The Stereoselective Synthesis of Heterocycles Through Cation-Triggered Annulation

A thesis submitted in partial fulfilment of the requirement

for the degree of Doctor of Philosophy (DPhil)

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Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from May 2019 until March 2023, under the supervision of Professor Timothy J. Donohoe. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

Lydia Cox

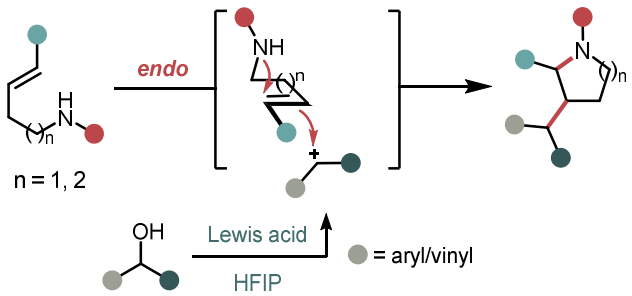
March 2023

Abstract

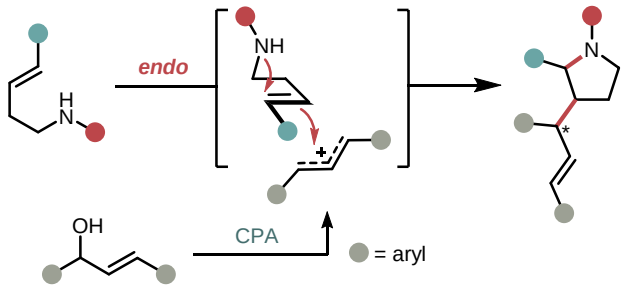
The work described herein details the development of new methodologies for the synthesis of 2,3-disubstituted pyrrolidines and piperidines *via* an *endo-trig* cyclisation. This was realised through two approaches: firstly, a Lewis acid catalysed cation triggered annulation strategy, and secondly an asymmetric Brønsted acid catalysed cation triggered annulation strategy.

Chapter 1 is a literature review, providing an overview of the current approaches and limitations associated with the synthesis azacycles, specifically focusing on methods which introduce maximum complexity around the ring in a single step. The lack of approaches which utilise an *endo-trig* cyclisation required an overview of potential solutions, with contemporary methods to generate carbocations discussed in detail, ultimately forming the basis of the research described in this thesis.

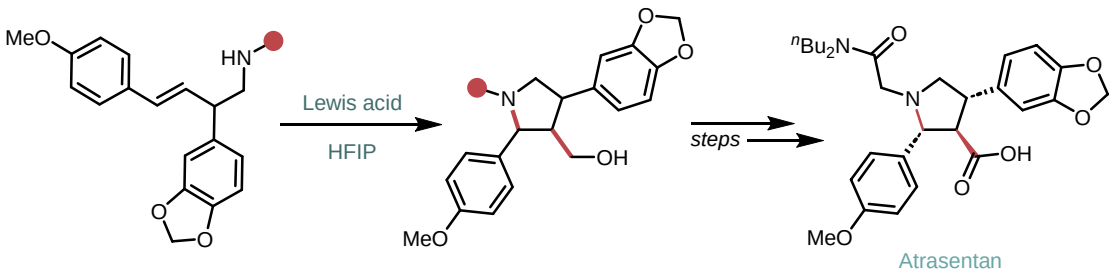
Chapter 2 details the development of a Lewis acid catalysed cation triggered annulation in HFIP which enabled the diastereoselective synthesis of a range of functionalised piperidine and pyrrolidine products. In this approach, a complementary protecting group strategy was developed, before utilising a range of alcohol and non-alcohol electrophiles which were able to act as alkylating agents following the generation of a carbocation.



Chapter 3 presents the extension of the work described in Chapter 2 to an enantioselective transformation. A series of approaches were tested, with chiral phosphoric acid catalysis shown to be the most successful. This method followed the same disconnection utilised previously, with an alcohol employed as an alkylating agent, this time in the absence of both the metal catalyst and HFIP as the solvent.



Chapter 4 documents studies towards the pharmaceutical molecule Atrasentan utilising the method developed in Chapter 2. An extensive optimisation of the substrate synthesis is discussed, along with multiple strategies to derivatise the pyrrolidine core towards Atrasentan.



Chapter 5 provides an overview of the major conclusions of this work and discusses potential future directions for this methodology.

Chapter 6 details the experimental procedures used and documents the spectroscopic data for all the compounds described in this work.

Chapter 7 lists the references cited within this work.

Acknowledgements

First of all, I would like to thank Professor Tim Donohoe for the opportunity to join your research group. I am very grateful not only for your supervision and support over the last four years but for giving me the freedom to try new things and become an independent researcher. Thank you for always being enthusiastic about chemistry, for validating my decisions when the results weren't coming and for supporting my professional development, I leave a more confident researcher because of it. Thank you to my industrial supervisor Mireia Sidera Portela and Vertex, your support when I was embarking on a new project greatly impacted my ability to carry out research.

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thank you both for your excellent contributions. More importantly, however, was the impact you had on my decision making; you encouraged me to try new things without over-thinking it, and taught me it is ok to stop when something isn't working. When I came to Oxford, a lot of me thought I did not belong here, so to Hamish thank you for your early advice, the phrase 'there is more than one way to be a good chemist' has kept me grounded on numerous occasions. Thank you for bringing me out of my shell, I truly believe that I would not be as confident now if it wasn't for you and for the opportunities that this has brought me, I will forever be grateful. Finally, to both you and Rebecca, thank you for your friendship, the summer of 2020 would have been a lot harder if it was not for you both.

The friends I made during my time in the lab have had a huge impact on my PhD experience. Elliot thank you for all the walks during lockdown and for your persistence in getting me to hang out whenever I'm having a hard time, I am always glad of it afterwards. To Bruno, I don't want to imagine what my time in F8 would have been like without you (minus maybe fewer whiny female vocalists on Spotify!), you have brought so much energy to the lab. Thank you for sharing you love of art, music and culture with me, in such a scientific environment our overlapping interests were a welcome change. Dani, I'm not sure I would have made it through the last four years without you and I worry how I will cope with the smallest (and biggest) of inconveniences and decisions without you so close. Sharing this journey with you has given me the validation I needed to truly speak up for what I believe. Your company continues to empower me, and the conviction I have towards supporting woman in science is because of your friendship. I hope we will both end up as the role models we wished were there for us. Francisco, you came into the lab when I was having a tough time and the joy you brought into my day-to-day life is no doubt some of the reason why it got better. Thank you for being my biggest hype-man, my ride or die and the most inappropriate person I have ever met. I know we come from very different backgrounds but I feel like you understood me more than most. To Andrew and Tim J, I may make fun of all the ridiculous things you love so much about Oxford but I am grateful to you both for your company, don't let the chemistry get you down, it isn't worth it.

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formatting!) skills which I still rely on every day, but I am most grateful for all the advice, support and friendship you have continued to give me in the years since. To those friends I made during my time in Oakfield, I don't see you as much as I would like but am grateful for every opportunity to be with you all. A special mention goes to Tom, Evie and Clare, thank you for always being there for me.

Although studying at university for over eight years is a far cry from normal in our family, I hope you know that we are, after all this time, still the same, my trade just happens to be chemistry. Growing up you were the best of role models and I hope I have made you all proud. I will forever be a Cox from Buckinghamshire and there will never be a place I feel as much like I belong as I do with you all. Sometimes you need a lucky break so to Wendy, Darren and Darren's Darren, thank you, without your help I would likely not be where I am today, I am proud that the nepotism I received was through two gardeners, it feels truly right.

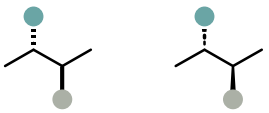
To my parents, I owe you both so much, thank you for endlessly fighting in my corner. I am so grateful that you never pushed me to follow dreams that were not truly mine, there is no doubt that I am much happier in my decisions because of the freedom you have given me. You taught me the importance of being both creative and practical and although I have spent so much of my life studying, I am certain that my success is a reflection of the way you both taught me to see the world. To Jake thank you for creating boogienitez, you have provided the best of soundtracks for my life for the last few years. You always know what to say and continue to have so much conviction in your beliefs, and I feel very lucky that you have no choice as my brother but to remain in my life.

Finally, to Bert, I know you may not count emotional support as one of your many, many strengths, but you have remained there for me through some of the hardest years of my life, I can only apologise for the countless times I have cried to you over the phone. Thank you for always challenging me, your continued belief that I can do things which I am afraid of has led me to try so many new things and more feels possible because of you. Navigating a long-distance relationship whilst both trying to get a PhD on top of a pandemic has often been a challenge, so I look forward to what (hopefully easier thing) will happen for us next.

Table of contents

Stereochemistry

Throughout this text, straight bonds are used to denote relative stereochemistry in racemic compounds, whereas wedged bonds are used to denote absolute and relative configuration in enantioenriched compounds. Where the absolute stereochemistry could not be determined in enantioenriched compounds a nominal absolute assignment has been given for ease of discussion.



racemic *enantioenriched*

Abbreviations and acronyms

α	Alpha
β	Beta
Å	Angstrom
°C	Degrees Celsius
γ	Gamma
ν_{max}	Infrared absorption maximum
μ	Micro
δ	NMR chemical shift
[α]	Specific rotation
(±)	Racemic
AAA	Asymmetric allylic alkylation
Ac	Acetyl
ACDC	Asymmetric counterion-directed catalysis
app.	Apparent
aq.	Aqueous
Ar	Aryl
ax.	Axial
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br.	Broad
Bu	Butyl
cat.	Catalytic
CBS	Corey–Bakshi–Shibata
Cbz	Carbobenzyloxy
CM	Cross metathesis

cm^{-1}	Wavenumber
CPA	Chiral phosphoric acid
cod	1,5-Cyclooctadiene
coe	Cyclooctene
d	Doublet
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DCAD	Di-(4-chlorobenzyl) azodicarboxylate
DCC	*N*,*N*'-Dicyclohexylcabodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DFT	Density Functional Theory
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	5-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulfoxide
dppf	1,1'-ferrocenediyl-bis(diphenylphosphine)
d.r.	Diastereomeric ratio
DTBAD	Di-*tert*-butyl azodicarboxylate
E	Electrophile
E	Entgegen
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
eq.	Equatorial
equiv.	Equivalents

e.r.	Enantiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron-withdrawing group
FCC	Flash column chromatography
g	Grams
G-I	Grubbs catalyst 1st generation
G-II	Grubbs catalyst 2nd generation
g	Grams
h	Hours
HBD	Hydrogen-bond donor
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HIR	Hypervalent iodine reagent
HMDS	Bis(trimethylsilyl)amine
HPLC	High-performance liquid chromatography
HOBt	Hydroxybenzotriazole
HRMS	High resolution mass spectrometry
Hz	Hertz
H-GII	Hoveyda-Grubbs 2nd generation catalyst
IDP	Imidodiphosphate
IDPi	Imidodiphosphorimidate
^{i}Pr	*iso*-propyl
IR	Infrared
J	Coupling constant
LDA	Lithium diisopropylamide
$LiAlH_4$	Lithium aluminium hydride

M	Molar
m	Multiplet
m/*z*	Mass to charge ratio
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
mol	Mole
mp	Melting point
MS	Molecular sieves
Ms	Methanesulfonyl
n	Normal (unbranched alkyl chain)
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
NPA	*N*-Phosphoramide
nOe	Nuclear Overhauser effect
Ns	Nitrophenylsulfonyl
Nu	Nucleophile
o	Ortho
p	Para
p	Pentet
PC	Photocatalyst
Ph	Phenyl
PIDA	(Diacetoxyiodo)benzene
PMP	*para*-Methoxy phenyl
q	Quartet
quant.	Quantitative
R	Unspecified organic group

rac	Racemic
rt	Room temperature
s	Singlet
sat.	Saturated
SET	Single electron transfer
SPINOL	(*S*)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol--hydrogen sulfide
T	Temperature
t	Time
t	Triplet
TEMPO	(2,2,6,6-Tetramethylpiperidinyl)oxyl
Tf	Trifluoromethylsulfonyl
t_R	Retention time
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diy
TBDPS	*tert*-Butyldiphenylsilyl
^{t}Bu	*tert*-Butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Toluenesulfonyl group
UV	Ultraviolet
wt.	By weight
X	Generic atom/counterion
Z	Zusammen

1

Introduction

1.1 The need for methods to access highly substituted azacycles

In 2014, an analysis by Njardarson and co-workers of over 1000 unique FDA approved small-molecule drugs revealed that 640 (59%) contain at least one nitrogen heterocycle.[1] The 640 drugs containing a nitrogen heterocycle can be subdivided into 24 different frameworks, of which only three are present more than 50 times, piperidines (72), pyridines (62) and piperazines (59), making up over a third of all occurrences. When the study is extended to a comparison of all ring structures in drugs, only benzene features more frequently; nitrogen heterocycles clearly have a privileged position within successful drug discovery.[2] Another conclusion which can be made from these analyses is that, despite the historical preference of the pharmaceutical industry to generate libraries of drug candidates using sp^2-sp^2 cross-coupling strategies, the most popular rings are not aromatic in nature. Only three of the 10 most prevalent rings are aromatic: benzene, pyridine and imidazole. In fact, a well-established link between a drug candidates' success and increased carbon-carbon bond saturation and three-dimensional character has been described.[3,4] Small azacycles not only satisfy these criteria, but additionally offer multiple vector points for introducing structural complexity, providing that the synthetic methods to access the required substitution are known. An analysis of the substitution patterns of existing piperidine and pyrrolidine drugs reveals the majority are only mono- and di- substituted, and this is likely a reflection of a lack of approaches to highly substituted azacycles rather than reduced activity with increasing substitution (**Figure 1**).

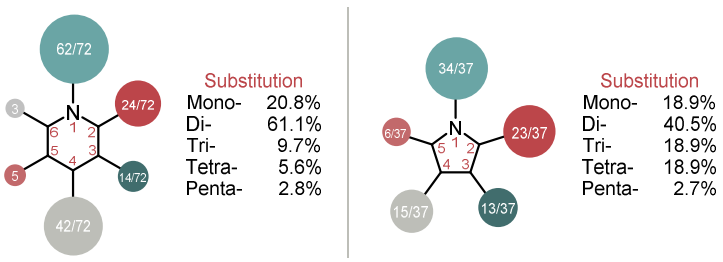


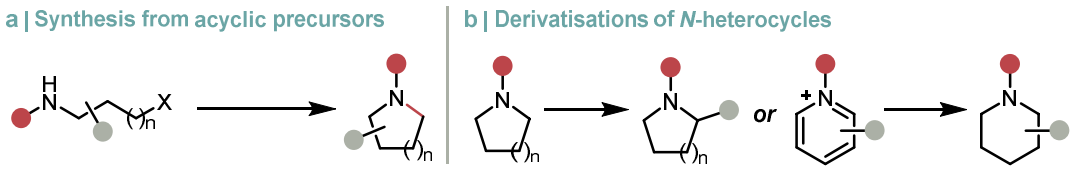
Figure 1. Substitution patterns of piperidines and pyrrolidines in FDA approved drugs.

To this effect research into the synthesis of highly substituted *N*-heterocycles has been of significant interest in recent years, no doubt enabling the introduction of more complex azacycles into drug targets. It is likely that the inclusion of azacycles in successful candidates will only increase with time. This introductory chapter with focus on outlining recent developments in the synthesis of pyrrolidines and piperidines, establishing the limitations of contemporary methods and potential strategies to overcome them.

1.2 Approaches to azacycles

Although the methods to synthesise pyrrolidines and piperidines will be discussed in parallel when overviewing the state-of-the art approaches within the literature, it would be remiss not the comment on the relative prevalence of strategies to access both. Some methods are, of course, limited to the synthesis of one, not both structures, owing to the mode of activation or disconnection approach. However, some methods which could easily be envisioned to allow access to both cycles often do not, and instead focus on pyrrolidines. A rational for this observation is far from straightforward, potentially substrate synthesis is easy for one but not the other, or for an asymmetric transformation, moving from one system to the other no longer leads to sufficiently high levels of enantioinduction. But considering that this trend is observed across very different reaction frameworks, it suggests that reactivity is a key factor, and that synthesis of the larger ring system is beyond the window of reactivity for some transformations, for this reason an effort will be made to highlight methods which readily access both pyrrolidines and piperidines.

Considering that the utility of a synthetic method in a drug discovery programme is often tied to the ease in which substrates with multiple substitution patterns can be accessed and this overview will comment on the relative ability of each approach to do so. Methods to access azacycles use a diverse range of disconnections, and providing an overview requires careful consideration into the ways in which ring substitution is introduced. Two distinct approaches can be separated: those from reaction of acyclic precursors (**Scheme 1a**) or those from further derivatisation of pre-existing ring systems, either through a dearomatisation strategy, or through elaboration of an existing saturated framework (**Scheme 1b**).[5,6] Although the derivatisation of existing *N*-heterocycles has been well studied, our overview will focus on the first approach: methods which go *via* the formation of a C-N bond.

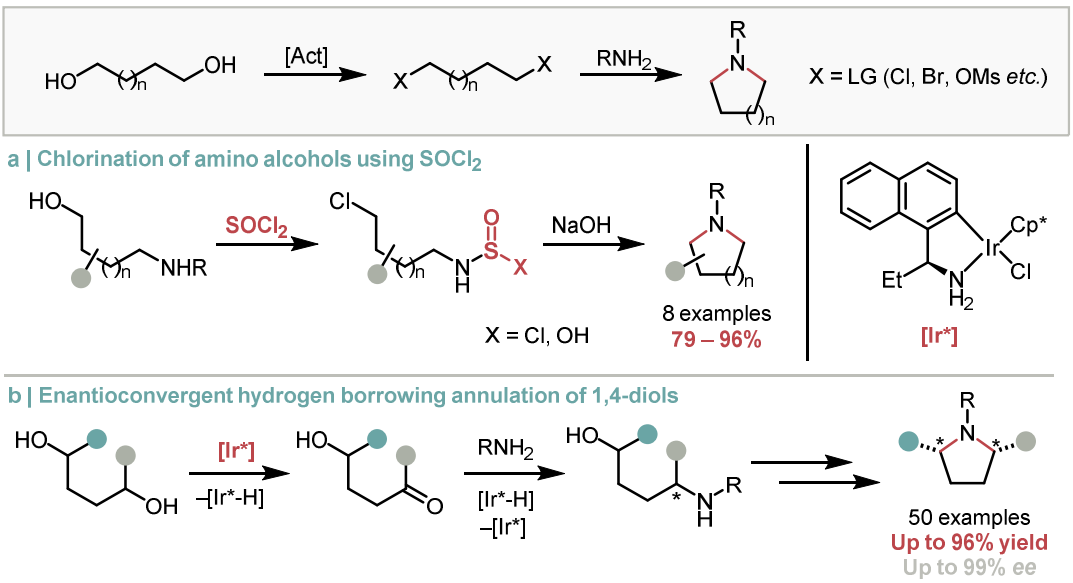


Scheme 1. Approaches to azacycles *via* an acyclic precursor (a), or derivatisation of a pre-existing heterocycle (b).

1.2.1 Nucleophilic substitution reactions

The simplest approach considered is the nucleophilic displacement of an internal electrophile *via* an S_N2 by a pendent amine (**Scheme 2**).[7] Traditionally this method requires the use of an activated leaving group, such as a halide, which can either be formed from the corresponding alcohol prior to the reaction or *in situ* as exemplified in the report by Xu and co-workers where $SOCl_2$ is used to chlorinate an amino alcohol giving the corresponding amino chloride during the reaction.[8] Treatment with base then leads to the cyclic amine (**Scheme 2a**).

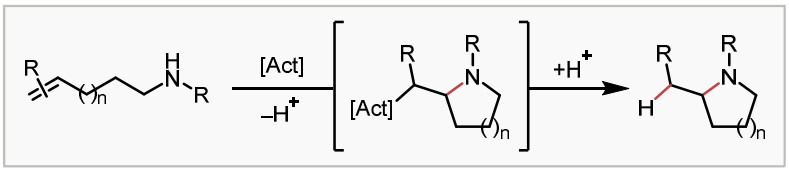
Instead of carrying out an indirect cyclodehydration, methods which use an alcohol directly have also been reported, including recent work by Zhao and co-workers who used a chiral iridium catalyst to carry out a 'hydrogen-borrowing' reaction (**Scheme 2b**).[9] Here a diol is oxidised to the corresponding ketone, which then undergoes condensation with an amine, the metal hydride generated during oxidation can then 'return' the hydrogen by reducing the imine, giving a secondary amine. The reductive amination sequence is then repeated on the second alcohol *via* an intramolecular condensation.



Scheme 2. Substitution approaches to azacycles *via* displacement of a halide (a) or by hydrogen-borrowing (b).

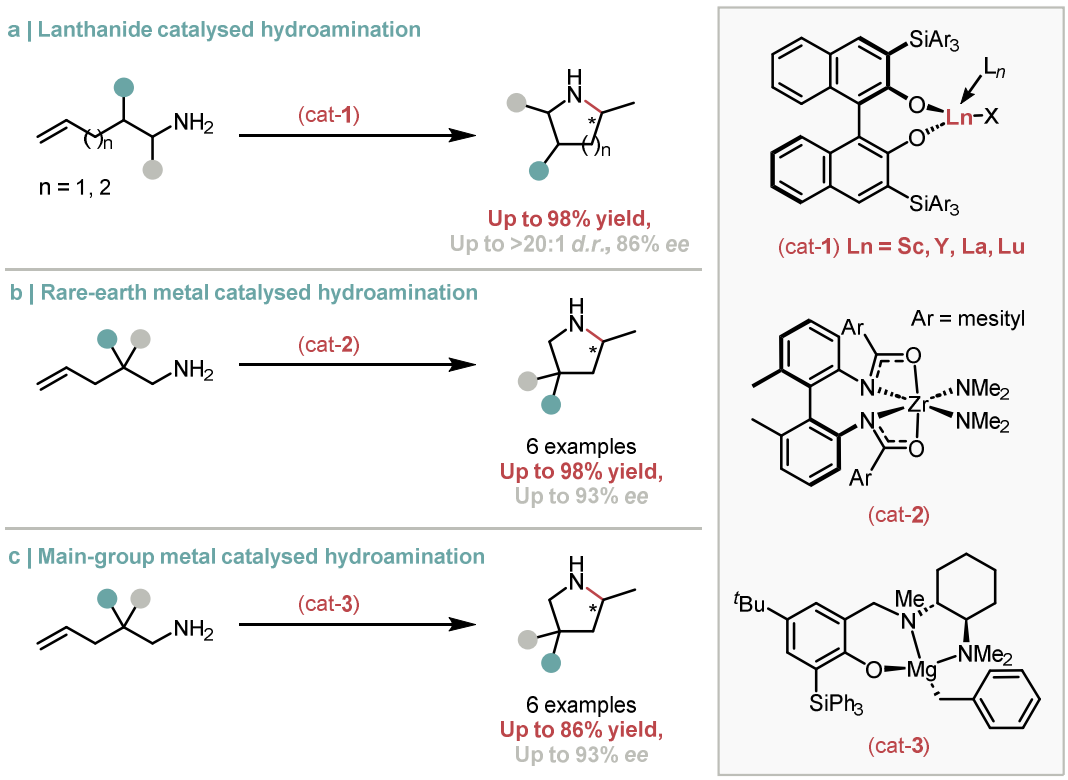
1.2.2 Hydroamination reactions

As an alternative to the activation of a leaving group, activation of a pendent alkene has become a popular method to generate 2-substituted azacycles *via* a hydroamination reaction. When compared to a displacement strategy, this approach is far superior, with 100% atom economy. A range of complementary routes using a catalytic transition metal or a Lewis or Brønsted acid have been established (**Scheme 3**).



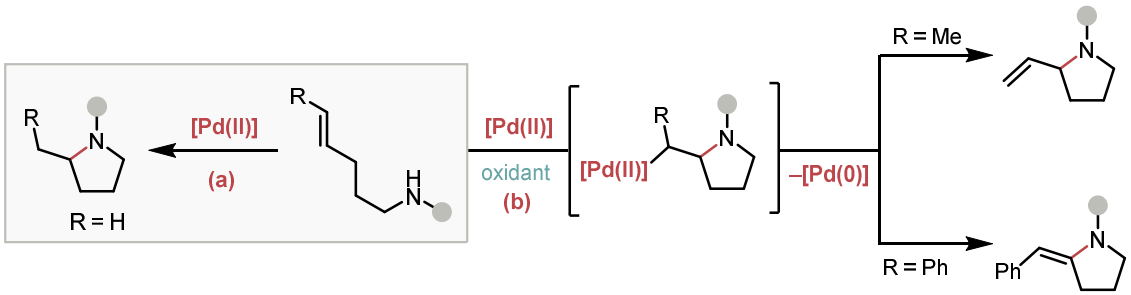
Scheme 3. A hydroamination reaction to form 2-substituted azacycles.

Initially, research into this approach centred heavily on the use of highly air- and moisture sensitive catalysts (**Scheme 4**). For example, lanthanides (cat-**1**), closely related rare-earth metals such zirconium (cat-**2**) and main-group metals including magnesium (cat-**3**) and lithium have all been used as catalysts.[10-12] However, these processes lack the generality to enable wide-scale uptake.



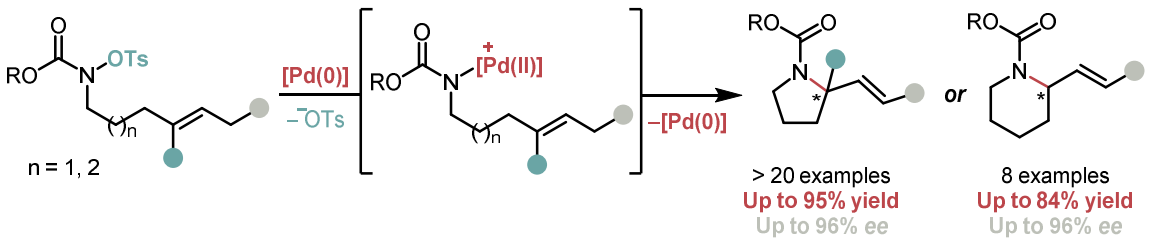
Scheme 4. Representative examples of hydroamination reactions catalysed by highly air- and moisture sensitive catalysts such as lanthanides (a), closely related rare-earth metals (b) and main-group metals (c).

Conversely, the use of late-transition metal catalysts and, in particular, palladium overcome many of these limitations, with broader functional group tolerance and increased generality.[13] Not only are these catalysts capable of generating the classical 2-methylated products (such as those accessible using the aforementioned catalysts, **Scheme 5a**), but through oxidative processes can engage in other transformations, giving products with additional functionality. For example, Wacker-type oxidative cyclisations using Pd(II) catalysts have been shown to give rise to pyrrolidines bearing an alkene *exo* to the ring (**Scheme 5b**).[14,15]



Scheme 5. Pd-catalysed hydroaminations to access 2-methyl pyrrolidines (a) and 2-olefin substituents (b).

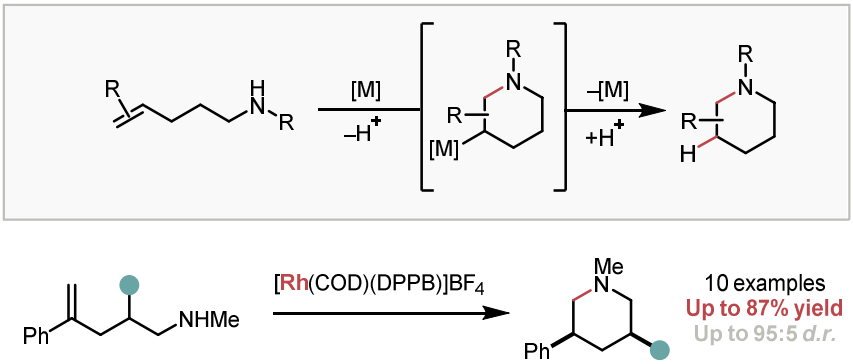
Rather than using an external oxidant, Bower and co-workers demonstrated that the *N*-*O* oxidative addition of a palladium catalyst can enable an enantioselective aza-Heck cyclisation (**Scheme 6**).[16] The synthesis of 2,2-disubstituted azacycles is possible through introduction of additional substituents onto the olefin. In addition, this report offers a rare example of a method which can access both 5- and 6-membered cycles, although the authors do comment on the additional challenges faced when extending the methodology to include piperidine examples, requiring re-optimisation of the chiral ligand to a less bulky phosphoramidate.



Scheme 6. Enantioselective aza-Heck cyclisations of *N*-(tosyloxy)carbamates.

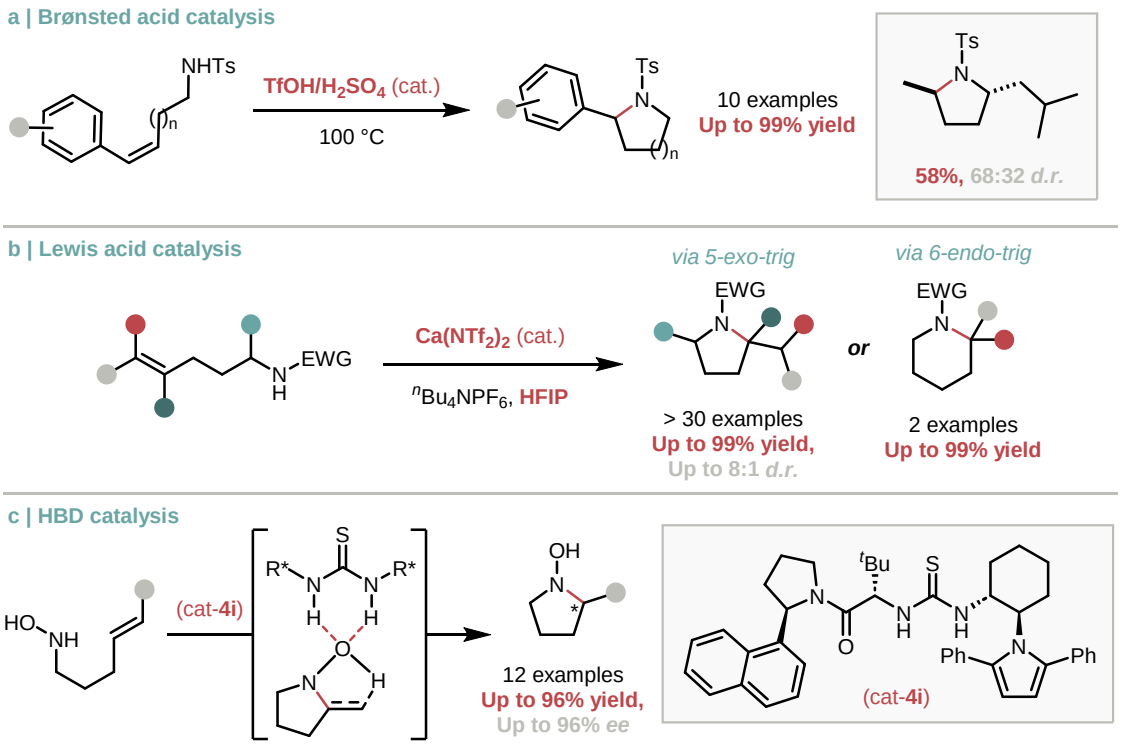
While Markovnikov 5-*exo*-*trig* cyclisations are well known, anti-Markovnikov 6-*endo*-*trig* cyclisations are limited, with only one transition metal catalysed approach reported by Hartwig and co-workers using a rhodium catalyst which is known to be selective in *inter*molecular transformations (**Scheme 7**).[17]

Subsequently further *endo-trig intra*molecular hydroaminations have been reported using photoredox catalysis including examples by Nicewicz and Hyster, however, this reactivity mode continues to remain more elusive than the corresponding *exo-trig* cyclisation.[18,19]



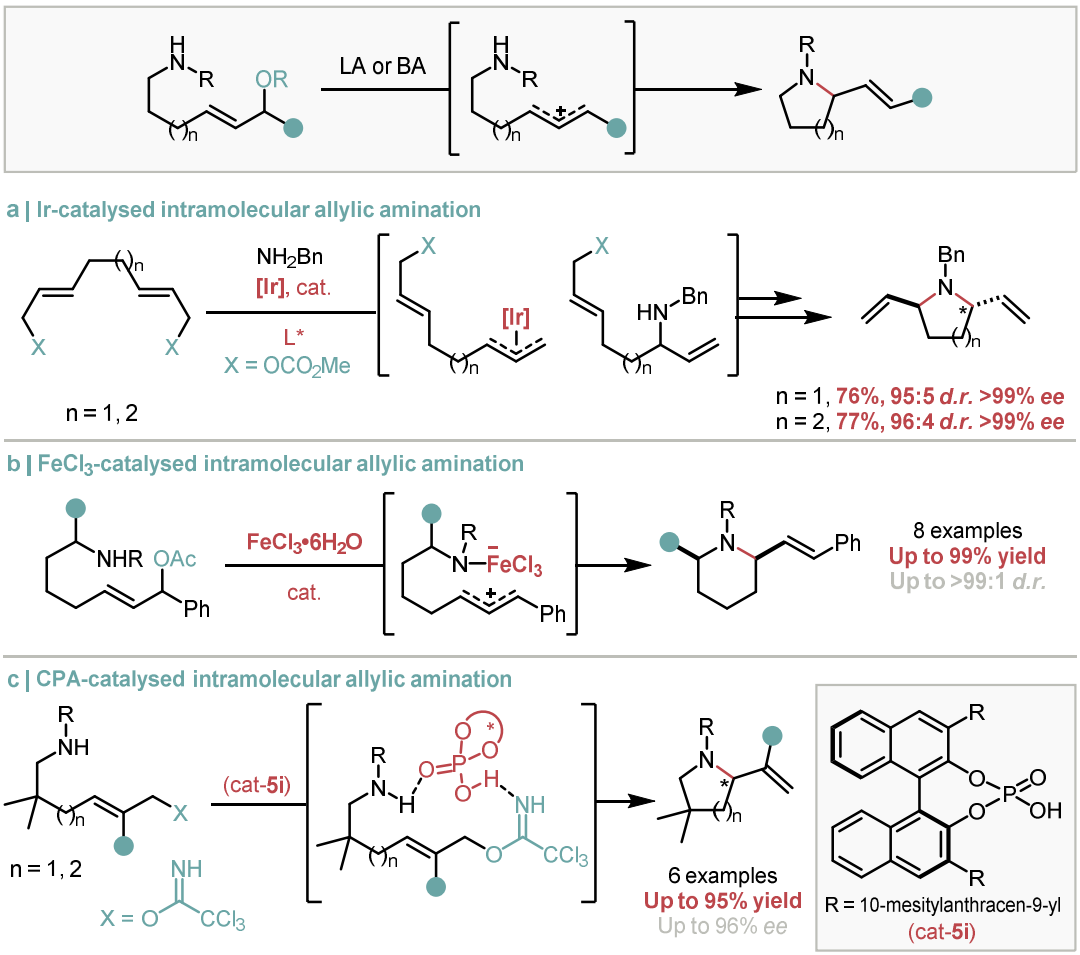
Scheme 7. Rhodium catalysed anti-Markovnikov hydroamination.

The scope of hydroaminations catalysed by traditional Brønsted and Lewis acids is smaller than what is possible using a late-transition metal catalyst, particularly when considering the formation of more complex azacycles. The conditions required for Brønsted acid catalysed processes are often too harsh, hindering the synthetic utility. For example, the 2002 report by Hartwig and co-workers employed either triflic or sulfuric acid at 100 ˚C for the preparation of 2-aryl azacycles and when additional substituents were introduced the diastereoselectivity was poor (**Scheme 8a**).[20,21] Lewis acids are often cited as insufficiently reactive to catalyse hydroamination reactions, however, Lebœuf and co-workers reported the use of a calcium (II) salt in combination with hexafluoroisopropanol (HFIP) as the solvent to increase activity.[22] This enabled the hydroamination of unactivated alkenes, accessing both pyrrolidines and piperidines depending on the nature of the alkene substituents (**Scheme 8b**). Recent years have seen the emergence of hydrogen-bond donor (HBD) catalysts, which typically activate electrophiles by binding to a leaving group, generating a stabilised ion pair (see **Section 1.4.2**). Jacobsen and co-workers applied a thiourea HBD catalyst (cat-**4i**) to a retro-Cope elimination of a hydroxylamine, enabling the formation of 2-substituted pyrrolidines with high levels of enantioinduction (**Scheme 8c**).[23]



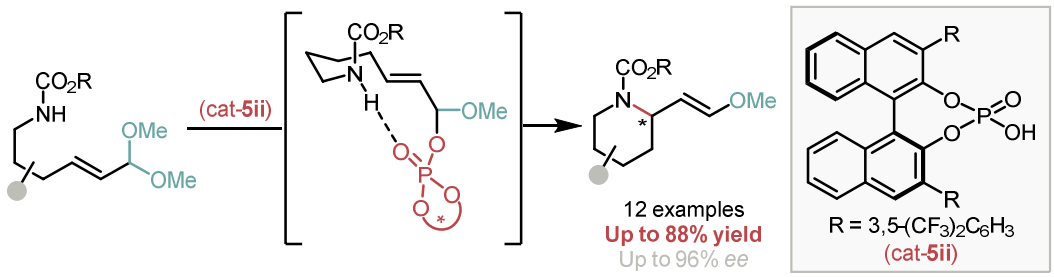
Scheme 8. Examples of azacycles synthesised using a Brønsted acid (a), Lewis acid (b), or HBD catalyst (c).

Rather than addition across a simple alkene, introduction of an α-hydroxy substituent enables addition of the amine to an allylic carbocation, giving products analogous to the aza-Heck reaction previously described (**Scheme 6**). This approach has been demonstrated with transition-metal catalysis along with both Brønsted and Lewis acid catalysis (**Scheme 9**). Intramolecular variants of Tsuji-Trost type allylic aminations have been successfully demonstrated with palladium and iridium catalysts as exemplified by Helmchen and co-workers, who carried out a double allylic substitution to form 2,5-vinyl substituted pyrrolidines and piperidines in excellent enantioselectivities (**Scheme 9a**).[24] Instead of using a carbonate leaving group, the Lewis acid catalysed process reported by Cossy and co-workers used an acetoxy group to enable the iron (III) catalysed synthesis of 2,5-*cis* disubstituted piperidines (**Scheme 9b**).[25] Finally, the use of a BINOL-derived chiral phosphoric acid (CPA, cat-**5i**) enabled an asymmetric Brønsted acid catalysed transformation as reported by Yamada and co-workers (**Scheme 9c**).[26] Mechanistically, this reaction proceeds *via* a S_N2' displacement of the trichloroacetimidate active alcohol instead of *via* formation and trapping of an allylic carbocation.



Scheme 9. Allylic aminations to synthesis 2-vinyl substituted azacycles using an Ir (a), Lewis acid (b) and Brønsted acid (c) catalyst.

Alternative CPA catalysed hydroaminations have been disclosed using starting materials with different functionality, for example introduction of a pendent unsaturated acetal unit enabled Nagorny co-workers to synthesise 2-substituted enol ether piperidines in high levels of enantioselectivity (**Scheme 10**).[27] Computational studies suggest a two-step mechanism whereby the CPA (cat-**5ii**) forms a mixed chiral phosphate acetal prior to an S_N2'-like displacement.

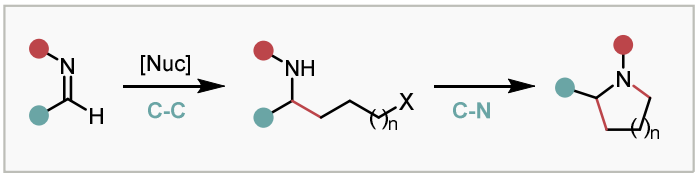


Scheme 10. Asymmetric synthesis of piperidines *via* a chiral mixed phosphoric acid acetal.

While both displacement and hydroamination strategies have been used in the synthesis of a range of azacycles, both are linear in character *i.e.* all of the substituents have to be installed in the acyclic precursor prior to cyclisation. As such, the accessibility of highly substituted azacycles is still limited given the requirement for a lengthy substrate synthesis, rather than one acyclic precursor being used to generate a variety of structures, requiring a C-C bond to form concomitantly to the C-N bond.

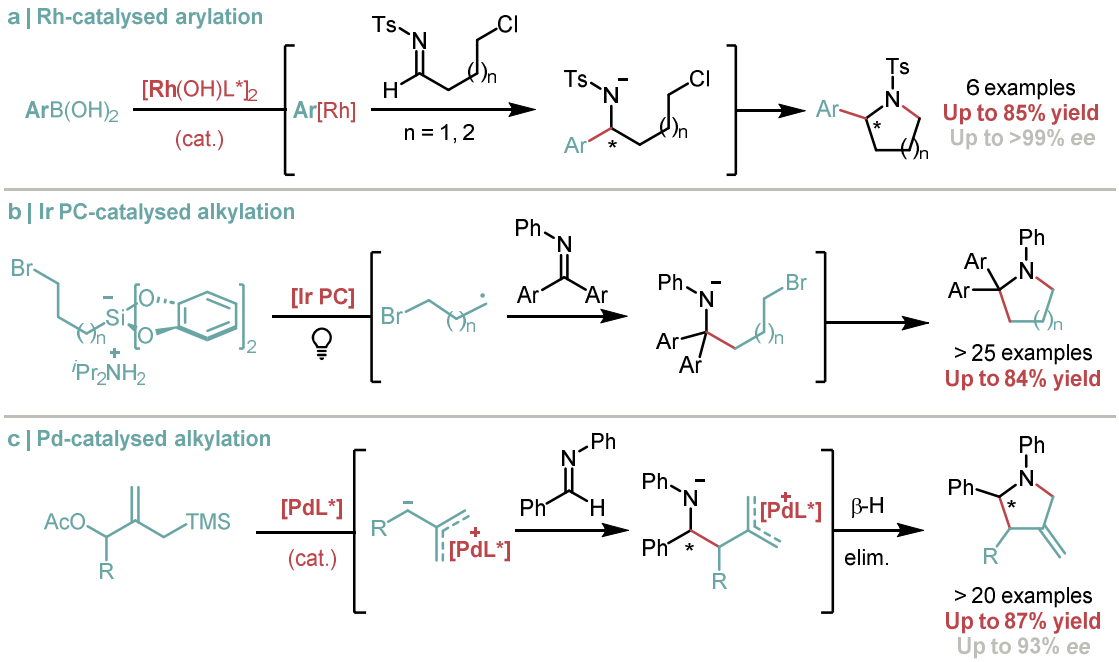
1.2.3 Azacycles *via* a 1,2-addition into imines

The reactions described so far have utilised a similar reaction framework, with the amine acting directly as a nucleophile, however, the use of an imine in the place of an amine enables additional reactivity. Here the nucleophilic amine is masked within the electrophile and can only be released following 1,2-addition, meaning the more challenging C-C bond is formed prior to the C-N bond formation (cyclisation) step (**Scheme 11**).



Scheme 11. 1,2-addition to an imine followed by cyclisation.

The 1,2-addition into imines is well established and application to the synthesis of azacycles simply relies upon the addition of pendent functionality which can be displaced/activated following the unmasking of the nucleophile. Representative examples include the work by Lin and co-workers who used a rhodium catalyst to arylate *N*-tosylimine with a boronic acid, with the following cyclisation generating a 2-aryl azacycle (**Scheme 12a**).[28] Whilst this approach has the pendent chloride pre-installed on the imine component, introduction of a halide on the nucleophilic component is also possible, as demonstrated by Molander and co-workers (**Scheme 12b**).[29] A silicate radical precursor is treated with an iridium photocatalyst (PC) to generate an alkyl radical which can react with the imine. The resulting *N*-radical then undergoes SET reduction to an anion prior to cyclisation, once again generating a 2-substituted azacycle. This approach is not limited to cyclisation *via* displacement of a halide, as exemplified by Trost and co-workers (**Scheme 12c**).[30] Here, following addition to the imine, the anionic amine attacks a palladium allyl complex, generating a pyrrolidine with an exocyclic alkene.



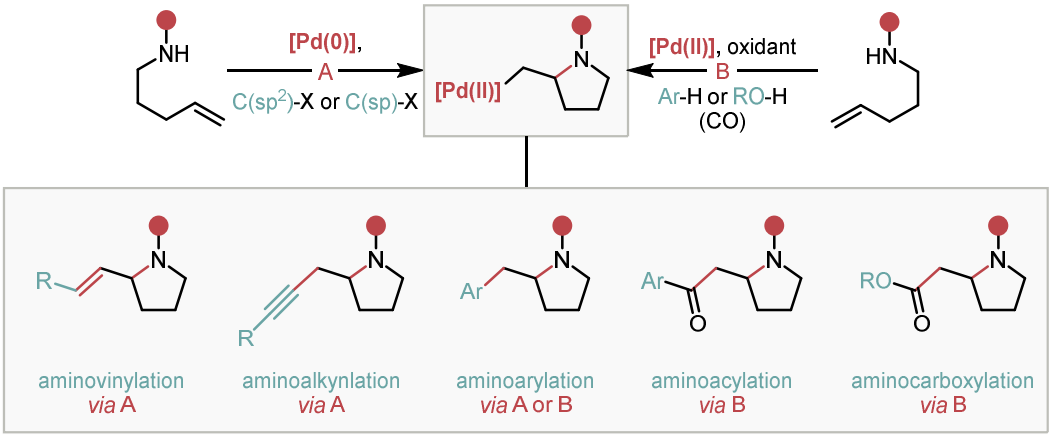
Scheme 12. Representative imine addition cyclisation cascades using Rh-catalysed arylation (a), Ir-photoredox alkylation (b) and Pd-catalysed alkylation (c).

This approach disconnects back to two similarly sized fragments, offering two opportunities to introduce additional substituents into the backbone of the ring. Imines are ideal starting materials; formation from the corresponding carbonyl compound is easy with the synthesis of substituted carbonyl compounds well developed in the literature. Unfortunately, this approach is limited by the reactivity of the nucleophile, and whereas hydroamination proceeded *via* activation of an alkene or allylic alcohol, addition into an imine requires the use of nucleophiles with poor atom economy.

1.2.4 Carboamination

Complementary to hydroamination reactions, carboamination approaches are a straightforward way to prepare azacycles, this time with the concomitant formation of a C-C bond in addition to the C-N bond. However, unlike the hydroamination approach which could be catalysed by both transition metals and Lewis/Brønsted acids, the carboamination approach is limited to late-transition metal catalysis. This cyclisation always proceeds *via* a 5-*exo*-*trig* addition introducing a substituent in the 2-exo position. Much of the work in this field is owed to early research by Wolfe and co-workers who have published extensively in this area, exploring the palladium-catalysed carboaminations of γ-aminoalkenes with aryl halides to access a range of substituted pyrrolidines (**Scheme 13**).[31] Despite numerous reports in this

area, at no point are the syntheses of piperidines disclosed in their work. Much like the oxidative palladium-catalysed hydroamination reactions, extension of carboamination approaches to introduce additional functionality has been carried out. For example, amination-Heck-type (aminovinylation) coupling cascades have been disclosed along with aminoalkynlation reactions.[32-33] Finally, amino-acylation and carboxylation are possible using a Pd(II) catalyst and an external oxidant.[34] Although this approach has been well explored using palladium, other transition metals have also been utilised.[35]



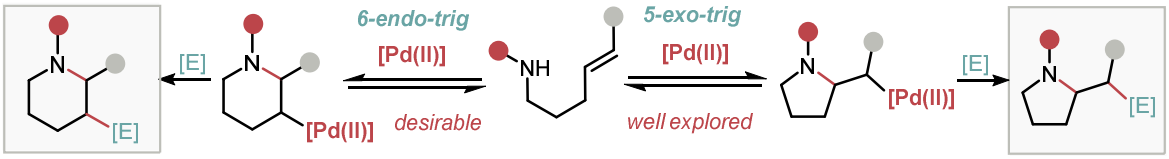
Scheme 13. Various carboamination approaches accessible through use of a palladium catalyst.

Although using a carboamination has been recognised as a powerful approach to access functionalised azacycles, the current literature has three notable weaknesses:

1. The transformations rely on late-transition metal catalysis.
2. 5-*exo-trig* cyclisations do not introduce substituents in other positions on the ring.
3. Piperidines are rarely synthesised *via* this approach.

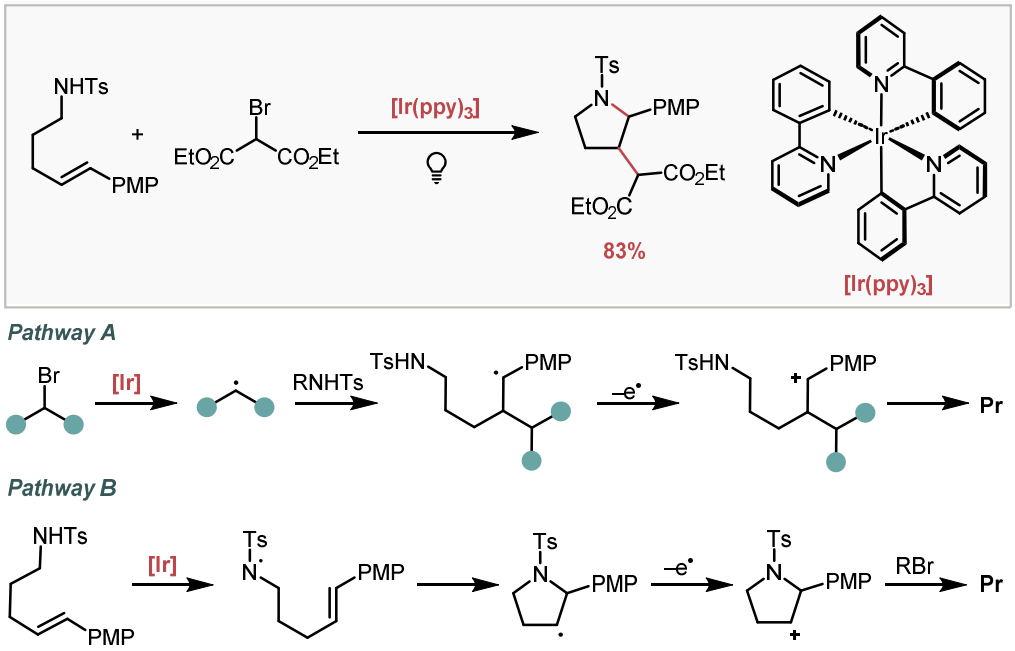
All three points are closely related, generally, 5-*exo-trig* cyclisations are preferred to the alternative 6-*endo-trig* cyclisation when a palladium catalyst, or other related metals (e.g. Cu, Ni, Rh) are used. Although, both modes of carbopalladation satisfy orbital overlap requirements, the reversibility of the carbopalladation means the less sterically congested 5-*exo-trig* palladium complex is preferred, and products deriving from a 6-*endo-trig* carbopalladation are observed only in rare cases with strong substrate bias (**Scheme 14**).[36] This means that not only are piperidines inaccessible from γ-aminoalkenes but that 3-substituents cannot be introduced in the ring using this approach. Finally, the corresponding 5-*endo-trig* cyclisation required to access 3-substituted pyrrolidines is 'disfavoured' according to Baldwins rules,

owing to the geometric constraints of the reactive functional groups not being able to achieve the Burgi-Dunitz angle.[37]



Scheme 14. 5-*exo-trig* vs. 6-*endo-trig* carbopalladations.

While 5-*endo-trig* reactions being disfavoured potentially prevents the use of transition metal catalysis for this transformation, Baldwin's rules are known to relax when a process is cationic, making Lewis and Brønsted acid catalysed 5-*endo-trig* cyclisations viable.[38] Although this approach has been successfully applied to the synthesis of other ring systems, examples which enable the formation of 3-substituted pyrrolidines remain limited. One example is the radical process 2015 report by Xia and co-workers using an iridium photocatalyst to enable a 5-*endo-trig* carboamination, introducing a malonate ester at the three position (**Scheme 15**).[39] The authors propose two potential pathways based on mechanistic studies, either: generation of a radical from cleavage of the bromide, followed by addition to the olefin, oxidation of the benzylic radical and then cyclisation (pathway A) or generation of a *N*-centered radical, followed by cyclisation, oxidation of the benzylic radical and reaction with the electrophile (pathway B). Both pathways proceed *via* a benzylic carbocation and there is no reason to suggest a comparable fully cationic transformation would not be possible *i.e.* through generation of a carbocation using a Lewis or Brønsted acid catalyst. Further investigations into this transformation are desirable, requiring the careful consideration of state-of-the-art methods to generate and stabilise a carbocation.



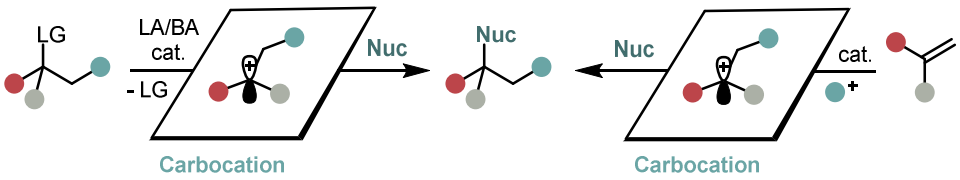
Scheme 15. Difunctionalisation of an electron-rich styrene *via* a 5-*endo-trig* cyclisation.

1.3 Carbocations in C-C bond forming reactions

1.3.1 Historical importance of carbocations in synthesis

Carbocations have long been recognised as potent intermediates to be harnessed in C-C bond forming reactions, and have found many applications both in industrial and academic chemistry, since being initially proposed by Meerwein in 1922.[40] Long before the carbocation was known, powerful reactions which proceed *via* a carbocation had been described, including early examples such as Friedel-Crafts alkylations, Pinacol rearrangements, and acid-catalysed polymerisation of olefins. Together, these three examples demonstrate the broad range of reactivity available through the generation of a carbocation with many alkylation, rearrangement and cascade reactions still relying heavily on carbocations today.[41]

Traditionally carbocations have been made using one of two strategies, either by activation of a leaving group or by addition of an electrophile across an olefin (**Scheme 16**). Of course, the substituents on this carbocation can vary, however, those adjacent to an aryl or alkene system have found the most general synthetic applications, owing to the increased stability from conjugation which ensures the carbocation can survive long enough to undergo reaction.



Scheme 16. Traditional approaches to form carbocations.

Despite the widespread application of carbocations within synthetic chemistry, the use of carbocations in complex target synthesis and asymmetric catalysis is comparably limited. This is likely a result of the harsh methods historically required to generate a carbocation, with conventional approaches typically engaging a strong Lewis or Brønsted acid catalyst, which, in turn limits the scope of the nucleophile that can be used. However, in recent years, several new approaches for the formation and stabilisation of carbocations have been established, suggesting that, despite often being seen as 'too reactive', the synthetic community remains interested in employing carbocations.

1.4 Contemporary methods to generate carbocations

1.4.1 Lewis acid catalysis

Despite the development of new classes of Lewis acids such as Boronic acids, the broad synthetic utility of these new classes remains to be seen and traditional Lewis acids continue to be the catalyst of choice for most transformations.[42] Although a diverse range of catalysts exist, if the electrophile is unreactive the requirement to use a strong Lewis acid remains, resulting in poor functional group tolerance. For example, strong Lewis acids are inherently incompatible with Lewis basic functionality which sequesters the catalyst, and as such examples using both in combination are severely limited.[43] One approach which by-passes this incompatibility is the introduction of a sacrificial reagent which can interact with the basic functionality, without effecting the reactivity of the Lewis acid. In fact, this method has already been discussed: the calcium (II) catalysed hydroamination reaction in HFIP (see **Section 1.2.2, Scheme 8b**) reported by Lebœuf and co-workers.[22] This transformation is one of many which cites the properties of HFIP as essential to enabling reactivity.

The last decade has seen the popularity of HFIP grow considerably, going from an obscure solvent to one included as standard during reaction optimisation, as reflected in the number of published reports featuring HFIP (**Figure 2**).[44] This success is, in turn, owed to the rare combination of intrinsic properties

which HFIP exhibits, allowing HFIP to not only find use as a solvent but as a promoter, (co)-catalyst or activator in many areas of organic synthesis.

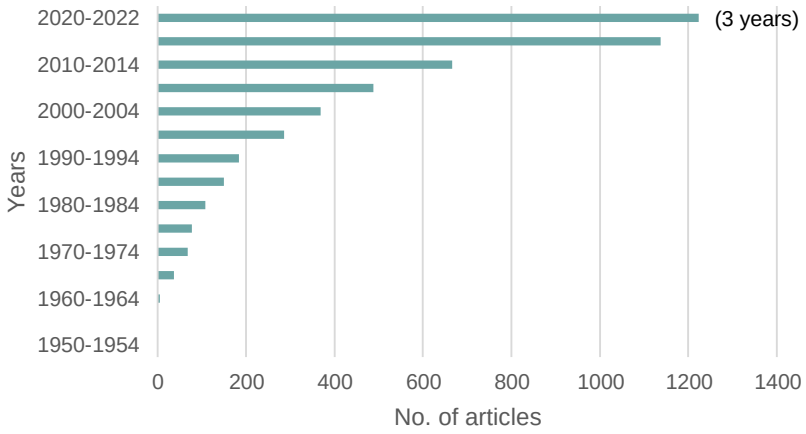


Figure 2. No. of articles that use HFIP by year (source: SciFinder).

Although the popularity of HFIP is often attributed to the cation stabilising ability, key studies by Berkessel and co-workers dispel this assumption, and is widely known that the behaviour of HFIP is often far more nuanced.[45] Extensive studies into the experimental properties of HFIP have been carried out, enabling a quantitative overview of the effect of the trifluoromethyl groups by direct comparison with isopropanol (*i*PrOH) (**Table 1**). These values can be broadly summarised as followed:

- HFIP shows **enhanced Brønsted acidity** and is > 10^7 times more acidic than *i*PrOH with an acidity scale (the acidities achievable in a given solvent i.e. for when a reaction is not carried out in aqueous media) in the same order of magnitude as water.
- The **reduced nucleophilicity** coupled with the high polarity means HFIP is a superior solvent for the generation and investigation of cationic species, however, whether HFIP stabilises cations (thermodynamic) or enables cations to persist for long enough to react (kinetic) is still not fully understood.
- HFIP is a **strong hydrogen-bond doner** but a poor hydrogen-bond acceptor. The donor ability of HFIP is enhanced by the formation of a H-bond network between molecules (predominantly as the dimer and trimer). HFIP is also known to form clusters with Lewis bases, including secondary and tertiary amines.

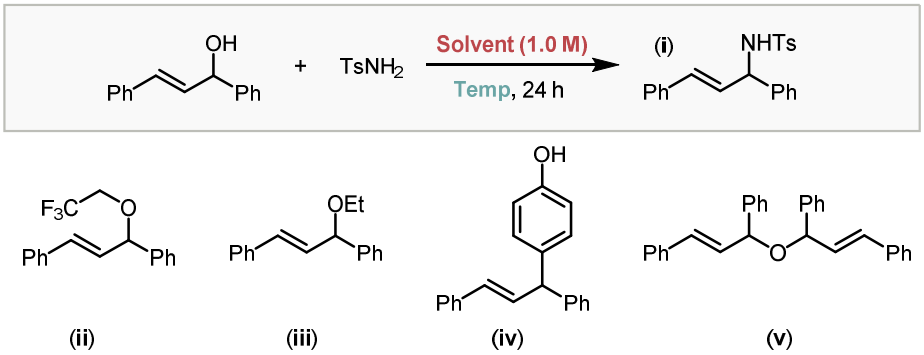
Table 1. Properties of ^{i}PrOH and HFIP.

Properties	^{i}PrOH	HFIP
pK_a (H_2O)[46,47]	17.1	9.3
dielectric constant (ε)[48]	19.4	16.7
polarity (E_T^N)[49]	0.546	1.608
nucleophilicity ($N_{t\text{-BuCl}}$)[50]	0.09	–3.93
ionising power ($Y_{t\text{-BuCl}}$)[50]	–2.73	2.46
dipole moment (μ)[48]	1.68	2.05
hydrogen-bond donor acidity (α)[51]	0.76	1.96
hydrogen-bond acidity (α_1)[52]	0.53	1.86
hydrogen-bond acidity (α_2^H)[47]	0.324	0.771
hydrogen-bond acceptor basicity (β)[51]	0.95	0.00
hydrogen-bond basicity (β_1)[52]	0.68	0.16

These properties are often cited to have varying degrees of contribution depending on the transformation; however, it is not uncommon for authors to report challenges with establishing the exact role of HFIP. The use of HFIP has been the subject of several comprehensive reviews, however, only those transformations related to the generation of a carbocation in the presence of a Lewis basic amine will be discussed here.[53]

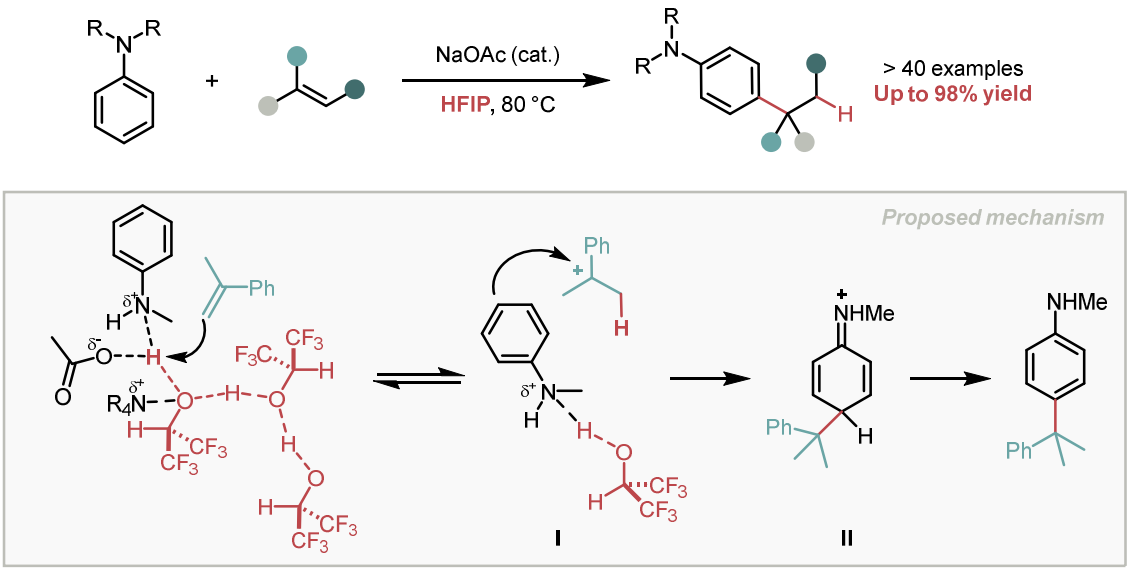
HFIP is known to catalyse reactions in the absence of a catalyst, acting as the sole promoter for a range of transformations, as exemplified by Nájera and co-workers, in the substitution of allylic alcohols with a range of nucleophiles, including sulfonamides, carbamates, carboxamides and anilines along with silylated nucleophiles and 1,3-dicarbonyl compounds (**Table 2**).[54,55] The reaction between (*E*)-1,3-diphenyl-2-propen-1-ol and tosyl amine in HFIP gave the desired substituted product **(i)** in high yields, however control reactions with other alcohol solvents during optimisation generally gave undesired reactivity (products (**ii**) – (**v**)).

Table 2. Solvent screen during the allylic substitution of an alcohol with tosylamine.



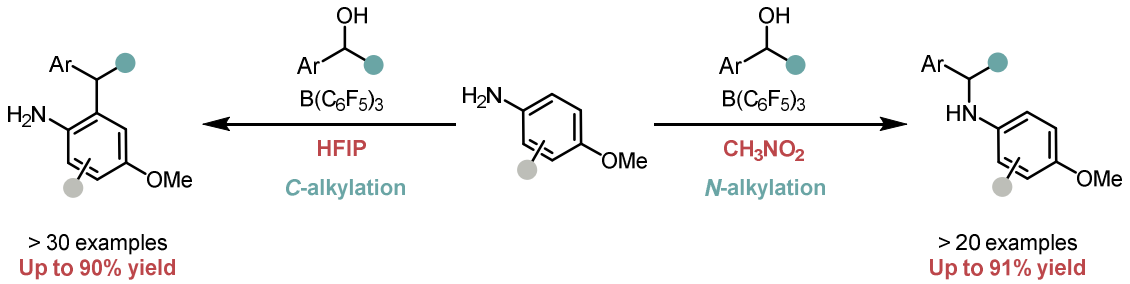
Entry	Solvent	Temp (°C)	Product	Product ratio
1	HFIP	50	**(i)**	>95
2	TFE	50	**(i)**/**(ii)**	84:16
3	TFE	70	**(i)**	>95
5	EtOH	70	**(iii)**	>95
6	PhOH	70	**(iv)**	>95
7	H_2O	70	**(v)**	90

In 2020, Colomer, employed HFIP as the solvent in the hydroarylation of an alkene using an aniline (**Scheme 17**).[56] Mechanistic studies led the author to propose a reaction pathway whereby a stable carbocationic intermediate **I** is formed from an alkene in HFIP, before reaction with the aniline, the Wheland intermediate **II** then undergoes rearomatisation. The amino group is 'protected' from *N*-alkylation by hydrogen bonding to the HFIP network.



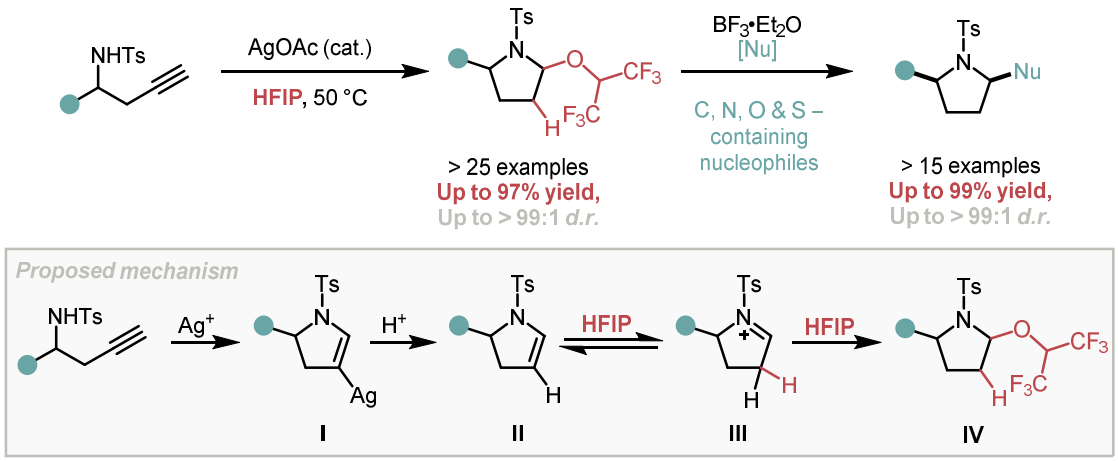
Scheme 17. Hydroarylation reaction in HFIP.

The *N*-'protection' effect is consistent with the chemoselective alkylation of anilines reported by others, including Chan and co-workers.[57,58] When HFIP is used as the solvent exclusively *C*-alkylation is observed, whereas switching to nitromethane as the solvent gives the *N*-alkylated product (**Scheme 18**).



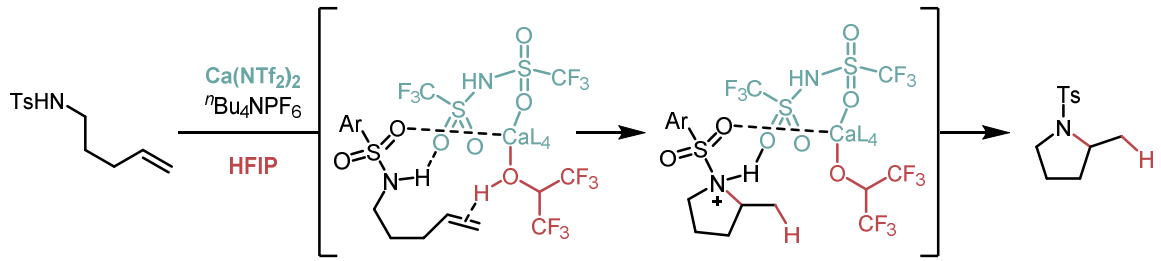
Scheme 18. Solvent dependent *C*- vs. *N*-alkylation using benzylic alcohols.

Despite the poor nucleophilicity of HFIP, Li and co-workers reported a two-step procedure to access 2,5-disubstituted pyrrolidines where the isolated intermediate arises from HFIP behaving as a nucleophilic reactant (**Scheme 19**).[59] The following mechanism is proposed, a Ag-catalyst hydroamination of the homopropargyl amine to generate a vinyl Ag species **I**, which then undergoes proto-demetallation to generate an enamine **II**. The enamine is then protonated using HFIP as the proton source to generate an imine **III** which is subsequently trapped by HFIP **IV**. The hemi-aminal can be isolated or used crude in a subsequent displacement with a range of nucleophiles proceeding with excellent diastereoselectivity. The authors describe the role of HFIP as fourfold: a solvent, proton donor, nucleophile and leaving group.



Scheme 19. A two-step hydroamination, nucleophilic displacement to access 2,5-disubstituted pyrrolidines.

The aforementioned report by Lebœuf and co-workers (see **Section 1.2.2, Scheme 8b**) is part of a larger area of work exploiting the reactivity a Lewis acid in combination with HFIP.[60] They have utilised $Ca(NTf_2)_2$ and $^nBu_4NPF_6$ in HFIP on numerous occasions and have studied the cooperative effect that the combination imparts. DFT calculations for the intramolecular hydroamination (**Scheme 20**) suggest the calcium has two roles. Firstly, coordinating to HFIP (which increases the Lewis acidity) to enable the protonation of the alkene and secondly bringing the NTf_2 ligand sufficiently close to interact with the N-H on the substrate, leading to increased rigidity of the transition state ultimately enabling cyclisation. Although $Ca(NTf_2)_2$ behaves primarily as a Lewis acid catalyst, mechanistic studies into other related transformations have revealed a potential secondary role, the metal catalyst enhances the Brønsted acidity of HFIP, leading to the formation of higher order aggregates, which could also be considered as active catalytic species *i.e.* hidden Brønsted acid catalysis.[61] Alongside the studies carried out by Lebœuf and co-workers, the Donohoe group has a long-standing history of utilising and studying the properties of HFIP and this work will be detailed in **Chapter 2**.



Scheme 20. Proposed key interactions in the Ca/HFIP enabled hydroamination of γ-aminoalkenes.

While HFIP has successfully enabled the formation of carbocations in a range of transformations, the ability to form strong H-bonds limits the application of HFIP in the formation of chiral cations. Fortunately, other contemporary catalyst systems exist which can be utilised.

1.4.2 Ion-pairing catalysis

The ability to induce enantioselectivity in transformations involving carbocations is intrinsically difficult as biasing the nucleophilic attack onto one of the two prochiral faces of a planar structure is challenging. This is exacerbated by the lack of strong, directional interactions present between a carbocation and a counterion when compared to other modes of catalytic activation through covalent or hydrogen bonding (**Figure 3**). Despite the associated issues, asymmetric counteranion-directed catalysis (ACDC), has

emerged as a powerful approach to induce enantioselectivity in transformations which proceed *via* a carbocation. The success of ACDC is the result of intelligent catalyst design, by recognising that ion-pairing interactions in isolation are insufficient to induce high levels of enantioselectivity. Therefore, pioneers in the field intentionally incorporated secondary structural elements which increase the number of specific attractive or repulsive interactions between substrate and catalyst. The field is subdivided into two: chiral anion-directed catalysis and anion-binding catalysis.[62]

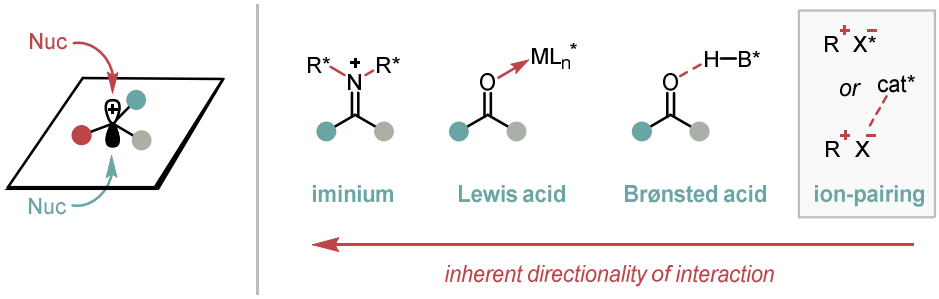
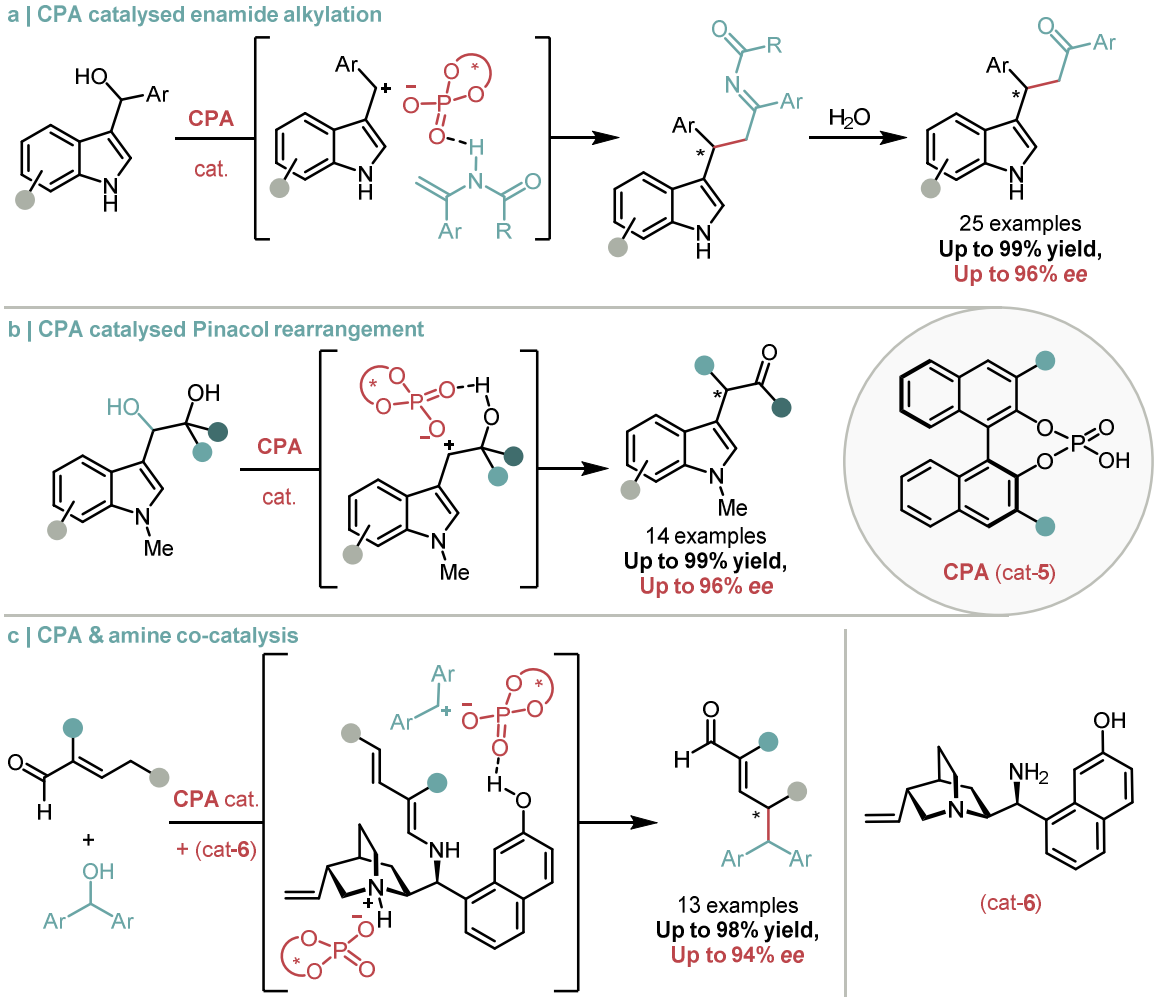


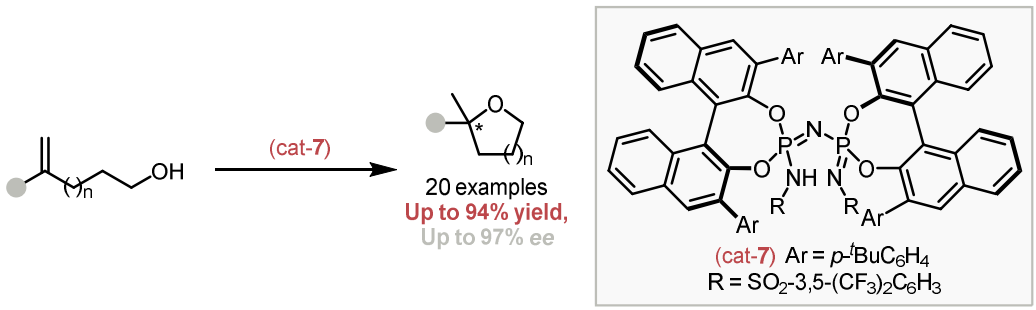
Figure 3. Challenges associated with generating a chiral carbocation (B* – chiral Brønsted acid, X*⁻ – chiral counterion).

Chiral anion-directed catalysis is perhaps best known because of BINOL-derived monophosphoric acids, which since being reported by Akiyama and Terada have become a widely used catalyst class.[63,64] Chiral phosphoric acids (CPAs) are capable of inducing enantioselectivity across a range of classical transformations including Friedel-Crafts (and related) alkylations and Pinacol rearrangements through activation of benzylic alcohols to the corresponding benzylic carbocations.[65] In 2009, Gong and co-workers reported a CPA catalysed alkylation reaction, here a 2-substitured indole benzylic alcohol forms a carbocation *in situ* before undergoing an enantioselective alkylation with an enamide (**Scheme 21a**).[66] Anitalla and co-workers also engaged a 2-substituted indole, here treatment with a CPA resulted in a Pinacol rearrangement generating a ketone (**Scheme 21b**).[67] CPAs can also be used in combination with other forms of organocatalysis and Melchiorre and co-workers reported the use of a CPA-primary amine (cat-**6**) co-catalysis system for the γ-alkylation of α-branched enals with a bis-benzylic alcohol (**Scheme 21c**).[68] In these examples, the carbocation not only forms an ion pair with the catalyst but an additional hydrogen bond is present between the substrate and a Brønsted basic site.



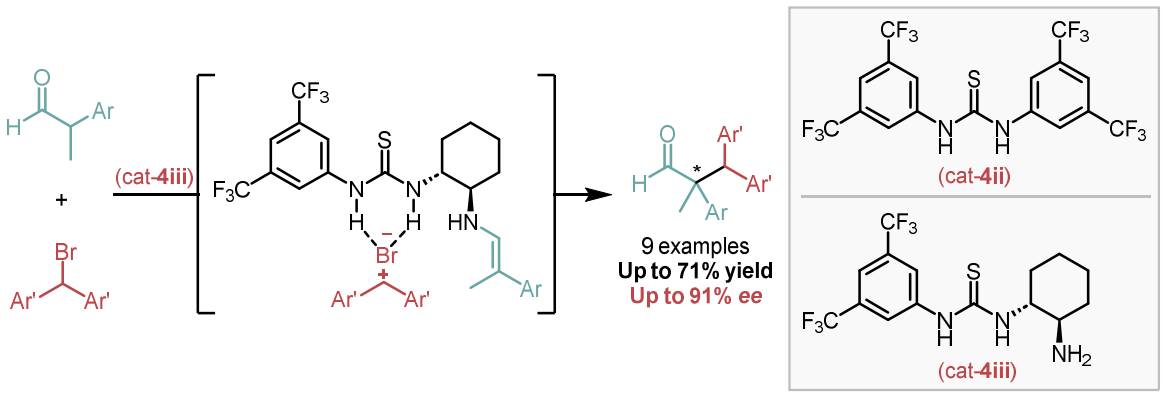
Scheme 21. Representative CPA catalysed reactions going *via* a carbocation including enamide alkylation (a), Pinacol rearrangement (b) and γ-alkylation (c) reactions.

BINOL-derived acid catalysts have also been used in reactions where the substrate lacks large aromatic groups which can sterically bias the system, and here catalyst design is of even greater importance, ensuring a confined pocket for the substrate which limits conformational freedom, thereby increasing selectivity. This has been a research focus for List and co-workers for many years, leading to the development of new catalyst classes such as imidodiphosphorimidate (IDPi) catalysts (cat-**7**).[69] In 2018, List and co-workers reported the application of IDPi catalysts to the hydroalkoxylation of unbiased olefins, giving 1,1-disubstituted tetrahydrofurans (**Scheme 22**).[70]



Scheme 22. IDPi catalysed hydroalkoxylation of unbiased olefins.

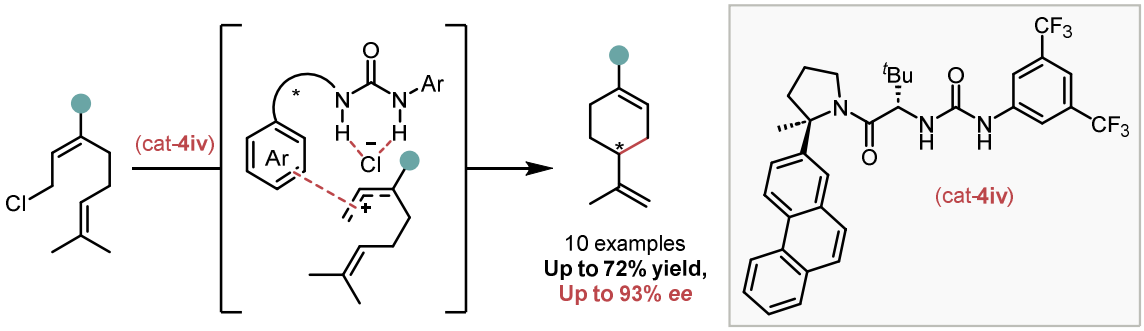
The other type of ACDC, anion-binding catalysis is comparatively less popular, however, chiral dual hydrogen-bond donors (HBDs) have emerged as the most promising class within the area for general applications. The anion-binding concept using ureas and thioureas was initially coined by Schreiner and Kotke, who employed an electron deficient thiourea (now known as Schreiner's catalyst cat-**4ii**).[71] Following this initial discovery, inclusion of chiral side chains enabled the application of the catalyst class to asymmetric catalysis. Many of the transformations which utilise this catalyst class have been carried out in the Jacobsen group, including the first report of a non-heterostabilised carbocation in an aldehyde alkylation reaction (**Scheme 23**).[72] The thiourea catalyst (cat-**4iii**) not only activates the bis-benzylic bromide, forming a carbocation but the pendent amine undergoes a condensation with the aldehyde to generate an enamine, which can then undergo α-alkylation.



Scheme 23. Enantioselective α-alkylation of aldehydes using a HBD catalyst.

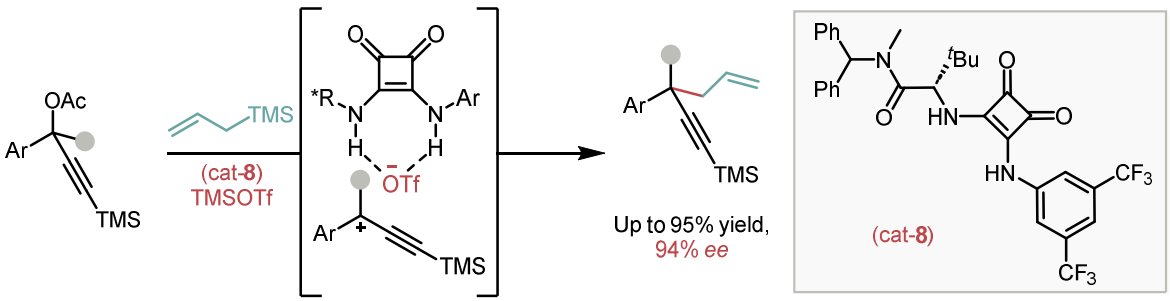
The ability to covalently bind a substrate to one component of the catalyst through incorporation of a secondary structural element is not always possible and alternative modes of interaction are required of the catalyst in these cases. This was demonstrated by Jacobsen and co-workers in the cyclisation of neryl chloride analogues (**Scheme 24**).[73] Kinetic analysis concluded that the phenanthrene aromatic system in

urea (cat-**4iv**) enabled stabilizing aromatic interactions which were at least partially responsible for enantioinduction.



Scheme 24. HBD catalysed cation-triggered cyclisation.

Although the generality of HBDs is less than that of CPAs, the ability to vary the catalyst framework and use other activated electrophiles, no doubt means that in the future more HBD catalysed processes will be disclosed. Such variations in reaction design are exemplified by the 2018 report by Jacobsen and co-workers, here rather than a (thio)urea, a squaramide derived catalyst (cat-**8**) provides the hydrogen bond donors, enabling an asymmetric allylation of propargyl acetates (**Scheme 25**).[74]

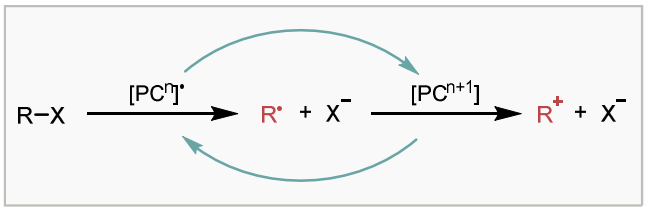


Scheme 25. Squaramide derived HBD catalyst for the generation of quaternary stereocentres.

Although other catalysts to generate chiral carbocations exist, asymmetric counteranion-directed catalysis (ACDC) presents the most general strategy available in the literature.

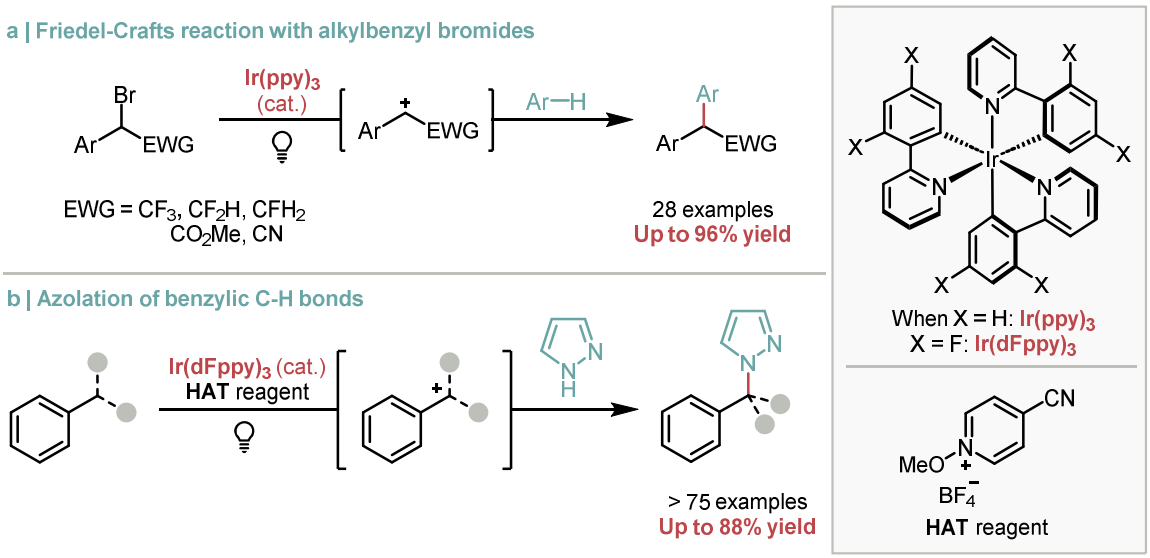
1.4.3 Radical processes

Although the majority of the ways to generate carbocations focus on the use of Lewis and Brønsted acid catalysis, one alternative strategy is to generate a carbocation *via* single electron oxidation of a radical (**Scheme 26**).[75] The biggest challenge here is to ensure that the highly reactive radical intermediates does not undergo side reactions (such as homocoupling and hydrogen abstraction) prior to oxidation.



Scheme 26. A radical approach to generate carbocations.

Despite these challenges, this approach has been successfully carried out using photoredox catalysis. For example, Hu and co-workers reported a photoredox-mediated Friedel Crafts alkylation where they indicate that a cation is generated from a benzyl bromide using the iridium photocatalyst (**Scheme 27a**).[76] The advantage of photoredox catalysis is that it enables the cleavage of bonds which are un-touched by traditional acid activation, for example benzylic C-H bonds, as demonstrated by Musacchio and co-workers (**Scheme 27b**).[77] They showed that secondary and tertiary benzylic sites could be activated using an iridium PC to give the corresponding carbocation, which could be intercepted by an azole. Finally, the carboamination reported by Xia and co-workers (see **Section 1.2.4, Scheme 15**) also uses photoredox catalysis to generate a carbocation.[39]



Scheme 27. Representative examples of photoredox catalysis to generate carbocations including a Friedel-Crafts alkylation (a) and azolation of a benzylic C-H bond (b).

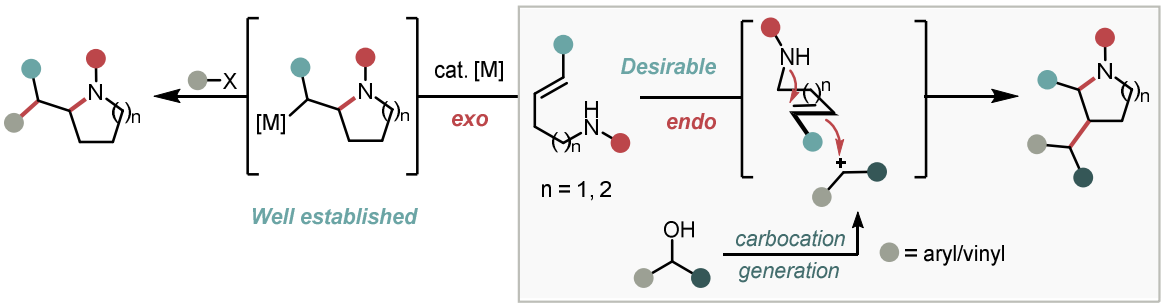
The three approaches covered, namely HFIP assisted Lewis acid catalysis, ion-pairing catalysis and photoredox catalysis offer the most potential for application in a cation-triggered *endo-trig* cyclisation to access piperidines and pyrrolidines.

1.5 Summary and thesis aims

Through reviewing state-of-the-art methods to access azacycles, it is clear that one key limitation prevails, namely the lack of approaches which introduce multiple substituents around the ring, and a general method remains desirable. One approach which offers the most potential is an *endo-trig* rather than *exo-trig* carboamination. Carboamination reactions share a number of advantages, being able to simultaneously generate a C-C and C-N bond in a single step is beneficial, and use of an external electrophile is preferable, providing it can be obtained commercially, negating the need to synthesise both precursors. Whilst methods catalysed by a late-transition metal are well established, the potential to use alternative catalyst system which does not share the strong inherent preference for an *exo-trig* reaction would enable the more useful 5- and 6-*endo*-trig cyclisation. Cationic approaches were proposed as a viable alternative.

Consideration of the contemporary methods available to generate a carbocation revealed not only mild-Lewis acid approaches mediated by HFIP as a potential catalyst system but ion-pairing catalysis as a feasible route to introduce asymmetry into the approach. Fortunately, both methods have been successfully demonstrated with alcohol electrophiles, which in combination with a carboamination annulation would lead to the generation of azacycles with water as the sole by-product.

The objective of the research described in this thesis was to design and develop a novel cation-triggered annulation to access both pyrrolidines and piperidines. It was key to our method that piperidines were accessible, despite being more prevalent in active pharmaceuticals than pyrrolidines, the number of methods which disclose the synthesis of the larger ring are notably lacking. Initial focus centres on the development of a diastereoselective transformation, and once the limits had been discovered, building on this approach to develop an enantioselective transformation, with both reactions proceeding *via* activation of an alcohol electrophile (**Scheme 28**).



Scheme 28. The key aim of this research.

2

Lewis acid catalysed synthesis of azacycles

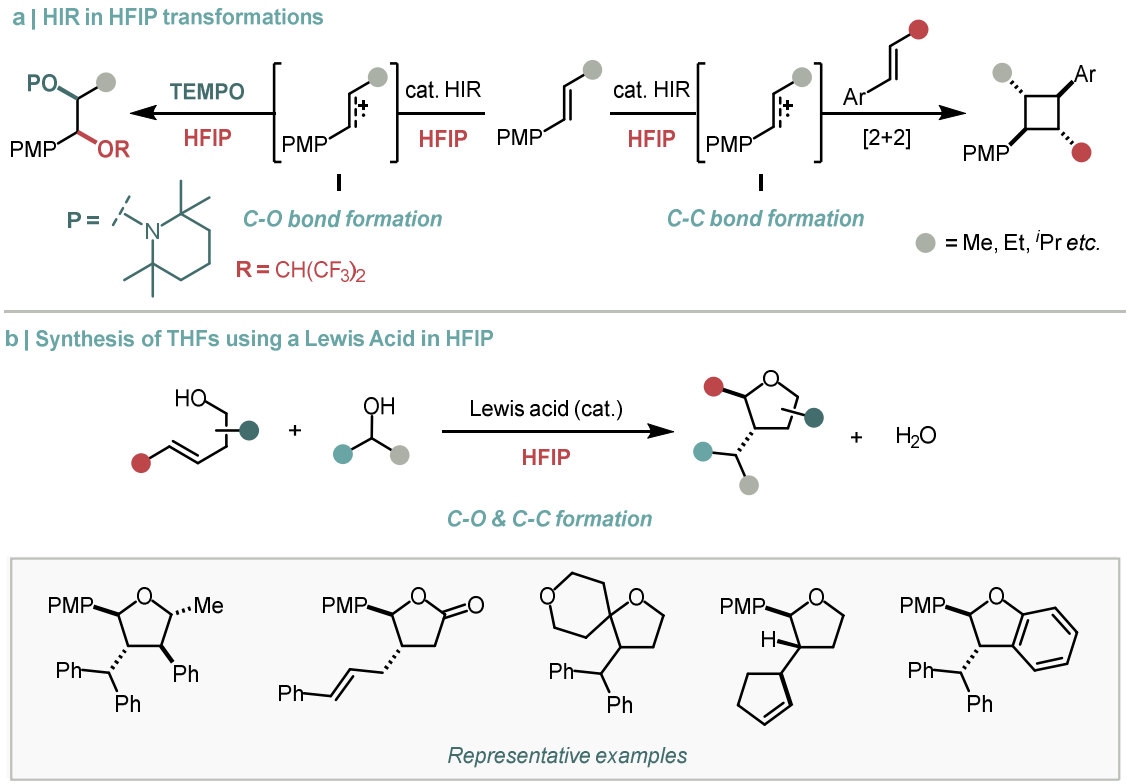
2.1 Chapter overview

The following chapter presents the synthesis of complex pyrrolidine and piperidine scaffolds through a cation triggered annulation strategy using alcohol electrophiles. Initially covered is the optimisation of the piperidine system, continuing work carried out by Yuxiang Zhu and Philip Smith before detailing an extensive substrate scope. Attention then shifted to demonstrating the applicability of the method to target synthesis through expansion of the work to non-alcohol electrophiles in addition to developing a 2-step derivatisation approach to further increase the functionality of our products. Finally, the potential targets envisioned to be synthetically possible using this approach were discussed.

2.2 Origin and outline of project

2.2.1 Use of HFIP as a solvent

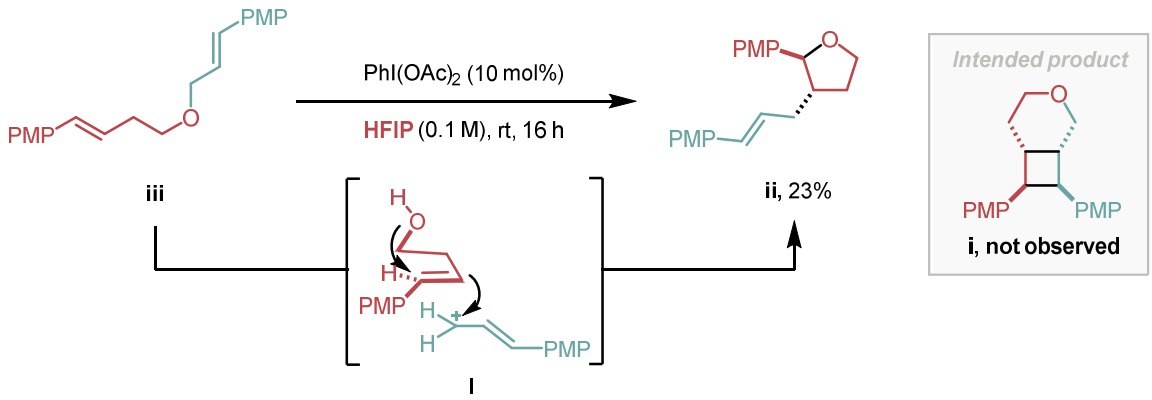
As discussed earlier (see **Chapter 1, Section 1.4.1**), the use of HFIP has increased dramatically in recent years owing to the wide range of properties exhibited and the Donohoe group has a longstanding history of using HFIP as a solvent, publishing several transformations enabled by HFIP (**Scheme 29a**).[78] This effort initially focused on the use of hypervalent iodine reagents (HIR), which when employed in HFIP, generates a stabilised radical cation **I** *via* oxidation of a styrene. **I** could then be trapped, either with an additional styrene in a formal (2+2)-cyclisation to generate a cyclobutane or undergo dihydroxylation using TEMPO to access a 1,2-diol.[79-80] In 2017, the cation triggered annulation of homoallylic alcohols was developed by Yuxiang Zhu, who showed that a sub-stoichiometric Lewis acid in HFIP could enable allylic and benzylic alcohols to act as alkylating agents *via* formation of a carbocation, triggering the formation of a C-C bond in addition to concomitant 5-*endo-trig* cyclisation and formation of a C-O bond (**Scheme 29b**).[81] This approach was used to access a diverse range of highly substituted complex oxygen heterocycles.



Scheme 29. Previous work from the Donohoe group including, HIR enabled transformations (a) and a cation triggered annulation to access THFs (b).

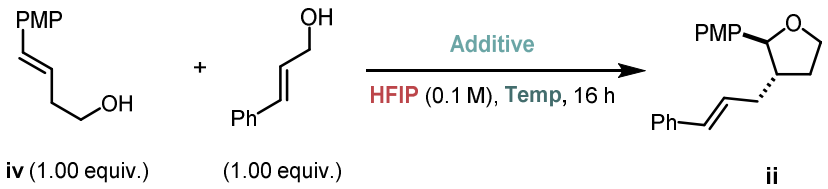
2.2.2 Alcohol system

The formation of tetrahydrofurans was a serendipitous discovery, initially the Donohoe group had hoped to extend the (2+2)-cycloaddition detailed above to the synthesis of fused bicyclic products **i** (**Scheme 30**).[82] However, instead of forming the desired cycle, instead a tetrahydrofuran **ii** was formed in 23% yield, suggesting that under the reaction conditions the starting material **iii** was cleaving to an homoallylic alcohol and a carbocation **I.** In this redox neutral process, the HIR was suspected to be simply acting as a Lewis acid. As such, a series of Lewis acid catalysts were screened for the reaction of **iv** with cinnamyl alcohol. Extensive optimisation revealed that 30 mol% $Ti(O^iPr)_4$ at 70 ˚C gave tetrahydrofuran **ii** in the highest yield (**Table 3**, Entry 6), HFIP was found to be essential for the transformation (**Table 3**, Entry 11).



Scheme 30. Initial hit.

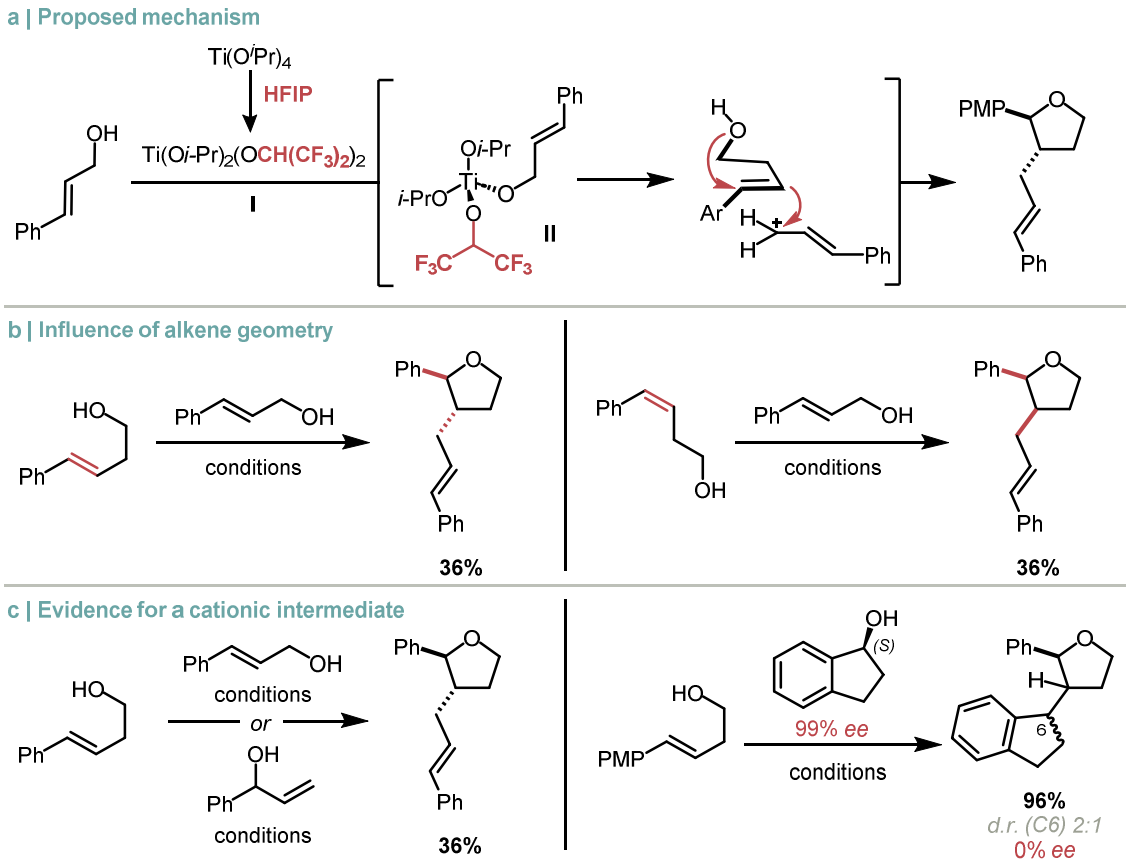
Table 3. Screening of reaction conditions for the cyclisation of **iv** with cinnamyl alcohol.



Entry	Additive	Temp (°C)	ii (%)
1	-	rt	3
2	10 mol% $Ti(O^iPr)_4$	rt	11
3	10 mol% $Ti(O^iPr)_4$	40	15
4	10 mol% $Ti(O^iPr)_4$	70	31
5	20 mol% $Ti(O^iPr)_4$	70	38
6	**30 mol% $Ti(O^iPr)_4$**	**70**	**52**
7	30 mol% $Cu(OTf)_2$	70	0
8	30 mol% $Sc(OTf)_2$	70	0
9	30 mol% $Zn(OAc)_2$	70	46
10	30 mol% Ph_4BF_4	70	47
11 (DCM)	30 mol% $Ti(O^iPr)_4$	70	0

[a]CH_2Cl_2 was used in place of HFIP. All reactions were carried out by Yuxiang Zhu.

A series of experiments were undertaken to probe the mechanism, which is proposed to proceed *via* a concerted addition (**Scheme 31a**). This is supported by an investigation into the influence of alkene geometry, which is reflected in the stereochemistry of the product *i.e. trans* alkenes give 2,3-*trans* products as the major diastereomer and *cis* alkenes give 2,3-*cis* products as the major diastereomer (**Scheme 31b**). The evidence of going *via* a carbocation intermediate is supported by the use of two different allyl alcohols converging on the same product, additionally, use of an enantiopure alcohol does not result in an enantiopure product, rather the tetrahydrofuran is isolated as a completely racemic mixture (**Scheme 31c**). Finally, NMR studies suggest **I** and **II** are key intermediates in the reaction pathway.



Scheme 31. The proposed mechanism (a) and supporting findings reflecting on the influence of alkene geometry (b) and evidence for a cationic intermediate (c). *Conditions:* $Ti(O^iPr)_4$ (30 mol%), HFIP (0.1 M) at 70 °C for 16 h.

The success of this approach led the Donohoe group to consider expanding the reaction conditions to other cation-triggered cyclisations, with the initial focus being the synthesis of azacycles.

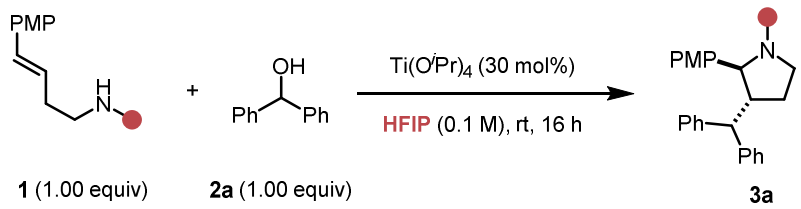
2.2.3 A note on collaboration

This project was initiated by Yuxiang Zhu, focusing solely on the optimisation of the pyrrolidine system, Philip Smith then briefly joined the project, focusing on initial optimisations of the piperidine system. These results are detailed in **Section 2.2.4** (Preliminary work). My involvement in the project commenced when Philip Smith left the group, continuing on the work on the piperidine system, as detailed in **Section 2.3**. Following optimisation, Yuxiang Zhu and I carried out the substrate scope and derivatisations alongside one another and **Sections 2.4 – 2.6** represent our combined findings with some additional results obtained once Yuxiang Zhu had completed his DPhil.

2.2.4 Preliminary work

The extension of this methodology to the synthesis of azacycles was started by Yuxiang Zhu using the previously reporting $Ti(O^iPr)_4$ in HFIP conditions.[82] Initially optimisation was carried out on homoallylic amine **1**, and benzhydrol **2a** (**Table 4**) and cinnamyl alcohol **2b** (**Table 5**) were both chosen as electrophiles to screen the *N*-protecting group, because of the reduced reactivity of **2b** reactions were carried out at elevated temperatures. A range of sulfonamide groups were evaluated, with *ortho*-nosyl giving the highest yields in both cases, outperforming the *para*-nosyl, *para*-tosyl and mesyl substrates, pyrrolidines **3a** and **3b** were accessed as single 2,3-*trans* diastereomers in all cases, as confirmed by nOe experiments. Further attempts to improve the yield of **3b** were unsuccessful, so these optimised conditions were then used for the synthesis of pyrrolidines.

Table 4. Protecting group screen using benzhydrol.

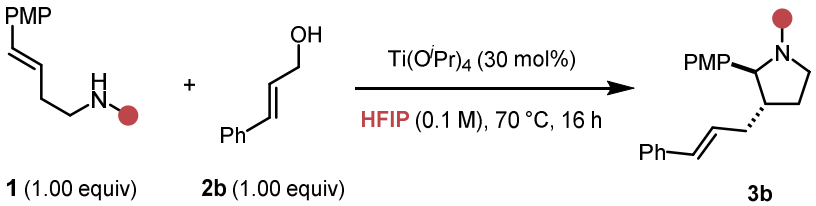


1 (1.00 equiv) **2a** (1.00 equiv) **3a**

Entry	Protecting group (1)	3a (%)
1	*para*-tosyl (**1a**)	64
2	mesyl (**1b**)	43
3	*ortho*-nosyl (**1c**)	99
4	*para*-nosyl (**1d**)	89

All reactions were carried out by Yuxiang Zhu.

Table 5. Protecting group screen using cinnamyl alcohol.

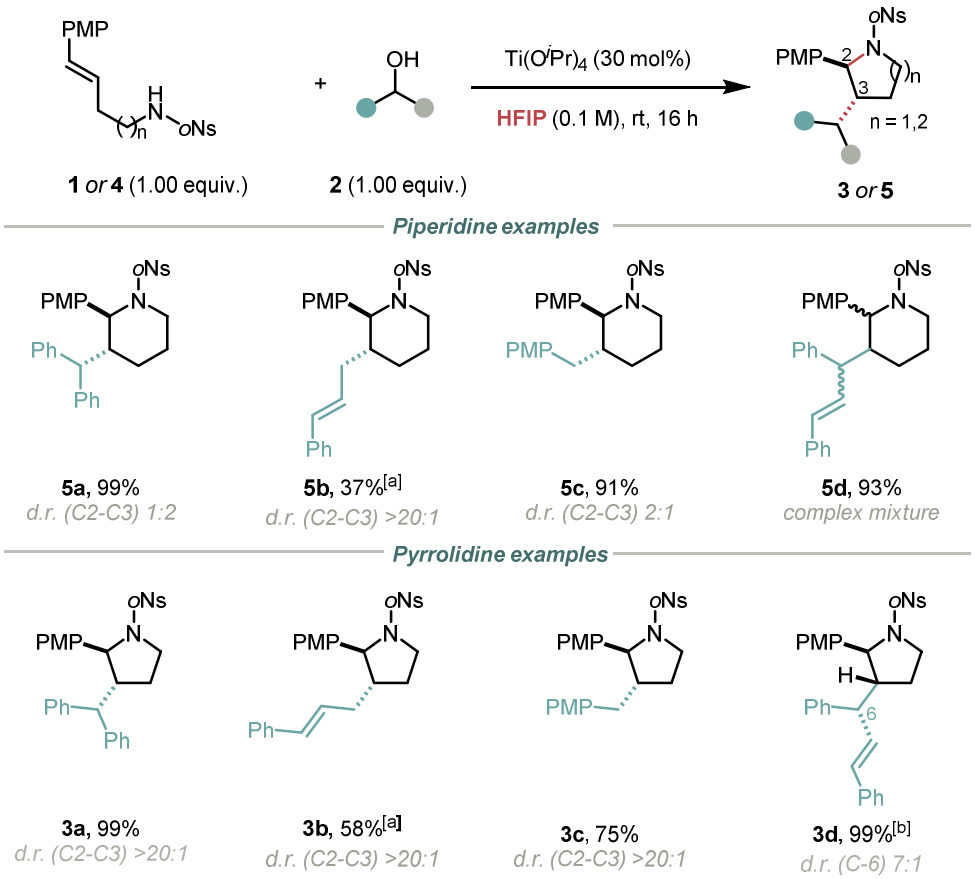


1 (1.00 equiv) **2b** (1.00 equiv) **3b**

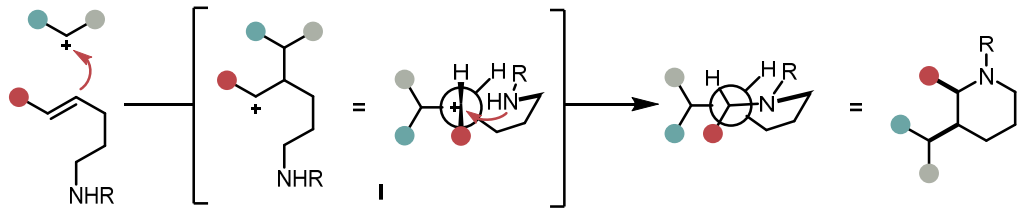
Entry	Protecting group (1)	3b (%)
1	*para*-tosyl (**1a**)	38
2	mesyl (**1b**)	55
3	*ortho*-nosyl (**1c**)	58
4	*para*-nosyl (**1d**)	56

All reactions were carried out by Yuxiang Zhu.

Unfortunately, translation of these conditions to the synthesis of piperidines proved to be challenging, this was unsurprising; despite several literature reports of carboamination reactions to form pyrrolidines, comparatively few examples which prepare piperidines have been published. Preliminary work carried out by Philip Smith utilising γ-aminoalkene **4** showed that the diastereoselectivities obtained when synthesising piperidines **5** were generally significantly lower than the directly related pyrrolidine analogue **3**, *i.e.* from >20:1 in **3c** to 2:1 in **5c** (**Scheme 32**).[83] It was hypothesised that if reaction of the olefin with the carbocation is faster than the *endo-trig* cyclisation a switch from a concerted to a stepwise pathway would occur (**Scheme 33**). If this is the case then the stereochemical information from the alkene is lost, with the benzylic cation **I** reacting unselectively with the nucleophile, likely leading to the formation of a significant amount of 2,3-*cis* substituted product in addition to the 2,3-*trans* substituted product.



Scheme 32. Initial piperidine results. [a]Corresponds to the yield and *d.r.* of pyrrolidine analogue. [b]Performed at 0 °C for 48 h. All reactions were conducted by Philip Smith and Yuxiang Zhu.

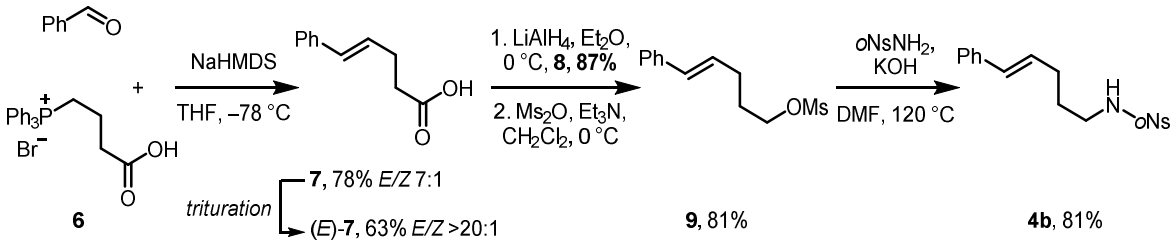


Scheme 33. Stereochemical model for the origin of the 2,3-*cis* diastereomer.

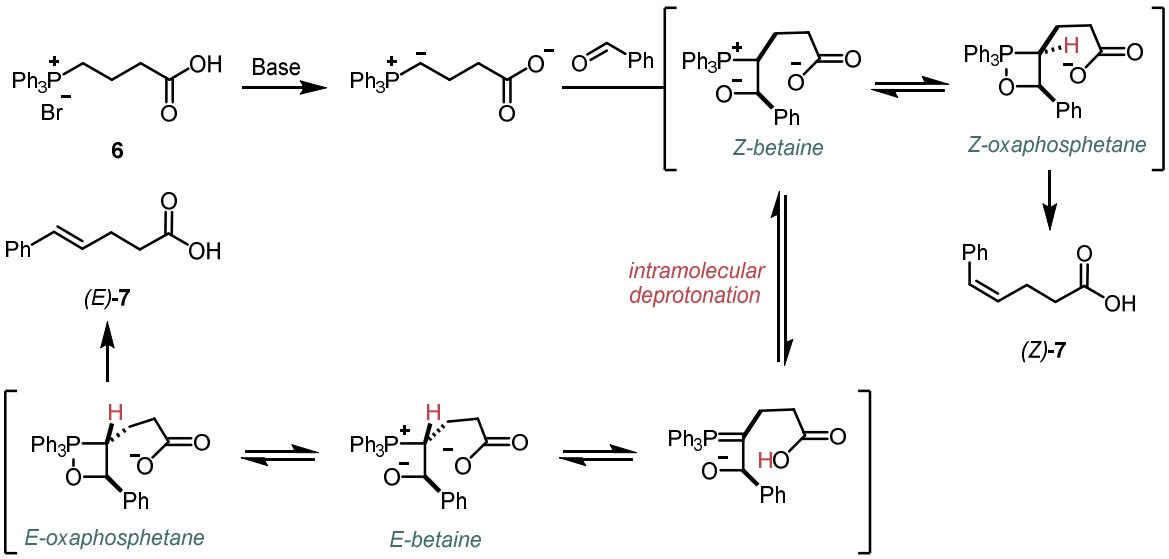
2.3 Optimisation of the piperidine system

2.3.1 Changing the nucleophile – I

It was at this point that I joined the project. In an attempt to moderate the reactivity of the alkene the electron rich paramethoxyphenyl (PMP) group in **4a** was replaced with a phenyl group **4b** in the hope this would lead to an improvement in the diastereoselectivity. Substrate **4b** was prepared in four steps, first benzaldehyde was reacted with bromide salt **6** in an *E*-selective Wittig olefination to afford carboxylic acid **7** high yield and a moderate 7:1 *E*/*Z* ratio (J = 16.0 Hz, major), the unwanted *Z* isomer could then selectively be removed by trituration with ice cold hexane (**Scheme 34**). The preference of the *E*-isomer is contrary to the result expected when using a non-stabilised ylide such as **6**, which would traditionally give high *Z* selectivity, however the carboxylate group on the phosphonium salt enables an intramolecular deprotonation leading to formation of the thermodynamically favoured *trans* product (*E*)-**7** (**Scheme 35**).[84] This principle is more widely known through utilising an external lithium salt as in the Schlosser modification.[85] Following the Witting reaction, reduction of **7** with lithium aluminium hydride gave alcohol **8** in high yield, before conversion to the corresponding mesylate **9** with mesyl anhydride. Finally, displacement of the mesylate with *ortho*-nosyl sulfonamide gave **4b** in moderate yield.

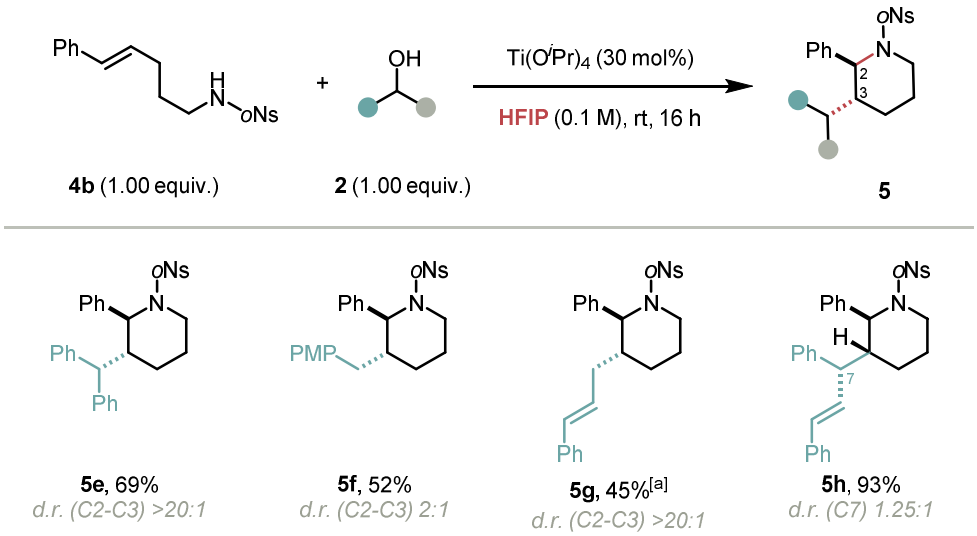


Scheme 34. Synthesis of substrate **4b**.



Scheme 35. Mechanism for *E*-selectivity when using Wittig salt **6.**

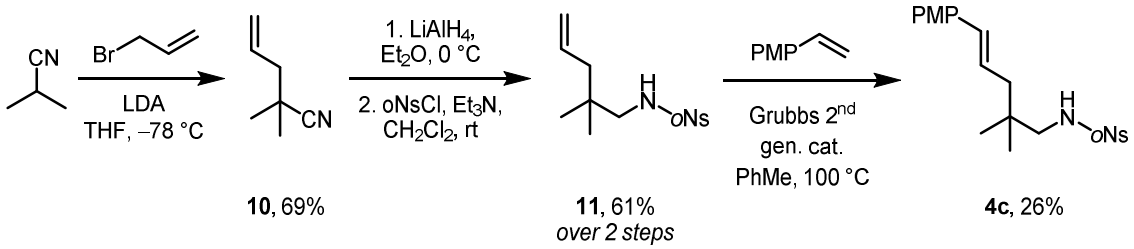
With γ-amino olefin **4b** in hand, a range of alcohols were screened in the cyclisation reaction (**Scheme 36**). As expected, the yields were lower than the corresponding PMP examples (*cf.* **Scheme 32**, **5a** – **5d**), but an improvement in diastereoselectivity was observed in some cases (an explanation of how the stereochemistry was assigned can be found in **Section 2.3.3**). However, this improvement was still far from the diastereoselectivity observed in the pyrrolidine system (*cf.* **Scheme 32**, **3a** – **3d**), whilst it was expected that the pyrrolidine system to be more reactive considering the relative rates of formation of 5- *vs* 6- rings, it was not anticipated that the diastereocontrol would differ so significantly. For this reason, alternative approaches were contemplated.



Scheme 36. Results using **4b** as the nucleophile. [a]Performed at 70 °C.

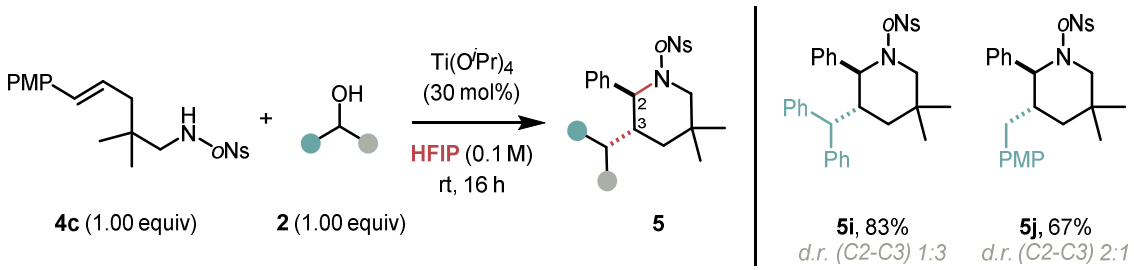
2.3.2 Changing the nucleophile – II

Firstly, it was hoped that invoking the Thorpe-Ingold effect through introduction of steric bulk onto the chain backbone would aid pre-organisation of the system into the required conformation. Based on ease of synthesis, introduction of a *gem*-dimethyl unit in the β-position was chosen as the substrate **4c** to investigate our hypothesis. **4c** was prepared in four steps from isobutyronitrile which was alkylated with allyl bromide to give **10** before reduction and protection to give **11**, finally cross-metathesis with PMP styrene afforded **4c** in >20:1 *E:Z* (J = 15.8 Hz) (**Scheme 37**).



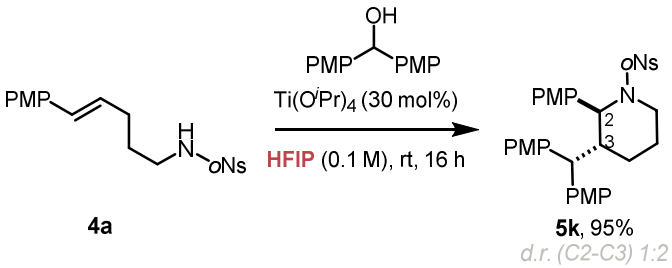
Scheme 37. Synthesis of substrate **4c**.

Unfortunately, reaction of **4c** with benzylic alcohols **2a** and **2c** did not improve the diastereoselectivity (**Scheme 38**) and once again reaction with benzhydrol had given piperidine **5i** with the 2,3-*cis* product as the major diastereomer as observed previously by Philip Smith (*cf.* **Scheme 32, 5a**).[83] Such reversal in selectivity was not observed in either the tetrahydrofuran or pyrrolidine system.



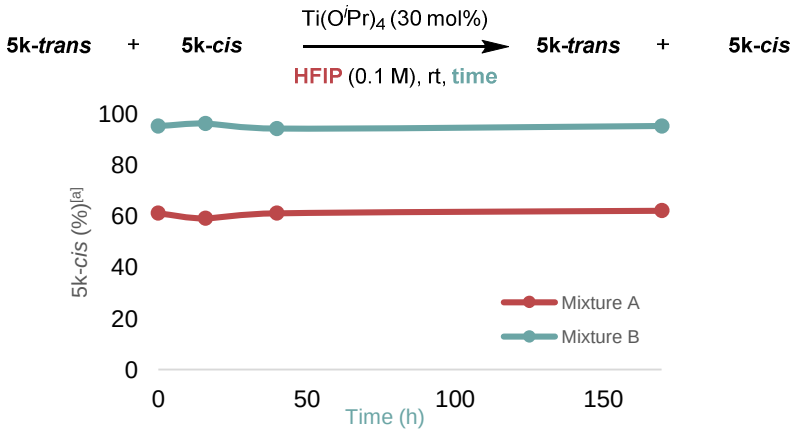
Scheme 38. Results from using **4c** as the nucleophile.

To probe the reason for our observations it was decided to resubject the cyclisation products to the reaction conditions to determine whether the cyclisation was reversable, leading to a thermodynamic ratio of diastereomers. Piperidine **5k** was used for this purpose, which was synthesised in a 1:2 (*trans:cis*) mixture of diastereomers which were partially separable (**Scheme 39**). Subjection of a 1:1.5 (*trans:cis*) and a 1:20 (*trans:cis*) mixture to the reaction conditions gave no change in product ratio over a range of time points, suggesting the formation of piperidines was not reversible (**Table 6**).



Scheme 39. Synthesis of **5k**. Substrate **4a** was prepared in a 4-step sequence analogous of that of **4b**.

Table 6. Resubjection experiments of **5k**.



[a]Calculated by quantitative ^{1}H NMR analysis of the crude reaction

2.3.3 Stereochemical assignments – I

At this stage it is worth noting the challenges associated with assigning the relative stereochemistry of the azacycle products. The 2,3-*trans* stereochemistry of the pyrrolidine products was easily determined through 2D NOESY analysis, with clear nOe correlations observed between C2-H & C6-H; providing a strong argument for the relative positions of the two groups. However, the crystal structure of **5e** revealed that 2D NOESY analysis would not be viable for corroborating the assignment of 2,3-*trans* piperidine products (**Figure 4**). The 2-substituent preferentially adopts an axial conformation, meaning C2-H is equatorial, facing away from the core of the ring so no diagnostic nOe correlations would be observed. The preference for an axial conformation is expected, protection of the piperidine nitrogen increases the *N* sp^2 hybridisation and planarity, and the resulting partial double-bond character leads to pseudoallylic strain, forcing the 2-substituent into an axial orientation.[86] In addition, in the *trans* products C3-H is also equatorial, preventing further insight through 2D NOESY data; for example if C3-H was axial an nOe correlation to C5-H$_{ax}$ would be observed, giving confirmation, at least, of the position of

the 3-substituent. The absence of an nOe correlation when C3-H is equatorial cannot be used as proof of the position of the 3-substituent. The 2,3-*trans* products instead have to be assigned through *J* coupling analysis which will be detailed later (see **Section 2.6.3**).

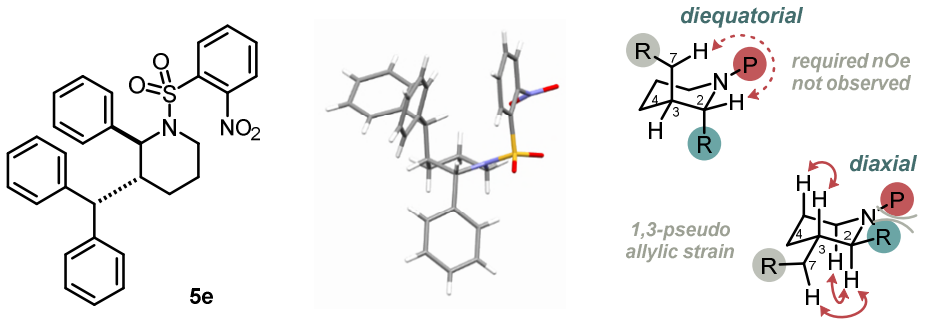
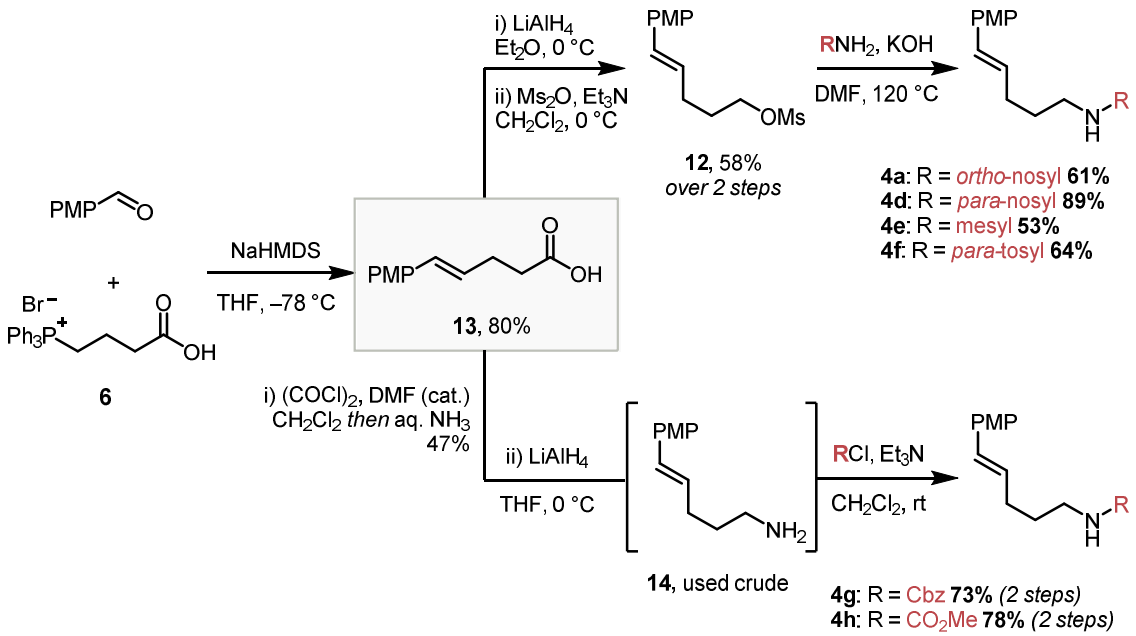


Figure 4. Approaches to the assignment of the piperidine stereochemistry.

2.3.4 Protecting group screen

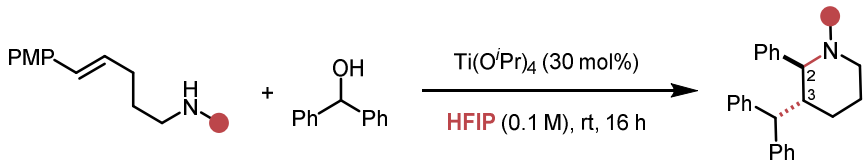
With no obvious insights into the reasons for the poor diastereoselectivity observed so far across the piperidine examples it was decided to re-evaluate the *N*-protecting group. Additional sulfonamides were prepared using the sequence described to synthesise **4b** (*cf.* **Scheme 34**), *via* an S_N2 reaction on mesylate **12** enabling the facile preparation of **4a** and **4d** – **4f**. However, the synthesis of carbamates required a different approach, here the nitrogen was introduced earlier in the synthesis *via* a two-step reductive amination of acid **13**. Crude amine **14** could then be reacted with chloroformates, enabling the preparation of two additional substrates **4g** and **4h** (**Scheme 40**).



Scheme 40. Protecting group screen substrate synthesis.

Initially benzhydrol **2a** was chosen as the electrophile for the optimisation (**Table 7**), however after promising results were observed additional alcohols were also subjected (see **Chapter 6**), ensuring that the *N*-protecting group exhibited broad reactivity for a range of alcohols. Initially switching from *ortho* to *para*-nosyl gave a moderate diastereoselectivity in favour of the expected 2,3-*trans* product (**Table 7**, Entry 2). It was hypothesised that steric bulk may be hindering the reaction, however when the smaller mesyl group was used a drop in diastereoselectivity was observed with tosyl proving to be the best of the sulfonamide protecting groups (**Table 7**, Entries 3 & 4), both in yield and diastereocontrol. However, carbamates were found to be superior, exhibiting excellent diastereoselectivity akin to the corresponding pyrrolidine examples. This supports the idea that the larger ring system requires a stronger nucleophile. As methyl carbamate (**Table 7**, Entry 6), gave higher yields than the benzyl carbamate (**Table 7**, Entry 5), this was the protecting group of choice for the piperidines going forward.

Table 7. Piperidine protecting group screen with benzhydrol.



4 (1.00 equiv.) **2a** (1.00 equiv.) **5**

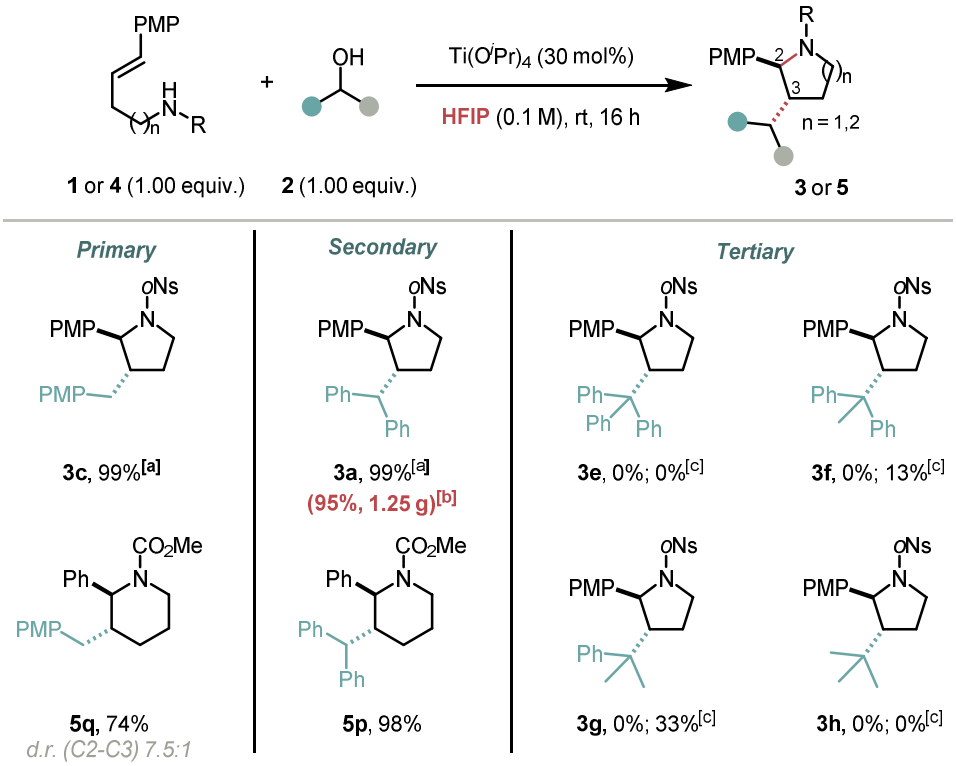
Entry	Protecting group	5 (%)	*d.r. (C2-C3)*
1	*ortho*-nosyl (**5a**)	84	1:2
2	*para*-nosyl (**5l**)	88	3:1
3	mesyl (**5m**)	64	2:1
4	tosyl (**5n**)	95	5:1
5	Cbz (**5o**)	86	>20:1
6	**CO_2Me** (**5p**)	98	>20:1

2.4 Scope of the electrophile

2.4.1 Alcohol scope

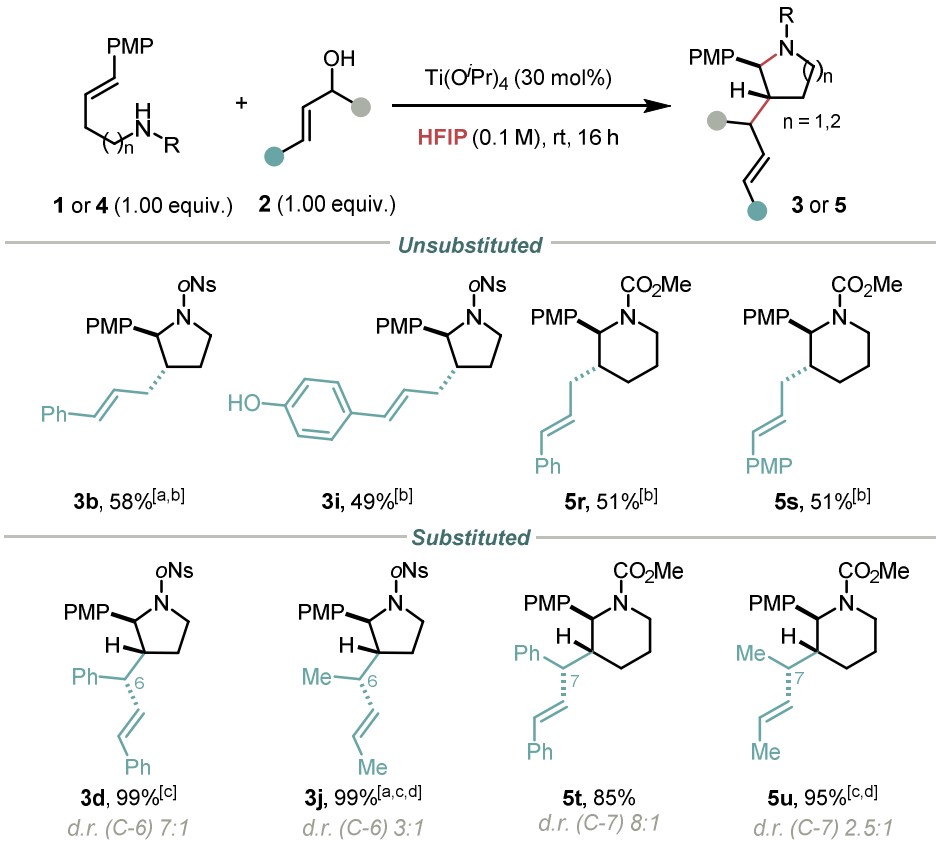
With complimentary *N*-protecting groups in hand the electrophile scope could be evaluated. Knowing that benzhydrol performed well in the reaction, other simple benzylic alcohols were employed (**Scheme 41**). Primary alcohols could be used, as demonstrated by 4-methoxybenzyl alcohol **2c** which gave a high yield and excellent to good diastereocontrol, **3c** and **5q**. When tertiary alcohols **2d** – **2f** were used only partial reactivity was observed; if the alcohol used was too bulky such as in the case of triphenylmethanol

no reaction took place **3e**, whereas replacing phenyl groups with a methyl group gave moderate reactivity **3f** and **3g**, requiring elevated temperatures. When *tert*-butanol was used no reactivity was observed, **3h**. At this stage it was also possible to demonstrate the scale up ability of the reaction, preparing 1.25 g of **3a** (2.50 mmol), with only a small reduction in yield when compared to the standard reaction scale.



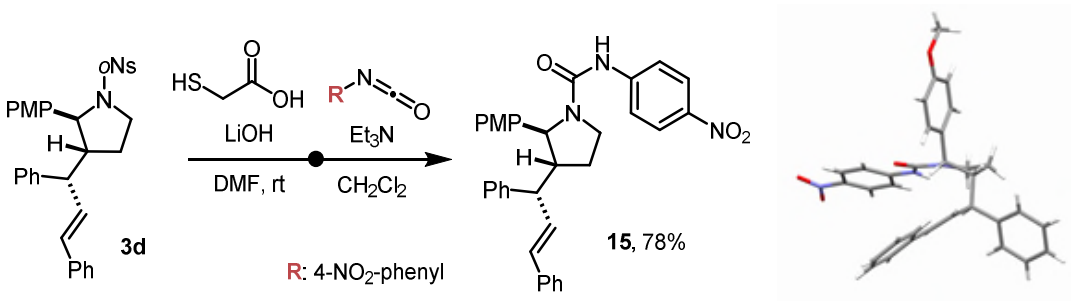
Scheme 41. Benzylic alcohol scope. [a]Conducted by Yuxiang Zhu. [b]Performed on a 2.50 mmol scale. [c]Performed at 70 °C. *d.r. (C2–C3) >20:1* unless otherwise stated.

Aromatic allylic alcohols could be used, however when compared to benzylic alcohols, allylic alcohols were more sluggish to react requiring elevated temperatures, not going to full conversion during the 16 h, **3b**, **3i** and **5r**, **5s** (**Scheme 42**). The reactivity could be improved significantly through the introduction of an additional α-substituent, enabling us to not only set the 2,3-*trans* ring stereochemistry but an additional exocyclic stereogenic centre, affording products with three contiguous stereocentres **3d, 3j** and **5t, 5u**. In each case complete 2,3-*trans* diastereoselectivity was observed with moderate to good diastereoselectivity at the *exo*cyclic stereocentre, here the bulk of the substituent plays a key role, for example a higher d.r. is observed using (*E*)-1,3-diphenyl-2-propen-1-ol **2g** *vs* 3-penten-2-ol **2h**.

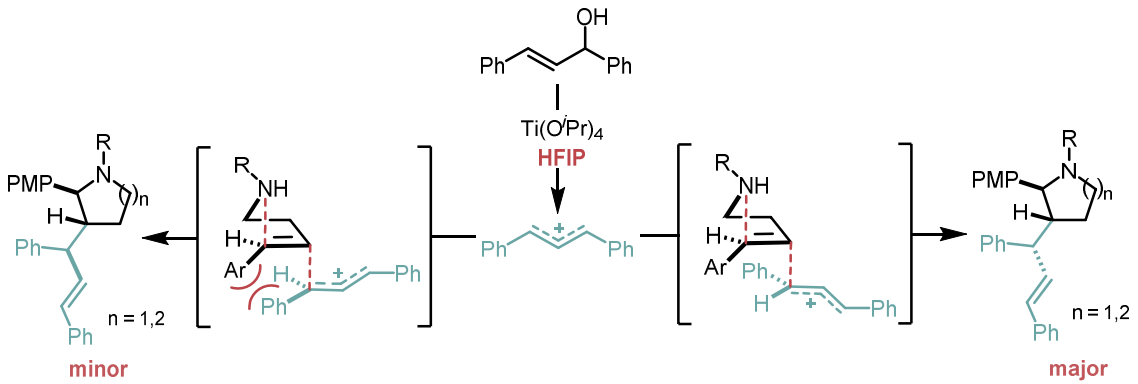


Scheme 42. Acyclic allylic alcohol scope. [a]Conducted by Yuxiang Zhu. [b]Performed at 70 ˚C. [c]Performed at 0 ˚C for 24 h. [d]Using 2.0 equiv. of electrophilic partner. *d.r. (C2–C3) >20:1* unless otherwise stated.

Assignment of the stereochemistry at the *exo*cyclic position required derivatisation of **3d**. Removal of the *ortho*-nosyl group using conditions developed by Yuxiang Zhu followed by reaction with 4-nitrophenylisocyanate to give **15** as a single diastereomer of which a crystal structure could be obtained (**Scheme 43**). The stereochemical outcome was primarily attributed to be a steric effect, with the approach by the allylic carbocation which minimises the clash between the aromatic groups giving the major diastereomer, *vs.* the alternative confirmation with the steric clash giving the minor diastereomer (**Scheme 44**). The rest of the compounds were assigned by analogy with **3d**.

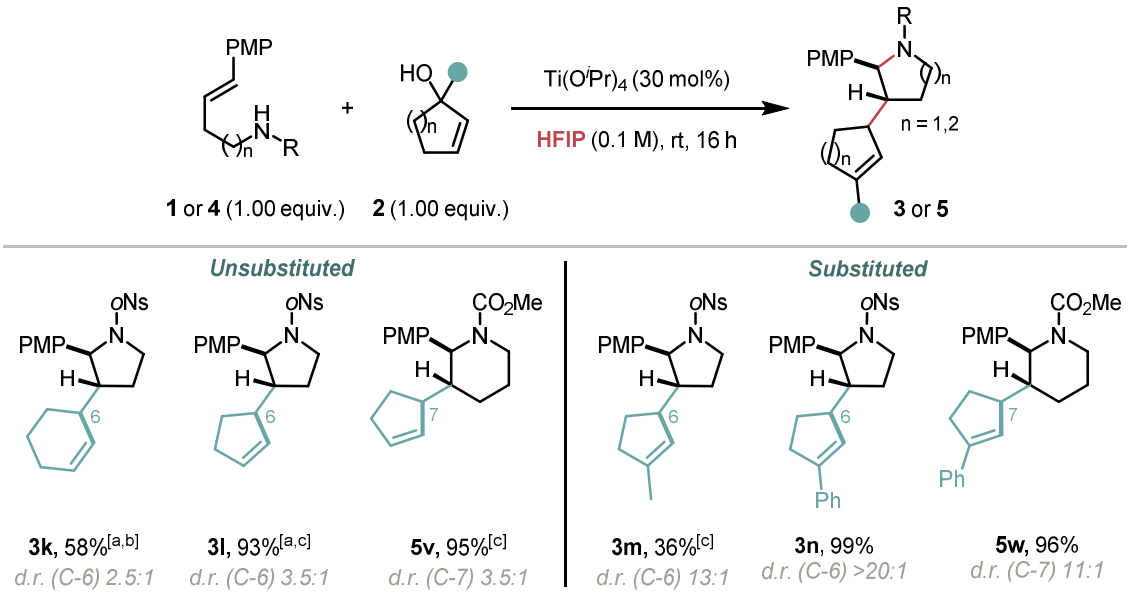


Scheme 43. Derivatisation of **3d** to generate a stereochemical assignment.



Scheme 44. Steric model for stereochemical outcome of **2g** as an electrophile.

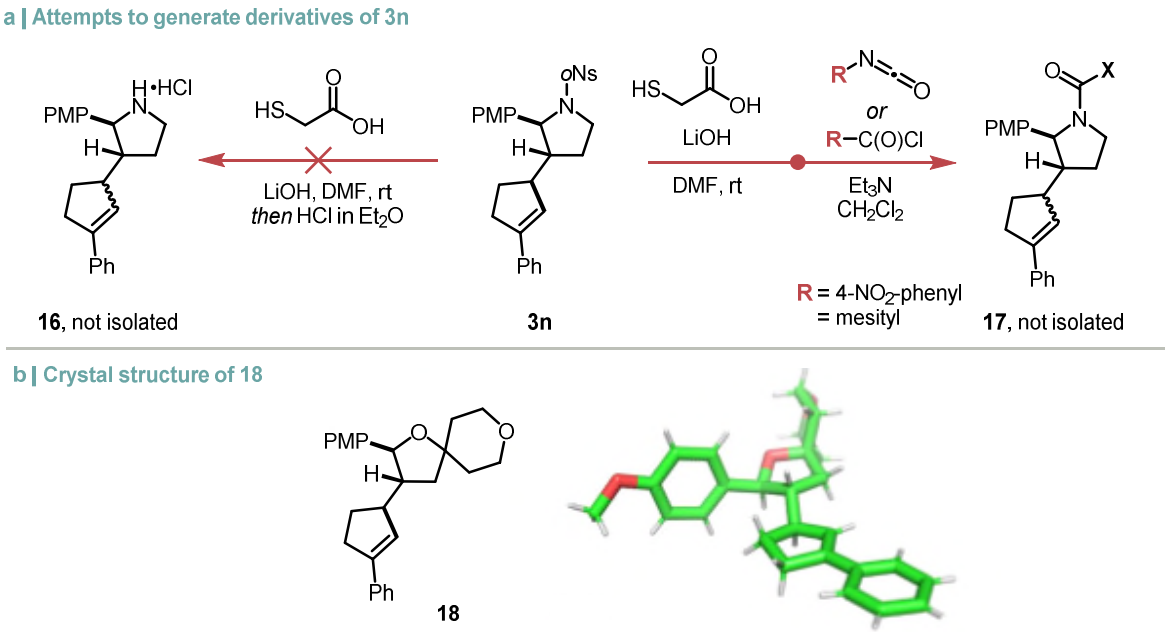
Finally, a diverse range of cyclic allylic alcohols were utilised, cyclohexenyl and cyclopentenyl alcohols gave moderate diastereoselectivity in the exocyclic centre **3k** – **3l** and **5v**, however introduction of a methyl or phenyl substituent gave a significant improvement in diastereocontrol coupled with complete regioselectivity **3m** – **3n** and **5w** (**Scheme 45**).



Scheme 45. Cyclic allylic alcohol scope. [a]Conducted by Yuxiang Zhu. [b]Performed at 70 ˚C. [c]Using 2.0 equiv. of electrophilic partner. *d.r. (C2–C3) >20:1* unless otherwise stated.

Attempts to assign the stereochemistry at the exocyclic position through derivatisation of **3n** were not possible, conditions to functionalise the pyrrolidine through deprotection and salt formation **16** or reaction to form a urea **17** led to a reduction in the d.r. observed at C6, either during the course of the reaction or upon standing in solution, as required to obtain a crystal structure (**Scheme 46**). Azacycles **3m** and **5w** could also not be used directly despite significant effort. Here assignments have been made

by analogy to a previously synthesised tetrahydrofuran product **18** through careful comparison of the NMR data with the corresponding heterocycles (See **Chapter 6, Section 6.2.6**).[81, 82]



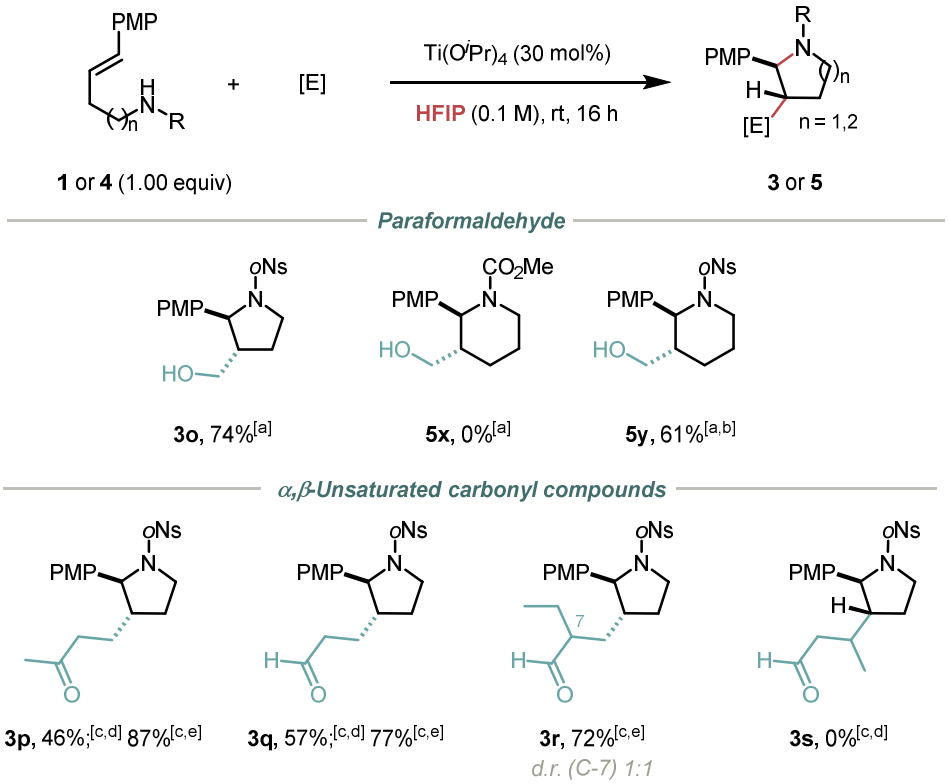
Scheme 46. Attempts to generate a stereochemical assignment for the exocylic stereocentre through derivatisation of **3n** (a) and the crystal structure of **18** used to assign by analogy (b).

2.4.2 Non-alcohol scope

Although it was demonstrated that a range of benzylic and allylic alcohols could be successfully utilised in our methodology, the requirement to form a stabilised carbocation indirectly means relying on the inclusion of multiple aromatic groups and ultimately the products exhibit high sp^2 character and lack some of the functionality desired for the method to be amenable to target oriented synthesis. It was hoped to improve this through the use of other activated electrophiles, further increasing the synthetic utility of our method.

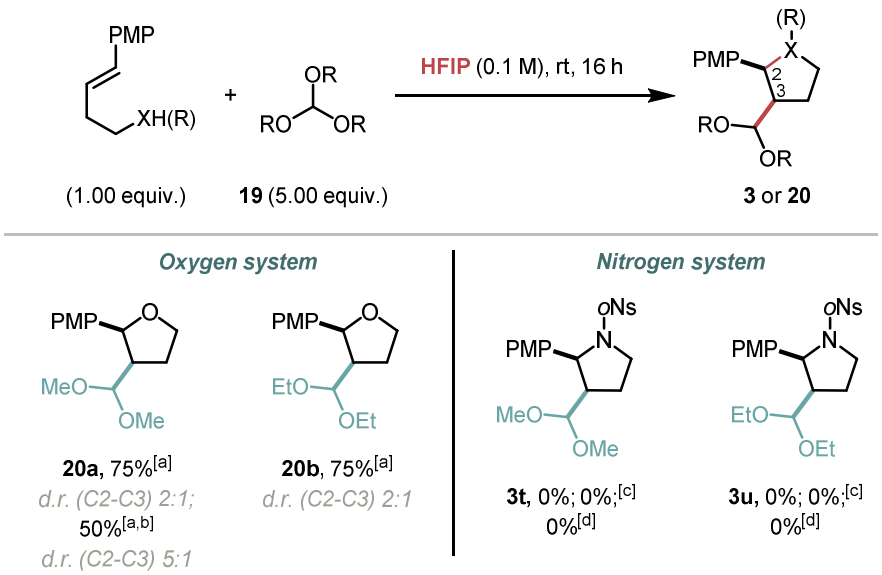
The first hit came through the use of paraformaldehyde to introduce a hydroxymethyl unit to our product (**Scheme 47**). No reactivity was observed with the methyl carbamate *N*-protecting group for the piperidine system **5x**, instead both cases used the *ortho*-nosyl group giving complete 2,3-*trans* selectivity and good yields **3o** and **5y**. The introduction of an alcohol into the products marks a significant step forward in terms of potential derivatisations available to us. It was pleasing to find that α,β-unsaturated carbonyl compounds could also be used successfully, here exclusively conjugate addition was observed,

giving the extended chain ketone and aldehyde products **3p** – **3r**, in moderate to good yield when 2.00 equiv. of electrophile are used, the yield could be improved further using 10.0 equiv. of electrophile. Unfortunately, only terminal olefins are tolerated; addition of a β-methyl group onto the alkene halted reactivity and no product **3s** was observed. Inclusion of an α-group on the alkene was successful, however no stereocontrol was imparted on the product **3r**.



Scheme 46. Non-alcohol electrophile scope. [a]Performed at 0 ˚C for 48 h using 20 equiv. of electrophilic partner. [b]Conducted by Philip Smith. [c]Performed at 70 ˚C. [d]Using 2.0 equiv. of electrophilic partner. [e]Using 10 equiv. of electrophilic partner. *d.r. (C2–C3) >20:1* unless otherwise stated.

During the investigation into the synthesis of *O*-heterocycles Yuixang Zhu showed that orthoformates **19** could be employed as electrophiles to give acetals **20a** and **20b** in high yield with a reversal in diastereoselectivity in favour of the *2,3*-cis product.[82] Unfortunately, switching to the nitrogen system gave no reactivity and **3t** and **3u** were not observed (**Scheme 47**).



Scheme 47. Orthoformates as electrophiles. [a]Conducted by Yuxiang Zhu. [b]Performed at 0 °C. [c]Performed at 70 °C. [d]Using 30 mol% $Ti(O^iPr)_4$.

A range of other classes of electrophile were then screened with limited success (**Figure 5**). It was hoped that iminium ions would be sufficiently reactive, however both preformed examples such as Eschenmoser's salt **21** and *in situ* generated iminium ions such as those made from the corresponding imine **22** or hydroxy-lactam **23** respectively were unreactive towards the reaction conditions, and the nucleophile remained untouched. Other unsuccessful electrophiles included epoxides, acyl chlorides, diazonium salts and nitrostyrenes. Despite extensive efforts it was clear that the nature of the electrophile was important and the method was only applicable to a limited selection of non-alcohol examples.

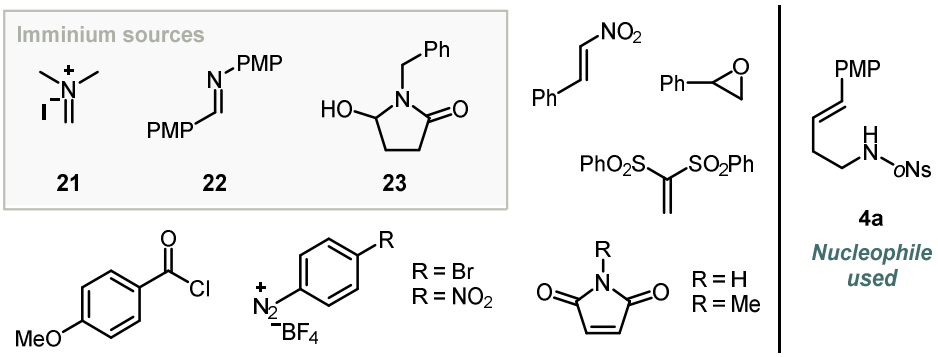
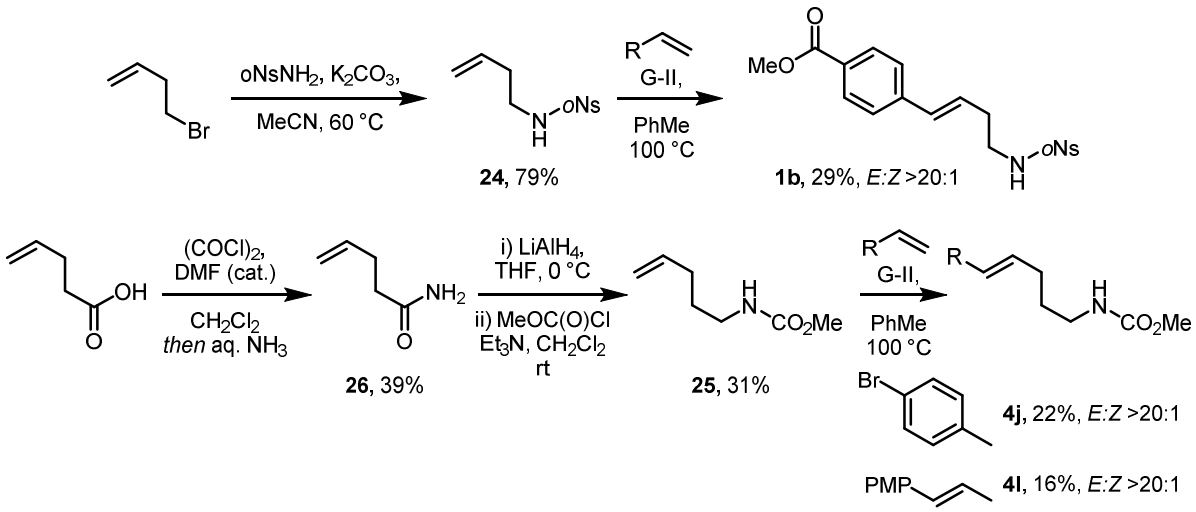


Figure 5. Failed electrophiles using sulfonamide **4a** as the nucleophile.

2.5 Nucleophile scope

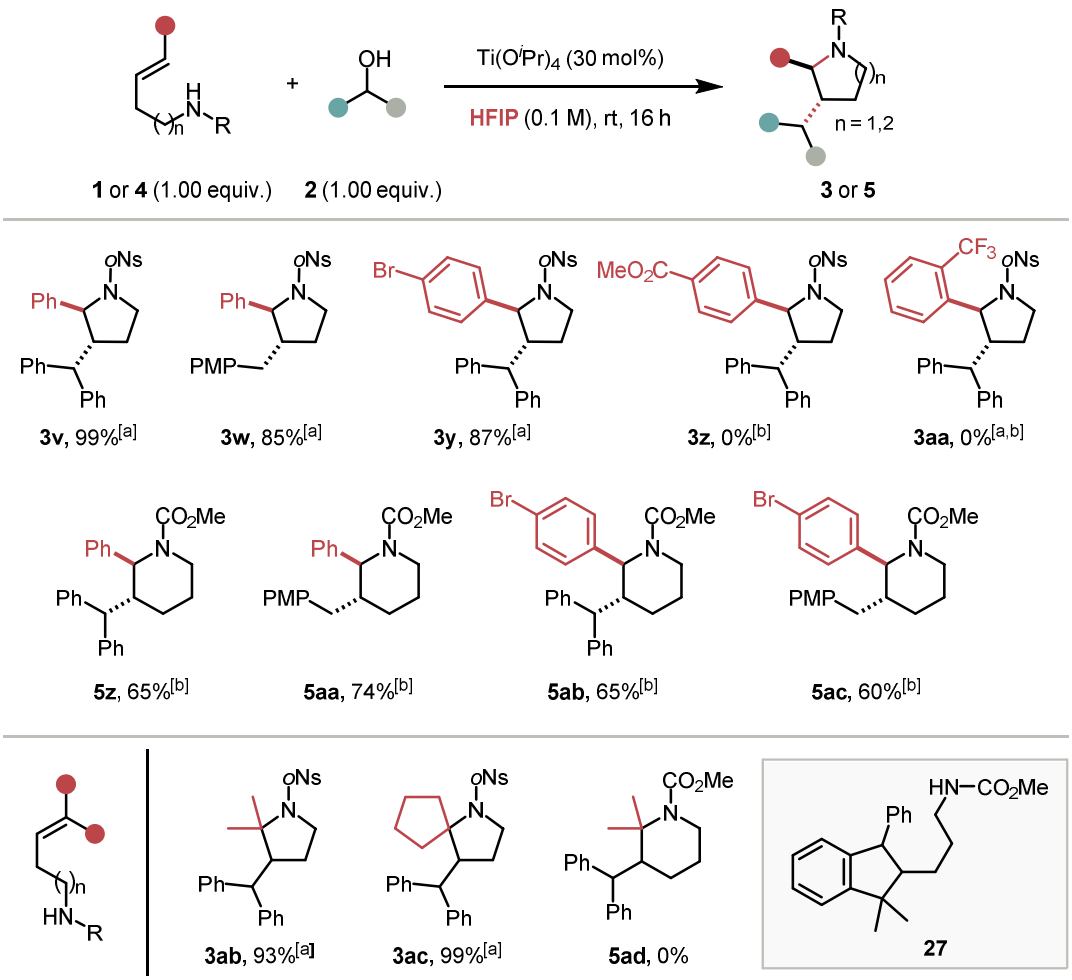
2.5.1 Nucleophile scope – I

Having explored the scope with respect to the electrophile attention moved to the nucleophile. Where possible substrates were prepared according to the sequence used to synthesis **4b** (*cf.* **Scheme 34**). However, in cases where this route was not viable, substrates were prepared from terminal alkenes **24** and **25**, through a cross-metathesis reaction, which were made either *via* the previously described reductive amination route or *via* a S_N2 reaction (**Scheme 48**).



Scheme 48. Synthesis of different nucleophiles.

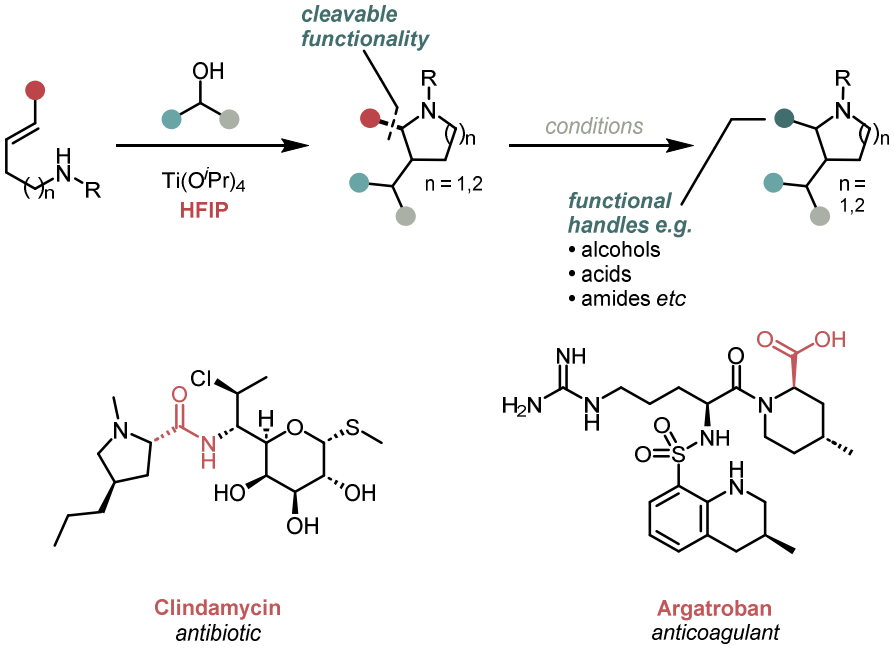
It was at this point that the largest difference in reactivity between the 5- and 6-membered systems was observed. Whilst it was still possible to access a range of pyrrolidines by varying the nucleophile, accessing piperidines proved to be more challenging. Firstly, the scope began by varying the aryl group on the alkene (**Scheme 49**), both systems tolerated the switch from PMP to Ph and 4-bromophenyl, with a reduction in yield for **5z** – **5ac** when compared to **3v** – **3y**. Unfortunately, inclusion of electron withdrawing functionality was not possible and both *para*-CO_2Me **3z** and *ortho*-CF_3 **3aa** were unreactive at elevated temperatures. It was encouraging to see that tri-substituted aliphatic alkenes were reactive in the pyrrolidine system giving products bearing a fully substituted center **3ab** including a spirocycle **3ac**. Attempts were also made to access **5ad**, however no cyclisation took place, instead side-product **27** was observed, resulting from an intramolecular Friedel-Crafts reaction.



Scheme 49. Aryl group scope. [a]Conducted by Yuxiang Zhu. [b]Performed at 70 ˚C. *d.r. (C2–C3) >20:1* unless otherwise stated.

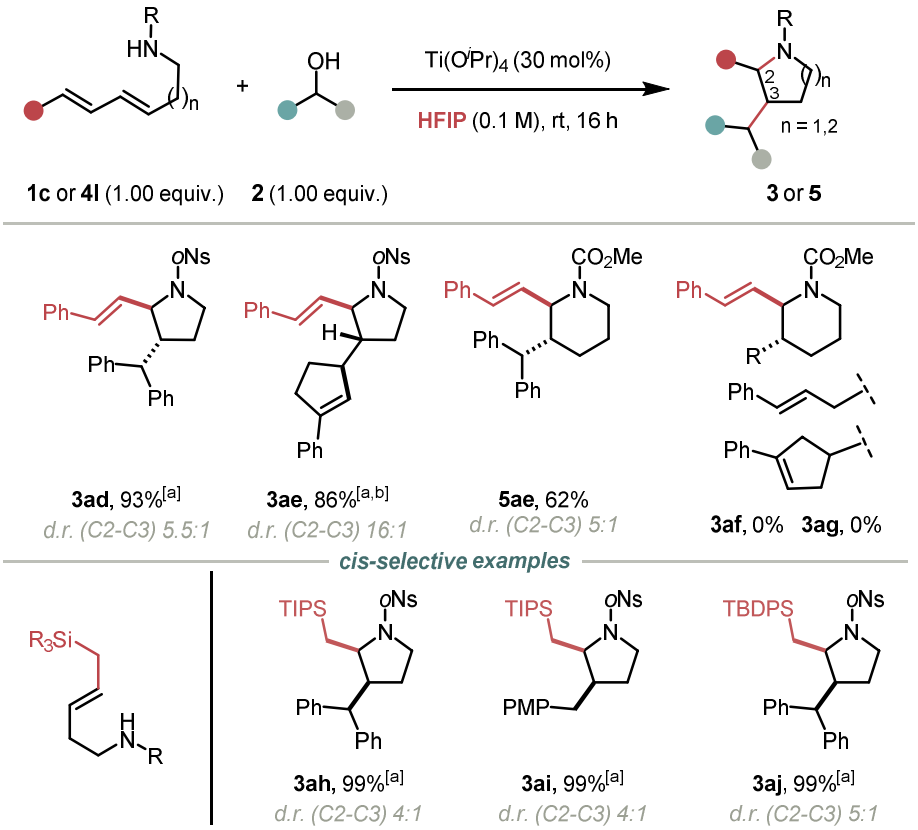
2.5.2 Nucleophile scope – II

A major limitation of this work is the requirement of the alkene substituent to stabilise a positive charge during the reaction, this significantly reduces the synthetic utility of our method when comparing to known biologically active molecules in the literature (**Scheme 50**). One way to circumvent this is a two-step strategy, whereby functionality is introduced in the C2-position which could easily be derivatised to access a wider range of functional groups.



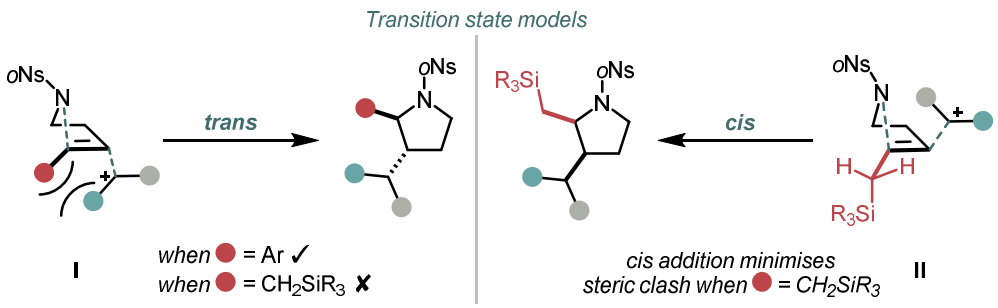
Scheme 50. 2-step strategy to increase functionality of our products.

To this end, two distinct tactics were established, firstly through the introduction of an *exo*-cyclic vinyl group using a diene precursor **1c** and **4l**. Both reacted with complete regioselectivity and good diastereocontrol **3ad** – **3ae** and **5ae** (**Scheme 51**). A range of electrophiles could be introduced in the pyrrolidine system, but the piperidine system was once again more limited, and only benzhydrol was able to trigger cyclisation **5af** – **5ag**. In the second approach, Yuxiang Zhu utilised nucleophilic vinyl silanes, which cyclised to give 2,3-*cis* products. Both TIPS- and TBDPS- silanes gave pyrrolidines in high yield and good *cis*-selectivity **3ah** – **3aj**.



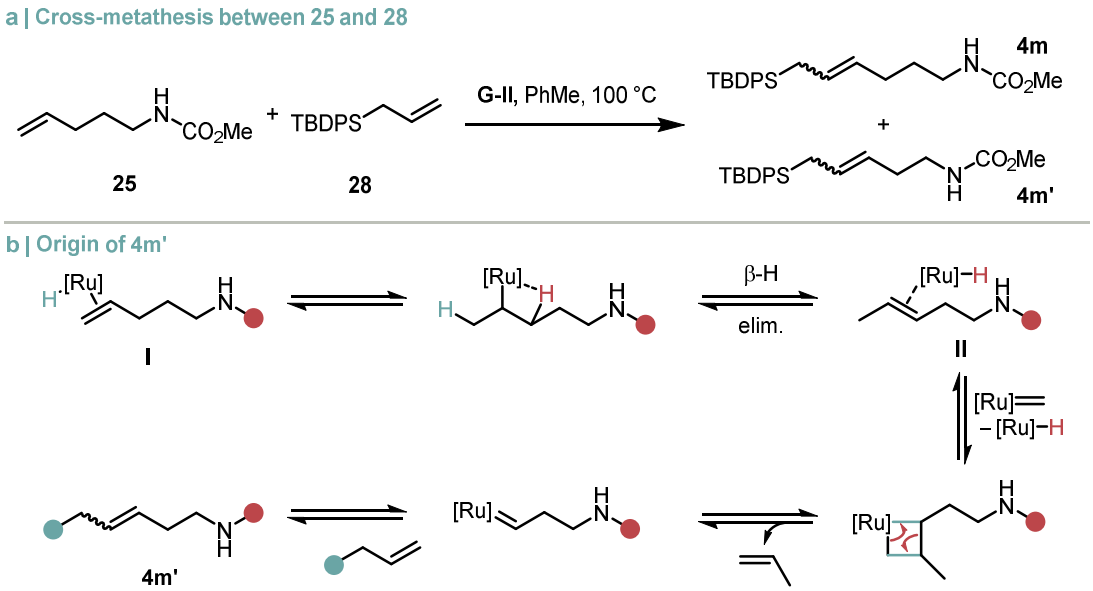
Scheme 51. Cleavable nucleophile scope. [a]Conducted by Yuxiang Zhu. [b]Performed at 0 °C for 48 h. *d.r.* Substrates were prepared according to the sequence described in **Scheme 48**.

The reversal in stereochemistry observed in the allyl silane system was rationalised using a transition state **I** and **II** (**Scheme 52**). It was proposed that the steric bulk of the silicon group plays a key role in dictating the selectivity, with a steric clash **I** between the silyl group (which is assumed to sit *syn*-periplanar to the *p*-orbitals of the alkene bond in order to maximise hyperconjugation) and the approaching electrophile. Consequently, addition of the cation from the face of the alkene anti to the silyl group **II** would minimise steric interactions and maximise stereoelectronic effects while leading to the *cis* heterocyclic product, as observed.



Scheme 52. Transition state models for the reversal in selectivity with vinyl silanes.

Unfortunately attempts to access substrate **4m** to extend this reaction to the piperidine system were hampered by the cross-metathesis between **25** and **28** which gave a complex, inseparable mixture of products (**Scheme 53a**). Although the desired product **4m** was observed, large amounts of the contracted product **4m'** were also obtained, arising from the ruthenium hydride mediated chain-walking of the external alkene **I** to internal alkene **II**, leading to the loss of a CH_2 unit in the product (**Scheme 53b**). Ruthenium hydride is a well-documented decomposition product of ruthenium metathesis catalysts.[87]



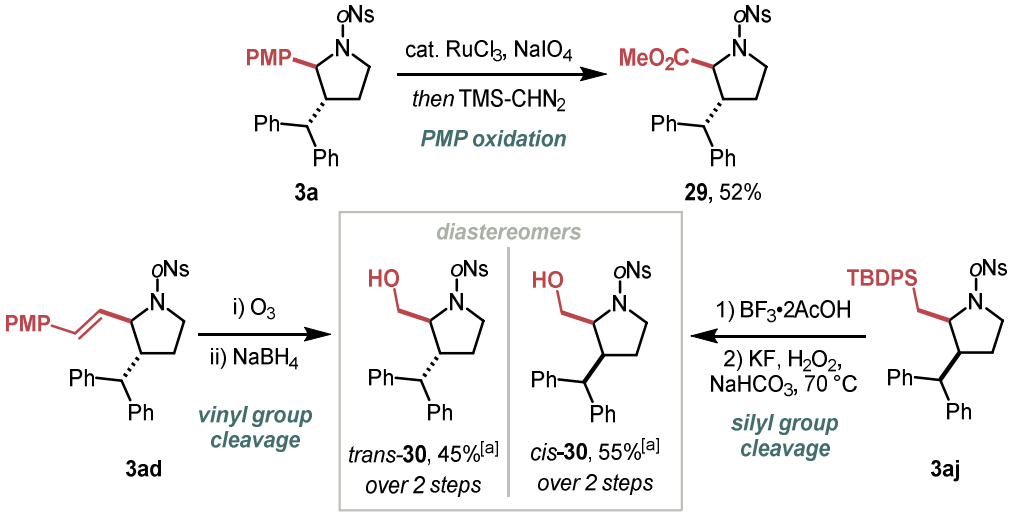
Scheme 53. Failed CM to access **4m** (a) and the mechanism to access side product **4m'** (b).

2.6 Derivatisations

2.6.1 C2 derivatisations

To demonstrate the viability of our 2-step strategy the products were subjected to a range of reactions to derivatise the C2-substituent to other functional groups (**Scheme 54**). Firstly, it was possible to oxidatively cleave the PMP group to the corresponding carboxylic acid, using catalytic ruthenium tetroxide, generated *in situ* by the oxidation of ruthenium (III) chloride with sodium periodate.[88] Unfortunately, direct purification of the carboxylic acid was not possible so the crude reaction mixture was treated with TMS diazomethane to give methyl ester **29** in moderate yield. Yuxiang Zhu was able to cleave the vinyl group of **3ad** using ozonolysis to access alcohol *trans*-**30**, the diastereomer of which could be accessed *via* Fleming-Tamao oxidation of the silyl group of **3aj** to give *cis*-**30**.[89] This

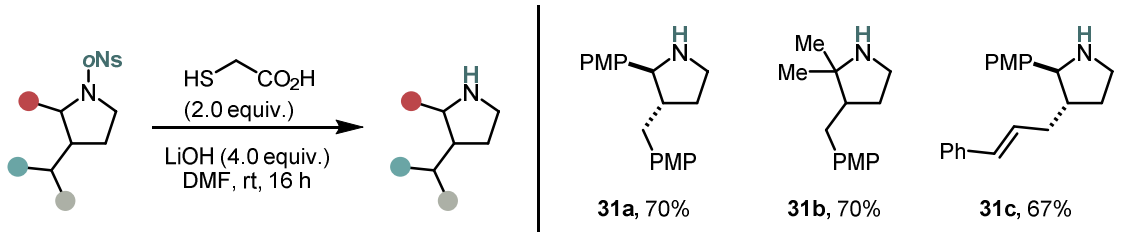
demonstrates how judicious choice of substrate allows the preferentially preparation of either *trans* or *cis* ring substituted products.



Scheme 54. C2 derivatisations. [a]Conducted by Yuxiang Zhu.

2.6.2 Protecting group removal

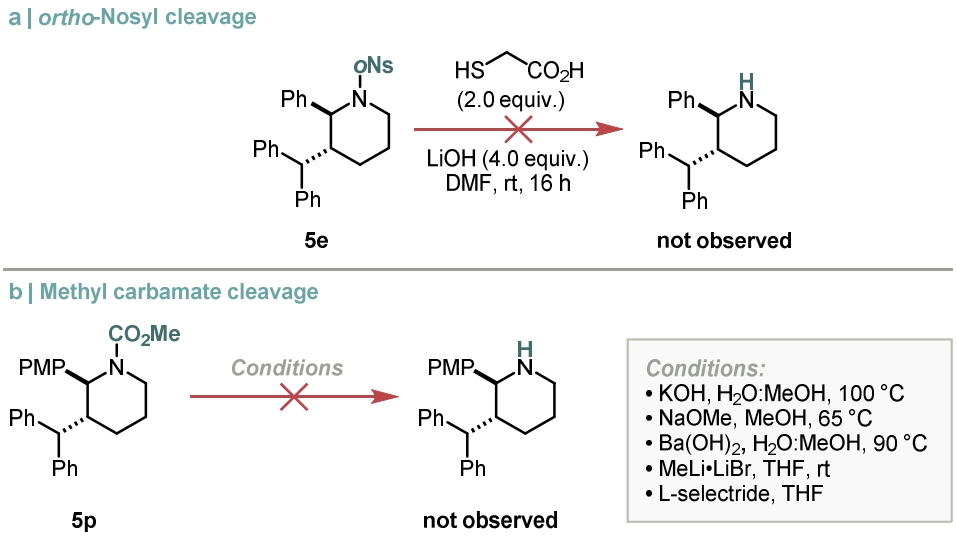
Finally, the fully demonstrate the utility of the method it was important to showcase removal of the *N*-protecting groups. Orthogonal strategies were required to remove the *ortho*-nosyl and methyl carbamate. Deprotection conditions for the pyrrolidine system were developed by Yuxiang Zhu, using mercaptoacetic acid and lithium hydroxide in DMF giving the corresponding free amines **31a** – **31c** in good yield (**Scheme 55**).



Scheme 55. Optimised conditions for *ortho*-nosyl removal. All reactions were conducted by Yuxiang Zhu.

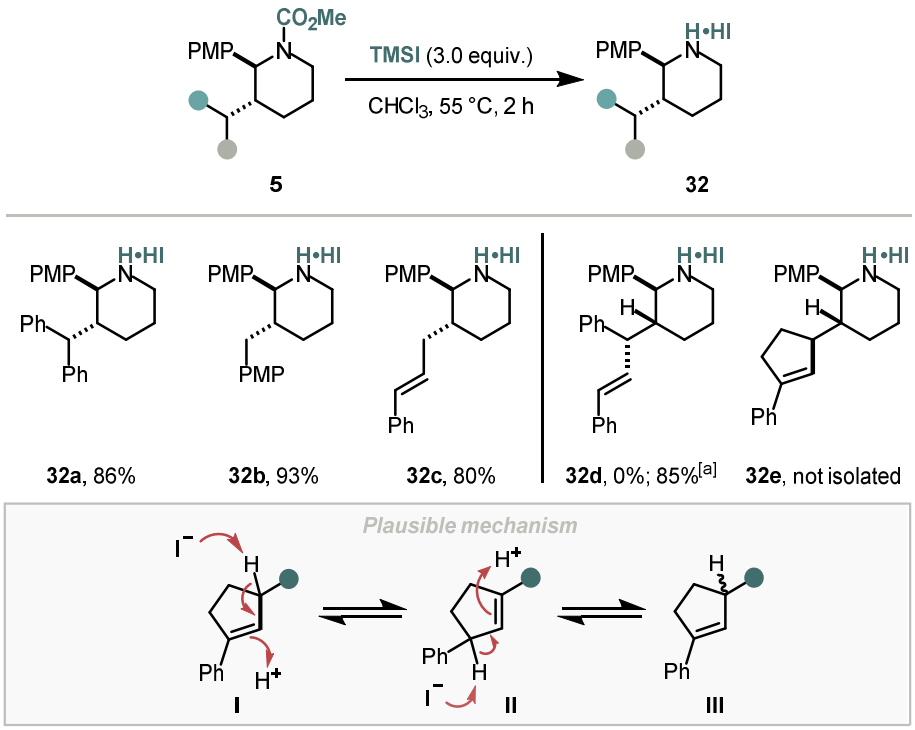
Despite an extensive arsenal of methods available to us in the literature for the removal of a methyl carbamate, the piperidine products were surprisingly resilient to derivatisation.[90] This was first discovered when the remove the *ortho*-nosyl group in **5e** was attempted, which remained untouched when subjected to the thiol/base conditions, leading us to hypothesise that the environment surrounding the nitrogen is sterically crowded with the reactive site being particularly encumbered (**Scheme 56a**). It was hoped that

the smaller carbamate projecting group would not exhibit the same problem, however treatment of **5p** to a variety of basic conditions were unsuccessful, in each case giving complete recovery of the **5p** (**Scheme 56b**).



Scheme 56. Failed attempts to cleave the piperidine *N*-protecting groups: *ortho*-nosyl (a), methyl carbamate (b).

Considering each of these conditions likely proceed *via* reaction at the carbonyl, attentions turned specifically to conditions which go *via* a different site of attack and found that reaction of **5p** with trimethylsilyl iodide (TMSI) in chloroform gave the corresponding iodide salt in high yield **32a** (**Scheme 57**).[91] A range of piperidines were then subjected to the conditions, both **32b** and **32c** gave similarly good yields, however, it was found that substrates containing a stereocentre at C7 underwent the reaction with a significant reduction in the diastereomeric ratio, **32d** – **32e**. It was hypothesised this was arising from HI in the reaction mixture reversibly adding across the double bond **I**, which could eliminate to alkene **II** before isomerisation back to the more stable **II**. Fortunately, addition of isoprene as a sacrificial alkene allowed us to access **32d** without stereoerosion at C7. As mentioned previously, the cyclopentenylphenyl moiety is particularly unstable and **32e** could not be isolated without scrambling of the stereocentre even under the moderated conditions.



Scheme 57. Optimised conditions for methyl carbamate cleavage with a proposed mechanism for the observed stereoerosion. [a]Using 10 equiv. of isoprene.

2.6.3 Stereochemical assignments – II

A crystal structure was obtained of **32c**, revealing that removal of the methyl carbamate shifts the conformation of the 2,3-substituents from diaxial (as observed in **5e**) to diequatorial, because there is no longer pseudoallylic strain between the 2-substituent and the nitrogen protecting group (**Figure 6**). Deprotection enabled a ^{1}H *J* coupling analysis, directly comparing key coupling constants between the protected and non-protected series (**Table 8**). Whereas previously the ^{1}H NMR of **5p** showed only small coupling constants (J = 2 – 5 Hz), aligning with a dihedral angle of 60 ° (*i.e.* axial-equatorial and di-equatorial relationships), the ^{1}H NMR of **32a** shows much larger coupling constants (J = 10 – 12 Hz), aligning with a dihedral angle of 180 ° (*i.e.* di-axial relationships). This was further corroborated through key nOe correlations observed in **32a** (**Figure 6**).

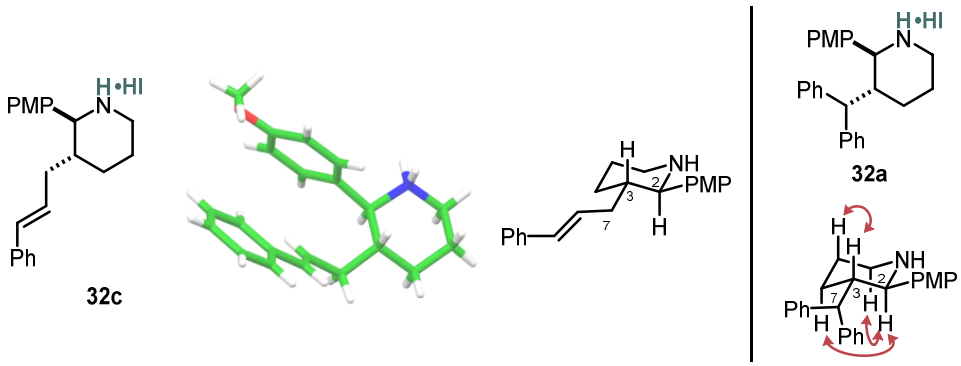
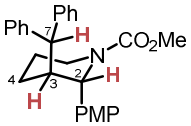


Figure 6 Crystal structure of **32c** and the nOes observed in **32a.**

Table 8. *J* coupling analysis comparing **5p** and **32a.**



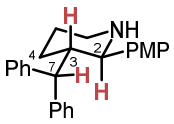
5p

$J_{C2\text{-}C3}$ = 2.2 Hz

$J_{C3\text{-}C7}$ = 11.9 Hz

$J_{C3\text{-}C4ax}$ = 4.2 Hz

$J_{C3\text{-}C4eq}$ = 2.2 Hz



32a

$J_{C2\text{-}C3}$ = 11.2 Hz

$J_{C3\text{-}C7}$ = 3.7 Hz

$J_{C3\text{-}C4ax}$ = 11.5 Hz

$J_{C3\text{-}C4eq}$ = 3.5 Hz

2.7 Preliminary investigations into target synthesis

At this stage in the development of the reaction it was felt that the synthetic utility was sufficient to apply the method to target synthesis. When carrying out a literature search of potential targets it was gratifying to find multiple molecules which showed the potential of being accessed *via* the methodology (**Figure 7**). Of these targets the drug Atrasentan **33** appeared closest in structure to what had already been demonstrated, and studies related to **33** will be detailed in **Chapter 4**. The other selected targets, Chelidonine **34** and Callophylline A **35** however, required us to explore different extensions to the methodology.[92,93] To establish if either were viable targets probing test reactions were carried out on both simultaneously.

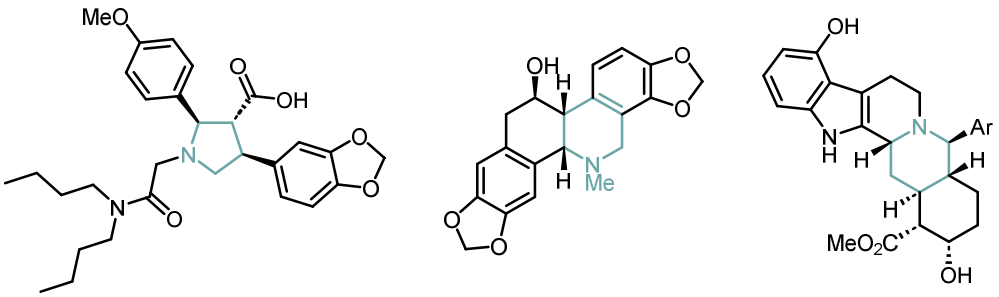
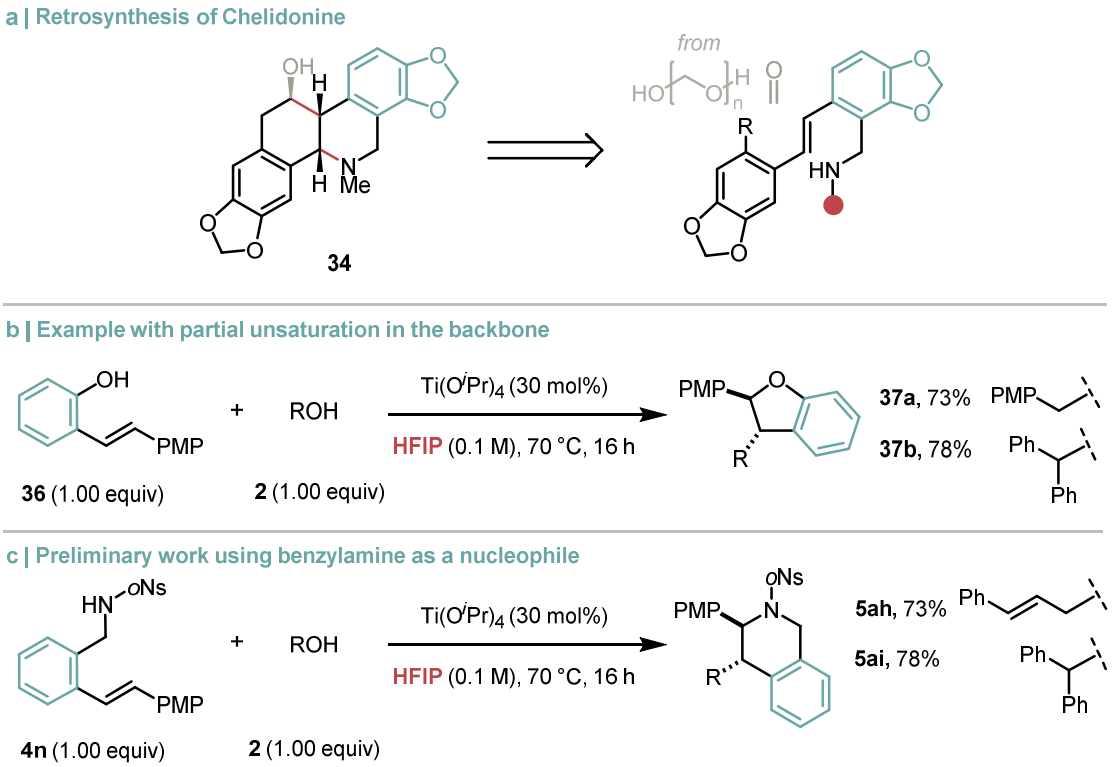


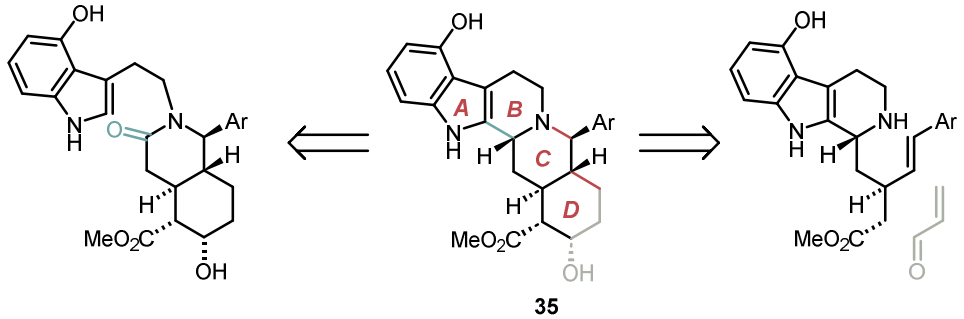
Figure 7. Potential targets for our methodology.

A carboamination approach to **34** using paraformaldehyde as the electrophile was proposed as the key disconnection, however inclusion of partial unsaturation into the nucleophile backbone would be required (**Scheme 58a**). Yuxiang Zhu had demonstrated this was possible in the oxygen system through use of phenol **36**, affording benzofurans **37a** and **38b** in good yield, however, the analogous reactivity of the nitrogen system had not been explored (**Scheme 58b**).[82] Preliminary work was carried out by Anna Miller, a placement student in the group, who demonstrated that benzylamine **4n** could undergo reaction with benzhydrol and cinnamyl alcohol to give **5af** and **5ag** in high yield (**Scheme 58c**).[94]



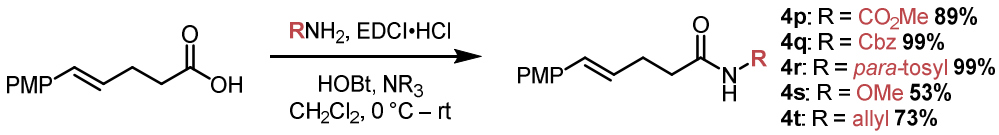
Scheme 58. Preliminary studies related to **34** including a retrosynthesis (a)**,** previous work on the oxygen system carried out by Yuxiang Zhu (b) and preliminary work carried out by Anna Miller (c).

For **35**, it was believed that inclusion of acrolein as the electrophile would enable the synthesis of the C and D rings *via* a carboamination approach (**Scheme 59**). It was proposed that reduction of an amide *via* an iminium ion followed by alkylation could be used to synthesise the B ring.



Scheme 59. Retrosynthesis of Callophylline A.

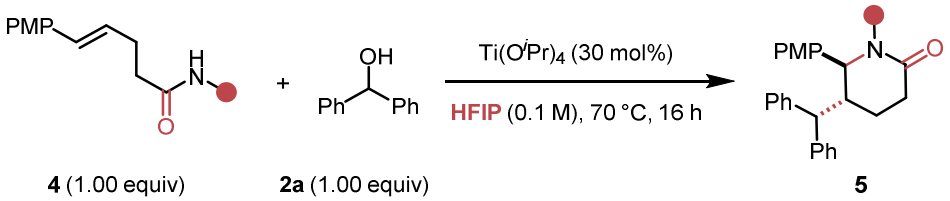
Although a carboxylic acid had be used in the oxygen system, using an unprotected amide **4o** was unsuccessful (**Table 9**, Entry 1) in preliminary investigations and introduction of an *N*-protecting groups was required for reactivity. Fortunately, synthesis of *N*-protected amides *via* an amide coupling of carboxylic acid **13** was facile enabling the preparation of five analogues in good yield **4x – 4ab** (**Scheme 60**).



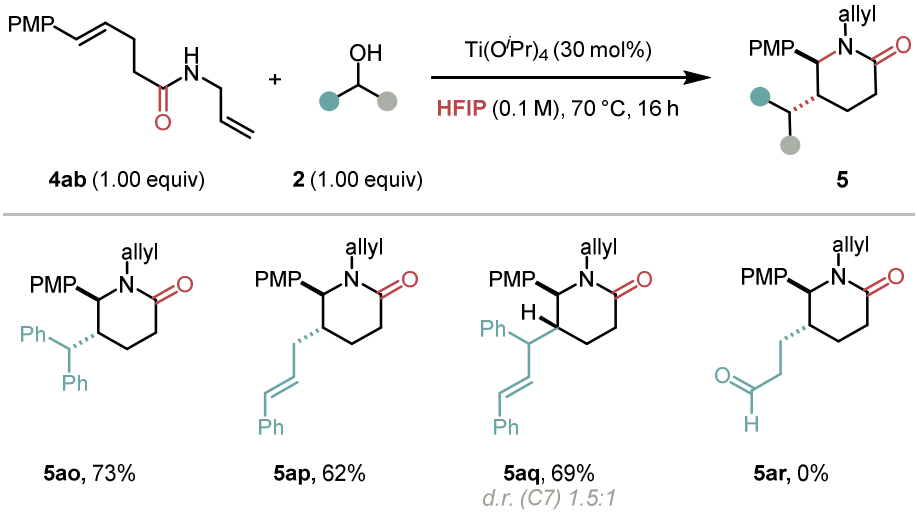
Scheme 60. Amide coupling reactions to access *N*-protected amides **4p – 4t** (NR_3 – *N*-methylmorpholine).

To our surprise, carbamates were unreactive (**Table 9**, Entries 2 & 3), and sulfonamides showed limited reactivity, with the tosyl amide affording **5am** in low yield (**Table 9**, Entries 2 – 4). The attention shifted towards less traditional *N*-activating groups, with methoxy giving a slightly improved yield **5an** and allyl giving the highest yield **5ao**. It is important to note that elevated temperatures were required to enable this transformation when compared to the standard use of benzhydrol, which usually triggers cyclisation at room temperature (*cf.* **Scheme 41**, **3a** & **3p**). Reaction of **4ab** with other alcohols was successful, affording **5ap** and **5aq** in moderate yield, however introduction of acrolein was not possible **5ar** (**Scheme 61**).

Table 9. Amide protecting group screen.



Entry	Protecting group (5)	5 (%)
1	- (**5aj**)	0
2	CO_2Me (**5ak**)	0
3	Cbz (**5al**)	0
4	tosyl (**5am**)	19
5	OMe (**5an**)	37
6	**allyl** (**5ao**)	73



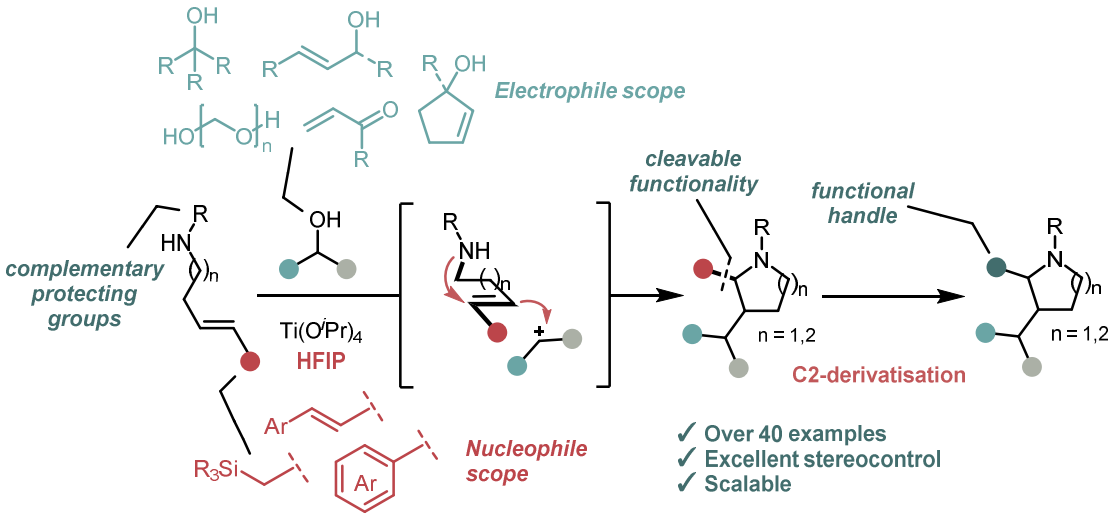
Scheme 61. Preliminary substrate scope using **4ab**.

Despite positive preliminary results for both targets, it was decided to focus on an enantioselective variant of our methodology prior to application to total synthesis.

2.8 Summary and outlook

In this chapter a complementary protecting group strategy has been developed to enable to the synthesis of complex pyrrolidines and piperidines using a range of allylic and benzylic alcohols (**Scheme 62**). Broadly excellent 2,3-*trans* stereoselectivity was observed and it was also demonstrated that an additional exocyclic stereocentre can be set affording products with three contiguous stereocentres. Although this work is a direct extension of the synthesis of THFs the ability to access the larger ring analogue marks a significant improvement in the method, especially when considering the limited approaches available in

the literature. Additionally, in an attempt to improve the synthetic utility of our method a range of non-alcohol electrophiles were screened, extending the scope to include paraformaldehyde and α,β-unsaturated carbonyl compounds, significantly increasing the functional groups observed in our products. In the same vein a 2-step approach to increase the functionality at the C2-position of our products was developed using a cleavable activating group, simultaneously enabling the synthesis of 2,3-*cis* substituted products through the use of an allyl silane precursor. Moreover, preliminary experiments to probe the application of this methodology to total synthesis have been carried. It is hoped that the strides made during our investigations could also be applied to the synthesis of other cyclic frameworks enabling access to a diverse range of products.



Scheme 62. Summary of carboamination methodology described in **Chapter 2**.

3

Enantioselective carboamination approaches to the synthesis of azacycles

3.1 Chapter overview

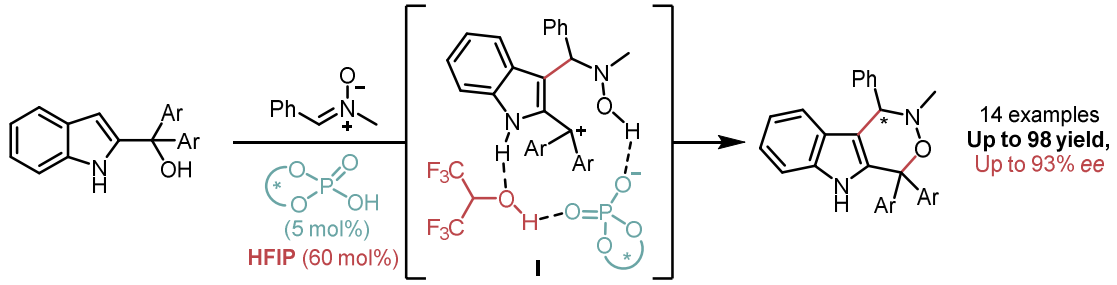
The following chapter presents attempts to translate the reaction described in **Chapter 2** into an enantioselective transformation. Initially detailed are the approaches considered when designing a reaction manifold before the initial hit was discovered. Extensive optimisation is then carried out on the transformation, alongside some experiments to establish the reaction mechanism. When insufficient enantioinduction was observed with the initial catalytic system further approaches were then screened.

3.2 Methodologies for the generation of chiral carbocations

3.2.1 The reliance on HFIP as a solvent

Despite the use of HFIP as a solvent across transition metal, Lewis acid and Brønsted acid catalysis, very few asymmetric transformations are reported, and if present, rather than being the sole solvent, HFIP is typically being engaged as a minor co-solvent or substoichiometrically as an additive or co-catalyst. This is unsurprising, the strong H-bond donating ability of HFIP has the potential to outnumber or saturate any potential interactions between a substrate and a chiral catalyst. This property can be used elegantly in some transformations, for example, the ability to form multiple hydrogen bonds can be an advantage in increasing the tightness of binding and rigidity of key transition states.[95] This is exemplified by the (3+3)-cycloaddition reported by Shi and co-workers, where HFIP was used as a co-catalyst (60 mol%), which according to computational modelling plays a key role in stabilising various transition states for example as in **I** (**Scheme 63**).[96] Unfortunately, predicting where and how HFIP will effect a transformation is challenging; reports which observe a positive effect on enantioselectivity when HFIP is added are often unable to rationalise why through mechanistic experiments or reaction modelling. For as many examples which found that HFIP had a positive influence on enantioselectivity as many, if not

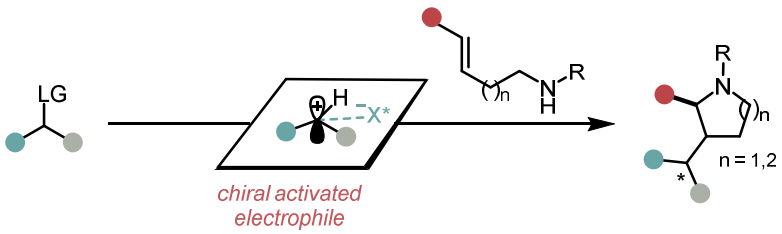
more, reported the opposite effect and for this reason reliance on HFIP as a solvent from the outset of developing an asymmetric carboamination process is undesirable.



Scheme 63. Representative example of HFIP use in asymmetric catalysis.

3.2.2 Potential approaches

Introduction of enantioselectivity into our transformation could be achieved *via* one of two approaches, activation of the nucleophile or activation of the electrophile. When considering catalyst systems to use, it became clear that focusing on activation of the electrophile would give us considerably more freedom with regards to the number of catalyst systems available to us (**Scheme 64**). This is not to say activation of the nucleophile is not possible, for example the work detailed earlier in the carboamination approaches (See **Chapter 1, Section 1.2.4**) by Wolfe and co-workers relies upon the formation of a bound chiral catalyst substrate complex *via* a carbopalladation prior to introduction of the electrophile.[31]

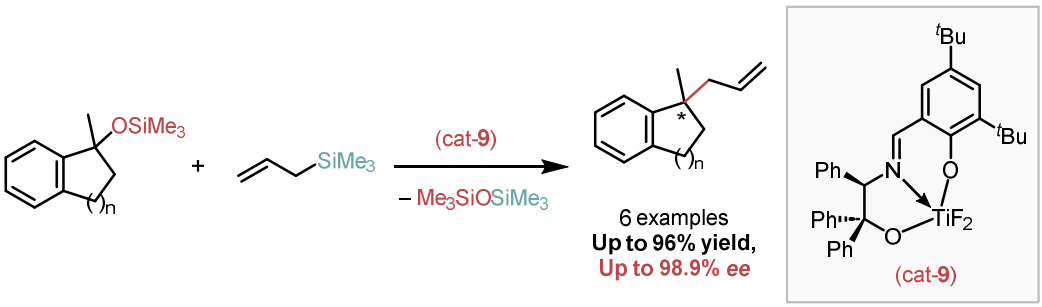


Scheme 64. Proposed asymmetric annulation.

Following an extensive review of the literature the main approaches available to activate the electrophile could be divided into three categories:

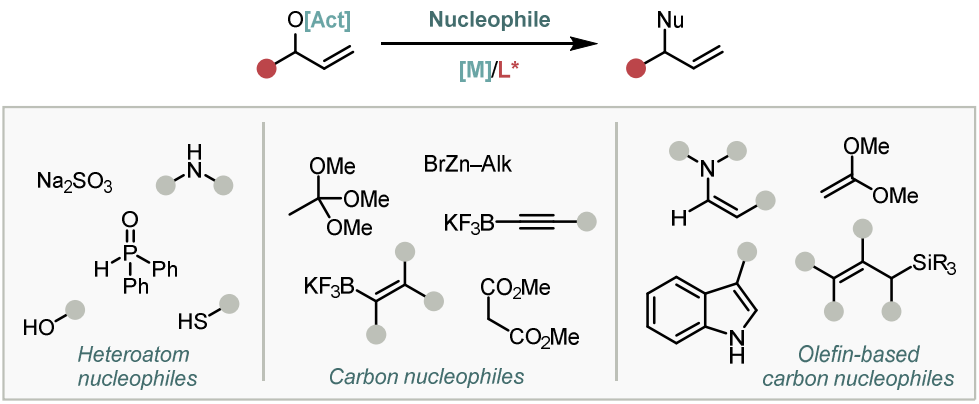
1. Chiral Lewis acid catalysis
2. Metal catalysed asymmetric allylic alkylation reactions
3. Chiral contact ion-pair catalysis
    a. Brønsted acid catalysis
    b. Thiourea organocatalysis

Whilst option one was clearly closely related to our previous conditions, an initial literature search revealed it was likely to be the most limited. Despite well-established transformations such as the Sharpless epoxidation, broadly, the complexation of chiral ligands to Lewis acids is lacking the generality which would enable the approach to become more commonplace. This is exemplified by the 2004 report by Braun and co-workers describing a Ti(IV)-catalysed carbon allylation onto alcohols; despite employing an effective chiral Ti complex (cat-**9**), capable of achieving >98% *ee*, no further reports of (cat-**9**) have been disclosed since (**Scheme 65**).[97] For this reason, this approach was considered with caution.



Scheme 65. Use of chiral titanium complex (cat-**9)**.

Conversely, option two is a more well-established approach, asymmetric allylic alkylations (AAAs) have been studied extensively and a diverse range of transition metals, chiral ligands and pro-electrophiles have been disclosed in the preceding years following the first report in 1977.[98,99] Despite the breadth of literature precedent, concerns associated with the requirement of the nucleophile were present, although a range of heteroatoms and carbon nucleophiles have been reported, the use of olefin-based nucleophiles is limited to activated systems for example using an enamine, or where the reaction is intramolecular, conversely it was believed that our system was significantly less reactive (**Scheme 66**).[100] This limitation was not unique to transition metal catalysed processes and one of our primary concerns when approaching this new transformation was the reactivity of the nucleophile.



Scheme 66. Examples of nucleophiles used in AAAs.

The final approach utilises catalysts discussed previously (See **Chapter 1, Section 1.4.2**), chiral ion-pairing catalysts, and specifically those related to chiral phosphoric acids (CPAs) and hydrogen-bond donors (HBDs) (**Figure 8**).[62] This method differs to AAA approach by the nature of the activated electrophile, while AAAs are considered to proceed *via* a bound intermediate ion-pairing catalysis utilises a true carbocation and is therefore the most similar in nature to our Ti/HFIP methodology. In addition to concerns with the reactivity of the nucleophile (chiral ion-pairing catalysis has a very similar nucleophile scope to that of AAA reactions), the variety of catalyst structures available also poses an issue. Whilst a series of well-described commercially available ligands exist which are broadly found in Tsuji-Trost allylations, the catalyst design for ion-pairing catalysis is far more bespoke. Not only are the frameworks rarely commercially available, but the aforementioned specificity associated with catalyst design means achieving high levels of enantioinduction potentially requires lengthy screening and catalyst synthesis. Despite our concerns, this approach was chosen to follow in the first instance.

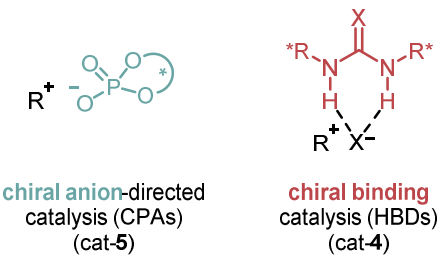
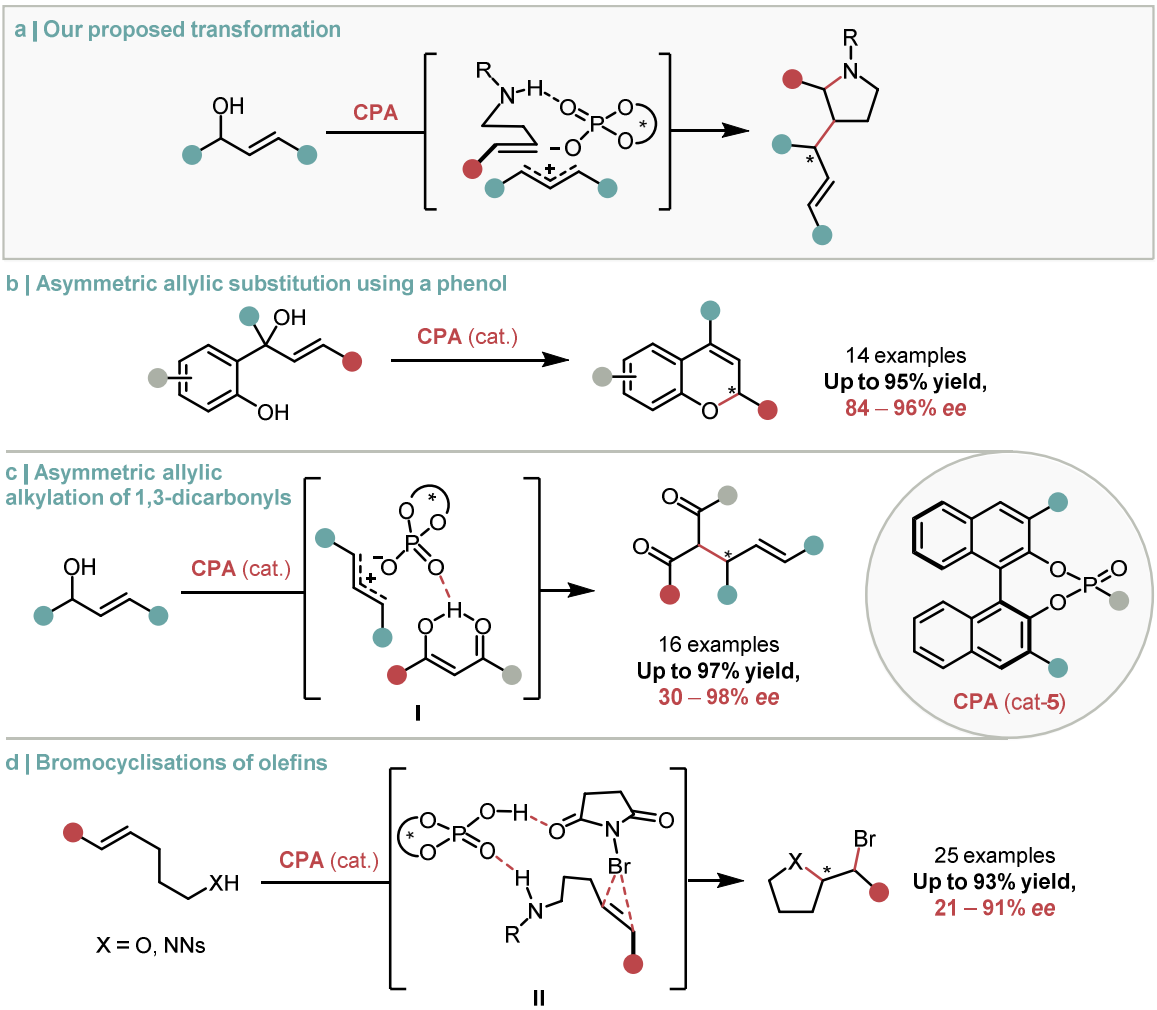


Figure 8. Chiral ion-pairing catalysis.

3.3 Reaction discovery

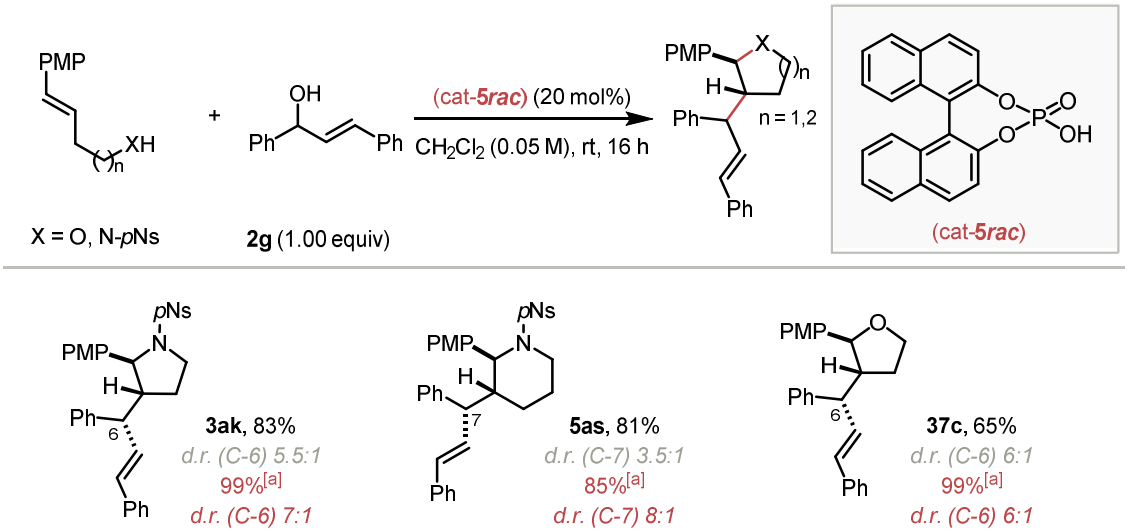
3.3.1 Initial hit

Initially, our efforts were focused on Brønsted acid catalysis and a comprehensive literature search revealed that many groups have studied allylic alcohols in inter- and intra-molecular reactions. Our envisioned transformation (**Scheme 67a**) is closely related to the 2011 report by Rueping and co-workers, with activation of a pendent 1,3-disubstituted allylic alcohol using a CPA triggering a cyclisation to generate a chromene with high levels of enantioenrichement (**Scheme 67b**).[101] Gong and co-workers reported a closely related intermolecular example, using 1,3-dicarbonyls as the nucleophile, here the catalyst behaves as a dual activator – coordinating both to the allylic carbocation and hydrogen bonding to the nucleophile *via* the basic site **I** (**Scheme 67c**).[102] Unfortunately, when the two transformations are compared, there is a significant drop in the enantioinduction achieved between the intra- and intermolecular examples, this is further supported by the report by Du and co-workers which reacts amines as the nucleophile with the allylic alcohol.[103] To the best of our knowledge allylic alcohols have not been used as electrophiles in an intermolecular cation triggered cyclisation, although NBS was used in the 2011 report by Shi and co-workers (**Scheme 67d**).[104] Dual coordination of the catalyst was proposed for the transition state this time *via* the succinimide **II**. We hoped to demonstrate the utility of this chemistry by having an allyl alcohol take the role of activating the double bond for cyclisation, leading to a novel C-C bond instead of a C-Br bond.



Scheme 67. Our proposed transformation (a) and key examples for our work**:** asymmetric allylic substitution to access chromenes (b) intermolecular allylic alkylation of 1,3-dicarbonyls (c) and bromocyclisations of olefins (d).

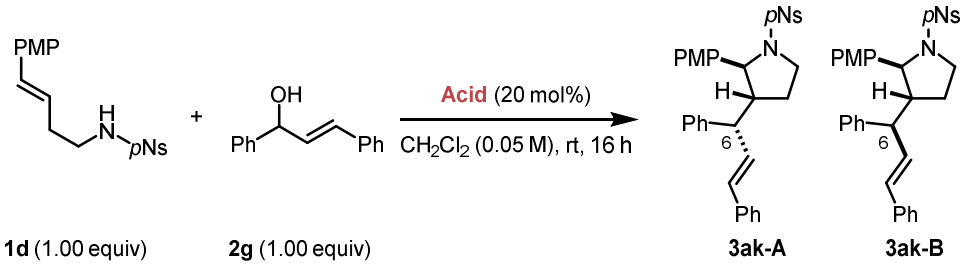
Initially (*E*)-1,3-diphenyl-2-propen-1-ol **2g** was used as the electrophile and a racemic phosphoric acid (cat-**5*rac***) was subjected to a test reaction using three nucleophiles. Due to the previously described issues with *ortho*-nosyl in the piperidine series (See **Chapter 2, Section 2.3**), and so that both nitrogen examples could be directly compared, the *para*-nosyl substrate was chosen at this early stage. Pleasingly all three reactions gave the desired product in good to high yields, in both nitrogen examples **3ak** and **5as** the diastereocontrol at the exocyclic centre was lower than the corresponding diastereomeric ratio observed using the old conditions, whereas the oxygen diastereoselectivity remained the same **37c** (**Scheme 68**). The use of (cat-**5*rac***) is the first successful *endo*-trig cyclisation carried out without using HFIP in our hands.



Scheme 68. Initial hit using (cat-**5*rac***) as a catalyst. [a]Corresponds to the yield and d.r. of the Ti/HFIP transformation.

However, this initial result did require us to establish two things: firstly, was (cat-**5*rac***) simply providing a proton, enabling an S_N2' displacement rather than forming an ion pair? If so, no enantioselectivity would be observed. As a control the reaction was repeated with a range of acids, whilst benzoic acid gave no product (**Table 10**, Entry 3), both diphenyl hydrogen phosphate (**Table 10**, Entry 2) and HCl in Et_2O (**Table 10**, Entry 4) afforded **3ak** in good yields.

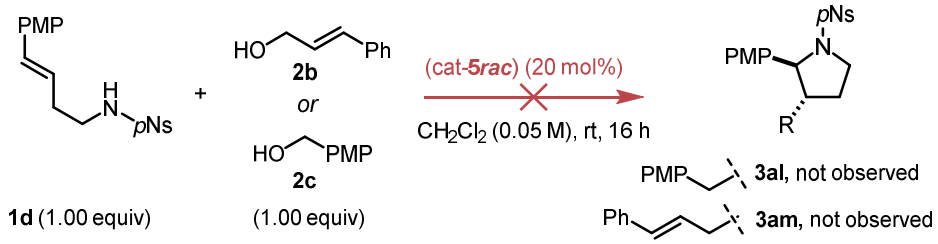
Table 10. Screen of different acids.



Entry	Acid	3ak (%)	*d.r. (C-6)*
1	(cat-**5*rac***)	83	5.5:1
2	$(PhO)_2PO_2H$	61	5.1:1
3	$PhCO_2H$	0	-
4	HCl (2.0 M in Et_2O)	77	5.5:1

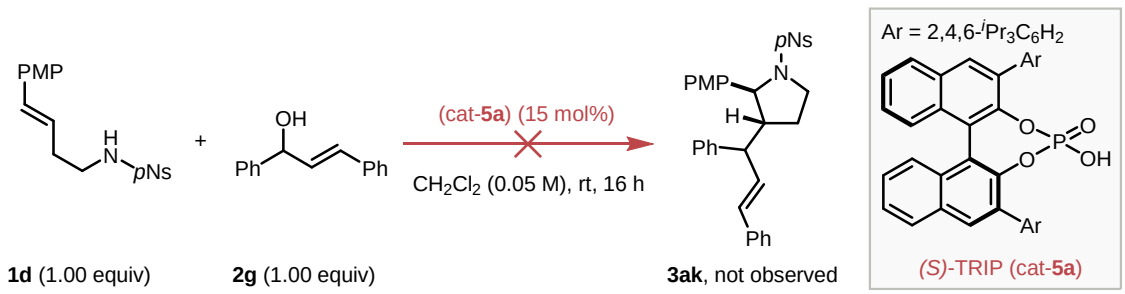
Secondly, optimisation of an enantioselective transformation becomes significantly more challenging when multiple diastereomers are made, primarily at this early stage due to the requirement to separate four rather than two stereoisomers during chiral HPLC analysis. For this reason, two additional

electrophiles were screened, cinnamyl alcohol **2b** and paramethoxybenzyl alcohol **2c**, neither giving any product (**Scheme 68**). This result was unsurprising, to the best our knowledge no reports exist where primary allylic and benzylic alcohols are used in CPA catalysed transformations, presumably because the CPA is unable to generate and stabilise the resulting carbocation.



Scheme 68. Failed attempt to use primary allylic and benzylic alcohols.

Therefore, it was decided to continue using **2g** as the alcohol and chose homoallylic amine **1d** as the substrate to carry out the first attempt of an enantioselective reaction. The amine system was chosen over oxygen because of the presence of the *N*-protecting group, an additional point of optimisation. The Donohoe group had no previous experience in the field of CPA catalysis and the only catalyst initially available to us was (*S*)-TRIP (cat-**5a**), where the BINOL 3,3'-substituents were the bulky 2,4,6-triisopropylphenyl groups. Unfortunately, when (cat-**5*rac***) was replaced with (cat-**5a**) no reaction was observed at room temperature, with complete recovery of **1d** (**Scheme 69**). Although this was initially disappointing, the fact that introducing steric bulk into the system hindered reactivity supported the formation of an ion pair between **2g** and (cat-**5**), dispelling the concerns associated with HCl also being able to catalyse the reaction.

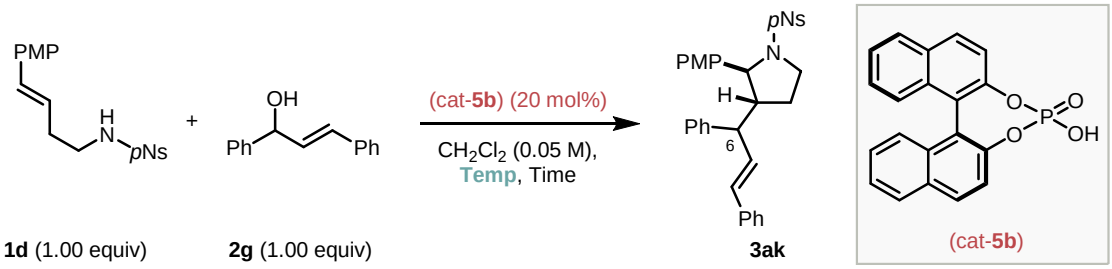


Scheme 69. Failed reaction using (cat-**5a**).

To force the reaction between the electrophile and the more sterically encumbered (cat-**5a**) it was decided to increase the reaction temperature. Prior to heating the reaction, a control experiment was carried out to offer an additional point of comparison, when the chiral, but unsubstituted (*S*)-BINOL phosphoric

acid catalyst (cat-**5b**) was used did it impart any enantioselectivity on the transformation and, if it did, what influence did lowering the temperature have (**Table 11**). As expected, reaction using (cat-**5b**) at room temperature gave full conversion to product and the same diastereoselectivity as with (cat-**5*rac***) (**Table 11**, Entry 1). Upon analysis of the mixture of four stereoisomers by HPLC using a chiral column, full base-line separation of all the isomers could not be achieved. Gratifyingly, the enantiomers of the major diastereomer **5ak-A** were separable. Although the enantiomeric ratio was slight, it was pleasing to see that **5ak-A** was not isolated as racemic mixture. To the best of our knowledge (cat-**5b**) is rarely reported as a chiral catalyst and is often seen in the early stages of optimisation.[63] Although reduction in temperature led to an improvement in diastereocontrol the enantiomeric ratio observed both at 0 °C and –20 °C remained the same (**Table 11**, Entry 2 & 3).

Table 11. Temperature studies using (cat-**5b**).



1d (1.00 equiv) **2g** (1.00 equiv) **3ak**

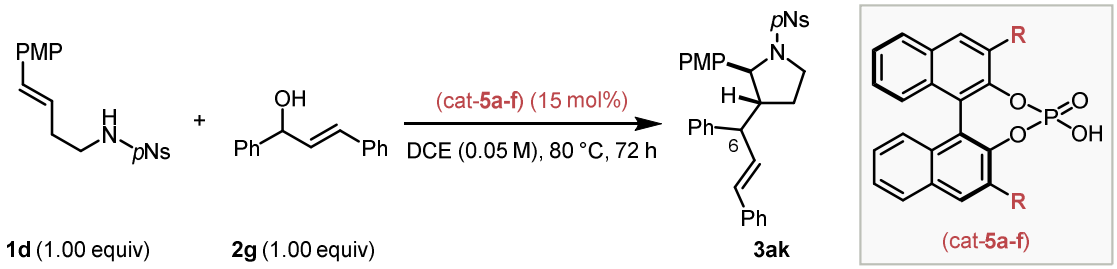
Entry	Temp (°C)	Time (h)	3ak (%)	*d.r. (C-6)*	*e.r. (3ak-A)*
1	rt	16	83	5.5:1	53:47
2	0	16	43	7:1	53:47
3	–20	72	36	8:1	53:47

e.r. corresponds to the major diastereomer.

The reaction with the bulky chiral catalyst (cat-**5a**) was repeated at higher temperatures, using DCE as the solvent, however only trace product was observed by TLC at 40 °C and 60 °C, and after 16 h at 80 °C the reaction had not progressed to completion; therefore, a prolonged reaction time of 72 h was used to ensure complete conversion. To our surprise the enantiomeric ratio was identical to that of the unsubstituted variant (53:47) (**Table 12**, Entry 1), in addition the diastereoselectivity at C-6 was significantly reduced from 5.5:1 to 2.5:1 (**Table 12**, Entry 2). At this stage, CPA catalysts bearing other aryl groups in the 3,3'-position were obtained (cat-**5c**) – (cat-**5f**), however in such small amounts that the reaction could not be carried out for more than one temperature. Instead, the reactions were monitored by TLC and when no reactivity was observed in any cases at room temperature or 40 °C (both for 4 h),

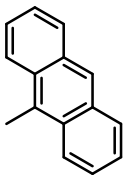
it was decided to carry out the reactions at 80 ˚C with the idea to screen at lower temperatures at a later stage when the reactivity was better understood. Unfortunately, varying the 3,3'-substitutent gave similarly low levels of enantioenrichment, the highest ratio (56:44) was observed when an anthracenyl group was present (cat-**5e/f**), aligning with the lowest diastereoselectivity (**Table 12**, Entries 5 & 6). It was evident from the catalyst screen that one or more components of the reaction needed to be more reactive, as heating reduced the diastereoselectivity without any appreciable enantioselectivity in return.

Table 12. Catalyst screen using **1d** as the nucleophile.

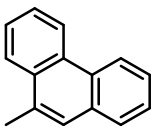


1d (1.00 equiv) **2g** (1.00 equiv) **3ak**

Entry	Ar	3ak (%)	*d.r. (C-6)*	*e.r. (3ak-A)*
1[a]	H (cat-**5b**)	83	5.5:1	53:47
2	2,4,6-$^{i}Pr_3C_6H_2$ (cat-**5a**)	65	2.5:1	53:47
3[b]	3,5-$(CF_3)_2C_6H_3$ (cat-**5c**)	69	4:1	51:49
4[b]	Ph (cat-**5d**)	79	2.5:1	55:45
5[b]	9-anthracenyl (cat-**5e**)	83	1.3:1	56:44
6[b]	9-phenanthryl (cat-**5f**)	83	1.6:1	56:44



9-anthracenyl



9-phenanthryl

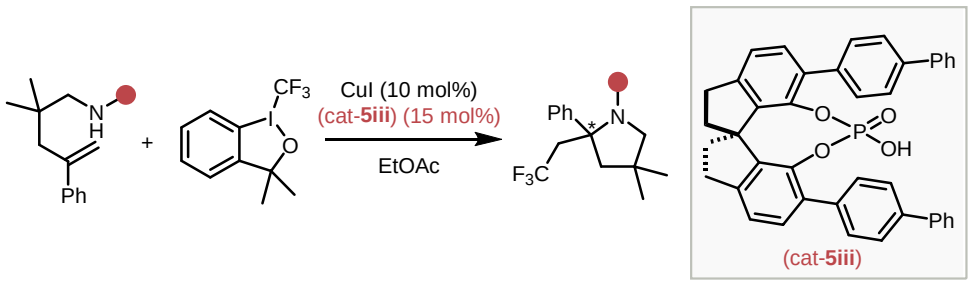
[a]Performed at rt. [b]Catalyst provided by another group within the Department of Chemistry. *e.r.* corresponds to the major diastereomer.

3.3.2 Improved substrate synthesis

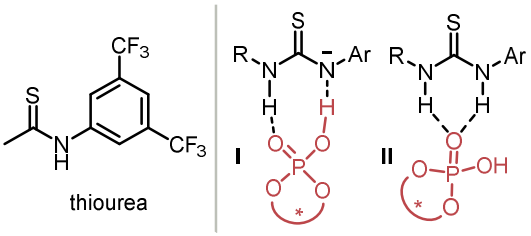
In 2016, Lin and co-workers reported a dual-catalytic strategy for the asymmetric radical trifluoromethylation of alkenes.[105] During optimisation, an examination of different *N*-protecting groups showed that, of a range of *N*-protected amines, most resulted in either no or low yields of desired product at both room temperature and 80 ˚C (**Table 13**). Conversely a 3,5-$(CF_3)_2$-phenylurea gave a significant improvement in yield and enantioselectivity, even at room temperature. The authors suggest the increase in reactivity was as a result of the increased nucleophilicity of the nitrogen when compared to the other activating groups. The increase in the enantioselectivity was proposed to arise from the additional acidic *N*-H site on the urea when compared to the other activating groups, with the introduction of further possible H-bonding interactions with the CPA (**I** & **II**). It was hoped that a similar trend would be

observed in our system through including the urea as an activating/protecting group. However, at present, the current route did not allow for introduction of such functionality.

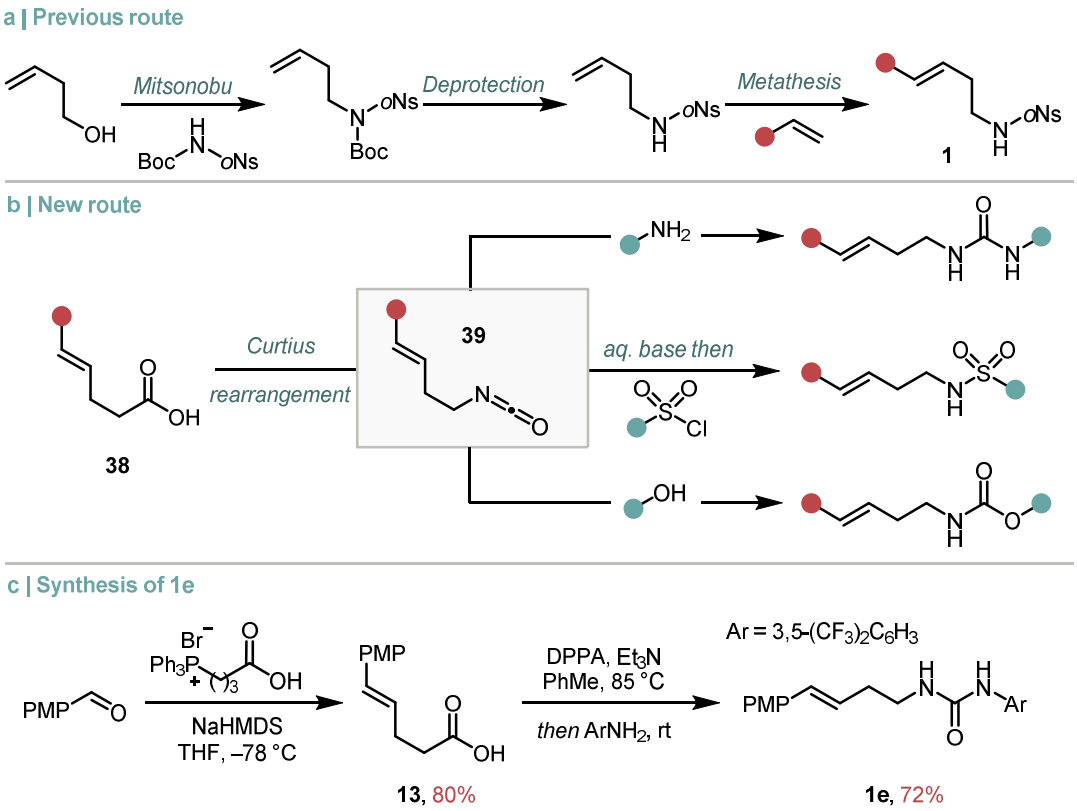
Table 13. Protecting group screen in the report by Lin and co-workers.



Entry	Protecting group	Temp (°C)	Yield (%)	*ee* (%)
1	H	rt / 80	0	-
2	C(O)Ph	rt / 80	0	-
3	Cbz	rt / 80	0	-
4	*para*-tosyl	80	46	20
5	thiourea	rt	90	56



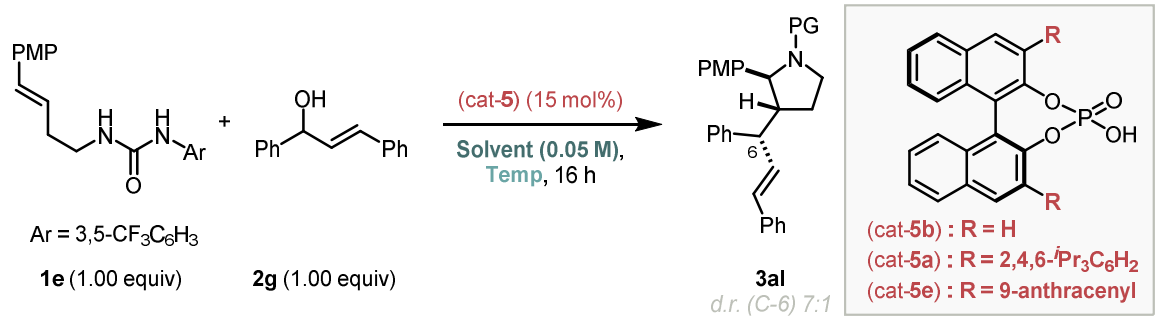
The route designed by Yuxiang Zhu to access homoallylic amines **1** prioritises diversification of the aromatic group with a metathesis as the final step enabling the use of a series of styrenes (**Scheme 70a**). However, a reversal in the order of steps was required, so a range of *N*-protecting groups could be introduced late on in the synthesis. Using a Mitsonobu reaction to introduce the nitrogen also limited what could be introduced as discussed earlier (See **Chapter 2, Section 2.3.4**). Fortunately, instead a carboxylic acid **38** could be subjected to a Curtius rearrangement to access crude isocyanate **38**, which could then be treated with a range of nucleophiles, amines to access ureas, alcohols to access carbamates, or treatment with aqueous base to access the free amine before introducing a sulfonyl chloride (**Scheme 70b**).[106] When compared to the initial route used by Yuxiang Zhu, which required additional steps and two challenging purifications, the new route allows for faster throughput of material (under 48 h from start to finish) with a single chromatography purification at the end. Overall, the new route offers a significant improvement to our previously disclosed methodology, when the ability to access starting materials is recognised as key to the overall synthetic utility of an approach. For the urea substrate **1e**, both carboxylic acid **13** and urea **1e** could be purified through recrystallisation, making the 2-step synthesis chromatography free (**Scheme 70c**).



Scheme 70. Substrate synthesis *via* the previous route by Yuxiang Zhu using a Mitsonubu reaction followed by a metathesis (a) or *via* the new route using a Curtius rearrangement (b) and the synthesis of **1e** (c). DPPA = diphenylphosphorylazide

With the substrate in hand, **1e** was subjected to reaction with a series of CPAs. As hoped, an increase in reactivity was observed, both bulky 3,3'-substituted catalysts (cat-**5a**) & (cat-**5e**) proceeded successfully at room temperature to generate **3al** (**Table 14**, Entries 2 & 3), however disappointingly with no significant enantioinduction, in fact (cat-**5a**) gave completely racemic material. It was decided to use catalyst (cat-**5e**) in a small solvent screen, and found that, although the conversion was lower, toluene gave slightly improved enantiomeric ratio 55:45 (**Table 14**, Entry 4). Both cyclohexane and fluorobenzene gave the same result as with CH_2Cl_2 52:48 (**Table 14**, Entries 5 & 6), cyclohexane was chosen as an example of a non-polar solvent and surprisingly resulting in no improvement in enantioinduction. Finally, reaction at 0 °C and in the presence of 4Å molecular sieves gave little to no change compared to the standard conditions (**Table 14**, Entries 7 & 8).

Table 14. Catalyst and condition screen using substrate **1e**.



Entry	Catalyst	Solvent	Temp (°C)	3al (%)	*e.r. (3al-A)*
1	(cat-**5b**)	CH_2Cl_2	rt	74	52:48
2	(cat-**5a**)	CH_2Cl_2	rt	74	50:50
3	(cat-**5e**)	CH_2Cl_2	rt	96	53:47
4	(cat-**5e**)	PhMe	rt	63	55:45
5	(cat-**5e**)	CyH	rt	60	52:48
6	(cat-**5e**)	C_6H_5F	rt	67	52:48
7	(cat-**5e**)	CH_2Cl_2	0	67	53:47
8[a]	(cat-**5e**)	CH_2Cl_2	rt	80	54:46

[a]Using 4Å molecular sieves.

3.3.3 Investigating the catalyst

The widespread use of CPAs is owed to the tuneable nature of catalyst structure, which can be altered in multiple ways (in addition to the 3,3'-substituent), leading to the development of several catalyst sub-classes, many of which are known to be more reactive (are stronger Brønsted acids), it was hoped one may prove successful in our transformation. Broadly, the steric environment primarily has an impact on the enantioselectivity rather than the yield of a transformation, meaning that the catalyst class is optimised prior to optimisation of 3,3'-substitutent. However, varying the BINOL backbone is more complicated, for example introducing partial saturation **(i)** has an impact on the pK_a and other axially chiral backbones such as vaulted biaryls **(ii)** or SPINOL **(iii)** differ not only in the pK_a but the steric environment, in fact, authors sometimes report limited reactivity with BINOL derived CPAs but find good reactivity with SPINOL derived CPAs (**Figure 9**).[107,108] Finding the balance between the use of steric bulk to impart enantioinduction without too great steric hindrance is clearly a challenge in our reaction. Investigating this effect is hampered by the availability of non-BINOL derived CPAs which, when compared to commercially available BINOL CPAs, can be lengthy to synthesise, therefore we were keen to consider other catalyst classes before expending time and on lengthy ligand synthesis.

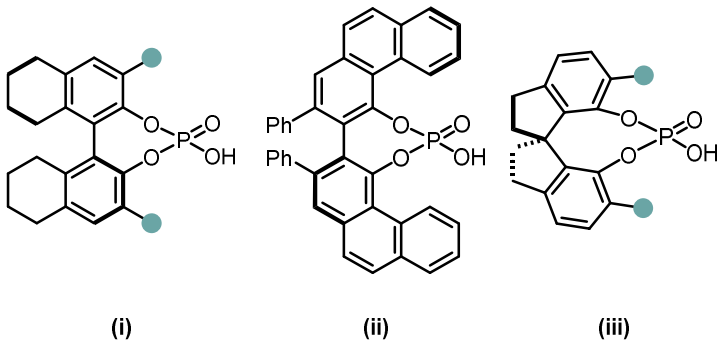


Figure 9. Non-BINOL derived CPAs.

Fortunately, the second point of variation has a much larger influence on the reactivity (according to the differences in pK_a), varying the heteroatoms directly bonded to the phosphorus. Both dithiophosphoric acids (cat-**10**), where the oxygens are replaced by sulfur and *N*-phosphoramides (NPAs) (cat-**11**), where an activated nitrogen (such as an *N*-trifyl group) is introduced, are stronger Brønsted acids and have found applications where the corresponding CPA shows no reactivity (**Figure 10**).[109,110] Whilst dithiophosphoric acids can be directly compared to CPAs, the introduction of a *N*-group influences both the steric environment and the Brønsted basicity. The presence of several different Brønsted basic sites gives rise to a large number of geometrically distinct ion pairs (compared to only one in a traditional CPA). Rotational freedom around the P-N and N-S bonds alters the relative positioning of the acidic and basic sites, meaning there is more than one catalytically active species capable of stabilising a transition state, often resulting in poor enantioselectivity. To fix the geometry into one active form, the List group has established a novel sub-class, the imidodiphosphates (cat-**12**), which are conformationally locked by the 3,3'-substituents so the highly rigid system only possesses a single catalytically active bifunctional ion pair.[111] Compared to traditional CPAs imidodiphosphates (IDPs) have a more sterically constrained active site, meaning they are often used to activate small substrates which do not possess sterically demanding protecting groups or other bulky (aromatic) substituents. For ease of synthesis, two unsubstituted catalysts were prepared, one dithiophosphoric acid (cat-**10a**) and one *N*-trifyl NPA (cat-**11a**) to gauge reactivity prior to considering more complex catalyst frameworks (**Scheme 71**).

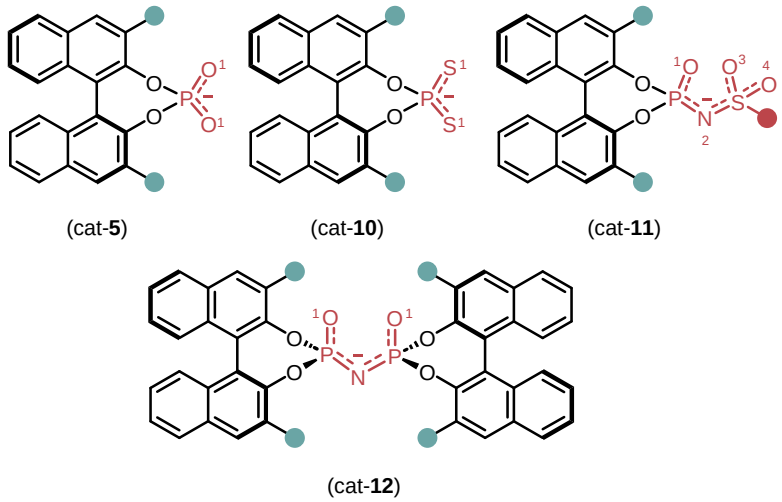
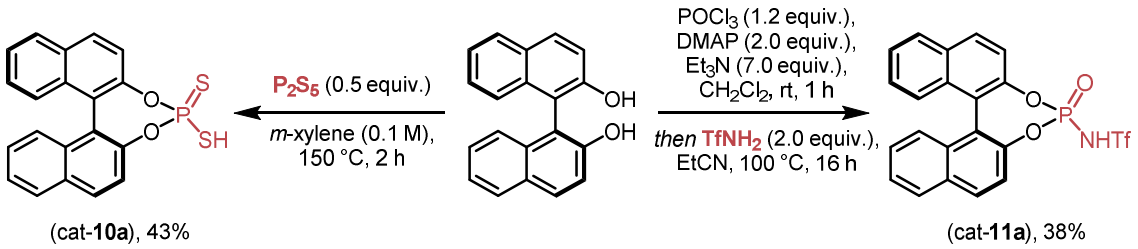


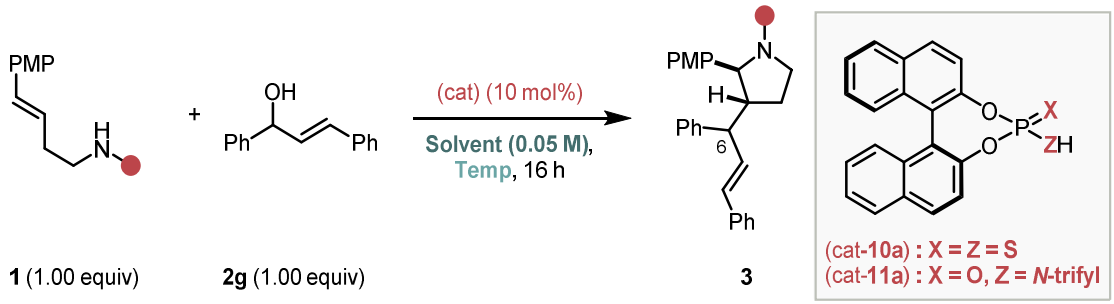
Figure 10. Sub-classes of CPAs with different heteroatoms. The different Brønsted basic sites are shown in red.



Scheme 71. Preparation of literature known catalysts (cat-**10a**) and (cat-**11a**).

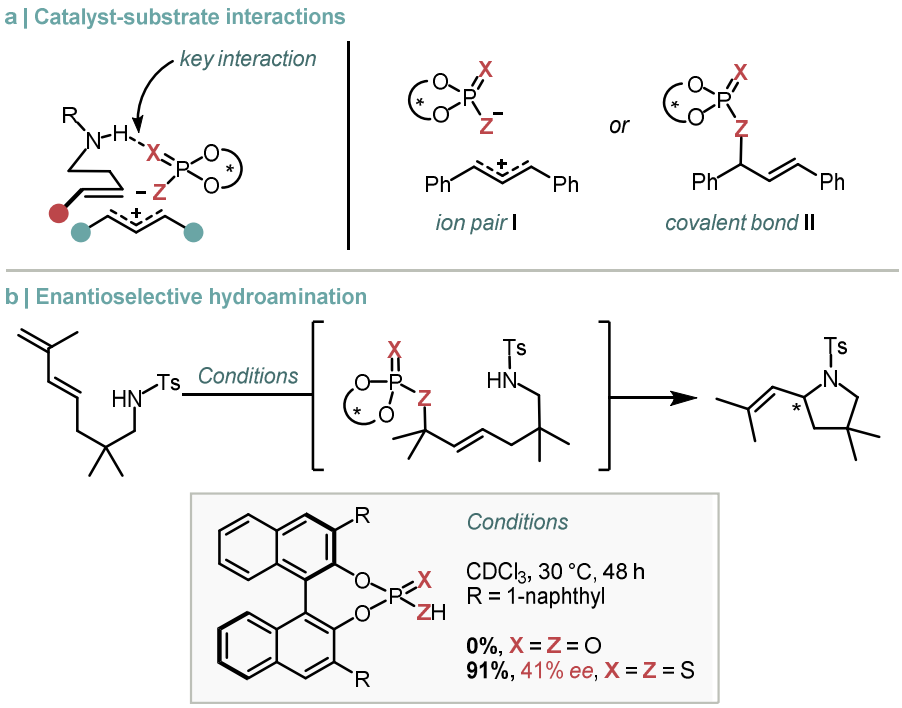
When sulfonamide **1d** was subjected to the reaction using both catalyst (cat-**10a**) and (cat-**11a**) at room temperature, no reactivity was observed, this was the first time no reaction was observed using an unsubstituted catalyst (**Table 15**, Entries 1 & 2). In fact, heating to 60 ˚C was required for appreciable conversion and **3ak** was isolated as a racemic mixture in both cases (**Table 15**, Entries 3 & 4). As it had been established from previous experiments that urea **1e** was more reactive, comparison of the reactivity using catalysts (cat-**10a**) and (cat-**11a**) was made, here both were able to generate **3al** at room temperature, however no enantioselectivity was observed.

Table 15. Catalyst and condition screen using (cat-**10a**) and (cat-**11a**).



Entry	*N-group*	Cat	Solvent	Temp (°C)	3 (%)	*d.r. (C-6)*	*e.r. (3-A)*
1	*p*-nosyl (**3ak**)	(cat-**10a**)	CH_2Cl_2	rt	0	-	-
2	*p*-nosyl (**3ak**)	(cat-**11a**)	CH_2Cl_2	rt	0	-	-
3	*p*-nosyl (**3ak**)	(cat-**10a**)	DCE	60	83	3.3:1	50:50
4	*p*-nosyl (**3ak**)	(cat-**11a**)	DCE	60	69	3:1	50:50
5	urea (**3al**)	(cat-**10a**)	CH_2Cl_2	rt	69	7.5:1	50:50
6	urea (**3al**)	(cat-**11a**)	CH_2Cl_2	rt	69	6:1	51:49

Although this was not the result we had hoped for, screening these two catalysts provided us with important information about our transformation. As both (cat-**10a**) and (cat-**11a**) are more acidic than (cat-**5b**), it is likely that in all cases activation of the alcohol was taking place, forming an ion pair **I**, this suggests the rate-determining step is addition of the nucleophile. If this is the true then the results in **Table 15** are unsurprising, whilst the catalysts may be more acidic, the dual-functionality is affected, both (cat-**10a**) and (cat-**11a**) are weaker Brønsted bases. We propose that in the case of sulfonamide **1d**, both catalysts were sufficiently poor H-bond acceptors that they were unable moderate the acidity of the nitrogen resulting in lower nucleophilicity and higher temperatures being required for reactivity. Conversely urea **1e** is a much more nucleophilic, requiring less basic activation from the catalyst, hence the observed reactivity at room temperature. What effect increasing the nucleophilicity of the conjugate base had on the carbocation of **2g** was also considered. The increased polarisability of sulphur makes (cat-**10a**) much more nucleophilic potentially leading to formation of **II** *via* covalent bonding (**Scheme 72a**). If this is the case, the reactivity of the electrophile is diminished when compared to the corresponding ion pair. These observations are consistent with the report of Toste and co-workers where activation of a diene using a covalent linkage was required before undergoing an enantioselective S_N2' displacement, here no reactivity was seen with a traditional CPA but reactivity was observed with the dithiophosphoric acid (**Scheme 72b**).[112]



Scheme 72. Key interactions between the substrate and the catalyst (a) and an example of covalent bonding using a dithiophosphoric acid (b).

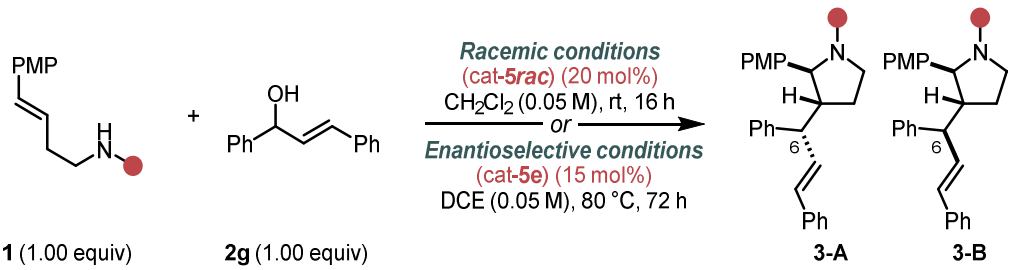
Considering that it was believed that the acidity of the amine was important for reactivity our focus was moved to the *N*-protecting group, in the hope to return to catalyst design at a later stage.

3.3.4 Investigating the nucleophile

To gain further insight into the effect of the *N*-protecting group, three additional substrates were made, two sulfonamides and a carbamate, using sequence described previously in 56 – 80% yield (See **Section 3.3.2, Scheme 70**). The 9-anthracenyl substituted CPA (cat-**5e**) was used for the screening having consistently performed comparably better in previous catalyst screens. Although mesylates had performed poorly under the Ti/HFIP conditions it was hoped that a smaller activating group may result in less steric encumbrance. The racemic reaction of **1f** gave **3am** in reduced yield and diastereocontrol when compared to the *para*-nosyl example (**Table 16**, Entry 1), when **1f** was subjected to the reaction with catalyst (cat-**5e**) at 80 °C a small reduction in the diastereoselectivity was observed (3.5:1 to 2:1 *vs* 5.5:1 to 2.5:1 as observed in **3ak**). For previous substrates separating all four products by HPLC using a chiral column was not possible, however it was for **3am**, revealing an interesting result: a higher enantiomeric ratio was observed for the *minor* diastereomer **3am-B** (66:34) than what was observed for the *major* diastereomer **3am-A** (51:49) (**Table 16**, Entry 2). When the tosyl substrate **1g** was subjected

the same trend was observed, here the 'minor' diastereomer was observed in a 1:0.9 ratio (**3an-B:3an-A)**, the enantiomeric ratio of **3an-B** was considerably higher (80:20) when compared to **3an-A** (61:39) (**Table 16**, Entry 3). Unfortunately, although methyl carbamate **1h** gave the best diastereoselectivity using the racemic catalyst (cat-**5*rac***), subjection to the enantioselective conditions gave **3ao** as a racemic mixture (**Table 16**, Entry 4). Two further carbamates were prepared, the Cbz amine **1i** and Boc amine **1j**. Disappointingly, the Cbz pyrrolidine **3ap** was not fully separable by chiral HPLC so no reaction with chiral catalyst was carried out (**Table 16**, Entry 5) and Boc pyrrolidine **3aq** was unstable in the reaction conditions leading to a complex mixture of products (**Table 16**, Entry 6). In the literature, sulfonamides are consistently chosen as the *N*-protecting groups for CPA catalysed hydroamination reactions, with very little mention of carbamates, so it was unsurprising to find that the functionality was unsuitable.

Table 16. *N*-protecting group screen I.



1 (1.00 equiv) **2g** (1.00 equiv) **3-A** **3-B**

Entry	*N*-group	Racemic conditions		Enantioselective conditions			
		3 (%)	***d.r. (C-6)***	**3 (%)**	***d.r. (C-6)***	***e.r. (3-A)***	***e.r. (3-B)***
1	*p*-nosyl (**3ak**)	83	5.5:1	78	2.5:1	56:44	-
2	mesyl (**3am**)	54	3.5:1	40	2:1	51:49	66:34
3	tosyl (**3an**)	92	4.5:1	78	0.9:1	61:39	80:20
4	CO_2Me (**3ao**)	80	14:1	33	12:1	50:50	50:50
5	Cbz (**3ap**)	80	6:1	-	-	-	-
6	Boc (**3aq**)	-	-	-	-	-	-

To establish whether the trend observed with the sulfonamide series was unique to the anthracenyl catalyst (cat-**5e**), tosyl substrate **1g** was treated with catalyst (*S*)-TRIP (cat-**5a**), in this case **3an** was isolated as a racemic mixture. Further investigations into the relationship between diastereoselectivity and enantioselectivity using catalyst (cat-**5e**) were required. A range of electron rich-, poor- and bulky-sulfonamides were prepared (**1k** – **1n**) using sequence described previously in 39 – 68% yield.

At this stage it is necessary to detail the nomenclature used for the major and minor diastereomers. Although in some cases the major product from the racemic reaction was not observed as the major

product using the chiral catalyst (such as for tosyl substrate **3an**) for ease of communication, a consistent assignment of major based on the racemic product distribution will be made, *i.e.* **-A** (major) and **-B** (minor) (**Figure 11**). Whilst the relative stereochemistry is known through 2D NOESY analysis and NMR comparison with the closely related **15** of which a crystal structure is known, the absolute stereochemistry is unproven and has been drawn as such nominally to aid consistency.

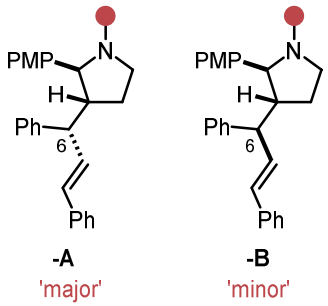
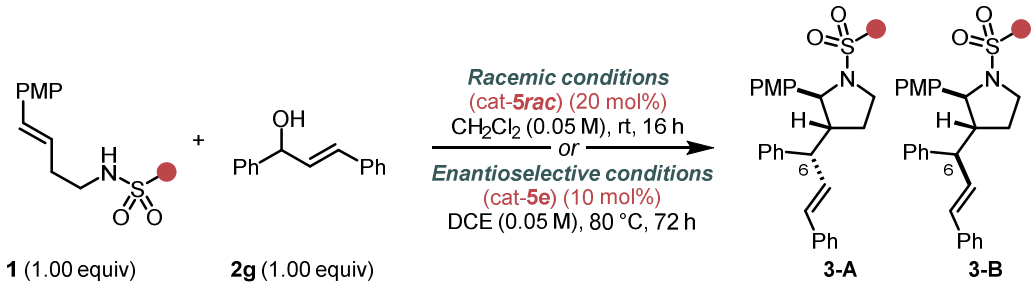


Figure 11. Stereochemical nomenclature.

Unfortunately, further issues with analysis occurred and two of the sulfonamides prepared **1m** and **1n** gave pyrrolidine products **3at** and **3au** which could not be fully separated by HPLC using a chiral column (**Table 17**, Entries 6 & 7). This left three additional sulfonamides products to use for comparison **3ar** – **3at** (**Table 17**, Entries 3 – 5). Across the five sulfonamides a clear relationship between the diastereoselectivity and the enantioselectivity was observed. A reduction in the diastereoselectivity corresponded with an increase in the enantioselectivity (across both diastereomers) – *i.e.* both napthyl **3ar** and tosyl **3an** had the lowest d.r. at ~1:1 but the highest e.r. of ~60:40 (A) and ~80:20 (B) compared to mesyl **3am** which had a higher d.r. at 2:1 but a lower e.r. This suggests a mismatch between substrate preference and catalyst preference. According to our proposed transition states used to rationalise the diastereoselectivity of alcohol **2g** in the Ti/HFIP transformation (**Scheme 73**), it was believed that the allylic carbocation orientates in such a way to minimise its steric clash with the nucleophile, leading to the observed preference. At elevated temperatures the increase in energy within the system leads to a lowering for this bias, enabling the formation of a higher proportion of the minor diastereomer. The link between the examples with the greatest reduction in diastereocontrol and the best enantioselectivity suggests an additive effect of the catalyst, preferentially generating the 'minor' diastereomer, presumably the steric clash with the catalyst outweighs whatever reduced substrate control there may be at elevated temperatures. To confirm this hypothesis reactions using the achiral catalyst (cat-**5*rac***) were repeated at

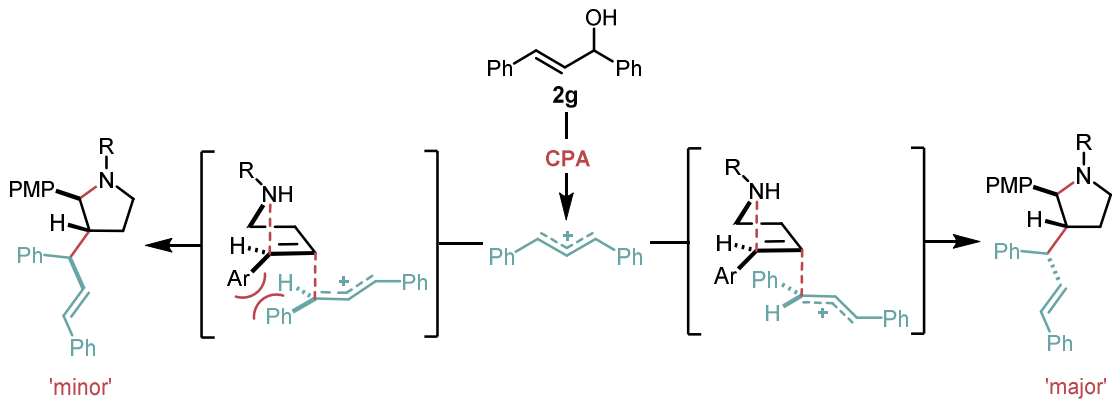
80 °C (**Table 17**, Entries 1 – 5, highlighted in red), and although a reduction in the diastereocontrol was observed when compared to the room temperature reaction, in all cases the d.r. was considerably higher than the corresponding d.r. when the chiral catalyst was used.

Table 17. *N*-protecting group screen II.



Entry	R group	Racemic conditions		Enantioselective conditions			
		3 (%)	*d.r. (C-6)*	3 (%)	*d.r. (C-6)*	*e.r. (3-A)*	*e.r. (3-B)*
1	Me (**3am**)	54	3.5:1 (2.5:1)[a]	40	2:1	51:49	66:34
2	4-MeC_6H_4 (**3an**)	95	4.5:1 (3.75:1)[a]	78	0.9:1	61:39	80:20
3	2-$NO_2C_6H_4$ (**3d**)	72	4:1 (2.5:1)[a]	58	1.25:1	56:44	80:20
4	Naphthyl (**3ar**)	79	5.5:1 (3.5:1)[a]	57	1:1	63:37	81:19
5	Ph* (**3as**)	83	5:1 (3.75:1)[a]	55	1.25:1	59:41	79:21
6	2,4-$(NO_2)_2C_6H_3$ (**3at**)	80	5:1	-	-	-	-
7	2-$MeOC_6H_4$ (**3au**)	96	5:1	-	-	-	-

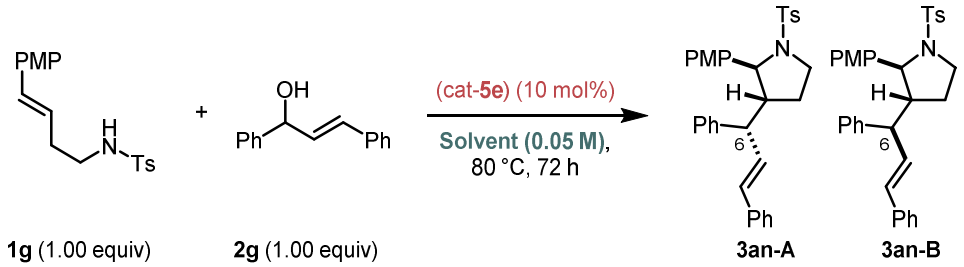
[a]Corresponds the *d.r. (C-6)* when the reaction was carried out at 80 °C.



Scheme 73. Steric model for stereochemical outcome of **2g** as an electrophile.

A brief solvent screen using tosyl substrate **1g** was carried out, toluene and fluorobenzene afforded **3an** in comparable yield and selectivity (**Table 18**, Entries 1 & 2), cyclohexane gave a slightly reduced yield, and a significant reduction in selectivity, which we were unable to rationalise (**Table 18**, Entry 3).

Table 18. Solvent screen with **1g**.

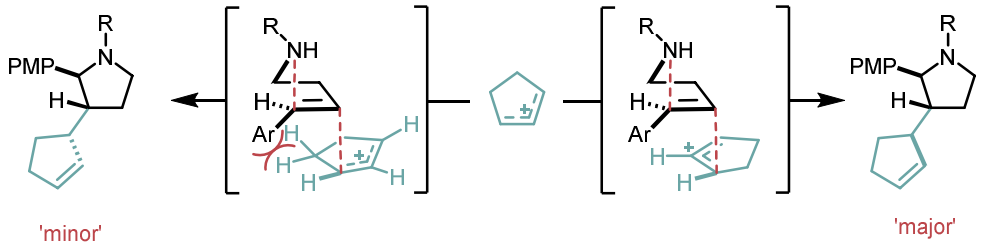


Entry	Solvent	3an (%)	*d.r. (C-6)*	*e.r. (3an-A)*	*e.r. (3an-B)*
1	PhMe	84	0.9:1	62:38	80:20
2	C_6H_5F	69	0.8:1	64:36	82:18
3	CyH	61	1.7:1	55:45	66:34

Although some of the enantiomeric ratios observed during the *N*-protecting group screen were significant as isolated results, considering that the ratio was of the 'minor' diastereomer and made in a ratio of ~1:1, it was still a significant way off of a desirable asymmetric transformation. For this reason, it was decided to investigate the alcohol component, hoping to improve our chances of getting enantioselectivity without the current issues associated with diastereoselectivity.

3.3.5 Investigating the electrophile

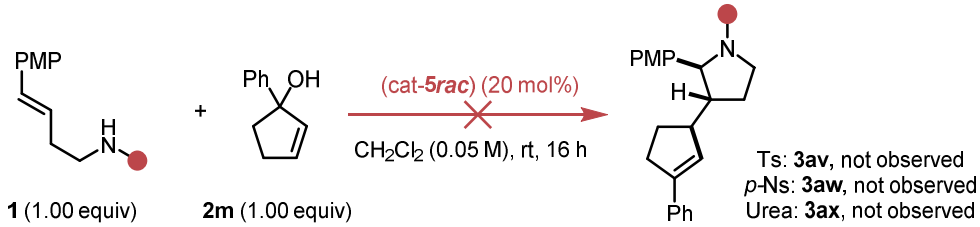
Initially the use of other allylic alcohols was considered; in our previous work a switch in the diastereoselectivity when going from acyclic to cyclic allylic alcohols was observed (**Scheme 74**), and it was hoped that the inherent substrate preference for the other diastereomer may in this case match with the diastereomeric preference of the catalyst.[81]



Scheme 74. Proposed origin of diastereoselectivity with cyclic allylic alcohols.

When a range of *N*-protected amines (**1d**, **1e** & **1g**) were subjected to a reaction with **2m**, no product **3av – 3ax** was formed and complete decomposition of alcohol **2m** was observed (**Scheme 75**). It had previously been found that **2m** was sensitive to acid, decomposing on silica unless base was added to the eluent, or if left in as a solution in deuterated chloroform for extended periods. Unfortunately, the

other cyclic alcohols available to us (See **Chapter 2, Section 2.4.1**) exhibited low diasteroselectivity in the Ti/HFIP conditions or required elevated temperatures for reactivity, for this reason, our attention moved to other classes of electrophiles.



Scheme 75. Failed attempt to use cyclic allylic alcohol **2m**.

Next, non-alcohol electrophiles were considered, literature searching revealed trichloroacetimidates **38** as potential alternatives, trichloroacetimidates have been using in combination with CPAs for a range of intramolecular transformations to good effect, showing reactivity where simple alcohols were not a sufficiently reactive leaving group.[113] However, our main concern was not increasing the reactivity of the electrophile, instead it was hoped to take advantage of the additional and different bonding interactions which the group imparts. It was proposed that switching the mechanism from S_N1 **I** to S_N2' **II**, with additional directional hydrogen bonding (rather than ion pair interactions) would introduce rigidity into the system during the addition and therefore lead to increased enantioinduction (**Figure 12**).

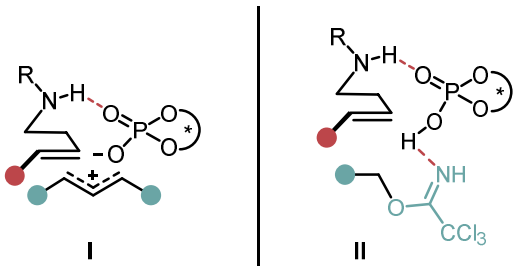
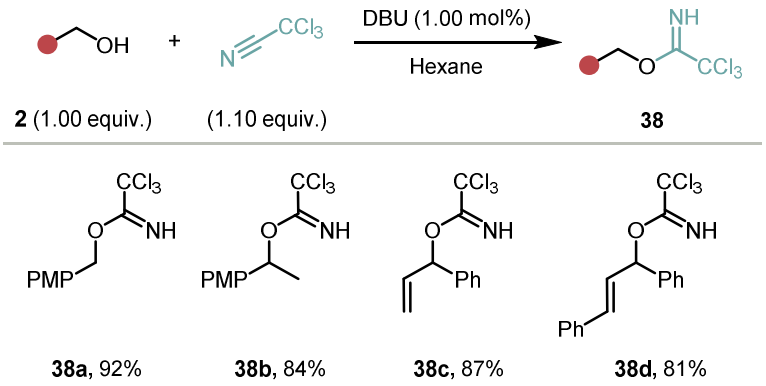


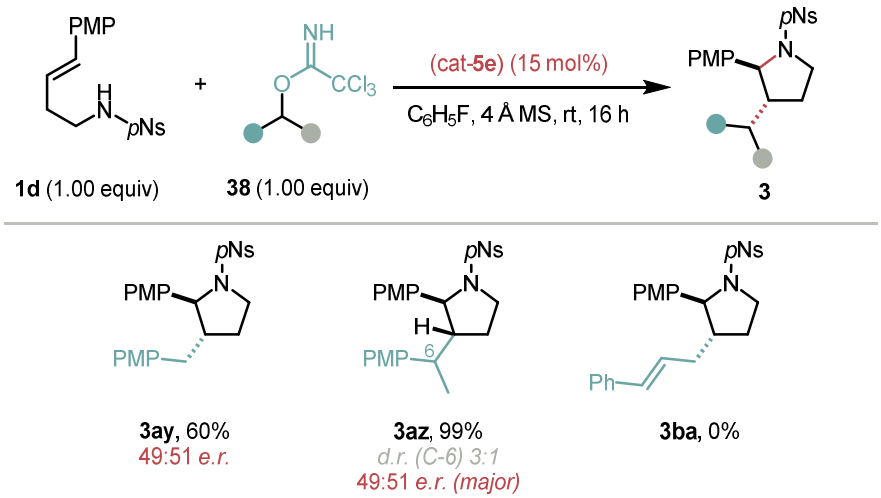
Figure 12. Different bonding modes when using trichloroacetimidates.

Using trichloroacetimidates gave us the opportunity to engage alcohols which did not introduce an additional exocyclic stereocentre, offering a solution to the diastereoselectivity issues. A series of trichloroacetimidates **38a – 38c** were prepared (**Scheme 76**), focusing on those related to alcohols which showed no reactivity during our earlier electrophile screening (See **Section 3.3.1, Scheme 68**), **38d** was also prepared as a control.



Scheme 76. Synthesis of trichloroacetimidates **38**.

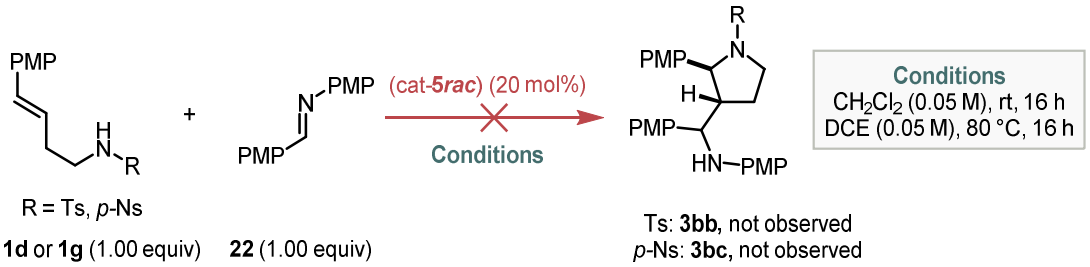
Pleasingly, introduction of the trichloroacetimidates allowed benzylic alcohols to be indirectly engaged as electrophiles using a phosphoric acid catalyst, unfortunately **38c** derived from the unsubstituted allylic alcohol remained unreactive (**Scheme 77**). Although tosyl amine **1g** had outperformed *p*-nosyl amine **1d** in the previous *N*-protecting group screening, when **1g** was reacted with the **38a** & **38b** only trace reactivity was observed, whereas *p*-nosyl amine **1d**, gave pyrrolidines **3ay** & **3az** in good to excellent yield. The conditions were adapted from the conditions reported by Yamada and co-workers for a transformation using trichloroacetimidates. Unfortunately, although chiral catalyst (cat-**5e**) was reactive at room temperature, significant enantioinduction was not observed in either case.



Scheme 77. Trichloroacetimidate scope.

Next use of imine **22** was considered, which had failed as an electrophile in the Ti/HFIP methodology. Similarly to the trichloroacetimidate series, it was hoped that activation of **22** *via* a directional H-bond

would offer a viable route to high enantioinduction.[62] Once again however was no reactivity observed at either room- or elevated temperatures (**Scheme 78**).

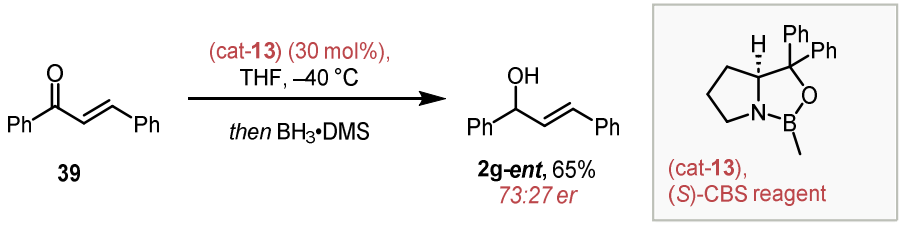


Scheme 78. Failed attempt using imine **22**.

Whilst this was by no means an extensive exploration into the electrophile source, it was felt that this catalyst system had been given due attention and our efforts were best placed in screening other potential modes of activation.

3.3.6 Mechanistic insights

Before looking into other catalyst systems, a series of experiments to disprove certain mechanisms which could be responsible for the low enantioinduction were carried out. Firstly, although it was believed that the reaction between **1g** and **2g** proceeds *via* a carbocation, two experiments were carried out to probe whether a kinetic resolution of the racemic alcohol *via* an S_N2' displacement could be the reaction mechanism. Firstly, an enantioenriched alcohol **2g-*ent*** was subjected to the reaction. A CBS-reduction of ketone **39** gave **2g-*ent*** in a moderate enantiomeric ratio (**Scheme 79**). However, when **2g-*ent*** was used in the standard reaction conditions (**Table 19**, Entry 2), the same enantioselectivity as before was observed. Further experiments, using **2g-*ent*** in combination with (cat-**5*rac***) in CH_2Cl_2 and cyclohexane gave completely racemic product (**Table 19**, Entries 3 & 4), suggesting that the reaction did proceed *via* a carbocation. This was consistent with the enantiomeric ratio observed when an excess of alcohol **2g** was used (5.0 equiv.), if a kinetic resolution was at play, an improvement in the enantiomeric ratio should be observed, however a reduction was seen instead (**Table 19**, Entry 5).

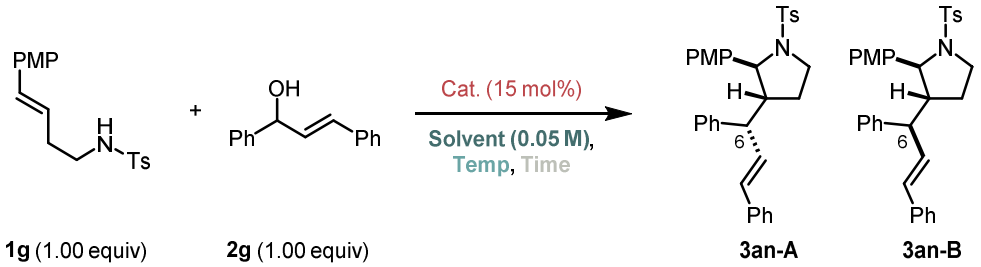


Scheme 79. Preparation of enantioenriched alcohol **2g-*ent***.

Following the initial hit, it had been confirmed that the reaction could take place using HCl as the catalyst (See **Section 3.3.1, Table 10**), therefore the possibility that following the first catalyst turnover, release of a proton may allow a background racemic reaction to take place was considered. The reaction was stopped before completion to determine if this was the case, however, after 4 h, both the diastereomeric and enantiomeric ratio observed were consistent with the ratios observed during standard reaction times (**Table 19**, Entry 6). This was further confirmed by increasing the catalyst loading to 50 mol%, again this gave no deviation from the standard enantioselectivity (**Table 19**, Entry 8).

The reaction was also carried out at a range of temperatures, further supporting the relationship between the diastereoselectivity and the enantioselectivity (**Table 19**, Entries 9 –11). Lowering the temperature gave a reduction in the enantioselectivity, aligning with the higher proportion of the major diastereomer **3an-A**. Increasing the temperature to 100 ˚C did not increase the enantioselectivity further and a drop off in enantioselectivity was observed (**Table 19**, Entry 11).

Table 19. Experiments to probe alternative mechanisms.

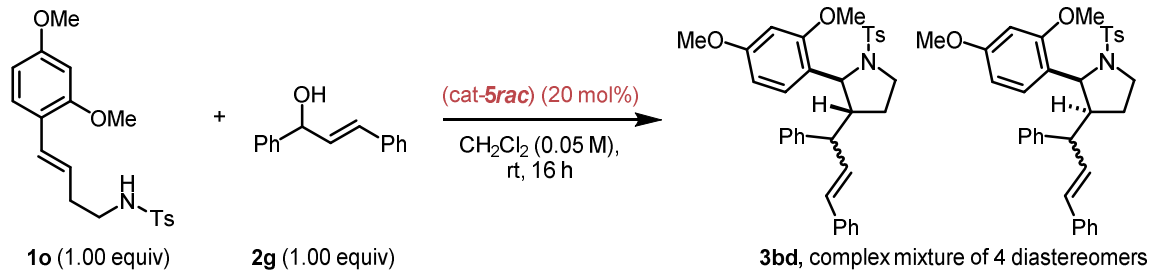


1g (1.00 equiv) **2g** (1.00 equiv) **3an-A** **3an-B**

Entry	Cat.	Solvent	Temp (°C)	Time (h)	3an (%)	*d.r. (C-6)*	*e.r. (3an-B)*
1	**(cat-5e)**	**DCE**	**80**	**72**	**78**	**0.9:1**	**80:20**
2[a]	(cat-**5e**)	DCE	80	72	77	0.9:1	80:20
3[a]	(cat-**5*rac***)	CH_2Cl_2	rt	16	76	5.5:1	50:50
4[a]	(cat-**5*rac***)	CyH	rt	16	54	5.5:1	50:50
5[b]	(cat-**5e**)	DCE	80	72	69	2:1	58:42
6	(cat-**5e**)	DCE	80	4	23	1:1.1	78:22
7	(cat-**5e**)	DCE	80	16	77	1:1.05	78:22
8[c]	(cat-**5e**)	DCE	80	72	81	1:1.15	78:22
9	(cat-**5e**)	DCE	40	72	38	1.6:1	71:29
10	(cat-**5e**)	DCE	60	72	76	1.1:1	74:26
11	(cat-**5e**)	DCE	100	72	84	1:1	76:24

[a]Using enantioenriched alcohol **2g-*ent***. [b]Using 5.00 equiv. **2g**. [c]Using 50 mol% (cat-**5e**).

Finally, for completeness the aryl group on the nucleophile was varied; we were reluctant to increase the electron richness of the ring at an earlier point, wary that this would likely lead to mismatched reactivity between the rate of olefin trapping and rate of cyclisation. This proved to be the case and reaction of **1o** gave **3bd** as a complex mixture of four diastereomers, from which no diastereomeric ratio could be obtained (**Scheme 80**). With these results in hand, we felt comfortable moving forward to other modes of activation.



1o (1.00 equiv) **2g** (1.00 equiv) **3bd**, complex mixture of 4 diastereomers

Scheme 80. Attempt to use a more electron-rich nucleophile **1o**.

3.4 Other approaches

3.4.1 Co-catalysis

Although the fields of Brønsted acid catalysis and transition metal catalysis have been independently established as powerful approaches to induce enantioselectivity across a range of allylic alkylation reactions, thanks to seminal papers by List, Hartwig and Gong, the merging of the two fields has enabled new reactivity and selectivity not accessible when either are used in isolation.[114] This multi-component approach harnesses the complementary activation modes of each method, with additional interactions also possible (**Figure 13**). Unlike the use of CPAs in isolation, combining CPAs with metal catalysis has regularly been applied to intermolecular transformations, so we were hopeful that our system would benefit from using both in combination.

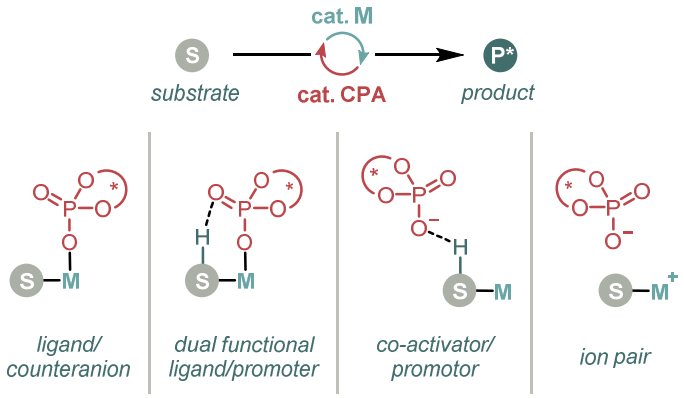
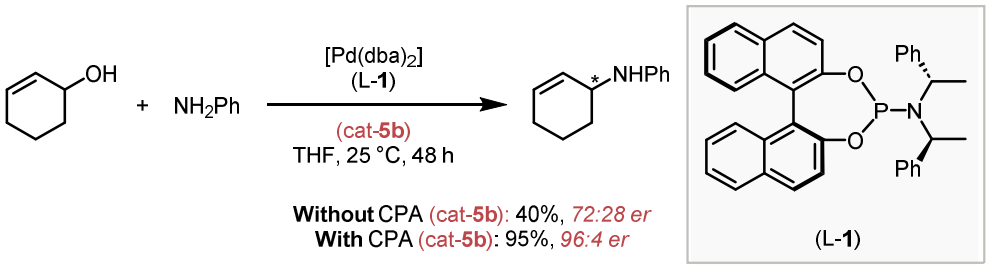


Figure 13. Plausible bonding modes from combining transition metal catalysis with CPA catalysis.

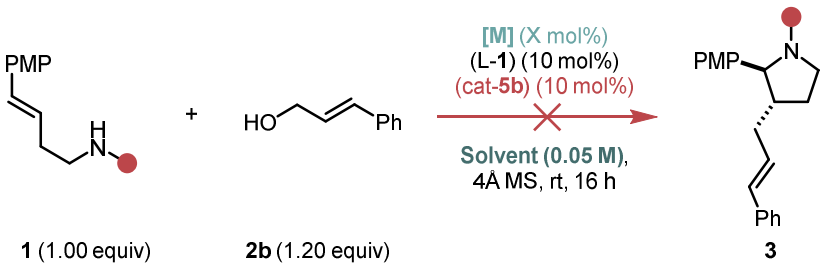
Authors often report an additive effect when the catalysts are used in combination, whilst the chiral ligand on the metal centre is responsible for controlling the absolute configuration, the CPAs interaction provides additional steric bulk about the metal centre and non-covalent interactions with the substrate, enhancing the enantioselectivity. CPAs are also known to facilitate the formation of the active allyl metal complex, negating the need to use activated electrophiles such as esters and carbonates in place of simple allylic alcohols. The closest transformation reported to what we were aiming for is the 2014 report by Beller and co-workers, who successfully demonstrated a highly asymmetric amination of racemic allylic alcohols (**Scheme 81**).[115]



Scheme 81. Asymmetric amination of allylic alcohols using transition metal catalysis in combination with a CPA.

Using three different *N*-protected amines, with cinnamyl alcohol **2b** as the electrophile the Beller conditions were applied to our system (**Table 20**). When no reactivity was observed additional transition metal catalysts were screened, however at no point was product observed and this approach was not pursued further.

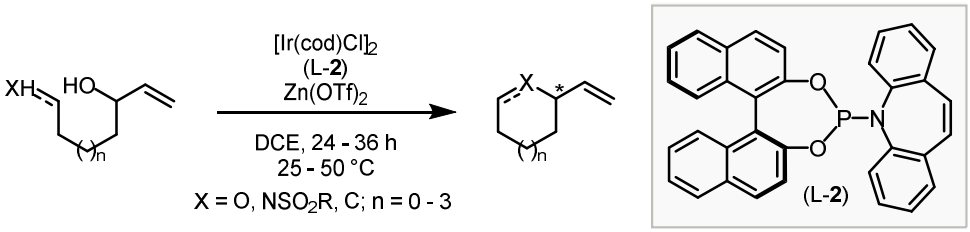
Table 20. Attempts to use transition metal, CPA co-catalysis on our system.



Entry	*N*-group	[M]	Solvent	3 (%)
1	tosyl (**3be**)	$[Pd(dba)_2]$ (5 mol%)	PhMe	-
2	tosyl (**3be**)	$[Ir(coe)_2Cl]_2$ (2.5 mol%)	PhMe	-
3	tosyl (**3be**)	$[Ir(cod)Cl]_2$ (2.5 mol%)	PhMe	-
4	tosyl (**3be**)	$[Pd(dba)_2]$ (5 mol%)	DCE	-
5	tosyl (**3be**)	$[Ir(coe)_2Cl]_2$ (2.5 mol%)	DCE	-
6	tosyl (**3be**)	$[Ir(cod)Cl]_2$ (2.5 mol%)	DCE	-
7	*o*-nosyl (**3ba**)	$[Pd(dba)_2]$ (5 mol%)	PhMe	-
8	*o*-nosyl (**3ba**)	$[Ir(coe)_2Cl]_2$ (2.5 mol%)	PhMe	-
9	*o*-nosyl (**3ba**)	$[Ir(cod)Cl]_2$ (2.5 mol%)	PhMe	-
10	urea (**3bf**)	$[Pd(dba)_2]$ (5 mol%)	PhMe	-
11	urea (**3bf**)	$[Ir(coe)_2Cl]_2$ (2.5 mol%)	PhMe	-
12	urea (**3bf**)	$[Ir(cod)Cl]_2$ (2.5 mol%)	PhMe	-

Next, another area of co-catalysis was considered, combining transition metal catalysis with Lewis acid catalysis, in recent years this approach has been a focus for the Carreira group, leading to the development of a privileged ligand scaffold (L-**2**) for such transformations (**Scheme 82**).[116] Traditionally, the Lewis acid used in these cases is either $Zn(OTf)_2$ or $Sc(OTf)_3$, in combination with iridium and the

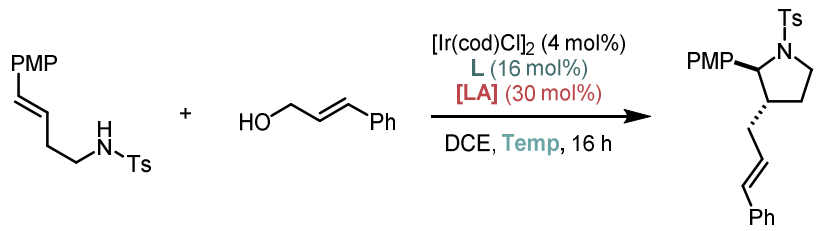
aforementioned phosphoramidite olefin ligand (L-**2**).[117] Compared to the Brønsted acid co-catalysis system, here the Lewis acid is solely used as an activator for the alcohol.



Scheme 82. Representative example of the work by Carriera in the field of Lewis acid co-catalysis.

Using the conditions reported by Carreira and co-workers as a starting point no reactivity was obsered, even at elevated temperatures (**Table 21**, Entries 1 & 2). A switch to a phosphoramidite ligand (L-**1**) led to the formation of **3be** in a low yield at elevated temperatures, albeit as a racemic mixture (**Table 21**, Entry 4). Screening of other Lewis acids was largely unsuccessful, however $Sc(OTf)_3$ gave a comparable result to $Zn(OTf)_2$ (**Table 21**, Entry 6). A control experiment in the absence of iridium was carried out and **3be** was observed in comparable amounts, suggesting that the Lewis acid was solely responsible for the reactivity (**Table 21**, Entries 11 & 12).

Table 21. Attempts to use a transition metal, Lewis acid co-catalysis on our system.

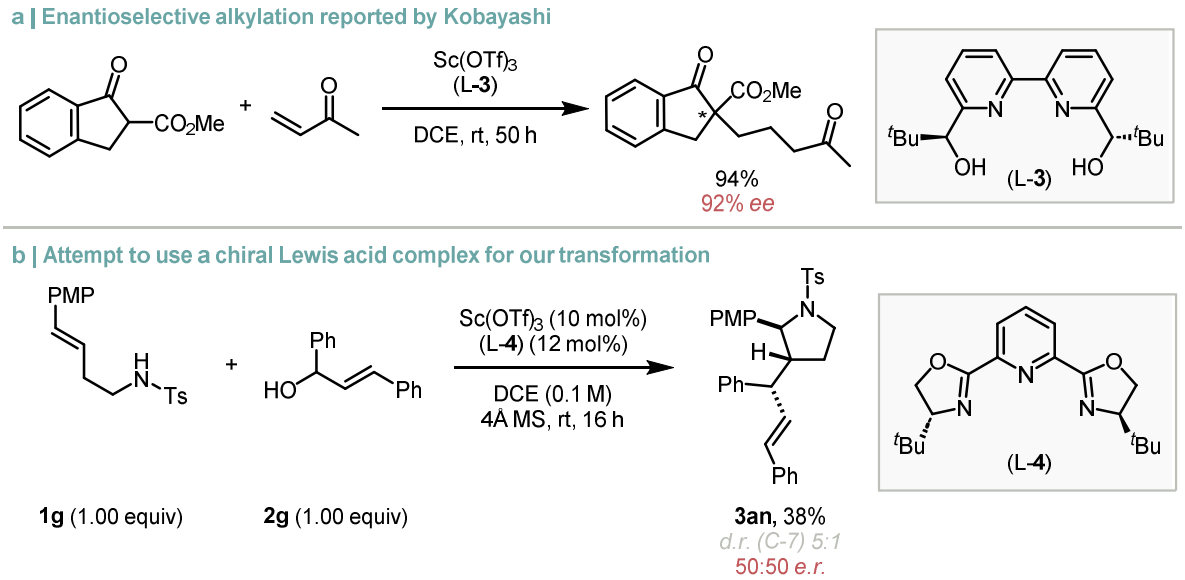


1g (1.00 equiv) **2b** (1.00 equiv) **3be**

Entry	Ligand	Lewis acid	Temp (°C)	3be (%)	*e.r. (3be)*
1	(L-**2**)	$Zn(OTf)_2$	rt	-	-
2	(L-**2**)	$Zn(OTf)_2$	50	-	-
3	(L-**1**)	$Zn(OTf)_2$	rt	-	-
4	(L-**1**)	$Zn(OTf)_2$	50	31	50:50
5	(L-**1**)	$Sc(OTf)_3$	rt	-	-
6	(L-**1**)	$Sc(OTf)_3$	50	29	50:50
7	(L-**1**)	$Ti(O^iPr)_4$	rt	-	-
8	(L-**1**)	$Ti(O^iPr)_4$	50	-	-
9	(L-**1**)	$Zn(OAc)_2$	rt	-	-
10	(L-**1**)	$Zn(OAc)_2$	50	-	-
11[a]	-	$Zn(OTf)_2$	50	40	-
12[a]	-	$Sc(OTf)_3$	50	38	-

[a]Carried out without [Ir].

For completeness one final approach was attempted, as mentioned previously, Lewis acids bearing chiral ligands are not commonplace when compared to traditional transition metal catalysis, however scandium being one of the strongest and most stable Lewis acids, has limited reports in combination with chiral ligands. For example, the Kobayashi group has reported a series of enantioselective transformations using a pre-mixed scandium bipyridine-ligand (L-**3**) complex (**Scheme 83a**).[118] Rather than synthesise (L-**3**), PyBOX ligand (L-**4**) was used, to test for reactivity. Unfortunately, **3an** was not formed with any level of enantioinduction (**Scheme 83b**).



Scheme 83. An example of a chiral scandium complex (a) and the failed attempt to utilised a chiral scandium complex in our system (b).

It was evident that, in terms of reactivity and selectivity, Brønsted acid catalysis was superior to both transition metal and Lewis acid catalysis, and without any significant leads to follow, it was decided to not proceed further with either approach.

3.4.2 Asymmetric aminocatalysis

Finally, it would be remiss not to consider a class of electrophile which had been successfully utilised in **Chapter 2** (**Section 2.4.2, Scheme 46**): α,β-unsaturated carbonyl compounds, for this functionality would enables us to try asymmetric aminocatalysis. This privileged field of organocatalysis differs from the activation modes previously attempted, rather than relying on hydrogen-bonding interactions, the reversible condensation with the aminocatalyst potentially offers increased chances for high levels of enantioinduction.[119] Three of the most utilised catalyst classes within the field were initially chosen, two

secondary amines: MacMillan catalyst (cat-**14**) and Jørgensen-Hayashi catalyst (cat-**15**), along with a cinchona-based primary amine (cat-**16**).

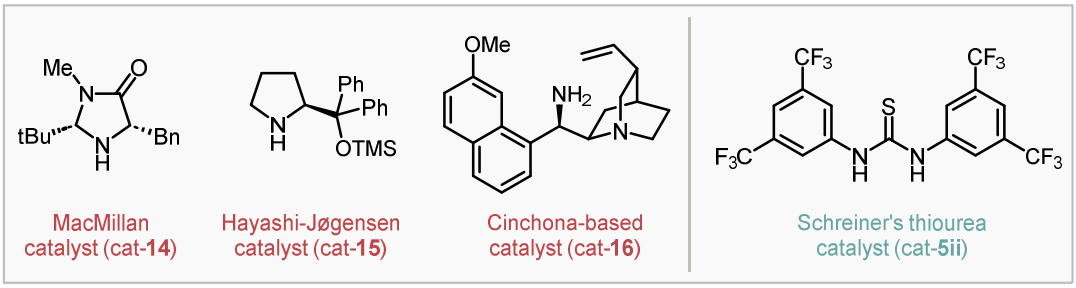
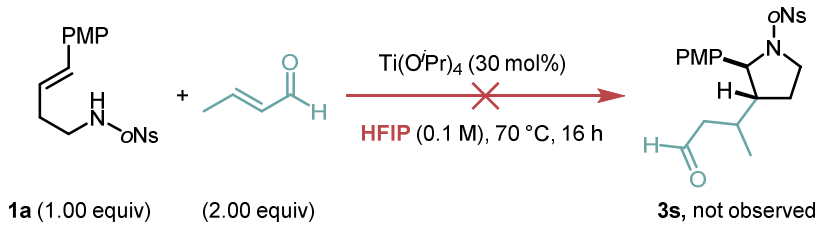


Figure 14. Commonly used aminocatalysts.

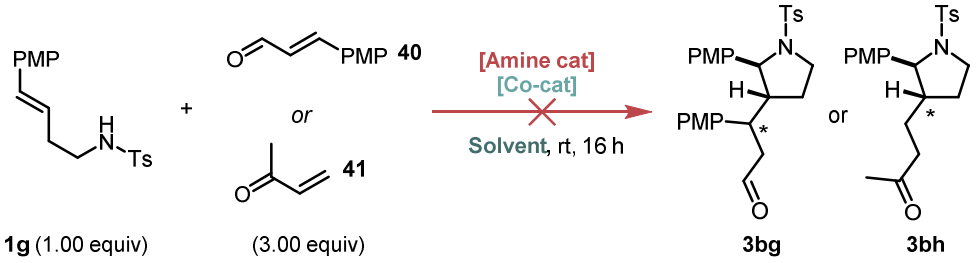
A potential discrepancy between the electrophiles utilised in the Ti/HFIP conditions and what was required for the organocatalysis was a concern; traditionally β-substituted alkenes are required for secondary amine activation, however no product was observed when such substitution was present, fortunately, primary amines have a broader scope (**Scheme 84**).[120]



Scheme 84. Failed synthesis of **3s** using a β-substituted alkene.

Initially, aldehyde **40** was selected, which from literature examples, was known to form an active iminium species under the reaction conditions. Unfortunately, each set of conditions, along with variations in co-catalyst and solvent were unreactive in our system, homoallylic amine **1g** remaining untouched (**Table 22**, Entries 1 – 6). Ketone **41** was then, which had been used successfully in our previous work, unfortunately, even at elevated temperatures, the same observation was made (**Table 22**, Entries 7 – 9).

Table 22. Failed attempt to use aminocatalysis for our transformation.



1g (1.00 equiv) (3.00 equiv) **3bg** **3bh**

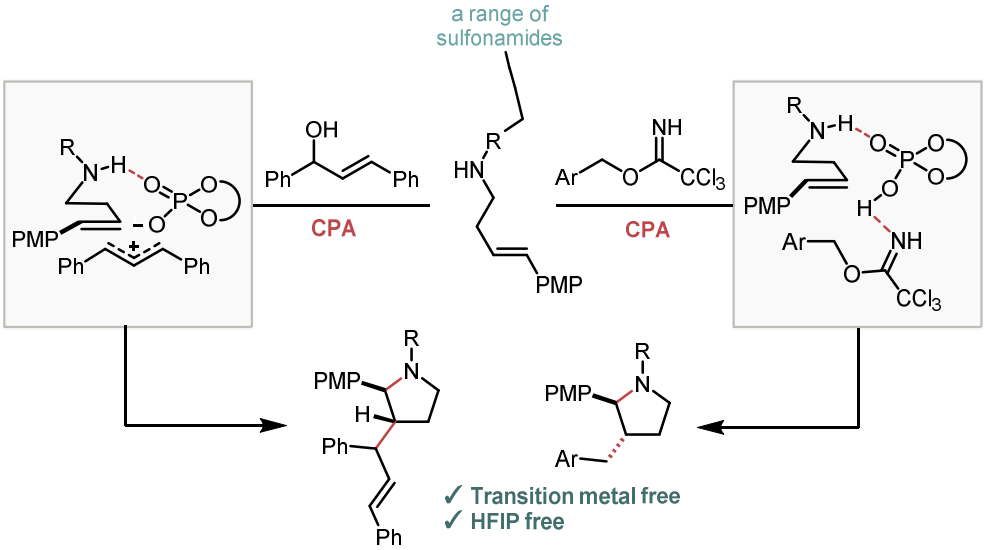
Entry	Electrophile	Amine catalyst	Co-catalyst	Solvent	3 (%)
1	**40**	(cat-**14**) (20 mol%)	TFA (20 mol%)	CH_2Cl_2:^{i}PrOH (85:15)	-
2	**40**	(cat-**14**) (20 mol%)	TFA (20 mol%)	CH_2Cl_2:HFIP (85:15)	-
3	**40**	(cat-**14**) (20 mol%)	(cat-**5b**) (30 mol%)	CH_2Cl_2:^{i}PrOH (85:15)	-
4	**40**	(cat-**14**) (20 mol%)	$PhCO_2H$ (30 mol%)	CH_2Cl_2:^{i}PrOH (85:15)	-
5	**40**	(cat-**15**) (20 mol%)	(cat-**4ii**) (30 mol%)	$CHCl_3$	-
6	**40**	(cat-16) (10 mol%)	TFA (30 mol%)	CH_2Cl_2	-
7[a]	**41**	(cat-**14**) (20 mol%)	TFA (20 mol%)	$CHCl_3$:^{i}PrOH (85:15)	-
8[a]	**41**	(cat-**15**) (20 mol%)	(cat-**4ii**) (30 mol%)	$CHCl_3$	-
9[a]	**41**	(cat-**16**) (10 mol%)	TFA (30 mol%)	$CHCl_3$	-

[a]Performed at 50 °C. (cat-**16**) was prepared by Bruno Marinic.

It was at this point that we decided to cease further attempts to establish an enantioselective variant of our carboamination approach. Whilst there was, of course, other conditions available to us to try, no reactivity was being observed consistently leading us to be wary of pursuing this reaction further.

3.5 Summary and outlook

Whilst ultimately, our primary aim to develop an appliable enantioselective transformation had failed, it was successfully demonstrated that significant levels of enantioinduction were possible through the use of a CPA catalyst. A cation-triggered annulation in the absence of HFIP was successfully carried out, something previously thought not possible, with a range of alcohols, either directly in the case of 1,3-disubstituted allylic alcohols or *via* pre-activation as the trichloroacetimidate for simple benzylic alcohols (**Scheme 85**). The transformation was also made transition metal free. Unfortunately, the mismatched diastereoselectivity and enantioselectivity relationship could not be overcome, ultimately preventing further optimisation of the CPA catalysed reaction despite our best efforts, with the highest enantioinduction being an 80:20 e.r. of the **3an-B**. When other modes of catalytic activation were attempted, the system was found to be consistently unreactive.



Scheme 85. Summary of carboamination methodology described in **Chapter 3**.

4

Studies towards the synthesis of Atrasentan

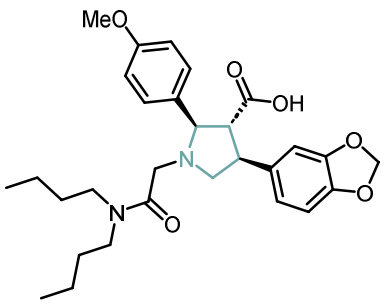
4.1 Chapter overview

The following chapter presents studies towards the synthesis of the experimental drug Atrasentan through application of the work detailed in **Chapter 2**, namely the cation triggered annulation of amines to access 2,3-disubstituted azacycles using $Ti(O^iPr)_4$ in HFIP. The following section will not only focus on the key cyclisation but also the optimisation of both substrate synthesis and product derivatisation with a brief discussion of potential points to introduce asymmetry into the route.

4.2 Atrasentan

4.2.1 Discovery and biological activity of Atrasentan

Since the 1990's the experimental drug Atrasentan has been linked to the treatment of various diseases, due to its selective and potent inhibition of endothelin A (ET_A), an endothelin cell membrane receptor (**Figure 15**).[121] First identified in 1987, the endothelins are 21-amino acid peptides that play a key role in regulating cell proliferation, hormone production and apoptosis. When overexpressed, endothelins can contribute to a range of diseases, particularly focused on the cardiovascular system including hypertension, heart disease and atherosclerosis.[122,123]



Atrasentan 33
endothelin A inhibitor

Figure 15. Structure of Atrasentan **33**.

Due to the role of endothelin A in tumour proliferation Atrasentan has been engaged in clinical trials targeting non-small cell lung cancer and prostate cancer, however it has received most attention in recent years as a therapy for diabetic kidney disease. In 2019, AbbVie published results of a phase 3 trial, demonstrating that patients with diabetic kidney disease had a significant reduction in proteinuria along with a reduced risk of progression to end-stage renal disease or kidney failure when Atrasentan was included alongside their standard therapy.[124] In the same year Atrasentan was acquired by Chinook Therapeutics, a Canadian biotech focused on medicines for kidney diseases, who immediately enrolled patients with Immunoglobulin A nephropathy (IgAN) in a phase 3 ALIGN trial.[125,126] Given the continuing interest in the potential applications of Atrasentan, the opportunity to synthesise this target along with flexible access to related structures is of interest to the scientific community.

Throughout the following sections, rather than drawing out the substituents on Atrasentan in full, the following notation will be used (**Figure 16**).

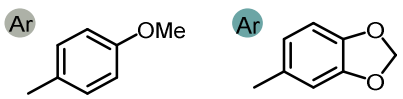
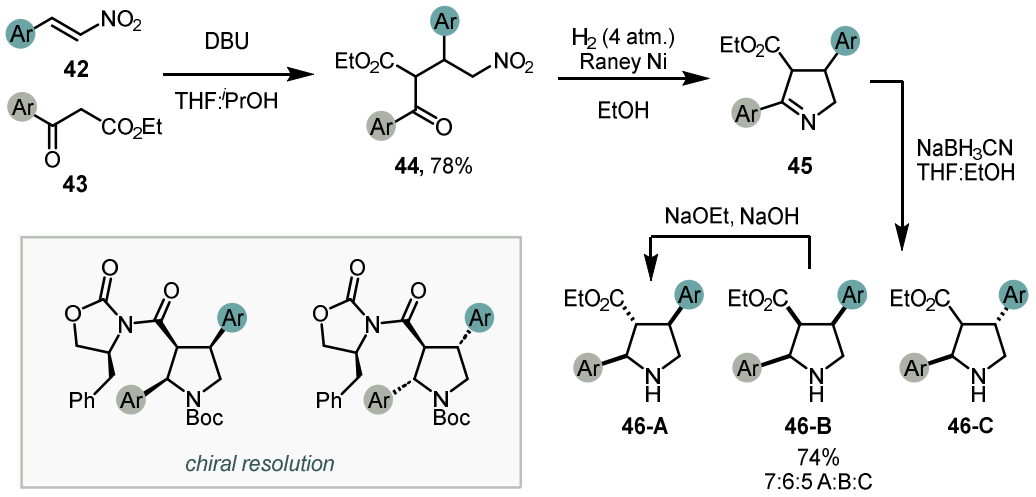


Figure 16. Notation used for the two ring substitutents on **33**.

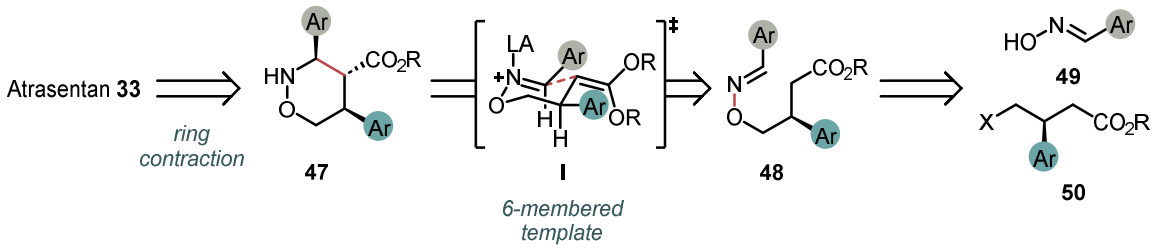
4.2.2 Previous synthetic routes

The first route to Atrasentan was reported by the research team at Abbott Laboratories in 1996.[127] The core of the structure was accessed in two steps: a Michael reaction between nitrostyrene **42** and β-ketoester **43** giving **44** as a mixture of diastereomers followed by treatment with Raney nickel affording dihydropyrrolidine **45** (**Scheme 86**). X-ray analysis of **45** confirmed the major diastereomer as *trans*. Reduction of **45** with cyanoborohydride gave three diastereomers **46-A-C** in a 7:6:5 ratio, with the desired *trans-trans* isomer **46-A** as the major product. Unfortunately, **46-A** co-eluted with **46-C**, so pure **46-A** was instead accessed *via* isomerisation of the separable **46-B** by heating in sodium ethoxide in ethanol. The **46-A/C** mixture could be carried forward and separated at a later stage. Introduction of the acetamide side chain followed by ester hydrolysis afforded **33** in five steps (not shown). However, an additional seven steps were required to access the enantiomerically pure target, using a late-stage resolution with (*S*)-(-)4-benzyl-2-oxazolidinone.



Scheme 86. First generation route to Atrasentan reported by Abbott Laboratories, showing a key chiral resolution to access the optically pure analogue.

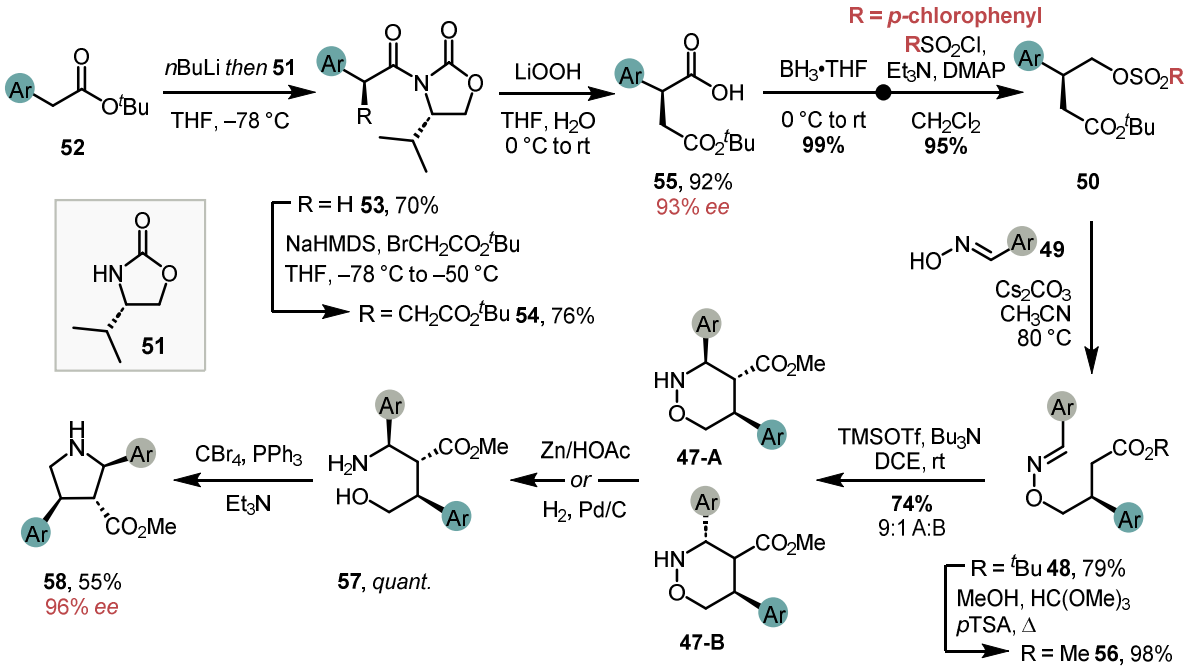
In 1999, Abbott Laboratories reported a second-generation route, addressing the issues of relative and absolute stereocontrol associated with their initial synthesis.[128] A new strategy was employed, using a six-membered ring template (**Scheme 87**). Here a key disconnection of the 1,2-oxazinane **47** back to oxime ether **48** was proposed, it was hoped that aryl groups would sit equatorially in the 6-*endo-trig* transition state **I** setting the relative stereochemistry. The disconnection of oxime ether **48** gave two similarly sized fragments **49** and **50**.



Scheme 87. Retrosynthetic strategy designed by Abbott Laboratories to improve the diastereoselectivity.

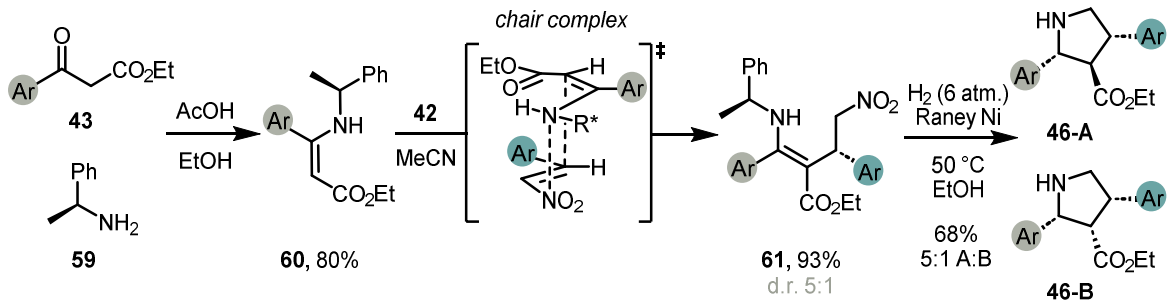
Absolute stereocontrol was introduced through Evans' asymmetric alkylation (**Scheme 88**). Once oxazolidinone **51** was reacted with *tert*-butyl ester **52** to give **53**, the key alkylation with *tert*-butyl bromoacetate was carried out affording **54**. Removal of the oxazolidinone with lithium hydroperoxide gave carboxylic acid **55** in 93% *ee*, which was subsequently reduced to the alcohol before activation to give the key coupling partner sulfonate ester **50**. Reaction of the two fragments **49** and **50** gave the oxime **48** in high yield, before transesterification to the methyl ester **56**. Treatment of **56** with TMSOTf gave 1,2-oxizinane **47** in high yield as a 9:1 mixture of diastereomers which could be separated. N-O bond

cleavage was possible *via* either metal promoted reduction (Zn/HOAc-THF) or hydrogenolysis (Pd/C, H_2, EtOH) affording **57** before cyclisation to pyrrolidine **58** *via* bromindation of the pendant alcohol with carbon tetrabromide and triphenylphosphine. The synthetic sequence could then follow the steps mentioned above.



Scheme 88. Second generation route to the core of Atrasentan using oxazolidone **51** as a chiral auxillary.

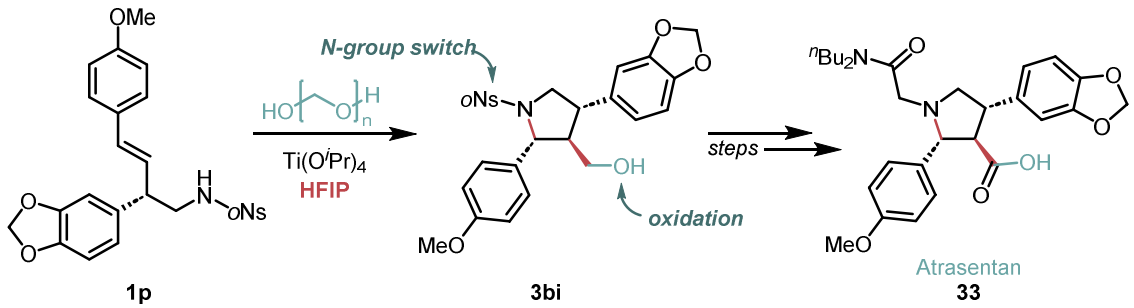
Whilst this strategy avoided the requirement for a late-stage resolution and solved the problem of diastereoselectivity, the route was much longer at 13 steps. Fortunately, a modification to the first-generation route was subsequently reported which enabled Atrasentan to be accessed in six steps and 99% *ee* (**Scheme 89**).[129] Condensation of **43** with (-)-α-methylbenzylamine **59** provided enaminoester **60** in good yield before conjugate addition with **42** gave adduct **61** with moderate diastereoselectivity, suggesting a preference for the chair-like transition state **I** over the corresponding boat-like transition state. Unfortunately, hydrogenation with Raney-Nickel gave the key *trans,trans*-isomer **46** in low yield, and in a similar way to the first-generation route, a three step isomerisation sequence was required to improve material recovery.



Scheme 89. Modification to the first-generation route to Atrasentan reported by Pfau and co-workers.

4.2.3 Project proposal

Despite considerable efforts towards improving the synthesis of Atrasentan each route ran into similar problems when it came to accessing the key 2,3,4-trisubstituted pyrrolidine core in high diastereoselectivity without the requirement to undergo a lengthy isomerisation sequence. An alternative approach was proposed based upon the previously described cation triggered annulation methodology (**Scheme 90**). It was hoped that treatment of the appropriately substituted homoallylic amine **1p** with paraformaldehyde in the presence of $Ti(O^iPr)_4$ in HFIP would deliver pyrrolidine **3bi** which could be further elaborated in three steps to Atrasentan; namely removal of the *ortho*-nosyl group, introduction of the acetamide side chain and finally oxidation of the alcohol.

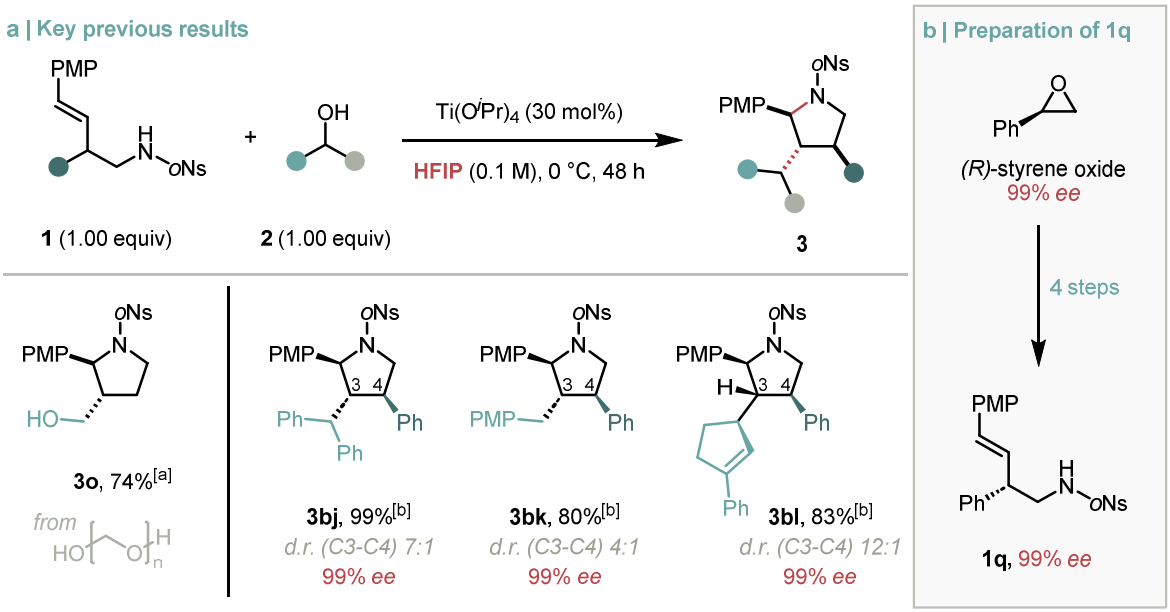


Scheme 90. Proposed carboamination of homoallylic amine **1p** to access Atrasentan.

4.2.4 Key previous results

The ability to introduce a hydroxymethyl group was previously established through the use of paraformaldehyde as the electrophile **3o** (see **Chapter 2, Section 2.4.2**). Investigations into the inclusion of a group in the 4-position of the pyrrolidine products had previously been carried out by Yuxiang Zhu, who demonstrated the reaction of **1q** with a range of electrophiles, affording **3bj – 3bl** in high yields and moderate to good diastereoselectivity across C3-C4 (**Scheme 91b**).[82] The introduction of a backbone

substituent also enabled the preparation of an enantiomerically pure substrate, through the use of commercially available (*S*)-styrene oxide as a starting material, substrate **1q** was isolated with complete retention of ee (**Scheme 91b**). Conversely, the styrene oxide required for Atrasentan is not commercially available, and initially the synthesis of **3bi-*rac*** was attempted, with the knowledge that the enantiopure analogue **3bi-*ent*** could be prepared providing **1p-*ent*** could be accessed.

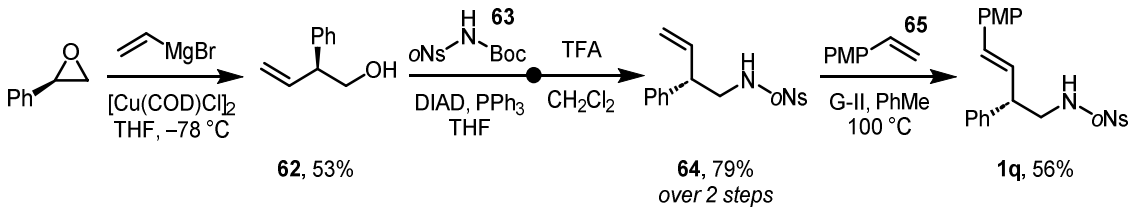


Scheme 91. Key previous results using the Ti/HFIP methodology (a) and the preparation of **1q** from (*S*)-styrene oxide (b). [a]Using 20 equiv. of electrophilic partner [b]Carried out by Yuxiang Zhu.

4.3 Substrate synthesis

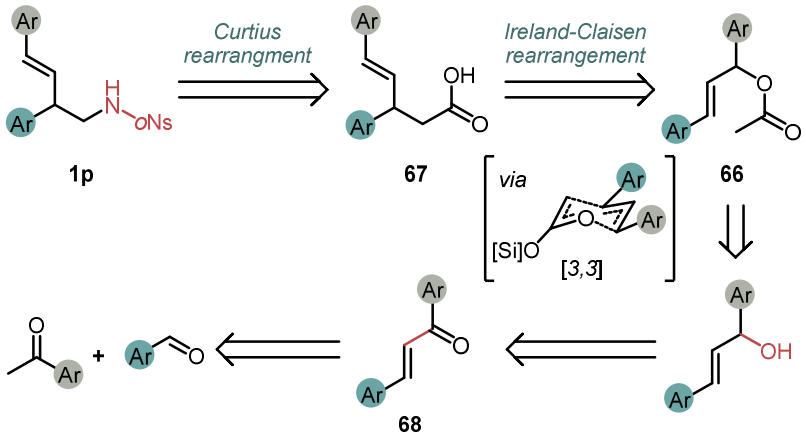
4.3.1 Previous route and retrosynthesis

The aforementioned substrate **1q** was prepared in four steps by Yuxiang Zhu (**Scheme 92**). At first (*R*)-styrene oxide was reacted with vinyl magnesium bromide in the presence of $[Cu(COD)Cl]_2$, to give homoallylic alcohol **62**. Introduction of the *ortho*-nosyl sulfonamide was realised through a Mitsonobu reaction of alcohol **62** using **63**, followed by removal of the Boc group using TFA. Finally, cross-metathesis between **64** and 4-methoxystyrene **65** afforded **1q** in moderate yield. Although this route delivered the required material, it was hoped the synthetic sequence could be improved to enable access to **1p** in larger amounts, namely by avoiding the requirement to carry out a low yielding metathesis as the final step and to introduce the nitrogen functionality with improved atom economy.



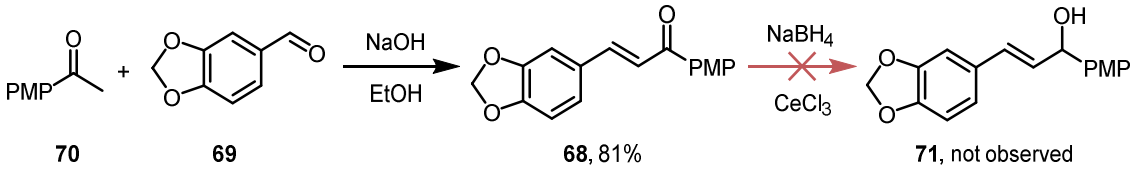
Scheme 92. Previous route used to access phenyl substituted substrate **1q**. All reactions were carried out by Yuxiang Zhu.

An alternative retrosynthesis was proposed (**Scheme 93**), with two rearrangements, an Ireland-Claisen rearrangement of allyl ester **66**, setting the *trans* double bond before a Curtius rearrangement of the carboxylic acid product **67** to install the nitrogen functionality. Allyl ester **66** can be prepared in only two steps from known enone **68**.



Scheme 93. Alternative potential strategy to access key substrate **1p**.

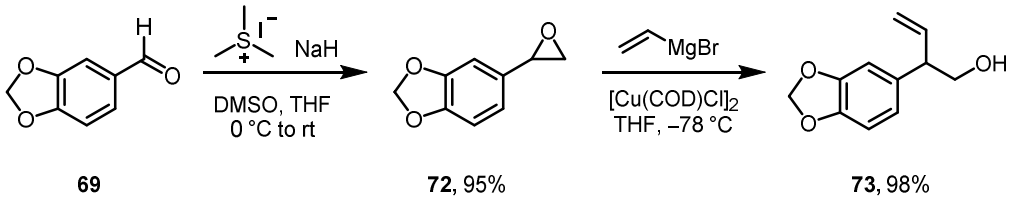
Unfortunately, although the Aldol reaction between piperonal **69** and methyl ketone **70** afforded enone **68** in good yield, subsequent reduction with sodium borohydride and cerium trichloride was unsuccessful (**Scheme 94**). Although monitoring of the reaction suggested consumption of starting material **68** and formation of alcohol **71**, isolation was not possible, presumably due to the instability of **71** with facile elimination to form a cation aided by the two electron rich aryl groups leading to decomposition.



Scheme 94. Attempted forward synthesis of the alternative strategy.

4.3.3 Forward synthesis

With this in mind, and with the interest of focusing on the key later steps, it was decided to use the initial route. Styrene oxide **72** was prepared in high yield from piperonal using sodium hydride and trimethylsulfonium iodide in a Corey-Chaykovsky reaction (**Scheme 95**).[130] On a large scale **72** was unstable to column chromatography, however, the material could be used crude in the following reaction. Treatment of **72** with vinyl magnesium bromide afforded alcohol **73** in excellent yield.

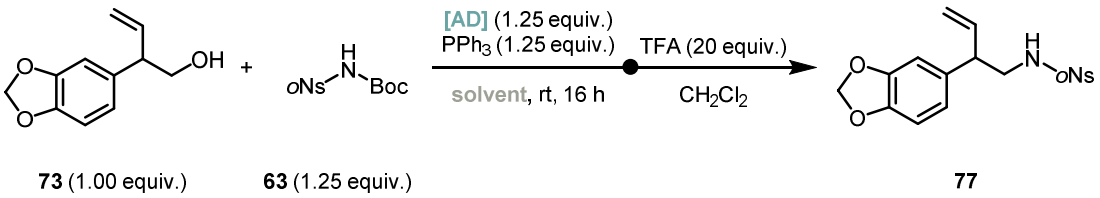


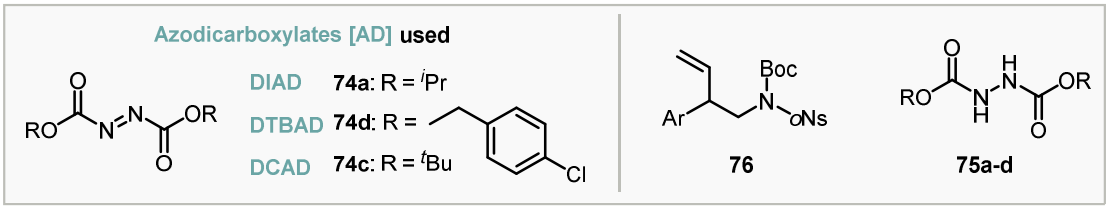
Scheme 95. Two-step sequence to alcohol **73**.

Next a Mitsonobu reaction between **73** and **63** was carried out (**Table 23**). Despite the widespread use of diisopropyl azodicarboxylate (DIAD) **74a** and other traditional azodicarboxylates (AD) such as diethyl azodicarboxylate (DEAD) **74b**, both potentially cause challenges during purification, as the corresponding hydrazine by-products are poorly soluble and are hard to remove using column chromatography. For this reason, alternative azodicarboxylate analogues were considered which had a hydrazine by-product **75** which could be removed prior to purification.[131] One such example investigated was di-(4-chlorobenzyl)azodicarboxylate (DCAD) **74c**. Here the by-product **75c** is insoluble in the reaction solvent (DCM) and can easily be filtered off. Despite this advantage, purification of **76** was not possible, and it was decided to submit the crude material directly to the Boc deprotection. Fortunately, purification at this stage was successful and **77** was isolated in 56% yield over two steps (**Table 23**, Entry 1); however, when this two-step procedure was scaled up the yield dropped to 39% (**Table 23**, Entry 2). Next, DIAD **74a** and di-*tert*-butyl azodicarboxylate (DTBAD) **74d** were screened (**Table 23**, Entries 3 & 4). Both showed good conversion to **76** but, once again, required carrying forward crude to the next step. As **74a** showed superior reactivity it was chosen for the scale-up (**Table 23**, Entry 5). On a larger scale, hydrazine **75a** could be partially removed prior to Boc deprotection by exploiting the low solubility. The crude reaction mixture **76** was dissolved in toluene and left for 30 min, after which **75a** partially

crystalised out of solution and could be removed by filtration. Although this did not remove all of **75a** it did significantly improve purification of **77**.

Table 23. Optimisation of azodicarboxylate source for the Mitsonobu reaction of **73**.

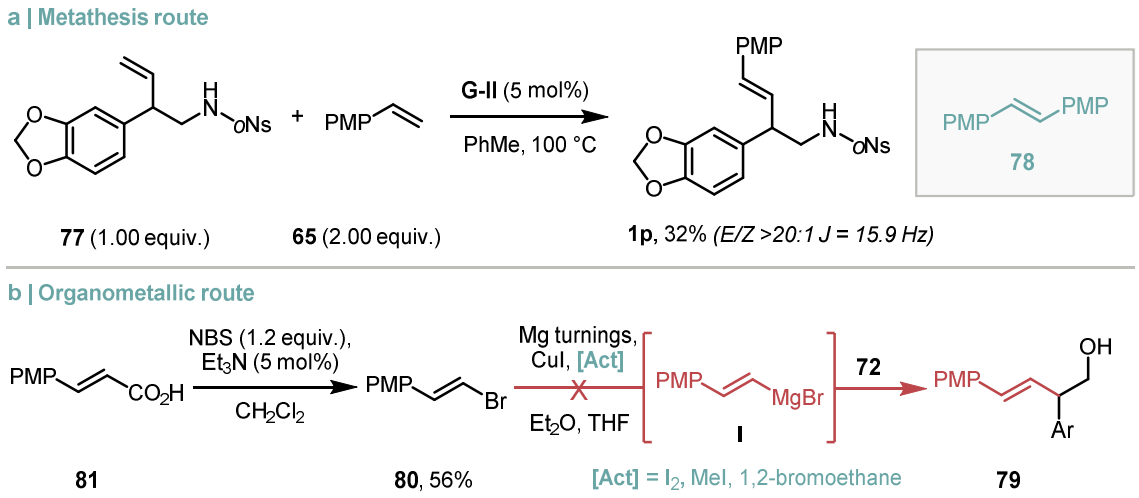




Entry	Azodicarboxylate [AD]	Solvent	mmol of 73	77 (%)
1	**74c**	CH_2Cl_2	1.00	56
2	**74c**	CH_2Cl_2	5.00	39
3	**74d**	THF	1.00	69
4	**74a**	THF	1.00	74
5	**74a**	THF	5.00	56

The final cross-metathesis step between **77** and **65** was low yielding, and the reaction had a very poor mass balance with only small amounts of **77** recovered (**Scheme 96a**). Furthermore, styrene **65** was used in excess to improve the statistical distribution of cross-metathesis products; unfortunately the additional equivalent lead to significant amounts of stilbene side-product **78**, which was challenging to remove by purification, further reducing the yield. This led to attempts to introduce the aryl group earlier in the synthesis, during the epoxide opening to afford **79** (**Scheme 96b**). Therefore, the synthesis of substituted vinyl magnesium bromide **I** was synthesised, through reaction of (*E*)-4-(2-bromo-vinyl)-anisole **80** with magnesium turnings. **80** was prepared in a moderate yield by treatment of 4-methoxycinnamic acid **81** with catalytic triethylamine and *N*-bromosuccinimide (NBS). This variation on the traditional Hunsdiecker reaction proceeds *via* a radical decarboxylation followed by recombination representing a facile method to access vinyl bromides from the corresponding cinnamic acids.[132] Unfortunately, the formation of the vinyl Grignard **I** was unsuccessful, even after screening a range of Grignard reagent activators, mechanical methods (*i.e.* vigorous stirring and sonication) and washing the magnesium turnings with acid. This is unsurprising, vinyl Grignard reagents are notoriously challenging to form and

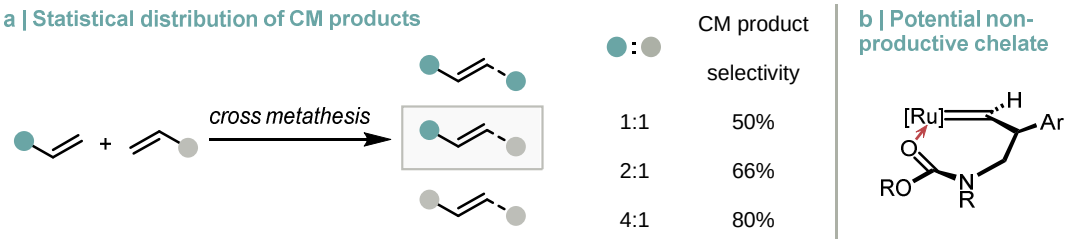
preparation is often unsuccessful.[133,134] Instead, the corresponding vinyl lithium species are used but, given the requirement for ^{t}BuLi in the preparation of this reagent, and the significant scale necessary at this point of the synthetic sequence, this route was discarded.



Scheme 96. Routes to introduce the PMP group, using a cross metathesis (a) or earlier in the synthesis using a Grignard reaction.

Our attention returned to optimising the cross-metathesis (CM). According to the report of Grubbs and co-workers both **77** and **65** should behave as Type II olefins, meaning the CM is non-selective.[135] This is traditionally overcome through altering the ratio of the two partners, as mentioned above, which has a marked effect on the statistically distribution of products (**Scheme 97a**). This was not however reflected in the product distribution observed, and none of the product resulting from homodimerisation of **77** was observed, and it is believed that **77** is actually a very poor substrate for CM, due to the steric bulk adjacent to the alkene, which likely clashes with the bulky ligand environment of the catalyst.[136] However, this does not explain the low recovery of **77**, which instead can be rationalised by the presence of the sulfonamide. It is well established that amine-containing systems have a propensity to coordinate to the metal centre, not only interfering un-productively with catalytic activity but making re-isolation challenging. Although it would be expected that suitable protection would decrease the likelihood of nitrogen coordination *via* the lone pair leading to an improvement in yield, this is often not observed. This strategy introduces additional sites for catalyst coordination for example *via* the carbonyl oxygen in a carbamate group, forming a non-productive chelate (**Scheme 97b**).[137] Whilst it has been reported that using a Lewis acid co-catalyst to saturate the coordination site of the nitrogen, out-competing the Ru

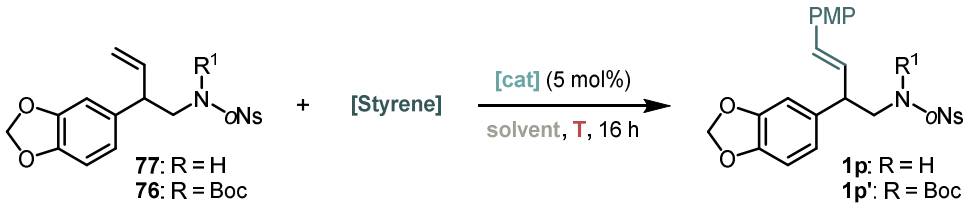
catalyst, has had a marked effect in a few cases, this approach has seen little application in the broader literature of CM reactions.[138]



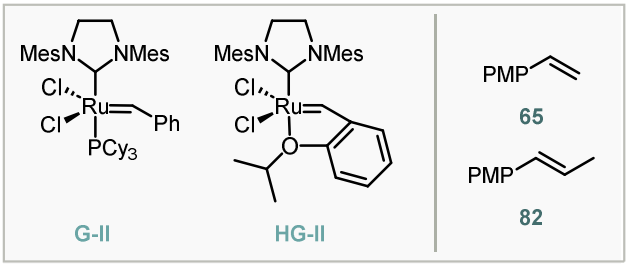
Scheme 97. Issues associated with CM reactions: the influence of starting material stoichiometry to product distribution (a) and unwanted coordination between the ruthenium centre and a carbonyl (b).

Despite the inherent nature of **77** as a poor substrate for CM, it was hoped that varying the reaction conditions would lead to an improvement in yield. Switching to HG-II catalyst was initially considered, the more reactive catalyst meaning less harsh conditions could be used *i.e.* lower temperatures. However no conversion to **1p** was observed (**Table 24**, Entry 2). The reactions did occur at an elevated temperature, however the yield was very similar to before and no starting material was recovered (**Table 24**, Entries 3 & 4). This opportunity was used to see if the amount of stilbene side-product **78** could be reduced, to aid purification. Anethole **82** was used, instead of **65**, the hope being that a 1,2-disubstituted olefin would reduce the rate of homodimerisation, unfortunately this did not appear to make an observable difference (**Table 24**, Entry 3). At this stage, it is important to note that although determining the exact ratio of products and starting materials using quantitative ^{1}H NMR would be useful, it was not possible due to a lack of isolated signals which could be compared directly. Doubling the equivalents of **82** gave a slight increase in yield, however the additional challenges associated with purification negated the minor improvement (**Table 24**, Entry 4). Finally, using **76** instead of **77** was attempted, here <20% NMR yield was observed in both cases (**Table 24**, Entries 5 & 6), this is not surprising considering the potential chelating ability of the Boc carbonyl as mentioned previously. At this point it was decided that, although this final step was low yielding, further optimisation was unlikely to result in significant improvement in the yield.

Table 24. Optimisation of the CM conditions.



Catalysts/Styrenes used



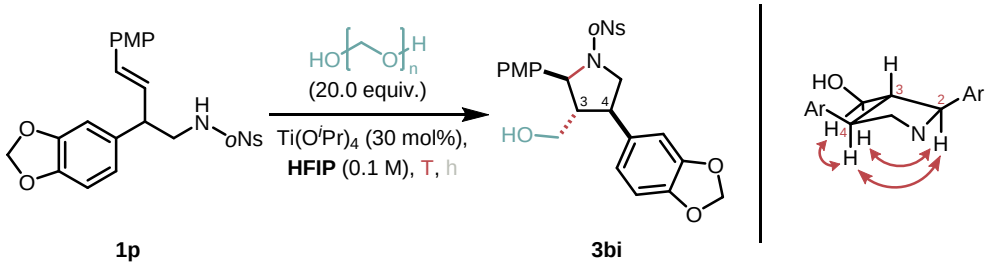
Entry	R^1	Styrene	A:B	Catalyst	Solvent	T (°C)	1p (%)
1	**H**	**65**	**1:2**	**G-II**	**PhMe**	**100**	**32**
2	H	**65**	1:2	HG-II	CH_2Cl_2	35	0
3	H	**82**	1:2	HG-II	DCE	70	29
4	H	**82**	1:4	HG-II	DCE	70	35
5	Boc	**65**	1:2	G-II	PhMe	100	15[a]
6	Boc	**82**	1:4	HG-II	DCE	70	18[a]

[a]Calculated by quantitative ^{1}H NMR analysis of the crude reaction mixture.

4.4 Cyclisation

Following preparation of the key substrate, **1p** was subjected to the reaction conditions optimised for the parent system **1a** (**Scheme 91a**). At 0 °C, no product **3bi** was observed, with complete recovery of **1p** (**Table 25**, Entry 1). Repeating the reaction at room temperature was promising, and **3bi** was isolated in a 29% yield and 5.5:1 d.r. across C3-C4 (determined by nOe analysis, highlighted in **Table 25**), pleasingly **1p** was also recovered in significant amounts (**Table 25**, Entry 2). Increasing the reaction temperature to 40 °C gave a small improvement in yield, however a marked improvement was observed through a further increase in the temperature to 50 °C (**Table 25**, Entries 3 & 4).

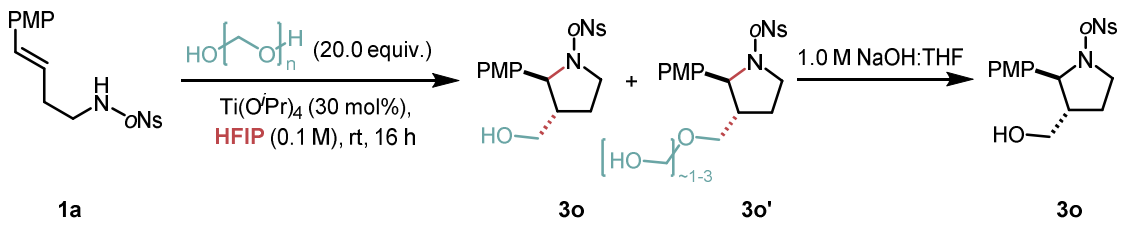
Table 25. Optimisation of the cyclisation of **1p** with paraformaldehyde with key nOes highlighted.



Entry	T (˚C)	t (h)	3bi (%)	d.r. (C3-C4)
1	0	48	0	-
2	rt	48	29	5.5:1
3	40	24	35	5.5:1
4	50	24	68	5.5:1

All reactions were carried out on 0.040 mmol scale.

It was decided not to increase the temperature further as only a trace amounts of **1p** was observed in the ^{1}H NMR of the crude reaction mixture. Additionally, when reaction of paraformaldehyde with **1a** was carried out at room temperature rather than 0 ˚C, side-product **3o'** was also formed; these short chain oligomers potentially arising from further *O*-alkylation of **3o** (**Scheme 98**). It was demonstrated that **3o'** could be cleaved back to **3o** with stirring in an aq. 1.0 M NaOH:THF 1:1 mixture albeit in reduced yields when compared to carrying out the cyclisation reaction directly at 0 ˚C. The major diastereomer was easily separated by column chromatography, enabling us to continue with the desired *trans-trans* 2,3,4-azacycle in the following steps. This result clearly demonstrates the utility of the method in the synthesis of the core of Atrasentan, especially when compared to the diastereoselectivity issues that arose during the previous routes.



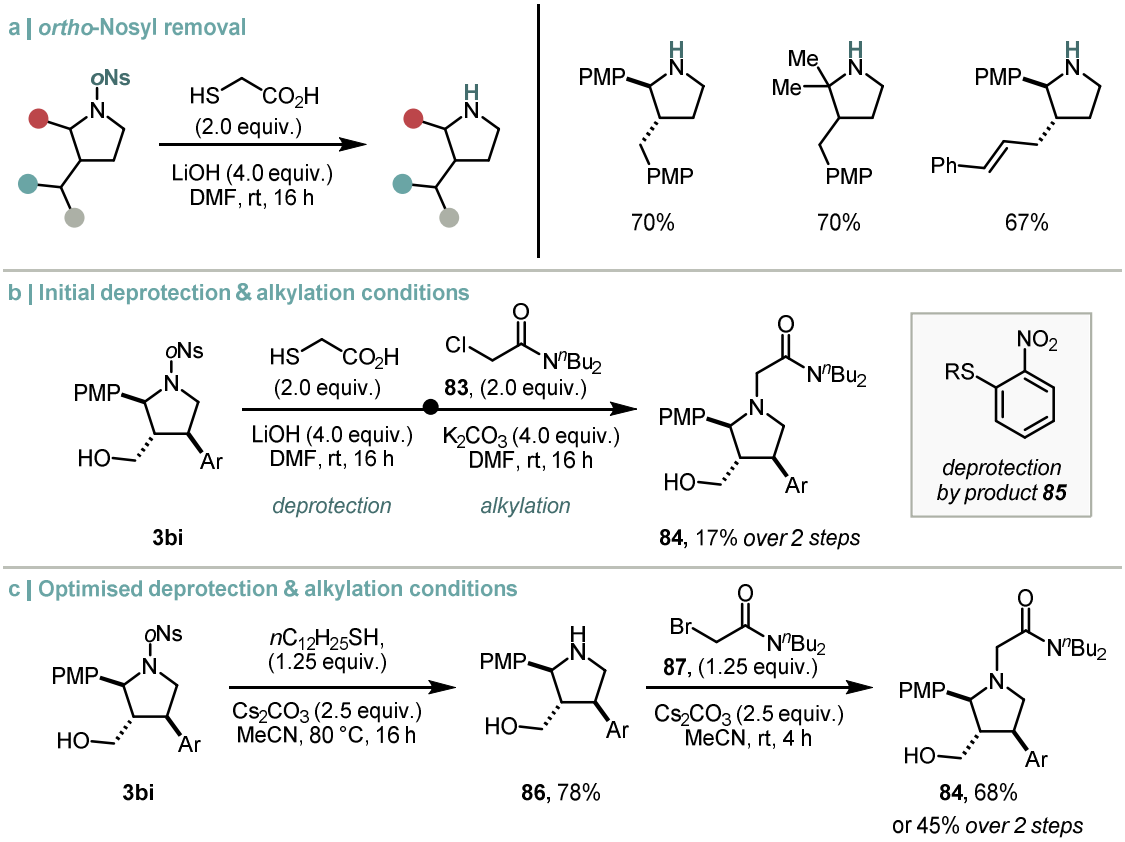
Scheme 98. Products observed when cyclisation of **1a** with paraformaldehyde was carried out at rt.

4.5 End game

4.5.1 First generation route

With **3bi** in hand, attention moved towards the steps required to make Atrasentan. As previously mentioned, the plan was to switch the group on the nitrogen before oxidation of the alcohol to the carboxylic acid. Conditions for the removal of the *ortho*-nosyl group had already been developed by Yuxiang Zhu, using mercaptoacetic acid and lithium hydroxide in DMF (**Scheme 99a**). However, when these conditions were applied to **3bi**, two things were observed which forced us to consider the reaction in greater detail. Whereas the deprotection reaction is typically clean, here the crude reaction mixture was complex, in addition, the target compound was very polar, both observations hinted at potential problems during work-up and purification. Owing to the second reason, it was decided to subject the crude material directly to the alkylation with 2-chloroacetamide **83** in DMF and **84** was isolated in low yield (**Scheme 99b**).

Mercaptoacetic acid was previously established as an ideal source of thiol for the deprotection; any unreacted acid is easily removed by aqueous workup and, although toxic, is significantly safer to handle than the more commonly used thiophenol. However, considering the potential requirement to carry the material through crude, avoiding aqueous work-up and column chromatography, a new thiol was required. The long chain thiol, 1-dodecanethiol was chosen as potential candidate, the toxicity is low, and both the thiol and thioether by-product **85** are comparably non-polar, making them easy to separate from **84** at a later stage. A further switch of the base was made from lithium hydroxide to caesium carbonate, a less hydroscopic alternative. Treatment of **3bi** under the new conditions provided a much cleaner reaction profile and following removal of caesium carbonate by filtration crude **86** could be directly subjected to the next step. Treatment of **86** with 2-bromoacetamide **87**, a more reactive electrophile compared to the chlorinated analogue **83**, in the presence of caesium carbonate provided **84** in a much higher yield of 45% (compared to 17% previously) (**Scheme 99c**). The yield could be improved slightly by purifying the deprotection material; using methanolic ammonia as a column co-eluent enabled the successful purification of **86**.



Scheme 99. Optimisation of the deprotection, previously utilised *ortho*-nosyl removal conditions by Yuxiang Zhu (a), using those conditions on the Atrasentan system (b) and the improved conditions (c).

Finally, oxidation from **84** to **33** was attempted. The direct conversion of primary alcohols to carboxylic acids has been well explored and traditional oxidants can be broadly divided into six categories, as summarised by Tojo and Fernández.[139]

1.Permanganate

2. Jones and other CrO_3-based oxidants

3. Pyridinium dichromate (PDC) in DMF

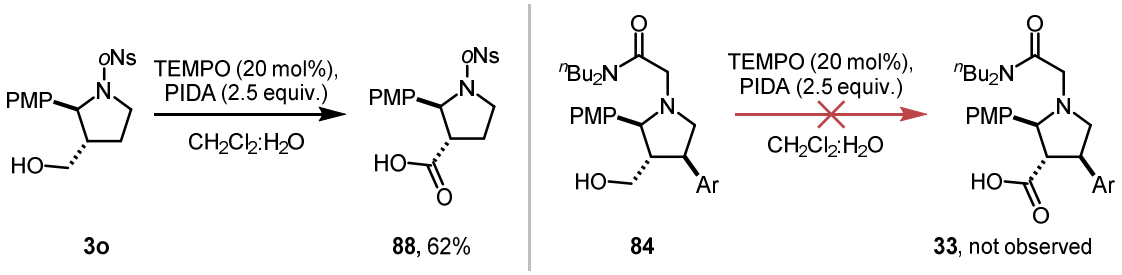
4. Heyns oxidation

5. Ruthenium tetroxide and related Ru compounds

6. TEMPO-mediated

Our initial approach followed method six, primarily as it a milder, greener and significantly less toxic alternative to many of the heavy metal approaches mentioned. Catalytic TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl radical) with (diacetoxyiodo)benzene (PIDA) as the stoichiometric oxidant was chosen, under a biphasic CH_2Cl_2:H_2O solvent system.[140] Testing this on the parent

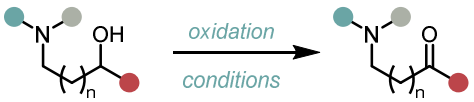
compound **3o** was successful **88** was isolated in good yield (**Scheme 100**). Unfortunately, when applied to the Atrasentan system, complete decomposition of **84** was observed.

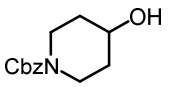
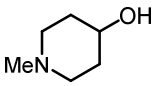
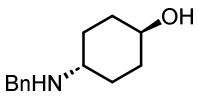


Scheme 100. TEMPO-mediated oxidation carried out on **3o** and **84**.

This observation was reflected in a search for reported oxidations in the presence of amines: whilst sulfonamides and other related protected-amines are reported to remain unaltered in TEMPO mediated oxidations, examples with electron-rich amines are limited, owing to increased susceptibility to oxidation.[141] This was demonstrated in a recent report by Iwabuchi and co-workers on the oxidation of amino alcohols to amino ketones.[142] When they compared their nitroxyl radical/copper co-catalysis approach to four more traditional oxidation methods it was evident that the presence of electron-rich amines has a detrimental effect on yield when compared to protected-amines (**Table 26**, Entries 1 – 3). This study clearly highlights the need for further investigation of oxidation conditions suitable for systems containing such amine functionality.

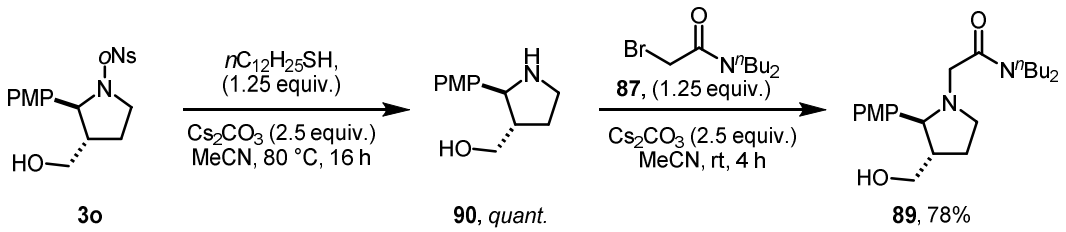
Table 26. Summary of the results reported by Iwabuchi and co-workers on the effect of amines on oxidations.



Entry	Amino alcohol	PCC[a]	Swern[b]	DMP[c]	TPAP[d]	AZADO/Cu[e]
1		92% / 2 h	95% / 0.75 h	97% / 2 h	90% / 0.75 h	97% / 1.5 h
2		16% / 1.5 h	65% / 1 h (10%)	20% / 3 h (17%)	32% / 3 h (29%)	96% / 3 h
3		26% / 1 h (<5%)	32% / 1.2 h	0% / 4 h (29%)	68% / 4 h (13%)	92% / 2 h

[a]PCC (1.5 equiv.), 4 Å MS, CH_2Cl_2, rt; [b]$(COCl)_2$ (2.0 equiv.), DMSO (4.0 equiv.), Et_3N (6.0 equiv.), CH_2Cl_2, –78 °C to rt; [c]DMP (1.5 equiv.), CH_2Cl_2, rt; [d]TPAP (5 mol%), NMO (1.5 equiv.), 4 Å MS, CH_2Cl_2, rt; [e]AZADO (5 mol%), CuCl (3 mol%), bpy (3 mol%), DMAP (6 mol%), MeCN, rt. Recovered starting material shown in brackets.

Rather than testing more oxidation conditions on **84**, test substrate **89** was prepared in two steps from cyclisation product **3o** (**Scheme 101**).



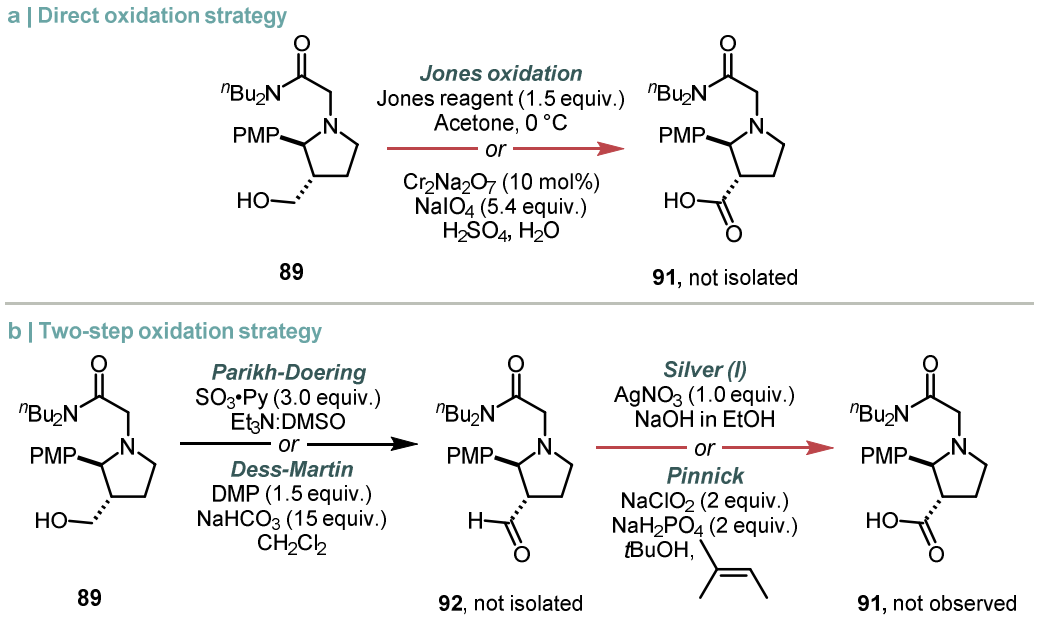
Scheme 101. Preparation of test substrate **89**.

Although literature examples of oxidations in the presence of electron-rich amines were narrow, Jones reagent had been successfully applied in limited examples.[139] Following the preparation of Jones reagent, **89** was subjected to the oxidation, analysis by TLC revealed consumption of starting material after 15 min and the presence of a more polar species, which was supported by the ESI spectrum of the crude material, which showed a clear product $[M+H]^+$ m/z. Unfortunately, purification was unsuccessful in separating tentative **91** from residual chromium which was present both after aqueous work up and column chromatography (**Scheme 102a**). The paramagnetic nature of chromium (III) resulted in broadening of the ^{1}H NMR signals, making further confirmation of the presence of **91** impossible. Due to the highly polar nature of **91** it was hoped that alternative purification techniques may prove successful, however, utilising a range of ion-exchange resins was similarly disappointing and for this reason no further attempts using the Jones oxidation were undertaken.

Rather than carrying out a direct oxidation procedure, a two-step route was considered, proceeding *via* the aldehyde. This approach is well established, it is reported that close to 40% of alcohol to acid transformations in the literature proceed *via* the aldehyde.[143] The popularity of this approach in complex-molecule synthesis reflects the increasing number of milder, and more selective conditions available. Much as with the direct procedure, an extensive array of approaches were available.

When assessing which conditions to use, the practical considerations associated with carrying out the reaction on a smaller scale were key. The Parikh-Doering oxidation was selected as a viable set of conditions, which was a preferable activated dimethyl sulfoxide source than the more commonly used Swern oxidation.[144] Initial attempts on **89** were successful, and the ^{1}H NMR of the crude showed

complete conversion to aldehyde **92**, however **92** was unstable to column chromatography and only trace material was recovered. It was decided to repeat the procedure, carrying **92** through crude to the second step but, unfortunately reproducibility issues were encountered and incomplete conversion to **92** was often observed. For this reason, Dess–Martin periodinane (DMP) was used instead to facilitate this transformation, reliably affording crude **92** which was deemed sufficiently clean to carry forward (**Scheme 102b**).[145] By far the most common approach utilised to oxidise an aldehyde to the corresponding carboxylic acid is the Pinnick oxidation. Despite multiple reports engaging Pinnick oxidation conditions on a substrate containing a tertiary amine, in our hands only decomposition was observed; although this is likely to be due to undesired oxidation, potentially having to use the aldehyde crude may be responsible.[146] Silver mediated oxidations are also known to be very mild, however, again only observed decomposition of **92** was observed under the reaction conditions. At this stage it was decided to stop investigating oxidation at this point in the sequence.

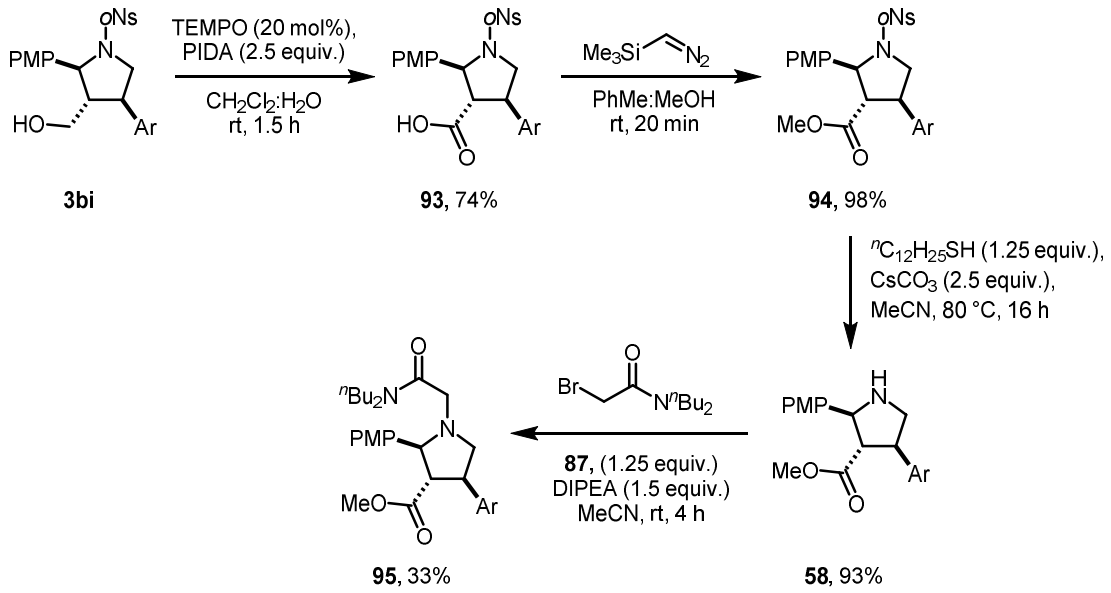


Scheme 102. Attempted oxidation of alcohol **89** using Jones reagent (a) or a 2-step strategy *via* aldehyde **92** (b).

4.5.2 Second generation route

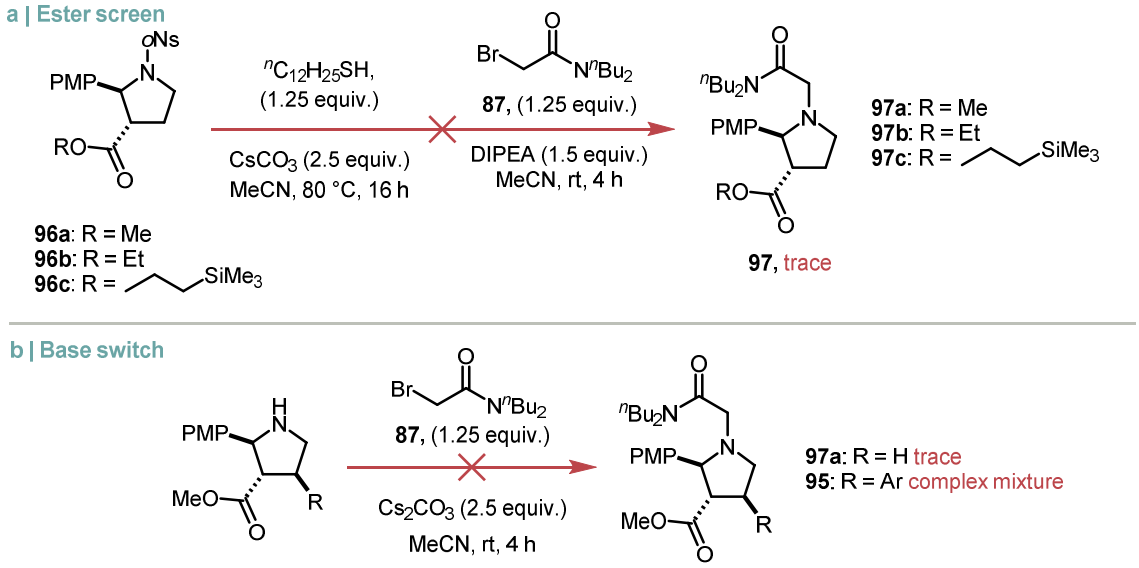
Having successfully demonstrated the oxidation of **3o**, it was decided to reverse the sequence of steps, first carrying out the oxidation before deprotection and introduction of the acetamide (**Scheme 103**). Although the initial route circumvented the need for protecting groups, it was required to convert the acid to the corresponding ester before carrying out the subsequent steps. Using the TEMPO-mediated

conditions as described previously, an oxidation of **3bi** was carried out to access **93**, again in good yield. It was decided to form methyl ester **94** which was more straightforward to install through the use of trimethylsilyldiazomethane rather than proceeding *via* the acid chloride or amide coupling approaches required to generate the ethyl ester. Formation of **94** proceeded in high yield, and the deprotection was also high yielding **58**. As intermediate **58** differs only in the nature of the ester to intermediate **46** disclosed in the industry route, the alkylation conditions they reported were followed, however **95** was isolated in a low 33% yield.



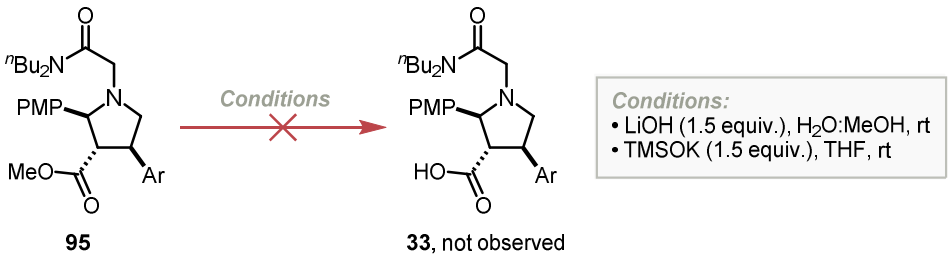
Scheme 103. Second generation route.

It was suggested that methyl ester may be susceptible to a S_N2-type attack by bromide generated during the reaction, leading to formation of the carboxylate and then ultimately decomposition. To test this hypothesis, three esters **96a** – **96c** were prepared, methyl, ethyl and TMS ethyl, before subjection to the deprotection, alkylation sequence. In all cases only trace product **97** was observed, suggesting that the ester substituent was not the issue (**Scheme 104a**). The alkylation was repeated with a different base: caesium carbonate rather than *N*,*N*-diisopropylethylamine (DIPEA) using methyl ester **96a**, once again only trace product was observed **98a** (**Scheme 104b**). When substrate **58** was subjected to the caesium carbonate conditions, monitoring the reaction using mass spectrometry showed complete consumption of starting material and **95** as major $[M+H]^+$ *m*/*z*, however, following work-up a complex reaction mixture was observed in the ^1H NMR of crude **95**.



Scheme 104. Attempts to improve the alkylation yield, using different esters (a) and Cs_2CO_3 as the base (b).

Although attempts to improve the yield of the alkylation of ester **95** were unsuccessful, our attention turned to the final ester hydrolysis step. Unfortunately, at this stage limited material and time meant only brief investigation into conditions for the hydrolysis were possible. Both use of aqueous lithium hydroxide and anhydrous potassium trimethylsilanolate conditions led to consumption of the ester starting material, however, isolation of acid **33** following an acidic workup was not possible (**Scheme 105**). If more time and material had been available, isolation of the corresponding carboxylate salt would have been attempted, as it was hypothesised that an acid-base work up on such small amounts of material was likely responsible for the loss of material.

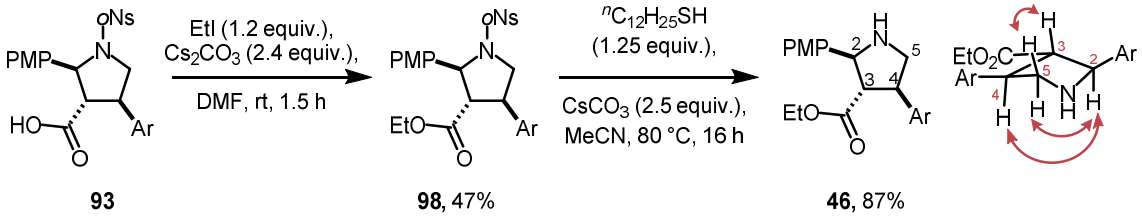


Scheme 105. Attempted ester hydrolysis of **95**.

4.5.3 Formal synthesis

Due to time constraints, it was decided to attempt a formal synthesis at this stage. Although the second-generation route reported by Abbott Laboratories proceeds *via* intermediate methyl ester **58**, the associated spectroscopic data was not made available during publication, so the synthesis ethyl ester **46**

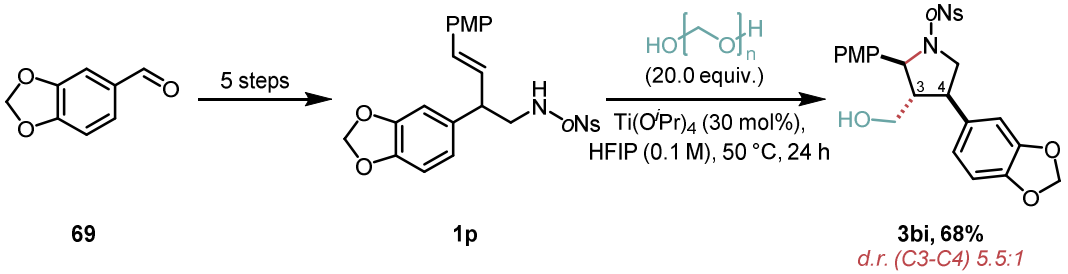
was carried out (**Scheme 106**).[128] Carboxylic acid **93** was treated with ethyl iodide with caesium carbonate to generate the corresponding ethyl ester **98** in moderate yield. **98** was then subjected to the standard deprotection conditions affording **46** in high yield. The relative stereochemistry of **46** was confirmed through nOe analysis with key correlations highlighted. A comparison of the ^{1}H and ^{13}C NMR data can be found in **Chapter 6, Section 6.4.5**.



Scheme 106. Formal synthesis of known intermediate **46**.

4.6 Summary and outlook

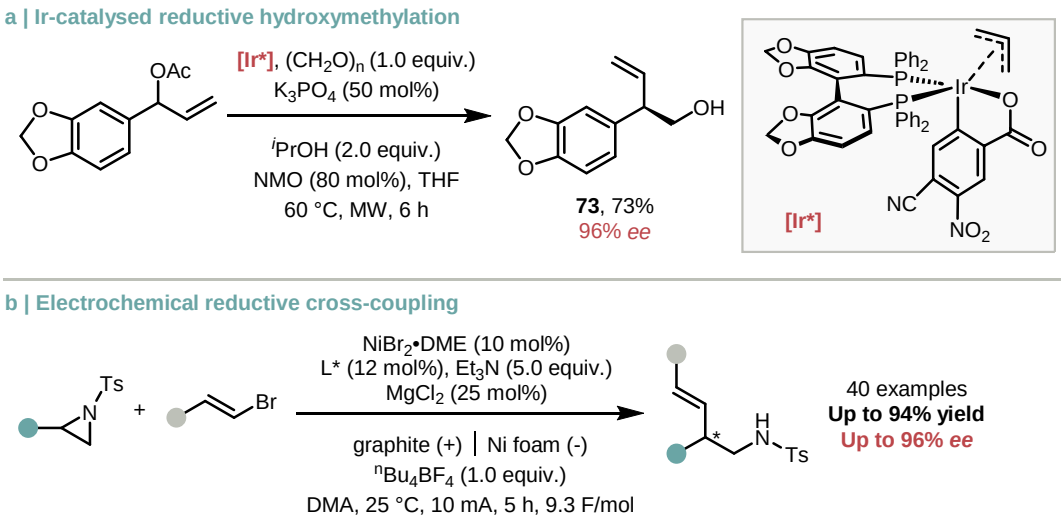
In summary, the $Ti(O^{i}Pr)_4$ in HFIP methodology disclosed in **Chapter 2** has successfully been applied to the synthesis of the core in Atrasentan with good diastereoselectivity and good yield (**Scheme 107**). Despite the longer route required to access the key substrate **1p** when compared to the industry routes, the cyclisation is clearly a superior way to access the pyrrolidine core with no need to introduce a lengthy sequence to separate and isomerise the undesired diastereomers. If a shorter, more scalable route to **1p** could be devised it would clearly put our method above the current literature sequence, however currently, the lack of cyclised material **3bi** ultimately hampered the derivatisations required to access Atrasentan.



Scheme 107. Summary of the route to the core of Atrasentan **3bi**.

In addition, a new route would offer potential points to access enantiomerically enriched material. Whilst homoallylic alcohol **73**, an intermediate on the current route can be accessed in 96% *ee* using conditions reported by Krische and co-workers (**Scheme 108a**), a recent report by Nevado and co-workers offers

a far superior alternative (**Scheme 108b**).[147,148] The nickel catalysed enantioselective electrochemical cross-coupling of aryl aziridines with alkenyl bromides potentially offering a facile method to access **1p**.



Scheme 108. Potential reductive coupling approaches to enantioenriched homoallylic amine.

Although the synthesis of Atrasentan was not achieved, accessing known intermediate **46** can be seen as a success considering the lack of material and issues associated with the oxidation and alkylation steps. It is likely that with more material and time the synthesis would be achievable.

5

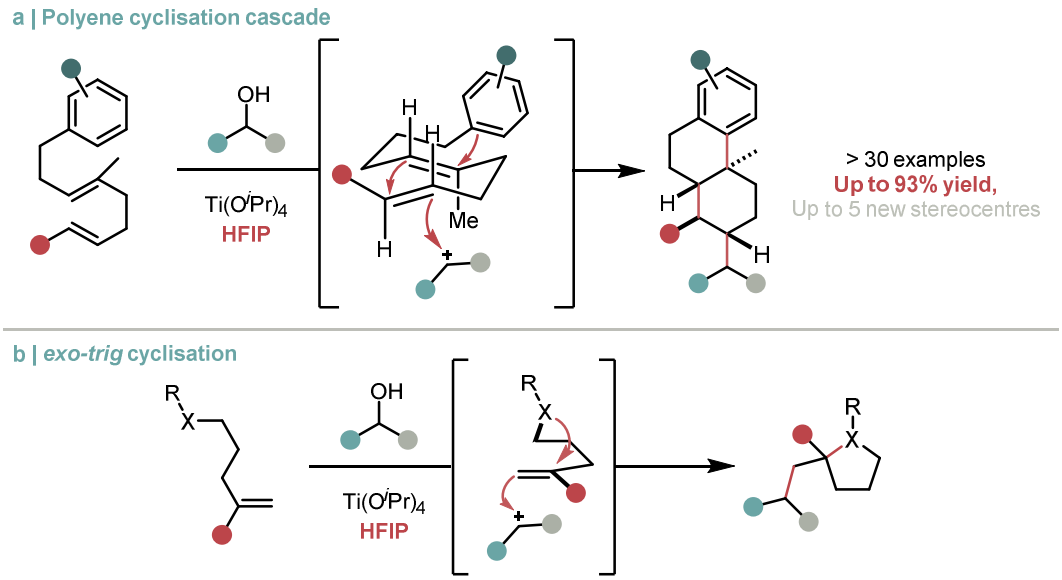
Conclusions and future work

An overview of the current methods in the literature to access pyrrolidines and piperidines clearly highlighted the requirement for approaches which enable the synthesis of azacycles with increasing ring substitution. The use of a cation-triggered annulation strategy was seen as a viable way to enable an *endo-trig* carboamination to occur, an otherwise poorly explored disconnection. Of the approaches considered to generate a carbocation, both the use of HFIP in combination with a Lewis acid catalyst and ion-pairing catalysis were found to be viable routes to access 2,3-disubstituted azacycles and through these complementary methods a diverse range of piperidines and pyrrolidines have been prepared.

Initially establishing a broad scope for the transformation was a central focus, and it was demonstrated that alongside allylic and benzylic alcohols other electrophiles could be used in the Ti/HFIP work. In addition, a 2-step strategy to diversify the C2-substitutent was established. These factors, in addition to the ability to access both the 5- and 6- ring systems in comparable yields and selectivity, mean this approach has improved upon what was previously achieved during the synthesis of tetrahydrofurans using these conditions.

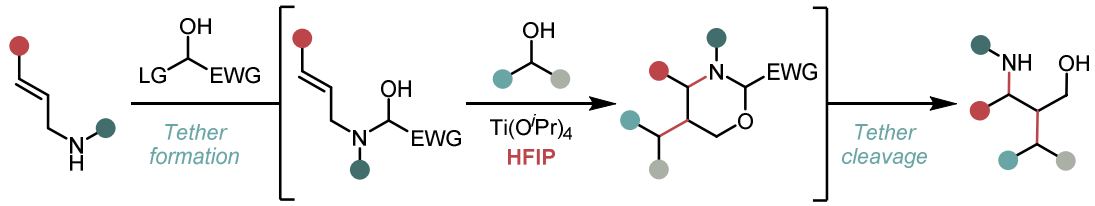
Whilst ultimately, achieving high levels of enantioselectivity using chiral phosphoric acid catalysis was complicated by diastereoselectivity issues, the ability to carry out the annulation in the absence of HFIP can be seen as a huge achievement, considering the low reactivity of the homoallylic amine when compared to established nucleophiles in the literature.

Alongside the undertaking of this work, the Donohoe group has studied other ring systems, and Daniya Aynetdinova successfully applied the Ti/HFIP conditions to a polyene cyclisation cascade, generating a library of steroid analogues (**Scheme 109a**).[149] Preliminary work has also been undertaken by Megan Jaschinski on a complementary *exo-trig* cyclisation reaction (**Scheme 109b**) and it is hoped that the alternative ring frameworks may prove amenable to an asymmetric transformation in the future.[150]



Scheme 109. New cyclisation reactions: a polyene cascade (a) and an *exo-trig* cyclisation (b).

Finally, one direction which could be explored through this method is a tethering strategy, as a method is access 1,3-aminoalcohols (**Scheme 110**). This approach would enable the excellent diastereocontrol obtained during cyclisation to be transferred to acyclic products.



Scheme 110. Proposed tethered strategy to access 1,3-aminoalcohols.

6

Experimental data and procedures

6.1 General experimental details

Reagents, solvents and techniques: All reactions were performed under an inert atmosphere with constant magnetic stirring, unless otherwise stated, using clean, oven dried glassware. Reagents and solvents were obtained from commercial supplies and were used without further purification. All inert gases were sourced from the University of Oxford's internal supplies and dried through $CaCl_2$ drying columns. Anhydrous solvents were obtained from the University of Oxford internal solvent system and dried by passing through alumina columns, manufactured by Innovative Technology Inc. PS-400-7. Temperatures of −78 °C and 0 °C were achieved with a CO_2(s)/acetone bath and ice/water bath respectively. Where a reaction was required to stay at 0 °C for 48 h a Thermo Scientific EK90 Immersion Cooler with Flex Probe and isopropanol bath was used.

Chromatography: Reactions were monitored by TLC using aluminium backed silica gel plates (Merck Kieselgel 60 PF254) with the appropriate solvent system and were visualised using UV fluorescence (254 nm) and developed with potassium permanganate, phosphomolybdic acid or vanillin. Flash column chromatography was performed on silica gel (60 Å, 230-400 mesh) under a positive pressure of nitrogen and the required eluent.

NMR Spectroscopy: ^{1}H and ^{13}C NMR samples were run on a Bruker AVIIIHD 400 MHz spectrometer, where required COSY and HSQC spectra were used to assign NMR spectra. In addition, Bruker AVIIIHD 500 MHz and Bruker NEO 600 MHz spectrometers were used to obtain NOESY and HMBC data where required. All NMR spectra were recorded at ambient temperature. Chemical shifts (δ) are recorded in parts per million (ppm). The residual protic solvent signal(s) acted as the internal reference for ^{1}H NMR spectra [$CDCl_3$ (δ 7.26) or MeOH-d4 (δ 3.31)], and the deuterated solvent signal acted as

the internal reference for ^{13}C NMR spectra [$CDCl_3$ (δ 77.16), MeOH-d4 (δ 49.0)]. All diastereomeric ratio values were based on the crude NMR unless otherwise stated.

Mass Spectroscopy: Mass spectra were obtained through the University of Oxford mass spectrometry service by electrospray ionisation (ESI) using a Bruker Daltonics microTOF spectrometer. The m/z values were all recorded in Daltons to four decimal places, the mass found was compared to the mass calculated from the monoisotopic molecular formula.

Infrared Spectroscopy: Infrared spectra were obtained using a Bruker Tensor 27 FT-IR spectrometer equipped with a diamond ATR module. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Melting Points: Melting points were obtained using Griffin melting point apparatus.

Optical Rotations: Optical rotations were recorded on a Schmidt Haensch Unipol L2000 polarimeter in a cell with a path length of 1 dm (using the sodium D line, 589 nm). Concentrations are reported in g/100 mL. Temperatures are reported in °C.

Chiral normal phase HPLC: Chiral normal phase HPLC was performed on an Agilent 1260 Series HPLC unit equipped with UV-vis diode-array detector, fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø × 25 cm) along with the corresponding guard column (0.4 cm ø × 1 cm). Wavelengths (λ) are reported in nm, retention times (tR) are reported in minutes and solvent flow rates are reported in mL min^{-1}.

6.2 Experimental details – Chapter 2

6.2.1 General procedures

General Procedure A: Wittig

According to the procedure of *Maryanoff.*[151] To a solution of (3-carboxypropyl)triphenyl-phosphonium bromide (1.2 equiv.) in anhydrous THF (2.0 mL/mmol) was added NaHMDS (2.0 M in THF, 2.4 equiv.) dropwise at 0 °C and left to stir for 30 min. The solution was cooled to –78 °C before addition of aldehyde (1.0 equiv.) dropwise. The reaction mixture was left to warm to rt over 16 h. The solution was diluted with EtOAc and water and the layers separated. The aqueous layer was acidified to pH 1 with 1.0 M HCl before extracting with EtOAc. The combined organic layers were washed with 1.0 M HCl and dried over $MgSO_4$ before concentrating *in vacuo* and purifying by FCC.

General Procedure B: Carboxylic acid reduction

To a suspension of $LiAlH_4$ (1.2 equiv.) in anhydrous THF (1.0 mL/mmol) was added a solution of acid (1.0 equiv.) in THF dropwise at 0 °C and left to stir for 3 h. The solution was quenched using a Fieser workup before concentrating *in vacuo* and purifying by FCC.

Fieser workup: The solution was diluted with Et_2O and cooled to 0 °C before subsequent addition of H_2O (1.0 mL/g of $LiAlH_4$), aq. NaOH (15 wt%, 1.0 mL/g of $LiAlH_4$) and H_2O (3.0 mL/g of $LiAlH_4$). The solution was warmed to rt and stirred for 15 min before addition of anhydrous $MgSO_4$, after a further 15 min the solid was removed by filtration before concentrating *in vacuo.*

General Procedure C: Mesylate formation

To a solution of alcohol (1.0 equiv.) in anhydrous CH_2Cl_2 (5.0 mL/mmol) was added triethylamine (1.5 equiv.) before cooling to 0 °C. Methanesulfonic anhydride (1.2 equiv.) was added portionwise before warming to rt. The reaction mixture was left to stir for 3 h before addition of 0.5 M HCl (4.5 mL/mmol). The aqueous later was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$ before concentrating *in vacuo* and purifying by FCC.

General Procedure D: S_N2

A suspension of sulfonamide (1.5 equiv.) and potassium hydroxide (1.5 equiv.) in DMF (10 mL/mmol) was stirred at 100 °C for 30 min before dropwise addition of mesylate (1.0 equiv.) in DMF. The reaction

mixture was left to stir at 100 °C for 1 h before cooling to rt and diluting with water. The aqueous layer was extracted with Et_2O and the organic layer washed with water and brine before drying over Na_2SO_4, concentrating *in vacuo* and purifying by FCC.

General Procedure E: Ru-catalysed metathesis

To a solution of the appropriate Ru catalyst (1.5 mol%) in anhydrous solvent (4 mL/mmol, previously degassed by bubbling through Ar for 30 min.) was added the alkene components in solution (1.0 mL/mmol) and the mixture heated at reflux. The reaction was monitored by TLC until completion, before the solvent was removed *in vacuo* and the crude material purified by FCC.

General Procedure F: Amide formation

To a solution of carboxylic acid (1.0 equiv.) in anhydrous CH_2Cl_2 (2 mL/mmol) was added oxalyl chloride (1.2 equiv.) dropwise at 0 °C followed by DMF (2 drops) and left to warm up to rt. After 45 min, 80% of the solvent was removed in vacuo before re-dissolving in CH_2Cl_2 (2 mL/mmol). Aq. ammonia (28% in H_2O, 4.0 mL/mmol) was added portionwise at 0 °C and left to warm up to rt and stirred for 16 h. The aqueous later was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over $MgSO_4$ before concentrating *in vacuo*. The crude amide was recrystallised from hot EtOAc.

General Procedure G: Amide reduction and protection sequence

To a solution of amide (1.0 equiv.) in anhydrous THF (3.0 mL/mmol) was added $LiAlH_4$ (1.0 M in THF, 1.5 equiv.) dropwise at 0 °C and left to warm up to rt and stirred for 16 h. Following a Fieser workup (see **General Procedure B**) crude amine was used directly in the following protection reaction. To a solution of amine (1.0 equiv.) in anhydrous CH_2Cl_2 (5.0 mL/mmol) was added triethylamine (1.25 equiv.). The solution was cooled to 0 °C before addition of the appropriate sulfonamide (as a solution) or chloroformate (1.25 equiv.). The reaction mixture was left to warm up to rt and stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 and water. The aqueous later was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over $MgSO_4$ before concentrating *in vacuo* and purifying by FCC.

Modification for low molecular weight amines: Following the Fieser workup, before concentrating in vacuo, the solution was cooled to 0 °C and HCl (2.0 M in Et_2O, 1.25 equiv.) was added dropwise and stirred for 15 min. The hydrochloride salt of the amine was then used directly in the following protection reaction. To a solution of hydrochloride salt of the amine (1.0 equiv.) in anhydrous CH_2Cl_2 (5.0 mL/mmol) at 0 °C was added triethylamine (3.0 equiv.) dropwise and left to stir for 30 min before addition of methylchloroformate (1.25 equiv.) dropwise. The normal procedure was then followed.

General procedure H: Amide coupling

To a solution of acid (1.00 equiv.) in CH_2Cl_2 (2 mL/mmol) at 0 ˚C was added EDCI.HCl (1.10 equiv.) and 1-hydroxybenzotriazole (1.10 equiv.). After stirring at 0 ˚C for 15 min. was added amine (1.15 equiv.) and *N*-methylmorpholine (1.20 equiv.) before stirring at rt for 16 h. The reaction mixture was concentrated *in vacuo*, redissolved in EtOAc and washed with 1.0 M HCl and brine. The solvent was removed *in vacuo* and the crude material purified by FCC.

General Procedure I: Cyclisation

To a microwave vial charged with a stirrer bar was added the appropriately protected amine (1.0 equiv.), alcohol (1.0 equiv.) and HFIP (10 mL/mmol) under argon. A solution of $Ti(O^iPr)_4$ in HFIP (30 mol%) was added and the reaction stirred at the given temperature for the given period of time. The reaction mixture was concentrated *in vacuo* and purified by FCC.

General Procedure J: *ortho*-nosyl removal

To a solution of pyrrolidine (1.0 equiv.) in anhydrous DMF (1.0 mL/mmol) under Ar was added LiOH (4.0 equiv.) and mercaptoacetic acid (2.0 equiv.) before stirring at rt for 16 h. The solution was diluted with EtOAc and water and the layers separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4 before concentrating *in vacuo* and purifying by FCC.

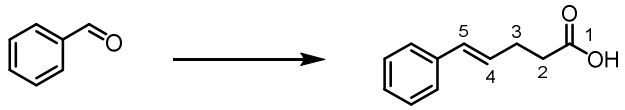
General Procedure K: Methyl carbamate removal

To a solution of cyclised product (1.0 equiv.) in $CHCl_3$ (25 mL/mmol) was added trimethylsilyl iodide (3.0 equiv.) before heating to 55 °C for 2 h. The reaction mixture was concentrated *in vacuo* and purified by FCC.

Modification for piperidines containing alkenes: Isoprene (10.0 equiv.) was added before heating to 55 °C.

6.2.2 Synthesis of nucleophiles

(7): (*E*)-5-Phenylpent-4-enoic acid

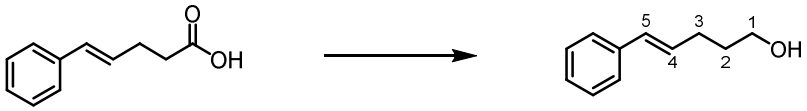


7

Prepared by **General Procedure A** using benzaldehyde (1.38 mL, 13.6 mmol), (3-carboxypropyl)-triphenylphosphonium bromide (7.00 g, 16.3 mmol), NaHMDS (2.0 M in THF, 16.3 mL, 32.6 mmol). Flash column chromatography (80% Et_2O/pentane + 1% acetic acid) followed by trituration with ice cold hexane (3 × 10 mL) afforded **7** as a crystalline white solid (1.52 g, 63%).

Data for **7**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.39 – 7.28 (4H, m, Ar), 7.22 (1H, m, Ar), 6.46 (1H, d, *J* = 16.0 Hz, C5-H), 6.24 (1H, m, C4-H), 2.61-2.49 (4H, m, 2 × C2-H_2 + 2 × C3-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 179.2 (C1) 137.3 (C Ar), 131.2 (C5), 128.5 (2 × C Ar), 128.0 (C4), 127.2 (2 × C Ar), 126.1 (C Ar), 33.8 (C2), 27.9 (C3). *The spectroscopic properties were consistent with the data available in the literature.*[152]

(8): (*E*)-5-Phenylpent-4-en-1-ol

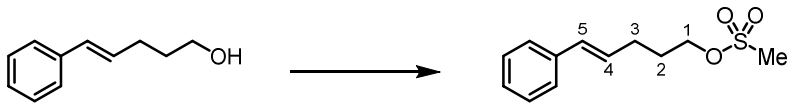


7 **8**

Prepared by **General Procedure B** using **7** (1.00 g, 5.67 mmol) and $LiAlH_4$ (6.8 mL, 1.0 M $LiAlH_4$ in THF, 6.8 mmol). Flash column chromatography (50% Et_2O – pentane) afforded **8** as a colourless liquid (799 mg, 87%).

Data for **8**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.40 – 7.28 (4H, m, Ar), 7.22 (1H, m, 1H, Ar), 6.44 (1H, d, *J* = 15.7 Hz, C5-H), 6.25 (1H, dt, *J* = 15.8, 7.0 Hz, C4-H), 3.71 (2H, t, *J* = 6.5 Hz, C1-H_2), 2.40 – 2.24 (2H, m, C3-H_2), 1.76 (2H, *app.* dq, *J* = 9.5, 6.5 Hz, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 137.6 (C Ar), 130.3 (C5), 130.0 (C4), 128.4 (2 × C Ar), 126.9 (2 × C Ar), 125.9 (Ar), 62.28 (C1), 32.2 (C2), 29.3 (C3). *The spectroscopic properties were consistent with the data available in the literature.*[153]

(9): (*E*)-5-Phenylpent-4-en-1-yl methanesulfonate

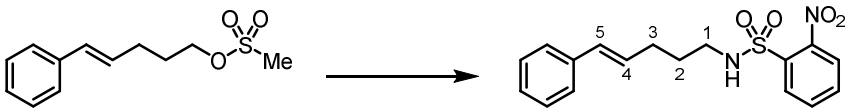


8 **9**

Prepared by **General Procedure C** using **8** (500 mg, 3.08 mmol), triethylamine (0.64 mL, 4.6 mmol) and methanesulfonic anhydride (644 mg, 3.70 mmol). Flash column chromatography (30% Et_2O – pentane) afforded **9** as a colourless liquid (600 mg, 81%).

Data for **9**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.40 – 7.28 (4H, m, Ar), 7.22 (1H, m, Ar), 6.45 (1H, d, *J* = 15.8 Hz, C5-H), 6.18 (1H, dt, *J* = 15.8, 7.0 Hz, C4-H), 4.28 (2H, t, *J* = 6.4 Hz, C1-H_2), 3.00 (3H, s, SO_2Me) 2.36 (2H, dt, *J* = 7.3, 7.0 Hz, C3-H_2), 1.99 – 1.89 (2H, m, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 137.2 (C Ar), 131.4 (C5), 128.5 (2 × C Ar), 128.2 (2 × C Ar), 127.2 (C4), 126.0 (C Ar), 69.2 (C1), 37.3 (SO_2Me), 28.7 (C2), 28.7 (C3). *The spectroscopic properties were consistent with the data available in the literature.*[154]

(4b): (*E*)-2-Nitro-*N*-(5-phenylpent-4-en-1-yl)benzenesulfonamide

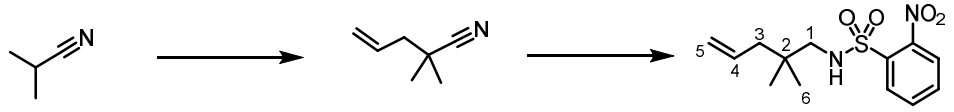


9 **4b**

Prepared by **General Procedure D** using **9** (1.2 g, 5.0 mmol), 2-nitrobenzenesulfonamide (1.52 g, 7.50 mmol) and potassium hydroxide (421 mg, 7.50 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **4b** as a white solid (902 mg, 52%).

Data for **4b**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.12 (1H, m, Ar), 7.82 (1H, m, Ar), 7.76 – 7.67 (2H, m, Ar), 7.31 – 7.27 (4H, m, Ar), 7.21 (1H, m, Ar), 6.35 (1H, d, *J* = 15.7 Hz , C5-H), 6.10 (1H, dt, *J* = 15.7, 7.0 Hz, C4-H), 5.32 (1H, t, *J* = 6.1 Hz, *N*H), 3.16 (2H, q, *J* = 6.1, 5.5 Hz, C1-H_2), 2.26 (2H, *app.* qd, *J* = 7.1, 1.5 Hz, C3-H_2), 1.73 (2H, p, *J* = 7.0 Hz, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.1 (C Ar), 137.3 (C Ar), 133.7 (C Ar), 133.5 (C Ar), 132.7 (C Ar), 131.2 (C5), 131.0 (C Ar), 128.6 (C4), 128.5 (2 × C Ar), 127.1 (C Ar), 126.0 (2 × C Ar), 125.3 (C Ar), 43.1 (C1), 29.7 (C3), 29.1 (C2). **HRMS** (ESI): calculated for $C_{17}H_{19}O_4N_2S$ $[M+H]^+$ requires *m/z* 347.1060, found *m/z* 347.1062. **IR** (film) ν_{max}: 3344, 3025, 2925, 1538, 1412, 1342, 1165, 740 cm^{-1}. **mp** (92 – 94 °C, EtOAc).

(11): *N*-(2,2-Dimethylpent-4-en-1-yl)-2-nitrobenzenesulfonamide



10 **11**

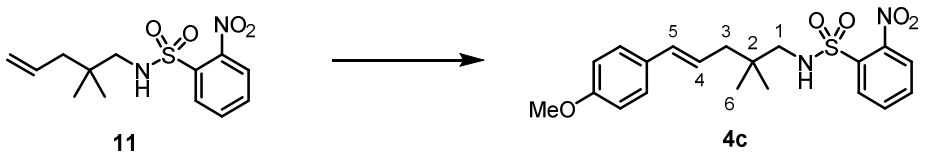
To a solution of freshly distilled diisopropylamine (5.26 mL, 37.5 mmol) in THF (100 mL) was added *n*-butyllithium (14.4 mL, 2.50 M in THF, 36.0 mmol) slowly at −78 °C before warming to rt. After stirring at rt for 15 min the solution was cooled to −78 °C before addition of isobutyronitrile (2.69 mL, 30.0 mmol) in THF (5 mL). The solution was stirred at −78 °C for 45 min before warming to rt and stirring for an additional 1 h. The solution was cooled to 0 °C before addition of allyl bromide (5.19 mL, 60.0 mmol) in THF (15 mL) and leaving to warm to rt and stir for a further 3 h. The solution was diluted with Et_2O and water and the layers separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$ before concentrating *in vacuo* and using **10** crude in the following reaction (2.25 g, 69%).

To a suspension of $LiAlH_4$ (695 mg, 18.3 mmol) in Et_2O (15 mL) was added 2,2-dimethyl-4-pentenenitrile (500 mg, 4.58 mmol) in Et_2O (5 mL) slowly at 0 °C before warming to rt overnight. The solution was quenched using a Fieser workup before concentrating *in vacuo*. The crude amine (272 mg, 2.40 mmol) was dissolved in CH_2Cl_2 (5 mL) before triethylamine (0.70 mL, 4.8 mmol) and 2-nitrobenzenesulfonyl chloride (585 mg, 2.64 mmol) were added at 0 °C and warming to rt overnight. The reaction mixture was quenched with H_2O (5 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 2.0 M HCl, water and brine and dried over $MgSO_4$ before concentrating *in vacuo.* Flash column chromatography (50% Et_2O – pentane) afforded **11** as a yellow oil (592 mg, 61%).

Data for **11**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.14 – 8.05 (1H, m, Ar), 7.90 – 7.80 (1H, m, Ar), 7.79 – 7.68 (2H, m, Ar), 5.84 – 5.68 (1H, m, C4-H), 5.33 (1H, t, *J* = 6.7 Hz, NH), 5.09 – 5.06 (1H, m, C5-H_A), 5.05 – 5.01 (1H, m, C5-H_B), 2.83 (2H, d, *J* = 6.7 Hz, C1-H_2), 2.00 (2H, d, *J* = 7.5 Hz, C3-H_2), 0.91 (6H, s, 2 × C6-H_3). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.2 (C Ar), 134.2 (C4), 133.7 (C Ar), 133.7 (C Ar), 132.9 (C Ar), 131.2 (C Ar), 125.5 (C Ar), 118.3 (C5), 53.3 (C1), 44.2 (C3), 34.4 (C2), 25.0 (C6). **HRMS**

(ESI): calculated for $C_{13}H_{19}O_4SN_2$ $[M+H]^+$ requires m/z 299.1060, found m/z 299.1062. **IR** (film) ν_{max}: 2963, 538, 1416, 1363, 1342, 1163, 1126, 1062, 854, 783 cm^{-1}.

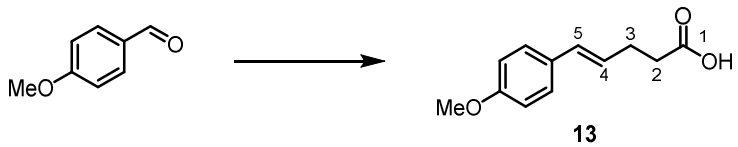
(4c): (*E*)-*N*-(5-(4-Methoxyphenyl)-2,2-dimethylpent-4-en-1-yl)-2-nitrobenzenesulfonamide



Prepared by **General Procedure E** using **11** (350 mg, 1.17 mmol), 4-vinylanisole (0.31 mL, 2.4 mmol), Grubbs II (48 mg, 0.056 mmol) in PhMe (6 mL). Flash column chromatography (20% EtOAc – pentane) afforded **4c** as a yellow oil (125 mg, 26%).

Data for **4c**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.14 – 8.04 (1H, m, Ar), 7.86 – 7.77 (1H, m, Ar), 7.76 – 7.64 (2H, m, Ar), 7.24 (2H, d, *J* = 8.6 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.34 (1H, d, *J* = 15.8 Hz, C5-H), 6.00 (1H, dt, *J* = 15.5, 7.6 Hz, C4-H), 5.34 (1H, t, *J* = 6.6 Hz, *N*H), 3.80 (3H, s, OMe), 2.86 (2H, d, *J* = 6.6 Hz, C1-H_2), 2.14 (2H, d, *J* = 7.6 Hz, C3-H_2), 0.96 (6H, s, 2 × C6-H_3).**^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.1 (C Ar), 133.6 (2 × C Ar), 132.9 (C Ar), 132.8 (C5), 131.3 (C Ar), 130.3 (C Ar), 127.4 (2 × C Ar), 125.5 (C Ar), 123.5 (C4), 114.1 (2 × C Ar), 55.5 (OMe), 53.3 (C1), 43.1 (C3), 35.1 (C2), 25.3 (C6). **HRMS** (ESI): calculated for $C_{20}H_{24}O_5SN_2Na$ $[M+Na]^+$ requires m/z 427.1298, found m/z 427.1297. **IR** (film) ν_{max}: 2961, 2361, 1608, 1540, 1511, 1468, 1364, 1250, 1174, 854 cm^{-1}.

(13): (*E*)-5-(4-Methoxyphenyl)pent-4-enoic acid

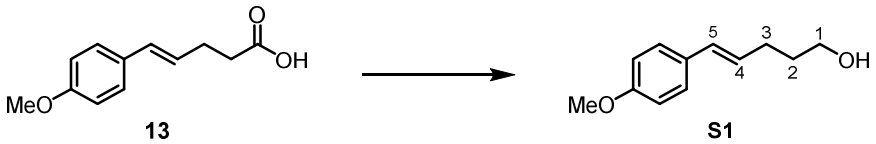


Prepared by **General Procedure A** using 4-methoxybenzaldehyde (1.22 mL, 10.0 mmol), (3-carboxypropyl)triphenylphosphonium bromide (5.15 g, 12.0 mmol), NaHMDS (2.0 M in THF, 12.0 mL, 24.0 mmol). Flash column chromatography (50% Et_2O – pentane + 1% acetic acid) afforded **13** as a crystalline white solid (1.65 g, 80%).

Data for **13**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27 (2H, d, *J* = 8.5 Hz, Ar), 6.84 (2H, d, *J* = 8.8 Hz, Ar), 6.39 (1H, d, *J* = 15.8 Hz, C5-H), 6.07 (1H, dt, *J* = 15.8, 7.0 Hz, C4-H), 3.80 (3H, s, OMe), 2.69 – 2.45

(4H, m, 2 × C2-H_2 + 2 × C3-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.2 (C Ar), 130.7 (C5), 130.3 (C Ar), 127.4 (C4), 126.0 (2 × C Ar), 114.1 (2 × C Ar), 55.5 (OMe), 33.9 (C2), 28.1 (C3). *The spectroscopic properties were consistent with the data available in the literature.*[155]

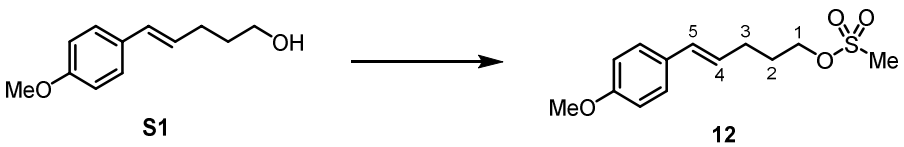
(S1): (*E*)-5-(4-Methoxyphenyl)pent-4-en-1-ol



Prepared by **General Procedure B** using **13** (1.00 g, 4.85 mmol) and $LiAlH_4$ (6.0 mL, 1.0 M $LiAlH_4$ in THF, 6.0 mmol). Flash column chromatography (50% Et_2O – pentane) afforded **S1** as a crystalline white solid (750 mg, 80%).

Data for **S1**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27 (2H, d, *J* = 8.6 Hz, Ar), 6.84 (2H, d, *J* = 8.8 Hz, Ar), 6.36 (1H, d, *J* = 15.7 Hz, C5-H), 6.09 (1H, dt, *J* = 15.8, 7.0 Hz, C4-H), 3.80 (3H, s, OMe), 3.70 (2H, t, *J* = 6.5 Hz, C1-H_2), 2.29 (2H, qd, *J* = 7.1, 1.5 Hz, C3-H_2), 1.82 – 1.65 (2H, m, C2-H_2), 1.58 – 1.56 (1H, m, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.9 (C Ar), 130.6 (C Ar), 129.9 (C5), 128.0 (C4), 127.2 (2 × C Ar), 114.1 (2 × C Ar), 62.6 (C1), 55.4 (OMe), 32.5 (C2), 29.4 (C3). *The spectroscopic properties were consistent with the data available in the literature.*[155]

(12): (*E*)-5-(4-Methoxyphenyl)pent-4-en-1-yl methanesulfonate

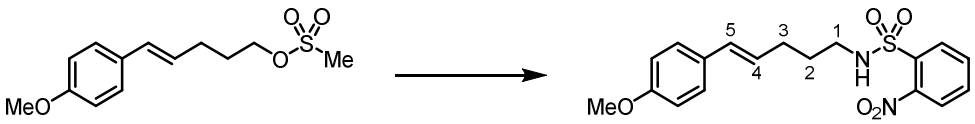


Prepared by **General Procedure C** using **S1** (711 mg, 3.70 mmol), triethylamine (0.77 mL, 5.6 mmol) and methanesulfonic anhydride (805 mg, 4.62 mmol). Flash column chromatography (30% Et_2O – pentane) afforded **12** as a crystalline white solid (730 mg, 73%).

Data for **12**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27 (2H, d, *J* = 8.9 Hz, Ar), 6.84 (2H, d, *J* = 8.8 Hz, Ar), 6.38 (1H, d, *J* = 15.8 Hz, C5-H), 6.02 (1H, dt, *J* = 15.8, 7.0 Hz, C4-H), 4.28 (2H, t, *J* = 6.4 Hz, C1-H_2), 3.80 (3H, s, OMe), 3.00 (3H, s, SO_2Me), 2.33 (2H, *app.* qd, *J* = 7.3, 1.5 Hz, C3-H_2), 1.93 (2H, *app.* dq, *J* = 7.8, 6.5 Hz, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.1 (C Ar), 131.0 (C5), 130.2 (C Ar), 127.3

(2 × C Ar), 126.2 (C4), 114.1 (2 × C Ar), 69.4 (C1), 55.4 (OMe), 37.5 (SO_2Me), 29.0 (C2), 28.9 (C3). *The spectroscopic properties were consistent with the data available in the literature.*[154]

(4a): (*E*)-*N*-(5-(4-Methoxyphenyl)pent-4-en-1-yl)-2-nitrobenzenesulfonamide

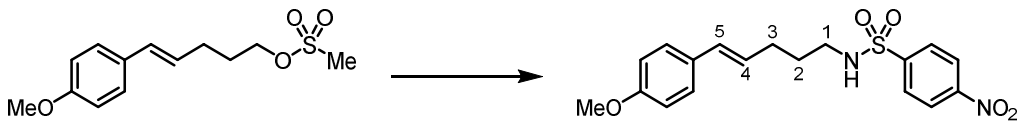


12 **4a**

Prepared by **General Procedure D** using **12** (200 mg, 0.740 mmol), 2-nitrobenzenesulfonamide (224 mg, 1.11 mmol) and potassium hydroxide (62 mg, 1.1 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **4a** as a white solid (169 mg, 61%).

Data for **4a**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.21 – 7.99 (1H, m, Ar), 7.88 – 7.79 (1H, m, Ar), 7.77 – 7.62 (2H, m, Ar), 7.22 (2H, d, *J* = 8.6 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.29 (1H, d, *J* = 15.9 Hz, C5-H), 5.94 (1H, dt, *J* = 15.8, 7.0 Hz, C4-H), 5.30 (1H, t, *J* = 6.1 Hz, *N*H), 3.80 (3H, s, OMe), 3.15 (2H, td, *J* = 7.0, 6.1 Hz, C1-H_2), 2.23 (2H, *app.* qd, *J* = 7.1, 1.5 Hz, C3-H_2), 1.71 (2H, p, *J* = 7.1 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.0 (C Ar), 133.6 (C Ar), 132.9 (C Ar), 131.2 (C Ar), 130.7 (C5), 130.2 (C Ar), 127.2 (2 × C Ar), 126.5 (C4), 125.5 (C Ar), 114.1 (2 × C Ar), 55.4 (OMe), 43.3 (C1), 29.9 (C3), 29.4 (C2). **HRMS** (ESI): calculated for $C_{18}H_{21}O_5NS$ $[M+H]^+$ requires *m/z* 377.1166, found *m/z* 377.1170. **IR** (film) ν_{max}: 3265, 2981, 2361, 2341, 1670, 1606, 1539, 1510, 1464, 1440, 1363, 1336, 1298, 1247, 1163 cm^{-1}. **mp** (86 – 88 °C, EtOAc).

(4d): (*E*)-*N*-(5-(4-Methoxyphenyl)pent-4-en-1-yl)-4-nitrobenzenesulfonamide

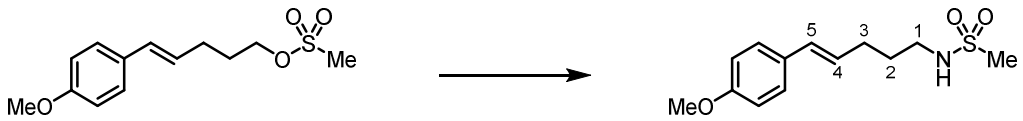


12 **4d**

Prepared by **General Procedure D** using **12** (250 mg, 0.920 mmol), 4-nitrobenzenesulfonamide (281 mg, 1.39 mmol) and potassium hydroxide (78 mg, 1.4 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **4d** as a white solid (308 mg, 89%).

Data for **4d**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.38 – 8.28 (2H, m, Ar), 8.08 – 7.99 (2H, m, Ar), 7.26 – 7.17 (2H, m, Ar), 6.90 – 6.79 (2H, m, Ar), 6.27 (1H, d, *J* = 15.7 Hz, C5-H), 5.92 (1H, dt, *J* = 15.8, 7.0 Hz, C4-H), 4.58 (1H, t, *J* = 6.1 Hz, *N*H), 3.81 (3H, s, OMe), 3.07 (2H, q, *J* = 6.7 Hz, C1-H_2), 2.21 (2H, *app.* qd, *J* = 7.1, 1.4 Hz, C3-H_2), 1.68 (2H, p, *J* = 7.1 Hz, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 146.1 (C Ar), 130.9 (C5), 130.0 (C Ar), 128.4 (2 × C Ar), 127.2 (2 × C Ar), 126.2 (C4), 124.5 (2 × C Ar), 114.2 (2 × C Ar), 55.5 (OMe), 42.9 (C1), 29.9 (C3), 29.4 (C2). *The spectroscopic properties were consistent with the data available in the literature.*[156]

(4e): (*E*)-*N*-(5-(4-Methoxyphenyl)pent-4-en-1-yl)methanesulfonamide

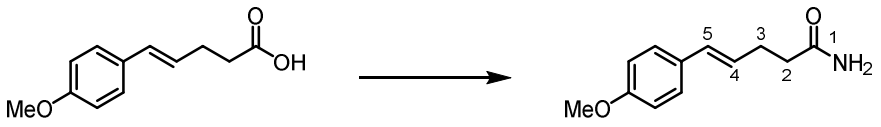


12 **4e**

Prepared by **General Procedure D** using **12** (100 mg, 0.370 mmol), methanesulfonamide (53 mg, 0.55 mmol) and potassium hydroxide (31 mg, 0.55 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **4e** as a white solid (53 mg, 53%).

Data for **4e**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28 (2H, d, *J* = 8.8 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.37 (1H, d, *J* = 15.8 Hz, C5-H), 6.03 (1H, dt, *J* = 15.7, 7.0 Hz, C4-H), 4.40 (1H, t, *J* = 6.3 Hz, *N*H), 3.81 (3H, s, OMe), 3.19 (2H, q, *J* = 6.8 Hz, C1-H_2), 2.96 (s, 3H, SO_2Me), 2.34 – 2.23 (2H, m, C3-H_2), 1.76 (p, *J* = 7.2 Hz, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.9 (C Ar), 130.5 (C Ar), 130.2 (C5), 127.1 (2 × C Ar), 126.6 (C4), 114.0 (2 × C Ar), 55.3 (OMe), 42.8 (C1), 40.4 (SO_2Me), 29.9 (C3), 29.9 (C2). **HRMS** (ESI): calculated for $C_{13}H_{19}O_3NNaS$ $[M+Na]^+$ requires *m/z* 292.0978, found *m/z* 292.0978. **IR** (film) ν_{max}: 3239, 2940, 2360, 1511, 1302, 1247, 1161, 1140, 1063, 1024 cm^{-1}. **mp** (90 – 92 °C, EtOAc).

(4o): (*E*)-5-(4-Methoxyphenyl)pent-4-enamide

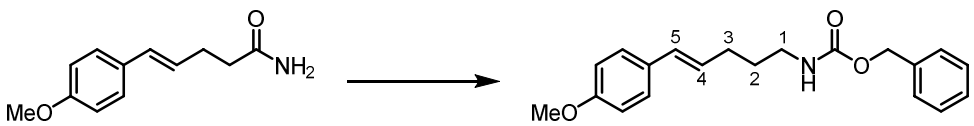


13 **4o**

Prepared by **General Procedure F** using **13** (1.67 g, 8.10 mmol) and oxalyl chloride (0.81 mL, 9.6 mmol). Recrystallisation from hot EtOAc afforded **4o** as a crystalline white solid (784 mg, 47%).

Data for **4o**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27 (2H, d, *J* = 8.8 Hz, Ar), 6.83 (2H, d, *J* = 8.8 Hz, Ar), 6.40 (1H, d, *J* = 15.9 Hz, C5-H), 6.07 (1H, dt, *J* = 15.8, 6.9 Hz, C4-H), 5.50 (2H, *br.* s, NH_2), 3.80 (3H, s, OMe), 2.53 (2H, *app.* q, *J* = 6.6, C3-H_2), 2.45 – 2.32 (2H, m, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 174.7 (C1), 159.1 (C Ar), 130.7 (C5), 130.2 (C Ar), 127.3 (C4), 126.4 (2 × C Ar), 114.1 (2 × C Ar), 55.4 (OMe), 35.8 (C2), 28.8 (C3). **HRMS** (ESI): calculated for $C_{12}H_{16}ON$ $[M+H]^+$ requires *m/z* 206.1176, found *m/z* 206.1176. **IR** (film) ν_{max}: 3386, 3191, 1648, 1604, 1510, 1440, 1282, 1174, 1029, 968, 847, 807 cm^{-1}. **mp** (165 – 167 °C, EtOAc).

(4g): Benzyl (*E*)-(5-(4-methoxyphenyl)pent-4-en-1-yl)carbamate



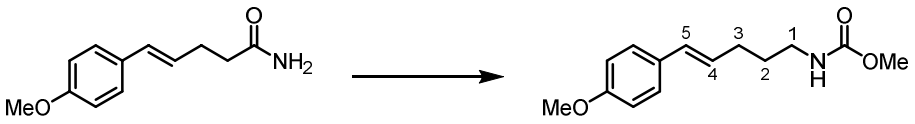
4o **4g**

Prepared by **General Procedure G** using **4o** (120 mg, 0.600 mmol) and $LiAlH_4$ (33 mg, 0.90 mmol). Crude amine **14** (80 mg, 0.42 mmol), triethylamine (0.07 mL, 0.5 mmol) and benzyl chloroformate (0.07 mL, 0.5 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **4g** as a white solid (107 mg, 73%).

Data for **4g**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.43 – 7.20 (5H, m, Ar), 7.28 – 7.19 (2H, m, Ar), 6.83 (2H, d, *J* = 8.8 Hz, Ar), 6.34 (1H, d, *J* = 15.8 Hz, C5-H), 6.04 (1H, dt, *J* = 15.5, 6.9 Hz, C4-H), 5.10 (2H, s, CH_2Ph), 4.77 (1H, *br.* s, *NH*), 3.80 (3H, s, OMe), 3.25 (2H, q, *J* = 6.7 Hz, C1-H_2), 2.31 – 2.15 (2H, m, C3-H_2), 1.68 (2H, p, *J* = 7.2 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 158.9 (C6), 136.8 (C Ar), 130.5 (C Ar), 130.1 (C5), 128.7 (2 × C Ar), 128.3 (C Ar), 128.3 (2 × C Ar), 127.5 (C Ar), 127.2 (2 × C Ar),

114.1 (2 × C Ar), 66.8 (CH_2Ph), 55.4 (OMe), 40.8 (C1), 30.3 (C2), 29.9 (C3). **HRMS** (ESI): calculated for $C_{20}H_{23}O_3NNa$ $[M+Na]^+$ requires m/z 348.1570, found m/z 348.1570. **IR** (film) ν_{max}: 3328, 2970, 2359, 1686, 1542, 1510, 1247, 1231, 1175, 1143 cm^{-1}. **mp** (68 – 70 °C, EtOAc).

(4h): Methyl (*E*)-(5-(4-methoxyphenyl)pent-4-en-1-yl)carbamate

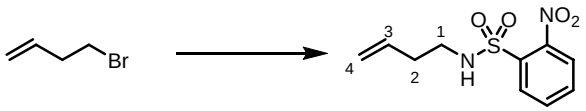


4o **4h**

Prepared by **General Procedure G** using **4o** (726 mg, 3.54 mmol) and $LiAlH_4$ (201 mg, 3.51 mmol). Crude amine **14** (411 mg, 2.15 mmol), triethylamine (0.37 mL, 2.7 mmol) and methyl chloroformate (0.21 mL, 2.7 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **4h** as a white solid (418 mg, 78%).

Data for **4h**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.26 (2H, d, *J* = 8.6 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.34 (1H, d, *J* = 15.8 Hz, C5-H), 6.04 (1H, dt, *J* = 15.8, 6.9 Hz, C4-H), 4.69 (1H, *br*. s, *N*H), 3.80 (3H, s, OMe), 3.66 (3H, s, OMe), 3.23 (2H, q, *J* = 6.8 Hz, C1-H_2), 2.28 – 2.17 (2H, m, C3-H_2), 1.67 (2H, p, *J* = 7.2 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 158.6 (CO), 130.5 (C Ar), 130.1 (C5), 127.5 (C4), 127.2 (2 × C Ar), 114.1 (2 × C Ar), 55.4 (OMe), 52.2 (OMe), 40.8 (C1), 30.3 (C3), 29.9 (C2). **HRMS** (ESI): calculated for $C_{14}H_{19}O_3NNa$ $[M+Na]^+$ requires m/z 272.1257, found m/z 272.1526. **IR** (film) ν_{max}: 3327, 2929, 1688, 1607, 2545, 1511, 1271, 1251, 1176, 1030 cm^{-1}. **mp** (74 – 76 °C, EtOAc).

(24): *N*-(But-3-en-1-yl)-2-nitrobenzenesulfonamide

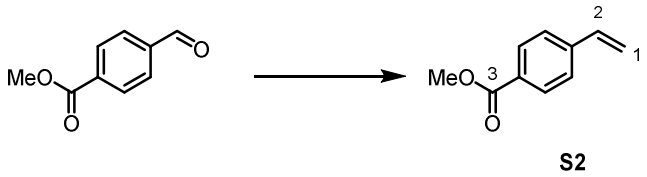


24

To a solution of 2-nitrobenzenesulfonamide (1.21 g, 6.00 mmol) and K_2CO_3 (829 mg, 6.00 mmol) in MeCN (20 mL) was added 4-bromo-1-butene (0.51 mL, 5.00 mmol) before heating to 60 °C for 16 h. After cooling to rt, aq. sat. NH_4Cl was added. The aqueous later was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$ before concentrating *in vacuo*. Flash column chromatography (30% EtOAc – pentane) afforded **24** as a white solid (1.01 g, 79%).

Data for **24**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.16 – 8.11 (1H, m, Ar), 7.89 – 7.84 (1H, m, Ar), 7.77 – 7.71 (2H, m, Ar), 5.66 (1H, ddt, *J* = 17.1, 10.3, 6.9 Hz, C3-H), 5.34 (1H, t, *J* = 6.5 Hz, NH), 5.10 – 5.00 (2H, m, 2 × C4-H), 3.18 (2H, q, *J* = 6.5 Hz, C1-H_2), 2.28 (2H, qt, J = 6.5, 1.3 Hz, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 134.0 (C Ar), 133.9 (C3), 133.7 (2 × C Ar), 132.9 (C Ar), 131.2 (C Ar), 125.5 (C Ar), 118.5 (C4), 43.0 (C1), 33.8 (C2). *The spectroscopic properties were consistent with the data available in the literature.*[157]

(S2): Methyl 4-vinylbenzoate

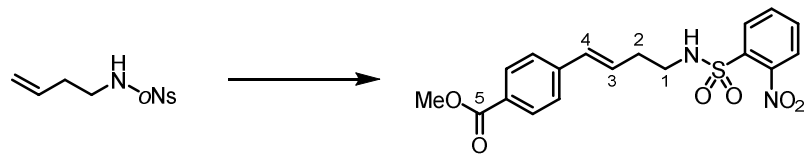


S2

To suspension of methyltriphenylphosphonium bromide (2.02 g, 6.00 mmol) in THF (20 mL) was added sodium hydride (60 wt%, 240 mg, 6.00 mmol) dropwise at 0 °C. After stirring at 0 °C for 1.5 h methyl 4-formylbenzoate (821 mg, 5.00 mmol) in THF (5 mL) was added slowly and allowed to warm up to rt. After 1 h, water was added. The aqueous later was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 before concentrating *in vacuo*. Flash column chromatography (100% hexane) afforded **S2** as a white solid (500 mg, 62%).

Data for **S2**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.01 – 7.98 (2H, m, Ar), 7.47 – 7.44 (2H, m, Ar), 6.75 (1H, dd, *J* = 17.6, 10.9 Hz, C2-H), 5.86 (1H, dd, J = 17.6, 0.7 Hz, 1 × C1-H), 5.38 (1H, dd, J = 10.9, 0.6 Hz, 1 × C1-H), 3.91 (3H, s, OMe). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.8 (C3), 141.9 (C Ar), 136.0 (C2), 129.9 (2 × C Ar), 129.3 (C Ar), 126.1 (2 × C Ar), 116.4 (C1), 52.0 (OMe). *The spectroscopic properties were consistent with the data available in the literature.*[158]

(1b): Methyl (*E*)-4-(4-((2-nitrophenyl)sulfonamido)but-1-en-1-yl)benzoate

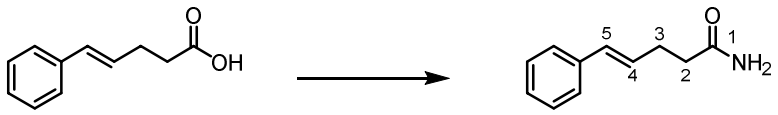


24 **1b**

Prepared by **General Procedure E** using **24** (320 mg, 1.25 mmol), **S2** (405 mg, 2.50 mmol), Grubbs II (53 mg, 0.063 mmol) in PhMe (5 mL). Flash column chromatography (20% EtOAc – pentane) afforded **1b** as an off-white solid (141 mg, 29%).

Data for **1b**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.13 (1H, dt, *J* = 7.5, 1.6 Hz, Ar), 7.98 – 7.90 (2H, m, Ar), 7.77 (1H, dt, *J* = 7.6, 1.9 Hz, Ar), 7.75 – 7.63 (2H, m, Ar), 7.33 – 7.27 (2H, m, Ar), 6.40 (1H, dd, *J* = 15.8, 1.7 Hz, C4-H), 6.14 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 5.41 (1H, *br.* s, *N*H), 3.91 (3H, s, OMe), 3.30 (2H, qd, *J* = 6.7, 1.0 Hz, C1-H_2), 2.47 (2H, qt, *J* = 6.8, 1.4 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 167.0 (C5), 148.1 (C Ar), 141.3 (C Ar), 133.7 (C Ar), 132.9 (C Ar), 132.7 (C4), 131.1 (C Ar), 130.0 (C Ar), 129.1 (2 × C Ar), 128.3 (C3), 126.4 (C Ar), 126.1 (2 × C Ar), 125.5 (C Ar), 52.2 (OMe), 43.3 (C1), 33.4 (C2). **HRMS** (ESI): calculated for $C_{18}H_{18}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 413.0778, found *m/z* 413.0790. **IR** (film) ν_{max}: 1712, 1348, 1179, 824, 758, 691, 657 cm^{-1}. **mp** (128 – 130 °C, EtOAc).

(S3): (*E*)-5-Phenylpent-4-enamide

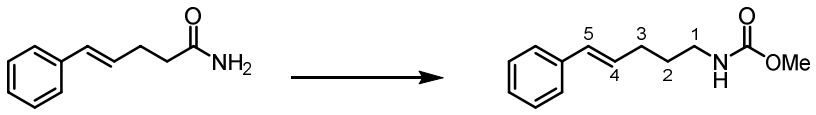


7 **S3**

Prepared by **General Procedure F** using **7** (500 mg, 2.84 mmol) and oxalyl chloride (0.29 mL, 3.4 mmol). Recrystallisation from hot EtOAc afforded **S3** as a crystalline white solid (350 mg, 70%).

Data for **S3**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.37 – 7.26 (4H, m, Ar), 7.24 – 7.17 (1H, m, Ar), 6.46 (1H, dt, *J* = 15.7, 1.5 Hz, C5-H), 6.22 (1H, dt, *J* = 15.8, 6.9 Hz, C4-H), 5.50 (2H, *br.* s, NH_2), 2.75 – 2.52 (2H, m, C3-H_2), 2.47 – 2.34 (2H, m, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 174.8 (C1), 137.4 (C Ar), 131.3 (C5), 128.7 (C4 + 2 × C Ar), 127.3 (C Ar), 126.2 (2 × C Ar), 35.6 (C2), 28.8 (C3). *The spectroscopic properties were consistent with the data available in the literature.*[159]

(4i): Methyl (*E*)-(5-phenylpent-4-en-1-yl)carbamate

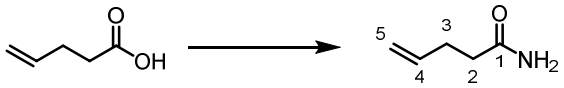


S3 **4i**

Prepared by **General Procedure G** using **S3** (300 mg, 1.71 mmol) and $LiAlH_4$ (97 mg, 2.6 mmol). Crude amine (270 mg, 1.67 mmol), triethylamine (0.29 mL, 2.1 mmol) and methyl chloroformate (0.16 mL, 2.1 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **4i** as a yellow oil (112 mg, 30%).

Data for **4i**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.37 – 7.25 (4H, m, Ar), 7.24 – 7.17 (1H, m, Ar), 6.41 (1H, d, *J* = 15.8, C5-H), 6.19 (1H, dt, *J* = 15.8, 6.9 Hz, C4-H), 4.85 (1H, *br.* s, *N*H), 3.66 (3H, s, C7-H_3), 3.23 (2H, q, *J* = 6.8 Hz, C1-H_2), 2.33 – 2.08 (2H, m, C3-H_2), 1.68 (2H, p, *J* = 7.3 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 157.2 (C6), 137.6 (C Ar), 130.6 (C5), 129.6 (C4), 128.6 (2 × C Ar), 127.1 (C Ar), 126.0 (2 × C Ar), 52.1 (C7), 40.7 (C1), 30.2 (C3), 29.7 (C2). **HRMS** (ESI): calculated for $C_{13}H_{18}O_2N$ $[M+H]^+$ requires *m/z* 220.1332, found *m/z* 220.1333. **IR** (film) ν_{max}: 3650, 3338, 3959, 3024, 2981, 2889, 2360, 2339, 1699, 1531, 1253, 966 cm^{-1}.

(26): Pent-4-enamide

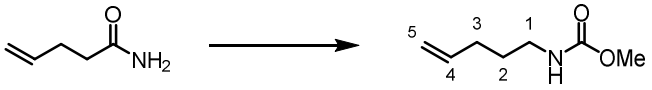


26

Prepared by **General Procedure F** using pent-4-enoic acid (2.04 mL, 20.0 mmol) and oxalyl chloride (2.04 mL, 24.0 mmol). Recrystallisation from hot EtOAc afforded **26** as a crystalline white solid (780 mg, 39%).

Data for **26**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.13 – 5.42 (2H, *br.* s, NH_2), 5.83 (1H, *app.* dddd, *J* = 16.6, 12.4, 8.0, 5.1 Hz, C4-H), 5.17 – 4.90 (2H, m, C5-H_2), 2.43 – 2.26 (4H, m, 2 × C2-H_2 + 2 × C3-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 175.3 (C1), 137.0 (C4), 115.8 (C5), 35.1 (C2), 29.4 (C3). *The spectroscopic properties were consistent with the data available in the literature.*[160]

(25): Methyl pent-4-en-1-ylcarbamate

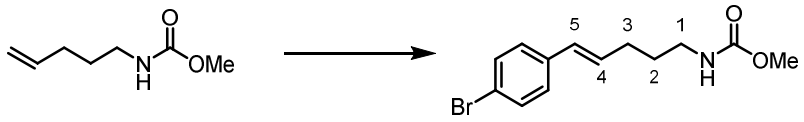


26 **25**

Prepared by **General Procedure G** *(with modification)* using **26** (1.00 g, 10.0 mmol) and $LiAlH_4$ (574 mg, 15.0 mmol). Crude amine hydrochloride salt (787 mg, 6.47 mmol), triethylamine (2.71 mL, 19.4 mmol) and methyl chloroformate (0.63 mL, 8.1 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **25** as a colourless oil (450 mg, 31%).

Data for **25**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.76 (1H, ddt, *J* = 16.9, 10.2, 6.6 Hz, C4-H), 5.00 (1H, dq, *J* = 17.1, 1.7 Hz, C5-H_A), 4.95 (1H, dq, *J* = 10.2, 1.4 Hz, C5-H_B), 4.82 (1H, *br.* s, *N*H), 3.62 (3H, s, OMe), 3.15 (2H, q, *J* = 6.8 Hz, C1-H_2), 2.05 (2H, td, *J* = 8.0, 6.0 Hz, C3-H_2), 1.57 (2H, p, *J* = 7.3 Hz, C2-H_2).**^{13}C NMR (101 MHz, $CDCl_3$) δ** 157.2 (CO), 137.8 (C4), 115.2 (C5), 52.0 (OMe), 40.6 (C1), 31.0 (C3), 29.2 (C2). **HRMS** (ESI): calculated for $C_7H_{14}O_2N$ $[M+H]^+$ requires *m/z* 144.1019, found *m/z* 144.1018. **IR** (film) ν_{max}: 3649, 3331, 3078, 2980, 2359, 2342, 1697, 1536, 1449, 1256 cm^{-1}.

(4j): Methyl (*E*)-(5-(4-bromophenyl)pent-4-en-1-yl)carbamate



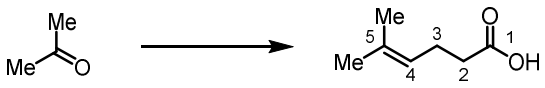
25 **4j**

Prepared by **General Procedure E** using **25** (200 mg, 1.40 mmol), 4-bromostyrene (0.37 mL, 2.80 mmol), Grubbs II (58 mg, 0.070 mmol) in PhMe (5 mL). Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) followed by recrystallisation from hot EtOAc afforded **4j** as a white solid (91 mg, 22%).

Data for **4j**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.48 – 7.34 (2H, m, Ar), 7.25 – 7.06 (2H, m, Ar), 6.34 (1H, d, *J* = 15.8 Hz, C5-H), 6.18 (1H, dt, *J* = 15.9, 6.8 Hz, C4-H), 4.69 (1H, *br.* s, *N*H), 3.66 (3H, s, OMe), 3.23 (2H, q, *J* = 6.8 Hz, C1-H_2), 2.40 – 2.10 (2H, m, C3-H_2), 1.68 (2H, p, *J* = 7.3 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 157.2 (CO), 136.6 (C Ar), 131.7 (2 × C Ar), 130.6 (C5), 129.6 (C4), 127.6 (2 × C Ar), 120.8 (C Ar), 52.2 (OMe), 40.7 (C1), 30.3 (C3), 29.7 (C2). **HRMS** (ESI): calculated for

$C_{13}H_{17}O_2N^{78}BrNa$ $[M+Na]^+$ requires m/z 336.0206, found m/z 336.0205. **IR** (film) ν_{max}: 3650, 3338, 2981, 2886, 2360, 2336, 1690, 1538, 1487, 1461 cm^{-1}. **mp** (78 – 80 °C, EtOAc).

(S4): 5-Methylhex-4-enoic acid

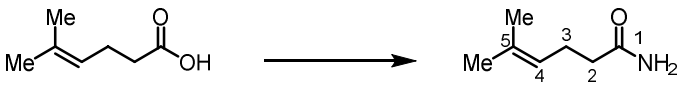


S4

Prepared by **General Procedure A** using acetone (0.73 mL, 10 mmol), (3-carboxypropyl)-triphenylphosphonium bromide (5.15 g, 12.0 mmol), NaHMDS (2.0 M in THF, 12.0 mL, 24.0 mmol). Flash column chromatography (80% Et_2O/pentane + 1% acetic acid) afforded **S4** as a yellow oil (903 mg, 70%).

Data for **S4**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.01 (1H, m, C4-H), 2.44 – 2.13 (4H, m, 2 × C2-H_2 + 2 × C3-H_2), 1.60 (3H, d, *J* = 1.3 Hz, Me), 1.53 (3H, d, *J* = 1.3 Hz, Me). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 179.2 (C1), 133.6 (C5), 122.2 (C4), 34.3 (C2), 25.8 (C3), 23.5 (Me), 17.8 (Me). *The spectroscopic properties were consistent with the data available in the literature.*[161]

(S5): 5-Methylhex-4-enamide

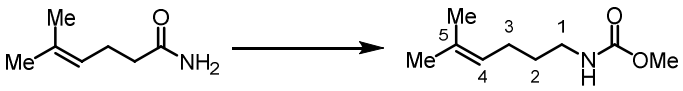


S4 **S5**

Prepared by **General Procedure F** using **S4** (500 mg, 3.90 mmol) and oxalyl chloride (0.40 mL, 4.70 mmol). Recrystallisation from hot EtOAc afforded **S5** as a crystalline white solid (418 mg, 84%).

Data for **S5**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.08 (1H, *br.* s, *N*H), 5.69 (1H, *br.* s, *N*H), 5.15 – 5.05 (1H, m, C4-H), 2.33 – 2.25 (2H, m, C3-H_2), 2.25 – 2.19 (2H, m, C2-H_2), 1.67 (3H, s, Me), 1.60 (3H, s, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 175.9 (C1), 133.5 (C5), 122.8 (C4), 36.1 (C2), 25.9 (Me), 24.3 (C3), 17.9 (Me). **HRMS** (ESI): calculated for $C_7H_{14}ON$ $[M+H]^+$ requires m/z 128.1070, found m/z 128.1070. **IR** (film) ν_{max}: 3366, 3186, 2969, 1678, 1657, 1452, 1411, 1318, 952, 817 cm^{-1}. **mp** (87 – 89 °C, EtOAc).

(4k): Methyl (5-methylhex-4-en-1-yl) carbamate

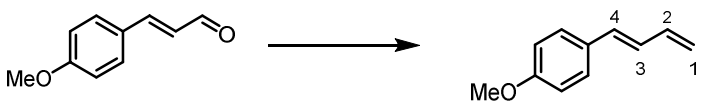


S5 **4k**

Prepared by **General Procedure G** *(with modification)* using **S5** (300 mg, 2.37 mmol) and $LiAlH_4$ (574 mg, 3.56 mmol). Crude amine hydrochloride salt (208 mg, 1.39 mmol), triethylamine (0.58 mL, 4.2 mmol) and methyl chloroformate (0.13 mL, 1.7 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **4k** as a colourless oil (90 mg, 27%).

Data for **4k**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.07 (1H, *app.* dddd, *J* = 7.2, 5.7, 2.9, 1.5 Hz, C4-H), 4.73 (1H, *br.* s, *N*H), 3.63 (3H, s, C8-H_3), 3.14 (2H, q, *J* = 6.7 Hz, C1-H_2), 1.99 (2H, q, *J* = 7.4 Hz, C3-H_2), 1.66 (3H, s, Me), 1.58 (3H, s, Me), 1.51 (2H, p, *J* = 7.4 Hz, C2-H_2).**^{13}C NMR (101 MHz, $CDCl_3$) δ** 157.2 (C7), 132.4 (C4), 123.6 (C5), 52.0 (C8), 40.8 (C1), 30.1 (C3), 25.8 (Me), 25.3 (C2), 17.8 (Me). **HRMS** (ESI): calculated for $C_9H_{17}O_2N$ $[M+H]^+$ requires *m/z* 172.1332, found *m/z* 172.1335. **IR** (film) ν_{max}: 3112, 1698, 1536, 1525, 1449, 1380, 1262, 1193, 1145, 779 cm^{-1}.

(S6): (*E*)-1-(Buta-1,3-dien-1-yl)-4-methoxybenzene



S6

Prepared according to the procedure reported by Doye et. al.[162] To suspension of methyltriphenylphosphonium bromide (8.57 g, 24.0 mmol) in THF (100 mL) was added *n*-butyllithium (2.5 M in hexanes, 9.60 mL, 24.0 mmol) dropwise at 0 °C. After stirring at 0 °C for 1.5 h 4-methoxy-cinnamaldehyde (3.24 g, 20.0 mmol) in THF (20 mL) was added slowly and allowed to warm up to rt. After 1 h, silica gel (10 g) and hexane (150 mL) was added. After stirring for 15 minutes the solid was removed by filtration and the filtrate concentrated *in vacuo*. Flash column chromatography (100% pentane) afforded **S6** as a crystalline white solid (2.34 g, 73%).

Data for **S6**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.25 (2H, d, *J* = 8.7 Hz, Ar), 6.77 (2H, d, *J* = 8.8 Hz, Ar), 6.67 – 6.54 (1H, m, C4-H), 6.49 – 6.34 (2H, m, C2-H + C3-H), 5.21 (1H, ddd, *J* = 16.9, 1.8, 0.9 Hz,

C1-H_A), 5.12 – 4.96 (1H, m, C1-H_B), 3.68 (s, 3H, OMe). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.5 (C Ar), 137.6 (C2), 132.6 (C3), 130.1 (C Ar), 127.8 (C4), 127.8 (2 × C Ar), 116.5 (C1), 114.2 (2 × C Ar), 55.3 (OMe). *The spectroscopic properties were consistent with the data available in the literature.*[162]

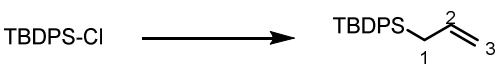
(4l): Methyl ((4*E*,6*E*)-7-(4-methoxyphenyl)hepta-4,6-dien-1-yl)carbamate

S6 **4l**

Prepared by **General Procedure E** using **S6** (400 mg, 2.86 mmol), **S6** (918 mg, 5.73 mmol), Grubbs I (115 mg, 0.140 mmol) in PhMe (12 mL) at 100 °C. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) followed by recrystallisation from hot EtOAc afforded **4l** as a crystalline white solid (125 mg, 16%).

Data for **4l**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.31 (2H, d, *J* = 8.7 Hz, Ar), 6.84 (2H, d, *J* = 8.8 Hz, Ar), 6.61 (1H, dd, *J* = 15.7, 10.3 Hz, C6-H), 6.40 (1H, d, *J* = 15.7 Hz, C7-H), 6.19 (1H, dd, *J* = 14.0, 10.3 Hz, C5-H), 5.73 (1H, dt, *J* = 14.7, 7.0 Hz, C4-H), 4.69 (1H, *br.* s, NH), 3.80 (3H, s, OMe), 3.66 (3H, s, OMe), 3.21 (2H, q, *J* = 7.0 Hz, C1-H_2), 2.17 (2H, td, *J* = 7.3, 1.5 Hz, C3-H_2), 1.63 (2H, p, *J* = 7.3 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.2 (CO), 133.0 (C4), 131.6 (C5), 130.5 (C Ar), 130.3 (C7), 127.5 (2 × C Ar), 127.2 (C6), 114.2 (2 × C Ar), 55.4 (OMe), 52.1 (OMe), 40.7 (C1), 30.1 (C3), 29.8 (C2). **HRMS** (ESI): calculated for $C_{16}H_{22}O_3N$ $[M+H]^+$ requires *m/z* 276.1594, found *m/z* 276.1596. **IR** (film) ν_{max}: 3331, 3015, 2363, 1692, 1602, 1552, 1510, 1284, 1254, 1030, 985, 834 cm^{-1}. **mp** (105 – 107 °C, EtOAc).

(28): Allyl(*tert*-butyl)diphenylsilane



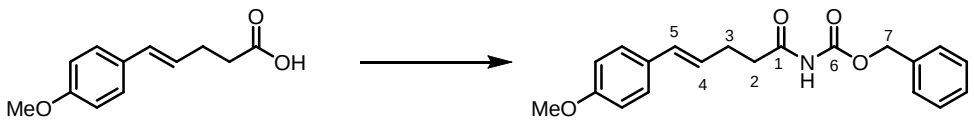
28

To a solution of *tert*-butylchlorodiphenylsilane (1.00 mL, 3.91 mmol) in anhydrous THF (2.3 mL) was added allylmagnesium bromide (1.0 M in Et_2O, 4.3 mL, 4.3 mmol) at 0 °C. After warming to rt, the reaction mixture was left to stir for 16 h. The reaction was cooled to 0 °C before addition of aq. sat. NH_4Cl. The aqueous later was extracted with Et_2O and the combined organic layers were washed with

brine and dried over $MgSO_4$ before concentrating *in vacuo*. Flash column chromatography (0% → 5% Et_2O – pentane) afforded **28** as a colourless oil (458 mg, 42%).

Data for **28**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.59 – 7.65 (4H, m, Ar), 7.32 – 7.43 (6H, m, Ar), 5.79 (1H, ddt, *J* = 17.0, 10.0, 7.9 Hz, C2-H), 4.92 (1H, dq, *J* = 17.0, 1.6 Hz, C3-H_A), 4.81 (1H, ddt, *J* = 10.0, 2.1, 1.2 Hz, C3-H_B), 2.20 (2H, dt, *J* = 7.9, 1.3 Hz, C1-H_2), 1.08 (9H, s, C(C**H$_3$**)$_3$). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 136.2 (4 × C Ar), 134.8 (2 × C Ar), 134.6 (C2), 129.2 (2 × C Ar), 127.7 (4 × C Ar), 114.6 (C3), 28.0 (C1), 18.9 (C(**C**H$_3$)$_3$), 18.6 (**C**(CH$_3$)$_3$). *The spectroscopic properties were consistent with the data available in the literature.*[162]

(4q): Benzyl (*E*)-(5-(4-methoxyphenyl)pent-4-enoyl)carbamate

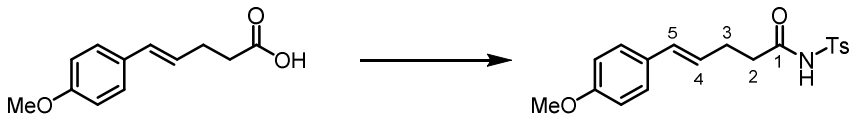


4o **4q**

Prepared according to **General Procedure H** using **4o** (360 mg, 1.75 mmol), benzyl carbamate (304 mg, 2.01 mmol), EDCI.HCl (370 mg, 1.93 mmol), 1-hydroxybenzotriazole (260 mg, 1.93 mmol) and *N*-methylmorpholine (0.23 mL, 2.10 mmol). Flash column chromatography (gradient elution 10% → 30% EtOAc – pentane) afforded **4q** as a white solid (589 mg, 99%).

Data for **4q**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.40 – 7.30 (5H, m, C Ar), 7.27 (2H, d, *J* = 8.8 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.39 (1H, d, *J* = 15.8 Hz, C5-H), 6.14 – 6.02 (1H, m, C4-H), 5.11 (2H, s, C7-H_2), 4.99 (1H, *br.* s, *N*H), 3.80 (3H, s, OMe), 2.55 – 2.49 (4H, m, C2-H_2 + C3-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 177.4 (C1), 159.0 (C Ar), 136.2 (C Ar), 130.5 (C5), 130.3 (C Ar), 128.7 (2 × C Ar), 128.4 (C Ar), 128.3 (2 × C Ar), 127.3 (2 × C Ar), 126.3 (C4), 114.1 (2 × C Ar), 67.2 (C7), 55.4 (OMe), 34.0 (C2), 28.2 (C3). *A signal corresponding to C6 was not observed.* **HRMS** (ESI): calculated for $C_{20}H_{22}NO_4$ $[M+H]^+$ requires *m/z* 340.1543, found *m/z* 340.1446. **IR** (film) ν_{max}: 1604, 1513, 1395, 1033, 956, 723, 669, 632 cm^{-1} **mp** (77 – 79 °C, EtOAc).

(4r): (*E*)-5-(4-Methoxyphenyl)-*N*-tosylpent-4-enamide

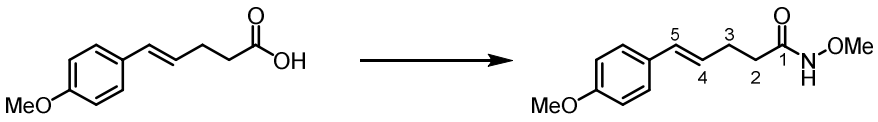


4o **4r**

Prepared according to **General Procedure H** using **4o** (360 mg, 1.75 mmol), toluene-4-sulfonamide (344 mg, 2.01 mmol), EDCI.HCl (370 mg, 1.93 mmol), 1-hydroxybenzotriazole (260 mg, 1.93 mmol) and *N*-methylmorpholine (0.23 mL, 2.10 mmol). Flash column chromatography (gradient elution 10% → 30% EtOAc – pentane) afforded **4r** as a white solid (622 mg, 99%).

Data for **4r**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.80 (2H, d, *J* = 8.4 Hz, Ar), 7.32 – 7.24 (4H, m, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.39 (1H, d, *J* = 15.7 Hz, C5-H), 6.12 – 6.00 (1H, m, C4-H), 4.98 (1H, *br.* s, *N*H), 3.79 (3H, s, OMe), 2.57 – 2.48 (4H, m, C2-H_2 + C3-H_2), 2.42 (3H, s, TsMe). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 171.4 (C1), 159.0 (C Ar), 143.7 (C Ar), 130.7 (C5), 130.2 (C Ar), 129.8 (2 × C Ar), 129.7 (C Ar), 127.3 (2 × C Ar), 126.6 (2 × C Ar), 126.0 (C4), 114.0 (2 × C Ar), 55.4 (OMe), 33.9 (C2), 28.1 (C3), 21.6 (TsMe). **HRMS** (ESI): calculated for $C_{19}H_{21}NO_4SNa$ $[M+Na]^+$ requires *m*/*z* 382.1084, found *m*/*z* 382.1072. **IR** (film) ν_{max}: 1735, 1601, 1374, 1249, 1091, 1044, 782, 665 cm^{-1}. **mp** (112 – 114 °C, EtOAc).

(4s): (*E*)-*N*-Methoxy-5-(4-methoxyphenyl)pent-4-enamide



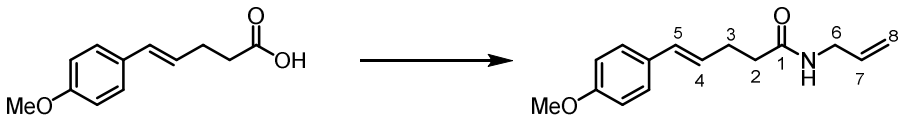
4o **4s**

Prepared according to **General Procedure H** using **4o** (285 mg, 1.38 mmol), methoxylamine hydrochloride (127 mg, 1.52 mmol), EDCI.HCl (291 mg, 1.52 mmol), 1-hydroxybenzotriazole (205 mg, 1.52 mmol) and Et_3N (0.43 mL, 3.11 mmol). Flash column chromatography (gradient elution 10% → 30% EtOAc – pentane) afforded **4s** as a colourless solid (290 mg, 89%).

Data for **4s**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.20 – 7.13 (2H, m, Ar), 6.75 (2H, d, *J* = 8.7 Hz, Ar), 6.30 (1H, d, *J* = 15.8 Hz, C5-H), 6.07 – 5.85 (1H, m, C4-H), 3.71 (3H, s, OMe), 3.65 (3H, s, OMe), 2.51 – 2.39 (2H, m, C3-H_2), 2.26 – 2.10 (2H, m, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 170.5 (C1), 159.0

(C Ar), 130.8 (C5), 130.0 (C Ar), 127.5 (2 × C Ar), 126.0 (C4), 114.1 (2 × C Ar), 66.6 (OMe), 55.4 (OMe), 33.2 (C2), 28.7 (C3). **HRMS** (ESI): calculated for $C_{13}H_{18}NO_3$ $[M+H]^+$ requires m/z 236.1281, found m/z 236.1273. **IR** (film) ν_{max}: 1778, 1576, 1511, 1442, 1362, 1250, 1177, 847, 645 cm^{-1}. **mp** (56 – 58 °C, EtOAc).

(4t): (*E*)-*N*-Allyl-5-(4-methoxyphenyl)pent-4-enamide



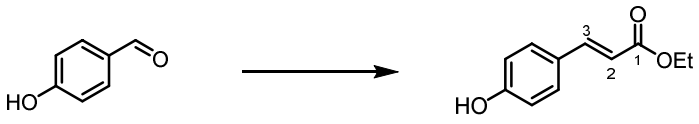
4o **4t**

Prepared according to **General Procedure H** using **4o** (360 mg, 1.75 mmol), allylamine (0.15 mL, 2.01 mmol), EDCI.HCl (370 mg, 1.93 mmol), 1-hydroxybenzotriazole (260 mg, 1.93 mmol) and *N*-methylmorpholine (0.23 mL, 2.10 mmol). Flash column chromatography (gradient elution 10% → 30% EtOAc – pentane) afforded **4t** as a yellow solid (410 mg, 79%).

Data for **4t**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.25 (2H, d, *J* = 8.7 Hz, Ar), 6.82 (2H, d, *J* = 8.8 Hz, Ar), 6.37 (1H, d, *J* = 15.9 Hz, C5-H), 6.05 (1H, dt, *J* = 15.8, 6.9 Hz, C4-H), 5.81 (1H, ddt, *J* = 17.2, 10.2, 5.6 Hz, C7-H), 5.65 (1H, s, *N*H), 5.16 (1H, dq, *J* = 17.2, 1.6 Hz, C8-H), 5.10 (1H, dq, *J* = 10.2, 1.4 Hz, C8-H), 3.88 (1H, tt, *J* = 5.8, 1.6 Hz, C6-H_2), 3.79 (3H, s, OMe), 2.57 – 2.49 (2H, m, C3-H_2), 2.35 (2H, dd, *J* = 8.1, 6.7 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 172.3 (C1), 159.0 (C Ar), 134.3 (C7), 130.6 (C5), 130.3 (C Ar), 127.3 (2 × C Ar), 126.6 (C4), 116.5 (C8), 114.1 (2 × C Ar), 55.4 (OMe), 42.0 (C6), 36.6 (C3), 29.1 (C2). **HRMS** (ESI): calculated for $C_{15}H_{19}NO_2Na$ $[M+Na]^+$ requires m/z 268.1308, found m/z 268.1301. **IR** (film) ν_{max}: 1638, 1605, 1511, 1440, 1250, 1175, 1031, 989, 846 cm^{-1}. **mp** (77 – 79 °C, EtOAc).

6.2.3 Synthesis of electrophiles

(S7): Ethyl (*E*)-3-(4-hydroxyphenyl)acrylate

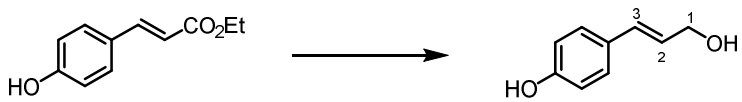


S7

To a solution of 4-hydroxybenzaldehyde (305 mg, 2.50 mmol) in CH_2Cl_2 (2.5 mL) was added ethyl(triphenylphosphoranylidene)acetate (1.34 g, 3.75 mmol) and stirred for 16 h. Consumption of aldehyde was monitored by TLC and upon completetion the solvent was removed *in vacuo*. Flash column chromatography (10% → 20% EtOAc – pentane) afforded **S7** as a white solid (364 mg, 76%).

Data for **S7**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.63 (1H, d, *J* = 16.0 Hz, C3-H), 7.50 – 7.35 (2H, m, Ar), 6.94 – 6.78 (2H, m, Ar), 6.30 (1H, d, *J* = 15.9 Hz, C2-H), 4.26 (2H, q, *J* = 7.1 Hz, C**H$_2$**CH$_3$), 1.34 (3H, t, *J* = 7.1 Hz, CH$_2$C**H$_3$**). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.8 (CO), 158.1 (C Ar), 144.9 (C3), 130.1 (2 × C Ar), 127.2 (C Ar), 116.0 (2 × C Ar), 115.5 (C2), 60.8 (**C**H$_2$CH$_3$), 14.5 (CH$_2$**C**H$_3$). *The spectroscopic properties were consistent with the data available in the literature.*[164]

(2i): (*E*)-4-(3-Hydroxyprop-1-en-1-yl)phenol



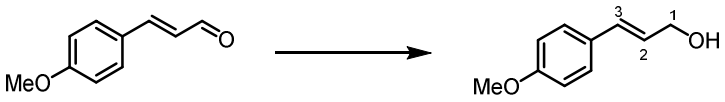
S7 **2i**

To a solution of **S7** (200 mg, 1.04 mmol) in CH_2Cl_2 (6.5 mL) was added DIBAL-H (1.0 M in CH_2Cl_2, 3.60 mL, 3.64 mmol) dropwise at –78 ˚C before warming to rt. After 1 h the solution was cooled to – 78 ˚C and aq. sat. Rochelle salts (3.5 mL) were added before warming to rt. To solution was stirred vigorously for 2 h before diluted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers washed with brine and dried over $MgSO_4$ before concentrating *in vacuo*. Flash column chromatography (10% → 35% EtOAc – pentane) afforded **2i** as a white solid (135 mg, 90%).

Data for **2i**: **^{1}H NMR (400 MHz, DMSO) δ** 9.44 (1H, s, OH), 7.22 (2H, d, *J* = 8.6 Hz, Ar), 6.70 (2H, d, *J* = 8.6 Hz, Ar), 6.42 (1H, dt, *J* = 16.0, 1.7 Hz, C3-H), 6.12 (1H, dt, *J* = 15.9, 5.4 Hz, C2-H), 4.06 (2H,

td, J = 5.5, 1.6 Hz, C1-H_2). **^{13}C NMR (101 MHz, DMSO) δ** 156.8 (C Ar), 128.7 (C3), 127.9 (C Ar), 127.4 (2 × C Ar), 127.2 (C2), 115.4 (2 × C Ar), 61.73 (C1). *The spectroscopic properties were consistent with the data available in the literature.*[165]

(2j): (2*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol

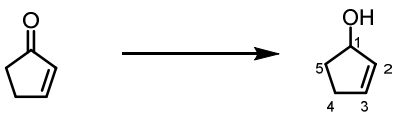


2j

To a solution of 4-methoxycinnamaldehyde (4.80 g, 29.6 mmol) in MeOH (56 mL) under Ar was added $NaBH_4$ (840 mg, 17.8 mmol) portionwise at 0 **°C. The reaction mixture was warmed to rt after 30 min at 0 °C. After an additional 1 h at rt the reaction was quenched with *aq. sat.* NH_4Cl.** The aqueous later was extracted with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$ before concentrating *in vacuo*. Recrystallisation from Et_2O afforded **2j** as a white solid (4.85 g, 98%).

Data for **2j**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.32 (2H, d, J = 8.7 Hz, Ar), 6.86 (2H, d, J = 8.7 Hz, Ar), 6.56 (1H, d, J = 15.9 Hz, C3-H), 6.24 (1H, dt, J = 15.8, 6.0 Hz, C2-H), 4.29 (2H, dd, J = 5.9, 1.2 Hz, C1-H_2), 3.81 (3H, s, OMe), 1.53 (1H, *br.* s, *O*H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.5 (C Ar), 131.1 (C3), 129.6 (C Ar), 127.8 (2 × C Ar), 126.4 (C2), 114.2 (2 × C Ar), 64.1 (C1), 55.43 (OMe). *The spectroscopic properties were consistent with the data available in the literature.*[166]

(2k): (±)-Cyclopent-2-en-1-ol



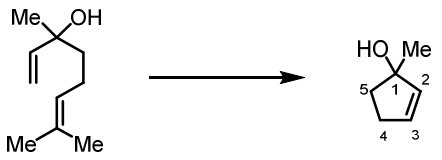
2k

To a solution of cerium trichloride (976 mg, 3.96 mmol) in MeOH (10 mL) was added cyclopent-2-enone (0.50 mL, 6.0 mmol). After 5 min, sodium borohydride (454 mg, 12.0 mmol) was added portionwise before stirring at rt for 15 min. H_2O was added until a clear solution was observed, the aqueous later was extracted with Et2O and the combined organic layers were washed with brine, dried

over $MgSO_4$ before concentrating *in vacuo*. Flash column chromatography (20% Et_2O – pentane) afforded **2k** as a colourless oil (368 mg, 73%).

Data for **2k**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.93 – 5.99 (1H, m, C3-H), 5.78 – 5.84 (1H, m, C2-H), 4.82-4.88 (1H, m, C1-H), 2.49 (1H, ddt, *J* = 16.5, 10.9, 5.4 Hz, C4-H_A), 2.17 – 2.31 (2H, m, 1 × C4-H_B + 1 × C5-H_A), 1.95 (1H, *br.* s, *OH*), 1.61 – 1.76 (1H, m, C5-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 135.2 (C3), 133.4 (C2), 77.6 (C1), 33.3 (C5), 31.1 (C4). *The spectroscopic properties were consistent with the data available in the literature.*[167]

(2l): (±)-1-Methylcyclopent-2-en-1-ol

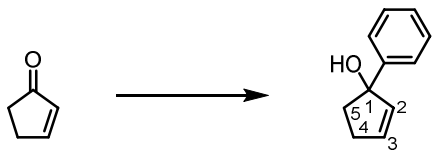


2l

Prepared according to **General Procedure E** using linalool (500 mg, 3.23 mmol) and Grubbs I (133 mg, 0.161 mmol) at rt in $CHCl_3$. Flash column chromatography (20% → 50% Et_2O – pentane) afforded **2l** as a yellow oil (250 mg, 79%).

Data for **2l**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.81 (1H, dt, *J* = 5.4, 2.3 Hz, C3-H), 5.69 (1H, dt, *J* = 5.4, 2.3 Hz, C2-H), 2.48 (1H, m, C4-H_A), 2.30 (1H, m, C4-H_B), 1.96 (1H, ddd, *J* = 13.4, 8.1, 4.8 Hz, C5-H_A), 1.89 (1H, ddd, *J* = 13.4, 8.1, 4.8 Hz, C5-H_B), 1.37 (3H, s, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 138.0 (C2), 132.8 (C3), 83.6 (C1), 39.8 (C5), 31.2 (C4), 27.6 (Me). *The spectroscopic properties were consistent with the data available in the literature.*[168]

(2m): (±)-1-Phenylcyclopent-2-en-1-ol



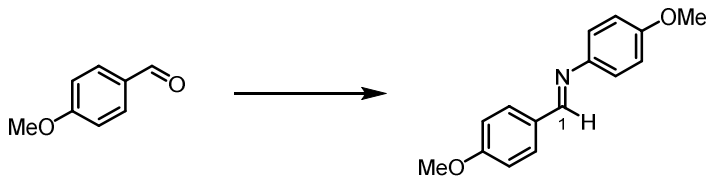
2m

To a solution of bromobenzene (0.63 mL, 6.0 mmol) in THF (30 mL) was added *n*-butyllithium (2.5 M in hexanes, 2.08 mL, 5.20 mmol) dropwise at -78 °C. After stirring at –78 °C for 30 min cyclopent-2-enone (0.34 mL, 4.0 mmol) in THF (5 mL) was added slowly. After 1 h stirring at –78 °C H_2O was added

and allowed to warm to rt. The aqueous later was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$ before concentrating *in vacuo*. Flash column chromatography (20% Et_2O – pentane) afforded **2m** as a white solid (0.564 g, 88%).

Data for **2m**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.43 – 7.47 (2H, m, Ar), 7.32 – 7.38 (2H, m, Ar), 7.23 – 7.28 (1H, m, Ar), 6.12 (1H, dt, *J* = 5.6, 2.4 Hz, C3-H), 5.88 (1H, dt, *J* = 5.5, 2.2 Hz, C2-H), 2.60 – 2.70 (1H, m, C4-H_A), 2.43 – 2.52 (1H, m, C4-H_B), 2.24 – 2.29 (2H, m, C5-H_2), 1.98 (1H, *br.* s, O*H*). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 147.0 (C Ar), 136.6 (C2), 134.9 (C3), 128.2 (2 × C Ar), 126.8 (C Ar), 124.9 (2 × C Ar), 87.0 (C1), 42.0 (C5), 31.5 (C4). *The spectroscopic properties were consistent with the data available in the literature.*[169]

(22): (*E*)-*N*,1-Bis(4-methoxyphenyl)methanimine



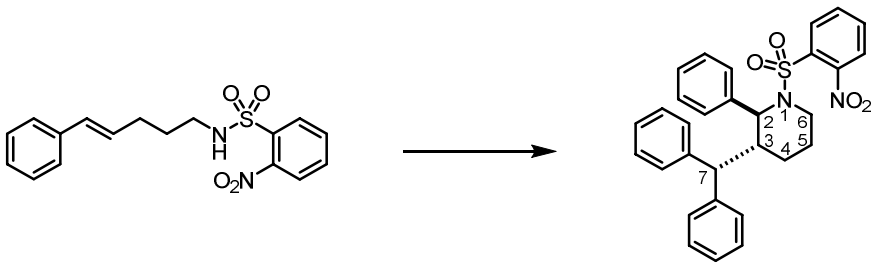
22

To a solution of 4-methoxybenzaldehyde (0.61 mL, 5.00 mmol) in CH_2Cl_2 (5.00 mL) was added 4-methoxyaniline (760 mg, 6.00 mmol). After 30 min was added $MgSO_4$ (750 mg, 6.00 mmol). After 2 h the solid was removed by filtration through celite. Flash column chromatography (20% EtOAc – pentane) afforded **22** as a crystalline colourless solid (1.01 g, 83%).

Data for **22**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.41 (1H, s, C1-H), 7.85 (2H, d, *J* = 7.8 Hz, Ar), 7.22 (2H, d, *J* = 8.4 Hz, Ar), 6.98 (2H, d, *J* = 8.9 Hz, Ar), 6.93 (2H, d, *J* = 8.9 Hz, Ar), 3.87 (3H, s, OMe), 3.83 (3H, s, OMe). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 158.1 (C Ar), 158.1 (C Ar), 130.6 (C Ar), 130.5 (C Ar), 122.2 (4 × C Ar), 114.5 (2 × C Ar), 114.3 (2 × C Ar), 55.6 (OMe), 55.6 (OMe). *A signal corresponding to C1 was not observed. The spectroscopic properties were consistent with the data available in the literature.*[170]

6.2.4 Cyclisations

(5e): (±)-(2*S*,3*R*)-3-Benzhydryl-1-((2-nitrophenyl)sulfonyl)-2-phenylpiperidine

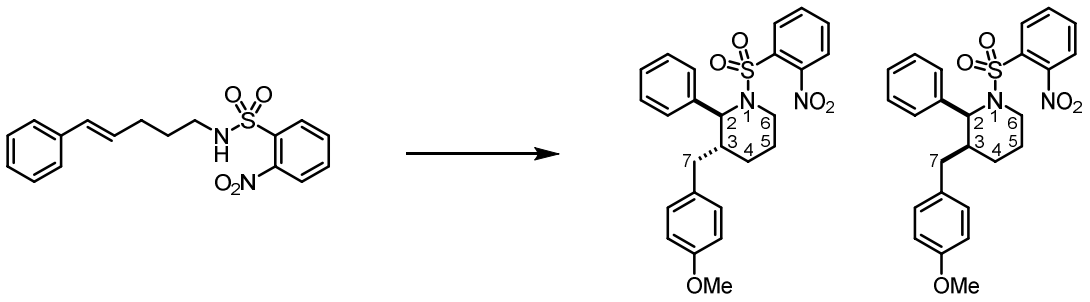


4b **5e**

Prepared according to **General Procedure I** using **4b** (28 mg, 0.080 mmol) and benzhydrol (15 mg, 0.080 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5e** as a colourless oil (31 mg, 69%).

Data for **5e**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.60 (1H, dd, *J* = 8.0, 1.5 Hz, Ar), 7.52 (1H, td, *J* = 7.5, 1.5 Hz, Ar), 7.42 (1H, dd, *J* = 8.0, 1.5 Hz, Ar), 7.36 – 7.07 (15H, m, Ar), 5.02 (1H, s, C2-H), 4.36 – 4.20 (2H, m, 1 × C6-H_A + 1 × C7-H), 3.53 (1H, td, *J* = 13.0, 3.0 Hz, C6-H_B), 3.09 – 3.05 (1H, m, C3-H), 1.98 – 1.95 (1H, m, C5-H_A), 1.51 – 1.45 (1H, m, C4-H_A), 1.45 – 1.35 (2H, m 1 × C4-H_B + 1 × C5-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 147.8 (C Ar), 143.5 (C Ar), 143.4 (C Ar), 140.1 (C Ar), 134.2 (C Ar), 133.0 (C Ar), 131.7 (C Ar), 131.7 (C Ar), 129.0 (2 × C Ar) 128.9 (2 × C Ar), 128.5 (2 × C Ar), 128.3 (2 × C Ar), 128.1 (2 × C Ar), 126.9 (C Ar), 126.8 (2 × C Ar), 126.6 (C Ar), 126.5 (C Ar), 123.9 (C Ar), 58.5 (C2), 51.9 (C7), 43.8 (C6), 42.7 (C3), 20.5 (C4), 19.7 (C5). **HRMS** (ESI): calculated for $C_{30}H_{32}O_4SN_2Na$ $[M+Na]^+$ requires *m/z* 535.1658, found *m/z* 535.1660. **IR** (film) ν_{max}: 2980, 2925, 1542, 1379, 1346, 1164, 1134, 942, 759, 706 cm^{-1}.

(5f): (±)-(2*S*,3*R*)-3-(4-Methoxybenzyl)-1-((2-nitrophenyl)sulfonyl)-2-phenylpiperidine and (±)-(2*S*,3*S*)-3-(4-Methoxybenzyl)-1-((2-nitrophenyl)sulfonyl)-2-phenylpiperidine



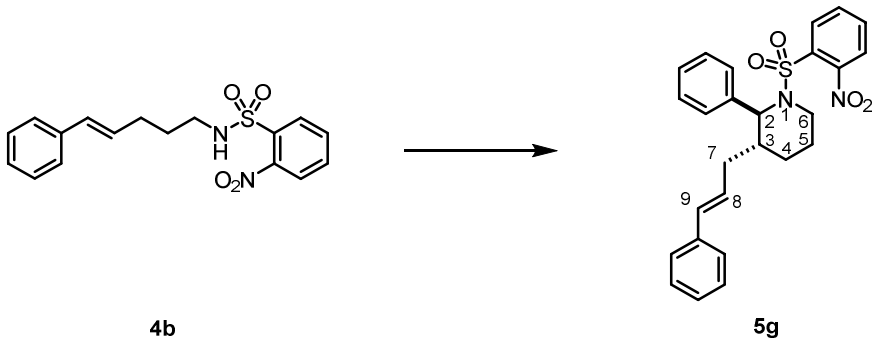
Prepared according to **General Procedure I** using **4b** (28 mg, 0.08 mmol), 4-methoxybenzyl alcohol (12.0 mg, 0.08 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded an inseparable 10:1 mixture of diastereomers **5f** as a yellow oil (20 mg, 52%). *An NMR of the crude reaction mixture indicated an initial dr of 2:1 A:B.*

Data for **5f-A** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.63 (1H, dd, *J* = 7.9, 1.2 Hz, Ar), 7.58 – 7.52 (2H, m, Ar), 7.35 (1H, ddd, *J* = 8.0, 7.0, 1.7 Hz, Ar), 7.17 – 7.02 (7H, m, Ar), 6.84 (2H, d, *J* = 8.7 Hz, Ar), 4.89 (1H, d, *J* = 3.6 Hz, C2-H), 4.03 (1H, dt, *J* = 12.9, 3.9 Hz, C6-H_A), 3.79 (3H, s, OMe), 3.53 (1H, ddd, *J* = 13.5, 11.6, 3.3 Hz, C6-H_B), 2.79 (1H, dd, *J* = 13.8, 6.5 Hz, C7-H_A), 2.53 (1H, dd, *J* = 13.8, 8.1 Hz, C7-H_B), 2.43 – 2.33 (1H, m, C3-H), 2.03 – 1.87 (1H, m, C5-H_A), 1.60 – 1.46 (2H, m, 1 × C4-H_A + 1 × C5-H_B), 1.45 – 1.34 (1H, m, C4-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 158.2 (C Ar), 139.2 (C Ar), 134.6 (C Ar), 133.1 (C Ar), 132.4 (C Ar), 131.6 (C Ar), 131.0 (C Ar), 130.2 (2 × C Ar), 128.4 (2 × C Ar), 127.4 (2 × C Ar), 127.2 (C Ar), 124.0 (C Ar), 114.1 (2 × C Ar), 61.6 (C2), 55.5 (OMe), 44.3 (C6), 41.7 (C3), 37.2 (C7), 23.4 (C4), 21.0 (C5).

Partial data for **5f-B** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 4.86 (1H, d, *J* = 3.4 Hz, C2-H), 3.89 (1H, d, *J* = 5.9 Hz, C6-H_A), 3.77 (3H, s, OMe), 2.75 – 2.70 (1H, m, C7-H_A), 2.49 – 2.43 (1H, m, C7-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 156.0 (C Ar), 139.2 (C Ar), 133.1 **(**2 × C Ar), 131.5 (2 × C Ar), 130.0 (2 × C Ar), 128.4 (2 × C Ar), 127.3 (2 × C Ar), 123.9 (2 × C Ar), 113.9 (2 × C Ar), 60.2 (C2), 55.4 (OMe), 41.6 (C3), 23.5 (C4), 20.9 (C5).

Data for **5f**: **HRMS** (ESI): calculated for $C_{25}H_{27}O_5SN_2$ $[M+H]^+$ requires m/z 467.1635, found m/z 467.1632. **IR** (film) ν_{max}: 2952, 1612, 1542, 1512, 1466, 1345, 1246, 1160, 950, 778, 729 cm^{-1}.

(5g): (±)-(2*S*,3*R*)-3-Cinnamyl-1-((2-nitrophenyl)sulfonyl)-2-phenylpiperidine

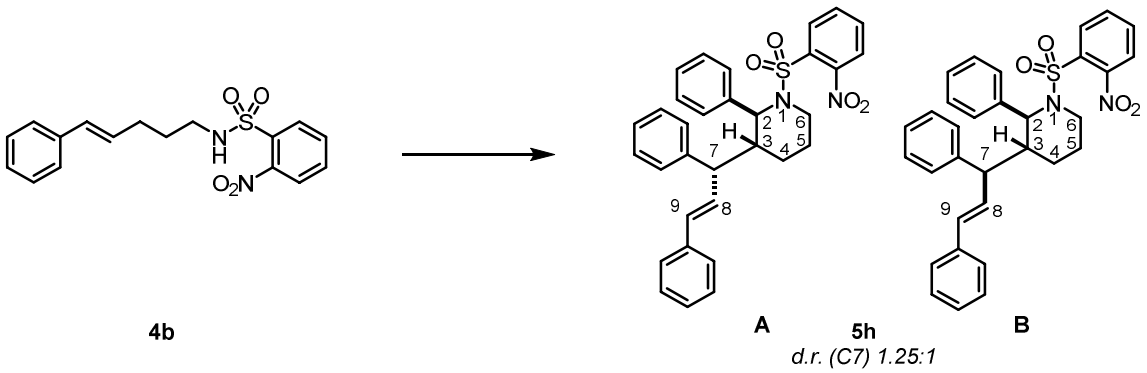


4b **5g**

Prepared according to **General Procedure I** using **4b** (14 mg, 0.040 mmol) and cinnamyl alcohol (5 mg, 0.04 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5g** as a colourless oil (9 mg, 49%).

Data for **5g**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.67 (1H, dd, *J* = 8.0, 1.5 Hz, 1H, Ar), 7.62 – 7.50 (2H, m, Ar), 7.43 – 7.01 (11H, m, Ar), 6.39 (1H, d, *J* = 16.0 Hz, C9-H), 6.16 (1H, dt, *J* = 16.0, 7.0 Hz, C8-H), 4.89 (1H, d, *J* = 4.0 Hz, C2-H), 3.99 (1H, dd, *J* = 13.5, 4.5 Hz, C6-H_A), 3.54 (1H, ddd, J = 13.5, 11.0, 3.5 Hz, 1H, C6-H_B), 2.43 (1H, m, C7-H_A), 2.33 – 2.27 (1H, m, C3-H), 2.27 – 2.17 (1H, m, C7-H_B), 1.53 (4H, m, 2 × C4-H_2 + 2 × C5-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 138.8 (C Ar), 137.5 (C Ar), 134.5 (C Ar). 134.4 (C Ar), 132.8 (C Ar), 132.3 (C9), 131.4 (2 × C Ar), 130.9 (2 × C Ar), 128.5 (2 × C Ar), 128.2 (2 × C Ar), 127.9 (C8), 127.3 (C Ar), 127.2 (C Ar), 127.0 (2 × C Ar), 126.1 (2 × C Ar), 123.8 (2 × C Ar), 61.5 (C2), 44.0 (C6), 39.4 (C3), 35.1 (C7), 23.8 (C5), 20.9 (C4). **HRMS** (ESI): calculated for $C_{26}H_{27}O_4SN_2$ $[M+H]^+$ requires *m/z* 463.1613, found *m/z* 463.1615. **IR** (film) ν_{max}: 3025, 2919, 2849, 1543, 1496, 1447, 1346, 1208, 1166, 745 cm^{-1}.

(5h): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-1-((2-nitrophenyl)sulfonyl)-2-phenylpiperidine and (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-Diphenylallyl)-1-((2-nitrophenyl)sulfonyl)-2-phenylpiperidine



Prepared according to **General Procedure I** using **4b** (28 mg, 0.080 mmol) and (*E*)-1,3-diphenylpropenol (18 mg, 0.08 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded an inseparable 1.25:1 mixture of diastereomers **5h** as a yellow oil (32 mg, 74%).

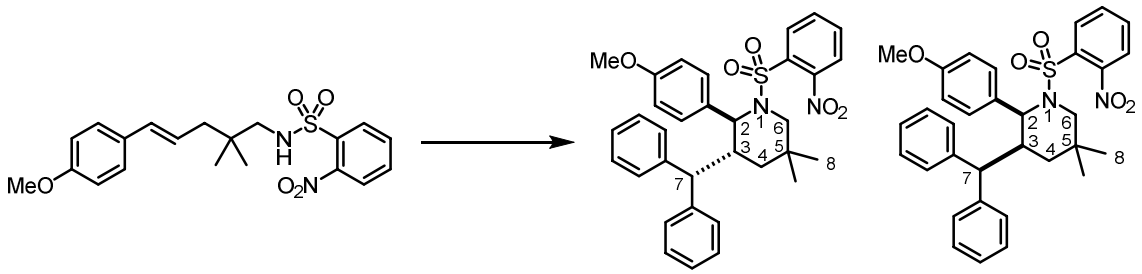
Data for **5h-A** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.58 (1H, d, *J* = 15.8 Hz, C9-H), 6.33 (1H, dd, *J* = 16.4, 9.3 Hz, C8-H), 5.40 (1H, *br.* s, C2-H), 4.20 (1H, ddd, *J* = 19.0, 12.5, 5.0 Hz, C6-H_A), 3.80 (2H, q, *J* = 9.4 Hz, C7-H_2), 3.53 (td, *J* = 13.0, 3.2 Hz, 1H, C6-H_B), 2.51 (1H, d, *J* = 11.0 Hz, C3-H), 1.82 (2H, td, *J* = 9.0, 5.2 Hz, C5-H_2), 1.41 – 1.32 (2H, m, C4-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 132.6 (C8), 132.2 (C9), 58.7 (C2), 49.1 (C7), 44.7 (C3), 43.7 (C6), 20.3 (C5), 20.1 (C4).

Partial data for **5h-B** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.48 (1H, d, *J* = 15.6 Hz, C9-H), 6.26 (1H, dd, *J* = 16.2, 10.6 Hz, C8-H), 4.84 (1H, d, *J* = 2.6 Hz, C2-H), 4.20 – 4.14 (1H, m, C6-H_A), 3.62 (1H, ddd, *J* = 13.2, 11.9, 3.4 Hz, C6-H_B), 2.63 – 2.54 (1H, m, C3-H), 2.00 (1H, m, C5-H_A), 1.59 (1H, m, C5-H_B), 1.42 – 1.13 (2H, m, 2H, C4-H_2) **^{13}C NMR (101 MHz, $CDCl_3$) δ** 131.2 (C8), 130.8 (C9), 58.2 (C2), 49.5 (C7), 44.7 (C3), 44.1 (C6), 20.3 (C5), 20.1 (C4)

Data for **5h: HRMS** (ESI): calculated for $C_{32}H_{30}O_4SN_2Na$ $[M+H]^+$ requires *m/z* 561.1843, found *m/z* 561.1815. **IR** (film) ν_{max}: 3026, 2943, 1542, 1369, 1346, 1164, 941, 909, 729, 699, 665 cm^{-1}. Aromatic signals for **5h-A+B** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.66 (dd, *J* = 8.0, 1.3 Hz), 7.57 (td, *J* = 8.1, 1.3 Hz), 7.53 – 7.46 (m), 7.41 (dd, *J* = 8.1, 1.3 Hz), 7.39 – 7.27 (m), 7.25 – 7.17 (m), 7.16 – 7.05 (m), 7.03 – 6.97 (m). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 156.1, 147.7, 143.3, 142.4, 140.0, 139.7, 137.6,

137.3, 134.2, 133.1, 133.0, 132.8, 132.4, 131.6, 131.5, 131.4, 131.4, 131.0, 129.0, 129.0, 128.6, 128.5, 128.4, 128.3, 128.1, 127.5, 127.4, 126.9, 126.9, 126.8, 126.7, 126.5, 126.4, 123.8.

(5i): (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)-5,5-dimethyl-1-((2-nitrophenyl)-sulfonyl)-piperidine and (±)-(2*S*,3*S*)-3-benzhydryl-2-(4-methoxyphenyl)-5,5-dimethyl-1-((2-nitrophenyl-)sulfonyl)-piperidine



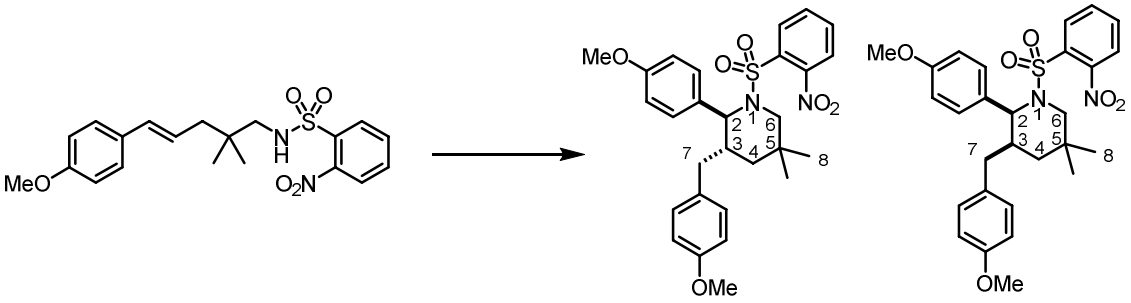
Prepared according to **General Procedure I** using **4c** (16 mg, 0.040 mmol) and benzhydrol (7.5 mg, 0.040 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded an inseparable 1:3 mixture of diastereomers **5i** as a yellow oil (19 mg, 83%).

Partial data for **5i-A** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.59 (2H, d, *J* = 7.8 Hz, Ar), 7.46 – 7.34 (5H, m, Ar), 7.31 – 7.06 (7H, m, Ar), 6.94 (2H, d, *J* = 8.7 Hz, Ar), 6.49 (2H, d, *J* = 8.8 Hz, Ar), 4.59 (1H, d, *J* = 7.4 Hz, C2-H), 4.09 (1H, d, *J* = 7.8 Hz, C7-H), 3.68 (3H, s, OMe), 3.53 (1H, d, *J* = 13.7 Hz, C6-H_A), 3.34 (1H, d, *J* = 13.7 Hz, C6-H_B), 3.07 – 2.97 (1H, m, C3-H), 1.63 – 1.54 (1H, m, C4-H_A), 1.40 (1H, dd, *J* = 13.9, 9.1 Hz, C4-H_B), 1.08 (3H, s, 1 × C8-H_3), 0.99 (3H, s, 1 × C8-H_3). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 61.8 (C2), 55.5 (OMe), 55.5 (C6), 53.1 (C7), 42.5 (C3), 37.6 (C4), 31.9 (C3), 28.4 (C8), 27.4 (C8).

Data for **5i-B** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.54 – 7.48 (2H, m, Ar), 7.32 – 7.05 (12H, m, Ar), 6.74 – 6.66 (2H, m, Ar), 6.66 – 6.55 (2H, m, Ar), 5.00 (1H, d, *J* = 5.7 Hz, C2-H), 3.77 (3H, s, OMe), 3.40 (1H, d, *J* = 14.1 Hz, C6-H_A), 3.34 – 3.26 (1H, m, C3-H), 3.22 (1H, d, *J* = 13.7 Hz, C6-H_B), 3.17 (1H, d, *J* = 11.9 Hz, C7-H), 1.64 (1H, t, *J* = 13.6 Hz, C4-H_A), 1.30 – 1.20 (1H, m, C4-H_B), 0.99 (3H, s, 1 × C8-H_3), 0.98 (3H, s, 1 × C8-H_3). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 58.0 (C2), 55.5 (OMe), 55.4 (C7), 52.1 (C6), 39.1 (C3), 38.0 (C4), 31.6 (C5), 29.2 (C8), 24.4 (C8).

Data for **5i**: **HRMS** (ESI): calculated for $C_{33}H_{34}O_6SN_2Na$ $[M+Na]^+$ requires m/z 593.2081, found m/z 593.2080. **IR** (film) ν_{max}: 3027, 2957, 2869, 1543, 1452, 1342, 1252, 1163, 908, 732 cm^{-1}. Aromatic signals for **5i-A+B** (from the mixture): **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.3, 148.0, 143.5, 142.2, 134.3, 133.1, 132.5, 131.5, 131.5, 131.3, 131.0, 129.7, 129.4, 129.0, 128.7, 128.7, 128.5, 128.4, 128.0, 126.7, 126.6, 126.4, 124.4, 123.9, 113.7, 113.4.

(5j): (±)-(2*S*,3*S*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-5,5-dimethyl-1-((2-nitrophenyl)-sulfonyl)piperidine and (±)-(2*S*,3*R*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-5,5-dimethyl-1-((2-nitrophenyl)sulfonyl)piperidine



Prepared according to **General Procedure I** using **4c** (16 mg, 0.040 mmol) and 4-methoxybenzyl alcohol (5.5 mg, 0.040 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded an inseparable 2:1 mixture of diastereomers **5j** as a yellow oil (14 mg, 67%).

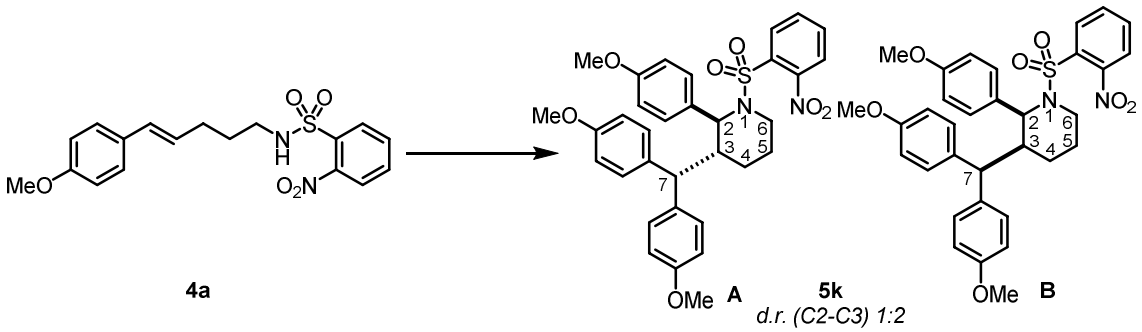
Data for **5j-A** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.98 – 6.58 (m, 10H), 6.51 (2H, d, J = 8.7 Hz, Ar), 4.21 (1H, d, J = 10.3 Hz, C2-H), 3.76 (3H, s, OMe), 3.70 (3H, s, OMe), 3.51 (1H, d, J = 13.2 Hz, C6-H_A), 3.34 (1H, d, J = 13.3 Hz, C6-H_B), 2.53 (1H, dd, J = 13.5, 3.3 Hz, C7-H_A), 2.17 – 2.08 (1H, m, C3-H), 2.02 (1H, dd, J = 14.0, 4.1 Hz, C7-H_B), 1.48 (1H, dd, J = 13.7, 3.3 Hz, C4-H_A), 1.13 – 1.08 (1H, m, C4-H_B), 1.06 (3H, s, 1 × C8-H_3), 0.96 (3H, s, 1 × C8-H_3). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 65.9 (C2), 55.9 (C6), 55.4 (OMe), 55.3 (OMe), 41.5 (C4), 41.2 (C3), 38.0 (C7), 31.9 (C5), 29.3 (C8), 26.0 (C8).

Partial data for **5j-B** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.01 (1H, d, J = 6.3 Hz, C2-H), 3.79 (3H, s, OMe), 3.69 (3H, s, OMe), 3.41 (1H, d, J = 13.6 Hz, C6-H_A), 3.23 (d, J = 13.6, C6-H_B), 2.37 (1H, dd, J = 14.0, 6.2 Hz, C7-H_A), 2.30 (1H, dd, J = 14.2, 6.5 Hz, C7-H_B), 1.02 (3H, s, 1 × C8-H_3), 0.88

(3H, s, 1 × C8-H_3). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 59.3 (C2), 55.4 (OMe), 55.3 (OMe), 52.7 (C6), 38.8 (C7), 29.1 (C8), 26.1 (C8).

Data for **5j**: **HRMS** (ESI): calculated for $C_{28}H_{32}O_6SN_2Na$ $[M+Na]^+$ requires m/z 547.1873, found m/z 547.1873. **IR** (film) ν_{max}: 1750, 1684, 1541, 1474, 1397, 1314, 1223, 1110, 851, 779 cm^{-1}. Aromatic signals for **5j-A+B** (from the mixture): **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.3, 158.0, 155.8, 135.2, 132.1, 131.7, 131.1, 131.0, 130.8, 130.2, 129.9, 123.8, 113.8, 113.7, 113.5.

(5k): (±)-(2*S*,3*R*)-3-(bis(4-Methoxyphenyl)methyl)-2-(4-methoxyphenyl)-1-((4-nitrophenyl)-sulfonyl)piperidine and (±)-(2*S*,3*S*)-3-(bis(4-Methoxyphenyl)methyl)-2-(4-methoxyphenyl)-1-((4-nitrophenyl)sulfonyl)piperidine and



Prepared by **General Procedure I** using **4a** (30 mg, 0.08 mmol) and 4,4'-dimethoxybenzhydrol (20 mg, 0.08 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 30% EtOAc – pentane) afforded a partially separable 2:1 mixture of diastereomers **5k** as a yellow oil (46 mg, 95%).

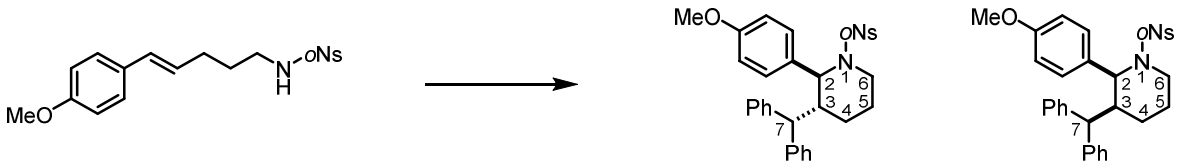
Partial data for **5k-A** (from a 1:1.5 B:A mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 4.96 (1H, s, C2-H), 4.22 – 4.12 (2H, m, 1 × C6-H_A + 1 × C7-H), 3.78 (3H, s, OMe), 3.74 (6H, s, 2 × OMe), 3.48 (1H, td, J = 13.5, 3.0 Hz, C6-H_B), 2.90 (1H, d, J = 11.8 Hz, C3-H), 1.97 – 1.91 (1H, m, C4-H_A), 1.46 – 1.34 (3H, m, 1 × C4-H_B + 2 × C5-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 158.3 (C Ar), 157.9 (C Ar), 147.7 (C Ar), 136.0 (C Ar), 135.7 (C Ar), 134.1 (C Ar), 132.8 (C Ar), 131.9 (C Ar), 131.5 (C Ar), 131.5 (C Ar), 128.9 (2 × C Ar), 128.8 (2 × C Ar), 127.8 (2 × C Ar), 123.7 (C Ar), 114.1 (2 × C Ar), 114.1 (2 × C Ar), 113.7 (2 × C Ar), 58.0 (C2), 55.2 (2 × OMe), 53.4 (OMe), 49.9 (C7), 43.6 (C6), 42.9 (C3), 20.4 (C5), 19.8 (C4).

Data for **5k-B** (from a >20:1 mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.62 (1H, dt, J = 8.0, 1.0 Hz, Ar), 7.58 – 7.53 (2H, m, Ar), 7.42 (1H, ddd, J = 8.0, 5.5, 3.5 Hz, Ar), 7.07 – 7.01 (2H, m, Ar), 7.01 – 6.94

(2H, m, Ar), 6.92 – 6.85 (2H, m, Ar), 6.82 – 6.77 (2H, m, Ar), 6.77 – 6.71 (2H, m, Ar), 6.69 – 6.63 (2H, m, Ar), 5.01 (1H, d, J = 5.5 Hz, C2-H), 3.82 – 3.76 (7H, m, OMe × 2 + C6-H_A), 3.71 (3H, s, OMe), 3.39 (1H, td, J = 13.0, 3.5 Hz, C6-H_B), 3.09 (1H, d, J = 12.0 Hz, C7-H), 2.83 (1H, qd, J = 8.0, 7.0, 3.0 Hz, 1H, C3-H), 1.87 (1H, dt, J = 9.5, 3.0 Hz, C5-H_A), 1.74 – 1.62 (2H, m, 1 × C4-H_A + 1 × C5-H_B), 1.59 (1H, m, C4-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.0 (C Ar), 158.1 (C Ar), 158.0 (C Ar), 147.9 (C Ar), 135.8 (C Ar), 134.3 (C Ar), 133.8 (C Ar), 132.9 (C Ar), 131.3 (C Ar), 131.3 (C Ar), 130.8 (C Ar), 129.3 (2 × C Ar), 129.0 (2 × C Ar), 128.6 (2 × C Ar), 124.1 (Ar), 114.0 (2 × C Ar), 114.0 (2 × C Ar), 113.2 (2 × C Ar), 58.4 (C1), 55.2 (2 × OMe), 55.2 (OMe), 53.4 (C7), 43.5 (C3), 41.3 (C6), 25.5 (C5), 23.4 (C4).

Data for **5k**: **HRMS** (ESI): calculated for $C_{33}H_{34}N_2O_7SNa$ $[M+Na]^+$ requires m/z 625.2003, found m/z 625.1998. **IR** (film) ν_{max}: 2850, 1609, 1543, 1510, 1441, 1345, 1302, 1248, 1182, 1032 cm^{-1}.

(5a): (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)piperidine and (±)-(2*S*,3*S*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)piperidine



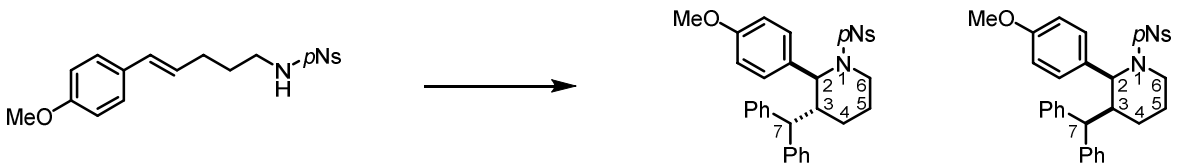
Prepared according to **General Procedure I** using **4a** (30 mg, 0.080 mmol) and benzhydrol (14 mg, 0.080 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5a** as a fully separable 1:2 mixture of diastereomers as a colourless oil (37 mg, 84%).

Data for **5a-A**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.62 (1H, dd, J = 8.0, 1.3 Hz, Ar), 7.54 (1H, td, J = 7.7, 1.4 Hz, Ar), 7.42 (1H, dd, J = 8.0, 1.3 Hz, Ar), 7.30 – 7.20 (11H, m, Ar), 7.19 – 7.16 (1H, m, Ar), 7.14 – 7.11 (3H, m, Ar), 6.77 – 6.75 (2H, m, Ar), 4.96 (1H, *br.* s, C2-H), 4.25 (1H, d, J = 11.8 Hz, C7-H), 4.20 (1H, dd, J = 13.6, 5.1 Hz, C6-H_A), 3.75 (3H, s, OMe), 3.48 (1H, td, J = 13.0, 3.3 Hz, C6-H_B), 3.03 (1H, *app.* d, J = 11.6 Hz, C3-H), 1.94 (1H, dtd, J = 14.5, 11.7, 10.5, 6.9 Hz, C4-H_A), 1.52 – 1.44 (1H, m, C5-H_A), 1.44 – 1.36 (2H, m, C4-H_B + C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.5 (C Ar), 143.5 (C Ar), 143.4 (C Ar), 134.3 (C Ar), 133.0 (C Ar), 131.9 (C Ar), 131.7 (2 × C Ar), 131.7 (C Ar), 128.9 (C Ar), 128.9 (2 × C Ar), 128.2 (2 × C Ar), 128.2 (2 × C Ar), 128.0 (2 × C Ar), 126.6 (C Ar), 126.5 (C

Ar), 123.9 (C Ar), 113.9 (2 × C Ar), 58.1 (C2), 55.4 (OMe), 51.7 (C7), 43.6 (C6), 42.5 (C2), 20.5 (C5), 19.9 (C4). **HRMS** (ESI): calculated for $C_{31}H_{30}O_5SN_2Na$ $[M+Na]^+$ requires m/z 565.1768, found m/z 565.1764. **IR** (film) ν_{max}: 2981, 2361, 2341, 1609, 1542, 1512, 1494, 1453, 1372, 1341 cm^{-1}.

Data for **5a-B**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.64 – 7.62 (1H, m, Ar), 7.58 – 7.54 (2H, m, Ar), 7.43 (1H, ddd, *J* = 7.9, 5.4, 3.4 Hz, Ar), 7.29 – 7.22 (3H, m, Ar), 7.20 – 7.16 (5H, m, Ar), 7.13 – 7.08 (3H, m, Ar), 6.89 – 6.85 (2H, m, Ar), 5.01 (1H, d, *J* = 5.5 Hz, C2-H), 3.79 (3H, s, OMe), 3.75 (1H, d, *J* = 2.4 Hz C6-H_A), 3.40 (1H, td, *J* = 13.1, 3.2 Hz, C6-H_B), 3.19 (1H, d, *J* = 11.9 Hz, C7-H), 2.94 (1H, *app.* qd, *J* = 7.0, 6.4, 4.4 Hz, C3-H), 1.89 – 1.86 (1H, m, C5-H_A), 1.73 – 1.69 (2H, m, C4-H_A + C5-H_B), 1.50 (1H, tt, *J* = 9.9, 2.7 Hz, C4-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 159.2 (C Ar), 148.0 (C Ar), 143.3 (C Ar), 141.9 (C Ar), 133.8 (C Ar), 133.1 (C Ar), 131.4 (3 × C Ar), 131.0 (C Ar), 129.3 (C Ar), 128.8 (2 × C Ar), 128.7 (2 × C Ar), 128.4 (2 × C Ar), 128.0 (2 × C Ar), 126.7 (C Ar), 126.5 (C Ar), 124.3 (C Ar), 113.4 (2 × C Ar), 58.5 (C2), 55.3 (OMe), 55.3 (C7), 43.2 (C3), 41.4 (C6), 25.5 (C5), 23.5 (C4). **HRMS** (ESI): calculated for $C_{31}H_{30}O_5SN_2Na$ $[M+Na]^+$ requires m/z 565.1768, found m/z 565.1766. **IR** (film) ν_{max}: 2981, 2361, 2341, 1609, 1542, 1512, 1494, 1453, 1372, 1341 cm^{-1}.

(5l): (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)piperidine and (±)-(2*S*,3*S*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)piperidine



Prepared according to **General Procedure I** using **4d** (15 mg, 0.040 mmol) and benzhydrol (7.5 mg, 0.040 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5l** as an inseparable 3:1 mixture of diastereomers as a colourless oil (19 mg, 88%).

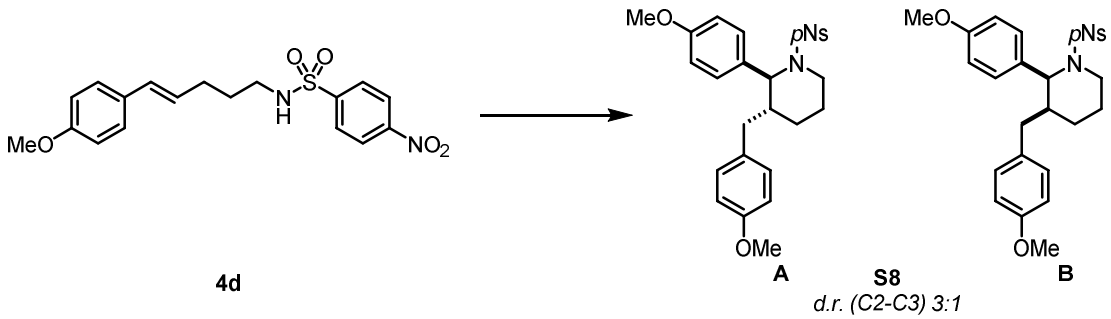
Data for **5l-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.11 (2H, d, *J* = 8.9 Hz, Ar), 7.63 (2H, d, *J* = 8.8 Hz, Ar), 7.47 – 7.32 (5H, m, Ar), 7.32 – 7.07 (5H, m, Ar), 6.91 – 6.77 (2H, m, Ar), 6.72 – 6.61 (2H, m, Ar), 5.03 (1H, *br.* s, C2-H), 4.25 (1H, d, *J* = 11.9 Hz, C7-H), 4.03 (1H, dd, *J* = 12.8, 5.3 Hz, C6-H_A), 3.73 (3H, s, OMe), 3.20 (1H, td, *J* = 12.8, 3.3 Hz, C6-H_B), 2.91 (1H, dt, *J* = 12.5, 3.2 Hz, C3-H),

1.98 – 1.81 (1H, m, C5-H_A), 1.70 – 1.51 (1H, m, C4-H_A), 1.51 – 1.38 (2H, m, C4-H_B + C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.8 (C Ar), 149.6 (C Ar), 145.9 (C Ar), 143.3 (C Ar), 143.0 (C Ar), 132.2 (C Ar), 129.0 (2 × C Ar), 129.0 (2 × C Ar), 128.4 (2 × C Ar), 128.3 (2 × C Ar), 128.2 (2 × C Ar), 128.1 (2 × C Ar), 127.1 (C Ar), 126.6 (C Ar), 123.8 (2 × C Ar), 113.9 (2 × C Ar), 58.0 (C2), 55.4 (OMe), 52.2 (C7), 42.7 (C3), 42.6 (C6), 19.9 (C4), 19.6 (C5).

Partial data for **5l-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.98 – 7.92 (2H, m, Ar), 7.40 (2H, d, *J* = 8.8 Hz, Ar), 6.59 – 6.50 (2H, m, Ar), 5.11 (1H, d, *J* = 5.4 Hz, C2-H), 3.95 – 3.86 (1H, m, C6-H_A), 3.75 (3H, s, OMe), 3.13 – 3.04 (2H, m, 1 × C6-H_B + 1 × C7-H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 159.5 (C Ar), 149.3 (C Ar), 145.2 (C Ar), 143.2 (C Ar), 141.7 (C Ar), 131.5 (2 × C Ar), 128.9 (2 × C Ar), 128.8 (2 × C Ar), 128.6 (C Ar), 128.3 (2 × C Ar), 128.0 (2 × C Ar), 126.9 (C Ar), 126.6 (C Ar), 123.4 (2 × C Ar), 113.2 (2 × C Ar), 58.7 (C2), 55.4 (OMe), 55.1 (C7), 43.7 (C3), 41.8 (C6), 25.5 (C5), 23.0 (C4).

Data for **5l**: **HRMS** (ESI): calculated for $C_{31}H_{30}O_5SN_2Na$ $[M+Na]^+$ requires *m/z* 565.1768, found *m/z* 565.1764. **IR** (film) ν_{max}: 3649, 3104, 3062, 3026, 2981, 2889, 2360, 2342, 1528, 1512 cm^{-1}.

(S8): (±)-(2*S*,3*R*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1-((4-nitrophenyl)sulfonyl)-piperidine and (±)-(2*S*,3*S*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1-((4-nitrophenyl)-sulfonyl)-piperidine

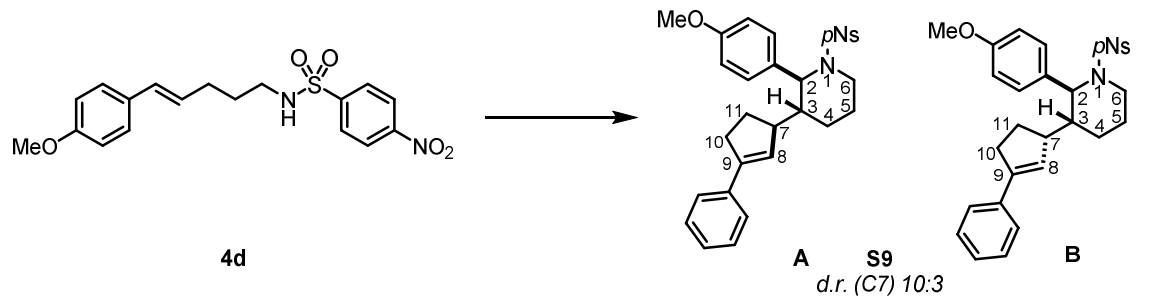


Prepared according to **General Procedure I** using **4d** (14 mg, 0.040 mmol) and 4-methoxybenzyl alcohol (5.5 mg, 0.040 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **S8** as a colourless oil (10 mg, 50%). *An NMR of the crude reaction mixture indicated the presence of a minor diastereomer (3:1 major:minor) which was not isolated.*

Data for **S8-A**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.16 (2H, d, *J* = 8.8 Hz, Ar), 7.73 (2H, d, *J* = 8.8 Hz, Ar), 7.08 (2H, d, *J* = 8.6 Hz, Ar), 6.91 (2H, d, *J* = 8.7 Hz, Ar), 6.84 (2H, d, *J* = 8.6 Hz, Ar), 6.66 (2H, d,

J = 8.8 Hz, Ar), 4.90 (1H, d, *J* = 3.5 Hz, C2-H), 3.86 (1H, ddd, *J* = 13.2, 5.6, 2.8 Hz, C6-H_A), 3.80 (3H, s, OMe), 3.73 (3H, s, OMe), 3.28 (1H, ddd, *J* = 13.0, 11.9, 3.8 Hz, C6-H_B), 2.81 (1H, dd, *J* = 13.8, 6.9 Hz, C7-H_A), 2.51 (1H, dd, *J* = 13.8, 7.8 Hz, C7-H_B), 2.28 (1H, tq, *J* = 7.7, 4.1 Hz, C3-H), 1.89 (1H, ddt, *J* = 16.9, 11.1, 5.6 Hz, C5-H_A), 1.63 (1H, ddt, *J* = 13.7, 11.1, 4.4 Hz, C4-H_A), 1.57 – 1.49 (1H, m, C5-H_B), 1.41 (1H, dq, *J* = 16.3, 4.7 Hz, C4-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.9 (C Ar), 158.2 (C Ar), 149.6 (C Ar), 146.6 (C Ar), 132.1 (C Ar), 131.5 (C Ar), 130.2 (2 × C Ar), 128.6 (2 × C Ar), 128.2 (2 × C Ar), 124.0 (2 × C Ar), 114.0 (2 × C Ar), 113.8 (2 × C Ar), 60.7 (C2), 55.4 (OMe), 55.4 (OMe), 42.8 (C6), 41.2 (C3), 37.5 (C7), 22.9 (C4), 20.7 (C5). **HRMS** (ESI): calculated for $C_{28}H_{27}O_6SN_2Na$ $[M+Na]^+$ requires *m/z* 519.1584, found *m/z* 519.1585. **IR** (film) ν_{max}: 2949, 2359, 1529, 1511, 1347, 1248, 1160, 1091, 1033, 755 cm^{-1}.

(S9): (±)-(2*S*,3*R*)-3-((*R*)-3-Phenylcyclopent-2-en-1-yl)-2-(4-methoxyphenyl)-1-((4-nitro-phenyl)-sulfonyl)piperidine and (±)-(2*S*,3*R*)-3-((*S*)-3-Phenylcyclopent-2-en-1-yl)-2-(4-methoxyphenyl)-1-((4-nitrophenyl)-sulfonyl)piperidine



Prepared according to **General Procedure I** using **4d** (14 mg, 0.040 mmol) and **2m** (6.5 mg, 0.040 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded an inseparable 10:3 mixture of diastereomers **S9** as a colourless oil (14 mg, 67%).

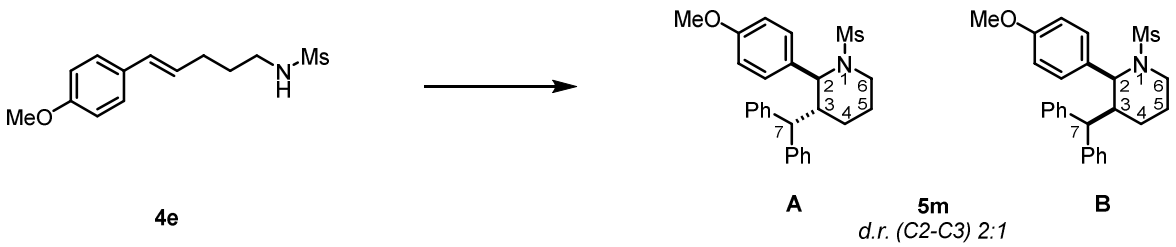
Data for **S9-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.21 (2H, d, *J* = 8.8 Hz, Ar), 7.82 (2H, d, *J* = 8.8 Hz, Ar), 7.46 – 7.40 (2H, m, Ar), 7.35 – 7.29 (3H, m, Ar), 7.01 (2H, d, *J* = 8.6 Hz, Ar), 6.72 (2H, d, *J* = 8.8 Hz, Ar), 6.11 (1H, d, *J* = 2.0 Hz, C8-H), 5.11 (1H, d, *J* = 3.2 Hz, C2-H), 3.94 – 3.85 (1H, m, C6-H_A), 3.76 (3H, s, OMe), 3.32 – 3.24 (1H, m, C6-H_B), 3.08 – 2.99 (1H, m, C7-H), 2.82 (1H, ddp, *J* = 13.5, 6.7, 2.1 Hz, C11-H_A), 2.77 – 2.66 (1H, m, C11-H_B), 2.40 (1H, dtd, *J* = 13.1, 8.7, 4.6 Hz, C10-H_A), 1.98 (1H, dq, *J* = 8.0, 3.8 Hz, C3-H), 1.92 – 1.83 (1H, m, C5-H_A), 1.83 – 1.74 (1H, m, C10-H_B), 1.73 – 1.67 (1H, m, C4-H_A), 1.66 – 1.50 (2H, m, 1 × C4-H_B + 1 × C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$)**

δ 158.8 (C Ar), 149.7 (C Ar), 146.8 (C Ar), 144.5 (C Ar), 137.0 (C Ar), 132.1 (C9), 128.5 (2 × C Ar), 128.4 (2 × C Ar), 128.2 (2 × C Ar), 127.5 (C8), 126.5 (C Ar), 125.8 (2 × C Ar), 124.1 (2 × C Ar), 114.0 (2 × C Ar), 59.9 (C2), 55.4 (OMe), 45.7 (C7), 44.5 (C3), 42.5 (C6), 32.6 (C11), 22.5 (C10), 21.5 (C4), 20.7 (C5).

Partial data for **S9-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.18 (2H, d, *J* = 8.9 Hz, Ar), 7.46 (2H, d, *J* = 8.4 Hz, Ar), 7.05 (2H, d, *J* = 8.7 Hz, Ar), 6.26 (1H, d, *J* = 1.9 Hz, C8-H), 5.20 (1H, d, *J* = 4.0 Hz, C2-H), 3.85 – 3.78 (1H, m, C6-H_A), 3.76 (3H, s, OMe), 2.91 (1H, m, C7-H), 2.86 – 2.83 (1H, m, C11-H_A), 2.69 – 2.60 (1H, m, C11-H_B), 2.11 (1H, dt, *J* = 7.9, 3.8 Hz, C10-H_A). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.9 (C Ar), 149.6 (C Ar), 143.7 (C Ar), 131.2 (C9), 128.6 (2 × C Ar), 128.5 (2 × C Ar), 128.4 (2 × C Ar), 128.2 (2 × C Ar), 127.5 (C8), 126.6 (C Ar), 125.8 (2 × C Ar), 124.0 (2 × C Ar), 113.9 (2 × C Ar), 60.4 (C2), 43.5 (C3), 42.4 (C6), 32.9 (C11), 20.9 (C4), 20.8 (C5).

Data for **S9**: **HRMS** (ESI): calculated for $C_{29}H_{30}O_5SN_2Na$ $[M+Na]^+$ requires *m/z* 541.1768, found *m/z* 541.1767. **IR** (film) ν_{max}: 2949, 2360, 1529, 1512, 1348, 1310, 1251, 1165, 1090, 757 cm^{-1}.

(5m): (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-(methylsulfonyl)piperidine and (±)-(2*S*,3*S*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-(methylsulfonyl)piperidine



Prepared according to **General Procedure I** using **4e** (28 mg, 0.10 mmol) and benzhydrol (18 mg, 0.10 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5m** as an inseparable 2:1 mixture of diastereomers as a colourless oil (28 mg, 64%).

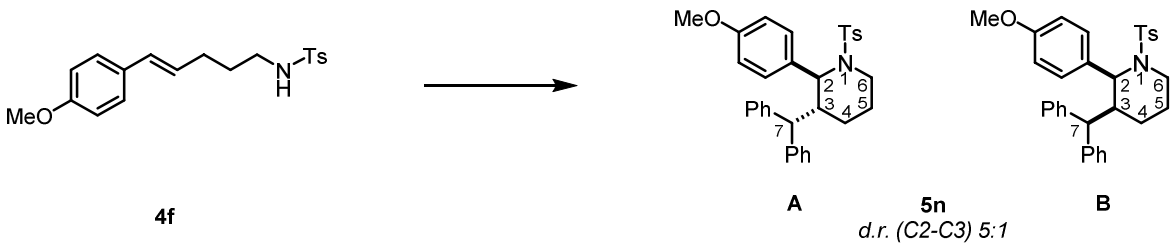
Data for **5m-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.49 – 7.44 (2H, d, *J* = 8.7 Hz, Ar), 7.39 – 7.14 (10H, m, Ar), 6.88 (2H, d, *J* = 8.7 Hz, 2H), 4.91 (1H, s, C2-H), 4.32 (1H, d, *J* = 11.9 Hz, C7-H), 3.87 (1H, dd, *J* = 13.1, 5.3 Hz, C6-H_A), 3.80 (3H, s, OMe), 3.28 (1H, td, *J* = 12.8, 3.4 Hz, C6-H_B), 2.99 – 2.94 (1H, m, C3-H), 2.62 (3H, s, SO_2Me), 1.98 – 1.91 (1H, m, C5-H_A), 1.72 – 1.65 (1H, m, C4-H_A), 1.60 – 1.53 (1H, m, C4-H_B), 1.50 – 1.41 (1H, m, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.8 (C Ar),

143.5 (C Ar), 143.3 (C Ar), 131.9 (C Ar), 128.9 (2 × C Ar), 128.8 (2 × C Ar), 128.5 (2 × C Ar), 128.3 (2 × C Ar), 128.1 (2 × C Ar), 126.9 (C Ar), 126.5 (C Ar), 114.2 (2 × C Ar), 57.3 (C2), 55.4 (OMe), 52.5 (C7), 42.0 (C6), 41.8 (C3), 39.5 (SO_2Me), 20.4 (C4), 19.9 (C5).

Partial data for **5m-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.08 – 7.04 (2H, m, Ar), 6.97 (2H, d, *J* = 8.7 Hz, Ar), 6.78 (2H, d, *J* = 8.7 Hz, Ar), 4.99 (1H, d, *J* = 5.5 Hz, C2-H), 3.82 (3H, s, OMe), 3.83 – 3.79 (1H, m, C7-H), 3.74 – 3.68 (1H, m, C6-H_A), 3.16 (1H, td, *J* = 12.4, 3.0 Hz, C6-H_B), 3.02 – 2.99 (1H, m, C3-H), 2.06 (3H, s, OMe), 1.91 – 1.83 (1H, m, C5-H_A), 1.83 – 1.74 (2H, m, C4-H_A + C5-H_B), 1.63 – 1.59 (1H, m, C4-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 159.4 (C Ar), 143.4 (C Ar), 141.8 (C Ar), 132.8 (C Ar), 129.0 (2 × C Ar), 128.7 (2 × C Ar), 128.5 (2 × C Ar), 128.3 (2 × C Ar), 128.0 (2 × C Ar), 126.7 (C Ar), 126.5 (C Ar), 113.7 (2 × C Ar), 58.3 (C2), 55.6 (OMe), 55.3 (C7), 43.5 (C6), 40.6, 37.3 (SO_2Me), 25.5 (C4), 23.8 (C5).

Data for **5m**: **HRMS** (ESI): calculated for $C_{26}H_{26}O_3SNNa$ $[M+Na]^+$ requires *m/z* 458.1760, found *m/z* 458.1756. **IR** (film) ν_{max}: 3026, 2935, 1609, 1512, 1451, 1333, 1251, 1151, 1031 cm^{-1}.

(5n): (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-tosylpiperidine and (±)-(2*S*,3*S*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-tosylpiperidine



Prepared according to **General Procedure I** using **4f** (14 mg, 0.040 mmol) and benzhydrol (7.5 mg, 0.040 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5n** as an inseparable 5:1 mixture of diastereomers as a colourless oil (20 mg, 95%).

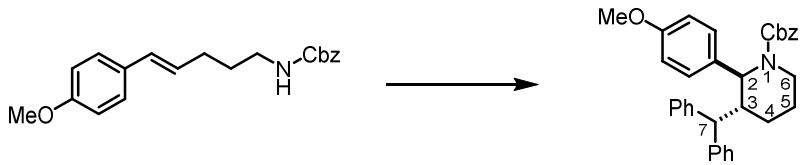
Data for **5n-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.50 (2H, d, *J* = 8.3 Hz, Ar), 7.45 – 7.39 (2H, m, Ar), 7.33 (2H, t, *J* = 7.7 Hz, Ar), 7.30 – 7.17 (8H, m, Ar), 7.04 – 6.95 (2H, m, Ar), 6.73 (2H, d, *J* = 8.7 Hz, Ar), 5.07 (1H, *br.* s, C2-H), 4.24 (1H, d, *J* = 11.9 Hz, C7-H), 3.93 (1H, dd, *J* = 13.2, 5.0 Hz, C6-H_A), 3.77 (3H, s, OMe), 3.15 (1H, td, *J* = 13.1, 3.4 Hz, C6-H_B), 3.02 – 2.96 (1H, m, C3-H), 2.41 (3H, s, TsMe), 1.93 – 1.69 (1H, m, C5-H_A), 1.52 (1H, tt, *J* = 13.8, 4.0 Hz, C4-H_A), 1.42 –

1.34 (1H, m, C4-H_B), 1.34 – 1.28 (1H, m, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.4 (C Ar), 143.6 (C Ar), 142.8 (C Ar), 138.0 (C Ar), 132.7 (C Ar), 131.6 (C Ar), 129.4 (2 × C Ar), 128.9 (2 × C Ar), 128.8 (2 × C Ar), 128.3 (2 × C Ar), 128.2 (2 × C Ar), 128.2 (2 × C Ar), 127.3 (2 × C Ar), 126.8 (C Ar), 126.4 (C Ar), 113.8 (2 × C Ar), 57.4 (C1), 55.4 (OMe), 52.1 (C7), 42.2 (C6), 41.9 (C3), 21.6 (TsMe), 20.4 (C4), 19.7 (C5).

Partial data for **5n-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.08 – 7.04 (2H, m, Ar), 6.78 (2H, d, J = 8.7 Hz, Ar), 6.61 (2H, d, J = 8.7 Hz, Ar), 5.04 (1H, d, J = 5.4 Hz, C2-H), 3.85 – 3.80 (1H, m, C6-H_A), 3.80 (3H, s, OMe), 3.11 – 3.05 (1H, m, C6-H_B), 2.88 – 2.79 (1H, m, C3-H), 2.33 (3H, s, TsMe), 1.73 – 1.68 (1H, m, C5-H_A), 1.62 (1H, td, J = 13.2, 3.8 Hz, C4-H_A). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 159.1 (C Ar), 143.5 (C Ar), 142.4 (C Ar), 142.0 (C Ar), 137.0 (C Ar), 129.4 (C Ar), 129.0 (2 × C Ar), 128.7 (2 × C Ar), 128.4 (2 × C Ar), 128.0 (C Ar), 127.3 (2 × C Ar), 126.7 (C Ar), 113.2 (2 × C Ar), 58.1 (C2), 55.3 (OMe), 55.2 (C7), 43.3 (C3), 41.1 (C6), 25.3 (C5), 23.4 (C4), 21.5 (TsMe).

Data for **5n**: **HRMS** (ESI): calculated for $C_{32}H_{33}O_3SNNa$ $[M+Na]^+$ requires m/z 534.2073, found m/z 534.2069. **IR** (film) ν_{max}: 3671, 3649, 3026, 2981, 2972, 2889, 2359, 2339, 1512, 1382 cm^{-1}.

(5o): (±)-Benzyl (2*S*,3*R*)-3-benzhydryl-2-(4-methoxyphenyl)piperidine-1-carboxylate



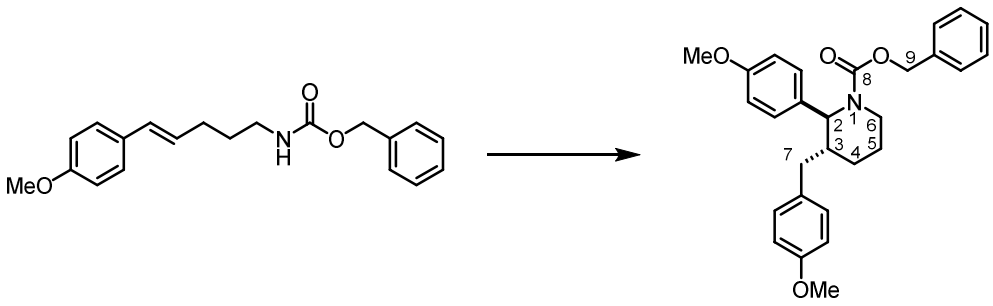
4g **5o**

Prepared according to **General Procedure I** using **4g** (13 mg, 0.040 mmol) and benzhydrol (7.5 mg, 0.040 mmol). Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5o** as a colourless oil (17 mg, 86%).

Data for **5o**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.42 – 7.05 (16H, m, Ar), 6.87 (2H, d, J = 8.8 Hz, Ar), 5.26 (1H, s, C2-H), 5.16 – 4.90 (2H, m, CH_2Ph), 4.32 – 4.14 (2H, m, C6-H_A + C7-H), 3.79 (3H, s, OMe), 3.22 (1H, ddt, J = 12.1, 4.3, 2.2 Hz, C3-H), 2.90 (1H, td, J = 13.2, 3.5 Hz, C6-H_B), 1.84 – 1.72 (1H, m, C5-H_A), 1.63 – 1.50 (1H, m, C4-H_A), 1.46 – 1.39 (1H, m, C4-H_B), 1.30 – 1.22 (1H, m, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.4 (C Ar), 144.0 (C Ar), 143.6 (C Ar), 132.1 (C Ar), 128.9 (2 × C Ar), 128.9

(2 × C Ar), 128.4 (2 × C Ar), 128.1 (2 × C Ar), 127.9 (2 × C Ar), 127.8 (2 × C Ar), 127.5 (2 × C Ar), 127.1 (2 × C Ar), 126.6 (2 × C Ar), 126.5 (2 × C Ar), 114.2 (2 × C Ar), 67.2 (CH_2Ph), 55.4 (OMe), 55.1 (C2), 52.3 (C7), 40.2 (C6), 39.4 (C3), 21.0 (C4), 19.7 (C5). *A signal corresponding to C(O) was not observed.* **HRMS** (ESI): calculated for $C_{33}H_{34}O_3N$ $[M+H]^+$ requires m/z 492.2533, found m/z 492.2533. **IR** (film) ν_{max}: 3028, 2947, 2360, 1691, 1511, 1423, 1245, 1127, 1035, 732 cm^{-1}.

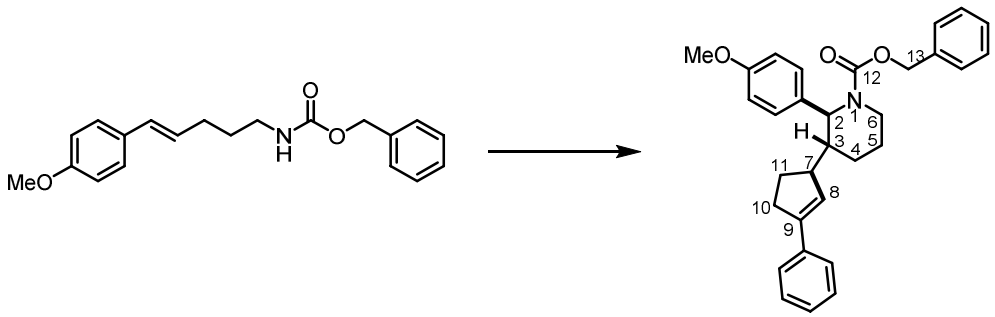
(S10): (±)-Benzyl (2*S*,3*R*)-3-(4-methoxybenzyl)-2-(4-methoxyphenyl)piperidine-1-carboxylate



Prepared according to **General Procedure I** using **4g** (6.5 mg, 0.020 mmol) and 4-methoxybenzyl alcohol (3.5 mg, 0.020 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **S10** as a colourless oil (6 mg, 67%).

Data for **S10**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.37 – 7.30 (5H, m, Ar), 7.11 – 7.03 (4H, m, Ar), 6.83 (2H, d, *J* = 8.8 Hz, Ar), 6.75 (2H, d, *J* = 8.6 Hz, Ar), 5.26 (1H, d, *J* = 12.4 Hz, C9-H_A), 5.22 (1H, *br.* s, C2-H), 5.17 (1H, d, *J* = 12.4 Hz, C9-H_B), 4.18 (1H, dd, *J* = 13.8, 4.6 Hz, C6-H_A), 3.78 (3H, s, OMe), 3.76 (3H, s, OMe), 2.93 – 2.78 (2H, m, 1 × C6-H_B + 1 × C7-H_A), 2.66 (1H, dd, *J* = 13.7, 6.8 Hz, C7-H_B), 2.55 – 2.46 (1H, m, C3-H), 1.80 (1H, ddt, *J* = 12.8, 9.1, 6.5 Hz, C5-H_A), 1.65 (1H, tt, *J* = 13.2, 4.3 Hz, C4-H_A), 1.52 – 1.44 (1H, m, C4-H_B), 1.38 (1H, d, *J* = 13.3 Hz, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.4 (C Ar), 158.1 (C Ar), 155.5 (C8), 132.9 (C Ar), 132.1 (C Ar), 130.2 (2 × C Ar), 127.7 (2 × C Ar), 114.1 (2 × C Ar), 113.9 (2 × C Ar), 67.4 (C9), 56.3 (C2), 55.4 (OMe), 55.4 (OMe), 40.3 (C6), 38.6 (C3), 37.2 (C7), 23.4 (C4), 20.3 (C5). **HRMS** (ESI): calculated for $C_{28}H_{32}O_4N$ $[M+H]^+$ requires m/z 446.2326, found m/z 446.2325. **IR** (film) ν_{max}: 2981, 2359, 2338, 1694, 1562, 1557, 1424, 1248 cm^{-1}.

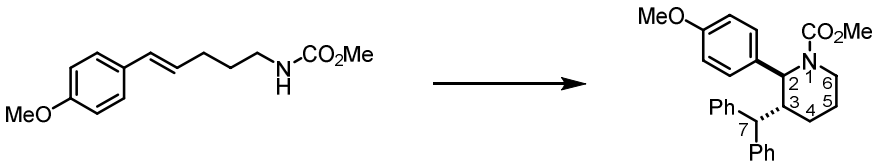
(S11): (±)-Benzyl (2*S*,3*R*)-2-(4-methoxyphenyl)-3-((*R*)-3-phenylcyclopent-2-en-1-yl)piperidine-1-carboxylate



Prepared according to **General Procedure I** using **4g** (6.5 mg, 0.020 mmol) and **2m** (3.0 mg, 0.040 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **S11** as a colourless oil (8 mg, 86%).

Data for **S11**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.49 – 7.41 (2H, m, Ar), 7.38 – 7.22 (8H, m, Ar), 7.18 – 7.12 (2H, m, Ar), 6.87 (2H, d, J = 8.8 Hz, Ar), 6.22 (1H, q, J = 2.0 Hz, C8-H), 5.39 (1H, s, C2-H), 5.27 (1H, d, J = 12.4 Hz, C13-H_A), 5.16 (1H, d, J = 12.4 Hz, C13-H_B), 4.17 (1H, dd, J = 14.3, 4.6 Hz, C6-H_A), 3.80 (3H, s, OMe), 3.22 – 3.09 (1H, m, C7-H), 2.89 (1H, td, J = 12.8, 3.6 Hz, C6-H_B), 2.83 – 2.74 (1H, m, C11-H_A), 2.74 – 2.61 (1H, m, C11-H_B), 2.37 – 2.26 (1H, m, C10-H_A), 2.19 – 2.09 (1H, m, C10-H_B), 1.89 – 1.63 (3H, m, 1 × C5-H_A + 2 × C4-H_B), 1.48 – 1.35 (1H, m, C5-H_A). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 158.4 (C Ar), 156.8 (C12), 143.5 (C Ar), 137.1 (C Ar), 136.7 (C Ar), 132.1 (C9), 128.6 (2 × C Ar), 128.5 (2 × C Ar), 128.0 (C Ar), 128.0 (2 × C Ar), 127.8 (2 × C Ar), 127.6 (C8), 127.3 (C Ar), 125.8 (2 × C Ar), 114.2 (2 × C Ar), 67.4 (C13), 56.2 (C2), 55.4 (OMe), 45.9 (C7), 41.8 (C3), 40.2 (C6), 32.7 (C11), 30.5 (C10), 22.3 (C4), 20.5 (C5). **HRMS** (ESI): calculated for $C_{31}H_{33}O_3NNa$ $[M+Na]^+$ requires m/z 490.2353, found m/z 490.2352. **IR** (film) ν_{max}: 2938, 2360, 1693, 1511, 1424, 1250, 1178, 1037 cm^{-1}.

(5p): (±)-Methyl (2*S*,3*R*)-3-benzhydryl-2-(4-methoxyphenyl)piperidine-1-carboxylate

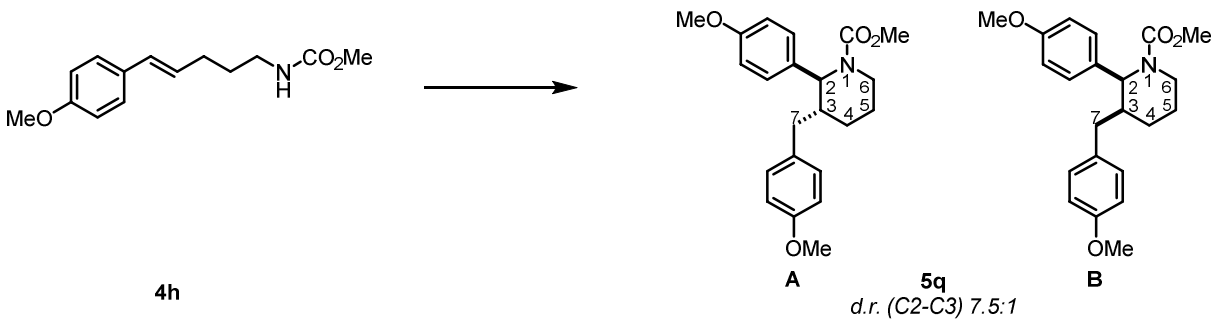


4h **5p**

Prepared according to **General Procedure I** using **4h** (25 mg, 0.10 mmol) and benzhydrol (19 mg, 0.10 mmol). Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5p** as a colourless oil (40 mg, 98%).

Data for **5p**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.43 – 7.36 (4H, m, Ar), 7.28 (4H, dt, *J* = 10.1, 7.7 Hz, Ar), 7.22 – 7.09 (4H, m, Ar), 6.91 – 6.86 (2H, m, Ar), 5.15 – 5.11 (1H, *br.* s, C2-H), 4.23 (1H, *br.* s, C6-H_A), 4.19 (1H, d, *J* = 11.9 Hz, C7-H), 3.79 (3H, s, OMe), 3.56 (3H, s, OMe), 3.20 (1H, ddt, *J* = 11.8, 4.2, 2.2 Hz, C3-H), 2.88 (1H, td, *J* = 13.2, 3.5 Hz, C6-H_B), 1.85 – 1.67 (1H, m, C5-H_A), 1.55 (1H, tt, *J* = 13.7, 4.2 Hz, C4-H_A), 1.46 – 1.37 (1H, m, C4-H_B), 1.29 – 1.21 (1H, m, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.4 (C Ar), 157.5 (CO), 144.2 (C Ar), 143.5 (C Ar), 132.0 (C Ar), 128.9 (2 × C Ar), 128.8 (2 × C Ar), 128.1 (2 × C Ar), 128.0 (2 × C Ar), 127.4 (2 × C Ar), 126.7 (C Ar), 126.5 (C Ar), 114.2 (2 × C Ar), 55.4 (OMe), 55.0 (C2), 52.5 (C7), 52.4 (OMe), 40.0 (C6), 39.8 (C3), 21.0 (C4), 19.7 (C5). **HRMS** (ESI): calculated for $C_{27}H_{30}O_3N$ $[M+H]^+$ requires *m/z* 416.2220, found *m/z* 416.2222. **IR** (film) ν_{max}: 2950, 2360, 1694, 1511, 1446, 1348, 1249, 1179, 1141, 706 cm^{-1}.

(5q): (±)-Methyl (2*S*,3*R*)-3-(4-methoxybenzyl)-2-(4-methoxyphenyl)piperidine-1-carboxylate and (±)-Methyl (2*S*,3*S*)-3-(4-methoxybenzyl)-2-(4-methoxyphenyl)piperidine-1-carboxylate



4h **A** **5q** **B**
d.r. (C2-C3) 7.5:1

Prepared according to **General Procedure I** using **4h** (25 mg, 0.10 mmol) and 4-methoxybenzyl alcohol (14 mg, 0.10 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 25%

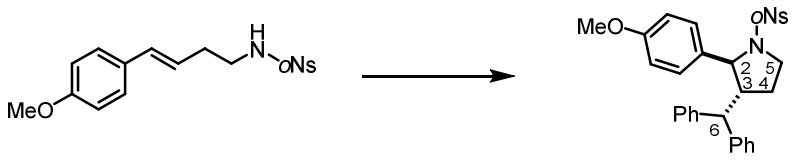
EtOAc – pentane) afforded **5q** a**s** an inseparable 7.5:1 mixture of diastereomers as a colourless oil (27 mg, 74%).

Data for **5q-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.19 – 7.13 (2H, m, Ar), 7.13 – 7.06 (2H, m, Ar), 6.88 – 6.82 (4H, m, Ar), 5.17 (1H, *br.* s, C2-H), 4.18 – 4.10 (1H, m, C6-H_A), 3.79 (3H, s, OMe), 3.78 (3H, s, OMe), 3.76 (3H, s, OMe), 2.88 – 2.82 (2H, m, C6-H_B + C7-H_A), 2.70 (1H, dd, J = 13.7, 7.0 Hz, C7-H_B), 2.53 (1H, tq, J = 6.8, 3.2 Hz, C3-H), 1.81 (1H, qt, J = 13.0, 4.6 Hz, C5-H_A), 1.68 – 1.58 (1H, m, C4-H_A), 1.52 – 1.44 (1H, m, C4-H_B), 1.41 – 1.33 (1H, m, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.4 (C Ar), 158.1 (C Ar), 157.5 (CO), 132.9 (C Ar), 132.1 (C Ar), 130.2 (2 × C Ar), 127.7 (2 × C Ar), 114.1 (2 × C Ar), 113.9 (2 × C Ar), 56.3 (C2), 55.4 (OMe), 55.4 (OMe), 52.9 (OMe), 40.1 (C6), 38.3 (C3), 37.3 (C7), 23.4 (C4), 20.3 (C5).

Partial data for **5q-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.01 – 6.89 (2H, d, J = 8.7 Hz, Ar), 6.78 (2H, d, J = 8.7 Hz, Ar), 3.81 (3H, s, OMe), 3.78 (3H, s, OMe), 3.63 (3H, s, OMe), 3.14 (1H, td, J = 13.4, 3.3 Hz, C6-H_A), 2.45 (1H, m, C7-H_A), 2.25 – 2.04 (2H, m, C3-H + C7-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.8 (C Ar), 158.0 (C Ar), 132.2 (C Ar), 130.1 (2 × C Ar), 113.8 (2 × C Ar), 113.6 (2 × C Ar), 55.4 (OMe), 55.3 (OMe), 52.6 (OMe), 41.9 (C6), 39.3 (C3).

Data for **5q**: **HRMS** (ESI): calculated for $C_{22}H_{27}O_4NNa$ $[M+Na]^+$ requires m/z 392.1832, found m/z 392.1832. **IR** (film) ν_{max}: 2938, 1694, 1611, 1511, 1443, 1408, 1247, 1179, 1125, 1037 cm^{-1}.

(1a): (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidine



1a **3a**

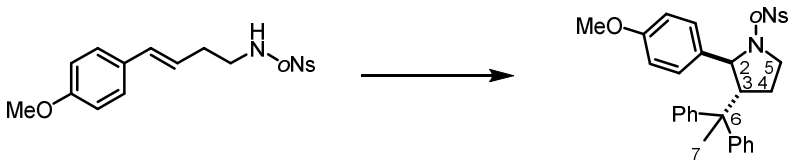
Prepared according to **General Procedure I** using **1a** (40 mg, 0.11 mmol) and benzhydrol (20 mg, 0.11 mmol). Flash column chromatography (gradient elution 15% → 25% Et_2O – pentane) afforded **3a** as a colourless oil (58 mg, 99%).

Data for **3a**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.47 – 7.55 (2H, m, Ar), 7.34 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.19 – 7.28 (6H, m, Ar), 7.06 – 7.18 (6H, m, Ar), 6.74 (2H, d, *J* = 8.7 Hz, Ar), 6.52 (2H, d, *J* = 8.7 Hz, Ar), 4.65 (1H, d, *J* = 3.6 Hz, C2-H), 3.97 (1H, dt, *J* = 10.2, 7.4 Hz, C5-H_A), 3.88 (1H, ddd, *J* = 10.2, 7.7, 5.0 Hz, C5-H_B), 3.79 (1H, d, *J* = 11.5 Hz, C6-H), 3.70 (3H, s, OMe), 3.05 (1H, m, C3-H), 3.01 – 3.09 (1H, m, C4-H_A), 1.72 (1h, ddt, *J* = 12.3, 7.2, 5.0 Hz, C4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.7 (C Ar), 147.7 (C Ar), 143.0 (C Ar), 142.9 (C Ar), 133.8 (C Ar), 133.6 (C Ar), 132.8 (C Ar), 131.2 (C Ar), 131.1 (C Ar), 128.9 (2 × C Ar),128.8 (2 × C Ar), 128.3 (2 × C Ar), 127.9 (2 × C Ar), 127.7 (2 × C Ar), 126.8 (C Ar), 126.8 (C Ar), 123.6 (C Ar), 113.6 (2 × C Ar), 67.0 (C2). 55.4 (OMe), 54.9 (C6), 53.6 (C3), 48.6 (C5), 28.3 (C4). **HRMS** (ESI): calculated for $C_{30}H_{28}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 551.1611, found *m/z* 551.1609. **IR** (film) ν_{max}: 2980, 1542, 1511, 1493, 1371, 1161 cm^{-1}.

Gram scale reaction:

To a solution of **1a** (906 mg, 2.50 mmol) in HFIP (25 mL) was added benzhydrol (461 mg, 2.50 mmol) before addition of $Ti(O^iPr)_4$ (0.22 mL, 30 mol%). Following stirring at rt for 16 h the solvent was removed *in vacuo*. Flash column chromatography (gradient elution 15% → 25% Et_2O – pentane) afforded **3a** as a colourless oil (1.25 g, 95%).

(3f): (±)-(2*S*,3*R*)-3-(1,1-Diphenylethyl)-2-(4-methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)-pyrrolidine



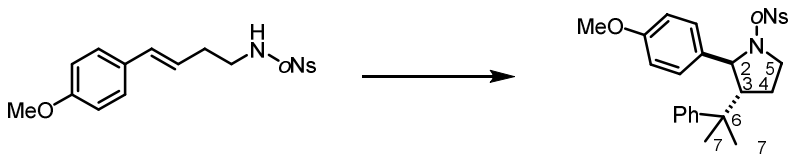
1a **3f**

Prepared according to **General Procedure I** using **1a** (36 mg, 0.10 mmol) and 1,1-diphenylethanol (20 mg, 0.10 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 10% → 20% EtOAc – pentane) afforded **3f** as a colourless oil (7 mg, 13%).

Data for **3f**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.45 – 7.38 (2H, m, Ar), 7.25 – 7.23 (2H, m, Ar), 7.22 – 7.17 (4H, m, Ar), 7.18 – 7.13 (5H, m, Ar), 7.10 (1H, ddd, *J* = 8.3, 7.2, 1.5 Hz, Ar), 6.51 (2H, d, *J* = 8.7 Hz, Ar), 6.41 (2H, d, *J* = 8.7 Hz, Ar), 4.73 (1H, d, *J* = 3.8 Hz, C2-H), 3.94 (1H, ddd, *J* = 9.9, 8.8, 4.1 Hz,

C5-H_A), 3.70 – 3.67 (1H, m, C5-H_B), 3.66 (3H, s, OMe), 3.27 (1H, dt, *J* = 8.3, 3.8 Hz, C3-H), 2.53 (1H, dq, *J* = 13.6, 8.7 Hz, C4-H_A), 2.16 (1H, ddt, *J* = 13.4, 8.0, 4.0 Hz, C4-H_B), 1.76 (3H, s, C7-H_3). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 158.8 (C Ar), 147.8 (C Ar), 147.8 (C Ar), 147.7 (C Ar), 135.0 (C Ar), 134.0 (C Ar), 132.7 (C Ar), 131.3 (C Ar), 131.0 (C Ar), 128.6 (2 × C Ar), 128.5 (2 × C Ar), 128.2 (3 × C Ar), 128.0 (2 × C Ar), 126.5 (C Ar), 126.4 (C Ar), 123.6 (2 × C Ar), 113.7 (2 × C Ar), 65.5 (C2), 57.6 (C3), 55.6 (OMe), 50.4 (C5), 50.1 (C6), 28.0 (C4), 23.0 (C7). **HRMS** (ESI): calculated for $C_{31}H_{30}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 565.1768, found *m/z* 565.1768. **IR** (film) ν_{max}: 2361, 1544, 1513, 1372, 1247, 1166, 1034, 912 cm^{-1}.

(3g): (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)-3-(2-phenylpropan-2-yl)pyrrolidine

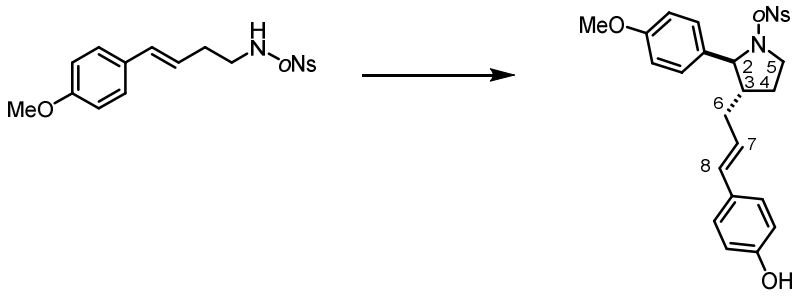


1a **3g**

Prepared according to **General Procedure I** using **1a** (36 mg, 0.10 mmol) and 1-methyl-1-phenylethyl alcohol (13.5 mg, 0.10 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 10% → 20% EtOAc – pentane) afforded **3g** as a colourless oil (16 mg, 33%).

Data for **3g**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.44 (1H, d, *J* = 7.6 Hz, Ar), 7.40 (1H, ddd, *J* = 7.9, 6.6, 2.3 Hz, Ar), 7.25 – 7.19 (4H, m, Ar), 7.16 – 7.09 (3H, m, Ar), 6.76 (2H, d, *J* = 8.5 Hz, Ar), 6.45 (2H, d, *J* = 8.5 Hz, Ar), 4.62 (1H, d, *J* = 6.6 Hz, C2-H), 3.89 (1H, ddd, *J* = 10.2, 7.8, 4.6 Hz, C5-H_A), 3.75 (1H, ddd, *J* = 10.1, 8.1, 7.0 Hz, C5-H_B), 3.68 (3H, s, OMe), 2.63 (1H, q, *J* = 7.5 Hz, C3-H), 1.98 – 1.90 (1H, m, C4-H_A), 1.90 – 1.85 (1H, m, C4-H_B), 1.31 (3H, s, C7-H_3), 1.27 (3H, s, C7-H_3). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 158.7 (C Ar), 147.8 (C Ar), 147.4 (C Ar), 134.4 (C Ar), 134.2 (C Ar), 132.3 (C Ar), 130.9 (C Ar), 130.8 (C Ar), 128.7 (2 × C Ar), 128.3 (2 × C Ar), 126.3 (2 × C Ar), 126.2 (C Ar), 123.4 (C Ar), 113.5 (2 × C Ar), 65.1 (C2), 60.4 (C3), 55.4 (OMe), 49.8 (C5), 39.9 (C6), 27.4 (C4), 26.2 (C7), 25.9 (C7). **HRMS** (ESI): calculated for $C_{26}H_{29}N_2O_5S$ $[M+H]^+$ requires *m/z* 481.1792, found *m/z* 481.1794. **IR** (film) ν_{max}: 2363, 1545, 1513, 1373, 1248, 1165, 1033, 765, 653 cm^{-1}.

(3i): (±)-4-((*E*)-3-((2*S*,3*S*)-2-(4-Methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)pyrrolidin-3-yl)prop-1-en-1-yl)phenol

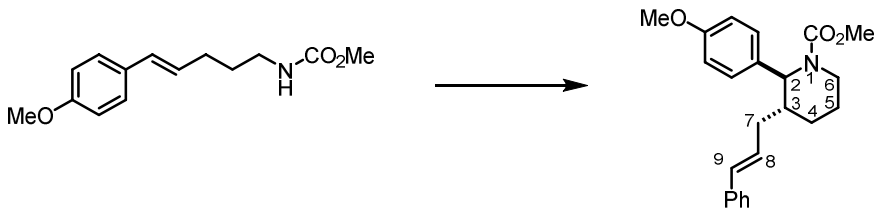


1a **3i**

Prepared according to **General Procedure I** using **1a** (18 mg, 0.050 mmol) and **2i** (7.5 mg, 0.050 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 10% → 30% EtOAc – pentane) afforded **3i** as a colourless oil (12 mg, 49%).

Data for **3i**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.51 (1H, dd, *J* = 7.9, 1.3 Hz, Ar), 7.46 (1H, ddd, *J* = 7.9, 7.3, 1.4 Hz, Ar), 7.25 (1H, d, *J* = 8.9 Hz, Ar), 7.19 (1H, ddd, *J* = 8.0, 7.4, 1.4 Hz, Ar), 7.14 (2H, d, *J* = 8.6 Hz, Ar), 7.05 (2H, d, *J* = 8.7 Hz, Ar), 6.74 (2H, d, *J* = 8.6 Hz, Ar), 6.60 (2H, d, *J* = 8.7 Hz, Ar), 6.27 (1H, dd, *J* = 15.8, 1.6 Hz, C8-H), 5.87 (1H, dt, *J* = 15.7, 7.1 Hz, C7-H), 4.78 (1H, *br.* s, O*H*), 4.48 (1H, d, *J* = 7.5 Hz, C2-H), 4.07 (1H, ddd, *J* = 10.8, 8.0, 3.2 Hz, C5-H_A), 3.78 (1H, ddd, *J* = 10.4, 9.5, 6.3 Hz, C5-H_B), 3.72 (3H, s, OMe), 2.36 – 2.24 (2H, m, C3-H + C6-H_A), 2.20 – 2.12 (2H, m, C5-H_A + C6-H_B), 1.74 (1H, dtd, *J* = 12.4, 9.5, 8.0 Hz, C5-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.2 (C Ar), 155.0 (C Ar), 147.5 (C Ar), 134.2 (C Ar), 132.6 (C Ar), 132.2 (C Ar), 131.6 (C8), 131.1 (C Ar), 131.0 (C Ar), 130.4 (C Ar), 128.9 (2 × C Ar), 127.5 (2 × C Ar), 125.2 (C7), 123.6 (C Ar), 115.5 (2 × C Ar), 113.8 (2 × C Ar), 68.7 (C2), 55.4 (OMe), 50.5 (C3), 49.6 (C5), 35.3 (C6), 30.6 (C4). **NOESY-2D (600 MHz, $CDCl_3$)**: between C2-H and C6-H_B, between C2-H and C7-H. **HRMS** (ESI): calculated for $C_{26}H_{27}N_2O_6S$ $[M+H]^+$ requires *m/z* 495.1584, found *m/z* 495.1585. **IR** (film) ν_{max}: 2923, 2852, 1611, 1542, 1513, 1371, 1247, 1160 cm^{-1}.

(5r): (±)-Methyl (2*S*,3*R*)-3-cinnamyl-2-(4-methoxyphenyl)piperidine-1-carboxylate

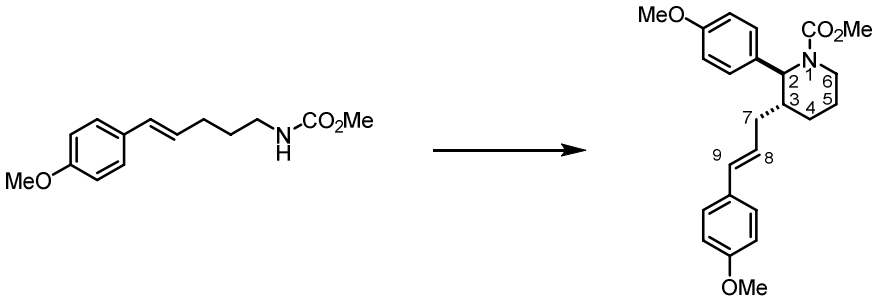


4h **5r**

Prepared according to **General Procedure I** using **4h** (21 mg, 0.080 mmol) and cinnamyl alcohol (11 mg, 0.080 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5r** as a colourless oil (15 mg, 51%).

Data for **5r**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.41 – 7.33 (2H, m, Ar), 7.31 – 7.28 (2H, m, Ar), 7.23 – 7.18 (1H, m, Ar), 7.18 – 7.14 (2H, m, Ar), 6.91 – 6.83 (2H, m, Ar), 6.46 (1H, d, *J* = 15.8 Hz, C9-H), 6.27 (1H, dt, *J* = 15.7, 7.2 Hz, C8-H), 5.24 (1H, *br.* s, C2-H), 4.18 – 4.05 (1H, m, C6-H_A), 3.80 (3H, s, OMe), 3.75 (3H, s, OMe), 2.84 (1H, td, *J* = 12.9, 3.5 Hz, C6-H_B), 2.52 (1H, dtd, *J* = 13.1, 7.2, 1.3 Hz, C7-H_A), 2.45 (1H, dq, *J* = 7.0, 3.1 Hz, C3-H), 2.38 (1H, dtd, *J* = 13.9, 7.0, 1.3 Hz, C7-H_B), 1.76 (1H, dt, *J* = 12.7, 4.5 Hz, C5-H_A), 1.69 (1H, tt, *J* = 12.9, 3.8 Hz, C4-H_A), 1.60 – 1.52 (1H, m, C4-H_B), 1.43 – 1.33 (1H, m, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.4 (C Ar), 157.5 (CO), 137.7 (C Ar), 132.2 (C9), 132.0 (C Ar), 128.8 (C8), 128.7 (2 × C Ar), 127.8 (2 × C Ar), 127.2 (2 × C Ar), 126.2 (2 × C Ar), 114.1 (2 × C Ar), 56.7 (C2), 55.4 (OMe), 52.9 (COMe), 40.0 (C6), 36.1 (C3), 35.5 (C7), 23.4 (C4), 20.2 (C5). **HRMS** (ESI): calculated for $C_{23}H_{27}O_3NNa$ $[M+Na]^+$ requires *m*/*z* 388.1883, found *m*/*z* 388.1884. **IR** (film) ν_{max}: 3649, 2981, 2360, 2342, 1693, 1511, 1443, 1407, 1248, 1178 cm^{-1}.

(5s): (±)-Methyl (2*S*,3*R*)-2-(4-methoxyphenyl)-3-((*E*)-3-(4-methoxyphenyl)allyl)piperidine-1-carboxylate

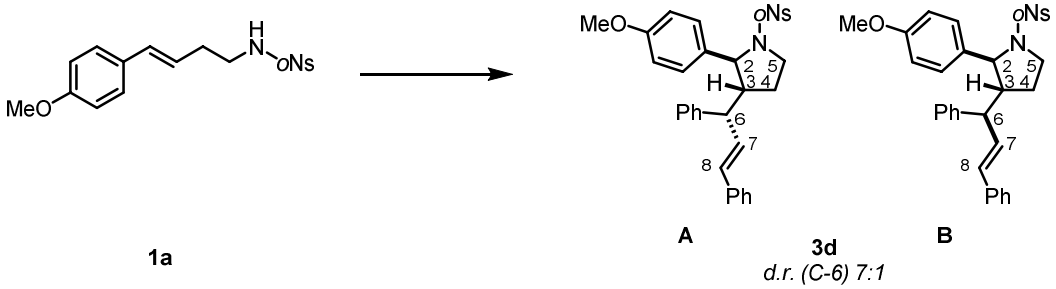


4h **5s**

Prepared according to **General Procedure I** using **4h** (10.5 mg, 0.040 mmol) and **2j** (6.5 mg, 0.040 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5s** as a colourless oil (8 mg, 51%).

Data for **5s**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.31 – 7.27 (2H, m, Ar), 7.20 – 7.11 (2H, m, Ar), 6.90 – 6.86 (2H, m, Ar), 6.86 – 6.81 (2H, m, Ar), 6.40 (1H, d, *J* = 15.7 Hz, C9-H), 6.11 (1H, dt, *J* = 15.6, 7.2 Hz, C8-H), 5.23 (1H, *br.* s, C2-H), 4.11 (1H, d, *J* = 13.1 Hz, C6-H_A), 3.80 (3H, s, OMe), 3.80 (3.80, s, OMe), 3.75 (3H, s, OMe), 2.83 (1H, td, *J* = 13.0, 3.5 Hz, C6-H_B), 2.49 (1H, dtd, *J* = 13.0, 7.2, 1.3 Hz, C7-H_A), 2.42 (1H, tq, *J* = 6.6, 3.0 Hz, C3-H), 2.38 – 2.31 (1H, m, C7-H_B), 1.81 – 1.62 (2H, m, C4-H_A + C5-H_A), 1.57 – 1.52 (1H, m, C4-H_B), 1.42 – 1.33 (1H, m, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 159.0 (C Ar), 158.4 (C Ar), 157.5 (CO), 132.1 (C Ar), 131.5 (C9), 130.5 (C Ar), 127.8 (2 × C Ar), 127.3 (2 × C Ar), 126.6 (C8), 114.0 (2 × C Ar), 114.1 (2 × C Ar), 56.7 (C2), 55.5 (OMe), 55.4 (OMe), 52.9 (OMe), 40.0 (C6), 36.2 (C3), 35.4 (C7), 23.4 (C4), 20.2 (C5). **HRMS** (ESI): calculated for $C_{24}H_{29}O_4NNa$ $[M+Na]^+$ requires *m/z* 418.1989, found *m/z* 418.1984. **IR** (film) ν_{max}: 3649, 2981, 2971, 2837, 2359, 2342, 1694, 1510, 1443, 1407 cm^{-1}.

(3d): (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*S*,2'*E*)-4-phenylbut-3-en-2-yl]pyrrolidine and (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*R*,2'*E*)-4-phenylbut-3-en-2-yl]pyrrolidine



Prepared according to **General Procedure I** using **1a** (40 mg, 0.11 mmol) and *trans*-1,3-diphenyl-2-propen-1-ol (23 mg, 0.11 mmol) at 0 ˚C for 48 h. Flash column chromatography (gradient elution 25% → 30% EtOAc – pentane) afforded **3d** as an inseparable 7:1 mixture of diastereomers as a colourless oil (61 mg, 99%).

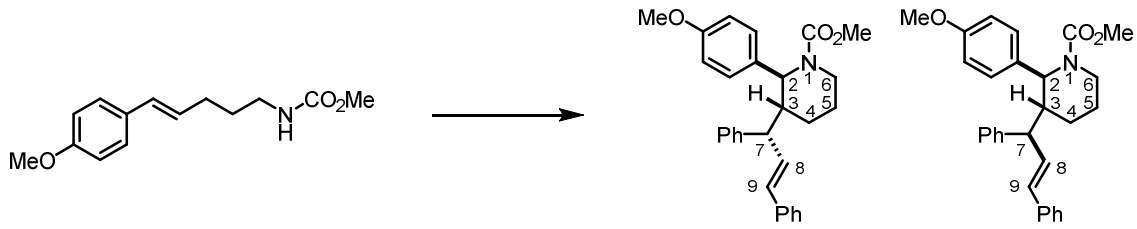
Data for **3d-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.43 – 7.52 (2H, m, Ar), 7.13 – 7.33 (12H, m, Ar), 7.02 (2H, d, *J* = 8.7 Hz, Ar), 6.55 (2H, d, *J* = 8.7 Hz, Ar), 6.37 (1H, d, *J* = 15.8 Hz, C8-H), 6.04 (1H, dd, *J* = 15.8, 9.3 Hz, C7-H), 4.84 (1H, d, *J* = 5.7 Hz, C2-H), 3.97 (1H, ddd, *J* = 10.3, 7.5, 5.2 Hz, C5-H_A), 3.81 (1H, dt, *J* = 10.3, 7.5 Hz, C5-H_B), 3.70 (3H, s, OMe), 3.39 (1H, t, *J* = 9.8 Hz, C6-H), 2.64 – 2.71 (1H, m, C3-H), 1.89 – 1.97 (1H, m, C4-H_A), 1.67 (1H, dq, *J* = 12.7, 7.5 Hz, C4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.9 (C Ar), 147.5 (C Ar), 142.4 (C Ar), 137.0 (C Ar), 133.9 (C Ar), 133.2 (C Ar), 132.6 (C Ar), 132.2 (C7), 131.06 (C8), 130.97 (2 × C Ar), 129.1 (2 × C Ar), 129.0 (2 × C Ar), 128.5 (2 × C Ar), 127.7 (2 × C Ar), 127.5 (C Ar), 126.94 (C Ar), 126.42 (2 × C Ar), 123.5 (C Ar), 113.7 (2 × C Ar), 67.2 (C2), 55.4 (OMe), 55.0 (C3), 53.5 (C6), 49.2 (C5), 29.1 (C4). **NOESY-2D (500 MHz, $CDCl_3$)**: between C2-H and C6-H, between C2-H and C7-H, between C2-H and C8-H.

Partial data for **3d-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.43 – 7.52 (2H, m, Ar), 7.13 – 7.33 (10H, m, Ar), 7.07 (2H, d, *J* = 6.9 Hz, Ar), 6.76 (2H, d, *J* = 8.7 Hz, Ar), 6.53 (2H, d, *J* = 8.7 Hz, Ar), 6.45 (1H, d, *J* = 15.7 Hz, C8-H), 6.29 (1H, dd, *J* = 15.7, 9.3 Hz, C7-H), 4.59 (1H, d, *J* = 5.3 Hz, C2-H), 4.04 (1H, ddd, *J* = 10.2, 7.4, 6.0 Hz, C5-H_A), 3.83 – 3.89 (1H, m, C5-H_B), 3.70 (3H, s, OMe), 3.38 (1H, d, *J* = 6.0 Hz, C6-H), 2.60 – 2.65 (1H, m, C3-H), 2.12 – 2.20 (1H, m, C4-H_A), 1.99 – 2.07 (1H, m, C4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.8 (C Ar), 147.6 (C Ar), 142.4 (C Ar), 137.0 (C Ar),

133.7 (C Ar), 133.1 (C Ar), 132.7 (C Ar), 132.0 (C8), 131.09 (C Ar), 130.3 (C7), 128.8 (2 × C Ar), 128.7 (2 × C Ar), 128.0 (2 × C Ar), 128.0 (2 × C Ar), 127.6 (C Ar), 126.9 (C Ar), 126.4 (C Ar), 126.4 (2 × C Ar), 123.5 (C Ar), 113.6 (2 × C Ar), 66.5 (C2), 55.4 (OMe), 54.8 (C3), 51.5 (C6), 48.9 (C5), 27.7 (C4).

Data for **3d: HRMS** (ESI): calculated for $C_{32}H_{30}N_2O_5SNa$ $[M+Na]^+$ requires m/z 577.1773, found m/z 577.1764. **IR** (film) ν_{max}: 2980, 2888, 1541, 1511, 1372, 1159 cm^{-1}.

(5t): (±)-Methyl (2*S*,3*R*)-3-((*S*,*E*)-1,3-diphenylallyl)-2-(4-methoxyphenyl)piperidine-1-carboxylate and (±)-Methyl (2*S*,3*R*)-3-((*R*,*E*)-1,3-diphenylallyl)-2-(4-methoxyphenyl)-piperidine-1-carboxylate



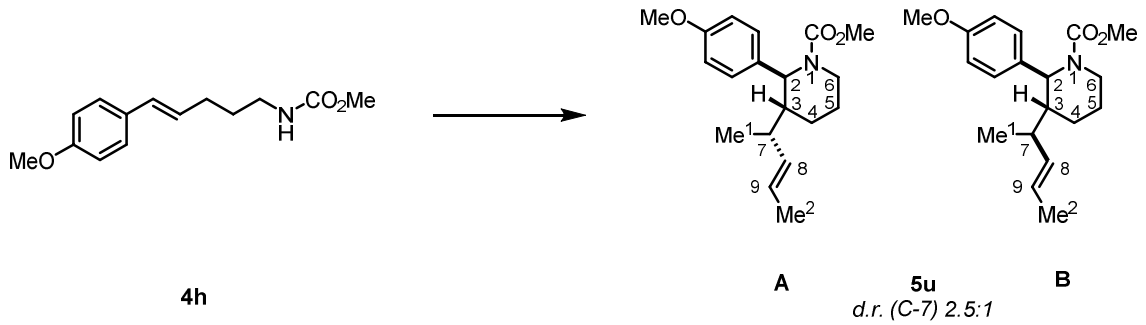
Prepared according to **General Procedure I** using **4h** (25 mg, 0.10 mmol) and (*E*)-1,3-diphenyl-2-propen-1-ol (21 mg, 0.10 mmol) at rt for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5t** a**s** an inseparable 8:1 mixture of diastereomers as a colourless oil (38 mg, 85%).

Data for **5t-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.39 – 7.29 (6H, m, Ar), 7.28 – 7.22 (3H, m, Ar), 7.19 – 7.15 (3H, m, Ar), 6.89 (2H, d, J = 8.8 Hz, Ar), 6.49 (1H, d, J = 15.6 Hz, C9-H), 6.37 (1H, dd, J = 15.7, 9.4 Hz, C8-H), 5.61 (1H, s, C2-H), 4.21 (1H, d, J = 14.0 Hz, C6-H_A), 3.80 (3H, s, OMe), 3.72 (3H, s, OMe), 3.67 (1H, d, J = 16.4 Hz, C7-H), 2.86 (1H, td, J = 13.2, 3.3 Hz, C6-H_B), 2.69 (1H, dp, J = 11.2, 2.2 Hz, C3-H), 1.71 (1H, dt, J = 13.0, 4.3 Hz, C5-H_A), 1.46 (1H, tt, J = 14.6, 4.2 Hz, C4-H_A), 1.30 – 1.16 (2H, m, C4-H_B + C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.4 (C Ar), 157.6 (CO), 143.0 (C Ar), 137.4 (C Ar), 132.9 (C8), 132.1 (C9), 129.1 (2 × C Ar), 128.6 (2 × C Ar), 127.9 (2 × C Ar), 127.6 (2 × C Ar), 127.4 (C Ar), 127.4 (C Ar), 126.6 (C Ar), 126.3 (2 × C Ar), 114.2 (2 × C Ar), 55.5 (OMe), 54.9 (C2), 52.9 (OMe), 50.3 (C7), 40.7 (C3), 39.9 (C6), 20.8 (C4), 20.0 (C5).

Partial data for **5t-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.11 – 7.01 (2H, m, Ar), 6.86 – 6.82 (2H, m, Ar), 4.99 (1H, *br.* s, C2-H), 3.78 (3H, s, OMe), 2.92 (1H, td, *J* = 13.1, 3.5 Hz, C6-H_B), 2.73 (1H, d, *J* = 11.6 Hz, C3-H), 1.85 (1H, m, C5-H_A), 1.36 (1H, d, *J* = 13.0 Hz, C5-H_B).**^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.4 (C Ar), 143. (C Ar), 132.2 (C9), 132.0 (C8), 130.6 (C Ar), 128.9 (2 × C Ar), 128.6 (2 × C Ar), 128.1 (2 × C Ar), 126.8 (C Ar), 126.3 (2 × C Ar), 114.1 (2 × C Ar), 55.4 (OMe), 54.6 (C7), 52.6 (OMe), 41.2 (C3), 21.4 (C4, 19.5 (C5).

Data for **5t**: **HRMS** (ESI): calculated for $C_{29}H_{31}O_3NNa$ $[M+Na]^+$ requires *m/z* 464.2196, found *m/z* 464.2195. **IR** (film) ν_{max}: 3649, 3059, 3025, 2981, 2954, 2836, 2358, 2338, 2246, 1691 cm^{-1}.

(5u): (±)-Methyl (2*S*,3*R*)-2-(4-methoxyphenyl)-3-((*S*,*E*)-pent-3-en-2-yl)piperidine-1-carboxylate and (±)-Methyl (2*S*,3*R*)-2-(4-methoxyphenyl)-3-((*R*,*E*)-pent-3-en-2-yl)piperidine-1-carboxylate



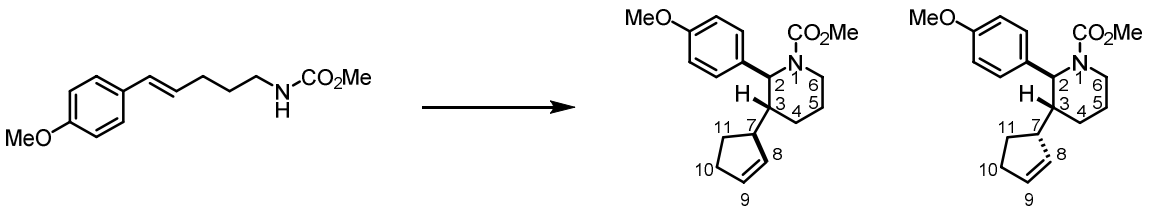
Prepared according to **General Procedure I** using **4h** (10 mg, 0.040 mmol) and 3-penten-2-ol (7 mg, 0.08 mmol, 2.0 equiv.) at 0 °C for 48 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5u** a**s** an inseparable 2.5:1 mixture of diastereomers as a colourless oil (12 mg, 95%).

Data for **5u-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.11 (2H, d, *J* = 8.9 Hz, Ar), 6.87 (2H, d, *J* = 8.8 Hz, Ar), 5.46 (1H, ddq, *J* = 15.0, 8.6, 6.3 Hz, C9-H), 5.36 (1H, *br.* s, C2-H), 5.31 (1H, ddd, *J* = 15.1, 8.8, 1.6 Hz, C8-H), 4.15 – 4.08 (1H, m, C6-H_A), 3.80 (3H, s, OMe), 3.70 (3H, s, OMe), 2.89 – 2.80 (1H, m, C6-H_B), 2.39 – 2.27 (1H, m, C7-H), 1.95 – 1.88 (1H, m, C3-H), 1.66 (3H, dd, *J* = 6.5, 1.6 Hz, Me^2), 1.69 – 1.57 (2H, m, C4-H_A + C5-H_A), 1.55 – 1.44 (1H, m, C4-H_B), 1.38 – 1.30 (1H, m, C5-H_B), 1.01 (3H, d, *J* = 6.7 Hz, Me^1). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.3 (C Ar), 157.4 (CO), 136.4 (C8), 132.7 (C Ar), 127.6 (2 × C Ar), 125.8 (C9), 114.1 (2 × C Ar), 55.5 (OMe), 55.4 (C2), 52.7 (OMe), 41.4 (C3), 40.1 (C6), 36.5 (C7), 20.6 (C4), 20.3 (C5), 18.5 (Me^1), 18.2 (Me^2).

Partial data for **5u-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.15 (2H, d, *J* = 8.9 Hz, Ar), 6.88 (2H, d, *J* = 9.0 Hz, Ar), 4.08 – 4.02 (1H, m, C6-H_A), 3.80 (3H, s, OMe), 3.73 (3H, s, OMe), 1.12 (3H, d, *J* = 6.6 Hz, Me^1). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.3 (C Ar), 157.4 (CO), 135.5 (C8), 132.5 (C Ar), 127.8 (2 × C Ar), 124.4 (C9), 55.4 (OMe), 54.9 (C2), 52.9 (OMe), 41.4 (C3), 39.8 (C6), 36.6 (C7), 21.5 (C4), 20.5 (Me^1), 20.1 (C5), 18.1 (Me^2).

Data for **5u**: **HRMS** (ESI): calculated for $C_{19}H_{28}O_3N$ $[M+H]^+$ requires *m/z* 318.2064, found *m/z* 318.2066. **IR** (film) ν_{max}: 3735, 3649, 2980, 2971, 2338, 4697, 1512, 1444, 1407, 1262 cm^{-1}.

(5v): (±)-Methyl (2*S*,3*R*)-3-((*R*)-cyclopent-2-en-1-yl)-2-(4-methoxyphenyl)piperidine-1-carboxylate and (±)-Methyl (2*S*,3*R*)-3-((*S*)-cyclopent-2-en-1-yl)-2-(4-methoxyphenyl)-piperidine-1-carboxylate



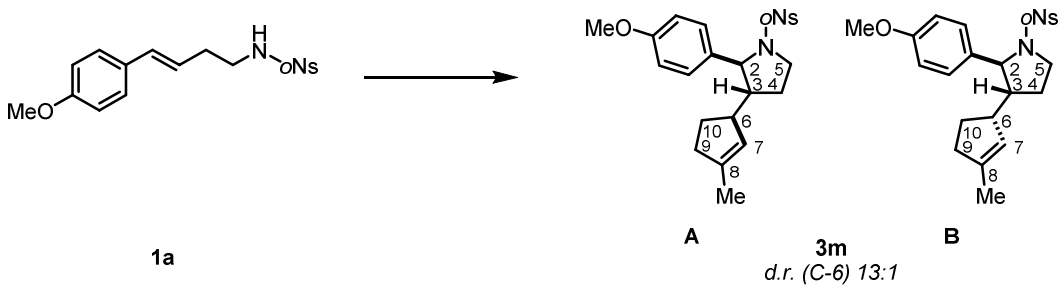
Prepared according to **General Procedure I** using **4h** (10 mg, 0.040 mmol) and **5v** (13 mg, 0.08 mmol, 2.0 equiv.) at 0 °C for 48 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5v** a**s** an inseparable 3.5:1 mixture of diastereomers as a colourless oil (12 mg, 95%).

Data for **5v-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.14 (2H, d, *J* = 8.9 Hz, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 5.83 (1H, dt, *J* = 6.4, 2.2 Hz, C8-H), 5.78 (1H, dq, *J* = 5.9, 2.1 Hz, C9-H), 5.31 (1H, s, C2-H), 4.14 – 4.04 (1H, m, C6-H_A), 3.80 (3H, s, OMe), 3.74 (3H, s, OMe), 3.07 – 2.96 (1H, m, C7-H), 2.86 (1H, td, *J* = 13.1, 3.5 Hz, C6-H_B), 2.45 – 2.38 (1H, m, C10-H_A), 2.38 – 2.30 (1H, m, C10-H_B), 2.25 (1H, ddd, *J* = 12.6, 8.3, 4.0 Hz, C11-H_A), 2.07 – 1.97 (1H, m, C3-H), 1.79 – 1.73 (1H, m, C5-H_A), 1.72 – 1.66 (1H, m, C4-H_A), 1.66 – 1.53 (2H, m, 1 × C4-H_B + 1 × C11-H_B), 1.36 (1H, ddd, *J* = 12.9, 5.2, 2.9 Hz, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.4 (C Ar), 157.5 (CO), 132.6 (C9), 132.2 (C8), 132.0 (C Ar), 127.7 (2 × C Ar), 114.1 (2 × C Ar), 56.3 (C2), 55.4 (OMe), 52.9 (COMe), 45.3 (C7), 41.9 (C3), 40.1 (C6), 32.2 (C10), 30.2 (C11), 22.2 (C4), 20.4 (C5).

Partial data for **5v-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 5.92 (1H, dq, *J* = 6.1, 2.1 Hz, C8-H), 5.82 – 5.80 (1H, m, C9-H), 5.42 (1H, d, *J* = 2.3 Hz, C2-H), 3.73 (3H, s, OMe), 2.09 – 2.05 (1H, m, C3-H), 1.51 – 1.45 (1H, m, C4-H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 157.4 (CO), 134.0 (C8), 131.6 (C9), 127.8 (2 × C Ar), 114.1 (2 × C Ar), 56.2 (C2), 45.3 (C7), 41.3 (C3), 40.0 (C6), 32.3 (C10), 29.9 (C11), 21.7 (C4), 20.3 (C3).

Data for **5v**: **HRMS** (ESI): calculated for $C_{19}H_{26}O_3N$ $[M+H]^+$ requires *m/z* 316.1907, found *m/z* 316.1910. **IR** (film) ν_{max}: 3735, 3649, 3050, 2981, 2971, 2954, 2868, 2380, 2341, 1697 cm^{-1}.

(3m): (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-[(1'*R*)-3-methylcyclopent-2-en-1-yl]-1-[(2-nitrophenyl)-sulfonyl]pyrrolidine and (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-[(1'*S*)-3-methylcyclopent-2-en-1-yl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidine



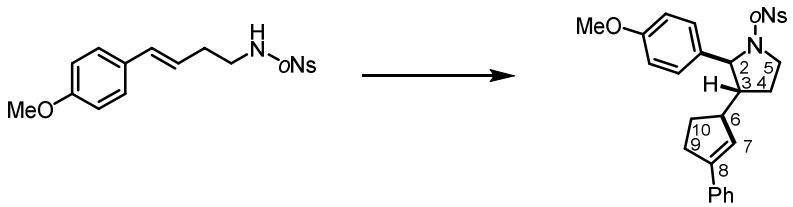
Prepared according to **General Procedure I** using **1a** (30 mg, 0.083 mmol) and **2l** (16 mg, 0.17 mmol, 2.0 equiv.) at 70 °C for 16 h. Flash column chromatography (gradient elution 10% → 20% EtOAc – pentane) afforded **3m** as an inseparable 13:1 mixture of diastereomers as a colourless oil (13 mg, 36%).

Data for **3m-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.42 – 7.51 (2H, m, Ar), 7.16 – 7.23 (2H, m, Ar), 7.04 (2H, d, *J* = 8.7 Hz, Ar), 6.58 (2H, d, *J* = 8.7 Hz, Ar), 5.20 – 5.24 (1H, m, C7-H), 4.54 (1H, d, *J* = 7.9 Hz, C2-H), 4.03 (1H, ddd, *J* = 10.7, 8.0, 3.0 Hz, C5-H_A), 3.73 – 3.79 (1H, m, C5-H_B), 3.72 (3H, s, OMe), 2.62 – 2.72 (1H, m, C6-H), 2.10 – 2.20 (3H, m, C3-H + C9-H_2), 2.05 (1H, dtd, *J* = 12.5, 6.2, 3.1 Hz, C4-H_A), 1.86 – 1.94 (1H, m, C10-H_A), 1.76 (dtd, J = 12.3, 9.8, 8.0 Hz, C4-H_B), 1.69 (1H, s, Me), 1.29 – 1.37 (1H, m, C10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 147.5 (C Ar), 142.8 (C Ar), 134.3 (C Ar), 133.0 (C8), 132.4 (C Ar), 131.0 (C Ar), 130.9 (C Ar), 129.1 (2 × C Ar), 125.3 (C7), 123.5 (C Ar), 113.6 (2 × C Ar), 67.6 (C2), 55.4 (C3 + OMe), 49.7 (C5), 47.1 (C6), 36.6 (C9), 29.5 (C10), 28.5 (C4), 16.8 (Me).

Partial data for **3m-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.42 – 7.51 (2H, m, Ar), 7.16 – 7.23 (2H, m, Ar), 7.04 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 5.03 – 5.07 (1H, m, C7-H), 4.57 (1H, d, *J* = 7.9 Hz, C2-H), 4.00 – 4.05 (1H, m, C5-H_A), 3.73 – 3.79 (1H, m, C5-H_B), 3.72 (3H, s, OMe), 2.62 – 2.72 (1H, m, C6-H), 2.10 – 2.20 (3H, m, C3-H + C9-H_2), 2.02 – 2.08 (1H, m, C4-H_A), 1.97 – 2.00 (1H, m, C10-H_A), 1.72 – 1.81 (1H, m, C4-H_B), 1.64 (1H, s, Me), 1.29 – 1.37 (1H, m, C10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 147.5 (C Ar), 141.9 (C Ar), 134.3 (C Ar), 133.0 (C8), 132.4 (C Ar), 131.0 (C Ar), 130.9 (C Ar), 129.0 (2 × C Ar), 126.3 (C7), 123.5 (C Ar), 113.7 (2 × C Ar), 67.7 (C2), 55.4 (OMe), 54.7 (C3), 49.4 (C5), 46.9 (C6), 36.4 (C9), 28.4 (C10), 27.7 (C4), 16.8 (Me).

Data for **3m**: **HRMS** (ESI): calculated for $C_{23}H_{27}N_2O_5S$ $[M+H]^+$ requires *m/z* 443.1641, found *m/z* 443.1635. **IR** (film) ν_{max}: 2980, 2889, 1543, 1512, 1374, 1249 cm^{-1}.

(3n): (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl)-3-[(1'*R*)-3-phenylcyclopent-2-en-1-yl]pyrrolidine



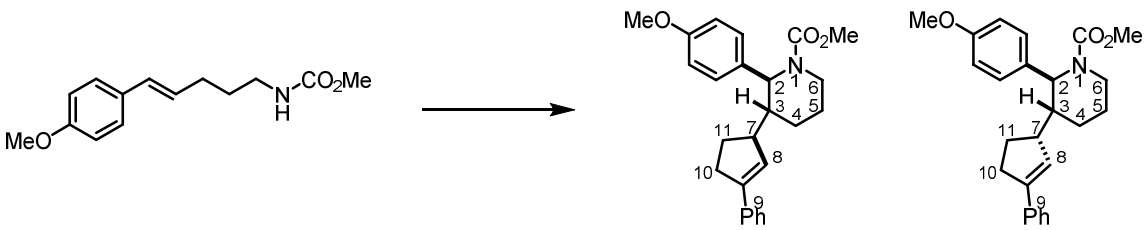
1a **3n**

Prepared according to **General Procedure I** using **1a** (31 mg, 0.086 mmol) and **2m** (14 mg, 0.086 mmol) at 0 °C for 48 h. Flash column chromatography (gradient elution 15% → 20% EtOAc – pentane) afforded **3n** as a colourless oil (43 mg, 99%).

Data for **3n: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.53 (1H, dd, *J* = 7.9, 1.4 Hz, Ar), 7.45 – 7.50 (1H, m, Ar), 7.38 – 7.42 (2H, m, Ar), 7.31 – 7.36 (2H, m, Ar), 7.24 – 7.28 (2H, m, Ar), 7.19 – 7.23 (1H, m, Ar), 7.10 (2H, d, *J* = 8.7 Hz, Ar), 6.62 (2H, d, *J* = 8.7 Hz, Ar), 6.07 (1H, q, *J* = 2.0 Hz, C7-H), 4.67 (1H, d, *J* = 8.0 Hz, C2-H), 4.09 (1H, ddd, *J* = 10.7, 8.0, 2.9 Hz, C5-H_A), 3.79 – 3.85 (1H, m, C5-H_B), 3.75 (3H, s, OMe), 2.93 – 3.00 (1H, m, C6-H), 2.61 – 2.72 (2H, m, C9-H_2), 2.35 (1H, ddt, *J* = 10.1, 8.0, 6.5 Hz, C3-H), 2.13 – 2.19 (1H, m, C4-H_A), 2.09 (1H, ddt, *J* = 13.2, 8.4, 4.2 Hz, C10-H_A), 1.82 – 1.91 (1H, m, C4-H_B), 1.54 (1H, ddt, *J* = 13.3, 8.6, 6.9 Hz, C10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar),

147.4 (C Ar), 144.2 (C Ar), 136.2 (C Ar), 134.2 (C Ar), 132.9 (C8), 132.5 (C Ar), 131.0 (C Ar), 130.9 (C Ar), 129.1 (2 × C Ar), 128.4 (C Ar), 127.5 (C7), 126.5 (2 × C Ar), 125.8 (C Ar), 123.6 (2 × C Ar), 113.7 (2 × C Ar), 67.8 (C2), 55.4 (OMe), 55.1 (C3), 49.7 (C5), 47.6 (C6), 32.9 (C9), 28.8 (C10), 28.7 (C4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between C2-H and C6-H, between C2-H and C7-H, between C2-H and C10-H_A, between C2-H and C10-H_B. **HRMS** (ESI): calculated for $C_{28}H_{29}N_2O_5S$ $[M+H]^+$ requires *m/z* 505.1797, found *m/z* 505.1792. **IR** (film) ν_{max}: 2980, 2889, 1729, 1514, 1369, 1150 cm^{-1}.

(5w): (±)-Methyl (2*S*,3*R*)-2-(4-methoxyphenyl)-3-((*R*)-3-phenylcyclopent-2-en-1-yl)piperidine-1-carboxylate and (±)-Methyl (2*S*,3*R*)-2-(4-methoxyphenyl)-3-((*S*)-3-phenylcyclopent-2-en-1-yl)-piperidine-1-carboxylate



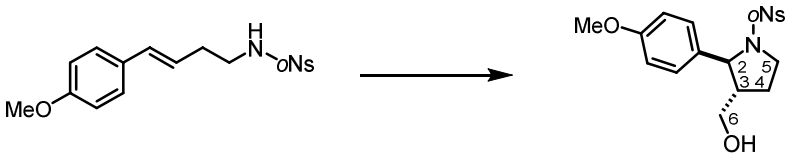
Prepared according to **General Procedure I** using **4h** (25 mg, 0.10 mmol) and **2m** (16 mg, 0.10 mmol). Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5w** a**s** an inseparable 11:1 mixture of diastereomers as a yellow oil (39 mg, 96%).

Data for **5w-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.51 – 7.43 (2H, m, Ar), 7.38 – 7.28 (2H, m, Ar), 7.28 – 7.21 (1H, m, Ar), 7.21 – 7.10 (2H, m, Ar), 6.93 – 6.84 (2H, m, Ar), 6.24 (1H, d, *J* = 2.0 Hz, C8-H), 5.36 (1H, s, C2-H), 4.21 – 4.06 (1H, m, C6-H_A), 3.81 (3H, s, OMe), 3.77 (3H, s, OMe), 3.23 – 3.14 (1H, m, C7-H), 2.89 (1H, td, *J* = 12.9, 3.5 Hz, C6-H_B), 2.84 – 2.80 (1H, m, C11-H_A), 2.77 – 2.70 (1H, m, C11-H_B), 2.43 (1H, dtd, *J* = 12.6, 8.5, 4.1 Hz, C10-H_A), 2.17 – 2.13 (1H, m, C3-H), 1.89 – 1.70 (3H, m, C4-H_A + C5-H_A + C10-H_B), 1.68 – 1.64 (1H, m, C4-H_B), 1.46 – 1.36 (1H, m, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.4 (C Ar), 157.5 (CO), 143.4 (C Ar), 136.7 (C Ar), 132.1 (C9), 128.5 (2 × C Ar), 127.7 (2 × C Ar), 127.6 (C8), 127.3 (C Ar), 125.8 (2 × C Ar), 114.1 (2 × C Ar), 56.1 (C2), 55.4 (OMe), 52.9 (OMe), 45.9 (C7), 41.9 (C3), 40.1 (C6), 32.7 (C11), 30.5 (C10), 22.3 (C4), 20.5 (C5).

Characteristic signals for **5w-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 6.37 (1H, s, C8-H), 5.52 (1H, s, C2-H), 3.74 (3H, s, OMe).

Data for **5w**: **HRMS** (ESI): calculated for $C_{25}H_{29}O_3NNa$ $[M+Na]^+$ requires *m/z* 414.2040, found *m/z* 414.2040. **IR** (film) ν_{max}: 2946, 1695, 1612, 1511, 1445, 1408, 1345, 1250, 1179, 1122 cm^{-1}.

(3o): (±)-((2*S*,3*S*)-2-(4-Methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)pyrrolidin-3-yl)methanol

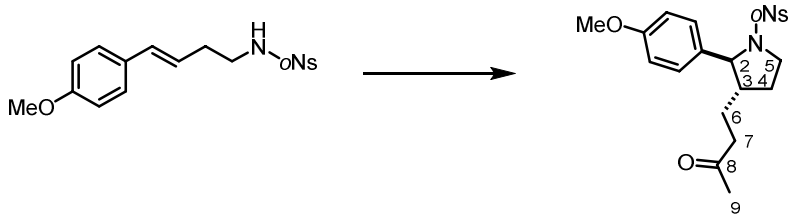


1a **3o**

Prepared according to **General Procedure I** using **1a** (26 mg, 0.071 mmol) and paraformaldehyde (prilled, 43 mg, 1.43 mmol, 20 equiv.) at 0 °C for 48 h. Flash column chromatography (gradient elution 20% → 30% EtOAc – pentane) afforded **3o** as a colourless oil (20 mg, 74%).

Data for **3o: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.46 – 7.53 (2H, m, Ar), 7.34 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.22 – 7.27 (1H, m, Ar), 7.07 (2H, d, *J* = 8.7 Hz, Ar), 6.62 (2H, d, *J* = 8.7 Hz, Ar), 4.70 (1H, d, *J* = 6.9 Hz, C2-H), 3.99 (1H, ddd, *J* = 10.3, 8.0, 4.2 Hz, C5-H_A), 3.76 – 3.84 (1H, m, C5-H_B), 3.72 (3H, s, OMe), 3.59 – 3.64 (1H, m, C6-H_A), 3.53 – 3.59 (1H, m, C6-H_B), 2.33 – 2.41 (1H, m, C3-H), 2.10 – 2.19 (1H, m, C4-H_A), 1.85 (1H, dq, *J* = 12.5, 8.4 Hz, C4-H_B), 1.60 (1H, *br.* s, *OH*). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 147.5 (C Ar), 133.8 (C Ar), 132.8 (C Ar), 132.6 (C Ar), 131.1 (C Ar), 131.1 (C Ar), 128.5 (2 × C Ar), 123.7 (C Ar), 113.8 (2 × C Ar), 65.7 (C2), 63.0 (C6), 55.4 (OMe), 52.3 (C3), 49.4 (C5), 27.7 (C4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between C2-H and C6-H_A, between C2-H and C6-H_B. **HRMS** (ESI): calculated for $C_{18}H_{20}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 415.0940, found *m/z* 415.0925. **IR** (film) ν_{max}: 3649, 2980, 2888, 2360, 1382, 1154 cm^{-1}.

(3p): (±)-4-((2*S*,3*S*)-2-(4-Methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)pyrrolidin-3-yl)butan-2-one

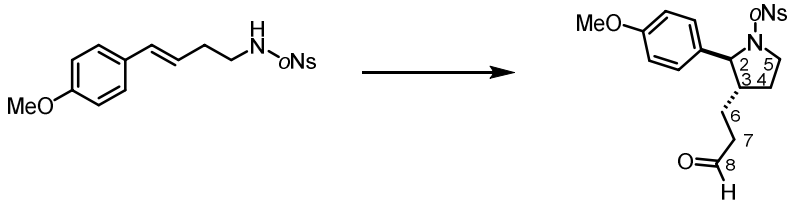


1a **3p**

Prepared according to **General Procedure I** using **1a** (36 mg, 0.10 mmol) and methyl vinyl ketone (70 mg, 1.0 mmol, 10 equiv.) at 70 °C for 16 h. Flash column chromatography (gradient elution 10% → 15% EtOAc – pentane) afforded **3p** as a colourless oil (38 mg, 87%).

Data for **3p**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.50 (1H, dd, *J* = 7.8, 1.3 Hz, Ar), 7.46 (1H, ddd, *J* = 8.0, 6.9, 1.8 Hz, Ar), 7.23 – 7.16 (2H, m, Ar), 7.04 (2H, d, *J* = 8.6 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 4.38 (1H, d, *J* = 7.9 Hz, C2-H), 4.06 (1H, ddd, *J* = 10.4, 8.0, 2.2 Hz, C5-H_A), 3.74 (1H, dt, *J* = 10.5, 5.3 Hz, C5-H_B), 3.72 (3H, s, OMe), 2.41 (1H, ddd, *J* = 17.5, 9.2, 6.1 Hz, C7-H_A), 2.36 – 2.29 (1H, m, C7-H_B), 2.17 – 2.07 (2H, m, C3-H + C4-H_A), 2.00 (3H, s, C9-H_3), 1.72 – 1.51 (3H, m, C4-HB + C6-H_2). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 207.9 (C8), 159.3 (C Ar), 147.4 (C Ar), 134.2 (C Ar), 132.6 (C Ar), 131.9 (C Ar), 131.0 (C Ar), 130.9 (C Ar), 129.0 (2 × C Ar), 123.6 (C Ar), 113.8 (2 × C Ar), 69.3 (C2), 55.4 (OMe), 49.6 (C5), 49.6 (C3), 41.7 (C7), 31.0 (C4), 29.9 (C9), 25.7 (C6). **NOESY- 2D (500 MHz, $CDCl_3$)**: between C2-H and C6-H_A, between C2-H and C6-H_B, between C2-H and C7-H_A. **HRMS** (ESI): calculated for $C_{21}H_{25}N_2O_6S$ $[M+H]^+$ requires *m/z* 433.1428, found *m/z* 433.1431. **IR** (film) ν_{max}: 2926, 1715, 1543, 1513, 1371, 1248, 1162, 1067, 1033, 779 cm^{-1}.

(3q): (±)-3-((2*S*,3*S*)-2-(4-Methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)pyrrolidin-3-yl)propanal

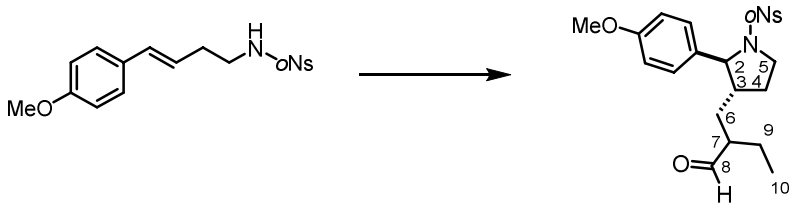


1a **3q**

Prepared according to **General Procedure I** using **1a** (36 mg, 0.10 mmol) and acrolein (56 mg, 1.0 mmol, 10.0 equiv.) at 50 °C for 16 h. Flash column chromatography (gradient elution 10% → 20% EtOAc – pentane) afforded **3q** as a colourless oil (32 mg, 77%).

Data for **1a**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 9.64 (1H, t, *J* = 1.3 Hz, C8-H), 7.51 (1H, dd, *J* = 7.6, 1.2 Hz, Ar), 7.46 (1H, ddd, *J* = 8.0, 6.1, 2.6 Hz, Ar), 7.24 – 7.16 (2H, m, Ar), 7.03 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 4.39 (1H, d, *J* = 7.9 Hz, C2-H), 4.07 (1H, ddd, *J* = 9.8, 7.2, 1.6 Hz, C5-H_A), 3.80 – 3.73 (1H, m, C5-H_B), 3.72 (3H, s, OMe), 2.49 – 2.27 (2H, m, C7-H_2), 2.23 – 2.07 (2H, m, C3-H + C4-H_A), 1.79 – 1.69 (1H, m, C6-H_A), 1.69 – 1.57 (2H, m, C4-H_B + C6-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 201.3 (C8), 159.4 (C Ar), 147.4 (C Ar), 134.1 (C Ar), 132.6 (C Ar), 131.6 (C Ar), 131.0 (C Ar), 131.0 (C Ar), 129.0 (2 × C Ar), 123.6 (C Ar), 113.8 (2 × C Ar), 69.3 (C2), 55.4 (OMe), 49.7 (C3), 49.5 (C5), 42.1 (C7), 30.9 (C4), 24.0 (C6). **NOESY-2D (600 MHz, $CDCl_3$)**: between C2-H and C6-H, between C2-H and C7-H. **HRMS** (ESI): calculated for $C_{20}H_{22}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 441.1091, found *m/z* 441.1089. **IR** (film) ν_{max}: 2933, 1720, 1544, 1513, 1372, 1249, 1163, 1033, 853, 779, 740 cm^{-1}.

(3r): (±)-(*R*)-2-(((2*S*,3*S*)-2-(4-Methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)pyrrolidin-3-yl)methyl)butanal and (±)-(*S*)-2-(((2*S*,3*S*)-2-(4-Methoxyphenyl)-1-((2-nitrophenyl)-sulfonyl)pyrrolidin-3-yl)methyl)butanal



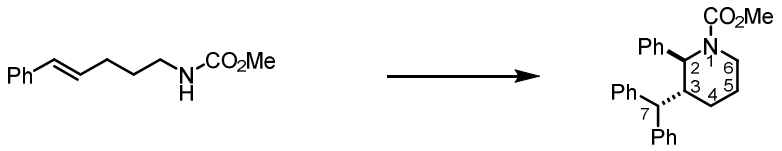
1a **3r-A + 3r-B**
d.r. (C-7): 1:1

Prepared according to **General Procedure I** using **1a** (36 mg, 0.10 mmol) and 2-ethyl acrolein (84 mg, 1.0 mmol, 10 equiv.) at 70 °C for 16 h. Flash column chromatography (gradient elution 10% → 15% EtOAc – pentane) afforded **3r** a**s** an inseparable 1:1 mixture of diastereomers as a colourless oil (32 mg, 72%).

Data for **3r-A** + **3r-B**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 9.46 (1H, d, *J* = 2.4 Hz, C8-$H_{A/B}$), 9.35 (1H, d, *J* = 3.2 Hz, C8-$H_{A/B}$), 7.51 (2H, ddd, *J* = 7.7, 3.1, 1.2 Hz, Ar, *A*+*B*), 7.49 – 7.42 (2H, m, Ar, *A*+*B*), 7.25 – 7.16 (2H, m, Ar, *A*+*B*), 7.03 (2H, d, *J* = 8.6 Hz, Ar, *A*/*B*), 7.02 (2H, d, *J* = 8.6 Hz, Ar, *A*/*B*), 6.60 (2H, d, *J* = 8.7 Hz, Ar, *A*/*B*), 6.59 (2H, d, *J* = 8.7 Hz, Ar, *A*/*B*), 4.40 (1H, d, *J* = 8.1 Hz, C2-H, *A*/*B*), 4.36 (1H, d, *J* = 8.0 Hz, C2-H, *A*/*B*), 4.07 (2H, dtd, *J* = 10.4, 7.9, 2.4 Hz, C5-H_A, *A*+*B*), 3.77 – 3.73 (2H, m, C5-H_B, *A*+*B*), 3.72 (6H, s, OMe, *A*+*B*), 2.21 – 2.09 (5H, m, C3-H + C6-H_A + C7-H_A, *A*+*B*), 1.77 – 1.66 (2H, m, C4-H_A, *A*+*B*), 1.66 – 1.60 (2H, m, C6-H_B, *A*+*B*), 1.59 – 1.49 (2H, m, C9-H_A, *A*+*B*), 1.49 – 1.37 (4H, m, C4-H_B + C9-H_B, *A*+*B*), 0.83 (3H, t, *J* = 7.5 Hz, C10-H_3, *A*/*B*), 0.76 (3H, t, *J* = 7.5 Hz, C10-H_3, *A*/*B*). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 204.5 (C8, *A*/*B*), 204.5 (C8, *A*/*B*), 159.4 (C Ar, *A*/*B*), 159.4 (C Ar, *A*/*B*), 147.4 (C Ar, *A*/*B*), 147.4 (C Ar, *A*/*B*), 134.2 (C Ar, *A*/*B*), 134.2 (C Ar, *A*/*B*), 132.6 (C Ar, *A*/*B*), 132.6 (C Ar, *A*/*B*), 131.6 (C Ar, *A*/*B*), 131.4 (C Ar, *A*/*B*), 131.0 (C Ar, *A*/*B*), 131.0 (C Ar, *A*/*B*), 131.0 (C Ar, *A*/*B*), 130.9 (C Ar, *A*/*B*), 129.1 (2 × C Ar, *A*/*B*), 129.0 (2 × C Ar, *A*/*B*), 123.7 (C Ar, *A*+*B*), 113.8 (2 × C Ar, *A*/*B*), 113.8 (2 × C Ar, *A*/*B*), 69.6 (C2, *A*/*B*), 69.4 (C2, *A*/*B*), 55.4 (OMe, *A*/*B*), 55.4 (OMe, *A*/*B*), 51.6 (C7, *A*/*B*), 51.6 (C7, *A*/*B*), 49.6 (C5, *A*/*B*), 49.5 (C5, *A*/*B*), 48.1 (C3, *A*/*B*), 47.8 (C3, *A*/*B*), 31.3 (C6, *A*/*B*), 31.1 (C6, *A*/*B*), 30.6 (C4, *A*/*B*), 30.2 (C4, *A*/*B*), 22.5 (C9, *A*/*B*), 22.0 (C9, *A*/*B*), 11.4 (C10, *A*/*B*), 11.1 (C10, *A*/*B*). **HRMS** (ESI): calculated for

$C_{22}H_{26}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 469.1404, found *m/z* 469.1405. **IR** (film) ν_{max}: 2964, 1720, 1544, 1371, 1249, 1163, 1032, 852, 778, 703 cm^{-1}.

(5z): (±)-Methyl (2*S*,3*R*)-3-benzhydryl-2-phenylpiperidine-1-carboxylate

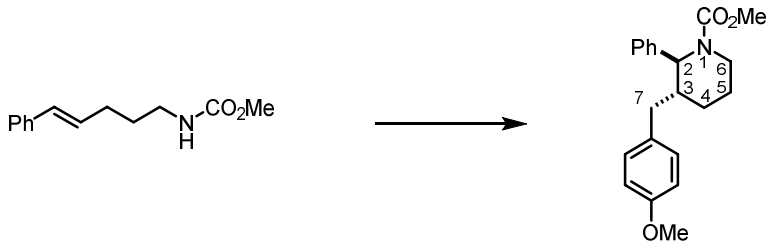


4i **5z**

Prepared according to **General Procedure I** using **4i** (18 mg, 0.08 mmol) and benzhydrol (15 mg, 0.08 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5z** as a colourless oil (20 mg, 65%).

Data for **5z**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.41 (4H, ddd, *J* = 8.1, 4.8, 1.4 Hz, Ar), 7.35 (2H, dd, *J* = 8.5, 6.6 Hz, Ar), 7.32 – 7.26 (4H, m, Ar), 7.25 – 7.20 (3H, m, Ar), 7.20 – 7.12 (2H, m, Ar), 5.18 (1H, s, C2-H), 4.27 (1H, *br.* s, C6-H_A), 4.20 (1H, d, *J* = 12.0 Hz, C7-H), 3.54 (3H, *br.* s, OMe), 3.25 (1H, ddt, *J* = 12.2, 4.3, 2.1 Hz, C3-H), 2.96 – 2.77 (1H, m, C6-H_B), 1.78 (1H, d, *J* = 13.3 Hz, C5-H_A), 1.52 (1H, tt, *J* = 13.5, 4.1 Hz, C4-H_A), 1.47 – 1.39 (1H, m, C4-H_B), 1.29 – 1.21 (2H, m, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 157.6 (CO), 144.1 (C Ar), 143.4 (C Ar), 140.2 (C Ar), 128.9 (2 × C Ar), 128.9 (2 × C Ar), 128.9 (2 × C Ar), 128.1 (2 × C Ar), 128.0 (2 × C Ar), 126.8 (C Ar), 126.7 (C Ar), 126.5 (C Ar), 126.3 (2 × C Ar), 55.5 (C2), 52.4 (OMe), 52.5 (C7), 40.1 (C6), 39.9 (C3), 21.0 (C4), 19.6 (C5). **HRMS** (ESI): calculated for $C_{26}H_{28}O_2N$ $[M+H]^+$ requires m/z 386.2115, found m/z 386.2118. **IR** (film) ν_{max}: 2948, 1696, 1599, 1494, 1446, 1408, 1348, 1266, 1191, 1132 cm^{-1}.

(5aa): (±)-Methyl (2*S*,3*R*)-3-(4-methoxybenzyl)-2-phenylpiperidine-1-carboxylate

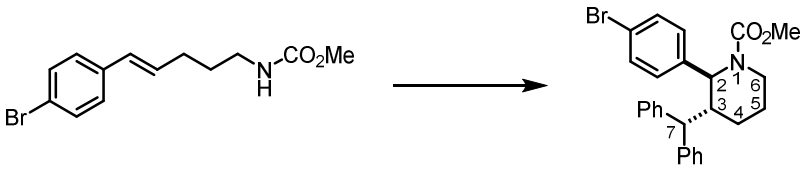


4i **5aa**

Prepared according to **General Procedure I** using **4i** (9 mg, 0.04 mmol) and 4-methoxybenzyl alcohol (5.5 mg, 0.040 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) afforded **5aa** as a colourless oil (10 mg, 74%).

Data for **5aa**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.32 (2H, t, *J* = 7.7 Hz, Ar), 7.24 – 7.12 (5H, m, Ar), 6.85 (2H, d, *J* = 8.6 Hz, Ar), 5.22 (1H, s, C2-H), 4.22 – 4.12 (1H, m, C6-H_A), 3.79 (3H, s, OMe), 3.77 (3H, s, OMe), 2.93 – 2.80 (2H, m, C6-H_B + C7-H_A), 2.72 (1H, dd, *J* = 13.7, 6.8 Hz, C7-H_B), 2.59 (1H, q, *J* = 6.8, 5.0 Hz, C3-H), 1.82 (1H, tdt, *J* = 13.0, 9.2, 4.6 Hz, C5-H_A), 1.69 – 1.55 (1H, m, C4-H_A), 1.49 (1H, dd, *J* = 13.5, 3.6 Hz, C4-H_B), 1.38 (1H, dq, *J* = 13.3, 3.4 Hz, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.1 (C Ar), 157.6 (C8), 140.2 (C Ar), 132.9 (C Ar), 130.2 (2 × C Ar), 128.7 (2 × C Ar), 126.7 (C Ar), 126.6 (2 × C Ar), 114.0 (2 × C Ar), 56.7 (C2), 55.4 (OMe), 52.9 (C9), 40.4 (C6), 38.4 (C3), 37.3 (C7), 23.5 (C4), 20.2 (C5). **HRMS** (ESI): calculated for $C_{21}H_{25}O_3N$ $[M+H]^+$ requires *m*/*z* 340.1907, found *m*/*z* 340.1908. **IR** (film) ν_{max}: 2942, 1697, 1512, 1445, 1408, 1247, 1179, 1126, 1035, 807 cm^{-1}.

(5ab): (±)-Methyl (2*S*,3*R*)-3-benzhydryl-2-(4-bromophenyl)piperidine-1-carboxylate

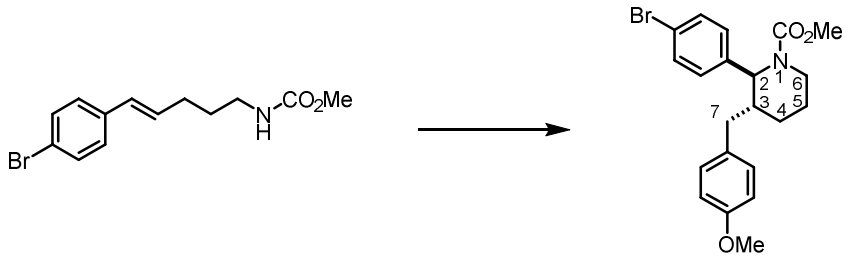


4j **5ab**

Prepared according to **General Procedure I** using **4j** (12 mg, 0.040 mmol) and benzhydrol (7.5 mg, 0.08 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) afforded **5ab** as a colourless oil (12 mg, 65%).

Data for **5ab**: **^{1}H NMR (500 MHz, $CDCl_3$)** 7.46 (2H, d, *J* = 8.6 Hz, Ar), 7.42 – 7.35 (4H, m, Ar), 7.29 (4H, td, *J* = 7.7, 5.8 Hz, Ar), 7.20 – 7.13 (2H, m, Ar), 7.09 (2H, d, *J* = 7.5 Hz, Ar), 5.11 (1H, *br.* s, C2-H), 4.25 (1H, *br.* s, C6-H_A), 4.17 (1H, d, *J* = 12.0 Hz, C7-H), 3.58 (3H, *br.* s, OMe), 3.17 (1H, ddt, *J* = 12.1, 4.0, 2.2 Hz, C3-H), 2.93 – 2.76 (1H, m, C6-H_B), 1.84 – 1.69 (1H, m, C5-H_A), 1.49 – 1.41 (2H, m, C4-H_2), 1.29 – 1.22 (1H, m, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 157.4 (CO), 143.9 (C Ar), 143.1 (C Ar), 139.4 (C Ar), 131.9 (2 × C Ar), 129.0 (2 × C Ar), 128.9 (2 × C Ar), 128.2 (2 × C Ar), 128.1 (2 × C Ar), 128.0 (2 × C Ar), 126.8 (C Ar), 126.6 (C Ar), 120.6 (C Ar), 55.2 (C2), 52.7 (OMe), 52.4 (C7), 40.0 (C3 + C6), 21.0 (C4), 19.5 (C6). **HRMS** (ESI): calculated for $C_{26}H_{27}O_2N^{78}Br$ $[M+H]^+$ requires *m/z* 464.1220, found *m/z* 464.1220. **IR** (film) ν_{max}: 2949, 1694, 1489, 1445, 1410, 1347, 1262, 1191, 1131, 1075 cm^{-1}.

(5ac): (±)-Methyl (2*S*,3*R*)-2-(4-bromophenyl)-3-(4-methoxybenzyl)piperidine-1-carboxylate



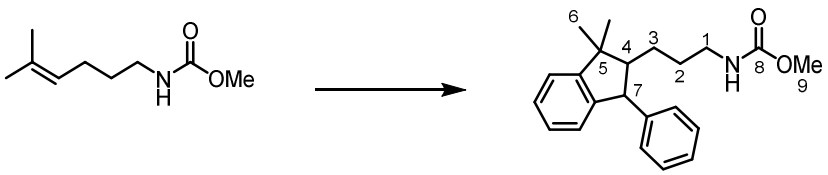
4j **5ac**

Prepared according to **General Procedure I** using **4j** (12 mg, 0.04 mmol) and 4-methoxybenzyl alcohol (5.5 mg, 0.040 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) afforded **5ac** as a colourless oil (10 mg, 60%).

Data for **5ac**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.43 (2H, d, *J* = 8.6 Hz, Ar), 7.15 (2H, d, *J* = 8.6 Hz, Ar), 7.04 (2H, d, *J* = 8.6 Hz, Ar), 6.85 (2H, d, *J* = 8.6 Hz, Ar), 5.15 (1H, *br.* s, C2-H), 4.21 – 4.12 (1H, m, C6-H_A), 3.79 (3H, s, OMe), 3.76 (3H, s, OMe), 2.86 – 2.80 (2H, m, C6-H_B + C7-H_A), 2.69 (1H, dd, *J* = 13.8, 6.8 Hz, C7-H_B), 2.56 – 2.43 (1H, m, C3-H), 1.88 – 1.73 (1H, m, C5-H_A), 1.57 (1H, tdd, *J* = 12.9, 8.7, 4.4 Hz, C4-H_A), 1.52 – 1.46 (1H, m, C4-H_B), 1.39 (1H, dd, *J* = 13.5, 3.7 Hz, C5-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.2 (C Ar), 157.4 (CO), 139.4 (C Ar), 132.6 (C Ar), 131.8 (2 × C Ar), 130.2 (2 × C Ar), 128.5 (2 × C Ar), 120.6 (C Ar), 114.0 (2 × C Ar), 56.4 (C2), 55.4 (OMe), 53.0 (OMe), 40.3 (C6), 38.5 (C3), 37.3 (C7), 23.4 (C4), 20.1 (C5). **HRMS** (ESI): calculated for $C_{21}H_{25}O_3N^{79}Br$ $[M+H]^+$

requires m/z 418.1012, found m/z 418.1012. **IR** (film) ν_{max}: 2941, 1696, 1512, 1488, 1443, 1409, 1247, 1179, 1127, 1037 cm^{-1}.

(4k): Methyl (3-(1,1-dimethyl-3-phenyl-2,3-dihydro-1H-inden-2-yl)propyl)carbamate

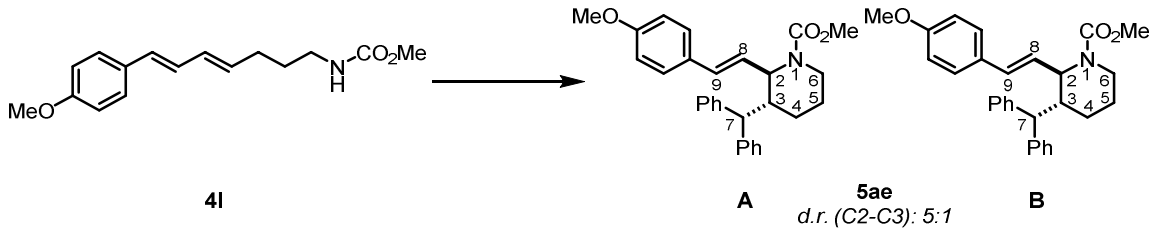


4k **27**

Prepared according to **General Procedure I** using **4k** (14 mg, 0.080 mmol) and benzhydrol (15 mg, 0.080 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) afforded **27** as a colourless oil (20 mg, 84%).

Data for **27**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.36 – 7.27 (2H, m, Ar), 7.29 – 7.16 (5H, m, Ar), 7.08 (1H, ddd, J = 7.5, 5.9, 2.4 Hz, Ar), 6.79 – 6.62 (1H, m, Ar), 4.43 (1H, *br.* s, NH), 3.87 (1H, dd, J = 10.5, 1.2 Hz, C7-H), 3.63 (3H, s, C9-H_3), 3.09 – 2.96 (2H, m, C1-H_2), 2.13 (1H, ddd, J = 10.6, 7.4, 6.1 Hz, C4-H), 1.72 – 1.44 (2H, m, C3-H_2), 1.42 (3H, s, 1 × C6-H_3), 1.41 – 1.21 (2H, m, C2-H), 1.09 (3H, s, 1 × C6-H_3). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 152.8 (C8), 145.5 (C Ar), 144.4 (C Ar), 129.1 (2 × C Ar), 128.6 (2 × C Ar), 127.1 (C Ar), 126.7 (C Ar), 126.7 (C Ar), 124.8 (C Ar), 121.8 (C Ar), 59.9 (C4), 56.4 (C7), 52.1 (C9), 41.5 (C2), 29.3 (C2), 27.7 (C6), 26.7 (C3), 24.0 (C6). **HRMS** (ESI): calculated for $C_{22}H_{28}O_2N$ $[M+H]^+$ requires m/z 338.2115, found m/z 338.2121. **IR** (film) ν_{max}: 3649, 3331, 3078, 2980, 2359, 2342, 1697, 1536, 1449, 1256 cm^{-1}.

(5ae): (±)-Methyl (2*R*,3*R*)-3-benzhydryl-2-((*E*)-4-methoxystyryl)piperidine-1-carboxylate and (±)-Methyl (2*R*,3*S*)-3-benzhydryl-2-((*E*)-4-methoxystyryl)piperidine-1-carboxylate



Prepared according to **General Procedure I** using **4l** (10 mg, 0.040 mmol) and benzhydrol (7.5 mg, 0.040 mmol) at 0 °C for 48 h. Flash column chromatography (gradient elution 0% → 25% EtOAc – pentane) afforded **5ae** as a colourless oil (12 mg, 65%).

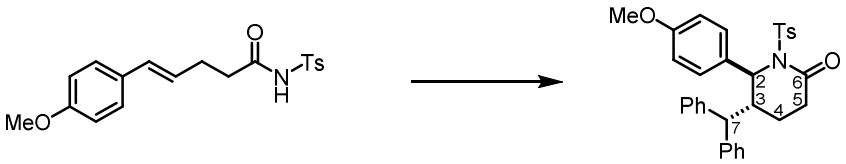
Characteristic data for **5ae-A**, 1.5:1 mixture of rotamers *A:B* (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.35 – 7.11 (12H, m, Ar), 6.92 – 6.85 (2H, m, Ar), 6.24 (1H, dt, *J* = 16.2, 8.2 Hz, C8-H, *A*+*B*), 5.99 (1H, d, *J* = 15.7 Hz, C9-H, *A*), 5.91 (1H, d, *J* = 15.7 Hz, C9-H, *B*), 4.93 (1H, *br.* s, C2-H, *A*), 4.75 (1H, *br.* s, C2-H, *B*), 4.17 – 4.07 (1H, m, C6-H_A, *A*), 4.01 – 3.94 (1H, m, C6-H_A, *B*), 3.83 (3H, s, OMe), 3.67 (1H, s, OMe, *A*), 3.64 (1H, s, OMe, *B*), 3.54 (1H, *br.* s, C7-H, *A*), 3.52 (1H, *br.* s, C7-H, *B*), 3.01 (1H, *ap.* q, *J* = 13.7 Hz, C6-H_B, *A*+*B*), 2.64 – 2.52 (1H, m, C3-H, *A*+*B*), 1.78 – 1.62 (1H, m, C5-H_A, *A*+*B*), 1.55 – 1.40 (2H, m, C4-H_A + C5-H_B, *A*+*B*), 1.40 – 1.29 (1H, m, C4-H_B, *A*+*B*). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 156.0 (CO, *A*+*B*), 134.6 (C9, *A*), 133.9 (C9, *B*), 119.6 (C8, *B*), 119.1 (C8, *A*), 55.8 (C2, *A*+*B*), 55.6 (C7, *A*+*B*), 55.5 (OMe, *A*), 55.4 (OMe, *B*), 52.8 (OMe, *B*), 52.6 (OMe, *A*), 43.4 (C3, *B*), 43.0 (C3, *A*), 40.0 (C6, *A*), 39.7 (C6, *B*), 26.0 (C5, *A*), 25.7 (C5, *B*), 24.9 (C4, *A*), 24.8 (C4, *B*).

Characteristic data for **5ae-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 6.11 (1H, dd, *J* = 4.9 Hz, C9-H), 4.74 (1H, *br.* s, C2-H), 4.13 (1H, d, *J* = 12.1 Hz, C8-H), 3.83 (3H, s, OMe), 2.72 (1H, *ap.* d, *J* = 12.2 Hz, C3-H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 156.4 (CO), 129.9 (C9), 129.8 (C8), 55.4 (OMe), 54.3 (OMe), 52.1 (C7), 41.8 (C3).

Data for **5ae**: **HRMS** (ESI): calculated for $C_{29}H_{31}O_3NNa$ $[M+Na]^+$ requires m/z 464.2196, found m/z 464.2193. **IR** (film) ν_{max}: 3027, 2953, 2858, 1695, 1607, 1511, 1445, 1250, 1032, 706 cm^{-1}. Aromatic signals for **5ae-A+B** (from the mixture): **^{13}C NMR (126 MHz, $CDCl_3$) δ** 159.4, 159.3, 143.8, 143.7,

143.4, 142.5, 142.2, 128.9, 128.8, 128.8, 128.4, 128.1, 128.1, 127.8, 127.7, 127.6, 126.6, 126.6, 126.4, 126.4, 114.2, 114.1, 114.1.

(5am): (±)-(5*R*,6*S*)-5-Benzhydryl-6-(4-methoxyphenyl)-1-tosylpiperidin-2-one

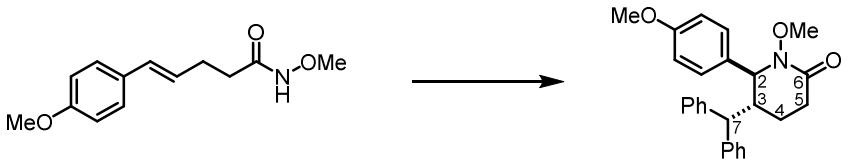


4r **5am**

Prepared according to **General Procedure I** using **4r** (36.0 mg, 0.100 mmol) and benzhydrol (18.5 mg, 0.100 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) afforded **5am** as a colourless oil (12 mg, 19%).

Data for **5am**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.60 (2H, d, *J* = 8.4 Hz, Ar), 7.51 – 7.48 (2H, m, Ar), 7.44 (2H, t, *J* = 7.7 Hz, Ar), 7.33 – 7.28 (3H, m, Ar), 7.28 – 7.23 (2H, m, Ar), 7.20 (2H, d, *J* = 8.2 Hz, Ar), 7.19 – 7.15 (1H, m, Ar), 6.92 (2H, d, *J* = 8.6 Hz, Ar), 6.82 (2H, d, *J* = 8.7 Hz, Ar), 5.47 (1H, *br.* s, C2-H), 3.92 (1H, d, *J* = 12.2 Hz, C7-H), 3.80 (3H, s, OMe), 2.92 – 2.80 (1H, m, C3-H), 2.51 (1H, ddd, *J* = 19.5, 12.3, 7.5 Hz, C5-H_A), 2.45 – 2.33 (4H, m, C5-H_B + TsMe), 1.82 (1H, dddd, *J* = 14.3, 11.7, 7.1, 4.1 Hz, C4-H_A), 1.43 – 1.34 (1H, m, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 170.7 (C6), 159.1 (C Ar), 144.8 (C Ar), 142.3 (C Ar), 142.1 (C Ar), 136.0 (C Ar), 133.6 (C Ar), 130.0 (2 × C Ar), 129.5 (2 × C Ar), 129.1 (2 × C Ar), 128.9 (2 × C Ar), 128.2 (2 × C Ar), 127.7 (2 × C Ar), 127.6 (C Ar), 127.4 (2 × C Ar), 127.0 (C Ar), 114.1 (2 × C Ar), 62.0 (C2), 55.5 (OMe), 52.2 (C7), 44.3 (C3), 29.4 (C5), 21.8 (Ts), 17.6 (C4). **HRMS** (ESI): calculated for $C_{32}H_{32}NO_4S$ $[M+H]^+$ requires *m*/*z* 526.2047, found *m*/*z* 526.2042. **IR** (film) ν_{max}: 2925, 1692, 1513, 1359, 1251, 1169, 1087, 833, 737, 677, 652 cm^{-1}.

(5an): (±)-(5*R*,6*S*)-5-Benzhydryl-1-methoxy-6-(4-methoxyphenyl)piperidin-2-one

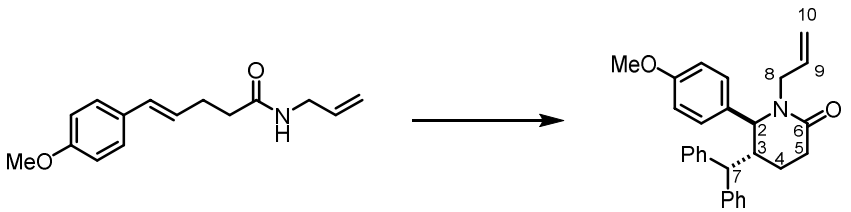


4s **5an**

Prepared according to **General Procedure I** using **4a** (24.0 mg, 0.100 mmol) and benzhydrol (18.5 mg, 0.100 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) afforded **5an** as a colourless oil (15 mg, 37%).

Data for **5an**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.53 – 7.45 (2H, m, Ar), 7.40 (2H, t, *J* = 7.7 Hz, Ar), 7.36 – 7.32 (2H, m, Ar), 7.31 – 7.25 (4H, m, Ar), 7.21 – 7.16 (1H, m, Ar), 7.02 (2H, d, *J* = 8.6 Hz, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 4.67 (1H, *br.* s, C2-H), 4.08 (1H, d, *J* = 12.0 Hz, C7-H), 3.79 (3H, s, OMe), 3.61 (3H, s, OMe), 2.90 (1H, dq, *J* = 12.1, 2.9 Hz, C3-H), 2.58 (1H, ddd, *J* = 18.1, 12.8, 6.7 Hz, C5-H_A), 2.44 (1H, ddd, *J* = 18.0, 6.4, 1.8 Hz, C5-H_B), 1.85 – 1.75 (1H, m, C4-H_A), 1.45 – 1.31 (1H, m, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 167.4 (C6), 159.2 (C Ar), 143.1 (C Ar), 142.1 (C Ar), 132.8 (C Ar), 129.5 (2 × C Ar), 129.1 (2 × C Ar), 128.0 (2 × C Ar), 127.7 (2 × C Ar), 127.4 (C Ar), 127.2 (2 × C Ar), 127.1 (C Ar), 114.2 (2 × C Ar), 64.4 (C2), 61.5 (OMe), 55.5 (OMe), 52.2 (C7), 45.4 (C3), 28.7 (C5), 17.8 (C4). **HRMS** (ESI): calculated for $C_{26}H_{28}NO_3$ $[M+H]^+$ requires *m/z* 402.2064, found *m/z* 402.2063. **IR** (film) ν_{max}: 2934, 1667, 1513, 1336, 1251, 1178, 979, 736, 708 cm^{-1}.

(5ao): (±)-(5*R*,6*S*)-1-Allyl-5-benzhydryl-6-(4-methoxyphenyl)piperidin-2-one

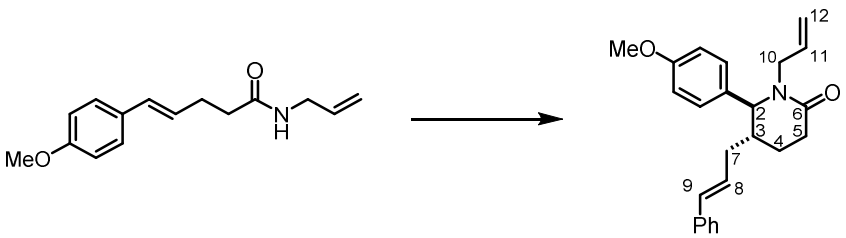


4t **5ao**

Prepared according to **General Procedure I** using **4t** (30 mg, 0.10 mmol) and benzhydrol (18.5 mg, 0.100 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) afforded **5ao** as a yellow oil (30 mg, 73%).

Data for **5ao**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.46 – 7.39 (2H, m, Ar), 7.39 – 7.30 (4H, m, Ar), 7.30 – 7.21 (3H, m, Ar), 7.20 – 7.12 (1H, m, Ar), 6.96 (2H, d, *J* = 8.6 Hz, Ar), 6.88 (2H, d, *J* = 8.6 Hz, Ar), 5.64 (1H, dddd, *J* = 17.0, 10.0, 8.3, 4.9 Hz, C9-H), 4.94 (1H, dd, *J* = 10.2, 1.6 Hz, C10-H), 4.86 (dq, *J* = 17.1, 1.3 Hz, C10-H), 4.72 (1H, ddt, *J* = 14.6, 5.1, 1.5 Hz, C8-H_A), 4.36 (1H, s, C2-H), 3.99 (1H, d, *J* = 12.2 Hz, C7-H), 3.80 (3H, s, OMe), 2.82 (1H, dd, *J* = 14.6, 8.3 Hz, C8-H_B), 2.75 (1H, dq, *J* = 12.2, 2.9 Hz, C3-H), 2.49 (1H, ddd, *J* = 19.4, 12.7, 7.0 Hz, C5-H_A), 2.39 (1H, ddd, *J* = 18.7, 6.9, 1.5 Hz, C5-H_B), 1.84 (1H, tdd, *J* = 13.0, 6.8, 3.8 Hz, C4-H_A), 1.43 – 1.34 (1H, m, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 170.3 (C6), 159.1 (C Ar), 143.2 (C Ar), 142.6 (C Ar), 133.7 (C Ar), 132.7 (C9), 129.1 (2 × C Ar), 129.0 (2 × C Ar), 128.3 (2 × C Ar), 127.7 (2 × C Ar), 127.5 (2 × C Ar), 127.1 (C Ar), 126.8 (C Ar), 118.8 (C10), 114.2 (2 × C Ar), 61.3 (C2), 55.4 (OMe), 52.1 (C7), 48.5 (C8), 43.7 (C3), 27.4 (C5), 17.5 (C4). **HRMS** (ESI): calculated for $C_{28}H_{30}NO_2$ $[M+H]^+$ requires *m/z* 412.2271, found *m/z* 412.2281. **IR** (film) ν_{max}: 2931, 1637, 1511, 1464, 1250, 1174, 1033, 925, 707 cm^{-1}.

(5ap): (±)-(5*R*,6*S*)-1-Allyl-5-cinnamyl-6-(4-methoxyphenyl)piperidin-2-one



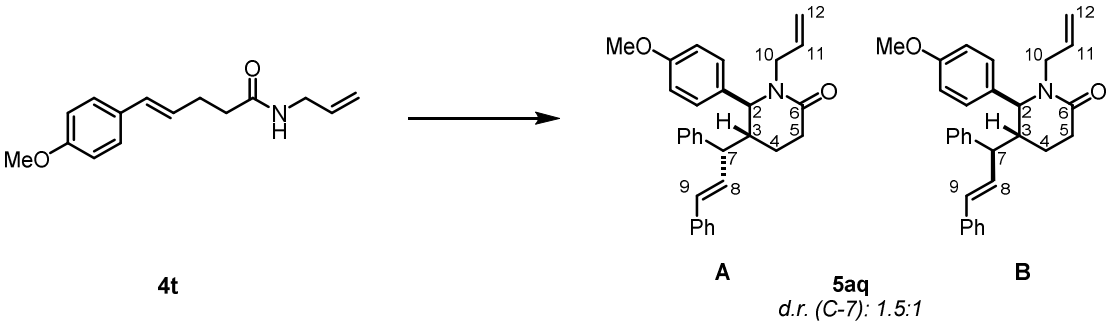
4t **5ap**

Prepared according to **General Procedure I** using **4t** (30 mg, 0.10 mmol) and cinnamyl alcohol (13.5 mg, 0.100 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) afforded **5ap** as a yellow oil (23 mg, 63%).

Data for **5ap**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.35 – 7.28 (4H, m, Ar), 7.22 (1H, td, *J* = 6.8, 1.7 Hz, Ar), 7.08 (2H, d, *J* = 8.6 Hz, Ar), 6.89 (2H, d, *J* = 8.6 Hz, Ar), 6.42 (1H, d, *J* = 15.9 Hz, C9-H), 6.13 (1H, dt, *J* = 15.2, 7.3 Hz, C8-H), 5.73 (1H, dddd, *J* = 17.7, 10.1, 8.0, 4.4 Hz, C11-H), 5.13 (1H, dt, *J* = 10.4, 1.7 Hz, C12-H), 5.04 – 4.97 (1H, m, C12-H), 4.75 (1H, ddt, *J* = 14.9, 4.3, 1.7 Hz, C10-H_A), 4.30 (1H, d, *J* = 5.0 Hz, C2-H), 3.81 (3H, s, OMe), 2.92 (1H, dd, *J* = 15.0, 8.0 Hz, C10-H_B), 2.62 – 2.43 (2H, m, C5-H_2), 2.43 – 2.33 (1H, m, C7-H_A), 2.26 – 2.19 (1H, m, C7-H_A), 1.94 (1H, ddtd, *J* = 23.6, 12.2, 6.0, 3.1 Hz, C4-H_A), 1.55 (1H, dq, *J* = 13.1, 6.4 Hz, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 170.4 (C6),

159.3 (C Ar), 137.4 (C Ar), 133.2 (C Ar), 133.1 (C11), 132.9 (C9), 128.7 (2 × C Ar), 128.3 (2 × C Ar), 127.5 (C Ar), 127.5 (C8), 126.2 (2 × C Ar), 118.0 (C12), 114.3 (2 × C Ar), 64.2 (C2), 55.5 (OMe), 47.5 (C10), 41.4 (C3), 35.5 (C7), 29.8 (C5), 22.1 (C4). **HRMS** (ESI): calculated for $C_{24}H_{28}NO_2$ $[M+H]^+$ requires *m/z* 362.2155, found *m/z* 362.2124. **IR** (film) ν_{max}: 1613, 1512, 1412, 1304, 1177, 1032, 928, 833, 699 cm^{-1}.

(5aq): (±)-(5*R*,6*S*)-1-Allyl-5-((*S*,*E*)-1,3-diphenylallyl)-6-(4-methoxyphenyl)piperidin-2-one and (±)-(5*R*,6*S*)-1-Allyl-5-((*R*,*E*)-1,3-diphenylallyl)-6-(4-methoxyphenyl)piperidin-2-one



Prepared according to **General Procedure I** using **4t** (30 mg, 0.10 mmol) and (*E*)-1,3-diphenyl-2-propen-1-ol (21 mg, 0.10 mmol) at 70 °C for 16 h. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) afforded **5aq** as an inseparable 1.5:1 mixture of diastereomers as a yellow oil (30 mg, 69%).

Data for **5aq-A** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.41 – 7.34 (3H, m, Ar), 7.34 – 7.26 (6H, m, Ar), 7.25 – 7.18 (3H, m, Ar), 7.07 (2H, d, *J* = 8.6 Hz, Ar), 6.92 – 6.86 (2H, m, Ar), 6.53 (1H, d, *J* = 15.6 Hz, C9-H), 6.36 (1H, dd, *J* = 15.6, 9.4 Hz, C8-H), 5.86 (1H, dddd, *J* = 17.1, 10.1, 8.5, 4.7 Hz, C11-H), 5.10 (1H, d, *J* = 10.2 Hz, C12-H), 5.08 – 5.02 (1H, m, C12-H), 4.84 (1H, ddt, *J* = 14.7, 4.8, 1.6 Hz, C10-H_A), 4.79 (1H, *br.* s, C2-H), 3.81 (3H, s, OMe), 3.59 – 3.50 (1H, m, C7-H), 2.95 (1H, dd, *J* = 14.6, 8.5 Hz, C10-H_B), 2.63 – 2.58 (1H, m, C5-H_A), 2.44 (1H, dd, *J* = 12.1, 6.8 Hz, C5-H_B), 2.25 – 2.20 (1H, m, C3-H), 1.83 – 1.69 (1H, m, C4-H_A), 1.25 – 1.17 (1H, m, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 170.4 (C6), 133.2 (C11), 132.6 (C9), 132.1 (C8), 118.8 (C12), 61.5 (C2), 55.4 (OMe), 50.1 (C7), 48.5 (C10), 44.7 (C3), 27.8 (C5), 17.6 (C4).

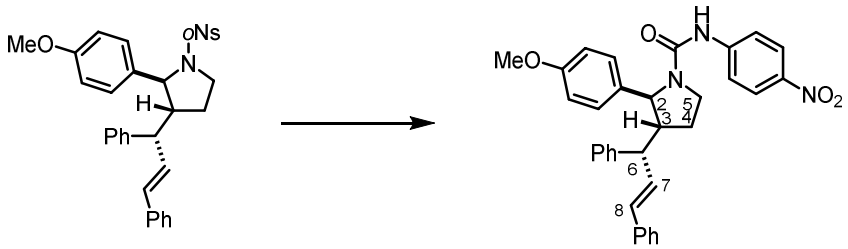
Partial data for **5aq-B** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 6.52 (1H, d, *J* = 15.7 Hz, C9-H), 6.28 (1H, dd, *J* = 15.6, 9.8 Hz, C8-H), 5.70 (1H, dddd, *J* = 17.1, 10.1, 8.3, 4.9 Hz, C11-H), 4.70

(1H, ddt, J = 14.6, 4.9, 1.5 Hz, C10-H_A), 4.23 (1H, s, C2-H), 3.80 (3H, s, OMe), 2.85 (1H, dd, J = 14.6, 8.3 Hz, C10-H_B), 2.36 (1H, dd, J = 6.9, 2.1 Hz, C5-H_B), 2.33 – 2.26 (1H, m, C3-H), 1.90 (1H, dddd, J = 15.1, 11.7, 6.5, 3.3 Hz, C4-H_A), 1.83 – 1.76 (1H, m, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 170.4 (C6), 132.8 (C11), 131.3 (C9), 130.9 (C8), 118.7 (C12), 61.4 (C2), 55.4 (OMe), 49.9 (C7), 48.4 (C10), 45.2 (C3), 27.8 (C5), 18.0 (C4).

Data for **5aq**: **HRMS** (ESI): calculated for $C_{30}H_{31}NO_2Na$ $[M+Na]^+$ requires m/z 460.2247, found m/z 460.2260. Aromatic signals for **5aq-A+B** (from the mixture): **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.1, 142.8, 142.0, 137.0, 133.6, 133.4, 129.1, 129.1, 128.7, 128.6, 128.1, 127.8, 127.6, 127.6, 127.6, 127.1, 126.9, 126.3, 114.2, 114.2. **IR** (film) ν_{max}: 1636, 1511, 1494, 1494, 1267, 1175, 1033, 927, 736, 646 cm^{-1}.

6.2.4 Product derivatisations

(15): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-*N*-(4-nitrophenyl)-pyrrolidine-1-carboxamide

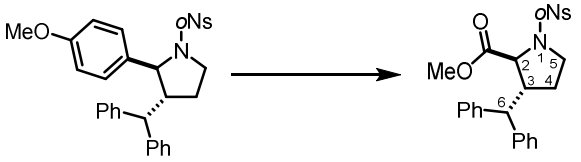


3d **15**

Prepared according to **General Procedure J** using **3d** (33 mg, 0.06 mmol), LiOH (4.5 mg, 0.18 mmol) and thioglycolic acid (0.008 mL, 0.088 mmol). The crude material was re-dissolved in CH_2Cl_2 (1 mL) and Et_3N (0.01 mL, 0.07 mmol) and 4-nitrophenylisocyanate (12 mg, 0.073 mmol) added. After 16 h the solvent was removed *in vacuo*. Flash column chromatography (gradient elution 1% → 5% MeOH – CH_2Cl_2) afforded **15** as a yellow solid (25 mg, 78%).

Data for **15**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.07 – 7.98 (3H, m, Ar), 7.36 – 7.14 (12H, m, Ar), 6.89 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (1H, d, *J* = 9.0 Hz, Ar), 6.51 (1H, d, *J* = 15.7 Hz, C8-H), 6.46 (1H, *br.* s, *N*H), 6.21 (1H, dd, *J* = 15.7, 9.3 Hz, C7-H), 4.76 – 4.64 (1H, *br.* s, C2-H), 3.89 (1H, dt, *J* = 11.0, 7.3 Hz, C5-H_A), 3.79 (3H, s, OMe), 3.74 – 3.65 (1H, m, C5-H_B), 3.44 (1H, t, *J* = 9.8 Hz, C6-H), 2.76 – 2.59 (1H, m, C3-H), 1.97 (1H, dq, *J* = 14.1, 7.2 Hz, C4-H_A), 1.61 (1H, ddt, *J* = 13.0, 7.4, 5.5 Hz, C4-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.7 (C Ar), 153.2 (CO), 145.3 (C Ar), 142.4 (C Ar), 142.3 (C Ar), 136.8 (C Ar), 132.1 (C7), 131.4 (C8), 129.1 (2 × C Ar), 128.7 (2 × C Ar), 128.0 (C Ar), 127.8 (2 × C Ar), 127.2 (C Ar), 126.5 (2 × C Ar), 126.4 (2 × C Ar), 125.1 (2 × C Ar), 118.0 (2 × C Ar), 115.0 (2 × C Ar), 113.5 (C Ar), 65.1 (C2), 55.5 (OMe), 55.5 (C3), 53.3 (C6), 46.4 (C5), 27.0 (C4). **HRMS** (ESI): calculated for $C_{33}H_{32}N_3O_4$ $[M+H]^+$ requires *m/z* 534.2387, found *m/z* 534.2388. **IR** (film) ν_{max}: 3655, 2981, 2918, 2850, 2361, 2341, 1380, 1250, 1137 cm^{-1}. **mp** (240 – 242 °C, EtOAc).

(29): (±)-Methyl (2*S*,3*R*)-3-benzhydryl-1-((2-nitrophenyl)sulfonyl)pyrrolidine-2-carboxylate

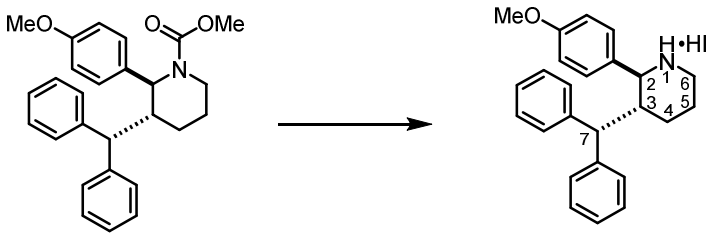


3a **29**

To a solution of **3a** (55 mg, 0.10 mmol) in a 2:2:3 mixture of CCl_4:MeCN:pH 7 buffer (Na_2HPO_4) (1.0 mL) was added $NaIO_4$ (445 mg, 2.08 mmol) at 0 °C. After 15 min $RuCl_3$ (1.0 mg, 5.0 mol%) was added and the reaction mixture allowed to warm up to rt before being stirred vigorously for 16 h. The reaction mixture was diluted with Et_2O and 1.0 M HCl. The aqueous later was extracted with Et_2O and the combined organic layers were washed with 1.0 M HCl and dried over $MgSO_4$ before concentrating *in vacuo*. The crude residue was re-dissolved in a 9:1 PhMe:MeOH mixture (1.0 mL) and trimethylsilyldiazomethane solution (2.0 M in Et_2O) was added dropwise until the yellow colour persisted. After 15 min the solvent was removed *in vacuo*. Flash column chromatography (gradient elution 10% → 25% EtOAc – pentane) afforded **29** as a colourless oil (25 mg, 52%).

Data for **29**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.99 (1H, dd, *J* = 7.9, 1.4 Hz, Ar), 7.73 – 7.67 (1H, m, Ar), 7.67 – 7.58 (2H, m, Ar), 7.28 – 7.23 (6H, m, Ar), 7.22 – 7.15 (4H, m, Ar), 4.27 (1H, d, *J* = 2.4 Hz, C2-H), 3.83 (1H, dt, *J* = 9.4, 7.7 Hz, C5-H_A), 3.71 (1H, d, *J* = 12.0 Hz, C6-H), 3.70 – 3.63 (1H, m, C5-H_B), 3.52 (3H, s, OMe), 3.31 (1H, ddt, *J* = 12.2, 6.5, 3.0 Hz, C3-H), 2.07 (1H, dtd, *J* = 16.3, 8.2, 5.7 Hz, C4-H_A), 1.71 (1H, ddt, *J* = 12.6, 7.8, 4.1 Hz, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 172.2 (CO), 148.2 (C Ar), 142.6 (C Ar), 142.4 (C Ar), 133.6 (C Ar), 133.1 (C Ar), 131.8 (C Ar), 131.2 (C Ar), 129.0 (4 × C Ar), 128.1 (2 × C Ar), 128.0 (2 × C Ar), 127.1 (C Ar), 127.0 (C Ar), 124.2 (C Ar), 64.5 (C2), 54.1 (C6), 52.6 (OMe), 48.4 (C3), 47.6 (C5), 28.6 (C4). **HRMS** (ESI): calculated for $C_{25}H_{25}N_2O_6S$ $[M+H]^+$ requires *m/z* 481.1429, found *m/z* 481.1428. **IR** (film) ν_{max}: 2981, 2361, 2312, 1745, 1544, 1453, 1372, 1215, 1032 cm^{-1}.

(32a): (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)piperidin-1-ium iodide

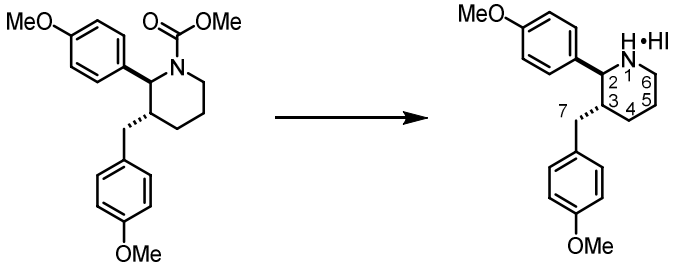


5p **32a**

Prepared according to **General Procedure K** using **5a** (37 mg, 0.089 mmol), trimethylsilyl iodide (38 μL, 0.27 mmol) in $CHCl_3$ (3.0 mL) at 55 °C for 2 h. Flash column chromatography (gradient elution 0% → 5% MeOH – CH_2Cl_2) afforded **32a** as an off white waxy solid (39 mg, 86%).

Data for **32a**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 8.75 – 8.41 (2H, m, Ar), 7.48 (2H, d, *J* = 8.2 Hz, Ar), 7.29 – 7.24 (3H, m, Ar), 7.22 (2H, t, *J* = 7.7 Hz, Ar), 7.17 – 7.12 (1H, m, Ar), 7.09 (2H, d, *J* = 8.3 Hz, Ar), 6.93 – 6.88 (2H, m, Ar), 6.87 – 6.79 (2H, m, Ar), 3.95 (1H, d, *J* = 3.7 Hz, C7-H), 3.77 (3H, s, OMe), 3.69 (1H, d, *J* = 11.2 Hz, C2-H), 3.17 (1H, tt, *J* = 11.5, 3.4 Hz, C3-H), 2.91 – 2.78 (1H, m, C6-H_A), 2.52 (1H, t, *J* = 12.7 Hz, C6-H_B), 2.18 – 2.00 (2H, m, C4-H_A + C5-H_A), 1.72 (1H, dt, *J* = 14.5, 2.9 Hz, C5-H_B), 1.36 (1H, qd, *J* = 13.1, 3.5 Hz, C4-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 160.0 (C Ar), 142.6 (C Ar), 140.4 (C Ar), 130.7 (C Ar), 130.6 (2 × C Ar), 128.4 (4 × C Ar), 128.2 (4 × C Ar), 127.0 (C Ar), 126.2 (C Ar), 114.4 (2 × C Ar), 64.7 (C7), 55.4 (OMe), 50.6 (C2), 46.0 (C6), 43.0 (C3), 26.4 (C5), 23.7 (C4). **NOESY-2D (600 MHz, $CDCl_3$)**: between C2-H and C6-H_B, between C2-H and C4-H_B, between C3-H and C5-H_A. **HRMS** (ESI): calculated for $C_{25}H_{28}ON$ $[M+H]^+$ requires *m*/*z* 358.2165, found *m*/*z* 358.2162. **IR** (film) ν_{max}: 2981, 2930, 2360, 2341, 1611, 1515, 1451, 1255, 1181, 1302 cm^{-1}.

(32b): (±)-(2*S*,3*R*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)piperidin-1-ium iodide

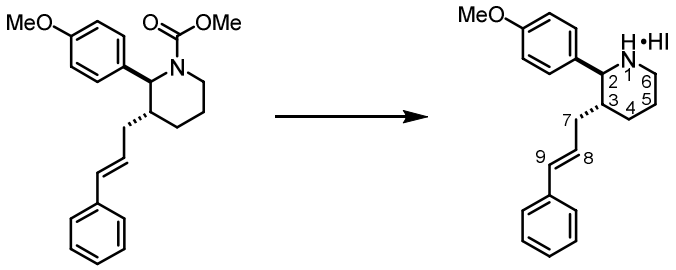


5q **32b**

Prepared according to **General Procedure K** using **5q** (38 mg, 0.10 mmol), trimethylsilyl iodide (44 μL, 0.30 mmol) in $CHCl_3$ (3.0 mL) at 55 °C for 2 h. Flash column chromatography (gradient elution 0% → 5% MeOH – CH_2Cl_2) afforded **32b** as an off white waxy solid (42 mg, 93%).

Data for **32b**: **^{1}H NMR (400 MHz, MeOD) δ** 7.47 (2H, d, *J* = 8.7 Hz, Ar), 7.06 (2H, d, *J* = 8.8 Hz, Ar), 6.92 (2H, d, *J* = 8.6 Hz, Ar), 6.79 (2H, d, *J* = 8.7 Hz, Ar), 3.93 (2H, d, *J* = 10.8 Hz, C2-H), 3.84 (3H, s, OMe), 3.74 (3H, s, OMe), 3.46 – 3.28 (1H, m, C6-H_A), 3.10 (1H, td, *J* = 12.9, 3.3 Hz, C6-H_B), 2.43 (1H, dd, *J* = 13.0, 2.8 Hz, C7-H_A), 2.26 – 2.04 (1H, m, C7-H_B), 1.99 – 1.83 (2H, m, 1 × C4-H_A + 1 × C5-H_A), 1.74 (1H, qt, *J* = 14.2, 4.0 Hz, C4-H_B), 1.44 – 1.25 (1H, m, C5-H_B). **^{13}C NMR (101 MHz, MeOD) δ** 162.1 (C Ar), 159.7 (C Ar), 131.8 (C Ar), 131.1 (2 × C Ar), 130.7 (2 × C Ar), 129.0 (C Ar), 115.9 (2 × C Ar), 114.9 (2 × C Ar), 66.4 (C2), 55.9 (OMe), 55.7 (OMe), 46.6 (C6), 42.6 (C3), 38.6 (C7), 29.5 (C5), 23.8 (C4). **HRMS** (ESI): calculated for $C_{20}H_{26}O_2N$ $[M+H]^+$ requires *m/z* 312.1958, found *m/z* 312.1957. **IR** (film) ν_{max}: 2935, 17096, 1692, 1676, 1586, 1513, 1349, 1363, 1247, 1198 cm^{-1}.

(32c): (±)-(2*S*,3*R*)-3-Cinnamyl-2-(4-methoxyphenyl)piperidin-1-ium iodide

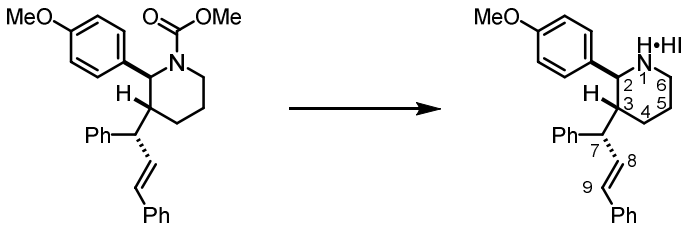


5r **32c**

Prepared according to **General Procedure K** using **5r** (46 mg, 0.13 mmol), trimethylsilyl iodide (50 μL, 0.39 mmol) in $CHCl_3$ (3.0 mL) at 55 °C for 2 h. Flash column chromatography (gradient elution 0% → 5% MeOH – CH_2Cl_2) afforded **32c** as a white waxy solid (44 mg, 80%).

Data for **32c**: **^{1}H NMR (400 MHz, MeOD) δ** 7.44 (2H, d, *J* = 8.7 Hz, Ar), 7.31 – 7.22 (4H, m, Ar), 7.20 – 7.14 (1H, m, Ar), 7.04 (1H, d, *J* = 8.8 Hz, Ar), 6.20 (1H, d, *J* = 15.8 Hz, C9-H), 6.03 (1H, ddd, *J* = 15.7, 8.1, 6.5 Hz, C8-H), 3.98 (1H, d, *J* = 11.2 Hz, C2-H), 3.81 (3H, s, OMe), 3.39 (1H, ddd, *J* = 12.6, 3.9, 1.8 Hz, C6-H_A), 3.15 (1H, td, *J* = 13.0, 3.4 Hz, C6-H_B), 2.26 – 2.04 (3H, m, 1 × C3-H + 1 × C5-H_A + 1 × C7-H_A), 2.04 – 1.93 (3H, m, 2 × C4-H_2 + 1 × C7-H_B), 1.93 – 1.82 (1H, m, C5-H_B). **^{13}C NMR (101 MHz, MeOD) δ** 162.3 (C Ar), 138.6 (C Ar), 134.0 (C9), 130.7 (2 × C Ar), 129.5 (2 × C Ar), 128.3 (C Ar), 128.2 (C Ar), 127.0 (2 × C Ar), 126.9 (C8), 115.9 (2 × C Ar), 66.0 (C2), 55.9 (OMe), 46.4 (C6), 40.7 (C3), 36.9 (C7), 29.8 (C5), 23.6 (C4). **HRMS** (ESI): calculated for $C_{21}H_{26}ON$ $[M+H]^+$ requires *m/z* 308.2009, found *m/z* 308.2012. **IR** (film) ν_{max}: 3024, 2957, 2934, 2837, 2069, 1612, 1516, 1256, 1182, 1030, 968, 826, 746 cm^{-1}.

(32d): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)piperidin-1-ium iodide



5w **32d**

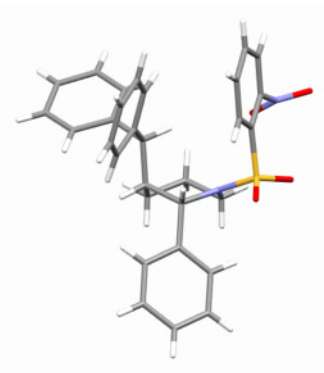
Prepared according to **General Procedure K** using **5w** (22 mg, 0.056 mmol), trimethylsilyl iodide (24 μL, 0.17 mmol), isoprene (0.060 mL, 0.58 mmol) in $CHCl_3$ (2.5 mL) at 55 °C for 2 h. Flash column chromatography (gradient elution 0% → 5% MeOH – CH_2Cl_2 + 1% Et_3N) afforded **32d** as a yellow oil (24 mg, 87%).

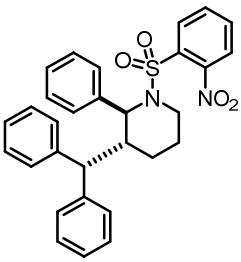
Data for **32d**: **^{1}H NMR (400 MHz, MeOD) δ** 7.48 (2H, d, *J* = 8.7 Hz, Ar), 7.34 – 7.27 (2H, m, Ar), 7.25 – 7.07 (8H, m, Ar), 6.97 (2H, d, *J* = 8.9 Hz, Ar), 6.28 (1H, dd, *J* = 15.8, 8.5 Hz, C8-H), 6.13 (1H, d, *J* = 15.8 Hz, C9-H), 3.97 (1H, d, *J* = 11.5 Hz, C2-H), 3.71 (3H, s, OMe), 3.48 – 3.42 (1H, m, C7-H), 3.36 – 3.32 (1H, m, C6-H_A), 3.11 – 2.99 (1H, m, C6-H_B), 2.72 (1H, tdd, *J* = 11.7, 5.8, 3.3 Hz, C3-H), 2.13 – 2.03 (1H, m, C5-H_A), 2.03 – 1.94 (1H, m, C4-H_A), 1.94 – 1.83 (1H, m, C4-H_B), 1.56 – 1.45 (1H, m, C5-H_B). **^{13}C NMR (101 MHz, MeOD) δ** 142.0 (C Ar), 138.6 (C Ar), 132.7 (C Ar), 131.6 (C Ar), 131.6 (C8), 131.5 (C9), 129.9 (2 × C Ar), 129.6 (2 × C Ar), 129.3 (2 × C Ar), 128.3 (C Ar), 128.1 (2 × C Ar), 127.8 (C Ar), 127.2 ((2 × C Ar), 115.9 (2 × C Ar), 65.4 (C2), 55.9 (OMe), 52.4 (C7), 46.2 (C6), 44.9 (C3),

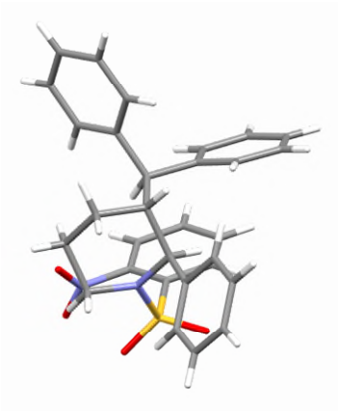
27.7 (C5), 23.5 (C4). **HRMS** (ESI): calculated for $C_{27}H_{30}ON$ $[M+H]^+$ requires m/z 384.2322, found m/z 384.2314. **IR** (film) ν_{max}: 2361, 1612, 1543, 1494, 1279, 1118, 1033, 969, 671 cm^{-1}.

6.2.5 X-ray crystallography

X-ray Crystallographic data for (5e): (±)-(2*S*,3*R*)-3-Benzhydryl-1-((2-nitrophenyl)-sulfonyl)-2-phenylpiperidine, 7372





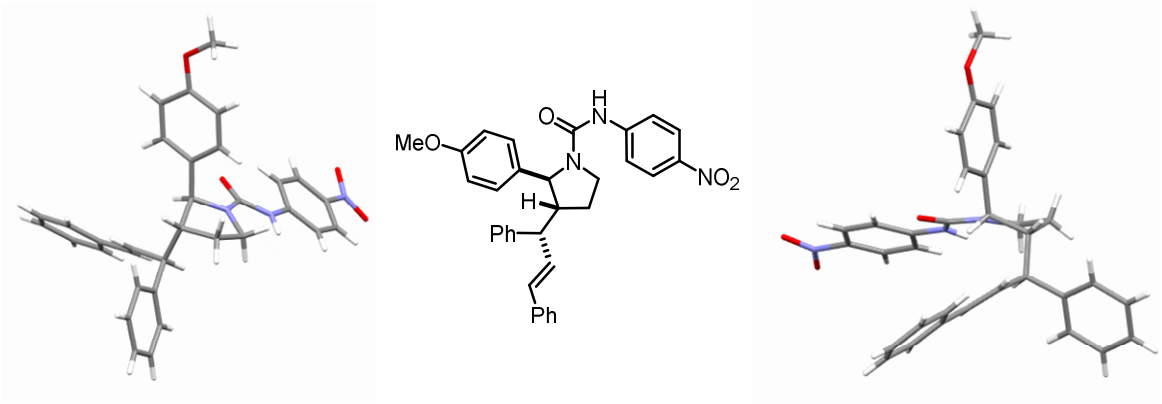


Crystals suitable for single crystal X-ray Crystallography were obtained *via* vapour diffusion of pentane into a solution of **5e** (10 mg) in EtOAc (0.5 mL).

Identification code	7372	
Empirical formula	C30 H28 N2 O4 S	
Formula weight	512.63	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 10.38990(10) Å	α= 90°.
	b = 23.2970(3) Å	β= 108.9135(16)°.
	c = 11.2415(2) Å	γ = 90°.
Volume	2574.13(7) Å^3	
Z	4	
Density (calculated)	1.323 Mg/m^3	
Absorption coefficient	1.437 mm^{-1}	
F(000)	1080	
Crystal size	0.20 x 0.18 x 0.09 mm^3	
Theta range for data collection	3.795 to 76.114°.	
Index ranges	-12<=h<=9, -29<=k<=28, -13<=l<=14	
Reflections collected	13843	
Independent reflections	5310 [R(int) = 0.026]	
Completeness to theta = 73.831°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.88 and 0.85	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5310 / 0 / 334	
Goodness-of-fit on F^2	0.9955	
Final R indices [I>2sigma(I)]	R1 = 0.0348, wR2 = 0.0885	

R indices (all data)	R1 = 0.0393, wR2 = 0.0935
Largest diff. peak and hole	0.43 and -0.45 e.Å^{-3}

X-ray Crystallographic data for (15): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxy-phenyl)-*N*-(4-nitrophenyl)-pyrro-lidine-1-carboxamide, 7493

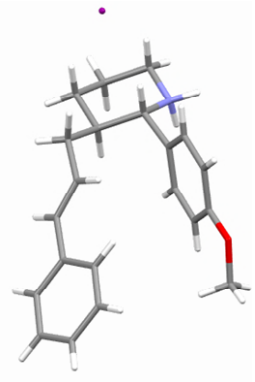


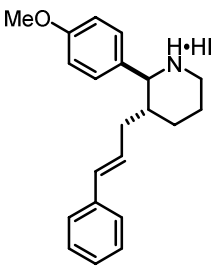
Crystals suitable for single crystal X-ray Crystallography were obtained *via* evaporation of a solution of **15** (18 mg) in heptane/EtOAc (0.5 mL).

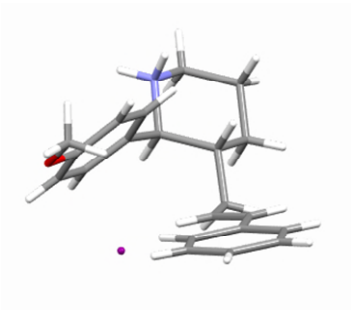
Identification code	7493	
Empirical formula	C33 H31 N3 O4	
Formula weight	533.62	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P c a 21	
Unit cell dimensions	a = 9.4987(7) Å	α= 90°.
	b = 14.7759(11) Å	β= 90°.
	c = 19.5458(13) Å	γ = 90°.
Volume	2743.3(3) Å^3	
Z	4	
Density (calculated)	1.292 Mg/m^3	
Absorption coefficient	0.689 mm^{-1}	
F(000)	1127.993	
Crystal size	0.16 x 0.05 x 0.03 mm^3	
Theta range for data collection	4.524 to 76.720°.	
Index ranges	-11<=h<=11, -16<=k<=18, -21<=l<=24	
Reflections collected	16415	
Independent reflections	4936 [R(int) = 0.062]	
Completeness to theta = 73.831°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.94	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	4932 / 1 / 362
Goodness-of-fit on F^2	1.0100
Final R indices [I>2sigma(I)]	R1 = 0.0556, wR2 = 0.1306
R indices (all data)	R1 = 0.0845, wR2 = 0.1602
Largest diff. peak and hole	0.19 and -0.15 e.Å^{-3}

X-ray Crystallographic data for (32c): (±)-(2*S*,3*R*)-3-Cinnamyl-2-(4-methoxyphenyl)piperidin-1-ium iodide, 7509







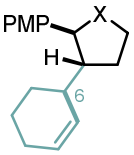
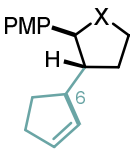
Crystals suitable for single crystal X-ray Crystallography were obtained *via* evaporation of **32c** (15 mg) in $CDCl_3$ (0.5 mL).

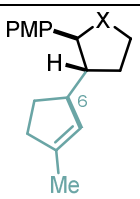
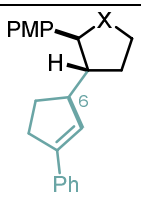
Identification code	7509
Empirical formula	C21 H26 I N O
Formula weight	435.35
Temperature	150 K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	Pccn
Unit cell dimensions	a = 45.0554(5) Å α= 90°. b = 10.23090(10) Å β= 90°. c = 8.46320(10) Å γ = 90°.
Volume	3901.17(7) Å^3
Z	8
Density (calculated)	1.482 Mg/m^3
Absorption coefficient	12.936 mm^{-1}
F(000)	1760
Crystal size	0.28 x 0.05 x 0.02 mm^3
Theta range for data collection	3.925 to 76.529°.
Index ranges	-56<=h<=56, -12<=k<=12, -10<=l<=10
Reflections collected	95997
Independent reflections	4096 [R(int) = 0.046]
Completeness to theta = 76.529°	99.8 %
Absorption correction	Semi-empirical from equivalents

Max. and min. transmission	0.77 and 0.07
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4095 / 0 / 217
Goodness-of-fit on F^2	0.9999
Final R indices [I>2sigma(I)]	R1 = 0.0709, wR2 = 0.1669
R indices (all data)	R1 = 0.0718, wR2 = 0.1691
Largest diff. peak and hole	2.68 and -0.38 e.$Å^{-3}$

6.2.6 Supporting document for assignment of the cyclic exocyclic stereocentre

A full comparison of the ^{1}H and ^{13}C NMR signals was made between selected pyrrolidine and tetrahydrofuran examples so that the exocyclic stereochemistry could be assigned by analogy. The following table summarises selected C2 and C7 ^{1}H NMR data, chosen because of the distinct ppm region both signals sit in across all examples.

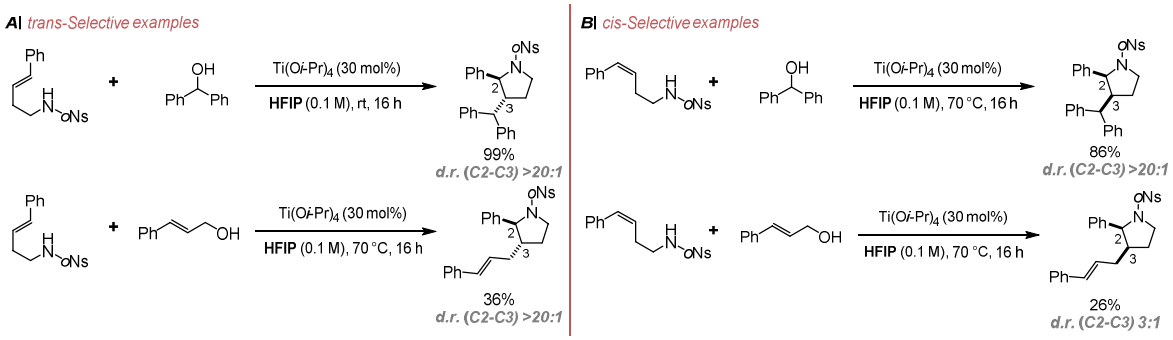
Substrate					
		major	**minor**	**major**	**minor**
d.r. (C6)	**N**	2.5	1	3.5	1
	O	2	1	3	1
C2 δ (ppm)	**N**	4.65 (d, *J* = 8.1 Hz)	4.67 (d, *J* = 8.4 Hz)	4.57 (d, *J* = 7.9 Hz)	4.58 (d, *J* = 8.1 Hz)
	O	4.56 (d, *J* = 7.5 Hz)	4.60 (d, *J* = 7.3 Hz)	4.48 (d, *J* = 6.3 Hz)	4.50 (d, *J* = 7.5 Hz)
C7 δ (ppm)	**N**	5.60 (dd, *J* = 10.5, 2.3 Hz)	5.39 (dd, *J* = 10.2, 2.3 Hz)	5.64 – 5.61 (m)	5.45 – 5.41 (m)
	O	5.71 – 5.66 (m)	5.47 – 5.41 (m)	5.83 – 5.79	5.69 – 5.67

Substrate					
		major	**minor**	**major**	**minor**
d.r. (C6)	**N**	13	1	>20	1
	O	7	1	>20	1
C2 δ (ppm)	**N**	4.54 (d, *J* = 7.9 Hz)	4.57 (d, *J* = 7.9 Hz)	4.67 (d, *J* = 8.0 Hz)	-
	O	4.46 (d, *J* = 7.3 Hz)	4.49 (d, *J* = 7.4 Hz)	4.56 (d, *J* = 7.2 Hz)	-
C7 δ (ppm)	**N**	5.24 – 5.20 (m)	5.07 – 5.03 (m)	6.07 (q, *J* = 2.0 Hz)	-
	O	5.33 – 5.28 (m)	5.11 – 5.08 (m)	6.15 (q, *J* = 2.0 Hz)	-

6.2.7 Supporting document for mechanistic hypothesis

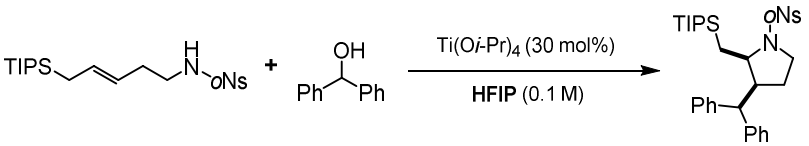
All experiments were carried out by Yuxiang Zhu.

(a) Influence of alkene geometry in the parent system



The role of the double bond geometry above shows that the *E* isomer gives exclusively the *trans* diastereomer with high stereoselectivity when reacted with benzhydrol and cinnamyl alcohol whereas the *Z* isomer leads to a major, but not exclusive, *cis* product when subjected to the same reaction suggesting a less stereoselective pathway.

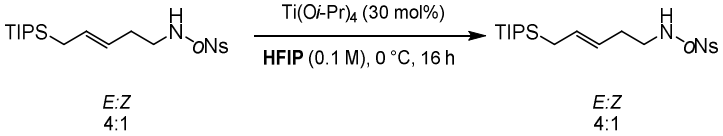
(b) Temperature experiments



Entry	Temp / ˚C	Time / h	Yield 3 / %	trans:cis
1	0	16	99	*1:4*
2	70	16	99	*1:2*
3	70	24	99	*1:1.4*
4	70	40	99	*1:1.1*

Higher temperature experiments support the equilibration at high temperature between the *trans* and *cis* diastereomers of **3aa**, with the *cis*-diastereomer being the kinetic product whereas the *trans*- diastereomer is the thermodynamically more stable product.

(c) Resubjection experiment



E:*Z*
4:1

E:*Z*
4:1

Finally, a control experiment confirmed that starting material was not simply being isomerised under the reaction conditions. Following 16 h at 0 °C the alkene geometry ratio was unchanged.

6.3 Experimental details – Chapter 3

6.3.1 General procedures

General Procedure L: Curtius rearrangement sequence

To a solution of acid (1.0 equiv.) in PhMe (4.0 mL/mmol) was added Et_3N (1.5 equiv.) followed by dropwise addition of diphenylphosphoryl azide (DPPA) (1.5 equiv.) before heating to 85 °C for 2 h.

(1) For ureas. The solution was cooled to rt before addition of amine and the reaction heated to reflux for 16 h. The solution was diluted with EtOAc and water and the layers separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$ before concentrating *in vacuo* and purifying by FCC.

(2) For alcohols. The solution was cooled to rt before addition of alcohol and the reaction heated to reflux for 16 h. The solution was diluted with EtOAc and water and the layers separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$ before concentrating *in vacuo* and purifying by FCC.

(3) For sulfonamides. The solution was cooled to rt before the addition of THF (4.0 mL/mmol) and aq. NaOH (2.0 M, 2.0 mL/mmol) and the reaction was left to stir vigorously for 16 h. The solution was diluted with EtOAc and water and the layers separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with 1.0 M NaOH and dried over $MgSO_4$ before concentrating in vacuo. The crude amine was re-dissolved in CH_2Cl_2 (5.00 mL/mmol) and Et_3N added (1.25 equiv.). The solution was cooled to 0 °C before addition of the appropriate sulfonamide (as a solution) or chloroformate (1.25 equiv.). The reaction mixture was left to warm up to rt and stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 and water. The aqueous later was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over $MgSO_4$ before concentrating *in vacuo* and purifying by FCC.

General Procedure M: Trichloroacetimidiate formation

To a solution of alcohol (1.00 equiv.) and trichloroacetonitrile (1.10 equiv.) in hexane (3 mL/mmol) at 0 °C was added DBU (1.00 mol%). After stirring for 30 min. the reaction mixture was diluted with hexane

before addition of aq. sat. ammonium chloride. The aqueous layer was extracted with hexane and the combined organic layers were dried over Na_2SO_4 before concentrating *in vacuo*.

General Procedure N: Racemic cyclisation

To a solution of homoallylic amine (1.0 equiv) and *trans*-1,3-diphenyl-2- propen-1-ol (1.0 equiv.) in CH_2Cl_2 (20 mL/mmol) was added 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (cat-**5*rac***) (20 mol%) and the reaction stirred at rt for 16 h. The reaction mixture was concentrated *in vacuo* and purified by FCC.

General Procedure O: Enantioselective cyclisation

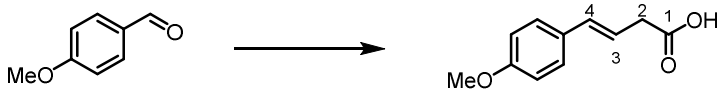
To a solution of homoallylic amine (1.0 equiv) and *trans*-1,3-diphenyl-2- propen-1-ol (1.0 equiv.) in DCE (20 mL/mmol) was added (cat-**5e**) (15 mol%) and the reaction stirred at 80 ˚C for 72 h. The reaction mixture was concentrated *in vacuo* and purified by FCC.

General Procedure P: Cyclisation with trichloroacetimidate

To a solution of homoallylic amine (1.0 equiv) and trichloroacetimidate (1.0 equiv.) in C_6H_5F (20 mL/mmol) and 4Å MS was added (cat-**5e**) (15 mol%) and the reaction stirred at rt for 16 h. The reaction mixture was concentrated *in vacuo* and purified by FCC.

6.3.2 Synthesis of nucleophiles

(S11): (*E*)-4-(4-Methoxyphenyl)but-3-enoic acid

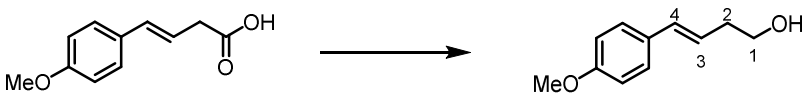


S11

Prepared by **General Procedure A** using *p*-anisaldehyde (2.44 mL, 20.00 mmol), (2-carboxyethyl)-triphenylphosphonium bromide (9.12 g, 22.00 mmol), NaHMDS (2.0 M in THF, 24.0 mL, 48.0 mmol). Flash column chromatography (80% Et_2O/pentane + 1% acetic acid) afforded **S11** as a crystalline white solid (1.71 g, 45%).

Data for **S11**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.31 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.46 (1H, d, *J* = 15.9 Hz, C4-H), 6.14 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 3.81 (3H, s, OMe), 3.28 (2H, dd, *J* = 7.1, 1.5 Hz, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 178.3 (CO), 159.4 (C Ar), 133.5 (C4), 129.6 (C Ar), 127.6 (2 × C Ar), 118.7 (C3), 114.1 (2 × C Ar), 55.4 (OMe), 38.2 (C2). *The spectroscopic properties were consistent with the data available in the literature.*[171]

(S12): (*E*)-4-(4-Methoxyphenyl)but-3-en-1-ol

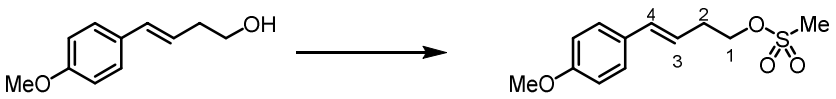


S11 **S12**

Prepared by **General Procedure B** using **S11** (1.71 g, 9.00 mmol) and $LiAlH_4$ (424 mg, 11.2 mmol). Flash column chromatography (50% Et_2O – pentane) afforded **S12** as a white solid (1.16 g, 72%).

Data for **S12**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.30 (2H, d, *J* = 8.9 Hz, Ar), 6.84 (2H, d, *J* = 8.8 Hz, Ar), 6.45 (1H, d, *J* = 15.9 Hz, C4-H), 6.05 (1H, dt, *J* = 15.8, 7.2 Hz, C3-H), 3.80 (3H, s, OMe), 3.75 (2H, t, *J* = 7.5 Hz, C1-H_2), 2.43 – 2.50 (2H, m, C2-H_2), 1.47 (1H, *br.* s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.0 (C Ar), 132.3 (C4), 130.1 (C Ar), 127.2 (2 × C Ar), 124.0 (C3), 114.0 (2 × C Ar), 62.1 (C1), 55.3 (OMe), 36.4 (C2). *The spectroscopic properties were consistent with the data available in the literature.*[172]

(S13): (*E*)-4-(4-Methoxyphenyl)but-3-en-1-yl methanesulfonate

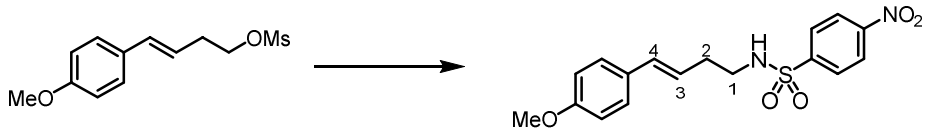


S12 **S13**

Prepared by **General Procedure C** using **S12** (760 mg, 4.26 mmol), triethylamine (0.89 mL, 6.4 mmol) and methanesulfonic anhydride (890 mg, 5.11 mmol). Flash column chromatography (30% Et_2O – pentane) afforded **S13** as a white solid (1.09 g, *quant.*).

Data for **S13**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28 (2H, d, *J* = 8.9 Hz, Ar), 6.85 (2H, d, *J* = 8.8 Hz, Ar), 6.45 (1H, d, *J* = 15.9 Hz, C4-H), 6.03 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 4.32 (2H, t, *J* = 7.5 Hz, C1-H_2), 3.81 (3H, s, OMe), 3.01 (3H, s, SO_2**Me**), 2.43 – 2.50 (2H, m, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.1 (C Ar), 132.9 (C4), 130.1 (C Ar), 127.3 (2 × C Ar), 124.1 (C3), 114.0 (2 × C Ar), 66.1 (C1), 55.1 (OMe), 37.3 (SO_2**Me**), 32.4 (C2). *The spectroscopic properties were consistent with the data available in the literature.*[173]

(1d): (*E*)-*N*-(4-(4-Methoxyphenyl)but-3-en-1-yl)-4-nitrobenzenesulfonamide



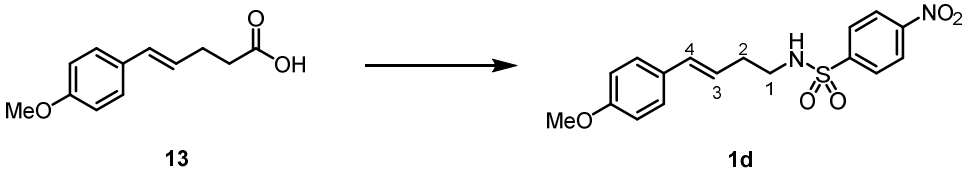
S13 **1d**

Prepared by **General Procedure D** using **S13** (1.09 g, 4.26 mmol), 4-nitrobenzenesulfonamide (1.29 g, 3.39 mmol) and potassium hydroxide (358 mg, 6.39 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **1d** as a pale-yellow solid (683 mg, 44%).

Data for **1d**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.28 (2H, d, *J* = 8.8 Hz, Ar), 8.01 (2H, d, *J* = 8.8 Hz, Ar), 7.17 (2H, d, *J* = 8.8 Hz, Ar), 6.82 (2H, d, *J* = 8.8 Hz, Ar), 6.30 (1H, d, *J* = 15.8 Hz, C4-H), 5.76 (1H, dt, *J* = 15.8, 7.2 Hz, C3-H), 4.70 (1H, t, *J* = 6.0 Hz, *NH*), 3.18 (2H, q, *J* = 6.3 Hz, C1-H_2), 2.37 (tdd, *J* = 7.6, 6.5, 1.4 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.5 (C Ar), 150.1 (C Ar), 146.1 (C Ar), 133.3 (C4), 129.4 (C Ar), 128.4 (2 × C Ar), 127.4 (2 × C Ar), 124.5 (2 × C Ar), 122.7 (C3), 114.2 (2 × C Ar), 55.5 (OMe), 43.0 (C1), 33.3 (C2). **HRMS** (ESI): calculated for $C_{17}H_{18}N_2O_5SNa$ $[M+Na]^+$ requires *m/z*

385.0829, found *m/z* 385.0826. **IR** (film) ν_{max}: 3294, 1667, 1529, 1521, 1348, 1248, 1092, 918 cm^{-1}. **mp** (104 – 106 °C, EtOAc).

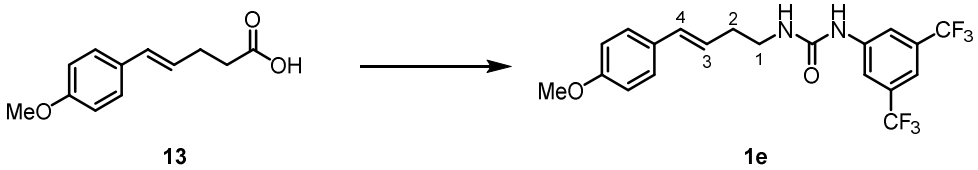
1d was also prepared by **General Procedure L**:



13 **1d**

Prepared by **General Procedure L3** using **13** (1.00 g, 4.85 mmol), Et_3N (1.00 mL, 7.28 mmol) and DPPA (1.50 mL, 7.28 mmol). Crude amine was then subjected to Et_3N (0.84 mL, 6.08 mmol) and 4-nitrobenzenesulfonyl chloride (1.35 g, 6.08 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **1d** as a white solid (1.35 mg, 71%).

(1e): (*E*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-(4-methoxyphenyl)but-3-en-1-yl)urea

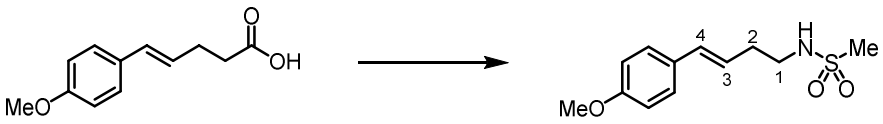


13 **1e**

Prepared by **General Procedure L1** using **13** (390 mg, 1.88 mmol), Et_3N (0.390 mL, 2.8 mmol), DPPA (0.60 mL, 2.8 mmol) and 3,5-bis(trifluoromethyl)aniline (0.96 mL, 5.6 mmol). Recrystallisation from hot EtOAc afforded **1e** as a crystalline white solid (594 mg, 72%).

Data for **1e**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.79 (2H, s, Ar), 7.46 (1H, s, Ar), 7.25 (d, *J* = 8.3 Hz, 2H), 6.99 (1H, *br.* s. NH), 6.82 (2H, d, *J* = 8.8 Hz, Ar), 6.39 (1H, d, *J* = 15.8 Hz, C4-H), 5.98 (1H, dt, *J* = 15.9, 7.2 Hz, C3-H), 3.79 (3H, s, OMe), 3.39 (2H, t, *J* = 6.5 Hz, C1-H_2), 2.42 (2H, q, *J* = 6.8 Hz, C2-H_2). **^{19}F NMR (377 MHz, $CDCl_3$) δ** -63.1. **HRMS** (ESI): calculated for $C_{20}H_{20}F_6N_2O_2$ $[M+H]^+$ requires *m/z* 433.1345, found *m/z* 433.1345. **IR** (film) ν_{max}: 2855, 2360, 1654, 1390, 1272, 1125, 1039, 681 cm^{-1}. **mp** (167 – 169 °C, EtOAc). *^{13}C characterisation was not possible, owing to the cyclisation which took place during the ^{13}C NMR experiment.*

(1f): (*E*)-*N*-(4-(4-Methoxyphenyl)but-3-en-1-yl)methanesulfonamide

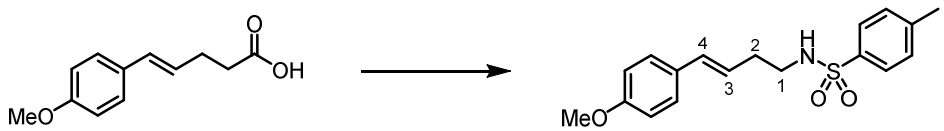


13 **1f**

Prepared by **General Procedure L3** using **13** (500 mg, 2.43 mmol), Et_3N (0.50 mL, 3.6 mmol) and DPPA (0.78 mL, 3.6 mmol). Crude amine was then subjected to Et_3N (0.420 mL, 3.04 mmol) and methanesulfonyl chloride (0.24 mL, 3.04 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **1f** as a white solid (382 mg, 56%).

Data for **1f**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.43 (1H, d, *J* = 15.8 Hz, C4-H), 5.97 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 4.50 (1H, t, *J* = 6.5 Hz, *N*H), 3.80 (3H, s, OMe), 3.09 (2H, q, *J* = 6.5 Hz, C1-H_2), 2.94 (3H, s, SO_2Me), 2.46 (2H, qd, *J* = 6.5, 1.4 Hz, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (C Ar), 132.9 (C4), 129.7 (C Ar), 127.4 (2 × C Ar), 123.3 (C3), 114.1 (2 × C Ar), 55.4 (OMe), 42.9 (C1), 40.5 (SO_2Me), 33.7 (C2). **HRMS** (ESI): calculated for $C_{12}H_{17}NO_3SNa$ $[M+Na]^+$ requires *m/z* 278.0827, found *m/z* 278.0821. **IR** (film) ν_{max}: 3283, 2980, 2360, 1576, 1511, 1313 cm^{-1}. **mp** (97 – 99 °C, EtOAc).

(1g): (3*E*)-*N*-[4-(4-Methoxyphenyl)but-3-en-1-yl]-4-methylbenzenesulfonamide



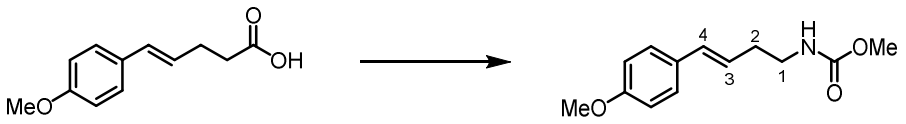
13 **1g**

Prepared by **General Procedure L3** using **13** (1.00 g, 4.85 mmol), Et_3N (1.00 mL, 7.28 mmol) and DPPA (1.50 mL, 7.28 mmol). Crude amine was then subjected to Et_3N (0.84 mL, 6.08 mmol) and 4-toluenesulfonyl chloride (1.16 g, 6.08 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **1g** as a white solid (1.08 g, 67%).

Data for **1g**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.74 (2H, d, *J* = 8.7 Hz, Ar), 7.29 (2H, d, *J* = 8.7 Hz, Ar), 7.21 (2H, d, *J* = 8.7 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.30 (1H, d, *J* = 15.8 Hz, C4-H), 5.82 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 4.41 (1H, t, *J* = 6.5 Hz, *N*H), 3.81 (3H, s, OMe), 3.09 (2H, q, *J* = 6.5 Hz, C1-H_2), 2.43 (3H, s, TsMe), 2.34 (2H, qd, *J* = 6.5, 1.4 Hz, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3

(2 × C Ar), 143.6 (2 × C Ar), 132.9 (C4), 129.9 (2 × C Ar), 127.4 (2 × C Ar), 127.3 (2 × C Ar), 123.3 (C3), 114.1 (2 × C Ar), 55.5 (OMe), 42.8 (C1), 33.1 (C-2), 21.7 (TsMe). *The spectroscopic properties were consistent with the data available in the literature.*[174]

(1h): Methyl (*E*)-(4-(4-methoxyphenyl)but-3-en-1-yl)carbamate

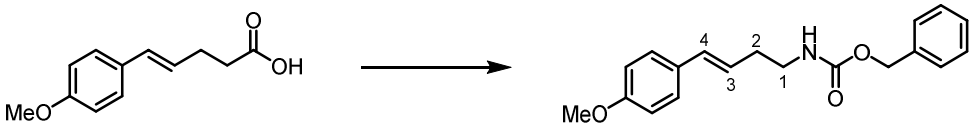


13 **1h**

Prepared by **General Procedure L2** using **13** (275 mg, 1.25 mmol), Et_3N (0.28 mL, 1.98 mmol), DPPA (0.43 mL, 1.98 mmol) and MeOH (0.5 mL, 12.5 mmol). Flash column chromatography (20% EtOAc – pentane) afforded **1h** as a white solid (235 mg, 80%).

Data for **1h**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27 (2H, d, *J* = 8.7 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.38 (1H, dt, *J* = 15.8, 1.4 Hz, C4-H), 5.98 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 4.83 (1H, *br.* s, *N*H), 3.79 (3H, s, OMe), 3.65 (3H, s, OMe), 3.30 (2H, q, *J* = 6.4 Hz, C1-H_2), 2.38 (2H, qd, *J* = 6.8, 1.4 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.1 (C Ar), 157.2 (CO), 131.9 (C4), 130.1 (C Ar), 127.3 (2 × C Ar), 124.6 (C3), 114.1 (2 × C Ar), 55.4 (OMe), 52.1 (OMe), 40.7 (C1), 33.6 (C2). **HRMS** (ESI): calculated for $C_{13}H_{17}NO_3Na$ $[M+Na]^+$ requires *m/z* 258.1101, found *m/z* 258.1105. **IR** (film) ν_{max}: 2924, 2361, 1686, 1511, 1308, 1043, 832, 681 cm^{-1}. **mp** (78 – 80 °C, EtOAc).

(1i): Benzyl (*E*)-(4-(4-methoxyphenyl)but-3-en-1-yl)carbamate



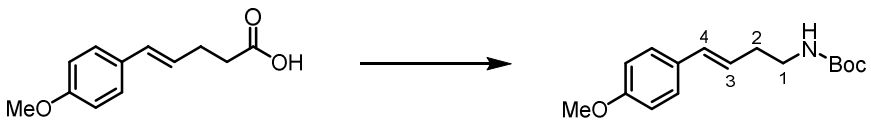
13 **1i**

Prepared by **General Procedure L2** using **13** (500 mg, 2.43 mmol), Et_3N (0.50 mL, 3.6 mmol), DPPA (0.78 mL, 3.6 mmol) and benzyl alcohol (0.76 mL, 7.29 mmol). Flash column chromatography (20% EtOAc – pentane) afforded **1i** as a white solid (614 mg, 75%).

Data for **1i**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.38 – 7.30 (5H, m, Ar), 7.28 – 7.24 (2H, m, Ar), 6.84 (2H, d, *J* = 8.8 Hz, Ar), 6.39 (1H, d, *J* = 16.0 Hz, C4-H), 5.99 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 5.10 (2H, s, OC**H_2**Ph), 4.83 (1H, *br.* s, *N*H), 3.80 (3H, s, OMe), 3.34 (2H, q, *J* = 6.5 Hz, C1-H_2), 2.40 (2H, q,

J = 6.8 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.1 (C Ar), 156.5 (CO), 136.7 (C Ar), 132.0 (C Ar), 130.1 (C Ar), 128.7 (2 × C Ar), 128.3 (C4), 128.2 (2 × C Ar), 127.4 (2 × C Ar), 124.5 (C3), 114.1 (2 × C Ar), 66.8 (O**C**H_2Ph), 55.4 (OMe), 40.8 (C1), 33.4 (C2). **HRMS** (ESI): calculated for $C_{19}H_{21}NO_3Na$ $[M+Na]^+$ requires m/z 334.1414, found m/z 334.1411. **IR** (film) ν_{max}: 2981, 2360, 1713, 1511, 1247, 907, 730, 650 cm^{-1}. **mp** (117 – 119 °C, EtOAc).

(1j): *tert*-Butyl (*E*)-(4-(4-methoxyphenyl)but-3-en-1-yl)carbamate

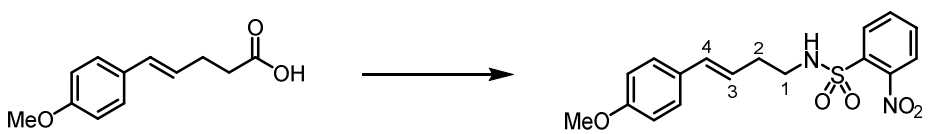


13 **1j**

Prepared by **General Procedure L2** using **13** (390 mg, 1.88 mmol), Et_3N (0.390 mL, 2.80 mmol) and DPPA (0.60 mL, 2.80 mmol) and ^{t}BuOH (8.00 mL). Crude amine was then subjected to Et_3N (0.330 mL, 2.35 mmol) and Boc_2O (513 mg, 2.35 mmol). Flash column chromatography (20% EtOAc – pentane) afforded **1j** as a white solid (370 mg, 71%).

Data for **1j**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27 (2H, d, J = 8.9 Hz, Ar), 6.83 (2H, d, J = 8.8 Hz, Ar), 6.38 (1H, dt, J = 15.9, 1.5 Hz, C4-H), 5.99 (1H, dt, J = 15.8, 7.1 Hz, C3-H), 3.79 (3H, s, OMe), 3.31 – 3.17 (2H, m, C1-H_2), 2.37 (2H, qd, J = 6.8, 1.4 Hz, C2-H_2), 1.43 (9H, s, C(C**H**$_3$)$_3$). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.1 (C Ar), 157.0 (CO), 131.8 (C4), 130.0 (C Ar), 127.3 (2 × C Ar), 124.9 (C3), 114.1 (2 × C Ar), 77.4 (**C**$(CH_3)_3$), 55.4 (OMe), 40.0 (C1), 33.7 (C2), 28.6 (C(**C**H_3)$_3$). *The spectroscopic properties were consistent with the data available in the literature.*[175]

(1a): (3*E*)-*N*-[4-(4-Methoxyphenyl)but-3-en-1-yl]-2-nitrobenzenesulfonamide

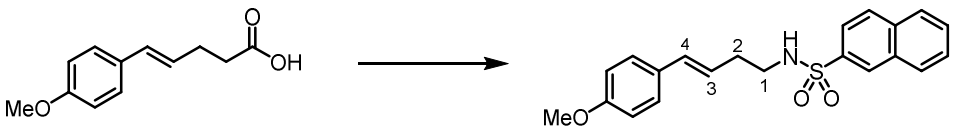


13 **1a**

Prepared by **General Procedure L3** using **13** (1.00 g, 4.85 mmol), Et_3N (1.00 mL, 7.28 mmol) and DPPA (1.50 mL, 7.28 mmol). Crude amine was then subjected to Et_3N (0.84 mL, 6.08 mmol) and 2-nitrobenzenesulfonyl chloride (1.35 g, 6.08 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **1a** as a white solid (1.30 mg, 68%).

Data for **1a**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.15 – 8.11 (1H, m, Ar), 7.79 – 7.63 (3H, m, Ar), 7.17 (2H, d, *J* = 8.6 Hz, Ar), 6.81 (2H, d, *J* = 8.8 Hz, Ar), 6.29 (1H, dt, *J* = 15.8, 1.5 Hz, C4-H), 5.82 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 5.39 (1H, t, *J* = 5.9 Hz, *N*H), 3.80 (3H, s, OMe), 3.27 (2H, td, *J* = 6.7, 5.9 Hz, C1-H_2), 2.40 (2H, qd, *J* = 6.7, 1.4 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.3 (C Ar), 134.0 (C Ar), 133.5 (C Ar), 133.0 (C Ar), 132.9 (C4), 131.1 (C Ar), 129.6 (C Ar), 127.4 (2 × C Ar), 125.5 (C Ar), 122.9 (C3), 114.1 (2 × C Ar), 55.4 (OMe), 43.7 (C1), 33.3 (C2). **HRMS** (ESI): calculated for $C_{17}H_{18}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 385.0829, found *m/z* 385.0826. **IR** (film) ν_{max}: 2981, 2360, 1521, 1441, 1342, 1126, 969 cm^{-1}. **mp** (111 – 113 °C, EtOAc).

(1k): (*E*)-*N*-(4-(4-Methoxyphenyl)but-3-en-1-yl)naphthalene-2-sulfonamide

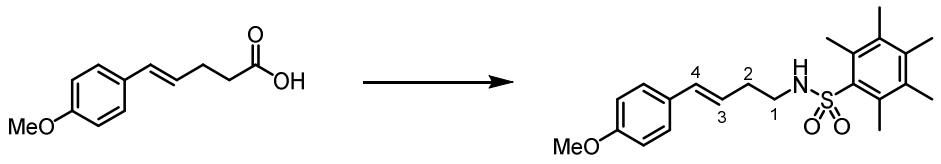


13 **1k**

Prepared by **General Procedure L3** using **13** (390 mg, 0.97 mmol), Et_3N (0.20 mL, 1.5 mmol) and DPPA (0.32 mL, 1.5 mmol). Crude amine was then subjected to Et_3N (0.17 mL, 1.2 mmol) and 2-naphthalenesulfonyl chloride (277 mg, 1.22 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **1k** as a white solid (179 mg, 49%).

Data for **1k**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.45 (1H, d, *J* = 1.9 Hz, Ar), 7.99 – 7.88 (3H, m, Ar), 7.83 (1H, dd, *J* = 8.7, 1.9 Hz, Ar), 7.70 – 7.57 (2H, m, Ar), 7.15 (2H, *J* = 8.8 Hz, Ar), 6.79 (2H, d, *J* = 8.7 Hz, Ar), 6.27 (1H, d, *J* = 15.8 Hz, C4-H), 5.79 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 4.75 (1H, *br.* s, *N*H), 3.79 (3H, s, OMe), 3.14 (2H, q, *J* = 6.1 Hz, C1-H_2), 2.34 (2H, qd, *J* = 6.7, 1.4 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.2 (C Ar), 136.9 (C Ar), 134.9 (C Ar), 132.8 (C4), 132.3 (C Ar), 129.6 (2 × C Ar), 129.4 (C Ar), 128.9 (C Ar), 128.6 (C Ar), 128.0 (C Ar), 127.7 (C Ar), 127.4 (2 × C Ar), 123.3 (C3), 122.5 (C Ar), 114.1 (2 × C Ar), 55.4 (OMe), 42.8 (C1), 33.1 (C2). **HRMS** (ESI): calculated for $C_{21}H_{22}NO_3S$ $[M+H]^+$ requires *m/z* 368.1315, found *m/z* 368.1317. **IR** (film) ν_{max}: 2928, 2855, 1606, 1511, 1244, 1032, 847, 799, 643 cm^{-1}. **mp** (125 – 127 °C, EtOAc).

(1l): (*E*)-*N*-(4-(4-Methoxyphenyl)but-3-en-1-yl)-2,3,4,5,6-pentamethylbenzenesulfonamide

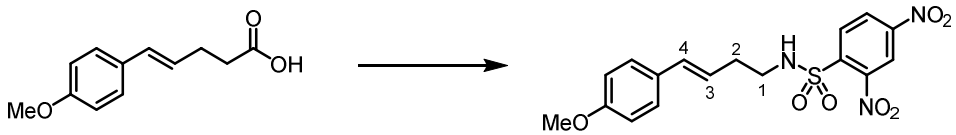


13 **1l**

Prepared by **General Procedure L3** using **13** (390 mg, 0.97 mmol), Et_3N (0.20 mL, 1.5 mmol) and DPPA (0.32 mL, 1.5 mmol). Crude amine was then subjected to Et_3N (0.17 mL, 1.22 mmol) and 2,3,4,5,6-pentamethylbenzenesulfonyl chloride (308 mg, 1.22 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **1l** as a white solid (260 mg, 69%).

Data for **1l**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.20 (2H, d, *J* = 8.7 Hz, Ar), 6.83 (2H, d, *J* = 8.8 Hz, Ar), 6.31 (1H, d, *J* = 15.8 Hz, C4-H), 5.83 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 4.57 (1H. *br.* s, *N*H), 3.81 (3H, s, OMe), 3.05 (2H, t, *J* = 6.5 Hz, C1-H_2), 2.57 (6H, s, 2 × ArMe), 2.35 (2H, qd, *J* = 6.6, 1.4 Hz, C2-H_2), 2.28 (3H, s, ArMe), 2.22 (6H, s, 2 × ArMe). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.3 (C Ar), 139.6 (C Ar), 136.0 (C Ar), 134.9 (2 × C Ar), 134.3 (2 × C Ar), 132.7 (C4), 129.8 (C Ar), 127.4 (2 × C Ar), 123.7 (C3), 114.1 (2 × C Ar), 55.4 (OMe), 42.4 (C1), 33.0 (C2), 19.1 (2 × ArMe), 17.9 (ArMe), 17.2 (2 × ArMe). **HRMS** (ESI): calculated for $C_{22}H_{30}NO_3S$ $[M+H]^+$ requires *m*/*z* 388.1941, found *m*/*z* 388.1944. **IR** (film) ν_{max}: 2929, 2856, 1607, 1422, 1149, 847, 806, 610 cm^{-1}. **mp** (118 – 120 °C, EtOAc).

(1m): (*E*)-*N*-(4-(4-Methoxyphenyl)but-3-en-1-yl)-2,4-dinitrobenzenesulfonamide



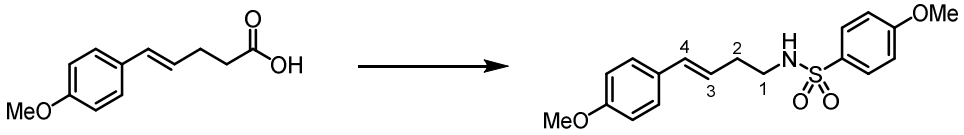
13 **1m**

Prepared by **General Procedure L3** using **13** (390 mg, 0.97 mmol), Et_3N (0.20 mL, 1.5 mmol) and DPPA (0.32 mL, 1.5 mmol). Crude amine was then subjected to Et_3N (0.17 mL, 1.22 mmol) and 2,4-dinitrobenzenesulfonyl chloride (333 mg, 1.22 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **1m** as a white solid (157 mg, 39%).

Data for **1m**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.37 – 8.31 (2H, m, Ar), 8.24 (1H, d, *J* = 9.2 Hz, Ar), 6.99 (2H, d, *J* = 8.6 Hz, Ar), 6.73 (2H, d, *J* = 8.7 Hz, Ar), 6.19 (1H, dd, *J* = 15.8, 1.5 Hz, C4-H), 5.62 (1H, dt,

J = 15.7, 7.3 Hz, C3-H), 5.39 (1H, t, *J* = 5.6 Hz, *N*H), 3.80 (3H, s, OMe), 3.44 (2H, q, *J* = 5.9 Hz, C1-H_2), 2.39 (2H, tdd, *J* = 7.3, 6.1, 1.3 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.5 (C Ar), 140.4 (C Ar), 140.0 (C Ar), 133.4 (C4), 132.0 (C Ar), 130.0 (C Ar), 129.0 (C Ar), 127.2 (2 × C Ar), 127.2 (C Ar), 122.9 (C3), 120.9, 114.1 (2 × C Ar), 55.4 (OMe), 44.2 (C1), 33.7 (C2). **HRMS** (ESI): calculated for $C_{17}H_{18}N_3O_7S$ $[M+H]^+$ requires *m/z* 408.0860, found *m/z* 408.0861. **IR** (film) ν_{max}: 2935, 1607, 1511, 1349, 1250, 1168, 746, 736 cm^{-1}. **mp** (105 – 107 °C, EtOAc).

(1n): (*E*)-4-Methoxy-*N*-(4-(4-methoxyphenyl)but-3-en-1-yl)benzenesulfonamide

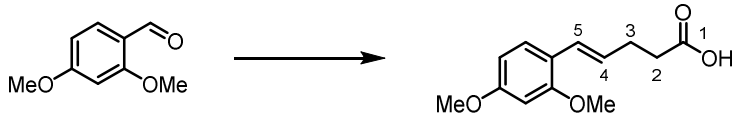


13 **1n**

Prepared by **General Procedure L3** using **13** (390 mg, 0.97 mmol), Et_3N (0.20 mL, 1.5 mmol) and DPPA (0.32 mL, 1.5 mmol). Crude amine was then subjected to Et_3N (0.17 mL, 1.2 mmol) and 3-methoxybenzene-1-sulfonyl chloride (289 mg, 1.22 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **1n** as a white solid (196 mg, 52%).

Data for **1n**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.79 (2H, d, *J* = 8.9 Hz, Ar), 7.21 (2H, d, *J* = 8.7 Hz, Ar), 6.96 (2H, d, *J* = 8.9 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.31 (1H, d, *J* = 15.8 Hz, C4-H), 5.82 (1H, dt, *J* = 15.8, 7.1 Hz, C3-H), 4.41 (1H, *br.* s, *N*H), 3.86 (3H, s, OMe), 3.81 (3H, s, OMe), 3.08 (2H, t, *J* = 6.6 Hz, C1-H_2), 2.34 (2H, qd, *J* = 6.7, 1.4 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 163.0 (C Ar), 159.3 (C Ar), 132.8 (C4), 131.7 (C Ar), 129.7 (C Ar), 129.4 (2 × C Ar), 127.4 (2 × C Ar), 123.3 (C3), 114.4 (2 × C Ar), 114.1 (2 × C Ar), 55.7 (OMe), 55.4 (OMe), 42.7 (C1), 33.1 (C2). **HRMS** (ESI): calculated for $C_{18}H_{21}NO_4SNa$ $[M+Na]^+$ requires *m/z* 370.1084, found *m/z* 370,1081. **IR** (film) ν_{max}: 3285, 2936, 1598, 1326, 1258, 1177, 1030, 805, 670 cm^{-1}. **mp** (115 – 117 °C, EtOAc).

(S14): (*E*)-5-(2,4-Dimethoxyphenyl)pent-4-enoic acid

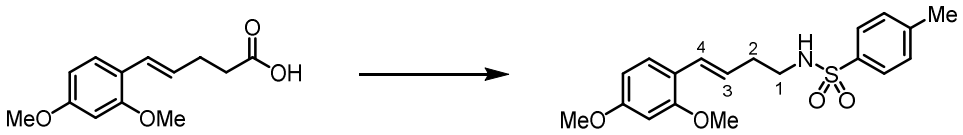


S14

Prepared by **General Procedure A** using 2,4-dimethoxybenzaldehyde (1.66 g, 10.0 mmol), (3-carboxy-propyl)-triphenylphosphonium bromide (5.15 g, 12.0 mmol), NaHMDS (2.0 M in THF, 12.0 mL, 24.0 mmol). Flash column chromatography (80% Et_2O/pentane + 1% acetic acid) followed by trituration with ice cold hexane (3 × 10 mL) afforded **S14** as a crystalline white solid (1.60 g, 67%).

Data for **S14**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.29 (1H, dd, *J* = 8.3, 7.2 Hz, Ar), 6.65 (1H, d, *J* = 16.0 Hz, C5-H), 6.49 – 6.38 (2H, m, Ar), 6.06 – 5.93 (1H, m, C4-H), 3.80 (3H, s, OMe), 3.79 (3H, s, OMe), 2.42 – 2.29 (4H, m, 2 × C2-H_2 + 2 × C3-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 160.3 (C Ar), 157.6 (C Ar), 127.4 (C Ar), 126.7 (C4), 125.6 (C5), 119.6 (C Ar), 104.9 (C Ar), 98.6 (C Ar), 55.6 (OMe), 55.5 (OMe), 34.1 (C2), 28.5 (C3). *The spectroscopic properties were consistent with the data available in the literature.*[176]

(1o): (*E*)-*N*-(4-(2,4-Dimethoxyphenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide



S14 **1o**

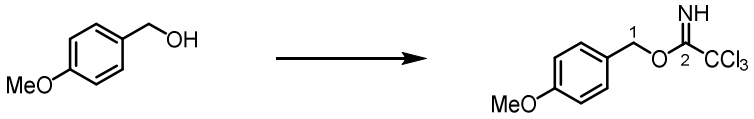
Prepared by **General Procedure L3** using **S14** (750 mg, 3.17 mmol), Et_3N (0.65 mL, 4.76 mmol) and DPPA (1.01 mL, 4.76 mmol). Crude amine was then subjected to Et_3N (0.55 mL, 3.97 mmol) and 4-toluenesulfonyl chloride (0. 76 mg, 3.97 mmol). Flash column chromatography (25% EtOAc – pentane) afforded **1o** as a white solid (584 mg, 51%).

Data for **1o**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.74 (2H, d, *J* = 8.4 Hz, Ar), 7.29 (2H, d, *J* = 7.9 Hz, Ar), 7.22 (1H, dd, *J* = 7.9, 0.8 Hz, Ar), 6.58 (1H, dt, *J* = 15.8, 1.5 Hz, C4-H), 6.44 (2H, d, *J* = 8.2 Hz, Ar), 5.83 (1H, dt, *J* = 16.0, 7.2 Hz, C3-H), 4.45 (1H, *br.* s, NH) 3.82 (3H, s, OMe), 3.81 (3H, s, OMe), 3.08 (2H, q, *J* = 6.3 Hz, C1-H_2), 2.42 (3H, s, TsMe), 2.33 (2H, qd, *J* = 6.7, 1.5 Hz, C2-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 160.4 (C Ar), 157.6, (C Ar) 143.4 (C Ar), 137.1 (C Ar), 129.8 (2 × C Ar), 129.6 (C Ar), 127.8 (C4), 127.5 (C Ar), 127.2 (2 × C Ar), 124.1 (C3), 104.8 (C Ar), 98.5 (C Ar), 55.5 (OMe),

55.5 (OMe), 42.8 (C1), 33.4 (C2), 21.6 (TsMe). **HRMS** (ESI): calculated for $C_{19}H_{23}NO_4SNa$ $[M+Na]^+$ requires m/z 384.1240, found m/z 384.1240. **IR** (film) ν_{max}: 2943, 2361, 1610, 1335, 1159, 667 cm^{-1}.

6.3.3 Synthesis of electrophiles

(38a): 4-Methoxybenzyl 2,2,2-trichloroacetimidate

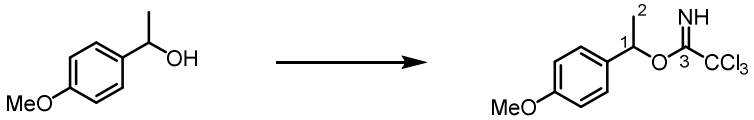


38a

Prepared according to **General Procedure M** using 4-methoxybenzyl alcohol (138 mg, 1.00 mmol), trichloroacetonitrile (90.0 μL, 1.10 mmol) and DBU (2.00 μL, 0.01 mmol). Concentrating *in vacuo* afforded **38a** as a colourless oil (259 mg, 92%).

Data for **38a**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.36 (1H, s, *N*H), 7.37 (2H, d, *J* = 8.8 Hz, Ar), 6.91 (2H, d, *J* = 8.7 Hz, Ar), 5.27 (2H, s, C1-H_2), 3.82 (3H, s, OMe). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 162.8 (C2), 159.9 (C Ar), 129.9 (2 × C Ar), 127.7 (C Ar), 114.1 (2 × C Ar), 90.9 (CCl_3), 70.8 (C1), 55.4 (OMe). *The spectroscopic properties were consistent with the data available in the literature.*[177]

(38b): 1-(4-Methoxyphenyl)ethyl 2,2,2-trichloroacetimidate

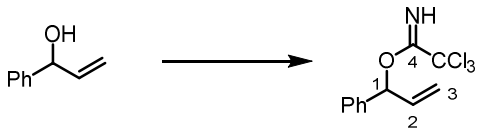


38b

Prepared according to **General Procedure M** using 1-(4-methoxyphenyl)ethanol (152 mg, 1.00 mmol), trichloroacetonitrile (90.0 μL, 1.10 mmol) and DBU (2.00 μL, 0.01 mmol). Concentrating *in vacuo* afforded **38b** as a colourless oil (248 mg, 84%).

Data for **38b**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.30 (1H, s, *N*H), 7.38 (2H, d, *J* = 8.9 Hz, Ar), 6.91 (2H, d, *J* = 8.8 Hz, Ar), 5.97 (1H, q, *J* = 6.5 Hz, C1-H), 3.82 (3H, s, OMe), 1.66 (3H, d, *J* = 6.6 Hz, C2-H_3). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 161.8 (C3), 159.4 (C Ar), 133.5 (C Ar), 127.4 (2 × C Ar), 113.9 (2 × C Ar), 90.9 (CCl_3), 77.1 (C1), 55.4 (OMe), 22.1 (C2). *The spectroscopic properties were consistent with the data available in the literature.*[178]

(38c): 1-Phenylallyl 2,2,2-trichloroacetimidate

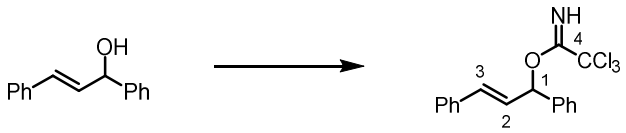


38c

Prepared according to **General Procedure M** using α-vinylbenzyl alcohol (134 mg, 1.00 mmol), trichloroacetonitrile (90.0 μL, 1.10 mmol) and DBU (2.00 μL, 0.01 mmol). Concentrating *in vacuo* afforded **38c** as a colourless oil (210 mg, 75%).

Data for **38c**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.38 (1H, s, *N*H), 7.50 – 7.28 (5H, m, Ar), 6.38 (1H, d, *J* = 5.8 Hz, C1-H), 6.09 (1H, dddd, *J* = 16.9, 10.5, 5.7, 0.6 Hz, C2-H), 5.43 (1H, ddt, *J* = 17.2, 1.4, 0.7 Hz, C3-H), 5.30 (1H, ddt, *J* = 10.5, 1.3, 0.6 Hz, C3-H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 161.5 (C4), 138.6 (C Ar), 135.9 (C2), 128.7 (2 × C Ar), 128.3 (C Ar), 127.0 (2 × C Ar), 117.3 (C3), 91.6 (CCl_3), 80.7 (C1). *The spectroscopic properties were consistent with the data available in the literature.*[179]

(38d): (*E*)-1,3-Diphenylallyl 2,2,2-trichloroacetimidate

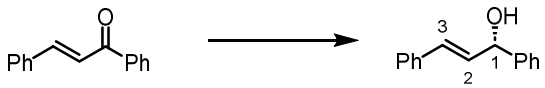


38d

Prepared according to **General Procedure M** using *(E)*-1,3-diphenylprop-2-en-1-ol (210 mg, 1.00 mmol), trichloroacetonitrile (90.0 μL, 1.10 mmol) and DBU (2.00 μL, 0.01 mmol). Concentrating *in vacuo* afforded **38d** as a colourless oil (287 mg, 81%).

Data for **38d**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.41 (1H, *br.* s, *N*H), 7.52 – 7.48 (2H, m, Ar), 7.42 – 7.36 (4H, m, Ar), 7.36 – 7.29 (3H, m, Ar), 7.29 – 7.24 (1H, m, Ar), 6.74 (1H, dd, *J* = 15.9, 1.2 Hz, C3-H), 6.55 (1H, dd, *J* = 6.6, 1.2 Hz, C1-H), 6.42 (1H, dd, *J* = 15.8, 6.6 Hz, C2-H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 161.1 (C4), 139.2 (C Ar), 136.0 (C Ar), 133.0 (C3), 129.3 (C Ar), 128.8 (2 × C Ar), 128.5 (2 × C Ar), 127.9 (C Ar), 127.2 (C2), 127.0 (2 × C Ar), 126.8 (2 × C Ar), 91.4 (CCl_3), 80.8 (C1). **HRMS** (ESI): calculated for $C_{17}H_{14}NOCl_3Na$ $[M+Na]^+$ requires *m/z* 376.0033, found *m/z* 376.0051. **IR** (film) ν_{max}: 1688, 1514, 1255, 1051, 796, 770, 695, 667 cm^{-1}. **mp** (122 – 124 °C, EtOAc).

(2g-*ent*): (*S*,*E*)-1,3-diphenylprop-2-en-1-ol

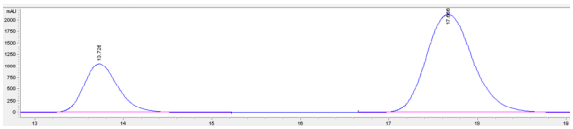


2g-*ent*

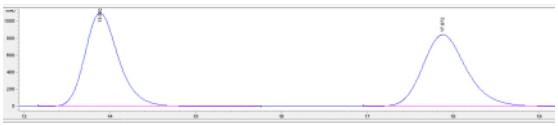
To a solution of *trans*-chalcone (125 mg, 0.600 mmol, 1.00 equiv.) in THF (1.5 mL) at –40 ˚C was added (*S*)-(+)-methyl-CBS (50 mg, 0.18 mmol, 30 mol%) and stirred for 30 min. BH_3•DMS (2.0 M in PhMe, 0.33 mL, 0.66 mmol, 1.1 equiv.) was added over 30 min before stirring at –40 ˚C for an additional 3 h. MeOH was added followed by aq sat $NaHCO_3$. The aqueous later was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over $MgSO_4$ before concentrating *in vacuo*. Flash column chromatography (15% EtOAc – pentane) afforded **2g-*ent*** as a colourless oil (82 mg, 65%).

Data for **2g-*ent***: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.45 (2H, d, *J* = 7.6 Hz, Ar), 7.42 – 7.35 (4H, m, Ar), 7.35 – 7.28 (3H, m, Ar), 7.26 – 7.23 (1H, m, Ar), 6.70 (1H, d, *J* = 16.0 Hz, C3-H), 6.40 (1H, dd, *J* = 16.0, 6.4 Hz, C2-H), 5.39 (1H, d, *J* = 6.4 Hz, C1-H), 2.15 (1H, *br.* s, *OH*). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 142.9 (C Ar), 136.6 (C Ar), 131.6 (C2), 130.7 (C3), 128.8 (C Ar), 128.7 (2 × C Ar), 128.0 (2 × C Ar), 127.9 (C Ar), 126.7 (2 × C Ar), 126.5 (2 × C Ar), 75.3 (C1). **[α]** $^{25}_{D}$ = –3.1 (0.01 g/mL, $CHCl_3$). *The spectroscopic properties were consistent with the data available in the literature.*[180]

Chiral HPLC: Chiralpak OD with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 μL injection.



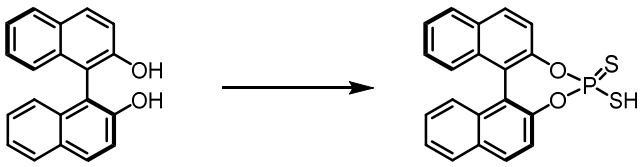
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.726	BB	28672.2	1066.2	0.4137	26.733	0.782
2	17.666	BB	78581	2127	0.573	73.267	0.837



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.882	BB	30019.6	1100.9	0.4181	49.968	0.783
2	17.872	BB	30058.5	845.1	0.545	50.032	0.807

6.3.4 Synthesis of catalysts

(cat-10a): (11b*S*)-4-Mercaptodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-sulfide

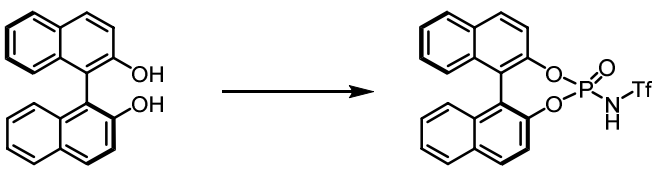


(cat-10a)

To a solution of phosphorus pentasulfide (76 mg, 0.25 mmol) in *m*-xylene (5.00 mL) was added (*S*)-BINOL (196 mg, 0.50 mmol). The solution was heated to 150 ˚C for 2 h, before cooling to rt and removing the solvent *in vacuo*. The crude material was dissolved in CH_2Cl_2 (5.0 mL) and hexane (50 mL) and concentrated *in vacuo* to 2.0 mL of solvent remained. The precipitate was collected, and washed with ice cold hexane (3 × 5.0 mL). **(cat-10a)** was isolated as a white solid (162 mg, 43%).

Data for **(cat-10a)**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.07 (2H, d, *J* = 8.8 Hz, Ar), 7.98 (2H, dt, *J* = 8.2, 1.0 Hz, Ar), 7.58 (2H, dd, *J* = 8.8, 1.4 Hz, Ar), 7.52 (2H, ddt, *J* = 8.0, 6.8, 1.1 Hz, Ar), 7.46 – 7.40 (2H, m, Ar), 7.33 (2H, ddd, *J* = 8.4, 6.7, 1.4 Hz, Ar), 3.43 (1H, s, *S*H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 147.3 (d, $J_{C\text{-}P}$ = 13.0 Hz, 2 × C Ar) 132.6 (2 × C Ar), 132.1 (2 × C Ar), 131.2 (2 × C Ar), 128.7 (2 × C Ar), 127.3(2 × C Ar), 127.0 (2 × C Ar), 126.2 (2 × C Ar), 122.8 (2 × C Ar), 121.2 (2 × C Ar). **^{31}P NMR (162 MHz, $CDCl_3$) δ** 97.2. **[α]** $^{25}_{D}$ = +418.3 (0.01 g/mL, $CHCl_3$). *The spectroscopic properties were consistent with the data available in the literature.*[181]

(cat-11a): 1,1,1-Trifluoro-*N*-((11b*S*)-4-oxidodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)-methanesulfonamide



(cat-11a)

To a solution of (*S*)-BINOL (171 mg, 0.60 mmol) in CH_2Cl_2 (3.0 mL) at 0 ˚C was added phosphorus oxychloride (67 μL, 0.72 mmol), DMAP (147 mg, 1.20 mmol) and triethylamine (0.59 mL, 4.20 mmol).

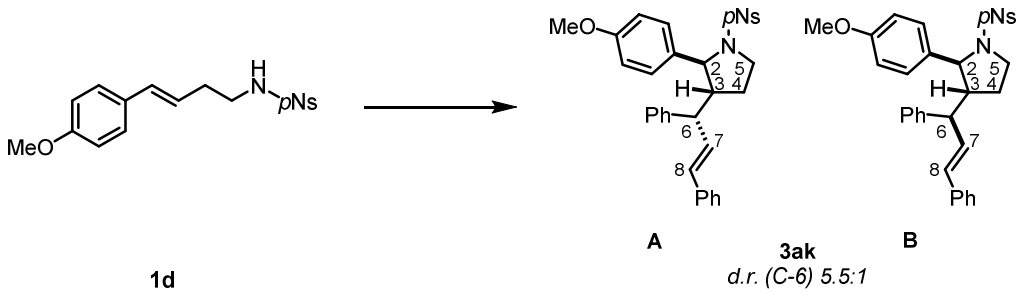
After stirring at rt for 1 h was added trifluoromethylsulfonylamide (179 mg, 1.20 mmol) and propiononitrile (3.0 mL) before heating to 100 ˚C for 16 h. After cooling to rt, the reaction was quenched with water, diluted with Et_2O and the layers separated. The organic layer was washed with sat. aq. $NaHCO_3$ and 4.0 M HCl, dried with $MgSO_4$ and concentrated *in vacuo*. The crude material underwent flash column chromatography (10% EtOAc – pentane), followed being re-dissolved in CH_2Cl_2 and acidifying with 4.0 M HCl. The organic layer was dried over Na_2SO_4 before concentrating *in vacuo*. **(cat-11a)** was isolated as a white solid (109 mg, 38%).

Data for **cat-11a**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.86 (1H, d, $J_{C\text{-}P}$ = 8.2 Hz, Ar), 7.76 (1H, d, $J_{C\text{-}P}$ = 8.2 Hz, Ar), 7.67 (1H, d, J = 8.2 Hz, Ar), 7.51 (2H, dd, J = 13.9, 8.2 Hz, Ar), 7.39 (1H, dt, J = 17.1, 8.9 Hz, Ar), 7.33 – 7.24 (3H, m, Ar), 7.20 (2H, d, J = 6.4 Hz, Ar), 7.08 (1H, dt, J = 16.2, 6.5 Hz, Ar). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 147.9 (d, $J_{C\text{-}P}$ = 10.6 Hz, C Ar), 146.8 (d, $J_{C\text{-}P}$ = 8.5 Hz, C Ar), 132.3 (C Ar), 132.2 (Ar), 131.7 (C Ar), 131.6 (C Ar), 130.9 (C Ar), 130.1 (C Ar), 128.9 (C Ar), 128.4 (C Ar), 128.2 (C Ar), 127.4 (C Ar), 127.3 (C Ar), 127.0 (C Ar), 126.7 (C Ar), 126.6 (C Ar), 125.8 (C Ar), 125.5 (C Ar), 121.9 (d, $J_{C\text{-}F}$ = 2.1 Hz) 121.5 (d, $J_{C\text{-}F}$ = 2.1 Hz), 120.0 (qd, $J_{C\text{-}F}$ = 320, 4.6 Hz, CF_3). **^{19}F NMR (377 MHz, $CDCl_3$) δ** -76.4. **^{31}P NMR (162 MHz, $CDCl_3$) δ** –3.5. **$[\alpha]_D^{25}$** = +330.7 (0.01 g/mL, $CHCl_3$).

The spectroscopic properties were consistent with the data available in the literature.[182]

6.3.5 Cyclisations

(3ak): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-((4-nitrophenyl)sulfonyl)-pyrrolidine and (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-((4-nitro-phenyl)-sulfonyl)pyrrolidine



Prepared according to **General Procedure N** using **1d** (18 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3ak** a**s** an inseparable 5.5:1 mixture of diastereomers as a colourless oil (23 mg, 83%).

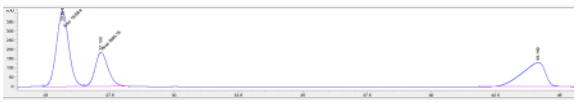
Data for **3ak-A** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 8.15 (2H, d, *J* = 8.9 Hz, Ar), 7.65 (2H, d, *J* = 8.8 Hz, Ar), 7.31 – 7.26 (4H, m, Ar), 7.24 – 7.17 (4H, m, Ar), 7.11 – 7.07 (2H, m, Ar), 6.97 (2H, d, *J* = 8.6 Hz, Ar), 6.67 (2H, d, *J* = 8.7 Hz, Ar), 6.28 (1H, d, *J* = 15.7 Hz, C8-H), 6.07 (1H, dd, *J* = 15.7, 9.1 Hz, C7-H), 4.75 (1H, d, *J* = 4.7 Hz, C2-H), 3.80 – 3.76 (1H, m, C5-H_A), 3.75 (3H, s, OMe), 3.56 (1H, dt, *J* = 9.9, 6.8 Hz, C5-H_B), 3.16 (1H, t, *J* = 9.5 Hz, C6-H), 2.62 (1H, dtd, *J* = 10.9, 6.4, 4.7 Hz, C3-H), 1.95 (1H, dq, *J* = 13.4, 6.8 Hz, C4-H_A), 1.64 – 1.55 (1H, m, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.1 (C Ar), 149.7 (C Ar), 145.5 (C Ar), 142.0 (C Ar), 136.8 (C Ar), 133.7 (C Ar), 131.7 (C7), 131.5 (C8), 129.0 (2 × C Ar), 128.7 (2 × C Ar), 128.7 (2 × C Ar), 128.3 (2 × C Ar), 127.8 (2 × C Ar), 127.7 (C Ar), 127.1 (C Ar), 126.4 (2 × C Ar), 123.9 (2 × C Ar), 113.9 (2 × C Ar), 67.1 (C2), 55.5 (OMe), 54.4 (C3), 53.1 (C6), 48.4 (C5), 28.5 (C4). **NOESY-2D (600 MHz, $CDCl_3$)**: between C2-H and C6-H, between C2-H and C7-H, between C2-H and C8-H.

Partial data for **3ak-B** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.69 (2H, d, *J* = 8.8 Hz, Ar), 7.04 – 6.99 (2H, m, Ar), 6.76 (2H, d, *J* = 8.6 Hz, Ar), 6.39 (1H, d, *J* = 15.6 Hz, C8-H), 6.17 (1H, dd, *J* = 15.7, 9.4 Hz, C7-H), 4.47 (1H, d, *J* = 4.5 Hz, C2-H), 3.75 (3H, s, OMe), 3.64 (1H, ddd, *J* = 10.0, 7.2, 5.9 Hz, C5-H_A), 2.13 (1H, dq, *J* = 13.6, 6.9 Hz, C4-H_A). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.0 (C Ar),

149.8 (C Ar), 145.2 (C Ar), 142.1 (C Ar), 133.7 (C Ar), 132.1 (C8), 130.1 (C7), 129.0 (2 × C Ar), 128.7 (2 × C Ar), 128.6 (2 × C Ar), 128.4 (2 × C Ar), 128.0 (2 × C Ar), 127.9 (C Ar), 127.1 (C Ar), 126.3 (2 × C Ar), 124.0 (2 × C Ar), 113.8 (2 × C Ar), 66.6 (C2), 55.4 (OMe), 54.2 (C3), 51.5 (C6), 48.3 (C5), 27.5 (C4).

3ak was also prepared according to **General Procedure O** using **1d** (9.0 mg, 0.025 mmol) and (*E*)-1,3-diphenyl-2-propen-1-ol (5.5 mg, 0.025 mmol) and (cat-**5e**) (2.5 mg, 15 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3ak** a**s** an inseparable 2.5:1 mixture of diastereomers as a colourless oil (11 mg, 78%).

Chiral HPLC: Chiralpak IA with guard, 15% IPA, 85% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 μL injection.

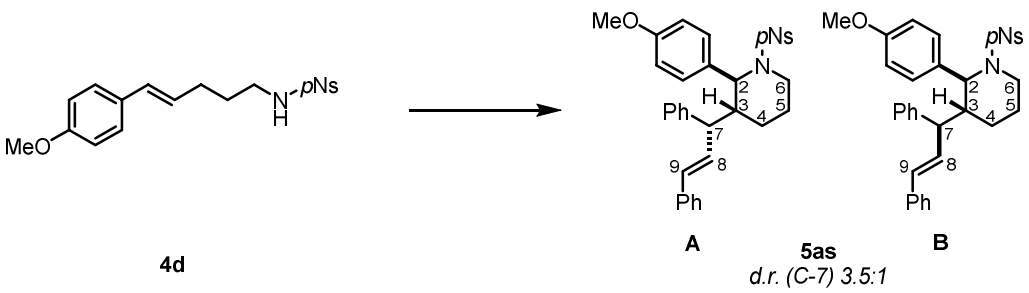


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.634	MF	13768.6	404.5	0.5673	47.542	0.968
2	27.13	FM	6595.2	185.4	0.5929	22.772	0.815
3	44.149	BB	8597.3	131.5	0.9629	29.686	2.269

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.893	BV	5899.6	158.3	0.5828	18.700	0.971
2	27.149	VB	12854.3	358.8	0.55	40.744	0.807
3	41.609	BB	12794.7	192.4	0.9778	40.555	2.781

3ak was also prepared according to **General Procedure P** using **1d** (9.0 mg, 0.025 mmol) and **38d** (9.0 mg, 0.025 mmol). Flash column chromatography (15% EtOAc – pentane) afforded **3ak** as an inseparable 2.5:1 mixture of diastereomers as a colourless oil (11 mg, 78%).

(5as): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-((4-nitrophenyl)sulfonyl)-piperidine and (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-((4-nitrophenyl)-sulfonyl)piperidine



Prepared according to **General Procedure N** using **4d** (19 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%).

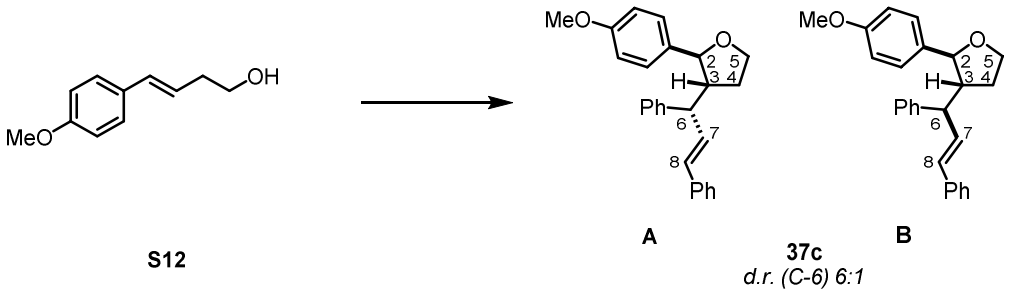
Flash column chromatography (15% EtOAc – pentane) afforded **5as** a**s** an inseparable 3.5:1 mixture of diastereomers as a colourless oil (23 mg, 81%).

Data for **5as-A** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 8.12 (2H, d, *J* = 8.9 Hz, Ar), 7.71 (2H, d, *J* = 8.9 Hz, Ar), 7.47 – 7.35 (5H, m, Ar), 7.34 – 7.28 (5H, m, Ar), 6.94 (2H, d, *J* = 8.7 Hz, Ar), 6.70 – 6.61 (3H, m, C9-H + 2 × Ar), 6.34 (1H, dd, *J* = 15.8, 9.0 Hz, C8-H), 5.44 (1H, d, *J* = 2.0 Hz, C2-H), 4.02 (1H, dd, *J* = 12.9, 5.8 Hz, C6-H_A), 3.82 – 3.78 (1H, m, C7-H), 3.73 (3H, s, OMe), 3.20 (1H, td, *J* = 12.7, 3.7 Hz, C6-H_B), 2.39 – 2.32 (1H, m, C3-H), 1.86 – 1.75 (1H, m, C5-H_A), 1.53 – 1.47 (1H, m, C4-H_A), 1.42 (1H, m, C5-H_B), 1.33 – 1.22 (1H, m, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 158.8 (C Ar), 149.6 (C Ar), 146.2 (C Ar), 142.3 (C Ar), 137.4 (C Ar), 132.9 (C9), 132.4 (C8), 132.2 (C Ar), 129.1 (2 × C Ar), 128.9 (2 × C Ar), 128.6 (2 × C Ar), 128.5 (2 × C Ar), 128.4 (2 × C Ar), 127.6 (C Ar), 126.8 (C Ar), 126.6 (2 × C Ar), 123.8 (2 × C Ar), 113.9 (2 × C Ar), 58.0 (C2), 55.5 (OMe), 49.9 (C7), 43.8 (C3), 42.6 (C6), 20.0 (C5), 19.8 (C4).

Partial data for **5as-B** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 8.08 (2H, d, *J* = 8.8 Hz, Ar), 7.61 (2H, d, *J* = 8.8 Hz, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 6.48 (1H, d, *J* = 15.6 Hz, C9-H), 6.27 (1H, dd, *J* = 15.6, 10.0 Hz, C8-H), 4.85 (1H, d, *J* = 2.7 Hz, C2-H), 3.94 – 3.88 (1H, m, C6-H_A), 3.82 – 3.79 (1H, m, C7-H), 3.71 (3H, s, OMe), 3.11 (1H, td, *J* = 12.6, 3.7 Hz, C6-H_B), 2.46 – 2.40 (1H, m, C3-H), 2.02 – 1.93 (1H, m, C5-H_A), 1.92 – 1.83 (1H, m, C4-H_A), 1.72 – 1.66(1H, m, C4-H_B), 1.49 – 1.44 (1H, m, C5-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 131.3 (C9), 131.1 (C8), 56.8 (C2), 55.4 (OMe), 49.9 (C7), 43.0 (C3), 42.0 (C6), 19.9 (C5), 19.8 (C4).

Data for **5as**: **HRMS** (ESI): calculated for $C_{33}H_{32}N_2O_5S$ $[M+Na]^+$ requires *m*/*z* 591.1924, found *m*/*z* 591.1943.

(37c): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)tetrahydrofuran and (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)tetrahydrofuran



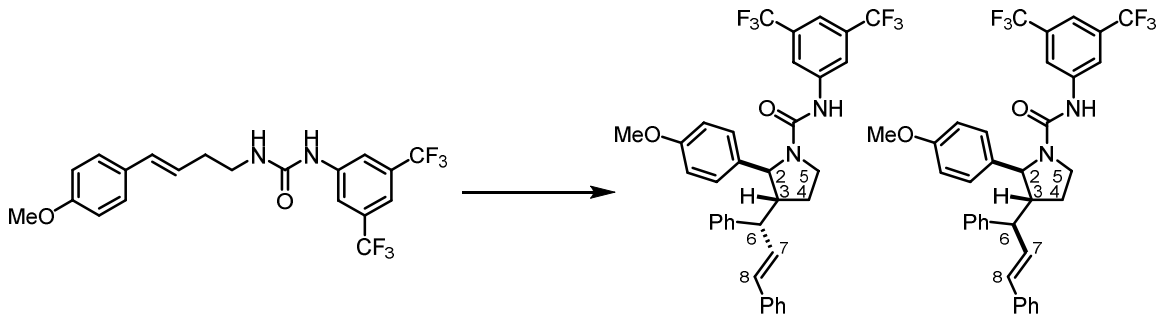
Prepared according to **General Procedure N** using **S12** (9 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **37c** as an inseparable 6:1 mixture of diastereomers as a colourless oil (12 mg, 65%).

Data for **37c-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.36 – 7.31 (2H, m, Ar), 7.29 – 7.15 (10H, m, Ar), 6.84 (2H, d, *J* = 8.7 Hz, Ar), 6.45 (1H, d, *J* = 15.7 Hz, C8-H), 6.12 (1H, dd, *J* = 15.7, 9.2 Hz, C7-H), 4.78 (1H, d, *J* = 6.0 Hz, C2-H), 4.11 (1H, td, *J* = 7.9, 5.8 Hz, C5-H_A), 3.96 (1H, dt, *J* = 8.4, 7.1 Hz, C5-H_B), 3.80 (3H, s, OMe), 3.49 (1H, t, *J* = 9.6 Hz, C6-H), 2.73 (1H, ddt, *J* = 10.3, 8.0, 6.1 Hz, C3-H), 2.08 – 1.96 (1H, m, C4-H_A), 1.72 (1H, ddt, *J* = 12.3, 7.6, 6.0 Hz, C4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.0 (C Ar), 143.4 (C Ar), 137.2 (C Ar), 135.20 (C Ar), 133.0 (C7), 130.4 (C8), 128.8 (2 × C Ar), 128.5 (2 × C Ar), 128.3 (2 × C Ar), 128.0 (2 × C Ar), 127.3 (C Ar), 126.7 (C Ar), 126.4 (2 × C Ar), 113.9 (2 × C Ar), 84.9 (C2), 67.9 (C5), 55.4 (OMe), 53.7 (C6), 52.5 (C3), 31.5 (C4).

Partial data for **37c-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.39 – 7.36 (2H, m, Ar), 6.95 (2H, d, *J* = 8.7 Hz, Ar), 6.77 (2H, d, *J* = 8.7 Hz, Ar), 6.49 (1H, d, *J* = 15.8 Hz, C8-H), 6.42 (1H, dd, *J* = 15.7, 8.7 Hz, C7-H), 4.60 (1H, d, J = 5.7 Hz, C2-H), 4.17 (1H, td, *J* = 8.0, 5.5 Hz, C5-H_A), 4.03 (1H, dt, *J* = 8.6, 7.3 Hz, C5-H_B), 3.79 (3H, s, OMe), 3.49 (1H, t, *J* = 9.6 Hz, C6-H), 2.69 – 2.66 (1H, m, C3-H), 2.19 – 2.15 (1H, m, C4-H_A), 2.12 – 2.06 (1H, m, C4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.8 (C Ar), 143.0 (C Ar), 137.3 (C Ar), 135.15 (C Ar), 131.6 (C7), 131.3 (C8), 128.7 (2 × C Ar), 128.6 (2 × C Ar), 128.3 (2 × C Ar), 128.2 (2 × C Ar), 127.5 (C Ar), 127.3 (C Ar), 126.3 (2 × C Ar), 113.7 (2 × C Ar), 84.1 (C2), 67.9 (C5), 55.4 (OMe), 53.9 (C6), 52.0 (C3), 30.2 (C4).

Data for **37c**: **HRMS** (CI): calculated for $C_{26}H_{25}O_2$ $[M+H]^+$ requires *m/z* 369.1849, found *m/z* 369.1848. **IR** (film) ν_{max}: 2979, 1511, 1451, 1244, 1030, 694 cm^{-1}.

(3al): (±)-(2*S*,3*R*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*,*E*)-1,3-diphenylallyl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxamide and (±)-(2*S*,3*R*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-3-((*R*,*E*)-1,3-diphenylallyl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxamide



Prepared according to **General Procedure N** using **1e** (22 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3al** a**s** an inseparable 7:1 mixture of diastereomers as a colourless oil (23 mg, 74%).

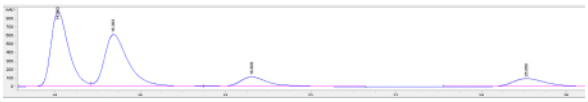
Data for **3al-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.62 (2H, s, Ar), 7.42 (1H, s, Ar), 7.38 – 7.27 (6H, m, Ar), 7.26 – 7.18 (6H, m, Ar), 6.92 (d, *J* = 8.7 Hz, Ar), 6.54 (1H, d, *J* = 15.6 Hz, C8-H), 6.34 (1H, *br.* s, *N*H), 6.25 (1H, dd, *J* = 15.7, 9.3 Hz, C7-H), 4.76 (1H, *br.* s, C2-H), 3.89 (1H, dt, *J* = 10.9, 7.6 Hz, C5-H_A), 3.81 (3H, s, OMe), 3.73 (1H, ddd, *J* = 10.8, 7.9, 5.3 Hz, C5-H_B), 3.46 (1H, t, *J* = 9.8 Hz, C6-H), 2.75 – 2.65 (1H, m, C3-H), 2.05 – 1.94 (1H, m, C4-H_A), 1.64 (1H, ddt, *J* = 12.8, 7.4, 5.3 Hz, C4-H_B). **^{19}F NMR (470 MHz, $CDCl_3$) δ** -63.03. **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.7 (C Ar), 153.5 (C Ar), 142.3 (C Ar), 140.6 (C Ar) 136.8 (C Ar), 132.1 (C7), 132.0 (q, *J* = 33.4 Hz, 2 × **C**-CF_3), 131.5 (C8), 129.1 (2 × C Ar), 128.7 (2 × C Ar), 127.9 (C Ar), 127.8 (2 × C Ar), 127.8 (2 × C Ar), 127.1 (C Ar), 126.4 (2 × C Ar), 123.3 (q, *J* = 272.8 Hz, 2 × **C**F_3), 118.8 (q, *J* = 3.4 Hz, C Ar), 115.94 (hept, *J* = 3.8 Hz, C Ar), 115.0 (2 × C Ar), 64.9 (C2), 55.4 (OMe), 55.4 (C3), 53.2 (C6), 46.3 (C5), 26.9 (C4).

Partial data for **3al-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.58 (2H, s, Ar), 6.97 (2H, d, *J* = 8.7 Hz, Ar), 6.87 (2H, d, *J* = 8.7 Hz, Ar), 4.46 (1H, *br.* s, C2-H), 3.98 – 3.90 (1H, m, C5-H_A), 3.81 (3H, s, OMe), 3.80 – 3.76 (1H, m, C5-H_B), 2.20 – 2.11 (1H, m, C4-H_A), 2.10 – 2.03 (1H, m, C4-H_B). **^{19}F NMR (470 MHz, $CDCl_3$) δ** -63.04. **^{13}C NMR (126 MHz, $CDCl_3$) δ** 142.6 (C Ar), 140.6 (C Ar), 136.9 (C Ar), 114.9 (2 × C Ar), 64.4 (C2), 55.5 (OMe), 55.0 (C3), 51.8 (C6), 46.2 (C5), 25.9 (C4).

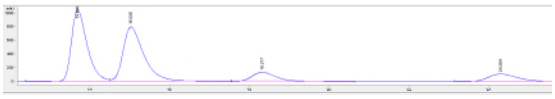
Data for **3al**: **HRMS** (ESI): calculated for $C_{35}H_{31}F_6N_2O_2$ $[M+H]^+$ requires *m/z* 625.2284, found *m/z* 625.2297. **IR** (film) ν_{max}: 1656, 1543, 1362, 1130, 910, 735, 700, 682 cm^{-1}.

3al was also prepared according to **General Procedure O** using **3al** (11 mg, 0.025 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (5.5 mg, 0.025 mmol) and (cat-**5e**) (2.5 mg, 15 mol%) at rt for 16 h. Flash column chromatography (15% EtOAc – pentane) afforded **3al** as an inseparable 7:1 mixture of diastereomers as a colourless oil (15 mg, 96%).

Chiral HPLC: Chiralpak IB with guard, 5% IPA, 95% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 μL injection.

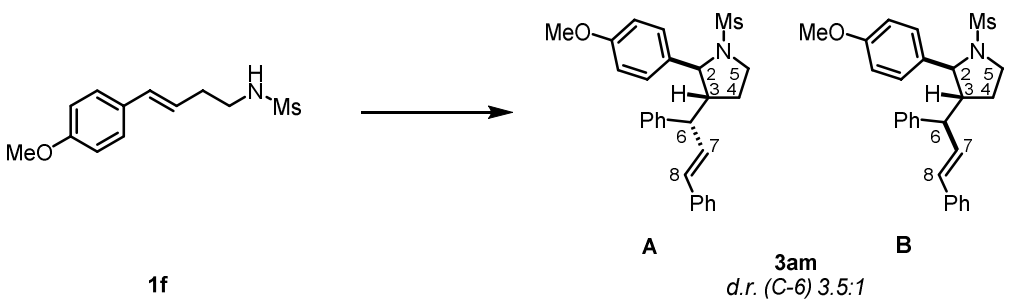


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.06	BV	25375.6	882.4	0.4355	42.711	0.624
2	15.363	VB	23492.9	610.4	0.573	39.542	0.581
3	18.608	BB	5119	110.6	0.692	8.616	0.645
4	25.05	BB	5424.9	95.9	0.8499	9.131	0.659



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.69	BV	29085.1	1054.7	0.4177	41.443	0.619
2	15.025	VB	29408	805.2	0.5461	41.903	0.567
3	18.317	BB	5748.5	134.8	0.6516	8.191	0.683
4	24.294	BB	5939.7	112.2	0.8037	8.463	0.663

(3am): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-(methylsulfonyl)-pyrrolidine and (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-(methyl-sulfonyl)-pyrrolidine



Prepared according to **General Procedure N** using **1f** (11 mg, 0.050 mmol) and (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%).

Flash column chromatography (15% EtOAc – pentane) afforded **3am** as an inseparable 2.5:1 mixture of diastereomers as a colourless oil (12 mg, 54%).

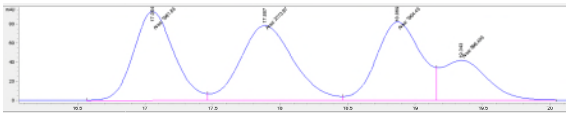
Data for **3am-A** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.34 – 7.29 (2H, m, Ar), 7.27 – 7.17 (10H, m, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.52 (1H, d, *J* = 15.7 Hz, C8-H), 6.15 (1H, dd, *J* = 15.7, 9.2 Hz, C7-H), 4.81 (1H, d, *J* = 4.5 Hz, C2-H), 3.78 (4H, s, C5-H_A + OMe), 3.52 (1H, ddd, *J* = 9.9, 7.2, 6.1 Hz, C5-H_B), 3.45 (1H, t, *J* = 9.8 Hz, C6-H), 2.69 (1H, dtd, *J* = 10.7, 6.3, 4.4 Hz, C3-H), 2.54 (3H, s, Ms), 1.97 (1H, dq, *J* = 13.6, 6.9 Hz, C4-H_A), 1.66 (1H, ddt, *J* = 13.3, 7.5, 6.0 Hz, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.0 (C Ar), 142.5 (C Ar), 137.0 (C Ar), 134.6 (C Ar), 132.1 (C7), 131.4 (C8), 129.0 (2 × C Ar), 128.6 (2 × C Ar), 128.5 (2 × C Ar), 127.9 (2 × C Ar), 127.5 (C Ar), 127.0 (C Ar), 126.5 (2 × C Ar), 114.2 (2 × C Ar), 66.5 (C2), 55.4 (OMe), 54.4 (C3), 53.3 (C7), 47.7 (C5), 39.9 (Ms), 28.7 (C4). **NOESY-2D (600 MHz, $CDCl_3$)**: between C2-H and C6-H, between C2-H and C7-H, between C2-H and C8-H.

Partial data for **3am-B** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 6.92 (2H, d, *J* = 8.6 Hz, Ar), 6.77 (2H, d, *J* = 8.7 Hz, Ar), 6.48 (1H, d, *J* = 15.7 Hz, C8-H), 6.29 (1H, dd, *J* = 15.7, 9.3 Hz, C7-H), 4.54 (1H, d, *J* = 3.7 Hz, C2-H), 3.86 – 3.81 (1H, m, C5-H_A), 3.77 (3H, s, OMe), 3.61 (1H, ddd, *J* = 9.8, 7.6, 4.9 Hz, C5-H_B), 3.45 – 3.38 (1H, m, C7-H), 2.68 – 2.60 (1H, m, C3-H), 2.60 (3H, s, Ms), 2.21 – 2.13 (1H, m, C4-H_A), 2.09 (1H, ddt, *J* = 12.5, 7.2, 4.9 Hz, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 158.9 (C Ar), 142.6 (C Ar), 137.0 (C Ar), 131.8 (C7), 130.8 (C8), 129.0 (2 × C Ar), 128.7 (2 × C Ar), 128.2 (2 × C Ar), 127.7 (C Ar), 127.6 (2 × C Ar), 127.0 (C Ar), 126.4 (2 × C Ar), 114.0 (2 × C Ar), 65.8 (C2), 55.4 (OMe), 54.2 (C3), 51.9 (C7), 47.5 (C5), 39.5 (Ms), 27.5 (C4).

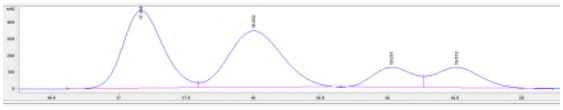
Data for **3am**: **HRMS** (ESI): calculated for $C_{27}H_{29}NO_3SNa$ $[M+Na]^+$ requires *m/z* 470.1760, found *m/z* 470.1768. **IR** (film) ν_{max}: 1612, 1328, 1248, 1149, 1031, 911, 829, 700 cm^{-1}.

3am was also prepared according to **General Procedure O** using **1f** (11 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and (cat-**5e**) (5.0 mg, 15 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3am** as an inseparable 2:1 mixture of diastereomers as a colourless oil (9.0 mg, 40%).

Chiral HPLC: Chiralpak IA with guard, 15% IPA, 85% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 7.0 µL injection.

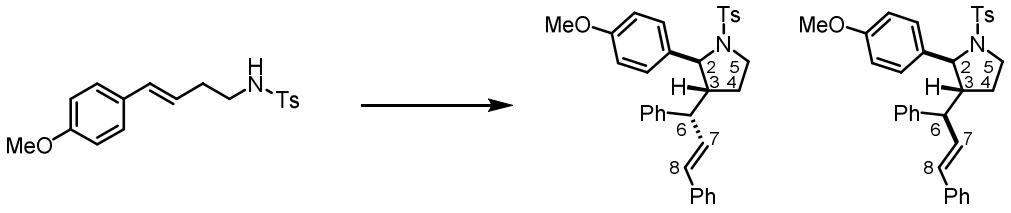


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.054	MF	1961.8	93.7	0.349	27.881	0.86
2	17.887	MF	2173.7	79.1	0.4582	30.892	0.841
3	18.869	MF	1904.4	82.5	0.3847	27.066	0.891
4	19.343	FM	996.4	42.2	0.3937	14.161	0.708



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.165	BV	9801.3	469.4	0.3236	39.309	0.806
2	18.002	VB	9556.4	341.7	0.4403	38.327	0.852
3	19.031	BV	2563.8	121.6	0.324	10.282	0.897
4	19.512	VB	3012.5	124.6	0.364	12.082	0.834

(3an): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-tosylpyrrolidine and (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-tosylpyrrolidine



1g **3an** *d.r. (C-6) 4.5:1*

Prepared according to **General Procedure N** using **1g** (16.5 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3an** as an inseparable 4.5:1 mixture of diastereomers as a colourless oil (25 mg, 92%).

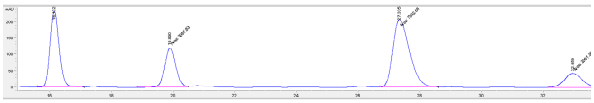
Data for **3an-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.69 (2H, d, *J* = 8.3 Hz, Ar), 7.40 – 7.21 (10H, m, Ar), 7.21 – 7.12 (2H, m, Ar), 7.03 – 6.95 (2H, m, Ar), 6.80 (2H, d, *J* = 8.7 Hz, Ar), 6.14 – 6.08 (2H, m, C7-H + C8-H), 4.70 (1H, d, *J* = 2.8 Hz, C2-H), 3.79 (3H, s, OMe), 3.64 (1H, ddd, *J* = 9.7, 7.7, 3.8 Hz, C5-H_A), 3.50 (1H, td, *J* = 9.4, 6.8 Hz, C5-H_B), 2.74 (1H, dd, *J* = 10.8, 7.7 Hz, C6-H), 2.49 (4H, s, C3-H + TsMe), 1.90 (1H, ddt, *J* = 13.0, 9.2, 7.4 Hz, C4-H_A), 1.38 (1H, ddt, *J* = 12.9, 7.1, 3.8 Hz, C4-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.7 (C Ar), 143.3 (C Ar), 142.2 (C Ar), 137.0 (C Ar), 135.8 (C Ajr), 135.4 (C Ar), 132.1 (C7/8), 131.6 (C7/8), 129.7 (2 × C Ar), 129.0 (2 × C Ar), 128.7 (2 × C Ar), 127.8 (2 × C Ar), 127.8 (2 × C Ar), 127.7 (2 × C Ar), 127.6 (C Ar), 126.9 (C Ar), 126.3 (2 × C Ar), 113.9 (2 × C Ar), 66.4 (C2), 55.4 (OMe), 54.2 (C3), 52.2 (C6), 48.0 (C5), 27.1 (C4), 21.8 (TsMe). **NOESY-2D (500 MHz, $CDCl_3$)**: between C2-H and C6-H, between C2-H and C7/8-H.

Partial data for **3an-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.64 (2H, d, *J* = 8.3 Hz, Ar), 6.96 – 6.88 (4H, m, Ar), 6.75 (2H, d, *J* = 8.7 Hz, Ar), 6.28 (1H, d, *J* = 15.6 Hz, C8-H), 4.37 (1H, d, *J* = 3.4 Hz, C2-H), 3.78 (3H, s, OMe), 3.69 (1H, ddd, *J* = 9.9, 7.5, 4.4 Hz, C5-H_A), 3.61 – 3.56 (1H, m, C5-H_B), 2.93 (1H, t, *J* = 9.6 Hz, C7-H), 2.46 (3H, s, TsMe), 2.10 – 1.98 (1H, m, C4-H_A), 1.88 – 1.77 (1H, m, C4-H_B). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 158.7 (C Ar), 142.4 (C Ar), 137.0 (C Ar), 135.2 (C Ar), 131.7 (C8), 128.9 (2 × C Ar), 128.7 (2 × C Ar), 113.8 (2 × C Ar), 66.0 (C2), 55.4 (OMe), 51.1 (C7), 26.6 (C4), 21.7 (TsMe).

Data for **3an**: **HRMS** (ESI): calculated for $C_{33}H_{33}NO_5SNa$ $[M+Na]^+$ requires *m/z* 546.2073, found *m/z* 546.2078. **IR** (film) ν_{max}: 2360, 1512, 1347, 1248, 1161, 1031, 735, 664 cm^{-1}.

3an was also prepared according to **General Procedure O** using **1g** (8 mg, 0.025 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (5.5 mg, 0.025 mmol) and (cat-**5e**) (2.5 mg, 15 mol%) at 80 ˚C for 72 h. Flash column chromatography (15% EtOAc – pentane) afforded **3an** a**s** an inseparable 0.9:1 mixture of diastereomers as a colourless oil (10.0 mg, 78%).

Chiral HPLC: Chiralpak IA with guard, 15% IPA, 85% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 μL injection.



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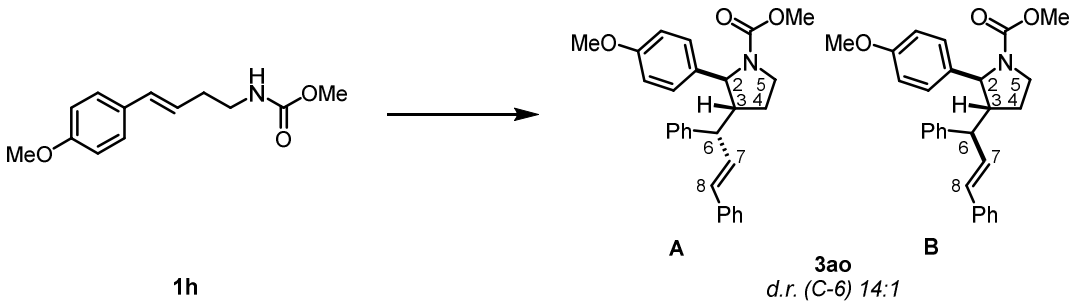
1	16.132	BB	4821.3	233.6	0.3168	27.005	0.798
2	19.89	MF	3097.6	121.6	0.4247	17.350	0.911
3	27.335	MM	7932.9	210.5	0.6281	44.433	0.658
4	32.959	MM	2001.6	45	0.7416	11.211	0.886

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	16.185	BB	16223.3	774.8	0.3203	39.016	0.763
2	19.986	BV R	16509	642	0.3877	39.703	0.891
3	27.543	BB	4411.9	119	0.5704	10.610	0.703
4	33.094	BB	4436.9	104.5	0.6551	10.670	0.85

3an was also prepared using **1g** (16 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.50 mmol), $Sc(OTf)_3$ (5.5 mg, 10 mol%) and (L-**4**) in DCE (1.0 mL) at rt for 16 h. Flash column chromatography (15% EtOAc – pentane) afforded **3an** as an inseparable 5:1 mixture of diastereomers as a colourless oil (10.0 mg, 38%).

(3ao): (±)-Methyl (2*S*,3*R*)-3-((S,*E*)-1,3-diphenylallyl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate and (±)-Methyl (2*S*,3*R*)-3-((*R*,*E*)-1,3-diphenylallyl)-2-(4-methoxy-phenyl)pyrrolidine-1-carboxylate



Prepared according to **General Procedure N** using **1h** (12 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3ao** as an inseparable 14:1 mixture of diastereomers as a colourless oil (17 mg, 80%).

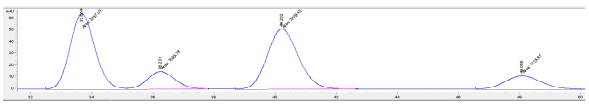
Data for **3ao-A** (from the mixture): **^{1}H NMR (500 MHz, PhMe) δ** 7.46 – 7.36 (4H, m, Ar), 7.31 – 7.22 (8H, m, Ar), 6.96 (2H, d, *J* = 8.6 Hz, Ar), 6.64 (1H, d, *J* = 15.7 Hz, C8-H), 6.50 (1H, dd, *J* = 15.7, 8.7 Hz, C7-H), 5.30 (1H, s, C2-H), 3.93 (1H, dd, *J* = 17.0, 7.4 Hz, C5-H$_A$), 3.81 – 3.73 (1H, m, C5-H$_B$), 3.72 (3H, s, OMe), 3.65 (3H, s, OMe), 3.51 (1H, t, *J* = 9.3 Hz, C6-H), 2.76 (1H, ddt, *J* = 10.2, 7.2, 3.8 Hz, C3-H), 1.96 (1H, dt, *J* = 14.9, 7.4 Hz, C4-H$_A$), 1.62 (1H, ddt, *J* = 12.6, 7.6, 4.7 Hz, C4-H$_B$). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 158.5 (C Ar), 157.6 (CO), 142.8 (C Ar), 137.2 (C Ar), 131.4 (C7), 129.1 (2 × C Ar), 128.7 (2 × C Ar), 128.1 (C8), 127.9 (2 × C Ar), 127.6 (2 × C Ar), 127.0 (C Ar), 126.8 (C Ar), 126.4 (2 × C Ar), 113.9 (2 × C Ar), 64.2 (C2), 55.4 (OMe), 53.3 (C3), 52.8 (C6), 52.5 (OMe), 46.0 (C5), 25.9 (C4). **NOESY-2D (500 MHz, PhMe)**: between C2-H and C7-H, between C2-H and C8-H.

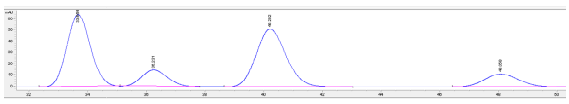
Characteristic data for **3ao-B** (from the mixture): **^{1}H NMR (500 MHz, PhMe) δ** 7.11 (2H, d, *J* = 8.3 Hz, Ar), 6.92 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (1H, d, *J* = 15.7 Hz, C8-H), 6.44 (1H, dd, *J* = 15.7, 8.8 Hz, C7-H), 5.00 (1H, s, C2-H), 3.64 (3H, s, OMe), 2.67 (1H, td, *J* = 6.7, 3.4 Hz, C3-H), 2.11 (1H, dd, *J* = 13.4, 7.1 Hz, C4-H$_A$), 2.03 (1H, dt, *J* = 8.6, 4.4 Hz, C4-H$_B$). ***3ao*** *shows rotameric character and the ^{13}C characterisation of minor diastereomer* ***3ao-B*** *was not possible.*

Data for **3ao**: **HRMS** (ESI): calculated for $C_{28}H_{30}NO_3$ $[M+H]^+$ requires m/z 428.2220, found m/z 428.2232. **IR** (film) ν_{max}: 2927, 1699, 1512, 1451, 1248, 1034, 967, 701, 656 cm^{-1}.

3ao was also prepared according to **General Procedure O** using **1h** (5.5 mg, 0.025 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (5.5 mg, 0.025 mmol) and (cat-**5e**) (2.5 mg, 15 mol%) at 80 °C for 72 h. Flash column chromatography (15% EtOAc – pentane) afforded **3ao** as an inseparable 12:1 mixture of diastereomers as a colourless oil (3.5 mg, 40%).

Chiral HPLC: Chiralpak IC with guard, 5% IPA, 95% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 μL injection.





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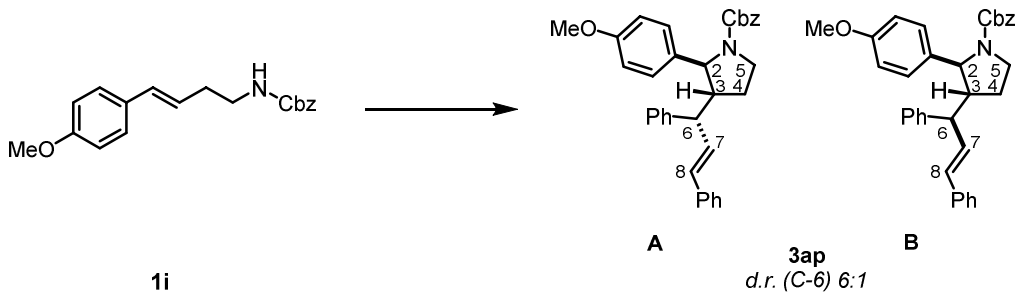
1	33.654	MF	3757.5	65.3	0.9589	38.904	0
2	36.231	FM	1005.8	14.9	1.126	10.414	0.878
3	40.202	MM	3779.4	51.9	1.2146	39.131	0.855
4	48.058	MM	1115.6	11.8	1.571	11.551	0.824

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	33.654	BB	3576.9	64.2	0.844	39.911	0.882
2	36.231	BB	848.8	13.8	0.8756	9.471	0.855
3	40.202	BB	3619.1	51.1	1.0602	40.382	0.84
4	48.058	BB	917.4	10.9	0.9954	10.236	0.844

(3ap): (±)-Benzyl (2*S*,3*R*)-3-((*S*,*E*)-1,3-diphenylallyl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate and Benzyl (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-diphenylallyl)-2-(4-methoxy-phenyl)-pyrrolidine-1-carboxylate



Prepared according to **General Procedure N** using **1i** (15.5 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3ap** as an inseparable 6:1 mixture of diastereomers as a colourless oil (20 mg, 80%).

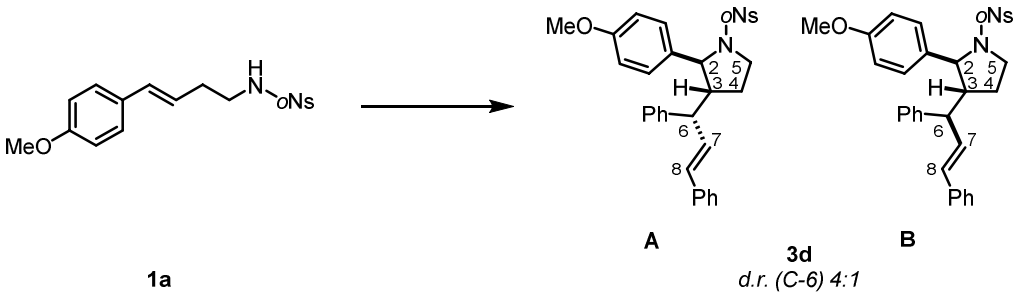
Data for **3ap-A** (from the mixture): **^{1}H NMR (500 MHz, PhMe) δ** 7.43 – 7.19 (17H, m, Ar), 6.94 (2H, d, *J* = 8.6 Hz, Ar), 6.61 (1H, d, *J* = 15.8 Hz, C8-H), 6.47 (1H, dd, *J* = 15.8, 8.8 Hz, C7-H), 5.46 – 5.26 (3H, m, C2-H + OC**H$_2$**Ph), 4.00 – 3.92 (1H, m, C5-H$_A$), 3.78 (1H, s, C5-H$_B$), 3.67 (3H, s, OMe), 3.49 (1H, t, *J* = 9.4 Hz, C6-H), 2.75 (1H, ddt, *J* = 10.3, 7.4, 4.0 Hz, C3-H), 1.95 (1H, dq, *J* = 14.8, 7.6 Hz,

C4-H_A), 1.66 – 1.56 (1H, m, C4-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 158.6 (C Ar), 154.9 (CO), 142.8 (C Ar), 137.2 (C Ar), 136.2 (C Ar), 132.6 (C7), 131.3 (C8), 129.0 (C Ar), 129.0 (2 × C Ar), 128.7 (2 × C Ar), 128.6 (2 × C Ar), 128.3 (C Ar), 127.9 (2 × C Ar), 127.5 (C Ar), 127.4 (2 × C Ar), 126.8 (C Ar), 126.5 (4 × C Ar), 113.9 (2 × C Ar), 66.7 (O**C**H_2Ph), 64.4 (C2), 55.4 (OMe), 53.8 (C3), 53.0 (C7), 46.3 (C5), 26.4 (C4). **NOESY-2D (500 MHz, PhMe)**: between C2-H and C7-H, between C2-H and C8-H.

Characteristic data for **3ap-B** (from the mixture): **^{1}H NMR (500 MHz, PhMe) δ** 6.92 – 6.87 (2H, m, Ar), 6.57 (1H, d, *J* = 15.7 Hz, C8-H), 5.25 (2H, s, OC**H_2**Ph), 3.66 (3H, s, OMe), 2.71 – 2.61 (1H, m, C3-H), 2.18 – 2.05 (1H, m, C4-H_A), 2.05 – 1.99 (1H, m, C4-H_B). ***3ap*** *shows rotameric character and the ^{13}C characterisation of minor diastereomer* ***3ap-B*** *was not possible.*

Data for **3ap**: **HRMS** (ESI): calculated for $C_{28}H_{30}NO_3$ $[M+H]^+$ requires *m/z* 428.2220, found *m/z* 428.2232. **IR** (film) ν_{max}: 2884, 1771, 1733, 1699, 1652, 1576, 1540, 1496, 1457, 1418, 953 cm^{-1}.

(3d): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)-pyrrolidine and (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-((2-nitro-phenyl)-sulfonyl)pyrrolidine



Prepared according to **General Procedure N** using **1a** (18 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3d** as an inseparable 4:1 mixture of diastereomers as a colourless oil (20 mg, 72%).

Data for **3d-A** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.43 – 7.52 (2H, m, Ar), 7.13 – 7.33 (12H, m, Ar), 7.02 (2H, d, *J* = 8.7 Hz, Ar), 6.55 (2H, d, *J* = 8.7 Hz, Ar), 6.37 (1H, d, *J* = 15.8 Hz, C8-H), 6.04 (1H, dd, *J* = 15.8, 9.3 Hz, C7-H), 4.84 (1H, d, *J* = 5.7 Hz, C2-H), 3.97 (1H, ddd, *J* = 10.3, 7.5,

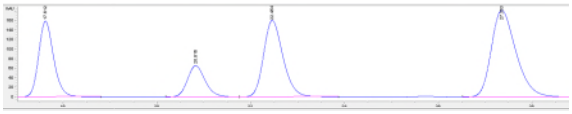
5.2 Hz, C5-H_A), 3.81 (1H, dt, *J* = 10.3, 7.5 Hz, C5-H_B), 3.70 (3H, s, OMe), 3.39 (1H, t, *J* = 9.8 Hz, C6-H), 2.64 – 2.71 (1H, m, C3-H), 1.89 – 1.97 (1H, m, C4-H_A), 1.67 (1H, dq, *J* = 12.7, 7.5 Hz, C4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.9 (C Ar), 147.5 (C Ar), 142.4 (C Ar), 137.0 (C Ar), 133.9 (C Ar), 133.2 (C Ar), 132.6 (C Ar), 132.2 (C7), 131.1 (C8), 131.0 (2 × C Ar), 129.1 (2 × C Ar), 129.0 (2 × C Ar), 128.5 (2 × C Ar), 127.7 (2 × C Ar), 127.5 (C Ar), 126.9 (C Ar), 126.4 (2 × C Ar), 123.5 (C Ar), 113.7 (2 × C Ar), 67.2 (C2), 55.4 (OMe), 55.0 (C3), 53.5 (C6), 49.2 (C5), 29.1 (C4). **NOESY-2D (500 MHz, $CDCl_3$)**: between C2-H and C6-H, between C2-H and C7-H, between C2-H and C8-H.

Partial data for **3d-B** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.43 – 7.52 (2H, m, Ar), 7.13 – 7.33 (10H, m, Ar), 7.07 (2H, d, *J* = 6.9 Hz, Ar), 6.76 (2H, d, *J* = 8.7 Hz, Ar), 6.53 (2H, d, *J* = 8.7 Hz, Ar), 6.45 (1H, d, *J* = 15.7 Hz, C8-H), 6.29 (1H, dd, *J* = 15.7, 9.3 Hz, C7-H), 4.59 (1H, d, *J* = 5.3 Hz, C2-H), 4.04 (1H, ddd, *J* = 10.2, 7.4, 6.0 Hz, C5-H_A), 3.83 – 3.89 (1H, m, C5-H_B), 3.70 (3H, s, OMe), 3.38 (1H, d, *J* = 6.0 Hz, C6-H), 2.60 – 2.65 (1H, m, C3-H), 2.12 – 2.20 (1H, m, C4-H_A), 1.99 – 2.07 (1H, m, C4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.8 (C Ar), 147.6 (C Ar), 142.4 (C Ar), 137.0 (C Ar), 133.7 (C Ar), 133.1 (C Ar), 132.7 (C Ar), 132.0 (C8), 131.09 (C Ar), 130.3 (C7), 128.8 (2 × C Ar), 128.7 (2 × C Ar), 128.0 (2 × C Ar), 128.0 (2 × C Ar), 127.6 (C Ar), 126.9 (C Ar), 126.4 (C Ar), 126.4 (2 × C Ar), 123.5 (C Ar), 113.6 (2 × C Ar), 66.5 (C2), 55.4 (OMe), 54.8 (C3), 51.5 (C6), 48.9 (C5), 27.7 (C4).

Data for **3d**: **HRMS** (ESI): calculated for $C_{32}H_{30}N_2O_5SNa$ $[M+Na]^+$ requires *m*/*z* 577.1773, found *m*/*z* 577.1764. **IR** (film) ν_{max}: 2980, 2888, 1541, 1511, 1372, 1159 cm^{-1}.

3d was also prepared according to **General Procedure O** using **1a** (9.0 mg, 0.025 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (5.5 mg, 0.025 mmol) and (cat-**5e**) (2.5 mg, 15 mol%) at 80 °C for 72 h. Flash column chromatography (15% EtOAc – pentane) afforded **3d** as an inseparable 1.25:1 mixture of diastereomers as a colourless oil (8.0 mg, 58%).

Chiral HPLC: Chiralpak IA with guard, 15% IPA, 85% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 μL injection.



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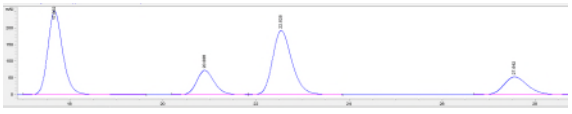
2	20.816	BB	1728.8	65.3	0.405	10.438	0.818
3	22.454	BB	4612.5	159.5	0.4455	27.849	0.767
4	27.353	BB	6673.4	180.8	0.5667	40.292	0.694



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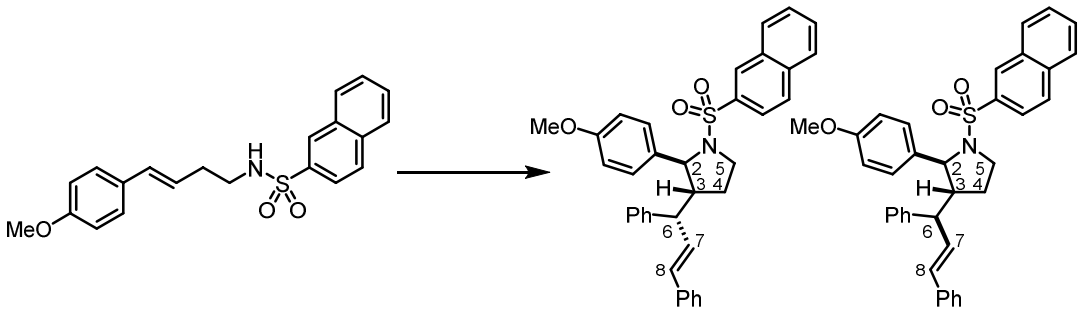
2	20.886	BB	1931.4	73.2	0.406	12.790	0.821
3	22.528	BB	5585.5	192.5	0.4444	36.989	0.759
4	27.542	BB	1942.4	53.8	0.5514	12.863	0.769

(3ar): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-(naphthalen-2-yl-sulfonyl)-pyrrolidine and (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-(naphthalen-2-ylsulfonyl)-pyrrolidine



1k

3ar
d.r. (C-6) 5.5:1

Prepared according to **General Procedure N** using **1k** (18 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3ar** a**s** an inseparable 5.5:1 mixture of diastereomers as a colourless oil (22 mg, 79%).

Data for **3ar-A** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 8.29 (1H, d, *J* = 2.2 Hz, Ar), 7.85 (1H, dd, *J* = 8.7, 2.3 Hz, Ar), 7.34 – 7.28 (5H, m, Ar), 7.25 – 7.21 (4H, m, Ar), 7.21 – 7.16 (4H, m, Ar), 7.10 – 7.07 (2H, m, Ar), 6.97 (2H, d, *J* = 8.7 Hz, Ar), 6.49 (2H, d, *J* = 8.7 Hz, Ar), 6.41 (1H, d, *J* = 15.7 Hz, C8-H), 5.95 (1H, dd, *J* = 15.7, 9.4 Hz, C7-H), 4.77 (1H, d, *J* = 7.0 Hz, C2-H), 4.03 (1H, ddd, *J* = 10.4, 7.7, 3.8 Hz, C5-H_A), 3.81 (1H, ddd, *J* = 10.4, 9.2, 6.4 Hz, C5-H_B), 3.66 (3H, s, OMe), 3.45 (1H, t, *J* = 9.7 Hz, C6-H), 2.79 – 2.69 (1H, m, C3-H), 1.96 (1H, dtd, *J* = 12.6, 6.3, 3.7 Hz, C4-H_A), 1.74 (1H, dtd, *J* = 12.7, 9.1, 7.8 Hz, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.4 (C Ar), 148.8 (C Ar), 147.2 (C Ar), 142.2 (C Ar), 142.0, 139.5 (C Ar), 136.8 (C Ar), 132.8 (C Ar), 132.6 (C Ar), 132.4 (C Ar), 132.0

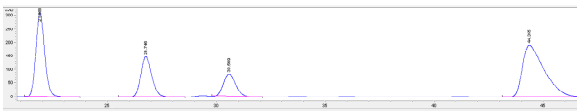
(C7), 131.0 (C8), 129.8 (2 × C Ar), 129.1 (2 × C Ar), 128.5 (2 × C Ar), 127.7 (2 × C Ar), 127.7 (2 × C Ar), 127.6 (C Ar), 127.1 (C Ar), 126.4 (3 × C Ar), 124.9 (C Ar), 118.9 (C Ar), 113.8 (2 × C Ar), 67.9 (C2), 55.4 (C3), 55.2 (OMe), 54.0 (C6), 49.9 (C5), 30.1 (C4). **NOESY-2D (600 MHz, $CDCl_3$)**: between C2-H and C6-H, between C2-H and C7-H, between C2-H and C8-H.

Partial data for **3ar-B** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 8.27 (1H, d, *J* = 2.2 Hz, Ar), 6.70 (2H, d, *J* = 8.6 Hz, Ar), 6.47 – 6.44 (2H, m, Ar), 6.31 (1H, dd, *J* = 15.7, 9.2 Hz, C7-H), 4.58 (1H, d, *J* = 6.7 Hz, C2-H), 4.11 – 4.06 (1H, m, C5-H_A), 3.89 – 3.85 (1H, m, C5-H_B), 3.66 (3H, s, OMe), 3.44 – 3.40 (1H, m, C6-H), 2.73 – 2.68 (1H, m, C3-H), 2.23 (1H, dtd, *J* = 12.8, 6.5, 4.4 Hz, C4-H_A), 2.09 – 2.01 (1H, m, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.2 (C Ar), 148.9 (C Ar), 147.2 (C Ar), 142.0 (C Ar), 139.3 (C Ar), 136.7 (C Ar), 132.4 (C Ar), 132.3 (C Ar), 113.6 (2 × C Ar), 67.3 (C2), 55.4 (OMe), 54.8 (C3), 51.9 (C6), 49.7 (C5), 28.8 (C4).

Data for **3ar**: **HRMS** (ESI): calculated for $C_{36}H_{33}NO_3SNa$ $[M+Na]^+$ requires *m/z* 582.2073, found *m/z* 582.2093. **IR** (film) ν_{max}: 1512, 1341, 1249, 1160, 909, 732, 662 cm^{-1}.

3ar was also prepared according to **General Procedure O** using **1k** (9.0 mg, 0.025 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (5.5 mg, 0.025 mmol) and (cat-**5e**) (2.5 mg, 15 mol%) at 80 °C for 72 h. Flash column chromatography (15% EtOAc – pentane) afforded **3ar** as an inseparable 1:1 mixture of diastereomers as a colourless oil (8.0 mg, 57%).

Chiral HPLC: Chiralpak IA with guard, 15% IPA, 85% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 μL injection.



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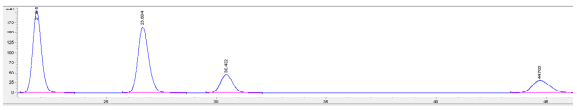
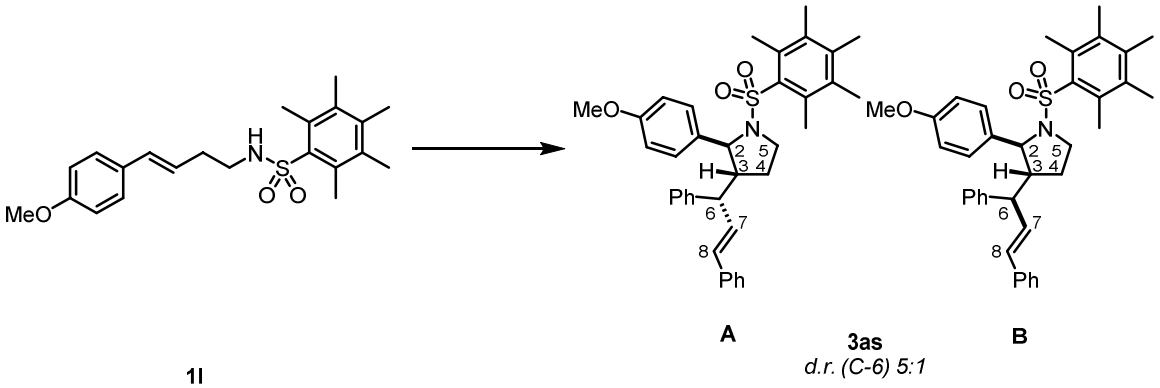
3	30.569	BB	3179.3	81.9	0.5989	10.549	0.844
4	44.355	BB	13190.4	190	1.0218	43.765	0.44



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	21.815	BB	5637	203.1	0.4277	38.108	0.843
2	26.634	BB	5665.1	165.2	0.5282	38.298	0.796
3	30.432	BB	1743.8	45.2	0.5956	11.788	0.879
4	44.7	BB	1746.2	29.5	0.8764	11.805	0.761

(3as): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-((2,3,4,5,6-pentamethyl-phenyl)sulfonyl)pyrrolidine and (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-Diphenylallyl)-2-(4-methoxy-phenyl)-1-((2,3,4,5,6-pentamethyl-phenyl)sulfonyl)pyrrolidine



Prepared according to **General Procedure N** using **1l** (19 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3as** as an inseparable 5:1 mixture of diastereomers as a colourless oil (24 mg, 83%).

Data for **3as-A** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.36 – 7.12 (10H, m, Ar), 6.82 (2H, d, *J* = 8.5 Hz, Ar), 6.54 – 6.41 (3H, m, C8-H + 2 × Ar), 6.05 (1H, dd, *J* = 15.7, 9.3 Hz, C7-H), 4.66 (1H, d, *J* = 4.7 Hz, C2-H), 3.89 (1H, dt, *J* = 10.2, 7.4 Hz, C5-H_A), 3.69 (3H, s, OMe), 3.57 – 3.43 (2H, m, C5-H_B + C7-H), 2.60 (1H, dq, *J* = 10.8, 5.4 Hz, C3-H), 2.45 (6H, s, ArMe), 2.12 (3H, s, ArMe), 2.05 (6H, s, ArMe), 1.97 (1H, dq, *J* = 14.5, 7.4 Hz, C4-H_A), 1.73 – 1.63 (1H, m, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 158.4 (C Ar), 142.8 (C Ar), 139.5 (C Ar), 137.3 (C Ar), 135.3 (2 × C Ar), 135.1 (C Ar), 134.4 (2 × C Ar), 134.1 (C Ar), 132.5 (C7), 131.1 (C8), 128.9 (2 × C Ar), 128.5 (2 × C Ar), 128.2 (2 × C Ar), 127.9 (2 × C Ar), 127.3 (C Ar), 126.8 (C Ar), 126.4 (2 × C Ar), 112.9 (2 × C Ar), 66.3 (C2), 55.2 (OMe), 54.4 (C3), 53.1 (C7), 47.3 (C5), 28.7 (C4), 18.9 (2 × Ar**Me**), 17.7 (Ar**Me**), 16.9 (2 × Ar**Me**). **NOESY-2D (600 MHz, $CDCl_3$)**: between C2-H and C7-H, between C2-H and C8-H.

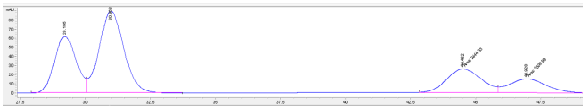
Partial data for **3as-B** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 6.30 (1H, dd, *J* = 15.7, 9.4 Hz, C7-H), 4.39 (1H, d, *J* = 4.4 Hz, C2-H), 3.98 – 3.92 (1H, m, C5-H_A), 3.56 (1H, ddd, *J* = 10.0, 5.0, 2.2 Hz, C5-H_B), 2.53 (1H, td, *J* = 8.4, 5.6 Hz, C3-H), 2.41 (6H, s, 2 × ArMe). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 158.3 (C Ar), 142.9 (C Ar), 137.2 (C Ar), 135.4 (2 × C Ar), 131.8 (2 × C Ar), 130.8 (2 × C Ar), 128.7

(2 × C Ar), 128.6 (2 × C Ar), 128.4 (2 × C Ar), 127.4 (C Ar), 126.8 (C Ar), 126.4 (2 × C Ar), 112.8 (2 × C Ar), 65.6 (C2), 55.2 (OMe), 54.4 (C3), 51.2 (C7), 47.0 (C5), 27.5 (C4), 18.8 (2 × Ar**Me**), 17.8 (Ar**Me**), 16.9 (2 × Ar**Me**).

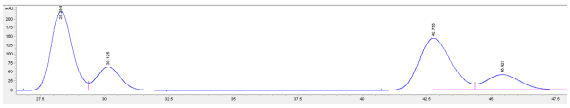
Data for **3as**: **HRMS** (ESI): calculated for $C_{37}H_{41}NO_3SNa$ $[M+Na]^+$ requires m/z 602.2699, found m/z 602.2719. **IR** (film) ν_{max}: 1512, 1303, 1248, 1142, 967, 732 cm^{-1}.

3as was also prepared according to **General Procedure O** using **1k** (9.5 mg, 0.025 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (5.5 mg, 0.025 mmol) and (cat-**5e**) (2.5 mg, 15 mol%) at 80 °C for 72 h. Flash column chromatography (15% EtOAc – pentane) afforded **3as** as an inseparable 1.25:1 mixture of diastereomers as a colourless oil (8 mg, 55%).

Chiral HPLC: Chiralpak IC with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 μL injection.

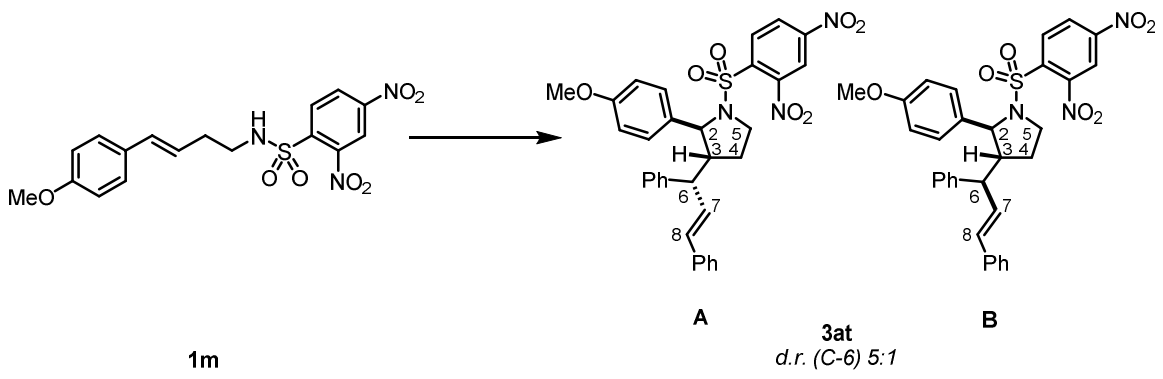


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	29.195	BV	3616.1	61.5	0.8975	26.845	0.879
2	30.963	VB	5899.8	88.9	1.0103	43.799	0.86
3	44.482	MF	2444.3	26.3	1.5467	18.146	0.868
4	46.928	FM	1510	14.9	1.6915	11.210	0.859



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	28.284	BV	12663.8	223.1	0.8761	37.892	0.824
2	30.125	VB	4107.4	65.7	0.9453	12.290	0.875
3	42.755	BV	12622.9	145.6	1.3213	37.769	0.787
4	45.427	VB	4026.8	42	1.2593	12.049	0.831

(3at): (±)-(2*S*,3*R*)-1-((2,4-Dinitrophenyl)sulfonyl)-3-((*S*,*E*)-1,3-diphenylallyl)-2-(4-methoxy-phenyl)-pyrrolidine and (±)-(2*S*,3*R*)-1-((2,4-Dinitrophenyl)sulfonyl)-3-((*R*,*E*)-1,3-diphenyl-allyl)-2-(4-methoxy-phenyl)pyrrolidine



Prepared according to **General Procedure N** using **1m** (20 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%).

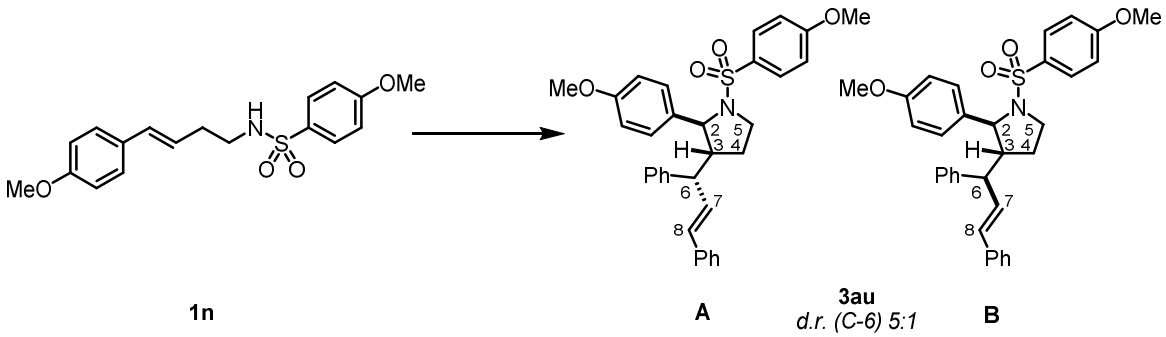
Flash column chromatography (15% EtOAc – pentane) afforded **3at** as an inseparable 5:1 mixture of diastereomers as a yellow oil (24 mg, 80%).

Data for **3at-A** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 8.23 (1H, dd, *J* = 1.6, 0.8 Hz, Ar), 7.99 – 7.93 (2H, m, Ar), 7.89 – 7.86 (1H, m, Ar), 7.79 (1H, dd, *J* = 8.6, 1.8 Hz, Ar), 7.68 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz, Ar), 7.62 (1H, ddd, *J* = 8.1, 6.9, 1.2 Hz, Ar), 7.26 – 7.23 (1H, m, Ar), 7.23 – 7.18 (3H, m, Ar), 7.17 – 7.12 (2H, m, Ar), 7.08 – 7.04 (1H, m, Ar), 6.96 – 6.92 (1H, m, Ar), 6.72 (2H, d, *J* = 8.6 Hz, Ar), 6.04 (1H, dd, *J* = 15.7, 9.1 Hz, C7-H), 5.88 (1H, d, *J* = 15.7 Hz, C8-H), 4.78 (1H, d, *J* = 3.1 Hz, C2-H), 3.71 (3H, s, OMe), 3.71 – 3.65 (2H, m, C5-H_2), 2.78 (1H, dd, *J* = 10.7, 9.1 Hz, C6-H), 2.52 (1H, ddt, *J* = 10.5, 7.0, 3.5 Hz, C3-H), 1.92 (1H, dtd, *J* = 13.0, 8.1, 6.6 Hz, C4-H_A), 1.45 (1H, ddt, *J* = 13.0, 6.8, 4.4 Hz, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 158.7 (C Ar), 142.2 (C Ar), 136.8 (C Ar), 136.0 (C Ar), 134.9 (C Ar), 134.8 (C Ar), 132.4 (C Ar), 132.0 (C7), 131.4 (C8), 129.5 (C Ar), 129.1 (2 × C Ar), 128.9 (2 × C Ar), 128.8 (C Ar), 128.5 (2 × C Ar), 127.6 (2 × C Ar), 127.5 (C Ar), 126.9 (C Ar), 126.3 (2 × C Ar), 123.0 (C Ar), 113.8 (2 × C Ar), 66.5 (C2), 55.3 (OMe), 54.3 (C3), 52.4 (C6), 48.2 (C5), 27.4 (C4). **NOESY-2D (600 MHz, $CDCl_3$)**: between C2-H and C7-H, between C2-H and C8-H.

Partial data for **3at-B** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 8.23 (1H, s, Ar), 6.92 (2H, d, *J* = 8.5 Hz, Ar), 6.71 (2H, d, *J* = 8.6 Hz, Ar), 6.22 (1H, d, *J* = 15.7 Hz, C8-H), 6.10 (1H, dd, *J* = 15.7, 9.3 Hz, C7-H), 4.48 (1H, d, *J* = 3.1 Hz, C2-H), 3.81 (1H, ddd, *J* = 9.8, 7.8, 4.1 Hz, C5-H_A), 2.87 (1H, t, *J* = 9.7 Hz, C6-H), 2.15 – 2.08 (1H, m, C4-H_A). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 131.5 (C9), 130.8 (C8), 66.1 (C2), 55.3 (OMe), 54.0 (C3), 51.4 (C6), 48.0 (C5), 26.8 (C4).

Data for **3at**: **HRMS** (ESI): calculated for $C_{32}H_{29}N_3O_7SNa$ $[M+Na]^+$ requires *m*/*z* 622.1618, found *m*/*z* 622.1606. **IR** (film) ν_{max}: 1553, 1513, 1350, 1250, 909, 733, 700 cm^{-1}.

(3au): (±)-(2*S*,3*R*)-3-((*S*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-((4-methoxyphenyl)-sulfonyl)-pyrrolidine and (±)-(2*S*,3*R*)-3-((*R*,*E*)-1,3-Diphenylallyl)-2-(4-methoxyphenyl)-1-((4-methoxyphenyl)-sulfonyl)pyrrolidine



Prepared according to **General Procedure N** using **1n** (17 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%). Flash column chromatography (15% EtOAc – pentane) afforded **3au** as an inseparable 5:1 mixture of diastereomers as a colourless oil (26 mg, 96%).

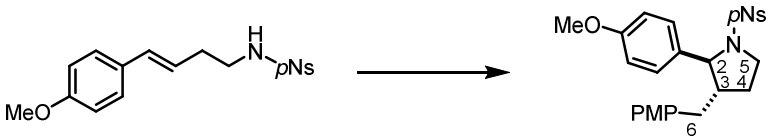
Data for **3au-A** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.72 (2H, d, *J* = 8.7 Hz, Ar), 7.33 – 7.21 (8H, m, Ar), 7.16 (2H, d, *J* = 8.6 Hz, Ar), 7.04 – 7.00 (2H, m, Ar), 6.98 (2H, d, *J* = 8.8 Hz, Ar), 6.80 (2H, d, *J* = 8.6 Hz, Ar), 6.17 – 6.11 (2H, m, C7-H + C8-H), 4.69 (1H, d, *J* = 2.9 Hz, C2-H), 3.89 (3H, s, OMe), 3.79 (3H, s, OMe), 3.63 (1H, ddd, *J* = 9.6, 7.6, 3.9 Hz, C5-H_A), 3.51 (1H, td, *J* = 9.4, 6.8 Hz, C5-H_B), 2.81 (1H, ddd, *J* = 10.8, 5.6, 2.6 Hz, C6-H), 2.50 (1H, ddt, *J* = 10.2, 6.7, 3.5 Hz, C3-H), 1.90 (1H, ddt, *J* = 14.1, 9.1, 7.3 Hz, C4-H_A), 1.41 (1H, ddt, *J* = 13.0, 7.2, 3.8 Hz, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 163.0 (C Ar), 158.8 (C Ar), 142.4 (C Ar), 137.1 (C Ar), 135.5 (C Ar), 132.2 (C7/8), 131.6 (C7/8), 130.7 (C Ar), 129.9 (2 × C Ar), 129.0 (2 × C Ar), 128.8 (2 × C Ar), 128.0 (2 × C Ar), 127.8 (2 × C Ar), 127.7 (C Ar), 127.0 (C Ar), 126.4 (2 × C Ar), 114.3 (2 × C Ar), 114.0 (2 × C Ar), 66.4 (C2), 55.9 (OMe), 55.5 (OMe), 54.3 (C3), 52.3 (C6), 48.1 (C5), 27.3 (C4). **NOESY-2D (500 MHz, $CDCl_3$)**: between C2-H and C6-H, between C2-H and C7/8-H.

Partial data for **3au-B** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.68 (2H, d, *J* = 8.8 Hz, Ar), 6.93 (2H, d, *J* = 8.8 Hz, Ar), 6.90 (2H, d, *J* = 8.6 Hz, Ar), 6.75 (2H, d, *J* = 8.6 Hz, Ar), 6.31 (1H, d, *J* = 15.6 Hz, C8-H), 4.38 (1H, d, *J* = 3.4 Hz, C2-H), 3.88 (3H, s, OMe), 3.77 (3H, s, OMe), 3.70 – 3.66 (1H, m, C5-H_A), 3.61 – 3.57 (1H, m, C5-H_B), 2.98 (1H, t, *J* = 9.6 Hz, C7-H), 2.09 – 2.01 (1H, m, C4-H_A),

1.88 – 1.81 (1H, m, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 158.8 (C Ar), 142.6 (C Ar), 137.1 (C Ar), 135.3 (C Ar), 131.8 (C Ar), 130.8 (C Ar), 129.9 (2 × C Ar), 129.0 (2 × C Ar), 128.8 (2 × C Ar), 127.5 (C Ar), 113.9 (2 × C Ar), 66.1 (C2), 55.9 (OMe), 55.5 (OMe), 54.3 (C3), 51.3 (C6), 48.0 (C5), 26.8 (C4)

Data for **3au**: **HRMS** (ESI): calculated for $C_{33}H_{33}NO_4SNa$ $[M+Na]^+$ requires m/z 562.2023, found m/z 562.2030. **IR** (film) ν_{max}: 2981, 2360, 1597, 1512, 1250, 1157, 910, 732 cm^{-1}.

(3ay): (±)-(2*S*,3*S*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1-((4-nitrophenyl)sulfonyl)-pyrrolidine



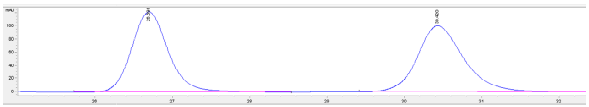
1d **3ay**

Prepared according to **General Procedure P** using **1d** (18 mg, 0.050 mmol), **38a** (14 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%) with 4Å MS (78 mg). Flash column chromatography (15% EtOAc – pentane) afforded **3ay** as a colourless oil (14 mg, 60%).

Data for **3ay**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 8.18 (2H, d, *J* = 8.8 Hz, Ar), 7.68 (2H, d, *J* = 8.8 Hz, Ar), 6.96 (2H, d, *J* = 8.6 Hz, Ar), 6.90 (2H, d, *J* = 8.6 Hz, Ar), 6.78 (2H, d, *J* = 8.6 Hz, Ar), 6.72 (2H, d, *J* = 8.7 Hz, Ar), 4.38 (1H, d, *J* = 5.8 Hz, C2-H), 3.85 – 3.82 (1H, m, C5-H_A), 3.78 (3H, s, OMe), 3.77 (3H, s, OMe), 3.55 (1H, ddd, *J* = 10.1, 7.7, 6.8 Hz, C5-H_B), 2.60 – 2.53 (1H, m, C6-H_A), 2.41 – 2.31 (2H, m, C3-H + C6-H_B), 1.99 (1H, ddt, *J* = 12.4, 6.5, 5.1 Hz, C4-H_A), 1.59 (1H, dq, *J* = 12.6, 7.6 Hz, C4-H_B). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.3 (C Ar), 158.4 (C Ar), 149.7 (C Ar), 145.5 (C Ar), 132.9 (C Ar), 131.1 (C Ar), 130.0 (2 × C Ar), 128.3 (2 × C Ar), 128.3 (2 × C Ar), 124.0 (2 × C Ar), 114.0 (2 × C Ar), 113.9 (2 × C Ar), 68.2 (C2), 55.5 (OMe), 55.4 (OMe), 51.5 (C3), 48.6 (C5), 37.2 (C6), 29.8 (C4). **NOESY-2D (600 MHz, $CDCl_3$)**: between C2-H and C6-H_A, between C2-H and C6-H_B. **HRMS** (ESI): calculated for $C_{25}H_{27}N_2O_6S$ $[M+H]^+$ requires m/z 483.1584, found m/z 483.1589. **IR** (film) ν_{max}: 1698, 1531, 1457, 1305, 1171, 1034, 738, 707 cm^{-1}.

3ay was also prepared according to **General Procedure P** using **1d** (18 mg, 0.050 mmol), **38a** (14 mg, 0.050 mmol) and (cat-**5e**) (5.0 mg, 15 mol%) with 4Å MS (78 mg). Flash column chromatography (15% EtOAc – pentane) afforded **3ay** as a colourless oil (15 mg, 64%).

Chiral HPLC: Chiralpak IC with guard, 5% IPA, 95% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 μL injection.



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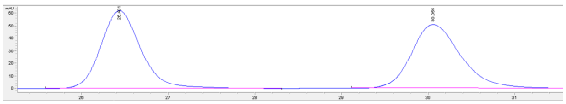
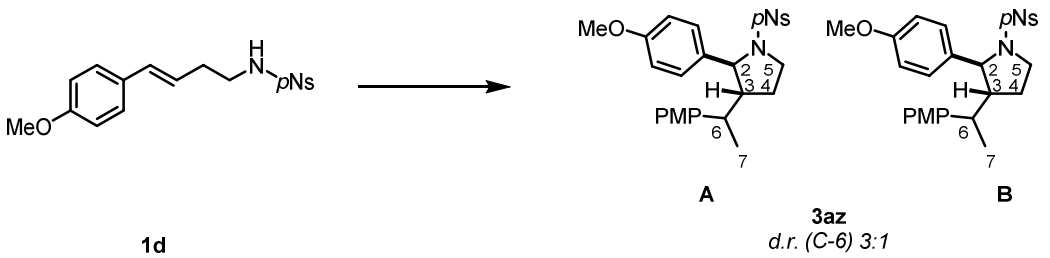
2	30.42	BB	4169.6	100	0.6285	50.960	0.747



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	26.431	BB	2022.3	62.5	0.4973	49.576	0.817
2	30.055	BB	2056.9	51.7	0.6001	50.424	0.749

(3az): (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-((*S*)-1-(4-methoxyphenyl)ethyl)-1-((4-nitrophenyl)-sulfonyl)pyrrolidine and (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-((*R*)-1-(4-methoxyphenyl)ethyl)-1-((4-nitrophenyl)-sulfonyl)pyrrolidine



Prepared according to **General Procedure P** using **1d** (18 mg, 0.050 mmol), **38b** (15 mg, 0.050 mmol) and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (3.5 mg, 20 mol%) in C_6H_5F (1.0 mL) with 4Å MS (78 mg). Flash column chromatography (15% EtOAc – pentane) afforded **3az** as an inseparable 3:1 mixture of diastereomers as a colourless oil (25 mg, 99%).

Data for **3az-A** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 8.13 (2H, d, *J* = 8.7 Hz, Ar), 7.60 (2H, d, *J* = 8.8 Hz, Ar), 7.11 (2H, d, *J* = 8.5 Hz, Ar), 6.93 (2H, d, *J* = 8.6 Hz, Ar), 6.80 (2H, d, *J* = 8.6 Hz, Ar), 6.76 (2H, d, *J* = 8.5 Hz, Ar), 4.51 (1H, d, *J* = 6.1 Hz, C2-H), 3.79 (3H, s, OMe), 3.79 (3H, s, OMe), 3.67 (1H, ddd, *J* = 10.4, 7.6, 4.6 Hz, C5-H_A), 3.46 (1H, ddd, *J* = 10.3, 8.2, 6.6 Hz, C5-H_B), 2.49 – 2.40 (1H, m, C6-H), 2.30 (1H, ddd, *J* = 14.4, 8.2, 6.3 Hz, C3-H), 1.81 (1H, dtd, *J* = 12.8, 6.4, 4.7 Hz, C4-H_A), 1.38 (1H, dq, *J* = 12.7, 8.1 Hz, C4-H_B), 1.15 (3H, d, *J* = 7.0 Hz, C7-H_3). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.3 (C Ar), 158.5 (C Ar), 149.6 (C Ar), 145.4 (C Ar), 135.8 (C Ar), 133.8 (C Ar), 128.8 (2 × C Ar), 128.7 (2 × C Ar), 128.2 (2 × C Ar), 123.9 (2 × C Ar), 114.0 (2 × C Ar), 114.0 (2 × C Ar), 67.1 (C2), 56.1

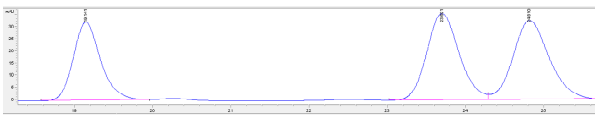
(C3), 55.5 (OMe), 55.4 (OMe), 48.4 (C5), 40.6 (C6), 28.1 (C4), 21.3 (C7). **NOESY-2D (600 MHz, $CDCl_3$)**: between C2-H and C6-H_A, between C2-H and C6-H_B.

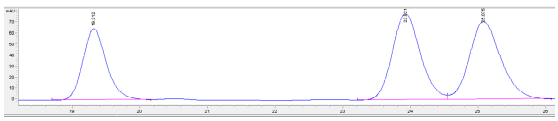
Partial data for **3az-B** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 6.72 (2H, d, *J* = 8.6 Hz, Ar), 6.63 (2H, d, *J* = 8.6 Hz, Ar), 6.55 (2H, d, *J* = 8.6 Hz, Ar), 4.38 (1H, d, *J* = 5.0 Hz, C2-H), 3.85 – 3.80 (1H, m, C5-H_A), 3.78 (3H, s, OMe), 3.72 (3H, s, OMe), 3.58 (1H, dt, *J* = 9.9, 6.9 Hz, C5-H_B), 2.37 – 2.33 (1H, m, C3-H), 2.16 (1H, dq, *J* = 12.9, 6.5 Hz, C4-H_A), 1.88 (1H, dq, *J* = 13.6, 7.0 Hz, C4-H_B), 1.17 (3H, d, *J* = 7.0 Hz, C7-H_3). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 158.8 (C Ar), 158.4 (C Ar), 149.6 (C Ar), 145.6 (C Ar), 136.9 (C Ar), 134.0 (C Ar), 128.5 (2 × C Ar), 128.3 (2 × C Ar), 128.0 (2 × C Ar), 123.9 (2 × C Ar), 113.5 (2 × C Ar), 67.1 (C2), 56.3 (C3), 55.4 (OMe), 48.5 (C5), 41.5 (C6), 28.2 (C4), 20.2 (C7).

Data for **3az**: **HRMS** (ESI): calculated for $C_{33}H_{33}NO_4SNa$ $[M+Na]^+$ requires *m/z* 562.2023, found *m/z* 562.2030. **IR** (film) ν_{max}: 2981, 2360, 1597, 1512, 1250, 1157, 910, 732 cm^{-1}.

3az was also prepared according to **General Procedure P** using **1d** (18 mg, 0.050 mmol), **38b** (15 mg, 0.050 mmol) and (cat-**5e**) (5.0 mg, 15 mol%) with 4Å MS (78 mg). Flash column chromatography (15% EtOAc – pentane) afforded **3az** a**s** an inseparable 3:1 mixture of diastereomers as a colourless oil (25 mg, 99%).

Chiral HPLC: Chiralpak IC with guard, 5% IPA, 95% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 μL injection.

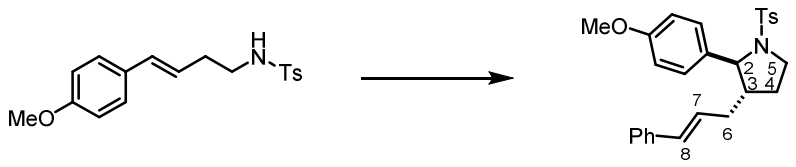




#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.141	BB	773	31.9	0.3727	27.324	0.807
2	23.691	BV	1019.5	35.5	0.4433	36.035	0.849
3	24.81	VB	1036.6	32.3	0.4927	36.641	0.807

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.312	BB	1593.8	64.8	0.3768	25.729	0.821
2	23.921	BV	2287.1	78.3	0.4488	36.921	0.837
3	25.075	VB	2313.7	70.8	0.4972	37.350	0.787

(3be): (±)-(2*S*,3*S*)-3-Cinnamyl-2-(4-methoxyphenyl)-1-((4-methylphenyl)sulfonyl)pyrrolidine

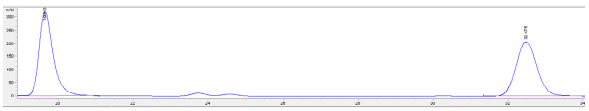


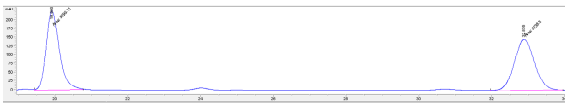
1g **3be**

Prepared according to **General Procedure I** using **1g** (16 mg, 0.050 mmol), (*E*)-1,3-diphenyl-2-propen-1-ol (11 mg, 0.50 mmol) and $Zn(OTf)_2$ (5.5 mg, 30 mol%) in DCE (1.0 mL) at 50 ˚C for 16 h. Flash column chromatography (15% EtOAc – pentane) afforded **3be** as a colourless oil (9.0 mg, 40%).

Data for **3be**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.63 (2H, d, *J* = 8.3 Hz, Ar), 7.32 – 7.20 (7H, m, Ar), 7.19 (2H, d, *J* = 8.7 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.18 (1H, d, *J* = 15.8 Hz, C8-H), 5.95 (1H, dt, *J* = 15.8, 7.1 Hz, C7-H), 4.29 (1H, d, *J* = 5.4 Hz, C2-H), 3.80 (3H, s, OMe), 3.65 – 3.57 (2H, m, C5-H_2), 2.42 (3H, s, TsMe), 2.20 – 2.13 (1H, m, C3-H), 2.07 – 1.98 (2H, m, C4-H_A + C6-H_A), 1.96 – 1.88 (1H, m, C6-H_B), 1.49 – 1.39 (1H, m, C4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.9 (C Ar), 143.3 (C Ar), 137.3 (C Ar), 135.5 (C Ar), 134.6 (C Ar), 132.4 (C8), 129.6 (2 × C Ar), 128.7 (2 × C Ar), 127.9 (2 × C Ar), 127.6 (2 × C Ar), 127.4 (C Ar), 127.3 (C7), 126.1 (2 × C Ar), 113.9 (2 × C Ar), 68.0 (C2), 55.4 (OMe), 49.6 (C3), 48.5 (C5), 35.5 (C6), 29.5 (C4), 21.7 (TsMe). **NOESY-2D (500 MHz, $CDCl_3$):** between C2-H and C6-H_B, between C2-H and C7-H. **HRMS** (ESI): calculated for $C_{27}H_{29}NO_3SNa$ $[M+Na]^+$ requires *m*/*z* 470.1766, found *m*/*z* 470.1761. **IR** (film) ν_{max}: 3648, 2980, 2360, 1612, 1382, 1095 cm^{-1}.

Chiral HPLC: Chiralpak IA with guard, 15% IPA, 85% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 μL injection.





#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.643	BB	8430.6	319.8	0.3975	51.140	0.679
2	32.475	BB	8054.8	207.5	0.5968	48.860	0.873

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.9	MM	5795.1	225.6	0.428	50.255	0.751
2	32.876	MM	5736.3	146.5	0.6527	49.745	0.927

6.4 Experimental Details – Chapter 4

6.4.1 General procedures

General Procedure Q: *ortho*-nosyl deprotection

To a solution of pyrrolidine (1.00 equiv.) in anhydrous MeCN (10.0 mL/mmol) was added thiol (1.25 equiv.) and caesium carbonate (2.50 equiv.) before heating to 80 °C for 16 h. The solution was cooled to rt and the solid removed by filtration before concentrating *in vacuo* and purifying by FCC.

General Procedure R: Alkylation

To a solution of amine (1.00 equiv.) in anhydrous MeCN (10.0 mL/mmol) was added bromoacetamide (1.25 equiv.) and caesium carbonate (2.50 equiv.) and left for stir for 4 h. The solid was removed by filtration before concentration *in vacuo* and purifying by FCC.

General Procedure S: TEMPO oxidation

To a solution of alcohol (1.0 equiv.) in CH_2Cl_2:water (2:1, 20 mL/mmol) was added TEMPO (0.2 equiv.) and PIDA (2.5 equiv.) before stirring vigorously for 1.5 h. The solution was quenched with *aq.* $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4 before concentrating *in vacuo* and purifying by FCC.

General Procedure T: Methyl ester formation

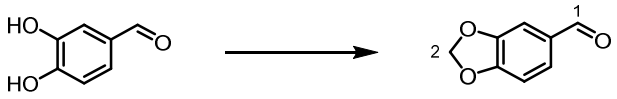
To a solution of acid (1.0 equiv.) in PhMe:MeOH (10:1, 10 mL/mmol) was added TMS diazomethane (2.0 M in Et_2O) dropwise until the yellow colour persists. The reaction was stirred for a further 20 min before concentration *in vacuo* and purifying by FCC.

General Procedure U: Steglich esterification

To a solution of acid (1.0 equiv.), alcohol (1.25 – 10.0 equiv.) and dimethylaminopyridine (0.1 equiv.) in DCM (20 mL/mmol) was added EDCI.HCl (1.5 equiv.) at 0 °C before leaving for 16 h. The solvent was removed *in vacuo* and the crude material was redissolved in EtOAc before washing with 1.0 M HCl, $NaHCO_3$ and brine before drying over Na_2SO_4, concentrating *in vacuo* and purifying by FCC.

6.4.2 Substrate synthesis

(69): Benzo[*d*][1,3]dioxole-5-carbaldehyde (Piperonal)

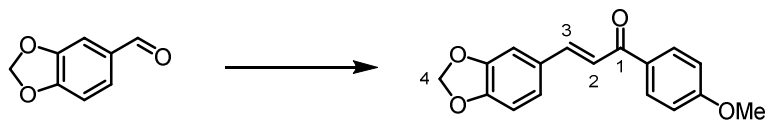


69

A solution of 3,4-dihydroxybenzaldehyde (5.00 g, 36.2 mmol, 1.00 equiv.), dibromomethane (3.60 mL, 50.7 mmol, 1.40 equiv.) and Cs_2CO_3 (13.3 g, 50.7 mmol, 1.00 equiv.) in DMF (60 mL) was heated to 110 °C for 2 h. The solution was cooled to rt before the addition of H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$ before concentrating *in vacuo*. Flash column chromatography (gradient elution 0% → 15% EtOAc – pentane) afforded **69** as a colourless solid (4.00 g, 85%).

Data for **69**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 9.80 (1H, s, C1-H), 7.41 (1H, dd, *J* = 7.9, 1.6 Hz, Ar), 7.32 (1H, dd, *J* = 1.6, 0.4 Hz, Ar), 7.01 – 6.87 (1H, m, Ar), 6.07 (2H, s, C2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.4 (C1), 153.2 (C Ar), 148.9 (C Ar), 132.0 (C Ar), 128.8 (C Ar), 108.5 (C Ar), 107.1 (C Ar), 102.2 (C2). *The spectroscopic properties were consistent with the data available in the literature.*[183]

(68): (*E*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)prop-2-en-1-one



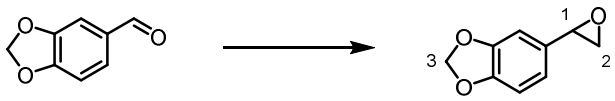
69 **69**

To a solution of 4-methoxyacetophenone (4.00 g, 26.6 mmol, 1.00 equiv.) in EtOH (10.0 mL) was added **69** (4.00 g, 26.6 mmol, 1.00 equiv.) and NaOH (10 wt%, 0.31 mL). After 1.5 h the solid was collected by filtration and washed with EtOH:H_2O (1:1) affording **68** as a yellow solid (6.07 g, 81%).

Data for **68**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.02 (2H, d, *J* = 8.9 Hz, Ar), 7.73 (1H, d, *J* = 15.5 Hz, C3-H), 7.38 (1H, d, *J* = 15.8 Hz, C2-H), 7.21 – 7.15 (1H, m, Ar), 7.15 – 7.08 (1H, m, Ar), 6.98 (2H, d, *J* = 9.0 Hz, Ar), 6.84 (d, *J* = 8.1 Hz, Ar), 6.02 (2H, s, C4-H_2), 3.89 (3H, s, OMe). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 188.7 (C1), 163.5 (C Ar), 149.9 (C Ar), 148.5 (C Ar), 143.9 (C3), 131.4, 130.8 (2 × C Ar), 129.7

(C Ar), 125.2 (C Ar), 120.1 (C2), 113.9 (2 × C Ar), 108.8 (C Ar), 106.8 (C Ar), 101.7 (C4), 55.6 (OMe). *The spectroscopic properties were consistent with the data available in the literature.*[184]

(72): 5-(Oxiran-2-yl)benzo[*d*][1,3]dioxole



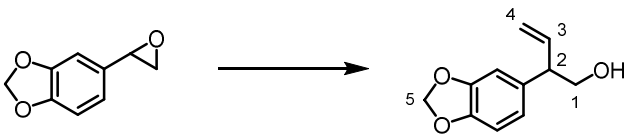
69 **72**

A solution of trimethylsulfonium iodide (13.56 g, 66.0 mmol, 2.00 equiv.) and sodium hydride (2.64 g, 60% w/w, 66.0 mmol, 2.00 equiv.) in DMSO (40 mL) and THF (30 mL) was stirred at rt for 20 min before cooling to 0 °C. A solution of **69** (5.00 g, 33.0 mmol, 1.00 equiv.) in THF (15 mL) was added. The solution stirred at 0 °C until consumption of aldehyde was observed before diluting with H_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with H_2O and brine and dried over Na_2SO_4 before concentrating *in vacuo*. The yellow oil was used crude in the following steps due to instability on silica.

Note: on a smaller scale purification was possible. Flash column chromatography (20% Et_2O – pentane).

Data for **72**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.82 – 6.75 (2H, m, Ar), 6.70 (1H, d, *J* = 1.5 Hz, Ar), 5.95 (2H, s, C3-H_2), 3.79 (1H, dd, *J* = 4.0, 2.6 Hz, C1-H), 3.10 (1H, dd, *J* = 5.4, 4.0 Hz, C2-H_A), 2.75 (1H, dd, *J* = 5.4, 2.6 Hz, C2-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 148.2 (C Ar), 147.8 (C Ar), 131.6 (C Ar), 119.8 (C Ar), 108.4 (C Ar), 105.6 (C Ar), 101.3 (C3), 52.5 (C1), 51.1 (C2). *The spectroscopic properties were consistent with the data available in the literature.*[185]

(73): 2-(Benzo[*d*][1,3]dioxol-5-yl)but-3-en-1-ol



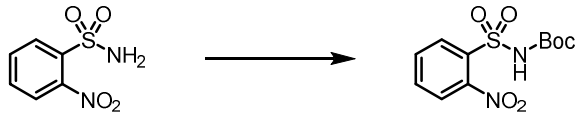
72 **73**

To a solution of **72** (1.90 g, 11.6 mmol, 1.00 equiv.) and $[Cu(COD)Cl]_2$ (240 mg, 0.580 mmol, 5 mol%) in THF (100 mL) at – 78 °C was added vinylmagnesium bromide (1.0 M in THF, 13.9 mL, 13.9 mmol, 1.20 equiv.). The reaction was allowed to warm to rt and stirred for 6 h before addition of aq. NH_4Cl

and dilution with EtOAc. The aqueous later was extracted with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$ before concentrating *in vacuo*. Flash column chromatography (10% → 20% EtOAc – pentane) afforded **73** as a yellow oil (1.28 mg, 57%).

Data for **73**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.78 (1H, d, *J* = 7.9 Hz, Ar), 6.76 – 6.66 (2H, m, Ar), 6.06 – 5.83 (3H, m, C3-H + C5-H_2), 5.29 – 5.08 (2H, m, C4-H_2), 3.78 (2H, d, *J* = 7.1 Hz, C1-H_2), 3.45 (1H, q, *J* = 7.3 Hz, C2-H), 1.56 (1H, *br.* s, *O*H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 148.1 (C Ar), 146.6 (C Ar), 138.4 (C3), 134.6 (C Ar), 121.2 (C Ar), 117.1 (C4), 108.6 (C Ar), 108.4 (C Ar), 101.1 (C5), 66.2 (C1), 52.2 (C2). *The spectroscopic properties were consistent with the data available in the literature.*[186]

(63): *tert*-Butyl [(2-nitrophenyl)sulfonyl]carbamate

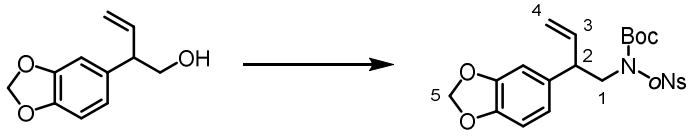


63

To a solution of 2-nitrobenzene sulfonamide (1.00 g, 4.95 mmol, 1.00 equiv.), DMAP (640 mg, 0.50 mmol, 0.1 equiv.), in CH_2Cl_2 (10 mL) was added Et_3N (0.83 mL, 5.95 mmol, 1.20 equiv.) followed by di-*tert*-butyl decarbonate (1.10 g, 4.95 mmol, 1.00 equiv.) at 0 °C. The mixture was stirred at rt for 8 h before concentrating *in vacuo* and re-dissolving in EtOAc. The solution was washed with 1.0 M HCl before drying over Na_2SO_4 and concentrating *in vacuo*. Recrystallisation from hot hexane afforded **63** as a crystalline white solid (1.34 g, 80%).

Data for **63**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.31 – 8.36 (1H, m, Ar), 7.83 – 7.88 (1H, m, Ar), 7.74 – 7.82 (2H, m, Ar), 1.43 (9H, s, C(C**H**$_3$)$_3$). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.8 (C(O)), 148.2 (C Ar), 134.8 (C Ar), 133.4 (C Ar), 132.6 (C Ar), 132.2 (C Ar), 125.2 (C Ar), 84.9 (**C**(CH$_3$)$_3$), 28.0 (C(**C**H$_3$)$_3$). *The spectroscopic properties were consistent with the data available in the literature.*[187]

(76): *tert*-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)but-3-en-1-yl)((2-nitrophenyl)sulfonyl)-carbamate



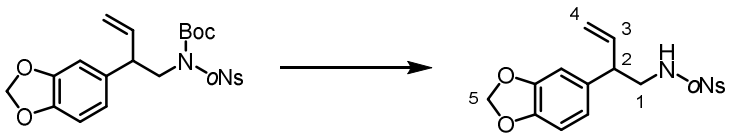
73 **76**

To a solution of **73** (1.00 g, 5.31 mmol, 1.00 equiv.), **63** (2.00 g, 6.63 mmol, 1.25 equiv.) and triphenylphosphine (1.74 g, 6.63 mmol, 1.25 equiv.) in THF (50 mL) at 0 °C was added DIAD (1.30 mL, 6.63 mmol, 1.25 equiv.). The solution was warmed to rt overnight before concentrating *in vacuo*. The yellow oil was used crude in the following steps.

Note: partial removal of the reduced DIAD was possible, the crude material was dissolved in PhMe and left for 30 min, DIAD-H₂ was then removed by filtration.

Data for **76 (from preparatory TLC)**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.34 – 8.20 (1H, m, Ar), 7.81 – 7.66 (3H, m, Ar), 6.84 – 6.73 (3H, m, Ar), 6.04 (1H, ddd, *J* = 17.0, 10.2, 8.6 Hz, C3-H), 5.93 (2H, s, C5-H_2), 5.26 – 5.15 (2H, m, C4-H_2), 4.04 (1H, dd, *J* = 14.6, 9.1 Hz, 1 × C1-H_2), 3.95 (1H, dd, *J* = 14.6, 6.8 Hz, 1 × C1-H_2), 3.74 (1H, td, *J* = 8.8, 6.7 Hz, C2-H), 1.33 (9H, s, C(C**H**$_3$)$_3$). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 150.4 (CO), 147.9 (C Ar), 147.7 (C Ar), 146.6 (C Ar), 138.1 (C3), 134.7 (C Ar), 134.2 (C Ar), 133.7 (C Ar), 133.5 (C Ar), 131.8 (C Ar), 124.5 (C Ar), 121.4 (C Ar), 117.6 (C4), 108.5 (2 × C Ar), 101.1 (C5), 85.1 (**C**(CH$_3$)$_3$), 52.7 (C1), 50.3 (C2), 49.7, 45.2, 27.9 (C(**C**H$_3$)$_3$). **HRMS** (ESI): calculated for $C_{22}H_{24}N_2O_8SNa$ $[M+Na]^+$ requires *m/z* 499.1146, found *m/z* 499.1151. **IR** (film) ν_{max}: 1731, 1541, 1364, 1172, 1120, 1039, 723, 695 cm^{-1}.

(77): *N*-(2-(Benzo[*d*][1,3]dioxol-5-yl)but-3-en-1-yl)-2-nitrobenzenesulfonamide



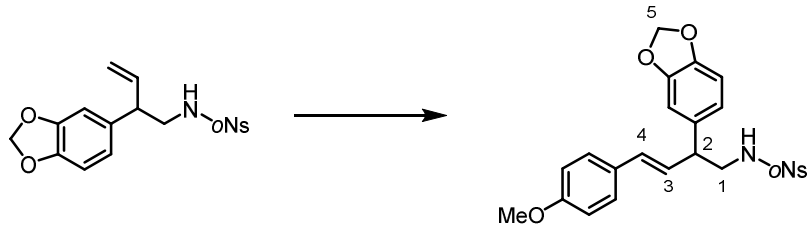
76 **77**

To a solution of **76** (3.17 g, 6.66 mmol, 1.00 equiv.) in CH_2Cl_2 (100 mL) was added trifluoracetic acid (10 mL, 133 mmol, 20.0 equiv.). When no starting material was observed by TLC was added H_2O. The aqueous layer was basified to pH 12 with 4.0 M aq. NaOH and extracted with CH_2Cl_2. The combined

organic layers were washed with water (30 mL) and brine (30 mL) before drying over Na_2SO_4. Flash column chromatography (20% EtOAc – pentane) afforded **77** as a colourless oil (1.87 g, 81%).

Data for **77**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.14 – 8.05 (1H, m, Ar), 7.89 – 7.81 (1H, m, Ar), 7.77 – 7.68 (2H, m, Ar), 6.73 – 6.62 (1H, m, Ar), 6.62 – 6.47 (2H, m, Ar), 5.91 (2H, s, C5-H_2), 5.83 (1H, ddd, *J* = 17.2, 10.4, 6.9 Hz, C3-H), 5.33 (1H, t, *J* = 5.2 Hz, *N*H), 5.15 (1H, dt, *J* = 10.3, 1.0 Hz, C4-H_A), 5.07 (1H, dt, *J* = 17.2, 1.2 Hz, C4-H_B), 3.51 – 3.20 (3H, m, C1-H_2 + C2-H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 171.3 (C Ar), 148.1 (C Ar), 148.0 (C Ar), 146.8 (C Ar), 137.8 (C3), 133.9 (C Ar), 133.6 (C Ar), 133.0 (C Ar), 131.0 (C Ar), 125.5 (C Ar), 121.0 (C Ar), 117.3 (C4), 108.7 (C Ar), 107.9 (C Ar), 101.2 (C5), 49.1 (C2), 48.1 (C1). **HRMS** (ESI): calculated for $C_{17}H_{17}N_2O_6S$ $[M+H]^+$ requires *m/z* 377.0802, found *m/z* 377.0804. **IR** (film) ν_{max}: 2981, 2360, 1542, 1442, 1169, 1040, 932, 741 cm^{-1}.

(1p): (*E*)-*N*-(2-(Benzo[*d*][1,3]dioxol-5-yl)-4-(4-methoxyphenyl)but-3-en-1-yl)-2-nitro-benz-ene-sulfonamide



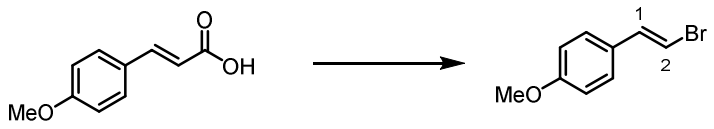
77 **1p**

Prepared according to **General Procedure E** using **77** (180 mg, 0.50 mmol), 4-methoxystyrene (0.13 mL, 1.0 mmol) and Grubbs II (21 mg, 0.025 mmol) in PhMe (2.0 mL) at 100 °C. Flash column chromatography (0% → 35% EtOAc – pentane) followed by recrystallisation from hot EtOAc afforded **1p** as a pale-yellow solid (77 mg, 32%).

Data for **1p: ^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.16 – 8.07 (1H, m, Ar), 7.87 – 7.77 (1H, m, Ar), 7.77 – 7.65 (2H, m, Ar), 7.20 (2H, d, *J* = 8.7 Hz, Ar), 6.81 (2H, d, *J* = 8.7 Hz, Ar), 6.70 (1H, d, *J* = 8.4 Hz, Ar), 6.63 – 6.56 (2H, m, Ar), 6.31 (1H, d, *J* = 15.9 Hz, C4-H), 5.99 (1H, dd, *J* = 15.9, 7.6 Hz, C3-H), 5.92 (2H, s, C5-H_2), 5.36 (1H, t, *J* = 5.8 Hz, *N*H), 3.80 (3H, s, OMe), 3.57 – 3.50 (1H, m, C2-H), 3.50 – 3.38 (2H, m, C1-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.5 (C Ar), 148.2 (C Ar), 146.9 (C Ar), 134.1 (C Ar), 134.1 (C Ar), 133.5 (C Ar), 132.9 (C Ar), 131.9 (C4), 131.0 (C Ar), 129.4 (C Ar), 127.6 (2 × C Ar), 126.9

(C3), 125.6, (C Ar) 121.0 (C Ar), 114.1 (2 × C Ar), 108.8 (C Ar), 107.9 (2 × C Ar), 101.2 (C5), 55.5 (OMe), 48.7 (C1/C2), 48.6 (C1/C2). **HRMS** (ESI): calculated for $C_{24}H_{22}N_2O_7SNa$ $[M+Na]^+$ requires *m/z* 505.1040, found *m/z* 505.1054. **IR** (film) ν_{max}: 1607, 1542, 1297, 1060, 93, 852, 755, 647 cm^{-1}. **mp** (176 – 178 °C, EtOAc).

(80): *(E)*-1-(2-Bromovinyl)-4-methoxybenzene

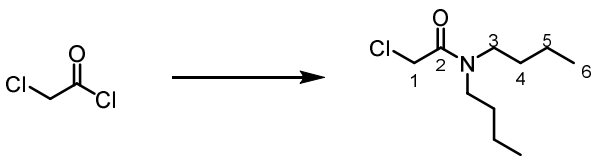


80

To a solution of 4-methoxycinnamic acid (1.78 g, 10.0 mmol. 1.00 equiv.) in CH_2Cl_2 (30 mL) was added triethylamine (80 µL, 0.50 mmol, 5.0 mol%). After stirring for 5 min *N*-bromosuccinimide (1.42 g, 12.0 mmol, 1.20 equiv.) was added. After 20 min the solvent was removed *in vacuo*. Flash column chromatography (100% CH_2Cl_2) afforded **80** as a colourless solid (1.19 g, 56%).

Data for **80**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.23 (2H, d, *J* = 8.6 Hz, Ar), 7.04 (1H, d, *J* = 13.9 Hz, C1-H), 6.86 (2H, d, *J* = 8.6 Hz, Ar), 6.61 (1H, d, *J* = 14.0 Hz, C2-H), 3.81 (3H, s, OMe). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.7 (C Ar), 136.6 (C Ar), 128.8 (2 × C Ar), 127.4 (C1), 114.2 (2 × C Ar), 104.0 (C2), 55.3 (OMe). *The spectroscopic properties were consistent with the data available in the literature.*[188]

(83): *N,N*-Dibutyl-2-chloroacetamide



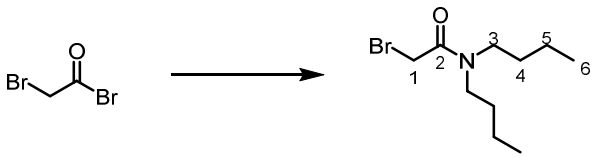
83

To a solution of chloroacetyl chloride (80.0 µL, 1.00 mmol, 1.00 equiv.) in THF (2.00 mL) was added a solution of dibutylamine (34.0 µL, 2.00 mmol, 2.00 equiv.) in THF (0.5 mL) before stirring at rt for 12 h. The solid was removed by filtration before concentrating *in vacuo* affording **83** as a yellow liquid (193 mg, 94%).

Data for **83**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 4.09 (2H, s, C1-H_2), 3.33 (4H, dt, *J* = 20.9, 7.6 Hz, 2 × C3-H_2), 1.70 – 1.48 (4H, m, 2 × C4-H_2), 1.35 (4H, dq, *J* = 11.8, 7.5 Hz, 2 × C5-H_2), 0.97 (6H, dt,

J = 14.4, 7.3 Hz, 2 × C6-H_3). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.6 (C2), 48.3 (C3), 46.3 (C3'), 41.2 (C1), 31.3 (C4), 29.5 (C4'), 20.2 (C5), 20.2 (C5'), 14.0 (C6), 13.9 (C6'). *The spectroscopic properties were consistent with the data available in the literature.*[189]

(87): *N,N*-Dibutyl-2-bromoacetamide



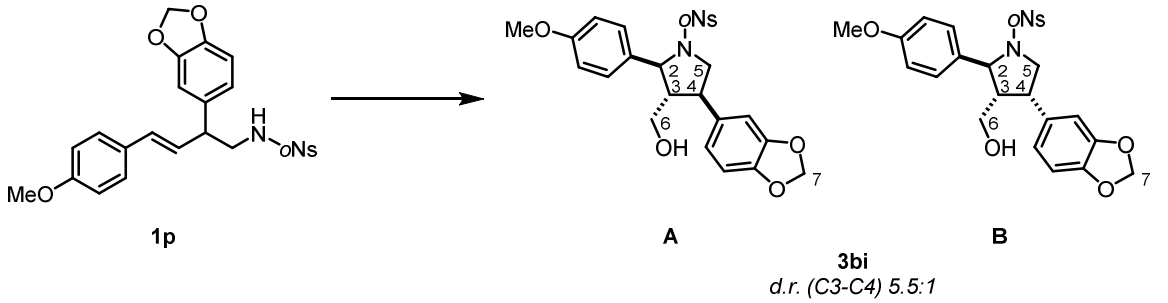
87

To a solution of dibutylamine (3.50 mL, 21.0 mmol, 2.10 equiv.) in DCE (10 mL) at –45 °C was added bromoacetyl bromide (0.87 mL, 10 mmol, 1.0 equiv.) in DCE (2.5 mL). The solution was kept at –45 °C for 25 min before stirring at rt for a further 25 min. The reaction mixture was diluted with DCE, washed with H_2O and concentrated *in vacuo*. The crude residue was redissolved in heptane and the solid removed by filtration affording **87** as a yellow liquid (2.26 g, 90%).

Data for **87**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 3.83 (2H, s, C1-H_2), 3.36 – 3.24 (4H, m, C3-H_2), 1.77 – 1.45 (4H, m, C4-H_2), 1.33 (4H, dtd, *J* = 15.2, 7.5, 5.8 Hz, C5-H_2), 0.94 (6H, dt, *J* = 14.9, 7.3 Hz, C6-H_3). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.6 (C2), 48.7 (C3), 46.1 (C3'), 31.4 (C4), 29.5 (C4'), 26.5 (C1), 20.2 (2 × C5), 14.0 (C6), 13.9 (C6'). *The spectroscopic properties were consistent with the data available in the literature.*[190]

6.4.3 Cyclisation

(3bi): (±)-((2*S*,3*S*,4*R*)-4-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)-1-((2-nitrophenyl)-sulfonyl)pyrrolidin-3-yl)methanol



Prepared according to **General procedure I** using **1p** (19 mg, 0.040 mmol) and paraformaldehyde (24 mg, 0.80 mmol) at 50 °C for 24 h. Flash column chromatography (gradient elution 0% → 20% EtOAc – CH_2Cl_2) afforded **3bi-A** + **3bi-B** as a colourless oil (15 mg, 73%).

Flash column chromatography (gradient elution 0% → 45% EtOAc – pentane) afforded **3bi-A** as a colourless oil (12 mg, 56%) and a 5.5:1 mixture of **3bi-A** + **3bi-B** as a colourless oil (3.0 mg, 15%).

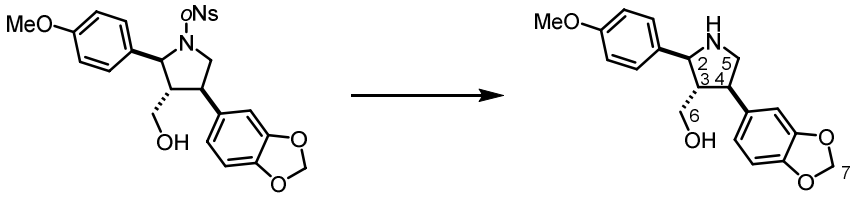
Data for **3bi-A**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.54 (1H, dd, *J* = 7.9, 1.2 Hz, Ar), 7.47 (1H, ddd, *J* = 7.7, 6.9, 1.8 Hz, Ar), 7.24 – 7.16 (2H, m, Ar), 7.15 (2H, d, *J* = 8.6 Hz, Ar), 6.85 – 6.74 (3H, m, Ar), 6.62 (2H, d, *J* = 8.6 Hz, Ar), 6.00 – 5.93 (2H, m, C7-H_2), 4.89 (1H, d, *J* = 9.6 Hz, C2-H), 4.39 (1H, dd, *J* = 10.8, 7.8 Hz, C5-H_A), 3.79 (1H, t, *J* = 11.0 Hz, C5-H_B), 3.74 (3H, s, OMe), 3.57 – 3.50 (2H, m, C6-H_2), 3.34 (1H, td, *J* = 11.5, 7.8 Hz, C4-H), 2.40 (1H, ddt, *J* = 11.6, 9.5, 3.9 Hz, C3-H). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.5 (C Ar), 148.3 (C Ar), 147.5 (C Ar), 147.1 (C Ar), 134.4 (C Ar), 132.6 (C Ar), 131.8 (C Ar), 131.7 (C Ar), 131.1 (C Ar), 131.0 (C Ar), 129.1 (2 × C Ar), 123.7 (C Ar), 121.3 (C Ar), 114.0 (2 × C Ar), 108.8 (C Ar), 107.8 (C Ar), 101.3 (C7), 65.8 (C2), 59.7 (C6), 58.7 (C3), 56.5 (C5), 55.5 (OMe), 45.5 (C4). **NOESY- 2D (600 MHz, $CDCl_3$):** between C2-H and C4-H, between C2-H and C6-H_2, between C4-H and C6-H_2. **HRMS** (ESI): calculated for $C_{25}H_{25}N_2O_8S$ $[M+H]^+$ requires *m/z* 513.1326, found *m/z* 513.1327. **IR** (film) ν_{max}: 2920, 2361, 1611, 1542, 1249, 1162, 1036, 780, 657 cm^{-1}.

Partial data for **3bi-B** (from the mixture): **^{1}H NMR (600 MHz, $CDCl_3$) δ** 5.91 (1H, dd, *J* = 11.0, 1.4 Hz, C7-H), 4.84 (1H, d, *J* = 7.3 Hz, C2-H), 4.24 (1H, dd, *J* = 10.4, 6.8 Hz, C5-H_A), 4.18 (1H, dd, *J* = 10.4, 4.9 Hz, C5-H_B), 3.73 (3H, s, OMe), 2.66 – 2.56 (1H, m, C3-H), 2.32 (td, *J* = 9.0, 4.3 Hz, C4-H). **^{13}C NMR**

(151 MHz, $CDCl_3$) δ 103.7 (C7), 64.8 (C2), 60.4 (C6), 58.4 (C4), 56.3 (C3), 54.4 (C5). *The stereochemistry of the minor isomer was not proven.*

6.4.4 Pyrrolidine reactions

(86): (±)-((2*S*,3*S*,4*R*)-4-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)pyrrolidin-3-yl)-methanol

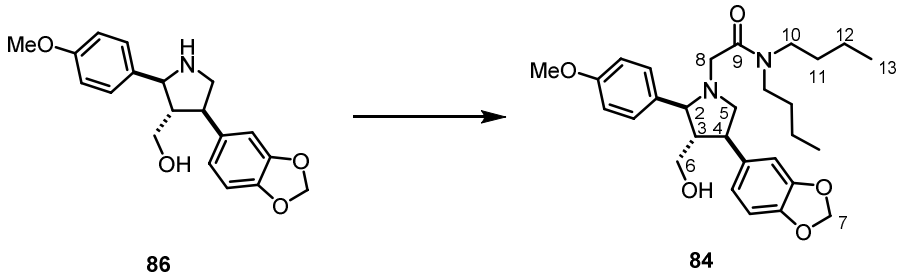


3bi **86**

Prepared according to **General procedure Q** using **3bi** (50 mg, 0.10 mmol), *n*-$C_{12}H_{25}SH$ (50 mg, 0.25 mmol) and $CsCO_3$ (163 mg, 0.50 mmol). Flash column chromatography (gradient elution 0% → 10% MeOH – CH_2Cl_2) afforded **86** as a yellow oil (25 mg, 78%).

Data for **86**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.44 (2H, d, *J* = 8.7 Hz, Ar), 6.91 (1H, d, *J* = 1.8 Hz, Ar), 6.85 (2H, d, *J* = 8.6 Hz, Ar), 6.80 (1H, dd, *J* = 8.0, 1.7 Hz, Ar), 6.76 (1H, d, *J* = 7.9 Hz, Ar), 5.94 (1H, q, *J* = 1.5 Hz, C7-H_2), 4.34 (1H, s, C2-H), 3.73 (3H, s, OMe), 3.57 (1H, dd, *J* = 11.3, 4.0 Hz, C6-H_A), 3.53 (1H, dd, *J* = 11.2, 3.8 Hz, C6-H_B), 3.44 (1H, dd, *J* = 10.1, 8.2 Hz, C5-H_A), 3.40 – 3.26 (2H, m, C4-H + C5-H_B), 2.32 (1H, tt, *J* = 9.9, 3.9 Hz, C3-H). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 159.9 (C Ar), 148.3 (C Ar), 146.8 (C Ar), 134.7 (C Ar), 130.2 (C Ar), 129.3 (2 × C Ar), 121.2 (C Ar), 114.4 (2 × C Ar), 108.6 (C Ar), 108.0 (C Ar), 101.2 (C7), 64.6 (C2), 59.8 (C6), 56.6 (C3), 55.4 (OMe), 52.1 (C5), 46.1 (C4). **HRMS** (ESI): calculated for $C_{19}H_{22}NO_4$ $[M+H]^+$ requires *m*/*z* 328.1543, found *m*/*z* 328.1549. **IR** (film) ν_{max}: 2924, 2852, 2360, 1611, 1376, 1250, 1178, 1038, 812 cm^{-1}.

(84): (±)-2-((2*S*,3*S*,4*R*)-4-(Benzo[*d*][1,3]dioxol-5-yl)-3-(hydroxymethyl)-2-(4-methoxy-phenyl)-pyrrolidin-1-yl)-*N*,*N*-dibutylacetamide



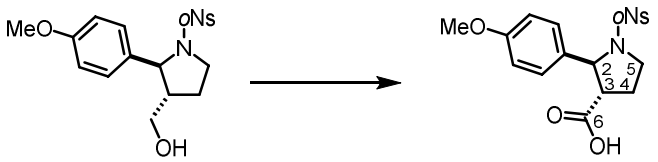
Prepared according to **General procedure R** using **86** (15 mg, 0.045 mmol), **87** (14 mg, 0.056 mmol) and $CsCO_3$ (37 mg, 0.11 mmol). Flash column chromatography (gradient elution 0% → 35% EtOAc – CH_2Cl_2) afforded **84** as a colourless oil (15 mg, 68%).

Data for **84**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.31 (2H, d, *J* = 8.4 Hz, Ar), 7.03 (1H, d, *J* = 1.7 Hz, Ar), 6.87 (2H, d, *J* = 8.4 Hz, Ar), 6.84 (1H, dd, *J* = 7.5, 1.5 Hz, Ar), 6.73 (1H, d, *J* = 7.9 Hz, Ar), 5.93 (2H, *br.* d, *J* = 7.3 Hz, C7-H_2), 3.80 (3H, s, OMe), 3.65 (1H, dd, *J* = 11.0, 5.0 Hz, C6-H_A), 3.60 (1H, dd, *J* = 11.0, 5.4 Hz, C6-H_B), 3.46 (2H, dt, *J* = 14.0, 7.6 Hz, 2 × C10-H_2), 3.41 (1H, d, *J* = 13.4 Hz, C8-H_A), 3.37 – 3.30 (3H, m, C2-H + C5-H_A + 1 × C10-H_2), 3.21 – 3.15 (1H, m, C4-H), 3.07 – 2.96 (4H, m, C5-H_B + C6-HB + 2 × C10-H_2), 2.75 (1H, d, *J* = 13.4 Hz, C8-H_B), 2.29 – 2.19 (1H, m, C3-H), 1.45 (1H, p, *J* = 8.0 Hz, 1 × C11-H_2), 1.40 – 1.36 (2H, 1 × C11-H_2), 1.33 – 1.21 (6H, m, 2 × C11-H_2 + 2 × C12-H_2), 1.08 (2H, h, *J* = 7.4 Hz, 2 × C12-H_2), 0.88 (3H, t, *J* = 7.4 Hz, 3 × C13-H_3), 0.81 (3H, t, *J* = 7.4 Hz, 3 × C13-H_3). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 169.8 (C9), 159.5 (C Ar), 148.1 (C Ar), 146.0 (C Ar), 140.7(C Ar), 133.0 (C Ar), 129.6 (2 × C Ar), 120.5 (C Ar), 114.2 (2 × C Ar), 108.2 (C Ar), 107.8 (C Ar), 101.0 (C7), 72.4 (C2), 63.3 (C6), 60.7 (C5), 59.9 (C3), 55.5 (C8), 55.4 (OMe), 47.0 (1 × C10), 45.3 (1 × C10), 45.1 (C4), 31.2 (1 × C11), 29.8 (1 × C11), 20.4 (1 × C12), 20.1 (1 × C12), 14.0 (1 × C13), 13.9 (1 × C13). **HRMS** (ESI): calculated for $C_{22}H_{37}N_2O_3$ $[M+Na]^+$ requires *m/z* 377.2799, found *m/z* 377.2797. **IR** (film) ν_{max}: 2959, 2360, 1636, 1514, 1250, 1039 832 cm^{-1}.

84 was also prepared using **General Procedure J: 3bi** (12.0 mg, 0.02 mmol), LiOH (3.0 mg, 0.04 mmol) and thioglycolic acid (3.5 mg, 0.040 mmol). The crude material was re-dissolved in DMF (0.5 mL) and **83** (5.0 mg, 0.025 mmol) and K_2CO_3 (7.0 mg, 0.050 mmol) added. After 16 h the solvent was removed

in vacuo. Flash column chromatography (gradient elution 0% → 35% EtOAc – CH_2Cl_2) afforded **84** as a colourless oil (1.7 mg, 17%).

(88): (±)-(2*S*,3*S*)-2-(4-Methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)pyrrolidine-3-carboxylic acid

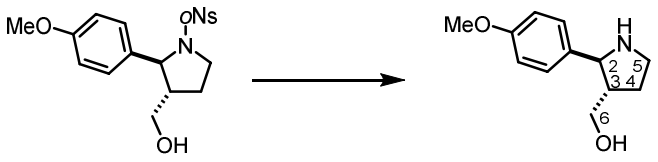


3o **88**

Prepared according to **General Procedure S** using **3o** (60 mg, 0.15 mmol), TEMPO (5 mg, 0.03 mmol), PIDA (126 mg, 0.380 mmol). Flash column chromatography (gradient elution 0% → 7% MeOH – CH_2Cl_2) afforded **88** as a yellow oil (38 mg, 62%).

Data for **88**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.59 – 7.46 (2H, m, Ar), 7.41 (1H, d, *J* = 7.9 Hz, Ar), 7.32 – 7.26 (1H, m, Ar), 7.10 (2H, d, *J* = 8.7 Hz, Ar), 6.64 (2H, d, *J* = 8.2 Hz, Ar), 5.23 (1H, d, *J* = 5.8 Hz, C2-H), 4.08 – 3.92 (1H, m, C5-H_A), 3.90 – 3.78 (1H, m, C5-H_B), 3.72 (3H, s, OMe), 3.11 – 2.98 (1H, m, C3-H), 2.43 – 2.17 (2H, m, C4-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 176.6 (C6), 159.4 (C Ar), 149.3 (C Ar), 137.6 (C Ar), 133.0 (C Ar), 131.2 (C Ar), 131.0 (C Ar), 130.4 (C Ar), 128.3 (2 × C Ar), 123.7 (C Ar), 114.0 (2 × C Ar), 65.3 (C2), 55.4 (OMe), 53.8 (C3), 49.3 (C5), 28.3 (C4). **HRMS** (ESI): calculated for $C_{18}H_{19}N_2O_7S$ $[M+H]^+$ requires *m*/*z* 407.0908, found *m*/*z* 407.0917. **IR** (film) ν_{max}: 1712, 1544, 1514, 1250, 1163, 1031, 743, 656 cm^{-1}.

(90): (±)-((2*S*,3*S*)-2-(4-Methoxyphenyl)pyrrolidin-3-yl)methanol

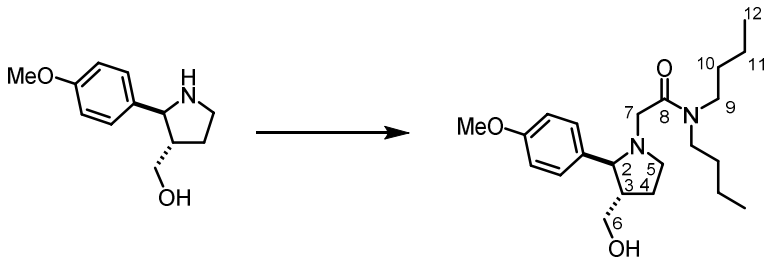


3o **90**

Prepared according to **General Procedure Q** using **3o** (45 mg, 0.11 mmol), *n*-$C_{12}H_{28}SH$ (28 mg, 0.14 mmol) and $CsCO_3$ (93 mg, 0.29 mmol). Flash column chromatography (gradient elution 0% → 10% ammonia 7.0 N methanol – CH_2Cl_2) afforded **90** as a yellow oil (24 mg, *quant.*).

Data for **90**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.30 (2H, *J* = 8.7 Hz, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 3.98 (1H, d, *J* = 8.0 Hz, C2-H), 3.78 (3H, s, OMe), 3.64 (1H, dd, *J* = 10.8, 5.2 Hz, C6-H_A), 3.58 (1H, dd, *J* = 10.8, 5.7 Hz, C6-H_B), 3.23 (1H, ddd, *J* = 10.5, 7.9, 6.1 Hz, C5-H_A), 3.12 – 3.02 (1H, m, C5-H_B), 2.31 (1H, dtd, *J* = 13.4, 7.8, 5.4 Hz, C3-H), 2.18 – 2.07 (1H, m, C4-H_A), 1.80 (1H, dddd, *J* = 13.1, 8.7, 7.2, 6.1 Hz, C4-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.4 (C Ar), 132.8 (C Ar), 128.6 (2 × C Ar), 114.3 (2 × C Ar), 64.9 (C2), 63.8 (C6), 55.4 (OMe), 48.7 (C3), 45.6 (C5), 28.4 (C4). **HRMS** (ESI): calculated for $C_{12}H_{18}NO_2$ $[M+H]^+$ requires *m/z* 208.1338, found *m/z* 208.1338. **IR** (film) ν_{max}: 2980, 1669, 1652, 1445, 967, 836, 699, 633 cm^{-1}.

(89): (±)-*N*,*N*-Dibutyl-2-((2*S*,3*S*)-3-(hydroxymethyl)-2-(4-methoxyphenyl)pyrrolidin-1-yl)-acetamide



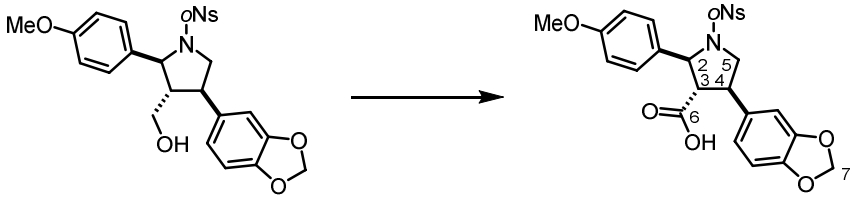
90 **89**

Prepared according to **General procedure R** using **90** (12 mg, 0.058 mmol), **87** (12 mg, 0.073 mmol) and Cs_2CO_3 (20 mg, 0.15 mmol). Flash column chromatography (gradient elution 0% → 20% EtOAc – CH_2Cl_2) afforded **89** as a colourless oil (16 mg, 78%).

Data for **89**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28 (2H, d, *J* = 8.3 Hz, Ar), 6.86 (2H, d, *J* = 8.3 Hz, Ar), 3.79 (3H, s, OMe), 3.68 – 3.53 (2H, m, C6-H_2), 3.43 – 3.24 (2H, m, C5-H_A + C7-H_A), 3.18 (1H, td, *J* = 9.8, 5.1 Hz, 1 × C9-H_2), 3.13 – 3.03 (2H, m, C2-H + 1 × C9-H_2), 2.97 (1H, ddd, *J* = 15.0, 10.0, 5.4 Hz, 1 × C9-H_2), 2.76 (1H, d, *J* = 13.1 Hz, C5-H_B), 2.61 (1H, *br.* s, C7-H_B), 2.29 (1H, *br.* s, C3-H), 2.20 – 2.09 (1H, m, C4-H_A), 1.83 – 1.75 (1H, m, C4-H_B), 1.54 – 1.17 (6H, m, 4 × C10-H_2 + 2 × C11-H_2), 1.07 (2H, h, *J* = 7.4 Hz, 2 × C11-H_2), 0.90 (3H, t, *J* = 7.3 Hz, 3 × C12-H_3), 0.81 (3H, t, *J* = 7.3 Hz, 3 × C12-H_3). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 159.3 (C Ar), 129.5 (C Ar), 129.4 (2 × C Ar), 114.0 (2 × C Ar), 71.9 (C2), 65.0 (C6), 55.4 (OMe), 55.4 (C5), 52.8 (C7), 49.6 (C3), 47.1 (1 × C9), 45.5 (1 × C9), 31.1 (1 × C10), 29.8 (1 × C10), 26.7 (C4), 20.4 (1 × C11), 20.0 (1 × C11), 14.0 (1 × C12), 14.0 (1 × C12).

HRMS (ESI): calculated for $C_{22}H_{37}N_2O_3$ $[M+H]^+$ requires m/z 377.2799, found m/z 377.2797. **IR** (film) ν_{max}: 3425, 2958, 2873, 1627, 1513, 1466, 1248, 823 cm^{-1}

(93): (±)-(2*S*,3*S*,4*R*)-4-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)-1-((2-nitrophenyl)-sulfonyl)pyrrolidine-3-carboxylic acid

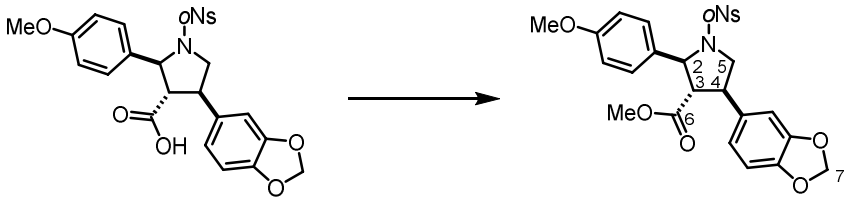


3bi **93**

Prepared according to **General Procedure S** using **3bi** (24 mg, 0.050 mmol), TEMPO (1.5 mg, 0.010 mmol), PIDA (40 mg, 0.125 mmol). Flash column chromatography (gradient elution 0% → 5% MeOH – CH_2Cl_2) afforded **93** a yellow oil (15 mg, 74%).

Data for **93**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.59 – 7.51 (1H, m, Ar), 7.49 (1H, ddd, *J* = 8.0, 5.8, 3.1 Hz, Ar), 7.24 – 7.17 (2H, m, Ar), 7.16 – 7.08 (2H, m, Ar), 6.79 – 6.72 (3H, m, Ar), 6.62 (2H, d, *J* = 8.7 Hz, Ar), 5.96 (2H, *br.* s, C7-H_2), 5.20 (1H, d, *J* = 9.3 Hz, C2-H), 4.45 (1H, dd, *J* = 10.9, 7.7 Hz, C5-H_A), 3.79 (1H, t, *J* = 11.1 Hz, C5-H_B), 3.73 (3H, s, OMe), 3.65 (1H, td, *J* = 11.4, 7.7 Hz, C4-H), 3.25 (1H, dd, *J* = 11.5, 9.3 Hz, C3-H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 175.5 (C6), 159.7 (C Ar), 148.2 (C Ar), 147.4 (C Ar), 147.4 (C Ar), 133.9 (C Ar), 132.9 (C Ar), 131.2 (C Ar), 131.1 (C Ar), 130.4 (C Ar), 130.3 (C Ar), 128.9 (2 × C Ar), 123.8 (C Ar), 121.1 (C Ar), 114.0 (2 × C Ar), 108.7 (C Ar), 107.7 (C Ar), 101.4 (C7), 66.7 (C2), 60.9 (C3), 56.5 (C5), 55.4 (OMe), 47.8 (C4). **HRMS** (ESI): calculated for $C_{25}H_{22}N_2O_9SNa$ $[M+Na]^+$ requires m/z 549.0944, found m/z 549.0949. **IR** (film) ν_{max}: 2360, 1712, 1543, 1368, 1251, 1126, 735 cm^{-1}.

(94): (±)-Methyl (2*S*,3*S*,4*R*)-4-(benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)-1-((2-nitrophenyl)-sulfonyl)pyrrolidine-3-carboxylate

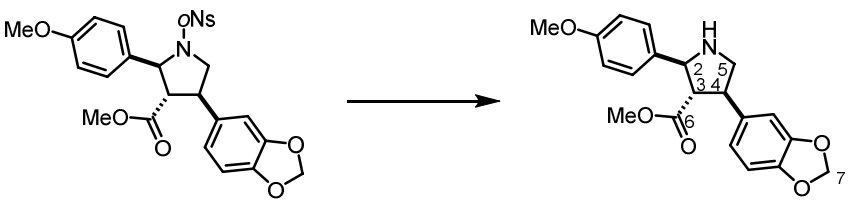


93 **94**

Prepared according to **General procedure T** using **93** (15 mg, 0.037 mmol). Flash column chromatography (15% EtOAc – pentane) afforded **94** as a white solid (15 mg, 98%).

Data for **94**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.56 (1H, dd, *J* = 7.5, 1.0 Hz, Ar), 7.50 (1H, ddd, *J* = 8.0, 5.0, 3.7 Hz, Ar), 7.23 – 7.18 (2H, m, Ar), 7.11 (2H, d, *J* = 8.7 Hz, Ar), 6.80 – 6.71 (3H, m, Ar), 6.62 (2H, d, *J* = 8.7 Hz, Ar), 5.95 (2H, *br.* s, C7-H_2), 5.20 (1H, d, *J* = 9.5 Hz, C2-H), 4.45 (1H, dd, *J* = 10.9, 7.7 Hz, C5-H_A), 3.80 (1H, t, *J* = 11.1 Hz, C5-H_B), 3.73 (3H, s, OMe), 3.72 – 3.62 (1H, m, C4-H), 3.53 (3H, s, OMe), 3.23 (1H, dd, *J* = 11.6, 9.5 Hz, C3-H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 171.2 (C6), 159.7 (C Ar), 148.2 (C Ar), 147.4 (C Ar), 147.3 (C Ar), 134.1 (C Ar), 132.9 (C Ar), 131.2 (C Ar), 131.1 (C Ar), 130.6 (C Ar), 130.6 (C Ar), 128.8 (2 × C Ar), 123.8 (C Ar), 121.0 (C Ar), 114.0 (2 × C Ar), 108.7 (C Ar), 107.6 (C Ar), 101.3 (C7), 67.1 (C2), 61.4 (C3), 56.3 (C5), 55.4 (OMe), 52.4 (OMe), 47.9 (C4). **HRMS** (ESI): calculated for $C_{26}H_{25}N_2O_9S$ $[M+H]^+$ requires *m/z* 541.1275, found *m/z* 541.1277. **IR** (film) ν_{max}: 1737, 1544, 1514, 1371, 1252, 1037, 736 cm^{-1}.

(58): (±)-Methyl (2*S*,3*S*,4*R*)-4-(benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)-pyrrolidine-3-carboxylate

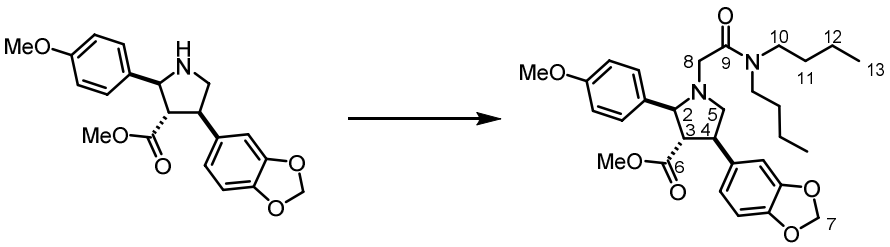


94 **58**

Prepared according to **General procedure Q** using **94** (70 mg, 0.13 mmol), *n*-$C_{12}H_{25}SH$ (70 mg, 0.33 mmol) and $CsCO_3$ (220 mg, 0.65 mmol). Flash column chromatography (gradient elution 0% → 7% MeOH – CH_2Cl_2) afforded **58** as a yellow oil (50 mg, 93%).

Data for **58**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.39 (2H, d, *J* = 8.7 Hz, Ar), 6.91 – 6.82 (3H, m, Ar), 6.77 – 6.70 (2H, m, Ar), 5.94 (2H, s, C7-H_2), 4.53 (1H, d, *J* = 9.4 Hz, C2-H), 3.77 (3H, s, OMe), 3.67 – 3.60 (1H, m, C4-H), 3.57 (3H, s, OMe), 3.54 – 3.47 (1H, m, C5-H_A), 3.23 (1H, dd, *J* = 11.0, 7.8 Hz, C5-H_B), 3.04 (1H, t, *J* = 9.4 Hz, C3-H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 159.6 (C Ar), 148.3 (C Ar), 148.1 (C Ar), 136.8 (C Ar), 131.6 (C Ar), 128.4 (2 × C Ar), 120.8 (C Ar), 114.9 (2 × C Ar), 108.7 (C Ar), 107.7 (C Ar), 101.3 (C7), 66.6 (C2), 60.6 (C3), 55.5 (OMe), 52.4 (C5), 52.2 (OMe), 50.1 (C4). *A signal corresponding to C6 was not observed.* **HRMS** (ESI): calculated for $C_{20}H_{22}NO_5$ $[M+H]^+$ requires *m/z* 356.1493, found *m/z* 356.1496. **IR** (film) ν_{max}: 2952, 1735, 1666, 1612, 1514, 1422, 1250, 1176, 1038, 735 cm^{-1}.

(95): (±)-Methyl (2*S*,3*S*,4*R*)-4-(benzo[*d*][1,3]dioxol-5-yl)-1-(2-(dibutylamino)-2-oxoethyl)-2-(4-methoxyphenyl)pyrrolidine-3-carboxylate

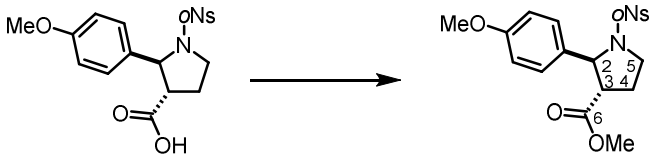


Prepared according to **General procedure R** using **58** (25 mg, 0.045 mmol), **87** (14 mg, 0.056 mmol) and DIPEA (12.0 μL, 0.068 mmol). Flash column chromatography (gradient elution 0% → 25% EtOAc – CH_2Cl_2) afforded **95** as a colourless oil (12 mg, 33%).

Data for **95**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.30 (2H, d, *J* = 8.4 Hz, Ar), 7.01 (1H, d, *J* = 1.8 Hz, Ar), 6.95 – 6.79 (2H, m, Ar), 6.73 (2H, d, *J* = 7.9 Hz, Ar), 5.95 – 5.91 (2H, m, C7-H_2), 3.79 (3H, s, OMe), 3.73 (1H, d, *J* = 9.5 Hz, C2-H), 3.57 (4H, s, C4-H + OMe), 3.50 – 3.35 (3H, m, C5-H_A + C8-H_A + 1 × C10-H_2), 3.30 (1H, ddd, *J* = 15.1, 10.0, 5.9 Hz, 1 × C10-H_2), 3.12 – 2.92 (4H, m, C3-H + C5-H_B + 2 × C10-H_2), 2.74 (1H, d, *J* = 13.3 Hz, C8-H_B), 1.44 (2H, q, *J* = 7.6 Hz, 1 × C11-H_2), 1.40 – 1.31 (2H, m, 1 × C11-H_2), 1.31 – 1.19 (4H, m, 2 × C11-H_2 + 2 × C12-H_2), 1.07 (2H, h, *J* = 7.5 Hz, 2 × C12-H_2), 0.87 (3H, t, *J* = 7.3 Hz, 3 × C13-H_3), 0.80 (3H, t, *J* = 7.3 Hz, 3 × C13-H_3). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 173.9 (C6), 169.5 (C9), 159.6 (C Ar), 146.2 (C Ar), 139.5 (C Ar), 131.7 (C Ar), 129.4 (2 × C Ar), 120.5 (C Ar), 114.1 (2 × C Ar), 108.3 (C Ar), 107.7 (C Ar), 101.0 (C7), 72.9 (C2), 61.9 (C3), 60.5 (C5), 55.4 (C8), 55.4 (OMe), 52.0 (OMe), 47.0 (C10), 46.0 (C4), 45.3 (C10), 31.2 (1 × C11), 29.8 (1 × C11), 20.4

(1 × C12), 20.0 (1 × C12), 14.0 (1 × C13), 13.9 (1 × C13). **HRMS** (ESI): calculated for $C_{30}H_{41}N_2O_6$ $[M+H]^+$ requires m/z 525.2959, found m/z 525.2963. **IR** (film) ν_{max}: 2959, 2873, 1736, 1649, 1486, 1249, 1213, 1037, 933, 831 cm^{-1}.

(96a): (±)-Methyl (2*S*,3*S*)-2-(4-methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)pyrrolidine-3 -carboxylate

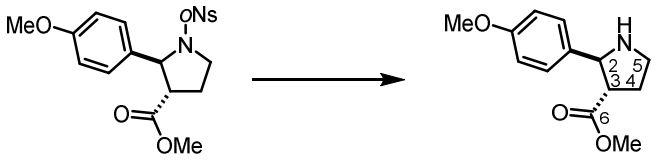


88 **96a**

Prepared according to **General procedure T** using **88** (22 mg, 0.054 mmol). Flash column chromatography (15% EtOAc – pentane) afforded **96a** as a white solid (22 mg, *quant.*).

Data for **96a**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.58 – 7.50 (2H, m, Ar), 7.47 – 7.39 (1H, m, Ar), 7.31 (1H, ddd, J = 8.1, 5.8, 2.9 Hz, Ar), 7.12 (2H, d, J = 8.6 Hz, Ar), 6.66 (2H, d, J = 8.7 Hz, Ar), 5.22 (1H, d, J = 6.3 Hz, C2-H), 4.02 (1H, ddd, J = 10.2, 7.5, 5.3 Hz, C5-H_A), 3.89 – 3.81 (1H, m, C5-H_B), 3.73 (3H, s, OMe), 3.63 (3H, s, OMe), 3.05 (1H, dt, J = 7.9, 6.6 Hz, C3-H), 2.35 – 2.19 (2H, m, C4-H_2). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 172.3 (C6), 159.4 (C Ar), 133.3 (C Ar), 133.0 (C Ar), 132.0 (C Ar), 131.2 (C Ar), 131.1 (C Ar), 128.3 (2 × C Ar), 127.6 (C Ar), 123.7 (C Ar), 113.9 (2 × C Ar), 65.7 (C2), 55.4 (OMe), 54.0 (C3), 52.4 (OMe), 49.4 (C5), 28.4 (C4). **HRMS** (ESI): calculated for $C_{19}H_{20}N_2O_7SNa$ $[M+Na]^+$ requires m/z 443.0884, found m/z 443.0891. **IR** (film) ν_{max}: 2956, 2855, 1738, 1547, 1374, 1176, 779, 629 cm^{-1}.

(S15): (±)-Methyl (2*S*,3*S*)-2-(4-methoxyphenyl)pyrrolidine-3-carboxylate

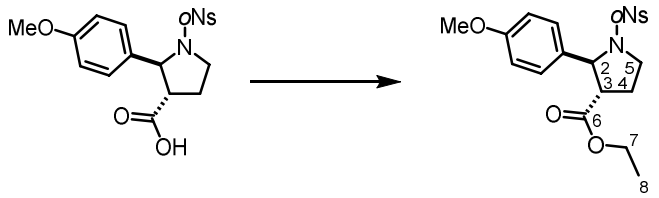


96a **S15**

Prepared according to **General Procedure Q** using **96a** (22 mg, 0.054 mmol), *n*-$C_{12}H_{28}SH$ (27 mg, 0.14 mmol) and $CsCO_3$ (88 mg, 0.27 mmol). Flash column chromatography (gradient elution 0% → 10% ammonia 7.0 N methanol – CH_2Cl_2) afforded **S15** as a yellow oil (12.5 mg, 98%).

Data for **S15**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.32 (2H, d, *J* = 8.7 Hz, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 4.36 (1H, d, *J* = 8.0 Hz, C2-H), 3.79 (3H, s, OMe), 3.66 (3H, s, OMe), 3.30 – 3.19 (1H, m, C5-H_A), 3.14 (1H, q, *J* = 8.5 Hz, C5-H_B), 2.93 (1H, dt, *J* = 9.4, 7.5 Hz, C3-H), 2.31 – 2.20 (1H, m, C4-H_A), 2.19 – 2.09 (1H, m, C4-H_B). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 176.5 (C6), 159.7 (C Ar), 134.1 (C Ar), 128.7 (2 × C Ar), 114.3 (2 × C Ar), 65.6 (C2), 55.4 (OMe), 52.3 (OMe), 50.8 (C3), 45.7 (C5), 29.9 (C4). **HRMS** (ESI): calculated for $C_{13}H_{18}NO_3$ $[M+H]^+$ requires *m*/*z* 236.1281, found *m*/*z* 236.1277. **IR** (film) ν_{max}: 2957, 2854, 1737, 1518, 1254, 1035, 883, 643 cm^{-1}.

(96b): (±)-Ethyl (2*S*,3*S*)-2-(4-methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)pyrrolidine-3-carboxylate



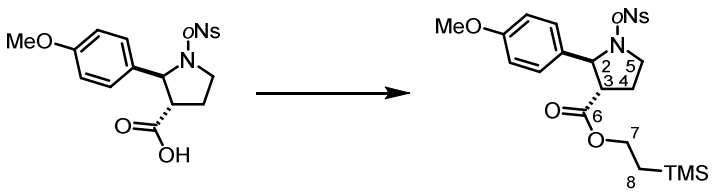
88 **96b**

Prepared according to **General Procedure U** using **88** (40 mg, 0.10 mmol), EtOH (60 μL, 1.0 mmol), DMAP (1.5 mg, 0.010 mmol) and ECDI.HCl (29 mg, 0.15 mmol). Flash column chromatography (15% EtOAc – pentane) afforded **96b** as a colourless oil (15 mg, 35%).

Data for **96b**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.56 – 7.49 (2H, m, Ar), 7.42 (1H, d, *J* = 8.0 Hz, Ar), 7.33 – 7.27 (1H, m, Ar), 7.12 (2H, d, *J* = 8.2 Hz, Ar), 6.65 (2H, d, *J* = 8.8 Hz, Ar), 5.21 (1H, d, *J* = 6.3 Hz,

C2-H), 4.08 (2H, q, J = 7.1 Hz, C7-H_2), 4.02 (1H, ddd, J = 10.6, 7.6, 5.2 Hz, C5-H_A), 3.85 (1H, dt, J = 10.4, 7.5 Hz, C5-H_B), 3.73 (3H, s, OMe), 3.03 (1H, q, J = 7.1 Hz, C3-H), 2.33 – 2.18 (2H, m, C4-H_2), 1.20 (3H, t, J = 7.2 Hz, C8-H_3). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 171.8 (OMe), 159.4 (C Ar), 147.7 (C Ar), 133.4 (C Ar), 132.9 (C Ar), 132.1 (C Ar), 131.2 (C Ar), 131.1 (C Ar), 128.3 (2 × C Ar), 123.7 (C Ar), 113.9 (2 × C Ar), 65.7 (C2), 61.3 (C7), 55.4 (OMe), 54.2 (C3), 49.5 (C5), 28.4 (C4), 14.2 (C8). **HRMS** (ESI): calculated for $C_{20}H_{22}N_2O_7SNa$ $[M+Na]^+$ requires m/z 457.1040, found m/z 457.1052. **IR** (film) ν_{max}: 2987, 2967, 1733, 1546, 1514, 1182, 1034 cm^{-1}.

(96c): (±)-2-(Trimethylsilyl)ethyl (2*S*,3*S*)-2-(4-methoxyphenyl)-1-((2-nitrophenyl)sulfonyl)-pyro-lidine-3-carboxylate

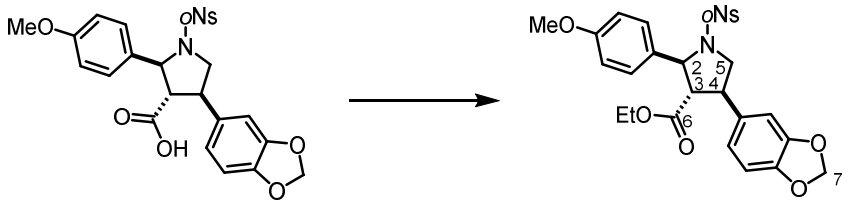


88 **96c**

Prepared according to **General Procedure U** using **88** (40 mg, 0.10 mmol), 2-(trimethylsilyl)ethanol (17 μL, 0.12 mmol), DMAP (1.5 mg, 0.010 mmol) and ECDI.HCl (29 mg, 0.15 mmol). Flash column chromatography (15% EtOAc – pentane) afforded **96c** as a colourless oil (17 mg, 34%).

Data for **96c**: **^{1}H NMR (600 MHz, $CDCl_3$) δ** 7.55 – 7.49 (2H, m, Ar), 7.41 (1H, dd, J = 7.9, 1.2 Hz, Ar), 7.32 – 7.27 (1H, m, Ar), 7.12 (2H, d, J = 8.6 Hz, Ar), 6.65 (2H, d, J = 8.7 Hz, Ar), 5.20 (1H, d, J = 6.4 Hz, C2-H), 4.15 – 4.06 (2H, m, C7-H_2), 4.02 (1H, ddd, J = 10.2, 7.6, 5.1 Hz, C5-H_A), 3.84 (1H, ddd, J = 10.2, 7.8, 6.7 Hz, C5-H_B), 3.73 (3H, s, OMe), 3.02 (1H, dt, J = 8.0, 6.7 Hz, C3-H), 2.32 – 2.17 (2H, m, C4-H_2), 0.01 (9H, s, $Si(CH_3)_3$). **^{13}C NMR (151 MHz, $CDCl_3$) δ** 172.0 (C6), 159.5 (C Ar), 133.6 (C Ar), 133.0 (C Ar), 132.2 (C Ar), 131.3 (C Ar), 131.2 (C Ar), 131.1 (C Ar), 128.5 (2 × C Ar), 123.8 (C Ar), 114.0 (2 × C Ar), 65.8 (C2), 63.8 (C7), 55.5 (OMe), 54.5 (C3), 49.6 (C5), 28.5 (C4), 17.5 (C8), -1.3 ($Si(\mathbf{C}H_3)_3$). **HRMS** (ESI): calculated for $C_{23}H_{31}N_2O_7SSi$ $[M+H]^+$ requires m/z 507.1616, found m/z 507.1627. **IR** (film) ν_{max}: 1731, 1545, 1514, 1371, 1250, 1166, 1034, 837, 742 cm^{-1}.

(98): (±)-Ethyl (2*S*,3*S*,4*R*)-4-(benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)-1-((2-nitro-phenyl)-sulfonyl)pyrrolidine-3-carboxylate

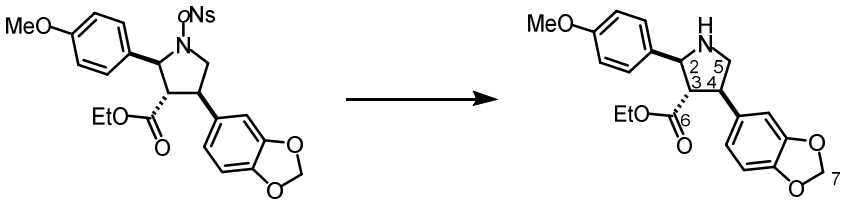


93 **98**

To a solution of **93** (12 mg, 0.023 mmol) in DMF (0.3 mL) was added ethyl iodide (4.0 mg, 0.027 mmol) in DMF (0.1 mL) and Cs_2CO_3 (18 mg, 0.055 mmol). After 16 the solid was removed by filtration and the solvent removed *in vacuo*. Flash column chromatography (15% EtOAc – pentane) afforded **98** as a colourless oil (6.0 mg, 47%).

Data for **98**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.56 (1H, dd, *J* = 7.6, 1.0 Hz, Ar), 7.50 (1H, ddd, *J* = 8.0, 4.9, 3.8 Hz, Ar), 7.21 (2H d, *J* = 3.9 Hz, Ar), 7.11 (2H, d, *J* = 8.7 Hz, Ar), 6.83 – 6.71 (3H, m, Ar), 6.61 (2H, d, *J* = 8.7 Hz, Ar), 5.95 (2H, s, C7-H_2), 5.19 (1H, d, *J* = 9.6 Hz, C2-H), 4.45 (1H, dd, *J* = 10.8, 7.7 Hz, C5-H_A), 4.00 (2H, *app.* dd, *J* = 7.1, 4.7 Hz, OC**H_2**CH_3), 3.79 (1H, d, *J* = 11.0 Hz, C5-H_B), 3.73 (3H, s, OMe), 3.66 (1H, td, *J* = 11.5, 7.7 Hz, C4-H), 3.20 (1H, dd, *J* = 11.6, 9.6 Hz, C3-H), 1.02 (3H, t, *J* = 7.1 Hz, OCH_2C**H_3**). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 170.6 (C6), 159.6 (C Ar), 148.2 (C Ar), 147.2 (C Ar), 134.1 (C Ar), 132.9 (C Ar), 131.2 (C Ar), 131.1 (C Ar), 130.7 (C Ar), 130.6 (C Ar), 128.9 (2 × C Ar), 123.8 (C Ar), 121.1 (C Ar), 113.9 (2 × C Ar), 108.6 (C Ar), 107.7 (C Ar), 101.3 (C7), 67.0 (C2), 61.5 (C3), 61.2 (O**C**H_2CH_3), 56.3 (C6), 55.4 (OMe), 47.8 (C4), 14.2 (OCH_2**C**H_3). **HRMS** (ESI): calculated for $C_{27}H_{27}N_2O_9S$ $[M+H]^+$ requires *m/z* 555.1432, found *m/z* 555.1433. **IR** (film) ν_{max}: 2359, 2337, 1737, 1543, 1252, 1038, 697, 663 cm^{-1}.

(46): (±)-Ethyl (2*S*,3*S*,4*R*)-4-(benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)-pyrrolidine-3-carboxylate



98 **46**

Prepared according to **General procedure Q** using **98** (6.0 mg, 0.014 mmol), *n*-$C_{12}H_{25}SH$ (3.0 mg, 0.028 mmol) and $CsCO_3$ (9.0 mg, 0.028 mmol). Flash column chromatography (gradient elution 0% → 5% MeOH – CH_2Cl_2) afforded **46** as a yellow oil (4.5 mg, 87%).

Data for **46**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.39 (2H, d, *J* = 8.8 Hz, Ar), 6.88 – 6.83 (3H, m, Ar), 6.76 – 6.71 (2H, m, Ar), 5.94 (2H, s, C7-H_2), 4.53 (1H, d, *J* = 9.7 Hz, C2-H), 4.04 (2H, q, *J* = 7.1 Hz, OC**H_2**CH_3), 3.77 (3H, s, OMe), 3.67 – 3.60 (1H, m, C4-H), 3.58 – 3.50 (1H, m, C5-H_A), 3.24 (1H, dd, *J* = 10.9, 8.0 Hz, C5-H_B), 3.02 (1H, t, *J* = 9.3 Hz, C3-H), 1.07 (3H, t, *J* = 7.1 Hz, OCH_2C**H_3**). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 159.6 (C Ar), 148.1 (C Ar), 146.7 (C Ar), 128.5 (2 × C Ar), 120.8 (C Ar), 114.2 (2 × C Ar), 108.5 (C Ar), 107.7 (C Ar), 101.2 (C7), 66.5 (C2), 61.0, 60.9 (O**C**H_2CH_3), 60.4 (C3), 55.4 (OMe), 53.4 (C6), 49.9 (C4), 14.3 (OCH_2**C**H_3). *A signal corresponding to C6 and 2 × C $Ar_{quat.}$ was not observed.* **NOESY- 2D (500 MHz, $CDCl_3$):** between C2-H and C4-H, between C2-H and C5-H_a, between C3-H and C5-H_b. **HRMS** (ESI): calculated for $C_{21}H_{24}NO_5$ $[M+H]^+$ requires *m*/*z* 370.1649, found *m*/*z* 370.1655. **IR** (film) ν_{max}: 2362, 1731, 1514, 1490, 1247, 1036, 736 cm^{-1}.

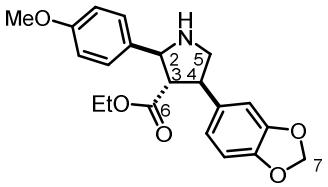
6.4.5 NMR signal comparison for 46

Table I – ^{1}H NMR shifts

Signal	**Literature**[128] (270 MHz)		**Observed** (500 MHz)		**Δ**
	δ (ppm)	***J* (Hz)**	**δ (ppm)**	***J* (Hz)**	
C2-H	4.45 (d)	8.8	4.53 (d)	9.7	-0.08
C3-H	2.99 (t)	8.8	3.02 (t)	9.3	-0.03
C4-H	3.73 – 3.44	-	3.67 – 3.60 (m)	-	-
C5-H_a			3.58 – 3.50 (m)	-	-
C5-H_b	3.18 (dd)	9.9, 6.3	3.24 (dd)	10.9, 8.0	-0.06
C7-H_2	5.91 (s)	-	5.94 (s)	-	-0.03
OMe	3.73 (s)	-	3.77 (s)	-	-0.04
O**CH_2**CH_3	4.04 – 3.88 (m)		4.04 (q)	7.1	-
OCH_2**CH_3**	1.09 (t)	7.0	1.07 (t)	7.1	+0.02

Table II – ^{13}C NMR shifts

Literature[129] (75.5 MHz) **δ (ppm)**	Observed (126 MHz) **δ (ppm)**	**Δ**
173.66	-	-
158.97	159.57	-0.60
147.86	148.11	-0.25
146.28	146.74	-0.46
136.37	-	-
134.16	-	-
127.77	128.51	-0.74
120.39	120.76	-0.37
113.87	114.19	-0.32
108.17	108.45	-0.28
107.49	107.73	-0.24
100.9	101.16	-0.26
66.68	66.52	+0.16
61.34	60.98	+0.36
60.56	60.44	+0.12
55.2	55.45	-0.25
53.53	53.38	+0.15
50.58	49.94	+0.64
14.19	14.29	-0.10



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