Short, efficient routes towards the synthesis of fluorinated nitrogen heterocycles

Thomas Cogswell M.Sci

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School of Chemistry

College of Science and Engineering

University of Glasgow

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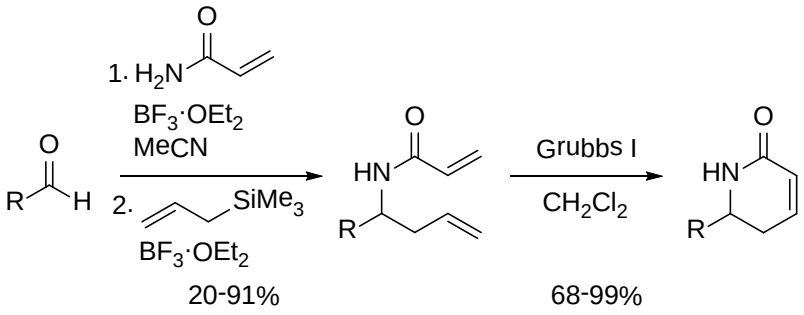
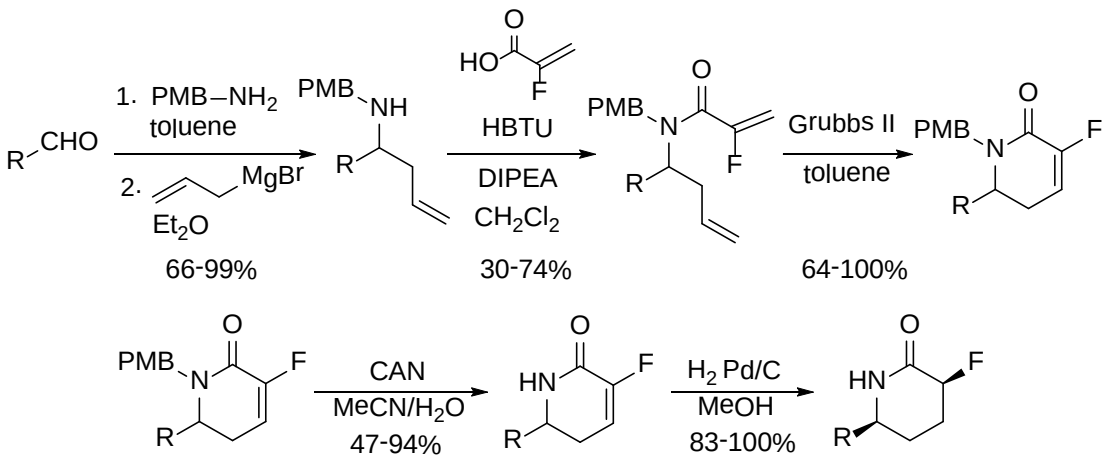
Abstract

Fluorinated compounds make up a large proportion of the output from both the pharmaceutical and agrochemical industries. However, there are still a limited number of methodologies involving the synthesis of such molecules. Six-membered nitrogen containing heterocycles such as pyridines and lactams are key compounds for medicinal chemistry. Therefore, there is much interest into the synthesis of fluorinated nitrogen heterocycle libraries which can be utilised effectively for numerous substrate screens.

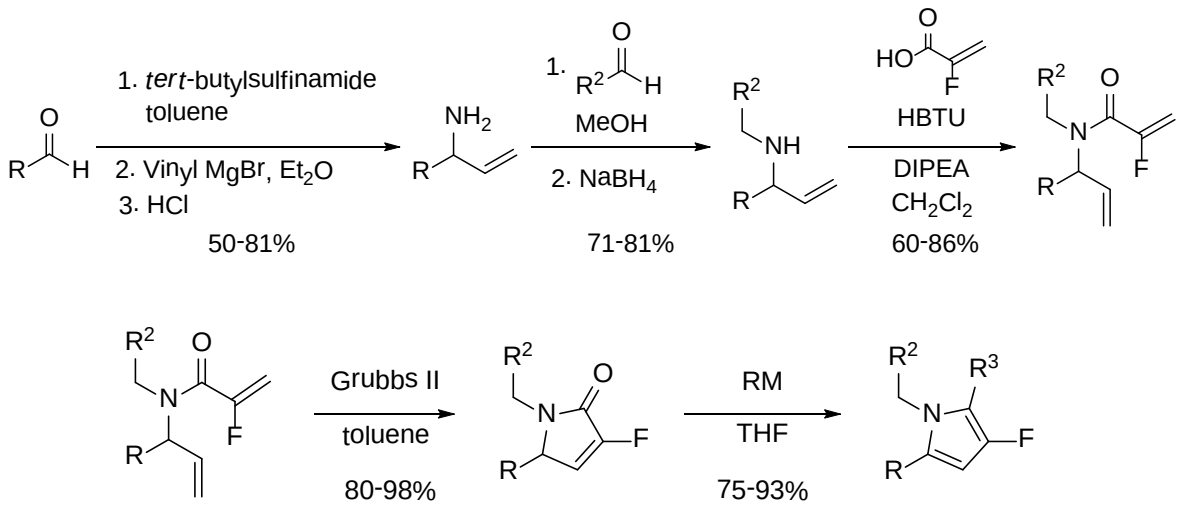
This thesis aims to produce a novel route for the generation of a host of fluorinated pyridines, lactams and piperidines. Work on non-fluorinated analogues has lead to a rapid two-pot process for the production of dihydropyridones, a potential intermediate for the above targets, starting from common aldehydes.



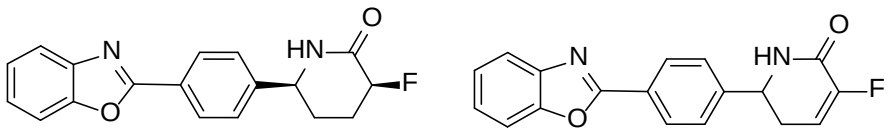
This methodology has been utilised in the synthesis of fluorinated lactams through an efficient ring-closing metathesis protocol of vinyl fluoride compounds. A variety of aldehydes, including aromatic, aliphatic and heterocyclic examples, could be converted in 6 efficient steps into novel fluorinated δ-lactams. The final hydrogenation occurred on the opposite face to the R groups giving a single diasteromer in all cases.



Taking inspiration from the δ-lactams series, a synthetic route was designed and implemented to grant access to an array of fluorinated polysubstituted pyrroles. The final step involved a novel addition-aromatisation reaction which allowed late-stage variation of the resulting fluorinated pyrroles. Installation of a hydride, *n*-butyl, phenyl and allyl moieties could be achieved, all in high yields of 75-93%.



Finally the synthesis of a number of interesting benzoxazole containing compounds was undertaken to produce a range of novel fluorinated poly(ADP-ribose) polymerase (PARP) inhibitors, yielding a group of potential anti-cancer agents.



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Author Declaration

I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow. All chemical synthesis and analysis was carried out, either in the Raphael lab at the University of Glasgow or in the research labs at AstraZeneca, Alderley Park, by the author.

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Abbreviations

Aq	aqueous
Ac	acetate
ADP	adenosine diphosphate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad peak
BRCA	breast cancer, early onset
CAN	ceric ammonium nitrate
CI	chemical ionisation
m-CPBA	*meta*-chloroperoxybenzoic acid
d	doublet
dd	doublet of doublets
DBSA	dodecylbenzene sulfonic acid
DBU	1,8-diazabicycloundec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl diazenedicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylthethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dr	diastereomeric ratio
ED_{50}	half maximal effective dose
ee	enantiomeric excess
EI	electron ionisation
Et	ethyl
eq	equivalents
F	bioavailability
F-TEDA	1-chloromethyl-4-fluoro-1, 4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
gBRCAm	germline breast cancer, early onset mutated
HBTU	*N*,*N*,*N*′,*N*′-Tetramethyl-O-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
IC_{50}	half maximal inhibitory concentration
IBX	2-iodoxybenzoic acid

IR	infrared spectroscopy
J	coupling constant
Ki	inhibition constant
liq	liquid
m	mulitplet
Me	methyl
m.p.	melting point
MW	microwave
NAD	nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NCS	*N*-chlorosuccinimide
NBS	*N*-bromosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
No	number
p	para
PARP	poly(ADP-ribose) polymerase
pin	pinacol ester
Ph	phenyl
pK_a	the logarithmic value of the acid dissociation constant
PMB	*para*-methoxybenzyl
ppm	parts per million
q	quartet
quant	quantitative
RCM	ring-closing metathesis
rt	room temperature
s	singlet
SAM	*S*-adenosylmethionine
sat	saturated
SEM	2-(Trimethylsilyl)ethoxymethyl
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBAF	tetra-*n*-butylammonium fluoride
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

Ts	tosyl
UV	ultraviolet
μM	micromolar
5’-FDA	5’-fluoro-5’deoxyfluoroadenosine
5-HT	5-hydroxytryptamine
9-BBN	9-borabicyclo[3.3.1]nonane

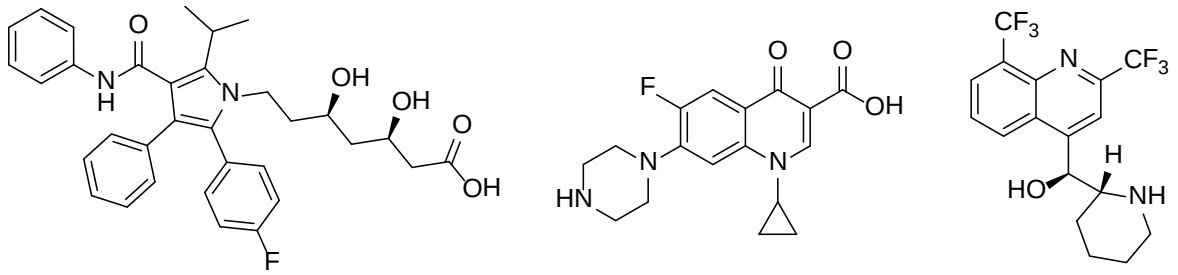
Contents

1. Introduction

1.1: Fluorine in organic chemistry

It has been well documented that the installation of fluorine atoms into organic molecules greatly changes their physical and pharmacological properties.[1] Fluorinated molecules are, therefore, highly sought after in industry, especially by medicinal and materials chemists hoping to fine tune the properties of their target molecules.[2]

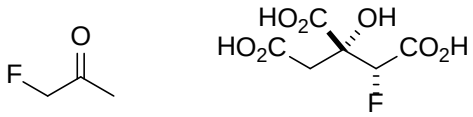
Cholesterol lowering drugs atorvastatin **1** (the worlds best-selling pharmaceutical between 1996 and 2012),[3] fluvastatin and rosuvastatin all have C-F bonds in their structures which is paramount to their efficiency.[4] Many other examples of fluorinated pharmaceuticals exist including the antibiotic ciprofloxacin **2** produced by Bayer and Roche's anti-malarial treatment mefloquine **3** (Figure 1).[5, 6]



1 **2** **3**

Figure 1. Cholesterol lowering drug atorvastatin **1**, antibiotic ciprofloxacin **2** and anti-malarial agent mefloquine **3**.[3, 6]

However, the installation of fluorine atoms is not a trivial matter for organic chemists. This is exemplified in nature, with little more than 30 naturally occurring organofluorine compounds and only one isolated enzyme, adenosyl-fluoride synthase, known to catalyse the production of C-F bonds (Figure 2).[7,8] In contrast, around 30% of all agrochemicals and 20% of all pharmaceuticals contain a C-F bond in their structure.[3] This shows the importance of the C-F bond in modern bio-organic chemistry as well as the significant need for new, efficient ways to install fluorine atoms into a large variety of environments with little inspiration from nature to guide the design of methodology.

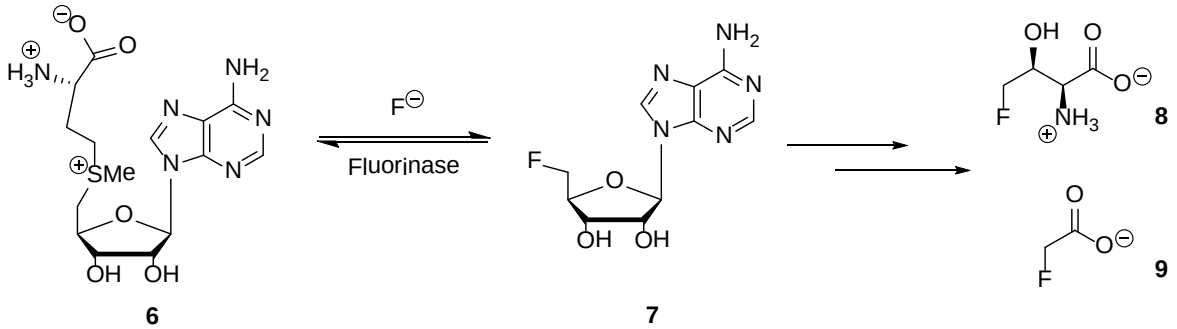


4 **5**

Figure 2. The chemical structures of two naturally occurring fluorinated compounds: 1-fluoro-propan-2-one **4** and 3-carboxy-2-fluoro-3-hydroxy-pentanedioic acid **5**.[7,8]

Fluorine is the most common halogen in the earth's crust contributing to 0.065% of the overall make up, this is significantly more than other halogens such as chlorine and bromine, which have abundances of 0.017% and 0.0003% respectively.[7] It is, therefore, surprising that there are upwards of 4,500 natural products containing these less common halogens compared to the 30 natural products containing fluorine.[9] Fluorine may be relatively abundant as an element, however the uptake of fluorine into biological systems is compromised by a number of factors. The naturally forming fluorine-containing minerals, such as fluorite, have poor solubility in aqueous media due to strong ionic bonds between the fluorine and the metal.[8] Once a fluorine atom is present in water, a very tight solvation shell means the anion has poor nucleophilicity.[8] Oxidation of halogens from X^- to X^+ is an important process in their incorporation into natural compounds. However, as the oxidation potential of fluoride (-2.87 eV) which is higher than hydrogen peroxide (-1.87 eV), this process can not take place.[8]

Even with these obstacles, nature has managed to incorporate fluorine into a limited number of natural products. Adenosyl-fluoride synthase, an enzyme identified from the bacteria *Streptomyces cattleya* was found to convert *S*-adenosylmethionine (SAM) **6** to 5'-fluoro-5'deoxyfluoroadenosine (5'-FDA) **7** (Scheme 1).[8] This transformation involves the nucleophilic attack of the fluoride ion onto the 5' carbon on the ribose ring eliminating the amino acid, methionine. 5'-FDA **7** can then be readily transformed into the fluorinated building blocks 4-fluorothreonine **8** and fluoroacetate **9**.[8]



6 **7** **8** **9**

Scheme 1. Nucleophilic fluorination reaction catalysed by enzyme, adenosyl-fluoride synthase. The resulting fluorinated sugar 5'-FDA **7** is further metabolised to produce fluorinated natural products, **8** and **9**.[8]

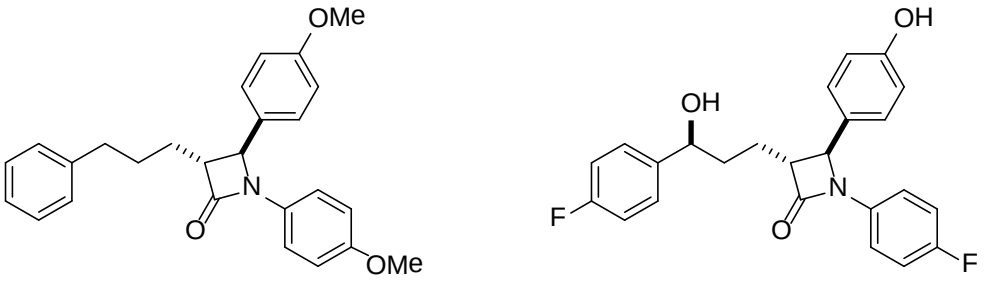
The special properties of organofluorine molecules that make them integral for medicinal chemistry are largely determined by the size and electronegativity of the fluorine atom.[1] Apart from hydrogen, fluorine has the smallest Van der Waals radius of any atom that can form a covalent bond with carbon. This generates a bond with very low steric strain, which coupled with a partial ionic nature produces very strong, short C-F interactions. The C-F bond can replace a C-H bond with very little change to the molecular sterics, which is important when modifying a drug candidate for a particular enzyme active site.[1]

The high electronegativity of the fluorine atom causes the C-F bond to be highly polarised, pulling electrons towards the fluorine and lowering the electron density of surrounding atoms.[1] This lowers the pK_a of α-hydrogen atoms and nearby acid functionalities as well as reducing the reactivity towards oxidising agents.[2,10] The lone pair of electrons on the fluorine atom is too strongly attracted to the electronegative centre to form any noteworthy hydrogen bonding interactions with proton donating functionalities.[1] This lack of polarisability of the fluorine atom leads to the general increase in the lipophilicity of molecules upon fluorination.[2,10] The physical properties, stated above, have a profound effect on the pharmacological properties of organofluorine compounds making them key compounds in the pharmaceutical industry.

As a consequence of the inclusion of fluorine atoms, organic molecules display an increase in metabolic stability. When administered to the body a lipophillic drug molecule will be modified by enzymes involved in the metabolic processes, changing the molecular structure. This often involves oxidation, which not only decreases the biological activity but can also lead to an increase in the hydrophilic nature of the compound causing an increased rate of expulsion from the body through urination.[11] The inclusion of fluorine atoms can be used to block such degradation by deactivating the labile sites prone to oxidation, by reducing the availability of electrons in the molecule which can interact with the metabolic enzymes.

An important example is the oxidation of phenyl groups by enzyme cytochrome P450. Cytochrome P450 oxidises phenyl rings at the *para* position which leads to an increase in the hydrophilic nature of the drug candidate. However, the inclusion of a fluorine atom at the *para* position deactivates the phenyl ring towards oxidation, hence slowing metabolism without changing the sterics of the drug molecule significantly.[11] This strategy was utilised in the production of the cholesterol-absorption inhibitor **11**. Compound **10** was identified as a lead compound for the inhibition of cholesterol-absorption mechanisms, however *in vivo* metabolism at certain labile sites hindered the activity of the compound. Fluorination at the *para* position of two of the phenyl rings was used to block the action of metabolic

enzymes and drastically improve the activity *in vivo* using a hamster model. This resulted in lowering the ED_{50} value from 2.20 mg Kg^{-1} for **10** to 0.04 mg Kg^{-1} for **11** (Figure 3).[11]



10 **11**

Figure 3. Cholesterol-absorption inhibitor: SCH 48461, **10**, undergoes oxidation of the phenyl ring during metabolism, which reduces the drug activity *in vivo*. However, addition of fluorine atoms, as shown in structure **11**, increases activity 400 fold by blocking this oxidation.[11]

Another crucial function of the C-F bond is to increase the ability of drug-like molecules to cross the lipid bilayer surrounding cells. Many biologically active molecules have modes of action that are carried out inside cells, targeting enzymes, DNA *etc*.[12] If a molecule is too lipophobic, it will not be able to diffuse through the internal lipid layer of the cell membrane and will have to enter the cell by other means, or be rendered ineffective. The increase in lipophilicity caused by the fluorination of drug-like molecules facilitates their transport into cells, therefore increasing the intracellular drug concentration.[12] Fluorination can also be used to make a drug viable for oral administration instead of less practical approaches. The increase in lipophilicity can be enough to facilitate transport across the gut and stomach linings and also make compounds more chemically stable towards the highly acidic environment of the stomach.[2,13]

The alteration of the pK_a of a molecule is another way the introduction of fluorine atoms can be used to tune potential drug candidates. If one of the forms, protonated or non-protonated, is the active form, then the change in pK_a can be used to shift the equilibrium to favour one isoform. Installation of fluorine can lower the pK_a of surrounding protons, so addition of a number of fluorine atoms can be used to tune the pK_a to favour the active form of a compound.[2,10] The change of basicity of nearby sites upon fluorination was demonstrated eloquently by van Niel and coworkers.[14] They found that fluorination of human 5-HT_{1D} receptor **12** reduced the pK_a, favouring the un-ionised species, and so significantly increased the compounds bioavailability and viability for oral administration (Figure 4).[14]

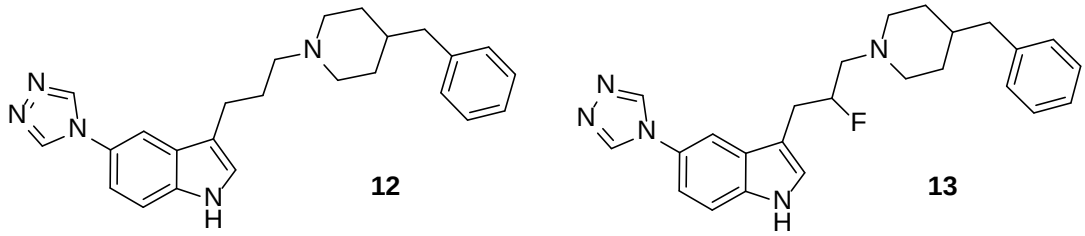


Figure 4. Fluorinated analogue **13** of human 5-HT_{1D} receptor **12** has a lower pK_a (9.7 for **12** and 8.7 for **13**) and improved bioavailability to a medium value (F = 14%).[14]

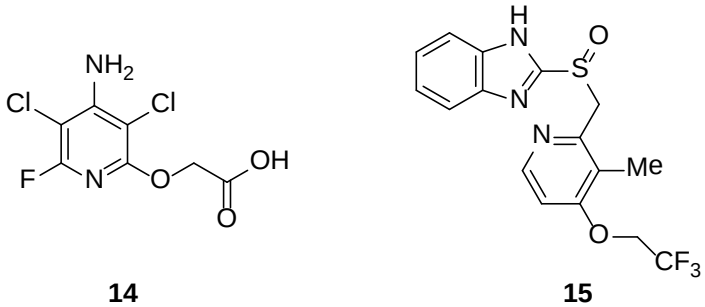
In summary, organofluorine compounds are of paramount importance in medicinal chemistry where the properties of the C-F bond are often used to turn highly active compounds into potential drug candidates that can survive in a biological environment.

1.2: Fluorinated nitrogen heterocycles

Nitrogen containing heterocycles are abundant in nature and increasingly, in synthetically produced molecules. They have diverse applications and are used as pharmaceutical drugs, pesticides and in the materials industry.

As previously discussed, the fluorination of certain molecules is highly desirable. Therefore, there is a high demand for cost-effective methodology for the construction of fluorinated nitrogen heterocycles. Although much progress has been made in this area there is still scope for improvement to make these compounds readily available and economically viable targets.

This thesis will focus on 5- and 6- membered fluorinated heterocycles such as pyridines, lactams and pyrroles. On the market there are already significant examples with both key agrochemicals and pharmaceuticals comprising such functionality. The herbicide fluroxypyr **14** is a prime example possessing a fluorine atom in the 2 position of a fully substituted pyridine unit (Figure 5).[15] Lansoprazole **15** is a proton pump inhibitor used in the treatment of stomach ulcers and gastric reflux disease (Figure 5).[16] Another important example discussed previously is atorvastatin **1** (Section 1.1), which has a *p*-fluorobenzene substituent on a pyrrole ring system (Figure 1).[3]



14 **15**

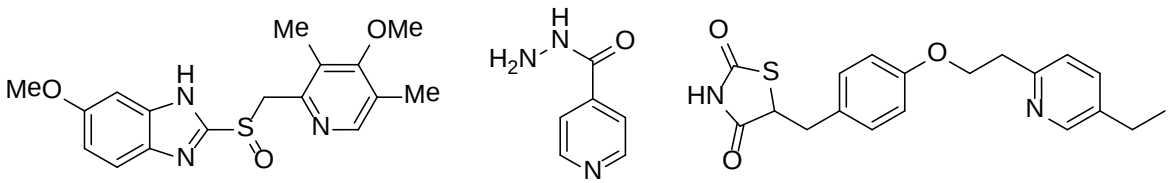
Figure 5. Herbicide fluroxypyr, **14**, and proton pump inhibitor lansoprazole, **15**.[15, 16]

1.3: Synthesis of fluorinated nitrogen heterocycles

As fluorinated compounds have become major targets for medicinal chemists,[2] there has been significant research dedicated to the synthesis of fluorinated nitrogen heterocycles. In the following sections, significant developments regarding fluorinated pyridines, δ- and γ-lactams, and finally pyrroles will be described.

1.3.1: Pyridines

The pyridine unit is a motif of high biological relevance and features in many naturally-occurring compounds, with examples including the human enzyme cofactor pyridoxyl phosphate (active form of vitamin B_6),[17] the NAD and NADP precursor niacin (vitamin B_3),[18] and the plant alkaloid nicotine.[19] Pyridines are also extensively used in medicinal chemistry as both key functional groups and scaffold structures.[20] They are also used in the pharmaceutical and material industries as solvents, bases, ligands and even components in molecular devices.[21] Thus, it is not surprising that the pyridine moiety features in several high selling pharmaceutical drugs such as the proton pump inhibitor Nexium® **16**, the anti-tuberculosis drug Isoniazid® **17** and the diabetes treatment Actos® **18** (Figure 6).[21, 22, 33, 24]

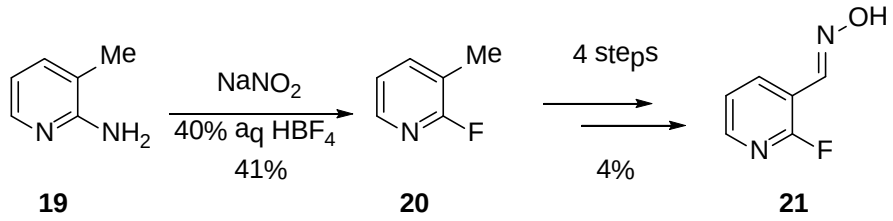


16 **17** **18**

Figure 6. Heartburn relief drug nexium® **16**, anti-tuberculosis agent isoniazid® **17** and diabetes treatment actos® **18**.[21, 22, 23, 24]

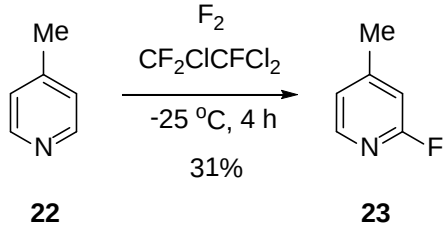
1.3.1.1: Direct fluorination of pyridine ring

An important reaction in the synthesis of fluorinated aromatics is the Balz-Schiemann reaction.[25] This reaction involves the direct production of a C-F bond from an amine starting material using HNO_2 and HBF_4 (Scheme 2). Timperley and co-workers used this approach to form an array of mono- and perfluorinated pyridine aldoximes as potential lead compounds for the treatment of organophosphorous nerve-agent poisoning.[26] Although Timperley was successful in producing a variety of different compounds for testing, the reported yields were low and one of the most problematic steps was the fluorination reaction which occurred in moderate yields (41-66%) (Scheme 2).[26]



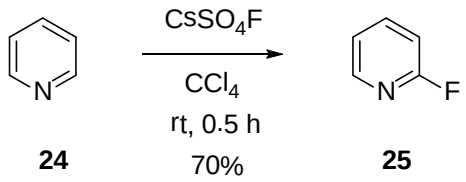
Scheme 2. The Balz-Schiemann reaction for the synthesis of fluorinated aldoximes such as **21**.[26]

Another approach for producing fluorinated pyridine units is the direct fluorination of pyridine with strong fluorinating agents. One example is elemental fluorine, F_2, which was reported by Van Der Puy to react with a number of pyridine derivatives producing 2-fluoro analogues in low to moderate yields (Scheme 3).[27]



Scheme 3. Fluorination of 4-methylpyridine **22** with elemental fluorine occurring at the 2 position to yield **23**.[27]

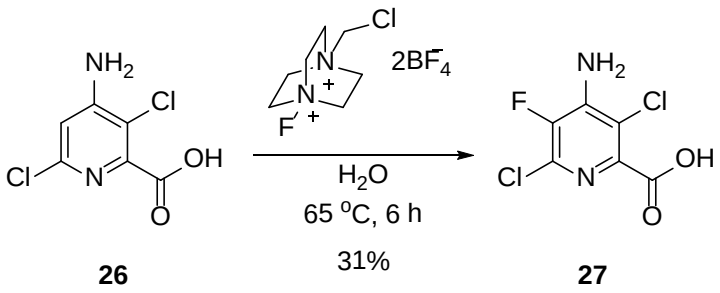
A more successful outcome can be achieved using cesium fluoroxysulfate (Scheme 4) which was shown by Stavber and Zupan to yield 2-fluoropyridine **25** with a 70% yield.[28] However, these types of reagents are not easy to handle, and their use is hindered by the intolerance of different functionalities in more complex pyridine systems.



24 **25**

Scheme 4. The direct fluorination of pyridine **24** with $CsSO_4F$ to form 2-fluoropyridne **25** as reported by Zupan *et al*.[28]

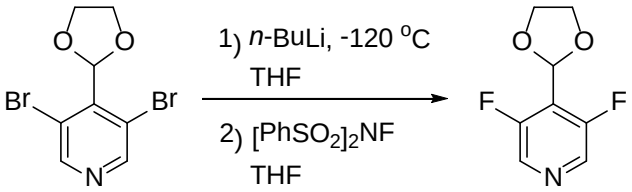
Fluorinated analogues of the herbicide aminopyralid have received some interest in recent years as there is the possibility of producing new active compounds with lower toxicity. Brewster managed to achieve an electrophilic fluorination using Selectfluor® producing the fluorinated analogue **27** in 31% yield (Scheme 5).[29]



26 **27**

Scheme 5. The fluorination of aminopyralid **26**, by Selectfluor® producing compound **27**.[29]

A popular route for the synthesis of fluorinated pyridine derivatives involves the lithium-halogen exchange of halopyridines to install the fluorine atom. One example, as developed by Shin and co-workers, involves bromine-lithium exchange followed by the addition of *N*-fluorobenzenesulfonimide (NFSI) (Scheme 6). Using this methodology, 3,5-difluoropyridine **28** was produced from the 3,5-dibromo-precursor **29** in a yield of 78%.[30]

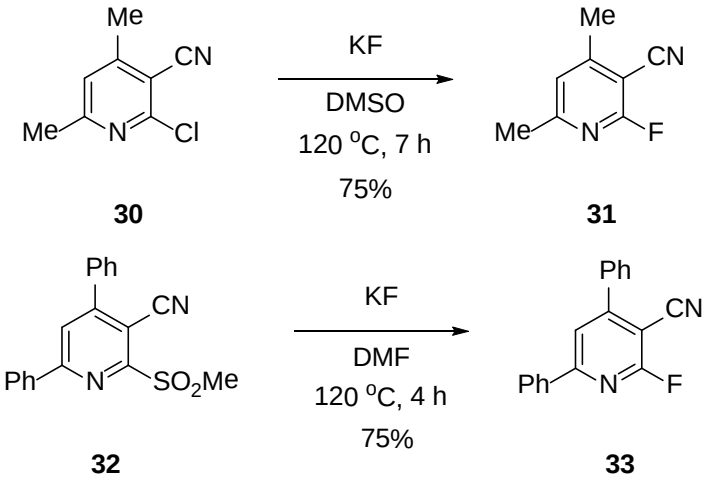


28 **29**

Scheme 6. Lithium-halogen exchange followed by addition of electrophilic fluorine source to produce difluoropyridines such as **29**.[30]

Another halogen exchange route, in which KF or Bu_4NF are used as sources of the fluoride anion to undergo nucleophilic substitution with halo-precursors, has been well documented in the literature. Shestopalov and co-workers used this approach for the synthesis of different 3-cyano-2-fluoropyridines as potential kinase inhibitors, K^+ channel inhibitors as well as acetylcholine receptor ligands.[31] It was demonstrated that starting

from 2-halo-3-cyanopyridnes, fluorination could be achieved in good yield (52-76%) using KF (Scheme 7). Increased yields were obtained using Bu_4NF and it was proposed that this was due to the increase in the organic solubility of the reagent. The authors also showed that the same method could be applied to substrates with a sulfonyl group or a tetrahydrothiophenium salt in the pyridine 2 position (Scheme 7).[31]

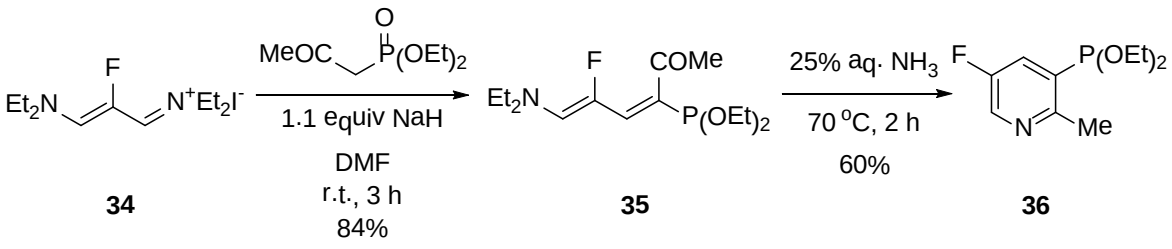


Scheme 7. Shestopalov approach for the production of 3-cyano-2-fluoropyridines **31** and **33**.[31]

1.3.1.2: Pyridine synthesis *via* cyclisation of fluorinated precursors

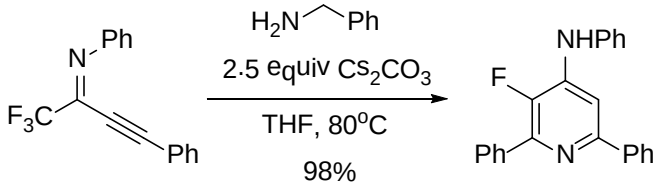
All the examples detailed so far have involved reactions on a preformed or pre-functionalised pyridine ring to install the fluorine atom. However, this is not always the most efficient route as this often requires the installation of a group, which may not be facile, just for it to be removed in favour of the fluorine. A more streamlined and expedient method could be achieved by the incorporation of the fluorination step into the pyridine ring synthesis.

This approach was elegantly demonstrated by Arimitsu, who used a *β*-fluorinated vinamidinium salt as a building block in their pyridine synthesis (Scheme 8).[32] Reaction of the vinamidinium salt **34** with a Horner-Wadsworth-Emmons reagent produced the organophosphorus compound **35**, which was then cyclised to form the fluorinated pyridine **36** in the presence of 25% aq. ammonia.[32]



Scheme 8. Synthesis of fluorinated pyridine **36** as reported by Arimitsu *et al*. [32]

In 2011, Gong and co-workers reported a cascade process to produce fluorinated pyridine analogues **38** from the reaction of fluoroalkyl alkynylimines **37**, with primary amines (Scheme 9).[33] The reaction involves the loss of two of the three fluorine atoms leaving one still intact on the pyridine backbone. The process worked in good to excellent yields, and the scope of the reaction was extended to the synthesis of other nitrogen based heterocycles such as pyrimidines.[33]



37 **38**

Scheme 9. Gong's synthesis of fluorinated pyridine **38.**[33]

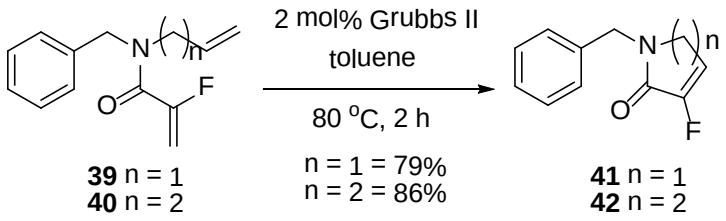
1.3.2: Lactams

Lactam moieties are present in a large number of biologically active molecules. It has been estimated that 25% of all pharmaceuticals contain an amide bond, and many of these are cyclic.[34] The production of fluorinated lactams is, therefore, of significant interest to the scientific community, with the aim of combining the lucrative pharmacological properties of the fluorine with this key scaffold.

1.3.2.1: Ring-closing metathesis routes to fluorinated nitrogen ring systems

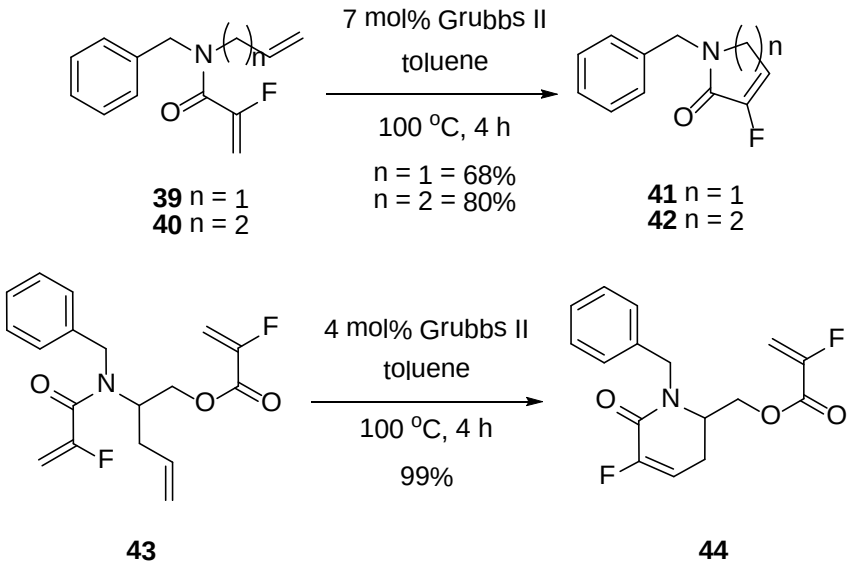
Fluorinated δ and γ-lactams are both species with limited documentation in the literature and at the time of writing there are still very few synthetic routes for such compounds. The most expedient method for the generation of these molecules proceeds *via* the ring-closing metathesis (RCM) of vinyl fluoride compounds to form the α,β-unsaturated lactams; however, there are only a few reported examples.

The first ring-closing metathesis reaction utilising a vinyl fluoride moiety in the production of nitrogen heterocycles was reported by two separate groups independently within a margin of 13 days. Haufe and co-workers found that Grubbs 2nd generation catalyst (2 mol%) could be used in the formation of fluorinated γ and δ-lactams, **41** and **42**, in high yields (Scheme 10).[35]



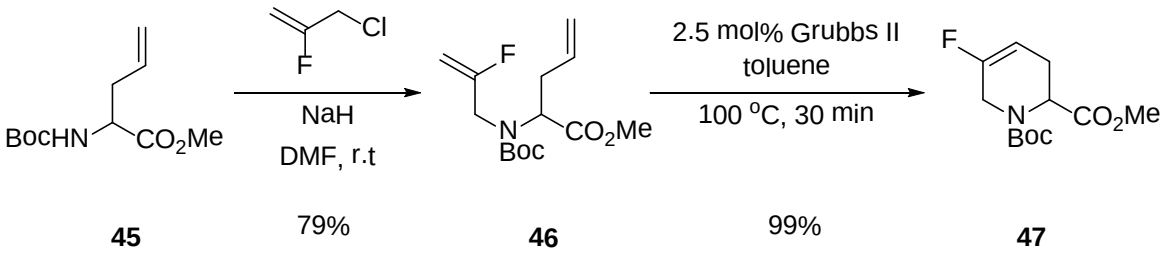
Scheme 10. RCM reaction to form γ and δ-lactams, **41** and **42**.[35]

Rutjes and co-workers also utilised Grubbs 2nd generation catalyst for the synthesis of fluorinated lactams.[36] Using the same RCM precursor as Haufe and co-workers, they could generate γ and δ-lactams, **41** and **42**, in 68 and 80% yield respectively (Scheme 11). An excellent yield of 99% was also reported for a triene analogue **44** which demonstrated a selective route for forming 6-membered rings over 7-membered variants (Scheme 11).



Scheme 11. RCM reaction, identical to Scheme 10, carried out with higher catalyst loading and higher temperatures.[36]

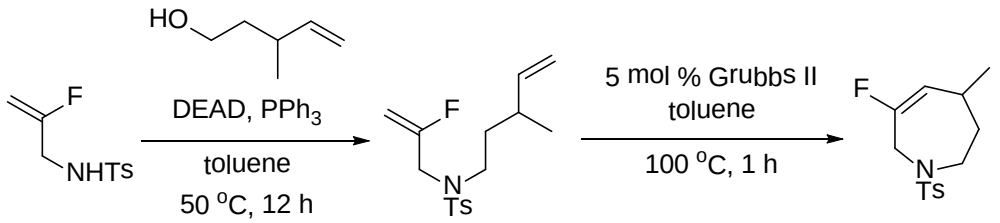
Rutjes and co-workers also utilised the RCM approach to produce a fluorinated piperidine **47**.[37] Alkylating amine **45** with 1-chloro-2-fluoro-2-propene they could produce the RCM precursor **46** in 79% yield. The RCM proceeded smoothly with Grubbs 2nd generation catalyst to afford the fluoro-piperidine **47** in 99% yield (Scheme 12).



45 79% **46** 99% **47**

Scheme 12. Synthetic route to fluorinated piperidine **47** with ester substituent.[37]

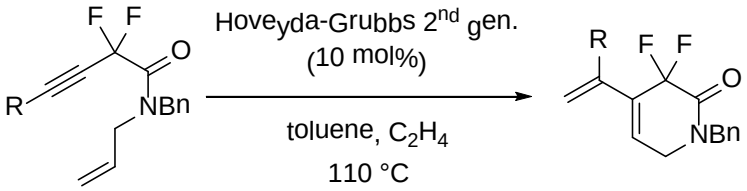
Rutjes and coworkers also managed to extend this methodology to synthesise a 7-membered ring variant. Using Mitsunobu chemistry, they synthesised the RCM precursor **49** in a 68% yield. With the vinyl fluoride in hand, treatment with Grubbs 2nd generation lead to rapid metathesis giving the 7-membered fluorinated piperidine **50** in a good 94% yield (Scheme 13).[38]



48 68% **49** 94% **50**

Scheme 13. Mitsunobu conditions were used to alkylate electron deficient sulfonyl amine **48** to form **49**, followed by ring closure to produce heterocycle **50**.[38]

Hammond and co-workers also used a RCM approach,[34] this time an ene-yne metathesis process to produce a number of difluorinated δ-lactams **54-56** in good yields (Scheme 14).



69-70%

51 R = H
52 R = n-Hex
53 R = Ph

54 R = H
55 R = n-Hex
56 R = Ph

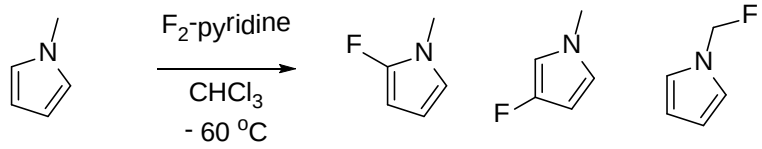
Scheme 14. Treatment with Hoveyda-Grubbs catalyst 2nd generation afforded the lactams **54-56** *via* an ene-yne metathesis reaction starting from the gem-difluoropropargyl amides **51-53**.[34]

1.3.3: Pyrrole

Pyrroles are historically one of the most important heterocyclic compounds, finding many uses in medicinal and pharmaceutical chemistry as key drug fragments.[39] As a result, the synthesis of these molecules has been widely explored with much success;[40] however the synthesis of fluorinated pyrroles, as with many fluorinated compounds, has lagged behind and routes are plagued with low yields and poor selectivity.

1.3.3.1: Direct fluorination of pyrrole rings

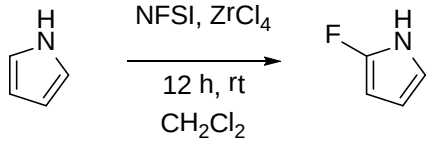
Direct fluorination of the pyrrole ring would be seen as the most atom-efficient route for yielding the target molecules. This has been explored by Fornarini and coworkers using elemental fluorine with *N*-methylpyrrole **57**, however, rapid polymerisation led to a mixture of products being formed.[41] Fornarini reported poor selectivity, forming the 2-fluoropyrrole **58**, 3-fluoropyrrole **59** as well as fluorination on the *N*-methyl group forming **60** (Scheme 15).



57 **58** **59** **60**

Scheme 15. Direct fluorination of *N*-methylpyrrole with elemental fluorine in pyridine. Yields were not given for the mixture of products obtained **58**-**60**.[41]

Yamamoto and co-workers reported a more useful Lewis acid catalysed fluorination of pyrrole **61** yielding 2-fluoropyrrole **62** in a moderate 53% yield.[42] Compared to many of the direct fluorination conditions, the reagents *N*-fluorobenzenesulfonimide (NFSI) and $ZrCl_4$ are reasonably easy to handle and convenient to use (Scheme 16).

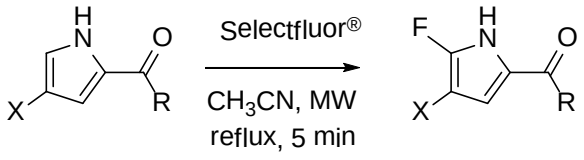


61 **62**

Scheme 16. Lewis acid catalysed fluorination of pyrrole **61** described by Yamamoto *et al.*[42]

Lindel and coworkers utilised microwave irradiation to convert a number of substituted pyrroles **63**-**66** into the corresponding 5-fluoro-pyrroles **67**-**70**.[43] The conditions were mild,

using Selectfluor® as the fluorinating source, however the yields were moderate to poor with large amounts of starting material recovered in all cases (Scheme 17). The pyrroles generated were then utilised in the synthesis of a number of fluorinated analogues of the serotonergic receptor antagonist, hymenidin.[43]

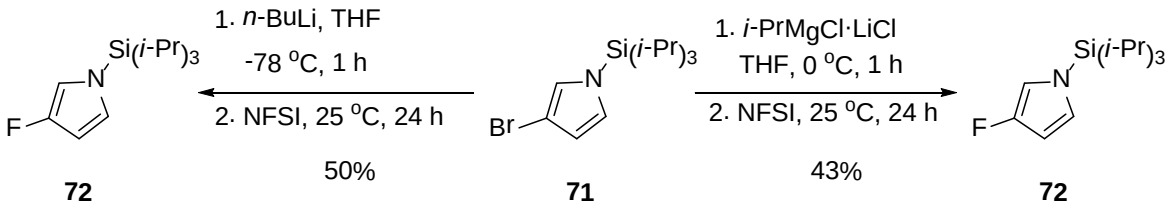


63 X = H, R = CCl_3
64 X = Br, R = CCl_3
65 X = H, R = *i*-Bu
66 X = H, R = NH_2

67 X = H, R = CCl_3
68 X = Br, R = CCl_3
69 X = H, R = *i*-Bu
70 X = H, R = NH_2

Scheme 17. Microwave irradiation of substituted pyrroles **63-66** with Selectfluor®, by Lindel and coworkers, produced the fluorinated pyrroles **67-70** in moderate yields.[43]

Metalation and addition to an electrophillic fluorine source is also a common way to fluorinate heterocycles. It is usually not as efficient as direct fluorination as the corresponding halo-pyrrole often has to be produced first; however good selectivity for fluorination can usually be achieved. Starting with 3-bromopyrrole **71** it has been shown that it is possible to form the equivalent 3-fluoropyrrole **72** *via* two different metalation conditions (Scheme 18). Exchange of the bromine atom for a lithium atom, before addition of the lithiated pyrrole to electrophilic fluorine source NFSI, can be used to yield 3-fluoropyrrole **72** in a moderate 50% yield.[44] Alternatively, it is also possible to form a Grignard reagent which can be added to NFSI yielding the same fluoropyrrole **72** in a slightly lower 43% yield.[45]



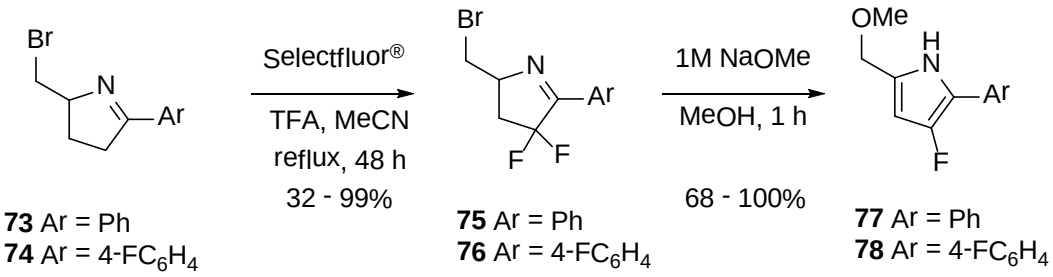
72 **71** **72**

Scheme 18. Metalation of the bromopyrrole **71** before treatment with NFSI to give the corresponding fluoropyrrole **72** in moderate yields.[44,45]

1.3.3.2: Pyrrole synthesis *via* cyclisation of fluorinated precursors

Aromatisation of 3,3-difluoro-1-pyrrolidine **75**-**76** *via* reaction with different sodium alkoxides was used by De Kimpe and coworkers to produce 3-fluoropyrroles **77**-**78** in variable yields.[46] Fluorination of the pyrrolidines **73**-**74** was undertaken using Selectfluor®

and a catalytic amount of TFA to ensure enamide formation could allow a second fluorination (Scheme 19).



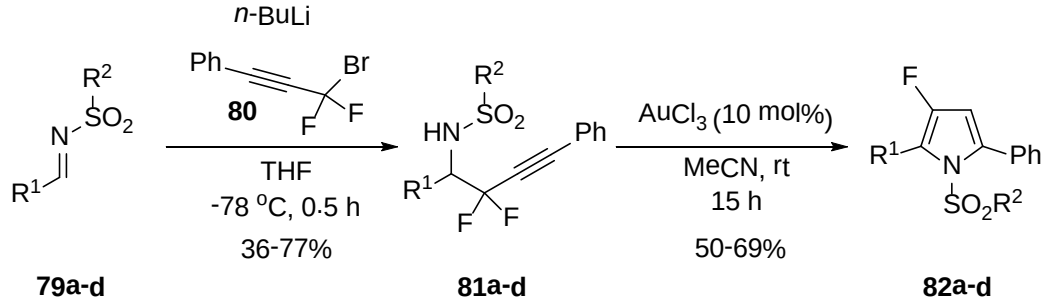
73 Ar = Ph
74 Ar = 4-FC_6H_4

75 Ar = Ph
76 Ar = 4-FC_6H_4

77 Ar = Ph
78 Ar = 4-FC_6H_4

Scheme 19. Fluorination followed by elimination allowed the conversion of pyrrolidine compounds **73-74** to 3-fluoropyrroles **77-78** as reported by De Kimpe *et al*.[46]

In a further report, De Kimpe *et al.* used gold catalysis to cyclise a range of fluorinated alkyne compounds **81a**-**d** to form the corresponding 3-fluoropyrroles **82a**-**d** in good yields.[47] Lithiation of a difluorobromoalkyne **80** followed by reaction with various sulfonimines **79a**-**d** formed the fluorinated cyclisation precursors **81a**-**d** in variable yields (Scheme 20).



79a-d **81a-d** **82a-d**

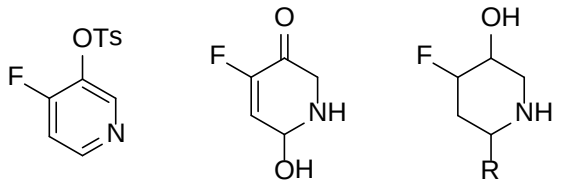
a R^1 = Ph, R^2 = 4-MeC_6H_4,
b R^1 = 4-ClC_6H_4, R^2 = 4-MeC_6H_4,
c R^1 = 4-MeC_6H_4, R^2 = 4-MeC_6H_4,
d R^1 = 4-ClC_6H_4, R^2 = Ph,

Scheme 20. Synthesis of 3-fluoropyrroles **82a-d** through a gold catalysed cyclisation reaction reported by De Kimpe *et al*.[47]

2: Aims

Over the past few years, there has been a developing interest in the synthesis of fluorinated nitrogen heterocycles and many successful routes have been proposed. However, most of the routes are either low yielding or require the use of starting materials that are not readily accessible. Therefore, there is a requirement for new routes that are efficient, short and generated from readily available starting materials.

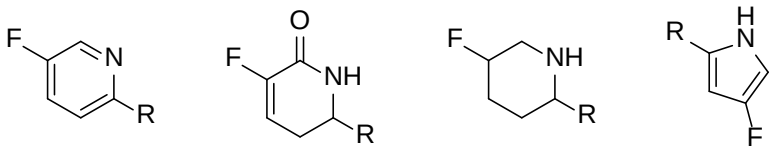
A key aim of the present work is to produce such a route and to synthesise an array of fluorinated nitrogen heterocycle analogues. One of our proposed routes involves the aza-Achmatowicz rearrangement as the key step. This would produce a novel fluorinated pyridone **84** that could in turn be converted to fluorinated pyridine or piperidine analogues, **83** and **85** (Figure 7).



83 **84** **85**

Figure 7. Examples of targeted fluorinated nitrogen heterocycles, **83**-**85**, to be accessed via an Achmatowicz rearrangement approach.

Another route that will be investigated, utilises a ring-closing metathesis protocol with vinyl fluorine precursors to give the desired fluorinated heterocycles. It is hoped that the flexibility of this methodology will allow for a variety of different ring sizes and heterocycle classes, **86**-**89**, to be accessed in a synthetically expedient manner (Figure 8).



86 **87** **88** **89**

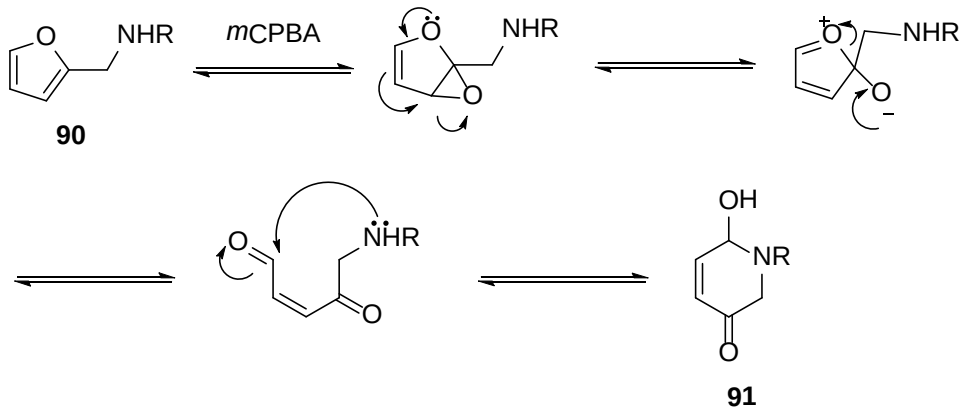
Figure 8. Examples of targeted fluorinated nitrogen heterocycles **86**-**89** to be accessed via an RCM approach.

Once an efficient and flexible route has been established, the next aim would be to utilise the methodology to produce some fluorinated biologically active compounds. A number of nitrogen heterocycles that are active in the inhibition of poly ADP ribose polymerase (PARP) enzymes are of interest in this respect.

3: Fluorinated nitrogen heterocycle synthesis *via* the aza-Achmatowicz rearrangement

3.1: Introduction

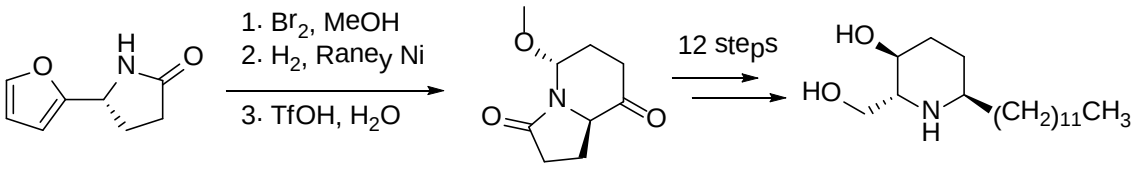
Nitrogen heterocycles can be formed by an oxidation cascade initiated by an oxidative ring expansion of α-furylamides to form hemiaminals.[48] The oxidative ring expansion in question is known commonly as the aza-Achmatowicz rearrangement.[48]



Scheme 21. The accepted mechanism for the aza-Achmatowicz rearrangement, R is an electron withdrawing group, for example a tosyl or a carbamate.[49, 50]

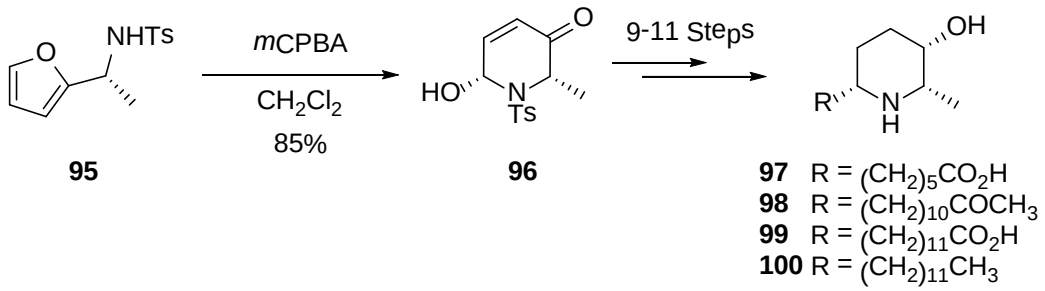
The mechanism, synonymous to the classic Achmatowicz rearrangement,[51] proceeds *via* a directed epoxidation followed by ring opening. Ring expansion occurs as the nitrogen atom is incorporated to yield a new heterocyclic structure **91** (Scheme 21).[49,50]

There has been significant attention given to this transformation in the field of total synthesis as it allows rapid access to some interesting families of natural products. Cuifolini and co-workers utilised this protocol in the synthesis of the piperidine alkaloid, desoxoprosopinine B, **94** (Scheme 22).[49] In 2006, Padwa and co-workers applied the aza-Achmatowicz rearrangement to the synthesis of the *Cassia* and *Prosopis* alkaloid family, **97**-**100** (Scheme 23).[50]



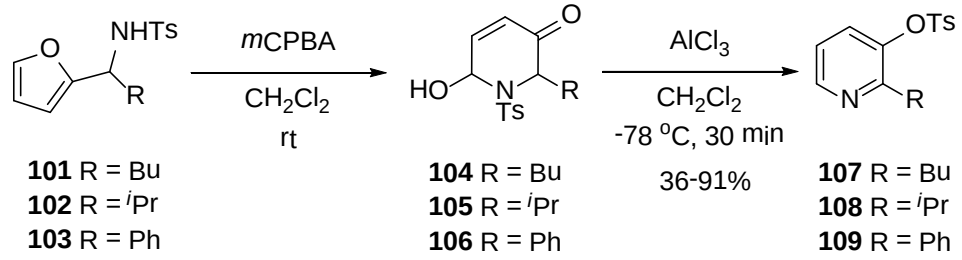
92 **93** **94**

Scheme 22. Cuifolini *et al*. published the synthesis of desoxoprosopinine B **94**, the key step being an aza-Achmatowicz rearrangement using Br_2 and MeOH.[49]



Scheme 23. *Cassia* and *Prosopis* alkaloid family, **97**-**100**, were accessed by Padwa and co-workers in 2006 through the rearrangement of furan **95** to hemiaminal **96** using *m*CPBA.[50]

Perry and co-workers utilised the aza-Achmatowicz rearrangement in the synthesis of a range of pyridines **107**-**109** (Scheme 24).[52] Oxidative rearrangement of furan precursors **101-103** was followed by Lewis acid promoted aromatisation to produce 3-tosylpyridines **107-109** in good yields over the two steps. The protecting group migrated from the nitrogen to the oxygen during the aromatisation procedure.



Scheme 24. Pyridine synthesis via aza-Achmatowicz rearrangement followed by Lewis acid promoted aromatisation in 36-91% yields the for **107**-**109** over the two steps.[52]

Our aim was to utilise this process in the synthesis of fluorinated nitrogen heterocycles such as pyridines, lactams and piperidines (Figure 9). Initial optimisation would focus on the development of a non-fluorinated analogue to validate the route before incorporation of a fluorine atom.

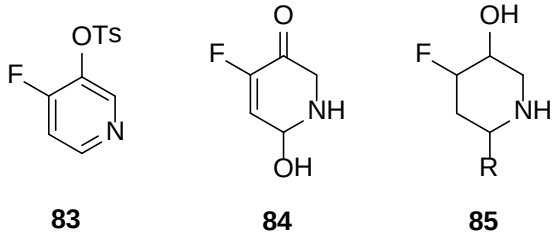
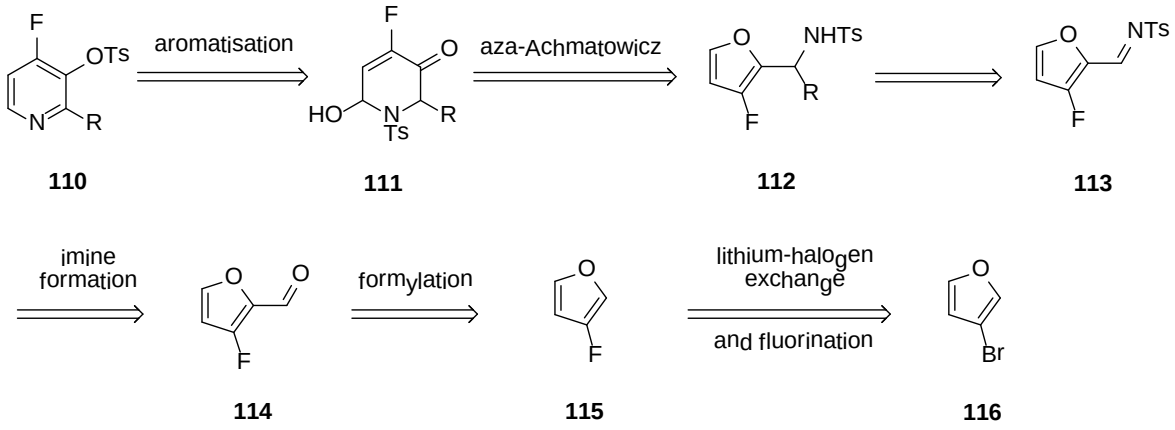


Figure 9. Examples of targeted fluorinated nitrogen heterocycles, **83**-**85**, to be accessed via an aza-Achmatowicz rearrangement approach.

3.2: Retrosynthetic analysis for the synthesis of fluorinated pyridines

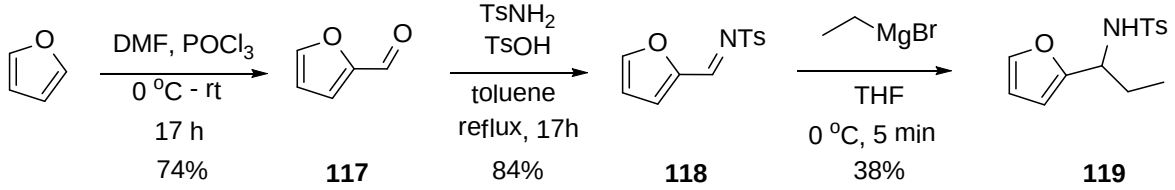
The retrosynthetic analysis proposed envisions the target pyridines **110** as originating from the aromatisation of pyridinones **111** (Scheme 25). Pyridinones **111** is the product of the aza-Achmatowicz rearrangement from precursors **112**. Furfuryl amines **112** can be formed from the aldehyde **113**, which is first converted to the imine followed by addition of a nucleophile to install various R groups. Aldehyde **114** will be produced from the fluorofuran **115**, which in turn could be produced from the commercially available 3-bromofuran **116** *via* lithium-halogen exchange.[53]



Scheme 25. Retrosynthetic analysis for the synthesis of fluorinated pyridine **110** the key step being an aza-Achmatowicz rearrangement.

3.3: Optimisation of non-fluorinated route – building the rearrangement precursor

Before adding a fluorine atom into the system, attempts were made to convert the furan starting material into the rearrangement precursor. This would be needed if the subsequent fluorinated route, starting from 3-bromofuran **116**, was to be carried out. The formylation of furan and subsequent conversion to the imine **118** were carried out using conditions reported by Padwa *et al* (Scheme 26).[54]



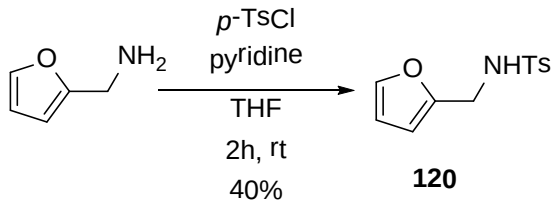
Scheme 26. The production of sulfonamide **119** from furan in 3 steps.[54,55]

With the formation of the imine in place, an array of different groups could be added in the form of Grignard reagents. This would provide the flexibility needed to prepare an array of

different pyridine analogues from a common intermediate. Following a procedure reported by Padwa and co-workers, ethyl magnesium bromide was added to imine **118** to produce amine **119**, the rearrangement precursor (Scheme 26).[54]

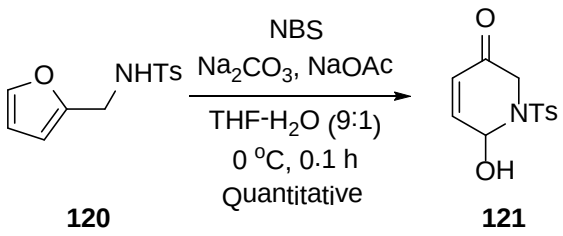
3.4: Optimisation of non-fluorinated route – rearrangement and aromatisation

Initial testing and optimisation of the rearrangement and aromatisation methodologies were undertaken. Furfurylamine was used as a model system due to its commercial availability and ease of conversion into a precursor for the rearrangement (Scheme 27). Furfurylamine was converted to the sulfonamide **120** through a reaction with *p*-toluenesulfonyl chloride and pyridine, in an unoptimised process, to give the sulfonamide **120** in a moderate yield.



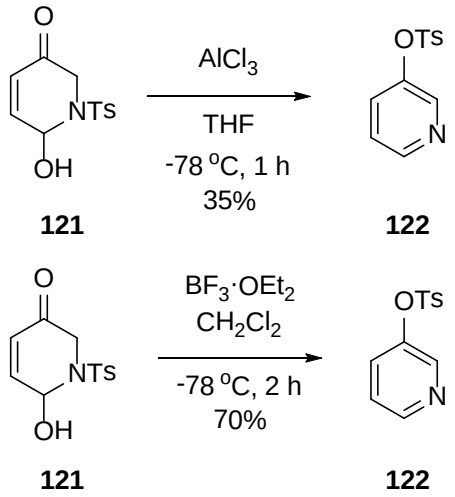
Scheme 27. Protection of furfurylamine with a tosyl group producing **120**.[56]

Having established a viable synthesis of the sulfonamide precursor, the aza-Achmatowicz rearrangement was attempted using *m*-CPBA as the oxidant.[57] The rearrangement proceeded smoothly with complete conversion to product after 7 hours. The use of *N*-bromosuccinamide (NBS) as a potential oxidant was also investigated. This accelerated the reaction, achieving complete conversion in less than 10 minutes without the need for anhydrous conditions (Scheme 28).[52] The cyclised product **121** was not purified due to fears over its instability; however, the crude material was of sufficient purity to move forward with the synthesis.



Scheme 28. aza-Achmatowicz rearrangement of amine **120** to generate hemi-aminal **121** using NBS as the oxidant.[52]

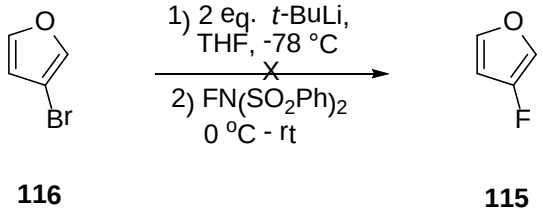
Following a literature procedure, the aromatisation step was carried out using $AlCl_3$ as a Lewis acid, however, only a low yield of **122** resulted (Scheme 29).[52] In an attempt to increase the aromatisation yield, the Lewis acid was switched to $BF_3{\cdot}OEt_2$ and the reaction re-attempted (Scheme 29). Under these conditions, a much improved 70% yield of pyridine **122** was achieved.



Scheme 29. Lewis acid promoted aromatisation of the pyridinone **121** to the analogous pyridine **122**.[52]

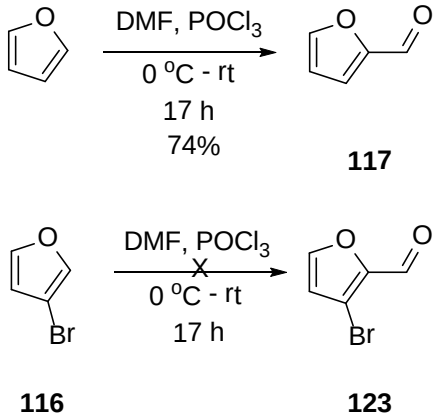
3.5: Optimisation of fluorinated route starting from 3-bromofuran

Following the successful production of a pyridine core and the development of a plausible synthetic route, investigations began into the fluorination of the furan and the conversion of the product into the rearrangement precursor. The initial plan was to use a lithium-halogen exchange reaction on commercially available 3-bromofuran and introduce the fluorine using an electrophilic fluorine source (Scheme 30).[53] This was attempted initially with *n*-butyllithium and subsequently *t*-butyllithium, however, no product was formed in either case. A complex mixture of products was formed in the reaction and the volatility of the desired compound lead difficulty in purification.



Scheme 30. Lithium-halogen exchange of 3-bromofuran **116** to yield the resulting fluorinated compound **115**, however **115** could not be isolated.[53]

Formylation of **116** was attempted, in order to functionalise the ring prior to fluorination. Thus, a Vilsmeir-Haack reaction was carried out on 3-bromofuran **116**, however, no product could be detected (Scheme 31).[55] Although other formylation techniques could be attempted they usually require the use of incompatible reagents. Thus, concerns about the stability of the starting material under these conditions prevented us pursuing this approach.

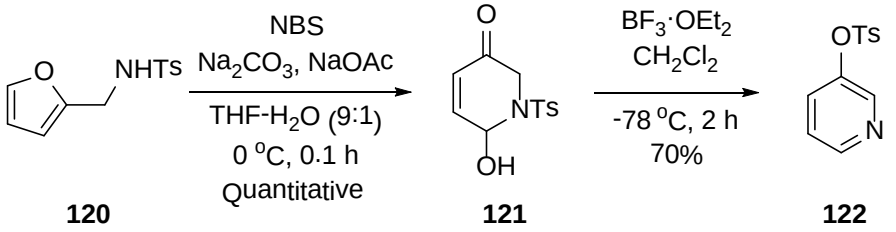


Scheme 31. The Vilsmier-Haack formylation on furan to yield furaldehyde **117**. However no product was attained from the brominated example **116**.[55]

At this stage, more promising developments with regards to other synthetic routes shifted our attention to different chemistry (*vide infra*) and no further work was carried out in this area.

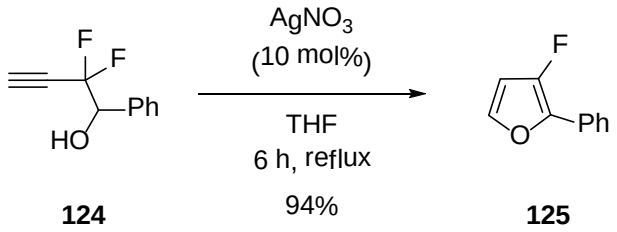
3.6: Conclusion and future work

Investigations into the use of the aza-Achmatowicz rearrangement as a tool to produce fluorinated nitrogen heterocycles were conducted. A non-fluorinated pyridine **122** was generated in a quick, efficient manner from a furan starting material **120** (Scheme 32). However, when the incorporation of a fluorine atom was probed, the synthesis of the fluorinated furan starting material proved non-trivial. As a result, the aza-Achmatowicz rearrangement on a fluorinated furan precursor could not be carried out.



Scheme 32. Synthesis of pyridine **122** in two steps from furan **120.**

Hammond and co-workers reported the synthesis of 3-fluorofuran compounds such as **125** in good yields from difluoroalkene starting materials, **124** (Scheme 33).[58] Utilising this chemistry to produce such starting 3-fluorofuran compounds, it may be possible to build the aza-Achmatowicz rearrangement precursor and produce fluorinated pyridines *via* this synthetic route.



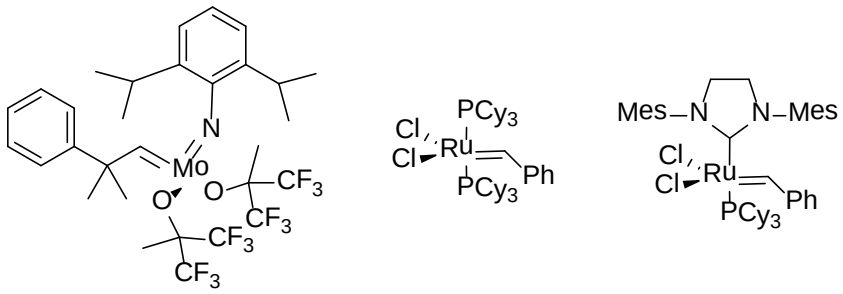
124 **125**

Scheme 33. 3-Fluorofuran synthesis reported by Hammond.[58]

4: The synthesis of 6-membered nitrogen heterocycles using ring-closing metathesis

4.1: Introduction

Ring-closing metathesis (RCM) is a type of olefin metathesis in which two alkene moieties, bound by a linker, are reacted together to form an unsaturated ring.[59] The process has been documented since 1980,[60] however pioneering work by Grubbs and Schrock in the early 90's brought it into mainstream organic chemistry with the development of stable metathesis pre-catalysts (Figure 10).[59] A Nobel Prize for chemistry was awarded to both Schrock and Grubbs for their contributions to this field along with Chauvin for his integral mechanistic insight into this process.[61]



126 **127** **128**

Figure 10. Structures of common metathesis precatalysts: Schrock A **126**, Grubbs 1st generation **127** and Grubbs 2nd generation **128** from left to right.[62,63,64]

Following *in situ* catalyst activation, the mechanism involves a [2+2] cycloaddition between the catalyst and an alkene to form a cycloruthenabutane intermediate. This ring then collapses to give the metal carbene with elimination of ethene. The metal carbene can now undergo another [2+2] cycloaddition to the second tethered alkene and the same process leads to elimination of the ring-closed product and regeneration of the active catalyst (Figure 11).[65]

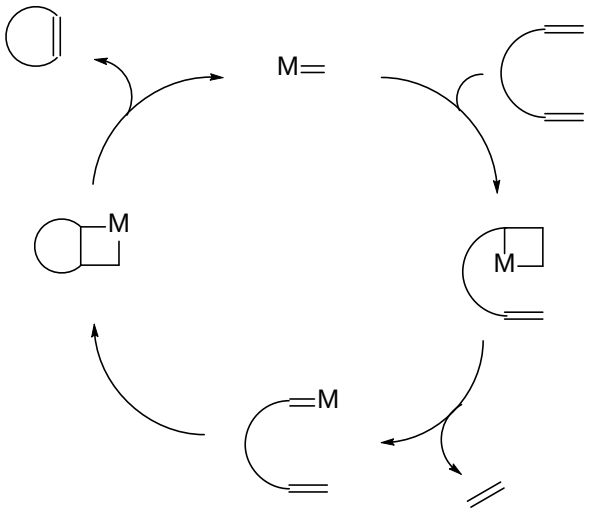
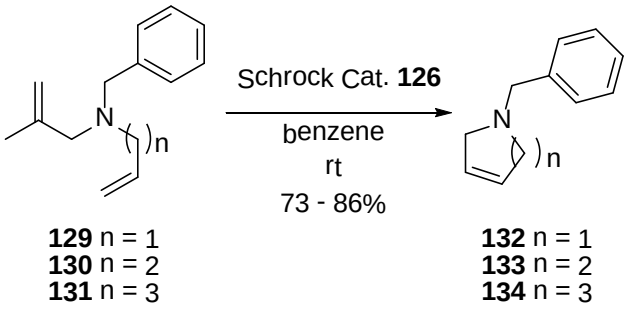


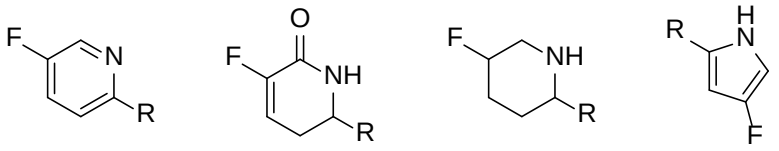
Figure 11. A simplified mechanism of the RCM reaction with activated metal catalyst**.**[65]

In 1992, the first nitrogen heterocycles were synthesised through a ring-closing metathesis approach by Grubbs and co-workers.[66] Using the molybdenum catalyst developed by Schrock **126** (Figure 10), they were able to produce an array of unsaturated nitrogen heterocycles, **132**-**134**, ranging from 5- to 7-membered rings in good yields (73-86%) (Scheme 34).



Scheme 34. RCM reactions perfomed by Grubbs and co-workers yielding a number of saturated nitrogen heterocycles **132**-**134**.[66]

One of our initial ideas focused on utilising a ring-closing metathesis (RCM) approach to access a range of fluorinated nitrogen heterocycles. Previous work in this area by the groups of Haufe, Rutjes and Hammond, amongst others, has demonstrated the potential of RCM for the production of fluorinated heterocycles (Section 1.3.2).[34-38] It is the aim of the present work to produce a route to a common α,β-unsaturated lactam intermediate **87** which could be converted late-stage into a number of heterocycle classes **86** and **88**. Initial attempts will focus on the synthesis of heterocycles featuring a 6-membered ring. Following this, attempts will be made to develop a more general procedure for the production of heterocycles containing different ring sizes, such as fluorinated pyrrole **89** (Figure 12).

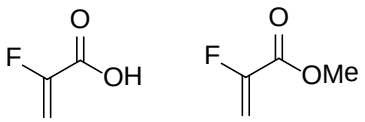


86 **87** **88** **89**

Figure 12. Examples of targeted fluorinated nitrogen heterocycles, **86**-**89**, to be accessed via an RCM approach.

4.2: Retrosynthetic analysis for the synthesis of fluorinated nitrogen heterocycles

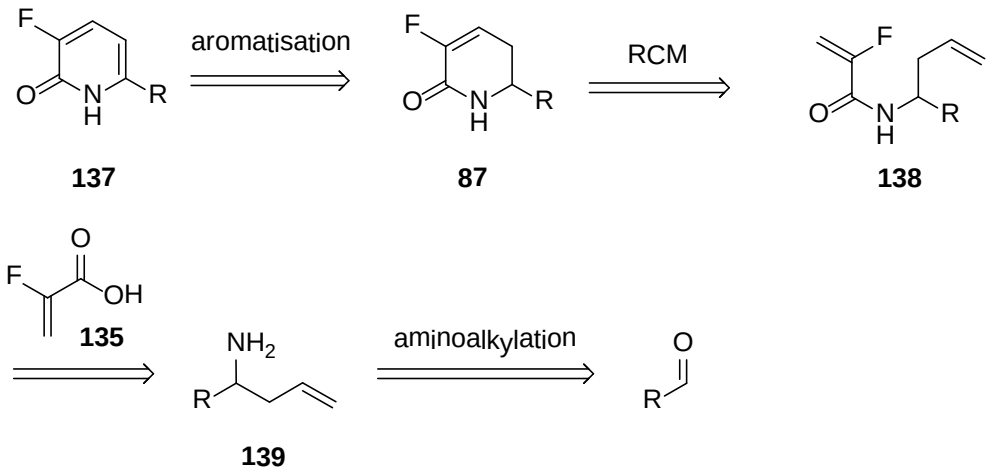
The commercial availability of a range of fluorinated alkenes, such as **135** and **136**, presented us with the opportunity to build fluorinated nitrogen heterocycles via an RCM process.



135 **136**

Figure 13. Commercially available fluorinated alkene compounds.

Retrosynthetically, we envisioned pyridone **137** as originating *via* an oxidative process from the unsaturated lactam **87** (Scheme 35). Ring-closing metathesis could be used to form the cyclic system from the diene **138**. Diene **137** could be formed through the coupling between allyl amine **139** and fluorinated acid **135**, with amine **139** being generated from a commercially available aldehyde.



137 **87** **138**

135

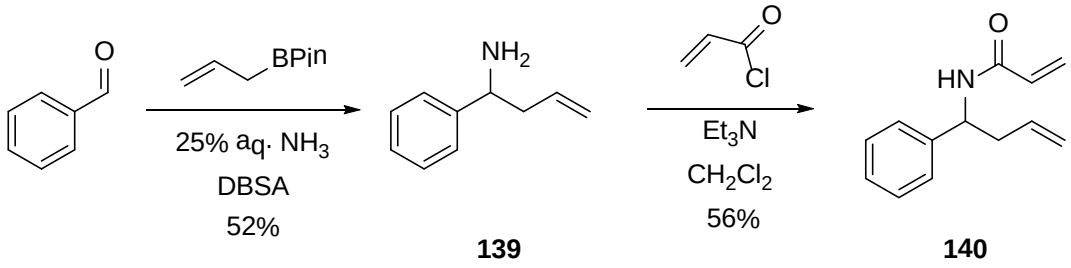
139

Scheme 35. Retrosynthetic analysis of potential route to fluorinated pyridones, **137**.

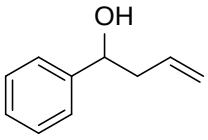
4.3: Production of nitrogen heterocycles using ring-closing metathesis methodology

Initial testing and optimisation of the ring-closing metathesis methodology for the synthesis of nitrogen heterocycles was first undertaken without inclusion of the fluorine functionality.

The first step in the forward synthesis was the generation of allyl amine **139** from benzaldehyde using aqueous ammonia and allylboronic acid pinacol ester (Scheme 36), under conditions reported by Kobayashi and co-workers.[67] Initial attempts resulted in the formation of amine **139** in a 52% yield. The main side product was alcohol **141**, which was formed by the reaction of the boronic ester with the starting material**,** in a reaction that competed with the desired process (Figure 14). However, alcohol **141** was easily removed via an acid-base extraction.[67] The allylic amine **139** was coupled with acryloyl chloride to produce diene **140** in a moderate yield of 56%.[68]



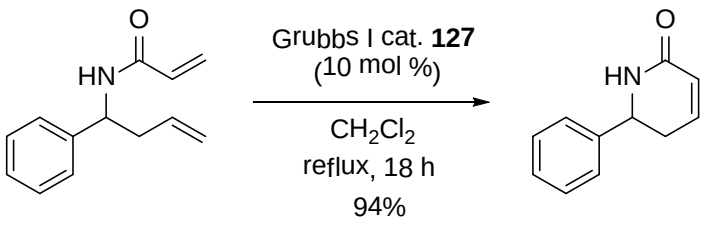
Scheme 36. Aminoalkylation of benzaldehyde, followed by acryloyl chloride addition to produce **140**. DBSA stands for dodecyl benzenesulfonic acid.[67, 68]



141

Figure 14. Alcohol **141**. The main side product of the amino-alkylation reaction.[67]

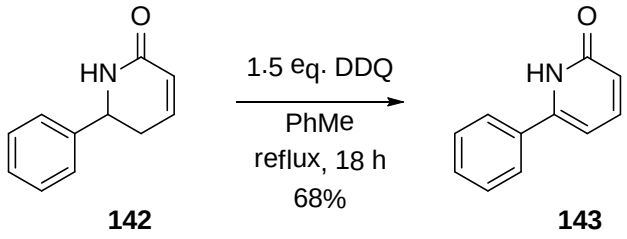
Ring-closing metathesis of diene **140** proceeded in high yield to give the bicyclic unit **142** (Scheme 37). As with all metathesis reactions, control of the concentration was vital to ensure the desired process occurred instead of the competing dimerisation that could occur through cross metathesis.[69] In an initial attempt, a concentration of diene in dichloromethane of 0.042 g mL^{-1} was used, however, only a 42% yield of **142** was isolated. The mixture was subsequently diluted to 0.01 g mL^{-1} and the desired RCM reaction occurred in a favourable 94% yield.



140 **142**

Scheme 37. The ring-closing metathesis on **140** to give dihydro-pyridinone **142**.[69]

The final step in the synthesis involved the oxidation of the dihydro-pyridinone **142** to the analogous pyridone **143**. For this to be achieved, a hydride at the 6- position needed to be extracted, requiring the use of a strong oxidising agent. For this purpose, we chose to treat our recently obtained α,β-unsaturated lactam **142** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2 at room temperature.[70] The reaction was not complete after 18 hours; however, a promising yield of around 30% was obtained. In order to increase the yield, the solvent was switched to toluene and the reaction heated to reflux. After stirring for 18 hours at reflux, an acceptable yield of 68% was achieved (Scheme 38).



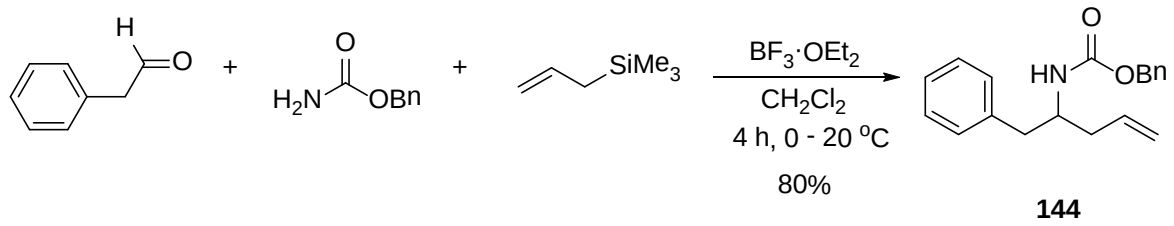
142 **143**

Scheme 38. The oxidation of ring-closed product **142** to the analogous pyridone **143**.[70]

4.4: Optimisation of one-pot diene synthesis

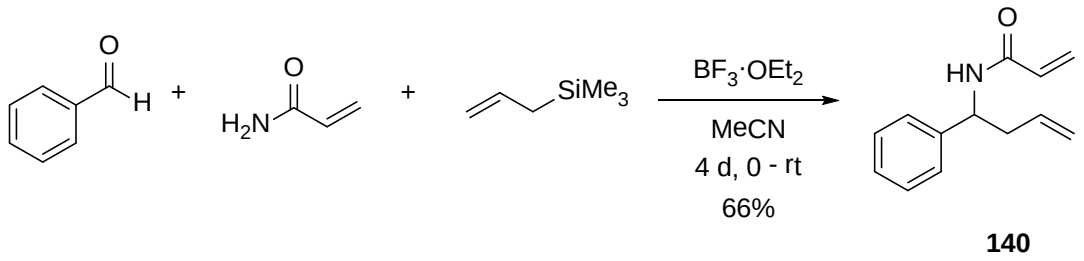
The success of the aromatisation reaction (Section 4.3) meant that a short 4 step synthesis of pyridones from a commercially available aldehyde had been completed. However, the yield of the first step was unacceptable, thus before attempting to develop the synthesis of fluorinated analogues a significant improvement to the route had to be made.

Veenstra and co-workers reported a one-pot procedure to synthesise a range of protected allylic amines, such as **144**, using allyltrimethylsilane and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 or MeCN in good yields of up to 95% (Scheme 39).[71] Hence, we proposed that if a similar coupling reaction could be carried out using acrylamide, the diene precursor **140** could be obtained in a single step (Scheme 40).

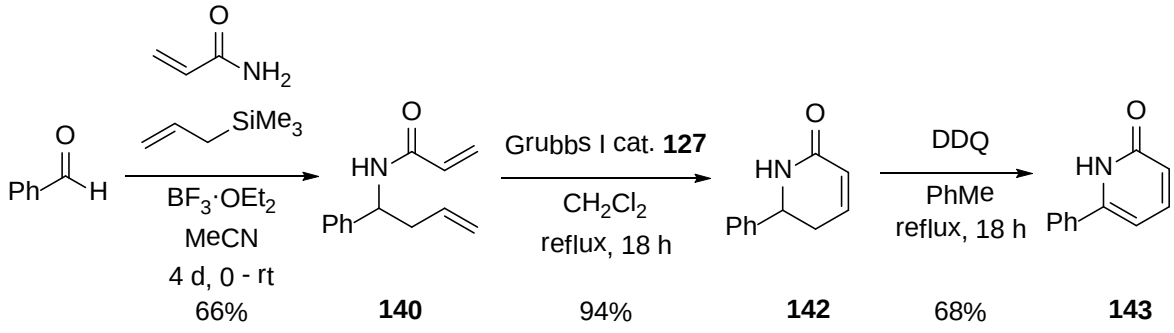


Scheme 39. Synthesis of benzyl carbamate **144** reported by Veenstra and co-workers.[71]

In order to test this hypothesis, benzaldehyde, acrylamide and allyltrimethylsilane were stirred together in acetonitrile with Lewis acid $BF_3{\cdot}OEt_2$ at room temperature (Scheme 40). The reaction was very slow and took four days to reach completion; however, the dialkene **140** was isolated in an excellent yield of 66%. The success of this one pot procedure meant that the target pyridone synthesis could be reduced to three steps (Scheme 41).



Scheme 40. The one pot production of dialkene **140**.

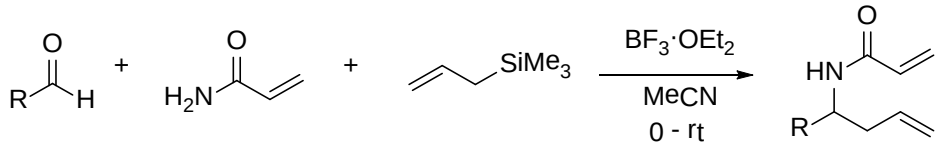


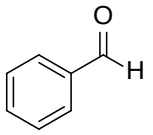
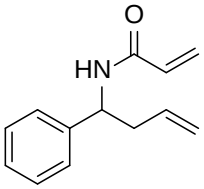
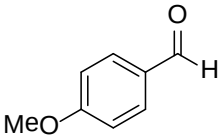
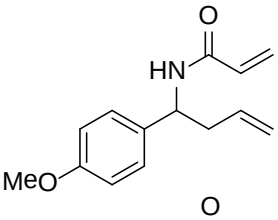
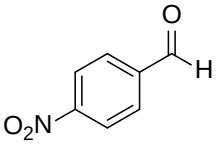
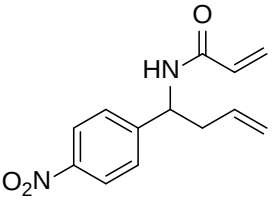
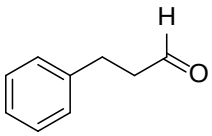
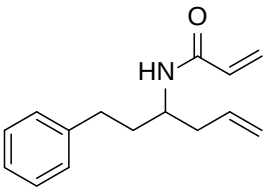
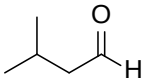
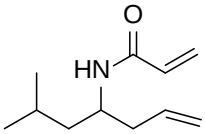
Scheme 41. The 3 step synthesis of pyridone **143**.

4.5: Scope of three component coupling reaction.

The next stage was to determine the scope of the methodology and produce an array of substituted pyridones. Therefore, the one pot dialkene formation was performed on a range of different aldehydes and the results are displayed in Table 1.

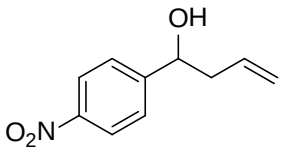
Table 1. Unoptimised yields for the one-pot aminoalkylation with various different aldehydes



Entry number	Aldehyde	Product		Time / d	Yield / %[a]
1			**140**	4	66
2			**145**	4	19
3			**146**	6	10
4			**147**	4	45
5			**148**	6	46

[a] Isolated Yield

As can be seen in Table 1, the results produced were mixed. Low yields were obtained when the electronics of the aromatic ring were changed from benzaldehyde (Entry 1) which exhibited the highest yield. In the presence of an electron-donating substituent (Entry 2), a poor yield of 19% of **145** was obtained due to poor reactivity of the starting aldehyde. In the presence of an electron-withdrawing substituent (Entry 3) a yield of 10% of **146** was obtained. In the case of the electron withdrawing group, a 52% yield of the alcohol **149** was obtained (Figure 15), showing that the highly electrophilic nature of the aldehyde favoured addition of the allyltrimethylsilane to the aldehyde before the desired imine formation could take place. Aliphatic examples, **147** (Entry 4) and **148** (Entry 5), were generated in moderate yields of 45% and 46% yields respectively.



149

Figure 15. Alcohol **149**. The main side product of the amino-alkylation reaction with *p*-nitrobenzaldehyde.

As the yields and time scale for the reaction were not satisfactory, further optimisation of this step was carried out. It was thought that the reason the reaction was so slow was due to the unreactive nature of acrylamide (Figure 16). The competition between the acrylamide and the allyltrimethylsilane to react with the aldehyde was severely lowering the reaction yields and dramatically reducing the routes scope.

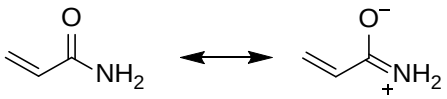
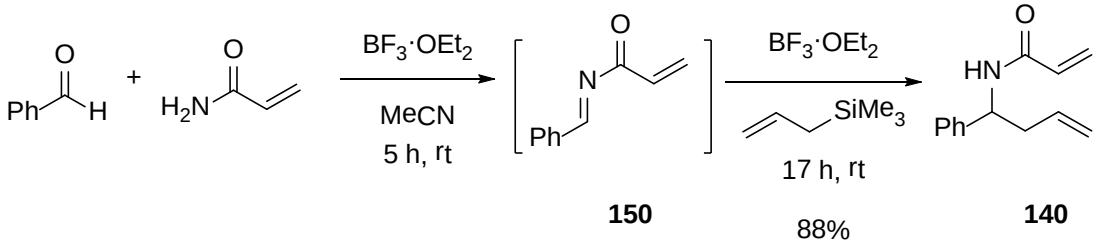


Figure 16. Resonance forms of acrylamide reducing the nucleophilicity of the nitrogen.

Taking this into account, the reaction was modified in order to increase the likelihood of the imine formation. Under the new procedure, the aldehyde was stirred with 3 equivalents of acrylamide and 1 equivalent of Lewis acid for 5 hours prior to subsequent addition of allyltrimethylsilane and a further equivalent of Lewis acid. This modification was first attempted on benzaldehyde and resulted in a dramatic increase in the yield to 88%, in addition to a reduction in the reaction time to a total of 22 hours (Scheme 42).

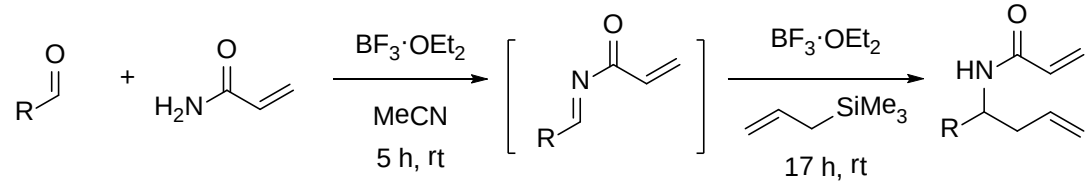


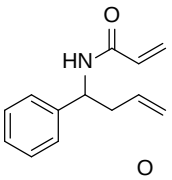
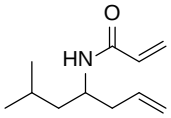
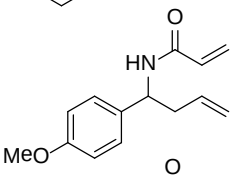
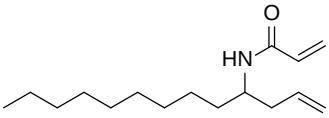
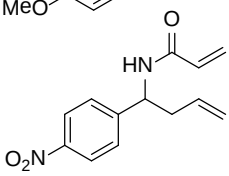
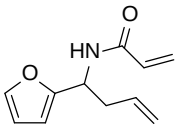
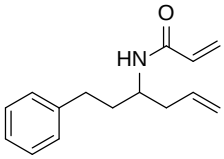
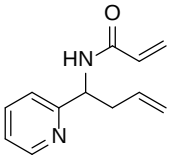
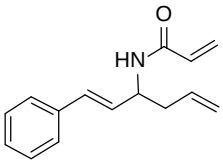
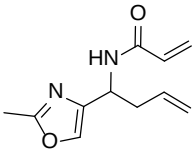
Scheme 42. Optimised one pot production of dialkene **140**.

4.6: Extension of methodology for non-fluorinated nitrogen heterocycle synthesis

Having developed an expedient methodology for heterocycle synthesis, a range of aldehydes were subjected to the reaction conditions and the results are displayed in Table 2.

Table 2. Results of the optimised one pot production of dialkene analogues **140**, **145**-**148** and **151**-**155**, using a range of aldehydes.



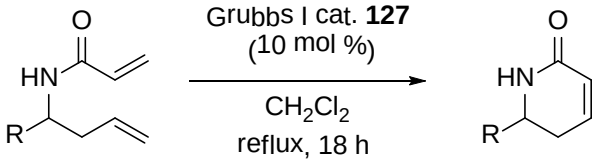
Entry no	Product		Yield / %[a]	Entry no	Product		Yield / %[a]
1		**140**	88	6		**148**	86
2		**145**	83	7		**152**	91
3		**146**	34	8		**153**	0
4		**147**	66	9		**154**	0
5		**151**	20	10		**155**	41

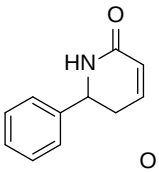
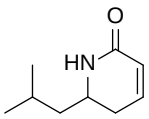
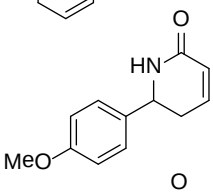
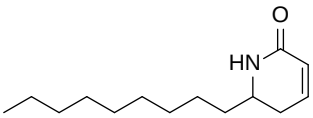
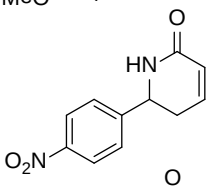
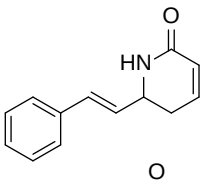
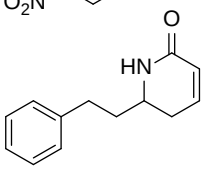
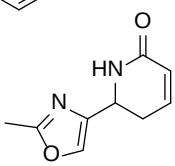
[a] Isolated Yield

The results were promising for a variety of aldehydes (Table 2). The electron rich 4-methoxybenzaldhyde was converted to amide **145** in an 83% yield (Entry 2), as compared with 19% under the previous conditions (Table 1, Entry 2). The electron poor 4-nitrobenzene analogue **146** (Entry 3) was obtained in an improved yield of 34%, however insolubitiy issues with the intermediate imine prevented higher conversion to the desired product. Aliphatic examples **148** (Entry 6) and **152** (Entry 7) worked especially well with yields of 86 and 91% obtained respectively. A few of the desired products were not formed under the reaction conditions including furan **153** (Entry 9) and pyridine **154** (Entry 10). This could be explained by the presence of heteroatoms in the ring systems, which could result in an interaction with the Lewis acid in the mixture. This is especially prevalent in the case of furfural (Entry 9) which in the presence of $BF_3{\cdot}OEt_2$ has the potential to ring open. However, in contrast, a 41% yield of the oxazole **155** was obtained (Entry 8).

Following the successful dialkene formation, the ring-closing metathesis was performed on the range of analogues (Table 3). This was carried out as previously described (Section 4.3) using 10 mol% Grubbs 1st generation catalyst **127** in dichoromethane at reflux.

Table 3. The products and yields of the ring closing metathesis reaction to generated α,β-unsaturated lactams **142**, **156**-**162**.



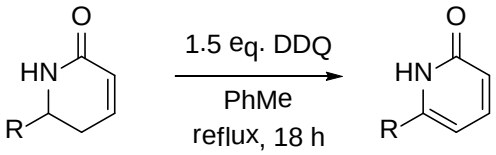
Entry no	RCM product		Yield / %[a,b]	Entry no	RCM product		Yield / %[a,b]
1		**142**	94	5		**159**	84
2		**156**	99	6		**160**	90
3		**157**	99	7		**161**	68
4		**158**	94	8		**162**	0

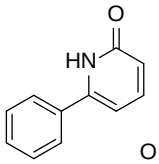
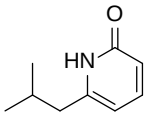
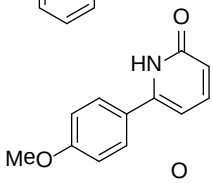
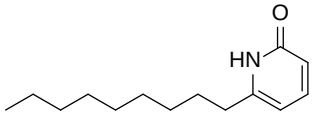
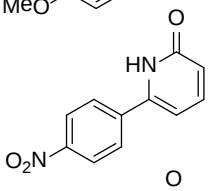
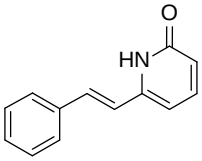
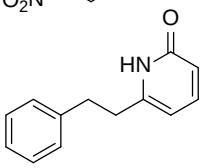
[a] Isolated Yield. [b] Concentration = 0.01 g ml^{-1}.

The RCM reaction proceeded efficiently with the majority of the analogues tested, producing the target dihydropyridones in good yields (Table 3). The analogues possessing electron donating and electron withdrawing groups, **156** and **157** respectively, (Entries 2 and 3) were both obtained in an excellent 99% yield. Ring closure occurred selectively in the case of the unsaturated diene **151** to produce **161** in a good yield of 68% (Entry 7). The one analogue that was not obtained was the substituted oxazole **162** (Entry 8); it is possible that the presence of electron rich heteroatoms may have poisoned the catalyst before the reaction could proceed.[72]

The next step involved an oxidation with DDQ to yield the relevant pyridone. Using the procedure as previously described (Section 4.3) with DDQ in toluene at reflux, the oxidations were attempted on the RCM products (Table 4).

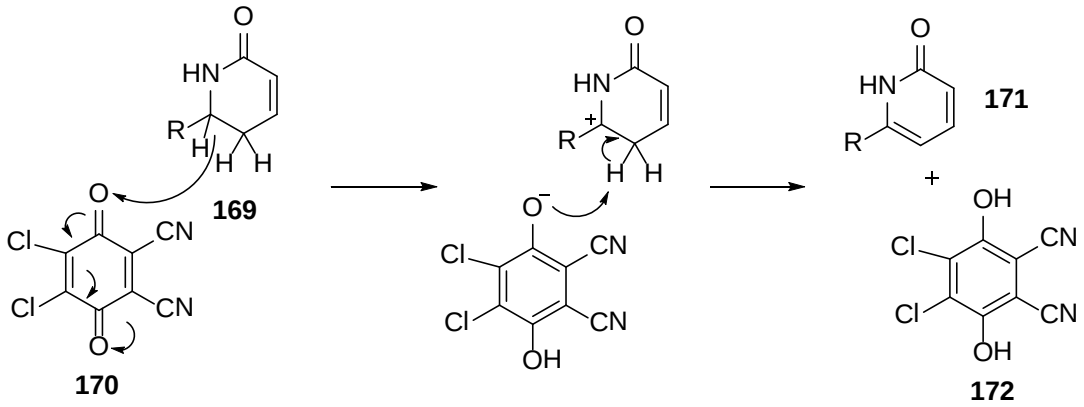
Table 4. The oxidation of RCM products with DDQ to form pyridone compounds **143** and **163**-**168**.



Entry no	RCM product		Yield / %[a]	Entry no	RCM product		Yield / %[a]
1		**143**	68	5		**166**	0
2		**163**	76	6		**167**	0
3		**164**	0	7		**168**	0
4		**165**	0				

[a] Isolated Yield

Disappointingly, the previously successful oxidation of the phenyl analogue (Entry 1) could not be replicated with the vast majority of the other analogues. It was evident from the results that the electronics of the R group were integral to the success of the oxidation reaction. With the phenyl and aromatic electron donating substituents **143** and **163** the reaction proceeded in reasonable yields (Entries 1 and 2), however with an aromatic electron withdrawing substituent or aliphatic substituents, **164** and **165**-**167**, the reaction did not proceed at all (Entries 3-7). It has been postulated by Linstead and co-workers that the mechanism of DDQ dehydrogenation proceeds initially via a hydride abstraction to leave a carbocation followed by a further adjacent proton removal to yield the saturated system (Scheme 43).[73] This being the case, a possible reason for the failed oxidation of most analogues could be due to a lack of stabilisation of the carbocation in the transition state, meaning hydride abstraction was disfavoured. This would also explain the good yield observed in the presence of the compound **163**, with the electron donating substituent, as in that instance the carbocation would be stabilised.

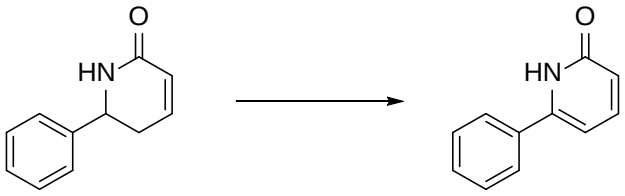


Scheme 43. Mechanism proposed by Linstead and co-workers for mechanism for DDQ dehydrogenation applied to the reaction carried out above.[73]

4.7: Optimisation of conditions for the oxidation of α,β-unsaturated lactam 142

With the DDQ reaction only oxidising two analogues, more general conditions were required if aromatic heterocylces were to be accessed via this route. The conditions attempted could be split into to two categories: firstly oxidisation of the ring directly and the second ring modification followed by elimination (Table 5).

Table 5. Reagents and conditions used to aromatise dihydropyridone **142** to pyridone **143** by direct oxidation.[74-77]

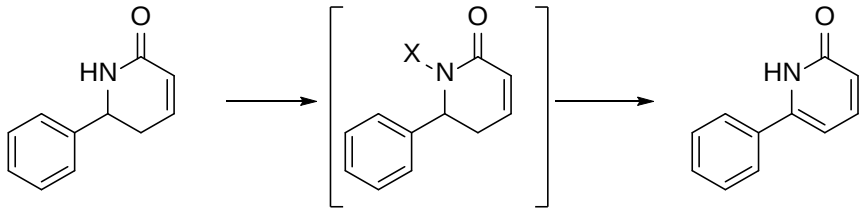


Entry No.	Reagents	Conditions	Yield / %[a]
1	DDQ	CH_2Cl_2, rt	30
2	DDQ	toluene, reflux	68
3	CAN	MeCN, reflux	0
4	IBX	DMSO, 45 to 80 °C	0
5	$Hg(OAc)_2$	H_2O/EtOH	0
6	DBU/CCl_3Br	CH_2Cl_2, rt	0

[a] Isolated Yield.

The direct oxidation of the ring was attempted with CAN (Entry 3),[74] IBX (Entry 4),[75] $Hg(OAc)_2$ (Entry 5),[76] and DBU/CCl_3Br (Entry 6),[77] however there was no reaction with any of these oxidising agents (Table 5).

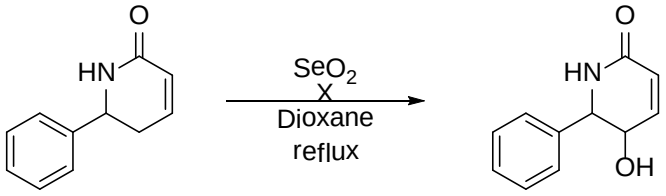
Table 6. Reagents and conditions used to aromatise dihydropyridone **142** to pyridone **143** *via* **173** using a halogenation-elimination approach.[78-79]



Entry No.	Reagents	Conditions	Yield / %[a]
1	*t*BuOK/NCS[b]	THF, rt	0
2	NBS/DBU[c]	CH_2Cl_2, rt	0
3	Br_2/DBU[c]	CH_2Cl_2, rt	0

[a] Isolated Yield. [b] X = Cl. [C] X = Br.

In the second category, halogenation of the amide followed by elimination was attempted under various conditions (Table 6). Chlorination was attempted with NCS, to form a N-Cl bond, before potassium *tert*-butoxide was added to eliminate the chlorine however no product was isolated (Entry 1).[78] Bromination was also attempted with firstly NBS followed by bromine elimination with DBU but again only starting material was isolated (Entry 2).[79] Bromine was also used to followed by DBU, however, this time there was evidence of new product characteristic of over brominated material and not the desired product (Entry 3).



142 **174**

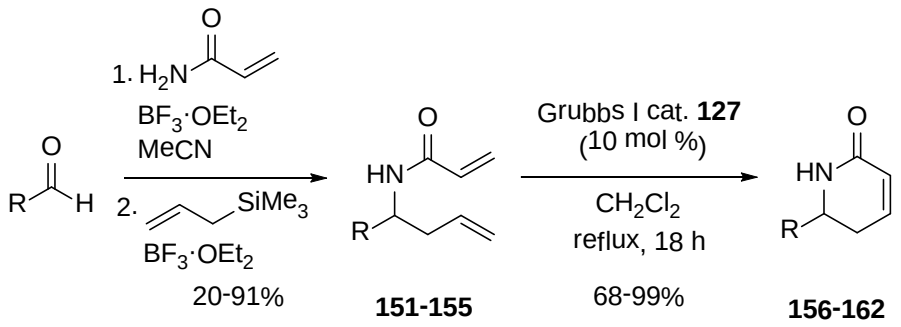
Scheme 44. Attempted allylic oxidation of dihydropyridone **142** using SeO_2.[80]

Finally, selenium dioxide was used as a stratergy to add an allylic alcohol, **174**, that could be eliminated to yield the desired product, however no oxidation was observed (Scheme 44).[80]

4.8 Conclusions and future work

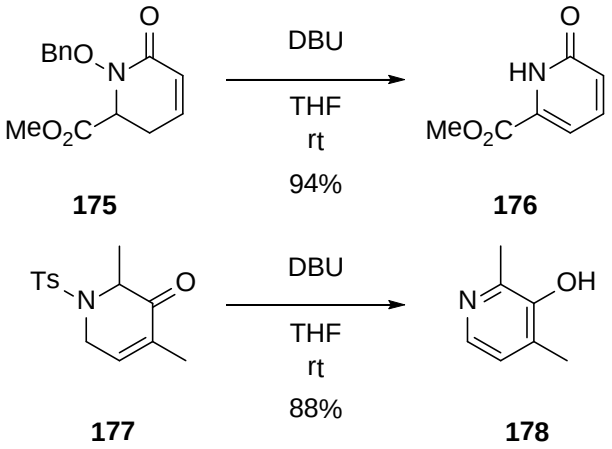
A three step, two-pot route to dihydropyridones was established and a library of compounds synthesised (Scheme 45). Imine formation followed by allylation yielded the intermediate diene compounds **151**-**155** in an efficient one-pot process. Ring-closing

metathesis could then occur smoothly on addition of Grubbs 1st generation catalyst **127** producing the dihydropyridones **156**-**162** in high yields.



Scheme 45. Rapid, protecting group free synthesis of dihydropyridones **156**-**162** starting from common aldehydes.

General conditions for oxidation from the dihydropyridone to the pyridone and subsequently the pyridine have not been achieved so far. Donohoe and co-workers produced the pyridone **176** and pyridine **178** *via* elimination reactions using 1,8-diazabicycloundec-7-ene (DBU); a similar approach in this work may lead to successful pyridine synthesis (Scheme 46).[79]

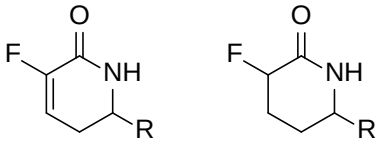


Scheme 46. Synthesis of pyridone **176** and pyridine **178** reported by Donohoe.[79]

5: Development of a route to fluorinated nitrogen heterocycles using a ring-closing metathesis protocol

5.1 Introduction

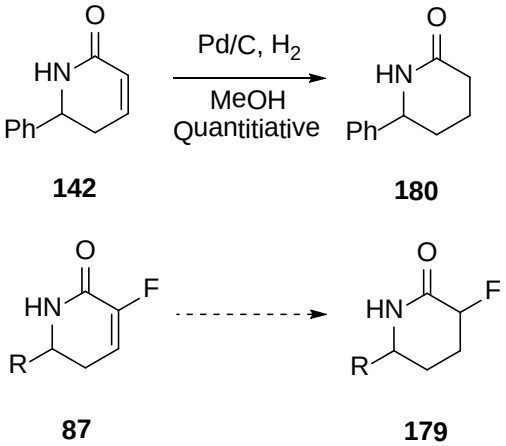
Novel synthetic routes to access fluorinated nitrogen heterocyclic are of keen interest to the scientific community. Compounds **87** and **179** are examples of nitrogen heterocycles that have been targeted in this thesis and it is our aim to synthesise such compounds *via* a ring-closing metathesis approach (Figure 17).



87 **179**

Figure 17. Examples of targeted fluorinated nitrogen heterocycles, **87** and **179**, to be accessed via an RCM approach.

Following the success of the two step synthesis of dihydropyridones (Section 4.6), our next aim was to introduce a fluorine atom into the system. The oxidation of the dihydropyridones **156**-**162** had not been achieved (Section 4.6), however reduction to the δ-lactam **180**, shown previously by Marquez and co-workers, had been demonstrated in quantitative yields (Scheme 47).[81] Therefore, a three step synthesis of fluorinated δ-lactams was targeted, with fluorinated lactam **87** being a key intermediate.



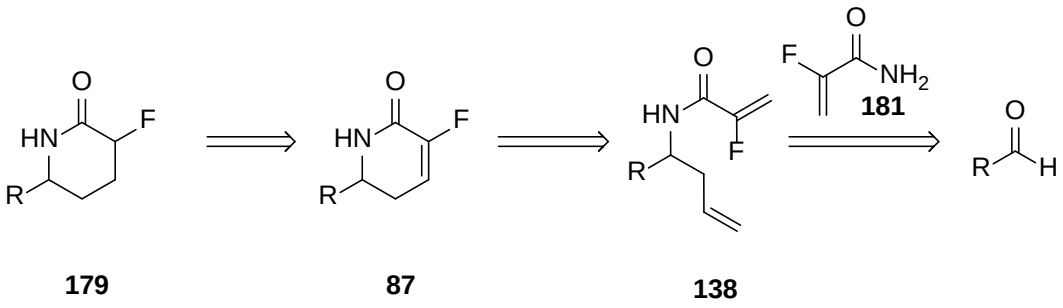
142 **180**

87 **179**

Scheme 47. Work within the Marquez group has shown the dihydropyridone **142** can be reduced to the lactam **180**.[81]

5.2 Retrosynthetic analysis

A new retrosynthetic approach was devised starting from the fluorinated δ-lactam **179** (Scheme 48). The δ-lactam **179** would be generated, as described, from the dihydropyridone **87**. This in turn would be produced through the ring-closing metathesis reaction of the dialkene **138**, with ring closure taking place between with the vinyl fluoride and allylic alkene. The RCM precursor was envisaged as originating from the commercially available aldehyde through a one-pot aminoalkylation as described previously, with 2-fluoroacrylamide **181** replacing the acrylamide.

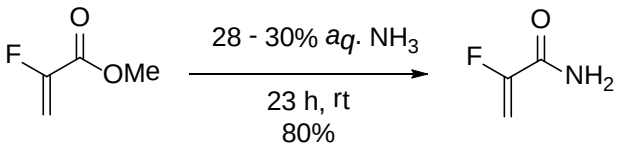


179 **87** **138**

Scheme 48. Retrosynthetic pathway for the synthesis of fluorinated δ-lactams.

5.3: Use of 2-fluoroacrylamide for the synthesis of the fluorinated ring-closing metathesis precursor

In order to commence this route, 2-fluoroacrylamide **181** was synthesised in one step from commercially available 2-fluoroacrylic acid methyl ester, **136** using conditions reported by Nagata.[82] The generation of the amide unit was accomplished in a good yield of 80% by stirring the ester **136** with aqueous ammonia (Scheme 49).

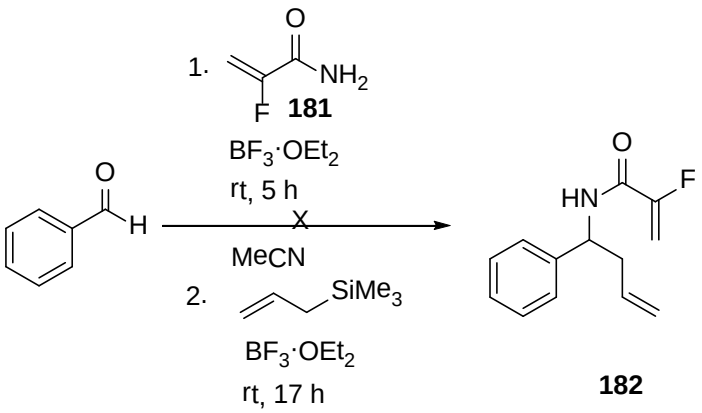


136 **181**

Scheme 49. Conversion of fluorinated ester **136** to the fluorinated amide **181**.[82]

2-Fluoroacrylamide **181** was then used in the one pot dialkene formation following the same conditions described previously (Section 4.4). However, after repeated attempts the reaction did not proceed as desired (Scheme 50). It was thought that the fluorine caused

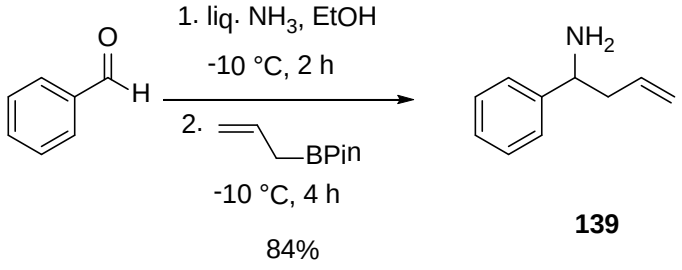
the amide to become more electron deficient and was rendered less reactive towards the aldehyde.



Scheme 50. Attempted one pot dialkene formation attempted with 2-fluoroacrylamide **181** in place of acrylamide.

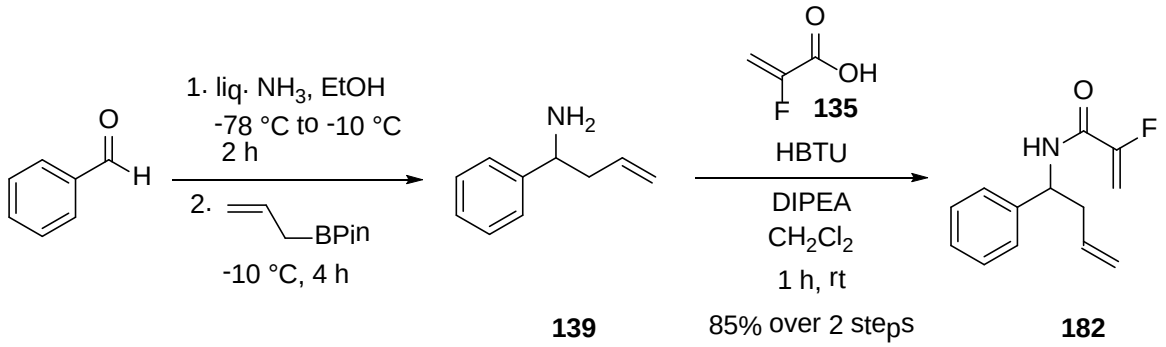
5.4: Synthesis of the fluorinated ring-closing metathesis precursor and initial attempts at fluorinated ring-closing metathesis reaction.

With the failure of the one-pot procedure, the synthetic route had to go *via* the amine **139**. In the first instance, an amino-allylation reaction could be attempted to form the allylic amine **139**, which could then be acylated to form the cyclisation precursor **182**. The synthesis of amine **139** had been attempted previously (Section 4.3, Scheme 36), using aqueous ammonia and allyl boronic pinacol ester to produce the homo-allylic amine **139**, however this only worked in low yields.[67] To improve this step, a procedure reported by Kobayashi and co-workers was utilised.[83] The authors used liquid ammonia to form an imine before treatment with allyl boronic pinacol ester to generate **139**. Kobayashi reported good yields for this reaction in the range of 80 to 90% for a variety of aldehydes (Scheme 51).[83]



Scheme 51. An example aminoalkylation reported by Koybayashi and colleagues forming **139** in a 84% yield.[83]

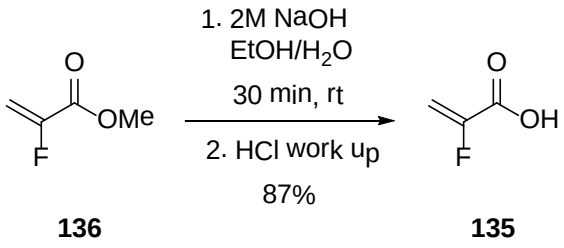
Following Kobayashi conditions, the amino-allylation reaction was carried out using benzaldehyde and the allylic amine **139** was formed.[83] The product was purified using an acid-base work up and the next step was carried out on the crude material (Scheme 52).



Scheme 52. Two step procedure to form diene **182** in 85% from the benzaldehyde.[83]

The addition of the vinyl fluorine to the system was our next goal. To do this an amide coupling reaction was performed with 2-fluoroacrylic acid **135** in the presence of HBTU. The coupling reaction proceeded efficiently with complete consumption of starting material in under an hour, producing the target dialkene **182** in an excellent yield of 85% from benzaldehyde (Scheme 52).

The free acid **135**, required to perform the amide coupling, was generated from the corresponding methyl ester **136**. This hydrolysis was carried out to form the sodium salt, followed by acidification to yield the free acid **135** in a high yield of 87% (Scheme 53).[84]

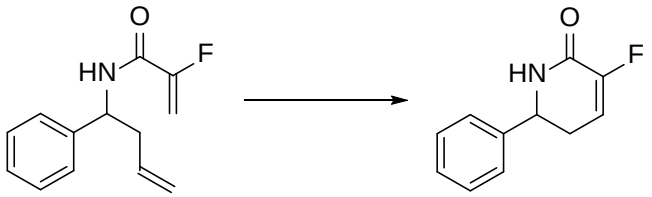


Scheme 53. Conversion of ester **136** to acid **135** in 87% yield.[84]

Following the successful production the dialkene **182**, ring-closing metathesis was then attempted to generate the cyclic amide **183**. Initially, the previously described conditions (Section 4.3, Scheme 37) were tested which utilised 10 mol% Grubbs 1st generation catalyst **127** at reflux in dichloromethane (Table 7, Entry 1). However, only cross metathesis products were identified and no cyclised product was isolated. The presence of the fluorine atom, as expected, caused the alkene to be more electron deficient thereby reducing its reactivity towards metathesis.[85] The adjacent alkene, however, had no such problem and it seemed it was interacting with the catalyst and cross coupling before coordination with the electron deficient alkene could occur. In an attempt to circumvent

this, the reactions were performed at a higher dilution and the catalyst was switched to the more reactive Grubbs 2nd generation catalyst **128** (Table 7, Entries 2 and 3).[85] Therefore, 7.5 mol% Grubbs 2nd generation catalyst **128** was used but under these modified conditions the reaction still did not proceed as desired (Entry 2). There was still evidence of cross-metathesis and starting material. The reaction was attempted under microwave irradiation (Entry 3) but no product was obtained. A different catalyst, Zhan 1B **184** (Figure 18), was also used but again no product was detected (Entry 4).[86]

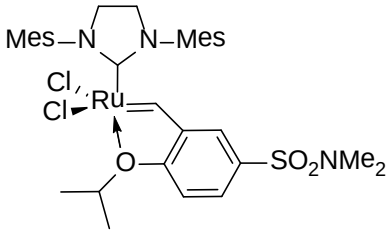
Table 7. Results for the attempted RCM reactions of **182** to **183**.[85,86]



182 **183**

Entry	Pre-catalyst	Conditions	Yield / %
1	Grubbs 1st gen. **127**	10 mol%, CH_2Cl_2, reflux[a]	0
2	Grubbs 2nd gen. **128**	7.5 mol%, toluene, 100 °C[b]	0
3	Grubbs 2nd gen. **128**	7.5 mol%, toluene, MW, 100 °C[b]	0
4	Zhan 1B **184**	7.5 mol%, toluene, 80 °C[b]	0

[a] concentration = 0.01 g mL^{-1}. [b] concentration = 0.0025 g mL^{-1}



184

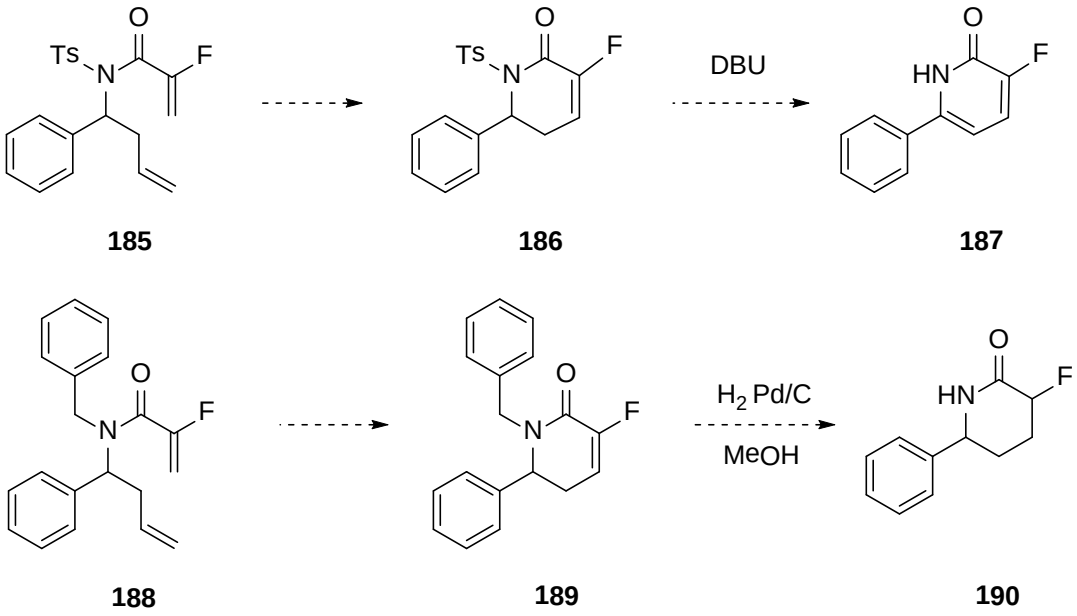
Figure 18. Zhan 1B catalyst, **184**.[86]

The observed failure of the metathesis reaction could be explained by the electron deficiency of the fluorinated olefin. However, this may not be the case as there are several examples of metathesis with vinyl fluorides in the literature.[35-38] On the other hand, examination of the literature revealed that there were no examples of ring-closing metathesis using substrates containing an unprotected amide within the ring that was to be formed.[35-38] It was proposed that the available alkene was coordinating to the ruthenium catalyst, but the second alkene was being held in position facing away from the reactive site preventing further metathesis. It was proposed that the RCM may work using a substrate in which the amide was protected. Amide protection could prevent the

unwanted interaction of the ruthenium centre with the amide,[72] and could also alter the conformation of the molecule to potentially bring the two alkenes into closer proximity, facilitating the desired reaction via a possible Thorpe-Ingold type effect.[87]

5.5: Protection of amide and ring-closing metathesis

Although the installation and removal of a protecting group would result in the lengthening of the proposed four step synthesis, it would allow for more flexibility and could potentially lead to the synthesis of different final products which could also be of synthetic interest. It was proposed that the installation of a protecting group that could be removed by elimination, for example tosyl, would allow access of aromatic fluorinated rings **187** (Scheme 54).[79] Alternatively, to access the lactam **190**, a benzyl group could be installed that could be potentially removed in the same step as the olefin under hydrogenative conditions (Scheme 54).



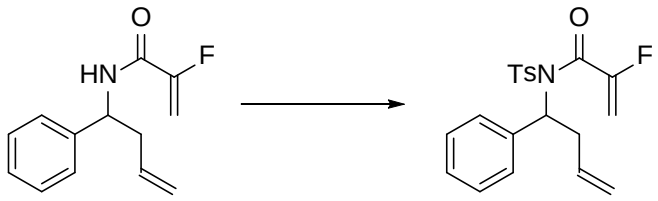
185 **186** **187**

188 **189** **190**

Scheme 54. Two strategies for using protecting groups to aid in the production of fluorinated heterocycles. The top scheme utilises the tosyl group where as the bottom uses a benzyl group.[79]

The first attempt at tosyl protection of amide **185** was carried out with *p*-toluenesulfonyl chloride, triethylamine and DMAP (Table 8, Entry 1), however, this reaction was unsuccessful. It was proposed that the amide nitrogen was sufficiently electron deficient that it would not attack the tosyl chloride directly following deprotonation. More rigorous conditions were then applied, using stronger bases including sodium hydride and *n*-butyllithium but only starting material was isolated in both cases (Entries 2 and 3).

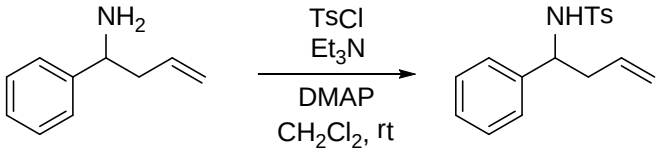
Table 8. Conditions used for the protection of dialkene **182** with a tosyl group.



182 **185**

Entry No.	Base	Conditions	Yield / %
1	Et_3N/DMAP	CH_2Cl_2, 0 °C to rt, 17 h	0
2	NaH	THF, 0 °C to rt, 2 h	0
3	*n*-BuLi	THF, -78 °C to rt, 1.5 h	0

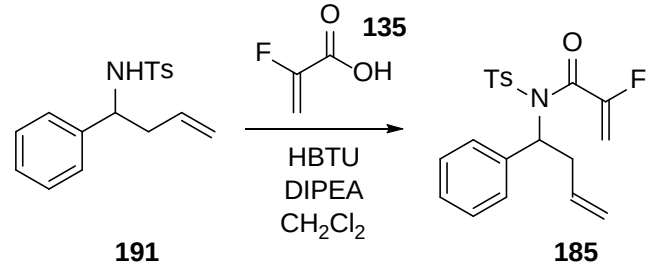
After failing to directly protect the amide **182**, protection of the allylic amine **139** followed by acylation was attempted. The tosyl protection proceeded in a good yield of 86%, however, the amide coupling of the resulting sulfonylamide **191** proved challenging (Scheme 55). The amide coupling failed both when heated to reflux (Table 9, Entry 2) and under microwave conditions (Entry 3).



139 **191**

Scheme 55. Tosyl protection of amine **139** to form sulfonamide **191**.

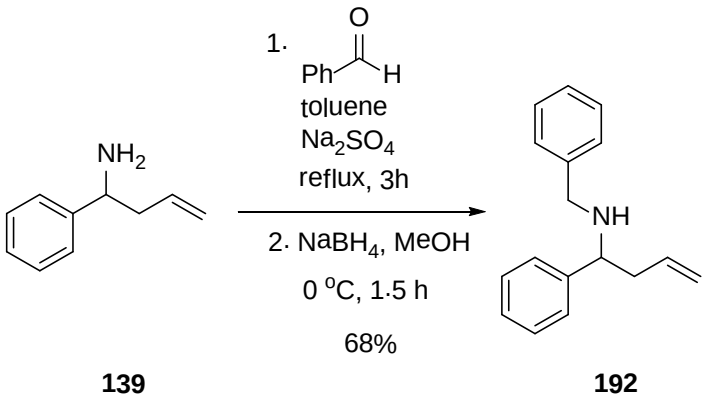
Table 9. Conditions attempted for amide coupling between fluorinated acid **135** with sulphonamide **191** to give diene **185**.



191 **185**

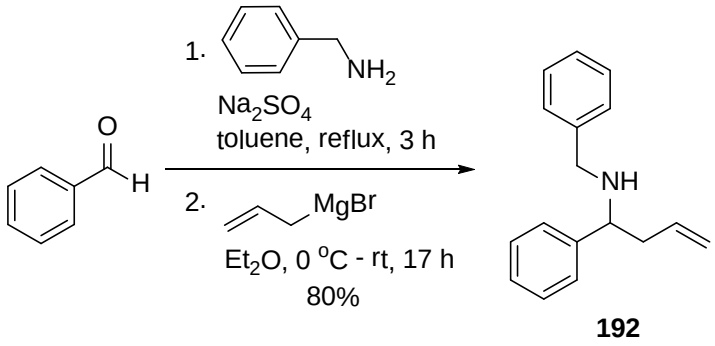
Entry No.	Conditions	Yield / %
1	rt, 17 h	0
2	reflux, 17 h	0
3	MW, 80 °C, 2 h	0

As previously described (*Vide Supra*), an alternative route using a benzyl protecting group was also proposed. This was attempted initially using the amine **139** with benzyl bromide, however, only product resulting from a double addition was obtained. A subsequent attempt using the same substrate utilised benzaldehyde to form the imine, followed by reduction with $NaBH_4$ to produce the benzyl protected amine **192**. This resulted in the isolation of **192** in 68% yield over the two steps (Scheme 56).[88]



Scheme 56. Two step synthesis of protected amine **192** in good yields of 68%.[88]

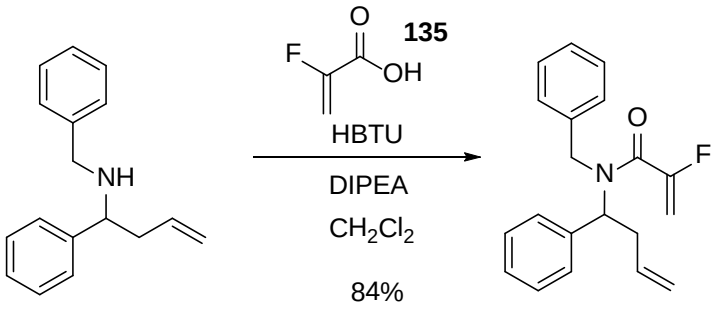
Whilst carrying out the above procedure, it was realised that an alternative protocol could be used to form the product **192** in one step. Treating benzaldehyde with benzylamine followed by alkylation should give **192**, thus removing the need to use liquid ammonia and the expensive allyl boronic pinacol ester.[89] Using this modified approach, benzaldehyde was cleanly converted into protected amine **192** in 80% yield in a single pot procedure (Scheme 57).



Scheme 57. One pot production of the benzyl protected amine **192** starting from benzaldehyde.[88]

The protected amine **192** could now be used in the amide coupling reaction with 2-fluoroacrylamide **135** (Table 10). The reaction was attempted at room temperature (Entry 1), reflux (Entry 2) and in the microwave (Entry 3) with the best result coming from refluxing overnight in CH_2Cl_2 (Entry 2). These conditions allowed formation of the amide in a good yield of 84% (Table 25).

Table 10. Conditions explored for amide coupling reaction to form the dialkene **188**

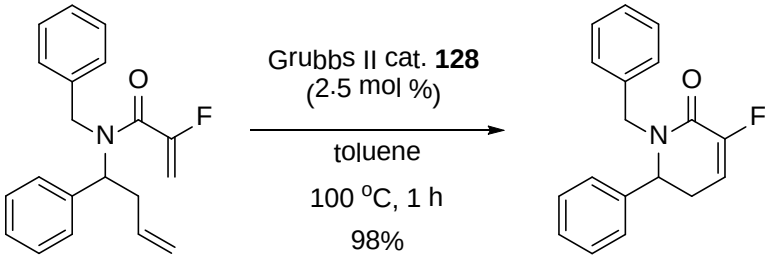


192 **188**

Entry No.	Conditions	Yield / %[a]
1	rt, 17 h	42
2	reflux, 17 h	84
3	MW, 80 °C, 2 h	71

[a] Isolated Yield

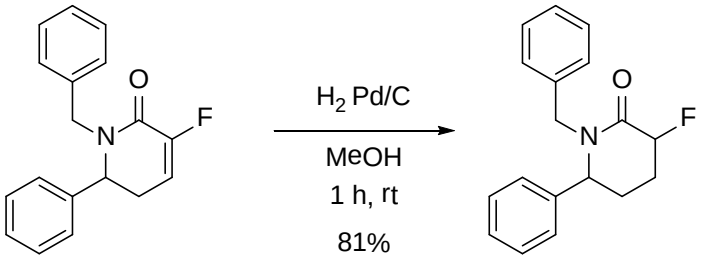
The ring-closing metathesis reaction was then attempted using the protected RCM precursor **188**. With the protecting group in place, the reaction proceeded efficiently and went to completion within an hour. Only 2.5 mol% of Grubbs 2nd generation catalyst **128** was needed to produce the cyclic amide **189** in 98% yield (Scheme 58).[35]



188 **189**

Scheme 58. Ring closing metathesis reaction to yield the cyclic amide **189** in 98%.[35]

A hydrogenation reaction was then carried out with the intention of reducing the alkene whilst removing the benzyl group simultaneously. Two different sources of H_2 were tested, ammonium formate with Pd/C in MeOH were used at reflux in the first instance. Under these conditions, the olefin was hydrogenated effectively but removal of the benzyl group was unsuccessful. It was, therefore, decided to use hydrogen instead of the ammonium formate to remove the benzyl group. This was also unsuccessful, hydrogenating the olefin but leaving the benzyl group to produce the protected lactam **193** in 81% yield (Scheme 59). Even when increasing the pressure of hydrogen, the benzyl group could not be removed.

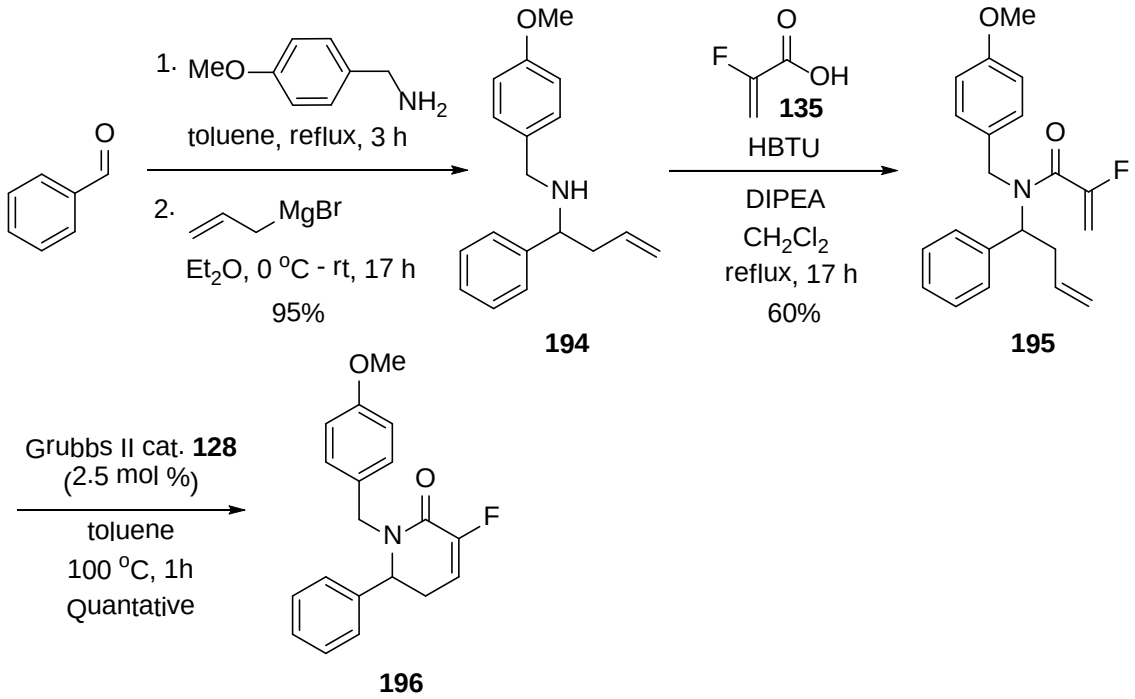


189 **193**

Scheme 59. Hydrogenation reaction to remove the olefin and the benzyl group however only the olefin could be removed to form **193**.

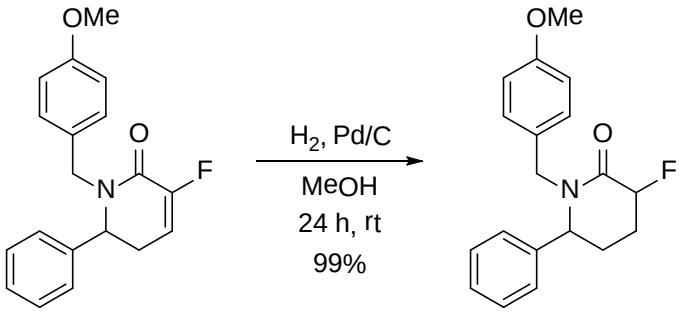
5.6: Protection of amide with *p*-methoxybenzyl group and synthesis of fluorinated δ-lactam

An alternative strategy for the removal of the benzyl group would be to employ a strong acid, however, this would restrict the scope of the methodology, precluding the use of substrates bearing acid labile groups. Therefore, it was decided to use a more easily removed protecting group. With this in mind we decided to use a *p*-methoxybenzyl group, which is similar in structure but could be more easily removed by hydrogenation or oxidation.[91]



Scheme 60. Four step synthesis of protected lactam **196** incorporating a *p*-methoxybenzyl group instead of a benzyl group.

The previous reaction sequence was carried out, this time with the installation of a *p*-methoxybenzyl protecting group instead of a benzyl protecting group (Scheme 60). Following allylmagnesium bromide addition, the protected amine **194** was formed in a high yield of 95%. Amide coupling was then carried out with identical conditions to those used in the benzyl example this time giving a 60% yield of **195**. The RCM reaction was then found to proceed in a quantitative yield to form the unsaturated lactam **196** (Scheme 60).

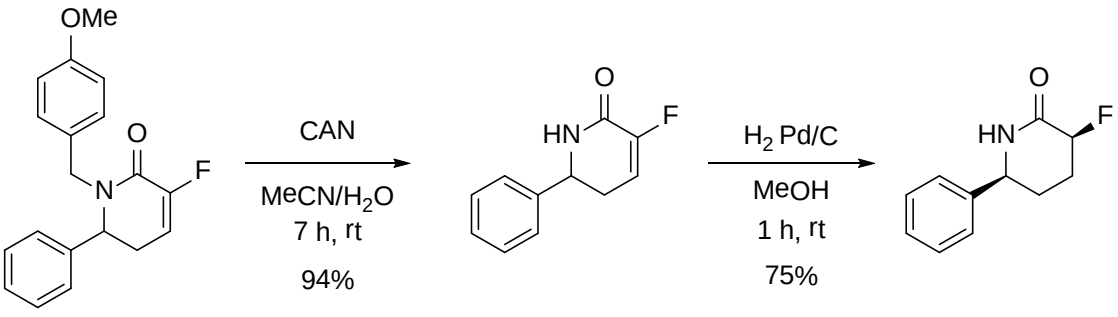


196 **197**

Scheme 61. Hydrogenation reaction to yield **197** in 99% yield.

The resulting unsaturated lactam **196** was then subjected to hydrogenation conditions in an attempt to remove both the alkene and the *p*-methoxybenzyl protecting group. However, yet again only the alkene was hydrogenated producing the protected lactam **197** in a 99% yield (Scheme 61).

The *p*-methoxybenzyl protecting group can also be removed by oxidation, therefore, the oxidising agent ceric ammonium nitrate (CAN) was used with this aim.[90] The deprotection went to completion in 7 hours and resulted in a yield of 94% of the deprotected unsaturated lactam **198**.[22] Hydrogenation was then undertaken, under the conditions used previously, to yield the fluorinated lactam **190** in 75% yield, isolated as a single diastereomer (Scheme 62).



196 **198** **190**

Scheme 62. Removal of the *p*-methoxybenzyl group followed by hydrogenation to yield the fluorinated lactam **190** in 42% yield over five steps.[90]

The hydrogenation of the unsaturated lactam was found to occur selectively on the opposite face to the phenyl ring, resulting in the fluorine and the phenyl group residing in a *cis* geometry to one another. This was confirmed by the ^{1}H NMR analysis and corroborated by crystal X-ray diffraction analysis (Figure 19).

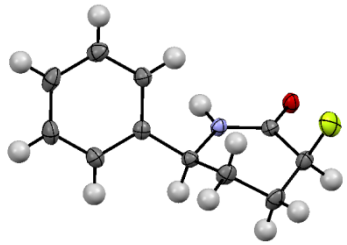


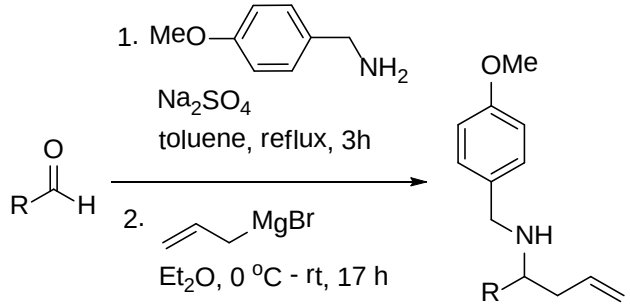
Figure 19. The crystal structure of lactam **190**. The fluorine atom in yellow is shown to be on the same face as the phenyl ring.

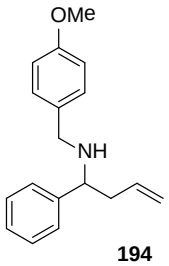
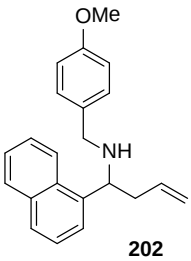
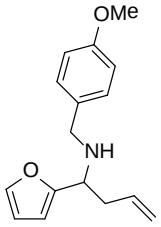
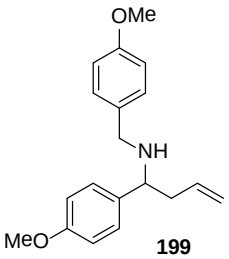
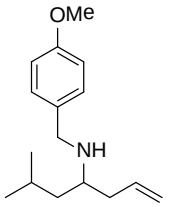
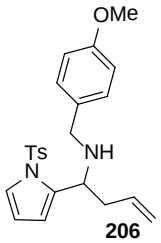
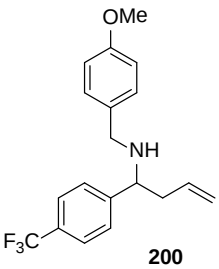
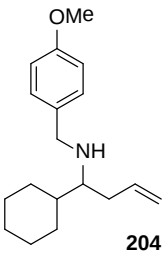
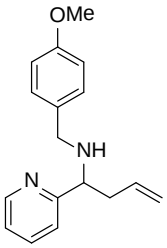
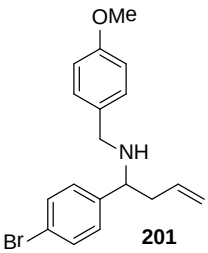
5.7: Extension of the methodology towards the synthesis of a family of fluorinated δ-lactams

5.7.1: Extension of the methodology – secondary amine synthesis

Having developed an efficient route to fluorinated lactams, attempts were made to extend the scope of the methodology, in order to incorporate a variety of functional groups on the lactam ring. Therefore, the amino-alkylation protocol was carried out on a range of aldehyde substrates, with good yields obtained in all cases (Table 11). The electronics of the aromatic substituent were varied and the effect on the yield investigated. In the presence of an electron donating substituent on the aryl ring (Entry 2) and electron withdrawing substituent (Entry 3), the desired products **199** and **200** were formed in good yields of 80% and 66% respectively. Further examples possessing aromatic substituents, 1-naphthaldehyde and 4-bromobenzaldehyde were also subjected to the conditions producing amines **201** and **202** in excellent 99% and 97% yields (Entries 4 and 5). Isovaleraldehyde and cyclohexanecarboxaldehyde were converted to the corresponding amines **203** and **204** in 76% and 74% respectively showing that aliphatic aldehydes could be incorporated easily (Entries 6 and 7). Finally, a variety of products possessing heteroaromatic substituents, **205**-**207**, were synthesised from the relevant aldehydes in good yields (Entries 8, 9 and 10).

Table 11. The production of amines **199**-**207** formed in a two step procedure from the corresponding aldehydes.



Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **194**	95	5	 **202**	99	8	 **205**	83
2	 **199**	80	6	 **203**	76	9	 **206**	85
3	 **200**	66	7	 **204**	74	10	 **207**	73
4	 **201**	97						

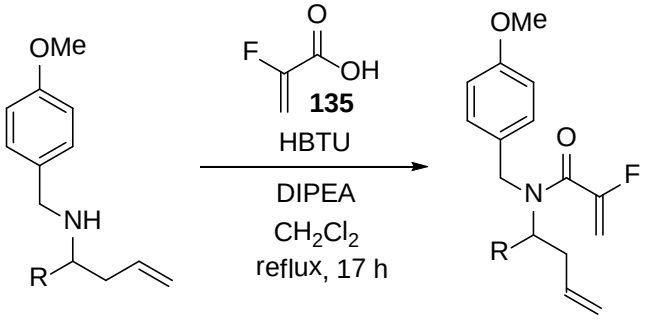
[a] Isolated Yield

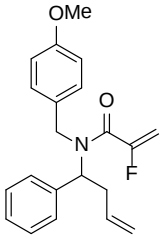
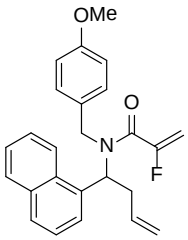
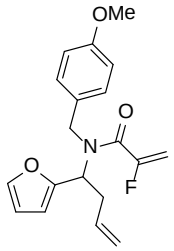
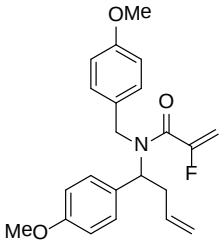
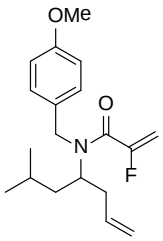
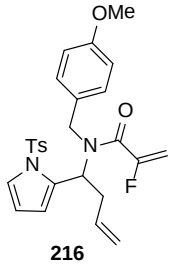
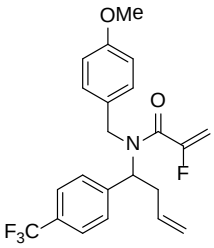
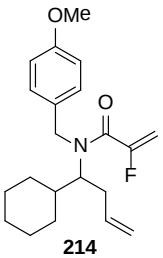
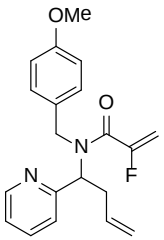
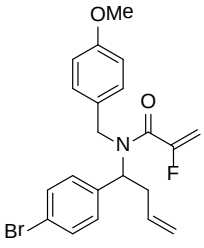
5.7.2: Extension of the methodology – amide coupling reaction

The previously described conditions for amide coupling (Section 5.6) were then applied to all the secondary amine analogues produced with varied results (Table 12). Compound **209** (Entry 2), possessing a 4-methoxybenzene substituent on the nitrogen, was generated in a good yield of 66%. The reaction proved troublesome in the presence of

other aromatic substituents, with a 45%, 54% and 34% yield for the trifluorobenzene, *p*-bromobenzene and naphthyl compounds **210**-**212** respectively (Entries 3, 4 and 5), a result of the lowered nucleophilic nature of their nitrogen atom. The compounds possessing aliphatic substituents (**213** and **214**) reacted efficiently, with yields greater than 70% obtained in both cases (Entries 6 and 7). The furan- and pyrrole-containing substrates **215** and **216** gave moderate yields, with only 28% and 50% yields obtained (Entries 8 and 9); however, a good yield was recorded for the pyridine analogue **217** (Entry 10).

Table 12. The amide coupling reaction of amines **199**-**207** with the fluorinated acid to produce the RCM precursors **208**-**217**.



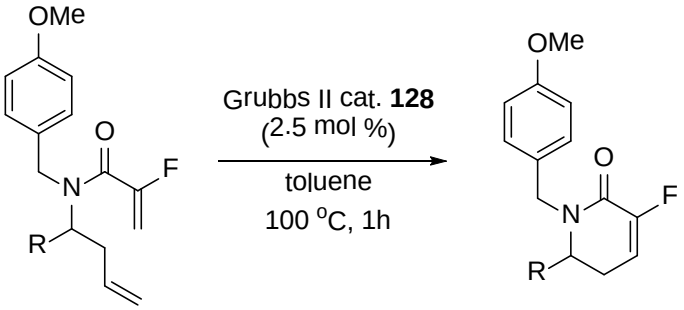
Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **195**	60	5	 **212**	34	8	 **215**	28
2	 **209**	66	6	 **213**	74	9	 **216**	50
3	 **210**	45	7	 **214**	70	10	 **217**	68
4	 **211**	54						

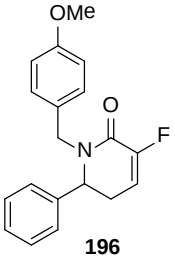
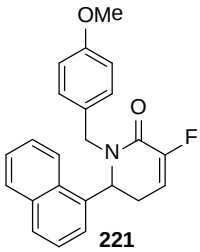
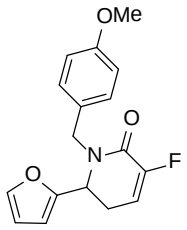
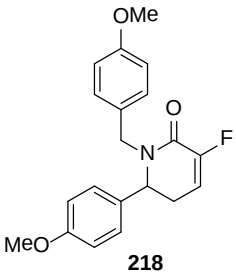
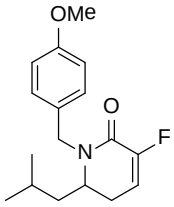
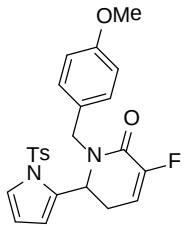
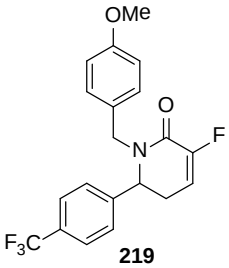
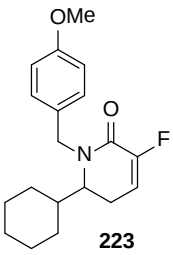
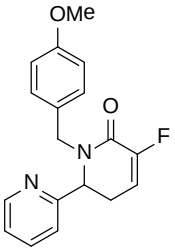
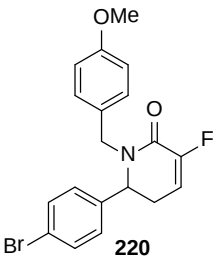
[a] Isolated Yield

5.7.3: Extension of the methodology – RCM reaction

Having obtained sufficient amounts of the appropriate fluorinated diene compounds (**209-217**), ring-closing metathesis reactions were attempted using previously described conditions (Section 5.6). The RCM reactions proceeded smoothly in nearly all cases (Table 13); quantitative yields were recorded for compounds bearing a 4-methoxybenzene substituent **218** (Entry 2), a trifluorobenzene substituent **219** (Entry 3) and a naphthyl substituent **221** (Entry 5). High yields were also obtained for the compounds **222**-**225**, which gave us access to a range of fluorinated aliphatic and heterocyclic substituted α,β-unsaturated lactams (Entries 6-9). In contrast, the 2-pyridyl substrate failed to undergo ring closure (Entry 10) and a quantitative yield of the starting material **217** was isolated. A possible explanation is that the nitrogen lone pair on the pyridine ring coordinated to the ruthenium centre, resulting in inhibition of the catalytic activity.[72]

Table 13. RCM of dienes **209**-**217** to produce the fluorinated α,β-unsaturated lactams **218**-**226**.



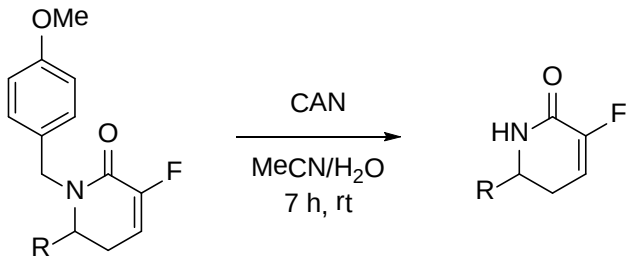
Entry No.	Product	Yield / %[a,b]	Entry No.	Product	Yield / %[a,b]	Entry No.	Product	Yield / %[a,b]
1	 **196**	quant	5	 **221**	quant	8	 **224**	64
2	 **218**	quant	6	 **222**	85	9	 **225**	77
3	 **219**	quant	7	 **223**	89	10	 **226**	0
4	 **220**	99						

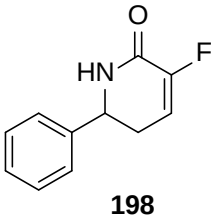
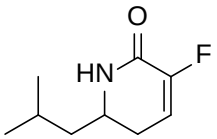
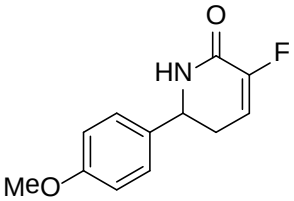
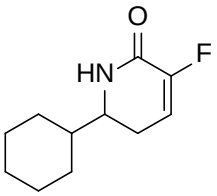
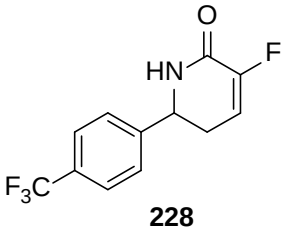
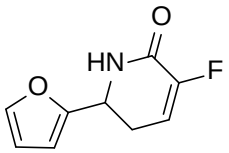
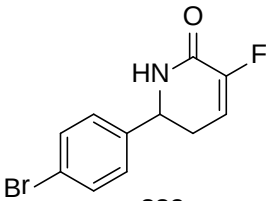
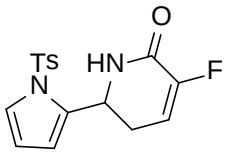
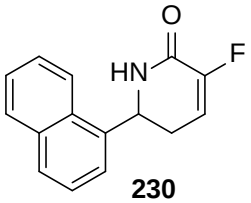
[a] Isolated Yield. [b] Concentration = 0.0025 g mL^{-1}.

5.7.4: Extension of the methodology – *p*-methoxybenzyl deprotection

The *p*-methoxybenzyl deprotection proved inconsistent when applied to a variety of analogues (Table 14); much lower yields were obtained for compounds with *p*-methoxybenzene **227** and *p*-trifluoromethanebenzene substiuents **228** of 40% and 47% respectively (Entries 2 and 3) compared to the original phenyl substituted compound **197** (Entry 1). The *p*-bromobenzene and naphthyl compounds **229** and **230** showed better conversions with 72% and 61% yields isolated respectively (Entries 4 and 5). The aliphatic analogues reacted efficiently under these conditions, with a 97% yield obtained for the isovaleryl lactam **231** (Entry 6) and a 79% yield achieved for the cyclohexyl lactam **232** (Entry 7). The use of heterocyclic compounds **233** and **234** resulted in no product formation on treatment with CAN; we believe that these heterocyclic compounds were not compatible with the oxidative conditions used and a complex mixture of breakdown products was generated (Entries 8 and 9).[91]

Table 14. Removal of *p*-methoxybenzyl group to give α,β-unsaturated lactams **227**-**234**.[90]



Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **198**	94	6	 **231**	97
2	 **227**	40	7	 **232**	79
3	 **228**	47	8	 **233**	0
4	 **229**	72	9	 **234**	0
5	 **230**	61			

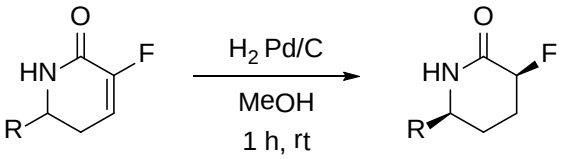
[a] Isolated Yield.

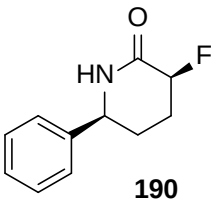
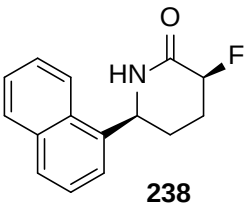
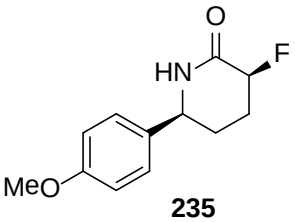
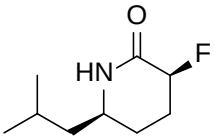
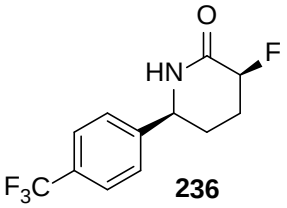
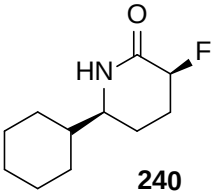
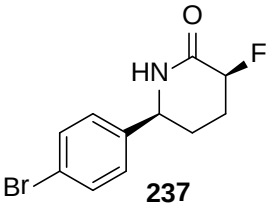
5.7.5: Extension of the methodology – hydrogenation to yield fluorinated δ-lactams

Hydrogenation of α,β-unsaturated lactams **227**-**234** to give the target fluorinated δ-lactams **235**-**240** proceeded efficiently for the majority of substrates (Table 15). In all cases, the

hydrogenation occurred selectively on the opposite face to the bulky group producing the desired δ-lactam exclusively as the *cis* diastereomer (Entries 1-7). Quantitative yields were obtained for the *p*-trifluoromethylbenzyl (Entry 3), 2-naphthyl (Entry 5), isovaleryl (Entry 6) and cyclohexyl (Entry 7) analogues **236, 238**-**240**. The presence of a bromine atom on the aromatic substituent was not tolerated under the reaction conditions and the desired product **237** was not formed, instead the bromine atom was lost and **190** was instead formed in a quantitative yield. This was due to hydrogenation of not only the olefin but also of the aromatic bromine atom.

Table 15. Hydrogenation of α,β-unsaturated lactams **227**-**234** to form the fluorinated δ-lactams **235**-**240**.



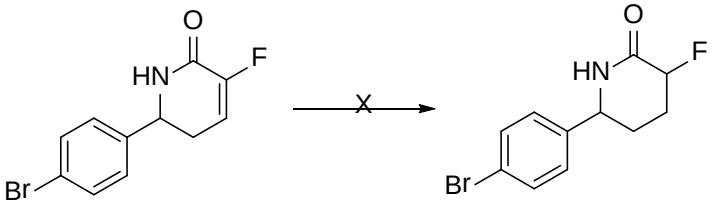
Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **190**	98	5	 **238**	quant
2	 **235**	83	6	 **239**	quant
3	 **236**	quant	7	 **240**	quant
4	 **237**	0[b]			

[a] Isolated yield. [b] Quantitative yield of **190** isolated.

5.8: Attempts to reduce bromo-analogue 229 and Suzuki cross-coupling

In order to achieve a selective reaction of **229**, in the presence of a 4-bromobenzyl functional group (Table 15, Entry 4), different conditions were applied to attempt the selective alkene hydrogenation (Table 16). In the first instance, the solvent was changed to ethyl acetate as it had been reported previously that aromatic halides did not undergo reduction under such conditions; however, no reduction of either the alkene or the halide were observed (Entry 2).[92] This was attributed to a lack of solubility of the starting material in the solvent. The catalyst was changed to the less reactive Wilkinson's Catalyst, with benzene as the solvent, but no product was isolated under these conditions (Entry 3).[93] Reduction was attempted through generation of a diimide species from the reaction between dipotassium azodicarboxylate and acetic acid, however when the resulting diimide was introduced to our unsaturated compound **229**, only starting material was recovered (Entry 4).[94] In a final attempt, a conjugate reduction was attempted using Stryker's reagent, however, no addition took place (Entry 5).[95]

Table 16. Conditions attempted for the hydrogenation of the α,β unsaturated lactam **229** however no product could be isolated in all cases.[92-15]



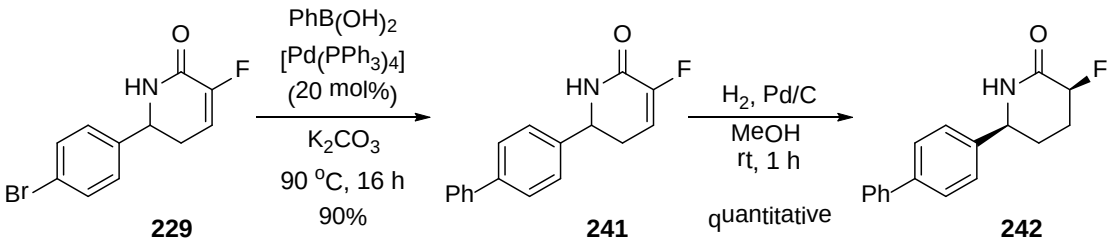
229 **237**

Entry No.	Conditions	Yield / %
1	H_2, Pd/C, MeOH	0
2	H_2, Pd/C, EtOAc	0
3	Wilkinson's Catalyst, H_2, C_6H_6	0
4	Dipotassium azodicarboxylate, AcOH	0
5	Stryker reagent, THF	0

[a] Isolated yield.

In the absence of suitable reduction conditions allowing the bromide to be retained as a molecular handle, a new strategy was devised whereby a cross-coupling reaction could be performed prior to reduction in order to exploit the bromide functionality. Hence, a

Suzuki coupling was carried out using phenyl boronic acid and $[Pd(PPh_3)_4]$ and resulted in the installation of a further phenyl ring in a quantitative yield.[96] Owing to the well-documented scope of palladium-catalysed cross-coupling reactions, a whole range of different groups could be installed, demonstrating the expedient nature of the methodology.[97] Once the Suzuki coupling had taken place, the alkene was reduced to yield the lactam **242** in a quantitative yield and with complete diastereocontrol (Scheme 63).



Scheme 63. Suzuki cross-coupling followed by hydrogenation to generate δ-lactam **242**.[96]

5.9: Towards the synthesis of fluorinated goniothalamin analogues

(*R*)-(+)-Goniothalamin **243** was first isolated from *Cryptocarya caloneura* in 1967 and since that time it has been shown to exhibit a wide range of biological activities.[98] The most interesting of these properties was the cytotoxicity towards a number of human cancer cell lines including leukaemia, kidney, ovarian and prostate.[99] The presence of a Michael acceptor in its structure is a key element in its activity and enzyme inhibition; therefore, we envisaged that the production of fluorinated analogues possessing a more reactive Michael acceptor could increase the biological activity.[99]

Using the methodology described previously (Section 5.6), it was thought we could access the racemic fluorinated analogue **244** by a similar route but with Grignard addition taking place onto an aldehyde rather than onto an imine.

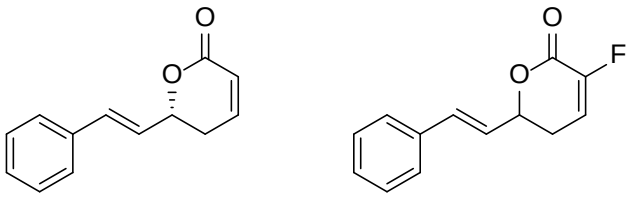
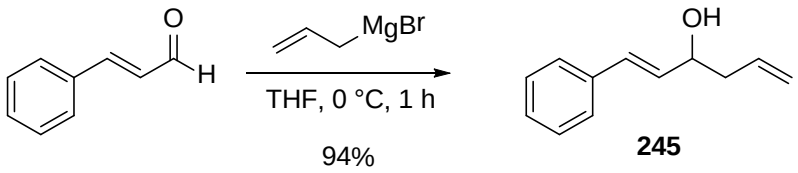


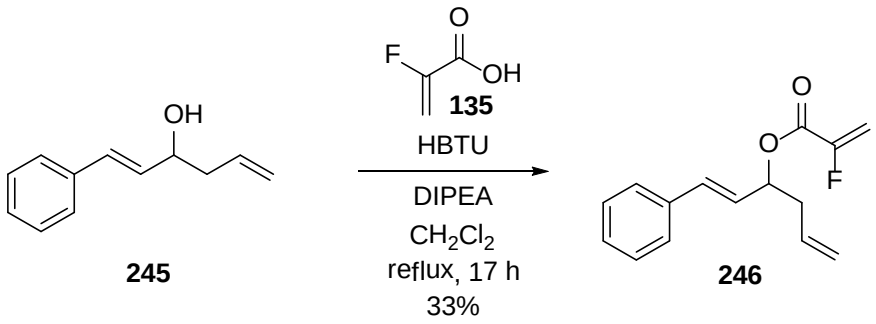
Figure 20. Anticancer compound (*R*)-(+)-goniothalamin **243** and target fluorinated analogue **244.**

In the first step, cinnamaldehyde was reacted with allylmagnesium bromide generating the desired alcohol **245** in 94% yield (Scheme 64).



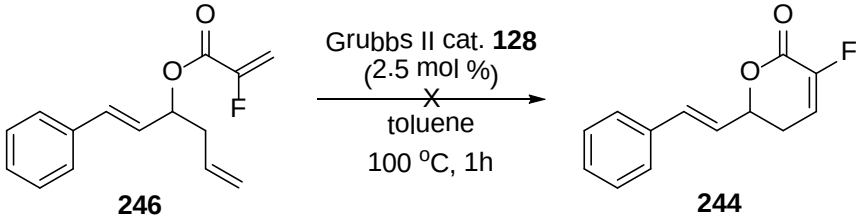
Scheme 64. The addition of a Grignard reagent to cinnamaldehyde to give alcohol **245** in a 94% yield.

Having obtained sufficient quantities of alcohol **245**, a coupling reaction between the alcohol **245** and fluorinated acid **135** was carried out using conditions developed for the equivalent amide coupling performed previously (Section 5.6). However, only a low yield of 33% of the resulting ester **246** was obtained (Scheme 65). This lower yield could be due to the reduced nucleophilicity of the alcohol compared to the secondary amine used previously as much unreactive starting material was recovered.



Scheme 65. Coupling of alcohol **245** to fluorinated acid **135** forming diene **246** in 33% yield.

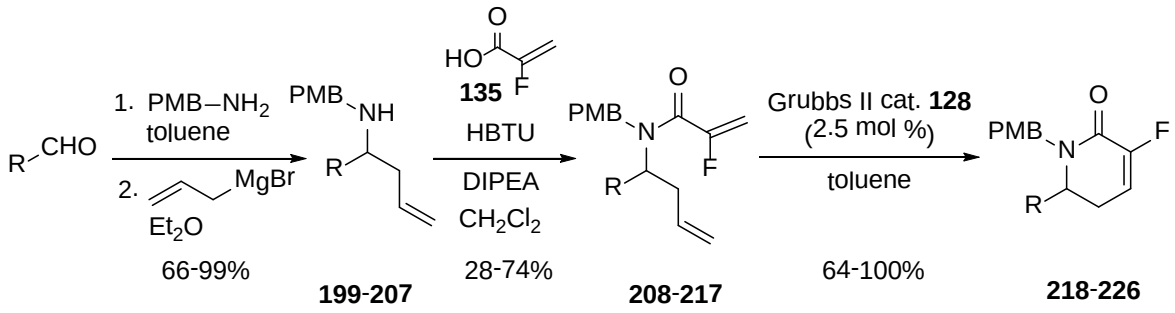
The fluorinated diene **246** was then subjected to the standard metathesis conditions, however, after heating for 72 h in the presence of 7.5 mol% catalyst **128** reaction occurred (Scheme 66). This was similar to the unprotected amine example (Section 5.4, Table 7) where the presence of coordinating heteroatoms and conformational issues were observed to be deleterious to the catalysis. Therefore, the diene was re-subjected to the metathesis conditions and an equivalent of Lewis acid, $Ti(O^iPr)_4$, was added to sequester the lone pairs on the oxygen atom and thus allowing catalysis to occur.[100] Unfortunately, this was unsuccessful and no reaction occurred under the revised conditions.



Scheme 66. Attempted RCM reaction to form fluorinated goniothalamin analogue **244** however only starting material was isolated.

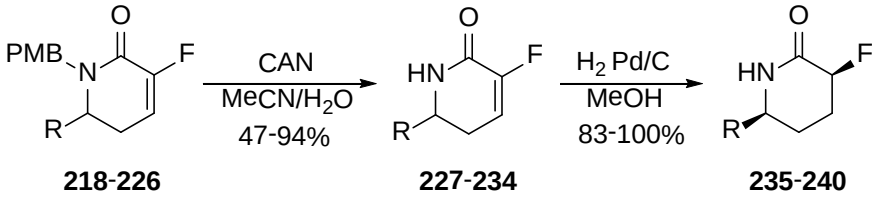
5.10: Conclusion and future work

A route to fluorinated α,β-unsaturated lactams was produced with the development of a four step protocol, starting from commercially available aldehydes. Imine formation and allylation gave the amines **199**-**207**, followed by amide coupling with fluorinated acid **135** to produce the RCM precursor compounds **208**-**217**. RCM reactions occurred rapidly, proceeding to completion in less than 1 hour on treatment of the substrate with Grubbs 2nd generation catalyst **128**. A number of fluorinated α,β-unsaturated lactams **218**-**226** were produced in excellent yields using this method (Scheme 67).



Scheme 67. Four step synthesis of fluorinated α,β-unsaturated lactams **218**-**226**.

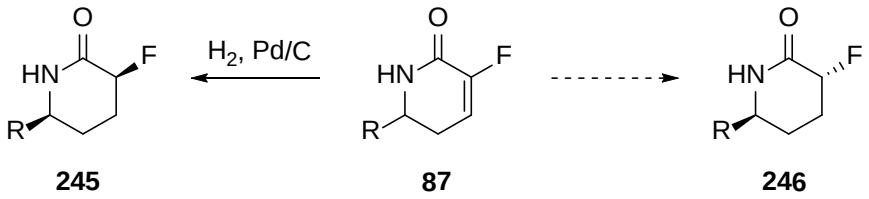
The α,β-unsaturated lactams **218**-**226** could be converted in two steps into an array of novel fluorinated δ-lactams **227**-**234**. Protecting group removal was carried out followed by a diastereoselective reduction to produce a number of novel fluorinated δ-lactams **235**-**240** (Scheme 68).



Scheme 68. Synthesis of fluorinated δ-lactams **235-240**.

The present work has detailed the development of a specific synthesis of a fluorinated δ-lactam as a single *cis* diastereomer (Section 5.6). It would be of greater synthetic utility to be able to generate both the *trans* and *cis* products selectively from the α,β-unsaturated lactam **87**, thus conditions will be sought whereby the *trans* product can be generated. The *cis* product is generated as the hydrogenation occurs on the unhindered side of the molecule placing the fluorine and R group on the same face. There is the potential to attempt this reduction with a copper hydride reagent, such as a modified Stryker's reagent.[101] Following addition of the hydride, an enol-type intermediate would be formed,

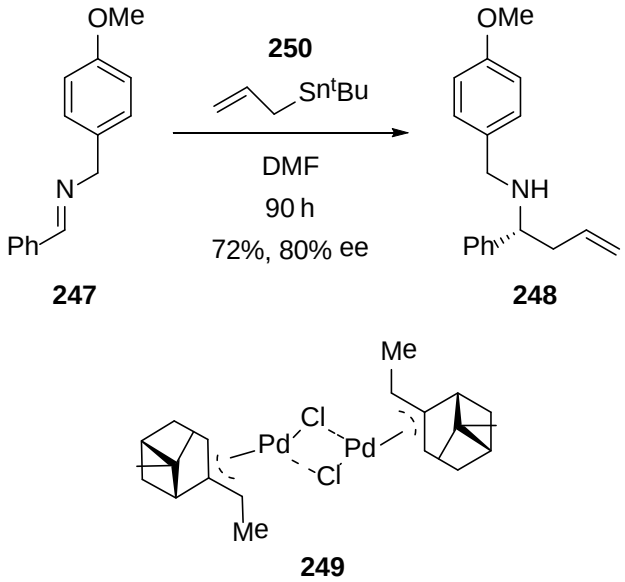
which on uptake of a hydrogen atom could give the *trans* relationship between the fluorine and R group.



245 **87** **246**

Scheme 69. Desired diastereoselective reduction to form *trans*-product **246**.

As stated above, the process as developed previously can produce a single diastereomer, however, it is not enantioselective. The stereochemistry of the C-N chiral centre could be installed early in the synthesis, ideally in a flexible manner allowing access to both the *R* and the *S* enantiomer. This enantioselective addition to the imine has been carried out previously by Yamamoto and co-workers using allyltributylstannane and chiral palladium complexes, such as **249**, to generate the *S* enantiomer **248** in yields of up to 80% and enantiomeric excesses of up to 82% (Scheme 70).[102] The conditions developed by Yamamoto and co-workers could be considered as a starting point for optimisation using our system.



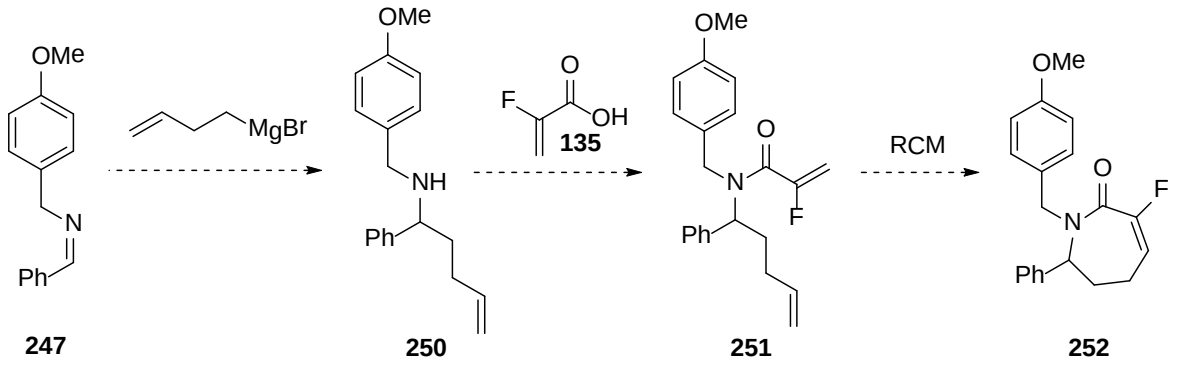
247 **248**

249

Scheme 70. Enantioselective addition to imine **247** reported by Yamamoto and co-workers using chiral palladium complex **249** to generate the *S* enatiomer of **248** in a 62% yield and 81% ee.[102]

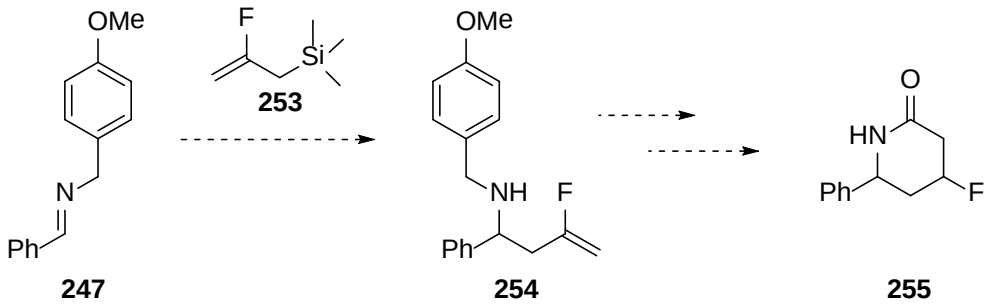
Work on this project so far has resulted in the synthesis of some specific fluorinated ring systems, however, there is scope to extend this methodology to allow for the generality that is required in modern organic synthesis. We have successfully produced 6-membered lactams, therefore, it would be of interest to develop a synthesis of fluorinated 7- and 8-

membered ring systems. Employing longer chains in the Grignard reagents would potentially give us access to such molecules (Scheme 71).

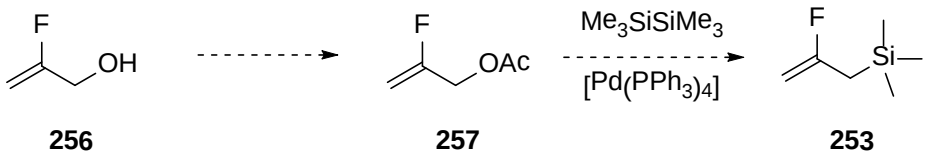


Scheme 71. Potential route to α,β-unsaturated ε-lactam **252**.

The ability to place fluorine atoms at multiple different positions on the ring is a further target for the development of this methodology. This would allow access to a variety of fluorinated lactams in addition to multi-fluorinated versions. A potentially fruitful approach would be to add a fluorinated allylsilane to the imine intermediate **247**; this would position the fluorine on carbon 4 or 5 of the nitrogen heterocycle **255** depending on the allylsilane used (Scheme 72). A proposed synthesis of a suitable allylsilane for use in this reaction is shown in scheme 73. These steps were developed by Usuki and co-workers for the synthesis of an analogous compound.[103]



Scheme 72. Potential synthesis of fluorinated nitrogen heterocycle **255**. The fluorine atom would be introduced via addition of fluorinated allyltrimethylsilane **253** to imine **247**.

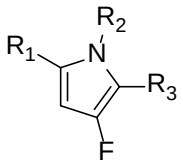


Scheme 73. Potential synthesis of the fluorinated allyltrimethylsilane **253** in two steps from fluorinated alcohol **256** using conditions reported by Usuki and co-workers.[103]

6: Synthesis of novel fluorinated pyrroles

6.1: Introduction

Following the success of the fluorinated 6-membered ring series (Section 5), work began on adapting the methodology to access 5-membered rings in the hope of generating a synthesis of novel fluorinated pyrroles. The target molecules are polysubstituted pyrroles with substituents in up to four sites on the pyrrole core (Figure 21). If successful this would generate a number of interesting compounds, and allow for the incorporation of the wide array of functionalities needed in medicinal chemistry.[39,40]

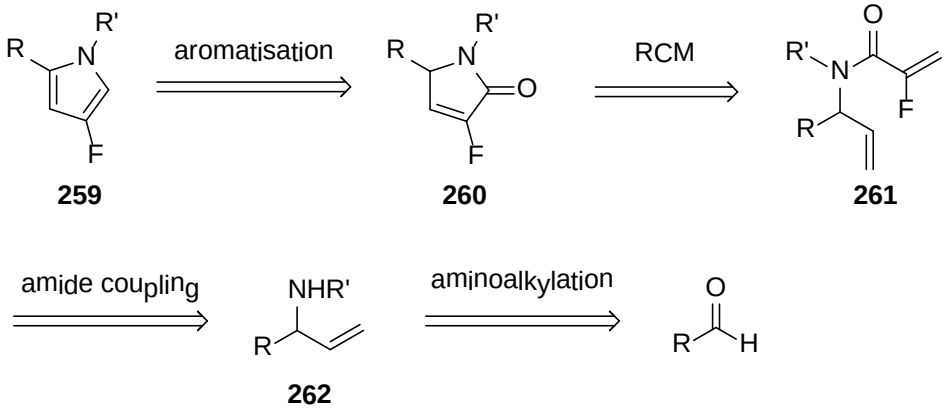


258

Figure 21. Target Polyfunctionalised fluorinated pyrrole **258**. A variety of different functionality at R^{1-3} will lead to an array of fluorinated pyrroles.

6.2: Retrosynthetic analysis

Following retrosynthetic analysis, it was envisaged that the target pyrrole **259** could be synthesised through the aromatisation of the α, β-unsaturated lactam **260** (Scheme 74). A similar ring-closing metathesis approach to previous work could be used to form the α, β-unsaturated lactam **260** from diene **261**. Diene **261** could be accessed from the amide coupling reaction between amine **262** and fluorinated acid **135**. The allylic amine **262** could be made by the same aminoalkylation protocol as in the 6-membered ring series but with the addition of vinyl Grignard reagent to the imine instead of the allyl Grignard used previously (Section 5.6).

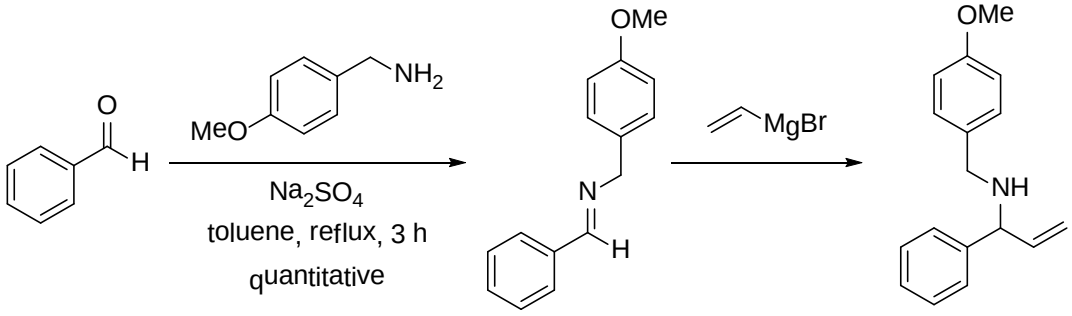


Scheme 74. Retrosynthetic analysis for fluorinated pyrrole series.

6.3: The development of an efficient route for the synthesis of fluorinated pyrroles

Using the same conditions as previously detailed in the 6-membered ring series (Section 5.6), benzaldehyde was reacted first with *p*-methoxybenzylamine to form the imine **247**, before the addition of 1.5 equivalents of vinyl bromide and stirred for 17 hours to give the amine **263** (Table 17, Entry 1). Unfortunately, the yield obtained was less than satisfactory, with only 4% of the desired product being isolated. Vinylmagnesium bromide exhibits reduced nucleophilicity compared with allylmagnesium bromide; in order to counter the poor reactivity the reaction was repeated with more equivalents of the vinyl Grignard (Entry 2). The yield only improved to 9% which demonstrated that the addition reaction was much slower than expected. The reaction time was increased to 48 h, with a considerable jump in yield to 29% (Entry 3), and after stirring for 7 days a more acceptable 62% yield was recorded (Entry 4). In an attempt to increase the yield of the addition reaction, the mixture was heated to 55 °C and as a result a 55% yield could be attained after 72 hours (Entry 5).

Table 17. Formation of imine **247** and optimisation of Grignard addition to imine **247** to form amine **263**.

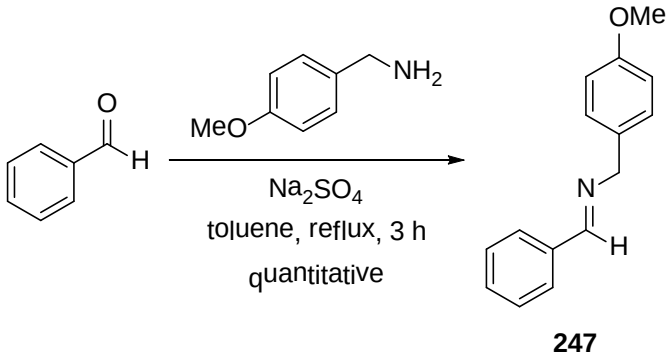


247 **263**

Entry No.	Conditions for Grignard reaction	Time	Yield / %[a]
1	1.5 eq, rt, Et_2O	17 h	4%
2	5 eq, rt, Et_2O	17 h	9%
3	5 eq, rt, Et_2O	48 h	29%
4	3 eq, rt, Et_2O	168 h	62%
5	3 eq, 55 °C, THF	72 h	55%

[a] Isolated Yield

Whilst the Grignard addition resulted in the production of sufficient material to explore subsequent synthetic steps, the long reaction times, low yields and poor reproducibility meant these conditions were not acceptable for the synthesis of an array of analogues. In an attempt to identify a viable alternative, the addition of vinyl lithium was explored. Therefore, the imine substrate **247** was synthesised in a quantitative yield (Scheme 75).

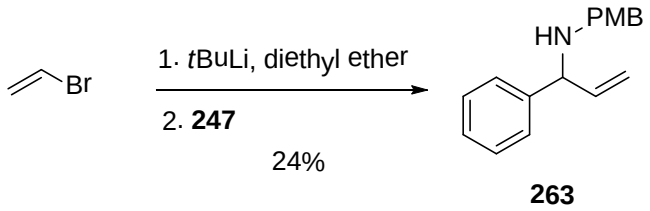


247

Scheme 75. Synthesis of imine **247** from benzaldehyde in quantitative yield.

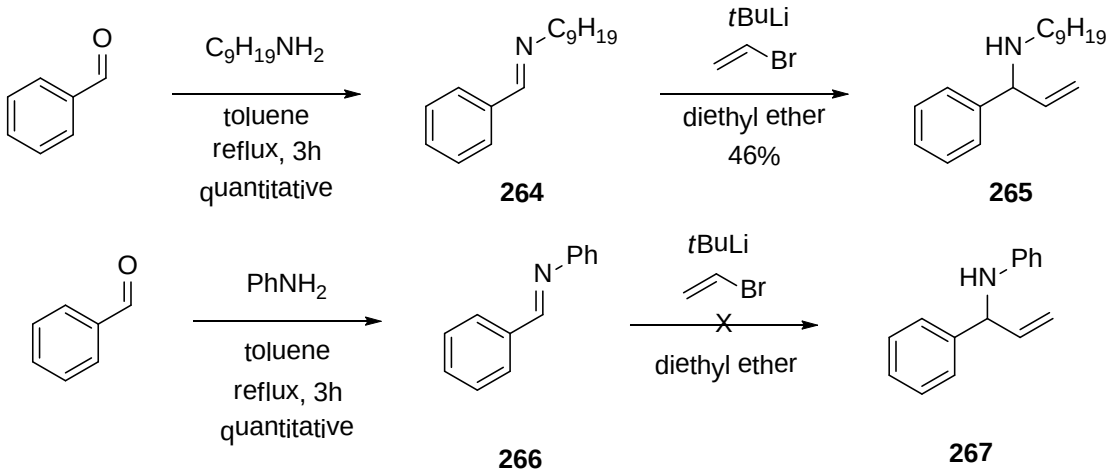
The vinyllithium was generated *in situ* from the reaction between *tert*-butyllithium and vinyl bromide following a literature procedure,[104] and a solution of imine **247** was added. After several attempts to affect the addition at varied temperatures, the highest yield recorded was a disappointing 24% (Scheme 76). A significant by-product in the reaction was *p*-methoxybenzaldehyde (~30%), the formation of which suggested that the vinyllithium was

acting as a base and removing a benzylic proton.[105] The resulting negative charge could be stabilised by delocalisation, before quenching and hydrolysis during the work up.



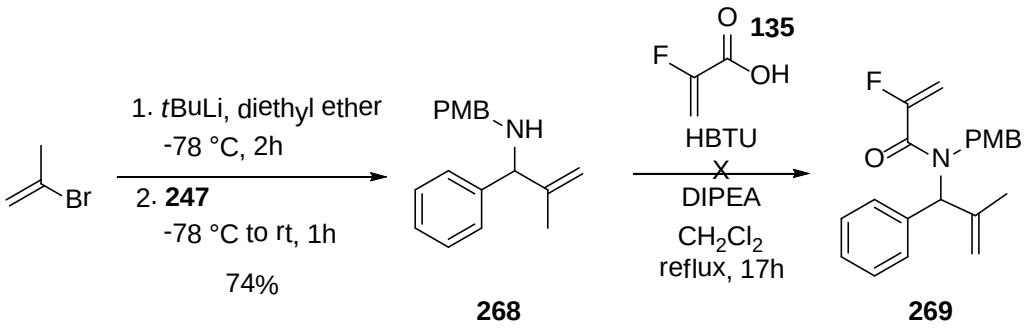
Scheme 76. Formation of vinyllithium and subsequent addition to imine **247** to form the amine **263** in 24% yield.[104]

In order to counter this problem, the reaction was attempted using two substrates that did not possess benzylic protons (**264** and **266**). The first, formed using nonylamine, produced a moderate but improved 46% yield of the desired amine **265**. However, the second imine, **266**, formed using phenylamine, did not react and full recovery of starting material was observed (Scheme 77).



Scheme 77. Attempted formation of amine compounds **265** and **267**, via imine formation and vinyl lithium addition.[104]

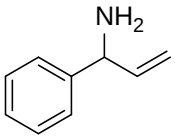
The reaction was also attempted, under these conditions, with the more nucleophilic 2-lithiumpropene and an improved yield of 74% was obtained in only 1 hour (Scheme 78). The amine **268** could now be used in the amide coupling step to generate the fluorinated diene **269**. However, the reaction did not proceed and only unreacted starting material was isolated. This was attributed to the increased steric hindrance present in the starting material due to the presence of the additional methyl group.



Scheme 78. Formation of amine **269** was achieved through addition of a vinyl lithium species to imine **247**. Amide coupling conditions were then applied to generate **269**, but no reaction occurred.[104]

6.4: Ellman's sulfinamide approach to give allylic amine

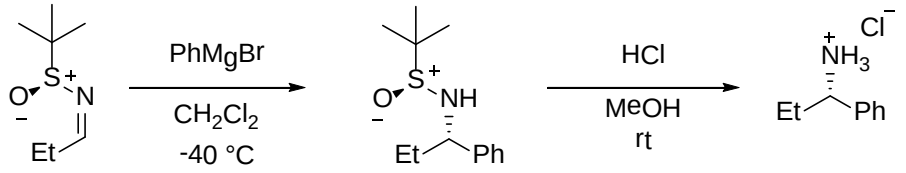
As a dependable route that would allow for a flexible pyrrole synthesis remained elusive, it was decided that a more convenient approach would be to access the primary amine **270** first before subsequent functionalisation.



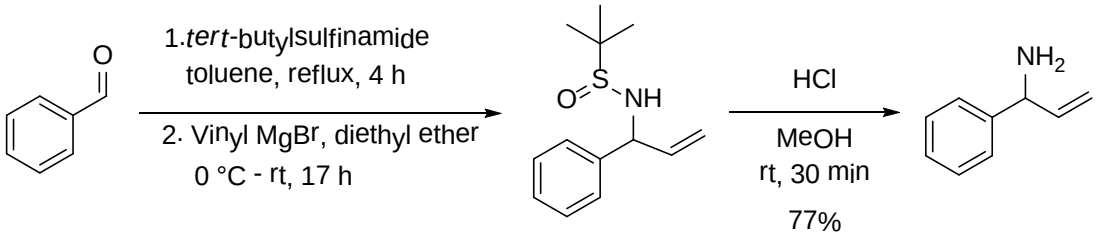
270

Figure 22. Target primary amine **270**.

Ellman's sulfinimide has been used widely in organic chemistry as an auxiliary to facilitate enantioselective additions for the formation of functionalised primary amines (Scheme 79).[106] It was our aim to utilise the electrophilic nature of the sulfinimide to facilitate a fast addition of the vinyl Gringard reagent. The resulting sulfinamide could then be readily deprotected to yield the desired primary amine **270** on reaction with acid. Therefore, benzaldehyde was reacted with *tert*-butylsulfinamide before addition of vinylmagnesium bromide was carried out to produce the sulfinamide **274**. The resulting sulfinamide **274** was stirred in acid before utilising an acid-base extraction to obtain the desired amine **270** in a good yield of 77% (Scheme 80).



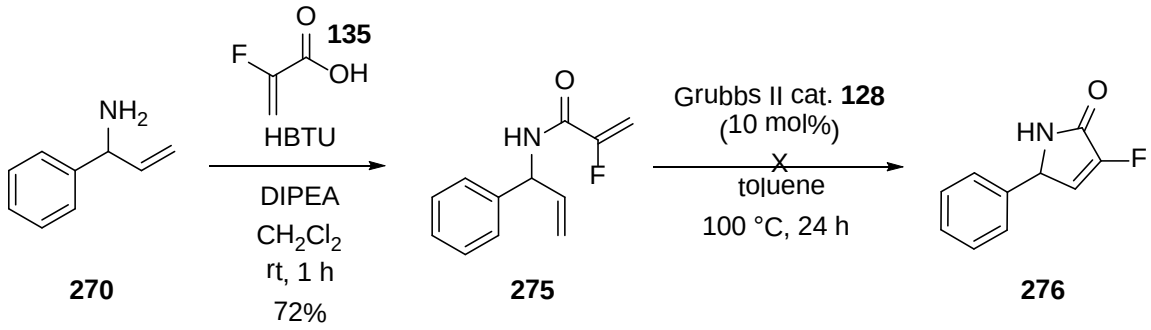
Scheme 79. Use of Ellmans sulfinimide to access primary amine **273** with high yield and diastereoselectivity.[106]



Scheme 80. Formation of primary amine **270** from benzaldehyde, via a sulfinamide intermediate **274**.[106]

6.5: Protecting group free amide coupling and ring-closing metathesis

The amine **270** was subjected to the amide coupling conditions yielding the fluorinated diene **275** in a good yield (Scheme 81). The RCM reaction could then be attempted, in order to determine whether this system could be ring-closed in the absence of a protecting group. Disappointingly, no product was obtained under these conditions (Scheme 81).

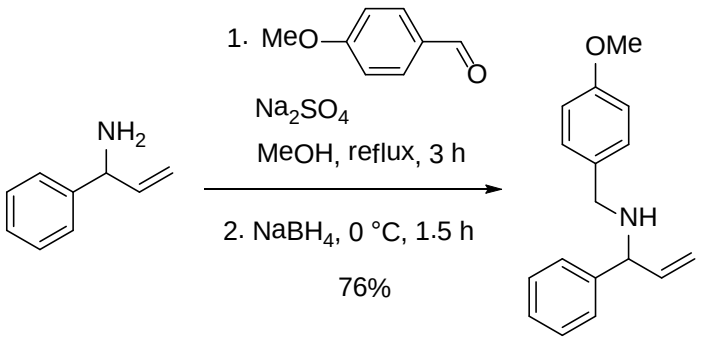


Scheme 81. Amide coupling reaction to form fluorinated amide **275**. A RCM reaction with fluorinated amide **275** to form α,β-unsaturated lactam **276** was attempted, however no product was isolated.

6.6: Formation of a fluorinated 5-membered α,β-unsaturated lactam

In previous examples where 6-membered rings were formed in the RCM step (Section 5.5), the presence of a protecting group on the amide was required in order to allow the metathesis reactions to proceed. An identical approach was adopted here, using the previously successful *p*-methoxybenzyl protecting group in an attempt to replicate the earlier procedure.

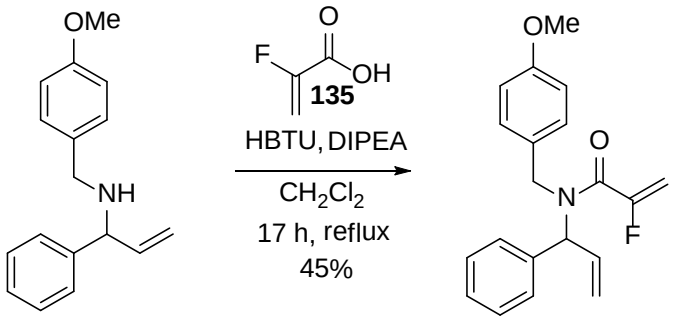
In order to achieve this, the amine **270** was initially reacted with *p*-methoxybenzaldehyde and the resulting imine was subsequently reduced to the secondary amine on addition of $NaBH_4$ (Scheme 82). A good yield of 76% was recorded of the desired amine **263**.



270 **263**

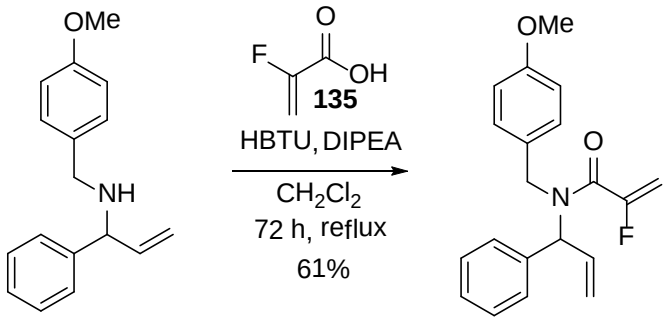
Scheme 82. Two step synthesis of secondary amine **263** from primary amine **270** in an 80% yield, via imine formation and reduction.

The previously described amide coupling conditions were applied, as used in the six-membered ring series (Section 5.6), however, only a moderate yield of 45% was achieved for **277** (Scheme 83). More forcing conditions were applied in an attempt to achieve a higher conversion to the product, resulting in an improved yield of 61% (Scheme 84).



263 **277**

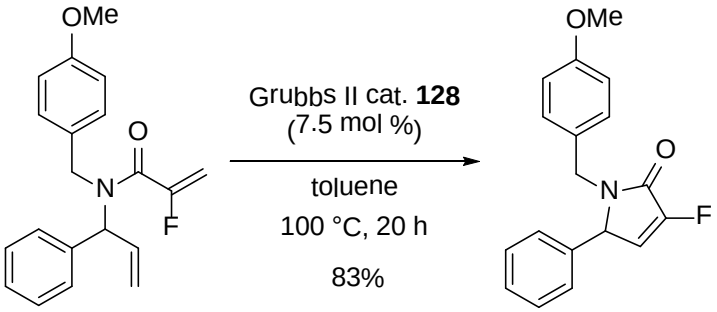
Scheme 83. Amide coupling of amine **263** with fluorinated acid **135** (1.5 equivalents) to form diene **277** in a 45% yield.



263 **277**

Scheme 84. Improved amide coupling of amine **263**, with increased reaction time (72 h) and increased equivalents of fluorinated acid **135** (2), to form diene **277** in a 61% yield.

The resulting diene compound **277** was subjected to ring-closing metathesis conditions, the reaction needed a catalyst loading of 7.5 mol% and reaction time of 20 h to go to completion. The α,β-unsaturated lactam **278** was isolated in a good yield of 83% (Scheme 85).[35]

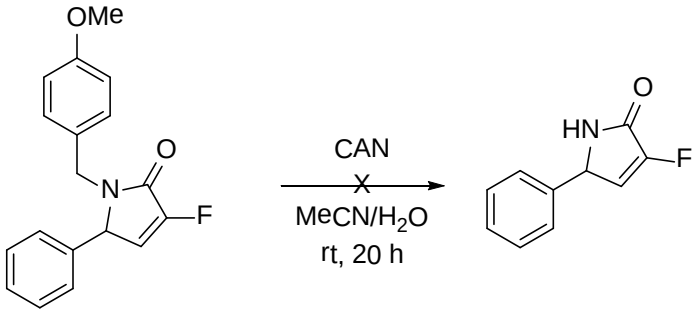


277 **278**

Scheme 85. The formation of α,β-unsaturated lactam **278** in 83% yield from diene **277**.[35]

6.7: Protecting group removal and aromatisation

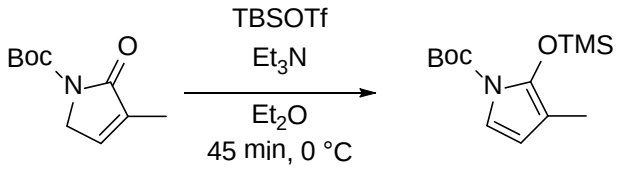
Having produced sufficient amounts of the α,β-unsaturated lactam **278**, an attempt to remove the *p*-methoxybenzyl group was made in order to obtain the unprotected lactam **276**. The protected lactam **278** was stirred with ceric ammonium nitrate (CAN) for 20 h however no product was detected (Scheme 86).[90]



278 **276**

Scheme 86. Attempted deprotection of *p*-methoxybenzyl group on α,β-unsaturated lactam **278** with CAN, however, no product was isolated.[90]

As the deprotection was unsuccessful at the initial attempt (Scheme 86), aromatisation conditions were probed and the protecting group would be removed afterwards. There are a number of examples in the literature in which α,β-unsaturated lactams are converted to the corresponding pyrrole via treatment with a base and a electrophile.[107] Bermajo and co-workers used this stratergy to convert Boc protected α,β-unsaturated lactam **279** to the pyrrole **280** in a excellent 95% yield (Scheme 87).[108]

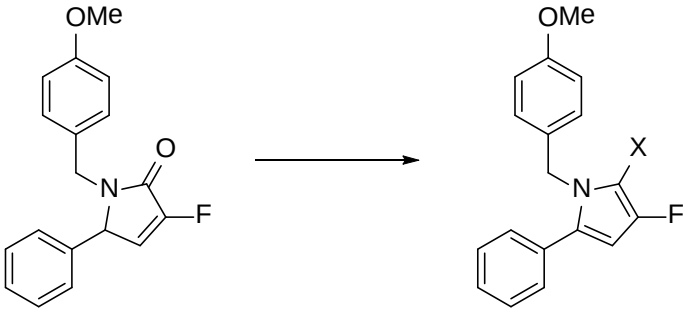


279 95% **280**

Scheme 87. Conversion of the α,β-unsaturated lactam **279** to the pyrrole **280** as reported by Bermejo and co-workers.[108]

Taking inspiration from the literature precedent,[108] conditions using triethylsilyl trifluoromethanesulfonate (TESOTf) and triethylamine were attempted however no reaction occurred (Table 18, Entry 1). This was also the case when the base was changed to DBU (Entry 2), and when the α,β-unsaturated lactam **278** was treated with DBU alone (Entry 3), a quantitative recovery of starting material was observed.

Table 18. Conditions attempted for conversion of α,β-unsaturated lactam **278** to a pyrrole ring system **281-282**.[108]



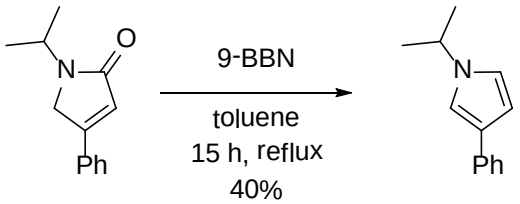
278

281 X = OTES
282 X = OH

Entry No.	Conditions[a]	X	Yield / %[b]
1	TESOTf, Et_3N, CH_2Cl_2, rt	OTES	0
2	TESOTf, DBU, CH_2Cl_2, rt	OTES	0
3	DBU, CH_2Cl_2, rt	OH	0

[a] Reaction times = 24 h. [b] Isolated Yield.

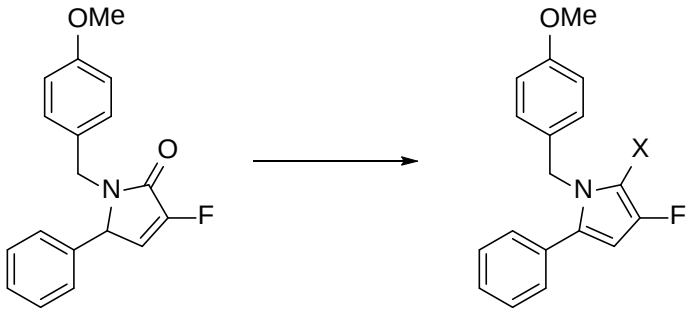
Looking at the problem from a different perspective, reducing the lactam could cause rearrangement into the aromatic ring system. There has been several examples in the literature of such reactions, De Kimpe and co-workers used this approach to synthesis a number of disubstituted pyrroles **284** (Scheme 88).[109] Therefore, the lactam **278** was treated with an equivalent of DIBAL, in an attempt to reduce the amide to the hemiaminal and subsequent elimination could generate the pyrrole unit. This was successful and an encouraging 35% yield was isolated of the desired pyrrole **285** (Table 19, Entry 1). Increasing the number of equivalents of DIBAL to three allowed the pyrrole **285** to be generated in an excellent yield of 85% (Entry 2).



283 **284**

Scheme 88. Reduction of α,β-unsaturated lactam **283** followed by aromatisation to yield pyrrole **284** as reported by De Kimpe.[109]

Table 19. Conditions attempted for conversion of **278** to a pyrrole ring system.



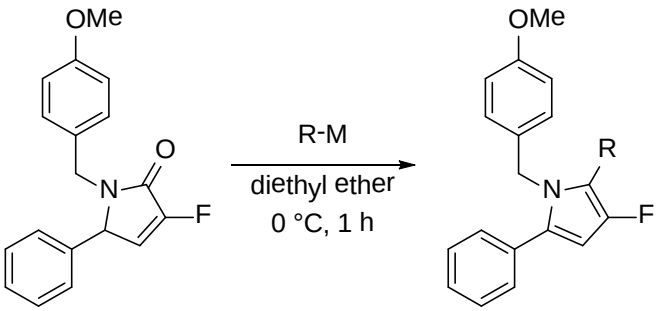
278 **285** X = H

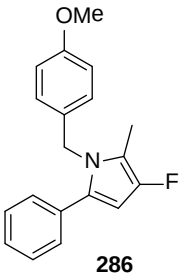
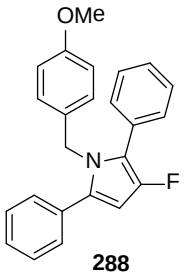
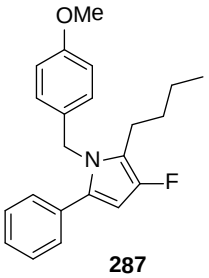
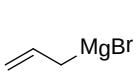
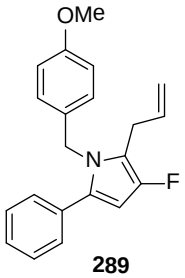
Entry No.	Conditions[a]	X	Yield / %[b]
1	DIBAL (1 eq), CH_2Cl_2, -78 °C to rt	H	35%
1	DIBAL (3 eq), CH_2Cl_2, -78 °C to rt	H	85%

[a] Reaction times = 17 h. [b] Isolated Yield.

In order to develop a more flexible methodology, attempts were made to extend the protocol to allow the incorporation of different nucleophiles (Table 20). This was first attempted with methyllithium, the α,β-unsaturated lactam was rapidly converted to the pyrrole **286** in an 86% yield after 1 hour (Entry 1). Alternative lithium reagents, *n*-butyllithium and phenyllithium, could be used in the same way forming the substituted pyrroles **287** and **288** in yields of 78% and 93% respectively (Entries 2 and 4). Finally, the addition of the Grignard reagent allylmagnesium bromide resulted in the facile transformation of the starting material to **289** in a good yield of 75% (Entry 4).

Table 20. Nucleophilic addition of organometallic reagents to lactam **278** to form pyrrole compounds **286**-**289**.



Entry No.	R-M	Product	Yield / %[a]	Entry No.	R-M	Product	Yield / %[a]
1	MeLi	 **286**	86	3	PhLi	 **288**	93
2	*n*BuLi	 **287**	78	4		 **289**	75

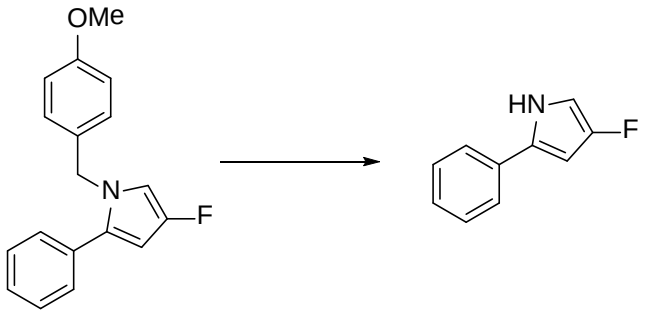
[a] Isolated Yield

6.8: Attempts at protecting group removal

In order to obtain the desired fluorinated pyrroles such as **290**, conditions for the removal of the protecting group were required. This, however, proved challenging and an array of conditions were used without success (Table 21). Initial attempts employed the typical CAN reagent, however, this failed to yield any product (Entry 1).[90] Another well-utilised reagent for PMB removal, DDQ, also failed to produce the desired product, returning starting material and a complex mixture of breakdown products (Entry 2).[110] The pyrrole **285** was treated with trifluoroacetic acid at reflux but still no product was detected (Entry 3).[111] A hydrogenation approach was employed, however, only starting material was recovered from the treatment of the pyrrole with Pd/C and H_2 (Entry 4).[112] Oxidising agent $SnCl_4$ was used in conjunction with PhSH, however, no reaction occurred (Entry 5).[113] Conditions using oxone with KBr (Entry 6),[114] $Hg(OAc)_2$ (Entry 7),[115] and $KMnO_4$ (Entry 8 and 9) were employed,[116] however, no product was formed in any of these cases. Finally, a Birch reduction was attempted (Entry 10). This proved unsuccessful due to the presence

of several aromatic rings, resulting in the degradation of the starting material into a complex mixture of breakdown products.[117]

Table 21. Conditions attempted for the removal of the *p*-methoxybenzyl group from **285** to give pyrrole **290**.[110-117]



285 **290**

Entry No.	Conditions	Yield / %
1	CAN, MeCN/H_2O, rt	0
2	DDQ, CH_2Cl_2/H_2O, rt	0
3	TFA, CH_2Cl_2, reflux	0
4	Pd/C, H_2, MeOH, rt	0
5	PhSH, $SnCl_4$, CH_2Cl_2, -78 °C	0
6	KBr, oxone, MeCN, rt	0
7	$Hg(OAc)_2$, H_2O/EtOH, 80 °C	0
8	$KMnO_4$, acetone/H_2O, rt	0
9	$KMnO_4$, acetone/H_2O, 50 °C	0
10	NH_3, Li wire, THF, -78 °C to rt	0

6.9: Extension of methodology to generate an array of novel fluorinated heterocycles

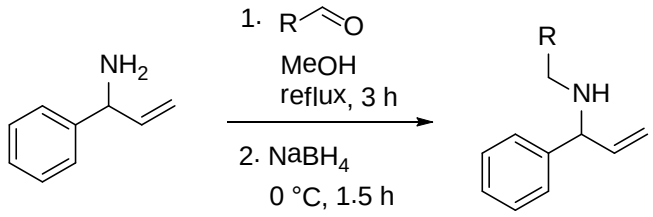
6.9.1: Extension of methodology – secondary amine synthesis

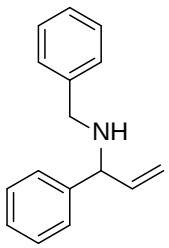
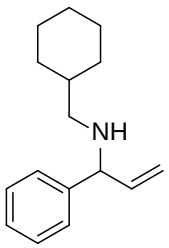
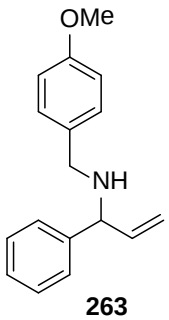
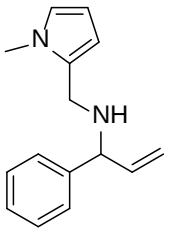
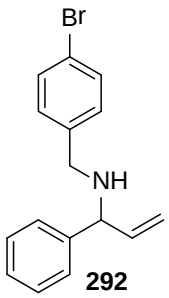
Many of the pyrroles in medicinal chemistry have substituents on the nitrogen that link to another building block or functional group.[118] Therefore, whilst working on deprotection conditions, the integration of different groups on the nitrogen was also explored to see

what different functionalities could be introduced. By changing the aldehyde that was condensed with the allylic amine **270**, different groups could be installed at this position.

In addition to the *p*-methoxybenzyl group already discussed, four other examples were chosen with varying properties to demonstrate the scope of the methodology (Table 22). Addition of a simple benzyl group was initially attempted, resulting in the formation of amine **291** in a 74% yield (Entry 1). Following this, a 4-bromobenzyl analogue was utilised as an electron withdrawing group as well as incorporating a synthetic handle for further chemistry (Entry 3). A 78% yield of the 4-bromobenzyl substituted amine **292** was recorded (Entry 3). Two further analogues including the aliphatic example **293** and heterocyclic methyl pyrrole **294** were also produced in good yields of 80% and 68% respectively (Entry 4 and 5).

Table 22. One-pot conversion of primary amine **270** into secondary amines **291-294.**



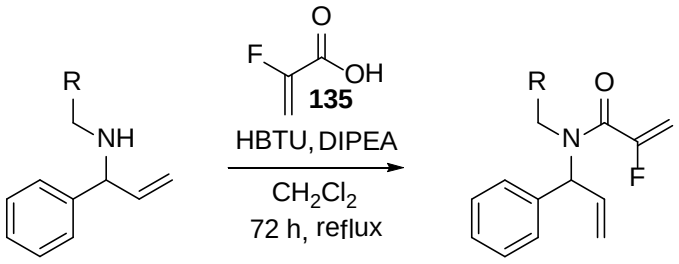
Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **291**	74	4	 **293**	80
2	 **263**	76	5	 **294**	68
3	 **292**	78			

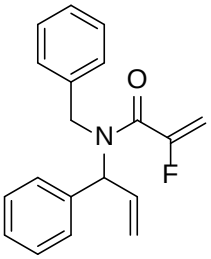
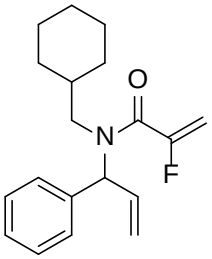
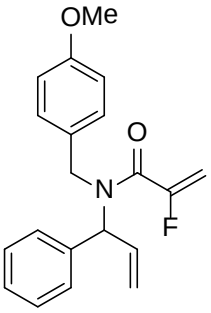
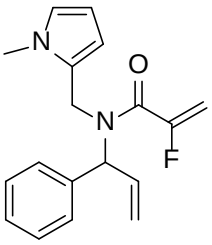
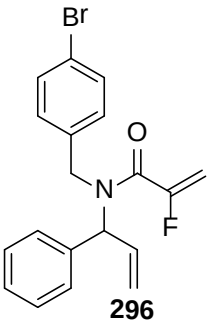
[a] Isolated Yield

6.9.2: Extension of methodology – amide coupling reaction

The secondary amines **291**-**294** could now be subjected to the amide coupling conditions (Table 23). The aromatic examples: **295** (Entry 1), **296** (Entry 3) and **298** (Entry 5) all underwent efficient amide coupling reactions with 73%, 71% and 63% yields recorded respectively. The aliphatic analogue **297** also worked well with a good yield of 86% recorded (Entry 4).

Table 23. Amide coupling reactions between secondary amines **291-294** and fluorinated acid **135** to form dienes **295-298.**



Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **295**	73	4	 **297**	86
2	 **277**	61	5	 **298**	63
3	 **296**	71			

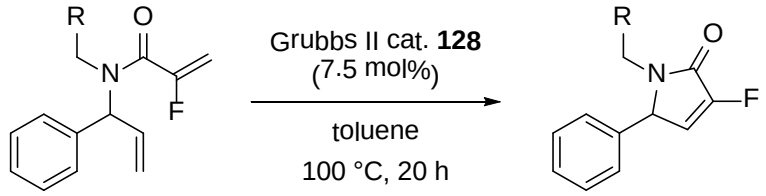
[a] Isolated Yield

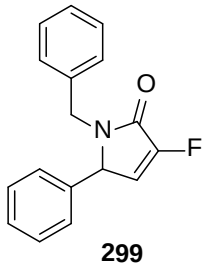
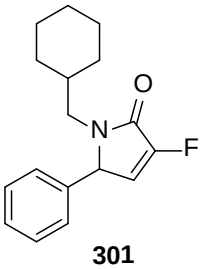
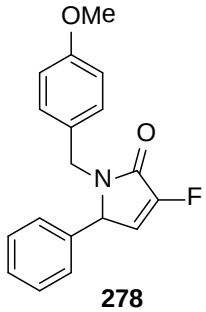
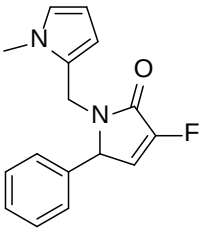
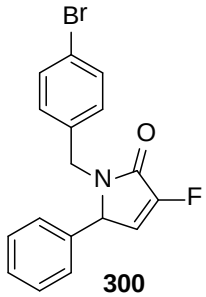
6.9.3: Extension of methodology – ring-closing metathesis

Ring-closing metathesis of the fluorinated dienes obtained in the previous step **295**-**298** yielded the α,β-unsaturated lactam series **299-302** in excellent yields in all cases (Table 24).[35] The benzyl **299** and 4-bromobenzyl examples **300** were isolated in excellent yields of 98% and 96% respectively (Entry 1 and 3). A 92% yield was achieved for the aliphatic

example **301** and the methyl pyrrole **302** was formed in a good yield of 81% (Entries 4 and 5).

Table 24. RCM reactions of **295-298** to form α, β-unsaturated lactams **299**-**302**.[35]



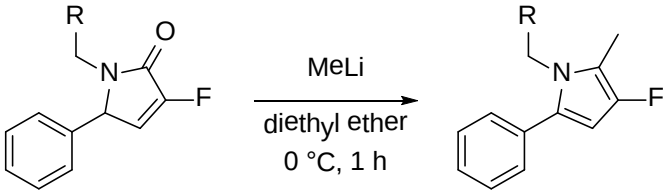
Entry No.	Product	Yield / %[a,b]	Entry No.	Product	Yield / %[a,b]
1	 **299**	98	4	 **301**	92
2	 **278**	83	5	 **302**	81
3	 **300**	96			

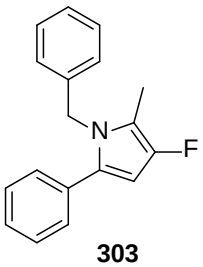
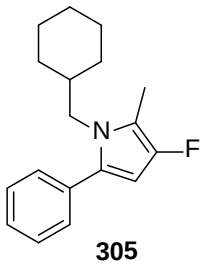
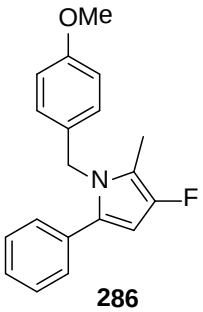
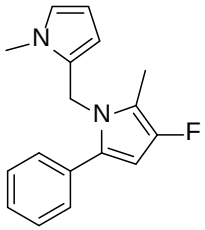
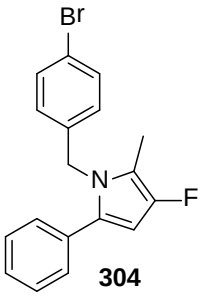
[a] Isolated Yield. [b] concentration = 0.005 g mL^{-1}.

6.9.4: Extension of methodology – addition-aromatisation reaction

Having synthesised a range of compounds with the 5-membered ring structure in place, the final step was to carry out the addition-aromatisation reaction (Table 25). We decided to carry out methyllithium addition on all the analogues as it provided a quick, efficient process unlike the DIBAL reduction, which required excess reagent and 17 h stirring. High yields for all the analogues in question generated an array of fluorinated pyrroles **303-306** (Table 25, Entries 1-5).

Table 25. Addition of methyllithium to lactams **299-302** to form the target pyrrole compounds **303-306**.



Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **303**	86	4	 **305**	84
2	 **286**	86	5	 **306**	75
3	 **304**	83			

[a] isolated Yield

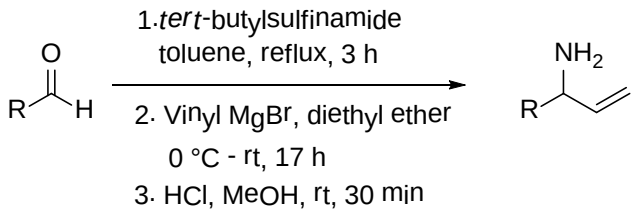
6.10: Synthesis of fluorinated pyrroles with alternate groups at the 5-position

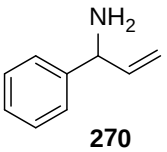
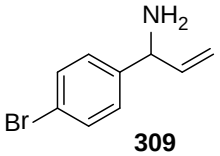
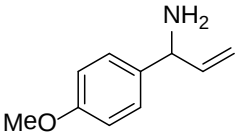
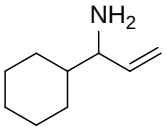
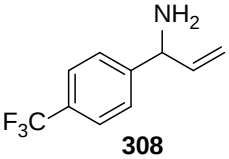
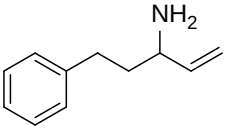
At this point two different groups had been successfully altered around the fluorinated pyrrole ring producing some interesting novel compounds. In all examples presented thus far, the 5 position of the pyrrole ring has borne a phenyl substituent. In order to expand the methodology further and construct more complex products, the starting amine could be altered to incorporate alternative functional groups at this position. A range of different amines to be used as starting materials could be synthesised using the Ellman protocol (Section 6.4).[106]

6.10.1: Extension of methodology – synthesis of allyl amines

In order to allow variation of the physical and electronic properties at the position in question, amines were formed from five different aldehydes (Table 26). The effect of the electronics of the benzene ring was initially probed using aldehydes bearing an electron donating group and an electron withdrawing substituent. The corresponding amines **307** and **308** were generated in reasonable yields of 71% and 61% respectively (Entries 2 and 3). Another aromatic example, 4-bromobenzene **309** was produced in a satisfactory yield of 75% (Entries 4). Finally, aliphatic analogues, cyclohexyl **310** and phenylpropyl **311**, were formed in moderate 50% and 58% yields (Entry 5 and 6).

Table 26. Three step synthesis of allyl amines **307**-**311**.[106]



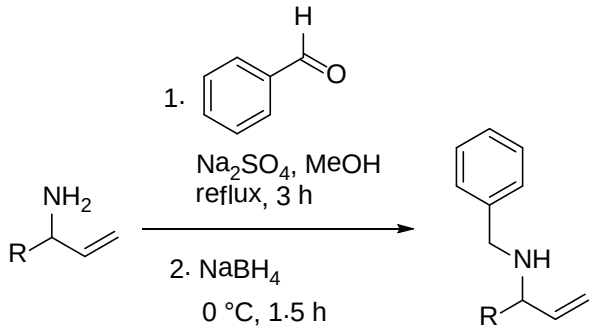
Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **270**	81	4	 **309**	75
2	 **307**	71	5	 **310**	50
3	 **308**	61	6	 **311**	58

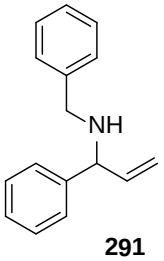
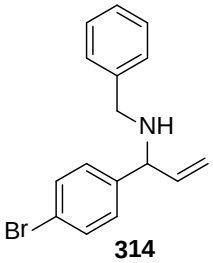
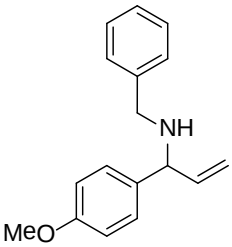
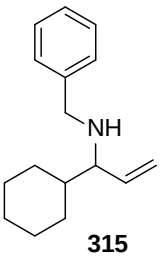
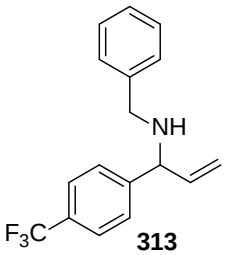
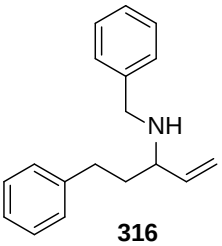
[a] Isolated Yield

6.10.2: Extension of methodology – synthesis of secondary amines

The allylic amines **307**-**311** could then be benzyl protected as described previously (Section 6.6). Good yields of 70-86% were established across the series to yield the fluorinated diene compounds **312**-**316** (Table 27).

Table 27. One-pot conversion of primary amines **307-311** into benzyl amines **312-316.**



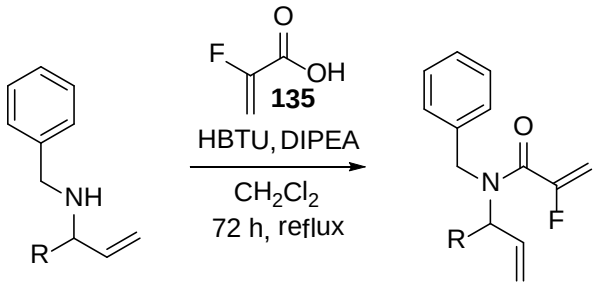
Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **291**	74	4	 **314**	84
2	 **312**	79	5	 **315**	70
3	 **313**	80	6	 **316**	86

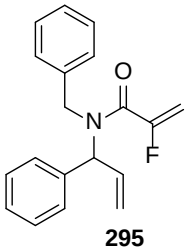
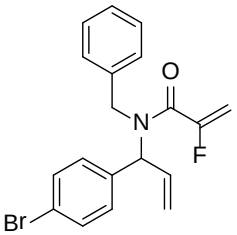
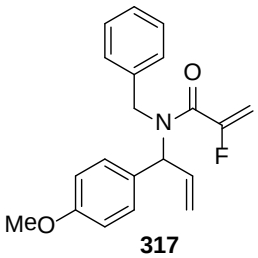
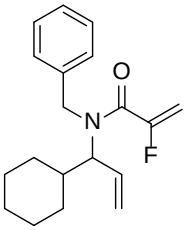
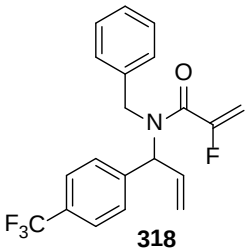
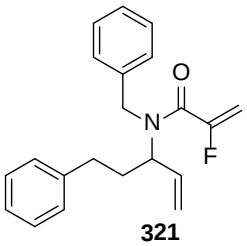
[a] Isolated yield

6.10.3: Extension of methodology – amide coupling reaction

The fluorinated RCM precursor could then be generated through the amide coupling protocol (Table 28). Reasonable yields of 62-76% were recorded for the analogues **317**, **319**-**321** (Entries 1, 2 and 4-6). The only exception was the example **318** which, consistent with results obtained for the 6-membered ring series, was coupled in a lower 45% yield due to reduced electron density on the nucleophilic nitrogen (Entry 3).

Table 28. Amide coupling reactions between secondary amines **312-316** and fluorinated acid **135** to form dienes **317-321.**



Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **295**	73	4	 **319**	62
2	 **317**	62	5	 **320**	76
3	 **318**	45	6	 **321**	75

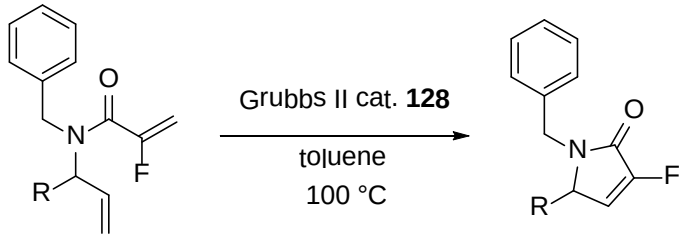
[a] Isolated Yield.

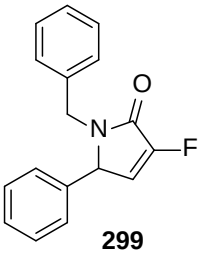
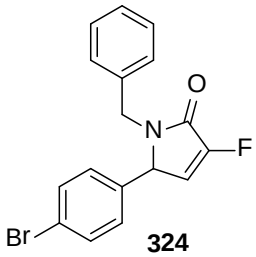
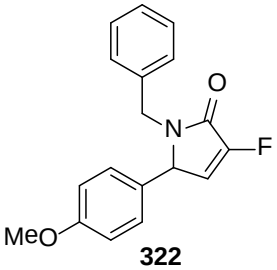
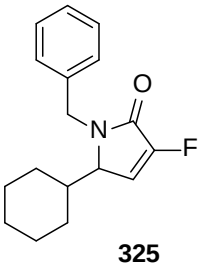
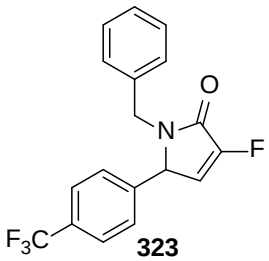
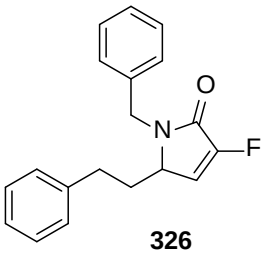
6.10.4: Extension of methodology – ring-closing metathesis

With sufficient quantities of the diene compounds **317**-**321** in hand, construction of the ring system through metathesis could now be carried out (Table 29). Elevated reaction times and catalyst loading are needed for several examples in this series. Namely, the 4-trifluoromethanebenzene **318** and 4-bromobenzene **319** analogues with their electron withdrawing properties hindered the metathesis reactions due a lower electron density at their reactive alkene site (Entries 3 and 4). The diene compound **318** required the harshest conditions taking 4 days and 15 mol% catalyst loading to achieve an 88% yield of **323** (Entry 3). The 4-bromobenzene example **319** took 48 h and 10 mol% catalyst to go to completion and produce **324** in a good yield of 96% (Entry 4). The standard conditions

of 20 h and 7.5 mol% catalyst were applied to the other analogues **317**, **320**-**321** yielding good results of between 78 and 98% of the α,β-unsaturated lactams **322, 325**-**326** (Entries 1, 2, 5 and 6).

Table 29. RCM reactions of **317-321** to form α, β-unsaturated lactams **322**-**326**.



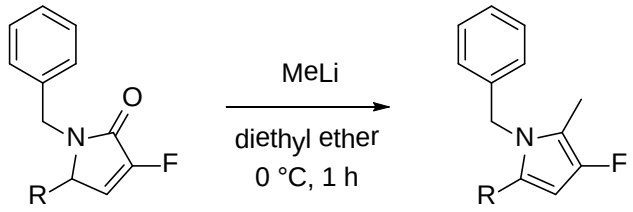
Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **299**	98[b]	4	 **324**	96[d]
2	 **322**	78[b]	5	 **325**	95[b]
3	 **323**	88[c]	6	 **326**	96[b]

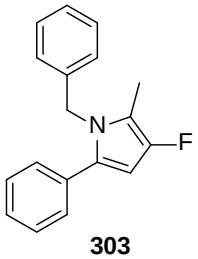
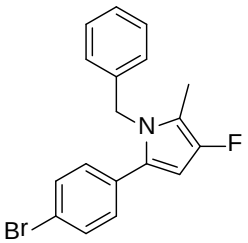
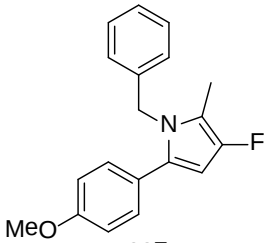
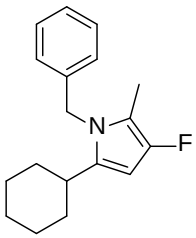
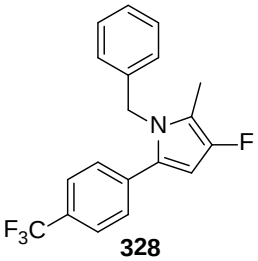
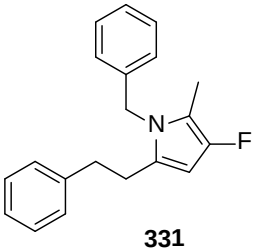
[a] Isolated Yield. [b] 7.5 mol% catalyst, 20 h, 0.005 g mL^{-1}. [c] 15 mol% catalyst, 96 h, 0.005 g mL^{-1}. [d] 10 mol%, 48 h, 0.005 g mL^{-1}.

6.10.5: Extension of methodology – addition-aromatisation reaction

Finally, aromatisation of the α,β-unsaturated lactam compounds **322**-**326** by methyllithium addition was carried out. Facile conversion to the corresponding fluorinated pyrrole **327-331** occurred in each case giving good yields of 73-92% (Table 30, Entries 1-6).

Table 30. Addition of methyllithium to lactams **322-326** to form the target pyrrole compounds **327-331**.

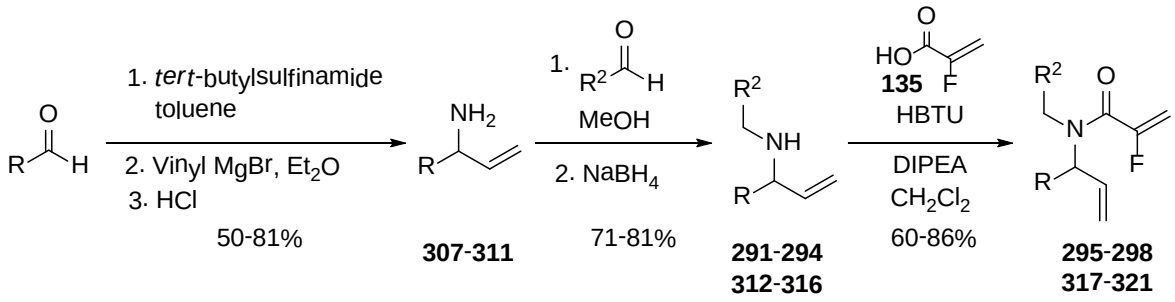


Entry No.	Product	Yield / %[a]	Entry No.	Product	Yield / %[a]
1	 **303**	86	4	 **329**	78
2	 **327**	88	5	 **330**	92
3	 **328**	73	6	 **331**	74

[a] Isolated Yield

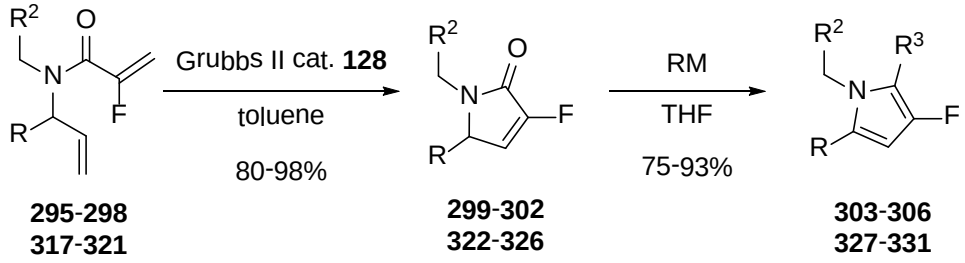
6.11: Conclusion and future work

A novel route for the synthesis of fluorinated polyfunctionalised pyrroles was investigated and optimised. Efficient conditions for the aromatisation of fluorinated α,β-unsaturated γ-lactams into the relevant fluorinated pyrrole was established using nucelophilic organometallics. The methodology could then be extended to produce a library to polysubstituted fluorinated pyrroles bearing aromatic, aliphatic and heterocyclic functionality.



Scheme 89. Synthesis of the fluorinated diene compounds **291-294** and **317-321**, key intermediates in the synthesis of fluorinated pyrroles.

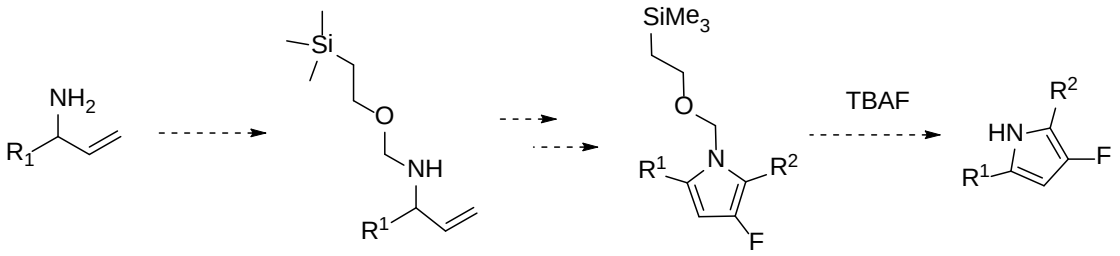
The fluorinated dienes **295**-**298** and **317**-**321** could be synthesised in six steps from commercially available aldehydes (Scheme 89). RCM reactions proceeded in excellent yields to give the fluorinated γ-lactams **299**-**302** and **322**-**326**. Treating the α,β-unsaturated γ-lactams with various nucleophiles, to allow late-stage variation, resulted in the rapid formation of fluorinated polyfunctionalised pyrroles **303**-**306** and **327**-**331** in high yields (Scheme 90).



Scheme 90. Ring-closing metathesis followed by aromatisation to yield the target fluorinated pyrrole compounds **303-306** and **327-331**.

Repeated attempts were made to remove the *p*-methoxybenzyl protecting group to unmask the fluorinated pyrrole series (Section 6.8), however, all conditions used were unsuccessful. Different protecting groups, that can be removed easily but do not hinder other steps in the synthesis, need to be investigated in this case. One example that is of

interest in this regard is a 2-(trimethylsilyl)ethoxymethyl (SEM) group as it should be viable to install onto the primary amine (Scheme 91), be compatible with all the synthetic steps and be easily removed.[119]



307-**311** **332** **333** **334**

Scheme 91. Potential synthesis of fluorinated pyrrole **334** using a SEM group as a protecting group. The SEM group could be removed easily using fluorine source, TBAF.[119,120]

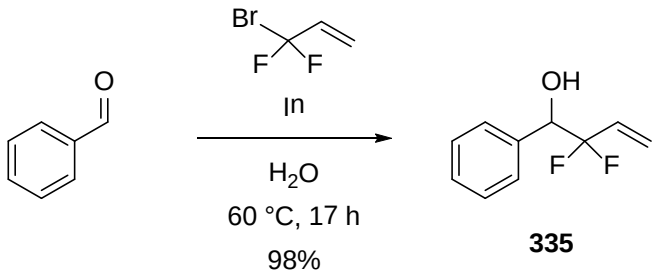
7: Other routes investigated towards the synthesis of fluorinated nitrogen heterocycles

Along with the successful routes to access fluorinated δ-lactams and pyrroles, the synthesis of nitrogen heterocycles with fluorine atoms present at different positions on the ring systems were investigated. The potential to develop synthetic pathways to novel fluorinated compounds for use in medicinal chemistry was the driving force behind this research.

7.1: Use of difluoroalkene in fluorinated nitrogen heterocycle synthesis

7.1.1: Introduction

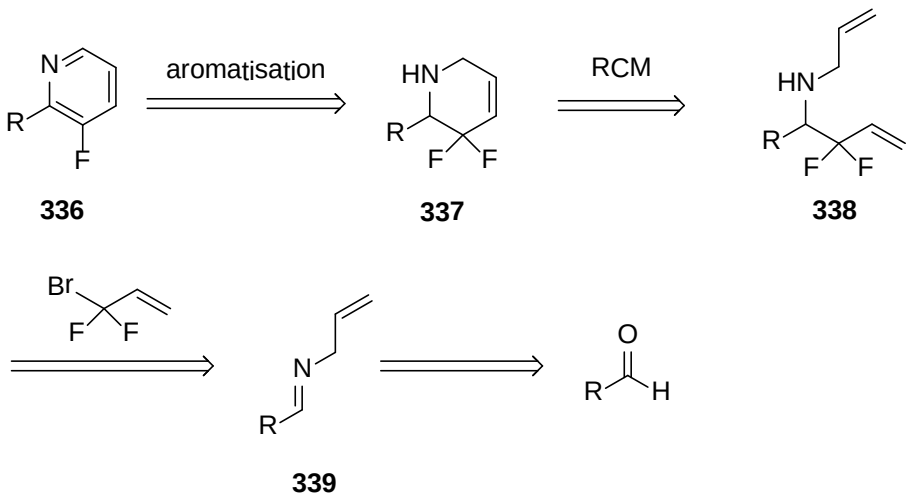
To access a number of nitrogen heterocycles with different sites of fluorination, some different fluorinated starting materials were evaluated. 3,3-difluoro-3-bromopropene was identified as a promising reagent as it has been shown, in the presence of indium, to undergo nucleophillic addition to aldehydes in water forming interesting fluorinated compounds such as **335** (Scheme 92).[121] It was envisaged that addition of 3,3-difluoro-3-bromopropene to a range of imines would provide the building blocks for a synthesis of fluorinated piperidenes and pyridines.



Scheme 92. Nucleophilic addition of 3,3-difluoro-3-bromopropene to benzaldehyde to give alcohol **335**.[121]

7.1.2: Retrosynthetic analysis

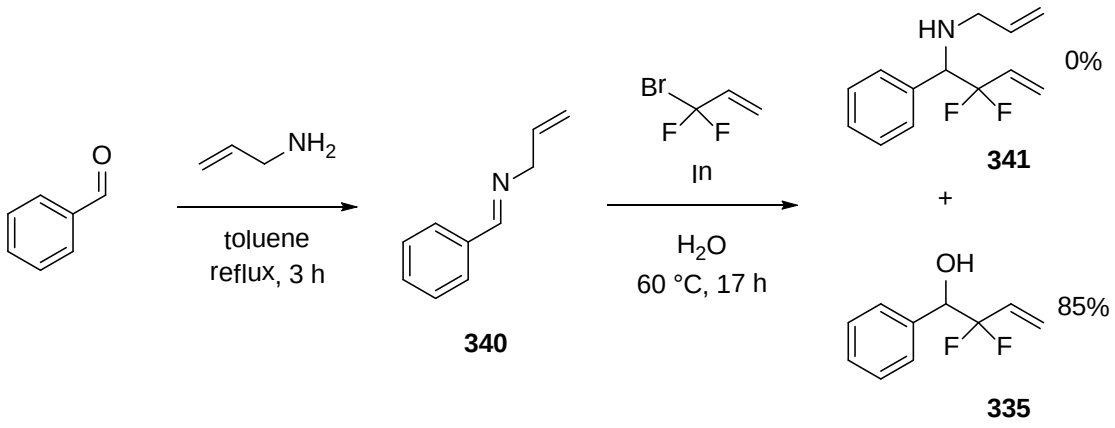
The retrosynthetic analysis starts with the pyridine **336** that is formed from aromatisation of the amine **337**, aided by loss of one of the fluorine atoms (Scheme 93). The ring would be formed in a RCM process from the diene **338**. Compound **338** in turn is produced from the reaction between the imine **339** and 3,3-difluoro-3-bromopropene.



Scheme 93. The retrosynthetic analysis for the synthesis of fluorinated pyridine **336**.

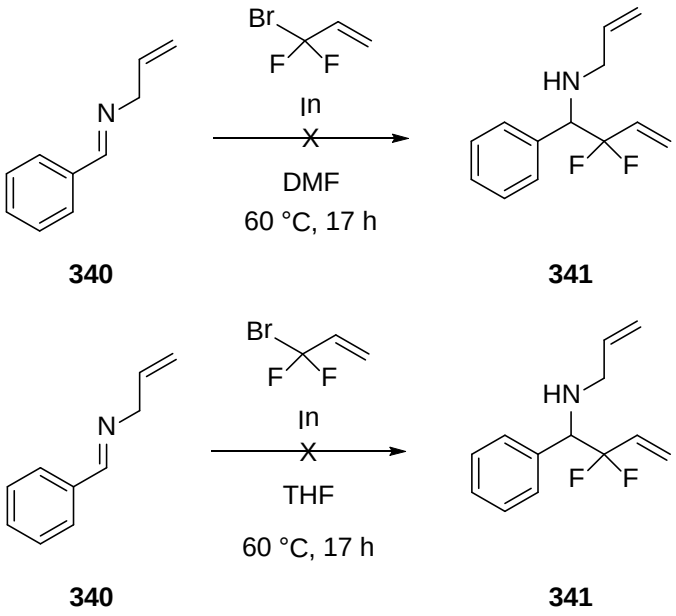
7.1.3: Development of 3,3-Difluoro-3-bromopropene addition to an imine

In order to begin the identified synthetic route, benzaldehyde was reacted with allylamine to form the imine **339**. The imine **339** was then subjected to an indium slurry in water and the difluorobromopropene, however, no product was detected and only the alcohol **335** was formed in an 85% yield (Scheme 94).[121]



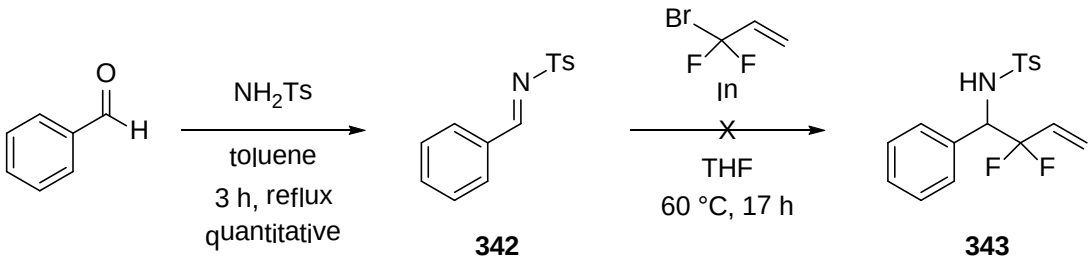
Scheme 94. Formation of imine **340** from allyl amine and benzaldehyde followed by attempted indium assisted addition of 3,3-difluoro-3-bromopropene to imine **340**. However only alcohol **335** was isolated in 85% yield.[121]

It was thought that performing the reaction in water lead to hydrolysis of the imine **340** before the desired addition reaction could take place. To prevent this, the reaction was carried out in anhydrous DMF and THF, however, the alcohol **335** was the only product in both cases (Scheme 95).[122]



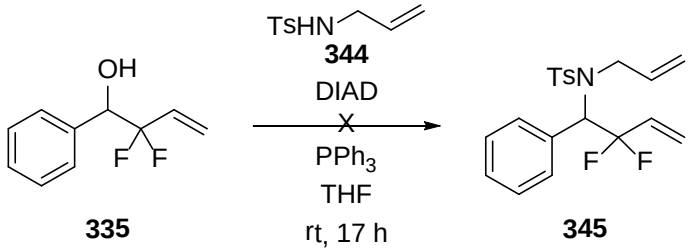
Scheme 95. Further attempts at indium assisted addition of 3,3-difluoro-3-bromopropene to imine **340** in different solvents**.** Unfortunately, only alcohol **335** was isolated in 70% and 81% yields respectively.[122]

Even under anhydrous conditions, it appeared that hydrolysis of the imine was faster than the desired addition. We decided to use a more reactive imine to enhance the addition reaction and reduce the efficacy of the competing hydrolysis. *p*-Toluenesulfonyl amine was reacted with benzaldehyde to give the imine **342**, before treatment with the fluorinated alkene in THF (Scheme 96). However, this was similarly unsuccessful, providing 97% of the unwanted alcohol **335**.



Scheme 96. Formation of imine **342** from the reaction between tosylamine and benzaldehyde. The imine **342** was then treated with indium and 3,3-difluoro-3-bromopropene however only alcohol **335** was isolated in a 97% yield.[122]

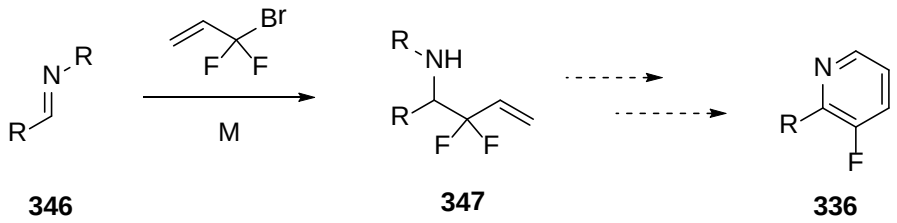
In an attempt to use the formation of the undesired alcohol **335** to our advantage, a Mistunobu reaction was attempted with the tosyl amine **344**, Diisopropyl azodicarboxylate (DIAD) and PPh_3 to form the sulfonamide **345**. However only starting material was isolated from the reaction (Scheme 97).[123]



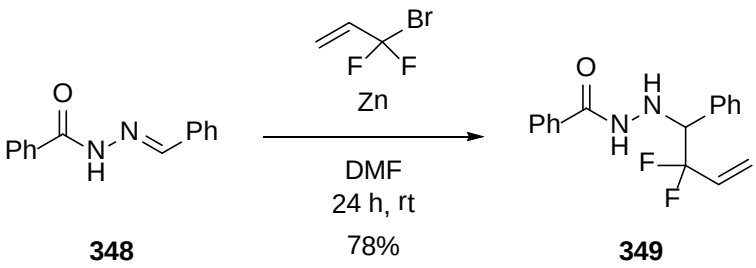
Scheme 97. The Mitsunobu reaction attempted on alcohol **335** to produce the sulfonamide **345** however only starting material was isolated.[123]

7.1.4: Conclusion and future work

Preliminary work has been carried out on the use of 3,3-difluoro-3-bromopropene to generate a difluorodiene compound for use in the synthesis of fluorinated nitrogen heterocycles. To date, there has been no success with the addition of 3,3-difluoro-3-bromopropene to any imine to generate the desired amine (Scheme 98). Future work in this area should involve screening alternative metals, such as zinc, and a range of imines in order to produce sufficient quantities of the desired amine **347**. In related work, Qing and co-workers reported the addition of bromodifluoropropene to a hydrazone **348** using Zn in good yields, which are conditions that we would like to apply to our system in the near future (Scheme 99).[124]



Scheme 98. A screening of metals and imines is required for the metal facilitated addition of bromodifluoropropene to imines **346** to find conditions for the generation of fluorinated amine compounds such as **247**.

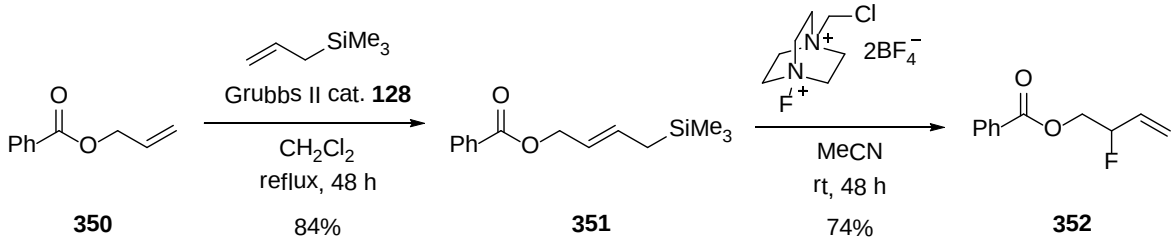


Scheme 99. Successful addition of 3,3-difluoro-3-bromopropene reported by Quing and co-workers.[124]

7.2: Electrophilic fluorination through reaction with allylsilane.

7.2.1: Introduction

In 2003, Gouverneur and co-workers developed an electrophillic fluorination reaction in which an allyl silane attacks the electrophilic fluorine present in Selectfluor®.[125] The authors developed a methodology that incorporated a cross metathesis between an unsaturated substrate and allyltrimethylsilane before fluorination with Selectfluor® to give the alkene product (Scheme 100).[126]



Scheme 100. Cross metathesis and electrophilic fluorination protocol published by Gouverneur and co-workers.[126]

It was our aim to extend this methodology to produce compounds such as **353**-**355** selectively by building in allyltrialkylsilane functionality when preparing the ring (Figure 23).

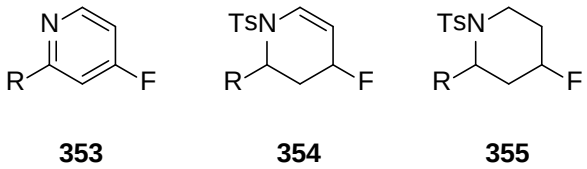
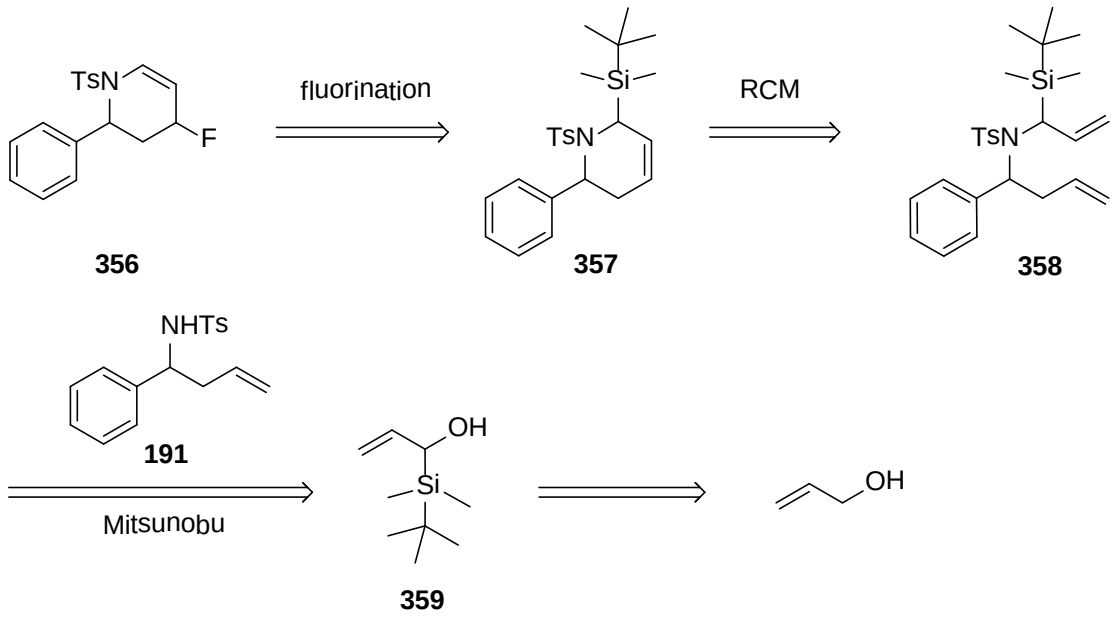


Figure 23. Target fluorinated nitrogen heterocycles **353-355**.

7.2.2: Retrosynthetic analysis

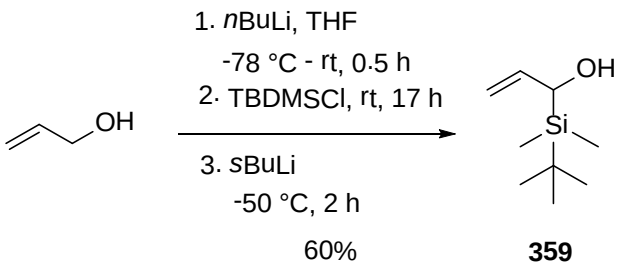
The fluorinated nitrogen heterocycle **356** could be synthesised from the relevant ring system with allyltrialkylsilane functionality in place such as **357** (Scheme 101). This in turn could be synthesised through a ring-closing metathesis procedure from the corresponding diene. The diene **358** could be produced from the allylic alcohol **359** and sulfonamide **360** in a Mitsunobu reaction.



Scheme 101. Retrosynthetic analysis for the synthesis of fluorinated nitrogen heterocycles, such as **356**, via electrophilic fluorination.

7.2.3: Forward synthesis to generate ring system with allyltrimethylsilane in place

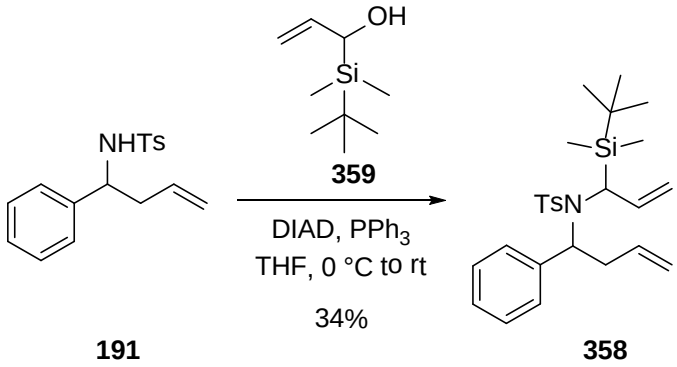
In order to generate the desired silylated compound **359**, allyl alcohol was first deprotonated and silylated with *t*-butlydimethylsilyl chloride (TBDMSCl). Addition of stronger base *sec*-butyllithium allowed deprotonation to occur alpha to the silylated alcohol, resulting in the subsequent migration of the silyl group from the oxygen to the carbon in a good yield over the three steps (Scheme 102).[127] This process was driven by formation of a more stable anion on the oxygen, rather than the higher energy carbanion.[128]



Scheme 102. One-pot silylation of allyl alcohol, firstly onto the alcohol before base mediated migration to form **359** in a 60% yield.[127]

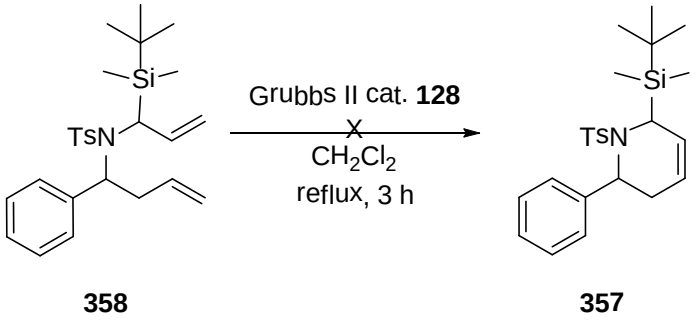
The sulfonamide coupling partner **191** had been previously synthesised in an 86% yield (Section 5.5, Scheme 57). With sufficient quantities of the alcohol **359** in place, a Mitsunobu reaction was attempted using diisopropyl azodicarboxylate and triphenylphosphine.[123] Unfortunately, a less than satisfactory result was obtained for this

step, with the diene **358** produced in a 34% yield (Scheme 103). Further optimisation would be needed to make this a plausible step, although it did result in enough material to attempt the next reaction.

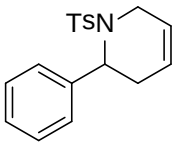


Scheme 103. Mitsunobu reaction between sulfonamide **190** and alcohol **359** to yield 34% of diene **358**.[123]

Diene **358** was subjected to Grubbs 2nd generation catalyst **128** and stirred at reflux for 3 hours (Scheme 104). However, even though a new product was formed seemingly very cleanly it was not the desired product **357** instead it was the desilylated compound **360** (Figure 24).



Scheme 104. Attempted RCM reaction on **358**, however none of the desired product **357** was isolated. Desilylated product **360** was formed in 81% yield.

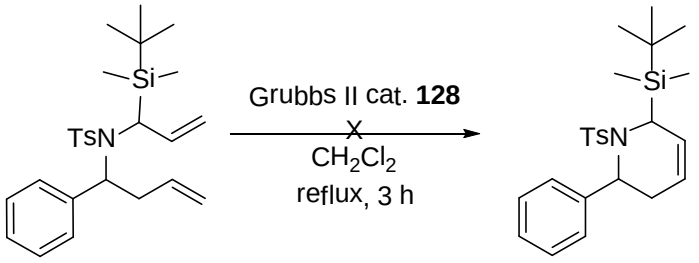


360

Figure 24. Desilylated product from the RCM reaction with diene **360**.

7.2.4: Conclusions and future work

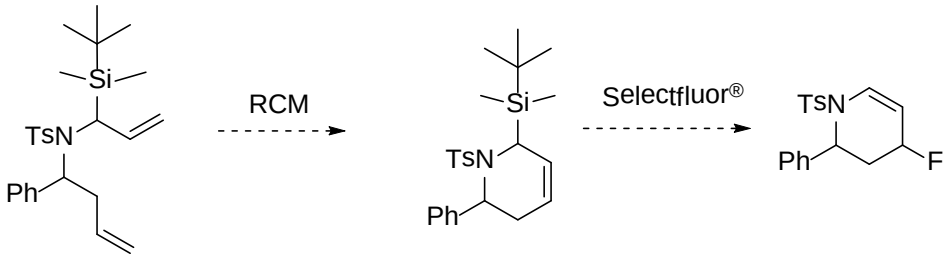
A preliminary investigation into an electrophilic nitrogen ring fluorination was carried out, however, the synthesis of the fluorination precursor proved problematic (Scheme 105). The planned RCM reaction occurred with loss of the all important silane.



358 **357**

Scheme 105. Attempted RCM reaction on **358**, however none of the desired product **357** isolated.

To investigate this further, alternative metathesis catalysts will be probed. Non-ruthenium based catalysts, such as Schrock's catalyst **126**, will be given particular attention, to see if the same process occurs (Scheme 106).[62] If the heterocyclic can be synthesised with the silane intact, a fluorination reaction will be attempted to try attain the fluorinated heterocycle **356**.



358 **357** **356**

Scheme 106. Screening of metathesis catalysts and conditions is needed to allow the RCM reaction to form nitrogen heterocycle **356,** prior to the fluorination step.

8: Synthesis of poly(ADP-ribose) polymerase (PARP) inhibitors

8.1: Introduction

Once an efficient methodology was established for the synthesis of fluorinated nitrogen heterocycles, it was our aim to use the methodology to produce fluorinated analogues of biologically active compounds. This would demonstrate the significance of the methodology as well as produce some interesting medically relevant structures. Therefore, it was decided to use the methodology established to generate δ-lactams (Section 5) for the synthesis of a number of fluorinated PARP inhibitors.

8.1.1 Poly(ADP-ribose) polymerase enzymes

Poly(ADP-ribose) polymerase (PARP) enzymes make up a family of 18 members that, as the name suggests, catalyse the polymerisation of ADP-ribose units.[129] This polymerisation is integral for the repair of double and single stranded DNA breaks, which in turn is essential for the healthy continuation of the cell cycle.[129] DNA is damaged internally during cell replication and also externally by a variety of conditions such as UV radiation, radiotherapy and chemotherapy. Prevention of DNA repair leads to cell death.[129]

In order to carry out this function, all PARP enzymes have an active site which is highly conserved throughout the family. This contains the PARP 'signature motif' which is 100% conserved within vertebrates.[128] The active site facilitates the transfer of nicotinamide adenine dinucleotide (NAD^+) to nuclear acceptor proteins; this occurs multiple times forming long, branched chains.[130] Following this activity, the PARP enzyme leaves the site of the damage and specific DNA repair enzymes recognise the nuclear acceptor proteins and so can repair the damage.[130] PARP-1, the most studied member of the family, can bind a wide variety of DNA structures including single and double strand breaks, crossovers, supercoils and cruciforms.[129]

8.1.2 PARP in cancer treatment

In recent years, there has been significant interest in inhibiting PARP enzymes as a treatment for cancer. Breast cancer, early onset (BRCA1 and BRCA2) genes are human tumour suppressor genes expressed in the breast and other tissue including the ovary,

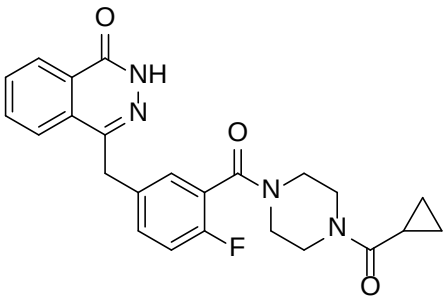
pancreas and lung.[131] The genes are important for the destruction of cells that cannot be repaired and the proteins coded by the genes are integral in the repair of double DNA strand breaks.[131] Certain people have hereditary mutations in the BRCA gene increasing their risk of gene malfunction and tumour growth. Research has found an 80% risk of developing breast cancer and 55% risk of developing ovarian cancer in women with BRCA mutations.[132]

The resulting tumours have a deficiency in BRCA genes which was a significant driving force behind the tumour growth.[131] However, this also leads to an innate weakness that can be exploited for the treatment of these specific tumours. The BRCA deficient tumours have a reduced capacity to repair double strand DNA breaks.[131] By inhibiting PARP enzymes, which is a key component of the cells protocol for fixing single strand breaks, the naturally occurring single strand breaks cannot be repaired efficiently. The single strand breaks are converted into double strand breaks during cell replication processes. This flooding of the cell DNA with double strand breaks, which BRCA deficient tumour cells cannot repair, is followed swiftly by cell death and tumour suppression.[131]

This treatment demonstrates cancer cell selectivity in two ways: firstly, healthy cells have a better ability to repair double strand breaks and secondly, healthy cells do not replicate as rapidly as cancer cells, therefore are less heavily dependant on DNA repair processes. DNA is also damaged during other cancer treatment programs, including both radiotherapy and chemotherapy, in the hope of killing the cancerous cells and thus suppressing the tumour. This being the case, PARP inhibitors could also be used in conjunction with other treatments to prevent the repair of the damaged DNA increasing the likelihood of cell death.[133]

8.1.3 Known PARP inhibitors

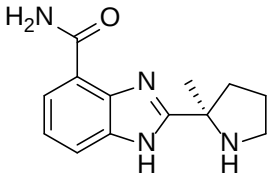
In late 2014, the first PARP inhibitor, Olaparib **361** (AstraZeneca), was approved for treatment of germline BRCA mutated (gBRCAm) advanced ovarian cancer (Figure 25). It is an inhibitor of both the PARP-1 and PARP-2 enzymes with IC_{50} values of 0.005 μM and 0.001 μM respectively and demonstrated a good oral exposure during pharmacokinetic studies.[134] It has only been approved for mono-therapy initially, however, there are presently investigations into duel therapy with traditional platinum cancer drugs which are ongoing.[133]



361

Figure 25. FDA approved PARP inhibitor (AstraZeneca) Olaparib **361**.[134]

Veliparib **362**, a PARP inhibitor produced by Abbott Laboratories, is currently in phase III clinical trials for both non-small cell lung cancer and breast cancer (Figure 26). With IC_{50} values of 0.005 μM for PARP-1 and 0.003 μM for PARP-2, it is a potent inhibitor and excellent drug candidate.[135] Similar to Olaparib **361**, there are many ongoing tests into combinational therapy approaches towards the treatment of a whole range of cancers.[135]

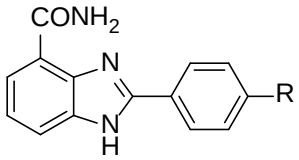


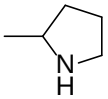
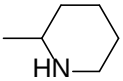
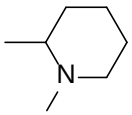
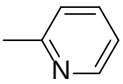
362

Figure 26. PARP inhibitor (Abbot), Veliparib **362**.[135]

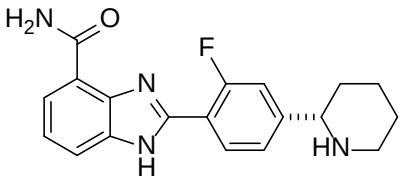
In 2010, Penning and co-workers reported an extended SAR of the veliparib benzimidazole scaffold, in which a benzene linker has been added between the eastern and western fragments (Table 31).[136] The eastern fragment was altered to incorporate various nitrogen heterocycles and the resulting changes in the cellular EC_{50} was tracked. The selection shown in Table 31 demonstrates the nitrogen heterocycle could be altered without a significant effect on the activity, with **363**-**366** (Entries 1-4) having cellular EC_{50} values ranging between 0.002 and 0.008 μM.[136]

Table 31. Enzyme binding and *in vitro* results for potential inhibitor compounds **363** to **366** reported by Penning and co-workers.[136]



Entry No.	Compound No.	R	PARP-1 (Ki, uM)	Cellular (EC_{50}, uM)
1	**363**		0·003	0·003
2	**364**		0·004	0·004
3	**364**		0·006	0·002
4	**365**		0·002	0·008

The crystal structure of PARP-1 with inhibitor **366** bound to the active site shows how the compounds interact with the enzyme (Figure 28).[136] The benzimidazole fragment forms strong interactions, primarily through hydrogen bonding, between the amide substituent and the nearby glycine and serine residues. The amine present in the imidazole ring forms a hydrogen bond to glutamine 988 and there is a stabilising π-π interaction between the benzene ring and a tyrosine residue. This inhibitor boasts a fluorine atom on the unsaturated linker which also forms hydrogen bond interactions to the enzyme.[136]



366

Figure 27. PARP inhibitor reported by Penning and co-workers.[136]

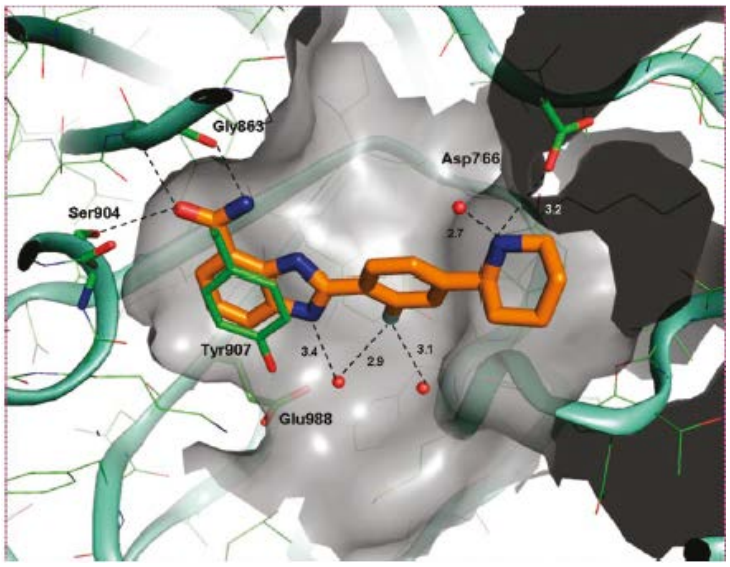
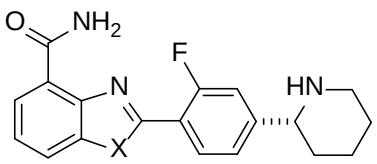


Figure 28. Cocrystal structure of PARP-1 active site with compound **366** bound, Ki = 0.006 μM.[136]

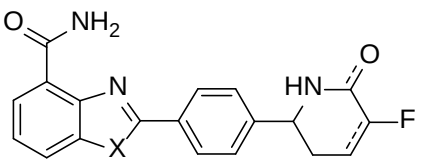
The eastern fragment, in comparison, has limited contact with the enzyme only forming hydrogen bond interactions through the available amine.[136] Upon examination of the active site, there appears to be space in this region to allow for further functionalisation on a potential inhibitor.[136] Development of next generation inhibitors could take advantage of this free space to increase the number of binding interactions and improve the pharmacokinetic properties (Figure 28).

8.2 Aims

Following the success of the fluorinated δ-lactam synthesis (Section 5), the opportunity arose to use the methodology to make some more specific targets with the aim of producing some biologically active compounds. The amides **366** and **367** are examples from a range of poly(ADP-ribose) polymerase 1 (PARP-1) inhibitors synthesised and tested by Penning *et al* (Figure 29).[136] The eastern side of the molecule bares a certain resemblance to the δ-lactams produced above and it was envisaged that using the brominated analogue **229** (Figure 30) we could readily access the complete compound via cross-coupling chemistry, a novel approach to this family of compounds.

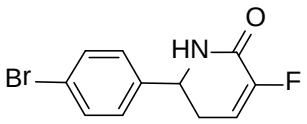


366 X = NH
367 X = O



368 X = NH
369 X = O

Figure 29. PARP inhibitors **366** and **367** reported by Penning and co-workers and potential fluorinated analogues **368** and **369**.[136]



229

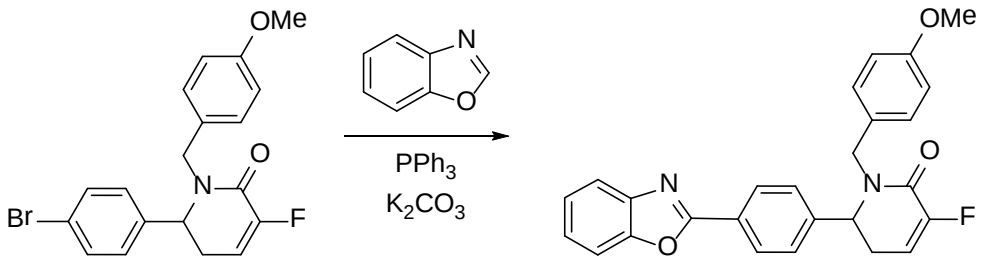
Figure 30. *Para* brominated α,β-unsaturated lactam **229**.

8.3: Results and Discussion

To develop the appropriate methodology we first attempted production of compounds which did not possess the amide side chain present on the western fragment of **367**. This would allow us to probe the cross coupling reaction with readily available starting materials, benzoxazole and benzimidazole. Therefore, the bromo α,β-unsaturated lactam **220**, was reacted with benzoxazole using a palladium-copper co-catalyst system in an attempt to activate a C-H bond on the benzoxazole and couple with the aromatic bromine (Table 32).[137]

The reaction was first attempted with 1 mol% palladium catalyst at reflux in toluene, in accordance with conditions developed Huang for the coupling of bromobenzene and benzoxazole (Entry 1).[137] However, under these preliminary conditions only starting material could be isolated. An increase to 10 mol% palladium catalyst under otherwise identical conditions resulted in a 24% yield of the desired coupled product (Entry 2). An increase of catalytic loading and time from 17 h to 48 h only improved the yield to 28% (Entry 3). Finally, the reaction was attempted in the microwave for 4 hours at 128 °C and to our delight an excellent 73% yield of **370** was produced (Entry 4).

Table 32. Conditions attempted for the C-H activation protocol to form benzoxazole product **370**.[137]

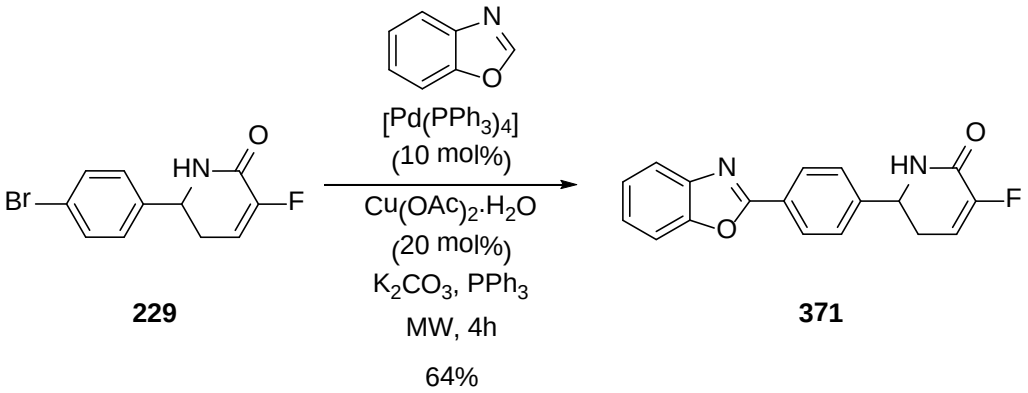


220 **370**

Entry No.	Catalytic System	Conditions	Yield / %[a]
1	Cu(II)$OAc_2.H_2O$ (20 mol%), $[Pd(PPh_3)_4]$ (1 mol%)	reflux, toluene, 17 h	0%
2	Cu(II)$OAc_2.H_2O$ (20 mol%), $[Pd(PPh_3)_4]$ (10 mol%)	reflux, toluene, 17 h	24%
3	Cu(II)$OAc_2.H_2O$ (50 mol%), $[Pd(PPh_3)_4]$ (20 mol%)	reflux, toluene, 48 h	28%
4	Cu(II)$OAc_2.H_2O$ (20 mol%), $[Pd(PPh_3)_4]$ (10 mol%)	128 °C, MW, toluene, 4 h	73%

[a] Isolated Yield

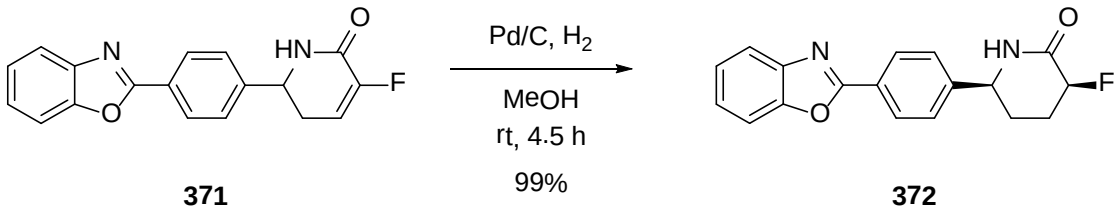
The reaction could then be attempted on the unprotected amide **229** forming **371** in a 70% yield (Scheme 107).



229 **371**

Scheme 107. C-H activation protocol to form benzoxazole product **371** in a 70% yield.

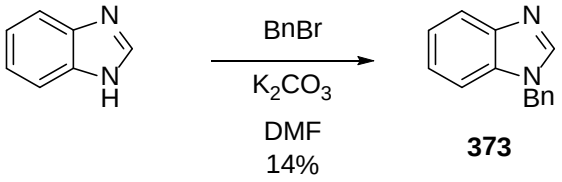
With the cross-coupled product **371** in hand, further interconversions could be carried out to form different compounds for testing. Firstly, the olefin was hydrogenated to give the δ-lactam **372** in a 99% yield. As in previous examples, this occurred on the opposite face to the bulky group producing a single diastereomer (Scheme 108).



371 **372**

Scheme 108. Reduction of α,β-unsaturated lactam **371** to δ-lactam **372** in a 99% yield.

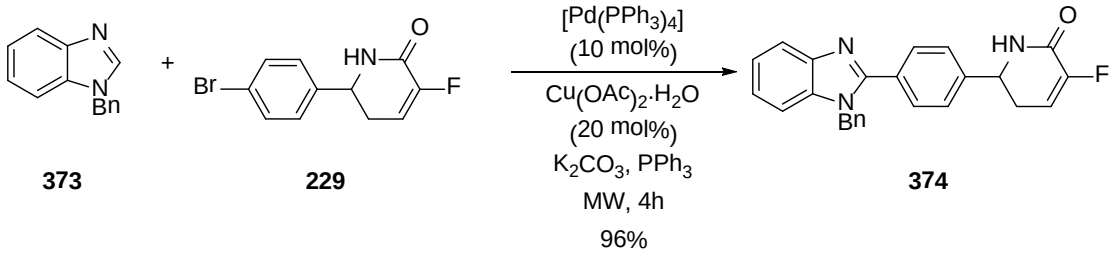
In order to access benzimidazole analogues, the amine present needed to be protected to allow for C-H activation. Therefore, benzimidazole was reacted with benzyl bromide under microwave irradiation in an unoptimised procedure to give the protected amine **373** in a poor 14% yield (Scheme 109).[138] Despite this, sufficient quantities of the protected benzimidazole **373** were obtained to test the next step, however, further optimisation on this step is required in order to provide an expedient synthetic route.



373

Scheme 109. Benzyl protection of benzimidazole to form **373** in a 14% yield.[138]

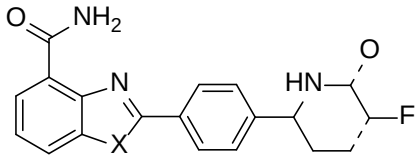
The cross-coupling reaction was carried out as previously described and proceeded in an excellent 96% yield (Scheme 110). This compound **374** can now be subjected to hydrogenation conditions to remove the protecting group and the alkene, giving us access to a key compound for testing. Reduction to the amine will also be carried out to produce a further analogue.



373 **229** **374**

Scheme 110. Cross-coupling reaction between benzyl protected benzimidazole **373** and **229** to produce the compound **374** in a 96% yield.

The compounds made will be tested in collaboration with Prof. A. Chalmers at the Cancer Research UK Beatson Institute, Glasgow. Further examples with the relevant amide side chain (Figure 31) are also under investigation and excellent binding properties to the PARP active site are expected.

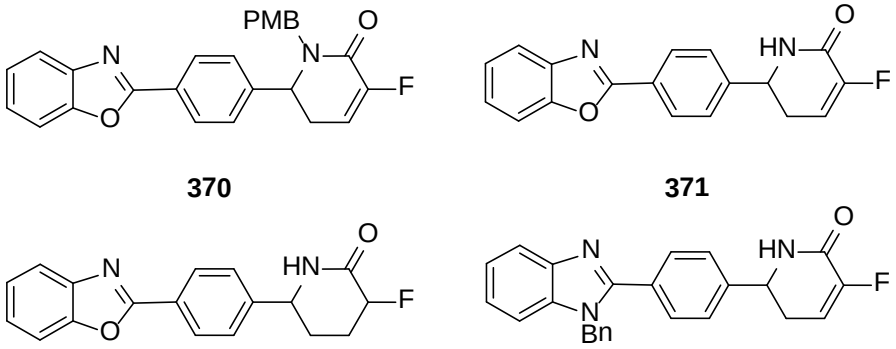


368 X = NH
369 X = O

Figure 31. Future PARP inhibitor targets **368** and **369** with primary amide side chain which is important in enzyme binding.

8.4: Conclusion and future work

An investigation into the synthesis of some potential fluorinated PARP inhibitors has been carried out and a C-H activation cross-coupling reaction has been utilised to produce the scaffold of the inhibitors. Several compounds have been synthesised and will be tested for biological activity in collaboration with Prof. A. Chalmers at the Cancer Research UK Beatson Institute (Figure 32).



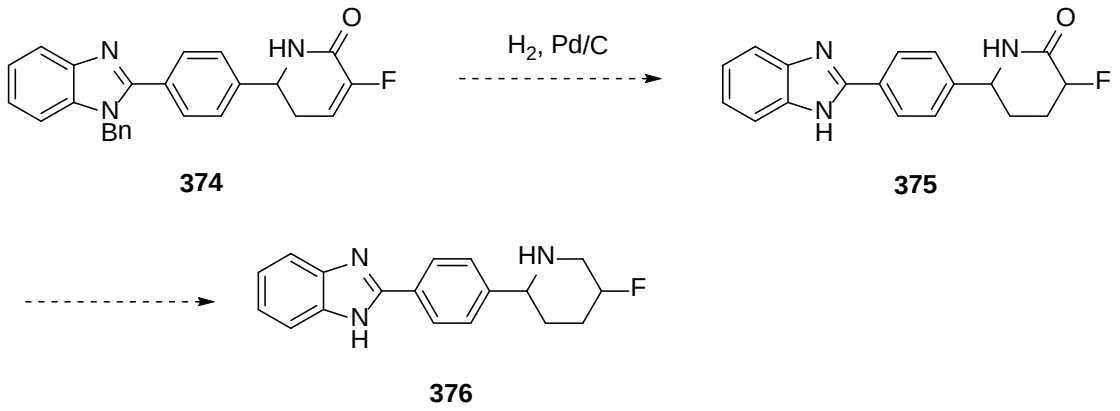
370 **371**

372 **374**

Figure 32. Fluorinated lactam compounds **370-372** and **374** to be tested for inhibition of PARP enzymes

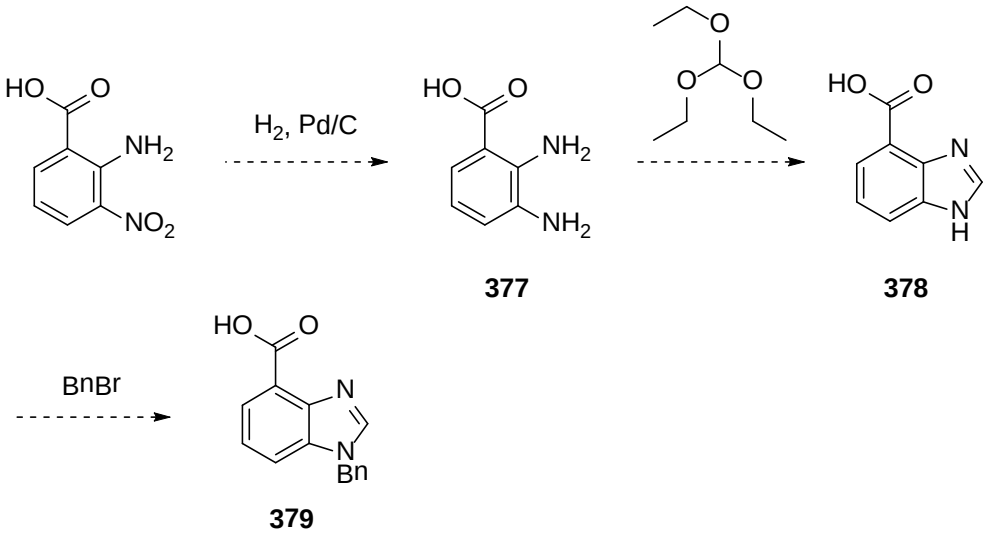
Conditions for the reduction of the fluorinated lactams need to be sought to yield the desired fluorinated amines that mimic previous inhibitors.

The synthesis of the benzimidazole analogues **375**-**376** needs to be completed before they can be submitted for testing. A hydrogenation reaction to remove the benzyl protecting group and the alkene will be carried out before the lactam will be reduced to the amine (Scheme 111).



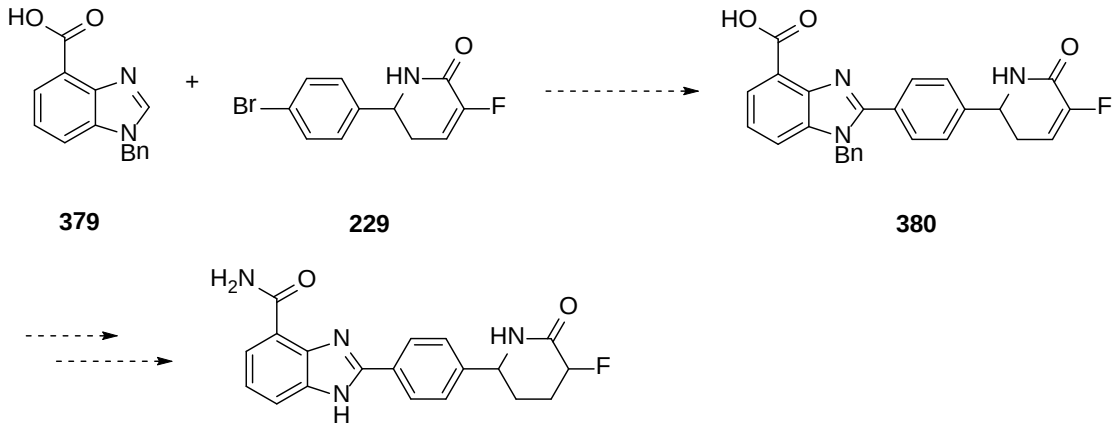
Scheme 111. Reduction of alkene and protecting group removal to unmask potential PARP inhibitor **375** and lactam reduction to give amine **376**.

The literature PARP inhibitors, synthesised by Penning and co-workers, all exhibit amide functionality on the benzimidazole fragment.[136] Our work so far has not incorporated this group which is key for good enzyme binding, therefore, the inclusion of this functionality is an important future aim. In this case, we need to synthesise the western fragment to include the amide group. A three step synthesis has been envisaged to form the acid **379** from commercially available 2-Amino-3-nitrobenzoic acid (Scheme 112).[139]



Scheme 112. Potential synthesis of acid **379** in three steps from commercially available 2-Amino-3-nitrobenzoic acid.[139]

The cross coupling reaction will be carried out with the acid **379** before conversion to the amide and protecting group removal to give the fluorinated PARP inhibitor **381** (Scheme 113).



379 **229** **380**

381

Scheme 113. The synthesis of the amide bearing PARP inhibitors will be completed with a cross-coupling of acid **379** to produce the fluorinated lactam **380** followed by amide formation and protecting group removal to give **381**.

9. Experimental

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether, toluene and dichloromethane were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40°C using a Buchi Rotavapor unless otherwise stated. IR spectra were recorded as thin films on NaCl plates using a JASCO FT/IR410 Fourier Transform spectrometer. Only significant absorptions (vmax) are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^{1}H NMR), fluorine magnetic resonance spectra (^{19}F) and carbon magnetic resonance spectra (^{13}C NMR) were respectively recorded at 400 MHz, 377 MHz and 100 MHz using a Bruker DPX Avance400 instrument. Proton magnetic resonance spectra (^{1}H NMR), fluorine magnetic resonance spectra (^{19}F) and carbon magnetic resonance spectra (^{13}C NMR) were respectively recorded at 500 MHz, 470 MHz and 125 MHz using a Bruker DPX Avance500 instrument. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br = broad), (3) and coupling constant (*J*) quoted in Hertz to the nearest 0.1 Hz. High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray (EI) chemical ionisation (CI) mass spectrometery operating at a resolution of 15000 full widths at half height. Flash chromatography was performed using silica gel (Flurochem Silica Gel 60, 40-63 micron) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F254) unless otherwise stated. The plates were visualised by the quenching of UV fluorescence (λmax254nm) and/or by staining with either anisaldehyde, potassium permanganate, iodine or cerium ammonium molybdate followed by heating.

General procedure A: Synthesis of PMB protected allylic amines, from aldehydes.

Na_2SO_4 (1.00 g) was dried under vacuum in a round bottom flask for 10 min. Aldehyde (1 eq) was then added, followed by toluene (15 mL) and 4-methoxybenzylamine (1.1 eq). The resulting reaction mixture was then heated to reflux for 3 h. The reaction was then cooled down to rt, and the solid residue filtered off.

The solvent was removed *in vacuo* and the residue was redissolved in anhydrous diethyl ether (20 mL). The solution was cooled down to 0 °C before allylmagnesium bromide (1.5 eq, 1 M in THF) was added dropwise. The resulting mixture was allowed to warm up to rt and was stirred for 17 h. The reaction was quenched with water (20 mL) and extracted

with diethyl ether (3 × 20 mL). The combined organic extracts were dried over sodium sulphate, and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography to afford the corresponding allylic amine.

General procedure B: Amide coupling of allylic amines

2-Fluoroacrylic acid (1.5 eq) and HBTU (1.5 eq) were dry mixed and then dissolved in CH_2Cl_2 (20 mL). DIPEA (1.5 eq) was added followed by the corresponding amine (1 eq). The solution was heated to reflux and stirred for 17 h. The reaction was cooled down to rt and the solvent was then removed *in vacuo*. The crude material was purified by flash column chromatography.

General procedure C: Ring-closing metathesis of fluorinated dialkene

A solution of the dialkene (1 eq) in toluene (2.5 mg mL^{-1}) was treated with Grubbs 2nd generation catalyst (2.5 mol%) and the resulting mixture was heated to 100 °C until completion (1-4 h). The reaction was cooled down to rt, the solvent was removed *in vacuo* and the crude material was purified by flash column chromatography.

General procedure D: Removal of *p*-methoxybenzyl protecting group

The cyclic amide (1 eq) was dissolved in a MeCN/H_2O (8:2, 4 mL) mixture and ceric ammonium nitrate was added portion wise. The solution was stirred at rt for 7 h. The reaction was quenched with *aq*. sat. $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 × 10 mL). The orgaincs were combined, dried (Na_2SO_4) and removed *in vacuo*. The crude material was purified flash column chromatography.

General procedure E: Hydrogenation of α,β-unsaturated lactam

A solution of dihydropyridone (1 eq) in MeOH (2 mL) was treated with palladium activated charcoal (10% by weight) and the suspension was stirred under a H_2 atmosphere until completion (1-4 h). The resulting mixture was filtered through celite, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography.

General procedure F: Synthesis of allylic amines, from aldehydes

Na_2SO_4 (1.00 g) was dried under vacuum in a round bottom flask for 10 min. Aldehyde (1 eq) was then added, followed by toluene (10 mL) and *tert*-butylsulfinamide (1.1 eq). The

resulting reaction mixture was then heated to reflux for 4 h. The reaction was then cooled down to room temperature, and the solid residue filtered off.

The solution was concentrated *in vacuo* and the residue was redissolved in anhydrous diethyl ether (10 mL). The solution was placed under argon and cooled down to 0 °C. The solution was then treated dropwise with vinylmagnesium bromide (3 eq) and the resulting mixture was allowed to warm up to room temperature for 17 h. The reaction was quenched with H_2O (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over sodium sulphate, and evaporated under reduced pressure.

The crude residue was dissolved in MeOH (20 mL) before HCl (6M) was added dropwise until a pH of 1 was reached. The solution was stirred for 1 h following which the reaction was diluted with H_2O (20 mL) and the mixture was extracted with diethyl ether (3 × 20 mL). The aqueous phase was basified to a pH of 14 with 15% NaOH and then extracted with CH_2Cl_2 (3 × 20 mL). The resulting organics were dried (Na_2SO_4) and the solvent was removed *in vacuo* to give the corresponding allylic amine without need for further purification.

General procedure G: Formation of secondary amines

Na_2SO_4 (1 g) was dried under vacuum in a round bottom flask for 10 min. Amine (1 eq) was then added, followed by MeOH (6 mL) and aldehyde (1.05 eq). The resulting reaction mixture was then heated to reflux and stirred for 3 h. The reaction was then cooled down to 0 °C, the solution was treated with $NaBH_4$ (1.5 eq) and the mixture was stirred for 1.5 h. Following this time, the reaction was quenched with H_2O (20 mL) and extracted with diethyl ether (3 × 20 mL). The organics were combined and dried (Na_2SO_4) before the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography to afford the corresponding secondary amine.

General procedure H: amide coupling to form diene

2-Fluoroacrylic acid (2 eq) and HBTU (2 eq) were dry mixed and then dissolved in CH_2Cl_2 (10 mL). DIPEA (2 eq) was added followed by the corresponding amine (1 eq). The resulting solution was heated to reflux for 72 h. The reaction was cooled down to rt and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography.

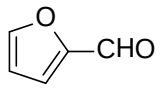
General procedure I: Ring-closing metathesis of fluorinated dialkene

A solution of the diene (1 eq) in toluene (5.0 mg mL^{-1}) and was heated to 100 °C. Grubbs 2nd generation catalyst was added in portions and the reaction was stirred until completion. The reaction was cooled down to rt, the solvent was removed *in vacuo* and the crude material was purified by flash column chromatography.

General procedure J: Nucleophilic addition and aromatisation to form pyrrole system

α,β-Unsaturated lactam (1 eq) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. Methyllithium (1.1 eq) was added dropwise and the mixture was stirred for 1 h. The reaction was quenched with H_2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified be flash column chromatography.

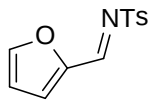
2-Furaldehyde, 117.[55]



$POCl_3$ (3.50 mL, 38.0 mmol) was added dropwise, ensuring the temperature did not rise above 25 °C, to DMF (6.27 mL, 75.1 mmol) at 0 °C. To the resulting mixture was gradually added furan (2.60 mL, 38.0 mmol) ensuring the temperature did not rise above 25 °C. The mixture was stirred for a further 1 h at 0 °C before being allowed to warm to rt and was stirred for 17 h. Sat. K_2CO_3 (10 mL) was added slowly to neutralise the mixture before extracting the aqueous phase with diethyl ether (3 × 15 mL). The combined organics were washed with H_2O (3 × 30 mL) and brine (2 × 30 mL) before being dried (Na_2SO_4) and removed *in vacuo* to yield the desired product **117** as a pale yellow oil (2.74 g, 28.5 mmol, 74%).

^{1}H ($CDCl_3$, 400 MHz) δ: 9.60 (1H, s, C*H*O), 7.69 (1H, d, J_H = 1.6, 0.8 Hz, OC*H*), 7.25 (1H dd, J_H = 3.6, 1.6 Hz, OC(CHO)C*H*), 6.60 (1H, dd, J_H = 3.6, 1.6 Hz (OCHC*H*).
^{13}C ($CDCl_3$, 125 MHz) δ: 177.9 (*C*HO), 153.0 (O*C*(CHO)CH), 148.1 (O*C*H), 121.0 (OC(CHO)*C*H), 112.6 (OCH*C*H).
The spectral data is in agreement with the literature values.[55]

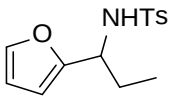
***N*-Furan-2-ylmethylene-4-methyl-benzenesulfonamide, 118.**[54]



To a solution of 2-furaldehyde **117** (0.89 mL, 10.4 mmol) in toluene (10 mL) was added *p*-toluenesulphonamide (1.8 g, 10.4 mmol) and *p*-toluenesulphonic acid (18 mg, 104 µmol). The mixture was heated to reflux for 17 h with the use of Dean-Stark apparatus. After this time, charcoal was added to the hot solution and it was further stirred for 1 h. The solids were filtered off, the solvent was removed *in vacuo* and the resulting material was recrystallised (benzene) to yield the desired product **118** as a brown solid (2.2 g, 8.83 mmol, 84%).

^{1}H ($CDCl_3$, 400 MHz) δ: 8.84 (1H, s, C*H*NTs), 7.89 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.75 (1H, s, OC*H*), 7.37-7.12 (3H, m, Ar-C*H* and OC(CHNTs)C*H*), 6.67 (1H, dd, J_H = 2.0, 1.6 Hz, OCHC*H*) 2.48 (3H, s, CH_3).
^{13}C ($CDCl_3$, 125 MHz) δ: 155.7 (*C*HN) 149.7 (CSO_2) 144.6 (O*C*(CHNTs), 135.2 (*C*CH_3) 129.8 (2C, Ar-*C*H) 128.3 (O*C*H) 128.1 (2C, Ar-*C*H) 126.5 (OC(CHNTs)*C*H), 113.7 (OCH*C*H), 21.7 (*C*H_3).
The spectral data is in agreement with the literature values.[54]

***N*-(1-Furan-2-yl-propyl)-4-methyl-benzenesulfonamide, 119.**[54]



The tosylated imine **118** (1.0 g, 4.01 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. Ethylmagnesium bromide (8.02 mmol, 2.7 mL of a 3 M solution in THF) was added to the solution and the reaction mixture was stirred for 5 min. The reaction was quenched with *aq.* $NaHCO_3$ (30 mL) and extracted with diethyl ether (3 × 30 mL). The combined organics were dried (Na_2SO_4), filtered and removed *in vacuo*. The crude product was purified by flash column chromatography (10% diethyl ether in petroleum ether) to yield the desired product **119** as a white solid (0.42 g, 1.51 mmol, 38%).

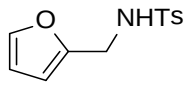
^{1}H ($CDCl_3$, 400 MHz) δ: 7.63 (2H, d, J_H = 8.0 Hz, Ar-*H*), 7.21 (2H, d, J_H = 8.0 Hz, Ar-H) 7.16 (1H, d, J_H = 1.2 Hz, OC*H*), 6.14 (1H, dd, J_H = 3.2, 1.8 Hz, OCHC*H*), 5.92 (1H, d, J_H = 3.2 Hz, OC(CHNTs)C*H*), 4.81 (1H, d, J_H = 8.8 Hz, N*H*), 4.34 (1H, quart, J_H = 8.8 Hz,

C*H*NH), 2.40 (3H, s, Ar-CH_3), 1.82 (2H, quint, J_H = 7.2 Hz, CH_2), 0.83 (3H, t, J_H = 7.6 Hz, CH_2CH_3).

^{13}C ($CDCl_3$, 125 MHz) δ: 152.7 (*C*SO_2), 143.0 (O*C*(CHNTs), 141.8 (O*C*H) 137.7 (*C*CH_3) 129.4 (2C, Ar-*C*H) 127.0 (2C, Ar-*C*H), 109.9 (OCH*C*H), 106.9 (OC(CHNTs)*C*H), 53.2 (*C*NHTs), 28.2 (*C*H_2), 21.7 (Ar-*C*H_3) 10.2 (*C*H_3)

The spectral data is in agreement with the literature values.[54]

_N_-Furan-2-ylmethyl-4-methyl-benzenesulfonamide, 120.[56]



Procedure A

To a solution of furfuryl amine (0.90 mL, 10.3 mmol) in CH_2Cl_2 (32 mL), triethylamine (3.8 mL, 26.0 mmol) was added and the reaction was stirred for 30 min. The mixture was then cooled to 0 °C before *p*-toluenesulfonyl chloride (2.98 g, 15 mmol) was added. The reaction was allowed to warm to rt before the mixture was stirred for 17 h. The solution was washed with sat. *aq*. $NaHCO_3$ (20 mL) and brine (20 mL). Following this, the organic phase was dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude product was recrystallised (diethyl ether) to yield the desired product **120** as a white solid (0.91 g, 3.62 mmol, 35%).

Procedure B

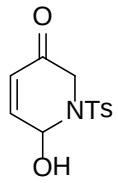
Pyridine (0.85 mL, 10.6 mmol) and *p*-toluenesulfonyl chloride (1.9 g, 10.5 mmol) were dissolved in THF (30 mL) at 0 °C. The solution was stirred for 15 min before furfurylamine (0.90 mL, 10.3 mmol) was added dropwise, not allowing the temperature to rise above 15 °C. The reaction mixture was stirred for a further 2 h. *aq*. NaOH (1M, 30 mL) was added and the resulting mixture was stirred for 30 min before extraction with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried (Na_2SO_4) and filtered through silica, eluting with EtOAc. The crude material was purified by flash column chromatography (20% diethyl ether in petroleum ether) to yield the desired product **120** as a white solid (1.0 g, 4.10 mmol, 40%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.74 (2H, d, J_H = 8.4 Hz, Ar-C*H*), 7.30 (2H, d, J_H = 8.4 Hz, Ar-C*H*), 7.25 (1H, d, J_H = 2.4 Hz, OC*H*), 6.24 (1H, dd, J_H = 3.2, 2.0 Hz, OCHC*H*), 6.10 (1H, d, J_H = 3.2 Hz, (OC(CH_2N)C*H)*, 4.72 (1H, br s, N*H*), 4.20 (2H, d, J_H = 6.1 Hz, CCH_2), 2.42 (3H, s, CH_3).

^{13}C ($CDCl_3$, 125 MHz) δ: 149.1 (SO_2C), 143.5 ($OC(CH_2N)CH$), 142.3 ($CHCHO$), 136.0 (CH_3C), 129.4 (2C, Ar-*C*H), 127.8 (2C, Ar-*C*H), 109.9 ($OCHCH$), 108.6 ($OC(CH_2N)CH$), 39.8 (CH_2), 21.0 (CH_3).

The spectral data is in agreement with the literature values.[56]

6-Hydroxy-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one, 121.[57]



Procedure A

Furfuryl tosylamine **120** (0.20 g, 0.79 mmol) was dried under vacuum for 1 h before the addition of CH_2Cl_2 (5 mL). The solution was cooled to 0 °C then treated with dropwise addition of *m*-CPBA (0.18 g, 1.1 mmol) not allowing the temperature to rise above 10 °C. After 20 min of stirring at the 0 °C, the reaction was allowed to warm to rt and stirring was continued for 7 h. The reaction mixture was washed with sat. *aq.* $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo*. This gave the desired product **121** as a pale yellow oil (0.21 g, 0.79 mmol, quantitative yield).

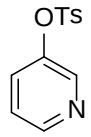
Procedure B

To a solution of furfuryl tosylamine **120** (0.10 g, 0.39 mmol) in THF-H_2O (8:2 mL) was added $NaHCO_3$ (60 mg, 0.80 mmol), NaOAc (30 mg, 0.40 mmol) and NBS (0.08 g, 0.44 mmol) in one portion at 0 °C. The reaction mixture was stirred until completion (0.1 h), before quenching with 30% *aq*. $Na_2S_2O_3$ (10 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organics were washed with sat. NH_4Cl (20 mL) and brine (20 mL). The solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to leave the desired product **121** as a pale yellow oil (0.12 g, 0.39 mmol, quantitative yield), which was not purified further due to instability.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.63 (2H, d, J_H = 8.0 Hz, Ar-C*H*), 7.21 (2H, d, J_H = 8.0 Hz, Ar-C*H*), 6.85 (1H, dd, J_H = 10.4, 5.2 Hz, C*H*CHCO), 6.24 (1H, d, J_H = 6.8 Hz, CHC*H*CO), 5.92 (1H, d, J_H = 4.8 Hz, C*H*OH), 3.96 (1H, d, J_H = 18 Hz, CH*H*), 3.93 (1H, d, J_H = 18 Hz, C*H*H), 2.32 (3H, s, CH_3).

The spectral data is in agreement with the literature values.[57]

3-(*p*-Toluenesulfonyloxy)pyridine, 122.[52]



Procedure A

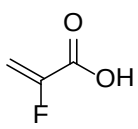
To a stirred solution of pyridone **121** (80 mg, 0.30 mmol) in THF (5 mL) was added $AlCl_3$ (0.36 mL, 1M solution in THF, 0.36 mmol) at -78 °C. After 1 h, the reaction was quenched with Et_3N (0.5 mL) and poured into H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and combined organics were dried (Na_2SO_4), filtered and removed *in vacuo*. The crude product was purified by flash column chromatography (30% EtOAc in hexane) to yield the desired product **122** as a yellow solid (24 mg, 96 µmol, 32%).

Procedure B

To a stirred solution of pyridone **121** (0.15 g, 0.56 mmol) in CH_2Cl_2 (7 mL) was added $BF_3{\cdot}OEt_2$ (90 µL, 0.70 mmol) at -78 °C. After 1 h, the reaction was quenched with Et_3N (0.5 mL) and poured into H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and combined organics were dried (Na_2SO_4), filtered and removed *in vacuo*. The crude product was purified by flash column chromatography (15% EtOAc in petroleum ether) to yield the desired product **122** as a yellow solid (70 mg, 0.28 mmol, 46%).

^{1}H ($CDCl_3$, 400 MHz) δ: 8.52 (1H, d, J_H = 3.6 Hz, NC*H*COTs), 8.17 (1H, d, J_H = 2.4 Hz, NC*H*CH), 7.72 (2H, d, J_H = 8.4 Hz, Ar-C*H*), 7.49 (1H, dq, J_H = 8.3, 1.2 Hz, C*H*COTs), 7.36 (2H, d, J_H = 8.4 Hz, Ar-C*H*), 7.31 (1H, dd, J_H = 8.3, 4.6 Hz, NCHC*H*), 2.46 (3H, s, CH_3).
^{13}C ($CDCl_3$, 125 MHz) δ: 148.9 (N*C*HCOTs), 146.6 (*C*SO_2), 146.1 (*C*OTs), 144.3 (N*C*HCH), 131.6 (CH_3*C*) 129.8 (*C*HCOTs), 129.7 (2C, Ar-*C*H), 127.8 (2C, Ar-*C*H), 123.8 (NCH*C*H), 21.0 (*C*H_3).
The spectral data is in agreement with the literature values.[52]

2-Fluoroacrylic Acid, 135.[140]

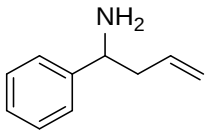


2-Fluoroacylic acid methyl ester **136** (0.87 mL, 9.61 mmol) was dissolved in EtOH/H_2O (8.7:1.3, 10 mL). *aq*. NaOH (2M) was then added dropwise until pH 11 was reached, and

the resulting mixture was stirred for 30 min. After which, the solvent was removed *in vacuo* to yield the sodium salt as a white solid. Diethyl ether (20 mL) was added to the salt, followed by *aq*. HCl (6M) dropwise until the solid dissolved. The layers were then separated, and the aqueous layer was extracted with diethyl ether (10 mL). The organics were combined, dried (Na_2SO_4) and removed *in vacuo to* yield the desired product **135** as a white solid (0.74 g, 8.20 mmol, 87%).

^{1}H ($CDCl_3$, 400 MHz) δ: 9.56 (1H, br s, OH), 5.85 (1H, dd, J_F = 42.8, J_H = 3.6 Hz, C*H*H), 5.51 (1H, dd, J_F = 12.4, J_H = 3.2 Hz, CH*H*).
^{19}F ($CDCl_3$, 377 MHz) δ: -118.3.
^{13}C ($CDCl_3$, 125 MHz) δ: 165.4 (d, J_F = 46.3, *C*OOH), 151.3 (d, J_F = 323.8 Hz, *C*F), 105.2 (d, J_F = 18.8, *C*H_2).
The spectral data is in agreement with the literature values.[140]

1-Phenyl-but-3-enylamine, 139.[141]



Procedure A

Allylboronic acid pinacol ester (1.2 g, 10.8 mmol) and dodecyl benzenesulfonic acid (10 mol%, 0.27 mL, 910 µmol) were added to 25-30% aqueous ammonia (10 mL) and the mixture was stirred for 30 min. After which, benzaldehyde (0.96 mL, 9.43 mmol) was added and the suspension was vigorously stirred for 4.5 h. The solution was then acidified to pH 1-2 and the organics extracted with CH_2Cl_2 (3 × 20 mL). The resulting aqueous phase was basified to pH 12-13 and the organics extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4), filtered and the solvent was removed in *vacuo*. This gave the desired product **139** as a colourless oil (0.72 g, 4.89 mmol, 52%).

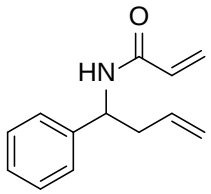
Procedure B

Benzaldehyde (0.21 g, 1.96 mmol) was dissolved in MeOH (4 mL) and the resulting solution was cooled to -78 °C. NH_3 (ca. 4 mL) was condensed into the solution, and the resulting reaction mixture was warmed to -10 °C and stirred until the excess ammonia had evaporated (3 h). Allyl boronic pinacol ester (0.76 mL, 3.93 mmol) was added and the reaction was stirred for 2 h. The reaction vessel was then allowed to warm up to rt and stirred for a further 1 h. *aq*. HCl (6 M) was added slowly to the solution until pH 1 and the mixture was extracted with diethyl ether (3 × 20 mL). The aqueous phase was collected,

and *aq*. NaOH (2 M) was added slowly until pH 14. The aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 phases were then dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* to yield the desired product **139** as a colourless oil (0.28 g, 1.90 mmol, 95%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.20-7.35 (5H, m, Ar-*H*), 5.65-5.75 (1H, m, CH_2CHCH_2), 5.04-5.17 (2H, m, $CHCH_2$), 3.99 (1H, dd, J_H = 8.0, 5.2 Hz, $CHNH_2$) 2.29-2.45 (2H, m, $CHCH_2CH$), 1.54 (2H, br s, NH_2).
^{13}C ($CDCl_3$, 125 MHz) δ: 145.8 (Ar*C*-CHN), 135.4 (*C*HCH_2) 128.4 (2C, Ar-*C*H), 127.9 (Ar-*C*H), 126.4 (2C, Ar-*C*H), 117.7 ($CHCH_2$), 55.4 (*C*HNH_2), 44.2 ($CHCH_2CH$).
The spectral data is in agreement with the literature values.[141]

_N_-(1-Phenyl-3-buten-1-yl)propenamide, 140.[142]



Procedure A

To a solution of acryloyl chloride (0.29 mL, 4.63 mmol) in CH_2Cl_2 (5 mL) was added a solution of allyl amine **139** (0.68 g, 4.63 mmol) with Et_3N (1.3 mL, 9.25 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at rt for 2 h. The reaction was quenched with sat. NH_4Cl (10 mL) and the phases separated. The organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to yield the desired product **140** as a white solid (0.54 g, 2.59 mmol, 56%).

Procedure B

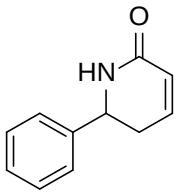
Benzaldehyde (0.50 g, 4.72 mmol), acrylamide (0.45 g, 7.08 mmol) and allyltrimethylsilane (1.1 mL, 7.08 mmol) were dissolved in MeCN (10 mL). The solution was cooled to 0 °C before $BF_3{\cdot}OEt_2$ (1.1 mL, 8.90 mmol) was added. The reaction mixture as stirred for 30 min at 0 °C, then allowed to warm to rt and stirred for a further 96 h. The solution was poured into sat. *aq*. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were then dried (Na_2SO_4), filtered and removed *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to yield the desired product **140** as a white solid (0.62 g, 3.11 mmol, 66%).

Procedure C

To a solution of benzaldehyde (0.20 g, 1.88 mmol) in MeCN (2 mL), acrylamide (0.38 g, 5.66 mmol) was added. After cooling to 0 °C, $BF_3{\cdot}OEt_2$ (0.23 mL, 1.88 mmol) was added slowly and the reaction mixture was stirred for 15 min. The solution was allowed to warm to rt and then stirred for a further 5 h. Following this time, allyltrimethylsilane (0.59 mL, 3.76 mmol) and $BF_3{\cdot}OEt_2$ (0.23 mL, 1.88 mmol) were added and the resulting mixture was stirred for 17 h. The solution was poured into sat. *aq*. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to yield the desired product **140** as a white solid (0.33 g, 1.65 mmol, 88%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.38-7.25 (5H, m, Ar-*H*), 6.31 (1H, dd, J_H = 16.8, 2.0 Hz, COCHCH*H*), 6.13 (1H, dd, J_H = 16.8, 10.0 Hz, COC*H*CH_2), 5.88 (1H, m, N*H*), 5.78-5.60 (2H, m, COCHC*H*H and CH_2C*H*CH_2), 5.22-5.10 (3H, m, CH_2CHCH_2 and C*H*NH), 2.64 (2H, t, J_H = 6.8 Hz, CHCH_2CH).
^{13}C ($CDCl_3$, 125 MHz) δ: 164.7 (*C*O), 141.4 (Ar*C*-CHN), 133.9 (*C*HCH_2), 130.8 (CO*C*H) 128.6 (2C, Ar-*C*), 127 4 (Ar-*C*), 126.7 (COCH*C*H_2) 126.5 (2C, Ar-*C*), 118.3 (CH*C*H_2), 52.1 (*C*HNH), 40.4 (CH*C*H_2CH).
The spectral data is in agreement with the literature values.[142]

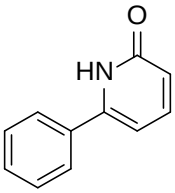
6-Phenyl-5,6-dihydro-1*H*-pyridin-2-one, 142.[143]



To a solution of dialkene **140** (0.10 g, 0.50 mmol) in CH_2Cl_2 (5.5 mL) was added Grubbs I catalyst (10 mol%, 40 mg, 50 µmol) and the reaction was stirred at reflux for 17 h. The solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (10 - 30% EtOAc in petroleum ether) to yield the desired product **142** as a grey solid (80 mg, 0.45 mmol, 90 %).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.39-7.42 (5H, m, Ar-*H*), 6.68 (1H, ddd, J_H = 10.0, 5.6, 3.2 Hz, COCHC*H*), 6.06 (1H, d, J_H = 10.0 Hz, COC*H*), 5.57 (1H, br s, N*H*) 4.77 (1H, dd, J_H = 10.8, 5.6 Hz, C*H*NH), 2.55 (2H, m, CHCH_2CH).
^{13}C ($CDCl_3$, 125 MHz) δ: 166.5 (*C*O), 141.1 (Ar*C*-CHN), 140.2 (COCH*C*H_2), 129.0 (2C, Ar-*C*), 128.4 (Ar-*C*) 126.4 (2C, Ar-*C*), 124.6 (CO*C*H), 55.9 (*C*HNH), 33.13 (CH*C*H_2CH).
The spectral data is in agreement with the literature values.[143]

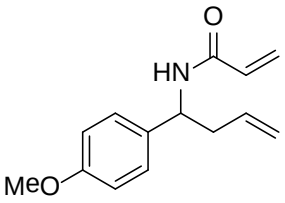
6-Phenyl-1*H*-pyridin-2-one, 143.[144]



To a solution of amide **142** (30 mg, 0.19 mmol) in toluene (5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (70 mg, 0.29 mmol) and the reaction was stirred at reflux for 17 h. The solvent was removed *in vacuo* and the crude residue purified by flash column chromatography (10 - 30% EtOAc in petroleum ether) to yield the desired product **143** as a white solid (20 mg, 0.13 mmol, 68%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.72 (1H, dd, J_H = 8.0, 1.6 Hz, COCHC*H*), 7.54-7.47 (5H, m, Ar-*H*), 6.56 (1H, d, J_H = 9.2 Hz, COC*H*), 6.51 (2H, d, J_H = 7.2 Hz, NHCC*H*).
^{13}C ($CDCl_3$, 125 MHz) δ: 164.7 (*C*O), 146.7 (*C*NH), 141.4 (COCH*C*H_2), 133.5 (Ar*C*-CHN), 130.1 (2C, Ar-*C*), 129.3 (Ar-*C*) 126.5 (2C, Ar-*C*), 118.8 (CO*C*H), 104.7 (NHC*C*H).
The spectral data is in agreement with the literature values.[144]

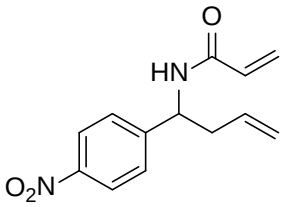
***N*-[1-(4-Methoxyphenyl)-3-buten-1-yl]-propenamide, 145.**[68]



To a solution of 4-methoxybenzaldehyde (0.17 mL, 1.46 mmol) in MeCN (2 mL), acrylamide (0.31 g, 4.38 mmol) was added. After cooling to 0 °C, $BF_3{\cdot}OEt_2$ (0.17 mL, 1.46 mmol) was added slowly and the reaction mixture was stirred for 15 min. The solution was allowed to warm to rt and then stirred for a further 6 h. Following this time, allyltrimethylsilane (0.46 mL, 2.92 mmol) and $BF_3{\cdot}OEt_2$ (0.17 mL, 1.46 mmol) were added and the resulting mixture was stirred for 17 h. The solution was poured into sat. *aq*. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to yield the desired product **145** as a white solid (0.27 g, 1.17 mmol, 83%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.27 (2H, d, J_H = 8.4 Hz, Ar-*H*), 6.81 (2H, d, J_H = 8.4 Hz, Ar-*H*), 6.27 (1H, dd, J_H = 16.8, 1.6 Hz, COCHCH*H*), 6.11 (1H, dd, J_H = 17.2, 10.4 Hz, COC*H*CH_2), 5.77-5.71 (1H, m, CH_2C*H*CH_2), 5.91 (1H, d, J_H = 7.6 Hz, N*H*), 5.64 (1H, dd, J_H = 10.4, 1.6 Hz, COCHC*H*H), 5.15-5.10 (3H, m, CH_2CHC*H*$_2$ and C*H*NH), 3.80 (3H, s, OCH_3), 2.64-2.60 (2H, m, CHC*H*$_2$CH).
^{13}C ($CDCl_3$, 125 MHz) δ: 164.7 (*C*O), 158.9 (*C*OMe), 134.1 (*C*HCH_2), 133.6 (Ar*C*-CHN), 130.9 (CO*C*H) 127.7 (2C, Ar-*C*), 126.7 (COCH*C*H_2) 118.1 (CH*C*H_2), 114.0 (2C, Ar-*C*), 55.3 (OCH_3), 52.0 (*C*HNH), 40.3 (CH*C*H_2CH).
The spectral data is in agreement with the literature values.[68]

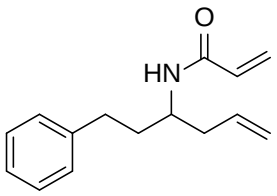
***N*-[1-(4-Nitro-phenyl)-but-3-enyl]-propenamide, 146.**



To a solution of 4-nitrobenzaldehyde (0.20 g, 1.3 mmol) in MeCN (2 mL), acrylamide (0.28 g, 4.0 mmol) was added. After cooling to 0 °C, $BF_3{\cdot}OEt_2$ (0.16 mL, 1.3 mmol) was added slowly and the reaction mixture was stirred for 15 min. The solution was allowed to warm to rt and then stirred for a further 6 h. Allyltrimethylsilane (0.41 mL, 2.64 mmol) and $BF_3{\cdot}OEt_2$ (0.40 mL, 3.4 mmol) were added and the resulting mixture was stirred for 17 h. The solution was poured into sat. *aq.* $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to yield the desired product **146** as a white solid (0.11 g, 0.44 mmol, 34%).

^{1}H ($CDCl_3$, 400 MHz) δ: 8.11 (2H, d, J_H = 8.5 Hz, Ar-*H*), 7.38 (2H, d, J_H = 8.5 Hz, Ar-*H*) 6.38 (1H, dd, J_H = 16.5, 1.0 Hz, COCHCH*H*), 6.14 (1H, d, J_H = 7.0 Hz, N*H*), 6.08 (1H, dd, J_H = 16.5, 10.0 Hz, COC*H*CH_2), 5.63-5.53 (2H, m, COCHC*H*H and CH_2C*H*CH_2), 5.13-5.07 (3H, m, CH_2CHC*H*$_2$ and C*H*NH), 2.53-2.50 (2H, m, CHC*H*$_2$CH).
^{13}C ($CDCl_3$, 125 MHz) δ: 165.0 (*C*O), 149.1 (*C*NO_2), 147.2 (Ar*C*-CHN), 132.7 (*C*HCH_2), 130.1 (CO*C*H), 127.6 (COCH*C*H_2), 127.3 (2C, Ar-*C*), 123.9 (2C, Ar-*C*), 119.5 (CH*C*H_2), 52.3 (*C*HNH), 40.2 (CH*C*H_2CH).
m/z [EI (+ve)] 246.2 $[M]^+$, HRMS found $[M]^+$ 246.1003, $C_{13}H_{14}N_2O_3$ requires 246.1004.
IR (thin film) ν_{max} = 3290, 3090, 2920, 1680, 1610, 1525, 1510 cm^{-1}.
m.p. 84-86 ˚C.

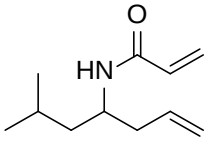
***N*-(1-Phenethyl-but-3-enyl)-propenamide, 147.**



To a solution of 3-phenylpropionaldehyde (0.20 mL, 1.49 mmol) in MeCN (2 mL), acrylamide (0.32 g, 4.47 mmol) was added. After cooling to 0 °C, $BF_3{\cdot}OEt_2$ (0.18 mL, 1.49 mmol) was added slowly and the reaction mixture was stirred for 15 min. The solution was allowed to warm to rt and then stirred for a further 6 h. Allyltrimethylsilane (0.47 mL, 2.98 mmol) and $BF_3{\cdot}OEt_2$ (0.18 mL, 1.78 mmol) were added and the resulting mixture was stirred for 17 h. The solution was poured into sat. *aq*. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (10% EtOAc in petroleum ether) to yield the desired product **147** as a white solid (0.22 g, 1.00 mmol, 66%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.32-7.19 (5H, m, Ar-*H*), 6.31 (1H, dd, J_H = 17.2, 1.2 Hz, COCHCH*H*), 6.08 (1H, dd, J_H = 17.2, 10.4 Hz, COC*H*CH_2), 5.85-5.75 (1H, m, CH_2C*H*CH_2), 5.66 (1H, dd, J_H = 10.4, 1.6 Hz, COCHC*H*H), 5.53 (1H, d, J_H = 8.4, N*H*), 5.13-5.09 (2H, m, CH_2CHCH_2), 4.17-4.15 (1H, m, C*H*NH), 2.70 (2H, t, J_H = 8.4 Hz, $PhCH_2$) 2.35-2.31 (2H, m, CHCH_2CH), 1.86-1.83 (2H, m, $PhCH_2CH_2$).
^{13}C ($CDCl_3$, 125 MHz) δ: 164.7 (*C*O), 141.7 (Ar*C*-CH_2), 134.0 (*C*HCH_2), 131.0 (CO*C*H), 128.5 (2C, Ar-*C*), 128.4 (2C, Ar-*C*), 126.4 (COCH*C*H_2) 125.9 (Ar-*C*), 118.2 (CH*C*H_2), 48.6 (*C*HNH), 39.2 (Ph-*C*H_2), 36.2 (CH*C*H_2CH), 32.4 ($PhCH_2$*C*H_2).
m/z [EI (+ve)] 229.2 $[M]^+$, HRMS found $[M]^+$ 229.1465, $C_{15}H_{19}NO$ requires 229.1467.
IR (thin film) ν_{max} = 3250, 3100, 2920, 1640, 1605, 1550 cm^{-1}.
m.p. 85-87 ˚C.

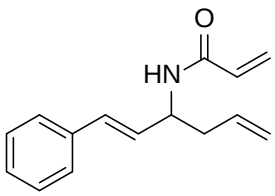
***N*-(1-Isobutyl-but-3-enyl)-propenamide, 148.**[145]



To a solution of isovaleraldehyde (0.25 mL, 2.33 mmol) in MeCN (2 mL), acrylamide (0.49 g, 6.99 mmol) was added. After cooling to 0 °C, $BF_3{\cdot}OEt_2$ (0.28 mL, 2.33 mmol) was added slowly and the reaction mixture was stirred for 15 min. The solution was allowed to warm to rt and then stirred for a further 6 h. Allyltrimethylsilane (0.72 mL, 4.66 mmol) and $BF_3{\cdot}OEt_2$ (0.28 mL, 2.33 mmol) were added and the resulting mixture was stirred for 17 h. The solution was poured into sat. *aq*. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to yield the desired product **148** as a white solid (0.36 g, 2.00 mmol, 86%).

^{1}H ($CDCl_3$, 400 MHz) δ: 6.29 (1H, dd, J_H = 17.2, 1.6 Hz, COCHCH*H*), 6.06 (1H, dd, J_H = 17.2, 10.4 Hz, COC*H*CH_2), 5.85-5.74 (1H, m, CH_2C*H*CH_2), 5.63 (1H, dd, J_H = 10.4, 1.6 Hz, COCHC*H*H), 6.15-6.13 (1H, m, N*H*), 5.08-5.06 (2H, m, CH_2CHC*H*$_2$), 4.19-4.17 (1H, m, C*H*NH), 2.31-2.28 (2H, m, CHC*H*$_2$CH), 1.66-1.64 (1H, m, C*H*$(CH_3)_2CH_2$), 1.35-1.32 (2H, m, CH$(CH_3)_2$C*H*$_2$), 0.98 (3H, d, J_H = 6.6 Hz, C*H*$_3$), 0.96 (3H, d, J_H = 6.6 Hz, C*H*$_3$).
^{13}C ($CDCl_3$, 125 MHz) δ: 165.0 (*C*O), 134.3 (*C*HCH_2), 131.1 (CO*C*H), 127.6 (COCH*C*H$_2$), 117.8 (CH*C*H$_2$), 46.8 (*C*HNH), 43.7 (CH*C*H$_2$CH), 39.7 (CH$(CH_3)_2$*C*H$_2$), 24.9 (*C*H$(CH_3)_2CH_2$) 23.1 (*C*H$_3$CHCH$_3$), 23.1 (CH$_3$CH*C*H$_3$).
The spectral data is in agreement with the literature values.[145]

(E)-*N*-(1-Phenylhexa-1,5-dien-3-yl)acrylamide, 151.[99]



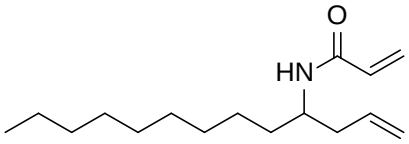
To a solution of cinnamaldehyde (0.20 mL, 1.5 mmol) in MeCN (2 mL), acrylamide (0.32 g, 4.5 mmol) was added. After cooling to 0 °C, $BF_3{\cdot}OEt_2$ (0.18 mL, 1.5 mmol) was added slowly and the reaction mixture was stirred for 15 min. The solution was allowed to warm to rt and then stirred for a further 6 h. Allyltrimethylsilane (0.48 mL, 3.0 mmol) and $BF_3{\cdot}OEt_2$ (0.37 mL, 3.0 mmol) were added and the resulting mixture was stirred for 17 h. The solution was poured into sat. *aq*. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (15% EtOAc in petroleum ether) to yield the desired product **151** as a white solid (70 mg, 0.16 mmol, 20%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.27-7.11 (5H, m, Ar-*H*), 6.45 (1H, dd, J_H = 16.8, 1.6 Hz, COCHCH*H*), 6.24 (1H, dd, J_H =10.8, 1.6 Hz, PhCHC*H*), 6.12 (1H, dd, J_H =16.8, 6.5 Hz, COC*H*CH_2), 6.03 (1H, d, J_H = 10.8 Hz, PhC*H*), 5.75-5.70 (2H, m, CH_2C*H*CH_2 and N*H*), 5.59 (1H, dd, J_H = 6.5, 1.6 Hz, COCHC*H*H), 5.14-5.08 (2H, m, CH_2CHCH_2), 4.76-4.74 (1H, m, C*H*NH), 2.41-2.37 (2H, m, CHCH_2CH).

^{13}C ($CDCl_3$, 125 MHz) δ: 164.8 (*C*O), 136.6 (Ar*C*-CH_2), 133.7 (*C*HCH_2), 130.9 (2C, Ph*C*H and CO*C*H), 128.9 (Ar-*C*), 128.6 (2C, Ar-*C*H), 127.7 (Ph*C*HCH) 126.7 (COCH*C*H_2), 126.4 (2C, Ar-*C*H), 118.6 (CH*C*H_2), 50.0 (*C*HNH), 39.4 (Ph-*C*H_2).

The spectral data is in agreement with the literature values.[99]

_N_-(1-Allyl-decyl)-propenamide, 152.



To a solution of decanal (0.24 mL, 1.28 mmol) in MeCN (2 mL), acrylamide (0.27 g, 3.84 mmol) was added. After cooling to 0 °C, $BF_3{\cdot}OEt_2$ (0.15 mL, 1.30 mmol) was added slowly and the reaction mixture was stirred for 15 min. The solution was allowed to warm to rt and then stirred for a further 6 h. Following this time, allyltrimethylsilane (0.40 mL, 2.56 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mL, 1.28 mmol) were added and the resulting mixture was stirred for 17 h. The solution was poured into sat. *aq*. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography (5% EtOAc in petroleum ether) to yield the desired product **152** as a white solid (0.29 g, 1.19 mmol, 91%).

^{1}H ($CDCl_3$, 400 MHz) δ: 6.18 (1H, dd, J_H = 16.8, 1.6 Hz, COCHCH*H*), 5.98 (1H, dd, J_H = 16.8, 10.4 Hz, COC*H*CH_2), 5.75-5.64 (1H, m, CH_2C*H*CH_2), 5.54 (1H, dd, J_H = 10.4, 1.6 Hz, COCHC*H*H), 5.26 (1H, d, J_H = 8.8 Hz, N*H*), 5.01-4.96 (2H, m, CH_2CHCH_2), 4.02-4.01 (1H, m, C*H*NH), 2.23-2.20 (2H, m, CHCH_2CH), 1.34-1.31 (2H, m, C$H_2(CH_2)_7$), 1.19-1.08 (14H, m, $CH_2(CH_2)_7CH_3$), 0.84-0.80 (3H, m, $CH_2(CH_2)_8CH_3$).

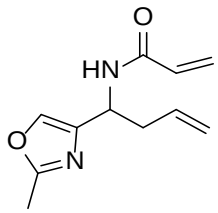
^{13}C ($CDCl_3$, 100 MHz) δ: 165.0 (*C*O), 134.3 (*C*HCH_2), 131.1 (CO*C*H), 126.1 (COCH*C*H_2), 117.9 (CH*C*H_2), 48.7 (*C*HNH), 39.1 (CH*C*H_2CH), 34.4 (*C*H_2), 31.9 (*C*H_2), 29.5 (*C*H_2), 29.5 (*C*H_2), 29.3 (*C*H_2), 25.9 (*C*H_2), 25.5 (*C*H_2), 22.7 (*C*H_2), 14.1 (*C*H_3).

m/z [EI (+ve)] 251.2 $[M]^+$, HRMS found $[M]^+$ 251.2244, $C_{16}H_{29}NO$ requires 251.2249.

IR (thin film) ν_{max} = 3267, 2924, 2854, 1654, 1548, 1263, 1099 cm^{-1}.

m.p. 56-58 ˚C.

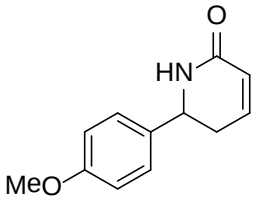
***N*-[1-(2-Methyl-oxazol-4-yl)-but-3-enyl]-propenamide, 153.**



To a solution of 2-methyl-oxazole-4-carbaldehyde (0.20 g, 1.8 mmol) in MeCN (2 mL), acrylamide (0.38 g, 5.4 mmol) was added. After cooling to 0 °*C*, $BF_3{\cdot}OEt_2$ (0.22 mL, 1.8 mmol) was added slowly and the reaction mixture was stirred for 15 min. The solution was allowed to warm to rt and then stirred for a further 6 h. Following this time, allyltrimethylsilane (0.57 mL, 3.6 mmol) and $BF_3{\cdot}OEt_2$ (0.22 mL, 1.8 mmol) were added and the resulting mixture was stirred for 17 h. The solution was poured into sat. *aq*. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc in petroleum ether) to yield the desired product **153** as a yellow oil (0.16 g, 0.76 mmol, 42%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.36 (1H, s, C*H*CO), 6.23 (1H, dd, J_H = 17.2, 1.6 Hz, COCHCH*H*), 6.15 (1H, m, N*H*), 6.01 (1H, dd, J_H = 17.2, 10.0 Hz, COC*H*CH_2), 5.70-5.60 (1H, m, CH_2C*H*CH_2), 5.57 (1H, dd, J_H = 10.0, 1.6 Hz, COCHC*H*H) 5.08-5.00 (3H, m, CH_2CHC*H*$_2$ and C*H*NH), 2.54-2.52 (2H, m, CHC*H*$_2$CH), 3.37 (3H, s, C*H*$_3$).
^{13}C ($CDCl_3$, 100 MHz) δ: 164.9 (*C*O), 161.9 (N*C*(CH_3)O), 139.8 (CH*C*(CH)N), 134.6 (*C*HCH_2), 133.7 (Ar-CH), 130.7 (CO*C*H), 126.7 (COCH*C*H_2), 118.2 (CH*C*H_2), 45.2 (*C*HNH), 38.6 (CH*C*H_2CH),14.0 (*C*H_3).
m/z [ESI (+ve)] 229.1 $[M+Na]^+$, HRMS found $[M+Na]^+$ 229.0943, $C_{11}H_{14}N_2O_2Na$ requires 229.0947.
IR (thin film) ν_{max} = 3267, 1656, 1539, 1408, 1244, 1099 cm^{-1}.

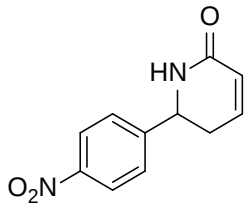
5,6-Dihydro-6-(4-methoxyphenyl)pyridin-2(1*H*)-one, 156.[68]



To a solution of dialkene **145** (0.10 g, 0.43 mmol) in CH_2Cl_2 (5.5 mL) was added Grubbs I catalyst (10 mol%, 40 mg, 40 µmol) and the reaction was stirred at reflux for 17 h. The mixture was removed *in vacuo* and the crude material was purified by flash column chromatography (10 - 30% EtOAc in petroleum ether) to yield the desired product **156** as a grey solid (90 mg, 0.43 mmol, quantitative).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.31 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.93 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.67 (1H, ddd, J_H = 10.0, 5.2, 3.6 Hz, COCHC*H*), 6.03 (1H, d, J_H = 10.0 Hz, COC*H*), 5.50 (1H, br s, N*H*), 4.70 (1H, dd, J_H = 10.0, 6.4 Hz, C*H*NH), 3.84 (3H, s, OCH_3), 2.52 (2H, m, CHCH_2CH).
^{13}C ($CDCl_3$, 125 MHz) δ: 166.5 (*C*O), 159.6 (Ar-*C*OCH_3), 140.3 (COCH*C*H), 133.1 (Ar*C*-CHN), 127.7 (2C, Ar-*C*), 124.6 (CO*C*H), 114.3 (2C, Ar-*C*), 55.4 (*C*HNH), 55.3 (OCH_3), 33.2 (CH*C*H_2CH).
The spectral data is in agreement with the literature values.[68]

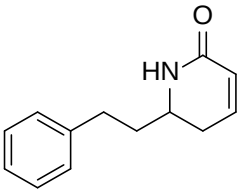
5,6-Dihydro-6-(4-nitrophenyl)pyridin-2(1*H*)-one, 157.[146]



To a solution of dialkene **146** (0.10 g, 0.40 mmol) in CH_2Cl_2 (5.5 mL) was added Grubbs I catalyst (10 mol%, 30 mg, 40 µmol) and the reaction was stirred at reflux for 17 h. The mixture was removed *in vacuo* and the crude material was purified by flash column chromatography (15 - 40% EtOAc in petroleum ether) to yield the desired product **157** as a grey solid (90 mg, 0.40 mmol, quantitative).

^{1}H ($CDCl_3$, 400 MHz) δ: 8.17 (2H, d, J_H = 8.8 Hz, Ar-*H*), 7.48 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.55 (1H, m, COCHC*H*), 6.15 (1H, br s, N*H*), 5.96 (1H, d, J_H = 8.0 Hz, COC*H*), 4.82 (1H, dd, J_H = 8.0, 4.8 Hz, C*H*NH), 2.63 (1H, m, CHC*H*HCH), 2.43 (1H, m, CHCH*H*CH).
^{13}C ($CDCl_3$, 125 MHz) δ: 166.3 (*C*O), 148.4 (Ar-*C*NO_2), 147.9 (Ar*C*-CHN), 139.5 (COCH*C*H), 127.3 (2C, Ar-*C*H), 124.8 (CO*C*H), 124.3 (2C, Ar–*C*H), 55.0 (*C*HNH), 32.6 (CH*C*H_2CH).
The spectral data is in agreement with the literature values.[146]

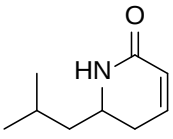
5,6-Dihydro-6-(phenylpropionyl)pyridin-2(1*H*)-one, 158.



To a solution of dialkene **147** (0.10 g, 0.44 mmol) in CH_2Cl_2 (5.5 mL) was added Grubbs I catalyst (10 mol%, 40 mg, 40 µmol) and the reaction was stirred at reflux for 17 h. The mixture was removed *in vacuo* and the crude material was purified by flash column chromatography (15 - 30% EtOAc in petroleum ether) to yield the desired product **158** as a grey solid (80 mg, 0.41 mmol, 94%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.34-7.20 (5H, m, Ar-*H*), 6.24-6.21 (1H, m, COCHC*H*), 5.93 (1H, dd, J_H = 9.6, 1.2 Hz, COC*H*), 5.84 (1H, br s, N*H*), 3.63-3.62 (1H, m, C*H*NH), 2.74-2.70 (2H, m, PhCH_2), 2.44-2.41 (1H, m, CHC*H*HCH), 2.26-2.24 (1H, m, CHCH*H*CH), 1.91-1.89 (2H, m, $PhCH_2CH_2$).
^{13}C ($CDCl_3$, 125 MHz) δ: 166.1 (*C*O), 140.6 (Ar*C*-CH_2), 140.1 (COCH*C*H), 128.6 (2C, Ar-*C*H), 128.2 (Ar-*C*H), 126.3 (2C, Ar-*C*H), 124.6 (CO*C*H), 50.5 (*C*HNH), 37.1 (CH_2), 31.6 (CH_2), 29.9 (CH_2).
m/z [EI (+ve)] 201.2 $[M]^+$, HRMS found $[M]^+$ 201.1153, $C_{13}H_{15}NO$ requires 201.1154.
IR (thin film) ν_{max} = 3059, 2922, 2868, 1676, 1608, 1415, 1325 cm^{-1}.
m.p. 116-118 ˚C.

5,6-Dihydro-6-(isobutyl)pyridin-2(1*H*)-one, 159.[145]



To a solution of dialkene **148** (0.12 g, 0.67 mmol) in CH_2Cl_2 (9.1 mL) was added Grubbs I catalyst (10 mol%, 60 mg, 70 µmol) and the reaction was stirred at reflux for 17 h. The mixture was removed *in vacuo* and the crude material purified by flash column chromatography (15 - 20% EtOAc in petroleum ether) to yield the desired product **159** as a grey solid (90 mg, 0.56 mmol, 84%).

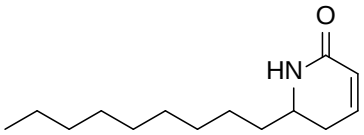
^{1}H ($CDCl_3$, 400 MHz) δ: 6.62 (1H, m, COCHC*H*), 5.92 (1H, d, J_H = 8.8 Hz, COC*H*), 5.61 (1H, br s, N*H*), 3.70-3.69 (1H, m, C*H*NH), 2.38-2.36 (1H, m, CHC*H*HCH), 2.16-2.14 (1H,

m, CHCH*H*CH), 1.71 (1H, quint, J_H = 6.8 Hz, C*H*$(CH_3)_2CH_2$), 1.45-1.43 (2H, m, $CH(CH_3)_2CH_2$), 0.96 (3H, d, J_H = 6.6 Hz, CH_3), 0.94 (3H, d, J_H = 6.6 Hz, CH_3).

^{13}C ($CDCl_3$, 125 MHz) δ: 165.0 (*C*O), 140.5 (COCH*C*H), 124.8 (CO*C*H), 49.1 (*C*HNH), 44.8 ($CHCH_2CH$), 30.5 ($CH(CH_3)_2CH_2$), 24.3 (CH_3CHCH_3), 22.7 (CH_3CHCH_3), 22.2 ($CH(CH_3)_2CH_2$).

The spectral data is in agreement with the literature values.[145]

5,6-Dihydro-6-(decanyl)pyridin-2(1*H*)-one, 160.



To a solution of dialkene **152** (0.10 g, 0.40 mmol) in CH_2Cl_2 (5.5 mL) was added Grubbs I catalyst (10 mol%, 30 mg, 40 μmol) and the reaction was stirred at reflux for 17 h. The mixture was removed *in vacuo* and the crude material was purified by flash column chromatography (15 - 20% EtOAc in petroleum ether) to yield the desired product **160** as a grey solid (80 mg, 0.35 mmol, 90%).

^{1}H ($CDCl_3$, 400 MHz) δ: 6.53 (1H, m, COCHC*H*), 5.83 (1H, dd, J_H = 8.0, 0.8 Hz, COC*H*), 5.54 (1H, br s, N*H*), 3.50 (1H, sept, J_H = 4.8 Hz, C*H*NH), 2.33-2.30 (1H, m, CHC*H*HCH), 2.08-2.06 (1H, m, CHCH*H*CH), 1.44-1.41 (2H, m, C$H_2(CH_2)_8CH_3$), 1.23-1.18 (14H, m, $CH_2(CH_2)_7CH_3$), 0.81 (3H, t, J_H = 5.6 Hz, $CH(CH_2)_8CH_3$).

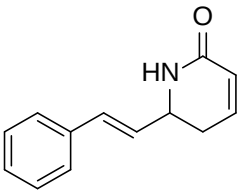
^{13}C ($CDCl_3$, 125 MHz) δ: 166.5 (*C*O), 140.7 (COCH*C*H), 124.5 (CO*C*H), 51.1 (*C*HNH), 35.5 (CH_2), 31.9 (CH_2), 30.0 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

m/z [EI (+ve)] 223.3 $[M]^+$, HRMS found $[M]^+$ 223.1933, $C_{14}H_{25}NO$ requires 223.1936.

IR (thin film) ν_{max} = 2924, 2852, 2360, 1678, 1610, 1419, 1309 cm^{-1}.

m.p. 38-40 ˚C.

(E)-6-Styryl-5,6-dihydropyridin-2(1*H*)-one, 161.[99]

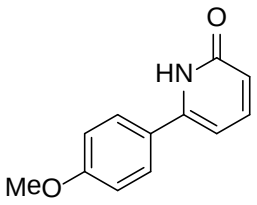


To a solution of dialkene **151** (80 mg, 0.35 mmol) in CH_2Cl_2 (5.5 mL) was added Grubbs I catalyst (10 mol%, 30 mg, 40 μmol) and the reaction was stirred at reflux for 17 h. The

mixture was removed *in vacuo* and the crude material was purified by flash column chromatography (15 - 30% EtOAc in petroleum ether) to yield the desired product **161** as a grey solid (50 mg, 0.24 mmol, 68%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.39-7.29 (5H, m, Ar-*H*), 6.69-6.59 (2H, m, COCHC*H* and PhC*H*), 6.22 (1 H, dd, J_H = 15.6, 7.6 Hz, PhCHC*H*), 5.99 (1H, d, J_H = 8.4 Hz, COC*H*), 5.68 (1H, br s, N*H*), 4.34-4.32 (1H, m, C*H*NH), 2.57-2.55 (1H, m, CHC*H*HCH), 2.42-2.39 (1H, m, CHCH*H*CH).
^{13}C ($CDCl_3$, 100 MHz) δ: 165.9 (*C*O), 139.8 (COCH*C*H), 135.9 (Ar*C*-CH_2), 134.3 (Ph*C*H), 128.8 (2C, Ar-*C*H), 128.5 (Ar-*C*H), 128.2 (PhCH*C*H), 126.6 (2C, Ar-*C*H), 124.7 (CO*C*H), 53.7 (*C*HNH), 30.6 (CH_2).
The spectral data is in agreement with the literature values.[99]

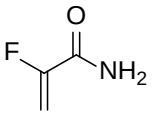
6-(4-Methoxyphenyl)-1*H*-pyridin-2-one, 163.



To a solution of amide **156** (60 mg, 0.30 mmol) in toluene (6 mL) was added 2, 3-dichloro-5,6-dicyano-1,4-benzoquinone (0.10 g, 0.45 mmol) and the reaction was stirred at reflux for 17 h. The solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (0 - 40% EtOAc in petroleum ether) to yield the desired product **163** as a white solid (50 mg, 0.23 mmol, 76%).

^{1}H ($CDCl_3$, 400 MHz) δ: 10.9 (1H, br s, N*H*), 7.63-7.34 (3H, m, Ar-*H* and COCHC*H*), 6.94 (2H, br s, Ar-*H*), 6.44 (1H, br s, COC*H*), 6.30 (1H, br s, PhCC*H*), 3.80 (3H, br s, OCH_3).
^{13}C ($CDCl_3$, 125 MHz) δ: 161.2 (2C, *C*O and Ar-*C*OCH_3), 128.14 (2C, Ar-*C*H), 126.0 (2C, Ar*C*-CHN and COCHC*H*), 114.7 (4C, CO*C*H, NH*C*CH and Ar-*C*H), 104.5 (NHC*C*H), 55.4 (O*C*H_3),
m/z [EI (+ve)] 201.1 $[M]^+$, HRMS found $[M]^+$ 201.0788, $C_{12}H_{11}O_2N$ requires 201.0790.
IR (thin film) ν_{max} = 2924, 1643, 1608, 1253 cm^{-1}.
m.p. 203-205 ˚C.

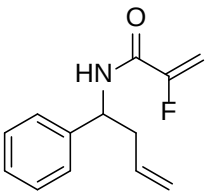
2-Fluoro-acrylamide, 181.[82]



Methyl ester **136** (0.89 mL, 9.61 mmol) was dissolved in a solution of 28-30% NH_4OH (10 mL) and the mixture stirred at rt until completion (20 h). The solvent was removed *in vacuo* and the resulting material azeotroped with $CHCl_3$ (3 × 2 mL) to leave **181** as a white solid (0.70 g, 7.86 mmol, 80%).

^1H ($CDCl_3$, 400 MHz) δ: 6.15 (2H, br s, NH_2), 5.73 (1H, dd, J_F = 47.2, J_H = 3.6 Hz, C*H*H), 5.20 (1H, dd, J_F = 14.8, J_H = 3.6 Hz, CH*H*).
^{19}F (D_2O, 400 MHz) δ: -118.5.
^{13}C (D_2O, 125 MHz) δ: 164.4 (d, J_F = 33.8 Hz, *C*O), 155.0 (d, J_F = 262.5 Hz, *C*F), 100.5 (d, J_F = 15.0, *C*H_2).
The spectral data is in agreement with the literature values.[82]

2-Fluoro-*N*-(1-phenyl-but-3-enyl)-propenamide, 182.

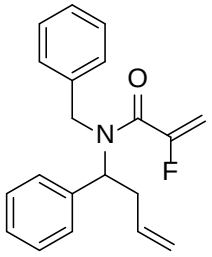


A solution of 2-fluoroacylic acid **135** (0.41 g, 4.50 mmol) in CH_2Cl_2 (25 mL) was treated with HBTU (2.6 g, 6.82 mmol) and was then cooled down to 0 °C. DIPEA (1.2 mL, 6.96 mmol) and amine **139** (0.80 g, 5.43 mmol) were sequentially added, and the reaction was stirred for 1 h. The solvent was removed *in vacuo*, and the crude residue was purified by flash column chromatography (0 - 5% EtOAc in petroleum ether) to yield the desired product **182** as a white solid (0.89 g, 4.06 mmol, 89%).

^1H ($CDCl_3$, 400 MHz) δ: 7.40-7.29 (5H, m, Ar-*H*), 6.57 (1H, br s, N*H*), 5.70 (2H, m, CFCH*H* and CH_2CHCH_2), 5.19-5.12 (4H, m, CFC*H*H, CH_2CHCH_2 and C*H*NH), 2.65 (2H, t, J_H = 6.8 Hz, $CHCH_2CH$).
^{19}F ($CDCl_3$, 400 MHz) δ: -121.3.

^{13}C ($CDCl_3$, 125 MHz) δ: 158.8 (d, J_F = 30.0 Hz, *C*O), 156.2 (d, J_F = 268.8 Hz, COCF) 140.8 (Ar-*C*CHN), 133.4 (*C*HCH_2), 128.8 (2C, Ar-*C*H), 127.7 (Ar-*C*H), 126.5 (2C, Ar-*C*H), 118.3 (CH*C*H_2), 99.1 (d, J_F = 15.0 Hz, COCF*C*H_2), 52.6 (*C*HNH), 40.3 (CH*C*H_2CH).
m/z [CI (+ve)] 220.3 $[M+H]^+$, HRMS found $[M+H]^+$ 220.1135, $C_{13}H_{15}FNO$ requires 220.1138.
IR (thin film) ν_{max} = 3338, 1651, 1529, 1190 cm^{-1}.
m.p. 63-65 ˚C.

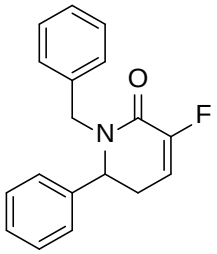
_N_-Benzyl-2-fluoro-N-(1-phenyl-but-3-enyl)-propenamide. 188.



2-Fluoroacrylic acid **135** (56 mg, 0.63 mmol) and HBTU (0.23 g, 0.63 mmol) were dissolved in CH_2Cl_2 (5 mL). DIPEA (0.11 mL, 0.63 mmol) was added followed by amine **192** (0.10 g, 0.42 mmol). The resulting solution was heated to reflux and stirred for 17 h. After which, the solvent removed *in vacuo* and the crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **188** (0.11 g, 0.38 mmol, 85%) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.37-7.05 (10H, m, Ar-*H*), 5.75-5.68 (1H, m, CH_2C*H*CH_2), 5.32 (1H, br. s, CFCH*H*), 5.28 (1H, br s, CFC*H*H), 5.11-5.04 (3H, m, CHCH_2 and PhC*H*H), 4.54 (1H, d, J_H = 16.0 Hz, PhCH*H*), 4.24 (1H, br. s, C*H*N), 2.75 (2H, br. s, CHCH_2CH).
^{19}F ($CDCl_3$, 400 MHz) δ: -102, -116.7.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.4 (d, J_F = 27.5 Hz, CO), 159.2 (d, J_F = 271.3, *C*F), 138.2 (Ar-*C*-CHN), 137.7 (Ar-*C*CH_2), 134.4 (*C*HCH_2,) 128.6 (2C, Ar-*C*H), 128.2 (2C, Ar-*C*H) 128.1 (2C, Ar-*C*H), 127.7 (2C, Ar-*C*H), 127.3 (Ar-*C*H), 127.2 (Ar-*C*H), 117.5 (CH*C*H_2), 99.4 (d, J_F = 15.0 Hz, CFCH_2), 61.3 (*C*HNH_2), 35.7 (CH*C*H_2CH), 28.6 (Ph*C*H_2).
m/z [EI (+ve)] 309.1 $[M]^+$, HRMS found $[M]^+$ 309.1526, $C_{20}H_{20}FNO$ requires 309.1529.
IR (thin film) ν_{max} = 3063, 1637, 1419, 1190, 1151 cm^{-1}.

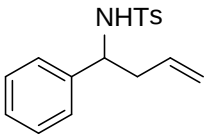
1-Benzyl-3-fluoro-6-phenyl-5,6-dihydro-1*H*-pyridin-2-one, 189.



Dialkene **188** (0.13 g, 0.44 mmol) was dissolved in toluene (52 mL). Grubbs 2nd generation catalyst (9.3 mg, 11 µmol, 2.5 mol%) was added and the resulting mixture was heated to 100 °C for 1 h The solvent was removed and the crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **189** as a colourless oil (0.12 g, 0.43 mmol, 98%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.37–7.05 (10H, m, Ar-*H*), 5.68 (1H, m, CFC*H*), 5.51 (1H, d, J_H = 14.8 Hz, PhC*H*H), 4.47 (1H, dd, J_H = 7.6, 2.4 Hz, C*H*N), 3.49 (1H, d, J_H = 14.8 Hz, PhCH*H*), 2.89 (1H, m, CHCH*H*CH), 2.40 (1H, m, CHC*H*HCH).
^{19}F ($CDCl_3$, 400 MHz) δ: -126.5.
^{13}C ($CDCl_3$, 125 MHz) δ: 159.9 (d, J_F = 30.0 Hz, *C*O), 149.4 (d, J_F = 252.5 Hz, COCF) 139.4 (Ar-*C*-CHN), 137.0 (Ar-*C*CH_2), 129.0 (2C, Ar-*C*H), 128.9 (Ar-*C*H), 128.7 (Ar-*C*H), 128.2 (Ar-*C*H), 128.1 (Ar-*C*H), 128.0 (Ar-*C*H), 127.7 (Ar-*C*H), 126.4 (Ar–*C*H), 125.3 (Ar-*C*H), 109.6 (d, J_F = 13.8 Hz, COCF*C*H), 57.4 (*C*HN), 47.9 (PhCH_2), 29.4 (d, J_F = 6.3 Hz, CHCH_2CH).
m/z [EI (+ve)] 281.2 $[M]^+$, HRMS found $[M]^+$ 281.1214, $C_{18}H_{16}FNO$ requires 281.1216.
IR (thin film) ν_{max} = 3066, 1653, 1452, 1219 cm^{-1}.

4-Methyl-*N*-(1-phenylbut-3-en-1-yl)methylbenzenesulfonamide, 191.[147]

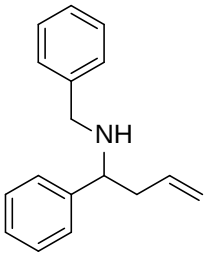


Amine **139** (0.10 g, 0.68 mmol) was dissolved in CH_2Cl_2 (5 mL). Et_3N (0.14 mL, 1.0 mmol) and DMAP (8.3 mg, 68 µmol) were added and the mixture was cooled to 0 °C. Tosyl chloride (0.19 g, 1.0 mmol) was added and the resulting solution was allowed to warm to rt and stirred for 17 h. The reaction mixture was diluted with CH_2Cl_2, washed with *aq*. $NaHCO_3$ (15 mL) and brine (15 mL). The organic phase was dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The crude residue was purified by flash column

chromatography (0 - 5% EtOAc in petroleum ether) to yield the desired product **191** as a white solid (0.13 g, 0.42 mmol, 86%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.56 (2H, d, J_H = 6.4 Hz, Ar-H), 7.24-7.02 (7H, m, Ar-*H*), 5.58-5.47 (1H, m, CH_2CHCH_2), 5.11-5.06 (2H, m, $CHCH_2$), 4.81 (1H, d, J_H = 6.4 Hz, N*H*), 4.39 (1H, q, J_H = 6.4 Hz, C*H*NH) 2.48 (2H, m, $CHCH_2CH$), 2.39 (3H, s, CH_3).
^{13}C ($CDCl_3$, 125 MHz) δ: 143.1 (Ar-*C*-CHN), 140.3 (Ar-*C*SO_2), 137.5 (Ar-*C*CH_3), 133.1 (*C*HCH_2,) 129.3 (2C, Ar-*C*H), 128.4 (2C, Ar-*C*H) 127.4 (2C, Ar-*C*H), 127.2 (2C, Ar-*C*H), 126.6 (Ar-*C*), 119.3 ($CHCH_2$), 57.1 (*C*HNH_2), 41.9 ($CHCH_2CH$), 21.4 (CH_3).
NMR data matches literature vales.[147]

_N_-Benzyl-1-phenylbut-3-en-1-amine, 192, [148]



Procedure A

Amine **139** (0.10 g, 0.68 mmol) and benzaldehyde (0.076 mL, 0.74 mmol) were added along with toluene (5 mL). The resulting mixture was heated to reflux and stirred for 3 h. The solution was filtered and the solvent was removed. The residue was redissovled in MeOH (5 mL), cooled to 0 °C and $NaBH_4$ (28 mg, 0.74 mmol) was added portionwise over 30 min. The reaction was stirred at 0 °C for 2 h followed by quenching with H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL) and the organic were combined, dried (Na_2SO_4), filtered and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 2.5% EtOAc in petroleum ether) to yield the desired product **192** as a pale yellow oil (0.11 g, 0.46 mmol, 68%).

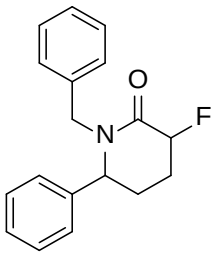
Procedure B

Benzaldehyde (0.95 mL, 9.43 mmol) was added along with toluene (15 mL). Benzamine (1.1 mL, 10.3 mmol) was added and the solution was heated to reflux for 3 h. After which, the mixture was filtered and the solvent was removed. The residue was redissolved in diethyl ether (20 mL) and cooled to 0 °C. Allyl magnesium bromide (1M in diethyl ether, 14.1 mmol, 14 mL) was added dropwise and the reaction was stirred at 0 °C for a further 1 h before being warmed to rt and stirred for 17 h. The reaction was quenched (H_2O, 10 mL) and extracted with diethyl ether (3 × 30 mL). The combined organics were dried (Na_2SO_4),

filtered and removed *in vacuo*. The crude product was purified by flash column chromatography (0 - 2.5% EtOAc in petroleum ether) to yield the desired product **192** as a pale yellow oil (1.8 g, 7.54 mmol, 80%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.41-7.28 (10H, m, Ar-*H*), 5.82-5.72 (1H, m, CH_2CHCH_2), 5.17-5.10 (2H, m, $CHCH_2$), 3.78 (2H, m, $CHNH_2$ and PhC*H*H), 3.58 (1H, d, J_H = 13.2 Hz, PhCH*H*), 2.43 (2H, m, $CHCH_2CH$), 1.79 (1H, br s, N*H*).
^{13}C ($CDCl_3$, 125 MHz) δ: 143.9 (Ar-*C*-CHN), 140.7 (Ar-*C*CH_2), 135.5 (*C*HCH_2), 128.4 (2C, Ar-*C*H), 128.4 (2C, Ar-*C*H) 128.1 (2C, Ar-*C*H), 127.3 (2C, Ar-*C*H), 127.1 (Ar-*C*H), 126.8 (Ar-*C*), 117.5 ($CHCH_2$), 61.7 ($CHNH_2$), 51.5 ($CHCH_2CH$), 43.2 (PhCH_2).
NMR data matches literature vales.[148]

1-Benzyl-3-fluoro-6-phenyl-piperidin-2-one, 193.



Procedure A

Fluoro-lactam **189** (42 mg, 0.14 mmol) was dissolved in MeOH (3 mL). Palladium on activated carbon (5.0 mg, 10% by weight) and ammonium formate (75 mg, 1.4 mmol) were added and the mixture was heated to reflux and stirred for 6 h. After this time, the suspension was filtered through celite and the filtrate was removed *in vacuo.* The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **193** as a white solid (23 mg, 82.0 μmol, 58%).

Procedure B

Palladium on activated carbon (11 mg, 10% by weight) was added to a solution of fluoro-lactam **189** (0.11 g, 0.38 mmol) in MeOH (5 mL) and the reaction was stirred under an atmosphere of H_2 for 6 h. After this time, the suspension was filtered through celite, the filtrate was removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **193** as a white solid (87 mg, 0.31 mmol, 81%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.35-7.03 (10H, m, Ar-*H*), 5.51 (1H, d, J_H = 14.8 Hz, PhC*H*H), 4.94 (1H, dt, J_F = 47.2 Hz, J_H = 7.2 Hz, CF*H*), 4.37 (1H, m, C*H*N), 3.33 (1H, dd, J_H = 14.8, 1.6 Hz, PhCH*H*), 2.00-1.88 (4H, m, CHCH_2CH$_2$ and CFHCH_2).

^{19}F ($CDCl_3$, 400 MHz) δ: -185.1.

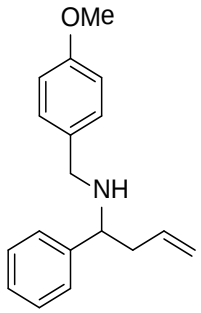
^{13}C ($CDCl_3$, 125 MHz) δ: 160.2 (d, J_F = 30.0 Hz, *C*O), 140.0 (Ar-*C*-CHN), 136.5 (Ar-*C*CH$_2$), 129.0 (2C, Ar-*C*H), 128.7 (2C, Ar-*C*H), 128.4 (2C, Ar-*C*H), 128.0 (2C, Ar-*C*H), 127.7 (Ar-*C*H), 126.7 (Ar-*C*H), 86.4 (d, J_F = 222.5 Hz, CO*C*F), 59.5 (*C*HN), 47.7 (PhCH_2), 27.6 (d, J_F = 10.0 Hz, CH$_2$CH_2), 23.8 (d, J_F = 25.0 Hz, CH$_2$CH_2).

m/z [EI (+ve)] 283.0 $[M]^+$, HRMS found $[M]^+$ 283.1373, $C_{18}H_{18}FNO$ requires 283.1372.

IR (thin film) ν_{max} = 2956, 1660, 1446, 1354, 1076 cm^{-1}.

m.p. 104-106 ˚C.

4'-Methoxy-*N*-(1-phenyl-3-butenyl)benzylamine, 194.[149]



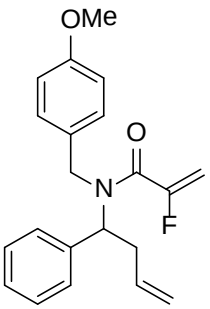
Following General Procedure A, benzaldehyde (0.95 mL, 9.43 mmol) reacted with 4-methoxybenzylamine (1.4 mL, 10.4 mmol) and allylmagnesium bromide (14 mL 1.0 M in THF, 14.3 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% EtOAc in petroleum ether) to yield the desired product **194** (2.4 g, 8.96 mmol, 95% yield) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.39-7.37 (4H, m, Ar-*H*), 7.30-7.28 (1H, m, Ar-*H*), 7.20 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.88 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.75-5.70 (1H, m, CH$_2$C*H*CH$_2$), 5.70-5.10 (2H, m, CHCH_2), 3.83 (3H, s, CH_3), 3.71 (1H, dd, J_H = 7.8, 5.9 Hz, C*H*N), 3.64 (1H, d, J_H = 13.2 Hz, ArC*H*H), 3.49 (1H, d, J_H = 13.2 Hz, ArCH*H*), 2.44-2.41 (2H, m, CHCH_2CH), 1.73 (1H, br s, N*H*).

^{13}C ($CDCl_3$, 125 MHz) δ: 158.5 (*C*OMe), 143.9 (Ar-*C*CH$_2$), 135.5 (*C*HCH$_2$) 132.8 (Ar-*C*CH), 129.3 (2C, Ar-*C*H), 128.4 (2C, Ar-*C*H), 127.3 (2C, Ar-*C*H), 127.0 (Ar-*C*H), 117.5 (CH*C*H$_2$), 113.7 (2C, Ar-*C*H), 61.5 (OCH$_3$), 55.3 (*C*HNH), 50.8 (*C*H$_2$NH), 43.1 (CH*C*H$_2$CH).

The spectral data is in agreement with the literature values.[149]

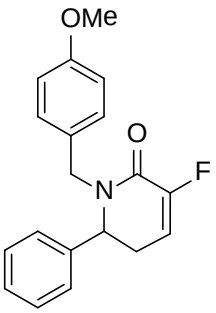
2'-Fluoro-*N*-(4''-methoxybenzyl)-*N*-(1-phenyl-3-butenyl)acrylamide, 195.



Amine **194** (0.50 g, 1.87 mmol) was coupled with 2-fluoroacrylic acid (0.25 g, 2.81 mmol) using HBTU (1.1 g, 2.81 mmol) following General Procedure B. The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **195** (0.38 g, 1.11 mmol, 60% yield) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.36-7.32 (5H, m, Ar-*H*), 6.97 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.76 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.75-5.66 (1H, m, CH_2CHCH_2), 5.35 (1H, br s, CFC*H*H), 5.26 (1H, br s, CFCH*H*), 5.08-4.99 (3H, m, ArC*H*H and CHCH_2), 4.47 (1H, d, J_H = 15.7 Hz, ArCH*H*), 4.16 (1H, br s, ArC*H*N), 3.78 (3H, s, CH_3), 2.74 (2H, br s, CHCH_2CH).
^{19}F ($CDCl_3$, 470 MHz) δ: -102.4, -114.2.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.3 (d, J_F = 30.0 Hz, CO), 158.7 (Ar-*C*OMe), 158.2 (d, J_F = 271.3, *C*F), 138.1 (Ar-*C*CHN), 134.3 (*C*HCH$_2$), 134.1 (2C, *C*HCH$_2$ and Ar-*C*CH2), 129.2 (2C, Ar-*C*H), 128.6 (2C, Ar-*C*H) 128.1 (2C, Ar-*C*H), 118.1 (CH*C*H$_2$), 113.6 (2C, Ar-*C*H), 99.4 (d, J_F = 16.3 Hz, CFCH_2), 55.2 (*C*H$_3$), 35.7 (PhCH_2), 33.5 (*C*HN), 28.6 (CH*C*H$_2$CH).
m/z [EI (+ve)] 339.2 $[M]^+$, HRMS found $[M]^+$ 339.1639, $C_{21}H_{22}FNO_2$ requires 339.1635.
IR (thin film) ν_{max} = 2937, 1637, 1512, 1417, 1246, 1176, 1033 cm^{-1}.

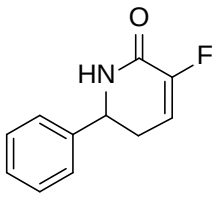
3-Fluoro-1-(4'-methoxybenzyl)-6-phenyl-5, 6-dihydro-1*H*-pyridin-2-one, 196.



Dialkene **195** (0.11 g, 0.32 mmol) was subjected to General Procedure C. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **196** (0.10 g, 0.32 mmol, quantitative yield) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.40-7.34 (3H, m, Ar-*H*), 7.19 (2H, d, J_H = 7.2 Hz, Ar-*H*), 7.15 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.86 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.77 (1H, m, CFC*H*), 5.54 (1H, d, J_H = 14.8 Hz, ArC*H*H), 4.57 (1H, dd, J_H = 7.7, 2.6 Hz, ArC*H*N), 3.83 (3H, s, OCH_3), 3.51 (1H, d, J_H = 14.8 Hz, ArCH*H*), 2.99-2.93 (1H, m, CHCH*H*CH), 2.50-2.44 (1H, m, CHC*H*HCH).
^{19}F ($CDCl_3$, 470 MHz) δ: -126.8.
^{13}C ($CDCl_3$, 125 MHz) δ: 159.8 (d, J_F = 30.0 Hz, *C*O), 159.2 (*C*OMe), 149.4 (d, J_F = 251.2 Hz, *C*F), 139.4 (Ar-*C*CHN), 129.6 (2C, Ar-*C*H), 129.0 (Ar-CH), 128.9 (2C, Ar-*C*H), 128.0 (Ar-*C*), 126.4 (2C, Ar-*C*H), 114.1 (2C, Ar-*C*H), 109.5 (CF*C*H, d, J_F = 14.6 Hz), 57.0 (*C*HN), 55.3 (O*C*H_3), 47.2 (N*C*H_2), 29.4 (CH*C*H_2CH, d, J_F = 6.0 Hz).
m/z [EI (+ve)] 311.2 $[M]^+$. HRMS found $[M]^+$ 311.1318, $C_{19}H_{18}FNO_2$ requires 311.1322.
IR (thin film) ν_{max} = 2933, 2837, 1651, 1512, 1247, 1176, 1031 cm^{-1}.

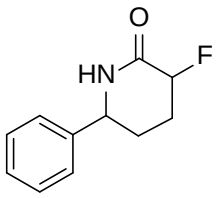
3-Fluoro-6-phenyl-5,6-dihydro-1*H*-pyridin-2-one, 198.



α,β-Unsaturated lactam **196** (96 mg, 0.31 mmol), was subjected to General Procedure D and treated with ceric ammonium nitrate (0.45 g, 2.7 eq, 0.86 mmol). The crude residue was purified by flash column chromatography (0 - 30% EtOAc in petroleum ether) to yield the desired product **198** (55 mg, 0.29 mmol, 94%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.45-7.37 (5H, m, Ar-*H*), 6.09 (1H, ddd, J_F = 11.1 Hz, J_H = 5.9, 3.3 Hz, CFC*H*), 5.62 (1H, br s, N*H*), 4.82 (1H, dd, J_H = 11.6, 5.8 Hz, C*H*NH), 2.75-2.60 (2H, m, CHCH_2CH).
^{19}F ($CDCl_3$, 470 MHz) δ: -129.9.
^{13}C ($CDCl_3$, 125 MHz) δ: 161.2 (d, J_F = 32.8 Hz, *C*O), 149.1 (d, J_F = 253.2 Hz, *C*F), 139.9 (Ar-*C*CH), 129.2 (2C, Ar-*C*H), 128.8 (Ar-CH), 126.4 (2C, Ar-*C*H), 113.5 (d, J_F = 13.8 Hz, CF*C*H), 56.1 (*C*HN), 31.2 (d, J_F= 5.0 Hz, CH*C*H_2CH).
m/z [EI (+ve)] 191.1 $[M]^+$, HRMS found $[M]^+$ 191.0748, $C_{11}H_{10}FNO$ requires 191.0746.
IR (thin film) ν_{max} = 2356, 1705, 1670, 1248 cm^{-1}.
m.p. 109-111 ˚C.

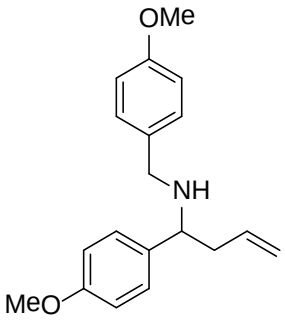
3-Fluoro-6-phenyl-piperidin-2-one, 190.



Dihydropyridone **198** (43 mg, 0.22 mmol) was subjected to General Procedure E. The crude residue was purified by flash column chromatography (0 - 30% EtOAc in petroleum ether) to yield the product **190** (32 mg, 0.17 mmol, 75%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.45-7.32 (5H, m, Ar-*H*), 5.93 (1H, br s, N*H*), 4.95 (1H, dt, J_F = 46.27 Hz, J_H = 5.28 Hz, C*H*F), 4.61-4.60 (1H, m, C*H*NH), 2.28-2.24 (1H, m, CH*H*), 2.17-2.03 (3H, m, C*H*H and CH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -180.3.
^{13}C ($CDCl_3$, 125 MHz) δ: 167.5 (d, J_F = 20.1 Hz, *C*O), 141.4 (Ar-*C*CH), 129.0 (2C, Ar-*C*H), 128.4 (Ar-*C*H), 126 1 (2C, Ar-*C*H), 85.7 (d, J_F = 175.1 Hz, *C*F), 57.3 (*C*HCN), 27.3 (d, J_F = 3.8 Hz, CH*C*H_2), 26.2 (d, J_F = 20.2 Hz, CF*C*H_2).
m/z [EI (+ve)] 193.1 $[M]^+$. HRMS found $[M]^+$ 193.0904, $C_{11}H_{12}FNO$ requires 193.0903.
IR (thin film) ν_{max} = 3194, 2066, 2958, 1666, 1329 cm^{-1}.
m.p. 149-151 ˚C.

4'-Methoxy-*N*-[1-(4''-methoxyphenyl)-3-butenyl]benzylamine, 199.[149]



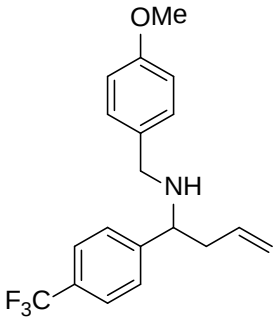
Following General Procedure A, 4-methoxybenzaldehyde (0.84 mL, 7.34 mmol) reacted with 4-methoxybenzylamine (1.1 mL, 8.03 mmol) and allylmagnesium bromide (11 mL 1.0 M in THF, 11.0 mmol). The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **199** (1.7 g, 5.62 mmol, 77% yield) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.29 (2H, d, J_H = 8.8 Hz, Ar-*H*), 7.18 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.92 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.87 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.75-5.70 (1H, m, CH_2CHCH_2), 5.12-5.04 (2H, m, $CHCH_2$), 3.85 (3H, s, OCH_3) 3.82 (3H, s, OCH_3), 3.68-3.60 (2H, m, ArC*H*H and NHC*H*), 3.47 (1H, d, J_H = 12.9 Hz, ArCH*H*), 2.44-2.39 (2H, m, $CHCH_2CH$)

^{13}C ($CDCl_3$, 125 MHz) δ: 158.6 (*C*OMe), 158.5 (*C*OMe), 135.9 (Ar-*C*CH_2), 135.6 (*C*HCH_2) 132.8 (Ar-*C*CH), 129.3 (2C, Ar-*C*H), 128.3 (2C, Ar-*C*H), 117.4 ($CHCH_2$), 113.7 (2C, Ar-*C*H), 113.6 (2C, Ar-*C*H), 60.81 (*C*HNH), 55.3 (OCH_3), 55.2 (OCH_3), 50.7 (CH_2NH), 43.2 ($CHCH_2CH$).

The spectral data is in agreement with the literature values.[149]

4'-Methoxy-*N*-[1-(4''-trifluoromethanephenyl)-3-butenyl]benzylamine, 200.



Following General Procedure A, 4-(trifluoromethyl)benzaldehyde (0.78 mL, 5.74 mmol) reacted with 4-methoxybenzylamine (0.83 mL, 6.32 mmol) and allylmagnesium bromide (8.6 mL 1.0 M in THF, 8.61 mmol). The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **200** (1.3 g, 3.79 mmol, 66% yield) as a pale yellow oil.

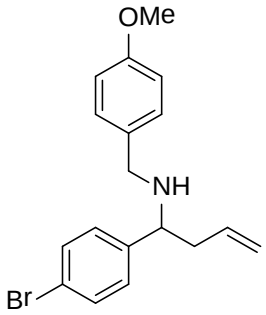
^{1}H ($CDCl_3$, 400 MHz) δ: 7.62 (2H, d, J_H = 8.2 Hz, Ar-*H*), 7.51 (2H, d, J_H = 8.2 Hz, Ar-*H*), 7.18 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.88 (2H, d, J_H = 8.8 Hz, Ar-*H*), 5.75-5.65 (1H, m, CH_2CHCH_2), 5.12-5.08 (2H, m, $CHCH_2$), 3.83 (3H, s, OCH_3), 3.77 (1H, dd, J_H = 7.6, 5.6 Hz, C*H*N), 3.64 (1H, d, J_H = 13.2 Hz, ArCH*H*), 3.45 (1H, d, J_H = 13.2 Hz, ArC*H*H), 2.45-2.34 (2H, m, $CHCH_2CH$).

^{19}F ($CDCl_3$, 400 MHz) δ: -62.3.

^{13}C ($CDCl_3$, 125 MHz) δ: 158.7 (Ar-*C*OMe), 148.2 (Ar-*C*CF_3), 134.8 (*C*HCH_2), 132.4 (*C*F_3), 129.8 (2C, Ar-*C*H), 127.7 (2C, Ar-*C*H), 125.7 (Ar-*C*CN), 125.4 (2C, Ar-*C*H), 125.3 (Ar-*C*CH_2), 118.2 ($CHCH_2$) 113.8 (2C, Ar-*C*H), 61.2 (*C*HN), 55.3 (OCH_3), 44.2 (CH_2), 33.6 (*C*H_2).

m/z [CI (+ve)] 336.1 $[M+H]^+$. HRMS found $[M+H]^+$ 336.1572, $C_{19}H_{21}F_3NO$ requires 336.1575.
IR (thin film) ν_{max} = 2935, 1612, 1512, 1323, 1246, 1120, 1066 cm^{-1}.

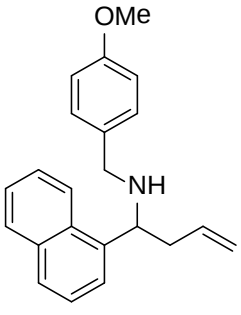
4'-Methoxy-*N*-[1-(4''-bromophenyl)-3-butenyl]benzylamine, 201.



Following General Procedure A, 4-bromobenzaldehyde (1.0 g, 5.40 mmol) reacted with 4-methoxybenzylamine (0.74 mL, 5.40 mmol) and allylmagnesium bromide (8.1 mL 1.0 M in THF, 8.11 mmol). The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **201** (1.8 g, 5.25 mmol, 97% yield) as a pale yellow oil.

^{1}H ($CDCl_3$, 500 MHz) δ: 7.48 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.27 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.15 (2H, d, J_H = 9.1 Hz, Ar-*H*), 6.87 (2H, d, J_H = 9.1 Hz, Ar-*H*), 5.72-5.63 (1H, m, CH_2CHCH_2), 5.10-5.05 (2H, m, CH_2CHCH_2), 3.82 (3H, s, OCH_3), 3.66 (1H, dd, J_H = 7.8, 6.3 Hz, C*H*NH), 3.61 (1H, d, J_H = 13.1 Hz, ArCC*H*H), 3.46 (1H, d, J_H = 13.1 Hz, ArCCH*H*), 2.40-2.35 (2H, m, $CHCH_2CH$).
^{13}C ($CDCl_3$, 125 MHz) δ: 158.7 (Ar-*C*OMe), 142.8 (Ar-*C*Br), 134.9 (*C*HCH_2), 132.2 (Ar-*C*), 131.4 (2C, Ar-*C*H), 129.2 (2C, Ar-*C*H), 129.1 (2C, Ar-*C*H), 120.7 (Ar-*C*), 117.9 ($CHCH_2$), 113.8 (2C, Ar-*C*H), 60.9 (OCH_3), 55.3 (*C*HN), 50.8 ($ArCCH_2$), 43.1 ($CHCH_2CH$).
m/z [CI (+ve)] 345.8 M^+, HRMS found $[M+H]^+$ 346.0804, $C_{18}H_{21}BrNO$ requires 346.0807.
IR (thin film) ν_{max} = 2945, 2835, 1511, 1245, 1035, 1009 cm^{-1}.

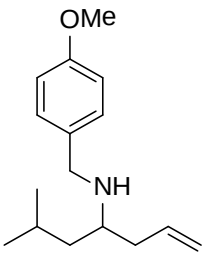
4'-Methoxy-*N*-[1-(naphthalen-1''-yl)-3-butenyl]benzylamine, 202.



Following General Procedure A, 1-napthaldehyde (0.86 mL, 6.40 mmol) reacted with 4-methoxybenzylamine (0.84 mL, 7.04 mmol) and allylmagnesium bromide (9.6 mL 1.0 M in THF, 9.60 mmol). The crude residue was purified by flash column chromatography (0 - 10% diethyl ether in petroleum ether) to yield the desired produce **202** (2.0 g, 6.38 mmol, 99% yield) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.10 (1H, appt d, J_H = 7.41 Hz, Ar-*H*), 7.81-7.79 (1H, m, Ar-*H*), 7.72-7.67 (2H, m, Ar-*H*), 7.44-7.38 (3H, m, Ar-*H*), 7.09 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.76 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.75-5.67 (1H, m, CH_2CHCH_2), 5.05-4.97 (2H, m, CH_2CHCH_2), 3.71 (3H, s, OCH_3), 3.60 (1H, d, J_H = 13.0 Hz, ArCCH*H*), 3.44 (1H, d, J_H = 13.0 Hz, ArCC*H*H), 2.59-2.54 (1H, m, CHC*H*HCH), 2.41-2.35 (1H, m, CHCH*H*CH).
^{13}C ($CDCl_3$, 125 MHz) δ: 158.6 (Ar-*C*OMe), 139.2 (Ar-*C*CHN), 138.9 ($CHCH_2$), 135.6 (Ar-*C*H), 134.1 (Ar-*C*), 132.8 (Ar-*C*), 131.6 (Ar-*C*), 129.4 (2C, Ar-*C*H), 129.0 (Ar-*C*H), 127.3 (Ar-*C*H), 125.7 (Ar-*C*H), 125.3 (Ar-*C*H), 123.9 (Ar-*C*H), 123.1 (Ar-*C*H), 117.6 ($CHCH_2$), 113.7 (2C, Ar-*C*H), 56.9 (*C*HN), 56.3 (OCH_3), 51.1 ($ArCCH_2$), 42.1 ($CHCH_2CH$).
m/z [CI (+ve)] 318.2 $[M+H]^+$, HRMS found $[M+H]^+$ 318.1862, $C_{22}H_{24}NO$ requires 318.1858.
IR (thin film) ν_{max} = 2960, 1511, 1246, 1035 cm^{-1}.

4'-Methoxy-*N*-(1-isobutyl-3-butenyl)benzylamine, 203.

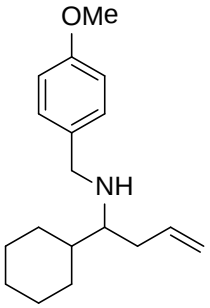


Following General Procedure A, isovaleraldehyde (1.25 mL, 11.6 mmol) reacted with 4-methoxybenzylamine (1.67 mL, 12.7 mmol) and allylmagnesium bromide (17.4 mL 1.0 M in THF, 17.4 mmol). The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **203** (2.06 g, 8.34 mmol, 76% yield) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.26 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.86 (2H, d, J_H = 8.8 Hz, Ar-*H*), 5.82-5.70 (1H, m, CH_2CHCH_2), 5.14-5.00 (2H, m, $CHCH_2$), 3.81 (3H, s, OCH_3), 3.73 (1H, quint, J_H = 6.4 Hz, C*H*NH), 2.70-2.65 (2H, m, CH_2), 2.25-2.03 (2H, m, $CHCH_2CH$), 1.62 (1H, appt sept, J_H = 6.8 Hz, $CH(CH_3)_2CH_2$), 1.46-1.23 (2H, m, $CH(CH_3)_2CH_2$), 0.88 (3H, d, J_H = 6.6 Hz, CH_3), 0.85 (3H, d, J_H = 6.6 Hz, CH_3).

^{13}C ($CDCl_3$, 100 MHz) δ: 158.5 (Ar-*C*OMe), 135.8 (*C*HCH$_2$), 133.0 (Ar-*C*CH$_2$), 129.4 (2C, Ar-*C*H), 118.8 (CH*C*H$_2$), 113.7 (2C, Ar-*C*H), 55.3 (O*C*H$_3$), 54.0 (*C*HN), 50.5 (Ar*C*H$_2$), 41.2 (*C*H$_2$), 38.6 (CH(CH$_3$)$_2$*C*H$_2$) 24.7 (*C*H(CH$_3$)$_2$CH$_2$), 22.5 (CH(*C*H$_3$)$_2$CH$_2$) .
m/z [CI (+ve)] 248.2 [M+H]$^+$, HRMS found [M+H]$^+$ 248.2018, $C_{16}H_{26}NO$ requires 248.2014.
IR (thin film) ν_{max} = 2953, 2906, 1612, 1512, 1464, 1246 cm^{-1}.

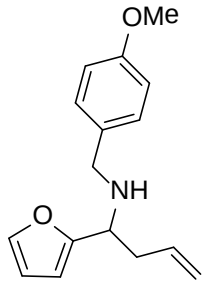
4'-Methoxy-*N*-(1-cyclohexyl-3-butenyl)benzylamine, 204.



Following General Procedure A, cyclohexanecarboxaldehyde (1.08 mL, 8.87 mmol) reacted with 4-methoxybenzylamine (1.16 mL, 9.76 mmol) and allylmagnesium bromide (13.3 mL 1.0 M in THF, 13.3 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **204** (1.81 g, 6.56 mmol, 74% yield) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.26 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.87 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.85-5.75 (1H, m, CH$_2$C*H*CH$_2$), 5.11-5.06 (2H, m, CHC*H*$_2$), 3.83 (3H, s, OC*H*$_3$), 3.71 (2H, s, ArC*H*$_2$), 2.42-2.38 (1H, m, C*H*NH), 2.32-2.26 (1H, m, CHC*H*HCH), 2.16-2.09 (1H, m, CHCH*H*CH), 1.81-1.70 (4H, m, CHC*H*$_2$CH$_2$), 1.47-1.43 (1H, m, CHC*H*CH$_2$), 1.31-1.18 (4H, m, CH$_2$C*H*$_2$CH$_2$), 1.10-1.00 (2H, m, C*H*$_2$).
^{13}C ($CDCl_3$, 125 MHz) δ: 158.5 (Ar-*C*OMe), 136.8 (C*H*CH$_2$), 133.3 (Ar-*C*CH$_2$), 129.3 (2C, Ar-*C*H), 116.7 (CH*C*H$_2$), 113.7 (2C, Ar-*C*H), 61.1 (O*C*H$_3$), 55.3 (*C*HN), 51.3 (Ar*C*H$_2$), 40.6 (*C*HCHN), 35.3 (CHC*H*$_2$CH), 29.7 (*C*H$_2$), 28.9 (*C*H$_2$), 26.8 (*C*H$_2$), 26.7 (*C*H$_2$), 26.7 (*C*H$_2$).
m/z [CI (+ve)] 274.2 [M+H]$^+$, HRMS found [M+H]$^+$ 274.2171, $C_{18}H_{28}NO$ requires 274.2168.
IR (thin film) ν_{max} = 2924, 1511, 1246, 1037 cm^{-1}.

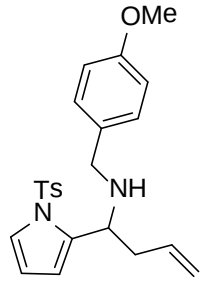
4'-Methoxy-*N*-[1-(furan-2''-yl)-3-butenyl]benzylamine, 205.



Following General Procedure A, 2-furaldehyde (0.86 mL, 10.4 mmol) reacted with 4-methoxybenzylamine (1.3 mL, 11.4 mmol) and allylmagnesium bromide (16 mL, 1.0 M in THF, 15.6 mmol). The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **205** (2.2 g, 8.59 mmol, 83% yield) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.42 (1H, dd, J_H = 1.8, 0.8 Hz, Ar-*H*), 7.23 (2H, d, J_H = 8.7 Hz, Ar-*H*), 6.88 (2H, d, J_H = 8.7 Hz, Ar-*H*), 6.36 (1H, dd, J_H = 3.7, 1.8 Hz, Ar-*H*), 6.21 (1H, d, J_H = 3.7 Hz, Ar-H), 5.79-5.62 (1H, m, CH_2CHCH_2), 5.14-5.06 (2H, m, CH_2CHCH_2), 3.83 (3H, s, OCH_3), 3.79 (1H, t, J_H = 6.8 Hz, C*H*NH), 3.72 (1H, d, J_H = 13.0 Hz, ArCC*H*H), 3.56 (1H, d, J_H = 13.0 Hz, ArCCH*H*), 2.58-2.53 (2H, m, $CHCH_2CH$).
^{13}C ($CDCl_3$, 125 MHz) δ: 158.6 (Ar-*C*OMe), 156.3 (Ar-*C*(O)CH), 141.6 (Ar-*C*H), 134.9 (*C*HCH_2), 132.4 (Ar-*C*), 129.4 (2C, Ar-CH), 117.5 ($CHCH_2$), 113.8 (2C, Ar-*C*H), 109.9 (Ar-*C*H), 106.6 (Ar-*C*H), 55.3 (OCH_3), 54.7 (*C*HN), 50.5 ($ArCCH_2$), 39.3 ($CHCH_2CH$).
m/z [CI (+ve)] 258.2 $[M+H]^+$, HRMS found $[M+H]^+$ 258.1492, $C_{16}H_{20}NO_2$ requires 258.1494.
IR (thin film) ν_{max} = 2930, 2850, 1511, 1441, 1246, 1035 cm^{-1}.

4'-Methoxy-*N*-[1-(1''-(toluene-4'''-sulfonyl)-1*H*-pyrrol-2''-yl)-3-butenyl]benzylamine, 206.

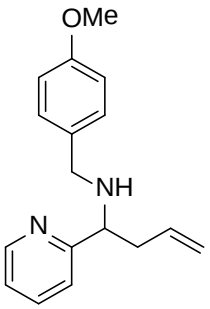


Following General Procedure A, 1-(toluene-4'-sulfonyl)-1*H*-pyrrol-2-carboxaldehyde (1.0 g, 4.02 mmol) reacted with 4-methoxybenzylamine (0.53 mL, 4.42 mmol) and

allylmagnesium bromide (6.0 mL 1.0 M in THF, 6.03 mmol). The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **206** (1.4 g, 3.42 mmol, 85% yield) as a brown oil.

^{1}H ($CDCl_3$, 500 MHz) δ: 7.62 (2H, d, J_H = 8.3 Hz, Ar-*H*), 7.36 (1H, dd, J_H = 3.2, 1.7 Hz, Ar-*H*), 7.25 (2H, d, J_H = 8.3 Hz, Ar-*H*), 7.15 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.84 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.35-6.33 (1H, m, Ar-*H*), 6.30 (1H, t, J_H = 3.3 Hz, Ar-*H*), 5.73-5.63 (1H, m, CH_2CHCH_2), 5.05-4.98 (2H, m, CH_2CHCH_2), 4.22 (1H, dd, J_H = 7.3, 5.1 Hz, C*H*NH), 3.84 (3H, s, OCH_3), 3.43 (1H, d, J_H = 12.6 Hz, ArCC*H*H), 3.25 (1H, d, J_H = 12.6 Hz, ArCCH*H*), 2.47-2.30 (2H, m, $CHCH_2CH$), 2.41 (3H, s, CH_3).
^{13}C ($CDCl_3$, 125 MHz) δ: 158.5 (Ar-*C*OMe), 144.8 (Ar-*C*SO_2), 137.9 (Ar-*C*), 136.8 (Ar-*C*), 135.0 (*C*HCH_2), 132.5 (Ar-*C*), 129.9 (Ar-*C*H), 129.1 (2C, Ar-*C*H), 126.7 (2C, Ar-*C*H), 122.9 (2C, Ar-*C*H), 117.4 ($CHCH_2$), 113.7 (2C, Ar-*C*H), 112.6 (Ar-*C*H), 111.5 (Ar-*C*H), 55.3 (OCH_3), 54.0 (*C*HN), 50.6 ($ArCCH_2$), 40.7 ($CHCH_2CH$), 21.6 (CH_3).
m/z [ESI] 433.1 $[M+Na]^+$, HRMS found $[M+Na]^+$ 433.1539, $C_{23}H_{26}N_2O_3SNa$ requires 433.1556.
IR (thin film) ν_{max} = 2975, 1512, 1247, 1172 cm^{-1}.

4'-Methoxy-*N*-[1-(pyridin-2''-yl)-3-butenyl]benzylamine, 207.



Following General Procedure A, pyridine-2-carboxaldehyde (0.89 mL, 9.30 mmol) reacted with 4-methoxybenzylamine (1.2 mL, 10.2 mmol) and allylmagnesium bromide (14 mL 1.0 M in THF, 14.0 mmol). The crude residue was purified by flash column chromatography (0 - 25% diethyl ether in petroleum ether) to yield the desired product **207** (1.8 g, 6.78 mmol, 73% yield) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.51 (1H, dq, J_H = 4.8, 0.9 Hz, Ar-*H*), 7.58 (1H, td, J_H = 7.7, 1.8 Hz, Ar-*H*), 7.30 (1H, d, J_H = 7.7 Hz, Ar-*H*), 7.12 (2H, d, J_H = 8.6 Hz, Ar-*H*), 7.08 (1H, ddd, J_H = 7.7, 4.8, 0.9 Hz, Ar-*H*), 6.76 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.70-5.60 (1H, m, CH_2CHCH_2), 4.99-4.92 (2H, m, CH_2CHCH_2), 3.75 (1H, dd, J_H = 7.8, 5.9 Hz, C*H*NH), 3.71

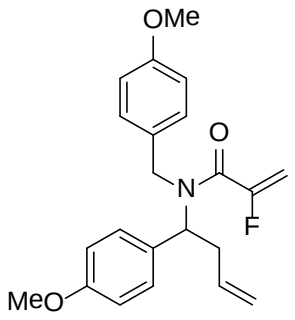
(3H, s, OCH_3), 3.54 (1H, d, J_H = 12.9 Hz, ArCC*H*H), 3.43 (1H, d, J_H = 12.9 Hz, ArCCH*H*), 2.50-2.43 (1H, m, CHC*H*HCH), 2.39-2.32 (1H, m, CHCH*H*CH).

^{13}C ($CDCl_3$, 125 MHz) δ: 163.3 (Ar-*C*(N)CH), 158.5 (Ar-*C*OMe), 149.4 (Ar-*C*H), 136.3 (Ar-*C*H), 135.3 (*C*HCH_2), 132.6 (Ar-*C*), 129.3 (2C, Ar-*C*H), 121.9 (2C, Ar-*C*H), 117.5 (CH*C*H_2), 113.7 (2C, Ar-*C*H), 62.9 (*C*HN), 55.3 (O*C*H_3), 51.0 (ArC*C*H_2), 41.6 (CH*C*H_2CH).

m/z [CI (+ve)] 269.1 $[M+H]^+$, HRMS found $[M+H]^+$ 269.1653, $C_{17}H_{21}N_2O$ requires 269.1654.

IR (thin film) ν_{max} = 2836, 1512, 1247, 905 cm^{-1}.

2'-Fluoro-*N*-(4''-methoxybenzyl)-*N*-[1-(4'''-methoxyphenyl)-3-butenyl]acrylamide, 209.



Amine **199** (0.55 g, 1.85 mmol) was coupled with 2-fluoroacrylic acid (0.25 g, 2.77 mmol) using HBTU (1.1 g, 2.77 mmol) following General Procedure B. The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **209** (0.44 g, 1.19 mmol, 66%) as a pale yellow oil.

^1H ($CDCl_3$, 400 MHz) δ: 7.27 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.98 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.89 (2H, d, J_H = 8.4 Hz, Ar-*H*), 6.77 (2H, d, J_H = 8.4 Hz, Ar-*H*), 5.73-5.64 (1H, m, CH_2CHCH_2), 5.35 (1H, br s, CFC*H*H), 5.23 (1H, br s, CFCH*H*), 5.07-4.92 (3H, m, ArC*H*H and CHCH_2), 4.46 (1H, d, J_H = 15.5 Hz, ArCH*H*), 4.14 (1H, br s, ArC*H*N), 3.83 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.69 (2H, br s, CHCH_2CH).

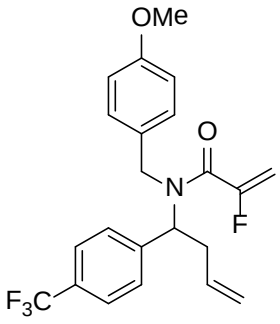
^{19}F ($CDCl_3$, 470 MHz) δ: -102.1, -104.2.

^{13}C ($CDCl_3$, 125 MHz) δ: 163.2 (d, J_F = 30.0 Hz, CO), 159.4 (Ar-*C*OMe), 159.3 (Ar-*C*OMe), 158.7 (Ar*C*), 158.5 (d, J_F = 271.3, *C*F), 134.2 (*C*HCH_2), 134.1 (Ar-*C*CH_2), 129.8 (2C, Ar-*C*H), 129.2 (2C, Ar-*C*H), 118.0 (CH*C*H_2), 113.9 (2C, Ar-*C*H), 113.6 (2C, Ar-*C*H), 99.3 (d, J_F = 15.0 Hz, CF*C*H_2), 77.3 (*C*HN), 65.9 (Ph*C*H_2), 55.3 (*C*H_3), 55.2 (*C*H_3), 33.5 (CH*C*H_2CH).

m/z [EI (+ve)] 369.2 $[M]^+$, HRMS found $[M]^+$ 369.1743, $C_{22}H_{24}FNO_3$ requires 369.1740.

IR (thin film) ν_{max} = 2933, 2837, 1635, 1512, 1246, 1178, 1033 cm^{-1}.

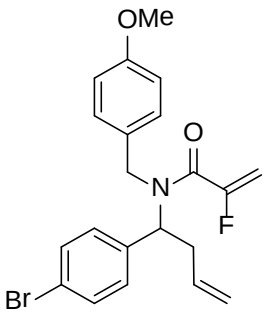
2'-Fluoro-*N*-(4''-methoxybenzyl)-*N*-[1-(4'''-trifluoromethanephenyl)-3-butenyl]acrylamide, 210.



Amine **200** (0.64 g, 1.8 mmol) was coupled with 2-fluoroacrylic acid (0.25 g, 2.7 mmol) using HBTU (1.1 g, 2.7 mmol) following General Procedure B. The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **210** (0.33 g, 0.80 mmol, 45%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.57 (2H, d, J_H = 8.0 Hz, Ar-*H*), 7.44 (2H, d, J_H = 8.0 Hz, Ar-*H*), 6.98 (2H, d, J_H = 8.4 Hz, Ar-*H*), 6.76 (2H, d, J_H = 8.4 Hz, Ar-*H*), 5.76–5.66 (1H, m, CH_2CHCH_2), 5.41 (1H, d, J_H = 3.2 Hz, CFCH*H*), 5.29 (1H, d, J_H = 3.2 Hz, CFC*H*H), 5.14-5.09 (3H, m, CHCH_2 and PhC*H*H), 4.43 (1H, d, J_H = 15.6 Hz, PhCH*H*), 4.34 (1H, br. s, C*H*N), 3.80 (3H, s, OCH_3), 2.79 (2H, br. s, CHCH_2CH).
^{19}F ($CDCl_3$, 400 MHz) δ: -62.3, -102.9.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.4 (d, J_F = 29.8 Hz, *C*O), 159.0 (Ar-*C*OMe), 158.0 (d, J_F = 273.0 Hz, *C*F), 142.5 (Ar-*C*CF_3), 139.0 (*C*F_3), 137.8 (*C*HCH_2), 133.9 (Ar-*C*CHN), 129.9 (Ar-*C*CH_2), 129.2 (2C, Ar-*C*H), 128.8 (2C, Ar-*C*H), 125.3 (2C, Ar-*C*H), 118.5 (CH*C*H_2), 113.7 (2C, Ar-*C*H), 99.8 (d, J_F = 12.5 Hz, CF*C*H_2), 66.7 (Ph*C*H_2), 59.8 (*C*HN), 55.2 (*C*H_3), 35.4 (CH*C*H_2CH).
m/z [EI (+ve)] 407.1 $[M]^+$, HRMS found $[M]^+$ 407.1504, $C_{22}H_{21}F_4NO_2$ requires 407.1508.
IR (thin film) ν_{max} = 2939, 1639, 1514, 1415, 1325, 1246, 1120, 1068 cm^{-1}.

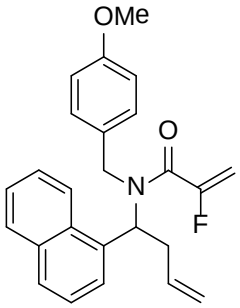
2'-Fluoro-*N*-(4''-methoxybenzyl)-*N*-[1-(4'''-bromophenyl)-3-butenyl]acrylamide, 211.



Amine **201** (0.50 g, 1.4 mmol) was coupled with 2-fluoroacrylic acid (0.19 g, 2.2 mmol) using HBTU (0.82 g, 2.2 mmol) following General Procedure B. The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **211** (0.24 g, 0.58 mmol, 41%) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.47 (2H, d, J_H = 8.1 Hz, Ar-*H*), 7.21 (2H, d, J_H = 8.1 Hz, Ar-*H*), 6.99 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.79 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.74-5.63 (1H, m, CH_2CHCH_2), 5.40-5.25 (2H, m, $CFCH_2$), 5.19-5.05 (3H, m, $CHCH_2$ and ArCHH), 4.44 (1H, d, J_H = 16.0 Hz, ArCH*H*), 4.25 (1H, m, C*H*N), 3.81 (3H, s, OCH_3), 2.74-2.69 (2H, m, CH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -102.3, -104.2.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.3 (d, J_F = 29.4 Hz, CO), 158.9 (Ar-*C*OMe), 157.9 (d, J_F = 273.3 Hz, *C*F), 137.3 (Ar-*C*Br), 133.9 (*C*HCH_2), 131.6 (2C, Ar-*C*H), 130.3 (2C, Ar-*C*H), 129.1 (2C, Ar-*C*H), 129.0 (Ar-*C*), 122.0 (Ar-*C*), 118.3 (CH*C*H_2), 113.7 (2C, Ar-*C*H), 99.7 (d, J_F = 15.6 Hz, CF*C*H), 59.4 (*C*HN), 55.3 (OCH_3), 35.6 (Ar*C*H_2), 23.9 (*C*H_2).
m/z [EI (+ve)] 417.0 $[M]^+$, HRMS found $[M]^+$ 417.0739, $C_{21}H_{21}BrFNO_2$ requires 417.0740.
IR (thin film) ν_{max} = 2940, 1639, 1513, 1247, 1176 cm^{-1}.

2'-Fluoro-*N*-(4''-methoxybenzyl)-*N*-[1-(naphthalen-1'''-yl)-3-butenyl]acrylamide, 212.

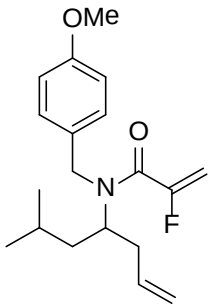


Amine **202** (0.50 g, 1.6 mmol) was coupled with 2-fluoroacrylic acid (0.21 g, 2.4 mmol) using HBTU (0.89 g, 2.4 mmol) following General Procedure B. The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **212** (0.21 g, 0.53 mmol, 34%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.07 (1H, d, J_H = 8.4 Hz, Ar-*H*), 7.87 (1H, br d, J_H = 8.4 Hz, Ar-*H*), 7.82 (1H, t, J_H = 4.6 Hz, Ar-*H*), 7.59-7.51 (2H, m, Ar-H), 7.44 (2H, d, J_H = 5.0 Hz, Ar-*H*), 6.76 (2H, d, J_H = 8.3 Hz, Ar-*H*), 6.63 (2H, d, J_H = 8.3 Hz, Ar-*H*), 6.57 (1H, br s, C*H*N), 5.87-5-76 (1H, m, CH_2CHCH_2), 5.32 (1H, br d, J_F = 47.8 Hz, CFC*H*H), 5.15-5.05 (3H, m, CFCH*H* and CHCH_2), 4.40 (1H, br d, J_H = 16.2 Hz, ArC*H*H), 3.91 (1H, dd, J_H = 16.2, 1.7 Hz, ArCH*H*), 3.76 (3H, s, OCH_3), 2.77 (2H, appt t, J_H = 6.7 Hz, $CHCH_2CH$).
^{19}F ($CDCl_3$, 376 MHz) δ: -103.7, -103.8.

^{13}C ($CDCl_3$, 100 MHz) δ: 162.9 (d, J_F = 30.4 Hz, CO), 158.7 (Ar-*C*OMe), 158.2 (d, J_F = 263.3 Hz, *C*F), 147.5 (Ar-*C*), 141.9 (Ar-*C*), 134.7 (*C*HCH$_2$), 134.0 (Ar-*C*), 132.6 (Ar-*C*), 129.3 (Ar-*C*H), 128.9 (Ar-*C*H), 128.6 (2C, Ar-*C*H), 126.9 (Ar-*C*H), 126.5 (Ar-CH), 126.0 (Ar-*C*H), 124.6 (Ar-*C*H), 123.4 (Ar-*C*H), 117.7 (CH*C*H$_2$), 113.4 (2C, Ar-*C*H), 99.9 (d, J_F = 15.8 Hz, CF*C*H$_2$), 61.2 (*C*HN), 55.2 (O*C*H$_3$), 48.2 (Ar-C*C*H$_2$), 35.6 (*C*H$_2$).
m/z [EI (+ve)] 389.2 [M]$^+$. HRMS found [M]$^+$ 389.1794, $C_{25}H_{24}FNO_2$ requires 389.1791.
IR (thin film) ν_{max} = 2970, 1632, 1513, 1246, 1176 cm^{-1}.

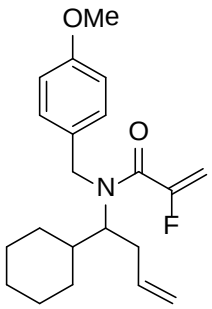
2'-Fluoro-*N*-(4''-methoxybenzyl)-*N*-(1-isobutyl-3-butenyl)acrylamide, 213.



Amine **203** (0.27 g, 1.1 mmol) was coupled with 2-fluoroacrylic acid (0.15 g, 1.7 mmol) using HBTU (0.63 g, 1.7 mmol) following General Procedure B. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **213** (0.26 g, 0.81 mmol, 74%) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.27 (2H, d, J_H = 8.0 Hz, Ar-*H*), 6.85 (2H, d, J_H = 8.0 Hz, Ar-*H*), 5.73-5.62 (1H, m, CH$_2$C*H*CH$_2$), 5.26 (1H, br s, CFCH*H*), 5.15 (1H, br s, CFC*H*H), 5.13-5.02 (2H, m, CHC*H*$_2$), 4.54-4.39 (2H, m, ArC*H*$_2$), 4.19-4.01 (1H, m, C*H*N), 3.81 (3H, s, OC*H*$_3$), 2.33-2.19 (2H, m, CHC*H*$_2$CH), 1.52-1.16 (3H, m, C*H*$_2$ and C*H*), 0.85 (3H, d, J_H = 6.4 Hz, C*H*$_3$), 0.74 (3H, d, J_H = 6.0 Hz, C*H*$_3$).
^{19}F ($CDCl_3$, 376 MHz) δ: -102.4, -103.6.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.9 (CO), 158.7 (Ar-*C*OMe), 158.3 (d, J_F = 270.0, *C*F), 135.4 (Ar-*C*CHN), 134.3 (*C*HCH$_2$), 130.3 (Ar-*C*CH$_2$), 129.2 (2C, Ar-*C*H), 118.0 (CH*C*H$_2$), 113.9 (2C, Ar-*C*H), 98.5 (CF*C*H$_2$), 57.7 (*C*HN), 55.3 (*C*H$_3$), 44.1 (Ph*C*H$_2$), 42.0 (CH*C*H$_2$CH), 38.9 (CH$_2$), 24.6 (CH), 22.7 (CH$_3$).
m/z [CI (+ve)] 320.2 [M+H]$^+$, HRMS found [M+H]$^+$ 320.2025, $C_{19}H_{27}FNO_2$ requires 320.2026.
IR (thin film) ν_{max} = 2958, 1637, 1514, 1246 cm^{-1}

2'-Fluoro-*N*-(4''-methoxybenzyl)-*N*-(1-cyclohexyl-3-butenyl)acrylamide, 214.



Amine **204** (0.48 g, 1.74 mmol) was coupled with 2-fluoroacrylic acid (0.24 g, 2.62 mmol) using HBTU (1.0 g, 2.62 mmol) following General Procedure B. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **214** (0.44 g, 1.27 mmol, 70%) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.32 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.84 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.63-5.56 (1H, m, CH_2CHCH_2), 5.27-4.91 (4H, m, $CFCH_2$ and $CHCH_2$), 4.44 (2H, s, $ArCH_2$), 3.81 (3H, s, OCH_3), 3.69 (1H, br t, J_H = 9.3 Hz, C*H*N), 2.51-2.44 (1H, m, CHC*H*HCH), 2.33-2.25 (1H, m, CHCH*H*CH), 1.85-1.51 (5H, m, CH_2 and C*H*), 1.20-1.05 (2H, m, CH_2), 0.97-0.81 (4H, m, CH_2).

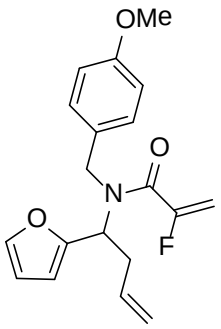
^{19}F ($CDCl_3$, 470 MHz) δ: -102.7.

^{13}C ($CDCl_3$, 125 MHz) δ: 164.7 (d, J_F = 30.0 Hz, CO), 158.7 (Ar-*C*OMe), 158.2 (d, J_F = 270.0 Hz, *C*F), 134.6 (*C*HCH_2), 130.1 (Ar*C*-C), 129.8 (2C, Ar-*C*H), 117.7 ($CHCH_2$), 113.7 (2C, Ar-*C*H), 98.5 (d, J_F = 15.0 Hz, $CFCH_2$), 64.7 (*C*HN), 55.3 (OCH_3), 44.8 (Ar-CCH_2), 40.9 (*C*H), 35.1 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 26.2 (CH_2) , 26.1 (CH_2), 26.0 (CH_2).

m/z [CI (+ve)] 346.3 $[M+H]^+$, HRMS found $[M+H]^+$ 346.2176, $C_{21}H_{29}FNO_2$ requires 346.2182.

IR (thin film) ν_{max} = 2924, 2852, 1635, 1513, 1442, 1246 cm^{-1}.

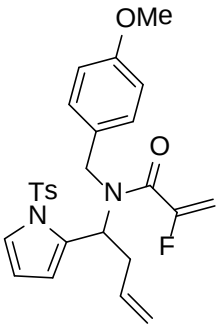
2'-Fluoro-*N*-(4''-methoxybenzyl)-*N*-[1-(furan-2'''-yl)-3-butenyl]acrylamide, 215.



Amine **205** (0.50 g, 1.9 mmol) was coupled with 2-fluoroacrylic acid (0.26 g, 2.9 mmol) using HBTU (1.10 g, 2.9 mmol) following General Procedure B. The crude residue was purified by flash column chromatography (0 - 10% diethyl ether in petroleum ether) to yield the desired product **215** (0.18 g, 0.54 mmol, 28%) as a yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.36 (1H, br s, Ar-*H*), 7.00 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.77 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.35-6.25 (2H, m, Ar-*H*), 5.72-5.64 (1H, m, CH_2CHCH_2), 5.38-5.24 (2H, m, $CFCH_2$), 5.10-5.05 (3H, m, $CHCH_2$ and ArC*H*H), 4.55 (1H, d, J_H = 15.7 Hz, ArCH*H*), 4.27 (1H, m, C*H*N), 3.80 (3H, s, OCH_3), 2.65-2.58 (2H, m, CH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -103.5, -105.3.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.2 (d, J_F = 29.4 Hz, CO), 158.6 (Ar-*C*OMe), 157.6 (d, J_F = 267.8 Hz, *C*F), 151.9 (Ar-*C*(O)CH), 142.4 (Ar-*C*), 133.1 (*C*HCH_2), 129.2 (2C, Ar-*C*), 118.6 ($CHCH_2$), 114.2 (Ar-CH), 113.6 (2C, Ar-*C*H), 110.4 (Ar-*C*H), 109.3 (Ar-*C*H), 99.4 ($CFCH_2$), 57.7 (*C*HN), 55.2 (OCH_3), 44.4 ($ArCH_2$), 23.8 (CH_2).
m/z [EI (+ve)] 329.2 $[M]^+$, HRMS found $[M]^+$ 329.1427, $C_{19}H_{20}FNO_3$ requires 329.1428.
IR (thin film) ν_{max} = 2956, 1699, 1513, 1246, 1117 cm^{-1}.

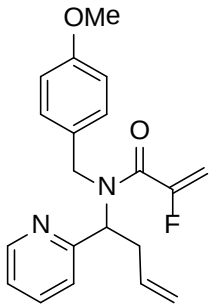
2'-Fluoro-*N*-(4''-methoxybenzyl)-*N*-[1-(1'''-(toluene-4''''-sulfonyl)-1*H*-pyrrol-2'''-yl)-3-butenyl]acrylamide, 216.



Amine **206** (0.66 g, 1.6 mmol) was coupled with 2-fluoroacrylic acid (0.22 g, 2.4 mmol) using HBTU (0.92 g, 2.4 mmol) following General Procedure B. The crude residue was purified by flash column chromatography (0 - 15% EtOAc in petroleum ether) to yield the desired product **216** (0.39 g, 0.81 mmol, 50%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.72 (2H, br s, Ar-*H*), 7.39 (1H, br s, Ar-*H*), 7.31 (2H, d, J_H = 8.3 Hz, Ar-*H*), 7.00 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.81 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.26-6.12 (2H, m, Ar-*H*), 5.75-5-65 (1H, m, C*H*N), 5.50-5.08 (3H, m, CH_2CHCH_2 and $CFCH_2$), 4.81-4.53 (3H, m, $CHCH_2$ and ArC*H*H), 4.09 (1H, d, J_H = 6.0 Hz, ArCH*H*), 3.81 (3H, s, OCH_3), 2.49-2.41 (5H, m, CH_3 and CH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -103.9.
^{13}C ($CDCl_3$, 125 MHz) δ: 162.4 (d, J_F = 29.4 Hz, CO), 159.3 (Ar-*C*OMe), 157.9 (d, J_F = 276.8 Hz, *C*F), 145.2 (Ar-*C*SO_2), 143.4 (Ar-*C*), 137.0 (Ar-*C*), 135.9 (Ar-*C*), 133.8 (*C*HCH_2), 130.0 (2C, Ar-*C*H), 129.7 (2C, Ar-CH), 129.3 (Ar-CH), 127.2 (2C, Ar-CH), 117.8 (Ar-CH), 117.4 (CH*C*H_2), 114.0 (Ar-CH), 113.5 (2C, Ar-CH), 98.9 (CF*C*H_2), 60.4 (CH_2), 55.2 (OCH_3), 51.8 (CH), 46.7 (CH_2), 21.6 (CH_3).
m/z [EI (+ve)] 482.1 $[M]^+$, HRMS found $[M]^+$ 482.1676, $C_{26}H_{27}FN_2O_2S$ requires 482.1676.
IR (thin film) ν_{max} = 2975, 1652, 1511, 1247 cm^{-1}.

2'-Fluoro-*N*-(4''-methoxybenzyl)-*N*-[1-(pyridin-2'''-yl)-3-butenyl]acrylamide, 217.



Amine **207** (0.50 g, 1.86 mmol) was coupled with 2-fluoroacrylic acid (0.25 g, 2.79 mmol) using HBTU (1.1 g, 2.79 mmol) following General Procedure B. The crude residue was purified by flash column chromatography (0 - 25% diethyl ether in petroleum ether) to yield the desired product **217** (0.42 g, 1.24 mmol, 67%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.55 (1H, s, Ar-*H*), 7.63 (1H, dt, J_H = 7.7, 1.8 Hz, Ar-*H*), 7.37 (1H, br s, Ar-*H*), 7.19 (1H, br s, Ar-*H*), 6.93 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.70 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.76-5.65 (1H, m, CH_2CHCH_2), 5.47-5.02 (5H, m, $CFCH_2$, $CHCH_2$ and C*H*N), 4.59 (2H, s, ArCH_2), 3.76 (3H, s, OCH_3), 3.04-2.95 (1H, m, CHCH*H*CH), 2.89-2.80 (1H, m, CHC*H*HCH).

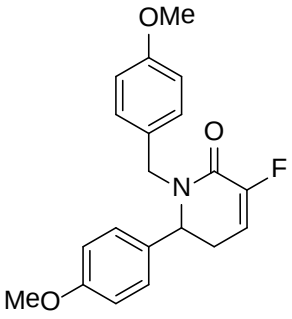
^{19}F ($CDCl_3$, 376 MHz) δ: -102.5, -105.1.

^{13}C ($CDCl_3$, 125 MHz) δ: 163.5 (d, J_F = 29.4 Hz, *C*O), 158.5 (Ar-*C*OMe), 158.0 (d, J_F = 271.5 Hz, *C*F), 157.6 (Ar-*C*), 149.0 (Ar-*C*H), 136.5 (Ar-*C*H), 134.4 (*C*HCH$_2$), 129.7 (2C, Ar-*C*H), 128.7 (Ar-*C*), 124.1 (Ar-*C*H), 122.9 (Ar-*C*H), 118.3 (CH*C*H$_2$), 113.5 (2C, Ar-*C*H), 99.5 (d, J_F = 16.5 Hz, CF*C*H$_2$), 62.5 (*C*H$_2$), 59.5 (*C*H), 55.1 (*C*H$_3$), 35.0 (*C*H$_2$).

m/z [CI (+ve)] 341.1 $[M+H]^+$, HRMS found $[M+H]^+$ 341.1669, $C_{20}H_{22}FN_2O_2$ requires 341.1665.

IR (thin film) ν_{max} = 1638, 1513, 1415, 1207, 1176 cm^{-1}.

3-Fluoro-1-(4'-methoxybenzyl)-6-(4''-methoxyphenyl)-5,6-dihydro-1*H*-pyridin-2-one, 218.



Dialkene **209** (0.22 g, 0.58 mmol) was subjected to General Procedure C. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **218** (0.19 g, 0.58 mmol, quantitative yield) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.05 (2H, d, J_H = 8.8 Hz, Ar-*H*), 7.00 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.80 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.77 (2H, d, J_H = 8.8 Hz, Ar-*H*), 5.70-5.66 (1H, m, CFC*H*), 5.65 (1H, d, J_H = 14.8 Hz, PhC*H*H), 4.41 (1H, dd, J_H = 7.6, 3.2 Hz, C*H*N), 3.84 (3H, s, OC*H*$_3$), 3.74 (3H, s, OC*H*$_3$), 3.39 (1H, d, J_H = 14.8 Hz, PhCH*H*), 2.84-2.79 (1H, m, CHCH*H*CH), 2.37-2.32 (1H, m, CHC*H*HCH).

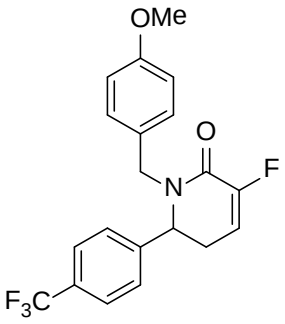
^{19}F ($CDCl_3$, 470 MHz) δ: -126.7.

^{13}C ($CDCl_3$, 125 MHz) δ: 159.7 (d, J_F = 30.0 Hz. *C*O), 159.4 (*C*OMe), 159.2 (*C*OMe), 149.4 (d, J_F = 252.5 Hz, *C*F), 131.2 (Ar*C*-CN), 129.6 (2C, Ar-CH), 129.0 (Ar*C*-CH$_2$), 127.6 (2C, Ar-*C*H), 114.2 (2C, Ar-*C*H), 114.1 (2C, Ar-*C*H), 109.6 (CF*C*H, d, J_F = 13.8 Hz), 56.6 (*C*HN), 55.4 (O*C*H$_3$), 55.3 (OCH$_3$), 47.1 (N*C*H$_2$), 29.6 (CH*C*H$_2$CH, d, J_F = 5.0 Hz).

m/z [EI (+ve)] 341.1 $[M]^+$. HRMS found $[M]^+$ 341.1420, $C_{20}H_{20}FNO_3$ requires 341.1427.

IR (thin film) ν_{max} = 2951, 2837, 1651, 1512, 1462, 1247, 1178, 1033 cm^{-1}.

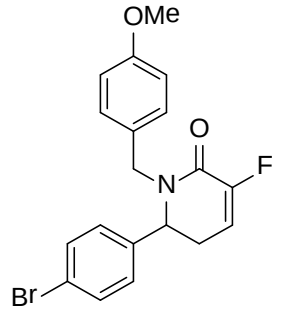
3-Fluoro-1-(4'-methoxybenzyl)-6-(4''-trifluoromethanephenyl)-5,6-dihydro-1*H*-pyridin-2-one, 219.



Dialkene **210** (0.20 g, 0.49 mmol) was subjected to General Procedure C. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **219** (0.18 g, 0.49 mmol, quantitative yield) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.64 (2H, d, J_H = 8.0 Hz, Ar-*H*), 7.30 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.14 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.85 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.78-5.75 (1H, m, CFC*H*), 5.52 (1H, d, J_H = 14.8 Hz, PhC*H*H), 4.62 (1H, dd, J_H = 7.6, 2.0 Hz, C*H*N), 3.82 (3H, s, OCH_3), 3.53 (1H, d, J_H = 14.8 Hz, PhCH*H*), 3.05-2.98 (1H, m, CHCH*H*CH), 2.48-2.43 (1H, m, CHC*H*HCH).
^{19}F ($CDCl_3$, 400 MHz) δ: -62.3, -126.1.
^{13}C ($CDCl_3$, 125 MHz) δ: 159.6 (d, J_F = 30.0 Hz. *C*O), 159.4 (*C*OMe), 149.4 (d, J_F = 253.8 Hz, *C*F), 143.5 (Ar-CCF_3), 130.6 (CF_3), 130.3 (Ar-*C*CHN), 129.6 (2C, Ar-CH), 128.5 (Ar*C*-CH_2), 126.8 (2C, Ar-*C*H), 124.9 (2C, Ar-CH), 114.2 (2C, Ar-*C*H), 109.3 (CF*C*H, d, J_F = 15.0 Hz), 56.7 (*C*HN), 55.3 (O*C*H_3), 47.5 (N*C*H_2), 29.2 (d, J_F = 6.3 Hz, CH*C*H_2CH).
m/z [EI (+ve)] 379.0 $[M]^+$, HRMS found $[M]^+$ 379.1198, $C_{20}H_{17}F_4NO_2$ requires 379.1195.
IR (thin film) ν_{max} = 2970, 1737, 1654, 1512, 1413, 1327, 1249, 1112, 1068 cm^{-1}.

3-Fluoro-1-(4'-methoxybenzyl)-6-(4''-bromophenyl)-5,6-dihydro-1*H*-pyridin-2-one, 220.



Dialkene **211** (0.17 g, 0.41 mmol) was subjected to General Procedure C. The crude residue was purified by flash column chromatography (0 - 15% EtOAc in petroleum ether) to yield the desired product **220** (0.15 g, 0.39 mmol, 96%) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.51 (2H, d, J_H = 8.5 Hz, Ar-*H*), 7.14 (2H, d, J_H = 8.6 Hz, Ar-*H*), 7.05 (2H, d, J_H = 8.5 Hz, Ar-*H*), 6.87 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.79-5.74 (1H, m, CFC*H*), 5.50 (1H, d, J_H = 14.6 Hz, ArC*H*H), 4.52 (1H, dd, J_H = 7.6, 2.4 Hz, C*H*NH), 3.83 (3H, s, OCH_3), 3.51 (1H, d, J_H = 14.6 Hz, ArCH*H*), 3.00-3.91 (1H, m, CHCH*H*CH), 2.46-2.38 (1H, m, CHC*H*HCH).

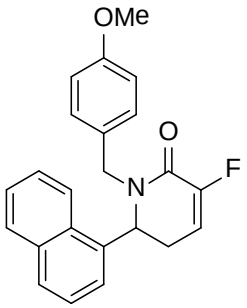
^{19}F ($CDCl_3$, 377 MHz) δ: -126.3.

^{13}C ($CDCl_3$, 100 MHz) δ: 159.6 (d, J_F = 31.0 Hz. *C*O), 159.3 (*C*OMe), 149.3 (d, J_F = 253.0 Hz, *C*F), 138.5 (Ar-*C*Br), 132.1 (2C, Ar-*C*H), 129.6 (2C, Ar-*C*H), 128.6 (Ar-*C*CH_2), 128.1 (2C, Ar-*C*H), 122.0 (Ar-*C*CH), 114.2 (2C, Ar-*C*H), 109.4 (d, J_F = 15.0 Hz, CF*C*H), 56.6 (*C*HN), 55.3 (O*C*H_3), 47.3 (N*C*H_2), 29.3 (d, J_F = 6.0 Hz, CH*C*H_2CH).

m/z [CI (+ve)] 391.7 $[M+H]^+$, HRMS found $[M+H]^+$ 390.0489, $C_{19}H_{18}BrFNO_2$ requires 390.0505.

IR (thin film) ν_{max} = 2950, 1653, 1512, 1247, 1217 cm^{-1}.

3-Fluoro-1-(4'-methoxybenzyl)-6-(naphthalen-1''-yl)-5,6-dihydro-1*H*-pyridin-2-one, 221.



Dialkene **212** (0.14 g, 0.36 mmol) was subjected to General Procedure C. The crude residue was purified by flash column chromatography (0 - 15% EtOAc in petroleum ether) to yield the desired product **221** (0.13 g, 0.36 mmol, quantitative yield) as a colourless oil.

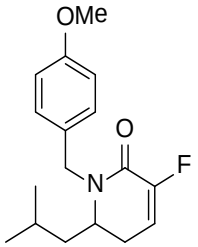
^{1}H ($CDCl_3$, 400 MHz) δ: 7.97-7.94 (1H, m, Ar-*H*), 7.88 (1H, d, J_H = 8.2 Hz, Ar-*H*), 7.78-7.75 (1H, m, Ar-*H*), 7.56-7.53 (2H, m, Ar-H), 7.49 (1H, br t, J_H = 7.7 Hz, Ar-H), 7.34 (1H, d, J_H = 7.2 Hz, Ar-H), 7.15 (2H, d, J_H = 8.5 Hz, Ar-*H*), 6.86 (2H, d, J_H = 8.5 Hz, Ar-*H*), 5.74-7.69 (1H, m, CFC*H*), 5.61 (1H, d, J_H = 14.8 Hz, ArC*H*H), 5.39 (1H, br d, J_H = 8.3 Hz, C*H*NH), 3.82 (3H, s, OCH_3), 3.47 (1H, d, J_H = 14.8 Hz, ArCH*H*), 3.12-3.04 (1H, m, CHCH*H*CH), 2.70-2.62 (1H, m, CHC*H*HCH).

^{19}F ($CDCl_3$, 400 MHz) δ: -127.5.

^{13}C ($CDCl_3$, 125 MHz) δ: 160.5 (d, J_F = 31.2 Hz. *C*O), 159.2 (*C*OMe), 149.1 (d, J_F = 255.0 Hz, *C*F), 134.4 (Ar-*C*), 133.5 (Ar-*C*), 130.2 (Ar-*C*), 129.7 (Ar-*C*H), 129.5 (2C, Ar-*C*H),

129.1 (Ar-*C*), 128.8 (Ar-*C*), 126.7 (Ar-*C*H), 125.8 (Ar-*C*H), 125.3 (Ar-*C*H), 123.9 (Ar-*C*H), 121.9 (Ar-*C*H), 114.1 (2C, Ar-*C*H), 109.9 (d, J_F = 14.7 Hz, CF*C*H), 55.3 (O*C*H_3), 53.7 (*C*HN), 47.3 (N*C*H_2), 27.8 (d, J_F = 5.5 Hz, CH*C*H_2CH).
m/z [EI (+ve)] 361.2 $[M]^+$. HRMS found $[M]^+$ 361.1480, $C_{23}H_{20}FNO_2$ requires 361.1478.
IR (thin film) ν_{max} = 2932, 1652, 1511, 1244, 1200 cm^{-1}.

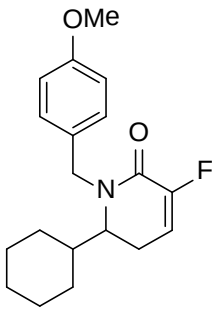
3-Fluoro-1-(4'-methoxybenzyl)-6-isobutyl-5,6-dihydro-1*H*-pyridin-2-one, 222.



Dialkene **213** (0.23 g, 0.71 mmol) was subjected to General Procedure C. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **222** (0.17 g, 0.60 mmol, 85%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.14 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.79 (2H, d, J_H = 8.8 Hz, Ar-*H*), 5.77-5.71 (1H, m, CFC*H*), 5.27 (1H, d, J_H = 14.8 Hz, ArC*H*H), 3.73 (3H, s, OCH_3), 3.66 (1H, d, J_H = 14.8 Hz, ArCH*H*), 3.31-3.26 (1H, m, C*H*N), 2.48-2.44 (1H, m, CHCH*H*CH), 2.14-2.07 (1H, m, CHC*H*HCH), 1.72-1.65 (1H, m, C*H*), 1.43-1.39 (1H, m, CH*H*), 1.27-1.17 (1H, m, C*H*H), 0.85 (3H, d, J_H = 6.8 Hz, CH_3), 0.76 (3H, d, J_H = 6.8 Hz, CH_3).
^{19}F ($CDCl_3$, 400 MHz) δ: -127.6.
^{13}C ($CDCl_3$, 125 MHz) δ: 159.2 (*C*OMe), 158.7 (d, J_F = 31.3 Hz. *C*O), 149.6 (d, J_F = 252.5 Hz, *C*F), 129.5 (Ar*C*-CH_2), 129.4 (2C, Ar-*C*H), 114.1 (2C, Ar-*C*H), 109.3 (d, J_F = 13.8 Hz, CF*C*H), 55.3 (O*C*H_3), 52.0 (*C*HN), 46.9 (N*C*H_2), 39.6 (CH_2), 25.1 (CH), 24.6 (d, J_F = 5.0 Hz, CH*C*H_2CH), 23.6 (CH_3), 21.5 (CH_3).
m/z [EI (+ve)] 291.2 $[M]^+$. HRMS found $[M]^+$ 291.1629, $C_{17}H_{22}FNO_2$ requires 291.1635.
IR (thin film) ν_{max} = 2955, 1651, 1512, 1249, 1201 cm^{-1}.

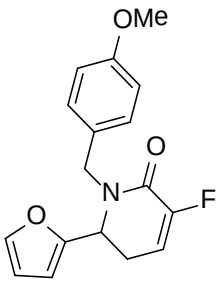
3-Fluoro-1-(4'-methoxybenzyl)-6-cyclohexane-5,6-dihydro-1*H*-pyridin-2-one, 223.



Dialkene **214** (0.35 g, 1.1 mmol) was subjected to General Procedure C. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **223** (0.30 g, 0.94 mmol, 89%) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.23 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.87 (2H, d, J_H = 8.8 Hz, Ar-*H*), 5.83-5.79 (1H, m, CFC*H*), 5.49 (1H, d, J_H = 14.9 Hz, PhC*H*H), 3.83 (3H, s, OCH_3), 3.79 (1H, d, J_H = 14.9 Hz, PhCH*H*), 3.18 (1H, br t, J_H = 6.8 Hz, C*H*N), 2.54-2.45 (1H, m, CHCH*H*CH), 2.36-2.28 (1H, m, CHC*H*HCH), 1.86-1.63 (6H, m, CH_2), 1.29-1.07 (4H, m, CH_2), 1.00-0.94 (1H, m, C*H*).
^{19}F ($CDCl_3$, 400 MHz) δ: -128.2.
^{13}C ($CDCl_3$, 125 MHz) δ: 159.2 (*C*OMe), 159.0 (d, J_F = 31.1 Hz. *C*O), 149.5 (d, J_F = 253.2 Hz, *C*F), 129.7 (Ar-*C*CH_2), 129.3 (2C, Ar-*C*H), 114.1 (2C, Ar-*C*H), 110.6 (d, J_F = 14.2 Hz, CF*C*H), 59.0 (*C*HN), 55.3 (O*C*H_3), 48.7 (N*C*H_2), 40.8 (*C*H), 30.3 (*C*H_2), 30.2 (*C*H_2), 26.4 (*C*H_2), 26.3 (*C*H_2), 26.2 (*C*H_2), 22.8 (d, J_F = 5.5 Hz, CH*C*H_2CH).
m/z [CI (+ve)] 318.2 $[M+H]^+$, HRMS found $[M+H]^+$ 318.1871, $C_{19}H_{25}FNO_2$ requires 318.1869.
IR (thin film) ν_{max} = 2925, 2850, 1645, 1511, 1247, 1198 cm^{-1}.

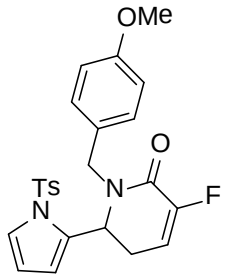
3-Fluoro-1-(4'-methoxybenzyl)-6-(furan-2''-yl)-5,6-dihydro-1*H*-pyridin-2-one, 224.



Dialkene **216** (0.37 g, 1.1 mmol) was subjected to General Procedure C. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **224** (0.21 g, 0.69 mmol, 62%) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.40 (1H, dd, J_H = 1.7, 0.6 Hz, Ar-*H*), 7.22 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.90 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.36 (1H, dd, J_H = 3.2, 1.7 Hz, Ar-*H*), 6.19 (1H, br d, J_H = 3.2 Hz, Ar-*H*), 5.91-5.86 (1H, m, CFC*H*), 5.48 (1H, d, J_H = 14.8 Hz, ArC*H*H), 4.59 (1H, dd, J_H = 7.0, 2.5 Hz, C*H*NH), 3.84 (3H, s, OCH_3), 3.75 (1H, d, J_H = 14.8 Hz, ArCH*H*), 2.84-2.75 (1H, m, CHCH*H*CH), 2.67-2.59 (1H, m, CHC*H*HCH).
^{19}F ($CDCl_3$, 470 MHz) δ: -126.3.
^{13}C ($CDCl_3$, 125 MHz) δ: 159.4 (d, J_F = 30.0 Hz, *C*O), 152.2 (*C*OMe), 149.1 (d, J_F = 252.5 Hz, *C*F), 142.5 (Ar-*C*H), 131.0 (Ar-*C*), 129.6 (2C, Ar-*C*H), 128.9 (Ar-*C*), 114.1 (2C, Ar-*C*H), 110.3 (Ar-*C*H), 110.1 (d, J_F = 16.5 Hz, CF*C*H), 107.5 (Ar-*C*H), 55.3 (O*C*H_3), 51.6 (*C*HN), 47.4 (N*C*H_2), 26.2 (d, J_F = 5.9 Hz, CH*C*H_2CH).
m/z [EI (+ve)] 301.2 $[M]^+$. HRMS found $[M]^+$ 301.1111, $C_{17}H_{16}FNO_3$ requires 301.1114.
IR (thin film) ν_{max} = 2957, 2364, 1654, 1513, 1415, 1248, 1117 cm^{-1}.

3-Fluoro-1-(4'-methoxybenzyl)-6-(1''-(toluene-4'''-sulfonyl)-1*H*-pyrrol-2''-yl)-5,6-dihydro-1*H*-pyridin-2-one, 225.



Dialkene **216** (0.23 g, 0.47 mmol) was subjected to General Procedure C. The crude residue was purified by flash column chromatography (0 - 30% EtOAc in petroleum ether) to yield the desired product **225** (0.16 g, 0.36 mmol, 77%) as a pale yellow oil.

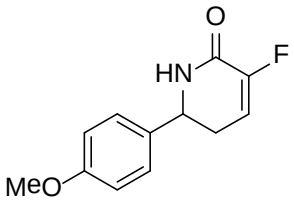
^{1}H ($CDCl_3$, 400 MHz) δ: 7.50 (2H, d, J_H = 8.5 Hz, Ar-*H*), 7.37 (1H, dd, J_H = 1.7, 1.5 Hz, Ar-*H*), 7.30 (2H, d, J_H = 8.5 Hz, Ar-*H*), 6.89 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.83 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.28 (1H, t, J_H = 3.3 Hz, Ar-*H*), 6.16-6.15 (1H, m, Ar-*H*), 5.76-5.72 (1H, m, CFC*H*), 5.30 (1H, d, J_H = 15.0 Hz, ArC*H*H), 4.95 (1H, d, J_H = 7.2 Hz, C*H*NH), 3.85 (3H, s, OCH_3), 3.12 (1H, d, J_H = 15.0 Hz, ArCH*H*), 2.94-2.87 (1H, m, CHCH*H*CH), 2.71-2.65 (1H, m, CHC*H*HCH), 2.47 (3H, s, CH_3).
^{19}F ($CDCl_3$, 400 MHz) δ: -127.9.

^{13}C ($CDCl_3$, 125 MHz) δ: 159.6 (d, J_F = 30.0 Hz. *C*O), 159.1 (*C*OMe), 148.8 (d, J_F = 252.5 Hz, *C*F), 145.4 (Ar-*C*SO_2), 136.1 (Ar-*C*(N)CH), 132.5 (Ar-*C*CH_2), 130.3 (2C, Ar-*C*H), 128.9 (2C, Ar-*C*H), 128.8 (Ar*C*), 126.4 (2C, Ar-*C*H), 124.8 (Ar-*C*H), 114.8 (Ar-*C*H), 114.0 (2C, Ar-*C*H), 112.0 (Ar-*C*H), 109.8 (d, J_F = 15.0 Hz, CF*C*H), 55.3 (O*C*H_3), 51.9 (*C*HN), 47.4 (N*C*H_2), 27.0 (d, J_F = 6.3 Hz, CH*C*H_2CH), 21.7 (*C*H_3).

m/z [ESI (+ve)] 477.1 $[M+Na]^+$, HRMS found $[M+Na]^+$ 477.1259, $C_{24}H_{23}FN_2O_4SNa$ requires 477.1255.

IR (thin film) ν_{max} = 2955, 1630, 1515, 1447, 1276, 1205 cm^{-1}.

3-Fluoro-6-(4'-methoxyphenyl)-5,6-dihydro-1*H*-pyridin-2-one, 227.



α,β-Unsaturated lactam **218** (0.14 g, 0.42 mmol) was subjected to General Procedure D and treated with ceric ammonium nitrate (1.30 g, 5.5 eq, 2.3 mmol). The crude residue was purified by flash column chromatography (0 - 25% EtOAc in petroleum ether) to yield the desired product **227** (37 mg, 0.17 mmol, 40%) as a yellow solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.21 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.84 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.01-5.97 (1H, m, CFC*H*), 5.57 (1H, br s, N*H*), 4.67 (1H, dd, J_H = 12.1, 5.6 Hz, C*H*NH), 3.81 (3H, s, OCH_3), 2.60-2.46 (2H, m, CHCH_2CH).

^{19}F ($CDCl_3$, 470 MHz) δ: -130.0.

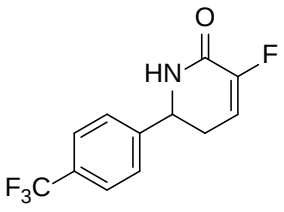
^{13}C ($CDCl_3$, 125 MHz) δ: 161.1 (d, J_F = 31.3 Hz, *C*O), 159.8 (Ar-*C*OMe), 149.8 (d, J_F = 253.8 Hz, *C*F), 131.9 (Ar-*C*CH), 127.6 (2C, Ar-*C*H), 114.4 (2C, Ar-*C*H), 113.6 (d, J_F = 13.8 Hz, CF*C*H), 55.6 (CHNH), 55.4 (OCH_3), 31.2 (d, J_F= 5.3 Hz, CH*C*H_2CH).

m/z [CI (+ve)] 222.1 $[M+H]^+$, HRMS found $[M+H]^+$ 222.0929, $C_{12}H_{13}FNO_2$ requires 222.09230.

IR (thin film) ν_{max} = 1695, 1630, 1250 cm^{-1}.

m.p. 133-135 ˚C.

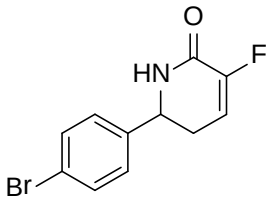
3-Fluoro-6-(4'-trifluoromethanephenyl)-5,6-dihydro-1*H*-pyridin-2-one, 228.



α,β-Unsaturated lactam **219** (0.16 g, 0.42 mmol) was subjected to General Procedure D and treated with ceric ammonium nitrate (1.1 g, 4.9 eq, 2.0 mmol). The crude residue was purified by flash column chromatography (0 - 20% EtOAc in petroleum ether) to yield the desired product **228** (50 mg, 0.20 mmol, 47%) as a white solid.

^{1}H ($CDCl_3$, 500 MHz) δ: 7.60 (2H, d, J_H = 8.2 Hz, Ar-*H*), 7.43 (2H, d, J_H = 8.2 Hz, Ar-*H*), 5.99 (1H, ddd, J_F = 11.8 Hz, J_H = 5.5, 3.6 Hz, CFC*H*), 5.93 (1H, br s, N*H*), 4.80 (1H, dd, J_H = 10.5, 6.1 Hz, C*H*NH), 2.67-2.53 (2H, m, CHCH_2CH).
^{19}F ($CDCl_3$, 470 MHz) δ: -62.4, -129.1.
^{13}C ($CDCl_3$, 125 MHz) δ: 161.1 (d, J_F = 31.3 Hz, *C*O), 149.6 (d, J_F = 253.8 Hz, *C*F), 144.0 (Ar-*C*CF_3), 131.1 (*C*F_3), 130.9 (Ar-*C*CH), 126.8 (2C, Ar-*C*H), 126.1 (2C, Ar-*C*H), 113.2 (d, J_F = 13.8 Hz, *C*HCF), 55.4 (*C*HNH), 30.9 (d, J_F = 5.0 Hz, CH_2).
m/z [EI (+ve)] 259.1 $[M]^+$, HRMS found $[M]^+$ 259.0623, $C_{12}H_9F_4NO$ requires 259.0620.
IR (thin film) ν_{max} = 1720, 1705, 1680, 1305, 1180 cm^{-1}.
m.p. 104-105 ˚C.

3-Fluoro-6-(4'-bromophenyl)-5,6-dihydro-1*H*-pyridin-2-one, 229.



α,β-Unsaturated lactam **220** (0.19 g, 0.47 mmol) was subjected to General Procedure D and treated with ceric ammonium nitrate (0.98 g, 3.8 eq, 1.8 mmol). The crude residue was purified by flash column chromatography (0 - 20% EtOAc in petroleum ether) to yield the desired product **229** (92 mg, 0.34 mmol, 72%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.56 (2H, d, J_H = 8.1 Hz, Ar-*H*), 7.27 (2H, d, J_H = 8.1 Hz, Ar-*H*), 6.09 (1H, dt, J_F = 10.9 Hz, J_H = 4.7 Hz, CFC*H*), 5.58 (1H, br s, N*H*), 4.79 (1H, t, J_H = 8.5 Hz, C*H*NH), 2.67-2.62 (2H, m, CHCH_2CH).

^{19}F ($CDCl_3$, 470 MHz) δ: -129.6.

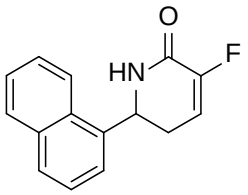
^{13}C ($CDCl_3$, 125 MHz) δ: 161.0 (d, J_F = 31.2 Hz, *C*O), 149.6 (d, J_F = 253.2 Hz, *C*F), 138.9 (Ar-*C*Br), 132.3 (2C, Ar-*C*H), 128.0 (2C, Ar-*C*H), 122.7 (Ar-*C*CH), 113.3 (d, J_F = 13.8 Hz, *C*HCF), 55.5 (*C*HNH), 31.0 (d, J_F = 5.0 Hz, *C*H_2).

m/z [CI (+ve)] 269.8 $[M+H]^+$, HRMS found $[M+H]^+$ 269.9945, $C_{11}H_{10}BrFNO$ requires 269.9930.

IR (thin film) ν_{max} = 1705, 1685, 1205, 1010 cm^{-1}.

m.p. 199-200 ˚C.

3-Fluoro-6-(naphthalen-1'-yl)-5,6-dihydro-1*H*-pyridin-2-one, 230.



α,β-Unsaturated lactam **221** (0.11 g, 0.30 mmol) was subjected to General Procedure D and treated with ceric ammonium nitrate (0.97 g, 5.9 eq, 1.8 mmol). The crude residue was purified by flash column chromatography (0 - 15% EtOAc in petroleum ether) to yield the desired product **230** (37 mg, 0.15 mmol, 51%) as a yellow solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.96 (1H, d, J_H = 8.1 Hz, Ar-*H*), 7.85 (1H, br d, J_H = 8.1 Hz, Ar-*H*), 7.79 (1H, d, J_H = 8.1 Hz, Ar-*H*), 7.55-7.41 (4H, m, Ar-*H*), 6.04 (1H, dt, J_F = 11.0 Hz, J_H = 4.6 Hz, CFC*H*), 5.74 (1H, br s, N*H*), 5.56 (1H, t, J_H = 8.5 Hz, C*H*NH), 2.81-2.76 (2H, m, CHCH_2CH).

^{19}F ($CDCl_3$, 470 MHz) δ: -129.6.

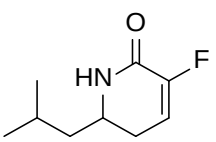
^{13}C ($CDCl_3$, 125 MHz) δ: 161.4 (d, J_F = 33.0 Hz, *C*O), 149.6 (d, J_F = 252.5 Hz, *C*F), 135.3 (Ar-*C*), 134.1 (Ar-*C*), 130.0 (Ar-*C*), 129.4 (Ar-*C*H), 129.2 (Ar-*C*H), 126.9 (Ar-*C*H), 126.2 (Ar-*C*H), 125.5 (Ar-*C*H), 123.9 (Ar-*C*H), 121.1 (Ar-*C*H), 113.7 (d, J_F = 12.5 Hz, *C*HCF), 52.3 (*C*HNH), 29.7 (d, J_F = 5.0 Hz, *C*H_2).

m/z [EI (+ve)] 241.1 $[M]^+$, HRMS found $[M]^+$ 241.0902, $C_{15}H_{12}FNO$ requires 241.0903.

IR (thin film) ν_{max} = 1715, 1797, 1320, 1180 cm^{-1}.

m.p. 135-137 ˚C.

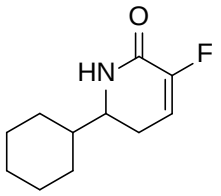
3-Fluoro-6-isobutyl-5,6-dihydro-1*H*-pyridin-2-one, 231.



α,β-Unsaturated lactam **222** (0.13 g, 0.44 mmol) was subjected to General Procedure D and treated with ceric ammonium nitrate (0.91 g, 3.8 eq, 1.7 mmol). The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **231** (70 mg, 0.41 mmol, 92%) as a white solid.

^{1}H ($CDCl_3$, 500 MHz) δ: 6.07 (1H, ddd, J_F = 11.1 Hz, J_H = 5.9, 3.3 Hz, CFC*H*), 5.59 (1H, br s, N*H*), 3.76-3.72 (1H, m, C*H*NH), 2.49-2.40 (1H, m, CHCH*H*CH), 2.34-2.25 (1H, m, CHC*H*HCH), 1.74-1.63 (1H, m, C*H*), 1.59-1.51 (1H, m, CH*H*), 1.45-1.36 (1H, m, C*H*H), 0.97 (3H, d, J_H = 6.6 Hz, CH_3), 0.96 (3H, d, J_H = 6.6 Hz, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -130.1.
^{13}C ($CDCl_3$, 100 MHz) δ: 161.2 (d, J_F = 28.0 Hz, *C*O), 149.7 (d, J_F = 253.0 Hz, *C*F), 113.7 (d, J_F = 13.0 Hz, *C*HCF), 49.3 (*C*HNH), 44.0 (CH_2), 28.3 (d, J_F = 5.0 Hz, CH_2), 24.4 (CH), 22.6 (CH_3), 22.3 (CH_3).
m/z [CI (+ve)] 172.1 $[M+H]^+$, HRMS found $[M+H]^+$ 172.1144, $C_9H_{15}FNO$ requires 172.1138.
IR (thin film) ν_{max} = 3219, 2934, 2906, 1696, 1669, 1264, 1206 cm^{-1}.
m.p. 61-63 ˚C.

3-Fluoro-6-cyclohexane-5,6-dihydro-1*H*-pyridin-2-one, 232.

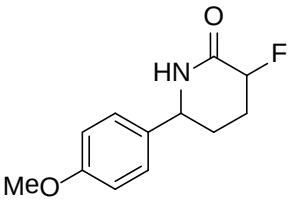


α,β-Unsaturated lactam **223** (0.22 g, 0.70 mmol) was subjected to General Procedure D and treated with ceric ammonium nitrate (1.4 g, 3.3 eq, 2.5 mmol). The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **232** (0.11 g, 0.55 mmol, 79%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 5.98 (1H, dt, J_F = 11.4 Hz, J_H = 4.3 Hz, CFC*H*), 5.54 (1H, br s, N*H*), 3.35 (1H, br q, J_H = 7.7 Hz, C*H*NH), 2.32-2.29 (2H, m, CHCH_2CH), 1.74-1.61 (5H, m, CH_2 and C*H*H), 1.43-1.32 (1H, m, C*H*), 1.19-0.97 (3H, m, CH_2 and CH*H*), 0.95-0.92 (2H, m, CH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -130.5.
^{13}C ($CDCl_3$, 125 MHz) δ: 161.3 (d, J_F = 31.3 Hz, *C*O), 149.6 (d, J_F = 252.5 Hz, *C*F), 114.0 (d, J_F = 13.8 Hz, *C*HCF), 56.0 (*C*HNH), 41.4 (*C*H), 28.8 (CH_2), 28.7 (CH_2), 26.1 (CH_2), 25.9 (d, J_F = 5.0 Hz, CH_2), 24.9 (CH_2), 24.8 (CH_2).

m/z [CI (+ve)] 198.1 $[M+H]^+$, HRMS found $[M+H]^+$ 198.1295, $C_{11}H_{17}FNO$ requires 198.1294.
IR (thin film) ν_{max} = 2927, 2855, 1691, 1652, 1208, 1199 cm^{-1}.
m.p. 108-110 ˚C.

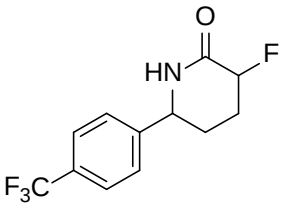
3-Fluoro-6-(4'-methoxyphenyl)-piperidin-2-one, 235.



Dihydropyridone **227** (24 mg, 0.11 mmol) was subjected to General Procedure E. The crude residue was purified by flash column chromatography (0 - 50% EtOAc in petroleum ether) to yield the desired product **235** (14 mg, 60 µmol, 58%) as a white solid.

^1H ($CDCl_3$, 400 MHz) δ: 7.25 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.94 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.83 (1H, s, N*H*), 4.94 (1H, dt, J_F = 47.1 Hz, J_H = 4.6 Hz, C*H*F), 4.56-4.51 (1H, m, C*H*NH), 3.84 (3H, s, OCH_3), 2.34-2.24 (1H, m, CH*H*), 2.13-1.96 (3H, m, C*H*H and CH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -184.8.
^{13}C ($CDCl_3$, 125 MHz) δ: 167.2 (d, J_F = 22 Hz, *C*O), 159.6 (Ar-*C*OMe), 133.4 (Ar-*C*CH), 127.3 (2C, Ar-*C*H), 114.4 (2C, Ar-*C*H), 85.7 (d, J_F = 176 Hz, *C*F), 57.0 (*C*HCN), 55.4 (O*C*H_3), 27.4 (d, J_F = 4.6 Hz, CH*C*H_2), 26.4 (d, J_F = 21 Hz, CF*C*H_2).
m/z [EI (+ve)] 223.1 $[M]^+$. HRMS found $[M]^+$ 223.0999, $C_{12}H_{14}FNO_2$ requires 223.1009.
IR (thin film) ν_{max} = 2930, 1695, 1510, 1230 cm^{-1}.
m.p. 159-161 ˚C.

3-Fluoro-6-(4'-trifluoromethanephenyl)-piperidin-2-one, 236.



Dihydropyridone **228** (29 mg, 0.11 mmol) was subjected to General Procedure E. The crude residue was purified by flash column chromatography (0 - 40% EtOAc in petroleum ether) to yield the desired product **236** (29 mg, 0.11 mmol, quantitative yield) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.60 (2H, d, J_H = 8.2 Hz, Ar-*H*), 7.38 (2H, d, J_H = 8.2 Hz, Ar-*H*), 5.93 (1H, s, N*H*), 4.86 (1H, dt, J_F = 47.1 Hz, J_H = 5.0 Hz, C*H*F), 4.59 (1H, br t, J_H = 5.7 Hz, C*H*NH), 2.22-2.12 (1H, m, CH*H*), 2.11-1.89 (3H, m, C*H*H and CH_2).

^{19}F ($CDCl_3$, 470 MHz) δ: -62.4, -185.0.

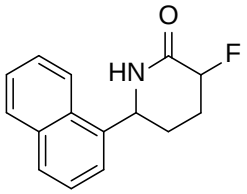
^{13}C ($CDCl_3$, 125 MHz) δ: 167.4 (d, J_F = 22.3 Hz, *C*O), 145.4 (Ar-*C*CF_3), 137.4 (*C*F_3), 130.6 (Ar-*C*CH), 126.6 (2C, Ar-*C*H), 126.1 (2C, Ar-*C*H), 85.5 (d, J_F = 176 Hz, *C*F), 57.0 (*C*HCN), 27.2 (d, J_F = 4.2 Hz, CH*C*H_2), 26.1 (d, J_F = 21 Hz, CF*C*H_2).

m/z [EI (+ve)] 261.1 $[M]^+$. HRMS found $[M]^+$ 261.0773, $C_{12}H_{11}F_4NO$ requires 261.0777.

IR (thin film) ν_{max} = 3005, 2970, 1675, 1430 cm^{-1}.

m.p. 122-124 ˚C.

3-Fluoro-6-(naphthalen-1'-yl)-piperidin-2-one, 238.



Dihydropyridone **230** (38 mg, 0.15 mmol) was subjected to General Procedure E. The crude residue was purified by flash column chromatography (0 - 40% EtOAc in petroleum ether) to yield the desired product **238** (29 mg, 0.12 mmol, 81%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.99-7.93 (2H, m, Ar-*H*), 7.87 (1H, d, J_H = 8.0 Hz, Ar-*H*), 7.62-7.51 (4H, m, Ar-*H*), 6.02 (1H, s, N*H*), 5.48-5.46 (1H, m, C*H*NH), 5.02 (1H, dt, J_F = 46.9 Hz, J_H = 5.7 Hz, C*H*F), 2.43-2.33 (1H, m, C*H*H), 2.28-2.23 (3H, m, CH*H* and CH_2).

^{19}F ($CDCl_3$, 377 MHz) δ: -186.1.

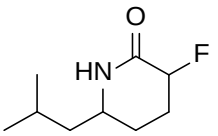
^{13}C ($CDCl_3$, 100MHz) δ: 168.3 (d, J_F = 19.9 Hz, *C*O), 136.6 (Ar-*C*), 134.0 (Ar-*C*), 129.8 (Ar-*C*), 129.4 (Ar-*C*H), 128.9 (Ar-*C*H), 126.8 (Ar-*C*H), 126.0 (Ar-*C*H), 125.4 (Ar-*C*H), 123.7 (Ar-*C*H), 121.9 (Ar-*C*H), 85.8 (d, J_F = 177.0 Hz, *C*F), 53.3 (*C*HCN), 25.9 (d, J_F = 6.0 Hz, CH*C*H_2), 25.7 (d, J_F = 20.0 Hz, CF*C*H_2).

m/z [CI (+ve)] 244.0 $[M+H]^+$, HRMS found $[M+H]^+$ 244.1137, $C_{15}H_{15}FNO$ requires 244.1138.

IR (thin film) ν_{max} = 3240, 2900, 1650, 1110 cm^{-1}.

m.p. 144-147 ˚C.

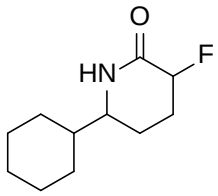
3-Fluoro-6-isobutyl-piperidin-2-one, 239.



Dihydropyridone **231** (39 mg, 0.23 mmol) was subjected to General Procedure E. The crude residue was purified by flash column chromatography (0 - 20% EtOAc in petroleum ether) to yield the desired product **239** (40 mg, 0.23 mmol, quantitative yield) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 6.00 (1H, s, N*H*), 4.80 (1H, dt, J_F = 48.6 Hz, J_H = 4.5 Hz, C*H*F), 3.40-3.37 (1H, m, C*H*NH), 2.16-2.13 (1H, m, CH*H*), 1.96-1.89 (1H, m, C*H*H), 1.81-1.77 (1H, m, C*H*), 1.64-1.58 (2H, m, CH_2), 1.40-1.31 (2H, m, CH_2), 0.87 (3H, d, J_H = 6.6 Hz, CH_3), 0.85 (3H, d, J_H = 6.6 Hz, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -185.0.
^{13}C ($CDCl_3$, 125 MHz) δ: 167.4 (d, J_F = 20.2 Hz, *C*O), 86.3 (d, J_F = 173.8 Hz, *C*F), 50.8 (*C*HCN), 45.6 (CH_2), 26.5 (d, J_F = 21.3 Hz, CF*C*H_2), 24.3 (*C*H), 24.0 (d, J_F = 3.8 Hz, CH*C*H_2), 22.6 (CH_3), 22.3 (CH_3).
m/z [CI (+ve)] 174.1 $[M+H]^+$, HRMS found $[M+H]^+$ 174.1300, $C_9H_{17}FNO$ requires 174.1294.
IR (thin film) ν_{max} = 2950, 2935, 1630 cm^{-1}.
m.p. 78-81 ˚C.

3-Fluoro-6-cyclohexane-piperidin-2-one, 240.



Dihydropyridone **232** (80 mg, 0.40 mmol) was subjected to General Procedure E. The crude residue was purified by flash column chromatography (0 - 20% EtOAc in petroleum ether) to yield the desired product **240** (81 mg, 0.40 mmol, quantitative yield) as a white solid.

^{1}H ($CDCl_3$, 500 MHz) δ: 5.93 (1H, s, N*H*), 4.74 (1H, dt, J_F = 47.2 Hz, J_H = 4.4 Hz, C*H*F), 3.13-3.09 (1H, m, C*H*NH), 2.21-2.13 (1H, m, CH*H*), 1.90-1.79 (1H, m, C*H*H), 1.74-1.62

(7H, m, CH_2 and CH), 1.35-1.30 (1H, m, CHH), 1.22-1.14 (2H, m, CH_2), 1.11-1.03 (1H, m, CHH), 0.99-0.89 (2H, m, CH_2).

^{19}F ($CDCl_3$, 470 MHz) δ: -184.6.

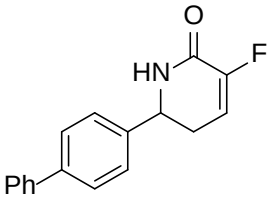
^{13}C ($CDCl_3$, 125 MHz) δ: 167.4 (d, J_F = 19.9 Hz, CO), 86.0 (d, J_F = 173.7 Hz, CF), 57.8 (CHCN), 42.6 (CH), 28.6 (CH_2), 28.4 (CH_2), 26.9 (d, J_F = 21.3 Hz, CFCH_2), 26.2 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 20.2 (d, J_F = 3.4 Hz, CHCH_2).

m/z [EI (+ve)] 199.1 $[M]^+$. HRMS found $[M]^+$ 199.1376, $C_{11}H_{18}FNO$ requires 199.1372.

IR (thin film) ν_{max} = 2926, 2870, 1664, 1410 cm^{-1}.

m.p. 148-159 ˚C.

3-Fluoro-6-(4'-phenylphenyl)-5,6-dihydro-1*H*-pyridin-2-one, 241.



Dihydropyridone **220** (98 mg, 0.36 mmol) was dissolved in toluene/H_2O (6:1, 14 mL). K_2CO_3 (0.11 g, 0.79 mmol), $PhB(OH)_2$ (88 mg, 0.72 mmol) and $Pd(PPh_3)_4$ (84 mg, 20 mol%) were then sequentially added and the resulting solution was heated at 90 °C for 16 h. The reaction was cooled down to rt and was filtered through celite and the celite was washed with EtOAc (30 mL). The organic layer was washed with H_2O (1 × 10 mL) and brine (1 × 10 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 20% EtOAc in petroleum ether) to yield the desired product **241** (87 mg, 0.33 mmol, 90%) as a white soild.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.58 (2H, d, J_H = 8.0 Hz, Ar-H), 7.52 (2H, d, J_H = 8.0 Hz, Ar-H), 7.40-7.31 (5H, m, Ar-H), 6.02 (1H, ddd, J_F = 11.0, J_H = 5.8, 3.3 Hz, CFCH), 5.59 (1H, s, NH), 4.77 (1H, dd, J_H = 11.3, 6.0 Hz, CHNH), 2.70-2.55 (2H, m, CHCH_2CH).

^{19}F ($CDCl_3$, 377 MHz) δ: -129.8.

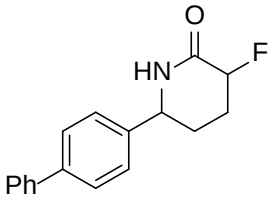
^{13}C ($CDCl_3$, 100 MHz) δ: 161.0 (d, J_F = 31.1 Hz, CO), 149.9 (d, J_F = 253.6 Hz, CF), 141.8 (Ar-C), 140.2 (Ar-C), 138.9 (Ar-CCH), 128.9 (2C, Ar-CH), 127.8 (2C, Ar-CH), 127.7 (Ar-CH), 127.1 (2C, Ar-CH), 126.8 (2C, Ar-CH), 113.5 (d, J_F = 14.0 Hz, CHCF), 55.8 (CHNH), 31.1 (d, J_F = 5.7 Hz, CH_2).

m/z [EI (+ve)] 267.1 $[M]^+$, HRMS found $[M]^+$ 267.1058, $C_{17}H_{14}FNO$ requires 267.1059.

IR (thin film) ν_{max} = 2358, 1693, 1658, 1258, 1198 cm^{-1}.

m.p. 199-201 ˚C.

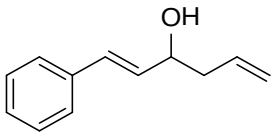
3-Fluoro-6-(4'-phenylphenyl)-piperidin-2-one, 242.



Dihydropyridone **241** (34 mg, 0.13 mmol) was subjected to General Procedure E. The crude residue was purified by flash column chromatography (0 - 40% EtOAc in petroleum ether) to yield the desired product **242** (34 mg, 0.13 mmol, quantitative) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.64 (2H, d, J_H = 7.5 Hz, Ar-*H*), 7.61 (2H, d, J_H = 7.5 Hz, Ar-*H*), 7.50-7.38 (5H, m, Ar-*H*), 5.91 (1H, s, N*H*), 4.97 (1H, dt, J_F = 43.7 Hz, J_H = 4.5 Hz, C*H*F), 4.67-4.63 (1H, m, C*H*NH), 2.36-2.27 (1H, m, C*H*H), 2.20-2.04 (3H, m, CH*H* and CH_2).
^{19}F ($CDCl_3$, 377 MHz) δ: -185.1.
^{13}C ($CDCl_3$, 100MHz) δ: 167.5 (d, J_F = 19.8 Hz, *C*O), 141.4 (Ar-*C*), 140.3 (Ar-*C*), 140.2 (Ar-*C*), 128.9 (2C, Ar-*C*H), 127.7 (2C, Ar-*C*H), 127.6 (Ar-*C*H), 127.1 (2C, Ar-*C*H), 126.6 (2C, Ar-*C*H), 85.7 (d, J_F = 176.0 Hz, *C*F), 57.2 (*C*HCN), 27.3 (d, J_F = 4.0 Hz, CH*C*H_2), 26.3 (d, J_F = 21.0 Hz, CF*C*H_2).
m/z [EI (+ve)] 269.0 $[M]^+$, HRMS found $[M]^+$ 269.1214, $C_{17}H_{16}FNO$ requires 269.1216.
IR (thin film) ν_{max} = 3239, 2949, 2356, 1676, 1486 cm^{-1}.
m.p. 171-173 ˚C.

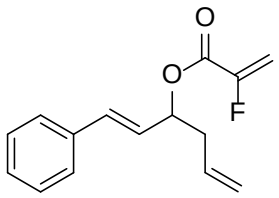
(1*E*)-1-Phenylhexa-1,5-diene-3-ol, 245.[150]



Cinnamaldehyde (0.47 mL, 3.78 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. Allylmagnesium bromide (4.2 mL, 4.16 mmol, 1M in diethyl ether) was added dropwise before the reaction mixture was stirred for 1 h at rt. Following this time, H_2O (15 mL) was added slowly at 0 °C and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organics were combined, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 5% EtOAc in petroleum ether) to yield the desired product **245** (0.62 g, 3.56 mmol, 94%) as a yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.43-7.25 (5H, m, Ar-*H*), 6.44 (1H, d, J_H = 15.9 Hz, PhC*H*CH), 6.27 (1H, dd, J_H = 15.9, 6.3 Hz, PhCHC*H*), 5.96-5.81 (1H, m, C*H*CH_2), 5.25-5.16 (2H, m, CHCH_2), 4.42-4.36 (1H, appt s, C*H*OH), 2.51-2.34 (2H, m, CHCH_2CH), 1.86 (2H, d, J_H = 3.6 Hz, CHO*H*).
^{13}C ($CDCl_3$, 125 MHz) δ: 136.7 (Ar*C*), 134.1 (*C*H), 131.5 (*C*H), 130.4 (*C*H), 128.6 (2C, Ar*C*-H), 127.7 (Ar*C*-H), 126.5 (2C, Ar*C*-H), 118.6 (CH_2), 71.7 (*C*HOH), 42.0 (CH_2).
The spectral data is in agreement with the literature values.[150]

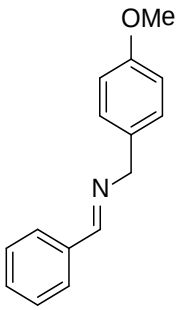
(1E)-1-Phenylhexa-1,5-dien-3-yl-2-fluoroprop-2'-enoate, 246.



2-Fluoroacrylic acid **135** (0.19 g, 2.2 mmol) and HBTU (0.82 g, 2.15 mmol) were dissolved in CH_2Cl_2 (10 mL). DIPEA (0.37 mL, 2.2 mmol) was added followed by alcohol **245** (0.25 g, 1.4 mmol). The resulting solution was heated to reflux and stirred for 17 h. After which, the solvent was removed *in vacuo* and crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) the desired product **246** (0.12 g, 0.47 mmol, 33%) as a yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.45-7.26 (5H, m, Ar-*H*), 6.71 (1H, d, J_H = 15.9 Hz, PhC*H*CH), 6.21 (1H, dd, J_H =15.9, 7.4 Hz, PhCHC*H*), 5.91-5.80 (1H, m, C*H*CH_2), 5.72 (1H, dd, J_F = 43.6 Hz, J_H = 3.2 Hz, CFC*H*H), 5.63 (1H, q, J_H = 6.4 Hz, C*H*O), 5.37 (1H, dd, J_F = 13.0 Hz, J_H = 3.2 Hz, CFCH*H*), 5.23-5.14 (2H, m, CHCH_2), 4.42-2.68-2.54 (2H, m, CHCH_2CH).
^{19}F ($CDCl_3$, 377 MHz) δ: -116.8 (d, J_H = 13.2 Hz), -116.9 (d, J_H = 13.2 Hz).
^{13}C ($CDCl_3$, 125 MHz) δ: 159.7 (d, J_F = 36.4 Hz, CO), 153.5 (d, J_F = 262.7 Hz, CF), 136.0 (Ar*C*), 133.4 (*C*H), 132.5 (*C*H), 128.6 (2C, Ar*C*-H), 128.4 (Ar*C*-H), 126.7 (2C, Ar*C*-H), 125.9 (*C*H), 118.7 (CH_2), 102.71 (d, J_F = 15.3 Hz, CF*C*H_2), 75.8 (*C*HO), 39.0 (CH_2).
m/z [EI (+ve)] 246.2 $[M]^+$, HRMS found $[M]^+$ 246.1058, $C_{15}H_{15}FO_2$ requires 246.1056.
IR (thin film) ν_{max} = 2924, 1736, 1654, 1313, 1165 cm^{-1}.

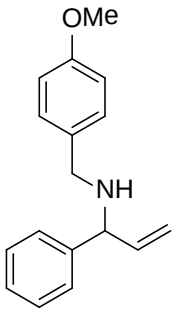
[(4-Methoxyphenyl)methyl](phenylmethylidene)amine, 247.[148]



Na_2SO_4 (1.0 g) was dried under vacuum in a round bottom flask for 10 min. Benzaldehyde (0.95 g, 9.43 mmol) was then added, followed by toluene (15 mL) and 4-methoxybenzylamine (1.4 mL, 10.3 mmol). The resulting reaction mixture was then heated to reflux and stirred for 3 h. The reaction was cooled down to rt, the solid residue filtered off and the solvent was removed *in vacuo* to yield the crude product **247** (2.1 g, 9.43 mmol, quantitative) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.40 (1H, s, C*H*N), 7.87-7.76 (2H, m, Ar-*H*), 7.49-7.38 (3H, m, Ar-*H*), 7.32-7.25 (2H, m, Ar-*H*), 6.91 (2H, d, J_H = 8.6 Hz, Ar-*H*), 4.80 (2H, CH_2N), 3.83 (3H, s, OCH_3).
^{13}C ($CDCl_3$, 125 MHz) δ: 161.7 (*C*N), 158.7 (Ar*C*), 136.2 (Ar*C*), 131.4 (Ar*C*), 130.8 (Ar*C*-H), 129.3 (2C, ArC-H), 128.6 (2C, ArC-H), 128.3 (2C, ArC-H), 114.0 (2C, ArC-H), 64.5 (*C*H_2), 55.3 (O*C*H_3).
The spectral data is in agreement with the literature values.[148]

***N*-(4'-Methoxyphenylmethyl)-1-phenyl-2-propenylamine, 263.**[151]



Procedure 1

Benzaldehyde (0.95 mL, 9.43 mmol) and *p*-methoxybenzylamine (1.4 mL, 10.3 mmol) were added to a suspension of Na_2SO_4 (1.0 g) in toluene (15 mL) and the resulting mixture was heated to reflux for 3 h. The solution was filtered and the solvent was removed *in vacuo*. The residue was redissovled in diethyl ether (20 mL) and vinylmagnesium bromide (28 mL, 28.2 mmol, 1M in diethyl ether) was added dropwise.

After the completed addition, the reaction heated to 50 °C for 72 h before quenching with H_2O (10 mL). The aqueous phase was extracted with diethyl ether (3 × 15 mL) and the organic were combined, dried (Na_2SO_4), filtered and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to the desired product **263** as a pale yellow oil (1.3 g, 5.10 mmol, 54%).

Procedure 2

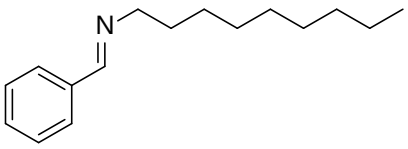
Following General Procedure G, amine **270** (0.11 g, 0.82 mmol) was reacted with *p*-methoxybenzaldehyde (0.11 mL, 0.86 mmol) and $NaBH_4$ (50 mg, 1.2 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **263** (0.16 g, 0.63 mmol, 76%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.41-7.24 (7H, m, Ar-*H*), 6.88 (2H, d, J_H = 8.4 Hz, Ar-*H*), 5.97 (1H, ddd, J_H = 17.2, 10.4, 7.2 Hz, C*H*CH_2), 5.25 (1H, appt dt, J_H = 17.2, 1.2 Hz, CHC*H*H), 5.14 (1H, ddd, J_H = 10.4, 1.6, 0.8 Hz, CHCH*H*), 4.24 (1H, d, J_H = 7.2 Hz, C*H*NH), 3.83 (3H, s, C*H*$_3$), 3.71 (1H, d, J_H = 13.6 Hz, C*H*HNH), 3.61 (1H, d, J_H = 13.6 Hz, CH*H*NH), 1.60 (1H, s, N*H*).

^{13}C ($CDCl_3$, 125 MHz) δ: 158.6 (Ar*C*-OMe), 142.8 (Ar*C*-CH_2), 141.00 (*C*HCH_2), 132.5 (Ar*C*-CH), 129.4 (2C, Ar*C*-H), 128.6 (2C, Ar*C*-H), 127.4 (2C, Ar*C*-H), 127.2 (Ar*C*-H), 115.2 (CH*C*H_2), 113.8 (2C, Ar*C*-H), 65.0 (*C*HNH_2), 55.3 (*C*H_3), 50.7 (*C*H_2).

The spectral data is in agreement with the literature values.[151]

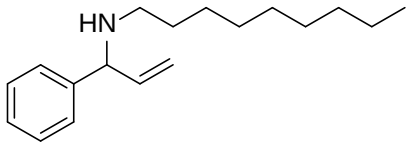
Nonyl(phenylmethylidene)amine, 264.[152]



Na_2SO_4 (1.0 g) was dried under vacuum in a round bottom flask for 10 min. Benzaldehyde (0.96 g, 9.43 mmol) was then added, followed by toluene (15 mL) and nonylamine (1.9 mL, 10.4 mmol). The resulting reaction mixture was then heated to reflux and stirred for 3 h. The reaction was cooled down to rt, the solid residue filtered off and the solvent was removed *in vacuo* to yield the desired product **264** (2.2 g, 9.43 mmol, quantitative) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.30 (1H, s, C*H*N), 7.77-7.72 (2H, m, Ar-*H*), 7.45-7.39 (3H, m, Ar-*H*), 3.63 (2H, td, J_H = 7.1, 1.2 Hz, NCH_2), 1.78-1.65 (2H, m, CH_2), 1.44-1.32 (12H, m, CH_2), 0.93-0.84 (3H, m, CH_3).
^{13}C ($CDCl_3$, 125 MHz) δ: 160.7 (*C*N), 136.4 (Ar*C*-C), 130.5 (Ar*C*-H), 128.6 (2C, Ar*C*-H), 128.0 (2C, Ar*C*-H), 61.4 (*C*H_2N), 31.9 (CH_2), 31.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.3 (CH_2), 22.7 (CH_2), 14.1 (CH_3).
The spectral data is in agreement with the literature values.[152]

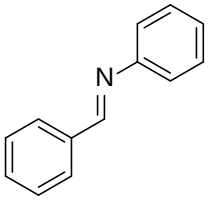
Nonyl(1-phenylprop-2-en-1-yl)amine, 265.



3-Bromopropene (3.2 mL, 3.23 mmol, 1 M in THF) was dissolved in THF (5 mL) and cooled to -78 °C. *tert*-Butyl lithium (3.8 mL, 6.45 mmol, 1.7 M in hexanes) was added slowly and the solution was stirred for 2 h at 0 °C. Imine **264** (0.50 g, 2.15 mmol) in THF (4 mL) was added the mixture was stirred for 30 min. After which, the reaction was allowed to warm to rt and stirred for 1 h before being quenched slowly with 1M HCl (5 mL) at 0 °C. The aqueous phase was extracted with diethyl ether (3 × 10 mL) which was subsequently dried (Na_2SO_4) and removed *in vacuo* at rt. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **265** (0.26 g, 1.00 mmol, 46%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.32-7.27 (4H, m, Ar-*H*), 7.23-7.17 (1H, m, Ar-*H*), 5.90 (1H, ddd, J_H = 17.2, 10.2, 7.2 Hz, C*H*CH_2), 5.17 (1H, dt, *J* = 13.6, 1.2 Hz, *C*H*CH*H), 5.06 (1H, ddd, J_H = 10.2, 1.5, 0.9 Hz, CHCH*H*), 4.14 (1H, d, J_H = 7.2 Hz, C*H*N), 2.65-2.41 (2H, m, NCH_2), 1.52-1.39 (3H, m, CH_2 and N*H*), 1.28-1.15 (12H, m, CH_2), 0.88-0.72 (3H, m, CH_3).
^{13}C ($CDCl_3$, 125 MHz) δ: 143.1 (Ar*C*), 141.2 (*C*HCH_2), 128.5 (2C, Ar*C*-H), 127.2 (2C, Ar*C*-H), 127.1 (Ar*C*-H), 114.9 (CH*C*H_2), 66.3 (*CH*), 47.7 (*C*H_2N), 31.9 (*C*H_2), 30.2 (*C*H_2), 29.6 (*C*H_2), 29.3 (2C, *C*H_2), 27.4 (*C*H_2), 22.7 (*C*H_2), 14.1 (*C*H_3).
m/z [ESI (+ve)] 260.2 $[M+H]^+$, HRMS found $[M+H]^+$ 260.2343, $C_{18}H_{30}N$ requires 260.2346.
IR (thin film) ν_{max} = 2955, 2924, 2854, 1454, 1116 cm^{-1}.

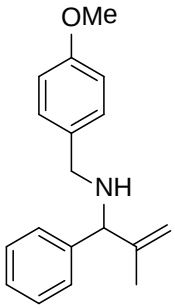
***N*-(Phenylmethylidene)aniline, 266.**[153]



Na_2SO_4 (1.00 g) was dried under vacuum in a round bottom flask for 10 min. Benzaldehyde (0.95 g, 9.43 mmol) was then added, followed by toluene (15 mL) and aniline (1.9 mL, 10.3 mmol). The resulting reaction mixture was then heated to reflux and stirred for 3 h. The reaction was cooled down to rt, the solid residue filtered off and the solvent was removed *in vacuo* to yield the crude product **266** (1.7 g, 9.43 mmol, quantitative) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.50 (1H, s, C*H*N), 7.97-7.91 (2H, m, Ar-*H*), 7.55-7.49 (3H, m, Ar-*H*), 7.47-7.40 (2H, m, Ar-*H*), 7.28-7.22 (3H, m, Ar-*H*).
^{13}C ($CDCl_3$, 125 MHz) δ: 160.5 (*C*N), 152.1 (ArC-N), 136.3 (Ar*C*-C), 131.5 (ArC-H), 129.3 (2C, ArC-H), 128.9 (2C, ArC-H), 128.8 (2C, ArC-H), 126.0 (ArC-H), 121.0 (2C, ArC-H).
The spectral data is in agreement with the literature values.[153]

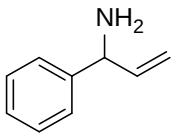
[(4'-Methoxyphenyl)methyl]-(2-methyl-1-phenylprop-2-en-1-yl)amine, 268.



2-Bromopropene (0.11 mL, 1.2 mmol) was dissolved in diethyl ether (5 mL) and cooled to -78 °C. *tert*-Butyl lithium (1.1 mL, 2.1 mmol, 1.9 M in hexanes) was added slowly and the resulting solution was stirred for 2 h. Imine **247** (0.25 g, 1.0 mmol) in diethyl ether (13 mL) was added the mixture was stirred for 20 min. After which, the reaction was allowed to warm to rt and stirred for 1 h before being quenched slowly with H_2O (10 mL) at 0 °C. The aqueous phase was extracted with diethyl ether (3 × 10 mL) which was subsequently dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **268** (0.20 g, 0.75 mmol, 74%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.33-7.28 (2H, m, Ar-*H*), 7.29-7.21 (2H, m, Ar-*H*), 7.18-7.12 (3H, m, Ar-*H*), 6.79 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.12-5.09 (1H, m, CC*H*H), 4.84-4.81 (1H, m, C*C*H*H*), 4.11 (1H, s, CHN), 3.73 (3H, s, OCH_3), 3.59 (1H, d, J_H = 13.0 Hz, C*H*HN), 3.54 (1H, d, J_H = 13.0 Hz, CH*H*N),1.62 (3H, s, CH_3), 1.59 (1H, br s, NH).
^{13}C ($CDCl_3$, 125 MHz) δ: 158.6 (Ar-*C*), 146.7 (*C*-CH_3), 142.3 (Ar-*C*), 132.8 (Ar-*C*), 129.3 (2C, Ar*C*-H), 128.3 (2C, Ar*C*-H), 127.4 (2C, Ar*C*-H), 127.0 (Ar*C*-H), 113.8 (2C, ArC-H), 111.3 (C*C*H_2), 67.7 (*C*HN), 55.3 (O*C*H_3), 51.0 (*C*H_2), 18.8 (*C*H_3).
m/z [ESI (+ve)] 268.2 $[M+H]^+$, HRMS found $[M+H]^+$ 268.1679, $C_{18}H_{22}NO$ requires 268.1696.
IR (thin film) ν_{max} = 2935, 2833, 1610, 1510, 1450, 1244, 1172, 1033 cm^{-1}.

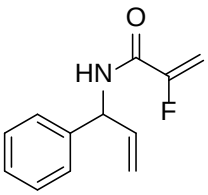
1-Phenyl-2-propenylamine, 270.[154]



Following General Procedure F, benzaldehyde (0.95 mL, 9.42 mmol) reacted with *tert*-butylsulfinamide (1.3 g, 10.6 mmol) and vinylmagnesium bromide (29 mL 1.0 M in THF, 28.5 mmol). Following acid-base work up the desired product **270** was yielded as a colourless oil (1.1 g, 7.96 mmol, 85%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.38-7.36 (4H, m, Ar-*H*), 7.29–7.28 (1H, m, Ar-*H*), 6.05 (1H, ddd, J_H = 17.1, 10.0, 6.1 Hz, C*H*CH_2), 5.27 (1H, dt, J_H = 17.1, 1.6 Hz, CHC*H*H), 5.14 (1H, dt, J_H = 10.0, 1.6 Hz, CHCH*H*), 4.56 (1H, dt, J_H = 6.1, 1.3 Hz, C*H*NH_2), 1.59 (2H, br s, NH_2).
^{13}C ($CDCl_3$, 125 MHz) δ: 144.5 (Ar*C*-CH), 142.3 (*C*HCH_2), 128.7 (2C, Ar*C*-H), 127.1 (Ar*C*-H), 126.6 (2C, Ar*C*-H), 113.6 (CH*C*H_2), 58.4 (*C*HNH_2).
The spectral data is in agreement with the literature values.[154]

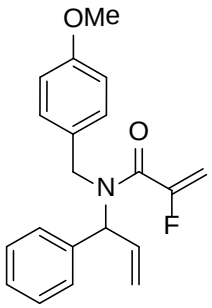
2-Fluoro-*N*-(1'-phenylprop-2'-en-1'-yl)prop-2-enamide, 275.



A solution of 2-fluoroacylic acid **135** (0.17 g, 1.85 mmol) in CH_2Cl_2 (10 mL) was treated with HBTU (0.95 g, 2.52 mmol). DIPEA (0.44 mL, 2.52 mmol) and amine **270** (0.22 g, 1.68 mmol) were sequentially added, and the reaction was stirred at rt for 1 h. The precipitate was filtered off and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **275** as a white solid (0.25 g, 1.22 mmol, 72%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.43-7.37 (2H, m, Ar-*H*), 7.36-7.31 (3H, m, Ar-*H*), 6.55 (1H, br s, N*H*), 6.07 (1H, ddd, J_H = 17.1, 10.4, 5.4 Hz, C*H*CH_2), 5.75 (1H, dd, J_F = 47.6 Hz, J_H = 3.2 Hz, CFC*H*H), 5.74-5.70 (1H, m, C*H*N), 5.35-5.26 (2H, m, CHCH_2), 5.17 (1H, dd, J_F = 15.3 Hz, J_H = 3.2 Hz, CFCH*H*).
^{19}F ($CDCl_3$, 377 MHz) δ: -121.2, -121.3.
^{13}C ($CDCl_3$, 100 MHz) δ: 158.6 (d, J_F = 31.0 Hz, *C*O), 156.2 (d, J_F = 270.0 Hz, *C*F), 139.7 (Ar*C*), 136.5 (*C*HCH_2), 128.9 (2C, Ar*C*-H), 128.0 (2C, Ar*C*-H), 127.3 (Ar*C*-H), 116.5 (CH*C*H_2), 99.3 (d, J_F = 14.8 Hz, CF*C*H_2), 55.1 (*C*HN).
IR (thin film) ν_{max} = 3331, 1651, 1523, 1311, 1182 cm^{-1}.
m/z [EI (+ve)] 205.2 $[M]^+$, HRMS found $[M]^+$ 205.0901, $C_{12}H_{12}FNO$ requires 205.0903.
m.p. 71-73 ˚C.

2-Fluoro-*N*-[(4''-methoxyphenyl)methyl]-*N*-[1'-phenylprop-2'-en-1'-yl]-prop-2-enamide, 277.



Amine **263** (0.12 g, 0.47 mmol) was coupled with 2-fluoroacrylic acid (90 mg, 0.95 mmol) using HBTU (0.35 g, 0.95 mmol) and DIPEA (0.16 mL, 0.95 mmol) following General Procedure H. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **277** (90 mg, 0.29 mmol, 61%) as a pale yellow oil.

^{1}H ($CDCl_3$, 500 MHz) δ: 7.27-7.19 (5H, m, Ar-*H*), 6.92 (2H, d, J_H = 8.2 Hz, Ar-*H*), 6.69 (2H, J_H = 8.2 Hz, Ar-*H*), 6.03 (1H, ddd, J_H = 17.0, 10.0, 7.2 Hz, C*H*CH_2), 5.72 (1H, d, J_H = 7.2 Hz, C*H*NH), 5.27-5.17 (3H, m, CFCH_2 and CHC*H*H), 5.01 (1H, dd, J_H = 17.0, 2.5 Hz,

CHCH*H*), 4.50 (1H, d, J_H = 16.0 Hz, C*H*HN), 4.27 (1H, d, J_H = 16.0 Hz, CH*H*N), 3.71 (3H, s, CH_3).

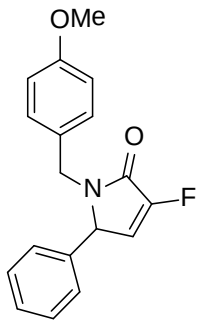
^{19}F ($CDCl_3$, 470 MHz) δ: -103.0, -105.5.

^{13}C ($CDCl_3$, 125 MHz) δ: 163.2 (d, J_F = 27.3 Hz, *C*O), 158.7 (Ar*C*-OMe), 157.9 (d, J_F = 272.4 Hz, *C*F), 138.2 (Ar*C*), 134.6 (*C*HCH$_2$), 129.4 (Ar*C*), 128.8 (2C, Ar*C*-H), 128.6 (2C, Ar*C*-H), 128.0 (2C, Ar*C*-H), 127.9 (Ar*C*-H), 119.2 (CH*C*H$_2$), 113.7 (2C, Ar*C*-H), 99.4 (CF*C*H$_2$), 63.3 (*C*HN), 55.2 (*C*H$_3$), 40.1 (Ph*C*H$_2$).

m/z [ESI (+ve)] 348.1 $[M+Na]^+$, HRMS found $[M+Na]^+$ 348.1356, $C_{20}H_{20}FNO_2Na$ requires 348.1359.

IR (thin film) ν_{max} = 2956, 1639, 1612, 1512, 1413, 1246, 1176 cm^{-1}.

3-Fluoro-1-[(4'-methoxyphenyl)methyl]-5-phenyl-2,5-dihydro-1*H*-pyrrol-2-one, 278.



Dialkene **277** (0.27 g, 0.84 mmol) was treated with 7.5 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude residue was purified by flash column chromatography (0 - 15% EtOAc in petroleum ether) to yield the desired product **278** (0.21 g, 0.71 mmol, 83%) as a pale yellow oil.

^1H ($CDCl_3$, 400 MHz) δ: 7.50-7.33 (3H, m, Ar-*H*), 7.20-7.09 (2H, m, Ar-*H*), 7.06 (2H, J_H = 8.6 Hz, Ar-*H*), 6.85 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.26 (1H, d, J_H = 1.6 Hz, C*H*CF), 5.12 (1H, d, J_H = 14.8 Hz, CH*H*N), 4.78 (1H, dd, J_F = 6.0 Hz, J_H = 2.4 Hz, C*H*N), 3.82 (3H, m, C*H*$_3$), 3.58 (1H, J_H = 14.8 Hz, C*H*HN).

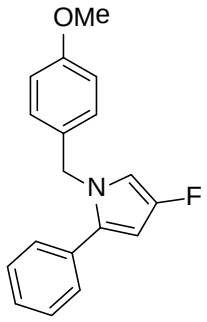
^{19}F ($CDCl_3$, 470 MHz) δ: -138.5.

^{13}C ($CDCl_3$, 125 MHz) δ: 163.0 (d, J_F = 31.2 Hz, CO), 159.2 (Ar*C*-OMe), 152.3 (d, J_F = 279.6 Hz, *C*F), 133.9 (d, J_F = 2.1 Hz, Ar*C*), 129.8 (2C, Ar*C*-H), 129.3 (2C, Ar*C*-H), 129.2 (Ar*C*-H), 128.6 (Ar*C*), 127.6 (2C, Ar*C*-H), 118.4 (d, J_F = 4.4 Hz, CH*C*F), 114.2 (2C, Ar*C*-H), 59.1 (d, J_F = 5.7 Hz, *C*HN), 55.3 (*C*H$_3$), 43.5 (Ar*C*H$_2$).

m/z [EI (+ve)] 297.2 $[M]^+$, HRMS found $[M]^+$ 297.1164, $C_{18}H_{16}FNO_2$ requires 297.1165.

IR (thin film) ν_{max} = 2355, 1710, 1666, 1514, 1247 cm^{-1}.

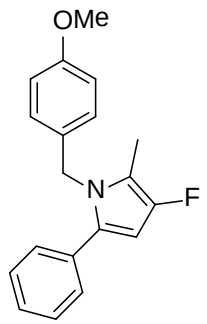
4-Fluoro-1-[(4'-methoxyphenyl)methyl]-2-phenyl-1*H*-pyrrole, 285.



α,β-Unsaturated lactam **278** (40 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (4 mL) and cooled to -78 °C. DIBAL (0.41 mL, 0.41 mmol, 1 M in hexanes) was added dropwise and the mixture was stirred for 16 h. Following this time, the reaction was quenched with H_2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **285** (30 mg, 0.11 mmol, 85%) as a yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.40-7.32 (5H, m, Ar-*H*), 6.98 (2H, d, J_H = 8.7 Hz, Ar-*H*), 6.86 (2H, d, J_H = 8.7 Hz, Ar-*H*), 6.46 (1H, dd, J_F = 3.2 Hz, J_H = 2.0 Hz, C*H*N), 6.04 (1H, d, J_F = 2.4 Hz, C*H*CF), 4.99 (2H, s, CH_2), 3.82 (3H, s, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -165.4.
^{13}C ($CDCl_3$, 125 MHz) δ: 159.0 (Ar*C*-OMe), 152.0 (d, J_F = 239.1 Hz, *C*F), 132.5 (d, J_F = 1.6 Hz, Ar*C*), 131.8 (d, J_F = 6.4 Hz, Ar-*C*N), 130.2 (Ar*C*-CH_2), 129.0 (2C, Ar*C*-H), 128.5 (2C, Ar*C*-H), 127.9 (2C, Ar*C*-H), 127.5 (Ar*C*-H), 114.1 (2C, Ar*C*-H), 105.5 (d, J_F = 27.3 Hz, *C*HN), 97.1 (d, J_F = 16.4 Hz, *C*HCF), 55.3 (O*C*H_3), 50.2 (Ar*C*H_2).
m/z [EI (+ve)] 281.1 $[M]^+$, HRMS found $[M]^+$ 281.1215, $C_{18}H_{16}FNO$ requires 281.1216.
IR (thin film) ν_{max} = 2956, 2837, 1701, 1612, 1512, 1247, 1176 cm^{-1}.

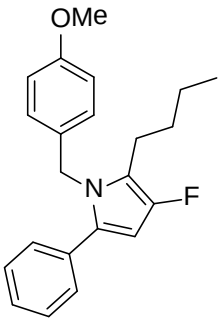
3-Fluoro-1-[(4'-methoxyphenyl)methyl]-2-methyl-5-phenyl-1*H*-pyrrole, 286.



α,β-Unsaturated lactam **278** (36 mg, 0.12 mmol) was reacted with methyl lithium (83 µL, 0.13 mmol, 1.6 M in diethyl ether) following General Procedure J. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **286** (30 mg, 0.10 mmol, 86%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.35-7.13 (5H, m, Ar-*H*), 6.78-6.76 (4H, m, Ar-*H*), 5.96 (1H, s, C*H*CF), 4.93 (2H, s, CH_2), 3.72 (3H, s, OCH_3), 1.98 (3H, d, J_F = 1.6 Hz, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -169.4.
^{13}C ($CDCl_3$, 125 MHz) δ: 158.7 (Ar*C*-OMe), 149.2 (d, J_F = 235.6 Hz, *C*F), 132.9 (Ar*C*), 130.6 (Ar*C*-CH_2), 130.1 (d, J_F = 6.9 Hz, Ar-*C*N), 128.8 (2C, Ar*C*-H), 128.5 (2C, Ar*C*-H), 127.1 (Ar*C*-H), 126.7 (2C, Ar*C*-H), 114.2 (2C, Ar*C*-H), 112.5 (d, J_F = 24.3 Hz, *C*CH_3), 96.4 (d, J_F = 16.4 Hz, *C*HCF), 55.3 (O*C*H_3), 47.2 (Ar*C*H_2), 8.2 (*C*H_3).
m/z [EI (+ve)] 295.2 $[M]^+$, HRMS found $[M]^+$ 295.1373 $C_{19}H_{18}FNO$ requires 295.1372.
IR (thin film) ν_{max} = 2928, 2359, 1614, 1599, 1512, 1352, 1249, 1174 cm^{-1}.
m.p. 73-75 ˚C.

2-Butyl-3-fluoro-1-[(4'-methoxyphenyl)methyl]-5-phenyl-1*H*-pyrrole, 287.



α,β-Unsaturated lactam **278** (38 mg, 0.13 mmol) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. *n*-Butyllithium (54 µL, 0.13 mmol, 2.5 M in hexanes) was added dropwise and the mixture was stirred for 1 h. Following this time, the reaction was quenched with H_2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **287** (34 mg, 0.10 mmol, 78%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.22-7.14 (5H, m, Ar-*H*), 6.75-6.73 (4H, m, Ar-*H*), 5.95 (1H, s, C*H*CF), 4.94 (2H, s, CH_2), 3.71 (3H, s, OCH_3), 2.37 (2H, t, J_H = 7.6 Hz, CH_2), 1.43-1.34 (2H, m, CH_2), 1.25-1.18 (2H, m, CH_2), 0.78 (3H, t, J_H = 7.3 Hz, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -168.0.

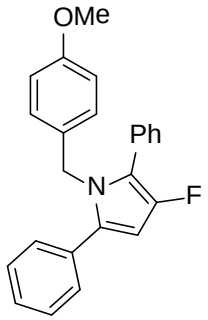
^{13}C ($CDCl_3$, 125 MHz) δ: 158.7 (Ar*C*-OMe), 149.5 (d, J_F = 236.1 Hz, *C*F), 133.0 (Ar*C*), 131.0 (Ar*C*-CH_2),130.0 (d, J_F = 7.0 Hz, Ar-*C*N), 128.9 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 127.1 (Ar*C*-H), 126.7 (2C, Ar*C*-H), 117.0 (d, J_F = 23.5 Hz, *C*CH_3), 114.1 (2C, Ar*C*-H), 96.7 (d, J_F = 16.6 Hz, *C*HCF), 55.3 (O*C*H_3), 47.1 (*C*H_2N), 31.3 (d, J_F = 2.0 Hz, *C*H_2), 23.1 (d, J_F = 2.6 Hz, *C*H_2), 22.4 (*C*H_2), 13.8 (*C*H_3).

m/z [EI (+ve)] 337.2 $[M]^+$, HRMS found $[M]^+$ 337.1840, $C_{22}H_{24}FNO$ requires 337.1842.

IR (thin film) ν_{max} = 2956, 2929, 2858, 1612, 1595, 1512, 1464, 1249 cm^{-1}.

m.p. 32-34 ˚C.

3-Fluoro-1-[(4'-methoxyphenyl)methyl]-2,5-diphenyl-1*H*-pyrrole, 288.



α,β-Unsaturated lactam **278** (45 mg, 0.15 mmol) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. Phenyl lithium (87 µL, 0.16 mmol, 1.9 M in di-n-butyl ether) was added dropwise and the mixture was stirred for 1 h. Following this time, the reaction was quenched with H_2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **288** (50 mg, 0.14 mmol, 93%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.39-7.36 (7H, m, Ar-*H*), 7.35-7.37 (3H, m, Ar-*H*), 6.66 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.55 (2H, d, J_H = 8.8 Hz, Ar-*H*), 6.17 (1H, br s, C*H*CF), 5.10 (2H, s, C*H*$_2$), 3.74 (3H, s, C*H*$_3$).

^{19}F ($CDCl_3$, 470 MHz) δ: -165.3.

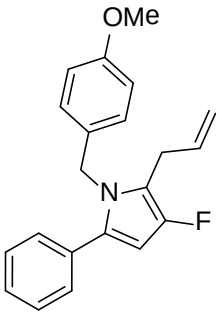
^{13}C ($CDCl_3$, 125 MHz) δ: 158.5 (Ar*C*-OMe), 149.6 (d, J_F = 242.5 Hz, *C*F), 133.0 (d, J_F = 7.1 Hz, Ar-*C*N), 132.9 (d, J_F = 1.8 Hz, Ar*C*), 130.8 (Ar*C*-CH_2), 129.9 (d, J_F = 3.3 Hz, Ar*C*), 129.5 (2C, Ar*C*-H), 129.1 (2C, Ar*C*-H), 128.5 (2C, Ar*C*-H), 128.5 (2C, Ar*C*-H), 127.5 (Ar*C*-H), 127.3 (2C, Ar*C*-H), 127.2 (Ar*C*-H), 119.1 (d, J_F = 21.0 Hz, *C*CH_3), 113.7 (2C, Ar*C*-H), 98.4 (d, J_F = 16.6 Hz, *C*HCF), 55.2 (O*C*H_3), 48.3 (Ar*C*H_2).

m/z [EI (+ve)] 357.0 $[M]^+$, HRMS found $[M]^+$ 357.1531, $C_{24}H_{20}FNO$ requires 357.1529.

IR (thin film) ν_{max} = 3063, 2955, 2835, 1610, 1512, 1492, 1435, 1247, 1176 cm^{-1}.

m.p. 84-86 ˚C.

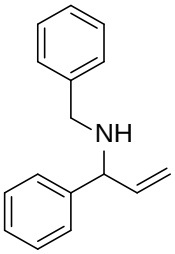
3-Fluoro-1-[(4''-methoxyphenyl)methyl]-5-phenyl-2-(prop-2'-en-1'-yl)-1*H*-pyrrole, 289.



α,β-Unsaturated lactam **278** (41 mg, 0.14 mmol) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. Allylmagnesium bromide (0.21 mL, 0.21 mmol, 1 M in diethyl ether) was added dropwise and the mixture was stirred for 1.5 h. Following this time, the reaction was quenched with H_2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **289** (34 mg, 0.11 mmol, 75%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.30-7.12 (5H, m, Ar-*H*), 6.76-6.74 (4H, m, Ar-*H*), 5.98 (1H, s, C*H*CF), 5.76 (1H, ddt, J_H = 16.1, 10.1, 6.0 Hz, C*H*CH_2), 5.00-4.84 (4H, m, CH_2N and CHCH_2), 3.71 (3H, s, OCH_3), 3.12 (2H, dd, J_H = 5.9, 0.8 Hz, CH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -168.0.
^{13}C ($CDCl_3$, 125 MHz) δ: 158.7 (Ar*C*-OMe), 149.5 (d, J_F = 237.3 Hz, *C*F), 135.3 (*C*HCH_2), 132.8 (Ar*C*), 130.8 (Ar*C*-CH_2), 130.7 (Ar-*C*N), 128.9 (2C, Ar*C*-H), 128.5 (2C, Ar*C*-H), 127.2 (Ar*C*-H), 126.7 (2C, Ar*C*-H), 115.4 (CH*C*H_2), 114.2 (2C, Ar*C*-H), 113.9 (d, J_F = 23.5 Hz, *C*CH_3), 96.6 (d, J_F = 16.3 Hz, *C*HCF), 55.3 (O*C*H_3), 47.1 (Ph*C*H_2), 27.5 (d, J_F = 2.1 Hz, *C*H_2).
m/z [EI (+ve)] 321.1 $[M]^+$, HRMS found $[M]^+$ 321.1526, $C_{21}H_{20}FNO$ requires 321.1529.
IR (thin film) ν_{max} = 2931, 1612, 1595, 1512, 1354, 1247, 1174 cm^{-1}.
m.p. 30-32 ˚C.

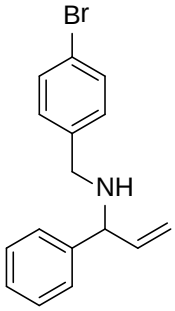
***N*-(1-Phenyl-2-propenyl)benzylamine, 291.**[155]



Following General Procedure G, amine **270** (0.40 g, 3.01 mmol) was reacted with benzaldehyde (0.32 mL, 3.16 mmol) and $NaBH_4$ (0.17 g, 4.51 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **291** (0.50 g, 2.25 mmol, 74%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.41-7.34 (7H, m, Ar-*H*), 7.31–7.26 (3H, m, Ar-*H*), 5.98 (1H, ddd, J_H = 17.2, 10.2, 7.2 Hz, C*H*CH_2), 5.25 (1H, dt, J_H = 17.2, 1.2 Hz, CHC*H*H), 5.15 (1H, dt, J_H = 10.2, 1.2 Hz, CHCH*H*), 4.26 (1H, d, J_H = 7.2 Hz, C*H*NH), 3.78 (1H, d, J_H = 13.2 Hz, C*H*HNH), 3.74 (1H, d, J_H = 13.2 Hz, CH*H*NH), 1.62 (1H, s, N*H*).
^{13}C ($CDCl_3$, 125 MHz) δ: 142.8 (Ar*C*-CH), 141.0 (*C*HCH_2), 140.5 (Ar*C*-CH_2), 128.6 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 128.2 (2C, Ar*C*-H), 127.4 (2C, Ar*C*-H), 127.2 (Ar*C*-H), 126.9 (Ar*C*-H), 115.2 (CH*C*H_2), 65.1 (*C*HNH_2), 51.3 (*C*H_2).
The spectral data is in agreement with the literature values.[155]

***N*-(4'-Bromophenylmethyl)-1-phenyl-2-propenylamine, 292.**



Following General Procedure G, amine **270** (0.26 g, 1.95 mmol) was reacted with 4-bromobenzaldehyde (0.40 g, 2.05 mmol) and $NaBH_4$ (0.11 g, 2.93 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **292** (0.46 g, 1.53 mmol, 78%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.46 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.40-7.27 (5H, m, Ar-*H*), 7.23 (2H, d, J_H = 8.4 Hz, Ar-*H*), 5.96 (1H, ddd, J_H = 17.2, 10.4, 7.2 Hz, C*H*CH_2), 5.25 (1H, appt dt, J_H

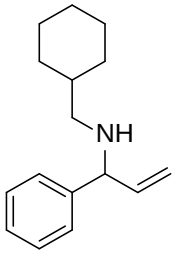
= 17.2, 1.2 Hz, CHC*H*H), 5.16 (1H, ddd, J_H = 10.4, 1.6, 1.2 Hz, CHCH*H*), 4.22 (1H, d, J_H = 6.8 Hz, C*H*NH), 3.73 (1H, d, J_H = 13.6 Hz, C*H*HNH), 3.68 (1H, d, J_H = 13.6 Hz, CH*H*NH), 1.63 (1H, s, N*H*).

^{13}C ($CDCl_3$, 125 MHz) δ: 142.6 (Ar*C*-Br), 140.8 (*C*HCH$_2$), 139.5 (Ar*C*-CH$_2$), 131.4 (2C, Ar*C*-H), 129.9 (2C, Ar*C*-H), 128.6 (2C, Ar*C*-H), 127.3 (2C, Ar*C*-H), 127.3 (ArC-H), 120.6 (Ar*C*-CH), 115.3 (CH*C*H$_2$), 65.0 (*C*HNH$_2$), 50.6 (*C*H$_2$).

m/z [EI (+ve)] 302.1 $[M]^+$, HRMS found $[M]^+$ 301.0469, $C_{16}H_{16}BrN$ requires 301.0466.

IR (thin film) ν_{max} = 3026, 2831, 1487, 1452, 1099, 1070 cm^{-1}.

_N_-(Cyclohexylmethyl)-1-phenyl-2-propenylamine, 293.



Following General Procedure G, amine **270** (0.27 g, 2.03 mmol) was reacted with cyclohexanecarboxaldehyde (0.27 mL, 2.13 mmol) and $NaBH_4$ (0.11 g, 3.04 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **293** (0.37 g, 1.61 mmol, 80% yield) as a pale yellow oil.

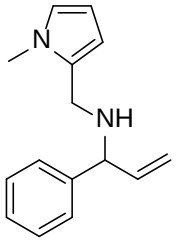
^{1}H ($CDCl_3$, 400 MHz) δ: 7.27-7.15 (5H, m, Ar-*H*), 5.84 (1H, ddd, J_H = 14.0, 8.4, 6.0 Hz, C*H*CH$_2$), 5.12 (1H, appt d, J_H = 13.6 Hz, CHC*H*H), 5.00 (1H, appt d, J_H = 8.0 Hz, CHCH*H*), 4.05 (1H, d, J_H = 6.0 Hz, C*H*NH), 2.35 (1H, dd, J_H = 9.2, 5.2 Hz, CH*H*NH), 2.25 (1H, dd, J_H = 9.2, 5.2 Hz, C*H*HNH), 1.69-1.55 (5H, m, C*H*$_2$ and N*H*), 1.42-1.33 (1H, m, CH), 1.15-1.01 (3H, m, CH*H* and C*H*$_2$), 0.87-0.76 (3H, m, C*H*H and C*H*$_2$).

^{13}C ($CDCl_3$, 125 MHz) δ: 143.3 (Ar*C*-CH), 141.5 (*C*HCH$_2$), 128.5 (2C, Ar*C*-H), 127.4 (2C, Ar*C*-H), 127.0 (ArC-H), 114.7 (CH*C*H$_2$), 66.3 (*C*HNH$_2$), 54.4 (NH*C*H$_2$), 38.2 (*C*HCH), 31.5 (*C*H$_2$), 31.4 (*C*H$_2$), 26.7 (*C*H$_2$), 26.1 (*C*H$_2$), 26.0 (*C*H$_2$).

m/z [EI (+ve)] 229.2 $[M]^+$, HRMS found $[M]^+$ 229.1827, $C_{16}H_{23}N$ requires 229.1830.

IR (thin film) ν_{max} = 2920, 2850, 1448, 1269, 1118 cm^{-1}.

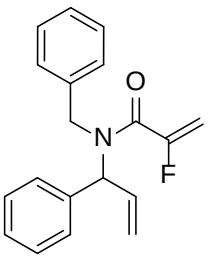
***N*-[(1'-methyl-1*H*-pyrrol-2'-yl)methyl]-1-phenyl-2-propenylamine, 294.**



Following General Procedure G, amine **270** (0.14 g, 1.1 mmol) was reacted with 1-methylpyrrole-2-carboxaldehyde (0.12 mL, 1.1 mmol) and $NaBH_4$ (60 mg, 1.6 mmol). The crude residue was purified by flash column chromatography (0-2.5% diethyl ether in petroleum ether) to yield the desired product **294** (0.16 g, 0.71 mmol, 68%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.42-7.35 (4H, m, Ar-*H*), 7.31-7.26 (1H, m, Ar-*H*), 6.01 (1H, dd, J_H = 2.4, 2.0 Hz, Ar-*H*), 6.01 (1H, m, Ar-*H*), 6.00 (1H, dd, J_H = 3.6, 2.0 Hz, Ar-*H*), 5.95 (1H, ddd, J_H = 17.2, 10.4, 7.2 Hz, C*H*CH_2), 5.27 (1H, dt, J_H = 17.2, 1.2 Hz, CHC*H*H), 5.15 (1H, ddd, J_H = 10.4, 1.6, 1.2 Hz, CHCH*H*), 4.27 (1H, d, J_H = 7.1 Hz, C*H*NH), 3.72 (1H, d, J_H = 13.6 Hz, C*H*HNH), 3.65 (3H, s, CH_3), 3.62 (1H, d, J_H = 13.6 Hz, CH*H*NH), 1.43 (1H, s, N*H*).
^{13}C ($CDCl_3$, 125 MHz) δ: 142.9 (Ar*C*-CH), 141.0 (*C*HCH_2), 131.20 (Ar*C*-CH_2), 128.5 (2C, Ar*C*-H), 127.3 (2C, Ar*C*-H), 127.2 (ArC-H), 122.3 (ArC-H), 115.1 (CH*C*H_2), 107.8 (Ar*C*-H), 106.4 (Ar*C*-H), 65.4 (*C*HNH_2), 43.2 (NH*C*H_2), 33.8 (*C*H_3).
m/z [EI (+ve)] 226.2 $[M]^+$, HRMS found $[M]^+$ 226.1469, $C_{15}H_{18}N_2$ requires 226.1470.
IR (thin film) ν_{max} = 2935, 2818, 1492, 1452, 1300, 1087 cm^{-1}.

***N*-Benzyl-2-fluoro-*N*-(1'-phenylprop-2'-en-1'-yl)-prop-2-enamide, 295.**

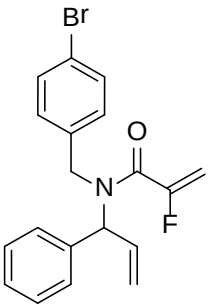


Amine **291** (0.30 g, 1.4 mmol) was coupled with 2-fluoroacrylic acid (0.24 g, 2.7 mmol) using HBTU (1.0 g, 2.7 mmol) and DIPEA (0.46 mL, 2.7 mmol) following General Procedure H. The crude product was purified by flash column chromatography (0 - 2.5%

diethyl ether in petroleum ether) to yield the desired product **295** (0.29 g, 0.98 mmol, 73%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.26-7.10 (8H, m, Ar-*H*), 7.01–6.98 (2H, m, Ar-*H*), 6.02 (1H, ddd, J_H = 17.2, 10.4, 7.2 Hz, C*H*CH_2), 5.77 (1H, d, J_H = 7.2 Hz, C*H*N), 5.30-5.18 (3H, m, CFCH_2 and CHC*H*H), 4.26 (1H, dd, J_H = 17.2 Hz, 2.8 Hz, CHCH*H*), 4.57 (1H, d, J_H = 16.1 Hz, C*H*HN), 4.35 (1H, d, J_H = 16.1 Hz, CH*H*N).
^{19}F ($CDCl_3$, 470 MHz) δ: -103.1, -105.5.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.3 (d, J_F = 29.6 Hz, *C*O), 157.8 (d, J_F = 273.3 Hz, *C*F), 138.1 (Ar*C*), 137.4 (Ar*C*), 134.6 (*C*HCH_2), 128.6 (2C, Ar*C*-H), 128.3 (2C, Ar*C*-H), 128.0 (2C, Ar*C*-H), 127.9 (Ar*C*-H), 127.3 (2C, Ar*C*-H), 126.9 (Ar*C*-H), 119.3 (CH*C*H_2), 99.6 (CF*C*H_2), 63.5 (*C*HN), 48.9 (Ph*C*H_2).
m/z [EI (+ve)] 294.9 $[M]^+$, HRMS found $[M]^+$ 295.1375, $C_{19}H_{18}FNO$ requires 295.1372.
IR (thin film) ν_{max} = 3030, 2251, 1635, 1450, 1417, 1153 cm^{-1}.

2-Fluoro-*N*-[(4''-bromophenyl)methyl]-*N*-[1'-phenylprop-2'-en-1'-yl]-prop-2-enamide, 296.



Amine **292** (0.28 g, 0.94 mmol) was coupled with 2-fluoroacrylic acid (0.17 g, 1.9 mmol) using HBTU (0.71 g, 1.9 mmol) and DIPEA (0.32 mL, 1.9 mmol) following General Procedure H. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **296** (0.25 g, 0.67 mmol, 71%) as a pale yellow oil.

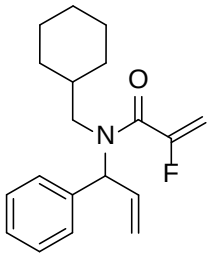
^{1}H ($CDCl_3$, 500 MHz) δ: 7.26-7.17 (7H, m, Ar-*H*), 6.82 (2H, d, J_H = 7.3 Hz, Ar-*H*), 5.99 (1H, ddd, J_H = 16.8, 10.0, 7.0 Hz, C*H*CH_2), 5.80 (1H, appt s, C*H*N), 5.31-5.21 (3H, m, CFCH_2 and CHC*H*H), 5.05 (1H, appt d, J_H = 16.8 Hz, CHCH*H*), 4.44 (1H, d, J_H = 15.8 Hz, C*H*HN), 4.32 (1H, d, J_H = 15.8 Hz, CH*H*N).
^{19}F ($CDCl_3$, 470 MHz) δ: -103.2, -106.4.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.2 (d, J_F = 33.0 Hz, *C*O), 157.7 (d, J_F = 275.0 Hz, *C*F), 137.8 (Ar*C*-Br), 136.5 (Ar*C*), 134.4 (*C*HCH_2), 131.3 (2C, Ar*C*-H), 129.1 (2C, Ar*C*-H), 128.7 (2C,

Ar*C*-H), 128.1 (Ar*C*-H), 128.0 (2C, Ar*C*-H), 120.9 (Ar*C*), 119.4 (CH*C*H_2), 99.8 (CF*C*H_2), 63.4 (*C*HN), 53.6 (Ph*C*H_2).

m/z [ESI (+ve)] 396.0 $[M+Na]^+$, HRMS found $[M+Na]^+$ 396.0351, $C_{19}H_{17}BrFNONa$ requires 396.0370.

IR (thin film) ν_{max} = 3030, 1641, 1489, 1404, 1209, 1072, 1010 cm^{-1}.

2-Fluoro-*N*-[cyclohexylmethyl]-*N*-[1'-phenylprop-2'-en-1'-yl]-prop-2-enamide, 297.



Amine **293** (0.27 g, 1.17 mmol) was coupled with 2-fluoroacrylic acid (0.21 g, 2.34 mmol) using HBTU (0.89 g, 2.34 mmol) and DIPEA (0.40 mL, 2.34 mmol) following General Procedure H. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **297** (0.30 g, 1.01 mmol, 86%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.39-7.28 (5H, m, Ar-*H*), 6.23 (1H, br s, C*H*CH_2), 5.74 (1H, br s, C*H*N), 5.44-5.21 (3H, m, CFCH_2 and CHC*H*H), 5.12 (1H, dd, J_H = 17.2 Hz, 3.5 Hz, CHCH*H*), 3.16 (2H, br s, CH_2N), 1.66-1.58 (4H, m, CH_2), 1.48-1.39 (1H, m, C*H*), 1.35-1.25 (1H, m, C*H*H), 1.06-0.98 (3H, m, CH*H* and CH_2), 0.90-0.74 (2H, m, CH_2).

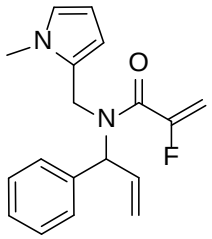
^{19}F ($CDCl_3$, 470 MHz) δ: -102.3, -104.2.

^{13}C ($CDCl_3$, 125 MHz) δ: 163.7 (*C*O), 158.2 (d, J_F = 272.0 Hz, *C*F), 138.6 (Ar*C*), 135.0 (*C*HCH_2), 128.6 (3C, Ar*C*-H), 127.9 (2C, Ar*C*-H), 118.9 (CH*C*H_2), 98.8 (CF*C*H_2), 63.6 (*C*HN), 40.9 (Ph*C*H_2), 36.9 (*C*H), 31.1 (*C*H_2), 30.8 (*C*H_2), 26.3 (*C*H_2), 25.9 (2C, *C*H_2).

m/z [ESI (+ve)] 324.2 $[M+Na]^+$, HRMS found $[M+Na]^+$ 324.1740, $C_{19}H_{24}FNONa$ requires 324.1735.

IR (thin film) ν_{max} = 2924, 2850, 1639, 1448, 1415, 1313, 1203, 1130 cm^{-1}.

2-Fluoro-*N*-[(1''-methyl-1H-pyrrol-2''-yl)methyl]-*N*-[1'-phenylprop-2'-en-1'-yl]-prop-2-enamide, 298.



Amine **294** (0.11 g, 0.48 mmol) was coupled with 2-fluoroacrylic acid (90 mg, 0.97 mmol) using HBTU (0.38 g, 0.97 mmol) and DIPEA (0.17 mL, 0.97 mmol) following General Procedure H. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **298** (90 mg, 0.30 mmol, 63%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.30-7.15 (5H, m, Ar-*H*), 6.45 (1H, appt t, J_H = 2.4 Hz, Ar-*H*), 5.91 (1H, dd, J_H = 3.2, 2.8 Hz, Ar-*H*), 5.79 (1H, m, C*H*CH_2), 5.70 (1H, br s, Ar-*H*), 5.63 (1H, d, J_H = 7.8 Hz, C*H*N), 5.25-5.09 (3H, m, CFCH_2 and CHC*H*H), 5.03 (1H, dd, J_F = 17.2 Hz, J_H = 3.6 Hz, CHCH*H*), 4.69 (1H, d, J_H = 15.6 Hz, C*H*HN), 4.17 (1H, br s, CH*H*N), 3.37 (3H, s, CH_3).

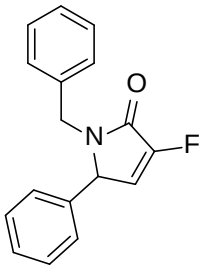
^{19}F ($CDCl_3$, 470 MHz) δ: -103.2.

^{13}C ($CDCl_3$, 125 MHz) δ: 163.0 (d, J_F = 30.3 Hz, *C*O), 157.8 (d, J_F = 271.8 Hz, *C*F), 138.1 (Ar*C*), 134.4 (*C*HCH_2), 128.6 (2C, Ar*C*-H), 127.8 (Ar*C*-H), 127.7 (2C, Ar*C*-H), 127.4 (Ar*C*), 122.7 (Ar*C*-H), 119.5 (CH*C*H_2), 110.0 (Ar*C*-H), 107.0 (Ar*C*-H), 99.0 (d, J_F = 15.3 Hz, CF*C*H_2), 63.1 (*C*HN), 40.1 (Ph*C*H_2), 38.9 (*C*H_3).

m/z [EI (+ve)] 298.2 $[M]^+$, HRMS found $[M]^+$ 298.1478, $C_{18}H_{19}FN_2O$ requires 298.1481.

IR (thin film) ν_{max} = 2362, 1643, 1494, 1415, 1303, 1195 cm^{-1}.

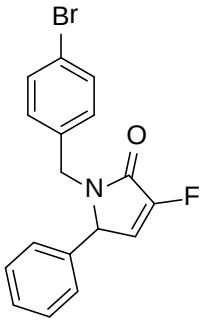
1-Benzyl-3-fluoro-5-phenyl-2,5-dihydro-1*H*-pyrrol-2-one, 299.



Dialkene **295** (0.11 g, 0.36 mmol) was treated with 7.5 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **299** (0.10 g, 0.35 mmol, 98%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.35-7.29 (3H, m, Ar-*H*), 7.26-7.20 (3H, m, Ar-*H*), 7.05-7.01 (4H, m, Ar-*H*), 6.19 (1H, d, J_H = 1.9 Hz, C*H*CF), 5.08 (1H, d, J_H = 15.0 Hz, C*H*HN), 4.70 (1H, dd, J_F = 5.8 Hz, J_H = 2.3 Hz, C*H*N), 3.53 (1H, d, J_H = 15.0 Hz, CH*H*N).
^{19}F ($CDCl_3$, 470 MHz) δ: -138.6.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.0 (d, J_F = 31.3 Hz, CO), 152.4 (d, J_F = 279.5 Hz, *C*F), 136.5 (Ar*C*), 133.8 (Ar*C*), 129.3 (2C, Ar*C*-H), 129.2 (Ar*C*-H), 128.8 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 127.8 (Ar*C*-H), 127.6 (2C, Ar*C*-H), 118.5 (d, J_F = 4.4 Hz, CH*C*F), 59.3 (d, J_F = 5.7 Hz, *C*HN), 44.1 (Ph*C*H_2).
m/z [ESI (+ve)] 290.1 $[M+Na]^+$, HRMS found $[M+Na]^+$ 290.0943, $C_{17}H_{14}FNONa$ requires 290.0940.
IR (thin film) ν_{max} = 3063, 1710, 1666, 1456, 1220, 1186 cm^{-1}.

3-Fluoro-1-[(4'-bromophenyl)methyl]-5-phenyl-2,5-dihydro-1*H*-pyrrol-2-one, 300.

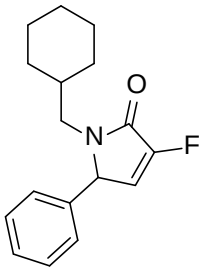


Dialkene **296** (0.12 g, 0.31 mmol) was treated with 7.5 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude residue was purified by flash

column chromatography (0 - 5% EtOAc in petroleum ether) to yield the desired product **300** (0.10 g, 0.29 mmol, 96%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.36 (2H, d, J_H = 8.3 Hz, Ar-*H*), 7.34-7.28 (3H, m, Ar-*H*), 7.03-7.00 (2H, m, Ar-*H),* 6.91 (2H, d, J_H = 8.3 Hz, Ar-*H*), 6.21 (1H, d, J_H = 2.0 Hz, C*H*CF), 4.98 (1H, J_H = 15.0 Hz, C*H*HN), 4.69 (1H, dd, J_F = 5.8 Hz, J_H = 2.2 Hz, C*H*N), 3.54 (1H, J_H = 15.0 Hz, CH*H*N).
^{19}F ($CDCl_3$, 470 MHz) δ: -138.5.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.0 (d, J_F = 31.3 Hz, CO), 152.3 (d, J_F = 279.8 Hz, *C*F), 135.5 (Ar*C*), 133.6 (d, J_F = 2.2 Hz, Ar*C*), 132.0 (2C, Ar*C*-H), 130.1 (2C, Ar*C*-H), 129.4 (2C, Ar*C*-H), 129.3 (Ar*C*-H), 127.5 (2C, Ar*C*-H), 121.9 (Ar*C*), 118.6 (d, J_F = 4.4 Hz, CH*C*F), 59.4 (d, J_F = 5.6 Hz, *C*HN), 43.6 (Ar*C*H_2).
m/z [EI (+ve)] 344.9 $[M]^+$, HRMS found $[M]^+$ 345.0167, $C_{17}H_{13}BrFNO$ requires 345.0165.
IR (thin film) ν_{max} = 2960, 1708, 1666, 1489, 1404, 1220, 1012 cm^{-1}.

3-Fluoro-1-(cyclohexylmethyl)-5-phenyl-2,5-dihydro-1*H*-pyrrol-2-one, 301.

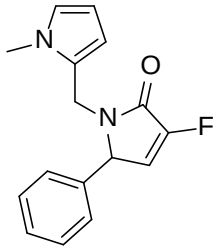


Dialkene **297** (0.15 g, 0.50 mmol) was treated with 7.5 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude residue was purified by flash column chromatography (0 - 7.5% EtOAc in petroleum ether) to yield the desired product **301** (0.13 g, 0.46 mmol, 92%) as a pale yellow oil.

^{1}H ($CDCl_3$, 500 MHz) δ: 7.37-7.22 (3H, m, Ar-*H*), 7.09-7.07 (2H, m, Ar-*H*), 6.20 (1H, d, J_H = 1.5 Hz, C*H*CF), 4.90 (1H, dd, J_F = 5.5 Hz, J_H = 2.0 Hz, C*H*N), 3.48 (1H, dd, J_H = 14.0, 8.7 Hz, C*H*HN), 2.46 (1H, dd, J_H = 14.0, 6.0 Hz, CH*H*N), 1.63-1.58 (2H, m, CH_2), 1.40-1.43 (3H, m, CH_2 and C*H*), 1.09-1.04 (3H, m, CH_2 and CH*H*), 0.87-0.79 (3H, m, CH_2 and C*H*H).
^{19}F ($CDCl_3$, 470 MHz) δ: -138.4.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.3 (d, J_F = 31.0 Hz, CO), 152.6 (d, J_F = 279.3 Hz, *C*F), 134.2 (Ar*C*), 129.3 (2C, Ar*C*-H), 129.1 (Ar*C*-H), 127.4 (2C, Ar*C*-H), 117.9 (d, J_F = 4.4 Hz, CH*C*F), 60.7 (d, J_F = 5.9 Hz, *C*HN), 46.6 (Cy*C*H_2), 37.0 (*C*H), 30.9 (*C*H_2), 30.4 (*C*H_2), 26.3 (*C*H_2), 25.7 (*C*H_2), 25.6 (*C*H_2).

m/z [EI (+ve)] 273.2 $[M]^+$, HRMS found $[M]^+$ 273.1528, $C_{17}H_{20}FNO$ requires 273.1529.
IR (thin film) ν_{max} = 2922, 2852, 1703, 1666, 1448, 1220, 1116 cm^{-1}.

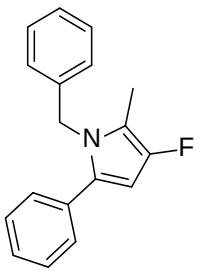
3-Fluoro-1-[(1'-methyl-1*H*-pyrrol-2'-yl)methyl]-5-phenyl-2,5-dihydro-1*H*-pyrrol-2-one, 302.



Dialkene **298** (80 mg, 0.27 mmol) was treated with 7.5 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude residue was purified by flash column chromatography (0 - 5% EtOAc in petroleum ether) to yield the desired product **302** (60 mg, 0.22 mmol, 81%) as a pale yellow solid.

^1H ($CDCl_3$, 400 MHz) δ: 7.45-7.27 (3H, m, Ar-*H*), 7.09-7.06 (2H, m, Ar-*H*), 6.51 (1H, appt t, J_H = 2.4 Hz, Ar-*H*), 6.18 (1H, d, J_H = 2.0 Hz, C*H*CF), 5.95 (1H, dd, J_H = 3.6, 2.8 Hz, Ar-*H*), 5.78 (1H, dd, J_H = 3.6, 2.0 Hz, Ar-*H*), 4.99 (1H, d, J_H = 15.5 Hz, C*H*HN), 4.74 (1H, dd, J_F = 5.9 Hz, J_H = 2.3 Hz, C*H*N), 3.60 (1H, d, J_H = 15.5 Hz, CH*H*N), 3.48 (3H, s, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -138.7.
^{13}C ($CDCl_3$, 125 MHz) δ: 162.4 (d, J_F = 31.3 Hz, CO), 151.9 (d, J_F = 279.8 Hz, *C*F), 133.7 (Ar*C*), 129.3 (2C, Ar*C*-H), 129.1 (Ar*C*-H), 127.6 (2C, Ar*C*-H), 126.8 (Ar*C*), 123.3 (Ar*C*-H), 118.8 (d, J_F = 4.2 Hz, CH*C*F), 110.3 (Ar*C*-H), 106.9 (Ar*C*-H), 58.9 (d, J_F = 5.5 Hz, *C*HN), 35.4 (CH_2), 34.1 (CH_3).
m/z [EI (+ve)] 270.1 $[M]^+$, HRMS found $[M]^+$ 270.1170, $C_{16}H_{15}FN_2O$ requires 270.1168.
IR (thin film) ν_{max} = 2960, 2359, 1716, 1666, 1417, 1217 cm^{-1}.
m.p. 92-94 ˚C.

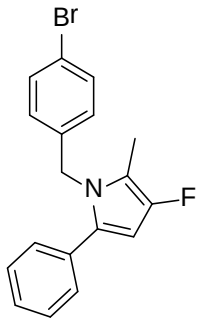
1-Benzyl-3-fluoro-2-methyl-5-phenyl-1*H*-pyrrole, 303.



α,β-Unsaturated lactam **299** (33 mg, 0.13 mmol) was reacted with methyl lithium (98 µL, 0.14 mmol, 1.4 M in diethyl ether) following General Procedure J. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **303** (29 mg, 0.11 mmol, 86%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.30-7.09 (8H, m, Ar-*H*), 6.87-6.84 (2H, m, Ar-*H*), 5.98 (1H, s, C*H*CF), 4.99 (2H, s, CH_2), 1.97 (3H, d, J_F = 1.6 Hz, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -169.3.
^{13}C ($CDCl_3$, 125 MHz) δ: 149.2 (d, J_F = 235.6 Hz, *C*F), 138.6 (Ar*C*-CH_2), 132.8 (Ar*C*), 130.2 (d, J_F = 3.3 Hz, Ph-*C*N), 128.8 (2C, Ar*C*-H), 128.8 (2C, Ar*C*-H), 128.5 (2C, Ar*C*-H), 127.2 (Ar*C*-H), 127.1 (Ar*C*-H), 125.6 (2C, Ar*C*-H), 112.6 (d, J_F = 24.4 Hz, *C*CH_3), 96.5 (d, J_F = 16.5 Hz, *C*HCF), 47.8 (Ph*C*H_2), 8.2 (*C*H_3).
m/z [EI (+ve)] 265.1 $[M]^+$, HRMS found $[M]^+$ 265.1269, $C_{18}H_{16}FN$ requires 265.1267.
IR (thin film) ν_{max} = 2924, 1662, 1599, 1452, 1352, 1118 cm^{-1}.
m.p. 44-46 ˚C.

1-[(4'-Bromophenyl)methyl]-3-fluoro-2-methyl-5-phenyl-1*H*-pyrrole, 304.

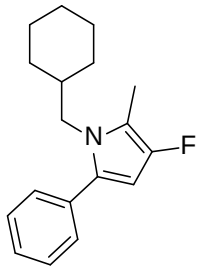


α,β-Unsaturated lactam **300** (38 mg, 0.11 mmol) was reacted with methyl lithium (74 µL, 0.12 mmol, 1.6 M in diethyl ether) following general procedure J. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **304** (31 mg, 90 µmol, 83%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.36 (2H, d, J_H = 8.6 Hz, Ar-*H*), 7.27-7.14 (5H, m, Ar-*H*), 6.72 (2H, d, J_H = 8.6 Hz, Ar-*H*), 5.98 (1H, s, C*H*CF), 4.93 (2H, s, CH_2), 1.97 (3H, d, J_F = 1.6 Hz, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -168.8.
^{13}C ($CDCl_3$, 125 MHz) δ: 149.3 (d, J_F = 236.2 Hz, *C*F), 137.7 (Ar*C*-CH_2), 132.6 (Ar*C*), 131.9 (2C, Ar*C*-H), 130.2 (d, J_F = 6.8 Hz, Ar-*C*N), 128.8 (2C, Ar*C*-H), 128.6 (2C, Ar*C*-H), 127.3 (2C, Ar*C*-H), 127.3 (Ar*C*-H), 121.0 (Ar*C*), 112.4 (d, J_F = 24.4 Hz, *C*CH_3), 96.8 (d, J_F = 16.5 Hz, *C*HCF), 47.2 (Ar*C*H_2), 8.1 (d, J_F = 2.1 Hz, *C*H_3).

m/z [EI (+ve)] 343.1 $[M]^+$, HRMS found $[M]^+$ 343.0367, $C_{18}H_{15}BrFN$ requires 343.0372.
IR (thin film) ν_{max} = 2924, 1680, 1599, 1489, 1363, 1072, 1010 cm^{-1}.
m.p. 98-100 ˚C.

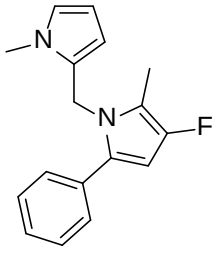
1-(Cyclohexylmethyl)-3-fluoro-2-methyl-5-phenyl-1*H*-pyrrole, 305.



α,β-Unsaturated lactam **301** (36 mg, 0.13 mmol) was reacted with methyl lithium (91 µL, 0.15 mmol, 1.6 M in diethyl ether) following general procedure J. The crude material was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **305** (29 mg, 0.11 mmol, 84%) as a white solid.

^{1}H ($CDCl_3$, 500 MHz) δ: 7.31-7.28 (2H, m, Ar-*H*), 7.25-7.20 (3H, m, Ar-*H*), 5.81 (1H, s, C*H*CF), 3.66 (2H, d, J_H = 7.0 Hz, CH_2N), 2.17 (3H, d, J_F = 1.6 Hz, CH_3), 1.50-1.45 (3H, m, CH_2 and C*H*), 1.28-1.23 (3H, m, CH_2 and C*H*H), 0.98-0.88 (3H, m, CH_2 and CH*H*), 0.56-0.49 (2H, m, CH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -170.1.
^{13}C ($CDCl_3$, 125 MHz) δ: 149.1 (d, J_F = 235.0 Hz, *C*F), 133.9 (Ar*C*), 130.0 (d, J_F = 7.2 Hz, Ar-*C*N), 128.3 (2C, Ar*C*-H), 128.3 (2C, Ar*C*-H), 126.8 (Ar*C*-H), 112.2 (d, J_F = 23.8 Hz, *C*CH_3), 96.3 (d, J_F = 16.3 Hz, *C*HCF), 50.2 (*C*H_2N), 39.2 (*C*H), 30.4 (2C, *C*H_2), 26.2 (*C*H_2), 25.7 (2C, *C*H_2), 8.5 (d, J_F = 1.9 Hz, *C*H_3).
m/z [EI (+ve)] 271.1 $[M]^+$, HRMS found $[M]^+$ 271.1733, $C_{18}H_{22}FN$ requires 271.1736.
IR (thin film) ν_{max} = 2926, 2852, 1597, 1450, 1348, 1112 cm^{-1}.
m.p. 73-75 ˚C.

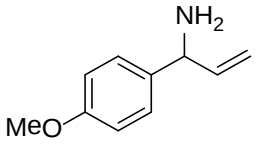
3-Fluoro-2-methyl-1-[(1'-methyl-1*H*-pyrrole-2'-yl)methyl]-5-phenyl-1*H*-pyrrole, 306.



α,β-Unsaturated lactam **302** (31 mg, 0.12 mmol) was reacted with methyl lithium (79 µL, 0.13 mmol, 1.6 M in diethyl ether) following general procedure J. The crude redidue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **306** (23 mg, 90 µmol, 75%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.28-7.23 (2H, m, Ar-*H*), 7.23-7.19 (3H, m, Ar-*H*), 6.46 (1H, appt t, J_H = 2.5 Hz, Ar-*H*), 5.95 (1H, appt t, J_H = 3.5 Hz, Ar-*H*), 5.92 (1H, s, C*H*CF), 5.70-5.69 (1H, m, Ar-*H*), 4.88 (2H, s, CH_2N), 3.26 (3H, s, NCH_3), 2.03 (3H, d, J_F = 1.6 Hz, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -169.5.
^{13}C ($CDCl_3$, 125 MHz) δ: 149.2 (d, J_F = 235.4 Hz, *C*F), 133.0 (Ar*C*), 129.9 (d, J_F = 6.9 Hz, Ph-*C*N), 128.8 (3C, Ar*C*-H and Ar*C*), 128.5 (2C, Ar*C*-H), 127.1 (Ar*C*-H), 122.3 (Ar*C*-H), 112.9 (d, J_F = 24.6 Hz, *C*CH_3), 107.9 (Ar*C*-H), 107.1 (Ar*C*-H), 96.4 (d, J_F = 16.5 Hz, *C*HCF), 41.6 (Ar*C*H_2), 33.7 (NCH_3), 8.2 (C*C*H_3).
m/z [EI (+ve)] 268.1 $[M]^+$, HRMS found $[M]^+$ 268.1380, $C_{17}H_{17}FN_2$ requires 268.1376.
IR (thin film) ν_{max} = 2922, 1705, 1599, 1469, 1361, 1301, 1089 cm^{-1}.
m.p. 69-71 ˚C.

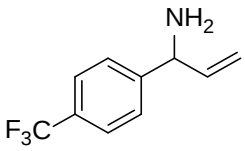
1-(4'-Methoxyphenyl)prop-2-en-1-amine, 307.[156]



Following General Procedure F, 4-methoxybenzaldehyde (0.42 mL, 3.67 mmol) reacted with *tert*-butylsulfinamide (0.48 g, 3.97 mmol) and vinylmagnesium bromide (11 mL, 1.0 M in THF, 10.8 mmol). Following acid-base work up the desired product **307** was yielded as a colourless oil (0.42 g, 2.60 mmol, 71%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.30 (2H, d, J_H = 8.4 Hz, Ar-*H*), 6.91 (2H, d, J_H = 8.4 Hz, Ar-*H*), 6.03 (1H, ddd, J_H = 17.2, 10.2, 6.1 Hz, C*H*CH_2), 5.24 (1H, dt, J_H = 17.2, 1.6 Hz, CHC*H*H), 5.12 (1H, dt, J_H = 10.2, 1.6 Hz, CHCH*H*), 4.51 (1H, d, J_H = 6.0 Hz, C*H*NH_2), 3.83 (3H, s, CH_3), 1.55 (2H, s, NH_2).
^{13}C ($CDCl_3$, 125 MHz) δ: 158.7 (Ar*C*-OMe), 142.6 (*C*HCH_2), 136.7 (Ar*C*-CH), 127.7 (2C, Ar*C*-H), 114.0 (2C, Ar*C*-H), 113.4 (CH*C*H_2), 57.8 (*C*HNH_2), 55.3 (*C*H_3).
The spectral data is in agreement with the literature values.[156]

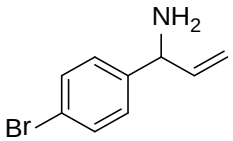
1-(4'-(Trifluoromethyl)phenyl)prop-2-en-1-amine, 308.[157]



Following General Procedure F, 4-(trifluoromethane)benzaldehyde (0.39 mL, 2.87 mmol) reacted with *tert*-butylsulfinamide (0.38 g, 3.16 mmol) and vinylmagnesium bromide (8.6 mL, 1.0 M in THF, 8.61 mmol). Following acid-base work up the desired product **308** was yielded as a colourless oil (0.35 g, 1.75 mmol, 61%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.53 (2H, d, J_H = 8.0 Hz, Ar-*H*), 7.42 (2H, d, J_H = 8.0 Hz, Ar-*H*), 5.91 (1H, ddd, J_H = 17.2, 10.4, 6.4 Hz, C*H*CH_2), 5.19 (1H, dt, J_H = 17.2, 1.2 Hz, CHC*H*H), 5.08 (1H, dt, J_H = 10.4, 1.2 Hz, CHCH*H*), 4.52 (1H, d, J_H = 6.4 Hz, C*H*NH_2), 1.51 (2H, s, NH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -62.4.
^{13}C ($CDCl_3$, 125 MHz) δ: 148.3 (Ar*C*-CF_3), 141.5 (*C*HCH_2), 129.4 (q, J_F = 32.3 Hz, CF_3), 127.1 (2C, Ar*C*-H), 125.5 (2C, Ar*C*-H), 122.8 (Ar*C*-CH), 114.6 (CH*C*H_2), 58.1 (*C*HNH_2).
The spectral data is in agreement with the literature values.[157]

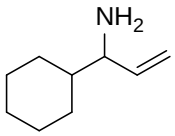
1-(4'-Bromophenyl)-2-propenylamine, 309.[156]



Following General Procedure F, 4-bromobenzaldehyde (0.50 g, 2.70 mmol) reacted with *tert*-butylsulfinamide (0.35 g, 2.97 mmol) and vinylmagnesium bromide (8.1 mL, 1.0 M in THF, 8.11 mmol). Following acid-base work up the desired product **309** was yielded as a colourless oil (0.43 g, 2.04 mmol, 75%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.46 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.25 (2H, d, J_H = 8.4 Hz, Ar-*H*), 5.99 (1H, ddd, J_H = 16.8, 10.0, 6.2 Hz, C*H*CH_2), 5.24 (1H, dt, J_H = 16.8, 1.2 Hz, CHC*H*H), 5.14 (1H, dt, J_H = 10.0, 1.2 Hz, CHCH*H*), 4.51 (1H, d, J_H = 6.2 Hz, C*H*NH_2), 1.54 (2H, s, NH_2).
^{13}C ($CDCl_3$, 125 MHz) δ: 153.4 (Ar*C*-Br), 141.8 (*C*HCH_2), 131.6 (2C, Ar*C*-H), 128.5 (2C, Ar*C*-H), 120.9 (Ar*C*-CH), 114.2 (CH*C*H_2), 57.9 (*C*HNH_2).
The spectral data is in agreement with the literature values.[156]

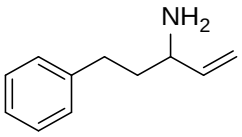
1-Cyclohexylprop-2-en-1-amine, 310.[156]



Following General Procedure F, cyclohexanecarboxaldehyde (0.53 mL, 4.44 mmol) reacted with *tert*-butylsulfinamide (0.59 g, 4.88 mmol) and vinylmagnesium bromide (13 mL, 1.0 M in THF, 13.3 mmol). Following acid-base work up the desired product **310** was yielded as a colourless oil (0.31 g, 2.22 mmol, 50%).

^{1}H ($CDCl_3$, 400 MHz) δ: 5.72 (1H, ddd, J_H = 17.3, 10.3, 7.2 Hz, C*H*CH_2), 5.04-4.95 (2H, m, CHC*H*$_2$), 2.98 (1H, dd, J_H = 7.2, 6.4 Hz, C*H*NH_2), 1.72-1.57 (6H, m, C*H*$_2$ and N*H*$_2$), 1.25-1.00 (5H, m, C*H* and C*H*$_2$), 0.95-0.85 (2H, m, C*H*$_2$).
^{13}C ($CDCl_3$, 125 MHz) δ: 142.1 (*C*HCH_2), 114.0 (CH*C*H_2), 59.6 (*C*HNH_2), 43.7 (*C*HCH), 29.3 (*C*H_2), 29.0 (*C*H_2), 26.6 (*C*H_2), 26.4 (*C*H_2), 26.3 (*C*H_2).
The spectral data is in agreement with the literature values.[156]

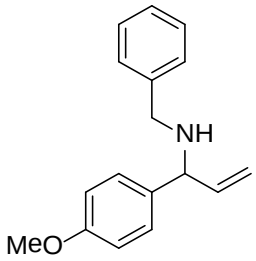
5-Phenylpent-1-en-3-amine. 311.[156]



Following General Procedure F, 3-phenylpropionaldehyde (0.46 mL, 3.73 mmol, 95%) reacted with *tert*-butylsulfinamide (0.49 g, 4.10 mmol) and vinylmagnesium bromide (11 mL, 1.0 M in THF, 11.1 mmol). Following acid-base work up the desired product **311** was yielded as a colourless oil (0.33 g, 2.05 mmol, 58%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.23-7.18 (2H, m, Ar-*H*), 7.13–7.09 (3H, m, Ar-*H*), 5.75 (1H, ddd, J_H = 17.2, 10.4, 6.8 Hz, C*H*CH_2), 5.04 (1H, dt, J_H = 17.2, 1.6 Hz, CHC*H*H), 4.98 (1H, dt, J_H = 10.4, 1.6 Hz, CHCH*H*), 3.27-3.22 (1H, m, C*H*NH_2), 2.62-2.58 (2H, m, C*H*$_2$), 1.71-1.65 (2H, m, C*H*$_2$), 1.14 (2H, s, N*H*$_2$).
^{13}C ($CDCl_3$, 125 MHz) δ: 143.3 (*C*HCH_2), 142.1 (Ar*C*-CH_2), 128.4 (2C, Ar*C*-H), 128.3 (2C, Ar*C*-H), 125.8 (Ar*C*-H), 113.7 (CH*C*H_2), 54.1 (*C*HNH_2), 39.2 (*C*H_2), 32.4 (*C*H_2).
The spectral data is in agreement with the literature values.[156]

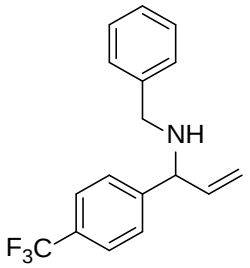
***N*-[1-(4'-Methoxyphenyl)-2-propenyl]benzylamine, 312.**[151]



Following General Procedure G, amine **307** (0.30 g, 1.84 mmol) was reacted with benzaldehyde (0.19 mL, 1.93 mmol) and $NaBH_4$ (0.11 g, 2.76 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **312** (0.36 g, 1.42 mmol, 79%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.29-7.17 (7H, m, Ar-*H*), 6.80 (2H, d, J_H = 8.8 Hz, Ar-*H*), 5.86 (1H, ddd, J_H = 17.2, 10.2, 7.2 Hz, C*H*CH_2), 5.13 (1H, dt, J_H = 17.2, 1.2 Hz, CHC*H*H), 5.03 (1H, dt, J_H = 10.2, 1.2 Hz, CHCH*H*), 4.09 (1H, d, J_H = 7.2 Hz, C*H*NH), 3.72 (3H, s, CH_3), 3.66 (1H, d, J_H = 13.6 Hz, C*H*HNH), 3.62 (1H, d, J_H = 13.6 Hz, CH*H*NH), 1.64 (1H, s, N*H*).
^{13}C ($CDCl_3$, 125 MHz) δ: 158.8 (Ar*C*-OMe), 141.2 (*C*HCH_2), 140.5 (Ar*C*-CH_2), 134.9 (Ar*C*-CH), 128.4 (2C, Ar*C*-H), 128.2 (2C, Ar*C*-H), 127.0 (Ar*C*-H), 126.9 (2C, Ar*C*-H), 114.8 (CH*C*H_2), 113.9 (2C, Ar*C*-H), 64.4 (*C*HNH_2), 55.3 (*C*H_3), 51.3 (*C*H_2).
The spectral data is in agreement with the literature values.[151]

***N*-[1-(4'-(Trifluoromethyl)phenyl)-2-propenyl]benzylamine, 313.**[158]



Following General Procedure G, amine **308** (0.26 g, 1.31 mmol) was reacted with benzaldehyde (0.14 mL, 1.38 mmol) and $NaBH_4$ (70 mg, 1.96 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **313** (0.30 g, 1.03 mmol, 80%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.53 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.44 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.28-7.16 (5H, m, Ar-*H*), 5.83 (1H, ddd, J_H = 17.2, 10.4, 7.2 Hz, C*H*CH_2), 5.09 (1H, dt, J_H =

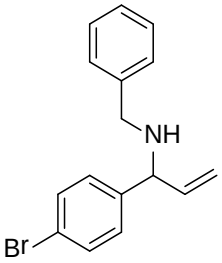
17.2, 1.2 Hz, CHC*H*H), 5.08 (1H, dt, J_H = 10.4, 1.2 Hz, CHCH*H*), 4.22 (1H, d, J_H = 7.2 Hz, C*H*NH), 3.67 (1H, d, J_H = 13.6 Hz, C*H*HNH), 3.61 (1H, d, J_H = 13.6 Hz, CH*H*NH), 1.56 (1H, s, N*H*).

^{19}F ($CDCl_3$, 470 MHz) δ: -62.4.

^{13}C ($CDCl_3$, 125 MHz) δ: 146.9 (Ar*C*-CF_3), 140.2 (*C*HCH_2), 140.0 (Ar*C*-CH_2), 129.6 (q, J_F = 32.3 Hz, CF_3), 128.5 (2C, Ar*C*-H), 128.1 (2C, Ar*C*-H), 127.7 (2C, Ar*C*-H), 127.1 (ArC-H), 125.5 (2C, Ar*C*-H), 122.9 (Ar*C*-CH), 116.0 (CH*C*H_2), 64.8 (*C*HNH_2), 51.3 (CH_2).

The spectral data is in agreement with the literature values.[158]

_N_-[1-(4'-Bromophenyl)-2-propenyl]benzylamine, 314.[159]



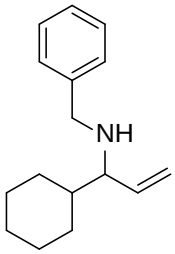
Following General Procedure G, amine **309** (0.30 g, 1.41 mmol) was reacted with benzaldehyde (0.15 mL, 1.49 mmol) and $NaBH_4$ (80 mg, 2.12 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **314** (0.36 g, 1.20 mmol, 84%) as a pale yellow oil.

^1H ($CDCl_3$, 400 MHz) δ: 7.49 (2H, d, J_H = 8.0 Hz, Ar-*H*), 7.38-7.26 (7H, m, Ar-*H*), 5.92 (1H, ddd, J_H = 17.2, 10.4, 7.2 Hz, C*H*CH_2), 5.24 (1H, dt, J_H = 17.2, 1.2 Hz, CHC*H*H), 5.16 (1H, dt, J_H = 10.4, 1.2 Hz, CHCH*H*), 4.23 (1H, d, J_H = 7.2 Hz, C*H*NH), 3.76 (1H, d, J_H = 13.2 Hz, C*H*HNH), 3.71 (1H, d, J_H = 13.2 Hz, CH*H*NH), 1.62 (1H, s, N*H*).

^{13}C ($CDCl_3$, 125 MHz) δ: 141.9 (Ar*C*-Br), 140.5 (*C*HCH_2), 140.2 (Ar*C*-CH_2), 131.6 (2C, Ar*C*-H), 129.1 (2C, Ar*C*-H), 128.5 (2C, Ar*C*-H), 128.1 (2C, Ar*C*-H), 127.0 (ArC-H), 121.0 (Ar*C*-CH), 115.6 (CH*C*H_2), 64.5 (*C*HNH_2), 51.3 (*C*H_2).

The spectral data is in agreement with the literature values.[159]

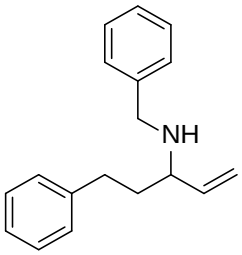
_N_-[1-Cyclohexyl-2-propenyl]benzylamine, 315.



Following General Procedure G, amine **310** (0.22 g, 1.50 mmol) was reacted with benzaldehyde (0.17 g, 1.65 mmol) and $NaBH_4$ (90 mg, 2.36 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **315** (0.24 g, 1.05 mmol, 70%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.32-7.15 (5H, m, Ar-*H*), 5.54 (1H, ddd, J_H = 14.0, 8.0, 7.2 Hz, C*H*CH_2), 5.11-5.09 (1H, m, CHC*H*H), 4.99-4.96 (1H, m, CHCH*H*), 3.76 (1H, d, J_H = 10.8 Hz, CH*H*NH), 3.52 (1H, d, J_H = 10.8 Hz, C*H*HNH), 2.69 (1H, dd, J_H = 7.2, 5.2 Hz, C*H*NH), 1.73-1.55 (5H, m, CH_2 and N*H*), 1.31-1.25 (2H, m, CH_2), 1.12-1.00 (3H, m, C*H* and CH_2), 0.95-0.85 (2H, m, CH_2).
^{13}C ($CDCl_3$, 125 MHz) δ: 140.9 (Ar*C*-CH_2), 139.6 (*C*HCH_2), 128.3 (2C, Ar*C*-H), 128.2 (2C, Ar*C*-H), 126.7 (ArC-H), 116.7 (CH*C*H_2), 66.3 (*C*HNH_2), 51.3 (Ar-*C*H_2), 42.3 (*C*HCH), 30.0 (*C*H_2), 29.2 (*C*H_2), 26.7 (*C*H_2), 26.4 (*C*H_2), 26.3 (*C*H_2).
m/z [EI (+ve)] 229.3 $[M]^+$, HRMS found $[M]^+$ 229.1832, $C_{16}H_{23}N$ requires 229.1830.
IR (thin film) ν_{max} = 2922, 2850, 1450, 1028 cm^{-1}.

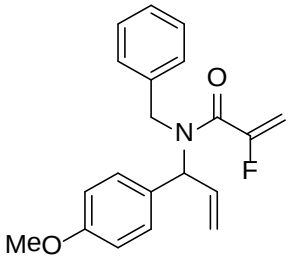
_N_-[5-Phenylpent-1-3-yl]benzylamine, 316.[160]



Following General Procedure G, amine **311** (0.24 g, 1.53 mmol) was reacted with benzaldehyde (0.16 mL, 1.60 mmol) and $NaBH_4$ (90 mg, 2.28 mmol). The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **316** (0.33 g, 1.31 mmol, 86%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.30-7.23 (4H, m, Ar-*H*), 7.21-7.07 (6H, m, Ar-*H*), 5.61 (1H, ddd, J_H = 17.2, 10.0, 8.4 Hz, C*H*CH_2), 5.15-5.05 (2H, m, CHCH_2), 3.75 (1H, d, J_H = 13.2 Hz, C*H*HNH), 3.56 (1H, d, J_H = 13.2 Hz, CH*H*NH), 3.03-2.97 (1H, m, C*H*NH), 2.64-2.52 (2H, m, CH_2), 1.81-1.63 (2H, m, CH_2).
^{13}C ($CDCl_3$, 125 MHz) δ: 142.2 (Ar*C*-CH_2), 141.0 (*C*HCH_2), 140.6 (Ar*C*-CH_2), 128.4 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 128.3 (2C, Ar*C*-H), 128.2 (2C, Ar*C*-H), 127.0 (ArC-H), 126.9 (ArC-H), 116.6 (CH*C*H_2), 60.8 (*C*HNH_2), 51.2 (Ar-*C*H_2), 37.3 (*C*H_2), 32.2 (*C*H_2).
The spectral data is in agreement with the literature values.[160]

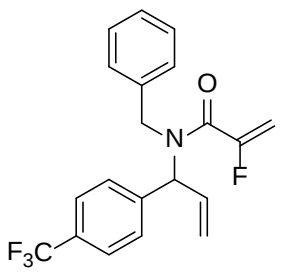
***N*-Benzyl-2-fluoro-*N*-[1'-(4''-methoxyphenyl)prop-2'-en-1'-yl]-prop-2-enamide, 317.**



Amine **312** (0.20 g, 0.79 mmol) was coupled with 2-fluoroacrylic acid (0.14 g, 1.6 mmol) using HBTU (0.60 g, 1.6 mmol) and DIPEA (0.28 mL, 1.6 mmol) following General Procedure H. The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **317** (0.16 g, 0.49 mmol, 62%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.29-7.16 (5H, m, Ar-*H*), 7.09–7.07 (2H, m, Ar-*H*), 6.85 (2H, J_H = 8.8 Hz, Ar-*H*), 6.09 (1H, ddd, J_H = 16.8, 10.4, 7.2 Hz, C*H*CH_2), 5.84 (1H, d, J_H = 7.2 Hz, C*H*N), 5.41-5.22 (3H, m, CFC*H*$_2$ and CHC*H*H), 5.11 (1H, dd, J_H = 16.8 Hz, 2.4 Hz, CHCH*H*), 4.61 (1H, d, J_H = 16.0 Hz, C*H*HN), 4.45 (1H, d, J_H = 16.0 Hz, CH*H*N), 3.81 (3H, s, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -102.9, -105.5.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.3 (d, J_F = 31.0 Hz, *C*O), 159.2 (Ar*C*-OMe), 157.9 (d, J_F = 272.0 Hz, *C*F), 137.5 (Ar*C*), 134.9 (*C*HCH_2), 130.0 (Ar*C*), 129.4 (2C, Ar*C*-H), 128.2 (2C, Ar*C*-H), 127.3 (2C, Ar*C*-H), 127.0 (Ar*C*-H), 118.8 (CH*C*H_2), 114.0 (2C, Ar*C*-H), 99.3 (CF*C*H_2), 62.9 (*C*HN), 55.3 (*C*H_3), 48.4 (Ph*C*H_2).
m/z [EI (+ve)] 325.1 $[M]^+$, HRMS found $[M]^+$ 325.1476, $C_{20}H_{20}FNO_2$ requires 325.1478.
IR (thin film) ν_{max} = 2252, 1633, 1421, 1249, 1178 cm^{-1}.

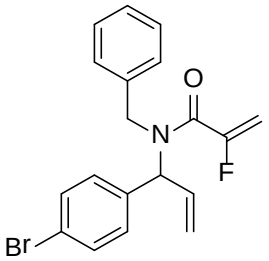
***N*-Benzyl-2-fluoro-*N*-[1'-(4''-trifluoromethanephenyl)prop-2'-en-1'-yl]-prop-2-enamide, 318.**



Amine **313** (0.22 g, 0.76 mmol) was coupled with 2-fluoroacrylic acid (0.15 g, 1.7 mmol) using HBTU (0.65 g, 1.7 mmol) and DIPEA (0.28 mL, 1.7 mmol) following General Procedure H. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **318** (0.13 g, 0.34 mmol, 45%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.47 (2H, J_H = 8.2 Hz, Ar-*H*), 7.28 (2H, J_H = 8.2 Hz, Ar-*H*), 7.23-7.11 (3H, m, Ar-*H*), 7.08–7.00 (2H, m, Ar-*H*), 6.12-6.00 (1H, m, C*H*CH_2), 5.64 (1H, appt s, C*H*N), 5.34-5.19 (3H, m, CFCH_2 and CHC*H*H), 5.05 (1H, dd, J_H = 13.6 Hz, 2.4 Hz, CHCH*H*), 4.58 (1H, d, J_H = 16.0 Hz, C*H*HN), 4.43 (1H, d, J_H = 16.0 Hz, CH*H*N).
^{19}F ($CDCl_3$, 470 MHz) δ: -62.6, -103.3, -105.7.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.1 (d, J_F = 30.4 Hz, *C*O), 157.6 (d, J_F = 272.6 Hz, *C*F), 142.3 (Ar*C*-CF_3), 140.2 (CF_3), 140.1 (Ar*C*), 136.9 (Ar*C*), 133.7 (*C*HCH_2), 128.5 (2C, Ar*C*-H), 128.1 (Ar*C*-H), 128.1 (2C, Ar*C*-H), 127.4 (2C, Ar*C*-H), 125.5 (2C, Ar*C*-H), 120.3 (CH*C*H_2), 100.3 (CF*C*H_2), 63.1 (*C*HN), 51.3 (Ph*C*H_2).
m/z [EI (+ve)] 363.1 $[M]^+$, HRMS found $[M]^+$ 363.1245, $C_{20}H_{17}F_4NO$ requires 363.1246.
IR (thin film) ν_{max} = 3020, 1639, 1417, 1325, 1166, 1126, 1068 cm^{-1}.

_N_-Benzyl-2-fluoro-_N_-[1'-(4''-bromophenyl)prop-2'-en-1'-yl]-prop-2-enamide, 319.



Amine **314** (0.24 g, 0.78 mmol) was coupled with 2-fluoroacrylic acid (0.14 g, 1.6 mmol) using HBTU (0.60 g, 1.6 mmol) and DIPEA (0.28 mL, 1.6 mmol) following General Procedure H. The crude residue was purified by flash column chromatography (0 - 5% diethyl ether in petroleum ether) to yield the desired product **319** (0.18 g, 0.48 mmol, 62%) as a pale yellow oil.

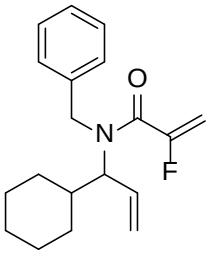
^{1}H ($CDCl_3$, 400 MHz) δ: 7.44 (2H, J_H = 8.5 Hz, Ar-*H*), 7.29-7.23 (3H, m, Ar-*H*), 7.16–7.11 (4H, m, Ar-*H*), 6.10 (1H, ddd, J_H = 17.2, 10.4, 7.2 Hz, C*H*CH_2), 5.72 (1H, d, J_H = 7.2 Hz, C*H*N), 5.42-5.26 (3H, m, CFCH_2 and CHC*H*H), 5.13 (1H, dd, J_H = 17.2 Hz, 3.4 Hz, CHCH*H*), 4.64 (1H, d, J_H = 16.2 Hz, C*H*HN), 4.47 (1H, d, J_H = 16.2 Hz, CH*H*N).
^{19}F ($CDCl_3$, 470 MHz) δ: -103.2, -105.8.

^{13}C ($CDCl_3$, 125 MHz) δ: 163.2 (d, J_F = 30.3 Hz, *C*O), 157.7 (d, J_F = 272.5 Hz, *C*F), 140.5 (Ar*C*-Br), 137.2 (Ar*C*), 137.1 (Ar*C*), 134.0 (*C*HCH$_2$), 131.7 (2C, Ar*C*-H), 129.6 (3C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 127.3 (2C, Ar*C*-H), 119.8 (CH*C*H$_2$), 100.0 (CF*C*H$_2$), 62.9 (*C*HN), 51.2 (Ph*C*H$_2$).

m/z [EI (+ve)] 373.2 $[M]^+$, HRMS found $[M]^+$ 373.0478, $C_{19}H_{17}BrFNO$ requires 373.0478.

IR (thin film) ν_{max} = 3030, 1639, 1487, 1415, 1209, 1074, 1010 cm^{-1}.

_N_-Benzyl-2-fluoro-_N_-[1'-cyclohexylprop-2'-en-1'-yl]-prop-2-enamide, 320.



Amine **315** (0.18 g, 0.78 mmol) was coupled with 2-fluoroacrylic acid (0.14 g, 1.6 mmol) using HBTU (0.59 g, 1.6 mmol) and DIPEA (0.26 mL, 1.6 mmol) following General Procedure H. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **320** (0.18 g, 0.59 mmol, 76%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.39-7.23 (5H, m, Ar-*H*), 6.00-5.68 (1H, m, C*H*CH$_2$), 5.34-4.94 (3H, m, CFC*H*$_2$ and CHC*H*H), 4.82-4.58 (1H, m, CHCH*H*), 4.55-4.30 (1H, m, C*H*HN), 4.14-3.80 (1H, m, CH*H*N), 2.04-1.51 (6H, m, C*H*$_2$ and C*H*), 1.38-1.03 (3H, m, CH*H* and C*H*$_2$), 0.97-0.68 (3H, m, C*H*H and C*H*$_2$).

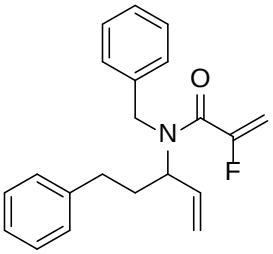
^{19}F ($CDCl_3$, 470 MHz) δ: -102.5, -104.6.

^{13}C ($CDCl_3$, 125 MHz) δ: 163.2 (d, J_F = 33.7 Hz, *C*O), 158.0 (d, J_F = 274.5 Hz, *C*F), 137.7 (Ar*C*), 135.2 (*C*HCH$_2$), 128.3 (2C, Ar*C*-H), 127.3 (2C, Ar*C*-H), 126.9 (Ar*C*-H), 119.3 (CH*C*H$_2$), 98.9 (CF*C*H$_2$), 67.2 (*C*HN), 51.5 (Ph*C*H$_2$), 39.3 (*C*H), 30.7 (*C*H$_2$), 29.9 (*C*H$_2$), 26.2 (*C*H$_2$), 26.0 (*C*H$_2$), 25.9 (*C*H$_2$).

m/z [ESI (+ve)] 373.2 $[M+Na]^+$, HRMS found $[M+Na]^+$ 373.1719, $C_{19}H_{24}FNONa$ requires 373.1719.

IR (thin film) ν_{max} = 2928, 2852, 1637, 1446, 1417, 1192 cm^{-1}.

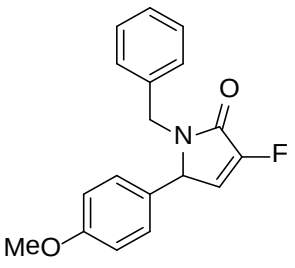
_N_-Benzyl-2-fluoro-_N_-[5'-phenylpent-1'-en-3'-yl]-prop-2-enamide, 321.



Amine **316** (0.24 g, 0.96 mmol) was coupled with 2-fluoroacrylic acid (0.17 g, 1.9 mmol) using HBTU (0.73 g, 1.9 mmol) and DIPEA (0.33 mL, 1.9 mmol) following General Procedure H. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **321** (0.23 g, 0.71 mmol, 75%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.34-7.20 (8H, m, Ar-*H*), 7.12–6.88 (2H, m, Ar-*H*), 6.02-5.84 (1H, m, C*H*CH_2), 5.34-5.14 (3H, m, CFCH_2 and C*H*N) 5.09 (1H, dd, J_H = 17.1 Hz, 3.5 Hz, CHC*H*H), 4.81-4.31 (3H, m, CHCH*H* and CH_2N), 2.59-2.44 (2H, m, CH_2), 2.07-1.93 (2H, m, CH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -103.1, -104.7.
^{13}C ($CDCl_3$, 125 MHz) δ: 163.6 (d, J_F = 32.8 Hz, *C*O), 158.0 (d, J_F = 270.9 Hz, *C*F), 141.1 (Ar*C*), 137.8 (Ar*C*), 136.2 (*C*HCH$_2$), 128.5 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 128.3 (2C, Ar*C*-H), 127.8 (Ar*C*-H), 127.4 (Ar*C*-H), 126.1 (2C, Ar*C*-H), 118.2 (CH*C*H$_2$), 99.1 (CF*C*H$_2$), 60.4 (*C*HN), 40.9 (PhCH$_2$), 32.8 (*C*H$_2$), 32.6 (*C*H$_2$).
m/z [EI (+ve)] 323.2 $[M]^+$, HRMS found $[M]^+$ 323.1683, $C_{21}H_{22}FNO$ requires 323.1685.
IR (thin film) ν_{max} = 2931, 1635, 1417, 1359, 1178, 1153 cm^{-1}.

1-Benzyl-3-fluoro-5-(4'-methoxyphenyl)-2,5-dihydro-1*H*-pyrrol-2-one, 322.



Dialkene **317** (0.10 g, 0.31 mmol) was treated with 7.5 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **322** (70 mg, 0.22 mmol, 71%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.35-7.29 (3H, m, Ar-*H*), 7.14-7.13 (2H, m, Ar-*H*), 7.03 (2H, d, J_H = 8.7 Hz, Ar-*H*), 6.93 (2H, d, J_H = 8.7 Hz, Ar-*H*), 6.25 (1H, d, J_H = 1.6 Hz, C*H*CF), 5.15 (1H, d, J_H = 15.0 Hz, C*H*HN), 4.75 (1H, dd, J_F = 5.8 Hz, J_H = 2.1 Hz, C*H*N), 3.85 (3H, s, CH_3), 3.61 (1H, d, J_H = 15.0 Hz, CH*H*N).

^{19}F ($CDCl_3$, 470 MHz) δ: -138.7.

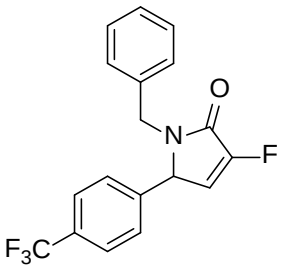
^{13}C ($CDCl_3$, 125 MHz) δ: 162.9 (d, J_F = 31.3 Hz, CO), 160.3 (Ar*C*-OMe), 152.3 (d, J_F = 279.3 Hz, *C*F), 136.7 (Ar*C*), 128.9 (2C, Ar*C*-H), 128.8 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 127.8 (Ar*C*-H), 125.4 (d, J_F = 2.1 Hz, Ar*C*), 118.5 (d, J_F = 4.0 Hz, CH*C*F), 114.6 (2C, Ar*C*-H), 58.7 (d, J_F = 5.8 Hz, *C*HN), 55.4 (*C*H_3), 43.9 (Ph*C*H_2).

m/z [EI (+ve)] 297.1 $[M]^+$, HRMS found $[M]^+$ 297.1169, $C_{18}H_{16}FNO_2$ requires 297.1165.

IR (thin film) ν_{max} = 2933, 1707, 1666, 1512, 1247, 1174, 1030 cm^{-1}.

m.p. 101-103 ˚C.

1-Benzyl-3-fluoro-5-[(4'-trifluoromethyl)phenyl]-2,5-dihydro-1*H*-pyrrol-2-one, 323.



Dialkene **318** (80 mg, 0.22 mmol) was treated with 15 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude residue was purified by flash column chromatography (0 - 15% EtOAc in petroleum ether) to yield the desired product **323** (70 mg, 0.20 mmol, 88%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.58 (2H, d, J_H = 8.1 Hz, Ar-*H*), 7.26-7.21 (3H, m, Ar-*H*), 7.16 (2H, d, J_H = 8.1 Hz, Ar-*H*), 7.03-7.01 (2H, m, Ar-*H),* 6.19 (1H, d, J_H = 1.2 Hz, C*H*CF), 5.09 (1H, d, J_H = 15.0 Hz, C*H*HN), 4.77 (1H, dd, J_F = 4.8 Hz, J_H = 2.0 Hz, C*H*N), 3.57 (1H, d, J_H = 15.0 Hz, CH*H*N).

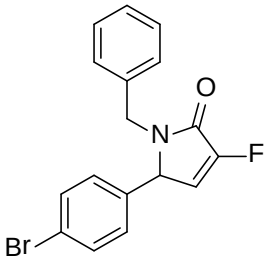
^{19}F ($CDCl_3$, 470 MHz) δ: -62.9, -137.2.

^{13}C ($CDCl_3$, 125 MHz) δ: 162.9 (d, J_F = 31.2 Hz, CO), 152.7 (d, J_F = 280.9 Hz, *C*F), 138.1 (CF_3), 136.1 (Ar*C*), 131.7 (Ar*C*), 131.4 (Ar*C*), 129.0 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 128.1 (Ar*C*-H), 128.0 (2C, Ar*C*-H), 126.3 (2C, q, J_F = 3.7 Hz, Ar*C*-H), 118.0 (d, J_F = 5.0 Hz, CH*C*F), 58.7 (d, J_F = 5.7 Hz, *C*HN), 44.4 (Ph*C*H_2).

m/z [EI (+ve)] 335.0 $[M]^+$, HRMS found $[M]^+$ 335.0932, $C_{18}H_{13}F_4NO$ requires 335.0933.

IR (thin film) ν_{max} = 2362, 2332, 1718, 1670, 1421, 1325, 1166, 1126, 1066 cm^{-1}.

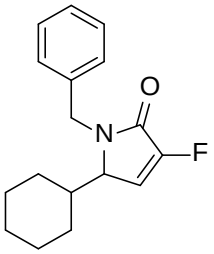
1-Benzyl-3-fluoro-5-(4'-bromophenyl)-2,5-dihydro-1*H*-pyrrol-2-one, 324.



Dialkene **319** (99 mg, 0.26 mmol) was treated with 10 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **324** (87 mg, 0.25 mmol, 96%) as a pale yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.54 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.36-7.30 (3H, m, Ar-*H*), 7.13-7.10 (2H, m, Ar-*H),* 7.00 (2H, d, J_H = 8.4 Hz, Ar-*H*), 6.26 (1H, d, J_H = 1.6 Hz, C*H*CF), 5.17 (1H, d, J_H = 15.0 Hz, C*H*HN), 4.76 (1H, dd, J_F = 5.8 Hz, J_H = 2.2 Hz, C*H*N), 3.62 (1H, d, J_H = 15.0 Hz, CH*H*N).
^{19}F ($CDCl_3$, 470 MHz) δ: -137.7.
^{13}C ($CDCl_3$, 125 MHz) δ: 162.9 (d, J_F = 31.2 Hz, CO), 152.5 (d, J_F = 280.5 Hz, *C*F), 136.3 (Ar*C*), 132.9 (d, J_F = 2.2 Hz, Ar*C*), 132.5 (2C, Ar*C*-H), 129.2 (2C, Ar*C*-H), 128.9 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 128.0 (Ar*C*-H), 123.2 (Ar*C*), 118.1 (d, J_F = 4.7 Hz, CH*C*F), 58.6 (d, J_F = 5.7 Hz, *C*HN), 44.2 (Ph*C*H_2).
m/z [EI (+ve)] 345.1 $[M]^+$, HRMS found $[M]^+$ 345.0165, $C_{17}H_{13}BrFNO$ requires 345.0165.
IR (thin film) ν_{max} = 3030, 1708, 1666, 1489, 1408, 1220, 1078, 1010 cm^{-1}.

1-Benzyl-3-fluoro-5-cyclohexyl-2,5-dihydro-1*H*-pyrrol-2-one, 325.



Dialkene **320** (0.10 g, 0.34 mmol) was treated with 7.5 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude residue was purified by flash column chromatography (0 - 5% EtOAc in petroleum ether) to yield the desired product **325** (88 mg, 0.32 mmol, 95%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.28-7.16 (5H, m, Ar-*H*), 6.12 (1H, d, J_H = 2.1 Hz, C*H*CF), 5.03 (1H, d, J_H = 15.2 Hz, C*H*HN), 4.01 (1H, d, J_H = 15.2 Hz, CH*H*N), 3.73-3.70 (1H, m, C*H*N), 1.83-1.69 (2H, m, CH_2), 1.66-1.54 (3H, m, CH_2 and C*H*), 1.31-1.18 (2H, m, CH_2), 1.05-0.97 (3H, m, CH_2 and C*H*H), 0.87-0.77 (1H, m, CH*H*).

^{19}F ($CDCl_3$, 470 MHz) δ: -136.9.

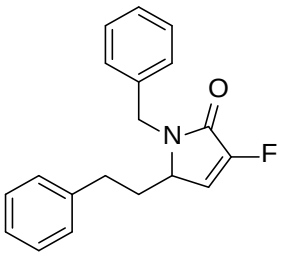
^{13}C ($CDCl_3$, 125 MHz) δ: 163.4 (d, J_F = 31.5 Hz, CO), 152.8 (d, J_F = 277.4 Hz, *C*F), 136.7 (Ar*C*), 128.3 (2C, Ar*C*-H), 128.0 (2C, Ar*C*-H), 127.7 (Ar*C*-H), 115.6 (d, J_F = 4.2 Hz, CH*C*F), 60.1 (d, J_F = 4.4 Hz, *C*HN), 44.2 (Ph*C*H_2), 37.8 (*C*H), 30.1 (*C*H_2), 36.5 (*C*H_2), 26.3 (*C*H_2), 25.7 (*C*H_2), 25.5 (*C*H_2).

m/z [EI (+ve)] 273.2 $[M]^+$, HRMS found $[M]^+$ 273.1527, $C_{17}H_{20}FNO$ requires 273.1529.

IR (thin film) ν_{max} = 2928, 2854, 1703, 1666, 1450, 1421, 1240, 1145 cm^{-1}.

m.p. 53-55 ˚C.

1-Benzyl-3-fluoro-5-(2'-phenylethyl)-2,5-dihydro-1*H*-pyrrol-2-one, 326.



Dialkene **321** (0.12 g, 0.38 mmol) was treated with 5 mol% Grubbs 2nd generation catalyst as described in General Procedure I. The crude residue was purified by flash column chromatography (0 - 10% EtOAc in petroleum ether) to yield the desired product **326** (0.11 g, 0.36 mmol, 96%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.26-7.11 (8H, m, Ar-*H*), 6.97-6.96 (2H, m, Ar-*H*), 6.17 (1H, d, J_H = 1.6 Hz, C*H*CF), 5.00 (1H, d, J_H = 15.2 Hz, C*H*HN), 4.06 (1H, d, J_H = 15.2 Hz, CH*H*N), 3.88-3.85 (1H, m, C*H*N), 2.49-2.31 (2H, m, CH_2), 2.11-2.04 (1H, m, C*H*H), 1.86-1.75 (1H, m, CH*H*).

^{19}F ($CDCl_3$, 470 MHz) δ: -137.0.

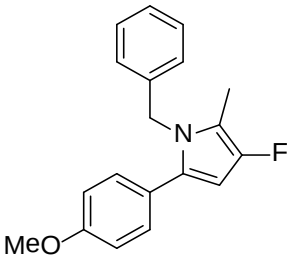
^{13}C ($CDCl_3$, 125 MHz) δ: 163.1 (d, J_F = 31.3 Hz, CO), 152.7 (d, J_F = 278.2 Hz, *C*F), 140.4 (Ar*C*), 136.5 (Ar*C*), 128.9 (2C, Ar*C*-H), 128.7 (2C, Ar*C*-H), 128.2 (2C, Ar*C*-H), 128.1 (2C, Ar*C*-H), 127.9 (Ar*C*-H), 126.4 (Ar*C*-H), 117.2 (d, J_F = 4.2 Hz, CH*C*F), 55.0 (d, J_F = 5.0 Hz, *C*HN), 44.3 (Ph*C*H_2), 31.7 (d, J_F = 2.0 Hz, *C*H_2CH), 30.0 (*C*H_2).

m/z [EI (+ve)] 295.2 $[M]^+$, HRMS found $[M]^+$ 295.1373, $C_{19}H_{18}FNO$ requires 295.1372.

IR (thin film) ν_{max} = 2935, 2364, 1707, 1666, 1454, 1226 cm^{-1}.

m.p. 62-65 ˚C.

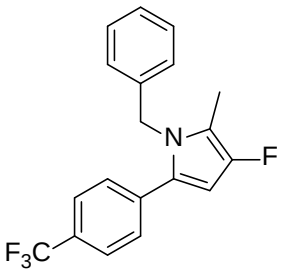
1-Benzyl-3-fluoro-5-(4'-methoxyphenyl)- 2-methyl-1*H*-pyrrole, 327.



α,β-Unsaturated lactam **322** (32 mg, 0.11 mmol) was reacted with methyl lithium (83 µL, 1.16 mmol, 1.4 M in diethyl ether) following general procedure J. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **327** (28 mg, 90 µmol, 88%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.25-7.16 (3H, m, Ar-*H*), 7.10 (2H, d, J_H = 8.9 Hz, Ar-*H*), 6.86-6.84 (2H, m, Ar-*H*), 6.76 (2H, d, J_H = 8.9 Hz, Ar-*H*), 5.91 (1H, s, C*H*CF), 4.95 (2H, s, CH_2), 3.71 (3H, s, OCH_3), 1.97 (3H, d, J_F = 1.6 Hz, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -169.6.
^{13}C ($CDCl_3$, 125 MHz) δ: 158.9 (Ar*C*-OMe), 149.1 (d, J_F = 235.4 Hz, *C*F), 138.7 (Ar*C*-CH_2), 130.2 (2C, Ar*C*-H), 129.9 (d, J_F = 3.3 Hz, Ar-*C*N), 128.8 (2C, Ar*C*-H), 127.1 (Ar*C*-H), 125.6 (2C, Ar*C*-H), 125.4 (d, J_F = 1.6 Hz, Ar*C*), 113.9 (2C, Ar*C*-H), 111.8 (d, J_F = 24.4 Hz, *C*CH_3), 96.0 (d, J_F = 16.4 Hz, *C*HCF), 55.3 (O*C*H_3), 47.6 (Ph*C*H_2), 8.1 (d, J_F = 2.0 Hz, *C*H_3).
m/z [EI (+ve)] 295.2 $[M]^+$, HRMS found $[M]^+$ 295.1373, $C_{19}H_{18}FNO$ requires 295.1372.
IR (thin film) ν_{max} = 2929, 1653, 1603, 1454, 1249, 1176 cm^{-1}.
m.p. 74-76 ˚C.

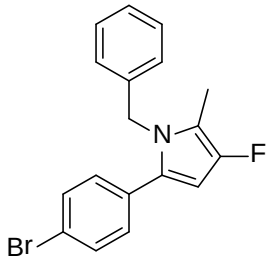
1-Benzyl-3-fluoro-2-methyl-5-[(4'-trifluoromethyl)phenyl]-1*H*-pyrrole, 328.



α,β-Unsaturated lactam **323** (22 mg, 60 µmol) was reacted with methyl lithium (51 µL, 70 µmol, 1.4 M in diethyl ether) following general procedure J. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **328** (16 mg, 50 µmol, 73%) as a yellow solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.46 (2H, d, J_H = 8.7 Hz, Ar-*H*), 7.32-7.17 (5H, m, Ar-*H*), 6.87-6.85 (2H, m, Ar-*H*), 6.05 (1H, s, C*H*CF), 5.01 (2H, s, CH_2), 2.00 (3H, d, J_F = 1.6 Hz, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -62.5, -168.5.
^{13}C ($CDCl_3$, 125 MHz) δ: 149.3 (d, J_F = 236.4 Hz, *C*F), 138.1 (Ar*C*-CH_2), 136.3 (*C*F_3), 129.0 (Ar*C*), 128.9 (2C, Ar*C*-H), 128.6 (d, J_F = 7.2 Hz, Ar-*C*N), 128.5 (2C, Ar*C*-H), 127.4 (2C, Ar*C*-H), 126.0 (d, J_F = 3.8 Hz, Ar*C*), 125.5 (Ar*C*-H), 125.4 (2C, Ar*C*-H), 114.1 (d, J_F = 24.4 Hz, *C*CH_3), 96.7 (d, J_F = 16.5 Hz, *C*HCF), 47.9 (Ph*C*H_2), 8.2 (d, J_F = 2.0 Hz, *C*H_3).
m/z [EI (+ve)] 333.2 $[M]^+$, HRMS found $[M]^+$ 333.1139, $C_{19}H_{15}F_4N$ requires 333.1141.
IR (thin film) ν_{max} = 2926, 1606, 1325, 1166, 1124 cm^{-1}.
m.p. 75-77 ˚C.

1-Benzyl-5-(4'-bromophenyl)-3-fluoro-2-methyl-1*H*-pyrrole, 329.

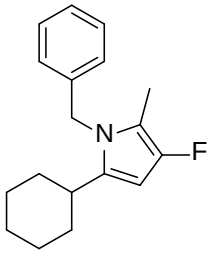


α,β-Unsaturated lactam **324** (43 mg, 0.13 mmol) was reacted with methyl lithium (98 µL, 0.14 mmol, 1.4 M in diethyl ether) following general procedure J. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **329** (34 mg, 0.10 mmol, 78%) as a brown solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.37 (2H, d, J_H = 8.6 Hz, Ar-*H*), 7.29-7.16 (3H, m, Ar-*H*), 7.04 (2H, d, J_H = 8.6 Hz, Ar-*H*), 6.85-6.83 (2H, m, Ar-*H*), 5.97 (1H, s, C*H*CF), 4.96 (2H, s, CH_2), 1.98 (3H, d, J_F = 1.6 Hz, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -168.9.
^{13}C ($CDCl_3$, 125 MHz) δ: 149.2 (d, J_F = 236.1 Hz, *C*F), 138.3 (Ar*C*-CH_2), 131.7 (d, J_F = 1.8 Hz, Ar-*C*N), 131.6 (2C, Ar*C*-H), 130.2 (2C, Ar*C*-H), 128.9 (2C, Ar*C*-H), 128.8 (Ar*C*), 127.3 (Ar*C*-H), 125.5 (2C, Ar*C*-H), 121.2 (Ar*C*), 113.2 (d, J_F = 24.3 Hz, *C*CH_3), 96.9 (d, J_F = 16.5 Hz, *C*HCF), 47.7 (Ph*C*H_2), 8.2 (d, J_F = 2.0 Hz, *C*H_3).
m/z [EI (+ve)] 343.1 $[M]^+$, HRMS found $[M]^+$ 343.0368, $C_{18}H_{15}BrFN$ requires 343.0372.

IR (thin film) ν_{max} = 2922, 1683, 1612, 1471, 1352 cm^{-1}.
m.p. 98-100 ˚C.

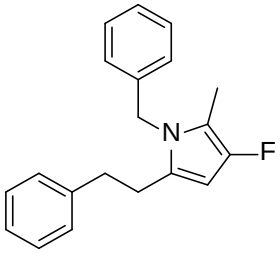
1-Benzyl-5-cyclohexyl-3-fluoro-2-methyl-1*H*-pyrrole, 330.



α,β-Unsaturated lactam **325** (32 mg, 0.12 mmol) was reacted with methyl lithium (92 µL, 0.13 mmol, 1.4 M in diethyl ether) following general procedure J. The crude residue was purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **330** (29 mg, 0.11 mmol, 92%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.25-7.13 (3H, m, Ar-*H*), 6.80-6.76 (2H, m, Ar-*H*), 5.64 (1H, s, C*H*CF), 4.90 (2H, s, CH_2), 2.33-2.24 (1H, m, C*H*), 1.91 (3H, d, J_F = 1.6 Hz, CH_3), 1.74-1.63 (4H, m, CH_2), 1.26-1.08 (6H, m, CH_2).
^{19}F ($CDCl_3$, 470 MHz) δ: -170.6.
^{13}C ($CDCl_3$, 125 MHz) δ: 148.6 (d, J_F = 233.9 Hz, *C*F), 138.7 (Ar*C*-CH_2), 134.8 (d, J_F = 5.7 Hz, Ar-*C*N), 128.7 (2C, Ar*C*-H), 127.1 (Ar*C*-H), 125.5 (2C, Ar*C*-H), 109.3 (d, J_F = 24.7 Hz, *C*CH_3), 91.8 (d, J_F = 16.8 Hz, *C*HCF), 46.4 (Ph*C*H_2), 35.6 (*C*H), 34.1 (2C, *C*H_2), 26.6 (2C, *C*H_2), 26.0 (*C*H_2), 7.8 (d, J_F = 2.1 Hz, *C*H_3).
m/z [EI (+ve)] 271.1 $[M]^+$, HRMS found $[M]^+$ 271.1737, $C_{18}H_{22}FN$ requires 271.1736.
IR (thin film) ν_{max} = 2926, 2852, 1616, 1446, 1365, 1348, 1112 cm^{-1}.
m.p. 55-57 ˚C.

1-Benzyl-3-fluoro-2-methyl-5-(2'-phenylethyl)-1*H*-pyrrole, 331.

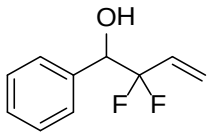


α,β-Unsaturated lactam **326** (34 mg, 0.11 mmol) was reacted with methyl lithium (91 µL, 0.12 mmol, 1.4 M in diethyl ether) following general procedure J. The crude residue was

purified by flash column chromatography (0 - 2.5% diethyl ether in petroleum ether) to yield the desired product **331** (24 mg, 80 µmol, 74%) as a yellow oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.24-7.08 (6H, m, Ar-*H*), 7.04-7.00 (2H, m, Ar-*H*), 6.80-6.76 (2H, m, Ar-*H*), 5.71 (1H, s, C*H*CF), 4.83 (2H, s, CH_2), 2.76-2.71 (2H, m, CH_2), 2.64-2.60 (2H, m, CH_2), 1.97 (3H, br s, CH_3).
^{19}F ($CDCl_3$, 470 MHz) δ: -170.5.
^{13}C ($CDCl_3$, 125 MHz) δ: 148.3 (d, J_F = 234.1 Hz, *C*F), 141.4 (Ar*C*), 138.2 (Ar*C*-CH_2), 128.8 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 128.3 (2C, Ar*C*-H), 127.9 (d, *J* = 6.3 Hz, Ph-*C*N), 127.2 (Ar*C*-H), 126.1 (Ar*C*-H), 125.5 (2C, Ar*C*-H), 110.0 (d, J_F = 24.6 Hz, *C*CH_3), 94.1 (d, J_F = 16.8 Hz, *C*HCF), 46.5 (Ph*C*H_2), 35.4 (*C*H_2), 28.4 (*C*H_2), 7.9 (d, J_F = 2.1 Hz, *C*H_3).
m/z [EI (+ve)] 293.1 $[M]^+$, HRMS found $[M]^+$ 293.1581, $C_{20}H_{20}FN$ requires 293.1580.
IR (thin film) ν_{max} = 2922, 1614, 1496, 1454, 1417, 1363, 1114 cm^{-1}.

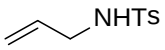
2,2-Difluoro-1-phenylbutan-1-ol, 335.[161]



3-Bromo-3,3-difluoroprop-1-ene (0.19 mL, 1.9 mmol) was added to a slurry of indium (0.22 g, 1.9 mmol) in H_2O (5 mL). Benzaldehyde (0.10 g, 0.94 mmol) in THF (0.6 mL) was added and the reaction was heated to 60 °C and stirred for 17 h. The mixture was diluted with H_2O (10 mL) and extracted with diethyl ether (3 × 10 mL). The organics were combined, dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 2% EtOAc in heptane) to give the desired product **335** (0.17 g, 0.92 mmol, 98%) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.48-7.42 (2H, m, Ar-*H*), 7.41-7.36 (3H, m, Ar-*H*), 5.88 (1H, ddt, J_{H+F} = 17.4, 12.4, 11.1 Hz, C*H*CH_2), 5.62 (1H, dtd, J_{H+F} = 17.4, 2.5, 0.9 Hz, C*H*H), 5.49 (1H, dd, J_H = 11.1, 0.9 Hz, CH*H*), 4.94 (1H, ddd, J_{H+F} = 10.3, 8.8, 3.9 Hz, C*H*OH), 2.46 (1H, dt, J_{H+F} = 3.9, 0.9 Hz, O*H*).
^{19}F ($CDCl_3$, 377 MHz) δ: -108.0 (dt, J_{H+F} = 21.2, 10.4 Hz), -109.4 (dt, J_{H+F} = 21.2, 10.4 Hz).
^{13}C ($CDCl_3$, 100 MHz) δ: 136.0 (dd, J_F = 3.4, 1.6 Hz, *C*F_2), 129.4 (t, J_F = 25.7 Hz, *C*HCH_2), 129.1 (Ar-*C*), 128.8 (Ar*C*-H), 128.2 (2C, Ar*C*-H), 127.6 (2C, Ar*C*-H), 121.6 (t, J_F = 9.2 Hz, *C*H_2), 75.9 (dd, J_F = 30.6, 29.1 Hz, *C*H).
The spectral data is in agreement with the literature values.[161]

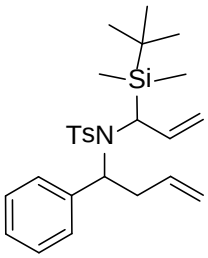
4-Methyl-*N*-(prop-2'-en-1'-yl)benzene-1-sulfonamide, 344.[162]



Allyl amine (1.31 mL, 17.5 mmol) was dissolved in CH_2Cl_2 (15 mL) and the solution was cooled to 0 °C. *p*-Toluenesulfonyl chloride (3.34 g, 17.5 mmol) and triethylamine (2.44 mL, 17.5 mmol) were added and the mixture was stirred for 17 h at rt. The reaction was diluted with H_2O (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organics were combined, dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 30% EtOAc in heptane) to yield the desired product **344** (3.32 g, 15.7 mmol, 90%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.78 (2H, d, J_H = 8.3 Hz, Ar-*H*), 7.33 (2H, d, J_H = 8.3 Hz, Ar-*H*), 5.73 (1H, ddt, J_H = 17.2, 10.2, 6.2 Hz, C*H*), 5.14 (1H, dd, J_H = 17.2, 1.5 Hz, CHC*H*H), 5.11 (1H, dd, J_H = 10.2, 1.5 Hz, CHCH*H*), 4.82 (1H, t, J_H = 6.2 Hz, N*H*), 3.59 (2H, tt, J_H = 6.2, 1.5 Hz, CH_2), 2.44 (3H, s, CH_3).
^{13}C ($CDCl_3$, 100 MHz) δ: 143.5 (Ar*C*-SO_2), 137.0 (Ar*C*-CH_3), 133.0 (*C*HCH_2), 129.7 (2C, Ar*C*-H), 127.2 (2C, Ar*C*-H), 117.7 (CH*C*H_2), 45.8 (*C*H_2), 21.6 (*C*H_3).
The spectral data is in agreement with the literature values.[162]

***N*-[1'-(*tert*-Butyldimethylsilyl)prop-2'-en-1'-yl]-4-methyl-*N*-(1''-phenylbut-3''-en-yl)benzene-1-sulfonamide, 358.**



Diisopropyl azodicarboxylate (0.20 mL, 1.0 mmol) was added dropwise to a solution of alcohol **359** (0.17 g, 0.99 mmol), PPh_3 (0.35 g, 1.3 mmol) and sulphonamide **191** (0.20 g, 0.66 mmol) in THF (5 mL) at 0 °C. The resulting mixture was stirred at rt for 17 h. The reaction was diluted with H_2O (10 mL) before being extracted with diethyl ether (3 × 10 mL). The organics were combined, dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified by flash column chromatography (1% EtOAc in heptane) to yield the desired product **358** (0.10 g, 0.22 mmol, 34%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.08-7.69 (2H, d, J_H = 8.3 Hz, Ar-*H*), 7.42-7.23 (7H, m, Ar-*H*), 5.89-5.62 (3H, m, C*H*Si, C*H*CH_2 and C*H*CH_2), 5.24 (1H, dd, J_H = 8.8, 6.9 Hz, C*H*N), 5.18-5.03 (2H, m, CH_2), 3.98 (1H, ddd, J_H = 16.7, 4.8, 1.2 Hz, CHC*H*H), 3.75 (1H, ddd, J_H = 16.8, 6.0, 1.2 Hz, CHCH*H*), 2.99-2.85 (1H, m, CHC*H*HCH), 2.77-2.65 (1H, m, CHC*H*HCH), 2.54 (3H, s, CH_3), 1.11-0.74 (9H, m, CH_3), 0.07– -0.07 (6H, m, CH_3).

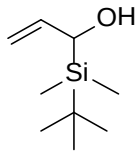
^{13}C ($CDCl_3$, 100 MHz) δ: 144.6 (*C*$CHCH_2$), 143.0 (Ar*C*), 138.6 (Ar*C*), 138.0 (Ar*C*), 134.7 (*C*$CHCH_2$), 129.7 (*C*H), 129.5 (2C, Ar*C*-H), 128.7 (2C, Ar*C*-H), 128.3 (2C, Ar*C*-H), 127.9 (Ar*C*-H), 127.4 (2C, Ar*C*-H), 117.5 (CH*C*H_2), 60.5 (*C*HN), 49.4 (*C*H_2), 36.4 (*C*H_2), 26.4 (3C, *C*H_3), 21.5 (CH_3), 16.5 (*C*CH_3), -6.2 (*C*H_3), -6.4 (*C*H_3).

m/z [ESI (+ve)] 478.2 $[M+Na]^+$, HRMS found $[M+Na]^+$ 478.2182, $C_{26}H_{37}NSSiO_2Na$ requires 478.2206.

IR (thin film) ν_{max} = 2953, 2926, 2854, 1452, 1338, 1159 cm^{-1}.

m.p. 75-77 ˚C.

1-(*tert*-Butyldimethylsilyl)prop-2-en-1-ol, 359.[163]



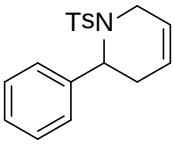
Allyl alcohol (0.29 mL, 4.31 mmol) was dissolved in THF (15 mL) and the solution was cooled to -78 °C. *n*-Butyl lithium (1.9 mL, 4.74 mmol, 2.5 M in hexanes) was added slowly and the mixture was stirred for 30 min. After this time, *tert*-butyldimethylsilyl chloride (0.71 g, 4.74 mmol) was added before the solution was allowed to warm to rt and stirred for 17 h. *sec*-Butyl lithium (6.2 mL, 8.62 mmol) was added slowly at -78 °C and the reaction was warmed to -50 °C and stirred for 2 h. The reaction mixture was quenched slowly at -78 °C with sat. NH_4Cl (20 mL) and then extracted with diethyl ether (3 × 10 mL). The organics were combined; dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 3% EtOAc in heptane) to yield the desired product **359** (0.44 g, 2.56 mmol, 60%) as a colourless oil.

^{1}H ($CDCl_3$, 400 MHz) δ: 5.98 (1H, ddd, J_H = 17.2, 10.7, 5.2 Hz, C*H*CH_2), 5.06-4.83 (2H, m, CHCH_2), 4.16-3.99 (1H, m, C*H*), 0.82 (9H, s, CH_3), -0.09 (3H, s, CH_3), -0.13 (3H, s, CH_3).

^{13}C ($CDCl_3$, 100 MHz) δ: 140.8 (*C*$CHCH_2$), 109.4 (*C*$CHCH_2$), 67.5 (*C*H), 26.9 (3C, *C*H_3), 17.0 (*C*CH_3), -7.6 (*C*H_3), -9.2 (*C*H_3).

The spectral data is in agreement with the literature values.[163]

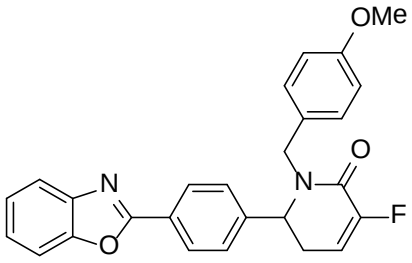
2-Phenyl-1-tosyl-1,2,3,6-tetrahydropyridine, 360.[164]



Diene **358** (66 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (26 mL). Grubbs 2nd generation catalyst (6.0 mg, 7.4 µmol, 5 mol%) was added and the mixture was heated to reflux for 3 h. The solvent was removed *in vacuo* and the crude residue purified by flash column chromatography (0 - 2.5% EtOAc in petroleum ether) to afford the desired product **360** (38 mg, 0.12 mmol, 81%).

^{1}H ($CDCl_3$, 400 MHz) δ: 7.61 (2H, d, J_H = 8.3 Hz, Ar-*H*), 7.31-7.23 (2H, m, Ar-*H*), 7.25-7.08 (5H, m, Ar-*H*), 5.71 (1H, ddd, J_H = 10.2, 5.0, 2.4 Hz, C*H*CH), 5.55-5.46 (1H, m, CHC*H*), 5.25-5.22 (1H, m, C*H*N), 4.10-3.97 (1H, m, NC*H*H), 3.38-3.22 (1H, m, NCH*H*), 2.43-2.20 (5H, m, CH_2 and CH_3).
^{13}C ($CDCl_3$, 100 MHz) δ: 143.1 (Ar*C*), 139.2 (Ar*C*), 137.1 (Ar*C*), 129.5 (2C, Ar*C*-H), 128.4 (2C, Ar*C*-H), 127.5 (Ar*C*-H), 127.4 (2C, Ar*C*-H), 127.0 (2C, Ar*C*-H), 123.9 (*C*HCH), 123.8 (CH*C*H), 52.8 (*C*HN), 40.8 (*C*H_2), 26.4 (*C*H_2), 21.5 (*C*H_3).
The spectral data is in agreement with the literature values.[164]

6-[4'-(1''',3'''-Benzoxazol-2'''-yl)phenyl]-3-fluoro-1-[(4''-methoxyphenyl)methyl]-1,2,5,6-tetrahydropyridin-2-one, 370.



Lactam **220** (30 mg, 77 µmol), benzoxazole (13 mg 0.11 mmol), K_2CO_3 (24 mg, 0.17 mmol), PPh_3 (12 mg, 40 µmol), Cu(II)OAc_2 (3.5 mg, 17 µmol) and Pd(PPh_3)$_4$ (10 mg, 9.0 µmol) were dry mixed. Toluene (3 mL) was added and the reaction was heated under microwave irradiation to 128 °C for 4 h. Following this time, the mixture was diluted with H_2O (5 mL) and extracted with diethyl ether (3 × 10 mL). The organics were combined, dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 20% EtOAc in petroleum ether) to yield the desired product **370** (24 mg, 56 µmol, 73%) as a white soild.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.28 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.86-7.76 (1H, m, Ar-*H*), 7.68-7.55 (1H, m, Ar-*H*), 7.46-7.37 (2H, m, Ar-*H*), 7.35 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.16 (2H, d, J_H = 8.5 Hz, Ar-*H*), 6.88 (2H, d, J_H = 8.5 Hz, Ar-*H*), 5.91-5.74 (1H, m, C*H*CF), 5.56 (1H, d, J_H = 14.8 Hz, C*H*HN), 4.65 (1H, dd, J_H = 7.7, 2.5 Hz, C*H*N), 3.83 (3H, s, CH_3), 3.51 (1H, d, J_H = 14.8 Hz, CH*H*N), 3.06-2.95 (1H, m, CHCH*H*CH), 2.57-2.47 (1H, m, CHC*H*HCH).

^{19}F ($CDCl_3$, 470 MHz) δ: -126.3.

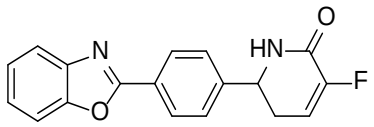
^{13}C ($CDCl_3$, 100 MHz) δ: 162.3 (N*C*O), 159.7 (d, J_F = 31.1 Hz, *C*O), 159.3 (Ar*C*-OMe), 150.8 (Ar*C*), 150.4 (Ar*C*), 149.4 (d, J_F = 255.2 Hz, *C*F), 143.1 (Ar*C*), 142.0 (Ar*C*), 129.6 (2C, Ar*C*-H), 128.6 (Ar*C*), 128.2 (2C, Ar*C*-H), 127.1 (2C, Ar*C*-H), 125.4 (Ar*C*-H), 124.8 (Ar*C*-H), 120.1 (Ar*C*-H), 114.2 (2C, Ar*C*-H), 110.7 (Ar*C*-H), 109.6 (d, J_F = 15.1 Hz, *C*HCF), 56.9 (O*C*H_3), 55.3 (*C*HN), 47.5 (N*C*H_2), 29.2 (d, J_F = 6.3 Hz, *C*H_2).

m/z [EI (+ve)] 428.3 $[M]^+$, HRMS found $[M]^+$ 428.1538, $C_{26}H_{21}FN_2O_3$ requires 428.1536.

IR (thin film) ν_{max} = 2928, 1651, 1512, 1452, 1244, 1199, 1057 cm^{-1}.

m.p. 117-119 ˚C.

6-[4'-(1'',3''-Benzoxazol-2''-yl)phenyl]-3-fluoro-1,2,5,6-tetrahydropyridin-2-one, 371.



α,β-Unsaturated lactam **229** (25 mg, 93 μmol), benzoxazole (13 mg, 0.11 mmol), K_2CO_3 (25 mg, 0.19 mmol), PPh_3 (12 mg, 40 μmol), Cu(II)OAc_2 (3.6 g, 17 μmol) and $Pd(PPh_3)_4$ (11 mg, 9.0 μmol) were dry mixed. Toluene (3 mL) was added and the reaction was heated under microwave irradiation to 128 °C for 4 h. Following this time, the mixture was diluted with H_2O (5 mL) and extracted with diethyl ether (3 × 10 mL). The organics were combined, dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 20% EtOAc in petroleum ether) to yield the desired product **371** (20 mg, 65 μmol, 70%) as a white soild.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.32 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.85-7.77 (1H, m, Ar-*H*), 7.66-7.60 (1H, m, Ar-*H*), 7.57 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.44-7.37 (2H, m, Ar-*H*), 6.12 (1H, dt, J_F = 10.9 Hz, J_H = 4.5 Hz, C*H*CF), 5.67 (1H, s, N*H*), 4.65 (1H, t, J_H = 8.6 Hz, C*H*N), 2.77-2.70 (2H, m, CHCH_2CH).

^{19}F ($CDCl_3$, 377 MHz) δ: -129.4.

^{13}C ($CDCl_3$, 100 MHz) δ: 162.2 (N*C*O), 161.0 (d, J_F = 31 Hz, *C*O), 150.8 (Ar*C*), 149.7 (d, J_F = 254 Hz, *C*F), 143.4 (Ar*C*), 142.0 (Ar*C*), 128.4 (2C, Ar*C*-H), 127.7 (ArC), 126.9 (2C, Ar*C*-

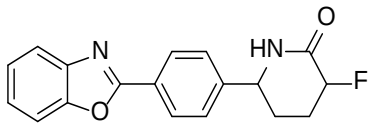
H), 125.4 (Ar*C*-H), 124.8 (Ar*C*-H), 120.2 (Ar*C*-H), 113.3 (d, J_F = 13 Hz, *C*HCF), 110.7 (Ar*C*-H), 55.8 (*C*HN), 31.0 (d, J_F = 6 Hz, *C*H_2).

m/z [EI (+ve)] 308.2 $[M]^+$, HRMS found $[M]^+$ 308.0963, $C_{18}H_{13}FN_2O_2$ requires 308.0961.

IR (thin film) ν_{max} = 3205, 2922, 1693, 1654, 1452, 1201 cm^{-1}.

m.p. 135-137 ˚C.

6-[4'-(1'',3''-Benzoxazol-2''-yl)phenyl]-3-fluoro-piperidin-2-one, 372.



A solution of benzoxazole **371** (0.11 g, 0.36 mmol) in MeOH (20 mL) was treated with palladium activated charcoal (11 mg, 10% by weight) and the suspension was stirred under a H_2 atmosphere for 4.5 h. The mixture was filtered through celite, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 40% EtOAc in petroleum ether) to yield the desired product **372** (0.11 g, 0.35 mmol, 99%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 8.31 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.84-7.78 (1H, m, Ar-*H*), 7.67-7.60 (1H, m, Ar-*H*), 7.51 (2H, d, J_H = 8.4 Hz, Ar-*H*), 7.44-7.37 (2H, m, Ar-*H*), 5.94 (1H, s, N*H*), 4.98 (1H, dt, J_F = 37.6 Hz, J_H = 4.0 Hz, C*H*F), 4.72-4.69 (1H, m, C*H*N), 2.39-1.99 (4H, m, CH_2CH_2).

^{19}F ($CDCl_3$, 470 MHz) δ: -185.2.

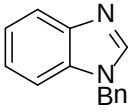
^{13}C ($CDCl_3$, 125 MHz) δ: 167.6 (d, J_F = 20 Hz, *C*O), 162.3 (N*C*O), 150.8 (Ar*C*), 144.9 (Ar*C*), 142.0 (Ar*C*), 128.3 (2C, Ar*C*-H), 127.3 (ArC), 126.7 (2C, Ar*C*-H), 125.4 (Ar*C*-H), 124.8 (Ar*C*-H), 120.1 (Ar*C*-H), 110.7 (Ar*C*-H), 85.6 (d, J_F = 176 Hz, *C*HF), 57.1 (*C*HN), 27.2 (d, J_F = 6 Hz, *C*H_2), 26.1 (d, J_F = 21.1 Hz, *C*H_2).

m/z [ESI (+ve)] 333.1 $[M+Na]^+$, HRMS found $[M+Na]^+$ 333.0989, $C_{18}H_{15}FN_2O_2Na$ requires 333.1010.

IR (thin film) ν_{max} = 2926, 2854, 1681, 1454, 1244, 1182, 1058 cm^{-1}.

m.p. 235-237 ˚C.

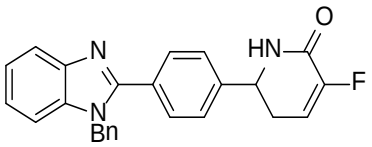
1-Benzyl-1*H*-1,3-benzodiazole, 373.[165]



DMF (5 mL) was added to a mixture of benzimidazole (0.20 g, 1.7 mmol) and K_2CO_3 (0.35 g, 2.5 mmol). Benzyl bromide (0.24 mL, 2.0 mmol) was added and the reaction was heated under microwave irradiation to 100 °C for 1 h. The mixture was diluted with H_2O (10 mL), extracted with diethyl ether (3 × 10 mL) followed by repeated washing with H_2O (3 × 10 mL) and brine (2 × 10 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 100% EtOAc in petroleum ether) to yield the desired product **373** (45 mg, 0.21 mmol, 14%) as a white solid.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.98 (1H, s, NC*H*), 7.88-7.84 (1H, m, Ar-*H*), 7.40-7.25 (6H, m, Ar-*H*), 7.23-7.19 (2H, m, Ar-*H*), 5.41 (2H, m, CH_2).
^{13}C ($CDCl_3$, 100 MHz) δ: 143.0 (Ar*C*), 143.2 (N*C*HO), 135.5 (Ar*C*), 134.0 (Ar*C*), 129.1 (2C, Ar*C*-H), 128.3 (Ar*C*-H), 127.1 (2C, Ar*C*-H), 123.1 (Ar*C*-H), 122.3 (Ar*C*-H), 120.5 (Ar*C*-H), 110.0 (Ar*C*-H), 48.9 (*C*H_2).
m.p. 114-115 ˚C.
The spectral data is in agreement with the literature values.[165]

6-[4'-(1''-Benzyl-1*H*-1'',3''-benzodiazol-2''-yl)phenyl]-3-fluoro-1,2,5,6-tetrahydropyridin-2-one, 374.



α,β-Unsaturated lactam **229** (30 mg, 0.10 mmol), benzimidazole **373** (28 mg 0.13 mmol), K_2CO_3 (31 mg, 0.20 mmol), PPh_3 (15 mg, 50 µmol), Cu(II)OAc_2 (4.4 mg, 20 µmol) and $Pd(PPh_3)_4$ (13 mg, 10 µmol) were dry mixed. Toluene (2.5 mL) was added and the reaction was heated under microwave irradiation to 128 °C for 4 h. Following this time, the mixture was diluted with H_2O (5 mL) and extracted with diethyl ether (3 × 10 mL). The organics were combined, dried (Na_2SO_4) and removed *in vacuo*. The crude residue was purified by flash column chromatography (0 - 60% EtOAc in petroleum ether) to yield the desired product **374** (39 mg, 96 µmol, 97%) as a white soild.

^{1}H ($CDCl_3$, 400 MHz) δ: 7.80 (1H, d, J_H = 8.0 Hz, Ar-*H*), 7.67 (2H, d, J_H = 8.2 Hz, Ar-*H*), 7.39 (2H, d, J_H = 8.2 Hz, Ar-*H*), 7.32-7.23 (4H, m, Ar-*H*), 7.23-7.11 (2H, m, Ar-*H*), 7.03 (2H, appt d, J_H = 6.5 Hz, Ar-*H*), 6.00 (1H, dt, J_F = 10.8, J_H = 4.5 Hz, C*H*CF), 5.54 (1H, s, N*H*), 5.40 (2H, s, CH_2N) 4.78 (1H, t, J_H = 8.5 Hz, C*H*N), 2.64-2.57 (2H, m, CHCH_2CH).
^{19}F ($CDCl_3$, 377 MHz) δ: -129.5.

^{13}C ($CDCl_3$, 100 MHz) δ: 161.0 (d, J_F = 31 Hz, *C*O), 153.2 (N*C*N), 149.7 (d, J_F = 255 Hz, *C*F), 143.2 (Ar*C*), 141.8 (Ar*C*), 136.19 (d, J_F = 6.9 Hz, Ar*C*), 130.7 (Ar*C*), 130.7 (2C, Ar*C*-H), 129.2 (2C, Ar*C*-H), 128.4 (Ar*C*), 127.9 (Ar*C*-H), 126.8 (2C, Ar*C*-H), 125.9 (2C, Ar*C*-H), 123.4 (Ar*C*-H), 122.9 (Ar*C*-H), 120.1 (Ar*C*-H), 113.3 (d, J_F = 14 Hz, *C*HCF), 110.5 (Ar*C*-H), 55.7 (*C*HN), 48.4 (N*C*H_2), 31.0 (d, J_F = 5 Hz, *C*H_2).

m/z [ESI (+ve)] 398.2 $[M+H]^+$, HRMS found $[M+H]^+$ 398.1643, $C_{25}H_{21}FN_3O$ requires 398.1639.

IR (thin film) ν_{max} = 2926, 2854, 1697, 1660, 1454, 1249, 1199 cm^{-1}.

m.p. 204-206 ˚C.

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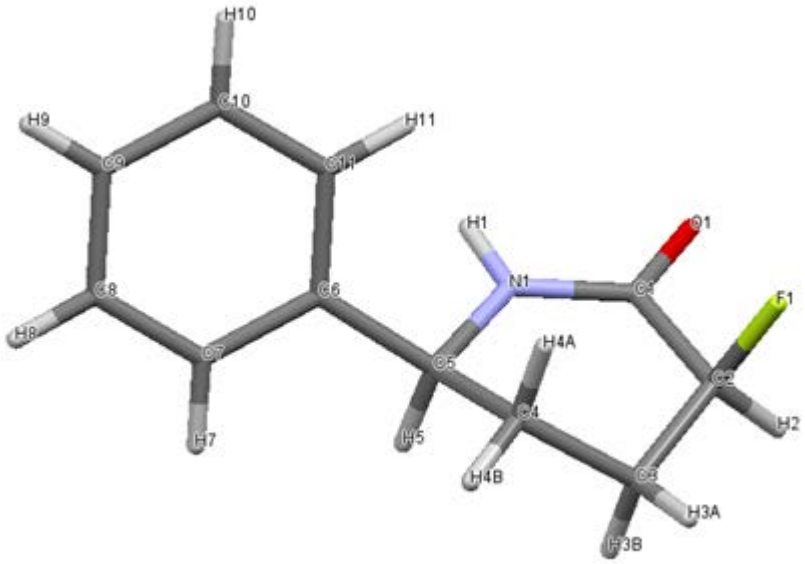
11. Appendix

Crystal Structure and Structural Refinement for 198



Chemical Formula: $C_{11}H_{12}FNO$

Space Group: P -1

Cell lengths: a 6.0469(2) b 9.1864(3) c 9.4011(3)

Cell angles: a 110.410(2) b 96.980(2) g 92.353(2)

Cell volume: -483.854

Z, Z': Z: 2 Z': 0

R factor (%): 3.49

Atoms

Number	Label	Charge	SybylType	Xfrac + ESD	Yfrac + ESD	Zfrac + ESD	Symm. op.
1	C1	0	C.2	0.9519(2)	0.69884(14)	0.67740(14)	x,y,z
2	C2	0	C.3	0.9134(2)	0.83934(15)	0.81542(15)	x,y,z
3	H2	0	H	0.955	0.8167	0.9114	x,y,z
4	C3	0	C.3	0.6782(2)	0.88681(16)	0.80997(15)	x,y,z
5	H3A	0	H	0.6759	0.9931	0.8858	x,y,z
6	H3B	0	H	0.5806	0.8145	0.8374	x,y,z
7	C4	0	C.3	0.5895(2)	0.88407(15)	0.65064(15)	x,y,z

8	H4A	0	H	0.6887	0.9541	0.6215	x,y,z
9	H4B	0	H	0.438	0.9211	0.6498	x,y,z
10	C5	0	C.3	0.5803(2)	0.71805(14)	0.53693(14)	x,y,z
11	H5	0	H	0.4674	0.6528	0.5635	x,y,z
12	C6	0	C.2	0.5099(2)	0.70444(14)	0.37274(14)	x,y,z
13	C7	0	C.2	0.2882(2)	0.65768(15)	0.30661(16)	x,y,z
14	H7	0	H	0.184	0.6333	0.3647	x,y,z
15	C8	0	C.2	0.2175(2)	0.64625(17)	0.15687(16)	x,y,z
16	H8	0	H	0.0653	0.6149	0.1133	x,y,z
17	C9	0	C.2	0.3677(2)	0.68038(17)	0.07054(16)	x,y,z
18	H9	0	H	0.3201	0.6706	-0.0327	x,y,z
19	C10	0	C.2	0.5883(2)	0.72897(17)	0.13642(16)	x,y,z
20	H10	0	H	0.6919	0.7541	0.0783	x,y,z
21	C11	0	C.2	0.6592(2)	0.74125(15)	0.28633(15)	x,y,z
22	H11	0	H	0.8108	0.775	0.3303	x,y,z
23	N1	0	N.am	0.79856(17)	0.65529(12)	0.55254(12)	x,y,z
24	H1	0	H	0.831	0.5813	0.4708	x,y,z
25	O1	0	O.2	1.12428(14)	0.63207(11)	0.68528(10)	x,y,z
26	F1	0	F	1.06059(14)	0.96212(10)	0.81591(10)	x,y,z

Bonds

Number	Atom1	Atom2	Type	Polymeric	Cyclicity	Length	SybylType
1	C1	C2	Unknown	no	cyclic	1.528(2)	1
2	C1	N1	Unknown	no	cyclic	1.332(2)	un
3	C1	O1	Unknown	no	acyclic	1.238(2)	2
4	C2	H2	Unknown	no	acyclic	1	1
5	C2	C3	Unknown	no	cyclic	1.505(2)	1
6	C2	F1	Unknown	no	acyclic	1.406(2)	1
7	C3	H3A	Unknown	no	acyclic	0.99	1

8	C3	H3B	Unknown	no	acyclic	0.99	1
9	C3	C4	Unknown	no	cyclic	1.520(2)	1
10	C4	H4A	Unknown	no	acyclic	0.99	1
11	C4	H4B	Unknown	no	acyclic	0.99	1
12	C4	C5	Unknown	no	cyclic	1.521(2)	1
13	C5	H5	Unknown	no	acyclic	1	1
14	C5	C6	Unknown	no	acyclic	1.510(2)	1
15	C5	N1	Unknown	no	cyclic	1.473(2)	1
16	C6	C7	Unknown	no	cyclic	1.390(2)	un
17	C6	C11	Unknown	no	cyclic	1.391(2)	un
18	C7	H7	Unknown	no	acyclic	0.95	1
19	C7	C8	Unknown	no	cyclic	1.387(2)	un
20	C8	H8	Unknown	no	acyclic	0.95	1
21	C8	C9	Unknown	no	cyclic	1.384(2)	un
22	C9	H9	Unknown	no	acyclic	0.95	1
23	C9	C10	Unknown	no	cyclic	1.386(2)	un
24	C10	H10	Unknown	no	acyclic	0.951	1
25	C10	C11	Unknown	no	cyclic	1.386(2)	un
26	C11	H11	Unknown	no	acyclic	0.95	1
27	N1	H1	Unknown	no	acyclic	0.88	1

All Angles

Number	Atom1	Atom2	Atom3	Angle
1	C2	C1	N1	118.0(1)
2	C2	C1	O1	119.0(1)
3	N1	C1	O1	123.0(1)
4	C1	C2	H2	109.2
5	C1	C2	C3	114.6(1)
6	C1	C2	F1	105.3(1)
7	H2	C2	C3	109.2
8	H2	C2	F1	109.2
9	C3	C2	F1	109.3(1)
10	C2	C3	H3A	109.6
11	C2	C3	H3B	109.5

12	C2	C3	C4	110.5(1)
13	H3A	C3	H3B	108.1
14	H3A	C3	C4	109.5
15	H3B	C3	C4	109.6
16	C3	C4	H4A	109.9
17	C3	C4	H4B	109.9
18	C3	C4	C5	108.9(1)
19	H4A	C4	H4B	108.3
20	H4A	C4	C5	109.9
21	H4B	C4	C5	109.9
22	C4	C5	H5	107.7
23	C4	C5	C6	113.2(1)
24	C4	C5	N1	110.0(1)
25	H5	C5	C6	107.8
26	H5	C5	N1	107.8
27	C6	C5	N1	110.2(1)
28	C5	C6	C7	119.3(1)
29	C5	C6	C11	122.0(1)
30	C7	C6	C11	118.7(1)
31	C6	C7	H7	119.6
32	C6	C7	C8	120.7(1)
33	H7	C7	C8	119.7
34	C7	C8	H8	119.9
35	C7	C8	C9	120.3(1)
36	H8	C8	C9	119.8
37	C8	C9	H9	120.4
38	C8	C9	C10	119.2(1)
39	H9	C9	C10	120.4
40	C9	C10	H10	119.7
41	C9	C10	C11	120.6(1)
42	H10	C10	C11	119.7
43	C6	C11	C10	120.4(1)
44	C6	C11	H11	119.8
45	C10	C11	H11	119.8
46	C1	N1	C5	126.8(1)
47	C1	N1	H1	116.6
48	C5	N1	H1	116.6

All Torsions

Number	Atom1	Atom2	Atom3	Atom4	Torsion
1	N1	C1	C2	H2	138.2
2	N1	C1	C2	C3	15.4(2)
3	N1	C1	C2	F1	-104.6(1)
4	O1	C1	C2	H2	-42.8
5	O1	C1	C2	C3	-165.6(1)
6	O1	C1	C2	F1	74.4(1)
7	C2	C1	N1	C5	-6.9(2)
8	C2	C1	N1	H1	173.1

9	O1	C1	N1	C5	174.2(1)
10	O1	C1	N1	H1	-5.8
11	C1	C2	C3	H3A	-164.3
12	C1	C2	C3	H3B	77.3
13	C1	C2	C3	C4	-43.5(2)
14	H2	C2	C3	H3A	72.9
15	H2	C2	C3	H3B	-45.5
16	H2	C2	C3	C4	-166.3
17	F1	C2	C3	H3A	-46.5
18	F1	C2	C3	H3B	-164.9
19	F1	C2	C3	C4	74.3(1)
20	C2	C3	C4	H4A	-57.7
21	C2	C3	C4	H4B	-176.9
22	C2	C3	C4	C5	62.7(1)
23	H3A	C3	C4	H4A	63.1
24	H3A	C3	C4	H4B	-56.1
25	H3A	C3	C4	C5	-176.5
26	H3B	C3	C4	H4A	-178.5
27	H3B	C3	C4	H4B	62.4
28	H3B	C3	C4	C5	-58.1
29	C3	C4	C5	H5	65.1
30	C3	C4	C5	C6	-175.8(1)
31	C3	C4	C5	N1	-52.1(1)
32	H4A	C4	C5	H5	-174.4
33	H4A	C4	C5	C6	-55.4
34	H4A	C4	C5	N1	68.4
35	H4B	C4	C5	H5	-55.3
36	H4B	C4	C5	C6	63.8
37	H4B	C4	C5	N1	-172.5
38	C4	C5	C6	C7	-97.9(1)
39	C4	C5	C6	C11	80.4(2)
40	H5	C5	C6	C7	21.1
41	H5	C5	C6	C11	-160.6
42	N1	C5	C6	C7	138.5(1)
43	N1	C5	C6	C11	-43.2(2)
44	C4	C5	N1	C1	25.9(2)
45	C4	C5	N1	H1	-154
46	H5	C5	N1	C1	-91.3
47	H5	C5	N1	H1	88.8
48	C6	C5	N1	C1	151.4(1)
49	C6	C5	N1	H1	-28.6
50	C5	C6	C7	H7	-0.9
51	C5	C6	C7	C8	179.0(1)
52	C11	C6	C7	H7	-179.3
53	C11	C6	C7	C8	0.7(2)
54	C5	C6	C11	C10	-179.3(1)
55	C5	C6	C11	H11	0.7
56	C7	C6	C11	C10	-1.0(2)
57	C7	C6	C11	H11	179

58	C6	C7	C8	H8	-179.5
59	C6	C7	C8	C9	0.4(2)
60	H7	C7	C8	H8	0.5
61	H7	C7	C8	C9	-179.6
62	C7	C8	C9	H9	178.7
63	C7	C8	C9	C10	-1.2(2)
64	H8	C8	C9	H9	-1.3
65	H8	C8	C9	C10	178.7
66	C8	C9	C10	H10	-179.1
67	C8	C9	C10	C11	0.9(2)
68	H9	C9	C10	H10	0.9
69	H9	C9	C10	C11	-179.1
70	C9	C10	C11	C6	0.2(2)
71	C9	C10	C11	H11	-179.8
72	H10	C10	C11	C6	-179.8
73	H10	C10	C11	H11	0.2