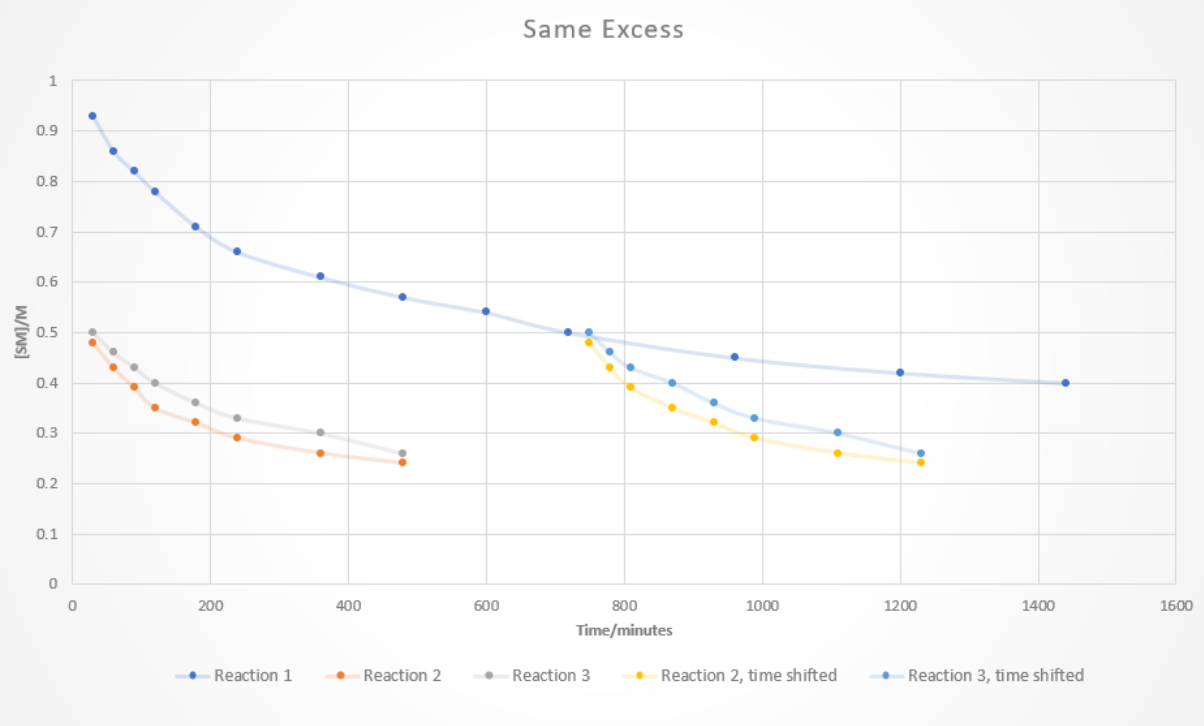
Three reactions were run under conditions to represent the same reaction, but started at different time points, **Table 4.4**. **Entry 1** is the reaction run under the standard conditions. **Entry 2** is the reaction at 50% conversion without the addition of the product, and **entry 3** at 50% conversion with the addition of the product. Given that the 3 entries have the same substrate concentration from 50% conversion onwards, it would be expected that in the absence of catalyst degradation or product inhibition their kinetic profiles would be identical.

Entries 1 and 2 will show if there is any catalyst deactivation or product inhibition, and entry 3 will distinguish between these two possibilities.

Reaction Number	**[SM]**	**[ArI]**	**[CsOAc]**	**[product]**
1	1	4	4	0
2	0.5	3.5	3.5	0
3	0.5	3.5	3.5	0.5

Table 4.4 Same excess parameters

The consumption of starting material was plotted against the time in minutes, **Graph 4.1**.



Graph 4.1 Same excess experiments

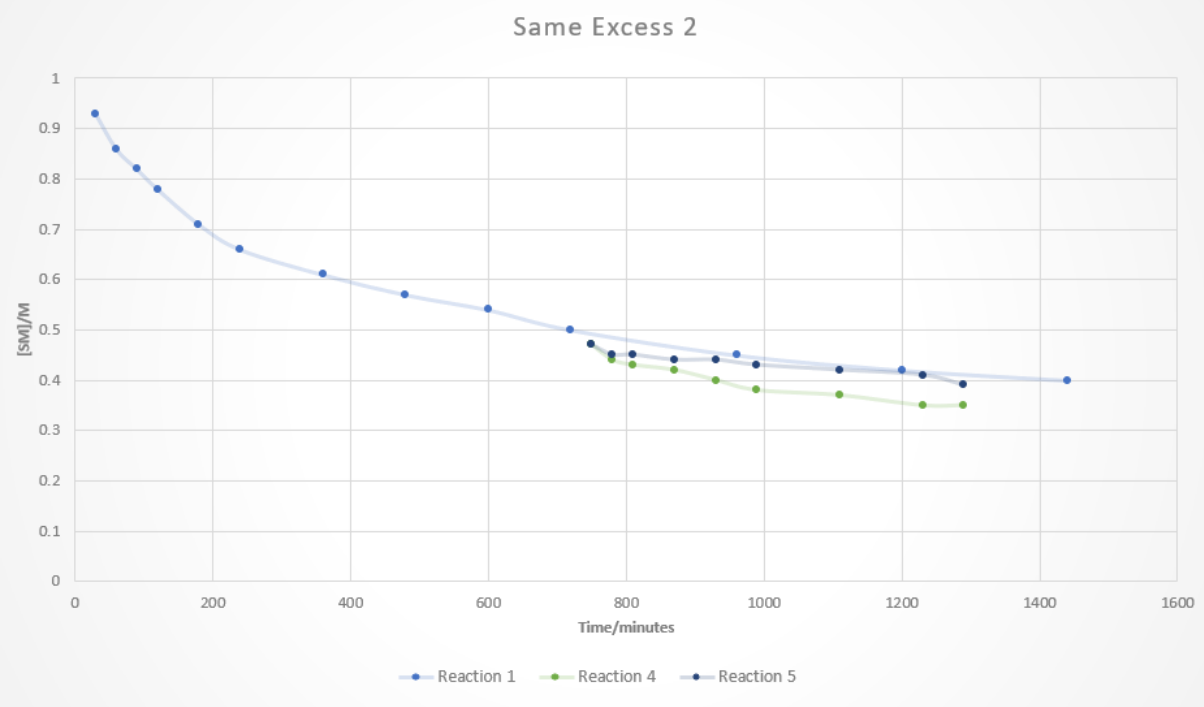
As the traces for **entries 2** and **3** roughly overlay, there is minimal product inhibition of the catalyst as the addition of product to the reaction mixture does not greatly affect the rate of reaction. **Entries 2** and **3** once time corrected do not overlay with **entry 1**. This shows that over the course of the reaction the catalyst is degrading. **Entry 1** proceeded more slowly from the 50% conversion point ([SM] = 0.5) than **entries 2** and **3** which had fresh catalyst. It appears that after the catalyst has done a certain amount of 'work' the rate of the reaction has slowed down.

This method does not take into account the formation of the two by-products of the reaction; cesium iodide and acetic acid. To include these in the same excess experiments, two more reactions were run (**table 4.5**). **Entry 4** includes the cesium iodide product, and **entry 5**

includes all three products of the reaction in the concentrations at which they would be present at 50% conversion.

Reaction Number	[SM]	[ArI]	[CsOAc]	[product X]	[CsI]	[AcOH]
1	1	4	4	0	0	0
4	0.5	3.5	3.5	0.5	0.5	0
5	0.5	3.5	3.5	0.5	0.5	0.5

Table 4.5 Same excess including side products

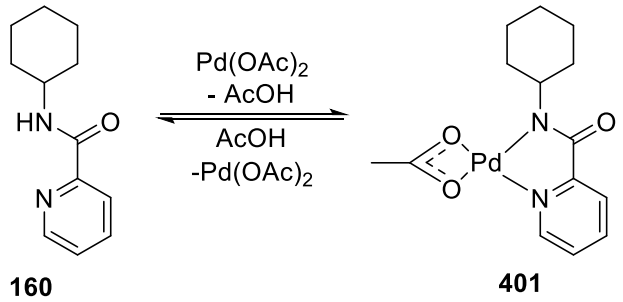


Graph 4.2 Same excess including side products

When these results are plotted, it becomes clear that these side products have a significant effect on the rate of reaction. The addition of cesium iodide plus the arylated product resulted in a slowing of the rate, when compared to entry 1 at [SM] = 0.5. When all three products are present, **entry 5**, the time corrected trace almost overlays with the original reaction, confirming product inhibition of the catalyst. There is no significant decomposition of the catalyst over the course of the reaction.

The same excess experiments have shown that while there may a small amount of catalyst decomposition taking place over the course of the reaction, there is significant inhibition of the catalyst by the side products cesium iodide and acetic acid. The presence of the arylated product does not have an effect on the rate of reaction and so it is not responsible for catalyst inhibition.

The coordination of the palladium acetate to the starting amide **160** to give the palladium complex **401** may be in equilibrium, with protodemetallation being possible in the presence of acetic acid, **Scheme 4.25**. The concentration of acetic acid increases over the course of the reaction, and so the protodemetallation becoming more likely as the reaction proceeds. This may explain why the addition of acetic acid into the reaction decreases the rate of reaction. Cesium iodide also appears to slow the reaction rate as it accumulated in the reaction. It is not clear why this is, but as it is insoluble in the reaction solvent it may be because it reduces the efficiency of the stirring.



160 **401**

Scheme 4.25 Equilibrium between starting amide and palladium complex

4.7 Conclusions

Potential palladium intermediates for the arylation of bornylamine were isolated and fully characterised. A crystal structure of a palladacycle showing a Pd-C bond and coordination of the picolinamide directing group to the palladium was obtained. Both isolated complexes were used as catalysts in the arylation reaction in the place of $Pd(OAc)_2$ and gave the arylated product in comparable yield suggesting that these complexes are viable intermediates for the reaction. However, they may also just be viable palladium (II) sources.

The reversibility of the cyclopalladation step of the mechanism was investigated. It was shown to not be reversible as no reaction was seen between the palladacycle and CD_3CO_2D.

The kinetics of the reaction were studied, and the rate dependence on both the palladium catalyst and the aryl iodide were determined. The order was 1 in the palladium acetate and 0.75 in aryl iodide.

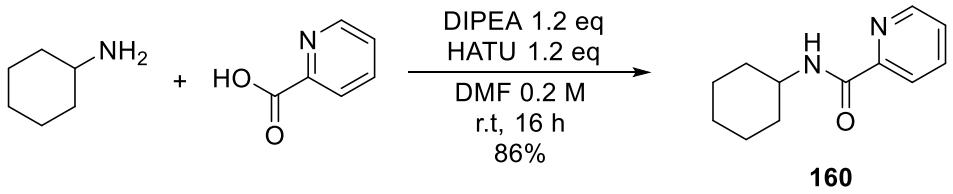
Same excess experiments showed that there is not significant degradation of the catalyst over the course of the reaction, but there is inhibition of the catalyst by the cesium iodide and acetic acid side products. The arylated product did not inhibit the catalyst.

Chapter 5

Sustainable Amide Synthesis

5.1 Project Aim and Background

It was necessary to synthesise the picolinamide substrates for C-H activation. While the majority of the amide substrates were synthesised using HATU, **Scheme 5.1**, this method was not atom economical and requires a lengthy work up procedure followed by purification using flash column chromatography. Due to these issues this method was not suitable for the synthesis of amides on a large scale.



Scheme 5.1 HATU amidation

Stoichiometric coupling reagents like HATU often have a high molecular weight and produce toxic by-products, **Figure 5.1**. Uronium salts are effective coupling agents which work by activating the carboxylic acid which then reacts with the amine.[145] These reagents are also costly so undesirable for the large scale synthesis of amides and result in the formation of large amounts of waste products.

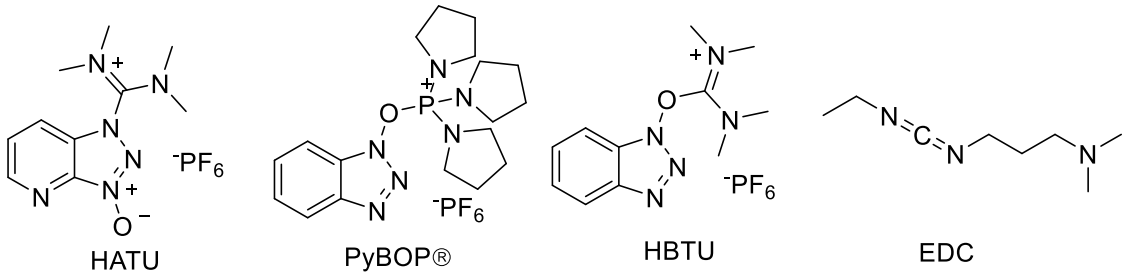


Figure 5.1 Stoichiometric amide coupling agents

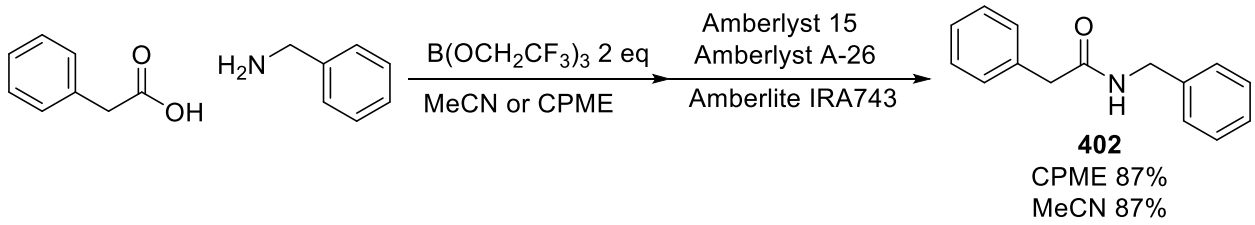
The aims of this part of the project were to expand on previous work on boron mediated amidation in the group[106] to improve the yields for the synthesis of amides from polar heterocyclic carboxylic acids, and to expand the substrate scope. As solvent is one of the large contributors to waste generated in a chemical process it was important to select a solvent that will reduce hazards associated with the reaction.[146]

It is preferable to employ an amidation method which allows for the direct condensation of an amine with a carboxylic acid without the need for stoichiometric activating agents or toxic solvents, such as DMF. Methods for catalytic amidation have attracted a considerable research effort, with common systems based around boronic acids, boric acid derivatives, boron heterocycles and group IV metal salts derived from titanium, zirconium or hafnium.

Amide bond formation accounts for 16% of all reactions performed during the drug discovery process, and so it is important to develop methods that are sustainable and safe.[147]

5.2 $B(OCH_2CF_3)_3$ for amide synthesis

Previous work in the group has identified $B(OCH_2CF_3)_3$ as an efficient reagent for the direct amidation of amines with carboxylic acids, **Scheme 5.2**. This method benefited from a solid phase work-up procedure, without the need for column chromatography or an aqueous work up and can be applied to pharmaceutically relevant substrates.[104,105]



Scheme 5.2 Amidation using $B(OCH_2CF_3)_3$

Using a catalytic amide coupling agent can improve the atom economy of the reaction, and make the amidation a more sustainable process.

Reagents containing group IV metals can be used as catalysts in amidation. $Ti(O^iPr)_4$[148], $Hf(Cp)_2Cl_2$[149], $ZrCl_4$ and $ZrCp_2Cl_2$[150,151] have been shown to be effective catalysts for the direct amidation of a range of amine and carboxylic acid substrates. These methods employ molecular sieves, which require dilute reaction conditions and large amounts of solvent to wash them at the end of the reaction to recover the amide products. The solvents employed include aromatic hydrocarbons and ethers which are not ideal with respect to safety and sustainability.[152] They are also unsuitable for the synthesis of amides from polar amines or carboxylic acids due to the insolubility of the substrates in non-polar solvents, and so were not suitable for the synthesis of the picolinamides required in C-H functionalisation reactions.

In 1996 *Yamamoto* showed that electron deficient boronic acids were effective catalysts for the synthesis of simple amide substrates[153] and since then a large number of boronic acid based amidation catalysts have been reported. Low catalyst loadings of 0.5 – 5 mol% can be achieved using a boron-based catalyst developed by Shibasaki. The DATB catalyst aids the direct coupling of amines with carboxylic acids, in toluene in the presence of molecular sieves and has a broad substrate scope which includes heterocyclic substrates and APIs.[154, 155] However, the synthesis of the catalyst is lengthy, which is a major drawback for using this method. Despite the broad substrate scope that can be achieved using a DATB catalyst, no amide products were observed with poorly nucleophilic anilines, or bulky carboxylic acids, **Figure 5.2**.

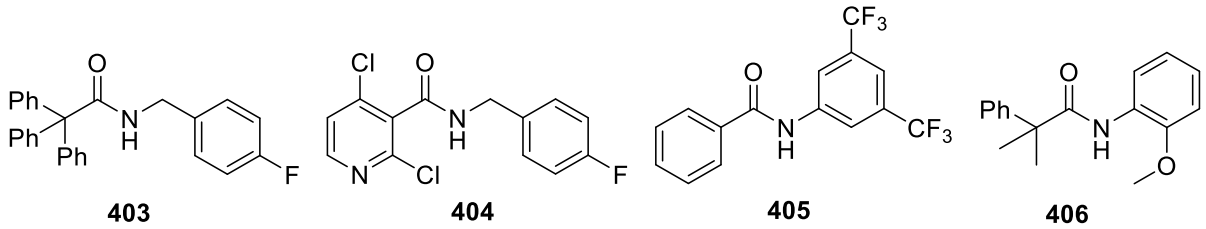
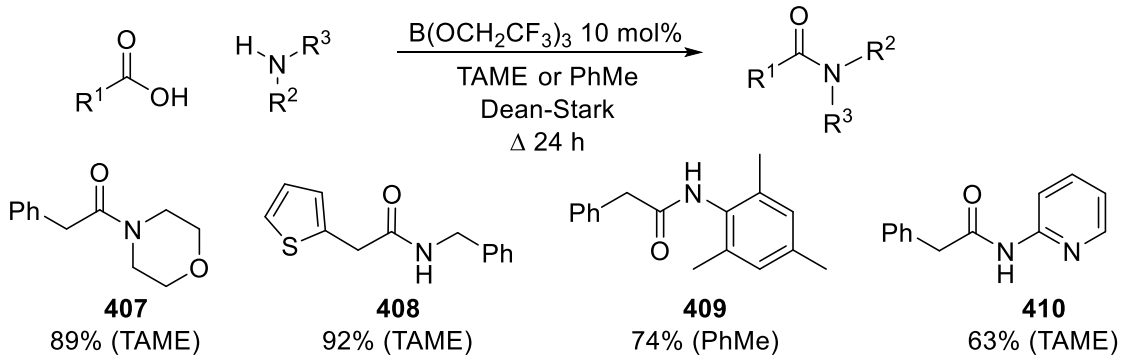


Figure 5.2 Examples of failed substrates under the DATB catalyst system

The Sheppard group showed that $B(OCH_2CF_3)_3$ was also an effective catalyst for the direct amidation of an amine with a carboxylic acid, producing only water as the by-product. The reaction could be carried out in toluene or TAME, of which the latter has been identified as a green solvent, **Scheme 5.3**.[106]

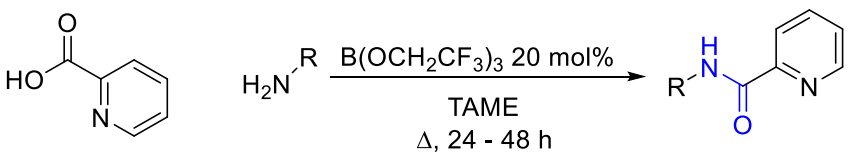


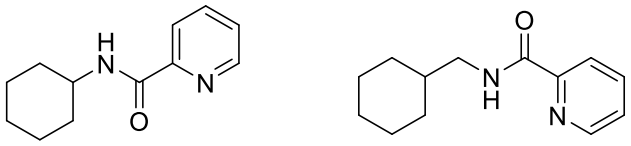
Scheme 5.3 Amidation using catalytic $B(OCH_2CF_3)_3$

The method gives excellent yields of complex amides, including those synthesised from unprotected amino acids but only moderate yields when using more polar carboxylic acids and poorly nucleophilic anilines.

5.2 Amidation in ester solvents

When the methodology for catalytic amidation developed in the group was applied to the synthesis of picolinamides to be used for C-H activation the yields were poor. The low yields of amides synthesised from 2-picolinic acid is likely due to the insolubility of the amine carboxylate salt in TAME, **Scheme 5.4**. The reactions also needed a higher loading of the borate catalyst.



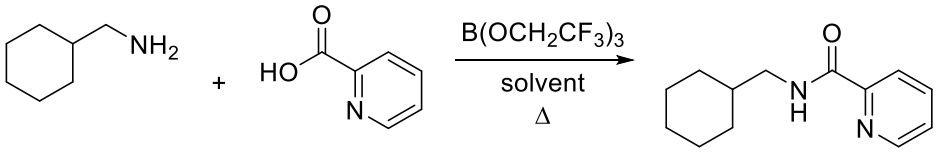


160 20%

159 71%

Scheme 5.4 Amidation using a borate ester catalyst in TAME

To overcome this issue, other solvents were screened to investigate if a change to a more polar, ester solvent could improve the yield. To identify a more suitable solvent for the direct amidation of a carboxylic acid with an amine the reaction of cyclohexylmethylamine with picolinic acid was used as a test reaction, **Scheme 5.5**. The reaction was performed at reflux in a Dean-Stark apparatus for the azeotropic removal of water. Esters were identified as potentially more suitable solvents, due to their increased polarity compared to ethers as well as their improved safety profile due to not being prone to peroxide formation.[152] There has been one previous report of a catalytic amidation performed in an ester solvent, using *n*-propyl acetate as the solvent and *n*BuB(OH)$_2$ as the catalyst.[156] A range of ester and nitrile solvents were screened, and the concentration and catalyst loading of the reaction was optimised, **Table 5.1**.[107]



1 equiv 1 equiv **159**

Scheme 5.5 Amidation of cyclohexylmethylamine

Entry	Solvent	B.p °C	Cat. Mol%	Concentration M	Yield[a] %
1	*t*BuOAc	97	20	1.0	92
2	*t*BuOAc	97	10	0.5	75
3	*i*PrOAc	89	10	0.5	52
4	EtOAc	77	10	0.5	9
5	*n*BuOAc	126	10	0.5	20
6	*t*BuOAc	97	10	0.5	75
7	***t*BuOAc**	**97**	**10**	**1.0**	**91**
8	EtCN	97	10	1.0	76
9	*n*PrCN	117	10	1.0	64
10	*n*PrOAc	102	10	0.5	27

Table 5.1 Optimisation of solvent and concentration. [a] isolated yields

Ester solvents gave variable yields, with ethyl acetate, *n*PrOAc and *n*BuOAc performing poorly (**entries 4, 5** and **10**). *i*PrOAc offered some improvement in yield of the amide product (**entry 3**). The solvent screen showed that *t*BuOAc was the best solvent for the reaction, with little difference in yield between 10 and 20 mol % of the borate catalyst (**entries 1** and **7**).

The concentration of the reaction was important, with an increase in yield from 75% to 91% for 0.5 M and 1 M respectively (**entries 6** and **7**), which reduced the solvent requirements for the reaction. The nitrile solvents (**entries 9** and **10**) gave moderate yields of the amide product and could provide an alternative for more polar substrates.

Solvents with high boiling points gave poor yields of the amide, most likely due to decomposition of the catalyst at elevated temperatures. The most effective solvents were those with a moderate boiling point, but a relatively high proportion of water in their azeotropes. *tert*-Butyl acetate and propionitrile were the most effective solvents, both with a boiling point of 97 °C, and containing 22 wt% and 24 wt% respectively of water present in the azeotrope. In contrast, ethyl acetate contains just 8 wt% of water in the azeotrope, and so is a poor solvent for amidation.[157]

A range of catalysts were then screened, with $B(OCH_2CF_3)_3$ giving the highest yield of the amide, **Table 5.2**. Trimethyl and triethyl borate gave disappointing yields of the amide, and titanium isopropoxide also gave a low yield. The use of a boronic acid, **entry 5**, also gave a good yield of the amide product.[153]

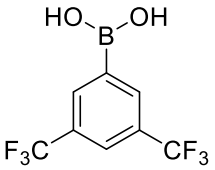
Entry	Catalyst 10 mol%	Yield % (isolated)
1	$B(OCH_2CF_3)_3$	92[a]
2	$B(OMe)_3$	8[a]
3	$B(OEt)_3$	10
4	$Ti(O^iPr)_4$	14[a]
5		73

Table 5.2 Catalyst screen. Conditions *t*BuOAc 1 M, Catalyst 10 mol%, 24 hours

The stability of the $B(OCH_2CF_3)_3$ catalyst in the chosen solvent was studied in collaboration with Dr Victor Laserna. An amidation reaction in *t*BuOAc was run for 24 hours, and samples were taken from both the reaction mixture and Dean-Stark trap to measure the quantity of trifluoroethanol present. The same reaction was run in the higher boiling *n*BuOAc to measure catalyst stability at elevated temperatures.

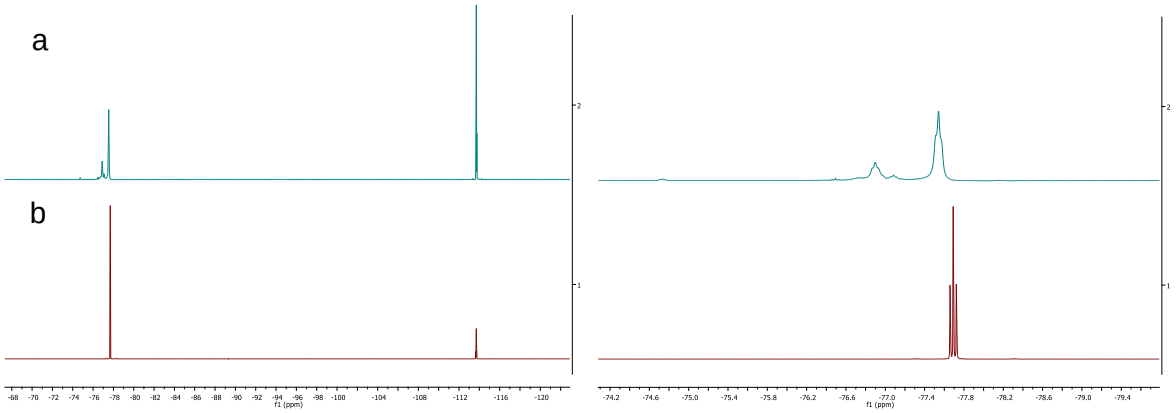


Figure 5.3 ^{19}F NMR of (a) Reaction flask and (b) Dean-Stark trap of the amidation in *t*BuOAc

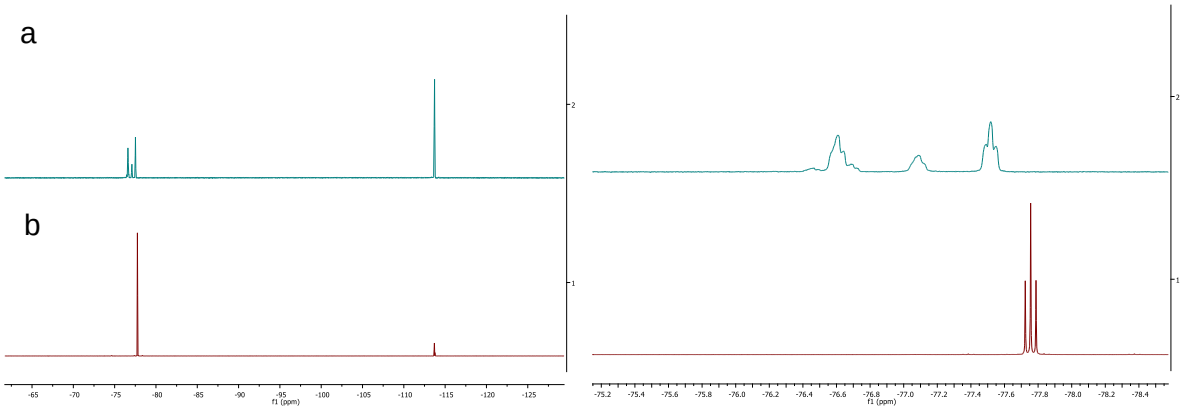


Figure 5.4 ^{19}F NMR of (a) Reaction flash and (b) Dean-Stark trap of the amidation in *n*BuOAc

Trifluoroethanol was present in both the Dean-Stark trap and the reaction flask in different quantities in the two different solvents.

*t*BuOAc: 49% of trifluroethanol was in the reaction flask, and 51% in the Dean-Stark

*n*BuOAc: 16% of trifluroethanol was in the reaction flask, and 84% in the Dean-Stark

In both solvents the triplet signal was broadened in the sample take from the reaction flask, potentially due to the exchange between the free trifluoroethanol and the trifluoroethoxy groups coordinated to boron. The high rate of catalyst decomposition in *n*BuOAc may account for the lower yield (20%) in this solvent, and shows that elevated temperatures do hinder the reaction.

5.2.1 Substrate scope

With the optimised conditions in hand, the substrate scope was explored, focussing on amides that had previously been difficult to synthesise under the previously reported conditions, **Figure 5.5**.

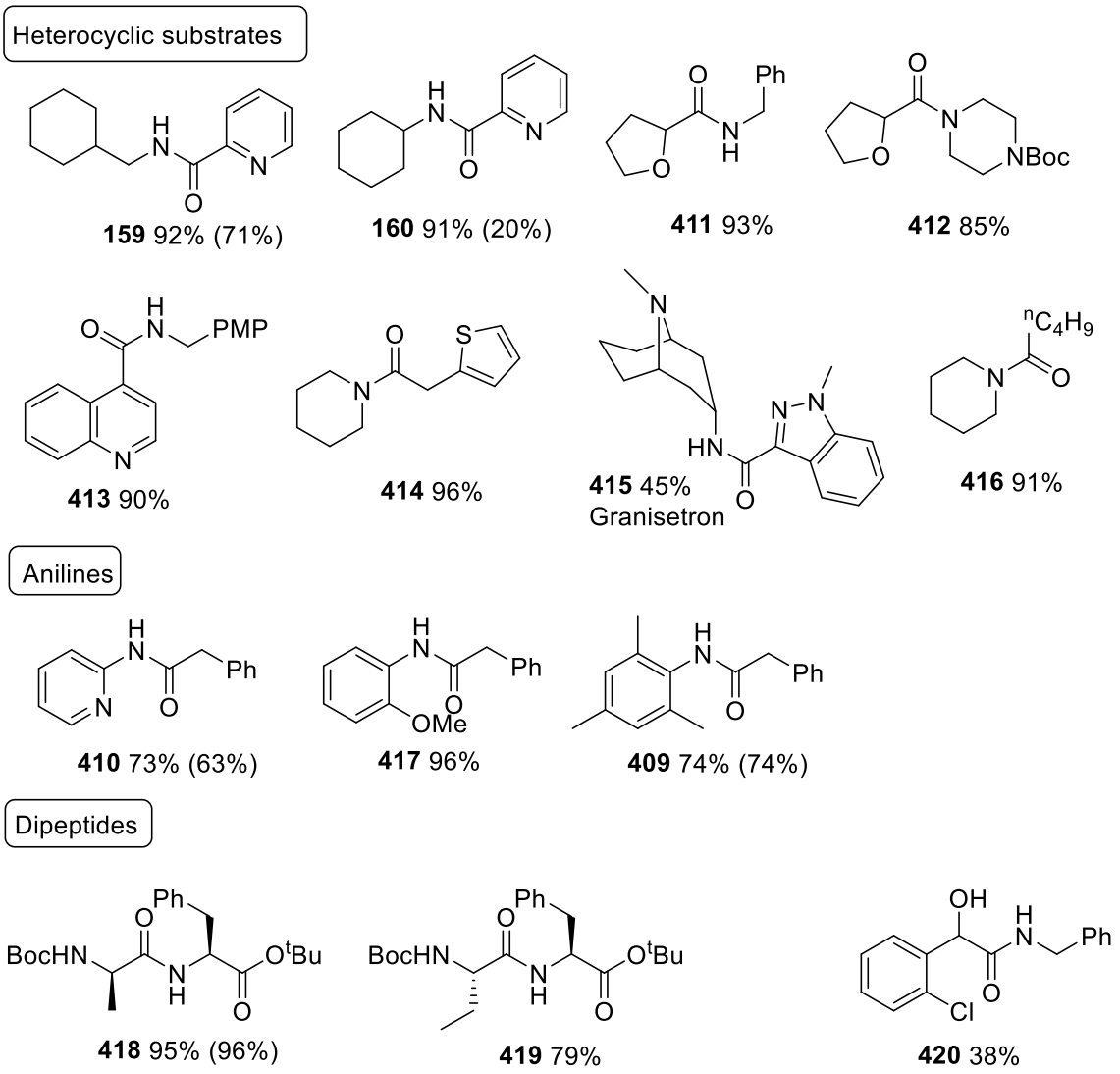
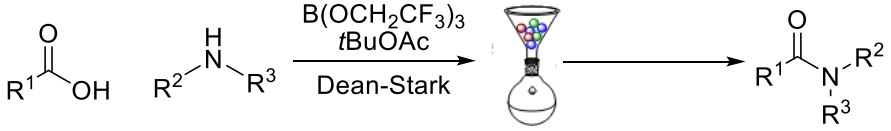


Figure 5.5 Substrate scope for amide synthesis. Conditions 1 eq amine, 1 eq acid, $B(OCH_2CF_3)_2$ 10 - 20 mol%, *t*BuOAc 1 M, Dean-Stark, reflux. Yields in TAME in parenthesis.

The substrate scope includes polar heterocyclic carboxylic acids and poorly nucleophilic, sterically hindered anilines. Carboxylic acids containing a pyridine (Compounds **159** and **160**), quinoline (Compound **413**), tetrahydrofuran (Compounds **411** and **412**) and a thiophene (compound **414**) were synthesised in good to excellent yields. Aniline derivatives (compounds **410**, **417** and **409**) were synthesised in good yields. The amide of 2-chloromadelic acid was only synthesised in a 38% yield due to the challenging nature of this substrate. Dipeptides **418** and **419** were synthesised from the Boc-protected alanine and the phenylalanine *tert*-butyl ester, with no observable epimerisation. Finally the drug molecule granisetron **415** was synthesised using 20 mol% of the catalyst (previously done using 1 equivalent of $B(OCH_2CF_3)_3$).

For the majority of substrates column chromatography for the purification of the products could be avoided using a solid phase work up. Scavenger resins to remove unreacted amine

(Amberlyst 15), carboxylic acid (Amberlyst A-26) and boron compounds (Amberlite IRA-743) were used, and the reaction could be filtered to give the pure amide, **Scheme 5.6**.



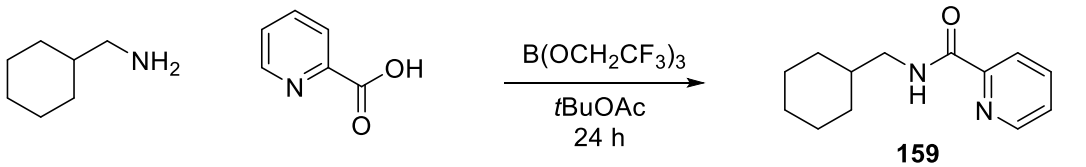
Scheme 5.6 Synthesis of amides using solid phase work up

Some products that contain amines can be scavenged by the Amberlyst 15, and thus these substrates were purified by column chromatography or recrystallisation.

5.3 PMI Calculations

The process mass intensity (PMI) of a process calculates the ratio between the total mass of materials used and the mass of the isolated product. All materials used are included in the calculation, including solvents, work up materials and reagents. It can be used as a measure of how efficient a process is.[158]

The synthesis of amide **159** was repeated on a 100 mmol scale, to calculate the PMI of the process, **Scheme 5.7**, to give 21.23 g of amide **159**, with a yield of 97%. A solid phase work up was carried out, adding the resins directly to the reaction mixture which reduces solvent requirements for the work up. Water is needed in the work up for the hydrolysis of boron compounds and can be removed using magnesium sulphate which is filtered at the same time as the resins. The resins and magnesium sulphate could be washed with ethyl acetate to give the pure amide.



[100 mmol] [100 mmol] **159** [21.23 g, 97.22 mmol, 97%]

Scheme 5.7 Large scale amidation

$$\textbf{Process Mass Intensity} = \frac{\textbf{total mass in a process or process step (kg)}}{\textbf{mass of product (kg)}}$$

Conditions	Input Reaction	Input Workup	Yield
Solvent (1 M)	*t*BuOAc (86.6 g)	Resins (12.5 g)	
Catalyst	$B(OCH_2CF_3)_3$ (3.079 g)	H_2O (10 g)	97%
Acid (1 eq)	2-Picolinic acid (12.311 g)	EtOAc (27.06 g)	21.23 g
Amine (1 eq)	Cyclohexanemethylamine (11.320 g)	$MgSO_4$ (10 g)	
24 h, 98 °C	*Total = 113.31 g*	*Total = 59.56 g*	

The PMI for the reaction shown in **Scheme 5.7** was calculated to be just 8. The typical PMI for an amidation reaction used for the synthesis of pharmaceutical intermediates is ~43, showing that this catalytic amidation could be a less wasteful method for large scale amidations.[159]

5.4 Conclusions

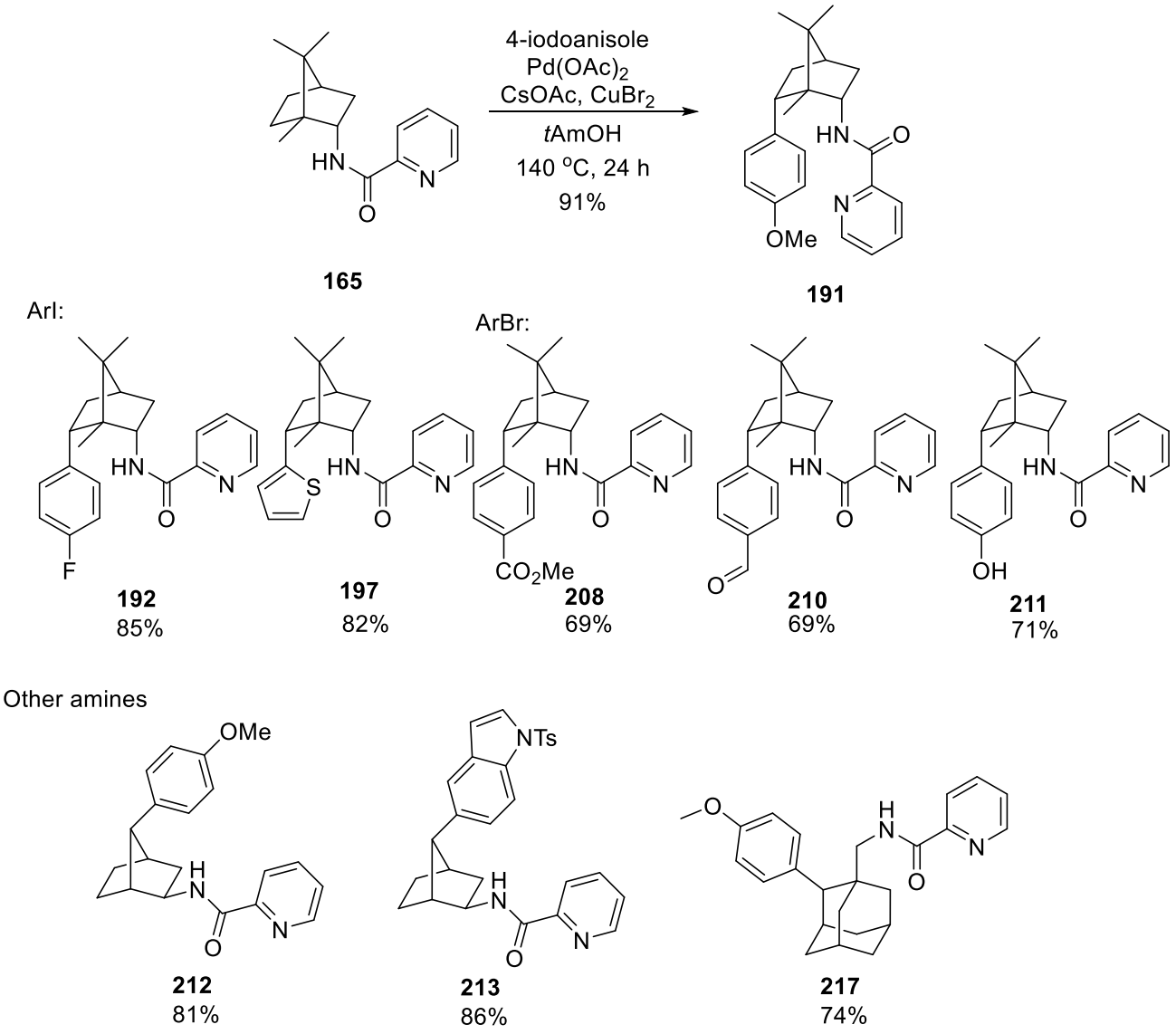
The existing methodology developed in the group for using $B(OCH_2CF_3)_3$ as a catalyst for direct amidation has been expanded upon. Performing the reactions in *t*BuOAc at a higher substrate concentration improved the green profile of the reaction, and allows for the synthesis of amides from polar carboxylic acids. Less nucleophilic and more hindered anilines have also been added to the substrate scope. Finally, the protocol was shown to be effective on a 100 mmol scale, demonstrating the low PMI of the reaction. This method allowed for the picolinamide substrates required for C-H functionalisation to be synthesised.

Chapter 6

Conclusions and Future work

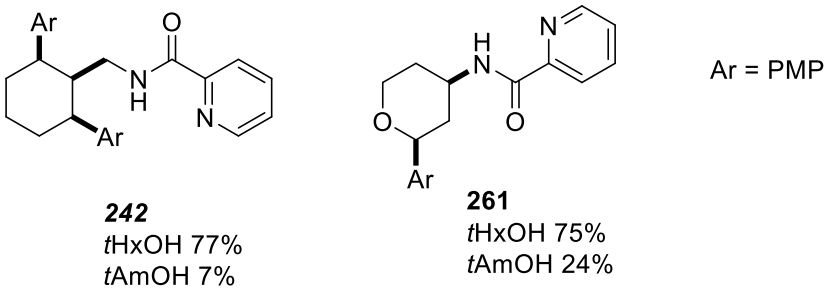
6.1 Conclusions

In summary, the amide directed C-H arylation of a range of saturated amine substrates has been demonstrated. A silver free arylation protocol directed by a picolinamide group was developed which used cesium carboxylate salts as alternative bases, which are cheaper and more sustainable. The reaction was shown to be compatible with a range of functionalities on the aryl iodide coupling partner, such as halogens, esters, ketones and simple heterocycles. In the arylation of bornylamine, it was also possible to use aryl bromides as the coupling partners, which are cheaper and more readily available than aryl iodides. As a wider range of aryl iodides are available, increased functionality on the aryl ring could be introduced, including free phenols and aldehydes.



Scheme 6.1 Arylation of bicyclic and tricyclic amines

For more challenging amine substrates, arylation could be achieved by changing from *t*AmOH to the higher boiling *t*HxOH as the solvent.

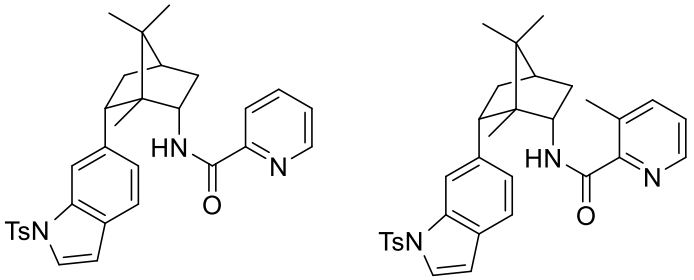


242
*t*HxOH 77%
*t*AmOH 7%

261
*t*HxOH 75%
*t*AmOH 24%

Figure 6.1 Arylation products synthesised in *t*HxOH

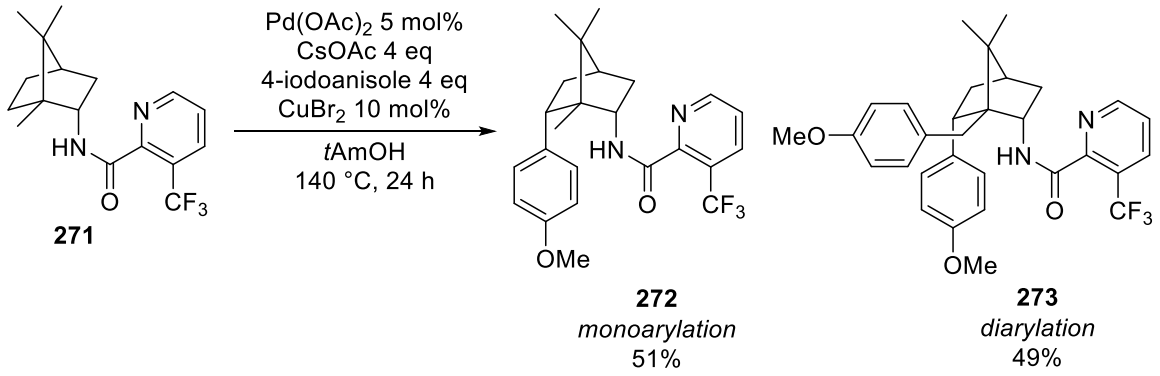
The effect of different directing groups on the selectivity and yields of C-H functionalisation reactions was investigated. It was shown that substituting the picolinamide directing group with a methyl group in the 3-position can result in improved yields of arylated products from a range of amines, **Scheme 6.2**. Electron donating and electron withdrawing substituents could have an effect on both the position and yield of C-H functionalisation reactions when there is more than one position available for C-H activation, **Scheme 6.2**.



201
44%

232
63%

Figure 6.2 Improved arylation yield using a 3-methylpicolinamide directing group



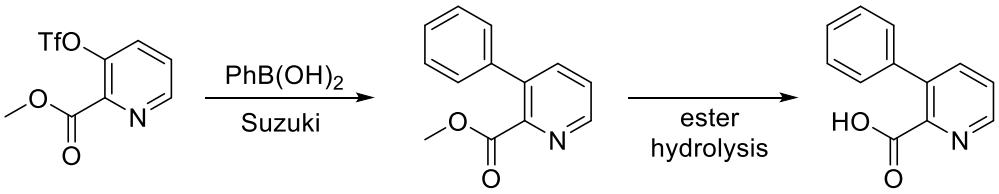
271

272
monoarylation
51%

273
diarylation
49%

Scheme 6.2 Change of selectivity when using a 3-CF_3 substituted picolinamide

As the arylation of the sterically crowded bornylamine system typically proceeded with higher yields than the arylation of less crowded systems such as cyclohexylamine and isobutylamine it may help to increase yields by introducing a bulkier directing group. As it was shown that having the 3-methylpicolinamide directing group led to improved yields for a number of arylated products. Increasing the steric bulk of the group may also lead to further enhanced yields. The methyl group could be replaced by a phenyl ring and a proposed synthesis of the picolinic acid required is shown in **Scheme 6.3**. A *tert*-butyl group is another alternative that could be used.



Scheme 6.3 Proposed synthesis of a substituted picolinic acid

The mechanism of the C-H functionalisation reaction was investigated. Viable palladium complex intermediates in the arylation of bornylamine were isolated. Both of these complexes were active as catalysts in the reaction. The kinetics of the reaction were also studied, and it was discovered that there was a positive rate dependence on both the concentration of the palladium catalyst and aryl iodide. A Pd^{II}/Pd^{IV} catalytic cycle was proposed, with the C-H activation step taking place *via* a CMD mechanism, followed by oxidative addition of the aryl halide and then reductive elimination to form the new C-C bond.

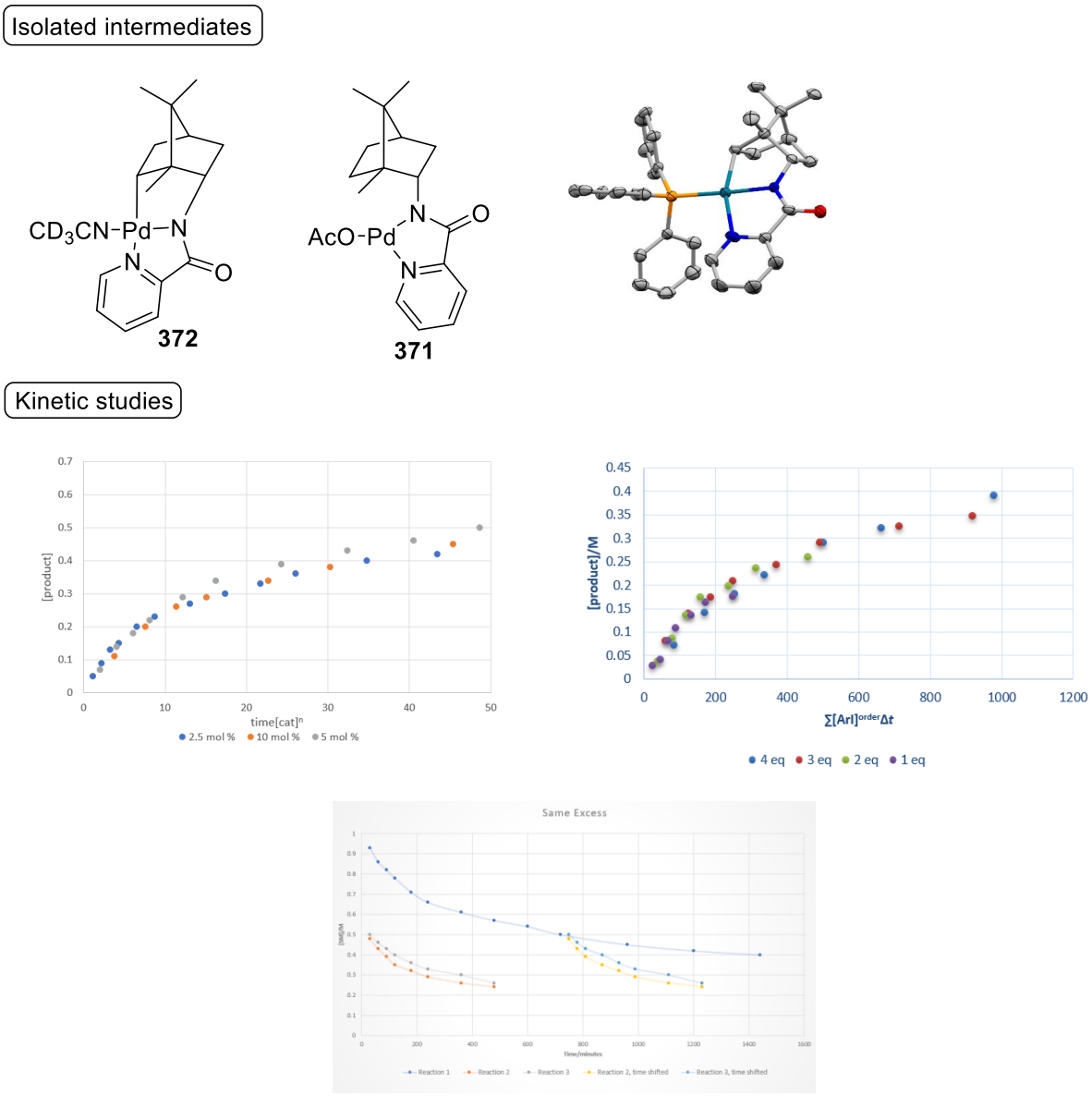
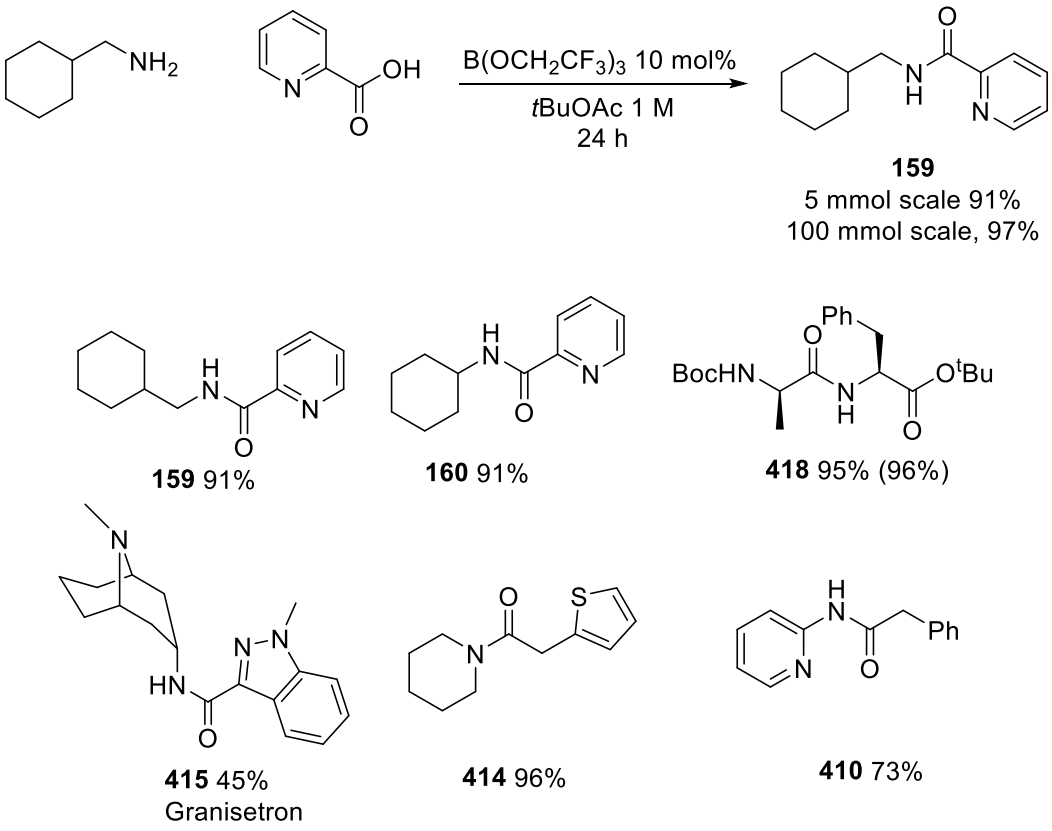


Figure 6.3 Summary of mechanistic work

Work in the group into developing sustainable methods for amidation using a borate ester catalyst was extended. The use of *t*BuOAc as the solvent can provide a useful alternative to hydrocarbon or ether solvents. This is of particular use when carrying out amidations using polar carboxylic acids or poorly nucleophilic anilines, **Scheme 6.4**. This method could then be used instead of a HATU coupling to synthesise the picolinamides required in C-H activation reactions without the need for an aqueous work up or column chromatography. This procedure also showed improved green metrics when compared to other amidation methods, with a PMI of 8.



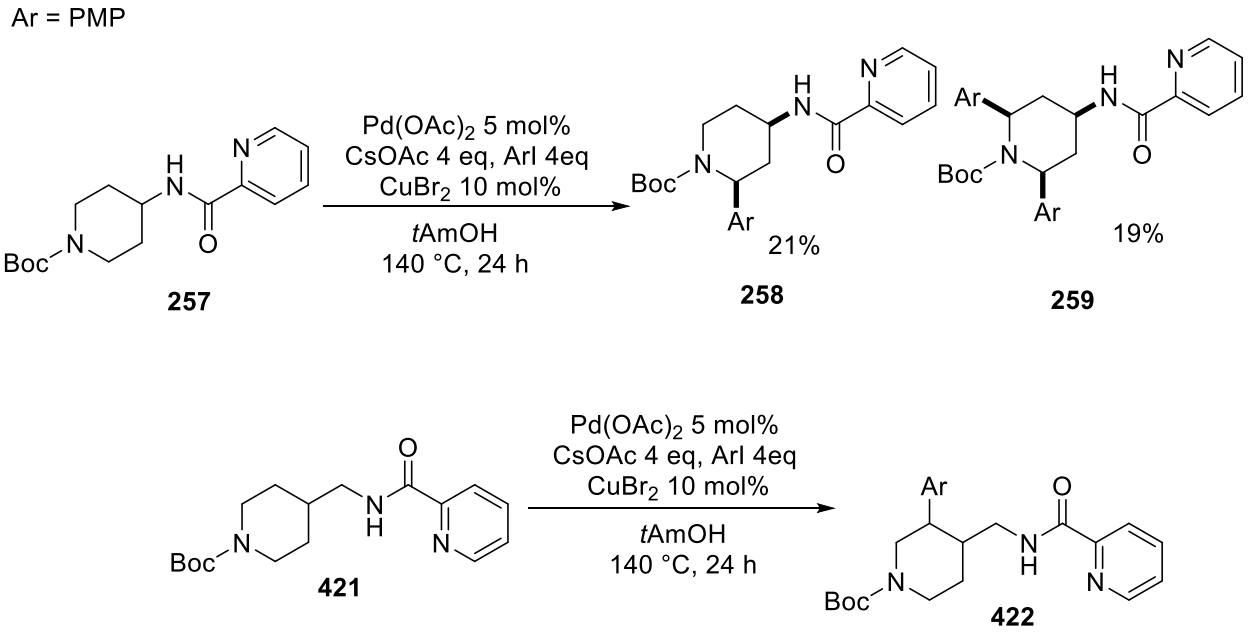
Scheme 6.4 Summary of amide synthesis

This amidation protocol is not suitable for small scale (<3 mmol) synthesis of amides, due to the Dean-Stark apparatus used to remove water from the reaction being inefficient when using small solvent volumes. It has been shown by Stoltz and coworkers that pressure equalised addition funnel containing molecular sieves and plugged with cotton wool can be used as an alternative to the Dean-Stark on small scales.[160] This method may allow for our amidation method to be used on a smaller scale.

Other borate esters may prove to be more efficient than $B(OCH_2CF_3)_3$ as catalysts for amidation. Borate esters synthesised from hexafluoroisopropanol or nonafluoro-*tert*-butyl alcohol can be synthesised and used as catalysts to investigate whether they can accelerate the rate of amidation.

6.2 Future work

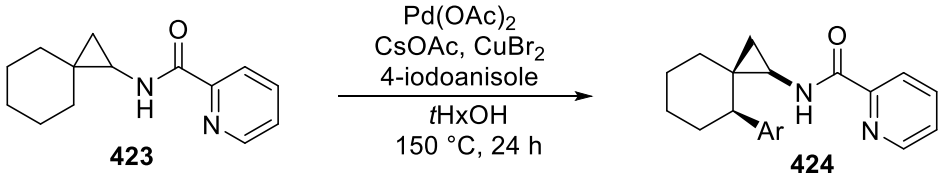
The C-H functionalisation of amino substituted nitrogen heterocycles remains a challenge. Due to the basic nitrogen of the heterocycle, it is necessary to install a protecting group. It became clear that the choice of protecting group was important for the reaction, with tosyl and CBz groups being ineffective, and resulting in no C-H arylation being observed. Low yields of arylated products were obtained using Boc protection.



Scheme 6.5 Piperidine arylation

The work on improving the directing group can be applied to attempt to obtain a higher yield of these arylated products. It may also be possible to improve this by using a different protecting group, such as an acetamide or Troc group, which is more stable than Boc to the elevated temperatures required for C-H functionalisation to take place. Preliminary results showed that amide **421** undergoes monoarylation to give compound **422**, unlike its analogous carbocyclic compound **159** which instead reacts to give the diarylated product (*vide supra*, Chapter 2).

Using *t*HxOH it became possible to observe the arylation of a spirocyclic amide **423** in moderate yield using *t*HxOH as the solvent, **Scheme 6.6**. Previously the arylation of this amide gave only trace quantities of product when performed in *t*AmOH. This reaction requires further optimisation, potentially by improving the directing group to give a higher conversion.



Scheme 6.6 Spirocycle arylation

Chapter 7

Experimental

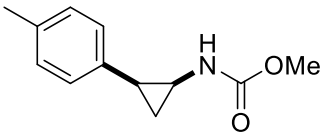
6.1 General Methods

All reagents and solvents were purchased and used as supplied unless otherwise stated. All reactions were carried out at atmospheric pressure with stirring and under inert atmosphere unless otherwise indicated. $Pd(OAc)_2$ was purchased from Sigma-Aldrich and CsOAc from Fisher Scientific. Piperidine was distilled before use. All resins were pre-washed with EtOAc, Et_2O and CH_2Cl_2 and dried in vacuo prior to use. *In vacuo* is used to describe evaporation of solvent by Büchi rotary evaporator between 17 ºC and 50 ºC at a pressure of ~ 10 mmHg. All reactions were monitored by TLC or ^1H NMR. TLC plates used were pre-coated with silica gel 60 F254 on aluminium (Merck KGaA). The spotted TLCs were visualised by UV light (254 nm or 365 nm) or chemically stained ($KMnO_4$, or Ninhydrin). ^1H NMR and ^{13}C NMR spectra were recorded at 400, 500, 600 or 700 MHz (for ^1H) and 100, 125 or 175 MHz (for ^{13}C) on a Bruker AMX400, AMX600 or NEO700 at ambient temperature, unless otherwise indicated. Deuterated solvents for NMR detection used were $CDCl_3$, MeCN- d3, MeOD-d4 or DMSO-d6, MeCN-d3 as stated in the spectrum. Peaks are assigned as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn) or multiplet (m). All shifts are reported in parts per million (ppm) and compared against residual solvent signals: $CDCl_3$ (δ = 7.26 ppm, s), MeCN (δ = 1.94, qn) DMSO (δ = 2.50 ppm, qn) or MeOD (δ = 3.31, qn) as the internal standard. Coupling constants (*J*) are quoted in Hertz (Hz) to one decimal place. Mass spectrometry was performed on VG70 SE (ES+, CI, ES- modes). Infrared spectra were obtained using a Perkin-Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode, all frequencies given in reciprocal centimetres (cm^{-1}). Melting points were measured with a Gallenkamp heating block and are uncorrected. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}, concentration (*c*) in g per 100 ml. Reactions performed above the solvent boiling point in sealed tubes were carried out in Radley Quick-Thread Glass Reaction Tube 24x150mm, and the solvent volume did not exceed 4 ml.

6.1 Experimental for Chapter Two

6.1.1 Preparation of amines

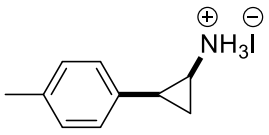
Methyl-2-(*p*-tolyl)cyclopropyl)carbamate 145



Triethyl orthoformate (9.60 ml, 57.6 mmol, 3.72 eq) was added dropwise via a syringe pump (1 ml h^{-1}) to a stirred mixture of methyl carbamate (3.70 g, 49.4 mmol, 3.19 eq), Zn (21.2 g, 324 mmol, 20.9 eq), Cu (1.40 g, 22.0 mmol, 1.45 eq), ZnCl (6.62 g, 48.6 mmol, 3.14 eq), TMSCl (22.4 ml, 176 mmol, 11.4 eq) and 4-methyl styrene (2.04 ml, 15.5 mmol, 1 eq) in Et_2O (80.0 ml). The reaction mixture was stirred at room temperature for 3 hours, then quenched with sat. aq. $NaHCO_3$. The resulting suspension was filtered and the solid washed with Et_2O (3 × 50 ml). The biphasic mixture was extracted with Et_2O (3 × 100 ml), the combined organic fractions washed with brine (80 ml), dried over $MgSO_4$ and concentrated. Potassium carbonate (6.64 g, 48 mmol) was added to the residue in MeOH (16 ml) and stirred at room temperature for 1 hour then concentrated *in vacuo*. Water (40 ml) was added and the aqueous layer extracted with CH_2Cl_2 (3 × 150 ml). The combined organic layers were washed with brine (80 ml), dried over $MgSO_4$ and concentrated. The crude reaction mixture was purified by flash column chromatography (0 – 30% ethyl acetate in petrol) to yield the carbamatocyclopropane as a white solid (1.72g, 8.37 mmol, 54%).

M.p 55 – 57 °C; $\boldsymbol{\nu_{max}}$ (film/cm^{-1}) 3246 (NH), 3134 (CH), 3016, 2944 (CH), 2915 (CH), 1707 (CO), 1514 (CC); **^{1}H NMR** (300 MHz, 330 K, $CDCl_3$); δ 7.07 (m, 4H, Ar*H*), 4.45 (br s, 1H, N*H*), 3.55 (s, 3H, OCH_3), 2.91 (m, 1H, NHC*H*), 2.30 (s, 3H, ArCH_3), 2.18 (dd, *J* = 15.9, 7.8 Hz, 1H, CH_2), 1.24 (dd, *J* = 15.2, 7.0 Hz, 1H, CH_2), 0.97 (dd, *J* = 10.8, 6.2 Hz, 1H, ArC*H*); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.7 (C), 136.3 (C), 129.2 (CH), 129.1 (C), 128.3 (CH), 52.1 (CH_3), 29.0 (CH), 21.4 (CH), 21.1 (CH_3), 12.2 (CH_2); **LRMS** (ES) $[M+H]^+$ 206.1; **HRMS** found (ES) $[M+H]^+$ 206.0749, $C_{12}H_{15}NO_2$+H requires 206.1176.

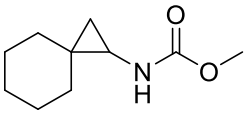
***p*-(2-Tolyl) cyclopropane-1-aminium iodide 146**



A solution of NaI (2.73 g, 18.2 mmol, 1.9 eq) and methyl 2-(*p*-tolyl)cyclopropyl)carbamate **145** (1.97 g, 9.59 mmol, 1.0 eq) in MeCN (10 ml) was treated with TMSCl (1.69 ml, 18.2 mmol, 1.9 eq), and heated to reflux for 1.5 hours. The solution was allowed to cool to room temperature, methanol (20 ml) was added and the reaction mixture heated to reflux for 0.5 hours, then concentrated. The resulting solid was washed with Et_2O to give the aminocyclopropane hydrogen iodide salt (2.57 g, 9.34 mmol, 97%).

M.p > 200 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3484 (NH), 2921 (CH), 1514 (CC); **^{1}H NMR** (500 MHz, CD_3OD); δ 7.26 - 7.17 (m, 4H, Ar*H*), 2.91 - 2.86 (m, 1H, NC*H*), 2.49 - 2.43 (m, 1H, ArC*H*), 2.32 (s, 3H, CH_3), 1.39 – 1.34 (m, 1H, CH_2), 1.26 – 1.21 (m, 1H, CH_2); **^{13}C NMR** (126 MHz, CD_3OD): δ 138.7 (C), 133.5 (C), 130.8 (CH), 130.6 (CH), 28.6 (CH), 21.1 (CH), 20.8 (CH_3), 9.2 (CH_2); **LRMS** (CI methane) $[M]^+$ 148.1; **HRMS** found (ES) $[M]^+$ 148.1128, $C_{10}H_{14}N$+ requires 148.1126.

Methyl spiro[2.5]octan-1-ylcarbamate 148

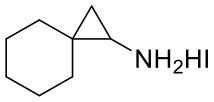


Triethyl orthoformate (9.60 ml, 57.6 mmol, 3.97 eq) and methylenecyclohexane (1.74 ml, 14.5 mmol, 1.0 eq) was added dropwise via a syringe pump (1 ml h^{-1}) to a stirred mixture of methyl carbamate (3.70 g, 49.4 mmol, 3.41 eq), Zn (21.2 g, 324 mmol, 22.3 eq), Cu (1.40 g, 22.0 mmol, 1.52 eq), ZnCl (6.62 g, 48.6 mmol, 3.35 eq), TMSCl (22.4 ml, 176 mmol, 12.1 eq) and in Et_2O (80.0 ml). The reaction mixture was stirred at room temperature for 3 hours, then quenched with sat. aq. $NaHCO_3$. The resulting suspension was filtered and the solid washed with Et_2O (3 × 50 ml). The biphasic mixture was extracted with Et_2O (3 × 100 ml), the combined organic fractions washed with brine (80 ml), dried over $MgSO_4$ and concentrated. Potassium carbonate (6.64 g, 48.0 mmol) was added to the residue in MeOH (16 ml) and stirred at room temperature for 1 hour then concentrated *in vacuo*. Water (40 ml) was added and the aqueous layer extracted with CH_2Cl_2 (3 × 150 ml). The combined organic layers were washed with brine (80 ml), dried over $MgSO_4$ and concentrated. The crude reaction mixture was purified by flash column chromatography (0 – 30% ethyl acetate in petrol) to yield the carbamatocyclopropane as a colourless oil (2.54 g, 13.9 mmol, 96%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3320 (NH), 2921 (CH), 2847 (CH), 1693 (CO); **^{1}H NMR** (400 MHz, 330 K, $CDCl_3$) δ 4.71 (s, 1H, N*H*), 3.69 – 3.60 (m, 3H, CH_3), 2.43 – 2.29 (m, 1H, NHC*H*), 1.55 (dd, *J* = 13.5, 8.0 Hz, 1H, Cy*H*), 1.51 – 1.42 (m, 5H, Cy*H*), 1.41 – 1.25 (m, 3H, Cy*H*), 1.22 – 1.12

(m, 1H, Cy*H*), 0.66 – 0.53 (m, 1H, NHCHC*H*$_2$), 0.33 (dt, *J* = 9.3, 5.0 Hz, 1H, NHCHC*H*$_2$); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 158.0 (C), 52.1 (CH_3), 35.5 (CH_2), 34.6 (CH), 29.8 (CH_2), 26.4 (C), 25.1 (CH_2), 19.2 (CH_2); **HRMS** found (ES) [M+H] 184.1331, $C_{10}H_{17}NO_2$+H requires 184.1332.

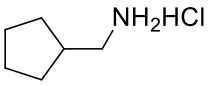
Spiro[2.5]octan-1-amine hydroiodide 149



To a solution of carbamate **148** (737 mg, 4.02 mmol, 1 eq) in MeCN (16 ml) was added NaI (1.15 g, 7.64 mmol, 1.9 eq) and TMSCl (0.96 ml, 7.64 mmol, 1.9 eq). The reaction mixture was heated to reflux for 1 hour, before being cooled and concentrated *in vacuo*. The resulting solid was washed with Et_2O to give the product as a light brown solid (672 mg, 2.65 mmol, 66%).

M.p >200 °C; **ν_{max}** (film/cm^{-1}) 3480 (NH), 3416 (NH), 2923 (CH); **^{1}H NMR** (600 MHz, MeOD) *δ* 2.38 (dd, *J* = 7.7, 4.1 Hz, 1H, NH_2CH), 1.69 – 1.43 (m, 10H, Cy*H*), 0.84 – 0.79 (m, 1H, NH_2CHCH_2), 0.64 (dd, *J* = 5.9, 4.3 Hz, 1H, NH_2CHCH_2); **^{13}C NMR** (151 MHz, MeOD) *δ* 36.0 (CH), 34.2 (C), 29.8 (CH_2), 27.0 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 24.4 (CH_2), 17.3 (CH_2).

Cyclopentylmethanamine hydrochloride 151



A solution of cyclopentanecarbonitrile (0.31 ml, 3.0 mmol, 1 eq) in diethyl ether (2.1 ml) was added dropwise to a solution of $LiAlH_4$ (1.9 ml, 7.5 mmol, 2.5 eq, 4 M in diethyl ether) in diethyl ether (4 ml) at 0 °C. The resulting suspension was stirred for 5 minutes, before the addition of $Na_2SO_4.10H_2O$ followed by $MgSO_4$. The mixture was filtered, and the solids washed with ether (3 × 5 ml). HCl (1 ml, 37%) was added dropwise to the filtrate and the solution concentrated to give the title compound as a white solid (401 mg, 2.96 mmol, 99%).

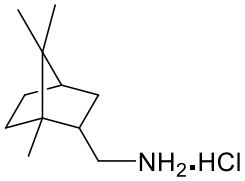
M.p > 200 °C; **ν_{max}** (film/cm^{-1}) 2903 (NH), 2652 (CH); **^{1}H NMR** (600 MHz, MeOD) *δ* 2.89 (d, *J* = 7.5 Hz, 2H, NHC*H*$_2$), 2.19 – 2.10 (m, 1H, $NHCH_2CH$), 1.91 – 1.85 (m, 2H), 1.75 – 1.67 (m, 2H), 1.67 – 1.59 (m, 2H), 1.26 (td, *J* = 15.2, 7.8 Hz, 2H); **^{13}C NMR** (151 MHz, MeOD) *δ* 45.5 (CH_2), 39.4 (CH), 31.3 (CH_2), 26.0 (CH_2).
Data in accordance with literature[161]

139 1,7,7-Trimethylbicyclo[2.2.1]heptane-2-carbonitrile[99] **152**

t-BuOK (8.42 g, 75.0 mmol, 5 eq) was added to a rapidly stirred solution of TosMIC (5.80 g, 30.0 mmol, 2 eq) in DMSO (22.2 ml) at 0 °C, before stirring for 5 minutes. (+/)-Camphor (2.25 g, 15.0 mmol, 1 eq) and methanol (0.75 ml) were added and the reaction mixture warmed to 45 °C and stirred for 72 hours. The reaction mixture was diluted with 2 M HCl (30 ml), water (30 ml) and extracted with petrol (5 × 40 ml). The combined organic fractions were dried over $MgSO_4$, concentrated and the residue purified by flash column chromatography (0 - 40% ethyl acetate in petrol) to yield the title compound as a white solid (1.88 g, 11.5 mmol, 77%).

M.p 138 – 141 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3019 (CH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.66 (ddd, *J* = 11.8, 5.1, 3.1 Hz, 1H, CNC*H*), 2.24 – 2.14 (m, 1H, CH_2CHCH_2), 1.93 – 1.85 (m, 1H, $CNCHCH_2$), 1.81 (ddd, *J* = 11.9, 7.9, 4.0 Hz, 1H, CCH_2CH_2), 1.76 (dd, *J* = 4.8, 2.6 Hz, 1H, CCH_2CH_2), 1.59 – 1.52 (m, 1H, CCH_2), 1.46 (dd, *J* = 13.0, 5.1 Hz, 1H, CCH_2), 1.30 (ddd, *J* = 11.8, 9.4, 4.5 Hz, 1H, $CNCHCH_2$), 0.98 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.84 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 123.1 (C), 49.7 (C), 48.0 (C), 45.1 (CH), 36.1 (CH), 34.2 (CH_2), 31.3 (CH_2), 27.9 (CH_2), 19.4 (CH_3), 18.5(CH_3), 14.3 (CH_3).

1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)methanamine hydrochloride[100] **153**

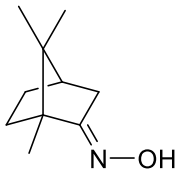


A solution of **152** (1.88 g, 11.5 mmol, 1 eq) in THF (17.3 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (34.5 ml, 1M in THF, 34.5 mmol, 3 eq) in THF (34.5 ml) at 0 °C. The resulting solution was heated to reflux for 7 hours. The reaction mixture was cooled to -10 °C and hydrated sodium sulphate (18 g) was added portionwise while stirring and the suspension dried over $MgSO_4$, filtered and concentrated. The residue was taken up in methanol (20 ml), cooled to 0 °C and acetyl chloride (3 ml) added dropwise. The solution

was concentrated, the resulting solid sonicated in Et_2O (30 ml) and filtered to yield the title compound as a white solid (1.37 g, 6.71 mmol, 58%). *d.r* 9:1

M.p > 200 °C; $\mathbf{v_{max}}$ (film/cm^{-1}) 3300 (NH), 2949 (CH), 1108 (CN); **^{1}H NMR** (600 MHz, MeOD) δ 3.07 – 3.02 (m, 1H, NH_2CH_2), 2.85 (dd, *J* = 20.7, 8.9 Hz, 1H, NH_2CH_2), 2.11 (dd, *J* = 15.8, 7.7 Hz, 1H, NH_2CH_2CH), 1.98 (d, *J* = 10.6 Hz, 1H, $(CH_3)_2CCH$), 1.78 (d, *J* = 4.2 Hz, 1H, $CHCH_2CH$), 1.69 (t, *J* = 4.3 Hz, 1H, $CHCCH_2CH_2$), 1.42 (dd, *J* = 14.4, 7.5 Hz, 2H, $CHCCH_2CH_2$ and $CHCCH_2$), 1.25 – 1.16 (m, 1H, $CHCCH_2$), 0.98 (dd, *J* = 12.6, 4.5 Hz, 1H, $CHCH_2CH$), 0.94 – 0.91 (m, 6H, 2 × CH_3), 0.90 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, DMSO) δ 48.5 (C), 47.2 (CH), 44.4 (CH), 41.6 (C), 41.4 (CH_2), 34.3 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 18.9 (CH_3), 18.3 (CH_3), 14.0 (CH_3).

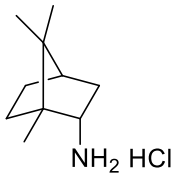
(+/-) Camphor oxime[162] **154**



A solution of (+/-)-camphor (2.03 g, 13.3 mmol, 1.0 eq) in ethanol (6.7 ml) was added to a stirred solution of hydroxylamine hydrochloride (1.39 g, 20.0 mmol, 1.50 eq) and sodium acetate (1.37 g, 16.7 mmol, 1.25 eq) in water (10 ml). The resulting suspension was stirred at 60 °C for 24 hours. The solution was cooled and concentrated until crystals of camphor oxime began to form then cooled to 4 °C to complete crystallisation. The crystals were collected by filtration, washing with ice cold water to yield camphor oxime as a colourless crystalline solid (1.99 g, 11.9 mmol, 89%).

M.p 116 – 119 °C; $\mathbf{v_{max}}$ (film/cm^{-1}) 3020 (CH), 1214 (CN); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.81 (s, 1H, OH), 2.55 (dt, *J* = 17.8, 3.8 Hz, 1H, $NCCH_2CH$), 2.05 (d, *J* = 17.8 Hz, 1H, $NCCH_2$), 1.91 (t, *J* = 4.4 Hz, 1H, $CHCH_2CH_2$), 1.83 (tdd, *J* = 11.9, 7.5, 4.2 Hz, 1H, $CHCH_2CH_2$), 1.70 (td, *J* = 12.1, 3.9 Hz, 1H, $CHCH_2CH_2$), 1.49 – 1.41 (m, 1H, $CHCH_2CH_2$), 1.23 (ddd, *J* = 9.3, 7.9, 4.2 Hz, 1H, NCCH), 1.00 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.80 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.1 (C), 51.9 (C), 48.4 (C), 43.8 (CH), 33.2 (CH_2), 32.7 (CH_2), 27.4 (CH_2), 19.6 (CH_3), 18.7 (CH_3), 11.2 (CH_3).

endo-(+/-)-Bornylamine hydrochloride[163] **155**



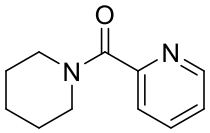
A solution of camphor oxime (668 mg, 4.0 mmol, 1.0 eq) in ethanol (10.3 ml) was warmed to 80 °C and treated portionwise with sodium (710 mg, 31 mmol, 7.75 eq). The resulting solution was stirred for 2 hours before being cooled to 0 °C and water (8 ml) carefully added. The reaction mixture was concentrated to ~10 ml and extracted with DCM (3 x 15 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude residue was taken up in 2 M HCl (20 ml) and the resulting precipitate was filtered off, washing with ether, to yield the product as a white solid (465 mg, 2.45 mmol, 61%).

M.p >200 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 2988 (CH), 2962 (CH), 2885 (NH); **^{1}H NMR** (400 MHz, MeOD) δ 3.40 (dd, *J* = 11.0, 4.0 Hz, 1H, NC*H*), 2.41 – 2.29 (m, 1H, CH_2CHCH_2), 1.89 – 1.81 (m, 1H, NCHCH_2), 1.76 (t, *J* = 4.6 Hz, 1H, NCHCH_2), 1.56 (dd, *J* = 8.9, 5.8 Hz, 2H, NCHCCH_2), 1.39 – 1.31 (m, 1H, CH_2CHCH_2), 1.13 (dd, *J* = 13.7, 4.4 Hz, 1H, CH_2CHCH_2), 0.98 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, DMSO) δ 48.6 (CH), 43.9 (C), 27.1 (C), 26.8 (CH), 20.1 (CH_2), 20.0 (CH_2), 19.4 (CH_2), 18.3 (CH_3), 13.1 (CH_3), 11.6 (CH_3).

6.2 Addition of directing groups to amines

6.2.1 Synthesis of amides using $B(OCH_2CF_3)_3$

Piperadin-1-yl(pyridine-2-yl)methanone[164] **156**



$B(OCH_2CF_3)_3$ (0.86 ml, 4.00 mmol, 2 eq) was added dropwise to a solution of piperidine (0.24 ml, 2.40 mmol, 1.2 eq) and picolinic acid (0.123g, 1.00 mmol, 0.5 eq) in CPME (4 ml). The reaction mixture was heated to 100 °C and stirred for 20 hours then cooled to room temperature. Amberlyst® A-26(OH), Amberlite® IRA743, water (1 ml) and ethyl acetate (4 ml) were added to the cooled reaction mixture and stirred for 30 minutes. The resins were removed by filtration, the solution concentrated *in vacuo* and the crude product purified by flash column chromatography (10-50% ethyl acetate in petrol) to yield the product as a pale orange oil (23 mg, 0.12 mmol, 12%).

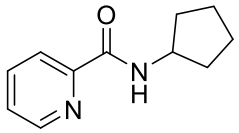
ν_{max} (film/cm^{-1}) 3337 (CH), 2919 (CH), 2852 (CH), 1620 (CO), 1582 (CC); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.6 Hz, 1H, pyNC*H*), 7.76 (ddd, *J* = 7.7, 6.0, 1.7 Hz, 1H, pyCC*H*), 7.55 (d, *J* = 7.8 Hz, 1H, pyCCHC*H*), 7.31 (ddd, *J* = 7.6, 4.9, 1.0 Hz, 1H, pyNCHC*H*), 3.72 (s, 2H, NCH_2), 3.46 – 3.35 (m, 2H, NCH_2), 1.71 – 1.63 (m, 4H, NCH_2CH_2), 1.58 – 1.52 (m, 2H, $NCH_2CH_2CH_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.8 (C), 154.9 (C), 148.6 (CH), 137.1 (CH), 124.3 (CH), 123.4 (CH), 48.4 (CH_2), 43.4 (CH_2), 26.6 (CH_2), 25.7 (CH_2), 24.7 (CH_2); **LRMS** Found (ES+) $[M+H]^+$ 191.1.

Catalytic borate:

Picolinic acid (0.492 g, 4.0 mmol, 1 eq), $B(OCH_2CF_2)$ (86 µl, 0.40 mmol, 10 mol%) and piperadine (0.55 ml, 4.80 mmol, 1.2 eq) were dissolved in toluene (4 ml) and heated to reflux in a Dean-Stark for 48 hours. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (0 – 10% methanol in DCM) to give the product as a yellow oil (103 mg, 0.54 mmol, 14%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 – 8.44 (m, 1H), 7.68 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 – 7.43 (m, 1H), 7.30 – 7.18 (m, 1H), 3.64 (s, 2H), 3.40 – 3.28 (m, 2H), 1.58 (s, 4H), 1.46 (s, 2H).

_N_-Cyclopentylpicolinamide 157



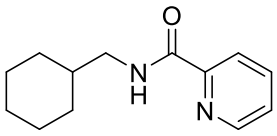
$B(OCH_2CF_3)_3$ (0.86 ml, 4.0 mmol, 2.0 eq) was added dropwise to a solution of cyclopentylamine (0.24 ml, 2.4 mmol, 1.2 eq) and picolinic acid (246 mg, 2.0 mmol, 1.0 eq) in CPME (4 ml). The reaction mixture was heated to 125 °C and stirred for 24 hours then cooled to room temperature. Amberlyst® A-26(OH), Amberlite® IRA743, water (1 ml) and ethyl acetate (4 ml) were added to the cooled reaction mixture and stirred for 30 minutes. The resins removed by filtration, the solution concentrated *in vacuo* and the crude product purified by flash column chromatography (10 - 50% ethyl acetate in petrol) to yield the product as a pale yellow solid (307 mg, 0.24 mmol, 81%).

Mp 84 – 87 °C; ν_{max} (film/cm^{-1}) 3313 (NH), 2954 (CH), 1646 (CO), 1587 (CC); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.50 – 8.41 (m, 1H, ArNC*H*), 8.14 (dd, *J* = 7.8, 0.9 Hz, 1H, ArCC*H*), 8.07 – 7.83 (m, 1H, N*H*), 7.77 (td, *J* = 7.7, 1.7 Hz, 1H, ArCCHC*H*), 7.35 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, ArNCHC*H*), 4.35 (dq, *J* = 13.6, 6.9 Hz, 1H, NHC*H*), 2.08 – 1.93 (m, 2H, NHCHCH_2),

1.77 – 1.43 (m, 6H, NHCH_2CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.8 (C), 150.2 (C), 148.0 (CH), 137.3 (CH), 126.0 (CH), 122.1 (CH), 51.1 (CH), 33.2 (CH_2), 23.9 (CH_2).

Data in accordance with literature[165]

***N*-(Cyclohexylmethyl)picolinamide 159**

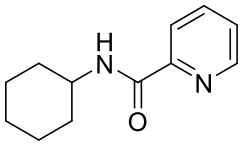


A suspension of 2-picolinic acid (616 mg, 5.0 mmol, 1 eq), cyclohexylmethylamine (650 µl, 5.0 mmol, 1 eq) and $B(OCH_2CF_3)_3$ (108 µl, 0.50 mmol, 10 mol%) in *t*BuOAc (5 ml, 1 M) with a Dean-Stark (side arm filled with *t*BuOAc) was heated to reflux. An air condenser was fitted and the reaction mixture heated for 24 hours. Upon completion, the reaction was cooled to room temperature and water (0.5 ml), DMC (5 ml) Amberlite IRA-743 (0.25 g) and A-26(OH) (0.5 g) resins were added and the resulting suspension was stirred for 30 min. $MgSO_4$ (~0.5 g) was added and the mixture filtered and the resins washed with EtOAc (2 × 5 ml). The combined filtrates were concentrated *in vacuo* to yield the amide as a white solid (1.004 g, 4.60 mmol, 92%).

M.p 65 - 67 °C; **ν_{max}** (solid/cm^{-1}) 3354 (NH), 2916 (CH), 2847 (CH), 1657 (CO), 1525 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.7 Hz, 1H, Ar*H*), 8.15 (d, *J* = 7.8 Hz, 1H, Ar*H*), 8.09 (s, 1H, N*H*), 7.78 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.35 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H, Ar*H*), 3.27 (t, *J* = 6.6 Hz, 2H, NHCH_2), 1.75 (dd, *J* = 13.6, 1.9 Hz, 2H, CHCH_2), 1.71 – 1.65 (m, 2H, CHCH_2CH_2), 1.61 (ddd, *J* = 12.5, 5.0, 2.6 Hz, 1H, CHCH_2CH_2CH_2), 1.55 (ttd, *J* = 10.5, 7.0, 3.4 Hz, 1H, C*H*), 1.23 – 1.15 (m, 2H, CHCH_2CH_2), 1.15 – 1.08 (m, 1H, CHCH_2CH_2CH_2), 0.96 (ddd, *J* = 24.5, 12.3, 3.3 Hz, 2H, CHCH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.4 (C), 150.2 (C), 148.1 (CH), 137.4 (CH), 126.1 (CH), 122.3 (CH), 45.7 (CH_2), 38.2 (CH), 31.0 (CH_2), 26.5 (CH_2), 26.0 (CH_2).

Data in accordance with literature[166]

***N*-Cyclohexylpicolinamide 160**

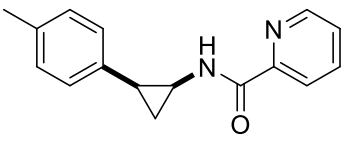


A suspension of 2-picolinic acid (616 mg, 5.0 mmol, 1 eq), cyclohexylamine (570 µl, 5.0 mmol) and $B(OCH_2CF_3)_3$ (108 µl, 0.50 mmol, 10 mol%) in *t*BuOAc (5 ml, 1 M) with a Dean-Stark (side arm filled with *t*BuOAc) was heated to reflux. An air condenser was fitted and the reaction mixture heated for 48 hours. Upon completion, the reaction was cooled to room temperature and water (0.5 ml), DMC (5 ml) Amberlite IRA-743 (0.25 g) and A-26(OH) (0.5 g) resins were added and the resulting suspension was stirred for 30 min. $MgSO_4$ (~0.5 g) was added and the mixture filtered and the resins washed with EtOAc (2 × 5 ml). The combined filtrates were concentrated *in vacuo* to yield the amide as a white solid (930 mg, 4.55 mmol, 91%).

M.p 54 – 56 °C; $\mathbf{\nu_{max}}$ (solid/cm^{-1}) 3379, 2935, 2857, 1666; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, Ar*H*), 8.18 (dt, *J* = 7.8, 1.1 Hz, 1H, Ar*H*), 7.93 (s, 1H, N*H*), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.39 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, Ar*H*), 4.03 – 3.89 (m, 1H, NHC*H*), 2.05 – 1.95 (m, 2H, NHCHCH_2), 1.80 – 1.70 (m, 2H, NHCHCH_2CH_2), 1.68 – 1.59 (m, 1H, NHCHCH_2CH_2CH_2), 1.48 – 1.16 (m, 5H, 3 × CH_2); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.4 (C), 150.4 (C), 148.1 (CH), 137.4 (CH), 126.1 (CH), 122.3 (CH), 48.3 (CH), 33.2 (CH_2), 25.7 (CH_2), 25.0 (CH_2).

Data in accordance with literature[50]

***N*-(2-(p-tolyl)cyclopropyl)picolinamide 161**

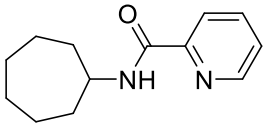


Saturated potassium carbonate solution (20.0 ml) was added to *p*-(2-tolyl) cyclopropane-1-aminium iodide (1.10 g, 4.00 mmol, 1 eq) and the aqueous layer extracted with DCM (3 x 20 ml), dried over $MgSO_4$ and concentrated to liberate the free amine. $B(OCH_2CH_3)_3$ (86 µl, 0.40 mmol, 10 mol%) and picolinic acid (0.492 g, 4.00 mmol, 1 eq) were added to the amine in toluene (4 ml). The reaction mixture was heated to reflux in a Dean-Stark for 24 hours,

before being concentrated and purified by flash column chromatography (0 – 5% methanol in DCM) to yield the product as a brown oil (112 mg, 0.44 mmol, 11%).

ν_{max} (film/cm^{-1}) 3352 (NH), 2983 (CH), 1647 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.37 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.11 (dt, *J* = 7.8, 1.1 Hz, 1H, pyCC*H*), 7.79 (br s, 1H, N*H*), 7.78 – 7.75 (m, 1H, pyCCHC*H*), 7.33 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 7.14 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.09 (d, *J* = 7.9 Hz, 2H, Ar*H*), 3.34 (tt, *J* = 7.6, 4.7 Hz, 1H, NHC*H*), 2.38 (dd, *J* = 16.4, 7.5 Hz, 1H, ArC*H*), 2.30 (s, 3H, ArCH_3), 1.46 (ddd, *J* = 9.1, 7.5, 6.2 Hz, 1H, NHCHCH_2), 1.15 – 1.10 (m, 1H, NHCHCH_2); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.8 (C), 149.7 (C), 148.1 (CH), 137.3 (CH), 136.1 (C), 133.4 (C), 129.2 (CH), 128.7 (CH), 126.2 (CH), 122.0 (CH), 28.8 (CH), 21.7 (CH_3), 21.2 (CH), 12.3 (CH_2); **LRMS** (ES) 253.1 ([M+H]$^+$) 527.2 ([2M+Na]$^+$); **HRMS** found (ES) [M+H]$^+$ 253.1344 $C_{16}H_{16}N_2O$+H requires 253.1335.

N-Cycloheptylpicolinamide 162

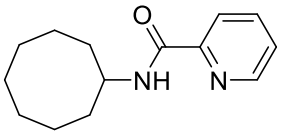


A suspension of 2-picolinic acid (616 mg, 5.0 mmol, 1 eq), cycloheptylamine (637 µl, 5.0 mmol, 1 eq) and $B(OCH_2CF_3)_3$ (215 µl, 0.50 mmol, 20 mol%) in *t*BuOAc (5 ml, 1 M) with a Dean-Stark (side arm filled with *t*BuOAc) was heated to reflux. An air condenser was fitted and the reaction mixture heated for 24 hours. Upon completion, the reaction was cooled to room temperature and water (0.5 ml), DMC (5 ml) Amberlite IRA-743 (0.25 g) and A-26(OH) (0.5 g) resins were added and the resulting suspension was stirred for 30 min. $MgSO_4$ (~0.5 g) was added and the mixture filtered and the resins washed with EtOAc (2 × 5 ml). The combined filtrates were purified by flash column chromatography (30% EtOAc in petrol) to give the product as a colourless oil (875 mg, 4.01 mmol, 80%).

ν_{max} (film/cm^{-1}) 3351 (NH), 2923 (CH), 2857 (CH), 1640 (CO), 1518 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.51 – 8.45 (m, 1H, pyNC*H*), 8.15 (d, *J* = 7.8 Hz, 1H, CC*H*), 7.99 (d, *J* = 6.3 Hz, 1H, N*H*), 7.80 – 7.76 (m, 1H, CCHC*H*), 7.37 – 7.33 (m, 1H, pyNCHC*H*), 4.14 – 4.09 (m, 1H, NHC*H*), 2.02 – 1.94 (m, 2H, NHCHCH_2), 1.68 – 1.48 (m, 10H, CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.1 (C), 150.4 (C), 148.1 (CH), 137.4 (CH), 126.1 (CH), 122.3 (CH), 50.5 (CH), 35.2 (CH_2), 28.2 (CH_2), 24.3 (CH_2).

Data in accordance with literature[166]

***N*-Cyclooctylpicolinamide 163**

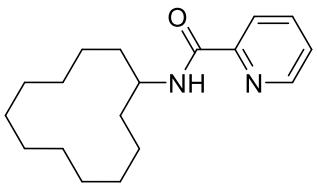


A suspension of 2-picolinic acid (616 mg, 5.0 mmol, 1 eq), cyclooctylamine (686 µl, 5.0 mmol, 1 eq) and $B(OCH_2CF_3)_3$ (215 µl, 0.50 mmol, 20 mol%) in *t*BuOAc (5 ml, 1 M) with a Dean-Stark (side arm filled with *t*BuOAc) was heated to reflux. An air condenser was fitted and the reaction mixture heated for 24 hours. Upon completion, the reaction was cooled to room temperature and water (0.5 ml), DMC (5 ml) Amberlite IRA-743 (0.25 g) and A-26(OH) (0.5 g) resins were added and the resulting suspension was stirred for 30 min. $MgSO_4$ (~0.5 g) was added and the mixture filtered and the resins washed with EtOAc (2 × 5 ml). The combined filtrates were purified by flash column chromatography (30% EtOAc in petrol) to give the product as a colourless oil (709 mg, 3.05 mmol, 61%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3381 (NH), 2918 (CH), 2852 (CH), 1666 (CO), 1512 (CC); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.18 (dt, *J* = 7.9, 1.1 Hz, 1H, CC*H*), 8.01 (s, 1H, N*H*), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H, CCHC*H*), 7.39 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 4.23 – 4.12 (m, 1H, NHC*H*), 1.97 – 1.88 (m, 2H, CH_2), 1.75 – 1.52 (m, 12H, CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.1 (C), 150.4 (C), 148.0 (CH), 137.4 (CH), 126.1 (CH), 122.3 (CH), 49.5 (CH), 32.3 (CH_2), 27.4 (CH_2), 25.6 (CH_2), 23.8 (CH_2).

Data in accordance with literature[166]

***N*-Cyclododecylpicolinamide 164**



A suspension of 2-picolinic acid (616 mg, 5.0 mmol, 1 eq), cyclododecylamine (916 mg, 5.0 mmol, 1 eq) and $B(OCH_2CF_3)_3$ (215 µl, 0.50 mmol, 20 mol%) in *t*BuOAc (5 ml, 1 M) with a Dean-Stark (side arm filled with *t*BuOAc) was heated to reflux. An air condenser was fitted and the reaction mixture heated for 24 hours. Upon completion, the reaction was cooled to room temperature and water (0.5 ml), DMC (5 ml) Amberlite IRA-743 (0.25 g) and A-26(OH) (0.5 g) resins were added and the resulting suspension was stirred for 30 min. $MgSO_4$ (~0.5 g) was added and the mixture filtered and the resins washed with EtOAc (2 × 5 ml). The

combined filtrates were purified by flash column chromatography (30% EtOAc in petrol) to give the product as a colourless oil (826 mg, 2.86 mmol, 57%).

ν_{max} (film/cm^{-1}) 3354 (NH), 2925 (CH), 2853 (CH), 1652 (CO), 1512 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.51 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H, pyNC*H*), 8.21 – 8.16 (m, 1H, CC*H*), 7.96 – 7.84 (m, 1H, N*H*), 7.82 (tt, *J* = 7.7, 1.7 Hz, 1H, CCHC*H*), 7.40 – 7.36 (m, 1H, pyNCHC*H*), 4.28 – 4.22 (m, 1H, NHC*H*), 1.77 – 1.69 (m, 2H, NHCHCH_2), 1.53 – 1.30 (m, 20H, CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.7 (C), 150.4 (C), 148.1 (CH), 137.4 (CH), 126.1 (CH), 122.3 (CH), 46.1 (CH), 30.5 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 23.6 (CH_2), 21.7 (CH_2).

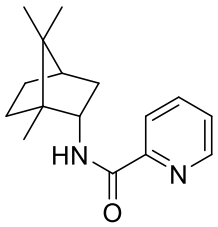
Data in accordance with literature[166]

6.2.2 Synthesis of amides using HATU

General Procedure for Amidation A (HATU coupling)

DIPEA (1.2 or 3 eq) was added dropwise to a solution of amine (1 eq), picolinic acid (1.2 eq) and HATU (1.2 eq) in dimethylformamide (0.2 M). The resulting solution was stirred at room temperature for 16 hours. Saturated aqueous lithium chloride was added and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography.

***N*((1*S*,2*S*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide**



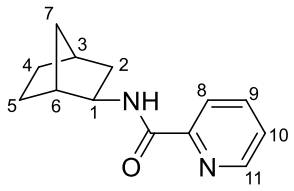
Prepared according to general amidation procedure A, using *R*-(+)-bornylamine (307 mg, 2.0 mmol) and 2-picolinic acid (295 mg, 2.4 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a white solid (387 mg, 1.51 mmol, 75%).

M.p 78 – 80 °C; **ν_{max}** (film/cm^{-1}) 3375 (NH), 2982 (CH), 1673 (CO); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.23 – 8.11 (m, 2H, N*H* and pyCC*H*),

7.84 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 4.48 – 4.39 (m, 1H, NHC*H*), 2.48 – 2.37 (m, 1H, NHCHCH_2), 1.83 (dtd, *J* = 12.2, 8.0, 4.0 Hz, 1H, CHCCH_2), 1.71 (ddd, *J* = 13.7, 8.2, 3.4 Hz, 2H, CH_2CHCH_2 and $CHCH_2CH_2$), 1.49 – 1.39 (m, 1H, $CHCH_2CH_2$), 1.36 – 1.29 (m, 1H, CHCCH_2), 1.03 – 0.96 (m, 4H, NHCHCH_2 and CH_3), 0.92 (s, 3H, CH_3), 0.88 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.3 (C), 150.3 (C), 148.1 (CH), 137.5 (CH), 126.1 (CH), 122.3 (CH), 53.9 (CH), 50.0 (C), 48.4 (C), 45.2 (CH), 37.7 (CH_2), 28.6 (CH_2), 28.2 (CH_2), 20.0 (CH_3), 18.9 (CH_3), 13.9 (CH_3); **LRMS** (CI) 259.2 ($[M+H]^+$).

Data in accordance with literature[113]

Exo-*N*-(Bicyclo[2.2.1]heptan-2-yl)picolinamide 166

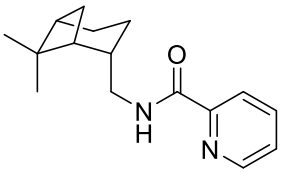


Prepared according to general amidation procedure A, using *exo*-aminonorborane (133 mg, 1.20 mmol) and 2-picolinic acid (178 mg, 1.44 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a white solid (225 mg, 1.04 mmol, 87%).

M.p 61-63 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.52 (ddd, *J* = 4.7, 1.7, 1.0 Hz, 1H, H11), 8.18 (ddd, *J* = 7.8, 2.4, 1.4 Hz, 1H, H8), 7.88 (s, 1H, N*H*), 7.83 (tdd, *J* = 7.7, 3.0, 1.7 Hz, 1H, H9), 7.40 (dddd, *J* = 7.5, 4.8, 2.5, 1.2 Hz, 1H, H10), 3.96 – 3.88 (m, 1H, H1), 2.33 (dd, *J* = 2.9, 1.5 Hz, 2H, H6 and H3), 1.88 (ddd, *J* = 13.1, 8.0, 2.4 Hz, 1H, H2), 1.59 – 1.53 (m, 1H, H5), 1.52 – 1.46 (m, 2H, H7 and H4), 1.41 – 1.36 (m, 1H, H2), 1.35 – 1.30 (m, 1H, H5), 1.27 – 1.23 (m, 1H, H7), 1.21 – 1.15 (m, 1H, H4). **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 163.5 (C), 150.2 (C), 148.1 (CH), 137.4 (CH), 126.1 (CH), 122.2 (CH), 52.8 (CH), 42.6 (CH), 40.4 (CH), 35.9 (CH_2), 35.9 (CH_2), 28.4 (CH_2), 26.7 (CH_2); **LRMS** (CI) 217.1 ($[M+H]^+$), 433.2 ($[2M+H]^+$).

Data in accordance with literature[113]

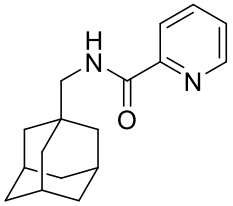
***N*-(((1*R*,2*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)picolinamide 167**



Prepared according to general amidation procedure A, using *cis*-myrtanylamine (307 mg, 2.0 mmol) and 2-picolinic acid (295 mg, 2.4 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a colourless oil (501 mg, 1.94 mmol, 97%).

ν_{max} (film/cm^{-1}) 3354 (NH), 3054 (CH), 2934 (CH), 1668 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.7 Hz, 1H, pyNC*H*), 8.18 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 8.16 – 8.01 (m, 1H, N*H*), 7.82 (td, *J* = 7.7, 1.6 Hz, 1H, pyCCHC*H*), 7.42 – 7.37 (m, 1H, pyNCHC*H*), 3.54 – 3.37 (m, 2H, NHCH_2), 2.39 – 2.28 (m, 2H, NHCH$_2$C*H*CH_2), 2.02 – 1.93 (m, 3H, NHCH$_2$CHC*H*CH_2CHCH_2), 1.90 (ddt, *J* = 7.8, 5.4, 2.5 Hz, 1H, CHCH$_2$C*H*CH$_2$), 1.89 – 1.83 (m, 1H, CHCH_2CH), 1.60 – 1.51 (m, 1H, CHCH_2CH$_2$), 1.19 (s, 3H, CH_3), 1.08 (s, 3H, CH$_3$), 0.90 (d, *J* = 9.6 Hz, 1H, NHCH$_2$CHCH_2); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.3 (C), 150.3 (C), 148.1 (CH), 137.4 (CH), 126.1 (CH), 122.3 (CH), 45.2 (CH$_2$), 44.0 (CH), 41.6 (CH), 41.5 (CH), 38.9 (C), 33.4 (CH$_2$), 28.1 (CH$_3$), 26.2 (CH$_2$), 23.3 (CH$_3$), 20.0 (CH$_2$); **LRMS** (ES) 259.2 ([M+H]$^+$), 517.3 ([2M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 259.1815 $C_{16}H_{22}N_2O$+H requires 259.1810.

***N*-(Adamantan-1-yl)methyl)picolinamide 168**

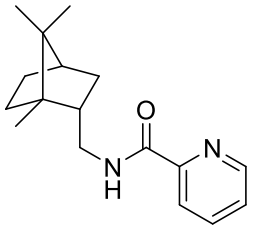


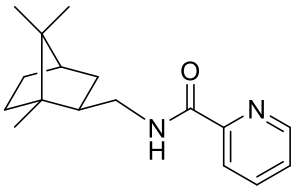
Prepared according to general amidation procedure A, using 1-adamantanemethylamine (198 mg, 1.20 mmol) and 2-picolinic acid (178 mg, 1.44 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a white solid (302 mg, 1.12 mmol, 93%).

M.p 84 – 86 °C; **ν_{max}** (film/cm^{-1}) 3386 (NH), 2969 (CH), 1669 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.7 Hz, 1H, pyNC*H*), 8.20 (m, 2H, N*H* and pyCC*H*), 7.85 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.42 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H, pyNCHC*H*), 3.17 (d, *J* = 6.7 Hz, 2H, NHCH_2), 1.99 (s, 3H, CCH$_2$C*H*), 1.71 (d, *J* = 12.2 Hz, 3H, CCH$_2$CHCH_2), 1.65 (d, *J* = 11.5 Hz, 3H, CCH$_2$CHCH_2), 1.58 (d, *J* = 2.2 Hz, 6H, CCH_2); **^{13}C NMR** (151 MHz, $CDCl_3$) δ

164.6 (C), 150.2 (C), 148.1 (CH), 137.5 (CH), 126.1 (CH), 122.4 (CH), 51.1 (CH_2), 40.4 (CH_2), 37.0 (CH_2), 34.2 (C), 28.4 (CH); **HRMS** (ES) m/z [M + H]+ found 271.1804, $C_{17}H_{22}N_2O$ requires 271.1805.

***endo-N*-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)methyl)picolinamide 158b** and ***exo-N*-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)methyl)picolinamide 158a**





Prepared according to amidation procedure A, using amine **153** and 2-picolinic acid. Purified by flash column chromatography (0 – 20% EtOAc in petrol) give the product as a mixture of *endo* and *exo* diastereoisomers. Separation of isomers was achieved using prep HPLC (performed by AZ at Gothenburg).

Endo white waxy solid.

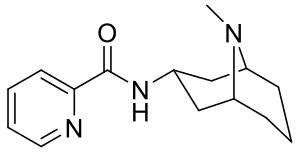
$\boldsymbol{\nu_{max}}$ (film/cm^{-1}) 3326 (NH), 2947 (CH), 2873 (CH), 1655 (CO), 1532 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.5 Hz, 1H, pyNC*H*), 8.20 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 8.07 – 7.92 (s, 1H, N*H*), 7.83 (td, *J* = 7.7, 1.6 Hz, 1H, pyCCHC*H*), 7.41 (ddd, *J* = 7.4, 4.8, 0.8 Hz, 1H, pyNCHC*H*), 3.55 (dt, *J* = 12.9, 5.3 Hz, 1H, NHCH_2), 3.45 (ddd, *J* = 13.1, 9.2, 6.0 Hz, 1H, NHCH_2), 2.09 – 1.98 (m, 2H, NHCH$_2$C*H*CH_2), 1.76 – 1.70 (m, 1H, CHCCH_2), 1.63 (t, *J* = 4.4 Hz, 1H, CH$_2$CH$_2$C*H*CH$_2$), 1.62 – 1.58 (m, 1H, CH$_2$CH_2CH), 1.42 – 1.36 (m, 1H, CH$_2$CH_2CH), 1.19 – 1.14 (m, 1H, CHCCH_2), 0.92 (dd, *J* = 11.9, 4.1 Hz, 1H, NHCH$_2$CHCH_2), 0.89 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.87 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.3 (C), 150.3 (C), 148.2 (CH), 137.5 (CH), 126.1 (CH), 122.3 (CH), 49.2 (C), 47.6 (C), 45.2 (CH), 43.7 (CH), 42.2 (CH_2), 35.2 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 19.4 (CH_3), 18.7 (CH_3), 14.9 (CH_3); **HRMS** found (ES) $[M+H]^+$ 273.1972, $C_{17}H_{24}N_2O$+H requires 273.1967.

Exo brown waxy solid.

$\boldsymbol{\nu_{max}}$ (film/cm^{-1}) 3320 (NH), 2923 (CH), 2853 (CH), 1656 (CO), 1532 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.2 Hz, 1H, pyNC*H*), 8.19 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 8.00 (s, 1H, N*H*), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.41 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H

pyNCHC*H*), 3.58 (dt, *J* = 13.2, 6.0 Hz, 1H, NHCH_2), 3.42 (ddd, *J* = 13.4, 9.8, 6.2 Hz, 1H, NHCH_2), 1.82 – 1.77 (m, 1H, NHCH$_2$C*H*), 1.75 – 1.71 (m, 2H, CH$_2$CH_2C*H*CH$_2$), 1.70 – 1.65 (m, 1H, CHCCH_2), 1.56 (m, 2H, CHCH_2CHCCH_2), 1.21 – 1.13 (m, 2H, CHCCH_2 and CHCH_2CH), 0.97 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.85 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.3 (C), 150.3 (C), 148.2 (CH), 137.5 (CH), 126.1 (CH), 122.3 (CH), 47.7 (CH), 47.6 (C), 47.3 (C), 45.2 (CH), 43.6 (CH_2), 39.7 (CH_2), 34.9 (CH_2), 27.4 (CH_2), 20.8 (CH_3), 20.8 (CH_3), 13.1 (CH_3); **HRMS** found (ES) $[M+H]^+$ 273.1969, $C_{17}H_{24}N_2O$+H requires 273.1967.

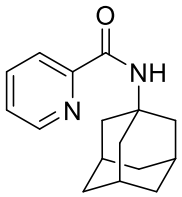
***N*-((1*R*,3*r*,5*S*)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)picolinamide 169**



Prepared according to general amidation procedure A, using 9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (154 mg, 1.0 mmol) and 2-picolinic acid (148 mg, 1.2 mmol). Purified by flash column chromatography (0 – 10% MeOH in DCM) to give the product as an off-white solid (235 mg, 0.91 mmol, 91%).

M.p >200 °C; **ν_{max}** (film/cm^{-1}) 3372 (NH), 3077 (CH), 2934 (CH), 1664 (CO), 1239 (CN); **^{1}H NMR** (600 MHz, MeOD) *δ* 8.65 (d, *J* = 4.4 Hz, 1H, pyNC*H*), 8.09 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.97 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.57 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H, pyNCHC*H*), 4.60 – 4.51 (m, 1H, NHC*H*), 3.67 (d, *J* = 10.2 Hz, 2H, CH$_3$NC*H*), 2.93 (s, 3H, NCH_3), 2.60 – 2.53 (m, 2H, NHCH_2), 2.20 (m, 3H, CH$_3$NCHCH_2), 1.99 – 1.91 (m, 2H, NHCH_2), 1.70 – 1.65 (m, 1H, CH$_3$NCHCH_2), 1.60 (d, *J* = 12.9 Hz, 2H, CHCH$_2$CH_2); **^{13}C NMR** (151 MHz, MeOD) *δ* 166.3 (C), 150.8 (C), 149.8 (CH), 138.9 (CH), 128.0 (CH), 123.2 (CH), 55.1 (CH), 39.7 (CH), 38.8 (CH_3), 31.5 (CH_2), 25.8 (CH_2), 12.9 (CH_2); **LRMS** (ES) 260.2 ([M+H]$^+$); **HRMS** found (ES) $[M+H]^+$ 260.1768 $C_{15}H_{21}N_3O$+H requires 260.1763.

***N*-(Adamantan-1-yl)picolinamide 170**

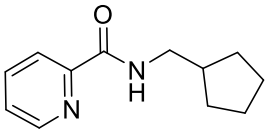


Prepared according to general amidation procedure A, using 1-amantadine (1.50 g, 9.93 mmol) and 2-picolinic acid (1.466 g, 11.9 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the amide as a white solid (1.92 g, 7.482 mmol, 75%).

M.p 117 – 118 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3350 (NH), 2904 (CH), 2847 (CH), 1668 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.51 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.17 (dt, *J* = 7.8, 1.1 Hz, 1H, pyCC*H*), 7.90 (s, 1H, N*H*), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.39 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 2.16 (d, *J* = 2.5 Hz, 6H, NHCCH_2), 2.13 (s, 3H, C*H*), 1.72 (dt, *J* = 23.7, 11.8 Hz, 6H, CHCH_2CH); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.2 (C), 151.0 (C), 147.8 (CH), 137.5 (CH), 125.9 (CH), 121.8 (CH), 51.7 (C), 41.6 (CH), 36.5 (CH_2), 29.6 (CH_2); **LRMS** (CI) 257.1 ([M+H]$^+$).

Data in accordance with literature[167]

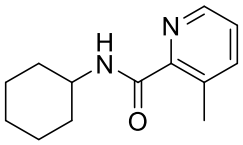
***N*-(Cyclopentylmethyl)picolinamide 186**



Prepared according to general amidation procedure A, using cyclopentylmethanamine hydrochloride (271 mg, 2.0 mmol) and picolinic acid (295 mg, 2.4 mmol). Purified by flash column chromatography (0 – 40 % EtOAc in petrol) to give the amide as a white solid (347 mg, 1.7 mmol, 85%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3374 (NH), 2984 (CH), 1661 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.57 – 8.52 (m, 1H, pyNC*H*), 8.21 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 8.18 – 8.03 (m, 1H, N*H*), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.44 – 7.39 (m, 1H, pyNCHC*H*), 3.42 (dd, *J* = 7.2, 6.2 Hz, 2H, NHCH_2), 2.19 (hept, *J* = 7.6 Hz, 1H, C*H*), 1.87 – 1.77 (m, 2H, CH_2), 1.70 – 1.63 (m, 2H, CH_2), 1.61 – 1.52 (m, 2H, CH_2), 1.36 – 1.24 (m, 2H, CH_2); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.3 (C), 150.2 (C), 148.1 (CH), 137.4 (CH), 126.1 (CH), 122.3 (CH), 44.4 (CH), 40.0 (CH_2), 30.5 (CH_2), 25.3 (CH_2); **LRMS** (CI NH_3) 205.13 ([M+H]$^+$); **HRMS** found (CI NH_3) [M+H]$^+$ 205.1335, $C_{12}H_{16}N_2O$+H requires 205.1335.

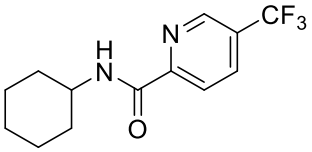
***N*-Cyclohexyl-3-methylpicolinamide 235**



Prepared according to general amidation procedure A, using cyclohexylamine (229 µl, 2.0 mmol) and 2-picolinic acid (329 mg, 2.4 mmol). Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a white solid (336 mg, 1.54 mmol, 77%).

M.p 72 – 74 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3302 (NH), 2933 (CH), 2851 (CH), 1641 (CO), 1529 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.36 (d, *J* = 3.9 Hz, 1H, pyNC*H*), 8.02 (s, 1H, N*H*), 7.56 (d, *J* = 7.6 Hz, 1H, pyNCHCHC*H*), 7.27 (dd, *J* = 7.7, 4.5 Hz, 1H, pyNCHC*H*), 3.95 – 3.87 (m, 1H, NHC*H*), 2.73 (s, 3H, CH_3), 2.02 – 1.97 (m, 2H, CHCH_2), 1.78 – 1.73 (m, 2H, $CHCH_2CH_2$), 1.66 – 1.61 (m, 1H, $CHCH_2CH_2CH_2$), 1.45 – 1.38 (m, 2H, CHCH_2), 1.30 (ddd, *J* = 15.0, 12.4, 3.4 Hz, 2H, $CHCH_2CH_2$), 1.26 – 1.19 (m, 1H, $CHCH_2CH_2CH_2$); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 165.2 (C), 147.7 (C), 145.4 (CH), 141.0 (CH), 135.5 (C), 125.6 (CH), 48.1 (CH), 33.3 (CH_2), 25.8 (CH_2), 25.1 (CH_2), 20.7 (CH_3); **HRMS** found (ES) $[M+H]^+$ 219.1495, $C_{13}H_{18}N_2O$+H requires 219.1497.

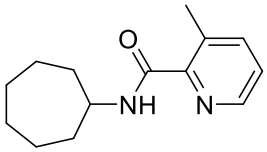
***N*-Cyclohexyl-5-(trifluoromethyl)picolinamide 239**



Prepared according to general amidation procedure A, using cyclohexylamine (229 µl, 2.0 mmol) and 5-trifluoromethylpicolinic acid (382 mg, 2.0 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a yellow oil (450 mg, 1.65 mmol, 83%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3336 (NH), 2933 (CH), 2854 (CH), 1649 (CO), 1527 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 1.4, 0.8 Hz, 1H, pyNC*H*), 8.33 (d, *J* = 8.2 Hz, 1H, CF_3CCHCH), 8.10 – 8.05 (m, 1H, CF_3CCHCH), 7.98 – 7.80 (s, 1H, N*H*), 4.01 – 3.93 (m, 1H, NHC*H*), 2.05 – 1.96 (m, 2H, NHCHCH_2), 1.79 – 1.74 (m, 2H, $CHCH_2CH_2$), 1.68 – 1.62 (m, 1H, $CHCH_2CH_2CH_2$), 1.47 – 1.40 (m, 2H, $CHCH_2CH_2$), 1.36 – 1.29 (m, 2H, NHCHCH_2), 1.24 (tt, *J* = 11.7, 4.1 Hz, 1H, $CHCH_2CH_2CH_2$); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 162.0 (C), 253.3 (C), 145.20 (q, *J* = 3.9 Hz, CH), 134.83 (q, *J* = 3.4 Hz, CH), 128.74 (q, *J* = 33.3 Hz, C), 123.35 (q, *J* = 272.7 Hz, C), 122.2 (CH), 48.5 (CH), 33.1 (C), 25.7 (C), 24.9 (C); **HRMS** found (ES) $[M+H]^+$ 273.1215, $C_{13}H_{15}N_2OF_3$+H requires 273.1215.

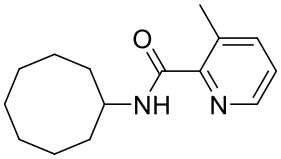
***N*-Cycloheptyl-3-methylpicolinamide 252**



Prepared according to general amidation procedure A, using cycloheptylamine (255 µl, 2.0 mmol) and 3-methylpicolinic acid (330 mg, 2.4 mmol). Purified by flash column chromatography (30% EtOAc in petrol) to give the product as a colourless oil (421 mg, 1.81 mmol, 91%).

ν_{max} (film/cm^{-1}) 3380 (NH), 2923 (CH), 2854 (CH), 1666 (CO), 1503 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.33 (d, *J* = 4.0 Hz, 1H, pyNC*H*), 8.18 – 7.98 (d, *J* = 6.6 Hz, 1H, N*H*), 7.52 (d, *J* = 7.7 Hz, 1H, CH_3CCH), 7.24 (dd, *J* = 7.7, 4.5 Hz, 1H, pyNCHC*H*), 4.06 (tt, *J* = 12.6, 6.2 Hz, 1H, NHC*H*), 2.71 (s, 3H, CH_3), 2.02 – 1.97 (m, 2H, NHCHCH_2), 1.69 – 1.49 (m, 10H, CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.9 (C), 147.7 (C), 145.5 (CH), 140.9 (CH), 135.4 (C), 125.5 (CH), 50.3 (CH), 35.2 (CH_3), 28.2 (CH_2), 24.4 (CH_2), 20.7 (CH_3); **HRMS** found (ES) $[M+H]^+$ 233.1648, $C_{14}H_{20}N_2O$+H requires 233.1654.

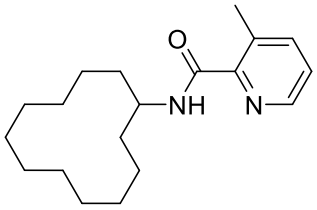
***N*-Cyclooctyl-3-methylpicolinamide 253**



Prepared according to general amidation procedure A, using cyclooctylamine (274 µl, 2.0 mmol) and 3-methylpicolinic acid (330 mg, 2.4 mmol). Purified by flash column chromatography (30% EtOAc in petrol) to give the product as a colourless oil (415 mg, 1.69 mmol, 84%).

ν_{max} (film/cm^{-1}) 3381 (NH), 2919(CH), 2851 (CH), 1667 (CO), 1501 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 2.7, 1.7 Hz, 1H, pyNC*H*), 8.10 (d, *J* = 6.6 Hz, 1H, N*H*), 7.57 – 7.52 (m, 1H, CH_3CCH), 7.26 (dd, *J* = 8.1, 4.2 Hz, 1H, pyNCHC*H*), 4.18 – 4.09 (m, 1H, NHC*H*), 2.73 (s, 3H, CH_3), 1.95 – 1.89 (m, 2H, NHCHCH_2), 1.73 – 1.64 (m, 4H, CH_2), 1.64 – 1.51 (m, 8H, CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.9 (C), 147.8 (C), 145.5 (CH), 140.9 (CH), 135.4 (C), 125.5 (CH), 49.2 (CH), 32.6 (CH_2), 27.3 (CH_2), 25.7 (CH_2), 24.0 (CH_2), 20.8 (CH_3); **HRMS** found (ES) $[M+H]^+$ 247.1810, $C_{15}H_{22}N_2O$+H requires 247.1810.

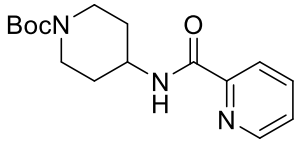
***N*-Cyclododecyl-3-methylpicolinamide 254**



Prepared according to general amidation procedure A, using cyclododecylamine (367 mg, 2.0 mmol) and 3-methylpicolinic acid (330 mg, 2.4 mmol). Purified by flash column chromatography (30% EtOAc in petrol) to give the product as a white solid (512 mg, 1.69 mmol, 85%).

M.p 89 – 90 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3348 (NH), 2926 (CH), 2844 (CH), 1644 (CO), 1519 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.38 – 8.34 (m, 1H, pyNC*H*), 8.00 (d, *J* = 8.3 Hz, 1H, N*H*), 7.56 (ddd, *J* = 7.7, 1.6, 0.7 Hz, 1H, CH_3CC*H*), 7.27 (dd, *J* = 7.8, 4.6 Hz, 1H, pyNCHC*H*), 4.24 – 4.16 (m, 1H, NHC*H*), 2.75 (s, 3H, CH_3), 1.72 (dq, *J* = 13.3, 6.8 Hz, 2H, NHCHCH_2), 1.54 – 1.30 (m, 20H, CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 165.4 (C), 147.8 (C), 145.5 (CH), 140.9 (CH), 135.4 (C), 125.5 (CH), 45.9 (CH), 30.4 (CH_2), 24.2 (CH_2), 23.9 (CH_2), 23.6 (CH_2), 23.6 (CH_2), 21.7 (CH_2), 20.8 (CH_3); **HRMS** found (ES) $[M+H]^+$ 303.2434, $C_{19}H_{30}N_2O$+H requires 303.2437.

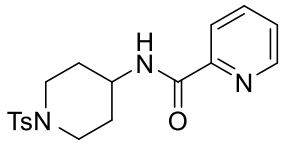
***tert*-Butyl 4-(picolinamido)piperidine-1-carboxylate 256**



Prepared according to general amidation procedure A, using 4-amino-1-Boc-piperidine (1.00 g, 5.0 mmol) and 2-picolinic acid (738 mg, 6.0 mmol). Purified by flash column chromatography (20 – 40% EtOAc in petrol) to give the amide as a white solid (1.32 g, 4.33 mmol, 87%).

M.p 105 – 107 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3259 (NH), 2977 (CH), 2840 (CH), 1698 (CO), 1651 (CO), 1529 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, ArNC*H*), 8.19 (dt, *J* = 7.8, 1.1 Hz, 1H, ArCC*H*), 7.98 (d, *J* = 8.0 Hz, 1H, N*H*), 7.84 (tt, *J* = 7.7, 2.5 Hz, 1H, ArCCHC*H*), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, ArNCHC*H*), 4.16 – 4.00 (m, 3H, NHC*H,* NCH_2), 2.96 (s, 2H, NCH_2), 2.02 – 1.98 (m, 2H, CHCH_2), 1.46 (s, 11H, C(CH_3)$_3$ and CHCH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.7 (C), 154.9 (C), 150.0 (C), 148.2 (CH), 137.5 (CH), 126.3 (CH), 122.4 (CH), 79.8 (C), 46.8 (CH), 42.8 (CH_2), 32.1 (CH_2), 28.6 (CH_3); **HRMS** found (ES) $[M+H]^+$ 306.1817, $C_{16}H_{23}N_3O_3$+H requires 306.1618.

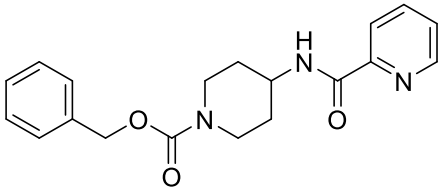
_N_-(1-Tosylpiperidin-4-yl)picolinamide



A solution of *tert*-Butyl 4-(picolinamido)piperidine-1-carboxylate (382 mg, 1.25 mmol) in DCM (3 ml) and TFA (1 ml) was stirred at room temperature for 30 minutes. Saturated $NaHCO_3$ (50 ml) and DCM (50 ml) were added, and the pH of the aqueous layer adjusted to pH ~ 12 using NaOH (1 M). The layers were separated and the aqueous layer washed with DCM (2 × 30 ml). The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated to give the free amine (169 mg, 0.823 mmol, 66%). The crude residue was dissolved in DCM (3.2 ml) and pyridine (133 µl 1.646 mmol, 2 eq), and a solution of TsCl (188 mg, 0.988 mg, 1.2 eq) in DCM (2 ml) was added dropwise. The resulting solution was stirred at room temperature for 5 hours. The reaction mixture was diluted with DCM and water and the layers separated. The aqueous layer was washed with DCM (2 × 30 ml), and the combined organic fractions washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (60% EtOAc in petrol) to give the title compound as a white solid (101 mg, 0.281 mmol, 34%).

M.p 191 – 193 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3379 (NH), 2958 (CH), 2860 (CH), 1670 (CO), 1518 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.54 (tdd, *J* = 4.8, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.20 – 8.13 (m, 1H, pyCC*H*), 7.97 (s, 1H, N*H*), 7.85 (dtd, *J* = 20.0, 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.70 – 7.62 (m, 2H, SO_2CC*H*), 7.44 (dddd, *J* = 13.6, 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 7.34 (dd, *J* = 8.5, 0.6 Hz, 2H, CH_3CC*H*), 3.89 (tdt, *J* = 12.3, 8.3, 4.1 Hz, 1H, NHC*H*), 3.80 (dd, *J* = 9.4, 3.0 Hz, 2H, NCH_2), 2.48 (td, *J* = 12.1, 2.6 Hz, 2H, NCH_2), 2.45 (s, 3H, ArCH_3), 2.20 – 2.05 (m, 2H, NHCHCH_2), 1.73 – 1.66 (m, 2H, NHCHCH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.8 (C), 149.7 (C), 148.2 (CH), 143.8 (C), 137.5 (CH), 133.1 (C), 129.9 (CH), 127.8 (CH), 126.5 (CH), 122.3 (CH), 46.1 (CH), 45.5 (CH_2), 31.6 (CH_2), 21.7 (CH_3); **HRMS** found (ES) $[M+H]^+$ 360.1367, $C_{18}H_{21}N_3O_3S$+H requires 360.1376.

Benzyl 4-(picolinamido)piperidine-1-carboxylate

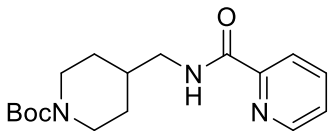


A solution of *tert*-Butyl 4-(picolinamido)piperidine-1-carboxylate (382 mg, 1.25 mmol) in DCM (4 ml) and TFA (1 ml) was stirred at room temperature for 30 minutes. The reaction mixture

was concentrated. The residue was taken up in DCM (25 ml) and water (25 ml), and the pH of the aqueous layer adjusted to pH ~ 12 using NaOH (1 M). The layers were separated, and the aqueous layer washed with DCM (2 × 30 ml). The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated to give the unprotected piperidine (218 mg, 1.06 mmol, 68%). CBz-Cl (284 µl, 2.0 mmol, 2.0 eq) was added dropwise to a suspension of the piperidine and Na_2CO_3 (233 mg, 2.2 mmol. 2.2 eq) in H_2O (3.8 ml) and THF (2 ml), and the mixture stirred for 5 hours. DCM (30 ml) and water (30 ml) were added and the layers separated. The aqueous layer was extracted with DCM (2 × 30 ml) and the combined organic fractions washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (40% EtOAc in petrol) to give the product as a white solid (250 mg, 0.74 mmol, 74%).

M.p 105 – 107 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3344 (NH), 2948 (CH), 2863 (CH), 1682 (CO), 1651 (CO), 1523 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.55 – 8.50 (m, 1H, pyNC*H*), 8.21 – 8.16 (m, 1H, PyCC*H*), 8.04 – 7.93 (m, 1H, N*H*), 7.85 – 7.82 (m, 1H, pyCCHC*H*), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 7.38 – 7.29 (m, 5H, Ar*H*), 5.14 (s, 2H, OCH_2), 4.23 – 4.08 (m, 3H, NHC*H* and NCH_2), 3.00 (br s, 2H, NCH_2), 2.06 – 2.00 (m, 2H, NCH_2CH_2), 1.54 (m, 2H, NCH_2CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.7 (C), 155.4 (C), 149.9 (C), 148.2 (CH), 137.6 (CH), 136.9 (C), 128.7 (CH), 128.2 (C), 128.0 (CH), 126.4 (CH), 122.4 (CH), 67.3 (CH_2), 46.6 (CH), 43.0 (CH_2), 32.1 (CH_2); **HRMS** found (ES) $[M+H]^+$ 340.1651, $C_{19}H_{21}N_3O_3$+H requires 340.1656

***tert*-Butyl 4-(picolinamidomethyl)piperidine-1-carboxylate 421**

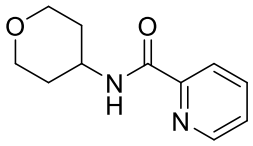


Prepared according to general amidation procedure A, using 2-picolinic acid (738 mg, 6.0 mmol) and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (1.07 g, 5.0 mmol). Purified by flash column chromatography (30 – 50% EtOAc in petrol) to give the product as a white solid (1.10 g, 3.45 mmol, 69%).

M.p 118 – 120 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3373 (NH), 2931 (CH), 2865 (CH), 1681 (CO), 1666 (CO), 1514 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.54 – 8.49 (m, 1H, NC*H*), 8.20 – 8.13 (m, 2H, N*H* and NCC*H*), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H, NCCHC*H*), 7.43 – 7.39 (m, 1H, NCHC*H*), 4.22 – 3.97 (s, 2H, NHCH_2), 3.36 (s, 2H, BocNCH_2), 2.68 (s, 2H, BocNCH_2), 1.82 – 1.75 (m, 1H, $NHCH_2CH$), 1.73 (d, *J* = 12.8 Hz, 2H, $BocNCH_2CH_2$), 1.44 – 1.41 (m, 9H), 1.24 – 1.16 (m,

2H, BocNCH$_2$C*H*$_2$); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.6 (C), 154.9 (C), 150.0 (C), 148.2 (CH), 137.5 (CH), 126.3 (CH), 122.4 (CH), 79.5 (C), 44.9 (CH_2), 43.7 (CH_2), 36.7 (CH), 30.0 (CH_2), 28.6 (CH_3); **HRMS** found (ESI) $[M+H]^+$ 320.1971, $C_{17}H_{25}N_3O_3$+H requires 320.1969.

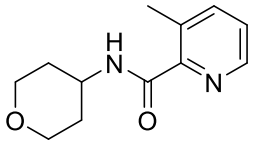
_N_-(tetrahydro-2_H_-pyran-4-yl)picolinamide 259



Prepared according to general amidation procedure A, using 4-aminotetrahydropyran (110 mg, 1 mmol) and 2-picolinic acid (148 mg, 1.2 mmol). Purified using 0 - 2% methanol in DCM to give the amide as a sticky white solid (179 mg, 0.87 mmol, 87%).

ν_{max} (film/cm^{-1}) 3398 (NH), 2954 (CH), 2838 (CH), 1648 (CO), 1522 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.58 – 8.53 (m, 1H, ArNC*H*), 8.20 (d, *J* = 7.8 Hz, 1H, ArCC*H*), 7.99 (s, 1H, N*H*), 7.86 (td, *J* = 7.7, 1.7 Hz, 1H, ArCC*H*), 7.44 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, ArNCHC*H*), 4.20 (tdt, *J* = 12.6, 8.5, 4.3 Hz, 1H, NHC*H*), 4.01 (dt, *J* = 12.0, 3.4 Hz, 2H, OC*H*$_2$), 3.56 (td, *J* = 11.7, 2.2 Hz, 2H, OC*H*$_2$), 2.00 (dd, *J* = 12.6, 2.2 Hz, 2H, OCH$_2$C*H*$_2$), 1.69 – 1.63 (m, 2H, OCH$_2$C*H*$_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.7 (C), 150.0 (CH), 148.1 (CH), 137.5 (CH), 126.3 (CH), 122.4 (CH), 66.9 (CH_2), 45.8 (CH), 33.2 (CH_2); **LRMS** (CI NH_3) 207.11 ([M+H]$^+$); **HRMS** found (CI NH_3) $[M+H]^+$ 207.1128, $C_{11}H_{14}N_2O_2$+H requires 207.1128.

3-methyl-_N_-(tetrahydro-2H-pyran-4-yl)picolinamide 262

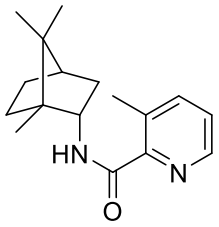


Prepared according to general amidation procedure A, using 4-aminotetrahydropyran (101 mg, 1.0 mmol) and 3-methylpicolinic acid (165 mg, 1.2 mmol). Purified by flash column chromatography (0 - 30% EtOAc in petrol) to give the product as colourless oil (91 mg, 0.41 mmol, 41%).

ν_{max} (film/cm^{-1}) 3380 (NH), 2964 (CH), 2877 (CH), 1664 (CO), 1512 (CC), 1156 (CO); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.38 – 8.32 (m, 1H, pyNC*H*), 8.15 – 8.00 (s, 1H, N*H*), 7.55 (dd, *J* = 7.7, 0.8 Hz, 1H, CH_3CC*H*), 7.29 – 7.24 (m, 1H, pyNCHC*H*), 4.15 – 4.07 (m, 1H, NHC*H*),

3.99 – 3.94 (m, 2H, OCH_2), 3.51 (td, *J* = 11.6, 2.2 Hz, 2H, OCH_2), 2.70 (d, *J* = 8.4 Hz, 3H, CH_3), 1.98 – 1.92 (m, 2H, OCH_2CH_2), 1.64 – 1.56 (m, 2H, OCH_2CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 165.4 (C), 147.2 (C), 145.5 (CH), 141.0 (CH), 135.6 (C), 125.8 (CH), 67.0 (CH_2), 45.6 (CH), 33.2 (CH_2), 20.7 (CH_3); **HRMS** found (ES) $[M+H]^+$ 221.1288, $C_{12}H_{16}N_2O_2$+H requires 221.1290.

3-Methyl-*N*-((1*S*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 232

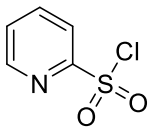


Prepared according to general amidation procedure A, using *R*-(+)-bornylamine (61 mg, 0.40 mmol) and 3-methylpicolinic acid (66 mg, 0.48 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a colourless oil (82 mg, 0.30 mmol, 75%).

$[\alpha]_D^{24}$ +4.67 (*c* = 0.3, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3384 (NH), 2976 (CH), 2876 (CH), 1666 (CO), 1506 (CC); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.42 – 8.39 (m, 1H, pyNC*H*), 8.31 (d, *J* = 8.6 Hz, 1H, N*H*), 7.57 (t, *J* = 7.7 Hz, 1H, pyNCHCHC*H*), 7.29 (dd, *J* = 7.7, 4.6 Hz, 1H, pyNCHC*H*), 4.43 – 4.35 (m, 1H, NHC*H*), 2.74 (s, 3H, ArCH_3), 2.46 – 2.37 (m, 1H, NHCHCH_2), 1.85 – 1.78 (m, 1H, CHCH_2CH_2), 1.73 – 1.68 (m, 2H, CH_2CH_2C*H*), 1.46 – 1.40 (m, 1H CH_2CH_2CH), 1.34 – 1.28 (m, 1H, CHCH_2CH_2), 1.01 (s, 3H, CH_3), 0.97 (dd, *J* = 13.4, 4.6 Hz, 1H, NHCHCH_2), 0.91 (s, 3H, CH_3), 0.88 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 166.1 (C), 147.6 (C), 145.5 (CH), 141.0 (CH), 135.5 (C), 125.6 (CH), 53.6 (CH), 49.9 (C), 48.3 (C), 45.2 (CH), 37.7 (CH_2), 28.8 (CH_2), 28.3 (CH_2), 20.9 (CH_3), 20.0 (CH_3), 18.8 (CH_3), 13.9 (CH_3). **LRMS** (CI NH_3) 273.20 ($[M+H]^+$); **HRMS** found (CI NH_3) $[M+H]^+$ 273.1961, $C_{17}H_{24}N_2O$+H requires 273.1961.

6.2.1 Synthesis of sulphonamides

Pyridine-2-sulphonyl chloride 172



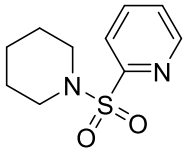
2-mercaptopyridine (1.25 g, 11.3 mmol) was dissolved in concentrated H_2SO_4 (31.3 ml) and cooled to -10 ˚C. Sodium hypochlorite solution (78.8 ml, 5% Cl) was added dropwise over 4

hours and the mixture maintained at -10 °C for a further 30 minutes. Water (50 ml) was added and the mixture extracted with DCM (3 x 50 ml). The combined organic fractions were washed with sat. $NaHCO_3$ (50 ml), water (50 ml), dried over $MgSO_4$ and concentrated to give the product as a colourless oil (1.12 g, 6.31 mmol, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (dt, *J* = 5.8, 3.0 Hz, 1H, Ar*H*), 8.09 – 8.04 (m, 2H, Ar*H*), 7.72 – 7.66 (m, 1H, Ar*H*).

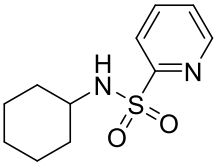
[Compound hydrolysed before further data could be collected.]

2-(Piperidin-1-ylsulphonyl)pyridine 173



A solution of pyridine-2-sulphonyl chloride (511 mg, 2.88 mmol, 1.2 eq) in MeCN (20 ml) was cooled to 0 °C. Piperidine (0.20 ml, 2.40 mmol, 1 eq) was added to the solution followed by the dropwise addition of NEt_3 (0.40 ml, 2.88 mmol, 1.2 eq). The resulting solution was allowed to warm to room temperature and stirred for 16 hours, before being concentrated. The crude residue was purified by flash column chromatography (0 – 60% ethyl acetate in petrol) to yield the title compound as a white solid (501 mg, 2.21 mmol, 92%).
M.p 60.7 – 62.3 °C; $\mathbf{v_{max}}$ (film/cm^{-1}) 3054 (CH), 2947 (CH), 1264 (SO), 1118 (SO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.71 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H, pyNC*H*), 7.95 – 7.86 (m, 2H, pyCC*H*C*H*), 7.48 (ddd, *J* = 7.4, 4.7, 1.4 Hz, 1H, pyNCHC*H*), 3.31 – 3.23 (m, 4H, NCH_2), 1.63 (dt, *J* = 11.4, 5.9 Hz, 4H, NCH_2CH_2), 1.52 – 1.45 (m, 2H, $NCH_2CH_2CH_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.8 (C), 150.1 (CH), 137.9 (CH), 126.5 (CH), 123.1 (CH), 47.5 (CH_2), 25.5 (CH_2), 23.8 (CH_2); **LRMS** (ES) 227.1 ([M+H]$^+$) 475.1 ([2M+Na]$^+$); **HRMS** found (ES) [M+H]$^+$ 227.0848 $C_{10}H_{14}N_2O_2$+H requires 227.0849.

***N*-Cyclohexylpyridine-2-sulphonamide 174**

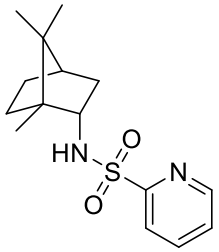


A solution of pyridine-2-sulphonyl chloride (511 mg, 2.88 mmol, 1.2 eq) in MeCN (20 ml) was cooled to 0 °C. Cyclohexylamine (0.27 ml, 2.40 mmol, 1 eq) was added to the solution followed by the dropwise addition of NEt_3 (0.40 ml, 2.88 mmol, 1.2 eq). The resulting solution

was allowed to warm to room temperature and stirred for 16 hours, before being concentrated. The crude residue was purified by flash column chromatography (0 – 60% ethyl acetate in petrol) to yield the title compound as a white solid (513 mg, 2.13 mmol, 89%).

M.p 87 – 89 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3056 (CH), 2937 (CH), 2859 (CH), 1333 (SO), 1175 (SO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.71 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H, ArNC*H*), 8.02 (dt, *J* = 7.8, 1.0 Hz, 1H, ArCC*H*), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H, ArCCHC*H*), 7.49 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H, ArNCHC*H*), 5.01 (d, *J* = 7.4 Hz, 1H, N*H*), 3.25 (qd, *J* = 10.1, 4.1 Hz, 1H, NHC*H*), 1.80 – 1.73 (m, 2H, NHCHCH_2), 1.67 – 1.60 (m, 2H, CHCH_2CH_2), 1.54 – 1.46 (m, 1H, CHCH_2CH_2CH_2), 1.27 – 1.07 (m, 5H, Cy*H*); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 158.7 (C), 150.1 (CH), 138.1 (CH), 126.6 (CH), 122.0 (CH), 53.3 (CH), 34.0 (CH_2), 25.2 (CH_2), 24.7 (CH_2); **LRMS** (ES) 241.1 ([M+H]$^+$), 503.2 ([2M+Na]$^+$); **HRMS** found (ES) [M+H]$^+$ 241.1004, $C_{11}H_{16}N_2O_2S$+H requires 241.1004.

***N*-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)pyridine-2-sulphonamide 175**

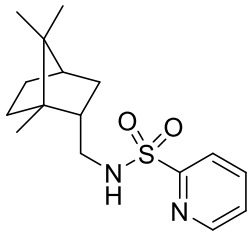


A solution of pyridine-2-sulphonyl chloride (169 mg, 0.95 mmol, 1.2 eq) in MeCN (6 ml) was cooled to 0 °C. Endo-(+/-)-Bornylamine hydrochloride (150 mg, 0.79 mmol, 1 eq) was added to the solution followed by the dropwise addition of NEt_3 (0.33 ml, 2.37 mmol, 3 eq). The resulting solution was allowed to warm to room temperature and stirred for 16 hours, before being concentrated. The crude residue was purified by flash column chromatography (0 – 60% ethyl acetate in petrol) to yield the title compound as a white solid (32 mg, 0.11 mmol, 14%).

M.p 153 – 155 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3019 (CH), 1214 (SO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.74 – 8.69 (m, 1H, ArNC*H*), 8.01 (dt, *J* = 7.8, 0.9 Hz, 1H, ArCC*H*), 7.93 – 7.88 (m, 1H, ArCCHC*H*), 7.48 (ddd, *J* = 7.5, 4.7, 1.0 Hz, 1H, ArNCHC*H*), 4.87 (d, *J* = 8.9 Hz, 1H, N*H*), 3.56 – 3.45 (m, 1H, NHC*H*), 1.98 – 1.90 (m, 1H, NHCHC*H*), 1.72 (ddd, *J* = 16.2, 8.3, 3.9 Hz, 1H, HNHCHCCH_2), 1.55 (dt, *J* = 13.7, 4.6 Hz, 2H, CH_2CHCH_2, $CH_2CHCH_2CH_2$), 1.39 (dd, *J* = 20.0, 8.1 Hz, 1H, NHCHCCH_2), 1.17 – 1.10 (m, 1H, $CH_2CHCH_2CH_2$), 0.85 (d, *J* = 4.0 Hz,

C*H*$_3$), 0.80 (s, 3H, C*H*$_3$), 0.79 (s, 3H, C*H*$_3$), 0.78 – 0.74 (m, 1H, NHCHC*H*); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 158.3 (C), 150.2 (CH), 138.0 (CH), 126.6 (CH), 122.2 (CH), 59.3 (CH), 49.4 (C), 47.8 (C), 44.8 (CH), 38.0 (CH_2), 28.2 (CH_2), 27.7 (CH_2), 19.9 (CH_3), 18.6 (CH_3), 13.1 (CH_3); **LRMS** (ES) 295.2 ([M+H]$^+$) 611.3 ([2M+Na]$^+$); **HRMS** found (ES) [M+H]$^+$ 295.1477, $C_{15}H_{22}N2O_2S$+H requires 295.1475.

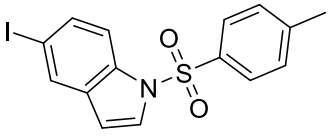
1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)methyl)pyridine-2-sulphonamide 176



A solution of pyridine-2-sulphonyl chloride (156 mg, 0.88 mmol, 1.2 eq) in MeCN (6 ml) was cooled to 0 °C. Amine **153** (150 mg, 0.74 mmol, 1 eq) was added to the solution followed by the dropwise addition of NEt_3 (0.31 ml, 2.21 mmol, 3 eq). The resulting solution was allowed to warm to room temperature and stirred for 16 hours, before being concentrated. The crude residue was purified by flash column chromatography (0 – 60% ethyl acetate in petrol) to yield the title compound as a white solid (73 mg, 0.24 mmol, 32%).

M.p 175 – 177 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 2948 (CH), 2927 (CH), 1311 (SO), 1176 (SO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.72 (dt, *J* = 7.3, 3.2 Hz, 1H, pyNC*H*), 8.04 – 7.99 (m, 1H, pyCC*H*), 7.95 – 7.91 (m, 1H, pyCCHC*H*), 7.50 (dtd, *J* = 5.9, 4.8, 1.1 Hz, 1H, pyNCHC*H*), 4.90 (s, 1H, N*H*), 3.17 – 3.10 (m, 1H, NHCH_2), 2.97 – 2.89 (m, 1H, NHCH_2), 1.93 (ddd, *J* = 12.6, 7.9, 4.0 Hz, 1H, CHCH_2CH), 1.84 – 1.76 (m, 1H, NHCH$_2$C*H*), 1.69 – 1.62 (m, 1H, CHCCH_2), 1.58 (t, *J* = 4.6 Hz, 1H, CH$_2$C*H*CH$_2$), 1.34 – 1.24 (m, 2H, CHCH_2CH$_2$), 1.04 – 0.97 (m, 1H, CHCCH_2), 0.82 (s, 3H, C*H*$_3$), 0.79 (s, 3H, C*H*$_3$), 0.78 (s, 3H, C*H*$_3$), 0.76 (dd, *J* = 8.7, 3.9 Hz, 1H, CHCH_2-CH); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.5 (C), 150.2 (CH), 138.2 (CH), 126.7 (CH), 122.4 (CH), 49.2 (C), 47.5 (C), 46.7 (CH_2), 45.0 (CH), 43.7 (CH), 35.0 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 19.2 (CH_3), 18.5 (CH_3), 14.7 (CH_3); **LRMS** (ES) 302.2 ([M+H]$^+$) 639.3 ([2M+Na+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 309.1635 $C_{16}H_{24}N_2O_2S$+H requires 309.1631.

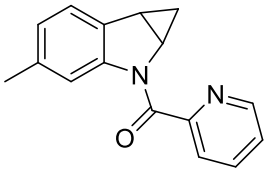
5-Iodo-1-tosyl-1*H*-indole[168] 200



A solution of 5-iodoindole (1.22 g, 5.0 mmol, 1 eq) in DMF (3.1 ml) was added dropwise over 10 minutes to a suspension of sodium hydride (60% dispersion in mineral oil, 300 mg, 7.5 mmol, 1.5 eq) in DMF (6.25 ml) at 0 °C. After 30 minutes tosyl chloride (1.15 g, 6.0 mmol, 1.2 eq) in DMF (3.1 ml) was added dropwise, the mixture was then allowed to warm to room temperature and stirred for 2 hours. The mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (3 × 20 ml) and the combined organic fractions washed with saturated $NaHCO_3$ (aq), brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (0 – 20% EtOAc in petrol) to yield the product as a white solid (1.32 g, 4.88 mmol, 98%).

M.p 139 – 141 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3374 (CH), 3116 (CH), 1523 (CC), 1368 (SO), 1166 (SO), 571 (CI); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.88 – 7.86 (m, *J* = 1.3 Hz, 1H, Ar*H*), 7.77 – 7.74 (m, *J* = 7.6, 5.2 Hz, 2H, Ar*H*), 7.74 – 7.72 (m, 1H, Ar*H*), 7.57 (dd, *J* = 8.7, 1.7 Hz, 1H, Ar*H*), 7.53 (d, *J* = 3.7 Hz, 1H, Ar*H*), 7.23 (d, *J* = 8.0 Hz, 2H, Ar*H*), 6.58 (d, *J* = 3.7 Hz, 1H Ar*H*), 2.35 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.4 (C), 145.4 (C), 135.1 (C), 134.2 (C), 133.2 (C), 130.4 (CH), 130.1 (CH), 127.3 (CH), 126.9 (CH), 115.5 (CH), 108.1 (CH), 87.6 (C), 21.7 (CH_3).

(4-methyl-1a,6b-dihydrocyclopropa[b]indol-2(1H)-yl)(pyridin-2-yl)methanone 177



A solution of amide **161** (112 mg, 0.44 mmol, 1 eq), $Pd(OAc)_2$ (5 mg, 0.022 mmol, 5 mol%), $PhI(OAc)_2$ (156 mg, 0.48 mmol, 1.1 eq) in Ac_2O (1.7 ml) and AcOH (1.7 ml) was stirred at 100 °C for 16 h. The reaction mixture was cooled and the solvent removed *in vacuo*. The residue was dissolved in DCM (20 ml) and sat. aq. $NaHCO_3$ (30 ml). The layers were separated and the aqueous extracted with DCM (3 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (10 – 50 % EtOAc in petrol) to give the product as a brown oil (24 mg, 0.096 mmol, 22%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 2991 (CH), 2903 (CH), 1634 (CO), 1515 (CC); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.73 – 8.67 (m, 1H, pyNC*H*), 8.17 (s, 1H, CH_3C*H*C), 7.88 (td, *J* = 16.3, 7.5 Hz, 2H, pyCC*HCH*), 7.48 – 7.39 (m, 1H, pyNCHC*H*), 7.21 (d, *J* = 7.1 Hz, 1H, CH_3CCHC*H*), 6.88 (d, *J*

= 7.4 Hz, 1H, CH_3CCHCH), 4.48 (s, 1H, NC*H*), 2.67 – 2.62 (m, 1H, ArC*H*), 2.37 (s, 3H, ArCH_3), 1.04 (dd, *J* = 13.3, 6.3 Hz, 1H, CH_2), 0.49 (s, 1H, CH_2); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.7 (C), 154.4 (C), 148.54 (C), 148.50 (CH), 142.2 (C), 138.0 (CH), 137.2 (CH), 132.0 (C), 125.2 (CH), 124.3 (CH), 123.6 (CH), 119.2 (CH), 40.8 (CH), 21.8 (CH_3), 20.1 (CH), 13.4 (CH_2); **LRMS (**ES) 251.1 ($[M+H]^+$) 501.2 ($[2M+H]^+$);

6.X Arylation reactions

General procedures for the arylation of picolinamides

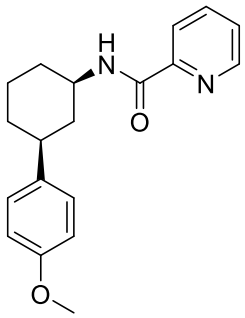
General arylation procedure A

A tube was charged with a picolinamide (1 eq), $CuBr_2$ (10 mol%), $Pd(OAc)_2$ (5 mol%), CsOAc (4 eq), *t*AmOH (1 M) and an aryl iodide or bromide (4 eq). The tube was sealed with a PTFE lined cap and heated to 140 °C for 24 hours. The reaction mixture was then cooled and filtered through a pad of Celite®, washing with EtOAc. The filtrate was concentrated *in vacuo* and the resulting crude residue purified by flash column chromatography.

General arylation procedure B

A tube was charged with a picolinamide (1 eq), $CuBr_2$ (10 mol%), $Pd(OAc)_2$ (5 mol%), CsOAc (4 eq), *t*HxOH (1 M) and an aryl iodide (4 eq). The tube was sealed with a PTFE lined cap and heated to 130 or 140 °C for 24 hours. The reaction mixture was then cooled and filtered through a pad of Celite®, washing with EtOAc. The filtrate was concentrated *in vacuo* and the resulting crude residue purified by flash column chromatography.

N-(3-(4-Methoxyphenyl)cyclohexyl)picolinamide 184

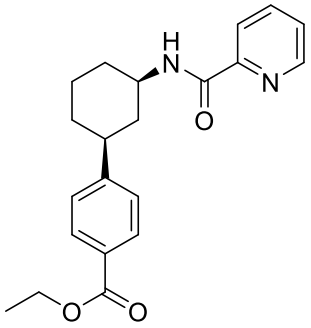


Prepared according to general arylation procedure A, using *N*-cyclohexylpicolinamide (97 mg, 0.50 mmol) and 4-iodoanisole (498 mg, 2.0 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a colourless oil (105 mg, 0.36 mmol, 68%).

ν_{max} (film/cm^{-1}) 3380 (NH), 3057 (CH), 2998 (CH), 2928 (CH), 2854 (CH), 1666 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.53 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H, pyNC*H*), 8.20 (dt, *J* = 7.8, 1.0 Hz, 1H, pyCC*H*), 7.97 (d, *J* = 8.5 Hz, 1H, N*H*), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 7.16 – 7.12 (m, 2H, OCCHC*H*), 6.85 – 6.81 (m, 2H, OCC*H*), 4.12 (tdt, *J* = 12.2, 8.3, 4.0 Hz, 1H, NHC*H*), 3.78 (s, 3H, OCH_3), 2.69 (tt, *J* = 12.2, 3.3 Hz, 1H, ArC*H*), 2.28 – 2.22 (m, 1H, CHCH_2CH), 2.15 (d, *J* = 12.3 Hz, 1H, NHCHCH_2CH$_2$), 1.98 – 1.92 (m, 1H, ArCHCH$_2$CH_2), 1.92 – 1.86 (m, 1H, ArCHCH_2CH$_2$), 1.63 – 1.54 (m, 1H, ArCHCH$_2$CH_2), 1.45 – 1.28 (m, 3H, Cy*H*); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.4 (C), 158.0 (C), 150.2 (C), 148.1 (CH), 138.6 (C), 137.5 (CH), 127.7 (CH), 126.2 (CH), 122.4 (CH), 113.9 (CH), 55.4 (CH_3), 48.9 (CH), 42.4 (CH), 41.2 (CH_2), 33.6 (CH_2), 32.9 (CH_2), 25.3 (CH_2).

Data in accordance with literature[50]

Ethyl 4-(3-(picolinamide)cyclohexyl)benzoate 185



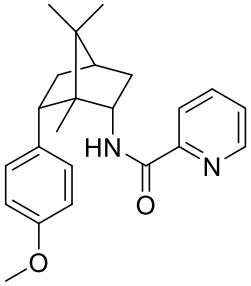
Prepared according to general arylation procedure A, using *N*-cyclohexylpicolinamide (97 mg, 0.50 mmol) and ethyl-4-iodobenzoate (550 mg, 2.0 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a colourless oil (126 mg, 0.36 mmol, 72%).

ν_{max} (film/cm^{-1}) 3371 (NH), 2927 (CH), 2858 (CH), 1711 (CO), 1655 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.55 – 8.51 (m, 1H, pyNC*H*), 8.19 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.97 (m, 3H, OCOCC*H* and N*H*), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H, pyNCHCHC*H*), 7.43 – 7.39 (m, 1H, pyNCHC*H*), 7.28 (d, *J* = 8.2 Hz, 2H, CyCC*H*), 4.35 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.14 (tdt, *J* = 12.2, 8.3, 4.0 Hz, 1H, NHC*H*), 2.80 (tt, *J* = 12.2, 3.2 Hz, 1H, ArC*H*), 2.29 (d, *J* = 12.4 Hz, 1H, NHCHCH_2CH), 2.16 (d, *J* = 12.4 Hz, 1H, CHCH_2CH$_2$), 2.01 – 1.95 (m, 1H, NHCHCH$_2$CH_2), 1.92 (d, *J* = 12.9 Hz, 1H, ArCHCH_2CH$_2$), 1.61 (qt, *J* = 13.2, 3.4 Hz, 1H, NHCHCH$_2$CH_2), 1.50 – 1.34 (m, 6H, NHCH_2CH$_2$ and OCH$_2$CH_3 and CHCH_2CH and ArCHCH_2CH$_2$); **^{13}C NMR** (151

MHz, $CDCl_3$) δ 166.7 (C), 163.5 (C), 151.5 (C), 150.1 (C), 148.1 (CH), 137.5 (CH), 129.9 (CH), 128.6 (C), 126.9 (CH), 126.2 (CH), 122.4 (CH), 60.9 (CH_2), 48.7 (CH), 43.3 (CH), 40.5 (CH_2), 33.1 (CH_2), 32.8 (CH_2), 25.2 (CH_2), 14.5 (CH_3).

Data in accordance with literature[50]

_N_-((1_S_,2_S_,4_R_,6_S_)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 191

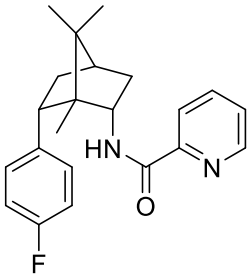


Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol) or 4-bromoanisole (50 µl, 0.40 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a white solid; 339 mg, 0.091 mmol, 91% (aryl iodide); 34 mg, 0.093 mmol, 93% (aryl bromide).

M.p 113 – 115 °C; **$[\alpha]_D^{18}$** +43.2 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3366 (NH), 2953 (CH), 2928 (CH), 1672 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.21 – 8.18 (m, 1H, pyNC*H*), 7.95 (dt, *J* = 7.8, 1.0 Hz, 1H, pyCC*H*), 7.74 (d, *J* = 9.2 Hz, 1H, N*H*), 7.68 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.35 (d, *J* = 8.4 Hz, 2H, OCCHC*H*), 7.26 (ddd, *J* = 7.6, 4.7, 1.4 Hz, 1H, pyNCHC*H*), 6.90 (d, *J* = 8.8 Hz, 2H, OCC*H*), 4.49 (dddd, *J* = 11.3, 9.3, 6.0, 1.9 Hz, 1H, NHC*H*), 3.79 (s, 3H, OCH_3), 3.29 (dd, *J* = 11.8, 4.8 Hz, 1H, ArC*H*), 2.58 – 2.50 (m, 1H, NHCHCH_2), 2.27 – 2.19 (m, 1H, ArCHCH_2), 2.00 (dt, *J* = 12.2, 6.1 Hz, 1H, ArCHCH_2), 1.92 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.28 – 1.24 (m, 1H, NHCHCH_2), 1.08 (d, *J* = 5.6 Hz, 6H, 2 × CH_3), 1.05 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.5 (C), 158.2 (C), 149.9 (C), 147.5 (CH), 136.9 (CH), 133.8 (C), 129.8 (CH), 125.7 (CH), 121.8 (CH), 114.5 (CH), 55.3 (CH_3), 54.5(CH), 53.8 (C), 51.0 (C), 46.8 (CH), 43.7 (CH), 36.9 (CH_2), 32.9 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 13.8 (CH_3); **LRMS** (CI) 365.2 ($[M+H]^+$), 729.0 ($[2M+H]^+$).

Data in accordance with literature[113]

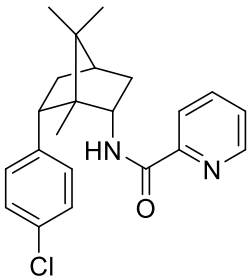
***N*-((1*S*,2*S*,4*R*,6*S*)-6-(4-Fluorophenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 192**



Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 4-iodofluorobenzene (46 µl, 0.40 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as an off-white solid (30 mg, 0.085 mmol, 85%).

M.p 112 – 115 °C; **$[\alpha]_D^{18}$** +24.6 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3364 (NH), 3064 (CH), 2954 (CH), 2924 (CH), 1667 (CO), 1508 (CC); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.26 (ddd, *J* = 4.7, 1.5, 0.9 Hz, 1H, pyNC*H*), 7.96 (dt, *J* = 7.8, 1.0 Hz, 1H, pyCC*H*), 7.70 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.61 (d, *J* = 8.8 Hz, 1H, N*H*), 7.40 (dd, *J* = 8.4, 5.4 Hz, 2H, FCC*H*), 7.29 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H, pyNCHC*H*), 7.04 (t, *J* = 8.8 Hz, 2H, FCCHC*H*), 4.50 (dddd, *J* = 11.4, 9.4, 6.0, 1.9 Hz, 1H, NHC*H*), 3.32 (dd, *J* = 11.8, 5.6 Hz, 1H, ArC*H*), 2.59 – 2.52 (m, 1H, NHCHCH_2), 2.31 – 2.24 (m, 1H, ArCHCH_2), 2.01 (dd, *J* = 13.2, 5.8 Hz, 1H, ArCHCH_2), 1.94 (t, *J* = 4.7 Hz, 1H, CH_2CHCH_2), 1.25 (dt, *J* = 8.8, 4.3 Hz, 1H, NHCHCH_2), 1.10 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.4 (C), 161.8 (d, J_{CF} = 243.8 Hz, C), 149.8 (C), 147.6 (CH), 137.7 (C), 136.9 (CH), 130.2 (d, *J* = 7.7 Hz, CH), 125.7 (CH), 121.7 (CH), 115.8 (d, *J* = 21.0 Hz, CH), 54.4 (C), 54.1 (CH), 51.0 (C), 47.1 (CH), 43.7 (CH), 37.0 (CH_2), 33.0 (CH_2), 20.2 (CH_3), 20.0 (CH_3), 13.8 (CH_3); **LRMS** (ES) 353.2 ($[M+H]^+$); **HRMS** found (ES) $[M+H]^+$ 353.2025, $C_{22}H_{25}N_2OF+H$ requires 353.2024.

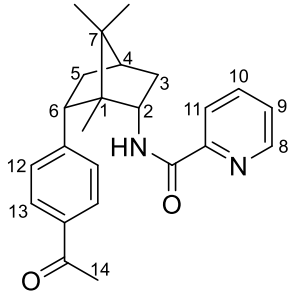
***N*-((1*S*,2*S*,4*R*,6*S*)-6-(4-Chlorophenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-,yl)picolinamide 193**



Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 4-iodochlorobenzene (95 mg, 0.40 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a pale yellow solid (31 mg, 0.084 mmol, 84%).

M.p 130 – 132 °C; **[α]$_D^{18}$** +18.2 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3373 (NH), 2978 (CH), 2950 (CH), 1672 (CO); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.34 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H, pyNC*H*), 7.96 (dt, *J* = 7.8, 1.0 Hz, 1H, pyCC*H*), 7.70 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.61 (d, *J* = 8.9 Hz, 1H, N*H*), 7.37 (d, *J* = 8.5 Hz, 2H, ClCCHC*H*), 7.34 – 7.28 (m, 3H, ClCC*H*, pyNCHC*H*), 4.50 (dddd, *J* = 11.3, 9.4, 6.0, 1.9 Hz, 1H, NHC*H*), 3.30 (dd, *J* = 11.7, 4.9 Hz, 1H, ArC*H*), 2.60 – 2.49 (m, 1H, NHCHCH_2), 2.26 (ddd, *J* = 16.2, 7.6, 3.9 Hz, 1H, ArCHCH_2), 2.01 (dd, *J* = 13.2, 5.8 Hz, 1H, ArCHCH_2), 1.94 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.27 – 1.21 (m, 1H, NHCHCH_2), 1.09 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.5 (C), 149.7 (C), 147.9 (CH), 140.8 (C), 137.0 (CH), 131.9 (C), 130.2 (CH), 129.2 (CH), 125.8 (CH), 121.7 (CH), 56.2 (C), 54.4 (CH), 51.1 (C), 47.2 (CH), 43.6 (CH), 37.0 (CH_2), 32.8 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 13.8 (CH_3); **LRMS** (ES) 369.2 ([M+H]$^+$) 737.3 ([2M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 369.1731, $C_{22}H_{25}N_2OCl$+H requires 369.1734.

N-((1*S*,2*S*,4*R*,6*S*)-6-(4-Acetylphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 194

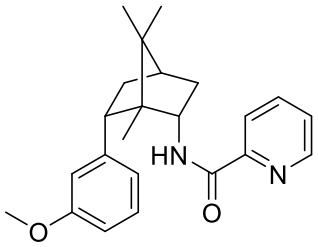


Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 4-iodoacetophenone (98 mg, 0.40 mmol). Purified by flash column chromatography (0 – 60% EtOAc in petrol) to give the product as an off-white solid (19 mg, 0.050 mmol, 50%).

M.p 178 – 181 °C; **[α]$_D^{18}$** +21.4 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3367 (NH), 3064 (CH), 2949 (CH), 1667 (CO) **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.06 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, H8), 7.94 – 7.90 (m, 3H, H11, H13, H11), 7.67 (td, *J* = 7.7, 1.7 Hz, 1H, H10), 7.55 (d, *J* = 8.0 Hz, 2H, H12), 7.48 (d, *J* = 8.8 Hz, 1H, NH), 7.22 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, H9), 4.56 – 4.50 (m, 1H, H2), 3.39 (dd, *J* = 11.5, 5.7 Hz, 1H, H6), 2.57 (ddd, *J* = 10.6, 6.9, 3.5 Hz, 1H, H3), 2.54 (s, 3H, H14), 2.32 – 2.26 (m, 1H, H5), 2.12 (dd, *J* = 13.3, 5.8 Hz, 1H, H5), 1.98 (t, *J* = 4.6 Hz,

1H, H4), 1.30 (dd, *J* = 13.4, 5.9 Hz, 1H, H3), 1.11 (m, 9H, 3 × CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 198.0 (CO), 164.3 (CO), 149.6 (ArC), 148.7 (ArC), 147.4 (ArC), 137.0 (ArC), 135.0 (ArC), 129.2 (ArC), 129.0 (ArC), 125.8 (ArC), 121.8 (ArC), 55.4 (C), 54.4 (CH), 51.2 (C), 48.0 (CH), 43.7 (CH), 37.0 (CH_2), 32.6 (CH_2), 26.7 (CH_3), 20.3 (CH_3), 20.0 (CH_3), 14.0 (CH_3); **LRMS** (ES) 377.2 ($[M+H]^+$) 753.4 ($[2M+H]^+$); **HRMS** found (ES) $[M+H]^+$ 377.2230, $C_{24}H_{28}N_2O_2$+H requires 377.2229.

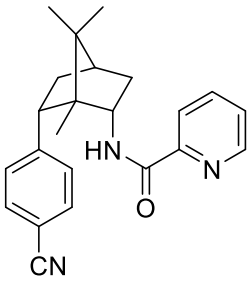
***N*-((1*S*,2*S*,4*R*,6*S*)-6-(3-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 195**



Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 3-iodoanisole (48 µl, 0.40 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as colourless oil (22 mg, 0.060 mmol, 60%).

$[\alpha]_D^{18}$ +50.9 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3358 (NH), 2951 (CH), 2836 (CH), 1665 (CO), 1509 (CC); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.24 (d, *J* = 4.7 Hz, 1H, pyNC*H*), 7.96 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.86 (d, *J* = 10.3 Hz, 1H, N*H*), 7.70 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.29 – 7.27 (m, 1H, pyNCHC*H*), 7.23 (t, *J* = 7.9 Hz, 1H, OCC*H*CH), 7.05 – 6.98 (m, 2H, OCC*H*CC*H*), 6.76 (dd, *J* = 8.2, 2.3 Hz, 1H, OCHCHC*H*), 4.54 (td, *J* = 9.6, 5.1 Hz, 1H, NHC*H*), 3.78 (s, 3H, OCH_3), 3.33 (dd, *J* = 11.5, 5.4 Hz, 1H, ArC*H*), 2.59 – 2.53 (m, 1H, NHCHCH_2), 2.29 – 2.23 (m, 1H, ArCHCH_2), 2.04 (dd, *J* = 13.2, 5.9 Hz, 1H, ArCHCH_2), 1.94 (t, *J* = 4.6 Hz, 1H, CH_2C*H*CH_2), 1.31 – 1.27 (m, 1H, NHCHCH_2), 1.11 (d, *J* = 5.0 Hz, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.5 (C), 160.3 (C), 154.1 (C), 150.0 (C), 147.3 (CH), 143.8 (CH), 136.9 (CH), 130.3 (CH), 129.9 (CH), 125.6 (CH), 121.8 (CH), 111.6 (CH), 55.2 (CH_3), 54.4 (CH), 54.4 (C) 51.1 (C), 47.8 (CH), 43.7 (CH), 37.1 (CH_2), 32.9 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 13.9 (CH_3); **LRMS** (ES) 365.2 ($[M+H]^+$); **HRMS** found (ES) $[M+H]^+$ 365.2230, $C_{23}H_{28}N_2O_2$+H requires 365.2229.

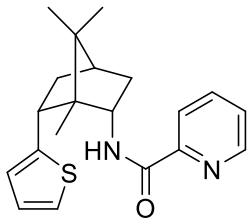
***N*-((1*S*,2*S*,4*R*,6*S*)-6-(4-Cyanophenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 196**



Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 4-iodobenzonitrile (92 mg, 0.40 mmol). Purified by flash column chromatography (0 – 50% Et_2O in petrol) to give the product as an off-white solid (26 mg, 0.072 mmol, 72%).

M.p 170 – 172 °C; **[α]$_D$** +55.5 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3374 (NH), 2947 (CH), 2924 (CH), 2222 (CN), 1670 (CO); **^{1}H NMR (**600 MHz, $CDCl_3$) *δ* 8.31 – 8.28 (m, 1H, pyNC*H*), 7.95 (dd, *J* = 7.8, 1.0 Hz, 1H, pyCC*H*), 7.72 (tdd, *J* = 7.7, 1.7, 1.0 Hz, 1H, pycCHC*H*), 7.60 (d, *J* = 8.1 Hz, 2H, NCCC*H*), 7.56 (d, *J* = 8.3 Hz, 2H, NCCCHC*H*), 7.36 – 7.29 (m, 2H, pyNCHC*H*, N*H*), 4.52 (dd, *J* = 15.8, 9.8 Hz, 1H, NHC*H*), 3.37 (dd, *J* = 11.5, 5.6 Hz, 1H, ArC*H*), 2.61 – 2.53 (m, 1H, NHCHCH_2), 2.33 – 2.25 (m, 1H, ArCHC*H*), 2.07 (dd, *J* = 13.3, 5.7 Hz, 1H, ArCHC*H*), 1.98 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.26 (dd, *J* = 13.5, 6.0 Hz, 1H, NHCHC*H*), 1.11 (s, 6H, 2 × CH_3), 1.10 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.2 (C), 149.5 (C), 148.7 (C), 147.5 (CH), 137.2 (CH), 132.7 (CH), 129.5 (CH), 126.2 (CH), 121.7 (CH), 119.3 (C), 109.5 (C), 55.6 (C), 54.3 (CH), 51.3 (C), 48.1 (CH), 43.6 (CH), 37.0 (CH_2), 32.5 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 14.0 (CH_3); **LRMS** (ES) 360.2 ([M+H]$^+$) 719.4 ([2M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 360.2071, $C_{23}H_{25}N_3O$+H requires 360.2076.

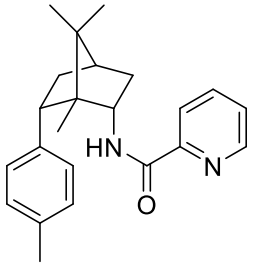
***N*-((1*S*,2*S*,4*R*,6*R*)-1,7,7-Trimethyl-6-(thiophen-2-yl)bicycle[2.2.1]heptan-2-yl)picolinamide 197**



Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 2-iodothiophene (44 µl, 0.40 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as an orange oil (28 mg, 0.082 mmol, 82%).

$[\alpha]_D^{18}$ +91.4 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3355 (NH), 2951 (CH), 1667 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.27 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.00 (dt, *J* = 7.8, 1.1 Hz, 1H, pyCC*H*), 7.97 – 7.91 (m, 1H, N*H*), 7.71 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.29 – 7.27 (m, 1H, pyNCHC*H*), 7.11 (dd, *J* = 5.2, 0.7 Hz, 1H, SC*H*), 7.06 (dt, *J* = 3.4, 1.2 Hz, 1H, SCC*H*), 7.00 (dd, *J* = 5.2, 3.5 Hz, 1H, SCHC*H*), 4.59 (dddd, *J* = 11.6, 9.9, 5.7, 2.0 Hz, 1H, NHC*H*), 3.50 (dd, *J* = 11.6, 6.0 Hz, 1H, ArC*H*), 2.56 – 2.50 (m, 1H, NHCHCH_2), 2.50 – 2.44 (m, 1H, ArCHCH_2), 1.96 (dd, *J* = 13.0, 6.0 Hz, 1H, ArCHCH_2), 1.92 (t, *J* = 4.7 Hz, 1H, CH_2CHCH_2), 1.25 (dd, *J* = 13.3, 5.7 Hz, 1H, NHCHCH_2), 1.19 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.05 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.4 (C), 150.1 (C), 147.5 (CH), 147.2 (C), 136.9 (CH), 127.3 (CH), 125.6 (CH), 124.4 (CH), 124.0 (CH), 121.8 (CH), 54.1 (C), 54.0 (CH), 50.8 (C), 43.8 (CH), 43.7 (CH), 37.4 (CH_2), 36.2 (CH_2), 20.2 (CH_3), 20.1 (CH_3), 13.6 (CH_3); **LRMS** (ES) 341.2 ($[M+H]^+$); **HRMS** found (ES) $[M+H]^+$ 341.1693, $C_{20}H_{24}N_2OS$+H requires 341.1688.

1,7,7-Trimethyl-6-(*p*-tolyl)bicyclo[2.2.1]heptan-2-yl)picolinamide 198

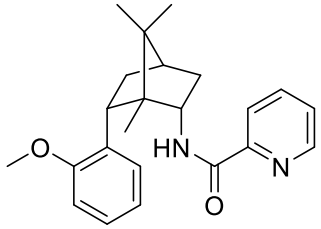


Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 4-iodotoluene (87 mg, 0.40 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a white solid (28 mg, 0.080 mmol, 80%).

M.p 150-153 °C; **$[\alpha]_D^{18}$** +37.5 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3354 (NH), 3054 (CH), 2951 (CH),1668 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.19 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H, pyNC*H*), 7.95 (dt, *J* = 7.8, 1.0 Hz, 1H, pyCC*H*), 7.74 (d, *J* = 9.4 Hz, 1H, N*H*), 7.69 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.33 (d, *J* = 7.9 Hz, 2H, $ArCH_3CCHCH$), 7.28 – 7.25 (m, 1H, pyNCHC*H*), 7.15 (d, *J* = 7.8 Hz, 2H, $ArCH_3CCH$), 4.51 (dddd, *J* = 11.4, 9.4, 6.0, 1.9 Hz, 1H, NHC*H*), 3.30 (dd, *J* = 11.7, 5.5 Hz, 1H, ArC*H*), 2.58 – 2.51 (m, 1H, NHCHC*H*), 2.27 – 2.21 (m, 1H, ArCHCH_2), 2.07 – 2.03 (m, 1H, ArCHCH_2), 1.93 (t, *J* = 4.7 Hz, 1H, CH_2CHCH_2), 1.29 (dd, *J* = 13.2, 5.9 Hz, 1H, NHCHCH_2), 1.11 – 1.04 (m, 9H, 3 × CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ*

164.5 (C), 150.0 (C), 147.4 (CH), 138.9 (C), 136.9 (CH), 135.6 (C), 129.8 (CH), 128.8 (CH), 125.5 (CH), 121.8 (CH), 54.5 (C), 54.0 (CH), 51.0 (C), 47.3 (CH), 43.7 (CH), 37.0 (CH_2), 32.7 (CH_2), 21.2 (CH_3), 20.3 (CH_3), 20.0 (CH_3), 13.8 (CH_3); **LRMS** (ES) 349.2 ($[M+H]^+$); **HRMS** found (ES) $[M+H]^+$ 349.2275, $C_{23}H_{28}N_2O$+H requires 349.2274.

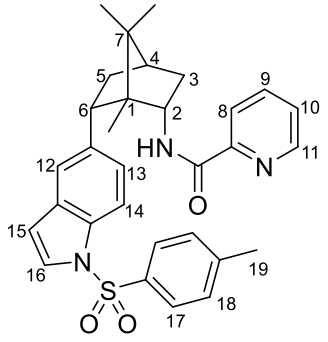
_N_-((1_S_,2_S_,4_R_,6_R_)-6-(2-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 199



Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 2-iodoanisole (52 µl, 0.40 mmol). Purified by flash column chromatography (0 – 60% EtOAc in petrol) to give the product as a white solid (16 mg, 0.044 mmol, 44%).

M.p 177 – 180 °C; **$[\alpha]_D^{18}$** +101.0 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3353 (NH), 3054 (CH), 2951 (CH), 1669 (C=O), 998 (C-O); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.24 (d, *J* = 4.3 Hz, 1H, pyNC*H*), 8.18 (d, *J* = 8.5 Hz, 1H, N*H*), 7.97 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.69 (td, *J* = 7.7, 1.4 Hz, 1H, pyCCHC*H*), 7.56 (d, *J* = 7.5 Hz, 1H, CH_3OCCC*H*), 7.28 – 7.25 (m, 1H, pyNCHC*H*), 7.22 (t, *J* = 7.3 Hz, 1H, OCCHC*H*), 7.01 (t, *J* = 7.4 Hz, 1H, OCCHCHC*H*), 6.86 (d, *J* = 8.1 Hz, 1H, OCC*H*), 4.52 (dd, *J* = 15.9, 9.8 Hz, 1H, NHC*H*), 3.79 (d, *J* = 12.0 Hz, 4H, OCH_3, ArC*H*), 2.60 – 2.51 (m, 1H, NHCHCH_2), 2.24 – 2.17 (m, 1H, ArCHCH_2), 2.04 (dd, *J* = 13.0, 5.8 Hz, 1H, ArCHCH_2), 1.92 (t, *J* = 4.5 Hz, 1H, CH_2CHCH_2), 1.42 (dd, *J* = 13.2, 6.2 Hz, 1H, NHCHCH_2), 1.13 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 0.94 (s, 3H, *CH* **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.6 (C), 158.3 (C), 150.2 (C), 147.4 (CH), 136.8 (CH), 130.6 (C), 130.3 (CH), 126.9 (CH), 125.5 (CH), 121.8 (CH), 121.4 (CH), 111.0 (CH), 55.0 (CH_3), 55.0 (CH), 54.9 (C), 51.2 (C), 44.1 (CH), 41.1 (CH), 36.4 (CH_2), 33.5 (CH_2), 20.5 (CH_3), 20.0 (CH_3), 13.9 (CH_3); **LRMS** (ES) 365.2 ($[M+H]^+$) 729.4 ($[2M+H]^+$); **HRMS** found (ES) $[M+H]^+$ 365.2231, $C_{23}H_{25}N_3O$+H requires 365.2229.

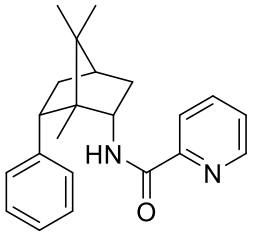
***N*-((1*S*,2*S*,4*R*,6*S*)-1,7,7-Trimethyl-6-(1-tosyl-1*H*-indol-5-yl)bicyclo[2.2.1]heptan-2-yl)picolinamide 201**



Prepared according to the general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 5-iodo-1-tosyl-1H-indole (159 mg, 0.40 mmol). Purified by flash column chromatography (0 – 50% Et_2O in petrol) to give the product as a yellow solid (23 mg, 0.044 mmol, 44%).

M.p 182 – 185 °C; **$[\alpha]_D^{18}$** +13.2 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3066 (CH), 2833 (CH), 1669 (CO), 1371 (SO), 1172 (SO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.6 Hz, 1H, H14), 7.85 (d, *J* = 7.8 Hz, 1H, H11), 7.78 (d, *J* = 8.4 Hz, 2H, H16), 7.69 – 7.62 (m, 2H, NH, H12), 7.59 – 7.55 (m, 2H, H10, H16), 7.42 (s, 1H, H8), 7.35 (d, *J* = 8.5 Hz, 1H, H11), 7.20 (d, *J* = 8.2 Hz, 2H, H18), 7.05 – 7.00 (m, 1H, H9), 6.64 (d, *J* = 3.6 Hz, 1H, H15), 4.51 (ddd, *J* = 15.6, 7.8, 3.0 Hz, 1H, H2), 3.40 (dd, *J* = 11.6, 5.4 Hz, 1H, H6), 2.59 – 2.53 (m, 1H, H3), 2.33 (s, 3H, H19), 2.30 – 2.23 (m, 1H, H5), 2.08 (dd, *J* = 13.2, 5.8 Hz, 1H, H5), 1.95 (t, *J* = 4.6 Hz, 1H, H4), 1.31 (dd, *J* = 13.3, 5.9 Hz, 1H, H3), 1.10 (d, *J* = 4.4 Hz, 9H, 3 × CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.5 (C), 149.5 (C), 147.4 (CH), 145.0 (C), 137.3 (C), 136.5 (CH), 135.5 (C), 133.6 (C), 131.9 (C), 130.0 (CH), 127.0 (CH), 126.5 (CH), 126.3 (CH), 125.5 (CH), 121.4 (CH), 120.9 (CH), 113.9 (CH), 109.5 (CH), 54.4 (CH), 54.2 (C), 51.1 (C), 47.6 (CH), 43.7 (CH), 37.0 (CH_2), 33.1 (CH_2), 21.7 (CH_3), 20.3 (CH_3), 20.0 (CH_3), 13.9 (CH_3); **LRMS** (ES) 528.2 ($[M+H]^+$); **HRMS** found (ES) $[M+H]^+$ 528.2322, $C_{31}H_{33}N_3O_3S$+H requires 528.2321.

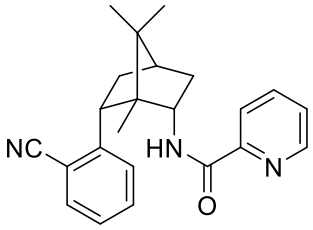
***N*-((1*S*,2*S*,4*R*,6*S*)-1,7,7-Trimethyl-6-phenylbicyclo[2.2.1]heptan-2-yl)picolinamide 204**



Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and bromobenzene (42 µl, 0.40 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a colourless oil (29 mg, 0.087 mmol, 87%).

[α]$_D^{18}$ +86.8 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3012 (CH), 2951 (CH), 1667 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.19 (d, *J* = 4.7 Hz, 1H, pyNC*H*), 7.94 (d, *J* = 7.8 Hz, 1H, CC*H*CH), 7.75 – 7.65 (m, 2H, N*H*, CCHC*H*), 7.45 (dd, *J* = 9.2, 4.4 Hz, 2H, Ar*H*), 7.34 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.26 – 7.24 (m, 1H, pyNCHC*H*), 7.22 (t, *J* = 7.4 Hz, 1H, Ar*H*), 4.53 (dddd, *J* = 11.3, 9.5, 6.0, 1.8 Hz, 1H, NHC*H*), 3.35 (dd, *J* = 11.6, 5.5 Hz, 1H, ArC*H*), 2.60 – 2.52 (m, 1H, NHCHCH_2), 2.26 (tt, *J* = 12.7, 3.9 Hz, 1H, ArCHCH_2), 2.08 (dd, *J* = 13.2, 5.8 Hz, 1H, ArCHCH_2), 1.95 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.30 (dd, *J* = 13.3, 5.9 Hz, 1H, NHCHCH_2), 1.09 (dd, *J* = 17.6, 6.5 Hz, 9H, 3 × CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.5 (C), 149.9 (C), 148.1 (C), 147.4 (CH), 142.1 (CH), 136.9 (CH), 129.1 (CH), 125.9 (CH), 125.5 (CH), 121.7 (CH), 54.3 (C), 51.1 (CH), 47.7 (C), 43.7 (CH), 37.0 (CH), 32.6 (CH_2), 28.6 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 13.8 (CH_3); **LRMS** (ES) 336.2 ([M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 335.2111, $C_{22}H_{26}N_2O$+H requires 335.2123.

_N_-((1_S_,2_S_,4_R_,6_S_)-6-(2-cyanophenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 205

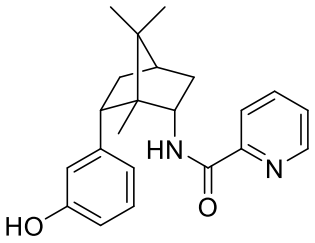


Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 2-bromobenzonitrile (73 mg, 0.40 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as an orange solid (28 mg, 0.078 mmol, 78%).

M.p 185 – 186 °C; **[α]$_D^{18}$** +151.8 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3378 (NH), 3060 (CH), 2954 (CH), 2222 (CN), 1669 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.20 – 8.17 (m, 1H, pyNC*H*), 7.99

(d, *J* = 7.8 Hz, 1H, CC*H*), 7.85 (d, *J* = 8.4 Hz, 1H, NCCCC*H*), 7.72 (td, *J* = 7.7, 1.7 Hz, 2H, CCHC*H* and N*H*), 7.65 – 7.61 (m, 2H, NCCCHCHC*H* and NCCC*H*), 7.33 (dd, *J* = 11.1, 4.1 Hz, 1H, NCCCHC*H*), 7.30 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H, pyNCHC*H*), 4.56 – 4.50 (m, 1H, NHC*H*), 3.82 (dd, *J* = 11.8, 4.7 Hz, 1H, ArC*H*), 2.69 – 2.62 (m, 1H, NHCHCH_2), 2.45 – 2.39 (m, 1H, ArCHCH_2), 2.01 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.95 (dd, *J* = 13.3, 5.6 Hz, 1H, ArCHCH_2), 1.43 (dd, *J* = 13.5, 6.3 Hz, 1H, NHCHCH_2), 1.18 (s, 3H, CH_3), 1.13 (s, 6H, 2 × CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.4 (C), 149.7 (C), 147.3 (CH), 146.6 (C), 137.2 (CH), 134.1 (CH), 133.5 (CH), 130.1 (CH), 126.3 (CH), 125.9 (CH), 121.9 (CH), 119.2 (C), 114.9 (CN), 57.1 (C), 55.0 (CH), 51.7 (C), 46.6 (CH), 43.8 (CH), 36.6 (CH_2), 35.1 (CH_2), 20.4 (CH_3), 20.0 (CH_3), 14.0 (CH_3); **LRMS** (ES) 360.2 ([M+H]$^+$) 719.4 ([2M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 360.2079, $C_{23}H_{25}N_3O$+H requires 360.2076.

N-((1*S*,2*S*,4*R*,6*S*)-6-(3-Hydroxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 206

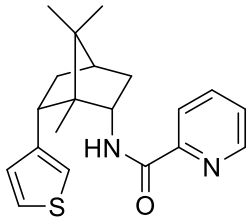


Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 3-bromophenol (69 mg, 0.40 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as a brown solid (20 mg, 0.057 mmol, 57%).

M.p 137 – 140 °C; **[α]$_D^{18}$** +40.6 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3326 (NH), 2951 (CH), 1651 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.32 – 8.28 (m, 1H, pyNC*H*), 8.03 (d, *J* = 9.7 Hz, 1H, N*H*), 7.94 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.64 (td, *J* = 7.7, 1.6 Hz, 1H, pyCCHC*H*), 7.23 (dd, *J* = 6.8, 4.8 Hz, 1H, pyNCHC*H*), 7.18 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.97 (s, 1H, O*H*), 6.92 (d, *J* = 2.1 Hz, 2H, Ar*H*), 6.78 – 6.74 (m, 1H, Ar*H*), 4.53 – 4.45 (m, 1H, NHC*H*), 3.22 (dd, *J* = 11.5, 5.3 Hz, 1H, ArC*H*), 2.48 – 2.40 (m, 1H, NHCHCH_2), 2.21 – 2.14 (m, 1H, ArCHCH_2), 1.92 (dd, *J* = 13.2, 5.7 Hz, 1H, ArCHCH_2), 1.81 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.13 (dd, *J* = 13.3, 5.9 Hz, 1H, NHCHCH_2), 1.03 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.8 (C), 157.0 (C), 149.8 (C), 147.6 (CH), 143.9 (C), 137.0 (CH), 130.2 (CH), 125.8 (CH), 121.8 (CH), 121.3 (CH), 115.7 (CH), 113.2 (CH), 54.4 (C), 54.3 (CH), 51.0 (C), 47.6 (CH), 43.6 (CH), 36.8 (CH_2), 32.8 (CH_2), 20.2 (CH_3), 19.9 (CH_3), 13.7 (CH_3); **LRMS**

(ES) 351.2 ([M+H]$^+$) 725.5 ([2M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 351.2076, $C_{22}H_{26}N_2O_2$+H requires 351.2072.

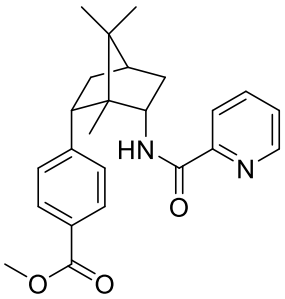
_N_-((1_S_,2_S_,4_R_,6_S_)-1,7,7-Trimethyl-6-(thiophen-3-yl)bicycle[2.2.1]hepten-2-yl)picolinamide 207



Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 3-bromothiophene (37 µl, 0.40 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as an orange oil (22 mg, 0.065 mmol, 65%).

[α]$_D^{18}$ +11.0 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3377 (NH), 3062 (CH), 2953 (CH), 1668 (CO); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.35 – 8.31 (m, 1H, pyNC*H*), 8.01 – 7.97 (m, 1H, pyCC*H*), 7.85 (s, 1H, N*H*), 7.71 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.28 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 7.25 – 7.22 (m, 2H, SCHC*H*, SC*H*CH), 7.05 (dd, *J* = 4.9, 1.5 Hz, 1H, SC*H*C), 4.56 (dd, *J* = 16.3, 10.6 Hz, 1H, NHC*H*), 3.33 (dd, *J* = 11.6, 5.9 Hz, 1H, ArC*H*), 2.53 (s, 1H, NHCHCH_2), 2.36 (dd, *J* = 16.1, 8.4 Hz, 1H, ArCHCH_2), 1.95 – 1.89 (m, 2H, ArCHCH_2, CH_2C*H*CH_2), 1.21 (dd, *J* = 13.3, 5.8 Hz, 1H, NHCHCH_2), 1.14 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.4 (C), 150.0 (C), 147.6 (CH), 144.1 (C), 137.0 (CH), 128.5 (CH), 126.8 (CH), 125.6 (CH), 121.8 (CH), 120.5 (CH), 54.2 (CH), 53.6 (C), 50.7 (C), 43.7 (CH), 43.7 (CH), 37.6 (CH_2), 34.8 (CH_2), 20.2 (CH_3), 20.0 (CH_3), 14.01 (CH_3); **LRMS** (ES) 341.2 ([M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 341.1693, $C_{20}H_{24}N_2OS$+H requires 341.6880.

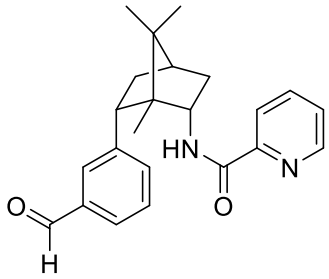
Methyl-4-((1_S_,2_S_,4_R_,6_S_)-1,7,7-trimethyl-6-(picolinamide)bicyclo[2.2.1]heptan-2-yl)benzoate 208



Prepared according general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and methyl 4-bromobenzoate (86 mg, 0.40 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as an off-white solid (27 mg, 0.069 mmol, 69%).

M.p 114 – 115 °C; **[α]$_D^{18}$** +43.8 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3016 (CH), 2953 (CH), 1714 (CO), 1660 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.12 – 8.10 (m, 1H, pyNC*H*), 8.00 (d, *J* = 8.3 Hz, 2H, OC(O)CC*H*), 7.91 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.66 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.52 (d, *J* = 8.0 Hz, 3H, N*H*, OC(O)CCHC*H*), 7.22 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H, pyNCHC*H*), 4.56 – 4.49 (m, 1H, NHC*H*), 3.92 (s, 3H, OCH_3), 3.38 (dd, *J* = 11.5, 5.5 Hz, 1H, ArC*H*), 2.58 – 2.52 (m, 1H, NHCHCH_2), 2.28 (ddd, *J* = 16.1, 7.6, 3.8 Hz, 1H, ArCHCH_2), 2.11 (dd, *J* = 13.2, 5.8 Hz, 1H, ArCHCH_2), 1.97 (t, *J* = 4.6 Hz, 1H, CH_2C*H*CH_2), 1.29 (dd, *J* = 13.4, 6.0 Hz, 1H, NHCHCH_2), 1.12 – 1.09 (m, 9H 3 × CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 167.3 (C), 164.4 (C), 149.6 (C), 148.3 (C), 147.5 (CH), 136.9 (CH), 130.4 (CH), 128.8 (CH), 127.8 (C), 125.7 (CH), 121.7 (CH), 55.3 (C), 54.3 (CH), 52.1 (CH_3), 51.2 (C), 48.0 (CH), 43.6 (CH), 37.0 (CH_2), 32.6 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 13.9 (CH_3); **HRMS** found (ES) $[M+H]^+$ 393.2172, $C_{24}H_{28}N_2O_3$+H requires 393.2178.

_N_-((1_S_,2_S_,4_R_,6_S_)-6-(3-Formylphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 209

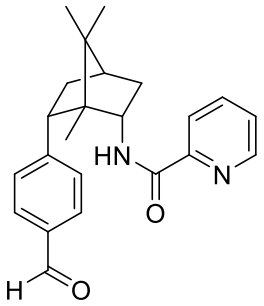


Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 3-bromobenzaldehyde (47 µl, 0.40 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a white solid (11 mg, 0.030 mmol, 30%).

M.p 108 – 110 °C; **[α]$_D^{18}$** +7.8 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 2952 (CH), 1696 (CO), 1670 (CO), 1518 (CC); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 10.03 (s, 1H, C*H*O), 8.06 (d, *J* = 4.2 Hz, 1H, pyNC*H*), 8.01 (s, 1H, CC*H*C), 7.92 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.72 (d, *J* = 7.6 Hz, 1H, H(O)CCC*H*CH), 7.67 (td, *J* = 7.7, 1.7, 1H, pyCCHC*H*), 7.64 (d, *J* = 7.8 Hz, 1H, H(O)CCCHC*H*), 7.48 (d, *J* = 8.6 Hz, 1H, N*H*), 7.43 (t, *J* = 7.6 Hz, 1H, CHCC*H*CH), 7.25 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H, pyNCHC*H*), 4.56 – 4.50 (m, 1H, NHC*H*), 3.41 (dd, *J* = 11.5, 5.7 Hz, 1H, ArC*H*), 2.62 – 2.55 (m, 1H, NHCHCH_2), 2.33 (ddd, *J* = 16.2, 7.7, 3.8 Hz, 1H,

ArCHCH_2), 2.14 (dd, *J* = 13.2, 5.9 Hz, 1H, ArCHCH_2), 2.00 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.34 (dd, *J* = 13.4, 5.9 Hz, 1H, NHCHCH_2), 1.12 (m, 9H, 3 × CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 192.8 (C), 164.2 (C), 149.5 (C), 147.3 (CH), 143.7 (C), 137.2 (CH), 137.0 (CH), 135.8 (CH), 130.1 (C), 129.5 (CH), 126.8 (CH), 125.8 (CH), 121.8 (CH), 54.8 (CH), 54.5 (C), 51.3 (C), 47.6 (CH), 43.6 (CH), 37.2 (CH_2), 32.7 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 14.0 (CH_3); **LRMS** (ES) 363.2 ([M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 363.2076, $C_{23}H_{26}N_2O_2$+H requires 363.2073.

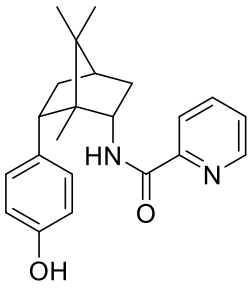
N-((1*S*,2*S*,4*R*,6*S*)-6-(4-Formylphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 210



Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 4-bromobenzaldehyde (74 mg, 0.40 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as an off-white solid (25 mg, 0.069 mmol, 69%).

M.p 148 – 150 °C; **[α]$_D^{18}$** +29.4 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3016 (CH), 1662 (CO), 1520 (CC); 3016 (CH), 1662 (CO), 1520 (CC); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 9.96 (s, 1H, C*H*O), 8.04 (d, *J* = 4.7 Hz, 1H, pyNC*H*), 7.91 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.84 (d, *J* = 8.0 Hz, 2H, H(O)CCC*H*), 7.66 (td, *J* = 7.7, 1.6 Hz, 1H, pyCCHC*H*), 7.62 (d, *J* = 7.9 Hz, 2H, H(O)CCHC*H*), 7.43 (d, *J* = 9.0 Hz, 1H, N*H*), 7.24 – 7.21 (m, 1H, pyNCHC*H*), 4.59 – 4.48 (m, 1H, NHC*H*), 3.40 (dd, *J* = 11.5, 5.6 Hz, 1H, ArC*H*), 2.61 – 2.52 (m, 1H, NHCHCH_2), 2.36 – 2.24 (m, 1H, ArCHCH_2), 2.13 (dd, *J* = 13.3, 5.8 Hz, 1H, ArCHCH_2), 1.99 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.30 (dd, *J* = 13.4, 6.0 Hz, 1H, NHCHCH_2), 1.13 – 1.10 (m, 9H, 3 × CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 192.1 (C), 164.3 (C), 150.5 (C), 149.5 (C), 147.4 (CH), 137.0 (CH), 134.6 (C), 130.5 (CH), 129.4 (CH), 125.9 (CH), 121.8 (CH), 55.7 (C), 54.3 (CH), 51.3 (C), 48.3 (CH), 43.6 (CH), 37.0 (CH_2), 32.6 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 14.0 (CH_3); **LRMS** (ES) 363.2 ([M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 363.2074, $C_{23}H_{27}N_2O_2$+H requires 363.2073.

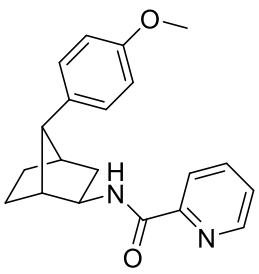
***N*-((1*S*,2*S*,4*R*,6*S*)-6-(4-Hydroxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 211**



Prepared according to general arylation procedure A using amide **165** (26 mg, 0.10 mmol) and 4-bromophenol (69 mg, 0.40 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as a yellow solid (25 mg, 0.071 mmol, 71%).

M.p 198 – 200 °C; **[α]$_D^{18}$** +20.2 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3327 (OH), 2950 (CH), 2809 (CH), 1651 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.35 (d, *J* = 4.7 Hz, 1H, pyNC*H*), 7.96 – 7.88 (m, 2H, PyCC*H*, N*H*), 7.65 (td, *J* = 7.7, 1.6 Hz, 1H, pyCCHC*H*), 7.29 (d, *J* = 8.2 Hz, 2H, HOCC*H*), 7.24 – 7.19 (m, 1H, pyNCHC*H*), 6.88 (d, *J* = 8.1 Hz, 2H, HOCCHC*H*), 6.16 (s, 1H, O*H*), 4.54 – 4.46 (m, 1H, NHC*H*), 3.28 (dd, *J* = 11.7, 5.4 Hz, 1H, ArC*H*), 2.58 – 2.50 (m, 1H, NHCHCH_2), 2.24 (ddd, *J* = 12.9, 7.3, 3.7 Hz, 1H, ArCHCH_2), 1.99 (dd, *J* = 13.1, 5.7 Hz, 1H, ArCHCH_2), 1.91 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.28 – 1.23 (m, 1H, NHCHCH_2), 1.07 (d, *J* = 1.6 Hz, 6H, 2 × CH_3), 1.03 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 164.9 (C), 154.9 (C), 149.6 (C), 147.9 (CH), 136.9 (CH), 133.3 (C), 130.0 (CH), 125.7 (CH), 121.7 (CH), 116.1 (CH), 54.7 (CH), 53.7 (C), 50.9 (C), 46.8 (CH), 43.7 (CH), 36.9 (CH_2), 32.9 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 13.8 (CH_3); **LRMS** (ES) 351.2 ([M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 351.2055, $C_{22}H_{26}N_2O_2$+H requires 351.2072.

***N*-7-(4-Methoxyphenyl)bicycle[2.2.1]heptan-2-yl)picolinamide 212**

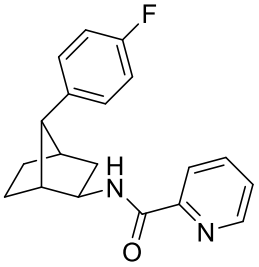


Prepared according to general arylation procedure A using amide **166** (22 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as a white solid (26 mg, 0.081 mmol, 81%).

M.p 99 – 101 °C; $\mathbf{v_{max}}$ (film/cm^{-1}) 3377 (NH), 2947 (CH), 2862 (CH), 1660 (C=O), 1507 (CC), 1028 (C-O); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.23 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H, pyNC*H*), 8.04 (dt, *J* = 7.8, 1.0 Hz, 1H, pyCC*H*), 7.73 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.34 (d, *J* = 8.7 Hz, 1H, N*H*), 7.28 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H, pyNCHC*H*), 7.26 – 7.23 (m, 2H, OCCHC*H*), 6.86 – 6.83 (m, 2H, OCC*H*), 4.12 (td, *J* = 9.0, 3.7 Hz, 1H, NHC*H*), 3.81 (s, 3H, OCH_3), 3.02 (s, 1H, ArC*H*), 2.78 (t, *J* = 4.1 Hz, 1H, NHCHC*H*), 2.73 (d, *J* = 4.4 Hz, 1H, NHCHCH$_2$C*H*), 1.97 (dd, *J* = 13.5, 8.6 Hz, 1H, NHCHCH_2), 1.83 (tt, *J* = 12.0, 4.4 Hz, 1H, CH$_2$CHCH_2CH$_2$), 1.75 (ddd, *J* = 14.5, 9.2, 5.6 Hz, 2H, NHCHCH_2, NHCHCHCH_2), 1.51 – 1.46 (m, 1H, CH$_2$CHCH_2CH$_2$), 1.36 (ddd, *J* = 11.9, 9.5, 4.2 Hz, 1H, NHCHCHCH_2); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.8 (C), 158.0 (C), 150.1 (C), 147.6 (CH), 137.0 (CH), 132.3 (C), 129.3 (CH), 125.7 (CH), 121.8 (CH), 114.2 (CH), 55.4 (CH_3), 52.9 (CH), 52.3 (CH), 47.2 (CH), 38.2 (CH), 38.1 (CH_2), 28.9 (CH_2), 28.2 (CH_2); **LRMS** (ES) 323.2 ([M+H]$^+$) 645.4 ([2M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 323.1762, $C_{20}H_{22}N_2O_2$+H requires 323.1760.

Data in accordance with literature[113]

***N*-7-(4-Fluorophenyl)bicyclo[2.2.1]heptan-2-yl)picolinamide 213**

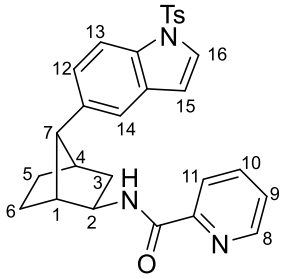


Prepared according to general arylation procedure A using amide **166** (22 mg, 0.10 mmol) and 4-iodofluorobenzene (46 µl, 0.40 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as an off-white solid (26 mg, 0.084 mmol, 84%).

M.p 125 – 128 °C; $\mathbf{v_{max}}$ (film/cm^{-1}) 3362 (NH), 2951 (CH), 2871 (CH), 1667 (CO), 1506 (CC), 1219 (CF); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.26 (d, *J* = 4.6 Hz, 1H, pyNC*H*), 8.04 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.74 (t, *J* = 7.7 Hz, 1H, CCHC*H*), 7.33 – 7.23 (m, 4H, N*H*, pyNCHC*H*, FCC*H*), 6.98 (t, *J* = 8.7 Hz, 2H, FCCHC*H*), 4.11 (td, *J* = 8.9, 3.8 Hz, 1H, NHC*H*), 3.03 (s, 1H, ArC*H*), 2.79 (s, 1H, NHCHC*H*), 2.75 (d, *J* = 4.2 Hz, 1H, NHCHCH$_2$C*H*), 1.99 (dd, *J* = 13.3,

8.6 Hz, 1H, NHCHCH_2), 1.84 (tt, *J* = 12.0, 4.4 Hz, 1H, $CH_2CHCH_2CH_2$), 1.79 – 1.69 (m, 2H, NHCHCHCH_2, NHCHCH_2), 1.54 – 1.47 (m, 1H, $CH_2CHCH_2CH_2$), 1.40 – 1.34 (m, 1H, NHCHCHCH_2); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 162.8 (C), 161.5 (d, *J* = 244.0 Hz, C), 160.7 (C), 149.8 (C), 147.8 (CH), 137.1 (CH), 136.0 (C), 136.0 (CH), 129.9 (d, *J* = 7.8 Hz, CH), 125.9 (CH), 121.8 (CH), 115.5 (d, *J* = 21.1, C), 52.8 (CH), 52.4 (CH), 47.4 (CH), 38.1 (CH), 38.1 (CH_2), 28.9 (CH_2), 28.1 (CH_2); **LRMS** (ES) 311.2 ([M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 311.1557, $C_{19}H_{19}N_2OF$+H requires 311.1560.

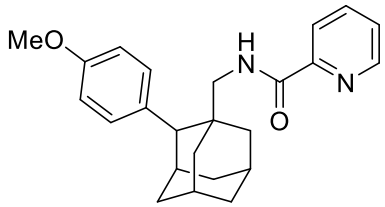
***N*-7-(1-Tosyl-1*H*-indol-5-yl)bicyclo[2.2.1]heptan-2-yl)picolinamide 214**



Prepared according to general arylation procedure A using amide **166** (22 mg, 0.10 mmol) and 5-iodo-1-tosyl-1H-indole (159 mg, 0.40 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as a white solid (42 mg, 0.086 mmol, 86%).

M.p 149 – 151 °C; **ν_{max}** (film/cm^{-1}) 3330 (NH), 2960 (CH), 2919 (CH), 1663 (CO), 1517 (CC), 1365 (SO); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 7.97 (dd, *J* = 7.2, 1.7 Hz, 1H, H8), 7.91 (d, *J* = 8.6 Hz, 1H, H13), 7.79 (d, *J* = 8.4 Hz, 2H, HTs), 7.68 – 7.64 (m, 2H, H9, H10), 7.54 (t, *J* = 4.3 Hz, 1H, H16), 7.50 (s, 1H, H14), 7.31 (d, *J* = 8.7 Hz, 1H, H12), 7.27 (d, *J* = 5.8 Hz, 1H, NH), 7.21 (d, *J* = 8.3 Hz, 2H, HTs), 7.16 – 7.12 (m, 1H, H11), 6.54 (d, *J* = 3.6 Hz, 1H, H15), 4.12 (td, *J* = 9.0, 3.6 Hz, 1H, H2), 3.12 (s, 1H, H7), 2.84 (d, *J* = 3.7 Hz, 1H, H4), 2.80 (d, *J* = 4.3 Hz, 1H, H1), 2.33 (s, 3H, CH_3), 1.99 (dd, *J* = 13.3, 8.5 Hz, 1H, H3), 1.85 (tt, *J* = 12.1, 4.3 Hz, 1H, H6), 1.79 – 1.71 (m, 2H, H3, H5), 1.54 – 1.48 (m, 1H, H6), 1.38 (ddd, *J* = 13.6, 9.5, 4.2 Hz, 1H, H5); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 162.8 (C), 149.6 (C), 147.7 (CH), 145.0 (C), 136.8 (CH), 135.5 (C), 135.4 (C), 133.5 (C), 131.4 (C), 130.0 (CH), 127.0 (CH), 126.4 (CH), 125.6 (CH), 125.2 (CH), 121.5 (CH), 121.0 (CH), 113.8 (CH), 109.2 (CH), 53.0 (CH), 52.8 (CH), 47.3 (CH), 38.3 (CH), 38.2 (CH_2), 28.9 (CH_2), 28.2 (CH_2), 21.7 (CH_3); **HRMS** found (ES) [M+H]$^+$ 486.1830, $C_{28}H_{27}N_2O_3S$+H requires 486.1852.

***N*-2-(4-Methoxyphenyl)adamantan-1-yl)methyl)picolinamide 218**



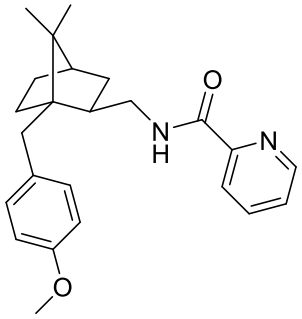
Prepared according to general arylation procedure A using amide **168** (27 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol), reaction time extended to 48 h. Purified using 0–40% EtOAc in petrol to give the product as a colourless oil (28 mg, 0.074 mmol, 74%)

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3389 (NH), 2902 (CH), 2850 (CH), 1675 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.56–8.52 (m, 1H, pyNC*H*), 8.14 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.94 (s, 1H, N*H*), 7.82 (td, *J* = 7.7, 1.7 Hz, pyCCHC*H*), 7.47–7.43 (m, 2H, OCCHC*H*), 7.40 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 6.90–6.85 (m, OCC*H*), 3.81 (s, 3H, OCH_3), 3.26 (dd, *J* = 13.7, 7.6 Hz, 1H, NCH_2), 2.95 (dd, *J* = 13.7, 5.8 Hz, 1H, NCH_2), 2.89 (s, 1H, ArC*H*), 2.25 (t, *J* = 12.2 Hz, 1H), 2.21 (d, *J*= 13.3 Hz, 1H), 2.14 (d, *J* = 14.0 Hz, 1H), 2.08–2.05 (m, 1H), 1.92 (s, 1H), 1.91–1.83 (m, 2H), 1.81–1.75 (m, 2H), 1.72 (dd, *J* = 12.5, 1.7 Hz, 2H), 1.59–1.54 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.5 (C), 158.1 (C), 150.2 (C), 148.1 (CH), 137.4 (CH), 136.4 (C), 130.6 (CH), 126.0 (CH), 122.3 (CH), 113.9 (CH), 55.3 (CH_3), 53.9 (CH_2), 48.5 (C), 43.8 (CH), 40.1 (CH), 38.1 (CH), 37.7 (CH), 35.5 (CH_2), 35.4 (CH_2), 31.1 (CH_2), 28.9 (CH_2), 28.0 (CH_2); **HRMS** found (ES) $[M + H]^+$ 377.2222, $C_{24}H_{28}N_2O_2$+H requires 377.2224.

Scale up arylation procedure and recovery of aryl bromide

A tube was charged with a picolinamide (258 mg, 1.0 mmol, 1 eq), $CuBr_2$ (22 mg, 0.1 mmol, 10 mol%), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), CsOAc (767 mg, 4.0 mmol), *t*AmOH (1.0 ml) and 2-bromobenzonitrile (728 mg, 4.0 mmol, 4 eq). The tube was sealed with a PTFE lined cap and heated to 140 °C for 24 hours. The reaction mixture was then cooled and filtered through a pad of Celite®, washing with EtOAc. The filtrate was concentrated *in vacuo* and the resulting crude residue purified by flash column chromatography (0 – 50 % EtOAc in petrol), to give the arylated product (262 mg, 0.73 mmol, 73%) and 3.12 mmol (568 mg) of recovered aryl bromide.

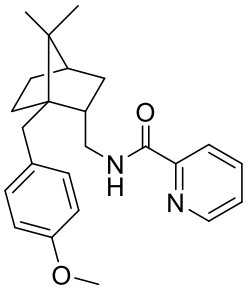
(+/-) *N*-1-(((4-Methoxybenzyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)picolinamide 225



Prepared according to general arylation procedure A, using amide **158a** (27 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography 0 – 20% EtOAc in petrol) to give the product as a viscous oil (33 mg, 0.087 mmol, 87%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3392 (NH), 2919 (CH), 2850 (CH), 1672 (CO), 1524 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.53 – 8.49 (m, 1H, pyNC*H*), 8.19 (dt, *J* = 7.8, 1.1 Hz, 1H, pyCC*H*), 7.86 (s, 1H, N*H*), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.40 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H, pyNCHC*H*), 7.24 – 7.19 (m, 2H, OCCHC*H*), 6.83 – 6.78 (m, 2H, OCC*H*), 3.83 – 3.79 (m, 1H, NHCH_2), 3.77 (s, 3H, OCH_3), 3.64 (ddd, *J* = 13.2, 11.4, 6.9 Hz, 1H, NHCH_2), 2.79 (d, *J* = 14.5 Hz, 1H, ArCH_2), 2.61 (d, *J* = 14.5 Hz, 1H, ArCH_2), 1.88 (tt, *J* = 11.0, 5.5 Hz, 1H, NHCH$_2$C*H*), 1.77 – 1.68 (m, 4H, NHCH$_2$CHCH_2C*H*CH_2CH_2), 1.54 (dd, *J* = 12.1, 9.4 Hz, 1H, NHCH$_2$CHCH_2), 1.22 – 1.19 (m, 1H, CHCCH_2CH$_2$), 1.13 (dd, *J* = 6.6, 2.9 Hz, 1H, CHCCH$_2$CH_2), 1.12 (s, 3H, CH_3), 0.87 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.4 (C), 157.8 (C), 150.2 (C), 148.1 (CH), 137.4 (CH), 132.0 (C), 131.1 (CH), 126.1 (CH), 122.3 (CH), 113.6 (CH), 55.3 (CH_3), 51.4 (C), 48.6 (C), 46.1 (CH), 45.5 (CH), 43.5 (CH_2), 36.8 (CH_2), 35.1 (CH_2), 33.3 (CH_2), 27.4 (CH_2), 21.4 (CH_3), 21.1 (CH_3); **HRMS** found (ES) $[M+H]^+$ 379.2371, $C_{24}H_{30}N_2O_2$+H requires 379.2380.

***N*-1-(4-Methoxybenzyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)methyl)picolinamide 227**



Prepared according to general arylation procedure A, using amide **158b** (27 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography 0 – 20% EtOAc in petrol) to give the product as a viscous oil (25 mg, 0.066 mmol, 66%).

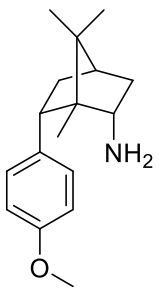
ν_{max} (film/cm^{-1}) 3391 (NH), 2922 (CH), 2851 (CH), 1671 (CO), 1511 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.53 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.18 (dt, *J* = 7.8, 1.1 Hz, 1H, pyCC*H*), 7.88 (s, 1H, N*H*), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.40 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 7.16 – 7.12 (m, 2H, OCCHC*H*), 6.82 – 6.79 (m, 2H, OCC*H*), 3.77 (s, 3H, OCH_3), 3.22 (ddd, *J* = 12.9, 11.1, 6.9 Hz, 1H, NHCH_2), 3.09 (ddd, *J* = 12.9, 4.7, 3.6 Hz, 1H, NHCH_2), 2.69 (d, *J* = 13.9 Hz, 1H, ArCH_2), 2.63 (d, *J* = 13.9 Hz, 1H, ArCH_2), 2.18 (ddd, *J* = 7.9, 6.4, 2.9 Hz, 1H, NHCH$_2$C*H*), 2.06 – 2.00 (m, 1H, CHCH_2CH), 1.80 – 1.74 (m, 1H, CHCH$_2$CH_2), 1.63 (ddd, *J* = 11.7, 5.2, 2.5 Hz, 2H, CHCH_2CH$_2$), 1.56 (t, *J* = 4.5 Hz, 1H, CH$_2$C*H*CH$_2$), 1.23 – 1.20 (m, 1H, CHCH$_2$CH_2), 0.96 (dd, *J* = 12.4, 4.1 Hz, 1H, CHCH_2CH), 0.90 (s, 3H, CH_3), 0.89 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.3 (C), 158.0 (C), 150.3 (C), 148.1 (CH), 137.4 (CH), 132.2 (C), 131.0 (CH), 126.1 (CH), 122.3 (CH), 113.6 (CH), 55.3 (CH_3), 51.4 (C), 50.0 (C), 45.8 (CH), 42.8 (CH), 42.6 (CH_2), 36.9 (CH_2), 35.6 (CH_2), 28.2 (CH_2), 27.7 (CH_3), 19.9 (CH_3), 19.3 (CH_3); **HRMS** found (ES) $[M+H]^+$ 379.2384, $C_{24}H_{31}N_2O_2$+H requires 379.2386.

Removal of the picolinamide auxiliary

Reaction performed in an air atmosphere.

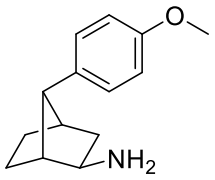
Water (2.0 ml) and HCl (0.50 ml, 12 M) were added to a solution of picolinamide (0.20 mmol, 1 eq) in THF (2.0 ml) and the solution stirred for 5 minutes. Zinc dust (196 mg, 3.0 mmol, 15 eq) was added portionwise over half an hour and the resulting suspension stirred for 16 hours. The reaction mixture was filtered through Celite®, and saturated $NaHCO_3$ (50 ml) was added to the filtrate. The organic layer was extracted with $CHCl_3$ (3 × 30 ml), and the combined organic layers were washed with aqueous HCl (1 M, 50 ml). Saturated aqueous $NaHCO_3$ was added to the aqueous layer to adjust the pH to ~8, and the product extracted into $CHCl_3$. The organic layer was washed with water (20 ml), brine (20 ml), dried over $MgSO_4$ and concentrated to give the free amine.

(1*S*,2*S*,4*R*,6*S*)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine 230



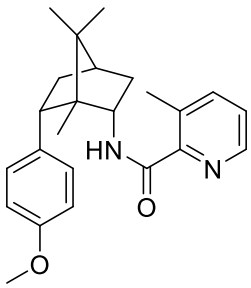
Yellow oil; 42 mg, 0.16 mmol, 81%; **[α]$_D^{18}$** +14.6 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 2981 (CH), 2948 (CH), 1512 (CC); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 7.31 (d, *J* = 8.6 Hz, 2H, OCCHC*H*), 6.86 (d, *J* = 8.7 Hz, 2H, OCC*H*), 3.80 (s, 3H, OCH_3), 3.21 (dd, *J* = 11.6, 5.7 Hz, 1H, ArC*H*), 3.10 (dd, *J* = 10.5, 6.2 Hz, 1H, NH_2CH), 2.43 – 2.36 (m, 1H, NH_2CHCH_2), 2.22 – 2.16 (m, 1H, ArCHCH_2), 1.94 (dd, *J* = 13.1, 5.9 Hz, 1H, ArCHCH_2), 1.82 (t, *J* = 4.7 Hz, 1H, CH_2CHCH_2), 1.13 – 1.10 (m, 1H, NH_2CHCH_2), 1.02 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.91 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 158.0 (C), 134.8 (C), 129.5 (CH), 114.0 (CH), 58.6 (CH), 55.4 (CH_3), 53.4 (C), 51.0 (C), 46.6 (CH), 43.4 (CH), 39.0 (CH_2), 32.9 (CH_2), 20.6 (CH_3), 19.8 (CH_3), 13.6 (CH_3); **LRMS** (ES) 260.2 ([M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 260.2012, $C_{17}H_{25}NO$+H requires 260.2014.

7-(4-Methoxyphenol)bicyclo[2.2.1]heptan-2-amine 231



Yellow oil; 32 mg, 0.15 mmol, 74%; **ν_{max}** (film/cm^{-1}) 2946 (CH), 1832 (CH), 1510 (CC) 1244 (CO); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 7.26 (d, *J* = 8.7 Hz, 2H, OCCHC*H*), 6.83 (d, *J* = 8.5 Hz, 2H, OCC*H*), 3.78 (s, 3H, OCH_3), 2.88 (s, 1H, ArC*H*), 2.82 (s, 1H, NH_2CH), 2.69 (m, 1H, NH_2CH_2CH), 2.50 (d, *J* = 2.6 Hz, 1H, NH_2CHCH), 1.83 (dd, *J* = 12.8, 8.2 Hz, 1H, NH_2CHCH_2), 1.72 (s, 1H, $NH_2CHCHCH_2$), 1.68 – 1.61 (m, 1H, $NH_2CHCHCH_2CH_2$), 1.56 – 1.38 (m, 3H, NH_2CH_2, NH_2), 1.25 – 1.21 (m, 2H, $NH_2CHCHCH_2CH_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 157.7 (C), 133.0 (C), 129.4 (CH), 113.9 (CH), 57.1 (CH), 55.3 (CH_3), 51.8 (CH), 49.7 (CH), 40.7 (CH_2), 38.1 (CH), 28.8 (CH_2), 28.7 (CH_2); **LRMS** (ES) 218.65 ([M+H]$^+$); **HRMS** found (ES) [M+H]$^+$ 218.1555, $C_{14}H_{19}NO$+H requires 218.1514.

***N*-((1*S*,2*S*,4*R*,6*S*)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-3-methylpicolinamide 233**

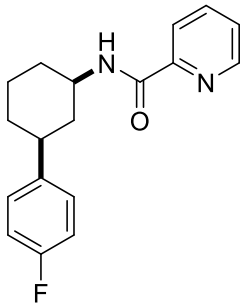


Prepared according to general arylation procedure A using amide **232** (26 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 30%

EtOAc in petrol) to give the product as a white solid; 36 mg, 0.097 mmol 97% (aryl iodide); 37 mg, 0.098 mmol, 98% (aryl bromide).

M.p 128 – 130 °C; **$[\alpha]_D^{24}$** +5.93 (*c* = 0.3, $CHCl_3$); **^{1}H NMR** (700 MHz, $CDCl_3$) *δ* 8.02 (ddd, *J* = 4.6, 1.6, 0.5 Hz, 1H, pyNC*H*), 7.72 (d, *J* = 9.0 Hz, 1H, N*H*), 7.44 – 7.39 (m, 1H, pyNCHCHC*H*), 7.34 (d, *J* = 8.5 Hz, 2H, OCCHC*H*), 7.14 (dd, *J* = 7.7, 4.6 Hz, 1H, pyNCHC*H*), 6.87 (d, *J* = 8.8 Hz, 2H, OCC*H*), 4.47 (dddd, *J* = 11.3, 9.3, 6.0, 2.0 Hz, 1H, NHC*H*), 3.77 (s, 3H, OCH_3), 3.28 (dd, *J* = 11.9, 4.5 Hz, 1H, ArC*H*), 2.60 (s, 3H, ArCH_3), 2.54 (dddd, *J* = 13.4, 11.4, 5.0, 3.3 Hz, 1H, NHCHCH_2), 2.24 (tt, *J* = 12.5, 3.9 Hz, 1H, ArCHCH_2), 1.99 (dd, *J* = 13.1, 5.8 Hz, 1H, ArCHCH_2), 1.91 (t, *J* = 4.7 Hz, CH_2CHCH_2), 1.24 (dd, *J* = 12.0, 4.7 Hz, 1H, NHCH_2), 1.09 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.05 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 166.3 (C), 158.1 (C), 147.5 (C), 144.9 (CH), 140.3 (CH), 134.7 (C), 134.0 (C), 129.9 (CH), 125.0 (CH), 114.4 (CH), 55.3 (CH_3), 54.1 (CH), 53.8 (C), 50.9 (C), 47.0 (CH), 43.7 (CH), 37.1 (CH_2), 33.0 (CH_2), 20.5 (CH_3), 20.3 (CH_3), 20.0 (CH_3), 13.8 (CH_3); **HRMS** found (ES) $[M+H]^+$ 379.2383, $C_{24}H_{30}N_2O_2$+H requires 379.2386.

***N*-(3-(4-fluorophenyl)cyclohexyl)picolinamide 238**

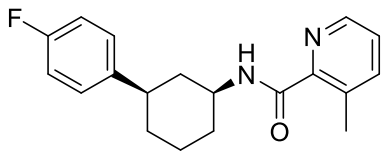


Prepared according to the general arylation procedure B using picolinamide **160** (40 mg, 0.20 mmol) and 4-fluoroiodobenzene (92 µl, 0.80 mmol) at 130 °C. Purified by flash column chromatography (0 – 40 % EtOAc in petrol) Product was further purified by recrystalisation from hot petrol/$CHCl_3$ to give the product as a white crystalline solid (48 mg, 0.16 mmol, 80%).

M.p 96 – 99 °C; **ν_{max}** (film/cm^{-1}) 3354 (NH), 2932 (CH), 2857 (CH), 1650 (CO), 1525 (CC); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 8.53 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.20 (dt, *J* = 7.8, 1.1 Hz, 1H, pyCC*H*), 7.97 (d, *J* = 8.1 Hz, 1H, N*H*), 7.90 – 7.77 (m, 1H, pyCCHC*H*), 7.46 – 7.36 (m, 1H, pyNCHC*H*), 7.23 – 7.12 (m, 2H, FCCHC*H*), 7.04 – 6.90 (m, 2H, FCC*H*), 4.12 (tdt, *J* = 12.3, 8.3, 4.0 Hz, 1H, NHC*H*), 2.72 (tt, *J* = 12.3, 3.3 Hz, 1H, ArC*H*), 2.32 – 2.23 (m, 1H, CHCH_2CH), 2.19 – 2.11 (m, 1H, NHCHCH_2CH_2), 2.00 – 1.93 (m, 1H, $CH_2CH_2CH_2$), 1.93 –

1.87 (m, 1H, ArCHCH_2CH$_2$), 1.59 (qt, *J* = 13.2, 3.5 Hz, 1H, CH$_2$CH_2CH$_2$), 1.47 – 1.29 (m, 3H, Cy*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) *δ* 163.1 (C), 161.0 (d, *J* = 243.5 Hz, C), 149.8 (C), 147.7 (CH), 141.6 (d, *J* = 3.1 Hz, C), 137.1 (C), 127.8 (d, *J* = 7.8 Hz, CH), 125.8 (CH), 121.9 (CH), 114.8 (d, *J* = 21.0 Hz, CH), 48.4 (CH), 42.1 (CH), 40.7 (CH$_2$), 33.09 (CH$_2$), 32.4 (CH$_2$), 24.8 (CH$_2$); **HRMS** found (ESI) $[M+H]^+$ 299.1554, $C_{18}H_{19}N_2O$+H requires 299.1557.

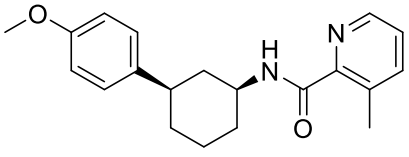
N-((1*S*,3*R*)-3-(4-Fluorophenyl)cyclohexyl)-3-methylpicolinamide 236



Prepared according to general arylation procedure **A** or **B**, using amide **235** (44 mg, 0.20 mmol) and 4-iodoanisole (188 mg, 0.80 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a colourless oil.
A (45 mg, 1.44 mmol, 72%)
B (57 mg, 1.84 mmol, 91%)

ν_{max} (film/cm^{-1}) 3329 (NH), 2981 (CH), 2862 (CH), 1651 (CO), 1515 (CC); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.36 (dd, *J* = 4.6, 1.1 Hz, 1H, pyNC*H*), 8.06 (d, *J* = 8.2 Hz, 1H, N*H*), 7.57 (ddd, *J* = 7.8, 1.5, 0.7 Hz, 1H, pyNCHCHC*H*), 7.29 (dd, *J* = 7.7, 4.6 Hz, 1H, pyNCHC*H*), 7.19 – 7.13 (m, 2H, FCCHC*H*), 6.99 – 6.92 (m, 2H, FCC*H*), 4.07 (tdt, *J* = 12.1, 8.2, 3.9 Hz, 1H, NHC*H*), 2.79 – 2.65 (m, 4H, ArCH_3, ArC*H*), 2.29 – 2.21 (m, 1H, CHCH_2CH), 2.13 (d, *J* = 12.4 Hz, 1H, Cy*H*), 1.95 (ddt, *J* = 13.2, 6.5, 3.3 Hz, 1H, Cy*H*), 1.91 – 1.85 (m, 1H, Cy*H*), 1.58 (qt, *J* = 13.1, 3.4 Hz, 1H, Cy*H*), 1.45 – 1.30 (m, 3H, CHCH_2CH, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 165.2 (C), 161.4 (d, *J* = 243.5 Hz, C), 147.4 (C), 145.4 (CH), 142.1 (d, *J* = 3.1 Hz, C), 141.1 (CH), 135.6 (C), 128.3 (d, *J* = 4.3 Hz, CH), 125.7 (CH), 115.2 (d, *J* = 20.1 Hz, CH), 48.7 (CH), 42.8 (CH), 41.2 (CH$_2$), 33.6 (CH$_2$), 32.9 (CH$_2$), 25.3 (CH$_2$), 20.7 (CH$_3$); **HRMS** (ES) m/z [M + H]+ found 313.13715, $C_{19}H_{20}N_2OF$+H requires 313.1716.

N-((3-(4-Methoxyphenyl)cyclohexyl)-3-methylpicolinamide 237

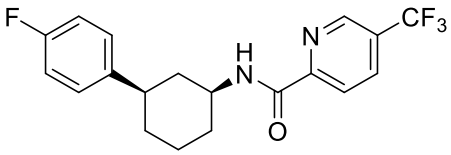


Prepared according to general arylation procedure B, using amide **235** (44 mg, 0.20 mmol) and 4-iodoanisole (188 mg, 0.80 mmol) at 130 °C. Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a colourless oil (55 mg, 0.170 mmol, 85%).

ν_{max} (film/cm^{-1}) 3379 (NH), 2924 (CH), 2861 (CH), 1675 (CO), 1512 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 4.6, 1.0 Hz, 1H, pyNC*H*), 8.12 – 7.99 (m, 1H, N*H*), 7.56 (ddd, *J* = 7.7, 1.6, 0.7 Hz, 1H, pyNCHCHC*H*), 7.28 (dd, *J* = 7.7, 4.6 Hz, 1H, pyNCHC*H*), 7.15 – 7.11 (m, 2H, OCCHC*H*), 6.86 – 6.80 (m, 2H, OCC*H*), 4.07 (tdt, *J* = 12.1, 8.2, 4.0 Hz, 1H, NHC*H*), 3.78 (d, *J* = 4.1 Hz, 3H, OCH_3), 2.74 (s, 3H, ArCH_3), 2.68 (tt, *J* = 12.2, 3.3 Hz, 1H, ArC*H*), 2.25 (dtd, *J* = 9.3, 3.5, 1.8 Hz, 1H, Cy*H*), 2.13 (dd, *J* = 7.2, 5.3 Hz, 1H, Cy*H*), 1.97 – 1.91 (m, 1H, Cy*H*), 1.91 – 1.86 (m, 1H, Cy*H*), 1.62 – 1.52 (m, 1H, Cy*H*), 1.46 – 1.34 (m, 2H, Cy*H*), 1.34 – 1.27 (m, 1H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 165.2 (C), 158.0 (C), 147.6 (C), 145.4 (CH), 141.0 (CH), 138.7 (C), 135.6 (C), 127.8 (CH), 125.6 (CH), 113.9 (CH), 55.4 (CH_3), 48.8 (CH), 42.5 (CH), 41.3 (CH_2), 33.7 (CH_2), 33.0 (CH_2), 25.4 (CH_2), 20.7 (CH_3); **HRMS** (ES) m/z [M + H]+ found 325.1916, $C_{20}H_{23}N_2O_2$+H requires 325.1916.

When prepared according to general arylation procedure A yield was 84%. Determined using 1,3,5-trimethoxybenzene as the internal standard.

***N*-3-(4-Fluorophenyl)cyclohexyl)-5-(trifluoromethyl)picolinamide 240**

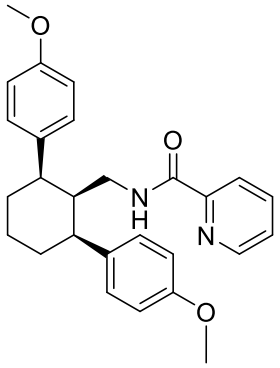


Prepared according to general arylation procedure B using amide **239** (54 mg, 0.20 mmol) and 4-fluoroiodobenzene (92 µl, 0.80 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a yellow oil (48 mg, 0.127 mmol, 63%).

ν_{max} (film/cm^{-1}) 3382 (NH), 2930 (CH), 2856 (CH), 1679 (CO), 1524 (CC); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.82 – 8.77 (m, 1H), 8.33 (d, *J* = 8.2 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H, N*H*), 7.20 – 7.13 (m, 2H, FCCHC*H*), 6.98 (ddd, *J* = 10.8, 5.9, 2.6 Hz, 2H, FCC*H*), 4.20 – 4.04 (m, 1H, NHC*H*), 2.79 – 2.67 (m, 1H, ArC*H*), 2.27 (d, *J* = 12.3 Hz, 1H, Cy*H*), 2.15 (d, *J* = 12.5 Hz, 1H, Cy*H*), 2.01 – 1.87 (m, 2H, Cy*H*), 1.66 – 1.58 (m, 1H, Cy*H*), 1.48 – 1.32 (m, 3H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 162.1 (C), 161.5 (d, *J* = 243.8 Hz), 153.1 (d, *J* = 1.1 Hz, C), 145.2 (q, *J* = 3.8 Hz, CH), 141.8 (d, *J* = 3.1 Hz, C), 134.9 (q, *J* = 3.4 Hz, CH), 128.8 (q, *J* = 33.3 Hz, C), 128.2 (d, *J* = 7.8 Hz, CH), 123.3 (q, *J* = 272.7 Hz,

C), 122.2 (CH), 115.3 (d, *J* = 21.0 Hz, CH), 49.1 (CH), 42.5 (CH), 41.2 (CH_2), 33.4 (CH_2), 32.8 (CH_2), 25.2 (CH_2); **HRMS** found (ES) $[M+H]^+$ 367.1431, $C_{19}H_{18}N_2OF_4$+H requires 367.1433.

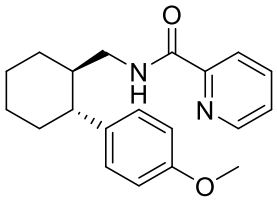
***N*-((2,6-Bis(4-methoxyphenyl)cyclohexyl)methyl)picolinamide 243**



A sealed tube was charged with amide **159** (43 mg, 0.20 mmol, 1 eq), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol%), $CuBr_2$ (4.4 mg, 0.02 mmol, 10 mol%), CsOAc (154 mg, 0.8 mmol, 4 eq), 4-iodoanisole (281 mg, 1.2 mmol, 6 eq) and 3-methyl-3-pentanol (0.2 ml). The mixture was heated at 150 °C for 24 hours, cooled and filtered through Celite®, washing with EtOAc. The crude product was purified by flash Column chromatography (10 – 70 % EtOAc in petrol) to give the title compound as a white solid (60 mg, 0.13 mmol, 65%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3377 (NH), 2926 (CH), 2856 (CH), 1666 (CO), 1509 (CC); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.21 (d, *J* = 4.7 Hz, 1H, pyNC*H*), 7.88 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.67 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.24 (ddd, *J* = 7.4, 4.8, 1.0 Hz, 1H, pyNCHC*H*), 7.20 (d, *J* = 8.6 Hz, 4H, OCCHC*H*), 6.78 – 6.73 (m, 4H, OCCiH), 6.72 (s, 1H, N*H*), 3.64 (s, 6H, OCH_3), 3.33 (t, *J* = 5.8 Hz, 2H, NHCH_2), 3.14 (dt, *J* = 12.7, 3.5 Hz, 2H, ArC*H*), 2.51 – 2.47 (m, 1H, $NHCH_2CH$), 2.17 – 2.12 (m, 1H, $ArCHCH_2CH_2$), 1.91 (dtd, *J* = **23.5, 13.0, 3.4** Hz, 4H, $ArCHCH_2$), 1.63 – 1.56 (m, 1H, $ArCHCH_2CH_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.2 (C), 158.0 (C), 149.8 (C), 147.4 (CH), 136.74 (C), 136.69 (CH), 128.1 (CH), 125.7 (CH), 121.5 (CH), 113.9 (CH), 55.1 (CH_3), 48.2 (CH), 46.2 (CH), 34.4 (CH_2), 26.7 (CH_2), 24.8 (CH_2); **LRMS** (CI NH_3) 431.24 ($[M+H]^+$); **HRMS** found (CI NH_3) $[M+H]^+$ 431.2250, $C_{27}H_{30}N_2O_3$+H requires 431.2251.

***N*-((2-(4-Methoxyphenyl)cyclohexyl)methyl)picolinamide 244**



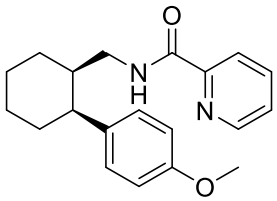
major

Colourless oil (10 mg, 0.032 mmol, 16%)

ν_{max} (film/cm^{-1}) 3389 (NH), 2922 (CH), 2851 (CH), 1671 (CO), 1510 (CC); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.3 Hz, 1H, pyNC*H*), 8.12 (t, *J* = 7.1 Hz, 1H, pyCC*H*), 7.81 (td, *J* = 7.7, 1.6 Hz, 2H, pyCCHC*H*, N*H*), 7.39 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H, NCHC*H*), 7.17 – 7.14 (m, 2H, OCCHC*H*), 6.84 (t, *J* = 5.7 Hz, 2H, OCC*H*), 3.77 (s, 3H, OCH_3), 3.27 – 3.22 (m, 1H, NHCH_2), 3.15 – 3.10 (m, 1H, NHCH_2), 2.28 (td, *J* = 11.6, 3.2 Hz, 1H, ArC*H*), 2.00 (d, *J* = 13.3 Hz, 1H, Cy*H*), 1.86 – 1.78 (m, 4H, NHCH$_2$C*H*, Cy*H*), 1.52 – 1.45 (m, 1H, Cy*H*), 1.39 – 1.33 (m, 2H, Cy*H*), 1.20 (m, 1H, Cy*H*); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.2 (C), 158.2 (C), 150.2 (C), 137.8 (CH), 137.2 (CH), 128.4 (C) 128.3 (CH), 126.0 (CH), 122.2 (CH), 114.2 (CH), 55.3 (CH_3), 48.4 (CH), 43.9 (CH), 43.4 (CH_2), 36.0 (CH_2), 31.2 (CH_2), 26.8 (CH_2), 26.2 (CH_2); **LRMS** (CI NH_3) 325.20 ([M+H]$^+$); **HRMS** found (CI NH_3) [M+H]$^+$ 325.1910, $C_{20}H_{24}N_2O_2$+H requires 325.1911.

IR and mass spec as a mixture of isomers

Minor isomer 245

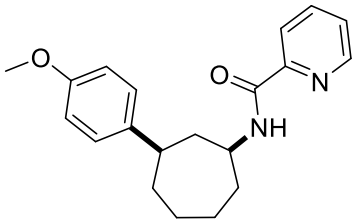


minor

Key NMR peaks for the identification of the minor isomer and stereochemistry

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.77 (s, 2H), 3.70 (ddd, *J* = 13.6, 9.4, 8.1 Hz, 1H), 3.02 (dt, *J* = 13.7, 4.8 Hz, 1H), 2.95 (dt, *J* = 11.8, 3.8 Hz, 1H), 2.21 (dd, *J* = 8.9, 4.6 Hz, 1H).

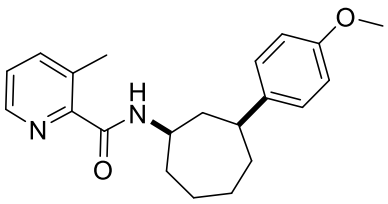
***N*-(3-(4-Methoxyphenyl)cycloheptyl)picolinamide 248**



Prepared according to general arylation procedure B, using amide **162** (109 mg, 0.50 mmol) and 4-iodoanisole (468 mg, 2.0 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a colourless oil (30 mg, 0.154 mmol, 31%). Mixture of diastereoisomers *d.r* = 92:8

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3372 (NH), 2925 (CH), 2872 (CH), 1661 (CO), 1509 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.52 (t, *J* = 9.1 Hz, 1H, pyNC*H*), 8.17 (d, *J* = 6.5 Hz, 1H, pyCC*H*), 8.01 (t, *J* = 12.6 Hz, 1H, N*H*), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.42 – 7.36 (m, 1H, pyNCHC*H*), 7.13 – 7.09 (m, 2H, OCCHC*H*), 6.82 – 6.79 (m, 2H, OCC*H*), 4.28 – 4.22 (m, 1H, NHC*H*), 3.77 (s, 3H, OCH_3), 2.85 – 2.80 (m, 1H, ArC*H*), 2.19 – 2.11 (m, 2H, CHCH_2CH and CH_2), 1.96 (ddd, *J* = 13.4, 7.2, 4.0 Hz, 1H, CH_2), 1.85 (dt, *J* = 13.2, 11.2 Hz, 1H, CHCH_2CH), 1.81 – 1.63 (m, 6H, CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.0 (C), 157.8 (C), 150.3 (C), 148.1 (CH), 141.2 (C), 137.4 (CH), 127.6 (CH), 127.6 (CH), 126.1 (CH), 122.3 (CH), 114.0 (CH), 113.9 (CH), 55.4 (CH_3), 50.2 (CH), 44.4 (CH), 42.8 (CH_2), 37.1 (CH_2), 35.2 (CH_2), 26.5 (CH_2), 23.9 (CH_2); **HRMS** (ES) m/z [M + H]+ found 325.1916, $C_{20}H_{23}N_2O_2$+H requires 325.1916.

***N*-(3-(4-methoxyphenyl)cycloheptyl)-3-methylpicolinamide 255**

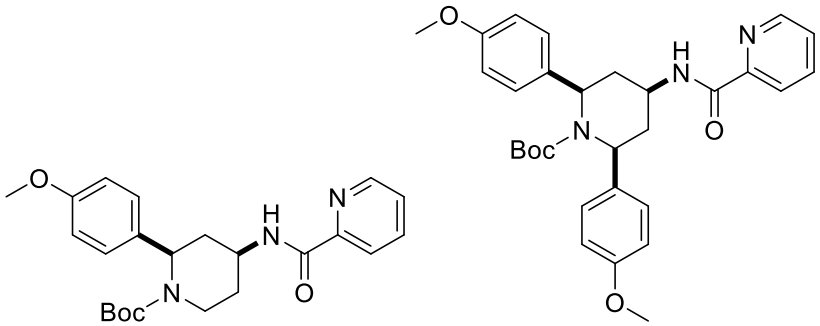


Prepared according to general arylation procedure B using amide **252** (116 mg, 0.50 mmol) and 4-iodoanisole (468 mg, 2.0 mmol). Purified by flash column chromatography (5 – 25% EtOAc in petrol) to give the product as a yellow oil (65 mg, 0.192 mol, 38%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3379 (NH), 2927 (CH), 2851 (CH), 1666 (CO), 1506 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.34 (ddd, *J* = 4.6, 1.6, 0.5 Hz, 1H, pyNC*H*), 8.11 (d, *J* = 8.2 Hz, 1H, N*H*), 7.56 – 7.53 (m, 1H, pyNCHCHC*H*), 7.26 (dd, *J* = 7.7, 4.6, 1H, pyNCHC*H*), 7.13 – 7.10 (m, 2H, OCCHC*H*), 6.82 – 6.79 (m, 2H, OCC*H*), 4.23 – 4.15 (m, 1H, NHC*H*), 3.77 (s, 3H,

OCH_2), 2.85 – 2.80 (m, 1H, ArC*H*), 2.72 (s, 3H, ArCH_3), 2.18 – 2.10 (m, 2H, CH_2), 1.98 – 1.93 (m, 1H, CH_2), 1.88 – 1.82 (m, 1H, CH_2), 1.81 – 1.66 (m, 6H, CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.8 (C), 157.8 (C), 147.6 (C), 145.4 (CH), 141.3 (C), 141.0 (CH), 135.5 (C), 127.6 (CH), 125.6 (C), 113.9 (CH), 55.4 (CH_3), 50.0 (CH), 44.5 (CH), 43.0 (CH_2), 37.1 (CH_2), 35.2 (CH_2), 26.4 (CH_2), 24.0 (CH_2), 20.7 (CH_3); **HRMS** found (ES) $[M+H]^+$ 339.2061, $C_{21}H_{26}N_2O_2$+H requires 339.2067.

***tert*-Butyl 2-(4-methoxyphenyl)-4-(picolinamido)piperidine-1-carboxylate 257** and ***tert*-butyl 2,6-bis(4-methoxyphenyl)-4-(picolinamido)piperidine-1-carboxylate 258**



Prepared according to general arylation procedure A, using amide **256** (92 mg, 0.30 mmol) and 4-iodoanisole (282 mg, 1.2 mmol). Purified by flash column chromatography (5 – 40% EtOAc in petrol) to give the separated monoarylated (yellow oil, 26 mg, 0.063 mmol, 21%) and diarylated (colourless oil, 29 mg, 0.057 mmol, 19%) products.

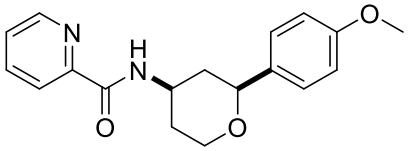
Monoarylation 257

ν_{max} (film/cm^{-1}) 3374 (NH), 2961 (CH), 2845 (CH), 1699 (CO), 1662 (CO), 1513 (CC); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.21 – 8.18 (m, 1H, pyNC*H*), 8.04 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.87 (s, 1H, N*H*), 7.75 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.31 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H, pyNCHC*H*), 7.14 (d, *J* = 8.1 Hz, 2H, OCCHC*H*), 6.87 – 6.82 (m, 2H, OCC*H*), 5.38 (s, 1H, ArC*H*), 4.43 – 4.35 (m, 1H, NHC*H*), 4.19 – 4.11 (m, 1H, NCH_2), 3.78 (s, 3H, OCH_3), 3.32 – 3.21 (m, 1H, NCH_2), 2.45 (d, *J* = 14.4 Hz, 1H, ArCHCH_2), 2.30 – 2.22 (m, 1H, ArCHCH_2), 2.00 – 1.92 (m, 1H, NCH_2CH_2), 1.82 (s, 1H, NCH_2CH_2), 1.42 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.7 (C), 158.3 (C), 156.8 (C), 149.7 (C), 148.0 (CH), 137.8 (CH), 137.0 (C), 128.1 (CH), 126.4 (CH), 122.5 (CH), 113.7 (CH), 80.3 (C), 55.8 (CH), 55.4 (CH_3), 42.9 (CH_2), 43.3 (CH), 35.6 (CH_2), 34.6 (CH_2), 28.3 (CH_3); **HRMS** found (ES) $[M+H]^+$ 412.2240, $C_{23}H_{29}N_3O_4$+H requires 412.2236

Diarylation 258

ν_{max} (film/cm^{-1}) 3352 (NH), 2991 (CH), 2872 (CH), 1695 (CO), 1669 (CO), 1511 (CC); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.2 Hz, 1H, pyNC*H*), 8.20 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 8.12 (d, *J* = 8.1 Hz, 1H, N*H*), 7.86 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.44 (ddd, *J* = 6.4, 4.8, 1.1 Hz, 1H, pyNC*H*), 7.20 (d, *J* = 8.6 Hz, 4H, OCCHC*H*), 6.85 – 6.79 (m, 4H, OCC*H*), 5.28 – 5.20 (m, 2H, ArC*H*), 4.46 (dd, *J* = 14.9, 6.6 Hz, 1H, NHC*H*), 3.79 (d, *J* = 6.8 Hz, 6H, OCH_3), 2.54 – 2.42 (m, 2H, NHCHCH_2), 2.15 (dt, *J* = 14.1, 8.7 Hz, 2H, NHCHCH_2), 1.24 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.7 (C), 158.3 (C), 156.8 (C), 149.7 (C), 148.0 (CH), 137.8 (CH), 137.0 (C), 128.1 (CH), 126.4 (CH), 122.5 (CH), 113.7 (CH), 80.3 (C), 55.8 (CH), 55.4 (CH_3), 43.3 (CH), 35.6 (CH_2), 28.3 (CH_3); **HRMS** found (ES) $[M+H]^+$ 518.2613, $C_{30}H_{35}N_3O_5$+H requires 518.2610.

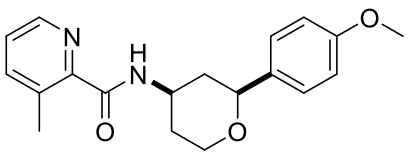
N-(2-(4-methoxyphenyl)tetrahydro-2H-pyran-4-yl)picolinamide 260



Prepared according to general arylation procedure B, using amide **259** (42 mg, 0.20 mmol) and 4-iodoanisole (188 mg, 0.80 mmol) at 150 °C. Purified by flash column chromatography (5 – 40% EtOAc in petrol) to give the product as a colourless oil (47 mg, 0.15 mmol, 75%).

ν_{max} (film/cm^{-1}) 3376 (NH), 2950 (CH), 2836 (CH), 1668 (CO), 1514 (CC), 1247 (CO); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.20 (dt, *J* = 7.9, 1.1 Hz, 1H, pyCC*H*), 7.99 (d, *J* = 8.1 Hz, 1H, N*H*), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*h*), 7.32 – 7.26 (m, 2H, OCCHC*H*), 6.90 – 6.84 (m, 2H, OCC*H*), 4.44 (dd, *J* = 11.3, 1.9 Hz, 1H, ArC*H*), 4.36 (tdd, *J* = 12.4, 8.1, 4.3 Hz, 1H, NHC*H*), 4.21 (ddd, *J* = 11.8, 4.7, 1.5 Hz, 1H, OCH_2), 3.79 (s, 3H, OCH_3), 3.74 (td, *J* = 12.2, 2.1 Hz, 1H, OCH_2), 2.27 (ddt, *J* = 12.7, 4.1, 2.0 Hz, 1H, OCHCH_2), 2.06 (ddd, *J* = 12.7, 4.2, 2.2 Hz, 1H, OCH_2CH_2), 1.76 – 1.66 (m, 1H, OCH_2CH_2), 1.63 – 1.59 (m, 1H, OCHCH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.6 (C), 159.2 (C), 149.9 (C), 148.1 (CH), 137.6 (CH), 134.3 (C), 127.3 (CH), 126.4 (CH), 122.5 (CH), 113.9 (CH), 78.6 (CH), 67.3 (CH_2), 55.4 (CH_3), 46.7 (CH), 40.5 (CH_2), 32.9 (CH_2); **HRMS** found (ES) $[M+H]^+$ 313.1552, $C_{18}H_{20}N_2O_3$+H requires 313.1552.

***N*-(2-(4-Methoxyphenyl)tetrahydro-2H-pyran-4-yl)-3-methylpicolinamide 263**



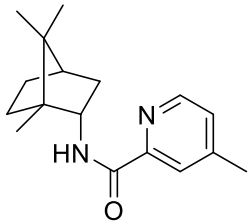
Prepared according to general arylation procedure B, using amide **262** (44 mg, 0.20 mmol) and 4-iodoanisole (188 mg, 0.80 mmol) at 150 °C. Purified by flash column chromatography (5 – 40% EtOAc in petrol) to give the product as a yellow oil (55 mg, 0.17 mmol, 85%).

ν_{max} (film/cm^{-1}) 3371 (NH), 2951 (CH), 2835 (CH), 1663 (CO), 1507 (CC), 1244 (CO); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 4.6, 1.1 Hz, 1H, pyNC*H*), 8.11 (d, *J* = 8.0 Hz, 1H, N*H*), 7.59 (ddd, *J* = 7.8, 1.6, 0.7 Hz, 1H, pyNCHCHC*H*), 7.33 – 7.25 (m, 3H, pyNCHC*H* and OCCHC*H*), 6.89 – 6.84 (m, 2H, OCC*H*), 4.43 (dd, *J* = 11.3, 1.9 Hz, 1H, ArC*H*), 4.37 – 4.25 (m, 1H, NHC*H*), 4.21 (ddd, *J* = 11.8, 4.7, 1.5 Hz, 1H, OCH_2), 3.79 (s, 3H, OCH_3), 3.73 (td, *J* = 12.1, 2.1 Hz, 1H, OCH_2), 2.74 (s, 3H, ArCH_3), 2.27 (ddt, *J* = 12.7, 4.1, 2.0 Hz, 1H, OCHCH_2), 2.05 (ddd, *J* = 12.7, 4.2, 2.0 Hz, 1H, OCH$_2$CH_2), 1.75 – 1.65 (m, 1H, OCH$_2$CH_2), 1.65 – 1.55 (m, 1H, OCHCH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 165.3 (C), 159.2 (C), 147.1 (C), 145.4 (CH), 141.2 (CH), 135.7 (C), 134.4 (C), 127.3 (CH), 125.8 (CH), 113.9 (CH), 78.7 (CH), 67.3 (CH_2), 55.4 (CH_3), 46.5 (CH), 40.7 (CH_2), 32.9 (CH_2), 20.7 (CH_3); **HRMS** found (ES) $[M+H]^+$ 327.1698, $C_{19}H_{22}N_2O_3$+H requires 327.1709.

6.2 Experimental for Chapter 3

6.2.1 Synthesis of substituted picolinamides

4-methyl-*N*-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 273

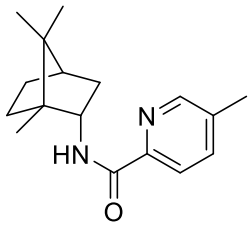


Prepared according to general amidation procedure A, using *R*-(+)-bornylamine (77 mg, 0.50 mmol) and 4-methylpicolinic acid (82 mg, 0.60 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a colourless oil (74 mg, 0.27 mmol, 54%).

$[\alpha]_D^{24}$ +4.20 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3384 (NH), 2952 (CH), 2880 (CH), 1673 (CO), 1516 (CC); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.9 Hz, 1H, pyNC*H*), 8.26 – 8.10 (m,

1H, N*H*), 8.04 – 8.00 (m, 1H, pyCC*H*C), 7.25 – 7.19 (m, 1H, pyNCHC*H*), 4.43 (dddd, *J* = 11.5, 9.6, 4.6, 2.3 Hz, 1H, NHC*H*), 2.46 – 2.39 (m, 4H, ArCH_3, NHCHCH_2), 1.87 – 1.78 (m, 1H, CH_2CH$_2$CH), 1.74 – 1.67 (m, 2H, CH$_2$CH_2C*H*), 1.43 (dqd, *J* = 14.9, 4.8, 2.5 Hz, 1H, CH$_2$CH_2CH), 1.36 – 1.28 (m, 1H, CH_2CH$_2$CH), 1.06 – 0.96 (m, 4H, CH_3, NHCHCH_2), 0.90 (s, 3H, CH_3), 0.87 (s, 3H, CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) *δ* 164.2 (C), 149.7 (C), 148.4 (C), 147.5 (CH), 126.5 (CH), 122.8 (CH), 53.5 (CH), 49.6 (C), 47.9 (C), 44.7 (CH), 37.2 (CH_2), 28.1 (CH_2), 27.8 (CH_2), 20.8 (CH_3), 19.6 (CH_3), 18.5 (CH_3), 13.5 (CH_3); **HRMS** found (ES) $[M+H]^+$ 273.1966, $C_{17}H_{24}N_2O$+H requires 273.1961.

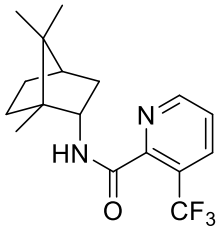
5-Methyl-*N*-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 276



Prepared according to general amidation procedure A, using *R*-(+)-bornylamine (77 mg, 0.50 mmol) and 5-methylpicolinic acid (82 mg, 0.60 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a colourless oil (118 mg, 0.43 mmol, 87%).

$[\alpha]_D^{24}$ +4.00 (*c* = 0.7, $CHCl_3$); **^{1}H NMR** (700 MHz, $CDCl_3$) *δ* 8.36 – 8.34 (m, 1H, pyNC*H*), 8.14 (d, *J* = 8.5 Hz, 1H, N*H*), 8.07 (d, *J* = 6.9 Hz, 1H, pyNCC*H*), 7.63 – 7.61 (m, 1H, pyCH$_3$CC*H*), 4.42 (dddd, *J* = 11.5, 9.5, 4.6, 2.3 Hz, 1H, NHC*H*), 2.44 – 2.37 (m, 4H, ArCH$_3$ and NHCHCH_2), 1.85 – 1.78 (m, 1H, CCH_2), 1.72 – 1.67 (m, 2H, CCH$_2$CH_2 and CH$_2$C*H*CH$_2$), 1.42 (dddd, *J* = 14.2, 12.2, 4.6, 2.3 Hz, 1H, CCH$_2$CH_2), 1.34 – 1.29 (m, 1H, CCH_2), 1.01 (s, 3H, CH_3), 0.98 (dd, *J* = 13.4, 4.6 Hz, 1H, NHCHCH_2), 0.90 (s, 3H, CH_3), 0.86 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.6 (C), 148.6 (CH), 147.9 (C), 137.8 (CH), 136.2 (C), 121.9 (CH), 53.9 (CH), 50.0 (C), 48.4 (C), 45.2 (CH), 37.7 (CH_2), 28.6 (CH_2), 28.3 (CH_2), 20.0 (CH_3), 18.9 (CH_3), 18.7 (CH_3), 13.9 (CH_3); **HRMS** found (ES) $[M+H]^+$ 273.1966, $C_{17}H_{24}N_2O$+H requires 273.1961.

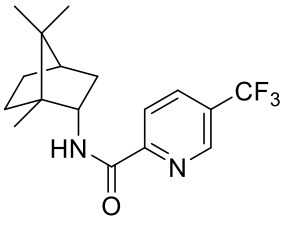
3-(Trifluoromethyl)-*N*-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 270



Prepared according to general amidation procedure A, using *R*-(+)-bornylamine (77 mg, 0.50 mmol) and 3-trifluoromethylpicolinic acid (115 mg, 0.60 mmol). Purified by flash column chromatography (0 – 5% MeOH in DCM) to give the product as an off-white solid (131 mg, 0.40 mmol, 80%).

M.p 95 – 96 °C; **$[\alpha]_D^{24}$** +5.20 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3043 (NH), 3078 (CH), 2943 (CH), 1690 (CO), 1513 (CC); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.77 – 8.72 (m, 1H, pyNC*H*), 8.16 (d, *J* = 8.0 Hz, 1H, pyNCHC*H*), 7.73 (d, *J* = 8.4 Hz, 1H, N*H*), 7.56 (dd, *J* = 8.0, 4.8 Hz, 1H, CF_3CCH), 4.45 (tdd, *J* = 9.6, 4.5, 2.2 Hz, 1H, NHC*H*), 2.45 (ddt, *J* = 14.1, 11.1, 3.9 Hz, 1H, NHCHCH_2), 1.82 (tq, *J* = 12.2, 4.1 Hz, 1H, CH_2CH_2CH), 1.73 (t, *J* = 4.5 Hz, 1H, CH_2CHCH_2), 1.65 (ddd, *J* = 13.8, 9.4, 4.4 Hz, 1H, CH_2CH_2CH), 1.50 – 1.40 (m, 1H, CH_2CH_2CH), 1.28 (ddd, *J* = 13.4, 9.3, 4.5 Hz, 1H, CH_2CH_2CH), 1.03 – 0.99 (s, 3H, CH_3), 0.97 (dd, *J* = 13.5, 4.6 Hz, 1H, NHCHCH_2), 0.90 (m, 6H, 2 × CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.9 (C), 150.2 (CH), 149.5 (C), 135.9 (q, *J* = 6.4 Hz, CH), 125.6 (q, *J* = 34.3 Hz, C), 123.7 (CH), 122.6 (q, *J* = 273.1 Hz, C), 53.8 (CH), 49.6 (C) , 48.0 (C), 44.7 (CH), 37.2 (CH_2), 28.1 (CH_2), 27.8 (CH_2), 19.5 (CH_3), 18.3 (CH_3), 13.4 (CH_3); **HRMS** found (ES) $[M+H]^+$ 327.1670, $C_{17}H_{21}N_2OF_3$+H requires 327.1679.

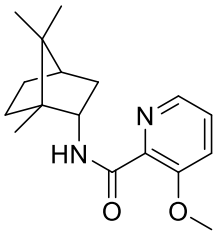
5-(Trifluoromethyl)-*N*-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 279



Prepared according to general amidation procedure A, using *R*-(+)-bornylamine (154 mg, 1.0 mmol) and 5-trifluoromethylpicolinic acid (230 mg, 1.2 mmol). Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a white solid (298 mg, 0.916 mmol, 92%).

M.p 78 – 80 °C; **[α]$_D^{24}$** +9.00 (*c* = 0.8, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3375 (NH), 2939 (CH), 2889 (CH), 1670 (CO), 1552 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) *δ* 8.84 (s, 1H, pyNC*H*), 8.33 (d, *J* = 8.1 Hz, 1H, CF_3CC*H*CH), 8.14 (d, *J* = 8.2 Hz, 1H, N*H*), 8.09 (d, *J* = 8.1 Hz, 1H, pyCC*H*CH), 4.43 (ddd, *J* = 11.2, 4.2, 2.2 Hz, 1H, NHC*H*), 2.48 – 2.40 (m, 1H, NHCHCH_2), 1.84 (ddd, *J* = 16.5, 8.4, 4.0 Hz, 1H, CH_2C*H*$_2$CH), 1.74 (t, *J* = 4.4 Hz, 1H, CH_2C*H*CH_2), 1.66 (dt, *J* = 9.5, 6.2 Hz, 1H, C*H*$_2CH_2$CH), 1.48 – 1.42 (m, 1H, C*H*$_2CH_2$CH), 1.34 – 1.29 (m, 1H, CH_2C*H*$_2$CH), 1.01 (s, 3H, C*H*$_3$), 0.98 (dd, *J* = 13.5, 4.4 Hz, 1H, NHCHCH_2), 0.93 – 0.90 (s, 3H, C*H*$_3$), 0.87 (s, 3H, C*H*$_3$). **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 162.9 (C), 153.2, 145.3 (q, *J* = 3.9 Hz, CH), 134.9 (q, *J* = 3.4 Hz, CH), 128.8 (q, *J* = 33.2 Hz, C), 123.4 (q, *J* = 272.7 Hz, C), 122.2 (CH), 54.2 (CH), 50.1 (C), 48.4 (C), 45.1 (CH), 37.7 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 19.9 (CH_3), 18.8 (CH_3), 13.9 (CH_3); **HRMS** found (ES) $[M+H]^+$ 327.1683, $C_{17}H_{22}N_2OF_3$+H requires 327.1684.

3-Methoxy-*N*-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 282

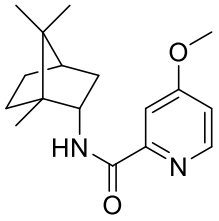


A solution of *R*-(+)-bornylamine (154 mg, 1.0 mmol, 1 equiv.) in DMF (1 ml) was added to DIPEA (209 µl, 1.2 mmol, 1.2 eq), 3-methyl-2-picolinic acid (184 mg, 1.2 mmol,1.2 eq) and HATU (456 mg, 1.2 mmol, 1.2 eq) in dimethylformamide (0.2 M). The resulting solution was stirred at room temperature for 16 hours. Saturated aqueous lithium chloride (20 ml) was added and the aqueous layer was extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed with water, sat. aq $NaHCO_3$ (20 ml), dilute aq AcOH (pH 4, 20 ml), brine (20 ml), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (0 – 5% MeOH in DCM) to give the product as a colourless oil (187 mg, 0.648 mmol, 65%).

[α]$_D^{24}$ +0.96 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3390 (NH), 2950 (CH), 2880 (CH), 1658 (CO), 1508 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) *δ* 8.20 (dd, *J* = 4.3, 1.4 Hz, 1H, pyNC*H*), 7.83 (s, 1H, N*H*), 7.38 (dd, *J* = 8.5, 4.3 Hz, 1H, pyNCHC*H*), 7.36 (dd, *J* = 8.5, 1.3 Hz, 1H, pyNCHCHC*H*), 4.43 (dddd, *J* = 11.3, 9.2, 4.6, 2.3 Hz, 1H, NHC*H*), 3.93 (s, 3H, OC*H*$_3$), 2.45 – 2.38 (m, 1H, NHCHCH_2), 1.83 – 1.77 (m, 1H, C*H*$_2CH_2$CH), 1.69 (t, *J* = 4.5 Hz, 1H, CH_2C*H*CH_2), 1.66 (ddd, *J* = 13.8, 9.5, 4.4 Hz, 1H, CH_2C*H*$_2$CH), 1.45 – 1.39 (m, 1H, CH_2C*H*$_2$CH), 1.29 – 1.25 (m, 1H, C*H*$_2CH_2$CH), 1.00 (s, 3H, C*H*$_3$), 0.94 (dd, *J* = 13.4, 4.6 Hz, 1H, NHCHCH_2), 0.90 (s, 3H, C*H*$_3$), 0.87 (s, 3H, C*H*$_3$); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.3 (C), 156.0 (C), 140.1 (CH),

139.6 (C), 126.8 (CH), 120.8 (CH), 56.2 (CH_3), 53.7 (CH), 49.8 (C), 48.3 (C), 45.2 (CH), 37.8 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 20.0 (CH_3), 18.9 (CH_3), 14.0 (CH_3).

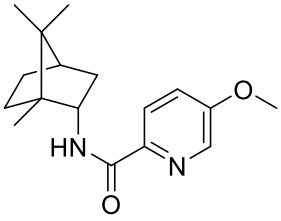
4-Methoxy-*N*-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 284



Prepared according to general amidation procedure A, using *R*-(+)-bornylamine (154 mg, 1.0 mmol) and 4-methoxypicolinic acid (184 mg, 1.2 mmol). Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a colourless oil (250 mg, 0.867 mmol, 87%).

$[\alpha]_D^{24}$ -7.00 (*c* = 0.4, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3384 (NH), 2952 (CH), 2880 (CH), 1672 (CO), 1509 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) *δ* 8.35 (d, *J* = 5.6 Hz, 1H, pyNC*H*), 8.20 (d, *J* = 8.5 Hz, 1H, N*H*), 7.73 (s, 1H, pyCC*H*C), 6.90 (dd, *J* = 5.2, 2.1 Hz, 1H, pyNCHC*H*), 4.44 – 4.39 (m, 1H, NHC*H*), 3.91 (s, 3H, OCH_3), 2.45 – 2.39 (m, 1H, NHCHCH_2), 1.81 (tt, *J* = 12.4, 4.0 Hz, 1H, C$H_2$$CH_2$CH), 1.72 (t, *J* = 4.5 Hz, 1H, CH_2C*H*CH_2), 1.71 – 1.67 (m, 1H, CH_2CH_2CH), 1.43 (ddd, *J* = 13.9, 4.4, 2.2 Hz, 1H, CH_2CH_2CH), 1.34 – 1.29 (m, 1H, C$H_2$$CH_2$CH), 1.01 (s, 3H, C$H_3$), 0.99 (dd, *J* = 13.5, 4.4 Hz, 1H, NHCHCH_2), 0.91 (s, 3H, CH_3), 0.87 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 167.1 (C), 164.3 (C), 152.4 (C), 149.3 (CH), 113.0 (CH), 107.4 (CH), 55.6 (CH_3), 54.0 (CH), 50.1 (C), 48.4 (C), 45.2 (CH), 37.6 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 20.0 (CH_3), 18.9 (CH_3), 13.9 (CH_3); **HRMS** found (ES) $[M+H]^+$ 289.1912, $C_{17}H_{25}N_2O_2$+H requires 289.1916.

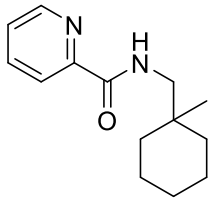
5-Methoxy-N-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 287



Prepared according to general amidation procedure A, using *R*-(+)-bornylamine (154 mg, 1.0 mmol) and 5-methoxypicolinic acid (184 mg, 1.2 mmol). Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a colourless oil (282 mg, 0.978 mmol, 98%).

[α]$_D^{24}$ +10.0 (*c* = 2.2, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3390 (NH), 2952 (CH), 2881 (CH), 1667 (CO), 1519 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) *δ* 8.22 (d, *J* = 2.2 Hz, 1H, pyNC*H*), 8.13 (t, *J* = 7.8 Hz, 1H, pyCC*H*CH), 7.98 (d, *J* = 8.6 Hz, 1H, N*H*), 7.29 – 7.26 (m, 1H, pyCCHC*H*), 4.44 – 4.38 (m, 1H, NHC*H*), 3.89 (s, 3H, OCH_3), 2.46 – 2.37 (m, 1H, NHCHCH_2), 1.86 – 1.78 (m, 1H, CH_2CH$_2$CH), 1.98 (m, 2H, CH$_2$CH_2C*H*) 1.46 – 1.40 (m, 1H, CH$_2$CH_2CH), 1.34 – 1.28 (m, 1H, CH_2CH$_2$CH), 1.00 (s, 3H, CH_3), 0.97 (dd, *J* = 13.4, 4.5 Hz, 1H, NHCHCH_2), 0.90 (s, 3H, CH_3), 0.86 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.3 (C), 157.8 (C), 143.1 (C), 136.5 (CH), 123.4 (CH), 120.3 (CH), 55.9 (CH_3), 53.8 (CH), 50.0 (C), 48.4 (C), 45.2 (CH), 37.7 (CH_2), 28.6 (CH_2), 28.3 (CH_2), 20.0 (CH_3), 18.9 (CH_3), 13.9 (CH_3); **HRMS** found (ES) $[M+H]^+$ 289.1911, $C_{17}H_{25}N_2O_2$+H requires 289.1916.

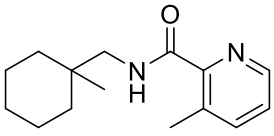
_N_-((1-Methylcyclohexyl)methyl)picolinamide 296



Prepared according to general amidation procedure A, using (1-methylcyclohexyl)methanamine (127 mg, 1.0 mmol) and 2-picolinic acid (148 mg, 1.2 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a colourless oil (209 mg, 0.900 mmol, 90%).

ν_{max} (film/cm^{-1}) 3393 (NH), 2925 (CH), 2851 (CH), 1675 (CO), 1527 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) *δ* 8.54 (d, *J* = 4.7 Hz, 1H, pyNC*H*), 8.20 (d, *J* = 7.81, 1H, pyCC*H*), 8.17 (b s, 1H, N*H*) 7.84 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.43 – 7.39 (m, 1H, pyNCHC*H*), 3.33 (d, *J* = 6.6 Hz, 2H, NHCH_2), 1.58 – 1.52 (m, 2H, Cy*H*), 1.51 – 1.43 (m, 3H, Cy*H*), 1.39 – 1.30 (m, 5H, Cy*H*), 0.97 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.5 (C), 150.2 (C), 148.1 (CH), 137.5 (CH), 126.1 (CH), 122.4 (CH), 49.6 (CH_2), 35.6 (CH_2), 34.8 (C), 26.4 (CH_2), 23.4 (CH_3), 22.0 (CH_2); **HRMS** found (ES) $[M+H]^+$ 233.1655, $C_{14}H_{20}N_2O$+H requires 233.1654.

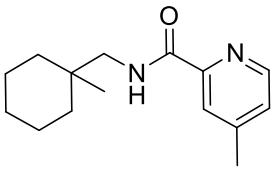
3-Methyl-_N_-((1-methylcyclohexyl)methyl)picolinamide 299



Prepared according to general Amidation procedure A, using (1-methylcyclohexyl)methanamine (127 mg, 1.0 mmol) and 3-methylpicolinic acid (165 mg, 1.2 mmol). Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a colourless oil (206 mg, 0.836 mmol, 84%).

ν_{max} (film/cm^{-1}) 3390 (NH), 2926 (CH), 2851 (CH), 1672 (CO), 1517 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.0 Hz, 1H, pyNC*H*), 8.22 (s, 1H, N*H*), 7.55 (d, *J* = 7.6 Hz, 1H, pyNCHCHC*H*), 7.27 (dd, *J* = 7.7, 4.6 Hz, 1H, pyNCHC*H*), 3.27 (d, *J* = 6.5 Hz, 2H, NHCH_2), 2.73 (s, 3H, ArCH_3), 1.57 – 1.50 (m, 2H, Cy*H*), 1.50 – 1.40 (m, 3H, Cy*H*), 1.38 – 1.28 (m, 5H, Cy*H*), 0.95 (s, 3H, CH_2CCH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 166.2 (C), 147.7 (C), 145.5 (CH), 140.9 (CH), 135.5 (C), 125.6 (CH), 49.4 (CH_2), 35.7 (CH_2), 34.7 (C), 26.5 (CH_2), 23.4 (CH_3), 22.0 (CH_2), 20.7 (CH_3); **HRMS** found (ES) $[M+H]^+$ 247.1802, $C_{15}H_{22}N_2O$+H requires 247.1810.

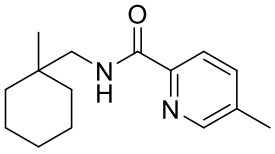
4-Methyl-*N*-((1-methylcyclohexyl)methyl)picolinamide 302



Prepared according to general amidation procedure A, using (1-methylcyclohexyl)methanamine (127 mg, 1.0 mmol) and 4-methylpicolinic acid (165 mg, 1.2 mmol). Purified by flash column chromatography (0 – 30 % EtOAc in petrol) to give the product as a colourless oil (110 mg, 0.447 mmol, 48%).

ν_{max} (film/cm^{-1}) 3390 (NH), 2924 (CH), 2852 (CH), 1672 (CO), 1526 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.8 Hz, 1H, pyNC*H*), 8.14 (s, 1H, N*H*), 8.03 (s, 1H, pyNCC*H*), 7.22 (d, *J* = 4.7 Hz, 1H, pyNCHC*H*), 3.31 (d, *J* = 6.6 Hz, 2H, NHCH_2), 2.42 (s, 3H, ArCH_3), 1.54 (dt, *J* = 11.3, 5.6 Hz, 2H, Cy*H*), 1.51 – 1.41 (m, 3H, Cy*H*), 1.40 – 1.28 (m, 5H, Cy*H*), 0.97 (s, 3H, CyCH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.8 (C), 150.0 (C), 148.9 (C), 148.0 (CH), 126.9 (CH), 123.3 (CH), 49.6 (CH_2), 35.6 (CH_2), 34.8 (C), 26.4 (CH_2), 23.4 (CH_3), 22.0 (CH_2), 21.2 (CH_3); **HRMS** found (ES) $[M+H]^+$ 247.1814, $C_{15}H_{22}N_2O$+H requires 247.1810.

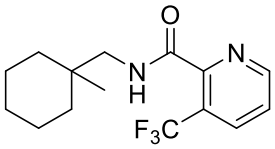
5-Methyl-*N*-((1-methylcyclohexyl)methyl)picolinamide 305



Prepared according to general amidation procedure A, using (1-methylcyclohexyl)methanamine (127 mg, 1.0 mmol) and 5-methylpicolinic acid (165 mg, 1.2 mmol). Purified by flash column chromatography (10 – 30 % EtOAc in petrol) to give the product as a colourless oil (201 mg, 0.816 mmol, 82%).

ν_{max} (film/cm^{-1}) 3396 (NH), 2923 (CH), 2850 (CH), 1675 (CO), 1522 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 1.4, 0.7 Hz, 1H, pyNC*H*), 8.15 – 8.06 (m, 2H, N*H*, pyNCC*H*), 7.65 – 7.60 (m, 1H, CH_3CCHCH), 3.32 (d, *J* = 6.6 Hz, 2H, $NHCH_2$), 2.39 (s, 3H, $ArCH_3$), 1.57 – 1.51 (m, 2H, Cy*H*), 1.50 – 1.42 (m, 3H, Cy*H*), 1.39 – 1.30 (m, 5H, Cy*H*), 0.96 (s, 3H, CCH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.7 (C), 148.6 (CH), 147.8 (C), 137.8 (CH), 136.2 (C), 122.0 (CH), 49.5 (CH_2), 35.6 (CH_2), 34.8 (C), 26.5 (CH_2), 23.4 (CH_3), 22.0 (CH_2), 18.6 (CH_3); **HRMS** found (ES) $[M+H]^+$ 247.1812, $C_{15}H_{22}N_2O$+H requires 247.1812.

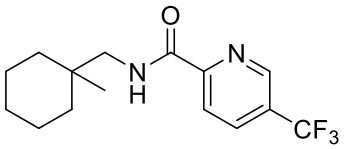
***N*-((1-Methylcyclohexyl)methyl)-3-(trifluoromethyl)picolinamide 308**



Prepared according to general amidation procedure A, using (1-methylcyclohexyl)methanamine (127 mg, 1.0 mmol) and 3-trifuoromethylpicolinic acid (229 mg, 1.2 mmol). Purified by flash column chromatography (20 – 40% EtOAc in petrol) to give the product as an off-white solid (279 mg, 0.929 mmol, 93%).

M.p 76 – 79 °C; **ν_{max}** (film/cm^{-1}) 3308 (NH), 2923 (CH), 2855 (CH), 1645 (CO), 1558 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.5 Hz, 1H, pyC*H*), 8.15 (d, *J* = 8.0 Hz, 1H, pyNCHCHC*H*), 7.64 (s, 1H, N*H*), 7.54 (dd, *J* = 8.0, 4.8 Hz, 1H, pyNCHC*H*), 3.33 (d, *J* = 6.6 Hz, 2H, $NHCH_2$), 1.56 – 1.51 (m, 2H, Cy*H*), 1.50 – 1.42 (m, 3H, Cy*H*), 1.38 – 1.29 (m, 5H, Cy*H*), 0.96 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.6 (C), 150.7 (CH), 150.1 (C), 136.3 (q, *J* = 5.9, CH), 126.1 (q, *J* = 34.4 Hz, C), 125.2 (CH), 123.0 (q, *J* = 273.2 Hz, C), 49.7 (CH_2), 35.6 (CH_2), 34.7 (C), 26.4 (CH_2), 23.4 (CH_3), 21.9 (CH_2); **HRMS** found (ES) $[M+H]^+$ 301.1521, $C_{15}H_{19}N_2OF_3$+H requires 301.1528.

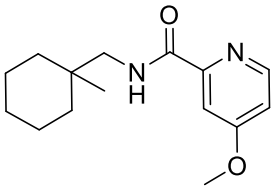
***N*-((1-Methylcyclohexyl)methyl)-5-(trifluoromethyl)picolinamide 311**



Prepared according to general amidation procedure A, using (1-methylcyclohexyl)methanamine (127 mg, 1.0 mmol) and 5-trifuoromethylpicolinic acid (229 mg, 1.2 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as an off-white solid (298 mg, 0.992 mmol, 99%).

M.p 75 – 77 °C; **ν_{max}** (film/cm^{-1}) 3362 (NH), 2919 (CH), 2853 (CH), 1657 (CO), 1529 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.82 (s, 1H, pyNC*H*), 8.34 (d, *J* = 8.1 Hz, 1H, CF_3CCHCH), 8.10 (m, 2H, pyNCC*H*, N*H*), 3.34 (d, *J* = 8.6 Hz, 2H, $NHCH_2$), 1.58 – 1.42 (m, 5H, Cy*H*), 1.41 – 1.29 (m, 5H, Cy*H*), 0.97 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.1 (C), 153.1 (C), 145.3 (q, *J* = 3.9 Hz, CH), 134.9 (q, *J* = 3.4 Hz, CH), 128.8 (q, *J* = 33.3 Hz, C), 123.3 (q, *J* = 272.7 Hz, C), 122.3 (CH), 49.7 (CH_2), 35.6 (CH_2), 34.8 (C), 26.4 (CH_2), 23.4 (CH_3), 21.9 (CH_2); **HRMS** found (ES) $[M+H]^+$ 301.1527, $C_{15}H_{22}N_2OF_3$+H requires 301.1528.

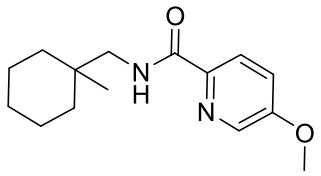
4-Methoxy-*N*-((1-methylcyclohexyl)methyl)picolinamide 315



Prepared according to general amidation procedure A, using (1-methylcyclohexyl)methanamine (127 mg, 1.0 mmol) and 4-methoxypicolinic acid (184 mg, 1.2 mmol). Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a colourless oil (201 mg, 0.766 mmol, 77%).

ν_{max} (film/cm^{-1}) 3385 (NH), 2924 (CH), 2850 (CH), 1674 (CO), 1597 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.32 (d, *J* = 5.8 Hz, 1H, pyNC*H*), 8.21 (s, 1H, N*H*), 7.73 (s, 1H, pyCC*H*C), 6.92 – 6.86 (m, 1H, pyNCHC*H*), 3.89 (s, 3H, OCH_3), 3.30 (d, *J* = 6.6 Hz, 2H, $NHCH_2$), 1.58 – 1.49 (m, 2H, Cy*H*), 1.49 – 1.40 (m, 3H, Cy*H*), 1.37 – 1.28 (m, 5H, Cy*H*), 0.95 (s, 3H, CCH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 167.1 (C), 164.5 (C), 152.3 (C), 149.2 (CH), 113.1 (CH), 107.5 (CH), 55.6 (CH_3), 49.6 (CH_2), 35.6 (CH_2), 34.8 (C), 26.4 (CH_2), 23.4 (CH_3), 21.9 (CH_2); **HRMS** found (ES) $[M+H]^+$ 263.1763, $C_{15}H_{23}N_2O_2$+H requires 263.1760.

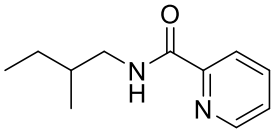
5-Methoxy-*N*-((1-methylcyclohexyl)methyl)picolinamide 318



Prepared according to general amidation procedure A, using (1-methylcyclohexyl)methanamine (127 mg, 1.0 mmol) and 5-methoxypicolinic acid (184 mg, 1.2 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a colourless oil (222 mg, 0.846 mmol, 85%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3400 (NH), 2923 (CH), 2848 (CH), 1669 (CO), 1524 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.20 (d, *J* = 2.2 Hz, 1H, pyNC*H*), 8.14 (d, *J* = 8.6 Hz, 1H, pyCC*H*CH), 8.05 – 7.88 (br s, 1H, N*H*), 7.27 (dd, *J* = 8.7, 2.2 Hz, 1H, pyCCHC*H*), 3.90 (s, 3H, OCH_3), 3.30 (d, *J* = 6.6 Hz, 2H, NHCH_2), 1.53 (dt, *J* = 11.6, 5.8 Hz, 2H, Cy*H*), 1.50 – 1.41 (m, 3H, Cy*H*), 1.38 – 1.29 (m, 5H, Cy*H*), 0.96 (s, 3H, CCH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.5 (C), 157.9 (C), 143.0 (C), 136.5 (CH), 123.5 (CH), 120.3 (CH), 55.9 (CH_3), 49.5 (CH_2), 35.6 (CH_2), 34.7 (C), 26.5 (CH_2), 23.4 (CH_3), 22.0 (CH_2); **HRMS** found (ES) $[M+H]^+$ 263.1764, $C_{15}H_{23}N_2O_2$+H requires 263.1760.

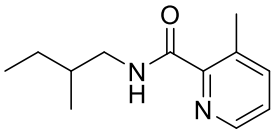
***N*-(2-Methylbutyl)picolinamide 323**



Prepared according to general amidation procedure A, using (2-methylbutyl)amine (87 mg, 1.0 mmol) and 2-picolinic acid (148 mg, 1.2 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a colourless oil (174 mg, 0.91 mmol, 91%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3369 (NH), 2971 (CH), 2912 (CH), 2873 (CH), 1661 (CO), 1519 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.8 Hz, 1H, pyNC*H*), 8.11 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 8.10 – 7.97 (s, 1H, N*H*), 7.74 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.31 (ddd, *J* = 7.6, 4.8, 1.0 Hz, 1H, pyNCHC*H*), 3.35 – 3.29 (m, 1H, NHCH_2), 3.21 (dt, *J* = 13.4, 6.7 Hz, 1H, NHCH_2), 1.64 – 1.57 (m, 1H, C*H*), 1.41 – 1.35 (m, 1H, CH_3CH_2), 1.16 – 1.10 (m, 1H, CH_3CH_2), 0.88 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.84 (t, *J* = 7.5 Hz, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.4 (C), 150.1 (C), 148.1 (CH), 137.4 (CH), 126.1 (CH), 122.2 (CH), 45.1 (CH_2), 35.2 (CH), 27.1 (CH_2), 17.3 (CH_3), 11.4 (CH_3); **HRMS** found (ES) $[M+H]^+$ 193.1343, $C_{11}H_{16}N_2O$+H requires 193.1341.

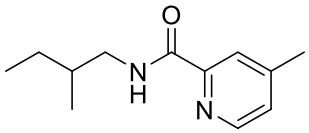
3-Methyl-*N*-(2-methylbutyl)picolinamide 326



Prepared according to general amidation procedure A, using (2-methylbutyl)amine (87 mg, 1.0 mmol) and 3-methylpicolinic acid (165 mg, 1.2 mmol). Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a colourless oil (166 mg, 0.81 mmol, 80%).

ν_{max} (film/cm^{-1}) 3389 (NH), 2962 (CH), 2929 (CH), 2875 (CH), 1667 (CO), 1517 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.33 (s, 1H, pyNC*H*), 8.25 – 8.12 (b s, 1H, N*H*), 7.52 (d, *J* = 7.7 Hz, 1H, pyNCHCHC*H*), 7.26 – 7.22 (m, 1H, pyNCHC*H*), 3.36 – 3.31 (m, 1H, NHCH_2), 3.20 (ddd, *J* = 13.4, 9.7, 3.7 Hz, 1H, NHCH_2), 2.70 (s, 3H, ArCH_3), 1.69 – 1.61 (m, 1H, C*H*), 1.49 – 1.40 (m, 1H, CH_3CH_2), 1.22 – 1.17 (m, 1H, CH_3CH_2), 0.93 (dd, *J* = 6.8, 1.4 Hz, 3H, CHCH_3), 0.90 (td, *J* = 7.4, 1.4 Hz, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 166.1 (C), 147.6 (C), 145.5 (CH), 140.9 (CH), 135.4 (C), 125.6 (CH), 45.0 (CH_2), 35.2 (CH), 27.3 (CH_2), 20.7 (CH_3), 17.4 (CH_3), 11.4 (CH_3); **HRMS** found (ES) $[M+H]^+$ 207.1497, $C_{12}H_{28}N_2O$+H requires 207.1497.

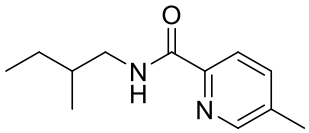
4-Methyl-*N*-(2-methylbutyl)picolinamide 329



Prepared according to general amidation procedure A, using (2-methylbutyl)amine (87 mg, 1.0 mmol) and 4-methylpicolinic acid (165 mg, 1.2 mmol). Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a colourless oil (180 mg, 0.87 mmol, 87%).

ν_{max} (film/cm^{-1}) 3389 (NH), 2960 (CH), 2926 (CH), 1668 (CO), 1523 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.8 Hz, 1H, pyNC*H*), 8.19 – 8.03 (m, 1H, N*H*), 8.00 (s, 1H, pyCC*H*C), 7.19 (d, *J* = 4.7 Hz, 1H, pyNCHC*H*), 3.41 – 3.35 (m, 1H, NHCH_2), 3.27 (dt, *J* = 13.4, 6.7 Hz, 1H, NHCH_2), 2.39 (s, 3H, ArCH_3), 1.71 – 1.63 (m, 1H, C*H*), 1.49 – 1.42 (m, 1H, CH_3CH_2), 1.23 – 1.17 (m, CH_3CH_2), 0.94 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.91 (t, *J* = 7.5 Hz, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.7 (C), 150.0 (C), 148.9 (C), 148.0 (CH), 126.9 (CH), 123.2 (CH), 45.1 (CH_2), 35.2 (CH), 27.2 (CH_2), 21.2 (CH_3), 17.4 (CH_3), 11.4 (CH_3); **HRMS** found (ES) $[M+H]^+$ 313.1917, $C_{19}H_{24}N_2O_2$+H requires 313.1916.

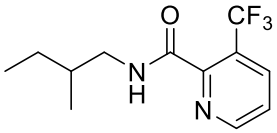
5-Methyl-*N*-(2-methylbutyl)picolinamide 332



Prepared according to general amidation procedure A, using (2-methylbutyl)amine (87 mg, 1.0 mmol) and 4-methylpicolinic acid (165 mg, 1.2 mmol). Purified by flash column chromatography (10 – 30% EtOAc in petrol) to give the product as a colourless oil (195 mg, 0.95 mmol, 94%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3394 (NH), 2960 (CH), 2927 (CH), 1667 (CO), 1522 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.34 (d, J = 0.7 Hz, 1H, pyNC*H*), 8.08 (d, J = 7.9 Hz, 1H, pyNCC*H*), 8.04 (s, 1H, N*H*), 7.62 (ddd, J = 7.9, 1.3, 0.7 Hz, 1H, pyNCCHC*H*), 3.42 – 3.37 (m, 1H, NHCH_2), 3.27 (dt, J = 13.4, 6.7 Hz, 1H, NHCH_2), 2.38 (s, 3H, ArCH_3), 1.72 – 1.64 (m, 1H, C*H*), 1.51 – 1.44 (m, 1H, CH_3CH_2), 1.25 – 1.18 (m, 1H, CH_3CH_2), 0.96 (dd, J = 6.7, 1.3 Hz, 3H, CHCH_3), 0.94 – 0.91 (m, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.7 (C), 148.6 (CH), 147.8 (C), 137.8 (CH), 136.3 (C), 122.0 (C), 45.1 (CH_2), 35.3 (CH), 27.2 (CH_2), 18.6 (CH_3), 17.4 (CH_3), 11.5 (CH_3); **HRMS** found (ES) $[M+H]^+$ 207.1495, $C_{12}H_{18}N_2O$+H requires 207.1497.

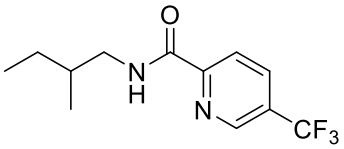
***N*-(2-Methylbutyl)-3-(trifluoromethyl)picolinamide 335**



Prepared according to general amidation procedure A, using (2-methylbutyl)amine (87 mg, 1.0 mmol) and 3-trifluoromethylpicolinic acid (229 mg, 1.2 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a white solid (229 mg, 0.880 mmol, 88%).

M.p 67 – 70 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3282 (NH), 2964 (CH), 2877 (CH), 1670 (CO), 1562 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.71 (m, 1H, pyNC*H*), 8.15 (t, J = 6.6 Hz, 1H, pyNCHC*H*), 7.77 – 7.58 (s, 1H, N*H*), 7.57 – 7.51 (m, 1H, CF_3CCH), 3.44 – 3.38 (m, 1H, NHCH_2), 3.31 – 3.25 (m, 1H, NHCH_2), 1.75 – 1.67 (m, 1H, C*H*CH_3), 1.51 – 1.43 (m, 1H, CH_3CH_2), 1.27 – 1.19 (m, 1H, CH_3CH_2), 0.99 – 0.95 (m, 3H, CHCH_3), 0.95 – 0.91 (m, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.4 (C), 150.6 (C), 149.9 (CH), 136.3 (q, J = 5.7 Hz, CH), 126.1 (q, J = 33.3 Hz, C), 125.3 (CH), 123.0 (q, J = 273.2 Hz, C), 45.2 (CH_2), 35.1 (CH), 27.2 (CH_2), 17.3 (CH_3), 11.4 (CH_3); **HRMS** found (ES) $[M+H]^+$ 261.1212, $C_{12}H_{15}N_2OF_3$+H requires 261.1215.

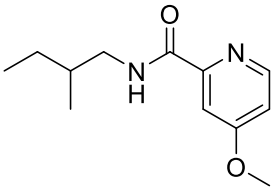
***N*-(2-Methylbutyl)-5-(trifluoromethyl)picolinamide 338**



Prepared according to general amidation procedure A, using (2-methylbutyl)amine (87 mg, 1.0 mmol) and 5-trifluoromethylpicolinic acid (229 mg, 1.2 mmol). Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a pale-yellow oil (253 mg, 0.972 mmol, 97%).

ν_{max} (film/cm^{-1}) 3400 (NH), 2963 (CH), 2930 (CH), 2877 (CH), 1670 (CO), 1527 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.79 (s, 1H, pyNC*H*), 8.32 (d, *J* = 8.2 Hz, 1H, CF_3CCHCH), 8.09 (m, 2H, N*H*, CF_3CCHCH), 3.45 – 3.39 (m, 1H, $NHCH_2$), 3.30 (dt, *J* = 13.3, 6.6 Hz, 1H, $NHCH_2$), 1.74 – 1.65 (m, 1H, C*H*), 1.49 – 1.41 (m, 1H, CH_3CH_2), 1.26 – 1.20 (m, 1H, CH_3CH_2), 0.95 (d, *J* = 6.7 Hz, 3H, $CHCH_3$), 0.91 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.0 (C), 153.1 (C), 145.2 (q, *J* = 3.8 Hz, CH), 134.9 (q, *J* = 3.4 Hz, CH), 128.8 (q, *J* = 33.3 Hz, C), 123.3 (q, *J* = 272.7 Hz, C), 122.2 (CH), 45.3 (CH_2), 35.2 (CH), 27.2 (CH_2), 17.3 (CH_3), 11.4 (CH_3); **HRMS** found (ES) $[M+H]^+$ 261.1212, $C_{15}H_{15}N_2OF_3$+H requires 261.1215.

4-Methoxy-*N*-(2-methylbutyl)picolinamide 342

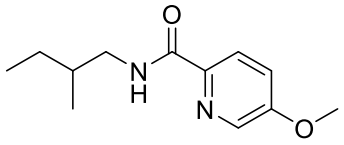


Prepared according to general amidation procedure A, using (2-methylbutyl)amine (87 mg, 1.0 mmol) and 4-methoxypicolinic acid (184 mg, 1.2 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a colourless oil (176 mg, 0.792 mmol, 79%).

ν_{max} (film/cm^{-1}) 3387 (NH), 2960 (CH), 2928 (CH), 1667 (CO), 1521 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.32 (d, *J* = 5.3 Hz, 1H, pyNC*H*), 8.19 – 8.06 (m, 1H, N*H*), 7.73 (d, *J* = 2.6 Hz, 1H, pyNCC*H*), 6.89 (dd, *J* = 5.6, 2.6 Hz, 1H, pyNCHC*H*), 3.90 (s, 3H, OCH_3), 3.39 (dt, *J* = 12.7, 6.2 Hz, 1H, $NHCH_2$), 3.28 (dt, *J* = 13.4, 6.7 Hz, 1H, $NHCH_2$), 1.68 (oct, *J* = 6.7 Hz, 1H, C*H*), 1.49 – 1.44 (m, 1H, CH_3CH_2), 1.24 – 1.19 (m, 1H, CH_3CH_2), 0.96 (d, *J* = 6.7 Hz, 3H, $CHCH_3$), 0.93 (t, *J* = 7.5 Hz, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 167.1 (C), 164.4 (C), 152.3 (C), 149.3 (CH), 113.0 (CH), 107.4 (CH), 55.6 (CH_3), 45.2 (CH_2), 35.2 (CH),

27.2 (CH_2), 17.4 (CH_3), 11.5 (CH_3); **HRMS** found (ES) $[M+H]^+$ 223.1450, $C_{12}H_{18}N_2O_2$+H requires 223.1447.

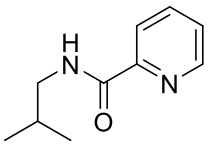
5-Methoxy-*N*-(2-methylbutyl)picolinamide 345



Prepared according to general amidation procedure A, using (2-methylbutyl)amine (87 mg, 1.0 mmol) and 5-methoxypicolinic acid (184 mg, 1.2 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the product as a colourless oil (169 mg, 0.760 mmol, 76%).

ν_{max} (film/cm^{-1}) 3396 (NH), 2960 (CH), 2929 (CH), 1664 (CO), 1523 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.16 (t, *J* = 2.5 Hz, 1H, pyNC*H*), 8.11 (dd, *J* = 8.6, 2.2 Hz, 1H, pyNCC*H*), 7.86 (s, 1H, N*H*), 7.24 (dt, *J* = 8.7, 2.5 Hz, 1H, pyNCCHC*H*), 3.86 (s, 3H, OCH_3), 3.38 – 3.34 (m, 1H, NHCH_2), 3.27 – 3.21 (m, 1H, NHCH_2), 1.68 – 1.61 (m, 1H, C*H*), 1.47 – 1.42 (m, 1H, CH_3CH_2), 1.21 – 1.16 (m, 1H, CH_3CH_2), 0.93 (dd, *J* = 6.7, 2.3 Hz, 3H, CHCH_3), 0.90 (td, *J* = 7.4, 2.3 Hz, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.4 (C), 157.8 (C), 143.0 (C), 136.5 (CH), 123.4 (CH), 120.2 (CH), 55.8 (CH_3), 45.1 (CH_2), 35.3 (CH), 27.2 (CH_2), 17.4 (CH_3), 11.4 (CH_3); **HRMS** found (ES) $[M+H]^+$ 223.1444, $C_{12}H_{19}N_2O_2$+H requires 223.1447.

***N*-Isobutylpicolinamide 351**

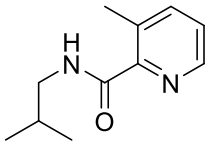


Prepared according to general amidation procedure A, using isobutylamine (0.2 ml, 2.0 mmol) and 2-picolinic acid (295 mg, 2.4 mmol) Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a colourless oil (322 mg, 1.81 mmol, 90%).

ν_{max} (solid/cm^{-1}) 3351 (NH), 2973 (CH), 2879 (CH), 1668 (CO), 1508 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H, pyNC*H*), 8.20 (dt, *J* = 7.8, 1.0 Hz, 1H, pyCC*H*), 8.18 – 8.06 (s, 1H, pyN*H*), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyCHC*H*), 3.33 – 3.28 (m, 2H, CH_2), 1.92 (non, *J* = 6.7 Hz, 1H, C*H*),

0.99 (d, *J* = 6.7 Hz, 6H, C*H*$_3$); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.4 (C), 150.2 (C), 148.1 (CH), 137.5 (CH), 126.1 (CH), 122.4 (CH), 46.9 (CH_2), 28.9 (CH), 20.3 (CH_3); **HRMS** found (ES) $[M+H]^+$ 179.1180, $C_{10}H_{14}N_2O$+H requires 179.1184.

_N_-Isobutyl-3-methylpicolinamide 352

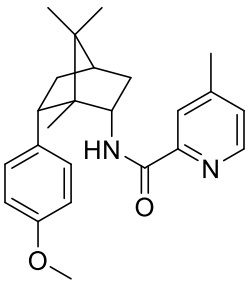


Prepared according to general amidation procedure A, using isobutylamine (0.2 ml, 2.0 mmol) and 3-methylpicolinic acid (330 mg, 2.4 mmol). Purified by flash column chromatography (20% EtOAc in petrol) to give the product as a colourless oil (355 mg, 1.85 mmol, 92%).

ν_{max} (solid/cm^{-1}) 3353 (NH), 2986 (CH), 2871 (CH), 1663 (CO), 1511 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) *δ* 8.37 (d, *J* = 4.5 Hz, 1H, pyNC*H*), 8.18 (s, 1H, N*H*), 7.60 – 7.53 (m, 1H, pyCC*H*), 7.30 – 7.26 (m, 1H, pyNCHC*H*), 3.27 – 3.23 (m, 2H, CH_2), 2.74 (s, 3H, ArCH_3), 1.91 (dp, *J* = 20.1, 6.7 Hz, 1H C*H*), 1.00 – 0.96 (m, 6H, CHCH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 166.1 (C), 147.6 (C), 145.5 (CH), 140.9 (CH), 135.5 (C), 125.6 (CH), 46.8 (CH_2), 28.8 (CH), 20.7 (CH_3), 20.4 (CH_3); **HRMS** found (ES) $[M+H]^+$ 193.1341, $C_{11}H_{16}N_2O$+H requires 193.1341.

6.2.2 Arylation of substituted picolinamides

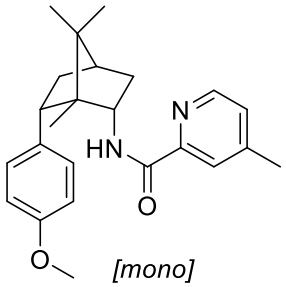
_N_-((*1S*,2*S*,4*R*,6*S*)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-4-methylpicolinamide 274



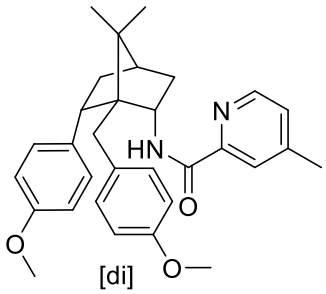
Prepared according to general arylation procedure A, using amide **273** (26 mg, 0.1 mmol) and 4-bromoanisole (50 µl, 0.4 mmol). Purified by flash column chromatography (0 – 30 % EtOAc in petrol) to give the product as colourless oil (32 mg, 0.085 mmol, 85%).

ν_{max} (film/cm^{-1}) 3360 (NH), 2927 (CH), 2853 (CH), 1665 (CO), 1509 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.05 (d, *J* = 4.9 Hz, 1H, pyNC*H*), 7.77 (s, 1H, pyCC*H*C), 7.69 (d, *J* = 9.0 Hz, 1H, N*H*), 7.35 (d, *J* = 8.4 Hz, 2H, OCCHC*H*), 7.07 (dd, *J* = 4.9, 0.8 Hz, 1H, pyNCHC*H*), 6.88 (d, *J* = 8.8 Hz, 2H, OCC*H*), 4.49 (dddd, *J* = 11.3, 9.2, 6.0, 1.9 Hz, 1H, NHC*H*), 3.79 (s, 3H, OCH_3), 3.29 (dd, *J* = 11.7, 5.1 Hz, 1H, ArC*H*), 2.59 – 2.50 (m, 1H, NHCHCH_2), 2.33 (s, 3H, ArCH_3), 2.24 (tt, *J* = 12.6, 3.8 Hz, 1H, ArCHCH_2), 2.04 – 1.98 (m, 1H, ArCHCH_2), 1.92 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.26 (dd, *J* = 13.0, 6.3 Hz, 1H, NHCHCH_2), 1.09 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.05 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.8 (C), 158.2 (C), 149.9 (C), 148.2 (C), 147.4 (CH), 133.9 (C), 129.8 (CH), 126.4 (CH), 122.6 (CH), 114.5 (CH), 55.3 (CH_3), 54.5 (CH), 53.9 (C), 50.9 (C), 46.9 (CH), 43.7 (CH), 37.0 (CH_2), 32.9 (CH_2), 21.2 (CH_3), 20.3 (CH_3), 20.0 (CH_3), 13.8 (CH_3); **HRMS** found (ES) $[M+H]^+$ 379.2375, $C_{24}H_{30}N_2O_2$+H requires 379.2386.

***N*-((1*S*,2*S*,4*R*,6*S*)-1-(4-Methoxybenzyl)-6-(4-methoxyphenyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)-4-methylpicolinamide 275** and ***N*-((*1S*,*2S*,4*R*,6*S*)-6-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-4-methylpicolinamide 274**



[mono]



[di]

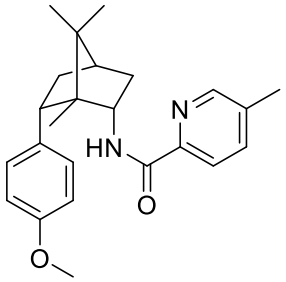
Prepared according to general arylation procedure A using amide **273** (26 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 30 % EtOAc in petrol) to give the title compounds as the mono aryl product and a mixture of mono and diarylated products; ratio in crude mono:di 88:12.
Isolated material overall (39 mg, 97%).

Mono (27 mg, 0.071 mmol, 71%)
Mixture (10 mg) Mono 0.016 mmol 16%; Di 0.010 mmol, 10%

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.9 Hz, 1H, N*H*) 8.08 – 8.04 (m, 1H, PyNC*H*)*, 7.89 – 7.87 (m, 1H, pyNCHC*H*), 7.45 (d, *J* = 8.6 Hz, 2H, OCCHC*H*), 7.11 – 7.09 (m, 1H, pyNCC*H*), 7.08 – 7.04 (m, 2H, OCHCC*H*), 6.93 (d, *J* = 8.7 Hz, 2H, OCC*H*), 6.78 – 6.75 (m, 2H, OCC*H*), 4.79 – 4.72 (m, 1H, NHC*H*), 3.85 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.50 (dd, *J* = 12.0, 5.4 Hz, 1H, ArC*H*), 3.06 (d, *J* = 14.3 Hz, 1H, ArCH_2), 2.82 (d, *J* = 14.3 Hz, 1H,

ArCH_2), 2.59 – 2.51 (m, 1H, NHCHCH_2), 2.36 (d, J = 6.9 Hz, 3H, ArCH_3), 2.28 – 2.21 (m, 1H, ArCHCH_2)*, 1.97 (dd, J = 13.1, 5.7 Hz, 1H, ArCHCH_2) 1.71 (t, J = 4.6 Hz, 1H, CH_2CHCH_2), 1.28 – 1.25 (m, 1H, NHCHCH_2)*, 1.19 (s, 3H, CH_3), 0.58 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.8, 158.5, 158.0, 150.0, 148.2, 147.5, 133.2, 130.8, 130.3, 129.8, 126.5, 122.7, 114.6, 113.6, 55.4, 55.3, 51.0, 50.7, 49.0, 45.6, 36.8, 35.4, 33.5, 21.2, 21.0, 20.4.
*Peaks overlapping with monoarylation compound.

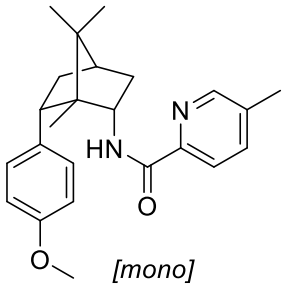
_N_-((1_S_,2_S_,4_R_,6_S_)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-5-methylpicolinamide 277



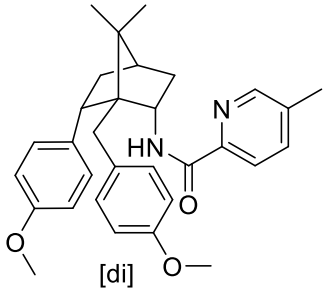
Prepared according to general arylation procedure A using amide **276** (26 mg, 0.10 mmol) and 4-bromoanisole (50 µl, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a colourless oil (26 mg, 0.0687 mmol, 69%).

$[\alpha]_D^{24}$ -10.0 (c = 0.1, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3367 (NH), 2927 (CH), 2851 (CH), 1669 (CO), 1513 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.01 (dd, J = 1.4, 0.7 Hz, 1H, pyNCH), 7.83 (d, J = 7.9 Hz, 1H, pyCH_3CCH), 7.63 (d, J = 9.0 Hz, 1H, NH), 7.49 – 7.46 (m, 1H, pyNCCH), 7.35 (d, J = 8.4 Hz, 2H, OCCHCH), 6.89 (d, J = 8.8 Hz, 2H, OCCH), 4.48 (dddd, J = 11.3, 9.3, 6.0, 2.0 Hz, 1H, NHCH), 3.80 (s, 3H, OCH_3), 3.29 (dd, J = 11.8, 4.6 Hz, 1H, ArCH), 2.57 – 2.50 (m, 1H, NHCHCH_2), 2.32 (s, 3H), 2.24 (tt, J = 12.5, 3.8 Hz, 1H, ArCHCH_2), 2.01 (dd, J = 13.1, 5.8 Hz, 1H, ArCHCH_2), 1.91 (t, J = 4.7 Hz, 1H, CH_2CHCH_2), 1.28 – 1.23 (m, 1H, NHCHCH_2), 1.08 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.05 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.7 (C), 158.2 (C), 148.0 (CH), 147.7 (C), 137.2 (CH), 135.5 (C), 133.9 (C), 129.8 (CH), 121.3 (CH), 114.5 (CH), 55.2 (CH_3), 54.4 (CH), 53.6 (C), 50.9 (C), 46.9 (CH), 43.7 (CH), 37.0 (CH_2), 32.9 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 18.6 (CH_3), 13.8 (CH_3); **HRMS** found (ES) $[M+H]^+$ 379.2388, $C_{24}H_{30}N_2O_2$+H requires 379.2380.

***N*-((1*S*,2*S*,4*R*,6*S*)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-5-methylpicolinamide 277** and ***N*-((1*S*,2*S*,4*R*,6*S*)-1-(4-Methoxybenzyl)-6-(4-methoxyphenyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)-5-methylpicolinamide 278**



[mono]

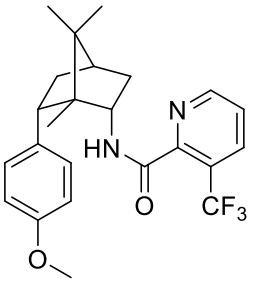


[di]

Prepared using general arylation procedure A using amide **276** (26 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the title compounds as an inseparable mixture (38 mg, 99%).
Mono (0.088 mmol, 88%)
Di (0.011 mmol, 11%)

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.03 – 8.00 (m, 2H, N*H* and pyNC*H*)*, 7.93 (d, *J* = 7.9 Hz, 1H, pyNCC*H*), 7.53 – 7.50 (m, 1H, pyNCCHC*H*), 7.48 – 7.43 (m, 2H, OCCHC*H*)*, 7.07 – 7.04 (m, 2H, OCCHC*H*), 6.95 – 6.92 (m, 2H, OCC*H*), 6.77 – 6.75 (m, 2H, OCC*H*), 4.78 – 4.72 (m, 1H, NHC*H*), 3.86 (s, 3H, OCH_3), 3.73 (d, *J* = 2.3 Hz, 3H, OCH_3), 3.51 – 3.48 (m, 1H, ArC*H*), 3.05 (d, *J* = 14.3 Hz, 1H, ArCH_2), 2.82 (d, *J* = 14.3 Hz, 1H, ArCH_2), 2.57 – 2.50 (m, 1H, NHCHCH_2)*, 2.33 (s, 3H, ArCH_3), 2.25 – 2.22 (m, 1H, ArCHCH_2)*, 1.98 – 1.95 (m, 1H, ArCHCH_2), 1.70 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.27 – 1.24 (m, 1H, NHCHCH_2)*, 1.15 (s, 3H, CH_3), 0.58 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.7, 158.5, 158.0, 148.1, 147.7, 137.3, 135.7, 133.3, 131.5, 131.0, 130.8, 130.3, 121.4, 113.6, 55.8, 55.3, 51.0, 50.7, 49.0, 45.6, 41.1, 36.8, 35.4, 29.8, 24.0, 21.0, 14.8.
*Peaks overlapping with monoarylation compound

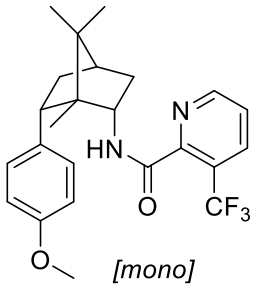
***N*-((1*S*,2*S*,4*R*,6*S*)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-3-(trifluoromethyl)picolinamide 271**



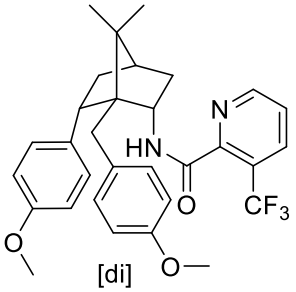
Prepared according to general arylation procedure A using amide **270** (66 mg, 0.20 mmol) and 4-bromoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol). Further purified by recrystallisation from hot petrol/DCM, to give the product as a yellow crystalline solid (29 mg, 0.068 mmol, 34%).

M.p 130 – 132 °C; $\mathbf{\nu_{max}}$ (film/cm^{-1}) 3363 (NH), 2923 (CH), 2860 (CH), 1673 (CO), 1512 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 4.7, 1.4 Hz, 1H, pyNC*H*), 8.00 (dd, *J* = 8.0, 1.1 Hz, 1H, pyNCHCHC*H*), 7.39 (dd, *J* = 7.9, 4.7 Hz, 1H, pyNCHC*H*), 7.32 (d, *J* = 8.5 Hz, 2H, OCCHC*H*), 7.21 (d, *J* = 9.1 Hz, 1H, N*H*), 6.79 (d, *J* = 8.9 Hz, 2H, OCC*H*), 4.51 – 4.46 (m, 1H, NHC*H*), 3.70 (s, 3H, OCH_3), 3.28 (dd, *J* = 11.9, 4.5 Hz, 1H, ArC*H*), 2.58 – 2.53 (m, 1H, NHCHCH_2), 2.24 (tt, *J* = 12.8, 3.9 Hz, 1H, ArCHCH_2), 1.99 (dd, *J* = 13.2, 5.8 Hz, 1H, ArCHCH_2), 1.92 (t, *J* = 4.7 Hz, 1H, CH_2CHCH_2), 1.25 (dd, *J* = 13.4, 5.9 Hz, 1H, NHCHCH_2), 1.07 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.3 (C), 158.1 (C), 150.1 (CH), 149.7 (C), 135.7 (q, *J* = 5.9 Hz, CH), 134.1 (C), 129.8 (CH), 125.3 (q, *J* = 34.2 Hz, C), 124.6 (CH), 123.0 (q, *J* = 273.2 Hz, C), 114.3 (CH), 55.2 (CH_3), 54.7 (CH), 54.0 (C), 50.9 (C), 46.8 (CH), 43.7 (CH), 36.8 (CH_2), 32.7 (CH_2), 20.2 (CH_3), 19.9 (CH_3), 13.7 (CH_3); **HRMS** found (ES) $[M+H]^+$ 433.2098, $C_{24}H_{27}N_2O_2F_3$+H requires 433.2103.

***N*-((1*S*,2*S*,4*R*,6*S*)-1-(4-Methoxybenzyl)-6-(4-methoxyphenyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)-3-(trifluoromethyl)picolinamide 272** and ***N*-((1*S*,2*S*,4*R*,6*S*)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-3-(trifluoromethyl)picolinamide 271**



[mono]



[di]

Prepared according to general arylation procedure A using amide **270** (33 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the title compounds as an inseparable mixture (48 mg, 99%).
Mono (0.051 mmol, 51%)
Di (0.048 mmol, 48%)

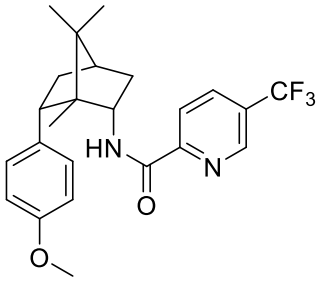
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 4.7, 1.4 Hz, 1H, pyNC*H*), 8.04 (dd, *J* = 8.0, 1.3 Hz, 1H, pyNCHCHC*H*), 7.56 – 7.50 (m, 2H, N*H*, pyNCHC*H*), 7.45 – 7.43 (m, 2H, OCCHC*H*), 7.07 – 7.04 (m, 2H, OCCHC*H*), 6.86 (d, *J* = 8.8 Hz, 2H, OCC*H*), 6.77 – 6.75 (m, 2H, OCC*H*), 4.75 – 4.70 (m, 1H, NHC*H*), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.48 (dd, *J* = 12.1, 4.5 Hz, 1H, ArC*H*), 3.00 (d, *J* = 14.3 Hz, 1H, ArCH_2), 2.80 (d, *J* = 14.3 Hz, 1H, ArCH_2), 2.59 – 2.52 (m, 1H, NHCHCH_2)*, 2.28 – 2.20 (m, 1H, ArCHCH_2)*, 2.01 – 1.97 (m, 1H, ArCHCH_2)*, 1.72 (t, *J* = 4.5 Hz, 1H, CH_2CHCH_2), 1.26 – 1.23 (m, 1H, NHCHCH_2)*, 1.19 (s, 3H, CH_3), 0.58 (s, 3H, CH_3);

^{13}C NMR (176 MHz, $CDCl_3$) δ 163.4, 158.4, 158.1, 150.6, 150.2, 133.4, 131.4, 130.9, 130.1, 125.20, 124.7, 114.3, 113.7, 55.8, 55.33, 55.2, 54.2, 51.0, 48.9, 37.6, 35.3, 34.0, 33.4, 20.91, 20.87.

*Peaks overlapping with monoarylated product

[not all ^{13}C signals were seen due to C-F splitting]

_N_-((1_S_,2_S_,4_R_,6_S_)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-5-(trifluoromethyl)picolinamide 280

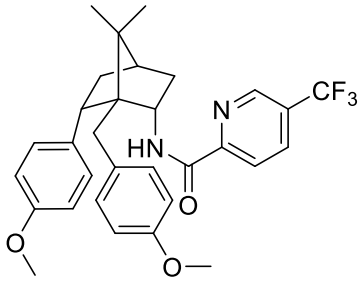


Prepared according to general arylation procedure A using amide **279** and 4-bromoanisole (50 µl, 0.4 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as a white solid (10 mg, 0.023 mmol, 23%).

M.p 117 – 118 °C; **$[\alpha]_D^{24}$** +58.8 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3353 (NH), 2943 (CH), 2849 (CH), 1691 (CO), 1508 (CC); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 1.4, 0.8 Hz, 1H, pyNC*H*), 8.08 (d, *J* = 8.2 Hz, 1H, pyCCHC*H*), 7.99 – 7.91 (m, 1H, pyCC*H*CH), 7.69 (d, *J* = 8.9 Hz, 1H, N*H*), 7.35 (d, *J* = 8.5 Hz, 2H, OCCHC*H*), 6.89 (d, *J* = 8.8 Hz, 2H, OCC*H*), 4.52 – 4.41 (m, 1H, NHC*H*), 3.78 (s, 3H, OCH_3), 3.31 (dd, *J* = 11.9, 4.5 Hz, 1H, ArC*H*), 2.61 – 2.49 (m, 1H, NHCHCH_2), 2.32 – 2.20 (m, 1H, ArCHCH_2), 2.03 (dd, *J* = 13.2, 5.7 Hz, 1H, ArCHCH_2), 1.94 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.29 – 1.26 (m, 1H, NHCHCH_2), 1.09 (s, 6H, 2 × CH_3), 1.06 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.0 (C), 158.3 (C), 152.9 (C), 144.61 (q, *J* = 4.0 Hz, CH), 134.28 (q, *J* = 3.3 Hz, CH), 133.8 (C), 129.8 (CH), 128.20 (q, *J* = 33.1 Hz, C), 123.40 (q, *J* = 272.6 Hz, C), 121.5 (CH), 114.6 (CH), 55.1 (CH_3), 54.8 (CH_2),

53.9 (C), 50.9 (C), 46.7 (CH), 43.7 (CH), 36.9 (CH_2), 32.7 (CH_2), 20.2 (CH_3), 20.0 (CH_3), 13.9 (CH_3); **HRMS** found (ES) $[M+H]^+$ 433.2100, $C_{24}H_{28}N_2O_2F_3$+H requires 433.2103.

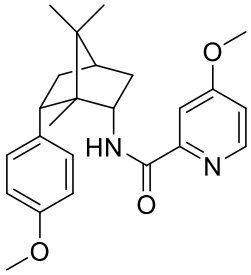
***N*-((1*S*,2*S*,4*R*,6*S*)-1-(4-Methoxybenzyl)-6-(4-methoxyphenyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)-5-(trifluoromethyl)picolinamide 281**



Prepared according to general arylation procedure A, using amide **279** (33 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 10% EtOAc in petrol) to give the product as a yellow oil (9 mg, 0.017 mmol, 17%). Also isolated the monoarylation product (24 mg, 0.056 mmol, 56%).

$[\alpha]_D^{24}$ +26.0 (*c* = 0.2, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3353 (NH), 2955 (CH), 2921 (CH), 1674 (CO), 1509 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 1.4, 0.8 Hz, 1H, pyNC*H*), 8.18 (d, *J* = 8.1 Hz, 1H, pyCC*H*), 8.04 (d, *J* = 8.9 Hz, 1H, N*H*), 8.00 – 7.98 (m, 1H, pyCCHC*H*), 7.45 (d, *J* = 8.6 Hz, 2H, OCCHC*H*), 7.05 – 7.03 (m, 2H, OCCHC*H*), 6.96 – 6.93 (m, 2H, OCC*H*), 6.78 – 6.75 (m, 2H, OCC*H*), 4.77 – 4.72 (m, 1H, NHC*H*), 3.85 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.52 (dd, *J* = 12.1, 4.4 Hz, 1H, ArC*H*), 3.04 (d, *J* = 14.4 Hz, 1H, ArCH_2), 2.84 (d, *J* = 14.4 Hz, 1H, ArCH_2), 2.60 – 2.54 (m, 1H, NHCHCH_2), 2.31 – 2.26 (m, 1H, ArCHCH_2), 1.99 (dd, *J* = 13.2, 5.6 Hz, 1H, ArCHCH_2), 1.73 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.29 – 1.28 (m, 1H, NHCHCH_2), 1.20 (s, 3H), 0.59 (s, 3H); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.0 (C), 158.7 (C), 158.1 (C), 153.0 (C), 144.7 (q, *J* = 4.2 Hz, CH), 134.4 (q, *J* = 3.5 Hz, CH), 133.1 (C), 131.4 (CH), 130.8 (CH), 130.1 (C), 128.4 (q, *J* = 33.1 Hz, C), 123.2 (q, *J* = 237.6 Hz, C), 121.6 (CH), 114.6 (CH), 113.7 (CH), 55.9 (C), 55.3 (CH_3), 55.2 (CH_3), 51.1 (C), 51.0 (CH), 48.8 (CH), 45.6 (CH), 36.7 (CH_2), 35.4 (CH_2), 33.3 (CH_2), 20.9 (CH_3), 20.4 (CH_3); **HRMS** found (ES) $[M+H]^+$ 539.2514, $C_{31}H_{33}N_2O_3F_3$+H requires 539.2516.

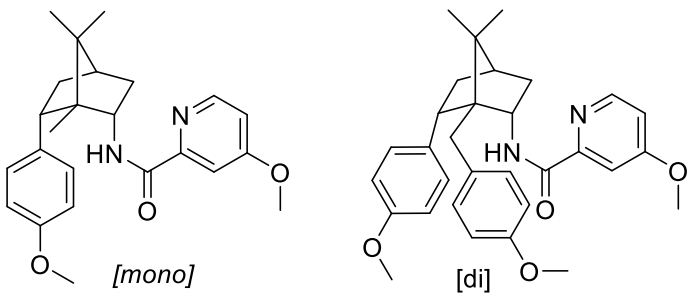
4-Methoxy-*N*-((1S,2S,4R,6S)-6-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 285



Prepared according to general arylation procedure A using amide **284** (29 mg, 0.10 mmol) and 4-bromoanisole (50 µl, 0.40 mmol). Product was purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as white solid (29 mg, 0.0735 mmol, 74%).

M. p 127 – 129 °C; **$[\alpha]_D^{24}$** +52.0 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3359 (NH), 2983 (CH), 2951 (CH), 1671 (CO), 1509 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) *δ* 7.99 (d, *J* = 5.6 Hz, 1H, pyNC*H*), 7.70 (d, *J* = 9.0 Hz, 1H, N*H*), 7.50 (d, *J* = 2.5 Hz, 1H, pyNCHC*H*), 7.34 (d, *J* = 8.4 Hz, 2H, OCCHC*H*C), 6.88 (d, *J* = 8.7 Hz, 2H, OCC*H*CHC), 6.78 – 6.74 (m, 1H, pyCC*H*C), 4.50 – 4.44 (m, 1H, NHC*H*), 3.83 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.28 (dd, *J* = 11.7, 5.3 Hz, 1H, ArC*H*), 2.53 (ddd, *J* = 14.4, 8.2, 4.6 Hz, 1H, NHCHCH_2), 2.24 (tt, *J* = 12.8, 3.8 Hz, 1H, ArCHCH_2), 2.01 (dd, *J* = 13.1, 5.8 Hz, 1H, ArCHCH_2), 1.91 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.28 – 1.25 (m, 1H, NHCHCH_2), 1.08 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.05 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 166.7 (C), 164.5 (C), 158.3 (C), 152.1 (C), 148.6 (CH), 133.8 (C), 129.8 (CH), 114.5 (CH), 112.5 (CH), 106.8 (CH), 55.5 (CH_3), 55.3 (CH_3), 54.6 (CH_2), 53.8 (C), 50.9 (C), 46.9 (CH), 43.7 (CH), 36.9 (CH_2), 32.9 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 13.8 (CH_3); **HRMS** found (ES) $[M+H]^+$ 395.2234, $C_{22}H_{30}N_2O_3$+H requires 395.2235.

4-Methoxy-*N*-((1S,2S,4R,6S)-1-(4-methoxybenzyl)-6-(4-methoxyphenyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 286 and **4-methoxy-*N*-((1S,2S,4R,6S)-6-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 285**

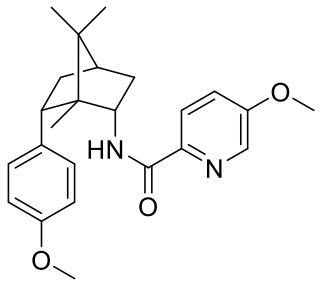


[mono] [di]

Prepared according to general arylation procedure A, using amide **284** (29 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a mixture of mono and diarylation products (31 mg, 75%).
Mono (0.066 mmol, 66%)
Di (0.009 mmol, 9%)

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.1 Hz, 1H, N*H*), 8.00 - 7.98 (m, 1H, pyNC*H*)*, 7.60 (d, *J* = 2.5 Hz, 1H, pyNCC*H*), 7.44 (t, *J* = 7.7 Hz, 2H, OCCHC*H*), 7.06 (d, *J* = 8.6 Hz, 2H, OCCHC*H*), 6.93 (d, *J* = 8.7 Hz, 2H, OCC*H*), 6.80 (dd, *J* = 5.6, 2.6 Hz, 1H, pyNCHC*H*), 6.78 – 6.76 (m, 1.21H, OCC*H*)*, 4.77 – 4.71 (m, 1H, NHC*H*), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.50 (dd, *J* = 11.9, 5.1 Hz, 1H, ArC*H*), 3.06 (d, *J* = 14.3 Hz, 1H, ArCH_2), 2.82 (d, *J* = 14.3 Hz, 1H, ArCH_2), 2.58 – 2.50 (m, 1H, NHCHCH_2)*, 2.30 – 2.20 (m, 1H, ArCHCH_2)*, 1.96 (dd, *J* = 13.1, 5.7 Hz, 1H, ArCHCH_2), 1.71 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.26 (dd, *J* = 13.4, 6.0 Hz, 1H, NHCHCH_2)*, 1.19 (s, 3H, CH_3), 0.58 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 166.8, 164.5, 158.5, 158.1, 152.2, 148.7, 133.2, 131.5, 130.8, 130.3, 114.6, 114.0, 113.6, 112.7, 55.8, 55.5, 55.4, 55.3, 51.0, 50.8, 49.0, 45.6, 36.8, 35.4, 33.5, 20.4, 14.8.
*Peaks overlapping with monoarylation product

5-Methoxy-*N*-((1*S*,2*S*,4*R*,6*S*)-6-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 288

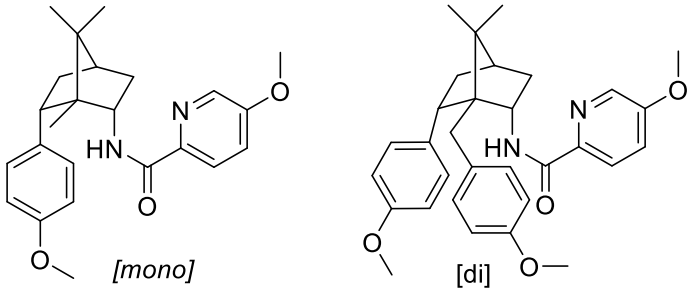


Prepared according to general arylation procedure A, using amide **287** (29 mg, 0.10 mmol) and 4-bromoanisole (50 µl, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a yellow solid. (34 mg, 0.086 mmol, 86%).

M.p 137 – 140 °C; **$[\alpha]_D^{24}$** +62.5 (*c* = 0.8, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 3384 (NH), 2954 (CH), 2931 (CH), 1672 (CO), 1508 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.91 – 7.88 (m, 1H, pyNC*H*), 7.87 (d, *J* = 2.9 Hz, 1H, pyCCHC*H*), 7.54 (d, *J* = 9.1 Hz, 1H, N*H*), 7.35 (d, *J* = 8.4 Hz, 2H, OCCHC*H*CCH), 7.13 (dd, *J* = 8.6, 2.9 Hz, 1H, pyCC*H*), 6.90 (d, *J* = 8.7 Hz, 2H,

OCC*H*CHCCH), 4.50 – 4.44 (m, 1H, NHC*H*), 3.85 (s, 3H, pyOCH_3), 3.81 (s, 3H, OCH_3), 3.29 (dd, *J* = 11.7, 5.2 Hz, 1H, ArC*H*), 2.53 (ddd, *J* = 14.4, 8.2, 4.7 Hz, 1H, NHCHCH_2), 2.24 (tt, *J* = 12.7, 3.8 Hz, 1H, ArCHCH_2), 2.01 (dd, *J* = 13.1, 5.7 Hz, 1H, ArCHCH_2), 1.91 (t, *J* = 4.6 Hz, 1H, CH_2CHCH_2), 1.25 – 1.23 (m, 1H, NHCHCH_2), 1.08 (2 × s, 6H, 2 × CH_3), 1.05 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.4 (C), 158.3 (C), 157.4 (C), 142.9 (C), 135.6 (CH), 133.9 (C), 129.8 (CH), 122.8 (CH), 120.0 (CH), 114.5 (CH), 55.7 (CH_3), 55.2 (CH_3), 54.4 (CH), 53.8 (C), 50.9 (C), 46.9 (CH), 43.7 (CH), 37.0 (CH_2), 32.9 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 13.8 (CH_3); **HRMS** found (ES) $[M+H]^+$ 395.2338, $C_{24}H_{31}N_2O_3$+H requires 395.2335.

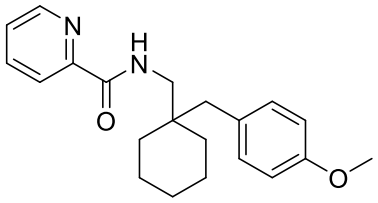
5-Methoxy-*N*-((1*S*,2*S*,4*R*,6*S*)-1-(4-methoxybenzyl)-6-(4-methoxyphenyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 289 and **5-Methoxy-*N*-((1*S*,2*S*,4*R*,6*S*)-6-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide 288**



Prepared according general arylation procedure A using amide **287** (29 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.4 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give a mixture of the mono and di arylated products (32 mg, 79%).
Mono (0.071 mmol, 71%)
Di (0.008 mmol, 8%)

^{1}H NMR (700 MHz, $CDCl_3$) *δ* 8.00 – 7.98 (m, 1H, pyNC*H*), 7.91 – 7.89 (m, 1H, N*H*)*, 7.88 – 7.85 (m, 1H, pyNCC*H*)*, 7.45 (d, *J* = 8.6 Hz, 2H, OCCHC*H*), 7.17 (dd, *J* = 8.6, 2.9 Hz, 1H, pyNCCHC*H*), 7.06 (d, *J* = 8.6 Hz, 2H, OCCHC*H*), 6.94 (d, *J* = 8.8 Hz, 2H, OCC*H*), 6.79 – 6.74 (m, 2H, OCC*H*), 4.76 – 4.71 (m, 1H, NHC*H*), 3.87 (s, 6H, OCH_3), 3.74 (s, 3H, OCH_3), 3.50 (dd, *J* = 12.0, 4.7 Hz, 1H, ArC*H*), 3.05 (d, *J* = 14.3 Hz, 1H, ArCH_2), 2.81 (d, *J* = 14.3 Hz, 1H, ArCH_2), 2.56 – 2.50 (m, 1H, NHCHCH_2)*, 2.29 – 2.21 (m, 1H, ArCHCH_2)*, 1.97 (dd, *J* = 13.2, 5.7 Hz, 1H, ArCHCH_2), 1.70 (t, *J* = 4.6 Hz, 0.1H, CH_2CHCH_2), 1.26 – 1.24 (m, 1H, NHCHCH_2), 1.19 (s, 3H, CH_3), 0.57 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.4, 158.7, 158.0, 157.5, 143.0, 135.7, 133.3, 131.5, 130.8, 130.3, 122.9, 120.1, 114.5, 113.6, 55.8, 55.7, 55.32, 55.26, 50.9, 50.7, 49.0, 36.9, 35.4, 33.5, 29.8, 21.0, 20.4.
*Peaks overlapping with the monoarylation product

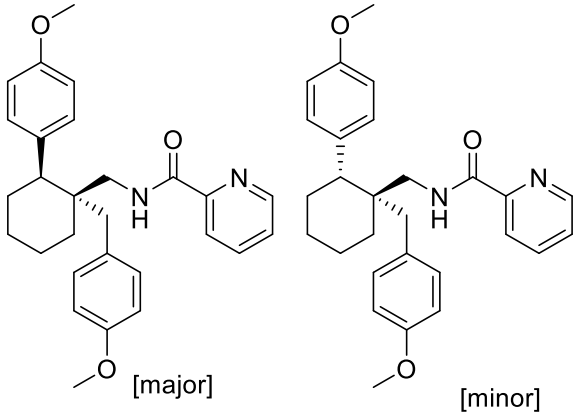
***N*-((1-(4-Methoxybenzyl)cyclohexyl)methyl)picolinamide 297**



Prepared according to general arylation procedure A using amide **296** (23 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 30% EtOAc in petrol) to give the monoarylation product as a colourless oil (20 mg, 0.059 mmol, 59%).

ν_{max} (film/cm^{-1}) 3372 (NH), 2958 (CH), 2921 (CH), 1668 (CO), 1512 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.19 (dt, *J* = 7.8, 1.1 Hz, 1H, pyCC*H*), 8.11 (s, 1H, N*H*), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 7.13 – 7.10 (m, 2H, OCCHC*H*), 6.85 – 6.82 (m, 2H, OCC*H*), 3.79 (s, 3H, OCH_3), 3.35 (d, *J* = 6.4 Hz, 2H, NHCH_2), 2.64 (s, 2H, ArCH_2), 1.58 (m, 4H, Cy*H*), 1.47 (dd, *J* = 11.7, 6.0 Hz, 1H, Cy*H*), 1.43 – 1.41 (m, 2H, Cy*H*), 1.40 – 1.36 (m, 3H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.4 (C), 158.2 (C), 150.2 (C), 148.2 (CH), 137.4 (CH), 131.5 (CH), 130.2 (C), 126.1 (CH), 122.3 (CH), 113.7 (CH), 55.3 (CH_3), 44.9 (CH_2), 42.8 (CH_2), 38.1 (C), 33.6 (CH_2), 26.3 (CH_2), 21.8 (CH_2); **HRMS** found (ES) $[M+H]^+$ 339.2066, $C_{21}H_{26}N_2O_2$+H requires 339.2072.

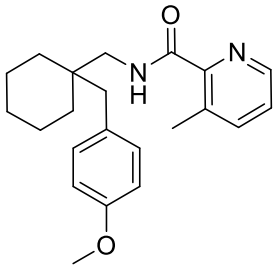
***N*-(1-(4-methoxybenzyl)-2-(4-methoxyphenyl)cyclohexyl)methyl)picolinamide 298**



Isolated from the same reaction as monoarylation product **296**. Yellow oil, mixture of diastereoisomers, *d.r* 85:15 (10 mg, 0.022 mmol, 22%).

[major diastereoisomer]. ν_{max} (film/cm^{-1}) 3361 (NH), 2922 (CH), 2853 (CH), 1672 (CO), 1508 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.24 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.04 (dt, *J* = 7.8, 1.0 Hz, 1H, pyCC*H*), 7.73 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.35 (m, 1H, N*H*), *7*.29 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H, pyNCHC*H*), 7.23 – 7.21 (m, 2H, OCCHC*H*), 7.07 – 7.04 (m, 2H, OCCHC*H*), 6.85 – 6.83 (m, 2H, OCC*H*), 6.82 – 6.79 (m, 2H, OCC*H*), 4.28 (dd, *J* = 13.1, 9.2 Hz, 1H, NHCH_2), 3.81 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.10 – 3.06 (m, 1H, NHCH_2), 2.75 (d, *J* = 13.5 Hz, 1H, ArCH_2), 2.64 (dd, *J* = 12.8, 3.5 Hz, 1H, ArC*H*), 2.50 (d, *J* = 13.5 Hz, 1H, ArCH_2), 2.17 (qd, *J* = 12.9, 3.9 Hz, 1H, Cy*H*), 1.92 – 1.85 (m, 2H, Cy*H*), 1.76 – 1.71 (m, 1H, Cy*H*), 1.54 – 1.51 (m, 1H, Cy*H*), 1.46 (dt, *J* = 13.4, 3.3 Hz, 1H, Cy*H*), 1.27 – 1.24 (m, 2H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.1 (C), 158.6 (C), 158.3 (C), 150.0 (C), 147.7 (CH), 137.1 (CH), 134.8 (C), 131.4 (CH), 130.5 (CH), 125.8 (CH), 121.8 (CH), 114.0 (CH), 113.4 (CH), 55.4 (CH_3), 55.3 (CH_3), 52.7 (CH), 47.0 (CH_2), 41.4 (C), 40.5 (CH_2), 34.4 (CH_2), 29.4 (CH_2), 27.0 (CH_2), 21.9 (CH_2); **HRMS** found (ES) $[M+H]^+$ 445.2462, $C_{28}H_{32}N_2O_3$+H requires 445.2491.

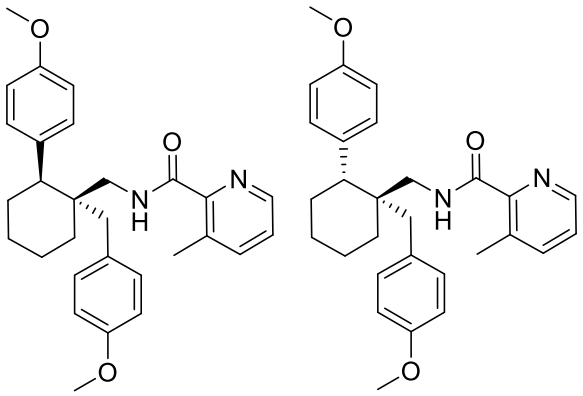
***N*-((1-(4-Methoxybenzyl)cyclohexyl)methyl)-3-methylpicolinamide 300**



Prepared according to general arylation procedure A using amide **299** (25 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a colourless oil (20 mg, 0.057 mmol, 57%)

ν_{max} (film/cm^{-1}) 3387 (NH), 2923 (CH), 2852 (CH), 1673 (CO), 1510 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 4.5, 1.0 Hz, 1H, pyNC*H*), 8.18 (s, 1H, N*H*), 7.57 (dd, *J* = 7.7, 0.8 Hz, 1H, CH_3CC*H*), 7.29 (dd, *J* = 7.7, 4.6 Hz, 1H, pyNCHC*H*), 7.10 (t, *J* = 5.7 Hz, 2H, OCCHC*H*), 6.84 – 6.81 (m, 2H, OCC*H*), 3.78 (s, 3H, OCH_3), 3.31 (d, *J* = 6.3 Hz, 2H, NHCH_2), 2.74 (s, 3H, CCH_3), 2.63 (s, 2H, ArCH_2), 1.59 – 1.55 (m, 4H, Cy*H*), 1.49 – 1.43 (m, 2H, Cy*H*), 1.42 (t, *J* = 4.9 Hz, 1H, Cy*H*), 1.37 (m, 3H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 166.1 (C), 158.2 (C), 147.6 (C), 145.5 (CH), 140.9 (CH), 135.4 (C), 131.5 (CH), 130.3 (C), 125.6 (CH), 113.7 (CH), 55.3 (CH_3), 44.7 (CH_2), 42.9 (CH_2), 38.1 (C), 33.6 (CH_2), 26.3 (CH_2), 21.8 (CH_2), 20.6 (CH_3); **HRMS** found (ES) $[M+H]^+$ 353.2230, $C_{22}H_{28}N_2O_2$+H requires 353.2229.

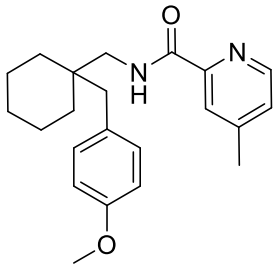
***N*-((1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)cyclohexyl)methyl)-3-methylpicolinamide 301**



Colourless oil. Mixture of diastereoisomers 84:16 (2 mg, 0.005 mmol, 5%)

ν_{max} (film/cm^{-1}) 3361 (NH), 2924 (CH), 2853 (CH), 1670 (CO), 1509 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 1H, pyNC*H*), 7.46 (ddd, *J* = 7.7, 1.6, 0.7 Hz, 1H, pyNCHCHC*H*), 7.43 (d, *J* = 7.4 Hz, 1H, N*H*), 7.23 – 7.21 (m, 2H, OCCHC*H*), 7.17 (dd, *J* = 7.7, 4.6 Hz, 1H, pyNCHC*H*), 7.07 – 7.04 (m, 2H, OCCHC*H*), 6.85 – 6.83 (m, 2H, OCC*H*), 6.80 – 6.78 (m, 2H, OCC*H*), 4.27 (dd, *J* = 12.9, 9.2 Hz, 1H, NHCH_2), 3.80 (d, *J* = 1.9 Hz, 3H, OCH_3), 3.76 (d, *J* = 1.4 Hz, 3H, OCH_3), 3.01 (dd, *J* = 13.9, 2.8 Hz, 1H, NHCH_2), 2.73 (d, *J* = 13.1, 1H, ArCH_2), 2.67 (s, 3H, ArCH_3), 2.65 – 2.62 (m, 1H, ArC*H*), 2.49 (d, *J* = 13.4 Hz, 1H, ArCH_2), 2.18 (qd, *J* = 13.0, 3.4 Hz, 1H, ArCHCH_2), 1.92 (d, *J* = 13.5 Hz, 1H, Cy*H*), 1.87 (d, *J* = 12.9 Hz, 1H, Cy*H*), 1.72 (d, *J* = 14.1 Hz, 1H, ArCHCH_2), 1.52 (s, 1H, Cy*H*), 1.50 – 1.44 (m, 1H, Cy*H*), 1.37 (ddt, *J* = 21.5, 12.8, 4.4 Hz, 1H, Cy*H*), 1.27 (dd, *J* = 8.0, 4.2 Hz, 1H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 165.7 (C), 158.4 (C), 158.2 (C), 147.3 (C), 145.1 (CH), 140.6 (CH), 134.93 (C), 134.87 (C), 131.5 (CH), 130.59 (CH), 130.55 (CH), 125.3 (CH), 113.9 (CH), 113.4 (CH), 55.34 (CH_3), 55.26 (CH_3), 52.8 (CH), 47.2 (CH_2), 41.5 (C), 40.1 (CH_2), 34.4 (CH_2), 29.4 (CH_2), 27.0 (CH_2), 21.9 (CH_2), 20.6 (CH_3); **HRMS** found (ES) $[M+H]^+$ 459.2659, $C_{28}H_{32}N_2O_3$+H requires 459.2648.

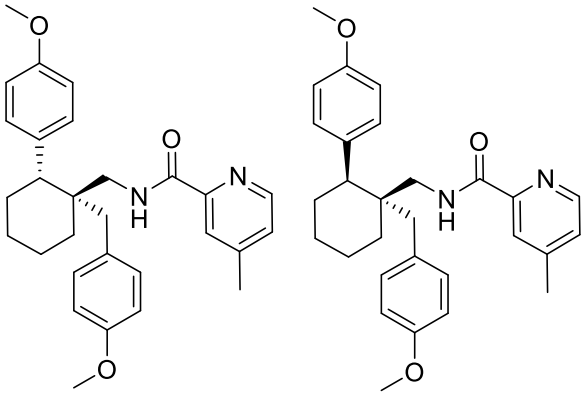
***N*-((1-(4-methoxybenzyl)cyclohexyl)methy l)-4-methylpicolinamide 303**



Prepared according to general arylation procedure A using amide **302** (25 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a white solid (27 mg, 0.077 mmol, 77%).

ν_{max} (film/cm^{-1}) 3376 (NH), 2908 (CH), 2865 (CH), 2850 (CH), 1663 (CO), 1511 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.38 (d, J = 4.9 Hz, 1H, pyNC*H*), 8.10 (s, 1H, N*H*), 8.02 (s, 1H, pyNCC*H*), 7.22 (d, J = 4.5 Hz, 1H, pyNCHC*H*), 7.10 (d, J = 8.2 Hz, 2H, OCCHC*H*), 6.83 (d, J = 8.2 Hz, 2H, OCC*H*), 3.78 (s, 3H, OCH_3), 3.33 (d, J = 6.3 Hz, 2H, NHCH_2), 2.62 (s, 2H, CCH_2Ar), 2.42 (s, 3H, ArCH_3), 1.60 – 1.53 (m, 4H, Cy*H*), 1.50 – 1.44 (m, 1H, Cy*H*), 1.43 – 1.33 (m, 5H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.7 (C), 158.2 (C), 150.0 (C), 148.9 (C), 148.0 (CH), 131.5 (CH), 130.2 (C), 126.9 (CH), 123.2 (CH), 113.7 (CH), 55.3 (CH_3), 44.8 (CH_2), 42.7 (CH_2), 38.1 (C), 33.5 (CH_2), 26.3 (CH_2), 21.8 (CH_2), 21.2 (CH_3). **HRMS** found (ES) $[M+H]^+$ 353.2221, $C_{22}H_{28}N_2O_2$+H requires 353.2229.

***N*-((1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)cyclohexyl)methyl)-4-methylpicolinamide 304**

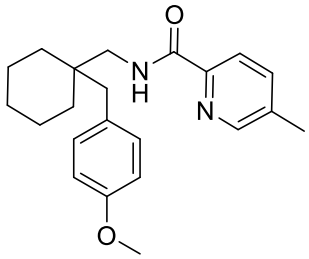


Isolated from the same reaction as the monoarylated compound as a colourless oil; Mixture of diastereoisomers *d.r* 85:15 (4 mg, 0.009 mmol, 9%).

ν_{max} (film/cm^{-1}) 3356 (NH), 2925 (CH), 2984 (CH), 1669 (CO), 1510 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.09 (d, J = 4.8 Hz, 1H, pyNC*H*), 7.87 (s, 1H, pyNCC*H*), 7.36 (d, J = 7.7 Hz, 1H, N*H*), 7.22 (d, J = 8.2 Hz, 2H, OCCHC*H*), 7.10 (d, J = 4.4 Hz, 1H, pyNCHC*H*), 7.04 (d, J = 8.1 Hz, 2H, OCCHC*H*), 6.84 (d, J = 7.9 Hz, 2H, OCC*H*), 6.80 (d, J = 8.0 Hz, 2H, OCC*H*), 4.26 (dd, J = 13.8, 9.2 Hz, 1H, NHCH_2), 3.81 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.07 (d, J = 14.0 Hz, 1H, NHCH_2), 2.74 (d, J = 13.5 Hz, 1H, ArCH_2), 2.67 – 2.61 (m, 1H, ArC*H*), 2.50 (d, J = 13.5 Hz, 1H, ArCH_2), 2.36 (s, 3H, ArCH_3), 2.21 – 2.13 (m, 1H, Cy*H*), 1.87 (t, J = 11.3 Hz, 2H, Cy*H*), 1.76 – 1.70 (m, 1H, Cy*H*), 1.51 – 1.43 (m, 2H, Cy*H*), 1.35 (tdd, J = 30.7, 19.2, 12.5 Hz, 3H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.3 (C), 158.5 (C), 158.3 (C), 149.8 (C),

148.4 (C), 147.6 (CH), 134.9 (C), 131.4 (CH), 130.6 (CH), 130.5 (CH), 126.6 (CH), 122.7 (CH), 113.9 (CH), 113.4 (CH), 55.3 (CH_3), 55.3 (CH_3), 52.7 (CH), 46.9 (CH_2), 41.5 (C), 40.5 (CH_2), 34.4 (CH_2), 29.4 (CH_2), 27.0 (CH_2), 21.9 (CH_2), 21.2 (CH_3); **HRMS** found (ES) $[M+H]^+$ 459.2625, $C_{29}H_{34}N_2O_3$+H requires 459.2648.

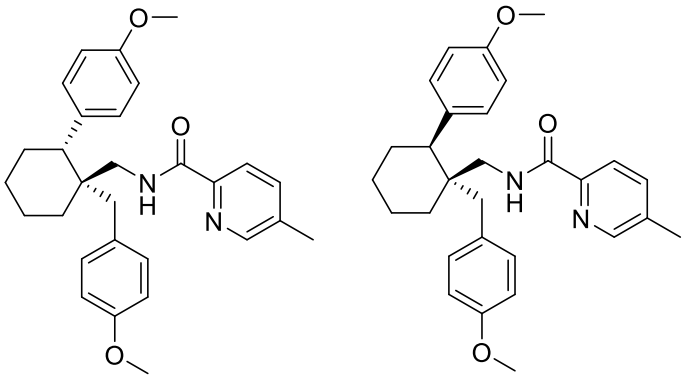
***N*-((1-(4-Methoxybenzyl)cyclohexyl)methyl)-5-methylpicolinamide 306**



Prepared according to general arylation procedure A, using amide **305** (25 mg, 0.1 mmol) and 4-iodoanisole (94 mg, 0.4 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a colourless oil (15 mg, 0.0426 mmol, 43%).

ν_{max} (film/cm^{-1}) 3392 (NH), 2923 (CH), 2850 (CH), 1674 (CO), 1510 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.35 (dd, J = 1.4, 0.7 Hz, 1H, pyNC*H*), 8.10 – 8.04 (m, 2H, pyNCC*H* and N*H*), 7.65 – 7.61 (m, 1H, CH_3CC*H*CH), 7.12 – 7.08 (m, 2H, OCCHC*H*), 6.86 – 6.79 (m, 2H, OCC*H*), 3.79 (s, 3H, OCH_3), 3.33 (d, J = 6.4 Hz, 2H, NHCH_2), 2.64 – 2.62 (m, 2H, ArCH_2), 2.40 (s, 3H, ArCH_3), 1.60 – 1.55 (m, 4H, Cy*H*), 1.50 – 1.44 (m, 1H, Cy*H*), 1.44 – 1.34 (m, 5H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.7 (C), 158.2 (C), 148.7 (CH), 147.8 (C), 137.7 (CH), 136.2 (C), 131.5 (CH), 130.2 (C), 121.9 (CH), 113.7 (CH), 55.3 (CH_3), 44.8 (CH_2), 42.7 (CH_2), 38.1 (C), 33.5 (CH_2), 26.3 (CH_2), 21.8 (CH_2), 18.7 (CH_3); **HRMS** found (ES) $[M+H]^+$ 353.2234, $C_{22}H_{28}N_2O_2$+H requires 353.2229.

***N*-((1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)cyclohexyl)methyl)-5-methylpicolinamide 307**



diastereoisomer 1 *diastereoisomer 2*

This compound was isolated as a mixture of diastereoisomers *dr* 85:15 (5 mg, 0.0109 mmol, 11%)

ν_{max} (film/cm^{-1}) 3364 (NH), 2926 (CH), 2854 (CH), 1673 (CO), 1511 (CC);

Diastereoisomer 1

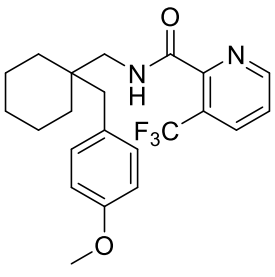
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.06 – 8.05 (m, Hz, 1H, pyNC*H*), 7.93 (d, *J* = 7.9 Hz, 1H, pyCC*H*CH), 7.52 (ddd, *J* = 7.9, 2.2, 0.7 Hz, 1H, pyCCHC*H*), 7.30 (d, *J* = 6.8 Hz, 1H, N*H*), 7.23 – 7.21 (m, 2H, OCCHC*H*), 7.07 – 7.04 (m, 2H, OCCHC*H*), 6.85 – 6.83 (m, 2H, OCC*H*), 6.82 – 6.79 (m, 2H, OCC*H*), 4.25 (dd, *J* = 13.6, 9.4 Hz, 1H, NHCH_2), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.07 (dd, *J* = 13.9, 3.0 Hz, 1H, NHCH_2), 2.74 (d, *J* = 13.5 Hz, 1H, ArCH_2), 2.66 – 2.61 (m, 1H, ArC*H*), 2.50 (d, *J* = 13.5 Hz, 1H, ArCH_2), 2.33 (s, 3H, ArCH_3), 2.17 (qd, *J* = 13.0, 3.9 Hz, 1H, ArCHCH_2), 1.88 (t, *J* = 12.5 Hz, 2H, Cy*H*), 1.72 (d, *J* = 11.0 Hz, 1H, ArCHCH_2), 1.54 – 1.52 (m, 1H, Cy*H*), 1.50 – 1.44 (m, 1H, Cy*H*), 1.36 (ddd, *J* = 12.2, 6.0, 3.0 Hz, 1H, Cy*H*), 1.28 – 1.26 (m, 1H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.3 (C), 158.5 (C), 158.3 (C), 148.3 (CH), 147.6 (C), 137.4 (CH), 135.8 (C), 134.9 (C), 131.4 (CH), 130.6 (CH), 130.5 (CH), 121.4 (CH), 113.9 (CH), 113.4 (CH), 55.33 (CH_3), 55.30 (CH_3), 52.7 (CH), 46.9 (CH_2), 41.4 (C), 40.4 (CH_2), 34.4 (CH_2), 29.4 (CH_2), 27.0 (CH_2), 21.9 (CH_2), 18.6 (CH_3).

Diastereoisomer 2

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 1.4, 0.7 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 5.6 Hz, 1H), 7.57 (ddd, *J* = 7.9, 2.2, 0.7 Hz, 1H), 7.21 – 7.19 (m, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.87 – 6.85 (m, 2H), 6.79 – 6.77 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.32 – 3.28 (m, 1H), 3.16 (d, *J* = 13.7 Hz, 1H), 3.11 (dd, *J* = 13.8, 5.3 Hz, 1H), 2.80 (dd, *J* = 12.8, 3.1 Hz, 1H), 2.45 (d, *J* = 13.6 Hz, 1H), 2.37 (s, 3H), 2.12 – 2.08 (m, 1H).

HRMS found (ES) $[M+H]^+$ 459.2652, $C_{29}H_{34}N_2O_3$+H requires 459.2648.

***N*-((1-(4-Methoxybenzyl)cyclohexyl)methyl)-3-(trifluoromethyl)picolinamide 309**

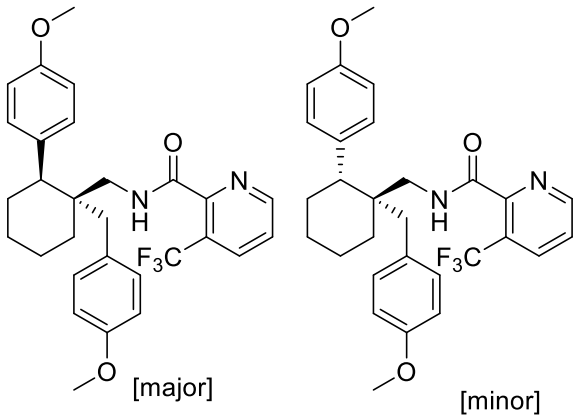


Prepared according to general arylation procedure A using amide **308** (30 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the mono and diarylated products as an inseparable mixture (15 mg, 35%).

Mono (12 mg, 0.03 mmol, 30%)

ν_{max} (film/cm^{-1}) 3363 (NH), 2923 (CH), 2852 (CH), 1689 (CO), 1510 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.67 (dd, *J* = 4.7, 1.4 Hz, 1H, pyNC*H*), 8.15 (dd, *J* = 8.1, 1.1 Hz, 1H, CF_3CCH), 7.54 (dd, *J* = 7.9, 4.8 Hz, 2H, N*H* and pyNCHC*H*), 7.11 – 7.08 (m, 2H, OCCHC*H*), 6.84 – 6.81 (m, 2H, OCC*H*), 3.78 (s, 3H, OCH_3), 3.37 (d, *J* = 6.3 Hz, 2H, $NHCH_2$), 2.62 (s, 2H, $ArCH_2$), 1.59 – 1.55 (m, 6H, Cy*H*), 1.47 (dd, *J* = 10.9, 5.0 Hz, 1H, Cy*H*), 1.43 – 1.40 (m, 1H, Cy*H*), 1.39 – 1.37 (m, 2H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.3 (C), 158.3 (C), 150.6 (CH), 149.9 (C), 136.3 (q, *J* = 6.0 Hz Hz, CH), 131.4 (CH), 130.2 (C), 126.0 (q, *J* = 34.4 Hz, C), 125.2 (CH), 123.0 (q, *J* = 273.2 Hz, C) 113.8 (CH), 55.3 (CH_3), 45.2 (CH_2), 43.2 (CH_2), 38.2 (C), 33.6 (CH_2), 26.3 (CH_2), 21.8 (CH_2); **HRMS** found (ES) $[M+H]^+$ 407.1932, $C_{22}H_{25}N_2O_2F_3$+H requires 407.1946.

_N_-((1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)cyclohexyl)methyl)-3-(trifluoromethyl)picolinamide 310

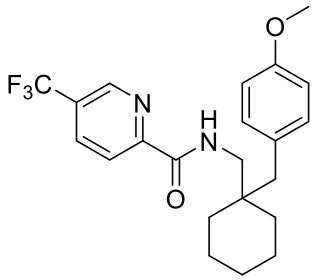


Isolated as an inseparable mixture with the mono arylated product. *d.r* = 88:12 (3 mg, 0.005 mmol, 5%).

[*major diastereoisomer*] **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.7, 1.4 Hz, 1H, pyNC*H*), 8.07 – 8.03 (m, 1H, CF_3CCH), 7.45 – 7.40 (m, 1H, pyNCHC*H*), 7.21 – 7.19 (m, 2H, OCCHC*H*), 7.06 – 7.02 (m, 2H, OCCHC*H*), 6.91 (d, *J* = 8.7 Hz, 1H, N*H*), 6.85 – 6.83 (m, 2H, OCC*H*), 6.79 – 6.76 (m, 2H, OCC*H*), 4.35 (dd, *J* = 13.9, 10.5 Hz, 1H, $NHCH_2$), 3.81 (s, 3H,

OCH_3), 3.74 (s, 3H, OCH_3), 3.02 – 2.99 (m, 1H, NHCH_2), 2.73 (d, J = 13.4 Hz, 1H, ArCH_2), 2.65 – 2.63 (m, 1H, ArCH), 2.49 (d, J = 12.9 Hz, 1H, ArCH_2), 2.21 – 2.13 (m, 1H, CyH), 1.92 (d, J = 13.5 Hz, 1H, CyH), 1.88 (d, J = 13.1 Hz, 1H, CyH), 1.82 – 1.77 (m, 1H, CyH), 1.73 (t, J = 16.0 Hz, 2H, CyH); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 162.6, 158.5, 158.3, 150.0, 136.0 134.7, 131.4, 130.6, 130.5, 124.9, 113.9, 113.4, 55.3, 52.9, 47.4, 46.0, 41.5, 40.6, 35.6, 34.4, 27.0, 21.9.

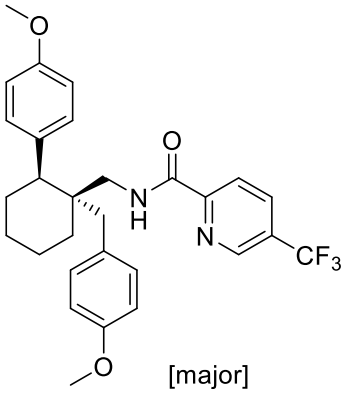
***N*-((1-(4-Methoxybenzyl)cyclohexyl)methyl)-5-(trifluoromethyl)picolinamide 212**



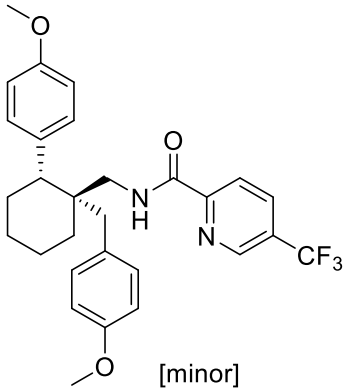
Prepared according to general arylation procedure A using amide **311** (30 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a colourless oil (16 mg, 0.039 mmol, 39%).

ν_{max} (film/cm^{-1}) 3396 (NH), 2924 (CH), 2852 (CH), 1681 (CO), 1512 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.81 – 8.78 (m, 1H, pyNCH), 8.32 (t, J = 8.9 Hz, 1H, CF_3CCHCH), 8.09 (dd, J = 8.2, 2.1 Hz, 1H, CF_3CCHCH), 8.05 – 7.92 (m, 1H, NH), 7.13 – 7.08 (m, 2H, OCCHCH), 6.86 – 6.82 (m, 2H, OCCH), 3.79 (s, 3H, OCH_3), 3.37 (d, J = 6.4 Hz, 2H, NHCH_2), 2.63 (s, 2H, ArCH_2), 1.60 – 1.54 (m, 4H, CyH), 1.48 (dd, J = 11.0, 5.2 Hz, 1H, CyH), 1.45 – 1.37 (m, 5H, CyH); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.0 (C), 158.3 (C), 153.0 (C), 145.2 (q, J = 3.9 Hz, CH), 134.9 (q, J = 3.4 Hz, CH), 131.4 (CH), 130.1 (C), 128.8 (q, J = 33.3 Hz, C), 123.4 (q, J = 272.7 Hz, C), 122.1 (CH), 113.8 (CH), 55.3 (CH_3), 45.2 (CH_2), 43.1 (CH_2), 38.2 (C), 33.6 (CH_2), 26.3 (CH_2), 21.8 (CH_2); **HRMS** found (ES) $[M+H]^+$ 407.1939, $C_{22}H_{25}N_2O_2F_3$+H requires 407.1946.

***N*-((1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)cyclohexyl)methyl)-5-(trifluoromethyl)picolinamide 313**



[major]

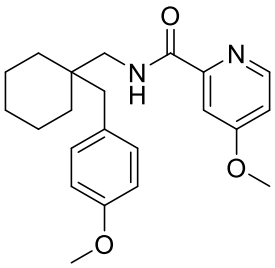


[minor]

Colourless oil (9 mg, 0.018 mmol, 18%). Mixture of diastereoisomers d.r = 17:83

ν_{max} (film/cm^{-1}) 3368 (NH), 2925 (CH), 2854 (CH), 1682 (CO), 1511 (CC);
[*major diastereoisomer*] **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 1.4, 0.7 Hz, 1H, pyNC*H*), 8.16 (d, *J* = 8.2 Hz, 1H, pyCC*H*), 7.99 (dd, *J* = 8.2, 2.2 Hz, 1H, pyCCHC*H*), 7.23 – 7.20 (m, 2H, OCCHC*H*), 7.05 – 7.03 (m, 2H, OCCHC*H*), 6.85 – 6.84 (m, 3H, OCC*H,* N*H*), 6.81 – 6.78 (m, 2H, OCC*H*), 4.28 (dd, *J* = 13.4, 9.7 Hz, 1H, NHCH_2), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.09 – 3.05 (m, 1H, NHCH_2), 2.78 – 2.74 (m, 1H, ArCH_2), 2.65 (dd, *J* = 12.9, 3.5 Hz, 1H, ArC*H*), 2.53 – 2.49 (m, 1H, ArCH_2), 2.21 – 2.13 (m, 1H, Cy*H*), 1.89 (s, 2H, Cy*H*), 1.74 (d, *J* = 12.6 Hz, 1H, Cy*H*), 1.53 (d, *J* = 4.3 Hz, 1H, Cy*H*), 1.43 (dd, *J* = 5.8, 2.7 Hz, 1H, Cy*H*), 1.36 (dddd, *J* = 19.3, 15.9, 9.9, 4.8 Hz, 2H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 162.6 (C), 158.6 (C), 158.4 (C), 152.8 (C), 144.8 (q, *J* = 3.9 Hz, CH), 134.6 (CH), 134.5 (q, *J* = 3.5 Hz, C), 131.4 (CH), 131.3 (C), 130.5 (CH), 130.4 (C), 121.6 (CH), 114.0 (CH), 113.5 (CH), 55.3 (CH_3), 55.2 (CH_3), 52.8 (CH), 47.2 (CH_2), 41.0 (C), 40.6 (CH_2) , 34.4 (CH_2), 29.3 (CH_2), 26.9 (CH_2), 21.9 (CH_2);
HRMS found (ES) $[M+H]^+$ 513.2310, $C_{29}H_{31}N_2O_3F_3$+H requires 513.2360.

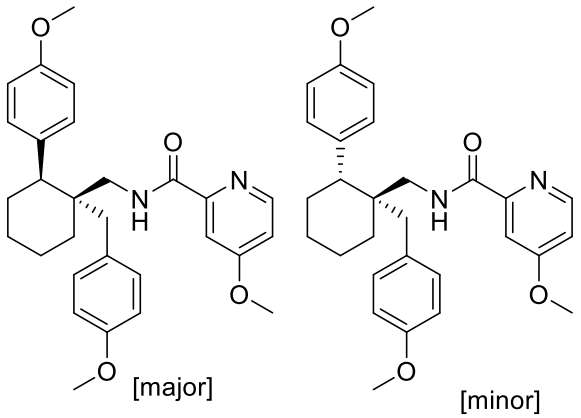
4-Methoxy-*N*-((1-(4-methoxybenzyl)cyclohexyl)methyl)picolinamide 316



Prepared according to general arylation procedure A using amide **315** (26 mg, 0.10 mmol) and 4-iodoanisole (0.40 mmol, 94 mg). Purified by flash column chromatography (0 – 40% EtOAc in petrol) to give the product as a colourless oil (20 mg, 0.054 mmol, 54%).

ν_{max} (film/cm^{-1}) 3385 (NH), 2921 (CH), 2851 (CH), 1677 (CO), 1511 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.35 – 8.31 (m, 1H, pyNC*H*), 8.18 (s, 1H, N*H*), 7.74 (d, *J* = 2.5 Hz, 1H, pyNCHC*H*), 7.12 – 7.09 (m, 2H, OCCHC*H*), 6.91 (dd, *J* = 5.6, 2.6 Hz, 1H, pyCC*H*C), 6.85 – 6.81 (m, 2H, OCC*H*), 3.91 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.33 (d, *J* = 5.6 Hz, 2H, NHCH_2), 2.63 (s, 2H, ArCH_2), 1.59 – 1.55 (m, 4H, Cy*H*), 1.47 (dt, *J* = 17.8, 5.8 Hz, 1H, Cy*H*), 1.43 – 1.34 (m, 5H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 167.1 (C), 164.4 (C), 158.2 (C), 152.3 (C), 149.3 (CH), 131.5 (CH), 130.2 (C), 113.7 (CH), 113.1 (CH), 107.3 (CH), 55.7 (CH_3), 55.3 (CH_3), 44.9 (CH_2), 42.7 (CH_2), 38.1 (C), 33.5 (CH_2), 26.3 (CH_2), 21.8 (CH_2); **HRMS** found (ES) $[M+H]^+$ 369.2176, $C_{22}H_{28}N_2O_3$ requires 369.2178.

4-Methoxy-*N*-((1-(4-methoxybenzyl)-2-(4-methoxyphenyl)cyclohexyl)methyl)picolinamide 317



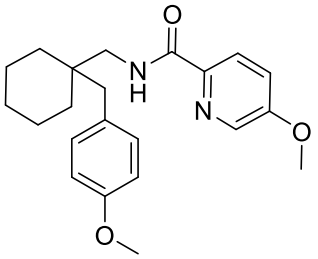
Colourless oil; mixture of diastereoisomers d.r = 19:81 (11 mg, 0.023 mmol, 23%).

ν_{max} (film/cm^{-1}) 3353 (NH), 2920 (CH), 2851 (CH), 1671 (CO), 1510 (CC);
[*major diastereoiomer*] **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.04 (d, *J* = 5.9 Hz, 1H, pyNC*H*), 7.59 (d, *J* = 4.2 Hz, 1H, pyCC*H*C), 7.40 – 7.36 (m, 1H, N*H*), 7.23 – 7.21 (m, 2H, OCCHC*H*), 7.07 – 7.03 (m, 2H, OCCHC*H*), 6.85 – 6.84 (m, 2H, OCC*H*), 6.80 (dd, *J* = 7.1, 1.5 Hz, 2H, OCC*H*), 6.79 (d, *J* = 3.9 Hz, 1H, Ar*H*), 4.26 (dd, *J* = 13.6, 9.4 Hz, 1H, NHCH_2), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.07 (dd, *J* = 13.9, 3.0 Hz, 1H, NHCH_2), 2.74 (d, *J* = 13.5 Hz, 1H, ArCH_2), 2.64 (dd, *J* = 12.8, 3.5 Hz, 1H, ArC*H*), 2.50 (d, *J* = 13.5 Hz, 1H, ArCH_2), 2.16 (qd, *J* = 13.0, 3.9 Hz, 1H, Cy*H*), 1.90 – 1.85 (m, 2H, Cy*H*), 1.71 (dd, *J* = 28.7, 13.1 Hz, 2H, Cy*H*), 1.53 (s, 1H, Cy*H*), 1.51 – 1.43 (m, 2H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 166.8 (C), 164.0 (C), 158.6 (C), 158.3 (C), 152.1 (C), 148.9 (CH), 134.8 (C), 131.4 (CH),

130.5 (CH), 130.4 (C), 114.0 (CH), 113.5 (CH), 112.7 (CH), 106.9 (CH), 55.5 (CH_3), 55.4 (CH_3), 55.3 (CH_3), 52.6 (CH), 46.9 (CH_2), 41.5 (C), 40.6 (CH_2), 34.4 (CH_2), 29.4 (CH_2), 26.9 (CH_2), 21.9 (CH_2);

HRMS found (ES) $[M+H]^+$ 475.2582, $C_{29}H_{34}N_2O_4$+H requires 475.2597.

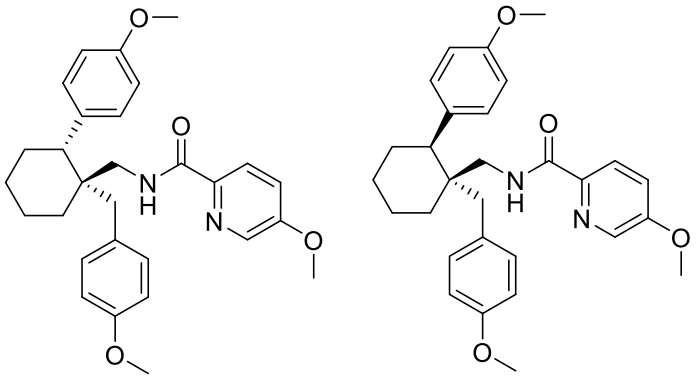
5-Methoxy-*N*-((1-(4-methoxybenzyl)cyclohexyl)methyl)picolinamide 319



Prepared according to general arylation procedure A, using amide **318** (26 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 40% EtOAc in petrol), to give the product as a colourless oil (14 mg, 0.038 mmol, 38%).

ν_{max} (film/cm^{-1}) 3393 (NH), 2924 (CH), 2850 (CH), 1671 (CO), 1510 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.20 (d, *J* = 2.5 Hz, 1H, pyNC*H*), 8.14 (d, *J* = 8.6 Hz, 1H, pyCC*H*CH), 7.92 (s, 1H, N*H*), 7.27 (dd, *J* = 8.6, 2.7 Hz, 1H, pyCCHC*H*), 7.10 (d, *J* = 8.3 Hz, 2H, OCCHC*H*), 6.82 (d, *J* = 9.6 Hz, 2H, OCC*H*), 3.90 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.32 (d, *J* = 6.3 Hz, 2H, NHCH_2), 2.62 (s, 2H, ArCH_2), 1.57 (dt, *J* = 11.4, 5.5 Hz, 4H, Cy*H*), 1.47 (td, *J* = 11.2, 5.3 Hz, 1H, Cy*H*), 1.43 – 1.33 (m, 5H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.4 (C), 158.2 (C), 157.9 (C), 143.0 (C), 136.5 (CH), 131.5 (CH), 130.2 (C), 123.4 (CH), 120.3 (CH), 113.7 (CH), 55.9 (CH_3), 55.3 (CH_3), 44.8 (CH_2), 42.8 (CH_2), 38.1 (C), 33.5 (CH_2), 26.3 (CH_2), 24.0 (CH_2), 21.8 (CH_2); **HRMS** found (ES) $[M+H]^+$ 369.2176, $C_{22}H_{28}N_2O_3$+H requires 369.2178.

5-Methoxy-*N*-((1-(4-methoxybenzyl)-2-(4-methoxyphenyl)cyclohexyl)methyl)picolinamide 320



diastereoisomer 1 *diastereoisomer 2*

This compound was isolated as a mixture of diastereoisomers *d.r* 86:14 (9 mg, 0.019 mmol, 19%).

ν_{max} (film/cm^{-1}) 3365 (NH), 2925 (CH), 2852 (CH), 1667 (CO), 1510 (CC);

Diastereoisomer 1

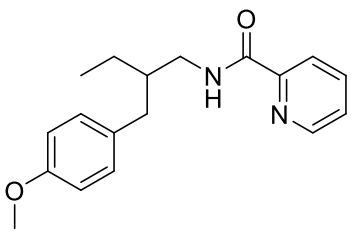
^{1}H NMR (700 MHz, $CDCl_3$) *δ* 7.99 (d, *J* = 8.6 Hz, 1H, pyNC*H*), 7.90 (d, *J* = 2.7 Hz, 1H, pyCC*H*), 7.24 – 7.20 (m, 2H, OCCHC*H*), 7.17 (dd, *J* = 8.7, 2.8 Hz, 1H, pyCCHC*H*), 7.15 (d, *J* = 7.7 Hz, 1H, N*H*), 7.05 (d, *J* = 8.4 Hz, 2H, OCCHC*H*), 6.84 (d, *J* = 8.4 Hz, 2H, OCC*H*), 6.80 (d, *J* = 8.4 Hz, 2H, OCC*H*), 4.25 (dd, *J* = 13.9, 9.3 Hz, 1H, NHCH_2), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.08 – 3.02 (m, 1H, NHCH_2), 2.74 (d, *J* = 13.5 Hz, 1H, ArCH_2), 2.66 – 2.60 (m, 1H, ArC*H*), 2.49 (d, *J* = 13.5 Hz, 1H, ArCH_2), 2.17 (qd, *J* = 13.2, 3.6 Hz, 1H, Cy*H*), 1.88 (t, *J* = 13.1 Hz, 2H, Cy*H*), 1.72 (d, *J* = 12.4 Hz, 1H, Cy*H*), 1.52 (d, *J* = 8.5 Hz, 1H, Cy*h*), 1.46 (d, *J* = 13.2 Hz, 1H, Cy*H*), 1.36 (dd, *J* = 7.9, 3.9 Hz, 1H, Cy*H*), 1.27 – 1.26 (m, 1H, Cy*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.0 (C), 158.5 (C), 158.3 (C), 157.6 (C), 142.8 (C), 136.0 (CH), 134.9 (C), 131.4 (CH), 130.6 (CH), 130.5 (CH), 122.9 (CH), 120.0 (CH), 113.9 (CH), 113.4 (CH), 55.8 (CH_3), 55.34 (CH_3), 55.26 (CH_3), 52.7 (CH), 47.0 (CH_2), 41.5 (C), 40.4 (CH_2), 34.4 (CH_2), 29.4 (CH_2), 27.0 (CH_2), 21.9 (CH_2).

Diastereoisomer 2

^{1}H NMR (700 MHz, $CDCl_3$) *δ* 8.06 (d, *J* = 2.7 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 5H), 7.58 (s, 1H), 7.11 (d, *J* = 4.1 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.77 (s, 3H), 3.15 (d, *J* = 13.6 Hz, 1H), 2.80 (d, *J* = 10.0 Hz, 1H), 2.45 (d, *J* = 13.6 Hz, 1H), 2.09 (d, *J* = 8.2 Hz, 1H), 2.00 (dt, *J* = 13.7, 6.9 Hz, 1H).

HRMS found (ES) $[M+H]^+$ 475.2591, $C_{29}H_{34}N_2O_4$+H requires 475.2597.

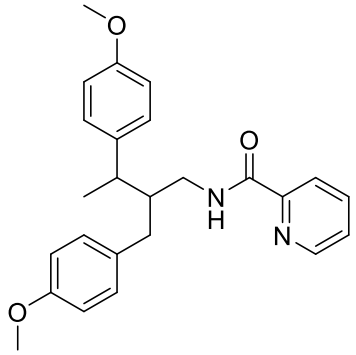
***N*-(2-(4-Methoxybenzyl)butyl)picolinamide 324**



Prepared according to general arylation procedure A, using amide **323** (19 mg, 0.10 mmol) and 4-iodoanisle (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a colourless oil (9 mg, 0.030 mmol, 30%).

ν_{max} (film/cm^{-1}) 3389 (NH), 2959 (CH), 2828 (CH), 1673 (CO), 1510 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.54 – 8.51 (m, 1H, pyNC*H*), 8.18 (dt, *J* = 7.8, 1.1 Hz, 1H, pyCC*H*), 8.10 – 7.98 (m, 1H, N*H*), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 7.13 – 7.10 (m, 2H, OCCHC*H*), 6.83 – 6.81 (m, 2H, OCC*H*), 3.77 (s, 3H, OCH_3), 3.45 (dt, *J* = 13.5, 6.3 Hz, 1H, NHCH_2), 3.39 (dt, *J* = 13.6, 6.1 Hz, 1H, NHCH_2), 2.64 (dd, *J* = 13.9, 6.9 Hz, 1H, ArCH_2), 2.58 (dd, *J* = 14.0, 7.4 Hz, 1H, ArCH_2), 1.92 – 1.85 (m, 1H, C*H*), 1.44 – 1.38 (m, 2H, CH_3CH_2), 0.98 (t, *J* = 7.5 Hz, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.5 (C), 158.0 (C), 150.2 (C), 148.1 (CH), 137.4 (CH), 132.6 (C), 130.1 (CH), 126.1 (CH), 122.3 (CH), 113.9 (CH), 55.4 (CH_3), 42.2 (CH), 42.1 (CH_2), 37.7 (CH_2), 24.4 (CH_2), 11.3 (CH_3); **HRMS** found (ES) $[M+H]^+$ 299.1758, $C_{18}H_{22}N_2O_2$+H requires 299.1758.

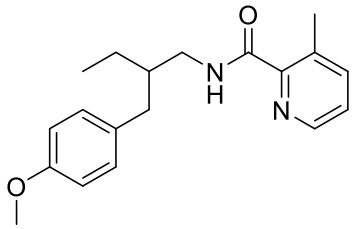
***N*-(2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)butyl)picolinamide 325**



Compound obtained in trace quantities along with the mono arylation product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.46 (m, 1H, pyNC*H*), 8.15 – 8.11 (m, 1H, pyCC*H*), 7.84 – 7.77 (m, 1H, pyCCHC*H*)*, 7.61 (s, 1H, N*H*), 7.39 – 7.36 (m, 1H, pyNCHC*H*)*, 7.20 – 7.16 (m, 2H, OCCHC*H*), 7.08 – 7.04 (m, 2H, OCCHC*H*), 6.87 – 6.83 (m, 2H, OCC*H*), 6.79 – 7.76 (m, 2H, OCC*H*), 3.78 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.54 (dd, *J* = 13.4, 6.4 Hz, 1H, NHCH_2), 3.14 (dt, *J* = 13.7, 5.7 Hz, 1H, NHCH_2), 2.94 – 2.86 (m, 1H, ArC*H*), 2.76 (dd, *J* = 14.1, 4.5 Hz, 1H, ArCH_2), 2.49 – 2.40 (m, 1H, ArCH_2), 2.16 – 2.10 (m, 1H, $ArCH_2CH$).
*Peak overlapping with monoarylation product

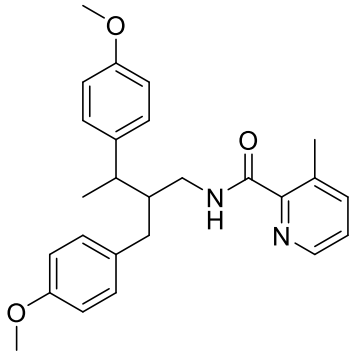
***N*-(2-(4-Methoxybenzyl)butyl)-3-methylpicolinamide 327**



Prepared according to general arylation procedure A, using amide **326** (21 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a mixture of mono and di arylated products (25 mg, 78%).
Monoarylation 0.073 mmol, 73%

ν_{max} (film/cm^{-1}) 3388 (NH), 2959 (CH), 2927 (CH), 1670 (CO), 1509 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.36 (ddd, *J* = 4.6, 1.6, 0.5 Hz, 1H, pyNC*H*), 8.12 (s, 1H, N*H*), 7.57 (ddd, *J* = 7.7, 1.6, 0.7 Hz, 1H, pyNCHCHC*H*), 7.30 – 7.27 (m, 1H, pyNCHC*H*), 7.13 – 7.09 (m, 2H, OCCHC*H*), 6.83 – 6.80 (m, 2H, OCC*H*), 3.77 (s, 3H, OCH_3), 3.42 (dt, *J* = 13.5, 6.2 Hz, 1H, NHCH_2), 3.34 (dt, *J* = 13.6, 6.2 Hz, 1H, NHCH_2), 2.74 (s, 3H, ArCH_3), 2.65 – 2.57 (m, 2H, ArCH_2), 1.91 – 1.84 (m, 1H, NHCH$_2$C*H*), 1.43 – 1.34 (m, 2H, CH$_3$CH_2), 0.99 – 0.96 (m, 3H, CH_3CH$_2$); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 166.1 (C), 158.0 (C), 147.5 (C), 145.5 (CH), 140.9 (CH), 135.4 (C), 132.7 (C), 130.1 (CH), 125.6 (CH), 113.9 (CH), 55.4 (CH_3), 42.1 (CH), 42.0 (CH_2), 37.7 (CH_2), 24.4 (CH_2), 20.7 (CH_3), 11.2 (CH_3); **HRMS** found (ES) $[M+H]^+$ 313.1915, $C_{19}H_{24}N_2O_2$+H requires 313.1916.

***N*-(2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)butyl)-3-methylpicolinamide 328**

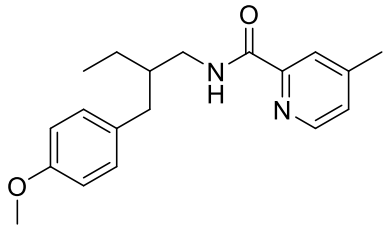


Isolated as a mixture with the monoarylated product (0.005 mmol, 5%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.39 – 8.37 (m, 1H, pyNC*H*), 7.92 (s, 1H, N*H*), 7.55 - 7.53 (m, 1H, pyNCHCHC*H*), 7.19 – 7.16 (m, 2H, OCCHC*H*), 7.07 – 7.05 (m, 3H, pyNCHC*H* and OCCHC*H*), 6.86 – 6.83 (m, 2H, OCC*H*), 6.79 – 6.77 (m, 2H, OCC*H*), 3.78 (s, 3H, OCH_3),

3.75 (s, 3H, OCH_3), 3.54 – 3.50 (m, 1H, NHCH_2), 3.24 (ddd, *J* = 13.4, 7.2, 6.3 Hz, 1H, NHCH_2), 3.14 – 3.09 (m, 1H, ArC*H*), 2.91 (dd, *J* = 13.4, 6.7 Hz, 1H, ArCH_2), 2.71 (s, 3H, ArCH_3), 2.46 (dd, *J* = 14.1, 9.0 Hz, 1H, ArCH_2), 2.41 – 2.33 (m, 1H, ArCHC*H*), 1.36 -1.35 (m, 3H, ArCHCH_3); **HRMS** found (ES) $[M+H]^+$ 419.2339, $C_{26}H_{30}N_2O_3$+H requires 419.2335.

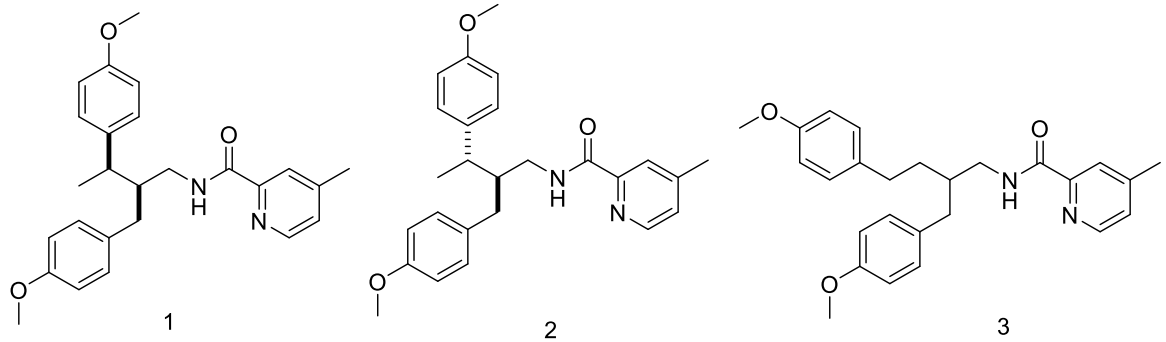
***N*-(2-(4-Methoxybenzyl)butyl)-4-methylpicolinamide 330**



Prepared according to general arylation procedure A, using amide **329** (21 mg, 0.1 mmol) and 4-iodoanisle (94 mg, 0.4 mmol). Purified by flash column chromatography to give the product as a colourless oil (8 mg, 0.0256 mmol, 26%).

ν_{max} (film/cm^{-1}) 3387 (NH), 2924 (CH), 2875 (CH), 1617 (CO), 1510 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.39 – 8.35 (m, 1H, pyNC*H*), 8.03 (s, 1H, N*H*), 8.02 – 8.01 (m, 1H, pyCC*H*C), 7.22 (dd, *J* = 4.9, 1.7 Hz, 1H, pyNCHC*H*), 7.13 – 7.09 (m, 2H, OCCHC*H*), 6.84 – 6.80 (m, 2H, OCC*H*), 3.77 (s, 3H, OCH_3), 3.44 (dt, *J* = 13.5, 6.3 Hz, 1H, NHCH_2), 3.39 (dt, *J* = 13.6, 6.1 Hz, 1H, NHCH_2), 2.63 (dd, *J* = 13.9, 6.9 Hz, 1H, ArCH_2), 2.57 (dd, *J* = 13.9, 7.4 Hz, 1H, ArCH_2), 2.42 (s, 3H, ArCH_3), 1.91 – 1.84 (m, 1H, C*H*), 1.43 – 1.38 (m, 2H, CH_3CH_2), 0.97 (t, *J* = 7.5 Hz, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.7 (C), 158. (C), 149.9 (C), 148.9 (C), 148.0 (CH), 132.6 (C), 130.1 (CH), 126.9 (CH), 123.2 (CH), 113.9 (CH), 55.4 (CH_3), 42.2 (CH), 42.0 (CH_2), 37.6 (CH_2), 24.4 (CH_2), 21.3 (CH_3), 11.2 (CH_3); **HRMS** found (ES) $[M+H]^+$ 313.1917, $C_{19}H_{24}N_2O_2$+H requires 313.1916.

***N*-(2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)butyl)-4-methylpicolinamide 331**



Separated from the monoarylation product. Yellow oil. 11 mg, 0.026 mmol, 26%

1 and 2

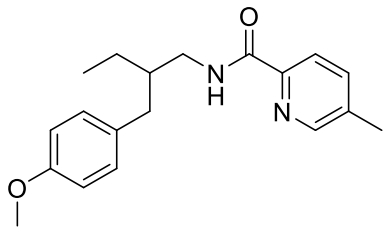
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 4.9, 0.5 Hz, 1H, pyNC*H*), 8.01 – 7.99 (m, 1H, pyNCC*H*), 7.93 (s, 1H, N*H*), 7.23 – 7.22 (m, 1H, pyNCHC*H*), 7.16 – 7.14 (m, 2H, OCCHC*H*), 7.07 (d, *J* = 2.1 Hz, 2H, OCCHC*H*), 6.85 – 6.84 (m, 2H, OCC*H*), 6.80 – 6.78 (m, 2H OCC*H*), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.52 – 3.50 (m, 1H, NHCH_2), 3.42 – 3.40 (m, 1H, NHCH_2), 2.85 – 2.82 (m, 1H, ArC*H*), 2.66 (s, 1H, ArCH_2), 2.43 (s, 3H, ArCH_3), 2.38 – 2.36 (m, 1H, ArCH_2), 2.13 – 2.11 (m, 1H, ArCHC*H*), 1.37 – 1.35 (m, 3H, CHCH_3).

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 4.9, 0.5 Hz, 1H, pyNC*H*), 7.98 – 7.97 (m, 1H, PyNCC*H*), 7.88 (s, 1H, N*H*), 7.21 – 7.20 (m, 1H, pyNCHC*H*), 7.19 – 7.17 (m, 2H, OCCHC*H*), 7.08 – 7.06 (m, 2H, OCCHC*H*), 6.86 – 6.84 (m, 2H, OCC*H*), 6.79 – 6.78 (m, 2H, OCC*H*), 3.79 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.56 – 3.52 (m, 1H, NHCH_2), 3.15 – 3.11 (m, 1H, NHCH_2), 2.92 – 2.88 (m, 1H, ArC*H*), 2.75 (dd, *J* = 14.1, 4.5 Hz, 1H, ArCH_2), 2.47 – 2.44 (m, 1H, ArCH_2), 2.41 (s, 3H, ArCH_3), 2.16 – 2.13 (m, 1H, ArCHC*H*), 1.39 – 1.36 (m, 3H, CHCH_3).

3

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 4.9, 0.8 Hz, 1H, pyNC*H*), 8.07 (s, 1H, N*H*), 8.03 – 8.02 (m, 1H, pyNCC*H*), 7.24 – 7.22 (m, 1H, pyNCHC*H*), 7.11 – 7.09 (m, 2H, OCCHC*H*), 7.07 - 7.05 (m, 2H, OCCHC*H*), 6.82 – 6.81 (m, 2H, OCC*H*), 6.79 – 6.78 (m, 2H, OCC*H*), 3.79 (s, 3H OCH_3), 3.78 (s, 3H, OCH_3), 3.51 – 3.48 (m, 1H, NHCH_2), 3.46 – 3.44 (m, 1H, NHCH_2), 2.69 – 2.61 (m, 4H, ArCH_2), 2.43 (s, 3H, ArCH_3), 2.00 – 1.96 (m, 1H, NHCH$_2$C*H*), 1.68 – 1.63 (m, 2H, CHCH_2CH$_2$).

***N*-(2-(4-Methoxybenzyl)butyl)picolinamide 333**

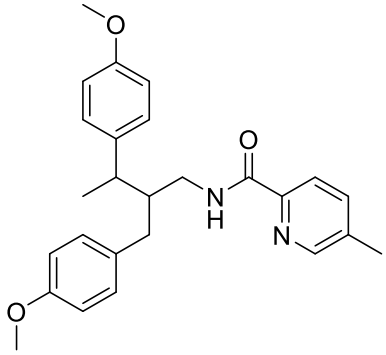


Prepared according to general arylation procedure A, using amide **332** (21 mg, 0.1 mmol) and 4-iodoanisle (94 mg, 0.4 mmol). Purified by flash column chromatography (0 – 15% EtOAc in petrol) to give the product as a yellow oil (27 mg, 0.087 mmol, 87%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.36 – 8.32 (m, 1H, CH$_3$CC*H*N), 8.07 (d, *J* = 8.0 Hz, 1H, CH$_3$CCHC*H*), 7.96 (s, 1H, N*H*), 7.64 – 7.61 (m, 1H, CH$_3$CC*H*CH), 7.13 – 7.09 (m, 2H, OCCHC*H*), 6.84 – 6.79 (m, 2H, OCC*H*), 3.77 (s, 3H, OCH$_3$), 3.46 – 3.41 (m, 1H, NHCH_2),

3.38 (dt, *J* = 13.6, 6.1 Hz, 1H, NHC*H*$_2$), 2.63 (dd, *J* = 13.9, 6.9 Hz, 1H, ArC*H*$_2$), 2.57 (dd, *J* = 13.9, 7.3 Hz, 1H, ArC*H*$_2$), 2.39 (s, 3H, ArC*H*$_3$), 1.91 – 1.84 (m, 1H, C*H*), 1.42 – 1.37 (m, 2H, CH$_3$C*H*$_2$), 0.97 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.7 (C), 158.0 (C), 148.6 (CH), 147.7 (C), 137.8 (CH), 136.3 (C), 132.6 (C), 130.1 (CH), 121.9 (CH), 113.9 (CH), 55.3 (CH_3), 42.2 (CH_2), 42.0 (CH), 37.6 (CH_2), 24.4 (CH_2), 18.6 (CH_3), 11.2 (CH_3); **HRMS** found (ES) $[M+H]^+$ 313.1914, $C_{19}H_{24}N_2O_2$+H requires 313.1916.

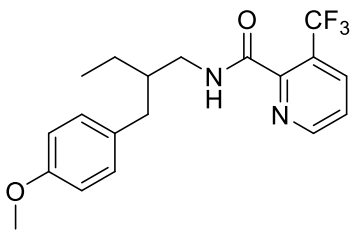
***N*-(2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)butyl)-5-methylpicolinamide 334**



Isolated as a mixture with the monoarylated product (0.011 mmol, 11%)

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.31 – 8.29 (m, 1H, pyNC*H*), 8.07 (d, *J* = 8.0 Hz, 1H, pyNCC*H*), 7.79 (s, 1H, N*H*), 7.60 (d, *J* = 6.5 Hz, 1H, pyNCCHC*H*), 7.18 (d, *J* = 8.6 Hz, 2H, OCCHC*H*), 7.07 – 7.05 (m, 2H, OCCHC*H*), 6.87 – 6.84 (m, 2H, OCC*H*), 6.79 – 6.76 (m, 2H, OCC*H*), 3.79 (s, 3H, OC*H*$_3$), 3.75 (s, 3H, OC*H*$_3$), 3.53 (dd, *J* = 13.4, 6.6 Hz, 1H, NHC*H*$_2$), 3.16 – 3.09 (m, 1H, NHC*H*$_2$), 2.93 – 2.88 (m, 1H, ArC*H*), 2.74 (dd, *J* = 14.1, 4.6 Hz, 1H, ArC*H*$_2$), 2.44 (dd, *J* = 14.0, 9.2 Hz, 1H, ArC*H*$_2$), 2.39 (s, 3H, ArC*H*$_3$), 1.37 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$).

***N*-(2-(4-Methoxybenzyl)butyl)-3-(trifluoromethyl)picolinamide 336**

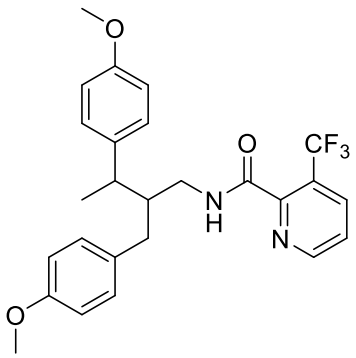


Prepared according to the general arylation procedure using amide **335** (26 mg, 0.10 mmol) and 4-iodoanisole (0.40 mmol, 94 mg). Purified by flash column chromatography (0 – 25% EtOAc in petrol) to give the monoarylated product as a colourless oil (17 mg) and a mixture of monoarylated and diarylated (7 mg).

Mono (17 mg, 0.046 mmol, 46%)

ν_{max} (film/cm^{-1}) 3370 (NH), 2941 (CH), 2870 (CH), 1621 (CO), 1508 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.68 (dd, J = 4.7, 1.4 Hz, 1H, pyNC*H*), 8.15 (dd, J = 8.0, 1.1 Hz, 1H, CF_3CCH), 7.57 – 7.50 (m, 2H, N*H* and pyNCHC*H*), 7.12 – 7.08 (m, 2H, OCCHC*H*), 6.83 – 6.79 (m, 2H, OCC*H*), 3.77 (s, 3H, OCH_3), 3.49 (dt, J = 13.6, 6.2 Hz, 1H, $NHCH_2$), 3.39 – 3.34 (m, 1H, $NHCH_2$), 2.65 (dd, J = 13.9, 6.9 Hz, 1H, $ArCH_2$), 2.57 (dd, J = 13.9, 7.4 Hz, 1H, $ArCH_2$), 1.93 – 1.86 (m, 1H, $ArCH_2CH$), 1.43 – 1.38 (m, 2H, CH_2CH_3), 0.98 (t, J = 7.5 Hz, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.3 (C), 158.0 (C), 150.6 (CH), 149.8 (C), 136.3 (q, J = 5.9 Hz, CH), 132.5 (C), 130.1 (CH), 126.0 (q, J = 34.3 Hz, C), 125.2 (CH), 123.0 (q, J = 273.3 Hz, C), 114.0 (CH), 55.4 (CH_3), 42.6 (CH_2), 42.0 (CH), 37.8 (CH_2), 24.5 (CH_2), 11.2 (CH_3); **HRMS** found (ES) $[M+H]^+$ 367.1633, $C_{19}H_{21}N_2O_2F_3$+H requires 367.1633.

***N*-(2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)butyl)-3-(trifluoromethyl)picolinamide 337**

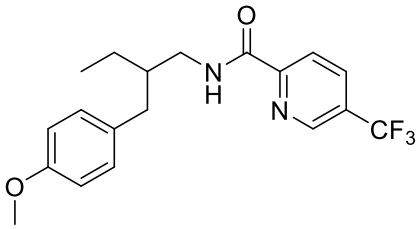


Isolated with the monoarylated compound (0.002 mmol, 2%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H, pyNC*H*), 8.35 (s, 1H, N*H*), 8.14 – 8.07 (m, 1H, CF_3CCH)*, 7.66 – 7.62 (m, 1HpyNCHC*H*)*, 7.18 – 7.14 (m, 2H, OCCHC*H*), 7.06 (d, J = 8.7 Hz, 2H, OCCHC*H*), 6.87 – 6.82 (m, 2H, OCC*H*), 6.77 – 6.75 (m, 2H, OCC*H*), 3.78 – 3.77 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.62- 3.54 (m, 1H, $NHCH_2$), 3.21 – 3.11 (m, 1H, $NHCH_2$), 2.91 (m, 1H, ArC*H*), 2.73 (m, 1H, $ArCH_2$), 2.50 – 2.40 (m, 1H, $ArCH_2$), 2.13 – 2.06 (m, 1H, ArCHC*H*), 1.35 – 1.34 (m, 3H, $CHCH_3$).

*Peaks overlapping with the monoarylation product

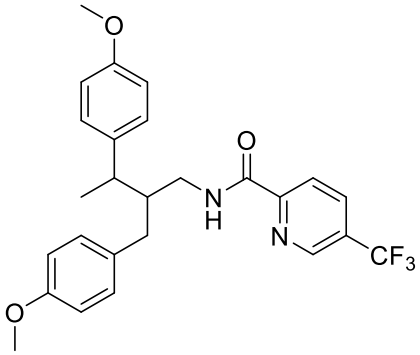
***N*-(2-(4-Methoxybenzyl)butyl)-5-(trifluoromethyl)picolinamide 339**



Prepared according to general arylation procedure A, using amide **338** (26 mg, 0.10 mmol) and 4-iodoanisle (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a colourless oil (15 mg, 0.041 mmol, 41%).

ν_{max} (film/cm^{-1}) 3370 (NH), 2941 (CH), 2870 (CH), 1621 (CO), 1508 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.79 – 8.77 (m, 1H, pyNC*H*), 8.31 (d, *J* = 8.2 Hz, 1H, CF_3CCHCH), 8.10 – 8.06 (m, 1H, CF_3CCHCH), 7.94 (s, 1H, N*H*), 7.12 – 7.09 (m, 2H, OCCHC*H*), 6.83 – 6.80 (m, 2H, OCC*H*), 3.77 (s, 3H, OCH_3), 3.50 – 3.46 (m, 1H, $NHCH_2$), 3.40 (dt, *J* = 13.6, 6.2 Hz, 1H, $NHCH_2$), 2.67 (dd, *J* = 14.0, 6.6 Hz, 1H, $ArCH_2$), 2.56 – 2.53 (m, 1H, $ArCH_2$), 1.92 – 1.87 (m, 1H, $NHCH_2CH$), 1.44 – 1.39 (m, 2H, CH_3CH_2), 0.99 (t, *J* = 7.5 Hz, 3H, CH_3CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.0 (C), 158.1 (C), 153.0 (C), 145.2 (q, *J* = 3.9 Hz, CH), 134.8 (q, *J* = 3.4 Hz, CH), 132.4 (C), 130.1 (CH), 128.8 (q, *J* = 33.3 Hz, C), 123.3 (q, *J* = 272.7, C), 122.1 (CH), 114.0 (CH), 55.3 (CH_3), 42.4 (CH_2), 42.1 (CH), 37.9 (CH_2), 24.6 (CH_2), 11.3 (CH_3); **HRMS** found (ES) $[M+H]^+$ 367.1621, $C_{19}H_{21}N_2O_2F_3$+H requires 367.1628

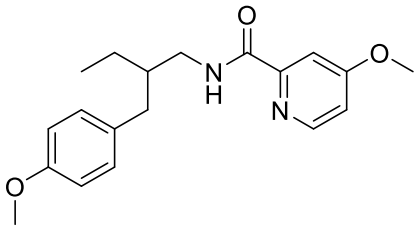
***N*-(2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)butyl)-5-(trifluoromethyl)picolinamide 340**



Isolated with the monoaryl compound (0.004 mmol, 4%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H, Ar*H*), 8.24 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.68 (s, 1H, N*H*), 7.17 (t, *J* = 5.4 Hz, 2H, Ar*H*), 6.88 – 6.83 (m, 2H, Ar*H*), 6.79 – 6.75 (m, 2H, Ar*H*), 3.78 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.60 – 3.52 (m, 1H), 3.22 – 3.13 (m, 1H), 2.89 – 2.79 (m, 1H), 2.47 – 2.33 (m, 1H), 2.19 – 2.12 (m, 1H), 2.00 (d, *J* = 6.1 Hz, 1H), 1.66 (dd, *J* = 15.5, 6.9 Hz, 1H); **HRMS** found (ES) $[M+H]^+$ 473.2033, $C_{26}H_{27}N_2O_3F_3$+H requires 473.2034

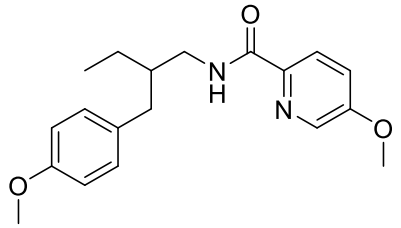
4-Methoxy-*N*-(2-(4-methoxybenzyl)butyl)picolinamide 343



Prepared according to general arylation procedure A, using amide **342** (22 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography (0 – 50% EtOAc in petrol) to give the product as a colourless oil (18 mg, 0.0548 mmol, 55%).

ν_{max} (film/cm^{-1}) 3386 (NH), 2923 (CH), 2853 (CH), 1672 (CO), 1511 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.32 – 8.30 (m, 1H, pyNC*H*), 8.06 (s, 1H, N*H*), 7.73 (d, *J* = 2.5 Hz, 1H, pyNCC*H*), 7.13 – 7.08 (m, 2H, OCCHC*H*), 6.91 – 6.89 (m, 1H, pyNCHC*H*), 6.84 – 6.81 (m, 2H, OCC*H*), 3.91 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.45 – 3.36 (m, 2H, NHCH_2), 2.63 (dd, *J* = 13.9, 6.9 Hz, 1H, ArCH_2), 2.57 (dd, *J* = 14.0, 7.4 Hz, 1H, ArCH_2), 1.91 – 1.83 (m, 1H, C*H*), 1.42 – 1.38 (m, 2H, CH_3CH_2), 0.98 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 167.1 (C), 164.4 (C), 158.0 (C), 152.2 (C), 149.2 (CH), 132.6 (C), 130.1 (CH), 113.9 (CH), 113.1 (CH), 107.3 (CH), 55.7 (CH_3), 55.4 (CH_3), 42.2 (CH), 42.1 (CH_2), 37.6 (CH_2), 24.4 (CH_2), 11.3 (CH_3); **HRMS** found (ES) $[M+H]^+$ 329.1864, $C_{19}H_{24}N_2O_3$+H requires 329.1865.

5-Methoxy-*N*-(2-(4-methoxybenzyl)butyl)picolinamide 346



Prepared according to general arylation procedure A, using amide **345** (22 mg, 0.10 mmol) and 4-iodoanisole (94 mg, 0.40 mmol). Purified by flash column chromatography to give a mixture of the mono and diarylated products (31 mg).

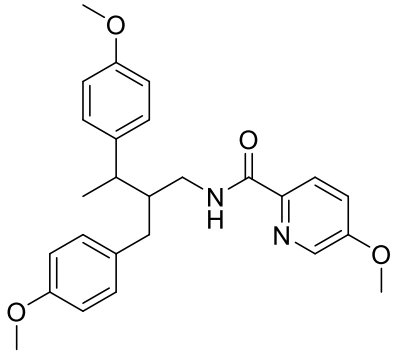
Isolated as a mixture with the diarylated product (0.082 mmol, 82%).

ν_{max} (film/cm^{-1}) 3391 (NH), 2923 (CH), 2853 (CH), 1669 (CO), 1511 (CC);

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 2.9, 0.5 Hz, 1H, pyNC*H*), 8.13 (dd, *J* = 8.6, 0.5 Hz, 1H, pyNCC*H*), 7.84 (s, 1H, N*H*), 7.28 – 7.26 (m, 1H, pyNCCHC*H*), 7.12 – 7.10 (m, 2H,

OCCHC*H*), 6.83 – 6.81 (m, 2H, OCC*H*), 3.90 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.45 – 3.41 (m, 1H, NHCH_2), 3.39 – 3.35 (m, 1H, NHCH_2), 2.62 (dd, *J* = 13.9, 6.9 Hz, 1H, ArCH_2), 2.57 (dd, *J* = 13.9, 7.3 Hz, 1H, ArCH_2), 1.90 – 1.83 (m, 1H, NHCH$_2$C*H*), 1.42 – 1.36 (m, 2H, CH$_3$CH_2), 0.97 (t, *J* = 7.5 Hz, 3H, CH_3CH$_2$); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 164.4 (C), 158.0 (C), 157.9 (C), 142.9 (C), 136.5 (CH), 132.6 (C), 130.1 (CH), 123.4 (CH), 120.3 (CH), 113.9 (CH), 55.9 (CH_3), 55.3 (CH_3), 42.2 (CH_2), 42.1 (CH), 37.7 (CH_2), 24.4 (CH_2), 11.3 (CH_3); **HRMS** found (ES) $[M+H]^+$ 329.1871, $C_{19}H_{24}N_2O_3$+H requires 329.1865.

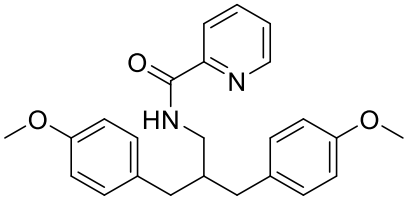
5-Methoxy-*N*-(2-(4-methoxybenzyl)-3-(4-methoxyphenyl)butyl)picolinamide 347



Isolated as a mixture with the monoarylated product (0.009 mmol, 9%).

^{1}H NMR (700 MHz, $CDCl_3$) *δ* 8.20 – 8.19 (m, 1H, pyNC*H*), 8.16 – 8.15 (m, 1H, pyNCC*H*), 8.08 (dd, *J* = 8.7, 0.5 Hz, 1H, pyNCCHC*H*), 7.68 (m, 1H, N*H*), 7.18 – 7.16 (m, 2H, OCCHC*H*), 7.07 – 7.05 (m, 2H, OCCHC*H*), 6.86 – 6.84 (m, 2H, OCC*H*), 6.79 – 6.77 (m, 2H, OCC*H*), 3.90 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.56 – 3.51 (m, 1H, NHCH_2), 3.12 (dt, *J* = 13.7, 5.6 Hz, 1H, NHCH_2), 2.90 (p, *J* = 7.1 Hz, 1H, ArC*H*), 2.74 (dd, *J* = 14.1, 4.5 Hz, 1H, ArCH_2), 2.44 (dd, *J* = 14.1, 9.3 Hz, 1H, ArCH_2), 2.38 – 2.33 (m, 1H, NHCH$_2$C*H*), 1.36 – 1.35 (m, 3H, CHCH_3); **HRMS** found (ES) $[M+H]^+$ 435.2261, $C_{26}H_{30}N_2O_4$+H requires 435.2284.

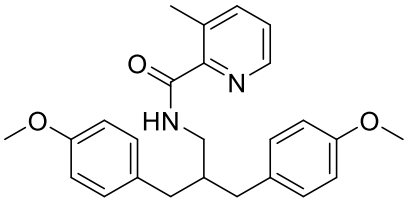
***N*-(2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)propyl)picolinamide 355**



Prepared according to general arylation procedure A, using amide **351** (36 mg, 0.20 mmol) and 4-iodoanisole (188 mg, 0.80 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as a yellow oil (53 mg, 0.136 mmol, 68%).

ν_{max} (solid/cm^{-1}) 3364 (NH), 2909 (CH), 2852 (CH), 1660 (CO), 1520 (CC); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, pyNC*H*), 8.17 (dt, *J* = 7.8, 1.1 Hz, 1H, pyCC*H*), 8.00 (s, 1H, N*H*), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.40 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, pyNCHC*H*), 7.14 – 7.06 (m, 4H, OCCHC*H*), 6.85 – 6.79 (m, 4H, OCC*H*), 3.77 (s, 6H, OCH_3), 3.41 (t, *J* = 6.2 Hz, 2H, NHCH_2), 2.67 – 2.56 (m, 4H, ArCH_2), 2.31 – 2.18 (m, 1H, C*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.3 (C), 158.1 (C), 149.9 (C), 147.9 (CH), 137.6 (C), 132.3 (CH), 130.1 (CH), 126.2 (CH), 122.4 (CH), 114.0 (CH), 55.4 (CH_3), 42.9 (CH_2), 42.4 (CH), 37.9 (CH_2); **HRMS** found (ES) $[M+H]^+$ 391.2007, $C_{24}H_{26}N_2O_3$+H requires 391.2016.

N-(2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)propyl)-3-methylpicolinamide 356



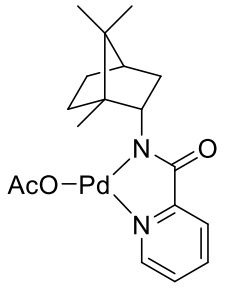
Prepared according to general arylation procedure A, using amide **352** (38 mg, 0.20 mmol) and 4-iodoanisole (188 mg, 0.80 mmol). Purified by flash column chromatography (0 – 20% EtOAc in petrol) to give the product as colourless oil (50 mg, 0.12 mmol, 62%).

ν_{max} (solid/cm^{-1}) 3351 (NH), 2952 (CH), 2871 (CH), 1664 (CO), 1518 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.33 (ddd, *J* = 4.6, 1.6, 0.5 Hz, 1H, pyNC*H*), 8.09 (t, *J* = 5.6 Hz, 1H, N*H*), 7.57 – 7.54 (m, 1H, pyNCHCHC*H*), 7.29 – 7.26 (m, 1H, pyNCHC*H*), 7.12 – 7.07 (m, 4H, OCCHC*H*), 6.83 – 6.79 (m, 4H, OCC*H*), 3.77 (s, 6H, OCH_3), 3.39 – 3.36 (m, 2H, NHCH_2), 2.73 (s, 3H, ArCH_3), 2.65 – 2.58 (m, 4H, ArCH_2), 2.26 – 2.19 (m, 1H, C*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 166.1 (C), 158.0 (C), 147.4 (C), 145.4 (CH), 140.9 (CH), 135.4 (C), 132.4 (CH), 130.2 (CH), 125.6 (C), 114.0 (CH), 55.4 (CH_3), 42.9 (CH_2), 42.3 (CH), 37.9 (CH_2), 20.7 (CH_3); **HRMS** found (ES) $[M+H]^+$ 405.2165, $C_{25}H_{28}N_2O_3$+H requires 405.2173.

6.3 Experimental for Chapter 4

6.3.1 Isolation of palladium complexes

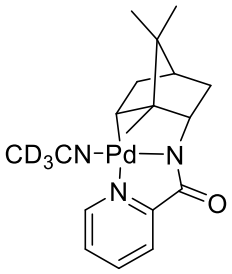
Palladium complex **371**



A sealed tube was charged with amide **165** (26 mg, 1.0 mmol, 1 eq), $Pd(OAc)_2$ (27 mg, 1.2 mmol, 1.2 eq) and CsOAc (23 mg, 0.12 mmol, 1.2 eq) in *t*AmOH (0.05 ml). The resulting mixture was heated at 140 °C for 1 hour, then cooled and filtered through Celite® washing with $CDCl_3$ and concentrated to give the palladium complex as an orange oil in quantitative yield (42 mg, 0.10 mmol).

$[\alpha]_D$ +35.4 (*c* = 1, $CHCl_3$); **ν_{max}** (film/cm^{-1}); 2949 (CH), 2924 (CH), 1673 (CO), 1516 (CC); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 7.97 – 7.92 (m, 2H, pyNC*H*CHC*H*), 7.57 – 7.53 (m, 1H, pyCC*H*), 7.35 (ddd, *J* = 7.2, 5.8, 1.6 Hz, 1H, pyNCHC*H*), 2.57 (dd, *J* = 12.0, 5.2 Hz, 1H, NHCHCH_2), 2.50 (ddd, *J* = 11.6, 5.1, 2.3 Hz, 1H, NHC*H*), 2.09 (s, 3H, PdOCCH_3), 1.70 – 1.65 (m, 1H, CH_2CH_2CH), 1.65 – 1.60 (m, 1H, CH_2CH_2CH), 1.57 – 1.52 (m, 2H, $CH_2CH_2CHCH_2$), 1.32 – 1.29 (m, 1H, NHCHCH_2), 1.28 (s, 3H, CH_3), 1.18 – 1.14 (m, 1H, CH_2CH_2CH), 0.83 (s, 3H, CH_3), 0.76 (s, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 184.3 (C), 170.2 (C), 157.0 (C), 145.8 (CH), 140.3 (CH), 126.4 (CH), 125.9 (CH), 71.3 (C), 64.8 (CH), 53.0 (C), 46.9 (CH), 30.1 (CH_2), 29.9 (CH_2), 28.8 (CH_3), 27.3 (CH_2), 19.8 (CH_3), 18.9 (CH_3), 14.6 (CH_3); **HRMS** (monomer) found (ES) $[M+H]^+$ 423.0895, $C_{18}H_{24}N_2O_3Pd$+H requires 423.0902.

Palladacycle 372



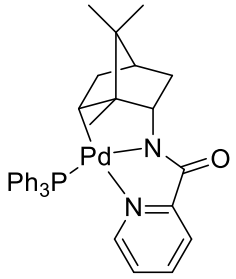
A sealed tube was charged with amide **165** (52 mg, 0.20 mmol, 1 eq), $Pd(OAc)_2$ (54 mg, 0.24 mmol, 1.2 eq) and CsOAc (115 mg, 0.30 mmol, 3 eq) in CD_3CN. The reaction mixture was heated at 60 °C for 1.5 hours, before being filtered through Celite® and concentrated.

The crude complex was dissolved in chloroform and washed with water (3 × 1 ml) before concentrating to give the product as a bright yellow solid (77 mg, 0.19 mmol, 95%).

M.p > 200 °C (decomp); **[α]$_D$** +141.1 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 2942 (CH), 2920 (CH), 1665 (CO); **^{1}H NMR** (600 MHz, CD_3CN) *δ* 8.30 – 8.28 (m, 1H, pyNC*H*), 7.97 (td, *J* = 7.7, 1.6 Hz, 1H, pyCCHC*H*), 7.86 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.48 (ddd, *J* = 7.5, 5.0, 1.3 Hz, 1H, pyNCHC*H*), 3.99 (dt, *J* = 9.5, 2.9 Hz, 1H, NC*H*CH_2), 2.63 (dt, *J* = 10.8, 3.3 Hz, 1H, PdC*H*), 2.35 (ddt, *J* = 13.0, 9.4, 3.9 Hz, 1H, NCHC*H*$_2$), 1.85 (ddt, *J* = 14.1, 10.8, 3.7 Hz, 1H, PdCHC*H*$_2$), 1.73 (t, *J* = 4.2 Hz, 1H, CH_2C*H*CH_2), 1.62 (dd, *J* = 13.6, 3.2 Hz, 1H, PdCHC*H*$_2$), 1.14 (dd, *J* = 12.7, 2.4 Hz, 1H, NCHC*H*$_2$), 1.04 (s, 3H, C*H*$_3$), 0.96 (s, 3H, C*H*$_3$), 0.85 (s, 3H, C*H*$_3$); **^{13}C NMR** (151 MHz, CD_3CN) *δ* 174.8 (C), 168.0 (C), 157.8 (C), 148.5 (CH), 139.8 (CH), 127.0 (CH), 124.5 (CH), 68.3 (CH), 64.0 (C), 48.0 (PdCH), 47.5 (CH), 47.3 (C), 41.0 (CH_2), 36.7 (CH_2), 22.5 (CH_3), 19.3 (CH_3), 15.2 (CH_3).

[It was not possible to obtain mass spectrometry data for this compound]

Palladacycle 374

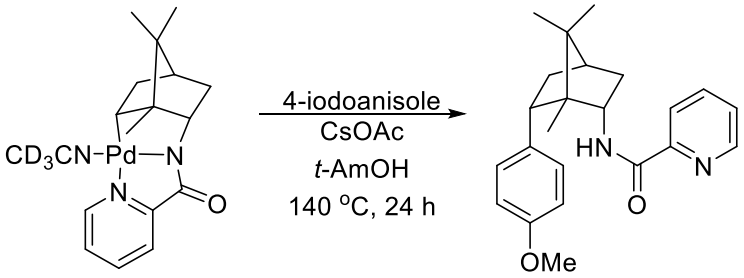


PPh_3 (26 mg, 0.10 mmol, 1 eq) was added to a solution of palladacycle **372** (41 mg, 0.10 mmol, 1 eq) in $CHCl_3$ (1 ml) and the resulting solution stirred at room temperature for 30 minutes, before filtering through Celite®, washing with $CHCl_3$. The filtrate was concentrated to give the desired palladacycle as a yellow solid in quantitative yield (62 mg, 0.10 mmol).

M.p 190 °C (decomp.); **[α]$_D$** +28.8 (*c* = 0.5, $CHCl_3$); **ν_{max}** (film/cm^{-1}) 2942 (CH), 2920 (CH), 1587 (CC), 1095 (CP); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 8.13 (d, *J* = 7.8 Hz, 1H, pyNC*H*), 7.78 – 7.72 (m, 1H, pyNCHC*H*), 7.71 – 7.65 (m, 6H, PPh), 7.47 (t, *J* = 7.4 Hz, 3H, PPh), 7.43 – 7.39 (m, 6H, PPh), 7.07 – 7.03 (m, 1H, pyCC*H*), 6.91 – 6.86 (m, 1H, pyCCHC*H*), 4.28 – 4.20 (m, 1H, NC*H*CH_2), 2.53 – 2.46 (m, 1H, NCHC*H*$_2$), 2.04 (tdd, *J* = 8.2, 5.8, 2.4 Hz, 1H, PdC*H*), 1.57 (t, *J* = 4.0 Hz, 1H, CH_2C*H*CH_2), 1.51 – 1.44 (m, 1H, PdCHC*H*$_2$), 1.30 (dd, *J* = 12.8, 2.1 Hz, 1H, NCHC*H*$_2$), 1.13 – 1.07 (m, 1H, PdCHC*H*$_2$), 1.04 (s, 3H, C*H*$_3$), 0.91 (s, 3H, C*H*$_3$), 0.47 (s, 3H, C*H*$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) *δ* 167.5 (C), 159.7 (C), 148.4 (CH), 138.1 (CH),

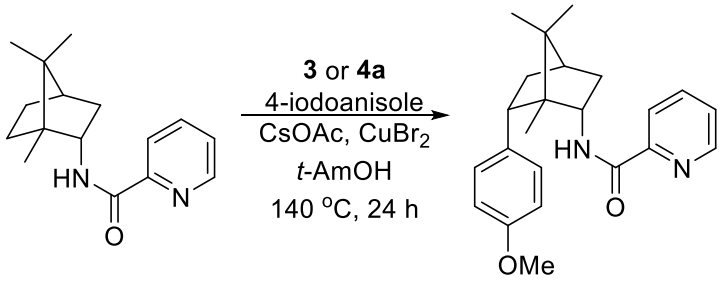
134.4 (d, *J* = 13.2 Hz, CH), 132.1 (d, *J* = 42.1 Hz , C), 130.7 (d, *J* = 1.9 Hz, CH), 128.7 (d, *J* = 10.1 Hz, CH), 124.9 (H), 65.7 (CH), 65.1 (C), 56.7 (PdCH), 47.2 (C), 46.6 (CH), 40.1 (CH_2), 35.6 (CH_2), 22.2 (CH_3), 18.8 (CH_3), 15.2 (CH_3); **^{31}P NMR** (300 MHz, $CDCl_3$) δ 33.68 (PPh_3); **HRMS** found (ES) $[M+H]^+$ 625.1594, $C_{34}H_{35}N_2OPPd+H$ requires 625.1607.

Arylation of palladacycle 6a



A tube was charged with palladacycle **372** (41 mg, 0.1 mmol, 1 eq), CsOAc (19 mg, 0.1 mmol, 1 eq), *t*AmOH (0.1 ml) and 4-iodoanisole (94 mg, 0.4 mmol, 4 eq). The tube was sealed with a PTFE lined cap and heated to 140 °C for 24 hours. The reaction mixture was then cooled and filtered through a pad of Celite®, washing with EtOAc. The filtrate was concentrated *in vacuo* and the resulting crude residue purified by flash column chromatography to give the arylated product **191** (0.043 mmol, 43%).

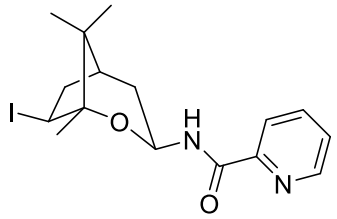
Arylation using palladium complexes as a catalyst



A tube was charged with picolinamide **165** (26 mg, 0.1 mmol, 1 eq), $CuBr_2$ (2.2 mg, 0.01 mmol, 10 mol%), palladium complex **371** or **372** (0.005 mmol, 5 mol%), CsOAc (77 mg, 0.4 mmol, 4 eq), *t*-AmOH (0.1 ml) and 4-iodoanisole (94 mg, 0.4 mmol, 4 eq). The tube was sealed with a PTFE lined cap and heated to 140 °C for 24 hours. The reaction mixture was then cooled and filtered through a pad of Celite®, washing with EtOAc. The filtrate was concentrated *in vacuo* and the resulting crude residue purified by flash column chromatography (0 – 40% EtOAc in petrol).

Yield using palladium complex **371** as a catalyst 87%; Yield using palladacycle **372** as a catalyst 80%

***N*-((1*R*, 3*S*, 5*S*,7*R*)-7-iodo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-yl)picolinamide 397**



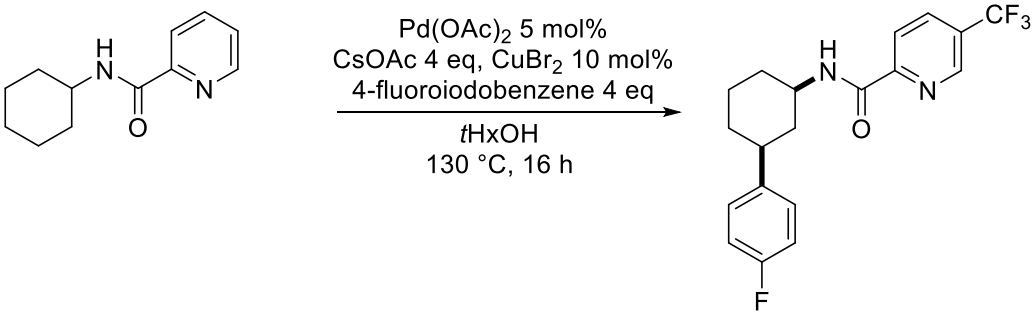
Iodine (26 mg, 0.10 mmol, 1 eq) was added to a solution of palladacycle **372** (40 mg, 0.10 mmol, 1 eq) in $CDCl_3$ (2 ml). The resulting suspension was stirred for 16 hours at room temperature, before being filtered through Celite®, and concentrated. The residue was purified by flash column chromatography (0 – 60% EtOAc in petrol) to the product as a brown oil (10 mg, 0.025 mol, 25%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.7 Hz, 1H, pyNC*H*), 8.39 (d, *J* = 9.1 Hz, 1H, N*H*), 8.20 (d, *J* = 7.8 Hz, 1H, pyCC*H*), 7.85 (td, *J* = 7.7, 1.7 Hz, 1H, pyCCHC*H*), 7.47 – 7.42 (m, 1H, pyNCHC*H*), 5.70 (td, *J* = 10.1, 4.9 Hz, 1H, NHC*H*), 4.93 (dd, *J* = 9.2, 6.3 Hz, 1H IC*H*), 2.65 – 2.61 (m, 1H, ICHCH_2), 2.50 (dd, *J* = 15.1, 9.2 Hz, 1H, ICHCH_2), 2.06 – 2.01 (m, 2H, CH_2CHCH_2CH), 1.69 (dt, *J* = 9.2, 4.3 Hz, 1H, NHCHCH_2), 1.42 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.17 (s, 3H, CH_3); **^{13}C NMR** (151d MHz, $CDCl_3$) δ 163.9 (C), 149.4 (C), 148.2 (CH), 137.5 (CH), 126.7 (CH), 122.8 (CH), 86.3 (C), 72.1 (CH), 44.9 (CH), 44.5 (C), 41.9 (CH_2), 34.3 (CH_2), 28.3 (CH), 25.6 (CH_3), 23.1 (CH_3), 19.9 (CH_3); **LRMS** 401.0 [M+H]; **HRMS** found (CI NH_3) $[M+H]^+$ 401.0720, $C_{16}H_{21}N_2O_2I$+H requires 401.0720.

6.3.2 Kinetic data

Kinetic studies

Order in catalyst



The reaction was run according to general arylation procedure **B**, using amide **160** and 4-fluoroiodobenzene, and 1,3,5-trimethoxybenzene as the internal standard (10 mol%). The reaction was run with 2.5 mol%, 5 mol% and 10 mol% of $Pd(OAc)_2$.

Time minutes	Yield %	time[cat]	[product]
30	5	0.75	0.05
60	9	1.5	0.09
90	13	2.25	0.13
120	15	3	0.15
180	20	4.5	0.2
240	23	6	0.23
360	27	9	0.27
480	29	12	0.29
600	33	15	0.33
720	36	18	0.36
960	40	24	0.4
1200	42	30	0.42
1440	41	36	0.41

2.5 mol% $Pd(OAc)_2$

Minutes	Yield	time[cat]	[product]
30	7	1.5	0.07
60	14	3	0.14
90	18	4.5	0.18
120	22	6	0.22
180	29	9	0.29
240	34	12	0.34
360	39	18	0.39
480	43	24	0.43
600	46	30	0.46
720	50	36	0.5
960	55	48	0.55
1200	58	60	0.58
1440	61	72	0.61

5 mol% $Pd(OAc)_2$

Minutes	Yield	time[cat]	[product]
30	11	3	0.11
60	20	6	0.2
90	26	9	0.26
120	29	12	0.29
180	34	18	0.34
240	38	24	0.38
360	45	36	0.45
480	49	48	0.49
600	52	60	0.52
720	55	72	0.55
960	58	96	0.58
1200	61	120	0.61
1440	62	144	0.62

10 mol% $Pd(OAc)_2$

Order in aryl iodide

Entry	Equivalents of ArI	Concentration of ArI (M)
1	4	4.00
2	3	2.69
3	2	1.49
4	1	0.74

Time	Yield	modified time	[product]	[ArI]
30	7	85.36936	0.07	4.065
60	14	170.2619	0.14	3.94
90	18	254.1584	0.18	3.94
120	22	337.6152	0.22	3.885
180	27	502.5251	0.29	3.815
240	31	663.8076	0.32	3.66
360	37	978.8997	0.39	3.585

Entry 1 - 4 eq

Time	Yield	modified time	[product]	[Arl]
30	7	62.78524	0.080738	2.664
60	12	125.2624	0.138408	2.655
90	15	187.5104	0.17301	2.638
120	18	249.2903	0.207612	2.602
180	21	372.1243	0.242215	2.597
240	25	492.7187	0.288351	2.476
360	28	715.9228	0.322953	2.099
480	30	919.0341	0.346021	2.279

Entry 2 – 3 eq

Time	Yield	modified time	[product]	[Arl]
30	3	40.78402	0.0369	1.487
60	7	80.3945	0.086101	1.41
90	11	119.8408	0.135301	1.471
120	14	158.9477	0.172202	1.377
180	16	237.1616	0.196802	1.471
240	19	314.4674	0.233702	1.333
360	21	459.0438	0.258303	1.231

Entry 3 – 2 eq

Time	Yield	modified t	[product]	[Arl]
30	2	24.79177	0.026918	0.654
60	3	46.79664	0.040377	0.669
90	6	69.07537	0.080754	0.676
120	8	91.16749	0.107672	0.654
180	10	134.0497	0.13459	0.624
240	12	174.3642	0.161507	0.553
360	13	249.7987	0.174966	0.524

Entry 4 – 1 eq

Same excess experiments data

Entry	[amide X]	[ArI]	[arylated product]	[CsI]	[AcOH]
1	**1**	**4**	**0**	**0**	**0**
2	**0.5**	**3.5**	**0**	**0**	**0**
3	**0.5**	**3.5**	**0.5**	**0**	**0**
4	**0.5**	**3.5**	**0.5**	**0.5**	**0.5**
5	**0.5**	**3.5**	**0.5**	**0.5**	**0**

Time	[SM]
30	0.93
60	0.86
90	0.82
120	0.78
180	0.71
240	0.66
360	0.61
480	0.57
600	0.54
720	0.50
960	0.45
1200	0.42
1440	0.40

Entry 1

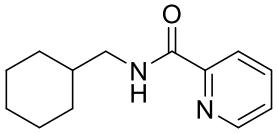
Time (corrected)	Time (original)	[SM] Entry 2	[SM] Entry 3	[SM] Entry 4	[SM] Entry 5
750	30	0.48	0.50	0.47	0.47
780	60	0.43	0.46	0.45	0.44
810	90	0.39	0.43	0.45	0.43
870	120	0.35	0.40	0.44	0.42
930	180	0.32	0.36	0.44	0.40
990	240	0.29	0.33	0.43	0.38
1110	300	0.26	0.30	0.41	0.37
1230	360	0.24	0.26	0.39	0.35

6.4 Experimental for Chapter 5 – Amides

General amidation procedure B

A suspension of carboxylic acid (5.0 mmol, 1 equiv.), amine (5.0 mmol, 1 equiv.) and $B(OCH_2CF_3)_3$ (108 µl, 0.5 mmol, 10 mol%) in *t*BuOAc (5 ml, 1 M) with a Dean-Stark apparatus (side arm filled with *t*BuOAc) was heated to reflux. An air condenser was fitted and the reaction mixture heated for 1 – 48 hours. Upon completion, the reaction was cooled to room temperature and water (0.5 ml), dimethyl carbonate (5 ml) Amberlite IRA-743 (0.25 g), Amberlyst A15 (0.5 g) and A-26(OH) (0.5 g) resins were added and the resulting suspension was stirred for 30 min. $MgSO_4$ (~0.5 g) was added and the mixture filtered and the resins washed with EtOAc (2 × 5 ml). The combined filtrates were concentrated *in vacuo* to yield the pure amide.

N-(Cyclohexylmethyl)picolinamide 159



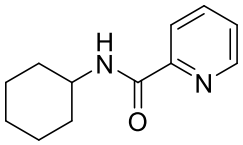
Prepared according to general amidation procedure B, using 2-picolinic acid (616 mg, 5.0 mmol), cyclohexylmethylamine (651 µl, 5.0 mmol) and heated to reflux for 24 h. Purified using the standard resin work-up, without the use of Amberlyst A15 to give the product as a white solid 5 mmol scale (1.004 g, 4.60 mmol, 92%).

M.p 65 - 67 °C; $\mathbf{\nu_{max}}$ (solid/cm^{-1}) 3354 (NH), 2916 (CH), 2847 (CH), 1657 (CO), 1525 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.7 Hz, 1H, Ar*H*), 8.15 (d, *J* = 7.8 Hz, 1H, Ar*H*), 8.09 (s, 1H, N*H*), 7.78 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.35 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H, Ar*H*), 3.27 (t, *J* = 6.6 Hz, 2H, NHCH_2), 1.75 (dd, *J* = 13.6, 1.9 Hz, 2H, CHCH_2), 1.71 – 1.65 (m, 2H, $CHCH_2CH_2$), 1.61 (ddd, *J* = 12.5, 5.0, 2.6 Hz, 1H, $CHCH_2CH_2CH_2$), 1.55 (ttd, *J* = 10.5, 7.0, 3.4 Hz, 1H, C*H*), 1.23 – 1.15 (m, 2H, $CHCH_2CH_2$), 1.15 – 1.08 (m, 1H, $CHCH_2CH_2CH_2$), 0.96 (ddd, *J* = 24.5, 12.3, 3.3 Hz, 2H, CHCH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 164.4 (C), 150.2 (C), 148.1 (CH), 137.4 (CH), 126.1 (CH), 122.3 (CH), 45.7 (CH_2), 38.2 (CH), 31.0 (CH_2), 26.5 (CH_2), 26.0 (CH_2).

Data in accordance with literature[166]

[100 mmol scale (21.23 g, 97 mmol, 97%)]

***N*-Cyclohexylpicolinamide 160**

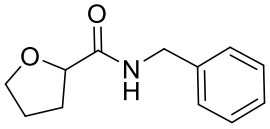


Prepared according to general amidation procedure B, using 2-picolinic acid (616 mg, 5.0 mmol), cyclohexylamine (573 µl, 5.0 mmol) and heated to reflux for 48 h. Purified using the standard resin work-up, without the use of Amberlyst A15 to give the product as a white solid (930 mg, 4.55 mmol, 91%)

M.p 54 – 56 °C; $\mathbf{\nu_{max}}$ (solid/cm^{-1}) 3379, 2935, 2857, 1666; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, Ar*H*), 8.18 (dt, *J* = 7.8, 1.1 Hz, 1H, Ar*H*), 7.93 (s, 1H, N*H*), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.39 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, Ar*H*), 4.03 – 3.89 (m, 1H, NHC*H*), 2.05 – 1.95 (m, 2H, NHCHCH_2), 1.80 – 1.70 (m, 2H, NHCHCH_2CH_2), 1.68 – 1.59 (m, 1H, NHCHCH_2CH_2CH_2), 1.48 – 1.16 (m, 5H, 3 × CH_2); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.4 (C), 150.4 (C), 148.1 (CH), 137.4 (CH), 126.1 (CH), 122.3 (CH), 48.3 (CH), 33.2 (CH_2), 25.7 (CH_2), 25.0 (CH_2).

Data in accordance with literature[50]

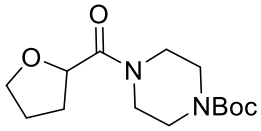
***N*-Benzyltetrahydrofuran-2-carboxamide 411**



Prepared according to general amidation procedure B, using tetrahydro-2-furoic acid (480 µl, 5.0 mmol), benzylamine (547 µl, 5.0 mmol) and heated to reflux for 2 h. Purified using the standard resin work-up to give the product as a yellow oil (950 mg, 4.63 mmol, 93%).

$\mathbf{\nu_{max}}$ (film/cm^{-1}) 3328 (NH), 2951 (CH), 2875 (CH), 1654 (CO), 1520 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.31 (dt, *J* = 8.3, 4.2 Hz, 2H, Ar*H*), 7.28 – 7.17 (m, 3H, Ar*H*), 7.15 – 6.91 (s, 1H, N*H*), 4.50 – 4.32 (m, 3H, NHCH_2, C*H*), 3.93 – 3.79 (m, 2H, OCH_2), 2.33 – 2.24 (m, 1H, CHCH_2), 2.11 – 2.03 (m, 1H, CHCH_2), 1.94 – 1.80 (m, 2H, OCH$_2$CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 173.3 (C), 138.3 (C), 128.8 (CH), 127.8 (CH), 127.6 (CH), 78.6 (CH), 69.5 (CH_2), 43.0 (CH_2), 30.4 (CH_2), 25.7 (CH_2).

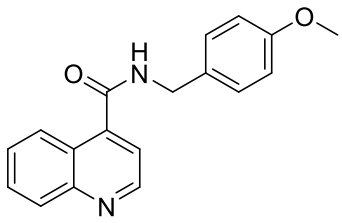
***tert*-Butyl 4-(tetrahydrofuran-2-carbonyl)piperazine-1-carboxylate 412**



Prepared according to general amidation procedure B, using tetrahydro-2-furoic acid (480 µl, 5.0 mmol), 1-Boc-piperazine (931 mg, 5.0 mmol) and heated to reflux for 1 h. Purified using the standard resin work-up to give the product as a white solid (1.21 g, 4.26 mmol, 85%).

M.p 55 – 58 °C; $\mathbf{v_{max}}$ (solid/cm^{-1}) 2974 (CH), 2868 (CH), 1683 (CO), 1644 (CO); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 4.44 (dd, *J* = 7.4, 5.8 Hz, 1H, OC*H*), 3.75 (dd, *J* = 14.8, 7.0 Hz, 1H, OCH_2), 3.67 (dd, *J* = 13.8, 7.6 Hz, 1H, OCH_2), 3.52 (m, 2H, NCH_2), 3.37 – 3.27 (m, 4H, NCH_2), 3.26 – 3.21 (m, 1H, NCH_2), 3.20 – 3.14 (m, 1H, NCH_2), 2.13 (dq, *J* = 12.2, 6.2 Hz, 1H, OCHCH_2), 1.90 – 1.79 (m, 2H, OCHCH_2, OCH_2CH_2), 1.77 – 1.71 (m, 1H, OCH_2CH_2), 1.29 (m, 9H, C(CH_3)$_3$); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 170.0 (C), 154.5 (C), 80.1 (C), 75.9 (CH), 69.0 (CH_2), 45.3 (CH_2), 43.6 (br, CH_2), 41.9 (CH_2), 28.3 (CH_2), 25.7 (CH_3); **HRMS** found (ESI) $[M+H]^+$ 285.1810, $C_{14}H_{24}N_2O_4$+H requires 285.1809.

***N*-(4-methoxybenzyl)quinoline-4-carboxamide 413**

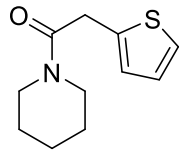


Prepared according to general amidation procedure B, using 4-quinolinecarboxylic acid (433 mg, 2.5 mmol), 4-methoxybenzylamine (327 µl, 2.5 mmol) and heated to reflux for 36 h. Purified using the standard resin work-up, without the use of Amberlyst A15. Further purified by recrystallisation from IPA to give the product as an off-white solid (658 mg, 2.25 mmol, 90%).

M.p 123 – 124 °C; $\mathbf{v_{max}}$ (solid/cm^{-1}) 3273 (NH), 2929 (CH), 2834 (CH), 1634 (CO), 1510 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.81 (d, *J* = 4.3 Hz, 1H, Ar*H*), 8.19 (d, *J* = 8.4 Hz, 1H, Ar*H*), 8.06 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.75 – 7.69 (m, 1H, Ar*H*), 7.56 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.35 (d, *J* = 4.3 Hz, 1H, Ar*H*), 7.29 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.90 – 6.86 (m, 2H, Ar*H*), 6.59 (br s, 1H, N*H*) 4.62 (d, *J* = 5.7 Hz, 2H, CH_2), 3.80 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ

167.2 (C), 159.4 (C), 149.9 (CH), 148.7 (C), 142.0 (C), 130.1 (CH), 129.9 (CH), 129.8 (C), 129.5 (CH), 127.8 (CH), 125.4 (CH), 124.6 (C), 118.5 (CH), 114.4 (CH), 55.5 (CH_3), 43.8 (CH_2); **HRMS** found (ESI) $[M+H]^+$ 293.1286, $C_{18}H_{16}N_2O_2$+H requires 293.1285.

1-(piperidin-1-yl)-2-(thiophen-2-yl)ethan-1-one 414

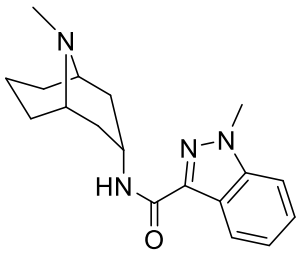


Prepared according to general amidation procedure B, using 2-thiopheneacetic acid (711 mg, 5.0 mmol), piperadine (494 µl, 5.0 mmol) and heated to reflux for 24 h. Purified using the standard resin work-up to give the product as a colourless oil (1.00 g, 4.79 mmol, 93%).

ν_{max} (film/cm^{-1}) 2932 (CH), 2852 (CH), 1630 (CO); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.14 (s, 1H, Ar*H*), 6.90 (d, *J* = 2.9 Hz, 1H, Ar*H*), 6.85 (s, 1H, Ar*H*), 3.86 (d, *J* = 5.6 Hz, 2H, COCH_2), 3.53 (s, 2H, NCH_2) 3.40 (s, 2H, NCH_2), 1.57 (s, 2H, $NCH_2CH_2CH_2$), 1.49 (s, 2H, NCH_2CH_2), 1.41 (s, 2H, NCH_2CH_2); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 168.3 (C), 137.1 (C), 126.9 (CH), 126.0 (CH), 124.7 (CH), 47.5 (CH_2), 43.2 (CH_2), 36.3 (CH_2), 26.4 (CH_2), 25.5 (CH_2), 24.5, (CH_2).

Data in accordance with literature[169]

1-Methyl-*N*-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)-1H-indazole-3-carboxamide 415



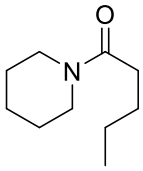
Prepared according to general amidation procedure B, using 1-methyl-1H-indazole-3-carboxylic acid (440 mg, 2.5 mmol), 9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (386 mg, 2.5 mmol) and $B(OCH_2CF_3)_3$ (56 µl, 20 mol%) for 72 h. Purified by flash column chromatography (0 – 10% MeOH in DCM) to give the product as a white waxy solid (350 mg, 1.12 mmol, 45%).

ν_{max} (solid/cm^{-1}) 3409 (NH), 2925 (CH), 2087 (CH), 1636 (CO), 1530 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.38 (dt, *J* = 8.2, 1.0 Hz, 1H, Ar*H*), 7.41 – 7.38 (m, 1H, Ar*H*), 7.37 (dt, *J* = 8.5, 0.9 Hz, 1H, Ar*H*), 7.25 (ddd, *J* = 7.8, 5.1, 1.1 Hz, 1H, Ar*H*), 6.78 (d, *J* = 8.2 Hz, 1H, N*H*), 4.55

(tdt, *J* = 11.4, 8.4, 6.7 Hz, 1H, NHC*H*), 4.07 (s, 3H, ArNCH_3), 3.08 (d, *J* = 10.9 Hz, 2H, NC*H*), 2.55 – 2.51 (m, 2H, NHCH_2), 2.50 (s, 3H, NCH_3), 2.01 – 1.92 (m, 3H, CH_2CH_2CH and CH_2CH_2CH), 1.54 – 1.50 (m, 1H, CH_2CH_2CH), 1.37 (ddd, *J* = 11.6, 8.9, 3.2 Hz, 2H, NHCH_2), 1.08 – 1.02 (m, 2H, CH_2CH_2CH); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 162.0 (C), 141.4 (C), 137.7 (C), 126.9 (CH), 123.2 (CH), 122.9 (C), 122.6 (CH), 109.1 (CH), 51.4 (CH), 40.83 (CH), 40.76 (CH_3), 36.0 (CH_3), 33.2 (CH_2), 25.0 (CH_2), 14.5 (CH_2)

Data in accordance with literature[106]

1-(Piperidin-1-yl)pentan-1-one 416

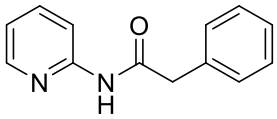


Prepared according to general amidation procedure B, using *n*-pentanoic acid (544 µl, 5.0 mmol), piperidine (494 µl, 5.0 mmol) and heated to reflux for 18 h. Purified using the standard resin work-up to give the product as a yellow oil (801 mg, 4.73 mmol, 95%).

ν_{max} (film/cm^{-1}) 2932 (CH), 2855 (CH), 1634 (CO); **^{1}H NMR** (700 MHz, $CDCl_3$) *δ* 3.40 (d, *J* = 4.3 Hz, 2H, NCH_2), 3.26 (d, *J* = 4.0 Hz, 2H, NCH_2), 2.18 (dd, *J* = 16.9, 9.9 Hz, 2H), 1.64 – 1.29 (m, 8H), 1.27 – 1.17 (m, 2H, CH_2CH_3), 0.79 (dt, *J* = 14.9, 7.4 Hz, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) *δ* 171.5 (C), 46.7 (CH_2), 42.6 (CH_2), 33.2 (CH_2), 27.6 (CH_2), 26.6 (CH_2), 25.6 (CH_2), 24.6 (CH_2), 22.6 (CH_2), 13.9 (CH_3).

Data in accordance with literature[170]

2-Phenyl-*N*-(pyridine-2-yl)acetamide 410



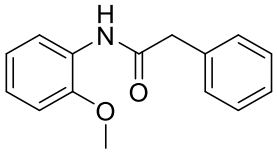
Prepared according to general amidation procedure B, using phenylacetic acid (681 mg, 5.0 mmol), 2-aminopyridine (471 mg, 5.0 mmol) and heated to reflux for 48 h. Purified using the standard resin work-up, without the use of Amberlyst A15 to give the product as a white solid (772 mg, 6.64 mmol, 73%).

M.p 122-123 °C; **ν_{max}** (solid/cm^{-1}) 3273 (NH), 2930 (CH), 1636 (CO), 1512 (CC); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.29 – 8.16 (m, 2H, Ar*H*), 7.98 (s, 1H, N*H*), 7.72 – 7.64 (m, 1H, Ar*H*),

7.43 – 7.36 (m, 2H, Ar*H*), 7.35 – 7.29 (m, 3H, Ar*H*), 7.05 – 6.97 (m, 1H, Ar*H*), 3.76 (s, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.6 (C), 151.3 (C), 147.8 (CH), 138.5 (CH), 134.0 (C), 129.6 (CH), 129.3 (CH), 127.8 (CH), 120.0 (CH), 114.0 (CH), 45.1 (CH_2).

Data in accordance with literature[104]

***N*-(2-methoxyphenyl)-2-phenylacetamide 417**

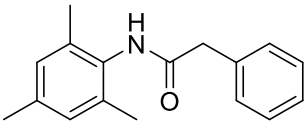


Prepared according to general amidation procedure B, using phenylacetic acid (681 mg, 5.0 mmol), *o*-anisidine (565 µl, 5.0 mmol) and heated to reflux for 40 h. Purified using the standard resin work-up to give the product as an off-white solid (528 mg, 1.915 mmol, 38%).

White Solid. 1.162 g, 96%; $\mathbf{v_{max}}$ (solid/cm^{-1}) 3259 (NH), 2932 (CH), 2839 (CH), 1643 (CO), 1527 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar*H*), 7.89 – 7.71 (m, 1H, N*H*), 7.43 – 7.37 (m, 2H, Ar*H*), 7.37 – 7.29 (m, 3H, Ar*H*), 7.01 (td, *J* = 7.9, 1.4 Hz, 1H, Ar*H*), 6.96 – 6.91 (m, 1H, Ar*H*), 6.80 (d, *J* = 8.1 Hz, 1H, Ar*H*), 3.78 (d, *J* = 21.9 Hz, 2H, CH_2), 3.69 (s, 3H, CH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 169.1 (C), 148.0 (C), 134.8 (C), 129.7 (C), 129.2 (CH), 127.7 (CH), 127.6 (CH), 123.9 (CH), 121.2 (CH), 119.7 (CH), 110.1 (CH), 55.8 (CH_3), 45.3 (CH_2).

Data in accordance with literature[105]

***N*-mesityl-2-phenylacetimide 409**



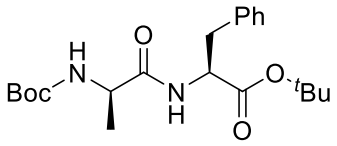
Prepared according to general amidation procedure B, using phenylacetic acid (681 mg, 5.0 mmol), 2,3,5-trimethylaniline (676 mg, 5.0 mmol) and heated to reflux for 20 h. Purified by flash column chromatography (20-60% EtOAc in petrol) to give the product as a white solid (916 mg, 3.62 mmol, 72%).

M.p 99-102 °C; $\mathbf{v_{max}}$ (solid/cm^{-1}) 3250 (NH), 2916 (CH), 1654 (CO), 1517 (CC); **^{1}H NMR** (400 MHz, DMSO) δ 9.35 (s, 1H, N*H*), 7.38 – 7.30 (m, 4H, Ar*H*), 7.27 – 7.24 (m, 1H, Ar*H*), 6.84 (s, 2H, Ar*H*), 3.61 (s, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.02 (s, 6H, 2 × CH_3); **^{13}C NMR** (101 MHz,

DMSO) δ 168.8 (C), 136.5 (C), 135.3 (C), 134.9 (CH), 132.5 (C), 129.0 (CH), 128.3 (CH), 128.2 (CH), 126.5 (CH), 42.6 (CH_2), 20.5 (CH_3), 18.0 (CH_3).

Data in accordance with literature[171]

***tert*-Butyl (tert-butoxycarbonyl)-D-alanyl-L-phenylalaninate 418**

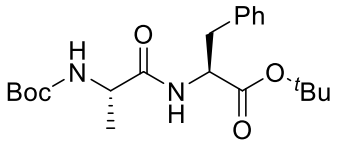


L-phenylalanine-*tert*-butyl ester hydrochloride (773 mg, 3.0 mmol) was washed with sat. aq. $NaHCO_3$ and the free base extracted into DCM. Prepared according to general amidation procedure B, using Boc-D-alanine (568 mg, 3.0 mmol), and heated to reflux for 16 h. Purified using the standard resin work-up to give the product as an off-white solid (1.12 g, 2.85 mmol, 95%).

$[\alpha]_D^{24.7}$ +43.6 (*c* 1.0, $CHCl_3$); **M.p** 96 - 99 °C; **ν_{max}** (solid/cm^{-1}) 3293 (NH), 2974 (CH), 2930 (CH), 1712 (CO), 1628 (CO); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.1 Hz, 2H, Ar*H*), 7.20 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.13 (d, *J* = 7.5 Hz, 2H, Ar*H*), 6.61 (d, *J* = 7.3 Hz, 1H, N*H*), 5.09 (s, 1H, N*H*), 4.69 (q, *J* = 6.2 Hz, 1H, C*H*CH_3), 4.15 (s, 1H, C*H*CH_2), 3.10 – 3.02 (m, 2H, CH_2), 1.41 (d, *J* = 11.1 Hz, 9H, C(CH_3)$_3$), 1.37 (s, 9H, C(CH_3)$_3$), 1.29 (t, *J* = 8.8 Hz, 3H, CHCH_3); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 172.4 (C), 170.4 (C), 155.5 (C), 136.2 (C), 129.7 (CH), 128.5 (CH), 127.1 (CH), 82.5 (C), 80.1 (C), 53.8 (CH), 50.3 (CH), 38.1 (CH_2), 28.4 (CH_3), 28.0 (CH_3), 18.6 (CH_3).

Data in accordance with literature[106]

***tert*-Butyl (tert-butoxycarbonyl)-L-alanyl-L-phenylalaninate 419**



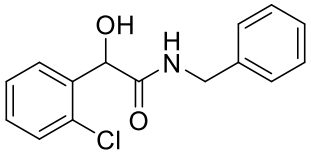
L-phenylalanine-*tert*-butyl ester hydrochloride (773 mg, 3.0 mmol) was washed with sat. aq. $NaHCO_3$ and the free base extracted into DCM. Prepared according to general amidation procedure B, using Boc-L-alanine (568 mg, 3.0 mmol), and heated to reflux for 16 h. Purified

using the standard resin work-up to give the product as an off-white waxy solid (927 mg, 2.36 mmol, 79%).

$[\alpha]_D^{24.7}$ -43.4 (*c* 1.0, $CHCl_3$); **ν_{max}** (solid/cm^{-1}) 3303 (NH), 2974 (CH), 2931 (CH), 2854 (CH), 1712 (CO), 1632 (CO); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.21 (m, 1H, Ar*H*), 7.14 (d, *J* = 7.4 Hz, 2H, Ar*H*), 6.58 (s, 1H, N*H*), 5.02 (d, *J* = 6.5 Hz, 1H, N*H*), 4.69 (q, 6.1 Hz, 1H, C*H*CH_3), 4.17 (s, 1H, C*H*CH_2), 3.14 – 3.02 (m, 2H, C*H*$_2$), 1.42 (s, 9H, (C*H*$_3$)$_3$), 1.39 (s, 9H, (C*H*$_3$)$_3$), 1.29 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 172.2 (C), 170.5 (C), 155.5 (C), 136.2 (C), 129.7 (CH), 128.5 (CH), 127.1 (CH), 82.5 (C), 80.2 (CH), 53.6 (CH), 50.2 (CH), 38.2 (CH_2), 28.4 (CH_3), 28.1 (CH_3), 18.8 (CH_3).

Data in accordance with literature[106]

***N*-Benzyl-2-(2-chlorophenyl)-2-hydroxyacetamide 420**



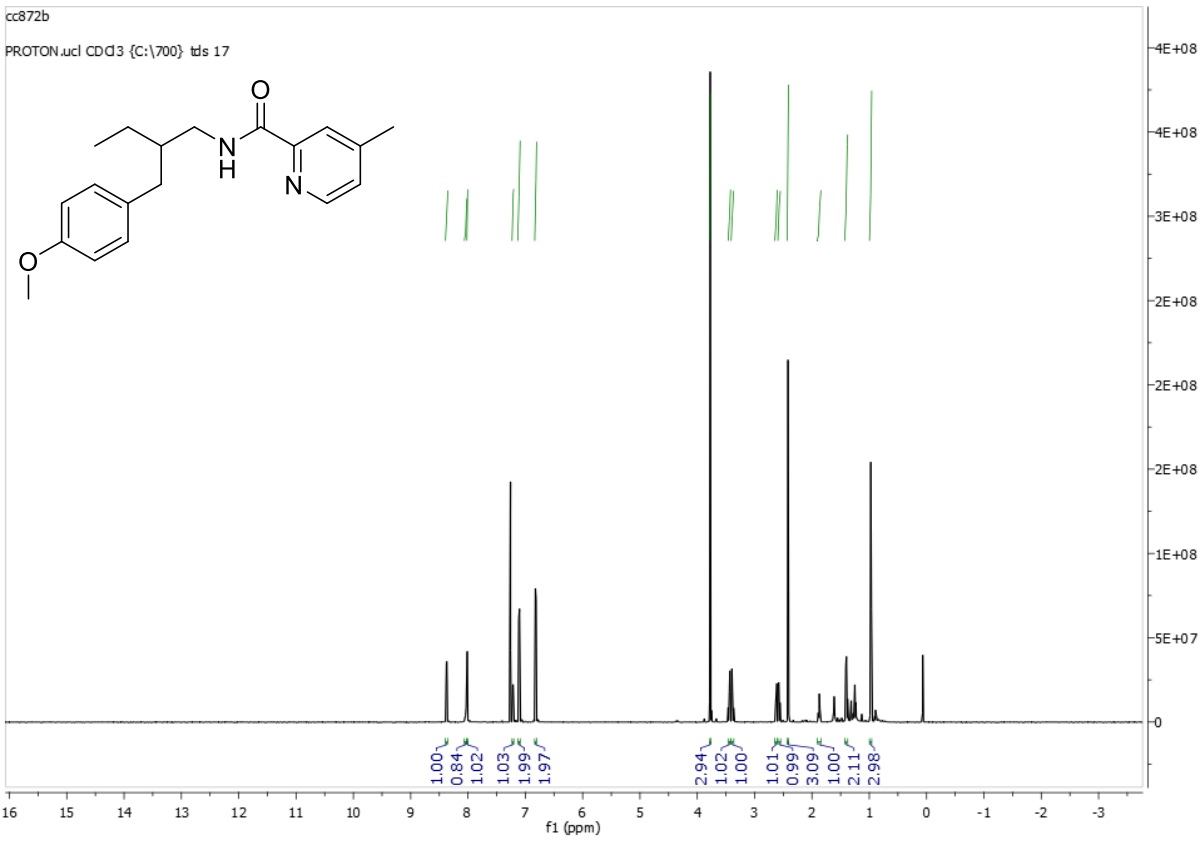
Prepared according to general amidation procedure B, using 2-chloromandelic acid (933 mg, 5.0 mmol), benzylamine (547 µl, 5.0 mmol) and heated to reflux for 40 h. Purified using the standard resin work-up to give the product as an off-white solid (528 mg, 1.915 mmol, 38%).

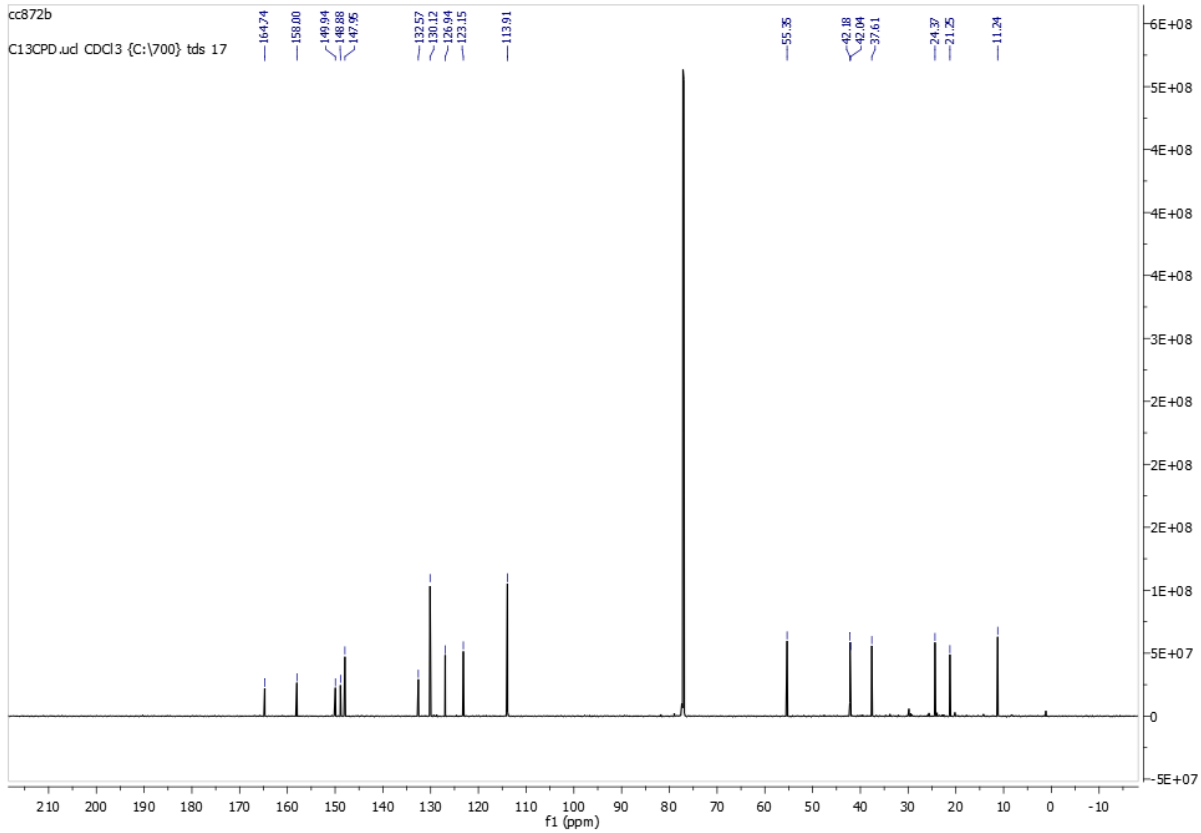
M.p 144 - 146 °C**;** **ν_{max}** (solid/cm^{-1}) 3264 (NH), 3195 (OH), 1919 (CH), 1633 (CO), 1532 (CC); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 7H, Ar*H*), 7.17 (d, *J* = 7.2 Hz, 2H, Ar*H*), 6.76 – 6.56 (m, 1H, N*H*), 5.03 (d, *J* = 2.4 Hz, 1H, C*H*), 4.45 – 4.36 (m, 2H, C*H*$_2$), 3.81 (d, *J* = 3.3 Hz, 1H, O*H*); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 171.8 (C), 138.0 (C), 137.7 (C), 134.6 (C), 129.1 (CH), 128.9 (CH), 128.2 (CH), 128.0 (CH), 127.84 (CH), 127.77 (CH), 127.7 (CH), 73.7 (CH), 43.6 (CH_2); **HRMS** found (ES) $[M+H]^+$ 276.0786, $C_{15}H_{14}NO_2Cl$+H requires 276.0786.

[It should be noted that the chemical shifts of the CH peak at 5.03 ppm and the OH at 3.81 are concentration dependent.]

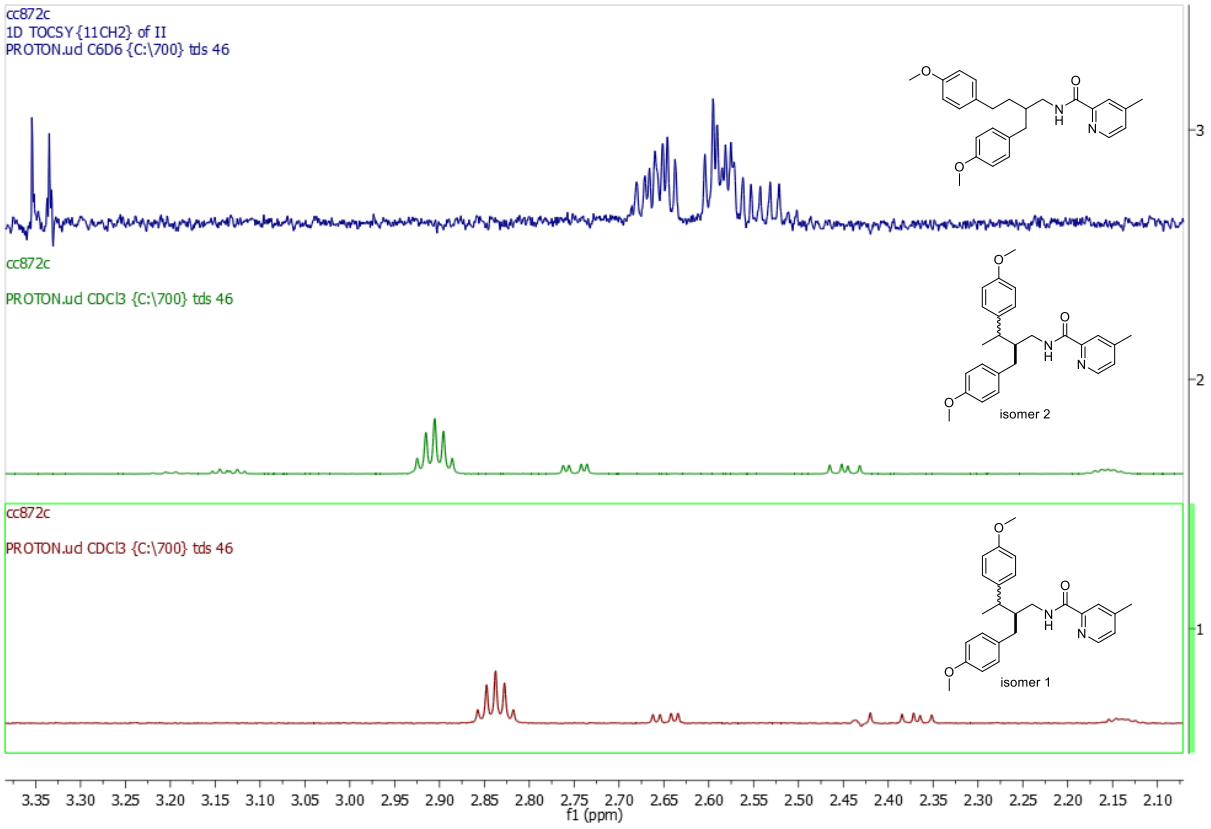
8. Appendix

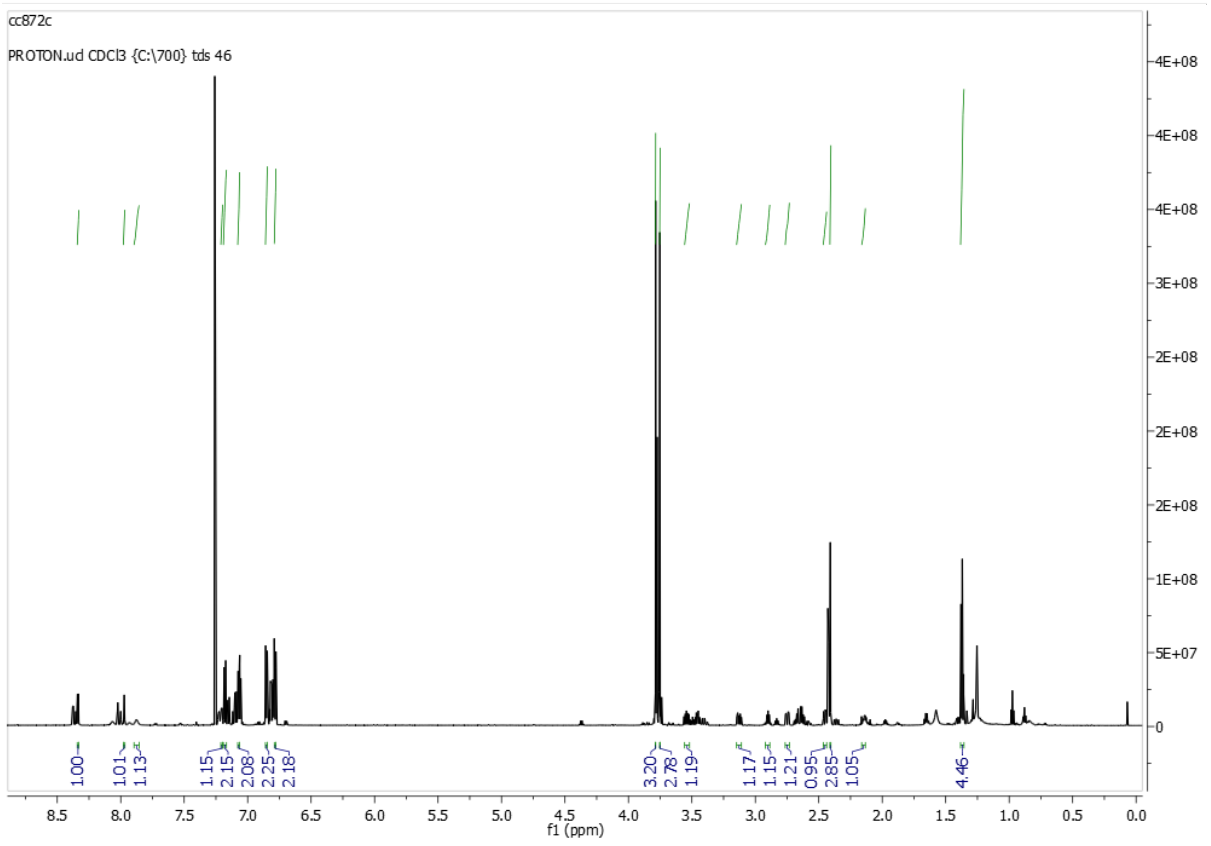
N-(2-(4-Methoxybenzyl)butyl)-4-methylpicolinamide 330





TOCSY Experiments for assignment of **331a**, **331b** and **331c**





9. References

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