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The Development of Pd(II)-Catalysed C–H Activation Cascades for the Synthesis of Polyheterocycles

The Development of Pd(II)-Catalysed C–H Activation Cascades for the Synthesis of Polyheterocycles

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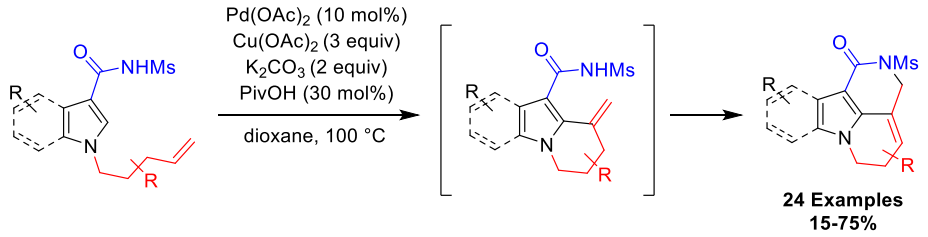
A thesis submitted to the University of Bristol in accordance with the requirements of the degree of Doctor of Philosophy in the Faculty of Science

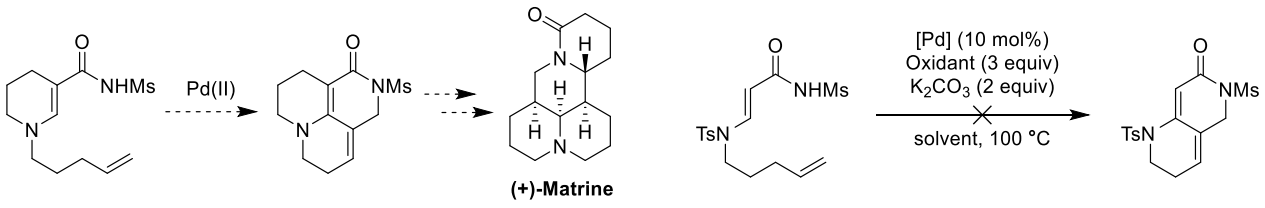
Abstract

A novel Pd(II)-catalysed C–H activation/aza-Wacker cascade sequence has been optimised for indoles bearing an *N*-tethered alkene and an *N*-acyl mesylamide group that serves dual purpose as a directing group and a C–N bond precursor. This optimisation was achieved by a combination of Design of Experiments and traditional reactant screening. The reaction is tolerant to functionalisation on the alkene and tether, as well as substitution at various positions around the indole ring. The methodology can also be applied to pyrrole systems. 24 successful examples of this Pd(II)-catalysed C–H activation methodology are described.



A number of studies have been carried out in order to probe the mechanism of this cascade sequence. As a result of this an oxidative Heck/aza-Wacker mechanism beginning with amide deprotonation can be proposed.

The application of this methodology to non-aromatic substrates, with a view to this being used as a potential key step towards the total synthesis of naturally occurring alkaloids and potential drug discovery scaffolds, was examined. The synthesis of the substrate necessary for the total synthesis of the alkaloid matrine was unsuccessful, so the Pd(II)-catalysed C–H activation of enamine test substrates were instead investigated. These substrates were found to be unsuitable for Pd(II)-catalysed C–H activation due to a lack of aromaticity and a lack of electron density.



Proof of concept for the oxidative Heck/aza-Wacker cascade cyclisation of aniline-derived substrates is also described.

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Author's declaration

The work described in this thesis was carried out at the School of Chemistry, University of Bristol, under the supervision of Professor Kevin Booker-Milburn between May 2016 and September 2019. I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

Signed…… Date ……..

List of Abbreviations

Ac	Acetyl
acac	Acetylacetone
Ala	Alanine
AQ	8-Aminoquinoline
atm	Atmospheres
BBBPY	4,4'-Di-*tert*-butyl-2,2'-dipyridyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
bipy	2,2'-Bipyridine
Bn	Benzyl
Boc	*tert*-Butyl carbamate
BQ	Benzoquinone
Bu	Butyl
Bz	Benzoyl
cat.	Catalyst
CDI	Carbonyldiimidazole
CMD	Concerted Metalation-Deprotonation
COD	1,5-Cyclooctadiene
CPA	Chiral phosphinic acid
DAF	4,5-Diazafluoren-9-one
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DHP	Dihydropyridine
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIH	1,3-Diiodo-5,5-Dimethyl hydantoin
DIPEA	*N*,*N'*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMPU	*N*,*N'*-Dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
DoE	Design of Experiments
dppb	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
Equiv(.)	Equivalents
Et	Ethyl
fmoc	Fluorenylmethyloxycarbonyl chloride
Gly	Glycine
HFIP	Hexafluoroisopropanol
IBX	2-Iodoxybenzoic acid

KIE	Kinetic isotope effect
Leu	Leucine
LiHMDS	Lithium bis(trimethyl)amide
Me	Methyl
MeCN	Acetonitrile
MPAA	Mono-protected amino acids
Ms	Mesylate, $MeSO_2$-
MS	Molecular sieves
NBS	*N*-Bromosuccinamide
NCS	*N*-Chlorosuccinamide
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
Ns	Nosyl, *o*-$NO_2(C_6H_4)SO_2$
OVAT	One variable at a time
Ph	Phenyl
phen	1,10-Phenanthroline
Piv	Pivalate, $(Me)_3CCO_2$-
PTS	PEG-600/alpha-Tocopherol-based diester of sebacic acid
rac	Racemic
r.t.	Room temperature
S_EAr	Electrophilic aromatic substitution
SM	Starting material
TBAB	Tetra-*n*-butylammonium bromide
TBAF	Tetrautylammoniumfluoride
TBAHS	Tetrabutylammonium hydrogen sulfate
TBAI	Tetrabutylammonium iodide
TBDMS/TBS	*tert*-Butyldimethylsilyl
*t*BuLi	*tert*-Butyl lithium
Tf	Triflyl, F_3CSO_2-
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFE	Tetrafluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
Thr	Threonine
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediame
TosMIC	Toluenesulfonylmethyl isocyanide
Ts	Tosyl, *p*-$Me(C_6H_4)SO_2$
Val	Valine
wt	weight

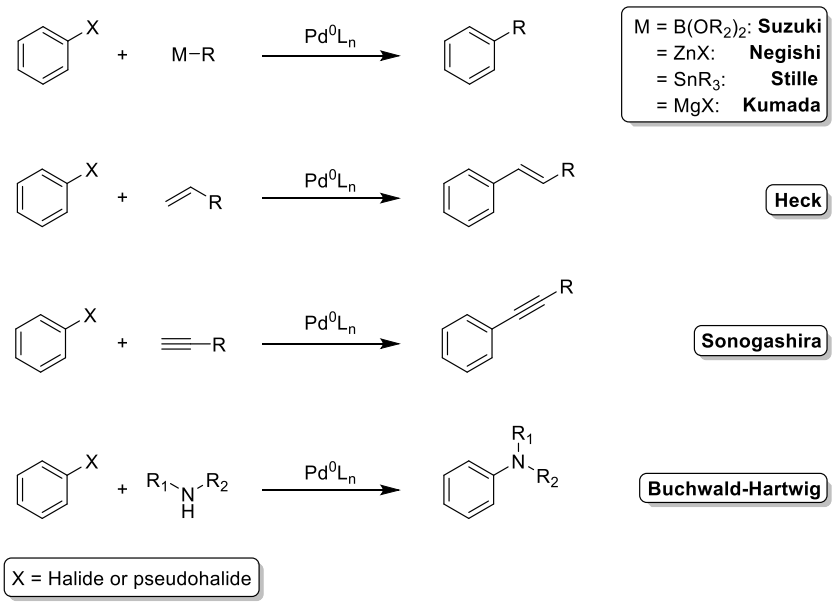
Contents

1. Introduction

Nitrogen containing polyheterocycles are an important class of compounds and can be found in a wide variety of natural products, drug molecules and other biologically active compounds. Their pharmacological activity is due to their similarity to structures found within the body, such as in DNA, and the ability of nitrogen-containing polyheterocycles to participate in hydrogen bonding interactions with structures in the body, such as proteins. Indole-containing compounds are particularly prevalent in nature as they can be synthesised from the amino acid tryptophan. Because of this, the development of efficient synthesis of nitrogen-containing polyheterocycles is essential in order to fully exploit their pharmacological properties. It is not clear whether natural products are synthesised in nature because those are the optimum compounds, or because they are easily synthesised by nature, so the synthesis and analysis of compounds seen in nature and novel compounds are both necessary areas of exploration. Pd(II)-catalysed C–H activation reactions are powerful tools in organic synthesis as they can be used to functionalise polyheterocycles, but can also be used in ring annulations towards the formation of polyheterocycles. C–H activation reactions are particularly useful when used as part of a cascade reaction as these can rapidly transform simple starting materials into much more complex products. This thesis investigates the development of Pd(II)-catalysed oxidative Heck/aza-Wacker cascade sequences for the generation of novel complex polyheterocycles.

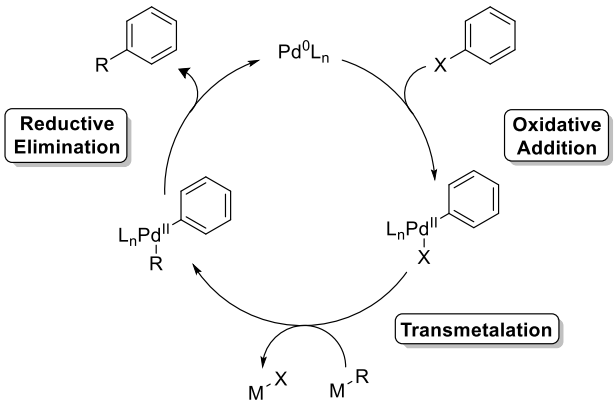
1.1 Pd(0)-Catalysed cross coupling reactions

Pd(0)-catalysed cross coupling reactions have revolutionised modern synthetic chemistry by allowing the efficient formation of C–C and C–N bonds. These reactions have therefore become vital tools in both academia and industry, particularly in the pharmaceutical, agrochemical, and fine chemical industries. This was highlighted in 2010 when the Nobel Prize was awarded to Heck, Suzuki and Negishi for their ground-breaking discoveries regarding Pd(0)-catalysed C–C bond formations. Over the years, examples of Pd(0)-catalysed cross-coupling reactions have grown in number and diversity. The most notable reactions include the Suzuki,[1] Heck,[2] Negishi,[3] Sonogashira,[4] Stille[5] and Kumada[6] reactions and Buchwald–Hartwig amination[7] (Scheme 1).



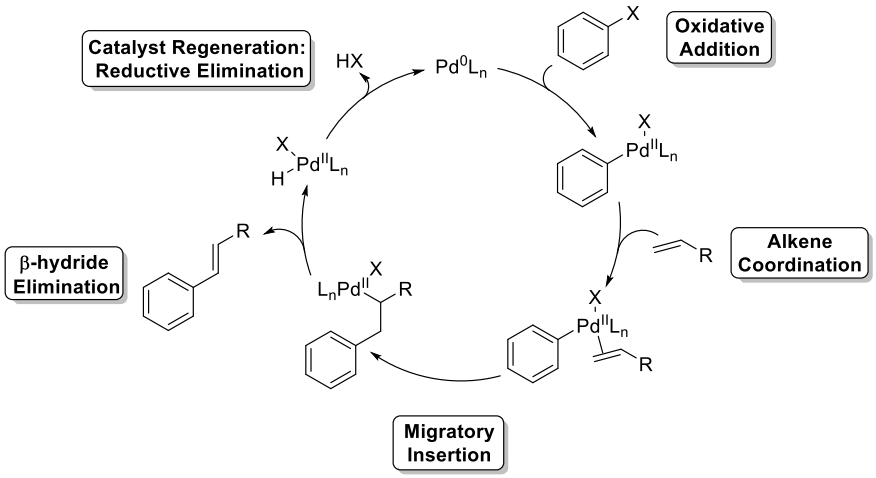
Scheme 1. Common Pd(0)-catalysed cross-coupling reactions

These reactions all follow a general mechanism based on a Pd(0)/Pd(II) catalytic cycle, involving oxidative addition, transmetalation, and reductive elimination (Scheme 2). The active Pd(0) catalyst is usually formed *in situ* by the reduction of a Pd(II) precatalyst such as $Pd(OAc)_2$. The generated Pd(0) species undergoes oxidative addition with an aryl halide or pseudo halide, where the Pd(0) species inserts itself into the aryl halide R–X bond producing a reactive organopalladium(II) halide complex. This complex then undergoes transmetalation with an organometallic coupling partner; it is this transmetalation step that distinguishes one cross-coupling reaction from another. While the Sonogashira reaction does not initially contain an organometallic reagent, a copper acetylide is formed *in situ* by the reaction of a base and a copper halide salt with the alkyne. The Suzuki reaction is also unique in that the addition of a base, such as sodium hydroxide, is necessary for the reaction to occur. It was originally thought that the base activates the boronic acid by forming a borate complex $[B(OR)_3R]^-$. However, it is now believed that the anionic hydroxide does not act as a base, but as a ligand for aryl-Pd(II) complexes.[8] The boron coupling partner is able to form a much stronger interaction with the oxygen of the hydroxyl ligand than it would with a halide ligand, allowing transmetalation to occur. The transmetalated species undergoes reductive elimination to form the product and regenerate the Pd(0) species, enabling it to undergo subsequent reaction cycles.



Scheme 2. General Pd(0)-catalysed reaction mechanism

The Heck reaction differs in mechanism to that of the other Pd(0)-catalysed cross coupling reactions as it does not include a transmetalation step. Instead, following oxidative addition, an alkene coupling partner coordinates to the Pd(II) centre. This then undergoes migratory insertion followed by *syn*-selective β-hydride elimination to form the desired product. The cycle is completed by the reductive elimination of the resulting Pd(II) species, regenerating the active Pd(0) species (Scheme 3).



Scheme 3. General Heck reaction mechanism

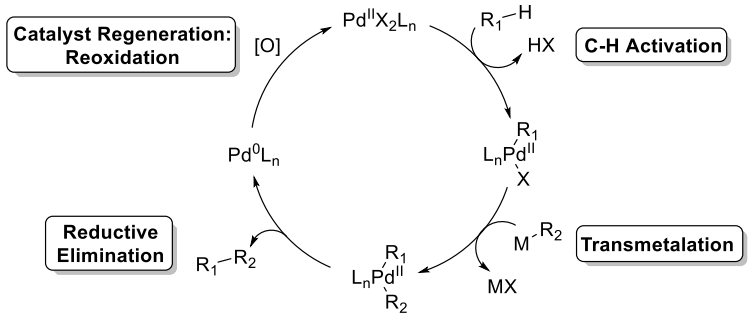
1.2 Pd(II)-Catalysed C–H activation reactions

While Pd(0)-catalysed cross-coupling reactions are crucial in modern synthetic chemistry, they require pre-functionalisation steps to access the aryl halides or pseudohalides. These pre-functionalisation steps can be costly with regard to both time and resources. The use of aryl halides also results in the generation of stoichiometric amounts of halide waste. C–H bonds are not traditionally reactive due to large kinetic barriers associated with C–H bond cleavage and due to the apolar nature of such bonds. There can also be selectivity issues due to the ubiquity of C–H bonds in organic molecules. However, the direct functionalisation of C–H bonds represents a more favourable alternative to traditional

Pd(0)-catalysed cross-coupling as no pre-functionalisation steps are required and no halide waste is produced. Instead of replacing aryl halides, C–H activation can also replace the use of organometallic reagents as coupling partners. This avoids the generation of a stoichiometric amount of metal waste and, again, avoids costly pre-functionalisation steps. Therefore, in recent years there has been significant advancement in this area and there are now a plethora of examples in the literature.[9]

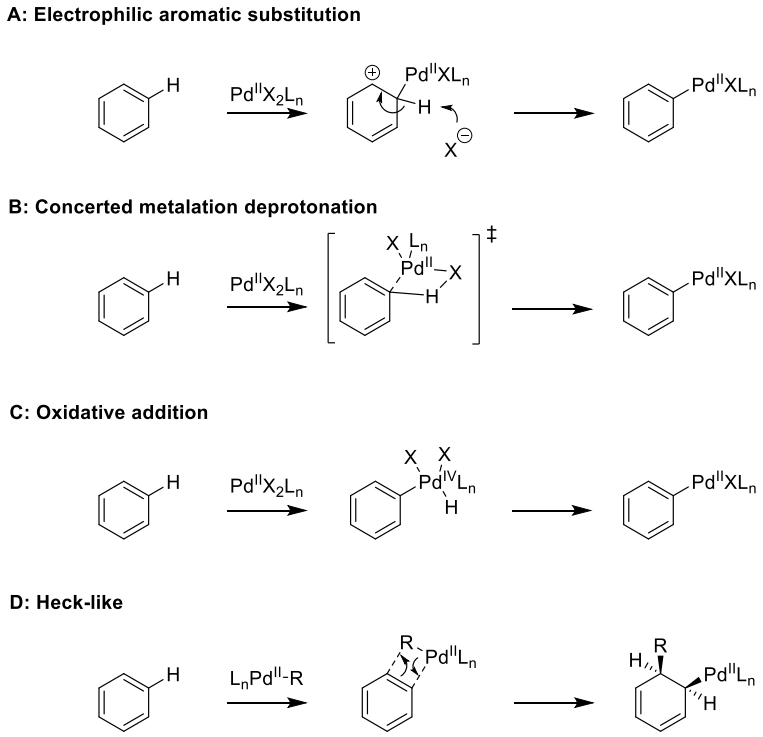
1.2.1 Mechanism of C–H activation

The mechanism of C–H activation bears similarity to that of the Pd(0)-catalysed cross-coupling reactions shown above (cf. Scheme 2, page 11). However, C–H activation differs in the fact that the reaction is catalysed by a Pd(II) species. An electrophilic Pd(II) catalyst can insert into a C–H bond. This C–H activation is followed by reaction with a coupling partner, such as an organometallic reagent or alkene, to generate the desired product. In contrast to Pd(0)-catalysed reactions, C–H activation requires the presence of an oxidant to reoxidise the resulting Pd(0) species back to the active Pd(II) catalyst (Scheme 4).



Scheme 4. General Pd(II)-catalysed CH activation reaction mechanism

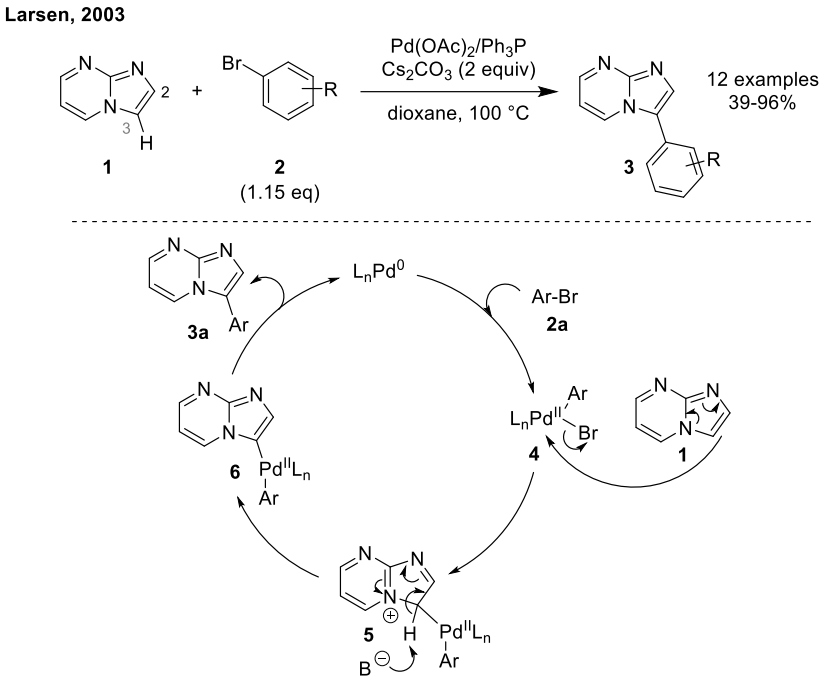
There have been a number of mechanisms proposed for the C–H activation step, including electrophilic aromatic substitution (S_EAr), concerted metalation deprotonation (CMD), oxidative C–H insertion and the Heck-like mechanism (Scheme 5), with S_EAr and CMD being the most common.



Scheme 5. Common mechanisms of C–H activation

S_EAr proceeds *via* Pd–C bond formation that results in a temporary loss of aromaticity (Scheme 5A). It is the most probable mechanism for the C–H activation of electron-rich, nucleophilic arenes and heteroarenes due to their ability to stabilise the intermediate carbocation.[10-12] Arylation usually occurs at the site most susceptible to electrophilic attack. However, the initial site of electrophilic attack is not necessarily where the functional group ends up due to the possibility of migration, for example the 2,3-migration of indoles.[13] No kinetic isotope effect (KIE) is observed for C–H activation reactions which proceed by S_EAr due to the rapid nature of the C–H cleavage step.

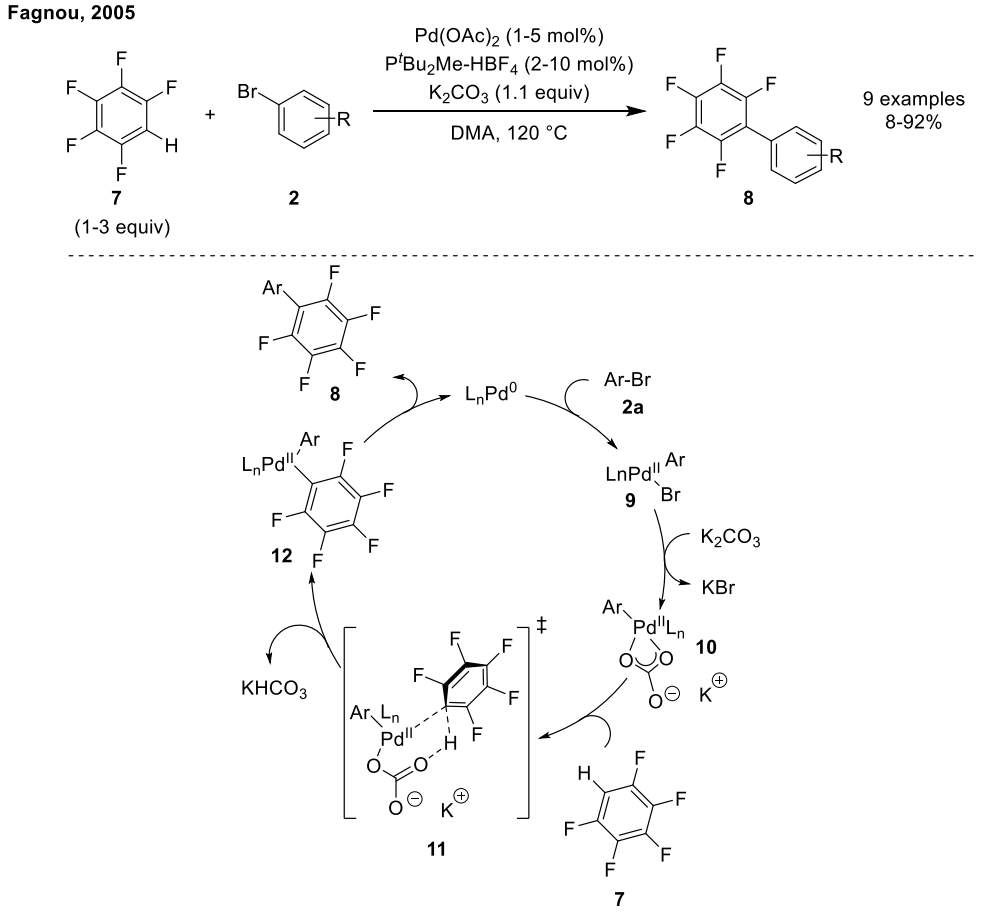
An example of S_EAr is the arylation of imidazole [1,2,*a*]pyrimidine **1** (Scheme 6).[10] This reaction proceeds with complete regioselectivity, with arylation occurring at the 3-position to give **3**. This is the site most susceptible to electrophilic attack as it gives rise to the most stable arenium ion. Attack at the 2-position is also possible but is unfavoured as the intermediate would be much less stable. The reaction was tolerant to a range of aryl bromide coupling partners, although those bearing electron-withdrawing substituents proceeded best.



Scheme 6. Arylation of imidazole [1,2,*a*]pyrimidines *via* S_EAr

CMD involves arene metalation and C–H bond cleavage occurring in a concerted manner (Scheme 5B). The hydrogen atom is abstracted by a base either in an intermolecular or intramolecular fashion. The accessibility of this mechanism is dependent on the acidity of the C–H bond. CMD is usually seen with simple and electron-deficient arenes which do not have sufficient electron density to undergo S_EAr. However, Fagnou has reported that the CMD pathway can also be used to predict the reactivity for a diverse set of arenes including some previously proposed to react *via* S_EAr.[14] A KIE is observed, indicating that C–H bond cleavage is a kinetically significant event.[15]

An example of CMD by Fagnou exemplifies the complementary reactivity of CMD to S_EAr,[16] in which the intermolecular direct arylation of electron-deficient perfluorobenzene **7** was demonstrated (Scheme 7). Computational studies showed that C–H activation proceeded *via* a concerted arene metalation and C–H bond cleavage process, with the proton being transferred to a carbonate ligand bound to the Pd-catalyst (**11**). This mechanism favours electron-deficient arenes with an acidic C–H bond, the complete opposite reactivity to S_EAr.



Scheme 7. Direct arylation of electron-deficient perfluorobenzenes

Another possible mechanism for electron-deficient arenes is oxidative addition. In this mechanism the Pd(II) species inserts itself into the C–H bond, increasing the oxidation state of Pd from II to IV. The Pd(IV) species then undergoes reductive elimination to form the common organometallic intermediate (Scheme 5C). This mechanism is most likely to occur when the metal catalyst is electron-rich and low valent, and a when a strong oxidant is present. It is most commonly observed for late transition metals due to their ability to accommodate higher oxidation states and changes in geometry. Compared with S_EAr and CMD, oxidative addition is a fairly uncommon pathway due to the instability and high energy of Pd(IV) species. Despite this there are still many examples in the literature.[17-19]

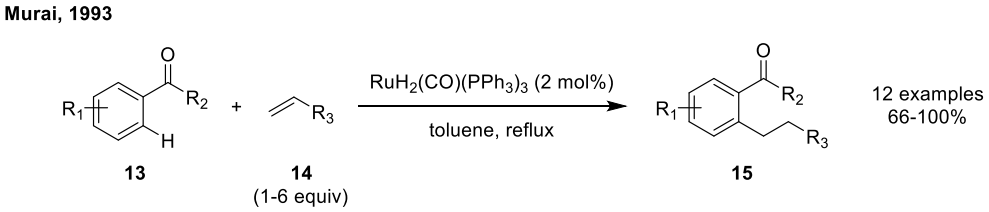
The Heck-like mechanism can occur in the presence of a pre-functionalised Pd(II) species (Scheme 5D). The Pd(II) species can add across the double bond of an alkene or an arene. This intermediate can then undergo either proton abstraction by a base, or β-hydride elimination to form the desired product.[20-21]

1.2.2 Directed C–H activation

A major challenge of C–H activation is achieving the selective functionalisation of a single C–H bond within a complex molecule, often containing multiple C–H bonds of similar reactivity. There are several strategies for overcoming this including the use of sterics[22-24] and intrinsic electronic properties.[25] However, the most successful strategy is the use of directing groups. This involves the use of substrates containing coordinating ligands, usually Lewis basic functional groups containing non-bonding electrons. These ligands bind to the metal centre allowing for the selective delivery of the catalyst to a proximal C–H bond. As well as controlling site selectivity, directing groups promote the formation of the agostic interaction due to the increase in effective concentration between the metal and the C–H bond, and they arrange the pre-transition state geometry in a favourable way for C–H cleavage. The key criterion for an effective directing group is to coordinate to a metal in a strong yet reversible manner, in order to promote C–H activation and then disassociate at the end of the reaction.

1.2.2.1 Oxygen-based directing groups

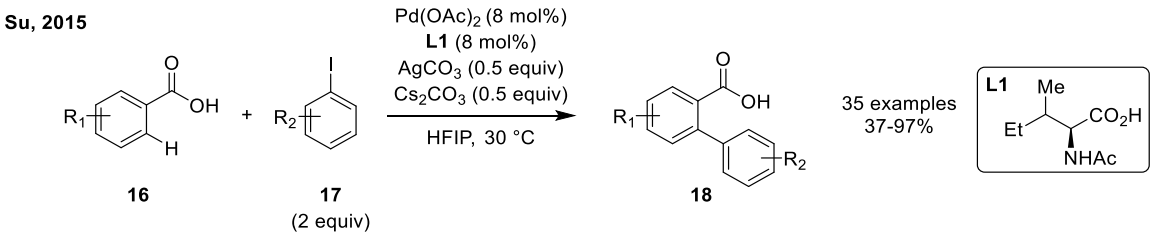
The use of directing groups for C–H activation was first made popular by Murai in the early 1990s.[26] It was demonstrated that the coupling of aromatic C–H bonds with alkenes could be carried out selectively at the *ortho*-position of the aromatic ring to form alkylarenes **15**, using a ruthenium catalyst (Scheme 8). This was achieved using a ketone directing group, which coordinated to the low-valent ruthenium complex and positioned it for the subsequent cleavage of the aromatic C–H bond. This reaction served as a blueprint for the field of directed C–H activation.



Scheme 8. Ketone-directed *ortho*-alkylation

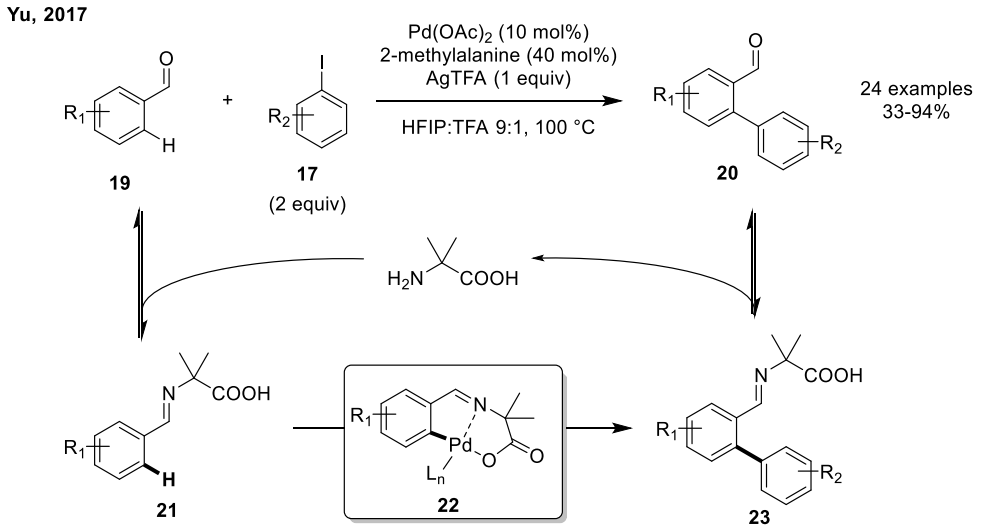
Since this work by Murai a wide range of Pd(II)-catalysed C–H activation reactions directed by oxygen-based directing groups have been reported. As well as ketones[27-29], esters[30-31], silanols[32] and ethers[33] have also been employed as effective directing groups. The use of carboxylic acids as directing groups can be challenging as they are weakly coordinating and they can undergo undesired side reactions such as hydrodecarboxylation. However, carboxylic acid are desirable directing groups as they are naturally occurring, easily installed and can be removed or serve as a handle for subsequent transformations. For these reasons there many examples of carboxylic acid directing groups in the literature.[34] One example is that reported by Su,[35] in which the Pd(II)-catalysed *ortho*-arylation of

benzoic acids **16** with aryl iodides **27** was achieved using a mono-protected amino acid (MPAA) ligand at ambient temperature to give biaryl products **18** (Scheme 9). A wide functional group tolerance was observed including substrates bearing esters and ketones, with the carboxyl group overriding any directing group ability of the ester or ketone allowing arylation to occur selectively at the *ortho*-position of the carboxyl only.



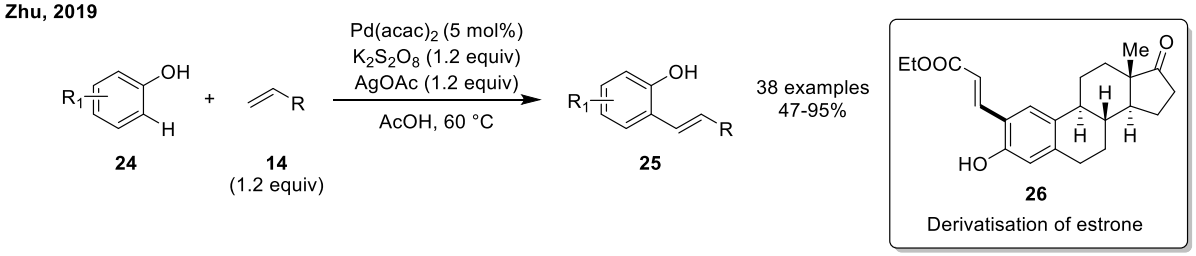
Scheme 9. *ortho*-Arylation of benzoic acids

Aldehydes are not commonly used as directing groups as they are weakly coordinating, susceptible to oxidation and prone to metal-insertion. However, they can be applied as part of transient directing group systems, in which a more strongly coordinating directing group is formed and cleaved *in situ*. This approach has been demonstrated by a number of groups.[36-38] The challenge lies with selecting the most appropriate transient directing group, as often the transient Pd(II) species is too stable, preventing functionalisation and/or dissociation from occurring. In 2017 Yu reported an example in which a catalytic amount of 2-methylalanine was used as a mediator to form the effective directing group (Scheme 10).[39] The use of an amino acid results in a carboxyl directing group attached to the substrate by an imine linkage (**21**). Carboxyl groups are not strongly coordinating, allowing functionalisation to occur. The nature of the amino acid used played a vital role towards the outcome of the reaction: α-amino acids performed better than β-amino acids, suggesting that a 5-membered palladacycle was more favourable, and the presence of the quaternary carbon centre in 2-methylalanine was beneficial due to the smaller bit angle helping to form the 5-membered palladacycle **22**. This transformation could be applied to a wide range of benzaldehydes **19** and was tolerant of a range of diverse aryl iodide coupling partners **17** to give a range of biaryl products **20**.



Scheme 10. The use of aldehydes as a transient directing group

The use of unprotected phenol as a directing group has recently been reported by Zhu.[40] In this reaction phenols **24** undergo highly selective *ortho*-alkenylation in good yields under mild reaction conditions (Scheme 11). It was found that $Pd(acac)_2$ was the most effective catalyst for the reaction and $K_2S_2O_8$ the best oxidant. Addition of a AgOAc additive gave a large increase in yield, and swapping from to DMSO to AcOH as the solvent gave a yield of 95% with no by-products for the parent system. The reaction had a broad substrate scope including unprotected tyrosine and its derivatives, and the drug molecules estrone (**26**), estradiol and ethinylestradiol. This demonstrated that the transformation was suitable for late-stage modifications of complex, biologically active, phenol-containing compounds and could be used for a tool for diversity-oriented drug discovery.[41]



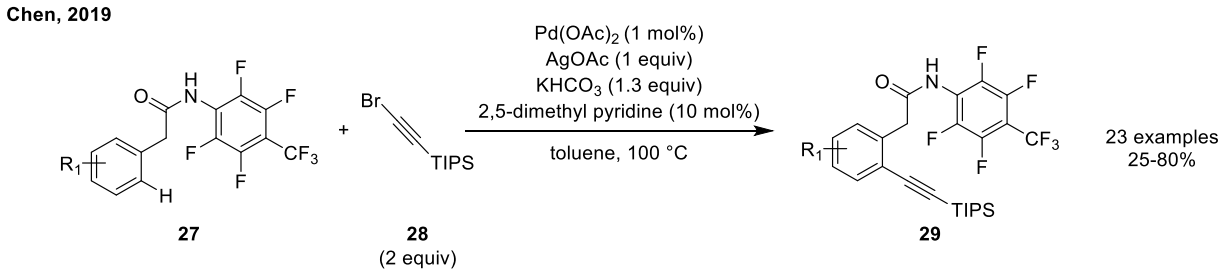
Scheme 11. *ortho*-Alkenylation of phenols

1.2.2.2 Nitrogen-based directing groups

Nitrogen-based directing groups represent the largest class of directing groups. Nitrogen possesses multiple binding modes and can bind up to 3 substituents, allowing its Lewis basicity to be fine-tuned. Nitrogen directing groups are also stable, easily accessible and easily removed.

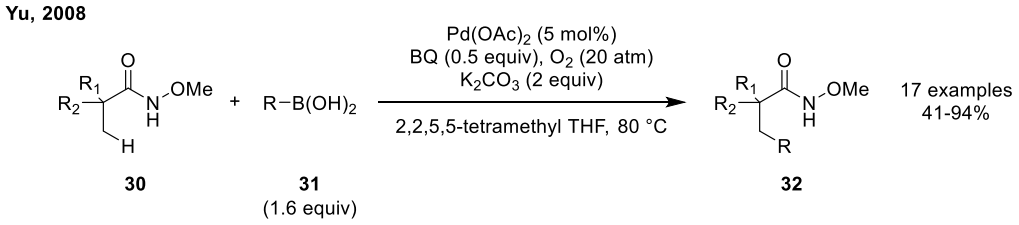
There are a plethora of examples of amide-directed Pd(II)-catalysed functionalisation reactions including alkenylations,[42] arylations,[43-44] acetylations[45] and halogenations.[46] A recent example of an

amide-directed C–H functionalisation reaction is the Pd(II)-catalysed alkynylation of phenylacetic acid derivatives **27** by Chen (Scheme 12).[47] Here a polyfluoroaniline auxiliary was used, which greatly increased the acidity of the N–H bond as a result of the strongly electron-withdrawing nature of fluorine. This was beneficial to *N*-coordination and allowed the Pd(II) catalyst to be delivered to the desired site of C–H activation. The efficiency of this reaction was increased by the addition of pyridine ligands. Investigation into the substitution pattern of the methyl groups on the pyridine showed 2,5-dimethyl pyridine to be the best ligand, allowing the Pd loading to be reduced to just 1 mol%. This transformation had a broad substrate scope and proved easy to scale up.



Scheme 12. Amide-directed alkynylation of phenylacetic acid derivatives

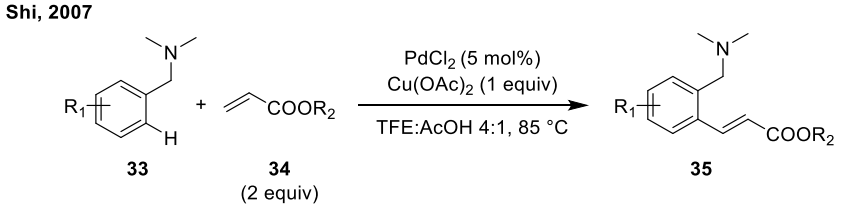
As well as standard amides, *N*-alkoxy amides have also been shown to act as versatile directing groups.[48] In 2008, Yu reported the use of *N*-alkoxyl amides as directing groups in the cross-coupling of sp^3 C–H bonds with both sp^2 and sp^3 boronic acids (Scheme 13).[49] In initial studies, cross-coupling with alkylboronic acids **31** did not result in the formation of desired product **32**. It was thought that this was due to an undesired β-hydride elimination pathway which would be supressed by the addition of sterically hindered ligands. In fact, the addition of such ligands prevented C–H activation. However, the use of 2,2,5,5-tetramethyltetrahydrofuran as the solvent did allow the transformation using alkylboronic acids to occur. It was also found that, instead of the AgO used in preliminary studies, oxygen could be used as the oxidant as an inexpensive and environmentally friendly alternative.



Scheme 13. *N*-Alkoxy amide-directed sp^2-sp^3 and sp^3-sp^3 cross-coupling

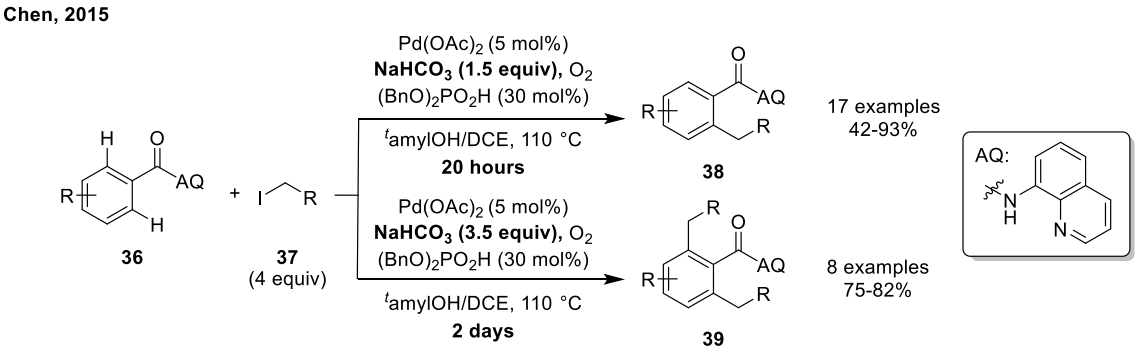
The use of amines as directing groups is challenging as their strong σ-donating ability and their excess relative to the transition metal catalyst mean they occupy the vacant coordination sites on the metal centre which are vital for C–H activation to occur. Amines also increase the electron density on the metal centre, reducing its electrophilicity. A solution to this was demonstrated by Shi in the

alkenylation of substrates such as **33** with acrylates **34** (Scheme 14).[50] AcOH was used to tune the concentration of free amines by an acid/base balance and to assist the dissociation of anionic ligands from the catalytic centre. The best solvent system for this transformation was 2,2,2-trifluoroethanol and AcOH, but the quantity of acid had to be carefully controlled. Both a decrease and increase in AcOH concentration from the range of 16-32 equiv. (relative to tertiary amine) lead to a decrease in the reaction yield, likely due to changing the concentration of tertiary amines and the electrophilicity of the metal centre. Use of the stronger acid TFA shut down the reaction completely, possibly due to the strong acid completely protonating the tertiary amine directing group and preventing binding to the metal.



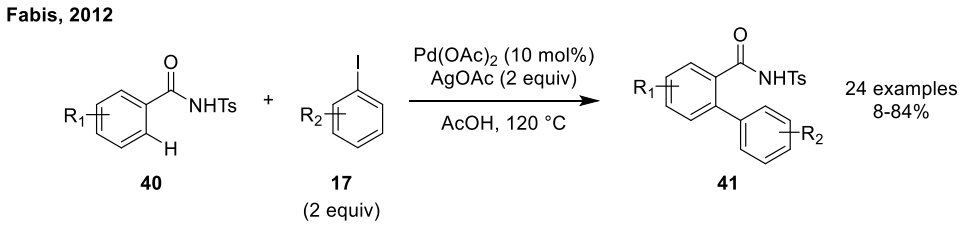
Scheme 14. Amine-directed *ortho*-alkenylation

Bidentate directing groups are also an important class of directing groups, with the *N*,*N*-bidentate group 8-aminoqunoline (AQ) being by far the most common bidentate auxiliary used in directed C–H activation. Since the first examples by Daugulis in 2005[51] there have been numerous examples in the literature.[52-53] One example is the *ortho*-C−H alkylation of *N*-quinolyl benzamides **36** by Chen (Scheme 15).[54] The key challenge for this transformation was to selectively form the monoalkylated product **38** without formation of the dialkylated derivative **39**. It was hoped that a second *ortho*-C–H alkylation would be sterically disfavoured relative to the first, however this disparity proved too small to allow for the selective formation of only **38**. It was found that the amount of $NaHCO_3$ was the crucial variable for achieving selectivity. The use of 1.5 equiv. of $NaHCO_3$ gave **38** in a yield of 81% with only 9% **39**. The use of a phosphate additive was also necessary to obtain a high yield. Interestingly, it was found that increasing the amount of $NaHCO_3$ to 3.5 equiv. and increasing the reaction time gave **39** in a yield of 82%. The scope of the reaction was examined, with a range of primary iodides forming the corresponding monoalkylated products **38** in good yield under the standard conditions. Reoptimisation of the reaction conditions allowed the coupling of secondary iodides. Mechanistic studies suggested that the functionalisation of the Pd(II) palladacycle with secondary iodides proceeded by a concerted oxidative addition pathway.



Scheme 15. AQ-directed mono- and dialkylation

There are also examples of *N*-acyl sulfonamides as *ortho*-directing groups for Pd(II)-catalysed transformations. Fabis and coworkers demonstrated the *N*-acyl sulfonamide-directed arylation of arenes **40** with aryl iodides **17** as an example of a new entry into biarylcarboxamides **41** (Scheme 16).[55] The reaction was carried out using a $Pd(OAc)_2$ catalyst and a AgOAc additive in an acidic medium. The scope of the reaction was investigated, and it was found that both electron-donating and -withdrawing substituents were well tolerated at the *ortho*- and *meta*-positions, but *para*-substitution lead to formation of the diarylated product, reducing the yield of the desired monoarylated product. The versatility of the directing group as a handle for further derivatisation was demonstrated, with examples including removal of the sulfonamide, basic hydrolysis of the sulfonamide, and intramolecular amination.



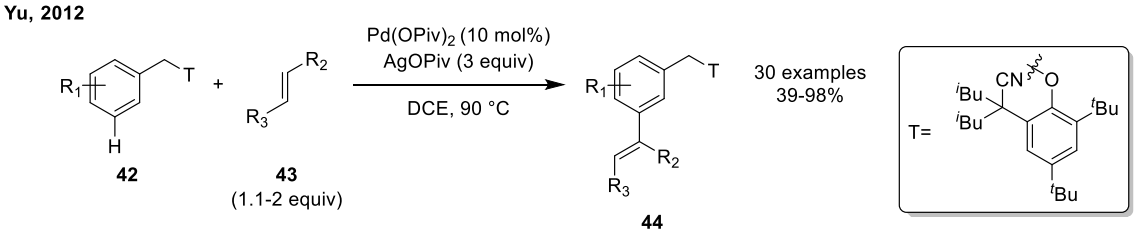
Scheme 16. *N*-Acyl sulfonamide-directed *ortho*-arylation

Further examples of *N*-acyl sulfonamides as directing groups include the use of *N*-tosylamide as a directing group for Pd(II)-catalysed arylation,[55] alkoxylation and halogenation.[56]

1.2.2.3 Remote C–H activation

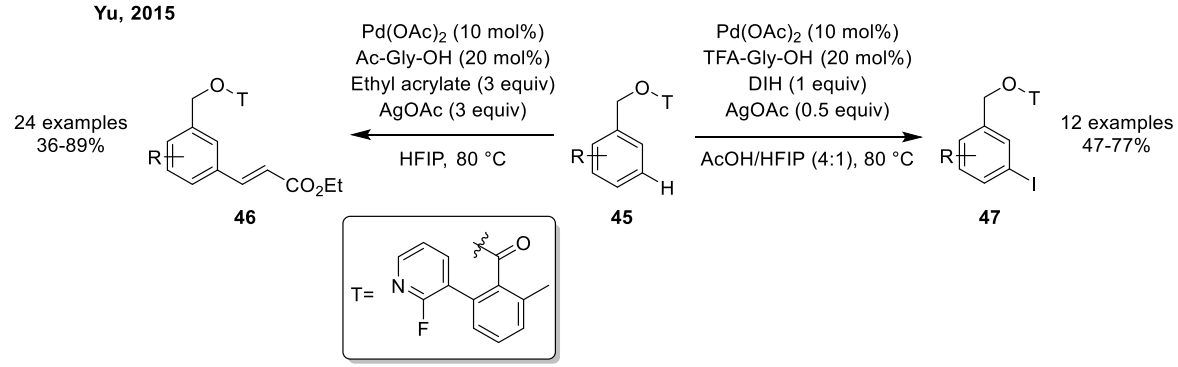
Despite the success and broad utility of *ortho*-directing groups, the activation of remote C–H bonds is also a key goal within C–H activation. The Yu group have developed an approach in which a nitrile-containing template is able to deliver the Pd(II) catalyst to a *meta*-C–H bond (Scheme 17).[57] This facilitates *meta*-olefination of arene C–H bonds with excellent selectivity. The nitrile group coordinates to the Pd(II) in an 'end-on' fashion and allows the formation of a macrocyclic cyclophane pre-transition state. This transition state overcomes any *ortho*-direction as well as any intrinsic steric

and electronic effects. This strategy has been shown to be effective for two distinct classes of substrate: toluene and hydrocinnamic acid derivatives.



Scheme 17. Nitrile-based template-directed *meta*-olefination

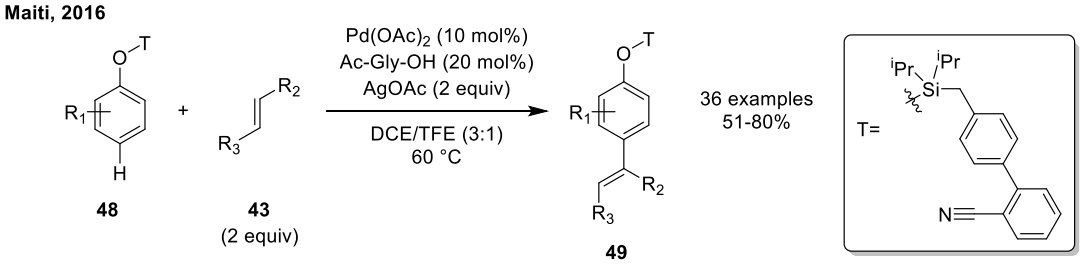
While the template approach by Yu has been a success, the use of a weakly coordinating nitrile group does have limitations: competing coordination of solvents or other functional groups. This has been overcome in a more recent example by the Yu group, which employs a more strongly σ-coordinating pyridine group to direct C–H activation (Scheme 18).[58] The template is attached by an easily removable ester linker. This pyridine-based template was successfully used for *meta*-olefination of **45** to give **46** and the reaction was tolerant to a wide range of functional groups. Another advantage to this template was the ability to direct *meta*-iodination, using 1,3-diiodo-5,5-dimethylhydantoin (DIH) as the iodine source, yielding *meta*-iodinated products **47**. *meta*-Iodination was a reaction that was unsuccessful with the previous nitrile-based template.



Scheme 18. Pyridyl-based template-directed *meta*-olefination

Despite being a greater challenge due to the difficulties associated with forming large cyclophane-like metallocycles, and the need for optimum chain length in order to deliver the catalyst to the correct position, the activation of *para*-arene C–H bonds can also be realised. Once again, this can be achieved using a template-based strategy using a nitrile coordinating group. This has been demonstrated by Maiti, who used a silyl biphenyl template to achieve *para*-functionalisation of phenol derivatives **48** (Scheme 19).[59] The *para*-selectivity was achieved by the end-on coordination of a nitrile group to the Pd catalyst and the formation of a cyclophane 17-membered transition state. Both electron-withdrawing and -donating substituents on the phenol derivatives were tolerated, including electron-

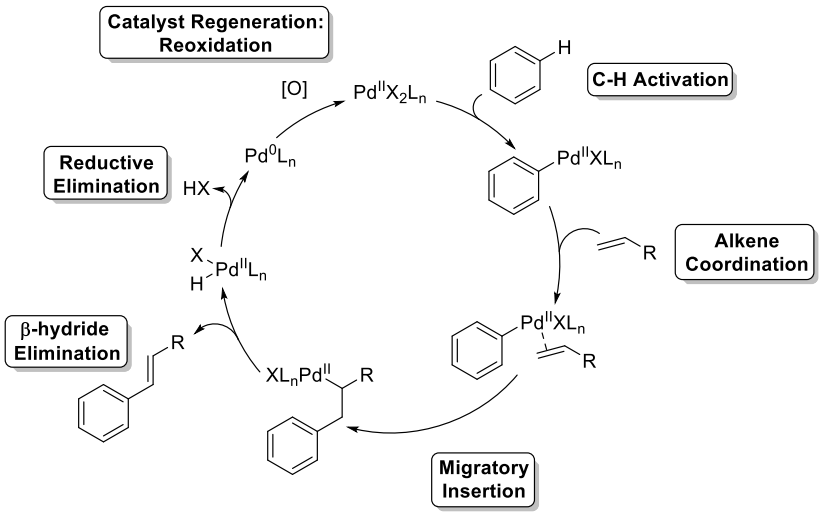
withdrawing groups *meta*-to the hydroxy group which would usually strongly deactivate the *para*-position. This ability to override electronic effects illustrates the crucial role of the template. Bulky substituents on the phenol derivatives and a range of olefins were also tolerated. The template was easily removed following functionalisation using TsOH or TBAF.



Scheme 19. Nitrile-based template-directed *para*-olefination

1.3 The Fujiwara–Moritani reaction

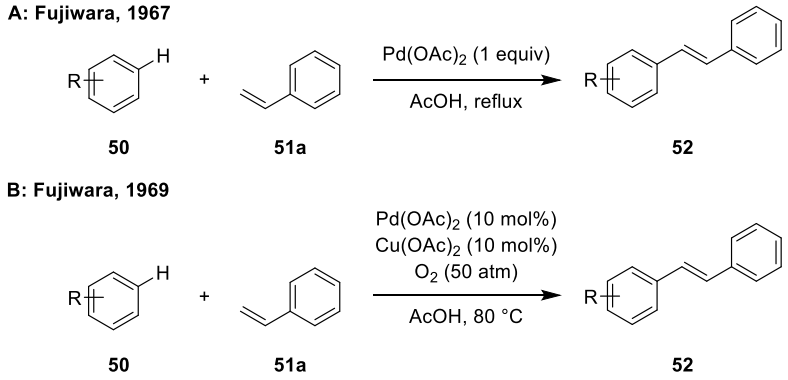
The Fujiwara–Moritani, or oxidative-Heck, reaction involves the coupling of arenes with alkenes through Pd(II)-assisted cleavage of a C–H bond. It is analogous to the Heck reaction and is an early example of a transition metal catalysed C–H activation reaction. The reaction begins with C–H activation of an aryl C–H bond. The alkene coupling partner can then coordinate to the Pd(II) centre, before undergoing migratory insertion into the C–Pd(II) bond. The product is formed by a *syn*-selective β-hydride elimination. The resulting Pd(II) species undergoes reductive elimination, forming a Pd(0) species, which is re-oxidised to regenerate the active Pd(II) catalyst (Scheme 20).



Scheme 20. The Fujiwara–Moritani reaction mechanism

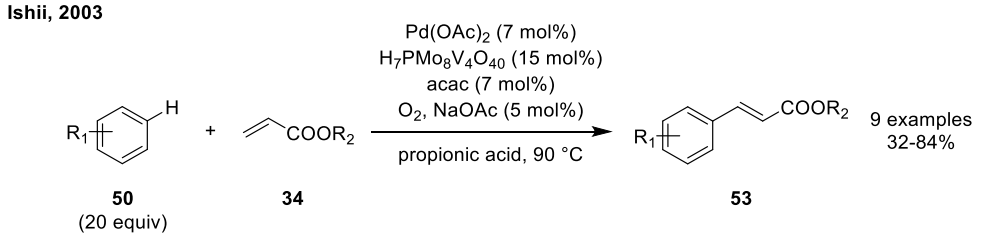
The first examples of the Fujiwara–Moritani reaction were reported by Fujiwara and in the late 1960's.[60-61] They demonstrated the coupling of benzene derivatives **50** with styrene **51a** using

stoichiometric amounts of Pd in the presence of acetic acid (Scheme 21A). Later developments allowed the reaction to be carried out catalytically using high pressure O_2 and $Cu(OAc)_2$ as an oxidant (Scheme 21B).[62]



Scheme 21. Early examples of the Fujiwara–Moritani reaction

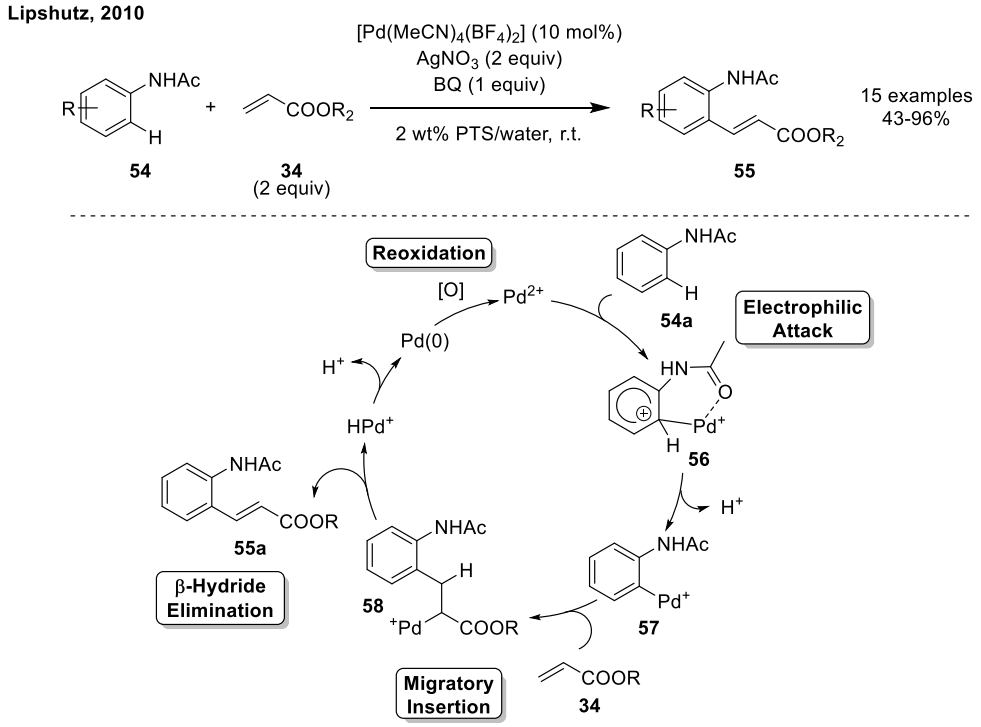
However, these early examples of the Fujiwara-Moritani reaction required harsh conditions including high pressures of O_2 as an oxidant and high temperatures. In 2003, Ishii reported an example of the Fujiwara-Moritani reaction using much milder conditions (Scheme 22).[63] They showed that arenes **50** can be directly coupled to acrylates **34** in the presence of a Pd(II) catalyst using an atmospheric pressure of O_2 as the terminal oxidant at temperatures less than 100 °C. For atmospheric O_2 to be used as the oxidant it had to be used in combination with molybdovanadophosphoric acid (HPMoV). It was found that the outcome of the reaction was heavily dependent on the Mo and V content. It was also found that the use of acetylacetone, either as an additive of in the form of $Pd(acac)_2$, was beneficial.



Scheme 22. Fujuwara-Moritani reaction under mild conditions

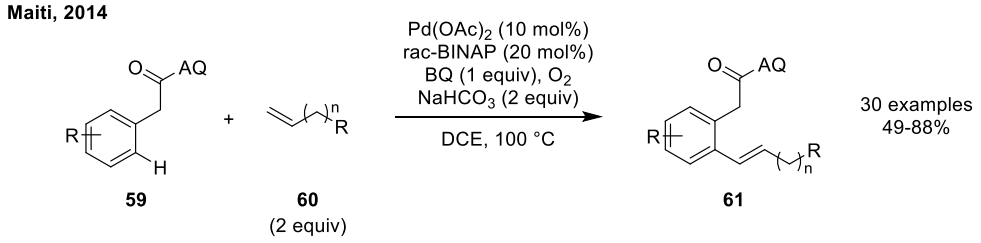
A later example by Lipshutz demonstrated even milder conditions, where the alkenylation of acetanilide substrates **54** with acrylates **34** could occur in water at ambient temperature without the need for external acid (Scheme 23).[64] Usually the presence of acid accelerates cross-coupling reactions as it increases the electrophilicity of the Pd centre, however in this example the use of the dicationic Pd catalyst $[Pd(MeCN)_4][BF4]_2$ negates this need for acid. The *ortho*-alkenylation of acetanilides using this catalyst was carried out using BQ as the oxidant and $AgNO_3$ as an additive in water with the surfactant PTS. The scope of the reaction was assessed, with a range of *meta*-substituted anilides and

acrylates with varying chain lengths undergoing the transformation in good yields. However, *para*-substituted derivatives proved unreactive.



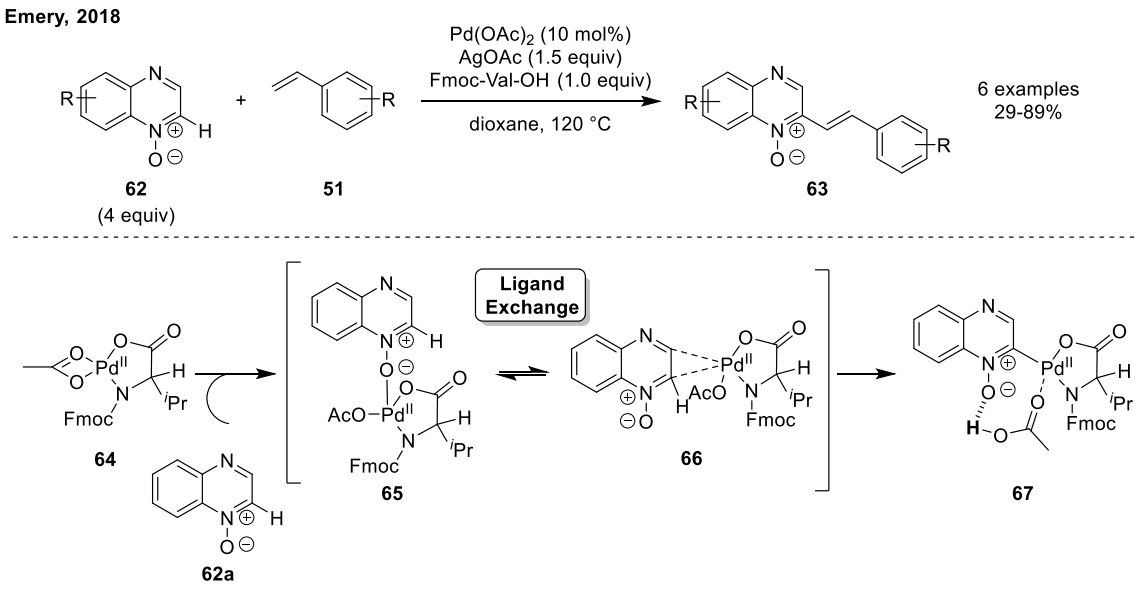
Scheme 23. $[Pd]^{2+}$-catalysed acid-free Fujiwara-Moritani reaction in water

Examples of the Fujiwara-Moritani are largely restricted to electronically activated olefins such as acrylates and styrenes.[62-64] In 2014 Maiti reported the *ortho*-alkenylation of phenylacetic acid derivatives **59** using unactivated aliphatic olefins **60** (Scheme 24).[65] This was achieved using the bidentate directing group AQ. It was thought that the rigid coordination and resulting 6-membered palladacycle helped incorporate unactivated olefins. Initial experiments resulted in the formation of a mixture of linear and branched products. In order to reduce the amount of the undesired branched product being formed a racemic BINAP ligand was added to saturate the coordination sites on the Pd centre. Once the linear product could be obtained selectively the scope of the reaction was analysed, with a wide range of olefins, functionalised olefins and substituted phenylacetic acids tolerated.



Scheme 24. Fujiwara-Moritani reaction with unactivated olefins

The scope of the Fujiwara-Moritani reaction is not limited to phenyl derivatives. A recent example by Emery showcases the alkenylation of quinoxaline *N*-oxides **62** with styrene derivatives **51** (Scheme 25).[66] Quinoxaline is a privileged heterocyclic motif that is present in a number of biologically active compounds.[67] Quinoxaline *N*-oxides possess increased C–H acidity at the α-position, which gives it excellent reactivity and selectivity for Pd(II)-catalysed cross-coupling reactions. The key variable for this reaction was the ligand and it was found that the use of the bidentate ligands 1,10-phenanthroline (phen) and BBBPY resulted in decreased yields compared to pyridine ligands. The most effective ligands proved to be MPAA's, with Fmoc-Val-OH giving the best result. It is thought that the MPAA forms a complex with Pd(II), coordinating both the N–H and COOH. The Pd(II) then coordinates to the oxygen of the *N*-oxide and can undergo reversible ligand exchange. Following CMD, a stable complex **67** is formed due to hydrogen bonding between the anionic oxygen and the acetate ligand. The mechanism continues in an analogous fashion to the general Fujiwara-Moritani mechanism (cf. Scheme 20, page 23).

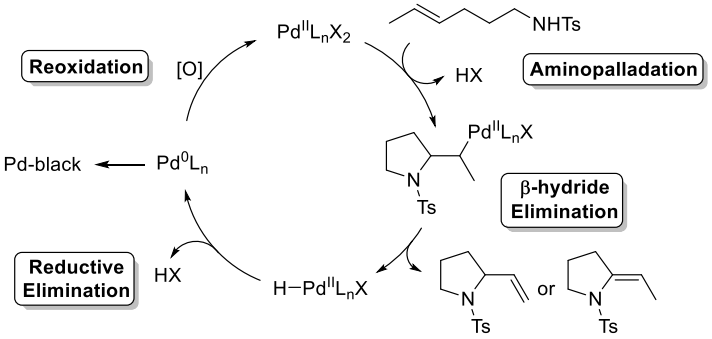


Scheme 25. Fujiwara-Moritani reaction of quinoxaline *N*-oxide

1.4 The aza-Wacker reaction

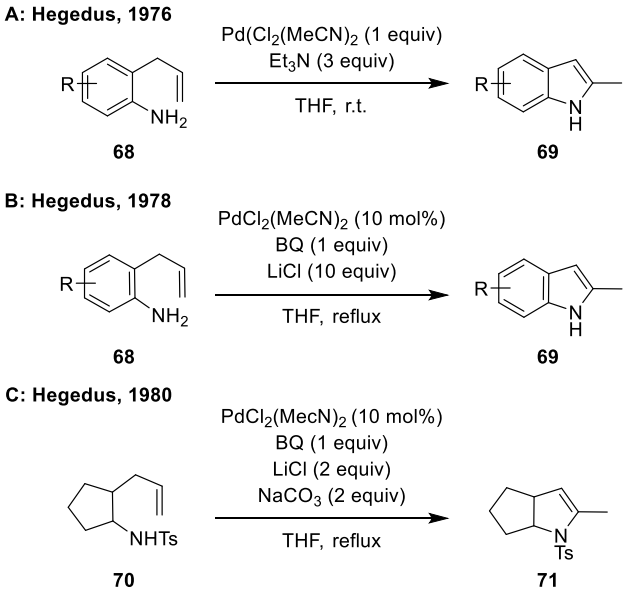
Pd(II)-catalysed oxidative coupling of alkenes with oxygen nucleophiles, such as water, have been known for over half a century.[68] An extension of these Wacker-type reactions is the aza-Wacker reaction, in which the oxygen nucleophile is replaced with a nitrogen nucleophile.[69] This is a powerful tool for the construction of nitrogen-containing heterocycles using mild conditions.

The reaction begins with aminopalladation of the alkene. The alkylpalladium(II) intermediate then undergoes β-hydride elimination to form either an enamine or an allylic amine (Scheme 26). Due to the oxidative nature of this process a stoichiometric amount of oxidant is needed.



Scheme 26. Aza-Wacker reaction mechanism

The aza-Wacker reaction was pioneered by Hegedus.[70-73] In 1976, Hegedus demonstrated the cyclisation of *ortho*-allyl anilines **68** to 2-methyl indoles **69** using a stoichiometric amount of $PdCl_2(MeCN)_2$ and Et_3N in THF (Scheme 27A).[70] While this reaction proceeded in good yields under mild conditions and tolerated a range of functional groups, the use of stoichiometric Pd was unfavourable. This was later overcome by the addition of 1 equiv. of BQ, allowing the generated Pd(0) species to be re-oxidised to Pd(II), so catalytic amounts of Pd could be used (Scheme 27B).[71]

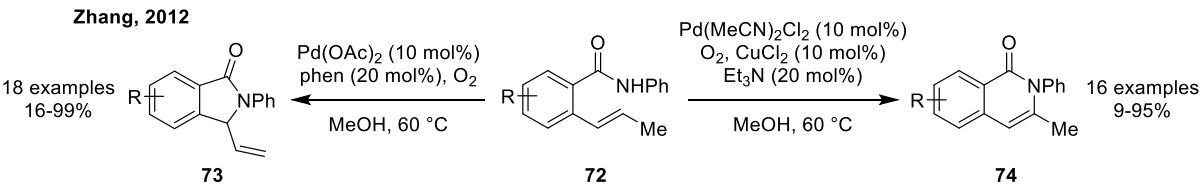


Scheme 27. Early examples of the aza-Wacker reaction

This methodology was also extended to aliphatic nucleophiles **70** (Scheme 27C).[73] In this case the increased basicity and nucleophilicity of the NH_2 group prevented the desired cyclisation from occurring and it was therefore necessary for an *N*-protecting group to be employed. *p*-Toluenesulfonamides were used as they are easily prepared and are reactive enough to be useful

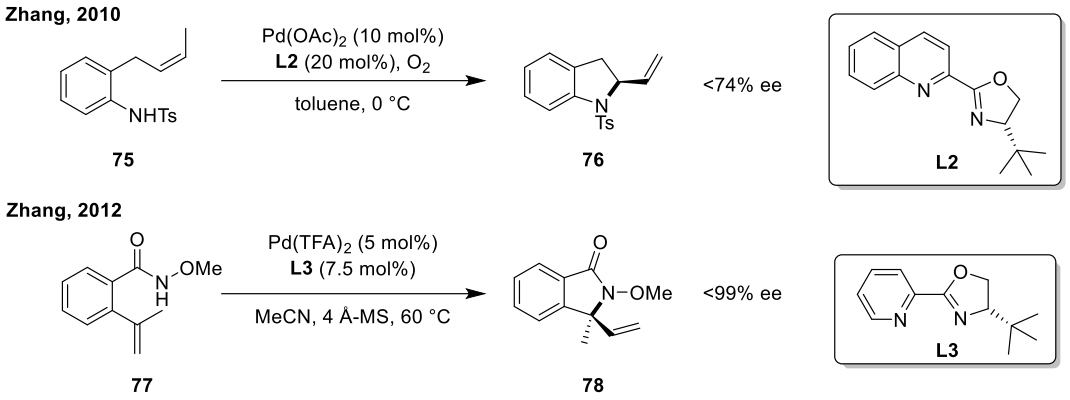
synthetic intermediates. This use of a protecting group allowed the cyclisation to be carried out in good yields under catalytic conditions.

Since their discovery, aza-Wacker-type cyclisations have been utilised in the formation of a wide range of nitrogen-containing heterocycles including pyrroles,[73] dihydroindoles and dihydroquinolines,[74] and imidazolidinones.[75] A switchable regioselective aza-Wacker cyclisation was developed by Zhang in which isoindolinones **73** or isoquinolin-1(2*H*)-ones **74** could be made from the same starting substrates **72** simply by changing the catalytic system (Scheme 28).[76] Initial studies focused on the formation of isoindolinones. When $Pd(OAc)_2$ with a pyridine ligand in toluene was used a 68% yield of **73** was obtained. The bidentate ligand phen was then employed to see if this could increase the yield, but the Pd-complexes generated were insoluble in toluene and the yield decreased. Switching the solvent to MeOH overcame this, resulting in a yield of 85%. Interestingly, in the absence of ligand it was found that the corresponding isoquinolin-1(2*H*)-one **74** was formed instead of the isoindolinone **73**. The conditions for this transformation were optimised by adding a $CuCl_2$ cocatalyst and a catalytic amount of triethylamine. Following a number of ligand studies it was concluded that the key to regiocontrol was the steric hinderance of the ligands.



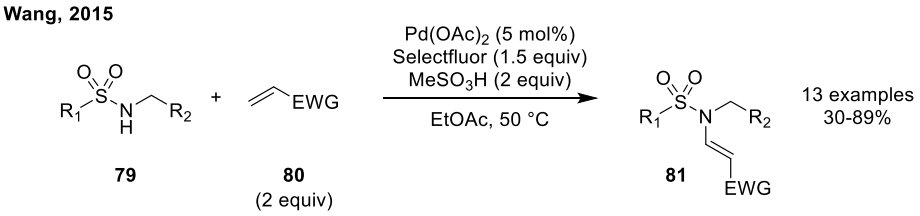
Scheme 28. Synthesis of isoindolinones and isoquinolin-1(2*H*)-ones by the aza-Wacker reaction

Interest has also turned to the addition of chiral ligands to achieve enantioselective aza-Wacker reactions. Zhang employed chiral quinolineoxazoline ligands (Scheme 29, **L2**) in the aza-Wacker-type cyclisation of olefinic tosylamides **75** to afford chiral nitrogen-containing heterocycles **76** in good yield with ee's of up to 74%.[77] Another example, also by Zhang, allowed the formation of isoindolines **78**, which contain a quaternary carbon stereocentre adjacent to the nitrogen. This was achieved by using the chiral pyridine-oxazoline ligand ^{t}Bu-pyrox (Scheme 29, **L3**).[78]



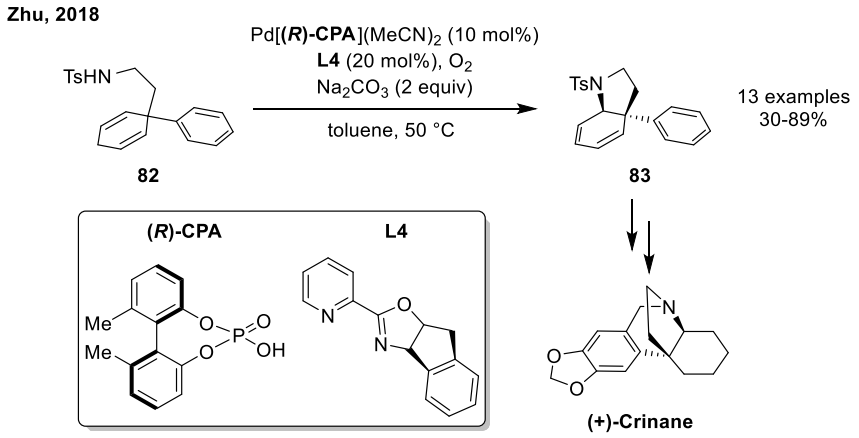
Scheme 29. Enantioselective aza-Wacker reactions using chiral ligands

All examples discussed so far have been intramolecular, however intermolecular aza-Wacker transformations are also possible. The reaction of *N*-alkylsulfonamides **79** with electron-deficient olefins **80** has been reported by Wang (Scheme 30).[79] This reaction was carried out under mild conditions using a green solvent and gave high levels of (*E*)-selectivity. It was found that a stoichiometric amount of methanesulfonic acid was required for the reaction to succeed. When lower quantities of methanesulfonic acid were used longer reaction times were required and lower yields were obtained. It was proposed that the reaction proceeds *via* a Pd(II)/Pd(0) catalytic pathway with Selectfluor® acting as a strong oxidant. The electronics of the sulfonyl group proved to have a significant effect on the outcome of the reaction, with substrates bearing strongly electron-withdrawing sulfonyl groups yielding no product. Investigations into the effect of the olefin also gave varied results with acrylates being well tolerated but alkenes such as styrene, acrylonitrile and BQ yielding no product.



Scheme 30. Intermolecular aza-Wacker reaction

A recent example by Zhu describes the desymmetrising aza-Wacker reaction of prochiral 3,3-disubstituted cyclohexa-1,4-dienes **82** to form enantioenriched tetrahydroindoles **83** (Scheme 31).[80] The key to this reaction was the use of a Pd catalyst bearing chiral phosphinic acid (CPA) ligands in combination with a chiral pyrox ligand, **L4**. The enantioselectivity was determined by the pyrox ligand and the matched CPA increased both the yield and the ee. The utility of this transformation was highlighted by its use in the total synthesis of (+)-crinane.



Scheme 31. Desymmetrising aza-Wacker cyclisation

1.5 C–H Activation of indoles

Indoles can be found in a wide range of products, across a diverse set of industries. Crucially, indole is seen as a privileged structure in medicinal chemistry due to its ubiquitous presence in both drug molecules and natural products (Figure 1).[81] Because of this, indole is of key interest in the design of new, synthetic molecules that possess biological activity. Consequently, the development of methodologies for the synthesis of functionalised indoles is crucial. There are three main routes towards the synthesis of functionalised indoles: *de novo* construction of the indole ring itself by reactions such as the Fischer[82] or Larock[83] indole synthesis, halogenation of the indole followed by Pd(0)-catalysed cross-coupling, or direct Pd(II)-catalysed C–H activation. The latter is by far the most attractive route due to its step and atom economy.

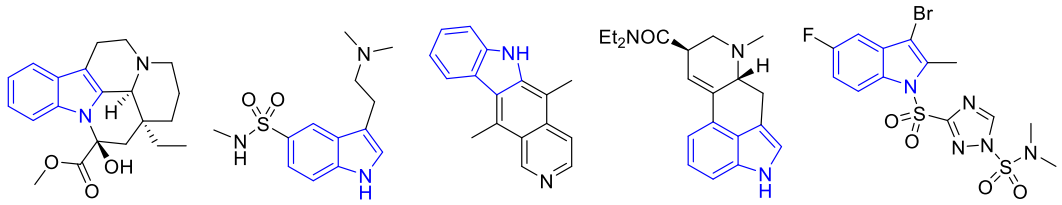


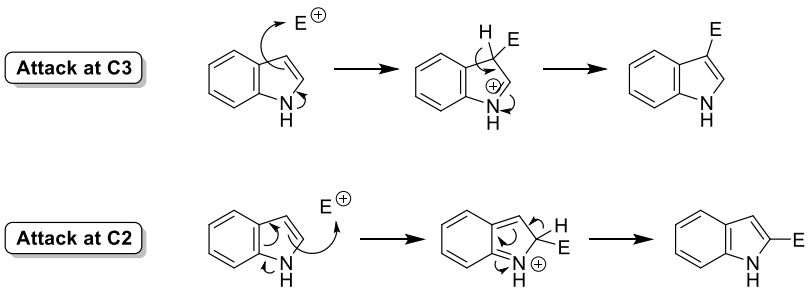
Figure 1. Important indole-containing molecules

1.5.1 Intermolecular C–H activation of indoles

1.5.1.1 C3-Functionalisation of indoles

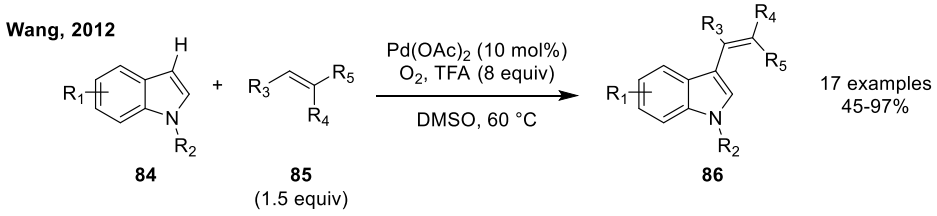
The nucleophilic nature of indole at the C3 position means that electrophilic palladation usually occurs preferentially at this position in the absence of a directing group. To understand this C3 *vs* C2 selectivity the mechanism of electrophilic attack at each position must be examined. Electrophilic attack at C2 requires breaking the aromaticity of the phenyl ring, whereas electrophilic attack at C3

does not. This means that electrophilic attack at the C3 position is much more thermodynamically favourable and C–H activation therefore occurs naturally at C3.



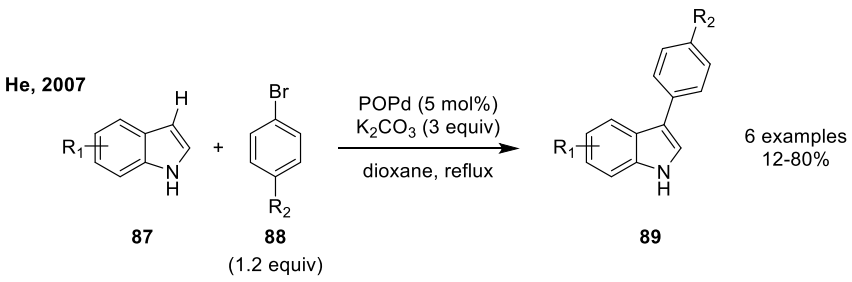
Scheme 32. Nucleophilic reactivity of indoles

An example of the alkenylation of indoles at the C3 position was reported by Wang in 2012 (Scheme 33).[84] The reaction proceeded with complete regio- and stereoselectivity with only O_2 as an oxidant, avoiding the generation of reduced oxidant waste. It was found that increasing the electrophilicity of the $Pd(OAc)_2$ catalyst by the addition of TFA improved the yield of the reaction. DMSO was the most effective solvent, and a temperature of 60 °C was found to be optimal as higher temperatures led to the decomposition of both the starting material and product. This transformation tolerated a large range of alkenes **85**, including mono- and disubstituted activated and unactivated olefins. Substitution on the indole ring with both electron-donating and -withdrawing groups was also well tolerated, with even the *N*-unprotected indole forming the desired product.



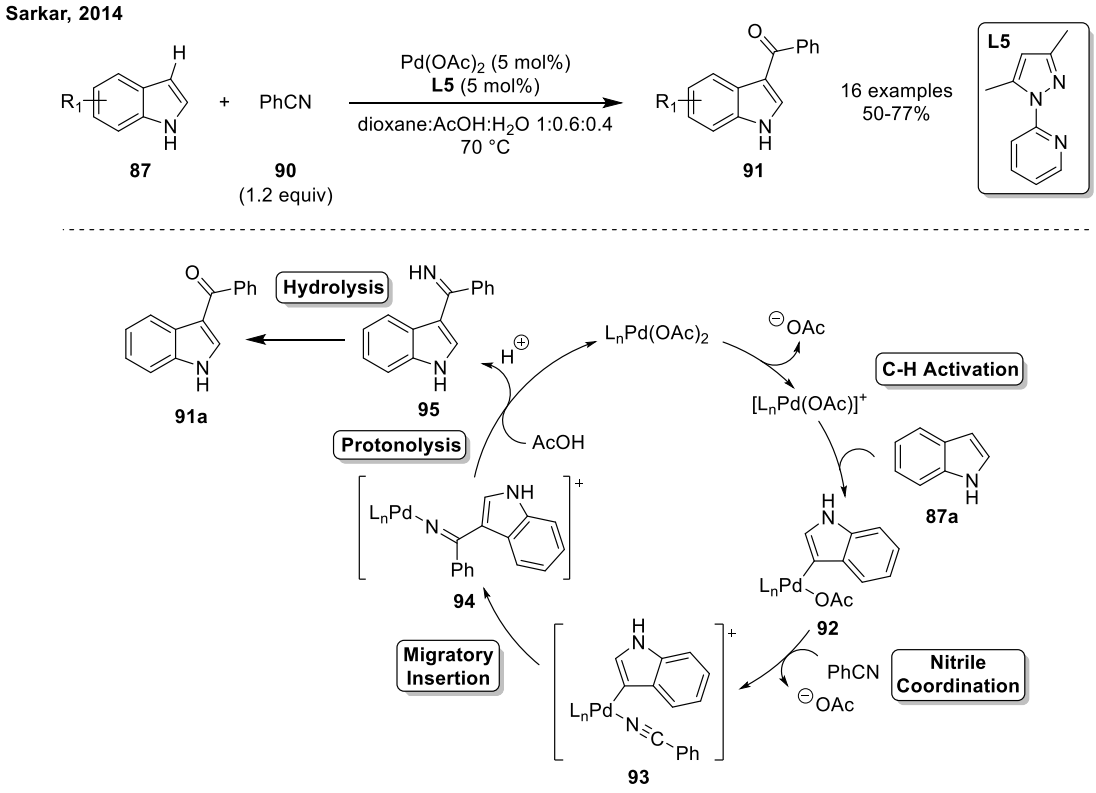
Scheme 33. C3-Alkenylation of indoles

Li has demonstrated the use of air stable Pd-phosphinous acid complexes as effective catalysts for transition-metal catalysed cross-coupling reactions.[85] This work was extended by He with the application of these catalysts to the C3-arylation of indoles **87** with aryl bromides **88** (Scheme 34).[86] The best Pd complex for this transformation was found to be $Pd[(^tBu)_2P(OH)_2]Cl_2$ (POPd). A base screen revealed weak bases such as K_2CO_3 to be the most effective. The biggest advantage of this reaction was that *N*-unprotected indoles were used, avoiding the need for *N*-protection and deprotection. The scope of this reaction was limited, with both electron-withdrawing and -donating groups on the bromobenzene coupling partner significantly decreasing the yield. Cyano- and nitro groups on the 5-position of the indole ring, and substitution at the 2 position also prevented reactivity.



Scheme 34. C3-Arylation of indoles

The Pd(II)-catalysed C3-acylation of indoles has also been realised (Scheme 35).[87] Initial studies focused on the acylation of phenyl boronic acid using nitriles, however it was hypothesised that the cationic intermediate may also be trapped with nucleophilic indoles **87** to yield 3-acylated indoles **91**. Indeed, using $Pd(OAc)_2$, **L5**, and K_2CO_3 in dioxane at 70 °C the desired product **91a** was formed in a yield of 70%. The reaction was successfully applied to a broad range of substrates. This represented a versatile, regioselective and non-hazardous (relative to standard acylating reagents) C3-acylation of *N*-unprotected indoles using nitriles.



Scheme 35. C3-Acylation of indoles

1.5.1.2 C2-Functionalisation of indoles

In recent years much work has been done on fine-tuning reaction conditions to selectively access the C2 position. A key strategy for this is to install a regiodirecting group on the indole nitrogen which

coordinates weakly to the Pd-centre and directs metalation to the adjacent position (Figure 2). Effective directing groups for the C2 functionalistion of indoles include *N*-(2-pyridyl)sulfonyl,[88-89] *N*-(2-pyridyl)methyl,[90] and *N*-2-aminophenyl.[91]

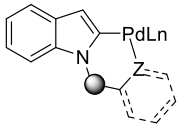
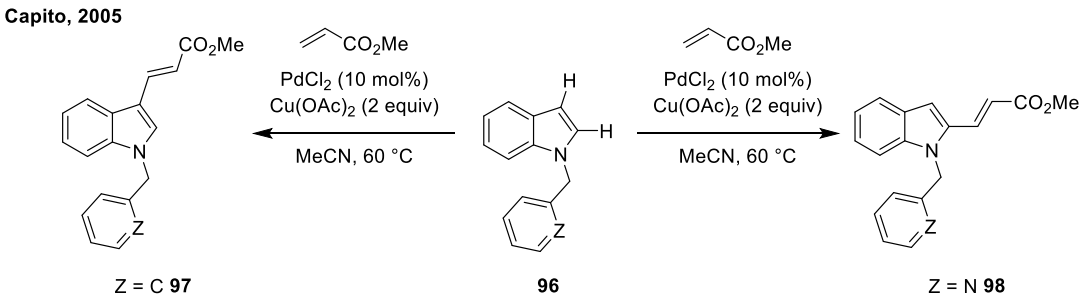


Figure 2. Directing group strategy for the C2-functionalisation of indole

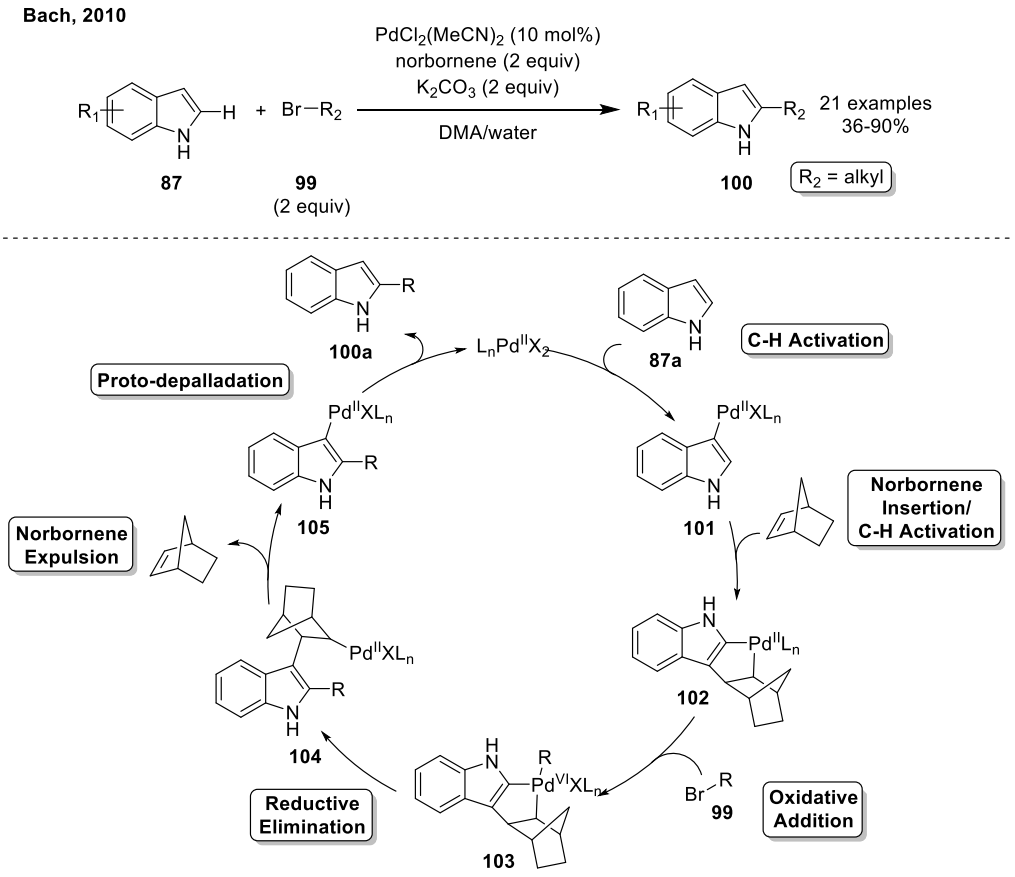
The directed Pd(II)-catalysed C2-alkenylation of indoles was exemplified by Capito.[90] It was demonstrated that when the indole nitrogen bore a benzyl-substituent the sole product was the 3-alkenylated indole **97**. The regioselectivity could be switched to the 2-position using a 2-pyridyl methyl substituent, giving the 2-alkenylated indole **98**. This selectivity arises because with the *N*-(2-pyridyl)methyl group present electrophilic attack of the Pd catalyst can occur reversibly at both the C3 and C2 positions, but attack at C2 results in the formation of a palladacycle due to ligation of the Pd to the directing group. This ligation increases the lifetime of the Pd-C intermediate causing subsequent reactivity to occur at this site. Lability of the cyclopalladated intermediate proved to be crucial as a catalytic turnover was only observed when the intermediate could not be isolated.



Scheme 36. *N*-substituent controlled C3 *vs* C2 selectivity for the alkenylation of indoles

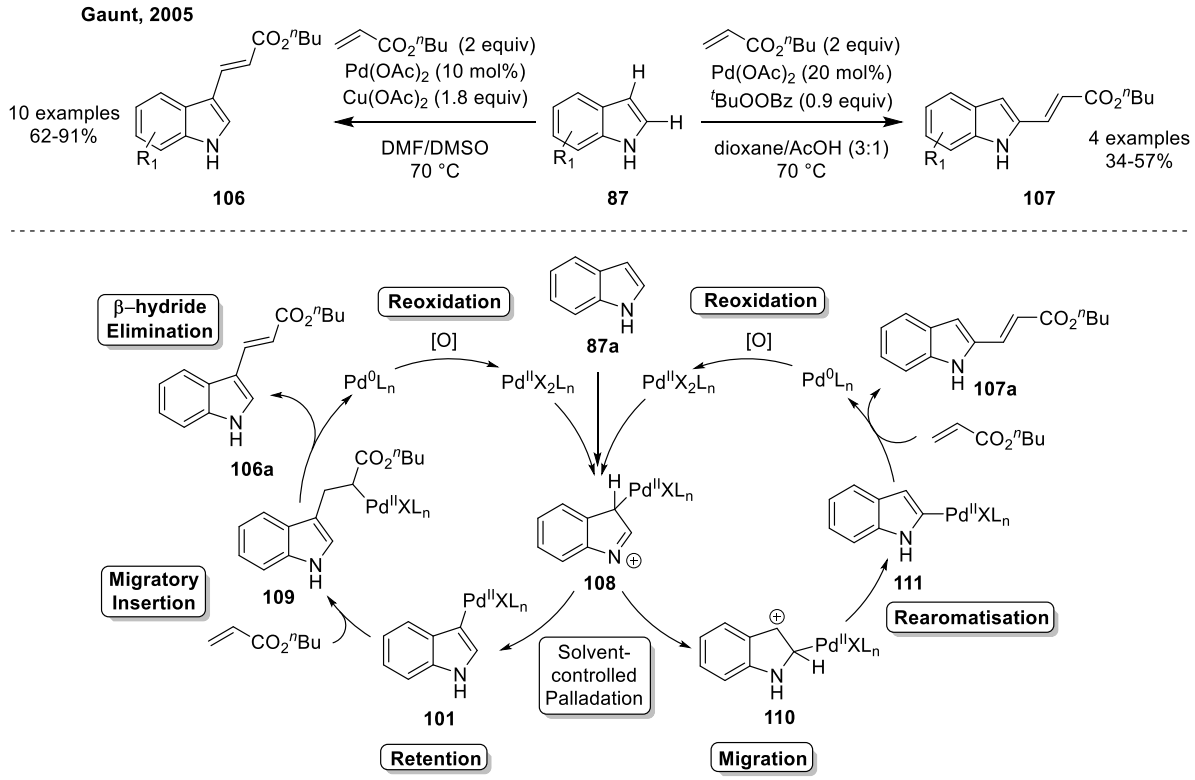
An alternative approach to the C2 functionalisation of indoles is the direct 2-alkylation of free N–H indoles **87** reported by Bach in 2010 (Scheme 37).[92] This was achieved *via* a norbornene-mediated cascade C–H activation process inspired by the norbornene-mediated alkylation of aryl halides reported by Lautens.[93] During reaction optimisation it was found that while the use of Cs_2CO_3 as a base gave the *N*-alkylated product, the use of K_2CO_3 resulted in the formation of the desired C2-alkylated product **100**. A screen of solvents revealed DMA to be the most effective, however a comparison of reagent grade DMA to freshly distilled DMA revealed that the reagent grade gave better yields. This led to studies to probe the effect of water, and it was found that the presence of a small amount of water accelerated the reaction. The scope of the reaction was assessed with a range of alkyl bromides and substituted indoles well tolerated. The reaction begins with the direct palladation of indole, which

occurs preferentially at the C3 position to give **101**. Norbornene then undergoes insertion into the Pd-indole bond which then allows a second C–H activation of the indole to occur at the 2-position, forming the indole-fused palladacycle **102**. Oxidative addition of the alkyl halide then occurs, forming Pd(IV) species **103**. This is followed by reductive elimination, norbornene expulsion, and proto-depalladation, generating the desired 2-alkylated indole species **100a**.



Scheme 37. Norborne-mediated direct C2-alkylation of indole

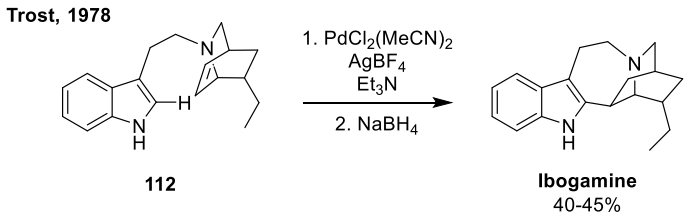
Work by Gaunt has shown that regioselective alkenylation of free N–H indoles **87** can be achieved by solvent-switching (Scheme 38).[94] It was found that the use of polar solvents resulted exclusively in C3-alkenylated indoles **106**. However, the use of AcOH as a co-solvent with dioxane lead to a complete reversal in selectivity, allowing the C2-alkenylated product **107** to be formed. Both reactions occur *via* intermediate **108**. For C3-alkenylation, rearomatisation occurs followed by a Heck-type reaction. Under these neutral conditions the acetate formed from the attack of indole on $Pd(OAc)_2$ is able to remove the C3 proton, allowing rearomatisation to occur. However, under acidic conditions, as in the C2-alkenylation reaction, this deprotonation is much slower. This enables migration of the C3–Pd bond to the more activated C2 position prior to rearomatisation. This is again followed by a Heck-type mechanism to give C2-alkenylated indoles.



Scheme 38. Solvent-controlled C3 *vs* C2 alkenylation of indoles

1.5.2 Intramolecular C–H activation of indoles

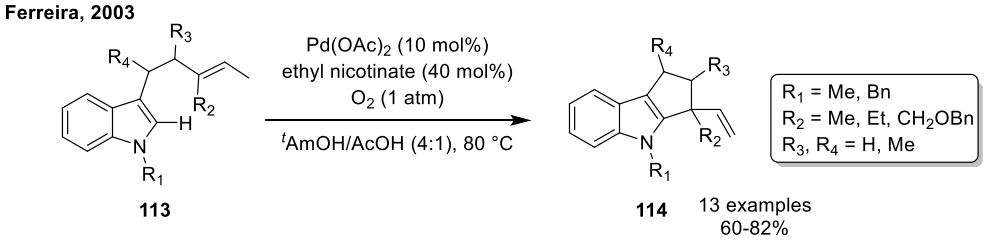
The first reported example of intramolecular C–H activation of indoles was by Trost in 1978.[95] He used stoichiometric amounts of $PdCl_2(MeCN)_2$ and $AgBF_4$ to activate the C2 position of indole **112**, followed by a $NaBH_4$ workup. This was used as the key step in the total synthesis of the alkaloid natural product ibogamine (Scheme 39). Since then a vast number of examples of intramolecular C–H activation of indoles have been reported in the literature.[96-100]



Scheme 39. Trosts's synthesis of ibogamine by the intramolecular alkenylation of indole

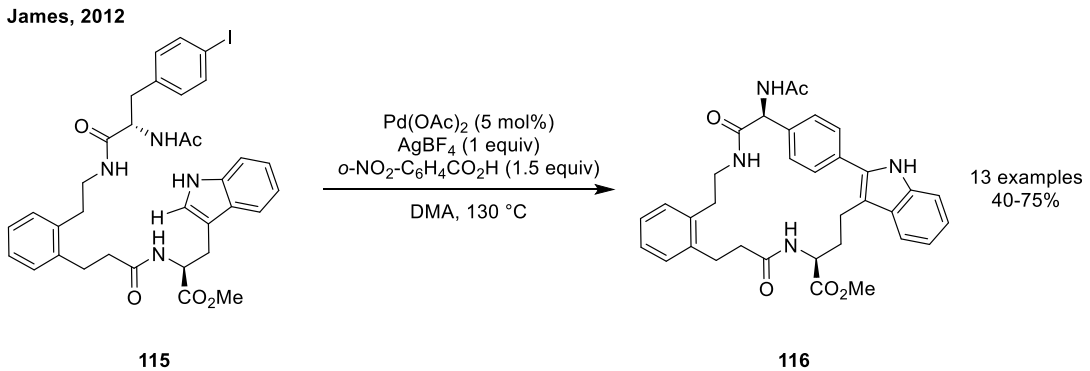
A more recent example is that by Ferriera, in which the intramolecular annulation of alkenyl indoles **113** resulted in the formation of carbocyclic 5-membered ring-fused indoles **114** (Scheme 40).[97] A correlation between the electronic properties of the pyridine ligands and their ability to facilitate cyclisation was observed. It was assumed that electron-poor ligands resulted in a more electrophilic Pd-catalyst, thus increasing its activity. However, ligands that were too electron-poor were unable to

ligate to the Pd-catalyst. A compromise between these factors was achieved by using ethyl nicotinate. It was also found that more polar solvents were more effective, most likely due to their ability to stabilise any charged intermediates. AcOH was also found to be a necessary additive. With these conditions in hand a range of substrates were cyclised, with substitutions on both the nitrogen and on the tethered alkene tolerated.



Scheme 40. Intramolecular C–H activation of indoles

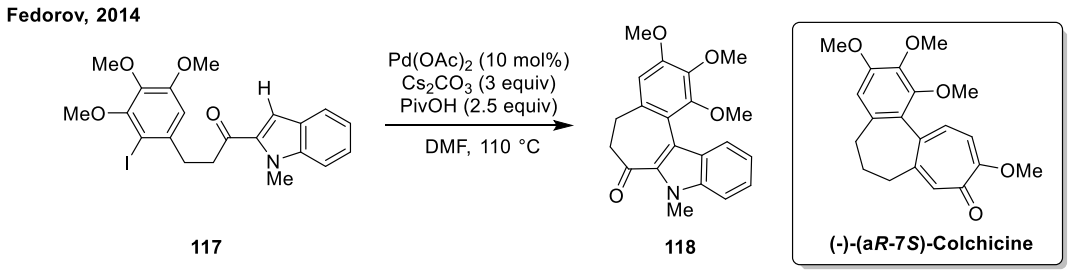
Macrocyclisation is traditionally achieved using ring closing olefin metathesis,[101] amide coupling[102] or copper-catalysed azide alkyne 'click' reactions.[103] The intramolecular Pd(II)-catalysed arylation of indoles has been shown to be an additional tool for macrocyclisation.[98] This was achieved by the cross-coupling of tryptophan and phenylanaline derivatives **115** to yield products such as **116**. The reaction was carried out using a $Pd(OAc)_2$ catalyst with a silver(I) additive. An acid additive was found to be beneficial to the reaction, and *ortho*-$NO_2C_6H_4COOH$ was found to be the most effective compared to the weak acids PivOH and *para*-$NO_2C_6H_4COOH$. The best solvent was DMA, and under these conditions a 90% yield by UV absorption from LC/MS was observed. This Pd(II)-catalysed macrocyclisation was applied to a range of substrates to form 15- to 25-membered peptidic rings. Both *meta*- and *para*-iodo-substituted phenylalanine derivatives were tolerated, but no macrocyclisation occurred using *ortho*-iodophenylalanine, likely due to the increased steric hinderance.



Scheme 41. Intramolecular arylation of indoles for macrocyclisation

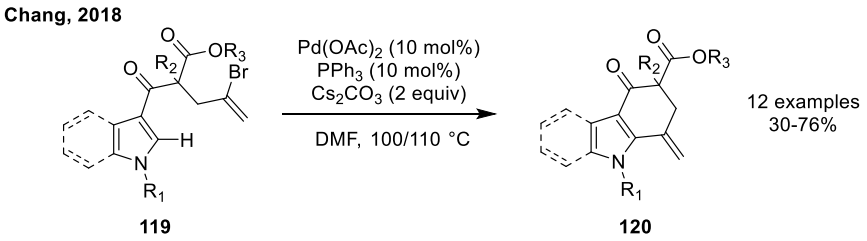
Intramolecular Pd(II)-catalysed C–H activation has also been used as they key step in the synthesis of a library of novel tetracyclic compounds, which are the lead structures in the design of new

antimitotics (Scheme 42).[99] Colchicine is a tubulin polymerisation inhibitor used in the treatment of acute gout and familial Mediterranean fever. It also has potential as an anticancer agent, but this is limited due to its high toxicity. The generation of analogues is therefore a key area of interest. A number of tubulin polymerisation inhibitors have been reported that contain indole as the key pharmacophore.[104] Such structures may be accessed by the intramolecular Pd(II)-catalysed arylation of specific indolyl ketones **117**. Importantly this cross-coupling reaction gives rise to the seven-membered ring seen in colchicine.



Scheme 42. Intramolecular arylation of indoles for drug design

A recent example of intramolecular Pd(II)-catalysed C–H activation of indoles is the synthesis of tetrahydroindolones and tetrahydrocarbazolones **120** (Scheme 43).[100] With $Pd(OAc)_2$ selected as the best catalyst, a variety of bases were trialled. Organic and strong inorganic bases were detrimental to the reaction yield, so the weak inorganic base Cs_2CO_3 was chosen. Using a catalyst loading of 5 mol% the reaction did not go to completion, however increasing the loading led to unproductive side reactions. The addition of PPh_3 overcame this issue, increasing the yield when using a 5 mol% catalyst loading. These conditions proved to be general for both indole and pyrrole substrates, although a higher temperature was required for indole substrates. It was feared that an absence of the R_2 substituent would lead to the formation of an undesired furan derivative, but pleasingly the desired product was isolated in a 30% yield.



Scheme 43. Intramolecular alkenylation of indoles towards the synthesis of tetrahydroindolones and tetrahydrocarbazolones

1.6 C–H Activation of pyrroles

Pyrrole is also a privileged heterocycle found in a number of drug molecules and natural products.[105] The synthesis of substituted pyrroles is therefore a key aim within medicinal chemistry. As with indoles, there are several key strategies towards the synthesis of substituted pyrroles: *de novo* synthesis of the pyrrole core *via* methods such as the Paal Knorr,[106] Hantzsch[107] and Van Leusen pyrrole synthesis,[108] halogenation followed by Pd(0)-catalysed cross coupling, or direct C–H activation. The instability of halopyrroles means that the development of effective direct C–H activation reactions is vital. However, the transition metal catalysed functionalisation of pyrroles poses a bigger challenge than that of indoles, as pyrroles are much less stable under acidic and oxidative conditions. Despite this there are a plethora of examples reported in the literature.[109-111]

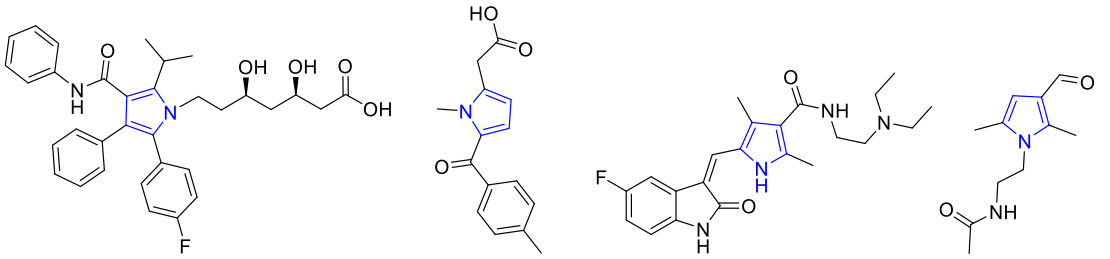
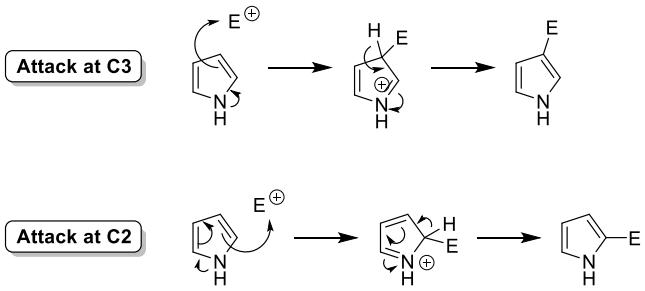


Figure 3. Important pyrrole-containing molecules

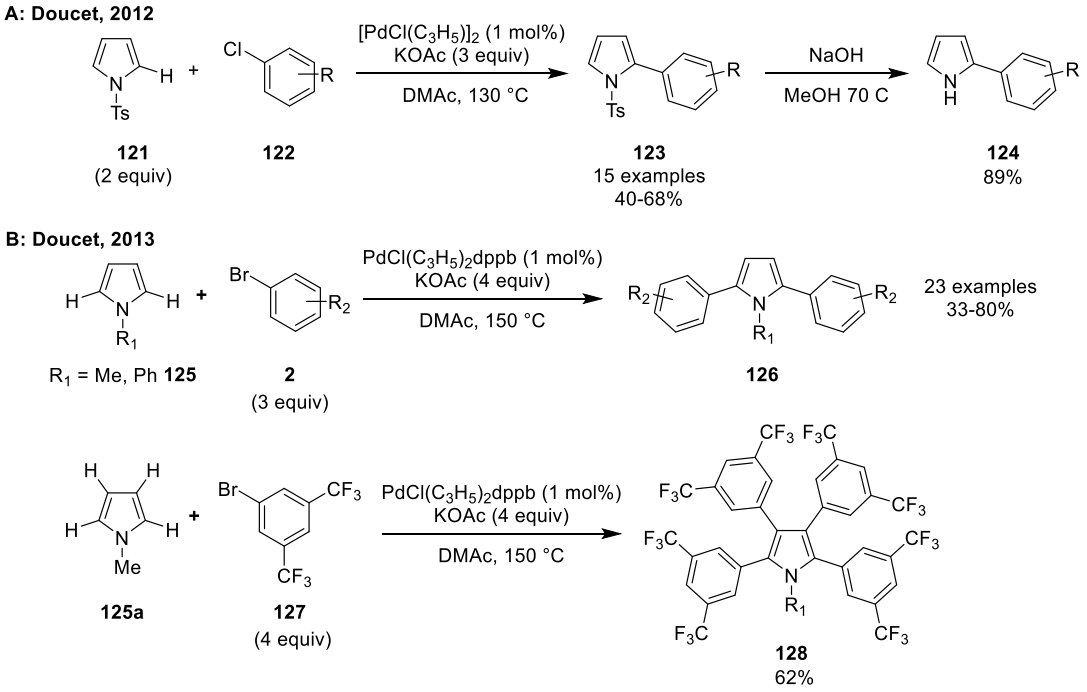
1.6.1.1 C2-Functionalisation of pyrroles

In contrast with indoles, pyrroles are most reactive towards electrophiles at the 2- and 5- positions. Electrophilic attack can easily occur at any position, but reaction at the 2- or 5- positions is slightly more favourable. One justification for this can be understood by looking at the intermediates formed by electrophilic attack. When attack occurs at C2 the intermediate formed has a linear conjugated system whereas attack at C3 gives a 'cross-conjugated' system. The linear conjugated system is slightly more favourable, thus making the C2 position more reactive.



Scheme 44. Nucleophilic reactivity of pyrroles

It is known that *N*-alkyl and *N*-aryl pyrrole substrates are effective substrates for C–H activation.[112] However, the formation of products with a free N–H is desirable as it would allow for subsequent functionalisation at this position. This has been investigated by Doucet, who compared the reactivity of *N*–H pyrrole with *N*-tosyl pyrrole in C2-arylation reactions with aryl chlorides.[113] The *N*-tosyl pyrrole is an attractive substrate as the tosyl can be easily removed following transition metal-catalysed functionalisation. Reaction optimisation studies revealed the *N*-tosyl substrate to give higher yields. A competition experiment was run, in which equal amounts of *N*–H and *N*-tosyl substrates were used. It was found that the *N*–H product was formed exclusively, demonstrating that the *N*–H substrate coordinates much faster than the *N*-tosyl. However, yields were low. It is likely that it is this coordination of the N–H that is poisoning the Pd-catalyst and hindering the reaction. Ultimately the *N*-tosyl substrate **121** was chosen to investigate the scope of the reaction, which was found to be general for a wide variety of aryl- and heteroaryl chlorides **122** (Scheme 45A). Following arylation, the tosyl group could then be removed easily by hydrolysis with NaOH in MeOH to give **124**.

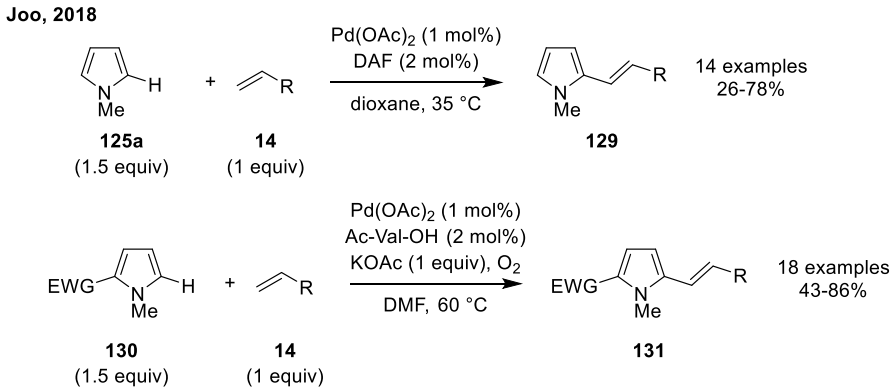


Scheme 45. C2-Arylation of pyrrole

The same group has also developed methodology for the Pd(II)-catalysed symmetric diarylation of pyrroles (Scheme 45B).[109] For this transformation a $PdCl(C_3H_5)$dppb catalyst was chosen over $Pd(OAc)_2$ as it formed Pd black less rapidly under the reaction conditions, and therefore gave increased yields. A broad substrate scope was observed for the 2,5-diarylation of *N*-methylpyrrole using *para*-substituted bromobenzenes, but *meta*-substituted aryl bromides were less tolerated. *N*-Phenylpyrrole was also tolerated, albeit with lower yields. An interesting result was observed when the strongly

electron-deficient 3,5-bis(trifluoromethyl)bromobenzene **125a** was employed: a mixture of di-, tri- and tetra-substituted products was formed. When the amount of this aryl bromide was increased to 4 equiv. the tetra-substituted product **128** was formed as the major product in a yield of 62%. This represented a novel strategy for the preparation of tetra-arylated pyrroles.

The Pd(II)-catalysed C2 alkenylation of pyrroles has also been investigated. Work by Joo describes the importance of electronically tailoring the catalytic system to be specific for either electron-rich or electron-poor pyrrole substrates (Scheme 46).[114] It was hypothesised that an electrophilic catalyst would be suitable for electron-rich pyrroles, whereas catalyst bearing basic ligands would be more suited to electron-poor pyrroles with acidic C–H bonds. Indeed, the alkenylation of *N*-methylpyrrole **125a** using $Pd(OAc)_2$ and 4,5-diazafluoren-9-one (DAF) as a ligand in dioxane gave the alkenylated product **129** in a yield of 80%, but under the same conditions the electron-poor substrate 2-acetyl-1-methylpyrrole **130** only resulted in a 19% yield of **131**. In contrast, the use of a mono-protected amino acid (MPAA) instead of DAF and the addition of KOAc in DMF gave **131** in a yield of 85% but **129** in only 14%. The addition of MPAA's to the DAF system did not improve the yield of **129**, highlighting the importance of electronic matching of the heterocycle and the catalytic system. Both systems tolerated a range of olefins, and the basic catalyst system was general for pyrroles bearing a range of electron-withdrawing groups.

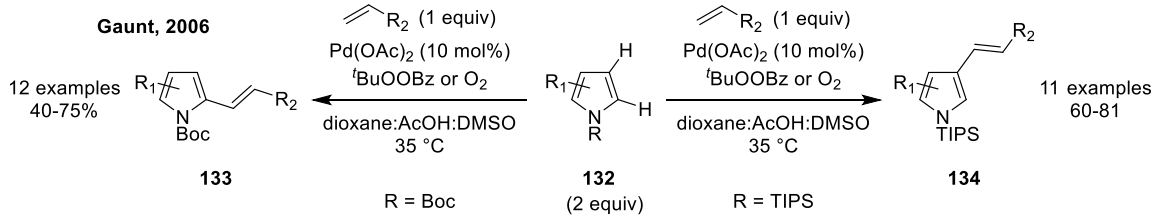


Scheme 46. C2-Alkenylation of pyrroles

1.6.1.2 C3-Functionalisation of pyrroles

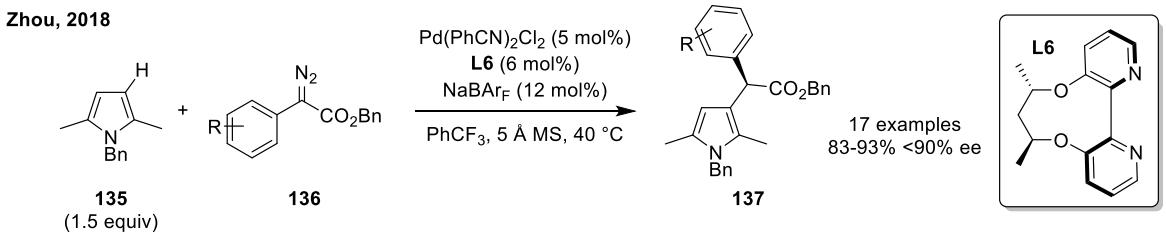
Gaunt has reported reaction conditions under which either C2 or C3 alkenylation can be achieved simply by the selection of a sterically or electronically tuned *N*-pyrrole protecting group (Scheme 47).[110] Initial work focused on achieving this selectivity *via* the choice of solvent as had been achieved with indoles (cf. Scheme 38, page 35). However, the increased reactivity of pyrroles meant that reactions proceeded with low selectivity and were prone to over alkenylation and polymerisation. This reactivity was harnessed and allowed for alkenylation to be carried out under much milder conditions. Using $Pd(OAc)_2$, in a dioxane/AcOH/DMSO solvent system with a ^{t}BuOOBz oxidant at only 35 °C,

alkenylation of *N*-benzylpyrrole was achieved, but with a disappointing 2:1 ratio of C2:C3. To enhance the natural reactivity of the pyrrole substrate an electron-withdrawing group was installed on the nitrogen to reduce reactivity and increase selectivity. Indeed, this allowed the selective alkenylation at the C2 position. In contrast, the use of a bulky TIPS group on the nitrogen gave selectively the C3-alkenylation product. Later it was found that the ^{t}BuOOBz oxidant could be replaced with the more environmentally friendly O_2 with little effect on the yield.



Scheme 47. *N*-Substituent controlled C2 *vs* C3 alkenylation of pyrroles

Stereoselective control during the C–H activation of pyrroles is a challenge due to the relatively small size of pyrrole resulting in weak steric interactions between it and the chiral catalyst and ligands. The Pd(II)-catalysed asymmetric C–H functionalisation of pyrroles using α-aryl-α-diazoacetates **136** has been reported (Scheme 48).[111] This was achieved using the bipy-derived chiral ligand **L6**. The effect of the structure of the pyrrole substrate on the enantioselectivity was investigated. It was found that increasing the steric bulk of the C2- and C5- substituents decreased the ee, as did switching the benzyl *N*-protecting group to 4-methoxyphenyl. Because of this, 1-benzyl-2,5-dimethyl-1*H*-pyrrole **135** was used as the substrate for all subsequent reactions, but the reaction was tolerant to a wide range of diazosubstrates.



Scheme 48. Asymmetric C3 functionalisation of pyrroles

1.7 C–H Activation of anilide derivatives

Anilides are an important class of compounds as they serve as ubiquitous structural motifs in a wide range of natural products, pharmaceuticals, agrochemicals and dyes. The development of efficient routes towards functionalised anilide derivatives is therefore crucial and the C–H functionalisation of aromatic compounds is a key goal in industry.[115] There are a plethora of Pd(II)-catalysed C–H activation reactions of such compounds currently in the literature.[116-118] Anilides are particularly useful

substrates for transition metal catalysed C–H activation reactions as the amide moiety can serve as a directing group, allowing for selective *ortho*-functionalisation.

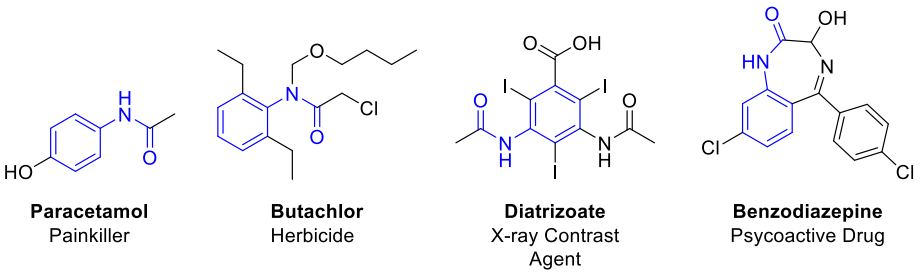
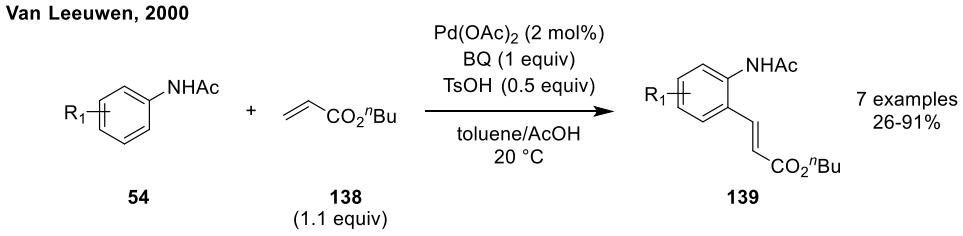


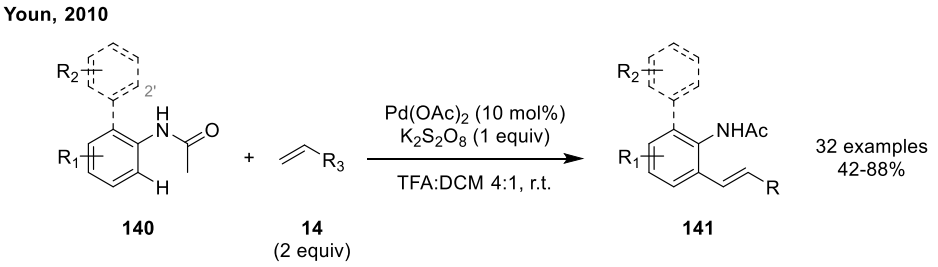
Figure 4. Important anilide-containing molecules

An early example of the Pd(II)-catalysed C–H functionalisation of anilides was reported by Van Leeuwen (Scheme 49).[117] This reaction enabled the coupling of acetanilide **54** with butyl acrylate **138** using cheap oxidants under mild conditions. Interestingly, the yields of **139** obtained were found to higher when the reaction was carried out at 20 °C compared with at 80 °C. It was also found that the addition of TsOH was beneficial, although use of more than 0.5 equiv. promoted undesired side reactions. The transformation displayed excellent *ortho*-selectivity, with no observation of *meta*- or *para*-substitution, nor any products derived from the activation of the amide N–H bond, demonstrating the importance of the amide directing group. A range of substituted acetanilides were tolerated although *ortho*-substitution was found to hamper the yields. When a methyl group was added to the amide nitrogen no product was formed under the standard reaction conditions.



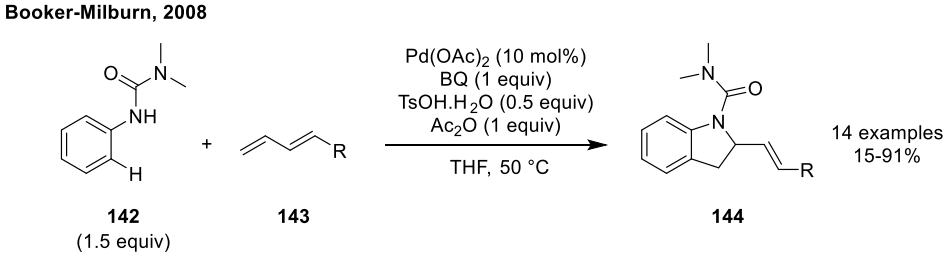
Scheme 49. Alkenylation of acetanilides

As previously noted, the C–H functionalisation of *ortho*-substituted anilides proves more of a challenge due to steric effects. A serendipitous result from work by Youn resulted in the *ortho*-alkenylation of *ortho*-phenyl-substituted acetanilides **140**.[118] This reactivity was as a result of the unique combination of the TFA:DCM (4:1) solvent system, the high concentration and the use of $K_2S_2O_8$ as the oxidant. Under these conditions a variety of 2-alkenyl-6-phenyl acetanilides **141** were formed. The only functionality not tolerated was strongly electron-withdrawing groups which required elevated heating and then reacted at the 2' position. The reaction conditions were also suitable for the alkenylation of simple acetanilides.



Scheme 50. Alkenylation of *ortho*-substituted acetanilides

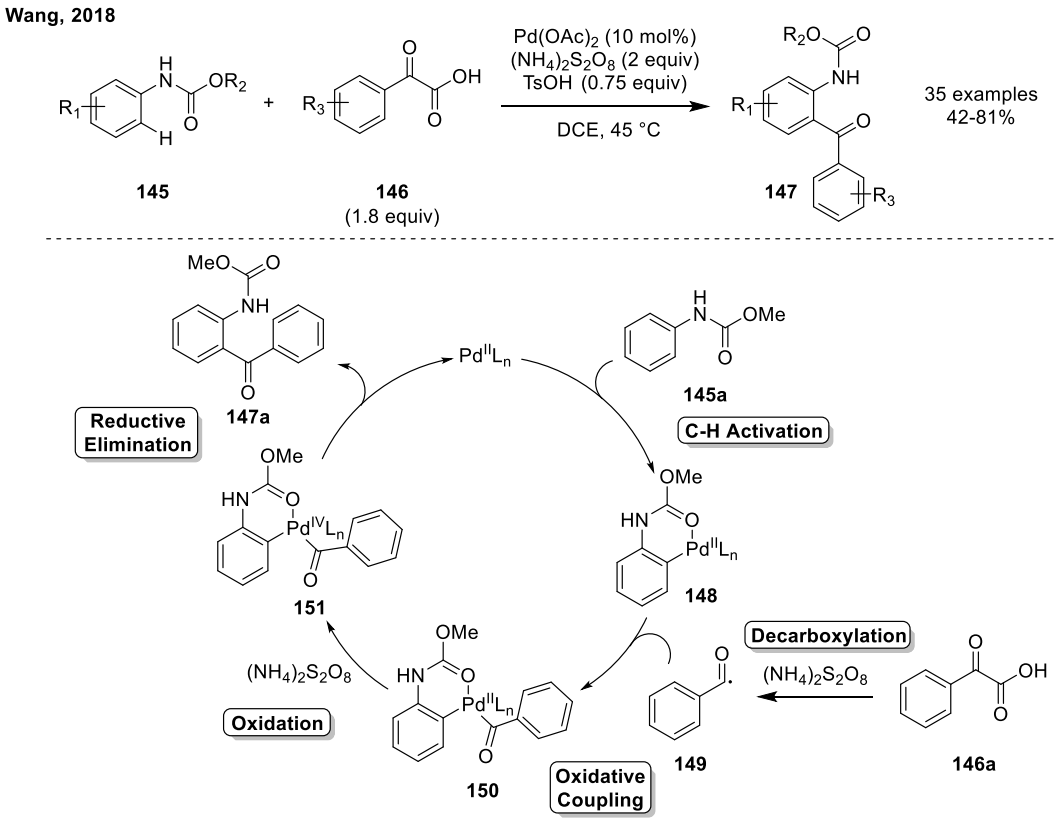
A urea moiety has also been shown to be an effective directing group in the Pd(II)-catalysed *ortho*-functionalisation of anilide-derivatives. Booker-Milburn and co-workers have reported the urea-directed C–H activation of anilides as part of a C–H insertion/carbopalladation cyclisation sequence (Scheme 51).[119] In this reaction the use of a diene results in the generation of a π-allyl intermediate which can then be trapped by the urea nitrogen to generate an indoline. The initial C–H insertion and oxidative Heck step is analogous to the reaction reported by Van Leeuwen[117] which required acidic reaction conditions and a TsOH additive. It was possible the urea or diene may have been sensitive to these acidic conditions so in an attempt to improve initial yields the reaction was carried out in the absence of acid. Interestingly, the absence of AcOH had no significant effect on the yield but the absence of TsOH resulted in no reaction. This suggested that TsOH was vital for the reaction to occur and was likely forming an active Pd tosylate species *in situ*. Another observation was the detrimental effect of water, so Ac_2O was added as a drying agent. The reaction conditions proved general for electron-deficient olefins and electron-donating phenyl substituents. *ortho*-Methyl substitution was not tolerated. It was thought that this was because it was preventing the urea from adopting the necessary conformation for Pd-complexation or C–H insertion.



Scheme 51. Urea-directed C–H functionalisation of anilides for the generation of indolines

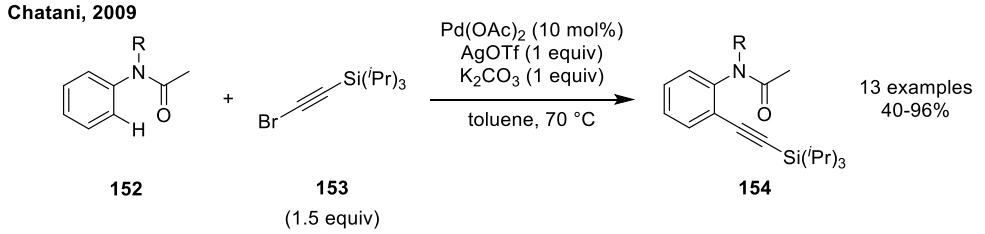
The directing group ability of aniline carbamates is an area less explored. A recent publication describes the use of aniline carbamates as directing groups for the *ortho*-acylation of anilides **145** with α-oxocarboxylic acids **146** (Scheme 52).[120] $Pd(OAc)_2$ was employed as the catalyst and ammonium persulfate as the oxidant. Once again, the use of a TsOH additive was necessary for an efficient reaction. A broad substrate scope was observed with respect to both coupling partners. Ammonium persulfate is also known to be a radical initiator, so a radical trapping experiment was carried out to

probe the reaction mechanism. Indeed, it was discovered that a free radical process is involved in the reaction mechanism. It was proposed that the reaction begins with *ortho*-palladation, resulting in the formation of the 6-membered palladacycle **148**. **148** then undergoes oxidative coupling with acyl radical **149** which is formed by decarboxylation of oxocarboxylic acid **146a** in the presence of ammonium persulfate. **150** is then oxidised to Pd(IV) and the product **147a** is then expelled by reductive elimination, which also regenerates the Pd(II) catalyst.



Scheme 52. *ortho*-Acylation of aniline carbamates

All examples described above contain an anilide N–H bond, which is true for the majority of examples found in the literature.[121] However there are also examples of Pd(II)-catalysed *ortho*-functionalisation of tertiary anilides **152**. An examples of this is the alkynylation reaction developed by Chatani (Scheme 53).[122] Silver salts were needed in order to increase the electrophilicity of the Pd species to allow it to react with the anilide substrates. The alkyne substituent **153** was found to have a significant effect on the outcome of the reaction. When the triisopropyl group was replaced with a TBS group the yield decreased by almost half, and groups such as phenyl, hexyl and ester groups shut down the reaction completely. The reaction conditions were general for anilides bearing both electron-donating and -withdrawing substituents, although electron-poor substrates gave slightly poorer yields.



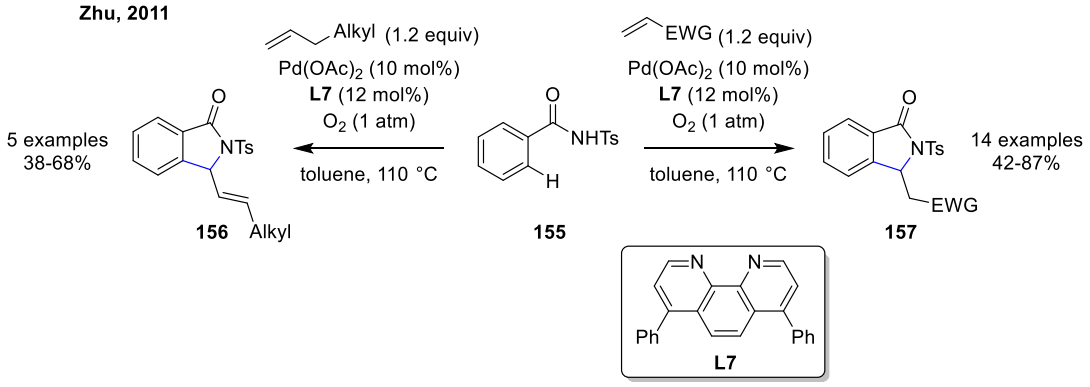
Scheme 53. *ortho*-Functionalisation of tertiary anilides

1.8 Cascade reactions

A cascade reaction is defined as a chemical process in which at least two reactions occur consecutively with each subsequent reaction occurring as a result of the functionality formed in the previous reaction. In such processes no intermediates are isolated and the reaction conditions do not change during the course of the reaction.[123] This differs from one-pot reactions, which involve at least two consecutive chemical reactions but additional reagents may be added following each step. Cascade reactions are powerful tools which can be used to rapidly generate complex, often polycyclic, molecules from relatively simple starting materials. Other advantages include high atom economy, shorter synthesis times and the generation of much less waste. A number of Pd(II)-catalysed cascade reactions are discussed below, with examples chosen to demonstrate the complexity which can be achieved. The following examples focus on cascade reactions beginning with a Heck-type reaction, as this is what the work in this project involves. The development of Pd(II)-catalysed cascade methodology within the KBM group is also discussed.

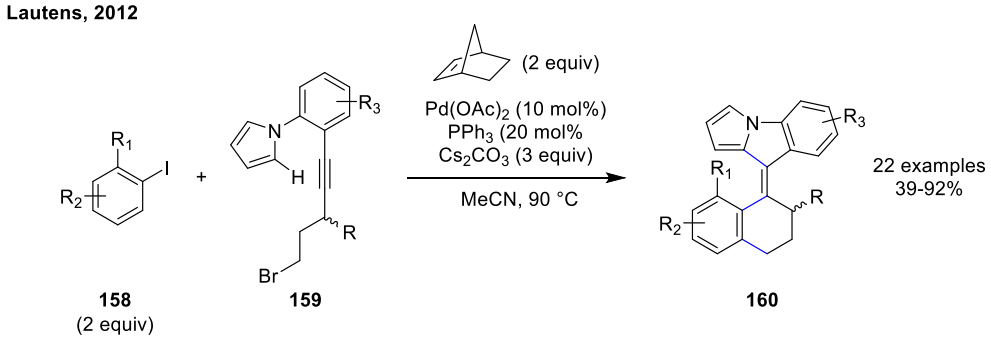
Work by Zhu exemplifies the advantages of using an *N*-acyl sulfonamide as a directing group in the tandem olefination/annulation reaction of *N*-tosylbenzamides **155** with olefins to form isoindolines **156** or **157** (Scheme 54).[124] This reaction was found to be compatible with both aliphatic and activated alkenes, with the product formed being dictated by the electronic properties of the alkene. Non-conjugated alkenes undergo an aza-Wacker type ring annulation followed by β-hydride elimination to give **156**, while electron-deficient alkenes participate in a Michael addition reaction to give **157**. A number of alternative directing groups were trialled, but only substrates bearing an *N*-acyl sulfonamide group were able to form any product. It is the acidic nature of the *N*-acyl sulfonamide N–H bond which allowed the reaction to occur and allowed the compatibility of a much wider range of alkenes than would normally be feasible. This acidity arises from the combined electron-withdrawing effect of the carbonyl and tosyl groups. The acidity of the N–H bond enables the formation of a Pd–N bond, which in turn promotes the formation of the intermediate palladacycle. The reaction was shown to be broadly compatible with a range of electron-donating and -withdrawing groups. It can be

considered an eco-friendly transformation as it can be carried out using molecular oxygen or even air as the oxidant.



Scheme 54. Tandem olefination/annulation of *N*-tosylbenzamides

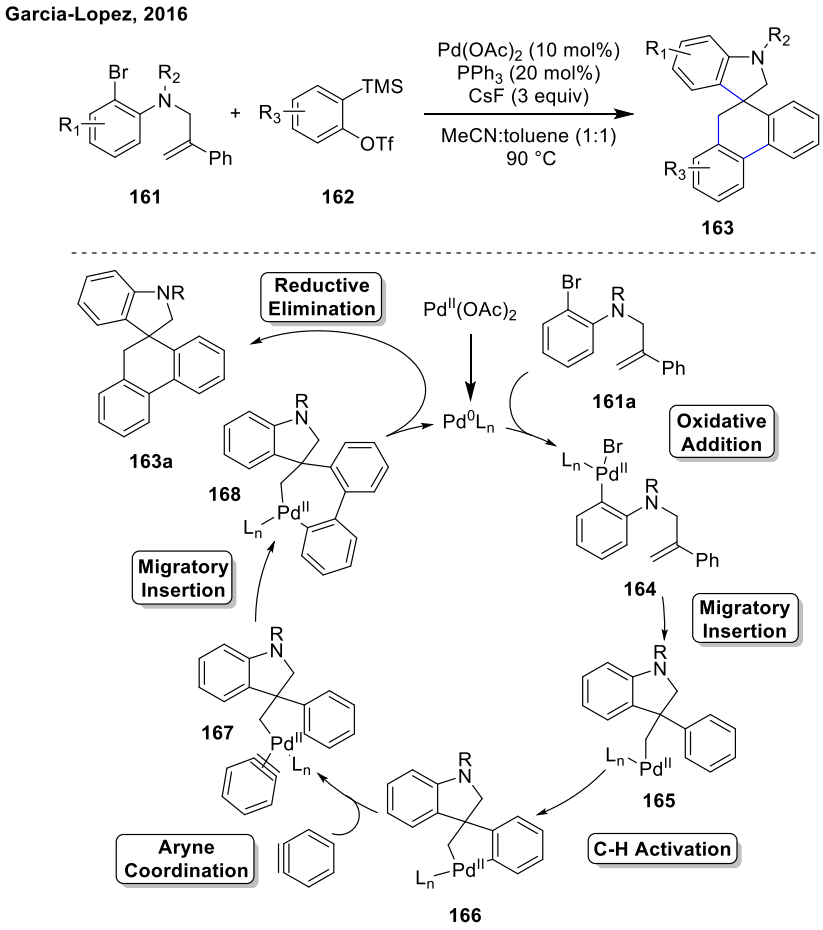
The utility of cascade reactions was later exploited in the synthesis of tetra-substituted helical alkenes **160** (Scheme 55).[125] The reaction mechanism is norbornene-mediated (cf. Scheme 37, page 34) and involves the formation of three new carbon-carbon bonds. Initial reactions gave a mixture of (*E*)- and (*Z*)-alkenes, likely due to acid-catalysed or light-induced isomerisation. In acid-free conditions in the absence of light the desired isomer was formed exclusively. The transformation was tolerant to a variety of *ortho*-substituents on the aryl iodide and substitution of the alkyne ring system. As well as the pyrrole used in the test substrate a number of other heterocycles could be used, including indole, furan and thiophene. When enantiomerically enriched substrates were employed complete retention of stereochemistry was observed, providing a route towards enantiomerically enriched helical alkenes.



Scheme 55. Cascade sequence for the synthesis of tetra-substituted helical alkenes

Another example that showcases the utility of cascade reactions in the formation of complex polycyclic molecules from relatively simple starting materials is that reported by Garcia-Lopez in 2016.[126] This reaction relies on the tapping of transient alkyl-Pd(II) species with arynes, and gives rise to complex spirocyclic structures. Benzyne is a privileged coupling partner as it contains two reactive

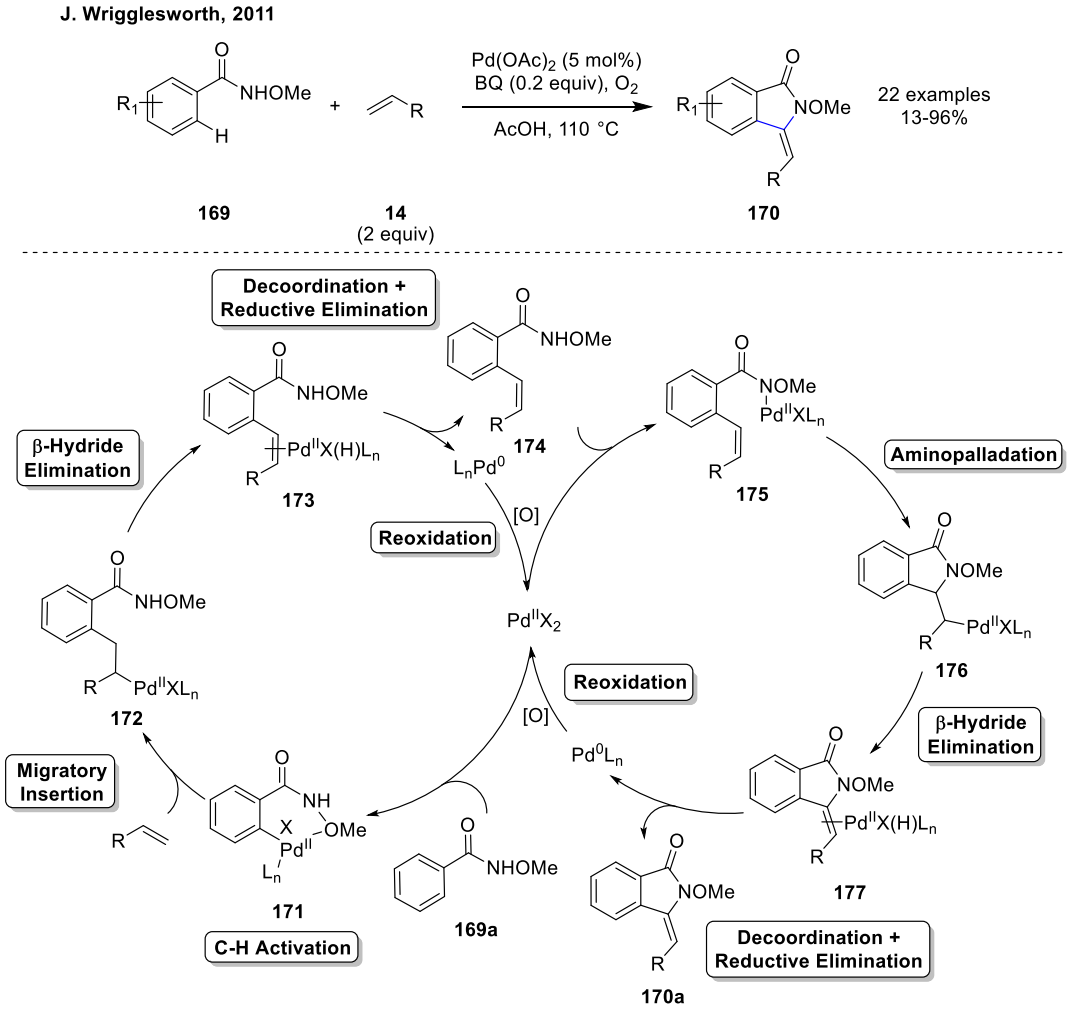
positions, allowing difunctionalisation, and it can be used to generate biaryl systems, a ubiquitous motif throughout functional material and medicinal chemistry. The best conditions for the reaction were found to be a $Pd(OAc)_2$ catalyst with PPh_3 as a ligand, CsF as a base and a 1:1 mixture of MeCN and toluene as the solvent. The scope of the reaction was investigated with respect to the tether, the presence of aryl substituents and the benzyne precursor and a range of interesting spirocyclic products in the form of **163** were generated. The reaction begins with an intramolecular Heck-type mechanism of the bromoaniline coupling partner to give **165**. The pendant phenyl group the undergoes C–H activation with the generated alkyl Pd(II) species to form **166**. Coordination followed by migratory insertion of the benzyne (generated *in situ*) to gives **168**. The product **163a** is formed by reductive elimination.



Scheme 56. Cascade reaction for the synthesis of spirocyclic compounds

The use of Pd(II)-catalysed C–H activation reactions as part of cascade sequences for the generation of complex polyheterocycles has long been a theme in the Booker-Milburn group.[119, 127-130] In the reaction of *N*-alkoxybenzamide **169** with butyl acrylate, instead of the expected Fujiwara-Moritani product, the annulated ring system **170** was formed. Investigation into the oxidant system revealed that in the absence of O_2 at least two equiv. of BQ were necessary for the reaction to proceed

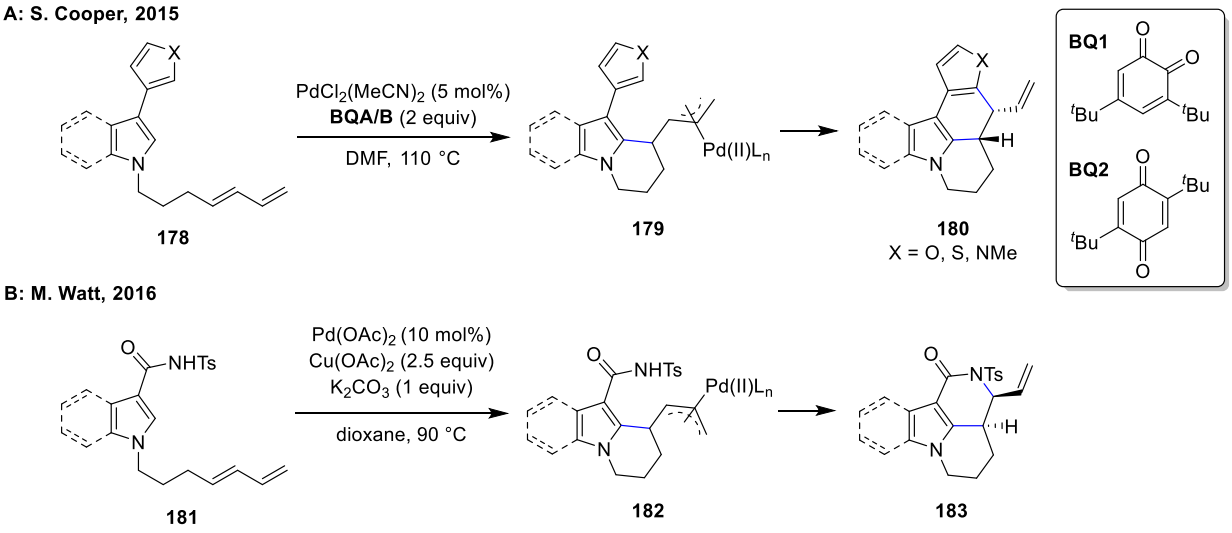
effectively, suggesting that there are two Pd(II) turnovers per reaction. The scope of the reaction was assessed, and a variety of olefins **14** were tolerated, with electron-deficient olefins performing the best. A range of substituted *N*-alkoxybenzamides **169** were also tolerated, although in two cases the saturated products were formed, a result of a Michael addition rather than the desired Pd(II)-catalysed transformation. The reaction displayed complete (*E*)-selectivity, and complete regioselectivity in the case of *meta*-substituted *N*-alkoxybenzamides. *ortho*-Substitution and the use of alternative alkoxy groups were not tolerated. The first catalytic cycle for this transformation is a standard Fujiwara-Moritani mechanism that forms intermediate **174**. **174** then undergoes a second Pd(II)-catalysed transformation, an aza-Wacker reaction. Following coordination of the Pd(II) catalyst to the *N*-alkoxy directing group, aminopalladation occurs to give intermediate **176**. The product is formed by β-hydride elimination.



Scheme 57. Fujiwara-Moritani/ aza-Wacker cascade sequence of *N*-alkoxybenzamides

The Booker-Milburn group has also used the C–H activation of heterocycles as part of cascade sequences. Starting from an indole or pyrrole core, an *N*-tethered diene could be used to generate a

π-allyl intermediate **179** which could then be trapped by a variety of internal heterocyclic nucleophiles to give complex polyheterocyclic products in the form of **180** (Scheme 58A).[127] It was found that the use of bulky quinone oxidants was necessary in order to prevent conjugate addition of the heterocyclic nucleophile to benzoquinone. DMF as a solvent and high temperatures were also found to be crucial for a successful reaction. This methodology was extended further by switching the internal heterocyclic nucleophile to an internal heteroatomic nucleophile, *N*-acyl tosylamide, which resulted in the formation of products in the form of **183** (Scheme 58B).[128] For this reaction $Cu(OAc)_2$ was needed as the oxidant and dioxane was used as the solvent. Both reactions are thought to proceed *via* a similar mechanism: C–H activation at the C2 position of the heterocyclic core, migratory insertion of the diene to generate the π-allyl intermediate, then trapping by the internal nucleophile to generate structures such as **180** and **183**.

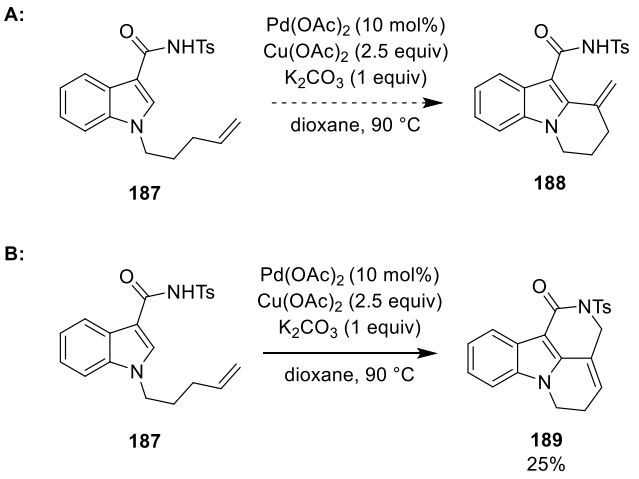


Scheme 58. Oxidative Heck/ π-allyl trapping cascade sequences

2. Results and discussion

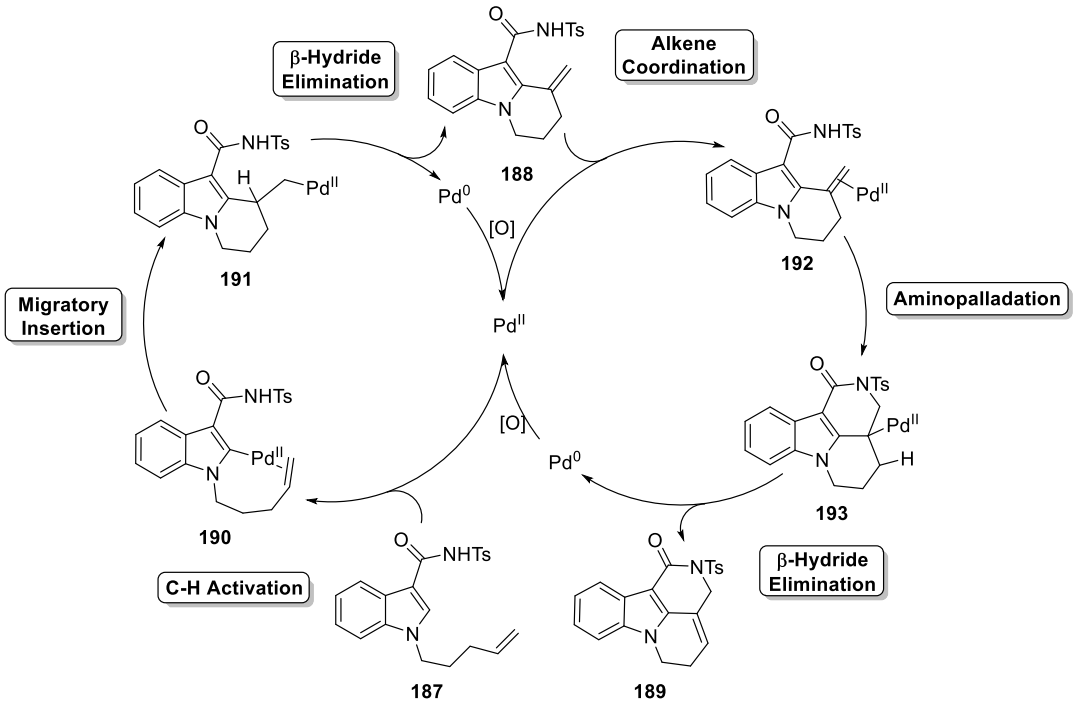
2.1 Aims

As discussed above, the Booker-Milburn group has developed a number examples of Pd(II)-catalysed cascade sequences for the synthesis of complex polyheterocycles (cf. Scheme 58, page 49). In the work using indole substrates bearing an *N*-acyl tosylamide nucleophile an unexpected result was observed when the tethered diene was replaced by a tethered alkene.[131] Without the second alkene of the diene a reactive π-allyl intermediate cannot be formed so it was thought that the reaction would stop after the oxidative-Heck step to give the oxidative-Heck product **188** (Scheme 59A). This would have been consistent with previous findings within the group.[132] However, when **187** was exposed to the standard reaction conditions, **188** was not formed. Instead, the only product observed was the fully cyclised product **189** in a yield of 25% (Scheme 59B).



Scheme 59. Expected and actual outcome of the cyclisation of alkene-tethered substrate **187**

It is thought that **189** was formed by an oxidative Heck reaction followed by an aza-Wacker reaction. The aza-Wacker reaction was able to occur due to the presence of the N–H bond of the *N*-acyl tosylamide and the *exo* alkene of the oxidative Heck product **188**. **188** begins this second catalytic cycle by coordination of the alkene to the Pd(II) catalyst. The coordinated species **192** then undergoes aminopalladation to give **193**, which then undergoes β-hydride elimination to give the fully cyclised oxidative Heck/aza-Wacker product **189**.



Scheme 60. Proposed mechanism for the formation of **189** (ligands omitted for clarity)

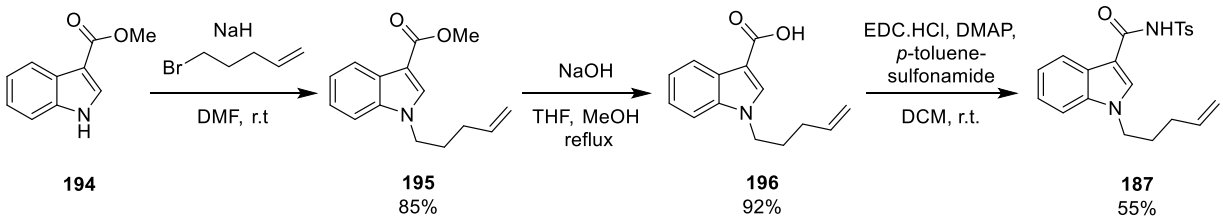
Initial optimisation studies carried out in the group saw the yield of this reaction increase from 25% to 49%.[133] The aim of the project described in this thesis was to explore this reaction further with a view to applying it to a range of distinct substrates. Reaction optimisation, substrate scope for indole and pyrrole systems and mechanistic studies are discussed. Attempts at expanding the methodology further for natural product synthesis is then explored, along with the synthesis of additional novel polyheterocyclic structures.

2.2 Reaction optimisation

The initial aim of the project was to optimise the reaction in order to increase the moderate yield of 49%.

2.2.1 Initial optimisation studies

The alkene-tethered indole substrate bearing an *N*-acyl tosylamide directing group could be easily synthesised in three steps from inexpensive, commercially available starting materials. Alkylation of indole **194** using NaH and 5-bromo-1-pentene in DMF gave the alkylated indole **195** in a yield of 85%. The methyl ester was then hydrolysed using NaOH in THF and MeOH to afford the free acid **196** in a yield of 92%. **196** was coupled with *p*-toluenesulfonamide in an amide coupling reaction using EDC.HCl to give the desired substrate **187** in a yield of 55%. (Scheme 61).



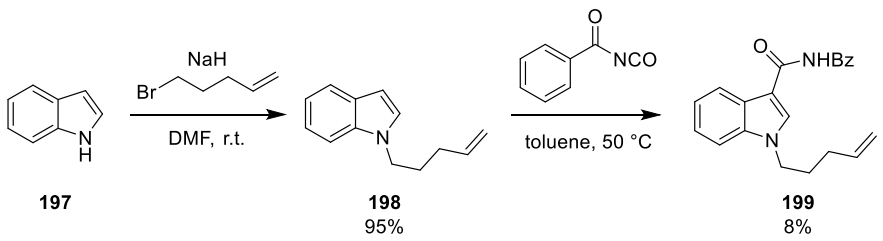
Scheme 61. Synthesis of substrate **187**

The optimum reported conditions for the diene tethered substrate (cf. Scheme 58B, page 49) were 10 mol% $Pd(OAc)_2$, 2.5 equiv. $Cu(OAc)_2$ and 1 equiv. K_2CO_3 in dioxane.[128] These conditions gave a 25% yield of **189** when applied to the alkene tethered indole **187** (Scheme 59). However, following initial optimisation studies, it was found that changing the conditions to 10 mol% $Pd(TFA)_2$, 2.5 equiv. $Cu(OAc)_2$, and 2.5 equiv. K_2CO_3 increased the yield of **189** to 49%.[133]

Throughout this work Quantitative ^{1}H NMR analysis was carried out following filtration of the crude reaction mixture over celite (to remove any copper species) and evaporation of the dioxane. The crude material was dissolved in $CDCl_3$ and a known amount of 1,4-dimethoxybenzene was added as an internal standard. ^{1}H NMR yields were calculated by comparing peak integration to that of the internal standard.

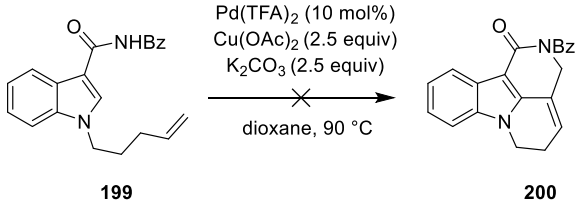
The previously optimised conditions were repeated, and gave a ^{1}H NMR yield of 20%, and an isolated yield of 49% after purification by flash column chromatography. This disparity between the ^{1}H NMR yield and the isolated yield was due to the insolubility of **189** in $CDCl_3$. **189** was also found to be highly insoluble in all other common laboratory solvents, so it was also unclear whether the isolated yields were accurate, as undissolved material could have been lost during filtration or column chromatography. Therefore, to begin the reaction optimisation process, the use of alternative directing groups was explored. It was hoped that replacing the *N*-acyl tosylamide with a group with similar electronic properties would allow the reaction to proceed with a similar yield but would improve product solubility.

The first directing group investigated was an *N*-benzoyl amide. To synthesise substrate **199**, indole was initially alkylated using NaH and 5-bromo-1-pentene in DMF to give **198** in an excellent yield of 95%. **198** was then reacted with benzoyl isocyanate to give the desired substrate **199** (Scheme 62). The reaction with benzoyl isocyanate proceeded in a poor yield of only 8%, however this generated enough material to trial the cyclisation reaction.



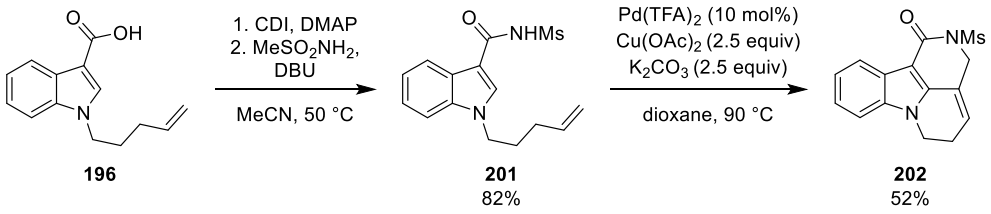
Scheme 62. Synthesis of *N*-benzoyl amide substrate **199**

The cyclisation reaction was carried out on **199** using the previously optimised conditions (Scheme 63). Unfortunately, no formation of the desired product **200** was observed. Only unreacted starting material was visible by TLC and ^{1}H NMR of the crude material, and on purification by flash column chromatography 57% of the unreacted starting material was recovered.



Scheme 63. Cyclisation of *N*-benzoyl amide substrate **199**

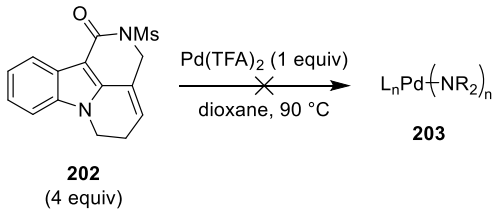
Another directing group investigated was an *N*-acyl mesylamide. This was a more promising directing group as it was expected to have more similar electronic properties to the *N*-acyl tosylamide. The *N*-acyl mesylamide substrate **201** was synthesised in an analogous fashion to the *N*-acyl tosylamide substrate **187**. The *N*-acyl mesylamide group was installed by an amide coupling reaction of acid **196** with methanesulfonamide using CDI, DMAP and DBU, giving **201** in a yield of 82%. Substrate **201** was subjected to the previously optimised cyclisation conditions and the desired cyclisation product **202** was obtained in a 52% isolated yield (59% yield by ^{1}H NMR) (Scheme 64). As well as this result being a slight improvement on the yields obtained using the *N*-acyl tosylamide substrate, the product was also much more soluble in $CHCl_3$. For these reasons an *N*-mesylamide directing group was used for all further studies.



Scheme 64. Synthesis and cyclisation of *N*-mesylamide substrate **201**

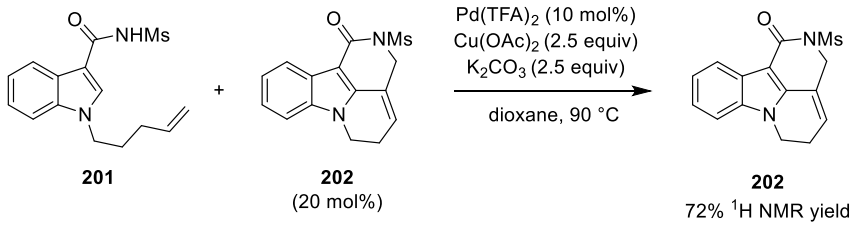
In all cyclisation reactions carried out thus far, complete mass balanced had not been observed (a 59% yield of product was observed by ^{1}H NMR of the crude reaction mixture, but the remaining 41% of the

material was unaccounted for). One explanation for this could be that the product was, as a result of containing nitrogen, acting like a ligand and coordinating to palladium. This would mean that on filtration through Celite® during the workup any palladium-coordinated product would be insoluble in organic solvent and would be lost on the Celite® pad. To investigate this, 4 equiv. of the cyclised product **202** were heated at 90 °C with 1 equiv. of the $Pd(TFA)_2$ catalyst for 16 hours in dioxane (Scheme 65). After filtration through celite® and washing with DCM and $CHCl_3$ all material was recovered. This demonstrated that the unaccounted material was not due to loss of material upon workup as a result of coordination of the product to palladium.



Scheme 65. Coordination study of cyclised product **202**

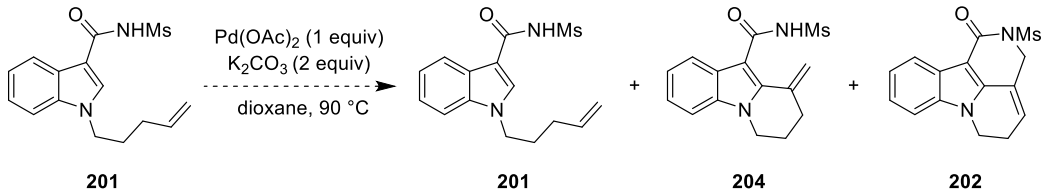
Another hypothesis for the low yield was product inhibition. It was possible that cyclised product could be ligating to the palladium catalyst during the reaction which would supress the catalyst turnover. This effect would increase with the amount of product generated. This theory was investigated by adding 20 mol% of the cyclised product **202** at the start of the reaction (Scheme 66). After 16 hours, a 72% ^{1}H NMR yield of **202** was observed (20% from the product added at the beginning plus ~50% formed during the reaction). This suggests that no significant product inhibition is in operation. This also supports the previous findings that the product does not coordinate to the catalyst.



Scheme 66. Product inhibition experiment

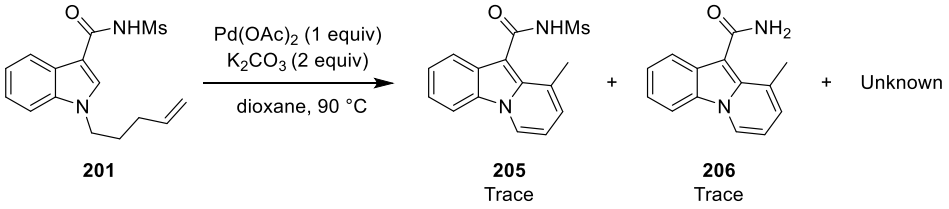
At this point, no further improvement on the yield of the reaction had been achieved. For this reason, more information on the reaction mechanism was sought. The proposed mechanism of the reaction (Scheme 60, page 51) involves two catalytic cycles, each requiring one equivalent of oxidant to re-oxidise the Pd(0) species to the active Pd(II) in order to allow the catalytic cycle to continue. A reaction was carried out using stoichiometric palladium in the absence of oxidant. It was hoped that this would give insight into the relative rates of reaction for each catalytic cycle. Using 1 equiv. of palladium it was expected that if the first cycle was significantly faster than the second the formation of

intermediate **204** would be observed, whereas if the second cycle was significantly faster 50% of the product **202** and 50% unreacted starting material **201** would be observed. It was envisaged that the ratio of these two products would shed light on the mechanism, thus allowing further optimisation to be more targeted (Scheme 67).



Scheme 67. Expected outcome of the cyclisation of **201** using stoichiometric palladium

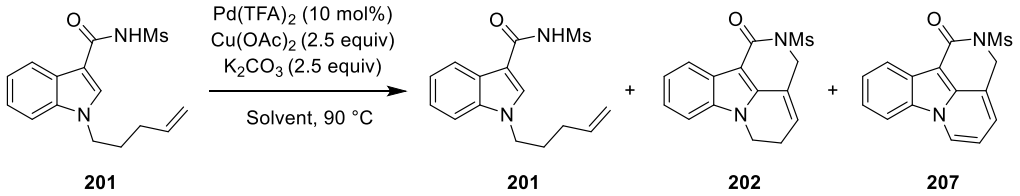
Unfortunately, on carrying out this reaction neither the fully cyclised product, nor the oxidative Heck product was observed. Instead, a complex mixture was formed, as observed by TLC analysis (6 spots observed). Analysis of the crude reaction mixture by ^{1}H NMR also showed a complex mixture of products. Flash column chromatography of the crude mixture lead to the isolation of trace amounts of the fully aromatised intermediate **205** and the fully aromatised demesylated intermediate **206** (Scheme 68). No other products were isolated in yields appreciable enough to be characterised. It is thought that most material was lost *via* a Pd(0)-catalysed decomposition pathway.



Scheme 68. Actual outcome of the cyclisation of **201** using stoichiometric palladium

A brief solvent screen was then performed (Table 1). Solvents with boiling points with over 90 °C were screened to allow the reaction to still be heated to this temperature. The results showed that the only solvent to yield a significant amount of the product **202** was dioxane (Table 1, entry 1). When toluene was used (Table 1, entry 2), no product was observed by ^{1}H NMR, nor any unreacted starting material or appreciable by-products. This suggests that all material polymerised or decomposed. Interestingly, when the more polar solvents DMSO and DMF were used (Table 1, entries 3 and 4) the unexpected by-product **207** was formed. This fully aromatised by-product suggests that the desired product was forming but continued to react further. A possible mechanism for this is Pd-insertion into an aliphatic C–H bond followed by β-hydride elimination. **207** was a particularly interesting by-product as it was bright yellow in colour, and a bright blue colour under UV. This suggests that it may have interesting electronic properties and may have used as a photosensitiser or fluorescent probe.

Table 1. Solvent screen for the cyclisation of **201**



Entry	Solvent	Yield (%)[a]		
		201	**202**	**207**
1	dioxane	>5	59	0
2	toluene	0	0	0
3	DMSO	30	0	24
4	DMF	20	16	20

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard

2.2.2 Statistical approach: Design of Experiments (DoE)

Traditionally, reaction optimisation is carried out in a 'one variable at a time' (OVAT) approach. This method has many drawbacks. The OVAT approach does not necessarily uncover the optimal conditions for a reaction as the outcome is highly dependent on the starting point. It also does not distinguish between any inherent run-to-run variations of a system and actual improvements unless a significant number of repeats of a reaction using identical reaction conditions are used. Design of Experiments (DoE) is a statistical approach to reaction optimisation, which allows the whole 'reaction space' of a system to be investigated by varying multiple factors simultaneously. A DoE approach overcomes the drawbacks faced by an OVAT approach as the whole chemical space is explored, so optimal conditions will not be missed unless they fall outside the space covered. DoE also eliminates any researcher bias. Another major advantage of a DoE approach is that much more information can be gained from a much smaller number of reactions run. For example, in a traditional OVAT approach if 3 variables were to be investigated at least 8 reactions would be required. In contrast, for a half-factorial DoE only 4 experiments would need to be carried out. This efficiency allows a much larger number of parameters to be explored in a relatively small number of experiments.[134-135]

A DoE was carried out, using the software MODDE, to provide an insight into which parameters most affected the yield of the desired product. Seven variables, with minimum and maximum values decided for quantitative variables, were chosen: temperature (80, 100 °C); concentration (0.025, 0.1 M); catalyst ($Pd(TFA)_2$, $Pd(OAc)_2$, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$; catalyst loading (10, 20 mol%); oxidant ($Cu(OAc)_2$, AgOAc); amount of oxidant (2, 4 equiv.); and amount of base (2, 4 equiv.). These variables were input into MODDE and the conditions for 21 experiments were generated, including those for three centre

point runs. These reactions were carried out and the ^{1}H NMR yields obtained. The results were input into MODDE and a coefficient plot was generated to illustrate the findings of the DoE (Figure 5). Each purple bar represents a variable and shows the effect of increasing that variable on the yield. A bar with a positive value means the yield will increase with an increase of that variable. Similarly, a negative value means the yield will decrease with an increase of that variable. However, only variables for which the confidence intervals do not include zero can be considered statistically significant (confidence intervals of 95% shown). For qualitative variables (catalyst and oxidant), the values show the effect of that variable compared with the average for all experiments.

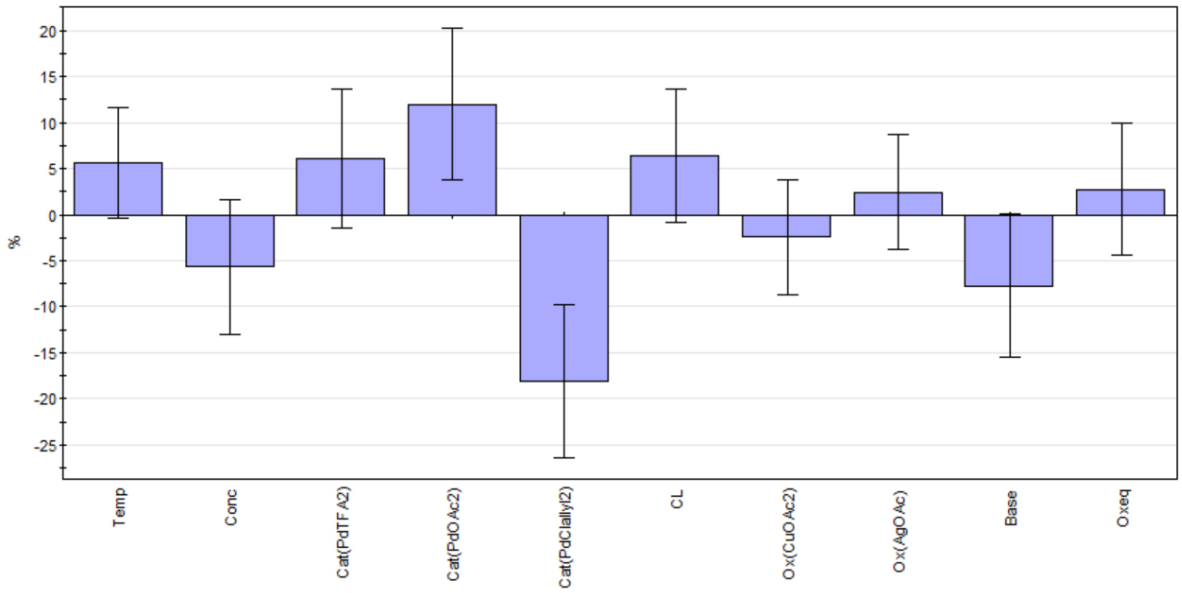


Figure 5. DoE coefficient plot

From the coefficient plot it could clearly be seen that the most significant factor was the catalyst used, with the use of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ resulting in a significant decrease in yield compared with the average for all experiments. Both $Pd(OAc)_2$ and $Pd(TFA)_2$ give a significant increase in yield. The previously optimised conditions used $Pd(TFA)_2$ as a catalyst, however these results showed that the use of $Pd(OAc)_2$ results in a better yield.

While no other factors could be considered statistically significant, due to their confidence intervals including zero, more information could be gained from the coefficient plot. Both an increase in temperature and an increase in catalyst loading both appeared to have a positive effect on the yield, while an increase in concentration and an increase in the amount of base appeared to have a negative effect. The oxidant used and the amount of oxidant had no significant impact on the yield, although AgOAc seemed to be marginally preferential to $Cu(OAc)_2$.

A graph of the experimentally observed results against the results predicted by the computer model is shown below (Figure 6). A positive correlation can be seen which validates the accuracy of the model.

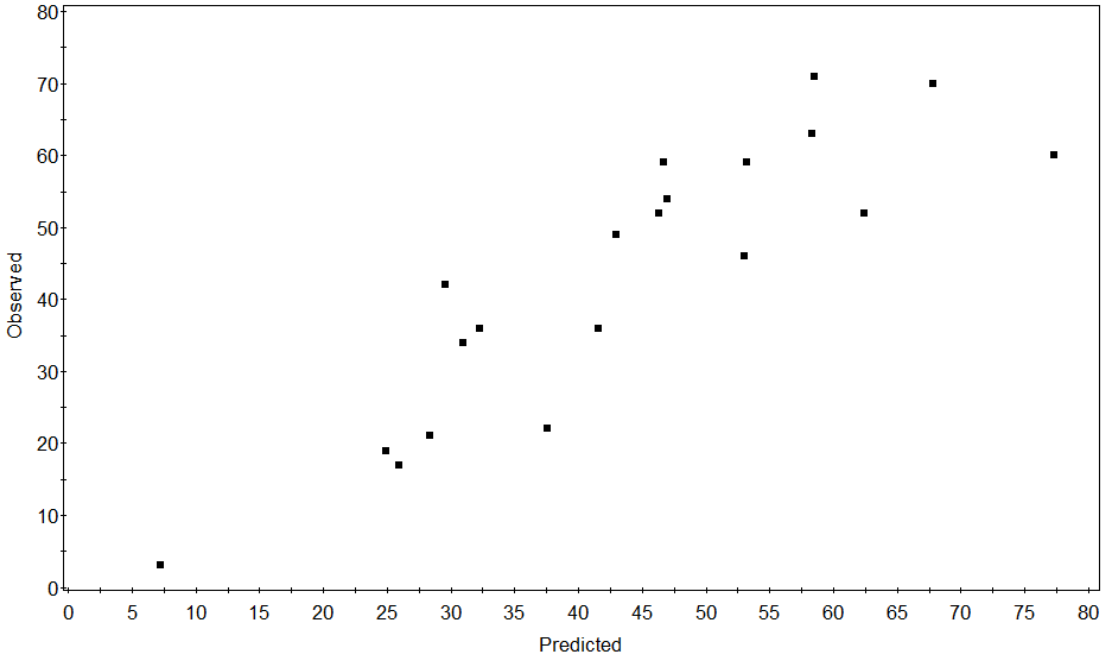
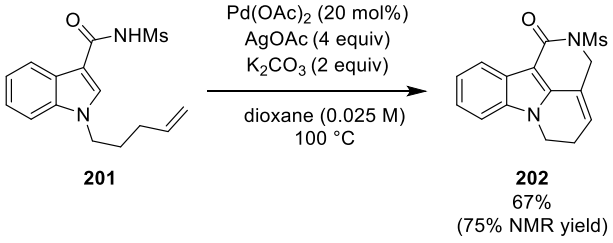


Figure 6. Observed *vs* Predicted results from DoE

The optimum conditions from the DoE were as follows: 20 mol% $Pd(OAc)_2$, 4 equiv. AgOAc, and 2 equiv. K_2CO_3 in dioxane (0.025 M) at 100 °C. The cyclisation of **201** was carried out under these conditions and pleasingly an ^{1}H NMR yield of 75% and an isolated yield of 67% of the cyclised product **202** were obtained (Scheme 69). This was a significant improvement on conditions used previously. However, limitations were evident; a high catalyst loading (20 mol%) and a large excess of costly AgOAc (4 equiv.) were required. A catalyst loading of 20 mol% was deemed too high, so was subsequently reduced to 10 mol%, and oxidant returned to 3 equiv. of $Cu(OAc)_2$. This gave an ^{1}H NMR yield of 60%. Therefore, although the DoE was a success, further optimisation was required.



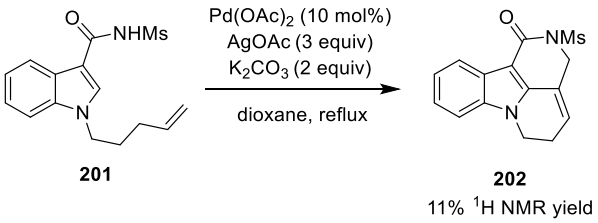
201

202
67%
(75% NMR yield)

Scheme 69. Optimum conditions from the DoE for the cyclisation of **201**

From the DoE studies it was shown that an increase in temperature proved beneficial. This could be for a number of reasons including increased substrate solubility or enhanced formation of the active

catalyst. The boiling point of dioxane (101 °C) limited the amount the temperature could be increased by, but the reaction was carried out at reflux to determine if this would result in any further improvement in yield (Scheme 70). Unfortunately, under these conditions a ^{1}H NMR yield of only 11% was obtained. No starting material remained, and no other products were detected.



201 **202**

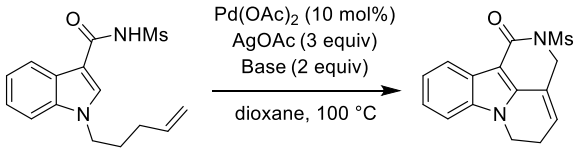
11% ^{1}H NMR yield

Scheme 70. Cyclisation of **203** under reflux conditions

2.2.3 Traditional reactant screening

The only parameter not investigated thus far was the base, so a base screen was performed. A variety of inorganic and organic bases were chosen and were employed at 2 equiv. as this was found to be the optimum amount from the DoE. The results are displayed below (Table 2). NaOAc and ^{t}BuOK (Table 2, entries 3 and 4) showed comparable yields to that when using K_2CO_3. However, no others showed any improvement, with the organic bases DBU and DIPEA (Table 2, entries 5 and 6) resulting in poor yields. Therefore, K_2CO_3 remained as the optimum choice of base and was used in all further cyclisation reactions.

Table 2. Base screen for the cyclisation of **201**



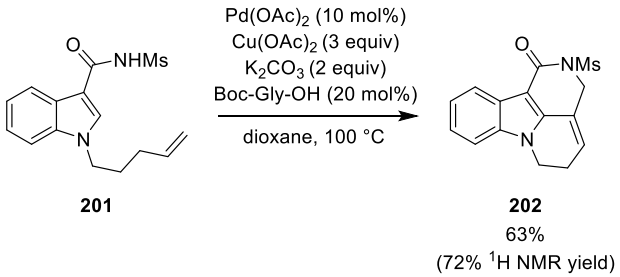
201 **202**

Entry	Base	Yield of 202 (%)[a]
1	K_2CO_3	60
2	Cs_2CO_3	39
3	NaOAc	55
4	^{t}BuOK	59
5	DBU	5
6	DIPEA	17

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard

MPAA ligands have been used extensively by Yu *et al*. in C–H activation methodology.[33, 136-138] Inspired by their success, cyclisation of **201** was carried out with the addition of 20 mol% Boc-Gly-OH (Scheme

71). At this point it was also decided to swap the AgOAc oxidant back to the cheaper and more environmentally friendly $Cu(OAc)_2$ as this had no significant detrimental effect on the yield. Pleasingly, this addition of an MPAA ligand resulted in a ^1H NMR yield of **202** of 72% and an isolated yield of 63%. This was close to the yields achieved by the DoE, but with a significantly lower catalyst loading, and a lower amount of the cheaper oxidant $Cu(OAc)_2$.

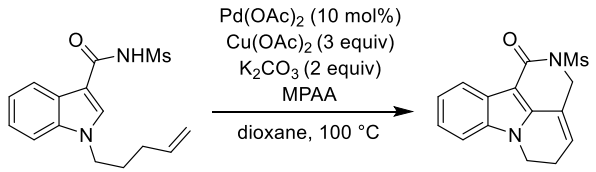


201 **202**
63%
(72% ^1H NMR yield)

Scheme 71. Addition of Boc-Gly-OH ligand

Following this success, the loading of Boc-Gly-OH was investigated (Table 3). It was found that both decreasing (Table 3, entries 1 and 2) and increasing the loading (Table 3, entry 4) from the original 20 mol% resulted in a slight decrease in the yield of **202**. Investigations were then carried out to identify the optimal amino acid backbone. A range of commercially available Boc-protected amino acids were examined (Table 3, entries 5-9). While all ligands performed well, there was no improvement seen on the ^1H NMR yield of **202** achieved by Boc-Gly-OH. It could be argued that this is due to steric factors as the least bulky MPAA's, such as glycine and alanine, (Table 3, entries 3 and 6) appeared to perform better than those with bulkier α-substituents such as valine (Table 3, entry 9). However, no firm conclusions can be drawn as the yields are all within 15% of each other, which are within the errors associated with ^1H NMR.

Table 3. Boc-Gly-OH loading and amino acid backbone screen for the cyclisation of **201**



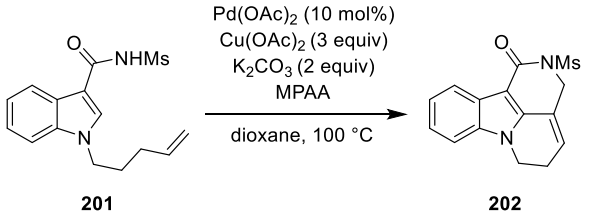
201 **202**

Entry	Mono-*N*-protected amino acid	Loading	Yield of 202 (%)[a] (Isolated yield)
1	Boc-Gly-OH	10 mol%	60
2	Boc-Gly-OH	15 mol%	67
3	Boc-Gly-OH	20 mol%	72 (63)
4	Boc-Gly-OH	30 mol%	69
5	Boc-Phe-OH	20 mol%	62
6	Boc-Ala-OH	20 mol%	71
7	Boc-Leu-OH	20 mol%	64
8	Boc-Thr(bzl)-OH	20 mol%	65
9	Boc-Val-OH	20 mol%	57

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard

Following the identification of glycine as the optimal amino acid backbone, optimisation of the *N*-protecting group was carried out (Table 4). An initial control reaction was carried out to assess whether an *N*-protecting group was required. In this reaction with a NH_2-Gly-OH additive (Table 4, entry 2) a ^{1}H NMR yield of 64% was observed. This revealed that *N*-protection was not necessary for the reaction to occur, but it did aid in increasing the yield. A range of *N*-protected glycine ligands were synthesised (Table 4, entries 3-8). Because Boc-protecting groups were found to be beneficial, other carbamate groups with different steric properties were trialled (Table 4, entries 3 and 4). However, no improvement was observed. Amide protecting groups were also investigated (Table 4, entries 5-8) and pleasingly several showed an improvement in yield, with the best being Ac-Gly-OH giving a ^{1} H NMR yield of **202** of 75% and an isolated yield of 69%. An *N*-tosyl protecting group was also trialled (Table 4, entry 9), but a ^{1}H NMR yield of only 55% was observed.

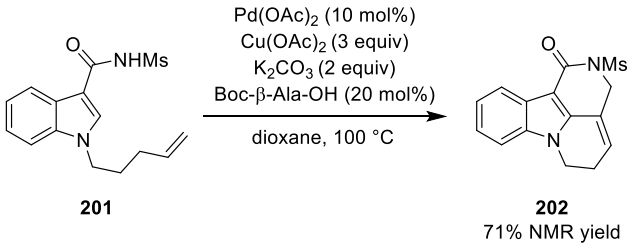
Table 4. MPAA *N*-protecting group screen for the cyclisation of **201**



Entry	MPAA	Yield of 202 (%)[a] (Isolated yield)
1	Boc-Gly-OH	72 (63)
2	NH_2-Gly-OH	64
3	Cbz-Gly-OH	67
4	EtO_2C-Gly-OH	59
5	Ac-Gly-OH	75 (69)
6	Formyl-Gly-OH	63
7	TFA-Gly-OH	70
8	Piv-Gly-OH	66 (67)
9	Ts-Gly-OH	55

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard

A mono-*N*-protected β-amino acid ligand, Boc-β-Ala-OH, was also examined (Scheme 72), thus increasing the length of the ligand backbone by one methylene unit. If the MPAA's were acting as bidentate ligands this would increase the chelate from a 5- to a 6-membered ring. It was expected that this would have a significant impact on the yield of the reaction. In fact, a 71% ^{1}H NMR yield was observed for this reaction, which is comparable to that when using Boc-Gly-OH. This result suggested that the MPAA's may not have been acting as bidentate ligands, but as acids.

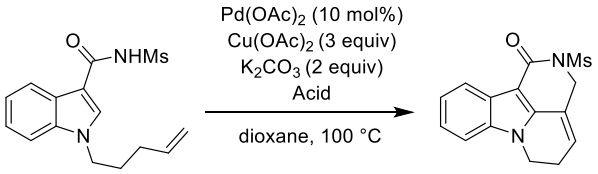


Scheme 72. Addition of Boc-β-Ala-OH ligand

To investigate the role of the additives the reaction was carried out using 30 mol% PivOH, conditions with literature precedent for C–H activation methodology.[139] Indeed, for this reaction a ^{1}H NMR yield of 71% was observed and an isolated yield of 68% was obtained (Table 5, entry 1). This was again comparable with that seen for Boc-Gly-OH. The amount of PivOH used was then investigated (Table 5, entries 1-3), but no further improvement was seen. A small sample of other acids were trialled

(Table 5, entries 4-6) and they all performed equally well, except for the more electron deficient TFA (Table 5, entry 4) for which the ^{1}H NMR yield dropped to 65%.

Table 5. Acid additive screen for the cyclisation of **201**



201 **202**

Entry	Acid	Loading	Yield of 202 (%)[a] (Isolated yield)
1	PivOH	30 mol%	71 (68)
2	PivOH	20 mol%	65
3	PivOH	1 equiv.	65
4	TFA	30 mol%	65
5	AcOH	30 mol%	70
6	AdOH	30 mol%	71

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard

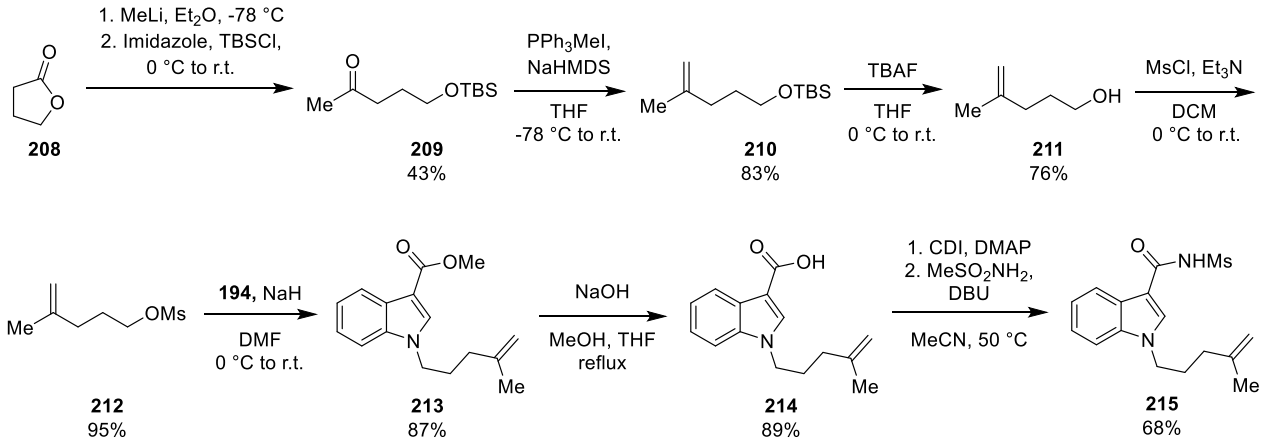
At this point a decision was made to finish the reaction optimisation as the DoE yields had been matched, but with a lower catalyst and using a lower amount of the cheaper oxidant $Cu(OAc)_2$. This was achieved by the use of MPAA or acid additives. It was decided that PivOH would be used as an additive over Ac-Gly-OH, despite the marginally higher yield resulting from the use of Ac-Gly-OH, because it was a more readily available and inexpensive reagent. Therefore, the optimised conditions were as follows: 10 mol% $Pd(OAc)_2$, 3 equiv. $Cu(OAc)_2$, 2 equiv. K_2CO_3, 30 mol% PivOH, dioxane (0.1 M), 100 °C, 16 hours.

2.3 Substrate scope

Following the optimisation process an investigation into the scope of the reaction was undertaken, starting with modifications of the alkene and tether. Such modifications would have the potential to lead to the formation of various sized rings or substituted rings.

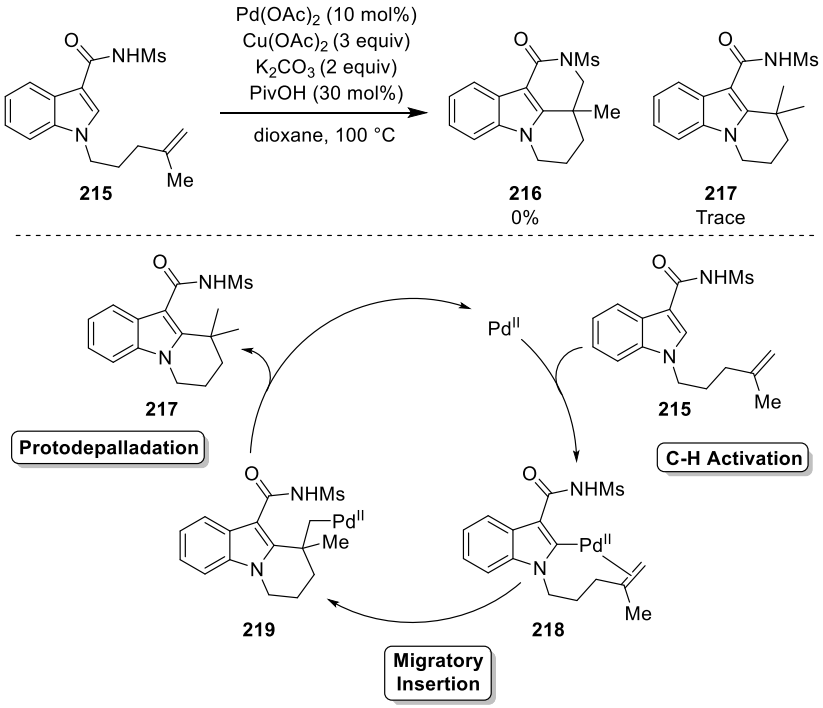
2.3.1 Alkene variation

The first substrate targeted was one with a methyl group at the internal position of the alkene. This substrate was not expected to perform well as the presence of the methyl substituent meant the β-hydride elimination step in the first cyclisation (cf. Scheme 60, page 51) could not occur. However, **215** was still a substrate of interest in order to see whether any alternative products would be formed, or whether the fully cyclised product would still be formed but *via* a different mechanism. The synthesis of **215** began with the opening of γ-butyrolactone **208** with MeLi to access 5-hydroxypentan-2-one which was immediately protected with TBSCl, due to instability of the alcohol in air. This was followed by a Wittig reaction to form alkene **210**. Subsequent TBS-deprotection and mesylation resulted in the formation of tether **212**, which was used to alkylate indole **194**. The synthesis was completed by hydrolysis of the methyl ester followed by amide coupling to afford **215**.



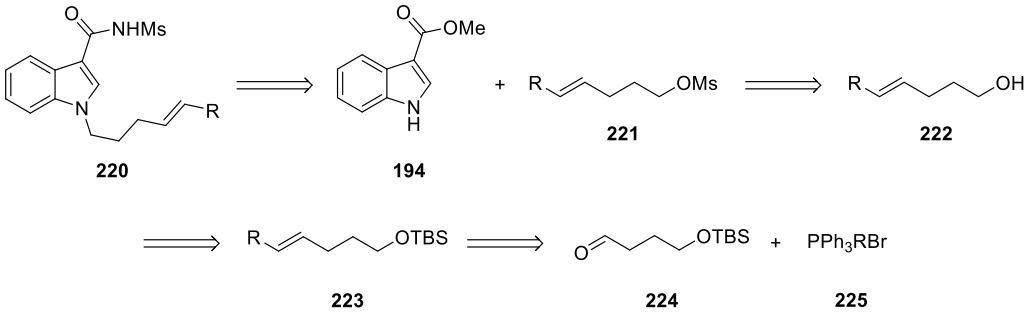
Scheme 73. Synthesis of and attempted cyclisation of **215**

Substrate **215** was then subjected to the standard cyclisation conditions. As expected, no formation of the desired cyclisation product **216** was observed. The only product formed was a trace amount of the mono-cyclised product **217** (Scheme 74). It is possible that this is a result of protodepalladation of intermediate **219**.[140]



Scheme 74. Cyclisation of **215** and proposed mechanism

The tolerance of the reaction to substitution on the terminal position of the alkene was also explored. It was envisaged that such substrates could be synthesised in a similar manner to that of **215** but starting from aldehyde **224**. A Wittig reaction between **224** and a variety of phosphonium salts **225** would enable access to alkenes bearing a range of terminal substituents (Scheme 75).

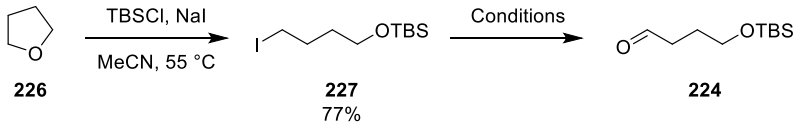


Scheme 75. Retrosynthetic analysis of **220**

For this to be realised, an efficient synthesis of **224** needed to be developed. A literature procedure was found in which THF could be ring-opened by NaI and TBS-protected to give **227** in one pot.[141] This reaction was carried out and a good yield of 77% was achieved on a 40 mmol scale. It was then envisaged that the iodide could be converted to the desired aldehyde by a Kornblum oxidation. A range of conditions were trialled, with limited success (Table 6). Initially, pyridine *N*-oxide and $NaHCO_3$ were used in toluene at 110 °C. After 5 hours ^1H NMR analysis of the crude mixture showed that only an 8% conversion to the product had occurred. This reaction was repeated but left for a prolonged amount of time in the hope that this would allow the reaction to go to completion. Unfortunately,

after 40 hours analysis by TLC showed a complex mixture of products, and by ^{1}H NMR of the crude reaction mixture no product was visible. Instead, DMSO and $NaHCO_3$ were used, as these Kornblum oxidation conditions are more commonly found in the literature.[142-144] Under these conditions at 150 °C only the TBS peaks were visible in the ^{1}H NMR, suggesting that the TBS group had been hydrolysed. These conditions were repeated at a lower temperature (110 °C) to supress this hydrolysis. Pleasingly, a 22% conversion to the product was observed by ^{1}H NMR. An increase in reaction time provided **224** in a 53% isolated yield. However, on scale-up, this yield dropped to 43%. It was decided that this route was not efficient enough to be used for the generation of terminally substituted alkene substrates.

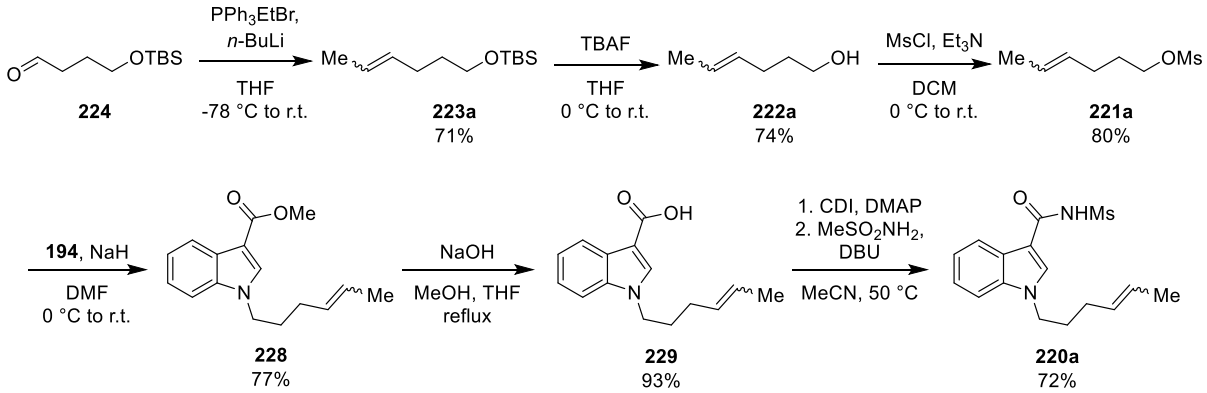
Table 6. Kornblum oxidation conditions for the synthesis of aldehyde **224**



226 **227** 77% **224**

Entry	Conditions	Solvent	Temperature	Time	Yield of 224 (%)
1	Pyridine *N*-oxide, $NaHCO_3$	toluene	110 °C	5 hours	8
2	Pyridine *N*-oxide, $NaHCO_3$	toluene	110 °C	40 hours	0
3	DMSO, $NaHCO_3$	NA	150 °C	2 minutes	0
4	DMSO, $NaHCO_3$	NA	110 °C	2 minutes	22
5	DMSO, $NaHCO_3$	NA	110 °C	20 minutes	53

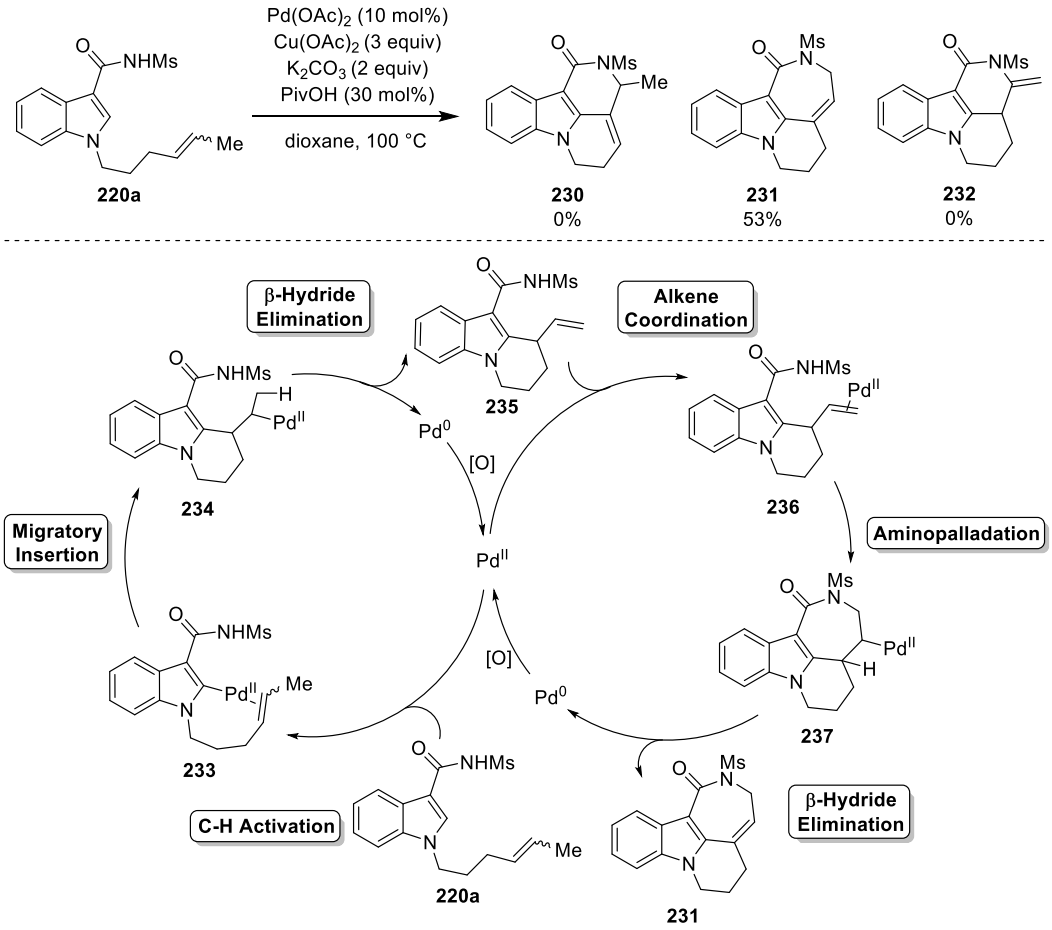
Fortunately, enough of aldehyde **224** was generated to take forward for the synthesis of the methyl substituted **220a**. This was achieved by a Wittig reaction between **224** and PPh_3EtBr to install a methyl substituent on the terminal position of the alkene. Alkene **223a** was formed as a mixture of stereoisomers. The remainder of the synthesis was the same as for substrate **215**: TBS deprotection followed by mesylation to form tether **221a**, then alkylation, hydrolysis, and amide coupling to give **220a** (Scheme 76).



Scheme 76. Synthesis and cyclisation of **220a**

An interesting result arose when **220a** was subjected to the standard cyclisation conditions. It was expected that the reaction would proceed in the normal manner to form **230**, with the usual [6,6] ring system but with a methyl substituent adjacent to the *N*-mesylamide. In fact, the seven-membered ring containing product **231** was formed in a moderate yield of 53% (Scheme 77).

It is thought that the mechanism for this reaction begins with an oxidative Heck reaction with β-hydride elimination to give intermediate **235** with a terminal alkene. The second catalytic cycle is an aza-Wacker type reaction. The presence of the additional methyl substituent on the alkene means that aminopalladation should be able to occur 6-*exo* or 7-*endo*. Both scenarios are allowed by Baldwin's rules, but it appears that the 7-*endo* reaction is much more favoured and so occurs preferentially, with **231** being form exclusively and no 6-*exo* product **232** observed. It is not currently known why this selectivity occurs.

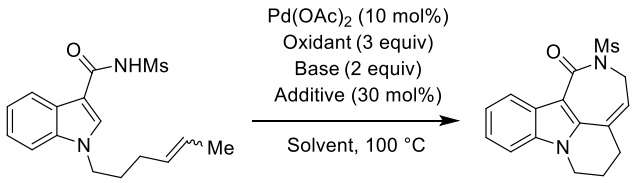


Scheme 77. Unexpected result from cyclisation of **220a** and proposed mechanism

Subsequent optimisation studies were carried out by another member of the group.[145] Initial investigation involved the screening of a number of parameters (selected results in Table 7). The initial experiment gave **231** in a ^{1}H NMR and isolated yield of 53% using the standard cyclisation conditions. Inspired by the literature[13] a solvent mixture of dioxane/AcOH (4:1 v:v) was trialled (Table 7, entry 2),

but this led only to complete degradation of the starting material. A brief oxidant screen was carried out to see if the catalytic turnover could be increased (Table 7, entries 3-5). The use of ^{t}BuOOBz resulted in degradation of the starting material, AgO gave a lower yield of 31% and BQ gave a comparable yield to that using $Cu(OAc)_2$. A base screen was then carried out, but all bases screened resulted in a decrease in yield (Table 7, entries 6-9). Inorganic bases proved more effective, with the organic base Et_3N giving a yield of only 13%. Lastly alternative additives were investigated (Table 7, entries 10-13). Unfortunately, still no increase in yield was achieved, so the original conditions were used in further studies.

Table 7. Optimisation studies for the cyclisation of **220a**



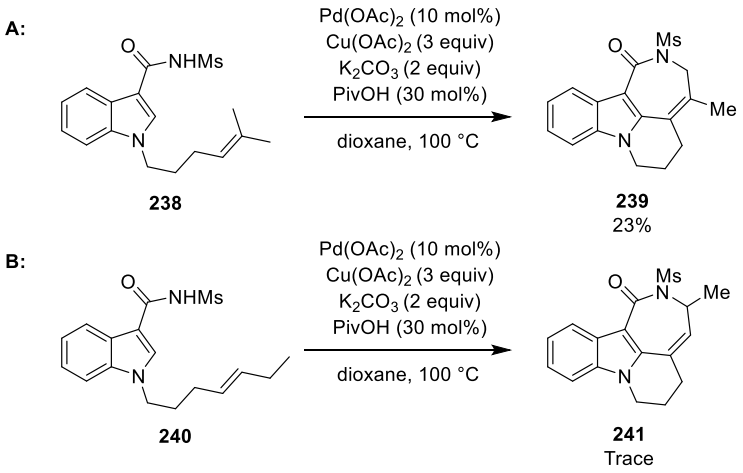
220a **231** 53%

Entry	Oxidant	Base	Additive	Solvent	Yield of 231 (%)[a]
1	$Cu(OAc)_2$	K_2CO_3	PivOH	dioxane	53
2[b]	$Cu(OAc)_2$	K_2CO_3	PivOH	dioxane/AcOH	0
3[b]	AgOAc	K_2CO_3	PivOH	dioxane	31
4[b]	BQ	K_2CO_3	PivOH	dioxane	52
5[b]	^{t}BuOOBz	K_2CO_3	PivOH	dioxane	0
6[b]	$Cu(OAc)_2$	^{t}BuOK	PivOH	dioxane	37
7[b]	$Cu(OAc)_2$	Et_3N	PivOH	dioxane	13
8[b]	$Cu(OAc)_2$	NaOAc	PivOH	dioxane	50
9[b]	$Cu(OAc)_2$	KOAc	PivOH	dioxane	32
10[b]	$Cu(OAc)_2$	K_2CO_3	Piv-Gly-OH	dioxane	37
11[b]	$Cu(OAc)_2$	K_2CO_3	Cbz-Gly-OH	dioxane	30
12[b]	$Cu(OAc)_2$	K_2CO_3	Ac-Gly-OH	dioxane	22
13[b]	$Cu(OAc)_2$	K_2CO_3	Boc-β-Ala-OH	dioxane	31

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard [b]Experiment conducted by J. Box

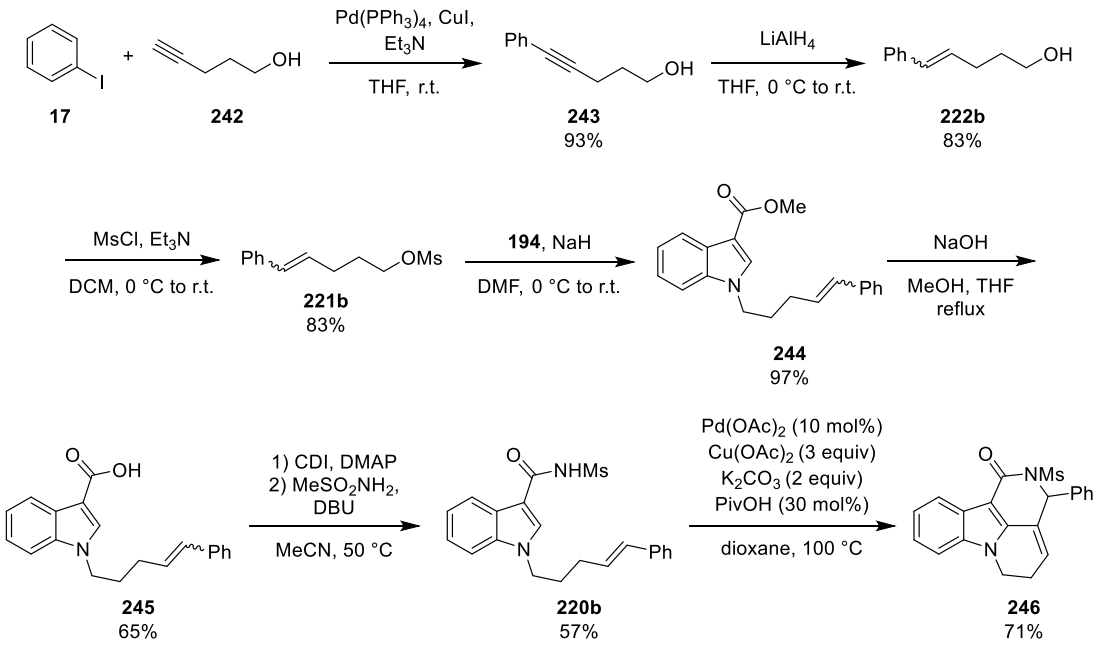
Further investigation into this reaction was conducted by another member of the group[145] to find out what would happen if two methyl groups were added to the terminal position of the alkene; whether it would go back to forming the [6,6] ring system or if it would still form the [6,7] ring system. When the dimethyl substrate **238** was subjected to the standard cyclisation conditions, once again the product with the [6,7] ring formation was formed exclusively in a yield of 23%, this time with a methyl substituent on the seven-membered ring (Scheme 78A). Addition of an ethyl group on the terminal

position of the alkene was also trialled to see whether a [6,6] ring system with an ethyl substituent, a [6,7] system with a methyl substituent or a [6,8] ring system would be formed. When **240** was subjected to the standard cyclisation conditions only a trace amount of the [6,7] system **241** was observed (Scheme 78B).



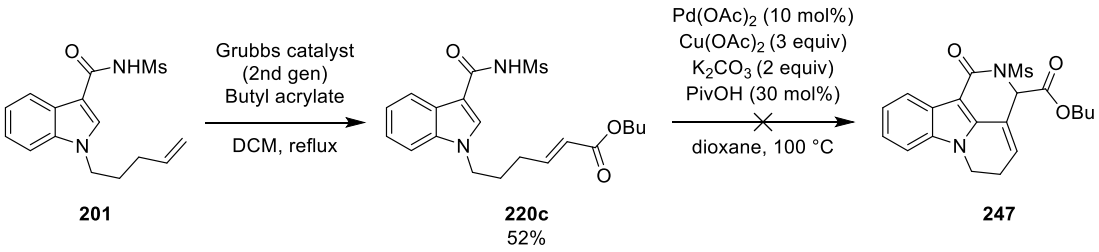
Scheme 78. Cyclisation of **238** and **240**. Work performed (and substrates synthesised) by J. Box

The addition of a phenyl ring to the terminal position of the alkene was then studied. The synthesis began with a Sonogashira reaction between iodobenzene and 4-pentyn-1-ol, followed by reduction of the resulting alkyne **243** to give alkene **222b** which was formed predominantly as the *trans* isomer. Alcohol **222b** was then mesylated to give the tethered alkene **221b** which was then suitable for alkylation with methyl indole-3-carboxylate. The synthesis was completed by the hydrolysis of the methyl ester followed by amide coupling. Substrate **220b** was recrystallised to give the *trans* isomer exclusively. When a methyl group was added to the terminal position of the alkene a change in mechanism resulted in the unexpected formation of a 7-membered ring (Scheme 77). However, the incorporation of a phenyl ring at this position does not allow for this alternative β-hydride elimination pathway, so it was expected that the standard [6,6] ring formation would occur. Indeed, when **220b** was subjected to the standard cyclisation conditions the polyheterocyclic product **246** was formed in a 71% yield (Scheme 79).



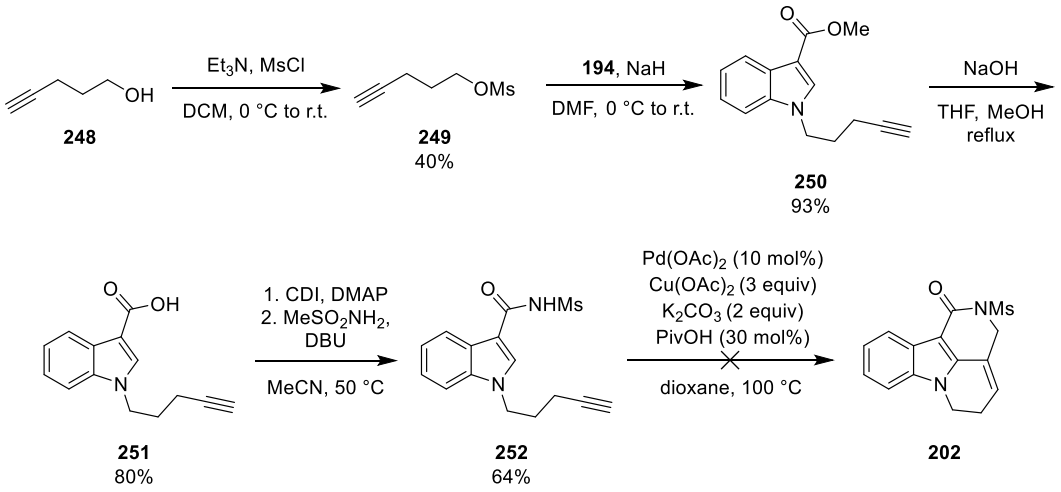
Scheme 79. Synthesis and cyclisation of **220b**

Functionalisation of the terminal position of the alkene was also achieved using Grubbs olefin metathesis. This allowed the alkene to be substituted with an ester group. Unfortunately, when **220c** was subjected to the standard cyclisation conditions complete decomposition of the starting material was observed and no formation of the desired product **247** was evident (Scheme 80).



Scheme 80. Synthesis and attempted cyclisation of **220c**

Another variation explored was the substitution of the alkene with an alkyne. Alkyne substrate **252** was easily synthesised in four steps from 4-pentyn-1-ol in an analogous fashion to previous examples. Unfortunately, when subjected to the standard cyclisation conditions, no formation of the cyclised product **202** was observed (Scheme 81).

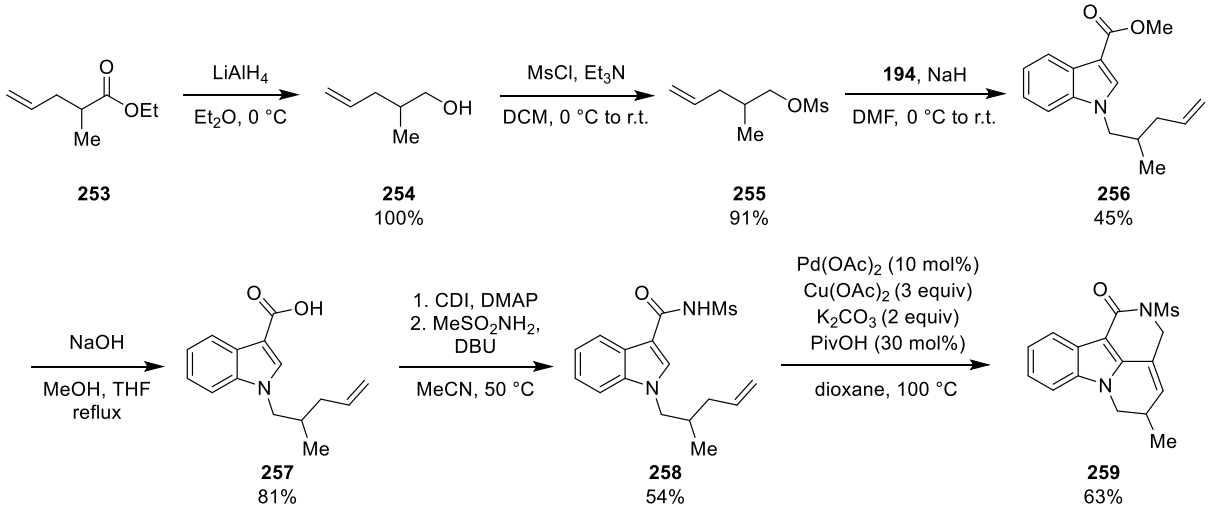


Scheme 81. Synthesis and attempted cyclisation of **252**

2.3.2 Tether variation

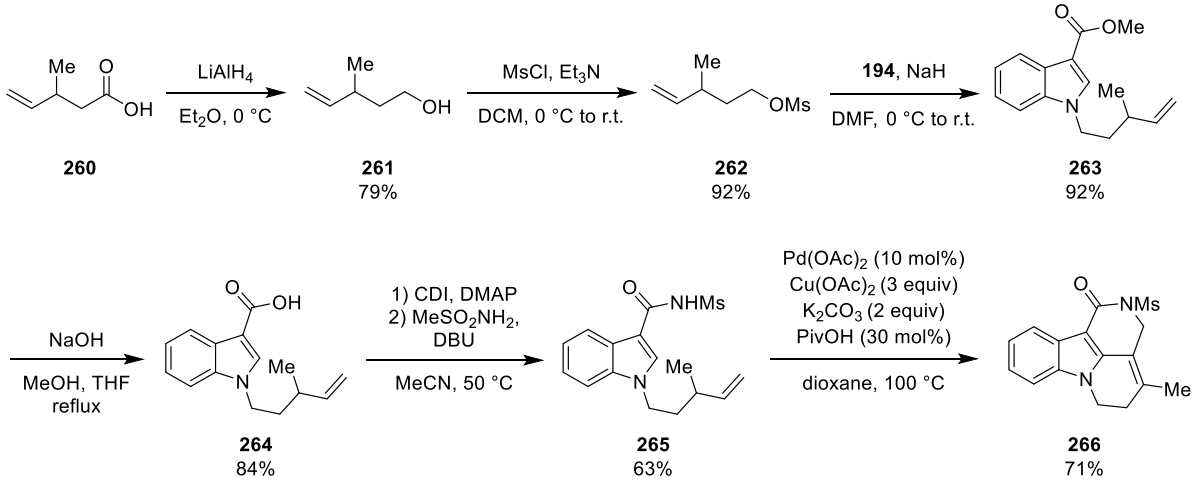
Following exploration of the alkene, an investigation into the *N*-tether was conducted. Initial investigations focused on the addition of substituents on the tether.

The tolerance to the presence of a methyl group β- to the nitrogen was first trialled. Synthesis of the tethered alkene portion **255** was achieved by reduction of the commercially available ester **253** to the corresponding alcohol **254** followed by mesylation, with both steps proceeding in excellent yields. Indole **194** was then alkylated using **255**, followed by hydrolysis of the methyl ester and amide coupling with methanesulfonamide to yield the desired substrate **258**. Pleasingly, under the standard cyclisation conditions, the cyclised product **259** was formed with an isolated yield of 63%. This was slightly less than that of the parent substrate, but that was to be expected due to the steric effects of the additional methyl group.



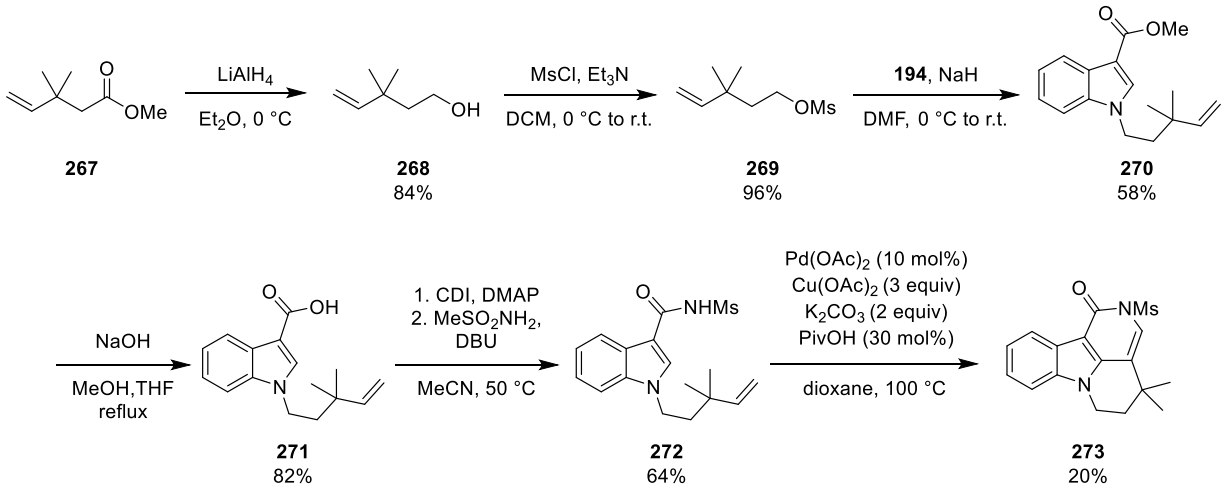
Scheme 82. Synthesis and cyclisation of **258**

Continuing with this theme, substitution on the tether of a methyl group γ- to the indole nitrogen was also trialled. Substrate **265** was synthesised in an analogous fashion to **258** but starting from acid **260** (Scheme 83). Under the standard cyclisation conditions, the cyclised product **266** was formed in an isolated yield of 71%; a yield comparable to that of the parent system.



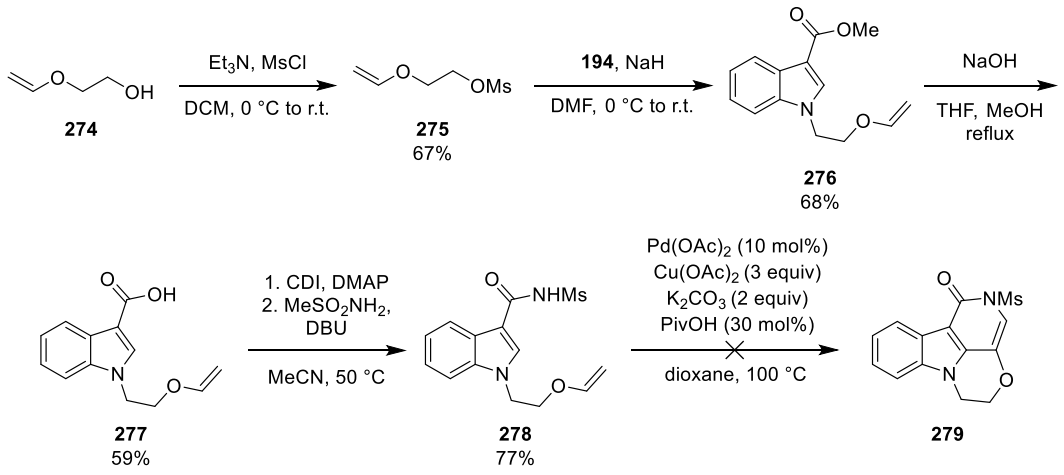
Scheme 83. Synthesis and cyclisation of **265**

A substrate with a gem-dimethyl group adjacent to the alkene was also synthesised. This was achieved by reduction of ester **267** to alcohol **268**. This was followed by mesylation, alkylation, ester hydrolysis and amide coupling as seen previously to give substrate **272** (Scheme 84). It was expected that, when subjected to the standard cyclisation conditions, substrate **272** would form a product similar to that seen with the parent substrate but with the double bond in a different place (Scheme 84). The gem-dimethyl group would prevent β-hydride elimination occurring in the usual manner, but there is still a β-hydrogen available for elimination. Indeed, cyclised product **273** was formed, albeit in a low yield of 20%.



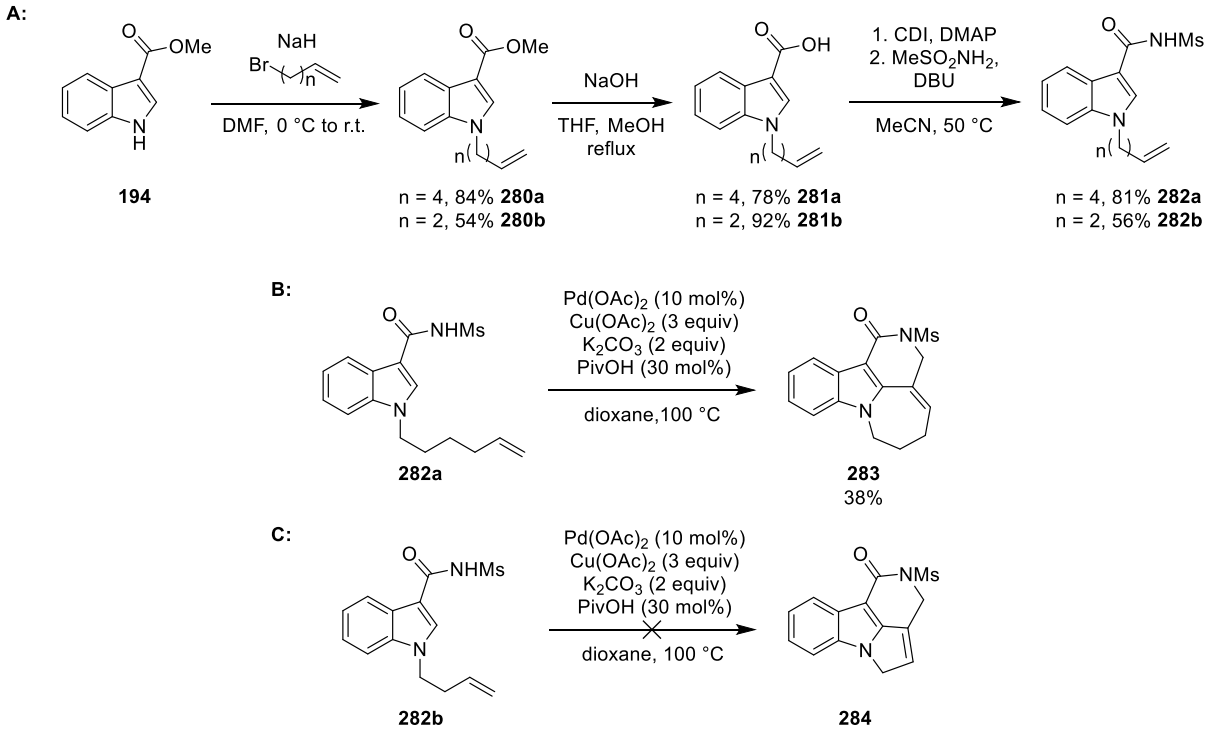
Scheme 84. Synthesis and cyclisation of **272**

The incorporation of an oxygen atom into the tether was investigated. Substrate **278** was easily synthesised from ethylene glycol vinyl ether in the usual manner (Scheme 85). This resulted in the incorporation of an oxygen atom adjacent to the alkene. Unfortunately, when exposed to the standard cyclisation conditions no desired cyclisation product **279** was formed. This is likely due to the instability of the vinyl ether under the reaction conditions.



Scheme 85**.** Synthesis and attempted cyclisation of **278**

The final tether variation explored was the tether length. It was hoped that this would allow access to a range of ring sizes of the bottom ring. Substrates **282a** and **282b** were synthesised in the usual way from commercially available bromoalkenes (Scheme 86A).

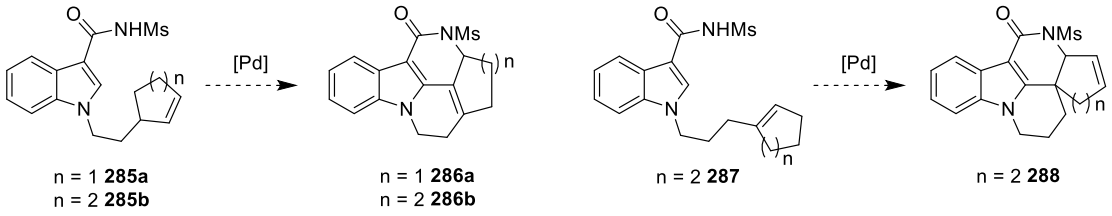


Scheme 86. Synthesis and cyclisation of **282a** and **282b**

Indoles **282a** and **282b** were both subjected to the standard cyclisation conditions. It was expected that, based on previous work within the group,[132] **282a** would perform poorly as it would have to go *via* an 8-membered transition state. Surprisingly, the reaction proceeded to give **283** in an isolated yield of 38% (Scheme 86B). In contrast, **282b** was expected to cyclise, but no formation of the cyclised product **284** was observed (Scheme 86C). The completed reaction mixture for **282b** was a black mess, which suggested that the material had polymerised.

2.3.3 Cyclic alkenes

Following the success of the investigation into substitution on the tether and alkene, more complex systems were targeted. It was envisaged that the incorporation of a ring in the alkene portion of the molecule would result in the formation of more complex polyheterocyclic structures, such as those shown below (Scheme 87).



n = 1 **285a**
n = 2 **285b**

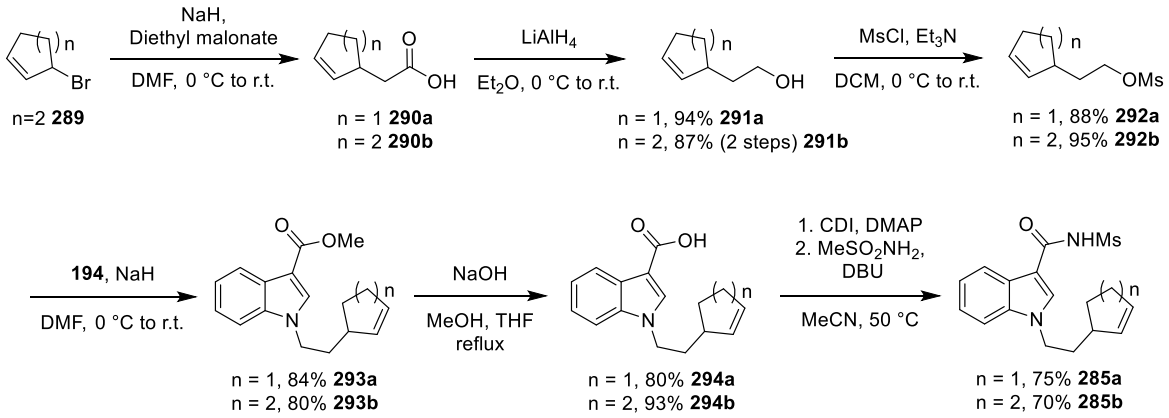
n = 1 **286a**
n = 2 **286b**

n = 2 **287**

n = 2 **288**

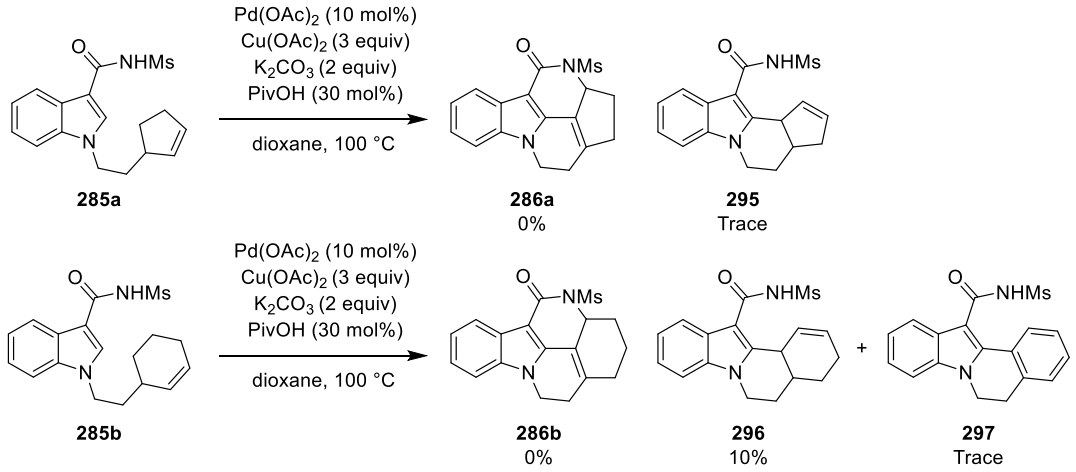
Scheme 87. Predicted formation of more complex polyheterocycles

First substrates **285a** and **285b** were synthesised, with the alkenes incorporated into 5- and 6-membered rings respectively. To begin the synthesis of **285b** 3-bromocyclohexene was reacted with diethyl malonate to give the corresponding carboxylic acid **290b**. For the synthesis of **285a** the necessary carboxylic acid **290a** was commercially available. The carboxylic acids were reduced to give alcohols **291a** and **291b** which were then mesylated to afford **292a** and **292b**. Indole 3-carboxylate **194** was then alkylated using the newly formed mesylates to give indoles **293a** and **293b**, and this was followed by hydrolysis of the methyl esters and amide coupling to give the desired substrates **285a** and **285b**.



Scheme 88. Synthesis and expected cyclisation of **285a** and **285b**

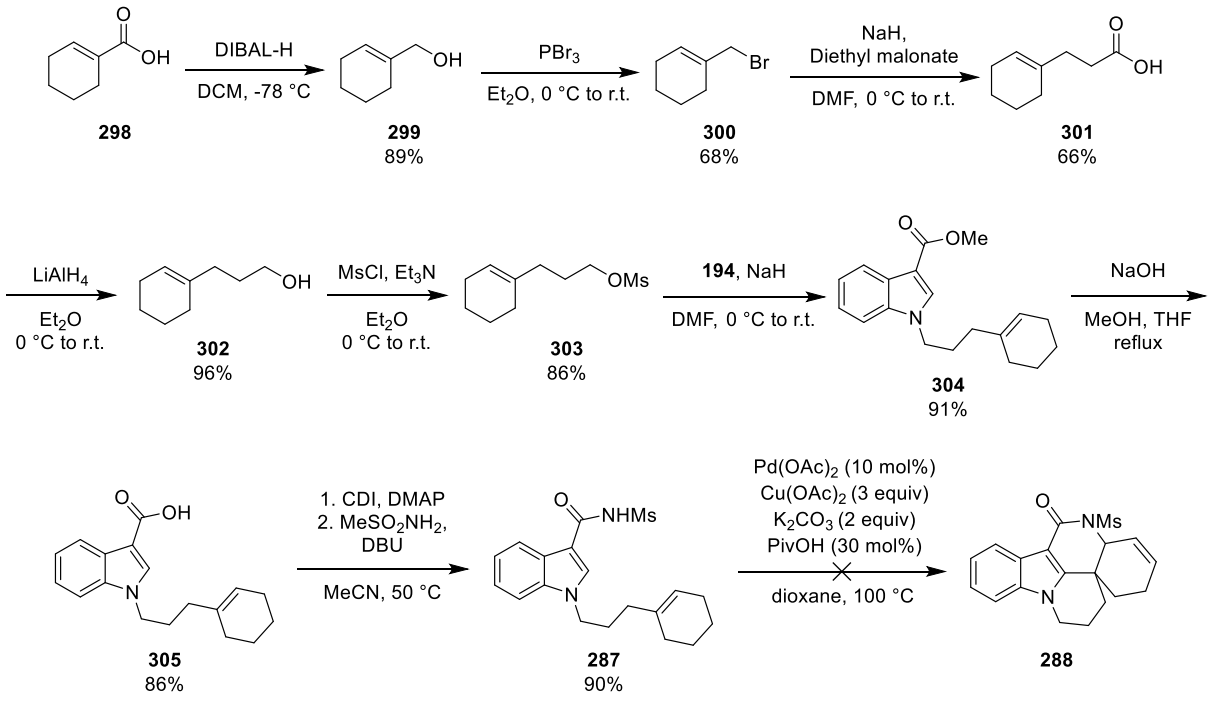
When **285b** was subjected to the standard cyclisation conditions formation of the fully cyclised product **286b** was not observed, only a 10% conversion to the oxidative Heck product **296** and a trace amount of the aromatised oxidative Heck product **297**. No starting material remained, so it is assumed that the rest of the material was lost to decomposition. Similarly, when **285a** was subjected to the standard cyclisation conditions, only trace amounts of the oxidative Heck product **295** were observed. It is likely that the desired fully cyclised products were not formed as a result of a reduction in conformational flexibility due to the additional rings.



Scheme 89. Cyclisation of **285a** and **285b**

Substrate **287** was then targeted (Scheme 90). Its synthesis began with reduction of the commercially available carboxylic acid **298** to alcohol **299**. This alcohol was homologated by bromination followed by reaction with diethyl malonate and then reduction to give **302**. As seen previously, the alcohol was then mesylated to form the desired tether portion of the substrate. Mesylate **303** was used to alkylate methyl indole-3-carboxylate **194** to give **304**. Hydrolysis of the methyl ester followed by amide coupling gave the desired substrate **287**. It was envisaged that upon exposure to the standard cyclisation conditions the spirocyclic product **288** would be formed. Unfortunately, none of this

product was formed, nor any other products, with only 22% of unreacted starting material observed by ^{1}H NMR analysis.

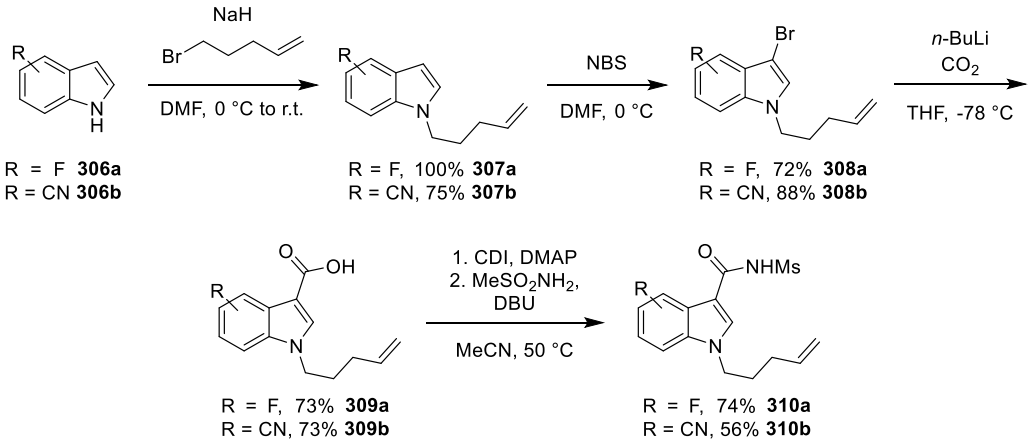


Scheme 90. Synthesis and expected cyclisation of **287**

2.3.4 Substitution on indole

The tolerance of the reaction to substitution around the indole ring was then explored.

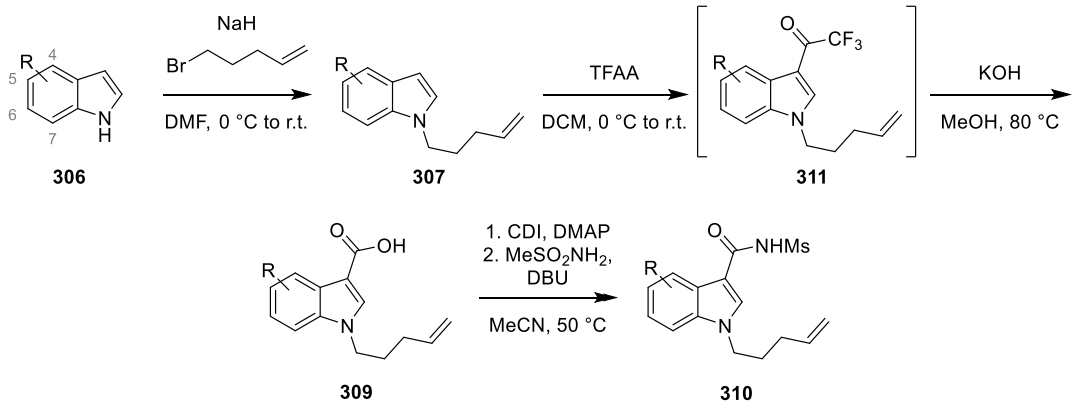
For this to be achieved a straightforward and robust method for the synthesis of such substrates needed to be developed. It was decided that designing a route from commercially available substituted indoles would be the simplest option, as opposed to adding functionality to the indoles at a later stage. Initially the route shown below was used (Scheme 91). The substituted indoles could be alkylated with 5-bromo-1-pentene using the standard alkylation conditions. The alkylated indoles **307** could then be brominated at the C3 position using NBS to give **308**. This then enabled a lithium-halogen exchange reaction to be carried out, during which trapping with CO_2 furnished the indoles with a carboxylic acid group. As seen previously the acid could then be coupled with methanesulfonamide to give the desired substrates **310**. Using this route two derivatives were synthesised; the 5-fluoro-substitued **310a** and the 5-cyano-substituted **310b**. A number of other substituted indoles were also trialled, but it was found that the brominated substrates were often very unstable, with some decomposing within minutes of isolation. The results of the lithium-halogen exchange reactions were also very variable, with some reactions only yielding the dehalogenated product. For these reasons, a more reliable way to installing the acid was necessary.



Scheme 91. Synthesis of substituted indole substrates **310**

It was found that the desired transformation could be achieved by treatment of the alkylated indole with TFAA, followed by hydrolysis with KOH.[146] This reaction was found to proceed with good to excellent yields of 65% and above, except in the case of indoles substituted at the 4 position (Table 8, entries 4 and 5) where the yield dropped significantly, likely due to steric effects. Utilising this new route, another eight examples were synthesised from commercially available indoles substituted with a variety of functional groups at different positions around the indole ring (Table 8).

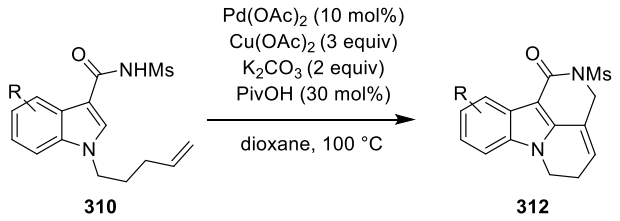
Table 8. Synthesis of substituted indole substrates **310**



Entry	Label	R	Yield (%)		
			307	**309**	**310**
1	c	5-Me	100	73	63
2	d	5-OMe	90	65	80
3	e	5-NO_2	100	88	76
4	f	4-Me	73	42	64
5	g	4-OMe	100	37	61
6	h	6-Cl	97	75	74
7	i	7-NO_2	75	86	84
8	j	7-aza	99	91	50

The substituted indole substrates were then subjected to the standard cyclisation conditions. Overall the reaction was tolerant of the different functional groups, with the majority of yields ranging from good to excellent. The reaction appeared to show a slight preference for electron-donating groups, particularly in the C5-substituted substrates, with the electron-donating methyl and ether substituents (Table 9, entries 3 and 4) giving rise to higher yields than the electron-withdrawing nitrile and halide substituents (Table 9, entries 1 and 2). This preference for more electron-rich substrates could be suggestive of an S_EAr-type mechanism. The tolerance to halide functionality is particularly useful due to its ability to serve as a handle for further functionalisation by cross-coupling reactions. The only substituent to perform poorly was the nitro group (Table 9, entries 5 and 9). It is thought that this was due to the high insolubility of the nitro substrates. It was expected that the 7-aza indole (Table 9, entry 10) would perform poorly due to the basic pyridine nitrogen and its ability to act as a ligand, which could deactivate the palladium catalyst. Surprisingly, even this example proceeded in a good yield of 58%.

Table 9. Cyclisation of substituted indole substrates



310 312

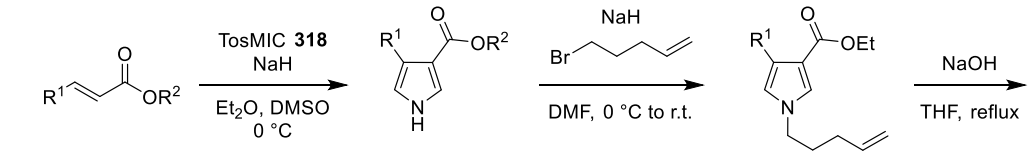
Entry	Label	R	Yield of 312 (%)
1	a	5-F	61
2	b	5-CN	64
3	c	5-Me	75
4	d	5-OMe	73
5	e	5-NO_2	15
6	f	4-Me	54
7	g	4-OMe	67
8	h	6-Cl	60
9	i	7-NO_2	22
10	j	7-aza	58

2.3.5 Pyrrole core

The next goal of the project was to switch the indole heterocyclic core to a pyrrole core as this would allow access to other novel polyheterocyclic structures. This had been successful for other cascade reactions developed previously within the group.[127-128]

The pyrrole moiety of the substrates could be constructed by a Van Leusen pyrrole synthesis, which has much literature precedence.[128, 147-148] This method was desirable as the ability to incorporate different R groups in the starting materials would allow for the synthesis of a variety of substrates with varying substitution around the ring. A Van Leusen pyrrole synthesis also generates pyrroles with an ester group at the 3-postion; an ideal handle for the synthesis of the *N*-acyl mesylamide.

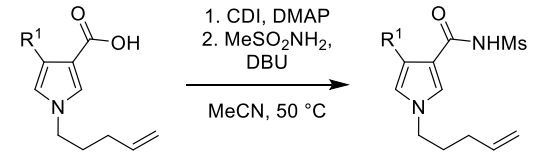
The viability of the route was demonstrated using the parent system **317a** (Scheme 92); reaction of TosMIC **318** and ethyl acrylate in the presence of NaH gave pyrrole **314a**, albeit in a disappointingly low yield of 20%. Alkylation and hydrolysis using the standard conditions both proceeded in excellent yields to give **316a**. The synthesis was completed by the formation of the mesylamide which gave the desired substrate **317a** in a 47% yield. Two 4-substituted pyrrole substrates were also synthesised using this route, albeit in low yields due to challenging purification of the Van Leusen products, and the low yields of the amide coupling reactions.



R^1 = H, R^2 = Et **313a**
R^1 = Me, R^2 = Me **313b**
R^1 = Ph, R^2 = Et **313c**

R^1 = H, R^2 = Et, 20% **314a**
R^1 = Me, R^2 = Me **314b**
R^1 = Ph, R^2 = Et, 76% **314c**

R^1 = H, R^2 = Et 83% **315a**
R^1 = Me, R^2 = Me, 60% (2 steps) **315b**
R^1 = Ph, R^2 = Et, 86% **315c**

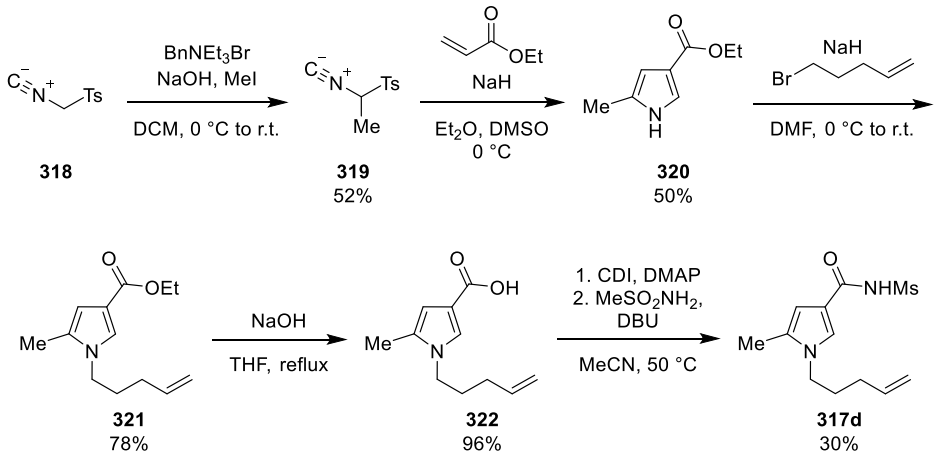


R^1 = H, 100% **316a**
R^1 = Me, 87% **316b**
R^1 = Ph, 95% **316c**

R^1 = H, 47% **317a**
R^1 = Me, 17% **317b**
R^1 = Ph, 60% **317c**

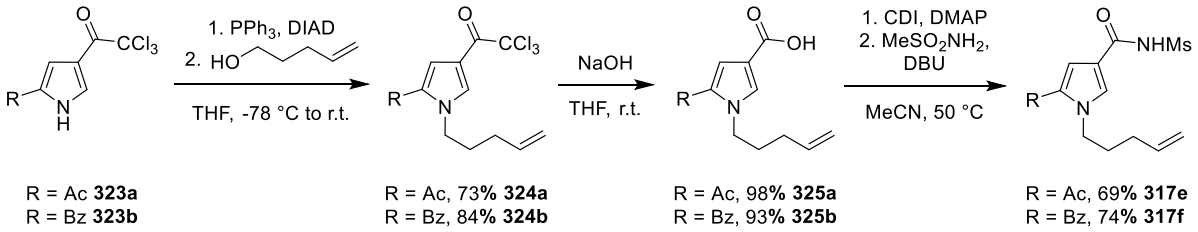
Scheme 92. Synthesis of 4-substituted pyrroles **317** *via* Van Leusen pyrrole synthesis

The synthesis of the 5-Me pyrrole substrate **317d** was achieved using an analogous sequence, following methylation of TosMIC with MeI using phase transfer conditions to give the methylated derivative of TosMIC **319** (Scheme 93).



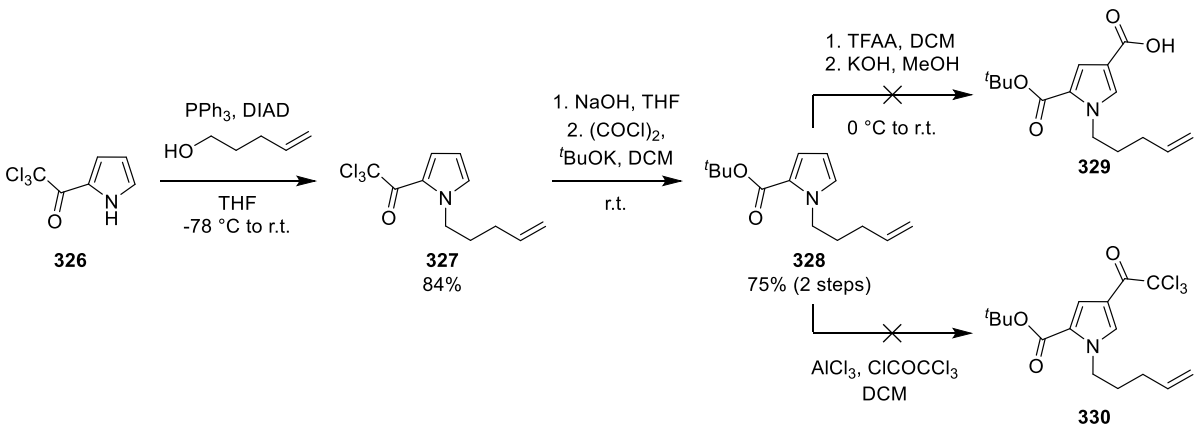
Scheme 93. Van Leusen pyrrole synthesis of **317d**

A number of 3,5-substituted pyrroles bearing electron-withdrawing groups at the 5-position and a trichloroacetyl group at the 3-position **323** were available within the group.[131] These served as ideal starting materials for the synthesis of 5-substituted pyrrole substrates as such pyrroles are known to cleanly undergo Mitsunobu alkylation, and the trichloroacetyl groups could be easily hydrolysed to give the corresponding acid derivatives **325** ready for amide coupling (Scheme 94). By this route two 5-susbstituted pyrrole substrates, **317e** and **317f**, were synthesised.



Scheme 94. Synthesis of 5-substituted pyrroles

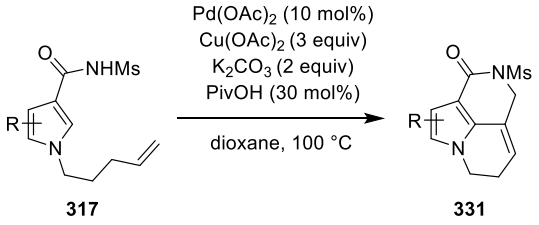
The synthesis of a pyrrole substrate bearing an ester substituent was also attempted. Commercially available 2-(trichloroacetyl)pyrrole **326** was alkylated using Mitsunobu conditions to give **327** in an excellent yield of 84%. The trichloroacetyl group was then hydrolysed and furnished with a *tert*-butyl ester using oxalyl chloride. It was envisaged that an acid group at the 3-position could be installed in an analogous fashion to the indole cores, using TFAA followed by KOH. Unfortunately, no formation of the product **329** was observed, with ^{1}H NMR analysis revealing a complex mixture containing no ^{t}BuO peak. An alternative method for installing functionality at the 3-position was trialled, utilising Friedel-Crafts chemistry. This reaction resulted in the degradation of the starting material, so again no formation of the desired product was observed, leading to the synthesis of this substrate being abandoned.



Scheme 95. Attempted synthesis of ester-substituted pyrrole substrate

The six successfully synthesised pyrrole substrates were subjected to the same cyclisation conditions used for the indole substrates. Pleasingly, all of the pyrrole substrates underwent cyclisation, generating a range of novel complex structures **331a-f** in moderate yields, demonstrating tolerance to substitution at both the 4- and 5-positions of the pyrrole ring (Table 10).

Table 10. Cyclisation of pyrrole substrates



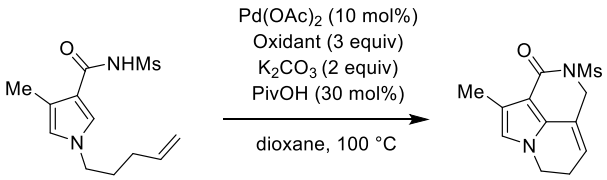
Entry	Label	R	Yield of 331 (%)
1	**a**	H	35
2	**b**	4-Me	50
3	**c**	4-Ph	40
4	**d**	5-Me	39
5	**e**	5-Ac	35
6	**f**	5-Bz	37

Despite all pyrrole substrates undergoing the desired cyclisation, the yields for these systems were less than that seen for indoles (Table 9). Factors which may have been contributing to the lower yields could be a lower catalytic turnover, or that the pyrrole substrates and products are more sensitive to decomposition under the reaction conditions due to their increased electron density.

Following the lower yields obtained for these pyrrole systems further optimisation was undertaken in the hope that the yields could be increased to those of the indoles. A screen of oxidants for the cyclisation of **317b** was carried out to see if an improved catalytic turnover could be achieved (Table

11). A variety of organic and inorganic oxidants were chosen. Unfortunately all oxidants other than $Cu(OAc)_2$ performed poorly, with the use of ^tBuOOBz and oxone (Table 11, entries 3 and 5) resulting in no formation of the desired product and BQ and IBX (Table 11, entries 2 and 6) resulting in only trace amounts of product formed, indicating no catalytic turnover. The only oxidant other than $Cu(OAc)_2$ to give a catalytic turnover was $AgBF_4$ (Table 11, entry 4) but even this only generated a yield of 15%.

Table 11. Oxidant screen for the cyclisation of **321b**



317b **331b**

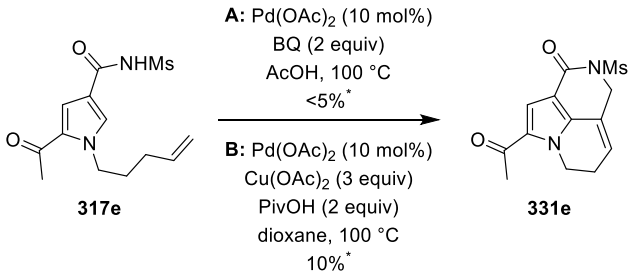
Entry	Oxidant	Yield of 331b (%)[a]
1	$Cu(OAc)_2$	50
2	BQ	5
3	^tBuOOBz	0
4	$AgBF_4$	15
5	Oxone	0
6	IBX	Trace

[a]As determined by ^1H NMR analysis with 1,4-dimethoxybenzene as an internal standard

It was noted that the mechanism for this cyclisation reaction (Scheme 60, page 51) had marked similarity to a reaction previously developed within the group in which alkylidine isoindolines were synthesised from *N*-alkoxybenzamides (Scheme 57, page 48).[129] Despite their obvious differences, in that the reaction of *N*-alkoxybenzamides has a different core and is an intermolecular reaction, both cascade sequences proceed by a C–H activation/oxidative Heck reaction followed by an aza-Wacker reaction and both sequences are directed by an acidic amide directing group. Interestingly, while the reaction in this work was carried out under basic conditions, the reaction of *N*-alkoxybenzamides was carried out under acidic conditions. Inspired by this, a variety of new conditions were trialled in the hope that the moderate yields obtained for the pyrrole substrates could be improved.

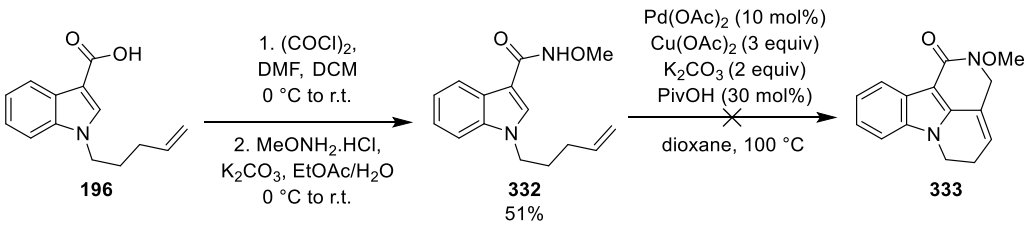
First, the cyclisation of the pyrrole substrate **317e** was carried out using $Pd(OAc)_2$ (10 mol%) and BQ (2 equiv.) in AcOH at 100 °C (**A**), conditions similar to those used in the reaction of *N*-alkoxybenzamides. BQ was chosen as the oxidant as O_2 was more difficult to obtain and during optimisation studies for the reaction of *N*-alkoxybenzamides BQ was shown to perform equally well. Under these conditions a yield of **331e** of less than 5% was observed by ^1H NMR analysis. This result

was unsurprising as BQ had previously performed poorly for this reaction (Table 11, entry 2), and previous investigations into the solvent have shown only dioxane to be an effective solvent (Table 1, page 56). For these reasons conditions more similar to those used normally were trialled; $Pd(OAc)_2$ (10 mol%), $Cu(OAc_2)$ (3 equiv.), PivOH (2 equiv.) in 1,4-dioxane at 100 °C (**B**). Here the oxidant and solvent were kept the same as usual, but K_2CO_3 was replaced with an excess of PivOH, making the conditions acidic rather than basic. These conditions produced a yield of **331e** of only 10%.



Scheme 96. Pyrrole cyclisation under acidic conditions (*As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as a standard)

Use of an *N*-alkoxyamide directing group was also trialled. Acid **196** was reacted with oxalyl chloride to give the corresponding acid chloride, which was then reacted with methylamine hydrochloride to afford **332** in a 51% yield over two steps. This *N*-alkoxyamide substrate **332** was subjected to the standard cyclisation conditions but no cyclisation to form the expected product **333** was observed (Scheme 97).

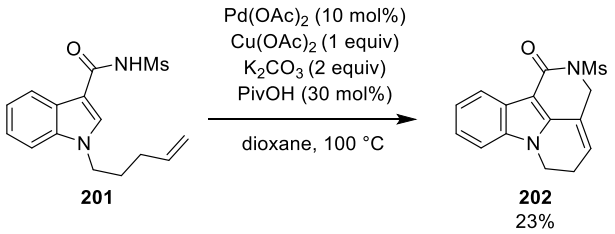


Scheme 97. Synthesis and attempted cyclisation of *N*-alkoxy amide substrate **332**

2.4 Mechanistic studies

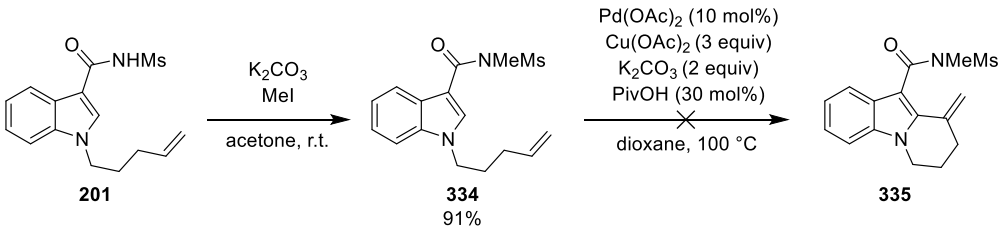
Having explored the scope of the reaction attention was turned to the reaction mechanism. Initially a C–H activated oxidative Heck reaction followed by an aza-Wacker reaction was proposed (Scheme 60, page 51). It was thought that this began with C–H activation at the C2 position of indole **187** to give **190**, followed by migratory insertion and then β-hydride elimination to give the intermediate **188**. It was thought that **188** then enters a second Pd(II)-catalysed cycle, with alkene coordination to the Pd(II) catalyst, aminopalladation to give **193** and then β-hydride elimination to yield the product **189**. A number of experiments were carried out in order to gain evidence towards this mechanism.

The proposed mechanism involves two catalytic cycles. In order to test this, **201** was subjected to the cyclisation conditions but with only 1 equiv. of $Cu(OAc)_2$. If two catalytic cycles are in operation the use of only 1 equiv. of $Cu(OAc)_2$ would only allow for a yield of up to 50%. Indeed, when the reaction was carried out a yield of only 23% of **202** was obtained, thus supporting two palladium turnovers per cascade sequence.



Scheme 98. Cyclisation of **201** using only 1 equiv. $Cu(OAc)_2$

The next investigation involved methylating the *N*-mesylamide of **201**. This transformation was easily achieved using MeI and K_2CO_3 to give the methylated substrate **334** in a 91% yield (Scheme 99). It was envisaged that subjecting **334** to the cyclisation conditions would reveal the importance of the free N–H in the mesylamide directing group. Substrate **334** would not be able to undergo the aza-Wacker cyclisation owing to the lack of N-H. It was thought that it would be possible, however, for **334** to undergo the oxidative Heck reaction to form **335**. In fact, when **334** was subjected to the standard cyclisation conditions, 100% of unreacted starting material was recovered. This result demonstrates that the mesylamide N-H is required to direct the Pd(II) centre to the C-2 position of the indole and indicates that the first step of the mechanism is not C–H activation of the indole as previously thought, but deprotonation and metalation of the *N*-mesylamide. This result also suggests that the role of the K_2CO_3 is to deprotonate the mesylamide in order to facilitate this coordination.

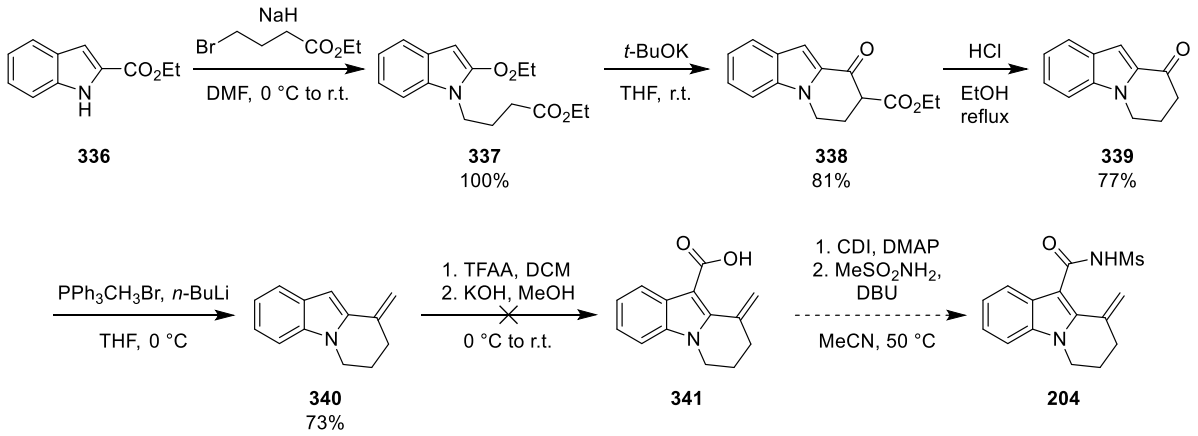


Scheme 99. Methylation of **201** and attempted cyclisation of **334**

As a key piece of mechanistic evidence, the synthesis of the putative intermediate **204** was targeted. If this could be achieved, subjection of **204** to the cyclisation conditions would elucidate its involvement in the cascade sequence.

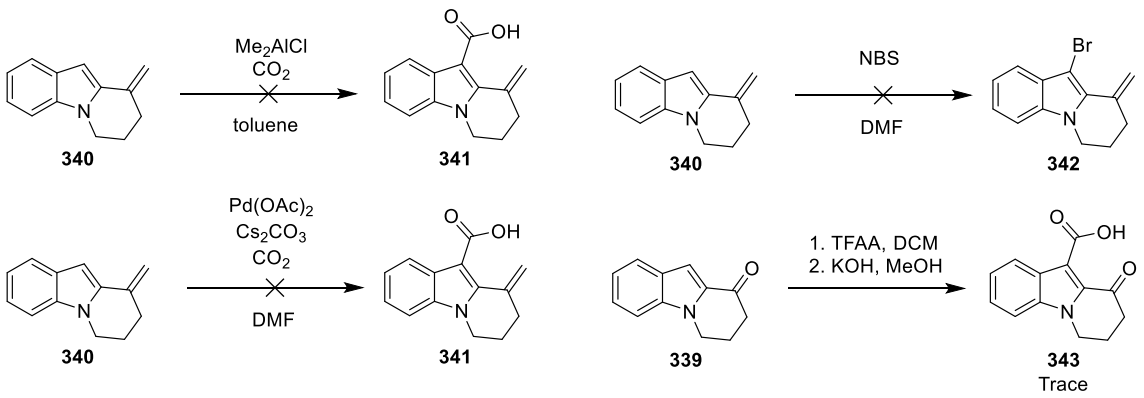
Following a search of the literature a straightforward synthesis of alkene **340** was found. It involved alkylation of ethyl indole-2-carboxylate **336** with ethyl 4-bromobutyrate followed by ring closure in

the presence of base to give **338**. An acidic decarboxylation reaction gave tricyclic ketone **340** which could then undergo a Wittig reaction to give the desired alkene moiety. All reactions proceeded in excellent yields (Scheme 100). It had been envisaged that a carboxylic acid group could then be installed at the C3 position of the indole using TFAA followed by KOH as had been used for the substituted indole substrates (cf. Table 8, page 77). When this reaction was carried out a complex mixture of products was observed by ^{1}H NMR analysis of the crude material. Unfortunately, no peaks were present in the alkene region of the spectrum meaning the mixture did not contain any of the desired product **341**.



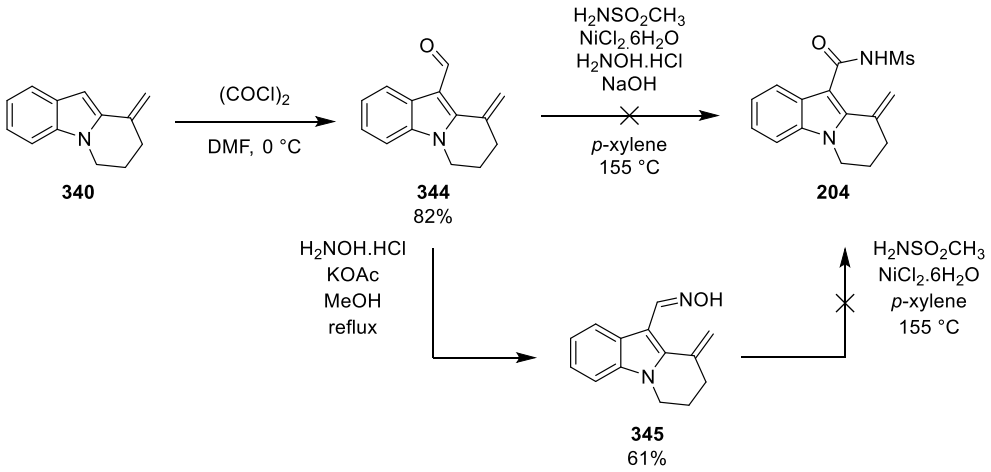
Scheme 100. Attempted synthesis of putative intermediate **204**

A number of other reaction conditions were trialled (Scheme 101), including bromination using NBS which would allow for a lithium-halogen exchange reaction followed by trapping with CO_2 to afford the desired acid **341**. Again, for all conditions trialled, only complex mixtures containing no alkene peaks were observed by ^{1}H NMR analysis. This decomposition of the alkene was likely due to the increased reactivity of the alkene as a result of conjugation to the indole. To circumvent this, installation of the acid prior to the formation of the alkene was attempted. Following reaction of **339** with TFAA it appeared that the formation of a trace amount of the product **343** had occurred, but not enough to take forward for the rest of the synthesis.



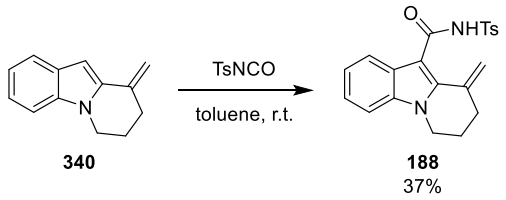
Scheme 101. Attempted functionalisation at indole C3

A reaction developed by Williams *et al.* was found in which aldehydes could be converted to amides in a one pot reaction.[149] Alkene **340** could easily be functionalised using a Vilsmeier-Haack to give the necessary aldehyde. Indole **344** was then treated with methanesulfonamide in the presence of $NiCl_2.6H_2O$, hydroxylamine hydrochloride and NaOH in *p*-xylene (Scheme 102). Unfortunately, no formation of the desired product **204** was observed. It was also reported that this transformation could be carried out in two steps *via* the formation of the oxime. Generation of the oxime **345** proceeded in a good yield of 61%, but again formation of the desired mesylamide was unsuccessful.



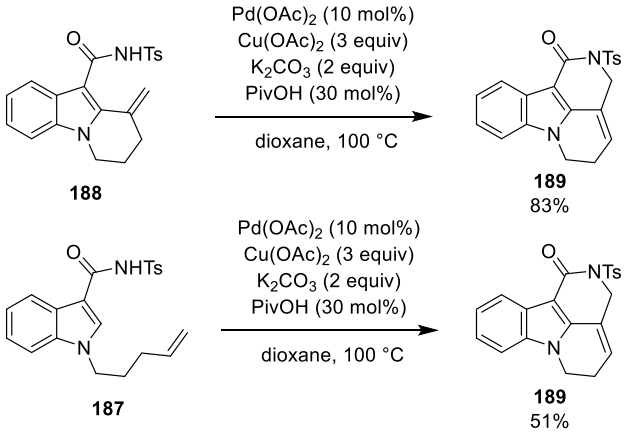
Scheme 102. Attempted functionalisation at indole C3 *via* a Vilsmeier Haack reaction

Following the lack of success in the synthesis of **204** it was decided that, instead of an *N*-acyl mesylamide group, an *N*-acyl tosylamide group would be used. Both groups have similar electronic properties, and it had been shown previously that substrates bearing an *N*-acyl tosylamide directing group also undergo the same cascade sequence (Scheme 59). It was hoped that this would make the synthesis more straightforward as an *N*-acyl tosylamide group can be installed directly by reaction of an indole with tosyl isocyante (the mesyl equivalent is not commercially available). Indeed, when alkene **340** was treated with tosyl isocyanate the desired tosylamide **188** was formed.



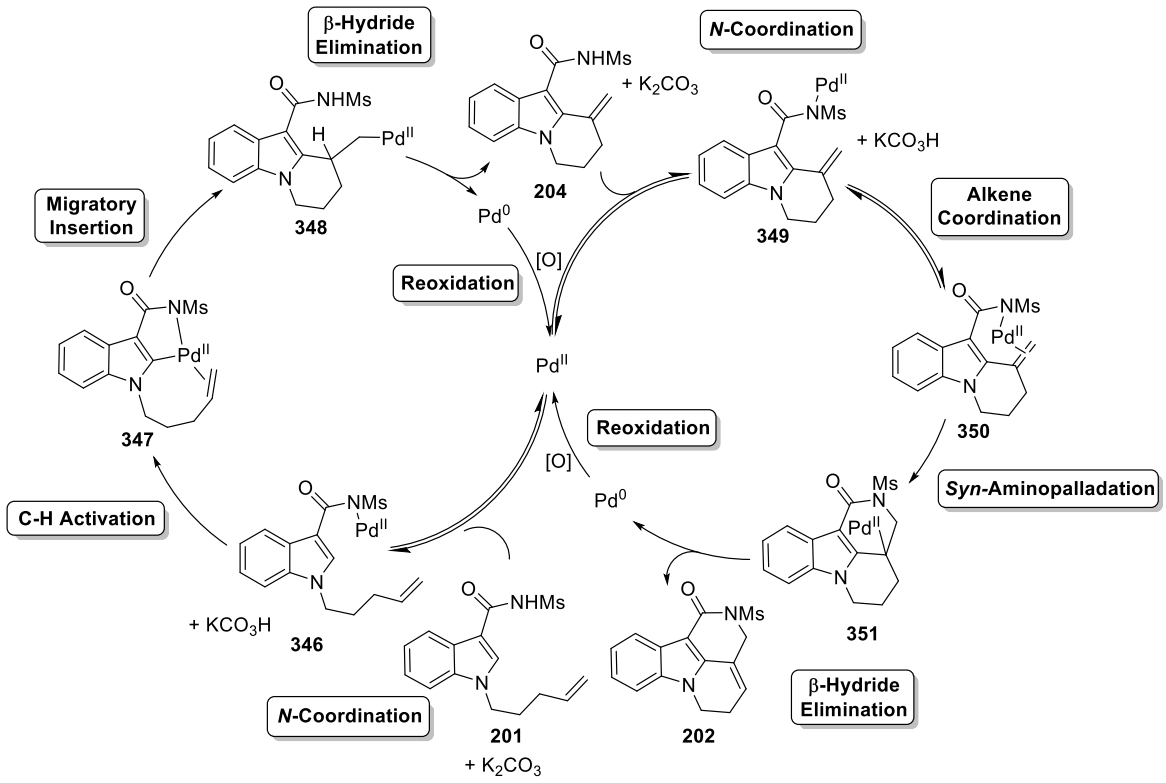
Scheme 103. Installation of *N*-acyl tosylamide group

The putative intermediate **188** was subjected to the standard cyclisation conditions and pleasingly gave the cyclised product **189** in a yield of 83%. This result is strong evidence that this intermediate is indeed involved in the cascade sequence. As a comparison, the tosylamide substrate **187** was also subjected to the optimised reaction conditions and gave **189** in a yield of 51%. This is another piece of evidence that supports two catalytic turnovers per cascade sequence.



Scheme 104. Cyclisation of putative intermediate **188** and *N*-tosylamide substrate **187**

As a result of these mechanistic studies, the following revised mechanism has been proposed (Scheme 105).



Scheme 105. Revised mechanism for the cyclisation of **203** (ligands omitted for clarity)

The catalytic cycle begins with coordination of the *N*-atom of **201** to the Pd(II) centre, which is facilitated by K_2CO_3. This directs C–H activation to the 2-position of the indole. Migratory insertion of **347** is followed by β-hydride elimination to give intermediate **204**. The active Pd(II) species is regenerated by oxidation with Cu(II). The intermediate **204** then enters a second catalytic cycle, undergoing *N*-coordination, alkene coordination and aminopalladation to give **351**. The product **202** is then generated by β-hydride elimination, and the resulting Pd(0) centre undergoes a second redox cycle with Cu(II). In addition to our observations, the mechanism for the aza-Wacker reaction is also supported by work done by Stahl that supports a *syn*-amino palladation mechanism for such processes.[150-152]

It must be noted that an alternative mechanism can also be proposed, involving nucleophilic addition of the indole to the alkene,[153] which does not process *via* C–H activation. A more comprehensive mechanistic study must be carried out in order to confirm which mechanism is in operation. Determination of a KIE using an indole substrate deuterated at the C2 position would determine which mechanism is occurring. If it is C–H activation by S_EAr no KIE would be observed as the C–H cleavage step is fast. if it is a nucleophilic addition a KIE would be observed. However, from the experiments conducted so far it is more likely that it is the C – H activation mechanism in operation due to the need for N–H bond in the directing group.

2.5 Natural product synthesis: Matrine alkaloids

The next aim of the project was to adapt the methodology for use as the key step in the synthesis of a natural product.

Matrine is a quinolizidine alkaloid which has been isolated from a number of plants from the Sophora genus, including *Sophora flavescens*, *Sophora tonkinensis*,[154] and *Sophora moorcroftiana*.[155] *Sophora flavescens* has long been used in traditional medicine in China, Japan and India for the treatment of conditions such as eczema, dysentery and pyogenic skin infections.[156] Modern analysis has shown that this is due to the presence of matrine-type alkaloids and flavonoids, which are the main components of this plant.[156] Over 40 matrine alkaloids have now been isolated from various Sophora plants. Recent pharmacological studies have shown that these alkaloids exhibit strong antiviral activities against Coxsackie virus B3 and B5, hepatitis B, and influenza virus A (H3N2).[157] Matrine has also displayed synergistic effects with several anti-cancer drugs, so could be used to reduce their therapeutic dose. This would reduce the side-effects of toxic drugs without compromising their efficacy.[158]

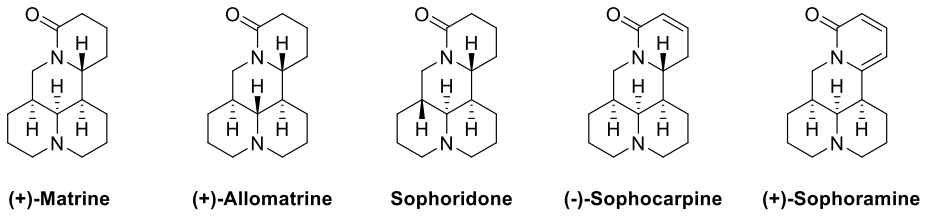
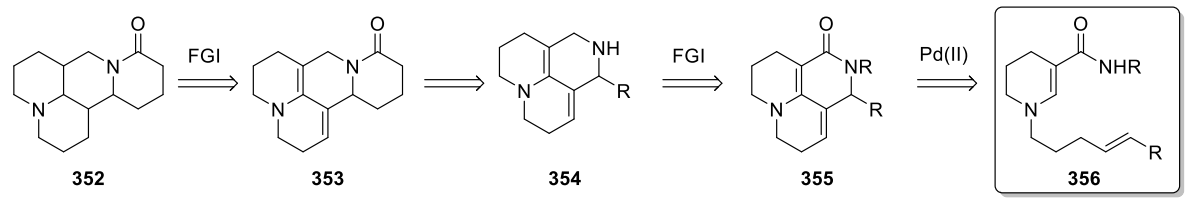


Figure 7. Matrine alkaloids

The matrine alkaloids and their derivatives are therefore considered ideal lead compounds in drug discovery, so the development of efficient syntheses towards such compounds is vital. Previous total syntheses of matrine alkaloids include the synthesis of matrine by Zard using a radical cyclisation methodology,[159] and the synthesis of (+)-allomatrine by Brown using an imino-aldol reaction and *N*-acyliminium cyclisation.[160] The matrine alkaloids are ideal targets for this work as they contain a diaza-tricyclic core that could be accessed using a Pd(II) cascade sequence similar to that described in the previous chapter of this thesis.

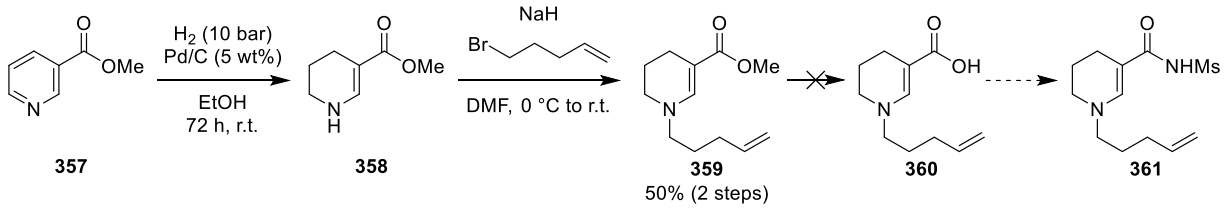
Retrosynthetically, the matrine alkaloid cores could be accessed by the hydrogenation of **353**. A potential route to **353** could be *N*-acylation of **354** followed by a ring closure with an appropriate pendant R group. Structure **354** would be formed from **355** *via* reduction of the amide and removal of the directing group. It is envisaged that the key step in this synthesis would be the Pd(II)-catalysed ring annulation of **356** to give **355**, similar to the Pd(II)-catalysed methodology described previously. Therefore, the initial focus was on developing an efficient and scalable route for the synthesis of substrates in the form of **356**.



Scheme 106. Retrosynthetic analysis of matrine alkaloid core **352**

2.5.1 Substrate synthesis: Reduction of pyridine derivatives

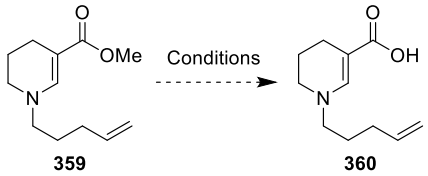
The most obvious route to **361** began with cheap, commercially available methyl nicotinate which could be partially hydrogenated to **358** using Pd/C under H_2 (10 bar) (Scheme 107). This formation of the desired core with a double bond preserved is as a result of the conjugation between the ester group and the *N*-atom which prevents overhydrogenation. Compound **358** was alkylated using the standard alkylation conditions to give **359** in a 50% yield over the two steps.



Scheme 107. Attempted synthesis of **361**

From here it was envisaged that the methyl ester could then be hydrolysed to give the corresponding acid, which would then be used in an amide coupling reaction with methanesulfonamide to afford the desired substrate **361**. Unfortunately, when **359** was treated with aqueous NaOH in MeOH and THF no formation of product **360** was observed (Table 12, entry 1), even after heating at reflux for several days. On increasing the excess of NaOH, decomposition of the starting material was observed (Table 12, entry 4). This lack of success was likely due to the highly electron rich nature of the ester, so acidic conditions were also trialled but again no product was formed (Table 12, entry 7). A variety of other conditions were screened, including Krapcho conditions, but these were also unsuccessful.

Table 12. Screen of conditions for the hydrolysis of **359**



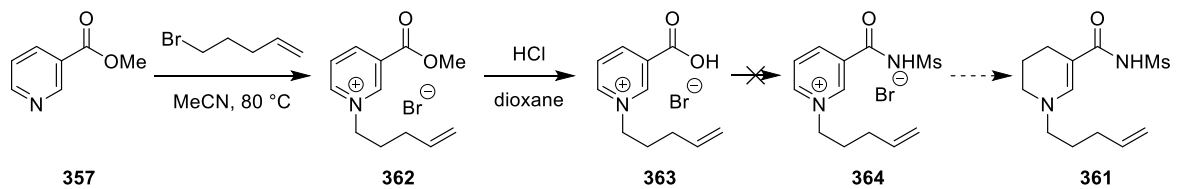
359 **360**

Entry	Conditions	Solvent	Temperature	Time	Yield of 360 (%)	Observations[a]
1	NaOH (10 equiv.)[b]	MeOH/THF	reflux	4 days	0	No reaction
2	KOH (10 equiv.)[b]	MeOH/THF	reflux	4 days	0	No reaction
3	LiOH (10 Equiv.)[b]	MeOH/THF	reflux	4 days	0	No reaction
4	NaOH (40 equiv.)[b]	MeOH/THF	reflux	3 days	0	Decomposition
5	LiCl (5 equiv.)	DMF	150 °C	18 hours	0	No reaction
6	LiCl (3 equiv.)	DMSO	150 °C	18 hours	0	No reaction
7	HCl (1.6 equiv.)[b]	THF	reflux	18 hours	0	Decomposition
8	TFA (14 equiv.)	Water	reflux	3 hours	0	Decomposition

[a]As observed by TLC and ^{1}H NMR analysis [b]As a 2 M aqueous solution

It was though that one way to circumvent this hydrolysis problem would be to perform the reactions in a different order (Scheme 108). Alkylation prior to reduction of the pyridine would result in the formation of pyridinium salt **362**. The electronics of the ester on the pyridinium salt would be very different to that of ester **360** so hydrolysis should be more facile. From here it was thought that the acid could be transformed to the mesylamide by standard amide coupling conditions and then the pyridinium core reduced to the desired 1,4,5,6- tetrahydropyridine core. Reduction using H_2 and Pd/C could be employed as this would also result in the reduction of the tethered alkene, but there are several examples in the literature in which similar systems are reduced using reducing agents such as $NaBH_4$.[161-162]

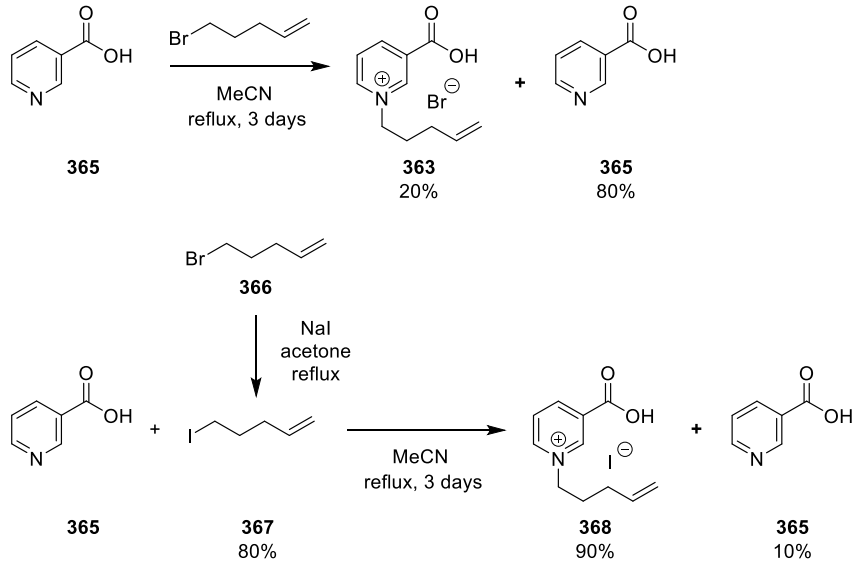
Unfortunately, pyridinium salts **362** and **363** proved difficult to work with, particularly during purification due to their high polarity and high water solubility. By ^{1}H NMR analysis of the crude hydrolysis product the methyl ester peak had disappeared, suggesting the hydrolysis had been successful, but there were many inseparable impurities present.



357 **362** **363** **364** **361**

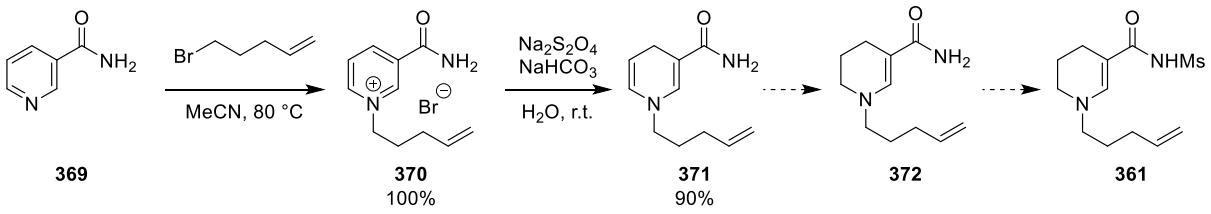
Scheme 108. Attempted synthesis of **361:** change of order of reaction

Instead, nicotinic acid was alkylated directly. It was hoped that this would circumvent any purification issues as once the reaction has gone to completion any solvent and unreacted bromide could simply be evaporated, leaving the pure product without need for aqueous workup or flash column chromatography. The only downside to this approach was that nicotinic acid is less nucleophilic than the methyl ester, so the alkylation reaction was much slower. After refluxing nicotinic acid with 5-bromo-1-pentene for 72 hours the reaction had reached only 20% completion. In order to increase the rate of reaction the bromide was first converted to the iodide using a Finkelstein reaction. Using this iodide, a 90% conversion to the pyridinium salt was observed after 72 hours at reflux. Despite this improvement in yield this route was not continued as there was still a significant amount of inseparable starting material present.



Scheme 109. Alkylation of nicotinic acid

There are many examples in the literature of dithionate reductions of pyridinium salts of nicotinamide and its derivatives.[163-165] Nicotinamide was alkylated by refluxing with 5-bromo-1-pentene in MeCN for 3 days, which gave the pyridinium salt **370** in a quantitative yield. Pyridinium salt **370** was then reacted with sodium dithionate in the presence of sodium hydrogen carbonate to give the corresponding 1,4-dihydropyridine **371** in a yield of 90%. From here it was hoped that this could be further reduced to the desired 1,4,5,6-tetrahydropyridine and then the amide transformed to the mesylamide to give the desired substrate **361** (Scheme 110).

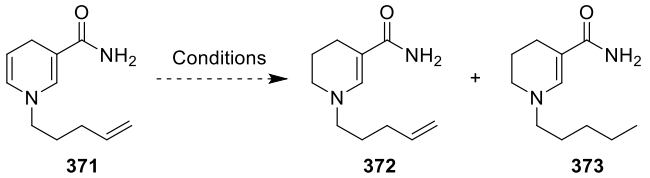


369 **370** 100% **371** 90% **372** **361**

Scheme 110. Attempted synthesis of **361** from nicotinamide

A variety of conditions were trialled for the reduction of the 1,4-dihydropyridine to the 1,4,5,6-tetrahydropyridine (Table 13). The use of sodium triacetoxyborohydride (STAB) with AcOH gave a complex mixture by TLC and ^{1}H NMR of the crude material (Table 13, entry 1). Following flash column chromatography, no product was observed. The amount of STAB and the reaction time were decreased (Table 13, entry 2) to see if a simpler reaction mixture could be observed in order to determine what reactions were occurring, but still a complex mixture, with no discernible products, was seen. Another reducing agent, $NaCNBH_3$, was also trialled (Table 13, entry 3) but once again only a complex mixture was formed. Lastly, literature precedent was found for reduction using $NaBH_4$ and $NiCl_2.6H_2O$.[166] Indeed, under these conditions the desired 1,4,5,6-tetrahydropyridine core was formed (Table 13), but unfortunately the tethered alkene was also reduced, giving **373** in a yield of 26%. The amount of $NaBH_4$ and $NiCl_2.6H_2O$ were reduced (Table 13, entry 4) in the hope that using only 1 equiv. of reducing agent would result only in the selective reduction of the tetrahydropyridine. Again, only the over reduced compound **373** was observed. The amount of reducing agent was reduced further (Table 13, entry 5), but this resulted in a complex mixture, still including the undesired product **373**.

Table 13. Reduction of 1,4-dihydropyridine **371**



371 **372** **373**

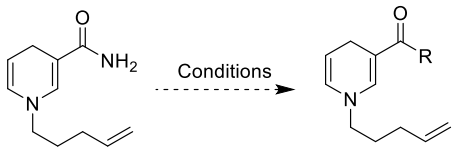
Entry	Conditions	Solvent	Temperature	Time	Yield of 372 (%)	Observations[a]
1	STAB (4 equiv.), AcOH (2 equiv.)	DCM	r.t.	48 hours	0	Complex mixture
2	STAB (1 equiv.), AcOH (2 equiv.)	DCM	r.t.	4 hours	0	Complex mixture
3	$NaCNBH_3$ (1.5 equiv.), AcOH (drop)	MeOH	r.t.	4 hours	0	Complex mixture
4	$NiCl_2.6H_2O$ (1 equiv.), $NaBH_4$ (4 equiv.)	MeOH	r.t.	3 hours	0	26% **373**
5	$NiCl_2.6H_2O$ (0.3 equiv.), $NaBH_4$ (1 equiv.)	MeOH	r.t.	3 hours	0	**373**
6	$NiCl_2.6H_2O$ (0.05 equiv.), $NaBH_4$ (0.5 equiv.)	MeOH	r.t.	3 hours	0	Complex mixture, including **373**

[a]As observed by TLC and ^{1}H NMR analysis

Attention was then turned to the dihydropyridine core. If the sulfonamide directing group could be installed then this may itself serve as a suitable substrate for Pd(II)-catalysis, without need for further reduction. A range of literature conditions were trialled for the installation of the sulfonamide group (Table 14). The use of the literature conditions KOH, TBAHS and K_2CO_3 followed by MsCl[167] were employed (Table 14, entry 1), but in the ^{1}H NMR of the crude material no dihydropyridine peaks were present, suggesting the starting material had degraded. The use of the stronger base NaH with TsCl under heating[168] was trialled (Table 14, entry 2), but only TsCl was recovered from the reaction mixture. A search of the literature found that 1,4-dihydropyridines are known to degrade at elevated temperatures,[169] so the reaction was repeated without heating for a much shorter reaction time (Table 14, entry 3). Still only TsCl was recovered from the reaction mixture. It was thought that NaH as a base may be too strong, so the reaction was attempted with the much weaker base Na_2CO_3 (Table 14, entry 4). Again, no dihydropyridine peaks were present in the ^{1}H NMR of the crude material. Instead of reacting the primary amide directly to form the *N*-acyl sulfonamide, hydrolysis of amide to the corresponding acid using NaOH was attempted (Table 14, entry 6). By ^{1}H NMR of the crude material a complex mixture was observed, with no obvious product peaks. From these results it appears that the 1,4-dihydropyridine core is highly unstable, so even if conditions were found in which the sulfonamide

directing group could be successfully installed it is unlikely that it would survive the likely high temperature of the Pd(II)-catalysed cyclisation.

Table 14. Reaction of primary amide



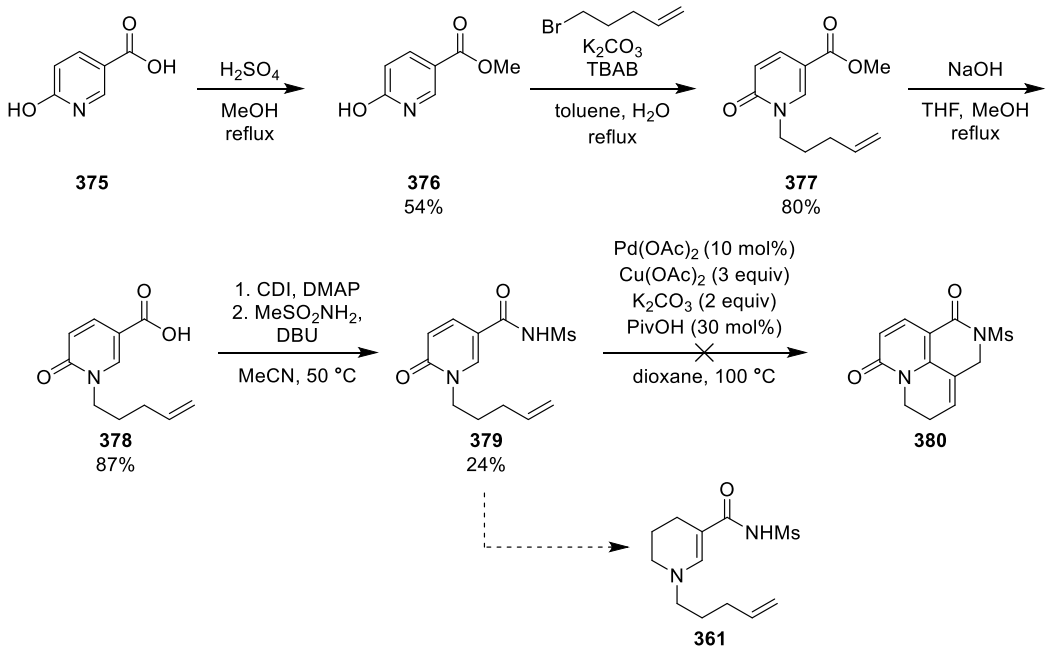
371 374

Entry	Conditions	R	Solvent	Temperature	Time	Yield of 374 (%)	Observations[a]
1	KOH, TBAHS, K_2CO_3, MsCl	NHMs	THF	55 °C	20 hours	0	No DHP peaks
2	NaH, TsCl	NHTs	THF	55 °C	20 hours	0	Only TsCl recovered
3	NaH, TsCl	NHTs	THF	r.t.	3.5 hours	0	Only TsCl recovered
4	Na_2CO_3, TsCl	NHTs	water, acetone	r.t.	20 hours	0	No DHP peaks
5	NaHMDS, MsCl	NHMs	THF	r.t.	20 hours	0	No Ts or DHP peaks
6	KOH	OH	MeOH, THF	reflux	20 hours	0	Mess

[a]As observed by TLC and ^{1}H NMR analysis

An alternative approach was to construct a substrate around a pyridone core. Such structures were easily accessible from 5-hydroxynicotinic acid **375** (Scheme 111). Following esterification to give **376**, the hydroxypyridine core was alkylated to give the *N*-alkylated pyridone **377** in an excellent yield of 80%. Hydrolysis of the methyl ester was then feasible due to the distinct electronic properties of the pyridone core compared to the 1,4,5,6-tetrahydropyridine core of **360**. Acid **378** was subjected to the standard amide coupling conditions to give the *N*-mesylamide substrate **379**. When **379** was subjected to the standard cyclisation conditions no cyclised product was observed, only decomposition. This result was unsurprising because the C6 position of pyridones is the most electron deficient position, and therefore not nucleophilic enough C–H activation.[170] While several transition metal catalysed Heck reactions have been reported at the C6 position[171-172] there are no examples using palladium, which prefers to react at the C3 and C5 positions.[173-174]

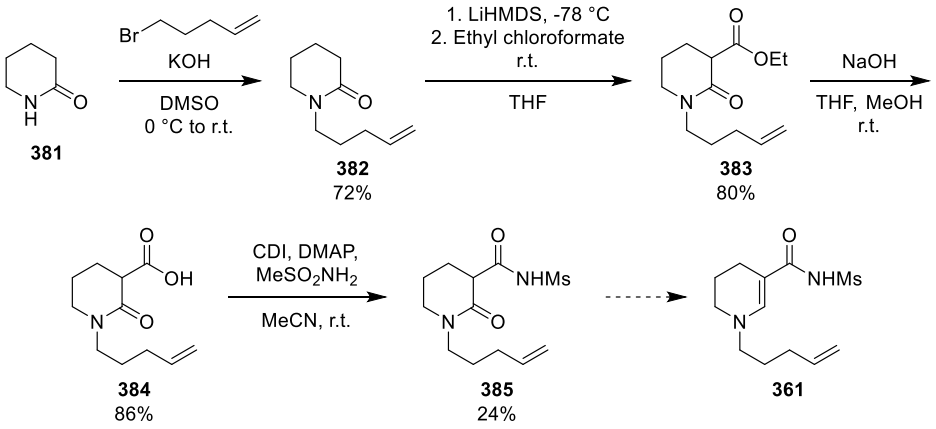
The ideal scenario would have been to reduce the 4,5-carbon-carbon double bond and the pyridine carbonyl to give the desired substrate. Unfortunately, following a search of the literature, attainment of this selectivity was deemed too challenging due to the presence of a number of other reducible functional groups.



Scheme 111. Synthesis and attempted cyclisation of 2-pyridone substrate **379**

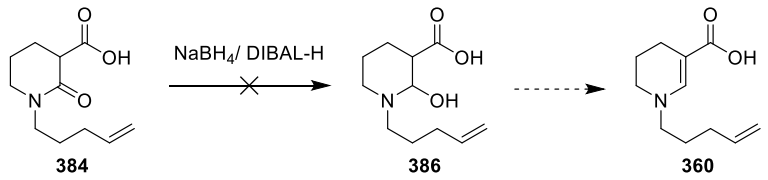
2.5.2 Substrate synthesis: Lactam reduction

An alternative route to the desired tetrahydropyridine substrate **361** was proposed, starting from δ-valerolacram (Scheme 112). It was envisaged that the carbonyl group at the 2-position of the ring would allow the hydrolysis step to occur, but then would be able to be reduced and then eliminated to give the desired double bond formed in a straightforward manner. δ-Valerolacram was alkylated using KOH in DMSO to give lactam **382** in a 72% yield. The ester moiety was then installed by treatment of **382** with LiHMDS and ethyl chloroformate in THF to give **383** in an excellent yield of 80%. As expected, the ethyl ester was hydrolysed successfully using the standard hydrolysis conditions; NaOH (as a 2 M aqueous solution) in THF and MeOH. Acid **384** then underwent an amide coupling reaction to give *N*-mesylamide **385**.



Scheme 112. Attempted synthesis of **361** from δ-valerolactam

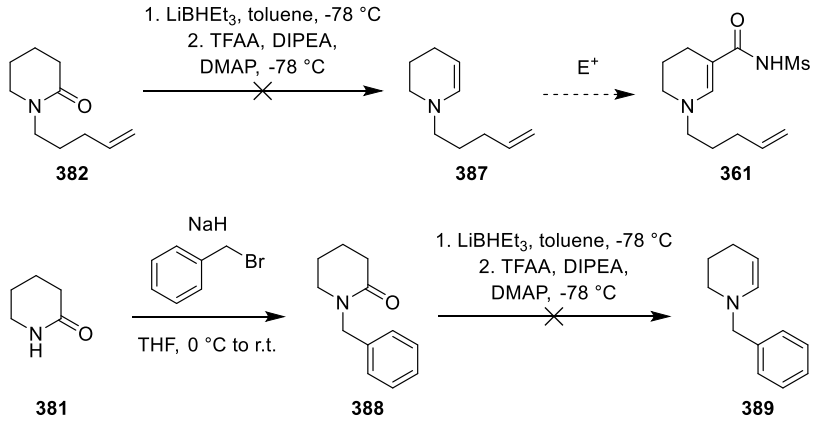
From here it was hoped that the desired substrate **361** would be formed by reduction of the carbonyl followed by elimination of the generated alcohol to give the desired carbon-carbon double bond (Scheme 113). Substrate **385** was reacted with $NaBH_4$ in MeOH. Unfortunately, the desired alcohol was not formed. In the ^1H NMR of the crude material there was no mesyl proton peak, and no obvious CH proton peak formed, suggesting that desired reduction had not occurred but the sulfonamide group had been removed. Because of this undesired reactivity of the mesylamide future reductions were performed on acid **384**. Again, $NaBH_4$ was trialled. By TLC no reaction was observed and after 20 hours the reaction was worked up but only a small mass recovery was obtained, with no appreciable peaks in the ^1H NMR. DIBAL was then trialled, and while a greater mass was obtained there were still no discernible peaks in the ^1H NMR. The material was reacted with H_2SO_4 in Et_2O in case it was the desired alcohol but following workup no material was recovered.



384 **386** **360**

Scheme 113. Attempted reduction/elimination sequence of **383**

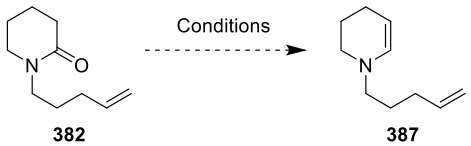
Literature conditions were found in which a benzyl-protected lactam is reduced using lithium triethylborohydride and the resulting alcohol eliminated using DMAP, DIPEA and TFAA.[175] It was thought that these conditions would also work for *N*-pentenyl lactam. It was hoped that the resulting enamine **387** could then be reacted with an electrophile to furnish the substrate at the 3-position (Scheme 114). *N*-Pentenyl lactam was subjected to the exact literature conditions, but by ^1H NMR only starting material was observed. The reaction was repeated, but stirred with lithium triethylborohydride for longer, however still no reaction was observed. The literature conditions were then repeated, with the literature substrate *N*-benzyl lactam **388**. This literature reaction was found to be irreproducible, with only starting material observed.



Scheme 114. Literature procedure for the reduction/elimination of lactams

A number of other reducing agents were trialled on the *N*-pentenyl substrate **382**, including DIBAL, but for all conditions only starting material was observed.

Table 15. Conditions for the reduction/elimination of **382**

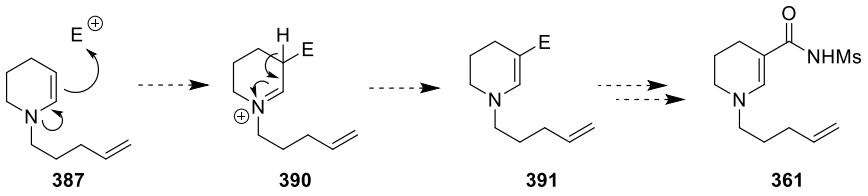


Entry	Conditions	Solvent	Temperature	Yield of 381 (%)	Observations[a]
1	1. $LiBHEt_3$ (1.05 equiv.) 2. DMAP (0.02 equiv.), DIPEA (5.7 equiv.), TFAA (1.2 equiv.)	toluene	-78 °C	0	SM
2	$LiBHEt_3$ (1.05 equiv.)	toluene	-78 °C	0	SM
3	DIBAL-H	DCM	-78 °C	0	SM
4	KO^tBu (0.05 equiv.), $Si(EtO)_3H$ (4 equiv.)	THF	65 °C	0	SM

[a]As observed by TLC and ^1H NMR analysis

2.5.3 Substrate synthesis: Electrophilic attack on enamine

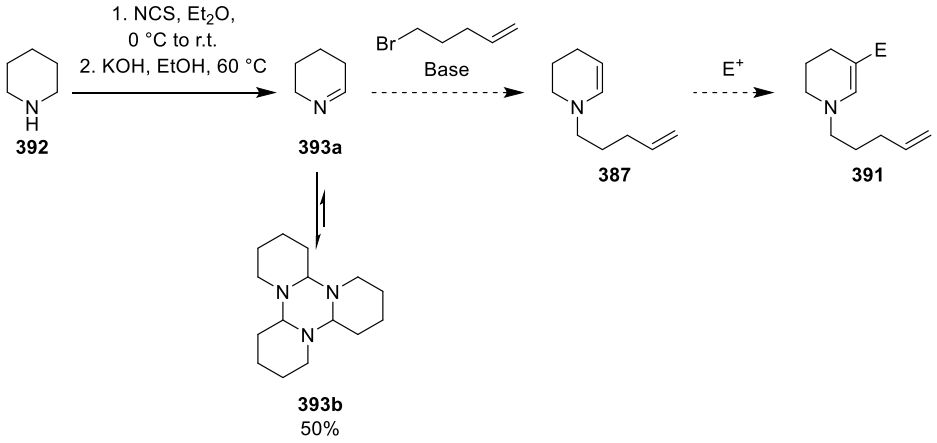
As mentioned previously, if enamine **387** could be accessed reaction with an electrophile may introduce functionality at the 3-position of the ring (Scheme 115). An electrophile such as TFAA would install a trifluoroacetyl group at the 3-position. This could then be hydrolysed and then coupled with an amine to give the *N*-acyl sulfonamide. Alternatively, a reaction with tosyl isocyanate would directly install the *N*-acyl sulfonamide directing group at the 3-position. Synthesis of enamine **387** was therefore targeted.



Scheme 115. Installation of 3-substituent by electrophilic attack

Imine **393a** was synthesised by reaction of piperidine with NCS, followed by KOH, which gave a yield of 50%. This imine exists in an equilibrium with the trimer **393b**. It was hoped that this imine could then be reacted with 5-bromo-1-pentene in the presence of base to install the tethered alkene and result in the desired enamine **387**. Following workup only peaks from the tethered alkene were observed in the ^{1}H NMR. This could be as a result of degradation of the generated enamine, so the reaction was repeated with tosyl isocyanate as an electrophile added *in situ* to see if any desired product could be generated. This was trialled with and without base. In the presence of base, a complex mixture was observed, with the major product being an undesired derivative of tosyl isocyanate, without base only tosyl proton peaks were observed. The reaction was trialled using MeI instead of 5-bromo-1-pentene, as it is a much stronger electrophile, to see if the reaction could work, but still no product was observed.

Table 16. Alkylation conditions

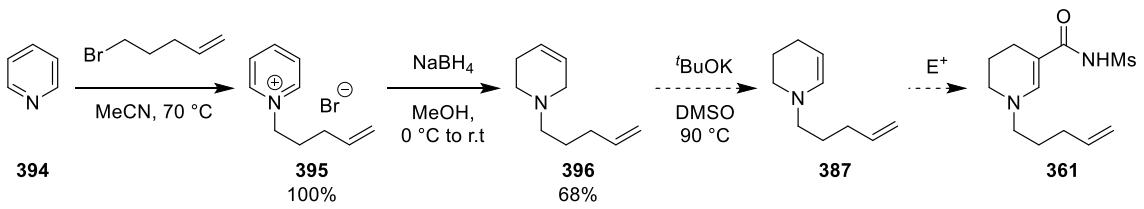


Entry	Conditions	Yield of 387 (%)	Observations[a]
1	5-Bromo-1-pentene, NEt_3, DMF	0	5-bromo-1-pentene peaks only
2	1. 5-Bromo-1-pentene, NEt_3, DMF 2. TsNCO	0	Complex mixture, mainly Ts
3	1. 5-Bromo-1-pentene, DMF 2. TsNCO	0	Just Ts peaks
4	MeI, NEt_3, DMF	0	No peaks in ^{1}H NMR

[a]As observed by TLC and ^{1}H NMR analysis

An alternative route to enamine **387** was devised starting from pyridine. Pyridine was alkylated by refluxing with 5-bromo-1-pentene in MeCN, which gave pyridiunium salt **395** in a quantitative yield. Reduction with $NaBH_4$ gave the 1,2,5,6-tetrahydropyridine **396** in a yield of 68%. A search of the literature found that stirring with ^{t}BuOK in DMSO should lead to isomerisation of the double bond to give the desired 1,4,5,6-tetrahydropyridine.[176] **396** was stirred at 90 °C with ^{t}BuOK in DMSO. After two days analysis by TLC suggested most of the starting material had reacted so 1 equiv. of tosyl isocyanate was added. Following work up, a mass spec of the crude mixture was taken, but no mass peaks corresponding to the desired product were present.

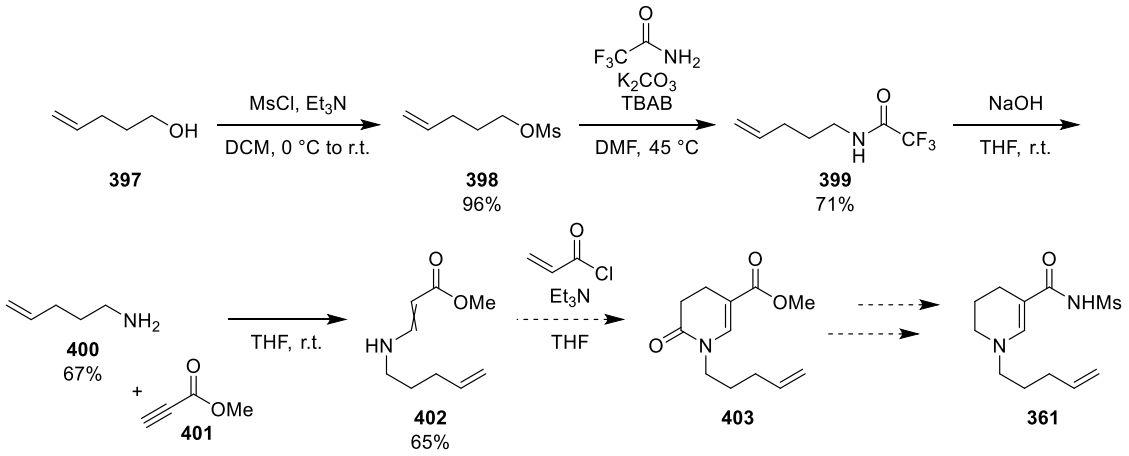
At this point, a route based on the electrophilic attack on a cyclic enamine was abandoned, as it appeared that the enamine was too unstable to be isolated and/or undergo subsequent reactions.



Scheme 116. Attempted synthesis of **361** from pyridine

2.5.4 Substrate synthesis: Construction of ring

The final route towards the synthesis of substrate **361** attempted involved construction of the 6-membered ring. This route had previously been undertaken by another member of the group but using a tethered diene instead of the tethered alkene, from which a 2% yield of the diene substrate was obtained over 6 steps.[131] The synthesis of the alkene derivative began with the mesylation of 4-penten-1-ol using standard the standard mesylation conditions, which gave mesylate **398** in an excellent yield of 96%. Mesylate **398** was reacted with trifluroacetamide under phase transfer conditions to give the secondary trifluoroacetamide **399**, which was hydrolysed to give amine **400**. The yield of this hydrolysis was lower than anticipated due to the low boiling point of the product. A Michael addition of amine **400** and methyl propiolate gave **402**. Unfortunately, despite the reasonable yield of 65%, this reaction gave the undesired *cis* alkene as the major product (*cis*:*trans* 75:25). The synthetic aim was to then react **402** with acryloyl chloride to construct the ring, which would make the desired 1,4,5,6-tetrahydropyridine with an ester group in the 3-position. Under these conditions, by ^{1}H NMR analysis, it appeared that some product had been formed. However due to the low yields this route was abandoned as the selectivity of the Michael addition meant that it would be challenging and/or wasteful to bring enough material through to make enough of the final substrate **404**.



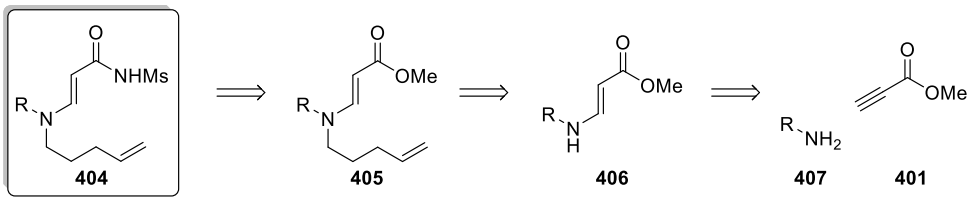
Scheme 117. Synthesis of substrate **361** by construction of core

2.6 Enamine-type test substrates

2.6.1 Substrate Synthesis

Due to the challenges associated with the synthesis of substrate **362** it was decided that attention should be turned to the synthesis of a test substrate in order to investigate whether or not the Pd(II)-catalysed C–H activation of non-aromatic substrates would be feasible. It was envisaged that the synthesis of a non-cyclic derivative would be more facile. Enamine-type substrates in the form of **404**

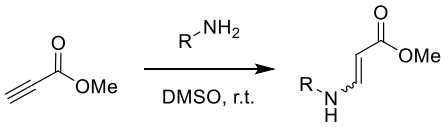
were targeted as they still contain an *N*-tethered alkene, the carbon-carbon double bond and the *N*-acyl mesylamide directing group. All that was needed was to establish the best substituent to have on the nitrogen. To obtain substrates in the form of **404**, **404** could be accessed by the functional group interconversion of **405**, which itself could be made by the alkylation of **406**. **406** is the product of a Michael addition reaction between methyl propiolate and a primary amine.



Scheme 118. Test substrate **404** and its retrosynthesis

The first aim was to investigate the Michael addition reaction, as it had the potential to form both the *cis* and *trans* isomers and only the trans isomer was desired. A range of primary amines were screened in order to see which gave the best selectivity (Table 17). In general, a preference for the *trans* stereoisomer was observed with roughly a 70%:30% *trans*:*cis* ratio calculated for most amines. There was a slight trend, in that a higher percentage of *trans* was observed for amines with smaller alkyl groups. Methylamine and ethylamine could not be used as in their pure form due to their low boiling points, so they had to be used in solution or as the hydrochloride (Table 17, entries 1-3). For both the use of the hydrochloride resulted in an unclear ^{1}H NMR spectrum. A solution of methylamine in EtOH gave a clean ^{1}H NMR spectrum and gave the highest ratio of the desired *trans* product. As shown previously, 4-pent-1-amine gave the *cis* isomer as the major product. It is unclear why there is such a large shift in selectivity when switching from the butylamine to the pentenylamine. *p*-Toluenesulfonamide, benzamide and acetamide were also trialled (Table 17, entries 8-10), but no reaction was observed. From these results methyl group was chosen as the best nitrogen substituent.

Table 17. *trans*:*cis* ratios of Michael addition products

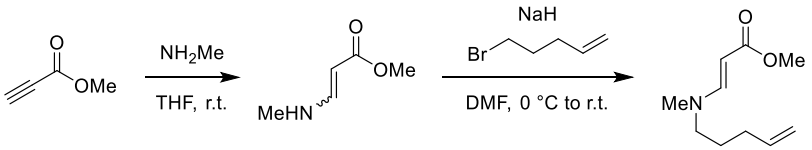


401 **406**

Entry	Amine	Solvent	*Trans*:Cis	Observations[a]
1	$MeNH_2$.HCl	MeCN	77:23	Messy
2	$MeNH_2$ (33% in EtOH)	THF	85:15	Clean
3	$EtNH_2$.HCl	MeCN	70:30	Messy
4	$^{i}PrNH_2$	DMSO	70:30	Clean
5	$BuNH_2$	THF	68:32	Clean
6	$BuNH_2$	DMSO	72:28	Clean
7	4-Penten-1-amine	THF	25:75	Clean
8	*p*-Toluenesulfonamide	DMSO	NA	No reaction
9	Benzamide	THF	NA	No reaction
10	Acetamide	THF	NA	No reaction

[a]As observed by TLC and ^{1}H NMR analysis

The next step was to alkylate the Michael addition product **406a**. Using the standard alkylation conditions of NaH and 5-bromo-1-pentene in DMF a 91% yield of **405a** was obtained. Interestingly only the desired *trans* stereoisomer was observed. This suggested that during the reaction the *cis* isomer isomerised to the desired *trans* isomer.

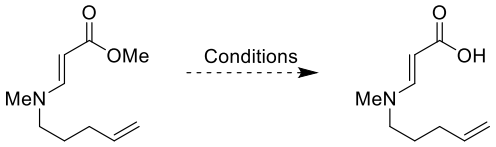


401 **406a** 76% **405a** 91%

Scheme 119. Synthesis of **405a**

From here it was thought that a functional group interconversion to transform the methyl ester to the acid and then to the mesylamide would complete the synthesis of **404a**. However, as experienced before with the cyclic derivative (cf. Table 12, page 91), hydrolysis of the methyl ester proved challenging. As before a range of conditions were trialled. Under basic and acidic conditions no reaction occurred, and only clean starting material was recovered. Using Krapcho conditions a complex mixture was observed by ^{1}H NMR (Table 18).

Table 18. Screen of conditions for the hydrolysis of **405a**

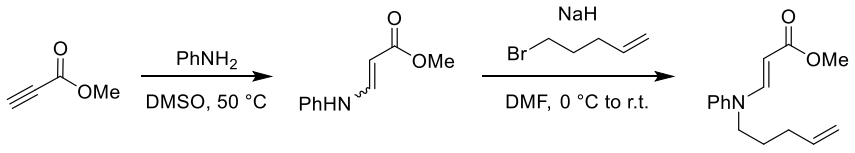


405a **408a**

Entry	Conditions	Yield of 408a (%)	Observations[a]
1	LiOH	0	Clean SM
2	NaOH	0	Clean SM
3	HCl	0	Clean SM
4	LiCl	0	Messy

[a]As observed by TLC and ^{1}H NMR analysis

A substrate was then synthesised bearing a phenyl substituent on the nitrogen instead of the methyl group. A phenyl group is electron-withdrawing by induction, so should take some of the electron density away from the methyl ester, making it more susceptible to base-catalysed hydrolysis. It was therefore hoped that this change in electronics would allow the ester hydrolysis step to occur. The phenyl derivative **406b** was again accessed from a Michael addition reaction. The resulting mixture of *cis* and *trans* isomers was subjected to the standard alkylation conditions, and pleasingly only the desired *trans* product was obtained, in a yield of 77%.

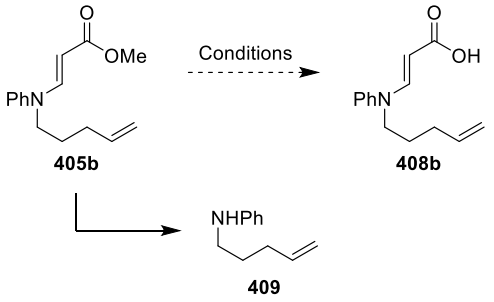


401 **406b** 93% **405b** 77%

Scheme 120. Synthesis of **405b**

As before, basic, acidic and Krapcho conditions were trialled for the hydrolysis of methyl ester **405b**. Under Kraphco conditions a complex mixture was observed. Under basic and acidic conditions **405b** was hydrolysed, but adjacent to the nitrogen, giving **409** (Table 19).

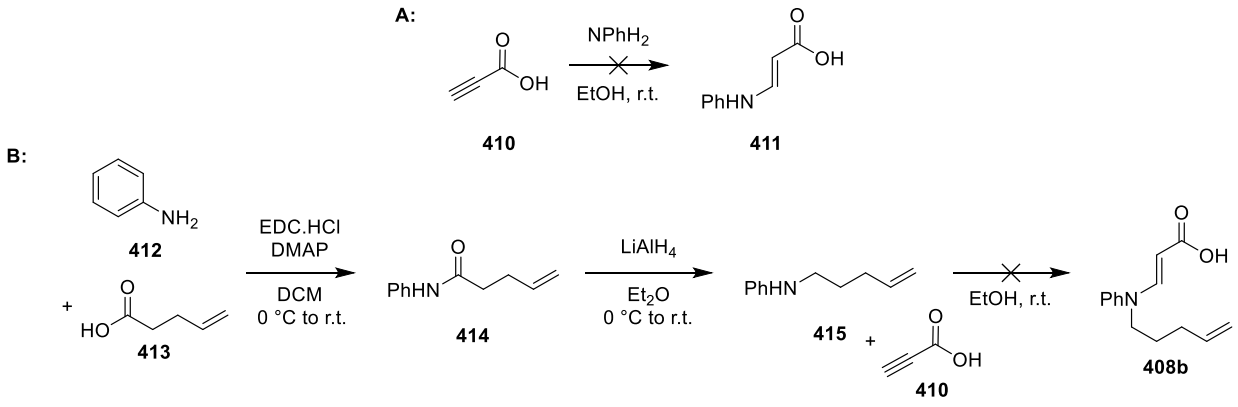
Table 19. Screen of conditions for the hydrolysis of **405b**



Entry	Conditions	Yield of 408b (%)	Observations[a]
1	NaOH	0	**409**
2	HCl	0	**409**
3	LiCl	0	Messy

[a]As observed by TLC and ^{1}H NMR analysis

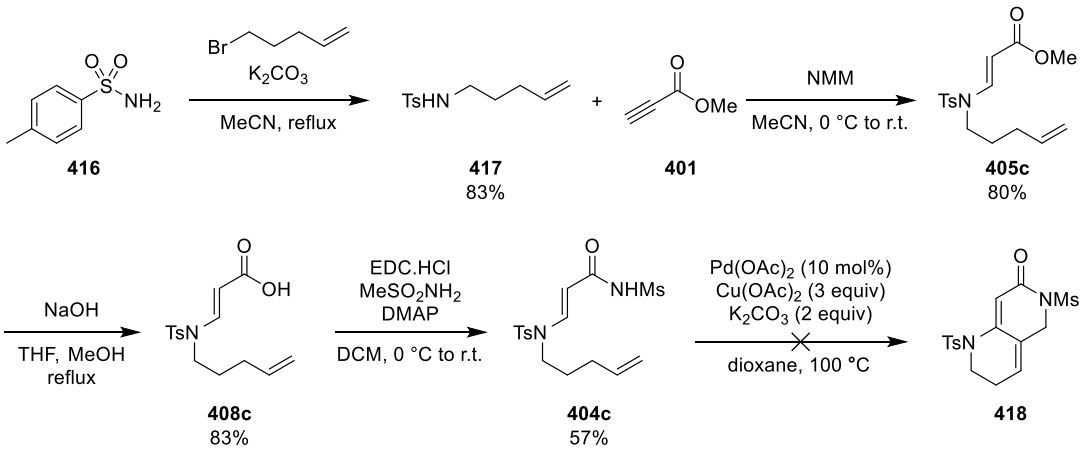
To remove the need for the hydrolysis step, the Michael addition was attempted using propiolic acid (Scheme 121A). Unfortunately, only a complex ^{1}H NMR spectrum was observed, containing no alkene peaks. The secondary amine **414** was synthesised by an amide coupling reaction between aniline and 4-pentenoic acid, followed by reduction using $LiAlH_4$ to give **415**. This secondary amine was also subjected to the Michael addition reaction conditions with propiolic acid but still no product was obtained (Scheme 121B).



Scheme 121. Attempted Michael addition reactions with propiolic acid

Due to the lack of success in the synthesis of substrates bearing alkyl and aryl substituents on the nitrogen, a substrate with tosyl group on nitrogen was then targeted. As seen previously the Michael addition doesn't work with *p*-toluenesulfonamide, so a secondary sulfonamide was synthesised as it should be more nucleophilic, making the Michael addition reaction more likely. To make the secondary sulfonamide, *p*-toluenesulfonamide was alkylated with 5-bromo-1-pentene using K_2CO_3 in MeCN. This gave **417** in an excellent yield of 83%. Pleasingly, **417** underwent the Michael addition reaction to give

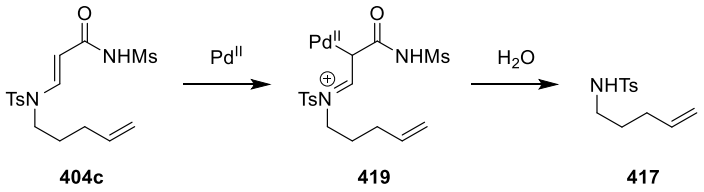
solely the desired *trans* product **405c** with a yield of 80%. **405c** was then readily hydrolysed using NaOH and then converted to the desired *N*-acyl sulfonamide **404c** by amide coupling.



Scheme 122. Synthesis of and attempted cyclisation **404c**

2.6.2 Pd(II)-Catalysed cyclisation of test substrate

The tosyl substrate **404c** was subjected to standard Pd(II)-catalysed cyclisation conditions (Scheme 122). The pivalic acid additive was omitted as it is known to not be vital for reaction to occur, so as to minimise the number of variables. No formation of the desired cyclisation product occurred, instead the hydrolysed derivative **416** was formed. It is thought that this occurred because the palladium catalyst can act as a Lewis acid to generate imine **419** which can then be hydrolysed by any trace amounts of water present in the reaction mixture.



Scheme 123. Hydrolysis of **404c**

To avoid this hydrolysis, all traces of water needed to be eliminated from the reaction mixture. Several methods for drying the reaction mixture were investigated. 1 equiv. of the chemical drying agent Ac_2O was added to the reaction mixture, prior to substrate addition, and the mixture stirred for 5 minutes. After 16 hours at 100 °C the ^1H NMR of the crude material revealed that indeed the addition of Ac_2O appeared to suppress the hydrolysis of the starting material. In the absence of Ac_2O there was no starting material present at the end of the reaction, but with 1 equiv. of Ac_2O there was some starting material left, along with some of the hydrolysed starting material and one other unknown derivative. The presence of these compounds could be monitored by looking at the aromatic region of the ^1H NMR's of the crude reaction mixtures (Figure 8). Pleasingly, when the amount of Ac_2O was increased

to 3 equiv., only unreacted starting material was observed. Molecular sieves were also trialled, but they were not as effective as Ac_2O.

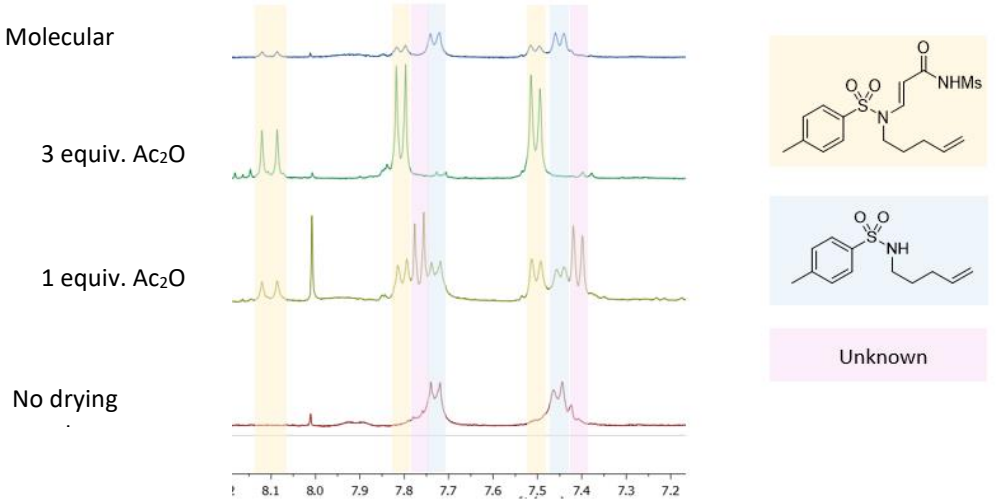
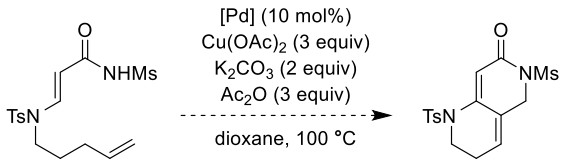


Figure 8. Comparison of aromatic region of ^{1}H NMR for different drying agents.

Having solved the hydrolysis problem, screening of reaction conditions was begun to see if any formation of the desired cyclisation product could be achieved. The first variable to be investigated was the source of palladium. A variety of palladium catalysts were screened, including more electrophilic sources of palladium such as $Pd(TFA)_2$. Unfortunately, no formation of the desired cyclisation product was observed for any of the catalysts trialled. TLC and ^{1}H NMR analysis of all reactions showed only unreacted starting material. $Pd(OAc)_2$ was kept as the catalyst of choice because it resulted in the least amount of starting material degradation.

Table 20. Palladium screen



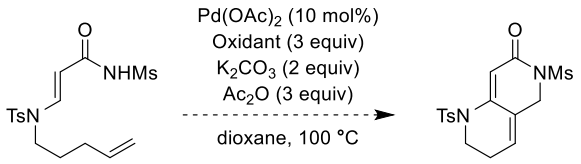
404c **418**

Entry	Pd Catalyst	Yield of 417 (%)[a]	Unreacted 404c (%)[a]
1	$Pd(OAc)_2$	0	58
2	$Pd(MeCN)_2(OTs)_2$	0	50
3	$Pd(TFA)_2$	0	45
4	$PdCl_2$	0	32
5	$[Pd(allyl)Cl]_2$	0	50
6	$Pd(MeCN)_2Cl_2$	0	46

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard

An oxidant screen was then carried out to see if improving the catalytic turnover could result in the formation of product. When $Cu(OAc)_2$ was swapped for AgOAc a higher amount of unreacted starting material remained, but there were unidentifiable impurities present. The common oxidant BQ was trialled, as was the bulky derivative 3,5-di^{t}Bu *p*-BQ but neither yielded any product. The stronger oxidant IBX was trialled to see if a Pd(II)/Pd(IV) pathway could be encouraged, but again no product was formed.

Table 21. Oxidant screen



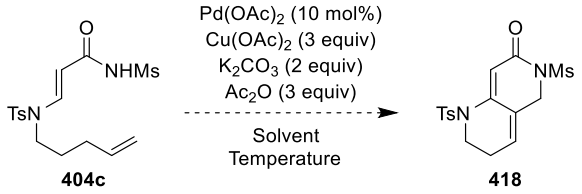
404c **418**

Entry	Oxidant	Yield of 417 (%)[a]	Unreacted 404c (%)[a]	Observations[a]
1	$Cu(OAc)_2$	0	58	-
2	AgOAc	0	82	Unidentified impurities
3	*p*-BQ	0	-[b]	-
4	3,5-^{t}Bu *p*-BQ	0	74	Some loss of Ms
5	IBX	0	60	Unidentified impurities

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard [b]Internal standard overlapped with BQ derivative so mass recovery could not be calculated by ^{1}H NMR

It is known that a change in solvent can drastically affect the outcome of a reaction. A number of solvents were screened, including the higher boiling point solvents DMF and DMSO so the reaction could be heated to a higher temperature (Table 22). Unfortunately, only starting material was observed for all solvents. It was expected that an increase in temperature would encourage either the product to form, the formation of another species, or increase the decomposition process by which the starting material was being lost. In fact, when the temperature was raised the amount of remaining starting material was higher, with no products observed.

Table 22. Solvent and temperature screen

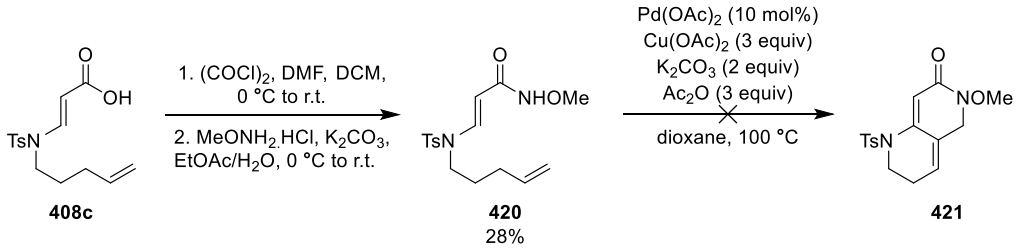


Entry	Solvent	Temperature	Yield of 418 (%)[a]	Unreacted 404c (%)[a]
1	DMF	100 °C	0	42
2	DMSO	100 °C	0	72
3	DMF	120 °C	0	65
4	DMSO	120 °C	0	77
5	THF	60 °C	0	56
6	toluene	100 °C	0	41

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard

2.6.3 Change of directing group

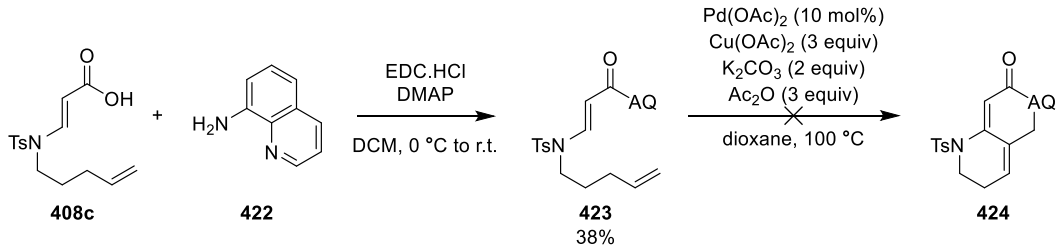
For Pd(II)-catalysed indole and pyrrole cyclisation methodology *N*-acyl mesylamide was an effective directing group. Other directing groups were trialled for the enamine-type substrates to see if there was a more suitable directing group for these substrates. The directing groups must still have been secondary amides to have the N–H available for aza-Wacker reaction. *N*-Alkoxy amide directing groups, such as *N*-methoxy amide, are known to be versatile directing groups.[48] The *N*-methoxy amide was easily accessed from the acid **408c** (Scheme 124). **408c** was first reacted with oxalyl chloride to form the acid chloride, which was then reacted with methoxy amine hydrochloride to give **420** in a yield of 28%. Despite the poor yield enough material was generated to trial the cyclisation reaction. Unfortunately, under the standard cyclisation conditions no cyclised product **421** was formed.



Scheme 124. Synthesis and attempted cyclisation of *N*-methoxy amide substrate **420**

There is also much literature precedent for the 8-aminoquinoline directing group.[52] This could be a more effective directing group as the two nitrogen atoms allow it to act as a bidentate directing group thus binding and delivering the Pd(II) catalyst more efficiently. The 8-aminoqinoline group possesses a relatively acidic N–H bond, so deprotonation and coordination to Pd should have been able to occur. Again, this substrate could be made from acid **408c**, this time using standard amide coupling

conditions (Scheme 125). This gave **423** in a yield of 38%. Under the standard cyclisation conditions, no product was observed.

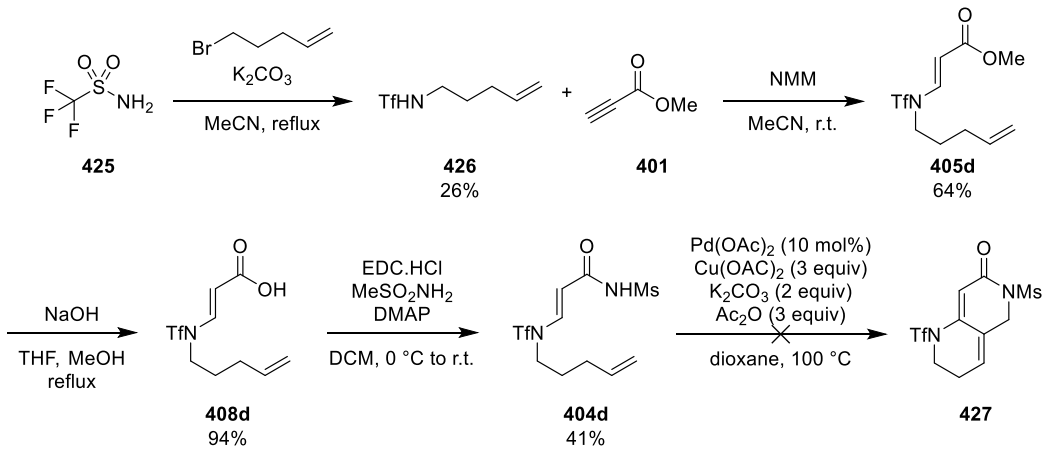


Scheme 125. Synthesis and cyclisation of 8-aminoquinoline substrate **422**

2.6.4 Change of *N*-substituent

At this stage, no C–H activation of the enamine-type substrate had been achieved. The next step was to investigate a change in *N*-substituent as this would change the electronics of the substrate and was expected to make the C–H bond more reactive.

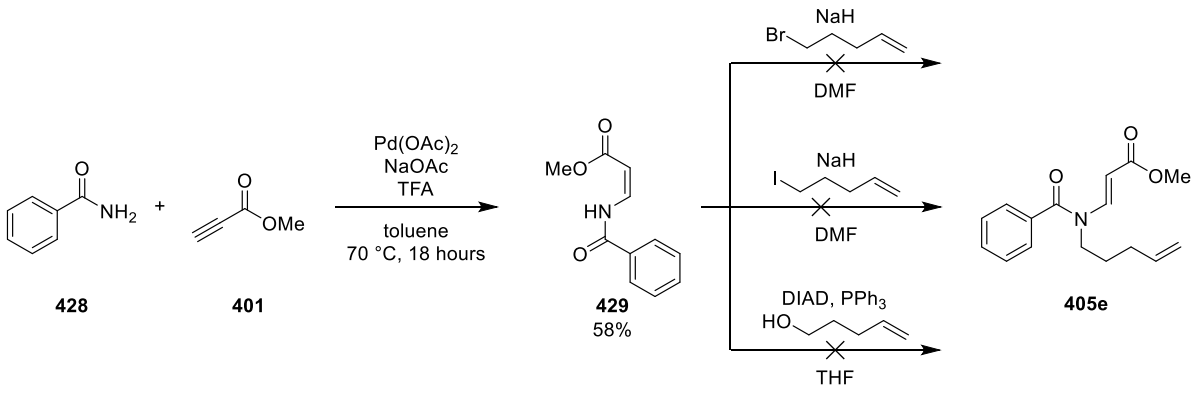
One substrate that was easily synthesised was one with a triflyl group on the nitrogen. This was made in the same way as the tosyl substrate. Reaction of trifluoromethanesulfonamide with 5-bromo-1-pentene gave the secondary sulfonamide **426**. The yield obtained was lower than that of tosyl derivative **416** as a triflyl group is more electron-withdrawing, so the reaction was more susceptible to dialkylation. The subsequent Michael addition, ester hydrolysis and amide coupling reactions proceeded in moderate to excellent yields to give the triflyl-substituted substrate **404d**. When **404d** was subjected to standard cyclisation conditions the desired cyclisation product was not formed. This result was unsurprising as the electron-withdrawing nature of triflyl removes electron density from the C–H bond making it less likely to be activated by the electrophilic Pd(II) catalyst.



Scheme 126. Synthesis of triflyl substrate **404d**

A substrate with a *N*-substituent less electron withdrawing than tosyl and triflyl was desired. As described previously substrates with methyl and phenyl substituents were inaccessible. The synthesis of an acetyl or benzoyl derivative was targeted as, despite still being electron-withdrawing groups, they are less electron withdrawing than tosyl and triflyl.

The Michael addition reaction of the primary amides acetamide and benzamide with methyl propiolate did not yield any product (Table 17, entries 9 and 10, page 103), due to the low nucleophilicity of these amides. A reaction was found in literature in which benzamide could be added to methyl propiolate using Pd catalysis. This reaction allowed **429** to be formed with a yield of 58%. However, instead of the desired *trans* product, only the *cis* isomer was formed. Previously it was found that upon alkylation the *cis* isomers isomerised to the desired trans-isomers, so it was hoped that following alkylation the desired *trans* product would be obtained. First the standard alkylation conditions of NaH and 5-bromo-1-pentene in DMF were trialled. The reaction was monitored by TLC, but no reaction was observed. After 1 week the reaction mixture was worked up and analysis by ^{1}H NMR showed a complex mixture, with no appreciable amount of the desired product. Due to this lack of reactivity, the reaction was repeated but with the iodide instead of the bromide. Again, no reaction was observed by TLC and by ^{1}H NMR of the crude material mainly unreacted starting material was present. In a distinct approach, Mitsunobu conditions were also trialled but once again a complex mixture was observed by ^{1}H NMR, with the major component being unreacted starting material.

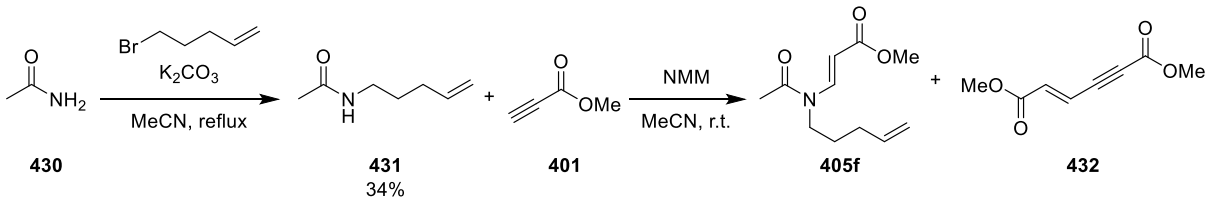


Scheme 127. Attempted synthesis of **405e**

Attention was then turned back to the use of a Michael addition reaction. When making the tosyl derivative the Michael addition reaction did not work for the primary sulfonamide but did for the secondary sulfonamide. The secondary amide **431** was synthesised to see if this was also the case for acetamide and its derivatives. Amide **431** was obtained by the alkylation of acetamide with 5-bromo-1-pentene using K_2CO_3 as a base which gave a yield of 34%. This low yield was due to the high proportion of the over alkylated by-product. The secondary amide **431** was stirred with methyl propiolate in the presence of *N*-methyl morpholine. In the ^{1}H NMR of the crude material the desired

product was present, along with unreacted starting material and a large amount of by-product **432**. A 20% conversion to product with respect to unreacted starting material was calculated, but the desired product **405f** accounted for only 7% of the total reaction mixture due to the presence of 61% by-product **432**, a dimer of methyl propiolate. To supress the formation of this by-product the reaction was repeated but with methyl propiolate added as a dilute solution in MeCN over a period of 30 minutes in order to keep the concentration of methyl propiolate low to encourage it to react with the amide rather than itself. Indeed, this did slightly improve the outcome of the reaction, giving a conversion of 25%, with **405f** accounting for 16% of the completed reaction mixture and **432** 36%. Unfortunately, this conversion was still poor, and the dimer was inseparable by flash column chromatography. This meant that the material could not be taken forward for subsequent reactions. The reaction was also trialled using the stronger base NaH, but this resulted in a complex ^{1}H NMR spectrum containing neither product nor by-product peaks.

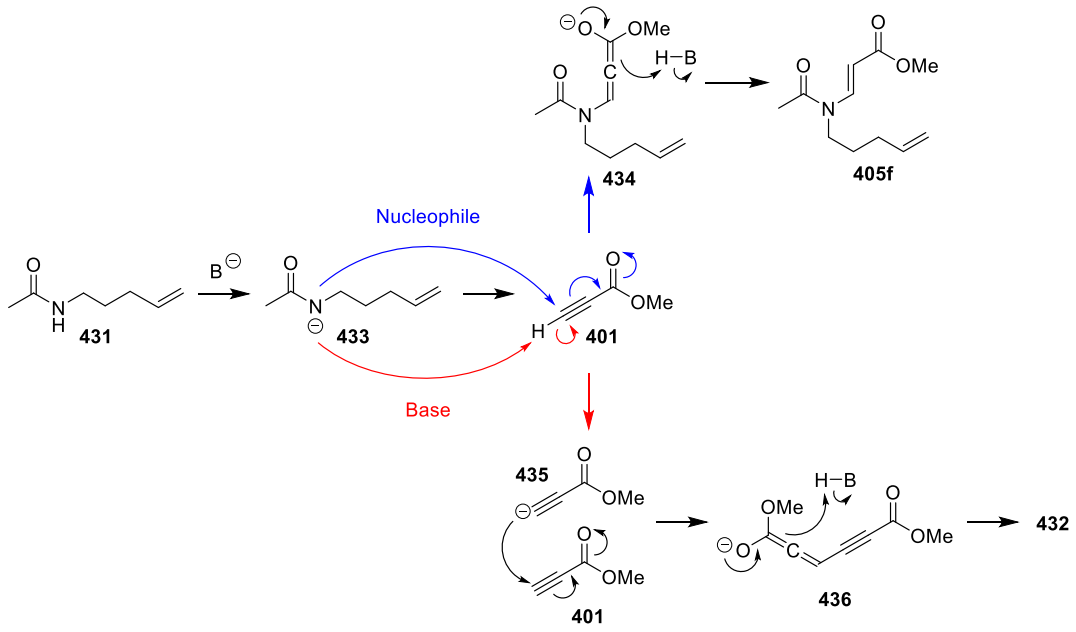
Table 23. Ratio of **405f**, **431** and **432**



430 **431** 34% **401** **405f** **432**

Entry	Conditions	% of reaction mixture by ^{1}H NMR			% Conversion to 405f wrt 431
		405f	431	432	
1	All added together	7	32	61	20
2	Dilute methyl propiolate added slowly	16	48	36	25

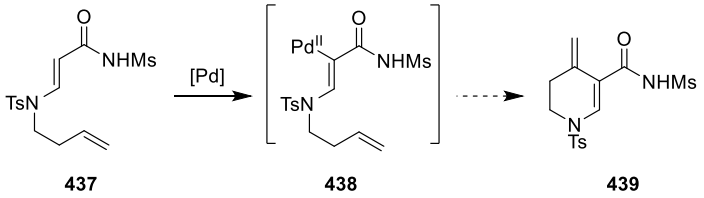
It is thought that the formation of this dimer by-product is as a result of the secondary amide being able to act as a base as well as a nucleophile. The deprotonated amide is able to deprotonate methyl propiolate, enabling it to act as the Michael donor and attack another equivalent of methyl propiolate. The increased basicity of **431** compared to that of the tosyl derivative **417** may be due to the amide having less resonance forms than the sulfonamide, making the anion less stable and therefore more basic.



Scheme 128. Nucleophilic *vs* basic reactivity of **431**

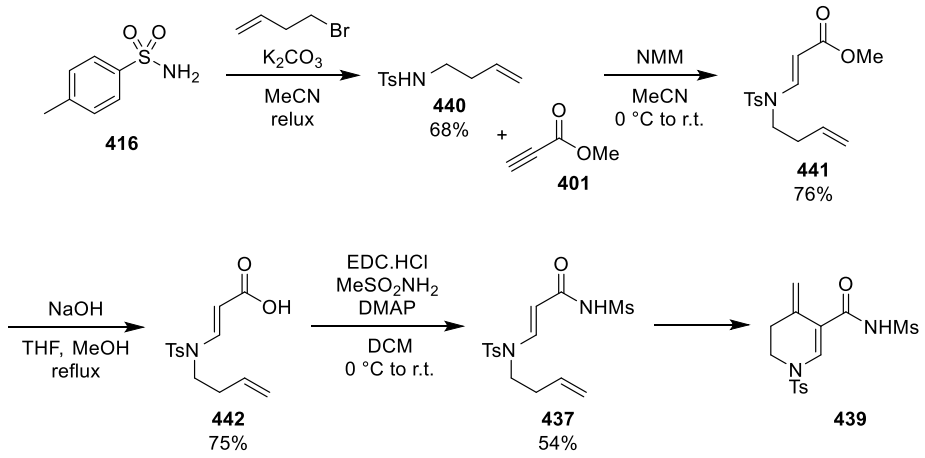
2.6.5 The use of a shorter tether

As discussed previously, it was hypothesised that the reason for the formation of undesired **417** when **404c** was subjected to the standard cyclisation conditions was due to Pd acting as a Lewis acid, and attacking β to the nitrogen (cf. Scheme 123, page 106). If the tether was one methylene unit shorter this may allow the alkene to coordinate to the Pd and then be inserted into the Pd–C bond to form a 6-membered ring, which may result in a novel distinct Pd-catalysed methodology (Scheme 129).



Scheme 129. Proposed cyclisation of **437**

The substrate with a shorter tether was synthesised in the same manner as tosyl substrate **404c**: alkylation of tosyl sulfonamide with 4-bromo-1-butene and K_2CO_3, Michael addition to methyl propiolate in the presence of NMM, hydrolysis of the methyl ester and then amide coupling. All of these steps proceeded in good yields.

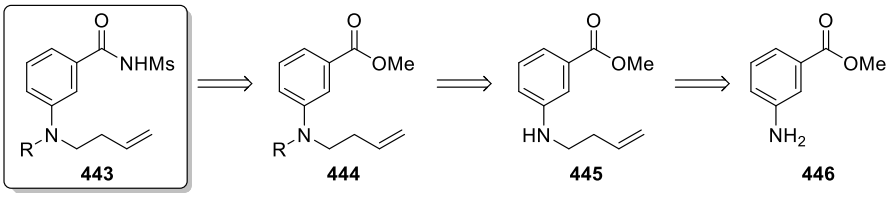


Scheme 130. Synthesis of **437**

Substrate **437** was subjected to the standard cyclisation conditions. Unfortunately, no product **439** was observed, with only unreacted starting material present in the ^{1}H NMR of the crude material.

2.7 Aniline-type substrates

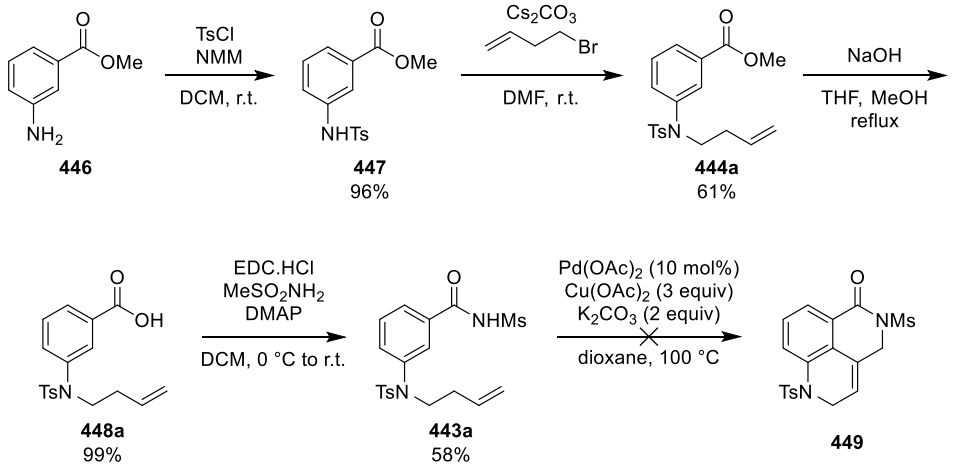
It is likely that the Pd(II)-catalysed C–H activation and cyclisation of the enamine-type substrates was unsuccessful due to their inability to undergo an S_EAr C–H activation mechanism. The lack of aromaticity combined with the lack of electron density on the C–H bond meant that it would be difficult for the C–H to be activated by the electrophilic palladium catalyst. Because of this, aniline-type substrates were then targeted. Anilines are aromatic and have a much greater electron density, so they are more likely to allow S_EAr to occur. This was a move away from a system which would allow the synthesis of the matrine alkaloids, but it had the potential to still lead to an oxidative Heck/aza-Wacker cascade sequence and would allow access to a new class of interesting novel polyheterocycles. It would also provide mechanistic information on the catalytic sequence. It was envisaged that such substrates could be easily synthesised from commercially available amino benzoate derivatives.



Scheme 131. Retrosynthetic analysis of aniline-type substrates **443**

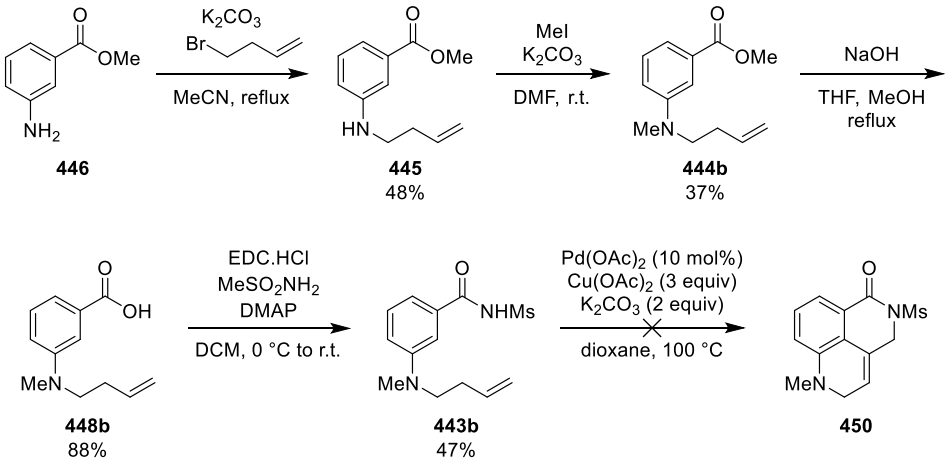
Once again, a substituent was needed on the nitrogen. Initially a substrate was synthesised with a tosyl substituent on the aniline nitrogen in order to more directly compare with the previous class of substrates. Methyl-3-aminobenzoate was reacted with TsCl in the presence of NMM to install the tosyl group, giving **447** in an excellent yield of 96%. The aniline nitrogen was then alkylated using 4-bromo-1-butene and Cs_2CO_3 in DMF. For these substrates a shorter tether was necessary to achieve the 6-

membered rings in the cyclisation reaction. Hydrolysis of the methyl ester to uncover the acid was facile and proceeded in a near-quantitative yield. The acid **448a** underwent an amide coupling reaction with methanesulfonamide to yield the desired substrate **443a**. When subjected to the standard cyclisation conditions no formation of cyclised product **449** was observed, with only unreacted starting material recovered. For these substrates a drying agent was no longer needed because such substrates are much less likely to form a hydrolysable imine.



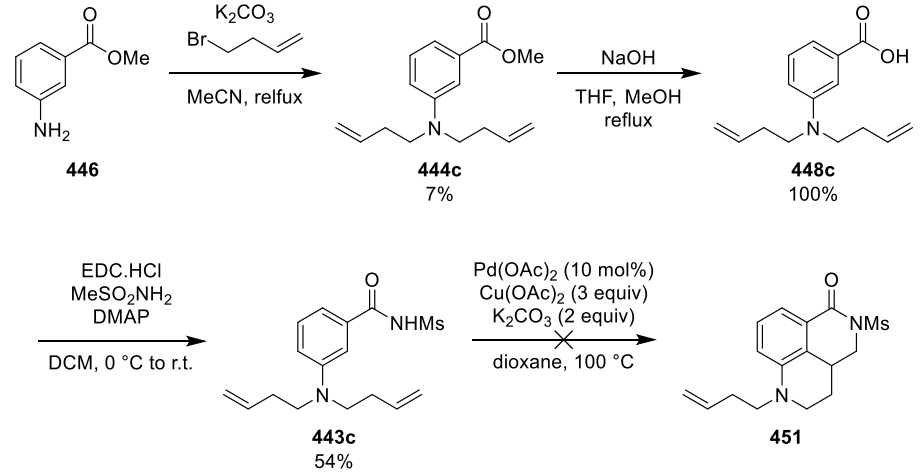
Scheme 132. Synthesis and cyclisation of tosyl-substituted aniline substrate **443a**

An aniline substrate with a methyl substituent on nitrogen was then targeted. The removal of the electron-withdrawing tosyl group should increase electron density of the aromatic ring, increasing the likelihood of C–H activation by S_EAr. The methyl group was necessary as a free N–H may interfere with the catalytic cycle, as it would have the possibility of coordinating to the Pd catalyst. Synthesis of an aniline substrate with a methyl group as the *N*-substituent was achieved in a similar manner to tosyl substrate **443a**, but the alkylation step was carried out before methylation. The alkylation step was slow, with a yield of **445** of only 48% despite heating at reflux for 72 hours. Methylation using MeI and K_2CO_3 was also low yielding, but subsequent functional group interconversion resulted in enough of the desired substrate **443b** to try the cyclisation reaction. Unfortunately, under the standard cyclisation conditions, no cyclisation occurred.



Scheme 133. Synthesis and cyclisation of methyl-substituted aniline substrate **443b**

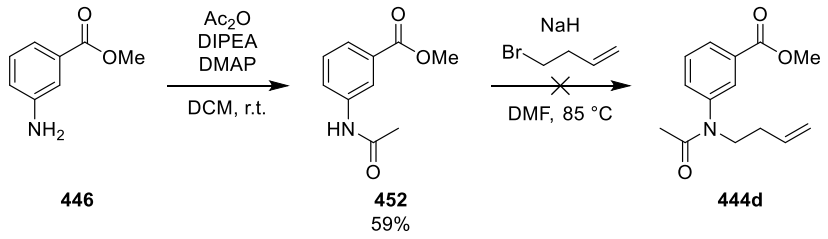
The by-product of the alkylation of methyl-3-aminobenzoate was the dialkylated product **444c**. This was also taken through to the mesylamide as it only involved two straightforward steps to get to the interesting substrate **443c**. The use of this substrate is effectively doubling the concentration of alkene present, so if any C–H activation is occurring it would increase the changes of subsequent alkene coordination and migratory insertion. The presence of a second tethered alkene may also lead to the formation of more complex products. However, once again, no cyclised product was formed under the standard cyclisation conditions.



Scheme 134. Synthesis and cyclisation of dialkylated aniline substrate **443c**

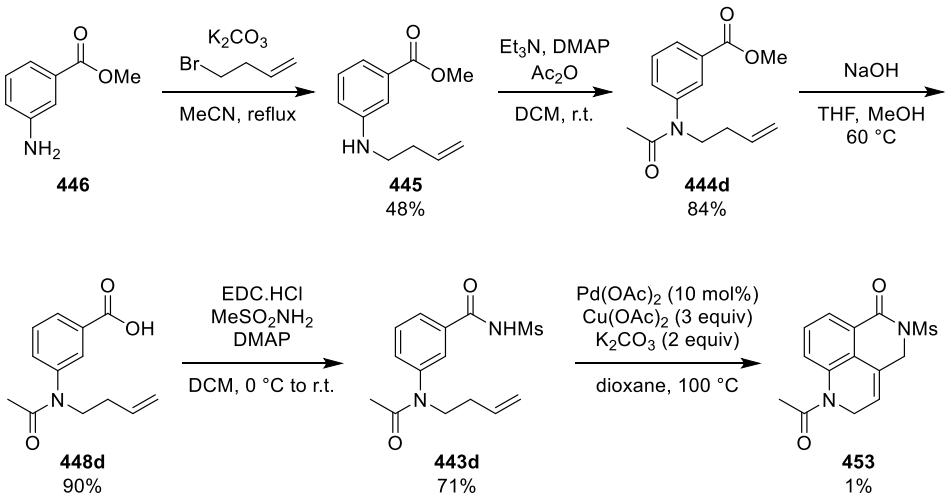
An aniline substrate with an acetyl substituent on the nitrogen was trialled. An acetyl substituent is less electron withdrawing than tosyl but more so than alkyl groups. As mentioned previously, the alkylation of methyl-3-amino benzoate gave only moderate yields even after heating at reflux for 72 hours. Therefore, in an attempt to improve the yields of the synthesis, the acetylation step was carried out first. Acetylation was achieved using Ac_2O, DIPEA and DMAP to give **452** in a yield of 59%. For the alkylation step the stronger base NaH could be used as there was no longer risk of over-alkylation.

However, under these conditions no alkylation occurred at room temperature, and after heating to 85 °C still only starting material was present. The bromide was converted to a tosyl group, as this would serve as a better leaving group, but still no reaction occurred. This could be because the substrate was not nucleophilic enough due to the electron withdrawing nature of both the acetyl and methyl benzoate groups.



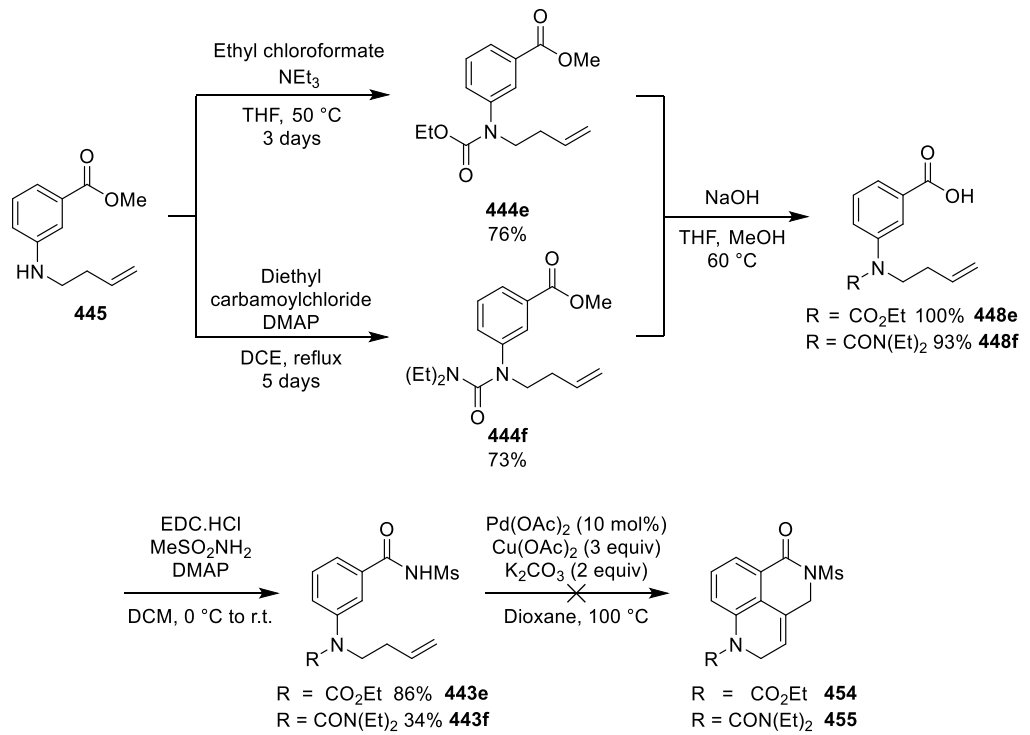
Scheme 135. Attempted acetylation and alkylation of **446**

It was therefore necessary to revert back to the alkylation of methyl-3-aminobenzoate followed by acetylation. This time acetylation was achieved using Et_3N instead of DIPEA, giving **444d** in a yield of 84%. The synthesis was completed by hydrolysis of the methyl ester and amide coupling with methanesulfonamide. Substrate **443d** was then subjected to the standard cyclisation conditions and 1% yield of the cyclised product **453** was observed by ^{1}H NMR. Despite this being a very poor yield, it served as a 'proof of concept' and demonstrated that C–H activation of these aniline-type substrates was possible. This supports the hypothesis that the C–H activation is occurring *via* an S_EAr-type mechanism.



Scheme 136. Synthesis and cyclisation of acetyl-substituted aniline substrate **443d**

Due to the success of the acetyl-substituted substrate, other substituents with similar pKa's to acetyl were selected for investigation. Substrates with a urea and a carbamate substituent were trialled (Scheme 137). These were both synthesised in an analogous fashion to previous aniline-type substrates. Unfortunately, under the standard cyclisation conditions neither substrate yielded any product.

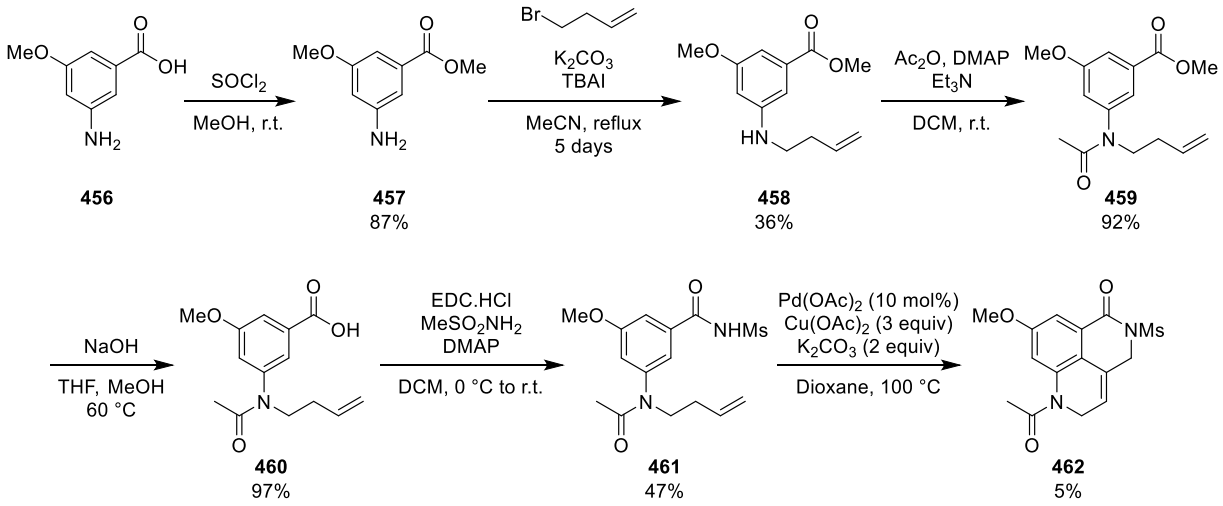


Scheme 137. Synthesis and attempted cyclisation of urea- and carbamate-substituted aniline substrates **443e** and **443f**

Another way of increasing the electron density of the aniline system was to introduce an electron donating substituent onto the aniline ring itself. A substrate with a methoxy group *para*- to the site of C–H activation was synthesised from commercially available 3-amino-5-methylbenzoic acid. First, the acid was protected by esterification using $SOCl_2$ and MeOH which gave methyl ester **457** in a yield of 87%. The aniline nitrogen of **457** was then alkylated using 4-bromo-1-butene, K_2CO_3 and TBAI in MeCN. As seen with previous alkylations of aniline substrates, this was a very slow reaction that required refluxing for 5 days and a yield of **458** of only 36% was obtained. The nitrogen was acetylated using Ac_2O, DMAP and Et_3N and then the methyl ester was converted to the mesylamide using the standard hydrolysis and amide coupling conditions, with all reactions proceeding in high yields to give the desired substrate **461**. Under the standard cyclisation conditions the cyclisation product **462** was observed with a ^{1}H NMR yield of 7%. Isolation of the cyclisation product by flash column chromatography gave an isolated yield of 5%. The fact that the addition of an electron-donating substituent resulted in an increase in yield further supports the theory that the C–H activation step is occurring by an S_EAr-type mechanism and that a high electron density is needed for the reaction to occur.

Unfortunately, full ^{13}C NMR data could not be obtained for **462**. This compound is very rich in quaternary carbons which have long T_1-relaxation times. T_1-relaxation is the rate of energy transfer from a nuclear spin-system to its neighbouring atoms. Quaternary carbons have much longer T_1-

relaxation times than other carbons because usually the main contribution to T_1-relaxation comes from ^{1}H-^{13}C dipole interactions. Initial ^{13}C NMR experiments were carried out with standard relaxation times, resulting in some missing peaks. When the NMR experiments were repeated with much longer relaxation times the compound appeared to have degraded significantly in the time since the previous NMR experiments. However, the NMR data obtained, along with mass spec and FTIR data, was enough to confidently confirm the structure of the cyclisation product **462**.



456

457 87%

458 36%

459 92%

460 97%

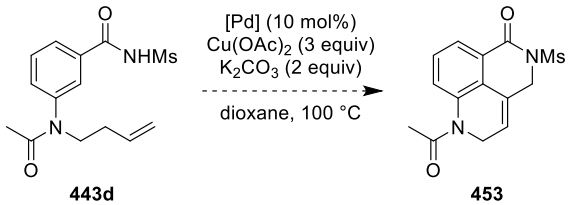
461 47%

462 5%

Scheme 138. Synthesis and cyclisation 4-methoxy substituted aniline substrate **461**

At this stage it was known that electronics were playing a significant role in whether or not C–H activation would occur. For this reason, a range of palladium sources were screened to see if a change in electrophilicity of the palladium would have an effect on the reaction outcome (Table 24). All catalysts trialled resulted in the formation of at least a trace amount of the cyclisation product, but none increased the ^{1}H NMR yield by any significant amount.

Table 24. Palladium screen



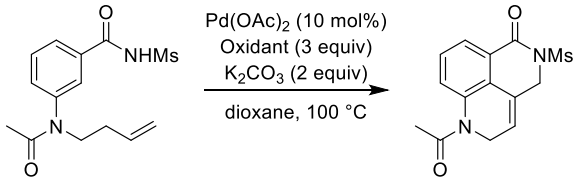
443d **453**

Entry	Catalyst	Yield of 453 (%)[a]	Unreacted 443d (%)[a]
1	$Pd(OAc)_2$	1	15
2	$Pd(TFA)_2$	<1	30
3	$PdCl_2$	<1	20
4	$Pd(MeCN)_2Cl_2$	2	10
5	$Pd(MeCN)_2(OTs)_2$	1	5

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard

An oxidant screen was then carried out to see if increasing catalytic turnover could increase the yield (Table 25). BQ was trialled as it is a common oxidant in oxidative Heck reactions, but no product formed and only 5% starting material remained (Table 25, entry 2). BQ was also trialled but as part of literature conditions using TsOH.H_2O in THF (Table 25, entry 3). Again, this yielded no product, and under these conditions complete degradation of starting material was observed. Several other oxidants were screened, but still only trace amounts of the desired cyclisation product were formed.

Table 25. Oxidant screen



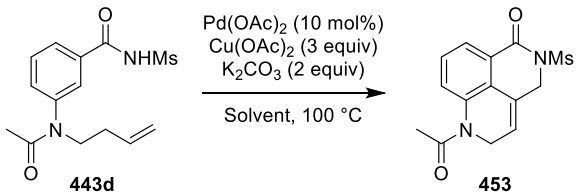
443d 453

Entry	Oxidant	Yield of 453 (%)[a]	Unreacted 443d (%)[a]
1	$Cu(OAc)_2$	1	15
2	BQ	0	5
3[b]	BQ	0	0
4	AgOAc	<1	25
5	oxone	<1	10
6	$K_2S_2O_8$	1	30

[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard [b] TsOH.H_2O (2 equiv.) and THF instead of K_2CO_3 and dioxane

It is known that a change in solvent can have a drastic effect on the outcome of the reaction, so a range of solvents were screened (Table 26). Unfortunately, for all solvents trialled, other than dioxane, no cyclisation product was observed.

Table 26. Solvent screen

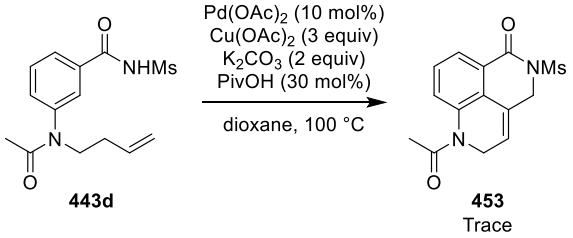


443d 453

Entry	Solvent	Yield of 453 (%)[a]	Unreacted 443d (%)[a]
1	Dioxane	1	15
2	DMF	0	13
3	DMSO	0	10
4	Toluene	0	1
5[b]	THF	0	8

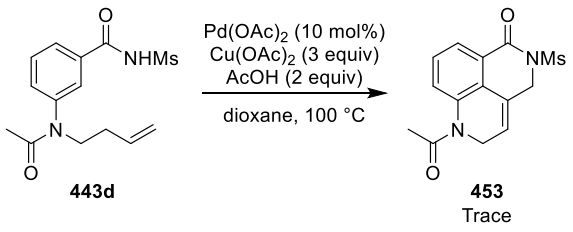
[a]As determined by ^{1}H NMR analysis with 1,4-dimethoxybenzene as an internal standard [b]50 °C

When optimising the conditions for the indole cyclisation methodology it was found that the addition of an organic acid additive gave an increase in yield. The cyclisation of **443d** was carried out with 30 mol% PivOH as an additive to see this would result in any increase in yield. Sadly, still only a trace amount of product was observed in the ^{1}H NMR of the crude material, along with 32% unreacted starting material.



Scheme 139. Cyclisation of **443d** with PivOH additive

There are examples in literature of similar reactions being carried out under acidic conditions.[117, 119] The cyclisation reaction was carried out under acidic conditions rather than basic conditions, with K_2CO_3 replaced with AcOH. This resulted in a complex mixture as observed by TLC and ^{1}H NMR analysis of the crude material, which appeared to include a trace amount of product. Purification of the crude mixture by flash column chromatography was attempted in order to elucidate the identity of the unknown by-products, however much coelution occurred so no by-products were isolated.

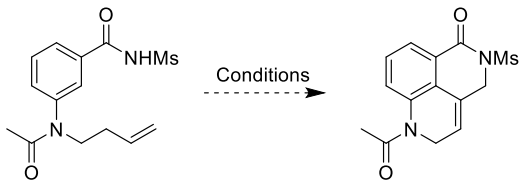


Scheme 140. Cyclisation of **443d** under acid conditions.

One thing that could be noted from these optimisation experiments was the consistent poor mass recovery. For each reaction only up to 30% of the original mass could be accounted for, meaning the remaining 70% was being lost. This loss was likely due to degradation or polymerisation pathways. A series of control experiments were carried to determine what was causing this loss of material. The usual conditions were repeated but with 3 equiv. of Ac_2O as a drying agent to see if elimination of all traces of water could improve the mass recovery. Indeed, the amount of unreacted starting material observed was increased to 75%, but under these conditions no product was formed. The reaction was then carried out in the absence of $Pd(OAc)_2$ as this is the reagent most likely to be causing loss of mass by unfavourable Pd-catalysed pathways. The amount of unreacted starting material increased, but only to 35% suggesting there are still other factors resulting in loss of mass. The reaction was carried

out in the absence of oxidant, with both a catalytic and stoichiometric amount of $Pd(OAc)_2$. For both reactions a trace amount of product was observed but the mass recovery was poor. In the absence of base, a complex mixture was observed by ^1H NMR, but with a high mass recovery. In the absence of both $Pd(OAc)_2$ and $Cu(OAc)_2$ 100% starting material was recovered.

Table 27. Control reactions for the cyclisation of **443d**



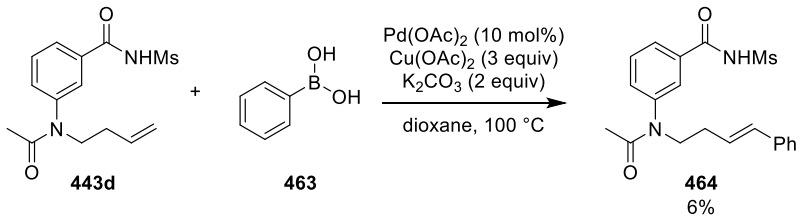
Entry	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	Heating	Yield of 453 (%)[a]	Unreacted 443d (%)[a]
1	✓	✓	✓	✓	Trace	15
2[b]	✓	✓	✓	✓	0	75
3	×	✓	✓	✓	0	35
4	✓	✓	✓	×	0	45
5	✓	×	✓	✓	Trace	10
6[c]	✓	×	✓	✓	Trace	7
7	✓	✓	×	✓	Trace	Complex mixture ~90% Mass
8	×	×	✓	✓	0	100
9	×	×	×	✓	0	100

[a]As determined by ^1H NMR analysis with 1,4-dimethoxybenzene as an internal standard [b] Ac_2O (3 equiv.) added.
[c]Stoichiometric $Pd(OAc)_2$, run for only 30 minutes

From these results it is still not clear what is the cause of the poor mass recovery. It is likely that it is not just one factor, but a combination. It was noticed previously that the isolated product appeared to be unstable, as when NMR experiments were repeated the sample appeared to have degraded. This may mean that the product is being formed during the reaction but then degrading before the end of the reaction.

The C–H activation of **443d** was then carried out with the addition of phenyl boronic acid. If any C–H activation was occurring, it was expected that the carbopalladated intermediate would be trapped out by the phenyl boronic acid and arylate the aniline. It was hoped that this would give information on which sites around the aniline ring were able to undergo C–H activation. If the yield of arylated product had been greater than 1% that would suggest that in the usual cyclisation reaction either C–H activation was occurring, but migratory insertion of alkene was inefficient, or the reaction was occurring, but the cyclisation product was degrading under the reaction conditions. In fact, no

arylation on the aniline ring occurred. Instead the phenyl ring was added to the terminal position of the alkene, and this product was obtained in a yield of 6%.

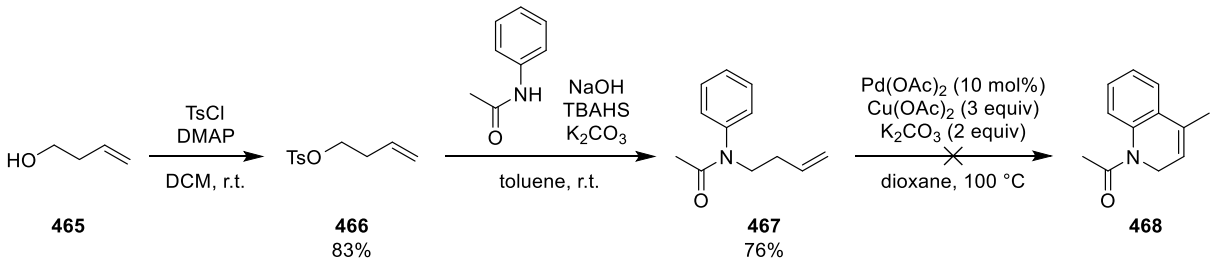


Scheme 141. Addition of phenyl boronic acid

2.8 Intramolecular C–H activation of acetanilides

There is much literature precedent for the C–H activation of acetanilides and phenylureas.[116] In these examples the amide/urea acts as the directing group to achieve *ortho*- C–H activation. This suggests for the C–H activation of substrates such as **443d**, the *N*-acyl mesylamide directing group should not be necessary for the initial oxidative Heck reaction to occur as the amide should also be able to serve as a directing group. Removal of the *N*-acyl sulfonamide would also increase the electron density of the aromatic ring, favouring the electrophilic attack of palladium. All examples found in the literature of acetanilide and phenylurea directed C–H activation are intermolecular.[116] It was thought that the presence of a tethered alkene on the nitrogen of the acetanilide, as seen in aniline substrates such as **467**, could mean that an intramolecular oxidative Heck reaction could be achieved.

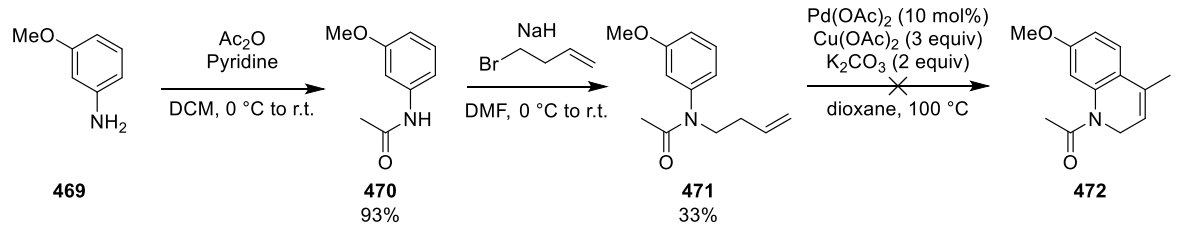
To synthesise the acetanilide with a tethered alkene literature conditions were found in which acetanilide could be alkylated using a tosylate.[177] Tosylate **466** was synthesised from 3-buten-1-ol using tosyl chloride and DMAP. **466** was then reacted with acetanilide in the presence of NaOH, TBAHS and K_2CO_3 to give the desired substrate **467** in a yield of 76%. Acetanilide substrate **467** was subjected to the standard cyclisation conditions. No formation of the desired product occurred and 93% of unreacted starting material remained.



Scheme 142. Synthesis and attempted cyclisation of **467**

To increase the electron density of the system and activate the C–H bond a substrate with a methoxy group *para*- to the C–H bond was synthesised. Commercially available *m*-anisidine was acetylated

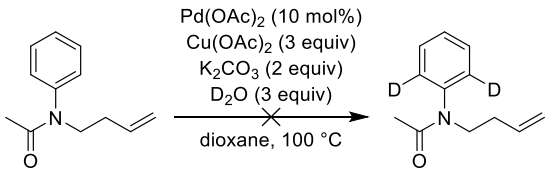
using Ac_2O and pyridine in DCM to give **470** in an excellent yield of 93%. **470** was then alkylated using NaH and 4-bromo-1-butene in DMF. Substrate **471** was subjected to the standard cyclisation conditions but, as with substrate **467**, no cyclisation occurred, and 90% unreacted starting material remained.



469 | **470** 93% | **471** 33% | **472**

Scheme 143. Synthesis and cyclisation of **471**

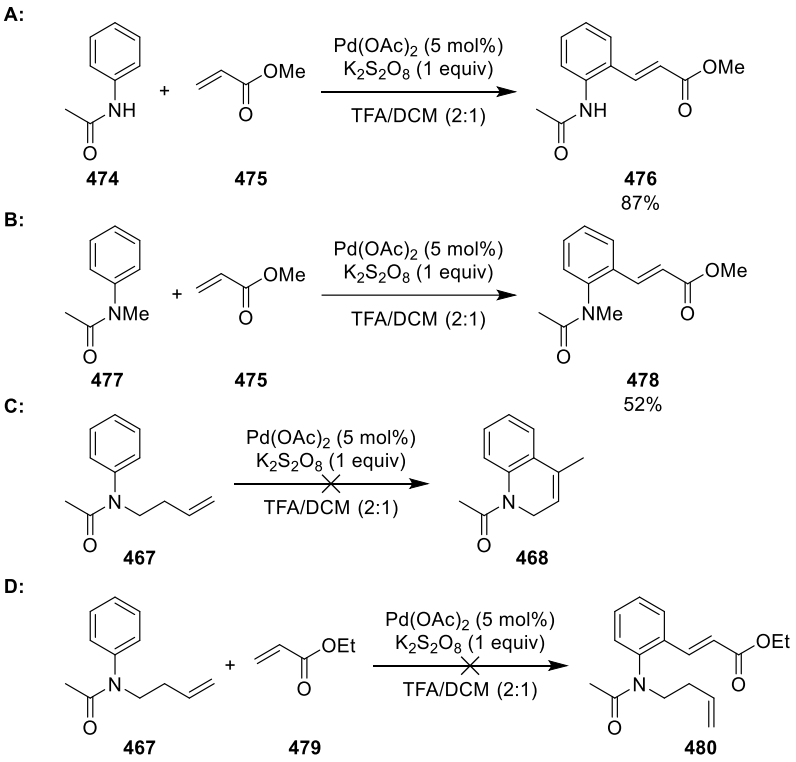
Given the complete lack of reactivity, it was not apparent whether it was the C–H activation step that was not occurring, or the incorporation of the alkene. The cyclisation of **467** was repeated but with the addition of D_2O. If the C–H activation step was occurring, deuterium incorporation *ortho*- to the directing group should occur, which would be observable by ^{1}H NMR. In the ^{1}H NMR spectrum of the crude material, following subjection to the cyclisation conditions, 100% of the starting material remained unreacted with no apparent deuterium incorporation. This implied that no C–H activation was occurring.



467 | **473**

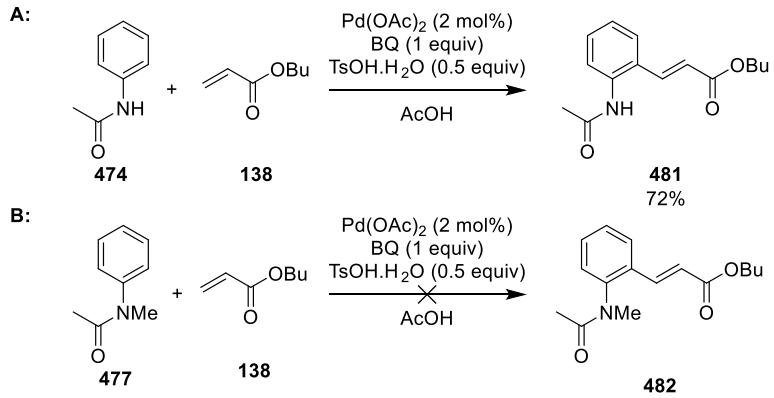
Scheme 144. Deuterium incorporation experiment

As it appeared that no C–H activation was occurring a change in conditions was investigated. An example was found in the literature that used a $Pd(OAc)_2$ catalyst, $K_2S_2O_8$ as the oxidant and a mixture of TFA and DCM as the solvent to couple methyl acrylate to the *ortho*-position of acetanilide (Scheme 145A).[118] The paper also included an example in which the reaction was directed by a tertiary amide (Scheme 145B), albeit in a much lower yield and with increased heating, which suggested that C–H activation of the alkene-tethered acetanilide substrate may be feasible using these conditions. When **467** was subjected to these literature conditions no cyclisation occurred (Scheme 145C). Another factor was the reactivity of the alkene: the majority of literature reactions use activated alkenes such as acrylates. The reaction was repeated but with the addition of 4 equiv. of ethyl acrylate, to give the substrate a more activated alkene to react with (Scheme 145D). Unfortunately, still no reaction was observed.



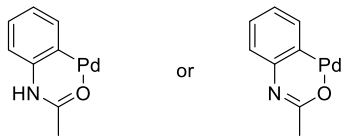
Scheme 145. Literature conditions for the C–H activation of acetanilides

Another search of the literature found an example of the oxidative coupling of acetanilide with butyl acrylate using a $Pd(OAc)_2$ catalyst, BQ as the oxidant and $TsOH.H_2O$ as an additive in AcOH (Scheme 146A).[117] Interestingly, this study reported that methylation of the amide directing group completely shut down the reaction (Scheme 146B).



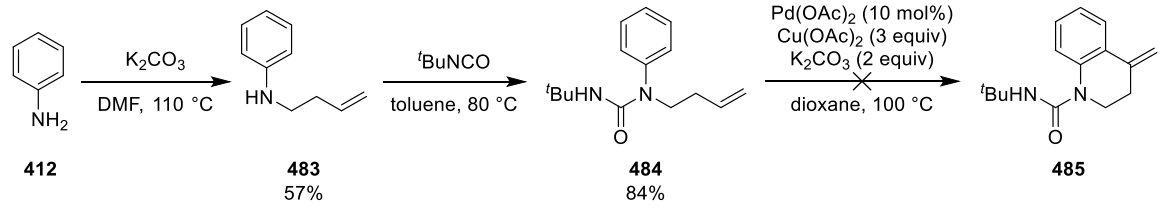
Scheme 146. Literature conditions for the C–H activation of acetanilides

This example of the necessity of the N–H bond, along with the fact that the majority of other examples in the literature are with secondary amides instead of tertiary amides may shed light onto why the reactions of alkene tethered amides were not working. It may be that the N–H is necessary to allow deprotonation so the amide can exist in its iminol form and bind the Pd more strongly (Scheme 147).



Scheme 147. Possible palladacycles

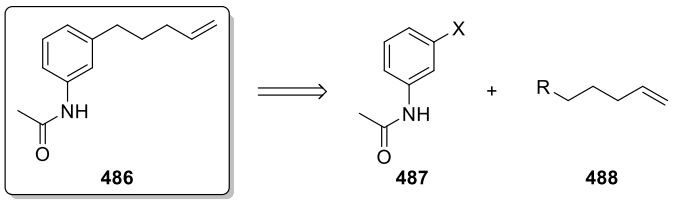
Substrates containing an N–H bond within the directing group were therefore targeted. The urea substrate **484** was synthesised. First alkylation of aniline using K_2CO_3 in DMF gave **483** in a yield of 57%. This was followed by reaction with *t*-butyl isocyanate which gave the urea substrate **484** in a yield of 84%. Substrate **484** was subjected to standard cyclisation conditions, but no cyclisation occurred.



412 **483** 57% **484** 84% **485**

Scheme 148. Synthesis and attempted cyclisation of urea substrate **484**

Another substrate targeted was **486**. This substrate is an acetamide with the free N–H with the alkene tethered to the phenyl ring rather than the acetanilide nitrogen. It was thought that this substrate could be easily accessed in one step by the coupling of the acetamide moiety with the tethered alkene moiety.



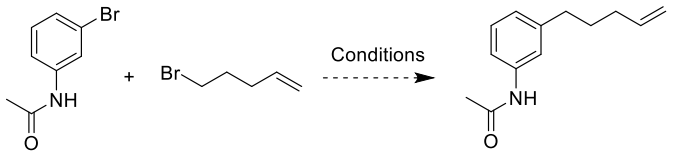
486 **487** **488**

Scheme 149. Retrosynthetic analysis of **486**

A wide range of transition metal-catalysed cross coupling conditions were employed in an attempt to obtain substrate **486** (Table 28.). Negishi coupling conditions were found for a very similar reaction in which 3-bromo acetanilide is coupled to an alkyl bromide.[178] These conditions were trialled (Table 28, entry 1) but by ^{1}H NMR analysis of the crude material mainly starting material remained with only a trace amount of the desired product. Upon flash column chromatography no product was isolated. The lack of reactivity of this reaction may have been caused by difficulties in activating the zinc. An alternative approach was to use a Kumada coupling reaction (Table 28, entries 2-6). A variety of conditions were trialled, utilising a number of different transition metal catalysts including Nickel, Iron and Copper,[179-180] but for all conditions no product was observed with starting material left unreacted.

3-Bromo aniline was also used as a substrate in case the lack of reactivity was being caused by the presence of the amide (Table 28,entry 6), but still no product was observed. A number of Suzuki reactions were also trialled (Table 28, entries 7-9) with the chloro- and iodoacetanilides trialled in addition to the bromoacetanilide, but once again no reaction occurred. Finally, a Heck reaction was attempted between 3-bromo acetanilide and 1,4-pentadiene (Table 28, entry 10) but once again no product was observed.

Table 28. Conditions for the coupling of **487** and **366**



487a **366** **486**

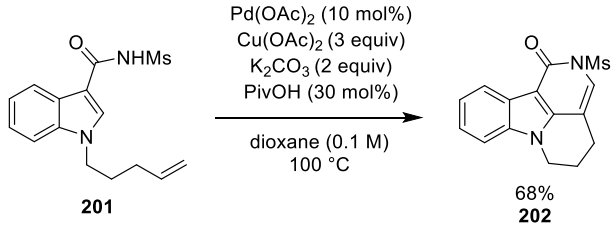
Entry	Conditions	Yield of 486 (%)	Observations[a]
1	$Ni(COD)_2$, bipy, Zn, NaI, pyridine, DMPU, 60 °C	0%	SM
2	Mg, $NiCl_2$(dppp), THF	0%	SM
3	Mg, $FeCl_3$, TMEDA, THF, 0 °C	0%	SM
4	Mg, $CoCl_3$, TMEDA, THF, 0 °C	0%	SM
5	Mg, Li_2CuCl_4, THF, reflux	0%	SM
6[b]	Mg, $NiCl_2$(dppp), THF	0%	SM
7[c]	$Pd(PPh_3)_4$, K_2CO_3, THF	0%	SM
8[c,d]	$Pd(PPh_3)_4$, K_2CO_3, THF	0%	SM
9[c,e]	$Pd(PPh_3)_4$, K_2CO_3, THF	0%	SM
8[f]	$PdCl_2(PPh_3)_2$, NEt_3, DMF, 90 °C	0%	SM

[a]As observed by TLC and ^{1}H NMR analysis [b]Bromo-aniline instead of acetamide [c]4-Pentenyl boronic acid instead used of bromide [c]3-Iodoacetanilide [e]3-Chloroacetanilide [f]Pentadiene used instead of bromide

3. Conclusions and Future Work

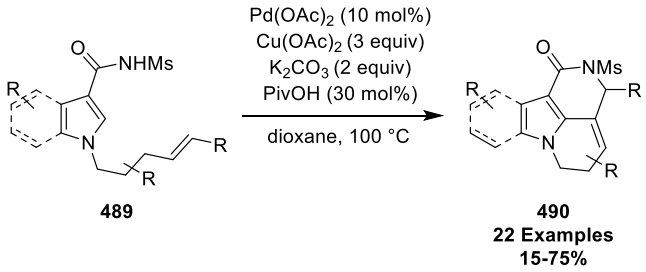
In conclusion, a novel Pd(II)-catalysed C–H activation/aza-Wacker cascade sequence has been optimised for indoles bearing an *N*-tethered alkene and an *N*-acyl mesylamide directing group. This allows for the generation of complex polycyclic heterocycles.

Following an investigation into directing groups, a DoE, and a screen of MPAA ligands and acid additives the following optimised conditions were established: 10 mol% $Pd(OAc)_2$, 3 equiv. $Cu(OAc)_2$, 2 equiv. K_2CO_3, 30 mol% PivOH, dioxane (0.1 M), 100 °C.



Scheme 150. Optimised reaction conditions for the oxidative Heck/aza-Wacker cyclisation of **201**

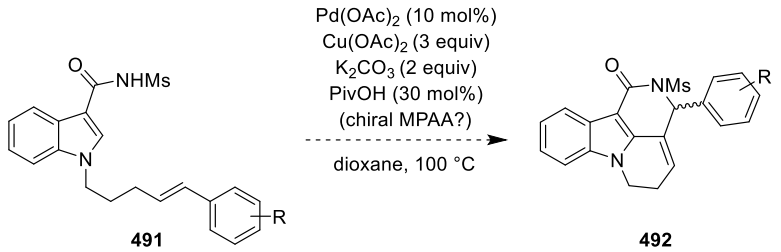
The scope of this cyclisation reaction was investigated. The reaction was shown to be tolerant to substituents on the tether and on the terminal position of the alkene, but with the methyl-substituted substrate **220a** resulting in the surprising formation of the seven-membered derivative **231**. The tolerance to substituents on the indole ring was also explored. A variety of substituents were chosen at different positions around the indole ring, including ether, nitrile and halide groups. The majority of these substrates underwent the cyclisation reaction in good yields, with the reaction showing a slight preference for electron-donating substituents in the C5 position. The scope of the reaction was then expanded by switching the indole core for a pyrrole core. Six examples were synthesised with substituents at both the 4- and 5-positions. The cyclisation of these pyrrole substrates proceeded in moderate yields, but less than those seen for indoles. Further optimisation studies were undertaken but no improvement in the yields was seen.



Scheme 151. Scope of the oxidative Heck/aza-Wacker cyclisation

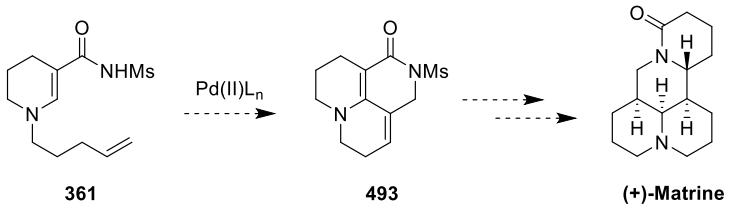
An area of further exploration could involve substrates bearing a phenyl ring at the terminal position of the alkene. Cyclisation of the phenyl substituted substrate **220b** gave the cyclised product **246** in

an excellent yield of 75%. Incorporation of electron-withdrawing and -donating groups onto the phenyl ring would be interesting as this would greatly change the electronics of the alkene. Any trends observed may give more information on the reaction mechanism. The products generated from these substrates also contain a chiral centre. The addition of chiral ligands may result in enantioselectivity. It is known that MPAA's can be used as additives in the cyclisation reaction, so may represent an excellent source of chirality.



A number of experiments have been carried out to gain evidence to support the proposed mechanism. When the cyclisation reaction was carried out using only one equiv. of the $Cu(OAc)_2$ oxidant the yield was poor. The need more than 1 equiv. of $Cu(OAc)_2$ supported a dual catalytic cycle. Cyclisation using the *N*-methylated mesylamide substrate **334** yielded only unreacted starting material, suggesting that the first step in the mechanism is pre-coordination of the Pd(II) centre to the *N*-atom, which is likely facilitated by K_2CO_3. Synthesis and cyclisation of the putative *N*-tosylamide intermediate **188** strongly suggested its involvement in the catalytic cycle. The mechanism was subsequently revised to reflect these observations. In order to confirm the reaction mechanism, kinetic studies must be carried out, as the determination of a KIE would provide further evidence for the mechanism in operation.

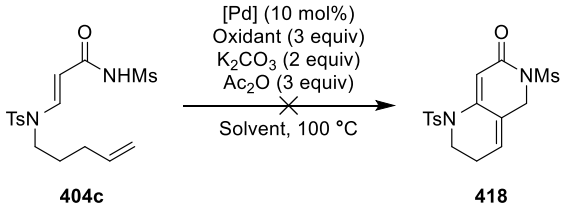
The use of the cyclisation reaction as the key step in the total synthesis of the Matrine alkaloids was then targeted. For this to be realised the development of a scalable and straightforward synthesis towards substrates in the form of **361**, containing a tetrahydropyridine core, was necessary. Unfortunately, despite a diverse range of routes trialled the synthesis of **361** was unsuccessful.



Scheme 152. Matrine synthesis *via* a Pd(II)-catalysed cascade reaction

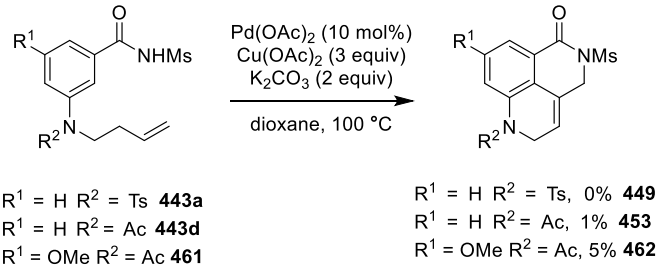
In order to test the C–H activation chemistry of non-aromatic substrates, the acyclic substrate **404c** was synthesised as a test substrate due to its similar electronic properties to **361**. Unfortunately, despite extensive reactant screening, no formation of the desired product was observed. It was

postulated that the lack of reactivity of these enamine-type substrates was due to the lack of electron density and the absence of aromaticity, prohibiting C – H activation *via* an S_EAr-type mechanism.



Scheme 153. Attempted oxidative Heck/aza-Wacker cyclisation of enamine-type substrates

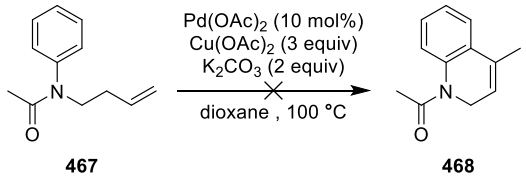
It was proposed that an aniline-type substrates **443** would be more likely to undergo C – H activation *via* an S_EAr-type mechanism. Indeed, under the standard cyclisation conditions, the acetyl substituted aniline substrate **443d** gave a 1% yield of the desired cyclisation product **453**. This served as a proof of concept. When the electron density of the system was increased by the addition of a methoxy group the yield increased, further supporting a S_EAr-type mechanism.



Scheme 154. Oxidative Heck/aza-Wacker cyclisation reaction of aniline-type substrates

A comprehensive screen for the cyclisation of aniline-type substrates was carried out, but to date no improvement on the initial yields has been achieved. Despite this, the optimisation of this methodology remains a key area of interest as it represents a route to a novel class of complex *N*-containing polyheterocycles, which are likely to possess biological activity.

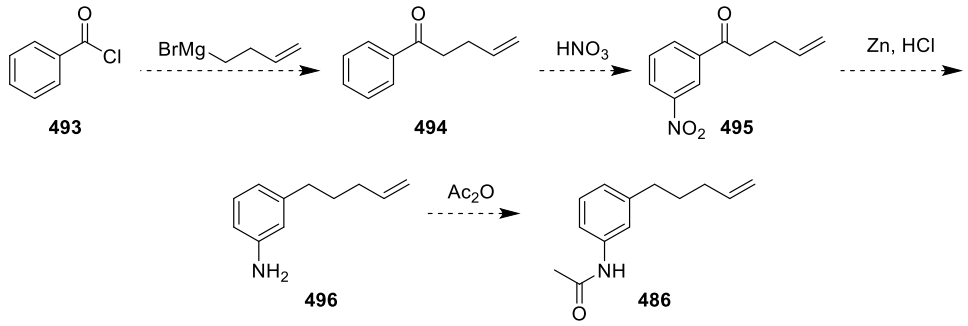
A brief investigation into the intramolecular C–H activation and cyclisation of acetanilide and its derivatives has also been undertaken, but to date no success has been achieved in this area.



Scheme 155. Attempted intramolecular C–H activation and cyclisation of acetanilide

It was hypothesised that substrates with a free N–H in the directing group may be more effective, so a substrate with the alkene tethered to the phenyl ring rather than the acetanilide nitrogen was

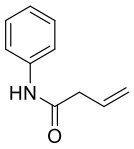
targeted. Initial attempts to synthesise **486** using transition metal catalysed cross-coupling reactions were unsuccessful. Another potential route is proposed below. If **486** could be accessed it would allow the investigation of it's potential as a substrate for C–H activation.



493 **494** **495** **496** **486**

Scheme 156. Potential route towards **492**

An alternative method of achieving substrates with a free amide N–H would be to incorporate the amide into the tether (Scheme 157).



497

Scheme 157. Alternative substrate with a free N–H

4. Experimental

4.1 General information

All reactions were performed in flame-dried glassware under N_2 using anhydrous solvents unless otherwise stated. Anhydrous THF, DCM, Et_2O and MeCN were dried using an Anhydrous Engineering Grubbs-type system (alumina columns). Other solvents (e.g. dioxane, DMF) were purchased in sureseal™ containers and transferred to a Straus flask prior to use. Chemicals were purchased from Acros Organics, Alfa Aesar, Fisher Scientific, Fluorochem, Sigma-Aldrich or TCI and were used without further purification. Flash column chromatography was performed using silica gel (Merck Kieselgel 60 F254 230-400 mesh (40-63 µm)). The crude material was applied to the column as a solution, or by pre-adsorption onto silica where necessary. Aluminium-backed silica plates (0.2 mm, 60 F254) were used for TLC analysis, and visualisation was achieved either by UV fluorescence or $KMnO_4$ solution and heat.

Melting points were obtained using Stuart Scientific SMP10 melting point apparatus and are uncorrected.

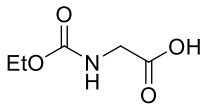
NMR spectra were recorded at 25 °C. Samples were prepared in Norell 502-7 standard series borosilicate tubes. NMR spectra were recorded using Jeol ECZ 400, Varian 400-MR and Bruker 400 spectrometers at 400 MHz (^{1}H) and 101 MHz (^{13}C). Selected NMR spectra were measured using a Bruker Advance III HD 500 Cryo instrument at 500 MHz (^{1}H) and 126 MHz (^{13}C). Chemical shifts are quoted in parts per million and are referenced to residual solvent peaks in the deuterated solvents ($CDCl_3$: 7.260 (^{1}H) 77.160 (^{13}C), DMSO-d_6: 2.500 (^{1}H), 39.520 (^{13}C), acetone-d_6: 2.050 (^{1}H), 29.840 (^{13}C)). Coupling constants (J) are given in Hz and are rounded to the nearest 0.5 Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet), br. (broad) and app. (apparent). Assignments were made with the assistance of gCOSY, gc2HSQC, gc2HMBC, and gc2H2BC.

Mass spectra were recorded by the University of Bristol Mass Spectrometry Service on a VG Analytical Autospec (ESI) spectrometer.

IR spectra were obtained on a Perkin-Elmer Spectrum TwoFTIR spectrometer, in the range 4000-600 cm^{-1}.

4.2 Ligand synthesis

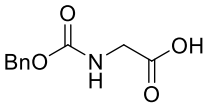
(Ethoxycarbonyl)glycine[181]



To a cooled solution of NaOH (22.0 mmol, 0.88 g) in water (20 mL) was added glycine methyl ester hydrochloride (8.0 mmol, 1.00 g). The solution was stirred until homogenous. A solution of ethyl chloroformate (10.5 mmol, 1.00 mL) in dioxane (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 16 hours. The solution was acidified with 3 M HCl and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was dissolved in MeOH (26 mL) and THF (14 mL). Aqueous NaOH (2 M, 20.0 mmol, 10.0 mL) was added, and the resulting solution was stirred at room temperature for 1 hour. On completion, the volatiles were removed, and the remaining mixture was acidified with 3 M HCl. This was extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the crude product. This was recrystallised from Et_2O to give the title compound (222 mg, 19% over two steps) as a colourless solid.

M.p. 74-75 °C (Et_2O); **^{1}H NMR (400 MHz, D_2O):** δ 4.12 (q, *J* = 7.5 Hz, 2H, OC*H*$_2$CH$_3$), 3.91 (s, 2H, NC*H*$_2$), 1.23 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); **^{13}C NMR (101 MHz, D_2O):** δ 174.2 (*C*O), 158.9 (*C*O), 62.1 (NCH$_2$), 42.0 (O*C*H$_2$CH$_3$), 13.7 (OCH$_2$*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_5H_9NO_4$ [M+Na]$^+$: 170.0424, found 170.0431; **IR ν_{max} (neat)/cm^{-1}:** 3314 (NH), 3072 (br. OH), 2987 (CH), 1686 (C=O).

((Benzyloxy)carbonyl)glycine[182]

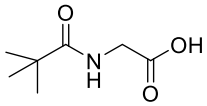


To a cooled solution of NaOH (22.0 mmol, 0.88 g) in water (20 mL) was added glycine methyl ester hydrochloride (8.0 mmol, 1.00 g). The solution was stirred until homogenous. A solution of benzyl chloroformate (10.5 mmol, 1.50 mL) in dioxane (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 16 hours. On completion, the solution was acidified with 3 M HCl, extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was dissolved in MeOH (26 mL) and THF (14 mL). Aqueous NaOH (2 M, 20.0 mmol, 10.0 mL) was then added, and the resulting solution was stirred at room temperature for 1 hour. The volatiles were removed, and the remaining mixture was acidified with 3 M HCl. This was extracted with Et_2O (3 × 30 mL), and the organic layers were combined, washed

with brine, dried over $MgSO_4$ and concentrated to afford the crude product. This was recrystallised from MeCN to give the title compound (1.53 g, 91% over two steps) as a colourless solid.

M.p. 121-122 °C (MeCN, lit. = 116-118 °C[183]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.29 (m, 5H, Ar*H*), 5.26 (s, 1H, N*H*), 5.15 (s, 2H, CH_2), 4.04 (d, *J* = 5.5 Hz, 2H, NCH_2); **IR ν_{max} (neat)/cm^{-1}:** 3328 (NH), 2972 (br. OH), 2573 (CH), 1726 (C=O), 1679 (C=O). Data are consistent with literature precedent.[182]

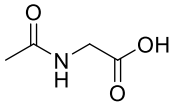
Pivaloylglycine



To a mixture of glycine methyl ester (8.0 mmol, 1.00 g) and triethylamine (9.6 mmol, 1.30 mL) in DCM (10 mL) was added pivaloyl chloride (9.6 mmol, 1.20 mL) dropwise at 0 °C. The reaction mixture was allowed to cool to room temperature and was stirred for 16 hours. Water (10 mL) was added, the organic layer separated, and the aqueous layer was washed with DCM (3 × 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. The resulting product was then dissolved in MeOH (26 mL) and THF (14 mL), and aqueous NaOH (2 M, 20.0 mmol, 10.0 mL) was added. The mixture was stirred at room temperature for 1 hour. The volatiles were then removed, and the remaining mixture acidified with 3 M HCl. This was extracted with Et_2O (3 × 30 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated to afford the title compound (163 mg, 12%) as an off-white solid.

M.p. 140-142 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.85 (s, 2H, NCH_2), 1.19 (s, 9H, 3 × CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 181.9 (*C*O), 173.2 (*C*O), 42.0 (N*C*H$_2$), 39.6 (*C*q), 27.2 (3 × *C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_7H_{13}NO_3$ $[M+H]^+$: 160.0968, found 160.0967; **IR ν_{max} (neat)/cm^{-1}:** 3405 (NH), 2965 (br. OH), 1742 (C=O), 1610 (C=O).

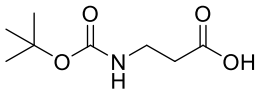
Acetylglycine[184]



To a solution of glycine (8.0 mmol, 601 mg) in MeOH (20 mL) was added acetic anhydride (21.6 mmol, 2.04 mL). The resulting mixture was stirred at reflux for 16 hours. On completion, the volatiles were removed to give the crude product. This was recrystallised from MeOH to afford acetylglycine (913 mg, 97%) as a white solid.

M.p. 203-205 °C (MeOH, lit. = 208 °C[184]); **^{1}H NMR (400 MHz, MeOD):** δ 3.88 (s, 2H, NCH_2), 1.98 (s, 3H, CH_3); **IR ν_{max} (neat)/cm^{-1}:** 3350 (NH), 1717 (C=O), 1581 (C=O). Data are consistent with literature precedent.[184]

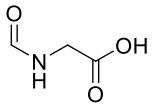
3-((*tert*-Butoxycarbonyl)amino)propanoic acid[185]



To a solution of NaOH (5.9 mmol, 236 mg) in water (3 mL) was added β-alanine (5.6 mmol, 500 mg), ^{t}BuOH (3 mL) and di-*tert*-butyl dicarbonate (5.9 mmol, 1.29 g), and the mixture was stirred for 16 hours at room temperature. On completion, the reaction mixture was diluted with water (20 mL) and washed with EtOAc (30 mL). The aqueous layer was acidified to pH 2 with acetic acid and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was recrystallised from EtOAc/Hex to give the title compound (94 mg, 8%) as a colourless solid.

M.p. 79-81 °C (EtOAc/Hex, lit. = 73-75 °C[186]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.24 (br. s, 1H, O*H*), 5.07 (br. s, 1H, N*H*), 3.48-3.27 (m, 2H, NCH_2), 2.64-2.44 (m, 2H, CH_2), 1.44 (s, 9H, 3 × CH_3); **IR ν_{max} (neat)/cm^{-1}:** 3440 (NH), 2967 (br. OH), 2911 (CH), 1701 (C=O). Data are consistent with literature precedent.[185]

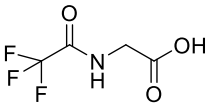
Formylglycine[187]



Formic acid (600 mmol, 23.0 mL) and acetic anhydride (80.0 mmol, 7.60 mL) were stirred at 45 °C for 1 hour. This was followed by the addition of glycine (8.0 mmol, 601 mg). The reaction mixture was stirred at room temperature for 72 hours. The volatiles were removed, and the resulting mixture was azeotroped with 70% Toluene/EtOH. The crude product was recrystallised from MeOH to yield formylglycine (765 mg, 93%) as a white solid.

M.p. 148-152 °C (MeOH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.17 (s, 1H, C*H*O), 4.06 (s, 2H, NCH_2); **IR ν_{max} (neat)/cm^{-1}:** 3311 (NH), 2931 (CH), 1699 (C=O), 1635 (C=O). Data are consistent with literature precedent.[187]

(2,2,2-Trifluoroacetyl)glycine[188]



To a solution of glycine (8.0 mmol, 600 mg) in MeOH (20 mL) was added trimethylamine (8.0 mmol, 1.12 mL). After stirring for 5 minutes, ethyl trifluoroacetate (10.0 mmol, 1.19 mL) was added dropwise. The reaction mixture was stirred at room temperature for 24 hours. On completion the volatiles were removed, and the crude residue dissolved in water. This was extracted with 1:2 MeOH:$CHCl_3$ (×3) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to afford the title compound (1.18 g, 86%) as a white solid.

M.p. 110-115 °C ($CHCl_3$, lit = 117-118 °C[188]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.83 (s, 2H, NC*H*$_2$); **IR ν_{max} (neat)/cm^{-1}:** 3314 (br. NH), 3104-2948 (CH), 2576 (br. OH), 1698 (C=O). Data are consistent with literature precedent.[188]

4.3 Substrate synthesis

4.3.1 General alkylation procedure

Synthesised using a modified literature procedure.[189]

Indole substrate (1 equiv.) was added portionwise to a suspension of NaH (1.2 equiv. as a 60% dispersion in mineral oil) in DMF (0.5 M) at 0 °C. This was stirred at room temperature for 30-60 minutes, until a clear solution formed. The reaction mixture was re-cooled to 0 °C, and a bromide or mesylate substrate (1 equiv.) was added dropwise. The mixture was then stirred at room temperature until complete consumption of the indole starting material was observed by TLC. On completion, the reaction mixture was quenched with water and extracted with EtOAc (×3). The combined organic extracts were washed with water (×3) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography.

4.3.2 General hydrolysis procedure

The alkylated indole substrate (1 equiv.) was dissolved in a mixture of aqueous NaOH (10 equiv. of a 2 M solution), THF (0.3 M), and MeOH (0.3 M), and heated at reflux until complete consumption of the indole starting material was observed by TLC. The reaction mixture was then cooled to room temperature and the volatile solvents removed. The mixture was diluted with water and washed with Et_2O. The aqueous layer was acidified with 3 M HCl to give a white suspension. This suspension was extracted with Et_2O (×3) and the organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated to give analytically pure product.

4.3.3 General amide coupling procedure

To a solution of the hydrolysed indole substrate (1 equiv.) in MeCN (0.1 M) was added CDI (2.2 equiv.) and DMAP (10 mol%). The resulting mixture was stirred at 50 °C until complete consumption of the indole starting material was observed by TLC. The reaction mixture was then allowed to cool to room temperature and methanesulfonamide (2.5 equiv.) and DBU (2.5 equiv.) were added. The reaction mixture was then stirred at 50 °C for 16 hours. On completion, acetic acid (5 mL) was added. The mixture was concentrated, redissolved in EtOAc and washed with water (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by recrystallisation from MeCN.

4.3.4 General mesylation procedure

To a solution of alcohol substrate (1 equiv.) and triethylamine (2 equiv.) in DCM (0.3 M) was added methanesulfonyl chloride (1.5 equiv.) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 5 minutes before being allowed to warm to room temperature, at which it was stirred for a further 2 hours. Water was added, and the phases separated. The aqueous layer was then extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography.

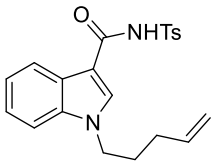
4.3.5 General carboxylation procedure

Synthesised using a modified literature procedure.[146]

To a solution of indole substrate (1 equiv.) in DCM at 0 °C was added TFAA (1.5 equiv.) dropwise. The reaction mixture was stirred at room temperature for 1 hour, and the volatiles were then removed. The crude residue was dissolved in MeOH (1 M) and aqueous KOH (5 equiv. of a 5 M solution) was added. The reaction mixture was stirred at 80 °C for 16 hours and was then allowed to cool to room temperature. The mixture was acidified to pH 1 with 3 M HCl, then extracted with EtOAc (×3). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by recrystallization from MeCN.

4.3.6 Indole and pyrrole substrate data

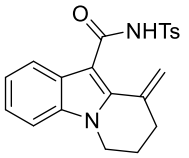
1-(Pent-4-en-1-yl)-*N*-tosyl-1*H*-indole-3-carboxamide 187



p-Toluenesulfonamide (4.5 mmol, 770 mg) was added dropwise to a stirred solution of EDC.HCl (4.5 mmol, 862 mg), DMAP (6.9 mmol, 843 mg) and 1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 688 mg) in DCM (12 mL). The resulting mixture was stirred at room temperature for 18 hours. On completion, the reaction mixture was washed with 1 M HCl, water (×2) and brine, dried over $MgSO_4$ and concentrated to give the title compound (631 mg, 55%) as a white solid (analytically pure), which was used without further purification.

M.p. 157-160 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 11.86 (s, 1H, N*H*), 8.40 (s, 1H, Ar*H*), 7.99-7.95 (m, 1H, Ar*H*), 7.92-7.87 (m, 2H, Ar*H*), 7.57 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.45-7.39 (m, 2H, Ar*H*), 7.23 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Ar*H*), 7.16 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar*H*), 5.84 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.09-4.97 (m, 2H, CH=CH_2), 4.22 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.38 (s, 3H, CH_3), 2.03 (q, *J* = 7.0 Hz, 2H, CH_2), 1.88 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 161.6 (*C*O), 143.7 (*C*q), 137.5 (*C*q), 137.4 (*C*H=CH_2), 136.2 (*C*q), 134.4 (*C*H), 129.4 (*C*H), 127.6 (*C*H), 126.6 (*C*q), 122.8 (*C*H), 121.8 (*C*H), 120.9 (*C*H), 115.5 (CH=*C*H_2), 110.8 (*C*H), 106.7 (*C*q), 45.6 (N*C*H_2), 30.2 (*C*H_2), 28.4 (*C*H_2), 21.1 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{21}H_{22}N_2O_3S$ [M+H]$^+$: 383.1424, found 383.1430; **IR ν_{max} (neat)/cm^{-1}:** 3200-2928 (CH), 1643 (C=O).

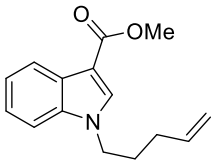
9-Methylene-*N*-tosyl-6,7,8,9-tetrahydro[1,2-*a*]indole-10-carboxamide 188



9-Methylene-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (1 mmol, 183 mg) was dissolved in toluene (2.5 mL). Tosyl isocyanate (1 mmol, 197 mg) was added dropwise and the reaction mixture was stirred at room temperature for 18 hours. On completion the mixture was filtered, and the filtrate concentrated. The crude residue was purified by recrystallisation from MeCN to yield the title compound (54 mg, 14%) as an off-white solid.

M.p. 175-177 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.48 (s, 1H, Ar*H*), 8.05 (m, 2H, Ar*H*), 8.01 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.35 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.25-7.20 (m, 2H, Ar*H*), 5.77 (s, 1H, C=C*H*H), 5.54 (s, 1H, C=CH*H*), 4.14 (t, *J* = 6.5 Hz, 2H, NCH_2), 2.66 (t, *J* = 6.5 Hz, 2H, CH_2), 2.44 (s, 3H, ArCH_3), 2.22 (qn, *J* = 6.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.1 (*C*O), 144.8 (*C*q), 139.1 (*C*q), 136.4 (*C*q), 135.8 (*C*q), 135.7 (*C*q), 129.6 (*C*H), 128.6 (*C*H), 127.2 (*C*q), 123.7 (*C*H), 122.8 (*C*H), 121.0 (*C*H), 119.6 (C=*C*H_2), 109.6 (*C*H), 104.6 (*C*q), 42.7 (N*C*H_2), 31.5 (*C*H_2), 23.9 (*C*H_2), 21.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{21}H_{20}N_2O_3S$ [M+H]$^+$: 381.1267, found 381.1280; **IR ν_{max} (neat)/cm^{-1}:** 3260-2930 (CH), 1644 (C=O).

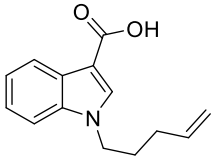
Methyl 1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylate 195



Methyl indole-3-carboxylate (17.0 mmol, 3.00 g) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (10% EtOAc/petrol) to afford the title compound (3.50 g, 85%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.14 (m, 1H, Ar*H*), 7.85 (s, 1H, Ar*H*), 7.42-7.36 (m, 1H, Ar*H*), 7.34-7.27 (m, 2H, Ar*H*), 5.82 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.12-5.08 (m, 1H, CH=C*H*H), 5.07-5.05 (m, 1H, CH=CH*H*), 4.18 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.94 (s, 3H, OCH_3), 2.14-2.07 (m, 2H, CH_2), 2.05-1.96 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.6 (*C*O), 136.9 (*C*H=CH_2), 136.6 (*C*q), 134.3 (*C*H), 126.9 (*C*q), 122.8 (*C*H), 121.9 (*C*H), 121.9 (*C*H), 116.2 (CH=*C*H_2), 110.1 (*C*H), 107.1 (*C*q), 51.1 (*C*H_3), 46.3 (N*C*H_2), 30.8 (*C*H_2), 28.9 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{17}NO_2$ $[M+H]^+$: 244.1332, found 244.1332; **IR ν_{max} (neat)/cm^{-1}:** 2946 (CH), 1694 (C=O).

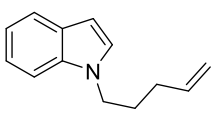
1-(Pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 196



Methyl 1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylate (14.0 mmol, 3.50 g) was subjected to the general hydrolysis conditions described above, to give the title compound (2.98 g, 92%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 123-125 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.32-8.25 (m, 1H, Ar*H*), 7.94 (s, 1H, Ar*H*), 7.43-7.36 (m, 1H, Ar*H*), 7.36-7.29 (m, 2H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.12-5.08 (m, 1H, CH=C*H*H), 5.08-5.06 (m, 1H, CH=CH*H*), 4.17 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.17-2.08 (m, 2H, CH_2), 2.05-1.96 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.7 (*C*O), 136.9 (*C*q), 136.8 (*C*H=CH_2), 135.7 (*C*H), 127.1 (*C*q), 123.0 (*C*H), 122.8 (*C*H), 122.1 (*C*H), 116.3 (CH=*C*H_2), 110.2 (*C*H), 106.5 (*C*q), 46.4 (N*C*H_2), 30.7 (*C*H_2), 28.8 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{15}NO_2$ $[M+Na]^+$: 252.0995, found 252.0998; **IR ν_{max} (neat)/cm^{-1}:** 2969 (CH), 2901 (br. OH), 1615 (C=O).

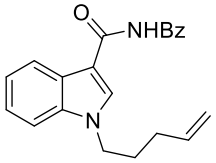
1-(Pent-4-en-yl)-1*H*-indole[190] 198



Indole (5.0 mmol, 585 mg) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (1% EtOAc/petrol) to afford the title compound (879 g, 95%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.61 (m, 1H, Ar*H*), 7.38-7.30 (m, 1H, Ar*H*), 7.21 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar*H*), 7.14-7.07 (m, 2H, Ar*H*), 6.50 (dd, *J* = 3.0, 1.0 Hz, 1H, Ar*H*), 5.82 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.10-5.01 (m, 2H, CH=CH_2), 4.14 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.13-2.05 (m, 2H, CH_2), 2.01-1.91 (m, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 3056-2871 (CH). Data are consistent with literature precedent.[190]

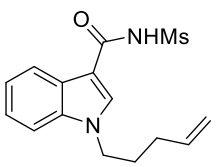
***N*-Benzoyl-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 199**



Benzoyl isocyante (2.4 mmol, 0.33 mL) was added dropwise to a solution of 1-(Pent-4-en-yl)-1*H*-indole (2.0 mmol, 474 mg) in toluene (5 mL). The reaction mixture was heated to 50 °C and stirred for 16 hours. The reaction mixture was diluted with EtOAc and washed with water (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (30% EtOAc/petrol) followed by recrystallisation from MeCN to afford the title compound (53 mg, 8%) as a white solid.

M.p. 162-163 °C (MeCN); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.74 (br. s, 1H, N*H*), 8.21-8.14 (m, 1H, Ar*H*), 8.03 (s, 1H, Ar*H*), 7.93-7.87 (m, 2H, Ar*H*), 7.63-7.57 (m, 1H, Ar*H*), 7.55-7.47 (m, 2H, Ar*H*), 7.44-7.40 (m, 1H, Ar*H*), 7.36-7.29 (m, 2H, Ar*H*), 5.80 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.12-5.02 (m, 2H, CH=CH_2), 4.20 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.12 (q, *J* = 7.0 Hz, 2H, CH_2), 2.01 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 166.8 (*C*O), 163.0 (*C*O), 136.8 (*C*q), 136.7 (*C*H), 134.8 (*C*H), 134.2 (*C*q), 132.8 (*C*H), 128.9 (*C*H), 128.0 (*C*H), 126.9 (*C*q), 123.4 (*C*H), 122.7 (*C*H), 121.5 (*C*H), 116.4 (CH=*C*H_2), 110.5 (*C*H), 109.4 (*C*q), 46.6 (N*C*H_2), 30.8 (*C*H_2), 28.9 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{21}H_{20}N_2O_2$ $[M+H]^+$: 333.1598, found 333.1595; **IR ν_{max} (neat)/cm^{-1}:** 3342 (br. NH), 3113-2934 (CH), 1695 (C=O), 1663 (C=O).

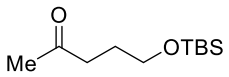
***N*-(Methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 201**



1-(Pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (2.0 mmol, 459 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (443 mg, 72%) as an off-white solid.

M.p. 216-217 °C (MeCN); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.33 (br. s, 1H, N*H*), 8.19-8.10 (m, 1H, Ar*H*), 7.78 (s, 1H, Ar*H*), 7.45-7.39 (m, 1H, Ar*H*), 7.37-7.30 (m, 2H, Ar*H*), 5.86-5.72 (m, 1H, C*H*=CH_2), 5.12-5.02 (m, 2H, CH=CH_2), 4.19 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.48 (s, 3H, SO_2CH_3), 2.10 (q, *J* = 7.0 Hz, 2H, CH_2), 2.00 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 162.7 (*C*O), 137.5 (*C*H=CH_2), 136.3 (*C*q), 134.5 (*C*H), 126.7 (*C*q), 122.8 (*C*H), 121.9 (*C*H), 121.0 (*C*H), 115.6 (CH=*C*H_2), 110.9 (*C*H), 106.8 (*C*q), 45.6 (N*C*H_2), 41.9 (SO_2*C*H_3), 30.2 (*C*H_2), 28.4 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{18}N_2O_3S$ $[M+Na]^+$: 329.0930, found 329.0926; **IR ν_{max} (neat)/cm^{-1}:** 3218 (NH), 2951 (CH), 1647 (C=O).

5-((*tert*-Butyldimethylsilyl)oxy)pentan-2-one[191] 209

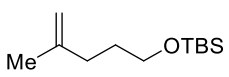


γ-Butyrolactone (15.0 mmol, 1.20 mL) was dissolved in Et_2O (30 mL) and the solution was cooled to -78 °C. Methyllithium (15.9 mmol, 9.90 mL, 1.6 M solution in Et_2O) was added dropwise over 10 minutes, and the reaction mixture was then stirred at -78 °C for 1 hour. This was quenched with saturated aqueous NH_4Cl and allowed to warm to room temperature. Brine was added and extracted with Et_2O (3 × 50 mL) and EtOAc (50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was used without further purification.

The crude alcohol was then dissolved in DMF (30 mL). Imidazole (18.0 mmol, 1.23 g) was added, and the solution was cooled to 0 °C. TBSCl (16.5 mmol, 2.49 g) was added and the reaction mixture was left to warm to room temperature and was stirred for 16 hours. On completion, water (50 mL) was added and the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were then washed with water (50 mL) and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (3% EtOAc/petrol) to yield the title compound (1.40 g, 43% over two steps) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61 (t, *J* = 6.0 Hz, 2H, OCH_2), 2.51 (t, *J* = 7.0 Hz, 2H, COCH_2), 2.15 (s, 3H, CH_3), 1.84-1.72 (m, 2H, CH_2), 0.88 (s, 9H, 3 × CH_3), 0.04 (s, 6H, 2 × CH_3); **IR ν_{max} (neat)/cm^{-1}:** 2954-2857 (CH), 1716 (C=O), 1254 (SiC), 1099 (SiO). Data are consistent with literature precedent.[191]

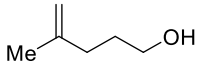
***tert*-Butyldimethyl((4-methylpent-4-en-1-yl)oxy)silane[192] 210**



NaHMDS (20.0 mmol, 10.0 mL, 2 M solution in THF) was added dropwise to a suspension of methyltriphenylphosphonium iodide (20.0 mmol, 8.09 g) in THF (50 mL) at -78 °C. The solution was allowed to warm to room temperature and was stirred for 1 hour before being re-cooled to -78 °C. 5-((*tert*-Butyldimethylsilyl)oxy)pentan-2-one (10.0 mmol, 2.15 g) in THF (15 mL) was added, and the reaction mixture was allowed to warm to room temperature and was then stirred for 16 hours. On completion, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with EtOAc (3 × 45 mL). The combined organic phases were washed with water (50 mL) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (2% EtOAc/petrol) to yield the title compound (1.77 g, 83%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72-4.66 (m, 2H, C=CH_2), 3.61 (t, *J* = 6.5 Hz, 2H, OCH_2), 2.05 (t, *J* = 8.0 Hz, 2H, CH_2), 1.73 (s, 3H, CH_3), 1.70-1.61 (m, 2H, CH_2), 0.90 (s, 9H, 3 × CH_3), 0.05 (s, 6H, 2 × CH_3); **IR ν_{max} (neat)/cm^{-1}:** 3075 (CH), 2951 (CH), 1650 (C=C), 1253 (SiC), 1101 (SiO). Data are consistent with literature precedent.[192]

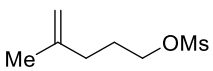
4-Methylpent-4-en-1-ol[193] 211



To a stirred solution of *tert*-butyldimethyl((4-methylpent-4-en-1-yl)oxy)silane (6.5 mmol, 1.39 g) in THF (8 mL) was added TBAF (13.0 mmol, 13.0 mL, 1M in THF) dropwise at 0 °C. The reaction mixture was left to warm to room temperature and was then stirred for 90 minutes. On completion, water (20 mL) was added and the mixture was extracted with Et_2O (3 × 45 mL). The combined organic layers were then washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (20% Et_2O/petrol) to yield the title compound (500 mg, 76%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74-4.70 (m, 2H, C=CH_2), 3.66 (t, *J* = 6.5 Hz, 2H, OCH_2), 2.10 (t, *J* = 7.5 Hz, 2H, CH_2), 1.76-1.68 (m, 5H, CH_2 + CH_3); **IR ν_{max} (neat)/cm^{-1}:** 3317 (br. OH), 3075 (CH), 2933 (CH), 1650 (C=C). Data are consistent with literature precedent.[193]

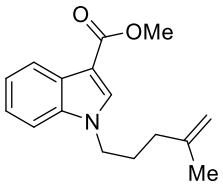
4-Methylpent-4-en-1-yl methanesulfonate[194] 212



4-Methylpent-4-en-1-ol (4.3 mmol, 435 mg) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (10% EtOAc/petrol) to yield the title compound (736 mg, 95%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78-4.75 (m, 1H, C=C*H*H), 4.73-4.69 (m, 1H, C=CH*H*), 4.22 (t, *J* = 6.5 Hz, 2H, OCH_2), 3.00 (s, 3H, SO_2CH_3), 2.13 (t, *J* = 7.5 Hz, 2H, CH_2), 1.94-1.85 (m, 2H, CH_2), 1.73 (s, 3H, CH_3); **IR ν_{max} (neat)/cm^{-1}:** 3076 (CH), 2970-2941 (CH), 1650 (C=C). Data are consistent with literature precedent.[194]

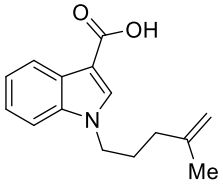
Methyl 1-(4-methylpent-4-en-1-yl)-1*H*-indole-3-carboxylate 213



Methyl indole-3-carboxylate (7.5 mmol, 1.31 g) was subjected to the general alkylation conditions described above with 4-methylpent-4-en-1-yl methanesulfonate. The crude material was purified by flash column chromatography (8% EtOAc/petrol) to afford the title compound (1.68 g, 87%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16-8.11 (m, 1H, Ar*H*), 7.76 (s, 1H, Ar*H*), 7.33-7.27 (m, 1H, Ar*H*), 7.25-7.19 (m, 2H, Ar*H*), 4.76-4.72 (m, 1H, C=C*H*H), 4.68-4.63 (m, 1H, C=CH*H*), 4.11-4.04 (m, 2H, NCH_2), 3.86 (s, 3H, OCH_3), 2.03-1.90 (m, 4H, 2 × CH_2), 1.66 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.9 (*C*O), 144.2 (*C*q), 136.9 (*C*q), 134.7 (*C*H), 127.1 (*C*q), 123.1 (*C*H), 122.2 (*C*H), 122.2 (*C*H), 111.5 (C=*C*H_2), 110.4 (*C*H), 107.4 (*C*q), 51.4 (O*C*H_3), 46.8 (N*C*H_2), 35.0 (*C*H_2), 27.9 (*C*H_2), 22.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{19}NO_2$ $[M+H]^+$: 258.1489, found 258.1494; **IR ν_{max} (neat)/cm^{-1}:** 3072 (CH), 2944 (CH), 1697 (C=O).

1-(Methylpent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 214

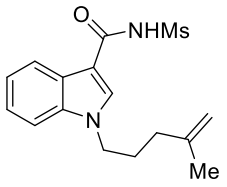


Methyl 1-(4-methylpent-4-en-1-yl)-1*H*-indole-3-carboxylate (6.5 mmol, 1.68 g) was subjected to the general hydrolysis conditions described above, to give the title compound (1.41 g, 89%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 111-113 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.29-8.23 (m, 1H, Ar*H*), 7.94 (s, 1H, Ar*H*), 7.42-7.37 (m, 1H, Ar*H*), 7.35-7.29 (m, 2H, Ar*H*), 4.84-4.79 (m, 1H, C=C*H*H), 4.76-4.69 (m, 1H, C=CH*H*), 4.23-4.11 (m, 2H, NCH_2), 2.10-2.03 (m, 4H, 2 × CH_2), 1.73 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.6 (*C*O), 144.0 (*C*q), 136.8 (*C*q), 135.7 (*C*H), 127.2 (*C*q), 123.0 (*C*H), 122.3 (*C*H), 122.1 (*C*H), 111.3 (C=*C*H_2),

110.2 (*C*H), 106.5 (*C*q), 46.6 (N*C*H$_2$), 34.7 (*C*H$_2$), 27.2 (*C*H$_2$), 22.5 (*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{17}NO_2$ [M+H]$^+$: 244.1332, found 244.1325; **IR ν_{max} (neat)/cm^{-1}:** 3050 (CH), 2926 (CH), 2689 (br. OH), 1656 (C=O).

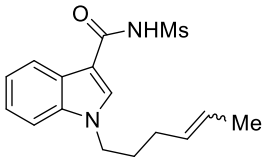
1-(4-Methylpent-4-en-1-yl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide 215



1-(Methylpent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 730 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (649 mg, 68%) as a white solid.

M.p. 146-147 °C (MeCN) **^{1}H NMR (400 MHz, acetone-d$_6$):** δ 8.29 (s, 1H, Ar*H*), 8.27-8.22 (m, 1H, Ar*H*), 7.59-7.50 (m, 1H, Ar*H*), 7.32-7.22 (m, 2H, Ar*H*), 4.78-4.63 (m, 2H, C=C*H*$_2$), 4.30 (t, *J* = 6.5 Hz, 2H, NC*H*$_2$), 3.38 (s, 3H, SO$_2$C*H*$_3$), 2.08-2.06 (m, 4H, 2 × C*H*$_2$), 1.70 (s, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, acetone-d$_6$):** δ 163.4 (*C*O), 145.4 (*C*q), 137.8 (*C*q), 134.3 (*C*H), 128.2 (*C*q), 123.9 (*C*H), 122.8 (*C*H), 122.4 (*C*H), 111.4 (*C*H), 111.1 (C=*C*H$_2$), 108.5 (*C*q), 47.1 (N*C*H$_2$), 42.2 (SO$_2$*C*H$_3$), 35.3 (*C*H$_2$), 28.5 (*C*H$_2$), 22.5 (*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{20}N_2O_3S$ [M+H]$^+$: 321.1267, found 321.1265; **IR ν_{max} (neat)/cm^{-1}:** 3226 (NH), 3118 (CH), 2952 (CH), 1645 (C=O), 1322 (S=O).

1-(Hex-4-en-1-yl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide 220a

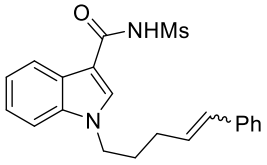


1-(Hex-4-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 730 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (694 mg, 72%, mixture of stereoisomers, cis:trans 16:14) as a white solid.

M.p. 176-178 °C (MeCN) **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 11.52 (s, 1H, N*H*), 8.42 (d, *J* = 4.0 Hz, 1H, Ar*H*), 8.16-8.11 (m, 1H, Ar*H*), 7.62-7.55 (m, 1H, Ar*H*), 7.31-7.19 (m, 2H, Ar*H*), 5.52-5.34 (m, 2H, C*H*=C*H*), 4.27-4.17 (m, 2H, NC*H*$_2$), 3.38 (s, 3H, SO$_2$C*H*$_3$), 2.06-1.92 (m, 2H, C*H*$_2$), 1.91-1.80 (m, 2H, C*H*$_2$), 1.62-1.59 (m, 1.4H, trans C*H*$_3$), 1.54-1.47 (m, 1.6H, cis C*H*$_3$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$):** δ 162.7 (*C*O), 136.4 (*C*q), 134.5 (*C*H), 129.9 (*C*H=CH, trans), 129.0 (*C*H=CH, cis), 126.7 (*C*q), 125.4 (CH=*C*H, trans), 124.7 (CH=*C*H, cis), 122.8 (*C*H), 121.9 (*C*H), 121.0 (*C*H), 110.9 (*C*H), 106.8 (*C*q), 45.7 (N*C*H$_2$), 41.8 (SO$_2$*C*H$_3$), 29.1 (*C*H$_2$), 23.5 (*C*H$_2$), 17.8 (*C*H$_3$, trans), 12.6 (*C*H$_3$, cis); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{20}N_2O_3S$

[M+Na]$^+$: 343.1087, found 343.1091; **IR ν_{max} (neat)/cm^{-1}:** 3225 (NH), 3116 (CH), 2945 (CH), 1650 (C=O), 1322 (S=O).

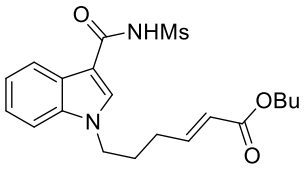
_N_-(Methylsulfonyl)-1-(5-phenylpent-4-en-yl)-1_H_-indole-3-carboxylate 220b



1-(5-Phenylpent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (2.5 mmol, 763 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (548 mg, 57%) as a white solid.

M.p. 146-148 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 10.06 (br. s, 1H, N*H*), 8.37 (s, 1H, Ar*H*), 8.27 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H, Ar*H*), 7.60 (dt, *J* = 8.5, 1.0 Hz, 1H, Ar*H*), 7.42-7.12 (m, 7H, Ar*H*), 6.47-6.39 (m, 1H, CH=C*H*Ph), 6.30 (dt, *J* = 16.0, 7.0 Hz, 1H, C*H*=CHPh), 4.39 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.39 (s, 3H, SO_2CH_3), 2.34-2.24 (m, 2H, CH_2), 2.12 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 163.3 (*C*O), 138.5 (*C*q), 137.7 (*C*q), 134.3 (*C*H), 131.7 (*C*H=CH), 129.9 (CH=*C*H), 129.3 (*C*H), 128.2 (*C*q), 127.8 (*C*H), 126.8 (*C*H), 123.9 (*C*H), 122.8 (*C*H), 122.4 (*C*H), 111.4 (*C*H), 108.5 (*C*q), 47.0 (*C*H_2), 42.3 (SO_2CH_3), 30.7 (*C*H_2), 30.2 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{21}H_{22}N_2O_3S$ [M+Na]$^+$: 405.1243, found 405.1249; **IR ν_{max} (neat)/cm^{-1}:** 3655 (NH), 2987 (CH), 2901 (CH), 1649 (C=O), 1399 (S=O), 1142 (S=O).

Butyl (_E_)-6-(3-((methylsulfonyl)carbamoyl)-1_H_-indole-1-yl)hex-2-enoate 220c

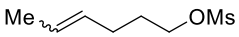


To a solution of *N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide (1.3 mmol, 400 mg) in DCM (50 mL) was added butyl acrylate (3.9 mmol, 0.56 mL). Grubbs catalyst 2nd generation was added (0.013 mmol, 11 mg), and the solution stirred at reflux for 2 hours. The reaction mixture was then concentrated directly onto silica and purified by flash column chromatography (60% EtOAc/petrol) to afford the title compound (273 mg, 52%) as an off-white solid.

M.p. 140-144 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.18-8.99 (m, 1H, N*H*), 8.27-8.17 (m, 1H, Ar*H*), 7.92 (s, 1H, Ar*H*), 7.42-7.28 (m, 3H, Ar*H*), 6.86 (dt, *J* = 15.5, 6.5 Hz, 1H, C*H*=CH), 5.81 (d, *J* = 15.5 Hz, 1H, CH=C*H*), 4.18 (t, *J* = 6.5 Hz, 2H, NCH_2), 4.12 (t, *J* = 6.5 Hz, 2H, OCH_2), 3.50 (s, 3H, SO_2CH_3), 2.27-2.15 (m, 2H, CH_2), 2.12-1.99 (m, 2H, CH_2), 1.62 (qn, *J* = 7.0 Hz, 2H, CH_2), 1.38 (h, *J* = 7.0 Hz, 2H, CH_2), 0.93 (t, *J* = 7.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 166.6 (*C*O), 162.5 (*C*O), 146.7 (*C*H=CH), 136.6 (*C*q), 133.2

(*C*H), 127.0 (*C*q), 123.7 (*C*H), 122.8 (*C*H), 122.6 (CH=*C*H), 121.8 (*C*H), 110.2 (*C*H), 107.6 (*C*q), 64.4 (O*C*H_2), 46.4 (N*C*H_2), 42.3 ($SO_2C$$H_3$), 30.7 (*C*$H_2$), 29.2 (*C*$H_2$), 28.0 (*C*$H_2$), 19.2 (*C*$H_2$), 13.8 (*C*$H_3$); **HRMS (ESI$^+$):** Calculated for $C_{20}H_{26}N_2O_5S$ $[M+H]^+$: 407.1635, found 407.1630; **IR ν_{max} (neat)/cm^{-1}:** 3230 (NH), 2965 (CH), 1716 (C=O), 1650 (C=O).

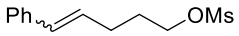
Hex-4-en-1-yl methanesulfonate[195] 221a



Hex-4-en-1-ol (6.9 mmol, 689 mg) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (10% EtOAc/petrol) to yield the title compound (1.03 g, 80%, mixture of stereoisomers, cis:trans 11:9) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.58-5.43 (m, 1H, C*H*=CH), 5.42-5.29 (m, 1H, CH=C*H*), 4.21 (t, *J* = 6.5Hz, 2H, O*C*H_2), 2.99 (s, 1.65H, $SO_2C$$H_3$), 2.99 (s, 1.35H, $SO_2C$$H_3$), 2.22-2.14 (m, 1.10H, cis CH_2), 2.14-2.06 (m, 0.90H, trans CH_2), 1.80 (dt, *J* = 7.5, 6.5 Hz, 2H, CH_2), 1.65 (d, *J* = 6.0 Hz, 1.35H, trans CH_3), 1.61 (d, *J* = 7.0 Hz, 1.65H, cis CH_3) ; **IR ν_{max} (neat)/cm^{-1}:** 2941 (CH), 1351 (S=O). Data are consistent with literature precedent.[195]

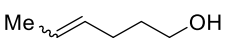
5-Phenylpent-4-en-1-yl methanesulfonate[196] 221b



5-Phenylpent-4-en-1-ol (6.9 mmol, 1.11 g) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (20% EtOAc/petrol) to yield the title compound (1.38 g, 83%, mixture of stereoisomers) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.15 (m, 5H, Ar*H*), 6.44 (d, *J* = 16.0 Hz, 1H, C*H*=CH), 6.17 (dt, *J* = 16.0, 7.0 Hz, 1H, CH=C*H*), 4.28 (t, *J* = 6.5 Hz, 2H, OCH_2), 3.00 (s, 3H, $SO_2C$$H_3$), 2.41-2.27 (m, 2H, C$H_2$), 1.99-1.87 (m, 2H, C$H_2$); **IR ν_{max} (neat)/cm^{-1}:** 3024 (CH), 2939 (CH), 1350 (S=O). Data are consistent with literature precedent.[196]

Hex-4-en-1-ol[197] 222a

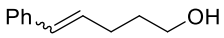


To a stirred solution of *tert*-butyl(hex-4-en-1-yloxy)dimethylsilane (9.8 mmol, 2.10 g) in THF (12 mL) was added TBAF (19.6 mmol, 19.6 mL, 1M in THF) dropwise at 0 °C. The reaction mixture was left to warm to room temperature and was then stirred for 60 minutes. On completion, water (20 mL) was added and the mixture was extracted with Et_2O (3 × 45 mL). The combined organic layers were then washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash

column chromatography (15% Et_2O/petrol) to yield the title compound (730 mg, 74%, mixture of stereoisomers) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.53-5.35 (m, 2H, C*H*=C*H*), 3.64 (td, *J* = 6.5, 4.0 Hz, 2H, OCH_2), 2.17-2.02 (m, 2H, CH_2), 1.69-1.52 (m, 5H, CH_2 + CH_3); **IR ν_{max} (neat)/cm^{-1}:** 2987 (CH), 2901 (CH). Data are consistent with literature precedent.[197]

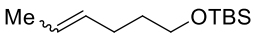
5-Phenylpent-4-en-1-ol[150] 222b



To a suspension of $LiAlH_4$ (17.5 mmol, 7.29 mL, 2.4 M solution in THF) in THF (10 mL) at 0 °C was added 5-phenylpent-4-yn-1-ol (5.0 mmol, 801 mg) dropwise. The reaction mixture was stirred at 0 °C for 20 minutes before slowly being heated to reflux and stirred for 18 hours. On completion, the mixture was cooled to 0 °C and quenched by the slow addition of water (1.00 mL), NaOH (2M, 1.00 mL), and water (2.00 mL) while stirring vigorously. The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (30% EtOAc/petrol) to yield the title compound (698 mg, 83%, mixture of stereoisomers) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.16 (m, 5H, Ar*H*), 6.42 (d, *J* = 15.5 Hz, 1H, C*H*=CH), 6.23 (dt, *J* = 15.5, 7.0 Hz, 1H, CH=C*H*), 3.71 (t, *J* = 7.0 Hz, 2H, OCH_2), 2.31 (q, *J* = 7.0 Hz, 2H, CH_2), 1.76 (qn, *J* = 7.0 Hz, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 3327 (OH), 2951 (CH). Data are consistent with literature precedent.[150, 196]

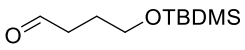
***tert*-Butyl(hex-4-en-1-yloxy)dimethylsilane[198] 223a**



Ethyl triphenylphosphonium bromide (2.2 mmol, 0.82 g) was dissolved in THF (5 mL) and cooled to -78 °C. *n*-Butyllithium (2.2 mmol, 0.88 mL, 2.5 M solution in hexane) was added dropwise, and the mixture was left to stir at -78 °C for 2 hours. The mixture was then left to warm to room temperature for 20 minutes, before being re-cooled to -78 °C. 4-((*tert*-Butyldimethylsilyl)oxy)butanal (2.0 mmol, 0.41 g) in THF (2.5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. On completion, the THF was removed *in vacuo* and saturated aqueous NH_4Cl (20 mL) was added to the crude residue. This was extracted with EtOAc (3 × 30 mL) and the organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (2% EtOAc/petrol) to yield the title compound (305 mg, 71%, mixture of stereoisomers) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.50-5.33 (m, 2H, C*H*=C*H*), 3.64-3.55 (m, 2H, OCH_2), 2.14-1.97 (m, 2H, CH_2), 1.66-1.52 (m, 5H, CH_2 + CH_3), 0.90 (s, 9H, 3 × CH_3), 0.05 (s, 6H, 2 × CH_3); **IR ν_{max} (neat)/cm^{-1}:** 2954-2857 (CH), 1253 (SiC), 1098 (SiO). Data are consistent with literature precedent.[198]

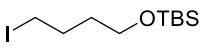
4-((*tert*-Butyldimethylsilyl)oxy)butanal[199] 224



A suspension of $NaHCO_3$ (18.9 mmol, 1.59 g) in DMSO (15 mL) was heated to 110 °C. *tert*-Butyl(4-iodobutoxy)dimethylsilane (3.2 mmol, 1.00 g) was added, and the reaction mixture was stirred at 110 °C for 20 minutes. The mixture was then rapidly cooled to room temperature and poured into water (30 mL). The mixture was extracted with Et_2O (3 × 40 mL) and EtOAc (40 mL) and the combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (2% EtOAc/petrol) to yield the title compound (341 mg, 53%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (t, *J* = 2.0 Hz, 1H, C*H*O), 3.65 (t, *J* = 6.0 Hz, 2H, OCH_2), 2.50 (td, *J* = 7.0, 2.0 Hz, 2H, CH_2), 1.90-1.81 (m, 2H, CH_2), 0.88 (s, 9H, 3 × CH_3), 0.04 (s, 6H, 2 × CH_3); **IR ν_{max} (neat)/cm^{-1}:** 2953-2857 (CH), 1726 (C=O), 1253 (SiC), 1097 (SiO). Data are consistent with literature precedent.[199]

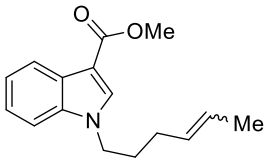
***tert*-Butyl(4-iodobutoxy)dimethylsilane[200] 227**



THF (145 mmol, 8 mL), TBS (40.0 mmol, 6.00 g), and NaI (80.0 mmol, 12.0 g) were dissolved in MeCN (80 mL). The resulting mixture was stirred at 55 °C for 20 hours. On completion, the reaction mixture was cooled to room temperature and the solvent was removed. The crude material was then diluted with water (50 mL) and extracted with 90% pentane/Et_2O (3 × 50 mL). The organic extracts were combined, washed with saturated $NaHCO_3$, 1M $NaSO_3$, and with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (2% EtOAc/ petrol) to yield the title compound (9.73 g, 77%) as a pale-orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (t, *J* = 6.0 Hz, 2H, OCH_2), 3.22 (t, *J* = 7.0 Hz, 2H, ICH_2), 1.97-1.84 (m, 2H, CH_2), 1.66-1.57 (m, 2H, CH_2), 0.89 (s, 9H, 3 × CH_3), 0.05 (s, 6H, 2 × CH_3); **IR ν_{max} (neat)/cm^{-1}:** 2953-2856 (CH) 1253 (SiC), 1100 (SiO). Data are consistent with literature precedent.[200]

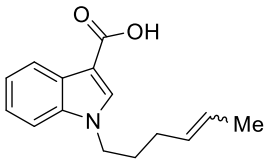
Methyl 1-(hex-4-en-1-yl)-1*H*-indole-3-carboxylate 228



Methyl indole-3-carboxylate (5.7 mmol, 999 mg) was subjected to the general alkylation conditions described above with hex-4-en-1-yl methanesulfonate. The crude material was purified by flash column chromatography (4% EtOAc/petrol) to afford the title compound (1.14 g, 77%, mixture of stereoisomers, cis:trans 17:13) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.12 (m, 1H, Ar*H*), 7.81 (s, 1H, Ar*H*), 7.41-7.33 (m, 1H, Ar*H*), 7.31-7.22 (m, 2H, Ar*H*), 5.61-5.32 (m, 2H, C*H*=C*H*), 4.20-4.08 (m, 2H, NCH_2), 3.91 (s, 3H, OCH_3), 2.14-1.87 (m, 4H, 2 × CH_2), 1.69-1.63 (m, 1.3H, trans CH_3), 1.61-1.53 (m, 1.7H, cis CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.7 (*C*O), 136.6 (*C*q), 134.4 (*C*H), 129.4 (*C*H=CH, trans), 128.6 (*C*H=CH, cis), 126.9 (*C*q), 126.8 (CH=*C*H, trans), 125.9 (CH=*C*H, cis), 122.8 (*C*H), 121.9 (*C*H), 121.9 (*C*H), 110.1 (*C*H), 107.0 (*C*q), 51.1 (*C*H_3), 46.4 (*C*H_2), 29.7 (*C*H_2), 23.9 (*C*H_2), 18.1 (*C*H_3, trans), 13.0 (*C*H_3, cis); **HRMS (ESI^+):** Calculated for $C_{16}H_{19}NO_2$ $[M+H]^+$: 258.1489, found 258.1487; **IR ν_{max} (neat)/cm^{-1}:** 2971 (CH), 2901 (CH), 1700 (C=O).

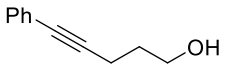
1-(Hex-4-en-1-yl)-1*H*-indole-3-carboxylic acid 229



Methyl 1-(hex-4-en-1-yl)-1*H*-indole-3-carboxylate (4.4 mmol, 1.07 g) was subjected to the general hydrolysis conditions described above, to give the title compound (990 mg, 93%, mixture of stereoisomers, cis:trans 17:13) as an off-white solid (analytically pure), which was used without further purification.

M.p. 102-104 °C (MeCN) **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.28-8.21 (m, 1H, Ar*H*), 7.92 (s, 1H, Ar*H*), 7.42-7.35 (m, 1H, Ar*H*), 7.34-7.29 (m, 1H, Ar*H*), 5.61-5.34 (m, 2H, C*H*=C*H*), 4.21-4.13 (m, 2H, NCH_2), 2.15-1.91 (m, 4H, 2 × CH_2), 1.67 (d, *J* = 5.5 Hz, 1.3H, trans CH_3), 1.58 (d, *J* = 7.0 Hz, 1.7H, cis CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.6 (*C*O), 136.8 (*C*q), 135.7 (*C*H), 129.3 (*C*H=CH, trans), 128.5 (*C*H=CH, cis), 127.2 (*C*q), 126.0 (CH=*C*H, trans), 123.0 (CH=*C*H, cis), 122.3 (*C*H), 122.1 (*C*H), 110.2 (*C*H), 106.4 (*C*q), 46.5 (*C*H_2), 29.5 (*C*H_2), 23.9 (*C*H_2), 18.1 (*C*H_3, trans), 13.1 (*C*H_3, cis); **HRMS (ESI^+):** Calculated for $C_{15}H_{17}NO_2$ $[M+Na]^+$: 266.1151, found 266.1144; **IR ν_{max} (neat)/cm^{-1}:** 2972 (CH), 2935 (CH), 2584 (br. OH), 1645 (C=O).

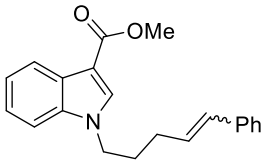
5-Phenylpent-4-yn-1-ol[150] 243



To a solution of iodobenzene (16.0 mmol, 1.78 mL), 4-pentyn-1-ol (8.0 mmol, 0.74 mL) and triethylamine (160 mmol, 22.3 mL) in THF (3 mL) was added $Pd(PPh_3)_4$ (1 mol%, 92.4 mg) and CuI (2 mol%, 30.5 mg). The reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was filtered, and the filtrate concentrated. The crude residue was purified by flash column chromatography (20% EtOAC/Petrol) to yield the title compound (1.19 g, 93%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.35 (m, 2H, Ar*H*), 7.29-7.23 (m, 3H, Ar*H*), 3.81 (t, *J* = 6.5 Hz, 2H, OCH_2), 2.53 (t, *J* = 6.5 Hz, 2H, CH_2), 1.85 (qn, *J* = 6.5 Hz, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 3327 (br. OH), 2950 (CH). Data are consistent with literature precedent.[150]

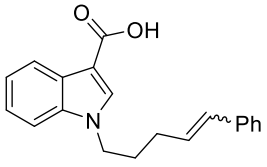
Methyl 1-(5-phenylpent-4-en-1-yl)-1*H*-indole-3-carboxylate 244



Methyl indole-3-carboxylate (5.0 mmol, 876 mg) was subjected to the general alkylation conditions described above with 5-phenylpent-4-en-1-yl methanesulfonate. The crude material was purified by flash column chromatography (5% EtOAc/petrol) to afford the title compound (1.55 g, 97%, mixture of stereoisomers trans:cis 15:1) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.15 (m, 1H, Ar*H*), 7.85 (s, 1H, Ar*H*), 7.43-7.16 (m, 8H, Ar*H*), 6.50 (d, *J* = 11.5 Hz, 0.06H, cis C*H*=CH), 6.40 (d, *J* = 16.0 Hz, 0.94H, trans C*H*=CH), 6.16 (dt, *J* = 16.0, 7.0 Hz, 0.94H, trans CH=C*H*), 5.63 (dt, *J* = 11.5, 7.5 Hz, 0.06H, cis CH=C*H*), 4.41-4.35 (m, 0.12H, cis NCH_2), 4.21 (t, *J* = 7.0 Hz, trans 1.88H, NCH_2), 3.92 (s, 2.82H, trans OCH_3), 3.90 (s, 0.18H, cis OCH_3), 2.29-2.20 (m, 2H, CH_2), 2.12-2.03 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.6 (*C*O), 137.4 (*C*q), 136.6 (*C*q), 134.4 (*C*H), 131.6 (*C*H=CH), 128.7 (*C*H), 128.5 (CH=*C*H), 127.4 (*C*H), 126.9 (*C*q), 126.1 (*C*H), 122.8 (*C*H), 122.0 (*C*H), 121.0 (*C*H), 110.1 (*C*H), 107.2 (*C*q), 51.1 (*C*H_3), 46.3 (*C*H_2), 30.1 (*C*H_2), 29.4 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{21}H_{21}NO_2$ $[M+Na]^+$: 342.1465, found 342.1470; **IR ν_{max} (neat)/cm^{-1}:** 3055 (CH), 2945 (CH), 1697 (C=O).

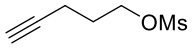
1-(5-Phenylpent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 245



Methyl 1-(5-phenylpent-4-en-1-yl)-1*H*-indole-3-carboxylate (4.5 mmol, 1.44 g) was subjected to the general hydrolysis conditions described above, to give the title compound (899 mg, 65%, mixture of stereoisomers trans:cis 15:1) as an off-white solid (analytically pure), which was used without further purification.

M.p. 157-159 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.23-8.16 (m, 1H, Ar*H*), 7.89 (s, 1H, Ar*H*), 7.35-7.13 (m, 8H, Ar*H*), 6.45 (d, *J* = 11.5 Hz, 0.06H, cis C*H*=CH), 6.35 (d, *J* = 15.5 Hz, 0.94H, trans C*H*=CH), 6.10 (dt, *J* = 15.5, 7.0 Hz, 0.94H, trans CH=C*H*), 5.57 (dt, *J* = 11.5, 7.0 Hz, 0.06 H, cis CH=C*H*), 4.33 (t, *J* = 7.0 Hz, 0.12H, cis NCH_2), 4.16 (t, *J* = 7.0 Hz, 1.88H, trans NCH_2), 2.20 (m, 2H, CH_2), 2.03 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.6 (*C*O), 137.3 (*C*q), 136.8 (*C*q), 135.6 (*C*H), 131.7 (*CH*=CH), 128.7 (*C*H), 128.5 (CH=*C*H), 127.4 (*C*H), 127.2 (*C*q), 126.2 (*C*H), 123.0 (*C*H), 122.3 (*C*H), 122.2 (*C*H), 110.2 (*C*H), 106.6 (*C*q), 46.5 (*C*H_2), 30.1 (*C*H_2), 29.4 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{20}H_{19}NO_2$ [M+Na]$^+$: 328.1308, found 328.1305; **IR ν_{max} (neat)/cm^{-1}:** 3675 (OH), 2988 (CH), 1655 (C=O).

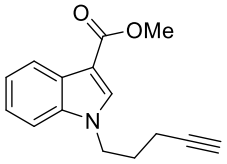
Pent-4-yn-1-yl methanesulfonate[201] 249



4-Pentyn-1-ol (10.0 mmol, 0.93 mL) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (40% Et_2O/ petrol) to yield 4-pentyn-1-yl methanesulfonate (694 mg, 40%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.35 (t, *J* = 6.0 Hz, 2H, OCH_2), 3.02 (s, 3H, SO_2CH_3), 2.36 (td, *J* = 7.0, 3.0 Hz, 2H, CH_2C≡CH), 2.01 (t, *J* = 3.0 Hz, 1H, C≡C*H*), 1.99-1.92 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 82.8 (*C*≡CH), 69.9 (C≡*C*H), 68.4 (O*C*H_2), 37.4 (*C*H_3), 27.9 (*C*H_2), 14.8 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_6H_{10}O_3S$ [M+Na]$^+$: 185.0243, found 185.0250; **IR ν_{max} (neat)/cm^{-1}:** 3286 (CH), 2940 (CH).

Methyl 1-(pent-4-yn-yl)-1*H*-indole-3-carboxylate 250

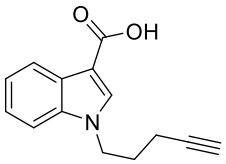


Methyl indole-3-carboxylate (7.4 mmol, 1.30 g) was subjected to the general alkylation conditions described above with 4-pentyn-1-yl methanesulfonate. The crude material was purified by flash column chromatography (10% EtOAc/ petrol) to yield the title compound (1.67 g, 93%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21-8.15 (m, 1H, Ar*H*), 7.86 (s, 1H, Ar*H*), 7.44-7.37 (m, 1H, Ar*H*), 7.32-7.27 (m, 2H, Ar*H*), 4.32 (t, *J* = 6.5 Hz, 2H, NCH_2), 3.92 (s, 3H, OCH_3), 2.23-2.16 (m, 2H, CH_2C≡CH), 2.12-

2.03 (m, 3H, CH_2 + C≡C*H*); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.6 (*C*O), 136.6 (*C*q), 134.5 (*C*H), 126.9 (*C*q), 122.9 (*C*H), 122.1 (*C*H), 122.0 (*C*H), 110.0 (*C*H), 107.3 (*C*q), 82.5 (*C*≡CH), 70.3 (C≡*C*H), 51.1 (O*C*H_3), 45.4 (N*C*H_2), 28.4 (*C*H_2), 15.8 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{15}NO_2$ [M+H]$^+$: 242.1176, found 242.1181; **IR ν_{max} (neat)/cm^{-1}:** 3273 (CH), 3121 (CH), 2947 (CH), 2114 (C≡C), 1684 (C=O).

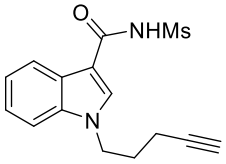
1-(Pent-4-yn-1-yl)-1*H*-indole-3-carboxylic acid 251



Methyl 1-(pent-4-yn-yl)-1*H*-indole-3-carboxylate (6.6 mmol, 1.60 g) was subjected to the general hydrolysis conditions described above. The crude material was recrystallised from MeCN to give the title compound (1.20 g, 80%) as an off-white solid.

M.p. 136-138 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.31-8.21 (m, 1H, Ar*H*), 7.97 (s, 1H, Ar*H*), 7.46-7.41 (m, 1H, Ar*H*), 7.34-7.29 (m, 2H, Ar*H*), 4.36 (t, *J* = 6.5 Hz, 2H, NCH_2), 2.22 (td, *J* = 6.5, 2.5 Hz, 2H, CH_2C≡CH), 2.14-2.06 (m, 3H, CH_2 + C≡C*H*); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.4 (*C*O), 136.7 (*C*q), 135.8 (*C*H), 127.2 (*C*q), 123.1 (*C*H), 122.4 (*C*H), 122.2 (*C*H), 110.2 (*C*H), 106.7 (*C*q), 82.5 (*C*≡CH), 70.4 (C≡*C*H), 45.5 (N*C*H_2), 28.4 (*C*H_2), 15.9 (*C*H_2); **HRMS (ESI$^-$):** Calculated for $C_{14}H_{13}NO_2$ [M-H]$^-$: 226.0874, found 226.0870; **IR ν_{max} (neat)/cm^{-1}:** 3299 (CH), 2953 (CH), 2571 (br. OH), 2118 (C≡C), 1659 (C=O).

***N*-(Methylsulfonyl)-1-(pent-4-yn-1-yl)-1*H*-indole-3-carboxamide 252**

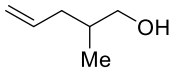


1-(Pent-4-yn-1-yl)-1*H*-indole-3-carboxylic acid (4.4 mmol, 1.00 g) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (860 mg, 64%) as a white solid.

M.p. 191-194 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 10.12 (br. s, 1H, N*H*), 8.32 (s, 1H, Ar*H*), 8.29-8.23 (m, 1H, Ar*H*), 7.64-7.52 (m, 1H, Ar*H*), 7.29 (dddd, *J* = 19.5, 8.0, 7.0, 1.0 Hz, 2H, Ar*H*), 4.42 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.40 (s, 3H, SO_2CH_3), 2.49 (t, *J* = 2.5 Hz, 1H, C≡C*H*), 2.24 (td, *J* = 6.5, 2.5 Hz, 2H, CH_2C≡CH), 2.15-2.07 (m, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 163.4 (*C*O), 137.7 (*C*q), 134.3 (*C*H), 128.2 (*C*q), 124.0 (*C*H), 122.9 (*C*H), 122.5 (*C*H), 111.4 (*C*H), 108.7 (*C*q), 83.6 (*C*≡CH), 71.2 (C≡*C*H), 46.2 (N*C*H_2), 42.3 (*C*H_3), 29.6 (*C*H_2), 16.2 (*CH*$_2$); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{16}N_2O_3S$ [M+Na]$^+$:

327.0774, found 327.0773; **IR ν_{max} (neat)/cm^{-1}:** 3297 (alkyne CH), 3212 (NH), 3117 (CH), 2930 (CH), 1650 (C=O).

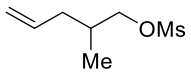
2-Methylpent-4-en-1-ol[202] 254



Ethyl 2-methylpent-4-enoate (10.0 mmol, 1.63 mL) in Et_2O (25 mL) was added slowly to a solution of $LiAlH_4$ (10.0 mmol, 4.20 mL, 2.4 M solution in THF) in Et_2O (25 mL) at 0 °C. The reaction mixture was stirred for 30 minutes, before being quenched by the slow addition of water (0.50 mL), NaOH (2 M, 0.50 mL) and water (1.00 mL) while stirring vigorously. The mixture was left to warm to room temperature and was stirred for a further 90 minutes. The reaction mixture was then filtered through Celite® and concentrated to yield the title compound (1.06 g, quantitative) as a colourless oil, without the need for further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 17.5, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.09-4.98 (m, 2H, CH=CH_2), 3.56-3.41 (m, 2H, OCH_2), 2.22-2.13 (m, 1H, C*H*H), 2.00-1.89 (m, 1H, CH*H*), 1.80-1.66 (m, 1H, C*H*), 0.95-0.89 (d, *J* = 6.5 Hz, 3H, CH_3); **IR ν_{max} (neat)/cm^{-1}:** 3324 (br. OH), 3077 (CH), 2958 (CH), 2911 (CH). Data are consistent with literature precedent.[202]

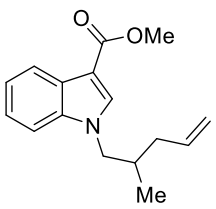
2-Methylpent-4-en-1-yl methanesulfonate 255



2-Methylpent-4-en-1-ol (10.0 mmol, 1.00 g) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (8% EtOAc/petrol) to yield the title compound (1.63 g, 91%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (dddd, *J* = 16.5, 12.5, 8.0, 6.0 Hz, 1H, C*H*=CH_2), 5.11-5.03 (m, 2H, CH=CH_2), 4.14-3.98 (m, 2H, OCH_2), 3.00 (s, 3H, SO_2CH_3), 2.23-2.14 (m, 1H, C*H*H), 2.06-1.93 (m, 2H, CH*H* + CH), 1.00 (d, *J* = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 135.4 (*C*H=CH_2), 117.4 (CH=*C*H_2), 74.0 (O*C*H_2), 37.3 (SO_2*C*H_3), 37.2 (*C*H_2), 32.9 (*C*H), 16.3 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_7H_{14}O_3S$ $[M+Na]^+$: 201.0556, found 201.0560; **IR ν_{max} (neat)/cm^{-1}:** 3078 (CH), 2972 (CH), 2901 (CH), 1350 (S=O).

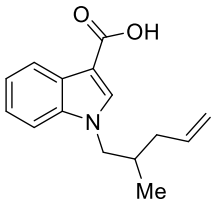
Methyl 1-(2-methylpent-4-en-1-yl)-1*H*-indole-3-carboxylate 256



Methyl indole-3-carboxylate (8.4 mmol, 1.47 g) was subjected to the general alkylation conditions described above with 2-methylpent-4-en-1-yl methanesulfonate. The crude material was purified by flash column chromatography (5% EtOAc/petrol) to afford the title compound (982 mg, 45%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25-8.08 (m, 1H, Ar*H*), 7.79 (s, 1H, Ar*H*), 7.39-7.31 (m, 1H, Ar*H*), 7.29-7.24 (m, 2H, Ar*H*), 5.78 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.12-5.04 (m, 2H, CH=CH_2), 4.11 (dd, *J* = 14.0, 6.0 Hz, 1H, NC*H*H), 3.91 (s, 3H, OCH_3), 3.86 (dd, *J* = 14.0, 8.0 Hz, 1H, NCH*H*), 2.23-2.06 (m, 2H, C*H*H + C*H*), 2.04-1.94 (m, 1H, CH*H*), 0.90 (d, *J* = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.7 (*C*O), 136.9 (*C*q), 135.6 (*C*H=CH_2), 134.9 (*C*H), 126.8 (*C*q), 122.8 (*C*H), 121.9 (*C*H), 121.9 (*C*H), 117.5 (CH=*C*H_2), 110.3 (*C*H), 107.0 (*C*q), 52.9 (N*C*H_2), 51.1 (O*C*H_3), 38.9 (*C*H_2), 33.9 (*C*H), 17.7 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{19}NO_2$ $[M+H]^+$: 258.1489, found 258.1494; **IR ν_{max} (neat)/cm^{-1}:** 3067 (CH), 2949 (CH), 1698 (C=O).

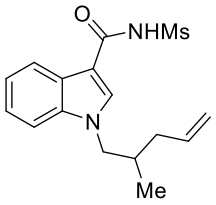
1-(2-Methylpent-4-en-1-yl)-1*H*-indole-carboxylic acid 257



Methyl 1-(2-methylpent-4-en-1-yl)-1*H*-indole-3-carboxylate (3.5 mmol, 901 mg) was subjected to the general hydrolysis conditions described above, to give title compound (733 mg, 81%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 110-113 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.30-8.18 (m, 1H, Ar*H*), 7.91 (s, 1H, Ar*H*), 7.39-7.35 (m, 1H, Ar*H*), 7.33-7.28 (m, 2H, Ar*H*), 5.80 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.17-4.99 (m, 2H, CH=CH_2), 4.15 (dd, *J* = 14.0, 6.0 Hz, 1H, NC*H*H), 3.90 (dd, *J* = 14.0, 8.0 Hz, 1H, NCH*H*), 2.28-2.09 (m, 2H, C*H*H + C*H*), 2.07-1.98 (m, 1H, CH*H*), 0.93 (d, *J* = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.7 (*C*O), 137.1 (*C*q), 136.2 (*C*H), 135.5 (*C*H=CH_2), 127.1 (*C*q), 123.0 (*C*H), 122.3 (*C*H), 122.1 (*C*H), 117.6 (CH=*C*H_2), 110.4 (*C*H), 106.5 (*C*q), 53.0 (N*C*H_2), 38.9 (*C*H_2), 33.8 (*C*H), 17.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{17}NO_2$ $[M+Na]^+$: 266.1151, found 266.1142; **IR ν_{max} (neat)/cm^{-1}:** 2917 (CH), 2588 (br. OH), 1644 (C=O).

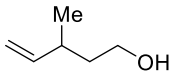
1-(2-Methylpent-4-en-1-yl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide 258



1-(2-Methylpent-4-en-1-yl)-1*H*-indole-carboxylic acid (2.5 mmol, 608 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (436 g, 54%) as a white solid.

M.p. 129-130 °C (MeCN); **^{1}H NMR (400 MHz, acetone-*d*$_6$):** δ 10.11 (br. s, 1H, N*H*), 8.31 (s, 1H, Ar*H*), 8.28-8.24 (m, 1H, Ar*H*), 7.67-7.50 (m, 1H, Ar*H*), 7.36-7.17 (m, 2H, Ar*H*), 5.84 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH$_2$), 5.11-4.97 (m, 2H, CH=C*H*$_2$), 4.25 (dd, *J* = 14.0, 6.0 Hz, 1H, NC*H*H), 4.08 (dd, *J* = 14.0, 8.0 Hz, 1H, NCH*H*), 3.40 (s, 3H, SO$_2$C*H*$_3$), 2.29-2.11 (m, 2H, C*H*H + C*H*), 2.03-1.94 (m, 1H, CH*H*), 0.90 (d, *J* = 6.5 Hz, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, acetone-*d*$_6$):** δ 163.3 (*C*O), 138.0 (*C*q), 137.0 (*C*H=CH$_2$), 134.7 (*C*H), 128.1 (*C*q), 123.9 (*C*H), 122.8 (*C*H), 122.4 (*C*H), 117.2 (CH=*C*H$_2$), 111.6 (*C*H), 108.4 (*C*q), 53.2 (N*C*H$_2$), 42.3 (SO$_2$C*H*$_3$), 39.3 (C*H*$_2$), 34.6 (C*H*), 17.5 (C*H*$_3$); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{20}N_2O_3S$ [M+Na]$^+$: 343.1087, found 343.1080; **IR ν_{max} (neat)/cm^{-1}:** 3225 (NH), 3116 (CH), 2976 (CH), 2927 (CH), 1646 (C=O), 1321 (S=O).

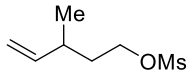
3-Methylpent-4-en-1-ol[203] 260



3-Methylpent-4-enoic acid (8.8 mmol, 1.00 g) in Et$_2$O (25 mL) was added slowly to a solution of LiAlH$_4$ (8.8 mmol, 3.67 mL, 2.4M solution in THF) in Et$_2$O (25 mL) at 0 °C. The reaction mixture was stirred for 30 minutes, before being quenched by the slow addition of water (0.50 mL), NaOH (2 M, 0.50 mL) and water (1.00 mL) while stirring vigorously. The mixture was allowed to warm to room temperature and was stirred for a further 90 minutes. The mixture was filtered through Celite®, and concentrated to yield the title compound (692 mg, 79%) as a colourless oil, without the need for further purification.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.72 (ddd, *J* = 17.0, 10.0, 8.0 Hz, 1H, C*H*=CH$_2$), 5.07-4.89 (m, 2H, CH=C*H*$_2$), 3.67 (t, *J* = 6.5 Hz, 2H, OC*H*$_2$), 2.31 (app. dt, 1H, C*H*), 1.63-1.54 (m, 2H, C*H*$_2$), 1.30 (br. s, 1H, O*H*), 1.03 (d, *J* = 7.0 Hz, 3H, CH$_3$); **IR ν_{max} (neat)/cm^{-1}:** 3663 (OH), 2970 (CH), 2901 (CH). Data are consistent with literature precedent.[203]

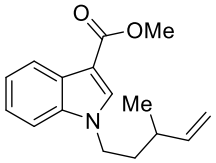
3-Methylpent-4-en-1-yl methanesulfonate 262



3-Methylpent-4-en-1-ol (6.5 mmol, 650 mg) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (20% EtOAc/petrol) to yield the title compound (1.07 g, 92%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH_2), 5.12-4.86 (m, 2H, CH=C*H*$_2$), 4.30-4.14 (m, 2H, OC*H*$_2$), 2.99 (s, 3H, SO_2CH_3), 2.33 (qn, *J* = 7.5 Hz, 1H, C*H*), 1.84-1.65 (m, 2H, C*H*$_2$), 1.05 (d, *J* = 7.0 Hz, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 142.7 (*C*H=CH_2), 114.4 (CH=*C*H$_2$), 68.5 (O*C*H$_2$), 37.4 (SO_2CH_3), 35.5 (*C*H$_2$), 34.5 (*C*H), 20.4 (*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_7H_{14}O_3S$ $[M+H]^+$: 201.0556, found 201.0563; **IR ν_{max} (neat)/cm^{-1}:** 3078 (CH), 2968 (CH), 1351 (S=O).

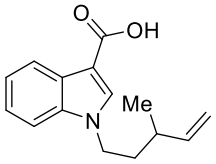
Methyl 1-(3-methylpent-4-en-1-yl)-1*H*-indole-3-carboxylate 263



Methyl indole-3-carboxylate (5.5 mmol, 963 mg) was subjected to the general alkylation conditions described above with 3-Methylpent-4-en-1-yl methanesulfonate. The crude material was purified by flash column chromatography (10% EtOAc/petrol) to afford the title compound (1.31 g, 92%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21-8.14 (m, 1H, Ar*H*), 7.82 (s, 1H, Ar*H*), 7.39-7.33 (m, 1H, Ar*H*), 7.32-7.25 (m, 2H, Ar*H*), 5.78-5.64 (m, 1H, C*H*=CH_2), 5.11-5.07 (m, 1H, CH=C*H*H), 5.07-5.03 (m, 1H, CH=CH*H*), 4.22-4.05 (m, 2H, NC*H*$_2$), 3.91 (s, 3H, OC*H*$_3$), 2.17 (qn, *J* = 7.0 Hz, 1H, C*H*), 1.98-1.75 (m, 2H, C*H*$_2$), 1.05 (d, *J* = 7.0 Hz, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.6 (*C*O), 142.9 (*C*H=CH_2), 136.5 (*C*q), 134.3 (*C*H), 126.9 (*C*q), 122.8 (*C*H), 121.9 (*C*H), 121.9 (*C*H), 114.7 (CH=*C*H$_2$), 110.1 (*C*H), 107.1 (*C*q), 51.1 (O*C*H$_3$), 45.1 (N*C*H$_2$), 36.4 (*C*H$_2$), 35.7 (*C*H), 20.7 (*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{19}NO_2$ $[M+H]^+$: 258.1489, found 258.1498; **IR ν_{max} (neat)/cm^{-1}:** 2950 (CH), 2952 (CH), 1698 (C=O).

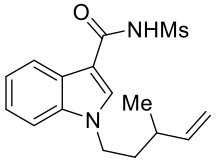
1-(3-Methylpent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 264



Methyl 1-(3-methylpent-4-en-1-yl)-1*H*-indole-3-carboxylate (5.0 mmol, 1.30 g) was subjected to the general hydrolysis conditions described above, to give the title compound (1.02 g, 84%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 102-104 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.28 (m, 1H, Ar*H*), 7.93 (s, 1H, ArH), 7.41-7.35 (m, 1H, Ar*H*), 7.34-7.28 (m, 2H, Ar*H*), 5.72 (ddd, *J* = 17.5, 10.0, 8.0 Hz, 1H, C*H*=CH_2), 5.12-5.08 (m, 1H, CH=C*H*H), 5.08-5.05 (m, 1H, CH=CH*H*), 4.27-4.06 (m, 2H, NCH_2), 2.19 (qn, *J* = 7.0 Hz, 1H, C*H*), 2.01-1.77 (m, 2H, CH_2), 1.07 (d, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.6 (*C*O), 142.7 (*C*H=CH_2), 136.6 (*C*q), 135.4 (*C*H), 127.0 (*C*q), 122.8 (*C*H), 122.1 (*C*H), 121.9 (*C*H), 114.7 (CH=*C*H_2), 110.1 (*C*H), 106.3 (*C*q), 45.1 (N*C*H_2), 36.2 (*C*H), 35.6 (*C*H_2), 20.6 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{17}NO_2$ $[M+Na]^+$: 266.1151, found 266.1153; **IR ν_{max} (neat)/cm^{-1}:** 3675 (OH), 2971 (CH), 2901 (CH), 1654 (C=O).

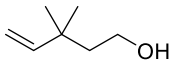
1-(3-Methylpent-4-en-yl)-*N*-indole-3-carboxamide 265



1-(3-Methylpent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 730 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (607 mg, 63%) as a white solid.

M.p. 148-149 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 11.50 (s, 1H, N*H*), 8.43 (s, 1H, Ar*H*), 8.14 (dt, *J* = 7.5, 1,0 Hz, 1H, Ar*H*), 7.57 (dt, *J* = 8.5, 1.0 Hz, 1H, ArH), 7.30-7.19 (m, 2H, Ar*H*), 5.79 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1H, C*H*=CH_2), 5.08-4.98 (m, 2H, CH=CH_2), 4.21 (dd, *J* = 8.0, 6.5 Hz, 2H, NCH_2), 3.38 (s, 3H, SO_2CH_3), 2.15 (qn, *J* = 7.0 Hz, 1H, C*H*), 1.82 (q, *J* = 7.0 Hz, 2H, CH_2), 1.03 (d, *J* = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, DSMO-d_6):** δ 162.6 (*C*O), 143.2 (*C*H=CH_2), 136.2 (*C*q), 134.3 (*C*H), 126.7 (*C*q), 122.8 (*C*H), 121.8 (*C*H), 121.0 (*C*H), 113.9 (CH=*C*H_2), 110.8 (*C*H), 106.8 (*C*q), 44.3 (N*C*H_2), 41.8 (SO_2CH_3), 35.6 (*C*H_2), 34.5 (*C*H), 19.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{20}N_2O_3S$ $[M+Na]^+$: 343.1087, found 343.1090; **IR ν_{max} (neat)/cm^{-1}:** 3680 (NH), 2969 (CH), 1637 (C=O), 1317 (S=O).

3,3-Dimethylpent-4-en-1-ol[204] 268

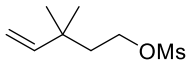


3,3-Dimethylpent-4-enoic acid (10.0 mmol, 1.58 mL) in Et_2O (25 mL) was added slowly to a solution of $LiAlH_4$ (10.0 mmol, 4.20 mL, 2.4 M solution in THF) in Et_2O (25 mL) at 0 °C. The reaction mixture was stirred for 30 minutes before being quenched by the slow addition of water (0.50 mL), NaOH (2 M, 0.50 mL) and water (1.00 mL) while stirring vigorously. The mixture was left to warm to room

temperature and was stirred for a further 90 minutes. The reaction mixture was then filtered through Celite®, and the solvent was removed. The crude residue was purified by flash column chromatography (15% Et_2O/petrol) to yield the title compound (957 mg, 84%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (ddt, *J* = 17.5, 11.0 Hz, 1H, C*H*=CH_2), 5.00-4.88 (m, 2H, CH=CH_2), 3.65 (t, *J* = 7.0 Hz, 2H, OCH_2), 1.67-1.57 (m, 2H, CH_2), 1.03 (s, 6H, C(CH_3)$_2$); **IR ν_{max} (neat)/cm^{-1}:** 2964 (CH). Data are consistent with literature precedent.[204]

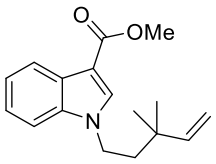
3,3-Dimethylpent-4-en-1-yl methanesulfonate[205] 269



3,3-Dimethylpent-4-en-1-ol (8.2 mmol, 950 mg) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (8% EtOAc/petrol) to yield the title compound (1.51 g, 96%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (dd, *J* = 17.5, 11.0 Hz, 1H, C*H*=CH_2), 5.04-4.92 (m, 2H, CH=CH_2), 4.20 (t, *J* = 7.5 Hz, OCH_2), 2.98 (s, 3H, SO_2CH_3), 1.79 (t, *J* = 7.5 Hz, 2H, CH_2), 1.06 (s, 6H, C(CH_3)$_2$); **IR ν_{max} (neat)/cm^{-1}:** 2965 (CH), 1352 (S=O). Data are consistent with literature precedent.[205]

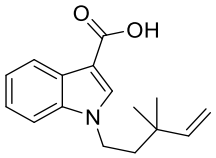
Methyl 1-(3,3-dimethylpent-4-en-1-yl)-1*H*-indole-3-carboxylate 270



Methyl indole-3-carboxylate (7.8 mmol, 1.37 g) was subjected to the general alkylation conditions described above with 3,3-dimethylpent-4-en-1-yl methanesulfonate. The crude material was purified by flash column chromatography (4% EtOAc/petrol) to afford the title compound (1.24 g, 58%) as a white solid.

M.p. 93-96 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.19-8.14 (m, 1H, Ar*H*), 7.81 (s, 1H, Ar*H*), 7.35-7.23 (m, 3H, Ar*H*), 5.85 (dd, *J* = 17.5, 11.0 Hz, 1H, C*H*=CH_2), 5.13-5.01 (m, 2H, CH=CH_2), 4.11-4.03 (m, 2H, NCH_2), 3.91 (s, 3H, OCH_3), 1.88-1.82 (m, 2H, CH_2), 1.12 (s, 6H, C(CH_3)$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.5 (*C*O), 146.6 (*C*H=CH_2), 136.5 (*C*q), 134.2 (*C*H), 126.9 (*C*H), 122.8 (*C*H), 121.9 (*C*H), 112.3 (CH=*C*H_2), 110.0 (*C*H), 107.1 (*C*q), 51.1 (O*C*H_3), 43.6 (N*C*H_2), 42.3 (*C*H_2), 36.1 (*C*(CH_3)$_2$), 26.9 (C(*C*H_3)$_2$); **HRMS (ESI$^+$):** Calculated for $C_{17}H_{21}NO_2$ $[M+H]^+$: 272.1645, found 272.1647; **IR ν_{max} (neat)/cm^{-1}:** 3107 (CH), 2928 (CH), 1684 (C=O).

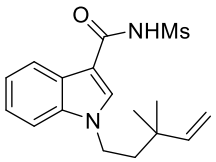
1-(3,3-Dimethylpent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 271



Methyl 1-(3,3-dimethylpent-4-en-1-yl)-1*H*-indole-3-carboxylate (4.5 mmol, 1.22 g) was subjected to the general hydrolysis conditions described above, to give the title compound (954 mg, 82%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 154-156 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.27-8.20 (m, 1H, Ar*H*), 7.92 (s, 1H, Ar*H*), 7.41-7.28 (m, 3H, Ar*H*), 5.86 (dd, *J* = 17.5, 11.0 Hz, 1H, C*H*=CH_2), 5.20-5.01 (m, 2H, CH=CH_2), 4.16-4.04 (m, 2H, NCH_2), 1.96-1.80 (m, 2H, CH_2), 1.13 (s, 6H, C(CH_3)$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.6 (*C*O), 146.5 (*C*H=CH_2), 136.7 (*C*q), 135.5 (*C*H), 127.2 (*C*q), 122.9 (*C*H), 122.3 (*C*H), 122.1 (*C*H), 112.4 (*C*H), 110.1 (CH=*C*H_2), 106.5 (*C*q), 43.8 (N*C*H_2), 42.2 (*C*H_2), 36.2 (*C*(CH_3)$_2$), 26.9 (C(CH_3)$_2$); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{19}NO_2$ [M+Na]$^+$: 280.1308, found 280.1230; **IR ν_{max} (neat)/cm^{-1}:** 2971 (br. OH), 2901 (CH), 1654 (C=O).

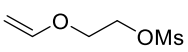
1-(3,3-Dimethylpent-4-en-1-yl)-*N*-(methylsulfonyl)-1*H*-indole-3-caboxamide 272



1-(3,3-Dimethylpent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 772 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (646 mg, 64%) as a white solid.

M.p. 152-154 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.89 (br. s, 1H, NH), 8.24-8.13 (m, 1H, Ar*H*), 7.89 (s, 1H, Ar*H*), 7.36-7.26 (m, 3H, Ar*H*), 5.83 (dd, *J* = 17.5, 11.0 Hz, 1H, C*H*=CH_2), 5.14-4.98 (m, 2H, CH=CH_2), 4.12-3.99 (m, 2H, NCH_2), 3.49 (s, 3H, SO_2CH_3), 1.89-1.82 (m, 2H, CH_2), 1.11 (s, 6H, C(CH_3)$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.0 (*C*O), 146.3 (*C*H=CH_2), 136.6 (*C*q), 132.7 (*C*H), 126.5 (*C*q), 123.4 (*C*H), 122.6 (*C*H), 121.4 (*C*H), 112.3 (CH=*C*H_2), 110.2 (*C*H), 107.4 (*C*q), 43.7 (N*C*H_2), 42.3 (SO_2CH_3), 41.9 (*C*H_2), 36.0 (*C*q), 26.7 (C(*C*H_3)$_2$); **HRMS (ESI$^+$):** Calculated for $C_{17}H_{22}N_2O_3S$ [M+Na]$^+$: 357.1243, found 357.1249; **IR ν_{max} (neat)/cm^{-1}:** 3154 (NH), 2962 (CH), 1640 (C=O), 1327 (S=O).

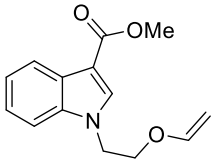
2-(Vinyloxy)ethyl methanesulfonate 275



Ethylene glycol vinyl ether (20.0 mmol, 1.79 mL) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (40% EtOAc/ petrol) to yield the title compound (2.22 g, 67%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 (dd, *J* = 14.5, 7.0 Hz, 1H, C*H*=CH_2), 4.47-4.42 (m, 2H, OCH_2), 4.22 (dd, *J* = 14.5, 2.5 Hz, 1H, CH=C*H*H), 4.09 (dd, *J* = 7.0, 2.5 Hz, 1H, CH=CH*H*), 3.98-3.93 (m, 2H, OCH_2), 3.05 (s, 3H, SO_2CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 151.1 (*C*H=CH_2), 87.9 (CH=*C*H_2), 68.0 (OCH_2), 65.7 (OCH_2), 37.8 (CH_3); **HRMS (ESI$^+$):** Calculated for $C_5H_{10}O_4S$ [M+Na]$^+$: 189.0192, found 189.0196.

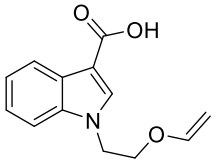
Methyl 1-(2-(vinyloxy)ethyl)-1*H*-indole-3-carboxylate 276



Methyl indole-3-carboxylate (18.0 mmol, 3.15 g) was subjected to the general alkylation conditions described above with 2-(vinyloxy)ethyl methanesulfonate. The crude material was purified by flash column chromatography (10% EtOAc/ petrol) to yield the title compound (2.99 g, 68%) as a white solid.

M.p. 66-68 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.22-8.16 (m, 1H, Ar*H*), 7.88 (s, 1H, Ar*H*), 7.41-7.36 (m, 1H, Ar*H*), 7.34-7.25 (m, 2H, Ar*H*), 6.41 (dd, *J* = 14.5, 7.0 Hz, 1H, C*H*=CH_2), 4.43 (t, *J* = 5.5 Hz, 2H, NCH_2), 4.16 (dd, *J* = 14.5, 2.5 Hz, 1H, CH=C*H*H), 4.04-3.99 (m, 3H, OCH_2 + CH=CH*H*), 3.91 (s, 3H, OCH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.6 (*C*O), 151.1 (*C*H=CH_2), 136.6 (*C*q), 135.0 (*C*H), 126.8 (*C*q), 123.0 (*C*H), 122.0 (*C*H), 109.8 (*C*H), 107.7 (*C*H), 87.6 (CH=*C*H_2), 66.0 (O*C*H_2), 51.2 (O*C*H_3), 46.1 (N*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{15}NO_3$ [M+H]$^+$: 246.1125, found 246.1128; **IR ν_{max} (neat)/cm^{-1}:** 2949 (CH), 1688 (C=O).

1-(2-(Vinyloxy)ethyl)-1*H*-indole-3-carboxylic acid 277

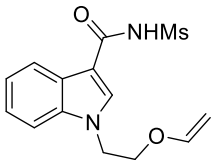


Methyl 1-(2-(vinyloxy)ethyl)-1*H*-indole-3-carboxylate (10.2 mmol, 2.50 g) was subjected to the general hydrolysis conditions described above. The crude material was recrystallised from MeCN to yield the title compound (1.38 g, 59%) as a white solid.

M.p. 140-141 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.28-8.22 (m, 1H, Ar*H*), 7.99 (s, 1H, Ar*H*), 7.45-7.36 (m, 1H, Ar*H*), 7.32 (dt, *J* = 6.5, 3.5 Hz, 2H, Ar*H*), 6.42 (dd, *J* = 14.5, 7.0 Hz, 1H, C*H*=CH_2), 4.45 (t, *J* =

5.5 Hz, 2H, NCH_2), 4.17 (dd, *J* = 14.5, 2.5 Hz, 1H, CH=C*H*H), 4.07-4.02 (m, 3H, OCH_2 + CH=CH*H*); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.5 (*C*O), 151.1 (*C*H), 136.8 (*C*q), 136.3 (*C*H), 127.1 (*C*q), 123.1 (*C*H), 122.4 (*C*H), 122.2 (*C*H), 109.9 (*C*H), 107.1 (*C*q), 87.6 (CH=*C*H_2), 65.9 (O*C*H_2), 46.2 (N*C*H_2); **HRMS (ESI^-):** Calculated for $C_{13}H_{13}NO_3$ $[M-H]^-$: 230.0823, found 230.0817; **IR ν_{max} (neat)/cm^{-1}:** 2923 (CH), 1661 (C=O).

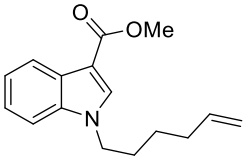
***N*-(Methylsulfonyl)-1-(2-vinyloxy)ethyl)-1*H*-indole-3-carboxamide 278**



1-(2-(Vinyloxy)ethyl)-1*H*-indole-3-carboxylic acid (4.3 mmol, 1.00 g) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (1.01 g, 77%) as a white solid.

M.p. 183-185 °C (MeCN); **^{1}H NMR (400 MHz, MeCN-d_3):** δ 9.22 (br. s, 1H, N*H*), 8.20-8.11 (m, 1H, Ar*H*), 8.01 (s, 1H, Ar*H*), 7.61-7.50 (m, 1H, Ar*H*), 7.39-7.23 (m, 2H, Ar*H*), 6.41 (dd, *J* = 14.5, 7.0 Hz, 1H, C*H*=CH_2), 4.47 (t, *J* = 5.0 Hz, 2H, NCH_2), 4.21 (dd, *J* = 14.5, 2.0 Hz, 1H, CH=C*H*H), 4.06 (t, *J* = 5.0 Hz, 2H, OCH_2), 4.00 (dd, *J* = 7.0 Hz, 2.0 Hz, 1H, CH=CH*H*), 3.34 (s, 3H, SO_2CH_3); **^{13}C NMR (101 MHz, MeCN-d_3):** δ 163.5 (*C*O), 152.2 (*C*H=CH_2), 137.8 (*C*q), 135.1 (*C*H), 127.8 (*C*q), 124.2 (*C*H), 123.2 (*C*H), 122.2 (*C*H), 111.7 (*C*H), 108.5 (*C*q), 88.0 (CH=*C*H_2), 67.4 (OCH_2), 47.0 (NCH_2), 42.4 (SO_2CH_3); **HRMS (ESI^+):** Calculated for $C_{14}H_{16}N_2O_4S$ $[M+H]^+$: 331.0723, found 331.0707; **IR ν_{max} (neat)/cm^{-1}:** 3168 (NH), 3110 (CH), 2932 (CH).

Methyl 1-(hex-5-en-1-yl)-1*H*-indole-3-carboxylate 280a

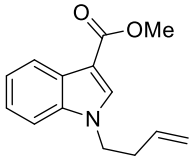


Methyl indole-3-carboxylate (10.0 mmol, 1.75 g) was subjected to the general alkylation conditions described above with 6-bromohex-1-ene. The crude material was purified by flash column chromatography (10% EtOAc/petrol) to afford the title compound (2.26 g, 84%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.15 (m, 1H, Ar*H*), 7.81 (s, 1H, Ar*H*), 7.39-7.32 (m, 1H, Ar*H*), 7.31-7.22 (m, 2H, Ar*H*), 5.74 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.04-4.90 (m, 2H, CH=CH_2), 4.13 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.91 (s, 3H, OCH_3), 2.08 (q, *J* = 7.0 Hz, 2H, CH_2), 1.87 (qn, *J* = 7.0 Hz, 2H, CH_2), 1.42 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.6 (*C*O), 138.0 (C*H*=CH_2), 136.6 (*C*q), 134.3 (*C*H), 126.8 (*C*H), 122.8 (*C*H), 121.9 (*C*H), 121.9 (*C*H), 115.4 (CH=*C*H_2), 110.1 (*C*H), 107.0 (*C*q), 51.1

(O*C*H$_3$), 47.0 (N*C*H$_2$), 33.3 (*C*H$_2$), 29.3 (*C*H$_2$), 26.2 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{19}NO_2$ [M+H]$^+$: 258.1489, found 258.1498; **IR ν_{max} (neat)/cm^{-1}:** 3116 (CH), 2939 (CH), 1699 (C=O).

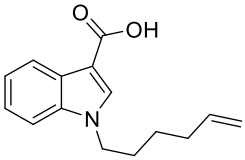
Methyl 1-(but-3-en-1-yl)-1*H*-indole-3-carboxylate 280b



Methyl indole-3-carboxylate (10.0 mmol, 1.75 g) was subjected to the general alkylation conditions described above with 4-bromo-1-butene. The crude material was purified by flash column chromatography (8% EtOAc/petrol) to afford the title compound (1.25 g, 54%) as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.21-8.15 (m, 1H, Ar*H*), 7.81 (s, 1H, Ar*H*), 7,39-7.35 (m, 1H, Ar*H*), 7.32-7.23 (m, 2H, Ar*H*), 5.76 (ddt, *J* = 17.5, 11.0, 7.0 Hz, 1H, C*H*=CH$_2$), 5.11-5.00 (m, 2H, CH=C*H*$_2$), 4.20 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 3.91 (s, 3H, OC*H*$_3$), 2.61 (app. qt, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$):** δ 165.6 (*C*O), 136.5 (*C*q), 134.3 (*C*H), 133.9 (*C*H=CH$_2$), 126.9 (*C*q), 122.8 (*C*H), 122.0 (*C*H), 121.9 (*C*H), 118.3 (CH=*C*H$_2$), 110.0 (*C*H), 107.1 (*C*q), 51.1 (O*C*H$_3$), 46.7 (N*C*H$_2$), 34.2 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{15}NO_2$ [M+Na]$^+$: 252.0995, found 252.0992; **IR ν_{max} (neat)/cm^{-1}:** 3109 (CH), 3053 (CH), 2952 (CH), 1684 (C=O).

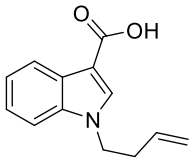
1-(Hex-5-en-1-yl)-1*H*-indole-3-carboxylic acid 281a



Methyl 1-(hex-5-en-1-yl)-1*H*-indole-3-carboxylate (8.4 mmol, 2.16 g) was subjected to the general hydrolysis conditions described above, to give the title compound (1.59 g, 78%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 119-120 °C (MeCN); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.29-8.22 (m, 1H, Ar*H*), 7.93 (s, 1H, Ar*H*), 7.42-7.36 (m, 1H, Ar*H*), 7.34-7.28 (m, 2H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH$_2$), 5.05-4.94 (m, 2H, CH=C*H*$_2$), 4.18 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 2.10 (q, *J* = 7.0 Hz, 2H, C*H*$_2$), 1.91 (qn, *J* = 7.0 Hz, 2H, C*H*$_2$), 1.46 (qn, *J* = 7.0 Hz, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$):** δ 170.6 (*C*O), 138.0 (*C*H=CH$_2$), 136.8 (*C*q), 135.6 (*C*H), 127.1 (*C*q), 123.0 (*C*H), 122.3 (*C*H), 122.1 (*C*H), 115.4 (CH=*C*H$_2$), 110.2 (*C*H), 106.5 (*C*q), 47.1 (N*C*H$_2$), 33.3 (*C*H$_2$), 29.3 (*C*H$_2$), 26.2 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{17}NO_2$ [M+Na]$^+$: 266.1151, found 266.1149; **IR ν_{max} (neat)/cm^{-1}:** 2934 (CH), 2585 (br. OH), 1645 (C=O).

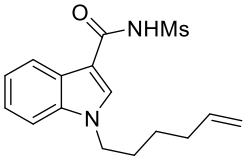
1-(But-3-en-1-yl)-1*H*-indole-3-carboxylic acid 281b



Methyl 1-(but-3-en-1-yl)-1*H*-indole-3-carboxylate (5.4 mmol, 1.24 g) was subjected to the general hydrolysis conditions described above, to give the title compound (1.07 g, 92%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 124-126 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.45-8.14 (m, 1H, Ar*H*), 7.93 (s, 1H, Ar*H*), 7.43-7.37 (m, 1H, Ar*H*), 7.35-7.29 (m, 2H, Ar*H*), 5.79 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.12-5.04 (m, 2H, CH=CH_2), 4.24 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.64 (q, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.4 (*C*O), 136.5 (*C*q), 135.5 (*C*H), 133.6 (*C*H=CH_2), 127.0 (*C*q), 122.9 (*C*H), 122.2 (*C*H), 121.9 (*C*H), 118.3 (CH=*C*H_2), 110.0 (*C*H), 106.3 (*C*q), 46.6 (N*C*H_2), 34.0 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{13}NO_2$ $[M+Na]^+$: 238.0838, found 238.0842; **IR ν_{max} (neat)/cm^{-1}:** 3116 (CH), 2945 (CH), 2606 (br. OH), 1644 (C=O).

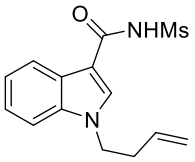
1-(Hex-5-en-1-yl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide 282a



1-(Hex-5-en-1-yl)-1*H*-indole-3-carboxylic acid (5.8 mmol, 1.41 g) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (1.52 g, 81%) as a white solid.

M.p. 181-182 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 10.06 (br. s, 1H, N*H*), 8.33 (s, 1H, Ar*H*), 8.30-8.21 (m, 1H, Ar*H*), 7.60-7.50 (m, 1H, Ar*H*), 7.37-7.15 (m, 2H, Ar*H*), 5.77 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.02-4.95 (m, 1H, CH=C*H*H), 4.94-4.89 (m, 1H, CH=CH*H*), 4.31 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.39 (s, 3H, SO_2CH_3), 2.09 (q, *J* = 7.0 Hz, 2H, CH_2), 1.91 (qn, *J* = 7.0 Hz, 2H, CH_2), 1.48-1.40 (m, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 163.3 (*C*O), 139.1 (*C*H=CH_2), 137.7 (*C*q), 134.2 (*C*H), 128.2 (*C*q), 123.9 (*C*H), 122.8 (*C*H), 122.4 (*C*H), 115.3 (CH=*C*H_2), 111.4 (*C*H), 108.4 (*C*q), 47.4 (N*C*H_2), 42.3 (SO_2CH_3), 33.9 (*C*H_2), 30.0 (*C*H_2), 26.7 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{20}N_2O_3S$ $[M+Na]^+$: 343.1087, found 343.1091; **IR ν_{max} (neat)/cm^{-1}:** 3231 (NH), 3116 (CH), 2927 (CH), 1645 (C=O), 1321 (S=O).

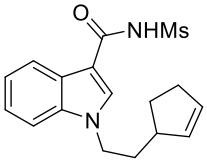
1-(But-3-en-1-yl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide 282b



1-(But-3-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 645 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (490 mg, 56%) as a white solid.

M.p. 186-188 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 10.06 (br. s, 1H, N*H*), 8.32 (s, 1H, Ar*H*), 8.29-8.24 (m, 1H, Ar*H*), 7.62-7.56 (m, 1H, Ar*H*), 7.34-7.21 (m, 2H, Ar*H*), 5.84 (ddt, *J* = 17.5, 9.5, 7.0 Hz, 1H, C*H*=CH_2), 5.09-4.97 (m, 2H, CH=CH_2), 4.37 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.39 (s, 3H, SO_2CH_3), 2.66 (app. qd, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 163.3 (*C*O), 137.7 (*C*q), 135.4 (*C*H=CH_2), 134.3 (*C*H), 128.2 (*C*q), 123.9 (*C*H), 122.8 (*C*H), 122.4 (*C*H), 118.0 (CH=*C*H_2), 111.4 (*C*H), 108.4 (*C*q), 47.0 (N*C*H_2), 42.3 (SO_2CH_3), 38.4 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{16}N_2O_3S$ [M+Na]$^+$: 315.0774, found 315.0770; **IR ν_{max} (neat)/cm^{-1}:** 3214 (NH), 3119 (CH), 2931 (CH), 1646 (C=O), 1321 (S=O).

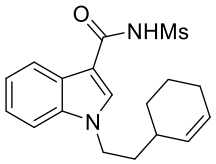
1-(2-(Cyclopent-2-en-1-yl)ethyl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide 285a



1-(2-(Cyclopent-2-en-1-yl)ethyl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 766 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (743 mg, 75%) as a white solid.

M.p. 164-165 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 10.07 (br. s, 1H, N*H*), 8.36 (s, 1H, Ar*H*), 8.27 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H, Ar*H*), 7.62-7.56 (m, 1H, Ar*H*), 7.35-7.22 (m, 2H, Ar*H*), 5.77-5.73 (m, 1H, C*H*=CH), 5.71-5.67 (m, 1H, CH=C*H*), 4.35 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.40 (s, 3H, SO_2CH_3), 2.72-2.62 (m, 1H, C*H*), 2.41-2.19 (m, 2H, CH_2), 2.13-1.97 (m, 2H, CH_2), 1.92-1.82 (m, 1H, C*H*H), 1.54-1.43 (m, 1H, CH*H*); **^{13}C NMR (101 MHz, acetone-d_6):** δ 163.4 (*C*O), 137.8 (*C*q), 134.8 (*C*H=CH), 134.3 (*C*H), 131.8 (CH=*C*H), 128.3 (*C*q), 124.0 (*C*H), 122.9 (*C*H), 122.5 (*C*H), 111.5 (*C*H), 108.6 (*C*q), 46.4 (N*C*H_2), 43.8 (*C*H), 42.4 (*C*H_3), 36.8 (*C*H_2), 32.6 (*C*H_2), 30.3 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{17}H_{20}N_2O_3S$ [M+H]$^+$: 333.1267, found 333.1253; **IR ν_{max} (neat)/cm^{-1}:** 3223 (br. NH), 3115 (CH), 2930 (CH), 1647 (C=O), 1321 (S=O), 1142 (S=O).

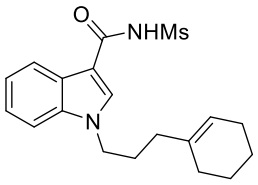
1-(2-(Cyclohex-2-en-1-yl)ethyl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide 285b



1-(2-(Cyclohex-2-en-1-yl)ethyl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 808 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (727 mg, 70%) as a white solid.

M.p. 135-138 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.31 (br. s, 1H, N*H*), 8.31-8.25 (m, 1H, Ar*H*), 8.02 (s, 1H, Ar*H*), 7.46-7.29 (m, 3H, Ar*H*), 5.84-5.74 (m, 1H, C*H*=CH), 5.67-5.63 (m, 1H, CH=C*H*), 4.23 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.54 (s, 3H, SO_2CH_3), 2.18-2.09 (m, 1H, C*H*), 2.04-1.99 (m, 2H, CH_2), 1.98-1.82 (m, 3H, 3 × C*H*H), 1.81-1.71 (m, 1H, C*H*H), 1.62-1.50 (m, 1H, C*H*H), 1.40-1.28 (m, 1H, C*H*H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.4 (*C*O), 136.7 (*C*q), 133.1 (*C*H), 130.0 (*C*H=CH), 128.6 (CH=*C*H), 126.9 (*C*q), 123.5 (*C*H), 122.7 (*C*H), 121.7 (*C*H), 110.3 (*C*H), 107.4 (*C*q), 45.0 (NCH_2), 42.3 (SO_2CH_3), 36.0 (*C*H_2), 32.6 (*C*H), 28.8 (*C*H_2), 25.2 (*C*H_2), 21.2 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{18}H_{22}N_2O_3S$ $[M+H]^+$: 347.1424, found 347.1413; **IR ν_{max} (neat)/cm^{-1}:** 3189 (br. NH), 3015 (CH), 2928-2836 (CH), 1634 (C=O), 1325 (S=O), 1157 (S=O).

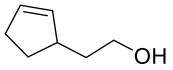
1-(3-(Cyclohex-1-en-1-yl)propyl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide 287



1-(3-Cyclohex-1-en-1-yl)propyl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 850 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (968 mg, 90%) as a white solid.

M.p. 149-150 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_3):** δ 10.06 (br. s, 1H, N*H*), 8.33 (s, 1H, Ar*H*), 8.29-8.23 (m, 1H, Ar*H*), 7.59-7.52 (m, 1H, Ar*H*), 7.35-7.21 (m, 2H, Ar*H*), 5.43-5.37 (m, 1H, C*H*=C), 4.28 (t, *J* = 6.5 Hz, 2H, NCH_2), 3.40 (s, 3H, SO_2CH_3), 2.05-1.85 (m, 8H, 4 × CH_2), 1.63-1.47 (m, 4H, 2 × CH_2); **^{13}C NMR (101 MHz, acetone-d_3):** δ 163.3 (*C*O), 137.7 (*C*q), 137.0 (*C*q), 134.2 (*C*H), 128.2 (*C*q), 123.8 (*C*H), 122.7 (*C*H), 122.5 (d, *C*H=C), 122.4 (*C*H), 111.4 (*C*H), 108.4 (*C*q), 47.1 (NCH_2), 42.2 (SO_2CH_3), 35.6 (*C*H_2), 28.7 (*C*H_2), 28.4 (*C*H_2), 25.8 (*C*H_2), 23.6 (*C*H_2), 23.1 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{19}H_{24}N_2O_3S$ $[M+H]^+$: 361.1580, found 361.1581; **IR ν_{max} (neat)/cm^{-1}:** 3304 (NH), 3126 (CH), 2923 (CH), 1668 (C=O), 1401 (S=O), 1168 (S=O).

2-(Cyclopent-2-en-1-yl)ethan-1-ol[206] 291a

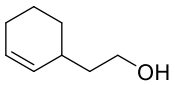


Synthesised using a modified literature procedure.[206]

To a solution of 2-cyclopentene-1-acetic acid (8.0 mmol, 0.96 mL) in Et_2O (40 mL) at 0 °C was added $LiAlH_4$ (16.0 mmol, 6.67 mL, 2.4 M solution in THF) dropwise. The reaction mixture was then allowed to warm to room temperature and was stirred for 3 hours. On completion, the mixture was re-cooled to 0 °C and quenched by the addition of water (0.42 mL), NaOH (2 M, 0.42 mL), and water (1.26 mL). The mixture was filtered through Celite®, washed with DCM, dried over $MgSO_4$ and concentrated to yield the title compound (846 mg, 94%) as a colourless oil (analytically pure), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77-5.72 (m, 1H, C*H*=CH), 5.71-5.66 (m, 1H, CH=C*H*), 3.76-3.64 (m, 2H, OCH_2), 2.83-2.72 (m, 1H, C*H*), 2.41-2.23 (m, 2H, CH_2), 2.13-2.01 (m, 1H, C*H*H), 1.75-1.65 (m, 1H, CH*H*), 1.63-1.53 (m, 1H, C*H*H), 1.50-1.38 (m, 1H, CH*H*); **IR ν_{max} (neat)/cm^{-1}:** 3312 (br. OH), 3050 (CH), 2927 (CH), 2850 (CH). Data are consistent with literature precedent.[206]

2-(Cyclohex-2-en-1-yl)ethan-1-ol[206] 291b



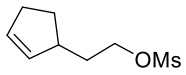
To a suspension of NaH (24.0 mmol, 960 mg, 60% dispersion in mineral oil) in THF (30 mL) was added diethyl malonate (24.0 mmol, 3.66 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 hour before the dropwise addition of 3-bromocyclohexene (12.0 mmol, 1.38 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 1 hour. On completion the mixture was poured into a solution of KOH (12 equiv.) in water/MeOH (1:1 v:v 30 mL), and stirred for a further 30 minutes. This was acidified with HCl (20 equiv.) and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was then refluxed in DMF for 3 hours. EtOAc was added, and the solution was washed with water (×3), washed with brine (×3), dried over $MgSO_4$ and concentrated. The crude product was used in the next step without further purification.

To a solution of crude 2-(cyclohex-2-en-1-yl)acetic acid (12.0 mmol) in Et_2O (55 mL) was added $LiAlH_4$ (20.0 mmol, 8.30 mL, 2.4 M solution in THF) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1 hour. On completion, the mixture was re-cooled to 0 °C and quenched by the addition of water (1.06 mL), NaOH (2 M, 1.06 mL), and water (3.18 mL). The mixture was filtered through Celite®, washed with DCM, dried over $MgSO_4$ and concentrated. The

crude residue was purified by flash column chromatography to yield the title compound (1.32 g, 87% over two steps) as a colourless oil.

^{1}H NMR (400 MHz, acetone-d_6): δ 5.73-5.65 (m, 1H, C*H*=CH), 5.62-5.55 (m, 1H, CH=C*H*), 3.79-3.69 (m, 2H, CH_2OH), 2.29-2.19 (m, 1H, C*H*), 2.02-1.94 (m, 2H, CH_2), 1.85-1.75 (m, 1H, C*H*H), 1.76-1.68 (m, 1H, CH*H*), 1.66-1.47 (m, 3H, 3 × C*H*H), 1.32-1.16 (m, 1H, CH*H*); **IR ν_{max} (neat)/cm^{-1}:** 3314 (br. OH), 3015 (CH), 2923 (CH). Data are consistent with literature precedent.[206]

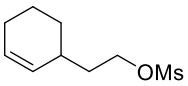
2-(Cyclopent-2-en-1-yl)ethyl methanesulfonate 292a



2-(Cyclopent-2-en-1-yl)ethan-1-ol (7.0 mmol, 785 mg) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (20% EtOAc/petrol) to yield the title compound (1.17 g, 88%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80-5.76 (m, 1H, C*H*=CH), 5.68-5.63 (m, 1H, CH=C*H*), 4.32-4.22 (m, 2H, OCH_2), 3.01 (s, 3H, SO_2CH_3), 2.84-2.75 (m, 1H, C*H*), 2.43-2.24 (m, 2H, CH_2), 2.15-2.06 (m, 1H, C*H*H), 1.93-1.83 (m, 1H, CH*H*), 1.79-1.68 (m, 1H, C*H*H), 1.49-1.38 (m, 1H, CH*H*); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 133.5 (*C*H=CH), 131.7 (CH=*C*H), 69.1 (O*C*H$_2$), 42.0 (SO_2CH_3), 37.6 (*C*H), 35.2 (*C*H$_2$), 32.0 (*C*H$_2$), 29.7 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_8H_{14}O_3S$ [M+Na]$^+$: 213.0556, found 213.0552; **IR ν_{max} (neat)/cm^{-1}:** 3048 (CH), 2938 (CH), 1345 (S=O), 1171 (S=O).

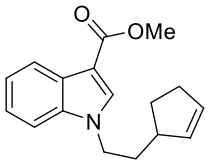
2-(Cyclohex-2-en-1-yl)ethyl methanesulfonate 292b



2-(Cyclohex-2-en-1-yl)ethan-1-ol (10.0 mmol, 1.26 g) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (5% EtOAc/petrol) to yield the title compound (1.94 g, 95%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76-5.69 (m, 1H, C*H*=CH), 5.57-5.50 (m, 1H, CH=C*H*), 4.30 (t, *J* = 6.5 Hz, 2H, OCH_2), 3.00 (s, 3H, SO_2CH_3), 2.31-2.21 (m, 1H, C*H*), 2.02-1.94 (m, 2H, CH_2), 1.86-1.77 (m, 2H, CH_2), 1.77-1.65 (m, 2H, CH_2), 1.59-1.48 (m, 1H, C*H*H), 1.30-1.20 (m, 1H, CH*H*); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 130.1 (*C*H=CH), 128.4 (CH=*C*H), 68.3 (O*C*H$_2$), 37.5 (SO_2CH_3), 35.4 (*C*H$_2$), 31.6 (*C*H), 28.7 (*C*H$_2$), 25.2 (*C*H$_2$), 21.2 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_9H_{16}O_3S$ [M+Na]$^+$: 227.0712, found 227.0714; **IR ν_{max} (neat)/cm^{-1}:** 2936 (CH).

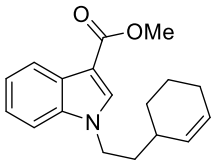
Methyl 1-(2-(cyclopent-2-en-1-yl)ethyl)-1*H*-indole-3-carboxylate 293a



Methyl indole-3-carboxylate (6.0 mmol, 1.05 g) was subjected to the general alkylation conditions described above with 2-(cyclopent-2-en-1-yl)ethyl methanesulfonate. The crude material was purified by flash column chromatography (5% EtOAc/petrol) to afford the title compound (1.35 g, 84%) as a white paste.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23-8.14 (m, 1H, Ar*H*), 7.83 (s, 1H, Ar*H*), 7.39-7.35 (m, 1H, Ar*H*), 7.32-7.24 (m, 2H, Ar*H*), 5.81-5.75 (m, 1H, C*H*=CH), 5.65-5.61 (m, 1H, CH=*CH*), 4.20-4.14 (m, 2H, NCH_2), 3.91 (s, 3H, OCH_3), 2.72-2.61 (m, 1H, C*H*), 2.44-2.24 (m, 2H, CH_2), 2.16-2.06 (m, 1H, CH*H*), 2.06-1.95 (m, 1H, C*H*H), 1.89-1.78 (m, 1H, C*H*H), 1.50-1.40 (m, 1H, CH*H*); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.7 (*C*O), 136.6 (*C*q), 134.3 (*C*H), 133.5 (*C*H=CH), 131.8 (CH=*C*H), 126.9 (*C*q), 122.8 (*C*H), 121.9 (*C*H), 121.9 (*C*H), 110.1 (*C*H), 107.1 (*C*q), 51.1 (*C*H_3), 45.7 (N*C*H_2), 43.0 (*C*H), 36.0 (*C*H_2), 32.1 (*C*H_2), 29.7 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{17}H_{19}NO_2$ [M+H]$^+$: 270.1489, found 270.1491; **IR ν_{max} (neat)/cm^{-1}:** 3109 (CH), 2945 (CH), 2854 (CH), 1686 (C=O).

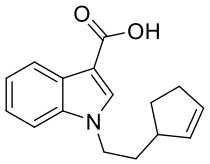
Methyl 1-2-(cyclohex-2-en-1-yl)ethyl)-1*H*-indole-3-carboxylate 293b



Methyl indole-3-carboxylate (9.0 mmol, 1.58 g) was subjected to the general alkylation conditions described above with 2-(cyclohex-2-en-1-yl)ethyl methanesulfonate. The crude material was purified by flash column chromatography (5% EtOAc/petrol) to afford the title compound (2.04 g, 80%) as a white solid.

M.p. 72-73 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.22-8.16 (m, 1H, Ar*H*), 7.84 (s, 1H, Ar*H*), 7.41-7.34 (m, 1H, Ar*H*), 7.31-7.24 (m, 2H, Ar*H*), 5.79-5.71 (m, 1H, C*H*=CH), 5.60-5.53 (m, 1H, CH=C*H*), 4.20 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.91 (s, 3H, OCH_3), 2.18-2.08 (m, 1H, C*H*), 2.04-1.96 (m, 2H, CH_2), 1.96-1.80 (m, 3H, 3 × C*H*H), 1.78-1.69 (m, 1H, CH*H*), 1.60-1.48 (m, 1H, C*H*H), 1.36-1.26 (m, 1H, CH*H*); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.6 (*C*O), 136.6 (*C*q), 134.2 (*C*H), 130.1 (*C*H=CH), 128.5 (CH=*C*H), 126.8 (*C*q), 122.8 (*C*H), 121.9 (*C*H), 121.9 (*C*H), 110.1 (*C*H), 107.1 (*C*q), 51.1 (O*C*H_3), 44.8 (N*C*H_2), 36.3 (*C*H_2), 32.7 (*C*H), 28.9 (*C*H_2), 25.3 (*C*H_2), 21.3 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{18}H_{21}NO_2$ [M+H]$^+$: 284.1645, found 284.1647; **IR ν_{max} (neat)/cm^{-1}:** 3113 (CH), 2987-2829 (CH), 1683 (C=O).

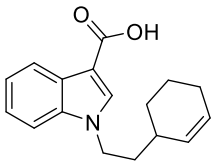
1-(2-(Cyclopent-2-en-1-yl)ethyl)-1*H*-indole-3-carboxylic acid 294a



Methyl 1-(2-(cyclopent-2-en-1-yl)ethyl)-1*H*-indole-3-carboxylate (5.0 mmol, 1.35 g) was subjected to the general hydrolysis conditions described above to give the title compound (1.02 g, 80%) as a white solid (analytically pure), which was used without further purification.

M.p. 152-153 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.30-8.23 (m, 1H, Ar*H*), 7.95 (s, 1H, Ar*H*), 7.44-7.37 (m, 1H, Ar*H*), 7.35-7.28 (m, 2H, Ar*H*), 5.84-5.77 (m, 1H, C*H*=CH), 5.68-5.62 (m, 1H, CH=C*H*), 4.24-4.17 (m, 2H, NCH_2), 2.74-2.64 (m, 1H, C*H*), 2.46-2.26 (m, 2H, CH_2), 2.17-1.98 (m, 2H, CH_2), 1.94-1.80 (m, 1H, C*H*H), 1.57-1.38 (m 1H, CH*H*); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.9 (*C*O), 136.8 (*C*q), 135.6 (*C*H), 133.5 (*C*H=CH), 131.8 (CH=*C*H), 127.1 (*C*q), 123.0 (*C*H), 122.3 (*C*H), 122.1 (*C*H), 110.2 (*C*H), 106.5 (*C*q), 45.9 (N*C*H_2), 43.0 (*C*H), 36.0 (*C*H_2), 32.1 (*C*H_2), 29.7 (*C*H_2); **HRMS (ESI^-):** Calculated for $C_{16}H_{17}NO_2$ $[M-H]^-$: 254.1187, found 254.1182; **IR ν_{max} (neat)/cm^{-1}:** 2988-2901 (CH), 2551 (br. OH), 1650 (C=O).

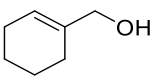
1-(2-(Cyclohex-2-en-1-yl)ethyl)-1*H*-indole-3-carboxylic acid 294b



Methyl 1-2-(cyclohex-2-en-1-yl)ethyl)-1*H*-indole-3-carboxylate (7.0 mmol, 1.98 g) was subjected to the general hydrolysis conditions described above to give the title compound (1.76 g, 93%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 144-145 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.28-8.22 (m, 1H, Ar*H*), 7.94 (s, 1H, Ar*H*), 7.44-7.37 (m, 1H, Ar*H*), 7.34-7.27 (m, 2H, Ar*H*), 5.80-5.71 (m, 1H, C*H*=CH), 5.62-5.53 (m, 1H, CH=C*H*), 4.22 (t, *J* = 7.5 Hz, 2H, NCH_2), 2.21-2.09 (m, 1H, C*H*), 2.05-1.81 (m, 5H, 5 × C*H*H), 1.79-1.70 (m, 1H, C*H*H), 1.61-1.49 (m, 1H, C*H*H), 1.39-1.27 (m, 1H, C*H*H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.6 (*C*O), 136.8 (*C*q), 135.5 (*C*H), 130.1 (*C*H=CH), 128.6 (CH=*C*H), 127.2 (*C*q), 123.0 (*C*H), 122.3 (*C*H), 122.1 (*C*H), 110.2 (*C*H), 106.6 (*C*q), 45.0 (N*C*H_2), 36.2 (*C*H_2), 32.8 (*C*H), 28.9 (*C*H_2), 25.3 (*C*H_2), 21.3 (*C*H_2); **HRMS (ESI^-):** Calculated for $C_{17}H_{19}NO_2$ $[M-H]^-$: 268.1343, found 268.1348; **IR ν_{max} (neat)/cm^{-1}:** 2926 (CH), 2584 (br. OH), 1651 (C=O).

Cyclohex-1-en-1-ylmethanol[207] 299

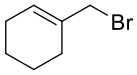


Synthesised using a modified literature procedure.[206]

To a solution of methyl 1-cyclohexene-1-carboxylate (20.0 mmol, 2.80 g) in DCM (40 mL) was added DIBAL-H (44 mmol, 44 mL, 1 M solution in hexane) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 3 hours before the addition of MeOH (40 mL) and saturated aqueous Rochelle's salt (40 mL). The mixture was allowed to warm to room temperature and then was stirred for 18 hours. The resulting phases were separated, and the aqueous phase extracted with EtOAc (×3). The combined organic extracts were dried over $MgSO_4$ and concentrated to yield the title compound (2.00 g, 89%) as a colourless oil (analytically pure), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71-5.66 (m, 1H, C*H*=C), 3.98 (s, 2H, CH_2OH), 2.06-1.98 (m, 4H, 2 × CH_2), 1.69-1.54 (m, 4H, 2 × CH_2); **IR ν_{max} (neat)/cm^{-1}:** 3305 (br. OH), 2922 (CH), 2856 (CH). Data are consistent with literature precedent.[207]

1-(Bromomethyl)cyclohex-1-ene[208] 300

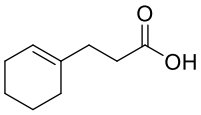


Synthesised using a modified literature procedure.[206]

To a solution of cyclohex-1-en-1-ylmethanol (17.0 mmol, 1.90 g) in Et_2O (80 mL) at 0 °C was added PBr_3. The reaction mixture was allowed to warm to room temperature and was stirred for 5 hours. On completion, the reaction mixture was poured into aqueous K_2CO_3 (17.0 mmol, 2.35 g). The resulting phases were separated, and the aqueous phase extracted with Et_2O (×2). The combined organic phases were dried over $MgSO_4$ and concentrated to yield the title compound (2.02 g, 68%) as a colourless oil (analytically pure), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90-5.85 (m, 1H, C*H*=C), 3.94 (s, 2H, CH_2Br), 2.16-2.09 (m, 2H, CH_2), 2.07-2.00 (m, 2H, CH_2), 1.72-1.63 (m, 2H, CH_2), 1.61-1.53 (m, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2927 (CH). Data are consistent with literature precedent.[208]

3-(Cyclohex-1-en-1-yl)propanoic acid[209] 301



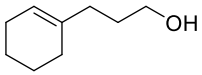
Synthesised using a modified literature procedure.[206]

To a suspension of NaH (22.0 mmol, 880 mg, 60% dispersion in mineral oil) in THF (30 mL) was added diethyl malonate (22.0 mmol, 3.34 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 hour before the dropwise addition of 1-(bromomethyl)cyclohex-1-ene (11.0 mmol, 1.93 g). The reaction mixture was allowed to warm to room temperature and was stirred for 1 hour. On completion, the

mixture was poured into a solution of KOH (12 equiv.) in water/MeOH (1:1 v:v 30 mL), and stirred for a further 30 minutes. The mixture was then acidified with HCl (20 equiv.) and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was then refluxed in DMF (30 mL) for 3 hours. EtOAc was added, and the solution was washed with water (×3), washed with brine (×3), dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (15% EtOAc/petrol) to yield the title compound (891 mg, 66%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46-5.41 (m, 1H, C*H*=C), 2.46 (dd, *J* = 9.0, 6.5 Hz, 2H, CH_2), 2.26 (t, *J* = 8.0 Hz, 2H, CH_2), 2.01-1.89 (m, 4H, 2 × CH_2), 1.66-1.50 (m, 4H, 2 × CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2926 (CH), 1709 (C=O). Data are consistent with literature precedent.[209]

3-(Cyclohex-1-en-1-yl)propan-1-ol[206] 302

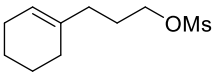


Synthesised using a modified literature procedure.[206]

To a solution of 3-(cyclohex-1-en-1-yl)propanoic acid (7.0 mmol, 1.08 g) in Et_2O (40 mL) was added $LiAlH_4$ (14.0 mmol, 5.80 mL, 2.4 M solution in THF) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1 hour. On completion, the mixture was re-cooled to 0 °C and quenched by the addition of water (0.63 mL), NaOH (2 M, 0.63 mL), and water (1.89 mL). The mixture was filtered through Celite®, washed with DCM, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography to yield the title compound (938 mg, 96%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49-5.39 (m, 1H, C*H*=C), 3.72-3.53 (m, 2H, CH_2), 2.08-1.84 (m, 6H, 3 × CH_2), 1.75-1.45 (m, 6H, 3 × CH_2); **IR ν_{max} (neat)/cm^{-1}:** 3316 (br. OH), 2923 (CH). Data are consistent with literature precedent.[206]

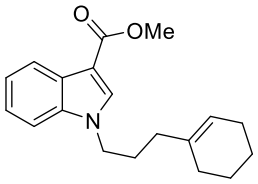
3-(Cyclohex-1-en-1-yl)propyl methanesulfonate[210] 303



3-(Cyclohex-1-en-1-yl)propan-1-ol (6.4 mmol, 897 mg) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (12% EtOAc/petrol) to yield the title compound (1.22 g, 86%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47-5.38 (m, 1H, C*H*=C), 4.20 (t, *J* = 6.5 Hz, 2H, OCH_2), 2.99 (s, 3H, SO_2CH_3), 2.04 (t, *J* = 7.5 Hz, 2H, CH_2), 2.01-1.95 (m, 2H, CH_2), 1.93-1.79 (m, 4H, 2 × CH_2), 1.66-1.58 (m, 2H, CH_2), 1.58-1.50 (m, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2930 (CH). Data are consistent with literature precedent.[210]

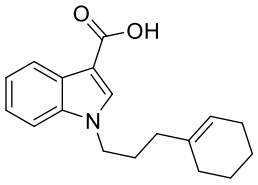
Methyl 1-(3-cyclohex-1-en-1-yl)propyl)-1*H*-indole-3-carboxylate 304



Methyl indole-3-carboxylate (5.5 mmol, 963 mg) was subjected to the general alkylation conditions described above with 3-(cyclohex-1-en-1-yl)propyl methanesulfonate. The crude material was purified by flash column chromatography (4% EtOAc/petrol) to afford the title compound (1.50 g, 91%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20-8.15 (m, 1H, Ar*H*), 7.82 (s, 1H, Ar*H*), 7.38-7.32 (m, 1H, Ar*H*), 7.31-7.23 (m, 2H, Ar*H*), 5.44-5.38 (m, 1H, C*H*=C), 4.16-4.08 (m, 2H, NCH_2), 2.03-1.94 (m, 6H, 3 × CH_2), 1.93-1.83 (m, 2H, CH_2), 1.68-1.50 (m, 4H, 2 × CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.7 (*C*O), 136.6 (*C*q), 136.0 (*C*q), 134.5 (*C*H), 126.8 (*C*q), 122.7 (*C*H), 122.4 (*C*H=C), 121.9 (*C*H), 121.9 (*C*H), 110.1 (*C*H), 107.0 (*C*q), 51.1 (O*C*H_3), 46.6 (N*C*H_2), 35.1 (*C*H_2), 28.4 (*C*H_2), 27.6 (*C*H_2), 25.3 (*C*H_2), 23.0 (*C*H_2), 22.6 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{19}H_{23}NO_2$ $[M+H]^+$: 298.1802, found 298.1809; **IR ν_{max} (neat)/cm^{-1}:** 2925 (CH), 1699 (C=O).

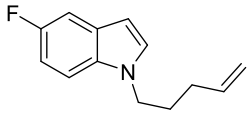
1-(3-Cyclohex-1-en-1-yl)propyl)-1*H*-indole-3-carboxylic acid 305



Methyl 1-(3-cyclohex-1-en-1-yl)propyl)-1*H*-indole-3-carboxylate (5.0 mmol, 1.49 g) was subjected to the general hydrolysis conditions described above to give the title compound (1.22 g, 86%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 136-138 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.29-8.22 (m, 1H, Ar*H*), 7.93 (s, 1H, Ar*H*), 7.41-7.34 (m, 1H, Ar*H*), 7.34-7.27 (m, 2H, Ar*H*), 5.47-5.41 (m, 1H, C*H*=C), 4.22-4.06 (m, 2H, NCH_2), 2.07-1.97 (m, 6H, 3 × CH_2), 1.94-1.86 (m, 2H, CH_2), 1.68-1.51 (m, 2H, 2 × CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.8 (*C*O), 136.8 (*C*q), 135.9 (*C*q), 135.7 (*C*H), 127.1 (*C*q), 122.9 (*C*H), 122.5 (*C*H=C), 122.2 (*C*H), 122.1 (*C*H), 110.2 (*C*H), 106.4 (*C*q), 46.7 (N*C*H_2), 35.1 (*C*H_2), 28.3 (*C*H_2), 27.5 (*C*H_2), 25.4 (*C*H_2), 23.0 (*C*H_2), 22.6 (*C*H_2); **HRMS (ESI$^-$):** Calculated for $C_{18}H_{21}NO_2$ $[M-H]^-$: 282.1500, found 282.1495; **IR ν_{max} (neat)/cm^{-1}:** 2925-2854 (CH), 2581 (br. OH), 1642 (C=O).

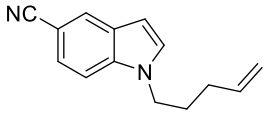
5-Fluoro-1-(pent-4-en-1-yl)-1*H*-indole 307a



5-Fluoroindole (10.0 mmol, 1.35 g) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (2% EtOAc/petrol) to afford the title compound (2.08g, 103%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.22 (m, 2H, Ar*H*), 7.13 (d, *J* = 3.0 Hz, 1H, Ar*H*), 6.96 (td, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 6.45 (dd, *J* = 3.0, 1.0 Hz, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.10-5.00 (m, 2H, CH=CH_2), 4.12 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.12-2.04 (m, 2H, CH_2), 2.00-1.89 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 157.9 (d, *J* = 234.0 Hz, *C*F), 137.3 (*C*H=CH_2), 132.7 (*C*q), 129.5 (*C*H), 128.9 (d, *J* = 10.0 Hz, *C*q), 115.9 (CH=*C*H_2), 110.0 (d, *J* = 10.0 Hz, *C*H), 109.9 (d, *J* = 26.5 Hz, *C*H), 105.7 (d, *J* = 23.5 Hz, *C*H), 101.1 (d, *J* = 4.5 Hz, *C*H), 46.0 (N*C*H_2), 30.9 (*C*H_2), 29.3 (*C*H_2); **^{19}F NMR (377 MHz, $CDCl_3$):** δ -125.67 (td, *J* = 10.0, 4.5 Hz, Ar*F*); **HRMS (ESI^+):** Calculated for $C_{13}H_{14}FN$ $[M+H]^+$: 204.1183, found 204.1182; **IR ν_{max} (neat)/cm^{-1}:** 3077 (CH), 2925 (CH), 1486 (CF).

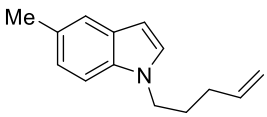
1-(Pent-4-en-1-yl)-1*H*-indole-5-carbonitrile 307b



5-Cyanoindole (10.0 mmol, 1.42 g) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (4% EtOAc/petrol) to give the title compound (1.57 g, 75%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H, Ar*H*), 7.47-7.32 (m, 2H, Ar*H*), 7.21 (d, *J* = 3.0 Hz, 1H, Ar*H*), 6.57 (dd, *J* = 3.0, 1.0 Hz, 1H, Ar*H*), 5.86-5.71 (m, 1H, C*H*=CH_2), 5.08-5.05 (m, 1H, CH=C*H*H), 5.05-5.02 (m, 1H, CH=CH*H*), 4.16 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.12-2.01 (m, 2H, CH_2), 1.95 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 137.6 (*C*q), 137.0 (*C*H=CH_2), 130.2 (*C*H), 128.4 (*C*q), 126.7 (*C*H), 124.5 (*C*H), 121.0 (*C*q), 116.2 (CH=*C*H_2), 110.3 (*C*H), 102.5 (*C*q), 102.4 (*C*H), 45.9 (N*C*H_2), 30.8 (*C*H_2), 29.3 (*C*H_2); **HRMS (ESI^+):** Calculated for $C_{14}H_{14}N_2$ $[M+H]^+$: 211.1230, found 211.1234; **IR ν_{max} (neat)/cm^{-1}:** 3071 (CH), 2973 (CH), 2931 (CH), 2217 (CN).

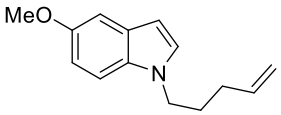
5-Methyl-1-(pent-4-en-1-yl)-1*H*-indole 307c



5-Methylindole (17 mmol, 2.23 g) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (5% DCM/petrol) to give the title compound (3.47 g, quantitative) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dt, *J* = 1.5, 1.0 Hz, 1H, Ar*H*), 7.26 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.09-7.03 (m, 2H, Ar*H*), 6.43 (dd, *J* = 3.0, 1.0 Hz, 1H, Ar*H*), 5.83 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.13-5.00 (m, 2H, CH=CH_2), 4.12 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.48 (s, 3H, CH_3), 2.13-2.02 (m, 2H, CH_2), 2.00-1.91 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 137.5 (*C*H), 134.5 (*C*q), 129.0 (*C*q), 128.5 (*C*q), 128.0 (*C*H=CH_2), 123.0 (*C*H), 120.7 (*C*H), 115.6 (CH=*C*H_2), 109.2 (*C*H), 100.5 (*C*H), 45.8 (N*C*H_2), 21.5 (*C*H_3), 30.1 (*C*H_2), 29.4 (*C*H_2); **HRMS (ESI^+):** Calculated for $C_{14}H_{17}N$ $[M+H]^+$: 200.1434, found 200.1443; **IR ν_{max} (neat)/cm^{-1}:** 2922 (CH), 1640 (C=C).

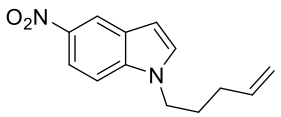
5-Methoxy-1-(pent-4-en-1-yl)-1*H*-indole 307d



5-Methoxyindole (10.0 mmol, 1.47 g) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (2% EtOAc/petrol) to give the title compound (1.93 g, 90%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (dt, *J* = 9.0, 0.5 Hz, 1H, Ar*H*), 7.10 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.07 (d, *J* = 3.0 Hz, 1H, Ar*H*), 6.88 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 6.41 (dd, *J* = 3.0, 1.0 Hz, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.10-4.97 (m, 2H, CH=CH_2), 4.10 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.86 (s, 3H, OCH_3), 2.11-2.03 (m, 2H, CH_2), 1.99-1.89 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 154.0 (*C*q), 137.5 (*C*H=CH_2), 131.4 (*C*q), 129.0 (*C*q), 128.4 (*C*H), 115.8 (CH=*C*H_2), 111.9 (*C*H), 110.2 (*C*H), 102.7 (*C*H), 100.6 (*C*H), 56.0 (O*C*H_3), 45.9 (N*C*H_2), 31.0 (*C*H_2), 29.4 (*C*H_2); **HRMS (ESI^+):** Calculated for $C_{14}H_{17}NO$ $[M+H]^+$: 216.1383, found 216.1390; **IR ν_{max} (neat)/cm^{-1}:** 2931 (CH).

5-Nitro-1-(pent-4-en-1-yl)-1*H*-indole 307e

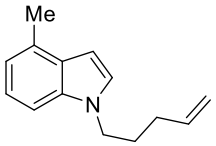


5-Nitroindole (10.0 mmol, 1.62 g) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (10% EtOAc/petrol) to give the title compound (2.30 g, quantitative) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 2.0 Hz, 1H, Ar*H*), 8.11 (dd, *J* = 9.0, 2.0, 1H, Ar*H*), 7.34 (dt, *J* = 9.0, 0.5 Hz, 1H, Ar*H*), 7.24 (d, *J* = 3.0 Hz, 1H, Ar*H*), 6.68 (dd, *J* = 3.5, 1.0 Hz, 1H, Ar*H*), 5.87-5.73 (m, 1H,

C*H*=CH_2), 5.11-4.95 (m, 2H, CH=CH_2), 4.18 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.12-2.03 (m, 2H, CH_2), 1.97 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 141.6 (*C*q), 138.9 (*C*q), 136.9 (*C*H=CH_2), 131.1 (*C*H), 127.8 (*C*q), 118.4 (*C*H), 117.3 (*C*H), 116.2 (CH=*C*H_2), 109.3 (*C*H), 104.1 (*C*H), 46.1 (N*C*H_2), 30.8 (*C*H_2), 29.3 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{14}N_2O_2$ $[M+Na]^+$: 253.0975 found 253.0955; **IR ν_{max} (neat)/cm^{-1}:** 3076 (CH), 2922-2852 (CH), 1512 (NO_2), 1330 (NO_2).

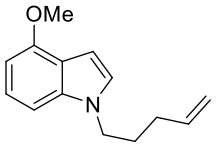
4-Methyl-1-(pent-4-en-1-yl)-1*H*-indole 307f



5-Methylindole (4.3 mmol, 0.48 mL) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (4% DCM/petrol) to give the title compound (634 g, 73%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.08 (m, 3H, Ar*H*), 6.92 (dt, *J* = 7.0, 1.0 Hz, 1H, Ar*H*), 6.52 (dd, *J* = 3.0, 1.0 Hz, 1H, Ar*H*), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.11-5.02 (m, 2H, CH=CH_2), 4.14 (t, *J* = 7.0 Hz, 1H, NCH_2), 2.58 (s, 3H, CH_3), 2.15-2.05 (m, 2H, CH_2), 1.97 (dt, *J* = 8.0, 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 137.5 (*C*H=CH_2), 135.8 (*C*q), 130.6 (*C*q), 128.6 (*C*q), 127.3 (*C*H), 121.7 (*C*H), 119.6 (*C*H), 115.7 (CH=*C*H_2), 107.2 (*C*H), 99.6 (*C*H), 45.9 (N*C*H_2), 31.0 (*C*H_2), 29.4 (*C*H_2), 18.9 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{17}N$ $[M+H]^+$: 200.1434, found 200.1439; **IR ν_{max} (neat)/cm^{-1}:** 2926 (CH).

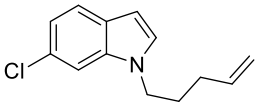
4-Methoxy-1-(pent-4-en-1-yl)-1*H*-indole 307g



4-Methoxyindole (10.0 mmol, 1.47 g) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (2% EtOAc/petrol) to give the title compound (2.15 g, quantitative) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.04-6.94 (m, 2H, Ar*H*), 6.60 (dd, *J* = 3.0, 1.0, 1H, Ar*H*), 6.53 (d, *J* = 7.5 Hz, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.11-5.00 (m, 2H, CH=CH_2), 4.11 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.97 (s, 3H, OCH_3), 2.13-2.04 (m, 2H, CH_2), 1.99-1.88 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 153.6 (*C*q), 137.6 (*C*H=CH_2), 137.5 (*C*H), 126.5 (*C*H), 122.3 (*C*H), 119.2 (*C*q), 115.7 (CH=*C*H_2), 103.1 (*C*H), 99.2 (*C*H), 98.4 (*C*H), 55.4 (O*C*H_3), 46.0 (N*C*H_2), 31.0 (*C*H_2), 29.4 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{17}NO$ $[M+H]^+$: 216.1383, found 216.1390; **IR ν_{max} (neat)/cm^{-1}:** 2928 (CH).

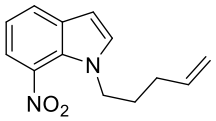
6-Chloro-1-(pent-4-en-1-yl)-1*H*-indole 307h



6-Chloroindole (3.6 mmol, 547 mg) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (5% EtOAc/petrol) to give the title compound (768 mg, 97%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.35-7.32 (m, 1H, Ar*H*), 7.11-7.05 (m, 2H, Ar*H*), 6.47 (dd, *J* = 3.0, 1.0 Hz, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.12-5.05 (m, 1H, CH=C*H*H), 5.05-5.02 (m, H, CH=CH*H*), 4.08 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.07 (q, *J* = 7.0 Hz, 2H, CH_2), 1.98-1.89 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 137.3 (*C*H=CH_2), 136.5 (*C*q), 128.6 (*C*H), 127.6 (*C*q), 127.2 (*C*q), 121.9 (*C*H), 120.1 (*C*H), 116.0 (CH=*C*H_2), 109.5 (*C*H), 101.4 (*C*H), 45.8 (N*C*H_2), 30.9 (*C*H_2), 29.2 (*C*H_2); **HRMS (ESI^+):** Calculated for $C_{13}H_{14}{}^{35}ClN$ $[M+H]^+$: 220.0888, found 220.0892; **IR ν_{max} (neat)/cm^{-1}:** 3076 (CH), 2930 (CH).

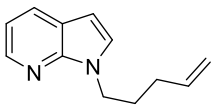
7-Nitro-1-(pent-4-en-1-yl)-1*H*-indole 307i



7-Nitroindole (5.0 mmol, 811 mg) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (4% EtOAc/petrol) to give the title compound (846 mg, 75%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.82 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.18 (d, *J* = 3.0 Hz, 1H, Ar*H*), 7.14 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.64 (d, *J* = 3.5 Hz, 1H, Ar*H*), 5.73 (ddt, *J* = 16.0, 11.0, 6.5 Hz, 1H, C*H*=CH_2), 5.04-4.99 (m, 1H, CH=C*H*H), 4.99-4.94 (m, 1H, CH=CH*H*), 4.27 (t, *J* = 7.0 Hz, 2H, NCH_2), 1.98-1.88 (m, 2H, CH_2), 1.77-1.68 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 137.2 (*C*H_2=CH_2), 137.2 (*C*q), 134.0 (*C*q), 133.0 (*C*H), 127.3 (*C*H), 126.3 (*C*q), 120.1 (*C*H), 118.6 (*C*H), 115.9 (CH=*C*H_2), 102.9 (*C*H), 49.6 (N*C*H_2), 30.7 (*C*H_2), 29.8 (*C*H_2); **HRMS (ESI^+):** Calculated for $C_{13}H_{14}N_2O_2$ $[M+Na]^+$: 253.0947, found 253.0904; **IR ν_{max} (neat)/cm^{-1}:** 2973-2901 (CH), 1512 (NO_2), 1320 (NO_2).

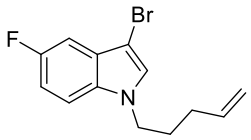
1-(Pent-4-en-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine 307j



7-Azaindole (10.0 mmol, 1.18 g) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (4% EtOAc/petrol) to give the title compound (1.84 g, 99%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar*H*), 7.90 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.21 (d, *J* = 3.5 Hz, 1H, Ar*H*), 7.05 (dd, *J* = 8.0, 4.5, Hz, 1H, Ar*H*), 6.45 (d, *J* = 3.5, 1H, Ar*H*), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.10-4.94 (m, 2H, CH=CH_2), 4.32 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.10 (q, *J* = 7.0 Hz, 2H, CH_2), 2.04-1.92 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 147.6 (*C*q), 142.8 (*C*H), 137.7 (*C*H=CH_2), 128.8 (*C*H), 128.1 (*C*H), 120.7 (*C*q), 115.7 (*C*H), 115.5 (CH=*C*H_2), 99.4 (*C*H), 44.1 (N*C*H_2), 31.1 (*C*H_2), 29.6 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{14}N_2$ $[M+H]^+$: 187.1230, found 187.1234; **IR ν_{max} (neat)/cm^{-1}:** 3056 (CH), 2925 (CH).

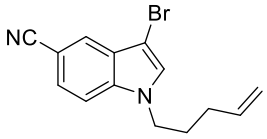
3-Bromo-5-fluoro-1-(pent-4-en-1-yl)-1*H*-indole 308a



To a solution of 5-fluoro-1-(pent-4-en-1-yl)-1*H*-indole (10.0 mmol, 2.03 g) in DMF (60 mL) was added NBS (10.0 mmol, 1.78 g) at 0 °C. The reaction mixture was shielded from light and stirred at 0 °C for 2 hours. The completed reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with water and extracted with Et_2O (×3). The combined organic layers were washed with water (×3), washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (100% petrol) to give the title compound (2.02 g, 72%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.19 (m, 2H, Ar*H*), 7.15 (s, 1H, Ar*H*), 6.99 (td, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 5.85-5.73 (m, 1H, C*H*=CH_2), 5.09-5.505 (m, 1H CH=C*H*H), 5.06-5.00 (m, 1H, CH=CH*H*), 4.09 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.10-2.03 (m, 2H, CH_2), 1.97-1.88 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 158.2 (d, *J* = 236.0 Hz, *C*F), 136.9 (*C*H=CH_2), 132.2 (*C*q), 128.2 (*C*H), 127.7 (d, *J* = 10.5 Hz, *C*q), 116.0 (CH=*C*H_2), 111.2 (d, *J* = 26.5 Hz, *C*H), 110.5 (d, *J* = 9.5 Hz, *C*H), 104.3 (d, *J* = 24.5 Hz, *C*H), 89.1 (d, *J* = 5.0 Hz, *C*q), 46.1 (N*C*H_2), 30.7 (*C*H_2), 29.1 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{13}{}^{79}BrFN$ $[M+H]^+$: 282.0288, found 282.0290; **IR ν_{max} (neat)/cm^{-1}:** 3077 (CH), 2974 (CH), 1486 (CF).

3-Bromo-1-(pent-4-en-1-yl)-1*H*-indole-5-carbonitrile 308b

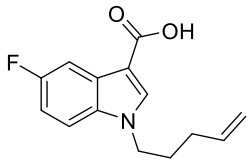


To a solution of 1-(pent-4-en-1-yl)-1*H*-indole-5-carbonitrile (7.5 mmol, 1.58 g) in DMF (45 mL) was added NBS (7.5 mmol, 1.34 g) at 0 °C. The reaction mixture was shielded from light and stirred at 0 °C

for 2 hours. The completed reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with water and extracted with Et_2O (×3). The combined organic layers were washed with water (×3), washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (15% Et_2O/petrol), to give the title compound as a colourless solid (1.83 g, 85%).

M.p. 64-66 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.93-7.90 (m, 1H, Ar*H*), 7.47 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 7.37 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.27-7.23 (m, 1H, Ar*H*), 5.78 (ddt, *J* = 17.0, 11.0, 7.0 Hz, 1H, C*H*=CH_2), 5.10-5.01 (m, 2H, CH=CH_2), 4.14 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.11-2.04 (m, 2H, CH_2), 1.94 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 137.3 (*C*q), 136.7 (*C*H=CH_2), 129.1 (*C*H), 127.4 (*C*q), 125.5 (*C*H), 125.4 (*C*H), 120.3 (*C*q), 116.4 (CH=*C*H_2), 110.8 (*C*H), 103.6 (*C*q), 90.9 (*C*q), 46.2 (NCH_2), 30.7 (*C*H_2), 29.2 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{13}{}^{79}BrN_2$ [M+H]$^+$: 289.0335, found 289.0337; **IR ν_{max} (neat)/cm^{-1}:** 3106 (CH), 2929 (CH), 2220 (CN).

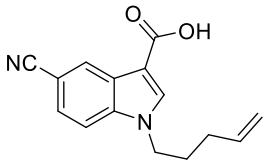
5-Fluoro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 309a



A solution of 3-bromo-5-fluoro-1-(pent-4-en-1-yl)-1*H*-indole (2.0 mmol, 564 mg) in THF (10 mL) was cooled to -78 °C. n-Butyllithium (2.2 mmol, 0.88 mL, 2.5 M solution in hexane) was added dropwise over 10 minutes. The reaction mixture was stirred at -78 °C for 30 minutes. CO_2 was bubbled through the mixture until complete consumption of indole starting material was observed by TLC. The completed reaction was allowed to warm to room temperature and was quenched with water (10 mL). The mixture was acidified to pH 1 with 3 M HCl and extracted with EtOAc (×3). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (30% EtOAc/petrol) to give the title compound (359 mg, 73%) as an off-white solid.

M.p. 167-168 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 8.08 (s, 1H, Ar*H*), 7.79 (dd, *J* = 10.0, 2.5 Hz, 1H, Ar*H*), 7.58 (dd, *J* = 9.0, 4.5 Hz, 1H, Ar*H*), 7.06 (td, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 5.86 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.04 (app. dq, 1H, CH=C*H*H), 5.00-4.93 (m, 1H, CH=CH*H*), 4.34 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.15-2.07 (m, 2H, CH_2), 2.04-1.96 (m, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 164.9 (*C*O), 159.0 (d, *J* = 235.0 Hz, *C*F), 137.4 (*C*H=CH_2), 136.3 (*C*H), 133.4 (*C*q), 127.8 (d, *J* = 11.0 Hz, *C*q), 114.9 (CH=*C*H_2), 111.7 (d, *J* = 10.0 Hz, *C*H), 110.5 (d, *J* = 26.5 Hz, *C*H), 106.5 (d, *J* = 4.5 Hz, *C*q), 106.0 (d, *J* = 25.0 Hz, *C*H), 46.2 (NCH_2), 30.5 (*C*H_2), 29.0 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{14}FNO_2$ [M+H]$^+$: 248.1081, found 248.1085; **IR ν_{max} (neat)/cm^{-1}:** 2941 (CH), 2567 (br. OH), 1656 (C=O).

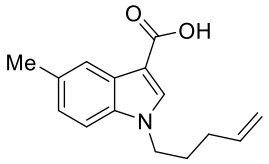
5-Cyano-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 309b



A solution of 3-bromo-1-(pent-4-en-1-yl)-1*H*-indole-5-carbonitrile (5.8 mmol, 1.66 g) in THF (25 mL) was cooled to -78 °C. n-Butyllithium (6.6 mmol, 2.64 mL, 2.5 M solution in hexane) was added dropwise over 10 minutes. The reaction mixture was stirred at -78 °C for 30 minutes. CO_2 was bubbled through the mixture until complete consumption of indole starting material was observed by TLC. The completed reaction was allowed to warm to room temperature and was quenched with water (10 mL). The mixture was acidified to pH 1 with 3 M HCl and extracted with EtOAc (×3). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (40% EtOAc/petrol) to give the title compound (632 mg, 73%) as an orange solid.

M.p. 169-169 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.61-8.54 (m, 1H, Ar*H*), 8.03 (s, 1H, Ar*H*), 7.53 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 7.45 (d, *J* = 8.5 Hz, 1H, Ar*H*), 5.79 (ddt, *J* = 16.0, 11.5, 7.0 Hz, 1H, C*H*=CH_2), 5.13-5.02 (m, 2H, CH=CH_2), 4.22 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.12 (q, *J* = 7.0 Hz, 2H, CH_2), 2.06-1.97 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 169.6 (*C*O), 138.3 (*C*q), 137.4 (*C*H), 136.4 (*C*H=CH_2), 127.6 (*C*H), 126.8 (*C*q), 126.1 (*C*H), 120.1 (*C*q), 116.8 (CH=*C*H_2), 111.2 (*C*H), 107.4 (*C*q), 105.8 (*C*q), 46.7 (N*C*H_2), 30.6 (*C*H_2), 28.9 (*C*H_2); **HRMS (ESI$^-$):** Calculated for $[M-H]^-$: 253.0983, found 253.0978; **IR ν_{max} (neat)/cm^{-1}:** 3109 (CH), 2945 (br. OH), 2225 (CN), 1656 (C=O).

5-Methyl-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 309c

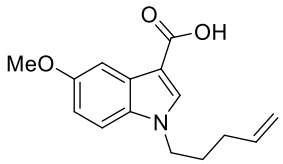


5-Methyl-1-(pent-4-en-1-yl)-1*H*-indole (5.0 mmol, 997 mg) was subjected to the general carboxylation conditions described above. The crude material was purified by recrystallization from MeCN to give the title compound (891 mg, 73%) as an off-white solid.

M.p. 135-138 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.06 (dt, *J* = 2.0, 1.0 Hz, 1H, Ar*H*), 7.88 (s, 1H, Ar*H*), 7.27 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.13 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 5.80 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.12-5.03 (m, 2H, CH=CH_2), 4.16 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.51 (s, 3H, CH_3), 2.14-2.06 (m, 2H, CH_2), 2.04-1.94 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.6 (*C*O), 136.9 (*C*H=CH_2), 135.6 (*C*H), 135.2 (*C*q), 131.9 (*C*q), 127.4 (*C*q), 124.5 (*C*H) 121.8 (*C*H), 116.3 (CH=*C*H_2), 109.9 (*C*H), 105.9 (*C*q), 46.5

(N*C*H$_2$), 30.8 (*C*H$_2$), 28.9 (*C*H$_2$), 21.7 (*C*H$_3$); **HRMS (ESI$^-$):** Calculated for $C_{15}H_{17}NO_2$ [M-H]$^-$: 242.1187, found 242.1188; **IR ν_{max} (neat)/cm^{-1}:** 2918 (CH), 2852 (CH), 2546 (br. OH), 1614 (C=O).

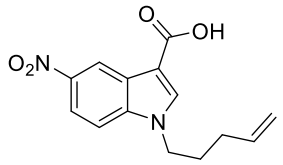
5-Methoxy-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 309d



5-Methoxy-1-(pent-4-en-1-yl)-1*H*-indole (5.0 mmol, 1.08 g) was subjected to the general carboxylation conditions described above. The crude material was purified by recrystallization from MeCN to give the title compound (843 mg, 65%) as an off-white solid.

M.p. 129-130 °C (MeCN); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.88 (s, 1H, Ar*H*), 7.72 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.26 (dd, *J* = 9.0, 0.5 Hz, 1H, Ar*H*), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 5.80 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH$_2$), 5.12-5.03 (m, 2H, CH=C*H*$_2$), 4.14 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 3.93 (s, 3H, OC*H*$_3$), 2.14-2.06 (m, 2H, C*H*$_2$), 2.03-1.94 (m, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$):** δ 170.0 (*C*O), 156.2 (*C*q), 136.9 (*C*H=CH$_2$), 135.6 (*C*H), 131.8 (*C*q), 128.0 (*C*q), 116.3 (CH=*C*H$_2$), 113.6 (*C*H), 111.1 (*C*H), 106.0 (*C*q), 103.3 (*C*H), 56.0 (O*C*H$_3$), 46.6 (N*C*H$_2$), 30.7 (*C*H$_2$), 28.9 (*C*H$_2$); **HRMS (ESI$^-$):** Calculated for $C_{15}H_{17}NO_3$ [M-H]$^-$: 258.1136, found 258.1135; **IR ν_{max} (neat)/cm^{-1}:** 2971 (CH), 2551 (br. OH), 1651 (C=O).

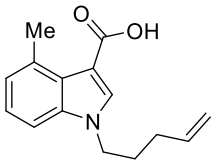
5-Nitro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 309e



5-Nitro-1-(pent-4-en-1-yl)-1*H*-indole (5.0 mmol, 1.15 g) was subjected to the general carboxylation conditions described above. The crude material was purified by recrystallization from MeCN to give the title compound (1.21 g, 88%) as a yellow solid.

M.p. 198-199 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 12.54 (s, 1H, O*H*), 8.89 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.36 (s, 1H, Ar*H*), 8.12 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 7.84 (d, *J* = 9.0 Hz, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH$_2$), 5.06-4.88 (m, 2H, CH=C*H*$_2$), 4.34 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 2.06-1.97 (m, 2H, C*H*$_2$), 1.90 (qn, *J* = 7.0 Hz, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$):** δ 164.8 (*C*O), 142.3 (*C*q), 139.3 (*C*q), 138.6 (*C*H), 137.4 (*C*H=CH$_2$), 125.7 (*C*q), 117.5 (*C*H), 117.2 (*C*H), 115.4 (CH=*C*H$_2$), 111.7 (*C*H), 108.7 (*C*q), 46.0 (N*C*H$_2$), 30.1 (*C*H$_2$), 28.6 (*C*H$_2$); **HRMS (ESI$^-$):** Calculated for $C_{14}H_{14}N_2O_4$ [M-H]$^-$: 273.0881, found 273.0885; **IR ν_{max} (neat)/cm^{-1}:** 2957 (CH), 2923 (CH), 2563 (br. OH), 1660 (C=O).

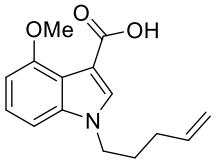
4-Methyl-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 309f



4-Methyl-1-(pent-4-en-1-yl)-1*H*-indole (3.0 mmol, 598 mg) was subjected to the general carboxylation conditions described above. The crude material was purified by recrystallization from MeCN to give the title compound (309 mg, 42%) as an off-white solid.

M.p. 96-100 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.01 (s, 1H, Ar*H*), 7.25-7.18 (m, 2H, Ar*H*), 7.11-7.04 (m, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.13-5.05 (m, 2H, CH=CH_2), 4.15 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.93 (s, 3H, CH_3), 2.16-2.08 (m, 2H, CH_2), 2.04-1.94 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.3 (*C*O), 137.6 (*C*q), 137.2 (*C*H), 136.9 (*C*H=CH_2), 133.1 (*C*q), 125.6 (*C*q), 124.3 (*C*H), 123.2 (*C*H), 116.3 (CH=*C*H_2), 107.8 (*C*H), 107.3 (*C*q), 46.4 (NCH_2), 30.8 (*C*H_2), 28.7 (*C*H_2), 22.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{17}NO_2$ $[M+Na]^+$: 266.1151, found 266.1165; **IR ν_{max} (neat)/cm^{-1}:** 2935 (CH), 2675 (br. OH), 1662 (C=O).

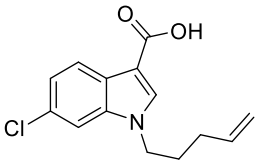
4-Methoxy-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 309g



4-Methoxy-1-(pent-4-en-1-yl)-1*H*-indole (5.0 mmol, 1.08 g) was subjected to the general carboxylation conditions described above. The crude material was purified by recrystallization from MeCN to give the title compound (482 mg, 37%) as an off-white solid.

M.p. 91-93 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 11.40 (s, 1H, COO*H*), 8.04 (s, 1H, Ar*H*), 7.31-7.22 (m, 2H, Ar*H*), 6.89 (dd, *J* = 6.0, 2.5 Hz, 1H, Ar*H*), 5.85 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.08-5.00 (m, 1H, CH=C*H*H), 5.00-4.95 (m, 1H, CH=CH*H*), 4.31 (t, *J* = 7.0 Hz, 2H, NCH_2), 4.15 (s, 3H, OCH_3), 2.15-2.04 (m, 2H, CH_2), 2.02-1.91 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.5 (*C*O), 152.0 (*C*q), 139.4 (*C*q), 138.3 (*C*H=CH_2), 137.4 (*C*H), 124.5 (*C*H), 115.8 (CH=*C*H_2), 115.2 (*C*q), 108.0 (*C*q), 106.3 (*C*H), 103.4 (*C*H), 57.0 (OCH_3), 47.0 (NCH_2), 31.4 (*C*H_2), 29.7 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{17}NO_3$ $[M+H]^+$: 260.1281, found 260.1284; **IR ν_{max} (neat)/cm^{-1}:** 3185 (CH), 2988 (CH), 1699 (C=O).

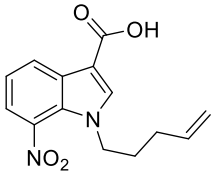
6-Chloro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 309h



6-Chloro-1-(pent-4-en-1-yl)-1*H*-indole (3.0 mmol, 659 mg) was subjected to the general carboxylation conditions described above. The crude material was purified by recrystallization from MeCN to give the title compound (599 mg, 75%) as an off-white solid.

M.p. 130-133 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 8.11 (d, *J* = 8.5 Hz, 1H, Ar*H*), 8.07 (s, 1H, Ar*H*), 7.64 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.22 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 5.87 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.09-5.01 (m, 1H, CH=C*H*H), 5.01-4.95 (m, 1H, CH=CH*H*), 4.34 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.17-2.08 (m, 2H, CH_2), 2.07-1.96 (m, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 165.8 (*C*O), 138.3 (*C*q), 138.1 (*C*H=CH_2), 136.7 (*C*H), 128.9 (*C*q), 126.6 (*C*q), 123.4 (*C*H), 122.7 (*C*H), 115.8 (CH=*C*H_2), 111.4 (*C*H), 107.7 (*C*q), 46.9 (N*C*H_2), 31.4 (*C*H_2), 29.8 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{14}{}^{35}ClNO_2$ $[M+Na]^+$: 286.0605, found 286.0612; **IR ν_{max} (neat)/cm^{-1}:** 3124 (CH), 2921 (CH), 2555 (br. OH), 1642 (C=O).

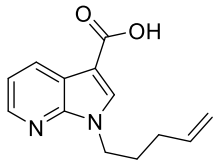
7-Nitro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid 309i



7-Nitro-1-(pent-4-en-1-yl)-1*H*-indole (3.1 mmol, 723 mg) was subjected to the general carboxylation conditions described above. The crude material was purified by recrystallization from MeCN to give the title compound (735 mg, 86%) as a yellow solid.

M.p. 127-128 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.59 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 8.01 (s, 1H, Ar*H*), 7.87 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.36 (t, *J* = 8.0 Hz, 1H, Ar*H*), 5.73 (ddt, *J* = 17.5, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.07-5.03 (m, 1H, CH=C*H*H), 5.03-4.99 (m, 1H, CH=CH*H*), 4.32 (t, *J* = 7.0 Hz, 2H, NCH_2), 1.99 (q, *J* = 7.0 Hz, 2H, CH_2), 1.80 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 169.7 (*C*O), 140.0 (*C*H), 137.7 (*C*q), 136.6 (*C*H=CH_2), 131.4 (*C*q), 127.9 (*C*H), 126.9 (*C*q), 121.6 (*C*H), 121.0 (*C*H), 116.5 (CH=*C*H_2), 107.4 (*C*q), 50.6 (N*C*H_2), 30.5 (*C*H_2), 29.4 (*C*H_2); **HRMS (ESI$^-$):** Calculated for $C_{14}H_{14}N_2O_4$ $[M-H]^-$: 273.0881, found 273.0882; **IR ν_{max} (neat)/cm^{-1}:** 2961 (CH), 2613 (br. OH), 1677 (C=O), 1523 (NO_2), 1315 (NO_2).

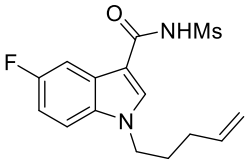
1-(Pent-4-en-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid 309j



1-(Pent-4-en-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (4.9 mmol, 911 mg) was subjected to the general carboxylation conditions described above. The crude material was purified by recrystallization from MeCN to give the title compound (1.03 mg, 91%) as a yellow solid.

M.p. 119-120 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.48 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 8.42 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar*H*), 8.05 (s, 1H, Ar*H*), 7.29-7.24 (m, 1H, Ar*H*), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.11-5.00 (m, 2H, CH=CH_2), 4.37 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.17-2.09 (m, 2H, CH_2), 2.09-2.02 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 169.8 (*C*O), 148.0 (*C*q), 144.2 (*C*H), 137.1 (*C*H=CH_2), 135.5 (*C*H), 130.3 (*C*H), 119.6 (*C*q), 118.4 (*C*H), 116.0 (CH=CH_2), 105.0 (*C*q), 45.0 (*C*H_2), 30.9 (*C*H_2), 29.2 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{14}N_2O_2$ $[M+H]^+$: 231.1128, found 231.1130; **IR ν_{max} (neat)/cm^{-1}:** 2923 (CH), 2583 (br. OH), 1655 (C=O).

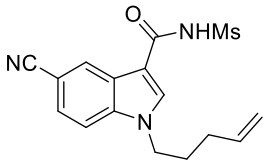
5-Fluoro-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 310a



5-Fluoro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 741 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (719 mg, 74%) as an off-white solid.

M.p. 197-198 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 10.13 (br. s, 1H, N*H*), 8.38 (s, 1H, Ar*H*), 7.92 (dd, *J* = 10.0, 2.5 Hz, 1H, Ar*H*), 7.59 (dd, *J* = 9.0, 4.5 Hz, 1H, Ar*H*), 7.10 (td, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 5.83 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.09-4.93 (m, 2H, CH=CH_2), 4.31 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.40 (s, 3H, SO_2CH_3), 2.15-1.95 (m, 4H, 2 × CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 163.1 (*C*O), 160.1 (d, *J* = 236.0 Hz, *C*F), 138.2 (*C*H=CH_2), 135.5 (*C*H), 134.3 (*C*q), 128.8 (d, *J* = 11.0 Hz, *C*q), 115.9 (CH=*C*H_2), 112.8 (d, *J* = 10.0 Hz, *C*H), 112.1 (d, *J* = 26.5 Hz, *C*H), 108.4 (d, *J* = 4.5 Hz, *C*q), 107.2 (d, *J* = 25.0 Hz, *C*H), 47.2 (N*C*H_2), 42.2 (d, *J* = 2.5 Hz, SO_2*C*H_3), 31.3 (*C*H_2), 29.8 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{17}FN_2O_3S$ $[M+H]^+$: 325.1017, found 325.1026; **IR ν_{max} (neat)/cm^{-1}:** 3225 (NH), 2931 (CH), 1643 (C=O), 1401 (CF)

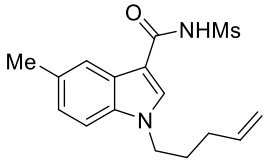
5-Cyano-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 310b



5-Cyano-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (2.3 mmol, 587 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (427 mg, 56%) as a pink solid.

M.p. 199 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 10.29 (br. s, 1H, N*H*), 8.59 (dd, *J* = 1.5, 0.5 Hz, 1H, Ar*H*), 8.51 (s, 1H, Ar*H*), 7.80 (dd, *J* = 8.5, 0.5 Hz, 1H, Ar*H*), 7.61 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 5.84 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.07-4.94 (m, 2H, CH=CH_2), 4.40 (t, *J* = 7.0, 2H, NCH_2), 3.42 (s, 3H, SO_2CH_3), 2.16-2.08 (m, 2H, CH_2), 2.07-1.99 (m, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 162.9 (*C*O), 139.3 (*C*q), 138.1 (*C*H=CH_2), 136. (*C*H), 127.8 (*C*q), 127.4 (*C*H), 126.7 (*C*H), 120.4 (*C*q), 116.0 (CH=*C*H_2), 113.0 (*C*H), 109.2 (*C*q), 106.1 (*C*q), 47.2 (N*C*H_2), 42.2 (SO_2CH_3), 31.3 (*C*H_2), 29.7 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{17}N_3O_3S$ [M+Na]$^+$: 354.0883, found 354.0881; **IR ν_{max} (neat)/cm^{-1}:** 3242 (CH), 3130 (CH), 2990 (CH), 2224 (CN), 1655 (C=O).

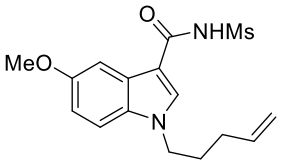
5-Methyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 310c



5-Methyl-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 730 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (601 mg, 63%) as an off-white solid.

M.p. 160-161 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 10.02 (br. s, 1H, N*H*), 8.27 (s, 1H, Ar*H*), 8.07 (dt, *J* = 1.5, 1.0 Hz, 1H, Ar*H*), 7.44 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.13 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 5.84 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.08-4.95 (m, 2H, CH=CH_2), 4.27 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.39 (s, 3H, SO_2CH_3), 2.45 (s, 3H, CH_3), 2.13-2.02 (m, 2H, CH_2), 2.02-1.94 (m, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 163.3 (*C*O), 138.3 (*C*H=CH_2), 136.1 (*C*q), 134.2 (*C*H), 132.1 (*C*q), 128.4 (*C*q), 125.4 (*C*H), 122.1 (*C*H), 115.8 (CH=*C*H_2), 111.1 (*C*H), 108.0 (*C*q), 46.9 (N*C*H_2), 42.2 (SO_2CH_3), 31.4 (*C*H_2), 29.7 (*C*H_2), 21.6 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{20}N_2O_3S$ [M+H]$^+$: 321.1267, found 321.1255; **IR ν_{max} (neat)/cm^{-1}:** 3304 (NH), 3126 (CH), 2923 (CH), 1668 (C=O), 1326 (S=O), 1168 (S=O).

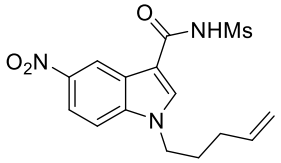
5-Methoxy-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 310d



5-Methoxy-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 778 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (812 mg, 80%) as an off-white solid.

M.p. 131-132 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 10.04 (br. s, 1H, N*H*), 8.27 (s, 1H, Ar*H*), 7.78 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.51-7.43 (m, 1H, Ar*H*), 6.92 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 5.83 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.10-5.00 (m, 1H, CH=C*H*H), 5.00-4.95 (m, 1H, CH=CH*H*), 4.26 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.40 (s, 3H, SO_2CH_3), 2.13-2.03 (m, 2H, CH_2), 2.02-1.93 (m, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 163.4 (*C*O), 157.0 (*C*q), 138.3 (*C*H=CH_2), 134.2 (*C*H), 132.6 (*C*q), 129.1 (*C*q), 115.9 (CH=*C*H_2), 114.1 (*C*H), 112.2 (*C*H), 107.9 (*C*q), 103.8 (*C*H), 55.9 (O*C*H_3), 47.1 (N*C*H_2), 42.3 (SO_2*C*H_3), 31.4 (*C*H_2), 29.8 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{20}N_2O_4S$ $[M+H]^+$: 337.1217, found 337.1192; **IR ν_{max} (neat)/cm^{-1}:** 3307 (NH), 3116 (CH), 2932 (CH), 1667 (C=O), 1131 (S=O).

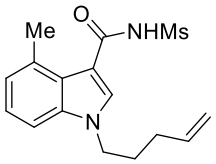
***N*-(Methylsulfonyl)-5-nitro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 310e**



5-Nitro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 823 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (800 mg, 76%) as a yellow solid.

M.p. 190-192 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 11.85 (s, 1H, N*H*), 9.00 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.63 (s, 1H, Ar*H*), 8.16 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 7.78 (d, *J* = 9.0 Hz, 1H, Ar*H*), 5.83 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.10-4.96 (m, 2H, CH=CH_2), 4.34 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.41 (s, 3H, SO_2CH_3), 2.04 (q, *J* = 7.0 Hz, 2H, CH_2), 1.91 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 162.7 (*C*O), 143.2 (*C*q), 139.8 (*C*q), 138.1 (*C*H), 137.8 (*C*H=CH_2), 126.4 (*C*q), 118.5 (*C*H), 117.8 (*C*H), 116.1 (CH=*C*H_2), 112.3 (*C*H), 109.3 (*C*q), 46.6 (N*C*H_2), 42.3 (SO_2*C*H_3), 30.5 (*C*H_2), 28.9 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{17}N_3O_5S$ $[M+H]^+$: 352.0962, found 352.0984; **IR ν_{max} (neat)/cm^{-1}:** 3274 (NH), 3123 (CH), 2928 (CH), 1674 (C=O), 1510 (NO_2), 1400 (S=O), 1321 (NO_2), 1138 (S=O).

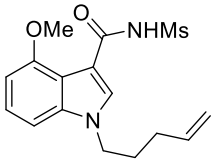
4-Methyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole 310f



4-Methyl-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (1.0 mmol, 243 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (140 mg, 64%) as a white solid.

M.p. 149 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 10.23 (br. s, 1H, N*H*), 8.14 (s, 1H, Ar*H*), 7.37 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.18 (dd, *J* = 8.5, 7.0 Hz, 1H, Ar*H*), 6.99 (dt, *J* = 7.0, 1.0 Hz, 1H, Ar*H*), 5.85 (ddt, 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.07-5.00 (m, 1H, CH=C*H*H), 5.00-4.95 (m, 1H, CH=CH*H*), 4.28 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.39 (s, 3H, SO_2CH_3), 2.72 (s, 3H, CH_3), 2.14-2.07 (m, 2H, CH_2), 2.02-1.93 (m, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 163.8 (*C*O), 138.4 (*C*H=CH_2), 138.2 (*C*q), 135.2 (*C*H), 132.8 (*C*q), 126.2 (*C*q), 124.4 (*C*H), 124.0 (*C*H), 115.8 (CH=*C*H_2), 110.4 (*C*q), 109.0 (*C*H), 46.8 (N*C*H_2), 41.9 (*C*H_3), 31.4 (*C*H_2), 29.7 (*C*H_2), 22.2 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{20}N_2O_3S$ $[M+H]^+$: 321.1267, found 321.1278 ; **IR ν_{max} (neat)/cm^{-1}:** 3069-2919 (CH), 1633 (C=O), 1336 (S=O), 1155 (S=O).

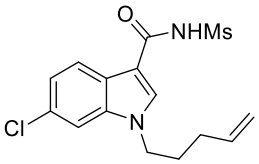
4-Methoxy-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 310g



4-Methoxy-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (1.5 mmol, 389 g) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (307 mg, 61%) as a white solid.

M.p. 138 °C (MeCN); **^{1}H NMR (400 MHz, acetone-d_6):** δ 11.65 (br. s, 1H, N*H*), 8.15 (s, 1H, Ar*H*), 7.31-7.25 (m, 2H, Ar*H*), 6.90 (dd, *J* = 5.5, 3.0 Hz, 1H, Ar*H*), 5.85 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.08-5.01 (m, 1H, CH=C*H*H), 5.00-4.95 (m, 1H, CH=CH*H*), 4.33 (t, *J* = 7.0 Hz, 2H, NCH_2), 4.11 (s, 3H, OCH_3), 3.39 (s, 3H, SO_2CH_3), 2.14-2.07 (m, 2H, CH_2), 1.99 (dt, *J* = 9.0, 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 162.2 (*C*O), 152.3 (*C*q), 139.8 (*C*q), 138.3 (*C*H=CH_2), 137.5 (*C*H), 124.7 (*C*H), 115.8 (CH=*C*H_2), 114.4 (*C*q), 109.7 (*C*q), 106.3 (*C*H), 104.1 (*C*H), 56.6 (O*C*H_3), 47.2 (N*C*H_2), 41.7 (SO_2CH_3), 31.4 (*C*H_2), 29.7 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{10}H_{13}NO_2$ $[M+Na]^+$: 180.1019, found 180.1020; **IR ν_{max} (neat)/cm^{-1}:** 3174 (br. NH), 3115 (CH), 2935 (CH), 1666 (C=O), 1327 (S=O), 1144 (S=O).

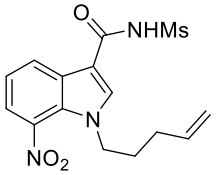
6-Chloro-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 310h



6-Chloro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (2.0 mmol, 527 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (507 mg, 74%) as an off-white solid.

M.p. 232-234 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 11.60 (s, 1H, N*H*), 8.44 (s, 1H, Ar*H*), 8.11 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.79 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.25 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 5.84 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH$_2$), 5.10-4.94 (m, 2H, CH=C*H*$_2$), 4.24 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 3.37 (s, 3H, SO$_2$C*H*$_3$), 2.09-1.98 (m, 2H, C*H*$_2$), 1.92-1.83 (m, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 162.4 (*C*O), 137.4 (*C*H=CH$_2$), 136.9 (*C*q), 135.2 (*C*H), 127.7 (*C*q), 125.4 (*C*q), 122.2 (*C*H), 122.2 (*C*H), 115.5 (CH=*C*H$_2$), 110.9 (*C*H), 107.0 (*C*q), 45.7 (N*C*H$_2$), 41.8 (SO$_2$*C*H$_3$), 30.1 (*C*H$_2$), 28.4 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for C$_{15}$H$_{17}$^{35}ClN$_2$O$_3$S [M+Na]$^+$: 363.0541, found 363.0541; **IR ν_{max} (neat)/cm^{-1}:** 3231 (NH), 3119 (CH), 2951 (CH), 1646 (C=O), 1321 (S=O), 1149 (S=O).

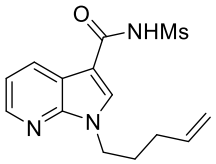
***N*-(Methylsulfonyl)-7-nitro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 310i**



7-Nitro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (2.0 mmol, 549 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from MeCN to give the title compound (592 mg, 84%) as a brown solid.

M.p. 173-175 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 11.83 (br. s, 1H, N*H*), 8.58 (s, 1H, Ar*H*), 8.56 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.93 (dd, *J* = 8.0, 1.0 Hz, 1H Ar*H*), 7.42 (t, *J* = 8.0 Hz, 1H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH$_2$), 5.04-4.90 (m, 2H, CH=C*H*$_2$), 4.21 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 3.40 (s, 3H, SO$_2$C*H*$_3$), 2.01-1.90 (m, 2H, C*H*$_2$), 1.81-1.65 (m, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 162.7 (*C*O), 139.2 (*C*H), 137.6 (*C*H=CH$_2$), 137.5 (*C*q), 131.4 (*C*q), 127.5 (*C*H), 126.4 (*C*q), 122.1 (*C*H), 121.0 (*C*H), 116.1 (CH=*C*H$_2$), 108.4 (*C*q), 49.9 (N*C*H$_2$), 42.2 (SO$_2$*C*H$_3$), 30.4 (*C*H$_2$), 29.2 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for C$_{15}$H$_{17}$N$_3$O$_5$S [M+H]$^+$: 352.0962, found 352.0957; **IR ν_{max} (neat)/cm^{-1}:** 3231 (NH), 3131 (CH), 2969 (CH), 1648 (C=O), 1524 (NO$_2$), 1397 (S=O), 1321 (NO$_2$), 1149 (S=O).

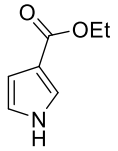
***N*-(Methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide 310j**



1-(Pent-4-en-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (3.0 mmol, 691 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallization from MeCN to give the title compound (461 mg, 50%) as a white solid.

M.p. 223-225 °C (MeCN); **^{1}H NMR (500 MHz, acetone-d_6):** δ 10.34 (br. s, 1H, N*H*), 8.52 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 8.49 (s, 1H, Ar*H*), 8.40 (dd, *J* = 4.5, 1.5 Hz, 1H, Ar*H*), 7.30 (dd, *J* = 8.0, 4.5 Hz, 1H, Ar*H*), 5.84 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH$_2$), 5.07-5.01 (m, 1H, CH=C*H*H), 4.98-4.93 (m, 1H, CH=CH*H*), 4.41 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 3.39 (s, 3H, SO$_2$C*H*$_3$), 2.13-2.07 (m, 2H, C*H*$_2$), 2.04-1.98 (m, 2H, C*H*$_2$); **^{13}C NMR (126 MHz, acetone-d_6):** δ 163.0 (*C*O), 148.9 (*C*q), 145.2 (*C*H), 138.3 (*C*H=CH$_2$), 134.3 (*C*H), 130.6 (*C*H), 120.3 (*C*q), 119.0 (*C*H), 115.7 (CH=*C*H$_2$), 107.2 (*C*q), 45.2 (N*C*H$_2$), 42.2 (SO$_2$*C*H$_3$), 31.4 (*C*H$_2$), 29.9 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{17}N_3O_3S$ [M+H]$^+$: 308.1063, found 308.1073; **IR ν_{max} (neat)/cm^{-1}:** 3230 (NH), 3107 (CH), 2927 (CH), 1651 (C=O), 1326 (S=O), 1156 (S=O).

Ethyl 1*H*-pyrrole-3-carboxylate[128] 314a

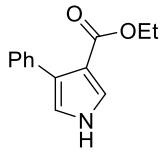


Synthesised using a modified literature procedure.[128]

A solution of TosMIC (11.0 mmol, 2.15 g) and ethyl acrylate (10.0 mmol, 1.09 mL) in Et$_2$O/DMSO (1:1 v:v 50 ml) was added dropwise to a suspension of NaH (11.0 mmol, 440 mg, 60% suspension in mineral oil) in Et$_2$O (20 mL) at 0 °C, over 30 minutes. The reaction mixture was stirred for a further 3 hours, before being quenched with water (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (×3). The combined organic layers were washed with water (×3) and brine, dried over MgSO$_4$ and concentrated. The crude material was purified by flash column chromatography (25% EtOAc/petrol) to yield the title compound (280 mg, 20%) as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.62 (br. s, 1H, N*H*), 7.45-7.41 (m, 1H, Ar*H*), 6.75 (dt, *J* = 3.0, 2.0 Hz, 1H, Ar*H*), 6.66 (td, *J* = 3.0, 1.5 Hz, 1H, Ar*H*), 4.29 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 1.34 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); **IR ν_{max} (neat)/cm^{-1}:** 3299 (br. NH), 2981-2906 (CH), 1671 (C=O). Data are consistent with literature precedent.[128]

Ethyl 4-phenyl-1*H*-pyrrole-3-carboxylate[128] 314c

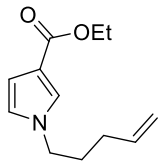


Synthesised using a modified literature procedure.[128]

A solution of TosMIC (8.0 mmol, 1.56 g) and ethyl cinnamate (8.0 mmol, 1.34 mL) in Et_2O/DMSO (1:2 v:v 30 ml) was added dropwise to a suspension of NaH (10.4 mmol, 416 mg, 60% suspension in mineral oil) in Et_2O (15 mL) at 0 °C over 30 minutes. The reaction mixture was stirred for a further 3 hours, before being quenched with water (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (×3). The combined organic layers were then washed with water (×3) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (20% EtOAc/petrol) to give the title compound (1.32 g, 76%) as a yellow solid.

M.p. 122-124 °C (EtOAc, lit. = 121-124 °C); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.58 (br. s, 1H, N*H*), 7.53-7.45 (m, 3H, Ar*H*), 7.35 (tq, *J* = 8.0, 1.5, 1,0 Hz, 2H, Ar*H*), 7.30-7.24 (m, 1H, Ar*H*), 6.76 (t, *J* = 2.5 Hz, 1H, Ar*H*), 4.22 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 1.24 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); **IR ν_{max} (neat)/cm^{-1}:** 3318 (NH), 2980 (CH), 1683 (C=O). Data are consistent with literature precedent.[128]

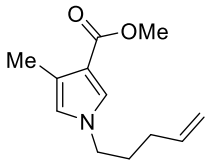
Ethyl 1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylate 315a



Ethyl 1*H*-pyrrole-3-carboxylate (3.5 mmol, 487 mg) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (20% EtOAc/petrol) to give the title compound (602 mg, 83%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (t, *J* = 2.0 Hz, 1H, Ar*H*), 6.59-6.6.56 (m, 2H, Ar*H*), 5.77 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH$_2$), 5.08-5.03 (m, 1H, CH=C*H*H), 5.03-5.01 (m, 1H, CH=CH*H*), 4.26 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 3.88 (t, *J* = 6.5 Hz, 2H, NC*H*$_2$), 2.04 (td, *J* = 7.5, 6.5 Hz, 2H, C*H*$_2$), 1.87 (qn, *J* = 7.5 Hz, 2H, C*H*$_2$), 1.33 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.0 (*C*O), 137.0 (*C*H=CH$_2$), 125.9 (*C*H), 121.6 (*C*H), 116.2 (CH=*C*H$_2$), 116.0 (*C*q), 110.2 (*C*H), 59.7 (O*C*H$_2$CH$_3$), 49.3 (N*C*H$_2$), 30.5 (*C*H$_2$), 30.3 (*C*H$_2$), 14.6 (OCH$_2$*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{17}NO_2$ [M+H]$^+$: 208.1332, found 208.1336; **IR ν_{max} (neat)/cm^{-1}:** 2978 (CH), 1701 (C=O).

Methyl 4-methyl-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylate 315b

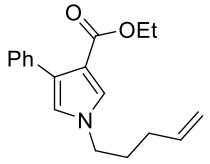


A solution of TosMIC (13.2 mmol, 2.58 g) and methyl crotonate (12.0 mmol, 1.28 mL) in Et_2O/DMSO (1:1 v:v 30 ml) was added dropwise to a suspension of NaH (26.4 mmol, 1.06 g, 60% suspension in mineral oil) in Et_2O (15 mL) at 0 °C over 30 minutes. The reaction mixture was stirred for a further 3 hours, before being quenched with water (50 mL). The layers were separated, and the aqueous layer extracted with EtOAc (×3). The combined organic layers were then washed with water (×3) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (0.5-2% DCM/petrol), but complete purification could not be achieved due to the presence of inseparable impurities. The material was therefore taken straight through to the next step.

The crude pyrrole was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (4% EtOAc/petrol) to give the title compound (1.49 g, 60% over two steps) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 2.5 Hz, 1H, Ar*H*), 6.37 (dd, *J* = 2.5, 1.0 Hz, 1H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.08-4.99 (m, 2H, CH=CH_2), 3.83-3.87 (m, 5H, NCH_2 + OCH_3), 2.25 (s, 3H, CH_3), 2.08-1.99 (m, 2H, CH_2), 1.89-1.78 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.9 (*C*O), 137.1 (*C*H=CH_2), 126.7 (*C*H), 121.7 (*C*q), 120.4 (*C*H), 116.0 (CH=*C*H_2), 113.9 (*C*q), 50.7 (O*C*H_3), 49.2 (N*C*H_2), 30.6 (*C*H_2), 30.2 (*C*H_2), 11.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{17}NO_2$ $[M+H]^+$: 208.1332, found 208.1337; **IR ν_{max} (neat)/cm^{-1}:** 2972-2901 (CH), 1702 (C=O).

Ethyl 1-(pent-4-en-1-yl)-4-phenyl-1*H*-pyrrole-3-carboxylate 315c

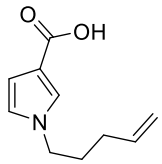


Ethyl 4-phenyl-1*H*-pyrrole-3-carboxylate (5.5 mmol, 1.18 g) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (2-20% EtOAc/petrol) to give the title compound (1.34 g, 86%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.46 (m, 2H, Ar*H*), 7.37-7.30 (m, 3H, Ar*H*), 7.29-7.22 (m, 1H, Ar*H*), 6.64 (t, *J* = 2.5 Hz, 1H, Ar*H*), 5.79 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.12-5.00 (m, 2H, CH=CH_2), 4.20 (q, *J* = 7.0 Hz, 2H, CH_2CH$_3$), 3.90 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.13-2.05 (m, 2H, CH_2), 1.96-1.88 (m, 2H, CH_2), 1.24 (t, *J* = 7.0, 3H, CH$_2$CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 164.8 (*C*O), 137.0 (*C*H=CH_2), 135.0 (*C*q),

129.4 (*C*H), 127.8 (*C*H), 127.7 (*C*q), 127.1 (*C*q), 126.5 (*C*H), 121.2 (*C*H), 116.1 (CH=*C*H_2), 113.3 (*C*q), 59.6 (O*C*H_2), 49.4 (N*C*H_2), 30.6 (*C*H_2), 30.2 (*C*H_2), 14.4 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{18}H_{21}NO_2$ $[M+Na]^+$: 306.1464, found 306.1463; **IR ν_{max} (neat)/cm^{-1}:** 2976 (CH), 1709 (C=O).

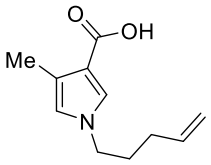
1-(Pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylic acid 316a



Ethyl 1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylate (2.5 mmol, 518 mg) was subjected to the general hydrolysis conditions described above, to give the title compound (508 mg, quantitative) as a pink solid (analytically pure), which was used without further purification.

M.p. 76-78 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36 (t, *J* = 2.0 Hz, 1H, Ar*H*), 6.66-6.58 (m, 2H, Ar*H*), 5.77 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.09-4.99 (m, 2H, CH=CH_2), 3.90 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.05 (q, *J* = 7.0 Hz, 2H, CH_2), 2.05 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.0 (*C*O), 136.9 (*C*H=CH_2), 127.2 (*C*H), 122.0 (*C*H), 116.2 (CH=*C*H_2), 115.1 (*C*q), 100.8 (*C*H), 49.5 (N*C*H_2), 30.5 (*C*H_2), 30.2 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{10}H_{13}NO_2$ $[M+H]^+$: 180.1019, found 180.1020; **IR ν_{max} (neat)/cm^{-1}:** 2977-2914 (CH), 2560 (br. OH), 1665 (C=O).

4-Methyl-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylic acid 316b

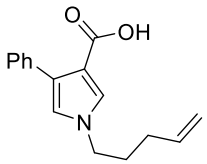


Methyl 4-methyl-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylate (3.0 mmol, 622 mg) was dissolved in MeOH (20 mL) and water (10 mL) and treated with aqueous NaOH (2 M, 30 mmol, 15 mL). The resulting solution was heated to reflux and stirred for 16 hours. On completion, the reaction mixture was cooled to room temperature and the volatiles were removed. The remaining solution was acidified to pH 1 with 3 M HCl and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to give the title compound (503 mg, 87%) as a brown solid (analytically pure), which was used without further purification.

M.p. 64-66 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.30 (d, *J* = 2.5 Hz, 1H, Ar*H*), 6.39 (dd, *J* = 2.5, 1.0 Hz, 1H, Ar*H*), 5.77 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.08-5.00 (m, 2H, CH=CH_2), 3.81 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.26 (app. d, 3H, CH_3), 2.09-2.00 (m, 2H, CH_2), 1.90-1.80 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.0 (*C*O), 137.1 (*C*H=CH_2), 128.1 (*C*H), 122.4 (*C*q), 120.6 (*C*H), 116.0 (CH=*C*H_2), 113.3

(*C*q), 49.2 (N*C*H$_2$), 30.6 (*C*H$_2$), 30.1 (*C*H$_2$), 11.9 (*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_{11}H_{15}NO_2$ [M+H]$^+$: 194.1176, found 194.1177; **IR ν_{max} (neat)/cm^{-1}:** 2951 (CH), 2602 (br. OH), 1659 (C=O).

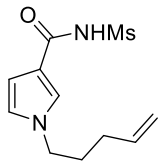
1-(Pent-4-en-1-yl)-4-phenyl-1*H*-pyrrole-3-carboxylic acid 316c



Ethyl 1-(pent-4-en-1-yl)-4-phenyl-1*H*-pyrrole-3-carboxylate (4.5 mmol, 1.28 g) was dissolved in EtOH (20 mL) and treated with aqueous NaOH (2 M, 45 mmol, 22.5 mL). The reaction mixture was heated to reflux and stirred for 18 hours. On completion, the reaction mixture was allowed to cool to room temperature and the volatiles were removed. The remaining aqueous solution was acidified to pH 1 with 3 M HCl and then extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to give the title compound (1.10 g, 95%) as a pale-yellow solid (analytically pure), which was used without further purification.

M.p. 101-104 °C (EtOAc); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.52-7.47 (m, 2H, Ar*H*), 7.43 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.34 (*J* = 7.5 Hz, 2H, Ar*H*), 7.29-7.25 (m, 1H, Ar*H*), 6.65 (d, *J* = 2.5 Hz, Ar*H*), 5.78 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH$_2$), 5.10-5.03 (m, 2H, CH=C*H*$_2$), 3.90 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 2.10 (q, *J* = 7.0 Hz, 2H, C*H*$_2$), 1.92 (qn, *J* = 7.0 Hz, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$):** δ 169.7 (*C*O), 136.9 (*C*H=CH$_2$), 134.6 (*C*q), 129.3 (*C*H), 129.3 (*C*H), 127.9 (*C*H), 127.5 (*C*q), 126.7 (*C*H), 121.6 (*C*H), 116.2 (CH=*C*H$_2$), 112.0 (*C*q), 49.5 (N*C*H$_2$), 30.6 (*C*H$_2$), 30.1 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{17}NO_2$ [M+H]$^+$: 256.1332, found 256.1328; **IR ν_{max} (neat)/cm^{-1}:** 2934 (CH), 2552 (br. OH), 1660 (C=O).

***N*-(Methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxamide 317a**

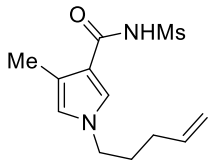


1-(Pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylic acid (2.3 mmol, 407 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from EtOAc to give the title compound (276 mg, 47%) as a white solid.

M.p. 98-101 °C (EtOAc); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.62 (br. s, 1H, N*H*), 7.38 (t, *J* = 2.0 Hz, 1H, Ar*H*), 6.62 (t, *J* = 2.5 Hz, 1H, Ar*H*), 6.52 (dd, *J* = 3.0, 1.5 Hz, 1H, Ar*H*), 5.76 (ddt, *J* = 17.5, 9.5, 7.0 Hz, 1H, *C*H=CH$_2$), 5.07-5.04 (m, 1H, CH=C*H*H), 5.03-5.01 (m, 1H, CH=CH*H*), 3.90 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 3.40 (s, 3H, SO$_2$C*H*$_3$), 2.03 (q, *J* = 7.0 Hz, 2H, C*H*$_2$), 1.87 (qn, *J* = 7.0 Hz, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$):**

δ 162.2 (*C*O), 136.8 (*C*H=CH_2), 126.0 (*C*H), 122.7 (*C*H), 116.6 (*C*q), 116.3 (CH=*C*H_2), 108.7 (*C*H), 49.6 (N*C*H_2), 42.1 (SO_2*C*H_3), 30.5 (*C*H_2), 30.1 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{11}H_{16}N_2O_3S$ $[M+H]^+$: 257.0954, found 257.0952; **IR ν_{max} (neat)/cm^{-1}:** 3162-2901 (CH), 1644 (C=O), 1323 (S=O), 1154 (S=O).

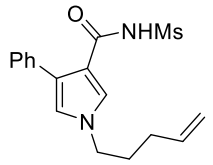
4-Methyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxamide 317b



4-Methyl-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylic acid (2.0 mmol, 386 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from EtOAc to give the title compound (94 mg, 17%) as a brown solid.

M.p. 105-106 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.23 (d, *J* = 2.5 Hz, 1H, Ar*H*), 6.42 (dq, *J* = 2.0, 1.0 Hz, 1H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.08-4.99 (m, 2H, CH=C*H*$_2$), 3.82 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 3.40 (s, 3H, SO_2C*H*$_3$), 2.27 (app. d, 3H, C*H*$_3$), 2.07-1.99 (m, 2H, C*H*$_2$), 1.89-1.80 (m, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.6 (*C*O), 136.9 (*C*H=CH_2), 125.4 (*C*H), 121.8 (*C*H), 121.6 (*C*q), 116.2 (CH=*C*H_2), 114.6 (*C*q), 49.4 (N*C*H_2), 42.3 (SO_2*C*H_3), 30.5 (*C*H_2), 30.0 (*C*H_2), 11.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{18}N_2O_3S$ $[M+H]^+$: 271.1111, found 271.1116; **IR ν_{max} (neat)/cm^{-1}:** 3165 (NH), 2938 (CH), 1646 (C=O), 1325 (S=O), 1151 (S=O).

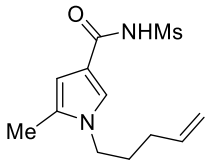
***N*-(Methylsulfonyl)-1-(pent-4-en-1-yl)-4-phenyl-1*H*-pyrrole-3-carboxamide 317c**



1-(Pent-4-en-1-yl)-4-phenyl-1*H*-pyrrole-3-carboxylic acid (3.0 mmol, 766 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from EtOAc to give the title compound (592 mg, 60%) as a white solid.

M.p. 106-107 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.80 (br. s, 1H, N*H*), 7.51-7.33 (m, 6H, Ar*H*), 6.62 (d, *J* = 2.5 Hz, 1H, Ar*H*), 5.78 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.12-5.05 (m, 1H, CH=C*H*H), 5.05-5.03 (m, 1H, CH=CH*H*), 3.91 (t, *J* = 7.0, 2H, NC*H*$_2$), 3.28 (s, 3*H*, SO_2C*H*$_3$), 2.09 (q, *J* = 7.0 Hz, 2H, C*H*$_2$), 1.92 (qn, *J* = 7.0 Hz, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.3 (*C*O), 136.7 (*C*H=CH_2), 133.4 (*C*q), 129.6 (*C*H), 129.2 (*C*H), 128.3 (*C*H), 128.1 (*C*H), 124.9 (*C*q), 121.6 (*C*H), 116.3 (CH=*C*H_2), 114.6 (*C*q), 49.6 (N*C*H_2), 42.0 (SO_2*C*H_3), 30.5 (*C*H_2), 30.0 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{17}H_{20}N_2O_3S$ $[M+H]^+$: 333.1267, found 333.1266; **IR ν_{max} (neat)/cm^{-1}:** 3219 (CH), 2901 (CH), 1664 (C=O), 1438 (S=O), 1154 (S=O).

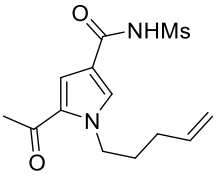
5-Methyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxamide 317d



5-Methyl-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylic acid (2.0 mmol, 387 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from EtOAc to give the title compound (160 mg, 30%) as a pale-yellow solid.

M.p. 90-92°C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.57 (br. s, 1H, N*H*), 7.31 (d, *J* = 2.0 Hz, 1H, Ar*H*), 6.23 (dq, *J* = 2.0, 1.0 Hz, 1H, Ar*H*), 5.77 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.10-4.96 (m, 2H, CH=CH_2), 3.80 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.39 (s, 3H, SO_2CH_3), 2.19 (app. d, 3H, CH_3), 2.10-2.00 (m, 2H, CH_2), 1.81 (qn, *J* = 7.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.3 (*C*O), 136.9 (*C*H=CH_2), 130.8 (*C*q), 125.7 (*C*H), 116.1 (CH=*C*H_2), 115.1 (*C*q), 106.8 (*C*H), 46.7 (N*C*H_2), 42.1 (SO_2*C*H_3), 30.5 (*C*H_2), 29.8 (*C*H_2), 12.0 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{18}N_2O_3$ $[M+H]^+$: 271.1111, found 271.1108; **IR ν_{max} (neat)/cm^{-1}:** 3153 (CH), 2987 (CH), 1644 (C=O), 1325 (S=O), 1147 (S=O).

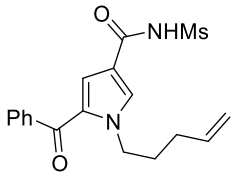
5-Acetyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxamide 317e



5-Acetyl-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylic acid (1.8 mmol, 387 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from EtOAc to give the title compound (359 mg, 69%) as a white solid.

M.p. 126-128 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.19 (br. s, 1H, N*H*), 7.54 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.42 (d, *J* = 2.0 Hz, 1H, Ar*H*), 5.77 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.07-4.97 (m, 2H, CH=CH_2), 4.33 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.43 (s, 3H, SO_2CH_3), 2.46 (s, 3H, COCH_3), 2.10-1.99 (m, 2H, CH_2), 1.88-1.77 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 188.9 (*C*O), 161.5 (*C*O), 137.1 (*C*H=CH_2), 132.9 (*C*H), 131.4 (*C*q), 119.4 (*C*H), 115.8 (CH=*C*H_2), 115.6 (*C*q), 50.2 (N*C*H_2), 42.2 (SO_2*C*H_3), 30.5 (*C*H_2), 30.1 (*C*H_2), 27.5 (CO*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{18}N_2O_4S$ $[M+H]^+$: 299.1060, found 299.1064; **IR ν_{max} (neat)/cm^{-1}:** 3288-2901 (CH), 1676 (C=O), 1656 (C=O), 1321 (S=O).

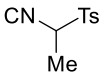
5-Benzoyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxamide 317f



5-Benzoyl-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylic acid (2.0 mmol, 567 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recrystallisation from EtOAc to give the title compound (533 mg, 74%) as a white solid.

M.p. 147-147 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.25 (s, 1H, N*H*), 7.80-7.74 (m, 2H, Ar*H*), 7.66 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.61-7.51 (m, 1H, Ar*H*), 7.50-7.45 (m, 2H, Ar*H*), 7.17 (d, *J* = 2.0 Hz, 1H, Ar*H*), 5.78 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.08-4.97 (m, 2H, CH=CH_2), 4.41 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.25 (s, 3H, SO_2CH_3), 2.09 (q, *J* = 7.0 Hz, 2H, CH_2), 1.91 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 186.4 (*C*O), 161. (*C*O), 138.8 (*C*q), 137.0 (*C*H=CH_2), 133.6 (*C*H), 132.3 (*C*H), 131.0 (*C*q), 129.4 (*C*H), 128.6 (*C*H), 121.6 (*C*H), 115.9 (CH=*C*H_2), 115.8 (*C*q), 49.9 (N*C*H_2), 42.0 (SO_2 *C*H_3), 30.6 (*C*H_2), 30.3 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{18}H_{20}N_2O_4S$ $[M+H]^+$: 361.1217, found 361.1218; **IR ν_{max} (neat)/cm^{-1}:** 3266 (NH), 2987-2901 (CH), 1682 (C=O), 1631 (C=O), 1147 (S=O).

1-((1-Isocyanoethyl)sulfonyl)-4-methylbenzene[128] 319

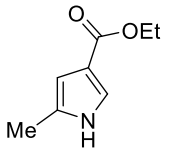


Synthesised using a modified literature procedure.[128]

To a solution of TosMIC (10.0 mmol, 1.95 g) and benzyl triethyl ammonium chloride (2.0 mmol, 456 mg) in DCM was added aqueous NaOH (6 M, 160 mmol, 26 mL). The resulting mixture was cooled to 0 °C and methyl iodide (12.0 mmol, 1.70 g) was added. The reaction mixture was stirred at room temperature for 2.5 hours and then diluted with water. The layers were separated, and the aqueous layer was extracted with EtOAc (×2). The organic layers were then combined, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (10% EtOAc/petrol) to give the title compound (1.08 g, 52%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.84 (m, 2H, Ar*H*), 7.46-7.39 (m, 2H, Ar*H*), 4.59 (q, *J* = 7.0 Hz, 1H, C*H*), 2.50 (s, 3H, ArCH_3), 1.75 (d, *J* = 7.0 Hz, 3H, CH_3); **IR ν_{max} (neat)/cm^{-1}:** 2989 (CH), 2133 (C≡N), 1330 (S=O), 1146 (S=O).Data are consistent with literature precedent.[128]

Ethyl 5-methyl-1*H*-pyrrole-3-carboxylate[128] 320

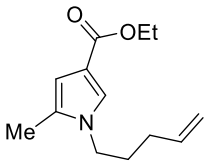


Synthesised using a modified literature procedure.[128]

A solution of 1-((1-isocyanoethyl)sulfonyl)-4-methylbenzene (7.7 mmol, 1.61 g) and ethyl acrylate (7.0 mmol, 0.76 mL) in Et_2O/DMSO (2:1 v:v 30 ml) was added dropwise to a suspension of NaH (14.0 mmol, 560 mg, 60% suspension in mineral oil) in Et_2O (15 mL) at 0 °C over 20 minutes. The reaction mixture was then stirred for a further 2 hours, before being quenched with water (30 mL). The layers were separated, and the aqueous layer extracted with EtOAc (×3). The combined organic layers were then washed with water (×3) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (25% EtOAc/petrol) to give the title compound (588 mg, 50%) as a yellow solid.

M.p. 69-70 °C (EtOAc, Lit. = 68-72 °C); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.50 (br. s, 1H, N*H*), 7.30-7.24 (m, 1H, Ar*H*), 6.29 (ddt, *J* = 2.5, 2.0, 1.0 Hz, 1H, Ar*H*), 4.26 (q, *J* = 7.0 Hz, 2H, OCH_2CH$_3$), 2.24 (app. d, 3H, ArCH_3), 1.32 (t, *J* = 7.0 Hz, 3H, OCH$_2$CH_3); **IR ν_{max} (neat)/cm^{-1}:** 3268 (NH), 2980-2870 (CH), 1672 (C=O). Data are consistent with literature precedent.[128]

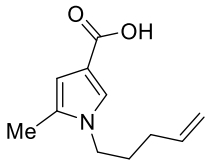
Ethyl 5-methyl-1-pentyl-1*H*-pyrrole-3-carboxamide 321



Ethyl 5-methyl-1*H*-pyrrole-3-carboxylate (3.5 mmol, 536 mg) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (8% EtOAc/petrol) to give the title compound (612 mg, 78%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 2.0 Hz, 1H, Ar*H*), 6.29 (dt, *J* = 2.0, 1.0 Hz, 1H, Ar*H*), 5.78 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH$_2$), 5.09-5.00 (m, 2H, CH=CH_2), 4.24 (q, *J* = 7.0 Hz, 2H, OCH_2CH$_3$), 3.81-3.74 (m, 2H, NCH_2), 2.19 (app. d, 3H, CH_3), 2.12-2.04 (m, 2H, CH_2), 1.87-1.76 (m, 2H, CH_2), 1.32 (t, *J* = 7.0 Hz, 3H, OCH$_2$CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.2 (*C*O), 137.1 (*C*H=CH$_2$), 129.6 (*C*q), 125.6 (*C*H), 116.0 (CH=*C*H$_2$), 114.7 (*C*q), 108.2 (*C*H), 59.6 (O*C*H$_2$CH$_3$), 46.5 (N*C*H$_2$), 30.7 (*C*H$_2$), 30.0 (*C*H$_2$), 14.7 (OCH$_2$*C*H$_3$), 12.0 (*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{19}NO_2$ [M+H]$^+$: 222.1489, found 222.1492; **IR ν_{max} (neat)/cm^{-1}:** 2977-2901 (CH), 1698 (C=O).

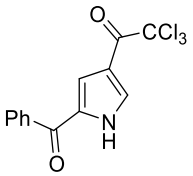
5-Methyl-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylic acid 322



Ethyl 5-methyl-1-pentyl-1*H*-pyrrole-3-carboxamide (2.5 mmol, 558 mg) was dissolved in THF (20 mL) and treated with aqueous NaOH (2 M, 25 mmol, 12.5 mL). The reaction mixture was then heated at reflux for 72 hours. On completion, the reaction mixture was allowed to cool to room temperature and the volatiles were removed. The remaining aqueous solution was acidified to pH 1 with 3 M HCl and then extracted with EtOAc (×3). The combined organic extracts were then washed with brine, dried over $MgSO_4$ and concentrated to give the title compound (465 mg, 96%) as a pale-orange solid (analytically pure), which was used without further purification.

M.p. 99-100 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.29 (d, *J* = 2.0 Hz, 1H, Ar*H*), 6.33 (s, 1H, Ar*H*), 5.78 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.10-5.01 (m, 2H, CH=CH_2), 3.81 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.21 (s, 3H, CH_3), 2.09 (q, *J* = 7.0 Hz, 2H, CH_2), 1.83 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.5 (*C*O), 137.0 (*C*H=CH_2), 130.0 (*C*q), 127.0 (*C*H), 116.0 (CH=*C*H_2), 113.7 (*C*q), 108.7 (*C*H), 46.6 (N*C*H_2), 30.6 (*C*H_2), 30.0 (*C*H_2), 12.0 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{11}H_{15}NO_2$ $[M+H]^+$: 194.1176, found 194.1173; **IR ν_{max} (neat)/cm^{-1}:** 2988-2901 (CH), 2565 (br. OH), 1645 (C=O).

1-(5-Benzoyl-1*H*-pyrrol-3-yl)-2,2,2-trichloroetan-1-one[128] 323b



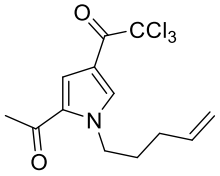
Synthesised using a modified literature procedure.[128]

To a suspension of aluminiumtrichloride (10.0 mmol, 1.33 g) in DCM (16 mL) was added trichloroacetyl chloride (6.0 mmol, 0.66 mL). The resulting solution was cooled to 0 °C and phenyl(1*H*-pyrrol-2-yl)methanone (4.0 mmol, 684 mg) was added. The reaction mixture was stirred at 0 °C for 10 minutes before being allowed to warm to room temperature and heated to reflux, at which it was stirred for 20 hours. On completion, the mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL). The volatiles were removed, and the resulting aqueous solution extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to yield the title compound (1.06 g, 84%) as a pale-pink solid.

M.p. 148-150 °C (EtOAc, lit = 150-151 °C[128]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.51 (br. s, 1H, N*H*), 8.06 (dd, *J* = 3.5, 1.5 Hz, 1H, Ar*H*), 7.97-7.90 (m, 2H, Ar*H*), 7.68-7.60 (m, 1H, Ar*H*), 7.59-7.50 (m, 3H, Ar*H*); **IR**

ν_{max} (neat)/cm^{-1}: 3249 (NH), 2977 (CH), 1695 (C=O), 1623 (C=O). Data are consistent with literature precedent.[128]

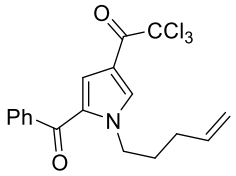
1-(5-Acetyl-1-(pent-4-en-1-yl)-1*H*-pyrrol-3-yl)-2,2,2-trichloroethan-1-one 324a



To a solution of triphenylphosphine (3.3 mmol, 865 mg) in THF (12 mL) at -78 °C was added DIAD (3.2 mmol, 0.62 mL). The resulting mixture was stirred for 1 hour. 4-Penten-1-ol (3.8 mmol, 0.39 mL) was added and the reaction mixture was stirred for a further hour. 1-(5-Acetyl-1*H*-pyrrol-3-yl)-2,2,2-trichloroethan-1-one (2.8 mmol, 720 mg) was added and the reaction mixture was stirred at -78 °C for a further 15 minutes, and then room temperature for 16 hours. The volatiles were removed, and the residue was triturated with cold Et_2O and petrol. The crude material was purified by flash column chromatography (2-5% EtOAc/petrol) to yield the title compound (689 mg, 73%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.59 (d, *J* = 2.0 Hz, 1H, Ar*H*), 5.79 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH_2), 5.09-5.01 (m, 2H, CH=CH_2), 4.39-4.33 (m, 2H, NCH_2), 2.51-2.47 (m, 3H, COCH_3), 2.09 (q, *J* = 7.5 Hz, 2H, CH_2), 1.88 (qn, *J* = 7.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 188.9 (*C*O), 176.5 (*C*O), 137.1 (*C*H=CH_2), 136.2 (*C*H), 131.1 (*C*q), 122.8 (*C*H), 116.0 (CH=*C*H_2), 113.8 (*C*q), 50.3 (N*C*H_2), 30.5 (*C*H_2), 30.1 (*C*H_2), 27.6 (CO*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{14}Cl_3NO_2$ $[M+H]^+$: 322.0163, found 322.0176; **IR ν_{max} (neat)/cm^{-1}:** 2987-2901 (CH), 1692 (C=O), 1665 (C=O).

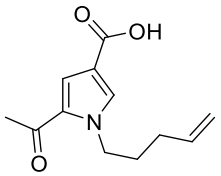
1-(5-Benzoyl-1-(pent-4-en-1-yl)-1*H*-pyrrol-3-yl)-2,2,2-trichloroethan-1-one 324b



To a solution of triphenylphosphine (3.3 mmol, 866 mg) in THF (12 mL) at -78 °C was added DIAD (3.2 mmol, 0.62 mL). The resulting mixture was stirred for 1 hour. 4-Penten-1-ol (3.8 mmol, 0.39 mL) was added and the reaction mixture was stirred for a further hour. 1-(5-Benzoyl-1*H*-pyrrol-3-yl)-2,2,2-trichloroetan-1-one (3.0 mmol, 950 mg) was added and the reaction mixture was stirred at -78 °C for a further 15 minutes, and then room temperature for 16 hours. The volatiles were removed, and the residue was triturated with cold Et_2O and petrol. The crude material was purified by flash column chromatography (4% EtOAc/petrol) to give the title compound (964 mg, 84%) as a viscous yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.79 (m, 3H, Ar*H*), 7.61 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.50 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.37 (d, *J* = 2.0 Hz, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.12-5.01 (m, 2H, CH=CH_2), 4.45 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.14 (q, *J* = 7.0 Hz, 2H, CH_2), 1.97 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 186.3 (*C*O), 176.4 (*C*O), 138.6 (*C*q), 136.9 (*C*H=CH_2), 136.2 (*C*H), 132.5 (*C*H), 130.6 (*C*q), 129.3 (*C*H), 128.4 (*C*H), 124.9 (*C*H), 116.0 (CH=*C*H_2), 113.8 (*C*q), 95.9 (*C*q), 49.8 (N*C*H_2), 30.5 (*C*H_2), 30.2 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{18}H_{16}Cl_3NO_2$ $[M+H]^+$: 384.0319, found 384.0348; **IR ν_{max} (neat)/cm^{-1}:** 2973 (CH), 1692 (C=O), 1639 (C=O).

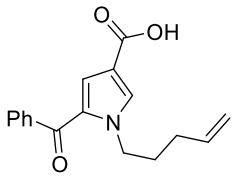
5-Acetyl-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylic acid 325a



1-(5-Acetyl-1-(pent-4-en-1-yl)-1*H*-pyrrol-3-yl)-2,2,2-trichloroethan-1-one (2.0 mmol, 665 mg) was dissolved in THF (10 mL) and treated with aqueous NaOH (1 M, 5 mmol, 5.00 mL). The resulting mixture was stirred at room temperature for 30 minutes. The volatiles were removed, and the aqueous solution was washed with Et_2O. The aqueous layer was acidified to pH 1 with 3 M HCl and extracted with EtOAc (×3). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (435 mg, 98%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 83-84 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 (d, *J* = 1.5 Hz, 1H, Ar*H*), 7.43 (d, *J* = 1.5 Hz, 1H, Ar*H*), 5.79 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH_2), 5.09-4.99 (m, 2H, CH=CH_2), 4.34 (t, *J* = 7.5 Hz, 2H, NCH_2), 2.47 (s, 3H, COCH_3), 2.07 (q, *J* = 7.5 Hz, 2H, CH_2), 1.86 (qn, *J* = 7.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 189.3 (*C*O), 169.5 (*C*O), 137.6 (*C*H=CH_2), 134.7 (*C*H), 131.5 (*C*q), 121.8 (*C*H), 116.1 (CH=*C*H_2), 114.5 (*C*q), 50.4 (N*C*H_2), 30.9 (*C*H_2), 30.5 (*C*H_2), 27.9 (CO*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{15}NO_3$ $[M+H]^+$: 222.1125, found 222.1130; **IR ν_{max} (neat)/cm^{-1}:** 2971 (CH), 1697 (C=O), 1625 (C=O).

5-Benzoyl-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxylic acid 325b

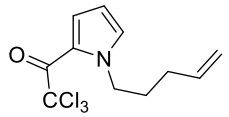


1-(5-Benzoyl-1-(pent-4-en-1-yl)-1*H*-pyrrol-3-yl)-2,2,2-trichloroethan-1-one (2.4 mmol, 923 mg) was dissolved in THF (12 mL) and treated with aqueous NaOH (1 M, 6 mmol, 6.00 mL). The resulting mixture was stirred at room temperature for 30 minutes. The volatiles were removed, and the aqueous

solution washed with Et_2O. The aqueous layer was acidified to pH 1 with 3 M HCl and extracted with EtOAc (×3). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (634 mg, 93%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 117-119 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.85-7.77 (m, 2H, Ar*H*), 7.62 (d, *J* = 1.5 Hz, 1H, Ar*H*), 7.61-7.54 (m, 1H, Ar*H*), 7.48 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.19 (d, *J* = 1.5 Hz, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.11-4.99 (m, 2H, CH=CH_2), 4.43 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.12 (q, *J* = 7.0 Hz, 2H, CH_2), 1.95 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 186.6 (*C*O), 169.1 (*C*O), 139.1 (*C*q), 137.2 (*C*H=CH_2), 134.7 (*C*H), 132.2 (*C*H), 130.9 (*C*q), 129.4 (*C*H), 128.5 (*C*H), 124.0 (*C*H), 115.9 (CH=*C*H_2), 114.4 (*C*q), 49.8 (N*C*H_2), 30.7 (*C*H_2), 30.5 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{17}H_{17}NO_3$ $[M+H]^+$: 284.1281, found 284.1270; **IR ν_{max} (neat)/cm^{-1}:** 2987 (CH), 1681 (C=O), 1634 (C=O).

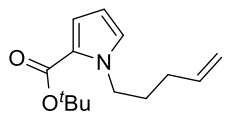
2,2,2-Trichloro-1-(1-(pent-4-en-yl)-1*H*-pyrrol-2-yl)ethan-1-one 327



To a solution of triphenylphosphine (6.6 mmol, 1.73 g) in THF (24 mL) at -78 °C was added DIAD (6.3 mmol, 1.24 mL). The resulting mixture was stirred for 1 hour. 4-Penten-1-ol (7.5 mmol, 0.78 mL) was added and the reaction mixture was stirred for a further hour. 2,2,2-Trichloro-1-(1*H*-pyrrol-2-yl)ethan-1-one (6.0 mmol, 1.28 g) was added and the reaction mixture was stirred at -78 °C for a further 15 minutes, and then room temperature for 16 hours. The volatiles were removed, and the residue was triturated with cold Et_2O and petrol. The crude material was purified by flash column chromatography (2% EtOAc/petrol) to yield the title compound (1.42 g, 84%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 4.5, 1.5 Hz, 1H, Ar*H*), 7.01 (t, *J* = 2.0 Hz, 1H, Ar*H*), 6.23 (dd, *J* = 4.5, 2.5 Hz, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.10-4.99 (m, 2H, CH=CH_2), 4.36-4.29 (m, 2H, NCH_2), 2.10 (q, *J* = 7.0 Hz, 2H, CH_2), 1.87 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.6 (*C*O), 137.5 (*C*H=CH_2), 133.2 (*C*H), 124.7 (*C*H), 121.2 (*C*q), 115.7 (CH=*C*H_2), 109.1 (*C*H), 96.6 (*C*q), 50.2 (N*C*H_2), 30.7 (*C*H_2), 30.3 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{11}H_{12}Cl_3NO$ $[M+H]^+$: 280.0057, found 280.0058; **IR ν_{max} (neat)/cm^{-1}:** 2928 (CH), 1665 (C=O).

***tert*-Butyl 1-(pent-4-en-1-yl)-1*H*-pyrrole-2-carboxylate 328**



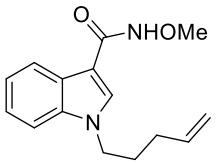
A solution of 2,2,2-trichloro-1-(1-(pent-4-en-yl)-1*H*-pyrrol-2-yl)ethan-1-one (8.0 mmol, 2.24 g) in THF (8 mL) and aqueous NaOH (2 M, 16.0 mmol, 8.00 mL) was stirred at room temperature for 1 hour. The

volatiles were then removed, and the remaining aqueous solution was acidified to pH 1 with 3 M HCl. This was extracted with Et_2O (×3), and the organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. The crude product was used without further purification.

To a solution of the crude acid in DCM (11 mL) at 0 °C was added oxalyl chloride (9.6 mmol, 0.81 mL) over 5 minutes. The reaction mixture was stirred at room temperature for 1 hour, before being re-cooled to 0 °C. ^{t}BuOK (24.0 mmol, 2.69 g) was added portionwise over 5 minutes, and the reaction mixture was stirred at room temperature for 18 hours. Water (20 mL) was added and the phases were separated. The aqueous layer was extracted with DCM (×3), and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (1% EtOAc/petrol) to give the title compound (1.41 g, 75% over two steps) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (dd, *J* = 4.0, 2.0 Hz, 1H, Ar*H*), 6.79-6.76 (m, 1H, Ar*H*), 6.08 (dd, *J* = 4.0, 2.5 Hz, 1H, Ar*H*), 5.80 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.07-4.97 (m, 2H, CH=CH_2), 4.28 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.09-2.01 (m, 2H, CH_2), 1.91-1.82 (m, 2H, CH_2), 1.55 (s, 9H, C(CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 160.7 (*C*O), 137.8 (*C*H=CH_2), 128.3 (*C*H), 123.4 (*C*q), 118.0 (*C*H), 115.4 (CH=*C*H_2), 107.6 (*C*H), 80.3 (*C*(CH$_3$)$_3$), 48.6 (N*C*H_2), 30.8 (*C*H_2), 30.8 (*C*H_2), 28.6 (C(*C*H_3)$_3$); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{21}NO_2$ [M+Na]$^+$: 258.1465, found 258.1467; **IR ν_{max} (neat)/cm^{-1}:** 2977 (CH), 1697 (C=O).

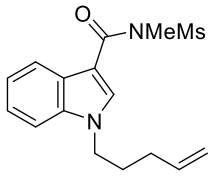
***N*-Methoxy-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 332**



To a solution of 1-(pent-4-en-1-yl)-1*H*-indole-3-carboxylic acid (3.0 mmol, 688 mg) in DCM (10 mL) at 0 °C was added oxalyl chloride (3.6 mmol, 0.31 mL) dropwise, followed by DMF (2 drops). The reaction mixture was allowed to warm to room temperature and was stirred for 20 hours. On completion, the volatiles were removed to yield the crude acid chloride. Methoxyamine hydrochloride (3.6 mmol, 301 mg) was added to a biphasic mixture of K_2CO_3 (6.0 mmol, 829 mg) in EtOAc/water (2:1 v:v 36 mL). The solution was cooled to 0 °C and the crude acid chloride dissolved in a minimum amount of EtOAc was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 4 hours. The phases were separated, and the aqueous phase extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (50% EtOAc/petrol) to yield the title compound (397 mg, 51%) as a colourless solid.

M.p. 100-103 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.34 (s, 1H, N*H*), 8.04-7.97 (m, 1H, Ar*H*), 7.79 (s, 1H, Ar*H*), 7.41-7.36 (m, 1H, Ar*H*), 7.32-7.42 (m, 2H, Ar*H*), 5.79 (ddt, *J* = 16.0, 11.0, 7.0 Hz, 1H, C*H*=CH_2), 5.09-5.05 (m, 1.5 Hz, 1H, CH=C*H*H), 5.05-5.02 (m, 1H, CH=CH*H*), 4.16 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.91 (s, 3H, OCH_3), 2.09 (q, *J* = 7.0 Hz, 2H, CH_2), 1.97 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.9 (*C*O), 136.9 (*C*H=CH_2), 136.5 (*C*q), 132.2 (*C*H), 125.8 (*C*q), 122.9 (*C*H), 121.9 (*C*H), 121.0 (*C*q), 116.2 (CH=*C*H_2), 110.4 (*C*H), 107.5 (*C*q), 64.9 (O*C*H_3), 46.3 (N*C*H_2), 30.8 (*C*H_2), 29.0 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{18}N_2O_2$ [M+H]$^+$: 259.1441, found 259.1452; **IR ν_{max} (neat)/cm^{-1}:** 3237 (NH), 3087 (CH), 2932 (CH), 1632 (C=O).

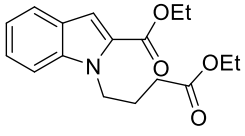
***N*-Methyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide 334**



To a suspension of *N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide (0.7 mmol, 200 mg) and K_2CO_3 (9.8 mmol, 1.34 g) in acetone (10 mL) was added iodomethane (9.8 mmol, 0.61 mL). The reaction mixture was stirred at room temperature for 96 hours, and then passed through a short silica pad eluted with DCM. The solution was then concentrated to yield the title compound (188 mg, 91%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 48-50 °C (MeCN); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.09-8.04 (m, 1H, Ar*H*), 7.75 (s, 1H, Ar*H*), 7.43-7.36 (m, 1H, Ar*H*), 7.35-7.28 (m, 2H, Ar*H*), 5.79 (ddt, *J* = 16.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.12-5.07 (m, 1H, CH=C*H*H), 5.06-5.03 (m, 1H, CH=CH*H*), 4.18 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.42 (s, 3H, SO_2CH_3), 3.30 (s, 3H, NCH_3), 2.11 (q, *J* = 7.0 Hz, 2H, CH_2), 2.05-1.93 (m, 2H, CH_2); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 167.8 (*C*O), 136.7 (*C*H=CH_2), 136.5 (*C*q), 135.5 (*C*H), 127.0 (*C*q), 123.6 (*C*H), 122.7 (*C*H), 121.8 (*C*H), 116.5 (CH=*C*H_2), 110.4 (*C*H), 109.1 (*C*q), 46.5 (N*C*H_2), 39.9 (N*C*H_3), 36.1 (SO_2CH_3) 30.7 (*C*H_2), 28.8 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{20}N_2O_3S$ [M+H]$^+$: 321.1267, found 321.1279; **IR ν_{max} (neat)/cm^{-1}:** 2928 (CH), 1639 (C=O), 1333 (S=O), 1157 (S=O).

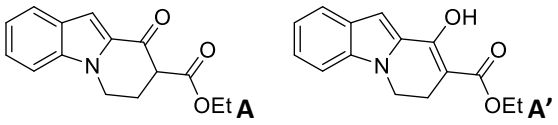
Ethyl 1-(4-ethoxy-4-oxobutyl)-1*H*-indole-2-carboxylate[211] 337



Ethyl indole-2-carboxylate (26.0 mmol, 5.00 g) was subjected to the general alkylation conditions described above with ethyl 4-bromobutyrate. The crude material was purified by flash column chromatography (10% EtOAc/petrol) to give the title compound (8.04 g mg, quantitative) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.45 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar*H*), 7.38-7.31 (m, 2H, Ar*H*), 7.14 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar*H*), 4.64 (t, *J* = 7.0 Hz, 2H, NCH_2), 4.37 (q, *J* = 7.0 Hz, 2H, OCH_2CH$_3$), 4.12 (q, *J* = 7.0 Hz, 2H, OCH_2CH$_3$), 2.34 (t, *J* = 7.0 Hz, 2H, CH_2), 2.15 (qn, *J* = 7.0 Hz, 2H, CH_2), 1.41 (t, *J* = 7.0 Hz, 3H, OCH$_2$CH_3), 1.24 (t, *J* = 7.0 Hz, 3H, OCH$_2$CH_3); **IR ν_{max} (neat)/cm^{-1}:** 2987 (CH), 1732 (C=O), 1708 (C=O). Data are consistent with literature precedent.[211]

Ethyl 9-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-8-carboxylate and ethyl 6,7-dihydro-9-hydroxypyrido[1,2-*a*]indole-8-carboxylate[211] 338



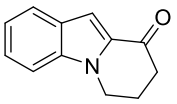
A **A'**

Synthesised using a modified literature procedure.[211]

A solution of ethyl 1-(4-ethoxy-4-oxobutyl)-1*H*-indole-2-carboxylate (26.0 mmol, 7.89 g) in THF (50 mL) was added to a stirred suspension of ^{t}BuOK (31.2, 3.50 g) in THF (40 mL) at room temperature. The resulting mixture was stirred for 16 hours before being quenched with water (50 mL). The volatiles were removed, and the remaining aqueous solution was extreacted with DCM (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (4% EtOAc/petrol) to give the title compounds (5.43 g, 81%(A:A' 1:4)) as a yellow solid.

M.p. 69-74 °C, (EtOAc, lit = 100-102 °C[211]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 12.17 (s, 0.8H, O*H* of A'), 7.74 (dt, *J* = 8.0, 1.0 Hz, 0.2H, Ar*H* of A), 7.67 (dd, *J* = 8.0, 1.0 Hz, 0.8 Hz, Ar*H* of A'), 7.44-7.27 (m, 2.2H, 3 × Ar*H* of A and 2 × Ar*H* of A'), 7.19 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 0.2H, Ar*H* of A), 7.13 (ddd, *J* = 8.0, 6.5, 1.0 Hz, 0.8H, Ar*H* of A'), 7.04 (s, 0.8H, Ar*H* of A'), 4.47-4.18 (m, 2.4H, NCH_2 of A, OCH_2CH$_3$ of A and A'), 4.12 (t, *J* = 7.0 Hz, 1.6H, NCH_2 of A'), 3.73 (dd, *J* = 8.5, 4.5 Hz, 0.2H, C*H* of A), 2.89 (t, *J* = 7.0 Hz, 1.6H, CH_2 of A'), 2.84-2.73 (m, 0.2H, C*H*H of A), 2.65-2.54 (m, 0.2H, CH*H* of A), 1.37 (t, *J* = 7.0 Hz, 0.6H, OCH$_2$CH_3 of A'), 1.30 (t, *J* = 7.0 Hz, 2.4H, CH$_2$CH_3 of A); **IR ν_{max} (neat)/cm^{-1}:** 2973 (CH), 1734 (C=O), 1674 (C=O), 1623 (C=O). ^{1}H NMR and IR data are consistent with literature precedent.[211]

7,8-Dihydropyrido[1,2-*a*]indol-9(6*H*)-one[211] 339



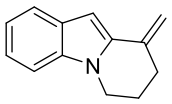
Synthesised using a modified literature procedure.[211]

To a solution of ethyl 9-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-8-carboxylate and ethyl 6,7-dihydro-9-hydroxypyrido[1,2-*a*]indole-8-carboxylate (21.1 mmol, 5.40 g) in EtOH (100 mL) was added 6 M HCl (100 mL) dropwise. The reaction mixture was stirred at reflux for 2.5 hours. The volatiles were

removed, and the remaining aqueous solution was extracted with DCM (×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (25-50% EtOAc/petrol) to yield the title compound (2.99 g, 77%) as an off-white solid.

M.p. 139-140 °C (MeCN, lit. = 140-142 °C[211]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.74 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.42-7.35 (m, 2H, Ar*H*), 7.32 (s, 1H, Ar*H*), 7.17 (ddd, *J* = 8.0, 5.5, 2,0 Hz, 1H, Ar*H*), 4.30-4.23 (m, 2H, NCH_2), 2.76 (dd, *J* = 7.0, 6.0 Hz, 2H, CH_2), 2.45-2.38 (m, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2969 (CH), 11669 (C=O). Data are consistent with literature precedent.[211]

9-Methylene-6,7,8,9-tetrahydropyrido[1,2-*a*]indole[211] 340

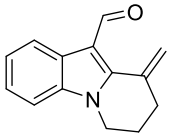


Synthesised using a modified literature procedure.[211]

To a solution of methyl triphenylphosphonium bromide (11.0 mmol, 3.93 g) in THF (35 mL) at 0 °C was added *n*-Butyllithium (11.0 mmol, 4.4 mL, 2.5 M solution in THF) dropwise. After stirring for 30 minutes a solution of 7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (10.0 mmol, 1.85 g) in THF (35 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 4 hours before being quenched with water (25 mL). The volatiles were removed, and the remaining aqueous solution extracted with DCM (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (5% EtOAc/petrol) to give the title compound (1.34 g, 73%) as a white solid.

M.p. 135-137 °C, (EtOAc, lit = 82-84 °C[211]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.30-7.25 (m, 1H, Ar*H*), 7.21-7.14 (m, 1H, Ar*H*), 7.10 (t, *J* = 7.5 Hz, 1H, Ar*H*), 6.75 (s, 1H, Ar*H*), 5.66-5.59 (m, 1H, C=C*H*H), 5.05-4.97 (m, 1H, C=CH*H*), 4.12 (t, *J* = 6.5 Hz, 2H, NCH_2), 2.66-2.58 (m, 2H, CH_2), 2.14 (qn, *J* = 6.5 Hz, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2954 (CH). ^{1}H NMR and IR data are consistent with literature precedent.[211]

9-Methylene-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-10-carboxaldehyde[212] 344



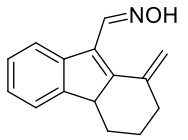
Synthesised using a modified literature procedure.[212]

To a portion of DMF (1 mL) at 0 °C was added $POCl_3$ (2.2 mmol, 0.20 mL) dropwise. A solution of 9-methylene-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (2.0 mmol, 366 mg) in DMF (2 mL) was then added

dropwise over a period of 5 minutes. The reaction mixture was stirred at 0 °C for 1 hour. The completed reaction mixture was poured onto ice and neutralised with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (×3), dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (10% EtOAc/petrol) to give the title compound (91 mg, 22%) as an orange solid.

M.p. 79-81 °C, (MeCN, lit = 84-86 °C[212]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.30 (s, 1H, C*H*O), 8.43-8.37 (m, 1H, Ar*H*), 7.35-7.29 (m, 3H, Ar*H*), 5.80 (s, 1H, C=C*H*H), 5.51 (s, 1H, C=CH*H*), 4.18 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.72-2.66 (m, 2H, CH_2), 2.28 (qn, *J* = 7.0 Hz, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2957 (CH), 1632 (C=O). Data are consistent with literature precedent.[212]

1-Methylene-2,3,4a-tetrahydro-1*H*-fluorene-9-carboxaldehyde oxime[212] 345

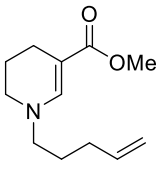


To a solution of 9-methylene-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-10-carboxaldehyde (0.8 mmol, 173 mg) in MeOH (3 mL) was added hydroxylamine hydrochloride (1.6 mmol, 114 mg) and KOAc (1.6 mmol, 161 mg). The reaction mixture was heated at reflux for 4 hours. On completion, the volatiles were removed, and the crude residue was purified by flash column chromatography (15% EtOAc/petrol) to yield the title compound (113 mg, 61%) as a yellow solid.

M.p. 167-168 °C, (MeCN, lit = 88-90 °C[212]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.62 (s, 1H, C*H*=N), 8.18 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.30-7.27 (m, 2H, Ar*H*), 7.25-7.20 (m, 1H, Ar*H*), 5.45 (s, 1H, C=C*H*H), 5.33 (s, 1H, C=CH*H*), 4.13 (t, *J* = 6.5 Hz, 2H, NCH_2), 2.67-2.54 (m, 2H, CH_2), 2.26-2.19 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 146.9 (*C*H), 138.0 (*C*q), 136.4 (*C*q), 136.1 (*C*q), 125.6 (*C*q), 123.3 (*C*H), 122.4 (*C*H), 121.7 (*C*H), 115.8 (C=*C*H_2), 109.2 (*C*H), 105.0 (*C*q), 42.5 (N*C*H_2), 31.8 (*C*H_2), 23.9 (*C*H_2); **IR ν_{max} (neat)/cm^{-1}:** 3262 (br. OH), 2956 (CH). NMR and IR data are consistent with literature precedent.[212]

4.3.7 Natural product synthesis substrate data

Methyl 1-(pent-4-en-1-yl)-1,4,5,6-tetrahydropyridine-3-carboxylate 359



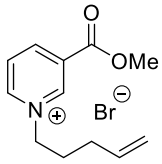
To a solution of methyl nicotinate (30.0 mmol, 4.12 g) in degassed EtOH (20 mL) was added 5% Pd/C (6 wt%, 248 mg). A magnetic stir bar was added, and the resulting suspension was sealed in an autoclave and pressurised with H_2 (10 bar). The reaction mixture was stirred at room temperature for

72 hours, before being filtered and concentrated. The product was inseparable from the remaining starting material so was used in the next step without further purification.

The crude material was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude product was purified by flash column chromatography (20% EtOAc/petrol) to afford the title compound (50% over two steps) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.31 (m, 1H, C=C*H*), 5.77 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.07-4.96 (m, 2H, CH=CH_2), 3.66 (s, 3H, OCH_3), 3.20-3.02 (m, 4H, 2 × NCH_2), 2.27 (tt, *J* = 5.5, 1.0 Hz, 2H, CH_2), 2.08-1.99 (m, 2H, CH_2), 1.85-1.77 (m, 2H, CH_2), 1.68-1.58 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 169.2 (*C*O), 146.3 (C=*C*H), 137.5 (*C*H=CH_2), 115.6 (CH=*C*H_2), 93.5 (*C*=CH), 55.3 (N*C*H_2), 50.6 (O*C*H_3), 45.8 (N*C*H_2), 30.7 (*C*H_2), 27.6 (*C*H_2), 21.5 (*C*H_2), 20.2 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{19}NO_2$ $[M+H]^+$: 210.1485, found 210.1488; **IR ν_{max} (neat)/cm^{-1}:** 2942 (CH), 1676 (C=O).

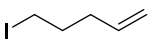
3-(Methoxycarbonyl)-1-(pent-4-en-1-yl)pyridine-1-ium bromide 362



To a solution of methyl nicotinate (10.0 mmol, 1.37 g) in MeCN (10 mL) was added 5-bromo-1-pentene (10.0 mmol, 1.20 mL). The resulting solution was stirred at reflux for 18 hours, after which a second portion of 5-bromo-1-pentene (10.0 mmol, 1.20 mL) was added. The reaction mixture was stirred for a further 30 hours at reflux and then cooled to toom temperature. The mixture was filtered, washed with Et_2O and dried *in vacuo* to give the title compound (2.86 g, quantitative) as a viscous orange oil, without need for further purification.

^{1}H NMR (400 MHz, acetone-d_6): δ 10.12 (dt, *J* = 6.0, 1.5 Hz, 1H, Ar*H*), 10.00-9.90 (m, 1H, Ar*H*), 9.13 (dt, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 8.47 (dd, *J* = 8.0, 6.0 Hz, 1H, Ar*H*), 5.94-5.83 (m, 1H, C*H*=CH_2), 5.26-5.18 (m, 2H, C=CH_2), 5.15-5.05 (m, 2H, NCH_2), 5.03-4.93 (m, 2H, CH_2), 4.02 (s, 3H, CH_3), 2.00-1.87 (m, 2H, CH_2); **^{13}C NMR (101 MHz, acetone-d_6):** δ 162.8 (*C*O), 149.9 (C*H*), 147.2 (*C*H), 146.3 (*C*H), 138.8 (*C*H=CH_2), 138.1 (*C*q), 129.8 (*C*H), 116.3 (CH=*C*H_2), 115.8 (N*C*H_2), 62.3 (O*C*H_3); 54.1 (N*C*H_2), 31.7 (*C*H_2), 28.5 (*C*H_2) **HRMS (ESI$^+$):** Calculated for $C_{12}H_{16}BrNO_2$ $[M-Br]^+$: 206.1176, found 206.1172.

5-Iodopent-1-ene[213] 367

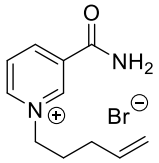


5-Bromo-1-pentene (20.0 mmol, 2.37 mL) was added to a solution of NaI (40.0 mmol, 6.00 g) in acetone (60 mL). The reaction mixture was heated at reflux for 3 hours. On completion, the mixture was allowed to cool to room temperature and diluted with water. The aqueous mixture was extracted

with pentane (×3), and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the title compound (3.10 g, 80%) as a colourless oil (analytically pure) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.18-5.04 (m, 1H, CH=C*H*H), 5.04-4.99 (m, 1H, CH=CH*H*), 3.19 (t, *J* = 7.0 Hz, 2H, IC*H*$_2$), 2.21-2.12 (m, 2H, C*H*$_2$), 1.92 (qn, *J* = 7.0 Hz, 2H, C*H*$_2$); **IR ν_{max} (neat)/cm^{-1}:** 2975 (CH). Data are consistent with literature precedent.[213]

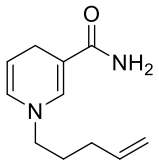
3-Carbamoyl-1-(pent-4-en-1-yl)pyridine-1-ium bromide 370



To a solution of nicotinamide (10.0 mmol, 1.22 g) in MeCN (20 mL) was added 5-bromo-1-pentene (12.0 mmol, 1.42 mL). The reaction mixture was stirred at reflux for 72 hours. On completion the mixture was concentrated to give the title compound (2.75 g, quantitative) as a yellow solid, without need for further purification.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.49 (s, 1H, Ar*H*), 9.21 (d, *J* = 6.0 Hz, 1H, Ar*H*), 8.93 (d, *J* = 8.0 Hz, 1H, Ar*H*), 8.55 (br. s, 1H, N*H*H), 8.27 (t, *J* = 7.0 Hz, 1H, Ar*H*), 8.16 (br. s, 1H, NH*H*), 5.81 (ddt, *J* = 16.5, 11.0, 6.0 Hz, 1H, C*H*=CH_2), 5.10-4.97 (m, 2H, CH=C*H*$_2$), 4.65 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 2.14-2.01 (m, 4H, 2 × C*H*$_2$); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 162.8 (*C*O), 146.5 (*C*H), 144.8 (*C*H), 143.5 (*C*H), 136.9 (*C*H=CH_2), 133.7 (*C*q), 127.9 (*C*H), 115.8 (CH=*C*H$_2$), 60.7 (N*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_{11}H_{15}BrNO_2$ [M-Br]$^+$: 191.1179, found 191.1186; **IR ν_{max} (neat)/cm^{-1}:** 3253 (NH_2), 3099-2934 (CH), 1693 (C=O).

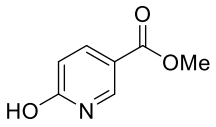
1-(Pent-4-en-1-yl)-1,4-dihydropyridine-3-carboxamide 371



To a solution of 3-carbamoyl-1-(pent-4-en-1-yl)pyridine-1-ium bromide (10.0 mmol, 2.71 g) and $NaHCO_3$ (40.0 mmol, 3.36 g) in EtOAc/water (1:1 v:v 100 mL) was added $Na_2S_2O_4$ (30.0 mmol, 5.22 g) slowly. The resulting mixture was stirred at room temperature for 6 hours. The layers were separated, and the aqueous layer was further extracted with EtOAc (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the title compound (1.72 g, 90%) as an orange oil (analytically pure), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 1.5 Hz, 1H, C*H*=CCONH$_2$), 5.81-5.68 (m, 2H, C*H*=CH$_2$ + NC*H*=CH), 5.23 (br. s, 2H, N*H*$_2$), 5.06-4.97 (m, 2H, CH=C*H*$_2$), 4.71 (dt, *J* = 8.0, 3.5 Hz, 1H, NCH=C*H*), 3.15 (dd, *J* = 3.5, 1.5 Hz, 2H, C*H*$_2$), 3.09 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 2.11-2.02 (m, 2H, C*H*$_2$), 1.63 (qn, *J* = 7.0 Hz, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.6 (*C*O), 139.8 (*C*H=CCONH$_2$), 137.3 (*C*H=CH$_2$), 129.1 (NC*H*=CH), 115.7 (CH=*C*H$_2$), 102.8 (NCH=*C*H), 98.0 (*C*q).53.3 (N*C*H$_2$), 30.4 (*C*H$_2$), 29.1 (*C*H$_2$), 22.9 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_{11}H_{16}N_2O$ [M+H]$^+$: 193.1335, found 193.1330; **IR ν_{max} (neat)/cm^{-1}:** 3333 (br. NH), 3202 (br. NH), 2928 (CH), 1680 (C=O), 1637 (C=C).

Methyl 6-hydroxynicotinate[214] 376

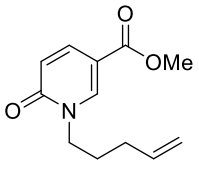


Synthesised using a modified literature procedure.

A mixture of 6-hydroxynicotinic acid (20.0 mmol, 2.78 g) and concentrated H_2SO_4 (2.0 mmol, 0.1 mL) in MeOH (25 mL) was heated at reflux for 24 hours. The reaction mixture was then allowed to cool to room temperature and $NaHCO_3$ (25 mL) was added dropwise until pH 11-12. The mixture was extracted with EtOAc (×3) and the combined organic layers were dried over $MgSO_4$ and concentrated. This gave the title compound (1.59 g, 54%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 166-167 °C, (EtOAc, lit = 164-165 °C[214]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 12.02 (br. s, 1H, O*H*), 8.17 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.99 (dd, *J* = 9.5, 2.5 Hz, 1H, Ar*H*), 6.57 (d, *J* = 9.5 Hz, 1H, Ar*H*), 3.87 (s, 3H, OC*H*$_3$); **IR ν_{max} (neat)/cm^{-1}:** 2912 (CH), 1724 (C=O), 1706 (C=O), 1688 (C=O), 1642 (C=O), 1610 (C=O). Data are consistent with literature precedent.[214]

Methyl 6-oxo-1-(pent-4-en-1-yl)-1,6-dihydropyridine-3-carboxylate[215] 377

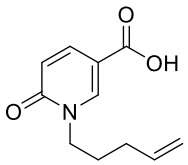


Synthesised using a modified literature procedure.[215]

To a solution of methyl 6-hydroxynicotinate (2.0 mmol, 306 mg) and 5-bromo-1-pentene (3.0 mmol, 0.34 mL) in toluene (16 mL) and water (0.5 mL) was added K_2CO_3 (4.0 mmol, 553 mg) and TBAB (0.2 mmol, 56 mg) and this was refluxed for 1 hour. The reaction mixture was then filtered, concentrated and purified by flash column chromatography (50% EtOAc/petrol) to give the title compound (524 mg, 80%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 2.5, 0.5 Hz, 1H, C*H*), 7.82 (dd, *J* = 9.5, 2.5 Hz, 1H, C*H*), 6.52 (dd, *J* = 9.5, 0.5 Hz, 1H, C*H*), 5.80 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.12-4.98 (m, 2H, CH=CH_2), 4.00-3.94 (m, 2H, NCH_2), 3.86 (s, 3H, OCH_3), 2.18-2.09 (m, 2H, CH_2), 1.92-1.83 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 164.9 (*C*O), 162.5 (*C*O), 143.1 (*C*H), 138.5 (*C*H), 137.0 (*C*H=CH_2), 120.0 (*C*H), 116.1 (CH=*C*H_2), 109.7 (*C*q), 52.2 (O*C*H_3), 50.2 (N*C*H_2), 30.7 (*C*H_2), 28.2 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{15}NO_3$ $[M+H]^+$: 222.1125, found 222.1128; **IR ν_{max} (neat)/cm^{-1}:** 2988 (CH), 1718 (C=O), 1667 (C=O).

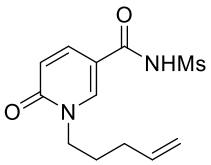
6-Oxo-1-(pent-4-en-yl)-1,6-dihydropyridine-3-carboxylic acid 378



Methyl 6-oxo-1-(pent-4-en-1-yl)-1,6-dihydropyridine-3-carboxylate (2.4 mmol, 524 mg) was subjected to the general hydrolysis conditions described above, to give the title compound (430 mg, 87%) as an off-white solid (analytically pure), which was used without further purification.

M.p. 166-167 °C, (EtOAc); **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** 12.80 (br. s, 1H, O*H*), 8.46-8.39 (m, 1H, C*H*), 7.77 (dd, *J* = 9.5, 2.5 Hz, 1H, C*H*), 6.40 (d, *J* = 9.5 Hz, 1H, C*H*), 5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, *C*H=CH_2), 5.06-5.01 (m, CH=C*H*H), 5.00-4.94 (m, 1H, CH=CH*H*), 3.99-3.92 (m, 2H, NCH_2), 2.07-1.99 (m, 2H, CH_2), 1.73 (tt, *J* = 8.5, 6.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-*d*$_3$):** δ 165.3 (*C*O), 161.5 (*C*O), 144.1 (*C*H), 138.7 (*C*H), 137.6 (*C*H=CH_2), 118.6 (*C*H), 115.3 (CH=*C*H_2), 109.2 (*C*q), 48.8 (N*C*H_2), 30.1 (*C*H_2), 27.6 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{11}H_{13}NO_3$ $[M+Na]^+$: 230.0788, found 230.0790; **IR ν_{max} (neat)/cm^{-1}:** 2996 (CH), 2488 (br. OH), 1701 (C=O), 1636 (C=O).

***N*-(Methylsulfonyl)-6-oxo-1-(pent-4-en-yl)-1,6-dihydropyridine-3-carboxamide 379**

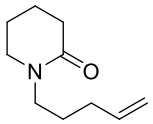


6-Oxo-1-(pent-4-en-yl)-1,6-dihydropyridine-3-carboxylic acid (2.0 mmol, 414 mg) was subjected to the general amide coupling conditions described above. The crude material was purified by recreystalisation from EtOAc to give the title compound (134 mg, 24%) as an off-white solid.

M.p. 118-119 °C, (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.64 (br. s, 1H, N*H*), 8.25 (d, *J* = 2.5 Hz, 1H, C*H*), 7.81 (dd, *J* = 9.5, 2.5 Hz, 1H, Ar*H*), 6.58 (d, *J* = 9.5 Hz, 1H, Ar*H*), 5.78 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.12-4.99 (m, 2H, CH=CH_2), 4.03-3.96 (m, 2H, NCH_2), 3.41 (s, 3H, $SO_2C$$H_3$), 2.17-2.09 (m, 2H, C$H_2$), 1.93-1.81 (m, 2H, C$H_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.9 (*C*O), 162.4 (*C*O), 143.1 (*C*H), 136.9 (*C*H), 136.8 (*C*HCH_2), 120.4 (*C*H), 116.3 (CH=*C*H_2), 110.6 (*C*q), 50.6 (N*C*H_2), 42.2 (SO_2*C*H_3), 30.7 (*C*H_2),

28.3 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{16}N_2O_4S$ $[M+H]^+$:285.0904, found 285.0900; **IR ν_{max} (neat)/cm^{-1}:** 3075 (br. NH), 2932 (CH), 1655 (C=O), 1646 (C=O).

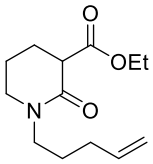
1-(Pent-4-en-1-yl)piperidin-2-one[216] 382



To a suspension of powdered KOH (40 mmol, 4.48 g) in DMSO (20 mL) was added δ-valerolactam (20.0 mmol, 2.00 g). The resulting mixture was cooled to 0 °C and 5-bromo-1-pentene (30.0 mmol, 3.55 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 hours. Water was added and the mixture was extracted with EtOAc (×3) and the combined organic layers were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (0.5-2% MeOH/DCM) to yield the title compound (2.41 g, 72%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.05-5.01 (m, 1H, CH=C*H*H), 4.99-4.93 (m, 1H, CH=CH*H*), 3.38-3.33 (m, 2H, NCH_2), 3.28-3.24 (m, 2H, NCH_2), 2.38-2.34 (m, 2H, CH_2), 2.09-2.02 (m, 2H, CH_2), 1.82-1.73 (m, 4H, 2 × CH_2), 1.68-1.59 (m, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2933 (CH), 1630 (C=O). Data are consistent with literature precedent.[216]

Ethyl 2-oxo-1-(pent-4-en-1-yl)piperidine-3-carboxylate 383

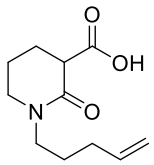


To a solution of 1-(pent-4-en-1-yl)piperidin-2-one (5.0 mmol, 835 mg) in THF (15 mL) at -78 °C was added LiHMDS (10.0 mmol, 10 mL, 1 M solution in hexane) dropwise. The mixture was stirred for 1 hour, and ethyl chloroformate (5.0 mmol, 0.48 mL) was added. The reaction mixture was stirred at room temperature for a further 18 hours, before being poured onto ice. This was extracted with EtOAc (×3) and the combined organic layers were then washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (1% MeOH/DCM) to give the title compound (919 mg, 77%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.04-5.00 (m, 1H, CH=C*H*H), 4.98-4.93 (m, 1H, CH=CH*H*), 4.27-4.12 (m, 2H, OC$H_2$$CH_3$), 3.45-3.22 (m, 5H, 2 × NCH_2 + C*H*), 2.15-1.90 (m, 5H, 2 × CH_2 + C*H*H), 1.82-1.71 (m, 1H, CH*H*), 1.65 (qn, *J* = 7.0 Hz, 2H, CH_2), 1.27 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.4 (*C*O), 165.7 (*C*O), 138.0 (C*H*=*C*H_2), 155.1 (CH=*C*H_2), 61.4 (O*C*$H_2$$CH_3$), 49.3 (*C*H), 47.8 (N*C*H_2), 47.2 (N*C*H_2), 31.1 (*C*H_2), 26.2 (*C*H_2), 25.3 (*C*H_2), 21.3 (*C*H_2), 14.2

(OCH_2CH_3); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{21}NO_3$ $[M+Na]^+$: 262.1414, found 262.1413; **IR ν_{max} (neat)/cm^{-1}:** 2935 (CH), 1732 (C=O), 1641 (C=O).

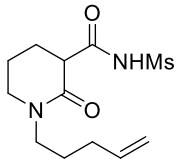
2-Oxo-1-(pent-4-en-1-yl)piperidine-3-carboxylic acid 384



To a stirring solution of ethyl 2-oxo-1-(pent-4-en-1-yl)piperidine-3-carboxylate (5.5 mmol, 1.32 g) in MeOH (10 mL) was added aqueous NaOH (2 M, 5.5 mmol, 2.70 mL) and water (8 mL). The reaction mixture was stirred at room temperature for 18 hours. On completion, the mixture was quenched with aqueous HCl (2 M) and extracted with DCM (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the title compound (935 mg, 80%) as an off-white solid (analytically pure), which was used without further purification.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.54 (br. s, 1H, COO*H*), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.07-4.93 (m, 2H, CH=CH_2), 3.31-3.19 (m, 5H, 2 × NCH_2 + C*H*), 2.03-1.95 (m, 3H, CH_2 + C*H*H), 1.93-1.77 (m, 2H, C*H*H + C*H*H), 1.71 (dddd, *J* = 12.5, 9.5, 7.0, 4.0 Hz, 1H, CH*H*), 1.55 (qn, *J* = 7.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-d_3):** δ 172.3 (*C*O), 165.5 (*C*O), 138.2 (*C*H=CH_2), 115.0 (CH=*C*H_2), 48.6 (*C*H), 47.1 (N*C*H_2), 46.0 (N*C*H_2), 30.5 (*C*H_2), 25.7 (*C*H_2), 24.7 (*C*H_2), 20.6 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{11}H_{17}NO_3$ $[M+H]^+$: 212.1281, found 212.1271; **IR ν_{max} (neat)/cm^{-1}:** 2973-2871 (CH), 2543 (br. OH), 1707 (C=O), 1593 (C=O).

***N*-(Methylsulfonyl)-2-oxo-1-(pent-4-en-1-yl)piperidine-3-carboxamide 385**

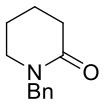


2-Oxo-1-(pent-4-en-1-yl)piperidine-3-carboxylic acid (4.0 mmol, 845 mg), EDC.HCl (6.0 mmol, 1.15 g) and DMAP (9.2 mmol, 1.12 g) were dissolved in DCM (15 mL). Methanesulfonamide (6.0 mmol, 571 mg) was added and the reaction mixture was stirred at room temperature for 18 hours. The mixture was washed with aqueous HCl (1 M), water (×2) and brine. The organic layer was dried over $MgSO_4$ and concentrated to give the title compound (775 mg, 60%) as an off-white solid.

M.p. 100-102 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 11.12 (br. s, 1H, N*H*), 5.80 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.13-4.89 (m, 2H, CH=CH_2), 3.48-3.40 (m, 1H, C*H*CON), 3.39-3.27 (m, 4H, 2 × NCH_2), 3.26 (s, 3H, SO_2CH_3), 2.29-2.18 (m, 1H, C*H*H), 2.13-2.03 (m, 3H, CH*H* + CH_2), 1.96-1.76 (m, 2H, CH_2), 1.67 (qn, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 167.9 (*C*O), 166.8 (*C*O), 137.4 (*C*H=CH_2), 115.6

(CH=*C*H_2), 48.4 (N*C*H_2), 48.0 (N*C*H_2), 47.4 (*C*H), 41.5 (SO_2*C*H_3), 31.1 (*C*H_2), 26.0 (*C*H_2), 22.4 (*C*H_2), 21.4 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{20}N_2O_4S$ $[M+H]^+$: 289.1217, found 289.1225; **IR ν_{max} (neat)/cm^{-1}:** 3185 (br. NH), 2922 (CH), 1686 (C=O), 1624 (C=O).

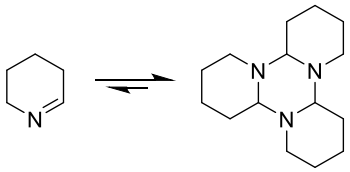
1-Benzylpiperidin-2-one[217] 388



To a solution of NaH (22.0 mmol, 880 mg, 60% dispersion in mineral oil) in THF (10 mL) at 0 °C was added a solition of δ-valerolactam (20.0 mmol, 2.00 g) in THF (30 mL) dropwise. The mixture was allowed to warm to room temperature and was stirred for two hours. Benzyl bromide (22.0 mmol, 2.60 mL) was added dropwise and the reaction mixture was stirred for a further 20 hours. Upon completion the mixture was diluted with water and extracted with EtOAc (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (50-80% EtOAc/petrol) to give the title compound (3.78 g, quantitative) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.29 (m, 2H, Ar*H*), 7.28-7.23 (m, 3H, Ar*H*), 4.60 (s, 2H, NC*H*$_2$Ar), 3.22-3.17 (m, 2H, C*H*$_2$), 2.47 (t, *J* = 6.5 Hz, 2H, C*H*$_2$), 1.84-1.72 (m, 2H, C*H*$_2$); **IR ν_{max} (neat)/cm^{-1}:** 2946 (CH), 1630 (C=O). Data are consistent with literature precedent.[217]

2,3,4,5-Tetrahydropyridine[218] 393

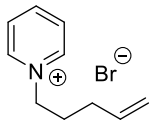


To a stirring solution of *N*-chlorosuccinimide (5.05 mmol, 674 mg) in Et_2O (5 mL) at 0 °C was added piperidine (5.0 mmol, 0.50 mL) dropwise. The resulting solution was stirred at room temperature for 2 hours. The reaction mixture was filterered and the filtrate was washed with water, dried and reduced to approximately 1/3 volume (without heating – potentially hazardous/explosive). EtOH (3 mL) and KOH (10.0 mmol, 560 mg) were added, and the mixture was heated at 60 °C for two hours. On completion the reaction mixture was diluted with water and the layers separated. The aqueous layer was further extracted with Et_2O (×2) and the combined organic layers dried over $MgSO_4$ and concentrated. This gave the title compound (233 mg, 56% as the trimer) as a colourless solid.

M.p. 82-84 °C (MeCN, lit = 59-61.5 °C); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.11 (dt, *J* = 10.5, 5.0 Hz, 3H, 3 × C*H*), 2.79 (d, *J* = 7.0 Hz, 3H, 3 × C*H*H), 2.05-1.97 (m, 3H, 3 × CH*H*), 1.77-1.64 (m, 9H, 3 × C*H*$_2$ + 3 × C*H*H),

1.59-1.51 (m, 6H, 3 × CH_2), 1.31-1.19 (m, 3H, 3 × CH*H*); **IR ν_{max} (neat)/cm^{-1}:** 2945 (CH). ^{1}H NMR and IR data are consistent with literature precedent.[218]

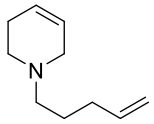
1-(Pent-4-en-1-yl)pyridin-1-ium bromide 395



To a solution of pyridine (10.0 mmol, 0.81 mL) in MeCN (20 mL) was added 5-bromo-1-pentene (20.0 mmol, 2.37 mL). The reaction mixture was stirred at 70 °C for 24 hours. On completion, the mixture was concentrated to give the title compound (2.51 g, quantitative) as an off-white solid (analytically pure), which was used without furher purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (d, *J* = 6.0 Hz, 2H, Ar*H*), 8.52 (t, *J* = 8.0 Hz, 1H, Ar*H*), 8.14 (t, *J* = 7.0 Hz, 2H, Ar*H*), 5.76 (ddt, *J* = 19.5, 12.5, 4.5 Hz, 1H, C*H*=CH_2), 5.10-4.95 (m, 4H, CH=CH_2 + NCH_2), 2.25-2.12 (m, 4H, 2 × CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 145.4 (*C*H), 145.4 (*C*H), 135.9 (*C*H=CH_2), 128.6 (*C*H), 116.8 (CH=*C*H_2), 61.4 (N*C*H_2), 30.9 (*C*H_2), 30.0 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{10}H_{14}BrN$ [M-Br]$^+$: 148.1121, found 148.1127; **IR ν_{max} (neat)/cm^{-1}:** 3050-2973 (CH).

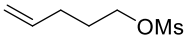
1-(Pent-4-en-1-yl)-1,2,3,6-tetrahydropyridine 396



To a solution of 1-(pent-4-en-1-yl)pyridin-1-ium bromide (20.0 mmol, 4.56 g) in EtOH (50 mL) at 0 °C was added $NaBH_4$ (30 mmol, 1.13 g) portionwise over 30 minutes. The mixture was allowed to warm to room temperature and was stirred for a further 18 hours. The reaction mixture was diluted with water and extracted with DCM (×3). The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (2.5 % MeOH/DCM) to give the title compound (2.19 g, 73%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 17.0 Hz, 10.0 Hz, 6.5 Hz, 1H, C*H*=CH_2), 5.76-5.62 (m, 2H, C*H*=C*H*), 5.03-4.99 (m, 1H, CH=C*H*H), 4.94 (ddt, *J* = 10.0, 2.5, 1.5 Hz, 1H, CH=CH*H*), 2.94 (dt, *J* = 5.0, 2.5 Hz, 2H, *N*CH_2), 2.53 (t, *J* = 5.5 Hz, 2H, NCH_2), 2.43-2.36 (m, 2H, NCH_2), 2.21-2.13 (m, 2H, CH_2), 2.12-2.03 (m, 2H, CH_2), 1.67-1.57 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 138.7 (*C*H=CH_2), 125.5 (*C*H=CH), 125.2 (CH=*C*H), 114.7 (CH=*C*H_2), 58.4 (N*C*H_2), 53.0 (N*C*H_2), 50.3 (N*C*H_2), 31.9 (*C*H_2), 26.4 (*C*H_2), 26.4 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{10}H_{17}N$ [M+H]$^+$: 152.1434, found 152.1430; **IR ν_{max} (neat)/cm^{-1}:** 2910 (CH), 2801 (CH).

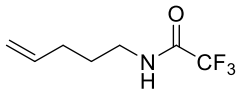
Pent-4-en-1-yl methanesulfonate[219] 398



4-Penten-1-ol (20.0 mmol, 2.06 mL) was subjected to the general mesylation conditions described above. The crude material was purified by flash column chromatography (15% EtOAc/petrol) to yield the title compound (3.15 g, 96%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.11-5.01 (m, 2H, CH=CH_2), 4.24 (t, *J* = 6.5 Hz, 2H, OCH_2), 3.00 (s, 3H, SO_2CH_3), 2.24-2.13 (m, 2H, CH_2), 1.92-1.79 (m, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2942 (CH), 1349 (S=O), 1171 (S=O). Data are consistent with literature precedent.[219]

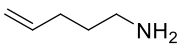
2,2,2-Trifluoro-*N*-(pent-4-en-1-yl)acetamide[220] 399



To a solution of trifluoroacetamide (25.0 mmol, 2.83 g), K_2CO_3 (25.0 mmol, 3.46 g) and TBAB (1.0 mmol, 322 mg) in DMF (35 mL) was added a solution of pent-4-en-1-yl methanesulfonate (10.0 mmol, 1.64 g) in DMF (15 mL). The resulting mixture was stirred vigorously at 45 °C for 48 hours. On completion the mixture was diluted with water and extracted with Et_2O (×3). The combined organic layers were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (5% EtOAc/petrol) to give the title compound (1.29 g, 71%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (br. s, 1H, N*H*), 5.79 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.11-4.99 (m, 2H, C*H*=CH_2), 3.38 (q, *J* = 7.0 Hz, 2H, NCH_2), 2.13 (q, *J* = 7.0 Hz, 2H, CH_2), 1.70 (qn, *J* = 7.0 Hz, 2H, CH_2); **ν_{max} (neat)/cm^{-1}:** 3304 (br. NH), 2942 (CH), 1701 (C=O), 1160 (CF)**.** Data are consistent with literature precedent.[220]

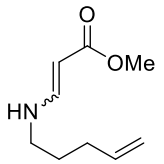
Pent-4-en-1-amine[221] 400



2,2,2-Trifluoro-*N*-(pent-4-en-1-yl)acetamide (7.0 mmol, 1.27 g) was dissolved in THF (25 mL) and treated with aqueous NaOH (2M, 35 mmol, 17.5 mL). The reaction mixture was stirred at room temperature for 18 hours, before being diluted with Et_2O and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O (×2), and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated (without heating). The crude product (400 mg, 67%) was obtained as a colourless oil and was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.07-4.83 (m, 2H, CH=CH_2), 2.75-2.67 (m, 2H, NCH_2), 2.17-2.03 (m, 2H, CH_2), 1.60-1.49 (m, 2H, CH_2); **ν_{max} (neat)/cm^{-1}:** 3277 (NH_2), 2928 (CH)**.** Data are consistent with literature precedent.[221]

Methyl-3-(pent-4-en-1-ylamino)acrylate 402

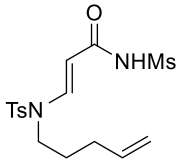


A solution of methyl propiolate (5.0 mmol, 0.44 mL) and pent-4-en-1-amine (5.0 mmol, 426 mg) in THF (20 mL) was stirred at room temperature for 20 hours. The reaction mixture was concentrated to give the title compound (547 mg, 65%, mixture of stereoisomers cis:trans 3:1) as a colourless oil, without need for further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 13.5, 8.5 Hz, 0.25H, trans C*H*=CH), 6.61 (dd, *J* = 13.5, 8.0 Hz, 0.75H, cis C*H*=CH), 5.84-5.70 (m, 1H, C*H*=CH_2), 5.09-4.96 (m, 2H, CH=CH_2), 4.73 (d, *J* = 13.5 Hz, 0.25H, trans CH=C*H*), 4.46 (d, *J* = 8.0 Hz, 0.75H, cis CH=C*H*), 3.66 (s, 0.75H, trans CH_3), 3.64 (s, 2.25H, cis CH_3), 3.17 (q, *J* = 7.5 Hz, 1.5H, cis NCH_2), 3.06 (q, *J* = 7.5 Hz, 0.5H, trans NCH_2), 2.15-2.05 (m, 2H, CH_2), 1.71-1.55 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.3 (cis *C*O), 170.1 (trans *C*O), 157.5 (trans *C*H=CH), 152.5 (cis *C*H=CH), 137.5 (*C*H=CH_2), 115.6 (CH=*C*H_2), 85.3 (trans CH=*C*H), 81.3 (cis CH=*C*H), 50.2 (O*C*H_3), 48.0 (N*C*H_2), 30.6 (*C*H_2), 30.3 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_9H_{15}NO_2$ $[M+Na]^+$: 192.0995, found 192.0993; **IR ν_{max} (neat)/cm^{-1}:** 3331 (NH), 2944 (CH), 1665 (C=O), 1610 (C=C).

4.3.8 Enamine-type substrate data

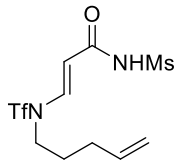
(*E*)-3-((-4-Methyl-*N*-(pent-4-en-1-yl)phenyl)sulfonamido)-*N*-(methylsulfonyl)acrylamide 404c



(*E*)-3-((4-Methyl-*N*-(pent-4-en-yl)phenyl)sulfonamido)acrylic acid (6.0 mmol, 1.86 g) was dissolved in DCM (40 mL) and cooled to 0 °C. EDC.HCl (9.0 mmol, 1.73 g), methanesulfonamide (6.6 mmol, 628 mg) and DMAP (9.0 mmol, 1.09 g) were added and the mixture was stirred at 0 °C for 15 minutes then at room temperature for 18 hours. On completion the reaction was quenched with 1 M HCl, and the volatiles were removed. The remaining aqueous mixture was extracted with DCM (×3), and the combined organic layers were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (0-1% MeOH/DCM) to give the title compound (1.31 g, 57%) as a pale-yellow solid.

M.p. 136-140 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 11.52 (br.s, 1H, N*H*), 7.88 (d, *J* = 14.0 Hz, 1H, NC*H*=CH), 7.77 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.48 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.79 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH_2), 5.40 (d, *J* = 14.0 Hz, NCH=C*H*), 5.09-4.92 (m, 2H, CH=CH_2), 3.40 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.27 (s, 3H, SO_2CH_3), 2.41 (s, 3H, ArCH_3), 2.02 (q, *J* = 7.5 Hz, 2H, CH_2), 1.55 (qn, *J* = 7.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 164.5 (*C*O), 145.1 (*C*q), 140.5 (N*C*H=CH), 137.2 (*C*H=CH_2), 134.5 (*C*q), 130.5 (*C*H), 127.0 (*C*H), 115.7 (CH=*C*H_2), 99.0 (NCH=*C*H), 45.6 (N*C*H_2), 41.3 (SO_2CH_3), 30.1 (*C*H_2), 25.2 (*C*H_2), 21.0 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{22}N_2O_5S_2$ $[M+H]^+$: 387.1043, found 387.1046; **IR ν_{max} (neat)/cm^{-1}:** 2952 (CH), 1704 (C=O), 1622 (C=C).

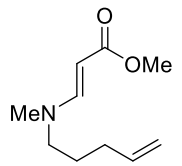
(*E*)-*N*-(Methylsulfonyl)-3-((1,1,1-trifluoro-*N*-(pent-4-en-1-yl)methyl)sulfonamido)acrylamide 404d



(*E*)-3-((1,1,1-Trifluoro-*N*-(pent-4-en-1-yl)sulfonamide)acrylic acid (1.0 mmol, 287 mg) was dissolved in DCM (10 mL) and the solution was cooled to 0 °C. EDC.HCl (1.5 mmol, 287 mg) was added, followed by methanesulfonamide (1.1 mmol, 105 mg) and DMAP (1.5 mmol, 183 mg). The reaction mixture was stirred at 0 °C for 15 minutes and then room temperature for 20 hours. The mixture was quenched by the addition of 1M HCl (1.5 mL). The phases were separated, and the aqueous layer was further extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (1% MeOH/DCM) to give the title compound (149 mg, 41%) as a pale-pink solid.

M.p. 101-108 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.66 (br. s, 1H, N*H*), 7.84 (d, *J* = 14.0 Hz, 1H, NC*H*=CH), 5.79 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.64 (d, *J* = 14.0 Hz, 1H, NCH=C*H*), 5.14-5.06 (m, 2H, CH=CH_2), 3.69 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.36 (s, 3H, SO_2CH_3), 2.14 (q, *J* = 7.0 Hz, 2H, CH_2), 1.82 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 163.3 (*C*O), 141.6 (N*C*H=CH), 136.2 (*C*H=CH_2), 116.8 (CH=*C*H_2), 102.4 (NCH=*C*H), 48.2 (N*C*H_2), 42.1 (SO_2CH_3), 30.5 (*C*H_2), 26.2 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{10}H_{15}F_3N_2O_5S_2$ $[M+H]^+$: 365.0447, found 365.0459; **IR ν_{max} (neat)/cm^{-1}:** 3224 (br. NH), 2930 (CH), 1694 (C=O), 1622 (C=C).

Methyl (*E*)-3-(methyl(pent-4-en-1-yl)amino)acrylate 405a



Method A

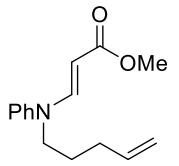
Methyl 3-(methylamino)acrylate (8.0 mmol, 921 mg) was subjected to the general alkylation conditions described above with 5-bromo-1-pentene. The crude material was purified by flash column chromatography (10% EtOAc/petrol) to afford the title compound (1.33 g, 96%) as a yellow oil.

Method B

A solution of 5-bromo-1-pentene (10.0 mmol, 1.18 mL) and methylamine (40.0 mmol, 4.80 mL, 33% in EtOH) in THF (15 mL) was stirred at room temperature for 18 hours. Methyl propiolate (20.0 mmol, 1.80 mL) was added and the mixture was stirred for a further 24 hours. The mixture was filtered, concentrated and the crude material purified by flash column chromatography (4-10% EtOAc/petrol) to afford the title compound (1.14 g, 62%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 13.0 Hz, 1H, NC*H*=CH), 5.76 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, NC*H*=CH_2), 5.08-4.98 (m, 2H, NCH=CH_2), 4.51 (d, *J* = 13.0 Hz, 1H, NCH=C*H*), 3.65 (s, 3H, OCH_3), 3.16 (t, *J* = 7.5 Hz, 2H, NCH_2), 2.79 (s, 3H, NCH_3), 2.03 (q, *J* = 7.0 Hz, 2H, CH_2), 1.72-1.54 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 168.6 (*C*O), 152.6 (N*C*H=CH), 137.8 (*C*H=CH_2), 115.3 (CH=*C*H_2), 82.4 (NCH=*C*H), 55.8 (N*C*H_2), 49.7 (O*C*H_3), 34.7 (N*C*H_3), 30.0 (*C*H_2), 27.3 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{10}H_{17}NO_2$ $[M+H]^+$: 184.1332, found 184.1338; **IR ν_{max} (neat)/cm^{-1}:** 2976-2869 (CH), 1686 (C=O), 1608 (C=C).

Methyl (*E*)-3-(pent-4-en-1-yl(phenyl)amino)acrylate 405b

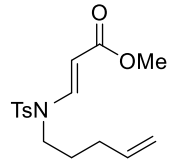


To a suspension of NaH (10.8 mmol, 432 mg, 60% dispersion in mineral oil) in DMF (27 mL) at 0 °C was added methyl 3-(phenylamino)acrylate (8.0 mmol, 1.41 g) dropwise. The resulting mixture was stirred at room temperature for 30 minutes. 5-Bromo-1-pentene (9.0 mmol, 1.07 mL) was added at 0 °C and the reaction mixture was stirred at room temperature for 21 hours. The mixture was quenched with water and extracted with EtOAc (×3). The combined organic layers were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (4% EtOAc/petrol) to yield the title compound (1.51 g, 77%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 13.5 Hz, 1H, NC*H*CH), 7.36-7.28 (m, 2H, Ar*H*), 7.15-7.07 (m, 3H, Ar*H*), 5.75 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.05-4.92 (m, 2H, CH=CH_2), 4.89 (d, *J* = 13.5 Hz, 1H, NCH=C*H*), 3.68 (s, 3H, OCH_3), 3.64-3.56 (m, 2H, NCH_2), 2.12-1.99 (m, 2H, CH_2), 1.80-1.68 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 169.9 (*C*O), 148.6 (N*C*H=CH), 145.5 (*C*q), 137.2 (*C*H=CH_2), 129.6 (*C*H), 124.9 (*C*H), 121.4 (*C*H), 115.9 (CH=*C*H_2), 89.3 (NCH=*C*H), 50.9 (O*C*H_3), 50.1 (N*C*H_2), 31.0 (*C*H_2), 25.7

(*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{19}NO_2$ [M+H]$^+$: 246.1494, found 246.1494; **IR ν_{max} (neat)/cm^{-1}:** 2945 (CH), 1695 (C=O), 1615 (C=C).

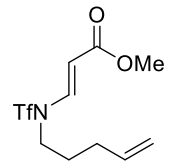
Methyl (*E*)-3-((4-methyl-*N*-(pent-4-en-yl)phenyl)sulfonamido)acrylate 405c



To a solution of 4-methyl-*N*-(pent-4-en-yl)benzenesulfonamide (17.0 mmol, 4.07 g) and methyl propiolate (22.1 mmol, 1.97 mL) in MeCN (70 mL) was added *N*-methylmorpholine (22.1 mmol, 2.43 mL) dropwise at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 2 hours. On completion the volatiles were removed, and the residue was diluted with EtOAc, washed with 1M HCl, washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (3-15% EtOAc/petrol) to give the title compound (4.40 g, 80%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 14.0 Hz, 1H, NC*H*=CH), 7.71-7.66 (m, 2H, Ar*H*), 7.35-7.30 (m, 2H, Ar*H*), 5.74 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.08-4.96 (m, 3H, CH=CH_2 + NCH=C*H*), 3.73 (s, 3H, OCH_3), 3.38-3.31 (m, 2H, NCH_2), 2.43 (s, 3H, ArCH_3), 2.09-2.01 (m, 2H, CH_2), 1.67 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 167.7 (*C*O), 144.9 (*C*q), 142.0 (N*C*H=CH), 136.8 (*C*H=CH_2), 135.5 (*C*q), 130.3 (*C*H), 127.3 (*C*H), 116.1 (CH=*C*H_2), 97.6 (NCH=*C*H), 51.6 (O*C*H_3), 45.7 (N*C*H_2), 30.8 (*C*H_2), 25.7 (*C*H_2), 21.7 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{21}NO_4S$ [M+H]$^+$: 324.1264, found 324.1257; **IR ν_{max} (neat)/cm^{-1}:** 2977-2901 (CH), 1712 (C=O), 1621 (C=C).

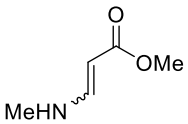
Methyl (*E*)-3-((1,1-trifluoro-*N*-(pent-4-en-1-yl)methyl)sulfonamido)acrylate 405d



To a solution of 1,1,1-trifluoro-*N*-(pent-4-en-1-yl)methanesulfonamide (2.5 mmol, 543 mg) in MeCN (10 mL) was added *N*-methylmorpholine (3.3 mmol, 0.36 mL) dropwise, followed by a solution of methyl propiolate (2.5 mmol, 0.22 mL) in MeCN (2 mL) over 30 minutes. The reaction mixture was stirred at room temperature for 3 hours. The volatiles were removed, and the remaining residue was redissolved in EtOAc, washed with 1 M HCl, washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (2% EtOAc/petrol) to yield the title compound (500 mg, 64%) as a colourless oil (ca. 7% inseparable impurity present).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 14.0 Hz, 1H, NC*H*=CH), 5.78 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.39 (d, *J* = 14.0 Hz, 1H, NCH=C*H*), 5.12-5.02 (m, 2H, CH=CH_2), 3.76 (s, 3H, OCH_3), 3.66 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.13 (q, *J* = 7.0 Hz, 2H, CH_2), 1.81 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 166.2 (*C*O), 139.7 (N*C*H=CH), 136.2 (*C*H=CH_2), 116.7 (CH=CH_2), 103.2 (NCH=*C*H). 52.0 (OCH_3), 47.6 (NCH_2), 30.5 (CH_2), 26.2 (CH_2); **HRMS (ESI^+):** Calculated for $C_{10}H_{14}F_3NO_4S$ $[M+H]^+$: 302.0668, found 302.0671; **IR ν_{max} (neat)/cm^{-1}:** 2955 (CH), 1723 (C=O), 1638 (C=C).

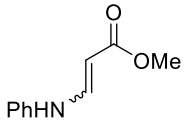
Methyl 3-(methylamino)acrylate 406a



A solution of methyl propiolate (10.0 mmol, 0.88 mL) and methylamine (10.0 mmol, 1.20 mL, 33% in EtOH) in DMSO (40 mL) was stirred at room temperature for 18 hours. The mixture was diluted with water and extracted with EtOAc (×3). The combined organic extracts were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. This gave the title compound (870 mg, 76%, mixture of stereoisomers, trans:cis 17:3) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 13.0 Hz, 7.5 Hz, 0.85H, trans NC*H*=CH), 6.58 (dd, *J* = 13.0, 8.0 Hz, 0.15H, cis NC*H*=CH), 4.70 (d, *J* = 13.0 Hz, 0.85H, trans NCH=C*H*), 4.46 (d, *J* = 8.0 Hz, 0.15H, cis NCH=C*H*), 3.66 (s, 2.55H, trans OCH_3), 3.63 (s, 0.45H, cis OCH_3), 2.95 (d, *J* = 5.0 Hz, 0.45H, cis NCH_3), 2.76 (d, *J* = 5.0 Hz, 2.55H, trans NCH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.3 (cis *C*O), 170.2 (trans *C*O), 153.6 (cis N*C*H=CH), 150.2 (trans N*C*H=CH), 85.2 (trans NCH=*C*H), 81.4 (cis NCH=*C*H), 50.6 (OCH_3), 41.0 (cis (NCH_3), 35.0 (trans N*C*H_3); **HRMS (ESI^+):** Calculated for $C_5H_9NO_2$ $[M+Na]^+$: 138.0525, found 138.0530; **IR ν_{max} (neat)/cm^{-1}:** 3342 (br. NH), 2950 (CH), 1664 (C=O), 1610 (C=C).

Methyl 3-(phenylamino)acrylate[222-223] 406b

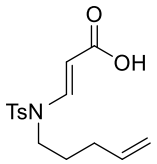


A solution of aniline (10.0 mmol, 0.90 mL) and methyl propiolate (10.0 mmol, 0.88 mL) in EtOH (40 mL) was stirred at 50 °C for 72 hours. On completion, water was added, and the mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to give the title zcompound (1.64 g, 93%, mixture of stereoisomers, trans:cis 6:4) as a yellow solid (analytically pure), which was used without further purification.

M.p. 113-114 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.84 (br. d, *J* = 12.5 Hz, 0.4H, cis N*H*), 7.98-7.85 (app. t, 0.6H, trans NC*H*=CH), 7.35-7.20 (m, 3H, Ar*H*), 7.07-6.90 (m, 2.6H, 2 × Ar*H* + trans N*H*), 6.55 (d,

J = 13.0 Hz, 0.4H, cis NC*H*=CH), 5.19 (d, *J* = 13.0 Hz, 0.6H, trans NCH=C*H*), 4.82 (d, *J* = 8.5 Hz, 0.4H, cis NCH=C*H*), 3.69 (s, 3H, OCH_3); **HRMS (ESI$^+$):** Calculated for $C_{10}H_{11}NO_2$ $[M+H]^+$: 178.0863, found 178.0864; **IR ν_{max} (neat)/cm^{-1}:** 3274 (br. NH), 2953 (CH), 1694 (C=O), 1614 (C=C). Data are consistent with literature precedent.[222-223]

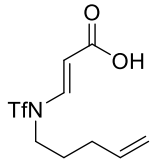
(*E*)-3-((4-Methyl-*N*-(pent-4-en-yl)phenyl)sulfonamido)acrylic acid 408c



A solution of methyl (*E*)-3-((4-methyl-*N*-(pent-4-en-yl)phenyl)sulfonamido)acrylate (5.0 mmol, 1.62 g) in THF (15 mL) and MeOH (15 mL) was treated with aqueous NaOH (4 M, 50.0 mmol, 12.5 mL). The mixture was stirred at reflux for 2 hours and then allowed to cool to room temperature. The volatiles were removed, and the aqueous solution was acidified with 3 M HCl, extracted with Et_2O (×3), washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (1.29 g, 83%) as a white solid (analytically pure), which was used without further purification.

M.p. 117-118 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.20 (d, *J* = 14.0 Hz,1H, NC*H*=CH), 7.75-7.64 (m, 2H, Ar*H*), 7.34 (*J* = 8.0 Hz, 2H, Ar*H*), 5.75 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.10-4.97 (m, 3H, CH=CH_2 + NCH=C*H*), 3.43 (m, 2H, NCH_2), 2.44 (s, 3H, ArCH_3), 2.06 (q, *J* = 7.0 Hz, 2H, CH_2), 1.68 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 173.1 (*C*O), 145.1 (*C*q), 144.0 (N*C*H=CH), 136.8 (*C*H=CH_2), 135.3 (*C*q), 130.3 (*C*H), 127.3 (*C*H), 116.1 (CH=*C*H_2), 96.7 (NCH=*C*H), 45.8 (N*C*H_2), 30.8 (*C*H_2), 25.8 (*C*H_2), 21.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{19}NO_4S$ $[M+H]^+$: 310.1108, found 310.1096; **IR ν_{max} (neat)/cm^{-1}:** 2946 (CH), 2640 (br. OH), 1668 (C=O), 1590 (C=C).

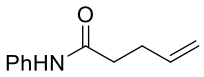
(*E*)-3-((1,1,1-Trifluoro-*N*-(pent-4-en-1-yl)sulfonamide)acrylic acid 408d



A solution of methyl (*E*)-3-((1,1-trifluoro-*N*-(pent-4-en-1-yl)methyl)sulfonamido)acrylate (1.6 mmol, 482 mg) in THF (10 mL) and MeOH (10 mL) was treated with aqueous NaOH (2 M, 16.0 mmol, 8 mL). The mixture was stirred at reflux for 3 hours and then allowed to cool to room temperature. The volatiles were removed, and the aqueous solution was acidified with 3 M HCl, extracted with EtOAc (×3), washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (428 mg, 94%) as a pale-yellow solid which was used without further purification (ca. 5% inseparable impurity present).

M.p. 66-69 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 7.46 (d, *J* = 14.0 Hz, 1H, NC*H*=CH), 5.88-5.78 (m, 1H, C*H*=CH$_2$), 5.76 (d, *J* = 14.0 Hz, 1H, NCH=C*H*), 5.10-4.96 (m, 2H, CH=C*H*$_2$), 3.80 (t, *J* = 7.5 Hz, 2H, NC*H*$_2$), 2.09 (q, *J* = 7.5 Hz, 2H, C*H*$_2$), 1.71 (qn, *J* = 7.5 Hz, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 166.5 (*C*O), 137.8 (N*C*H=CH), 137.1 (*C*H=CH$_2$), 115.7 (CH=*C*H$_2$), 105.7 (NCH=*C*H), 47.3 (N*C*H$_2$), 29.6 (*C*H$_2$), 25.8 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_9H_{12}F_3NO_4S$ $[M+H]^+$: 288.0512, found 288.0498; **IR ν_{max} (neat)/cm^{-1}:** 2958 (CH), 2565 (br. OH), 1682 (C=O), 1616 (C=C).

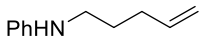
***N*-Phenylpent-4-enamide[224] 414**



EDC.HCl (13.0 mmol, 2.49 g) and DMAP (14.0 mmol, 1.71 g) were dissolved in DCM (25 mL). The solution was cooled to 0 °C and 4-pentenoic acid (10.0 mmol, 1.02 mL) was added. The mixture was stirred for 5 minutes at 0 °C and then aniline (12.0 mmol, 1.09 mL) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 18 hours. On completion, the reaction mixture was quenched with 1M HCl (25 mL). The layers were separated, and the aqueous layer was extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was recrystallised from hexane/EtOAc to give the title compound (1.37 g, 78%) as a pale-orange solid.

M.p. 82-85 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.31 (t, *J* = 8.0 Hz, 2H, Ar*H*), 7.10 (t, *J* = 7.5 Hz, 1H, Ar*H*), 5.89 (ddt, *J* = 16.5, 10.5, 6.0 Hz, 1H, C*H*=CH), 5.18-5.10 (m, 1H, CH=C*H*H), 5.08-5.04 (m, 1H, CH=CH*H*), 2.48 (m, 4H, 2 × C*H*$_2$); **IR ν_{max} (neat)/cm^{-1}:** 3317 (NH), 2978 (CH), 1645 (C=O). Data are consistent with literature precedent.[224]

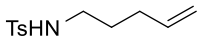
***N*-(Pent-4-en-1-yl)aniline[225] 415**



N-Phenylpent-4-enamide (7.5 mmol, 1.31 g) was dissolved in Et_2O (25 mL). The solution was cooled to 0 °C and $LiAlH_4$ (18.8 mmol, 7.80 mL, 2.4 M solution in THF) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 18 hours. The reaction mixture was quenched at 0 °C by the sequential addition of water (0.71 mL), 2M NaOH (0.71 mL), water (2.13 mL) and $MgSO_4$. After stirring vigorously for 1 hour the mixture was filtered and washed with EtOAc. The filtrate was washed with a saturated aqueous solution of $NaHCO_3$. The aqueous later was further extracted with EtOAc (×2), washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (949 mg, 78%) as a yellow oil (analytically pure) which was used withour further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.14 (m, 2H, Ar*H*), 6.69 (tt, *J* = 7.5, 1.0 Hz, 1H, Ar*H*), 6.64-6.60 (m, 2H, Ar*H*), 5.85 (ddt, *J* = 17.0, 10.1, 6.5 Hz, 1H, C*H*=CH_2), 5.10-5.03 (m, 1H, CH=C*H*H), 5.03-4.98 (m, 1H, CH=CH*H*), 3.14 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.23-2.13 (m, 2H, CH_2), 1.73 (qn, *J* = 7.0 Hz, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2924 (CH). Data are consistent with literature precedent.[225]

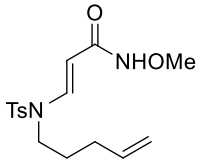
4-Methyl-*N*-(pent-4-en-yl)benzenesulfonamide[226] 417



To a solution of toluenesulfonamide (10.0 mmol, 1.71 g) in MeCN (30 mL) was added K_2CO_3 (10.0 mmol, 1.38 g) and 5-bromo-1-pentene (11.0 mmol, 1.30 mL). The resulting mixture was heated at reflux for 24 hours. On completion the mixture was filtered over Celite® and concentrated. The crude material was purified by flash column chromatography (5-20% EtOAc/petrol) to give the title compound (2.00 g, 83%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.31 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.70 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.02-4.88 (m, 2H, CH=CH_2), 4.51 (br. t, *J* = 6.5 Hz, 1H, N*H*), 2.95 (q, *J* = 7.0 Hz, 2H, NCH_2), 2.43 (s, 3H, ArCH_3), 2.04 (q, *J* = 7.0 Hz, 2H, CH_2), 1.56 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 143.5 (*C*q), 137.3 (*C*H=CH_2), 137.1 (*C*q), 129.8 (*C*H), 127.2 (*C*H), 115.7 (CH=*C*H_2), 42.8 (N*C*H_2), 30.8 (*C*H_2), 28.8 (*C*H_2), 21.7 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{17}NO_2S$ $[M+H]^+$: 240.1053, found 240.1050; **IR ν_{max} (neat)/cm^{-1}:** 3277 (br. NH), 2975-2870 (CH), 1322 (S=O), 1157 (S=O).

(*E*)-*N*-Methoxy-3-((4-methyl-*N*-(pent-4-en-1-yl)phenyl)sulfonamido)acrylamide 420

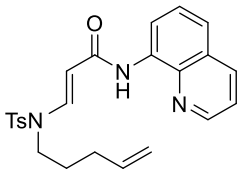


To a solution of (*E*)-3-((4-methyl-*N*-(pent-4-en-yl)phenyl)sulfonamido)acrylic acid (3.0 mmol, 928 mg) in DCM (10 mL) at 0 °C was added oxalyl chloride (3.6 mmol, 0.31 mL) dropwise, followed by a catalytic amount of DMF. The reaction mixture was allowed to warm to room temperature and stirred for 27 hours. The solvent was removed to give the crude acid chloride. Methoxyamine hydrochloride (3.6 mmol, 301 mg) was added to a biphasic mixture of K_2CO_3 (6.0 mmol, 829 mg) in EtOAc/water (2:1 v:v 36 mL). The mixture was cooled to 0 °C and the crude acid chloride dissolved in a minimum amount of EtOAc was added dropwise. The reaction mixture was stirred at room temperature for 24 hours. On completion the phases were separated, and the aqueous layer was extracted with EtOAc (×2). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude

material was purified by flash column chromatography (40% EtOAc/petrol) to yield the title compound (289 mg, 28%) as a white solid.

M.p. 113-114 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.34 (br. s, 1H, N*H*), 8.12 (d, *J* = 14.0 Hz, 1H, NC*H*=CH), 7.70 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.31 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.37-5.18 (br. m, 1H, NCH=C*H*), 5.08-4.95 (m, 2H, CH=CH_2), 3.74 (s, 3H, OCH_3), 3.43-3.34 (m, 2H, NCH_2), 2.42 (s, 3H, ArCH_3), 2.07 (q, *J* = 7.0 Hz, 2H, CH_2), 1.69 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 144.8 (*C*q), 141.1 (N*C*H=CH), 137.0 (*C*H=CH_2), 135.6 (*C*q), 130.2 (*C*H), 127.3 (*C*H), 116.1 (CH=*C*H_2), 95.6 (NCH=*C*H), 65.1 (O*C*H_3), 45.9 (N*C*H_2), 30.8 (*C*H_2), 25.9 (*C*H_2), 21.7 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{22}N_2O_4S$ [M+H]$^+$: 339.1373, found 339.1388; **IR ν_{max} (neat)/cm^{-1}:** 3137 (br. NH), 2938 (CH), 1659 (C=O), 1610 (C=C), 1357 (S=O), 1163 (S=O).

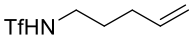
(*E*)-3-((4-Methyl-*N*-(pent-4-en-1-yl)phenyl)sulfonamido)-*N*-(quinoline-8-yl)acrylamide 423



To a solution of (*E*)-3-((4-methyl-*N*-(pent-4-en-yl)phenyl)sulfonamido)acrylic acid (2.0 mmol, 619 mg) in DCM (20 mL) at 0 °C was added EDC.HCl (3.0 mmol, 574 mg), 8-aminoquinoline (2.2 mmol, 317 mg) and DMAP (3.0 mmol, 367 mg). The reaction mixture was stirred at 0 °C for 15 minutes and then room temperature for 18 hours. The mixture was quenched with 1M HCl (3 mL) and the layers were separated. The aqueous layer was extracted with DCM (×2) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (10-20% EtOAc/petrol) to give the title compound (332 mg, 38%) as a yellow solid.

M.p. 158-160 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.66 (br. s, 1H, N*H*), 8.84 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 8.80 (dd, *J* = 4.5 Hz, 1H, Ar*H*), 8.20 (d, *J* = 13.5 Hz, 1H, NC*H*=CH), 8.19-8.15 (m, 1H, Ar*H*), 7.74 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.59-7.48 (m, 2H, Ar*H*), 7.46 (dd, *J* = 8.5, 4.0 Hz, 1H, Ar*H*), 7.32 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.84 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.45 (d, *J* = 13.5 Hz, 1H, NCH=C*H*), 5.17-5.00 (m, 2H, CH=CH_2), 3.52-3.39 (m, 2H, NCH_2), 2.42 (s, 3H, ArCH_3), 1.79 (q, *J* = 7.0 Hz, 2H, CH_2), 1.79 (qn, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 164.5 (*C*O), 148.1 (*C*H), 144.7 (*C*q), 140.3 (N*C*H=CH), 138.5 (*C*q), 137.2 (*C*H=CH_2), 136.6 (*C*H), 135.8 (*C*q), 135.0 (*C*q), 130.2 (*C*H), 128.1 (*C*q), 127.7 (*C*H), 127.3 (*C*H), 121.7 (*C*H), 121.4 (*C*H), 116.8 (*C*H), 116.0 (CH=*C*H_2), 101.6 (NCH=*C*H), 46.2 (N*C*H_2), 30.9 (*C*H_2), 26.2 (*C*H_2), 21.7 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{24}H_{25}N_3O_3S$ [M+H]$^+$: 436.1689, found 436.1678; **IR ν_{max} (neat)/cm^{-1}:** 3273 (br. NH), 2921 (CH), 1661 (C=O), 1356 (S=O), 1156 (S=O).

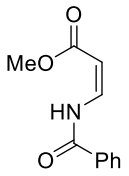
1,1,1-Trifluoro-*N*-(pent-4-en-1-yl)methanesulfonamide[227] 426



To a solution of trifluoromethanesulfonamide (10.0 mmol, 1.49 g) in MeCN (30 mL) was added K_2CO_3 (10.0 mmol, 1.38 g) and 5-bromo-1-pentene (11.0 mmol, 1.30 mL). The resulting mixture was heated at reflux for 24 hours. On completion the mixture was filtered over Celite® and concentrated. The crude material was purified by flash column chromatography (3-20% EtOAc/petrol) to give the title compound (561 mg, 26%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.12-5.01 (m, 2H, CH=CH_2), 4.84 (br. s, 1H, N*H*)), 3.33 (q, *J* = 7.0 Hz, 2H, NCH_2), 2.21-2.09 (m, 2H, CH_2), 1.73 (qn, *J* = 7.0 Hz, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 3317 (br. NH), 2949 (CH), 1368 (S=O), 1188 (S=O). Data are consistent with literature precedent.[227]

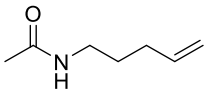
Methyl (*Z*)-3-benzamidoacrylate[228] 429



Benzamide (5.0 mmol, 606 mg), $Pd(OAc)_2$ (0.05 mmol, 11.2 mg), NaOAc (10.0 mmol, 820 mg), TFA (5.0 mmol, 1.90 mL) and toluene (20 mL) were stirred together for 5 minutes at room temperature. Methyl propiolate (7.5 mmol, 630 mg) was added and the reaction mixture was stirred at 70 °C for 18 hours. The mixture was diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate (×2) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (5% EtOAc/petrol) to give the title compound (598 mg, 58%) as an off-white solid.

M.p. 65-67 °C (MeCN, lit = 70 °C[228]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.98-7.94 (m, 2H, Ar*H* + NC*H*=CH), 7.75 (dd, *J* = 11.0, 9.0 Hz, 1H, Ar*H*), 7.60 (ddt, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 7.53-7.48 (m, 2H, Ar*H*), 5.28 (d, *J* = 9.0 Hz, 1H, NCH=C*H*), 3.78 (s, 3H, OCH_3); **HRMS (ESI$^+$):** Calculated for $C_{11}H_{11}NO_3$ $[M+H]^+$: 206.0812, found 206.0802; **IR ν_{max} (neat)/cm^{-1}:** 3326 (NH), 2961 (CH), 1694 (C=O), 1683 (C=O), 1623 (C=C). Data are consistent with literature precedent.[228]

***N*-(Pent-4-en-1-yl)acetamide[229] 431**

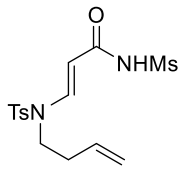


To a suspension of NaH (11.0 mmol, 440 mg, 60% dispersion in mineral oil) in DMF (30 mL) at 0 °C was added acetamide (10.0 mmol, 590 mg) portionwise. The resulting mixture was stirred at 0 °C for 30

minutes. 5-Bromo-1-pentene (11.0 mmol, 1.30 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature and was stirred for 40 hours. On completion, the reaction was quenched with water and extracted with EtOAc (×3). The combined organic layers were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (30-80% EtOAc/petrol) to give the title compound (438 mg, 34%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.06-5.00 (m, 1H, CH=C*H*H), 4.99-4.95 (m, 1H, CH=CH*H*), 3.25 (td, *J* = 7.5, 6.0 Hz, 2H, NCH_2), 2.12-2.05 (m, 2H, CH_2), 1.96 (s, 3H, COCH_3), 1.65-1.55 (m, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 3288 (NH), 2962 (CH), 1633 (C=O). Data are consistent with literature precedent.[229]

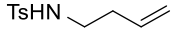
(*E*)-3-((*N*-(But-3-en-1-yl)-4-methylphenyl)sulfonamido)-*N*-(methylsulfonyl)acrylamide 437



(*E*)-3-((*N*-(But-3-en-1-yl)-4-methylphenyl)sulfonamido)acrylic acid (5.0 mmol, 1.48 g) was dissolved in DCM (50 mL) and the solution was cooled to 0 °C. EDC.HCl (7.5 mmol, 1.44 g) was added, followed by methanesulfonamide (5.5 mmol, 523 mg) and DMAP (7.5 mmol, 916 mg). The reaction mixture was stirred at 0 °C for 15 minutes and then room temperature for 20 hours. The mixture was quenched by the addition of 1M HCl (7.5 mL). The phases were separated, and the aqueous layer was further extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (20-60% EtOAc/petrol) to give the title compound (963 mg, 52%) as a pale-yellow solid.

M.p. 137-138 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.66 (br.s, 1H, N*H*), 8.18 (d, *J* = 13.5 Hz, 1H, NC*H*=CH), 7.71 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.35 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.76-5.62 (m, 1H, C*H*=CH_2), 5.14 (d, *J* = 13.5 Hz, 1H, NCH=C*H*), 5.10-5.03 (m, 2H, CH=CH_2), 3.51-3.39 (m, 2H, NCH_2), 3.34 (s, 3H, SO_2CH_3), 2.44 (s, 3H, ArCH_3), 2.30 (q, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 164.7 (*C*O), 145.4 (*C*q), 143.5 (N*C*H=CH), 135.0 (*C*q), 133.4 (C*H*=CH_2), 130.5 (*C*H), 127.4 (*C*H), 118.2 (CH=*C*H_2), 97.0 (NCH=*C*H), 46.0 (N*C*H_2), 42.1 (SO_2CH_3), 31.2 (*C*H_2), 21.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{20}N_2O_5S_2$ $[M+H]^+$: 373.0886, found 373.0881; **IR ν_{max} (neat)/cm^{-1}:** 3110 (br. NH), 2888 (CH), 1670 (C=O).

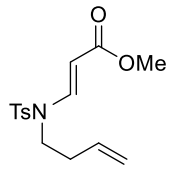
***N*-(But-3-en-1-yl)-4-methylbenzenesulfonamide[230] 440**



To a solution of toluenesulfonamide (10.0 mmol, 1.71 g) in MeCN (30 mL) was added K_2CO_3 (10.0 mmol, 1.38 g) and 4-bromo-1-butene (11.0 mmol, 1.12 mL). The resulting mixture was heated at reflux for 18 hours. On completion the mixture was filtered over Celite® and concentrated. The crude material was purified by flash column chromatography (3-20% EtOAc/petrol) to give the title compound (1.56 g, 68%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.71 (m, 2H, Ar*H*), 7.33-7.28 (m, 2H, Ar*H*), 5.62 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.08-4.99 (m, 2H, CH=C*H*$_2$), 4.57 (br. t, *J* = 6.5 Hz, N*H*), 3.01 (q, *J* = 6.5 Hz, 2H, NC*H*$_2$), 2.42 (s, 3H, ArC*H*$_3$), 2.23-2.15 (m, 1H, C*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 143.6 (*C*q), 137.0 (*C*q), 134.3 (*C*H=CH_2), 129.8 (*C*H), 127.2 (*C*H), 118.3 (CH=*C*H_2), 42.2 (N*C*H_2), 33.7 (*C*H_2), 21.7 (*C*H_3); **IR ν_{max} (neat)/cm^{-1}:** 3273 (br. NH), 2929 (CH), 1322 (S=O), 1157 (S=O). Data are consistent with literature precedent.[230]

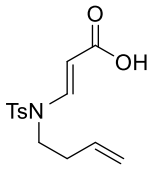
Methyl (*E*)-3-((*N*-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)acrylate 441



To a solution of *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (6.0 mmol, 1.35 g) and methyl propiolate (7.8 mmol, 0.69 mL) in MeCN (25 mL) was added *N*-methylmorpholine (7.8 mmol, 0.86 mL) dropwise at 0 °C. The mixture was allowed to warm to room temperature and was stirred for two hours. On completion the volatiles were removed, and the residue was diluted with EtOAc, washed with 1M HCl, washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (3-15% EtOAc/petrol) to give the title compound (1.41g, 76%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 14.0 Hz, 1H, NC*H*=CH), 7.73-7.65 (m, 2H, Ar*H*), 7.36-7.30 (m, 2H, Ar*H*), 5.74-5.63 (m, 1H, C*H*=CH_2), 5.11-5.02 (m, 3H, CH=C*H*$_2$ + NCH=C*H*), 3.73 (s, 3H, OC*H*$_3$), 3.44-3.37 (m, 2H, NC*H*$_2$), 2.43 (s, 3H, ArC*H*$_3$), 2.35-2.27 (m, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 167.6 (*C*O), 145.0 (*C*q), 141.9 (N*C*H=CH), 135.5 (*C*q), 133.6 (*C*H=CH_2), 130.3 (*C*H), 127.3 (*C*H), 118.0 (CH=*C*H_2), 97.8 (NCH=*C*H), 51.6 (O*C*H_3), 45.6 (N*C*H_2), 31.1 (*C*H_2), 21.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{19}NO_4S$ [M+Na]$^+$: 332.0927, found 332.0941; **IR ν_{max} (neat)/cm^{-1}:** 2949 (CH), 1708 (C=O), 1621 (C=C), 1365 (S=O), 1163 (S=O).

(*E*)-3-((*N*-(But-3-en-1-yl)-4-methylphenyl)sulfonamido)acrylic acid 442

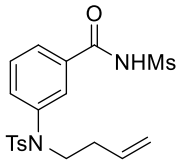


A solution of methyl (*E*)-3-((*N*-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)acrylate (4.5 mmol, 1.39 g) in THF (10 mL) and MeOH (10 mL) was treated with aqueous NaOH (6 M, 45.0 mmol, 7.5 mL). The mixture was stirred at reflux for 2 hours and then allowed to cool to room temperature. The volatiles were removed, and the aqueous solution was acidified with 3 M HCl, extracted with EtOAc (×3), washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (1.00 g, 75%) as a pale-yellow solid (analytically pure), which was used without further purification.

M.p. 118-119 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.20 (d, *J* = 14.0 Hz, 1H, NC*H*=CH), 7.77-7.63 (m, 2H, Ar*H*), 7.39-7.31 (m, 2H, Ar*H*), 5.70 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.15-5.01 (m, 3H, CH=CH_2 + NCH=C*H*), 3.49-3.40 (m, 2H, NCH_2), 2.45 (s, 3H, ArCH_3), 2.38-2.27 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.7 (*C*O), 145.2 (q), 143.9 (N*C*H=CH), 135.3 (*C*q), 133.4 (*C*H=CH_2), 130.4 (*C*H), 127.4 (*C*H), 118.1 (CH=*C*H_2), 96.7 (NCH=*C*H), 45.7 (N*C*H_2), 31.1 (*C*H_2), 21.8 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{17}NO_4S$ $[M+H]^+$: 296.0951, found 296.0959; **IR ν_{max} (neat)/cm^{-1}:** 2899 (CH), 2601 (br. OH), 1667 (C=O), 1161 (S=O).

4.3.9 Aniline-type substrate data

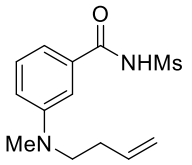
3-((*N*-(But-3-en-en-1-yl)-4-methylphenyl)sulfonamido)-*N*-(methysulfonyl)benzamide 443a



3-((*N*-(But-3-en-1-yl)-4-methylphenyl)sulfonamido)benzoic acid (3.0 mmol, 1.04 g) was dissolved in DCM (30 mL) and the solution was cooled to 0 °C. EDC.HCl (4.5 mmol, 863 mg) was added, followed by methanesulfonamide (3.3 mmol, 314 mg) and DMAP (4.5 mmol, 550 mg). The reaction mixture was stirred at 0 °C for 15 minutes and then room temperature for 20 hours. The mixture was quenched by the addition of 1M HCl (4.5 mL). The phases were separated, and the aqueous layer was further extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (2% MeOH/DCM) to give the title compound (740 mg, 58%) as a pale-yellow solid.

M.p. 95-100 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.82 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.56-7.54 (m, 1H, Ar*H*), 7.49-7.43 (m, 3H, Ar*H*), 7.31-7.26 (m, 3H, Ar*H*), 5.70 (ddt, *J* = 17.0, 10.5, 7.5 Hz, C*H*=CH_2), 5.09-4.94 (m, 2H, CH=CH_2), 3.61 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.43 (s, 3H, SO_2CH_3), 2.44 (ArCH_3), 2.16 (q, *J* = 7.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 164.8 (*C*O), 144.2 (*C*q), 140.1 (*C*q), 134.8 (*C*q), 134.1 (*C*H=CH_2), 133.8 (*C*H), 132.4 (*C*q), 129.9 (*C*H), 129.8 (*C*H), 128.7 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 117.6 (CH=*C*H_2), 49.9 (N*C*H_2), 41.9 (SO_2*C*H_3), 32.8 (*C*H_2), 21.7 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{19}H_{22}N_2O_5S_2$ $[M+H]^+$: 423.1043, found 423.1045; **IR ν_{max} (neat)/cm^{-1}:** 3125 (br. NH), 2984 (CH), 1681 (C=O), 1335 (S=O), 1157 (S=O).

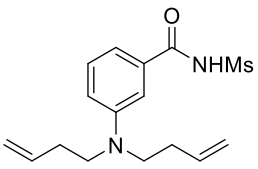
3-(But-3-en-1-yl(methyl)amino)-*N*-(methylsulfonyl)benzamide 443b



3-(But-3-en-1-yl(methyl)amino)benzoic acid (1.5 mmol, 308 mg) was dissolved in DCM (15 mL) and the solution was cooled to 0 °C. EDC.HCl (2.3 mmol, 421 mg) was added, followed by methanesulfonamide (1.7 mmol, 157 mg) and DMAP (2.3 mmol, 275 mg). The reaction mixture was stirred at 0 °C for 15 minutes and then room temperature for 16 hours. The mixture was quenched by the addition of 1M HCl (2.25 mL). The phases were separated, and the aqueous layer was further extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (0.5% MeOH/DCM) to give the title compound (198 mg, 47%) as a pale-yellow solid.

M.p. 124-126 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.60 (br.s, 1H, N*H*), 7.33-7.27 (m, 1H, Ar*H*), 7.15 (dd, *J* = 3.0, 1.5 Hz, 1H, Ar*H*), 7.00 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 6.91 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H, Ar*H*), 5.88-5.75 (m, 1H, C*H*=CH_2), 5.15-5.03 (m, 2H, CH=CH_2), 3.49-3.40 (m, 5H, SO_2CH_3 + NCH_2), 2.99 (s, 3H, NCH_3), 2.37-2.30 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 166.3 (*C*O), 149.6 (*C*q), 135.5 (*C*H=CH_2), 132.0 (*C*q), 129.9 (*C*H), 117.1 (*C*H), 117.1 (CH=*C*H_2), 114.4 (*C*H), 111.2 (*C*H), 52.3 (N*C*H_2), 41.9 (SO_2*C*H_3), 38.6 (N*C*H_3), 31.2 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{18}N_2O_3S$ $[M+H]^+$: 283.1111, found 283.1114; **IR ν_{max} (neat)/cm^{-1}:** 3187 (br. NH), 2896 (CH), 1656 (C=O), 1337 (S=O), 1151 (S=O).

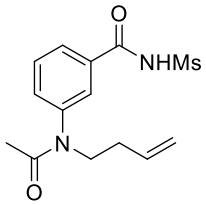
3-(Di(but-3-en-1-yl)amino)-*N*-(methylsulfontl)benzamide 443c



3-(Di(but-3-en-1-yl)amino)benzoic acid (3.0 mmol, 736 mg) was dissolved in DCM (30 mL) and the solution was cooled to 0 °C. EDC.HCl (4.5 mmol, 863 mg) was added, followed by methanesulfonamide (3.3 mmol, 314 mg) and DMAP (4.5 mmol, 550 mg). The reaction mixture was stirred at 0 °C for 15 minutes and then room temperature for 16 hours. The mixture was quenched by the addition of 1M HCl (4.5 mL). The phases were separated, and the aqueous layer was further extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (1% MeOH/DCM) to give the title compound (522 mg, 54%) as a pale-pink solid.

M.p. 89-91 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.62 (br. s, 1H, N*H*), 7.29 (t, *J* = 8.5 Hz, 1H, Ar*H*), 7.19-7.16 (m, 1H, Ar*H*), 6.96 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.87 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar*H*), 5.88-5.76 (m, 2H, 2 × C*H*=CH_2), 5.15-5.05 (m, 4H, 2 × CH=CH_2), 3.44-3.38 (m, 7H, SO_2CH_3 + 2 × NCH_2), 2.34 (q, *J* = 7.0 Hz, 4H, 2 × CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 166.3 (*C*O), 148.3 (*C*q), 135.4 (*C*H=CH_2), 132.1 (*C*q), 129.9 (*C*H), 117.1 (CH=*C*H_2), 117.0 (*C*H), 113.9 (*C*H), 111.2 (*C*H), 50.7 (SO_2CH_3), 41.9 (NCH_2), 31.6 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{22}N_2O_3S$ $[M+H]^+$: 323.1424, found 323.1424; **IR ν_{max} (neat)/cm^{-1}:** 3195 (br. NH), 2953 (CH), 1652 (C=O), 1339 (S=O), 1154 (S=O).

3-(*N*-(But-3-en-1-yl)acetamido)-*N*-(methylsulfonyl)benzamide 443d

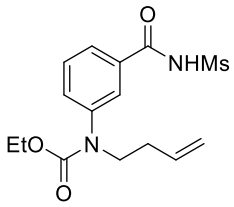


3-(*N*-But-3-en-1-yl)acetamido)benzoic acid (3.0 mmol, 700 mg) was dissolved in DCM (16 mL) and the solution was cooled to 0 °C. EDC.HCl (4.5 mmol, 863 mg) was added, followed by methanesulfonamide (3.3 mmol, 314 mg) and DMAP (4.5 mmol, 550 mg). The reaction mixture was stirred at 0 °C for 15 minutes and then room temperature for 16 hours. The mixture was quenched by the addition of 1M HCl (4.5 mL). The phases were separated, and the aqueous layer was further extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (5% MeOH/DCM) to give the title compound (667 mg, 71%) as a white solid.

M.p. 158-159 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.38 (br. s, 1H, N*H*), 7.86 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.77 (s, 1H, Ar*H*), 7.58 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.46-7.42 (m, 1H, Ar*H*), 5.72 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH_2), 5.08-5.00 (m, 2H, CH=CH_2), 3.78 (t, *J* = 7.5 Hz, NCH_2), 3.44 (s, 3H, SO_2CH_3), 2.25 (q, *J* = 7.5 Hz, 2H, CH_2), 1.82 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.7 (*C*O), 164.8 (*C*O), 143.6 (*C*q), 134.9 (*C*H=CH_2), 133.5 (*C*q), 133.1 (*C*H), 130.6 (*C*H), 128.2 (*C*H), 127.9 (*C*H), 117.3 (CH=*C*H_2), 48.5 (NCH_2), 42.0

(SO_2CH_3), 32.2 (CH_2), 23.1 (CH_3); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{18}N_2O_4S$ $[M+H]^+$: 311.1060, found 311.1059; **IR ν_{max} (neat)/cm^{-1}:** 3027 (br. NH), 2852 (CH), 1694 (C=O), 1625 (C=O), 1339 (S=O), 1162 (S=O).

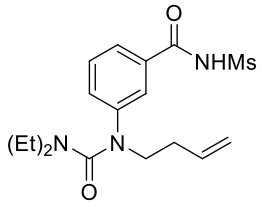
Ethyl but-3-en-1-yl(3-((methylsulfonyl)carbamoyl)phenyl)carbamate 443e



3-(But-3-en-1-yl(ethoxycarbonyl)amino)benzoic acid (3.0 mmol, 789 mg) was dissolved in DCM (18 mL) and the solution was cooled to 0 °C. EDC.HCl (4.5 mmol, 863 mg) was added, followed by methanesulfonamide (3.3 mmol, 314 mg) and DMAP (4.5 mmol, 550 mg). The reaction mixture was stirred at 0 °C for 15 minutes and then room temperature for 16 hours. The mixture was quenched by the addition of 1M HCl (4.5 mL). The phases were separated, and the aqueous layer was further extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to yield the title compound (879 mg, 86%) as a white gum (analytically pure). The gum was dissolved in a minimum amount of DCM, hexane was added, and the solution was concentrated. This was repeated a further 2 times in order to transform the white gum into a white solid.

M.p. 140-143 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.75-7.72 (m, 1H, Ar*H*), 7.70-7.66 (m, 1H, Ar*H*), 7.46-7.39 (m, 2H, Ar*H*), 5.78-5.66 (m, 1H, C*H*=CH_2), 5.08-5.01 (m, 2H, CH=CH_2), 4.19 (q, *J* = 7.0 Hz, 2H, OC$H_2$$CH_3$), 3.76 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.40 (s, 3H, SO_2CH_3), 2.29 (q, *J* = 7.5 Hz, 2H, CH_3), 1.30-1.21 (m, 3H, OCH_2CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.6 (*C*O), 155.9 (*C*O), 142.4 (*C*q), 134.7 (*C*H=CH_2), 132.5 (*C*H), 132.3 (*C*q), 129.5 (*C*H), 127.4 (*C*H), 126.4 (*C*H), 117.3 (CH=*C*H_2), 62.3 (O*C*H_2), 49.5 (N*C*H_2), 41.7 (SO_2CH_3), 32.8 (CH_2), 14.6 (CH_3); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{20}N_2O_5S$ $[M+H]^+$: 341.1166, found 341.1164; **IR ν_{max} (neat)/cm^{-1}:** 3080 (br. NH), 2981 (CH), 1682 (C=O), 1669 (C=O), 1339 (S=O), 1156 (S=O).

3-(1-(But-3-en-1-yl)-3,3-diethylureido)-*N*-(methylsulfonyl)benzamide 443f

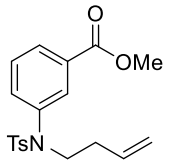


3-(1-(But-3-en-1-yl)-3,3,-diethylureido)benzoic acid (3.0 mmol, 871 mg) was dissolved in DCM (18 mL) and the solution was cooled to 0 °C. EDC.HCl (4.5 mmol, 863 mg) was added, followed by methanesulfonamide (3.3 mmol, 314 mg) and DMAP (4.5 mmol, 550 mg). The reaction mixture was

stirred at 0 °C for 15 minutes and then room temperature for 16 hours. The mixture was quenched by the addition of 1M HCl (4.5 mL). The phases were separated, and the aqueous layer was further extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to yield the title compound (380 mg, 34%) as a white gum (analytically pure). The gum was dissolved in a minimum amount of DCM, hexane was added, and the solution was concentrated. This was repeated a further 2 times in order to transform the white gum into a white solid.

M.p. 114-116 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.76 (br. s, 1H, N*H*), 7.75 (t, *J* = 2.0 Hz, 1H, Ar*H*), 7.71 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.44 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.31 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.06-4.96 (m, 2H, CH=CH_2), 3.64 (dd, *J* = 8.5, 7.0 Hz, 2H, NCH_2), 3.45 (s, 3H, SO_2CH_3), 3.12 (q, *J* = 7.0 Hz, 4H, N(CH_2CH_3)$_2$), 2.34 (q, *J* = 7.0 Hz, 2H CH_2), 0.94 (t, *J* = 7.0 Hz, 6H, N(CH_2CH_3)$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.4 (*C*O), 161.2 (*C*O), 147.0 (*C*q), 135.6 (*C*H=CH_2), 132.5 (*C*q), 130.1 (*C*H), 129.1 (*C*H), 124.2 (*C*H), 123.8 (*C*H), 116.9 (CH=*C*H_2), 51.7 (N*C*H_2), 41.9 (N(*C*H_2CH_3)$_2$), 41.9 (SO_2CH_3), 33.3 (*C*H_2), 12.8 (N(CH_2CH_3)$_2$); **HRMS (ESI$^+$):** Calculated for $C_{17}H_{25}N_3O_4S$ $[M+H]^+$: 368.1639, found 368.1634; **IR ν_{max} (neat)/cm^{-1}:** 3067-2936 (CH), 1689 (C=O), 1595 (C=O), 1339 (S=O), 1153 (S=O).

Methyl 3-((*N*-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)benzoate 444a



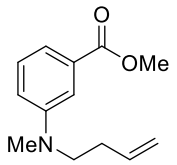
Synthesised using a modified literature procedure.[231]

To a suspension of methyl 3-((4-methylphenyl)sulfonamido)benzoate (9.5 mmol, 2.90 g) and Cs_2CO_3 (19.0 mmol, 6.19 g) in DMF (40 mL) was added 4-bromo-1-butene (19 mmol, 1.93 mL). The reaction mixture was stirred at room temperature for 18 hours. Water (40 mL) was added and the mixture was extracted with EtOAc (×3). The combined organic layers were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (5-10% EtOAc/petrol) to give the title compound (2.07 g, 61%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (dt, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.67 (t, *J* = 2.0 Hz, 1H, Ar*H*), 7.47-7.44 (m, 2H, Ar*H*), 7.41 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.32 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 7.26-7.23 (m, 2H, Ar*H*), 5.71 (ddt, *J* = 17.0, 10.5, 7.5 Hz, 1H, C*H*=CH_2), 5.06-4.93 (m, 2H, CH=CH_2), 3.90 (s, 3H, OCH_3), 3.61 (t, *J* = 7.5 Hz, 2H, NCH_2), 2.42 (s, 3H, $ArCH_3$), 2.17 (q, *J* = 7.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 166.3 (*C*O), 143.8 (*C*q), 139.6 (*C*q), 135.2 (*C*q), 134.4 (*C*H=CH_2), 134.0 (*C*H), 131.3 (*C*q), 129.6 (*C*H), 129.6 (*C*H), 129.2 (*C*H), 129.1 (*C*H), 127.8 (*C*H), 117.4 (CH=*C*H_2), 52.4 (O*C*H_3), 49.9 (N*C*H_2), 32.8 (*C*H_2), 21.7

(CH_3); **HRMS (ESI$^+$):** Calculated for $C_{19}H_{21}NO_4S$ [M+H]$^+$: 360.1264, found 360.1261; **IR ν_{max} (neat)/cm^{-1}:** 2952 (CH), 1723 (C=O), 1348 (S=O), 1165 (S=O).

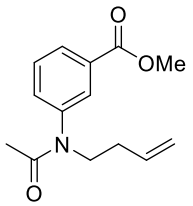
Methyl 3-(but-3-en-1-yl(methyl)amino)benzoate 444b



To a solution of methyl 3-(but-3-en-1-ylamino)benzoate (6.0 mmol, 1.23 g) in DMF (6 mL) was added K_2CO_3 (15.0 mmol, 2.07 g) and MeI (7.2 mmol, 0.45 mL). The reaction mixture was stirred at room temperature for 20 hours and a subsequent portion of MeI was added (3.0 mmol, 0.19 mL). After stirring at room temperature for a further 18 hours the reaction mixture was diluted with water and extracted with EtOAc (×3). The combined organic extracts were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (10% EtOAc/petrol) to give the title compound (493 mg, 37%) as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34-7.26 (m, 1H, Ar*H*), 7.24-7.18 (m, 2H, Ar*H*), 7.01-6.93 (m, 1H, Ar*H*), 5.84 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.11-5.05 (m, 1H, CH=C*H*H), 5.04-4.99 (m, 1H, CH=CH*H*), 3.82 (s, 3H, OCH_3), 3.47-3.39 (m, 2H, NCH_2), 2.29 (s, 3H, NCH_3), 2.32-2.20 (m, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 167.4 (*C*O), 149.3 (*C*q), 136.6 (*C*H=CH_2), 130.9 (*C*q), 129.9 (*C*H), 117.2 (CH=*C*H_2), 117.1 (*C*H), 116.7 (*C*H), 112.3 (*C*H), 52.5 (O*C*H_3), 51.7 (N*C*H_2), 38.5 (N*C*H_3), 31.0 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{17}NO_2$ [M+H]$^+$: 220.1332, found 220.1329; **IR ν_{max} (neat)/cm^{-1}:** 2949 (CH), 1717 (C=O).

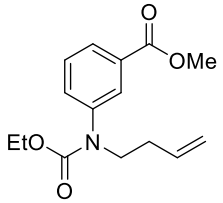
Methyl 3-(*N*-(but-3-en-1-yl)acetamido)benzoate 444d



To a solution of methyl 3-(but-3-en-1-ylamino)benzoate (6.0 mmol, 1.23 g) in DCM (30 mL) was added triethylamine (18.0 mmol, 2.39 mL), DMAP (1.2 mmol, 146 mg) and acetic anhydride (9.0 mmol, 918 mg). The reaction mixture was stirred at room temperature for 16 hours. On completion the mixture was washed with water, 1M NaOH, 1M HCl and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (20% EtOAc/petrol) to give the title compound (1.29 g, 84%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.85 (t, *J* = 2.0 Hz, 1H, Ar*H*), 7.50 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.36 (dt, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 5.73 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH_2), 5.08-4.98 (m, 2H, CH=CH_2), 3.93 (s, 3H, OCH_3), 3.79 (t, *J* = 7.5 Hz, 2H, NCH_2), 2.26 (q, *J* = 7.5 Hz, 2H, CH_2), 1.81 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.0 (*C*O), 166.1 (*C*O), 143.3 (*C*q), 135.1 (*C*H=CH_2), 132.8 (*C*H), 131.9 (*C*q), 129.8 (*C*H), 129.3 (*C*H), 129.0 (*C*H), 116.8 (CH=*C*H_2), 52.4 (O*C*H_3), 48.2 (N*C*H_2), 32.2 (*C*H_2), 22.9 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{17}NO_3$ $[M+H]^+$: 248.1281, found 248.1284; **IR ν_{max} (neat)/cm^{-1}:** 2951(CH), 1723 (C=O), 1661 (C=O).

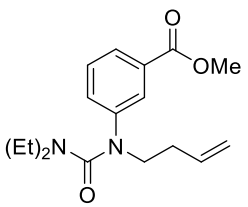
Methyl 3-(but-3-en-1-yl(ethoxycarbonyl)amino)benzoate 444e



To a solution of methyl 3-(but-3-en-1-ylamino)benzoate (9.0 mmol, 1.85 g) in THF (50 mL) at 0 °C was added triethylamine (9.9 mmol, 1.31 mL) and ethyl chloroformate (27.0 mmol, 2.58 mL). The reaction mixture was then heated to 50 °C and stirred for 72 hours. The solvent was removed, and the residue was dissolved in DCM and 2 M NaOH. The phases were separated, and the aqueous portion was further extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (2-10% EtOAc/petrol) to yield the title compound (1.90 g, 76%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dt, *J* = 7.0, 1.5 Hz, 1H, Ar*H*), 7.88 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.46-7.37 (m, 2H, Ar*H*), 5.74 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH_2), 5.08-5.00 (m, 2H, CH=CH_2), 4.15 (q, *J* = 7.0 Hz, OC$H_2$$CH_3$), 3.92 (s, 3H, OC$H_3$), 3.79-3.74 (m, 2H, NC$H_2$), 2.34-2.26 (m, 2H, C$H_2$), 1.21 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 166.5 (*C*O), 155.4 (*C*O), 1421. (*C*q), 134.9 (*C*H=CH_2), 132.1 (*C*H), 131.1 (*C*q), 128.9 (*C*H), 128.3 (*C*H), 127.6 (*C*H), 117.0 (CH=*C*H_2), 61.7 (O*C*$H_2$$CH_3$), 52.3 (O*C*$H_3$), 49.4 (N*C*$H_2$), 32.7 (*C*$H_2$), 14.5 ($OCH_2$*C*$H_3$); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{19}NO_4$ $[M+H]^+$: 278.1387, found 278.1383; **IR ν_{max} (neat)/cm^{-1}:** 2979 (CH), 1702 (C=O).

Methyl 3-(1-(but-3-en-1-yl)-3,3-diethylureido)benzoate 444f

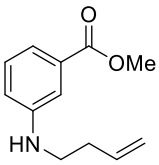


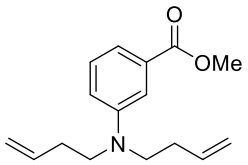
Methyl 3-(but-3-en-1-ylamino)benzoate (9.0 mmol, 1.85 g), diethylcarbamoyl chloride (27.0 mmol, 3.42 mL) and DMAP (9.5 mmol, 1.15 g) were dissolved in DCE (50 mL). The reaction mixture was heated

to reflux and stirred for 5 days. After cooling to room temperature, the mixture was washed with 1 M HCl and the aqueous layer was extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (4-20% EtOAc/petrol) to yield the title compound (2.00 g, 73%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79-7.74 (m, 2H, Ar*H*), 7.38 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.26-7.22 (m, 1H, Ar*H*), 5.80 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.08-4.99 (m, 2H, CH=CH_2), 3.91 (s, 3H, OCH_3), 3.68-3.62 (m, 2H, NCH_2), 3.10 (q, *J* = 7.0 Hz, 4H, N(C$H_2$$CH_3$)$_2$), 2.39-2.29 (m, 2H, C$H_2$), 0.92 (t, *J* = 7.0 Hz, 6H, N(CH_2CH_3)$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 166.5 (*C*O), 160.8 (*C*O), 146.4 (*C*q), 135.7 (*C*H=CH_2), 131.4 (*C*q), 129.3 (*C*H), 128.6 (*C*H), 125.3 (*C*H), 125.1 (*C*H), 116.4 (CH=*C*H_2), 52.2 (O*C*H_3), 51.5 (N*C*H_2), 41.7 (N(*C*$H_2$$CH_3$)$_2$), 33.1 (*C*$H_2$), 12.7 (N($CH_2$*C*$H_3$)$_2$); **HRMS (ESI$^+$):** Calculated for $C_{17}H_{24}N_2O_3$ $[M+H]^+$: 305.1860, found 305.1855; **IR ν_{max} (neat)/cm^{-1}:** 2972 (CH), 1724 (C=O), 1649 (C=O).

Methyl 3-(but-3-en-1-ylamino)benzoate 445





To a solution of 3-methyl aminobenzoate (50.0 mmol, 7.56 g) in MeCN (150 mL) was added 4-bromo-1-butene (75.0 mmol, 7.61 mL), K_2CO_3 (60.0 mmol, 8.29 g) and TBAI (5.0 mmol, 1.85 g). The reaction mixture was heated at reflux for 72 hours and was then filtered and concentrated. The crude material was purified by flash column chromatography (2-10% EtOAc/petrol) to give the biproduct (909 mg, 7%) as a pale-yellow oil.

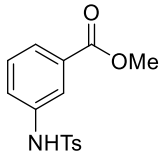
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.33 (m, 1H, Ar*H*), 7.31-7.26 (m, 1H, Ar*H*), 6.78 (dd, *J* = 8.0, 2.5 Hz, 1H, Ar*H*), 5.86 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 2H, 2 × C*H*=CH_2), 5.18-5.06 (m, 2H, 2 × CH=CH_2), 3.92 (s, 3H, OCH_3), 3.45-3.39 (m, 2H, 2 × NCH_2), 2.37 (q, *J* = 7.0 Hz, 2H, 2 × CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 167.9 (*C*O), 147.8 (*C*q), 135.7 (*C*H=CH_2), 131.2 (*C*q), 129.3 (*C*H), 116.9 (*C*H), 116.8 (CH=*C*H_2), 116.4 (*C*H), 112.9 (*C*H), 52.2 (O*C*H_3), 50.8 (N*C*H_2), 31.7 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{21}NO_2$ $[M+H]^+$: 260.1645, found 260.1643; **IR ν_{max} (neat)/cm^{-1}:** 2987 (CH), 1720 (C=O).

Further elution afforded the desired title compound (4.93 g, 48%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dt, *J* = 7.5, 1.0 Hz, 1H, Ar*H*), 7.21-7.18 (m, 1H, Ar*H*), 7.14 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.72-6.68 (m, 1H, Ar*H*), 5.75 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.11-5.02 (m, 2H, CH=CH_2), 3.81 (s, 3H, OCH_3), 3.15 (t, *J* = 6.5 Hz, 2H, NCH_2), 2.32 (q, *J* = 6.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 167.7 (*C*O), 148.4 (*C*H), 135.7 (*C*H=CH_2), 131.2 (*C*q), 129.3 (*C*H), 118.6 (*C*H), 117.5 (*C*H),

117.4 (CH=*C*H$_2$), 113.5 (*C*H), 52.1 (O*C*H$_3$), 42.8 (N*C*H$_2$), 33.6 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{15}NO_2$ $[M+H]^+$: 206.1176, found 206.1171; **IR ν_{max} (neat)/cm^{-1}:** 3394 (br. NH), 2949 (CH), 1711 (C=O).

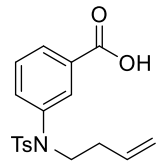
Methyl 3-((4-methylphenyl)sulfonamido)benzoate[232] 447



To a solution of methyl 3-aminobenzoate (10.0 mmol, 1.51 g) in DCM (20 mL) was added *N*-methylmorpholine (11.0 mmol, 1.21 mL) followed by tosyl chloride (11.0 mmol, 2.16 g). The reaction mixture was stirred at room temperature for 18 hours and then quenched with 1 M HCl (30 mL). The layers were separated, and the aqueous layer was extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (2.93 g, 96%) as a pale-pink solid (analytically pure) which was used without further purification.

M.p. 153-155 °C (MeCN); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.77 (dt, *J* = 7.5 Hz, 1H, Ar*H*), 7.72-7.69 (m, 1H, Ar*H*), 7.67 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.42-7.38 (m, 1H, Ar*H*), 7.33 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.22 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.05 (br. s, 1H, N*H*), 3.90 (s, 3H, OC*H*$_3$), 2.37 (s, 3H, ArC*H*$_3$); **^{13}C NMR (101 MHz, CDCl$_3$):** δ 166.6 (*C*O), 144.3 (*C*q), 137.2 (*C*q), 136.0 (*C*q), 131.4 (*C*q), 129.9 (*C*H), 129.6 (*C*H), 127.4 (*C*H), 126.3 (*C*H), 125.6 (*C*H), 122.2 (*C*H), 52.5 (O*C*H$_3$), 21.7 (*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{15}NO_4S$ $[M+H]^+$: 306.0795, found 306.0793; **IR ν_{max} (neat)/cm^{-1}:** 3227 (NH), 2960 (CH), 1703 (C=O), 1334 (S=O), 1156 (S=O).

3-((*N*-(But-3-en-1-yl)-4-methylphenyl)sulfonamido)benzoic acid 448a

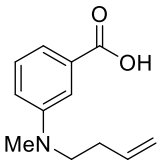


A solution of methyl 3-((*N*-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)benzoate (5.5 mmol, 1.98 g) in THF (15 mL) and MeOH (15 mL) was treated with aqueous NaOH (6 M, 55.0 mmol, 9.0 mL). The mixture was stirred at reflux for 90 minutes and then allowed to cool to room temperature. The volatiles were removed, and the aqueous solution was acidified with 3 M HCl, extracted with EtOAc (×3), washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (1.877 g, 99%) as a pale-yellow solid (analytically pure), which was used without further purification.

M.p. 118-120 °C (MeCN); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.05 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.74-7.66 (m, 1H, Ar*H*), 7.52-7.38 (m, 4H, Ar*H*), 7.32-7.22 (m, 2H, Ar*H*), 5.72 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*=CH$_2$), 5.07-4.97 (m, 2H, CH=C*H*$_2$), 3.63 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$), 2.43 (s, 3H, ArC*H*$_3$), 2.19 (q, *J* = 7.0 Hz, 2H,

CH_2); **^{13}C NMR (101 MHz, CDCl$_3$):** δ 171.3 (*C*O), 143.9 (*C*q), 139.7 (*C*q), 135.0 (*C*q), 135.0 (*C*H), 134.3 (*C*H=CH$_2$), 130.4 (*C*q), 130.0 (*C*H), 129.7 (*C*H), 129.7 (*C*H), 129.4 (*C*H), 127.7 (*C*H), 117.4 (CH=*C*H$_2$), 49.9 (N*C*H$_2$), 32.8 (*C*H$_2$), 21.7 (*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_{18}H_{19}NO_4S$ [M+H]$^+$: 346.1108, found 346.1109; **IR ν_{max} (neat)/cm^{-1}:** 2922 (CH), 2551 (br. OH), 1694 (C=O), 1347 (S=O), 1163 (S=O).

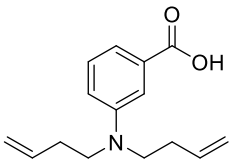
3-(But-3-en-1-yl(methyl)amino)benzoic acid 448b



Methyl 3-(but-3-en-1-yl(methyl)amino)benzoate (2.0 mmol, 439 mg) was dissolved in MeOH (15 mL) and THF (15 mL). The Solution was treated with aqueous NaOH (1 M, 10.0 mmol, 10 mL) and was stirred at reflux for 30 minutes. The volatiles were removed, and the remaining aqueous solution was acidified with 3M HCl. The mixture was extracted with EtOAc (×3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (362 mg, 88%) as an off-white solid (analytically pure) which was used without further purification.

M.p. 73-74 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 7.30-7.19 (m, 3H, Ar*H*), 6.97-6.93 (m, 1H, Ar*H*), 5.84 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH$_2$), 5.12-5.00 (m, 2H, CH=C*H*$_2$), 3.46-3.39 (m, 2H, NC*H*$_2$), 2.92 (s, 3H, NC*H*$_3$), 2.26 (q, *J* = 7.0 Hz, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$):** δ 167.9 (*C*O), 148.6 (*C*q), 136.0 (*C*H=CH$_2$), 131.5 (*C*q), 129.2 (*C*H), 116.6 (C*H*), 166.6 (CH=*C*H$_2$), 116.3 (*C*H), 112.2 (*C*H), 51.3 (N*C*H$_2$), 38.0 (N*C*H$_3$), 30.4 (*C*H$_2$); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{15}NO_2$ [M+H]$^+$: 206.1176, found 206.1174; **IR ν_{max} (neat)/cm^{-1}:** 2883 (CH), 2657 (br. OH), 1677 (C=O).

3-(Di(but-3-en-1-yl)amino)benzoic acid 448c



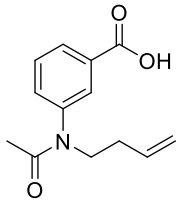
Methyl 3-(di(but-3-en-1-yl)amino)benzoate (3.5 mmol, 908 mg) was dissolved in MeOH (20 mL) and THF (20 mL). The Solution was treated with aqueous NaOH (1M, 17.5 mmol, 17.5 mL) and was stirred at reflux for 30 minutes. The volatiles were removed, and the remaining aqueous solution was acidified with 3M HCl. The mixture was extracted with EtOAc (×3) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (940 mg, quantitative) as an off-white solid (analytically pure) which was used without further purification.

M.p. 59-60 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 7.32-7.16 (m, 3H, Ar*H*), 6.98-6.86 (m, 1H, Ar*H*), 5.85 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 2H, 2 × C*H*=CH$_2$), 5.14-5.00 (m, 4H, 2 × CH=C*H*$_2$), 3.39 (t, *J* = 7.5 Hz, 4H,

2 × NCH_2), 2.27 (q, *J* = 7.5 Hz, 4H, 2 × CH_2); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 167.8 (*C*O), 135.8 (*C*H=CH$_2$), 131.6 (*C*q), 129.3 (*C*H), 116.6 (CH=*C*H$_2$), 49.8 (NCH_2), 31.0 (CH_2)*; **HRMS (ESI$^+$):** Calculated for $C_{15}H_{19}NO_2$ [M+H]$^+$: 246.1489, found 246.1489; **IR ν_{max} (neat)/cm^{-1}:** 2936 (CH), 2534 (br. OH), 1680 (C=O).

*Some peaks missing from ^{13}C NMR despite increased number of scans, increased relaxation time and increased temperature.

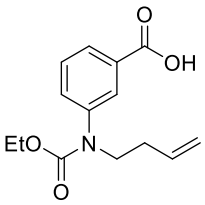
3-(*N*-But-3-en-1-yl)acetamido)benzoic acid 448d



Methyl 3-(*N*-(but-3-en-1-yl)acetamido)benzoate (5.0 mmol, 1.23 g) was dissolved in THF (7 mL) and MeOH (7 mL), and the resulting solution was treated with aqueous NaOH (1M, 5.0 mmol, 5 mL). The reaction mixture was stirred at 60 °C for 30 minutes. On completion the volatiles were removed, and the remaining aqueous solution was acidified with 3M HCl. The mixture was extracted with EtOAc (×3) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (1.06 g, 90%) as a pale-yellow solid (analytically pure), which was used without further purification.

M.p. 137-138 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.12 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.97-7.93 (m, 1H, Ar*H*), 7.56 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.46-7.40 (m, 1H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH$_2$), 5.11-5.02 (m, 2H, CH=CH_2), 3.83 (t, *J* = 7.5 Hz, 2H, NCH_2), 2.29 (q, *J* = 7.5 Hz, 2H, CH_2), 1.87 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.8 (*C*O), 169.8 (*C*O), 143.3 (*C*H), 135.1 (*C*H=CH$_2$), 133.5 (*C*H), 131.7 (*C*q), 130.1 (*C*H), 129.9 (*C*H), 129.8 (*C*H), 117.1 (CH=*C*H$_2$), 48.6 (N*C*H$_2$), 32.2 (*C*H$_2$), 22.9 (*C*H$_3$); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{15}NO_3$ [M+H]$^+$: 234.1125, found 234.1123; **IR ν_{max} (neat)/cm^{-1}:** 2979 (CH), 2597 (br. OH), 1717 (C=O), 1618 (C=O).

3-(But-3-en-1-yl(ethoxycarbonyl)amino)benzoic acid 448e

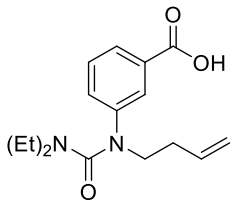


Methyl 3-(but-3-en-1-yl(ethoxycarbonyl)amino)benzoate (6.0 mmol, 1.66 g) was dissolved in MeOH (10 mL) and THF (10 mL) and treated with NaOH (1 M, 6.0 mmol, 6 mL). The reaction mixture was heated at 60 °C for 2 hours and the volatiles were then removed. The remaining aqueous mixture was

acidified with 3 M HCl and extracted with EtOAc (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the title compound (1.62 g, quantitative) as a viscous yellow oil (analytically pure) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (td, *J* = 4.5, 1.5 Hz, 1H, Ar*H*), 7.96 (q, *J* = 1.5 Hz, 1H, Ar*H*), 7.49-7.45 (m, 2H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H, C*H*CH_2), 5.10-5.01 (m, 2H, CH=CH_2), 4.17 (q, *J* = 7.0 Hz, 2H, OC$H_2$$CH_3$), 3.84-3.75 (m, 2H, NC$H_2$), 2.35-2.28 (m, 2H, C$H_2$), 1.22 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.3 (*C*O), 155.6 (*C*O), 142.4 (*C*q), 135.0 (*C*H=CH_2), 133.0 (*C*H), 130.5 (*C*q), 129.2 (*C*H), 129.0 (*C*H), 128.3 (*C*H), 117.2 (CH=*C*H_2), 62.0 (O*C*$H_2$$CH_3$), 49.6 (N*C*$H_2$), 32.9 (*C*$H_2$), 14.6 ($OCH_2$*C*$H_3$); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{17}NO_4$ $[M+H]^+$: 264.1230, found 264.1227; **IR ν_{max} (neat)/cm^{-1}:** 2980 (CH), 2600 (br. OH), 1697 (C=O).

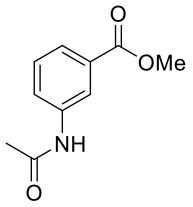
3-(1-(But-3-en-1-yl)-3,3,-diethylureido)benzoic acid 448f



Methyl 3-(1-(but-3-en-1-yl)-3,3-diethylureido)benzoate (6.0 mmol, 1.83 g) was dissolved in MeOH (10 mL) and THF (10 mL) and treated with NaOH (1 M, 6.0 mmol, 6 mL). The reaction mixture was heated at reflux for 6 hours and the volatiles were then removed. The remaining aqueous mixture was acidified with 3 M HCl and extracted with EtOAc (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the title compound (1.62 g, 93%) as a viscous yellow oil (analytically pure) which was used without further purification.

M.p. 85-87 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88-7.82 (m, 2H, Ar*H*), 7.41 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.30 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.07-4.98 (m, 2H, CH=CH_2), 3.71-3.65 (m, 2H, NCH_2), 3.12 (q, *J* = 7.0 Hz, 4H, N(C$H_2$$CH_3$)$_2$), 2.41-2.33 (m, 2H, C$H_2$), 0.94 (t, *J* = 7.0 Hz, 6H, N(CH_2CH_3)$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.7 (*C*O), 161.1 (*C*O), 146.6 (*C*q), 135.9 (*C*H=CH_2), 131.1 (*C*q), 129.6 (*C*H), 129.4 (*C*H), 126.2 (*C*H), 125.8 (*C*H), 116.7 (CH=*C*H_2), 51.8 (N(*C*$H_2$$CH_3$)$_2$), 42.0 (N*C*$H_2$), 33.3 (*C*$H_2$), 12.8 (N($CH_2$*C*$H_3$)$_2$); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{22}N_2O_3$ $[M+H]^+$: 291.1703, found 291.1702; **IR ν_{max} (neat)/cm^{-1}:** 2968 (CH), 2932 (CH), 2610 (br. OH), 1709 (C=O), 1601 (C=O).

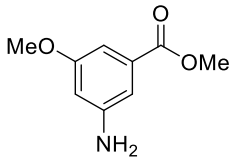
Methyl 3-acetamidobenzoate[233] 452



Methyl 3-aminobenzoate (10.0 mmol, 1.51 g) was dissolved in DCM (40 mL) and DIPEA (13.0 mmol, 2.26 mL) and acetic anhydride (1.2 mmol, 1.13 mL) were added. DMAP (10.0 mmol, 1.22 g) was added and the reaction mixture was stirred at room temperature for 20 hours. Water was added and the layers were separated. The organic layer was washed with 1M NaOH, 1M HCl, water and brine, dried and concentrated. The crude material was purified by flash column chromatography (40-75% EtOAc/petrol) to yield the title compound (1.15 g, 59%) as a pale-orange solid.

M.p. 132-135 °C (MeCN, lit = 136-137 °C); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.91 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.78 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.40 (t, *J* = 8.0 Hz, 1H, Ar*H*), 3.91 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3); **IR ν_{max} (neat)/cm^{-1}:** 3295 (br. NH), 2952 (CH), 1736 (C=O), 1663 (C=O). Data are consistent with literature precedent.[233]

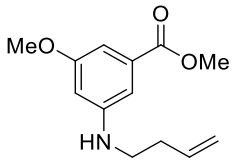
Methyl 3-amino-5-methoxybenzoate[234] 457



To a solution of 3-amino-5-methylbenzoic acid (29.9 mmol, 5.00 g) in MeOH (75 mL) at 0 °C was added thionyl chloride (180 mmol, 21.4 g) dropwise. The reaction mixture was stirred at room temperature for 5 hours and on completion was filtered and washed with Et_2O. The filtrate was triturated with MeOH and Et_2O, filtered and washed with Et_2O. This trituration/filtreation was repeated a futher three times. The combined solids were suspended in DCM and basified with saturated $NaHCO_3$ with vigorous stirring. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated. This gave the title compound (4.71 g, 87%) as a pale-yellow solid.

M.p. 80-83 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.98 (dq, *J* = 2.5, 1.5 Hz, 2H, Ar*H*), 6.41 (t, *J* = 2.5 Hz, 1H, Ar*H*), 3.88 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); **IR ν_{max} (neat)/cm^{-1}:** 3445 (br. NH), 3353 (br. NH), 2950-2842 (CH), 1709 (C=O). Data are consistent with literature precedent.[234]

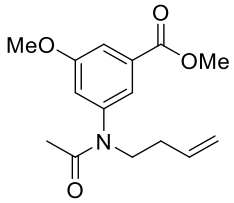
Methyl 3-(but-3-en-1-ylamino)5-methoxybenzoate 458



To a solution of methyl 3-amino-5-methoxybenzoate (25.0 mmol, 4.53 g) in MeCN (75 mL) was added 4-bromo-1-butene (25.0 mmol, 2.54 mL), K_2CO_3 (30.0 mmol, 4.15 g) and TBAI (2.5 mmol, 923 mg). The reaction mixture was heated at reflux for 5 days and was then filtered and concentrated. The crude material was purified by flash column chromatography (4-10% EtOAc/petrol) to give the title compound (2.11 g, 36%) as a white solid.

M.p. 53-55 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.92 (s, 2H, Ar*H*), 6.32 (s, 1H, Ar*H*), 5.81 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.23-5.06 (m, 2H, CH=CH_2), 3.88 (s, 3H, CO_2CH_3), 3.81 (s, 3H, OCH_3), 3.20 (t, *J* = 7.0 Hz, 2H, NCH_2), 2.38 (q, *J* = 7.0 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 167.5 (*C*O), 160.8 (*C*q), 149.5 (*C*q), 135.6 (*C*H=CH_2), 132.0 (*C*q), 117.5 (CH=*C*H_2), 107.6 (*C*H), 103.6 (*C*H), 103.0 (*C*H), 55.5 (O*C*H_3), 52.2 (CO_2*C*H_3), 42.9 (N*C*H_2), 33.6 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{17}NO_3$ $[M+H]^+$: 236.1281, found 236.1279; **IR ν_{max} (neat)/cm^{-1}:** 3397 (NH), 3010-2843 (CH), 1704 (C=O).

Methyl 3-(*N*-(but-3-en-1-yl)acetamido)-5-methoxybenzoate 459

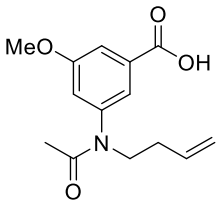


To a solution of methyl 3-(but-3-en-1-ylamino)5-methoxybenzoate (8.5 mmol, 2.00 g) in DCM (40 mL) was added triethylamine (25.5 mmol, 3.55 mL), DMAP (1.7 mmol, 208 mg) and acetic anhydride (12.8 mmol, 1.19 mL). The reaction mixture was stirred at room temperature for 20 hours. On completion the mixture was washed with water, 1M NaOH, 1M HCl and brine, dried over $MgSO_4$ and concentrated. This gave the title compound (2.18 g, 92%) as a viscous colourless oil (analytically pure) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 2.5, 1.5 Hz, 1H, Ar*H*), 7.44 (t, *J* = 1.5 Hz, 1H, Ar*H*), 6.90 (t, *J* = 2.0 Hz, 1H, Ar*H*), 5.74 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.08-4.99 (m, 2H, CH=CH_2), 3.93 (s, 3H, CO_2CH_3), 3.87 (s, 3H, OCH_3), 3.81-3.73 (m, 2H, NCH_2), 2.30-2.22 (m, 2H, CH_2), 1.84 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.1 (*C*O), 166.1 (*C*O), 160.6 (*C*q), 144.3 (*C*q), 135.3 (*C*H=CH_2), 132.8 (*C*q), 121.8 (*C*H), 119.6 (*C*H), 117.0 (CH=*C*H_2), 113.5 (*C*H), 55.9 (O*C*H_3), 52.6 (CO_2*C*H_3), 48.3 (N*C*H_2), 32.3 (*C*H_2), 22.9

(*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{19}NO_4$ [M+H]$^+$: 278.1387, found 278.1384; **IR ν_{max} (neat)/cm^{-1}:** 2950 (CH), 1722 (C=O), 1661 (C=O).

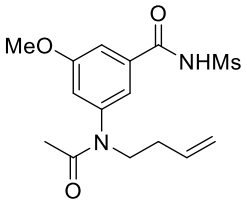
3-(*N*-(But-3-en-1-yl)acetamido)-5-methoxybenzoic acid 460



Methyl 3-(*N*-(but-3-en-1-yl)acetamido)-5-methoxybenzoate (7.5 mmol, 2.08 g) was dissolved in MeOH (10 mL) and THF (10 mL) and treated with NaOH (1 M, 15.0 mmol, 15 mL). The reaction mixture was heated at 60 °C for 3 hours and the volatiles were then removed. The remaining aqueous mixture was acidified with 3 M HCl and extracted with EtOAc (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the title compound (1.72 g, 97%) as an off-white solid (analytically pure) which was used without further purification.

M.p. 98-100 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.63 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.54 (t, *J* = 1.5 Hz, 1H, Ar*H*), 7.00-6.91 (m, 1H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH_2), 5.12-4.99 (m, 2H, CH=CH_2), 3.89 (s, 3H, OCH_3), 3.81 (t, *J* = 7.5 Hz, 2H, NCH_2), 2.30 (q, *J* = 7.5 Hz, 2H, CH_2), 1.90 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.7 (*C*O), 169.8 (*C*O), 160.7 (*C*q), 144.2 (*C*q), 135.2 (*C*H=CH_2), 132.4 (*C*q), 122.3 (*C*H), 120.2 (*C*H), 117.1 (CH=*C*H_2), 114.1 (*C*H), 56.0 (O*C*H_3), 48.5 (N*C*H_2), 32.3 (*C*H_2), 22.9 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{14}H_{17}NO_2$ [M+H]$^+$: 264.1230, found 264.1227; **IR ν_{max} (neat)/cm^{-1}:** 2941 (CH), 2603 (br. OH), 1706 (C=O).

3-(*N*-(but-3-en-1-yl)acetamide)-5-methoxy-*N*-(methylsulfonyl)benzamide 461

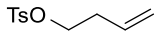


3-(*N*-(But-3-en-1-yl)acetamido)-5-methoxybenzoic acid (3.0 mmol, 790 mg) was dissolved in DCM (18 mL) and the solution was cooled to 0 °C. EDC.HCl (4.5 mmol, 863 mg) was added, followed by methanesulfonamide (3.3 mmol, 314 mg) and DMAP (4.5 mmol, 550 mg). The reaction mixture was stirred at 0 °C for 15 minutes and then room temperature for 18 hours. The mixture was quenched by the addition of 1M HCl (4.5 mL). The phases were separated, and the aqueous layer was further extracted with DCM (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and

concentrated. The crude material was purified by flash column chromatography (3% MeOH/DCM) to give the title compound.

M.p. 184-186 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 12.21 (br. s, 1H, N*H*), 7.48 (s, 1H, Ar*H*), 7.44 (s, 1H, Ar*H*), 7.19 (s, 1H, Ar*H*), 5.80-5.70 (m, 1H, C*H*=CH_2), 5.09-4.98 (m, 2H, CH=CH_2), 3.85 (s, 3H, OCH_3), 3.70 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.39 (s, 3H, SO_2CH_3), 2.17 (q, *J* = 7.5 Hz, 2H, CH_2), 1.77 (s, 3H, CH_3); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 168.8 (*C*O), 165.4 (*C*O), 160.0 (*C*q), 143.9 (*C*q), 135.6 (*C*H=CH_2), 133.8 (*C*q), 120.4 (*C*H), 119.4 (*C*H), 116.6 (CH=*C*H_2), 112.5 (*C*H), 55.8 (O*C*H_3), 47.2 (N*C*H_2), 41.3 (SO_2*C*H_3), 31.8 (*C*H_2), 22.6 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{20}N_2O_5S$ $[M+H]^+$: 341.1166, found 341.1162; **IR ν_{max} (neat)/cm^{-1}:** 2987-2901 (CH), 1698 (C=O), 1595 (C=O), 1342 (S=O), 1153 (S=O).

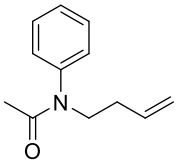
But-3-en-1-yl 4-methylbenzenesulfonate[235] 466



To a solution of tosyl chloride (11.0 mmol, 2.10 g) and DMAP (1.5 mmol, 183 mg) in DCM (50 mL) was added triethylamine (20.0 mmol, 2.79 mL) and 3-buten-1-ol (10.0 mmol, 0.86 mL). The reaction mixture was stirred at room temperature for 3 hours and then quenched with water. The phases were separated, and the organic layer was washed with saturated aqueous NH_4Cl (×2), washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (5-10% EtOAc/petrol) to give the title compound (1.87 g, 83%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.35 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.67 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, C*H*=CH_2), 5.12-5.03 (m, 2H, CH=CH_2), 4.06 (t, 7.0 Hz, 2H, OCH_2), 2.45 (s, 3H, ArCH_3), 2.43-2.37 (m, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2982 (CH), 1357 (S=O), 1175 (S=O). Data are consistent with literature precedent.[235]

***N*-(But-3-en-1-yl)-*N*-phenylacetamide[177] 467**



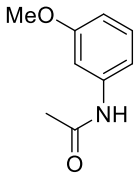
Synthesised using a modified literature procedure.[177]

To a solution of acetanilide (6.0 mmol, 811 mg) in toluene (24 mL) was added K_2CO_3 (6.1 mmol, 845 mg), tetrabutylammonium hydrogen sulfate (0.30 mmol, 102 mg) and NaOH (24.0 mmol, 960 mg). The resulting suspension was stirred for 1 hour at room temperature and then 80 °C for 15 minutes. But-3-en-1-yl 4-methylbenzenesulfonate (7.3 mmol, 1.65 g) was added and the reaction mixture was stirred at 80 °C for a further 18 hours. The mixture was allowed to cool to room temperature and 1M HCl was added. The layers were separated, and the aqueous potion was extracted with Et_2O (×3). The

combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (15-20% EtOAc/petrol) to give the title compound (860 mg, 76%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.39 (m, 2H, Ar*H*), 7.38-7.31 (m, 1H, Ar*H*), 7.19-7.15 (m, 2H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.10-4.97 (m, 2H, CH=CH_2), 3.81-3.74 (m, 2H, NCH_2), 2.31-2.23 (m, 2H, CH_2), 1.82 (s, 3H, CH_3); **IR ν_{max} (neat)/cm^{-1}:** 2977 (CH), 2930 (CH), 1655 (C=O). Data are consistent with literature precedent.[177]

***N*-(3-Methoxyphenyl)acetamide[236] 470**

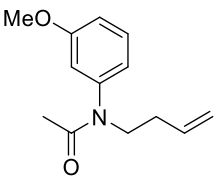


Synthesised using a modified literature procedure.[236]

To a solution of *m*-anidsidine (10.0 mmol, 1.23 g) and pyridine (6.0 mmol, 0.48 mL) in DCM (15 mL) at 0 °C was added acetic anhydride (11.0 mmol, 1.04 mL) dropwise. The mixture was allowed to warm to room temperature and was stirred for 16 hours. Water was added and the layers were separated. The aqueous portion was extracted with DCM (×2) and the combined organic extracts were washed with saturates $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (20-50% EtOAc/petrol) to give the title compound (1.54 g, 93%) as a pink solid.

M.p. 78-80 °C (EtOAc/Hex, lit. = 81-83 °C[236]); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41 (br. s, 1H, N*H*), 7.27 (t, *J* = 2.5 Hz, 1H, Ar*H*), 7.20 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.96 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 6.65 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar*H*), 3.79 (s, 3H, OCH_3), 2.16 (s, 3H, CH_3); **IR ν_{max} (neat)/cm^{-1}:** 3257 (br. NH), 2973-2901 (CH), 1662(C=O). Data are consistent with literature precedent.[236]

***N*-(But-3-en-1-yl)-*N*-(3-methoxyphenyl)acetamide 471**

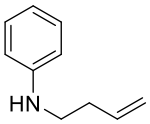


To a suspension of NaH (26.0 mmol, 1.04 g, 60% dispertion in mineral oil) in DMF (30 mL) at 0 °C was added *N*-(3-methoxyphenyl)acetamide (2.0 mmol, 330 mg) portionwise. The mixture was stirred at room temperature for 20 minutes and then recooled to 0 °C. 4-Bromo-1-butene (26.0 mmol, 2.64 mL) was added dropwise and the reaction mixture was stirred at room temperature for 72 hours. On

completion, the reaction mixture was quenched with water and then extracted with Et_2O (×3). The combined organic portions were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. The crude mixture was purified by flash column chromatography (15-40% EtOAc/petrol) to give the title compound (143 mg, 33%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.91-6.86 (m, 1H, Ar*H*), 6.75 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 6.70 (t, *J* = 2.0 Hz, 1H, Ar*H*), 5.75 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.08-4.99 (m, 2H, CH=CH_2), 3.81 (s, 3H, OCH_3), 3.79-3.73 (m, 2H, NCH_2), 2.31-2.24 (m, 2H, CH_2), 1.84 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 170.3 (*C*O), 160.6 (*C*q), 144.3 (*C*q), 135.5 (*C*H=CH_2), 130.4 (*C*H), 120.6 (*C*H), 116.7 (CH=*C*H_2), 114.3 (*C*H), 113.3 (*C*H), 55.5 (O*C*H_3), 48.3 (N*C*H_2), 32.4 (*C*H_2), 22.9 (*C*H_3); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{17}NO_2$ $[M+H]^+$: 220.1332, found 220.1327; **IR ν_{max} (neat)/cm^{-1}:** 2973 (CH), 1655 (C=O).

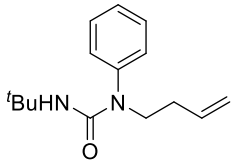
***N*-(But-3-en-1-yl)aniline[237] 483**



To a solution of aniline (12.0 mmol, 1.09 mL) and K_2CO_3 (20.0 mmol, 2.76 g) in DMF (30 mL) was added 4-bromo-1-butene (10.0 mmol, 1.01 mL) dropwise. The reaction mixture was stirred at 110 °C for 6 hours. On completion the mixture was allowed to cool to room temperature and water was added. The mixture was extracted with EtOAc (×3) and the combined organic layers were washed with water (×2) and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by flash column chromatography (0.25-1% EtOAc/petrol) to give the title compound (842 mg, 57%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.14 (m, 2H, Ar*H*), 6.71 (tt, *J* = 7.5, 1.0 Hz, 1H, Ar*H*), 6.65-6.58 (m, 2H, Ar*H*), 5.83 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.19-5.08 (m, 2H, CH=CH_2), 3.67 (br. s, 1H, N*H*), 3.19 (t, *J* = 6.5 Hz, 2H, NCH_2), 2.39 (app. qt, 2H, CH_2); **IR ν_{max} (neat)/cm^{-1}:** 2979 (CH). Data are consistent with literature precedent.[237]

1-(But-3-en-1-yl)-3-(*tert*-butyl)-1-phenylurea 484



N-(But-3-en-1-yl)aniline (5.0 mmol, 736 mg) and ^{t}Bu-isocyanate (15.0 mmol, 1.71 mL) were dissolved in toluene (10 mL) and stirred at 80 °C for 5 days. The reaction mixture was concentrated and purified by flash column chromatography (3-10% EtOAc/petrol) to give the title compound (1.04 g, 84%) as a colourless solid.

M.p. 26 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44-7.37 (m, 2H, Ar*H*), 7.33-7.28 (m, 1H, Ar*H*), 7.22-7.17 (m, 2H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 5.07-4.95 (m, 2H, CH=CH_2), 4.05 (br. s, 1H, N*H*), 3.75-3.68 (m, 2H, NCH_2), 2.29-2.20 (m, 2H, CH_2), 1.23 (s, 9H, C(CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 156.3 (*C*O), 142.5 (*C*q), 135.9 (*C*H=CH_2), 130.1 (*C*H), 128.8 (*C*H), 127.5 (*C*H), 116.4 (CH=*C*H_2), 50.8 (*C*(CH_3)$_3$), 48.2 (*C*H_2), 33.2 (*C*H_2), 29.5 (C(*C*H_3)$_3$); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{27}N_2O$ $[M+H]^+$: 247.1805, found 247.1796; **IR ν_{max} (neat)/cm^{-1}:** 2964 (CH), 1654 (C=O).

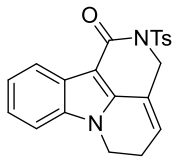
4.4 Cyclisation products

4.4.1 General cyclisation procedure

A flame-dried Schlenk tube under N_2 was charged with indole substrate (1 equiv.), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (3 equiv.), K_2CO_3 (2 equiv.), and PivOH (30 mol%). Dioxane (0.1 M) was added and the reaction was heated to 100 °C and stirred for 16 hours. The reaction mixture was cooled to room temperature and filtered through Celite®. The filter-cake was washed with DCM and $CHCl_3$, and the filtrate was then concentrated. The crude material was purified by flash column chromatography to give the product.

4.4.2 Compound data

2-Tosyl-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]naphthyridin-1-one 189



Reaction optimization

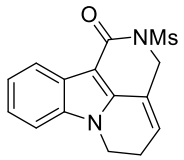
A flame-dried Schlenk tube under N_2 was charged with 1-(pent-4-en-1-yl)-N-tosyl-1H-indole-3-carboxamide (0.30 mmol, 115 mg), $Pd(TFA)_2$ (10 mol%, 10.0 mg), $Cu(OAc)_2$ (0.75 mmol, 136 mg) and K_2CO_3 (0.75 mmol, 104 mg). Dioxane (3 mL) was added and the reaction was heated to 100 °C and stirred for 16 hours. The reaction mixture was cooled to room temperature and filtered through Celite®. The filter-cake was washed with DCM and $CHCl_3$, and the filtrate was then concentrated. The crude material was purified by flash column chromatography (5% Et_2O/30% petrol/$CHCl_3$) to give the title compound (56 mg, 50%) as an off-white solid.

Cyclization of putative intermediate 188

9-Methylene-*N*-tosyl-6,7,8,9-tetrahydro[1,2-*a*]indole-10-carboxamide (0.30 mmol, 114 mg) was subjected to the general cyclization conditions described above. The crude material was purified by flash column chromatography to yield the title compound (101 mg, 83%) as an off-white solid.

M.p. 250 °C, decomp. (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.02 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.99 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.31 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.27 (d, *J* = 4.0 Hz, 2H, Ar*H*), 7.20 (dq, *J* = 8.0, 4.5 Hz, 1H, Ar*H*), 6.08 (tt, *J* = 4.5 Hz, 1H, C=C*H*), 4.98 (app. q, 2H, SO_2NCH_2), 4.12 (t, *J* = 7.5 Hz, 2H, NCH_2), 2.87-2.79 (m, 2H, CH_2), 2.41 (s, 3H, CH_3); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 161.4 (*C*O), 144.3 (*C*q), 140.2 (*C*q), 137.9 (*C*q), 137.2 (*C*q), 129.5 (*C*H), 128.5 (*C*H), 125.9 (*C*q), 124.2 (*C*H), 122.7 (*C*H), 122.1 (*C*q), 121.9 (*C*H), 121.0 (C=*C*H), 109.6 (*C*H), 102.5 (*C*q), 49.0 (SO_2NCH_2), 39.0 (NCH_2), 24.8 (CH_2), 21.8 (CH_3); **HRMS (ESI$^+$):** Calculated $C_{21}H_{18}N_2O_3S$ for $[M+Na]^+$: 401.0930, found 401.0943; **IR ν_{max} (neat)/cm^{-1}:** 3056-2933 (CH), 1673 (C=O), 1350 (S=O), 1159 (S=O).

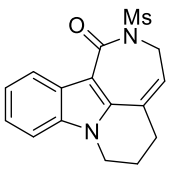
2-(Methylsulfonyl)-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]naphthyridin-1-one 202



N-(Methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide (0.30 mmol, 92 mg) was subjected to the general cyclisation conditions described above. The crude material was purified by flash column chromatography to yield the title compound (61.4 mg, 68%) as an off-white solid.

M.p. 185 °C, decomp. (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.33-7.23 (m, 3H, Ar*H*), 6.05 (tt, *J* = 4.5, 2.0 Hz, 1H, C*H*=C), 4.88-4.79 (m, 2H, SO_2NCH_2), 4.14 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.47 (s, 3H, SO_2CH_3), 2.89-2.81 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.6 (*C*O), 140.4 (*C*q), 138.0 (*C*q), 125.8 (*C*q), 124.4 (*C*H), 123.0 (*C*H), 121.7 (*C*q), 121.7 (*C*H), 121.4 (*C*H=C), 109.8 (*C*H), 102.1 (*C*q), 48.0 (SO_2NCH_2), 42.6 (SO_2CH_3), 39.0 (NCH_2), 24.8 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{14}N_2O_3S$ $[M+Na]^+$:325.0617, found 325.0621; **IR ν_{max} (neat)/cm^{-1}:** 2981 (CH), 1655 (C=O), 1329 (S=O), 1151 (S=O).

2-(Methylsulfonyl)-3,5,6,7-tetrahydroazepino[5,4,3-*hi*]benzo[*b*]indolizine-1(2*H*)-one 231

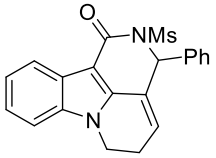


1-(Hex-4-en-1-yl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide (0.30 mmol, 96.1 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column

chromatography (10% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (50.1 mg, 53%) as a yellow solid.

M.p. 150 °C, decomp. (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.38-8.27 (m, 1H, Ar*H*), 7.43-7.29 (m, 3H, Ar*H*), 6.26 (tt, *J* = 7.0, 1.5 Hz, 1H, C*H*=C), 4.26 (d, *J* = 6.5 Hz, 2H, SO_2NCH_2), 4.18 (t, *J* = 6.0 Hz, 2H, NCH_2), 3.45 (s, 3H, SO_2CH_3), 2.73-2.63 (m, 2H, CH_2), 2.30-2.18 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 165.3 (*C*O), 139.0 (*C*q), 136.7 (*C*q), 134.7 (*C*q), 127.9 (*C*q), 126.1 (*C*H), 124.5 (*C*H), 123.1 (*C*H), 122.9 (*C*H), 109.6 (*C*H), 108.4 (*C*q), 42.7 (SO_2NCH_2), 42.5 (NCH_2), 42.5 (SO_2CH_3), 28.6 (CH_2), 23.0 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{16}N_2O_3S$ [M+Na]$^+$: 339.0774, found 339.0771; **IR ν_{max} (neat)/cm^{-1}:** 3018 (CH), 2931 (CH), 2857 (CH), 1643 (CO), 1335 (S=O), 1160 (S=O).

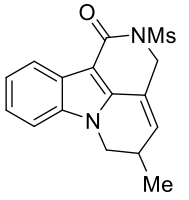
2-(Methylsulfonyl)-3-phenyl-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]naphthyridin-1-one 246



N-(Methylsulfonyl)-1-(5-phenylpent-4-en-yl)-1*H*-indole-3-carboxylate (0.30 mmol, 114.7 mg was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (5% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (80.7 mg, 71%) as a pale-yellow solid.

M.p. 238-240 °C (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.17 (dt, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.42-7.27 (m, 8H, Ar*H*), 6.34 (s, 1H, C*H*), 6.11 (ddd, *J* = 6.0, 3.0, 1.0 Hz, 1H, C*H*=C), 4.31 (ddd, *J* = 12.5, 8.0, 2.5 Hz, 1H, NC*H*H), 3.88 (td, *J* = 12.5, 6.5 Hz, 1H, NCH*H*), 3.11 (s, 3H, SO_2CH_3), 2.99-2.87 (m, 1H, C*H*H), 2.76-2.68 (m, 1H, CH*H*); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.5 (*C*O), 141.3 (*C*q), 139.7 (*C*q), 138.2 (*C*q), 129.3 (*C*H), 128.7 (*C*H), 126.0 (*C*q), 126.0 (*C*H), 125.9 (*C*q), 124.4 (*C*H=C), 123.1 (CH), 122.7 (*C*H), 121.9 (*C*H), 109.8 (*C*H), 102.3 (*C*q), 63.6 (*C*H), 43.3 (SO_2CH_3), 39.0 (NCH_2), 25.0 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{21}H_{18}N_2O_3S$ [M+H]$^+$: 379.1111, found 379.1115; **IR ν_{max} (neat)/cm^{-1}:** 2980 (CH), 2906 (CH), 1667 (CO), 1335 (S=O), 1149 (S=O).

5-Methyl-2-(methylsulfonyl)-2,3,5,6-tetrahydro-1*H*indolo[3,2,1-*ij*][1,6]napthyridin-1-one 259

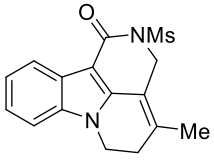


1-(2-Methylpent-4-en-1-yl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide (0.30 mmol, 96.1 mg), was subjected to the general cyclisation conditions described above. The crude product was purified by

flash column chromatography (10% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (60.2 mg, 63%) as a yellow solid.

M.p. 155 °C, decomp. (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.12-8.06 (m, 1H, Ar*H*), 7.34-7.23 (m, 3H, Ar*H*), 5.96 (dt, *J* = 4.0, 2.0 Hz, 1H, C*H*=C), 4.89-4.75 (m, 2H, SO_2NCH_2), 4.23 (dd, *J* = 12.5, 7.0 Hz, 1H, NC*H*H), 3.75 (dd, *J* = 12.5, 8.5 Hz, 1H, NCH*H*), 3.48 (s, 3H, SO_2CH_3), 3.13-3.02 (m, 1H, C*H*), 1.28 (d, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.2 (*C*O), 140.3 (*C*q), 138.0 (*C*q), 127.8 (*C*H=C), 126.0 (*C*q), 124.4 (*C*H), 123.0 (*C*H), 121.7 (*C*H), 120.8 (*C*q), 109.8 (*C*H), 102.1 (*C*q), 47.9 (SO_2NCH_2), 46.1 (NCH_2), 42.7 (SO_2CH_3), 31.1 (*C*H), 18.9 (CH_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{16}N_2O_3S$ $[M+Na]^+$: 339.0774, found 339.0789; **IR ν_{max} (neat)/cm^{-1}:** 2927 (CH), 1669 (CO), 1333 (S=O), 1149 (S=O).

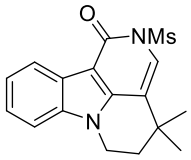
4-Methyl-2-(methylsulfonyl)-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]naphthyridin-1-one 266



1-(3-Methylpent-4-en-yl)-*N*-indole-3-carboxamide (0.30 mmol, 96.1 mg was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (6% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (67.5 mg, 71%) as a yellow solid.

M.p. decomp. 200 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 7.90-7.86 (m, 1H, Ar*H*), 7.57-7.53 (m, 1H, Ar*H*), 7.32-7.25 (m, 1H, Ar*H*), 7.23 (td, *J* = 7.5, 1.0 Hz, 1H, Ar*H*), 4.84-4.80 (m, 2H, SO_2NCH_2), 4.22 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.48 (s, 3H, SO_2CH_3), 2.82-2.75 (m, 2H, CH_2), 1.99-1.95 (m, 2H, CH_3); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 161.9 (*C*O), 141.5 (*C*q), 137.3 (*C*q), 133.7 (*C*q), 125.4 (*C*q), 123.3 (*C*H), 122.2 (*C*H), 119.9 (*C*H), 114.0 (*C*q), 110.6 (*C*H), 99.4 (*C*q), 46.0 (SO_2NCH_2), 41.4 (SO_2CH_3), 38.9 (NCH_2), 30.0 (CH_2), 18.2 (CH_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{16}N_2O_3S$ $[M+H]^+$: 317.0954, found 317.0960; **IR ν_{max} (neat)/cm^{-1}:** 2931 (CH), 1660 (CO), 1334 (S=O), 1156 (S=O).

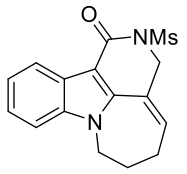
4,4-Dimethyl-2-(methylsulfonyl)-2,4,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]napthyridin-1-one 273



1-(3,3-Dimethylpent-4-en-1-yl)-*N*-(methylsulfonyl)-1*H*-indole-3-caboxamide (0.30 mmol, 100.3 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (10% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (18.1 mg, 20%) as a red solid.

M.p. 136-138 °C, (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.29 (dq, *J* = 7.5 Hz, 1.0 Hz, 1H, ArH), 7.78 (s, 1H, C=C*H*), 7.45-7.42 (m, 2H, Ar*H*), 7.37 (dq, *J* = 8.0, 4.5 Hz, 1H, Ar*H*), 4.28-4.18 (m, 2H, NCH_2), 3.72 (s, 3H, SO_2CH_3), 2.09-2.04 (m, 2H, CH_2), 1.41 (s, 6H, C(CH_3)$_2$); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 158.3 (*C*O), 142.9 (*C*q), 138.2 (*C*q), 124.8 (*C*q), 124.8 (*C*H), 123.1 (*C*H), 122.7 (*C*H), 122.1 (*C*H), 116.2 (*C*q), 109.4 (*C*H), 104.9 (*C*q), 42.8 (SO_2CH_3), 38.8 (NCH_2), 37.0 (CH_2), 31.0 (*C*(CH$_3$)$_2$), 28.1 (C(*C*H$_3$)$_2$); **HRMS (ESI$^+$):** Calculated for $C_{17}H_{18}N_2O_3S$ $[M+H]^+$: 331.1111, found 331,1135; **IR ν_{max} (neat)/cm^{-1}:** 2962 (CH), 1678 (C=O), 1347 (S=O), 1164 (S=O).

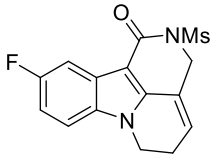
2-(Methylsulfonyl)-3,5,6,7-tetrahydro-2,7a-diazacyclohepta[*jk*]fluoren-1(2*H*)-one 283



1-(Hex-5-en-1-yl)-*N*-(methylsulfonyl)-1*H*-indole-3-carboxamide (0.30 mmol, 96.2 mg was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (10% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (36.3 mg, 38%) as a yellow solid.

M.p. 150 °C, decomp. (MeCN); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.30-8.18 (m, 1H, Ar*H*), 7.38-7.27 (m, 3H, Ar*H*), 6.22-6.15 (m, 1H, C*H*=C), 4.68 (d, *J* = 2.0 Hz, 2H, SO_2NCH_2), 4.33-4.28 (m, 2H, NCH_2), 3.46 (s, 3H, SO_2CH_3), 2.73-2.64 (m, 2H, CH_2), 2.20-2.13 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.9 (*C*O), 142.0 (*C*q), 138.2 (*C*q), 132.1 (*C*H=C), 125.5 (*C*q), 124.4 (*C*H), 123.0 (*C*H), 121.8 (*C*H), 121.6 (*C*q), 109.7 (*C*H), 106.3 (*C*q), 51.3 (SO_2NCH_2), 46.0 (NCH_2), 42.5 (SO_2CH_3), 31.1 (CH_2), 25.7 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{16}N_2O_3S$ $[M+Na]^+$: 339.0774, found 229.0780; **IR ν_{max} (neat)/cm^{-1}:** 2924 (CH), 1667 (CO), 1334 (S=O), 1154 (S=O).

10-Fluoro-2-(methylsulfonyl)-2,3,5,6-tetraheydro-1*H*-indolo[3,2,1-*ij*][1,6]napthiridin-1-one 312a

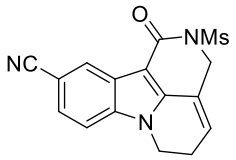


5-Fluoro-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide (0.30 mmol, 97.3 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (10% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (58.7 mg, 61%) as a pale-green solid.

M.p. decomp. 247 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 7.63 (dd, *J* = 9.0, 4.5 Hz, 1H, Ar*H*), 7.55 (dd, *J* = 9.5, 2.5 Hz, 1H, Ar*H*), 7.19 (ddd, *J* = 9.5, 9.0, 2.5 Hz, 1H, Ar*H*), 6.36 (tt, *J* = 4.5, 2.0 Hz, 1H, C*H*=C),

4.83 (app. q, 2H, SO_2NCH_2), 4.22 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.47 (s, 3H, SO_2CH_3), 2.84-2.79 (m, 2H, CH_2) ; **^{13}C NMR (101 MHz, DMSO-*d*$_6$):** δ 161.8 (*C*O), 158.6 (d, *J* = 236.5 Hz, *C*F), 142.0 (*C*q), 134.3 (*C*q), 125.6 (*C*q), 124.1 (*C*H=C), 120.4 (*C*q), 112.2 (d, *J* = 10.0 Hz, *C*H), 111.6 (d, *J* = 26.0 Hz, *C*H), 105.2 (d, *J* = 25.0 Hz, *C*H), 100.7 (*C*q), 47.9 (SO_2NCH_2), 41.4 (SO_2CH_3), 38.8 (NCH_2), 24.2 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{13}FN_2O_3S$ $[M+H]^+$: 321.0704, found 321.0709; **IR ν_{max} (neat)/cm^{-1}:** 2924 (CH), 1655 (CO), 1334 (S=O), 1154 (S=O).

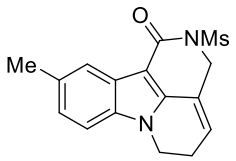
2-(methylsulfonyl)-1-oxo-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]napthyridine-10-carbonitrile 312b



5-Cyano-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide (0.30 mmol, 99.4 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (2% MeOH/DCM) to yield the title compound (63.0 mg, 64%) as a pale-yellow solid.

M.p. decomp. 240 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.21 (dd, *J* = 1.5, 0.5 Hz, 1H, Ar*H*), 7.80 (dd, *J* = 8.5, 0.5 Hz, 1H, Ar*H*), 7.72 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 6.45 (tt, *J* = 4.5, 2.0 Hz, 1H, C*H*=C), 4.86 (app. q, 2H, SO_2NCH_2), 4.29 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.48 (s, 3H, SO_2CH_3), 2.87-2.81 (m, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-*d*$_6$):** δ 162.0 (*C*O), 143.1 (*C*q), 139.9 (*C*q), 127.3 (*C*H), 126.2 (*C*H=C), 125.3 (*C*q), 124.9 (*C*H), 120.5 (*C*q), 120.2 (*C*q), 112.8 (*C*H), 104.9 (*C*q), 101.3 (*C*q), 48.4 (SO_2NCH_2), 41.8 (SO_2CH_3), 39.3 (NCH_2), 24.6 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{13}N_3O_3S$ $[M+H]^+$: 328.0750, found 328.0745; **IR ν_{max} (neat)/cm^{-1}:** 2987-2901 (CH), 2221 (CN), 1669 (C=O), 1354 (S=O), 1159 (S=O).

10-Methyl-2-(methylsulfonyl)-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]naphthyridin-1-one 312c

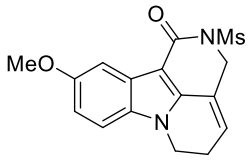


5-Methyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide (0.30 mmol, 96.1 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (5% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (71.1 mg, 75%) as a pale-yellow solid.

M.p. decomp. 221 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-*d*$_6$):** δ 7.70 (dd, *J* = 1.5, 1.0 Hz, 1H, Ar*H*), 7.46 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.22-7.08 (m, 1H, Ar*H*), 6.30 (tt, *J* = 4.5, 2.0 Hz, 1H, C*H*=C), 4.80 (app. q, 2H,

SO_2NCH_2), 4.17 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.46 (s, 3H, SO_2CH_3), 2.84-2.74 (m, 2H, CH_2), 2.42 (s, 3H, CH_3); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 162.0 (*C*O), 140.7 (*C*q), 135.9 (*C*q), 131.4 (*C*q), 125.2 (*C*q), 125.1 (*C*H), 123.1 (*C*H=C), 120.6 (*C*q), 119.9 (*C*H), 110.5 (*C*H), 100.2 (*C*q), 47.8 (SO_2NCH_2), 41.4 (SO_2CH_3), 38.6 (NCH_2), 24.1 (CH_2), 21.2 (CH_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{16}N_2O_3S$ $[M+H]^+$: 317.0954, found 317.0962; **IR ν_{max} (neat)/cm^{-1}:** 2923 (CH), 1666 (C=O), 1333 (S=O), 1151 (S=O).

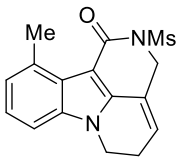
10-Methoxy-2-(methylsulfonyl)-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]napthyridin-1-one 312d



5-Methoxy-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide (0.30 mmol, 101 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (10% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (72.3 mg, 73%) as a pale-yellow solid.

M.p. decomp. 215 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 7.50 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.38 (d, *J* = 2.5 Hz, 1H, Ar*H*), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 6.29 (tt, *J* = 4.5, 2.0 Hz, 1H, C*H*=C), 4.81 (app. q, 2H, SO_2NCH_2), 4.17 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.80 (s, 3H, OCH_3), 3.46 (s, 3H, SO_2CH_3), 2.83-2.75 (m, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 162.1 (*C*O), 155.7 (*C*q), 140.8 (*C*q), 132.5 (*C*q), 125.9 (Cq), 122.9 (*C*H=C), 120.6 (*C*q), 113.2 (*C*H), 111.8 (*C*H), 102.1 (*C*H), 100.4 (*C*q), 55.4 (OCH_3), 47.9 (SO_2NCH_2), 41.4 (SO_2CH_3), 36.7 (NCH_2), 24.2 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{16}N_2O_4S$ $[M+H]^+$: 333.0904, found 333.0900; **IR ν_{max} (neat)/cm^{-1}:** 2921 (CH), 1662 (C=O), 1331 (S=O), 1159 (S=O).

11-Methyl-2-(methylsulfonyl)-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]naphthyridin-1-one 312f

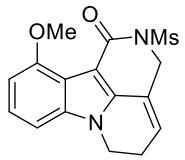


4-Methyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole (0.30 mmol, 96 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (10% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (50.9 mg, 54%) as a pale-yellow solid.

M.p. decomp. 239 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 7.28 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.21 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.00 (d, *J* = 7.0 Hz, 1H, Ar*H*), 6.35 (tt, *J* = 4.5 Hz, 2.0 Hz, 1H, C*H*=C), 4.79 (app. q, 2H, SO_2NCH_2), 4.17 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.46 (s, 3H, SO_2CH_3), 2.83 (s, 3H, CH_3), 2.81-2.75 (m, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 162.3 (*C*O), 141.5 (*C*q), 138.6 (*C*q), 132.0 (*C*q), 125.2 (*C*q), 124.5 (*C*H),

124.5 (*C*H), 124.0 (*C*H), 121.4 (*C*q), 108.5 (*C*q), 102.4 (*C*H), 47.8 (SO_2NCH_2), 42.1 (SO_2CH_3), 39.0 (NCH_2), 24.3 (CH_2), 22.6 (CH_3); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{16}N_2O_3S$ $[M+H]^+$: 317.0954, found 317.0961; **IR ν_{max} (neat)/cm^{-1}:** 2988-2901 (CH), 1658 (C=O), 1334 (S=O), 1151 (S=O).

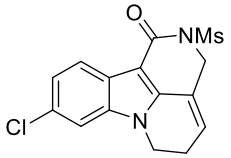
11-Methoxy-2-(methylsulfonyl-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]naphthyridin-1-one 312g



4-Methoxy-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide (0.30 mmol, 101 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (10% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (67.3 mg, 67%) as a pale-yellow solid.

M.p. decomp. 188 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 7.26 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar*H*), 7.15 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar*H*), 6.76 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 6.31 (tt, *J* = 4.5, 2.0 Hz, 1H, C*H*=C), 4.76 (app. q, 2H, SO_2NCH_2), 4.16 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.86 (s, 3H, OCH_3), 3.44 (s, 3H, SO_2CH_3), 2.81-2.73 (m, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 160.7 (*C*O), 154.4 (*C*q), 140.6 (*C*q), 139.8 (*C*q), 125.7 (*C*H), 123.4 (*C*H), 121.3 (*C*q), 115.4 (*C*q), 104.4 (*C*H), 103.9 (*C*H), 102.0 (*C*q), 56.1 (OCH_3), 47.9 (SO_2NCH_2), 42.0 (SO_2CH_3), 39.2 (NCH_2), 24.3 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{16}H_{16}N_2O_4S$ $[M+H]^+$: 333.0904, found 333.0917; **IR ν_{max} (neat)/cm^{-1}:** 2988-2901 (CH), 1677 (C=O), 1331 (S=O), 1153 (S=O).

9-Chloro-2-(methylsulfonyl)-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]naphthyridin-1-one 312h

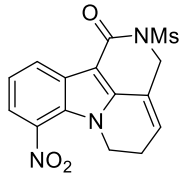


6-Chloro-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide (0.30 mmol, 102 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (10% Et_2O/25% petrol/$CHCl_3$) to yield the title compound (60.9 mg, 60%) as a pale-yellow solid.

M.p. decomp. 237 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 7.86-7.82 (m, 1H, Ar*H*), 7.77-7.75 (m, 1H, Ar*H*), 7.26 (dd, *J* = 8.5, 2,0 Hz, 1H, Ar*H*), 6.36 (tt, *J* = 4.5, 2.0 Hz, 1H, C*H*=C), 4.83 (app. q, 2H, SO_2NCH_2), 4.21 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.46 (s, 3H, SO_2CH_3), 2.80 (tdt, *J* = 7.5, 4.5, 2.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 161.7 (*C*O), 141.5 (*C*q), 138.2 (*C*q), 128.2 (*C*q), 124.2 (*C*H=C), 123.8 (*C*q), 122.6 (*C*H), 121.2 (*C*H), 120.3 (*C*q), 111.1 (*C*H), 100.6 (*C*q), 47.9 (SO_2NCH_2), 41.3 (SO_2CH_3), 38.7 (NCH_2),

24.1 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{13}{}^{35}ClN_2O_3S$ [M+Na]$^+$: 359.0228, found 359.0242; **IR ν_{max} (neat)/cm^{-1}:** 2923 (CH), 1670 (C=O), 1347 (S=O), 1156 (S=O).

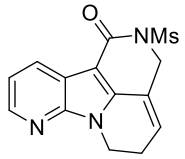
2-(Methylsulfonyl)-8-nitro-2,3,5,6-tetrahydro-1*H*-indolo[3,2,1-*ij*][1,6]naphthyridin-1-one 312i



N-(Methylsulfonyl)-7-nitro-1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamide (0.30 mmol, 105 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (10% Et_2O/$CHCl_3$) to yield the title compound (23.3 mg, 22%) as a pale-yellow solid.

M.p. decomp. 236 °C (MeCN); **^{1}H NMR (500 MHz, DMSO-d_6):** δ 8.31 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.99-7.92 (m, 1H, Ar*H*), 7.42 (td, *J* = 8.0, 0.5 Hz, 1H, Ar*H*), 6.49 (tt, *J* = 4.5, 2.0 Hz, 1H, C=C*H*), 4.85 (app. q, 2H, SO_2NCH_2), 4.27 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.49 (s, 3H, SO_2CH_3), 2.77 (tdt, *J* = 7.0, 4.5, 2.5 Hz, 2H, CH_2); **^{13}C NMR (126 MHz, DMSO-d_6):** δ 161.7 (*C*O), 143.0 (*C*q), 136.7 (*C*q), 128.9 (*C*q), 128.6 (*C*q), 126.3 (C=*C*H), 126.0 (*C*H), 121.9 (*C*H), 120.9 (*C*H), 120.4 (*C*q), 101.6 (*C*q), 47.8 (SO_2NCH_2), 42.7 (NCH_3), 41.3 (SO_2CH_3), 24.8 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{15}H_{13}N_3O_5S$ [M+Na]$^+$: 370.0468, found 370.0484; **IR ν_{max} (neat)/cm^{-1}:** 2922 (CH), 1669 (C=O), 1528 (NO_2), 1342 (S=O), 1333 (NO_2), 1158 (S=O)

2-(Methylsulfonyl)-2,3,5,6-tetrahydro-1*H*-pyrido[3',2':4,5]pyrrolo[3,2,1-*ij*][1,6]naphthyridin-1-one 312j

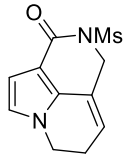


N-(Methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide (0.30 mmol, 92.1 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (2% MeOH/DCM) to yield the title compound (53.2 mg, 58%) as a pale-green solid.

M.p. 235-237 °C (MeCN); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.36 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H, Ar*H*), 8.20 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.29 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar*H*), 6.44 (tt, *J* = 4.5, 2.0 Hz, 1H, C=C*H*), 4.85 (app. q, 2H, SO_2NCH_2), 4.25 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.48 (s, 3H, SO_2CH_3), 2.83 (tdt, *J* = 7.5, 5.0, 2.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-d_6):** δ 161.4 (*C*O), 148.5 (*C*q), 144.3 (*C*H), 141.1 (*C*q), 128.2 (*C*H), 125.7 (C=*C*H), 120.1 (*C*q), 118.5 (*C*H), 118.1 (*C*q), 99.0 (*C*q), 47.8 (SO_2NCH_2), 41.3 (SO_2CH_3), 37.3 (NCH_2),

24.1 (*C*H_2); **HRMS (ESI$^+$):** Calculated for $C_{14}H1_3N_3O_3S$ [M+H]$^+$: 304.0750, found 304.0755; **IR ν_{max} (neat)/cm^{-1}:** 2958 (CH), 1725 (C=O), 1334 (S=O), 1155 (S=O).

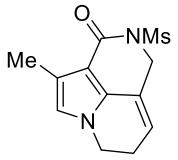
2-(Methylsulfonyl)-1,2,7,8-tetrahydro-3*H*-pyrrolo[3,2,1-*ij*][1,6]naphthyridin-3-one 331a



N-(Methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxamide (0.30 mmol, 76.8 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (15% Et_2O/ petrol 25%/ $CHCl_3$) to yield the title compound (27 mg, 35%) as a pale-yellow solid.

M.p. 92-94 °C, (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.63 (d, *J* = 3.0 Hz, 1H, Ar*H*), 6.55 (d, *J* = 3.0 Hz, 1H, Ar*H*), 5.76 (tt, *J* = 4.5, 2.0 Hz, 1H, C*H*=C), 4.76 (app. q, 2H, SO_2NCH_2), 3.99 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.41 (s, 3H, SO_2CH_3), 2.68 (tdt, *J* = 7.0, 4.5, 2.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.7 (*C*O), 135.0 (*C*q), 123.6 (*C*H), 121.6 (*C*q), 116.1 (*C*H=C), 110.2 (*C*q), 107.9 (*C*H), 48.4 (SO_2NCH_2), 42.5 (NCH_2), 42.5 (SO_2CH_3), 25.0 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{11}H_{12}N_2O_3S$ [M+H]$^+$: 253.0641, found 253.0645; **IR ν_{max} (neat)/cm^{-1}:** 2928 (CH), 1673 (C=O), 1322 (S=O), 1156 (S=O).

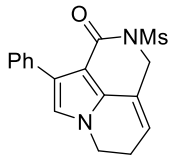
4-Methyl-2-(methylsulfonyl)-1,2,7,8-tetrahydro-3*H*-pyrrolo[3,2,1-*ij*][1,6]naphthyridin-3-one 331b



4-Methyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxamide (0.30 mmol, 81 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (5% Et_2O/ $CHCl_3$) to yield the title compound (40 mg, 50%) as a white solid.

M.p. 165-166 °C, (EtOAc); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 6.39 (q, *J* = 1.0 Hz, 1H, Ar*H*), 5.70 (tt, *J* = 4.5, 2.0 Hz, 1H, C*H*=C), 4.72 (app. q, 2H, SO_2NCH_2), 3.90 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.41 (s, 3H, SO_2CH_3), 2.67-2.60 (m, 2H, CH_2), 2.27 (app. d, 3H, CH_3); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 163.4 (*C*O), 135.0 (*C*q), 121.7 (*C*q), 121.4 (*C*H), 121.3 (*C*q), 115.5 (C=*C*H), 108.5 (*C*q), 48.3 (SO_2NCH_2), 42.6 (SO_2CH_3), 42.2 (NCH_2), 24.9 (CH_2), 11.0 (CH_3); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{14}N_2O_3S$ [M+H]$^+$: 267.0798, found 267.0809; **IR ν_{max} (neat)/cm^{-1}:** 2922 (CH), 1670 (C=O), 1334 (S=O), 1155 (S=O).

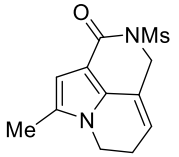
2-(Methylsulfonyl)-4-phenyl-1,2,7,8-tetrahydro-3*H*-pyrrolo[3,2,1-*ij*][1,6]naphthyridin-3-one 331c



N-(Methylsulfonyl)-1-(pent-4-en-1-yl)-4-phenyl-1*H*-pyrrole-3-carboxamide (0.30 mmol, 98 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (4% Et_2O/ $CHCl_3$) to yield the title compound (40 mg, 40%) as a white solid.

M.p. 218 °C (EtOAc); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.71-7.66 (m, 2H, Ar*H*), 7.39-7.33 (m, 2H, Ar*H*), 7.30-7.27 (m, 1H, Ar*H*), 6.78 (s, 1H, Ar*H*), 5.82 (tt, *J* = 4.5, 2.0 Hz, 1H, C*H*=C), 4.79 (app. q, 2H, SO_2NCH_2), 4.02 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.41 (s, 3H, SO_2CH_3), 2.71 (tdt, *J* = 7.5, 4.5, 2.5 Hz, 2H, CH_2); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 162.7 (*C*O), 136.0 (*C*q), 133.1 (*C*q), 128.5 (*C*H), 128.3 (*C*H), 127.2 (*C*H), 127.0 (*C*q), 121.9 (*C*H), 116.6 (C=*C*H), 106.9 (*C*q), 48.0 (SO_2NCH_2), 42.8 (SO_2CH_3), 42.5 (NCH_2), 24.8 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{17}H_{16}N_2O_3S$ $[M+Na]^+$: 351.0774, found 351.0774; **IR ν_{max} (neat)/cm^{-1}:** 2972 (CH), 1675 (C=O), 1337 (S=O), 1157 (S=O).

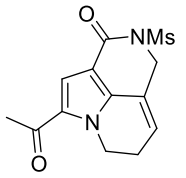
5-Methyl-2-(methylsulfonyl)-1,2,7,8-tetrahydro-3*H*-pyrrolo[3,2,1-*ij*][1,6]napthyridin-3-one 331d



5-Methyl-N-(methylsulfonyl)-1-(pent-4-en-1-yl)-1H-pyrrole-3-carboxamide (0.30 mmol, 81 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (3-5% Et_2O/ $CHCl_3$) to yield the title compound (31 mg, 39%) as a white solid.

M.p. 147-148 °C, (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44 (t, *J* = 1.5 Hz, 1H, Ar*H*), 6.51-6.47 (m, 1H, C*H*=C), 3.95-3.90 (m, 2H, SO_2NCH_2), 3.62 (s, 3H, SO_2CH_3), 2.73 (ddd, *J* = 7.5, 5.0, 1.5 Hz, 2H, NCH_2), 2.33 (d, *J* = 1.0 Hz, 3H, CH_3), 2.22-2.14 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 158.7 (*C*O), 138.0 (*C*q), 134.0 (*C*q), 119.5 (*C*H), 112.3 (*C*q), 107.3 (*C*q), 103.6 (*C*H=C), 42.5 (SO_2CH_3), 41.6 (SO_2NCH_2), 23.2 (CH_2), 21.6 (NCH_2), 11.8 (CH_3); **HRMS (ESI$^+$):** Calculated for $C_{12}H_{14}N_2O_3S$ $[M+H]^+$: 267.0798, found 267.0803; **IR ν_{max} (neat)/cm^{-1}:** 2931 (CH), 1659 (C=O), 1340 (S=O), 1158 (S=O).

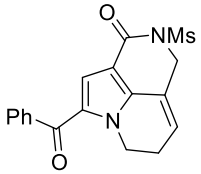
5-Acetyl-2-(methylsulfonyl)-1,2,7,8-tetrahydro-3*H*-pyrrolo[3,2,1][*ij*][1,6]naphthyridin-3-one 331e



5-Acetyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxamide (0.30 mmol, 89.4 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (25% Et_2O/ 25% petrol/ $CHCl_3$) to yield the title compound (30.9 mg, 35%) as a pale-yellow solid.

M.p. decomp. 222 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.27 (s, 1H, Ar*H*), 5.99 (tt, *J* = 4.0, 2.0 Hz, 1H, C*H*=C), 4.76 (app. q, 2H, SO_2NCH_2), 4.50 (t, *J* = 8.0 Hz, 2H, NCH_2), 3.42 (s, 3H, SO_2CH_3), 2.68 (tdt, *J* = 7.5, 4.5, 2.5 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 189.6 (*C*O), 161.9 (*C*O), 138.7 (*C*q), 133.0 (*C*q), 121.6 (*C*H), 120.8 (*C*q), 117.4 (*C*H), 110.3 (*C*q), 48.1 (SO_2CH_2), 42.5 (SO_2CH_3), 42.5 (NCH_2), 27.3 (CH_3), 24.9 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{13}H_{14}N_2O_4S$ $[M+H]^+$: 295.0747, found 295.0747; **IR ν_{max} (neat)/cm^{-1}:** 2988-2901 (CH), 1678 (C=O), 1651 (C=O), 1327 (S=O), 1157 (S=O).

5-Benzoyl-2-(methylsulfonyl)-1,2,7,8-tetrahydro-3*H*-pyrrolo[3,2,1-*ij*][1,6]naphthyridin-3-one 331f



5-Benzoyl-*N*-(methylsulfonyl)-1-(pent-4-en-1-yl)-1*H*-pyrrole-3-carboxamide (0.30 mmol, 108 mg) was subjected to the general cyclisation conditions described above. The crude product was purified by flash column chromatography (5% Et_2O/ 25% petrol/ $CHCl_3$) to yield the title compound (39.6 mg, 37%) as a pale-yellow solid.

M.p. decomp. 192 °C (EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.84-7.77 (m, 2H, Ar*H*), 7.71-7.63 (m, 1H, Ar*H*), 7.60-7.50 (m, 2H, Ar*H*), 6.92 (s, 1H, Ar*H*), 6.27 (tt, *J* = 4.5, 2.5 Hz, 1H, C*H*=C), 4.80 (app. q, 2H, SO_2NCH_2), 4.47 (t, *J* = 8.0 Hz, 2H, NCH_2), 3.43 (s, 3H, SO_2CH_3), 2.77-2.69 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 186.7 (*C*O), 162.0 (*C*O), 139.1 (*C*q), 138.5 (*C*q), 132.7 (*C*H), 132.6 (*C*q), 129.3 (*C*H), 128.6 (*C*H), 121.8 (*C*H), 120.9 (*C*q), 120.1 (*C*H), 110.5 (*C*q), 48.1 (SO_2NCH_2), 42.5 (SO_2CH_3), 42.3 (NCH_2), 25.1 (CH_2); **HRMS (ESI$^+$):** Calculated for $C_{18}H_{16}N_2O_4S$ $[M+H]^+$: 357.0904, found 357.0911; **IR ν_{max} (neat)/cm^{-1}:** 2981 (CH), 1684 (C=O), 1643 (C=O), 1340 (S=O), 1154 (S=O).

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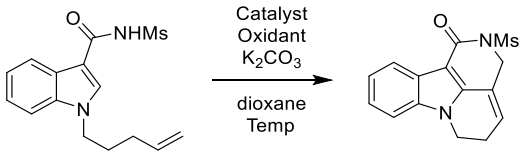
6. Appendix

DOE experiments



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Entry	Temperature (°C)	Concentration (M)	Catalyst	Catalyst loading (mol %)	Oxidant	Oxidant Equiv.	Base Equiv.	NMR yield* (%)
1	100	0.0625	$Pd(OAc)_2$	20	$Cu(OAc)_2$	2	3	52
2	80	0.025	$[PdCl(allyl)]_2$	20	AgOAc	4	4	42
3	80	0.025	$Pd(TFA)_2$	10	$Cu(OAc)_2$	2	2	52
4	90	0.0625	$Pd(TFA)_2$	15	$Cu(OAc)_2$	3	3	59
5	90	0.0625	$Pd(TFA)_2$	15	$Cu(OAc)_2$	3	3	54
6	100	0.2	$Pd(OAc)_2$	10	AgOAc	3	2	71
7	80	0.0625	$Pd(TFA)_2$	10	$Cu(OAc)_2$	4	3	22
8	80	0.0625	$Pd(OAc)_2$	15	AgOAc	2	4	36
9	100	0.0625	$Pd(TFA)_2$	15	AgOAc	4	2	70
10	80	0.0625	$[PdCl(allyl)]_2$	20	$Cu(OAc)_2$	3	2	36
11	90	0.0625	$Pd(TFA)_2$	15	$Cu(OAc)_2$	3	3	54
12	80	0.1	$[PdCl(allyl)]_2$	10	AgOAc	2	3	3
13	100	0.025	$Pd(OAc)_2$	10	$Cu(OAc)_2$	4	4	59
14	100	0.1	$[PdCl(allyl)]_2$	15	$Cu(OAc)_2$	4	3	17
15	100	0.1	$Pd(TFA)_2$	20	$Cu(OAc)_2$	2	4	49
16	80	0.1	$Pd(OAc)_2$	20	$Cu(OAc)_2$	4	2	63
17	80	0.025	$Pd(OAc)_2$	15	$Cu(OAc)_2$	3	3	46
18	100	0.0625	$[PdCl(allyl)]_2$	10	$Cu(OAc)_2$	4	3	19
19	100	0.025	$[PdCl(allyl)]_2$	15	$Cu(OAc)_2$	2	3	34
20	100	0.025	$Pd(TFA)_2$	20	AgOAc	3	2	60
21	80	0.1	$Pd(TFA)_2$	15	$Cu(OAc)_2$	3	4	21
22	100	0.025	$Pd(OAc)_2$	20	AgOAc	4	2	75

*As measured by ^{1}H-NMR analysis with 1,4-dimethoxybenzene as a standard