Design and Synthesis of 3-D Fragments to Explore New Areas of Pharmaceutical Space

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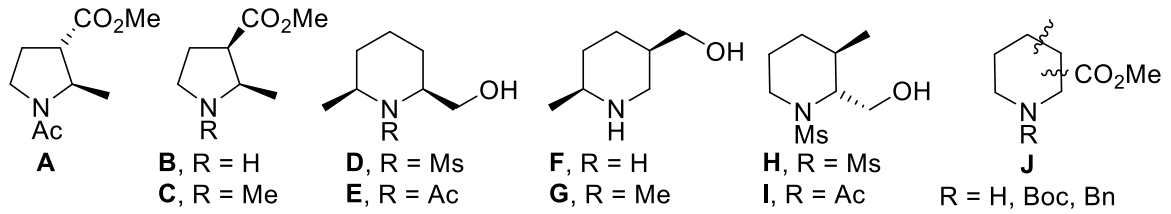
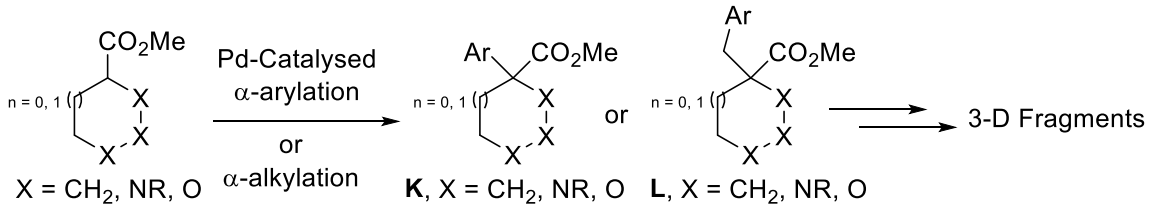
Abstract

The thesis is focused on the design and synthesis of 3-D fragments to explore new areas of pharmaceutical space. Chapter 1 provides an overview of fragment-based drug discovery including, fragment design, screening and synthesis. The diastereoselective synthesis of nine pyrrolidine and piperidine fragments **A**-**I** is described in Chapter 2. These fragments were identified as suitable 3-D fragments based on a 3-D shape analysis using principal moments of inertia. The key step in the synthesis of the 2,3-disubstituted pyrrolidines was the stereoselective reduction of the dihydropyrrole to afford the *cis*-diastereoisomer, with the *trans*-isomers accessed *via* epimerisation. The piperidines were synthesised *via* hydrogenation of the pyridine to give the *cis*-diastereoisomer as the major product, with the *trans* again access *via* epimerisation of the methyl ester. Chapter 3 covers of methodology for the synthesis of all 20 regio- and diastereosiomers of piperidines **J**. The syntheses were completed using three main types of methodology: pyridine hydrogenation, epimerisation and lithiation-trapping of *N*-Boc piperidines.



In Chapter 4, a different approach to 3-D fragment design and synthesis was developed. Here, the focus was on the identification of synthetic methodology that would allow the incorporation of different scaffolds and a range of aromatic/heteroaromatic groups. Ester enolate α-arylation and α-alkylation were the two approaches used to design fragments **K** and **L** which had their shapes analysed, with the most 3-D fragments selected and synthesised.



Finally, the entire York 3-D fragment library was compared against a set of commercial fragment libraries to evaluate their usefulness in drug discovery, with the analysis fully summarised in chapter 5.

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Author’s Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References

Chapter 1 Introduction

1.1 Fragment Based Drug Discovery (FBDD)

1.1.1 Introduction

The emergence of fragment based drug discovery (FBDD) over the last 20 years has opened the door for medicinal chemists to explore more challenging biological targets for the development of new drugs.[1] The first notion of fragments goes back to 1981, with Jencks' work on the attribution and additivity of binding energies. In that work, it was proposed that a molecule can be considered as containing two or more smaller molecules (fragments) which have the ability to bind to a target.[2] Over 10 years later, the technology behind FBDD started to be shaped by Fesik *et al.* from Abbot Pharmaceuticals. They developed a NMR-based method to determine structure-activity relationship (SAR) which offered the ability to screen a large quantity of fragments against a target protein.[3] The binding interactions of low affinity fragments could be detected at adjacent binding sites and structural information such as the binding region and the orientation of the bound fragment could be determined from the NMR spectrum. Once two fragments were determined to bind to the target at adjacent binding sites, they could then be linked to produce a higher affinity binding ligand.

FBDD offers a different approach to previous drug discovery methods such as high throughput screening (HTS), which is widely used by pharmaceutical companies to obtain lead compounds for their drug discovery programs.[4] HTS libraries often contain 100,000s of drug-like molecules, broadly obeying Lipinski's 'Rule of five', which have been adopted as a guideline for orally available drugs.[5] The rules are used as a general guide and consist of four parameters: molecular weight (MW) $\leq$ 500, ClogP $\leq$ 5, hydrogen bond donors $\leq$ 5 and hydrogen bond acceptors $\leq$ 10, where ClogP is a measure of the lipophilicity expressed as a ratio of octanol solubility to aqueous solubility. These rules were proposed based on the fact that 90% of orally active drugs in phase II clinical trials at the time were within these parameters, meaning that the molecules show acceptable solubility and intestinal permeability, so that they can enter the bloodstream. In comparison, fragments are often defined as obeying the 'Rule of three' with MW $\leq$ 300, ClogP $\leq$ 3, hydrogen bond donors $\leq$ 3 and hydrogen bond acceptors $\leq$ 3.[6] Researchers at Astex have since refined these guidelines and proposed that fragments should ideally have MW between 140-230, heavy atom count (HAC) 10-16 and ClogP 0-2.[7] Molecular weight and ClogP typically increase in size during

the optimisation of the fragment to a more lead-like compound before ultimately reaching the optimal drug-like space (Figure 1.1).

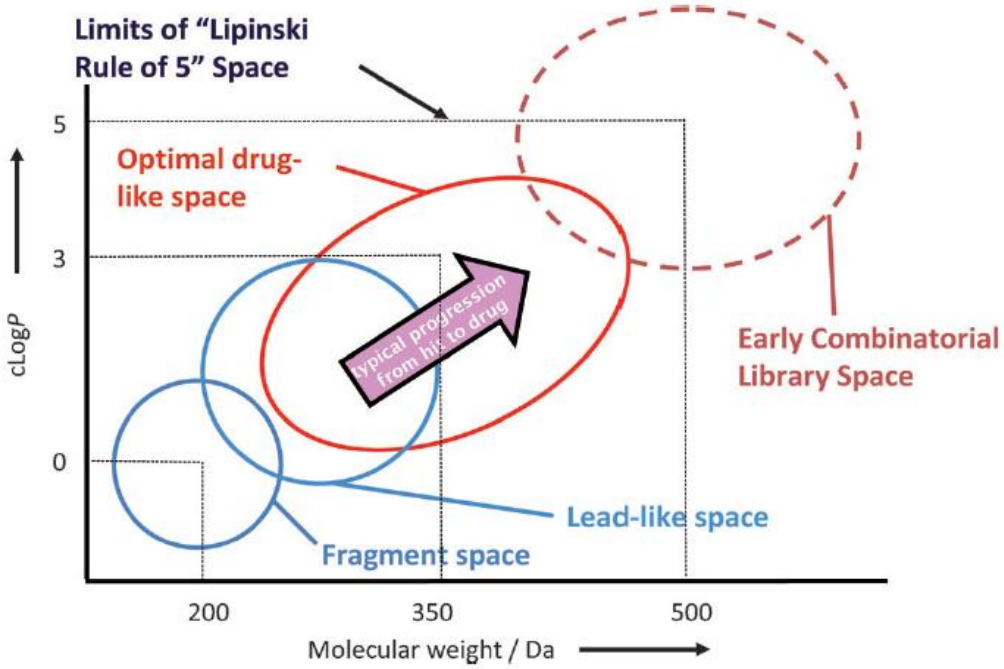


Figure 1.1 – Drug-like chemical space, which generally could be defined within the red dotted oval. As MW and ClogP increases (arrow), a suitable starting point would be the fragment space region of the graph (small blue circle).[8]

1.1.2 High Throughput Screening *versus* Fragment Based Drug Discovery

High throughput screening (HTS) is a highly successful method for initiating drug discovery and involves the screening of typically 100,000 or more lead-like compounds (MW > 350 typically). The advantage of this method comes from the high binding affinities that can be achieved, which removes the need for sensitive screening methods. However, the disadvantage of this approach is that the compounds being screened are complex and often non-drug-like with poor physicochemical properties, thus requiring further optimisation. The size of the molecules means that the potential chemical space is vast, with an estimated 10^{60} organic molecules possible with a MW < 500. As a result, HTS libraries containing 100,000 compounds seem extremely small compared to the large amount of chemical space that remains unoccupied with these libraries.[9]

For comparison, Reymond *et al*. computationally analysed the chemical space of molecules with a HAC of ≤ 17 i.e. within fragment space.[10] With the use of mathematical graphs, geometrical strain and functional group criteria, to ensure that the produced molecules made

chemical sense, they enumerated 166 billion different organic molecules containing carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine and iodine.[11–13] Therefore, the sampling of chemical space is more efficient with fragments, compared to molecules within HTS libraries, which makes them more appealing as a starting point. Another consideration is the simplicity of fragments and their lack of molecular complexity compared to larger molecules which may lead to higher hit rates with fragments. Hann *et al.*[14,15] studied the correlation between molecular complexity and the probability of finding hit compounds. A simple molecular interaction model was used based on the assumption of two types of interactions. If the receptor and the ligand are mismatched, then this indicated no affinity of the ligand to the receptor. A series of simulations was run using these assumptions to predict the probability of a ligand with a pre-determined number of interaction features binding to a receptor with a random sequence of interaction features. The results showed that as molecules increase in size, then the probability of measuring the binding interactions increased, but the probability of finding a hit decreased, as there are fewer ways of obtaining favourable interactions (Figure 1.2). Therefore, the probability of useful events (purple line) describes an interaction that is both favourable and measurable. The maximum can be seen to peak at about 5 interaction features. Thus, smaller fragments with lower complexity and fewer points for interaction should be able to bind to a greater number of sites and as a result lead to higher hit rates.

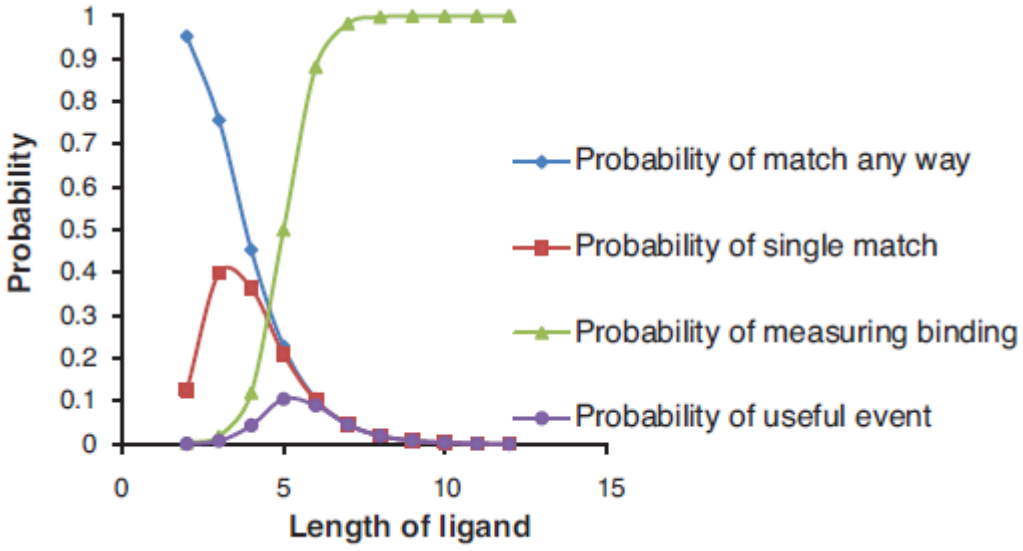
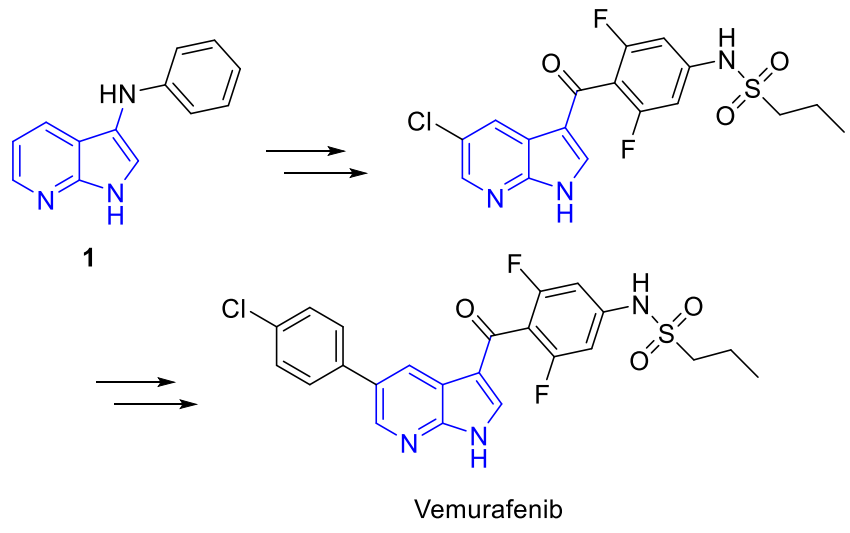


Figure 1.2 – The graph shows the probability of a match *vs* probability of measuring binding, which is represented by the probability of a useful event (purple line).[15]

Hann's molecular complexity model also highlights one of the main disadvantages with FBDD, namely that weaker binding affinities are observed with smaller molecules. The binding affinities are usually in the region of mM or high μM. Therefore, there is a requirement to use sensitive screening methods such as NMR-based approaches and X-ray crystallography, which can be more time consuming.[7] Despite this, FBDD has been a huge development for the discovery of lead compounds for a variety of diseases and has already led to the discovery of new drugs.

1.1.3 Fragment Based Drug Discovery Successes

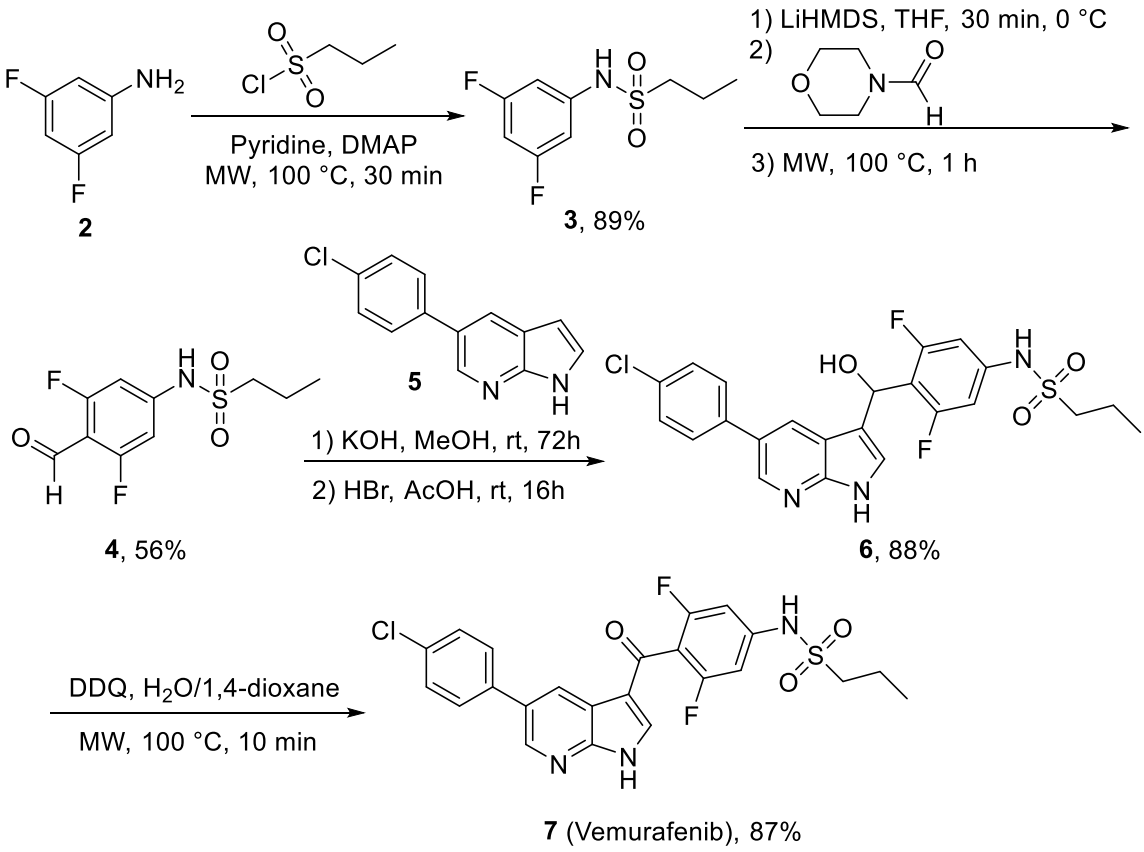
The first drug which emerged from FBDD was Vemurafenib (Zelboraf), which is a treatment for late-stage melanoma.[16] The drug targets BRAF^{V600E}, a kinase found in many types of cancer. Preclinical studies showed that proliferation of melanoma could be stimulated by BRAF^{V600E}, with its suppression leading to the regression of the tumour.[16] A fragment library of 20,000 compounds was initially screened against a family of five kinases. This screening identified 238 compounds for follow-up studies. The use of 3-dimensional structural analysis enabled scaffold selection based on the number of sites for chemical growth, along with the position and interaction within the binding pocket. This was accompanied with biological assays that allowed selection of a series of potent compounds. Vemurafenib was selected after optimisation of binding affinity, selectivity and pharmacokinetics. Vemurafenib was optimised starting from a 3-substituted 7-azaindole initial fragment hit **1** (Scheme 1.1).



Scheme 1.1

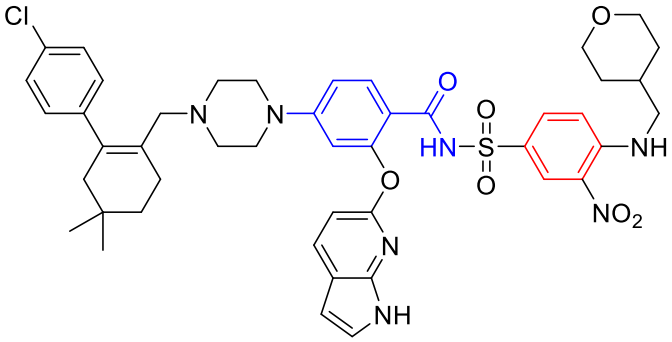
The route that was developed for the synthesis of Vemurafenib for preclinical research is shown in Scheme 1.2.[17] The first step involved sulfonylation of aniline **2** to afford

sulfonamide **3**. Formylation to give aldehyde **4** was achieved using *ortho*-metallation of the aromatic ring using LiHMDS and a morpholine amide under microwave conditions. Addition of the 3-substituted aza-indole **5** was achieved by nucleophilic attack of the aza-indole onto aldehyde **4** and then rearomatisation to give alcohol **6**. Finally, oxidation of the secondary alcohol in **6** to the ketone using DDQ gave the desired Vemurafenib.[17]



Scheme 1.2

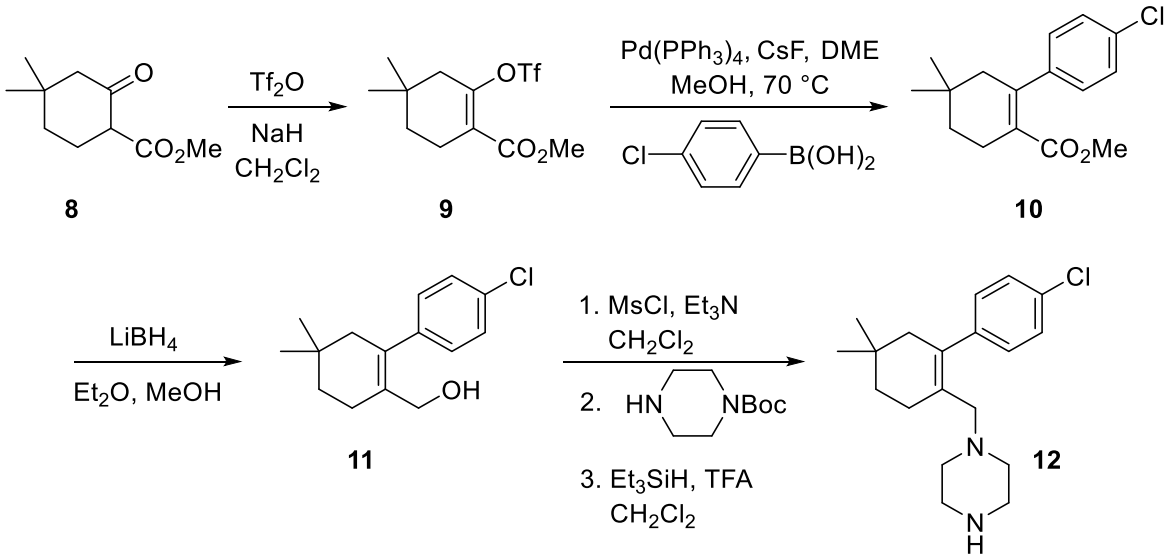
The second drug to be discovered using FBDD was Ventoclax, which has been approved in the USA as a treatment for chronic lymphocytic leukaemia.[18,19] Ventoclax was found to be an inhibitor of proteins in the B cell CLL/lymphoma 2 (BCL-2) which are key in the apoptotic process. The initial fragment hits were the two aromatic rings highlighted in Figure 1.3.



Ventoclax

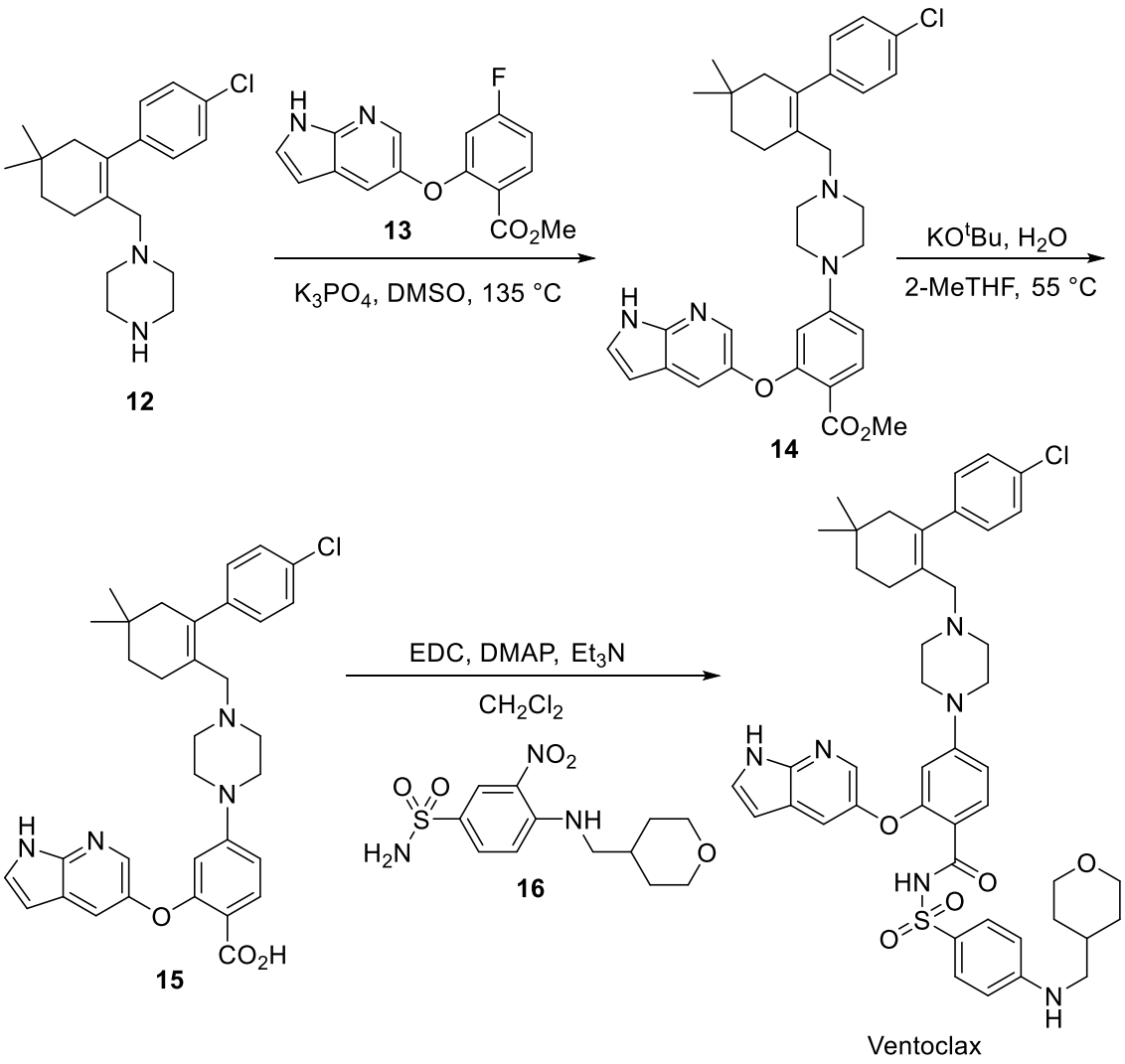
Figure 1.3 – Ventoclax, an approved treatment for chronic lymphocytic leukaemia.

The original route to Ventoclax, started with the conversion of β-ketoester **8** into enol triflate **9**. Next, Suzuki-Miyaura cross coupling to give **10** followed by reduction of the ester with $LiBH_4$ furnished primary alcohol **11**. Mesylation and then subsequent nucleophilic substitution with *N*-Boc piperazine and Boc group removal gave intermediate **12** (Scheme 1.3).



Scheme 1.3

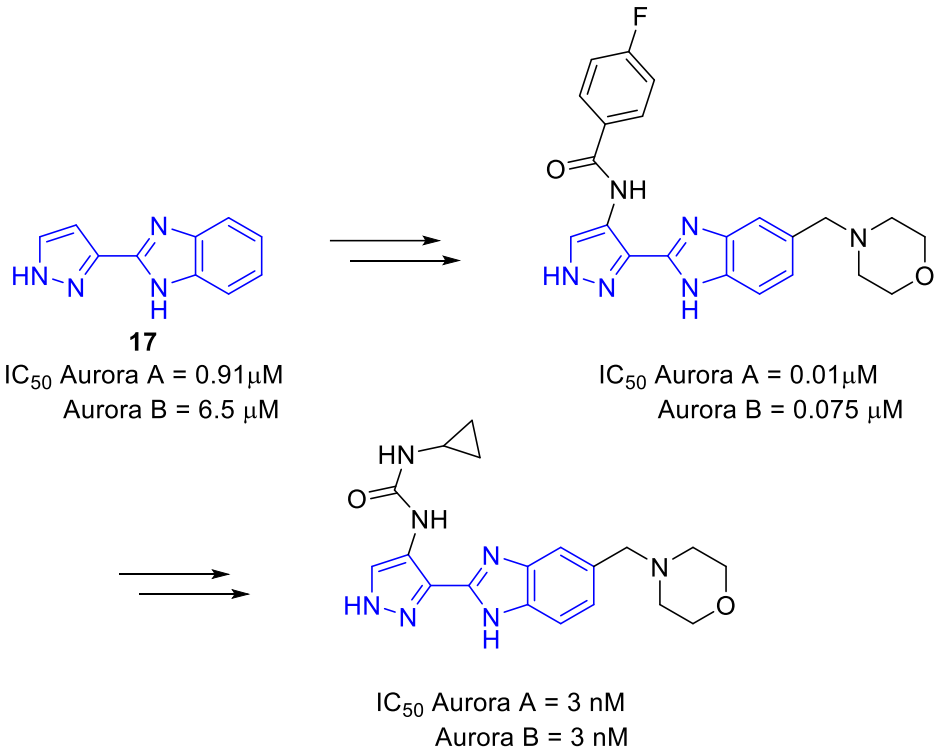
A S_NAr reaction of intermediate **12** with 7-azaindole **13** then afforded disubstituted piperazine **14**, which underwent ester hydrolysis to afford carboxylic acid **15**. The final step of the synthesis involved amide coupling of carboxylic acid **15** with sulfonamide **16** using EDC to give the desired drug molecule Ventoclax (Scheme 1.4).



Scheme 1.4

As of July 2016, along with Vemurafenib and Ventoclax, there were a further 30 lead compounds which were in either phase I or II clinical trials.[1] For example, Astex developed a drug candidate, which was in phase II clinical trials, targeting the Aurora and JAK2 kinases.[20] The initial target was the Aurora kinase which consists of the two isoforms, Aurora A and B, which are linked to the regulation of mitosis. As a consequence, drugs targeting the inhibition of the Aurora kinase have become popular anticancer treatments. Astex's initial fragment hit was pyrazole-benzimidazole **17**, which showed high affinity towards Aurora A. The key interactions were the three-hydrogen bonds with the carbonyl of an alanine residue and the NH of a glycine residue within the hinge region. Installation of the basic morpholine group on the benzimidazole core, combined with the *para*-fluorobenzamide, afforded a ten-fold increase in affinity for Aurora B. Replacement of the amide linker with the urea offered a folded conformation, placing the urea substituent closer

to the benzimidazole. Finally, optimisation led to the inclusion of a cyclopropane which kept the proximity to the benzimidazole and reduced the lipophilicity of the molecule (Scheme 1.5).



Scheme 1.5

The remaining 27 lead compounds included four where the structural information had not been shared within the public domain. However, analysis of the remaining 23 compounds revealed that they contained between 2-5 aromatic rings, with some of the compounds containing relatively few sp^3 centres (Figure 1.4).

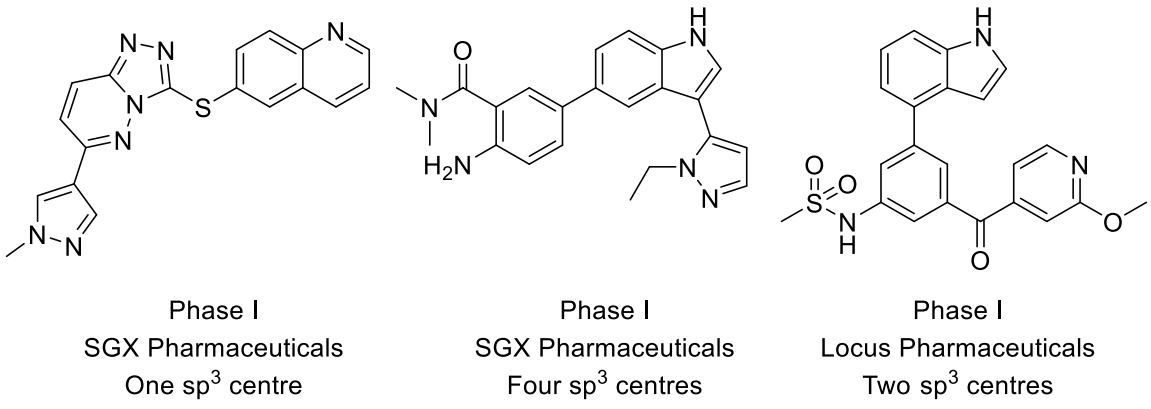


Figure 1.4 – Lead compounds with one, two or four sp^3 centres.

Despite the high number of aromatic rings, 16 of the lead compounds also contained saturated heterocycles. Over half of the current lead compounds derived from fragments incorporated morpholine, pyrrolidine, piperazine, piperidine, lactam, cyclohexane and tetrahydropyran (THP) saturated rings; selected examples are shown in Figure 1.5.

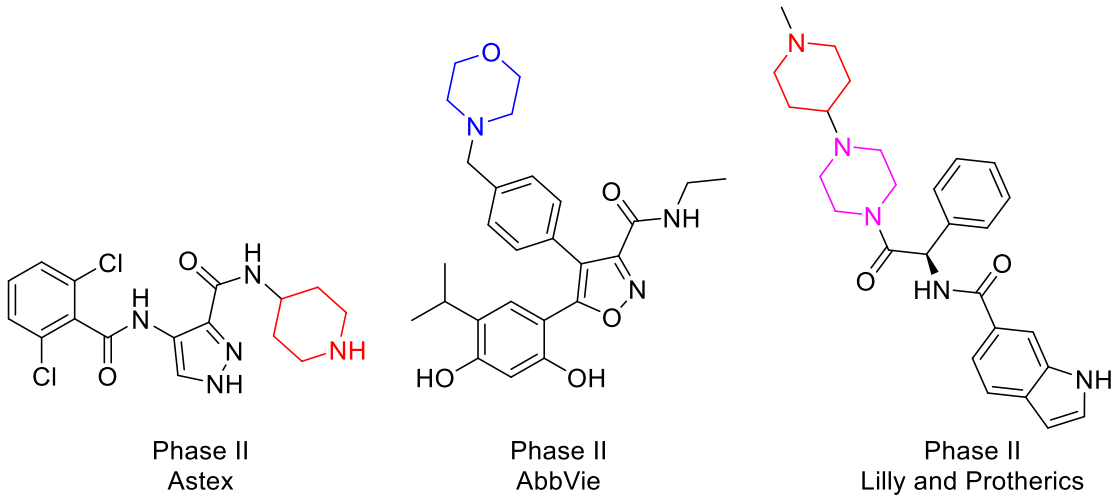


Figure 1.5 – Lead compounds containing saturated heterocycles, such as piperidine (red), morpholine (blue) and piperazine (pink).

1.2 'Escape from Flatland'

'Escape from Flatland' is part of the title of a paper published by Lovering *et al*. in 2009[21] which describes an analysis of molecules as they proceed through the different stages of the drug discovery process. Specifically, the analysis explored the correlation between molecules making it through clinical trials and how this related to the number of sp^3 hybridised carbon atoms and stereogenic centres within the molecule.

Traditionally, the properties assessed during the discovery-to-drug process focused on polar surface area (PSA), MW, rotatable bonds and hydrogen bond donors and acceptors. However, the complexity of the molecules was not considered. Lovering proposed fractional sp^3 (Fsp^3) as a descriptor for the saturation of a molecule, which could be used as a measure of molecular complexity. Fsp^3 is defined as the number of sp^3 hybridised carbon atoms divided by the total number of carbon atoms within the molecule. Lovering proposed that an increase in molecular complexity and saturation may offer the ability to access a wider region of chemical space which may not be accessible with flat aromatic rings. Therefore, this could lead to an increase in the selectivity and potency of the drug.

The paper analysed all of the compounds, in the period 1980-2009, which have either been reported to have biological activity or were described within a medicinal chemistry patent. The results showed a correlation between increasing Fsp^3 and the progression of a drug candidate through clinical studies, with a 31% increase in saturation when comparing discovery molecules to drugs. The second method they used for accessing molecular complexity was the presence of stereocentres. The paper revealed a 33% increase in the number of stereocentres when comparing discovery molecules to drugs.

Finally, the effect of increased saturation on the physical properties such as solubility and melting points of the compounds were compared. There was a correlation between increased Fsp^3 and increased solubility, with a reduction in melting points. The improved solubility for molecules with increased saturation and complexity could be attributed to the observed trend, as molecules with high solubility are more likely to succeed as suitable drug candidates.

A further study reported by Ritchie *et al*.[22] focused on the number of aromatic rings within drug molecules and whether that was detrimental to drug design. The study selected compounds within the GlaxoSmithKline pipeline over a period of time and revealed that the

average number of aromatic rings in a compound at the preclinical stage was 3.3. The number then decreased to 2.3 for compounds that were in proof-of-concept trials. The decreasing trend in the number of aromatic rings as a drug got closer to the market suggested a detrimental effect on the number of aromatic rings within drug molecules. However, there are benefits for inclusion of aromatic rings, as they can offer an increase in the ligand-receptor binding energy, due to the fewer degrees of freedom that aromatic rings possess. It has also been shown that aromatic rings do have an effect on the physical properties of the drug molecule. Ritchie *et al*. analysed over 26,000 compounds within the GlaxoSmithKline compound library and were able to show a correlation between the number of aromatic rings and ClogP. It was found that the inclusion of an aromatic ring gave a significant increase in ClogP, with fewer compounds having ClogP < 3 upon addition of an aromatic ring. Decreasing the starting ClogP value is an important feature as, increasingly, there have been studies showing a trend in logP drift owing in part to the difficulties associated with polar molecules and the dearth of methodology available to synthesise such molecules.[8]

The studies from Lovering and Ritchie demonstrated the improvement in progression of a molecule through clinical trials, when the molecule contained an increased amount of sp^3 centres and fewer aromatic rings. These papers are both focused on the progression of drug candidates through clinical trials and support the idea that by increasing the 3-D shape of drug candidates, the likelihood of the molecule making it through clinical trials could be increased.

1.3 Characterisation of 3-D Molecular Shape

Lovering *et al.* used Fsp^3 as a method to assess molecular complexity, proposing that it would enable the design of out-of-plane substituents and, in that respect, increase the 3-D shape of a molecule. However, Fsp^3 has limitations, as it does not characterise whether or not the sp^3 carbon is connected to a bond which deviates from the molecule in a way that increases the 3-D shape. Furthermore, a molecule containing no sp^3 carbon centres does not necessarily adopt a flat 2-D structure, which is an assumption made with using Fsp^3.

Sauer and Schwarz, introduced principal moment of inertia (PMI) plots as an alternative method for classifying the shapes of molecules.[23] Their aim was to develop a method that would allow analysis of the shape diversity between compound libraries of varying size and complexity. With the aid of a 3-D descriptor they wanted to show the benefits of having a library containing multiple scaffolds *versus* a library derived from a single scaffold, which it was proposed would have limited shape diversity.

A PMI plot is created in the following way. To start with, using molecular mechanics typically within conformation generating software, the conformations of a molecule are computationally generated and used to calculate the three principal moments of inertia I_1, I_2 and I_3. The values are then normalised by dividing the two smaller values I_1 and I_2 by the largest value I_3 to obtain two normalised principal moments of inertia (NPR1 and NPR2) for each molecule. Normalising the values eliminates variation arising from the size (or MW) of the molecule. The two normalised values NPR1 and NPR2 are then plotted onto a triangular plot. The plots can be used to visualise the degree to which a molecule is rod-, disc- or sphere-shaped. The top left apex represents rod-like molecules such as bis-alkynes with coordinates (NPR1 = 0 , NPR2 = 1), the bottom apex shows disc-like compounds such as benzene (NPR1 = 0.5 , NPR2 = 0.5) and the top right apex represents sphere-like molecules such as adamantane (NPR1 = 1 , NPR2 = 1) (Figure 1.6). The PMI plots can then be analysed to determine the overall 3-D shape of a compound collection. The rod-disc axis will contain molecules which are more 2-D in character with compounds becoming more 3-D in shape as they occupy the region towards the right apex.

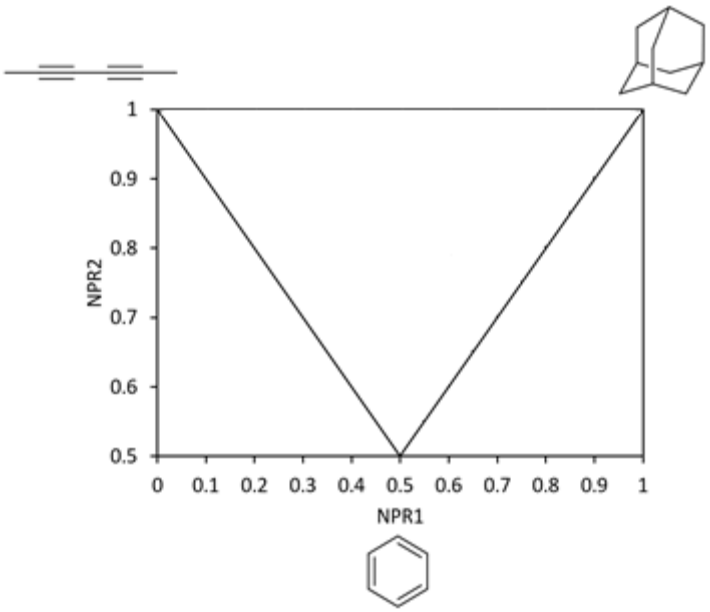


Figure 1.6 – PMI plot with the top left apex, bottom apex and top right apex representing rod-like, disc-like and sphere-like molecules respectively.

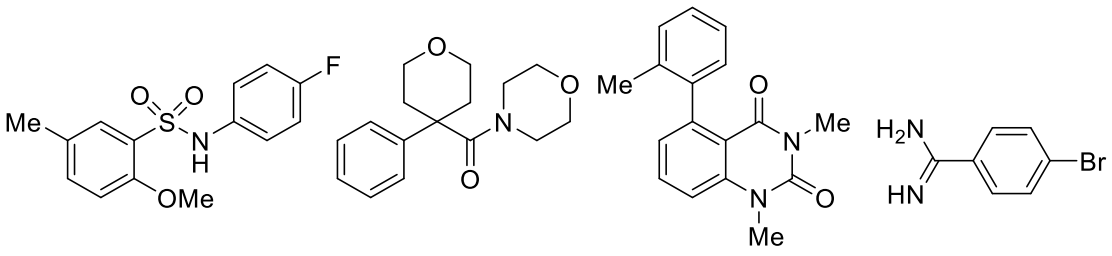
In order for Sauer and Schwarz to determine whether a small library containing multiple scaffolds was more 3-D shaped than a single scaffold library, they created three different libraries to analyse. The first library contained a single scaffold (benzodiazopine) with 13 diverse functional groups to afford a library of 2197 molecules. The second library contained the same single scaffold, but this time incorporated 50 diverse functional groups to afford 125,000 molecules. The final library increased the number of scaffolds to 50 but retained the initial 13 functional groups from the first library. Analysis of their respective PMI plots revealed that a single scaffold had access to a limited region of chemical space, and that a combination of a smaller library consisting of multiple scaffolds produced a library with higher levels of shape diversity and coverage. This study highlighted the potential usefulness of using PMI plots to assess 3-D shape.

Prior to the introduction of PMI analysis, an alternative descriptor of 3-D shape was proposed by Meyer. In 1985, Meyer described a computational procedure for predicting volumes, surface areas and cross-sectional areas of molecules. The data can then describe molecular globularity using the visual descriptor of globularity.[24] The theory is based on the radii of three spheres around the molecule to give a ratio $R_{M.}$ The first sphere of radius R_1 corresponds to a sphere that is equal in volume to the van der Waals volume. R_2 is the radius of the sphere which has a volume equal to the molecular volume and R_3 is the radius of the sphere that encapsulates the whole molecule. The shape descriptor is then defined by R_M =

$(R_3 - R_2) / (R_2 - R_1)$, with smaller values of R_M corresponding to the molecule being more spherical.

A new 3-D shape analysis tool, the plane of best-fit (PBF), was developed in 2012 by Firth, Brown and Bragg. In order to differentiate between flat and non-flat molecules, the following descriptions were employed: 1-D molecules consist of all the heavy atoms lying in a straight line; 2-D molecules have all of their heavy atoms in the same plane. Therefore, they proposed to describe and define how 3-D a molecule was by measuring how much it deviated from the 2-D plane.[25]

The molecules were assessed using CORINA to generate a single reference conformation.[26] The coordinates calculated for each conformer are used to determine the plane-of-best-fit which is solved using a least squares-method.[27] The equation of best-fit can then be used to give the distance, Δ, of each heavy atom from the plane-of-best-fit. The PBF score is then given as an average of all these distances measured in Å. The values can range from 0 to ∞, but values ranging from 0-2 are expected for small drug-like molecules. Some examples of molecules with differing PBF values are shown in Figure 1.7. The molecule which deviated the most from the PBF was sulfonamide **18**, which highlights the issues with Fsp^3 as a 3-D descriptor, as the molecule only contains two sp^3 carbons compared to morpholine **19** which deviated less from the plane but contains nine sp^3 carbons. The 3-D shape of the sulfonamide **18** arises due to the sulfonamide linker, which causes the molecule to fold back in on itself. The next most 3-D molecule was morpholine **19**, followed by bicycle **20** where the 3-D shape was directed by the *ortho* methyl group which rotates the biaryl bond. As expected, planar monocyclic aromatic fragments were completely flat. For example, amidine **21** had a PBF score of 0 Å.



18, 1.06 Å **19**, 0.805 Å **20**, 0.402 Å **21**, 0 Å

Figure 1.7 – Plane-of-best-fit values for four molecules contained within the Institute of Cancer Research (ICR) fragment library

The PBF approach was then applied to nine diverse compound libraries ranging from small fragment libraries to larger compound libraries and then compared against PMI and molecular globularity. The results showed good correlation with molecular globularity and PMI. Hence, PBF can also be considered a useful tool for analysing the 3-D shape of molecules within compound libraries. The one drawback with PBF is that larger molecules tend to have larger PBF values, which can make comparisons across different classes difficult.

1.4 Brief Overview of Fragment Libraries

Library design is an important aspect of FBDD. In terms of fragment properties, the 'Rule of three' (MW < 300, HBD < 3, HBA < 3 and ClogP < 3) is important, but there are other considerations which need to be taken into account. Fragment libraries should contain a diverse set of scaffolds which may allow for better sampling of chemical space.[28] Synthetic tractability is also an important feature, along with the ability to grow the fragment with suitably accessible growth vectors. A final consideration is the avoidance of highly reactive functional groups such as acyl chlorides, anhydrides, aziridines and epoxides, which can produce false positives in biochemical assays.[29,30]

One of the early approaches to library design, was detailed by Fejzo *et al*. from Vertex with their SHAPES library.[31] The library was developed to comprise shapes that would represent frameworks most commonly found within drug molecules and as a result should have favourable physicochemical and biological properties. Commercially available therapeutics were analysed and broken down into rings, linkers and sidechains. The rings were classified as an array of cyclic atoms, with the linkers being the bonds connecting the rings. Overall, the rings and linkers were classified as frameworks with some examples represented in Figure 1.8.

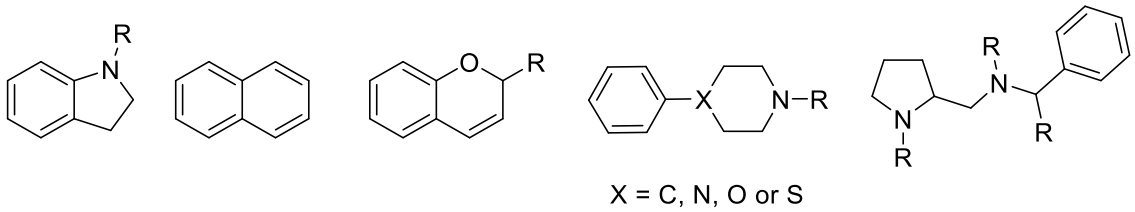


Figure 1.8 – Examples of frameworks used for the SHAPES library.

Within the SHAPES library, focus was placed on the cost, synthetic tractability, solubility and separation of the signals in ^{1}H NMR spectra of the frameworks. The fragments were screened by ^{1}H NMR spectroscopy to determine any weak affinity binding. Any hits could then be used to bias the filtering of a larger chemical database to select a large group of molecules for purchase or synthesis followed by HTS. The one drawback with using frameworks from commercial therapeutics is the lack of IP and novelty, which leads to regions of chemical space being unexplored and not exploited.

Fragment libraries designed for screening by NMR spectroscopy have been widely employed due to the high screening sensitivity of the technique and the ability to screen

multiple fragments at once. In 2004, Vernalis developed four libraries consisting of commercial fragments for screening by NMR spectroscopy.[32] The four main library design aspects were: fragments should have good aqueous solubility for the binding experiments; fragments needed to be stable in stock solution and should not degrade over time; fragments should show chemical diversity and fragments should contain points for diversification for growth of the fragments into potential lead or drug candidates. The four designed libraries were to be used within their SeeDs (Selection of Experimental Exploitable Drug Starting Point) strategy which covers fragment selection, NMR spectroscopy screening and determination of the X-ray crystal structure of the fragment bound to the protein. The information obtained from the crystal structure can then be used to direct the evolution of the fragment into a higher affinity hit. The four designed libraries contained 1315 compounds and were selected with the help of *in silico* filters to remove undesirable functionality, along with the help of medicinal chemists to remove any likely insoluble fragments.

Another approach to library design is to consider the synthetic tractability of the fragments. Novartis previously published their approach to designing fragment libraries for screening by NMR spectroscopy.[33] However, a few years later, they reported the design of a third generation library which offered improved chemical tractability. Functional groups in fragments offer potential binding interactions and points for diversification and elaboration of the fragment. However, modification of the functionality can cause a reduction in the binding interaction of the linked fragments. Therefore, it may be necessary to have fragments which have multiple functional groups to allow for fragment linking without loss in potency. The other solution is to have a masked functional group, which would resemble the group in the linked fragment. Functional group masking has already been applied by Ellman *et al*. with the development of the first highly selective inhibitor of c-Scr which is a key signalling kinase in cancer.[34,35] The aldehydes were masked with *O*-methyl oximes *via* a condensation reaction to resemble the functionality in the linked fragment (Figure 1.9)

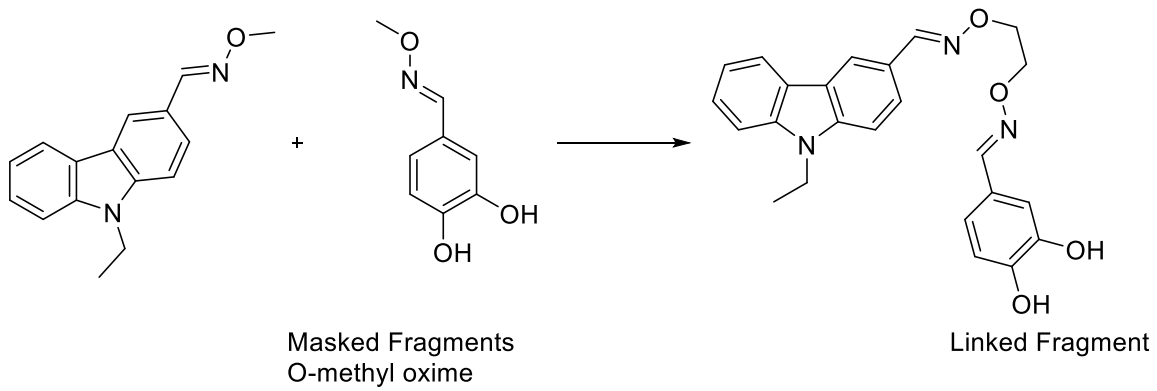


Figure 1.9 – Example of masked functional groups for a fragment linking stratergy.

Therefore, Novartis developed a fragment pair approach, where fragments would be screened with masked functionality, closely resembling the group in the linked fragment.[36] The two fragments would include the 'masked screening fragment' which would be derivatised with a simple and low MW group, and the 'synthesis fragment' which would be the main building block. The 'synthesis fragment' can contain reactive functional groups to allow for a range of chemistry to be undertaken to improve the binding interaction. Examples of the types of 'synthesis fragments' and 'screening fragments' included within the library are shown in Figure 1.10. In the first example, the piperazine is masked as the acetamide for screening, whereas in the second example the acyl chloride is masked as a secondary amide.

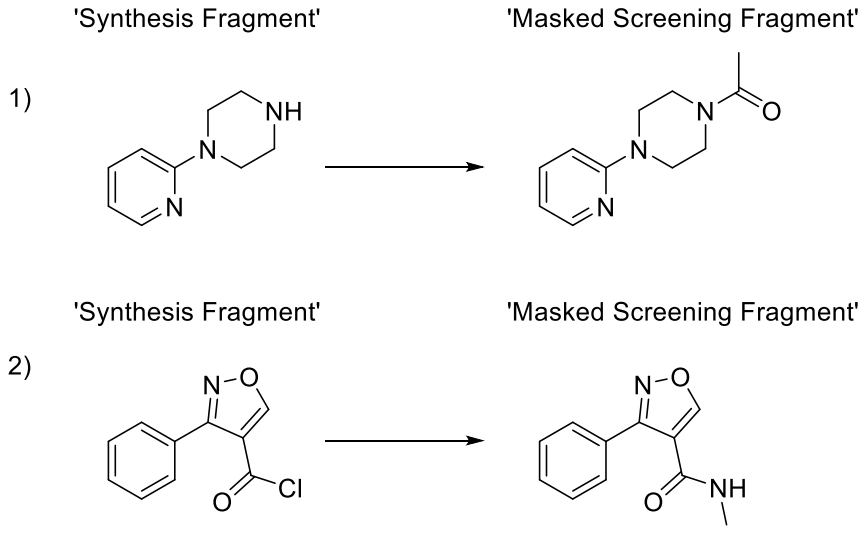


Figure 1.10 – Examples of 'synthesis fragments' and 'screening fragments'.

In recent years, pharmaceutical companies have been reviewing their fragment libraries to try and improve hit rates. In 2009, AstraZeneca reported the design of two generic fragment

libraries, one containing 20,000 fragments, and another focused on NMR screening and containing 1,200 fragments.[37] More recently, AstraZeneca have further re-evaluated their fragment library.[38] The library re-design has constituted the removal of compounds which have been found to decompose, cause assay interference or had poor aqueous solubility, which would not suit screening by X-ray, NMR or surface plasmon resonance (SPR). In the ten years since the first-generation library was designed, synthetic methodology has evolved significantly and, as a result, new fragments were added. Recently, attention has turned to evaluating 3-D molecular shape of the fragments in the library, with the use of methods such as PMI and PBF. Analysis of their library revealed gaps in the chemical space coverage of the current library, which were filled using shape analysis to identify new fragments. In total, the second-generation library contained over 15,000 fragments which all largely obeyed the 'Rule of three'.

A comparison of 3-D and 2-D fragments embedded within drug molecules was carried out by Chan *et al.* who took account of different ring sizes and structures.[39] A 2-D fragment was defined as having no sp^3 hybridised carbons, with a 3-D fragment having at least one sp^3 hybridised carbon within the ring. 1297 Drug molecules were analysed and showed a total of 433 unique ring fragments, with 101 2-D and 322 3-D fragments. The fragments showed a variety of ring sizes with the most common being the 5- and 6-membered rings, with the most-used ring systems being bicyclic and spirocyclic fragments. The 3-D fragments showed a good distribution of 3-D shape, supporting the theory that 3-D fragments allow for the sampling of a larger region of chemical space.

In Chan's study, a fragment target class analysis was also carried out, comparing the difference in binding between the 2-D and 3-D fragments against 15 different targets *e.g* GPCRs, ion channels and nuclear receptors. The findings showed that for fragments derived from nuclear receptors, 92% were 3-D fragments. The 3-D fragments were also found to have a high percentage (86%) in cellular proteins. Perhaps the most interesting finding was that the 2-D fragments failed to show a higher percentage contribution for any of the 15 target classes, underlining the potential benefit of 3-D fragments.

In 2013, in order to take advantage of the potential of 3-D fragments, a 3-D Fragment Consortium was set up. The consortium consists of not-for-profit organisations, and they outlined their goal of developing a fragment screening library which would have enhanced 3-D character.[40] The aim was to create a library of between 500-3000 fragments which would

contain fragments from current libraries and fragments which had enhanced 3-D shape. It was proposed that the flatness of current fragment libraries may be a reason for their poor success rate for certain protein targets.

To start with, the 3-D Fragment Consortium analysed a current fragment library consisting of 1000 compounds supplied by one of the members of the consortium, and compared them to fragments which are embedded in drug compounds which have been evaluated in humans (Figure 1.11). The two sets of data were evaluated using a PMI analysis. The results showed that the 1000 fragments occupied the region of the PMI plot along the rod-disc axis with limited spread across the plot (Figure 1.11a). This contrasted with the PMI plot shown in Figure 1.11b, which contained fragments which are embedded in current drug candidates.

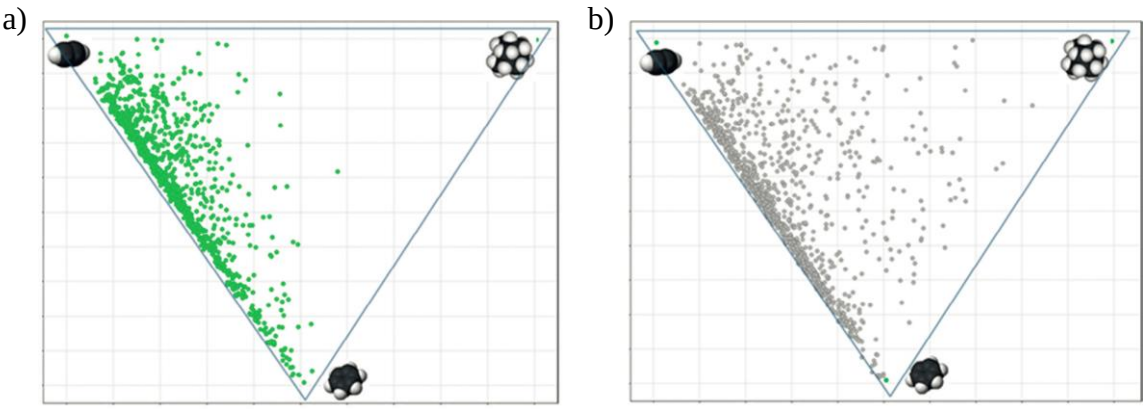


Figure 1.11- PMI plot of 1000 fragments within a current fragment library (a) and fragments which are embedded in current drug candidates (b).

The 3-D Fragment Consortium concluded that the different positional vectors that are possible with 3-D fragments might allow for alternative pharmacophore relations, which flat fragments cannot obtain. To selected 3-D fragments, the eMolecules and ZINC databases were combined to give a combined total of 13.4 million molecules. The molecules were then filtered to only include molecules with a HAC of 9-18, and to remove any undesirable functionality, which afforded 180,000 molecules. Then, 200 molecules were selected based on a 3-D shape analysis of the 180,000 molecules. After the removal of certain molecules due to supplier issues or failed quality checks, the library was reduced to 170 fragments. Three example 3-D fragments are shown in Figure 1.12.

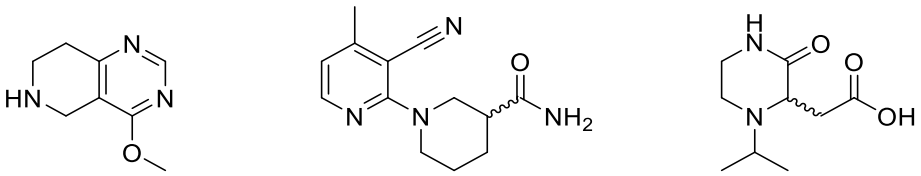


Figure 1.12 – Three fragments inlcuded within the 3-D Fragment Consortium library.

In the intervening five years, the consortium has grown the library to contain 609 fragments, which are publicly accessible *via* Diamond light source.[41] In combination with the library, the consortium also designed and developed 3DFIT (3-D Fragment Idea Tool) which is computational software that enables users to evaluate the 3-D shape and predict physicochemical properties of molecules. The program predicts the seven lowest energy conformations for PMI analysis and flags up any parameters that lie outside the boundaries which have been established by the consortium. 3DFIT offers a quick and instant assessment of the suitability of the molecule, which can help guide synthetic work and offer a useful tool for fragment-based drug discovery.

1.5 Recent Approaches to Fragment Synthesis

There is a growing interest in the development of 3-D fragment libraries and synthetic methodology related to 2-D and 3-D fragments. This section provides a detailed overview of the key work in these areas.

One of the main disadvantages with FBDD often can be the ability to follow up hits, due to the limited availability of chemically accessible growth vectors for fragment elaboration. Therefore, Brennan *et al*. proposed the creation of a poised fragment library, which would allow for fast and effective fragment optimisation once a fragment hit had been identified.[42] A poised fragment was defined as a fragment which could be separated into two separate synthons linked *via* the formation of a 'poised bond'. Chemically similar, commercially available synthons could then be bought, and in one synthetic step, follow-up fragment analogues could be synthesised and screened (Figure 1.13).

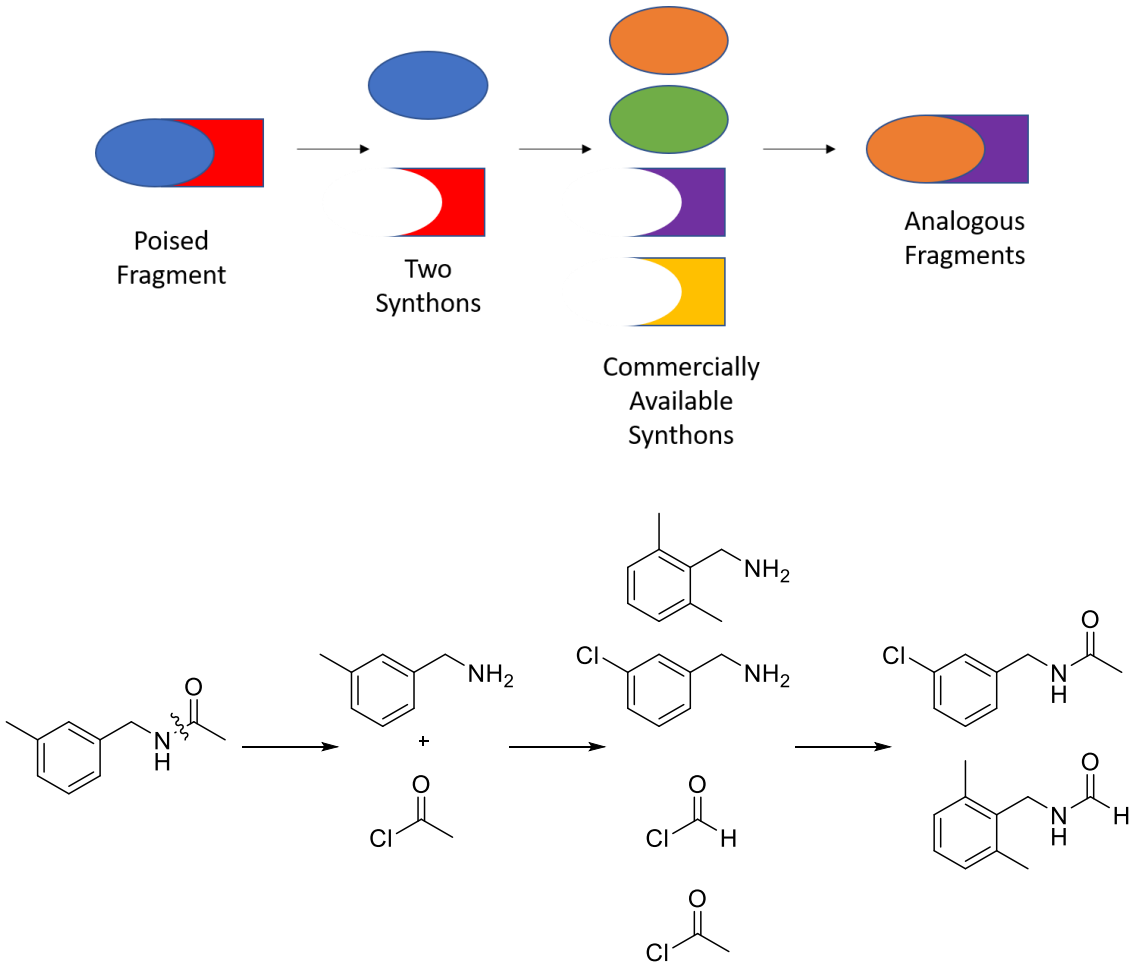
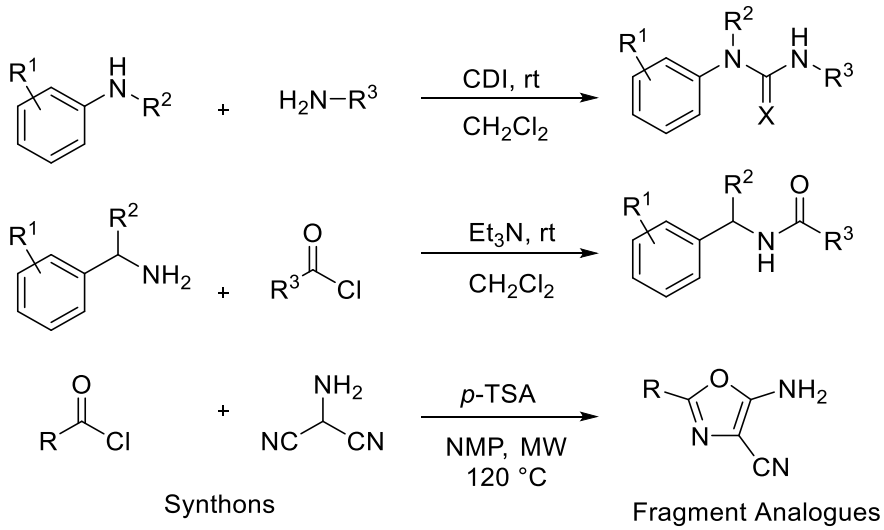


Figure 1.13 – A schematic overview of the poised fragment approach, with an example of a poised fragment strategy.

The ‘poised bond’ forming reaction required reliable and robust chemistry in order to tolerate a wide variety of commercially available compounds. Suitable reactions were selected based on the ten most common reactions used by medicinal chemists, which included amide coupling, reductive amination and Sonogashira coupling.[43] They also included 12 heterocycle forming reactions and a new oxazole synthesis that had been developed within their group.[44]

A library of 11,677 fragments from the Structural Genomics Consortium was collected from in-house libraries and collaborators. The fragments were then assessed based on poised fragments and prevalent synthons to create a library of 2347 fragments. To ensure diversity, a subset consisting of 407 poised fragments was identified. The 407 fragments were screened against pleckstrin homology domain interacting protein (PHIP), which had been identified as being overexpressed in metastatic melanomas, and against the PHIP(2) bromindomain using X-ray crystallography. For PHIP(2) bromindomain, three fragment hits were identified. The three poised fragment hits were in three different classes: thioureas, *N*-benzyl amides and oxazoles. Using the poised fragment strategy, a set of analogues for each class was synthesised (Scheme 1.6).



Scheme 1.6

In addition, Brennan *et al*. created a poised fragment library based on the 192,000 compounds within the ZINC fragment-like library which was reduced to 41,271 when drug-like property filters were applied. A poised fragment analysis was used and a library of 28,438 fragments were selected. They were surprised to find that 68% of ZINC compounds

could be synthesised using 21 different reactions, which highlighted the limited amount of synthetic reactions used by medicinal chemists.

Despite efforts to expand the scope of fragment methodology there are still issues with fragment-oriented synthesis. For example, Astex highlighted the issue of fragment elaboration and the need for synthetic methodology research to focus on fragment design and the elaboration of a fragment hit into a high affinity lead. As a representative example, they focused on dihydroisoquinolone **22**, as it has ideal fragment properties with a MW = 147, ClogP = 1.0 and one HBD and HBA. The synthesis of dihydroisoquinolone derivatives can be achieved using Rh C-H activation reactions. Rees *et al.* from Astex designed a series of dihydroisoquinolone derivatives, expanding on the current synthetic methodology to allow for the elaboration of the fragment to afford an array of near neighbours with alternative growth vectors (Figure 1.14).[45]

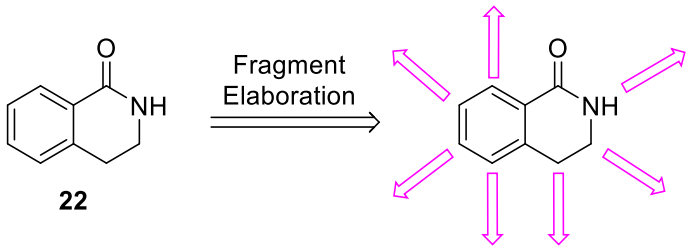
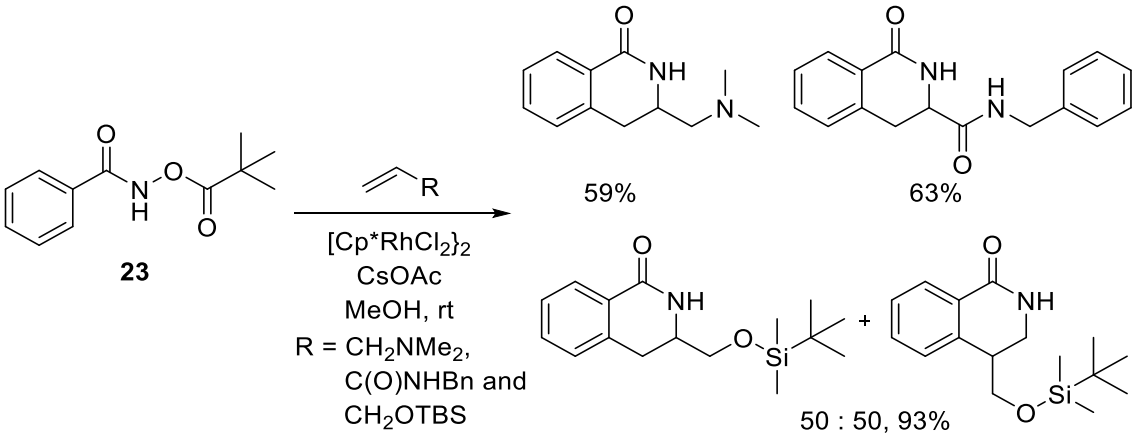


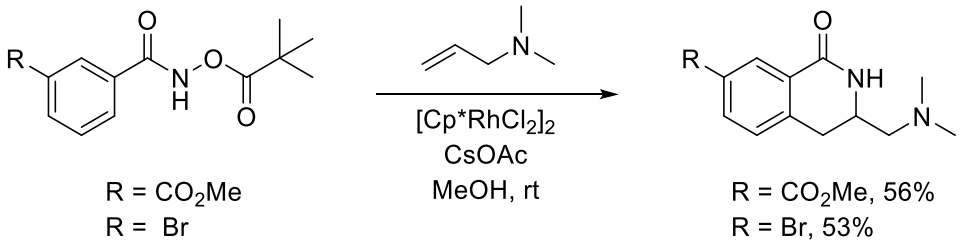
Figure 1.14 – Potential fragment elaboration points of the dihydroisoquinolone.

Starting from aryl-hydroxamate **23**, dihydroisoquinolones were synthesised generally with high regioselectivity when reacted with monosubstituted alkenes. The mechanism for the reaction is believed to involve the coordination of the Rh to the nitrogen which directs the cyclometalation to the *ortho* C-H bond. Reductive elimination and N-O bond cleavage affords the dihydroisoquinolone product.[46] Reaction of substituted alkenes enabled installation of protected polar functional groups which could facilitate future elaboration. The installation of monosubstituted alkenes largely afforded a single regioisomer. Insertion of the silyl protected alcohol afforded a 50:50 mixture of regioisomers which were separable. Despite the low regioselectivity, the route offered access to both regioisomers in good yields (Scheme 1.7).

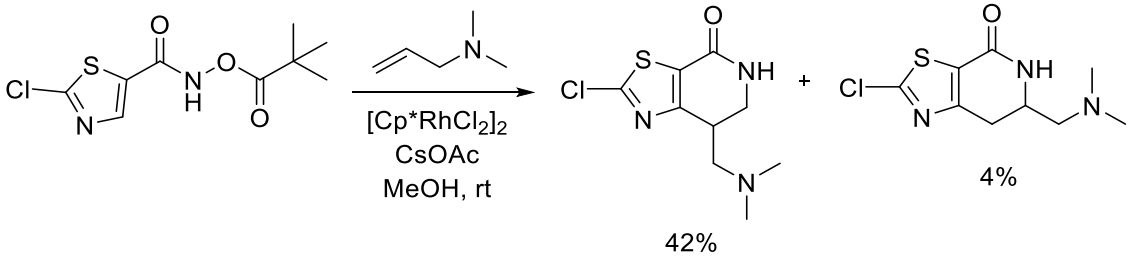


Scheme 1.7

Aryl substituted hydroxamates were also explored to give compounds with a bromide or methyl ester. Cyclisation of the *meta*-methyl ester afforded a single regioisomer, with the *meta*-bromide giving the desired product along with a small amount of the *ortho*-Br product (Scheme 1.8). Incorporation of heteroaromatics can modify the physicochemical properties of the fragments. Cyclisation was known with thiophenes and pyridines and the scope was expanded to include thiazoles, albeit in low yields. Cyclisation with chlorothiazole hydroxamate afforded an 80:20 mixture of regioisomers (Scheme 1.9).



Scheme 1.8



Scheme 1.9

The products of the reactions shown in Scheme 1.8 and Scheme 1.9 are not considered to be fragments, but rather they are building blocks offering points for elaboration *via* cross-

coupling or reduction. Thus, Rees *et al*. had been able to show that the dihydroisoquinolone fragment had the potential to be derivatised and elaborated by offering differing synthetic handles or regions for protein binding. However, the work undertaken to synthesise near-neighbours for just the one fragment demonstrates the challenges faced by medicinal chemists and the need for newly designed fragments to incorporate accessible points for fragment elaboration.

Fragment libraries often contain 'privileged scaffolds' derived from known drugs and this results in similar regions of chemical space being covered by the libraries. Another approach to fragment design would be to consider natural products, which have already been biologically validated in nature. Waldmann *et al.* outlined and demonstrated an approach towards the design and synthesis of a natural product inspired library.[47] Natural products benefit from having a high number of sp^3 centres and offer access to regions of chemical space currently unoccupied by commercial compounds. The natural product derived fragments would retain high numbers of sp^3 centres and resemble natural scaffolds. Thus, fragmentation of natural products was undertaken with the position and substitution patterns retained from the natural product, but with an alteration of the functional groups. The deconstruction of Renieramycin P into five fragments is shown in Figure 1.15.

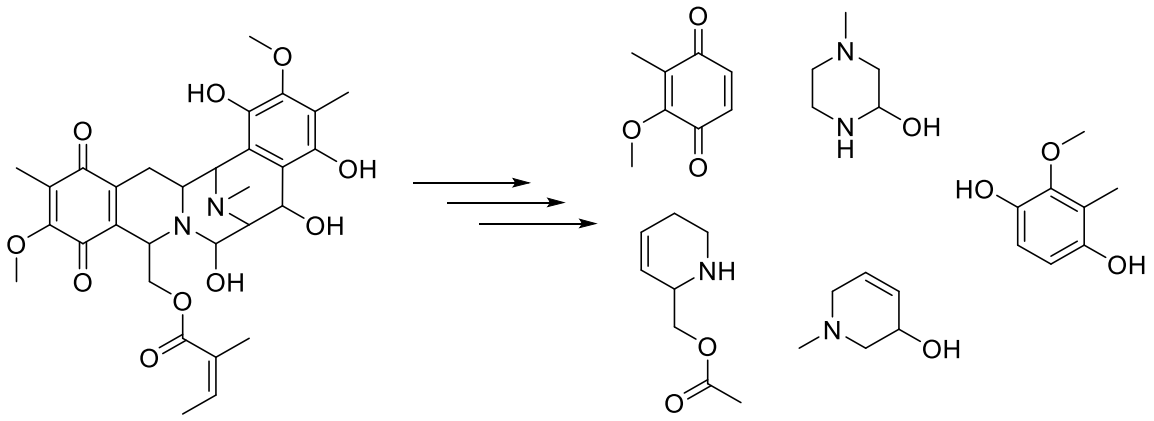
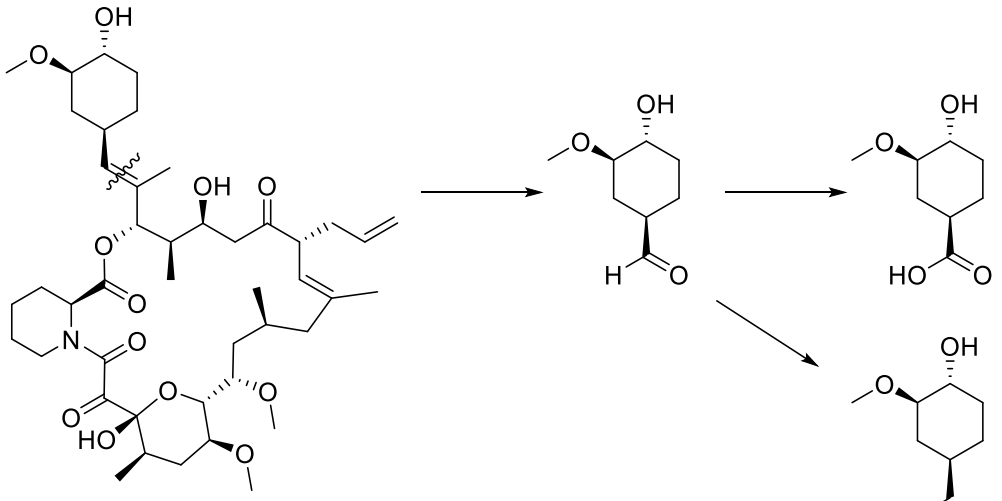


Figure 1.15 – Deconstruction of Renieramycin P to afford five fragments.

In total, 751,577 natural product derived fragments were generated and then filtered based on toxicity, stability and 'Rule of three' compliancy to afford roughly 160,000 fragments. To further refine the library, iterative clustering was performed to produce 2,000 clusters each showing high diversity and a richness in sp^3 centres. The chemical space coverage of the natural product library was then compared to a commercial ZINC fragment library. Analysis of the two libraries revealed that the two shared little overlap in chemical space.

In order to demonstrate that the natural product derived library could be applied to a drug target, the fragments were screened against p38α MAP kinase. A subset containing 193 fragments (or close analogues) was selected from the initial 2,000 fragments based on their availability. Screening of the library revealed unique binding to the allosteric pocket with bicyclic cytisine/sparteine derivatives, which offered a new starting point for future kinase inhibition.

Fragments inspired by natural products have also been reported by researchers at Novartis with their development of a fragment library consisting of 3-D and nature-inspired fragments.[48] An in-house library of 17,000 natural products was subjected to *in silico* fragment generation, yielding 66,000 fragments. Natural products were selected based on ease of cleavage, introduction of sp^3 centres and potential rearrangements. The known degradation of Tacrolimus is an example of their fragmentation approach. Ozonolysis of Tacrolimus followed by reduction or oxidation yield aldehyde, alcohol or carboxylic acid fragments (Scheme 1.10).



Tacrolimus

Scheme 1.10

The method of deconstruction *via* known routes of degradation was applied to other natural products, affording a library of 150 3-D and natural product-like fragments. The library was then compared against a Novartis in-house library for 3-D shape and natural product-likeness. The data revealed that the new library occupied novel areas of chemical space and showed a greater degree of natural product-likeness.

The biological relevance of sp^3 rich fragments which are distantly related to natural products has been shown by Nelson *et al*. with their 'top-down' synthetic approach towards natural product-like frameworks.[49] Starting from complex, but easily available intermediates, they synthesised 22 scaffolds which contained natural product-like features. The 22 scaffolds were then derivatised to create a library of 52 fragments, which were assessed against a commercial fragment library, showing increased natural-product likeness and greater shape diversity. In order to show the biological relevance of the fragments, they screened the library against three different protein targets, and obtained 17 hits (Figure 1.16 -). Screening a conventional fragment library, containing 700 compounds, against one of the protein targets achieved nine hits compared to the seven hits achieved with their own library. Thus, a higher hit rate was achieved with the shape-diverse natural product-like fragments compared to the conventional flat fragment library.

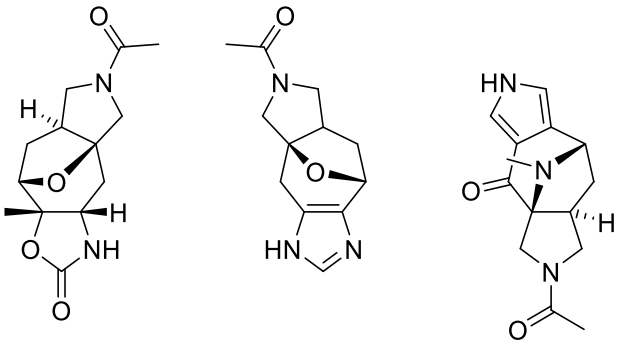


Figure 1.16 - Three shape-diverse natural product-like fragment hits.

The work on fragments inspired by nature has indeed offered a greater coverage of biologically relevant chemical space. However, the synthesis of natural product-derived fragments remains challenging, with the development of novel and innovative chemistry often required to synthesise the fragments of interest.

The ability to introduce diversity within fragment libraries can often prove challenging. However, there are synthetic strategies that have attempted to address the issue. For example, diversity oriented synthesis (DOS) can enable the synthesis of a series of compounds containing structural complexity and diversity.[50] Starting from simple building blocks, molecular complexity and diversity can be introduced in four to five steps to create a library of fragment-sized molecules which have the ability to be further elaborated. In 2011, Young *et al.* reported the first example of a DOS approach to synthesise fragments which had structural and stereochemical diversity, focusing on bicyclic and spirocyclic systems.[51]

Young *et al*. started from a selection of proline building blocks such as *cis*-**24**, *trans*-**25** and **26** and the different stereoisomers were used to incorporate stereochemical diversity into the fragments that were synthesised (Figure 1.17).

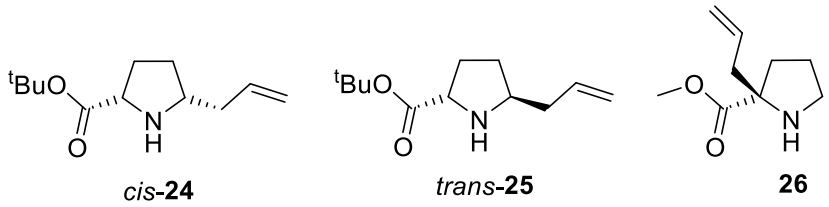
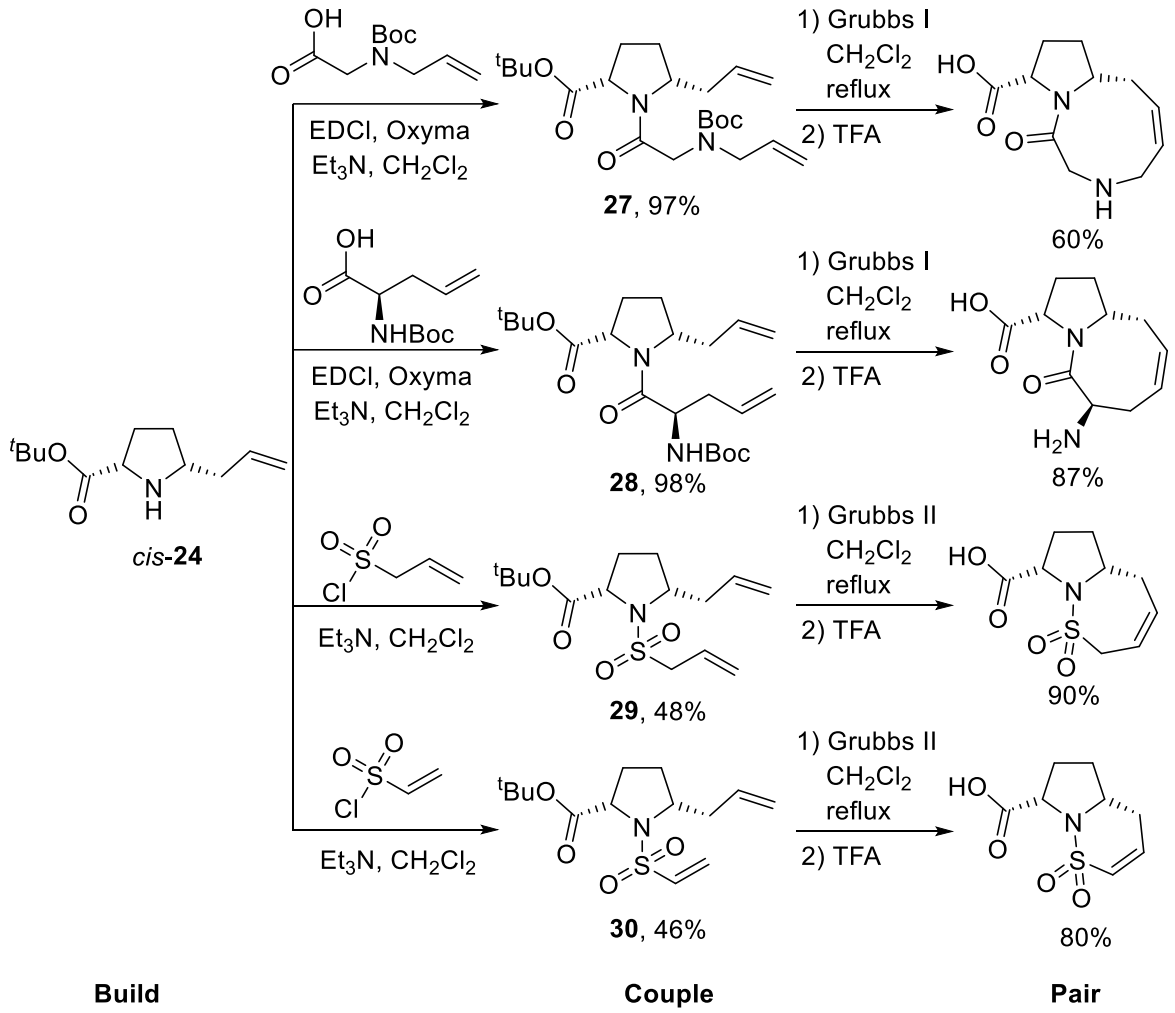


Figure 1.17– Examples of stereochemical diverse 3-D building blocks.

Young's strategy used proline-like building blocks *cis*-**24**, *trans*-**25** and **26** as the starting point for a build/couple/pair approach. Starting with chemically diverse starting materials, coupling with differing functional groups would offer the diversity before the final 'pair' phase in which the molecules would be subjected to coupling conditions to afford a higher degree of complexity within the molecule. This led to small fused bicyclic fragments which all obeyed the 'Rule of three'. Coupling of proline derivative *cis*-**24** with *N*-Boc amino acids gave amides **27** and **28**, whereas *N*-sulfonylation gave sulfonamides **29** and **30**. The substrates all had varying alkyl chain lengths with terminal alkenes, allowing for subsequent ring-closing metathesis with Grubbs I or II catalyst. The esters were cleaved with TFA to afford carboxylic acids with a range of different fused ring systems (Scheme 1.11).



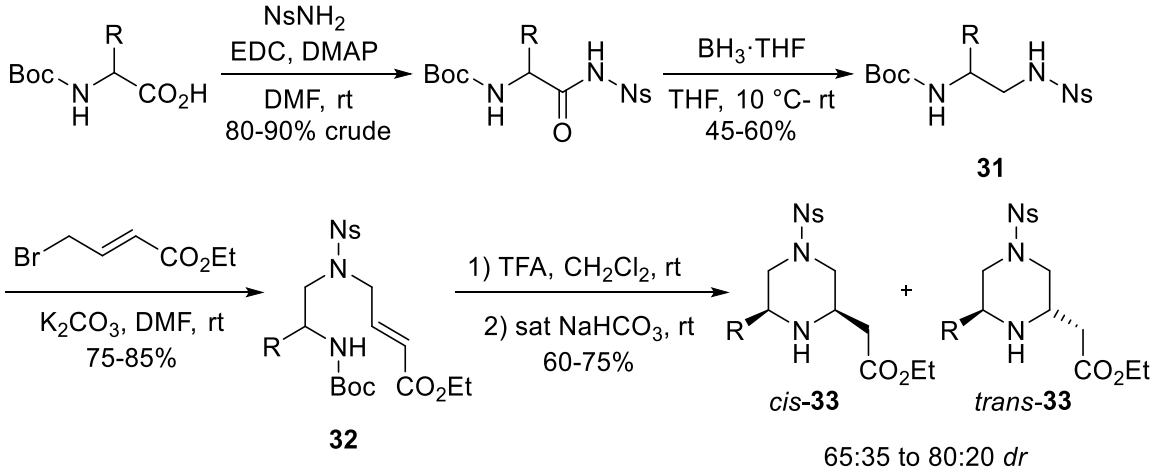
Scheme 1.11

The fragments synthesised all had a high degree of complexity, with the DOS approach offering control of each position on the ring. An advantage of the approach is that derivatisation of the initial building block can access new derivatives without changing the overall synthetic route. In addition, increasing the number of sp^3 centres could provide unique growth vectors and increased selectivity in protein binding. Finally, incorporation of polar functional groups can increase the solubility of the fragments which is important as high aqueous concentrations are necessary for protein screening.

Young *et al*. analysed 35 of their 3-D fragments against a sub-set within the ZINC library (18,534 compounds). PMI analysis of the two libraries revealed that the 3-D fragments occupied a broader region of the plot, with the ZINC fragments largely focused around the rod-disc axis. In order to analyse a smaller subset of the ZINC library, the 3-D fragments were compared against the best-match ZINC fragments, regarding HAC and similar physical

properties. The two comparisons showed that the ZINC fragments occupied the region around the rod-disc axis and the top left apex. Therefore, the ZINC fragments could be considered less diverse compared to the more 3-D fragments synthesised using the DOS approach.

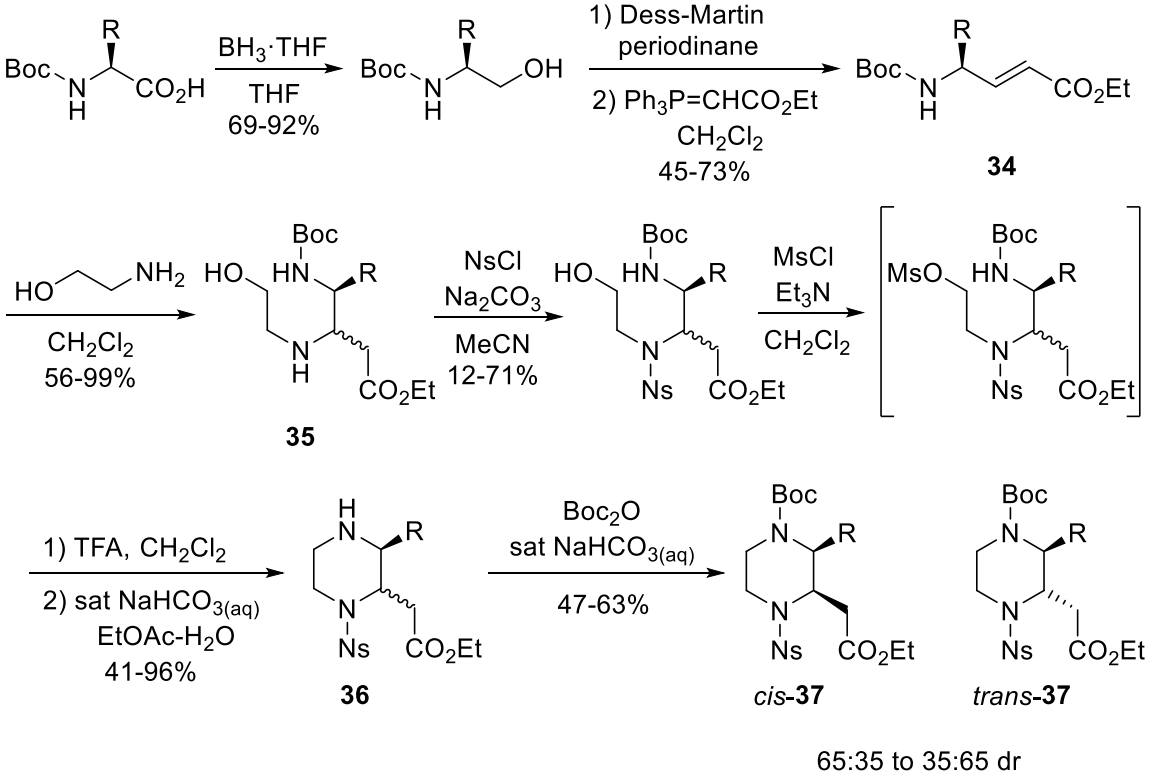
Young's group has also published work on the synthesis of enantiopure *cis*- and *trans*-2,3- and 2,6-disubstituted piperazines, sub-structures which are common in drug molecules. The outlined approach started from enantiopure amino acids, with the stereochemistry retained in the piperazines.[52,53] The 2,6-piperazine synthesis involved amide coupling of amino acids to afford amides which were directly reduced with BH_3 to afford protected diamines **31**. Alkylation gave acrylates **32** which, after deprotection and neutralisation, cyclised to give mixtures of 2,6-disubstituted piperazines *cis*-**33** and *trans*-**33** (Scheme 1.12). The diastereoisomers were separable using chromatography and a further 13 amino acids (both (*S*) and (*R*)) were reacted affording 24 2,6-piperazine analogues as single enantiomers. The (*S*)- and (*R*)-phenylglycine products were the only examples where the starting stereochemistry was not retained with high *ee* in the final product.



Scheme 1.12

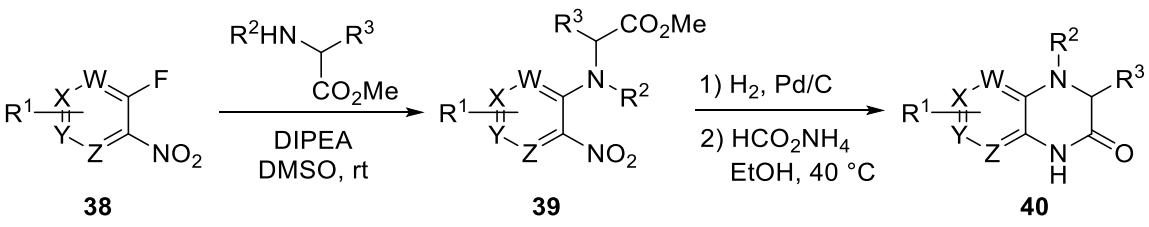
The synthesis of the 2,3-piperazines started from the reduction of the carboxylic acid in amino acids to the alcohol, followed by oxidation to the aldehyde and Wittig reaction to afford acrylates **34**. Aza-Michael addition with hydroxy amine afforded alcohols **35**, which then underwent *N*-protection and *O*-activation. Removal of the Boc protecting group allowed cyclisation to afford mixtures of 2,3-disubstituted piperazine **36**. Protection of the nitrogen then aided separation of the two diastereoisomers affording piperazines *cis*-**37** and *trans*-**37**,

with reactions of ten different amino acids (both (*S*) and (*R*)) giving 20 disubstituted 2,3-piperazines (Scheme 1.13).



Scheme 1.13

A different example of the Base/Couple/Pair approach was used by Young's group in a FBDD approach towards the inhibition of glycogen synthase kinase 3*β* (GSK3*β*), which had been found to be overexpressed in cancer and Alzheimer's diseases.[54] A series of fragments were synthesised starting from arylnitrofluoride **38** as the building block. S_NAr reaction with a range of amino acids afforded the coupled products **39**. The final step was the 'pairing' phase, with reduction of the nitro group giving an aniline which cyclised to afford the final amide fragments **40** (Scheme 1.14).



Scheme 1.14

Using this route, a series of fragments (Figure 1.18) were prepared and screened against GSK3*β*. The DOS approach enabled the rapid derivatisation and variation of the amino acid to install different functionality into the piperazinone ring, which led to an increase in the binding affinity towards GSK3*β*.

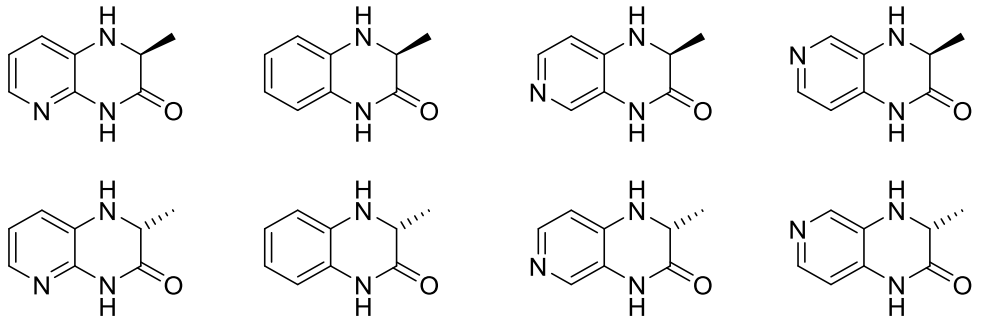
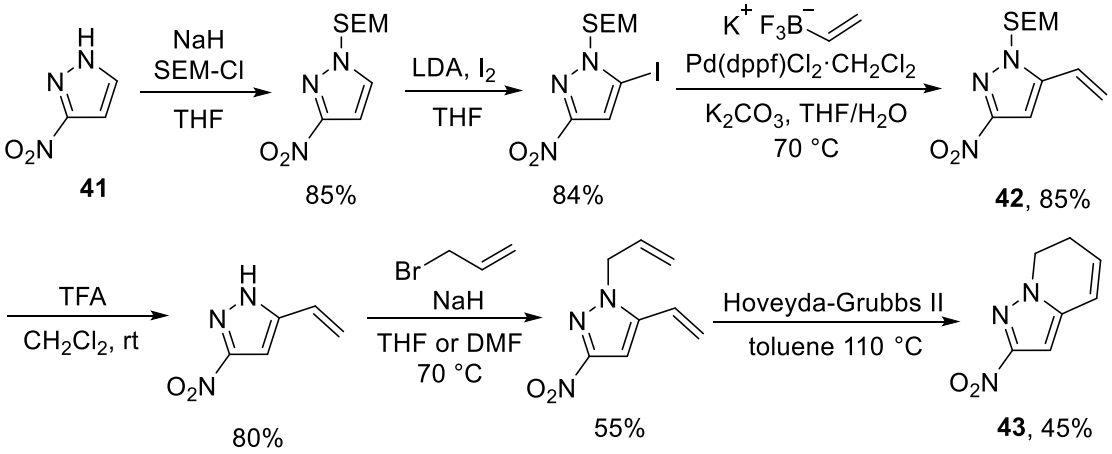


Figure 1.18 – Subset of eight fragments synthesised with differing aromatic groups.

In recent years, new methodology and synthetic strategies have been developed to accommodate the need for fragments to have multiple, accessible growth vectors. Spring *et al*. reported a synthetic approach to sp^3-rich fragments, focusing on partially saturated bicyclic heteroaromatics containing pyrazoles and pyridines.[55] The route for the synthesis of the bicyclic pyrazole system is shown in Scheme 1.15. Pyrazole **41** was initially SEM-protected and iodinated, allowing for Suzuki-Miyaura coupling which gave vinyl pyrazole **42** in 85% yield. The SEM group was removed to reveal a pyrazole which then underwent *N*-alkylation to give an alkene. Ring-closing metathesis using Hoveyda-Grubbs II catalyst gave bicyclic pyrazole **43** in 45% yield.



Scheme 1.15

With bicyclic pyrazole **43** prepared, a series of one-step reactions such as aziridination, dibromination, allylic oxidation, dihydroxylation, difluorocyclopropanation, hydroxybromination, epoxidation and hydroboration were performed on the alkene to introduce functionality at the 4-, 5- and 6- positions on the fused pyrazole system (Figure 1.19). These fragments were also derivatised further to install bromine, fluorine and nitrogen substituents. Nucleophilic attack of the epoxide with hydride or fluoride offered fragment diversification. The nitro group could also be reduced to afford the amine which offers another synthetic growth vector for the fragments. The ability to quickly build up a fragment library using the pyrazole and pyridine building blocks *via* simple and direct introduction of new functionality makes the route very attractive.

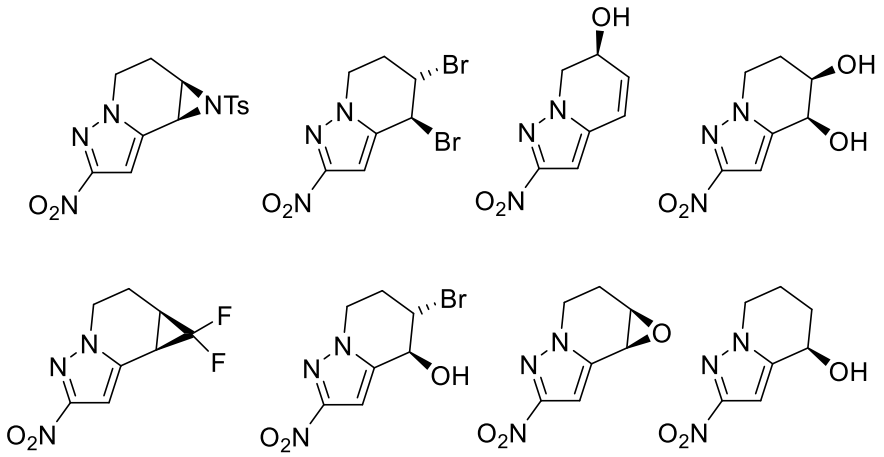


Figure 1.19– Example of eight products from one-step reactions to functionalise pyrazole **43**.

Using this approach, Spring *et al.* synthesised 42 fragments and analysed the physicochemical properties, with the mean value of the fragments being compared. The results showed that the fragment properties lay within the ranges set out by Astex, with MW between 140-230, hydrogen bond donors ≤ 3 and hydrogen bond acceptors ≤ 3. The ease of introducing functionality makes this route appealing, but some of the functionality in the fragments shown in Figure 1.19 such as epoxides and aziridines which are classed as reactive intermediates may not be suitable for use in drug discovery.

Spring *et al.* have also developed a DOS approach, starting from α,α-disubstituted propargyl amino ester **44**, for the synthesis of fragments which could feature 3-D growth vectors and allow the installation of polar functional groups.[56] The aim was to create a library of nitrogen-containing fragments with quaternary centres which would be synthesised using known chemistry based on the reactivity of amines, esters and terminal alkynes.

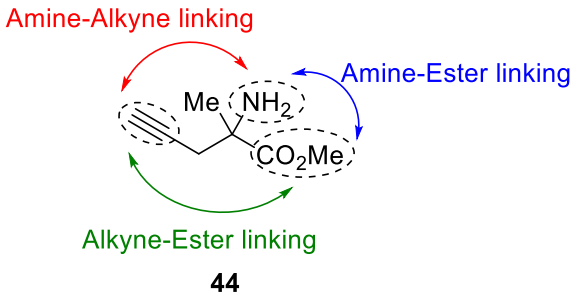
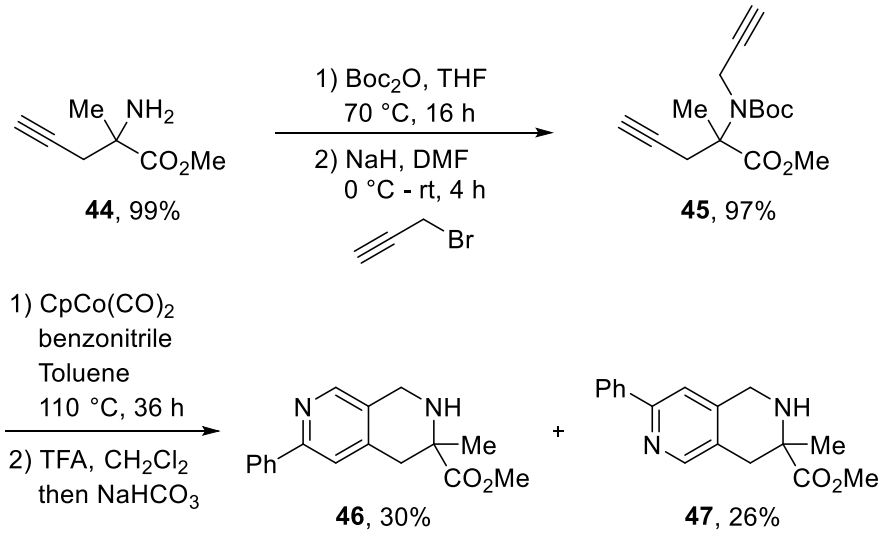


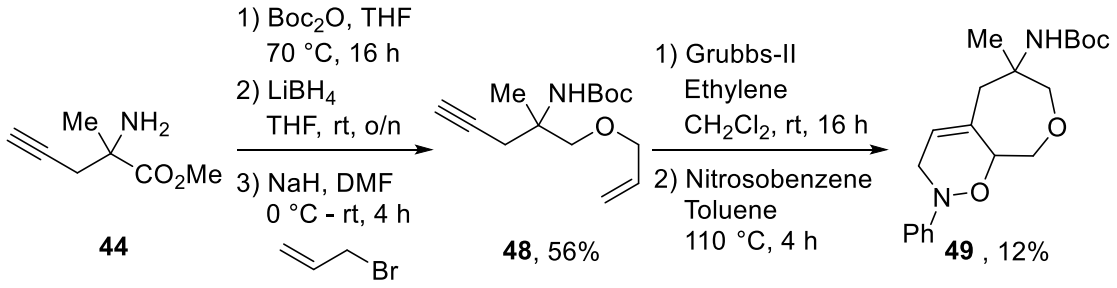
Figure 1.20 – Synthetic versatility of α,α-disubstituted amino esters.

One type of scaffold was prepared as shown in Scheme 1.16. Reaction of amine **44** with Boc_2O and alkylation with propargyl bromide gave **45**. Then, Co-induced [2+2+2] cyclotrimerization with benzonitrile afforded two bicyclic regioisomers, which were subsequently treated with TFA to afford **46** and **47**.



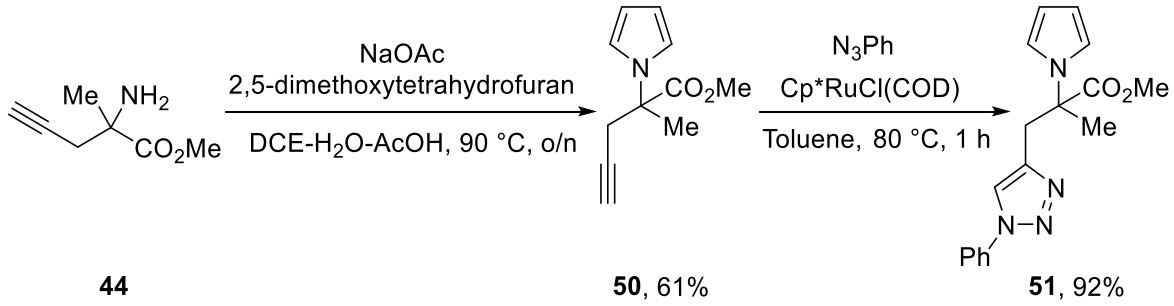
Scheme 1.16

A different scaffold could be prepared from amine **44** using different reactions. After Boc protection, reduction of the ester afforded a primary alcohol which was *O*-alkylated with allyl bromide to give **48**. Cyclisation of ether **48** *via* ring-closing enyne metathesis and Diels-Alder cycloaddition with nitrosobenzene afforded oxepine **49** in 12% yield over the two steps (Scheme 1.17).



Scheme 1.17

Alternatively, pairing of the amine and the ester was achieved either by alkylation and subsequent Dieckmann condensation to generate the cyclic compounds or by a Paal-Knorr reaction to generate a pyrrole. The Paal-Knorr reaction results in the alkyne functional group remaining intact, which can be further functionalised using 1,3-dipolar cycloadditions to install triazoles. From example, amine **44** was subjected to standard Paal-Knorr reaction conditions to afford pyrrole **50** which was then converted into triazole **51** (Scheme 1.18).

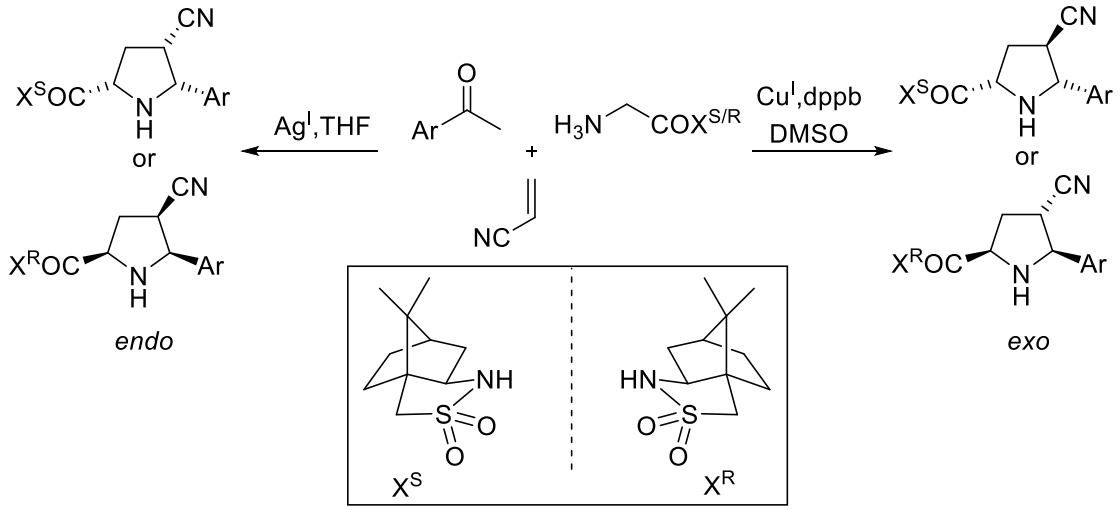


Scheme 1.18

Expanding on the methodology described in Scheme 1.17 and Scheme 1.18, 40 fragments were synthesised starting from α,α-disubstituted propargyl amino ester **44** in five or less steps. The molecular shapes of the 40 fragments were assessed using PMI analysis. The plots showed that the fragments occupied a wide region of chemical space and importantly avoided the rod-disc axis. A computationally derived library was also analysed, with the methyl group of the quaternary centre replaced with a phenyl substituent. Modification of the sp^3 quaternary centre altered the coverage of chemical space of the 40 fragments, highlighting the potential ability to tune the 3-D molecular shape of the fragments.

The approaches so far have addressed issues of elaboration, novelty and diversity. In the remainder of the chapter, methodology that affords compounds with suitable fragment properties will be presented. For example, AbbVie have recently published a paper focused on the design and synthesis of 3-D fragments, with the development of a stereoselective

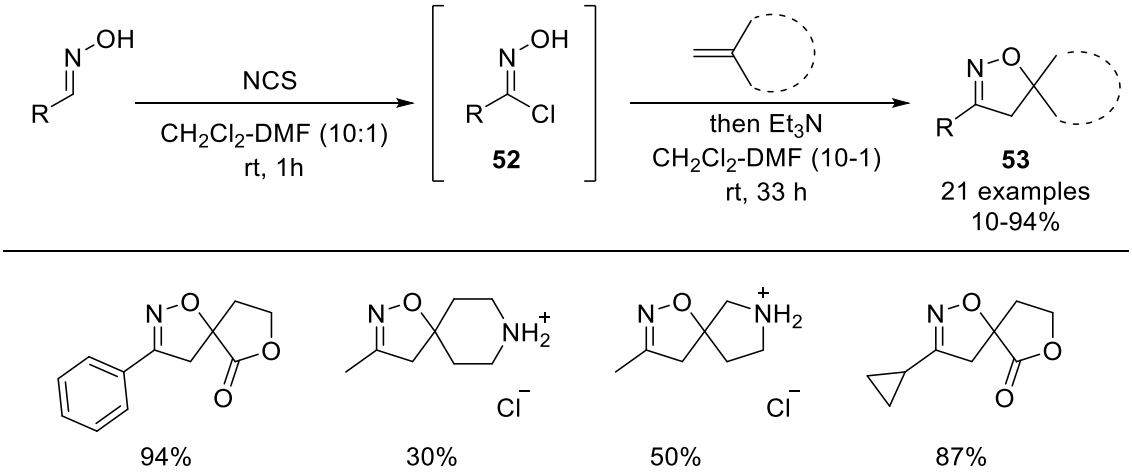
route to 48 enantiomerically pure pyrrolidine fragments.[57] The pyrrolidine scaffold is a popular moiety in drug molecules and natural products, and has the ability to access a wide region of chemical space due to the energetically accessible conformations arising from pseudorotation. AbbVie established a metal-catalysed asymmetric 1,3-dipolar cycloaddition with the incorporation of a chiral auxiliary and either Au(I) for *endo*-selectivity or Cu(I) for *exo*-selectivity (Scheme 1.19).



Scheme 1.19

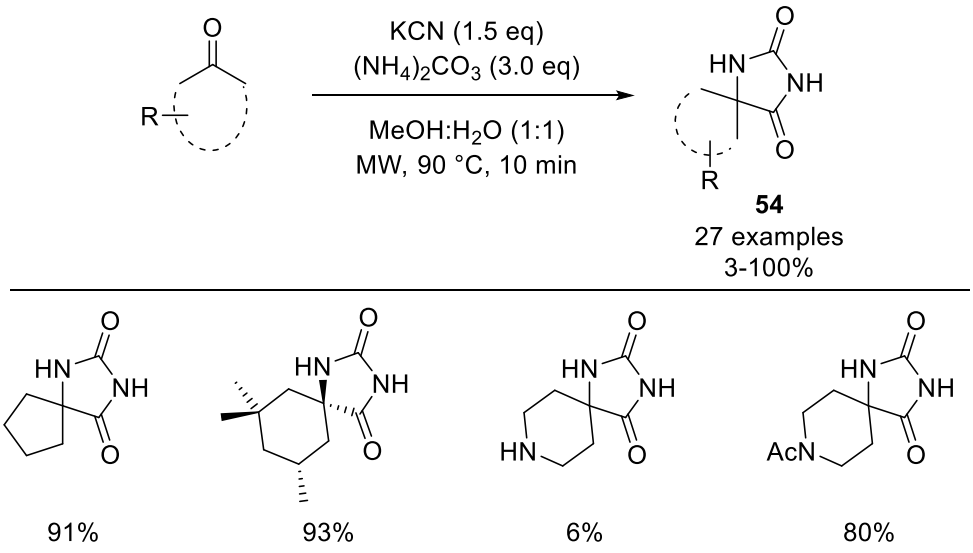
The enantiomerically pure pyrrolidine scaffolds were then derivatised to incorporate a methyl ester group and primary alcohol substituent to afford the 48 pyrrolidine fragments. The fragments were designed to comply with Astex's 'Rule of three', with the shape of the fragments analysed using PBF and PMI scores. The fragments were assessed based on Firth *et al.*[25] description of 3-D space which had been defined as ΣNPR ≥ 1.07 and PBF ≥ 0.6, resulting in all but one of the fragments occupying 3-D space. It was shown that from a relatively simple pyrrolidine scaffold, a wide region of chemical space could be accessed.

Willand *et al.* have also reported the synthesis of sp^3 rich fragments, composed of spirocyclic isoxazoles. Isoxazoles are prevalent in many natural products and have been shown to exhibit activity against a broad range of biological targets.[58] Spirocycles are popular drug scaffolds due to their conformational rigidity, which can potentially reduce off-target affects.[59] A small library of 21 fragments were synthesised using a one-pot strategy which proceeded *via* chloro oxime **52**, which underwent 1,3-dipolar cycloaddition with geminal disubstituted alkenes to afford substituted isoxazoles **53** (Scheme 1.20).



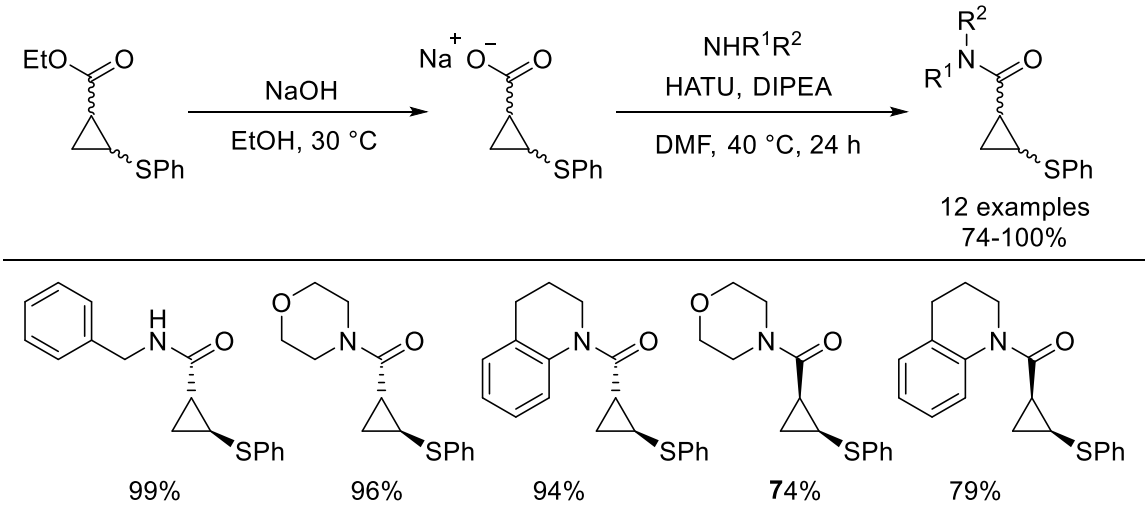
Scheme 1.20

The work was then further expanded to spirohydrantoin fragments.[60] The synthesis was achieved using microwave-assisted conditions. Cyclic ketones were reacted with $(NH_4)_2CO_3$ and KCN in a 1:1 mixture of MeOH-H_2O to afford the desired spirohydrantoins **54**. The ketone was varied to include, 4-, 5- and 6-membered rings along with substituted and hindered ketones containing ester and ether functional groups. The presence of a substituent on the ring led to mixtures of diastereoisomers, but substituents at the α- or β-position to the carbonyl in the cyclohexane series afforded single diastereoisomers. Presumably, steric hindrance directed the nucleophilic attack of the cyanide to the least hindered face. *N*-heterocycles were also attempted and tolerated under the same conditions. The 3-D shape of the 27 spirohydrantoin fragments were analysed using PMI plots, revealing that the fragments covered a broad region of chemical space. 24 of the fragments also showed suitable solubility with all the fragments fitting the 'Rule of three'.



Scheme 1.21

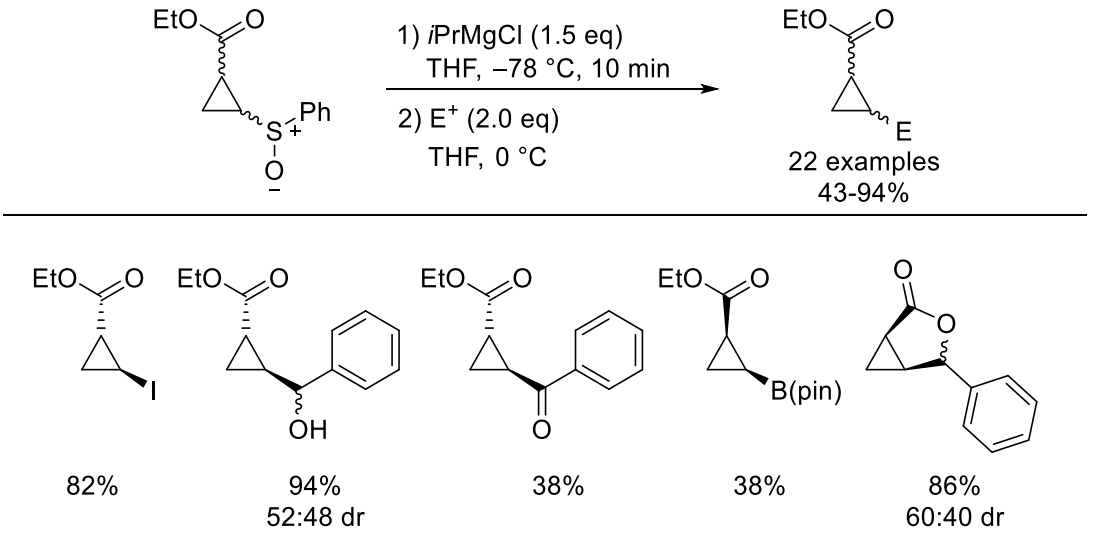
The Bull group have synthesised a library of 56 cyclopropanes using methodology discovered within the group.[61] Co-catalysed cyclopropanation of phenyl vinyl sulfides with ethyl diazoacetate afforded access to a 50:50 mixture of *cis*- and *trans*-cyclopropanes. The diastereoisomers offer differing growth vectors and, once separated, allowed for orthogonal derivatisation of the ester and the sulfide functional groups. For example, the ester group was hydrolysed to afford the carboxylic acid which could then undergo amide coupling to afford a range of amides (Scheme 1.22).



Scheme 1.22

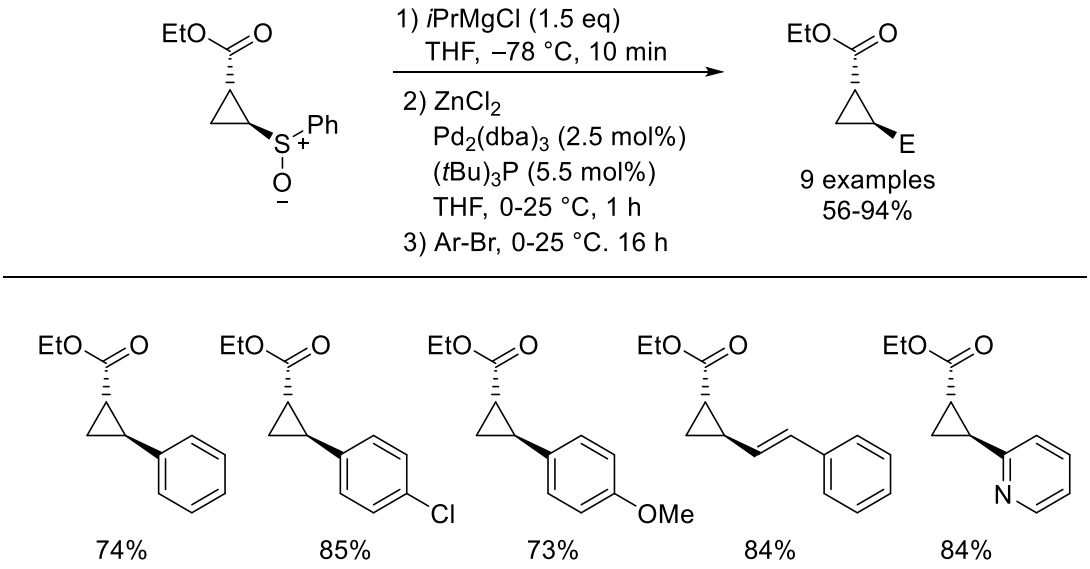
Oxidation of the sulfide using excess *m*-CPBA afforded a set of sulfones in quantitative yield. The sulfide could also be oxidised to a sulfoxide with 1.0 eq of *m*-CPBA which

allowed for sulfoxide-metal exchange reactions. Generation of the *cis*-/*trans*-cyclopropane Grignard intermediates were achieved with *i*PrMgCl and electrophilic trapping with aldehydes, halogens, acyl chlorides and boronates worked well (Scheme 1.23). Trapping to give a boronate allows for further functionalisation of the ring using Suzuki-Miyaura cross-coupling. As expected, trapping of the *cis*-cyclopropanes with aldehydes was followed by *in situ* lactonisation to afford bicyclic lactones.



Scheme 1.23

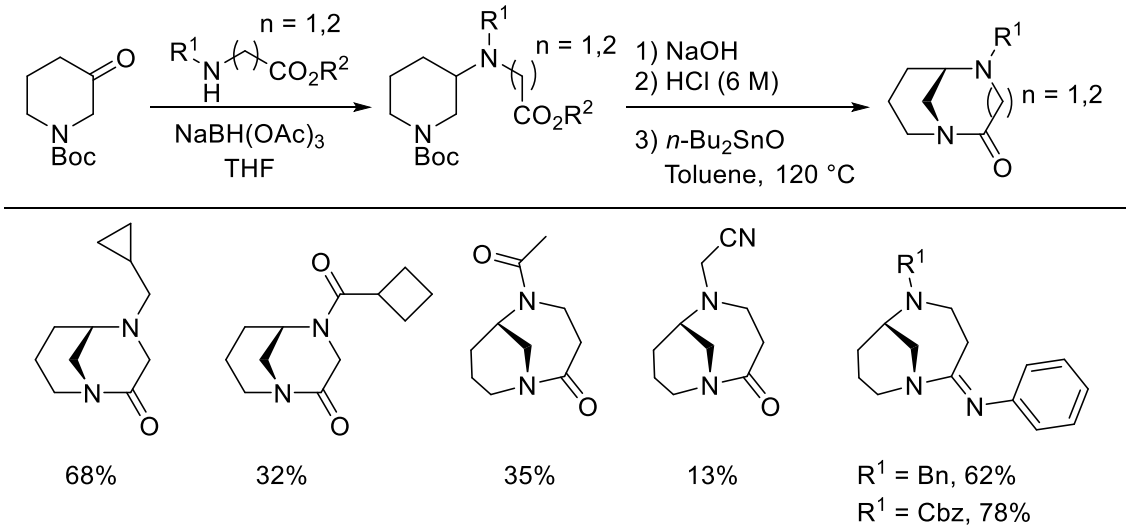
The *trans*-cyclopropane Grignard intermediate was also transmetallated with $ZnCl_2$ to enable Negishi cross-couplings. Thus, the *trans*-cyclopropane Grignard intermediate was charged with a mixture of $Pd_2(dba)_3$, (*t*Bu)$_3$P and $ZnCl_2$ followed by the aryl/heteroaryl bromides. Electron donating and electron withdrawing groups on the aryl bromide both worked well (Scheme 1.24).



Scheme 1.24

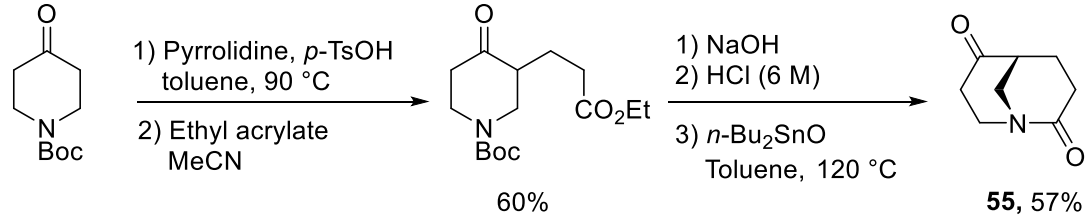
The MW and AlogP values of the synthesised cyclopropanes were analysed to assess their coverage of lead-like and fragment properties. The six cyclopropanes that contained iodides, aldehydes, boronates or ethoxysilanes were removed from the analysis due to the presence of reactive functional groups. The remaining 50 cyclopropanes showed a wide coverage of lead-like and fragment properties. The 56 cyclopropanes were also elaborated virtually using the Lead-likeness and Molecular Analysis (LLAMA) software developed by Nelson and Marsden.[62] The elaboration was restricted to 44 reactions with a maximum of two reactions on the scaffold. The virtual elaboration generated 1187 compounds with 392 compounds having a MW < 300 and 1033 compounds having a MW < 500. The Bull group has also published methodology synthesising arylated 3,4-pyrrolidines and piperidines along with oxetane ethers, all of which afford interesting fragments.[63,64,65]

The Marsden and Nelson groups have published methodology to access twisted bicyclic lactams containing a bridgehead nitrogen, which modulates the electronic properties of the amide, and could offer alterative interactions with proteins.[66] Starting from *N*-Boc piperidine-3-one, reductive amination followed by ester hydrolysis, Boc removal and Sn-mediated cyclisation gave access to bicyclo[3.3.1]nonane and bicyclo[4.3.1]decane bicyclic rings. Derivatisation of the amine was carried out using acylation and alkylation on both ring systems to afford a range of fragments. The amide could also be derivatised to afford amidines (Scheme 1.25).

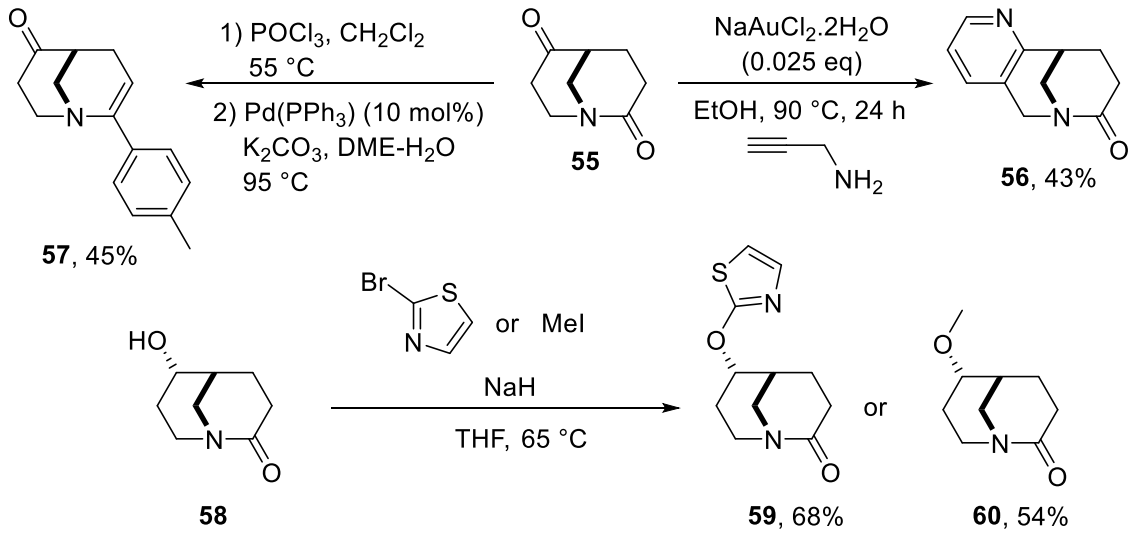


Scheme 1.25

Alternatively, condensation of *N*-Boc piperidine-4-one with pyrrolidine gave the enamine which was reacted with ethyl acrylate followed by lactam formation using the same procedure as above to afford bicyclo[3.3.1]nonane (Scheme 1.26). Lactam 55 could be derivatised to give a series of fragments. Au-catalysed hetaryl-annulation with propargylamine afforded pyrido-fused lactam **56**. The amide could be functionalised through formation of the chloroenamine and subsequent Suzuki-Miyaura cross-coupling to afford **57**. Diastereoselective reduction of lactam **55** with $NaBH_4$ occurred on the less hindered face to give alcohol **58** which was *O*-alkylated to furnish fragments **59** and **60** (Scheme 1.27). A diverse set of 22 bicyclic lactam fragments were synthesised with assessment of the fragment-like properties undertaken comparing the MW against AlogP. Analysis of the shape diversity using PMI plots revealed the bridged scaffold resulted in fragments with a high degree of 3-D shape.



Scheme 1.26



Scheme 1.27

In recent years, academic groups have responded to the need for more synthetic methodology focused on the synthesis of diverse and easily accessible fragments. Various approaches for accessing fragments have been undertaken, including the design of fragments to include predetermined growth vectors allowing for rapid fragment elaboration, the generation of fragments inspired by natural products and the use of DOS. The greater understanding of physicochemical properties and the need for fragments to have high aqueous solubility has led to an array of methodology being researched. This has led to the synthesis of small libraries of sp^3 rich fragments which have favourable 'Rule of three' and solubility properties.

1.6 Previous Work on 3-D Fragments in the O'Brien Group

Prior to starting the research described in this PhD thesis, work within the O'Brien group had led to the design and selection of a set of disubstituted pyrrolidine and piperidine fragments based on their 3-D shape. A previous member of the O'Brien group, Mary Wheldon, had created a protocol to analyse the 3-D shape of fragments and their conformations in order to identify suitably shaped fragments with a view to creating a library of 3-D fragments. In collaboration with Paul Bond and Rob Hubbard from the York Structural Biology Laboratory, Mary Wheldon developed a protocol within Pipeline pilot, using the BEST algorithm, to generate conformations and PMI data.[67] To carry out PMI analysis, the SMILE files of the fragments were uploaded to Pipeline Pilot. The SMILE files contain SMILE strings for each fragment and all the conformations with a relative energy < 7 kcal mol^{-1} and root-mean-square deviation (RMSD) of 0 Å were computationally generated. The conformations each have different normalised ratios of the principal moments of inertia, NPR1 and NPR2, which were plotted on the *x*/*y*-axis to give a final PMI plot. As well as conformation generation, the predicted physicochemical properties of the fragments such as the number of HBD/HBA, HAC and AlogP were also generated in the Pipeline Pilot protocol.

As an example, the protocol was applied to a commercial fragment library from Maybridge containing 1000 compounds obeying the 'Rule of three'. A PMI analysis of this set of compounds would enable the 3-D shape of the fragments to be evaluated.[68] The 1000 compounds in the Maybridge fragment library were uploaded to the Pipeline Pilot protocol and a PMI analysis was carried out. The lowest energy ground state conformations of each of the 1000 Maybridge fragments are shown in the PMI plot in Figure 1.21. The large number of fragments being analysed meant that plotting all the conformations with a relative energy below 7 kcal mol^{-1} would have afforded a large number of points on the plot, making analysis of the PMI plot difficult. The PMI plot in Figure 1.21 shows that the majority of the fragments occupy the region along or very close to the rod-disc axis indicating that the library consists of 2-D fragments. The plot also shows that these ground state conformations occupy less than half of the 3-D chemical space. The most spherical fragment was tricyclic alcohol **61**. However, despite its spherical shape, fragment **61** lacks certain functionality compared to the other fragments which contain at least two different moieties, offering diversity and easily accessible growth vectors for the fragment. The structures of three fragments lying on or close to the rod-disc axis, namely amine **62**, amide **63** and methoxy

ether **64**, indicated each contained an aromatic ring and they are 2-D shaped. The main conclusion drawn from PMI analysis of the Maybridge fragment library was the large area of chemical space currently unoccupied and therefore under-represented within the library.

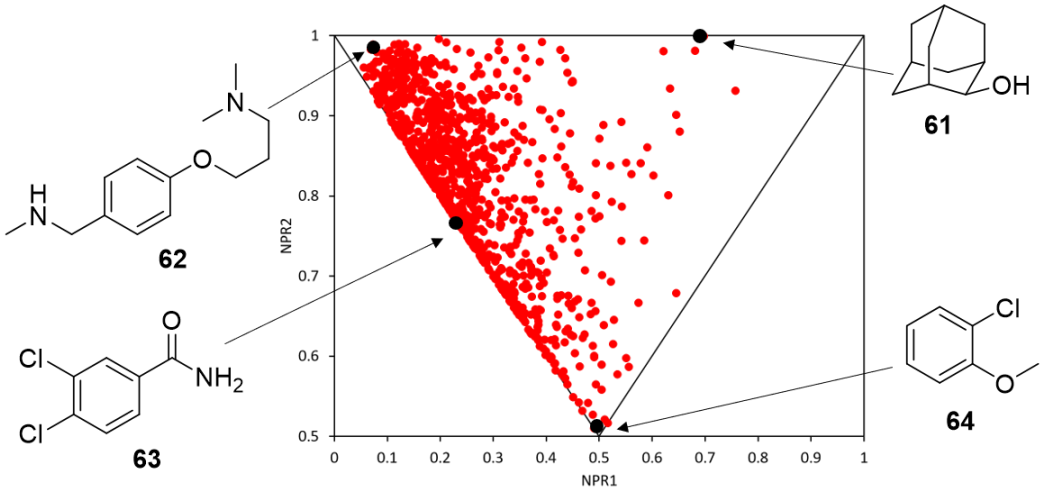


Figure 1.21 - PMI plot showing the ground state conformations of the 1000 Maybridge fragment library.

In order to access the regions of chemical space unoccupied within the Maybridge library, the previous work in the group focused on the design and selection of disubstituted pyrrolidine and piperidine fragments using the protocol developed within Pipeline Pilot to select compounds with the most 3-D conformations. The pyrrolidine ring is the fifth most popular saturated nitrogen heterocycle in FDA approved drugs.[69] Hence, pyrrolidines provide a good starting point for designing new 3-D fragments. For the initial set of fragments, the pyrrolidine scaffold was decorated with a methyl group and a methyl ester substituent. A methyl substituent provides a hydrophobic group and the methyl ester can engage in hydrogen bonding interactions, both of which could be important in protein-fragment binding interactions. The approach adopted in our group was to enumerate all the possible isomers of the pyrrolidine with these two substituents and then to use PMI analysis to select compounds for the synthetic work. Excluding enantiomers, there are 14 different isomers of a pyrrolidine with methyl and methyl ester substituents (Figure 1.22). However, the plan was to synthesise racemic mixtures of the fragments, as this would increase the size of the library and remove the need for asymmetric fragment synthesis which could prove challenging.

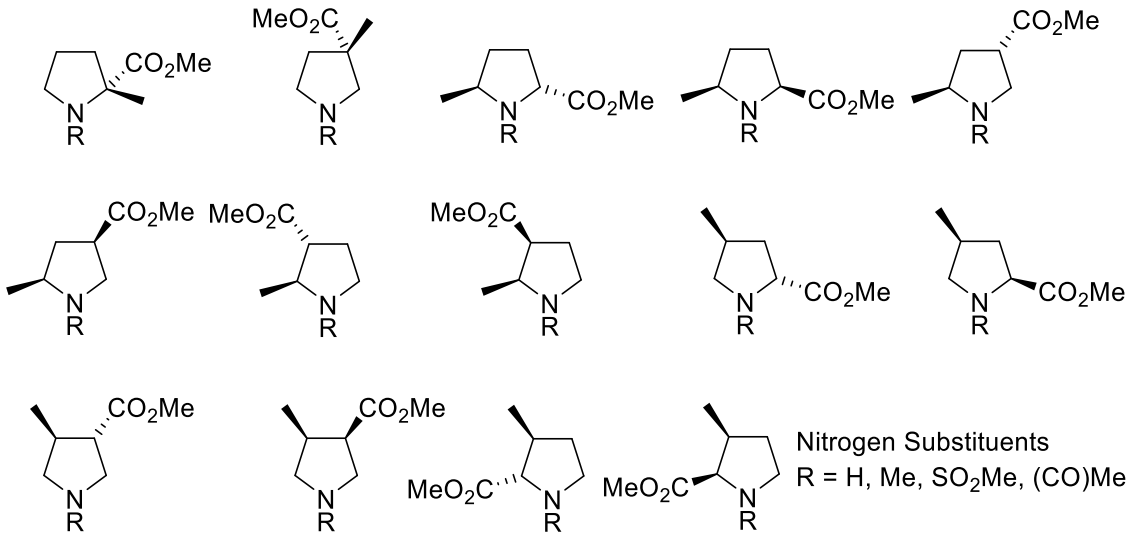


Figure 1.22 - 14 Pyrrolidine isomers gives 56 compounds with four different nitrogen substituents.

To introduce more structural diversity into the fragments, it was decided that the nitrogen would be functionalised in four different ways, so that the fragment would contain NH, NMe, NSO_2Me and N(CO)Me groups. It was envisaged that substituents could be easily installed onto the nitrogen using protecting group removal, reductive amination, mesylation or acylation. These substituents also provide potential for additional binding interactions with proteins. For example, the sulfonamide and amide can be involved in hydrogen bonding interactions and the amine, which will be protonated at physiological pH, can interact *via* electrostatic interactions and/or hydrogen bonding. In total, 56 pyrrolidine 3-D fragments were enumerated. The physicochemical properties were assessed to check whether the enumerated pyrrolidine fragments fitted within the Astex 'Rule of three' guidelines (see Section 1.1.1). Indeed, all the pyrrolidine fragments were compliant with the guidelines, having MW < 300, HBD/A < 3 and ClogP < 3. The MW and ClogP values are likely to increase during a lead optimisation process, with high ClogP values leading to poor aqueous solubility. Therefore, ClogP values < 3 allow for greater elaboration of hit compounds during optimisation.

The ground state PMI plot of the 56 pyrrolidine fragments are shown in Figure 1.23. The ground state conformations of the fragments are fairly spread over the plot, with few conformations in the top right apex which represents the most spherical fragments. Of note, none of the ground state conformations occupy the region near to the rod-disc axis which was the region densely occupied by the fragments in the Maybridge library (see Figure 1.21).

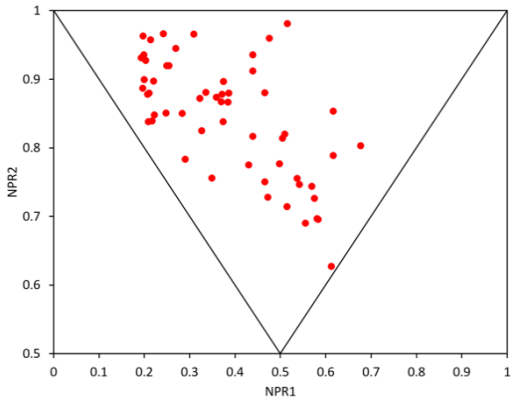
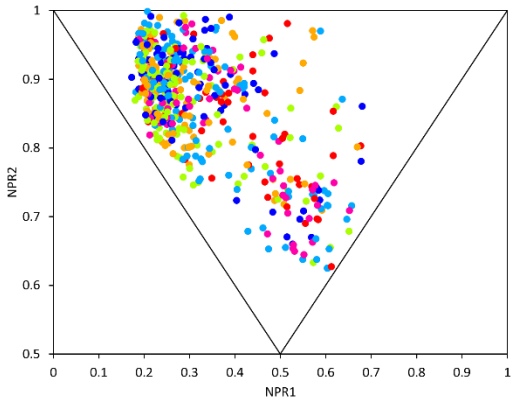


Figure 1.23 - PMI plot of the ground state conformations of the 56 pyrrolidine fragments.

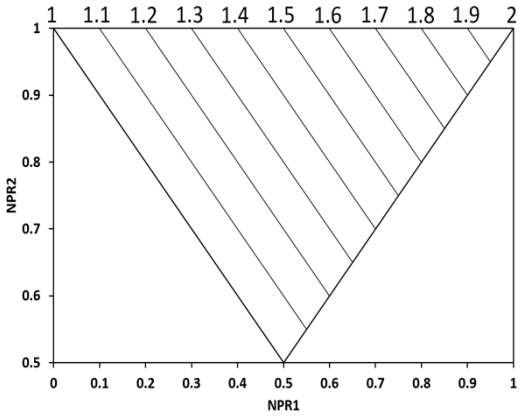
The 3-D shape of the pyrrolidine fragments was further analysed by considering a PMI analysis of all conformations with an energy of up to 1.5 kcal mol^{-1} above the energy of the ground state conformation for each molecule. The energy difference was selected based on a Boltzmann distribution calculation at physiological temperature, which revealed that the probability of the compounds occupying a conformation with an energy difference > 1.5 kcal mol^{-1} was < 8%. Considering conformations above the ground state conformation allows for conformational diversity and is appropriate since it is not necessarily the ground state conformation that will bind to the protein. The analysis gave a total of 582 conformations for the 56 fragments, which gave a wide spread across the PMI plot. The conformations did cluster near the top left apex suggesting that some of the conformations were flatter and possessed similar shapes (Figure 1.24).



Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

Figure 1.24 - PMI plot of the pyrrolidines with all conformations that have relative energy ≤ 1.5 kcal mol^{-1}.

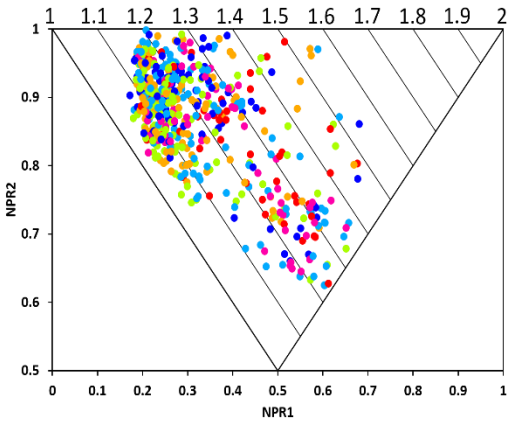
These 582 conformations were then used to select compounds for synthesis. Our intention was to identify compounds which had conformations as far away from the rod-disc axis as possible. This would allow us to target areas of fragment space that are under-represented in current fragment libraries. To identify compounds, the PMI plot was divided into 10 sections with lines parallel to the rod-disc axis (Figure 1.25). The diagonal lines correspond to the sum of NPR1 and NPR2 (ΣNPR) with ΣNPR = 1.00 describing the most rod-disc-like molecules and the region between 1.90-2.00 containing the most spherical molecules.



Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

Figure 1.25 - PMI plot showing the ΣNPR values

In order to select compounds for synthesis, the approach was to identity compounds with conformations in which the ΣNPR values were the highest. Figure 1.26 shows the 583 conformations on a PMI plot with the 10 sections of ΣNPR values highlighted. This PMI plot was used to select compounds and since it was felt unnecessary to synthesise all 56 compounds, a compromise between ΣNPR values and number of compounds was required. Thus, the region was analysed between ΣNPR values of 2.00-1.34. With ΣNPR ≥ 1.40, eight fragments would be selected for synthesis, which increased to 17 fragments when ΣNPR was set to ≥ 1.34 (Table 1.1). A closer inspection of the region between 1.40 to 1.34 was carried out in order to identify a suitable number of compounds for the initial synthetic work. Ultimately, an ΣNPR value of 1.36 was chosen and 14 fragments were selected, corresponding to 25% of the initially designed pyrrolidine fragments.



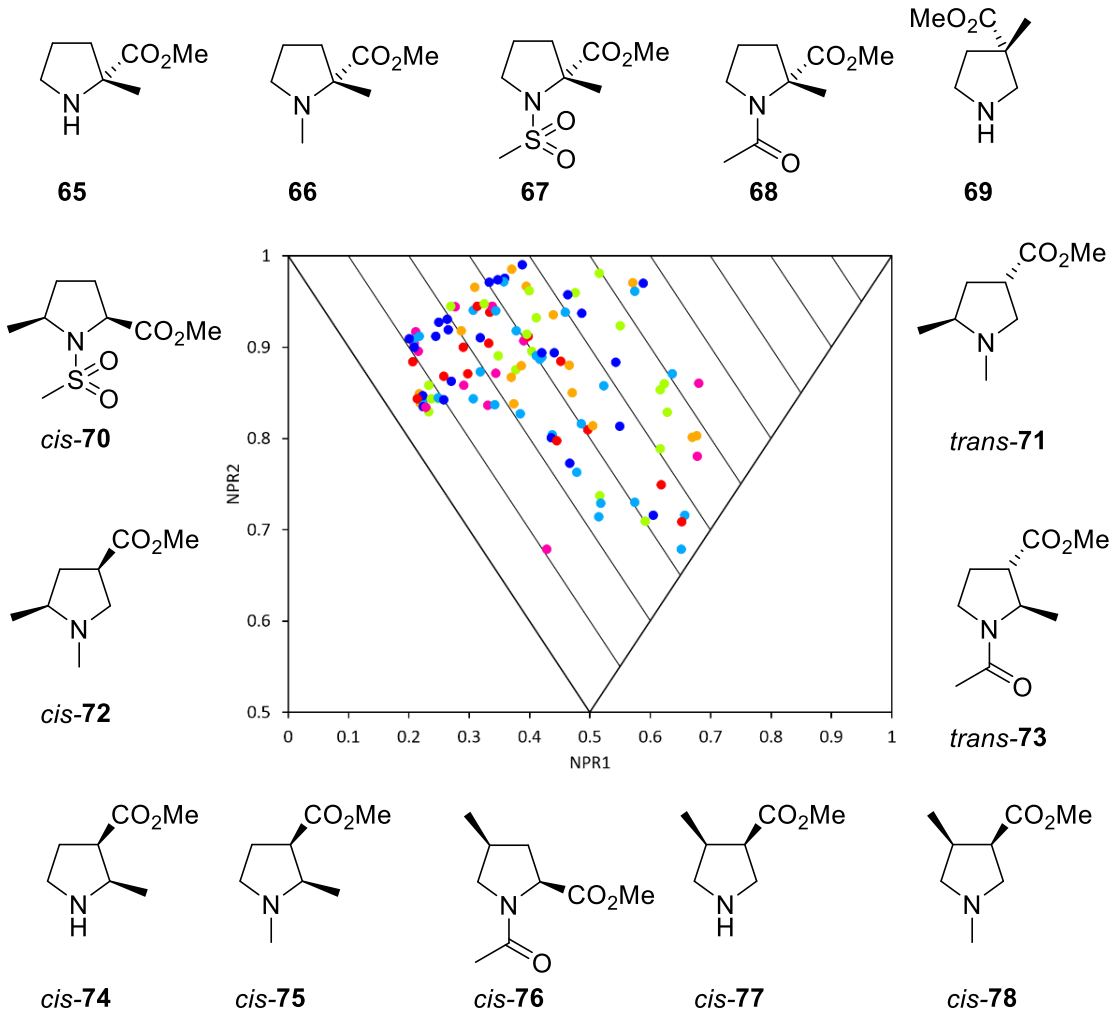
Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

Figure 1.26 - 582 Pyrrolidine conformations with a relative energy ≤ 1.5 kcal mol^{-1}.

ΣNPR value	**Number of Fragments**
≥ 1.40	8
≥ 1.39	9
≥ 1.38	9
≥ 1.37	10
≥ 1.36	14
≥ 1.35	15
≥ 1.34	17

Table 1.1 - Analysis of ΣNPR pyrrolidine values.

The selected 14 fragments have a total of 117 conformations with an energy of ≤ 1.5 kcal mol^{-1} above the ground state energy for each fragment; the structures of the fragments together with their associated PMI plot is shown in Figure 1.27. Each fragment has at least one conformation with a ΣNPR value ≥ 1.36. The fragments incorporate a range of regio- and diastereoisomers, with each of the four different nitrogen substituents present. Overall, the 14 selected fragments showed positional, stereochemical and functional group diversity, despite the relatively simple design criteria.



Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

Figure 1.27 - The selected 14 pyrrolidine fragments, and the PMI plot containing all of their 117 conformations with a relative energy ≤ 1.5 kcal mol^{-1}.

A similar design protocol and 3-D shape analysis was carried out with a set of piperidine fragments. In this set, the piperidine ring was decorated with a methyl group and a primary alcohol substituent. The primary alcohol was chosen instead of the methyl ester to help diversify the library, whilst keeping a hydrogen bonding group which would be useful for protein-fragment interactions. The piperidine scaffold was enumerated with the methyl and primary alcohol substituents to give 23 isomers. The nitrogen was substituted with NH, NMe, NSO_2Me and N(CO)Me, which afforded 92 fragments (Figure 1.28).

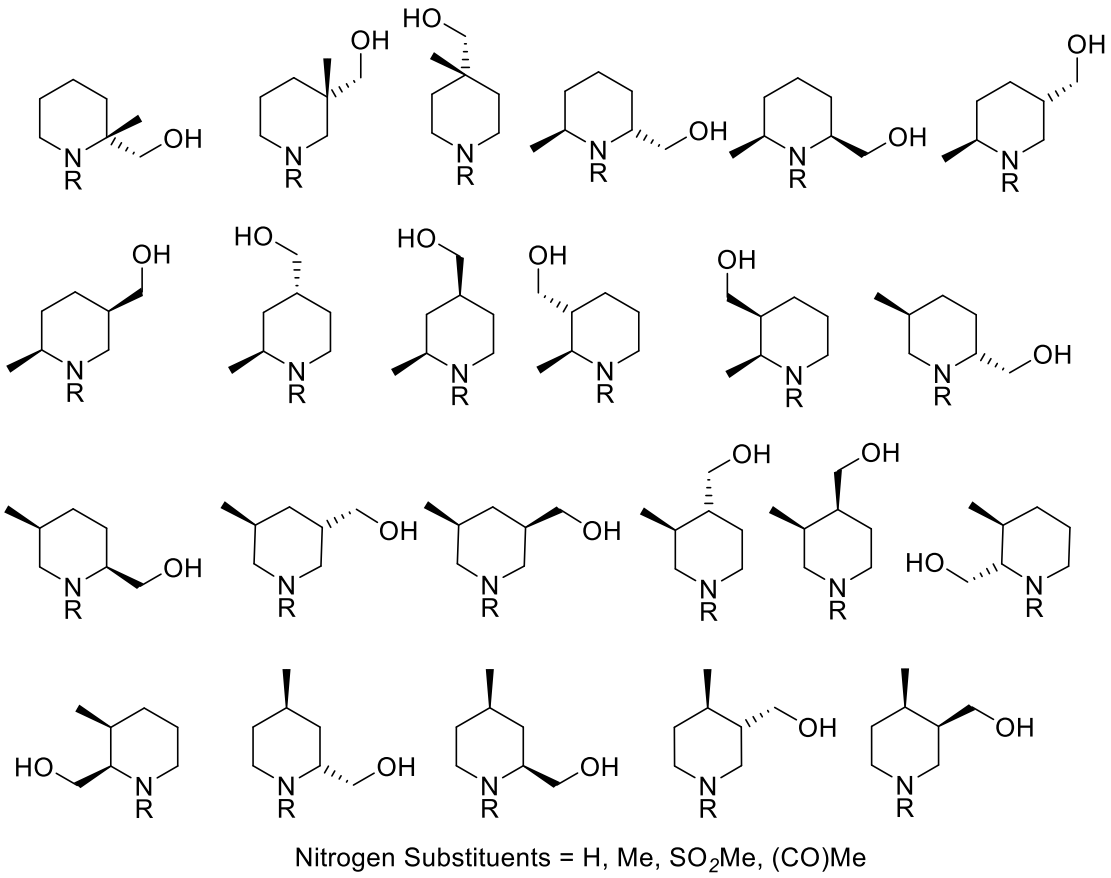


Figure 1.28 - 23 piperidine isomers gives 92 with four different nitrogen substituents.

The physicochemical properties were assessed, with the fragments all complying with the Astex 'Rule of three' guidelines. PMI analysis of the ground state energy of the 92 fragments (Figure 1.29) allowed comparisons to be made with the ground state conformations of the Maybridge library (see Figure 1.21). As with the pyrrolidine ground state conformations, none of the piperidine ground state conformations occupied the region along the rod-disc axis. The piperidine ground state conformations have a much more even spread across the plot compared to the ground state conformations of the 56 pyrrolidine fragments (see Figure 1.23). The piperidine conformations with a relative energy of ≤ 1.5 kcal mol^{-1} were assessed, which gave 373 conformations (Figure 1.30).

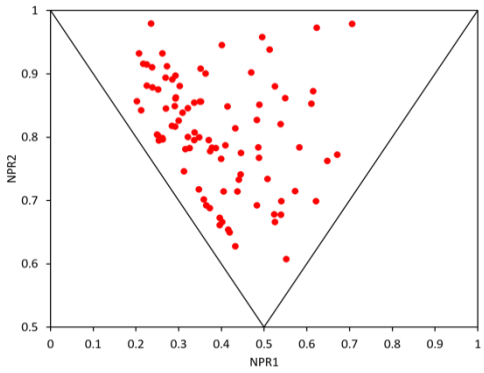
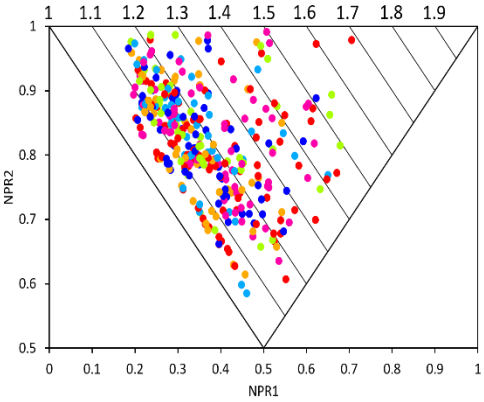


Figure 1.29 - PMI plot of the 92 ground state conformations.



Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

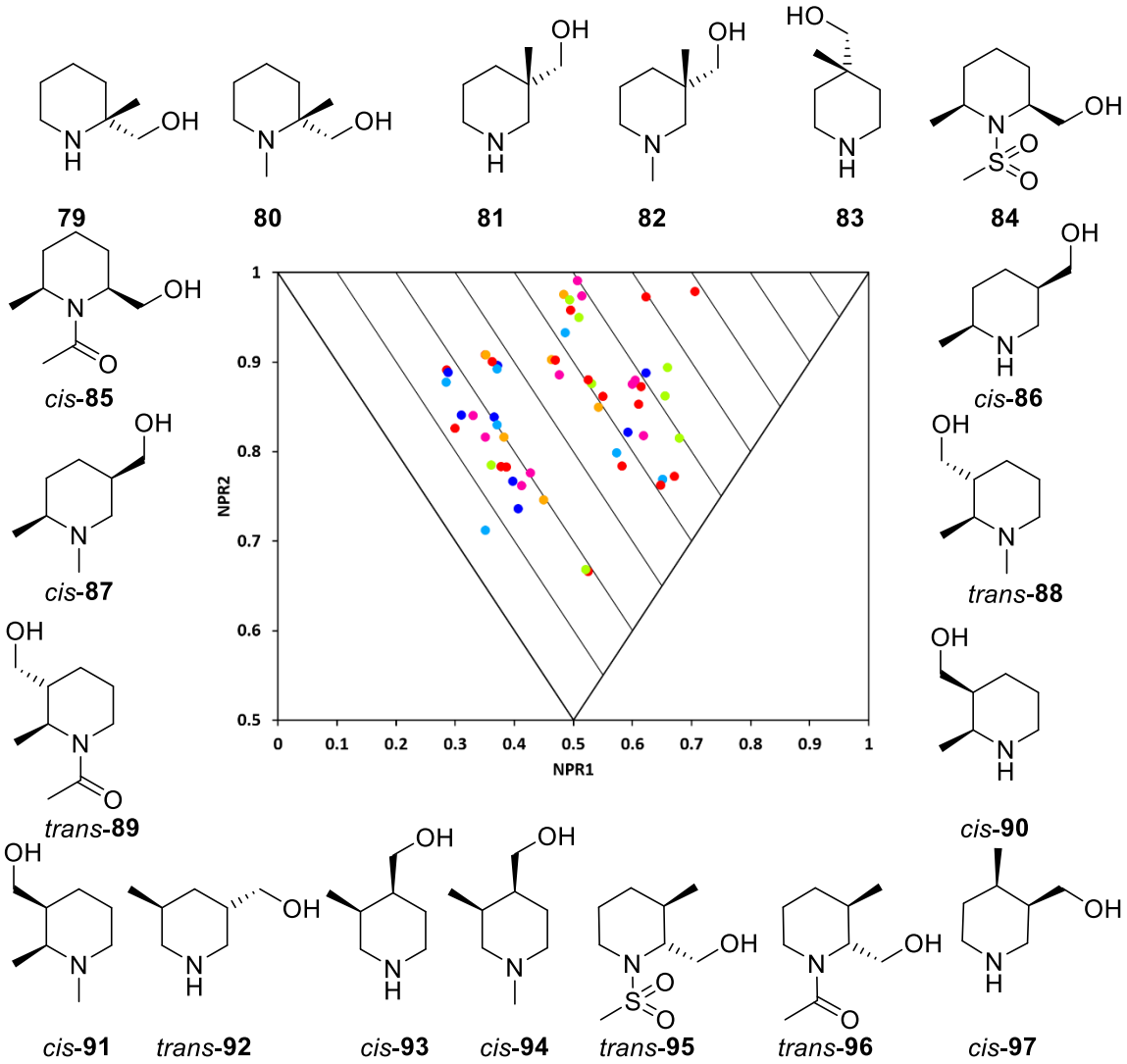
Figure 1.30 - PMI plot of the 373 conformations with relative energy ≤ 1.5 kcal mol^{-1}.

With 52 conformations lying above a ΣNPR value of 1.30 the region between ΣNPR values of 2.00-1.34 was assessed. When the ΣNPR was set to ≥ 1.4, 18 fragments were selected which increased to 28 fragments when the ΣNPR was set to ≥ 1.34, as shown in Table 1.2. Closer inspection of the region between 1.4 to 1.34 led to a ΣNPR value of ≥ 1.39 being selected affording 19 fragments, which was 20% of the initially designed piperidine fragments (Table 1.2).

ΣNPR value	Number of Fragments
≤ 1.4	18
≤ 1.39	19
≤ 1.38	19
≤ 1.37	23
≤ 1.36	24
≤ 1.35	26
≤ 1.34	28

Table 1.2 - Analysis of ΣNPR piperidine values

The 19 fragments gave a total of 58 conformations with a relative energy ≤ 1.5 kcal mol^{-1}. The 19 selected fragments show a similar structural diversity to that of the pyrrolidines (see Figure 1.27), with a range of regioisomers, diastereoisomers and *N*-substituents selected (Figure 1.31).



Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

Figure 1.31 – PMI plot of the selected 19 pyrrolidine fragments and all the conformations with a relative energy ≤ 1.5 kcal mol^{-1}.

In total, this PMI analysis led to 14 pyrrolidines and 19 piperidines being selected for synthesis and inclusion in the groups fragment library. Part of the work described later on within this PhD thesis is focussed on the development of synthetic routes to some of these pyrrolidine and piperidine fragments.

1.7 Project Outline

The long-term aim of this project is to build a fragment library of ~300 3-D compounds with shapes in the under-represented areas of 3-D space and to ultimately evaluate their protein binding properties. Following on from the previous work in the group outlined in Section 1.6, the design process will involve computational analysis of 3-D shapes using PMI plots to select compounds for synthesis. In order to occupy chemical space currently not covered by current fragment libraries, the plan was to select compounds with conformations which lie away from the rod-disc axis of the PMI plot.

The initial focus was placed on the synthesis of disubstituted pyrrolidine and piperidine fragments of the types shown in Figure 1.32, since such heterocycles are the first and fifth most popular nitrogen-containing saturated heterocycles within FDA approved drugs.[69] Previous analysis of the pyrrolidine and piperidine datasets had revealed that, despite our relatively simple design criteria, a range of shape-diverse fragments could be identified. Out of the 14 pyrrolidine and 19 piperidine fragments that were selected by the analysis, we focused our attention on the synthesis of the three pyrrolidines *trans*-**73**, *cis*-**74** and *cis*-**75** and the six piperidines *cis*-**84**, *cis*-**85**, *cis*-**86**, *cis*-**87**, *trans*-**95** and *trans*-**96** (Figure 1.33). The results of this part of the project are discussed in Chapter 2.

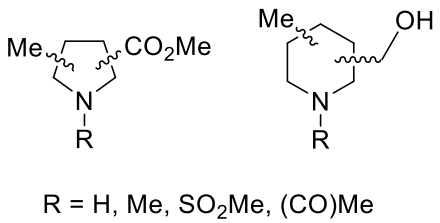


Figure 1.32 – Disubstituted pyrrolidines and piperidines with four differing nitrogen substituents.

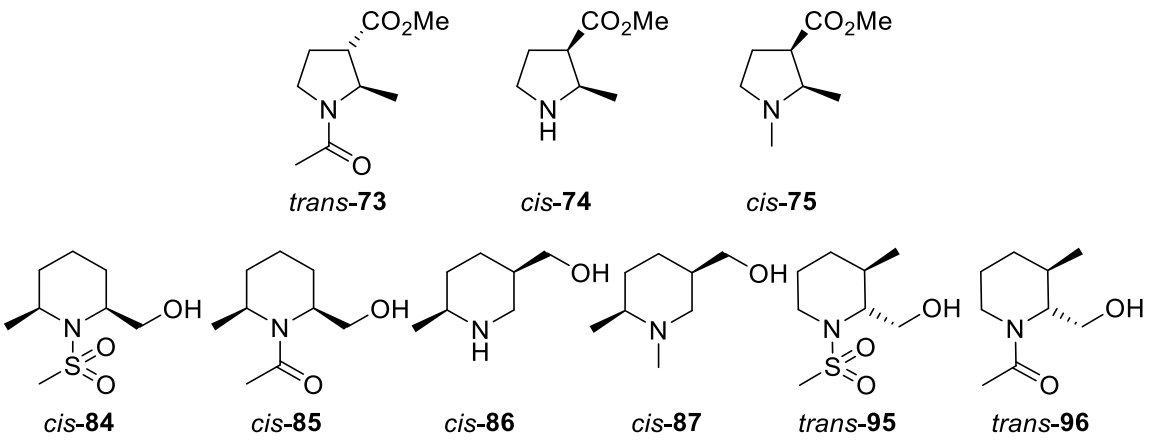
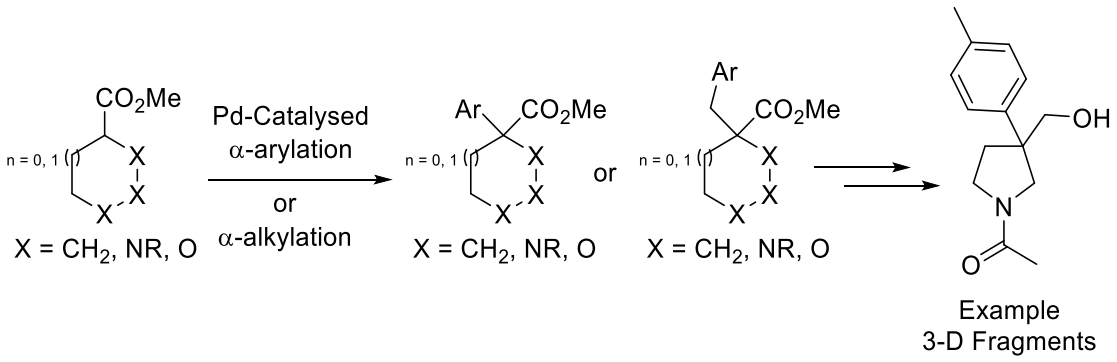


Figure 1.33 – Three pyrrolidine and six piperidine fragments.

Alongside the synthesis of specific fragments, we also explored whether it would be possible to develop some simple and general approaches for the synthesis of all of the possible 20 disubstituted piperidine regio- and diastereoisomers (excluding the geminal disubstituted piperidines). In the end, three different pieces of methodology were required to achieve our aim: pyridine hydrogenation, base-mediated epimerisation and lithiation-trapping and the results are described in Chapter 3.

As the project evolved, we identified some limitations in our design process. As a result, a different approach was adopted where there was a focus on two key transformations that could be applied to a wide range of scaffolds. This approach delivered a significant number of novel 3-D fragments with interesting PMI plot profiles in a short period of time. A key aspect of these fragments was that they contained aromatic functionality as this can help in fragment screening using ^{1}H NMR spectroscopy. An overview of our general approach is summarised in Scheme 1.28. The two main reactions that we focused on were ester enolate α-arylation and α-alkylation chemistry to install the required aromatic substituents. The results are presented in Chapter 4.



Scheme 1.28

Finally, we analysed the physicochemical properties of all the fragments within the library, and then compared the data against current commercial fragment libraries focusing on MW, HAC, Fsp^3 and ClogP. The main aim of our project was to design and synthesise fragments with shapes that are under-represented within current fragment libraries. Therefore, to validate the 3-D nature our library, we compared the PMI plot of our fragments with the PMI plots of commercial libraries, and other 3-D fragment libraries that were either commercially available or had been developed by academic groups. Our findings are described in Chapter 5.

Chapter 2 Synthesis of Disubstituted Pyrrolidine and Piperidine Fragments

In this Chapter, the development of methods for the synthesis of three of the designed pyrrolidine 3-D fragments and six of the designed piperidine 3-D fragments are described. The structures of the 3-D fragments that were the focus of our efforts are shown in Figure 2.1.

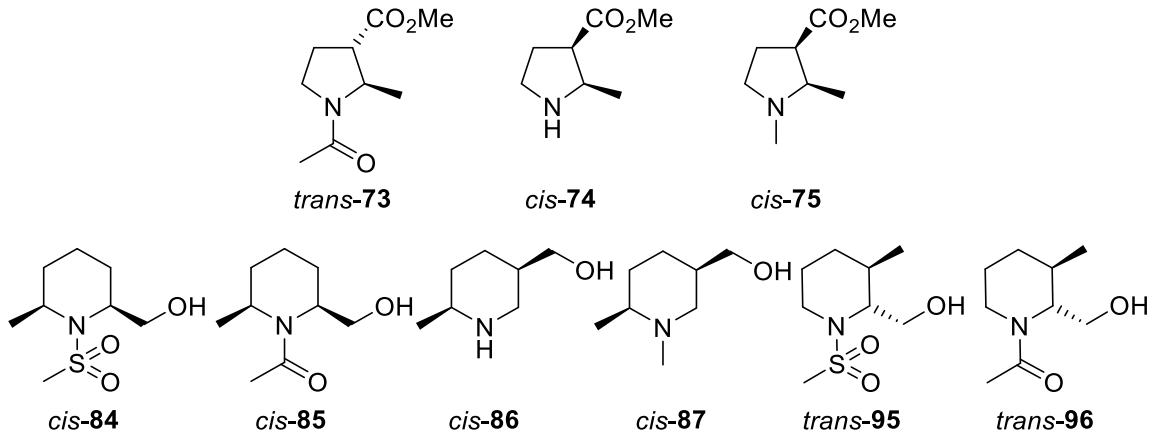
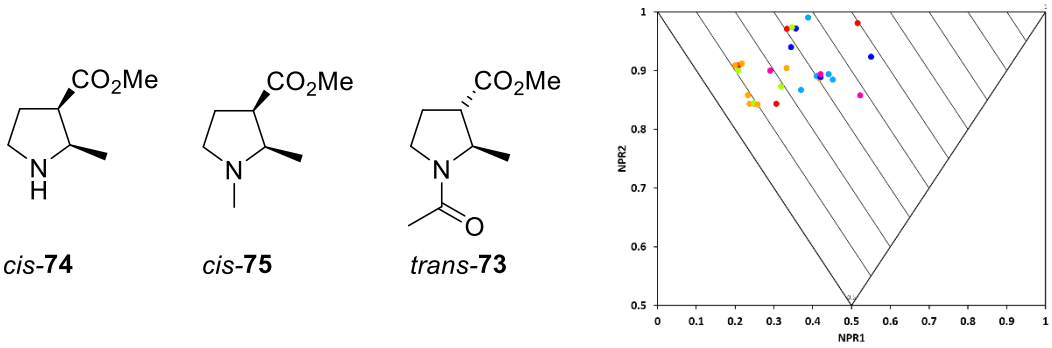


Figure 2.1 - Three pyrrolidine and six piperidine fragments.

Chapter 2.1 covers the synthesis of the pyrrolidine 3-D fragments, including an overview of the relevant background literature on approaches to *cis*- and *trans*-2,3-disubstituted pyrrolidines. The synthesis of the piperidine 3-D fragments and the related literature are described in Chapter 2.2. For each set of fragments, reduction chemistry was optimised for access to the *cis*-diastereoisomers. This was complemented by an epimerisation strategy to synthesise the corresponding *trans*-diastereoisomers.

2.1 Synthesis of 2,3-Disubstituted Pyrrolidine Fragments

The 14 selected pyrrolidine fragments were divided up for synthesis between the 3-D fragment team in the O'Brien group. The pyrrolidines that will be discussed within this section are the 2,3-disubstituted pyrrolidines *cis*-**74**, *cis*-**75** and *trans*-**73**. The PMI plot of their conformations with an energy that is ≤ 1.5 kcal mol^{-1} above the ground state energy is shown in Figure 2.2.



Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

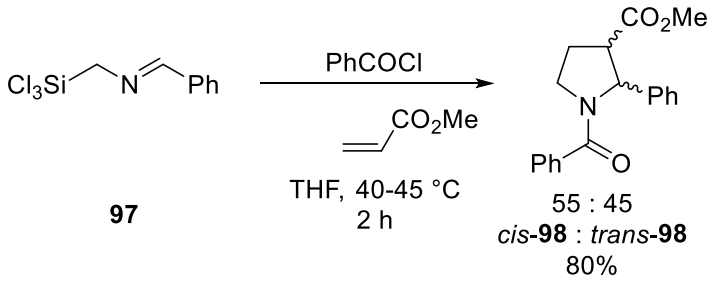
Figure 2.2 – Conformations of *cis*-**74**, *cis*-**75** and *trans*-**73**, which have a relative energy ≤ 1.5 kcal mol^{-1}.

2.1.1 Overview of Previous Approaches for the Synthesis of *cis*- and *trans*-2,3-Disubstituted Pyrrolidines

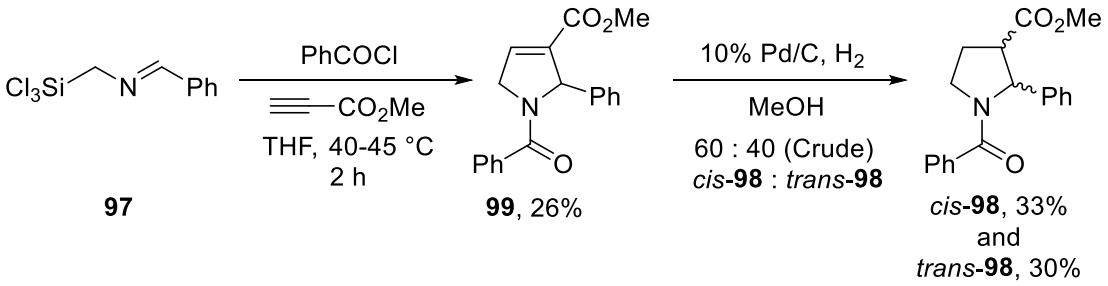
The three target fragments *cis*-**74**, *cis*-**75** and *trans*-**73** all contain 2,3-disubstitution, with *cis* or *trans* relative stereochemistry. In this section, an overview of previously described syntheses of 2,3-disubstituted pyrrolidines is discussed.

Sekiya *et al*. investigated a 1,3-dipolar cycloaddition route to *N*-acylated pyrrolidines and dihydropyrroles.[70] Disubstituted pyrrolidines *cis*-**98** and *trans*-**98** were synthesised directly *via* the reaction of imine **97** with methyl acrylate after the generation of the 1,3-dipole reagent from *N*-acylation and desilylation. However, the stereoselectivity was poor and a 55:45 mixture of pyrrolidines *cis*-**98** and *trans*-**98** was isolated in 80% yield (Scheme 2.1). An alternative two-step route is 1,3-dipolar cycloaddition with an alkyne to give a dihydropyrrole, which could be subsequently reduced to afford the pyrrolidine. This approach was also investigated and methyl propiolate was reacted with imine **97** to afford dihydropyrrole **99** in 26% yield. Reduction of dihydropyrrole **99** afforded a 60:40 mixture

of pyrrolidines *cis*-**98** and *trans*-**98** (Scheme 2.2).

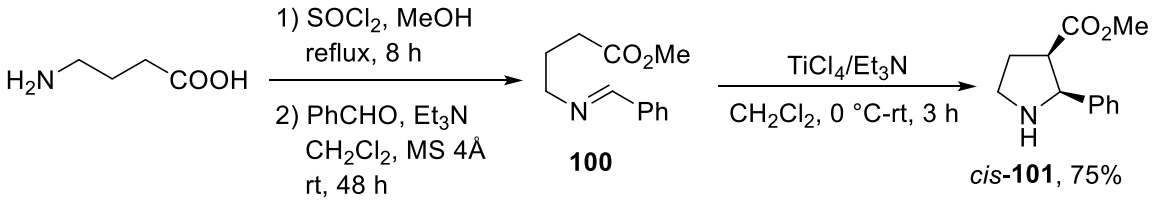


Scheme 2.1



Scheme 2.2

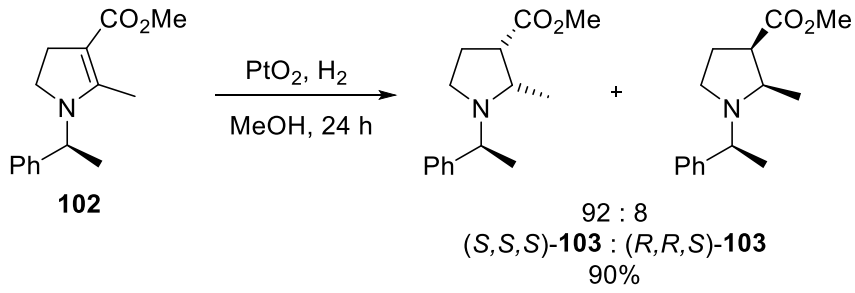
In 2004, Suresh and Periasamy reported a route for the synthesis of 2,3-disubstituted pyrrolidines such as *cis*-**101** *via* the stereoselective cyclisation of γ-imino esters using $TiCl_4/Et_3N$.[71] γ-Imino ester **100** was formed by esterification and imine formation. Subsequent reaction of γ-imino ester **100** with $TiCl_4/Et_3N$ gave pyrrolidine *cis*-**101** in 75% yield over three steps (Scheme 2.3). This reaction presumably involves nucleophilic attack of a titanium enolate onto the imine. The cyclisation reaction was repeated with five imines with different aromatic rings containing electron donating and withdrawing groups, affording pyrrolidines in 64-76% yields. The reactions each time gave purely the *cis*-diastereoisomer, making it a very attractive route to such *cis*-pyrrolidines.



Scheme 2.3

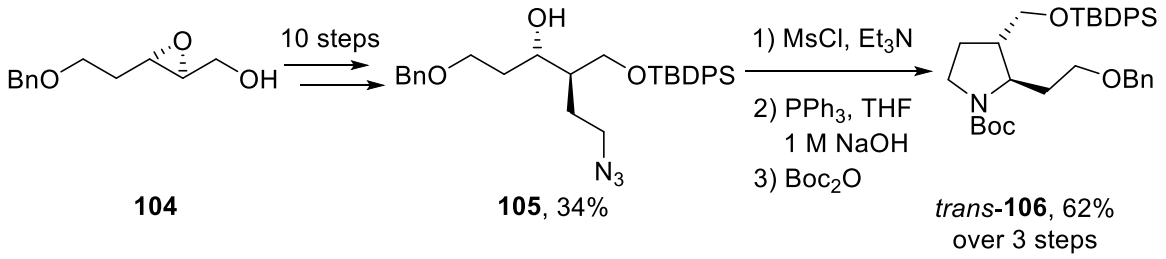
Another route to 2,3-disubstituted *cis*-pyrrolidine uses the stereoselective catalytic reduction of dihydropyrrole **102** reported by Gardette *et al.*[72] Hydrogenation of dihydropyrrole **102** with 10% Pd/C was found to be very slow, with removal of the *N*-α-methylbenzyl group occurring faster than the rate of hydrogenation. In contrast, use of PtO_2 as the catalyst

afforded a 92:8 mixture of (*S*,*S*,S)-**103** and (*R*,*R*,S)-**103** in 90% yield (Scheme 2.4).



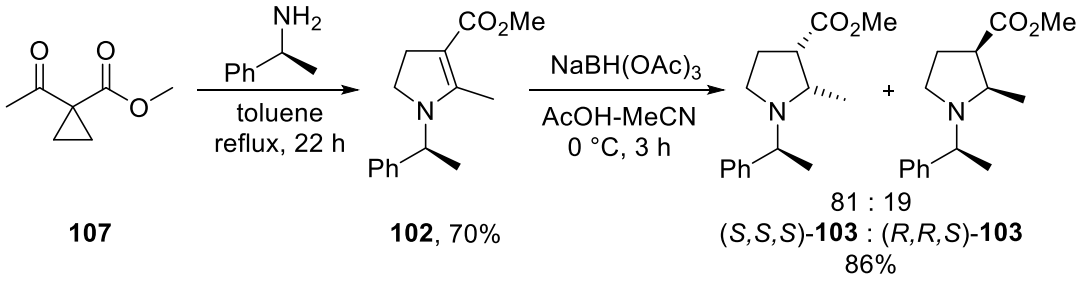
Scheme 2.4

Stereoselective routes to 2,3-disubstituted *trans*-pyrrolidines are also known. For example, Basu *et al*. reported a synthesis of pyrrolidine *trans*-**106** in 21% yield over 13 steps starting from epoxide **104** (Scheme 2.5).[73] The stereochemistry was set up at the start of the synthesis and retained throughout. Pyrrolidine formation was achieved through mesylation of alcohol **105**, followed by conversion of the azide into the amine and subsequent cyclisation to afford the *trans*-pyrrolidine. Boc protection of the secondary amine then gave pyrrolidine *trans*-**106**. The main disadvantage of this synthetic approach is the length of the overall route.



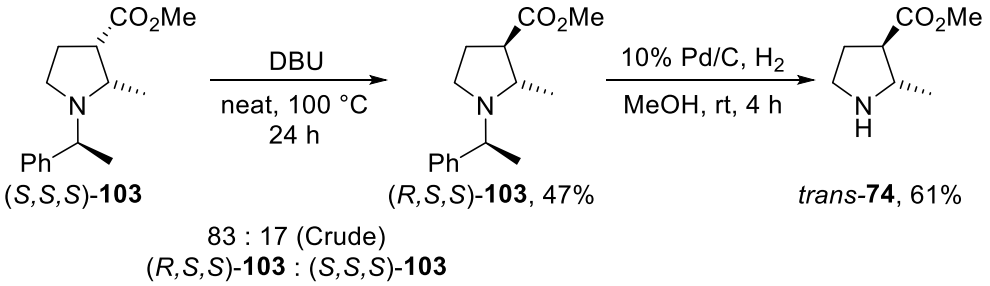
Scheme 2.5

A different synthetic route to 2,3-disubstituted *trans*-pyrrolidines was published by Zhang *et al*. starting from a 2,3-disubstituted *cis*-pyrrolidine, which had been previously synthesised by Gardette *et al.* Nucleophilic attack of (*S*)-α-methylbenzylamine on cyclopropane **107** and subsequent condensation gave dihydropyrrole **102** in 70% yield. Then, stereoselective reduction of dihydropyrrole **102** was achieved with $NaBH(OAc)_3$ to give the two *cis* diastereoisomers. Under these conditions, an 81:19 mixture of (*S*,*S*,*S*)-**103** and (*R*,*R*,*S*)-**103** was obtained in 86% yield (Scheme 2.6). The diastereoselectivity of this reduction reaction is slightly worse than that reported by Gardette *et al*. (see Scheme 2.4).



Scheme 2.6

In order to prepare the *trans*-pyrrolidine, pyrrolidine (*S*,*S*,*S*)-**103** was epimerised in neat DBU at 100 °C, which gave an 83:17 mixture of pyrrolidines (*R*,*S*,*S*)-**103** and (*S*,*S*,*S*)-**103**. Pyrrolidine (*R*,*S*,*S*)-**103** was isolated in 47% yield, with hydrogenolysis using 10% Pd/C being used to cleave the *N*-α-methylbenzyl group to give amine *trans*-**74** in 61% yield (Scheme 2.7).

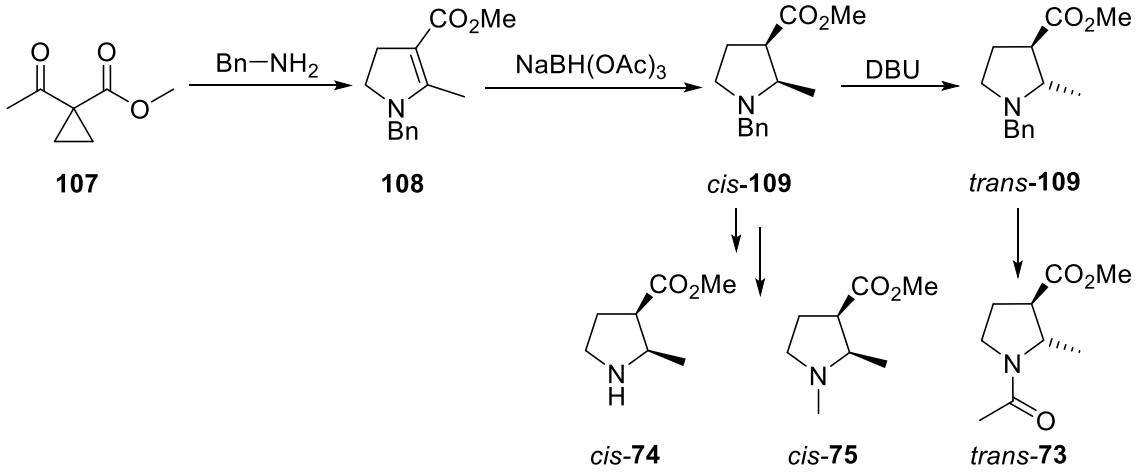


Scheme 2.7

The routes summarised here represent the main approaches that have been previously used for the synthesis of the 2,3-disubstituted *cis*- and *trans*-pyrrolidines. The 1,3-dipolar cycloaddition route described by Sekiya *et al.* lacked diastereoselectivity. In contrast, the titanium enolate methodology reported by Suresh and Periasamy was highly diastereoselective. However, in both of these routes, the examples only include an aromatic substituent α to the nitrogen. The most versatile approach is the one that proceeded *via* dihydropyrrole **102**. Using a combination of Gardette's and Zhang's work, access to both 2,3-disubstituted *cis*- and *trans*-pyrrolidines is possible. In addition, use of the α-methylbenzylamine chiral auxiliary would provide access to the enantiopure products and the methyl group α to the nitrogen in pyrrolidines (*S*,*S*,*S*)-**103** and (*R*,*S*,*S*)-**103** is exactly the substituent needed in the pyrrolidine fragments that were our initial targets.

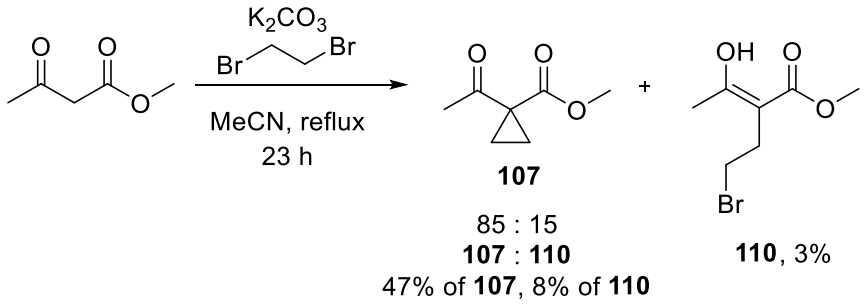
2.1.2 Synthesis of Pyrrolidine Fragments

Our initial plan for the synthesis of the target pyrrolidine 3-D fragments *cis*-**74**, *cis*-**75** and *trans*-**73** is set out in Scheme 2.8. It is based on the previous work reported by Gardette and Zhang. The route reported by Zhang *et al.* afforded the most promising route to the *trans*-pyrrolidine, whilst also affording access to the *cis*-pyrrolidine. (*S*)-α-Methylbenzylamine had been used in order to access single enantiomers. However, we only required access to the racemic *cis*- and *trans*-pyrrolidines since this would mean that both enantiomers for each diastereoisomer would be available for fragment screening. Therefore, we proposed to use benzylamine. Nucleophilic cyclopropane ring opening with benzylamine followed by condensation should afford dihydropyrrole **108**. Stereoselective reduction would hopefully give pyrrolidine *cis*-**109** which we anticipated could be epimerised to *trans*-**109** using Zhang's DBU conditions. Hydrogenolysis or hydrogenolysis/*N*-methylation of pyrrolidine *cis*-**109** should then generate fragments *cis*-**74** and *cis*-**75** respectively. Acylation of pyrrolidine *trans*-**109** should give pyrrolidine fragment *trans*-**73**.



Scheme 2.8

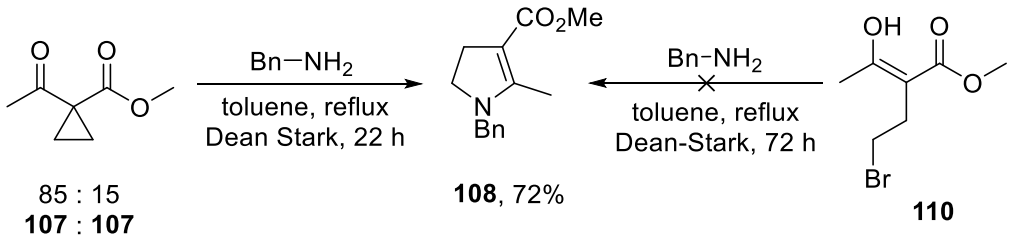
The synthesis of pyrrolidines *cis*-**74** and *cis*-**75** was initially targeted. Thus, methyl acetoacetate was reacted with 1,2-dibromoethane and K_2CO_3 in refluxing MeCN, adapted from the procedure by Zhang *et al.*[74] This afforded an 85:15 mixture of cyclopropane **107** and enol-bromide **110** as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. After purification, it was not possible to fully separate cyclopropane **107** and enol-bromide **110** and an 85:15 mixture of cyclopropane **107** and enol-bromide **110** was isolated. Based on this ratio and the isolated mass, a 47% yield of cyclopropane **107** was calculated for this reaction. Pure enol-bromide **110** was also isolated in 3% yield (Scheme 2.9).



Scheme 2.9

The observation of a reasonable amount of enol-bromide **110** indicated that the second alkylation was not going to completion. Attempts were made to force enol-bromide **110** to react further. For example, refluxing for 72 h or changing the base to Cs_2CO_3 was explored but this led to similar amounts of enol-bromide **110** being formed during the reaction.

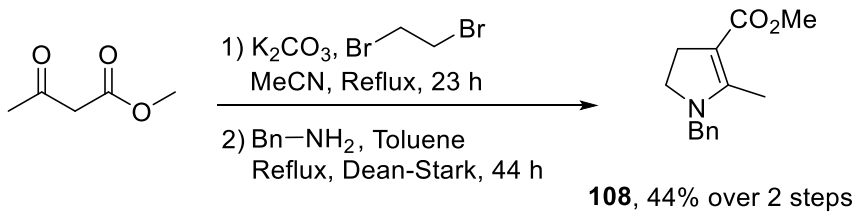
It is possible that reaction of enol-bromide **110** with benzylamine could afford dihydropyrrole **108**, which would mean that its formation is of no consequence for the next step of the synthesis. To explore this idea, enol-bromide **110** was reacted with benzylamine under reflux. However, this failed to yield any of the desired dihydropyrrole **108** (Scheme 2.10). Therefore, in the knowledge that enol-bromide **110** was unreactive with benzylamine, our attention turned to the next step, which was the nucleophilic ring-opening of cyclopropane **107** and subsequent condensation to afford dihydropyrrole **108**. Reaction of benzylamine with the 85:15 mixture of cyclopropane **107** and enol-bromide **110** in refluxing toluene gave dihydropyrrole **108** in 72% yield, calculated based on the amount of cyclopropane **107** present in the starting material (Scheme 2.10).



Scheme 2.10

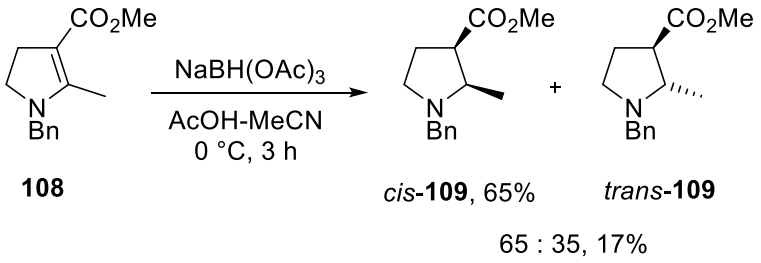
To streamline the synthesis of dihydropyrrole **108**, the first two steps were re-investigated in order to determine whether the dialkylation and dihydropyrrole steps could be telescoped. Thus, the crude mixture of cyclopropane **107** and enol-bromide **110** after the dialkylation step was taken through and subjected to reaction with benzylamine. This afforded a 44%

yield of dihydropyrrole **108** over two steps. This two-step process represents an improvement in the overall yield and a reduction in the time taken to synthesise dihydropyrrole **108** (Scheme 2.11).



Scheme 2.11

Zhang *et al.* achieved diastereoselective reduction of dihydropyrrole **102** using $NaBH(OAc)_3$ (see Scheme 2.6). Therefore, dihydropyrrole **108** was treated with $NaBH(OAc)_3$ in AcOH-MeCN and this gave an 85:15 mixture of pyrrolidines *cis*-**109** and *trans*-**109** as determined by ^1H NMR spectroscopic analysis. Purification by column chromatography gave pyrrolidine *cis*-**109** in 65% yield along with a 65:35 mixture of pyrrolidines *cis*-**109** and *trans*-**109** in 17% yield (Scheme 2.12). The stereoselective reduction of dihydropyrrole **108** can be explained by the formation of iminium ion **111** and preferential reduction on the face opposite to the sterically bulky methyl ester in **111** (Figure 2.3). The stereochemistry was proven by X-ray crystallography of a sulfonamide derivative synthesised from pyrrolidine *cis*-**109** (see Figure 2.4).



Scheme 2.12

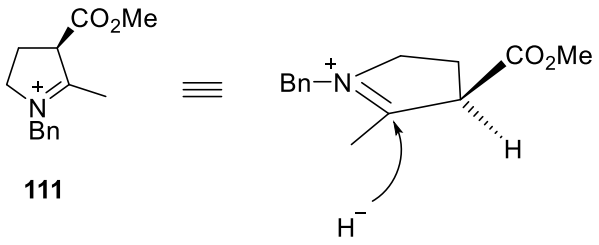
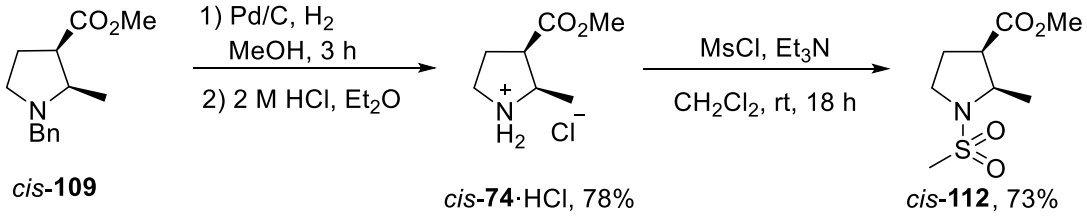


Figure 2.3 – Stereoselective reduction *via* hydride addition on the opposite face to the ester.

Hydrogenolysis of *N*-benzyl pyrrolidine *cis*-**109** would afford the first 3-D fragment, pyrrolidine *cis*-**74**. Treatment of pyrrolidine *cis*-**109** with 10% Pd/C and H_2 in MeOH gave pyrrolidine *cis*-**74**. However, upon attempted isolation of pyrrolidine *cis*-**74** in the work-up, we observed a low mass recovery. Given the low molecular weight of *cis*-**74**, we realised that it is likely to be somewhat volatile and was probably lost during the rotary evaporation step. Therefore, the hydrogenolysis was repeated and after removal of the Pd/C catalyst by filtration, a 2 M solution of HCl in Et_2O was added and rotary evaporation gave pyrrolidine *cis*-**74**·HCl directly, which was isolated in 78% yield (Scheme 2.13). The *cis* relative stereochemistry in *N*-benzyl pyrrolidine *cis*-**74** was proven by converting pyrrolidine *cis*-**74**·HCl into a crystalline derivative. Reaction of pyrrolidine *cis*-**74**·HCl with mesyl chloride and Et_3N afforded sulfonamide pyrrolidine *cis*-**112** in 73% yield. A crystal of sulfonamide pyrrolidine *cis*-**112** suitable for X-ray crystallography was grown and the *cis*-stereochemistry was confirmed (Figure 2.4).



Scheme 2.13

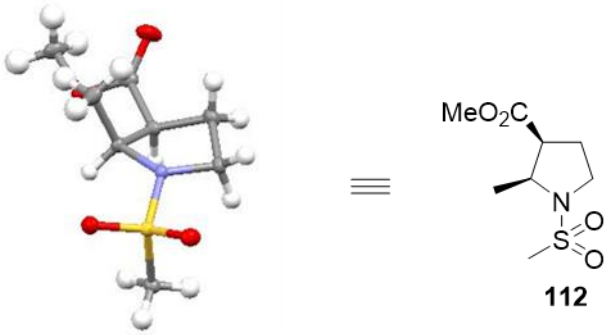
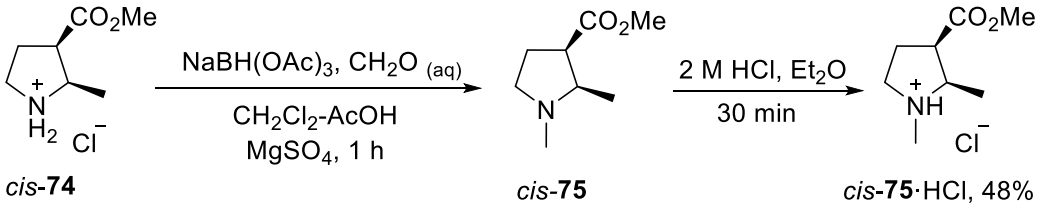


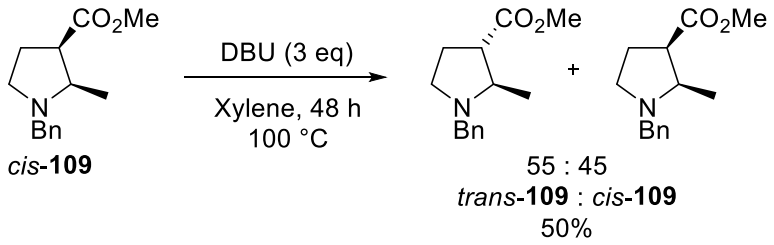
Figure 2.4

Access to *N*-methyl pyrrolidine *cis*-**75** was also required. Using a reductive amination procedure developed in the group, pyrrolidine *cis*-**74**·HCl was reacted with aqueous formaldehyde and $NaBH(OAc)_3$ in the presence of $MgSO_4$ to afford *N*-methyl pyrrolidine *cis*-**75**. However, due to the anticipated volatility of this compound, *N*-methyl pyrrolidine *cis*-**75** was taken through after work-up and stirred in 2 M HCl in Et_2O. This gave *N*-methyl pyrrolidine *cis*-**75**·HCl in 48% yield over two steps (Scheme 2.14).



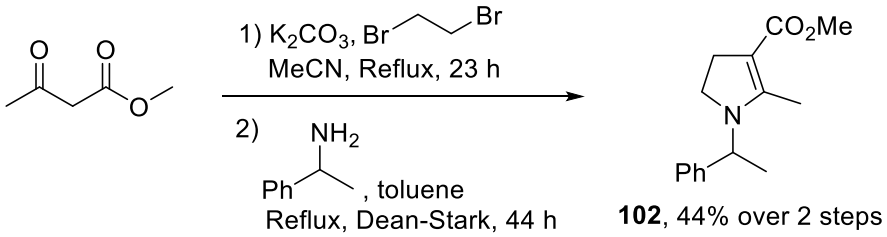
Scheme 2.14

With the successful synthesis of the two *cis*-pyrrolidine fragments, our attention switched to the synthesis of pyrrolidine *trans*-**73** for which, as outlined earlier (see Scheme 2.8), an epimerisation strategy would be explored. We decided to use the base-mediated epimerisation conditions outlined by Zhang *et al*. (see Scheme 2.7). In our hands, 3.0 equivalents of DBU in xylene were used instead of neat DBU, due to the unworkably small quantity of DBU that would be required. Reaction of pyrrolidine *cis*-**109** with DBU gave a 55:45 mixture of pyrrolidine *trans*-**109** and *cis*-**109** (by ^{1}H NMR spectroscopy of the crude reaction mixture). Unfortunately, it was not possible to separate the two diastereoisomers despite trialling multiple solvent systems (Scheme 2.15).



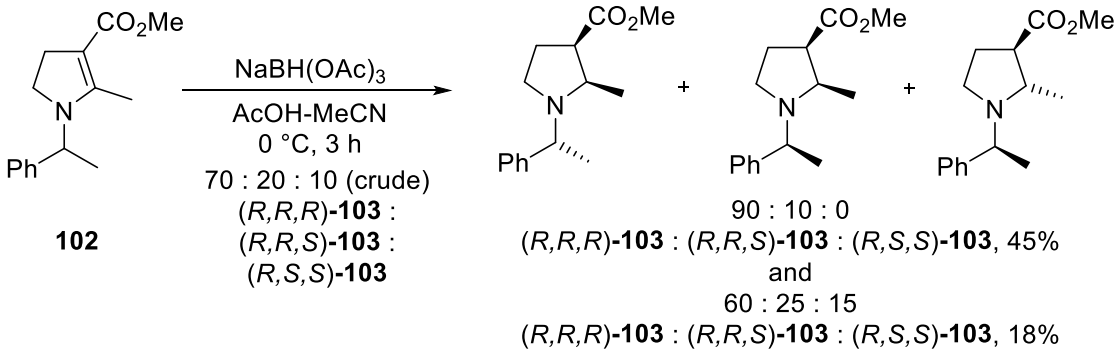
Scheme 2.15

The difficulty in separation of the two diastereoisomers, and the poor diastereoselectivity for *trans*-**109** after epimerisation, led us to use Zhang's α-methylbenzylamine-derived dihydropyrrole **102**. Thus, racemic α-methylbenzylamine was used as the nucleophile for the ring opening and subsequent intramolecular condensation. The telescoped two-step reaction afforded dihydropyrrole **102** in 44% yield (Scheme 2.16).



Scheme 2.16

Dihydropyrrole **102** was reduced using $NaBH(OAc)_3$ under the standard conditions. The ^1H NMR spectrum of the crude product showed a 70:20:10 mixture of pyrrolidine (*R*,*R*,*R*)-**103**, (*R*,*R*,*S*)-**103** and (*R*,*S*,*S)*-**103** (Figure 2.5). The methyl ester singlet appears at 3.69 ppm peak for (*R*,*S*,*S*)-**103**, at 3.67 ppm for (*R*,*R*,*R*)-**103** peak and at 3.63 ppm for (*R*,*R*,*S*)-**103**. Purification afforded a 45% yield of a 90:10 mixture of pyrrolidines (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103**, together with a 60:25:15 mixture of pyrrolidines (*R*,*R*,*R*)-**103**, (*R*,*R*,*S*)-**103** and (*R*,*S*,*S*)-**103** in 18% yield (Scheme 2.17). The stereochemistry of these three diastereoisomers was assigned by comparison of the NMR spectroscopic data with those reported by Zhang *et al*.[74]



Scheme 2.17

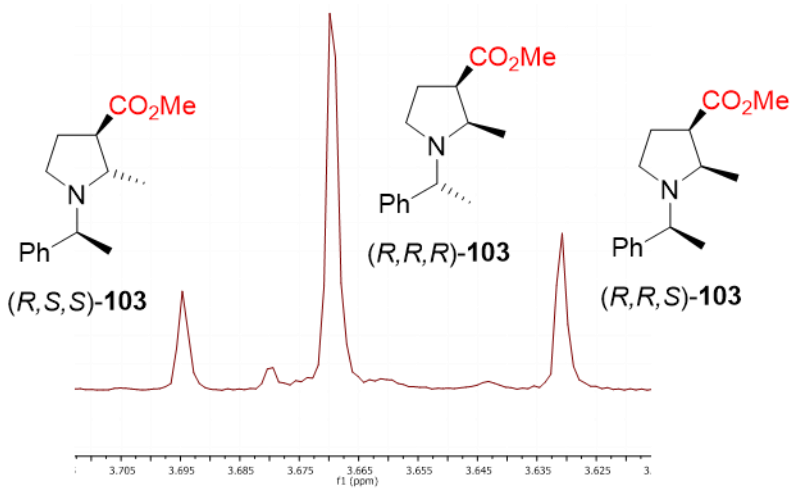
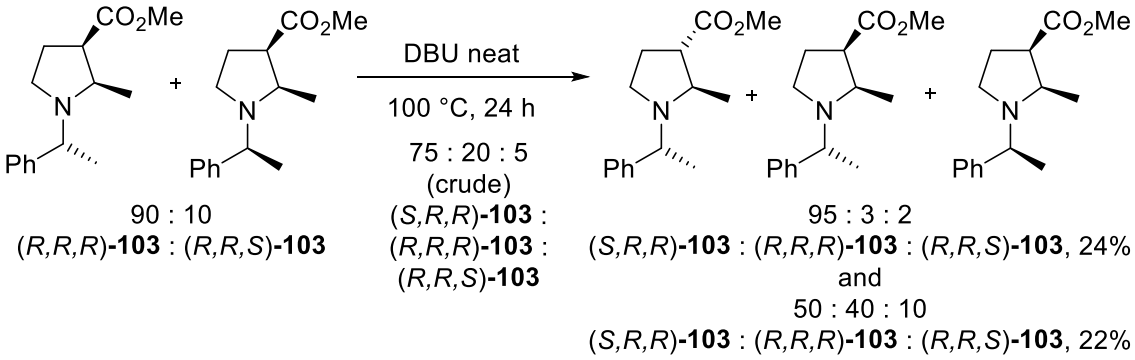


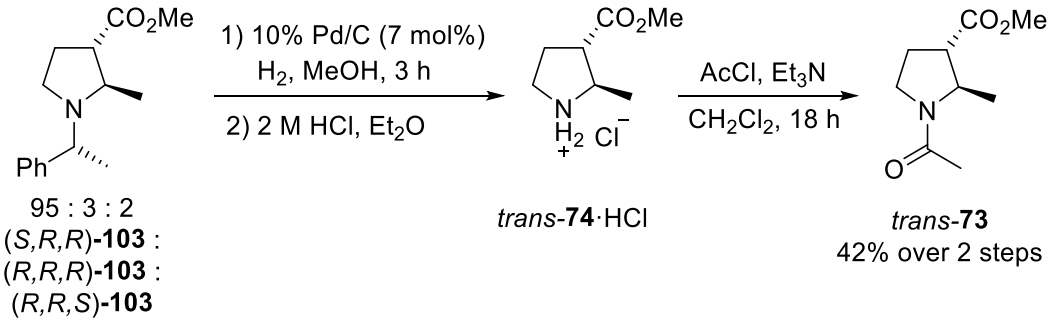
Figure 2.5 – ^{1}H NMR spectrum of a 70:20:10 mixture of (*R*,*R*,*R*)-**103**, (*R*,*R*,*S*)-**103** and (*R*,*S*,*S*)-**103**.

Epimerisation was then attempted by reacting the 90:10 mixture of pyrrolidines (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103** with neat DBU at 100 °C for 48 h. The crude reaction mixture contained a 75:20:5 mixture of pyrrolidines (*S*,*R*,*R*)-**103**, (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103**, demonstrating that a good degree of epimerisation had occurred. Separation of the diastereoisomers *via* column chromatography was not straightforward and gave a 95:3:2 mixture of pyrrolidines (*S*,*R*,*R*)-**103**, (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103**, in 24% yield, and a 50:40:10 mixture of pyrrolidines (*S*,*R*,*R*)-**103**, (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103**, in 22% yield (Scheme 2.18).



Scheme 2.18

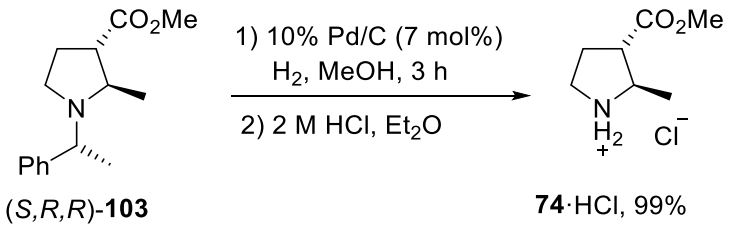
The last two steps in the synthesis of pyrrolidine fragment *trans*-**73** proceeded uneventfully. Hydrogenolysis with Pd/C and H_2 in MeOH removed the α-methylbenzyl to give pyrrolidine *trans*-**74**·HCl as the major component after treatment with 2 M HCl in Et_2O. Pyrrolidine *trans*-**74**·HCl was then acylated with acetyl chloride in the presence of Et_3N, which gave *N*-acyl pyrrolidine *trans*-**73** in 42% yield over two steps (Scheme 2.19).



Scheme 2.19

An important consideration with fragments that are stored as part of a library is their long-term stability in DMSO solution, as this is typically how they are stored. Thus, the stability of pyrrolidine fragments *cis*-**74**·HCl, *cis*-**75**·HCl and *trans*-**73** was inspected by dissolving 2 mg of each fragment in d_6-DMSO (2 mL). The samples were then analysed by ^{1}H NMR spectroscopy every two weeks in order to explore whether any degradation due to instability had occurred. *N*-Methyl pyrrolidine *cis*-**75**·HCl and *N*-acetyl pyrrolidine *trans*-**73** showed no stability issues after six weeks. However, on inspection of the sample of NH pyrrolidine *cis*-**74**·HCl in DMSO, after initially making up the solution, we noticed the presence of a small amount of a second methyl doublet (occurring at 1.22 ppm) in the ^{1}H NMR spectrum. It was initially considered that this signal could be due to partial epimerisation of pyrrolidine *cis*-**74**·HCl to pyrrolidine *trans*-**74**·HCl. Therefore, for comparison, pyrrolidine *trans*-

74·HCl was synthesised starting from pyrrolidine (*S*,*R*,*R*)-**103**. Hydrogenolysis of (*S*,*R*,*R*)-**103** with 10% Pd/C under H_2, and subsequent treatment with 2 M HCl in Et_2O gave pyrrolidine *trans*-**74**·HCl in 99% yield (Scheme 2.20).



Scheme 2.20

The ^{1}H NMR spectra of the aged sample of pyrrolidine *cis*-**74**·HCl and the freshly synthesised *trans*-**74**·HCl were compared (Figure 2.6). For pyrrolidine *trans*-**74**·HCl, there was a methyl doublet at 1.34 ppm and the C*H*CO_2Me appeared at 2.89 ppm. Both of these signals were not present in the aged sample of pyrrolidine *cis*-**74**·HCl which clearly indicated that epimerisation of *cis*-**74**·HCl had not occurred.

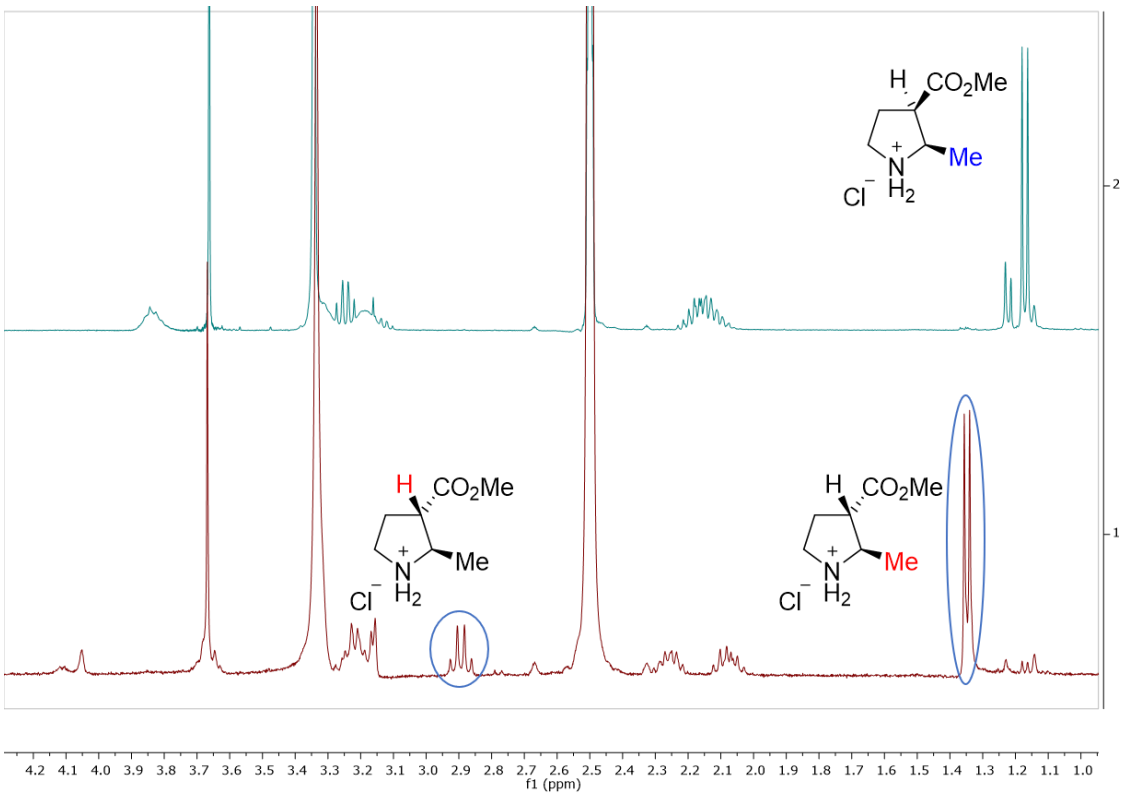


Figure 2.6 - ^{1}H NMR spectra of pyrrolidine *cis*-**74**·HCl (blue) and pyrrolidine *trans*-**74**·HCl (red).

We also considered whether the instability of pyrrolidine *cis*-**74**·HCl was due to hydrolysis of the ester to a carboxylic acid. Analysis of the downfield region of the ^{1}H NMR spectrum

of the aged sample of *cis*-**74**·HCl revealed that there were two signals at 9.74 pm and 8.80 ppm corresponding to the two NH protons and a third signal at 12.91 ppm. The 12.91 ppm signal was found to integrate to 1H with the signal at 1.22 ppm set to 3H integration. Signals within this region are usually associated with the hydroxy group of a carboxylic acid, supporting the suggestion that *cis*-**74**·HCl had partially hydrolysed to the carboxylic acid (Figure 2.7).

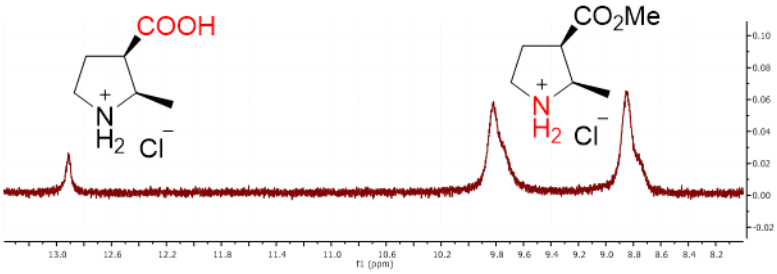
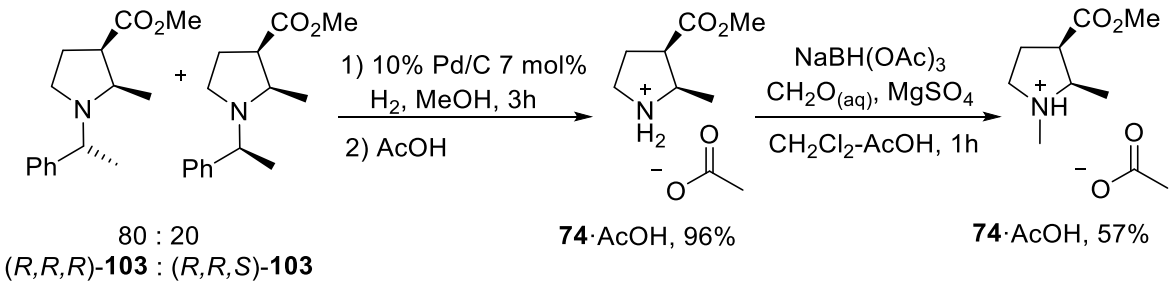


Figure 2.7 - The downfield region of the 1H NMR spectrum of **74**·HCl showing the two NH protons right, and the hydroxy signal left.

As a result of these findings, pyrrolidine fragments *cis*-**74** and *cis*-**75** were re-synthesised and converted into AcOH salts for long-term storage. In this case an 80:20 mixture of pyrrolidine (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103** was reacted with H_2 and 10% Pd/C followed by treatment with AcOH to afford pyrrolidine *cis*-**103**·AcOH in 96% yield. Reductive amination of pyrrolidine *cis*-**74**·AcOH gave pyrrolidine *cis*-**74**·AcOH in 57% yield (Scheme 2.21). The stability of pyrrolidines *cis*-**74**·AcOH and *cis*-**74**·AcOH was assessed by dissolving 2 mg of each fragment in d_6-DMSO (2 mL). Analysis of the ^{1}H NMR spectrum after six weeks showed that no ester hydrolysis or epimerisation of the pyrrolidines had occurred.

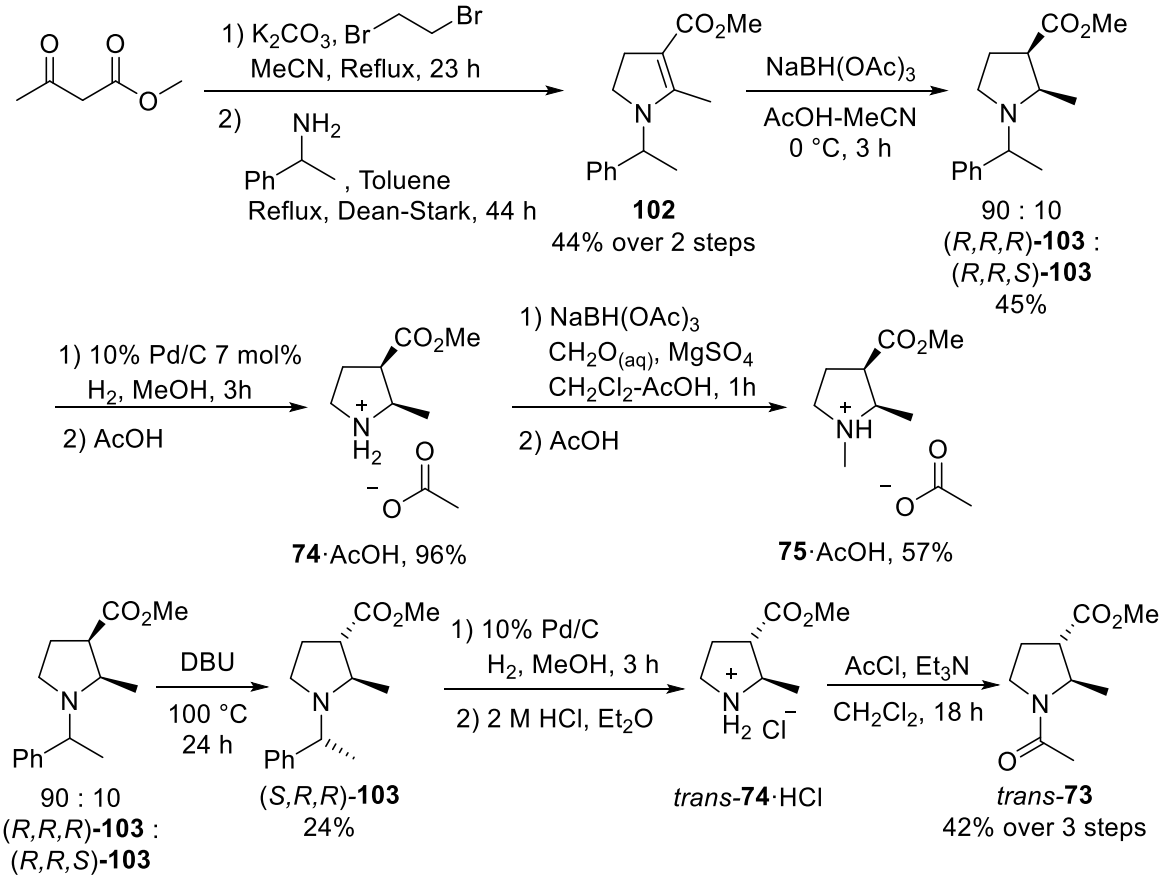


Scheme 2.21

2.1.3 Conclusion

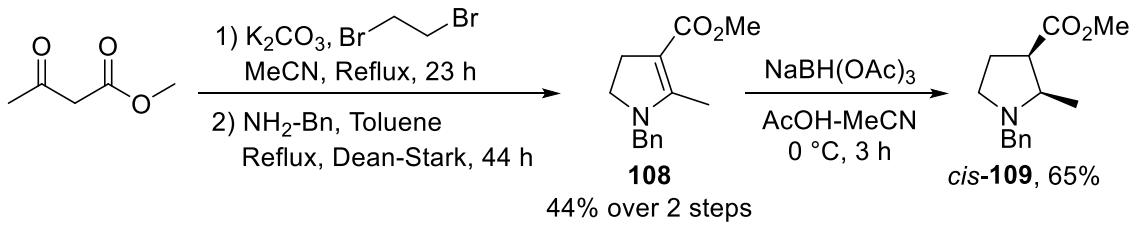
Previous work by Gardette *et al.* and Zhang *et al.* had offered routes to access pyrrolidine 3-D fragments *cis*-**74**, *cis*-**75** and *trans*-**73**. Telescoping the first two steps to obtain dihydropyrrole **108** avoided the difficult separation of cyclopropane **107** and enol-bromide **110** formed from the monoalkylation of dibromoethane. Hydrogenolysis or hydrogenolysis/*N*-methylation then gave the NH and *N*-methyl fragments, which were stored as the AcOH salts due to the volatility and stability issues we had encountered.

The synthesis of pyrrolidine *trans*-**73** used the base-mediated approach outlined by Zhang *et al.* Epimerisation with the inclusion of the *N*-benzyl substituent afforded marginal selectivity for the *trans*-pyrrolidine. However, the inclusion of the *N*-α-methylbenzyl substituent aided the separation of the diastereoisomers and gave pyrrolidine (*S,R,R*)-**103** in 24% yield with 95% purity. Hydrogenolysis, HCl salt formation and acylation gave pyrrolidine *trans*-**73** in 42% yield over the three steps (Scheme 2.22).



Scheme 2.22

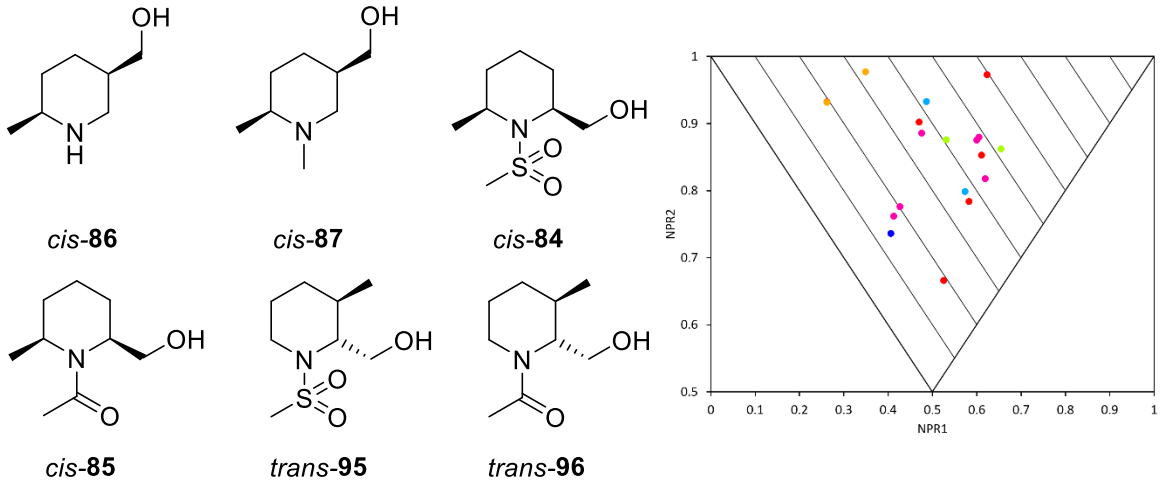
Synthesis of the three pyrrolidine 3-D fragments was possible using the route outlined above in Scheme 2.22. However, we observed that the reduction of *N*-benzyl dihydropyrrole **108** gave a higher yield of pyrrolidine *cis*-**109** compared to the reduction of *N*-α-methylbenzyl dihydropyrrole **102**. Pyrrolidine *cis*-**109** was isolated in 65% yield (see Scheme 2.23), whereas reduction of *N*-α-methylbenzyl dihydropyrrole **102** afforded a 90:10 mixture of pyrrolidine (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103** in 45% yield. Therefore, a higher yielding route to the *cis*-pyrrolidine fragments was achievable using *N*-benzyl dihydropyrrole **108**.



Scheme 2.23

2.2 Synthesis of 2,5-, 2,3- and 2,6-Disubstituted Piperidine Fragments

The 19 selected piperidine fragments were synthesised by different members of the O'Brien group. In this section, the syntheses of disubstituted piperidines *cis*-**86**, *cis*-**87**, *cis*-**84**, *cis*-**85**, *trans*-**95** and *trans*-**96** are discussed. The PMI plot for these six fragments (up to an energy of 1.5 kcal mol^{-1} above the ground state) showed that all of their conformations occupied different regions of chemical space, suggesting broad shape diversity of the conformations (Figure 2.8).



Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

Figure 2.8 – Conformations of *cis*-**86**, *cis*-**87**, *cis*-**84**, *cis*-**85**, *trans*-**95** and *trans*-**96**, which have a relative energy ≤ 1.5 kcal mol^{-1}.

2.2.1 Overview of Previous Approaches to 2,3-, 2,5- and 2,6-Disubstituted Piperidines

In this section, an overview of the synthesis of disubstituted piperidines with either a methyl group and a methyl ester/acid substituent, a methyl group and a hydroxyl methyl group or two esters in the 2,3-, 2,5- and 2,6-positions is provided (Figure 2.9). This included a summary of the previous synthetic routes to the *cis* and *trans*-diastereoisomers for these piperidines.

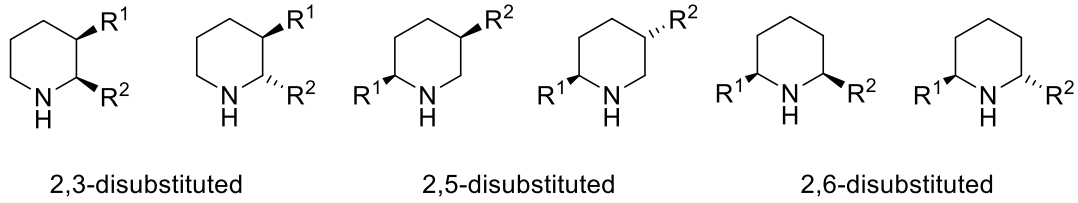
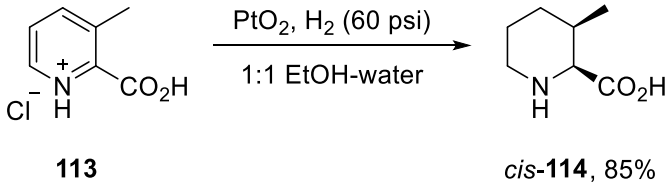
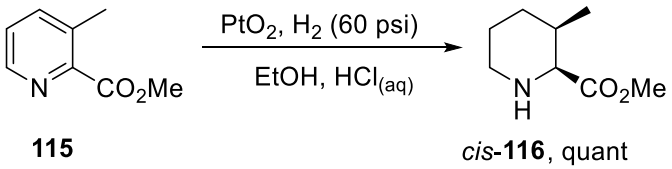


Figure 2.9 – Substitution patterns included in this section.

The most widely used strategy for the synthesis of 2,3-disubstituted *cis*-piperidines is hydrogenation of substituted pyridines. For example, in 1990, Shuman *et al*. reported the hydrogenation of pyridine **113** using 44 mol% PtO_2 at 60 psi to give piperidine *cis*-**114** which was isolated as the HCl salt (Scheme 2.24).[75] Another example of the hydrogenation of pyridine **113** used 10% Pd/C in MeOH and HCl at 50 psi for 1 h, which gave a quantitative yield of piperidine *cis*-**114**.[76] In a similar way, hydrogenation of 3-methylpyridine-2-methyl ester **115**, reported by Subramanyan *et al*.,[77] used 44 mol% PtO_2 at 60 psi in EtOH with $HCl_{(aq)}$. This gave piperidine *cis*-**116** in quantitative yield (Scheme 2.25).

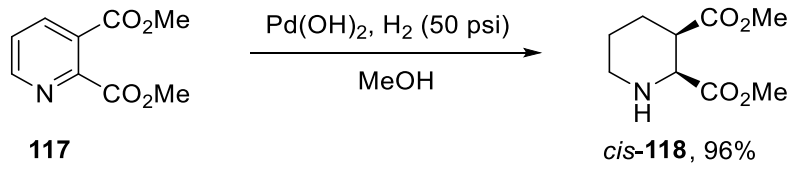


Scheme 2.24



Scheme 2.25

The hydrogenations shown in Scheme 2.24 and Scheme 2.25 were carried out under acidic conditions. However, pyridines can also be reduced in the absence of acid. For example, Whitten *et al.* reported the hydrogenation of 2,3-diester **117** using $Pd(OH)_2$ at 50 psi, which gave piperidine *cis*-**118** in high yield (Scheme 2.26).[78]

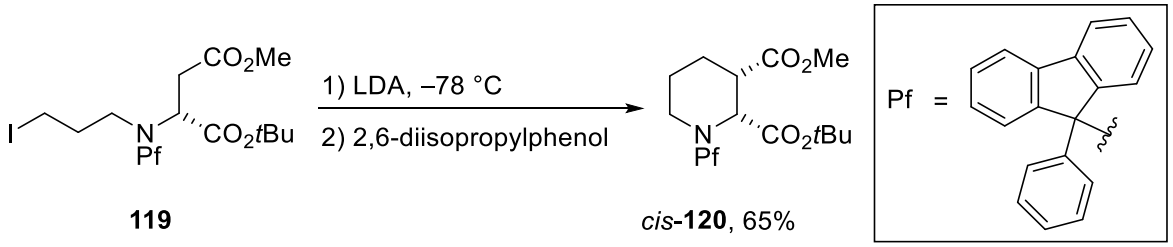


117 *cis*-**118**, 96%

Scheme 2.26

Hydrogenation of disubstituted pyridines offers high levels of *cis*-diastereoselectivity. Presumably, coordination of the pyridine ring to the surface of the catalyst results in hydrogen addition to one face of the pyridine ring to give the *cis*-piperidine as the major product. The minor *trans*-piperidine could result from the partially reduced pyridine ring dissociating from the catalyst surface and then re-coordinating on the opposite face.

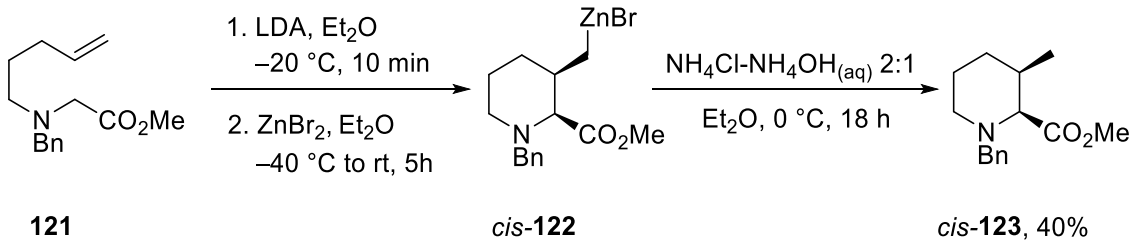
A non-hydrogenation route for the synthesis of a 2,3-disubstituted *cis*-piperidine was also developed by Whitten and co-workers. Deprotonation of iodide **119** using LDA at –78 °C, warming to –35 °C for cyclisation and quenching with 2,6-diisopropylphenol exclusively gave piperidine *cis*-**120** in 65% yield (Scheme 2.27).[78]



119 *cis*-**120**, 65%

Scheme 2.27

In 1998, Normant *et al.* designed a diastereoselective amino zinc enolate carbocyclisation as a route to piperidine *cis*-**123**. Subsequent epimerisation also allowed access to piperidine *trans*-**123**. Treatment of ester **121** with LDA followed by transmetalation with $ZnBr_2$ gave zincate *cis*-**122**. Protonation of zincate *cis*-**122** afforded piperidine *cis*-**123** in 40% yield over three steps as a single diastereoisomer (Scheme 2.28).[79] The cis stereochemistry is controlled *via* an intramolecular olefinic aldol reaction with the $ZnBr_2$ enolate, which selectively gave piperidine *cis*-**122** (Figure 2.10). Coordination of $ZnBr_2$ with the olefin results in a 6-exo-trig ring cyclisation affording the *cis*-stereochemistry.



121 *cis*-**122** *cis*-**123**, 40%

Scheme 2.28

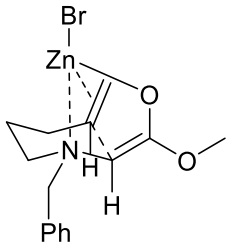
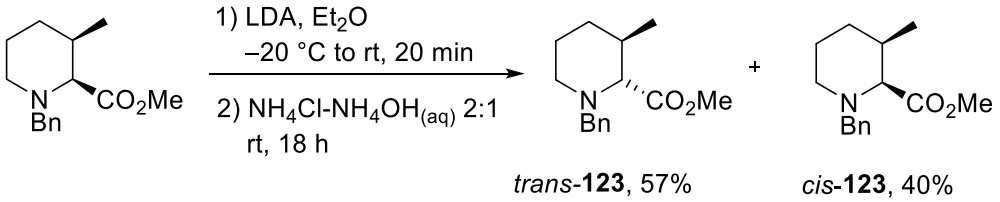


Figure 2.10 – 6-exo-trig cyclisation and coordination of the Zn(II)Br enolate with the olefin.

Epimerisation of piperidine *cis*-**123** was achieved using LDA which gave a 65:35 mixture of piperidines *trans*-**123** and *cis*-**123**. The diastereoisomers were separable and piperidine *trans*-**123** was isolated in 57% yield (Scheme 2.29).



trans-**123**, 57% *cis*-**123**, 40%

Scheme 2.29

Epimerisation of piperidine *cis*-**123** affords piperidine *trans*-**123** due to the 2,3-related substitution pattern. As shown in Figure 2.11, *cis*-**116** is likely to adopt a conformation with the ester group axial and the sterically larger methyl group equatorial. Thus, upon treatment with base, enolate **124** will be formed and protonation could give either *cis*-**116** or *trans*-**116**. Since the substituents are 2,3-related then formation of *trans*-**116** will be favoured as its conformation can have both substituents in equatorial positions. Thus, it would be expected that there would be a thermodynamic driving force for the formation of *trans*-**116**.

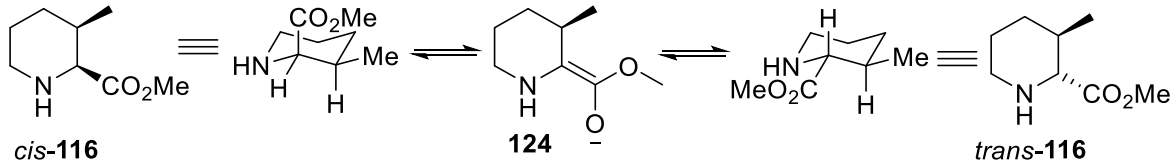
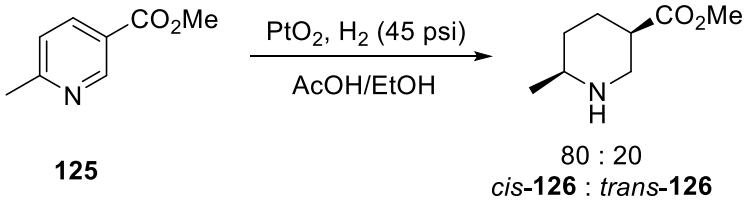


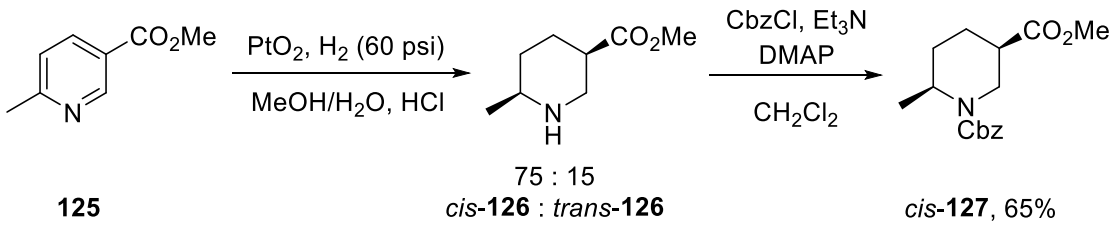
Figure 2.11 – Protonation of enolate **124** to give *trans*-**116**.

The synthesis of the 2,5-disubstituted *cis*-piperidine methyl/ester system has also been reported using pyridine hydrogenation. For example, as reported in a patent, hydrogenation of pyridine **125** with 5 mol% PtO_2 at 45 psi in AcOH/EtOH afforded an 80:20 mixture of piperidines *cis*-**126** and *trans*-**126** in quantitative yield (Scheme 2.30).[80]



Scheme 2.30

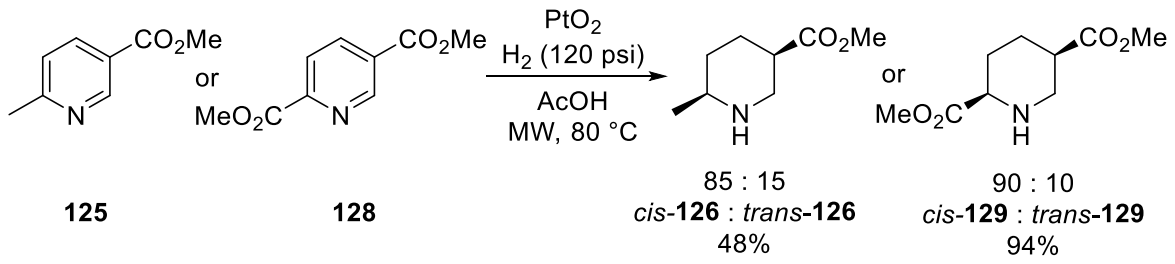
Hydrogenation of pyridine **125** was also reported in a further three patents using 10% Pd/C at H_2 pressures of 45-200 psi.[81,82,83] In all cases, the reactions were carried out under acidic conditions. In addition, Medina *et al*. reported the hydrogenation of pyridine **125** using 5 mol% PtO_2 at rt and 60 psi for 4.5 h. This gave a 75:25 mixture of piperidines *cis*-**126** and *trans*-**126**. Subsequent Cbz protection and separation of the diastereoisomers by chromatography afforded piperidine *cis*-**127** in 65% yield over the two steps (Scheme 2.31).[84]



Scheme 2.31

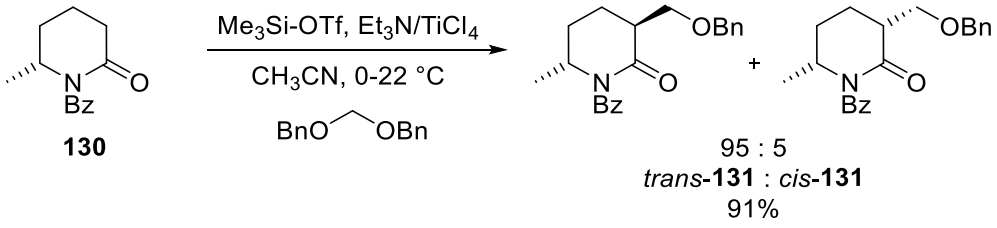
More recently, microwave hydrogenation conditions for the synthesis of 2,5-disubstituted piperidines have been developed by Taddei *et al.* (based on the initial microwave work by Vanier *et al*.).[85,86] Hydrogenation of pyridine **125** with 10 mol% PtO_2 at 120 psi and 80 °C under microwave conditions gave an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126**.

The hydrogenation of diester pyridine **128** was also studied and this gave a 90:10 mixture of piperidines *cis*-**129** and *trans*-**129** (Scheme 2.32).



Scheme 2.32

The synthesis of a 2,5-disubstituted *trans*-piperidine was reported by Chung *et al*. where the key step was a Mukaiyama aldol reaction of lactam **130** which installed the primary alcohol functionality.[87] This afforded a 95:5 mixture of lactams *trans*-**131** and *cis*-**131** in 91% yield (Scheme 2.33). The preferred formation of piperidine *trans*-**131** in the Mukaiyama aldol reaction can be explained by considering the steric hindrance between the carbonyl from the *N*-benzoyl and the methyl group. In order to minimise the $A^{1,3}$ strain, the methyl group is placed axial and the aldol reaction then proceeds in a *trans*-diaxial fashion to give the *trans* stereochemistry (Figure 2.12).



Scheme 2.33

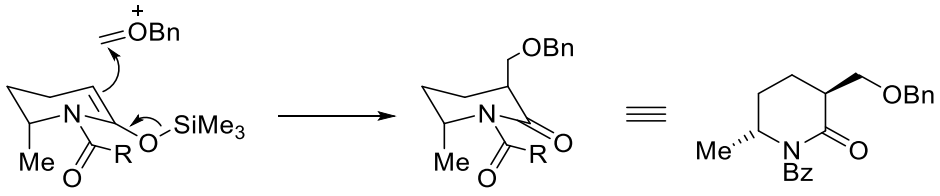
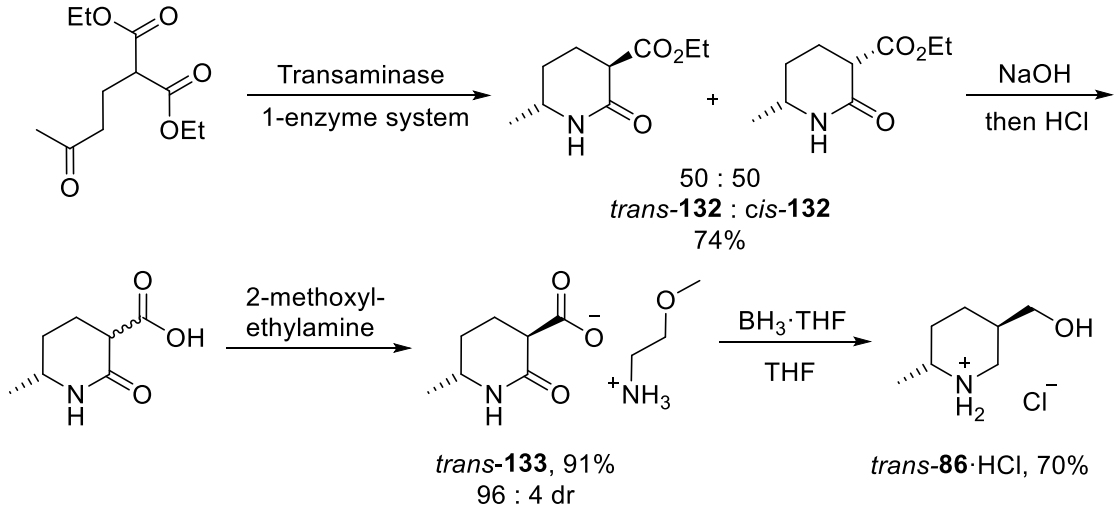


Figure 2.12 – Explanation of diastereoselectivity in the Mukaiyama aldol reaction to give *trans*-**131**.

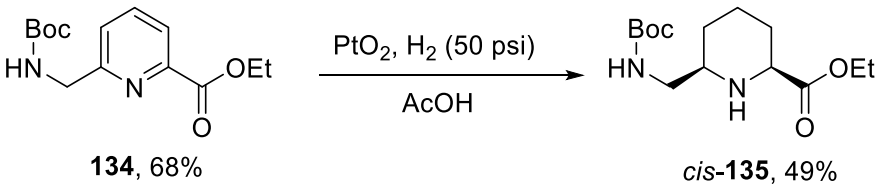
The same group developed a more cost-effective synthesis of piperidine *trans*-**86**·HCl which could be used in the manufacturing process (based on the work of Girardin *et al*.[88]). Single enzyme transamination gave a 50:50 mixture of lactams *trans*-**132** and *cis*-**132**. Then, lactams *trans*-**132** and *cis*-**132** were saponified using NaOH followed by HCl to give

carboxylic acids. Crystallised-induced dynamic resolution of the carboxylic acid with methoxyethylamine gave a 96:4 dr of lactams *trans*-**133** and *cis*-**133** in 91% yield. Finally, reduction of lactams *trans*-**133** and *cis*-**133** with BH_3·THF afforded piperidine *trans*-**86**·HCl (Scheme 2.34).[89]



Scheme 2.34

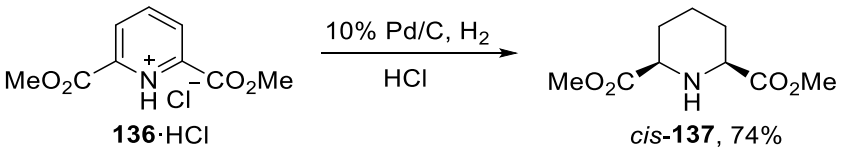
The main synthetic route used for the synthesis of 2,6-disubstituted *cis*-piperidines is also the hydrogenation of substituted pyridines. As early as 1961, Ryan and Ainsworth reported the hydrogenation of pyridine **134** using 5% Rh-alumina at 3960 psi, which gave piperidine *cis*-**135** in 82% yield.[90] Six years later in 1967, Crabb and Newton reported the hydrogenation of pyridine **134** using PtO_2 in AcOH, although no yields or catalyst loadings were provided. The only observation noted was the selective formation of piperidine *cis*-**135**.[91,92] More recently, work by Hausch *et al*. described the hydrogenation of pyridine **134** with PtO_2 at 50 psi in AcOH. This gave piperidine *cis*-**135** in 49% yield (Scheme 2.35).[93]



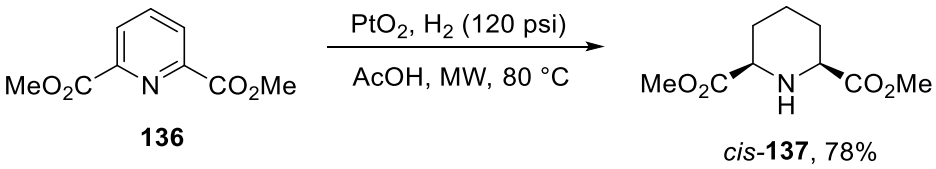
Scheme 2.35

The hydrogenation of 2,6-diester pyridine **136**·HCl was studied by Chênvert and Dickman. Using 10% Pd/C at 45 psi piperidine *cis*-**137** was isolated in 74% yield (Scheme 2.36).[94] Taddei *et al.* had also studied the hydrogenation of the 2,6-diester pyridine **136** using their developed microwave conditions (see Scheme 2.32). Hydrogenation with 10 mol% PtO_2 at

120 psi for 40 min afforded piperidine *cis*-**137** in 78% yield as a single diastereoisomer (Scheme 2.37).

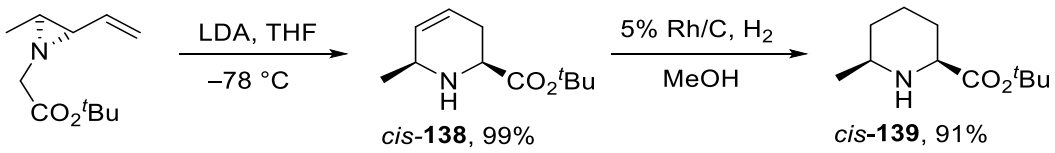


Scheme 2.36



Scheme 2.37

A route to access 2,6-*cis*-disubstituted piperidines without using pyridine hydrogenation was developed by Somfai *et al*. The key step was an aza-(2,3)-Wittig rearrangement upon treatment of the aziridine with LDA at –78 °C to give piperidine *cis*-**138** in excellent yield. Reduction of the alkene in piperidine *cis*-**138** with 5% Rh/C in MeOH then gave the *t*-butyl ester piperidine *cis*-**139** (Scheme 2.38).[95] The explanation for the observed *cis*-diastereoselectivity in the aza-(2,3)-Wittig rearrangement was discussed in an earlier paper by Somfai *et al*.[96] In order to facilitate bond formation, the *t*-butyl ester and the methyl group are *cis* with the enolate orientated to minimise steric interaction with the aziridine substituents (Figure 2.13).



Scheme 2.38

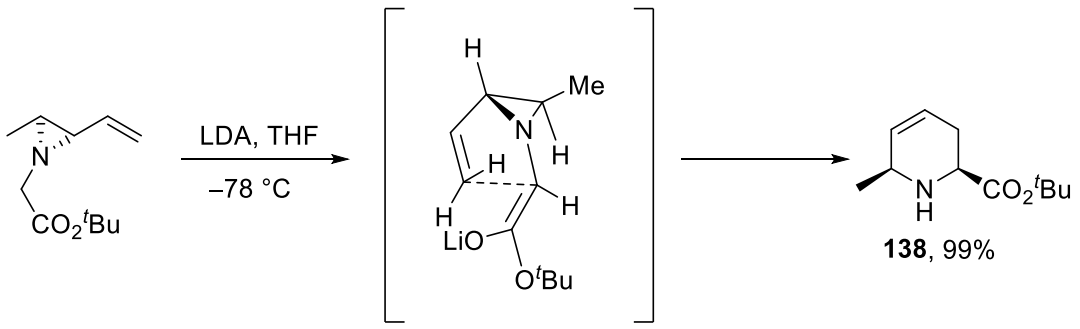
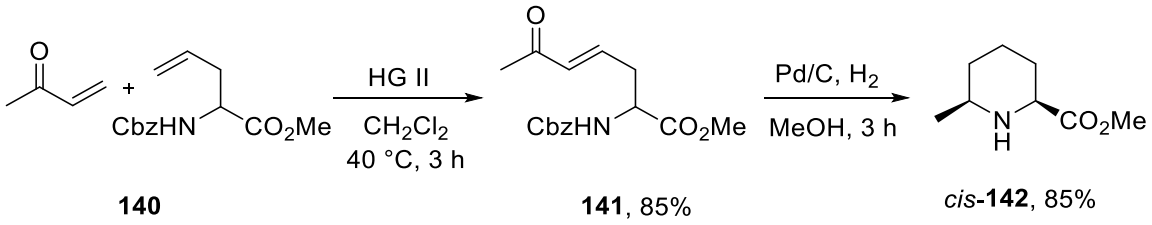


Figure 2.13 – Model to explain the *cis*-stereoselectivity

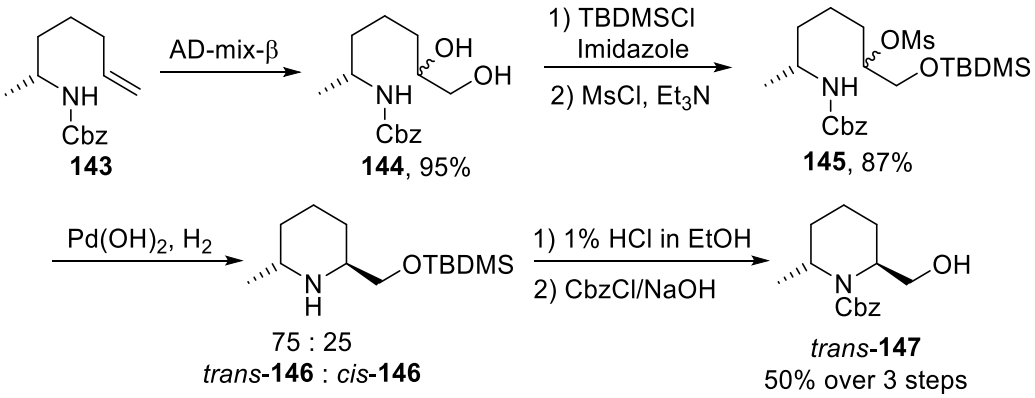
Blechert *et al*. has reported a stereoselective synthesis to access *N*-heterocycles *via* cross-metathesis and subsequent reductive cyclisation.[97] Cross-metathesis of methyl vinyl ketone with alkene-containing amino acid derivative **140** using 10 mol% Hoveyda-Grubbs II catalyst, afforded ketone **141**. Reduction of ketone **141** with H_2 and 5% Pd/C gave piperidine *cis*-**142** as a single diastereoisomer in 85% yield (Scheme 2.39). This transformation involves several steps: alkene hydrogenation, Cbz protecting group cleavage, cyclisation to an imine and hydrogenation. The imine hydrogenation occurs from the face opposite to the methyl ester group due to steric hinderance and this places the methyl group and the methyl ester substituents *cis* to each other.



Scheme 2.39

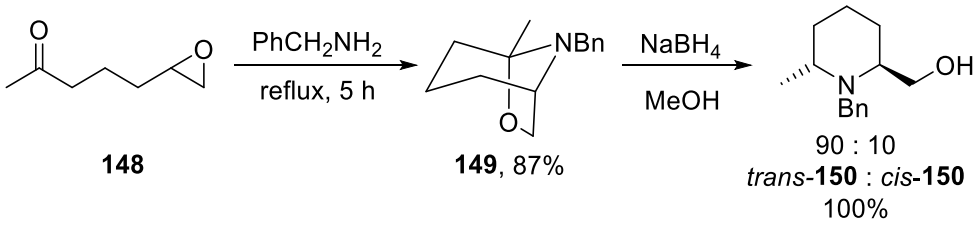
In 1994, Momose *et al.* reported a route towards piperidine *trans*-**147** starting from carbamate **143**, which was synthesised from *D*-alanine. Asymmetric dihydroxylation gave a mixture of diastereoisomeric diols **144**. Selective protection of the primary alcohol with TBDMSCl followed by reaction with MsCl gave carbamate **145**. Then, hydrogenolysis of the Cbz group in carbamate **145** with $Pd(OH)_2$ resulted in cyclisation *via* substitution of the mesylate group to give a 75:25 mixture of piperidines *trans*-**146** and *cis*-**146**. Removal of the TBDMS protecting group and Cbz protection of the free piperidine allowed the separation of the two diastereoisomers, with piperidine *trans*-**147** isolated in 50% yield (Scheme 2.40).[98] The diastereoselectivity is controlled by the asymmetric dihydroxylation

reaction and stereospecific inversion of the stereochemistry upon substitution of the mesylate group.



Scheme 2.40

A related approach to 2,6-disubstituted *trans*-piperidines was report by Wasserman *et al.* in 1988.[99] Reaction of epoxide **148** with benzylamine in refluxing benzene gave oxatropane **149** in 87% yield. Reduction of oxatropane **149** with $NaBH_4$ gave a 90:10 mixture of piperidines *trans*-**150** and *cis*-**150** which were acetylated to enable separation of the diastereomeric piperidines (Scheme 2.41).



Scheme 2.41

In this approach, the stereochemistry was controlled by the $A^{1,2}$-type strain between the substituent on the nitrogen and the primary alcohol (Figure 2.14). With a bulky *N*-benzyl group, the primary alcohol substituent will be orientated in an axial position **151** (rather than in an equatorial position **152**) to minimise steric interactions. Axial attack of hydride on the iminium ion then leads to the observed formation of *trans*-**150**.[100]

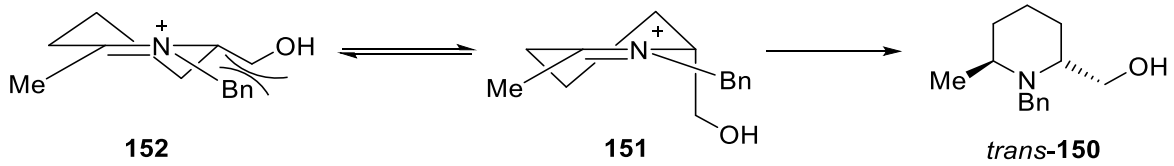
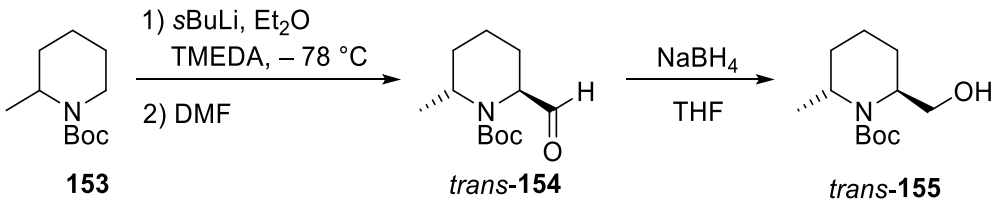


Figure 2.14 – Model to explain the formation of *trans*-**150**.

A completely different approach to synthesise 2,6-disubstituted *trans*-piperidines is the lithiation-trapping of *N*-Boc 2-methylpiperidine **153** using conditions reported by Beak in 1993.[101] For example, Pissarnitski *et al*. treated *N*-Boc 2-methylpiperidine **153** with *s*BuLi and TMEDA at –78 °C. Subsequent electrophilic trapping with DMF afforded piperidine *trans*-**154**, which was reduced using $NaBH_4$ to give alcohol *trans*-**155** (Scheme 2.42).[102]



Scheme 2.42

The *trans*-stereochemistry results from equatorial lithiation and subsequent trapping. Due to the Boc group, the C-2 substituent in *N*-Boc piperidine **153** is axial to reduce the $A^{1,3}$-type strain between the two substituents. The Boc group also directs the deprotonation to the equatorial proton, *via* coordination of the carbonyl group to the *s*BuLi to give **156**. Finally, electrophilic trapping proceeds with retention to give the two substituents *trans* to each other (Figure 2.15).

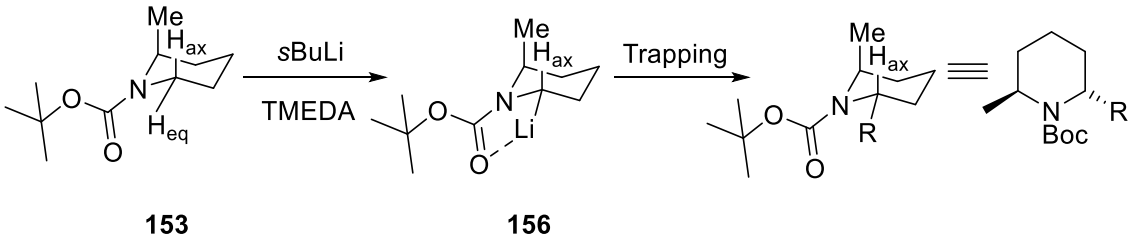
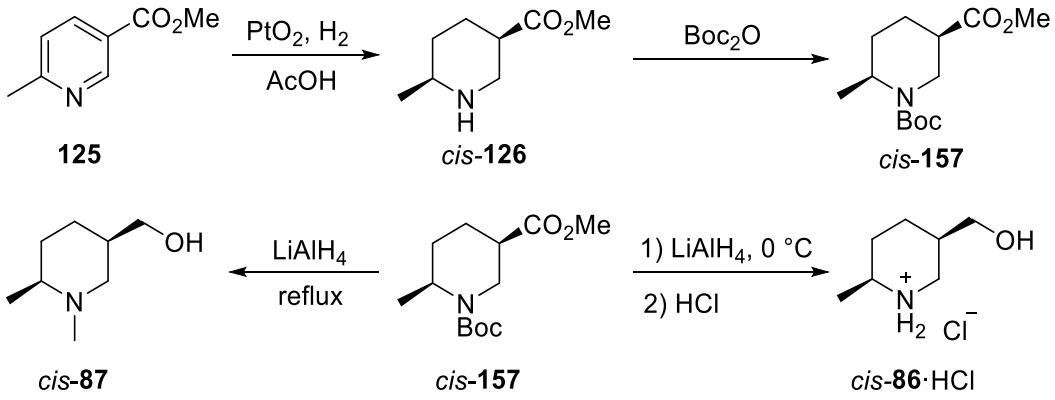


Figure 2.15 – Lithiation-trapping to obtain the 2,6-disubstituted *trans*-piperidine.

In summary, the most common method for synthesising the 2,3- 2,5- and 2,6-*cis*-disubstituted piperidines is hydrogenation of the corresponding disubstituted pyridines. Typical reaction conditions use PtO_2 under high H_2 pressure and acidic conditions to give the *cis*-piperidines as the major products. In contrast, the *trans*-piperidines required individual routes to obtain the desired diastereoselectivity, and no overall general approaches for the synthesis of 2,3-, 2,5- and 2,6-*trans*-disubstituted piperidines have been reported.

2.2.2 Synthesis of 2,5-Disubstituted Piperidine Fragments

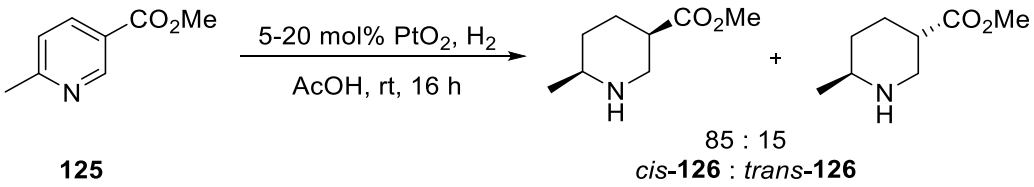
The approach planned for the synthesis of the piperidine 3-D fragments *cis*-**86** and *cis*-**87** is shown in Scheme 2.43. We proposed to use hydrogenation of 2,5-disubstituted pyridine **125**, which based on the literature precedent discussed in the previous section, should give piperidine *cis*-**126** as the major product. To aid with the separation of the diastereoisomers a Boc group would be installed to give *cis*-**157** and this should also allow access to both fragments. Chemoselective reduction of the ester in *cis*-**157** to the primary alcohol should be possible using $LiAlH_4$ at 0 °C[103] and subsequent removal of the Boc group would then afford 3-D fragment *cis*-**86**·HCl. In contrast, starting from *N*-Boc piperidine *cis*-**157**, reduction of the Boc group and methyl ester using $LiAlH_4$ at reflux should give *N*-methyl piperidine *cis*-**87**. These planned syntheses would allow both fragments to be accessed in three steps starting from the corresponding pyridine **125**.



Scheme 2.43

To start, 2-methylpyridine-5-methyl ester **125** was hydrogenated in AcOH using 5-20 mol% PtO_2 and a H_2 balloon at rt for 16 h. After filtration, with a CH_2Cl_2 wash, and work-up with $NH_4OH_{(aq)}$, the crude product was analysed by ^1H NMR spectroscopy to determine whether the reaction had gone to completion and establish the ratio of piperidines *cis*-**126** and *trans*-**126**. The results are shown in Table 2.1. In each case, an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** was observed, with the crude yield being reported as purification was not required. Confirmation that the major product was indeed *cis*-**126** is provided in Scheme 2.45. Using 20 mol% and 10 mol% PtO_2, piperidines *cis*-**126** and *trans*-**126** were each isolated in 74% yield with no pyridine **125** remaining (entries 1 and 2). With 5 mol% PtO_2, complete hydrogenation of the pyridine ring was observed after 16 h, to give piperidines *cis*-**126** and *trans*-**126** albeit in a slightly lower 65% yield (entry 3). The reaction was repeated for scale up with 10 mol% PtO_2 to ensure complete reduction of the pyridine ring after 16 h.

This gave a 76% yield of an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** (entry 2). As described above, the work-up for the reactions initially involved removing the PtO_2 catalyst by filtering through Celite and then washing the Celite pad with CH_2Cl_2 (entries 1-3). We suspected that some of the product was sticking on the Celite pad. Therefore, the work-up was modified and the Celite pad was washed with MeOH instead of CH_2Cl_2. This increased the yield of piperidines *cis*-**126** and *trans*-**126** to 93% (entry 4), which represented the optimised conditions.

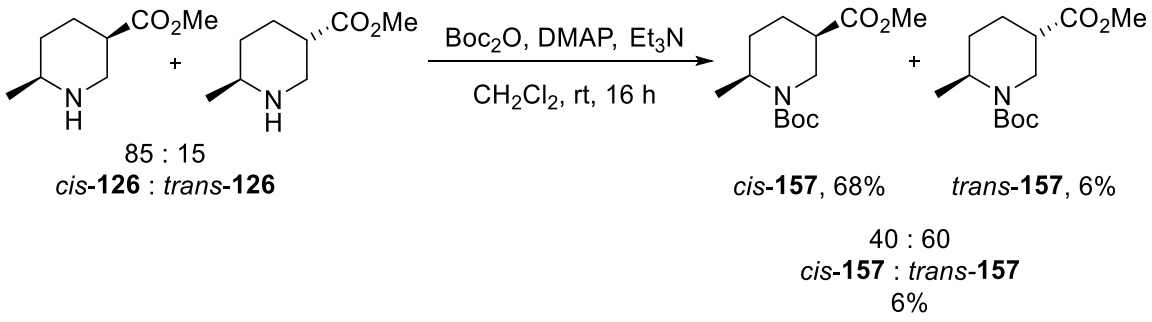


Entry	PtO_2 (mol %)	*cis*-126 : *trans*-126 [a]	Yield (%)[b]
1	20	85:15	74
2	10	85:15	74 (76[c])
3	5	85:15	65
4[d]	10	85:15	93

Table 2.1 – Hydrogenation of pyridine **125** using different loadings of PtO_2.

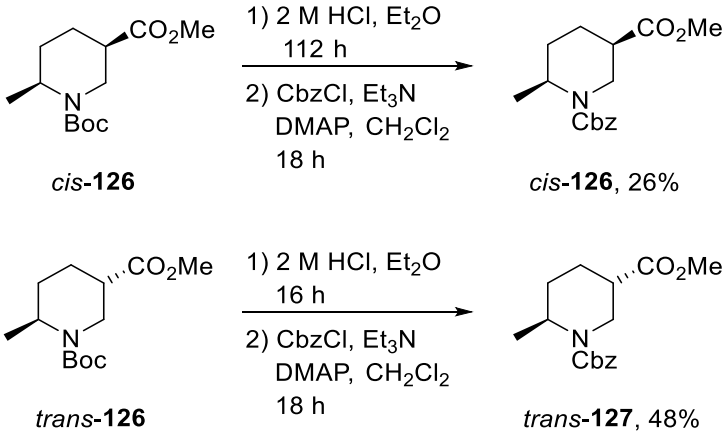
a) Ratio of diastereoisomers was determined by ^{1}H NMR spectroscopy of the crude product; b) Yield of crude product; c) Reaction carried out on 13.2 mmol scale. (d) Celite pad washed with MeOH instead of CH_2Cl_2.

Piperidines *cis*-**126** and *trans*-**126** could not be separated using column chromatography. Therefore, the crude 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** was reacted with Boc_2O and DMAP. Purification by column chromatography afforded Boc piperidine *cis*-**157** in 68% yield. In addition, a 60:40 mixture of Boc piperidines *trans*-**157** and *cis*-**157** (6% yield) and Boc piperidine *trans*-**157** (6% yield) were also isolated (Scheme 2.44).



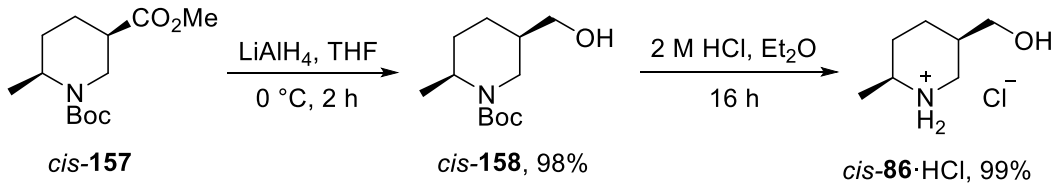
Scheme 2.44

Piperidines *cis*-**126** and *trans*-**126** had been synthesised previously and full data had been reported with a Cbz group present on the nitrogen.[84] The relative stereochemistry had been established using an X-ray structure of a *cis*-piperidine derivative bound to their target kinase. In order to compare the data, we synthesised the Cbz analogues for each diastereoisomer. The Boc group was removed with 2 M HCl in Et_2O and the HCl salts were Cbz protected to afford the corresponding piperidines *cis*-**127** and *trans*-**127** in 26% and 48% yields respectively (Scheme 2.45). Comparison of the ^{1}H NMR spectra for *cis*-**127** and *trans*-**127** with the literature data allowed unequivocal assignment of the relative stereochemistry.



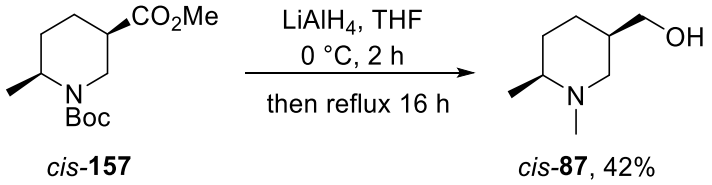
Scheme 2.45

With the relative stereochemistry assigned, the synthesis of the two 2,5-disubstituted piperidine 3-D fragments was completed. Reduction of the methyl ester in *cis*-**157** was carried out with $LiAlH_4$ at 0 °C for 2 h and ^{1}H NMR spectroscopic analysis after work-up revealed that no purification was required. Removal of the Boc group with 2 M HCl in Et_2O afforded piperidine fragment *cis*-**86**·HCl in 97% yield over two steps (Scheme 2.46) Alternatively, *N*-Boc piperidine *cis*-**157** was treated with $LiAlH_4$ at 0 °C for 2 h to reduce the methyl ester and then refluxed for 16 h to reduce the Boc group to afford the *N*-methyl substituent. Purification by column chromatography gave *N*-methyl piperidine *cis*-**87** in 42% yield (Scheme 2.47).



cis-**157** *cis*-**158**, 98% *cis*-**86**·HCl, 99%

Scheme 2.46

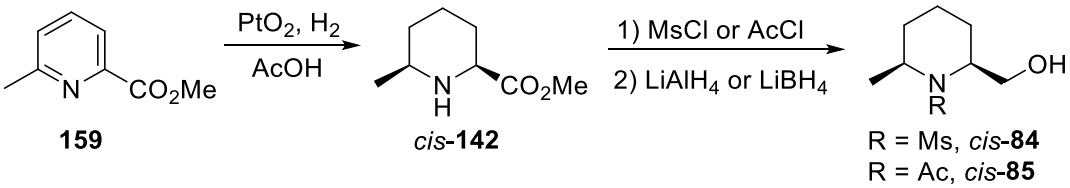


cis-**157** *cis*-**87**, 42%

Scheme 2.47

2.2.3 Synthesis of 2,6-Disubstituted Piperidine Fragments

A pyridine hydrogenation route was envisaged for the synthesis of 2,6-disubstituted piperidines *cis*-**84** and *cis*-**85** as outlined in Scheme 2.48. Thus, hydrogenation of 2,6-disubstituted pyridine **159** should afford piperidine *cis*-**142** selectively based on literature precedent (see Scheme 2.37).[90–93] Then, mesylation or acylation of *cis*-**142** followed by ester reduction to the primary alcohol should give 3-D piperidine fragments *cis*-**84** and *cis*-**85**.

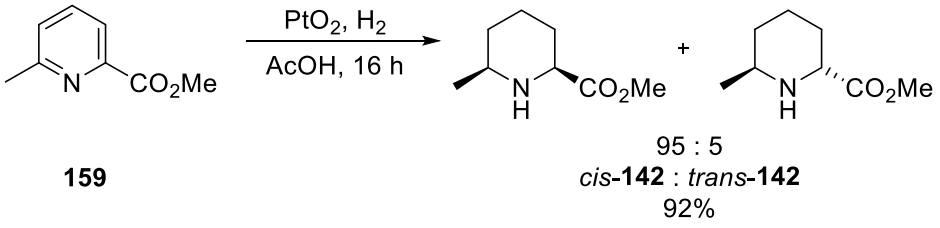


159 *cis*-**142**

Scheme 2.48

Starting from commercially available 2,6-pyridine methyl ester **159**, hydrogenation with 10 mol% PtO_2 in AcOH gave, after work-up, the crude product which required no further purification. Analysis by ^{1}H NMR spectroscopy showed that the crude product contained a 95:5 mixture of piperidines *cis*-**142** and *trans*-**142** (92% yield) (Scheme 2.49). The stereochemistry of piperidines *cis*-**142** and *trans*-**142** was assigned based on $^3J_{HH}$ values of the protons at the C-2 and C-6 positions (Figure 2.16). The C-2 proton exhibited $^3J_{HH}$ values of 12.5 and 2.5 Hz (as well as coupling to the methyl group), which suggested that the C-2 proton was axial. The C-6 proton showed $^3J_{HH}$ values of 11.0 and 3.0 Hz which suggested that it was also axial, thus confirming the *cis*-stereochemistry. Confirmation that the major

product was *cis*-**142** was obtained by X-ray crystallography of the 3-D sulfonamide fragment *cis*-**84** (see Figure 2.17).



Scheme 2.49

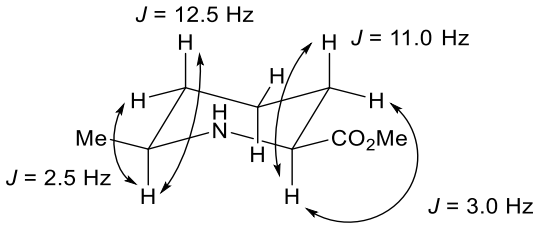
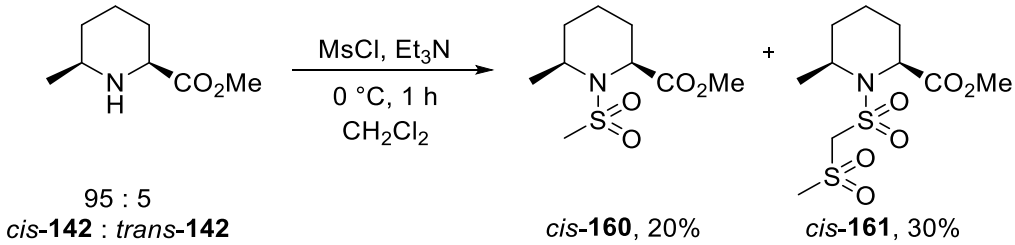


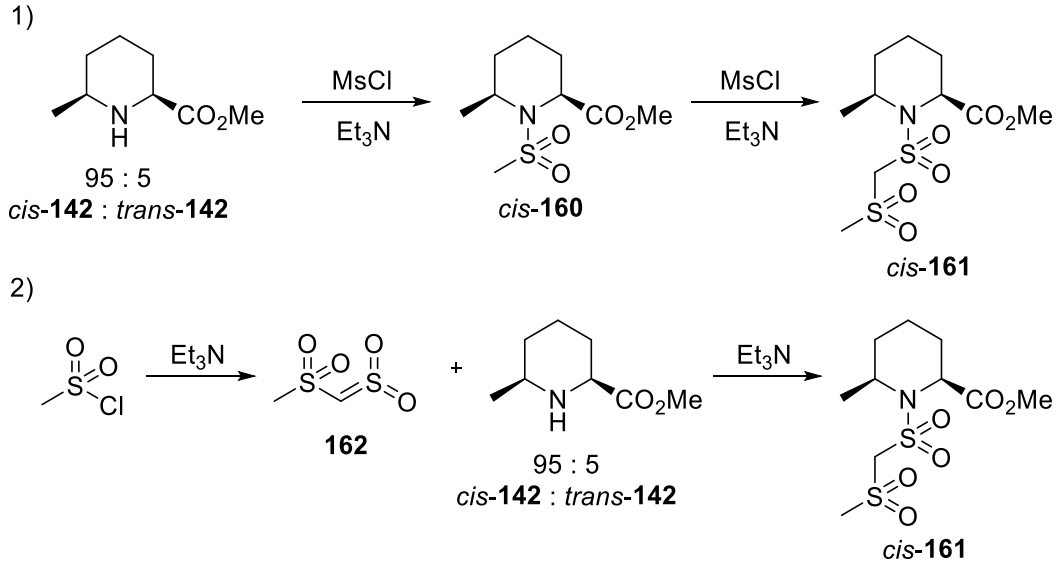
Figure 2.16 – Confirmation of stereochemistry *via* $^{3}J_{HH}$ coupling constants.

With a view to completing the synthesis of 3-D sulfonamide fragment *cis*-**84**, the 95:5 mixture of piperidines *cis*-**142** and *trans*-**142** was reacted with mesyl chloride and Et_3N (0 °C, 1 h). ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed the formation of two main products. Purification afforded sulfonamide piperidine *cis*-**160** in 20% yield and what we initially suspected was the corresponding *trans*-diastereoisomer. However, mass spectrometry showed a mass ion of *m/z* 336, which did not correspond to sulfonamide piperidine *trans*-**160**. Analysis of the ^{1}H NMR spectrum showed the presence of two doublets at 4.75 and 4.49 ppm which based on the *m/z* value, was consisted with a pair of diastereotopic CH_2 protons adjacent to two sulfur atoms. This, together with full characterisation by ^{1}H and ^{13}C NMR spectroscopy indicated that bismethanesulfonamide piperidine *cis*-**161** (assumed relative stereochemistry) had been formed and isolated in 30% yield (Scheme 2.50).



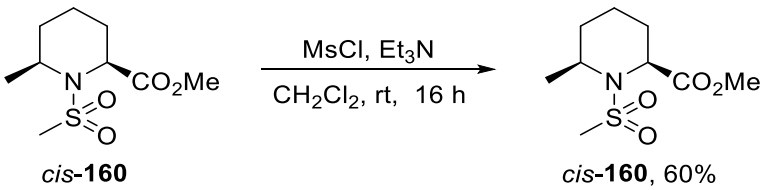
Scheme 2.50

We suggested that there are two possible pathways in which bismethanesulfonamide piperidine *cis*-**161** could be formed. The first starts with the formation of sulfonamide piperidine *cis*-**160** which can then react with another equivalent of mesyl chloride to afford bismethanesulfonamide *cis*-**161**. The second involves the initial formation of sulfonylidene **162**, (precedented in the work of Shealy *et al*.[104]), which can then react with piperidine *cis*-**142** to afford bismethanesulfomaide piperidine *cis*-**161** (Scheme 2.51).



Scheme 2.51

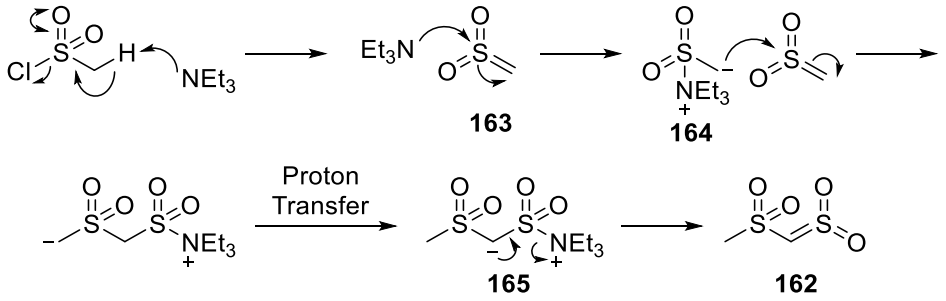
To investigate the first proposed route for the formation of bismethanesulfonamide piperidine *cis*-**161**, we re-subjected sulfonamide piperidine *cis*-**160** to mesyl chloride and Et_3N at rt for 16 h. ^1H NMR spectroscopic analysis of the crude reaction mixture revealed that no bismethanesulfonamide piperidine *cis*-**161** was present, and the starting sulfonamide piperidine *cis*-**160** was isolated in 60% yield after purification (Scheme 2.52).



Scheme 2.52

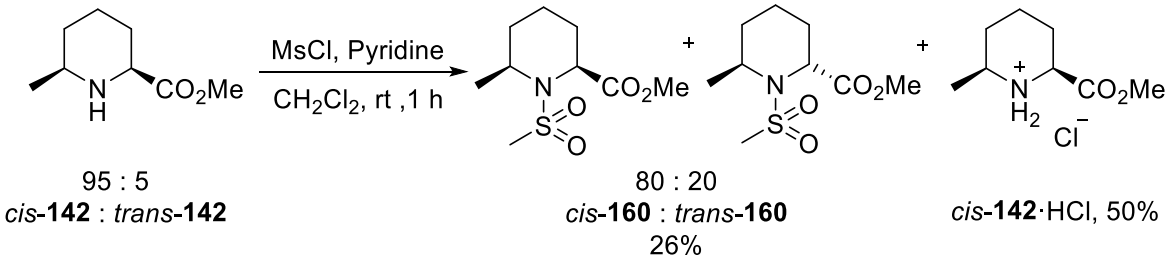
Therefore, we believe that the formation of bismethanesulfonamide piperidine *cis*-**161** proceeds *via* the second proposed route, with the initial formation of sulfonylidene **162**. We presume that the sterically hindered nature of the amine, due to the 2,6-substitution, results in a slow mesylation, which allows for the formation of sulfonylidene **162**. The proposed

mechanism for the formation of sulfonylidene **162** was reported in 1991 by Shealy *et al.*[104] Initial deprotonation of mesyl chloride affords sulfene **163** which then gets attacked by Et_3N to give **164**. Nucleophilic attack by **164** onto another molecule of sulfene **163**, followed by proton exchange gives the Et_3N adduct **165**, which had been previously isolated by Opitz and Bücher in 1966.[105] Subsequent elimination of Et_3N then affords sulfonylidene **162** (Scheme 2.53).



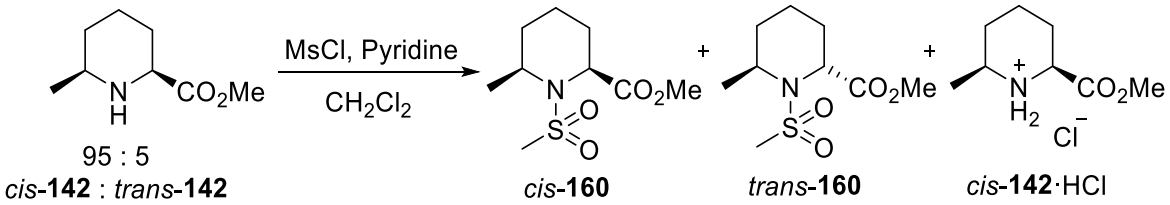
Scheme 2.53

To minimise the formation of bismethanesulfonamide piperidine *cis*-**161** we decided to change the base to pyridine, which should prevent the formation of sulfene **162** as it is a weaker base than Et_3N. Thus, pyridine was added to a CH_2Cl_2 solution containing a 95:5 mixture of piperidines *cis*-**142**/*trans*-**142** and mesyl chloride and stirred at rt for 1 h. ^{1}H NMR spectroscopic analysis revealed an 80:20 mixture of sulfonamide piperidines *cis*-**160** and *trans*-**160** with no presence of bismethanesulfonamide piperidine *cis*-**161**. Purification afforded an 80:20 mixture of sulfonamide piperidines *cis*-**160** and *trans*-**160** in 26% yield. In addition, and rather unexpectedly, piperidine *cis*-**142**·HCl was isolated (50% yield) (Scheme 2.54). Thus, the use of pyridine had two effects: first, partial epimerisation occurred during the sulfonylation reaction and, second, the generated HCl protonated the starting amine and prevented the mesylation reaction going to completion.



Scheme 2.54

In an attempt to optimise the formation of the desired sulfonamide *cis*-**160**, we decided to vary the reaction time, base and temperature using the results shown in Scheme 2.54 as the starting point (Table 2.2, entry 1). The relative amount of each product was determined by integration of the three methyl ester singlets in the ^{1}H NMR spectrum of the crude reaction mixture. Reaction for 24 h gave no improvement in the overall yield of sulfonamide piperidines *cis*-**160** and *trans*-**160** (entry 2). Use of 3.0 eq for 24 h afforded a higher overall yield of sulfonamide piperidines *cis*-**160** and *trans*-**160** (37%, entry 3). The base was changed to 2,6-lutidine and this gave 28% yield of sulfonamide piperidines *cis*-**160** and *trans*-**160** (entry 4). Running the reaction in neat pyridine for 24 h and 72 h was then investigated (entries 5 and 6). After 24 h, we obtained a 45:10:50 mixture of *cis*-**160**, *trans*-**160** and *cis*-**142**·HCl (entry 5). When the reaction was left for 72 h, a 60:5:35 mixture of *cis*-**160**, *trans*-**160** and *cis*-**142**·HCl was achieved, with sulfonamide piperidine *cis*-**160** isolated in 60% yield, along with a 90:10 mixture of sulfonamide piperidine *trans*-**160** and *cis*-**160** in (4% yield) (entry 6). We also explored elevating the reaction temperature to 60 °C, although this did not lead to any improvement (entries 7 and 8). The conditions used in entry 5 (neat pyridine, rt, 72 h) afforded the highest yield of sulfonamide piperidine *cis*-**160** and these conditions were then scaled up to give sulfonamide piperidine *cis*-**160** in 52% yield (entry 9).

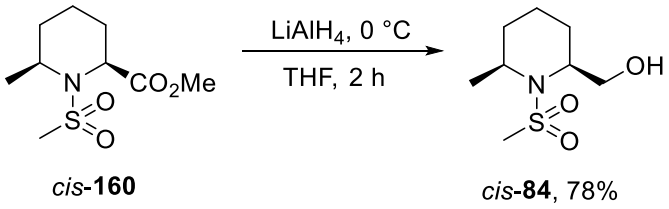


Entry	Time (h)	Temp (°C)	Base (eq)	*cis*-160:*trans*-160 :*cis*-142[a]	*cis*-160 (%)[b]	*cis*-160: *trans*-160 (%)[c]
1	1	25	1	25:5:70	-	26, 80:20[d]
2	24	25	1	20:5:75	19	3, 55:45[d]
3	24	25	3	35:5:60	-	37, 80:20[d]
4[e]	24	25	3	35:5:60	-	28, 80:20[d]
5	24	25	Neat	45:10:45	43	4, 20:80[d]
6	72	25	Neat	60:5:35	60	4, 10:90[d]
7	16	60	Neat	45:5:50	-	38, 90:10[d]
8	24	60	Neat	50:5:45	-	44, 90:10[d]
9[f]	72	25	Neat	55:5:40	52	-

Table 2.2 – Optimisation of the synthesis of piperidine sulfonamide *cis*-**160**.

a) Ratio determined by ^{1}H NMR spectroscopy of the crude product; b) % yield of *cis*-**160** after chromatography; c) % yield of *cis*-**160** and *trans*-**160** after chromatography; d) Ratio determined by ^{1}H NMR spectroscopy after chromatography; e) 2,6-Lutidine used; f) Scale-up reaction using entry 5 conditions.

The final step to synthesise piperidine *cis*-**84** was ester reduction to give the primary alcohol. Therefore, sulfonamide piperidine *cis*-**160** was treated with $LiAlH_4$ in THF at 0 °C for 2 h which gave sulfonamide piperidine 3-D fragments *cis*-**84** in 78% yield (Scheme 2.55). The final product was crystalline and crystals suitable for X-ray crystallography were grown. The X-ray crystal structure of sulfonamide piperidine *cis*-**84** (Figure 2.17) proved the *cis* stereochemistry. Interestingly, in the solid-state, the sulfonamide was planar (sp^2 hybridised) with both substituents in axial positions that are tilted slightly outwards, presumably to avoid steric clashes with the sulfonyl group.



Scheme 2.55

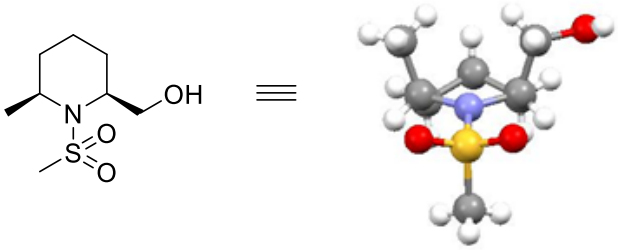
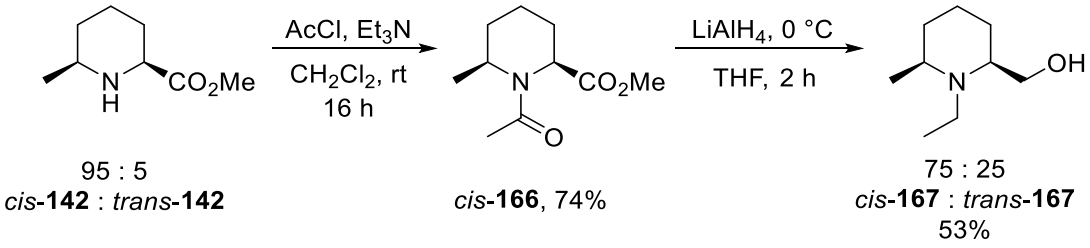


Figure 2.17 - X-ray crystal structure of sulfonamide *cis*-**84.**

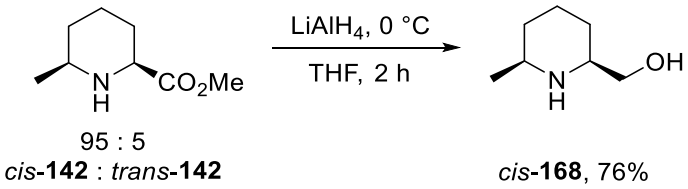
To gain access to acetamide piperidine *cis*-**85**, a similar route to that used to synthesise sulfonamide piperidine *cis*-**84** was envisaged. The 95:5 mixture of piperidines *cis*-**142** and *trans*-**142** was reacted with AcCl and Et_3N at rt for 16 h. Purification by chromatography afforded piperidine *cis*-**166** in 74% yield, with no evidence of any epimerisation (Scheme 2.56). Reduction of acetamide piperidine *cis*-**166** with $LiAlH_4$ at 0 °C for 2 h, led to reduction of both the ester and the acetamide, together with some epimerisation. ^1H NMR spectroscopic analysis revealed that a 75:25 mixture of amino alcohols *cis*-**167** and *trans*-**167** (53% yield) had been generated. To explain the facile amide reduction, it is possible that the carbonyl group of the amide is not fully conjugated with the nitrogen lone pair due to the steric hindrance cause by the 2,6-*cis*-disubstitution. As a result, this amide carbonyl group would be more electrophilic than typical amides and so readily reduced.



Scheme 2.56

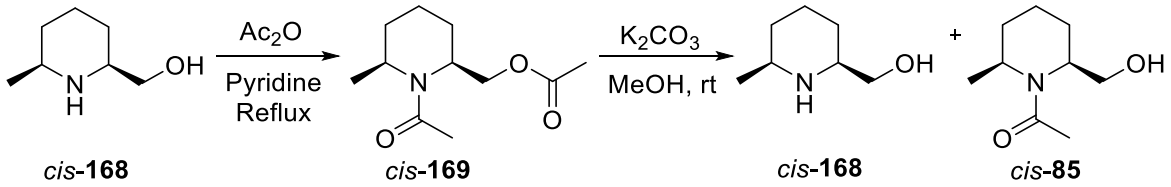
In the reaction to form amino alcohol *cis*-**167** and *trans*-**167**, it is assumed that the *cis*-diastereoisomer is the major product and, since some epimerisation was also occurring during the reduction, we decided to explore an alternative route rather than trying to optimise

the chemoselective reduction of the ester over the acetamide. The plan was to reduce piperidine *cis*-**142** to afford amino alcohol *cis*-**168**. Then, acylation of the alcohol and the amine would afford the doubly acylated product, in which the more labile *O*-acyl group could be selectively removed to afford acetamide piperidine *cis*-**85**. Reduction of the 95:5 mixture of piperidines *cis*-**142** and *trans*-**142** proceeded smoothly, to give, after purification, alcohol piperidine *cis*-**168** in 76% yield (Scheme 2.57).



Scheme 2.57

Refluxing piperidine alcohol *cis*-**168** with Ac_2O in pyridine gave crude diacylated product *cis*-**169**, which was subsequently treated with K_2CO_3 in MeOH at rt for 2 h. Purification led to the isolation of the fully deprotected piperidine alcohol *cis*-**168** in 66% yield (Table 2.3, entry 1). The cleavage of both the amide and ester group was unexpected although the ease of amide cleavage in this case was at least consistent with its ready reduction described above (see Scheme 2.56). To address this issue, shorter reaction times were explored. In contrast to the 2 h reaction, reaction for 30 min led to a mixture of acetamide piperidine *cis*-**85** and *cis*-**168** isolated in 28% and 12% yields respectively (entry 2). With a 10 min reaction time the ^{1}H NMR spectrum of the crude product showed formation of only the desired acetamide piperidine *cis*-**85**. Purification then gave acetamide piperidine 3-D fragment *cis*-**85** in 60% yield (entry 3).



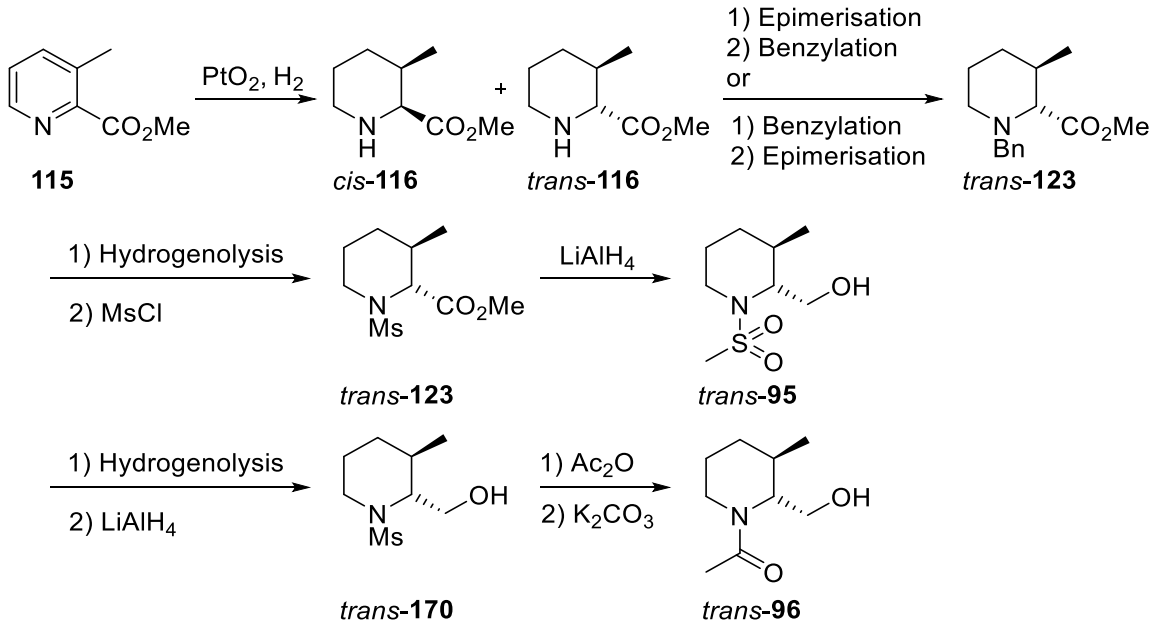
Entry	Time (min)	*cis*-168 (%)[a]	*cis*-85 (%)[b]
1	120	66	-[c]
2	30	12	28
3	10	-[c]	60

Table 2.3 – Optimisation of the synthesis of acetamide piperidine 3-D fragment *cis*-**85**.

a) % yield of *cis*-**168** after chromatography; b) % yield of *cis*-**85** after chromatography; c) No product observed from the ^{1}H NMR spectrum of the crude.

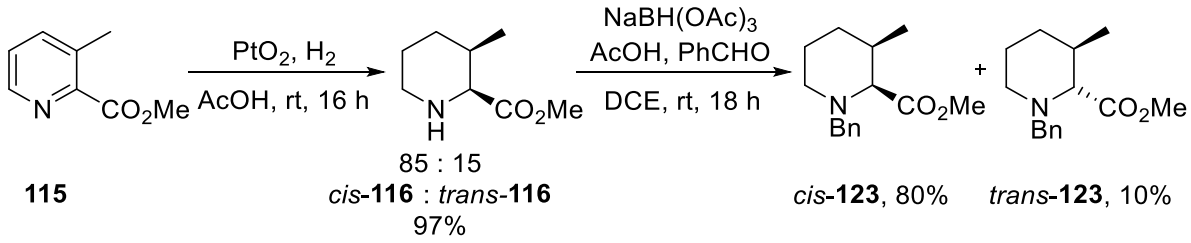
2.2.4 Synthesis of 2,3-Disubstituted Piperidine Fragments

Our proposed approach to access piperidine 3-D fragments *trans*-**95** and *trans*-**96** is summarised in Scheme 2.58. Hydrogenation of pyridine methyl ester **115** would give a mixture of piperidines *cis*-**116** and *trans*-**116** (presumably with *cis*-**116** as the major product). Then, the conversion of this mixture into *N*-benzyl ester *trans*-**123** would be investigated using base-mediated epimerisation with the formation of the more stable *trans*-diastereoisomer providing the driving force. There was literature precedent for epimerisation of NH and *N*-benzyl esters providing routes to 2,3-*trans*-piperidines[79,106] and both approaches could be studies. Starting from *N*-benzyl ester *trans*-**123**, hydrogenolysis to remove the benzyl group, mesylation and reaction with $LiAlH_4$ should give the 3-D sulfonamide fragment *trans*-**95**. The synthesis of the acetamide fragment would proceed using the route used to synthesis acetamide piperidine *cis*-**85**. Hydrogenolysis and ester reduction would afford the primary alcohol which would be doubly acylated. Removal of the more labile *O*-acyl group should then afford acetamide piperidine *trans*-**96**.



Scheme 2.58

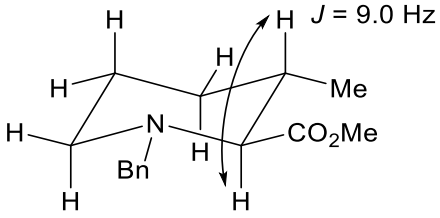
Hydrogenation of pyridine **115** was carried out with PtO_2 in AcOH for 16 h using our standard conditions. An 85:15 mixture of piperidines *cis*-**116** and *trans*-**116** was generated as determined by ^{1}H NMR spectroscopic analysis. This crude mixture was clean enough to react on without further purification (Scheme 2.59). With a view to exploring Normant *el al.*'s epimerisation method on *N*-benzyl piperidine esters *cis*-**123** and *trans*-**123** (see Scheme 2.29), benzylation using reductive amination was carried out. Thus, reaction of PhCHO with the 85:15 mixture of piperidines *cis*-**116** and *trans*-**116**, $NaBH(OAc)_3$ and AcOH in DCE gave, after chromatography, *N*-benzyl piperidine *cis*-**123** (80% yield) and *trans*-**123** (10% yield) (Scheme 2.59).



Scheme 2.59

The assignment of the *cis* and *trans* stereochemistry was assigned based on ^{1}H NMR *J*-values. The C-2 hydrogen had a $^3J_{HH}$ coupling constant of 9.0 Hz which supports the two hydrogens being in axial positions and therefore having the *trans*-stereochemistry. This

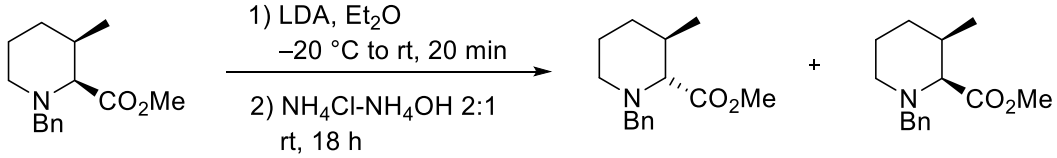
assignment meant that piperidine *cis*-**123** could be inferred as the major product after hydrogenation (Figure 2.18).



trans-**123**

Figure 2.18 – Diagnostic $^{3}J_{HH}$ coupling constant in piperidine *trans*-**123**.

N-Benzyl piperidine *cis*-**123** was then subjected to the epimerisation conditions reported by Normant *et al*.[79] A pre-made solution of LDA was added dropwise to a solution containing *cis*-**123** in Et_2O at –20 °C. The reaction was then warmed to rt over 20 min and stirred at rt for a further 20 min. After cooling to 0 °C, it was quenched with a 2:1 solution of sat $NH_4Cl_{(aq)}$-$NH_4OH_{(aq)}$. The solution was then allowed to warm to rt and left to stir for 18 h. The reaction mixture was then worked-up and the crude product was analysed by ^{1}H NMR spectroscopy, which showed a 50:50 mixture of *N*-benzyl piperidines *cis*-**123** and *trans*-**123**. Purification afforded *trans*-**123** in 34% yield and *cis*-**123** in 31% yield (Scheme 2.60).



cis-**123**

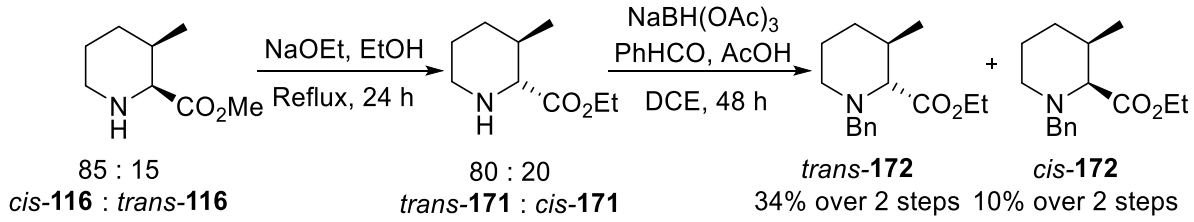
trans-**123**, 34%

cis-**123**, 31%

Scheme 2.60

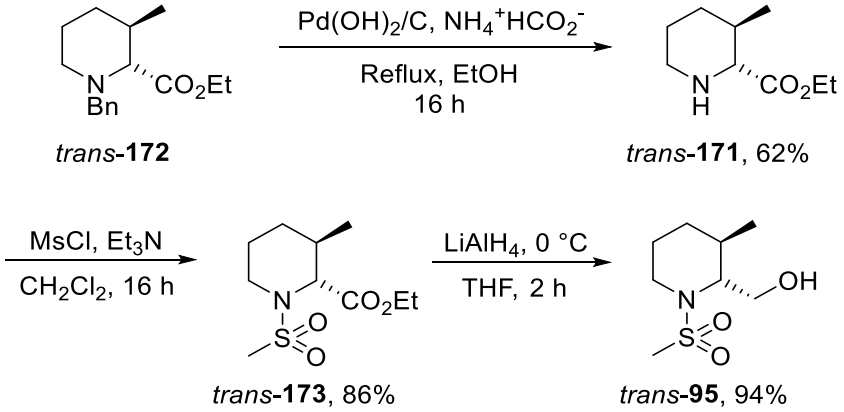
Since these LDA epimerisation conditions gave a 50:50 mixture *N*-benzyl piperidines *cis*-**123** and *trans*-**123**, it was decided to carry out the alternative approach of epimerisation and then benzylation. In a 2010 patent, researchers at Merck had reported that epimerisation of 2,3-piperidine ethyl ester *cis*-**171** using NaOEt in EtOH at 50 °C for 24 h gave a 90:10 mixture of piperidines *trans*-**171** and *cis*-**171**.[107] Since we had the methyl ester in hand, we decided to attempt the epimerisation using the NaOEt/EtOH conditions expecting that transesterification to the ethyl ester would occur to give the same products as reported by Merck. Thus, the 85:15 mixture of piperidines *cis*-**116** and *trans*-**116** was refluxed with NaOEt in EtOH for 24 h. This gave an 80:20 mixture of the ethyl ester piperidines *trans*-**171** and *cis*-**171** with no methyl ester observed. As these piperidines were inseparable, the crude

reaction mixture was *N*-benzylated. After chromatography, *N*-benzyl piperidines *trans*-**172** and *cis*-**172** were isolated in 34% and 10% yields respectively over the two steps (Scheme 2.61).



Scheme 2.61

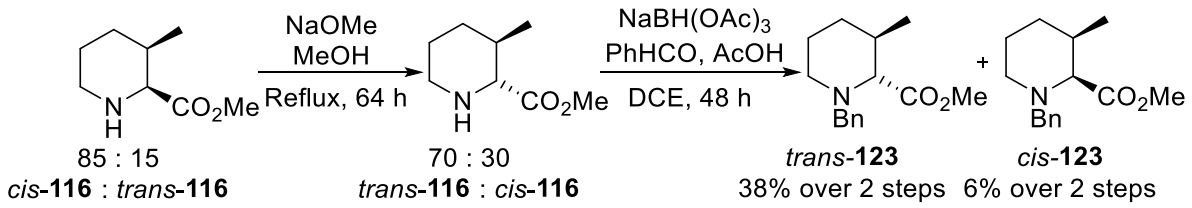
To remove the *N*-benzyl group from *trans*-**172**, transfer hydrogenolysis using 20% $Pd(OH)_2/C$ and $NH_4^+HCO_2^-$ in EtOH was used. This afforded 2,3-piperidine *trans*-**171** in 62% yield. Subsequent sulfonylation with MsCl and Et_3N for 16 h gave sulfonamide *trans*-**173** in 86% yield, with no epimerisation. Reduction of the ester with $LiAlH_4$ at 0 °C for 2 h then gave sulfonamide piperidine 3-D fragment *trans*-**95** in 94% yield (Scheme 2.62).



Scheme 2.62

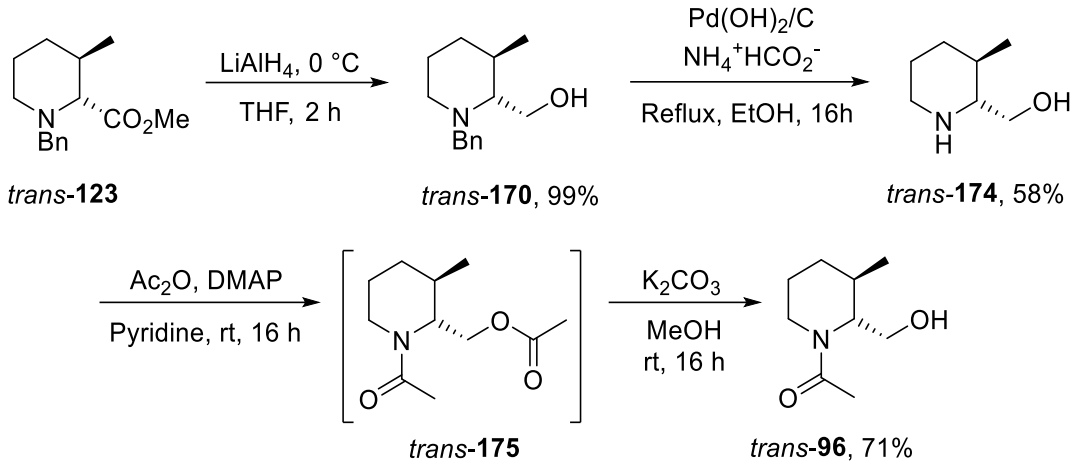
The synthesis of acetamide piperidine *trans*-**96** required repeating the NaOEt epimerisation shown in Scheme 2.61 to bring through more material. Unfortunately, using apparently identical conditions, we did not get the same outcome. It appeared that piperidine ester *cis*-**171** had hydrolysed to the acid, which was supported by the MS data. ^{1}H NMR spectroscopic analysis of the crude reaction mixture also showed no evidence of the ethyl ester peaks. The NaOEt used was a commercial 21% solution in EtOH and, presumably in the time between doing the two experiments, water had been absorbed into the solution and this led to ester hydrolysis. As a result, we decided to use NaOMe which would also avoid the transesterification.

The 85:15 mixture of piperidines *cis*-**116** and *trans*-**116** was reacted with NaOMe refluxing in MeOH and the reaction was monitored by ^{1}H NMR spectroscopy. After 24 h, the ^{1}H NMR spectrum showed a 50:50 mixture of piperidines *cis*-**116** and *trans*-**116**. The reaction was left for a further 40 h and the ^{1}H NMR spectrum showed a 70:30 mixture of piperidines *trans*-**116** and *cis*-**116**. The crude reaction mixture was *N*-benzylated to give piperidine *trans*-**123** in a similar yield (38% over two steps) as observed in the original NaOEt route (see Scheme 2.61) and piperidine *cis*-**123** in 6% yield (Scheme 2.63).



Scheme 2.63

Acetamide piperidine *trans*-**96** was synthesised following the double acylation route previously discussed for acetamide piperidine *cis*-**85** (see Table 2.2). The route avoided the possibility of any epimerisation and selective removal of the *O*-acyl group was established. Methyl ester piperidine *trans*-**123** was treated with $LiAlH_4$ at 0 °C for 2 h to give *N*-benzyl amino alcohol *trans*-**170** in 99% yield. Transfer hydrogenolysis then afforded amino alcohol *trans*-**174** in 58% yield (Scheme 2.64). Piperidine alcohol *trans*-**174** was stirred with Ac_2O and DMAP in pyridine to give amido ester *trans*-**175**. The crude product was treated with K_2CO_3 in MeOH which after 16 h, gave acetamide piperidine *trans*-**96** in 71% yield (Scheme 2.64). In contrast to the 2,6-disubstituted system *cis*-**85** (see Table 2.2), the cleavage of the *O*-acyl this time proceeded without removal of the amide even though the reaction was left for 16 h.



Scheme 2.64

Within this section the synthesis of disubstituted piperidines *cis*-**86**, *cis*-**87**, *cis*-**84**, *cis*-**85**, *trans*-**95** and *trans*-**95** were all discussed. We were able to access the *cis*-diastereoisomers *via* pyridine hydrogenation and subsequent protection to aid separation of the major *cis*-piperidine. Access to the 2,3-disubstituted *trans*-piperidine was achievable using base-mediated epimerisation to afford the more thermodynamically favoured *trans*-diastereoisomer. Finally, derivatisation of the nitrogen gave the six fragments in 3-6 steps.

2.3 Conclusions and Overview

We were able to synthesise three disubstituted pyrrolidine and six disubstituted piperidine fragments using the approaches outlined within the chapter. The three pyrrolidine fragments were synthesised *via* nucleophilic ring opening and condensation to afford the dihydropyrrole. Stereoselective reduction of the dihydropyrrole afforded the *cis*-diastereoisomer stereoselectively, with access to the *trans*-diastereoisomer possible *via* base-mediated epimerisation with neat DBU at reflux for 24 h.

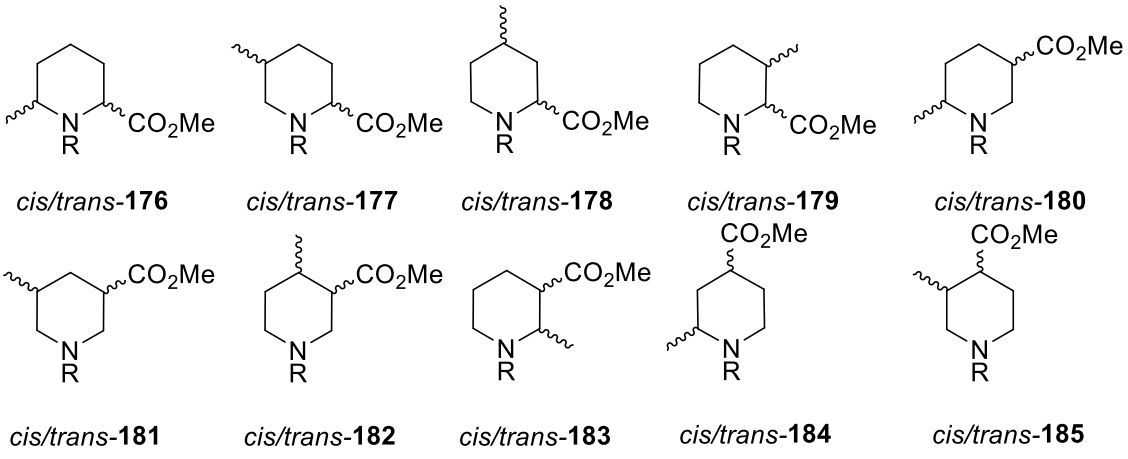
The six piperidine fragments were all synthesised starting from the hydrogenation of the corresponding disubstituted pyridine, which afforded the *cis*-diastereoisomers as the major products. Protection of the 2,5-disubstituted *cis*-piperidine aided the separation of the diastereoisomers, with hydrogenation of the 2,6-disubstituted piperidine selectively affording the *cis*-piperidine. The 2,3-disubstituted *trans*-piperidine was synthesised *via* base mediated epimerisation of the *cis*-piperidine using either NaOEt or NaOMe at reflux, which afforded the *trans*-diastereoisomer selectively.

Along with the other O'Brien group members, 32 fragments were synthesised. Full analysis of the physicochemical properties and 3-D shape of the 32 fragments is described in Chapter 5.

Chapter 3 Synthesis of Disubstituted Piperidines with Methyl and Methyl Ester Substituents

In order to carry out the synthesis of the six piperidine 3-D fragments described in Chapter 2, we had developed ways of carrying out the diastereoselective synthesis of 2,3-*trans*-, 2,3-*cis*-, 2,5-*cis*- and 2,6-*cis*-disubstituted piperidines. Other members of the group had also developed approaches to some of the other regio- and diastereoisomers during the synthesis of some of the other 19 piperidine 3-D fragments. Hence, it was decided to try to develop general methodology that would allow the synthesis of all possible regio- and diastereoisomers of disubstituted piperidines with methyl and methyl ester substituents.

If geminal disubstituted isomers are excluded, there are 20 regio- and diastereoisomers of disubstituted piperidines. The aim was to identify the fewest number of different pieces of synthetic methodology that could be used to access all 20 isomers. This Chapter describes our efforts towards that goal and demonstrates that using three main strategies, diastereoselective access to each of the 20 piperidines was possible.



cis/trans-**176** *cis/trans*-**177** *cis/trans*-**178** *cis/trans*-**179** *cis/trans*-**180**

cis/trans-**181** *cis/trans*-**182** *cis/trans*-**183** *cis/trans*-**184** *cis/trans*-**185**

3.1 Overview of the Three Planned Strategies to Disubstituted Piperidines

The work in Chapter 2 focused on the synthesis of disubstituted piperidine fragments with a methyl substituent and a primary alcohol group (accessed *via* reduction of a methyl ester). In the work described in Chapter 2 and work by other members of the group, two main strategies were used to control the relative stereochemistry in the fragments: pyridine hydrogenation gave disubstituted *cis*-piperidines with good levels of diastereoselectivity and epimerisation (*via* an enolate formation and protonation) gave access to disubstituted *trans*-piperidines. As a result of these studies, we had accessed several regioisomers of the disubstituted *cis*- and *trans*-piperidines containing methyl and methyl ester substituents. Therefore, we considered developing a general approach that would allow access to all of the 20 possible regio- and diastereoisomers of such disubstituted piperidines, either as the free amines or protected versions (*e.g.* with Bn or Boc protecting groups). As shown in Figure 3.1, there are ten different regioisomeric disubstituted *cis*-piperidines. The plan was to access the disubstituted *cis*-piperidines using the pyridine hydrogenation method developed within Chapter 2, which had already led to the synthesis of piperidines *cis*-**176** (R = H), *cis*-**179** (R = Bn) and *cis*-**180** (R = Boc). Furthermore, other members of the group had also synthesised piperidines *cis*-**182** (R = Boc), *cis*-**183** (R = Bn) and *cis*-**185** (R = Boc) starting from pyridines using the same approach.[108,109] We would thus focus on synthesising piperidines *cis*-**177**, *cis*-**178**, *cis*-**181** and *cis*-**184**.

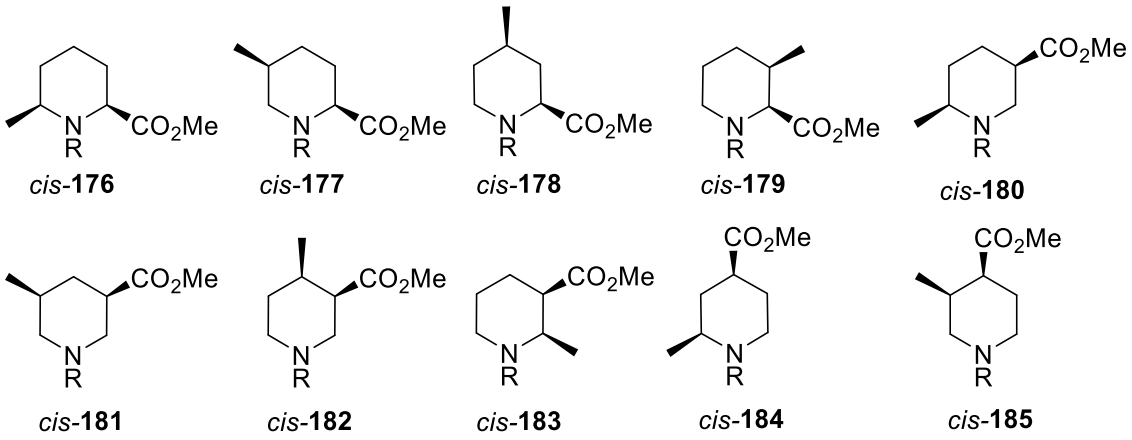


Figure 3.1 – Structures of the ten disubstituted *cis*-piperidines accessible by pyridine hydrogenation.

To access eight of the ten possible *trans*-piperidines, epimerisation using enolate formation was envisaged. Depending on the substitution pattern and substituent on the nitrogen, two different variants of epimerisation would be used. For example, base-mediated epimerisation of 2,3-. 2,5- and 3,4-*cis*-disubstituted piperidines with a free amine or *N*-benzyl group should

give diastereoselective access to the corresponding disubstituted piperidines *trans*-**177**, *trans*-**179**, *trans*-**180**, *trans*-**182**, *trans*-**183** and *trans*-**185** where R = H or Bn (Figure 3.2). As explained in Section 2.2.4, due to the substitution pattern around the piperidine ring, the thermodynamic driving force for both substituents to be equatorial should give access to the *trans* diastereoisomers stereoselectively. As the synthesise of piperidine *trans*-**179** had already been achieved in Chapter 2 and with another member of the group synthesising piperidine *trans*-**183** using base-mediated epimerisation focus would be placed on piperidines *trans*-**177**, *trans*-**180**, *trans*-**182** and *trans*-**185**.

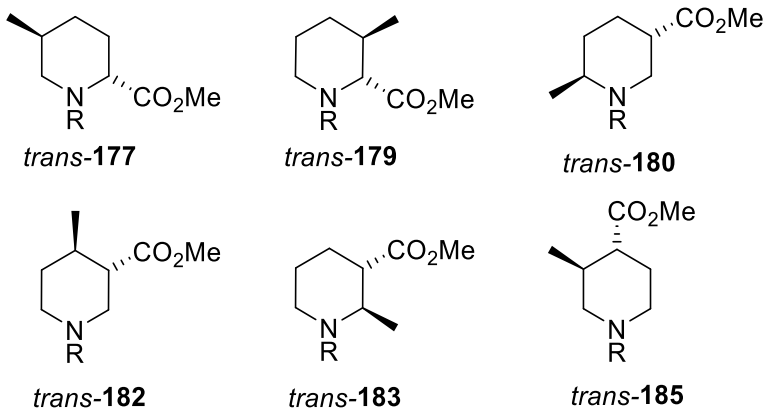
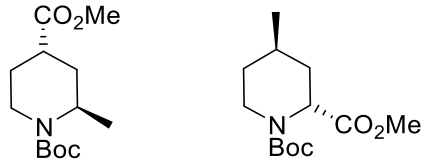


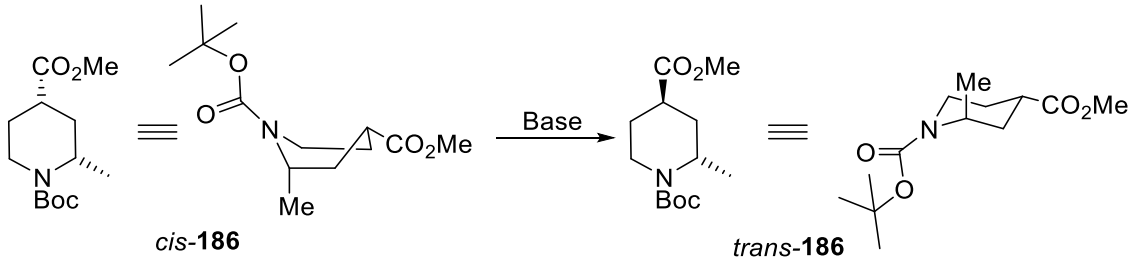
Figure 3.2 – Structures of six disubstituted *trans*-piperidines accessible by epimerisation.

A different type of base-mediated epimerisation could be used to synthesise the 2,4-disubstituted *trans*-piperidines *trans*-**186** and *trans*-**187** which have a Boc-protected amine (Figure 3.3). With 2,4-disubstituted *cis*-piperidines having a NH or *N*-benzyl group, both substituents can be in the more favoured equatorial positions. However, installation of a Boc group on the nitrogen forces the substituent at the C-2 position to adopt an axial position to minimise the steric interaction between the Boc group and the substituent ($A^{1,3}$-type strain). The C-4 substituent would then be forced into an axial position in a chair conformation as it is a *cis*-piperidine or, more likely, it would adopt an equatorial position in a boat conformation. Upon epimerisation, the formation of a thermodynamic chair-conformation with an equatorial C-4 substituent provides the driving force to afford piperidine *trans*-**186** (Figure 3.4). The same situation applies to the other 2,4-disubstituted *N*-Boc piperidine *trans*-**187**.



trans-**186** *trans*-**187**

Figure 3.3 – Structures of two 2,4-disubstituted *trans*-piperidines.



cis-**186** *trans*-**186**

Figure 3.4 – Base-mediated epimerisation to access *N*-Boc piperidine *trans*-**186**.

Finally, a lithiation-trapping strategy could be used to access some of the disubstituted *N*-Boc piperidines. Indeed, a diastereoselective lithiation-trapping approach to 2,6-*trans* disubstituted *N*-Boc piperidines has been reported[102] (Scheme 2.42) and use of this approach for the synthesis of *N*-Boc piperidine *trans*-**188** was developed by another member of the group. Selective lithiation of an equatorial proton α to the *N*-Boc group occurs from a conformation in which the already-present substituent at the 3- and 4-positions is in an equatorial position. As a result, this lithiation-trapping strategy could also give access to disubstituted piperidines *trans*-**189** and *cis*-**187** (Figure 3.5). However, we anticipated that lithiation-trapping would only be explored if the initial epimerisation and hydrogenation routes to these piperidines failed to afford the *trans* and *cis*-diastereoisomers stereoselectively. It should be noted that the lithiation of *N*-Boc 3-methylpiperidine **190** could occur at the C-2 or C-6 position. However, the steric hindrance of the methyl substituent hinders the C-2 position resulting in lithiation occurring at the C-6 position, which leads to high regioselectivity being observed for the formation of organolithium and hence *trans*-**189** after trapping with methyl chloroformate (Figure 3.6).[101]

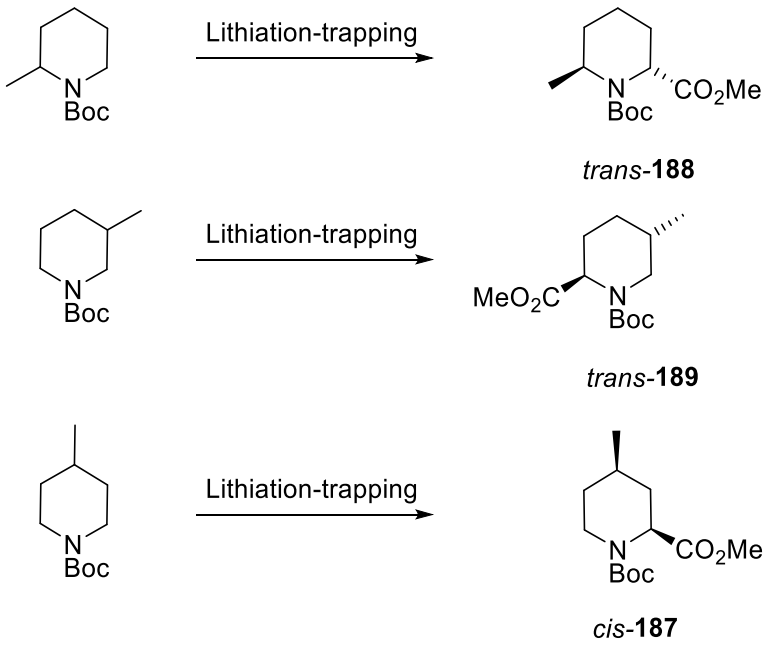


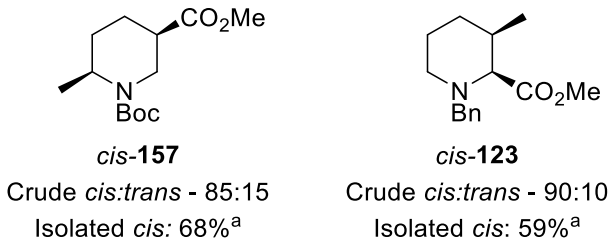
Figure 3.5 – Structures of piperidines *trans*-**188**, *trans*-**189** and *cis*-**187** accessible by lithiation-trapping.

Figure 3.6 – Lithiation-trapping to give piperidine *trans*-**189**.

Thus, using only three strategies, namely pyridine hydrogenation, base-mediated epimerisation and lithiation-trapping, we believed that it should be possible to synthesise 19 out of the possible 20 disubstituted *cis*-/*trans*-piperidines containing methyl/methyl ester substituents, with some of the piperidines potentially accessible *via* more than one approach. At the outset, it appeared that the synthesis of the 3,5-disubstituted piperidine *trans*-**181** would be challenging to synthesise due its substitution pattern and the inability to access it *via* base-mediated epimerisation. This will be discussed in more detail in Section 3.2.

3.2 Strategy One: Pyridine Hydrogenation Route to *cis*-Disubstituted Piperidines

The stereoselective synthesis of 2,5- and 2,3-disubstituted piperidines *cis*-**157** and *cis*-**123** using hydrogenation of the corresponding disubstituted pyridines was described in Chapter 2 along with proof of stereochemistry (see Scheme 2.45 and Figure 2.18). In that work, the hydrogenation conditions were optimised and involved the use of H_2 and 10 mol% PtO_2 in AcOH for 16 h at rt. Using these conditions, 2,5- and 2,3-disubstituted piperidines *cis*-**157** and *cis*-**123** were synthesised (Figure 3.7).

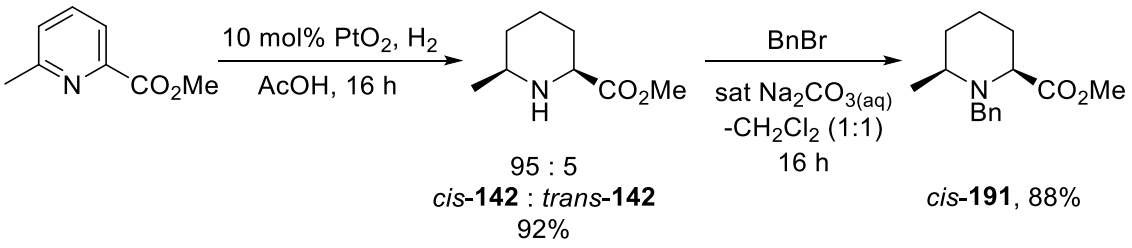


cis-**157**
Crude *cis:trans* - 85:15
Isolated *cis:* 68%[a]

cis-**123**
Crude *cis:trans* - 90:10
Isolated *cis*: 59%[a]

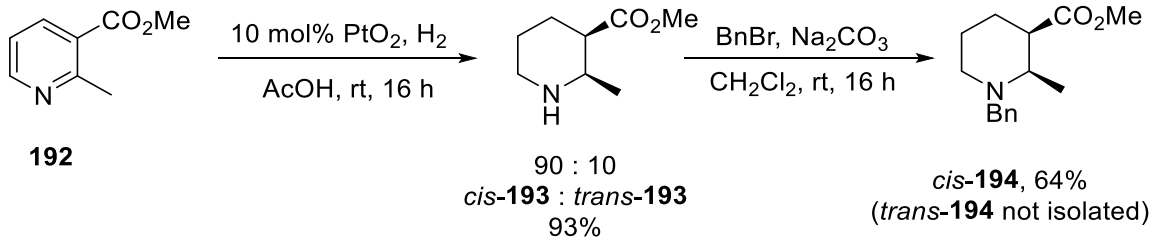
Figure 3.7 – Piperidines *cis*-**157** and *cis*-**123** accessed using pyridine hydrogenation.
a) Yield of *cis*-piperidine over the two steps of hydrogenation and amine protection.

In Chapter 2, the synthesis of the 2,6-disubstituted piperidine fragments were described. As part of that approach, the corresponding 2,6-disubstituted piperidine *cis*-**142** had been synthesised diastereoselectively using pyridine hydrogenation (see Scheme 2.49). To isolate the *cis*-piperidine, the 95:5 mixture of crude piperidines *cis*-**142** and *trans*-**142** was directly benzylated, which gave *N*-benzyl piperidine *cis*-**191** in 88% yield (Scheme 3.1).



Scheme 3.1

The next system to be investigated was 2,3-disubstituted pyridine **192** which, using our standard hydrogenation conditions (10 mol% PtO_2), afforded a 90:10 mixture of piperidines *cis*-**193** and *trans*-**193** in 93% yield. *N*-Benzylation, using alkylation, enabled the diastereoisomers to be separated, with *N*-benzyl piperidine *cis*-**194** isolated in 64% yield (Scheme 3.2).



Scheme 3.2

The relative stereochemistry of piperidine *cis*-**194** was assigned by comparing the $^{3}J_{HH}$ values between the protons at the C-2 and C-3 positions. There are two potential conformations for *cis*-**194** (Figure 3.8), but whichever conformation is adopted, the $^{3}J_{HH}$ value of 5.0 Hz for the coupling between the protons on C-2 and C-3 was consistent with an axial-equatorial coupling.

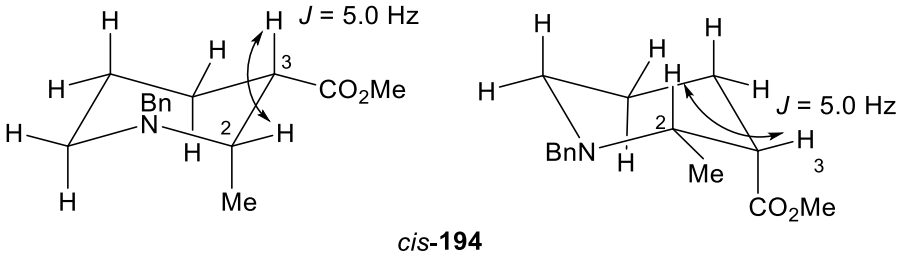
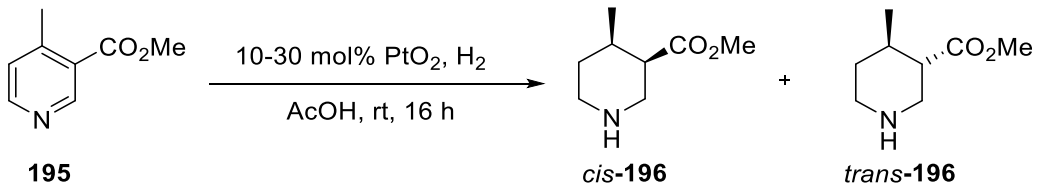


Figure 3.8 – Diagnostic $^{3}J_{HH}$ coupling constants for 2,3-disubstituted piperidine *cis*-**194**.

A system which had not been studied previously during the group's 3-D fragment synthesis efforts was the 3,4-disubstituted piperidines. Hydrogenation of 4-methylpyridine-3-methyl ester **195** using our standard hydrogenation conditions (10 mol%, PtO_2) failed to afford complete reduction. ^{1}H NMR spectroscopic analysis of the crude reaction mixture after a 136 h reaction time showed a 50:35:15 mixture of piperidines *cis*-**196**, *trans*-**196** and pyridine **195** (Table 3.1, entry 1). The PtO_2 catalyst loading was increased to 20 mol% and reacted for 16 h. The ^{1}H NMR spectrum of the crude reaction mixture showed a 40:20:40 mixture of piperidines *cis*-**196**, *trans*-**196** and pyridine **195** (entry 2). Therefore, the catalyst loading was finally increased to 30 mol% PtO_2, which gave full reduction of pyridine **195** and afforded a 65:35 mixture of piperidines *cis*-**196** and *trans*-**196** in 97% crude yield (entry 3).

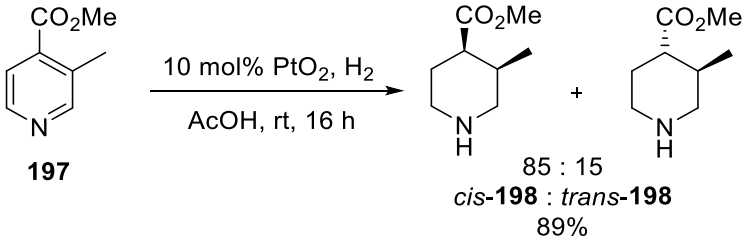


Entry	PtO_2 mol %	Time (h)	*cis*-196 : *trans*-196 : 195[a]	Yield *cis*-196 and *trans*-196 (%)[b]
1	10	136	35:15:50	N/A
2	20	16	40:20:40	N/A
3	30	16	65:35:0	97

Table 3.1 – Hydrogenation of pyridine **195** using different catalyst loadings of PtO_2.

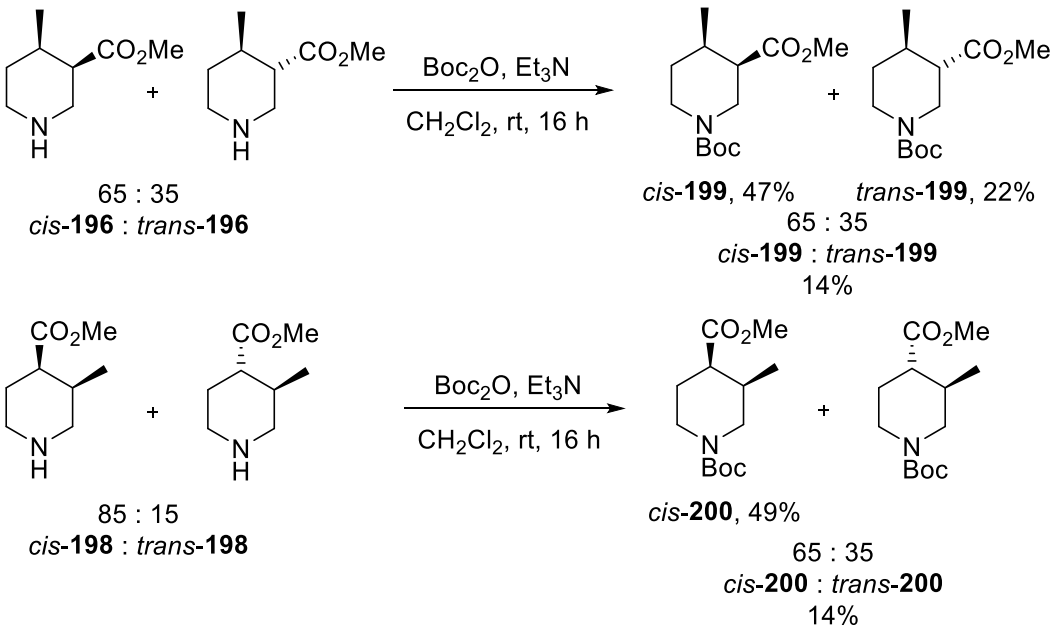
a) Ratio determined by ^{1}H NMR spectroscopic analysis; (b) Yield of crude product.

In contrast, the hydrogenation of pyridine **197**, which has the methyl and methyl ester groups swapped over, gave no problems with full reduction achieved within 16 h using the standard conditions (10 mol% PtO_2). In this case, an 85:15 mixture of piperidines *cis*-**198** and *trans*-**198** was isolated in 89% crude yield (Scheme 3.3).



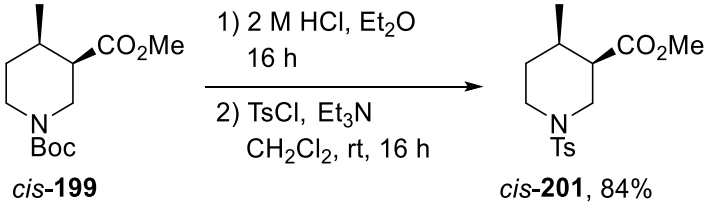
Scheme 3.3

The two 3,4-disubstituted piperidine mixtures were then converted into their *N*-Boc analogues to enable separation of the diastereoisomers. Starting from a 65:35 mixture of piperidines *cis*-**196** and *trans*-**196**, purification by chromatography afforded *N*-Boc piperidines *cis*-**199** in 47% yield, *trans*-**199** (22% yield) and a 65:35 mixture of *cis*-**199** and *trans*-**199** (14% yield). Similarly, from piperidines *cis*-**198** and *trans*-**198**, purification gave *N*-Boc piperidine *cis*-**200** in 49% yield and an 80:20 mixture of *N*-Boc piperidines *cis*-**200** and *trans*-**200** (14% yield) (Scheme 3.4).



Scheme 3.4

To aid with assigning the stereochemistry, the Boc protecting group in each of cis piperidine was converted into their *N*-tosyl analogues. *N*-Tosyl piperidine *cis*-**201** was synthesised in 84% yield (Scheme 3.5). The relative stereochemistry was assigned as *cis*-**201** by X-ray crystallography (Figure 3.9). As shown in Figure 3.9, the methyl substituent occupied an axial position and the methyl ester was equatorial, confirming their *cis*-relationship.



Scheme 3.5

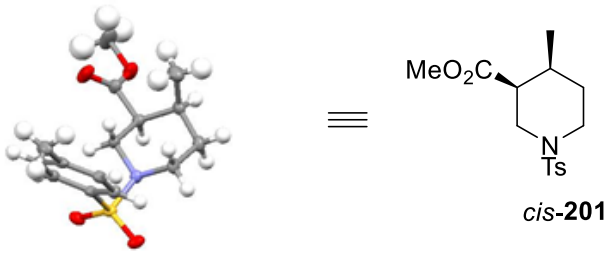
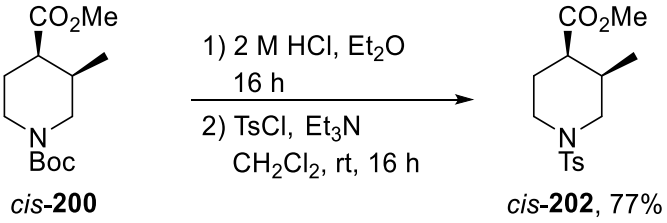


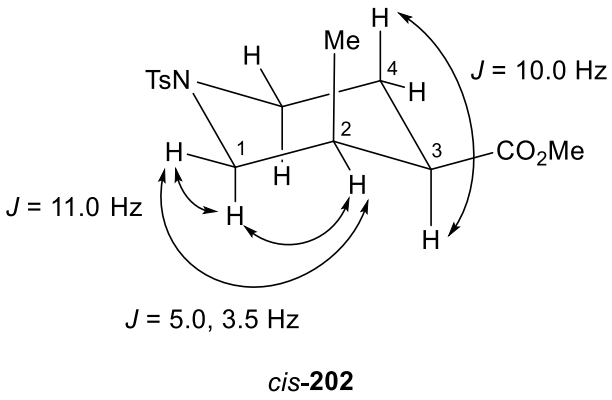
Figure 3.9 - X-ray crystal structure of *N*-tosyl piperidine *cis*-**201**

N-Boc piperidine *cis*-**200** was converted into *N*-tosyl piperidine *cis*-**202** in 77% yield (Scheme 3.6). On this occasion, the stereochemistry was determined based on $^{3}J_{HH}$ values

(Figure 3.10). The two protons on C-1 showed a $^{2}J_{HH}$ value of 11.0 Hz and $^{3}J_{HH}$ values of 5.0 and 3.5 Hz to the proton on C-2. These $^{3}J_{HH}$ values suggested that the proton at the C-2 position was in an equatorial position (with the methyl group in an axial position). The axial proton at the C-4 position showed a $^{2}J_{HH}$ value of 14.0 Hz and $^{3}J_{HH}$ values of 10.0, 10.0 and 4.0 Hz, which indicated that the C-3 proton was in an axial position (with the methyl ester in an equatorial position). All this analysis confirmed the *cis*-stereochemistry in piperidine *cis*-**202**.



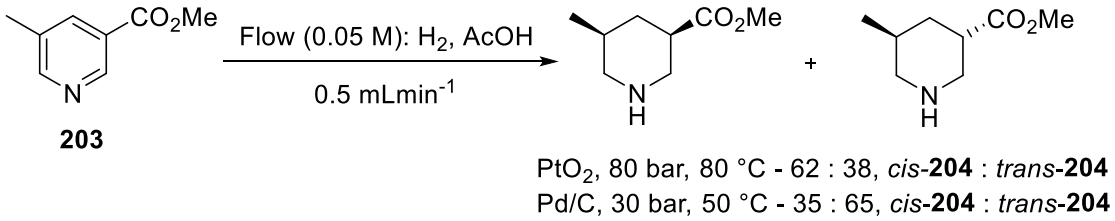
Scheme 3.6



cis-**202**

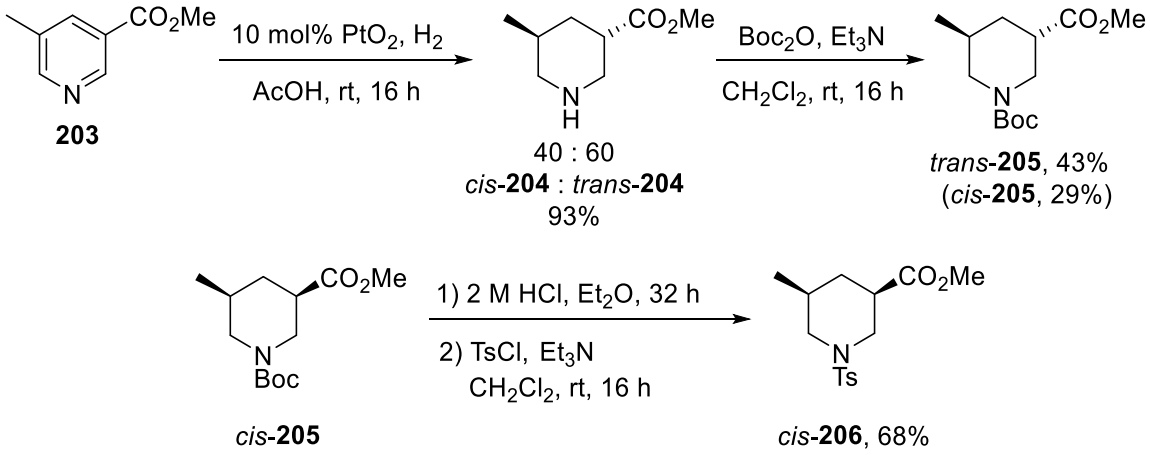
Figure 3.10 - Confirmation of stereochemistry of *cis*-**202** *via* $^{3}J_{HH}$ values.

Next, we planned to investigate the hydrogenation of 3-methylpyridine-5-methyl ester **203**. Kappe *et al.* had in fact studied the hydrogenation of pyridine ester **203** under flow hydrogenation conditions and were able to selectively obtain the *cis* and *trans*-piperidines by varying the catalyst, pressure and temperature of the hydrogenation reactions. The selective hydrogenation to afford the *cis*-piperidine used 10% w/w PtO_2 at 80 bar and 80 °C and gave a 63:37 mixture of piperidines *cis*-**204** and *trans*-**204**. In contrast, hydrogenation using 10% w/w Pd/C at 30 bar and 50 °C gave a 65:35 mixture of the piperidines *trans*-**204** and *cis*-**204** (Scheme 3.7). No explanation was put forward to explain the diastereoselectivity of these hydrogenation reactions.



Scheme 3.7

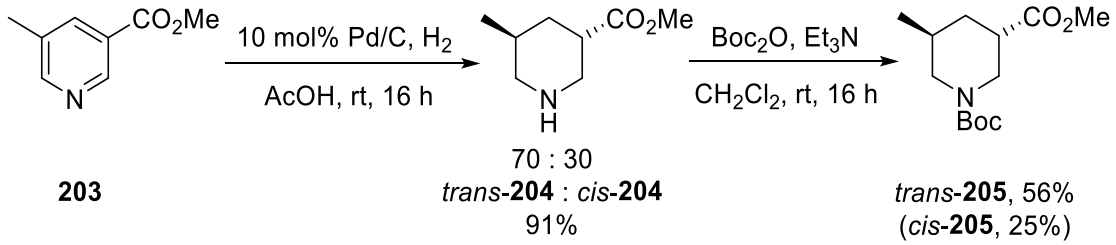
For comparison with Kappe's results, we explored the use of our standard hydrogenation conditions (10 mol% PtO_2) with pyridine methyl ester **203**. This gave a 60:40 mixture of piperidines *trans*-**204** and *cis*-**204** in 93% crude yield. The reaction mixture was treated with Boc_2O and the diastereoisomeric *N*-Boc compounds were separated to give *N*-Boc piperidines *cis*-**205** in 43% yield and *N*-Boc piperidine *trans*-**205** in 29% yield (Figure 3.8). The stereochemistry of *N*-Boc piperidines *trans*-**205** and *cis*-**205** was assigned as follows. Kappe had used NOE NMR experiments to assign the stereochemistry of *N*-tosyl piperidines *trans*-**206** and *cis*-**206**.[110] Therefore, the minor diastereomeric *N*-Boc piperidine was converted into the *N*-tosyl analogue and, by comparing the ^{1}H NMR spectroscopic data with those reported by Kappe, it was established that this was *N*-tosyl piperidine *cis*-**206** (Figure 3.8). In contrast to all other substitution patterns, this pyridine hydrogenation reaction gave the *trans*-piperidine as the major product, contrasting with Kappe's results using PtO_2 under pressure (see Figure 3.7).



Scheme 3.8

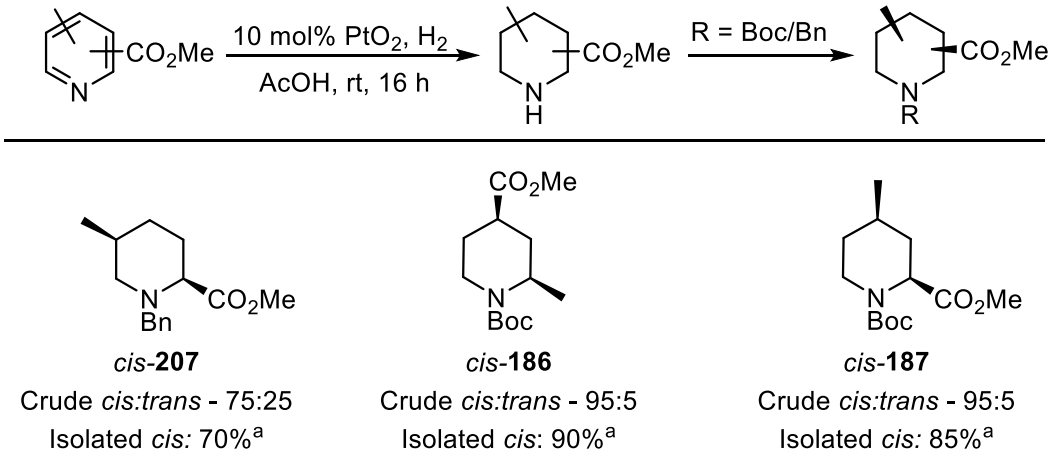
Since Kappe *et al.* had obtained the highest *trans*-diastereoselectivity using Pd/C as the calalyst (see Figure 3.8), we wondered whether this would also lead to an even more selective approach to *N*-Boc piperidine *trans*-**205**. Thus, using 10 mol% Pd/C under

otherwise identical conditions to the PtO_2 reactions, hydrogenation of pyridine ester **203** gave a 70:30 mixture of piperidines *trans*-**204** and *cis*-**204** in 91% crude yield, which was a slight improvement on the ratio obtained by Kappe *et al*. The 70:30 mixture of piperidines *trans*-**204** and *cis*-**204** was subsequently reacted with Boc_2O to enable separation of the diastereoisomers. Purification afforded *N*-Boc piperidine *trans*-**205** in 56% yield and *cis*-**205** in 25% yield (Scheme 3.9). Hence, this pyridine hydrogenation strategy afforded a stereoselective route to 3,5-disubstituted piperidine *trans*-**205**. This was in fact the diastereoisomer that we anticipated would be difficult to access since neither base-mediated epimerisation nor lithiation-trapping could offer a stereoselective route.



Scheme 3.9

The remaining three substitution patterns, the 2,5- and both 2,4-disubstituted *cis*-piperidines were studied by another member of the group, with the *cis*-piperidine being the major diastereoisomer after hydrogenation. These three results are summarised in Figure 3.10 and the *cis*-piperidines, *cis*-**207**, *cis*-**186** and *cis*-**187**, were isolated as either the *N*-Boc or *N*-Bn derivatives in good yields (Scheme 3.10).

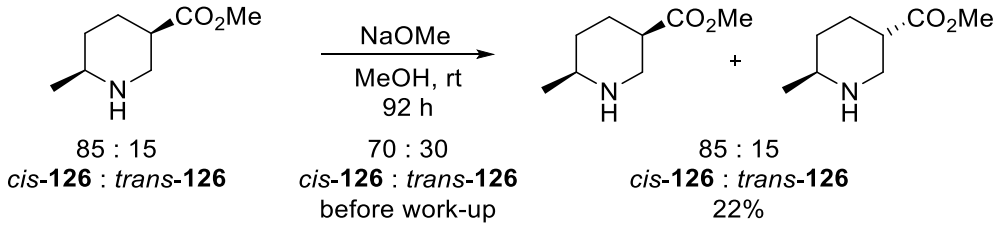


Scheme 3.10 – a) The isolated *cis*-yields are reported over two steps (hydrogenation and amine protection).

Hydrogenation using the use of H_2 and either 10 mol% PtO_2, or 30 mol% PtO_2 for pyridine **195**, in AcOH for 16 h at rt afforded nine out of ten *cis*-piperidines selectively. The hydrogenation strategy afforded a route to the 3,5-disubstituted *trans*-piperidine **204**, with 10 mol% Pd/C giving the highest diastereoselectivity after hydrogenation.

3.3 Strategy Two: Base-Mediated Epimerisation

Base-mediated epimerisation using enolate formation could offer a stereoselective route to six of the ten disubstituted *trans*-piperidines with the free amine or *N*-benzyl group. The synthesis of 2,3-disubstituted piperidine *trans*-**116** had already been established using epimerisation (NaOMe in MeOH at reflux for 24 h) followed by benzylation to separate out the diastereoisomers (see Scheme 2.63). A similar epimerisation approach was envisaged for the selective synthesis of piperidine *trans*-**180**. To start, an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** was reacted with NaOMe in MeOH at rt. After 92 h, ^{1}H NMR spectroscopic analysis of the crude reaction mixture obtained after evaporation of the MeOH solvent showed a 70:30 mixture of piperidines *cis*-**126** and *trans*-**126**. After a subsequent work-up with water and saturated $NaHCO_{3(aq)}$, an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** was isolated in 22% crude yield (Scheme 3.11).

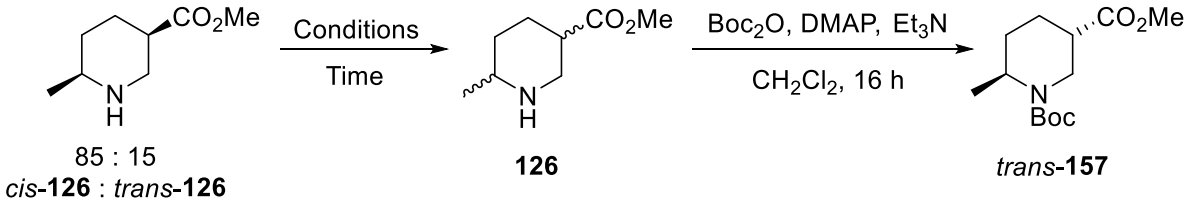


Scheme 3.11

The outcome of this reaction highlighted two issues. First, there was limited epimerisation observed from performing the reaction at rt. Second, the isolated yield after the work-up was low. We considered that this could be due to the piperidines **126** undergoing ester hydrolysis to the carboxylic acid to generate a water-soluble amino acid. Thus, the aqueous layer was analysed by mass spectrometry and a peak corresponding to the *m/z* value of the carboxylic acid was observed, supporting our theory. To try and increase the rate of epimerisation, reactions at higher temperatures were explored. In addition, we decided to remove the aqueous work-up by evaporating the reaction mixture after treatment with NaOMe in MeOH and took the crude product directly on for Boc protection. Table 3.2 summarises the results of these reactions; entry 1 shows the result at rt.

An 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** was reacted with NaOMe in MeOH at reflux (80 °C). After 24 h, ^{1}H NMR spectroscopic analysis of the crude reaction mixture (no aqueous work-up) showed a 70:30 mixture of piperidines *trans*-**126** and *cis*-**126** (entry 2), clearly indicating that a significant amount of epimerisation had occurred. The crude

reaction mixture was Boc protected and purified by chromatography. This afforded *N*-Boc piperidine *trans*-**157** in 27% yield, *cis*-**157** (10% yield) and a 70:30 mixture of *N*-Boc piperidines *trans*-**157** and *cis*-**157** (4% yield). A similar reaction using K_2CO_3 in MeOH at 80 °C for 24 h gave an 80:20 mixture of piperidines *trans*-**126** and *cis*-**126**. After Boc protection and purification, *N*-Boc piperidine *trans*-**157** was isolated in 18% yield, with no other products isolated (entry 3). Even though an aqueous work-up was avoided, the mass recovery from these two experiments was very low and we suspected that ester hydrolysis was occurring due to traces of water in the reactions. Epimerisation with DBU was then trialled at 50 and 80 °C. In both cases, ^{1}H NMR spectroscopic analysis of the crude reaction mixture obtained after evaporation of the toluene solvent showed that no epimerisation of the piperidine reaction mixture had occurred (entries 4-5). Thus, using NaOMe at 25 °C and DBU at 50 or 80 °C, little epimerisation was observed. In contrast, with NaOMe or K_2CO_3 in MeOH at 80 °C for 24 h, epimerisation occurred readily to give piperidine *trans*-**157** as the major product, but mass recovery was poor.



85 : 15 *cis*-**126** : *trans*-**126** | **126** | *trans*-**157**

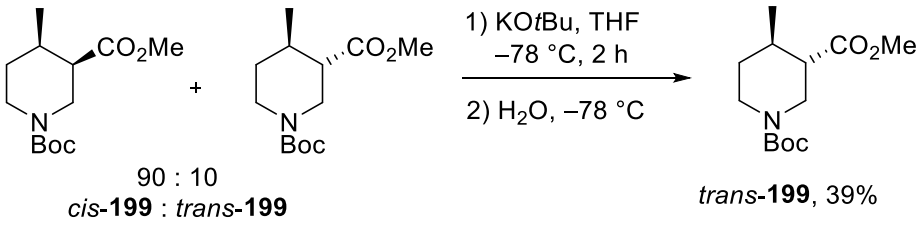
Entry	Base	Temp (°C)	Time (h)	*cis*-126 : *trans*-126[a]	Yield of *trans*-157 (%)
1	NaOMe	25	96	70:30	N/A
2	NaOMe	80	24	30:70	27[b]
3	K_2CO_3	80	24	20:80	18[b]
4	DBU	50	96	85:15	N/A
5	DBU	80	24	80:20	N/A

Table 3.2 – Epimerisation of an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126**.

a) Ratio determined by ^{1}H NMR spectroscopy of the crude NH piperidines, b) No aqueous work-up was performed after base-mediated epimerisation.

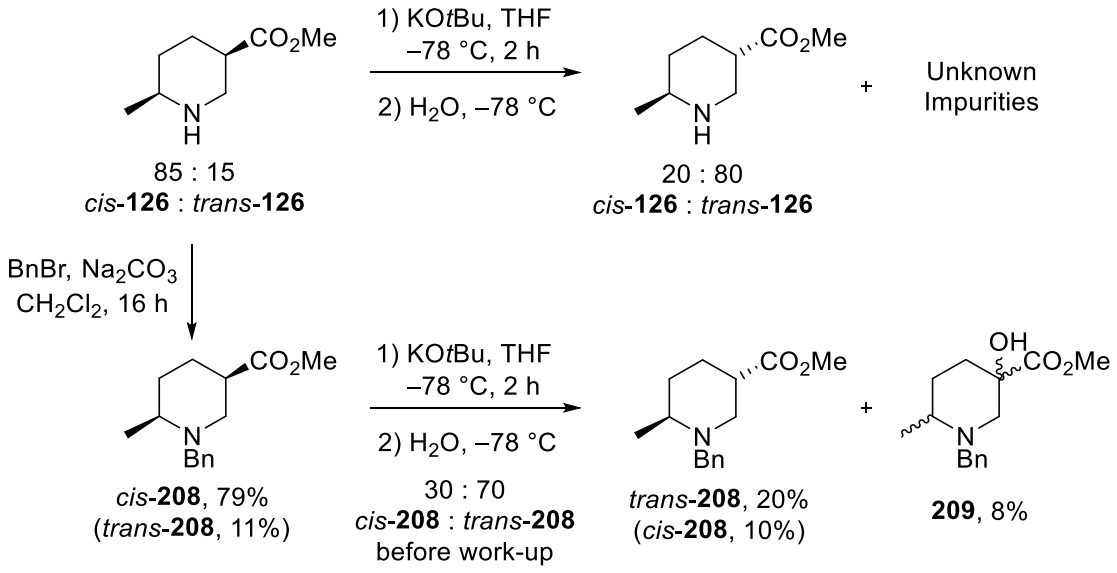
Given the poor mass recovery, alternative epimerisation conditions were explored and an example with a 3,4-disubstituted piperidine system was found. In 2010, work from a patent reported that reaction of a 90:10 mixture of *N*-Boc piperidines *cis*-**199** and *trans*-**199** with KO*t*Bu in THF at –78 °C gave a 39% yield of *N*-Boc piperidine *trans*-**199** (Scheme 3.12).[81] Despite the very low –78 °C reaction temperature, a yield of *N*-Boc piperidine *trans*-**199**

above the 10% that was present to start with showed that some epimerisation had been achieved.



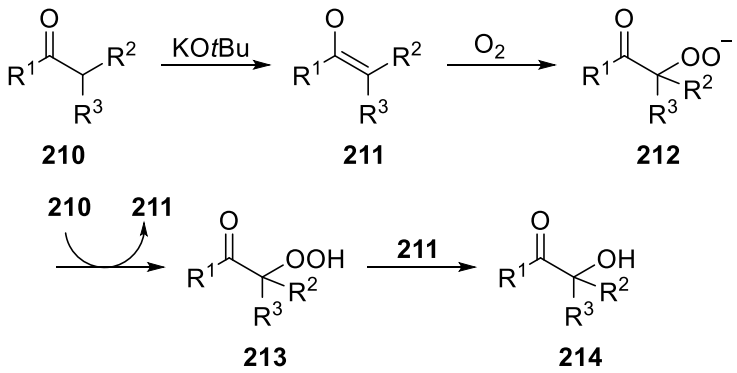
Scheme 3.12

Therefore, these conditions were explored. A 1 M solution of KO*t*Bu in THF was added to an 85:15 mixture of piperidine *cis*-**126** and *trans*-**126** in THF at –78 °C and reacted for 2 h. The reaction mixture was quenched with water at –78 °C and it was allowed to warm gradually to rt. After an aqueous work-up, the ^{1}H NMR spectrum of the crude product showed an 80:20 mixture of piperidines *trans*-**126** and *cis*-**126** together with some unidentified impurities (Scheme 3.13). However, the mass recovery was low, and in this case, we suspected that the amino esters **126** may be water soluble. An aqueous work-up was necessary with the KO*t*Bu epimerisation conditions since the reaction was quenched with water. Therefore, the corresponding benzylated piperidine was investigated. Benzylation of an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** with BnBr afforded, after purification, *N*-benzyl piperidine *cis*-**208** in 79% yield and *N*-benzyl piperidine *trans*-**208** (11% yield) (Scheme 3.13). *N*-Benzyl piperidine *cis*-**208** was treated with KO*t*Bu at –78 °C for 2 h and the ^{1}H NMR spectrum after an aqueous work-up showed a 70:30 mixture of piperidines *trans*-**208** and *cis*-**208**. Purification afforded *N*-benzyl piperidines *trans*-**208** in 20% yield along with *cis*-**208** (10% yield); a single unknown diastereoisomer of hydroxy ester **209** was also isolated in 8% yield (Scheme 3.13).



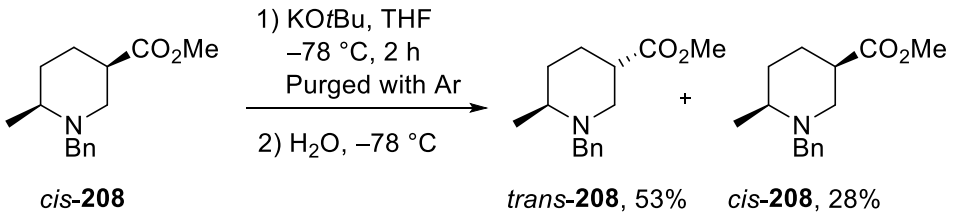
Scheme 3.13

The structure of hydroxyl ester **209** was established by MS, IR, ^{1}H and ^{13}C NMR spectroscopic data. The IR spectrum confirmed the presence of the hydroxy group, with a broad peak at 3456 cm^{-1}. The ^{1}H NMR spectrum showed two doublets at 2.93 and 2.38 ppm which correspond to the NCH_2 protons. The peaks only showed geminal coupling (^{2}J = 11.5 Hz). Mass spectrometry showed a *m/z* peak corresponding to hydroxy ester **209**. The ^{1}H NMR spectrum after work-up was re-analysed and showed a 50:25:25 mixture of *trans*-**208**, *cis*-**208** and hydroxy ester **209**. Enolate hydroxylation is precedented in the work of Gnanaprakasam *et al.* who explored a series of hydroxylations α to carbonyl groups using only KO*t*Bu in air with no other additives or oxidants.[111] Their proposed reaction mechanism proceeds *via* deprotonation of **210** to form enolate **211**, followed by trapping with O_2 to give the superoxide anion **212**. Deprotonation of **210** forms peroxide **213** which is then cleaved by **211** to give hydroxy ketone **214** (Scheme 3.14).



Scheme 3.14

In an attempt to avoid the formation of hydroxy ester **209**, the reaction of *N*-benzyl piperidine *cis*-**208** with KO*t*Bu was repeated with the rigorous exclusion of O_2. The reaction vessel was purged and back-filled with Ar three times to remove any O_2 within the system before the addition of KO*t*Bu. Pleasingly, reaction of *N*-benzyl piperidine *cis*-**208** with KO*t*Bu at –78 °C gave a 70:30 mixture of piperidines *trans*-**208** and *cis*-**208** with no evidence of the formation of hydroxyl ester **209**. After purification, *N*-benzyl piperidine *trans*-**208** was isolated in 53% yield along with *N*-benzyl piperidine *cis*-**208** in 28% yield (Scheme 3.15). Of note, this was our best result so far in terms of mass recovery (81%) from an epimerisation reaction. Thus, starting from amino esters **126**, we accessed *N*-benzyl piperidine *trans*-**208** in 41% yield over the two steps (benzylation and epimerisation). This is higher than the 27% yield of *N*-Boc piperidine *trans*-**157** obtained using NaOMe in MeOH at 80 °C for 24 h followed by Boc protection (see Table 3.2, entry 2).



cis-**208** *trans*-**208**, 53% *cis*-**208**, 28%

Scheme 3.15

Next, the KO*t*Bu epimerisation conditions were explored with five other disubstituted piperidines and the results are shown in Table 3.3. Therefore, for future epimerisations the KO*t*Bu conditions were used (Table 3.3). *N*-Benzyl piperidine *cis*-**207** (prepared by another member of the group *via* pyridine hydrogenation and benzylation) was reacted with KO*t*Bu at –78 °C for 2 h to give a 50:50 mixture of *N*-benzyl piperidine *cis*-**207** and *trans*-**207**. Purification afforded *N*-benzyl piperidine *cis*-**207** in 48% yield and *N*-benzyl piperidine *trans*-**207** in 40% yield (entry 1). The stereochemistry for piperidine *trans*-**207** was confirmed by $^3J_{HH}$ coupling constants. The lowest energy *trans*-conformation will have both substituents equatorial (Figure 3.11). Therefore, $^3J_{HH}$ coupling constants of 11.0 and 3.0 Hz, between the C-2 and C-3 positions and also between the C-5 and C-6 positions allowed for the *trans*-stereochemistry to be assigned.

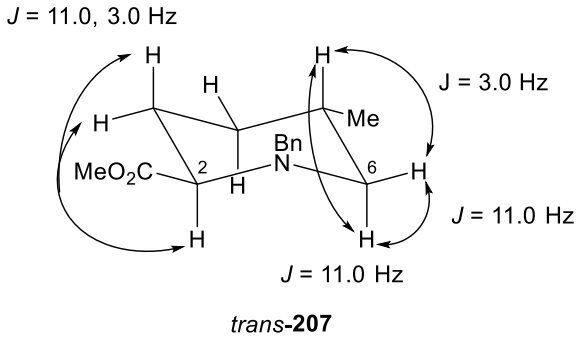


Figure 3.11 - Diagnostic $^{3}J_{HH}$ coupling constants for 2,3-disubstituted piperidine *cis*-**207**.

Unfortunately, this is the worst diastereoselectivity of all the base-mediated epimerisations that we have studied. For comparison, a reaction using NaOMe in MeOH at 80 °C for 24 h gave a 90:10 mixture of piperidines *cis*-**207** and *trans*-**207**, an even worse result.

Next, the synthesis of 2,3-*trans*-piperidines was explored. Treatment of *N*-benzyl piperidine *cis*-**194** with KO*t*Bu at –78 °C for 2 h afforded a 65:35 mixture of *N*-benzyl piperidines *trans*-**194** and *cis*-**194**. Purification then gave *N*-benzyl piperidine *trans*-**194** in 56% yield and an 80:20 mixture of *N*-benzyl piperidines *cis*-**194** and *trans*-**194** in 41% yield (entry 2). This is a 97% total recovery of piperidines *cis*-**194** and *trans*-**194** after purification. The relative stereochemistry was assigned based on the $^{3}J_{HH}$ coupling between the C-2 and C-3 positions from *trans*-piperidine **193**. The lowest energy conformation of piperidine *trans*-**193** (Figure 3.12) will have both substituents equatorial and identification of a $^{3}J_{HH}$ value of 10.0 Hz between the protons on C-2 and C-3 allowed the stereochemistry to be assigned.

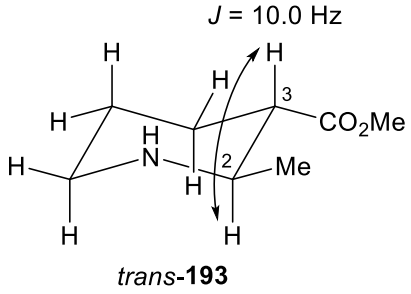
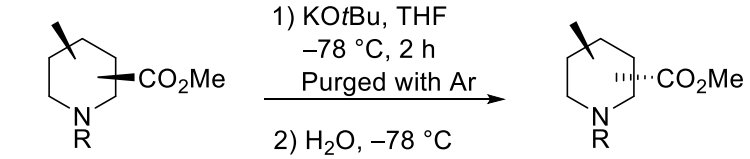


Figure 3.12 - Diagnostic $^{3}J_{HH}$ coupling constants for 2,3-disubstituted piperidine *cis*-**193**.

The 2,3-*trans*-piperidine with the methyl and methyl ester groups transposed was then studied. Epimerisation to afford piperidine *trans*-**123** had been achieved during the synthesis of piperidine 3-D fragments *trans*-**95** and *trans*-**96** (see Scheme 2.63). Use of the KO*t*Bu conditions with *N*-benzyl piperidine *cis*-**123** afforded a 70:30 mixture of piperidine *trans*-**123** and *cis*-**123** from which piperidines *trans*-**123** (60% yield) and *cis*-**123** (23% yield) were

isolated (entry 3). Thus, piperidine *trans*-**123** was synthesised in 48% yield over two steps from pyridine **115**, which is a 10% improvement over the approach using the NaOMe epimerisation conditions (see Scheme 2.63).



R = Bn or Boc

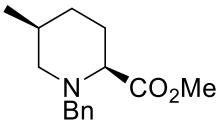
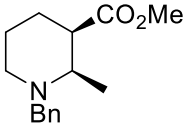
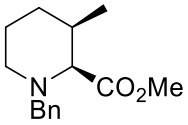
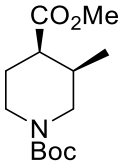
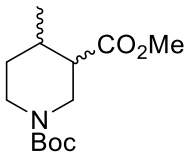
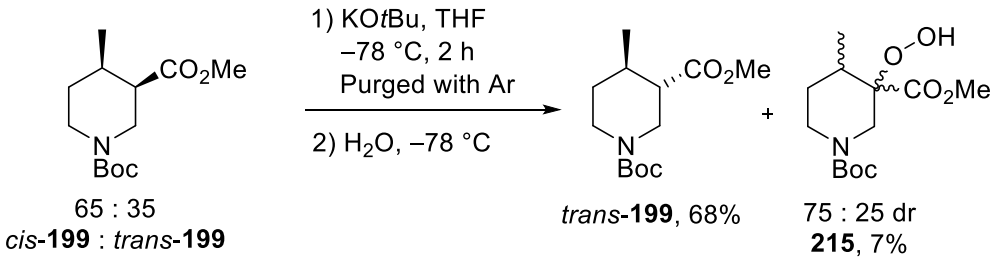
Entry	Piperidine	*trans* : *cis*[b]	Yield of *trans* (%)
1	 (**207**)	50 : 50	40[c], **207**
2	 (**194**)	65 : 35	56[d], **194**
3	 (**123**)	70 : 30	60[e], **123**
4	 (**200**)	90 : 10	90[f], **200**
5[a]	 (**199**)	90 : 10	68[g], **199**

Table 3.3 – Base-mediated epimerisation with K*t*OBu.

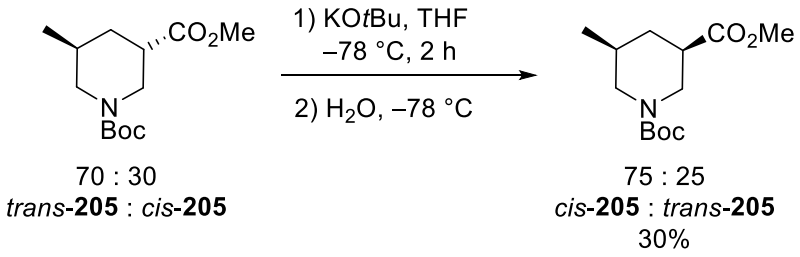
a) 65:35 mixture of piperidine *cis*-**199** and *trans*-**199**; b) Ratio determined by ^{1}H NMR spectroscopy of the crude product; c) Isolated *cis*-**207** in 48% yield; d) Isolated an 80:20 mixture of *N*-benzyl piperidines *cis*-**194** and *trans*-**194** in 41% yield; e) Isolated *cis*-**123** in 23% yield; f) Isolated a 90:10 mixture of piperidines *cis*-**200** and *trans*-**200**; g) Isolated a 75:25 mixture of peroxy ester **215** in 7% yield.

Similarly, successful results were obtained with the 3,4-disubstituted piperidines. Thus, reaction of *N*-Boc piperidine *cis*-**200** with KO*t*Bu at −78 °C for 2 h gave a 90:10 mixture of *N*-Boc piperidines *trans*-**200** and *cis*-**200** in 90% crude yield, which was not purified further as the diastereomers were not separable (entry 4). As shown in Scheme 3.12, epimerisation of the regioisomeric 3,4-disubstituted piperidines **199** with KO*t*Bu had already been reported.[81] In our hands, a 65:35 mixture of *N*-Boc piperidines *cis*-**199** and *trans*-**199** was treated with KO*t*Bu at –78 °C for 2 h to give a 90:10 mixture of *N*-Boc piperidines *trans*-**199** and *cis*-**199**. Purification by chromatography afforded *N*-Boc piperidine *trans*-**199** in 68% yield (entry 6). A second product was also isolated and the ^{1}H NMR spectrum had features that suggested that α-substitution of the enolate had occurred. For example, there were two doublets at 4.33 and 3.23 ppm corresponding to NCH_2 protons, which showed geminal coupling ($^2J_{HH}$ = 15.0 Hz) only. However, α-hydroxylation was ruled out as the mass spectrometry showed a *m/z* peak corresponding to α-peroxy ester **215**, which was isolated as a 75:25 mixture of diastereoisomers in 7% yield (Scheme 3.16). This further supported the mechanism proposed by Gnanaprakasam *et al.* with peroxide **213** being formed and subsequently cleaved to give the hydroxyl ketone (see Scheme 3.14).



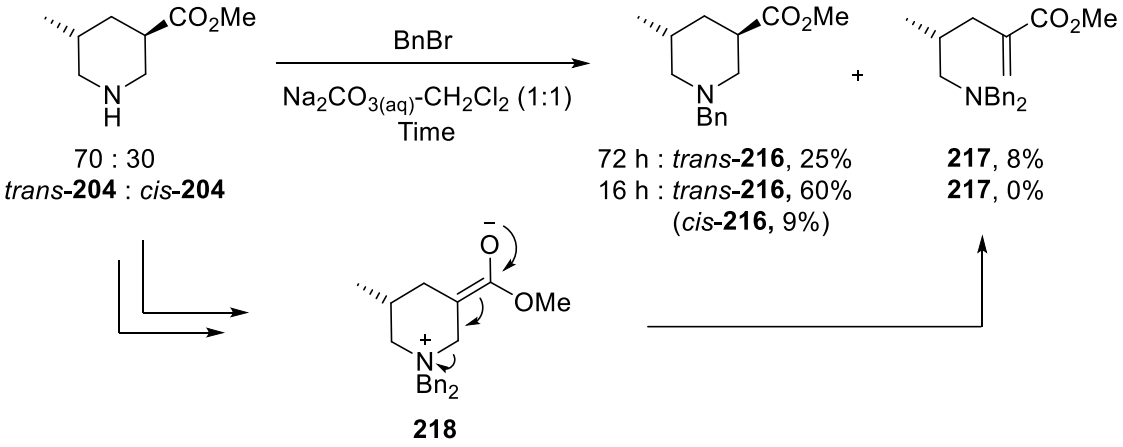
Scheme 3.16

As described in Section 3.2, hydrogenation of 3,5-disubstituted pyridine **203** had provided a stereoselective route to the 3,5-disubstituted piperidine *trans*-**205**. This opened up the opportunity to attempt to access the *cis*-piperidine stereoselectively using base-mediated epimerisation. Therefore, a 70:30 mixture of *N*-Boc piperidines *trans*-**205** and *cis*-**205** was subjected to the standard KO*t*Bu conditions. After work-up, a 75:25 mixture of *N*-Boc piperidines *cis*-**205** and *trans*-**205** was formed but in only 30% yield (Scheme 3.17). This was surprising as the KO*t*Bu epimerisation conditions had generally given high mass recovery (75-97%).



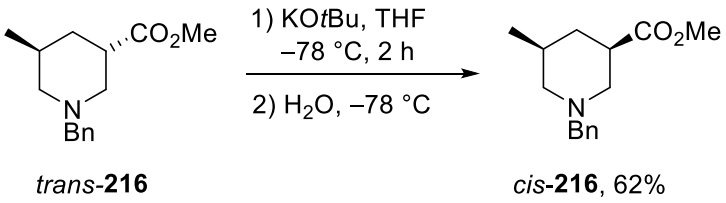
Scheme 3.17

Hence, the corresponding 3,5-disubstituted *N*-benzyl piperidines **216** were explored. *N*-Benzyl piperidine *trans*-**216** was synthesised from a 70:30 mixture of piperidines *trans*-**204** and *cis*-**204** using BnBr in a 1:1 mixture of saturated $Na_2CO_{3(aq)}$ and CH_2Cl_2 at rt for 72 h. Purification afforded *N*-benzyl piperidine *trans*-**216** in only 25% yield along with the doubly benzylated ring-opened amino acrylate **217** in 8% yield (Scheme 3.18). Presumably, the long reaction time had resulted in a second benzylation and elimination from enolate **218** would account for the formation of amino acrylate **217**. With a view to reducing the amount of formation of amino acrylate **217**, the reaction time was reduced to 16 h. In this way, *N*-benzyl piperidine *trans*-**216** was generated in an improved 60% yield with no formation of amino acrylate **217** (Scheme 3.18).



Scheme 3.18

With *N*-benzyl piperidine *trans*-**216** in hand, epimerisation to *cis*-**216** was then attempted with KO*t*Bu at –78 °C for 2 h. Pleasingly, this afforded *N*-benzyl piperidine *cis*-**216** in 62% yield, along with a small amount of a mixture of *N*-benzyl piperidine *trans*-**216** and other undetermined impurities (Scheme 3.19). Thus, a higher mass recovery than with the Boc protected piperidine was possible using the *N*-benzyl group.



trans-**216** *cis*-**216**, 62%

Scheme 3.19

The remaining two 2,4-disubstituted piperidines *trans*-**186** and *trans*-**187** were synthesised by another member of the group. In both cases, it was necessary to use a *N*-Boc group as the epimerisation is driven by placing the 2-substituent in an axial position (as discussed in section 3.1, see Figure 3.4). The best result in each case was obtained using a different base and the results are briefly summarised in Figure 3.13. Using LDA in THF at –78 °C, piperidine *trans*-**186** was selectively prepared in 65% yield. In contrast, the standard KO*t*Bu conditions were applied to synthesise *N*-Boc piperidine *trans*-**187** selectively in 53% yield with > 95% purity

trans-**186,** 65%
LDA, THF, –78 °C, 2 h

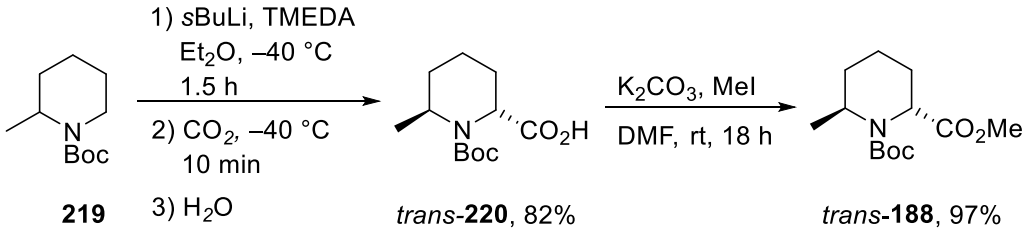
trans-**187**, 53%
KO*t*Bu, THF, –78 °C, 2 h

Figure 3.13 – Epimerisation to access piperidine *trans*-**186** and **187**.

Optimisation of the epimerisation approach led to the stereoselective synthesise of seven disubstituted *trans*-piperidines, along with the 3,5-disubstituted *cis*-piperidines. The only epimerisation which failed to afford the *trans*-piperidine as the major diastereoisomer, was the 2,5-disubstituted piperidine, which gave a 50:50 mixture of diastereoisomers.

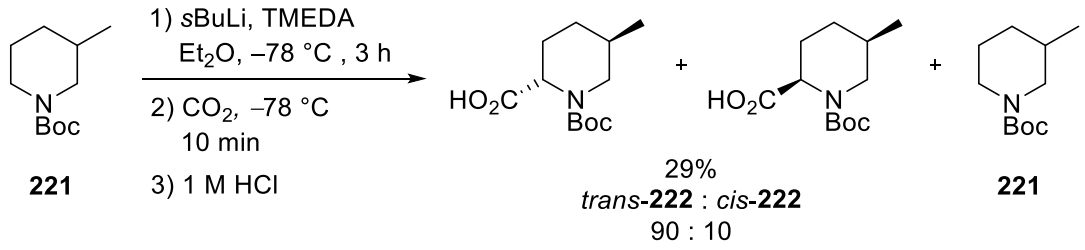
3.4 Strategy Three: Lithiation-Trapping of *N*-Boc Methyl piperidines

The final strategy that we proposed to use to stereoselectively access disubstituted piperidines was Beak's lithiation of *N*-Boc methyl piperidines and subsequent trapping with CO_2 or methyl chloroformate. The 2,6-disubstituted *trans*-piperidine was one of the systems that could be synthesised using this lithiation-trapping approach. This example was performed by another member of the group and, as outlined in Scheme 3.20, *N*-Boc 2-methylpiperidine **219** was converted into *N*-Boc piperidine ester *trans*-**188** in 79% yield over the two steps, *via N*-Boc acid *trans*-**220** (Scheme 3.20).



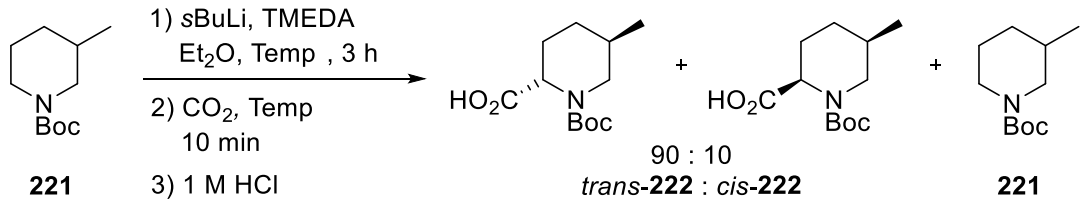
Scheme 3.20

This lithiation-trapping approach was investigated for the synthesis of the 2,5-*trans*-piperidine system since this substitution pattern had given the worst diastereoselectivity in the KO*t*Bu-mediated epimerisation reactions: a 50:50 mixture of *N*-benzyl piperidines *trans*-**207** and *cis*-**207** had been obtained (see Table 3.3, entry 1). Lithiation-trapping of *N*-Boc 3-methylpiperidine **221** with CO_2 had been reported in 2013 by Brewer *et al*. with acid *trans*-**222** isolated in 78% yield.[112] In our reaction, lithiation of *N*-Boc methyl piperidine **221** was carried out using *s*BuLi and TMEDA in Et_2O at –78 °C for 3 h. Then, dry $CO_{2(g)}$ was bubbled into the solution for 10 min to give, after work-up, a 60:40 mixture of starting *N*-Boc 2-methylpiperidine **221** and acids *trans*-/*cis*-**222**. Purification afforded a 29% yield of a 90:10 mixture of piperidines *trans*-**222** and *cis*-**222** and a 42% yield of recovered starting material **221** (Scheme 3.21). Analysis of the ^{1}H NMR spectrum after purification, showed the presence of two doublets at 1.10 and 0.97 ppm, corresponding to the minor and major acid products respectively. Piperidine *trans*-**222** had been fully characterised in the literature[112] and therefore the doublet at 0.97 ppm was assigned to the methyl substituent of piperidine *trans*-**222**. The doublet at 1.10 ppm was assumed to be the methyl group in piperidine *cis*-**222**, as minor downfield signals at 3.97, 2.94 and 2.51 ppm were identified for the NCH signals. Confirmation that the minor product was piperidine *cis*-**222** was obtained by its conversion into *N*-benzyl piperidine *cis*-**207** of known stereochemistry (see Scheme 3.22).



Scheme 3.21

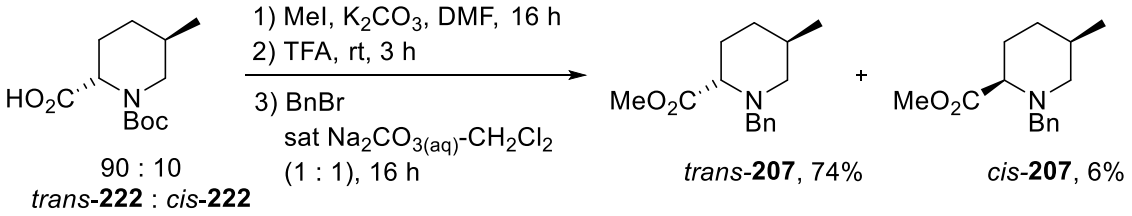
Despite isolating a 90:10 mixture of piperidines *trans*-**222** and *cis*-**222** in only 29% yield, the ratio was an improvement over the 50:50 mixture obtained after epimerisation of *N*-benzyl piperidines *cis*-**207** and *trans*-**207** (see Table 3.3, entry 1). The hope was that, after methylation of the carboxylic acid, separation of the diastereoisomers may be possible. Therefore, attempts were made to improve the conversion to products in the lithiation-trapping reaction. Table 3.4 summarises our results, including the initial reaction shown in Scheme 3.21 (entry 1). Initially, the temperature was raised from –78 to –60 °C which gave an improved 81:9:10 mixture of piperidines *trans*-**222**, *cis*-**222** and **221**, with a 90:10 mixture of piperidine *trans*-**222** and *cis*-**222** isolated in 57% yield (entry 2). Extending the lithiation time at –60 °C to 6 h in an attempt to fully consume the starting material was not successful and a 56% yield of a 90:10 mixture of piperidines *trans*-**222** and *cis*-**222** was obtained (entry 3). At –40 °C, a worse result was obtained with a 36:4:60 ratio of piperidines *trans*-**222**, *cis*-**222** and **221** and a 90:10 mixture of piperidine *trans*-**222** and *cis*-**222** isolated in 29% yield (entry 4). Thus, in our hands, the best result involved carrying out the lithiation at –60 °C for 3 h to give a 90:10 mixture of piperidines *trans*-**222** and *cis*-**222** in 57% yield.



Entry	Temp (°C)	Time (h)	*trans*-**222** : *cis*-**222** : **221**[a]	Yield of *trans*-**222** and *cis*-**222** (%)[b]
1	– 78	3	36 : 4 : 60	29
2	– 60	3	81 : 9 : 10	57
3	– 60	6	81 : 9 : 10	56
4	– 40	3	36 : 4 : 60	29

Table 3.4 – Lithiation-trapping of **221** with CO_2; a) Ratio determined by ^{1}H NMR spectroscopic analysis of the crude product; b) *trans*-**222** and *cis*-**222** were isolated as a 90:10 mixture as determined by ^{1}H NMR spectroscopic analysis.

Finally, the 90:10 mixture of piperidines *trans*-**222** and *cis*-**222** was methylated with MeI and K_2CO_3 in DMF at rt for 16 h. Upon purification by chromatography, it was not possible to separate the two methyl ester diastereoisomers. Since we knew that the corresponding *N*-benzyl piperidines *trans*-**207** and *cis*-**207** were separable, we converted the Boc group into the benzyl group. Thus, removal of the Boc protecting group using TFA and installation of the benzyl group using BnBr and sat $Na_2CO_{3(aq)}$ gave *N*-benzyl piperidines *trans*-**207** (74% yield) and *cis*-**207** (6% yield) over three steps (Scheme 3.22).



Scheme 3.22

Comparison of the base-mediated epimerisation route (see Table 3.3, entry 1) with the lithiation-trapping route to access *N*-benzyl piperidine *trans*-**207** reveal that the latter gave *N*-benzyl piperidine *trans*-**207** in 42% yield over four steps. The initial route of hydrogenation, protection and subsequent epimerisation afforded piperidine *trans*-**207** in a slightly lower 36% yield over four steps. However, the ability to access both

diastereoisomers in good yields is clearly an advantage of the hydrogenation/epimerisation approach.

3.7 Conclusions and Overview

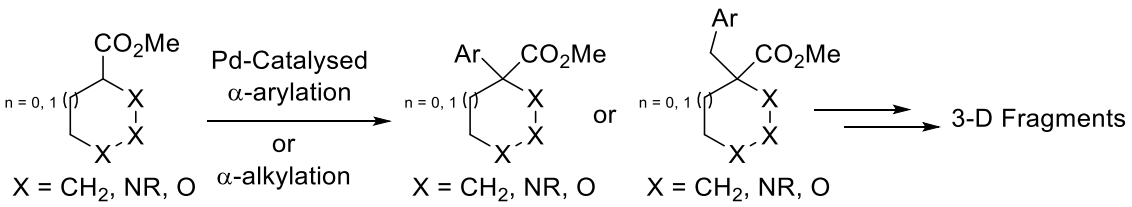
We have developed simple and general approaches for the synthesis of all of the possible 20 disubstituted regio- and diastereoisomeric piperidines using the four strategies outlined in Section 3.1. Hydrogenation using 10 or 30 mol% PtO_2/Pd/C in AcOH under H_2 afforded nine of the ten disubstituted *cis*-piperidines, with hydrogenation of the 3,5-disubstituted pyridine affording the *trans*-piperidine as the major product. We were unable to determine an overall trend for predicting the diastereoselectivity for the hydrogenations. However, the highest diastereoselectivity was achieved for the three systems with a substituent at the 2- or 6-positions and where the two substituents were able occupy the more favourable equatorial positions, i.e 2,6- and 2,4-disubstituted piperidines.

Epimerisation using KO*t*Bu at –78 °C for 2 h gave a selective route to piperidines *trans*-**208**, *trans*-**207**, *trans*-**194**, *trans*-**123**, *trans*-**200**, *trans*-**199** and *cis*-**216** in good yields (Table 3.3). The final approach we outlined was lithiation-trapping to afford piperidine *trans*-**188**, which had been performed by another member of the group. The approach also offered an alternative route to the 2,5-*trans* piperidine, affording a higher overall yield compared to base-mediated epimerisation approach. Therefore, with the use of four simple and general approaches, access to all 20 disubstituted regio- and diastereoisomeric piperidines was possible. The work complements our piperidine fragment library with access possible to all the disubstituted piperidines, which would allow for the rapid elaboration of the piperidine core.

Chapter 4 Design and Synthesis of 3-D Fragments *via* α-Arylation and α-Alkylation of Cyclic Esters

In this Chapter, we present a strategy for synthesising 3-D fragments that is different to that described in Chapter 2. Our plan was to develop an approach that would allow the more rapid synthesis of a wide range of 3-D fragments. PMI plots would still be a key part of the design process so that new areas of fragment chemical space were accessed. It was also decided to synthesise 3-D fragments based on different cyclic scaffolds that contained at least one aromatic substituent. This is because aromatic groups can help in fragment screening using ^{1}H NMR spectroscopy. The final design aspect was to focus on key pieces of synthetic methodology which could be easily extended to other scaffolds.

We planned to use two different synthetic methodologies, namely ester enolate α-arylation and α-alkylation, as the key steps in our 3-D fragment syntheses (Scheme 4.1). After setting out the challenges and limitations with the first-generation fragments (Chapter 4.1), we go on to describe the design and synthesis of 3-D fragments using α-arylation (Chapter 4.2) and α-alkylation (Chapter 4.3) methodology. In total, 42 novel 3-D fragments were synthesised using this approach.



Scheme 4.1

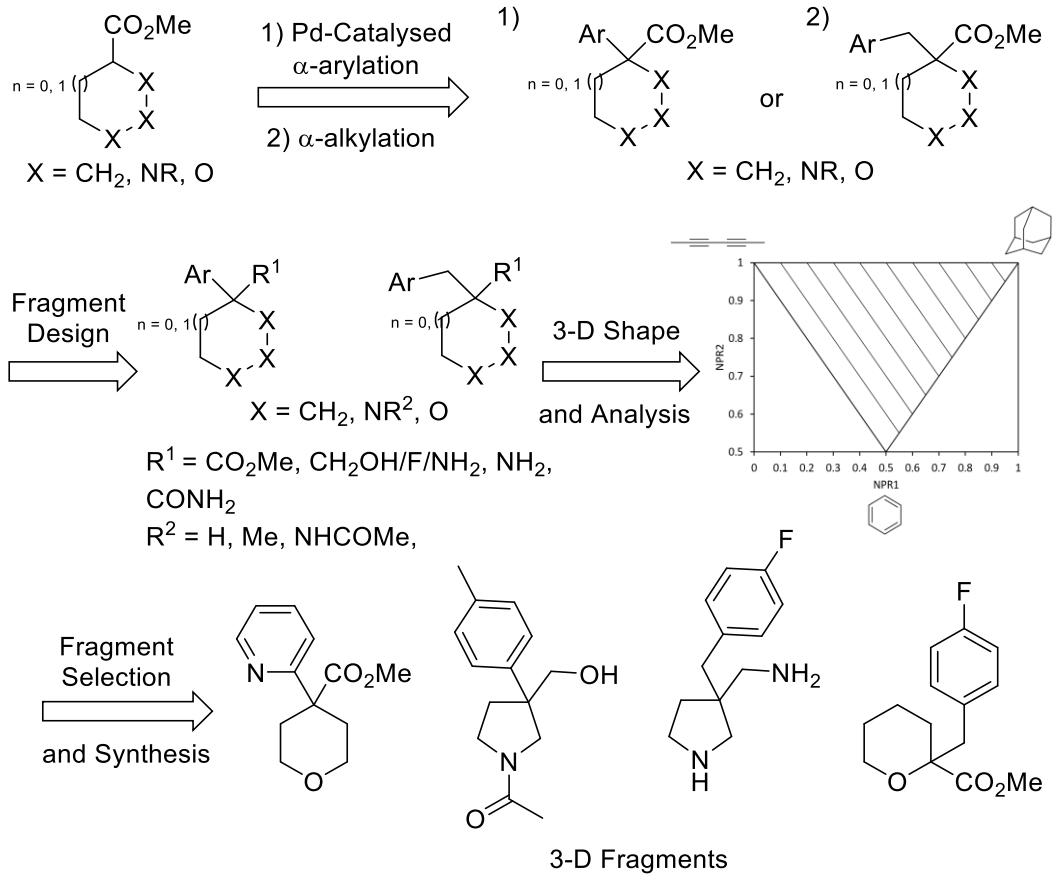
4.1 Challenges and Limitations with First-Generation 3-D Fragments and Development of a New Approach for the Synthesis of 3-D Fragments

The main challenge with the synthesis of the first-generation pyrrolidine and piperidine 3-D fragments arose from the range of regioisomers that were selected. The pyrrolidine regioisomers required bespoke methodology to access the various substitution patterns, with six different routes utilised to synthesise the 14 selected pyrrolidine fragments. The piperidines were easier to synthesise, although extensive optimisation was required to access some of the *trans*-diastereoisomers. The need for stereoselective routes to access either the *cis* or *trans*-diastereoisomers resulted in issues with both synthesis and purification. Finally, there were inherent limitations with the first-generation 3-D fragments when it came to screening using NMR spectroscopy. The absence of aromatic groups within the fragments made analysis of the ^{1}H NMR spectroscopic data difficult, since the signals due to the fragments overlapped with those of the target proteins. In this context, aromatic groups are ideal for fragment screening by ^{1}H NMR spectroscopy due to the occurrence of signals in the 6-8 ppm region.

As a result of these challenges and limitations, we decided to modify the fragment design and selection process. For fragment design, we wanted to avoid the presence of two stereogenic centres within the molecules and this in turn removed the need for the development of diastereoselective routes. For the new design approach, 3-D fragments would either be achiral or contain only one stereogenic centre. The incorporation of an aromatic group was also an important design aspect as this would help future fragment screening attempts using ^{1}H NMR spectroscopy. Finally, the design of the new 3-D fragments would be led by the identification of synthesis methodology that would allow aromatic substituents to be readily introduced onto cyclic and heterocyclic saturated nitrogen and oxygen scaffolds. Two pieces of synthetic methodology were identified for this purpose. These were the α-arylation of cyclic esters using palladium catalysis and more classical α-alkylation of cyclic esters *via* the reaction of enolates with benzylic halides. Using these two approaches, together with modification of the ester functional group and where applicable the *N*-substituent, 3-D fragments would be designed. Before synthesis, their 3-D shape would be analysed using our standard PMI protocol and only fragments in unexplored areas of 3-D fragment space would be targeted for synthesis. Crucially, design of 3-D fragments

would be based on the capability of the chemistry, which should streamline the synthesis of the 3-D fragments.

An overview of this approach is summarised in Scheme 4.2. Starting from cyclic and heterocyclic esters, palladium-catalysed ester enolate α-arylation and classical α-alkylation chemistry would be explored. The successful scaffolds would then be derivatised and their 3-D shape would be analysed using the PMI protocol. Finally, fragments with shapes occupying unexplored regions of chemical space would be selected and synthesised.

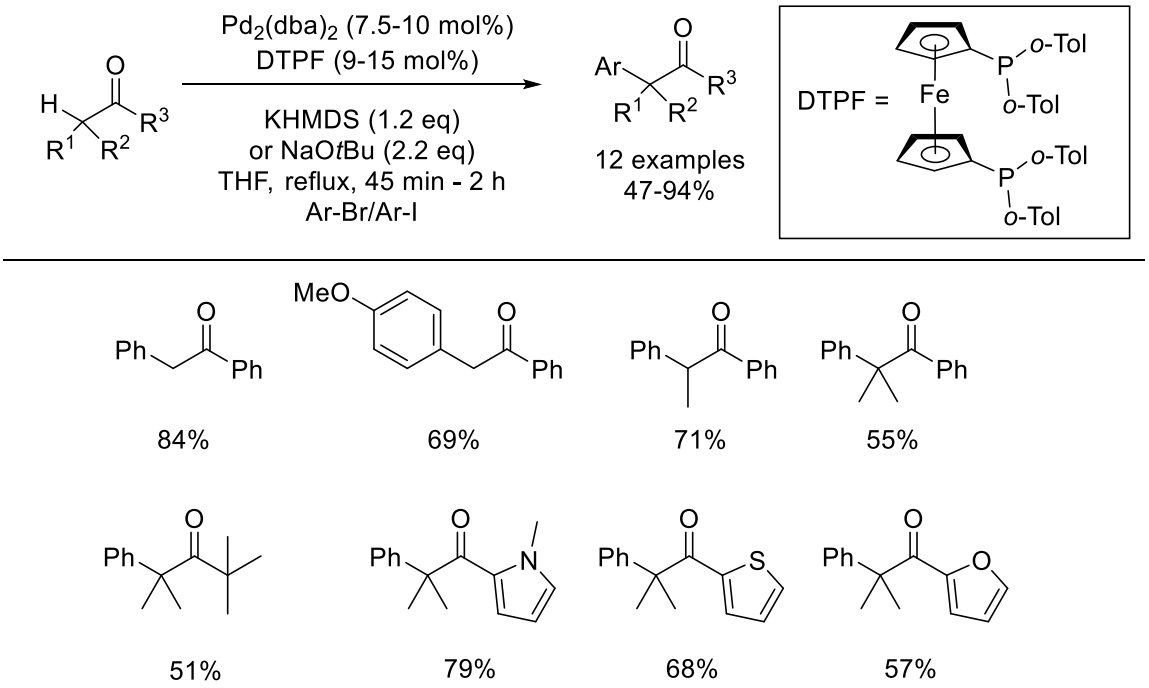


Scheme 4.2

4.2 Synthesis of 3-D Fragments *via* α-Arylation of Cyclic Esters

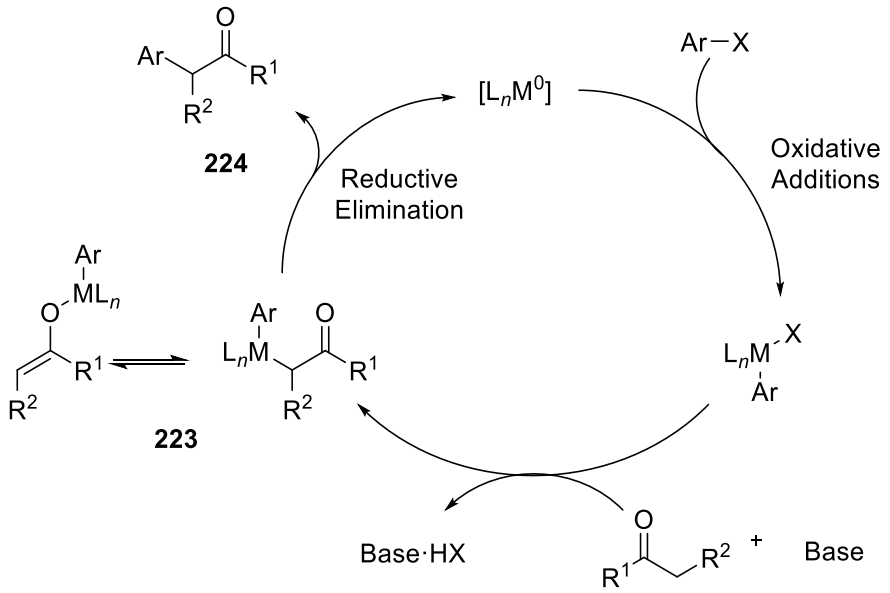
4.2.1 Overview of Palladium-Catalysed α-Arylation of Ketones, Amides and Esters

Palladium-catalysed α-arylation was first reported with ketones in 1984 by Migita *et al.*[113] In their work, tributyltin enolates were utilised to access a variety of arylated ketones. One of the main drawbacks was the need to pre-form the tributyltin enolates by reacting enol acetates with tributyltin methoxide. In 1997, Hartwig *et al.* reported arylation α to ketones to form secondary, tertiary and quaternary carbon centres without the need to pre-form the enolates.[114] Utilising $Pd(dba)_2$ with 1,1'-bis(di-*o*-tolylphosphino)ferrocene (DTPF) and either KHMDS or NaO*t*Bu it was possible to couple electron rich and poor aryl bromides/iodides. Selected examples are shown in Scheme 4.3.



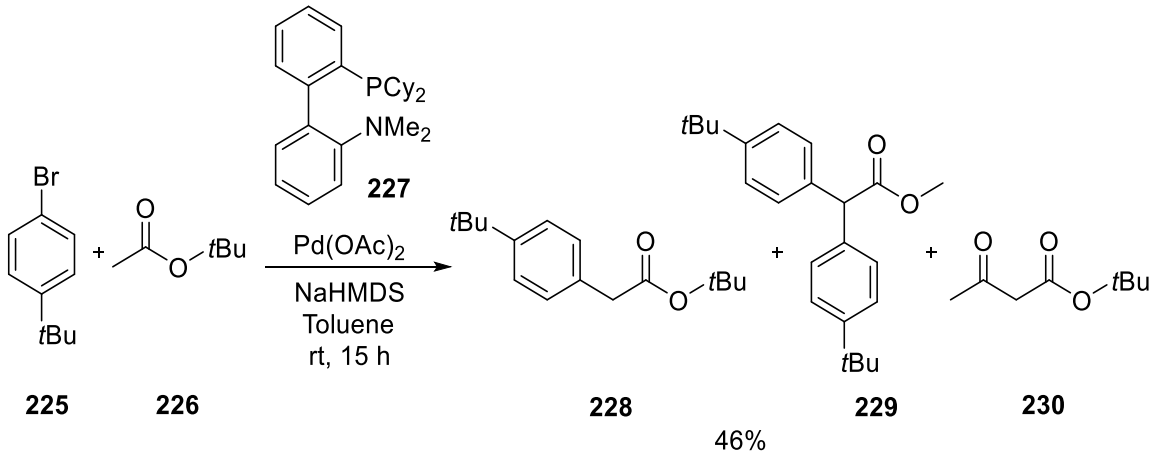
Scheme 4.3

The mechanism proposed for this α-arylation reaction, starts with the oxidative addition of the aryl halide and is followed by transmetallation to give enolate intermediate **223**. The final step consists of C-C bond formation *via* reductive elimination to afford the desired α-arylated compound **224** (Scheme 4.4).[115] It has been shown that the reductive elimination step is in competition with a β-hydride elimination process which forms an enone.



Scheme 4.4

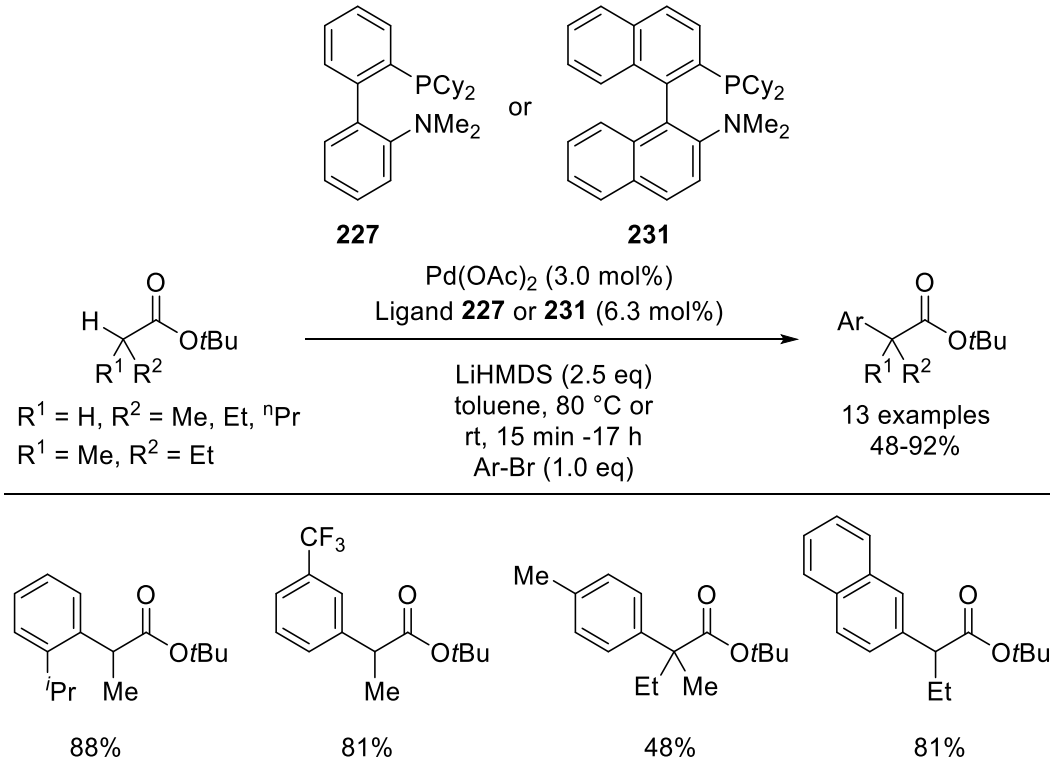
Numerous groups have since investigated the α-arylation of esters using different palladium sources and ligands. Buchwald *et al*. used either $Pd(OAc)_2$ or $Pd(dba)_2$ in combination with *o*-biphenyl phosphine ligands.[116] The electron richness and bulky size of the *o*-biphenyl phosphine ligands reduced the amount of β-hydride elimination. In an initial example, α-arylation of 1-bromo-4-*t*-butyl benzene **225** with *t*-butyl acetate **226** in the presence of NaHMDS, $Pd(OAc)_2$, and *o*-biphenyl phosphine **227** was studied. This gave both monoarylated product **228** and diarylated product **229** in a combined 46% yield. The Claisen self-condensation product **230** was also isolated but a yield was not reported (Scheme 4.5).



Scheme 4.5

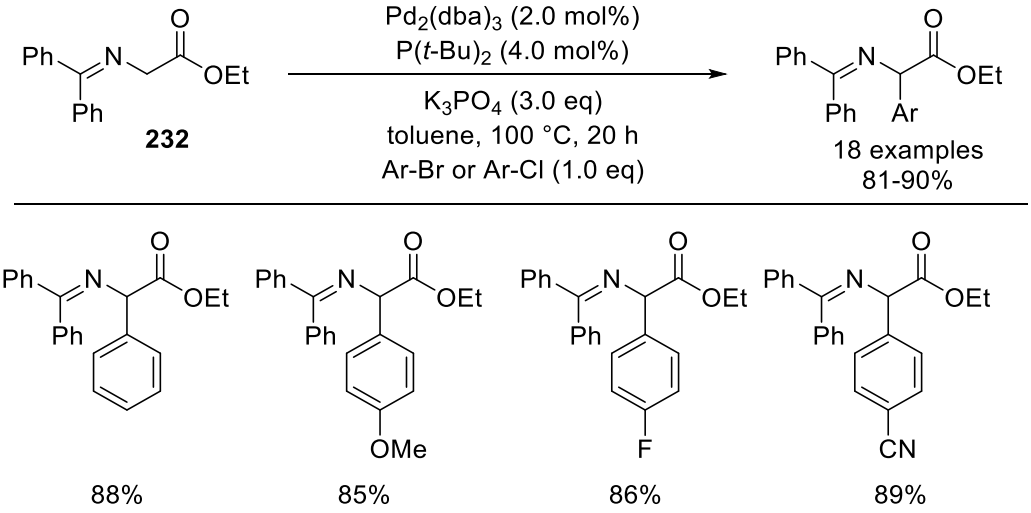
Buchwald *et al*. found that LiHMDS was the most effective base, with only trace amounts of diarylated product observed. The rationale behind the finding was connected to the

increase in covalency of the Li^+ *versus* Na^+ cation. The Li^+ cations are able form more covalent Li-O bonds, which reduced the formation of the diarylated product. Finally, with their optimised conditions in hand, the scope was expanded to include the formation of tertiary and quaternary carbon centres with *ortho*-, *meta*- and *para*-substituted aryl groups (Scheme 4.6).



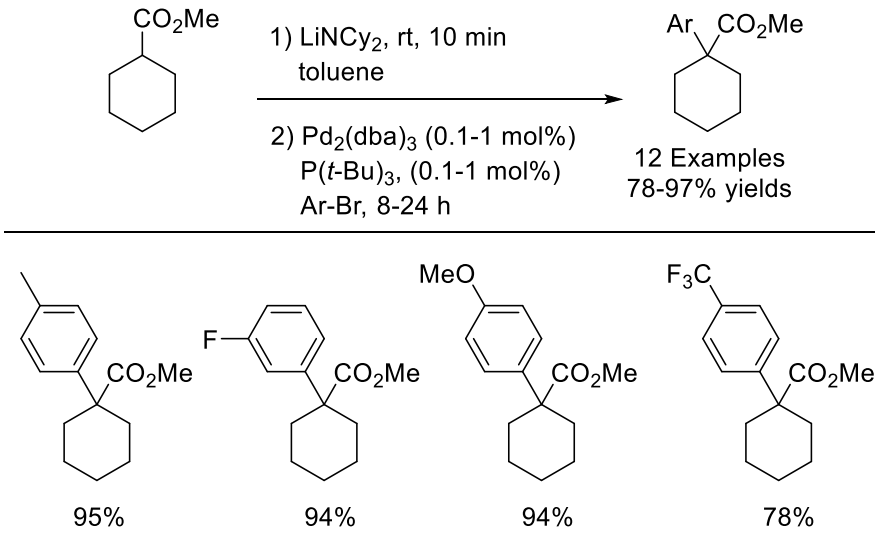
Scheme 4.6

The ester α-arylation reaction was extended by Hartwig *et al.* to the synthesis of α-aryl amino acids *via* the α-arylation of protected amino acids.[117] Mechanistic studies revealed that the rate limiting step was the formation of the palladium enolate complex which depended on the stability of the alkali metal enolate. The α-arylation of *N*-(diphenylmethylene)-glycinate **232** with electron rich and poor aryl bromides in the presence of $Pd_2(dba)_3$, P(*t*-Bu)$_3$ and K_3PO_4, gave the arylated products in high yields (Scheme 4.7).



Scheme 4.7

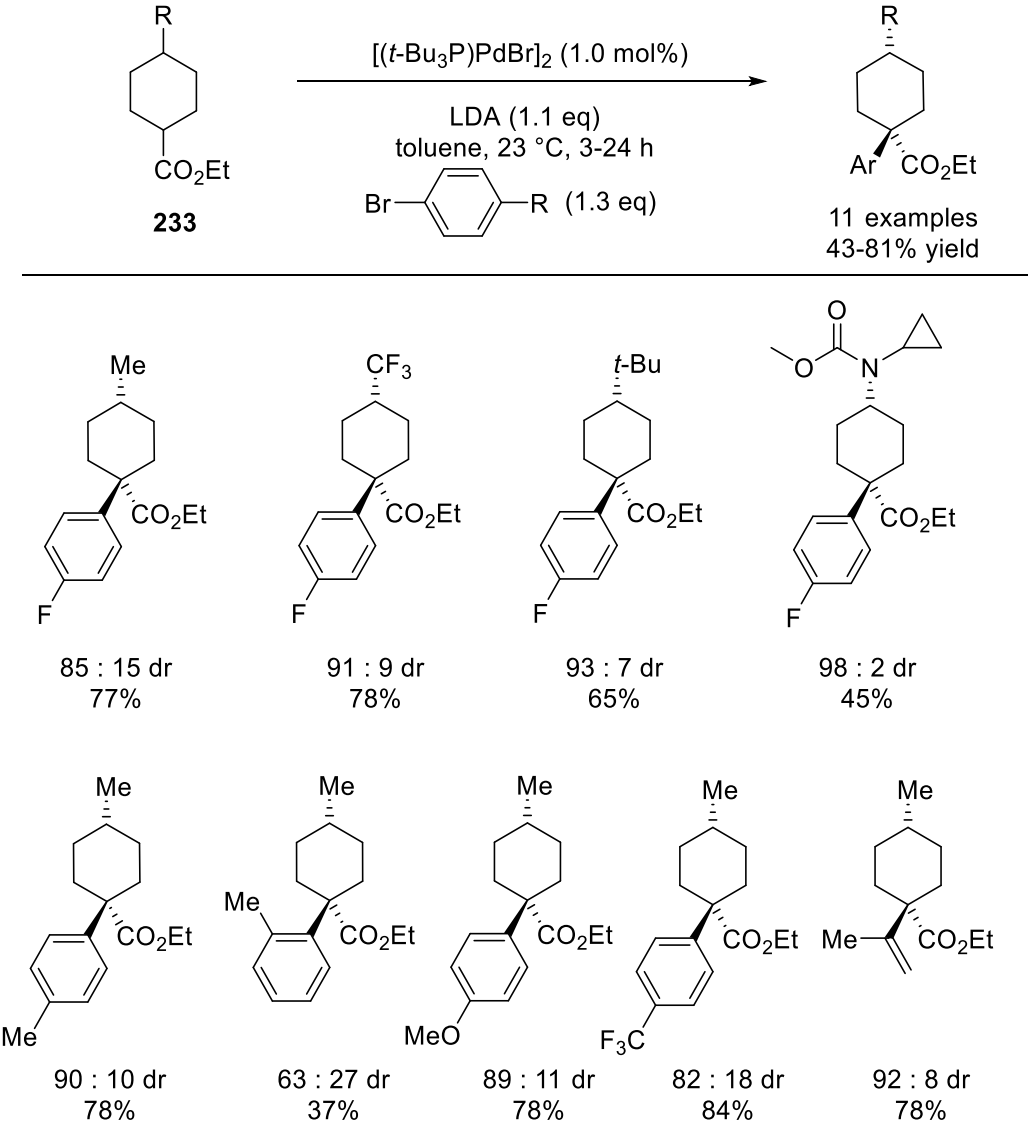
In 2002, Hartwig *et al.* described the α-arylation of cyclohexane-derived esters (Scheme 4.8).[118] The installation of electron rich and poor aromatics was possible, although no studies were carried out with sterically hindered *ortho*-substituted aromatics. In these reactions, the lithium enolate was pre-formed and the choice of solvent was found to be a key factor for successful α-arylation reactions. The best yields were obtained in aromatic solvents, whereas none of the α-arylated product was observed in reactions in ether solvents such as Et_2O and THF.



Scheme 4.8

In related work, Bercot *et al.* investigated the diastereoselective α-arylation of 1,4-disubstituted cyclohexanes **233**. Using LDA in toluene, with $[(t\text{-}Bu_3P)PdBr]_2$ as catalyst, a wide range of *cis*-α-arylated esters were generated (Scheme 4.9).

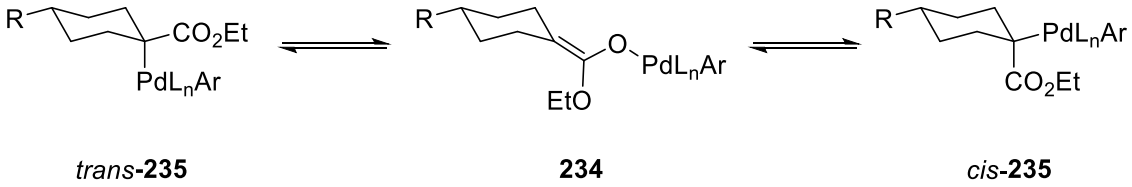
High *cis*-diastereoselectivity was generally observed for different 4-substituents and different aryl and vinyl halides. Reduced diastereoselectivity was found with sterically hindered *ortho*-substituted aryl bromides.



Scheme 4.9

Bercot *et al.* proposed the following explanation to explain the highly diastereoselective formation of *cis*-α-arylated esters. Initially, Pd enolate **234** would form, which could be transformed into α-palladyl esters *cis*-**235** and *trans*-**235** (Scheme 4.10). Due to both the sterically bulky 4-substituent and PdL_nAr groups being equatorial, it was proposed that *cis*-

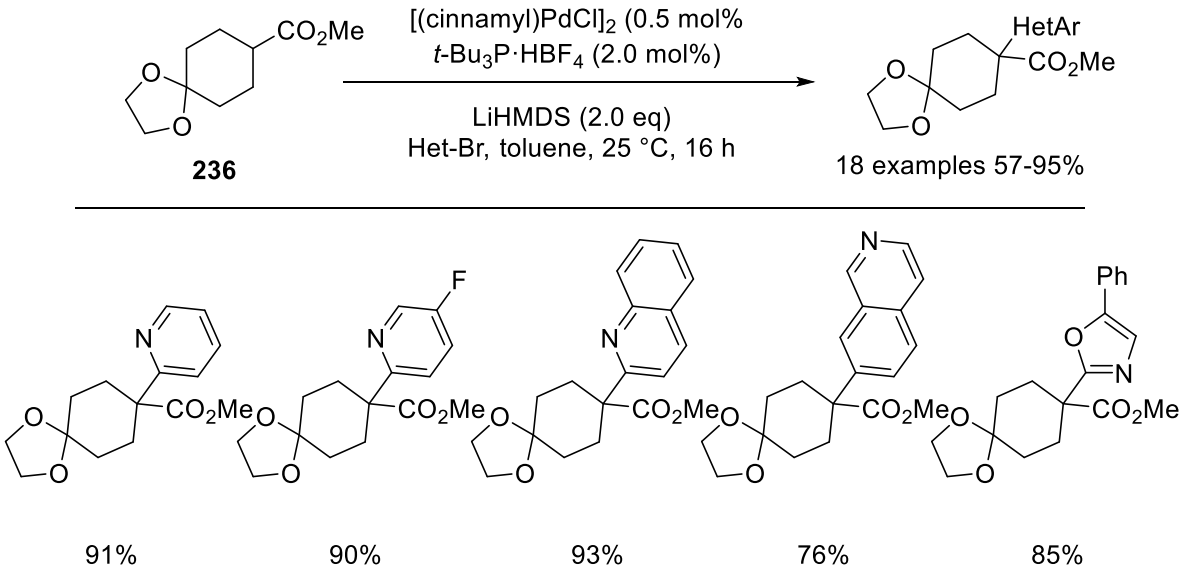
235 would preferentially form. Subsequent reductive elimination from *cis*-**235** would generate the *cis*-α-aryl esters.



trans-**235** **234** *cis*-**235**

Scheme 4.10

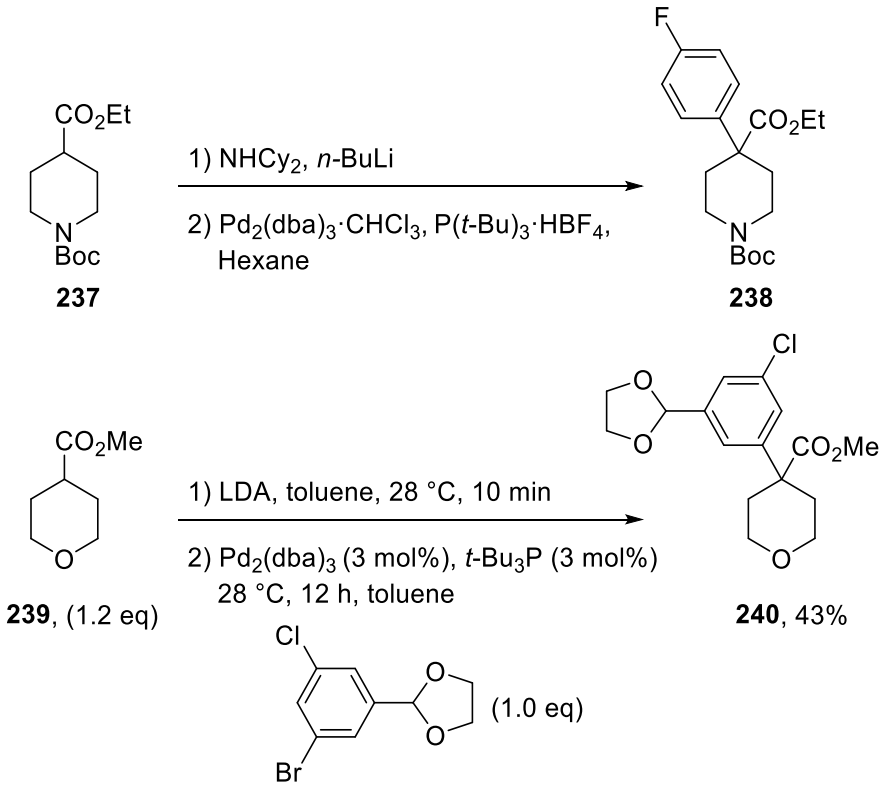
A more recent publication by Zhou *et al.* investigated the palladium-catalysed α-arylation of a 4-ketal-substituted cyclohexanone **236**.[119] α-Arylation was accomplished using LiHMDS, $[(\text{cinnamyl})\text{PdCl}]_2$, and *t*-$Bu_3P{\cdot}HBF_4$ and different heteroaromatic groups were introduced, including pyridyl, 3-substituted pyridyl, quinolinyl, *iso*-quinolinyl and isoxazolyl (Scheme 4.11).



Scheme 4.11

To the best of our knowledge, there are only two examples of the α-arylation of cyclic esters on saturated nitrogen and oxygen heterocycles (Scheme 4.12). Risatti *et al.* reported the α-arylation of *N*-Boc 4-ethyl ester piperidine **237** during the development of a scalable route to a duel NK-1/serotonin receptor antagonist.[120] Pre-formation of the enolate was followed by addition of $Pd_2(dba)_3$ and $P(t\text{-}Bu_3){\cdot}HBF_4$ to afford α-arylated ester **238** but unfortunately the yield was not reported. The only other example of the palladium-catalysed α-arylation of a heterocyclic ester was for 4-methyl ester THP **239**, reported within a patent from Indalo Therapeutics.[121] 4-Methyl ester THP **239** was added to a solution of LDA and stirred for 10

min to pre-form the enolate prior to the addition of the catalyst/aryl bromide solution. This gave α-aryl THP ester **240** in 43% yield.



Scheme 4.12

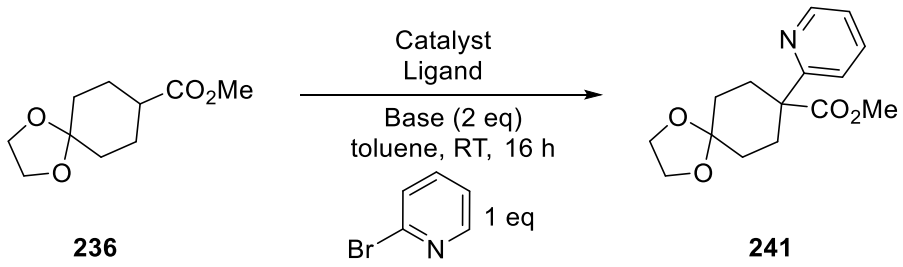
This brief overview reveals that a range of catalysts and ligands have been reported for the palladium-catalysed α-arylation of ketones, amides and esters. The most common bases used were either LiHMDS or LDA, with the reactions being conducted in aromatic solvents. Of note, examples with cyclohexane, a piperidine and a THP were described, including the use of heteroaromatic bromides as the coupling partner.

4.2.2 Investigation of the Scope and Limitations of the α-Arylation of Cyclic Esters

In order to explore the potential for 3-D fragment synthesis, the scope of the α-arylation of cyclic esters needed to be established. As outlined in the previous section, there are a few known examples of ester α-arylation of cyclic substrates, in particular the work of Zhou and Bercot on cyclohexyl esters (see Scheme 4.9 and Scheme 4.11). Therefore, their reaction conditions were used as a starting point for our optimisation studies. The main differences between the conditions reported by Bercot and Zhou was the formation of the enolate. In Bercot's work, the ester had been added to the base to pre-from the enolate prior to the addition of the catalyst/aryl bromide mixture. In contrast, Zhou *et al.* had added the base to

a mixture of the ester and heteroaryl bromide and subsequently added the catalyst solution. To start with, we attempted to carry out the reaction between cyclohexyl ketal **236** and 2-bromopyridine to give α-arylated ester **241** (Table 4.1), a reaction that Zhou *et al*. had reported on the corresponding ethyl ester. Using $[(cinnamyl)PdCl]_2$ (0.5 mol%) and *t*-$Bu_3P.HBF_4$ (2 mol%) with LiHMDS (1 M in THF), none of the desired α-arylated product **241** was formed (entry 1). The reaction was repeated with a higher catalyst and ligand loading of 2 and 4 mol% respectively. On this occasion, some 2-pyridyl ester **241** was identified in the ^1H NMR spectrum of the crude product but, after purification, none was isolated (entry 2). Disappointingly, under apparent identical reaction conditions, 2-pyridyl ester **241** could not be synthesised.

On closer inspection of the reaction conditions reported by Zhou *et al.*, we realised that they did not specify the solvent for the LiHMDS solution. Both THF and toluene solutions of LiHMDS are commercially available. Therefore, considering the observation made by Hartwig *et al*. about the importance of conducting the α-arylation reactions in aromatic solvents (see Scheme 4.8), the base was switched to a toluene solution of LiHMDS. Pleasingly, using LiHMDS (1 M in toluene), 2-pyridyl ester **241** was isolated in 74% yield (entry 3), slightly lower than the 91% yield reported by Zhou *et al*. for the corresponding ethyl ester.



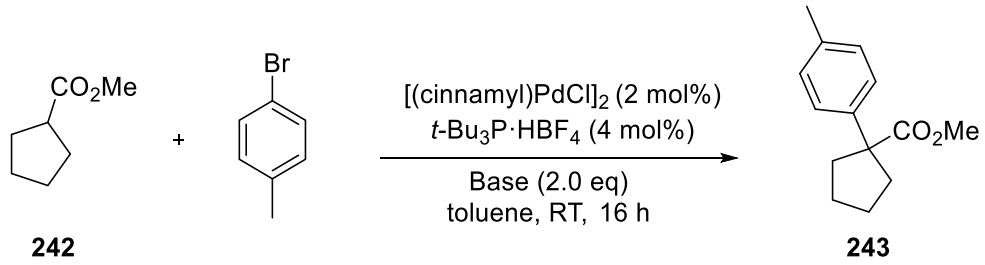
236 **241**

Entry	Catalyst	Ligand	Base	Yield of 241 (%)[a]
1	$[(cinnamyl)PdCl]_2$ (0.5 mol%)	*t*-$Bu_3P.HBF_4$ (2 mol%)	LiHMDS (1 M THF)	-
2	$[(cinnamyl)PdCl]_2$ (2 mol%)	*t*-$Bu_3P.HBF_4$ (4 mol%)	LiHMDS (1 M THF)	-
3	$[(cinnamyl)PdCl]_2$ (2 mol%)	*t*-$Bu_3P.HBF_4$ (4 mol%)	LiHMDS (1 M toluene)	74

Table 4.1 – Investigation of the synthesis of **241**.

a) % yield after chromatography.

Encouraged by this result, attention was turned to other cyclic esters and aryl bromides. Initially, the α-arylation of cyclopentane ester **242** with 4-bromotoluene was investigated (Table 4.2). LiHMDS (1 M in THF) and NaHMDS (2 M in THF) both failed to yield any of the desired α-arylated product **243** (Table 4.2, entries 1 and 2) which is in line with our previous findings. However, even with the toluene solution of LiHMDS, α-arylated ester **243** was isolated in only 5% yield (entry 3). We had better success with LDA (prepared in toluene) which gave **243** in 20% yield (entry 4).



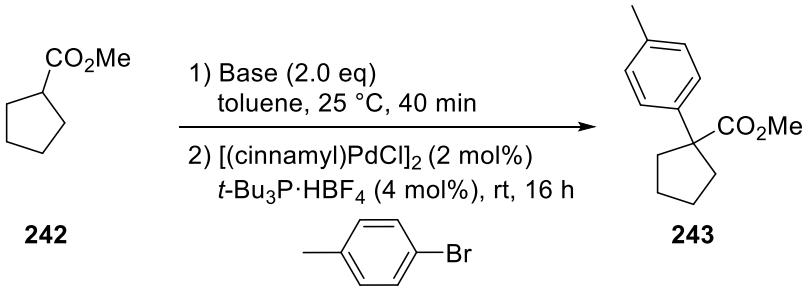
242 **243**

Entry	Base	Yield of 243 (%)[a]
1	LiHMDS (1 M THF)	-
2	NaHMDS (2 M THF)	-
3	LiHMDS (1 M toluene)	5
4	LDA (toluene)[b]	20

Table 4.2 – Investigation of the α-arylation of cyclopentane ester with 4-bromotoluene.

a) % yield after chromatography; b) LDA solution was formed at 0 °C for 30 min in toluene followed by addition of ester **242**.

The low yielding reaction for the α-arylation of cyclopentane ester **242** was a cause for concern. In the procedure, the base was added to the ester and aryl bromide solution and we considered that this could lead to some Claisen self-condensation. To reduce the chance of this occurring, the order of addition of the ester and the base was altered, in line with the procedure reported by Bercot *et al*.[122] Thus, ester **242** would be added to a solution of the base to pre-form the enolate. Then, this enolate solution would be added to a suspension of [(cinnamyl)PdCl]$_2$, *t*-Bu$_3$P·HBF$_4$ and 4-bromotoluene in toluene and stirred at rt for 16 h. The results with three different bases are shown in Table 4.3.



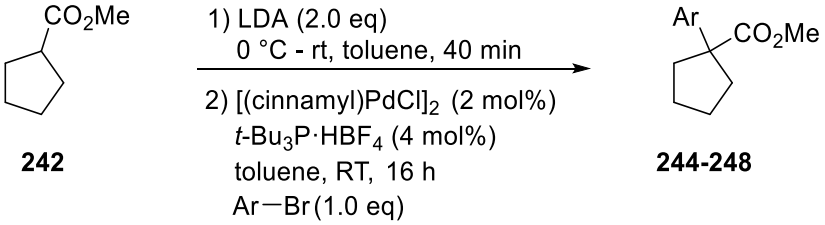
242 **243**

Entry	Base	Yield of 243 (%)[a]
1	LDA[b]	58
2	$LiNCy_2$[b]	59
3	LiHMDS (1 M THF)	No product detected
4	LiHMDS (1 M toluene)	34

Table 4.3 – Pre-formation of the cyclopentane enolate prior to α-arylation with 4-bromotoluene.

a) % yield after chromatography; b) The lithium amide solution was formed a at 0 °C for 30 min in toluene followed by addition of ester **242**.

Using LDA, α-aryl ester **243** was obtained in 58% yield (entry 1), a significant improvement on our previous result (20%, see Table 4.2 entry 4). $LiNCy_2$ was also explored since Hartwig *et al.*[118] had found that pre-formation of the enolate with $LiNCy_2$ represented their optimised conditions (see Scheme 4.8). This gave a 59% yield of **243** (entry 2). Changing the base to the THF solution of LiHMDS failed to afford any of the α-aryl ester (entry 3), whereas the toluene solution of LiHMDS gave α-aryl ester **243** in 34% yield (entry 4), which similar to LDA, was an improvement over our previous result using LiHMDS (1 M in toluene) (see Table 4.2 entry 3). At this point, pre-formation of the enolate using LDA was identified as the best conditions with cyclopentane ester **242**. Thus, using these conditions (LDA, $[(cinnamyl)PdCl]_2$ (2 mol%), t-$Bu_3P{\cdot}HBF_4$ (4 mol%)), the aryl bromide was varied (Table 4.4). Electron rich and poor aryl bromides worked well although yields were variable (**244-247**, 38-72%) (entries 1-4). An *ortho*-methyl substituent was reasonably well tolerated and gave α-aryl ester **247** in 36% yield (entry 4). Unfortunately, we had less success with heteroaryl bromides. Bromides containing pyrimidine and imidazole groups both failed to afford any of the desired α-arylated products based on analysis of the crude reaction mixtures by ^1H NMR spectroscopy and mass spectrometry (entries 5 and 6). However, ester enolate α-arylation with 2-bromopyridine gave α-aryl ester product **248**, albeit in 6% yield (entry 7).



242 **244-248**

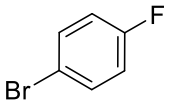
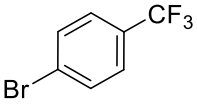
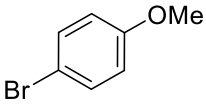
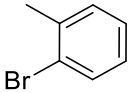
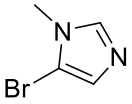
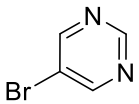
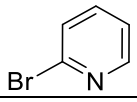
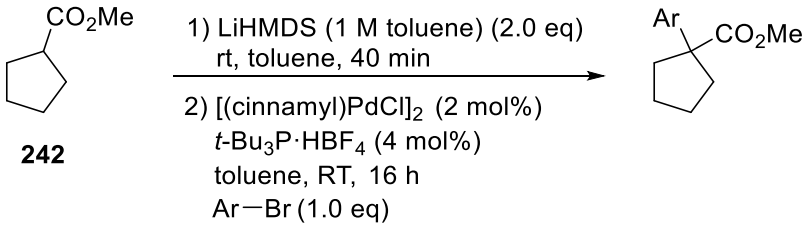
Entry	Ar-Br	Product	Yield (%)[a]
1		**244**	34
2		**245**	72
3		**246**	68
4		**247**	36
5		-	No product formation
6		-	No product formation
7		**248**	6

Table 4.4 – Investigation of the α-arylation of cyclopentane ester with aryl bromides; a) % yield after chromatography.

The yields for the *para*-fluorophenyl and *ortho*-methylphenyl derivatives **244** and **247** were relatively low (Table 4.4, entries 1 and 4). This led us to investigate the α-arylations with LiHMDS (1 M in toluene) *via* pre-formation of the enolate prior to addition of the catalyst and aryl bromide. For this study, five aryl bromides were used, and the results are shown in Table 4.5. Using these conditions, a 27% yield of *para*-fluorophenyl ester **244** was isolated, with none of *ortho*-methylphenyl ester **247** observed (entries 1 and 2). In contrast, and to our surprise, the α-arylation with 2-bromopyridine led to a 72% yield of 2-pyridyl ester **248**, which was not affected upon scale-up (entry 3). Unfortunately, α-arylation with the pyrimidinyl and imidazolyl bromides still failed to yield any of the desired α-arylated products (entries 4 and 5)



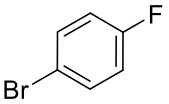
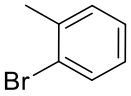
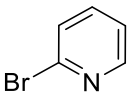
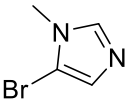
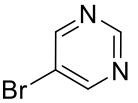
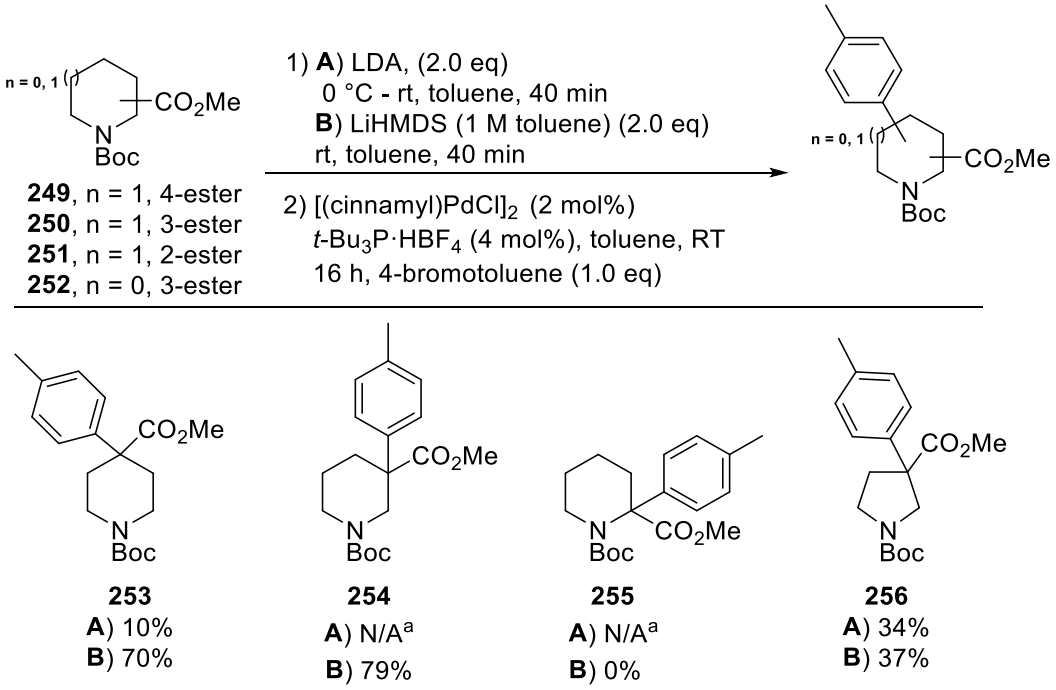
Entry	Ar-Br	Product	Yield (%)[a]
1		**244**	27
2		**247**	No product formation
3		**248**	72 (71[b])
4		-	No product formation
5		-	No product formation

Table 4.5 – Investigation of the α-arylation of cyclopentane ester with aryl bromides using LiHMDS (1 M in toluene); a) % yield after chromatography; b) 7.8 mmol scale.

With a preliminary study of the scope of the aryl bromides and with two sets of promising conditions, either LDA or LiHMDS (1 M in toluene), different heterocyclic esters were explored. To determine the best set of conditions, we attempted some using LDA (conditions A) and some using LiHMDS (conditions B) with a pre-formed enolate in toluene. The results with *N*-Boc esters are shown in Scheme 4.13.

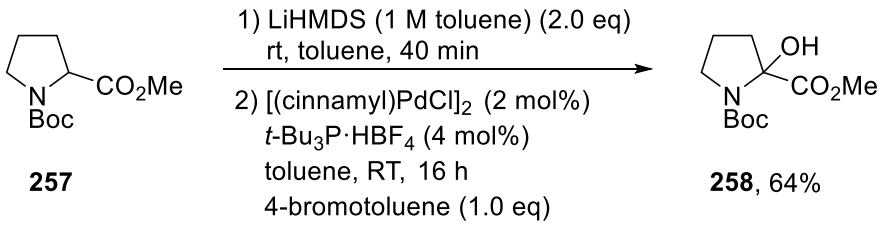
LiHMDS (1 M in toluene) and LDA were initially trialled on 4-methyl ester piperidine **249** with the former giving 4-α-tolyl piperidine **253** in 70% yield. The use of LDA was found to only give **253** in a 10% yield. Therefore, conditions B using LiHMDS (1 M in toluene) were applied to the 3-methyl ester piperidine which afforded 3-α-tolyl piperidine **254** in a 79% yield. However, using the same conditions, none of the desired 2-α-tolyl piperidine **255** was observed. Next, the *N*-Boc pyrrolidines were explored, with both sets of conditions applied to the 3-methyl ester pyrrolidine. On this occasion, both sets of conditions afforded similar yields, with 3-α-tolyl pyrrolidine **256** isolated in 34% and 37% yields respectively using

conditions A and B. However, the lower yields could be attributed to the poor solubility observed of the ester enolate, which had not been seen with the piperidine ester enolates.



Scheme 4.13 – a) Conditions not carried out.

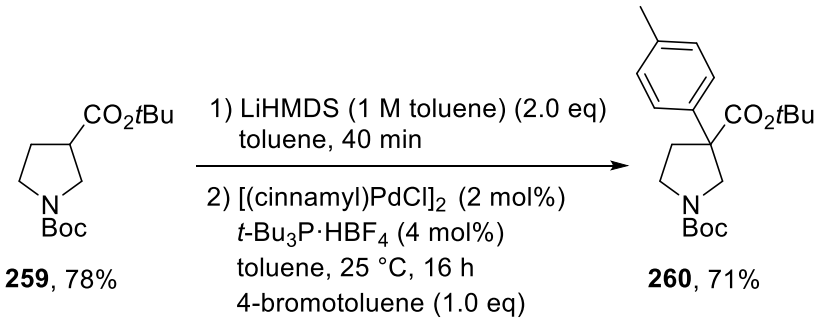
Conditions B (LiHMDS (1 M in toluene)) were applied to the 2-methyl ester pyrrolidine **257** and, surprisingly, gave 2-methyl ester pyrrolidine alcohol **258** in 64% yield, with none of the desired α-aryl pyrrolidine observed (Scheme 4.14). We presume that the formation of the α-hydroxy ester was due to the presence of oxygen within the reaction flask which led to an α-hydroxylation process.



Scheme 4.14

The poor solubility of the 3-methyl ester pyrrolidine enolate potentially contributed to the low yields observed. Therefore, to try and improve the enolate solubility and hinder the formation of the Claisen self-condensation product, the more sterically hindered *t*-butyl enolate was investigated. 3-*t*-Butyl ester pyrrolidine **259** was prepared by another member of the group starting from the corresponding carboxylic acid.[123] α-Arylation of 3-*t*-butyl ester

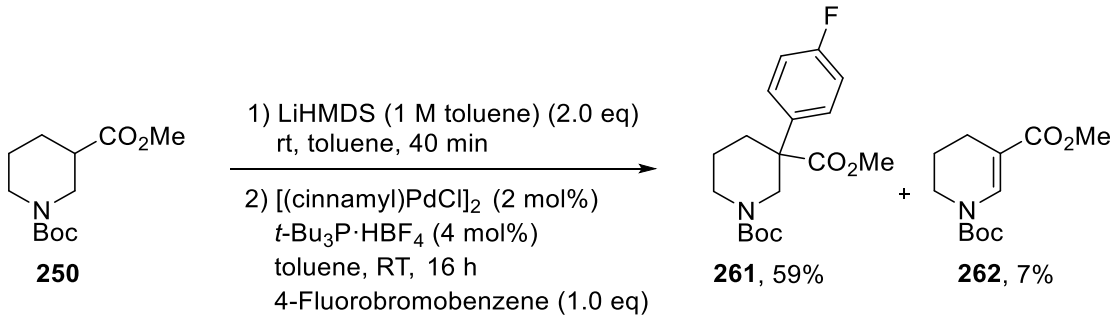
pyrrolidine **259** afforded 3-α-tolyl pyrrolidine **260** in 71% yield with the *t*-butyl enolate showing improved solubility; none of the Claisen self-condensation product was observed (Scheme 4.15).



259, 78% **260**, 71%

Scheme 4.15

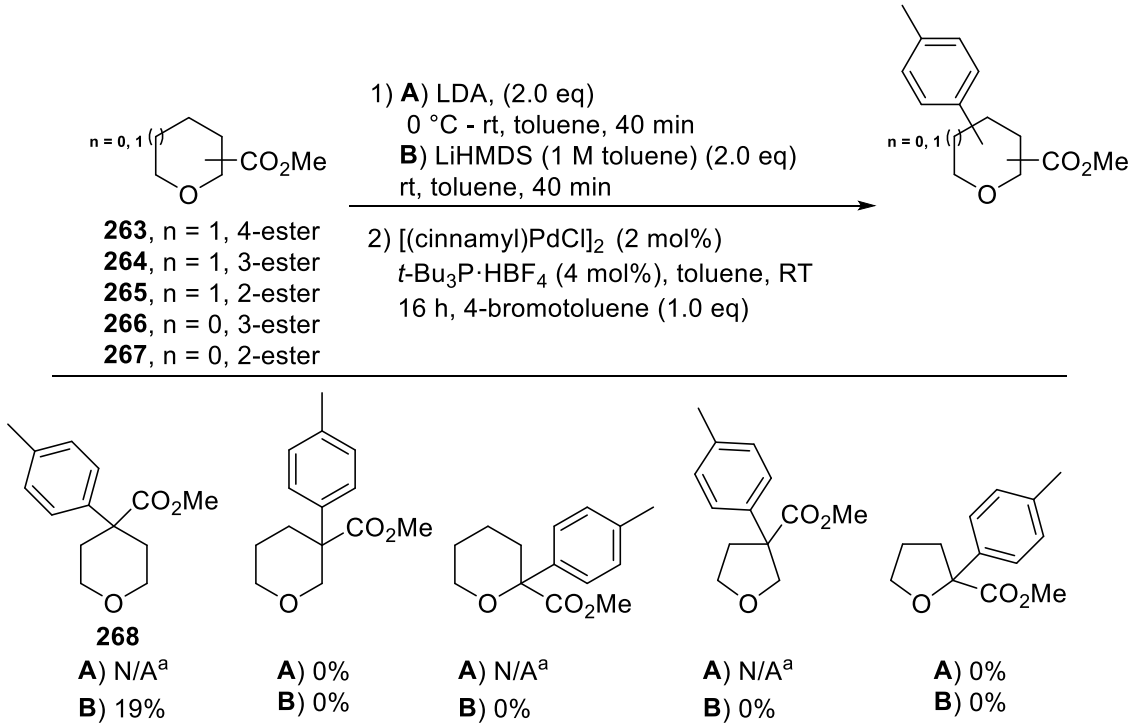
The final area we wanted to explore was the installation of different aryl bromides. Therefore, the α-arylation of 3-methyl ester piperidine **250** using LiHMDS (1 M in toluene) with 4-fluorobromobenzene was attempted and gave α-aryl piperidine **261** in 59% yield, along with dihydropyridine ester **262** in 7% yield. Presumably, formation of dihydropyridine **262** proceeded through β-hydride elimination, which is an alternative catalytic pathway to reductive elimination (Scheme 4.16).



250 **261**, 59% **262**, 7%

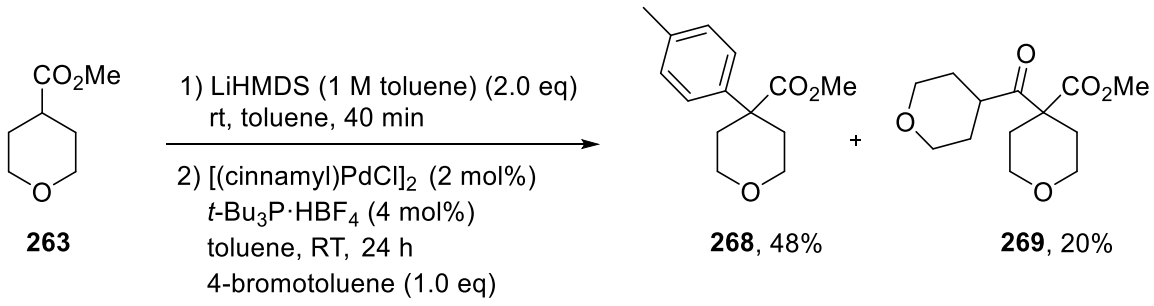
Scheme 4.16

Next, the α-arylation of THF and THP esters was investigated, with some attempted using LDA (conditions A) and some with LiHMDS (conditions B) with a pre-formed enolate in toluene. However, neither set of conditions yielded any of the desired α-arylated products, with the only exception being the 4-methyl ester THP **263**. In this case, α-tolyl THP **268** was isolated in 19% yield along with 4-methyl ester THP **263** in 28% yield (Scheme 4.17).



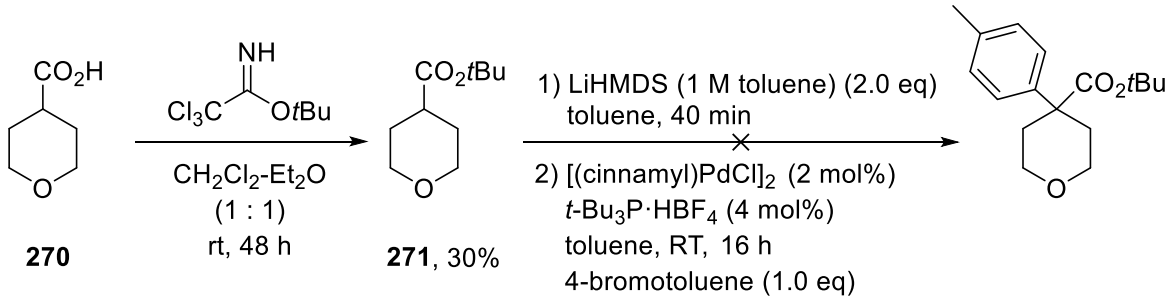
Scheme 4.17 – a) Conditions were not attempted.

Due to the low yield of α-tolyl THP **268** and the recovery of starting material, we decided to extend the reaction time to 24 h. This gave the desired product **268** in 48% yield along with Claisen self-condensation product **269** in 20% yield (Scheme 4.18).



Scheme 4.18

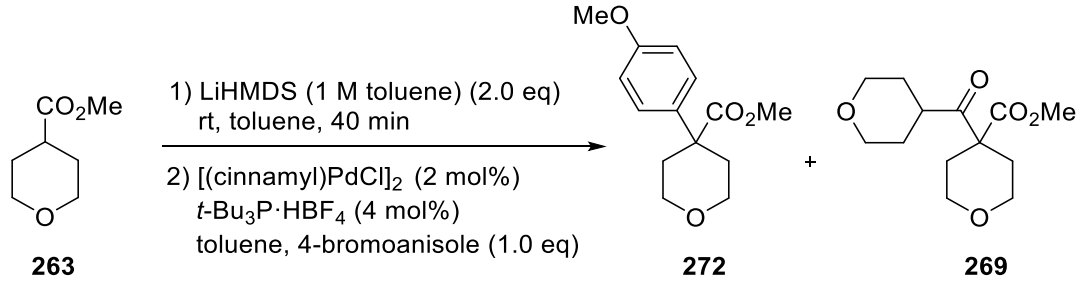
However, similar to the 3-methyl ester pyrrolidine **252** (see Scheme 4.15), we were observing poor solubility of the ester enolate. Therefore, the α-arylation of the *t*-butyl ester THP **271** was explored to see whether an improvement in solubility and overall yield could be achieved. The *t*-butyl ester was synthesised by reacting THP acid **270** with *t*-butyl-2,2,2-trichloroacetimidate at rt for 4 days. Purification afforded 3-*t*-butyl ester THP **271** in 30% yield. However, despite the improved solubility of the ester enolate, only starting material along with some minor undetermined impurities were detected (Scheme 4.19).



270 **271**, 30%

Scheme 4.19

Therefore, we returned to the 4-methyl ester THP **265** and decided to explore α-arylation with 4-bromoanisole and 2-bromopyridine using LiHMDS (1 M in toluene). Reaction with 4-bromoanisole at rt for 24 h gave α-aryl THP **272** in 18% yield (Table 4.6, entry 1). Unlike α-arylation with 4-bromotoluene, analysis of the ^{1}H NMR spectrum for the α-arylation with 4-bromoanisole showed unreacted starting material. As a result, the reaction time was increased to 64 h, which gave 4-methyl ester THP **272** in an improved 57% yield (entry 2). The reaction temperature was also increased to 50 °C, allowing for a shorter reaction time, affording 4-methyl ester THP **272** in a higher 63% yield (entry 3). Next, the α-arylation of 4-methyl ester THP **265** with 2-bromopyridine was explored. Using the optimised reaction conditions from Table 4.6 of 50 °C for 16 h, α-aryl THP **273** was isolated in 53% yield along with Claisen self-condensation **269** (20%) (Scheme 4.20).

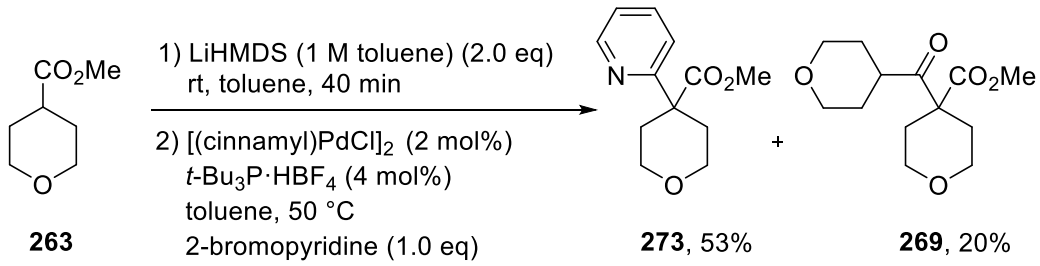


263 **272** **269**

Entry	Temperature (° C)	Time (h)	Yield 272 (%)[a]	Yield 269 (%)[a]
1	25	24	18	-
2	25	64	57	9
3	50	16	63	21

Table 4.6 – Optimisation of the synthesis of THP **272**.

a) % yield after chromatography.



Scheme 4.20

Investigation into the α-arylation of cyclic and heterocyclic esters had revealed the limitations of the chemistry, with only the cyclopentane, 3-pyrrolidine, 3- and 4-piperidine and the 4-THP esters successfully arylated. The aryl group could be interchanged to incorporate electron rich and poor aryls, along with the coupling of 2-pyridyl. Therefore, a series of potential fragments were designed which we anticipated would be accessible using the ester enolate α-arylation chemistry.

4.2.3 Design and Analysis of 3-D Fragments from α-Arylated Cyclic Esters

With knowledge of the scope and limitations of the α-arylation of cyclic esters, both in terms of the cyclic esters and the aryl bromides, we could design 3-D fragments that should be synthetically accessible. Then, 3-D shape analysis using PMI plots, together with ensuring that the fragments were 'Rule of three' compliant, would be used to identify the 3-D fragments that would be synthesised. Therefore, a series of fragments were designed based on the five cyclic scaffolds shown in Figure 4.1. They included cyclopentane, 3-substituted pyrrolidine, 3- and 4-substituted piperidines and THP. As well as the ester group, other substituents were incorporated such as carboxylic acid, primary alcohol and amine, secondary amine and amide since these groups should be accessible using simple transformations from the ester. The third point of diversification was the aryl group and the seven aromatic groups which had been successfully introduced by ester α-arylation (see Section 4.2.2). As a result of these three points of diversification, 210 3-D fragments were designed.

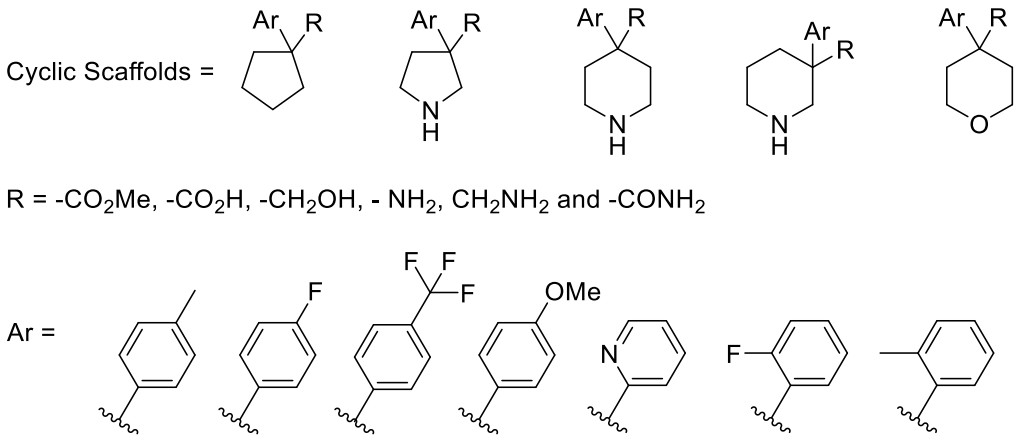
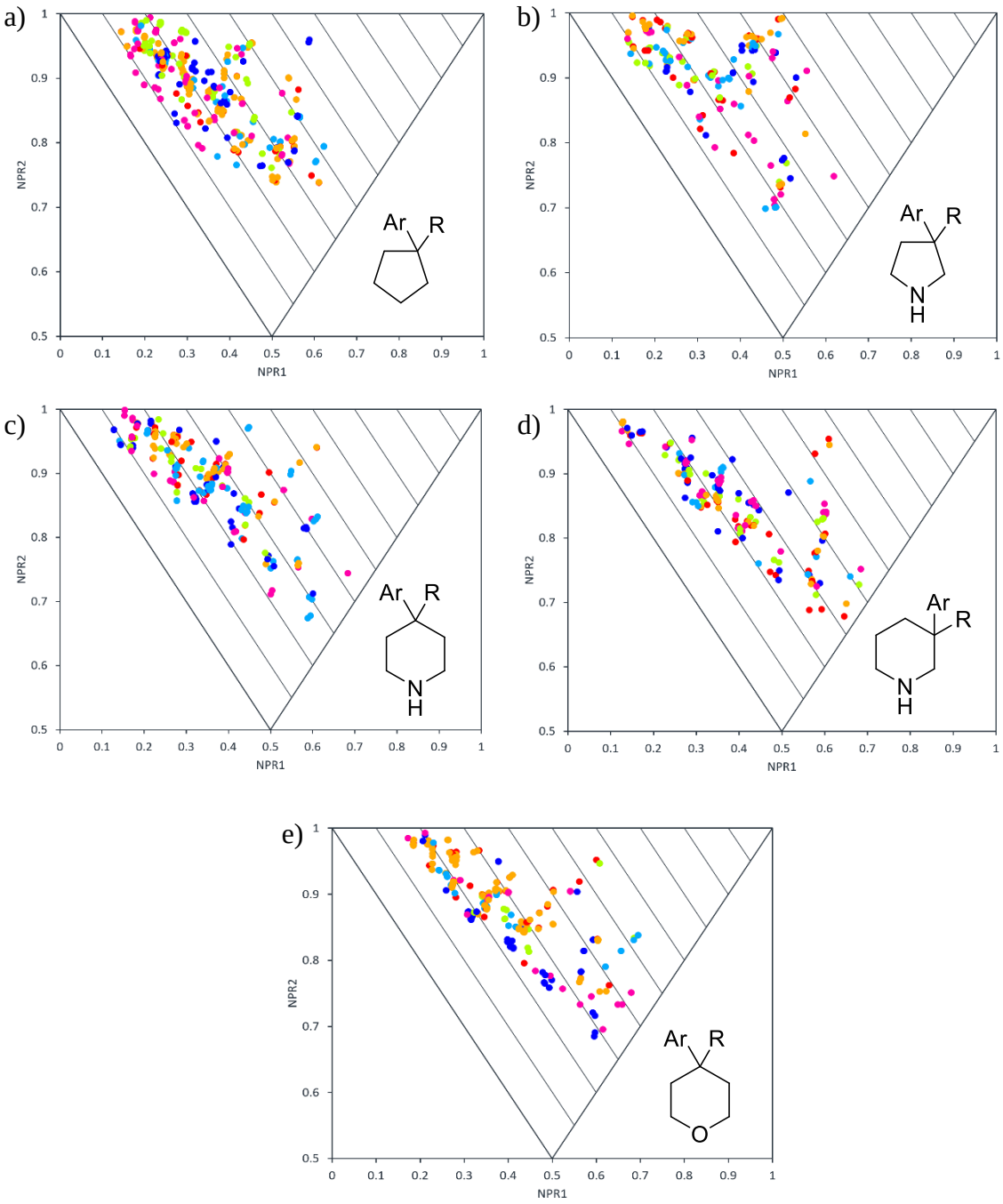


Figure 4.1 – Structures of 210 3-D fragments.

The PMI plot of the conformations with a relative energy of ≤ 1.5 kcal mol^{-1} of the 210 3-D fragments are shown in Figure 4.2. Pleasingly, these 3-D fragments showed good levels of shape diversity, with only 18 out of the 1176 conformations occupying the ΣNPR region between 1.0-1.1. For all five scaffolds, the 3-D fragments had almost all conformations in the most interesting regions of chemical space, normally ΣNPR ≥ 1.1. Hence, any of the 210 3-D fragments were of interest for synthesis. A sub-set of these were selected based on their anticipated ease of synthesis.



Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

Figure 4.2 –PMI analysis of (a) cyclopentane, (b) 3-substituted pyrrolidine, (c) 4-substituted piperidine, (d) 3-substituted piperidine and (e) 4-substituted THP showing all conformations which have a relative energy ≤ 1.5 kcal mol^{-1}. The Ar- and R- groups are shown in Figure 4.1.

4.2.4 Synthesis of Ester Enolate α-Arylated 3-D Fragments

The α-arylation of cyclic esters set out in Section 4.2.2 provided several 3-D fragments directly. The structures of these eight 3-D fragments are shown in Figure 4.3 and they were directly added to the 3-D fragment library.

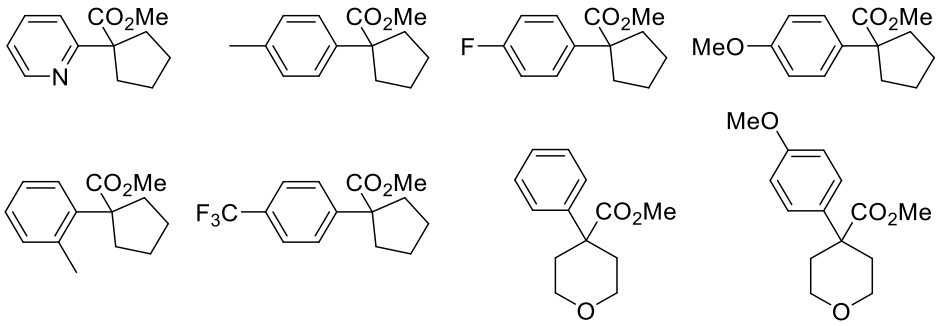
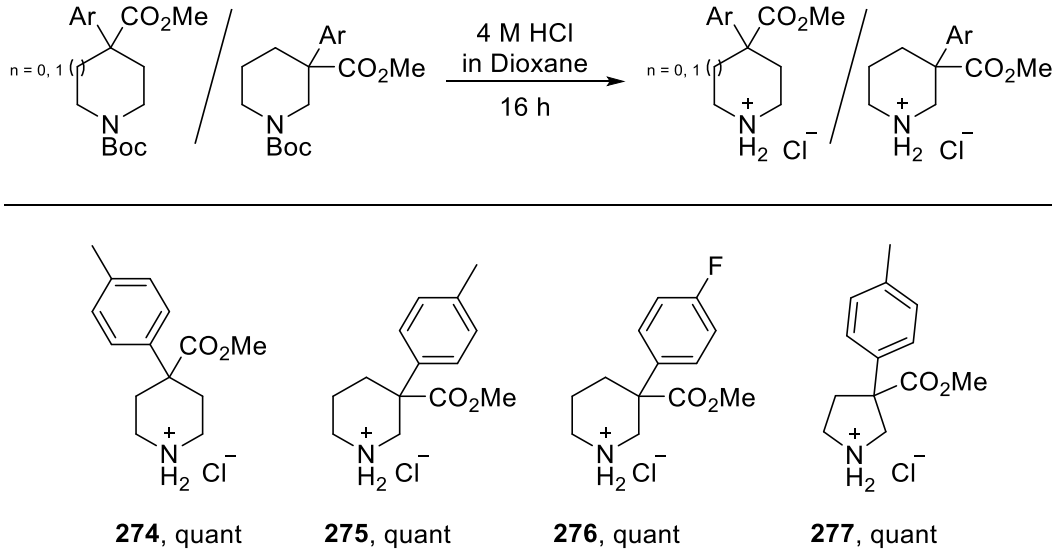


Figure 4.3 – Structures of eight 3-D fragments synthesised directly using α-arylation.

The α-arylation chemistry also afforded three *N*-Boc piperidine and one *N*-Boc pyrrolidine scaffolds, which required deprotection before inclusion within the library. The *N*-Boc protected scaffolds were treated with 4 M HCl in dioxane and stirred for 16 h, which gave the desired final fragments, all in quantitative yields (Scheme 4.21).

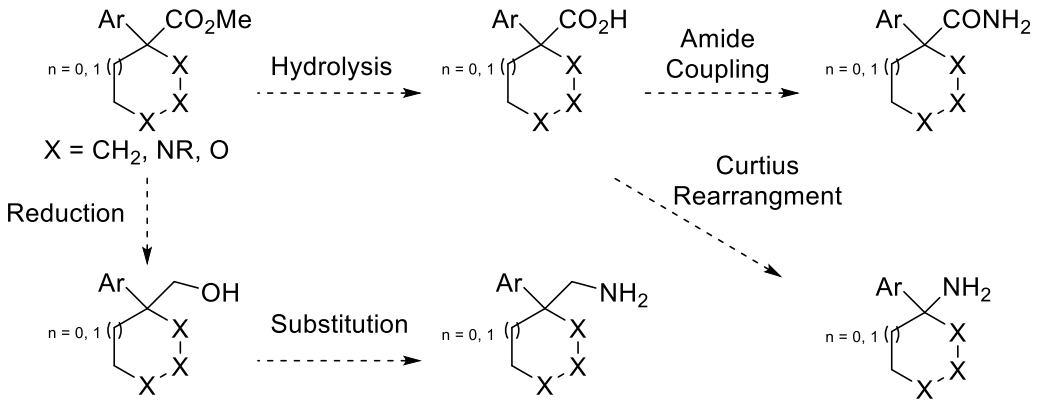


274, quant **275**, quant **276**, quant **277**, quant

Scheme 4.21

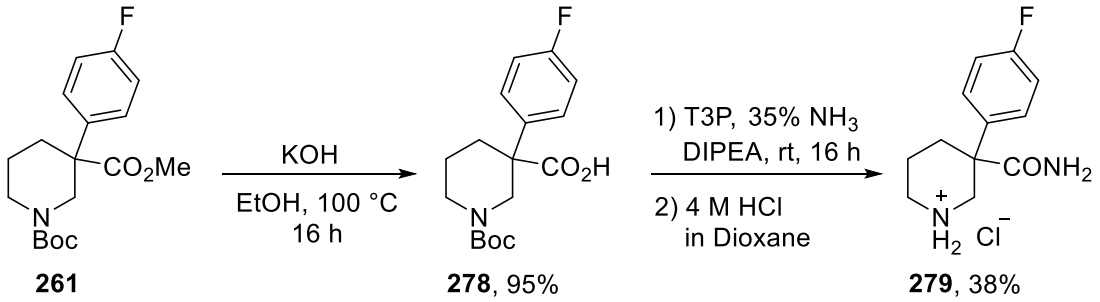
We also imagined a range of reactions that could be carried out on the α-arylated ester fragments to generate other 3-D fragments. Our planned reactions are summarised in Scheme 4.22. For example, ester hydrolysis would give the corresponding carboxylic acid which could be converted into an amide *via* coupling with an amine or into a secondary

amine *via* Curtius rearrangement. Alternatively, reduction of the ester would give a primary alcohol. Subsequently, activation and nucleophilic substitution should give a primary amine functionality.



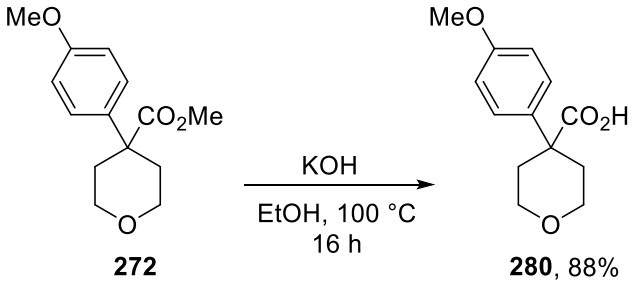
Scheme 4.22

The 4-fluorophenyl piperidine **261** was derivatised by ester hydrolysis and subsequent amide coupling followed by Boc removal to give amide piperidine **279** in 36% yield over the three steps (Scheme 4.23). Ester hydrolysis was also performed on the 4-methoxy THP **272** to afford carboxylic acid **280** in 88% yield (Scheme 4.24).



261 **278**, 95% **279**, 38%

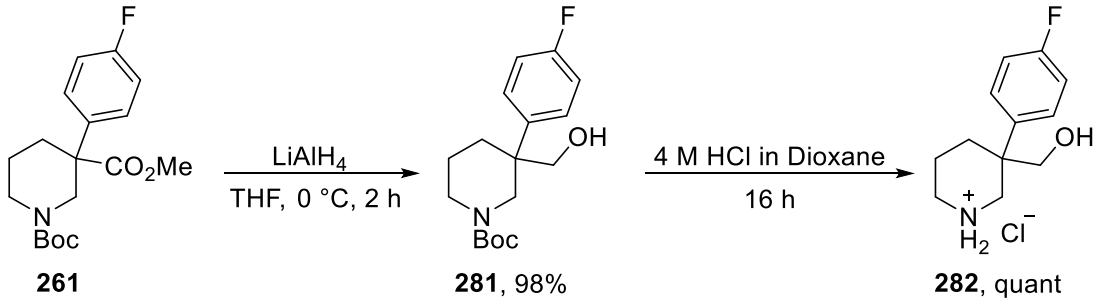
Scheme 4.23



272 **280**, 88%

Scheme 4.24

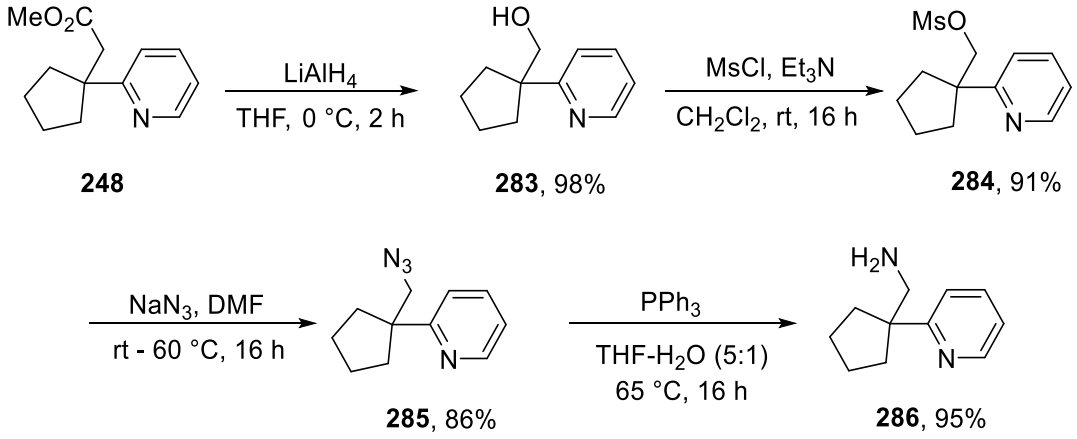
As well as ester hydrolysis, the ester in 4-fluorophenyl piperidine **261** was also reduced to the primary alcohol with $LiAlH_4$ at 0 °C for 2 h. After purification, this afforded *N*-Boc piperidine **281** in 98% yield. The Boc group was then removed to afford 3-D fragment **282** (Scheme 4.25).



261 **281**, 98% **282**, quant

Scheme 4.25

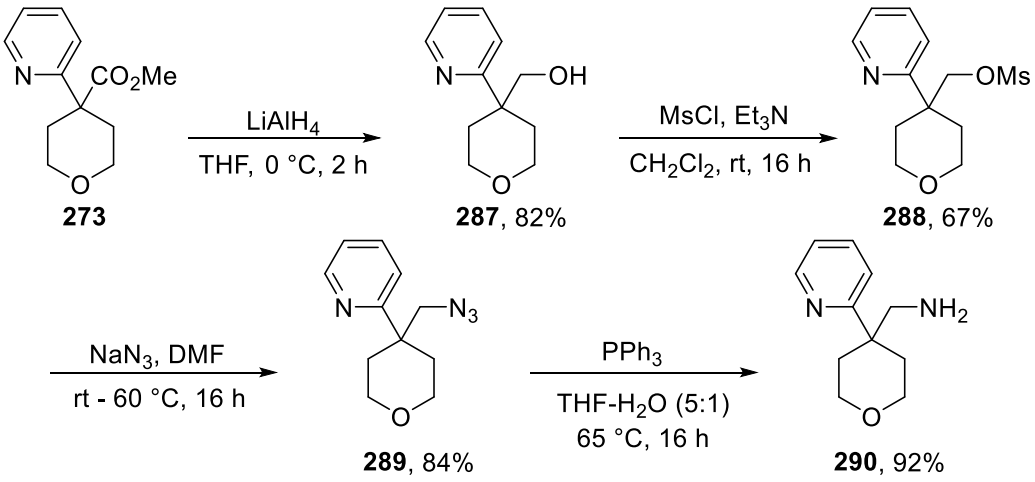
The primary alcohol could also be converted into a primary amine over three steps *via* mesylation, azide insertion and Staudinger reduction. After reduction of ester **248** using our standard conditions ($LiAlH_4$, 0°C, 2 h), cyclopentane alcohol **283** was reacted with MsCl and Et_3N at rt for 16 h to afford cyclopentane mesylate **284** in 91% yield. Nucleophilic substitution with NaN_3 at 60 °C for 16 h gave azide **285** in 86% yield, which was reduced to the amine using a Staudinger reaction to afford amine **286** in 95% yield (Scheme 4.26). In the same way, THP ester **273** underwent the same reaction sequence. THP alcohol **287** was converted into THP mesylate **288** and then in two steps to afford THP amine **289** in 42% over four steps from methyl ester **273** (Scheme 4.27).



248 **283**, 98% **284**, 91%

285, 86% **286**, 95%

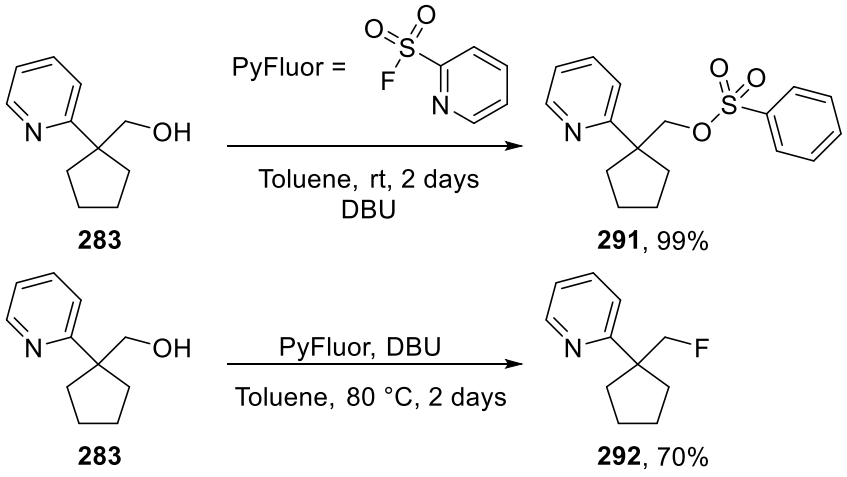
Scheme 4.26



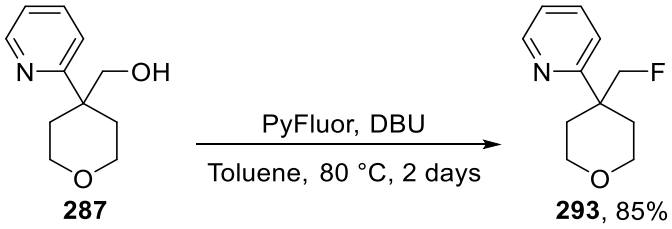
Scheme 4.27

As well as synthesising some of the designed 3-D fragments from Section 4.2.3, we also decided to carry out the synthesis of a few other 3-D fragments. The shape of the fragments was initially analysed using PMI plots, and their synthesis is described in the remainder of this section. For example, the conversion of the primary alcohol into a fluoroalkyl group was considered since fluorine is a common feature in potential drug molecules and is also used as an NMR handle in NMR screening of fragments.

A convenient method for deoxyfluorination using PyFluor had been developed by Doyle *et al.*[124] Hence, cyclopentane alcohol **283** was treated with PyFluor and DBU at rt for two days. ^{1}H NMR spectroscopic analysis of the reaction mixture revealed the formation of the pyridine sulfonate **291**, which was subsequently isolated in 99% yield. We reasoned that the lack of reactivity could be due to the neopentyl alcohol resulting in a slow rate of nucleophilic substitution. Therefore, the reaction temperature was increased to 80 °C, which gave the desired fluorinated product **292** in 70% yield (Scheme 4.28). Deoxyfluorination was also applied to THP alcohol **287** to afford fluorinated product **293** in 85% yield (Scheme 4.29).

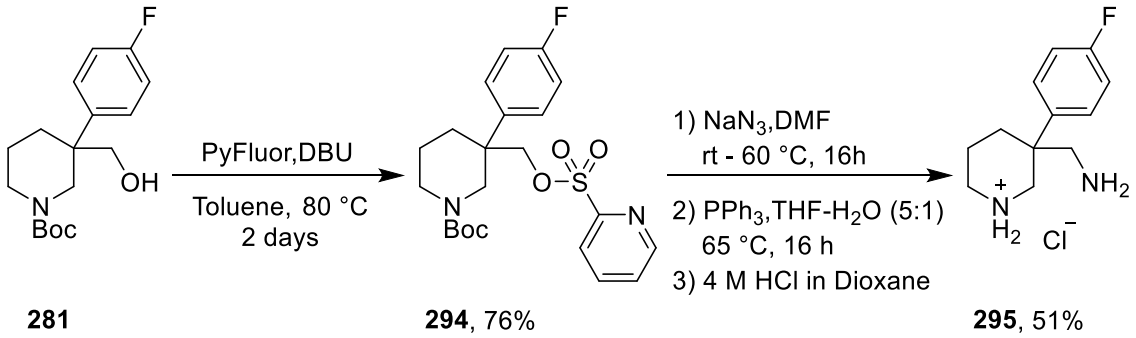


Scheme 4.28



Scheme 4.29

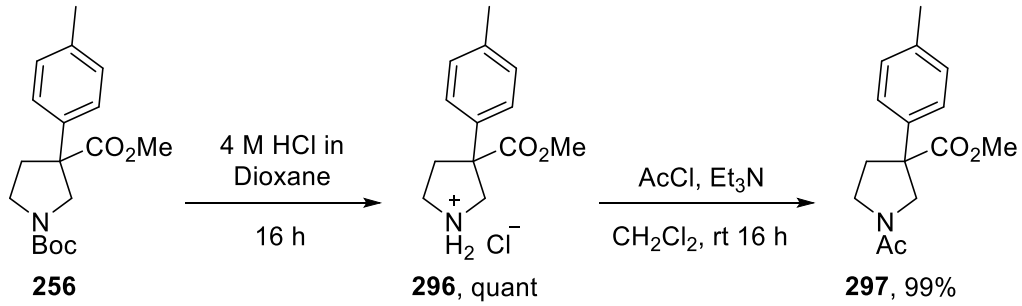
Fluorination was then attempted on 4-fluorophenyl *N*-Boc piperidine **281** using the conditions outlined above. However, on this occasion, we failed to form the fluorinated product and instead isolated the piperidine sulfonate intermediate **294** in 76% yield. We decided to take the intermediate and displace the sulfonate to from the primary amine using azide insertion and the Staudinger reaction. The Boc protecting group was then removed to afford piperidine **295** in a 51% yield over three steps from sulfonate **294** (Scheme 4.30).



Scheme 4.30

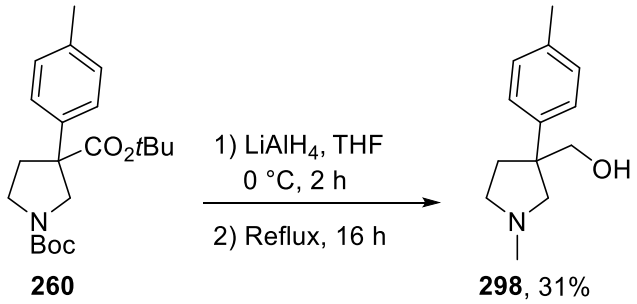
4-Methylphenyl pyrrolidine ester **256** was converted into the acetamide using 4 M HCl in dioxane to remove the Boc group, followed by acylation with acetyl chloride and Et_3N. This

gave acetyl pyrrolidine **297** in 99% yield (Scheme 4.31). We were also able to simultaneously reduce the *tert*-butyl ester and the Boc group in pyrrolidine **260** to afford *N*-methyl pyrrolidine alcohol **298** in 31% yield (Scheme 4.32).



256 **296**, quant **297**, 99%

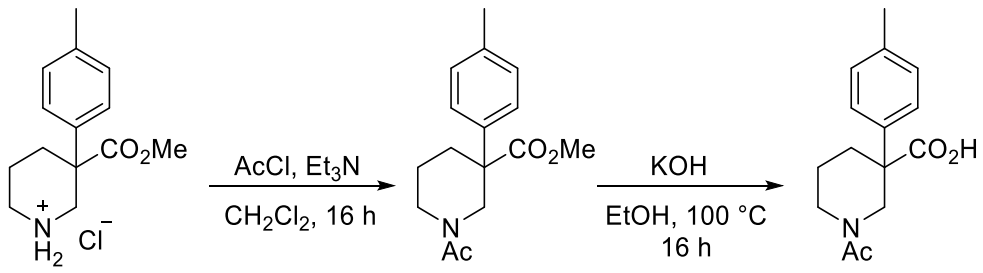
Scheme 4.31



260 **298**, 31%

Scheme 4.32

The final α-arylated fragment synthesised was piperidine acetamide **300**. This was synthesised starting from piperidine **275** in two steps *via* acylation and then subsequent base hydrolysis to give **300** in 88% yield over two steps (Scheme 4.33).



275 **299**, 88% **300**, quant

Scheme 4.33

In total, 26 α-arylated 3-D fragments were synthesised and included within the fragment library. The structures of the synthesised 3-D fragments are shown in Figure 4.4.

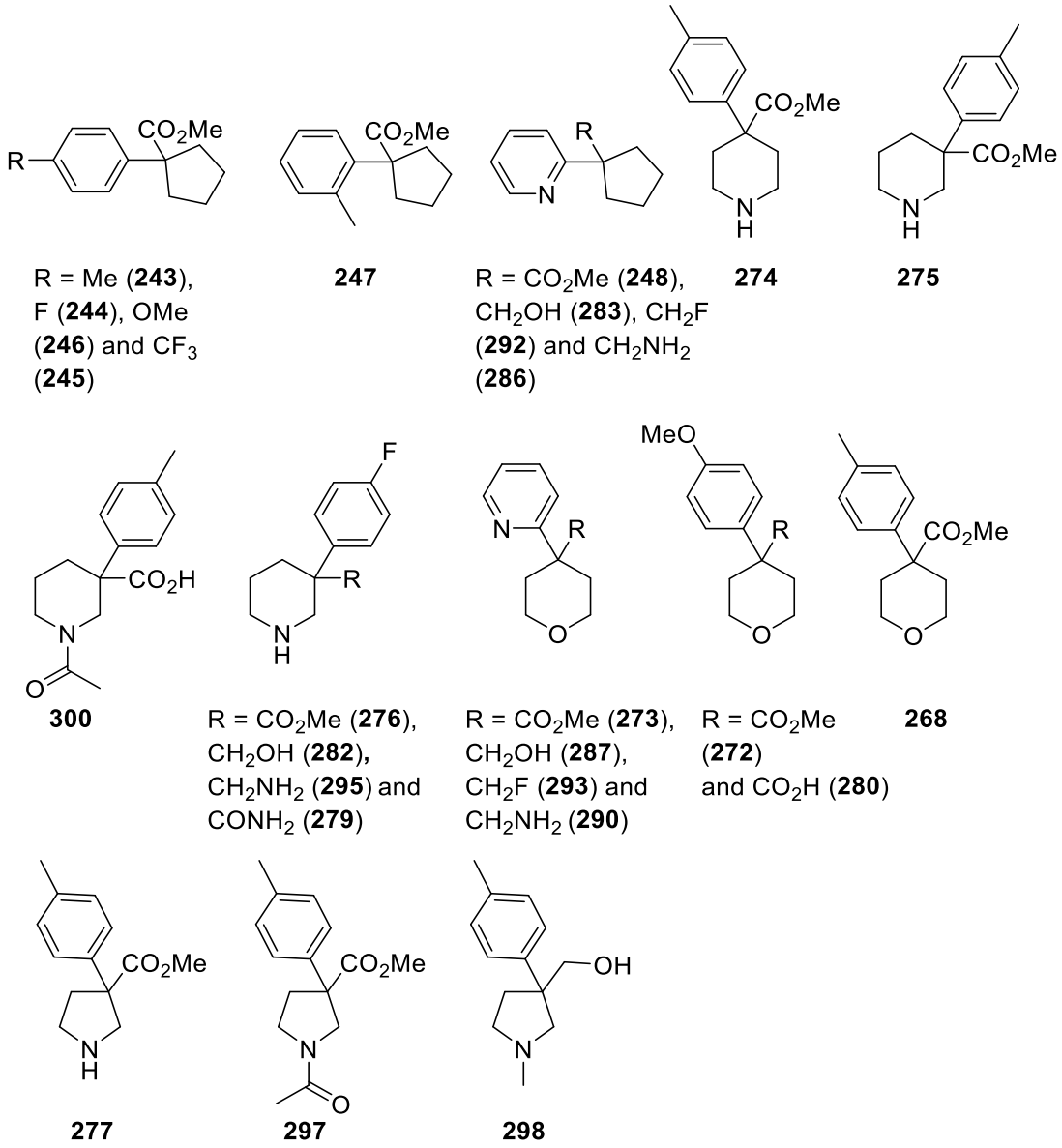
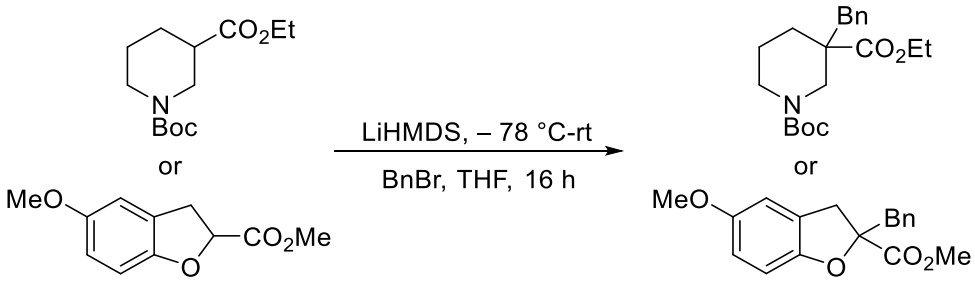


Figure 4.4 – Structures of 26 α-arylated 3-D fragments.

4.3 Synthesis of 3-D Fragments *via* α-Alkylation of Cyclic Esters

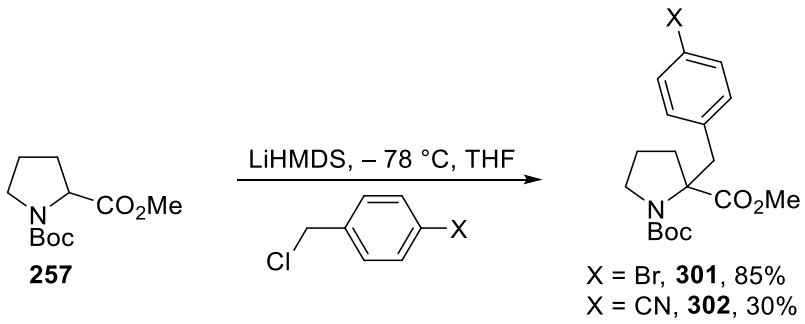
4.3.1 Overview of α-Alkylation of Cyclic Esters

The α-alkylation of cyclic esters is a classical reaction that has been widely used in synthesis, with typical reaction conditions using LiHMDS at –78 °C and trapping with either alkyl chlorides or bromides. Numerous examples have been reported within patents, with both 3-piperidine ethyl ester and dihydrobenzofuran methyl esters alkylated with benzyl bromide (Scheme 4.34).[125–130]



Scheme 4.34

Substituted benzyl derivatives have also been introduced by alkylation. For example, Dodd *et al*. alkylated 2-methyl ester pyrrolidine **257** with both 4-bromo and 4-nitrile benzyl chlorides to give α-alkylated products **301** and **302** in 85% and 30% yields respectively (Scheme 4.35).[131]

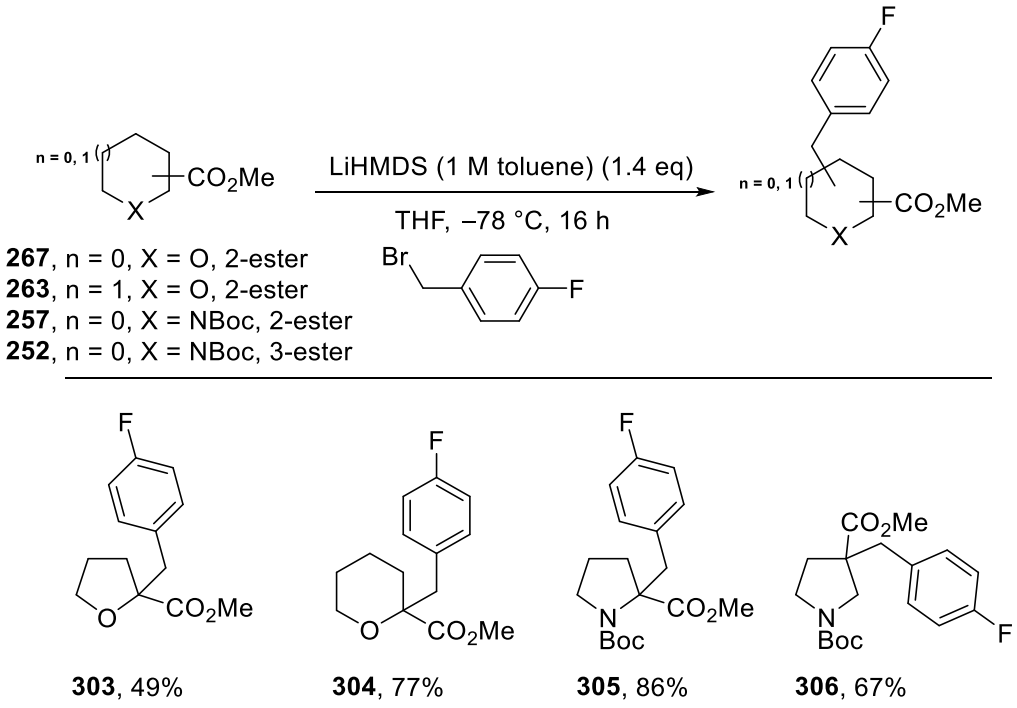


Scheme 4.35

The previous literature revealed that a range of heterocyclic esters have been α-alkylated with different benzyl bromides/chlorides. A range of substituents on the benzyl halide have been used.

4.3.2 Investigation of the Scope of the α-Alkylation of Cyclic Esters

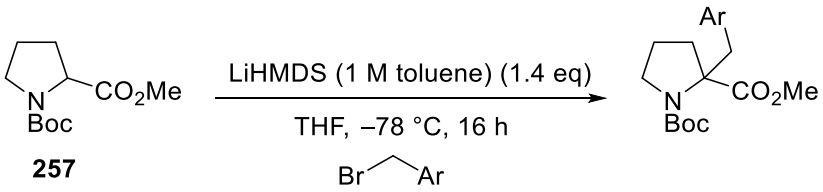
In order to explore the potential for 3-D fragment synthesis, the scope of the α-alkylation chemistry was briefly investigated. We decided to start with the cyclic esters which were less successful in the α-arylation chemistry. Thus, 2-methyl ester THF **267**, 2-methyl ester THP **263**, 2-methyl ester pyrrolidine **257** and 3-methyl ester pyrrolidine **252** were all explored (Scheme 4.36). Using the conditions outlined by Dodd *et al*., 2-methyl ester THF **267** was reacted with LiHMDS (1 M in toluene) in THF at –78 °C for 1.5 h to generate the enolate. 4-Fluorobenzyl bromide was then added and the reaction mixture was warmed to rt and stirred for 16 h. This gave α-alkylated THF **303** in 49% yield. Similarly, 2-methyl THP ester **263** was alkylated to afford **304** in 77% yield. The final two heterocycles explored were the 2- and 3-pyrrolidine methyl esters **257** and **252** and the alkylated products **305** and **306** were isolated in 86% and 67% yields respectively.



Scheme 4.36

Different benzyl bromides were then used, focusing on the 2-methyl ester pyrrolidine **257**. The *meta*- and *ortho*-fluorobenzyl bromides gave alkylated products **307** and **308** in 90% and 92% yields respectively (Table 4.7, entries 1 and 2). The benzyl group was varied to incorporate the *para*- and *meta*-methoxybenzyl bromides giving **309** and **310** in 68% and 91% yields (entries 3 and 4). The *ortho*-bromobenzyl bromide was also successfully installed to afford **311** in 89% yield (entry 5). As with α-arylation, we were less successful with the

installation of a pyridinyl substituent. Alkylation with 2-(bromomethyl) pyridine (generated by treating 2-(bromomethyl) pyridine·HBr with base) gave alkylated pyrrolidine **312** in only 33% yield (entry 6).



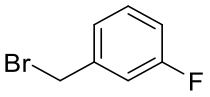
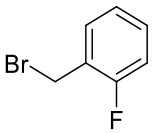
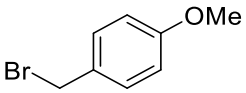
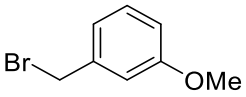
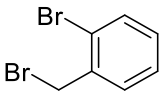
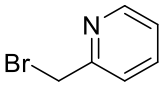
Entry	Hetero/Ar-Br	Yield[a] (%)
1		**307**, 92
2		**308**, 90
3		**309**, 91
4		**310**, 68
5		**311**, 89
6		**312**, 33

Table 4.7 – Investigation of the α-alkylation of pyrrolidine ester with aryl bromides using LiHMDS (1 M in toluene); a) % yield after chromatography.

4.3.3 Design and Analysis of 3-D Fragments from α-Alkylated Cyclic Esters

As with the α-arylated fragments, once the scope of the α-alkylation of cyclic esters had been explored, we designed 3-D fragments that should be synthetically accessible. Then, 3-D shape analysis using PMI plots, together with the 'Rule of three' guidelines, the 3-D fragments would be selected and synthesised. Therefore, a series of fragments were designed based on the four cyclic scaffolds shown in Figure 4.5. They included 2-substituted THF, THP and pyrrolidine and 3-substituted pyrrolidine. The ester group was derivatised to include, carboxylic acid, primary alcohol/amine, amide and secondary amine. The third point of diversification was the aryl group and the seven aromatic groups which had been

successfully introduced by ester α-alkylation were included. As a result of these three points of diversification, 140 3-D fragments were designed.

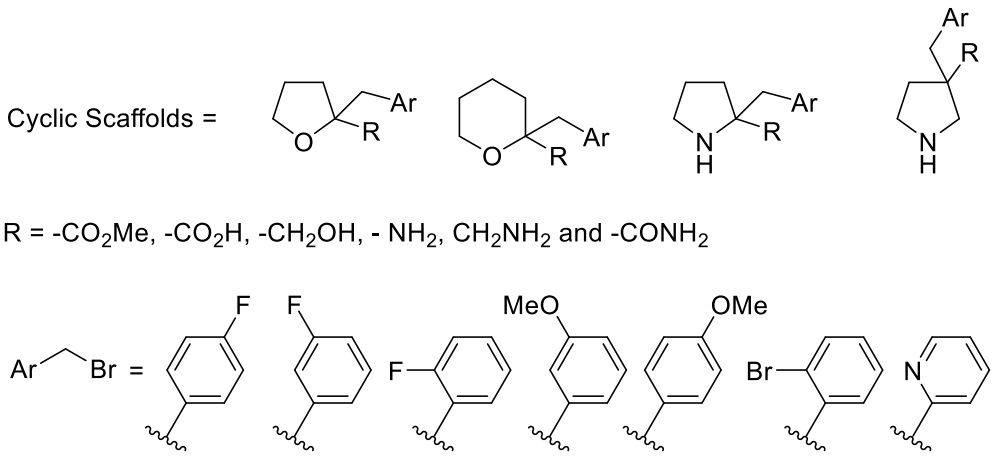
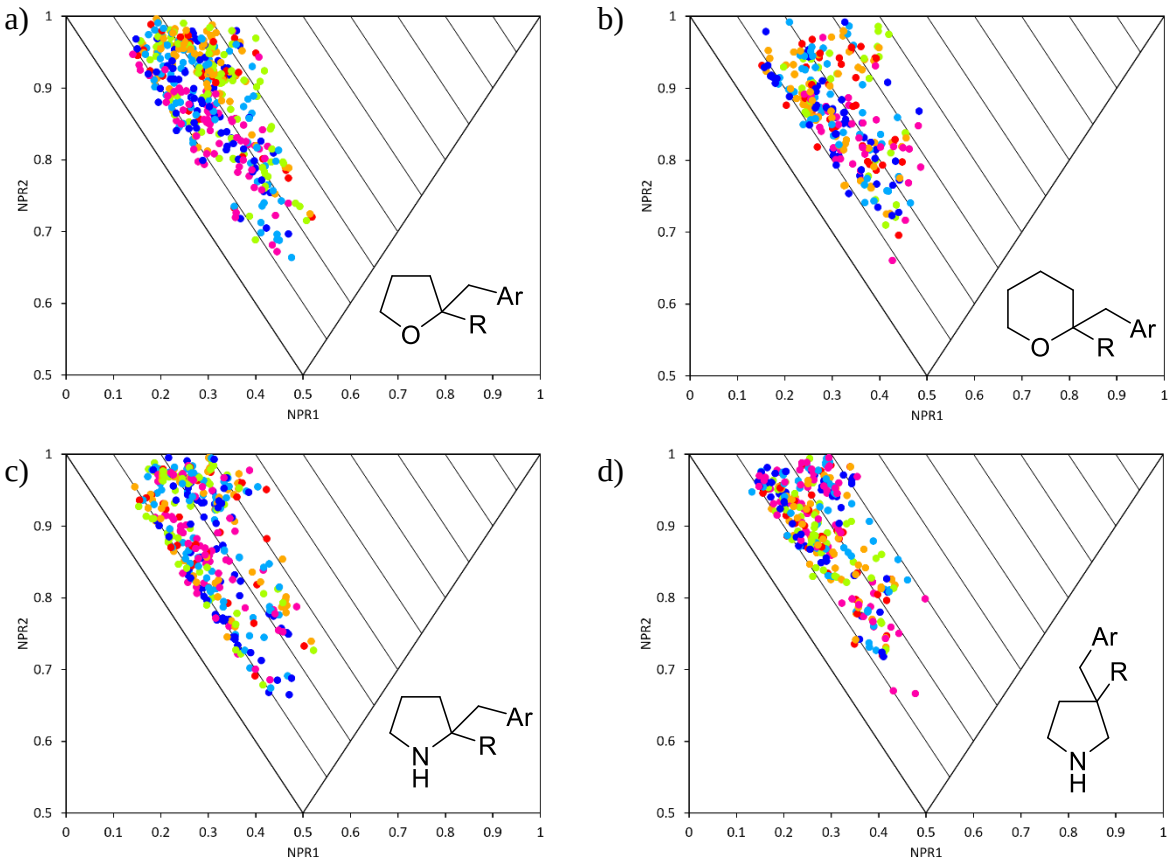


Figure 4.5 - Structures 140 3-D fragments.

The PMI plots of the conformations with a relative energy of ≤ 1.5 kcal mol^{-1} of the 140 3-D fragments are shown in Figure 4.5. The α-alkylated fragments, showed less diversity compared to the α-arylated fragments, with the conformations clustering around the top left-hand corner of the PMI plot. However, for all four scaffolds, the 3-D fragments had almost all conformations in the more interesting region of chemical space, ΣNPR ≥ 1.1. Therefore, a sub-set of these fragments were selected based on their proposed ease of synthesis.



Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

Figure 4.6 – PMI analysis of a) 2-substituted THF, b) 2-substituted THP, c) 2-substituted pyrrolidine and d) 3-substituted pyrrolidine showing all conformations which have a relative energy ≤ 1.5 kcal mol^{-1}. The Ar- and R- groups are shown in Figure 4.5.

4.3.4 Synthesis of Ester Enolate α-Alkylated 3-D Fragments

The α-alkylation of cyclic esters in Section 4.3.2 provided the THP and THF fragments **303** and **304**, which were directly added to the 3-D fragment library (Figure 4.7).

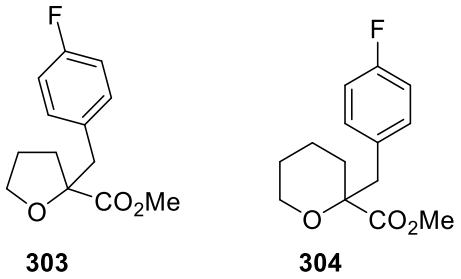
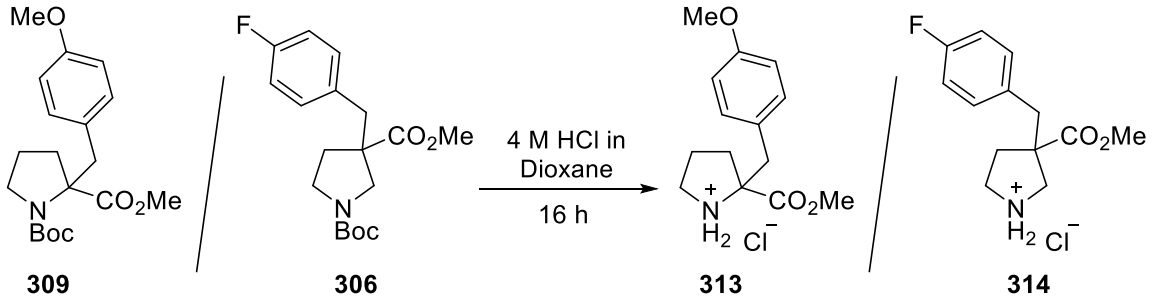


Figure 4.7 - Structures of two 3-D fragments synthesised directly using α-alkylation.

The α-alkylation chemistry also afforded eight *N*-Boc pyrrolidines, which required deprotection before inclusion within the library. The *N*-Boc pyrrolidines **309** and **306** were treated with 4 M HCl in dioxane and stirred for 16 h, which gave the desired final fragments, both in quantitative yields (Scheme 4.37). The remaining six *N*-Boc pyrrolidine scaffolds were deprotected by another member of the group, using the same conditions (Figure 4.8).



Scheme 4.37

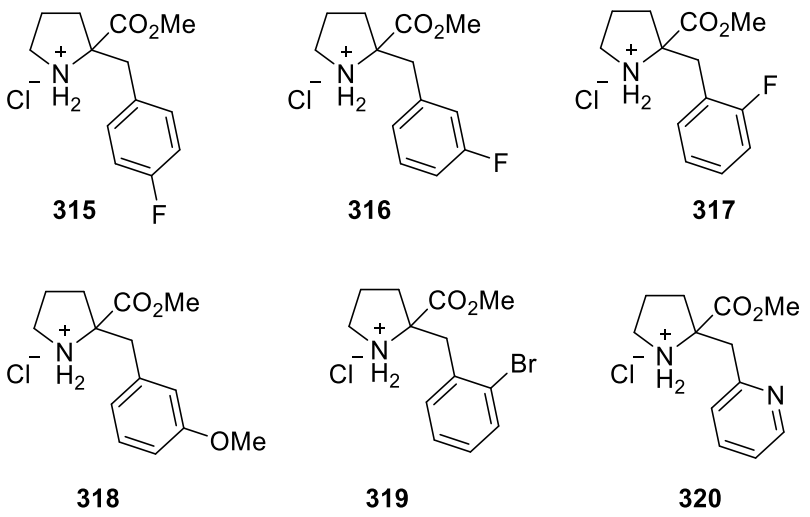
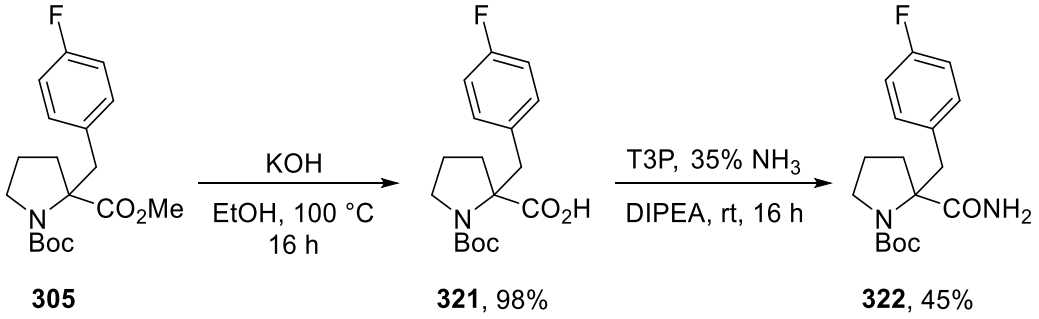


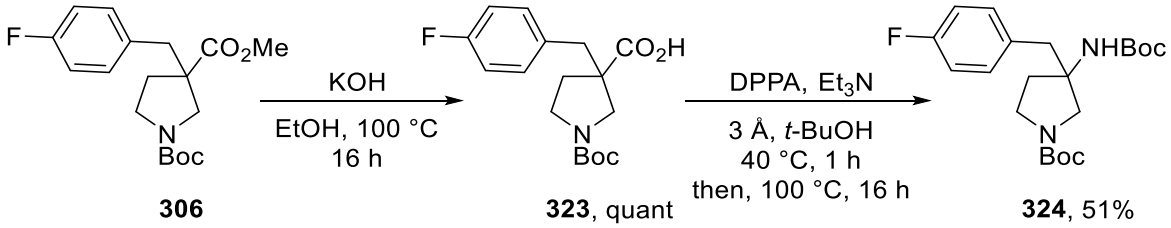
Figure 4.8 – Six deprotected pyrrolidine fragments.

We briefly explored some derivatisation chemistry with two of the α-alkylated esters. For example, 4-fluorobenzyl pyrrolidine **305** was hydrolysed using KOH to access carboxylic acid **321**. Then, acid **321** was converted into the amide to afford **322** in 44% yield over the two sets (Scheme 4.38). The Boc group was subsequently removed by another member of the group to give the final fragment.



Scheme 4.38

Similarly, the regioisomeric 4-fluorobenzyl pyrrolidine **306** was treated with KOH at 100 °C to afford carboxylic acid **323** in quantitative yield. Next, a Curtius rearrangement was explored. Acid **323** was reacted with DPPA in the presence of Et_3N to give amine **324** in 51% yield (Scheme 4.39). The two Boc groups were subsequently removed by another member of the group to afford the final fragment.



Scheme 4.39

In total, 14 α-alkylated 3-D fragments were synthesised and included within the fragment library. The structures of the synthesised 3-D fragments are shown in Figure 4.9.

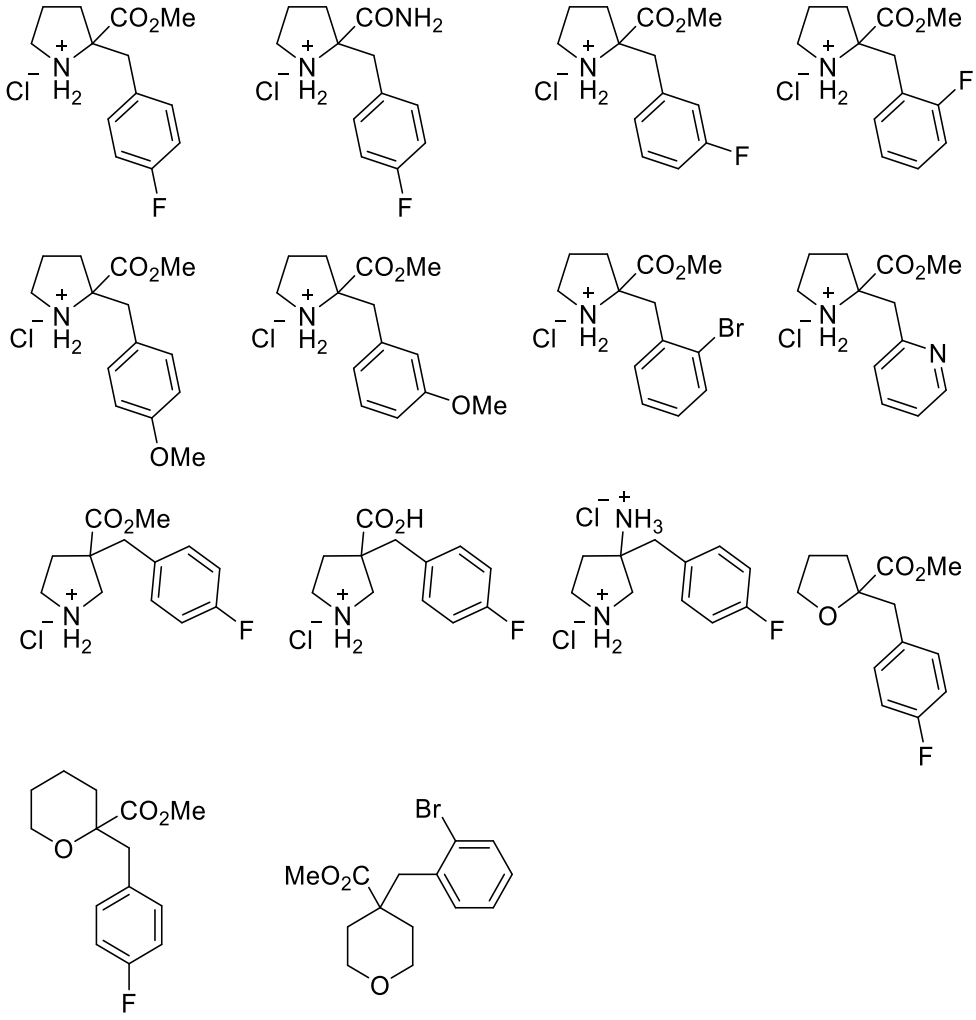
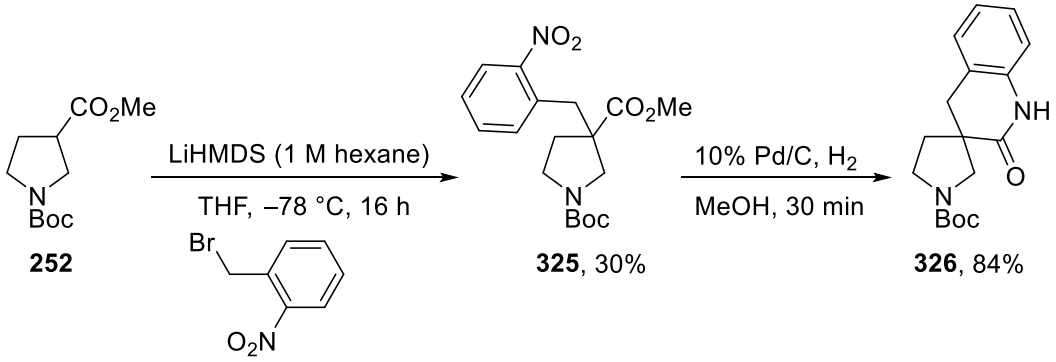


Figure 4.9 – Structures of 14 α-alkylated 3-D fragments.

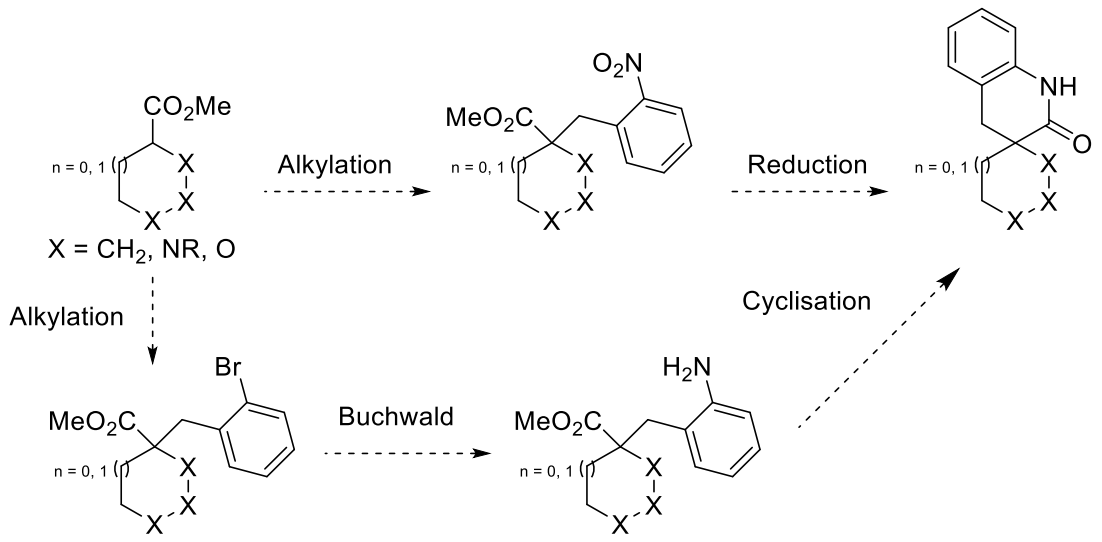
4.3.5 Synthesis of Ester Enolate α-Alkylated 3-D Fragments *via* Spirocyclisation

Spirocyclic scaffolds have become popular within drug molecules due to their ability to introduce conformational restriction within the molecule, which can modulate a drug's binding potency.[59] Numerous examples of the use of spirocycles in drug discovery have been reported, including aza-oxetane spirocycles.[132–134] As a result, we were interested in synthesising spirocyclic scaffolds and envisaged that α-alkylation could offer a potential route. Indeed, a patent by Kemp *et al.*[135] had reported the synthesis of spirocycles using the alkylation of *N*-Boc pyrolidine 3-ester **252** with 2-nitrobenzyl bromide. The nitro group in **325** was reduced to afford the aniline, which subsequently cyclised to give pyrrolidine spirocycle **326** in 25% yield over the two steps (Scheme 4.40).



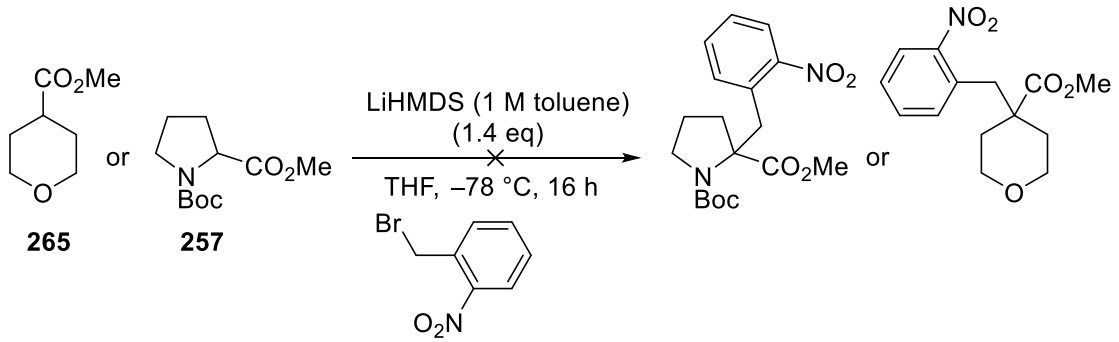
Scheme 4.40

Based on Kemp *et al.*'s precedent, two potential routes towards a range of spirocyclic scaffolds were proposed. In the first route, we planned to use α-alkylation to install the nitrobenzyl group with a variety of cyclic esters. Subsequent reduction would give the spirocycles. Alternatively, α-alkylation would be used to introduce a 2-bromobenzyl group from which Buchwald amination and lactamisation would then generate the same spirocycles (Scheme 4.41).



Scheme 4.41

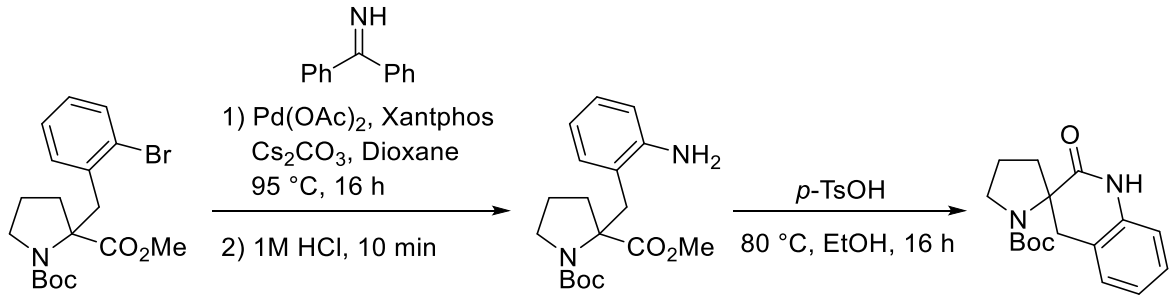
To start, the alkylation of 2-methyl ester pyrrolidine **257** and 4-methyl ester THP **265** with 2-nitrobenzyl bromide were attempted using our standard conditions. However, after analysing the crude reaction mixtures using ^{1}H NMR spectroscopy, the α-alkylated products could not be identified (Scheme 4.42).



Scheme 4.42

The lack of success with α-alkylation using 2-nitrobenzyl bromide led us to investigate the second proposed route. We had already synthesised 2-bromobenzyl *N*-Boc pyrrolidine **311** (see Table 4.7). Buchwald coupling of 2-bromobenzyl *N*-Boc pyrrolidine **311** with benzophenone imine was performed using a procedure reported by Winkler *et al.*[136] with $Pd(OAc)_2$, Xantphos and Cs_2CO_3 in dioxane at 95 °C for 16 h. Pyrrolidine **311** was reacted under these conditions, followed by subsequent imine hydrolysis which, after purification, afforded aniline **327** in an excellent 87% yield (Scheme 4.43). Following the successful installation of the aniline, cyclisation was attempted by heating aniline **327** at 50 °C in MeOH. However, ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that

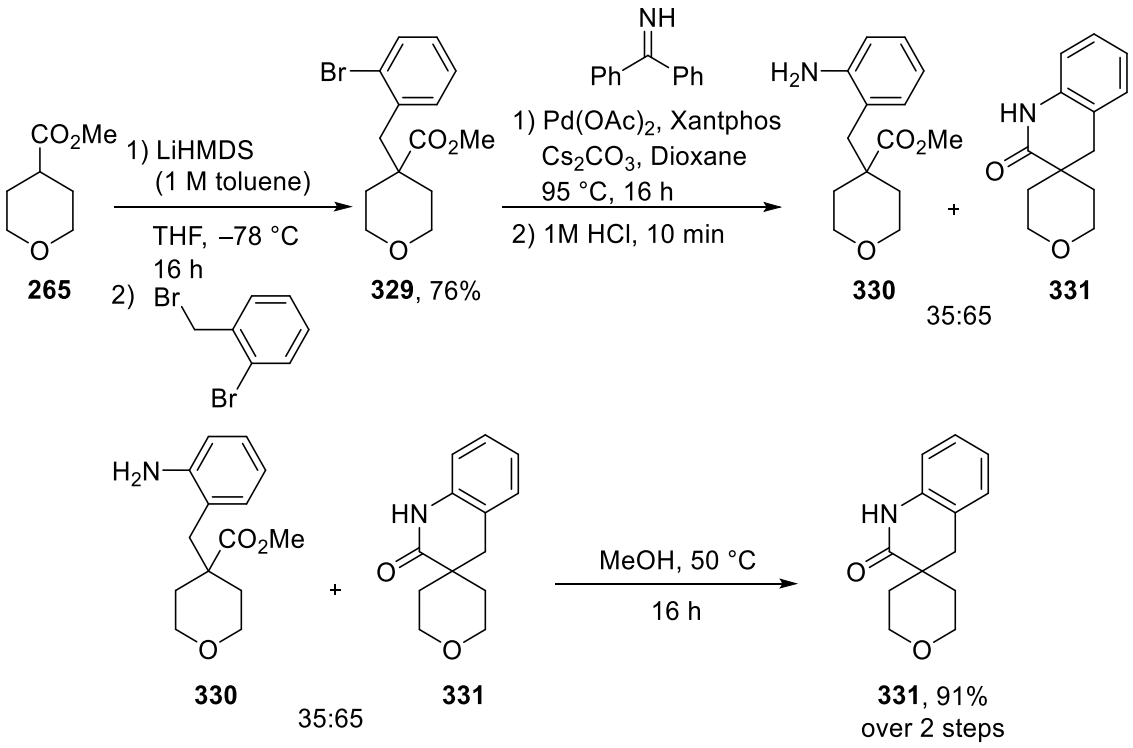
no cyclisation had occurred. The solvent was switched to EtOH allowing for the reaction to be heated to 80 °C for 16 h, but this also failed to yield any of the cyclised product. Finally, the cyclisation was attempted in the presence of *p*-TsOH, to promote acid catalysed cyclisation, which successfully afforded spirocycle **328** in 74% yield (Scheme 4.43).



311 **327**, 87% **328**, 74%

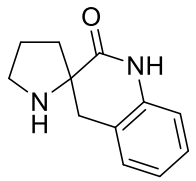
Scheme 4.43

Next, 4-methyl ester THP **265** was subjected to the spirocyclisation sequence. Reaction of 4-methyl ester THP **265** with 2-bromobenzyl bromide gave α-alkylated THP **329** in 76% yield (Scheme 4.44). Buchwald coupling using benzophenone imine gave good conversion to aniline **330** as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. However, upon purification by chromatography, some spirocyclisation occurred to give a 35:65 mixture of aniline **330** and spirocycle **331** based on the ^{1}H NMR spectrum. We propose that the acidic nature of the silica had promoted some spirocyclisation. The 35:65 mixture of aniline **330** and spirocycle **331** was then heated in MeOH at 50 °C for 16 h. This gave spirocycle **331** in 91% yield over the two steps (Scheme 4.44).

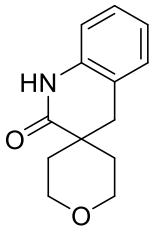


Scheme 4.44

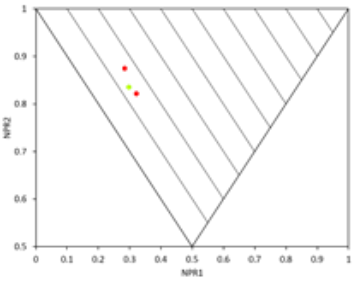
Thus, after removal of the Boc group, which was conducted by another member of the group, we had successfully synthesised two spirocyclic 3-D fragments **332** and **331** *via* α-alkylation, amination and cyclisation. The PMI plot of the conformations with a relative energy of ≤ 1.5 kcal mol^{-1} for these two 3-D fragments is shown in Figure 4.10. The conformations avoided the ΣNPR 1.0-1.1 region of the plot. These two fragments were also added to the fragment library.



332



331



Colour						
Conformation energy difference (kcal mol^{-1})	0	< 0.3	< 0.6	< 0.9	< 1.2	< 1.5

Figure 4.10 - PMI analysis of spirocycle fragemnts **332** and **331**, showing all conformations which have a relative energy ≤ 1.5 kcal mol^{-1}.

4.4 Conclusions and Overview

We were able to adopt two approaches to synthesise novel 3-D fragments using ester enolate α-arylation and α-alkylation. Due to the limitations we had identified with the design process of our initial fragments, we wanted to initially investigate the chemistry prior to designing potential fragments. We were also keen to include aromatic groups which can help fragment screening using ^{1}H NMR spectroscopy.

Investigation into ester enolate α-arylation revealed that we could couple electron rich/poor and sterically hindered aromatics. However, out of the 11 cyclic esters we investigated, only the cyclopentane, 3-pyrrolidine, 3-piperidine, 4-piperidine and 4-THP methyl esters afforded the desired products. The other issue we encountered was with the installation of heteroaromatics and only the 2-bromopyridine was successfully introduced. Despite the difficulties, we were able to synthesise 26 fragments using the α-arylation chemistry.

We had been unable to α-arylate at the 2-position on the heterocyclic esters and this led to the investigation of α-alkylation with benzyl bromides. The 2-methyl ester pyrrolidine, THF and THP scaffolds were all successfully alkylated. The benzyl bromide could be changed to include electron rich and poor aromatics, including alkylation with the 2-pyridyl group albeit in a low yield. The ester was also derivatised successfully, showing that further elaboration of the fragments could be carried out. Finally, we were interested in the formation of spirocycles *via* alkylation and subsequent cyclisation. Buchwald-Hartwig amination of the aryl bromide gave access to the corresponding aniline, which was subsequently cyclised, *via* acid-catalysis, to afford the 5,6- and 6,6-spirocycles in excellent yields. In total, our two approaches gave 42 novel 3-D fragments which were included within our fragment library.

Chapter 5 Properties and PMI Analysis of the York 3-D Fragment Library

During the course of the work described in this thesis, researchers in the O'Brien group have carried out the synthesis of numerous 3-D fragments. In this chapter, the 123 York 3-D fragments are compared with a set of commercial fragment libraries. This includes a comparison of MW, HAC and ClogP together with 3-D shape analysis using PMI plots. This has allowed us to evaluate the usefulness of the York 3-D fragments for use in drug discovery. Some example York 3-D fragments in the library are shown in Figure 5.1.

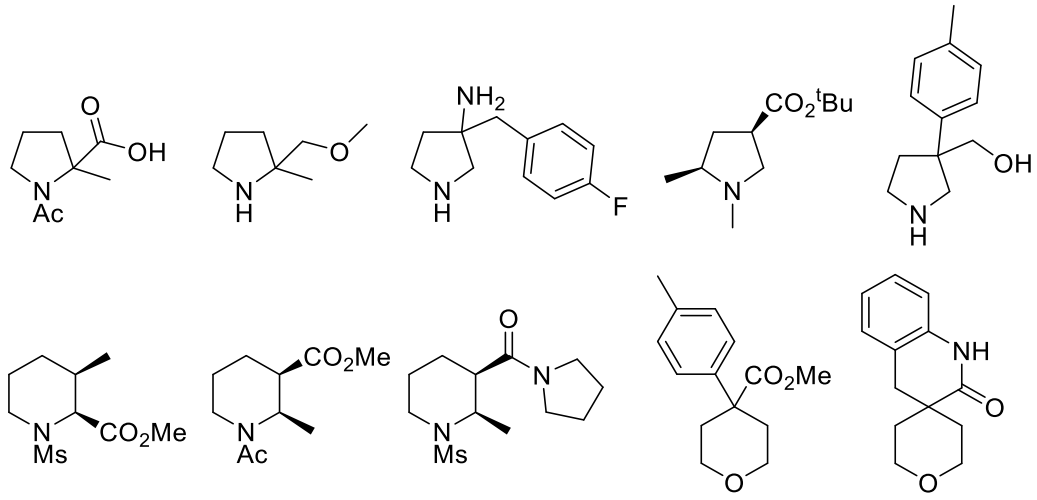


Figure 5.1

5.1 Properties and PMI Analysis of the First-Generation Fragment Library

In Chapter 2, we outlined the design and selection of 33 pyrrolidine and piperidine 3-D fragments, with the synthesis of three pyrolidine and six piperidine fragments discussed in detail. The remaining fragments were synthesised by other members of the O'Brien group. However, due to difficulties encountered with the synthesis of the 2,4-disubstituted *cis*-pyrrolidines this fragment was removed from the library to give a total of 32 fragments. Another member of the O'Brien group was able to further derivatise the methyl ester substituent on some of the selected pyrrolidine and piperidines to introduce carboxylic acids, amides, ethers and nitriles (Figure 5.2).

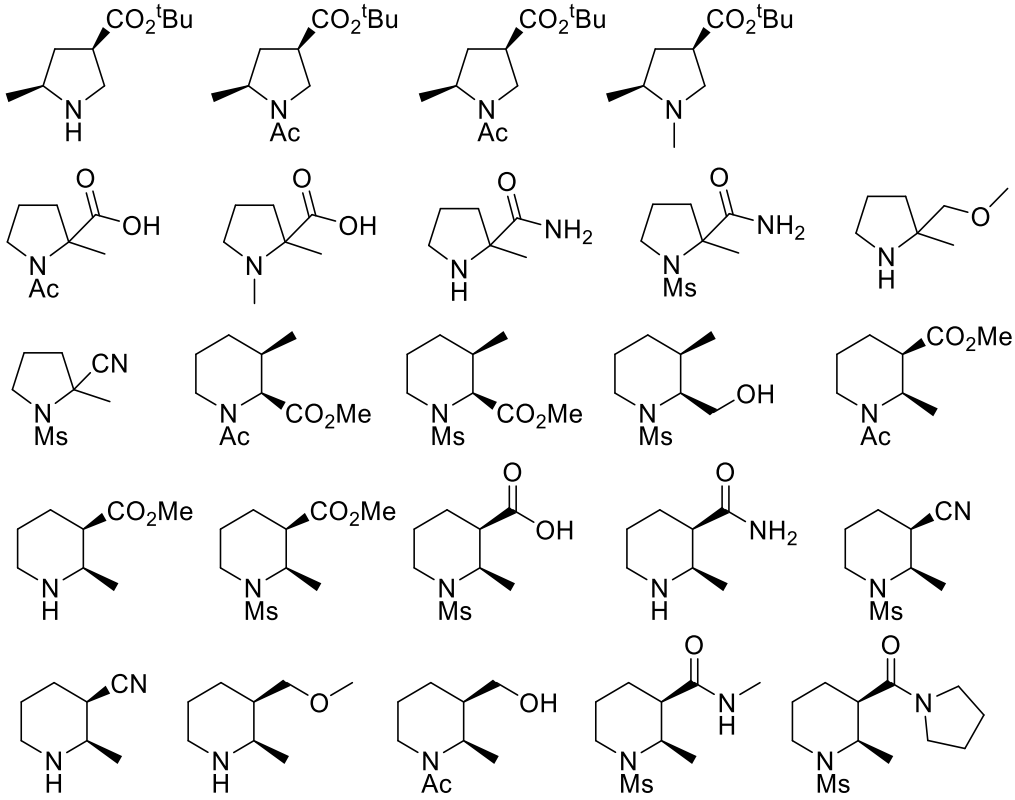


Figure 5.2 – Structures of 24 disubstituted pyrrolidines and piperidines accessible by ester derivatisation.

These 24 fragments were combined with the initial 32 fragments to create a first-generation fragment library containing 56 pyrrolidine/piperidine 3-D fragments. The PMI plot of these 56 3-D fragments is shown in Figure 5.3. The ground state conformations are coloured in red and all other conformations ≤ 1.5 kcal mol^{-1} in energy are in blue. Due to our design criteria, these fragments provided a good spread of conformations across the PMI plot with few conformations in the rod-disc area. The physicochemical properties of the 3-D fragments

were assessed against Astex's 'Rule of three' guidelines (Table 5.1) The properties were all within the limits set out by Astex.

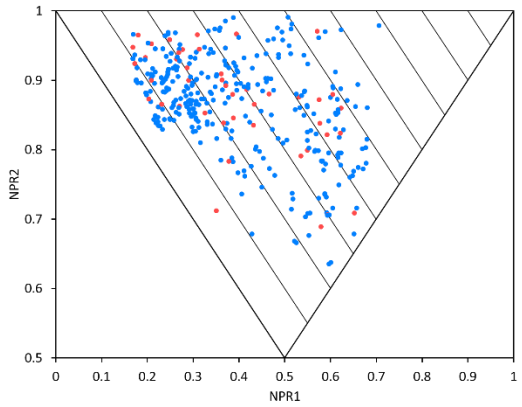


Figure 5.3 – PMI plot of the 56 first-generation pyrrolidines and piperidines with all conformations that have relative energy ≤ 1.5 kcal mol^{-1}.

Parameters	First-Generation Fragments	'Rule of 3'
MW	173.4 ± 38.5	< 300
HAC	11.8 ± 2.3	-
ClogP	0.52 ± 0.66	0-3
HBA	2.7 ± 0.73	< 3
HBD	0.9 ± 0.70	< 3

Table 5.1 – Average physicochemical properties of the 56 first-generation fragments.

These 56 3-D fragments were also subjected to a quality control (QC) study. Another member of the O'Brien group performed purity, stability and solubility studies using NMR spectroscopy. The purity of each fragment was assessed by ^{1}H NMR spectroscopic analysis of a 2 mM solution in DMSO. Two fragments failed the purity test (Figure 5.4) and were removed from the library

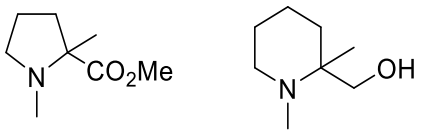


Figure 5.4 – Failed due to purity

The stability and solubility of the remaining 54 fragments were then assessed. The stability was assessed in 20 mM phosphate buffer (pH 7.48) (1 mM concentration of fragment) and DMSO (2 mM concentration of fragment) solutions. In 20 mM phosphate buffer, fragments

74 and **75** (Figure 5.5) were unstable due to hydrolysis of the ester to the carboxylic acid, which is not unexpected since hydrolysis was seen during fragment synthesis (see Figure 2.7) A further two fragments, **69** and **77** (Figure 5.5), were also unstable in solution. The remaining 49 fragments had showed no signs of decomposition after 6 weeks in DMSO solution.

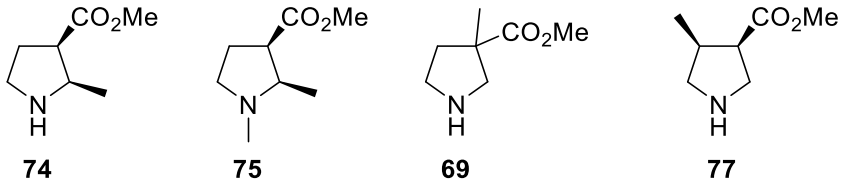


Figure 5.5 – Fragments removed due to stability in solution

Finally, the solubility of the 3-D fragments was determined, since precipitation due to poor solubility can interfere with fragment screening. The solubility was determined in 20 mM phosphate buffer solution (pH 7.48) using a 1 mM concentration of the fragment and a calibration compound. From this, four of the fragments (Figure 5.6) had poor solubility, < 0.5 mM, and were not included in the final library.

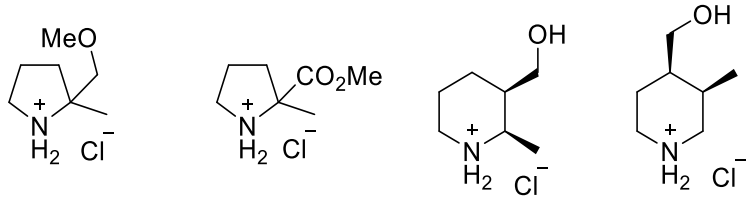


Figure 5.6 – Failed due to poor solubility

5.2 Properties and PMI Analysis of the Second-Generation Fragment

In Chapter 4, we described the synthesis of 42 3-D fragments using enolate α-arylation and α-alkylation. A similar strategy, focusing on one piece of synthetic methodology, was developed by another member of the O'Brien group. This approach produced the 25 3-D fragments shown in Figure 5.7.

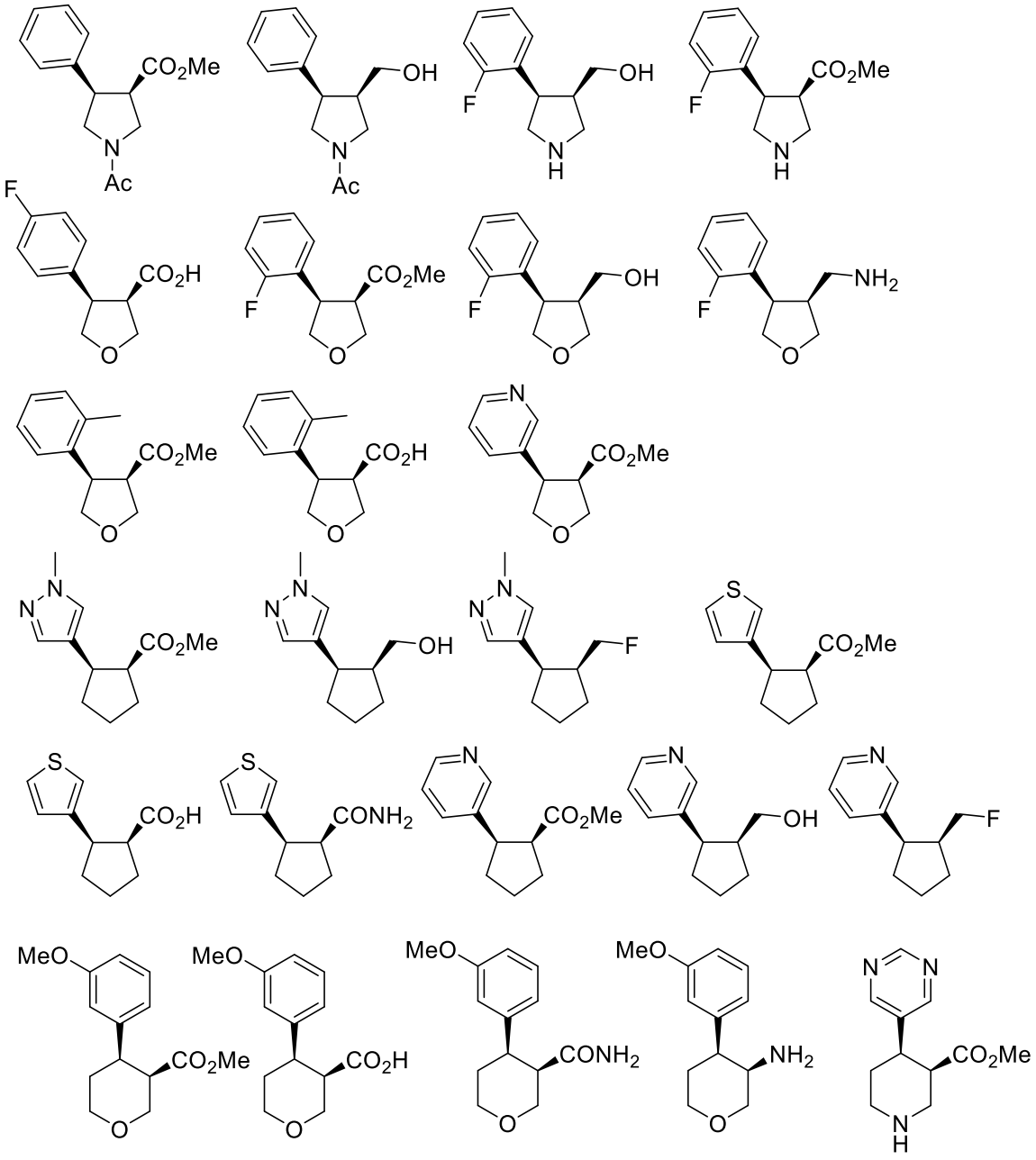


Figure 5.7 – Structures of 25 fragments synthesised using Suzuki-Miyaura cross-coupling.

The PMI plot of the 67 3-D second-generation fragments is shown in Figure 5.8. These fragments gave 553 conformations with a relative energy ≤ 1.5 kcal mol^{-1}. Analysis of the

PMI plot revealed that only 1.5% of the conformations lay within the initial ΣNPR region of 1.0-1.1, with the conformations ranging from a ΣNPR value of 1.07 to 1.54. The average physicochemical properties of the second-generation 3-D fragments were compared against Astex's guidelines (Table 5.2).

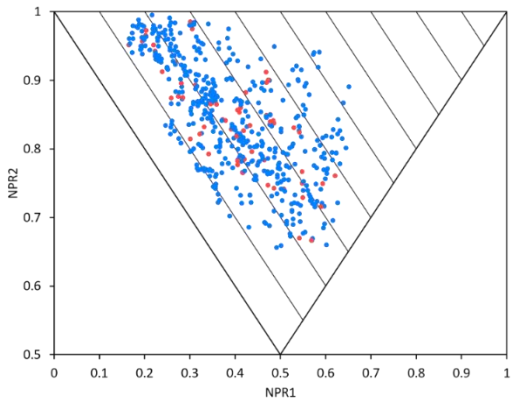


Figure 5.8 – PMI plot of the 67 second-generation fragment conformations with a relative energy ≤ 1.5 kcal mol^{-1} (blue) and ground state energy conformations (red).

Parameters	Second-Generation Fragments	'Rule of three'
MW	218.3 ± 26	< 300
HAC	15.7 ± 1.7	N/A
ClogP	1.64 ± 1.0	0-3
HBA	2.4 ± 0.86	< 3
HBD	0.6 ± 0.65	< 3

Table 5.2 – Physicochemical properties of the 67 second-generation fragments.

The second-generation 3-D fragments were all within the guidelines set out by Astex. A comparison of the first-generation 3-D fragments (Table 5.1) with the second-generation 3-D fragments (Table 5.2) shows that MW and ClogP are higher for the second-generation fragments. This is not unexpected since our design criteria for the second-generation included the additions of a heavier and more lipophilic aryl substituent.

5.3 Analysis of 123 York 3-D fragments

An analysis of the combined first- and second-generation 3-D fragments has been carried out. For this analysis, all 123 3-D fragments were included (even though some of the first-generation fragments had failed the QC analysis). From the PMI analysis, the 123 3-D fragments (Figure 5.9), had a total of 940 conformations with a relative energy ≤ 1.5 kcal mol^{-1} above the ground state. Only 2.4% of the conformations occupied the initial ΣNPR region of 1.0-1.1, with the fragments occupying ΣNPR regions from 1.07 to 1.68. This set of 123 3-D fragments provided a broad coverage of 3-D chemical space.

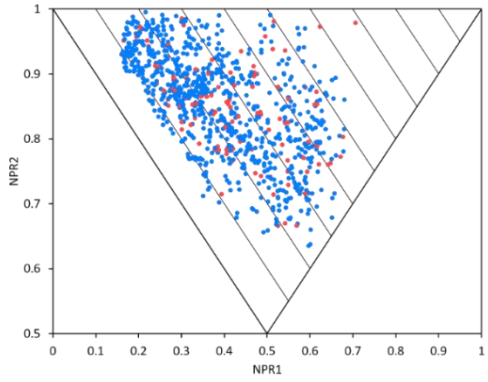


Figure 5.9 – PMI plot of all 123 fragments within the York 3-D fragment library, with all conformations with a relative energy ≤ 1.5 kcal mol^{-1} (blue) and ground state energy conformations (red).

The average physicochemical properties for the 123 3-D fragments were within Astex's 'Rule of three' guidelines (Table 5.3). Analysis of the individual fragments revealed that 84 (68%) of the 123 fragments fully complied with the 'Rule of three' with the remaining 39 (32%) of the fragments failing either one or multiple criteria. The decision to include the 39 fragments was supported by Mortenson *et al.*'s study where data from 85 lead campaigns undertaken between 2015-2017 had been collated.[137] The results revealed that ~5% of the fragments taken through had ClogP values > 3, which lies outside the criteria set out by Astex.

Parameters	First-Generation Fragments	Second-Generation Fragments	Combined Library	'Rule of 3'
MW	173.4	220.7	199.2 ± 40.4	< 300
HAC	11.8	15.7	13.9 ± 2.8	N/A
ClogP	0.52	1.64	1.0 ± 1.0	0-3
HBA	2.7	2.4	2.6 ± 0.82	< 3
HBD	0.9	0.6	0.76 ± 0.70	< 3

Table 5.3 – Average physicochemical properties of the 123 3-D fragments.

The physicochemical properties of the 123 York 3-D fragments were compared with four commercial fragment libraries: Maybridge 'Rule of three' (RO3), Chembridge, Enamine RO3 and Enamine sp^3. A plot of % of the library *versus* MW is shown in Figure 5.10. The York 3-D fragments showed a similar trend in MW to the Maybridge fragments, but a lower MW compared to the two Enamine and Chembridge fragment libraries.

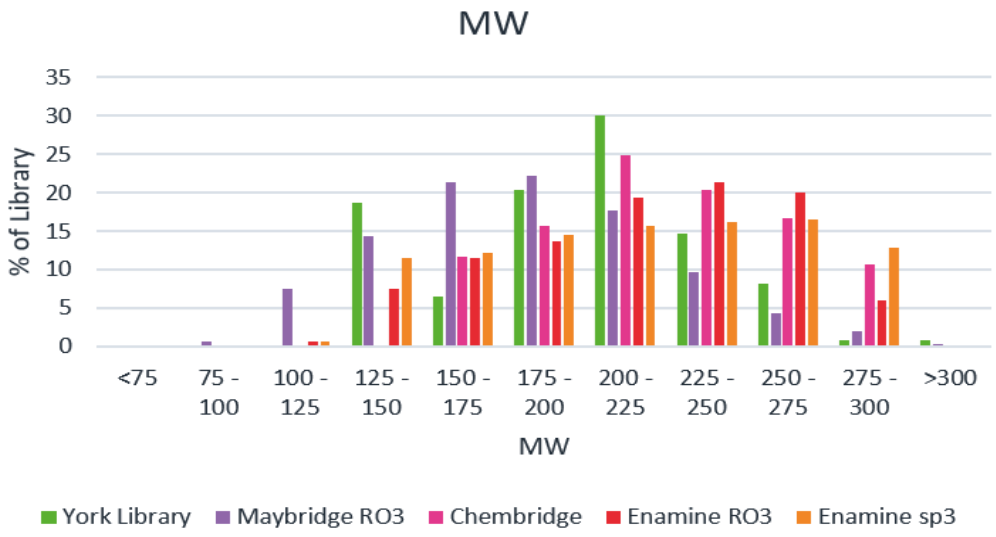


Figure 5.10 – MW analysis comparing the York 3-D (green), Maybridge (purple) and Chembridge (pink), Enamine RO3 (red) and Enamine sp^3 (orange) fragments libraries.

A similar set of trends was observed from the plots of % of library *versus* HAC (Figure 5.11). For the York 3-D fragments, 80% had a HAC < 16, which is the recommended upper limit put forward by Astex using updated guidelines.[138] In contrast, all four commercial libraries contained a number of fragments with HAC > 16, with 39% of the fragments within the two Enamine libraries having a HAC > 16.

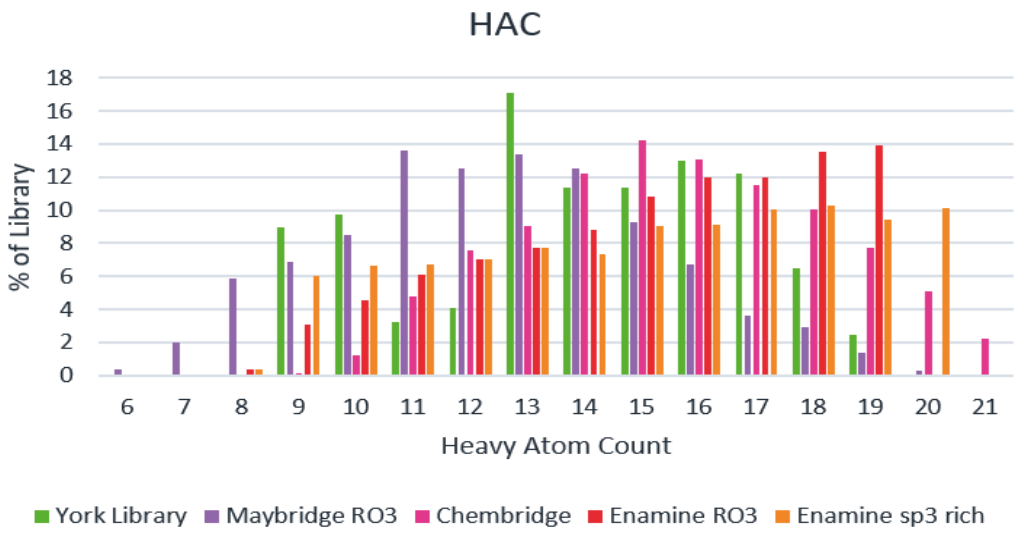


Figure 5.11 - HAC analysis comparing the York 3-D (green), Maybridge (purple) and Chembridge (pink), Enamine RO3 (red) and Enamine sp^3 (orange) fragment libraries.

The plot of % of library *versus* Fsp^3 is shown in Figure 5.12. The Maybridge RO3, Chembridge and Enamine RO3 libraries had relatively low Fsp^3 values, with over half of the fragments having an Fsp^3 value < 0.5. Unsurprisingly, the Enamine sp^3 library contained fragments with Fsp^3 values ranging from 0.5-1.0. This trend is mirrored by the York 3-D fragments, with 99.2% of the fragments having Fsp^3 values > 0.5. On closer inspection, 45% of the York 3-D fragments had an Fsp^3 values of 0.8-1.0, with the next best library being the Enamine sp^3, with 28% of their fragments within the same region. Despite Fsp^3 not correlating with 3-D shape, the analysis does show that the York 3-D fragments have increased complexity and saturation compared to three of the four commercial libraries and that they are similar to Enamine sp^3 fragments.

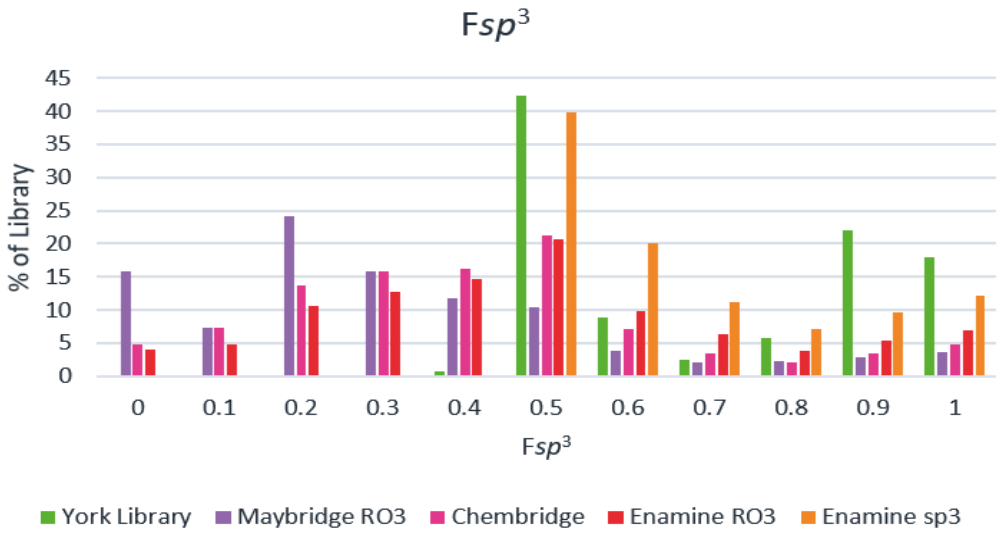


Figure 5.12 - Fsp^3 analysis comparing the York 3-D (green), Maybridge (purple) and Chembridge (pink), Enamine RO3 (red) and Enamine sp^3 (orange) fragments libraries.

We have also compared ClogP with the Maybridge and Chembridge libraries (Figure 5.13). On average, the York fragments had lower ClogP values, with 58% of the fragments having a ClogP < 1.0. In contrast, only 24% of the Maybridge and 35% of the Chembridge fragments had values < 1.0. Lower values of ClogP can indicate improved aqueous solubility of the fragments, allowing them to be screened at higher concentrations and avoiding any issues with precipitation of the fragments that can affect fragment screening.

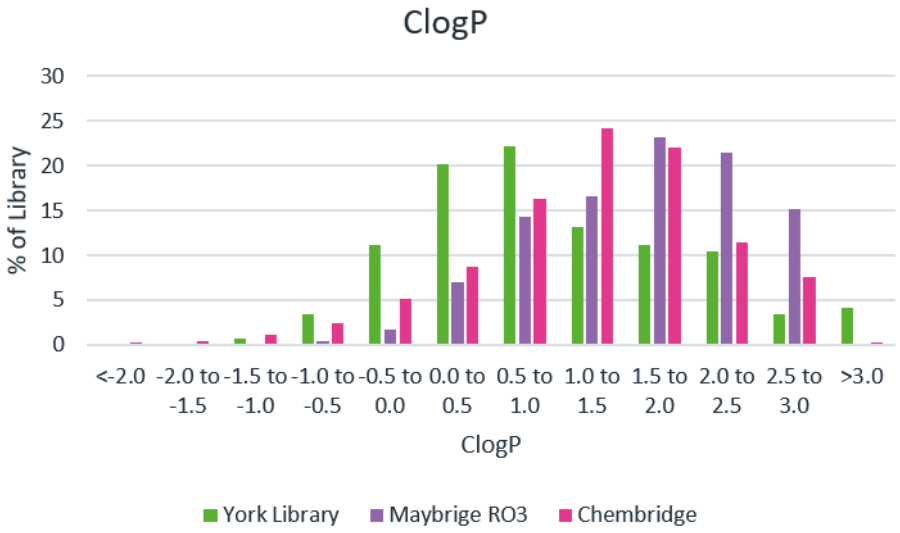


Figure 5.13 - ClogP analysis comparing the York 3-D (green), Maybridge (purple) and Chembridge (pink) fragments libraries.

Finally, since the overall aim of the project was to design and synthesise fragments with shapes in under-represented areas of 3-D space, we compared the PMI plot of the York 3-D fragments with those that we generated from current commercial libraries. In order to obtain direct comparisons, a cumulative % of fragments with conformations up to 1.5 kcal mol^{-1} above the ground state for the commercial fragment libraries with a defined distance from the rod-disc axis (ΣNPR) was carried out. Along with the commercial libraries already discussed, we have carried out a comparison with other 3-D fragment libraries from both industry and academia, which are accessible from the Diamond light source webpages.[139] The first was a commercial 3-D fragment library from Life Chemicals, containing 1,500 fragments which had been evaluated for 3-D shape using PMI plots.[140] The remaining three libraries included the 3-D Fragment Consortium[141] which was discussed in Section 1.4, a Leeds 3-D library (Nelson/Marsden groups) which contained diverse natural-product like fragments with high levels of Fsp^3/3-D shapes[142,143] and a library from the Spring group at Cambridge University who had designed a DOS library containing fragments with high levels of Fsp^3. The eight libraries were directly compared with the 123 York 3-D fragments and the cumulative PMI plot is shown in Figure 5.14.

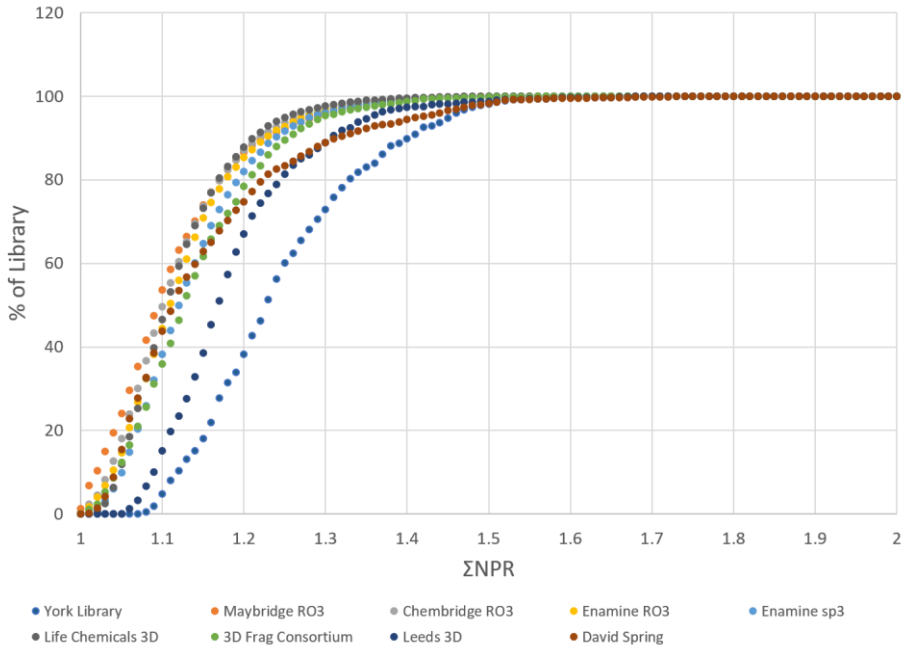


Figure 5.14 – Cumulative PMI plot of the York 3-D fragment library and eight fragment libraries.

Analysis revealed that for seven out of the eight libraries, roughly 50% of the conformations were within the initial ΣNPR 1.0-1.1 region. The Leeds 3-D fragments had the best conformational distribution out of the eight libraries, with 50% of their fragment

conformations lying between the ΣNPR region 1.0-1.17. In contrast, the York 3-D fragments had greater conformational distribution, with 50% of the library having a ΣNPR value > 1.23. Therefore, the main conclusion drawn from the PMI analysis was that the York 3-D fragments were able to offer a greater coverage of chemical space. The fragments were able to access regions of the PMI plot that are less-densely occupied by the other fragment libraries, potentially offering the opportunity to access different protein targets.

5.4 Conclusions and Overview

The work described in this thesis, together with other O'Brien group members, has contributed 117 fragments to the York 3-D fragment library, with 84 of the 3-D fragments complying with the Astex 'Rule of three' guidelines. Comparison of the physicochemical properties of the York 3-D fragments against four commercial libraries showed that our fragments followed similar trends. However, the average ClogP value was lower for our fragments compared to the commercial libraries. This can be explained by the low number of aromatic rings and the increase in the number of sp^3 carbon centres within our molecules compared to the commercial libraries. The lower ClogP often can be considered beneficial allowing for greater control of the ClogP during a hit-lead optimisation.

The aim of our work was to create a library containing molecules with a high degree of 3-D shape. Therefore, we compared the PMI plots of eight fragment libraries, of which four were described as 3-D fragment libraries, with our 3-D fragments. The data showed that using our approach of assessing the shapes of fragments prior to synthesis, we were able to produce a more focused 3-D fragment library, with fewer fragments lying within the region of chemical space most commonly occupied by current commercial fragment libraries. We look forward to the results of protein screening campaigns using the 3-D fragments described in this thesis.

Chapter 6 Conclusions and Future Work

We have created a new approach towards the design and synthesis of a 3-D fragment library by generating conformations of potential fragments and then using PMI analysis to assess and select the most 3-D fragments to synthesise and include within the 3-D fragment library. The fragments were designed based on pyrrolidine and piperidine cores, with the inclusion of two substituents to increase the shape and functional group diversity, with four differing substituents on the nitrogen, affording 56 pyrrolidine and 92 piperidine fragments.

The chemical space coverage of the 56 pyrrolidine and 92 piperidine fragments was analysed using principal moment of inertia (PMI) plots. A protocol developed in Pipeline Pilot by a previous member of the O'Brien group used molecular mechanics to generate conformations, which were used to create the PMI plots and predict the fragments physicochemical properties. Initially, we analysed a Maybridge 'Rule of three' compliant fragment library containing 1000 fragments, which showed limited coverage of chemical space and occupied the region along the rod-disc axis. In contrast, the pyrrolidine and piperidine fragments occupied a much wider region of chemical space despite our very simple design criteria. Fragment selection was achieved through PMI analysis with the plot being divided into ten regions to allow for selection and synthesis of the most 3-D fragments, with 14 pyrrolidine and 19 piperidine fragments selected.

The pyrrolidine and piperidine fragments were grouped and synthesised by members within the O'Brien group, with emphasis placed on investigating known synthetic routes to increase the ease of synthesis. In Chapter 2, the synthesis of three 2,3-disubstituted pyrrolidine fragments was presented. A previous route had been reported by Zhang *et al*. with the key step being the stereoselective reduction of the corresponding dihydropyrrole to afford the *cis*-pyrrolidine which could be epimerised to access the *trans*-pyrrolidine. After investigating the stereoselective reduction of *N*-benzyl dihydropyrrole **108**, the two *cis*-fragments were accessed. The epimerisation of *N*-benzyl pyrrolidine *cis*-**109** failed to afford the *trans*-pyrrolidine selectively, and therefore we reverted to the procedure reported by Zhang *et al.* with the epimerisation conditions optimised (DBU, 100 °C, 24 h) to afford the *trans*-pyrrolidine, which was acylated to afford pyrrolidine *trans*-**109**.

The synthesis of 2,5-, 2,6- and 2,3-disubstituted piperidines was also successfully completed, with access to the *cis*-piperidines achieved through hydrogenation of the corresponding

pyridine. The *trans*-diastereoisomer was required for the 2,3-disubstituted piperidine, which was accessed *via* epimerisation of the *cis* diastereoisomer. The 1,2-relationship of the substituents resulted in the *cis*-piperidine adopting conformations with one group axial and one group equatorial. Therefore, we were able to use base-mediated epimerisation to obtain the *trans*-diastereoisomer as the major product. Derivatisation of the nitrogen proceeded smoothly, with only the installation of the sulfonyl group onto the *cis*-2,6-piperidine proving problematic. The steric hindrance around the nitrogen potentially reduced the rate of mesylation and resulted in the formation of a bismethanesulfonate product. However, altering the base and reaction time led to an improvement in the reaction with the 2,6-piperidine sulfonamide isolated in good yield with no formation of the bismethanesulfonate **161**.

In Chapter 3, we outlined that, along with lithiation-trapping, we could apply our simple hydrogenation and epimerisation conditions to access all 20 disubstituted piperidine regio- and diastereoisomers. Hydrogenation, under our mild conditions, contrasted with the literature conditions which often employed a higher catalyst loading, elevated reaction temperatures and higher pressures. We were able to access nine *cis*-piperidines and the *trans*-3,5-piperidine using 10-30 mol% PtO_2 in AcOH at rt under a H_2 balloon. Optimisation of epimerisation conditions and manipulation of the protecting group on the nitrogen gave eight *trans*-piperidines and the *cis*-3,5-piperidine. The *trans*-2,6-disubstituted piperidine had been synthesised previously within the O'Brien group *via* lithiation-trapping and meant we were able to selectively access all 20 disubstituted piperidines in 2-3 steps.

The second-generation fragments (Chapter 4) were designed to incorporate a single stereogenic centre to avoid the issues we had encountered with diastereoselectivity and separation of diastereoisomers with the first-generation fragments. Two pieces of synthetic methodology were identified: α-arylation of cyclic esters using palladium catalysis and α-alkylation of cyclic esters *via* the reaction of enolates with benzylic halides. The design of 3-D fragments was based on the capability of the synthetic chemistry, which streamlined the synthesis of the 3-D fragments. With α-arylation, we could couple electron rich/poor and sterically hindered aromatics. However, out of the 11 cyclic esters investigated, only the cyclopentane, 3-pyrrolidine, 3-piperidine, 4-piperidine and 4-THP methyl esters afforded the desired products. The other issue we encountered was with the installation of heteroaromatics with only 2-bromopyridine being successfully introduced. Despite the difficulties, 26 fragments were efficiently synthesised using the α-arylation chemistry.

We had been unable to α-arylate at the 2-position on the heterocyclic esters, which led to us investigating α-alkylation with benzyl bromides. The 2-methyl ester pyrrolidine, THF and THP were all successfully alkylated. Electron rich and poor benzyl bromides were used as well as installation of a 2-pyridyl. Finally, we were interested in the formation of spirocycles *via* alkylation and subsequent cyclisation. Buchwald-Hartwig amination of the aryl bromide gave access to the corresponding aniline, which afforded the 5,6- and 6,6-spirocycles. This approach gave 16 novel 3-D fragments which were included within our fragment library.

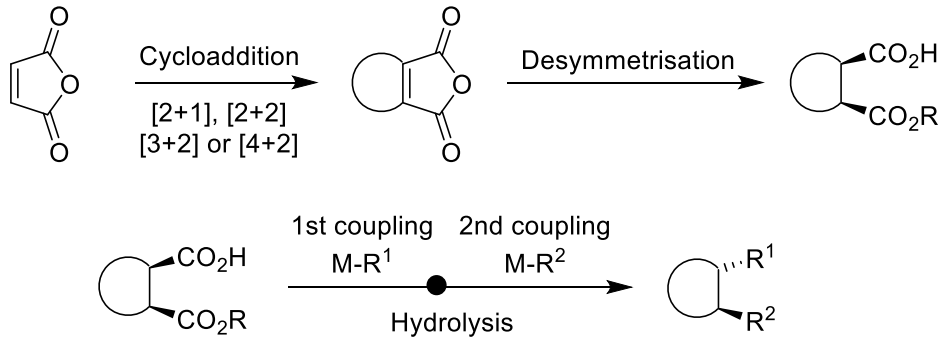
Combination of the first- and second-generation 3-D fragments gave a total of 123 York 3-D fragments, which all largely obeyed the 'Rule of three'. The York 3-D fragments were compared against four commercial libraries, which showed that they followed similar trends. The main difference between our 3-D fragments and the commercial libraries was the lower ClogP, which can often be considered beneficial allowing for greater control of ClogP during a hit-lead optimisation.

Finally, we conducted a % cumulative PMI analysis of the York 3-D fragments against the four commercial libraries, as well as four 3-D focused fragment collections from both industry and academia. The analysis revealed that the York 3-D fragments contained fewer conformations within the initial regions of the PMI plot along the rod-disc axis (ΣNPR 1.0-1.1), which showed we were able to produce a more 3-D focused fragment library. We hope that the design of fragments which access areas of chemical space currently under-represented within fragment libraries will offer an alternative starting point for the pharmaceutical industry and support the drug discovery process.

The future work within the project will involve making the library available for screening campaigns both in-house and externally, and we look forward to seeing the screening results with the York 3-D fragments.

The initial approach towards the synthesis of 3-D fragments was limited by the bespoke nature of the designed disubstituted pyrrolidine and piperidine fragments. The need for stereoselective routes to access either the *cis* or *trans*-diastereoisomers resulted in issues with synthesis and purification. The second-generation 3-D fragments were prepared by initially investigating the scope and limitations of the synthetic methodology. Fragments were then designed based on the capabilities of the chemistry, which streamlined their synthesis. Therefore, future work would look to identify suitable pieces of methodology that could install aryl groups and incorporate differing scaffolds. One potential route has recently been

reported by Baran *et al.*,[144] where they synthesised a series of sp^3 rich scaffolds *via* cycloaddition and subsequent C-C cross coupling. Cycloaddition with maleic anhydride was followed by desymmetrisation and radical decarboxylative cross-coupling (Suzuki, Negishi or Kumada). Hydrolysis of the ester allowed for a second radical decarboxylative cross coupling, which gave the *trans*-stereoisomers in high *ee* (> 92%) (Scheme 6.1). We envisage that this chemistry could offer the potential to access bridged fragments with the installation of heteroaryl substituents, which we had previously found difficult to install *via* α-arylation (Figure 6.1).



Scheme 6.1

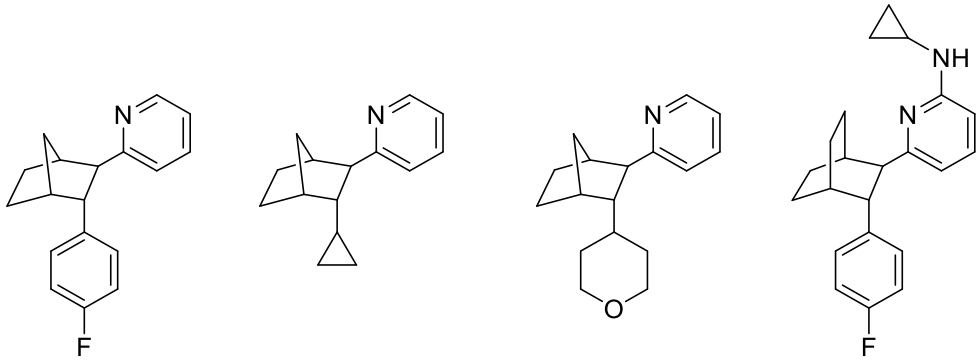
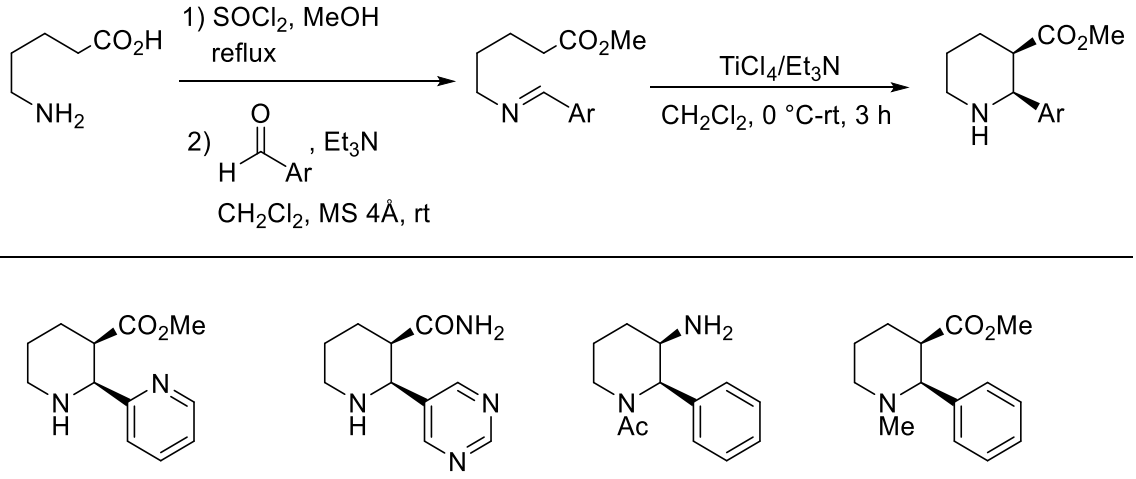


Figure 6.1 – Four proposed fragments

Another piece of methodology that had been identified during investigation into the synthesis of 2,3-disubstituted pyrrolidines was the stereoselective cyclisation of γ-imino esters using $TiCl_4/Et_3N$ to afford *cis* 2,3-disubstituted pyrrolidines.[71] The plan would be to expand the methodology to synthesise disubstituted piperidines and vary the aldehyde to incorporate differing aryl groups, along with derivatisation of the ester (Scheme 6.1). A selection of potential 3-D fragments that could be accessed are also shown in Scheme 6.1.


CO2H
NH2
1) SOCl2, MeOH
reflux
2)
, Et3N
CH2Cl2, MS 4Å, rt
CO2Me
N
Ar
TiCl4/Et3N
CH2Cl2, 0 °C-rt, 3 h
CO2Me
N
H
Ar
CO2Me
N
H
N
CONH2
N
H
N
N
NH2
N
Ac
CO2Me
N
Me

Scheme 6.2

Chapter 7 Experimental

7.1 Computational Methods

7.1.1 Shape Analysis Protocol

Prior to conformer generation a wash step was performed, which involved stripping salts and ionising the molecule at pH 7.4. Any stereocentre created here was left with undefined stereochemistry. SMILES strings were converted to their canonical representation. A list of allowed chirality at each centre is generated and a SMILES file with all possible stereoisomers was written. Conformers were generated using the BEST method in Catalyst using the rel option, run directly on the server and not through the built-in Conformation Generator component with a chosen maximum relative energy threshold of 20 kcal mol^{-1}, maximum of 255 conformers for each compound. Conformations were read, ones that cannot be represented by the canonical SMILES are discarded, with the remaining ones standardised to a single enantiomer. Duplicates were filtered with a RMSD threshold of 0.1. Minimisation with 200 steps of Conjugate Gradient minimisation with an RMS gradient tolerance of 0.1 was performed using the CHARMm forcefield with Momany-Rone partial charge estimation and a Generalised Born implicit solvent model. Duplicates were filtered again with a RMSD threshold of 0.1.

7.1.2 Physical Properties

The physical properties were calculated using Pipeline Pilots built in generator.

7.1.3 ClogP Calculations

The ClogP data reported for the fragments was generated using Astra Zeneca's protocol.

7.2 Synthetic Methods

7.2.1 General Methods

Non-aqueous reactions were purged and back filled with Ar three times in flame dried glassware. Et_2O and THF were distilled over sodium and benzophenone respectively. Alkyllithiums were titrated using *N*-benzylbenzamide prior to use.[145] CO_2 was dried over $CaCl_2$ before use in lithiation reactions. Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out

using commercially available Merk F254 aluminium backed silica plates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.0, central line of triplet). For samples recorded in d_6-DMSO, chemical shifts are quoted on parts per million relative to d_6-DMSO (δ_H 2.50, central line of quintet) and d_6-DMSO (δ_C 39.52, central line of septet). For samples recorded in d_4-MeOH, chemical shifts are quoted on parts per million relative to d_4-MeOH (δ_H 3.31, central line of quintet) and d_4-MeOH (δ_C 50-41, central line of septet). Carbon NMR spectra were recorded with broad band decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics micrOTOF spectrometer.

Some experimental procedures were adapted from methods reported by other group members (Mary Wheldon, Masakazu Atobe, Thomas Downes, James Firth and Hanna Klein).

7.2.2 General Procedures

General procedure A: Pyridine Hydrogenation without MeOH wash

PtO_2 (5-10 mol%) was added to a stirred solution of pyridine ester (100 mg, 0.66 mmol) in AcOH (1.0 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After the final evacuation, H_2 was charged and the reaction mixture was stirred vigorously under a balloon of H_2 for 24 h. The solids were removed by filtration through Celite and washed with CH_2Cl_2 (30 mL). $NH_4OH_{(aq)}$ (20 mL) was added to the filtrate and the two layers were separated. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure B: Pyridine Hydrogenation with MeOH wash

PtO_2 (5-33 mol%) was added to a stirred solution of pyridine ester (100 mg, 0.66 mmol) in AcOH (1.0 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After the final evacuation, H_2 was charged and the reaction mixture was stirred vigorously under a balloon of H_2 for 24 h. The solids were removed by filtration through Celite and washed with MeOH (30 mL). The filtrate was evaporated under

reduced pressure to give the crude product. The crude product was dissolved in CH_2Cl_2 (5 mL) and $NH_4OH_{(aq)}$ (2 mL) was added. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General procedure C: Mesylation with Pyridine in CH_2Cl_2

MsCl (0.06 mL, 0.77 mmol, 1.2 eq) was added dropwise to a stirred solution of piperidine (100 mg, 0.64 mmol, 1.0 eq) and pyridine (0.05 mL, 0.64 mmol, 1.0 eq or 0.27 mL, 1.91 mmol, 3.0 eq) in CH_2Cl_2 (8.5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h or rt for 24 h. The reaction mixture was evaporated under reduced pressure to give the crude product.

General procedure D: Mesylation with Pyridine

MsCl (0.03 mL, 0.38 mmol, 1.2 eq) was added dropwise to a stirred solution of piperidine (50 mg, 0.32 mmol, 1.0 eq) in pyridine (3.2 mL) at 0 °C under Ar. The resulting solution was stirred at rt or 60 °C for 16-72 h. The reaction mixture was evaporated under reduced pressure to give the crude product.

General Procedure E: Piperidine epimerisation *via* KO*t*Bu

N-Benzyl/*N*-Boc piperidine (50 mg, 0.20 mmol, 1.0 eq) was added to a flask containing dry THF (3 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and the solution was cooled to –78 °C. KO*t*Bu (0.24 mL of a 1 M solution in THF, 0.24 mmol, 1.2 eq) was added dropwise. The resulting solution was stirred at –78 °C for 2 h. Then, water (1 mL) was added at –78 °C and the reaction mixture was allowed to warm to rt. The mixture was extracted with EtOAc (3 x 5 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure F: Enolate arylation using LiHMDS (1 M THF or toluene)

A solution of cyclic ester (0.2 mL, 1.56 mmol, 1.2 eq) in toluene (1 mL) was added dropwise to a stirred solution of LiHMDS (2.6 mL of a 1.0 M solution in THF or toluene, 2.6 mmol, 2.0 eq) in toluene (2 mL) at rt under Ar. The resulting solution was stirred at rt for 40 min. In a separate reaction flask, [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$

(15 mg, 0.052 mmol, 0.04 eq) and aryl bromide (1.30 mmol, 1.0 eq) were added, followed by dry toluene (5 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The LiHMDS/ester solution was then added dropwise to the reaction flask and the resulting solution was stirred at rt for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (20 mL) and sat $NaHCO_{3(aq)}$ (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure G: Enolate arylation using LDA

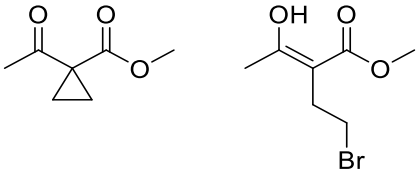
n-BuLi (1.0 mL of a 2.3 M solution in hexane, 2.3 mmol, 2.0 eq) was added dropwise to a stirred solution of diisopropylamine (0.32 mL, 2.3 mmol, 2.0 eq) in dry toluene (1 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. A solution of cyclic ester (0.2 mL, 1.56 mmol, 1.2 eq) in toluene (1 mL) was added dropwise to the LDA solution at 0 °C under Ar. The solution was stirred at 0 °C for 10 min and then allowed to warm to rt and stirred at rt for 10 min. In a separate reaction flask, [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) and aryl bromide (1.30 mmol, 1.0 eq) were added, followed by dry toluene (5 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The LDA/ester solution was then added dropwise to the reaction flask and the resulting solution was stirred at rt for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (20 mL) and sat $NaHCO_{3(aq)}$ (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure H: Enolate alkylation using LiHMDS (1 M in toluene)

LiHMDS (0.61 mL of a 1.0 M solution in toluene, 0.61 mmol, 1.4 eq) was added dropwise to a stirred solution of cyclic ester (100 mg, 0.43 mmol, 1.0 eq) in THF (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1.5 h. Then, a solution of benzyl bromide (152 mg, 0.61 mmol, 1.4 eq) in THF (1 mL) was added dropiwise –78 °C under Ar. The resulting solution was stirred at –78 °C and slowly warmed up to rt over 16 h. The solution was poured into sat $NH_4Cl_{(aq)}$ (10 mL) and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

7.2.3 Experimental Procedures and Characterisation Data

Methyl 1-acetylcyclopropane-1-carboxylate 107 and methyl 2-(2-bromoethyl)-3-hydroxybut-2-enoate 110



107 **110**

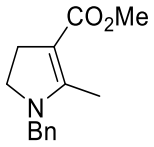
Methyl acetoacetate (3.0 mL, 27.8 mmol, 1.0 eq) was added dropwise to a stirred suspension of 1,2-dibromoethane (4.7 mL, 55.6 mmol, 2.0 eq) and K_2CO_3 (9.5 g, 69.5 mmol, 2.5 eq) in MeCN (50 mL, 0.55 M) at rt under Ar. The resulting suspension was stirred and heated at reflux for 23 h. After being allowed to cool to rt, the solids were removed by filtration and the filtrate was evaporated under reduced pressure to give an orange oil. The residue was dissolved in EtOAc (50 mL) and the solution was washed with brine (2 × 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow/orange oil. Purification by flash column chromatography on silica with 8:1 hexane-EtOAc as eluent gave enol-bromide **110** (130 mg, 3%) as a colourless oil, R_F (1:1 hexane-EtOAc) 0.55; IR (ATR) 2949 (OH), 1709 (C=O), 1435, 1269, 1138, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H, OH), 4.06 (t, 2H, J = 6.0 Hz, $BrCH_2$), 3.66 (s, 3H, OMe), 3.55 (t, J = 6.0 Hz, CH_2CH_2Br), 2.31 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) 171.7 (C=O or =COH), 168.1 (C=O or =COH), 91.7 (=CCH_2), 67.7 (CH_2Br), 51.0 (OMe), 28.2 (CH_2CH_2Br), 18.9 (Me); MS (ESI) *m/z* 245 $(M + Na)^+$; HRMS *m/z* calcd for $C_7H_{11}{}^{79}BrO_3$ $(M + Na)^+$ 244.9777, found 244.9784 (+2.6 ppm error) and a 85:15 mixture (by ^1H NMR spectroscopy) of cyclopropane **107** and enol-bromide **110** (2.37 g, 1.85 g of cyclopropane **107** (47%); 520 mg of enol-bromide **110** (8%)) as a colourless oil, R_F (1:1 hexane-EtOAc) 0.5; IR (ATR) 2955, 1698 (C=O, CO_2Me), 1625 (C=O, C(O)Me), 1436, 1120, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) of **107**: δ 3.69 (s, 3H, OMe), 2.42 (s, 3H, Me), 1.44-1.39 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) of **107**: 203.3 (C=O, C(O)Me), 171.7 (C=O, CO_2Me), 52.4 (OMe), 35.1 (C), 30.0 (Me), 19.5 (CH_2); MS (ESI) *m/z* 165 $(M + Na)^+$; HRMS *m/z* calcd for $C_7H_{10}O_3$ $(M + Na)^+$ 165.0522, found 165.0524 (–1.2 ppm error). Spectroscopic data for **107** consistent with those reported in the literature.[146]

Lab Book - PJ-01-35.

Methyl acetoacetate (0.25 mL, 2.3 mmol, 1.0 eq) was added dropwise to a stirred suspension of 1,2 dibromoethane (0.39 mL, 4.6 mmol, 2.0 eq) and Cs_2CO_3 (1.89 g, 5.7 mmol, 2.5 eq) in MeCN (20 mL, 0.1 M) at rt under Ar. The resulting suspension was stirred and heated at reflux for 23 h. After being allowed to cool to rt, the solids were removed by filtration and the filtrate was evaporated under reduced pressure to give an orange oil. The residue was dissolved in EtOAc (50 mL) and the solution was washed with brine (2 × 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow/orange oil. Purification by flash column chromatography on silica with 19:1 hexane-EtOAc as eluent gave an 80:20 mixture (by ^{1}H NMR spectroscopy) of cyclopropane **107** and enol-bromide **110** (150 mg, 83 mg of cyclopropane **107** (25%); 67 mg of enol-bromide **110** (7%)) as a colourless oil.

Lab Book - PJ-01-56.

Methyl 1-benzyl-2-methyl-4,5-dihydro-1H-pyrrole-3-carboxylate 108



108

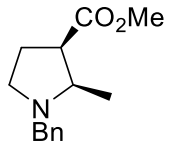
Benzylamine (1.26 mL, 11.6 mmol, 1.6 eq) was added to a stirred solution a 95:5 mixture of cyclopropane **107** and enol-bromide **110** (1.10 g i.e. 1.04 g, 7.3 mmol, 1.0 eq of cyclopropane **110**) in toluene (30 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 23 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 5:1 hexane-EtOAc as eluent gave dihydropyrrole **108** (1.23 g, 72%) as a yellow oil, R_F (5:1 hexane-EtOAc) 0.24; IR (ATR) 2946, 1668 (C=O), 1421, 1128, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 2H, Ph), 7.29-7.25 (m, 1H, Ph), 7.19-7.14 (m, 2H, Ph), 4.28 (s, 2H, NCH_2Ph), 3.65 (s, 3H, OMe), 3.29 (t, J = 9.5, 2H, NCH_2), 2.70 (t, J = 9.5, 2H, NCH_2CH_2), 2.29 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.8 (C=O), 161.7 (C=*C*Me), 137.3 (*ipso*-Ph), 128.8 (Ph), 127.5 (Ph), 127.2 (Ph), 96.4 (C=*C*CO_2Me), 50.7 (NCH_2Ph), 50.5 (NCH_2), 50.2 (OMe), 27.0 (CH_2), 21.2 (Me); MS (ESI) *m/z* 232 $(M + H)^+$; HRMS *m/z* calcd for $C_{14}H_{17}NO_2$ $(M + H)^+$ 232.1332, found 232.1337 (–1.5 ppm error). Spectroscopic data consistent with those reported in the literature.[147]

Lab Book - PJ-01-15.

Benzylamine (0.03 mL, 0.5 mmol, 1.5 eq) was added to a stirred solution of enol-bromide **110** (50 mg, 0.2 mmol, 1.0 eq) in toluene (5 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 72 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give a brown oil (178 mg, crude). No dihydropyrrole **108** was detected by ^{1}H NMR spectroscopy.
Lab Book - PJ-01-38.

Methyl acetoacetate (3.0 mL, 26.0 mmol, 1.0 eq) was added dropwise to a stirred suspension of 1,2-dibromoethane (4.7 mL, 53.0 mmol, 2.0 eq) and K_2CO_3 (9.5 g, 66.0 mmol, 2.5 eq) in MeCN (50 mL, 0.55 M) at rt under Ar. The resulting suspension was stirred and heated at reflux for 23 h. After being allowed to cool to rt, the solids were removed by filtration and the filtrate was evaporated under reduced pressure to give the crude product as an orange oil. Benzylamine (4.26 mL, 39.0 mmol, 1.5 eq) was added to a stirred solution of the crude product in toluene (30 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 48 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 19:1 hexane-EtOAc as eluent gave dihydropyrrole **108** (2.88 g, 44% over 2 steps) as a colourless oil.
Lab Book - PJ-01-71.

Methyl 1-benzyl-2-methylpyrrolidine-3-carboxylate *cis*-109



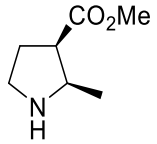
cis-**109**

$NaBH(OAc)_3$ (2.47 g, 1.17 mmol, 3.0 eq) was added to a stirred solution of dihydropyrrole **108** (900 mg, 3.9 mmol, 1.0 eq) in 1:1 AcOH-MeCN (12 mL) at rt under Ar. The resulting solution was cooled to 0 °C and stirred at 0 °C for 3 h. Then, the solvent was evaporated under reduced pressure to give an orange oil. The residue was dissolved in CH_2Cl_2 (30 mL) and sat $NaHCO_{3(aq)}$ (70 mL) was added. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow/orange oil which contained an 85:15 mixture of pyrrolidines *cis*-**109** and *trans*-**109**

(by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave pyrrolidine *cis*-**109** (590 mg, 65%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.1; IR (ATR) 2970, 1736 (C=O), 1434, 1164, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.14 (m, 5H, Ph), 3.85 (d, J = 13.5 Hz, 1H, NCHPh), 3.65 (s, 3H, OMe), 3.33 (d, J = 13.5 Hz, 1H, NCHPh), 3.02 (ddd, J = 8.0, 8.0, 8.0 Hz, 1H, $CHCO_2$) 2.94-2.80 (m, 2H, C*H*Me and NCH) 2.26 (ddd, J = 9.0, 9.0, 7.0 Hz, 1H, NCH), 2.23-2.14 (m, 1H, CH), 1.92-1.83 (m, 1H, CH), 0.99 (d, J = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.4 (C=O), 139.2 (*ipso*-Ph), 128.9 (Ph), 128.3 (Ph), 127.0 (Ph), 60.1 (NCH), 57.4 (NCH_2Ph), 52.3 (NCH_2), 51.6 (OMe), 47.4 (*C*HCO_2Me), 25.9 (CH_2), 14.7 (Me); MS (ESI) *m/z* 234 $(M + H)^+$; HRMS *m/z* calcd for $C_{14}H_{19}NO_2$ $(M + H)^+$ 234.1489, found 234.1498 (–3.9 ppm error) and a 65:35 mixture (by ^{1}H NMR spectroscopy) of pyrrolidines *trans*-**109** and *cis*-**109** (162 mg, 17%) as a yellow oil. Diagnostic signal for *trans*-**109**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 6.0 Hz, 3H, CH*Me*).

Lab Book - PJ-01-23.

3-(Methoxycarbonyl)-2-methylpyrrolidin-1-ium chloride *cis*-74

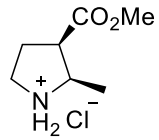


cis-**74**

A suspension of 20% $Pd(OH)_2$/C in MeOH (1 mL) was added to a stirred solution of benzyl pyrrolidine *cis*-**109** (50 mg, 0.21 mmol, 1.0 eq) and $NH_4^+HCO_2^-$ (68 mg, 1.05 mmol, 5.0 eq) in MeOH (1 mL). The resulting suspension was stirred and heated at reflux for 2 h. After being allowed to cool to rt, the solids were removed by filtration through Celite and washed with MeOH (10 mL). The solvent was evaporated under reduced pressure to give the crude product as a clear oil. Purification by flash column chromatography on silica with 95:4:1 CH_2Cl_2-MeOH-NH_4OH as eluent unfortunately did not afford *cis*-**74** due to volatility.

Lab Book - PJ-01-25

3-(Methoxycarbonyl)-2-methylpyrrolidin-1-ium chloride *cis*-74·HCl



cis-**74**·HCl

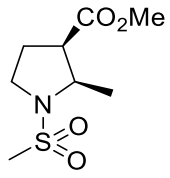
10% Pd/C (160 mg, 0.15 mmol, 0.7 eq) was added to a stirred solution of benzyl pyrrolidine *cis*-**109** (500 mg, 2.15 mmol, 1.0 eq) in MeOH (10 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After the final evacuation, H_2 was charged and the reaction mixture was stirred vigorously under a H_2 balloon at rt for 3 h. The solids were removed by filtration through Celite and washed with Et_2O (30 mL). HCl (5.3 mL of a 2 M solution in Et_2O, 5.3 mmol, 5.0 eq) was added dropwise to the filtrate. The resulting solution was stirred at rt for 30 min. Then, the solvent was evaporated under reduced pressure to give pyrrolidine *cis*-**74**·HCl (300 mg, 78%) as a red oil, IR (ATR) 2912, 1730 (C=O), 1437, 1177, 731 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOH) δ 3.96-3.82 (m, 1H, NC*H*Me), 3.72 (s, 3H, OMe), 3.58-3.46 (m, 1H, NCH), 3.42-3.32 (m, 1H, NCH), 3.32-3.24 (m, 1H, $CHCO_2$), 2.38-2.23 (m, 2H, CH_2), 1.33 (d, *J* = 6.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, d_4-MeOD) δ 173.5 (C=O), 58.7 (N*C*HMe), 52.8 (OMe), 47.6 (*C*HCO_2), 45.2 (NCH_2), 28.2 (CH_2), 13.9 (CH*Me*); MS (ESI) *m/z* 144 (M^+); HRMS *m/z* calcd for $C_7H_{14}NO_2$ (M^+) 144.1019, found 144.1023 (–2.2 ppm error). Spectroscopic data for consistent with those reported in the literature.[148]

Lab Book - PJ-02-04.

10% Pd/C (120 mg, 1.13 mmol, 0.7 eq) was added to a stirred solution of an 80:20 mixture of α-methyl benzyl pyrrolidine *cis,trans*-**103** and *cis,cis*-**103** (400 mg, 1.62 mmol, 1.0 eq.) in MeOH (9 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After the final evacuation, H_2 was charged and the reaction mixture was stirred vigorously under a H_2 balloon at rt for 3 h. The solids were removed by filtration through Celite and washed with Et_2O (30 mL). HCl (4 mL of a 2 M solution in Et_2O, 8.27 mmol, 5.0 eq) was added dropwise to the filtrate. The resulting solution was stirred at rt for 30 min. Then, the solvent was evaporated under reduced pressure to give pyrrolidine *cis*-**74**·HCl (280 mg, 97%) as a red oil.

Lab Book - PJ-02-55.

Methyl 2-methyl-1-(methylsulfonyl)pyrrolidine-3-carboxylate *cis*-112

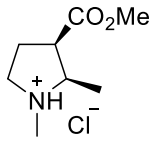


cis-**112**

Et_3N (0.23 mL, 1.68 mmol, 3.0 eq) was added dropwise to a stirred solution of *cis*-**74**·HCl (100 mg, 0.56 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) at rt under Ar. The resulting mixture was stirred at rt for 10 min and MsCl (0.13 mL, 1.68 mmol, 3.0 eq) was added dropwise. The resulting mixture was stirred at rt for 18 h. The reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the crude product as an orange solid. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc as eluent gave *N*-sulfonamide pyrrolidine *cis*-**112** (90 mg, 73%) as a white solid, mp 83-86 °C; R_F (1:1 hexane-EtOAc) 0.23; IR (ATR) 2973, 1745 (C=O), 1316, 1147, 1130, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (dq, *J* = 13.0, 6.5 Hz, 1H, NC*H*Me), 3.72 (s, 3H, OMe), 3.60-3.50 (m, 1H, NCH), 3.30 (ddd, *J* = 10.0, 10.0, 7.0 1H, NCH), 3.15-3.06 (m, 1H, C*H*CO_2Me), 2.85 (s, 3H, SO_2Me), 2.41-2.30 (m, 1H, CH), 2.18-2.10 (m, 1H, CH), 1.17 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.2 (C=O), 56.5 (N*C*HMe), 52.2 (OMe), 47.9 (*C*HCO_2Me), 46.9 (NCH_2), 36.7 (SO_2Me), 26.0 (CH_2), 18.2 (CH*Me*); MS (ESI) *m/z* 244 $(M + H)^+$; HRMS *m/z* calcd for $C_8H_{15}NO_4S$ $(M + Na)^+$ 244.0614, found 244.0617 (–3.8 ppm error).

Lab Book - PJ-02-57.

3-(Methoxycarbonyl)-1,2-dimethylpyrrolidin-1-ium chloride *cis*-75·HCl

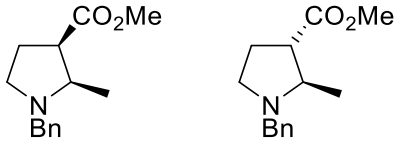


cis-**75**·HCl

37% aqueous formaldehyde (0.5 mL, 17.6 mmol, 10.0 eq) was added dropwise to a stirred suspension of pyrrolidine **74**·HCl (300 mg, 1.7 mmol, 1.0 eq), $NaBH(OAc)_3$ (1.06 g, 5.0 mmol, 3.0 eq) and $MgSO_4$ (500 mg, 4.15 mmol) in 4:1 CH_2Cl_2-AcOH (16 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. The reaction mixture was dissolved in CH_2Cl_2 (30 mL) and sat $NaHCO_{3(aq)}$ (70 mL) was added. The two layers were separated, and

the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$) to give a solution of the crude *cis*-**75**. HCl (4.25 mL of a 2 M solution in Et_2O, 8.5 mmol, 5.0 eq) was added dropwise to the solution of crude *cis*-**75**. The resulting solution was stirred at rt for 30 min. Then, the solvent was evaporated under reduced pressure to give *N*-methyl pyrrolidine *cis*-**75**·HCl (160 mg, 48%) as an orange solid, mp 42-45 °C; IR (ATR) 2952, 1736 (C=O), 1436, 1202, 780 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOD) δ 3.89-3.80 (m, 1H, NC*H*Me), 3.73 (s, 3H, OMe), 3.71-3.63 (m, 1H, NCH), 3.44-3.36 (m, 1H, NCH), 3.26-3.18 (m, 1H, $CHCO_2$), 2.91 (s, 3H, NMe), 2.45-2.33 (m, 1H, CH), 2.31-2.19 (m, 1H, CH), 1.36 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, d_4-MeOH) δ 173.9 (C=O), 67.4 (N*C*HMe), 56.5 (NCH_2), 52.9 (OMe), 47.9 (*C*HCO_2), 40.6 (NMe), 26.9 (CH_2), 12.4 (Me); MS (ESI) *m/z* 158 (M^+); HRMS *m/z* calcd for $C_8H_{16}NO_2$ (M^+) 158.1176, found 158.1171 (+2.9 ppm error).
Lab Book - PJ-02-05.

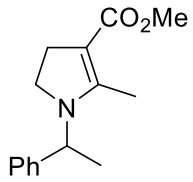
Methyl 1-benzyl-2-methylpyrrolidine-3-carboxylate *cis*-109 and *trans*-109



cis-**109** *trans*-**109**

A solution of a 90:10 mixture of pyrrolidines *cis*-**109** (50 mg, 0.29 mmol, 1.0 eq) in DBU (0.1 mL, 0.64 mmol, 3.0 eq) and xylene (1 mL) was stirred and heated at 100 °C for 48 h under Ar. After being allowed to cool to rt, water (50 mL) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give a 50:50 mixture of pyrrolidines *cis*-**109** and *trans*-**109** (25 mg, 50%) as a colourless oil, R_F (75:25 hexane-EtOAc) 0.23. Diagnostic signal for *cis*-**109**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.5 Hz, 1.5H, CH*Me*). Diagnostic signal for *trans*-**109**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.0 Hz, 1.5H, CH*Me*).
Lab Book - PJ-01-19.

Methyl 2-methyl-1-(1-phenylethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate 102

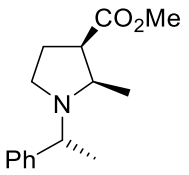


102

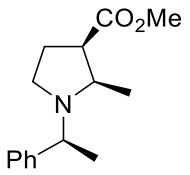
Methyl acetoacetate (3.0 mL, 27.8 mmol, 1.0 eq) was added dropwise to a stirred suspension of 1,2-dibromoethane (4.7 mL, 55.6 mmol, 2.0 eq) and K_2CO_3 (9.5 g, 69.5 mmol, 2.5 eq) in MeCN (50 mL, 0.55 M) at rt under Ar. The resulting suspension was stirred and heated at reflux for 23 h. After being allowed to cool to rt, the solids were removed by filtration and the filtrate was evaporated under reduced pressure to give the crude product as an orange oil. α-Methylbenzylamine (4.45 mL, 39.0 mmol, 1.5 eq) was added to a stirred solution of the crude product in toluene (130 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 48 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 19:1 hexane-EtOAc as eluent gave α-methyl dihydropyrrole **102** (3.04 g, 44%) as an orange oil, R_F (1:1 hexane-EtOAc) 0.29; IR (ATR) 2976, 2942, 1667 (C=O), 1417, 1130, 1025, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 2H, Ph), 7.28-7.20 (m, 3H, Ph), 4.88 (q, *J* = 7.0 Hz, 1H, NC*H*Me), 3.66 (s, 3H, OMe), 3.46-3.37 (m, 1H, NCH), 3.18-3.11 (m, 1H, NCH), 2.71-2.64 (m, 2H, CH), 2.32 (s, 3H, Me), 1.54 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.9 (C=O), 160.9 (C=*C*Me), 141.2 (*ipso*-Ph), 128.7 (Ph), 127.4 (Ph), 126.4 (Ph), 95.7 (C=*C*CO_2Me), 52.6 (N*C*HMe), 50.2 (OMe), 45.2 (NCH_2), 26.6 (CH_2), 17.6 (Me), 12.2 (CH*Me*); MS (ESI) *m/z* 246 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{20}NO_2$ $(M + H)^+$ 246.1489, found 246.1497 (–3.2 ppm error). Spectroscopic data consistent with those reported in the literature.[72]

Lab Book - PJ-01-80.

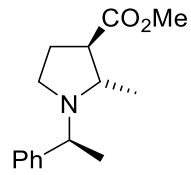
Methyl 2-methyl-1-(1-phenylethyl)pyrrolidine-3-carboxylate (*R*,*R*,*R*)-103, (*R*,*R*,*S*)-103 and (*R*,*S*,*S*)-103



(*R*,*R*,*R*)-**103**



(*R*,*R*,*S*)-**103**

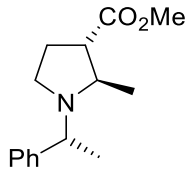


(*R*,*S*,*S*)-**103**

$NaBH(OAc)_3$ (1.3 g, 6.12 mmol, 3.0 eq) was added to a stirred solution of dihydropyrrole **102** (500 mg, 2.04 mmol, 1.0 eq) in 1:1 AcOH-MeCN (8 mL) at rt under Ar. The resulting solution was cooled and stirred at 0 °C for 3 h. Then, the solvent was evaporated under reduced pressure to give an orange oil. The residue was dissolved in CH_2Cl_2 (50 mL) and sat $NaHCO_{3(aq)}$ (50 mL) was added. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow/orange oil which contained a 70:20:10 mixture of (*R*,*R*,*R*)-**103**, (*R*,*R*,*S*)-**103** and (*R*,*S*,*S*)-**103** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave a 90:10 mixture of α-methyl benzyl pyrrolidines (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103** (230 mg, 45%) as a yellow oil, R_F (7:3 hexane-EtOAc) 0.22; IR (ATR) 2971, 1736 (C=O), 1452, 1163, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.19 (m, 5H, Ph), 3.67 (s, 2.7H, OMe), 3.63 (s, 0.3H, OMe), 3.58 (q, *J* = 6.5 Hz, 1H, PhC*H*Me), 3.53-3.44 (m, 1H, NC*H*Me), 3.15-3.06 (m, 1H, $CHCO_2$), 2.70 (ddd, *J* = 9.0, 9.0, 4.0 Hz, 1H, NCH), 2.53 (ddd, *J* = 9.0, 8.0, 8.0 Hz, 1H, NCH), 2.24-2.12 (m, 1H, CH), 1.93-1.82 (m, 1H, CH), 1.36 (d, *J* = 6.5, 0.3H, PhCH*Me*), 1.35 (d, *J* = 6.5, 2.7H, PhCH*Me*), 0.81 (d, *J* = 7.0 Hz, 0.3H, NCH*Me*), 0.75 (d, *J* = 7.0 Hz, 2.7H, NCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) for (*R*,*R*,*R*)-**103** δ 173.8 (C=O), 145.6 (*ipso*-Ph), 128.3 (Ph), 127.5 (Ph), 127.0 (Ph), 60.9 (Ph*C*HMe), 57.1 (N*C*HMe), 51.6 (OMe), 48.9 (NCH_2), 47.6 (*C*HCO_2), 25.0 (CH_2), 21.1 (PhCH*Me*), 12.7 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1647 (–0.3 ppm error) and a 60:25:15 mixture of pyrrolidines (*R*,*R*,*R*)-**103**, (*R*,*R*,*S*)-**103** and (*R*,*S*,*S*)-**103** (162 mg, 18%) as a yellow oil. Diagnostic signals for pyrrolidine (*R*,*R*,*S*)-**103**: ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 60.2 (Ph*C*HMe), 56.4 (N*C*HMe), 48.1 (NCH_2), 24.8 (CH_2), 23.3 (PhCH*Me*), 11.9 (CH*Me*). Diagnostic signal for (*R*,*S*,*S*)-**103**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.0 Hz, 3H, NCH*Me*). Spectroscopic data for (*R*,*R*,*R*)-**103**, (*R*,*R*,*S*)-**103** and (*R*,*S*,*S*)-**103** consistent with those reported in the literature.[74]

Lab Book - PJ-02-02.

Methyl 2-methyl-1-(1-phenylethyl)pyrrolidine-3-carboxylate (*S*,*R*,*R*)-103

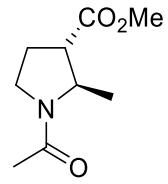


(*S*,*R*,*R*)-**103**

A solution of a 90:10 mixture of pyrrolidines (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103** (1.8 g, 7.3 mmol, 1.0 eq) in DBU (4.3 mL, 29.1 mmol, 4.0 eq) was stirred and heated at 100 °C for 16 h under Ar. After being allowed to cool to rt, water (50 mL) was added and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave a 60:30:10 mixture (by ^{1}H NMR spectroscopy) of α-methyl benzyl pyrolidines (*S*,*R*,*R*)-**103**, (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103** (530 mg, 30%) and a 95:3:2 mixture (by ^{1}H NMR spectroscopy) of α-methyl benzyl pyrolidines (*S*,*R*,*R*)-**103**, (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103** (380 mg, 24%) as an orange oil, R_F (9:1 hexane-EtOAc) 0.1; IR (ATR) 2971, 1731 (C=O), 1452, 1168, 908, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for (*S*,*R*,*R*)-**103**: δ 7.39-7.35 (m, 2H, Ph), 7.33-7.27 (m, 2H, Ph), 7.24-7.20 (m, 1H, Ph), 3.81 (q, *J* = 6.5 Hz, 1H, PhC*H*Me), 3.70 (s, 3H, OMe), 3.06-2.99 (m, 1H, NC*H*Me), 2.79-2.74 (m, 1H, NCH), 2.61 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 1H, NCH), 2.56 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H, $CHCO_2$), 2.01-1.94 (m, 2H, CH), 1.34 (d, *J* = 6.5 Hz, 3H, PhCH*Me*), 1.00 (d, *J* = 6.0 Hz, 3H, NCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) for (*S*,*R*,*R*)-**103**: δ 175.9 (C=O), 145.2 (*ipso*-Ph), 128.2 (Ph), 127.7 (Ph), 126.8 (Ph), 60.4 (N*C*HMe), 58.8 (Ph*C*HMe), 51.9 (OMe), 50.8 (*C*HCO_2), 48.0 (NCH_2), 26.4 (CH_2), 19.7 (PhCH*Me*), 16.3 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1640 (+2.0 ppm error).

Lab Book - PJ-02-08.

Methyl 1-acetyl-2-methylpyrrolidine-3-carboxylate *trans*-73

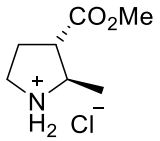


trans-**73**

10% Pd/C (106 mg, 1.0 mmol, 0.7 eq) was added to a stirred solution of a 95:3:2 mixture of pyrrolidines (*S*,*R*,*R*)-**103**, (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103** (350 mg, 1.3 mmol, 1.0 eq.) in MeOH (7 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After the final evacuation, H_2 was charged and the reaction mixture was stirred vigorously at rt under a H_2 balloon for 3 h. The solids were removed by filtration through Celite and washed with the MeOH (20 mL). AcCl (0.49 mL, 6.9 mmol, 5.0 eq) was added to the reaction mixture and the reaction was stirred at rt under Ar for 18 h. Then, the solvent was evaporated under reduced pressure to give crude pyrrolidine **74**·HCl (250 mg). Et_3N (0.8 mL, 5.8 mmol, 3.0 eq) was added dropwise to a stirred solution of crude pyrrolidine **74**·HCl (250 mg) in CH_2Cl_2 (30 mL) and the mixture was stirred at rt for 10 min under Ar. Then, AcCl (0.4 mL, 5.8 mmol, 3.0 eq) was added dropwise and the resulting mixture was stirred at rt for 18 h. The solution was poured into water (50 mL) and the two layers were separated. The organic layer was collected, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave *N*-acyl pyrrolidine *trans*-**73** (140 mg, 42%) as a yellow oil, R_F (8:2 hexane-EtOAc) 0.1; IR (ATR) 2955, 1731 (C=O, CO_2Me), 1634 (C=O, acetamide), 1412, 1171, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 4.40 (qd, *J* = 6.5, 2.5 Hz, 0.65H, NC*H*Me), 4.25 (dq, *J* = 6.5, 2.5 Hz, 0.35H, NC*H*Me), 3.70 (s, 1.05H, OMe), 3.68 (s, 1.95H, OMe), 3.63-3.54 (m, 1H, NCH), 3.53-3.46 (m, 0.65H, NCH), 3.45-3.38 (m, 0.35H, NCH), 2.77 (ddd, *J* = 6.0, 6.0, 3.0 Hz, 0.65H, $CHCO_2$), 2.72-2.65 (m, 0.35H, $CHCO_2$), 2.26-2.14 (m, 2H, CH), 2.09 (s, 1.05H, MeCO), 2.01 (s, 1.95H, MeCO), 1.31-1.25 (s, 3H, NCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 173.9 (C=O), 169.1 (C=O), 56.1 (N*C*HMe), 52.2 (OMe), 49.4 (*C*HCO_2), 46.7 (NCH_2), 26.9 (CH_2), 23.0 (*Me*CO), 20.2 (CH*Me*); MS (ESI) *m/z* 208 $(M + Na)^+$; HRMS *m/z* calcd for $C_9H_{15}NO_3$ $(M + Na)^+$ 208.0944, found 208.0951 (–3.5 ppm error).

Lab Book - PJ-02-11/13.

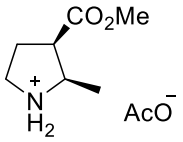
3-(Methoxycarbonyl)-2-methylpyrrolidin-1-ium chloride *trans*-74·HCl



trans-**74**·HCl

10% Pd/C (30 mg, 0.028 mmol, 0.7 eq) was added to a stirred solution of a 95:3:2 mixture of *N*-α-methyl benzyl pyrrolidine (*S*,*R*,*R*)-**103**, (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103** (100 mg, 0.4 mmol, 1.0 eq) in MeOH (2 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After the final evacuation, H_2 was charged and the reaction mixture was stirred vigorously under a H_2 balloon at rt for 3 h. The solids were removed by filtration through Celite and washed with Et_2O (10 mL). HCl (1 mL of a 2 M solution in Et_2O, 2.0 mmol, 5.0 eq) was added dropwise to the filtrate. The resulting solution was stirred at rt for 30 min. Then, the solvent was evaporated under reduced pressure to give pyrrolidine *trans*-**74**·HCl (70 mg, 99%) as a green oil, IR (ATR) 2921, 1723 (C=O), 1386, 1196, 1083, 800 cm^{-1}; ^{1}H NMR (400 MHz, d_4-MeOH) δ 3.89-3.80 (m, 1H, NC*H*Me), 3.72 (s, 3H, OMe), 3.34-3.29 (m, 2H, NCH_2), 2.92 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 1H, $CHCO_2$), 2.38 (dddd, *J* = 14.5, 7.5, 7.5, 7.5 Hz, 1H, CH), 2.22 (dddd, *J* = 14.5, 7.5, 7.5, 7.5 Hz, 1H, CH), 1.42 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, d_4-MeOH) δ 173.0 (C=O), 59.3 (N*C*HMe), 53.9 (OMe), 49.9 ($CHCO_2$), 46.8 (NCH_2), 29.3 (CH_2), 18.1 (CH*Me*); MS (ESI) *m/z* 144 (M^+); HRMS *m/z* calcd for $C_7H_{14}NO_2$ (M^+) 144.1019, found 14.1019 (–0.3 ppm error). Spectroscopic data consistent with those reported in the literature.[74]
Lab Book - PJ-02-01.

3-(Methoxycarbonyl)-2-methylpyrrolidin-1-ium chloride *cis*-74·AcOH



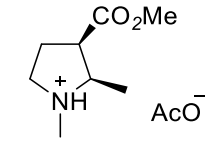
cis-**74**·AcOH

10% Pd/C (149 mg, 0.14 mmol, 0.07 eq) was added to a stirred solution of an 80:20 mixture of pyrrolidines (*R*,*R*,*R*)-**103** and (*R*,*R*,*S*)-**103** (500 mg, 2.0 mmol, 1.0 eq) in MeOH (20 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After the final evacuation, H_2 was charged and the reaction mixture was stirred vigorously at rt under a H_2 balloon for 3 h. The solids were removed by filtration through Celite and washed with the Et_2O (10 mL). AcOH (0.11 mL, 2.0 mmol, 1.0 eq) was

added dropwise to the filtrate and stirred at rt for 30 min. The solvent was evaporated under reduced pressure to give pyrrolidine *cis*-**74**·AcOH (392 mg, 96%) as a yellow oil, IR (ATR) 2955, 1733 (C=O), 1553, 1390, 1009, 654 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOH) δ 3.82 (dq, *J* = 7.0, 7.0 Hz, 1H, NC*H*Me), 3.70 (s, 3H, OMe), 3.46 (ddd, *J* = 8.0, 6.0, 6.0 Hz, 1H, $CHCO_2$), 3.35-3.20 (m, 2H, NCH), 2.31-2.18 (m, 2H, CH), 1.91 (s, 3H, $MeCO_2$), 1.29 (d, *J* = 7.0 Hz, 3H, NCH*Me*); ^{13}C NMR (100.6 MHz, d_4-MeOH) δ 178.0 (C=O, $MeCO_2$), 173.6 (C=O), 58.4 (N*C*HMe), 52.6 (OMe), 47.7 (*C*HCO_2), 45.0 (NCH_2), 28.2 (CH_2), 22.5 (*Me*CO_2), 14.0 (CH*Me*); MS (ESI) *m/z* 144 $(M)^+$; HRMS *m/z* calcd for $C_7H_{14}NO_2$ (M^+) 144.1019, found 144.1023 (–2.7 ppm error).

Lab Book - PJ-02-91.

3-(Methoxycarbonyl)-1,2-dimethylpyrrolidin-1-ium chloride *cis*-75·AcOH

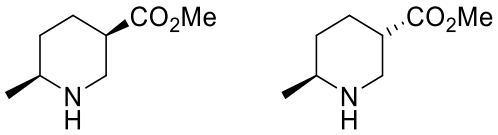


cis-**75**·AcOH

37% aqueous formaldehyde (0.55 mL, 7.4 mmol, 10.0 eq) was added dropwise to a stirred suspension of pyrrolidine **74**·AcOH (150 mg, 0.74 mmol, 1.0 eq), $NaBH(OAc)_3$ (466 mg, 2.2 mmol, 3.0 eq) and $MgSO_4$ (550 mg, 4.5 mmol) in 4:1 CH_2Cl_2-AcOH (7.4 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. The residue was dissolved in CH_2Cl_2 (30 mL) and sat $NaHCO_{3(aq)}$ (80 mL) was added. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined and dried ($MgSO_4$), AcOH (0.04 mL, 0.74 mmol, 1.0 eq) was added dropwise to the filtrate and stirred at rt for 30 min. The solvent was evaporated under reduced pressure to give *N*-methyl pyrrolidine *cis*-**75**·AcOH (91mg, 0.42 mmol, 57%) as an orange oil, IR (ATR) 2917, 1734 (C=O), 1562, 1366, 1256, 2008, 659 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOH) δ 3.65-3.53 (m, 1H, NCH), 3.63 (s, 3H, OMe), 3.47 (dq, *J* = 7.0, 7.0 Hz, 1H, C*H*Me), 3.28 (ddd, *J* = 7.5, 6.0, 6.0 Hz, 1H, $CHCO_2$), 3.05 (ddd, *J* =8.0, 6.0, 6.0 Hz, 1H, NCH), 2.72 (s, 3H, NMe), 2.23-2.15 (m, 2H, CH), 1.84 (s, 3H, $MeCO_2^-$), 1.21 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, d_4-MeOH) δ 176.8 (C=O, $MeCO_2^-$), 173.8 (C=O), 66.4 (N*C*HMe), 55.9 (NCH_2), 52.7 (OMe), 47.8 (*C*HCO_2), 40.0 (NMe), 26.6 (CH_2), 21.9 (*Me*CO_2^-), 12.35 (CH*Me*); MS (ESI) *m/z* 158 M^+; HRMS *m/z* calcd for $C_8H_{16}NO_2$ $(M)^+$ 158.1176, found 158.1179 (–0.9 ppm error).

Lab Book - PJ-02-100.

Methyl-6-methylpiperidine-3-carboxylate *cis*-126 and *trans*-126



cis-**126** *trans*-**126**

Table 2.1, Entry 1

Using general procedure A, PtO_2 (37 mg, 0.2 mmol, 20 mol%) and methyl-6-methylnicotinate (100 mg, 0.66 mmol) in AcOH (1.0 mL) gave the crude product which contained an 85:18 mixture of piperidines *cis*-**126** and *trans*-**126** (76 mg, 74%) as a colourless oil.

Lab Book - PJ-02-18.

Table 2.1, Entry 2

Using general procedure A, PtO_2 (15 mg, 0.1 mmol, 10 mol%) and methyl-6-methylnicotinate (100 mg, 0.66 mmol) in AcOH (1.0 mL) gave the crude product which contained an 85:18 mixture of piperidines *cis*-**126** and *trans*-**126** (76 mg, 74%) as a colourless oil.

Lab Book - PJ-02-18.

Table 2.1, Entry 3

Using general procedure A, PtO_2 (7.5 mg, 0.05 mmol, 5 mol%) and methyl-6-methylnicotinate (100 mg, 0.66 mmol) in AcOH (1.0 mL) gave the crude product which contained an 85:18 mixture of piperidines *cis*-**126** and *trans*-**126** (68 mg, 65%) as a colourless oil.

Lab Book - PJ-02-21.

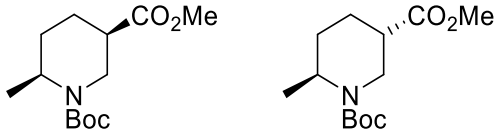
Table 2.1, Entry 4

Using general procedure B, PtO_2 (60 mg, 0.26 mmol, 10 mol%) and methyl-6-methylnicotinate (400 mg, 2.64 mmol, 1.0 eq) in AcOH (4 mL) gave the crude product which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of piperidines *cis*-**126** and *trans*-**126** (386 mg, 93%) as a colourless oil.

Lab Book – PJ-04-56.

Using general procedure A, PtO_2 (300 mg, 1.3 mmol, 10 mol%) and methyl-6-methylnicotinate (2.0 g, 13.2 mmol) in AcOH (20 mL) gave the crude product which contained an 85:18 mixture of piperidines *cis*-**126** and *trans*-**126** (1.58 g, 76%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 2.55H, OMe), 3.65 (s, 0.45H, OMe), 3.41 (ddd, *J* = 13.0, 2.5, 2.5 Hz, 1H, NCH), 2.81 (dd, *J* = 13.0, 4.0 Hz, 1H, NCH), 2.64 (dqd, *J* = 13, 6.5, 3.0 Hz, 1H, NC*H*Me), 2.48-2.44 (m, 1H, CH), 2.20-2.12 (m, 1H, CH), 2.09 (br, 1H, NH), 1.71-1.61 (m, 1H, CH), 1.54 (ddd, *J* = 13.5, 7.0, 3.5 Hz, 1H, CH), 1.23-1.12 (m, 1H, CH), 1.07-1.02 (m, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.2 (C=O), 51.8 (OMe), 51.8 (CH), 47.4 (NCH_2), 39.1 (CH), 31.5 (CH_2), 26.1 (CH_2), 22.7 (Me). The crude product was sufficiently pure for use in the next step. Spectroscopic data for *cis*-**126** and *trans*-**126** consistent with those reported in the literature.[84]
Lab Book - PJ-02-29.

1-(*tert*-Butyl) 3-methyl-6-methylpiperidine-1,3-dicarboxylate *cis*-157 and *trans*-157



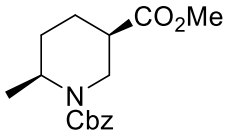
cis-**157** *trans*-**157**

Et_3N (4.15 mL, 29.8 mmol, 3.0 eq) was added dropwise to an 85:15 mixture of piperidines *cis*- **126** and *trans*-**126** (1.5 g, 9.93 mmol, 1.0 eq), Boc_2O (2.16 g, 9.93 mmol, 1.0 eq) and DMAP (60 mg, 4.97 mmol, 0.05 eq) in CH_2Cl_2 (100 mL) at rt under Ar. The reaction mixture was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-Boc piperidine *cis*-**157** (1.73 g, 68%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.22; IR (ATR) 2973, 1734 (C=O, CO_2Me), 1688 (C=O, Boc), 1408, 1161, 871 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52-4.29 (m, 1H, NC*H*Me), 4.29-4.04 (m, 1H, NCH), 3.69 (s, 3H, OMe), 2.97-2.82 (m, 1H, NCH), 2.45-2.33 (m, 1H, $CHCO_2$), 1.98-1.85 (m, 1H, CH), 1.79-1.65 (m, 2H, CH), 1.59-1.50 (m, 1H, CH), 1.45 (s, 9H, CMe_3), 1.12 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.1 (C=O, CO_2Me), 154.7 (C=O, Boc), 79.6 (*C*Me_3), 51.7 (OMe), 45.0 (N*C*HMe), 41.9 ($CHCO_2$), 39.7 (NCH_2), 29.1 (CH_2), 28.4 (C*Me*$_3$), 22.1 (CH_2), 15.5 (Me); MS (ESI) *m/z* 280

(M + Na)$^+$; HRMS *m/z* calcd for $C_{13}H_{23}NO_4$ (M + Na)$^+$ 280.1519, found 280.1507 (+4.4 ppm error), a 65:35 mixture of *N*-Boc piperidines *trans*-**157** and *cis*-**157** (144 mg, 6%) and *N*-Boc piperidine *trans*-**157** (150 mg, 6%), R_F (9:1 hexane-EtOAc) 0.17; IR (ATR) 2972, 1735 (C=O, CO_2Me), 1686 (C=O, Boc), 1414, 1152, 865 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45-4.29 (m, 2H, NC*H*Me and NCH), 3.67 (s, 3H, OMe), 3.04 (dd, *J* = 14.0, 4.0 Hz, 1H, NCH), 2.58 -2.53 (m, 1H, $CHCO_2$), 2.04-1.96 (m, 1H, CH), 1.92-1.72 (m, 2H, CH), 1.43 (s, 9H, CMe_3), 1.37-1.30 (m, 1H, CH), 1.11 (d, *J* = 7.0 Hz, 1H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.9 (C=O, CO_2Me), 154.9 (C=O, Boc), 77.5 (*C*Me_3), 51.9 (OMe), 45.9 (N*C*HMe), 39.4 (NCH_2), 39.2 (*C*HCO_2), 28.6 (C*Me*$_3$), 26.6 (CH_2), 20.2 (CH_2), 16.0 (Me); MS (ESI) *m/z* 280 (M + Na)$^+$; HRMS *m/z* calcd for $C_{13}H_{23}NO_4$ (M + Na)$^+$ 280.1519, found 280.1519 (–0.3 ppm error). Spectroscopic data for *cis*-**157** and *trans*-**157** consistent with those reported in the literature.[149]

Lab Book - PJ-02-32.

1-Benzyl 3-methyl-6-methylpiperidine-1,3-dicarboxylate *cis*-127



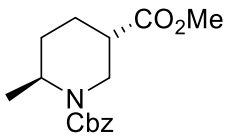
cis-**127**

HCl (3.9 mL of a 2 M solution in Et_2O, 7.8 mmol, 10.0 eq) was added dropwise to piperidine *cis*-**157** (200 mg, 0.78 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 112 h. Then, the solvent was evaporated under reduced pressure to give the hydrochloride salt (100 mg). Et_3N (0.14 mL, 1.04 mmol, 2.0 eq) was added dropwise to a solution of the hydrochloride salt (100 mg, 0.52 mmol, 1.0 eq) and DMAP (6 mg, 0.052 mmol, 0.1 eq) in CH_2Cl_2 (5 mL) under Ar. The reaction mixture was cooled to 0 °C and stirred for 1 h. Cbz-Cl (0.08 mL, 0.57 mmol, 1.1 eq) was then added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then warmed to rt and stirred at rt for 16 h. 2 M $HCl_{(aq)}$ (5 mL) was added and the solvent was evaporated under reduced pressure to give a colourless oil. The oil was partitioned between toluene (10 mL), Et_2O (10 mL) and water (20 mL). The two layers were separated, and the organic layer was washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-Cbz piperidine *cis*-**127** (59 mg, 26%) as a colourless oil, R_F (8:2

hexane-EtOAc) 0.2; IR (ATR) 2950, 1732 (C=O, CO_2Me), 1688 (C=O, Cbz), 1421, 1171, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H, Ph), 5.13 (s, 2H, CH_2Ph), 4.49 (br s, 1H, NCH), 4.38-4.13 (br s, 1H, NC*H*Me), 3.68 (s, 3H, OMe), 3.05-2.91 (m, 1H, NCH), 2.48-2.35 (m, 1H, $CHCO_2$), 1.99-1.84 (m, 1H, CH), 1.81-1.62 (m, 2H, CH), 1.62-1.54 (m, 1H, CH), 1.16 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.0 (C=O, CO_2Me), 155.2 (C=O, Cbz), 136.9 (*ipso*-Ph), 128.6 (Ph), 128.1 (Ph), 128.0 (Ph), 67.3 (NCH_2Ph), 51.9 (OMe), 45.9 (CH), 41.9 (CH), 40.0 (NCH_2), 29.2 (CH_2), 22.2 (CH_2), 15.8 (Me); MS (ESI) *m/z* 314 $(M + Na)^+$; HRMS *m/z* calcd for $C_{16}H_{21}NO_4$ $(M + Na)^+$ 314.1363, found 314.1353 (+2.6 ppm error). Spectroscopic data consistent with those reported in the literature.[84]

Lab Book - PJ-02-44.

1-Benzyl 3-methyl-6-methylpiperidine-1,3-dicarboxylate *trans*-127



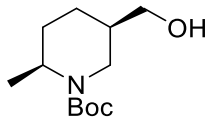
trans-**127**

HCl (1.95 mL of a 2 M solution in Et_2O, 3.9 mmol, 10.0 eq) was added dropwise to piperidine *trans*-**157** (100 mg, 0.39 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the hydrochloride salt (60 mg). Et_3N (0.09 mL, 0.62 mmol, 2.0 eq) was added dropwise to a solution of the hydrochloride salt (60 mg, 0.31 mmol, 1.0 eq) and DMAP (4 mg, 0.031 mmol, 0.1 eq) in CH_2Cl_2 (5 mL) under Ar. The reaction mixture was cooled to 0 °C and stirred for 1 h. Cbz-Cl (0.05 mL, 0.34 mmol, 1.1 eq) was then added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then warm to rt and stirred at rt for 16 h. 2 M $HCl_{(aq)}$ (2 mL) was added and the solvent was evaporated under reduced pressure to give a yellow oil. The oil was partitioned between toluene (10 mL), Et_2O (10 mL) and water (20 mL). The two layers were separated, and the organic layer was washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-Cbz piperidine *trans*-**127** (55 mg, 48%) as a colourless oil, R_F (8:2 hexane-Et_2O) 0.2; IR (ATR) 2949, 1732 (C=O, CO_2Me), 1690 (C=O, Boc), 1421, 1155, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 4H, Ph), 7.34-7.27 (m, 1H,

Ph), 5.18 (d, *J* = 12.5 Hz, 1H, C*H*Ph), 5.08 (d, *J* = 12.5 Hz, 1H, C*H*Ph), 4.49 (m, 1H, NCH), 4.46-4.40 (m, 1H, C*H*Me), 3.61 (s, 3H, OMe), 3.12 (dd, *J* = 14.0, 4.0 Hz, 1H, NCH), 2.60-2.58 (m, 1H, $CHCO_2$), 2.09-2.00 (m, 1H, CH), 1.95-1.75 (m, 2H, CH_2), 1.42-1.36 (m, 1H, CH), 1.16 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.7 (C=O, CO_2Me), 155.5 (C=O, Cbz), 137.2 (*ipso*-Ph), 128.6 (Ph), 128.0 (Ph), 127.8 (Ph), 67.1 (NCH_2Ph), 52.0 (OMe), 46.4 (CH), 39.6 (NCH_2), 39.1 (CH), 26.6 (CH_2), 20.1 (CH_2), 16.0 (Me); MS (ESI) *m/z* 314 $(M + Na)^+$; HRMS *m/z* calcd for $C_{16}H_{21}NO_4$ $(M + Na)^+$ 314.1363, found 314.1364 (–1.0 ppm error). Spectroscopic data consistent with those reported in the literature.[84]

Lab Book - PJ-02-54.

tert-Butyl-5-(hydroxymethyl)-2-methylpiperidine-1-carboxylate _cis_-158

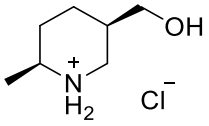


cis-**158**

$LiAlH_4$ (0.97 mL of a 1 M solution in THF, 0.97 mmol, 1.0 eq) was added dropwise to a stirred solution of *N*-Boc piperidine *cis*-**157** (250 mg, 0.97 mmol, 1.0 eq) in THF (15 mL) at rt under Ar. The reaction mixture was stirred at 0 °C for 2 h. Water (4 mL), 20% $NaOH_{(aq)}$ (4 mL) and water (4 mL) were added sequentially (CARE – vigorous reaction). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give alcohol *cis*-**158** (218 mg, 98%) as a colourless oil, IR (ATR) 3415 (OH), 2929, 1687 (C=O), 1411, 1142, 867 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46-4.30 (m, 1H, NC*H*Me), 4.07-3.96 (m, 1H, NCH), 3.58-3.41 (m, 2H, CH_2OH), 2.56-2.48 (m, 1H, NCH), 1.72-1.48 (m, 4H, CH), 1.46-1.40 (m, 9H, CMe_3), 1.36-1.20 (m, 1H, CH), 1.08 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.2 (C=O), 79.5 (*C*Me_3), 66.0 (CH_2OH), 46.2 (N*C*HMe), 41.5 (NCH_2), 39.3 (CH), 29.7 (CH_2), 28.6 (C*Me*$_3$), 22.0 (CH_2), 15.8 (Me); MS (ESI) *m/z* 252 $(M + Na)^+$; HRMS *m/z* calcd for $C_{12}H_{23}NO_3$ $(M + Na)^+$ 252.1570, found 252.1573 (–1.0 ppm error). The crude piperidine *cis*-**158** was sufficiently pure for the next step.

Lab Book - PJ-02-33.

5-(Hydroxymethyl)-2-methylpiperidin-1-ium *cis*-86·HCl

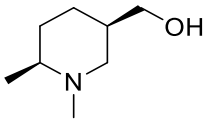


cis-**86**·HCl

HCl (2.1 mL of a 2 M solution in Et_2O, 4.37 mmol, 5.0 eq) was added dropwise to piperidine *cis*-**158** (200 mg, 0.87 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give piperidine *cis*-**86**·HCl (143 mg, 99%) as a colourless oil, IR (ATR) 3360 (OH), 2940, 1450, 1053 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOH) δ 3.68-3.54 (m, 2H, CH), 3.46-3.37 (m, 1H, NC*H*Me), 3.23-3.12 (m, 2H, NCH), 2.00-1.93 (m, 1H, C*H*CH_2OH), 1.89-1.80 (m, 1H, CH), 1.77-1.65 (m, 3H, CH), 1.33 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, d_4-MeOH) δ 63.9 (CH_2OH), 51.9 (*C*HMe), 44.2 (CH_2), 35.5 (CH), 28.0 (CH_2), 23.1 (CH_2), 17.1 (Me); MS (ESI) *m/z* 130 $(M)^+$; HRMS *m/z* calcd for $C_7H_{16}NO$ $(M)^+$ 130.1226, found 130.1229 (–1.7 ppm error).

Lab Book - PJ-02-37.

1,6-Dimethylpiperidin-3-yl)methanol *cis*-87



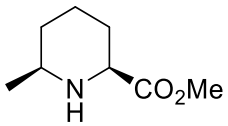
cis-**87**

A solution of *N*-Boc piperidine *cis*-**158** (400 mg, 1.56 mmol, 1.0 eq) in THF (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (295 mg, 7.78 mmol, 5.0 eq) in THF (10 mL) at 0 °C under Ar. The resulting suspension was stirred at 0 °C for 2 h. The reaction mixture was then allowed to warm up to rt, stirred and heated at reflux for 16 h. The reaction mixture was cooled to 0 °C, water (3 mL), 20% $NaOH_{(aq)}$ (3 mL) and water (3 mL) were added sequentially (CARE – vigorous reaction). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude product as a green oil. Purification by flash column chromatography on silica with 85:14:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$ as eluent gave *N*-methyl piperidine *cis*-**87** (93 mg, 42%) as a red oil, R_F (85:14:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$) 0.15; IR (ATR) 3333 (OH), 2925, 1446, 1046, 597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (dd, *J* = 11.0, 5.0 Hz, 1H, OCH), 3.74 (dd, *J* = 11.0, 5.0 Hz,

1H, OCH), 2.85 (dd, *J* = 11.0, 3.0 Hz, 1H, NCH), 2.37 (dd, *J* = 11.0, 3.0 Hz, 1H, NCH), 2.22 (s, 3H, NMe), 2.13-2.04 (m, 1H, C*H*Me), 1.81-1.74 (m, 1H, CH), 1.69-1.52 (m, 4H, CH), 1.05 (d, *J* = 6.5 Hz, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 67.8 (OCH_2), 58.88 (NCH_2), 58.81 (N*C*HMe), 43.3 (NMe), 35.4 (CH), 31.8 (CH_2), 27.4 (CH_2), 18.9 (Me); MS (ESI) *m/z* 144 $(M + H)^+$; HRMS *m/z* calcd for $C_8H_{17}NO$ $(M + H)^+$ 144.1383, found 144.1379 (+3.1 ppm error).

Lab Book - PJ-02-50.

Methyl 6-methylpiperidine-2-carboxylate *cis*-142

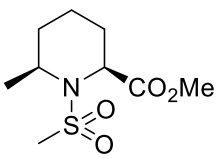


cis-**142**

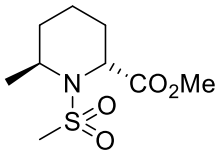
Using general procedure B, PtO_2 (30 mg, 0.13 mmol, 10 mol%) and 6-methyl-pyridine-2-methyl ester **159** (0.18 mL, 1.32 mmol, 1.0 eq) in AcOH (4.9 mL) gave the crude product which contained (by ^{1}H NMR spectroscopy) only piperidine *cis*-**142** (200 mg, 97%) as a colourless oil. IR (ATR) 2929, 1737 (C=O), 1436, 1212, 1056, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H, OMe), 3.34 (dd, *J* = 11.0, 3.0 Hz, 1H, $NCHCO_2$), 2.62 (dqd, *J* = 12.5, 6.5, 2.5 Hz, 1H, NC*H*Me), 1.99-1.92 (m, 1H, CH), 1.88-1.80 (m, 1H, CH), 1.62-1.54 (m, 1H, CH), 1.45-1.26 (m, 2H, CH), 1.08 (d, *J* = 6.5 Hz, 3H, CH*Me*), 1.06-0.96 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.8 (C=O), 59.4 (NCH), 52.0 (OMe), 51.9 (N*C*HMe), 33.8 (CH_2), 29.0 (CH_2), 24.6 (CH_2), 22.9 (CH*Me*); MS (ESI) *m/z* 158 $(M + H)^+$; HRMS *m/z* calcd for $C_8H_{15}NO_2$ $(M + H)^+$ 158.1176, found 158.1174 (+1.3 ppm error).

Lab Book - PJ-05-88.

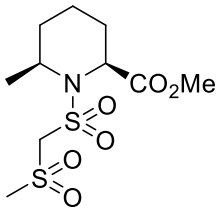
Methyl 1-methanesulfonyl-6-methylpiperidine-2-carboxylate *cis*-160, *trans*-160 and methyl 1-methanesulfonylmethanesulfonyl-6-methylpiperidine-2-carboxylate *cis*-161



cis-**160**



trans-**160**

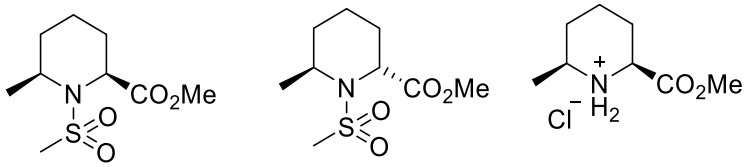


cis-**161**

MsCl (0.19 mL, 2.52 mmol, 4.0 eq) was added dropwise to a stirred solution of piperidine *cis*-**142** (100 mg, 0.64 mmol, 1.0 eq) and Et_3N (0.09 mL, 0.64 mmol, 1.0 eq or 0.27 mL, 1.91 mmol, 3.0 eq) in CH_2Cl_2 (6.3 mL) at rt or 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. The solution was poured into water (50 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave sulfonamide piperidine *cis*-**160** (34 mg, 20%) as a yellow oil , R_F (60:40 hexane-EtOAc) 0.33; IR (ATR) 2944, 1734 (C=O), 1315, 1160, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77-4.71 (m, 1H, $NCHCO_2$), 4.31-4.23 (m, 1H, NC*H*Me), 3.74 (s, 3H, OMe), 3.01 (s, 3H, SO_2Me), 2.35-2.28 (m, 1H, CH), 1.74-1.50 (m, 5H, CH), 1.15 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.2 (C=O), 52.8 (NCH), 52.5 (OMe), 48.4 (N*C*HMe), 41.2 (SO_2Me), 30.5 (CH_2), 26.4 (CH_2), 18.2 (CH*Me*), 15.3 (CH_2); MS (ESI) *m/z* 258 $(M + Na)^+$; HRMS *m/z* calcd for $C_9H_{17}NO_4S$ $(M + Na)^+$ 258.0770, found 258.0769 (+0.5 ppm error) and impure bismethanesulfonamide piperidine *cis*-**161** (102 mg). Purification of the impure bismethanesulfonamide piperidine *cis*-**161** by flash column chromatography on silica with 50:50 hexane-EtOAc as eluent gave bismethanesulfonamide piperidine *cis*-**161** (66 mg, 30%) as a white solid, mp 100-102 °C; R_F (50:50, hexane-EtOAc) 0.34; IR (ATR) 2980, 1733 (C=O), 1320, 1165, 966, 488 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75 (d, *J* = 15.0 Hz, $CHSO_2$), 4.72 (dd, *J* = 6.0, 1.5 Hz, 1H, $NCHCO_2$), 4.49 (d, *J* = 15 Hz, 1H, $CHSO_2$), 4.29-4.19 (m, 1H, NC*H*Me), 3.79 (s, 3H, OMe), 3.23 (s, 3H, SO_2Me), 2.38-2.31 (m, 1H, CH), 1.86-1.74 (m, 2H, CH), 1.73-1.58 (m, 3H, CH), 1.23 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C=O), 71.0 (CH_2SO_2), 54.2 (NCH), 52.9 (OMe), 50.6 (N*C*HMe), 42.5 (SO_2Me), 30.4 (CH_2), 25.9 (CH_2), 21.3 (CH*Me*), 15.1 (CH_2); MS (ESI) *m/z* 336 $(M + Na)^+$; HRMS *m/z* calcd for $C_{10}H_{19}NO_6S_2$ $(M + Na)^+$ 336.0546, found 336.0536 (+3.0 ppm error).

Lab Book - PJ-04-02.

Methyl 1-methanesulfonyl-6-methylpiperidine-2-carboxylate *cis*-160, *trans*-160 and methyl 6-methylpiperidine-2-carboxylate *cis*-142·HCl



cis-**160** *trans*-**160** *cis*-**142**·HCl

Table 2.2, Entry 1

Using general procedure C, MsCl (0.06 mL, 0.77 mmol, 1.2 eq), piperidine *cis*-**142** (100 mg, 0.64 mmol, 1.0 eq) and pyridine (0.05 mL, 0.64 mmol, 1.0 eq) in CH_2Cl_2 (8.5 mL) at 0 °C for 1 h gave a 25:5:70 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160**, sulfonamide piperidine *trans*-**160** and piperidine *cis*-**142**·HCl. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc followed by 85:15 CH_2Cl_2-MeOH as eluent gave an 80:20 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160** and *trans*-**160** (40 mg, 26%) as a colourless oil, and piperidine *cis*-**142**·HCl (63 mg, 50%) as a cream solid, mp 208-210 °C IR (ATR) 2980, 2698, 1749 (C=O), 1224, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (dd, *J* = 12.5, 3.0 Hz, 1H, NCHCO$_2$), 3.82 (s, 3H, OMe), 3.25-3.15 (m, 1H, NC*H*Me), 2.30-2.23 (m, 1H, CH), 1.97-1.87 (m, 2H, CH), 1.72-1.51 (m, 2H, CH), 1.42-1.26 (m, 1H, CH), 1.33 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4 (C=O), 58.5 (NCH), 54.4 (N*C*HMe), 53.7 (OMe), 30.9 (CH_2), 26.9 (CH_2), 23.3 (CH_2), 19.2 (CH*Me*); MS (ESI) *m/z* 158 (M^+); HRMS *m/z* calcd for $C_8H_{15}NO_2$ (M^+) 158.1176, found 158.1179 (+0.2 ppm error).

Lab Book - PJ-04-40.

Table 2.2, Entry 2

Using general procedure C, MsCl (0.06 mL, 0.77 mmol, 1.2 eq), piperidine *cis*-**142** (100 mg, 0.64 mmol, 1.0 eq) and pyridine (0.05 mL, 0.64 mmol, 1.0 eq) in CH_2Cl_2 (6.5 mL) at rt for 24 h gave a 20:5:75 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160**, sulfonamide piperidine *trans*-**160** and piperidine *cis*-**142**·HCl. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave sulfonamide piperidine *cis*-**160** (28 mg, 19%) as a colourless oil and a 55:45 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidines *cis*-**160** and *trans*-**160** (5 mg, 3%) as a colourless oil.

Lab Book - PJ-04-41.

Table 2.2, Entry 3

Using general procedure C, MsCl (0.03 mL, 0.38 mmol, 1.2 eq), piperidine *cis*-**142** (50 mg, 0.32 mmol, 1.0 eq) and pyridine (0.08 mL, 0.96 mmol, 3.0 eq) in CH_2Cl_2 (3.2 mL) at rt for 24 h gave a 30:5:65 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160**, sulfonamide piperidine *trans*-**160** and piperidine *cis*-**142**·HCl. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave an 80:20 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidines *cis*-**160** and *trans*-**160** (28 mg, 37%) as a colourless oil.

Lab Book - PJ-04-53.

Table 2.2, Entry 4

Using general procedure D, MsCl (0.03 mL, 0.38 mmol, 1.2 eq) and piperidine *cis*-**142** (50 mg, 0.32 mmol, 1.0 eq) in pyridine (3.2 mL) at rt for 24 h gave a 45:10:45 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160**, sulfonamide piperidine *trans*-**160** and piperidine *cis*-**142**·HCl. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave sulfonamide piperidine *cis*-**160** (32 mg, 43%) as a colourless oil and an 80:20 mixture (by ^{1}H NMR spectroscopy) of sulfonamides piperidines *trans*-**160** and *cis*-**160** (3 mg, 4%) as a colourless oil.

Lab Book - PJ-04-54.

Table 2.2, Entry 5

Using general procedure D, MsCl (0.03 mL, 0.38 mmol, 1.2 eq) and piperidine *cis*-**142** (50 mg, 0.32 mmol, 1.0 eq) in pyridine (3.2 mL) at rt for 72 h gave a 60:5:35 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160**, sulfonamide piperidine *trans*-**160** and piperidine *cis*-**142**·HCl. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave sulfonamide piperidine *cis*-**160** (45 mg, 60%) as a colourless oil and a 90:10 mixture (by ^{1}H NMR spectroscopy) of sulfonamides piperidine *trans*-**160** and sulfonamide piperidine *cis*-**160** (3 mg, 4%) as a colourless oil.

Lab Book - PJ-04-62.

Table 2.2, Entry 6

Using general procedure D, MsCl (0.03 mL, 0.38 mmol, 1.2 eq) and piperidine *cis*-**142** (50 mg, 0.32 mmol, 1.0 eq) in pyridine (3.2 mL) at 60 °C for 16 h gave a 45:5:50 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160**, sulfonamide piperidine *trans*-**160** and piperidine *cis*-**142**·HCl. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave an 80:20 mixture (by ^{1}H NMR spectroscopy) of sulfonamides piperidine *cis*-**160** and sulfonamide piperidine *trans*-**160** (28 mg, 38%) as a colourless oil.

Lab Book - PJ-04-73.

Table 2.2, Entry 7

Using general procedure D, MsCl (0.03 mL, 0.38 mmol, 1.2 eq) and piperidine *cis*-**142** (50 mg, 0.32 mmol, 1.0 eq) in pyridine (3.2 mL) at 60 °C for 24 h gave a 50:5:45 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160**, sulfonamide piperidine *trans*-**160** and piperidine *cis*-**142**·HCl. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave a 90:10 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160** and sulfonamide piperidine *trans*-**160** (33 mg, 44%) as a colourless oil.

Lab Book - PJ-04-74.

Table 2.2, Entry 8

Using general procedure D, MsCl (0.15 mL, 1.83 mmol, 1.2 eq) and piperidine *cis*-**142** (240 mg, 1.53 mmol, 1.0 eq) in pyridine (15 mL) at rt for 72 h gave a 55:5:40 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160**, sulfonamide piperidine *trans*-**160** and piperidine *cis*-**142**·HCl. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave sulfonamide piperidine *cis*-**160** (187 mg, 52%) as a colourless oil.

Lab Book - PJ-04-82.

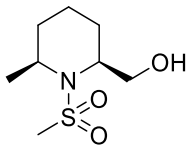
Table 2.2, Entry 9

MsCl (0.04 mL, 0.40 mmol, 1.2 eq) was added dropwise to a stirred solution of piperidine *cis*-**142** (54 mg, 0.34 mmol, 1.0 eq) and lutidine (0.12 mL, 1.02 mmol, 3.0 eq) in CH_2Cl_2 (3.4 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h then warmed to

rt and stirred at rt for 24 h. The reaction mixture was evaporated under reduced pressure to afford the crude product as a cream solid. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave an 80:20 mixture (by ^{1}H NMR spectroscopy) of sulfonamide piperidine *cis*-**160** and sulfonamide piperidine *trans*-**160** (23 mg, 28%) as a colourless oil.

Lab Book - PJ-04-60.

(1-Methanesulfonyl-6-methylpiperidin-2-yl)methanol *cis*-84

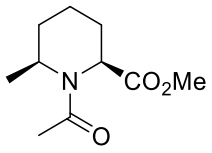


cis-**84**

A solution of sulfonamide piperidine *cis*-**160** (92 mg, 0.39 mmol, 1.0 eq) in THF (4 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (30 mg, 0.79 mmol, 2.0 eq) in THF (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 2 h. Water (0.1 mL), 20% $NaOH_{(aq)}$ (0.2 mL) and water (0.1 mL) were added sequentially (CARE – vigorous reaction). Then, $MgSO_4$ was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product as a green oil. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-acetone as eluent gave sulfonamide *cis*-**84** (63 mg, 78%) as a white solid, mp 58-60 °C; R_F (95:5 CH_2Cl_2-acetone) 0.06; IR (ATR) 3505 (OH), 2941, 1305, 1138, 966, 766 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21-4.13 (m, 1H, NC*H*Me), 4.03-3.98 (m, 1H, NCH), 3.79 (ddd, *J* = 11.0, 8.0, 5.5 Hz, 1H, OCH), 3.66-3.59 (m, 1H, HOC*H*), 2.89 (s, 3H, SO_2Me), 2.03 (dd, *J* = 8.0, 8.0 Hz, 1H, OH), 1.82-1.76 (m, 1H, CH), 1.73-1.51 (m, 5H, CH), 1.34 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 64.6 (OCH_2), 53.7 (NCH), 48.1 (N*C*HMe), 40.0 (SO_2Me), 30.3 (CH_2), 25.4 (CH_2), 22.2 (CH*Me*), 14.3 (CH_2); MS (ESI) *m/z* 230 $(M + Na)^+$; HRMS *m/z* calcd for $C_8H_{17}NO_3S$ $(M + Na)^+$ 230.0821, found 230.0814 (+3.7 ppm error).

Lab Book - PJ-03-60.

Methyl-1-acetyl-6-methylpiperidine-2-carboxylate *cis*-166

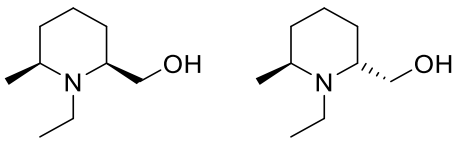


cis-**166**

AcCl (0.27 mL, 3.82 mmol, 3.0 eq) was added dropwise to a solution of piperidine *cis*-**160** (200 mg, 1.27 mmol, 1.0 eq) and Et_3N (0.54 mL, 3.82 mmol, 3.0 eq) in CH_2Cl_2 (10 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The solution was poured into water (10 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 5:5 hexane-EtOAc as eluent gave acetamide piperidine *cis*-**166** (188 mg, 85%) as a yellow oil, R_F (1:1 hexane-EtOAc) 0.17; IR (ATR) 2943, 1732 (C=O, CO_2Me), 1636 (C=O, NCO), 1409, 1210, 1021, 613 cm^{-1}; ^1H NMR (400 MHz, DMSO *d*-6) (55:45 mixture of rotamers) δ 5.16-5.06 (m, 0.55H, C*H*CO_2), 4.73-4.67 (m, 0.45H, C*H*CO_2), 4.64-4.56 (m, 0.45H, C*H*Me), 4.18-4.09 (m, 0.55H, C*H*Me), 3.64 (s, 1.35H, CO_2Me), 3.59 (s, 1.65H, CO_2Me), 2.21-2.11 (m, 1H, CH), 2.07 (s, 1.65H, COMe), 2.00 (s, 1.35H, COMe), 1.65-1.42 (m, 5H, CH), 1.07 (d, *J* = 7.0 Hz, 1.65H, CH*Me*), 0.87 (d, *J* = 7.0 Hz, 1.35H, CH*Me*); ^{13}C NMR (100.6 MHz, DMSO *d*-6) (rotamers) δ 172.6 (C=O, CO_2Me), 172.5 (C=O, CO_2Me), 170.3 (C=O, NCO), 169.6 (C=O, NCO), 53.5 (*C*HCO_2), 52.2 (OMe), 51.9 (OMe), 48.8 (*C*HCO_2), 48.1 (*C*HMe), 43.1 (*C*HMe), 29.9 (CH_2), 29.3 (CH_2), 25.7 (CH_2), 25.4 (CH_2), 21.9 (CO*Me*), 21.3 (CO*Me*), 18.8 (CH*Me*), 16.9 (CH*Me*), 15.2 (CH_2); MS (ESI) *m/z* 222 $(M + Na)^+$; HRMS *m/z* calcd for $C_{10}H_{17}NO_3$ $(M + Na)^+$ 222.1101, found 222.1105 (–2.3 ppm error).

Lab Book - PJ-05-63.

1-Ethyl-6-methylpiperidin-2-yl)methanol *cis*-167 and *trans*-167

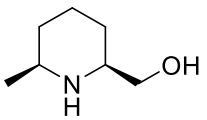


cis-**167** *trans*-**167**

A solution of piperidine *cis*-**166** (75 mg, 0.48 mmol, 1.0 eq) in THF (2 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (36 mg, 0.95 mmol, 2.0 eq) in THF (2 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 2 h. Water (0.1 mL), 20% $NaOH_{(aq)}$

(0.2 mL) and water (0.1 mL) were added sequentially (CARE – vigorous reaction). Then, $MgSO_4$ was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product as a green oil. Purification by flash column chromatography on silica with 90:9:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$ as eluent gave a 75:25 mixture of piperidines *cis*-**167** and *trans*-**167** (39 mg, 53%) as a colourless oil, R_F (90:9:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$) 0.11; IR (ATR) 3302 (OH), 2926, 1454, 1377, 1032, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *cis*-**167** δ 3.78 (dd, *J* = 11.0, 4.0 Hz, 1H, OCH), 3.36 (dd, *J* = 11.0, 2.5 Hz, 1H, OCH), 2.87-2.74 (m, 2H, NC*H*$_2$CH$_3$), 2.57-2.47 (m, 2H, C*H*Me and NCH), 1.71-1.64 (m, 1H, CH), 1.63-1.51 (m, 3H, CH), 1.39-1.25 (m, 1H, CH), 1.24-1.14 (m, 1H, CH), 1.09 (d, *J* = 6.0 Hz, 3H, Me), 0.94 (t, *J* = 7.0 Hz, 3H, NCH$_2$C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 63.5 (OCH_2), 59.5 (C*H*Me or NCH), 54.5 (C*H*Me or NCH), 41.7 (N*C*H$_2$CH$_3$), 34.3 (CH_2), 29.0 (CH_2), 23.9 (CH_2), 21.5 (CH*Me*), 9.41 (NCH$_2$*C*H$_3$); MS (ESI) *m/z* 158 $(M + Na)^+$; HRMS *m/z* calcd for $C_9H_{19}NO$ $(M + H)^+$ 158.1539, found 158.1540 (–1.5 ppm error). Diagnostic signal for *trans*-**167**: ^1H NMR (400 MHz, $CDCl_3$) *δ* 3.60 (ddd, *J* = 10.5, 4.0, 1.5 Hz, 1H, OCH) and 3.41 (dd, *J* = 10.5, 8.0 Hz, 1H, OCH).
Lab Book - PJ-05-64.

(6-Methylpiperidin-2-yl)methanol *cis*-168



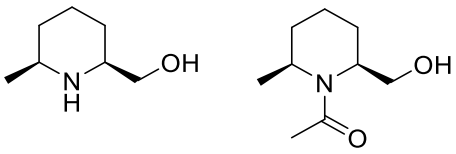
cis-**168**

A solution of piperidine *cis*-**142** (800 mg, 5.1 mmol, 1.0 eq) in THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (380 mg, 10.0 mmol, 2.0 eq) in THF (53 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 2 h. Water (0.4 mL), 20% $NaOH_{(aq)}$ (0.8 mL) and water (0.4 mL) were added sequentially (CARE – vigorous reaction). Then, $MgSO_4$ was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product as a green oil. Purification by flash column chromatography on silica with 90:9:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$ as eluent gave alcohol *cis*-**168** (490 mg, 76%) as a white solid, mp 62-64 °C; R_F (90:9:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$) 0.03; IR (ATR) 3117 (OH or NH), 2927, 1488, 1061, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.62 (dd, *J* = 10.5, 4.0 Hz, 1H, OCH), 3.43 (dd, *J* = 10.5, 8.0 Hz, 1H, OCH), 2.77-2.62 (m, 2H, NCH), 2.30 (br s, 2H, OH and NH) 1.84-1.76 (m, 2H, CH), 1.67-

1.59 (m, 1H, CH), 1.56-1.49 (m, 1H, CH), 1.38 (ddddd, *J* = 13.0, 13.0, 13.0, 4.0, 4.0 Hz, 1H, CH), 1.09 (d, *J* = 6.5 Hz, 3H, CH*Me*), 1.14-0.98 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 67.1 (OCH_2), 58.3 (NCH), 52.1 (N*C*HMe), 34.4 (CH_2), 28.1 (CH_2), 24.5 (CH_2), 23.1 (CH*Me*); MS (ESI) *m/z* 130 $(M + H)^+$; HRMS *m/z* calcd for $C_7H_{16}NO$ $(M + H)^+$ 130.1226, found 130.1224 (+2.8 ppm error). Spectroscopic data for piperidines alcohol *cis*-**168** consistent with those reported in the literature.[95]

Lab Book - PJ-03-72.

(6-Methylpiperidin-2-yl)methanol *cis*-168 and 1-[2-(hydroxymethyl)-6-methylpiperidin-1-yl]ethanone *cis*-85



cis-**168** *cis*-**85**

Table 2.3, Entry 1

Ac_2O (0.12 mL, 1.3 mmol, 6.0 eq) was added dropwise to a stirred solution of alcohol *cis*-**168** (28 mg, 0.21 mmol, 1.0 eq) in pyridine (2 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The reaction mixture was evaporated under reduced pressure to give an orange oil. CH_2Cl_2 (20 mL) was added and the solution was washed with 15% $CuSO_{4(aq)}$ (3 x 20 mL) and saturated $EDTA_{(aq)}$ (3 x 20 mL). The organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give crude piperidine *cis*-**169** (29 mg, 67%) as a colourless oil. K_2CO_3 (57 mg, 0.41 mmol, 3.0 eq) was added to a stirred solution of *cis*-**169** (29 mg, 0.14 mmol, 1.0 eq) in MeOH (1.4 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. The solution was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give *cis*-**168** (12 mg, 66%) as a white solid.

Lab Book - PJ-03-19/22.

Table 2.3, Entry 2

Ac_2O (0.08 mL, 0.93 mmol, 6.0 eq) was added dropwise to a stirred solution of piperidine *cis*-**168** (20 mg, 0.16 mmol, 1.0 eq) in pyridine (1.6 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The reaction mixture was evaporated under reduced pressure to give an orange oil. CH_2Cl_2 (20 mL) was added and the solution was washed with 15%

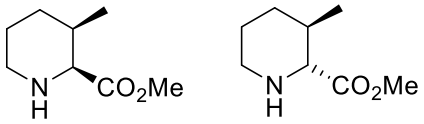
$CuSO_{4(aq)}$ (3 x 20 mL) and saturated $EDTA_{(aq)}$ (3 x 20 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give crude piperidine *cis*-**169** (31 mg, 92%) as a colourless oil. K_2CO_3 (62 mg, 0.45 mmol, 3.0 eq) was added to a stirred solution of *cis*-**169** (31 mg, 0.15 mmol, 1.0 eq) in MeOH (1.5 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. The solution was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 90:9:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$ as eluent gave *cis*-**169** (7 mg, 28%) as a colourless oil and *cis*-**85** (2 mg, 12%) as a white solid.
Lab Book - PJ-03-23/28.

Table 2.3, Entry 3

Ac_2O (0.44 mL, 4.65 mmol, 6.0 eq) was added dropwise to a stirred solution of piperidine *cis*-**168** (100 mg, 0.78 mmol, 1.0 eq) in pyridine (7.8 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The reaction mixture was evaporated under reduced pressure to give an orange oil. CH_2Cl_2 (20 mL) was added and the solution was washed with 15% $CuSO_{4(aq)}$ (3 x 80 mL) and saturated $EDTA_{(aq)}$ (3 x 20 mL). The organic layer was combined, dried ($MgSO_4$) and evaporated under reduced pressure to give crude piperidine *cis*-**169** (147 mg, 89%) as a colourless oil. K_2CO_3 (165 mg, 1.2 mmol, 3.0 eq) was added to a solution of *cis*-**169** (85 mg, 0.4 mmol, 1.0 eq) in MeOH (4 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. The solution was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-MeOH as eluent gave *cis*-**85** (39 mg, 60%) as a colourless oil, R_F (95:5, CH_2Cl_2-MeOH) 0.21; IR (ATR) 3368 (OH), 2936, 1606 (C=O), 1416, 1372, 1049, 1009, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 4.79-4.66 (m, 1H, NCH), 4.11-3.99 (m, 0.75H, NC*H*Me), 3.99-3.88 (m, 0.25H, NC*H*Me), 3.72-3.59 (m, 2H, OCH), 3.06-2.92 (m, 0.75H, OH), 2.92-2.74 (m, 0.25H, OH), 2.13 (s, 3H, NCOMe), 1.84-1.77 (m, 1H, CH), 1.70-1.44 (m, 5H, CH), 1.24 (d, J = 7.0 Hz, 2.25H, CH*Me*), 1.17–1.08 (m, 0.75H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8 (C=O), 66.1 (OCH_2), 50.1 (NCH), 48.6 (N*C*HMe), 30.5 (CH_2), 25.0 (CH_2), 22.0 (CO*Me*), 21.2 (CH*Me*), 14.4 (CH_2); MS (ESI) *m/z* 194 $(M + Na)^+$; HRMS *m/z* calcd for $C_9H_{17}NO_2$ $(M + Na)^+$ 194.1151, found 194.1146 (+2.5 ppm error).

Lab Book - PJ-03-50/68.

Methyl 3-methylpiperidine-2-carboxylate *cis*-116 and *trans*-116

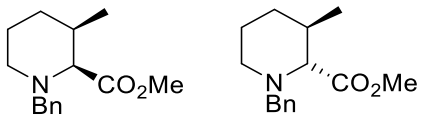


cis-**116** *trans*-**116**

Using general procedure B, PtO_2 (150 mg, 0.099 mmol, 10 mol%) and methyl-3-methylpicolinate (0.13 mL, 0.99 mmol, 1.0 eq) in AcOH (1.5 mL) gave the crude product which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of piperidines *cis*-**116** and *trans*-**116** (150 mg, 97%) as a colourless oil, IR (ATR) 2929, 1741 (C=O), 1435, 1202 1005, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 0.45H, OMe), 3.71 (s, 2.55H, OMe), 3.52 (d, *J* = 3.5 Hz, 0.85H, $NCHCO_2$), 3.16-3.08 (m, 1H, NCH), 2.96 (d, *J* = 10.0 Hz, 0.15H, $NCHCO_2$), 2.65-2.57 (m, 1H, NCH), 2.24-2.13 (m, 1H, C*H*Me), 1.68-1.57 (m, 3H, CH), 1.39-1.32 (m, 1H, CH), 0.93 (d, *J* = 7.0 Hz, 2.55H, CH*Me*), 0.87 (d, *J* = 7.0 Hz, 0.45H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) for *cis*-**116**: δ 173.6 (C=O), 62.2 ($NCHCO_2$), 51.8 (OMe), 46.1 (NCH_2), 30.9 (CH_2), 30.6 (*C*HMe), 21.2 (CH_2), 13.6 (CH*Me*); for *trans*-**116**: 66.5 ($NCHCO_2$), 45.9 (CH_2), 34.9 (CH), 33.1 (CH_2), 26.7 (CH_2), 19.0 (CH*Me*); MS (ESI) *m/z* 158 $(M + H)^+$; HRMS *m/z* calcd for $C_8H_{15}NO_2$ $(M + H)^+$ 158.1176, found 158.1177 (–1.3 ppm error).

Lab Book - PJ-04-37.

Methyl 1-benzyl-3-methylpiperidine-2-carboxylate *cis*-123 and *trans*-123



cis-**123** *trans*-**123**

PhCHO (0.36 mL, 3.5 mmol, 1.1 eq) was added dropwise to a stirred solution of an 85:15 mixture of piperidines *cis*-**116** and *trans*-**116** (500 mg, 3.18 mmol, 1.0 eq), $NaBH(OAc)_3$ (1.35 g, 6.37 mmol, 2.0 eq) and AcOH (0.03 mL, 0.64 mmol, 0.2 eq) in DCE (30 mL) at rt under Ar. The resulting mixture was stirred at rt for 18 h. The reaction mixture was poured into sat $NaHCO_{3(aq)}$ (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a green oil which contained a 90:10 mixture (by ^{1}H

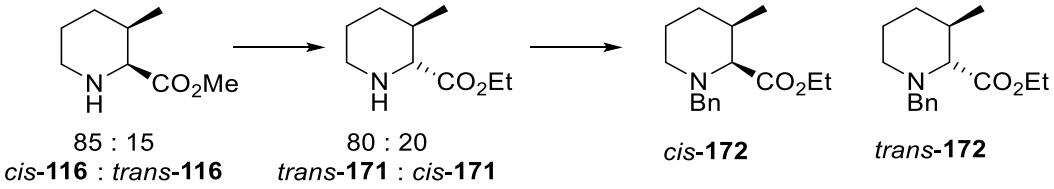
NMR spectroscopy) of piperidines *cis*-**123** and *trans*-**123**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave *N*-benzyl piperidine *cis*-**123** (626 mg, 80%) as a yellow oil, R_F (95:5 hexane-EtOAc) 0.23; IR (ATR) 2928, 1728 (C=O), 1453, 1148, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 4H, Ph), 7.25-7.22 (m, 1H, Ph), 3.69 (s, 3H, OMe), 3.61 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.56 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.45 (d, *J* = 5.0 Hz, 1H, $NCHCO_2$), 3.00-2.92 (m, 1H, NCH), 2.54-2.45 (m, 1H, NCH), 2.03-1.93 (m, 1H, C*H*Me), 1.71-1.64 (m, 1H, CH), 1.60-1.46 (m, 3H, CH), 0.90 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0 (C=O), 139.1 (*ipso*-Ph), 128.9 (Ph), 128.3 (Ph), 127.1 (Ph), 66.2 (N*C*HCO_2), 60.2 (NCH_2Ph), 50.5 (OMe), 47.0 (NCH_2), 33.2 (*C*HMe), 27.8 (CH_2), 25.2 (CH_2), 18.2 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1643 (–0.7 ppm error) and piperidine *trans*-**123** (82 mg, 10%) as a yellow oil, R_F (95:5 hexane-EtOAc) 0.1; IR (ATR) 2928, 1727 (C=O), 1453, 1147, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 4H, Ph), 7.26-7.22 (m, 1H, Ph), 3.76 (s, 3H, OMe), 3.71 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.25 (d, *J* = 13.5 Hz, 1H, NCHPh), 2.87 (ddd, *J* = 11.0, 5.5, 5.5 Hz, 1H, NCH), 2.64 (d, *J* = 9.0 Hz, 1H, $NCHCO_2$), 1.95-1.86 (m, 2H, CH), 1.76-1.68 (m, 1H, CH), 1.61-1.53 (m, 2H, CH), 1.05-0.94 (m, 1H, CH), 0.90 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.3 (C=O), 137.7 (*ipso*-Ph), 129.6 (Ph), 128.3 (Ph), 127.2 (Ph), 73.7 (N*C*HCO_2), 61.2 (NCH_2Ph), 51.8 (OMe), 51.3 (NCH_2), 34.4 (*C*HMe), 32.0 (CH_2), 24.6 (CH_2), 18.9 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1641 (+1.3 ppm error). Spectroscopic data for *N*-benzyl piperidines *cis*-**123** and *trans*-**123** consistent with those reported in the literature.[79]

Lab Book - PJ-02-45.

n-BuLi (0.75 mL of a 2.15 M solution in hexane, 1.62 mmol, 4.0 eq) was added dropwise to a stirred solution of diisopropylamine (0.36 mL, 1.62 mmol, 4.0 eq) in THF (1 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. The LDA solution was added dropwise to a stirred solution of *cis*-**123** (100 mg, 0.404 mmol, 1.0 eq) in Et_2O (20 mL) at –20 °C under Ar. The resulting solution was allowed to warm to rt over 20 min and then stirred at rt for 20 min. The solution was cooled to 0 °C and a 2:1 solution of sat $NH_4Cl_{(aq)}$-$NH_4OH_{(aq)}$ (10 mL) was added. The resulting mixture was then allowed to warm to rt over 30 min and stirred at rt for 18 h. The mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated

under reduced pressure to give the crude product, which contained a 50:50 mixture (by ^{1}H NMR spectroscopy) of piperidines *cis*-**123** and *trans*-**123**. Purification by flash column chromatography on silica with 90:10 and then 50:50 hexane-Et_2O as eluent gave piperidine *cis*-**123** (31 mg, 31%) as a yellow oil and piperidine *trans*-**123** (34 mg, 34%) as a yellow oil. Lab Book - PJ-02-48.

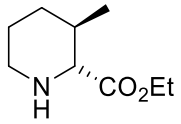
Ethyl 1-benzyl-3-methylpiperidine-2-carboxylate *cis*-172 and *trans*-172



NaOEt (2.5 mL of a 13 M solution in EtOH, 32.5 mmol, 3.0 eq) was added dropwise to an 85:15 mixture of piperidines *cis*-**116** and *trans*-**116** (1.7 g, 10.8 mmol, 1.0 eq) in EtOH (108 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 24 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give an orange oil. CH_2Cl_2 (100 mL) and water (100 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude piperidines (1.04 g, 6.62 mmol assumed) as an orange oil which contained an 80:20 mixture (by ^{1}H NMR spectroscopy) of piperidines *trans*-**171** and *cis*-**171**. PhCHO (0.74 mL, 7.28 mmol, 1.1 eq) was added dropwise to a stirred solution of the crude piperidines, $NaBH(OAc)_3$ (2.8 g, 13.2 mmol, 2.0 eq) and AcOH (0.08 mL, 1.32 mmol, 0.2 eq) in DCE (66 mL) at rt under Ar. The resulting mixture was stirred at rt for 18 h. The reaction mixture was poured into sat $NaHCO_{3(aq)}$ (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil which contained a 75:25 mixture (by ^{1}H NMR spectroscopy) of *N*-benzyl piperidines *trans*-**172** and *cis*-**172**. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-benzyl piperidine *trans*-**172** (975 mg, 36%) as a yellow oil, R_F (9:1 hexane-EtOAc) 0.18; IR (ATR) 2927, 1730 (C=O), 1453, 1176, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H, Ph), 7.26-7.21 (m, 1H, Ph), 4.25 (q, *J* = 7.0 Hz, 2H, OCH), 3.73 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.24 (d, *J* = 13.5 Hz, 1H, NCHPh), 2.89-2.83 (m, 1H, NCH), 2.61 (d, *J* = 9.0 Hz, 1H, $NCHCO_2$), 1.96-1.85 (m, 2H, CH), 1.76-1.68 (m, 1H, CH), 1.60-1.53 (m, 2H, CH), 1.31 (t,

J = 7.0 Hz, 3H, OCH_2*Me*), 1.05-0.94 (m, 1H, CH), 0.91 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.8 (C=O), 137.9 (*ipso*-Ph), 129.6 (Ph), 128.2 (Ph), 127.2 (Ph), 73.8 ($NCHCO_2$), 61.0 (OCH_2Me), 60.6 (NCH_2Ph), 51.3 (CH_2), 34.3 (*C*HMe), 32.1 (CH_2), 24.6 (CH_2), 18.8 (CH*Me*), 14.5 (OCH_2*Me*); MS (ESI) *m/z* 262 $(M + H)^+$; HRMS *m/z* calcd for $C_{16}H_{23}NO_2$ $(M + H)^+$ 262.1802, found 262.1804 (–0.5 ppm error) and an 85:15 mixture of piperidines *cis*-**172** and benzaldehyde (320 mg). This mixture was purified by flash column chromatography on silica with 9:1 to 10:0 n-hexane-CH_2Cl_2 as eluent to give *N*-benzyl piperidine *cis*-**172** (268 mg, 10%) as a yellow oil, R_F (9:1 hexane-CH_2Cl_2) 0.04; IR (ATR) 2929, 1725 (C=O), 1146, 1026, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 4H, Ph), 7.25-7.20 (m, 1H, Ph), 4.18 (q, *J* = 7.0 Hz, 2H, OCH), 3.63 (d, *J* = 13.5 Hz, 1H, C*H*Ph), 3.58 (d, *J* = 13.5 Hz, 1H, C*H*Ph), 3.42 (d, *J* = 5.0 Hz, 1H, $NCHCO_2$), 3.03-2.93 (m, 1H, NCH), 2.53-2.46 (m, 1H, NCH), 2.05-1.92 (m, 1H, C*H*Me), 1.73-1.63 (m, 1H, CH), 1.61-1.44 (m, 3H, CH), 1.29 (t, *J* = 7.0 Hz, 3H, OCH_2*Me*), 0.91 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C=O), 139.2 (*ipso*-Ph), 128.9 (Ph), 128.3 (Ph), 127.0 (Ph), 66.2 (N*C*HCO_2), 60.1 (*C*H_2Ph), 59.5 (O*C*H_2Me), 47.1 (NCH_2), 33.2 (*C*HMe), 27.9 (CH_2), 25.2 (CH_2), 18.2 (CH*Me*), 14.7 (OCH_2*Me*); MS (ESI) *m/z* 262 $(M + H)^+$; HRMS *m/z* calcd for $C_{16}H_{23}NO_2$ $(M + H)^+$ 262.1802, found 262.1797 (–2.7 ppm error). Lab Book - PJ-02-83/85.

Ethyl 3-methylpiperidine-2-carboxylate *trans*-171



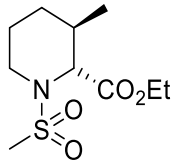
trans-**171**

A suspension of 20% $Pd(OH)_2$/C (106 mg, 0.12 mmol, 10 mol%) in EtOH (10 mL) was added to a stirred solution of *N*-benzyl piperidine *trans*-**172** (395 mg, 1.51 mmol, 1.0 eq) and $NH_4^+HCO_2^-$ (1.91 g, 30.3 mmol, 20.0 eq) in EtOH (13 mL) at rt under Ar. The resulting suspension was stirred and heated at reflux for 16 h. After being allowed to cool to rt, the solids were removed by filtration through Celite and washed with EtOH (40 mL). The filtrate was evaporated under reduced pressure to give piperidine *trans*-**171** (159 mg, 62%) as a colourless oil, R_F (9:1 CH_2Cl_2-MeOH) 0.23; IR (ATR) 2926, 1731 (C=O), 1187, 1031, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$Me), 3.11-3.04 (m, 1H, NCH), 2.93 (d, *J* = 10.0 Hz, 1H, $NCHCO_2$), 2.55 (ddd, *J* = 12.0, 12.0, 4.0 Hz, 1H, NCH),

1.84-1.77 (m, 1H, CH), 1.66-1.54 (m, 2H, CH), 1.45 (ddddd, *J* = 12.0, 12.0, 12.0, 4.0, 4.0 Hz 1H, CH), 1.26 (t, *J* = 7.0 Hz, 3H, OCH_2*Me*), 1.14 (dddd, *J* = 12.0, 12.0, 12.0, 4.0 Hz, 1H, CH), 0.87 (d, *J* = 6.5 Hz, 1H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.5 (C=O), 66.6 (N*C*HCO_2), 60.7 (O*C*H_2Me), 45.9 (NCH_2), 34.9 (*C*HMe), 33.2 (CH_2), 26.8 (CH_2), 19.0 (CH*Me*), 14.4 (OCH_2*Me*); MS (ESI) *m/z* 172 $(M + H)^+$; HRMS *m/z* calcd for $C_9H_{17}NO_2$ $(M + H)^+$ 172.1332, found 172.1336 (+2.3 ppm error).

Lab Book - PJ-03-09.

Ethyl 1-methanesulfonyl-3-methylpiperidine-2-carboxylate *trans*-173

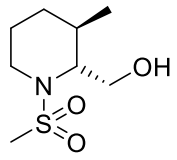


trans-**173**

MsCl (0.07 mL, 0.96 mmol, 3.3 eq) was added dropwise to a stirred solution of piperidine *trans*-**171** (50 mg, 0.29 mmol, 1.0 eq) and Et_3N (0.13 mL, 0.96 mmol, 3.3 eq) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The solution was poured into water (50 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave sulfonamide piperidine *trans*-**173** (62 mg, 86%) as a yellow oil, R_F (9:1 hexane-EtOAc) 0.2; IR (ATR) 2938, 1731 (C=O), 1320, 1139, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (br s, 1H, N$CHCO_2$), 4.25-4.17 (m, 2H, OC*H*$_2$Me), 3.72-3.68 (m, 1H, NCH), 3.19 (ddd, *J* = 12.0, 12.0, 3.0 Hz, 1H, NCH), 2.93 (s, 3H, SO_2Me), 2.58-2.50 (m, 1H, C*H*Me), 1.89-1.77 (m, 1H, CH), 1.53-1.50 (m, 1H, CH), 1.49-1.46 (m, 1H, CH), 1.46-1.41 (m, 1H, CH), 1.30 (t, *J* = 7.0 Hz, 3H, OCH_2*Me*), 1.20 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5 (C=O), 61.6 (OC*H*$_2$Me), 61.1 (N*C*HCO_2), 42.5 (NCH_2), 38.9 (SO_2Me), 29.7 (*C*HMe), 26.3 (CH_2), 19.2 (CH_2), 17.2 (OCH_2*Me*), 14.4 (CH*Me*); MS (ESI) *m/z* 250 $(M + H)^+$; HRMS *m/z* calcd for $C_{10}H_{19}NO_4S$ $(M + H)^+$ 250.1108, found 250.1114 (+2.7 ppm error).

Lab Book - PJ-03-14.

(1-Methanesulfonyl-3-methylpiperidin-2-yl)methanol *trans*-95

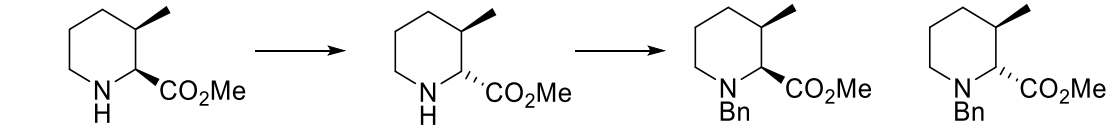


trans-**95**

A solution of sulfonamide piperidine *trans*-**173** (148 mg, 0.59 mmol, 1.0 eq) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (45 mg, 1.18 mmol, 2.0 eq) in THF (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 2 h. Water (0.1 mL), 20% $NaOH_{(aq)}$ (0.2 mL) and water (0.1 mL) were added sequentially (CARE – vigorous reaction). Then, $MgSO_4$ was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give crude product as a yellow oil. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-MeOH as eluent gave fragment **95** (100 mg, 82%) as a white solid, mp 40-42 °C; R_F (95:5 CH_2Cl_2-MeOH) 0.2 ; IR (ATR) 3500 (OH), 2933, 1307, 1133, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (ddd, *J* = 11.0, 9.5, 6.0 Hz, 1H, NCH), 3.78-3.72 (m, 1H, NCH), 3.67-3.59 (m, 2H, OCH), 3.08-2.99 (ddd, *J* = 12.0, 12.0, 4.0 Hz, 1H, NCH), 2.97 (s, 3H, SO_2Me), 2.00-1.94 (m, 1H, OH), 1.90-1.82 (m, 1H, C*H*Me), 1.82-1.72 (m, 1H, CH), 1.69-1.66 (m, 2H, CH), 1.49-1.38 (m, 2H, CH), 1.13 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 61.6 (OCH_2), 61.1 (NCH), 40.7 (NCH_2), 40.0 (SO_2Me), 28.1 (*C*HMe), 25.7 (CH_2), 20.1 (CH_2), 18.5 (CH*Me*); MS (ESI) *m/z* 230 $(M + Na)^+$; HRMS *m/z* calcd for $C_8H_{17}NO_3S$ $(M + Na)^+$ 230.0821, found 230.0822 (0.0 ppm error).

Lab Book - PJ-03-34.

Methyl 1-benzyl-3-methylpiperidine-2-carboxylate *cis*-123 and *trans*-123



85 : 15
cis-**116** : *trans*-**116**

75 : 15
trans-**116** : *cis*-**116**

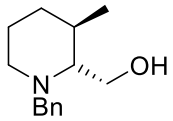
cis-**123**

trans-**123**

A solution of an 85:15 mixture of piperidines *cis*-**116** and *trans*-**116** (442 mg, 2.8 mmol, 1.0 eq) in MeOH (10 mL) was added dropwise to a stirred solution of NaOMe (152 mg, 2.8 mmol, 1.2 eq) in MeOH (20 mL) at rt under Ar. The resulting solution was stirred and heated

at reflux for 64 h. After being allowed to cool to rt, 1 M $HCl_{(aq)}$ was added until pH 7 was reached. The solids were removed by filtration through Celite and washed with CH_2Cl_2 (50 mL). The filtrate was evaporated under reduced pressure to give the crude product as a white solid. MeOH (20 mL) was added and the solids were removed by filtration and washed with CH_2Cl_2 (50 mL). The filtrate was evaporated under reduced pressure to give the crude piperidines as a white solid which contained a 75:25 mixture (by ^{1}H NMR spectroscopy) of piperidines *trans*-**116** and *cis*-**116**. PhCHO (0.31 mL, 3.08 mmol, 1.1 eq) was added dropwise to a stirred solution of the crude piperidines, $NaBH(OAc)_3$ (1.19 g, 5.6 mmol, 2.0 eq) and AcOH (0.03 mL, 0.56 mmol, 0.2 eq) in DCE (21 mL) at rt under Ar. The resulting mixture was stirred at rt for 18 h. The reaction mixture was poured into sat $NaHCO_{3(aq)}$ (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a green oil which contained a 70:30 mixture (by ^{1}H NMR spectroscopy) of *N*-benzyl piperidines *trans*-**123** and *cis*-**123**. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave *N*-benzyl piperidine *cis*-**123** (43 mg, 6%) as a yellow oil and *N*-benzyl piperidine *trans*-**123** (265 mg, 38%) as a yellow oil.
Lab Book - PJ-02-71/73.

(1-Benzyl-3-methylpiperidin-2-yl)methanol *trans*-170



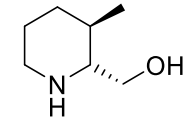
trans-**170**

A solution of *N* –benzyl piperidine *trans*-**123** (370 mg, 1.5 mmol, 1.0 eq) in THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (114 mg, 3.0 mmol, 2.0 eq) in THF (20 mL) at 0 °C under Ar. The reaction mixture was stirred at 0 °C for 2 h. Water (0.1 mL), 20% $NaOH_{(aq)}$ (0.2 mL) and water (0.1 mL) were added sequentially (CARE – vigorous reaction). Then, $MgSO_4$ was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give alcohol *trans*-**170** (330 mg, 100%) as a colourless oil, IR (ATR) 3401 (OH), 2926, 1452, 1061, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H, Ph), 4.09 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.94 (dd, *J* = 11.5, 3.5 Hz, 1H, OCH), 3.69 (dd, *J* = 11.5, 2.0 Hz, 1H, OCH), 3.23 (d, *J* = 13.5 Hz, 1H, NCHPh), 2.91 (br s, 1H, OH), 2.86 (dddd, *J* = 12.0, 4.0, 4.0, 2.0 Hz, 1H, NCH), 2.11 (ddd, *J* = 11.5, 11.5, 4.0 Hz, 1H,

NCH), 2.05 (ddd, *J* = 9.0, 3.0, 3.0 Hz, 1H, NCH), 1.85-1.70 (m, 2H, CH), 1.52-1.45 (m, 2H, CH), 1.11-1.00 (m, 1H, CH), 0.97 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.1 (*ipso*-Ph), 128.9 (Ph), 128.5 (Ph), 127.1 (Ph), 68.2 (NCH), 58.8 (OCH_2), 57.1 (NCH_2Ph), 52.0 (NCH_2), 33.2 (CH_2), 30.5 (*C*HMe), 24.1 (CH_2), 20.0 (CH*Me*); MS (ESI) *m/z* 220 $(M + H)^+$; HRMS *m/z* calcd for $C_{14}H_{21}NO$ $(M + H)^+$ 220.1696, found 220.1691 (+2.5 ppm error).

Lab Book - PJ-03-79.

(3-Methylpiperidin-2-yl)methanol *trans*-174

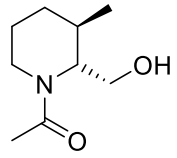


trans-**174**

20% $Pd(OH)_2/C$ (124 mg, 0.18 mmol, 10 mol%) was added to a stirred solution of *trans*-**170** (389 mg, 1.78 mmol, 1.0 eq) and $NH_4^+HCO_2^-$ (2.24 g, 35.6 mmol, 20.0 eq) in EtOH (35.6 mL) at rt under Ar. The resulting suspension was stirred and heated at reflux for 16 h. After being allowed to cool to rt, the solids were removed by filtration through Celite. The filtrate was evaporated under reduced pressure to give alcohol *trans*-**174** (172 mg, 73%) as an orange oil, IR (ATR) 3314 (OH), 2924, 1455, 1055, 829, 578 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (dd, *J* = 11.0, 3.0 Hz, 1H, OCH), 3.44 (dd, *J* = 11.0, 8.0 Hz, 1H, OCH), 3.07 (dddd, *J* = 12.0, 4.0, 2.0, 2.0 Hz, 1H, NCH), 2.87 (br s, 2H, OH and NH), 2.56 (ddd, *J* = 12.0, 12.0, 3.0 Hz, 1H, NCH), 2.25 (ddd, *J* = 10.0, 8.0, 3.0 Hz, 1H, NHC*H*), 1.77-1.68 (m, 1H, CH), 1.66-1.58 (m, 1H, CH), 1.52-1.37 (m, 1H, CH), 1.37-1.25 (m, 1H, C*H*Me), 1.12-1.00 (m, 1H, CH), 0.85 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 64.1 (NCH), 63.9 (OCH_2), 46.5 (NCH_2), 33.9 (CH_2), 33.2 (*C*HMe), 26.7 (CH_2), 18.6 (CH*Me*); MS (ESI) *m/z* 130 $(M + H)^+$; HRMS *m/z* calcd for $C_7H_{15}NO$ $(M + H)^+$ 130.1226, found 130.1233 (–4.9 ppm error).

Lab Book - PJ-03-06.

1-[2-(Hydroxymethyl)-3-methylpiperidin-1-yl]ethanone *trans*-96

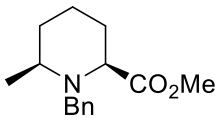


trans-**96**

Ac_2O (0.48 mL, 5.12 mmol, 6.0 eq) was added dropwise to a stirred solution of alcohol *trans*-**174** (100 mg, 0.85 mmol, 1.0 eq) and DMAP (95 mg, 0.85 mmol, 1.0 eq) in pyridine (8.5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The reaction mixture was evaporated under reduced pressure to give an orange oil. The crude product was dissolved in CH_2Cl_2 (50 mL) and washed with 15% $CuSO_{4(aq)}$ (3 x 40 mL). The combined organics were washed with sat $EDTA_{(aq)}$ (2 x 50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. K_2CO_3 (352 mg, 2.60 mmol, 3.0 eq) was added to the crude product in MeOH (8.5 mL). The resulting solution was stirred at rt for 16 h. The solution was poured into water (100 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (7 x 30 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give **96** (106 mg, 71%) as a yellow oil, IR (ATR) 3256 (OH), 2918, 1624 (C=O), 1440, 1076, 522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 4.57-4.48 (m, 0.45H, CH), 4.33 (ddd, *J* = 9.0, 4.5, 4.5 Hz, 0.55H, CH), 4.02 (dd, *J* = 11.5, 10.0 Hz, 0.45H, CH), 3.80-3.66 (m, 1.55H, CH), 3.61-3.55 (m, 0.45H, CH), 3.56-3.52 (m, 0.45H, CH), 3.27-3.17 (m, 0.55H, CH), 2.66-2.56 (m, 0.55H, NH), 2.13 (s, 1.55H, NCOMe), 2.13 (s, 1.45H, NCOMe), 1.91-1.81 (m, 1H, C*H*Me), 1.76-1.61 (m, 2H, CH), 1.54-1.46 (m, 0.55H, CH), 1.45-1.33 (m, 1.45H, CH), 1.07 (d, *J* = 7.0 Hz, 1.35H, CH*Me*), 1.02 (d, *J* = 7.0 Hz, 1.65H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.3 (C=O, COMe), 171.7 (C=O, COMe), 62.6 (OCH_2), 61.9 (NCH), 61.5 (OCH), 58.3 (NCH), 42.8 (NCH_2), 36.5 (NCH_2), 28.5 (*C*HMe), 28.2 (*C*HMe), 26.7 (CH_2), 25.9 (CH_2), 22.2 (NCO*Me*), 22.0 (NCO*Me*), 21.1 (CH_2), 19.6 (CH_2), 18.8 (CH*Me*), 18.3 (CH*Me*); MS (ESI) *m/z* 194 $(M + Na)^+$; HRMS *m/z* calcd for $C_9H_{17}NO_2$ $(M + Na)^+$ 194.1151, found 194.1146 (+2.7 ppm error).

Lab Book - PJ-03-81/86.

Methyl-1-benzyl-6-methylpiperidine-2-carboxylate *cis*-191

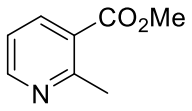


cis-**191**

BnBr (0.23 mL, 1.91 mmol, 3.0 eq) was added dropwise to a stirred solution of a 95:5 mixture of piperidines *cis*-**142** and *trans*-**142** (100 mg, 0.64 mmol, 1.0 eq) in sat $Na_2CO_{3(aq)}$ (2 mL) and CH_2Cl_2 (2 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave *N*-benzyl piperidine *cis*-**191** (139 mg, 88%) as a yellow oil, R_F (95:5 hexane-EtOAc) 0.04; IR (ATR) 2932, 1747 (C=O), 1453, 1163, 729, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 4H, Ph), 7.24-7.19 (m, 1H, Ph), 3.84 (d, *J* = 15.5 Hz, 1H, CHPh), 3.73 (d, *J* = 15.5 Hz, 1H, CHPh), 3.60 (s, 3H, OMe), 3.17 (dd, *J* = 10.5, 3.5 Hz, 1H, $CHCO_2$), 2.41 (dqd, *J* = 13.0, 6.0, 3.0 Hz, 1H, C*H*Me), 1.85-1.78 (m, 1H, CH), 1.76-1.66 (m, 2H, CH), 1.64-1.56 (m, 1H, CH), 1.46-1.35 (m, 1H, CH), 1.29 (dddd, *J* = 13.0, 8.0, 2.0, 2.0 Hz, 1H, CH), 1.14 (d, *J* = 6.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.9 (CO_2Me), 138.5 (*ipso*-Ph), 129.2 (Ph), 128.1 (Ph), 126.9 (Ph), 66.0 ($NCHCO_2$), 56.4 (CH_2Ph), 55.7 (N*C*HMe), 51.8 (OMe), 34.2 (CH_2), 30.3 (CH_2), 23.2 (CH_2), 21.4 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1648 (–1.5 ppm error).

Lab Book - PJ-05-91.

Methyl 2-methylpyridine-3-carboxylate 192

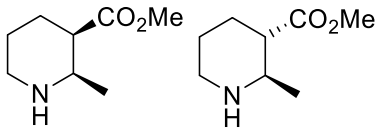


192

$SOCl_2$ (0.77 mL, 10.60 mmol, 3.0 eq) was added dropwise to a stirred solution of 2-methyl-nicotinic acid (485 mg, 3.54 mmol, 1.0 eq) in MeOH (20 mL) at 0 °C under Ar. The reaction mixture was warmed to rt, stirred and heat at reflux for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as an orange oil. The reaction mixture was poured into sat $NaHCO_{3(aq)}$ (10 mL) and extracted with CH_2Cl_2 (5 x 10 mL).

The combined organic layers were, dried (Na_2SO_4) and evaporated under reduced pressure to give pyridine **192** (443 mg, 82%) as an orange oil, IR (ATR) 1722 (C=O), 1571, 1433, 1278, 1084, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar), 8.19 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar), 7.21 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar), 3.92 (s, 3H, OMe), 2.83 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.1 (C=O), 160.1 (*ipso*-Ar), 152.0 (Ar), 138.6 (Ar), 125.5 (*ipso*-Ar), 121.0 (Ar), 52.4 (OMe), 25.0 (Me); MS (ESI) *m/z* 152 $(M + H)^+$; HRMS *m/z* calcd for $C_8H_{10}NO_2$ $(M + H)^+$ 152.0706, found 152.0703 (+1.8 ppm error). Spectroscopic data for piperidines **192** consistent with those reported in the literature.[150]
Lab Book - PJ-05-50.

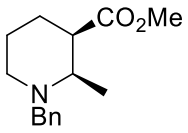
Methyl 2-methylpiperidine-3-carboxylate *cis*-193 and *trans*-193



cis-**193** *trans*-**193**

Using general procedure B, PtO_2 (10 mg, 0.05 mmol, 10 mol%) and pyridine **192** (70 mg, 0.45 mmol, 1.0 eq) in AcOH (5 mL) gave the crude product which contained a 90:10 mixture of piperidines *cis*-**193** and *trans*-**193** (65 mg, 93%) as a yellow oil, ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H, OMe), 3.10-3.03 (m, 1H, NCH), 2.96 (qd, *J* = 7.0, 3.5 Hz, 1H, C*H*Me), 2.66 (ddd, *J* = 13.5, 10.0, 3.5 Hz, 1H, NCH), 2.56-2.51 (m, 1H, $CHCO_2$), 2.02-1.94 (m, 1H, CH), 1.80-1.71 (m, 1H, CH), 1.71-1.60 (m, 2H, CH and NH), 1.42-1.33 (m, 1H, CH), 1.11 (d, *J* = 7.0 Hz, 2.7H, CH*Me*), 1.06 (d, *J* = 6.0 Hz, 0.3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *cis* δ 174.8 (C=O), 52.4 (*C*HMe), 51.3 (OMe), 45.3 (NCH_2), 44.1 ($CHCO_2$), 26.4 (CH_2), 22.8 (CH_2), 19.2 (CH*Me*). Spectroscopic data for piperidines *cis*-**193** and *trans*-**193** consistent with those reported in the literature.[151]
Lab Book - PJ-05-51.

Methyl 1-benzyl-2-methylpiperidine-3-carboxylate *cis*-194



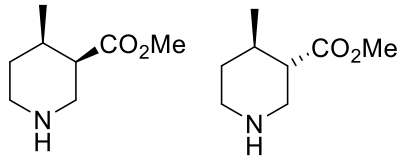
cis-**194**

BnBr (0.14 mL, 1.20 mmol, 3 eq) was added dropwise to a 90:10 solution of piperidine *cis*-**193** and *trans*-**193** (63 mg, 0.40 mmol, 1.0 eq) in 1:1 CH_2Cl_2-sat $Na_2CO_{3(aq)}$ (4 mL) at rt

under Ar. The resulting solution was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave *N*-benzyl piperidine *cis*-**194** (63 mg, 64%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.13; IR (ATR) 2943, 1732, 1138, 732, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 4H, Ph), 7.26-7.21 (m, 1H, Ph), 3.66 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.65 (s, 3H, OMe), 3.54 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.42 (qd, *J* = 6.5, 5.0 Hz, 1H, NC*H*Me), 2.84 (ddd, *J* = 12.5, 5.0, 5.0 Hz, 1H, $CHCO_2$), 2.48-2.37 (m, 2H, NCH), 1.82-1.73 (m, 1H, CH), 1.73-1.58 (m, 2H, CH), 1.56-1.45 (m, 1H, CH), 0.91 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.7 (C=O), 139.8 (*ipso*-Ph), 128.6 (Ph), 128.4 (Ph), 126.9 (Ph), 59.3 (NCH_2Ph), 54.1 (N*C*HMe), 51.6 (OMe), 46.1 (*C*HCO_2), 44.6 (NCH_2), 24.5 (CH_2), 20.7 (CH_2), 6.2 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1652 (-2.0 ppm error).

Lab Book - PJ-05-53.

Methyl 4-methylpiperidine-3-carboxylate *cis*-196 and *trans*-196



cis-**196** *trans*-**196**

Table 3.1, Entry 3

Using general procedure B, PtO_2 (45 mg, 0.20 mmol, 30 mol%) and methyl-4-methylnicotinate (100 mg, 0.66 mmol, 1.0 eq) in AcOH (1 mL) gave the crude product which contained a 65:35 mixture (by ^1H NMR spectroscopy) of piperidines *cis*-**196** and *trans*-**196** (93 mg, 90%) as a yellow oil, IR (ATR) 3314 (NH), 2952, 1726 (C=O), 1435, 1197, 1139, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H, OMe), 3.20-3.10 (m, 1H, NCH), 3.07-2.96 (m, 1H, NCH), 2.86-2.79 (m, 0.65H, NCH), 2.69-2.57 (m, 1.65H, CH), 2.55-2.50 (m, 0.65H, CH), 2.15 (br m, 1H, NH), 2.12-2.04 (m, 0.35H, CH), 2.04-1.93 (m, 0.65H, CH), 1.83-1.72 (m, 0.35H, CH), 1.66 (dddd, *J* = 7.0, 7.0, 5.0, 2.0, Hz, 0.35H, CH), 1.59-1.46 (m, 1H, CH), 1.16-1.03 (m, 0.35H, CH), 0.94 (d, *J* = 7.0 Hz, 1.95H, CH*Me*), 0.90 (d, *J* = 6.5 Hz, 1.05H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.9 (C=O), 174.7 (C=O), 51.6 (OMe), 51.3 (OMe), 49.1 (NCH_2), 46.6 (NCH_2), 46.3 (NCH_2), 45.4 (NCH_2), 44.7 (*C*HCO_2), 34.4

(CH_2), 33.4 (*C*HMe), 31.5 (*C*HMe), 31.2 (CH_2), 20.6 (CH*Me*), 18.2 (CH*Me*); MS (ESI) *m/z* 158 $(M + H)^+$; HRMS *m/z* calcd for $C_8H_{16}NO_2$ $(M + H)^+$ 158.11776, found 158.1173 (+1.9 ppm error). Spectroscopic data for piperidines *cis*-**196** and *trans*-**196** consistent with those reported in the literature.[152]

Lab Book - PJ-04-43.

Table 3.1, Entry 1

Using general procedure B, PtO_2 (30 mg, 0.13 mmol, 10 mol%) and methyl-4-methylnicotinate (200 mg, 1.32 mmol, 1.0 eq) in AcOH (2 mL) after 136 h, gave the crude product which contained a 30:50:20 mixture (by ^{1}H NMR spectroscopy) of methyl-4-methylnicotinate, piperidine *cis*-**196** and *trans*-**196** as an orange oil.

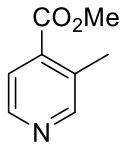
Lab Book - PJ-05-07.

Table 3.1, Entry 2

Using general procedure B, PtO_2 (30 mg, 0.13 mmol, 20 mol%) and methyl-4-methylnicotinate (100 mg, 0.66 mmol, 1.0 eq) in AcOH (5 mL) gave the crude product which contained a 40:40:20 mixture (by ^{1}H NMR spectroscopy) of methyl-4-methylnicotinate piperidine *cis*-**196** and *trans*-**196** as a yellow oil.

Lab Book - PJ-05-29.

Methyl 3-methylpyridine-4-carboxylate 197



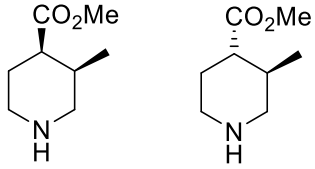
197

$SOCl_2$ (0.23 mL, 3.16 mmol, 1.1 eq) was added dropwise to a solution of 3-methyl-isonicotinic acid (393 mg, 2.87 mmol, 1.0 eq) in MeOH (20 mL) at 0 °C under Ar. The reaction mixture was warmed to rt and stirred and heated at reflux for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as an orange oil. The reaction mixture was poured into sat $NaHCO_{3(aq)}$ (10 mL) and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic were dried (Na_2SO_4) and evaporated under reduced pressure to give pyridine **197** (345 mg, 80%) as an orange oil, ^{1}H NMR (400 MHz, d_4-MeOH) δ 8.66-8.51 (m, 2H, Ar), 7.77 (d, *J* = 5.0 Hz, 1H, Ar), 3.94 (s, 3H, OMe), 2.56 (s, 3H, Me); ^{13}C

NMR (100.6 MHz, d_4-MeOH) δ 167.6 (C=O), 153.2 (Ar), 148.3 (Ar), 138.9 (*ipso*-Ar), 135.3 (*ipso*-Ar), 124.7 (Ar), 53.0 (OMe), 18.1 (Me). Spectroscopic data consistent with those reported in the literature.[153]

Lab Book - PJ-04-79.

Methyl 3-methylpiperidine-4-carboxylate *cis*-198 and *trans*-198

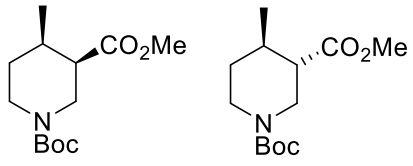


cis-**198** *trans*-**198**

Using general procedure B, PtO_2 (24 mg, 0.11 mmol, 10 mol%) and pyridine **197** (163 mg, 1.1 mmol, 1.0 eq) in AcOH (2 mL) gave the crude product which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of piperidines *cis*-**198** and *trans*-**198** (147 mg, 89%) as a colourless oil, IR (ATR) 3319 (NH), 2951, 1726 (C=O), 1434, 1269, 1171 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *cis*-**198** δ 3.66 (s, 3H, OMe), 3.07 (ddd, *J* = 12.5, 4.5, 4.5 Hz, 1H, NCH), 2.89-2.76 (m, 2H, NCH, $CHCO_2$), 2.64-2.56 (m, 2H, NCH), 2.26-2.19 (m, 0.15H, C*H*Me), 2.14-2.06 (m, 0.85H, C*H*Me), 1.79 (dddd, *J* = 14.5, 10.5, 10.5, 4.0 Hz, 1H, CH), 1.65-1.58 (m, 1H, CH), 1.53 (br s, 1H, NH), 0.94 (d, *J* = 7.0 Hz, 2.55H, CH*Me*), 0.82 (d, *J* = 7.5 Hz, 0.45H, CH*Me*).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1 (C=O), 52.0 (NCH_2), 51.5 (OMe), 45.4 (NCH_2), 44.7 (*C*HCO_2), 31.3 (*C*HMe), 24.5 (CH_2), 13.8 (CH*Me*); MS (ESI) *m/z* 158 $(M + H)^+$; HRMS *m/z* calcd for $C_8H_{16}NO_2$ $(M + H)^+$ 158.1176, found 158.1178 (–1.3 ppm error).

Lab Book - PJ-05-09.

1-*tert*-Butyl 3-methyl 4-methylpiperidine-1,3-dicarboxylate *cis*-199 and *trans*-199



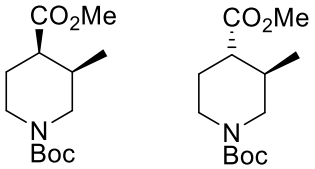
cis-**199** *trans*-**199**

Et_3N (0.14 mL, 0.98 mmol, 2.0 eq) was added dropwise to a stirred solution of a 65:35 mixture of piperidines *cis*-**196** and *trans*-**196** (77 mg, 0.49 mmol, 1.0 eq) and Boc_2O (214 mg, 0.98 mmol, 2.0 eq) in CH_2Cl_2 (5 mL) at rt under Ar. The reaction mixture was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude

product as an orange oil. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-Boc piperidine *trans*-**199** (28 mg, 22%) as a colourless oil, a 65:35 mixture of *N*-Boc piperidines *cis*-**199** and *trans*-**199** (22 mg, 18%) and a 90:10 mixture of *N*-Boc piperidines *cis*-**199** and *trans*-**199** (67 mg, 54%). The 65:35 and 90:10 mixtures of *N*-Boc piperidines *cis*-**199** and *trans*-**199** were combined and purified by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent to give a 65:35 mixture (by ^{1}H NMR spectroscopy) of *N*-Boc piperidines *cis*-**199** and *trans*-**199** (18 mg, 14%) as a colourless oil and *N*-Boc piperidine *cis*-**199** (59 mg, 47%) as a colourless oil, R_F (99:1 CH_2Cl_2-acetone) 0.18; IR (ATR) 2971, 1734 (C=O, CO_2Me), 1689 (C=O, Boc), 1422, 1365, 1163, 1138, 866 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (br s, 3H, OMe), 3.61-3.55 (m, 2H, NCH), 3.47-3.40 (m, 1H, NCH), 3.40-3.32 (m, 1H, NCH), 2.60-2.53 (m, 1H, $CHCO_2$), 2.19-2.10 (m, 1H, C*H*Me), 1.72-1.64 (m, 1H, CH), 1.61-1.54 (m, 1H, CH), 1.45 (s, 9H, CMe_3), 0.97 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.2 (C=O, CO_2Me), 154.5 (C=O, Boc), 79.6 (*C*Me_3), 51.6 (OMe), 44.7 (*C*HCO_2), 42.9 (CH_2), 40.5 (CH_2), 30.5 (*C*HMe), 30.3 (CH_2), 28.5 (C*Me*$_3$), 15.6 (CH*Me*); MS (ESI) *m/z* 280 (M + Na)$^+$; HRMS *m/z* calcd for $C_{13}H_{23}NO_4$ (M + Na)$^+$ 280.1519, found 280.1523 (–1.5 ppm error). Spectroscopic data for *N*-Boc piperidines *cis*-**199** consistent with those reported in the literature.[152]

Lab Book - PJ-05-15.

1-*tert*-Butyl 4-methyl 3-methylpiperidine-1,4-dicarboxylate *cis*-200 and *trans*-200



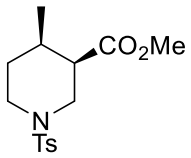
cis-**200** *trans*-**200**

Et_3N (0.16 mL, 1.16 mmol, 2.0 eq) was added dropwise to a stirred solution of an 85:15 mixture of piperidines *cis*-**198** and *trans*-**198** (91 mg, 0.58 mmol, 1.0 eq) and Boc_2O (252 mg, 1.16 mmol, 2.0 eq) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as a green oil. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-acetone as eluent gave an 65:35 mixture (by ^{1}H NMR spectroscopy) of *N*-Boc piperidines *cis*-**200** and *trans*-**200** (20 mg, 14%) as a colourless oil and *N*-Boc piperidine *cis*-**200** (73 mg, 49%) as a colourless oil, R_F (99:1 CH_2Cl_2-acetone) 0.14; IR (ATR) 2970, 1733

(C=O, CO_2Me), 1687 (C=O, Boc), 1425, 1161, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 4.12-3.97 (m, 0.6H, NCH), 3.97-3.83 (m, 0.4H, NCH), 3.81-3.72 (m, 1H, NCH), 3.67 (s, 1.8H, OMe), 3.67 (s, 1.2H, OMe), 3.09-3.01 (m, 1H, NCH), 3.00-2.88 (m, 0.4H, NCH), 2.88-2.77 (m, 0.6H, NCH), 2.59 (ddd, *J* = 10.5, 6.5, 3.0 Hz, 1H, $CHCO_2$), 2.18 (br m, 1H, C*H*Me), 1.89-1.76 (m, 1H, CH), 1.75-1.59 (m, 1H, CH), 1.44 (s, 5.4H, CMe_3), 1.43 (s, 3.6H, CMe_3), 0.88 (d, *J* = 7.0 Hz, 1.8H, CH*Me*), 0.87 (d, *J* = 7.0 Hz, 1.2H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 174.4 (C=O, CO_2Me), 155.3 (C=O, Boc), 79.6 (*C*Me_3), 51.7 (OMe), 49.6 (NCH_2), 48.3 (NCH_2), 44.7 ($CHCO_2$), 43.0 (NCH_2), 42.3 (NCH_2), 31.3 (*C*HMe), 28.5 (C*Me*$_3$), 23.4 (CH_2), 22.9 (CH_2), 13.2 (CH*Me*); MS (ESI) *m/z* 280 $(M + Na)^+$; HRMS *m/z* calcd for $C_{13}H_{23}NO_4$ $(M + Na)^+$ 280.1519, found 280.1517 (+0.6 ppm error).

Lab Book - PJ-05-21.

Methyl-4-methyl-1-tosyl piperidine-3-carboxylate 201



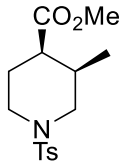
cis-**201**

HCl (0.78 mL of a 2 M solution in Et_2O, 1.56 mmol, 10.0 eq) was added dropwise to *N*-Boc piperidine *cis*-**199** (40 mg, 0.15 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the hydrochloride salt (33 mg). Et_3N (0.065 mL, 0.47 mmol, 3.0 eq) was added dropwise to a solution of the hydrochloride salt (33 mg, 0.95 mmol, 1.0 eq) and TsCl (6 mg, 0.052 mmol, 0.1 eq) in CH_2Cl_2 (5 mL) under Ar. The reaction mixture was stirred at rt for 16 h. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave *N*-tosyl piperidine *cis*-**201** (41 mg, 84%) as a white solid, mp 65-67 °C; R_F (0.12, 8:2 hexane-EtOAc); IR (ATR) 2929, 1726 (C=O),1340, 1161, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H, Ph), 7.32 (d, *J* = 8.0 Hz, 1H, Ph), 3.66 (s, 3H, OMe), 3.50 (ddd, *J* = 11.5, 3.0, 1.0 Hz, 1H, NCH), 3.31 (dddd, *J* = 11.5, 4.5, 4.5, 1.5 Hz, 1H, NCH), 2.86-2.73 (m, 2H, NCH and $CHCO_2$), 2.66 (ddd, *J* = 11.5, 11.5, 3.0 Hz, 1H, NCH), 2.43 (s, 3H, Ar*Me*), 2.26-2.17 (m, 1H, C*H*Me), 1.88-1.78 (m, 1H, CH),

1.70-1.62 (m, 1H, CH), 0.78 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C=O), 143.7 (*ispo*-Ph), 132.3 (*ipso*-Ph), 129.9 (Ph), 127.8 (Ph), 51.8 (OMe), 44.6 ($CHCO_2$), 43.3 (NCH_2), 42.0 (NCH_2), 30.7 (NCH_2), 28.7 (*C*HMe), 21.7 (Ph*Me*), 13.9 (CH*Me*); MS (ESI) *m/z* 334 $(M + Na)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_4S$ $(M + Na)^+$ 334.1083, found 334.1089 (–1.4 ppm error).

Lab Book - PJ-05-55.

Methyl-3-methyl-1-tosylpiperidine-4-carboxylate 202

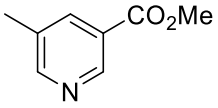


***cis*-202**

HCl (1.25 mL of a 2 M solution in Et_2O, 2.50 mmol, 10.0 eq) was added dropwise to *N*-Boc piperidine *cis*-**200** (64 mg, 0.25 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 32 h. Then, the solvent was evaporated under reduced pressure to give the hydrochloride salt. Et_3N (0.1 mL, 0.75 mmol, 3.0 eq) was added dropwise to a solution of the hydrochloride salt and TsCl (143 mg, 0.75 mmol, 3.0 eq) in CH_2Cl_2 (5 mL) under Ar. The reaction mixture was stirred at rt for 16 h. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave *N*-tosyl piperidine *cis*-**200** (60 mg, 77%) as a white solid, mp 76-80 °C; R_F (8:2 hexane-EtOAc) 0.17; IR (ATR) 2976, 1722 (C=O), 1288, 1158, 921, 545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.5 Hz, 2H, Ph), 7.30 (d, *J* = 8.0 Hz, 2H, Ph), 3.63 (s, 3H, OMe), 3.55-3.48 (m, 1H, NCH), 3.31 (dd, *J* = 11.5, 5.0 Hz, 1H, NCH), 2.68 (dd, *J* = 11.5, 3.5 Hz, 1H, NCH), 2.56 (ddd, *J* = 11.5, 10.0, 3.5 Hz, 1H, NCH), 2.44-2.38 (m, 4H, Ph*Me* and $CHCO_2$), 2.31-2.21 (m, 1H, C*H*Me), 1.97 (dddd, *J* = 14.0, 10.0, 10.0, 4.0 Hz, 1H, CH), 1.78 (dddd, *J* = 14.0, 5.0, 5.0, 3.5 Hz, 1H, CH), 0.98 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.9 (C=O), 143.6 (*ipso*-Ph), 133.4 (*ipso*-Ph), 129.8 (Ph), 127.7 (Ph), 51.8 (CO_2Me), 51.1 (NCH_2), 44.9 (NCH_2), 43.5 ($CHCO_2$), 31.0 (*C*HMe), 23.5 (CH_2), 21.7 (PhMe), 13.9 (CH*Me*); MS (ESI) *m/z* 334 $(M + Na)^+$; HRMS *m/z* calcd for 334.1083 $C_{15}H_{21}NO_4S$ $(M + Na)^+$, found 334.1087 (+0.1 ppm error).

Lab Book - PJ-05-70.

Methyl 3-methylpyridine-5-carboxylate 203

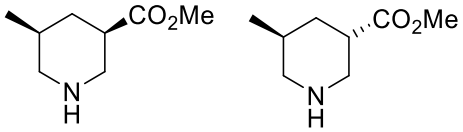


203

$SOCl_2$ (0.06 mL, 0.80 mmol, 1.1 eq) was added dropwise to a stirred solution of methyl 3-methylpyridine-5-carboxylate (100 mg, 0.73 mmol, 1.0 eq) in MeOH (5 mL) at 0 °C under Ar. The reaction mixture was warmed to rt and stirred and heated at reflux for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as an orange oil. The reaction mixture was poured into saturated $NaHCO_{3(aq)}$ (10 mL) and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give pyridine **203** (106 mg, 96%) as a white solid, mp 37-39 °C; IR (ATR) 2960, 1712 (C=O), 1574, 1293, 1108, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 2.0 Hz, 1H, Ph), 8.61 (d, *J* = 2.0 Hz, 1H, Ph), 8.13-8.09 (m, 1H, Ph), 3.95 (s, 3H, OMe), 2.40 (s, 3H, Me); ^{13}C NMR (100.6 MHz, d_4-MeOH) δ 166.9 (C=O), 154.3 (Ar), 148.2 (Ar), 139.1 (Ar), 135.7 (Ar), 127.5 (Ar), 52.9 (OMe), 18.2 (Me); MS (ESI) *m/z* 151 $(M + H)^+$; HRMS *m/z* calcd for $C_8H_9NO_2$ $(M + H)^+$ 152.0706, found 152.0702 (+2.7 ppm error). Spectroscopic data consistent with those reported in the literature.[154]

Lab Book - PJ-04-81.

Methyl 5-methylpiperidine-3-carboxylate *cis*-204 and *trans*-204



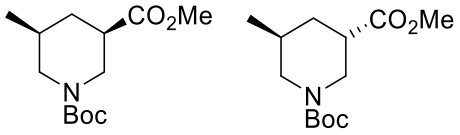
cis-**204** *trans*-**204**

Using general procedure B, 10% Pd/C (70 mg, 0.07 mmol, 10 mol%) and pyridine **203** (100 mg, 0.66 mmol, 1.0 eq) in AcOH (5 mL), gave the crude product which contained a 70:30 mixture (by ^1H NMR spectroscopy) of piperidines *trans*-**204** and *cis*-**204** (94 mg, 91%) as a colourless oil, IR (ATR) 2951, 1725 (C=O), 1435, 1198, 1177, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 2.1H, OMe), 3.65 (s, 0.9H, Ome), 3.30-3.23 (m, 1H, NCH), 2.97-2.90 (m, 1H, NCH), 2.73 (dd, *J* = 13.0, 3.5 Hz, 0.70H, NCH), 2.59-2.54 (m, 1H, $CHCO_2$), 2.51-2.43 (m, 0.3H, NCH), 2.24 (dd, *J* = 13.0, 10.0 Hz, 0.7H, NCH), 2.15-2.04 (m, 1.3H, NCH, CH), 1.69-1.57 (m, 0.7H, C*H*Me), 1.57-1.47 (m, 0.3H, C*H*Me), 1.39-1.30 (m, 0.7H, NCH), 1.17 (m, 0.3H, CH), 0.86 (d, *J* = 6.6 Hz, 0.9H, CH*Me*), 0.84 (d, *J* = 6.7 Hz, 2.1H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.4 (C=O), 174.7 (C=O), 53.8 (NCH_2), 53.7

(NCH_2), 51.8 (Ome), 51.7 (Ome), 48.3 (CH_2), 47.4 (CH_2), 43.4 (*C*HCO_2), 39.7 (*C*HCO_2), 36.2 (CH_2), 34.5 (CH_2), 31.8 (*C*HMe), 28.8 (*C*HMe), 19.5 (CH*Me*), 19.1 (CH*Me*); MS (ESI) *m/z* 158 $(M + H)^+$; HRMS *m/z* calcd for $C_8H_{16}NO_2$ $(M + H)^+$ 158.1176, found 158.1171 (–1.5 ppm error).
Lab Book - PJ-05-25.

Using general procedure B, PtO_2 (15 mg, 0.066 mmol, 10 mol%) and pyridine **203** (100 mg, 0.66 mmol, 1.0 eq) in AcOH (5 mL), gave the crude product which contained a 60:40 mixture (by ^{1}H NMR spectroscopy) of piperidines *trans*-**204** and *cis*-**204** (96 mg, 93%) as a colourless oil.
Lab Book - PJ-05-28.

1-*tert*-Butyl 3-methyl 5-methylpiperidine-1,3-dicarboxylate *cis*-205 and *trans*-205



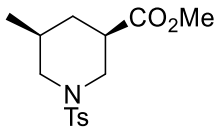
cis-**205** *trans*-**205**

A solution of Boc_2O (225 mg, 1.03 mmol, 3.0 eq) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of a 70:30 mixture of piperidines *trans*-**204** and *cis*-**204** (54 mg, 0.34 mmol, 1.0 eq), DMAP (4 mg, 0.034 mmol, 0.1 eq) and Et_3N (0.15 mL, 1.03 mmol, 3.0 eq) in CH_2Cl_2 (3 mL) at rt under Ar. The reaction mixture was stirred at rt for 16 h. Then, the reaction mixture was evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc piperidine *cis*-**205** (22 mg, 25%) as a colourless oil and *N*-Boc piperidine *trans*-**205** (49 mg, 56%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.16; IR (ATR) 2954, 1735 (C=O, CO_2Me), 1688 (C=O, Boc), 1422, 1160, 1136, 867 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 4.02-3.88 (br s, 0.4H, NCH), 3.66 (br, s, 3H, OMe), 3.73-3.55 (m, 1H, NCH), 3.43-3.33 (m, 0.6H, NCH), 3.33-3.22 (m, 0.6H, NCH), 3.13-2.99 (m, 0.4H, NCH), 2.78-2.68 (m, 1H, NCH), 2.68-2.58 (m, 1H, $CHCO_2$), 2.08-1.98 (m, 0.6H, CH), 1.98-1.84 (m, 1.4H, C*H*Me and CH), 1.43 (s, 10H, CH and CMe_3), 0.90 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 174.1 (C=O, CO_2Me), 154.8 (C=O, Boc), 79.6 (*C*Me_3), 51.8 (OMe), 50.5 (NCH_2), 49.7 (NCH_2), 45.4 (NCH_2), 45.1 (NCH_2), 38.8 (*C*HCO_2), 38.0 (*C*HCO_2), 33.9 (CH_2), 28.5 (C*Me*$_3$), 27.5 (*C*HMe), 18.2 (CH*Me*), 17.8

(CH*Me*); MS (ESI) *m/z* 258 $(M + H)^+$; HRMS *m/z* calcd for $C_{13}H_{23}NO_4$ $(M + H)^+$ 258.1700, found 258.1704 (–1.2 ppm error).

Lab Book - PJ-05-27.

Methyl 5-methyl-1-(4-methylbenzenesulfonyl)piperidine-3-carboxylate *cis*-206

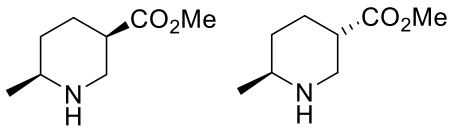


cis-**206**

HCl (0.88 mL of a 2 M solution in Et_2O, 1.75 mmol, 10.0 eq) was added dropwise to *N*-Boc piperidine *cis*-**205** (45 mg, 0.18 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 32 h. Then, the solvent was evaporated under reduced pressure to give the hydrochloride salt (32 mg). Et_3N (0.07 mL, 0.52 mmol, 3.0 eq) was added dropwise to a solution of the hydrochloride salt (32 mg) in CH_2Cl_2 (5 mL) at rt under Ar. The reaction mixture was stirred at rt for 30 min. TsCl (99 mg, 0.52 mmol, 3.0 eq) was then added dropwise to the reaction mixture which was stirred at rt for 16 h. The solution was poured into water (10 mL) and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL) and the combined organics were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-tosyl piperidine *cis*-**206** (37 mg, 68%) as a white solid, mp 84-86 °C; R_F (9:1 hexane-EtOAc) 0.08; IR (ATR) 2914, 1736 (C=O), 1335, 1150, 810, 548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H, Ph), 7.33 (d, *J* = 8.0 Hz, 2H, Ph), 4.06-4.00 (m, 1H, NCH), 3.77-3.71 (m, 1H, NCH), 3.67 (s, 3H, OMe), 2.68 (dddd, *J* = 11.5, 11.5, 4.0, 4.0 Hz, 1H, $CHCO_2$), 2.43 (s, 3H, Ph*Me*), 2.17 (dd, *J* = 11.5, 11.5 Hz, 1H, NCH), 2.00-2.07 (m, 1H, CH), 1.85-1.75 (m, 1H, C*H*Me), 1.72 (dd, *J* = 11.0, 11.0 Hz, 1H, NCH), 0.99-0.86 (m, 1H, CH), 0.89 (d, *J* = 6.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.4 (C=O), 143.8 (*ipso*-Ph), 133.2 (*ispo*-Ph), 129.9 (Ph), 127.8 (Ph), 52.8 (NCH_2), 52.1 (OMe), 47.4 (NCH_2), 41.5 (*C*HCO_2), 35.3 (CH_2), 30.5 (*C*HMe), 21.7 (Ph*Me*), 18.9 (CH*Me*); MS (ESI) *m/z* 334 $(M + Na)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_4S$ $(M + Na)^+$ 334.1083, found 334.1079 (–0.8 ppm error). Spectroscopic data consistent with those reported in the literature.[110]

Lab Book - PJ-05-46.

Methyl 2-methylpiperidine-5-carboxylate *cis*-126 and *trans*-126



cis-**126** *trans*-**126**

Table 3.2, Entry 1

NaOMe (21 mg, 0.38 mmol, 1.2 eq) was added to a stirred solution of an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** (50 mg, 0.32 mmol, 1.0 eq) in MeOH (5 mL) at rt under Ar. The resulting solution was stirred at rt for 96 h. The reaction mixture was evaporated under reduced pressure and water (2 mL) and sat $NaHCO_{3(aq)}$ (2 mL) were added. The mixture was extracted with CH_2Cl_2 (5 x 5 mL) and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give an 85:15 mixture (by ^{1}H NMR spectroscopy) of piperidines *cis*-**126** and *trans*-**126** (11 mg, 22%) as a colourless oil.
Lab Book - PJ-04-92.

Table 3.2, Entry 4

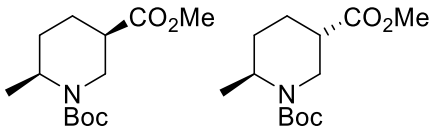
DBU (0.14 mL, 0.96 mmol, 3.0 eq) was added dropwise to a stirred solution of an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** (50 mg, 0.32 mmol, 1.0 eq) in toluene (5 mL) at rt under Ar. The resulting solution was stirred at 50 °C for 96 h. The reaction mixture was cooled to rt and evaporated under reduced pressure to give a colourless oil. Water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4) and evaporated under reduced pressure to give an 85:15 mixture (by ^{1}H NMR spectroscopy) of piperidines *cis*-**126** and *trans*-**126** (169 mg, impure) as an orange oil.
Lab Book - PJ-05-10.

Table 3.2, Entry 5

DBU (0.14 mL, 0.96 mmol, 3.0 eq) was added dropwise to a stirred solution of an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** (50 mg, 0.32 mmol, 1.0 eq) in toluene (5 mL) at rt under Ar. The resulting solution was stirred at 85 °C for 24 h. The reaction mixture was cooled to rt and evaporated under reduced pressure to give an 80:20 mixture (by ^{1}H NMR spectroscopy) of piperidines *cis*-**126** and *trans*-**126** (150 mg, impure) as a colourless oil.
Lab Book - PJ-05-18.

KO*t*Bu (0.38 mL of a 1 M solution in THF, 0.38 mmol, 1.2 eq) was added dropwise to a stirred solution of an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** (50 mg, 0.32 mmol, 1.0 eq) in THF (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 h. Then, water (1 mL) was added at –78 °C and the reaction mixture was allowed to warm to rt. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organics were dried (Na_2SO_4) and evaporated under reduced pressure to give an 80:20 mixture (by ^{1}H NMR spectroscopy) of piperidines *trans*-**126** and *cis*-**126** (16 mg, impure) as a colourless oil.
Lab Book - PJ-04-80.

1-*tert*-Butyl 3-methyl 6-methylpiperidine-1,3-dicarboxylate *trans*-157 and *cis*-157



cis-**157** *trans*-**157**

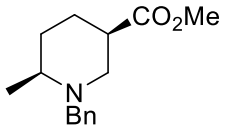
Table 3.2, Entry 2
NaOMe (62 mg, 1.15 mmol, 1.2 eq) was added to a stirred solution of an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** (150 mg, 0.96 mmol, 1.0 eq) in MeOH (9 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 24 h. The reaction mixture was cooled to rt and evaporated under reduced pressure to give the crude product as a white solid which contained a 70:30 mixture (by ^{1}H NMR spectroscopy) of piperidines *trans*-**126** and *cis*-**126**. The crude product was dissolved in CH_2Cl_2 (10 mL) and added to DMAP (59 mg, 0.48 mmol, 0.5 eq), Et_3N (0.4 mL, 2.87 mmol, 3.0 eq) and Boc_2O (627 mg, 2.88 mmol, 3.2 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. The reaction mixture was evaporated under reduced pressure to give the crude product as a yellow oil/solid. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-Boc piperidines *cis*-**157** (24 mg, 10%) as a colourless oil, a 70:30 mixture of *N*-Boc piperidine *trans*-**157** and *cis*-**157** (11 mg, 4%) as a colourless oil and *N*-Boc piperidine *trans*-**157** (66 mg, 27%) as a colourless oil.
Lab Book - PJ-04-57/58.

Table 3.2, Entry 3

K_2CO_3 (53 mg, 0.38 mmol, 1.2 eq) was added to a stirred solution of an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** (50 mg, 0.32 mmol, 1.0 eq) in MeOH (5 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 24 h. The reaction mixture was cooled to rt and evaporated under reduced pressure to give the crude product as a colourless oil which contained an 80:20 mixture (by ^{1}H NMR spectroscopy) of piperidines *trans*-**126** and *cis*-**126**. The crude product was dissolved in CH_2Cl_2 (5 mL) and added to a solution of DMAP (20 mg, 0.16 mmol, 0.5 eq), Et_3N (0.13 mL, 0.96 mmol, 3.0 eq) and Boc_2O (222 mg, 1.02 mmol, 3.2 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. The reaction mixture was evaporated under reduced pressure to give a yellow oil/solid. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-Boc piperidine *trans*-**157** (15 mg, 18%) as a colourless oil.

Lab Book - PJ-04-93/97.

Methyl 1-benzyl-6-methylpiperidine-3-carboxylate *cis*-208



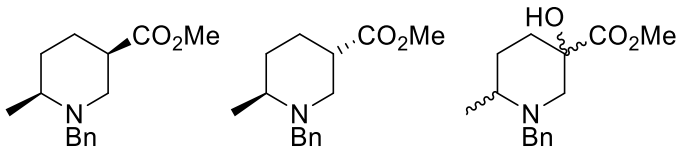
cis-**208**

BnBr (0.24 mL, 1.99 mmol, 1.2 eq) was added dropwise to a stirred solution of an 85:15 mixture of piperidines *cis*-**126** and *trans*-**126** (260 mg, 1.66 mmol, 1.0 eq) in saturated $Na_2CO_{3(aq)}$ (2 mL) and CH_2Cl_2 (2 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-benzyl piperidine *cis*-**208** (325 mg, 79%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.1; IR (ATR) 2947, 1732 (C=O), 1434, 1192, 1149, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H, Ph), 7.22 (m, 1H, Ph), 3.78 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.62 (s, 3H, OMe), 3.37 (d, *J* = 13.5 Hz, 1H, NCHPh), 2.83 (dd, *J* = 11.5, 7.5 Hz, 1H, NCH), 2.74-2.65 (m, 1H, NC*H*Me), 2.57-2.49 (m, 1H, $CHCO_2$), 2.44 (dd, *J* = 11.5, 4.0 Hz, 1H, NCH), 1.92-1.82 (m, 1H, CH), 1.74-1.63 (m, 2H, CH), 1.57 (m, 1H, CH), 1.06 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.9 (C=O), 139.8 (*ipso*-Ph), 128.8 (Ph), 128.2 (Ph), 126.9 (Ph), 58.7

(NCH_2Ph), 53.9 (N*C*HMe), 51.5 (OMe), 50.1 (NCH_2), 41.3 ($CHCO_2$), 31.1 (CH_2), 23.4 (CH-$_2$), 14.2 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{22}NO_2$ $(M + H)^+$ 248.1645, found 248.1636 (+4.1 ppm error) and *N*-benzyl piperidine *trans*-**208** (48 mg, 11%) as a colourless oil.

Lab Book - PJ-06-23.

Methyl 1-benzyl-6-methylpiperidine-3-carboxylate *cis*-208, *trans*-208 and methyl 1-benzyl-3-hydroxy-6-methylpiperidine-3-carboxylate 209



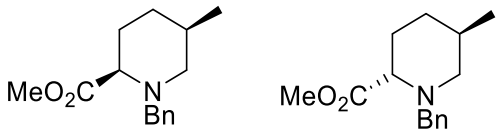
cis-**208** *trans*-**208** **209**

KO*t*Bu (0.24 mL of a 1 M solution in THF, 0.24 mmol, 1.2 eq) was added dropwise to a stirred solution of *N*-benzyl piperidine *cis*-**208** (50 mg, 0.20 mmol, 1.0 eq) in THF (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 h. Then, water (1 mL) was added at –78 °C and the reaction mixture was allowed to warm to rt. The reaction mixture was then concentrated under reduced pressure to give an orange oil. The solution was taken up into water (2 mL) and extracted with EtOAc (3 x 5 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a pale yellow oil which contained a 50:25:25 mixture (by ^{1}H NMR spectroscopy) of piperidines *trans*-**208**, *cis*-**208** and hydroxy ester **209**. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave *N*-benzyl piperidine *cis*-**208** (5 mg, 10%) as a colourless oil, *N*-benzyl piperidine *trans*-**208** (10 mg, 20%) as a colourless oil and a single unknown diastereoisomer of hydroxy ester **209** (5 mg, 8%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.04; IR (ATR) 3456 (OH), 2949, 1733 (C=O), 1451, 1373, 1223, 1027, 737, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 4H, Ph), 7.27-7.22 (m, 1H, Ph), 3.73 (s, 3H, OMe), 3.64 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.56 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.41 (br s, 1H, OH), 2.98-2.92 (m, 1H, NC*H*Me), 2.93 (d, *J* = 11.5 Hz, 1H, NCH), 2.38 (dd, *J* = 11.5, 2.0 Hz, 1H, NCH), 2.07-1.96 (m, 2H, CH), 1.69-1.62 (m, 1H, CH), 1.52-1.45 (m, 1H, CH), 1.07 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.3 (C=O), 138.9 (*ipso*-Ph), 128.9 (Ph), 128.5 (Ph), 127.3 (Ph), 72.9 (HOC), 58.7 (NCH_2Ph), 54.0 (NCH_2), 52.4 (OMe), 52.1 (N*C*HMe), 29.2 (CH_2), 27.6 (CH_2),

10.4 (CH*Me*); MS (ESI) *m/z* 264 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{22}NO_3$ $(M + H)^+$ 264.1594, found 264.1584 (+3.3 ppm error).
Lab Book - PJ-04-91.

Using general procedure E, *N*-benzyl piperidine *cis*-**208** (150 mg, 0.61 mmol, 1.0 eq) and. KO*t*Bu (0.73 mL of a 1 M solution in THF, 0.73 mmol, 1.2 eq) in THF (5 mL) gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of *N*-benzyl piperidines *trans*-**208** and *cis*-**208**. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave an 85:15 mixture of *N*-benzyl piperidine *cis*-**208** and *trans*-**208** (43 mg, 28%) as a colourless oil and *N*-benzyl piperidine *trans*-**208** (80 mg, 53%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.18; IR (ATR) 2947, 1732 (C=O), 1329, 1144, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.58 (s, 3H, OMe), 3.16 (d, *J* = 13.5 Hz, 1H, NCHPh), 2.98 (dd, *J* = 11.5, 3.5 Hz, 1H, NCH), 2.49 (dddd, *J* = 11.5, 11.5, 3.5, 3.5 Hz, 1H, $CHCO_2$), 2.28-2.19 (m, 1H, NC*H*Me), 2.04 (dd, *J* = 11.5, 11.5 Hz, 1H, NCH), 1.99-1.92 (m, 1H, CH), 1.74-1.68 (m, 1H, CH), 1.50 1.31 (m, 2H, CH), 1.18 (d, *J* = 6.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.0 (C=O), 139.2 (*ipso*-Ph), 129.1 (Ph), 128.3 (Ph), 126.9 (Ph), 57.9 (NCH_2Ph), 56.4 (NC*H*Me), 54.1 (NCH_2), 51.6 ($CHCO_2$), 42.2 (OMe), 34.0 (CH_2), 27.7 (CH_2), 20.7 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1638 (+2.3 ppm error).
Lab Book - PJ-06-25.

Methyl 1-benzyl-5-methylpiperidine-2-carboxylate *cis*-207 and *trans*-207

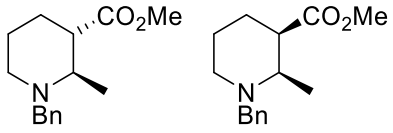


cis-**207** *trans*-**207**

Using general procedure E, *N*-benzyl piperidine *cis*-**207** (50 mg, 0.20 mmol, 1.0 eq) and KO*t*Bu (0.24 mL of a 1 M solution in THF, 0.24 mmol, 1.2 eq) in THF (3 mL) gave a 50:50 mixture (by ^{1}H NMR spectroscopy) of *N*-benzyl piperidines *trans*-**207** and *cis*-**207**. Purification by flash column chromatography on silica with 90:10 hexane-Et_2O as eluent gave *N*-benzyl piperidine *cis*-**207** (23 mg, 48%) as a colourless oil, R_F (90:10 hexane-Et_2O) 0.25; IR (ATR) 2950, 1734 (C=O), 1453, 1155, 1136, 735, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H, Ph), 7.26-7.21 (m, 1H, Ph), 3.82 (d, *J* = 13.5 Hz, 1H, NCHPh),

3.76 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.69 (s, 3H, OMe), 3.49 (dd, *J* = 5.5, 3.0 Hz, 1H, NCHCO$_2$), 2.65 (dd, *J* = 11.0, 11.0 Hz, 1H, NCH), 2.56 (dd, *J* = 11.0, 4.0 Hz, 1H, NCH), 2.00 (m, 1H, CH), 1.83 (dddd, *J* = 13.5, 13.5, 5.5, 4.0 Hz, 1H, CH), 1.71-1.62 (m, 1H, C*H*Me), 1.62-1.54 (m, 1H, CH), 1.10-0.98 (m, 1H, CH), 0.84 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.0 (C=O), 139.5 (*ipso*-Ph), 128.7 (Ph), 128.4 (Ph), 127.0 (Ph), 60.1 (N*C*HCO$_2$), 59.8 (NCH$_2$Ph), 54.9 (NCH$_2$), 51.1 (OMe), 30.9 (*C*HMe), 29.8 (CH$_2$), 28.3 (CH$_2$), 19.5 (CH*Me*); MS (ESI) *m/z* 248 (M + H)$^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ (M + H)$^+$ 248.1645, found 248.1648 (–0.9 ppm error) and *N*-benzyl piperidine *trans*-**207** (20 mg, 40%) as a colourless oil, R_F (90:10 hexane-Et$_2$O) 0.07; IR (ATR) 2927, 1746 (C=O), 1436, 1161, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 4H, Ph), 7.29-7.23 (m, 1H, Ph). 3.76 (d, *J* = 13.0 Hz, 1H, NCHPh), 3.75 (s, 3H, OMe), 3.21 (d, *J* = 13.0 Hz, 1H, NCHPh), 2.91 (dd, *J* = 11.0, 3.0 Hz, 1H, NCHCO$_2$), 2.83 (ddd, *J* = 11.0, 3.0, 1.5 Hz, 1H, NCH), 1.94-1.87 (m, 1H, CH), 1.81-1.70 (m, 2H, CH), 1.69-1.58 (m, 1H, C*H*Me), 1.55 (dd, *J* = 11.0, 11.0 Hz, 1H, NCH), 0.96-0.84 (m, 1H, CH), 0.79 (d, *J* = 6.5 Hz, 1H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.9 (C=O), 137.4 (*ipso*-Ph), 129.7 (Ph), 128.2 (Ph), 127.2 (Ph), 66.3 (N*C*HCO$_2$), 61.0 (NCH$_2$Ph), 59.3 (NCH$_2$), 52.1 (OMe), 32.1 (CH$_2$), 30.5 (*C*HMe), 30.1 (CH$_2$), 19.6 (CH*Me*); MS (ESI) *m/z* 248 (M + H)$^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ (M + H)$^+$ 248.1645, found 248.1647 (–0.6 ppm error).
Lab Book - PJ-05-32.

Methyl 1-benzyl-2-methylpiperidine-3-carboxylate *cis*-194 and *trans*-194



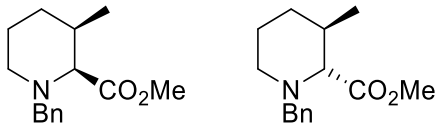
trans-**194** *cis*-**194**

Using general procedure E, a 90:10 mixture of *N*-Benzyl piperidine *cis*-**194** and *trans*-**194** (150 mg, 0.61 mmol, 1.0 eq) and KO*t*Bu (0.73 mL of a 1 M solution in THF, 0.73 mmol, 1.2 eq) in THF (5 mL) gave the crude product as an orange oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave an 80:20 mixture of *N*-benzyl piperidine *cis*-**194** and *trans*-**194** (61 mg, 41%) and *N*-benzyl piperidine *trans*-**194** (84 mg, 56%) as a colourless oil, R_F (80:20 hexane-Et$_2$O) 0.19; IR (ATR) 2943, 2795, 1732 (C=O), 1434, 1138, 732, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 4H, Ph), 7.24-7.20 (m, 1H, Ph), 3.95 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.67 (s, 3H, OMe), 3.25 (d, *J* =

13.5 Hz, 1H, NCHPh), 2.76-2.68 (m, 2H, NC*H*Me and NCH), 2.35 (ddd, *J* = 10.0, 9.0, 4.0 Hz, 1H, $CHCO_2$), 2.12-2.04 (m, 1H, NCH), 1.88-1.81 (m, 1H, CH), 1.65-1.56 (m, 2H, CH), 1.51-1.44 (m, 1H, CH), 1.15 (d, *J* = 6.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.7 (C=O), 139.5 (*ipso*-Ph), 129.0 (Ph), 128.3 (Ph), 126.9 (Ph), 57.6 (NCH_2Ph), 57.2 (*C*HMe), 51.7 (OMe), 51.2 (NCH_2), 49.5 (*C*HCO_2), 27.3 (CH_2), 24.0 (CH_2), 17.3 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1646 (-2.9 ppm error).

Lab Book - PJ-06-22.

Methyl 1-benzyl-3-methylpiperidine-2-carboxylate *cis*-123 and *trans*-123



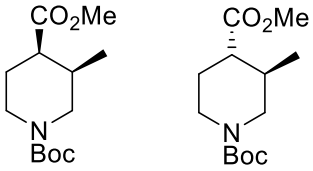
cis-**123** *trans*-**123**

PhCHO (0.36 mL, 3.5 mmol, 1.1 eq) was added dropwise to a stirred solution of an 85:15 mixture of piperidines *cis*-**116** and *trans*-**116** (500 mg, 3.18 mmol, 1.0 eq), $NaBH(OAc)_3$ (1.35 g, 6.37 mmol, 2 eq) and AcOH (0.03 mL, 0.64 mmol, 0.2 eq) in DCE (30 mL) at rt under Ar. The resulting mixture was stirred at rt for 18 h. The reaction mixture was poured into sat $NaHCO_{3(aq)}$ (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a green oil which contained a 90:10 mixture (by ^1H NMR spectroscopy) of piperidines *cis*-**123** and *trans*-**123**. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave *N*-benzyl piperidine *cis*-**123** (626 mg, 80%) as a yellow oil, R_F (95:5 hexane-EtOAc) 0.23; IR (ATR) 2928, 1728 (C=O), 1453, 1148, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 4H, Ph), 7.25-7.22 (m, 1H, Ph), 3.69 (s, 3H, OMe), 3.61 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.56 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.45 (d, *J* = 5.0 Hz, 1H, $NCHCO_2$), 3.00-2.92 (m, 1H, NCH), 2.54-2.45 (m, 1H, NCH), 2.03-1.93 (m, 1H, C*H*Me), 1.71-1.64 (m, 1H, CH), 1.60-1.46 (m, 3H, CH), 0.90 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0 (C=O), 139.1 (*ipso*-Ph), 128.9 (Ph), 128.3 (Ph), 127.1 (Ph), 66.2 (N*C*HCO_2), 60.2 (NCH_2Ph), 50.5 (OMe), 47.0 (NCH_2), 33.2 (*C*HMe), 27.8 (CH_2), 25.2 (CH_2), 18.2 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1643 (–0.7 ppm error) and piperidine *trans*-**123** (82 mg, 10%) as a yellow oil, R_F (95:5 hexane-EtOAc) 0.1; IR (ATR)

2928, 1727 (C=O), 1453, 1147, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 4H, Ph), 7.26-7.22 (m, 1H, Ph), 3.76 (s, 3H, OMe), 3.71 (d, *J* = 13.5 Hz, 1H, NCHPh), 3.25 (d, *J* = 13.5 Hz, 1H, NCHPh), 2.87 (ddd, *J* = 11.0, 5.5, 5.5 Hz, 1H, NCH), 2.64 (d, *J* = 9.0 Hz, 1H, $NCHCO_2$), 1.95-1.86 (m, 2H, CH), 1.76-1.68 (m, 1H, CH), 1.61-1.53 (m, 2H, CH), 1.05-0.94 (m, 1H, CH), 0.90 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.3 (C=O), 137.7 (*ipso*-Ph), 129.6 (Ph), 128.3 (Ph), 127.2 (Ph), 73.7 ($NCHCO_2$), 61.2 (NCH_2Ph), 51.8 (OMe), 51.3 (NCH_2), 34.4 (*C*HMe), 32.0 (CH_2), 24.6 (CH_2), 18.9 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1641 (+1.3 ppm error).Spectroscopic data for *N*-benzyl piperidines *cis*-**123** and *trans*-**123** consistent with those reported in the literature.[79]
Lab Book - PJ-02-45.

Using general procedure E, *N*-benzyl piperidine *cis*-**123** (173 mg, 0.70 mmol, 1.0 eq) and KO*t*Bu (0.84 mL of a 1 M solution in THF, 0.84 mmol, 1.2 eq) in THF (5 mL) gave a 70:30 mixture (by ^1H NMR spectroscopy) of *N*-benzyl piperidines *trans*-**123** and *cis*-**123**. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave *N*-benzyl piperidine *cis*-**123** (40 mg, 23%) as a colourless oil and *N*-benzyl piperidine *trans*-**123** (104 mg, 60%) as a colourless oil.
Lab Book - PJ-06-08.

1-*tert*-Butyl 4-methyl 3-methylpiperidine-1,4-dicarboxylate *cis*-200 and *trans*-200



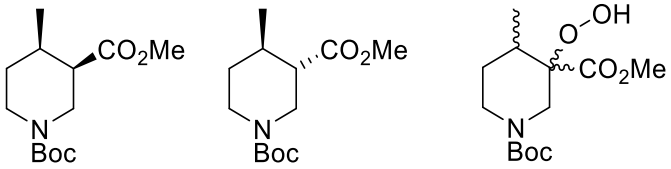
cis-**200** *trans*-**200**

Et_3N (0.16 mL, 1.16 mmol, 2.0 eq) was added dropwise to a stirred solution of an 85:15 mixture of piperidines *cis*-**198** and *trans*-**198** (91 mg, 0.58 mmol, 1.0 eq) and Boc_2O (253 mg, 1.16 mmol, 2.0 eq) in CH_2Cl_2 (5 mL) at rt under Ar. The reaction mixture was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as a green oil. Purification by flash column chromatography on silica with 90:10 hexane-Et_2O as eluent gave a 90:10 mixture (by ^1H NMR spectroscopy) of *N*-Boc piperidines *cis*-**200** and *trans*-**200** (117 mg, 78%) as a colourless oil.

Lab Book - PJ-04-100.

Using general procedure E, a 90:10 mixture of *N*-Boc piperidines *cis*-**200** and *trans*-**200** (50 mg, 0.19 mmol, 1.0 eq) and KO*t*Bu (0.23 mL of a 1 M solution in THF, 0.23 mmol, 1.2 eq) in THF (5 mL) gave a 90:10 mixture (by ^{1}H NMR spectroscopy) of *N*-Boc piperidine *trans*-**200** and *cis*-**200** (45 mg, 0.17 mmol, 90%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.14; IR (ATR) 2931, 1735 (C=O, CO_2Me), 1689 (C=O, Boc), 1420, 1158, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *trans*-**200**; δ 4.17-3.92 (m, 2H, NCH), 3.68 (s, 3H, OMe), 2.73-2.63 (m, 1H, NCH), 2.41-2.24 (m, 1H, NCH), 2.08 (ddd, *J* = 12.0, 11.0, 4.0 Hz, 1H, $CHCO_2$), 1.87-1.75 (m, 2H, CH and C*H*Me), 1.69-1.57 (dddd, *J* = 12.5, 12.5, 12.5, 4.5 Hz, 1H, CH), 1.45 (s, 9H, CMe_3), 0.87 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *trans*-**200**; δ 175.3 (C=O, CO_2Me), 154.7 (C=O, Boc), 79.8 (*C*Me_3), 51.8 (OMe), 50.0 (NCH_2), 49.5 (*C*HCO_2), 43.2 (NCH_2), 33.1 (C*H*Me), 28.8 (CH_2), 28.6 (C*Me*$_3$), 17.1 (CH*Me*); MS (ESI) *m/z* 280 $(M + Na)^+$; HRMS *m/z* calcd for $C_{13}H_{23}NO_4$ $(M + Na)^+$ 280.1519, found 280.1523 (–1.7 ppm error).
Lab Book - PJ-05-17.

1-*tert*-Butyl 3-methyl 4-methylpiperidine-1,3-dicarboxylate *trans*-199, *cis*-199 and 3-methyl 3-hydroperoxy-4-methylpiperidine-1,3-dicarboxylate 215



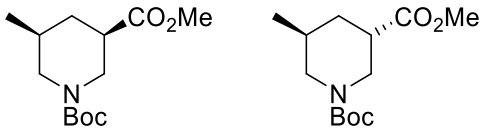
cis-**199** *trans*-**199** **215**

Et_3N (0.94 mL, 6.78 mmol, 2.0 eq) was added dropwise to a stirred solution of a 65:35 mixture of piperidines *cis*-**196** and *trans*-**196** (533 mg, 3.39 mmol, 1.0 eq) and Boc_2O (1.5 g, 6.78 mmol, 2.0 eq) in CH_2Cl_2 (10 mL) at rt under Ar. The reaction mixture was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave a 65:35 mixture of Boc piperidines *cis*-**199** and *trans*-**199** (740 mg, 84%) as a colourless oil.
Lab Book - PJ-04-71.

Using general procedure E, a 65:35 mixture of *N*-Boc piperidines *cis*-**199** and *trans*-**199** (150 mg, 0.58 mmol, 1.0 eq) and KO*t*Bu (0.47 mL of a 1 M solution in THF, 0.47 mmol, 1.2 eq) in THF (9 mL) gave the crude product as an orange oil. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave Boc piperidine *trans*-**199** (68 mg, 68%) as a colourless oil, R_F (90:10 hexane-Et_2O) 0.19; IR (ATR) 2930, 1733 (C=O, CO_2Me), 1692 (C=O, Boc), 1419, 1241, 1145, 963 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32-3.98 (m, 2H, NCH), 3.68 (s, 3H, OMe), 2.86-2.61 (m, 2H, NCH and $CHCO_2$), 2.14-2.05 (m, 1H, NCH), 1.86-1.73 (m, 1H, C*H*Me), 1.71-1.58 (m, 1H, CH), 1.44 (s, 9H, CMe_3), 1.20-1.05 (m, 1H, CH), 0.92 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.1 (C=O, CO_2Me), 154.6 (C=O, Boc), 79.9 (*C*Me_3), 51.7 (OMe), 49.8 (*C*HCO_2), 46.2 (NCH_2), 44.0 (CH_2), 33.7 (C*H*Me), 33.0 (CH_2), 28.5 (C*Me*$_3$), 20.1 (CH*Me*); MS (ESI) *m/z* 280 $(M + H)^+$; HRMS *m/z* calcd for $C_8H_{15}NO_2$ $(M + H)^+$ 280.1519, found 280.1519 (+0.3 ppm error) and a 70:30 mixture of diastereotopic peroxides **215** (8 mg, 7%) as a colourless oil, R_F (90:10 hexane-Et_2O) 0.14; IR (ATR) 2975, 1740 (C=O, CO_2Me), 1654 (C=O, Boc), 1428, 1274, 1147, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) **215** δ 10.81 (s, 1H, OOH), 10.68 (s, 0.3H), 4.44 (dd, *J* = 15.0, 2.0 Hz, 0.3H, NCH), 4.33 (d, *J* = 15.0 Hz, 1H, NCH), 3.83-3.76 (m, 1H, NCH), 3.81 (s, 0.9H, CO_2Me), 3.79 (s, 3H, OMe), 3.23 (d, *J* = 15.0 Hz, 1H, NCH), 3.17 (d, *J* = 15.0 Hz, 0.3H, NCH), 2.96 (ddd, *J* = 13.5, 13.5, 3.0 Hz, 1H, NCH), 2.87 (ddd, *J* = 13.5, 13.5, 3.0 Hz, 0.3H, NCH), 2.22-2.11 (m, 1H, C*H*Me), 2.07-2.00 (m, 0.3H, CH), 1.89 (dddd, *J* = 13.5, 13.5, 5.0, 5.0 Hz, 1H, CH), 1.48 (s, 9H, CMe_3) 1.19-1.13 (m, 1H, CH), 0.98 (d, *J* = 7.5 Hz, 3H, CH*Me*), 0.94 (d, *J* = 7.0 Hz, 0.9H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5 (C=O, CO_2Me), 158.5 (C=O, Boc), 86.0 (HOOC), 81.4 (*C*Me_3), 52.4 (OMe), 41.9 (NCH_2), 41.2 (NCH_2), 32.2 (*C*HMe), 28.5 (C*Me*$_3$), 27.3 (CH_2), 15.0 (CH*Me*); MS (ESI) *m/z* 290 $(M + H)^+$; HRMS *m/z* calcd for $C_{13}H_{24}NO_6$ $(M + H)^+$ 290.1598, found 290.1598 (–1.2 ppm error).

Lab Book - PJ-05-26.

1-*tert*-Butyl 3-methyl 5-methylpiperidine-1,3-dicarboxylate *cis*-205 and *trans*-205

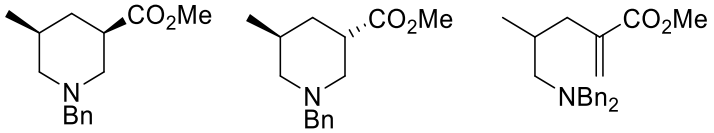


cis-**205** *trans*-**205**

A 70:30 mixture of piperidines *trans*-**205** and *cis*-**205** (100 mg, 0.38 mmol, 1.0 eq) was added to a flask containing dry THF (5 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and the solution was cooled to –78 °C. KO*t*Bu (0.47 mL of a 1 M solution in THF, 0.47 mmol, 1.2 eq) was added dropwise. The resulting solution was stirred at –78 °C for 2 h. Then, water (1 mL) was added at –78 °C and the reaction mixture was allowed to warm to rt. The mixture was extracted with EtOAc (3 x 5 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give a 75:25 mixture (by ^{1}H NMR spectroscopy) of *N*-Boc piperidines *cis*-**205** and *trans*-**205** (30 mg, 30%).

Lab Book - PJ-05-74.

Methyl 1-benzyl-5-methylpiperidine-3-carboxylate *cis*-216, *trans*-216 and 217



cis-**216** *trans*-**216** **217**

BnBr (0.16 mL, 1.35 mmol, 3.0 eq) was added dropwise to a 70:30 solution of piperidine *trans*-**204** and *cis*-**204** (70 mg, 0.45 mmol, 1.0 eq) in CH_2Cl_2:$Na_2CO_{3(aq)}$ (1:1, 4 mL) at rt under Ar. The resulting solution was stirred at rt for 72 h. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-benzyl **217** (12 mg, 8%) as a yellow oil, R_F (90:10 hexane-EtOAc) 0.34; IR (ATR) 3027, 295, 1719 (C=O), 1214, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 4H, Ph), 7.32-7.26 (m, 4H, Ph), 7.23-7.18 (m, 2H, Ph), 6.13 (d, *J* = 1.5 Hz, 1H, CH), 5.40 (s, 1H, CH), 3.68 (s, 3H, CO_2Me), 3.56 (d, *J* = 13.5 Hz, 2H, CHPh), 3.46 (d, *J* = 13.5 Hz, 2H, CHPh), 2.72 (dd, *J* = 13.0, 4.0 Hz, 1H, NCH), 2.20 (m, 2H, CH_2), 2.01-1.91 (m, 1H, C*H*Me), 1.71 (dd, *J* = 13.0, 9.5 Hz, 1H, NCH), 0.79 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6

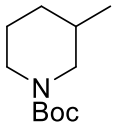
MHz, $CDCl_3$) δ 168.0 (C=O), 139.9 (*ipso*-Ph) 139.6 ($C=CH_2$), 129.0 (Ph), 128.2 (Ph), 126.9 (Ph), 126.4 (CH_2) 60.6 (CH_2Ph), 58.8 (NCH_2), 51.8 (OMe), 37.8 (CH_2), 30.2 (*C*HMe), 17.8 (CH*Me*); MS (ESI) *m/z* 338 $(M + H)^+$; HRMS *m/z* calcd for $C_{22}H_{28}NO_2$ $(M + H)^+$ 338.2115, found 338.2115 (0.2 ppm error) and *N*-benzyl piperidine *trans*-**216** (28 mg, 25%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.14; IR (ATR) 2949, 1732 (C=O), 1453, 1199, 1150, 697 cm^{-1}; ^1H NMR (400 MHz,) δ 7.31-7.28 (m, 4H, Ph), 7.25-7.22 (m, 1H, Ph), 3.67 (s, 3H, CO_2Me), 3.56 (d, *J* = 13.5 Hz, 1H, CHPh), 3.39 (d, *J* = 13.5 Hz, 1H, CHPh), 2.96-2.88 (m, 1H, NCH), 2.69-2.63 (m, 1H, $CHCO_2$), 2.63-2.57 (m, 1H, NCH), 2.31-2.23 (m, 1H, NCH), 2.06-1.94 (m, 2H, C*H*Me and CH), 1.91-1.83 (m, 1H, NCH), 1.24-1.14 (m, 1H, CH), 0.92 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.9 (C=O), 138.8 (*ipso*-Ph), 128.9 (Ph), 128.2 (Ph), 127.0 (Ph), 63.1 (CH_2Ph), 61.3 (NCH_2), 54.9 (NCH_2), 51.6 (OMe), 39.7 (*C*HCO_2), 33.4 (CH_2), 28.1 (*C*HMe), 19.2 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{22}NO_2$ $(M + H)^+$ 248.1645, found 248.1646 (–0.9 ppm error). Lab Book - PJ-06-04.

Pd/C (450 mg, 10 mol%) was added to a stirred solution of pyridine ester (600 mg, 4.0 mmol, 1.0 eq) in AcOH (30 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. After the final evacuation, H_2 was charged and the reaction mixture was stirred vigorously under a balloon of H_2 for 16 h. The solids were removed by filtration through Celite and washed with MeOH (30 mL). The filtrate was evaporated under reduced pressure to give the crude product. The crude product was dissolved in 1:1 CH_2Cl_2-sat $Na_2CO_{3(aq)}$ (12 mL) and BnBr (1.4 mL, 12.0 mmol, 3.0 eq) was added dropwise at rt under Ar. The resulting solution was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-benzyl piperidine *trans*-**216** (590 mg, 60%) as a colourless oil and *N*-benzyl piperidine *cis*-**216** (88 mg, 9%) as a yellow oil, R_F (90:10 hexane-EtOAc) 0.05; IR (ATR) 2951, 1732 (C=O), 1434, 1136, 1154, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.29 (m, 4H, Ph), 7.280-7.24 (m, 1H, Ph), 3.64 (s, 3H, OMe), 3.52 (s, 2H, CHPh), 3.12-3.06 (m, 1H, NCH), 2.84-2.79 (m, 1H, NCH), 2.64 (dddd, *J* = 12.0, 12.0, 4.0, 4.0 Hz, 1H, $CHCO_2$), 2.04-1.98 (m, 1H, CH), 1.95 (dd, *J* = 12.0, 12.0 Hz, 1H, NCH), 1.78-1.66 (m, 1H, C*H*Me), 1.55 (d, *J* = 12.0, 4.0 Hz, 1H, NCH), 1.02 (ddd, *J* = 12.0,

12.0, 12.0 Hz, 1H, CH), 0.87 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.9 (C=O), 140.1 (*ipso*-Ph), 129.2 (Ph), 128.4 (Ph), 127.1 (Ph), 63.2 (CH_2Ph), 61.2 (NCH_2), 55.1 (NCH_2), 51.7 (OMe), 42.3 ($CHCO_2$), 35.9 (CH_2), 30.6 (*C*HMe), 19.5 (CH*Me*); MS (ESI) *m/z* 248 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{21}NO_2$ $(M + H)^+$ 248.1645, found 248.1647 (–1.1 ppm error).
Lab Book - PJ-06-10.

Using general procedure E, *N*-benzyl piperidine *trans*-**216** (150 mg, 0.61 mmol, 1.0 eq) and KO*t*Bu (0.73 mL of a 1 M solution in THF, 0.73 mmol, 1.2 eq) in THF (5 mL) gave a crude 85:15 mixture (by ^{1}H NMR spectroscopy) of *N*-benzyl piperidines *cis*-**216** and *trans*-**216** (149 mg). Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-benzyl piperidine *cis*-**216** (93 mg, 62%) as a yellow oil.
Lab Book - PJ-06-16.

***tert*-Butyl 3-methylpiperidine-1-carboxylate 221**



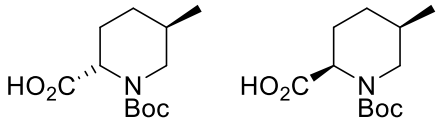
221

A solution of Boc_2O (1.3 g, 6.0 mmol, 1.2 eq) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of piperidines (0.59 mL, 5.0 mmol, 1.0 eq), and Et_3N (2.1 mL, 15.0 mmol, 3.0 eq) in CH_2Cl_2 (15 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the reaction mixture was evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 99:1 hexane-EtOAc as eluent gave *N*-Boc piperidine **221** (975 mg, 98%) as a colourless oil, R_F (99:1 hexane-EtOAc) 0.1; IR (ATR) 2959, 1690 (C=O), 1416, 1149, 1075, 969 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07-3.74 (m, 2H, NCH), 2.68 (ddd, *J* = 13.0, 11.5, 3.0 Hz, 1H, NCH), 2.49-2.21 (m, 1H, CH), 1.80-1.71 (m, 1H, CH), 1.68-1.50 (m, 2H, NCH and C*H*Me), 1.45 (s, 9H, CMe_3), 1.43-1.35 (m, 1H, CH), 1.09-0.97 (m, 1H, CH), 0.86 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1 (C=O), 79.3 (*C*Me_3), 51.5 (NCH_2), 50.8 (NCH_2), 44.5 (NCH_2), 43.8 (NCH_2), 33.1 (CH_2), 31.1 (*C*HMe), 28.6 (C*Me*$_3$), 25.3 (CH_2), 19.1 (CH*Me*); MS (ESI) *m/z* 222 $(M + Na)^+$; HRMS *m/z* calcd for $C_{11}H_{21}NO_2$ $(M + Na)^+$

222.1464, found 222.1471 (–3.8 ppm error). Spectroscopic data consistent with those reported in the literature.[155]

Lab Book - PJ-05-79.

1-(*tert*-butoxycarbonyl)-5-Methylpiperidine-2-carboxylic acid *trans*-222 and *cis*-222



trans-**222** *cis*-**222**

Table 3.4, Entry 1

s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq) was added drop wise to a stirred solution of *N*-Boc piperidine **221** (199 mg, 1.0 mmol, 1.0 eq) and TMEDA (0.19 mL, 1.3 mmol, 1.3 eq) in Et_2O (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Then, CO_2 (excess) was bubbled through the reaction mixture at –78 °C for 10 min. 1 M $HCl_{(aq)}$ (10 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 98:2 CH_2Cl_2-acetic acid as eluent gave a 90:10 mixture of piperidine carboxylic acid *trans*-**222** and *cis*-**222** (71 mg, 29%) as a white solid and *N*-Boc piperidine (85 mg, 42%) as a colourless oil.

Lab Book - PJ-05-85.

Table 3.4, Entry 2

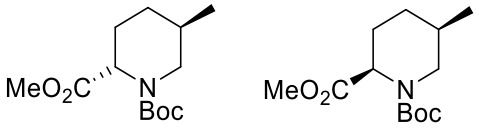
s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq) was added drop wise to a stirred solution of *N*-Boc piperidine **221** (199 mg, 1.0 mmol, 1.0 eq) and TMEDA (0.19 mL, 1.3 mmol, 1.3 eq) in Et_2O (4 mL) at –60 °C under Ar. The resulting solution was stirred at –60 °C for 3 h. Then, CO_2 (excess) was bubbled through the reaction mixture at –60 °C for 10 min. 1 M $HCl_{(aq)}$ (10 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 99:1 to 99:2 CH_2Cl_2-acetic acid as eluent gave a 90:10 mixture of piperidine carboxylic acid *trans*-**222** and *cis*-**222** (140 mg, 57 %) as a white solid, m.p 99-101 °C; R_F (95:5 CH_2Cl_2-AcOH) 0.22; IR (ATR) 2936, 1725 (C=O, CO_2H), 1622 (C=O, Boc), 1438, 1365, 1151, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *trans*-**222**: δ 11.56-10.82 (m, 1H, CO_2H), 4.97-4.51 (m, 1H,

NCHCO$_2$), 3.69-3.45 (m, 1H, NCH), 3.18 (dd, *J* = 13.0, 3.0 Hz, 1H, NCH), 1.97-1.93 (m, 2H, CH$_2$), 1.92-1.82 (m, 1H, C*H*Me), 1.68-1.54 (m, 1H, CH), 1.53-1.34 (m, 10H, CMe$_3$ and CH), 0.97 (d, *J* = 7.0 Hz, 2.7H, CH*Me*); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 178.0 (C=O, CO$_2$H), 156.5 (C=O, Boc), 80.5 (*C*Me$_3$), 53.9 (NCHCO$_2$), 47.5 (NCH$_2$), 28.4 (C*Me*$_3$), 27.1 (*C*HMe), 27.0 (CH$_2$), 21.6 (CH$_2$), 16.7 (CH*Me*); MS (ESI) *m/z* 266 (M + Na)$^+$; HRMS *m/z* calcd for C$_{12}$H$_{21}$NO$_4$ (M + Na)$^+$ 266.1363, found 266.1367 (–3.8 ppm error). Spectroscopic data consistent with those reported in the literature.[112]
Lab Book - PJ-05-90.

Table 3.4, Entry 3
s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq) was added drop wise to a stirred solution of *N*-Boc piperidine **221** (199 mg, 1.0 mmol, 1.0 eq) and TMEDA (0.19 mL, 1.3 mmol, 1.3 eq) in Et$_2$O (4 mL) at –40 °C under Ar. The resulting solution was stirred at –40 °C for 3 h. Then, CO$_2$ (excess) was bubbled through the reaction mixture at –40 °C for 10 min. 1 M HCl$_{(aq)}$ (10 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 99:1 to 99:2 CH$_2$Cl$_2$-acetic acid as eluent gave 3-methyl piperidine (69 mg, 35%) as a yellow oil and a 90:10 mixture of piperidine carboxylic acid *trans*-**222** and *cis*-**222** (70 mg, 29%) as a white solid.
Lab Book - PJ-05-93.

Table 3.4, Entry 4
s-BuLi (1.0 mL of a 1.3 M solution in hexane, 1.3 mmol, 1.3 eq) was added drop wise to a stirred solution of *N*-Boc piperidine **221** (199 mg, 1.0 mmol, 1.0 eq) and TMEDA (0.19 mL, 1.3 mmol, 1.3 eq) in Et$_2$O (4 mL) at –60 °C under Ar. The resulting solution was stirred at –60 °C for 6 h. Then, CO$_2$ (excess) was bubbled through the reaction mixture at –60 °C for 10 min. 1 M HCl$_{(aq)}$ (10 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 99:1 to 99:2 CH$_2$Cl$_2$-acetic acid as eluent gave a 90:10 mixture of piperidine carboxylic acid *trans*-**222** and *cis*-**222** (140 mg, 56 %) as a white solid.
Lab Book - PJ-05-97.

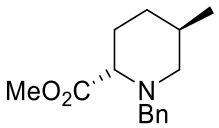
1-(*tert*-butyl) 2-Methyl-5-methylpiperidine-1,2-dicarboxylate *trans*-189 and *cis*-189



trans-**189** *cis*-**189**

Potassium carbonate (86 mg, 0.62 mmol, 3.0 eq) was added to a stirred solution of *N*-Boc piperidine carboxylic acid **222** (50 mg, 0.21 mmol, 1.0 eq) in dimethylformamide (3 mL) at rt. The resulting suspension was stirred at rt for 30 min before the addition of methyl iodide (0.038 mL, 0.62 mmol, 3.0 eq). The mixture was then stirred at rt for 18 h. The reaction mixture was taken up into water (3 mL) and extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with brine (4 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 90:10 hexane-EtOH as eluent gave a 90:10 mixture of piperidine ester *trans*-**189** and *cis*-**189** (47 mg, 87%) as a yellow oil, R_F (90:10, hexane-EtOH) 0.17; IR (ATR) 2940, 1743 (C=O, CO_2Me), 1690 (C=O, Boc), 1363, 1147, 864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.86-4.59 (m, 1H, $NCHCO_2$), 3.72 (s, 3H, OMe), 3.64-3.55 (m, 1H, NCH), 3.20-3.11 (m, 1H, NCH), 1.97-1.90 (m, 2H, CH), 1.90-1.83 (m, 1H, C*H*Me), 1.59-1.50 (m, 1H, CH), 1.44 (s, 9H, CMe_3), 1.41-1.32 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.7 (C=O, CO_2Me), 156.3 (C=O, Boc), 80.1 (*C*Me_3), 54.5 ($NCHCO_2$), 52.2 (OMe), 47.3 (NCH_2), 28.4 (C*Me*$_3$), 27.2 (*C*HMe), 27.1 (CH_2), 21.8 (CH_2), 16.7 (CH*Me*); MS (ESI) *m/z* 280 $(M + Na)^+$; HRMS *m/z* calcd for $C_{13}H_{23}NO_4$ $(M + Na)^+$ 280.1519, found 280.1525 (–2.0 ppm error).
Lab Book - PJ-05-95.

Methyl-1-benzyl-5-methylpiperidine-2-carboxylate *trans*-207

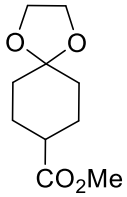


trans-**207**

TFA (1 mL) was added to a stirred solution of a 90:10 mixture of piperidine ester *trans*-**189** and *cis*-**189** (47 mg, 0.18 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) at 0 °C under Ar. The resulting solution was warmed to rt and stirred for 3 h at rt, then evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL) and sat $Na_2CO_{3(aq)}$ (2 mL) and benzyl bromide

(0.06 mL, 0.54 mmol, 3.0 eq) were added. The resulting mixture was stirred at rt for 16 h. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-benzyl piperidine *cis*-**207** (4 mg, 7%) as a colourless oil and *N*-benzyl piperidine *trans*-**207** (38 mg, 85%) as a colourless oil.
Lab Book - PJ-05-98.

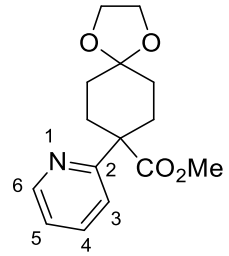
Methyl 1,4-dioxaspiro[4.5]decane-8-carboxylate 236



236

Ethylene glycol (1.14 mL, 20.4 mmol, 3.5 eq) was added dropwise to a stirred solution of methyl 4-oxocyclohexanecarboxylate (910 mg, 5.83 mmol, 1.0 eq) and *p*-TsOH (111 mg, 0.53 mmol, 0.1 eq) in dry toluene (30 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Et_2O (30 mL) was added and the combined organics were washed with water (20 mL) and sat $NaHCO_{3(aq)}$ (20 mL), dried (Na_2CO_3) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave ketal **236** (954 mg, 81%) as a colourless oil, R_F (80:20 hexane-Et_2O) 0.21; IR (ATR) 2950, 1730 (C=O), 1098, 923 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 4H, OCH_2), 3.66 (s, 3H, OMe), 2.34 (tt, *J* = 10.5, 4.0 Hz, 1H, CH), 1.97-1.87 (m, 2H, CH), 1.85-1.72 (m, 4H, CH), 1.54 (ddd, *J* = 13.0, 13.0, 4.5 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.8 (C=O), 108.2 (OCO), 64.4 (OCH_2), 51.7 (OMe), 41.6 (CH), 33.8 (CH_2), 26.4 (CH_2); MS (ESI) *m/z* 223 $(M + Na)^+$; HRMS *m/z* calcd for $C_{10}H_{16}O_4$ $(M + Na)^+$ 223.0941, found 223.0935 (+0.9 ppm error). Spectroscopic data consistent with those reported in the literature.[156]
Lab Book - PJ-06-47

Methyl 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decane-8-carboxylate 241



241

Table 4.1, entry 1

LiHMDS (0.83 mL of a 1.0 M solution in THF, 0.83 mmol, 2.0 eq) was added dropwise to a solution of ketal **236** (100 mg, 1.56 mmol, 1.2 eq) and 2-bromopyridine (0.04 mL, 0.42 mmol, 1.0 eq) in dry toluene (5 mL) at rt under Ar. The reaction mixture was then added dropwise to a solution of $[(cinnamyl)PdCl]_2$ (1.1 mg, 0.002 mmol, 0.005 eq) and *t*-$Bu_3P{\cdot}HBF_4$ (2.4 mg, 0.008 mmol, 0.02 eq) in dry toluene (1 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The resulting solution was stirred at rt for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine (10 mL), sat $NaHCO_{3(aq)}$ (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give crude product as an orange oil which contained no product by ^1H NMR spectroscopic analysis.

Lab Book - PJ-06-35.

Table 4.1, entry 2

LiHMDS (3.74 mL of a 1.0 M solution in THF, 3.74 mmol, 2.0 eq) was added dropwise to a solution of ketal **236** (450 mg, 2.25 mmol, 1.2 eq) and 2-bromopyridine (0.18 mL, 1.9 mmol, 1.0 eq) in dry toluene (5 mL) at rt under Ar. The reaction mixture was then added dropwise to a solution of $[(cinnamyl)PdCl]_2$ (19 mg, 0.037 mmol, 0.02 eq) and *t*-$Bu_3P{\cdot}HBF_4$ (21.7 mg, 0.075 mmol, 0.04 eq) in dry toluene (1 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The resulting solution was stirred at rt for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine (10 mL) and sat $NaHCO_{3(aq)}$ (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil which contained an 80:20 mixture of 2-bromopyridine and aryl ketal **241** by ^1H NMR spectroscopy.

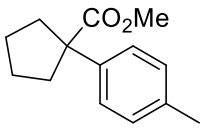
Lab Book - PJ-06-37.

Table 4.1, entry 3

LiHMDS (1.7 mL of a 1.0 M solution in toluene, 1.7 mmol, 2.0 eq) was added dropwise to a solution of ketal **236** (200 mg, 1.0 mmol, 1.2 eq) and 2-bromopyridine (0.08 mL, 0.83 mmol, 1.0 eq) in dry toluene (6 mL) at rt under Ar. The reaction mixture was then added dropwise to a solution of $[(cinnamyl)PdCl]_2$ (8.8 mg, 0.017 mmol, 0.02 eq) and *t*-$Bu_3P{\cdot}HBF_4$ (9.9 mg, 0.034 mmol, 0.04 eq) in dry toluene (1 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The resulting solution was stirred at rt for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine (10 mL) and sat $NaHCO_{3(aq)}$ (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give an orange oil. Purification by flash column chromatography on silica with 80:20-70:30 hexane-EtOAc as eluent gave aryl ketal **241** (171 mg, 74%) as a colourless oil, R_F (70:30 hexane-EtOAc) 0.17; IR (ATR) 2950, 1726 (C=O), 1220, 1194, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, 6-py), 7.65 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, 4-py), 7.36 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H, 3-py), 7.15 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, 5-py), 3.99-3.91 (m, 4H, OCH_2), 3.69 (s, 3H, OMe), 2.53-2.45 (m, 2H, CH), 2.28-2.19 (m, 2H, CH), 1.78-1.71 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.8 (C=O), 161.7 (*ipso*-Ar), 149.2 9 (Ar), 136.7 (Ar), 122.0 (Ar), 120.6 (Ar), 108.3 (C), 64.4 (OCH_2), 53.4 (C), 52.4 (OMe), 32.2 (CH_2), 31.4 (CH_2); MS (ESI) *m/z* 278 $(M + H)^+$; HRMS *m/z* calcd for $C_{15}H_{19}NO_4$ $(M + H)^+$ 278.1387, found 278.1383 (+1.5 ppm error). Spectroscopic data consistent with those reported in the literature.[119]

Lab Book - PJ-07-55.

Methyl 1-phenylcyclopentane-1-carboxylate 243



243

Table 4.2, entry 1

LiHMDS (2.6 mL of a 1.0 M solution in THF, 2.6 mmol, 2.0 eq) was added dropwise to a solution of cyclopentane ester **242** (0.2 mL, 1.56 mmol, 1.2 eq) and 4-bromotoluene (222 mg, 1.30 mmol, 1.0 eq) in dry toluene (5 mL) at rt under Ar. The reaction mixture was then added dropwise to a solution of $[(cinnamyl)PdCl_2]$ (13 mg, 0.026 mmol, 0.02 eq) and *t*-

$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) in dry toluene (1 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The resulting solution was stirred at rt for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (20 mL) and sat $NaHCO_{3(aq)}$ (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil which contained no product by ^{1}H NMR spectroscopy.
Lab Book - PJ-06-39.

Table 4.2, entry 2
NaHMDS (1.3 mL of a 2.0 M solution in THF, 2.6 mmol, 2.0 eq) was added dropwise to a solution of cyclopentane ester **242** (0.2 mL, 1.56 mmol, 1.2 eq) and 4-bromotoluene (222 mg, 1.30 mmol, 1.0 eq) in dry toluene (5 mL) at rt under Ar. The solution was then added dropwise to a solution of [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq) and *t*-$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) in dry toluene (1 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The resulting solution was stirred at rt for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (20 mL) and sat $NaHCO_{3(aq)}$ (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil which contained no product by ^{1}H NMR spectroscopy.
Lab Book - PJ-06-43.

Table 4.2, entry 3
LiHMDS (2.6 mL of a 1.0 M solution in toluene, 2.6 mmol, 2.0 eq) was added dropwise to a solution of cyclopentane ester **242** (0.2 mL, 1.56 mmol, 1.2 eq) and 4-bromotoluene (222 mg, 1.30 mmol, 1.0 eq) in dry toluene (5 mL) at rt under Ar. The reaction mixture was then added dropwise to a solution of [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq) and *t*-$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) in dry toluene (1 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The resulting solution was stirred at rt for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (20 mL) and sat $NaHCO_{3(aq)}$ (20 mL), dried ($MgSO_4$) and evaporated under

reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 90:10 hexane-Et_2O as eluent gave aryl cyclopentane ester **243** (15 mg, 5%) as a white solid and cyclopentane ester **242** (138 mg).
Lab Book - PJ-06-41.

Table 4.2, entry 4
n-BuLi (1.0 mL of a 2.3 M solution in hexane, 2.3 mmol, 2.0 eq) was added dropwise to a stirred solution of diisopropylamine (0.32 mL, 2.3 mmol, 2.0 eq) in dry toluene (1 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. A solution of cyclopentane ester **242** (0.2 mL, 1.56 mmol, 1.2 eq) and 4-bromotoluene (222 mg, 1.30 mmol, 1.0 eq) in toluene (5 mL) was added dropwise to the LDA solution under Ar. The solution was stirred at 0 °C for 10 min and then allowed to warm to rt and stirred at rt for 10 min. The solution was then added dropwise to a solution of [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq) and *t*-$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) in dry toluene (1 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The resulting solution was stirred at rt for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (20 mL) and sat $NaHCO_{3(aq)}$ (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 98:2-90:10 hexane-Et_2O as eluent gave aryl cyclopentane ester **243** (58 mg, 20%) as a white solid, mp 46-48 °C; R_F (90:10 hexane-Et_2O) 0.37; IR (ATR) 2947, 1720 (C=O), 1193, 1157, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 2H, Ar), 7.13 (d, *J* = 8.0 Hz, 2H, Ar), 3.62 (s, 3H, OMe), 2.68-2.60 (m, 2H, CH_2), 2.34 (s, 3H, C_6H_4*Me*), 1.96-1.87 (m, 2H, CH_2), 1.78-1.68 (m, 4H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.8 (C=O), 140.5 (*ipso*-Ar), 136.4 (*ipso*-Ar), 129.1 (Ar), 126.8 (Ar), 58.8 (OMe), 52.5 (C), 36.3 (CH_2), 23.7 (CH_2), 21.1 (C_6H_4*Me*); MS (ESI) *m/z* 241 (M + Na)$^+$; HRMS *m/z* calcd for $C_{14}H_{18}O_2$ (M + Na)$^+$ 241.1199, found 241.1191 (+0.8 ppm error). Spectroscopic data consistent with those reported in the literature.[157]
Lab Book - PJ-07-54.

Table 4.3, entry 1
Using general procedure G, *n*-BuLi (1.0 mL of a 2.3 M solution in hexane, 2.3 mmol, 2.0 eq), diisopropylamine (0.32 mL, 2.3 mmol, 2.0 eq), cyclopentane ester **242** (0.2 mL, 1.56

mmol, 1.2 eq), [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) and 4-bromotoluene (222 mg, 1.30 mmol, 1.0 eq) in dry toluene (7 mL) at rt for 16 h gave the crude product as an orange oil. Purification by flash column chromatography on silica with 98:2-90:10 hexane-Et_2O as eluent gave aryl cyclopentane ester **243** (58 mg, 58%) as a white solid.
Lab Book - PJ-06-44.

Table 4.3, entry 2
n-BuLi (1.0 mL of a 2.3 M solution in hexane, 2.3 mmol, 2.0 eq) was added dropwise to a stirred solution of dicyclohexylamine (0.46 mL, 2.3 mmol, 2.0 eq) in dry toluene (1 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. A solution of cyclopentane ester **242** (0.2 mL, 1.56 mmol, 1.2 eq) in toluene (1 mL) was added dropwise to the $LiNCy_2$ solution at 0 °C under Ar. The solution was stirred at 0 °C for 10 min and then allowed to warm to rt and stirred at rt for 10 min. The solution was then added dropwise to a solution of [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) and 4-bromotoluene (222 mg, 1.30 mmol, 1.0 eq) in dry toluene (5 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The resulting solution was stirred at rt for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (20 mL) and sat $NaHCO_{3(aq)}$ (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a green oil. Purification by flash column chromatography on silica with 98:2-90:10 hexane-Et_2O as eluent gave aryl cyclopentane ester **243** (58 mg, 59%) as a white solid.
Lab Book - PJ-06-46.

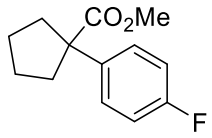
Table 4.3, entry 3
Using general procedure F, cyclopentane ester **242** (0.2 mL, 1.56 mmol, 1.2 eq), LiHMDS (2.6 mL of a 1.0 M solution in THF, 2.6 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) and 4-bromotoluene (222 mg, 1.30 mmol, 1.0 eq) in toluene (7 mL) at rt for 16 h gave the crude product as an orange oil which contained no product by ^1H NMR spectroscopy.
Lab Book - PJ-06-48.

Table 4.3, entry 4

Using general procedure F, cyclopentane ester **242** (0.2 mL, 1.56 mmol, 1.2 eq), LiHMDS (2.6 mL of a 1.0 M solution in toluene, 2.6 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) and 4-bromotoluene (222 mg, 1.30 mmol, 1.0 eq) in toluene (7 mL) at rt for 16 h gave the crude product as an orange oil. Purification by flash column chromatography on silica with 98:2-90:10 hexane-Et_2O as eluent gave aryl cyclopentane ester **243** (98 mg, 34%) as a white solid.

Lab Book - PJ-06-55.

Methyl 1-(4-fluorophenyl)cyclopentane-1-carboxylate 244



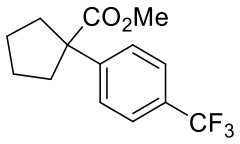
244

Table 4.4, entry 1

Using general procedure G, *n*-BuLi (0.57 mL of a 2.3 M solution in hexane, 1.32 mmol, 2.0 eq), diisopropylamine (0.19 mL, 1.32 mmol, 2.0 eq), cyclopentane ester **242** (0.1 mL, 0.79 mmol, 1.2 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromofluorobenzene (0.07 mL, 0.66 mmol, 1.0 eq) in dry toluene (6 mL) at rt for 16 h gave the crude product as a black oil. Purification by flash column chromatography on silica with 80:20 CH_2Cl_2-hexane as eluent gave aryl cyclopentane ester **244** (50 mg, 34%) as a colourless oil, R_F (CH_2Cl_2) 0.19, IR (ATR) 2952, 1726 (C=O), 1508, 1228, 1154, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 9.0, 5.5 Hz, 2H, Ar), 7.02-6.95 (dd, *J* = 9.0, 9.0 Hz, 2H, Ar), 3.61 (s, 3H, OMe), 2.69-2.58 (m, 2H, CH), 1.93-1.81 (m, 2H, CH), 1.77-1.66 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.4 (C=O), 161.7 (d, *J* = 245.0 Hz, *ipso*-Ar), 139.2 (d, *J* = 3.0 Hz, *ipso*-Ar), 128.6 (d, *J* = 8.0 Hz, Ar), 115.1 (d, *J* = 21.0 Hz, Ar), 58.6 (C), 52.5 (OMe), 36.4 (CH_2), 23.6 (CH_2); MS (ESI) *m/z* 223 $(M + H)^+$; HRMS *m/z* calcd for $C_{13}H_{15}FO_2$ $(M + H)^+$ 223.1129 found 223.1125 (+1.9 ppm error). Spectroscopic data consistent with those reported in the literature.[158]

Lab Book - PJ-06-67.

Methyl 1-(4-(trifluoromethyl)phenyl)cyclopentane-1-carboxylate 245



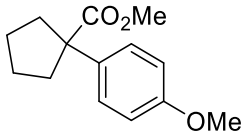
245

Table 4.4, entry 2

Using general procedure G, *n*-BuLi (0.57 mL of a 2.3 M solution in hexane, 1.32 mmol, 2.6 eq), diisopropylamine (0.19 mL, 1.32 mmol, 2.6 eq), cyclopentane ester **242** (0.1 mL, 0.79 mmol, 1.6 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.026 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.052 eq) and 4-bromobenzotrifluoride (0.07 mL, 0.66 mmol, 1.0 eq) in dry toluene (6 mL) at rt for 16 h gave the crude product as a black oil. Purification by flash column chromatography on silica with 98:2 hexane-Et_2O as eluent gave aryl cyclopentane ester **245** (97 mg, 72%) as a white solid, mp 52-54 °C; R_F (90:10 hexane-Et_2O) 0.3, IR (ATR) 2967, 1730 (C=O), 1320, 1158, 1122, 1101, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H, Ar), 7.47 (d, *J* = 8.0 Hz, 2H, Ar), 3.62 (s, 3H, OMe), 2.71-2.63 (m, 2H, CH), 1.96-1.87 (m, 2H, CH), 1.79-1.70 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.8 (C=O), 147.4 (*ipso*-Ar), 129.6 (q, *J* = 32.5 Hz, *ipso*-Ar), 127.4 (Ar), 125.3 (q, *J* = 4.0 Hz, Ar), 124.3 (q, *J* = 272.0 Hz, CF_3), 59.2 (C), 52.6 (OMe), 36.3 (CH_2), 23.6 (CH_2); MS (ESI) *m/z* 273 $(M + H)^+$; HRMS *m/z* calcd for $C_{14}H_{16}F_3O_2$ $(M + H)^+$ 273.1097 found 273.1098 (–2.2 ppm error).

Lab Book - PJ-06-62.

Methyl 1-(4-methoxyphenyl)cyclopentane-1-carboxylate 246



246

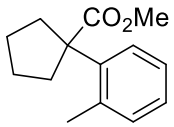
Table 4.4, entry 3

Using general procedure G, *n*-BuLi (0.57 mL of a 2.3 M solution in hexane, 1.32 mmol, 2.0 eq), diisopropylamine (0.19 mL, 1.32 mmol, 2.0 eq), cyclopentane ester **242** (0.1 mL, 0.79 mmol, 1.2 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromoanisole (0.08 mL, 0.66 mmol, 1.0 eq) in dry toluene (6

mL) at rt for 16 h gave the crude product as a black oil. Purification by flash column chromatography on silica with 98:2 hexane-Et_2O as eluent gave aryl cyclopentane ester **246** (106 mg, 68%) as a yellow oil, R_F (95:5 hexane-EtOAc) 0.08, IR (ATR) 2950, 1725 (C=O), 1511, 1247, 1181, 1034, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 9.0 Hz, 2H, Ar), 6.84 (d, *J* = 9.0 Hz, 2H, Ar), 3.79 (s, 3H, OMe), 3.60 (s, 3H, OMe), 2.71-2.55 (m, 2H, CH), 2.07-1.80 (m, 2H, CH), 1.79-1.61 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.8 (C=O), 158.4 (*ipso*-Ar), 135.5 (*ipso*-Ar), 128.0 (Ar), 113.7 (Ar), 58.4 (C), 55.3 (OMe), 52.4 (OMe), 36.3 (CH_2), 23.6 (CH_2); MS (ESI) *m/z* 257 $(M + Na)^+$; HRMS *m/z* calcd for $C_{14}H_{18}O_3$ $(M + Na)^+$ 257.1148 found 257.1146 (+0.8 ppm error).

Lab Book - PJ-06-68.

Methyl 1-(o-tolyl)cyclopentane-1-carboxylate 247



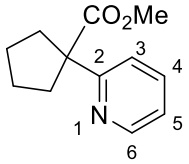
247

Table 4.4, entry 4

Using general procedure G, *n*-BuLi (0.57 mL of a 2.3 M solution in hexane, 1.32 mmol, 2.0 eq), diisopropylamine (0.19 mL, 1.32 mmol, 2.0 eq), cyclopentane ester **242** (0.1 mL, 0.79 mmol, 1.2 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 2-bromotoluene (0.08 mL, 0.66 mmol, 1.0 eq) in dry toluene (6 mL) at rt for 16 h gave the crude product as a black oil. Purification by flash column chromatography on silica with 98:2 hexane-Et_2O as eluent gave aryl cyclopentane ester **247** (52 mg, 36%) as a yellow oil, R_F (90:10 hexane-Et_2O) 0.27, IR (ATR) 2949, 1725 (C=O), 1231, 1152, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.32 (m, 1H, Ar), 7.20-7.11 (m, 3H, Ar), 3.61 (s, 3H, OMe), 2.55-2.47 (m, 2H, CH), 2.23 (s, 3H, C_6H_4*Me*), 2.08-1.98 (m, 2H, CH), 1.83-1.66 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.8 (C=O), 142.2 (*ipso*-Ar), 136.7 (*ipso*-Ar), 131.7 (Ar), 126.8 (Ar), 125.9 (Ar), 125.8 (Ar), 58.1 (C), 52.5 (OMe), 36.9 (CH_2), 24.7 (CH_2), 20.9 (C_6H_4*Me*); MS (ESI) *m/z* 241 $(M + Na)^+$; HRMS *m/z* calcd for $C_{14}H_{18}O_2$ $(M + Na)^+$ 241.1199 found 241.1198 (+0.3 ppm error).

Lab Book - PJ-06-63.

Methyl 1-(pyridin-2-yl)cyclopentane-1-carboxylate 248

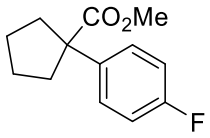


248

Table 4.4, entry 7

Using general procedure G, *n*-BuLi (1.0 mL of a 2.3 M solution in hexane, 2.3 mmol, 2.0 eq), diisopropylamine (0.32 mL, 2.3 mmol, 2.0 eq), cyclopentane ester **242** (0.2 mL, 1.56 mmol, 1.2 eq), [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) and 4-bromotoluene (222 mg, 1.30 mmol, 1.0 eq) in dry toluene (7 mL) at rt for 16 h gave give the crude product as a black oil. Purification by flash column chromatography on silica with 90:10 to 70:30 hexane-Et_2O, followed by 98:2 CH_2Cl_2-Et_2O as eluent gave aryl cyclopentane ester **248** (15 mg, 6%) as a yellow oil, R_F (80:20 hexane-Et_2O) 0.12, IR (ATR) 2950, 1727 (C=O), 1429, 1153, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, 6-py), 7.64 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, 4-py), 7.29 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H, 3-py), 7.14 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, 5-py), 3.66 (s, 3H, OMe), 2.57-2.48 (m, 2H, CH), 2.24-2.16 (m, 2H, CH), 1.79-1.70 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.3 (C=O), 162.6 (*ipso*-Ar), 148.9 (Ar), 136.5 (Ar), 121.7 (Ar), 121.1 (Ar), 61.7 (C), 52.4 (OMe), 36.2 (CH_2), 24.6 (CH_2); MS (ESI) *m/z* 206 $(M + H)^+$; HRMS *m/z* calcd for $C_{12}H_{15}NO$ $(M + Na)^+$ 206.1170, found 206.0964 (+3.7 ppm error).
Lab Book - PJ-06-52.

Methyl 1-(4-fluorophenyl)cyclopentane-1-carboxylate 244



244

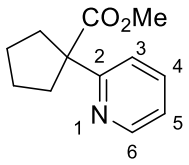
Table 4.5, entry 1

Using general procedure F, cyclopentane ester **242** (0.1 mL, 0.79 mmol, 1.2 eq), LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromofluorobenzene (0.07 mL, 0.66 mmol, 1.0 eq) in toluene (6 mL) at rt for 16 h gave the

crude product as a yellow oil. Purification by flash column chromatography on silica with 95:5-80:20 hexane-Et_2O as eluent gave aryl cyclopentane ester **244** (40 mg, 27%) as a yellow oil.

Lab Book - PJ-06-58.

Methyl 1-(pyridin-2-yl)cyclopentane-1-carboxylate 248



248

Table 4.5, entry 3

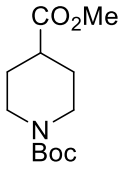
Using general procedure F, cyclopentane ester **242** (0.2 mL, 1.56 mmol, 1.2 eq), LiHMDS (2.6 mL of a 1.0 M solution in toluene, 2.6 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (13 mg, 0.026 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (15 mg, 0.052 mmol, 0.04 eq) and 2-bromopyridine (0.12 mL, 1.30 mmol, 1.0 eq) in toluene (7 mL) at rt for 16 h gave the crude product as an orange oil. Purification by flash column chromatography on silica with 90:10-80:20 hexane-Et_2O as eluent gave aryl cyclopentane ester **248** (193 mg, 72%) as a yellow oil, R_F (80:20 hexane-Et_2O) 0.12, IR (ATR) 2950, 1727 (C=O), 1429, 1153, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, 6-py), 7.64 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, 4-py), 7.29 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H, 3-py), 7.14 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, 5-py), 3.66 (s, 3H, OMe), 2.57-2.48 (m, 2H, CH), 2.24-2.16 (m, 2H, CH), 1.79-1.70 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.3 (C=O), 162.6 (*ipso*-Ar), 148.9 (Ar), 136.5 (Ar), 121.7 (Ar), 121.1 (Ar), 61.7 (C), 52.4 (OMe), 36.2 (CH_2), 24.6 (CH_2); MS (ESI) *m/z* 206 $(M + H)^+$; HRMS *m/z* calcd for $C_{12}H_{15}NO$ $(M + Na)^+$ 206.1170, found 206.0964 (+3.7 ppm error).

Lab Book - PJ-06-56.

Using general procedure F, cyclopentane ester **242** (1.18 mL, 9.36 mmol, 1.2 eq), LiHMDS (15.6 mL of a 1.0 M solution in toluene, 15.6 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (80 mg, 0.156 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (90 mg, 0.312 mmol, 0.04 eq) and 2-bromopyridine (0.74 mL, 7.8 mmol, 1.0 eq) in toluene (36 mL) at rt for 16 h gave the crude product as an orange oil. Purification by flash column chromatography on silica with 90:10-80:20 hexane-Et_2O as eluent gave aryl cyclopentane ester **248** (1.13 g, 71%) as a yellow oil.

Lab Book - PJ-07-15.

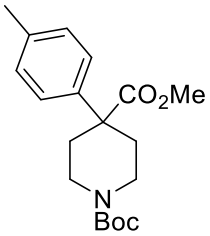
1-(*tert*-Butyl) 4-methyl piperidine-1,4-dicarboxylate 249



249

Potassium carbonate (724 mg, 5.24 mmol, 3.0 eq) was added to a stirred solution of piperidine-4-carboxylic acid (400 mg, 1.75 mmol, 1.0 eq) in DMF (10 mL) at rt. The resulting suspension was stirred at rt for 30 min and methyl iodide (0.33 mL, 5.24 mmol, 3.0 eq) was added. The mixture was then stirred at rt for 18 h. Water (3 mL) was added and the mixture was extracted with EtOAc (4 x 10 mL). The combined organic were washed with brine (4 x 80 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give *N*-Boc piperidine-4-methyl ester **249** (399 mg, 94%) as a colourless oil, IR (ATR) 2953, 1734 (C=O, CO_2Me), 1689 (C=O, Boc), 1419, 1158, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.08-3.92 (m, 2H, NCH), 3.67 (s, 3H, OMe), 2.87-2.75 (m, 2H, NCH), 2.43 (tt, *J* = 11.0, 4.0 Hz, 1H, CH), 1.90-1.81 (m, 2H, CH), 1.60 (dddd, *J* = 13.5, 11.0, 11.0, 4.0 Hz, 2H, CH), 1.43 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.2 (C=O, CO_2Me), 154.8 (C=O, Boc), 79.7 (*C*Me_3), 51.9 (OMe), 43.2 (NCH_2), 41.1 (CH), 28.5 (CH_2), 28.1 (C*Me*$_3$); MS (ESI) *m/z* 266 $(M + Na)^+$; HRMS *m/z* calcd for $C_{12}H_{21}NO_4$ $(M + Na)^+$ 266.1363, found 266.1359 (+1.3 ppm error). Spectroscopic data consistent with those reported in the literature.[159]
Lab Book - PJ-06-86.

1-(*tert*-Butyl) 4-methyl 4-(p-tolyl)piperidine-1,4-dicarboxylate 253



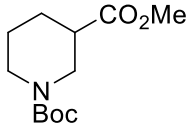
253

Using general procedure G, *n*-BuLi (0.57 mL of a 2.3 M solution in hexane, 1.32 mmol, 2.0 eq), diisopropylamine (0.19 mL, 1.32 mmol, 2.0 eq), *N*-Boc piperidine-4-methyl ester **249** (191 mg, 0.79 mmol, 1.2 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromotoluene (113 mg, 0.66 mmol, 1.0

eq) in dry toluene (6 mL) at rt for 16 h gave the crude product as an orange oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl piperidine-4-methyl ester **253** (22 mg, 10%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.27, IR (ATR) 2973, 1727 (C=O, CO_2Me), 1690 (C=O, Boc), 1421, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.0 Hz, 2H, Ar), 7.15 (d, *J* = 8.0 Hz, 2H, Ar), 4.04-3.85 (m, 2H, NCH), 3.65 (s, 3H, OMe), 3.11-2.91 (m, 2H, NCH), 2.55-2.44 (m, 2H, CH), 2.32 (s, 3H, C_6H_4*Me*), 1.93-1.76 (m, 2H, CH), 1.49-1.39 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 174.8 (C=O, CO_2Me), 155.0 (C=O, Boc), 139.3 (*ipso*-Ar), 137.1 (*ipso*-Ar), 129.5 (Ar), 125.8 (Ar), 79.6 (*C*Me_3), 52.4 (OMe), 49.2 (C), 42.0 (NCH_2), 41.3 (NCH_2), 34.1 (CH_2), 33.5 (CH_2), 28.5 (C*Me*$_3$), 21.1 (C_6H_4*Me*); MS (ESI) *m/z* 356 $(M + Na)^+$; HRMS *m/z* calcd for $C_{19}H_{27}NO_4$ $(M + Na)^+$ 356.1832, found 356.1832 (+0.1 ppm error) and *N*-Boc piperidine-4-methyl ester **249** (108 mg, 0.33 mmol) as a colourless oil.
Lab Book - PJ-06-87.

Using general procedure F, *N*-Boc piperidine-4-methyl ester **249** (150 mg, 0.62 mmol, 1.2 eq), LiHMDS (1.02 mL of a 1.0 M solution in toluene, 1.02 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (5.2 mg, 0.010 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (5.8 mg, 0.020 mmol, 0.04 eq) and 4-bromotoluene (87 mg, 0.51 mmol, 1.0 eq) in toluene (6 mL) at rt for 16 h gave the crude product as an orange oil. Purification by flash column chromatography on silica with 85:15 hexane-EtOAc as eluent gave *N*-Boc aryl piperidine-4-methyl ester **253** (120 mg, 70%) as a colourless oil.
Lab Book - PJ-06-89.

1-(*tert*-Butyl) 3-methyl piperidine-1,3-dicarboxylate 250



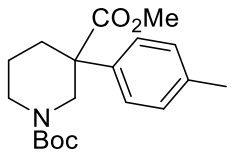
250

Potassium carbonate (724 mg, 5.24 mmol, 3.0 eq) was added to a stirred solution of *N*-Boc piperidine-3-carboxylic acid (400 mg, 1.75 mmol, 1.0 eq) in DMF (10 mL) at rt. The resulting suspension was stirred at rt for 30 min and methyl iodide (0.33 mL, 5.24 mmol, 3.0 eq) was added. The mixture was then stirred at rt for 18 h. Water (3 mL) was added and the mixture was extracted with EtOAc (4 x 10 mL). The combined organic were washed with

brine (4 x 80 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give *N*-Boc piperidine-3-methyl ester **250** (383 mg, 90%) as a white solid, mp 38-40 °C; IR (ATR) 2952, 1734 (C=O, CO_2Me), 1690 (C=O, Boc), 1421, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24-3.97 (m, 1H, NCH), 3.95-3.83 (m, 1H, NCH), 3.67 (s, 3H, OMe), 3.08-2.85 (m, 1H, NCH), 2.79 (ddd, *J* = 13.5, 11.0, 3.0 Hz, 1H, NCH), 2.49-2.38 (m, 1H, CH), 2.06-1.97 (m, 1H, CH), 1.74-1.65 (m, 1H, CH), 1.64-1.54 (m, 1H, CH), 1.50-1.37 (m, 10H, CMe_3 and CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.1 (C=O, CO_2Me), 154.8 (C=O, Boc), 79.8 (*C*Me_3), 51.9 (OMe), 45.8 (NCH_2), 43.9 (NCH_2), 41.5 (CH), 28.5 (C*Me*$_3$), 27.5 (CH_2), 24.4 (CH_2); MS (ESI) *m/z* 266 $(M + Na)^+$; HRMS *m/z* calcd for $C_{12}H_{21}NO_4$ $(M + Na)^+$ 266.1363, found 266.1360 (0.8 ppm error). Spectroscopic data consistent with those reported in the literature.[160]

Lab Book - PJ-06-90.

1-(*tert*-Butyl) 3-methyl 3-(p-tolyl)piperidine-1,3-dicarboxylate 254

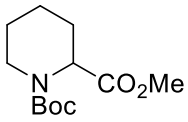


254

Using general procedure F, *N*-Boc piperidine-3-methyl ester **250** (191 mg, 0.76 mmol, 1.2 eq), LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromotoluene (113 mg, 0.66 mmol, 1.0 eq) in toluene (6 mL) at rt for 16 h gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 95:5-90:10 hexane-EtOAc as eluent gave *N*-Boc aryl piperidine-3-methyl ester **254** (174 mg, 79%) as a yellow oil, R_F (90:10 hexane-EtOAc) 0.13, IR (ATR) 2950, 1730 (C=O, CO_2Me), 1688 (C=O, Boc), 1424, 1147, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.23 (m, 2H, Ar), 7.13 (d, *J* = 8.0 Hz, 2H, Ar), 4.38 (d, *J* = 13.5 Hz, 1H, NCH), 3.76-3.65 (m, 1H, NCH), 3.62 (s, 3H, OMe), 3.47 (d, *J* = 13.5 Hz, 1H, NCH), 3.04 (ddd, *J* = 13.0, 6.5, 6.5 Hz, 1H, NCH), 2.49-2.40 (m, 1H, CH), 2.31 (s, 3H, C_6H_4*Me*), 1.99-1.88 (m, 1H, CH), 1.68-1.56 (m, 2H, CH), 1.51-1.41 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.2 (C=O, CO_2Me), 154.7 (C=O, Boc), 137.3 (*ipso*-Ar), 137.1 (*ipso*-Ar), 129.4 (Ar), 126.2 (Ar), 79.7 (*C*Me_3), 52.3 (OMe), 50.6 (C), 50.1 (NCH_2), 43.1 (NCH_2), 33.1 (CH_2), 28.5 (C*Me*$_3$), 22.5

(CH_2), 21.0 (C_6H_4*Me*); MS (ESI) *m/z* 356 $(M + Na)^+$; HRMS *m/z* calcd for $C_{19}H_{27}NO_4$ $(M + Na)^+$ 356.1838, found 356.1837 (–0.3 ppm error).
Lab Book - PJ-06-92.

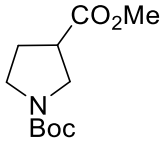
1-(*tert*-Butyl) 2-methyl piperidine-1,2-dicarboxylate 251



251

A solution of Boc_2O (1.22 g, 5.59 mmol, 2.0 eq) in CH_2Cl_2 (7.5 mL) was added dropwise to a stirred solution of piperidine-2-methyl ester (400 mg, 2.79 mmol, 1.0 eq) and Et_3N (1.16 mL, 8.37 mmol, 3.0 eq) in CH_2Cl_2 (7.5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the reaction mixture was evaporated under reduced pressure to give the crude product as a white solid. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc piperidine-2-methyl ester **251** (650 mg, 95%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.11, IR (ATR) 2938, 1742 (C=O, CO_2Me), 1693 (C=O, Boc) 1364, 1155 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.90-4.79 (m, 0.5H, NCH), 4.71-4.63 (m, 0.5H, NCH), 4.06-3.83 (m, 1H, NCH), 3.69 (s, 3H, OMe), 3.00-2.74 (m, 1H, NCH), 2.23-2.08 (m, 1H, CH), 1.70-1.52 (m, 3H, CH), 1.50-1.29 (m, 10H, CH and CMe_3), 1.28-1.10 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 172.7 (C=O, CO_2Me), 172.5 (C=O, CO_2Me), 156.0 (C=O, Boc), 155.6 (C=O, Boc), 80.0 (*C*Me_3), 55.0 (NCH), 53.8 (NCH), 52.1 (OMe), 42.1 (NCH_2), 41.2 (NCH_2), 28.4 (C*Me*$_3$), 26.8 (CH_2), 24.9 (CH_2), 24.6 (CH_2), 20.9 (CH_2); MS (ESI) *m/z* 266 $(M + Na)^+$; HRMS *m/z* calcd for $C_{12}H_{21}NO_4$ $(M + Na)^+$ 266.1363, found 266.1361 (+0.5 ppm error). Spectroscopic data consistent with those reported in the literature.[161]
Lab Book - PJ-06-98.

1-(*tert*-Butyl) 3-methyl pyrrolidine-1,3-dicarboxylate 252



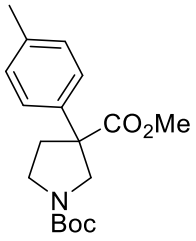
252

A solution of Boc_2O (1.04 g, 4.8 mmol, 2.0 eq) in CH_2Cl_2 (7.5 mL) was added dropwise to a stirred solution of pyrrolidine-3-methyl ester (400 mg, 2.4 mmol, 1.0 eq), and Et_3N (1.0

mL, 4.8 mmol, 3.0 eq) in CH_2Cl_2 (7.5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the reaction mixture was evaporated under reduced pressure to give the crude product as a white solid. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave *N*-Boc pyrrolidine-3-methyl ester **252** (445 mg, 81%) as a colourless oil, R_F (80:20 hexane-Et_2O) 0.14, IR (ATR) 2976, 1736 (C=O, CO_2Me), 1691 (C=O, Boc) 1400, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H, OMe), 3.65-3.41 (m, 3H, CH), 3.39 -3.29 (m, 1H, CH), 3.09-2.98 (m, 1H, CH), 2.19-2.05 (m, 2H, CH), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.7 (C=O, CO_2Me), 154.4 (C=O, Boc), 79.6 (*C*Me_3), 52.2 (OMe), 48.2 (CH_2), 45.2 (CH_2), 43.3 (CH), 42.4 (CH_2), 28.6 (C*Me*$_3$); MS (ESI) *m/z* 252 $(M + Na)^+$; HRMS *m/z* calcd for $C_{11}H_{19}NO_4$ $(M + Na)^+$ 252.1206, found 252.1208 (–0.9 ppm error). Spectroscopic data consistent with those reported in the literature.[162]

Lab Book - PJ-06-82.

1-(*tert*-Butyl) 3-methyl 3-(*p*-tolyl)pyrrolidine-1,3-dicarboxylate 256



256

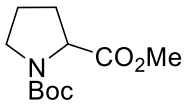
Using general procedure G, *n*-BuLi (0.57 mL of a 2.3 M solution in hexane, 1.32 mmol, 2.0 eq), diisopropylamine (0.19 mL, 1.32 mmol, 2.0 eq), *N*-Boc pyrrolidine-3-methyl ester **252** (180 mg, 0.79 mmol, 1.2 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromotoluene (113 mg, 0.66 mmol, 1.0 eq) in dry toluene (6 mL) at rt for 16 h gave the crude product as an orange oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl pyrrolidine-3-methyl ester **256** (72 mg, 34%) as a white solid, mp 102-104 °C; R_F (80:20 hexane-EtOAc) 0.20, IR (ATR) 2971, 1721 (C=O, CO_2Me), 1686 (C=O, Boc), 1406, 1170, 1151, 1123, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.20 (d, *J* = 8.0 Hz, 2H, Ar), 7.14 (d, *J* = 8.0 Hz, 2H, Ar), 4.36 (d, *J* = 11.0 Hz, 0.5H, NCH), 4.32 (d, *J* = 11.0 Hz, 0.5H, NCH), 3.67-3.58 (m, 3.5H, OMe and NCH), 3.53-3.46 (m, 1H, NCH), 3.45-3.31 (m, 1.5H, NCH), 2.91-2.80 (m, 1H, CH), 2.33 (s, 3H, C_6H_4Me), 2.21-2.08 (m, 1H,

CH), 1.48 (s, 4.5H, CMe_3), 1.46 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 174.2 (C=O, CO_2Me), 154.5 (C=O, Boc), 137.5 (*ipso*-Ar), 137.4 (*ipso*-Ar), 136.8 (*ipso*-Ar), 136.7 (*ipso*-Ar), 129.5 (Ar), 126.5 (Ar), 126.4 (Ar), 79.7 (CMe_3), 79.6 (CMe_3), 57.1 (C), 56.2 (NCH_2), 53.9 (OMe), 53.3 (OMe), 52.9 (NCH_2), 44.9 (NCH_2), 44.5 (NCH_2), 34.9 (CH_2), 33.9 (CH_2), 28.6 (CMe_3), 21.2 (C_6H_4Me); MS (ESI) *m/z* 342 $(M + Na)^+$; HRMS *m/z* calcd for $C_{18}H_{25}NO_4$ $(M + Na)^+$ 342.1676, found 342.1167 (–0.1 ppm error).

Using general procedure F, *N*-Boc pyrolidine-3-methyl ester **252** (180 mg, 0.76 mmol, 1.2 eq), LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromotoluene (113 mg, 0.66 mmol, 1.0 eq) in toluene (6 mL) at rt for 16 h gave the crude product as an orange oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl pyrolidine-3-methyl ester **256** (78 mg, 37%) as a white solid.

Lab Book - PJ-06-85.

1-(*tert*-Butyl) 2-methyl pyrrolidine-1,2-dicarboxylate 257



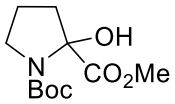
257

Potassium carbonate (579 mg, 4.2 mmol, 3.0 eq) was added to a stirred solution of *N*-Boc pyrrolidine-2-carboxylic acid (300 mg, 1.4 mmol, 1.0 eq) in DMF (6 mL) at rt. The resulting suspension was stirred at rt for 30 min and methyl iodide (0.26 mL, 4.2 mmol, 3.0 eq) was added. The mixture was then stirred at rt for 18 h. Water (3 mL) was added and the mixture was extracted with EtOAc (4 x 10 mL). The combined organics were washed with brine (4 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash chromatography on silica with 80:20 hexane-EtOAc as eluent gave *N*-Boc pyrrolidine-2-methyl ester **257** (270 mg, 84%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.15, IR (ATR) 2975, 1746 (C=O, CO_2Me), 1695 (C=O, Boc) 1391, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 60:40 mixture of rotamers δ 4.32 (dd, *J* = 8.5, 3.5 Hz, 0.4H, CH), 4.22 (dd, *J* = 8.5, 4.0 Hz, 0.6H, CH), 3.72 (s, 3H, OMe), 3.59-3.33 (m, 2H, CH), 2.28-2.11 (m, 1H, CH), 2.02-1.91 (m, 2H, CH), 1.91-1.81 (m, 1H, CH), 1.46 (s, 3.6H, CMe_3), 1.41 (s, 5.4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 173.9 (C=O,

CO_2Me), 153.9 (C=O, Boc), 80.0 (*C*Me_3), 79.9 (*C*Me_3), 59.2 (OMe), 58.8 (OMe), 52.3 ($CHCO_2$), 52.1 ($CHCO_2$), 46.7 (CH_2), 46.5 (CH_2), 31.0 (CH_2), 30.1 (CH_2), 28.6 (C*Me*$_3$), 28.4 (C*Me*$_3$), 24.5 (CH_2), 23.8 (CH_2); MS (ESI) *m/z* 252 $(M + Na)^+$; HRMS *m/z* calcd for $C_{11}H_{19}NO_4$ $(M + Na)^+$ 252.1206, found 252.1207 (–0.7 ppm error). Spectroscopic data consistent with those reported in the literature.[163]

Lab Book - PJ-06-79.

1-(*tert*-Butyl) 2-methyl 2-hydroxypyrrolidine-1,2-dicarboxylate 258

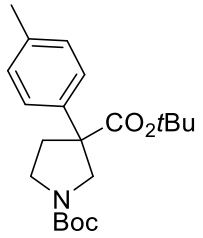


258

Using general procedure G, *n*-BuLi (0.57 mL of a 2.3 M solution in hexane, 1.32 mmol, 2.0 eq), diisopropylamine (0.19 mL, 1.32 mmol, 2.0 eq), *N*-Boc pyrrolidine-2-methyl ester **257** (180 mg, 0.79 mmol, 1.2 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromotoluene (113 mg, 0.66 mmol, 1.0 eq) in dry toluene (6 mL) at rt for 16 h gave the crude product as an orange oil. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave *N*-Boc pyrrolidine hydroxy ester **258** (104 mg, 64%) as a yellow oil, R_F (70:30 hexane-EtOAc) 0.15, IR (ATR) 3483 (OH), 2977, 1747 (C=O, CO_2Me), 1701 (C=O, Boc), 1394, 1367, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 4.45 (s, 0.5H, OH), 4.02 (s, 0.5H, OH), 3.80 (s, 1.5H, OMe), 3.80 (s, 1.5H, OMe), 3.67 (ddd, *J* = 11.0, 7.5, 4.0 Hz, 0.5H, NCH), 3.59 (ddd, *J* = 10.5, 7.5, 5.0 Hz, 0.5H, NCH), 3.52-3.41 (m, 1H, NCH), 2.28-2.15 (m, 1H, CH), 2.15-2.01 (m, 2H, CH), 1.99-1.89 (m, 1H, CH), 1.44 (s, 4.5H, CMe_3), 1.41 (s, 4.5H, CMe_3), ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 173.7 (C=O, CO_2Me), 173.3 (C=O, CO_2Me), 152.6 (C=O, Boc), 88.9 (C), 88.0 (C), 81.4 (*C*Me_3), 80.9 (*C*Me_3), 53.3 (OMe), 47.2 (NCH_2), 39.8 (CH_2), 38.3 (CH_2), 28.4 (C*Me*$_3$), 23.0 (CH_2), 22.4 (CH_2); MS (ESI) *m/z* 268 $(M + Na)^+$; HRMS *m/z* calcd for $C_{11}H_{19}NO_5$ $(M + Na)^+$ 268.1161, found 268.1157 (–1.49 ppm error).

Lab Book - PJ-06-72.

***tert*-Butyl 3-(*p*-tolyl)pyrrolidine-1,3-dicarboxylate 260**

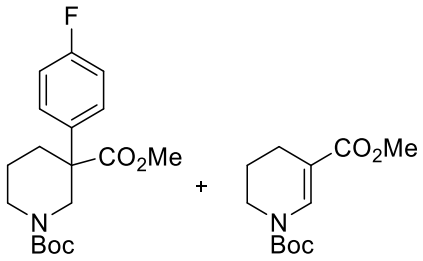


260

Using general procedure F, *N*-Boc pyrolidine-3-*t*-butyl ester **259** (205 mg, 0.76 mmol, 1.2 eq), LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromotoluene (113 mg, 0.66 mmol, 1.0 eq) in toluene (6 mL) at rt for 16 h gave the crude product as an orange oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl pyrolidine-3-*t*-butyl ester **260** (170 mg, 71%) as a white solid, mp 84-86 °C; R_F (70:30 hexane-EtOAc) 0.38, IR (ATR) 2974, 1714 (C=O, CO_2tBu), 1687 (C=O, Boc), 1410, 1147 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.17 (d, *J* = 8.0 Hz, 2H, Ar), 7.12 (d, *J* = 8.0 Hz, 2H, Ar), 4.30 (d, *J* = 11.0 Hz, 1H, NCH), 3.54 (d, *J* = 11.0 Hz, 0.5H, NCH), 3.52-3.43 (m, 0.5H, NCH), 3.43-3.30 (m, 2H, NCH), 2.83-2.72 (m, 1H, CH), 2.31 (s, 3H, C_6H_4*Me*), 2.19-2.01 (m, 1H, CH), 1.47 (s, 4.5H, C*Me*$_3$), 1.44 (s, 4.5H, CMe_3), 1.34 (s, 4.5H, CMe_3), 1.33 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 178.1 (C=O, CO_2tBu), 172.8 (C=O, Boc), 154.5 (*ipso*-Ar), 137.1 (*ipso*-Ar), 129.6 (Ar), 126.2 (Ar), 81.9 (*C*Me_3), 79.6 (*C*Me_3), 57.9 (C), 57.0 (C), 53.8 (NCH_2), 53.3 (NCH_2), 44.9 (NCH_2), 44.5 (NCH_2), 34.9 (CH_2), 33.9 (CH_2), 28.6 (C*Me*$_3$), 27.8 (C*Me*$_3$), 21.1 (C_6H_4*Me*); MS (ESI) *m/z* 284 $(M + Na)^+$; HRMS *m/z* calcd for $C_{21}H_{31}NO_4$ $(M + Na)^+$ 384.2145, found 384.2138 (+0.9 ppm error).

Lab Book - PJ-07-45.

1-(*tert*-Butyl) 3-methyl 3-(4-fluorophenyl)piperidine-1,3-dicarboxylate 261 and 1-(*tert*-butyl) 3-methyl 5,6-dihydropyridine-1,3(4H)-dicarboxylate 262

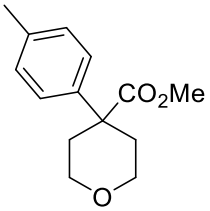


261 **262**

Using general procedure F, *N*-Boc piperidine-3-methyl ester **250** (192 mg, 0.76 mmol, 1.2 eq), LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-fluorobromobenzene (0.07 mL, 0.66 mmol, 1.0 eq) in toluene (6 mL) at rt for 16 h gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 90:10-80:20 hexane-EtOAc as eluent gave dihydropyridine **262** (15 mg, 7%) as a colourless oil, R_F (70:30 hexane-EtOAc) 0.32; IR (ATR) 2950, 1717 (C=O, CO_2Me), 1631 (C=O, Boc), 1366, 1241, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21-7.82 (m, 1H, =CH), 3.72 (s, 3H, OMe), 3.58-3.51 (m, 2H, NCH), 2.29 (ddd, *J* = 6.0, 6.0, 1.5 Hz, 2H, CH), 1.93-1.76 (m, 2H, CH), 1.51 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.3 (C=O, CO_2Me), 152.0 (C=O, Boc), 136.2 (=CH), 107.4 (=C), 82.4 (*C*Me_3), 51.5 (OMe), 41.8 (NCH_2), 28.3 (C*Me*$_3$), 21.0 (CH_2), 20.8 (CH_2); MS (ESI) *m/z* 264 $(M + Na)^+$; HRMS *m/z* calcd for $C_{12}H_{19}NO_4$ $(M + Na)^+$ 264.1212, found 264.1209 (–1.1 ppm error) and *N*-Boc aryl piperidine-3-methyl ester **261** (132 mg, 59%) as an orange oil, R_F (70:30 hexane-EtOAc) 0.24; IR (ATR) 2951, 1731 (C=O, CO_2Me), 1688 (C=O, Boc), 1511, 1423, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (s, 2H, Ar), 7.01 (dd, *J* = 9.0, 9.0 Hz, 2H, Ar), 4.34-4.16 (m, 1H, NCH), 3.62 (s, 3H, OMe), 3.75-3.45 (m, 2H, NCH) , 3.30-2.94 (s, 1H, NCH), 2.47-2.33 (m, 1H, CH), 1.99 (ddd, *J* = 13.5, 7.0, 7.0 Hz, 1H, CH), 1.75-1.54 (m, 2H, CH), 1.49-1.37 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.9 (C=O, CO_2Me), 162.0 (d, *J* = 246.5 Hz, *ipso*-Ar), 154.6 (C=O, Boc), 135.7 (d, *J* = 3.5 Hz, *ipso*-Ar), 128.3 (d, *J* = 8.0 Hz, Ar), 115.6 (d, *J* = 21.0 Hz, Ar), 79.9 (*C*Me_3), 52.4 (OMe), 50.6 (C), 49.8 (NCH_2), 43.1 (NCH_2), 33.1 (CH_2), 28.5 (C*Me*$_3$), 22.3 (CH_2); MS (ESI) *m/z* 360 $(M + Na)^+$; HRMS *m/z* calcd for $C_{18}H_{24}NO_4$ $(M + Na)^+$ 360.1582, found 360.1589 (–2.5 ppm error).

Lab book - PJ-07-11.

Methyl 4-(*p*-tolyl)tetrahydro-2H-pyran-4-carboxylate 268

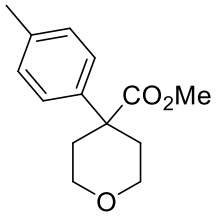


268

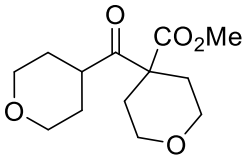
Using general procedure F, THP-4-methyl ester **263** (0.1 mL, 0.76 mmol, 1.2 eq), LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromotoluene (113 mg, 0.66 mmol, 1.0 eq) in toluene (6 mL) at rt for 16 h gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 75:25 hexane-EtOAc as eluent gave aryl THP-4-methyl ester **268** (29 mg, 19%) as a yellow solid, mp 58-60 °C; R_F (75:25 hexane-EtOAc) 0.31; IR (ATR) 2949, 1719 (C=O), 1445, 1125, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.0 Hz, 2H, Ar), 7.16 (d, *J* = 8.0 Hz, 2H, Ar), 3.92 (ddd, *J* = 11.5, 4.0, 4.0 Hz, 2H, OCH), 3.66 (s, 3H, OMe), 3.55 (ddd, *J* = 11.5, 11.0, 2.0 Hz, 2H, OCH), 2.56-2.45 (m, 2H, CH), 2.33 (s, 3H, Ar Me), 1.97 (ddd, *J* = 13.5, 11.0, 4.0 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1 (C=O), 139.6 (*ipso*-Ar), 137.1 (*ipso*-Ar), 129.5 (Ar), 125.7 (Ar), 65.8 (OCH_2), 52.4 (OMe), 48.4 (C), 34.6 (CH_2), 21.1 (C_6H_4*Me*); MS (ESI) *m/z* 257 $(M + Na)^+$; HRMS *m/z* calcd for $C_{14}H_{18}O_3$ $(M + Na)^+$ 257.1148, found 257.1146 (+1.3 ppm error).

Lab Book - PJ-06-93.

Methyl 4-(*p*-tolyl)tetrahydro-2H-pyran-4-carboxylate 268 and methyl 4-(tetrahydro-2H-pyran-4-carbonyl)tetrahydro-2H-pyran-4-carboxylate 269



268

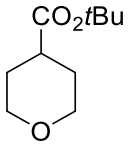


269

Using general procedure F, THP-4-methyl ester **263** (0.1 mL, 0.76 mmol, 1.2 eq), LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromotoluene (113 mg, 0.66 mmol, 1.0 eq) in toluene (6 mL) at rt for 24 h gave the crude product as a yellow

oil. Purification by flash column chromatography on silica with 75:25 hexane-EtOAc as eluent gave aryl THP-4-methyl ester **268** (75 mg, 48%) as a yellow solid and THP-keto-ester **269** (40 mg, 20%) as a colourless oil, R_F (70:30 hexane-EtOAc) 0.08; IR (ATR) 2954, 2848, 1731 (C=O, ketone), 1707 (C=O CO_2Me), 1119, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00-3.92 (m, 2H, OCH), 3.82-3.72 (m, 2H, OCH), 3.76 (s, 3H, OMe), 3.59 (ddd, *J* = 12.0, 9.0, 3.0 Hz, 2H, OCH), 3.38 (ddd, *J* = 12.0, 12.0, 2.0 Hz, 2H, OCH), 2.91 (tt, *J* = 12.0, 4.0 Hz, 1H, CH), 2.19-2.11 (m, 2H, CH), 1.99 (ddd, *J* = 13.5, 9.0, 4.0 Hz, 2H, CH), 1.80 (dddd, *J* = 12.0, 12.0, 12.0, 4.5 Hz, 2H, CH), 1.45 (ddd, *J* = 12.0, 4.0, 2.0 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.5 (C=O, ketone), 171.9 (C=O, CO_2Me), 67.1 (NCH_2), 64.8 (NCH_2), 58.8 (C), 52.8 (OMe), 43.6 (CH), 30.2 (CH_2), 29.7 (CH_2); MS (ESI) *m/z* 279 $(M + Na)^+$; HRMS *m/z* calcd for $C_{13}H_{20}O_5$ $(M + Na)^+$ 279.1208, found 279.1202 (–2.1 ppm error).
Lab Book - PJ-06-94.

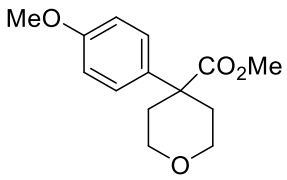
tert-Butyl tetrahydro-2H-pyran-4-carboxylate 271



271

Trichloroacetimidate (2.2 mL, 12.3 mmol, 2.0 eq) was added dropwise to a stirred solution of THP-4-carboxylic acid **270** (800 mg, 6.15 mmol, 1.0 eq) in 1:1 CH_2Cl_2-Et_2O (8 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the reaction mixture was evaporated under reduced pressure to give a white solid. Sat $NaHCO_{3(aq)}$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a white solid. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave THP-4-*t*butyl ester **271** (340 mg, 30%) as a colourless oil, R_F (70:30 hexane-EtOAc) 0.53, IR (ATR) 2957, 1724 (C=O), 1366, 1154, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00-3.89 (m, 2H, OCH), 3.41 (ddd, *J* = 11.5, 10.5, 3.0 Hz, 2H, OCH), 2.42 (tt, *J* = 10.5, 4.5 Hz, 1H, CH), 1.97-1.65 (m, 4H, CH), 1.44 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.1 (C=O), 80.4 (CMe_3), 67.3 (OCH_2), 41.2 (CH), 28.9 (CH_2), 28.2 (CMe_3); MS (ESI) *m/z* 209 $(M + Na)^+$; HRMS *m/z* calcd for $C_{10}H_{18}O_3$ $(M + Na)^+$ 209.1148, found 209.1148 (+0.4 ppm error).
Lab Book - PJ-07-60.

Methyl 4-(4-methoxyphenyl)tetrahydro-2H-pyran-4-carboxylate 272



272

Table 4.6, entry 1

Using general procedure F, THP-4-methyl ester **263** (0.1 mL, 0.76 mmol, 1.2 eq), LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromoanisole (0.083 mL, 0.66 mmol, 1.0 eq) in toluene (6 mL) at rt for 24 h gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave aryl THP-4-methyl ester **272** (31 mg, 18%) as a yellow solid.

Lab Book - PJ-07-07.

Table 4.6, entry 2

Using general procedure F, THP-4-methyl ester **263** (0.1 mL, 0.76 mmol, 1.2 eq), LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq), [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromoanisole (0.083 mL, 0.66 mmol, 1.0 eq) in toluene (6 mL) at rt for 64 h gave the crude product as a yellow oil. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave aryl THP-4-methyl ester **272** (98 mg, 57%) as a yellow solid and Claisen THP-keto-ester **269** (18 mg, 9%) as a colourless oil.

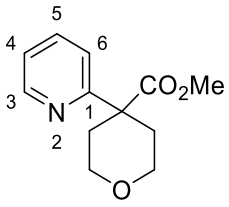
Lab Book - PJ-07-17.

Table 4.6, entry 3

A solution of 4-methyl THP ester **263** (0.1 mL, 0.76 mmol, 1.2 eq), in toluene (1 mL) was added dropwise to a stirred solution of LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq) in 95:5 toluene-THF (2.1 mL) at rt under Ar. The resulting solution was vigorously stirred at rt for 40 min. In a separate reaction flask, [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 4-bromoanisole (0.083 mL, 0.66 mmol, 1.0 eq) were added, followed by dry toluene (5 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The

LiHMDS/ester solution was then added dropwise to the reaction flask and the resulting solution was stirred and heated at 50 °C for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (20 mL) and sat $NaHCO_{3(aq)}$ (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave aryl THP-4-methyl ester **272** (104 mg, 63%) as a yellow solid, mp 56-58 °C; R_F (70:30 hexane-EtOAc) 0.25; IR (ATR) 2928, 1720 (C=O), 1512, 1100, 1027, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz, 2H, Ar), 6.87 (d, *J* = 9.0 Hz, 2H, Ar), 3.91 (ddd, *J* = 12.0, 4.0, 4.0 Hz, 2H, OCH), 3.79 (s, 3H, OMe), 3.65 (s, 3H, OMe), 3.53 (ddd, *J* = 12.0, 12.0, 2.0 Hz, 2H, OCH), 2.57-2.44 (m, 2H, CH), 1.94 (ddd, *J* = 13.0, 12.0, 2.0 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1 (C=O), 158.8 (*ipso*-Ar), 134.7 (*ipso*-Ar), 126.9 (Ar), 114.1 (Ar), 65.8 (OCH_2), 55.4 (OMe), 52.4 (OMe), 34.6 (CH_2); MS (ESI) *m/z* 273 $(M + Na)^+$; HRMS *m/z* calcd for $C_{14}H_{18}O_4$ $(M + Na)^+$ 273.1097, found 273.1094 (+3.5 ppm error). and THP-keto-ester **269** (41 mg, 21%) as a colourless oil.
Lab Book - PJ-07-26.

Methyl 4-(pyridin-2-yl)tetrahydro-2H-pyran-4-carboxylate 273

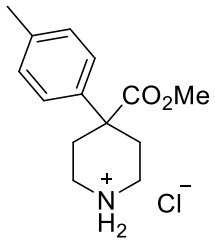


273

A solution of THP-4-methyl ester **263** (0.1 mL, 0.76 mmol, 1.2 eq), in toluene (1 mL) was added dropwise to a stirred solution of LiHMDS (1.32 mL of a 1.0 M solution in toluene, 1.32 mmol, 2.0 eq) in 95:5 toluene-THF (2.1 mL) at rt under Ar. The resulting solution was vigorously stirred at rt for 40 min. Io a separate reaction flask, [(cinnamyl)$PdCl_2$] (6.8 mg, 0.013 mmol, 0.02 eq), *t*-$Bu_3P{\cdot}HBF_4$ (7.5 mg, 0.026 mmol, 0.04 eq) and 2-bromopyridine (0.063 mL, 0.66 mmol, 1.0 eq) were added, followed by dry toluene (5 mL). The reaction flask was then evacuated under reduced pressure and back-filled with Ar three times. The LiHMDS/ester solution was then added dropwise to the reaction flask and the resulting solution was stirred and heated at 50 °C for 16 h. The solution was poured into 1 M $AcOH_{(aq)}$ (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined

organics were washed with brine (20 mL) and sat $NaHCO_{3(aq)}$ (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave aryl THP-4-methyl ester **273** (77 mg, 53%) as a yellow oil, R_F (80:20 hexane-EtOAc) 0.07; IR (ATR) 2954, 1726 (C=O), 1430, 1127, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61-8.53 (m, 1H, 6-py), 7.67 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, 4-py), 7.32 (m, 1H, 3-py), 7.17 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, 5-py), 3.87 (ddd, *J* = 12.0, 4.0, 4.0 Hz, 2H, OCH), 3.70 (s, 3H, OMe), 3.62 (ddd, *J* = 12.0, 10.0, 2.5 Hz, 2H, OCH), 2.47 (ddd, *J* = 14.0, 4.0, 2.5 Hz, 2H, CH), 2.16 (ddd, *J* = 14.0, 10.0, 4.0 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.4 (C=O), 161.3 (*ipso*-Ar), 149.3 (Ar), 136.9 (Ar), 122.2 (Ar), 120.6 (Ar), 65.5 (OCH_2), 52.5 (OMe), 33.8 (CH_2); MS (ESI) *m/z* 244 $(M + Na)^+$; HRMS *m/z* calcd for $C_{12}H_{15}NO_3$ $(M + Na)^+$ 244.0944, found 244.0940 (+0.2 ppm error) and THP-keto-ester **269** (39 mg, 20%) as a colourless oil.
Lab Book - PJ-07-30.

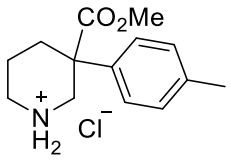
Methyl 4-(*p*-tolyl)piperidine-4-carboxylate 274·HCl



274

HCl (1 mL of a 4 M solution in dioxane) was added dropwise to *N*-Boc aryl piperidine-4-methyl ester **253** (111 mg, 0.3 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give aryl piperidine-4-methyl ester **274**·HCl (80 mg, 99%) as an orange solid, mp 230-232 °C; IR (ATR) 2934, 2730, 1725 (C=O), 1144, 495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (br s, 1H, NH), 9.53 (br s, 1H, NCH), 7.22-7.10 (m, 4H, Ar), 3.67 (s, 3H, OMe), 3.45-3.36 (m, 2H, NCH), 3.13-2.98 (m, 2H, NCH), 2.73 -2.61 (m, 2H, CH), 2.40-2.32 (m, 2H, CH), 2.31 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.6 (C=O, CO_2Me), 137.8 (*ipso*-Ar), 137.0 (*ipso*-Ar), 129.8 (Ar), 125.5 (Ar), 52.9 (OMe), 47.9 (C), 41.8 (NCH_2), 30.5 (CH_2), 21.0 (C_6H_4*Me*); MS (ESI) *m/z* 234 $(M)^+$; HRMS *m/z* calcd for $C_{14}H_{20}NO_2$ $(M)^+$ 234.1489, found 234.1493 (–1.6 ppm error).
Lab Book - PJ-07-98.

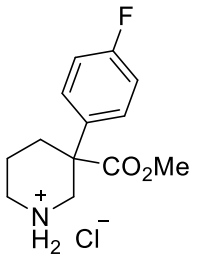
Methyl 3-(*p*-tolyl)piperidine-3-carboxylate 275·HCl



275

HCl (1 mL of a 4 M solution in dioxane) was added dropwise to *N*-Boc aryl piperidine-3-methyl ester **254** (60 mg, 0.18 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give aryl piperidine-3-methyl ester **275**·HCl (47 mg, 97%) as an orange oil, IR (ATR) 2951, 1728 (C=O, CO_2Me), 1449, 1239, 1151, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H, NH), 8.65 (s, 1H, NH), 7.17 (s, 4H, Ar), 4.18 (d, *J* = 13.0 Hz, 1H, NCH), 3.82 (s, 3H, OMe), 3.67-3.53 (m, 1H, NCH), 3.07-2.94 (m, 1H, NCH), 2.95-2.81 (m, 1H, NCH), 2.81-2.61 (m, 1H, CH), 2.32 (s, 3H, C_6H_4*Me*), 2.09-1.80 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8 (C=O), 138.4 (*ipso*-Ar), 135.6 (*ipso*-Ar), 129.9 (Ar), 125.3 (Ar), 53.7 (OMe), 49.7 (NCH_2), 48.6 (C), 43.6 (NCH_2), 30.7 (CH_2), 21.1 (C_6H_4*Me*), 20.4 (CH_2); MS (ESI) *m/z* 234 $(M)^+$; HRMS *m/z* calcd for $C_{14}H_{21}NO_2$ $(M)^+$ 234.1489, found 234.1490 (+0.4 ppm error). Lab Book - PJ-08-89.

Methyl 3-(4-fluorophenyl)piperidine-3-carboxylate 276·HCl

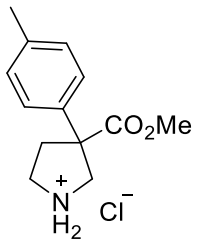


276

HCl (1 mL of a 2 M solution in Et_2O) was added dropwise to *N*-Boc aryl piperidine-3-methyl ester **261** (100 mg, 0.3 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 40 h. Then, the solvent was evaporated under reduced pressure to give aryl piperidine-3-methyl ester **276**·HCl (82 mg, 100%) as a brown solid, mp 122-124 °C; IR (ATR) 2955, 1728 (C=O), 1513, 1145, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.49-10.30 (m, 1H, NH), 8.93-8.56 (m, 1H, NH), 7.29 (dd, *J* = 9.0, 5.0 Hz, 2H, Ar), 7.05 (dd, *J* = 9.0, 9.0 Hz, 2H, Ar), 4.18 (d, *J* = 13.0 Hz, 1H, NCH), 3.82 (s, 3H, OMe), 3.69-3.52 (m, 1H, NCH), 3.14-2.95 (m, 1H, NCH), 2.98-2.83 (m, 1H, NCH), 2.80-2.70 (m, 1H, CH), 2.07-1.80 (m, 3H,

CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C=O), 162.5 (d, *J* = 248.5 Hz, *ipso*-Ar), 134.4 (d, *J* = 3.5 Hz, *ipso*-Ar), 127.4 (d, *J* = 8.5 Hz, Ar), 116.2 (d, *J* = 21.5 Hz, Ar), 53.8 (OMe), 49.6 (NCH_2), 48.4 (C), 43.6 (NCH_2), 30.8 (CH_2), 20.3 (CH_2); MS (ESI) *m/z* 238 $(M)^+$; HRMS *m/z* calcd for $C_{13}H_{17}FNO_2$ $(M)^+$ 238.1238, found 238.1237 (–0.3 ppm error).
Lab Book - PJ-07-75.

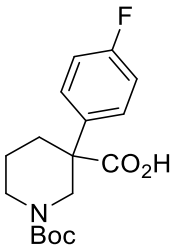
Methyl 3-(*p*-tolyl)pyrrolidine-3-carboxylate 277·HCl



277

HCl (1 mL of a 4 M solution in dioxane) was added dropwise to *N*-Boc aryl pyrrolidine-3-methyl ester **256** (72 mg, 0.23 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give aryl pyrrolidine-3-methyl ester **277**·HCl (58 mg, 99%) as a cream solid, mp 50-52 °C; IR (ATR) 2918, 1728 (C=O), 1212, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19-10.08 (m, 1H, NH), 10.00-9.87 (m, 1H, NH), 7.20-7.12 (m, 4H, Ar), 4.48-4.26 (m, 1H, NCH), 3.71 (s, 3H, OMe), 3.65-3.48 (m, 2H, NCH), 3.46-3.36 (m, 1H, NCH), 3.06-2.95 (m, 1H, CH), 2.40-2.21 (m, 1H, CH), 2.31 (s, 3H, C_6H_4*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C=O), 138.2 (*ipso*-Ar), 134.7 (*ipso*-Ar), 129.8 (Ar), 126.4 (Ar), 57.5 (C), 53.6 (OMe), 51.8 (NCH_2), 44.3 (NCH_2), 34.1 (CH_2), 21.1 (C_6H_4*Me*); MS (ESI) *m/z* 220 $(M)^+$; HRMS *m/z* calcd for $C_{13}H_{18}NO_2$ $(M)^+$ 220.1332, found 220.1333 (–0.2 ppm error).
Lab Book - PJ-07-92.

1-(*tert*-Butoxycarbonyl)-3-(4-fluorophenyl)piperidine-3-carboxylic acid 278

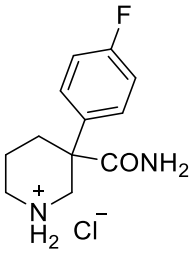


278

KOH (476 mg, 8.47 mmol, 10.0 eq) was added to a stirred solution of *N*-Boc aryl piperidine-3-methyl ester **261** (250 mg, 0.74 mmol, 1.0 eq) in EtOH (10 mL) at rt. The resulting mixture was stirred and heated at 100 °C for 16 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as an orange solid. The solid was taken up into water (20 mL) and washed with CH_2Cl_2 (3 x 10 mL). The aqueous layer was acidified with 1 M $HCl_{(aq)}$ (1 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give *N*-Boc aryl piperidine-3-carboxylic acid **278** (226 mg, 95%) as an orange solid, mp 178-180 °C; IR (ATR) 2978, 1717 (C=O, CO_2H), 1663 (C=O, Boc), 1436, 1149, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.36 (m, 2H, Ar), 7.01 (dd, *J* = 9.0, 9.0 Hz, 2H, Ar), 4.36-4.16 (m, 1H, NCH), 3.72-3.43 (m, 2H, NCH), 3.32-2.92 (m, 1H, NCH), 2.67-2.23 (m, 1H, CH), 2.16-1.87 (m, 1H, CH), 1.72-1.51 (m, 2H, CH), 1.43 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.9 (C=O, CO_2H), 162.2 (d, *J* = 247.0 Hz, *ipso*-Ar), 154.8 (C=O, Boc), 135.0 (d, *J* = 3.5 Hz, *ipso*-Ar), 128.4 (d, *J* = 8.0 Hz, Ar), 115.6 (d, *J* = 21.0 Hz, Ar), 80.2 (*C*Me_3), 50.6 (NCH_2), 49.5 (C), 43.1 (NCH_2), 32.6 (CH_2), 28.4 (C*Me*$_3$), 22.2 (CH_2); MS (ESI) *m/z* 346 $(M + Na)^+$; HRMS *m/z* calcd for $C_{17}H_{22}FNO_4$ $(M + Na)^+$ 346.1425, found 346.1458 (–4.8 ppm error).

Lab Book - PJ-07-76.

3-(4-Fluorophenyl)piperidine-3-carboxamide 279



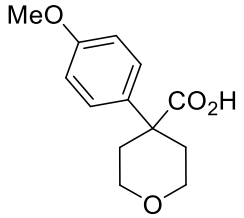
279

T3P (0.31 mL of a 50% wt. solution in EtOAc, 1.07 mmol, 1.7 eq) was added dropwise to a stirred solution of *N*-Boc aryl piperidine-3-carboxylic acid **278** (200 mg, 0.62 mmol, 1.0 eq), 35% $NH_{3(aq)}$ (0.031 mL, 0.78 mmol, 1.2 eq) and DIPEA (0.37 mL, 2.1 mmol, 3.4 eq) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The reaction mixture was poured into water (10 mL) and acidified using 1 M $HCl_{(aq)}$ (5 mL) was added. The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organics were washed with 2 M $NaOH_{(aq)}$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-MeOH as eluent gave *N*-Boc aryl piperidine-3-amide (76 mg, 38%) as an orange solid, mp 150-152 °C; R_F (99:1 CH_2Cl_2-MeOH) 0.23, IR (ATR) 2951, 1666 (C=O), 1626 (C=O), 1434, 1156, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.32 (m, 2H, Ar), 7.03 (dd, *J* = 9.0, 9.0 Hz, 3H, Ar and NH), 5.36-5.19 (m, 1H, NH), 4.63-4.44 (m, 1H, NCH), 4.05-3.78 (m, 1H, NCH), 3.16-3.05 (m, 1H, NCH), 3.03-2.86 (m, 1H, NCH), 2.85-2.74 (m, 1H, CH), 1.87-1.69 (m, 1H, CH), 1.67-1.58 (m, 2H, CH), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.9 (C=O, $CONH_2$), 162.1 (d, *J* = 247.0 Hz, *ipso*-Ar), 155.5 (C=O, Boc), 137.2 (*ipso*-Ar), 127.8 (Ar), 115.7 (d, *J* = 21.0 Hz, Ar), 80.8 (*C*Me_3), 50.3 (C), 49.8 (NCH_2), 44.5 (NCH_2), 33.6 (CH_2), 28.5 (C*Me*$_3$), 23.1 (CH_2); MS (ESI) *m/z* 345 $(M + Na)^+$; HRMS *m/z* calcd for $C_{17}H_{23}FN_2O_3$ $(M + Na)^+$ 345.1585, found 345.1581 (+0.6 ppm error). HCl (1 mL of a 4 M solution in dioxane) was added dropwise to *N*-Boc aryl piperidine-3-amide (76 mg, 0.24 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give aryl piperidine-3-amide **279**·HCl (63 mg, 99%) as a cream solid, mp 230-231 °C; IR (ATR) 2954, 1650 (C=O, $CONH_2$), 1510, 1229, 1165, 814 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOH) δ 7.46-7.39 (m, 2H, Ar), 7.14 (dd, *J* = 9.0, 9.0 Hz, 2H, Ar), 3.87 (dd, *J* = 12.5, 2.5 Hz, 1H, NCH), 3.37-3.30 (m, 1H, NCH), 2.98 (ddd, *J* = 12.5, 12.5, 3.5 Hz, 1H, NCH), 2.80 (d, *J* = 12.5 Hz, 1H, NCH), 2.61-2.44 (m, 1H, CH), 2.32

(ddd, *J* = 13.5, 13.5, 3.5 Hz, 1H, CH), 2.06 (ddddd, *J* = 15.0, 3.5, 3.5, 3.5, 3.5 Hz, 1H, CH), 1.92-1.76 (m, 1H, CH); ^{13}C NMR (100.6 MHz, d_4-MeOH) δ 176.8 (C=O, $CONH_2$), 162.6 (d, *J* = 246.5 Hz, *ipso*-Ar), 135.6 (d, *J* = 3.0 Hz, *ipso*-Ar), 128.1 (d, *J* = 8.0 Hz, Ar), 115.5 (d, *J* = 22.0 Hz, Ar), 50.5 (NCH_2), 48.1 (C), 43.1 (NCH_2), 29.2 (CH_2), 19.7 (CH_2); MS (ESI) *m/z* 223 $(M)^+$; HRMS *m/z* calcd for $C_{12}H_{16}FN_2O$ $(M)^+$ 223.1241, found 223.1240 (+1.3 ppm error).

Lab Book - PJ-07-79/PJ-08-01.

4-(4-Methoxyphenyl)tetrahydro-2H-pyran-4-carboxylic acid 280

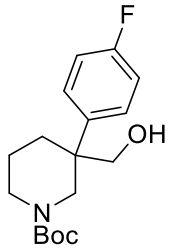


280

KOH (444 mg, 7.92 mmol, 10.0 eq) was added to a stirred solution of aryl THP-4-methyl ester **272** (198 mg, 0.79 mmol, 1.0 eq) in EtOH (10 mL) at rt. The resulting mixture was stirred and heated at 100 °C for 16 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as an orange solid. The solid was taken up into water (20 mL) and washed with CH_2Cl_2 (3 x 10 mL). The aqueous layer was acidified with 1M $HCl_{(aq)}$ (1 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give aryl THP-4-carboxylic acid **280** (164 mg, 88%) as a cream solid, mp 160-162 °C; IR (ATR) 2972, 1673 (C=O), 1511, 1257, 1239, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 9.0 Hz, 2H, Ar), 6.89 (d, *J* = 9.0 Hz, 2H, Ar), 3.91 (ddd, *J* = 12.0, 4.0, 4.0 Hz, 2H, OCH), 3.80 (s, 3H, OMe), 3.66-3.56 (m, 2H, OCH), 2.62-2.42 (m, 2H, CH), 1.96 (ddd, *J* = 14.0, 11.0, 4.0 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.2 (C=O), 159.0 (*ipso*-Ar), 133.8 (*ipso*-Ar), 127.2 (Ar), 114.2 (Ar), 65.6 (OCH_2), 55.4 (OMe), 47.6 (C), 34.2 (CH_2); MS (ESI) *m/z* 259 $(M + Na)^+$; HRMS *m/z* calcd for $C_{13}H_{16}O_4$ $(M + Na)^+$ 259.0941, found 259.0929 (+2.9 ppm error). Spectroscopic data consistent with those reported in the literature.[164]

Lab Book - PJ-07-83.

***tert*-Butyl 3-(4-fluorophenyl)-3-(hydroxymethyl)piperidine-1-carboxylate 281**

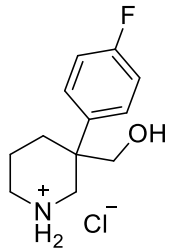


281

A solution of *N*-Boc aryl piperidine-3-methyl ester **261** (300 mg, 0.89 mmol, 1.0 eq) in THF (7 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (77 mg, 2.03 mmol, 2.0 eq) in THF (8 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 2 h. Water (0.1 mL), 20% $NaOH_{(aq)}$ (0.2 mL) and water (0.1 mL) were added sequentially (CARE – vigorous reaction). Then, $MgSO_4$ was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give *N*-Boc aryl piperidine alcohol **281** (268 mg, 98%) as a white solid, mp 98-100 °C; R_F (70:30 hexane-EtOAc) 0.12; IR (ATR) 3517 (OH), 2859, 1666 (C=O, Boc), 1431, 1156, 1060, 834 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOH) (50:50 mixture of rotamers) δ 7.47 (dd, *J* = 9.0, 5.0 Hz, 2H, Ar), 7.13-6.99 (m, 2H, Ar), 4.30 (d, *J* = 13.5 Hz, 0.5H, NCH), 4.16 (d, *J* = 13.5 Hz, 0.5H, NCH), 3.83-3.59 (m, 1H, NCH), 3.61-3.47 (m, 2H, OCH_2), 3.30-3.22 (m, 1H, NCH), 3.18-3.13 (m, 0.5H, NCH), 3.07-2.94 (m, 0.5H, NCH), 2.26-2.03 (m, 1H, CH), 1.95-1.78 (m, 1H, CH), 1.67-1.53 (m, 1H, CH), 1.54-1.36 (m, 10H, C*Me*$_3$ and CH); ^{13}C NMR (100.6 MHz, d_4-MeOH) (rotamers) δ 161.48 (d, *J* = 243.5 Hz, *ipso*-Ar), 155.0 (C=O , Boc), 138.2 (*ipso*-Ar), 129.1 (Ar), 114.40 (d, *J* = 21.0 Hz, Ar), 79.93 (*C*Me$_3$), 79.92 (*C*Me$_3$), 69.2 (OCH_2), 68.8 (OCH_2), 49.7 (NCH_2), 48.4 (NCH_2), 44.4 (NCH_2), 43.8 (C), 43.5 (NCH_2), 30.9 (CH_2), 30.5 (CH_2), 27.4 (C*Me*$_3$), 20.9 (CH_2); MS (ESI) *m/z* 332 $(M + Na)^+$; HRMS *m/z* calcd for $C_{17}H_{24}FNO_3$ $(M + Na)^+$ 332.1632, found 332.1622 (+4.5 ppm error).

Lab Book - PJ-07-78.

(3-(4-Fluorophenyl)piperidin-3-yl)methanol 282

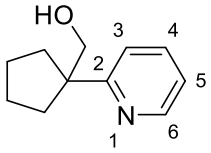


282

HCl (1 mL of a 4 M solution in dioxane) was added dropwise to *N*-Boc aryl piperidine alcohol **281** (90 mg, 0.29 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give aryl piperidine alcohol **282**·HCl (70 mg, 99%) as a white solid, mp 100-102 °C; IR (ATR) 3346 (OH), 2950, 1513, 1234, 832, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99-9.62 (m, 1H, NH), 8.98-8.65 (m, 1H, NH), 7.35-7.28 (m, 2H, Ar), 7.04 (dd, *J* = 8.5, 8.5 Hz, 2H, Ar), 4.17 (d, *J* = 12.0 Hz, 1H, OCH), 4.02 (d, *J* = 13.0 Hz, 1H, NCH), 3.71 (d, *J* = 12.0 Hz, 1H, OCH), 3.55-3.44 (m, 1H, NCH), 3.02 (d, *J* = 13.0 Hz, 1H, NCH), 2.93-2.81 (m, 1H, NCH), 2.30-2.05 (m, 2H, CH), 1.98-1.77 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.9 (d, *J* = 247.0 Hz, *ipso*-Ar), 138.6 (d, *J* = 3.0 Hz, *ipso*-Ar), 127.5 (d, *J* = 8.0 Hz, Ar), 115.7 (d, *J* = 21.0 Hz, Ar), 66.4 (OCH_2), 48.5 (NCH_2), 43.7 (NCH_2), 40.3 (C), 30.7 (CH_2), 19.3 (CH_2); MS (ESI) *m/z* 210 $(M)^+$; HRMS *m/z* calcd for $C_{12}H_{18}FNO$ $(M)^+$ 210.1289, found 210.1287 (+0.7 ppm error).

Lab Book - PJ-07-87.

(1-(Pyridin-2-yl)cyclopentyl)ethanol 283

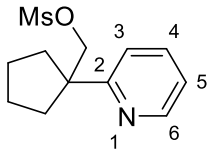


283

A solution of aryl cyclopentane ester **248** (100 mg, 0.49 mmol, 1.0 eq) in THF (2.5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (37 mg, 0.98 mmol, 2.0 eq) in THF (2.5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 2 h. Water (0.1 mL), 20% $NaOH_{(aq)}$ (0.2 mL) and water (0.1 mL) were added sequentially (CARE – vigorous reaction). Then, $MgSO_4$ was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give aryl cyclopentane alcohol **283** (85 mg, 98%)

as an orange oil, IR (ATR) 3350 (OH), 2949, 1590, 1471, 1048, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-8.42 (m, 1H, 6-py), 7.67-7.60 (m, 1H, 4-py), 7.30-7.26 (m, 1H, 3-py), 7.14-7.08 (m, 5-py), 3.73 (s, 2H, C*H*$_2$OH), 2.01-1.93 (m, 2H, CH), 1.91-1.82 (m, 2H, CH), 1.8-1.76 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.0 (*ipso*-Ar), 147.8 (Ar), 137.0 (Ar), 121.2 (Ar), 121.0 (Ar), 69.2 (C), 53.6 (OCH_2), 36.5 (CH_2), 25.5 (CH_2); MS (ESI) *m/z* 178 $(M + H)^+$; HRMS *m/z* calcd for $C_{11}H_{15}NO$ $(M + H)^+$ 178.1226, found 178.1226 (+0.3 ppm error). Spectroscopic data consistent with those reported in the literature.[165]
Lab Book - PJ-07-23.

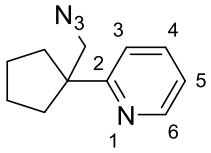
(1-(Pyridin-2-yl)cyclopentyl)methyl methanesulfonate 284



284

MsCl (0.026 mL, 0.34 mmol, 1.2 eq) was added dropwise to a stirred solution of aryl cyclopentane alcohol **283** (50 mg, 0.28 mmol, 1.0 eq) and Et_3N (0.08 mL, 0.56 mmol, 2.0 eq) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The reaction mixture was evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 70:30 hexane-EtOAc as eluent gave aryl cyclopentane mesylate **284** (66 mg, 91%) as a colourless oil, R_F (70:30 hexane-EtOAc) 0.09; IR (ATR) 2960, 1350, 1171, 941, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, 6-py), 7.63 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H, 4-py), 7.31 (m, 1H, 3-py), 7.13 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, 5-py), 4.42 (s, 2H, CH_2O), 2.70 (s, 3H, SO_2Me), 2.31-2.00 (m, 2H, CH), 2.05-1.88 (m, 2H, CH), 1.85-1.64 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.1 (*ipso*-Ar), 149.0 (Ar), 136.4 (Ar), 121.6 (Ar), 121.4 (Ar), 76.1 (CH_2O), 53.4 (C), 36.7 (Me), 34.7 (CH_2), 24.5 (CH_2); MS (ESI) *m/z* 256 $(M + H)^+$; HRMS *m/z* calcd for $C_{12}H_{17}NO_3S$ $(M + H)^+$ 256.1002, found 256.0998 (1.7 ppm error). Spectroscopic data consistent with those reported in the literature.[165]
Lab Book - PJ-07-28.

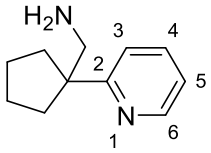
2-(1-(Azidomethyl)cyclopentyl)pyridine 285



285

A solution of aryl cyclopentane mesylate **284** (100 mg, 0.39 mmol, 1.0 eq) in DMF (1 mL) was added dropwise to a stirred solution of NaN_3 (76 mg, 1.18 mmol, 3.0 eq) in DMF (1 mL) at rt under Ar. The resulting mixture was stirred and heated at 60 °C for 24 h and then at 120 °C for 24 h. The reaction mixture was allowed to cool to rt and poured into water (10 mL) and Et_2O (10 mL). The two layers were separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave aryl cyclopentane azide **285** (68 mg, 86%) as a colourless oil, R_F (70:30 hexane-EtOAc) 0.42; IR (ATR) 2956, 2093 (N_3), 1587, 1469, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62-8.53 (m, 1H, 6-py), 7.63 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, 4-py), 7.37-7.27 (m, 1H, 3-py), 7.13 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, 5-py), 3.60 (s, 2H, N_3CH), 2.19-2.04 (m, 2H, CH), 2.00-1.86 (m, 2H, CH), 1.79-1.63 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.2 (*ipso*-Ar), 149.1 (Ar), 136.3 (Ar), 121.5 (Ar), 121.3 (Ar), 60.4 (N_3CH_2), 54.6 (C), 35.6 (CH_2), 24.5 (CH_2); MS (ESI) *m/z* 203 $(M + H)^+$; HRMS *m/z* calcd for $C_{11}H_{14}N_4$ $(M + H)^+$ 203.1291, found 203.1292 (–2.1 ppm error).
Lab Book - PJ-07-74.

(1-(Pyridin-2-yl)cyclopentyl)methanamine 286

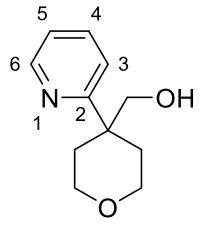


286

PPh_3 (166 mg, 0.63 mmol, 2.0 eq) was added to a stirred solution of aryl cyclopentane azide **285** (64 mg, 0.32 mmol, 1.0 eq) in 5:1 THF-water (6 mL) at rt. The resulting mixture was stirred and heated at 65 °C for 16 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 85:14:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$ as eluent gave aryl cyclopentane amine **286** (53 mg, 95%) as a green oil, R_F (85:14:1 CH_2Cl_2-MeOH-

$NH_4OH_{(aq)}$) 0.43; IR (ATR) 3066 (NH), 1474, 1430, 740, 690, 489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58-8.41 (m, 1H, 6-py), 7.70-7.54 (m, 1H, 4-py), 7.32-7.25 (m, 1H, 3-py), 7.16-7.05 (m, 1H, 5-py), 2.97 (s, 2H, NCH_2), 2.64 (br s, 2H, NH_2) 2.12-2.02 (m, 2H, CH), 1.97-1.84 (m, 2H, CH), 1.80-1.61 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.8 (*ipso*-Ar), 148.7 (Ar), 136.6 (Ar), 121.4 (Ar), 121.2 (Ar), 54.3 (NCH_2), 50.9 (C), 35.9 (CH_2), 24.6 (CH_2); MS (ESI) *m/z* 177 $(M + H)^+$; HRMS *m/z* calcd for $C_{11}H_{16}N_2$ $(M + H)^+$ 177.1386, found 177.1386 (–0.4 ppm error).
Lab Book - PJ-07-81.

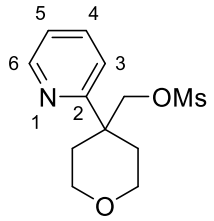
(4-(Pyridin-2-yl)tetrahydro-2H-pyran-4-yl)methanol 287



287

A solution of aryl THP-4-methyl ester **273** (430 mg, 1.95 mmol, 1.0 eq) in THF (7 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (147 mg, 3.89 mmol, 2.0 eq) in THF (8 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 2 h. Water (0.1 mL), 20% $NaOH_{(aq)}$ (0.2 mL) and water (0.1 mL) were added sequentially (CARE – vigorous reaction). Then, $MgSO_4$ was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 100% EtOAc as eluent gave aryl THP alcohol **287** (312 mg, 82%) as a colourless oil, R_F (EtOAc) 0.17; IR (ATR) 3378 (OH), 2952, 1432, 1043, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59-8.49 (m, 1H, 6-py), 8.01-7.62 (m, 1H, 4-py), 7.48-7.29 (m, 1H, 3-py), 7.22-7.09 (m, 1H, 5-py), 4.10-3.95 (m, 1H, OH), 3.91-3.75 (m, 4H, OCH), 3.73-3.54 (m, 2H, OCH), 2.38-2.11 (m, 2H, CH), 1.95-1.81 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.4 (*ipso*-Ar), 148.8 (Ar), 137.1 (Ar), 121.7 (Ar), 120.9 (Ar), 68.4 (OCH_2), 64.3 (OCH_2), 42.5 (C), 32.4 (CH_2); MS (ESI) *m/z* 194 $(M + H)^+$; HRMS *m/z* calcd for $C_{11}H_{15}NO_2$ $(M + H)^+$ 194.1176, found 194.1176 (+0.2 ppm error).
Lab Book - PJ-07-82.

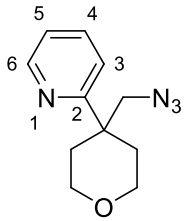
(4-(Pyridin-2-yl)tetrahydro-2H-pyran-4-yl)methyl methanesulfonate 288



288

MsCl (0.07 mL, 0.93 mmol, 1.2 eq) was added dropwise to a stirred solution of aryl THP alcohol **287** (150 mg, 0.78 mmol, 1.0 eq) and Et_3N (0.11 mL, 1.55 mmol, 2.0 eq) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. The reaction mixture was evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 80:20 EtOAc-heaxane as eluent gave aryl THP mesylate **288** (143 mg, 67%) as a colourless oil, R_F (80:20 EtOAc-heaxane) 0.26; IR (ATR) 2958, 1350, 1172, 952, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, 6-py), 7.76-7.65 (m, 1H, 4-py), 7.35 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H, 3-py), 7.19 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, 5-py), 4.33 (s, 2H, OCH_2), 3.83 (ddd, *J* = 12.0, 4.5, 4.5 Hz, 2H, OCH), 3.50 (ddd, *J* = 12.0, 9.5, 3.0 Hz, 2H, OCH), 2.66 (s, 3H, Me), 2.36 (dddd, *J* = 13.5, 4.5, 3.0 Hz, 2H, CH), 1.95 (ddd, *J* = 13.5, 9.5, 4.5 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.8 (*ipso*-Ar), 149.7 (Ar), 136.6 (Ar), 122.4 (Ar), 122.1 (Ar), 76.9 ($MsOCH_2$), 64.1 (OCH_2), 42.8 (C), 36.8 (Me), 31.8 (CH_2); MS (ESI) *m/z* 272 $(M + H)^+$; HRMS *m/z* calcd for $C_{12}H_{17}NO_4S$ $(M + H)^+$ 272.0951, found 272.0944 (+2.1 ppm error).
Lab Book - PJ-07-85.

2-(4-(Azidomethyl)tetrahydro-2H-pyran-4-yl)pyridine 289

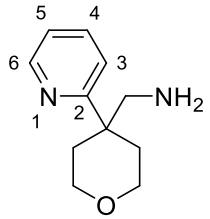


289

A solution of aryl THP mesylate **288** (120 mg, 0.44 mmol, 1.0 eq) in DMF (2 mL) was added dropwise to a stirred solution of NaN_3 (86 mg, 1.33 mmol, 3.0 eq) in DMF (1 mL) at rt under Ar. The resulting mixture was stirred and heated at 120 °C for 24 h. The reaction mixture was allowed to cool to rt and poured into water (10 mL) and Et_2O (10 mL). The two layers were separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined

organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave aryl THP azide **289** (80 mg, 84%) as a yellow oil, R_F (50:50 hexane-EtOAc) 0.32; IR (ATR) 2954, 2095 (N_3), 1587, 1105, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, 6-py), 7.70 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H, 4-py), 7.34 (ddd, *J* = 7.5, 1.0, 1.0 Hz, 1H, 3-py), 7.19 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, 5-py), 3.82 (ddd, *J* = 12.0, 4.5, 4.5 Hz, 2H, OCH), 3.52 (s, 2H, N_3CH_2), 3.48 (ddd, *J* = 12.0, 10.0, 2.5 Hz, 2H, OCH), 2.42-2.33 (m, 2H, CH), 1.89 (ddd, *J* = 14.0, 10.0, 4.5 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.8 (*ipso*-Ar), 149.7 (Ar), 136.5 (Ar), 122.1 (Ar), 121.9 (Ar), 64.4 (OCH_2), 62.0 (N_3CH_2), 43.6 (C), 33.1 (CH_2); MS (ESI) *m/z* 219 $(M + H)^+$; HRMS *m/z* calcd for $C_{11}H_{14}N_4O$ $(M + H)^+$ 219.1240, found 219.1239 (+0.8 ppm error).
Lab Book - PJ-07-88.

(4-(Pyridin-2-yl)tetrahydro-2H-pyran-4-yl)methanamine 290

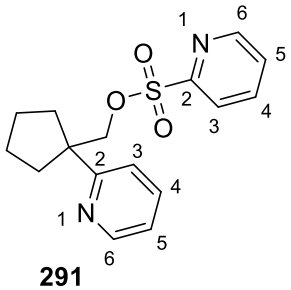


290

PPh_3 (194 mg, 0.74 mmol, 2.0 eq) was added to a stirred solution of aryl THP azide **289** (80 mg, 0.37 mmol, 1.0 eq) in 5:1 THF-water (6 mL) at rt. The resulting mixture was stirred and heated at 65 °C for 16 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:9:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$ as eluent gave aryl THP amine **290** (66 mg, 92%) as a yellow oil, R_F (90:9:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$) 0.18, IR (ATR) 3368 (NH), 2926, 2852, 1587, 1105, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64-8.59 (m, 1H, 6-py), 7.72-7.62 (m, 1H, 4-py), 7.32-7.27 (m, 1H, 3-py), 7.17-7.11 (m, 1H, 5-py), 3.87-3.77 (m, 2H, OCH), 3.50-3.41 (m, 2H, OCH), 2.88 (s, 2H, NCH_2), 2.38-2.29 (m, 2H, CH), 1.84-1.75 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.5 (*ipso*-Ar), 149.4 (Ar), 136.5 (Ar), 121.8 (Ar), 121.3 (Ar), 64.7 (OCH_2), 53.5 (NCH_2), 44.1 (C), 33.4 (CH_2); MS (ESI) *m/z* 193 $(M + H)^+$; HRMS *m/z* calcd for $C_{11}H_{16}N_2O$ $(M + H)^+$ 193.1335, found 193.1333 (+1.6 ppm error). Spectroscopic data consistent with those reported in the literature.[166]

Lab Book - PJ-07-94.

(1-(Pyridin-2-yl)cyclopentyl)methyl pyridine-2-sulfonate 291

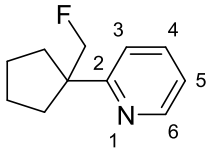


291

DBU (0.08 mL, 0.56 mmol, 2.0 eq) was added dropwise to a stirred solution of aryl cyclopentane alcohol **283** (50 mg, 0.28 mmol, 1.0 eq) and PyFluor (50 mg, 0.31 mmol, 1.1 eq) at rt under Ar. The resulting solution was stirred at rt for 48 h. The reaction mixture was evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 60:40 EtOAc-hexane as eluent gave aryl cyclopentane sulfonate **291** (89 mg, 99%) as a white solid, mp 64-66 °C; R_F (60:40 EtOAc-hexane) 0.07; IR (ATR) 2959, 1354, 1182, 936, 595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 5.0, 1.5, 1.5 Hz, 1H, 6-py), 8.38 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, 6-py), 7.86-7.80 (m, 2H, 4-py and 3-py), 7.55 (ddd, *J* = 7.5, 7.5, 2.0 1H, 4-py), 7.49 (ddd, *J* = 6.0, 5.0, 2.0 Hz, 1H, 5-py), 7.26 (ddd, *J* = 7.5, 1.0, 1.0 Hz, 1H, 3-py), 7.03 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, 5-py), 4.50 (s, 2H, OCH_2), 2.18-1.98 (m, 2H, CH), 2.01-1.84 (m, 2H, CH), 1.80-1.57 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.8 (*ipso*-Ar), 154.5 (*ipso*-Ar), 150.2 (Ar), 148.9 (Ar), 138.1 (Ar), 136.2 (Ar), 127.4 (Ar), 123.1 (Ar), 121.6 (Ar), 121.4 (Ar), 78.1 (OCH_2), 53.6 (C), 34.5 (CH_2), 24.4 (CH_2); MS (ESI) *m/z* 341 $(M + Na)^+$; HRMS *m/z* calcd for $C_{16}H_{18}N_2O_3S$ $(M + Na)^+$ 341.0930, found 341.0928 (+1.7 ppm error).

Lab Book - PJ-07-27.

2-(1-(Fluoromethyl)cyclopentyl)pyridine 292



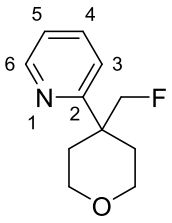
292

DBU (0.08 mL, 0.56 mmol, 2.0 eq) was added dropwise to a stirred solution of aryl cyclopentane alcohol **283** (50 mg, 0.28 mmol, 1.0 eq) and PyFluor (50 mg, 0.31 mmol, 1.1 eq) in toluene (5 mL) at rt under Ar. The resulting solution was stirred and heated at 80 °C

for 48 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as a yellow solid. Purification by flash column chromatography on silica with 60:40 hexane-EtOAc as eluent gave aryl cyclopentane fluoride **292** (35 mg, 70%) as a yellow oil, R_F (60:40 hexane-EtOAc) 0.57; IR (ATR) 2954, 1588, 1470, 1431, 991, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, 6-py), 7.61 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H, 4-py), 7.44-7.29 (m, 1H, 3-py), 7.11 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, 5-py), 4.51 (d, *J* = 48.0 Hz, 2H, FCH_2), 2.26-2.03 (m, 2H, CH), 2.03-1.85 (m, 2H, CH), 1.80-1.68 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.0 (d, *J* = 2.0 Hz, *ipso*-Ar), 149.0 (Ar), 136.2 (Ar), 121.7 (Ar), 121.4. (Ar), 88.7 (d, *J* = 175.0 Hz, FCH_2), 54.4 (d, *J* = 16.5 Hz, C), 34.1 (d, *J* = 4.5 Hz, CH_2), 25.0 (CH_2); MS (ESI) *m/z* 179 $(M + H)^+$; HRMS *m/z* calcd for $C_{11}H_{14}FN$ $(M + H)^+$ 180.1183, found 180.1180 (+2.0 ppm error).

Lab Book - PJ-07-34.

2-(4-(Fluoromethyl)tetrahydro-2H-pyran-4-yl)pyridine 293



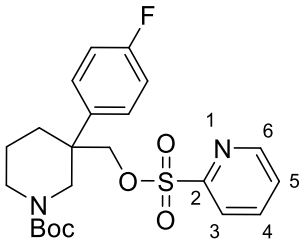
293

DBU (0.25 mL, 1.03 mmol, 2.0 eq) was added dropwise to a stirred solution of aryl THP alcohol **287** (100 mg, 0.52 mmol, 1.0 eq) and PyFluor (92 mg, 0.57 mmol, 1.1 eq) at rt under Ar. The resulting solution was stirred and heated at 80 °C for 48 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as an orange solid. Purification by flash column chromatography on silica with 60:40 hexane-EtOAc as eluent gave aryl THP fluoride **293** (86 mg, 85%) as a colourless oil, R_F (60:40 hexane-EtOAc) 0.35; IR (ATR) 2956, 1588, 1469, 1235, 1106, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, 6-py), 7.69 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H, 4-py), 7.39-7.33 (m, 1H, 3-py), 7.18 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, 5-py), 4.45 (d, *J* = 47.5 Hz, 2H, FCH_2), 3.84 (ddd, *J* = 12.0, 4.0, 4.0 Hz, 2H, OCH), 3.50 (ddd, *J* = 12.0, 10.0, 2.5 Hz, 2H, OCH), 2.41-2.31 (m, 2H, CH), 1.96 (ddd, *J* = 14.0, 10.0, 4.0 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.2 (*ipso*-Ar), 149.6 (Ar), 136.4 (Ar), 122.4 (Ar), 121.8 (Ar), 90.3 (d, *J* = 176.5 Hz, FCH_2), 64.3 (OCH_2), 43.8 (d, *J* = 17.5 Hz, C), 31.2 (d, *J* = 5.0 Hz,

CH_2); MS (ESI) *m/z* 196 $(M + H)^+$; HRMS *m/z* calcd for $C_{11}H_{14}FNO$ $(M + H)^+$ 196.1132, found 196.1127 (+3.1 ppm error).

Lab Book - PJ-07-84.

***tert*-Butyl 3-(4-fluorophenyl)-3-(((pyridin-2-ylsulfonyl)oxy)methyl)piperidine-1-carboxylate 294**

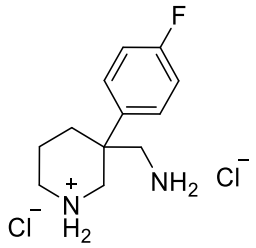


294

DBU (0.12 mL, 0.80 mmol, 2.0 eq) was added dropwise to a stirred solution of *N*-Boc aryl piperidine alcohol **281** (124 mg, 0.40 mmol, 1.0 eq) and PyFluor (71 mg, 0.44 mmol, 1.1 eq) at rt under Ar. The resulting solution was stirred and heated at 80 °C for 48 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 99:1 CH_2Cl_2-acetone as eluent gave *N*-Boc aryl piperidine sulfonate **294** (137 mg, 76%) as a colourless oil, R_F (99:1 CH_2Cl_2-acetone) 0.17; IR (ATR) 2976, 1638 (C=O), 1427, 1364, 1154, 830, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (ddd, *J* = 5.0, 1.0, 1.0 Hz, 1H, 6-py), 7.90-7.76 (m, 1H, 4-py and 3-py), 7.50 (ddd, *J* = 7.0, 5.0, 1.0 Hz, 1H, 5-py), 7.32-7.20 (m, 2H, Ar), 6.89 (dd, *J* = 8.5, 8.5 Hz, 2H, Ar), 4.33 (s, 2H, OCH_2), 4.11-3.91 (m, 1H, NCH), 3.61-3.37 (m, 2H, NCH), 3.27-3.17 (m, 1H, NCH), 2.19-1.84 (m, 2H, CH), 1.64-1.50 (m, 1H, CH), 1.51-1.30 (m, 10H, CMe_3 and CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 161.7 (d, *J* = 246.0 Hz, *ipso*-Ar), 154.8 (C=O or *ipso*-Ar), 154.4 (C=O or *ipso*-Ar), 150.2 (Ar), 138.2 (Ar), 136.0 (d, *J* = 3.5 Hz, Ar), 128.7 (d, *J* = 8.0 Hz, Ar), 127.6 (Ar), 123.0 (Ar), 115.29 (d, *J* = 21.0 Hz, Ar), 80.1 (CMe_3), 77.4 (OCH_2), 49.4 (NCH_2), 48.4 (NCH_2), 44.4 (NCH_2), 43.5 (NCH_2), 42.2 (C), 31.0 (CH_2), 28.5 (CMe_3), 21.0 (CH_2); MS (ESI) *m/z* 473 $(M + Na)^+$; HRMS *m/z* calcd for $C_{22}H_{27}FN_2O_5S$ $(M + Na)^+$ 473.1517, found 473.1512 (+1.7 ppm error).

Lab Book - PJ-07-80.

(3-(4-Fluorophenyl)piperidin-3-yl)methanamine 295·HCl



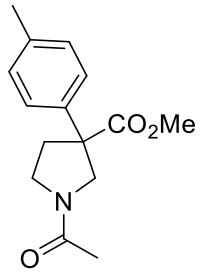
295

A solution of *N*-Boc aryl piperidine sulfonate **294** (137 mg, 0.30 mmol, 1.0 eq) in DMF (3 mL) was added dropwise to a stirred solution of NaN_3 (59 mg, 0.91 mmol, 3.0 eq) in DMF (1 mL) at rt under Ar. The resulting mixture was stirred and heated at 120 °C for 24 h. The reaction mixture was allowed to cool to rt and poured into water (10 mL) and Et_2O (10 mL). The two layers were separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. Purification by flash column chromatography on silica with 95:5-80:20 hexane-EtOAc as eluent gave *N*-Boc aryl piperidine azide (66 mg, 65%) as a colourless oil, R_F (95:5 hexane-EtOAc) 0.06; IR (ATR) 2935, 2098 (N_3), 1683 (C=O), 1425, 1153, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.29 (m, 2H, Ar), 7.03 (dd, *J* = 9.0, 9.0 Hz, 2H, Ar), 3.89 (d, *J* = 13.5 Hz, 1H, NCH), 3.51-3.42 (m, 2H, NCH), 3.40-3.36 (m, 2H, N_3CH), 3.36-3.25 (m, 1H, NCH), 2.07-1.96 (m, 1H, CH), 1.94-1.83 (m, 1H, CH), 1.72-1.52 (m, 2H, CH), 1.52-1.35 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 161.8 (d, *J* = 246.0 Hz, *ipso*-Ar), 155.2 (C=O or *ipso*-Ar) 154.6 (C=O or *ipso*-Ar), 137.6 (d, *J* = 2.5 Hz, *ipso*-Ar), 128.54 (d, *J* = 8.0 Hz, Ar), 115.45 (d, *J* = 21.0 Hz, Ar), 80.1 (*C*Me_3), 59.7 (N_3CH_2), 50.3 (NCH_2), 49.5 (NCH_2), 44.5 (NCH_2), 43.5 (NCH_2), 42.5 (C), 32.5 (CH_2), 32.2 (CH_2), 28.5 (C*Me*$_3$), 21.3 (CH_2); MS (ESI) *m/z* 357 $(M + Na)^+$; HRMS *m/z* calcd for $C_{17}H_{23}FN_4O_2$ $(M + Na)^+$ 357.1697, found 357.1695 (+0.0 ppm error). PPh_3 (103 mg, 0.40 mmol, 2.0 eq) was added to a stirred solution of *N*-Boc aryl piperidine azide (66 mg, 0.20 mmol, 1.0 eq) in 5:1 THF-water (6 mL) at rt. The resulting mixture was stirred and heated at 65 °C for 16 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-MeOH as eluent gave *N*-Boc aryl piperidine amine (49 mg, 79%) as a white solid, mp 82-84 °C; R_F (95:5 CH_2Cl_2-MeOH) 0.05; IR (ATR) 3360 (NH), 2979, 1676 (C=O), 1431, 1120, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 9.0, 5.5 Hz, 2H, Ar), 7.01 (dd, *J* = 9.0, 9.0 Hz, 2H, Ar), 3.85-3.70 (m, 1H, NCH), 3.68-3.45 (m, 1H, NCH), 3.45-3.19

(m, 2H, NCH), 2.92-2.58 (m, 2H, NCH), 2.10-1.87 (m, 1H, CH), 1.86-1.73 (m, 1H, CH), 1.66-1.54 (m, 1H, CH), 1.54-1.31 (m, 10H, CMe_3 and CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 161.4 (d, *J* = 245.5 Hz, *ipso*-Ar), 155.2 (C=O, Boc), 154.6 (C=O, Boc), 139.1 (*ipso*-Ar), 138.8 (*ipso*-Ar), 128.5 (d, *J* = 6.0 Hz, Ar), 115.4 (d, *J* = 21.0 Hz, Ar), 79.8 (*C*Me_3), 50.5 (NCH_2), 50.1 (NCH_2), 49.0 (NCH_2), 44.8 (NCH_2), 43.9 (NCH_2), 43.3 (C), 33.6 (CH_2), 33.2 (CH_2), 28.5 (C*Me*$_3$), 21.6 (CH_2), 21.5 (CH_2); MS (ESI) *m/z* 309 $(M + H)^+$; HRMS *m/z* calcd for $C_{17}H_{25}FN_2O_2$ $(M + H)^+$ 309.1973, found 309.1974 (–0.6 ppm error). HCl (1 mL of a 4 M solution in dioxane) was added dropwise to *N*-Boc aryl piperidine amine (49 mg, 0.15 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give aryl piperidine amine **295**·HCl (36 mg, 99%) as a white solid, mp 242-244 °C; IR (ATR) 3391 (NH), 2827, 1607, 1513, 1227, 1173, 842 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOD) δ 7.57 (dd, *J* = 9.0, 5.0 Hz, 2H, Ar), 7.27 (dd, *J* = 9.0, 9.0 Hz, 2H, Ar), 3.87 (d, *J* = 13.5 Hz, 1H, NCH), 3.46 (d, *J* = 13.5 Hz, 1H, NCH), 3.26 (s, 2H, NCH), 3.18-3.12 (m, 2H, NCH), 2.57-2.47 (m, 1H, CH), 2.05-1.90 (m, 2H, CH), 1.88-1.74 (m, 1H, CH); ^{13}C NMR (100.6 MHz, d_4-MeOH) δ 164.1 (d, *J* = 247.0 Hz, *ipso*-Ar), 133.6 (d, *J* = 3.0 Hz, *ipso*-Ar), 130.5 (d, *J* = 8.5 Hz, Ar), 117.9 (d, *J* = 21.5 Hz, Ar), 50.3 (NCH_2), 49.9 (NCH_2) 45.3 (NCH_2), 40.8 (C), 29.8 (CH_2), 19.7 (CH_2); MS (ESI) *m/z* 209 $(M)^+$; HRMS *m/z* calcd for $C_{12}H_{18}FN_2$ $(M)^+$ 209.1449, found 209.1449 (+2.9 ppm error).

Lab Book - PJ-07-91/PJ-08-02/PJ-08-11.

Methyl 1-acetyl-3-(*p*-tolyl)pyrrolidine-3-carboxylate 297

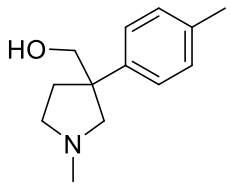


297

Et_3N (0.32 mL, 2.3 mmol, 10.0 eq) was added dropwise to a stirred solution of aryl pyrrolidine-3-methyl ester **296**·HCl (59 mg, 0.23 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, AcCl (0.02 mL, 0.34 mmol, 1.5 eq) was added dropwise and the solution was stirred at rt for 16 h. The solution was poured into water (10 mL) and the two layers were separated. The aqueous layer was extracted with

CH_2Cl_2 (3 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 70:29:1-50:49:1 hexane-EtOAc-$NH_4OH_{(aq)}$ as eluent gave *N*-acyl aryl pyrrolidine-3-methyl ester **297** (60 mg, 99%) as a yellow solid, mp 64-66 °C, R_F (70:29:1 hexane-EtOAc- $NH_4OH_{(aq)}$) 0.07; IR (ATR) 2957, 1723 (C=O, CO_2Me), 1634 (C=O, MeCO), 1416, 1193, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.23-7.03 (m, 4H, Ar), 4.51 (d, *J* = 11.5 Hz, 0.5H, NCH), 4.48 (d, *J* = 11.5 Hz, 0.5H, NCH), 3.70 (d, *J* = 11.5 Hz, 0.5H, NCH), 3.65 (s, 1.5H, OMe), 3.68-3.61 (m, 0.5H, NCH), 3.62 (s, 1.5H, OMe), 3.57-3.49 (m, 1.5H, OMe), 3.43 (ddd, *J* = 12.5, 10.0, 7.0 Hz, 0.5H, NCH), 3.03-2.91 (m, 0.5H, CH), 2.95-2.83 (m, 0.5H, CH), 2.33 (s, 1.5H, C_6H_4*Me*), 2.32 (s, 1.5H, C_6H_4*Me*), 2.2- 2.13 (m, 1H, CH), 2.10 (s, 1.5H, MeCO), 2.03 (s, 1.5H, MeCO); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 174.0 (C=O, CO_2Me), 173.8 (C=O, CO_2Me), 169.5 (C=O, *C*OMe), 169.3 (C=O, *C*OMe), 137.9 (*ipso*-Ar), 137.7 (*ipso*-Ar), 136.4 (*ipso*-Ar), 136.0 (*ipso*-Ar), 129.6 (Ar), 129.6 (Ar), 126.5 (Ar), 126.3 (Ar), 57.5 (C), 55.7 (NCH_2), 55.2 (OMe), 53.1 (NCH_2), 53.0 (OMe), 46.1 (NCH_2), 44.4 (NCH_2), 35.1 (CH_2), 33.2 (CH_2), 22.6 (CO*Me*), 22.2 (CO*Me*), 21.2 (C_6H_4*Me*); MS (ESI) *m/z* 284 $(M + Na)^+$; HRMS *m/z* calcd for $C_{15}H_{19}NO_3$ $(M + Na)^+$ 284.1257, found 284.1253 (+1.8 ppm error).
Lab Book - PJ-07-95.

(1-Methyl-3-(*p*-tolyl)pyrrolidin-3-yl)methanol 298



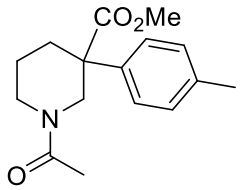
298

A solution of *N*-Boc aryl pyrolidine-3-*tert*-butyl ester **260** (120 mg, 0.33 mmol, 1.0 eq) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (63 mg, 1.66 mmol, 5 eq) in THF (5 mL) at 0 °C under Ar. The resulting suspension was stirred at 0 °C for 2 h. Then, the reaction mixture was allowed to warm to rt. The reaction mixture was then stirred and heated at reflux for 16 h. After the reaction mixture was cooled to 0 °C, water (0.1 mL), 20% $NaOH_{(aq)}$ (0.2 mL) and water (0.1 mL) were added sequentially (CARE – vigorous reaction). Then, $MgSO_4$ was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product as a green oil. Purification by

flash column chromatography on silica with 90:9:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$ as eluent gave *N*-methyl aryl pyrrolidine alcohol **298** (20 mg, 31%) as a colourless oil, R_F (90:9:1 CH_2Cl_2-MeOH-$NH_4OH_{(aq)}$) 0.17, IR (ATR) 3347 (OH), 2921, 1515, 1449, 1049, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.0 Hz, 2H, Ar), 7.07 (d, *J* = 8.0 Hz, 2H, Ar), 3.69 (d, *J* = 10.0 Hz, 1H, OCH), 3.51 (dd, *J* = 10.0, 2.0 Hz, 1H, OCH), 3.40 (d, *J* = 9.0 Hz, 1H, NCH), 3.27-3.20 (m, 1H, NCH), 2.64 (dd, *J* = 9.0, 2.0 Hz, 1H, NCH), 2.52-2.43 (m, 1H, CH), 2.40 (s, 3H, NMe), 2.32 (s, 3H, C_6H_4*Me*), 2.31-2.19 (m, 2H, CH and NCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.9 (*ipso*-Ar), 136.2 (*ipso*-Ar), 129.2 (Ar), 126.6 (Ar), 75.3 (OCH_2), 66.0 (NCH_2), 55.9 (NCH_2), 51.1 (C), 41.8 (NMe), 34.3 (CH_2), 21.0 (C_6H_4*Me*); MS (ESI) *m/z* 206 $(M + H)^+$; HRMS *m/z* calcd for $C_{13}H_{19}NO$ $(M + H)^+$ 206.1539, found 206.1537 (+1.0 ppm error).

Lab Book - PJ-07-90.

Methyl 1-acetyl-3-(*p*-tolyl)piperidine-3-carboxylate 299



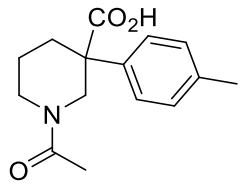
299

Et_3N (0.4 mL, 2.89 mmol, 10.0 eq) was added dropwise to a stirred solution of aryl piperidine-3-methyl ester **275**·HCl (78 mg, 0.28 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, AcCl (0.03 mL, 0.43 mmol, 1.5 eq) was added dropwise and the solution was stirred at rt for 16 h. The solution was poured into water (10 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 50:50-70:30 EtOAc-hexane as eluent gave *N*-acyl aryl piperidine-3-methyl ester **299** (68 mg, 88%) as a yellow oil, R_F (70:30 EtOAc-hexane) 0.1; IR (ATR) 2949, 1726 (C=O, CO_2Me), 1631 (C=O, MeCO), 1430, 1271, 1233, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.34-7.29 (m, 0.6H, Ar), 7.25-7.22 (m, 1.4H, Ar), 7.1-7.11 (m, 2H, Ar), 4.65-4.58 (m, 0.7H, NCH), 4.59-4.48 (m, 1H, NCH), 3.71 (d, *J* = 13.5 Hz, 0.3H, NCH), 3.67 (s, 2.1H, OMe), 3.61 (s, 0.9H, OMe), 3.55-3.46 (m, 0.3H, NCH), 3.23 (ddd, *J* = 13.0, 8.5, 4.0 Hz, 0.3H, NCH), 3.09 (d, *J* = 13.5 Hz,

0.7H, NCH), 2.74-2.66 (m, 0.7H, CH), 2.54 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 0.7H, NCH), 2.33 (s, 2.1H, C_6H_4*Me*), 2.31 (s, 0.9H, C_6H_4*Me*), 2.27 (s, 2.1H, MeCO), 2.11-2.02 (m, 0.3H, CH), 2.07 (s, MeCO), 1.91-1.75 (m, 1.4H, CH), 1.70-1.60 (m, 0.6H, CH), 1.61-1.46 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 174.2 (C=O, CO_2Me), 173.8 (C=O, CO_2Me), 170.0 (C=O, Me*C*O), 169.3 (C=O, Me*C*O), 137.8 (*ipso*-Ar), 137.2 (*ipso*-Ar), 136.8 (*ipso*-Ar), 129.7 (Ar), 129.5 (Ar), 126.3 (Ar), 125.6 (Ar), 53.9 (NCH_2), 52.5 (OMe), 52.4 (OMe), 51.0 (C), 49.9 (C), 47.4 (NCH_2), 46.6 (NCH_2), 41.3 (NCH_2), 33.1 (CH_2), 32.6 (CH_2), 23.1 (CH_2), 22.8 (CH_2), 21.9 (*Me*CO), 21.4 (*Me*CO), 21.1 (C_6H_4*Me*); MS (ESI) *m/z* 298 (M + Na)$^+$; HRMS *m/z* calcd for $C_{16}H_{21}NO_3$ (M + Na)$^+$ 298.1414, found 298.1408 (+1.6 ppm error).

Lab Book - PJ-07-97.

1-Acetyl-3-(*p*-tolyl)piperidine-3-carboxylic acid 300



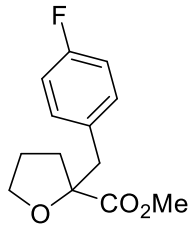
300

KOH (139 mg, 2.47 mmol, 10.0 eq) was added to a stirred solution of *N*-acyl aryl piperidine-3-methyl ester **299** (68 mg, 0.24 mmol, 1.0 eq) in EtOH (10 mL) at rt. The resulting mixture was stirred and heated at 100 °C for 16 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as an orange solid. The solid was taken up into water (10 mL) and washed with CH_2Cl_2 (3 x 10 mL). The aqueous layer was acidified with 1 M $HCl_{(aq)}$ (1 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give *N*-acyl aryl piperidine-3-carboxylic acid **300** (63 mg, 100%) as a white solid, mp 58-60 °C; IR (ATR) 2933, 2863, 1714 (C=O, CO_2H), 1591 (C=O, Me*C*O), 726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (70:30 mixture of rotamers) δ 7.33 (d, *J* = 8.0 Hz, 0.6H, Ar), 7.30 (d, *J* = 8.0 Hz, 1.4H, Ar), 7.16 (d, *J* = 8.0 Hz, 1.4H, Ar), 7.13 (d, *J* = 8.0 Hz, 0.6H, Ar), 4.72 (d, *J* = 13.5 Hz, 0.3H, NCH), 4.67-4.60 (m, 0.7H, NCH), 4.54 (dd, *J* = 13.5, 2.0 Hz, 0.7H, NCH), 3.58 (ddd, *J* = 13.0, 4.5, 4.5 Hz, 0.3H, NCH), 3.45 (d, *J* = 13.5 Hz, 0.3H, NCH), 3.17 (ddd, *J* = 13.0, 9.0, 4.0 Hz,0.3H, NCH), 3.07 (d, *J* = 13.5 Hz, 0.7H, NCH), 2.75.2.67 (m, 0.7H, CH), 2.58-2.46 (m, 1.0H, NCH and CH), 2.32 (s, 2.1H, C_6H_4*Me*), 2.30 (s, 0.9H,

C_6H_4*Me*), 2.26 (s, 2.1H, MeCO), 2.07 (s, 0.9H, MeCO), 1.99 (ddd, *J* = 13.5, 10.0, 4.5 Hz, 0.3H, CH), 1.86-1.73 (m, 1.7H, CH), 1.73-1.57 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 176.9 (C=O, CO_2H), 176.6 (C=O, CO_2H), 171.3 (C=O, Me*C*O), 170.3 (C=O, Me*C*O), 137.8 (*ipso*-Ar), 137.4 (*ipso*-Ar), 137.1 (*ipso*-Ar), 136.6 (*ipso*-Ar), 129.7 (Ar), 129.5 (Ar), 126.3 (Ar), 125.7 (Ar), 53.8 (NCH_2), 50.7 (C), 47.8 (NCH_2), 46.7 (NCH_2), 41.7 (NCH_2), 32.6 (CH_2), 23.0 (CH_2), 21.8 (*Me*CO), 21.3 (*Me*CO), 21.1 (C_6H_4*Me*); MS (ESI) *m/z* 284 $(M + Na)^+$; HRMS *m/z* calcd for $C_{15}H_{19}NO_3$ $(M + Na)^+$ 284.1257, found 284.1255 (+1.2 ppm error).

Lab Book - PJ-07-100.

Methyl 2-(4-fluorobenzyl)tetrahydrofuran-2-carboxylate 303

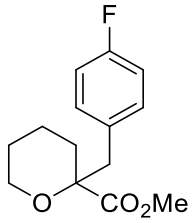


303

Using general procedure H, LiHMDS (1.08 mL of a 1.0 M solution in toluene, 1.08 mmol, 1.4 eq), THF-2-methyl ester **267** (0.09 mL, 0.77 mmol, 1.0 eq) and 4-fluorobenzyl bromide (0.13 mL, 1.08 mmol, 1.4 eq) in THF (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave aryl THF-2-methyl ester **303** (89 mg, 49%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.14; IR (ATR) 2952, 1729 (C=O), 1508, 1218, 1098, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.16 (m, 2H, Ar), 6.99-6.90 (m, 2H, Ar), 3.98-3.82 (m, 2H, OCH), 3.66 (s, 3H, OMe), 3.17 (d, *J* = 14.0 Hz, 1H, CHAr), 2.93 (d, *J* = 14.0 Hz, 1H, CHAr), 2.31-2.20 (m, 1H, CH), 1.94-1.76 (m, 2H, CH), 1.74-1.61 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.2 (C=O), 162.0 (d, *J* = 244.5 Hz, *ipso*-Ar), 132.2 (d, *J* = 3.5 Hz, *ipso*-Ar), 131.8 (d, *J* = 8.0 Hz, Ar), 115.0 (d, *J* = 21.0 Hz, Ar), 86.8 (C), 69.4 (OCH_2), 52.3 (OMe), 42.6 (CH_2Ar), 35.0 (CH_2), 25.4 (CH_2); MS (ESI) *m/z* 261 $(M + Na)^+$; HRMS *m/z* calcd for $C_{13}H_{15}FO_3$ $(M + Na)^+$ 261.0897, found 261.0892 (+2.3 ppm error).

Lab Book - PJ-07-22.

Methyl 2-(4-fluorobenzyl)tetrahydro-2H-pyran-2-carboxylate 304

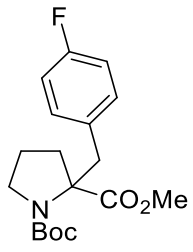


304

Using general procedure H, LiHMDS (1.08 mL of a 1.0 M solution in toluene, 1.08 mmol, 1.4 eq), THP-2-methyl ester **263** (0.1 mL, 0.77 mmol, 1.0 eq) and 4-fluorobenzyl bromide (0.13 mL, 1.08 mmol, 1.4 eq) in THF (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave aryl THP-2-methyl ester **304** (151 mg, 77%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.19; IR (ATR) 2947, 1729 (C=O), 1508, 1218, 1073, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16-7.09 (m, 2H, Ar), 6.98-6.89 (m, 2H, Ar), 3.93-3.86 (m, 1H, OCH), 3.68-3.59 (m, 4H, OMe and OCH), 2.91 (s, 2H, CHAr), 2.20-2.12 (m, 1H, CH), 1.76-1.67 (m, 1H, CH), 1.56-1.31 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.9 (C=O), 162.0 (d, *J* = 244.5 Hz, *ipso*-Ar), 131.8 (d, *J* = 8.0 Hz, Ar), 131.6 (d, *J* = 3.5 Hz, *ipso*-Ar), 114.9 (d, *J* = 21.0 Hz, Ar), 81.0 (C), 65.2 (OCH_2), 51.9 (OMe), 45.8 (CH_2Ar), 32.5 (CH_2), 25.2 (CH_2), 20.8 (CH_2); MS (ESI) *m/z* 275 $(M + Na)^+$; HRMS *m/z* calcd for $C_{14}H_{17}FO_3$ $(M + Na)^+$ 275.1054, found 275.1051 (+1.2 ppm error).

Lab Book - PJ-07-35.

1-(*tert*-Butyl) 2-methyl 2-(4-fluorobenzyl)pyrrolidine-1,2-dicarboxylate 305



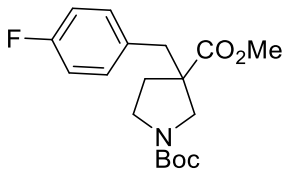
305

Using general procedure H, LiHMDS (0.42 mL of a 1.0 M solution in toluene, 0.42 mmol, 1.4 eq), *N*-Boc pyrrolidine-2-methyl ester **257** (69 mg, 0.3 mmol, 1.0 eq) and 4-fluorobenzyl bromide (0.052 mL, 0.42 mmol, 1.4 eq) in THF (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl pyrrolidine-2-methyl ester **305** (89 mg, 86%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.14; IR (ATR) 2976, 1739 (C=O, CO_2Me), 1692 (C=O, Boc), 1509,

1386, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.13-7.06 (m, 2H, Ar), 7.01-6.92 (m, 2H, Ar), 3.75 (s, 1.8H, OMe), 3.74 (s, 1.2H, OMe), 3.74-3.68 (m, 0.4H, CHAr), 3.56-3.45 (m, 1.2H, CHAr and NCH), 3.40 (ddd, *J* = 10.5, 7.0, 7.0 Hz, 0.4H, NCH), 3.08-2.96 (m, 1.6H, CHAr and NCH), 2.89 (ddd, *J* = 10.5, 7.5, 5.5 Hz, 0.4H, NCH), 2.12-1.97 (m, 2H, CH), 1.69-1.54 (m, 1H, CH), 1.50 (s, 3.6H, CMe_3), 1.48 (s, 5.4H, CMe_3), 1.06-0.96 (m, 0.4H, CH), 0.96-0.86 (m, 0.6H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 175.3 (C=O, CO_2Me), 175.1 (C=O, CO_2Me), 162.1 (d, *J* = 245.0 Hz, *ipso*-Ar), 161.9 (d, *J* = 244.5 Hz *ipso*-Ar), 154.3 (C=O, Boc), 153.7 (C=O, Boc), 133.07 (d, *J* = 3.0 Hz, *ipso*-Ar), 132.7 (d, *J* = 3.0 Hz, *ipso*-Ar), 132.3 (d, *J* = 7.5 Hz, Ar), 132.2 (d, *J* = 7.5 Hz, Ar), 115.3 (d, *J* = 21.0 Hz, Ar), 115.0 (d, *J* = 21.0 Hz, Ar), 80.6 (*C*Me_3), 79.8 (*C*Me_3), 68.4 (C), 68.0 (C), 52.5 (OMe), 52.4 (OMe), 48.4 (NCH_2), 48.4 (NCH_2), 39.1 (CH_2Ar), 37.8 (CH_2Ar), 36.7 (CH_2), 35.5 (CH_2), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$), 22.9 (CH_2), 22.3 (CH_2); MS (ESI) *m/z* 360 $(M + Na)^+$; HRMS *m/z* calcd for $C_{18}H_{24}FNO_4$ $(M + Na)^+$ 360.1582, found 360.1574 (+1.9 ppm error).

Lab Book - PJ-07-29.

1-(*tert*-Butyl) 3-methyl 3-(4-fluorobenzyl)pyrrolidine-1,3-dicarboxylate 306

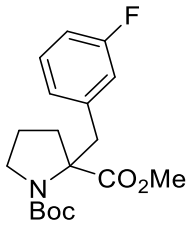


306

Using general procedure H, LiHMDS (0.61 mL of a 1.0 M solution in toluene, 0.61 mmol, 1.4 eq), *N*-Boc pyrrolidine-3-methyl ester **252** (100 mg, 0.43 mmol, 1.0 eq) and 4-fluorobenzyl bromide (0.08 mL, 0.61 mmol, 1.4 eq) in THF (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl pyrrolidine-3-methyl ester **306** (97 mg, 67%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.16; IR (ATR) 2976, 1732 (C=O, CO_2Me), 1691 (C=O, Boc), 1509, 1398, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.06-6.98 (m, 2H, Ar), 6.96-6.88 (m, 2H, Ar), 3.83-3.73 (m, 0.5H, NCH), 3.70-3.58 (m, 3.5H, OMe and NCH), 3.51-3.41 (m, 0.5H. NCH), 3.40-3.25 (m, 2.5H, NCH), 3.03-2.85 (m, 2H, CH_2Ar), 2.33-2.17 (m, 1H, CH), 1.92-1.79 (m, 1H, CH), 1.46-1.41 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 174.7 (C=O, CO_2Me), 174.6 (C=O, CO_2Me), 162.1 (d, *J* = 245.5 Hz, *ipso*-Ar), 154.5 (C=O, Boc), 154.4 (C=O, Boc), 132.7

(*ipso*-Ar), 131.0 (d, *J* = 8.0 Hz, Ar), 115.4 (d, *J* = 21.0 Hz, Ar), 79.7 (*C*Me$_3$), 79.9 (*C*Me$_3$), 54.7 (C), 54.0 (C), 53.1 (NCH$_2$), 52.3 (OMe), 44.8 (NCH$_2$), 44.3 (NCH$_2$), 41.2 (CH$_2$Ar), 41.0 (CH$_2$Ar), 33.7 (CH$_2$), 32.8 (CH$_2$), 28.6 (C*Me$_3$*); MS (ESI) *m/z* 360 (M + Na)$^+$; HRMS *m/z* calcd for $C_{18}H_{24}FNO_4$ (M + Na)$^+$ 360.1582, found 360.1577 (+1.5 ppm error).
Lab Book - PJ-07-71.

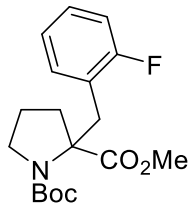
1-(*tert*-Butyl) 2-methyl 2-(3-fluorobenzyl)pyrrolidine-1,2-dicarboxylate 307



307

Using general procedure H, LiHMDS (0.61 mL of a 1.0 M solution in toluene, 0.61 mmol, 1.4 eq), *N*-Boc pyrrolidine-2-methyl ester **257** (100 mg, 0.43 mmol, 1.0 eq) and 3-fluorobenzyl bromide (0.075 mL, 0.61 mmol, 1.4 eq) in THF (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl pyrrolidine-2-methyl ester **307** (133 mg, 92%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.13; IR (ATR) 2976, 1739 (C=O, CO$_2$Me), 1691 (C=O, Boc), 1386, 1247, 1163 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) (60:40 mixture of rotamers) δ 7.29-7.15 (m, 1H, Ar), 6.98-6.89 (m, 2H, Ar), 6.88-6.82 (m, 1H, Ar), 3.79-3.72 (m, 0.4H, CHAr), 3.74 (s, 3H, OMe), 3.54 (d, *J* = 14.0 Hz, 0.6H, CHAr), 3.51-3.45 (m, 0.6H, NCH), 3.40 (ddd, *J* = 10.5, 7.0, 7.0 Hz, 0.4H, NCH), 3.08-2.98 (m, 1.6H, CHAr and NCH), 2.91 (ddd, *J* = 10.5, 7.5, 6.0 Hz, 0.4H, NCH), 2.09-1.98 (m, 2H, CH), 1.68-1.55 (m, 1H, CH), 1.49 (s, 3.6H, CMe$_3$), 1.47 (s, 5.4H, CMe$_3$), 1.09-0.87 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CDCl$_3$) (rotamers) δ 175.2 (C=O, CO$_2$Me), 175.1 (C=O, CO$_2$Me), 162.8 (d, *J* = 245.5 Hz, *ipso*-Ar), 154.3 (C=O, Boc), 153.6 (C=O, Boc), 140.0 (d, *J* = 7.5 Hz, *ipso*-Ar), 139.6 (d, *J* = 7.5 Hz, *ipso*-Ar), 129.9 (d, *J* = 8.0 Hz, Ar), 129.4 (d, *J* = 8.0 Hz, Ar), 126.6 (d, *J* = 3.0 Hz, Ar), 126.5 (d, *J* = 3.0 Hz, Ar), 117.8 (d, *J* = 2.5 Hz, Ar), 117.6 (d, *J* = 2.5 Hz, Ar), 113.8 (d, *J* = 21.0 Hz, Ar), 113.5 (d, *J* = 21.0 Hz, Ar), 80.6 (*C*Me$_3$), 79.9 (*C*Me$_3$), 68.3 (C), 68.0 (C), 52.5 (OMe), 52.4 (OMe), 48.4 (NCH$_2$), 39.8 (CH$_2$Ar), 38.4 (CH$_2$Ar), 36.8 (CH$_2$), 35.5 (CH$_2$), 28.6 (C*Me$_3$*), 28.5 (C*Me$_3$*), 22.9 (CH$_2$), 22.4 (CH$_2$); MS (ESI) *m/z* 360 (M + Na)$^+$; HRMS *m/z* calcd for $C_{18}H_{24}FNO_4$ (M + Na)$^+$ 360.1582, found 360.1579 (+0.1 ppm error).
Lab Book - PJ-07-68.

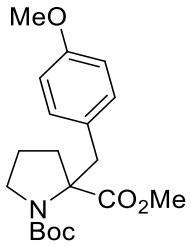
1-(*tert*-Butyl) 2-methyl 2-(2-fluorobenzyl)pyrrolidine-1,2-dicarboxylate 308



308

Using general procedure H, LiHMDS (0.61 mL of a 1.0 M solution in toluene, 0.61 mmol, 1.4 eq), *N*-Boc pyrrolidine-2-methyl ester **257** (100 mg, 0.43 mmol, 1.0 eq) and 2-fluorobenzyl bromide (0.07 mL, 0.61 mmol, 1.4 eq) in THF (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl pyrrolidine-2-methyl ester **308** (130 mg, 90%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.11; IR (ATR) 2976, 1740 (C=O, CO_2Me), 1693 (C=O, Boc), 1385, 1165, 1103, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers δ 7.27-7.13 (m, 1H, Ar), 7.17-7.06 (m, 1H, Ar), 7.10-6.94 (m, 2H, Ar), 3.74 (s, 1.2H, OMe), 3.74 (s, 1.8H, OMe), 3.58 (d, *J* = 13.5 Hz, 0.8H, CHAr), 3.51-3.32 (m, 2.6H, CHAr and NCH), 3.05-2.98 (m, 0.6H, NCH), 2.97-2.89 (m, 0.4H, NCH), 2.14-1.97 (m, 2H, CH), 1.67-1.57 (m, 1H, CH), 1.49-1.45 (m, 9H, CMe_3), 1.10-0.89 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 175.2 (C=O, CO_2Me), 175.0 (C=O, CO_2Me), 161.8 (d, *J* = 245.0 Hz, *ipso*-Ar), 154.3 (C=O, Boc), 153.7 (C=O, Boc), 133.2 (d, *J* = 4.5 Hz, Ar), 132.9 (d, *J* = 4.5 Hz, Ar), Ar, 128.6 (d, *J* = 8.0 Hz, Ar), 128.4 (d, *J* = 8.0 Hz, Ar), 124.5 (*ipso*-Ar), 124.3 (*ipso*-Ar), 124.1 (d, *J* = 4.0 Hz, Ar), 123.9 (d, *J* = 4.0 Hz, Ar), 115.4 (d, *J* = 22.5 Hz, Ar), 115.1 (d, *J* = 22.5 Hz, Ar), 80.5 (*C*Me_3), 79.7 (*C*Me_3), 68.6 (C), 68.2 (C), 52.4 (OMe), 52.3 (OMe), 48.3 (NCH_2), 48.2 (NCH_2), 36.7 (CH_2), 35.6 (CH_2), 32.5 (CH_2Ar), 31.4 (CH_2Ar), 28.5 (C*Me*$_3$), 28.4 (C*Me*$_3$), 23.1 (CH_2), 22.5 (CH_2); MS (ESI) *m/z* 360 $(M + Na)^+$; HRMS *m/z* calcd for $C_{18}H_{24}FNO_4$ $(M + Na)^+$ 360.1582, found 360.1576 (+1.7 ppm error). Lab Book - PJ-07-64.

1-(*tert*-Butyl) 2-methyl 2-(4-methoxybenzyl)pyrrolidine-1,2-dicarboxylate 309

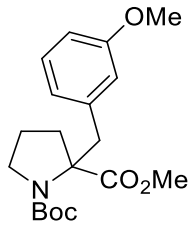


309

Using general procedure H, LiHMDS (0.61 mL of a 1.0 M solution in toluene, 0.61 mmol, 1.4 eq), *N*-Boc pyrrolidine-2-methyl ester **257** (100 mg, 0.43 mmol, 1.0 eq) and 4-methoxybenzyl bromide (123 mg, 0.61 mmol, 1.4 eq) in THF (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl pyrrolidine-2-methyl ester **309** (137 mg, 91%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.09; IR (ATR) 2973, 1738 (C=O, CO_2Me), 1691 (C=O, Boc) 1512, 1387, 1246, 1166 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOD) (55:45 mixture of rotamers) δ 7.06-7.02 (m, 2H, Ar), 6.86-6.80 (m, 2H, Ar), 3.76 (s, 1.35H, OMe), 3.754 (s, 1.65H, OMe), 3.749 (s, 1.65H, OMe), 3.72 (s, 1.35H, OMe), 3.58 (d, *J* = 14.0 Hz, 0.45H, CHAr), 3.46 (d, *J* = 14.0 Hz, 0.55H, CHAr), 3.42-3.33 (m, 1H, NCH), 2.97 (d, *J* = 14.0 Hz, 0.55H, CHAr), 2.95 (d, *J* = 14.0 Hz, 0.45H, CHAr), 2.88 (ddd, *J* = 10.0, 7.5, 5.0, Hz, 1H, NCH), 2.20-1.93 (m, 2H, CH), 1.66-1.52 (m, 1H, CH), 1.50 (s, 4.05H, CMe_3), 1.48 (s, 4.95H, CMe_3), 1.05-0.88 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 175.5 (C=O, CO_2Me), 175.3 (C=O, CO_2Me), 158.5 (*ipso*-Ar), 158.3 (*ipso*-Ar), 154.2 (C=O, Boc), 153.6 (C=O, Boc), 131.8 (Ar), 131.6 (Ar), 129.3 (*ipso*-Ar), 128.8 (*ipso*-Ar), 113.8 (Ar), 113.5 (Ar), 80.4 (*C*Me_3), 79.6 (*C*Me_3), 68.5 (C), 68.1 (C), 55.3 (OMe), 52.4 (OMe), 52.3 (OMe), 48.3 (NCH_2), 48.3 (NCH_2), 38.9 (CH_2Ar), 37.6 (CH_2Ar), 36.6 (CH_2), 35.4 (CH_2), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$), 22.9 (CH_2), 22.3 (CH_2); MS (ESI) *m/z* 372 $(M + Na)^+$; HRMS *m/z* calcd for $C_{19}H_{27}NO_5$ $(M + Na)^+$ 372.1781, found 372.1775 (+1.5 ppm error).

Lab Book - PJ-08-15.

1-(*tert*-Butyl) 2-methyl 2-(3-methoxybenzyl)pyrrolidine-1,2-dicarboxylate 310

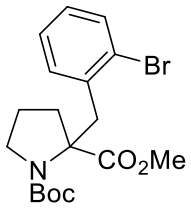


310

Using general procedure H, LiHMDS (0.61 mL of a 1.0 M solution in toluene, 0.61 mmol, 1.4 eq), *N*-Boc pyrrolidine-2-methyl ester **257** (100 mg, 0.43 mmol, 1.0 eq) and 3-methoxybenzyl bromide (0.085 mL, 0.61 mmol, 1.4 eq) in THF (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl pyrrolidine-2-methyl ester **310** (103 mg, 68%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.12; IR (ATR) 2974, 1739 (C=O, CO_2Me), 1692 (C=O, Boc), 1388, 1249, 1166, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.21-7.15 (m, 1H, Ar), 6.81-6.66 (m, 3H, Ar), 3.79 (s, 1.2H, OMe), 3.77 (s, 1.8H, OMe), 3.75 (s, 3H, OMe), 3.75-3.70 (m, 0.4H, CHAr), 3.56 (d, *J* = 14.0 Hz, 0.6H, CHAr), 3.49 (ddd, *J* = 10.5, 7.5, 7.5 Hz, 0.6H, NCH), 3.41 (ddd, *J* = 10.5, 7.5, 7.5 Hz, 0.4H, NCH), 3.05-2.97 (m, 1.6H, CHAr and NCH), 2.97-2.90 (m, 0.4H, NCH), 2.14-1.93 (m, 2H, CH), 1.64-1.53 (m, 1H, CH), 1.50 (s, 3.6H, CMe_3), 1.49 (s, 5.4H, CMe_3), 1.07-0.90 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 175.4 (C=O, CO_2Me), 175.3 (C=O, CO_2Me), 159.5 (*ipso*- Ar), 159.4 (*ipso*-Ar), 154.2 (C=O, Boc), 153.6 (C=O, Boc), 138.9 (*ipso*-Ar), 138.5 (*ipso*-Ar), 129.2 (Ar), 128.9 (Ar), 123.4 (Ar), 123.2 (Ar), 116.4 (Ar), 116.1 (Ar), 112.4 (Ar), 112.1 (Ar), 80.4 (*C*Me_3), 79.7 (*C*Me_3), 68.4 (C), 68.0 (C), 55.3 (OMe), 55.2 (OMe), 52.4 (OMe), 52.3 (OMe), 48.4 (NCH_2), 48.3 (NCH_2), 39.8 (CH_2Ar), 38.6 (CH_2Ar), 36.7 (CH_2), 35.4 (CH_2), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$), 22.9 (CH_2), 22.3 (CH_2); MS (ESI) *m/z* 372 $(M + Na)^+$; HRMS *m/z* calcd for $C_{19}H_{27}NO_5$ $(M + Na)^+$ 372.1781, found 372.1780 (+0.5 ppm error).

Lab Book - PJ-07-59.

1-(*tert*-Butyl) 2-methyl 2-(2-bromobenzyl)pyrrolidine-1,2-dicarboxylate 311

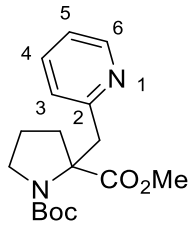


311

Using general procedure H, LiHMDS (3.19 mL of a 1.0 M solution in toluene, 3.19 mmol, 1.4 eq), *N*-Boc pyrrolidine-2-methyl ester **257** (500 mg, 2.28 mmol, 1.0 eq) and 2-bromobenzyl bromide (796 mL, 3.19 mmol, 1.4 eq) in THF (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 90:10 hexane-EtOAc as eluent gave *N*-Boc aryl pyrrolidine-2-methyl ester **311** (813 mg, 89%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.19; IR (ATR) 2974, 1739 (C=O, CO_2Me), 1692 (C=O, Boc), 1384, 1163, 1024, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.58-7.51 (m, 1H, Ar), 7.25-7.18 (m, 1H, Ar), 7.17-7.12 (m, 1H, Ar), 7.12-7.05 (m, 1H, Ar), 3.79-3.72 (m, 3H, OMe), 3.73-3.61 (m, 1.4H, CHAr and NCH), 3.58-3.39 (m, 1.6H, CHAr and NCH), 3.08-3.00 (m, 0.6H, NCH), 2.99-2.91 (m, 0.4H, NCH), 2.26-2.12 (m, 1H, CH), 2.10-1.96 (m, 1H, CH), 1.72-1.57 (m, 1H, CH), 1.53-1.48 (m, 3.6H, CMe_3), 1.49-1.45 (m, 5.4H, CMe_3), 1.09-0.90 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 175.0 (C=O, CO_2Me), 174.9 (C=O, CO_2Me), 154.4 (C=O, Boc), 153.7 (C=O, Boc), 137.5 (*ipso*-Ar), 137.1 (*ipso*-Ar), 133.1 (Ar), 132.9 (Ar), 132.9 (Ar), 132.6 (Ar), 128.5 (Ar), 128.2 (Ar), 127.6 (Ar), 127.3 (Ar), 126.4 (*ipso*-Ar), 80.6 (*C*Me_3), 79.9 (*C*Me_3), 69.2 (C), 68.8 (C), 52.5 (OMe), 52.5 (OMe), 48.3 (NCH_2), 48.2 (NCH_2), 38.2 (CH_2Ar), 37.1 (CH_2Ar), 36.4 (CH_2), 35.3 (CH_2), 28.6 (C*Me*$_3$), 28.5 (C*Me*$_3$), 23.2 (CH_2), 22.6 (CH_2); MS (ESI) *m/z* 420 $(M + Na)^+$; HRMS *m/z* calcd for $C_{18}H_{24}{}^{79}BrNO_4$ $(M + Na)^+$ 420.0781, found 420.0774 (+0.6 ppm error).

Lab Book - PJ-08-09.

1-(*tert*-Butyl) 2-methyl 2-(pyridin-2-ylmethyl)pyrrolidine-1,2-dicarboxylate 312



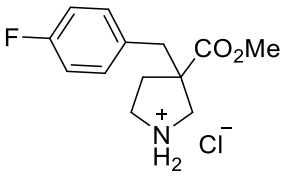
312

LiHMDS (0.61 mL of a 1.0 M solution in toluene, 0.61 mmol, 1.4 eq) was added dropwise to a stirred solution of *N*-Boc pyrrolidine-2-methyl ester **257** (100 mg, 0.43 mmol, 1.0 eq) in THF (4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1.5 h. In a separate flask sat $NaHCO_{3(aq)}$ (5 mL) was added to 2(bromomethyl)pyridine·HBr (153 mg, 0.61 mmol) and the solution was extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried (Na_2CO_3) and evaporated under reduced pressure to give a red oil. The oil was taken up into THF (2 mL) and added dropwise to the enolate reaction mixture at –78 °C under Ar. The resulting solution was stirred at –78 °C and slowly warmed up to rt over 16 h. The solution was poured into sat $NH_4Cl_{(aq)}$ (10 mL) and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 60:40 hexane-EtOAc as eluent gave *N*-Boc aryl pyrrolidine-2-methyl ester **312** (45 mg, 33%) as a colourless oil, R_F (90:10 hexane-EtOAc) 0.11; IR (ATR) 2974, 1739 (C=O, CO_2Me), 1691 (C=O, Boc), 1387, 1162, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 8.54-8.48 (m, 1H, 6-py), 7.61-7.53 (m, 1H, 4-py), 7.17-7.12 (m, 1H, 3-py), 7.12-7.06 (m, 1H, 5-py), 3.83 (d, *J* = 13.5 Hz, 0.4H, CHAr), 3.74 (s, 3H, OMe), 3.64 (d, *J* = 13.5 Hz, 0.6H, CHAr), 3.48 (ddd, *J* = 10.5, 7.0, 7.0 Hz, 0.6H, NCH), 3.40 (ddd, *J* = 10.5, 7.0, 7.0 Hz, 0.4H, NCH), 3.32 (d, *J* = 13.5 Hz, 0.6H, CHAr), 3.30 (d, *J* = 13.5 Hz, 0.4H, CHAr), 2.88 (ddd, *J* = 10.5, 7.5, 6.0 Hz, 0.6H, NCH), 2.81 (ddd, *J* = 10.5, 7.0, 7.0 Hz, 0.4H, NCH), 2.63-2.49 (m, 1H, CH), 2.12-1.99 (m, 1H, CH), 1.70-1.60 (m, 1H, CH), 1.49 (s, 5.6H, CMe_3), 1.46 (s, 3.4H, CMe_3), 1.08 (ddddd, *J* = 13.5, 7.0, 7.0, 7.0, 7.0 Hz, 0.4H, CH), 0.98-0.84 (m, 0.6H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 175.1 (C=O, CO_2Me), 157.9 (*ipso*-Ar), 153.7 (C=O, Boc), 149.1 (Ar), 148.8 (Ar), 136.3 (Ar), 136.0 (Ar), 125.6 (Ar), 125.3 (Ar), 121.8 (Ar), 121.6 (Ar), 80.6 (CMe_3), 79.7 (CMe_3), 68.4 (C), 68.0 (C), 52.5 (OMe), 52.4 (OMe), 48.4 (NCH_2), 48.3 (NCH_2), 42.2 (CH_2Ar), 41.0 (CH_2Ar), 36.4 (CH_2), 35.3 (CH_2), 28.6 (CMe_3), 22.9 (CH_2),

22.4 (CH_2); MS (ESI) *m/z* 321 $(M + H)^+$; HRMS *m/z* calcd for $C_{17}H_{25}N_2O_4$ $(M + H)^+$ 321.1809, found 321.1807 (+0.7 ppm error).

Lab Book - PJ-07-48.

Methyl 3-(4-fluorobenzyl)pyrrolidine-3-carboxylate 314·HCl

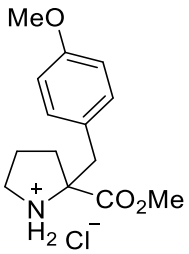


314

HCl (1 mL of a 4 M solution in dioxane) was added dropwise to *N*-Boc aryl pyrrolidine-3-methyl ester **306** (50 mg, 0.15 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give aryl pyrrolidine-3-methyl ester **314**·HCl (40 mg, 99%) as a red oil, IR (ATR) 3406 (NH), 2906, 2725, 1729 (C=O), 1509, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (br s, 1H, NH), 9.74 (br s, 1H, NH), 7.17-7.00 (m, 2H, Ar), 7.00-6.86 (m, 2H, Ar), 3.68 (s, 3H, OMe), 3.68-3.63 (m, 1H, NCH), 3.55-3.46 (m, 1H, NCH), 3.37-3.25 (m, 2H, NCH), 3.12 (d, *J* = 14.0 Hz, 1H, CHAr), 3.03 (d, *J* = 14.0 Hz, 1H, CHAr), 2.41 (ddd, *J* = 13,0, 7.5, 5.0 Hz, 1H, CH), 2.07 (ddd, *J* = 13.5, 8.5, 8.5 Hz, 1H, CH Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C=O), 162.2 (d, *J* = 246.0 Hz, *ipso*-Ar), 131.7 (d, *J* = 3.5 Hz, *ipso*-Ar), 131.0 (d, *J* = 8.0 Hz, Ar), 115.7 (d, *J* = 21.5 Hz, Ar), 55.1 (C), 52.9 (OMe), 50.8 (NCH_2), 44.4 (NCH_2), 40.9 (CH_2Ar), 33.9 (CH_2); MS (ESI) *m/z* 238 $(M)^+$; HRMS *m/z* calcd for $C_{13}H_{17}FNO_2$ $(M)^+$ 238.1238, found 238.1238 (+0.4 ppm error).

Lab Book - PJ-08-16.

Methyl 2-(4-methoxybenzyl)pyrrolidine-2-carboxylate 313·HCl

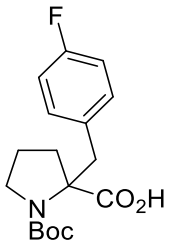


313

HCl (1 mL of a 4 M solution in dioxane) was added dropwise to *N*-Boc aryl pyrrolidine-2-methyl ester **309** (50 mg, 0.14 mmol, 1.0 eq) at rt under Ar. The resulting solution was stirred

at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give aryl pyrrolidine-2-methyl ester **313**·HCl (39 mg, 99%) as a white solid, mp 172-174 °C; IR (ATR) 2884, 2704, 1755 (C=O), 1513, 1255, 1202, 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.55 (s, 1H, NH), 8.24 (s, 1H, NH), 7.32-7.27 (m, 2H, Ar), 6.84-6.79 (m, 2H, Ar), 3.80-3.68 (m, 8H, OMe, NCH and CHAr), 3.47-3.34 (m, 2H, NCH and CHAr), 2.57-2.46 (m, 1H, CH), 2.35-2.15 (m, 2H, CH), 1.95-1.81 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5 (C=O), 159.3 (*ipso*-Ar), 130.8 (Ar), 125.8 (*ipso*-Ar), 114.4 (Ar), 74.7 (C), 55.3 (OMe), 53.7 (OMe), 45.5 (NCH_2), 39.5 (CH_2Ar), 34.1 (CH_2), 22.3 (CH_2); MS (ESI) *m/z* 250 $(M)^+$; HRMS *m/z* calcd for $C_{14}H_{20}NO_3$ $(M)^+$ 250.1438, found 250.1436 (+0.7 ppm error).
Lab Book - PJ-08-15.

1-(*tert*-Butoxycarbonyl)-2-(4-fluorobenzyl)pyrrolidine-2-carboxylic acid 321

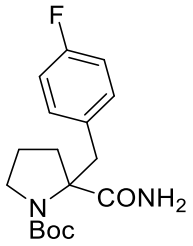


321

KOH (90 mg, 1.6 mmol, 10.0 eq) was added to a stirred solution of *N*-Boc aryl pyrrolidine-2-methyl ester **305** (55 mg, 0.16 mmol, 1.0 eq) in EtOH (10 mL) at rt. The resulting mixture was stirred and heated at 100 °C for 16 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as an orange solid. The solid was taken up into water (10 mL) and washed with CH_2Cl_2 (3 x 50 mL). The aqueous layer was then acidified with 1 M $HCl_{(aq)}$ (1 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give *N*-Boc aryl pyrrolidine-2-carboxylic acid **321** (50 mg, 98%) as a white solid, mp 178-180 °C; IR (ATR) 2984, 1739 (C=O, CO_2H), 1636 (C=O, Boc), 1419, 1219, 1148, 847, 770 cm^{-1}; ^{1}H NMR (400 MHz, d_4-MeOH) (60:40 mixture of rotamers) δ 7.19-7.14 (m, 2H, Ar), 7.05-6.98 (m, 2H, Ar), 3.68 (d, *J* = 14.0 Hz, 0.4H, CHAr), 3.52 (d, *J* = 14.0 Hz, 0.6H, CHAr), 3.46-3.36 (m, 1H, NCH), 3.05-2.99 (m, 1H, CHAr), 2.95-2.86 (m, 1H, NCH), 2.18-2.04 (m, 2H, CH), 1.70-1.58 (m, 1H, CH), 1.51 (s, 3.4H, C*Me*$_3$), 1.50 (s, 5.6H, C*Me*$_3$), 1.07-0.88 (m, 1H, CH); ^{13}C NMR (100.6 MHz, d_4-MeOH) (rotamers) δ 177.8 (C=O, CO_2H), 177.7 (C=O, CO_2H), 163.4 (d, *J* = 244.0 Hz, *ipso*-Ar), 163.3 (d, *J* = 244.0 Hz, *ipso*-Ar) 155.8 (C=O, Boc), 155.7 (C=O, Boc), 134.5 (d, *J* = 3.5 Hz, *ipso*-Ar), 134.4 (d,

J = 3.5 Hz, *ipso*-Ar), 133.4 (d, *J* = 8.0 Hz, Ar), 133.3 (d, *J* = 8.0 Hz, Ar), 115.9 (d, *J* = 21.5 Hz, Ar), 115.7 (d, *J* = 21.5 Hz, Ar), 82.2 (*C*Me$_3$), 81.1 (*C*Me$_3$), 69.5 (C), 69.5 (C), 49.7 (NCH$_2$), 49.5 (NCH$_2$), 39.8 (CH$_2$Ar), 38.5 (CH$_2$Ar), 37.8 (CH$_2$), 36.7 (CH$_2$), 28.9 (C*Me$_3$*), 28.7 (C*Me$_3$*), 23.6 (CH$_2$), 23.1 (CH$_2$); MS (ESI) *m/z* 346 $(M + Na)^+$; HRMS *m/z* calcd for $C_{17}H_{22}FNO_4$ $(M + Na)^+$ 346.1425, found 346.1420 (+1.5 ppm error).
Lab Book - PJ-07-44.

tert-Butyl 2-carbamoyl-2-(4-fluorobenzyl)pyrrolidine-1-carboxylate 322

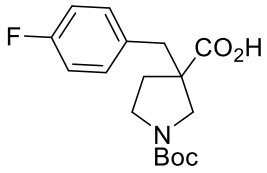


322

T3P (0.07 mL of a 50% wt solution in EtOAc, 0.23 mmol, 1.5 eq) was added dropwise to a stirredsolution of *N*-Boc aryl pyrrolidine-2-carboxylix acid **321** (50 mg, 0.15 mmol, 1.0 eq), DIPEA (0.08 mL, 0.46 mmol, 3.0 eq) and 35% $NH_{3(aq)}$ (0.018 mL, 0.47 mmol, 3.0 eq) in CH_2Cl_3 (3 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, water (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organics were washed with 2 M $NaOH_{(aq)}$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated under redued pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with EtOAc as eluent gave *N*-Boc aryl pyrrolidine amide **322** (21 mg, 45%) as a colourless oil, R_F (EtOAc) 0.36; IR (ATR) 3381 (NH), 2982, 1658 (C=O), 1509, 1395, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.41 (br s, 0.6H, NH), 7.15-7.04 (m, 2H, Ar), 7.01-6.92 (m, 2H, Ar), 5.80 (br s, 0.4H, NH). 5.39 (br s, 1H, NH), 3.70 (d, *J* = 14.0 Hz, 0.6H, CHAr), 3.54 (d, *J* = 14.0 Hz, 0.4H, CHAr), 3.51-3.45 (m, 0.4H, NCH), 3.40 (ddd, *J* = 11.0, 8.0, 3.0 Hz, 0.6H, NCH), 3.16 (d, *J* = 14.0 Hz, 0.4H, CHAr), 3.11 (d, *J* = 14.0 Hz, 0.6H, CHAr), 3.02-2.86 (m, 1H, NCH), 2.44 (ddd, *J* = 12.5, 6.5, 3.5 Hz, 0.6H, CH), 2.17-2.10 (m, 0.6H, CH), 1.81 (ddd, *J* = 13.0, 11.0, 7.0 Hz, 0.6H, CH), 1.60-1.56 (m, 1.2H, CH), 1.53 (s, 3.6H, C*Me$_3$*), 1.52 (s, 5.4H, C*Me$_3$*), 1.38-1.29 (m, 0.6H, CH), 1.04-0.94 (m, 0.4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 177.8 (C=O, CONH), 176.9 (C=O, CONH), 161.94 (d, *J* = 245.0 Hz, *ipso*-Ar), 155.5 (C=O, Boc), 153.6 (C=O, Boc), 132.9 (d, *J* = 3.0 Hz, *ipso*-Ar), 132.4 (d, *J* = 3.0 Hz, *ipso*-Ar), 132.1 (d, *J* = 8.0 Hz, Ar), 131.9 (d, *J* =

8.0 Hz, Ar), 115.4 (d, *J* = 21.0 Hz, Ar), 115.1 (d, *J* = 21.0 Hz, Ar), 81.5 (*C*Me$_3$), 80.6 (*C*Me$_3$), 70.8 (C), 69.1 (C), 49.5 (NCH$_2$), 48.5 (NCH$_2$), 37.9 (CH$_2$Ar), 37.8 (CH$_2$Ar), 37.4 (CH$_2$), 34.2 (CH$_2$), 28.6 (C*Me$_3$*), 22.2 (C*Me$_3$*), 22.0 (CH$_2$); MS (ESI) *m/z* 345 $(M + Na)^+$; HRMS *m/z* calcd for $C_{17}H_{23}FN_2O_3$ $(M + Na)^+$ 345.1585, found 345.1581 (+1.0 ppm error). Lab Book - PJ-07-61.

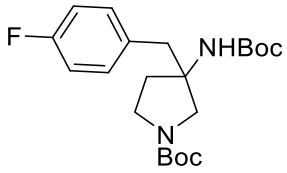
1-(*tert*-Butoxycarbonyl)-3-(4-fluorobenzyl)pyrrolidine-3-carboxylic acid 323



323

KOH (83 mg, 1.5 mmol, 10.0 eq) was added to a stirred solution of *N*-Boc aryl pyrrolidine-3-methyl ester **306** (50 mg, 0.15 mmol, 1.0 eq) in EtOH (10 mL) at rt. The resulting mixture was stirred and heated at 100 °C for 16 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give the crude product as an orange solid. The solid was taken up into water (10 mL) and washed with CH_2Cl_2 (3 x 50 mL). The aqueous layer was then acidified with 1 M $HCl_{(aq)}$ (1 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give *N*-Boc aryl pyrrolidine-3-carboxylic acid **323** (48 mg, 100%) as a white solid, mp 122-124 °C; IR (ATR) 2915, 1717 (C=O, CO_2H), 1632 (C=O, Boc), 1433, 1141, 893 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.17-7.04 (m, 2H, Ar), 7.02-6.89 (m, 2H, Ar), 3.82 (d, *J* = 11.5 Hz, 0.5H, CHAr), 3.71 (d, *J* = 11.5 Hz, 0.5H, CHAr), 3.55-3.28 (m, 3H, NCH and CHAr), 3.09-2.91 (m, 2H, CH), 2.35-2.25 (m, 1H, CH), 1.96-1.83 (m, 1H, CH), 1.46 (s, 9H, C*Me$_3$*); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 179.3 (C=O, CO_2H), 179.2 (C=O, CO_2H), 162.1 (d, *J* = 246.0 Hz, *ipso*-Ar), 154.6 (C=O, Boc), 132.4 (*ipso*-Ar), 131.1 (d, *J* = 8.0 Hz, Ar), 115.4 (d, *J* = 21.0 Hz, Ar), 80.0 (*C*Me$_3$), 79.9 (*C*Me$_3$), 54.4 (C), 53.7 (C), 52.9 (CH$_2$Ar), 44.8 (NCH$_2$), 44.3 (NCH$_2$), 40.8 (CH$_2$), 40.6 (CH$_2$), 33.5 (CH$_2$), 32.9 (CH$_2$), 28.6 (C*Me$_3$*); MS (ESI) *m/z* 346 $(M + Na)^+$; HRMS *m/z* calcd for $C_{17}H_{22}FNO_4$ $(M + Na)^+$ 346.1425, found 346.1427 (–1.4 ppm error). Lab Book - PJ-08-07.

***tert*-Butyl 3-((*tert*-butoxycarbonyl)-l2-azanyl)-3-(4-fluorobenzyl)pyrrolidine-1-carboxylate 324**

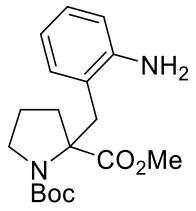


324

Et_3N (0.06 mL, 0.44 mmol, 2.0 eq) was added dropwise to a stirred solution of *N*-Boc pyrrolidine-3-carboxylic acid **323** (72 mg, 0.22 mmol, 1.0 eq), DPPA (0.06 mL, 0.27 mmol, 1.2 eq) and 3Å MS (50 mg) in *t*BuOH (10 mL) at rt under Ar. The resulting solution was stirred and heated at 40 °C for 1 h and then at 100 °C for 16 h. The reaction mixture was allowed to cool to rt and the solids were removed by filtration through Celite and washed with MeOH (10 mL). The filtrate was evaporated under redued pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 95:5-80:20 hexane-EtOAc as eluent gave *N*-Boc aryl pyrrolidine amine **324** (44 mg, 51%) as a colourless oil, R_F (80:20 hexane-EtOAc) 0.25; IR (ATR) 2977, 1627 (C=O), 1509, 1404, 1216, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.11-7.02 (m, 2H, Ar), 7.00-6.90 (m, 2H, Ar), 3.61-3.06 (m, 5H, NCH and CHAr), 3.00-2.83 (m, 1H, CHAr), 2.43-2.22 (m, 0.5H, CH), 2.04-1.92 (m, 0.5H, CH), 1.86 (ddd, *J* = 12.5, 8.5, 8.5 Hz, 1H, CH), 1.53-1.37 (m, 18H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 161.9 (d, *J* = 244.5 Hz, *ipso*-Ar), 154.7 (C=O, Boc), 133.2 (*ipso*-Ar), 131.4 (d, *J* = 7.0 Hz, Ar), 115.2 (d, *J* = 21.0 Hz, Ar), 79.7 (CMe_3), 79.6 (CMe_3), 61.9 (C), 61.5 (C), 56.1 (NCH_2), 44.3 (NCH_2), 43.7 (NCH_2), 39.5 (CH_2Ar), 39.2 (CH_2Ar), 35.3 (CH_2), 34.9 (CH_2), 28.6 (CMe_3), 28.6 (CMe_3), 28.5 (CMe_3); MS (ESI) *m/z* 417 $(M + Na)^+$; HRMS *m/z* calcd for $C_{21}H_{31}FN_2O_4$ $(M + Na)^+$ 417.2160, found 417.2160 (+0.0 ppm error).

Lab Book - PJ-07-70.

1-(*tert*-Butyl) 2-methyl 2-(2-aminobenzyl)pyrrolidine-1,2-dicarboxylate 327

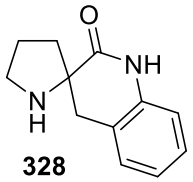


327

$Pd(OAc)_2$ (2.8 mg, 0.013 mmol, 0.05 eq) was added to a stirred solution of *N*-Boc aryl pyrrolidine-3-methyl ester **311** (100 mg, 0.25 mmol, 1.0 eq), benzophenone imine (0.063 mL, 0.38 mmol, 1.5 eq), Cs_2CO_3 (246 mg, 0.76 mmol, 3.0 eq) and Xantphos (14.5 mg, 0.025 mmol) in dioxane (6 mL) at rt. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. The resulting mixture was stirred and heated at 95 °C for 16 h. The reaction mixture was allowed to cool to rt and 1 M $HCl_{(aq)}$ (3 mL) was added. The resulting solution was stirred at rt for 10 min. 2 M $NaOH_{(aq)}$ (1 mL) was then added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried (Na_2CO_3) and evaporated under reduced pressure to give the crude product as a black oil. Purification by flash column chromatography on silica with 80:20 hexane-EtOAc as eluent gave aniline *N*-Boc pyrrolidine-2-methyl ester **327** (73 mg, 87%) as a yellow solid, mp 80-82 °C; R_F (80:20 hexane-EtOAc) 0.11; IR (ATR) 3488 (NH), 3371 (NH). 2976, 1741 (C=O, CO_2Me), 1692 (C=O, Boc), 1395, 1250, 1121, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.05-6.99 (m, 1H, Ar), 6.70-6.59 (m, 1H, Ar), 6.71-6.58 (m, 2H, Ar), 3.74 (s, 1.8H, OMe), 3.73 (s, 1.2H, OMe), 3.63 (d, *J* = 14.5 Hz, 0.4H, CHAr), 3.51 (ddd, *J* = 10.5, 7.5, 7.5 Hz, 0.6H, NCH), 3.43-3.34 (m, 1H, CHAr and NCH), 3.18 (ddd, *J* = 10.5, 7.5, 4.5 Hz, 0.6H, NCH), 3.11-3.01 (m, 1.4H, CHAr and NCH), 2.28-2.15 (m, 1H, CH), 2.08-1.96 (m, 1H, CH), 1.73-1.57 (m, 1H, CH), 1.45 (s, 3.6H, C*Me*$_3$), 1.41 (s, 5.4H, C*Me*$_3$), 1.27-1.14 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 175.7 (C=O, CO_2Me), 175.5 (C=O, CO_2Me), 155.2 (C=O, Boc), 153.7 (C=O, Boc), 146.5 (*ipso*-Ar), 145.9 (*ipso*-Ar), 132.8 (Ar), 132.6 (Ar), 127.9 (Ar), 127.8 (Ar), 121.4 (*ipso*-Ar), 121.1 (*ipso*-Ar), 118.7 (Ar), 117.9 (Ar), 116.1 (Ar), 115.7 (Ar), 80.7 (*C*Me$_3$), 79.9 (*C*Me$_3$), 69.2 (C), 68.9 (C), 52.5 (OMe), 52.4 (OMe), 48.4 (NCH_2), 37.1 (CH_2), 35.9 (CH_2), 35.3 (CH_2Ar), 34.5 (CH_2Ar), 28.5 (C*Me*$_3$), 28.4 (C*Me*$_3$), 23.3 (CH_2), 22.7 (CH_2); MS (ESI) *m/z* 335 $(M + H)^+$; HRMS *m/z* calcd for $C_{18}H_{26}N_2O_4$ $(M + H)^+$ 335.1965, found 335.1973 (–2.1 ppm error).

Lab Book - PJ-08-10.

1',4'-Dihydro-2'H-spiro[pyrrolidine-2,3'-quinolin]-2'-one 328

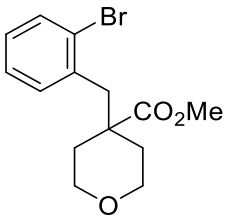


328

p-TsOH (36 mg, 0.21 mmol, 1.0 eq) was added to a stirred solution of aniline *N*-Boc pyrrolidine-2-methyl ester **327** (70 mg, 0.21 mmol, 1.0 eq) in EtOH (5 mL) at rt. The resulting solution was stirred and heated at 90 °C for 16 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to give an orange oil. Sat $NaHCO_{3(aq)}$ (10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organics were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with 95:5 CH_2Cl_2-MeOH as eluent gave 5,6-spirocycle **328** (31 mg, 74%) as a cream soild, mp 116-118 °C, R_F (95:5 CH_2Cl_2-MeOH) 0.11; IR (ATR) 3057 (NH), 2927, 1668 (C=O), 1492, 1369, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (br s, 1H, NH) 7.22-7.09 (m, 2H, Ar), 6.97 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.83 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar), 3.29-3.18 (m, 1H, NCH), 3.11-2.99 (m, 2H, NCH and CHAr), 2.86 (d, *J* = 15.5 Hz, 1H, CHAr), 1.91-1.69 (m, 4H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.8 (C=O), 136.8 (*ipso*-Ar), 128.7 (Ar), 127.7 (Ar), 123.8 (*ipso*-Ar), 123.2 (Ar), 115.2 (Ar), 63.9 (C), 47.6 (NCH_2), 39.8 (CH_2Ar), 35.5 (CH_2), 26.1 (CH_2); MS (ESI) *m/z* 203 $(M + H)^+$; HRMS *m/z* calcd for $C_{12}H_{14}N_2O$ $(M + H)^+$ 203.1179, found 203.1179 (–0.4 ppm error).

Lab Book - PJ-08-13.

Methyl 4-(2-bromobenzyl)tetrahydro-2H-pyran-4-carboxylate 329



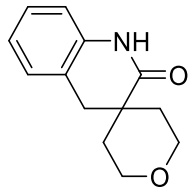
329

Using general procedure H, LiHMDS (2.1 mL of a 1.0 M solution in toluene, 2.1 mmol, 1.4 eq), THP-4-methyl ester **265** (0.2 mL, 1.5 mmol, 1.0 eq) in THF (10 mL) and 2-bromobenzyl bromide (525 mg, 2.1 mmol, 1.4 eq) in THF (5 mL) gave the crude product as a colourless oil. Purification by flash column chromatography on silica with 19:1 CH_2Cl_2-acetone as

eluent gave aryl THP-4-methyl ester **329** (368 mg, 76%) as a white solid, mp 44-46 °C; R_F (19:1 CH_2Cl_2-acetone) 0.25; IR (ATR) 2956, 1713 (C=O), 1438, 1210, 1134, 1104, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.48 (m, 1H, Ar), 7.23-7.17 (m, 1H, Ar), 7.09-7.01 (m, 2H, Ar), 3.88-3.80 (m, 2H, OCH), 3.69 (s, 3H, OMe), 3.35 (ddd, *J* = 12.0, 12.0, 2.0 Hz, 2H, OCH), 3.06 (s, 2H, CH_2Ar), 2.11-2.04 (m, 2H, CH), 1.72 (ddd, *J* = 13.5, 12.0, 4.5 Hz, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.4 (C=O), 136.2 (*ipso*-Ar), 133.2 (Ar), 131.8 (Ar), 128.5 (Ar), 127.1 (Ar), 125.8 (*ipso*-Ar), 65.6 (OCH_2), 52.0 (OMe), 47.2 (C), 45.3 (CH_2Ar), 34.1 (CH_2); MS (ESI) *m/z* 335 $(M + Na)^+$; HRMS *m/z* calcd for $C_{14}H_{17}{}^{79}BrO_3$ $(M + Na)^+$ 335.0253, found 335.0249 (–1.7 ppm error).

Lab Book - PJ-08-12.

1',2,3,4',5,6-Hexahydro-2'H-spiro[pyran-4,3'-quinolin]-2'-one 331



331

$Pd(OAc)_2$ (3.5 mg, 0.016 mmol, 0.05 eq) was added to a stirred solution of aryl THP-4-methyl ester **329** (100 mg, 0.31 mmol, 1.0 eq), benzophenone imine (0.08 mL, 0.46 mmol, 1.5 eq), Cs_2CO_3 (304 mg, 0.93 mmol, 3.0 eq) and Xantphos (18 mg, 0.031 mmol) in dioxane (6 mL) at rt. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times. The resulting mixture was stirred and heated at 95 °C for 16 h. The reaction mixture was allowed to cool to rt and 1 M $HCl_{(aq)}$ (3 mL) was added. The resulting solution was stirred at rt for 10 min. 2 M $NaOH_{(aq)}$ (1 mL) was then added and the two the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried (Na_2CO_3) and evaporated under reduced pressure to give the crude product as a black oil. Purification by flash column chromatography on silica with 80:20-60:40 hexane-EtOAc as eluent gave a 65:35 mixture (by ^1H NMR spectroscopy) of spirocycle **331** and aniline THP-4-methyl ester **330** (66 mg) as a white solid. The solid was taken up into MeOH (5 mL) and the resulting solution was stirred and heated at 50 °C for 16 h. The reaction mixture was allowed to cool to rt and evaporated under reduced pressure to afford spirocycle THP **330** (61 mg, 91%) as a white solid, mp 188-190 °C; R_F (80:20 hexane-EtOAc) 0.04; IR (ATR) 3058 (NH), 2984, 1662 (C=O), 1490, 1239, 747, 486 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H, NH), 7.23-7.11 (m, 2H, Ar), 7.05-6.92 (m, 1H, Ar), 6.86-6.64 (m, 1H, Ar), 3.90 (ddd, *J* = 11.5, 7.5, 3.5 Hz, 2H, OCH), 3.74 (ddd, *J* = 11.5, 7.0, 4.0 Hz, 2H, OCH), 2.92 (s, 2H, CH_2Ar), 2.01 (ddd, *J* = 14.0, 7.0, 4.0 Hz, 2H, CH), 1.47 (ddd, *J* = 14.0, 7.5, 3.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.4 (C=O), 136.5 (*ipso*-Ar), 128.7 (Ar), 127.8 (Ar), 123.3 (Ar), 122.3 (*ipso*-Ar), 114.8 (Ar), 64.0 (OCH_2), 37.7 (C), 37.3 (CH_2Ar), 32.2 (CH_2); MS (ESI) *m/z* 240 $(M + Na)^+$; HRMS *m/z* calcd for $C_{13}H_{15}NO_2$ $(M + Na)^+$ 240.0995, found 240.0996 (–1.6 ppm error).

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Abbreviations

Aq - Aqueous

Bn - Benzyl

Br - Broad

Cbz - Carboxybenzyl

cm^{-1} - Wavenumber

d - Doublet

DBU - 1,8-Diazabicyclo[5.4.0]undec-7-ene

DDQ - 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DIPEA - *N*,*N*-Diisopropylethylamine

DMAP - 4-Dimethylaminopyridine

DOS - Diversity Orientated Synthesis

DPPA - Diphenyl phosphoryl azide

dppf - 1,1'-Bis(diphenylphosphino)ferrocene

DTPF - 1,1’-Bis(di-o-tolylphosphino)ferrocene

Eq. - Equivalents

ESI - Electrospray ionisation

FBDD - Fragment based drug discovery

FDA - Food and drug administration

FG - Functional group

g - Gram(s)

GSK3β - Glycogen synthase kinase 3β

h - Hour(s)

H bond - Hydrogen bond

HAC - Heavy atom count

HBA - Hydrogen bond acceptor

HBD - Hydrogen bond donor

HRMS - High resolution mass spectrometry

HTS - High throughput screening

Hz - Hertz

ICR - Institute of Cancer Research

IP - Intellectual properties

IR - Infra-red

J - Coupling constant in Hz

kcal mol^{-1} - Kilocalories per mole

KHMDS - Potassium hexamethyldisilazide

LLAMA - Lead-likeness and Molecular Analysis

m - Multiplet

M - Molar

MAP - Mitogen protein kinase

m-CPBA - meta-Chloroperoxybenzoic acid

m/z - Mass to charge ratio

M+ - Molecular ion

mg - Milligrams

μM - Micromolar

min - Minute(s)

mL - Millilitre(s)

mmol - Millimole(s)

MS - Mass spectrometry

MW - Molecular weight

MW - Microwave

NCA - *N*-carboxyanhydrides

nM - Nanomolar

NMR - Nuclear Magnetic Resonance

NMP - *N*-Methyl-2-pyrrolidone

NPR - Normalised PMI ratio

Ns - Nosyl

Oxyma - Ethyl cyanohydroxyiminoacetate

PAINS - Pan-assay interference compounds

PBF - Plane of Best Fit

PHIP - Pleckstrin homology domain interacting protein

PMI - Principal moment of inertia

ppm - Parts per million

PSA - Polar Surface Area

p-TSA - para-Toluenesulfonic acid

q - Quartet

R_f - Retention Factor

RO3 - Rule of three

RMSD - Root-mean-square deviation

rt - Room Temperature

s - Singlet

SAR - Structure Activity Relationship

SeeD - Selection of Experimental Exploitable Drug Starting Point

SEM - [2-(Trimethylsilyl)ethoxy]methyl acetal

SMILES - Simplified molecular-input line-entry system

SPR - Surface plasmon resonance

t - Triplet

TFA - Trifluoroacetic acid

TMEDA - N',N',N',N'-Tetramethylethylenediamine

QC - Quality control

3-D FIT - 3-D Fragment idea Tool

Chapter 8 References

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