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Title:
Development of new classes of aza-Heck cyclisation for the synthesis of nitrogen heterocycles

Development of new classes of aza-Heck cyclisation for the synthesis of nitrogen heterocycles

Ian Hazelden

A thesis submitted to the University of Bristol in accordance with the requirements for award of the degree of PhD in the Faculty of Science

School of Chemistry, September 2018

(133,242 words)

Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific references in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others is indicated as such. Any views expressed in the dissertation are those of the author.

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Abstract

Two novel classes of aza-Heck reactions have been developed. These processes generate 2-alkenyl-*N*-heterocycles through the palladium-catalysed cyclisation of substrates containing an activated N–O bond and a pendant olefin. The first of these, based on the cyclisation of *N*-acyloxysulfonamides, is only the second reported class of aza-Heck reaction and is effective for the synthesis of complex bicyclic *N*-heterocycles commonly found in the core structures of natural products. Subsequently, an aza-Heck reaction of *N*-acyloxycarbamates was developed that provides considerable improvements in terms of efficiency compared to the sulfonamide-based reaction. Through the cyclisation of *N*-acyloxycarbamates, pyrrolidines and piperidines, as well as related 5- and 6-membered *N*-heterocycles, can be prepared in good to excellent yields. Furthermore, the diastereoselectivities achieved in these processes are generally much greater than those observed with aza-Heck cyclisations of *N*-acyloxysulfonamides. A number of mechanistic experiments have validated the aza-Heck pathway proposed for these transformations.

A highly asymmetric variant of the aza-Heck reaction was also developed, based on the cyclisation of *N*-sulfonyloxycarbamates. Through the use of SPINOL-based phosphoramidite ligands, pyrrolidines and piperidines can be prepared in good yields and with high enantioselectivities from substrates containing a diverse range of alkenes.

Additionally, palladium(0)-catalysed cascade reactions using the previously developed N–O bond donors have been demonstrated. These processes initiate with N–O oxidative addition and aminopalladation of a pendant alkene but terminate with trapping of the resulting organopalladium(II) intermediate, as opposed to β-hydride elimination. In collaboration with co-workers, a variety of alkene 1,2-aminofunctionalisation cascades have been achieved using this strategy. The application of these cascade reactions to the total synthesis of natural products has also been attempted.

Acknowledgements

First of all, my supervisor, John. Without his influence, this thesis would be incomparable. I hope that the quality of the results presented within are an accurate reflection of his significant intellectual input, and I know their quantity would be greatly reduced without his encouragement. I am confident that my abilities in synthetic organic chemistry, both in terms of a practical and theoretical basis, have improved massively over the course of my PhD, something which I also attribute significantly to him. Additionally, during writing up, his suggestions were invaluable at improving my confusing and cumbersome writing style. Finally, I thank him for his honesty.

I'd also like to thank Thomas Langer, my industrial supervisor at AstraZeneca, who was a great help to me during my placement. While I was there, he was crucial in getting me acquainted with how they do things, and also introduced me to the many people who helped me with my work. Furthermore, his advice on synthesis, as well as the fact that he ordered all the chemicals I needed, was much appreciated.

Due to the paucity of synonyms for gratitude available to my vocabulary, from here on, I have broken down my thanks into a list format. I can only apologise if this doesn't accurately portray the sincerity of my sentiments. I am extremely grateful to the following people at Bristol:

Jess Eastwood, Gabriele Fumagalli, Jamie Cadge, Giacomo Crisenza (despite only managing to read 5 pages in 7 weeks), Andrew Dalling, Phillippa Cooper and Ben Jones, for proofreading drafts of individual chapters. Of these, a special mention goes out to the first two, who had the misfortune of reading my work before I had learnt even the basic rules of punctuation. Xiaofeng Ma, Rafa Carmona, Charly Faradji, Josh Farndon and Tim Shuttleworth, for allowing me to make use of compounds they prepared. Xiaofeng Ma, Rafa Carmona and Ben Jones, whose results I discuss in this thesis. Professor Paul Pringle, for helpful discussions with regards to trioxaphosphaadamantane ligands, as well as providing the precursor required to prepare a variety of these. Alex Fawcett, for advice on the derivatisation of boronic esters.

Conducting my research was made considerably easier by the excellent facilities available in the Chemistry department. Although this is the result of the efforts of a large number of people, specific thanks to:

Paul Lawrence, Tom Leman and Professor Craig Butts, for running the NMR facilities, which were great, as well as providing help with the more technical aspects of NMR. Dr Paul Gates and Tom Leman, who were incredibly accommodating towards my tendency to submit an unreasonable number of MS samples in one go. Dr Hazel Sparkes and Dr Natalie Pridmore, for running all of my crystal structures.

Tony Rogers, for keeping everything in the lab working (my fume hood aside). Paul Egan and everyone in the stores.

I'd like to thank all the people at AstraZeneca who were so welcoming and friendly towards me; I really appreciated working in such a positive environment. In addition to this, many people generously gave their time to help me out while I was there, for which I am incredibly grateful:

Rachel Munday, Fiona Bell and Kevin Leslie, who provided a lot of help with chiral ligand screening during my industrial placement. David Whittaker and Michael Nunn, for their assistance with reaction monitoring (not to mention allowing me to put a sealed tube of THF in a spectrometer at 130 °C in the first place). Alex Telford, for help with hydrogenation apparatus. Anthony Bristow, for obtaining HRMS data for me. Lyn Powell (and his team) for welcoming me to their meetings, during which I gained valuable insights into the field of process chemistry. The other CASE students undertaking placements at the same time as me, thanks to you guys, I always knew what time to have lunch.

Thanks also to all the students in the Bower group, as well as anyone else who worked in N518. The tolerance with which my musical proclivities were accepted always surprised me, and this surpassed what Jenny offers me in this regard. I like to think that if I taught you guys anything, it's that good music doesn't have to be aesthetically pleasing, or that I don't like good music. Either one is fine with me. Outside of the lab, I had many good times with you guys, and I was lucky to be in such a social group. More specifically, I need to mention the following people:

Giacomo, while I found your lab behaviour infuriating, your proofreading non-existent and your views on women troubling, your company was never dull. I can honestly say, you are a friend to me unlike any other, and, for that, I am eternally grateful. Andrew, who had the misfortune of sharing with me what were potentially the two worst fume hoods in the department, and for keeping me entertained with jokes like, "United are going to win the league this year." Xiaofeng, who contributed so much to the development of the aza-Heck reactions. Rafa, who was a pleasure to work with, and never seemed to be in a bad mood. Phillippa, for asking challenging questions about my lifestyle. Lauren and Jamie, who continued to invite me to their house, despite my lack of respect towards it. Gangwei, for showing me cute pictures of his baby. Eric and Zedong, for keeping a close watch over my fume hood. Finally, thanks (and apologies) to the unfortunate people for whom I had some kind of supervisory responsibility towards.

Having covered my working life, I'm also appreciative of the following people who enriched (what was left of) my personal life:

My former housemates, Ollie and Sam. Their unfailing enthusiasm for weekly sessions of solvent and interpersonal abuse, over a few games of simulated association football, was a much-needed distraction

from the unimaginable horror encountered during a privileged life in the first-world. Discussions with Ollie were invaluable for identifying new music to inflict upon my long-suffering colleagues. Additionally, I appreciate Sam's frequent decisions to behave strangely in social situations so that I might look normal by comparison. His capacity for self-sacrifice is truly unparalleled. They have continued to demonstrate their generosity to me by letting me stay with them during my frequent visits to Bristol. Steve Stanton and Stephen Luckham, who organised a weekly game of football, as this was the closest my body got to doing the physical exercise it supposedly evolved to do. My pub quiz team, this event is the closest my mind gets to doing what I have carefully nurtured it to do: abusing quizmasters.

I am also indebted to my parents, for taking me (and my things) to and from my industrial placement in Macclesfield, and also for graciously storing my things (and my hair) while I am of no fixed abode. I am also grateful to Jenny's mother, Silvia, for letting me stay with her and Jenny as I complete my thesis.

Finally, I'd like to thank Jenny. The last six years have been the best of my life, and although I can't prove a causal link, I'm confident that this is due to her. Without her unwavering love and support, obtaining my first and (God willing) second degrees would have been a much harder and less rewarding task. I know I can count on her continued love and support in the future, particularly as I pursue my dream of becoming a professional footballer.

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Abbreviations

^{F}Bz	pentafluorobenzoyl
Cat	catecholato
CDI	carbonyl diimidazole
COD	1,5-cyclooctadiene
d.r.	diastereomeric ratio
dba	dibenzylideneacetone
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
dppb	1,4-bis(diphenylphosphino)butane
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
Im	imidazyl
MTBE	methyl *tert*-butyl ether
NBS	*N*-bromosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
Pin	pinacolato
Piv	pivaloyl
TFAA	trifluoroacetic anhydride

Standard abbreviations are not stated here.

Chapter 1 - Introduction

1.1 The importance of *N*-heterocycles

Nitrogen-based heterocycles are prevalent in bioactive molecules; a recent analysis of over a thousand FDA-approved drugs conducted by Njardarson and co-workers found that 59 % contained at least one *N*-heterocycle, with many of these containing more.[1] Furthermore, one of the major classes of natural products, alkaloids, contain *N*-heterocycles by definition.[2] It has been suggested that around 20 % of plant species produce alkaloids, which can display a wide variety of biological activities.[3] Considering this, it is perhaps unsurprising that out of the top ten most commonly used recreational drugs in the UK,[I] half have *N*-heterocycles at their cores, with four of these being alkaloids. Examples of each of these classes of compound are provided in Figure 1.

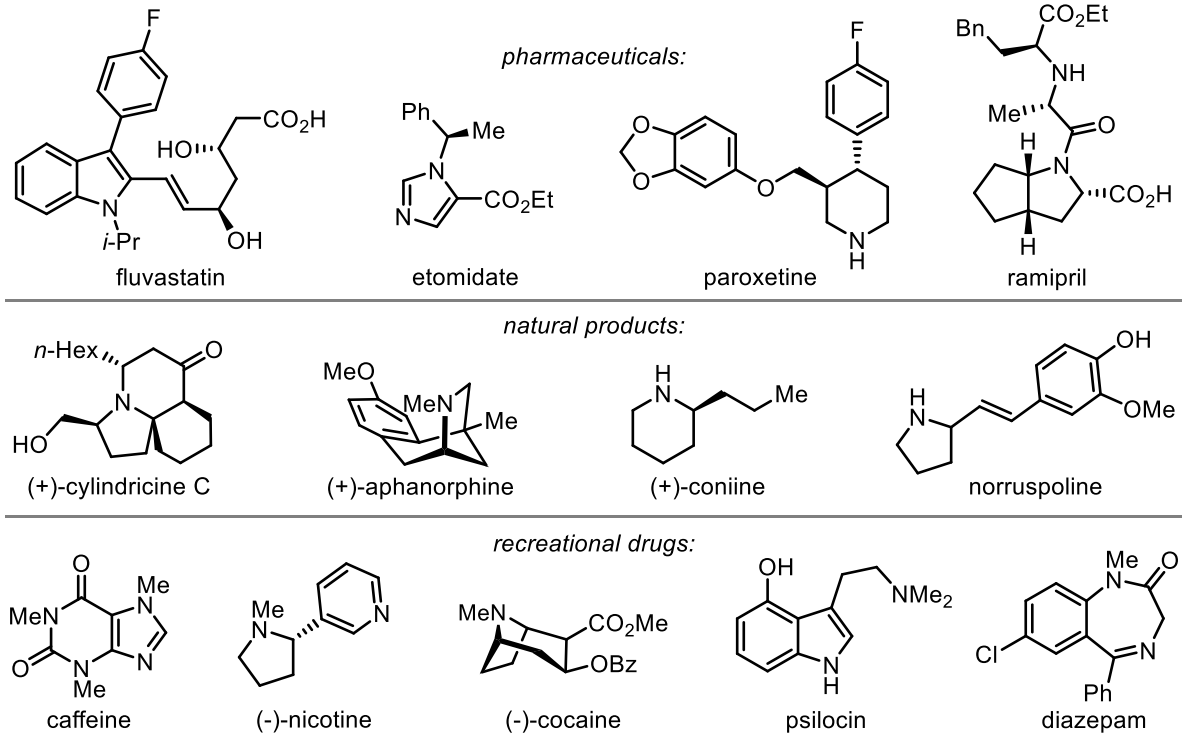


Figure 1 – Examples of pharmaceuticals,[1] natural products[9-13] and recreational drugs[8,14-17] containing N-heterocycles.

While analyses such as that by Njardarson are interesting, they only provide insight into successful drug candidates. Very little can be said about the compounds which might have been successful but were not amenable to synthesis. One of the aims of developing synthetic methodology is to limit the uncertainty in this area by enabling access to a greater diversity of molecules in a practical manner. The ubiquity of

[I] This list has been compiled from a variety of sources[4-7] and is as follows: caffeine, alcohol, nicotine, cannabis, cocaine, MDMA, amphetamines, amyl nitrite, hallucinogenic mushrooms and tranquilisers. Psilocin is one of the active components of hallucinogenic mushrooms,[8] and the structure of diazepam has been provided as an example of a tranquiliser.

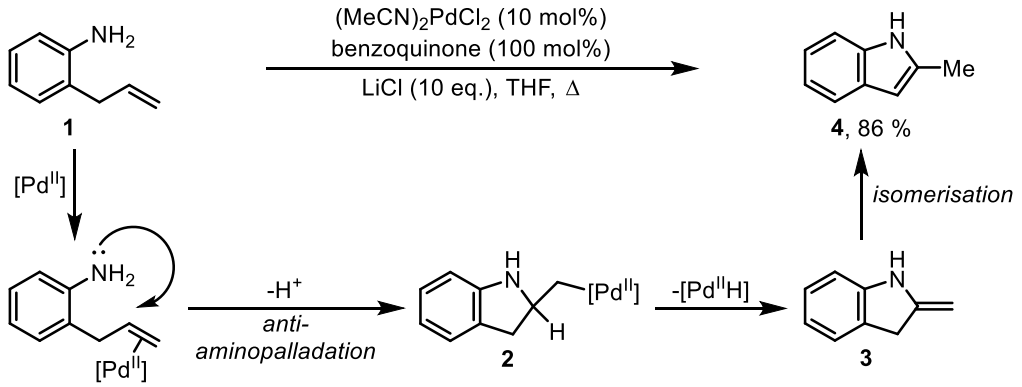
N-heterocycles in both pharmaceutical agents and bioactive natural products suggests that they are valuable targets for these efforts, and that methods which allow the preparation of previously difficult to access structures would be highly valuable.

Because of the importance of *N*-heterocycles, a variety of methods have been devised for their preparation. Key amongst these are palladium-catalysed cyclisations, and a brief overview of three classes of this kind of reaction is presented below. The first two classes are relatively well-developed strategies, whereas the final one is comparatively less developed and represents the focus of this thesis.

1.2 The aza-Wacker reaction

1.2.1 Initial reports and reaction development

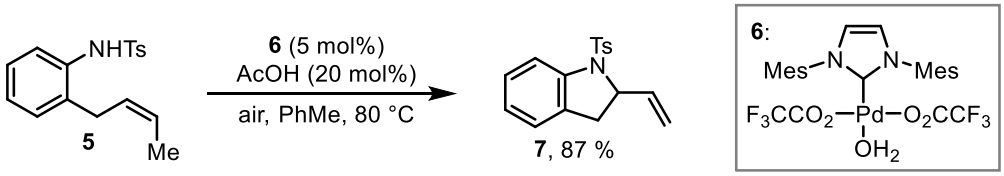
The palladium(II)-catalysed oxidative cyclisation of *o*-allylanilines to indoles was reported by Hegedus in 1978 (Scheme 1),[18] based on an earlier study of a stoichiometric transformation.[19] The reaction is proposed to proceed through intramolecular nucleophilic attack by nitrogen onto the palladium(II)-activated alkene of **1**, to afford intermediate **2**. From **2**, β-hydride elimination provides enamine **3**, which isomerises to indole **4**. The palladium hydride by-product requires oxidation to re-enter the catalytic cycle, as, although it is formally in the +2 oxidation state, deprotonation affords a palladium(0) species.



*Scheme 1 – Palladium(II)-catalysed oxidative cyclisation of o-allylaniline (**1**).[18]*

The palladium(II)-catalysed oxidative substitution of alkenes with a nitrogen nucleophile in the manner presented in Scheme 1 is known as the aza-Wacker reaction.[20] This terminology is used because of the analogy to the Wacker process, which involves palladium(II)-catalysed oxidation of ethylene to acetaldehyde.[21,22] Following the initial report from Hegedus,[18] further developments were made to improve the utility of the process. Early work focused on the use of free anilines and amines, but these bind too strongly to palladium(II), inhibiting catalytic activity.[23] Consequently, the use of protected nitrogen sources was found to be beneficial.[24] Improvements were also made with respect to the terminal

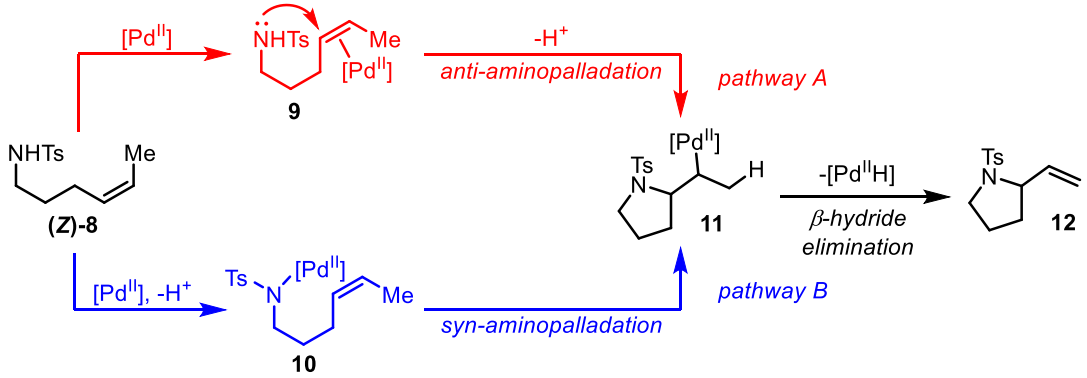
oxidant, and systems where the catalytic cycle is closed by molecular oxygen were reported.[25-27] Following this, Stahl demonstrated that palladium(II)-NHC catalyst **6** is highly effective for aza-Wacker cyclisations, allowing air to be used as the terminal oxidant in the conversion of **5** to indole **7** (Scheme 2).[28]



*Scheme 2 – Palladium(II)-catalysed oxidative cyclisation of substrate **5**, using air as the terminal oxidant.*[28]

1.2.2 Distinction between *syn*- and *anti*-aminopalladation pathways

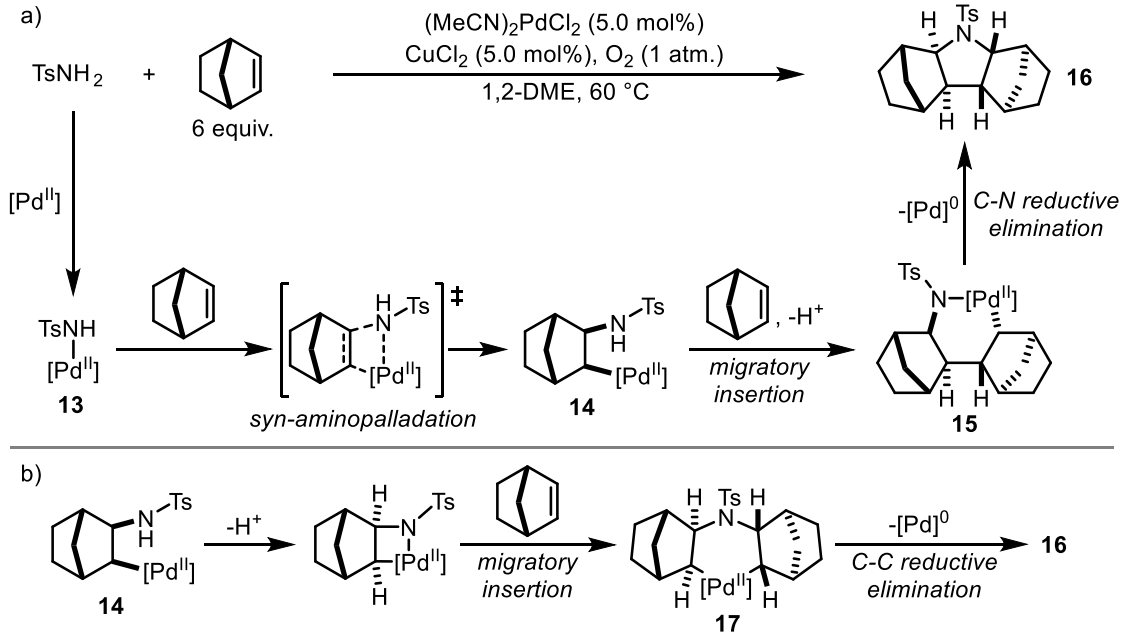
Early reports of aza-Wacker reactions invoked *anti*-aminopalladation in the key C–N bond forming step; here, palladium(II) activates the alkene for nucleophilic attack (Scheme 1 and Scheme 3, pathway A). However, *syn*-aminopalladation is an alternative possibility (Scheme 3, pathway B); in this case, ligand exchange produces aminopalladium(II) complex **10**, and the pendant alkene inserts into the Pd–N bond. Pioneering investigations into the aminopalladation of alkenes determined that the stereochemistry of products was consistent with an *anti*-aminopalladation step, although these studies were carried out on intermolecular reactions.[29,30] For some time, despite some indication that *syn*-aminopalladation is possible,[31] there was no evidence for it being operative in aza-Wacker reactions.[32]



Scheme 3 – The two distinct mechanisms possible for the aza-Wacker reaction. Pathway A: anti-aminopalladation. Pathway B: syn-aminopalladation.

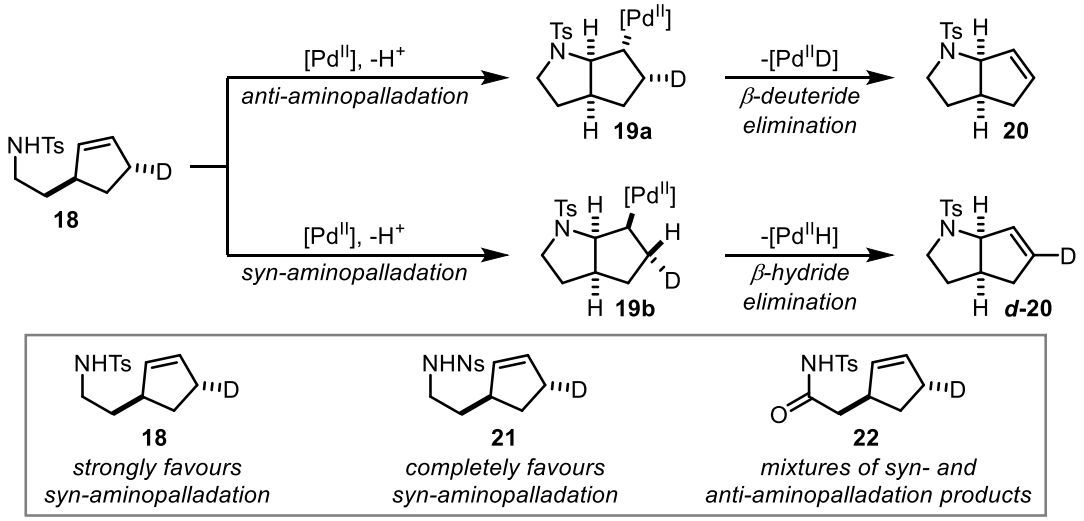
In the course of developing an intermolecular aza-Wacker reaction of unactivated alkenes, Stahl observed norbornene-derived product **16**, which can only result from *syn*-aminopalladation (Scheme 4a).[33] The initially proposed mechanism for the formation of **16** involves two sequential migratory insertions of norbornene, first into the Pd–N bond of **13** and then into the Pd–C bond of **14**. It was suggested that palladium(II) intermediate **15** undergoes C–N bond-forming reductive elimination

to afford **16**. However, C_{sp3}-N reductive eliminations from palladium(II) complexes are very rarely observed;[34] hence, complexes similar to **15** can be isolated.[35] Another mechanism has also been suggested, which involves norbornene inserting into a Pd–N bond twice, followed by C–C reductive elimination from **17** (Scheme 4b).[36]



*Scheme 4 – a) Observation of **16** from the aza-Wacker reaction of norbornene with p-toluenesulfonamide, and the initially proposed mechanism for its formation.[33] b) Alternative mechanism for the formation of **16**.[36]*

Following the observation of **16**, Stahl examined the geometry of aminopalladation in intramolecular aza-Wacker reactions under a number of conditions.[37] In the cyclisation of deuterium-labelled substrate **18**, *anti*-aminopalladation affords intermediate **19a**, whereas *syn*-aminopalladation affords intermediate **19b** (Scheme 5). From **19a**, β-deuteride elimination occurs to afford **20**. In contrast, only the hydrogen atom is available for elimination in intermediate **19b**, so ***d*-20** results. By comparing the ratio of **20** to ***d*-20**, the preference for *anti*- or *syn*-aminopalladation under a set of reaction conditions was determined. The majority of conditions examined were found to favour *syn*-aminopalladation, although conditions similar to those detailed in Scheme 2 (Section 1.2.1) resulted in a 1:1 mixture of *syn*- and *anti*-aminopalladation products. The selectivity for a given reaction pathway was found to be highly dependent on the pH of the reaction conditions, with acidic conditions favouring *anti*- and basic conditions favouring *syn*-aminopalladation. The nature of the substrate has an effect too: substrate **21**, the *N*-nosyl analogue of **18**, was found to afford *syn*-aminopalladation products with complete selectivity. This was rationalised as being due to the more acidic N–H bond facilitating formation of the key aminopalladium(II) intermediate (analogous to **10** in Scheme 3). However, the dependence of reaction pathway on substrate pK_a is not completely predictable, and substrate **22**, which is more acidic than both **18** and **21**, afforded mixtures of *syn*- and *anti*-aminopalladation products, with the ratio of products being highly dependent on the conditions used.

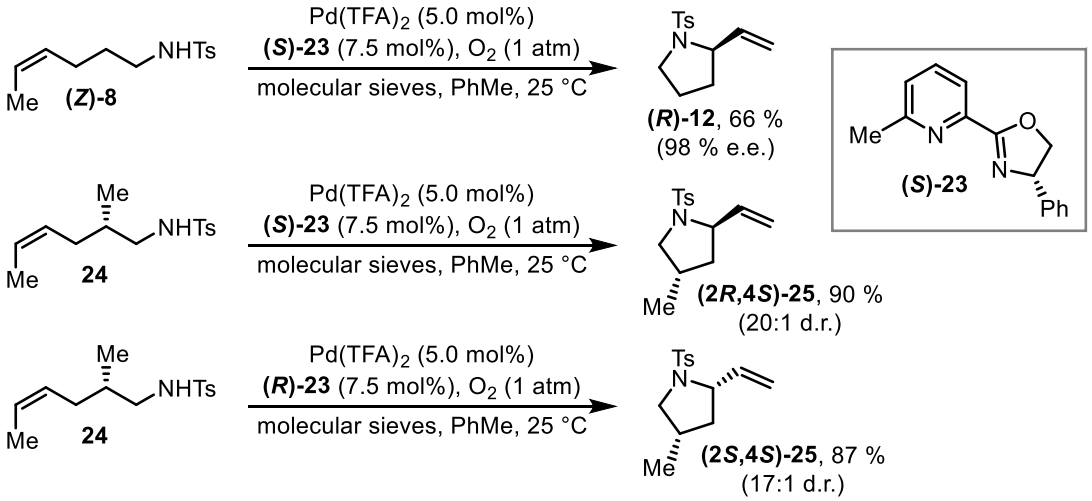


*Scheme 5 – Stahl's deuterium-labelled substrate (**18**) for probing the stereochemical course of aminopalladation in aza-Wacker cyclisations.*[37]

In aza-Wacker reactions, *syn*- and *anti*-aminopalladation pathways generally afford the same product. However, the stereochemical course of these processes has a bearing on enantioselective reactions. Due to the differing nature of intermediates **9** and **10** (Scheme 3), it is unlikely one chiral ligand could provide high levels of asymmetric induction in both a *syn*- and an *anti*-aminopalladation step. Consequently, reactions for which both pathways are operative are unlikely to proceed with high enantioselectivity. Furthermore, the fact that the aminopalladation mechanism is highly substrate dependent could limit the generality of any enantioselective aza-Wacker reaction. Finally, in related palladium(II)-catalysed cyclisations that do not terminate in β-hydride elimination,[38-42] the geometry of the aminopalladation step determines which diastereomer of product is obtained.

1.2.3 Enantioselective aza-Wacker cyclisations

The first highly enantioselective aza-Wacker reaction was reported by Stahl in 2011.[43] Using pyrox-based ligand **23**, enantioenriched pyrrolidines were prepared in good to excellent yields and with high enantioselectivities (Scheme 6). For substrates with a defined stereocentre in the β-position, the catalyst can override the inherent substrate-controlled diastereoselectivity. For example, starting from **24**, either diastereomer of **25** can be prepared, simply by using the (*S*)- or the (*R*)-enantiomer of ligand **23**. This strategy is not effective, however, for substrates containing either α- or γ-substitution. An alternative strategy for the preparation of enantioenriched pyrrolidines makes use of an enantiopure sulfinamide protecting group in two successive diastereoselective reactions, organometallic addition to an imine followed by an aza-Wacker cyclisation.[44]



Scheme 6 – Enantioselective aza-Wacker cyclisations.[43]

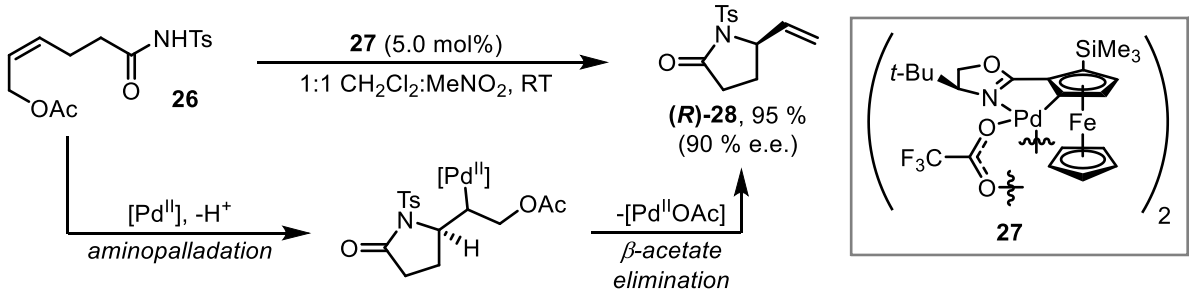
The process in Scheme 6 was initially proposed to proceed *via syn*-aminopalladation, as this step had been confirmed under similar conditions. However, in another example of the finely balanced nature of the two pathways, *anti*-aminopalladation was found to be operative in the enantioselective reaction.[45] Just by replacing pyridine with ligand **23**, the selectivity for *syn- versus anti*-aminopalladation was completely reversed. Reactions using the palladium(II)/**23** catalytic system that proceeded through *syn*-aminopalladation resulted in significantly lowered enantioselectivity.[45] This observation presumably explains the fact that a nosyl-protected substrate cyclised with significantly reduced enantioselectivity compared to the analogous tosyl-protected substrate (see Scheme 5).[43]

The significant delay between the discovery of the first aza-Wacker reaction (1978) and the demonstration of high enantioselectivity (2011) can be attributed, at least in part, to the need for oxidising conditions, which generally preclude the use of phosphine ligands. Transition metal complexes bearing phosphine ligands have been fundamental to the development of asymmetric catalysis and are responsible for the rapid growth of this field over the past 40 years or so.[46-48]

1.2.4 Redox-neutral variants of the aza-Wacker reaction

Aza-Wacker reactions can be rendered redox-neutral with the incorporation of an allylic acetate group (Scheme 7).[49] In this case, the reaction terminates in a β-acetate elimination (as opposed to β-hydride elimination); this results in a palladium(II) complex which does not require oxidation to re-enter the catalytic cycle. With the use of the dimeric palladium(II) catalyst **27**, the cyclisation products can be obtained in excellent yield and with good enantioselectivity. The overall transformation is equivalent to an intramolecular Tsuji-Trost amination, and such reactions have been reported.[50-53] While affording the same products, the two are mechanistically distinct; in Tsuji-Trost reactions, palladium cycles between the 0 and +2 oxidation states, whereas the process outlined in Scheme 7 proceeds *via* an isohypsic mechanism. Despite the absence of external oxidants, the need to prepare substrates

containing an acetate group reduces the attractiveness of this methodology compared to oxidative aza-Wacker reactions. Furthermore, the tolerance of other substitution patterns on the alkene has not been demonstrated, and only products containing a terminal alkene have been prepared.



*Scheme 7 – Redox-neutral palladium(II)-catalysed cyclisation of substrate **26**.*[49]

1.2.5 Overview of substrate scope in aza-Wacker processes

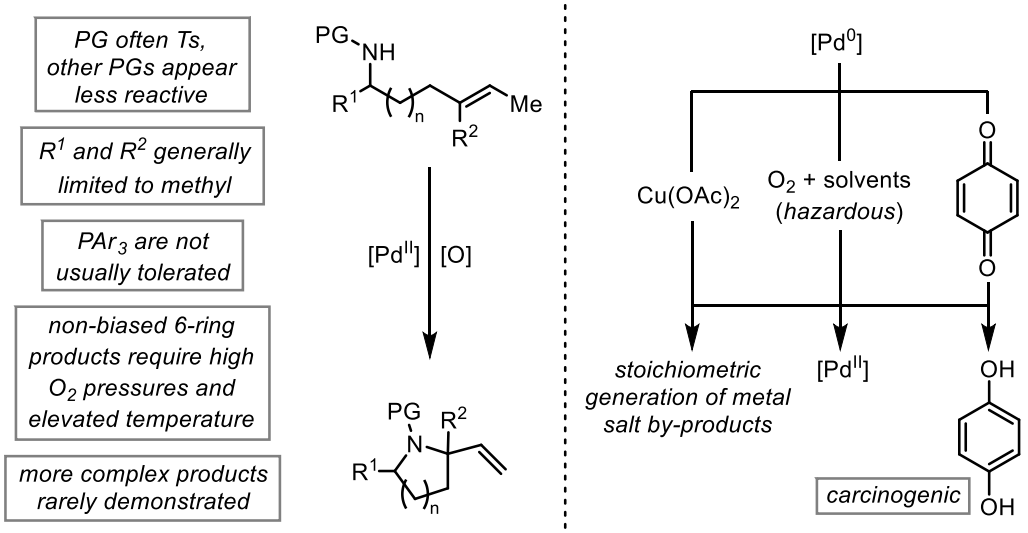
Heterocycles available: The aza-Wacker reaction can provide access to a number of different nitrogen heterocycles, the majority of these containing 5-membered rings, as cyclisations to form this ring size tend to be most facile. The following heterocycles have been prepared in this way: pyrroles,[54] pyrrolidines,[27,28,55] pyrrolidinones,[49] indoles,[18,55] indolines,[27,28,55] isoindolinones,[56] imidazolidines,[25] oxazolidines,[57] cyclic carbamates[49] and cyclic sulfamides.[58] While 5-membered rings are the most common target, larger ring sizes have been prepared, often with the use of conformationally biased benzo-fused substrates.[56,59,60] Access to morpholines and piperazines, as well as individual examples of piperidine and diazepane synthesis, has been demonstrated by Stahl, although these processes required high pressures of oxygen as the terminal oxidant.[61]

Alkene scope: Good substrate scope with respect to the alkene partner is very rarely demonstrated, and substrates containing trisubstituted alkenes with substituents larger than methyl groups are seldom used. With the exception of the reaction of sulfinamide-protected substrates,[44] substitution α to nitrogen appears to be limited to methyl groups or α,β-fused rings. Furthermore, transannular cyclisations to afford complex bicyclic systems are uncommon.

Protecting group scope: The majority of aza-Wacker cyclisations make use of a sulfonyl protecting group; aza-Wacker reactions of carbamate- and amide-protected substrates are known but are comparatively rare.[II] Under identical conditions, carbamate-based substrates have been shown to be less reactive than the analogous tosyl-based substrates, requiring longer reaction times to go to completion.[55] While seemingly being more suitable for cyclisations, sulfonamide-based protecting groups limit the further synthetic use of the products, as they are generally more difficult to remove than carbamates.

[II] Examples of aza-Wacker cyclisations of substrates containing carbamate[25,55,57] and amide[56,62] protecting groups.

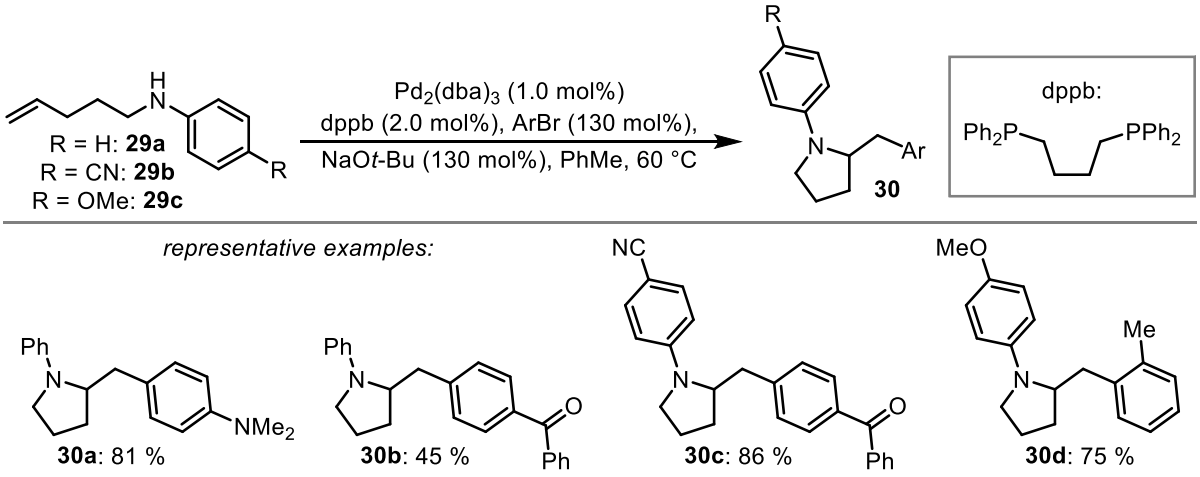
Issues with the oxidant: As a final point, the necessity of an external oxidant has implications on more than just the choice of ligand in these reactions. Aza-Wacker reactions that use reagent-based oxidants, typically benzoquinone or $Cu(OAc)_2$, generate stoichiometric by-products (Scheme 8). Those that use aerobic oxidation present obvious safety concerns, given the combination of flammable solvents with oxygen atmospheres, often at elevated temperatures. One recent study of a palladium-catalysed aerobic oxidative amination found that the active oxidant was the peroxide of the ethereal solvent the reaction was conducted in;[63] peroxides are notorious in synthetic chemistry for their tendency to cause explosions.[64] Consequently, the requirement for an external oxidant limits the attractiveness of these processes for anything greater than laboratory-scale reactions.



Scheme 8 – Summary of the major limitations of aza-Wacker reactions.

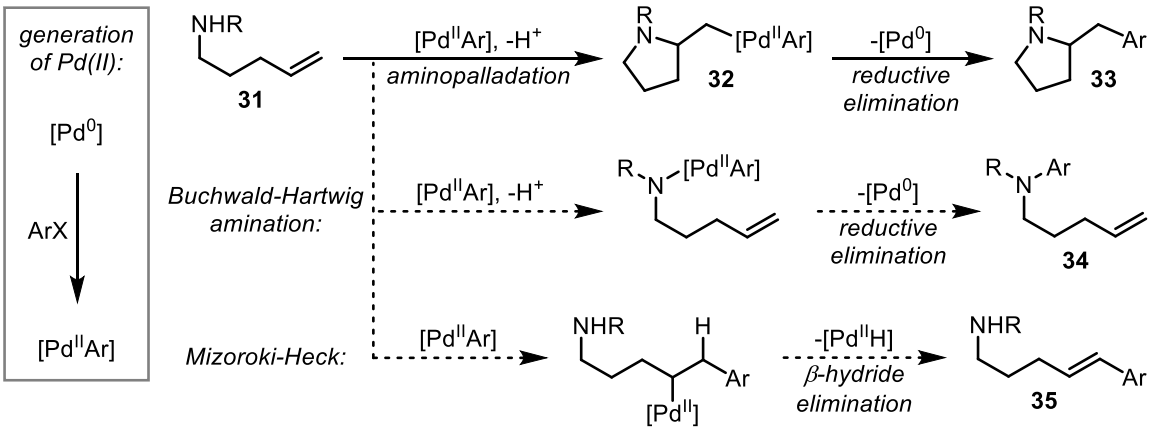
1.3 Nitrogen-based heterocycles *via* electrophilic 1,2-aminofunctionalisation of alkenes

In 2004, Wolfe reported a palladium-catalysed cyclisation, conceptually related to the aza-Wacker reaction, to form *N*-aryl pyrrolidines (Scheme 9).[65] The reaction constitutes a 1,2-aminoarylation of the alkene in **29**; the amination occurs in an intramolecular fashion and the aryl unit is provided by an external aryl bromide. While the initial report focused on the use of aniline-based substrates, the downstream flexibility of the products was improved by switching to amide- and carbamate-based protecting groups.[66,67]



*Scheme 9 – Palladium(0)-catalysed 1,2-aminoarylation of alkenes **29a-c**.*[65]

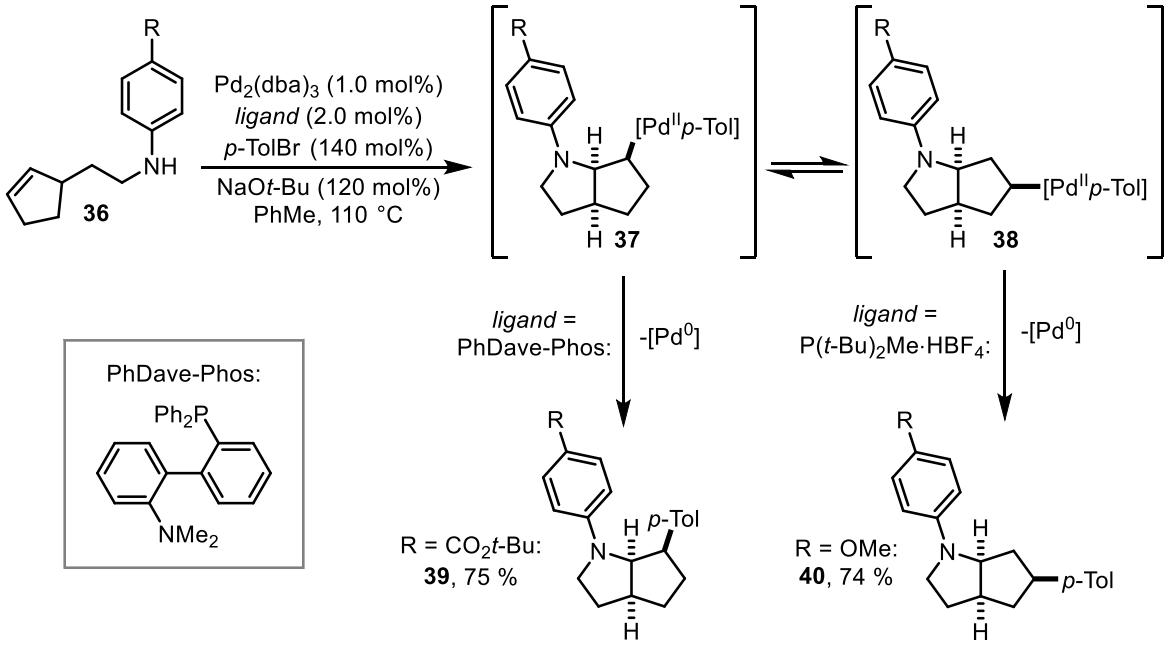
The mechanism of the general reaction is given in Scheme 10.[66] Oxidative addition of the aryl halide affords a palladium(II) species that promotes aminopalladation of the pendant alkene of **31**. Reductive elimination from intermediate **32** releases heterocyclic product **33** and palladium(0), which can re-enter the catalytic cycle. In contrast to the aza-Wacker reaction, which is an oxidative process, the 1,2-aminoarylation reaction couples a nucleophile with an electrophile across an alkene, making the overall transformation redox-neutral.



Scheme 10 – Mechanism of the palladium(0)-catalysed 1,2-aminoarylation of alkenes, as well as possible competing pathways.[66]

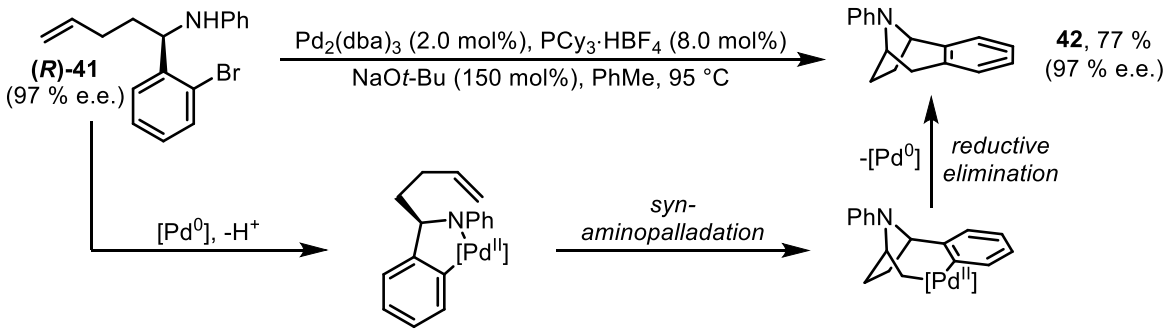
The ability to prepare pyrrolidines in this way is notable because the reaction conditions could conceivably result in either Buchwald-Hartwig amination of the N–H bond or Mizoroki-Heck functionalisation of the alkene (**34** and **35**, respectively, in Scheme 10); the latter has been observed under similar conditions.[68] The fact that this reaction does not require an external oxidant is key to the success of this strategy; by varying the phosphine ligand used, selectivity for either Buchwald-Hartwig amination or 1,2-aminoarylation products was achieved.[38] Additionally, in the reaction of **36**, ligand choice affects the isomerisation of intermediate **37** to **38**, allowing selective access to either **39** or **40** (Scheme 11).[38] The relative stereochemistry of **39** and **40** demonstrates that this transformation proceeds

through *syn*-aminopalladation; the strongly basic conditions used in these reactions are likely to favour this pathway with respect to *anti*-aminopalladation.[37]



*Scheme 11 – Catalyst-controlled selectivity for products **39** and **40** in the palladium(0)-catalysed aminoarylation of substrate **36**.[38]*

In a similar manner to the aza-Wacker cyclisation, this kind of aminoarylation has been extended to a variety of *N*-heterocycles, including aziridines,[69] pyrazolidines,[70] oxazolidines,[71] isoxazolidines,[72,73] cyclic ureas,[74] cyclic guanidines,[75,76] piperazines,[77,78] morpholines,[79] tetrahydroquinolines,[80] tetrahydroisoquinolines,[80] tetrahydroquinoxalines[80] and benzodiazepines.[81] The reaction can also be adapted to accommodate other classes of electrophiles that undergo oxidative addition with palladium(0); in this way, aminoalkenylation[82] and aminoalkynylation[83,84] have been achieved.



Scheme 12 – Synthesis of tropane derivatives[III] through palladium(0)-catalysed intramolecular 1,2-aminoarylation.[85]

[III] For aesthetic reasons, the structures in Scheme 12 have been depicted as enantiomeric to the reaction contained in reference 85.

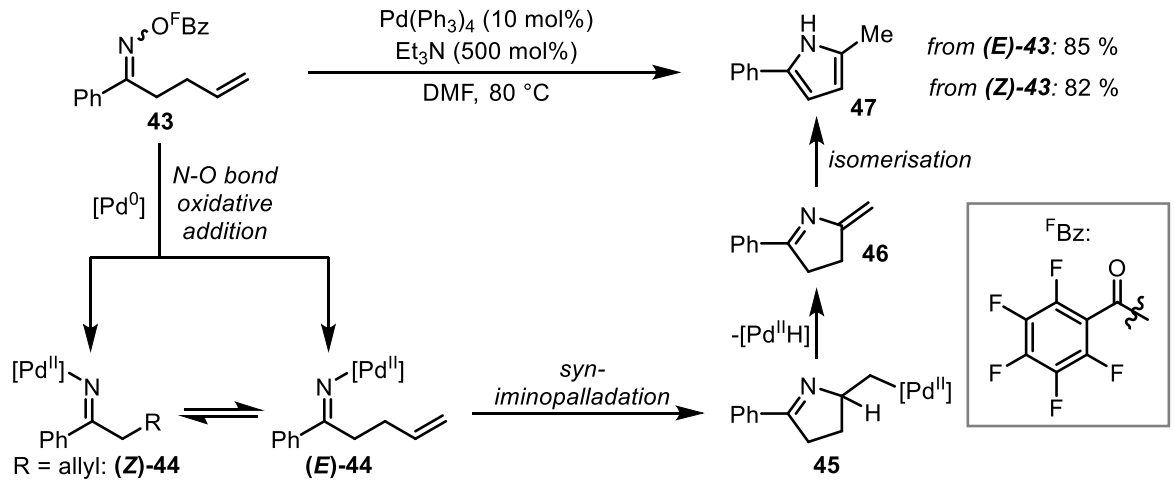
Wolfe has also reported the synthesis of tropane derivatives in an intramolecular reaction (Scheme 12).[85] This process made use of enantiopure substrates, such as **41**, and afforded products, such as **42**, with complete enantioretention. In addition to this enantioretentive cyclisation, enantioselective variants have also been developed. Using chiral phosphoramidite ligands, moderate to high levels of asymmetric induction have been achieved in cyclisations to form 5-membered[74,86] and 6-membered rings.[80]

Despite a good number of nitrogen-based heterocycles being available through this general strategy, and a wide variety of aryl halides being suitable for it, the scope with respect to the alkene partner is somewhat limited, with the vast majority of cyclisations involving terminal alkenes. In a rare case where tolerance of 1,2-disubstituted alkenes was demonstrated, products were obtained in relatively low yield (43-62 %), although they were formed with excellent diastereoselectivity.[39] Substrates containing 1,1-disubstituted alkenes appear to be more amenable to cyclisation.[39] It should be noted, however, that for both classes of disubstituted alkene, only sterically non-demanding examples have been demonstrated. Furthermore, for some processes, the complete failure of substrates containing trisubstituted alkenes was reported.[39]

1.4 Aza-Heck reactions

1.4.1 The Narasaka-Heck reaction

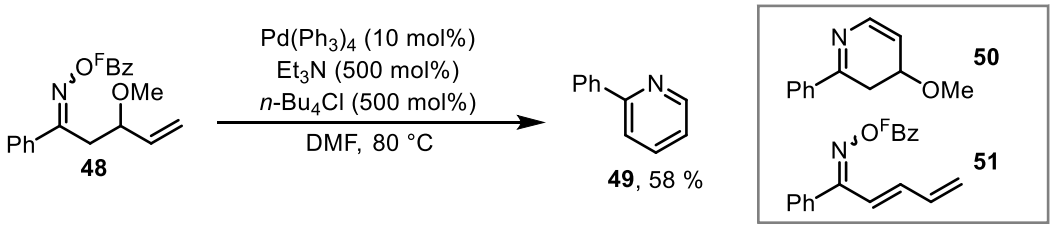
In 1999, Narasaka reported the palladium(0)-catalysed cyclisation of *O*-pentafluorobenzoyl (^{F}Bz) oxime esters containing pendant alkenes (Scheme 13),[87] a transformation which has subsequently been termed the Narasaka-Heck reaction.[88] The mechanism involves insertion of palladium(0) into the N–O bond of **43** to afford iminopalladium(II) species **44**; insertion of the pendant alkene into the Pd–N bond



Scheme 13 – The Narasaka-Heck reaction: synthesis of pyrroles via the palladium(0)-catalysed cyclisation of oxime esters.[87]

of **44** generates intermediate **45**. β-Hydride elimination from **45** provides dihydropyrrole **46** as the initially formed product, which then undergoes isomerisation to pyrrole **47**. Interestingly, the geometry of the starting oxime is inconsequential, as interconversion between **(*Z*)-44** and **(*E*)-44** appears to occur readily. This is evidenced by the fact that **47** can be prepared in essentially the same yield from either **(*E*)-43** or **(*Z*)-43**. As the transformation involves steps analogous to the Mizoroki-Heck reaction[89] – insertion of palladium(0) into an C–X bond, carbopalladation of an alkene and β-hydride elimination – but initiates with an N–X bond, it can be considered an example of an aza-Heck reaction, and the Narasaka-Heck cyclisation was the first reported example of this class of reaction.

Following the initial report detailing the synthesis of pyrroles, the process has been extended to provide access to pyridines,[90] isoquinolines,[90] azaanulenes[91] and imidazoles.[92] A relatively uncommon 6-*endo* cyclisation is observed in the reaction to form pyridines (Scheme 14), in contrast to the 5-*endo* mode operative in the other examples. The exact mechanism of the transformation outlined in Scheme 14 is unclear,[93] although **49** is likely formed from either **50** or **51**. When independently prepared, substrate **51** was shown to be equally capable of participating in the cyclisation to afford **49**.[90]



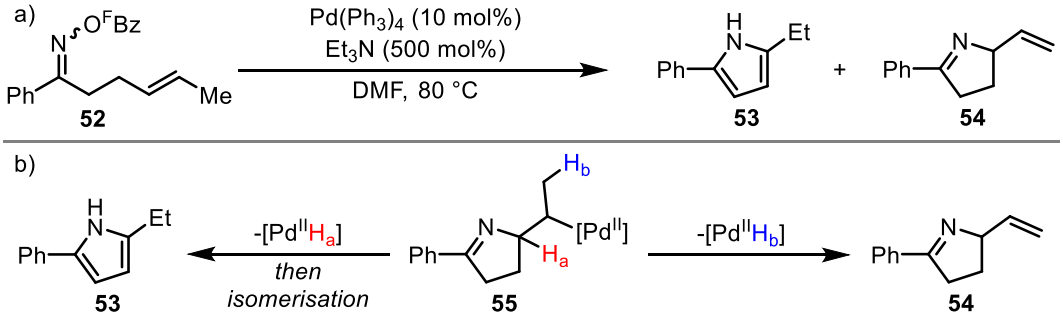
*Scheme 14 – Synthesis of pyridine **49** through the palladium(0)-catalysed 6-endo cyclisation of substrate **48**.[90]*

1.4.2 Bower group work: chiral heterocycles from the Narasaka-Heck reaction

Recently, it has been noted that the average degree of chirality[IV] in drug candidates increases at each stage of the development process.[95] Assuming a causal link,[V] this implies that candidates with a higher degree of chirality have a higher chance of success. Furthermore, these considerations suggest that medicinal chemists are making too many "flat" molecules; indeed, by one reported measure,[IV] the degree of chirality in discovery compounds has been decreasing since 1990.[97] This trend has been associated with the rise of compound libraries synthesised *via* palladium-catalysed sp^2–sp^2 couplings.[95] These combined observations suggest that methodologies which enable efficient synthesis of complex scaffolds would be highly desirable. With this in mind, research at Bristol has focused on taking processes that typically generate achiral products, such as the Narasaka-Heck reaction, and modifying them to allow access to chiral products.[98]

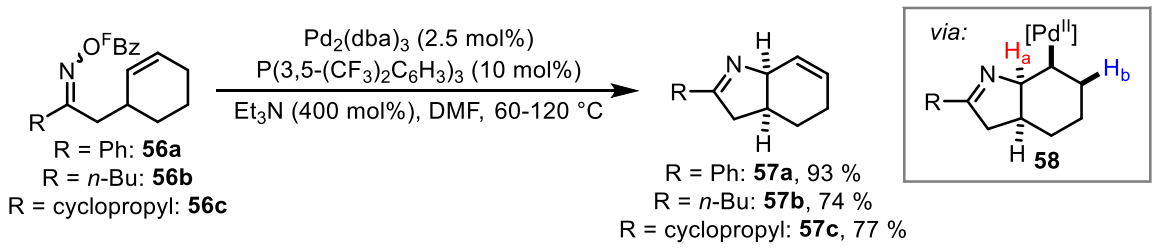
[IV] The fraction of sp^3 carbon atoms in a given structure has been proposed as a measure for this.[94,95]
[V] Suggestions as to the reason for this have been proposed.[96]

One example of a chiral product was observed in Narasaka's work: in the cyclisation of **52**, as well as desired pyrrole **53**, dihydropyrrole **54** was isolated as a minor product[VI] (Scheme 15a).[87] The formation of **54** is the result of β-hydride elimination of H_b, rather than H_a, from intermediate **55** (Scheme 15b); while under these conditions this is clearly unfavoured, by employing strategies to eliminate H_b selectively, the Narasaka-Heck reaction might be adapted to generate chiral products.[VII]



*Scheme 15 – a) Observation of chiral dihydropyrrole **54** in the Narasaka-Heck cyclisation of substrate **52**.[87] b) β-Hydride elimination from **55** is the key step in determining product distribution between **53** and **54**.*

A number of strategies to achieve selective access to dihydropyrrole products were examined; the first of these was the use of substrates with cyclic alkenes (Scheme 16).[100] Substitution of the imine (R in **56**) and in the α-position was well tolerated, and substrates with cyclic alkenes with ring sizes of 5 to 7 participated in the reaction in good yields. The key to the success of these cyclisations was the use of electron-deficient phosphine ligands, and, of these, $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ was optimal. The selectivity achieved in the case of **57** is due to H_a in **58** not being available for *syn*-β-hydride elimination.

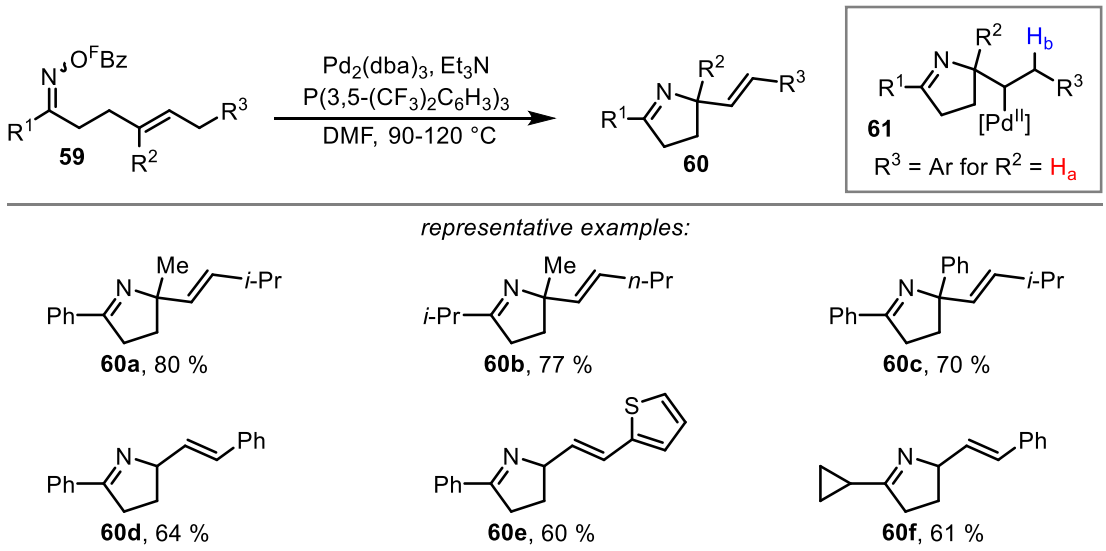


Scheme 16 – Access to bicyclic dihydropyrrole products through the use of substrates containing cyclic alkenes.[100]

Other approaches to chiral products were also developed (Scheme 17); substrates containing trisubstituted alkenes ($R^2 \neq H$ in **59**) lack H_a, so elimination of H_b from intermediate **61** occurs. A number of substrates containing relatively sterically congested alkenes cyclised to afford products **60a-c** in good yields.[101] Selectivity in processes involving linear 1,2-disubstituted alkenes was also achieved

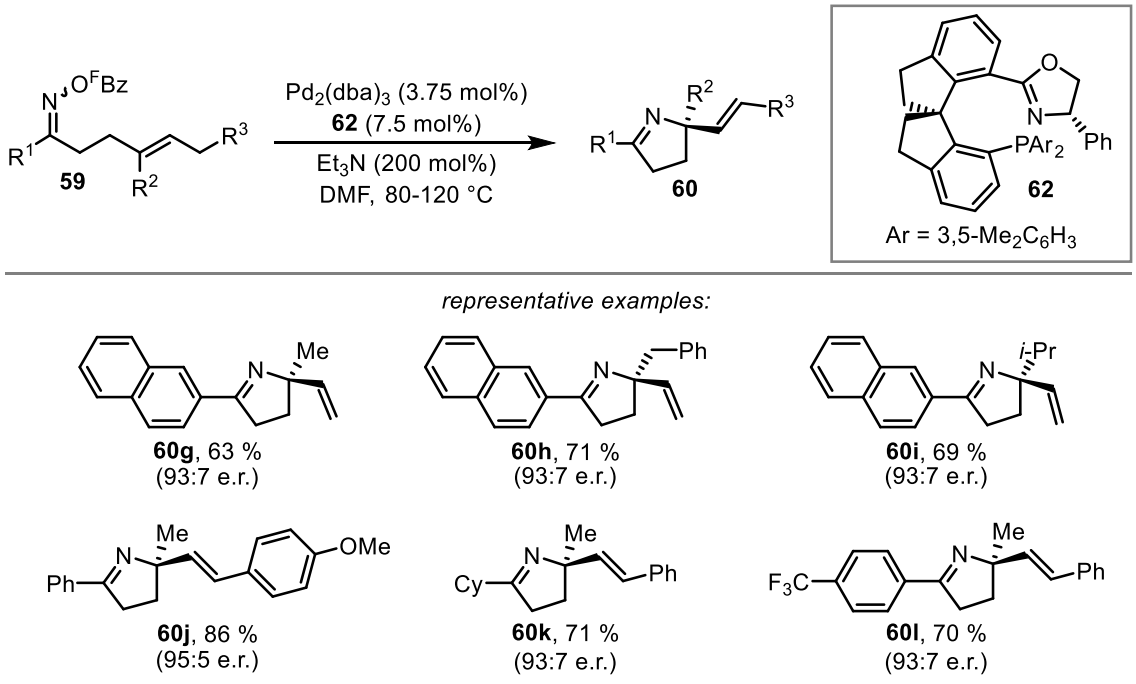
[VI] The ratio of **53** and **54** is given as 2:1 in the original publication.[87] However, under what appear to be the same conditions, a subsequent review gives a higher yield for **53**, without mentioning **54**.[99]
[VII] While the dihydropyrrole and pyrrole products possess the same fraction of sp^3 carbon atoms, the presence of a chiral carbon atom was also found to correlate to a greater chance of success in drug discovery.[95]

(**60d-f**);[102] in this case, the incorporation of an aryl group in the R^3 position of **59** leads to the activation of the adjacent hydrogen atoms in **61**, favouring elimination of H_b.

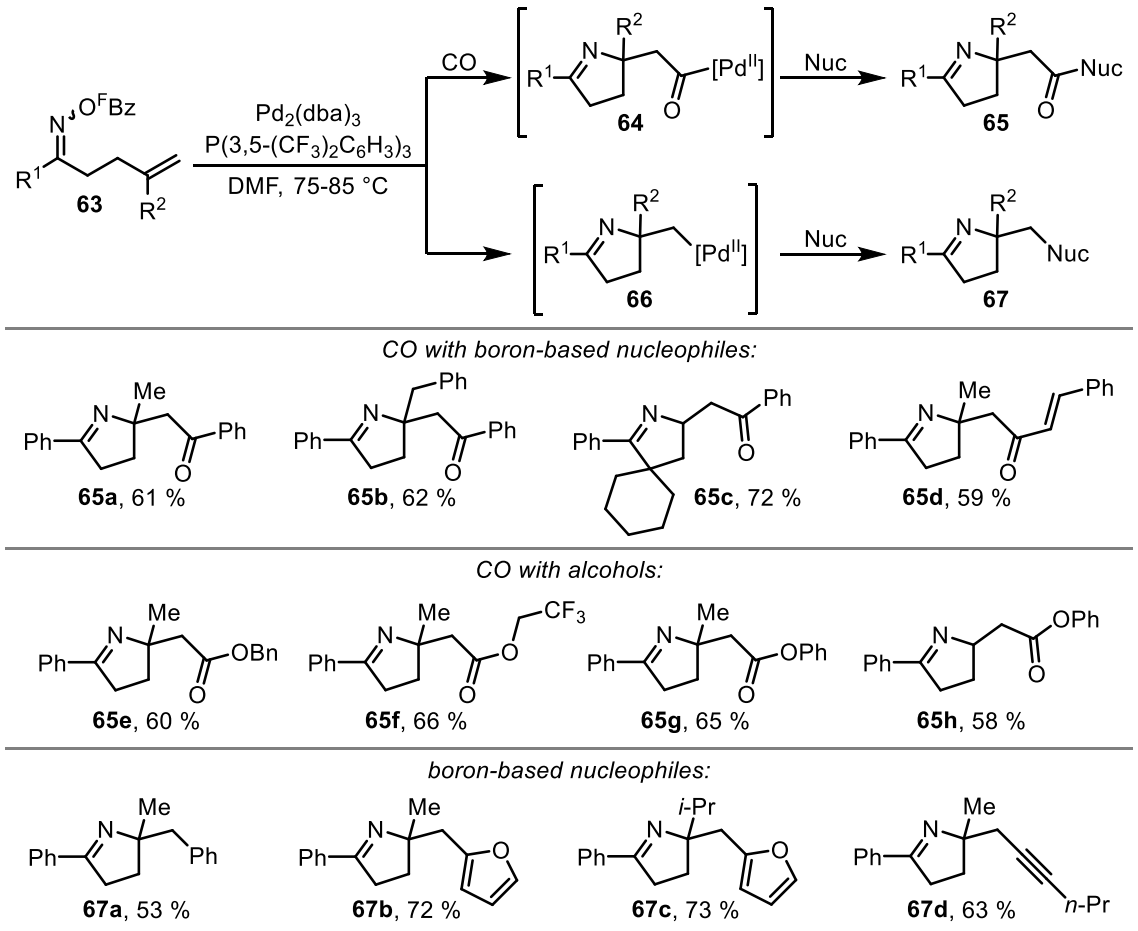


Scheme 17 – Further strategies for achieving selectivity for dihydropyrrole products.[101,102]

Having demonstrated the applicability of the Narasaka-Heck reaction to the synthesis of chiral products, the next logical target was an asymmetric variant that would allow the preparation of enantiopure dihydropyrroles. Through the use of P,N-based ligand **62**, products were obtained with good levels of enantioselectivity and in good yields (Scheme 18).[103] Although 1,2-disubstituted alkenes were not compatible with this methodology, trisubstituted alkenes were effective partners, generating products containing sterically congested tetrasubstituted C–N stereocentres.



Scheme 18 – Palladium(0)-catalysed enantioselective Narasaka-Heck cyclisations.[103]



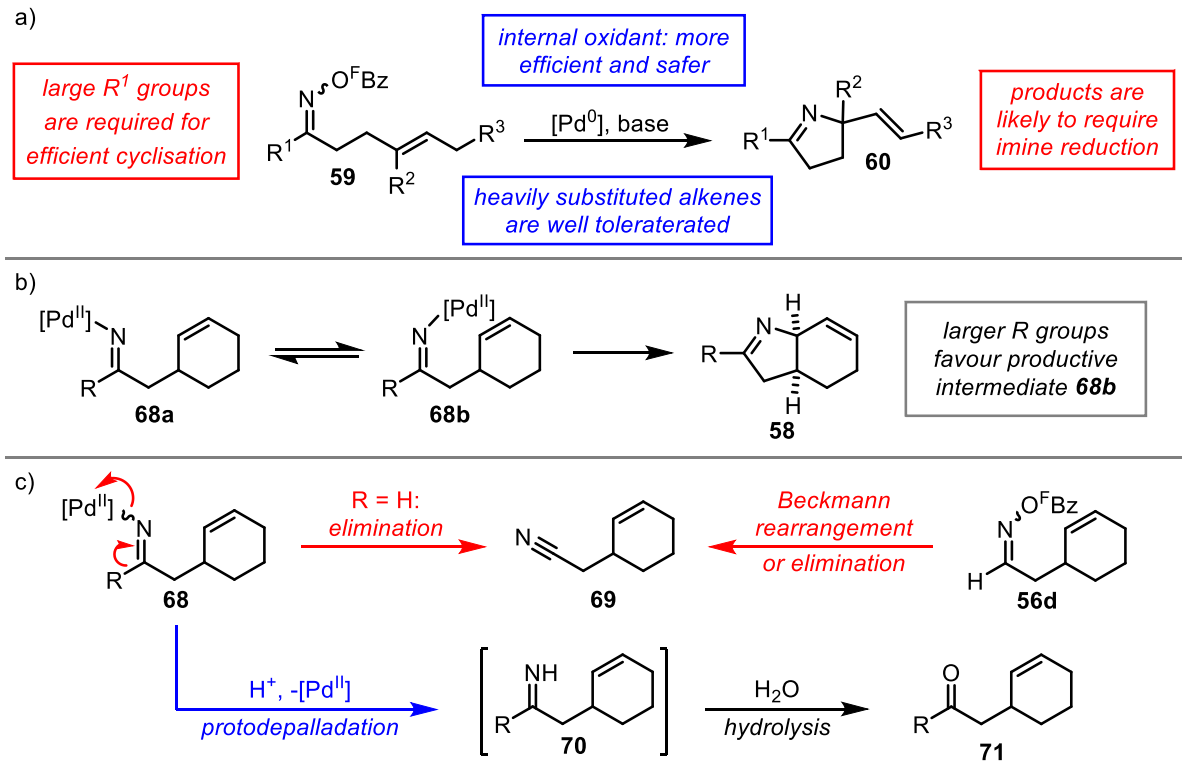
Scheme 19 – Application of the Narasaka-Heck initiation mode to a variety of partially intermolecular 1,2-iminofunctionalisation reactions.[104]

While distinct from aza-Heck reactions, intermolecular cascades using the initiation mode of the Narasaka-Heck reaction were also developed (Scheme 19).[104] For substrates containing *exo*-methylene or terminal alkenes, the intermediates resulting from oxidative addition and *syn*-iminopalladation (**64** and **66**) could, in theory, be intercepted by suitable nucleophiles. This objective was achieved under carbonylative conditions by using boron-based nucleophiles to deliver aryl, alkenyl and alkynyl groups to intermediate **64** (products **65a-d**), or through trapping **64** with alcohols (products **65e-h**). Alternatively, under non-carbonylative conditions, intermediate **66** can be intercepted directly with boron- or tin-based nucleophiles to provide 1,2-imino-arylation, -alkenylation and -alkynylation products (products **67a-d**).

Although some of the products obtained from these cascades are similar to those detailed in Section 1.3, the approach is distinct because the exogenous component is nucleophilic, as opposed to electrophilic. Organometallic nucleophiles cannot be used in palladium(II)-catalysed cyclisations of substrates containing free N–H bonds, as these reagents effect reduction of the palladium(II) species required for

the initial cyclisation. Consequently, oxidative cascades coupling N–H substrates with nucleophiles are rare.[VIII]

The work presented in this section demonstrates the success achieved in applying the Narasaka-Heck reaction to the synthesis of chiral products. The developed methodology exhibits good substrate scope, particularly with regard to the alkene partner, which comfortably outstrips what is tolerated in the reactions presented in Sections 1.2 and 1.3. Additionally, through adaptation of the reaction conditions, a wide variety of cascade processes were demonstrated. However, the use of the Narasaka-Heck initiation mode has a number of limitations (Scheme 20a). The first of these is that the cyclic imine products are arguably less useful than the saturated products obtained from the aza-Wacker reaction.[IX] Furthermore, successful cyclisations generally require a large substituent α to nitrogen. The reason for this is twofold. Firstly, in the equilibrium of **68a** with **68b**, large R groups favour **68b**, from which the desired reaction proceeds (Scheme 20b). Without competing decomposition from **68a**, the position of the equilibrium would only be of consequence to the rate of reaction, but decomposition of **68** evidently does occur, as ketones analogous to **71** are the most commonly observed side products.[100] Ketone **71**



*Scheme 20 – a) Summary of the advantages and limitations of the Narasaka-Heck reaction. b) Larger substituents favour the productive isomer of **68** in the Narasaka-Heck reaction. c) Competitive decomposition pathways available to **68**.[100]*

[VIII] Exceptions to this include a tandem aminocarbonylation/Friedel-Crafts acylation which uses a bimetallic catalytic system along with $CuCl_2$[105] and a reaction which uses organometallic nucleophiles but is stoichiometric in palladium.[106]

[IX] In Njardarson's analysis of FDA-approved drugs, pyrrolidines were found to be the 5th most common *N*-heterocycle, in comparison, dihydropyrroles were at least ten-times less prevalent.[1]

most likely arises from hydrolysis of imine **70**, the product of protodepalladation from **68** (Scheme 20c). While protodepalladation could conceivably proceed from either **68a** or **68b**, by favouring **68a**, the rate of productive reaction decreases, and hence the ratio of **57** to **71** decreases.[X] Secondly, aldoxime substrates (R = H in **56**) predominantly afford nitrile elimination products (**69** in Scheme 20c).[100] This has been proposed to result from Beckmann rearrangement from **56d**.[100] However, a number of alternative elimination mechanisms could be envisaged for the formation of **69**, such as β-hydride elimination from **68a**, E2 elimination from either **68b** or **(*E*)-56d**, and *syn*-elimination from **(*Z*)-56d**.

1.5 Project objectives

A timeline of the development of aza-Heck reactions is presented in Figure 2. Following its initial disclosure, the Narasaka-Heck reaction was soon applied to a variety of aromatic heterocycles (Section 1.4.1). Further advances were subsequently achieved by our group, and the reaction was adapted to the synthesis of chiral dihydropyrroles (Section 1.4.2). Despite this progress, at the outset of the studies contained in this thesis (2014), essentially no new classes of N–O bond donors had been reported in aza-Heck reactions in the 15 years since the publication of Narasaka's seminal paper. Consequently, the primary objective of the project was to develop further N–O bond donors suitable for aza-Heck reactions (Scheme 21) in the hope of overcoming some of the limitations associated with the Narasaka-Heck reaction (Scheme 20a). The possibility of introducing the preactivated N–O bond in one step, by means of a Mitsunobu alkylation, was also considered. Secondary objectives included achieving highly enantioselective aza-Heck cyclisations, and the application of new initiation modes to aza-Heck cascade reactions, similar to those outlined in Scheme 19 (Section 1.4.2).

Two novel classes of aza-Heck reactions were devised. The first of these was based on *N*-acyloxysulfonamides (PG = sulfonyl in **72**), and the development of this reaction is described in Chapter 2. The key results from this study were reported in 2016.[107] Following this, aza-Heck cyclisations of *N*-acyloxycarbamates (PG = carbamate in **72**) were successfully achieved. This work is contained in Chapter 3, and these efforts were published in 2018.[108] Chapter 4 details attempts to establish an enantioselective variant of the reactions contained in the preceding two chapters. A manuscript based on this work is being prepared for submission. The application of these novel N–O bond donors to a variety of cascade processes was also explored, and Chapter 5 contains the results of this.

[X] Assuming any changes to the relative rate of protodepalladation from **68a** and **68b** are less significant than the change in the position of equilibrium between the two.

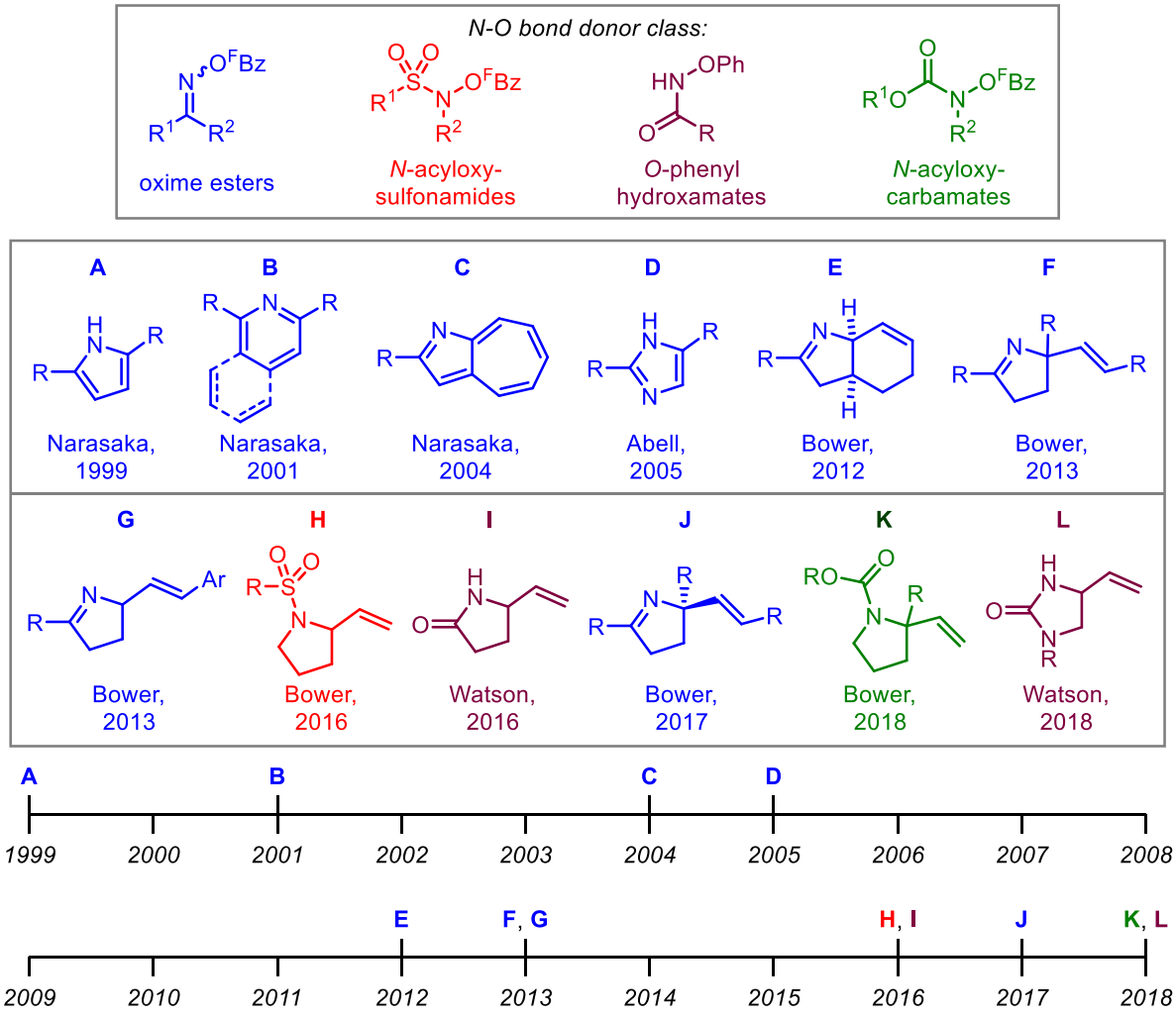
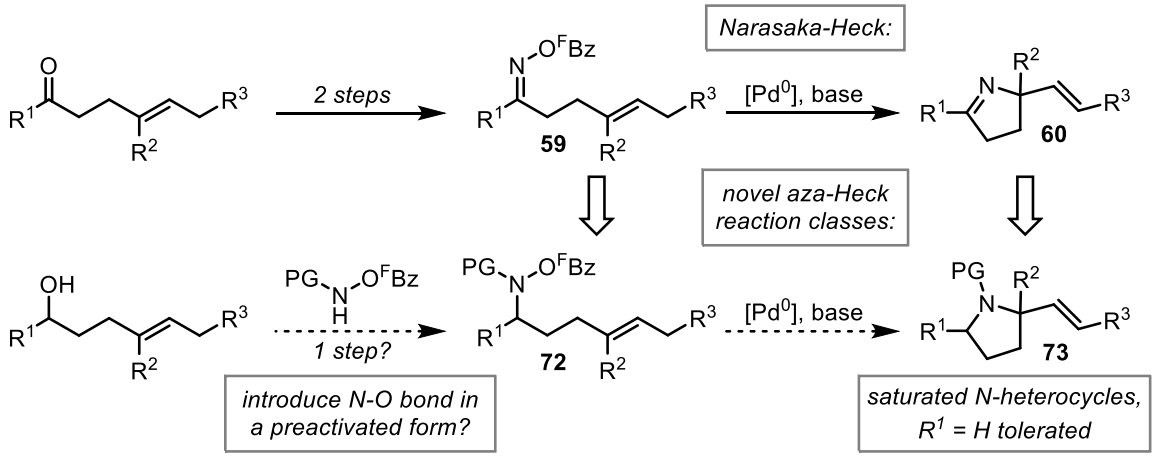


Figure 2 – Timeline of selected advances in the development of aza-Heck reactions.[XI]

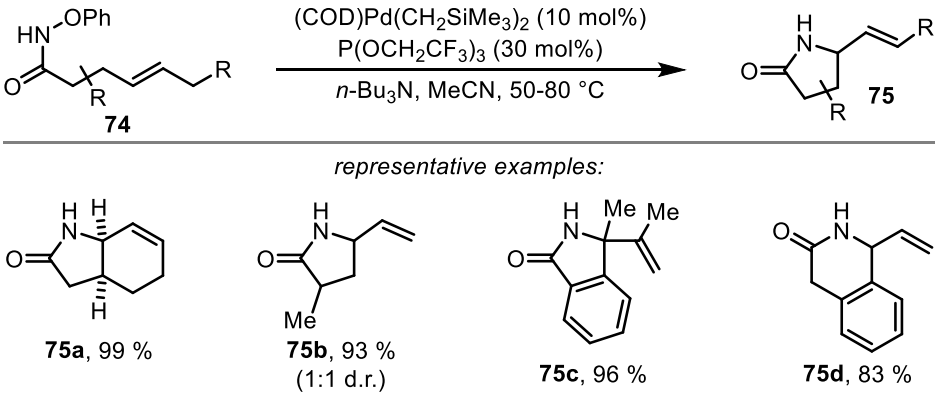


Scheme 21 – Proposed application of the aza-Heck concept to further classes of N–O bond donors.

[XI] References: **A**,[87] **B**,[90] **C**,[91] **D**,[92] **E**,[100] **F**,[101] **G**,[102] **H**,[107] **I**,[109] **J**,[103] **K**,[108] **L**.[110]

1.5.1 Aza-Heck reactions of *O*-phenyl hydroxamates

Before presenting the work contained in this thesis, it is pertinent to highlight a report from Watson detailing a further class of aza-Heck reaction;[109] this was published after the completion of the studies in Chapter 2. Watson's process made use of *O*-phenyl hydroxamate substrates (**74**) and afforded 5-membered lactams in generally excellent yield (Scheme 22). The reaction tolerates a good variety of alkene partners, including the first use of a tetrasubstituted alkene in an aza-Heck reaction (**75c**). One example of the synthesis of a benzo-fused 6-membered lactam was also disclosed (**75d**). However, further substitution on nitrogen is not tolerated, and the reason for this was not speculated upon. While a detailed mechanistic investigation was not carried out, the reaction is proposed to proceed through an aza-Heck mechanism. Compared to previous aza-Heck methodology, the substrates used in this reaction contained the relatively weakly activating *O*-phenyl group; stronger activating groups were found to promote Lossen rearrangement.[111] Recently, this methodology was extended to the synthesis of cyclic ureas (**L** in Figure 2).[110]



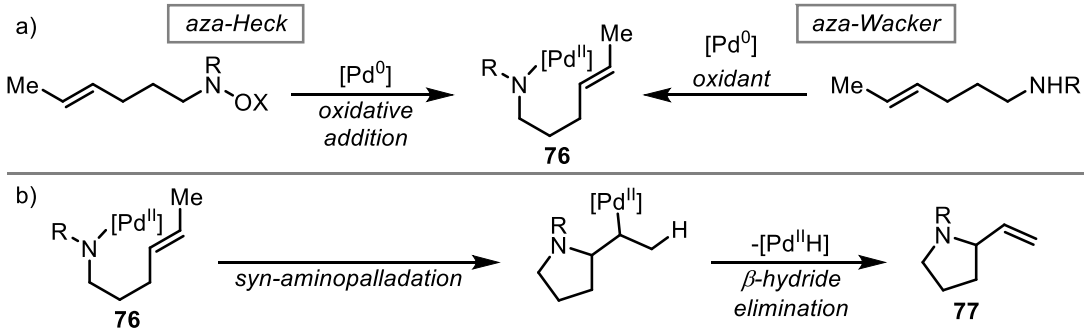
Scheme 22 – Aza-Heck cyclisations of O-phenylhydroxamate substrates.[109]

Chapter 2 - Aza-Heck reactions of *N*-acyloxysulfonamides

The contents of this chapter have been communicated: Hazelden, I. R.; Ma, X.; Langer, T.; Bower, J. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 11198-11202. Parts of this chapter have been reproduced from the aforementioned publication.

2.1 Introduction

Before commencing our studies, aza-Heck reactions had been applied to a wide variety of products (Figure 2, Section 1.5). However, all known classes were based on oxime esters, leading to partially unsaturated *N*-heterocycles. Our objective was to apply the aza-Heck concept to a new class of substrates, containing a C–N single bond, as this would generate potentially more useful saturated products. The proposed reaction appeared feasible, so long as access to key intermediate **76** could be achieved (Scheme 23a); **76** is known to be a productive intermediate in aza-Wacker reactions (Scheme 23b), where it is generated under oxidative conditions.



*Scheme 23 – a) Access to intermediate **76** through aza-Heck and aza-Wacker pathways. b) Generation of pyrrolidine **77** from intermediate **76**.*

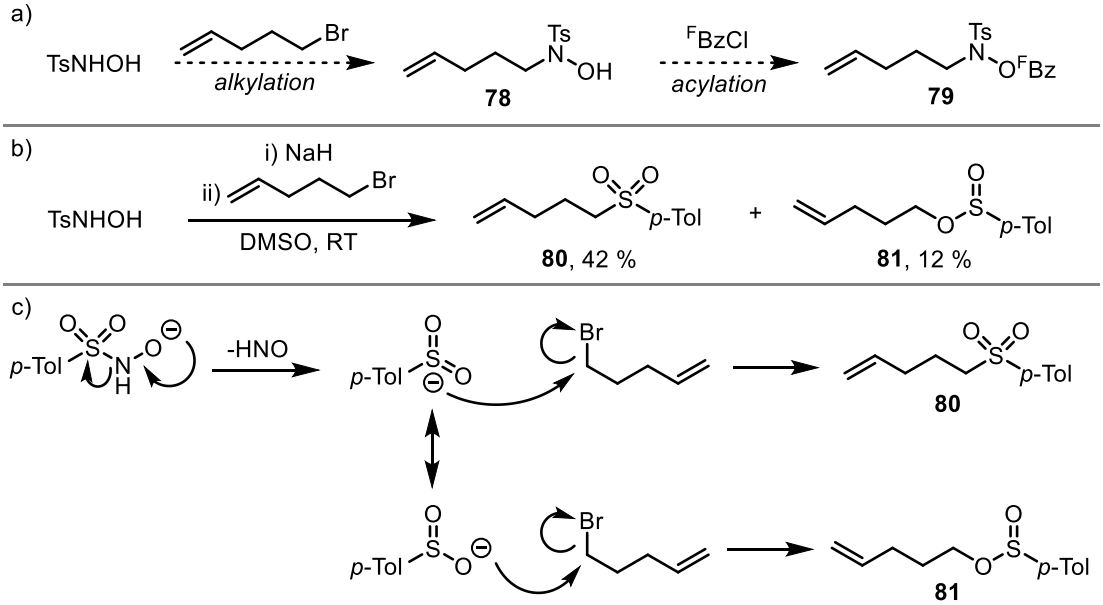
While the products of the reaction proposed in Scheme 21 (Section 1.5) are, in theory, available to aza-Wacker reactions, a redox-neutral approach would have a number of advantages over oxidative alternatives. As mentioned previously (Section 1.2.5), the scalability of oxidative processes can be limited due to issues with safety in the case of aerobic oxidation, or stoichiometric waste generation with reagent-based oxidants. External oxidants typically possess more promiscuous reactivity in comparison to internal N–O bond-based oxidants, as the former could conceivably react with many of the species in the reaction mixture, and oxidation of palladium could occur at a number of stages of the catalytic cycle. Furthermore, the ability to use highly-tuneable phosphine ligands could confer benefits over aza-Wacker reactions with respect to substrate scope, as this is somewhat limited in certain areas (Section 1.2.5).

Given the prevalence of sulfonamide-based substrates in aza-Wacker reactions, and the effectiveness of the pentafluorobenzoate activating group in aza-Heck reactions, a substrate combining both of these elements was seen as a logical starting point to initiate our studies.

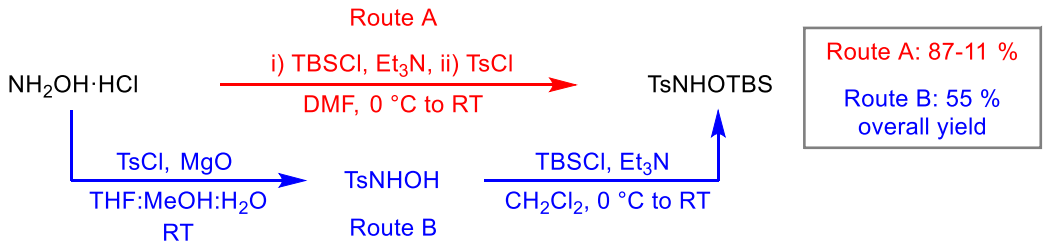
2.2 Substrate synthesis

2.2.1 First-generation routes to aza-Heck substrates

In order to test the feasibility of the proposed transformation, substrate **79** was targeted. The initial route devised to synthesise **79** relied on *N*-alkylation of TsNHOH to afford *N*-hydroxysulfonamide **78**, followed by acylation to provide **79** (Scheme 24a). The advantage of this approach was that substrates activated with a variety of leaving groups could be prepared from **78**, should pentafluorobenzoyl-based substrate **79** prove unsuitable for the reaction. Although there was no literature precedence for alkylation of TsNHOH, an analogous alkylation of $TsNHNH_2$ has been reported.[112] Alkylation of $TsNHNH_2$ proceeds with good regioselectivity, as the $-NH_2$ unit is significantly less acidic than the sulfonamide N–H bond. In contrast, there is a far smaller difference in the acidity of the NH and OH units of TsNHOH. It was hoped that by varying the reaction conditions and, if necessary, using two equivalents of base it would be possible to achieve a reaction with the desired selectivity. In the event, a different problem was encountered; when the alkylation was conducted in DMSO, the only products isolated were sulfone **80** and sulfinate ester **81** (Scheme 24b). Products **80** and **81** resulted from *S*- and *O*-alkylation, respectively, of *p*-toluenesulfinate, which presumably forms by elimination from the *O*-anion of TsNHOH (Scheme 24c). This kind of elimination has been used in a similar context to generate oximes from *O*-silyl-*N*-oxysulfonamides; here, the *O*-anion is generated by fluoride-mediated silyl deprotection, and the resulting alkyl-nitroso species tautomerises to give an oxime.[113] This reaction highlights an issue with the proposed synthesis of **79**: strongly basic conditions must be avoided in the formation and subsequent reactions of **78**.

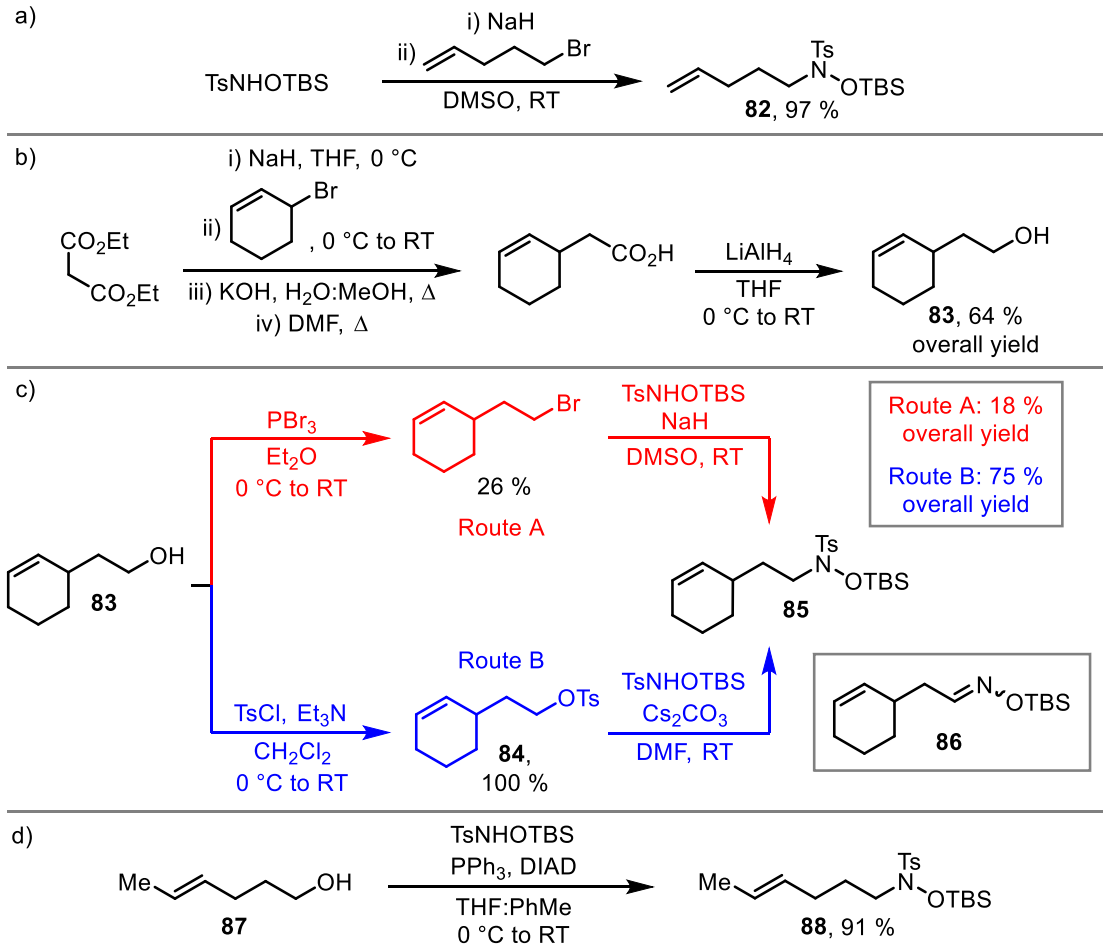


*Scheme 24 – a) Proposed synthesis of test substrate **79**. b) Observation of **80** and **81** in the attempted alkylation of TsNHOH. c) Proposed mechanism for the formation of **80** and **81**.*



Scheme 25 – Synthesis of TsNHOTBS.

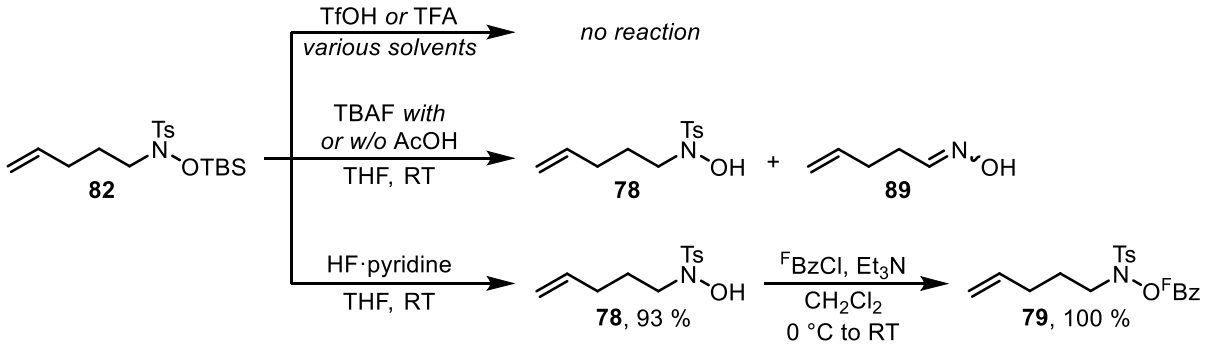
To avoid the formation of an *O*-anion during the alkylation step, the silyl-protected reagent TsNHOTBS was prepared (Route A, Scheme 25).[113] While this one-step synthesis initially provided TsNHOTBS in high yield, it proved poorly reproducible, and a two-step synthesis was devised which, although only proceeding in 55 % overall yield, offered a more practical and scalable route (Route B, Scheme 25).



*Scheme 26 – a) Synthesis of **82** through alkylation of TsNHOTBS. b) Synthesis of alcohol **83**. c) Synthesis of **85** from alcohol **83**. d) Synthesis of **88** through Mitsunobu alkylation.*

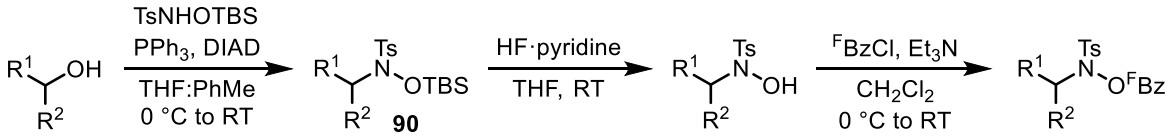
Alkylation of TsNHOTBS using NaH and 1-bromopent-4-ene in DMSO generated **82** in 97 % yield (Scheme 26a). However, this route proved unsatisfactory for the synthesis of other substrates, as bromination of the corresponding alcohols, such as **83** (Scheme 26b), proceeded in disappointing yield (Scheme 26c). Attempts were made to improve the bromination step, but these were ultimately

unsuccessful. It was found that converting alcohol **83** to tosylate **84** was a more practical alternative, as it allowed the use of a procedurally simpler alkylation method and was higher yielding. In another example of the relative ease with which the tosyl group eliminates, *O*-TBS-protected oxime **86** was observed in significant quantities when the alkylation was conducted at elevated temperature in rigorously dried solvent. The final improvement in the synthesis of *O*-TBS-*N*-oxysulfonamides (such as **82**, **85** and **88**) was the use of a Mitsunobu reaction (Scheme 26d). Starting from the requisite alcohol, this provides the desired compounds in one step in usually excellent yield, and hence was used for all of the other substrates which were prepared by the first-generation route.



*Scheme 27 – O-TBS deprotection conditions evaluated for the synthesis of **78**, and acylation of **78** to afford test substrate **79**.*

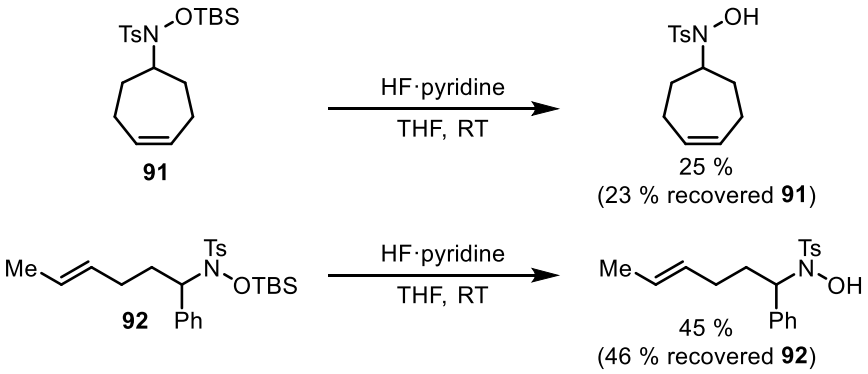
With access to **82** achieved, *O*-TBS deprotection was examined (Scheme 27). Acid-catalysed solvolysis proved unsuccessful, despite some literature precedence.[114] The resistance of the *O*-TBS group in **82** to acidic solvolysis is likely to be due to the electron-withdrawing sulfonamide group reducing the basicity of the oxygen atom; as the first step in this mechanism is protonation at oxygen, this results in a substantially reduced rate of reaction.[115] It was also confirmed that TBAF is too basic, as this generated oxime **89** along with **78**, even in the presence of acetic acid.[116] Finally, the mildly acidic fluoride source HF·pyridine proved effective in removing the *O*-TBS group selectively to afford **78** in 93 % yield. Acylation of **78** was not problematic, and treatment with ^{F}BzCl and Et$_3$N in CH$_2$Cl$_2$ afforded test substrate **79** in quantitive yield (Scheme 27). In this chapter, when a substrate is described as being prepared by the first-generation route, this refers to Mitsunobu alkylation using TsNHOTBS, deprotection with HF·pyridine and then acylation with ^{F}BzCl and Et$_3$N (Scheme 28).



Scheme 28 – First-generation route for the synthesis of aza-Heck substrates.

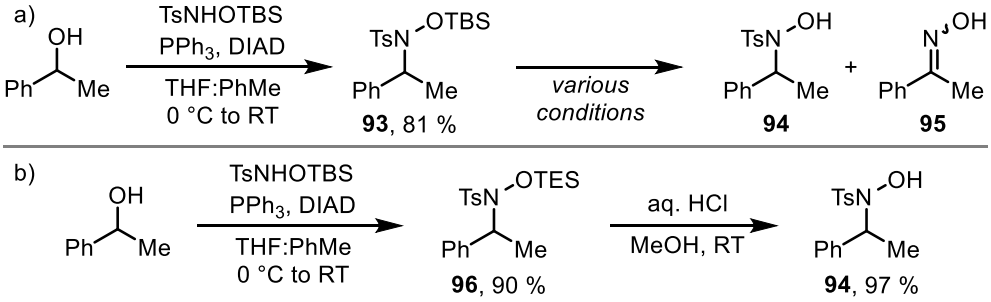
2.2.2 Second-generation route to aza-Heck substrates

The removal of the *O*-TBS group of **90** could be achieved for most substrates using HF·pyridine (Scheme 28), but in cases where the substrate contained a secondary carbon atom adjacent to the *O*-TBS-*N*-oxysulfonamide group, such as **91** and **92**, the reaction did not go to completion (Scheme 29). The extra steric congestion of this kind of system likely provides further stability to the oxygen-silicon bond by energetically disfavouring the pentavalent ate complex intermediate formed during deprotection.



*Scheme 29 – Problematic deprotection of **91** and **92**.*

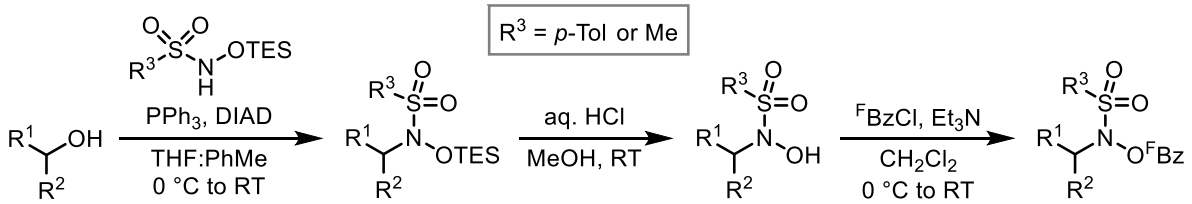
To improve the deprotection step, model system **93** was prepared (Scheme 30a). However, an extensive screen of conditions for cleaving the *O*-TBS group failed to identify a suitable procedure for converting **93** to **94** selectively. These reactions either led to no observed reaction, elimination of the tosyl group to form oxime **95**, or mixtures of **94** and **95**. Given the need to avoid basic deprotection conditions (Scheme 24b, Section 2.2.1), the resistance of these intermediates to acidic solvolysis, and the failure of HF·pyridine-mediated cleavage in sterically congested substrates, a modification to the synthesis was clearly required.



*Scheme 30 – a) Synthesis and attempted O-TBS deprotection of model system **93**. b) Synthesis and O-TES deprotection of model system **96**.*

It was reasoned that changing the nature of the silyl protecting group might lead to more success in the deprotection step. The triethylsilyl (TES) group is a more labile alternative to TBS, as the silicon atom is less sterically congested.[116] The reagent TsNHOTES could be synthesised analogously to

TsNHOTBS. Although TsNHOTES proved far more susceptible to hydrolysis in air, this problem could be overcome by either preparing it as required or storing it in a glovebox. Model substrate **96** was prepared by Mitsunobu alkylation of 1-phenylethanol and subsequently deprotected with aqueous HCl in MeOH to afford **94** (Scheme 30b). In this chapter, when a substrate is described as being prepared by the second-generation route, this refers to Mitsunobu alkylation using either TsNHOTES or MsNHOTES, deprotection with HCl and then acylation with ^{F}BzCl and Et_3N (Scheme 31).

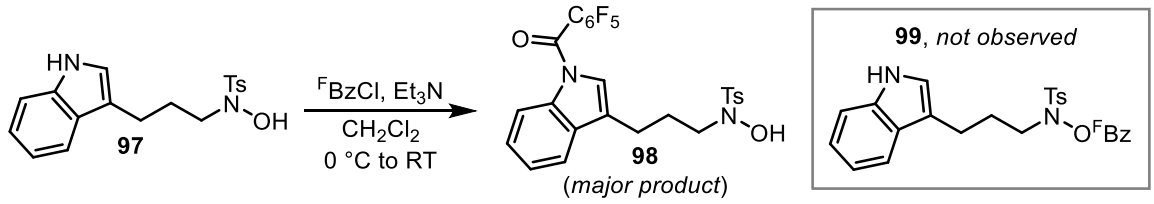


Scheme 31 – Second-generation route for the synthesis of aza-Heck substrates.

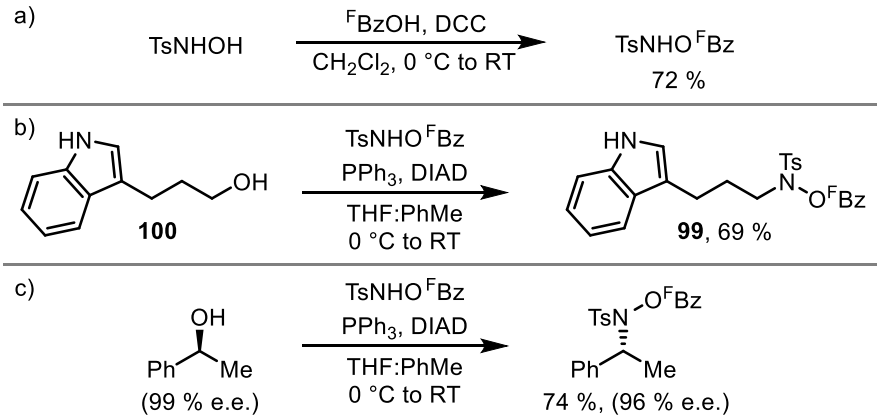
2.2.3 Third-generation route to aza-Heck substrates

The results in this section were obtained by Dr Xiaofeng Ma and hence are not detailed in the experimental section.

Although the problems encountered in the alkylation and deprotection steps of substrate synthesis were solved satisfactorily by the development of the first- and second-generation routes, respectively, there remained an issue in the acylation step. In the course of developing a dearomatisation reaction of indoles and phenols, substrate **99** was sought.[117] In the case of **97**, acylation can occur on either oxygen or nitrogen, and it was found that the major product resulted from *N*-acylation (**98**, Scheme 32). This problem could likely have been circumvented with the use of an orthogonal nitrogen-protecting group; however, this was not pursued, as it would further decrease the atom and step economy of substrate synthesis. Instead, a more direct synthesis was sought, and the preactivated reagent TsNHO^{F}Bz was prepared (Scheme 33a). TsNHO^{F}Bz participates in Mitsunobu reactions, albeit in slightly lower yields than TsNHOTBS and TsNHOTES, and afforded target substrate **99** in one step from alcohol **100** (Scheme 33b). Clean stereoinversion is typically observed in Mitsunobu reactions, and this was confirmed to be the case in the reaction of (*S*)-1-phenyl-ethan-1-ol (Scheme 33c).

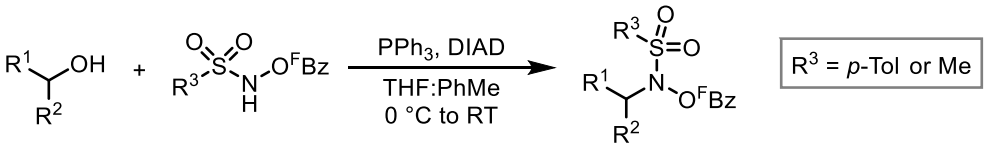


*Scheme 32 – Attempted synthesis of dearomatisation substrate **99**.*



*Scheme 33 – a) Synthesis of TsNHO^{F}Bz. b) Synthesis of **99** by Mitsunobu alkylation using TsNHO^{F}Bz. c) Demonstration of stereoinversion in the Mitsunobu reaction.*

This development was a major breakthrough, as it not only allowed the preparation of a wider variety of substrates but also significantly increased the atom and step economy. In this chapter, when a substrate is described as being prepared by the third-generation route, this refers to Mitsunobu alkylation using either TsNHO^{F}Bz or MsNHO^{F}Bz (Scheme 34).[XII]



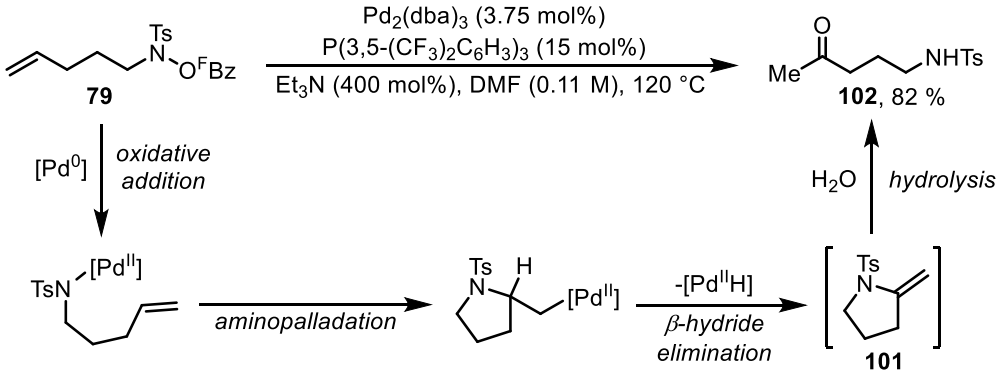
Scheme 34 – Third-generation route for the synthesis of aza-Heck substrates.

2.3 Development of the *N*-acyloxysulfonamide-based aza-Heck reaction

2.3.1 Reaction discovery

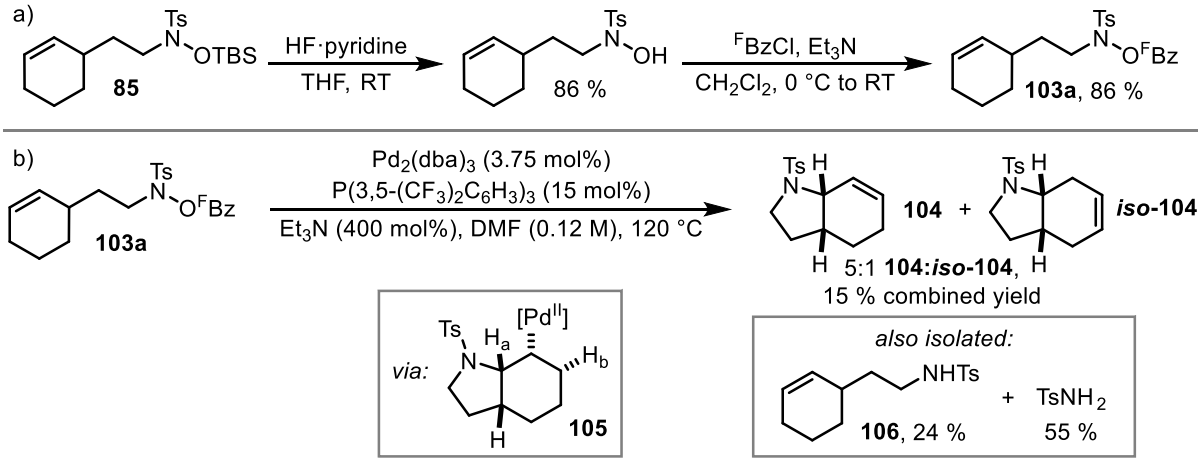
With test substrate **79** in hand, the desired aza-Heck reaction was investigated. When **79** was subjected to conditions previously identified as effective for promoting aza-Heck cyclisation of oxime esters,[101] ketone **102** was generated in 82 % yield (Scheme 35). Ketone **102** likely forms *via* hydrolysis of the initially formed enamine **101**, evidenced by the fact that **101** could be observed in the ^{1}H NMR spectrum of the crude reaction mixture. This promising result suggested the feasibility of the desired transformation; note that the overall reaction constitutes a formal Tsuji-Wacker oxidation of the pendant alkene, using the N–O bond as an internal oxidant.[118,119] For the continued development of the desired reaction, other substrates, which would generate more stable aza-Heck products, were evaluated.

[XII] MsNHO^{F}Bz was prepared by an analogous route to TsNHOFBz. The syntheses of both compounds are provided in the experimental section.



*Scheme 35 – Initial attempt at the palladium(0)-catalysed cyclisation of test substrate **79**.*

For the further development of the aza-Heck cyclisation, substrate **103a** was prepared from **85** (Scheme 36a). In this case, formation of an unstable enamine is not possible, as only H_b is in the correct configuration for β-hydride elimination in intermediate **105**.[100] When substrate **103a** was submitted to the aza-Heck reaction conditions, a 15 % yield of **104** and ***iso*-104** in a 5:1 ratio was obtained (Scheme 36b), with **iso-104** likely formed *via* palladium hydride-mediated isomerisation of initially formed **104**.

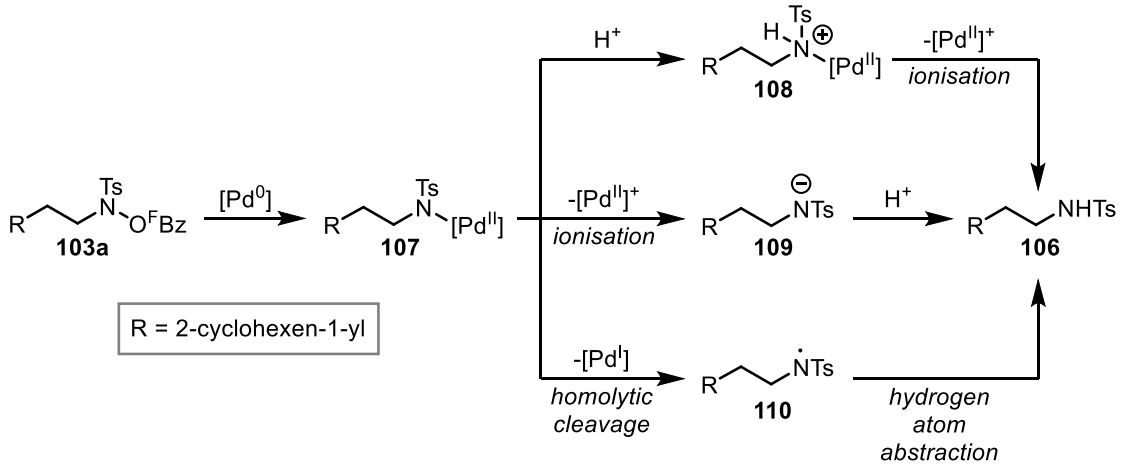


*Scheme 36 – a) Synthesis of substrate **103a**. b) Initial attempt at the palladium(0)-catalysed cyclisation of substrate **103a**.*

2.3.2 Observation of side products in the aza-Heck reaction

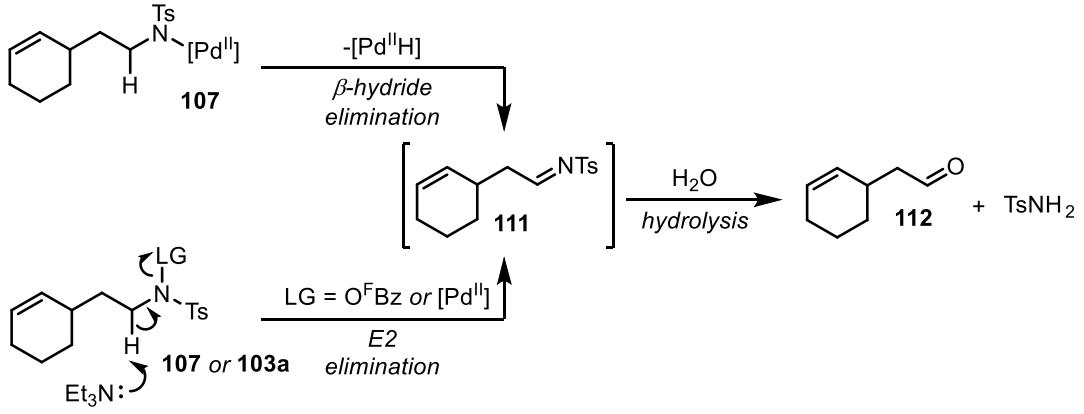
The yield of **104** and ***iso*-104** obtained from the initial cyclisation of **103a** was low, and formation of significant quantities of two side products was also observed (Scheme 36b). These were sulfonamide **106** and *p*-toluenesulfonamide. Sulfonamide **106**, the product of reduction of the N–O bond of **103a**, possibly forms by protodepalladation of intermediate **107** (Scheme 37). The mechanism of protodepalladation is unclear, with the most likely possibility being heterolytic cleavage of the Pd–N bond, followed by protonation of the resulting nitrogen anion **109**. Alternatively, protonation of nitrogen, to afford **108**, could precede heterolytic cleavage. It is also possible that **106** forms through

homolytic Pd–N cleavage, followed by hydrogen atom abstraction of the resulting nitrogen-centred radical **110**.[XIII]



*Scheme 37 – Proposed mechanisms for the formation of protodepalladation product **106** in the cyclisation of **103a**.*

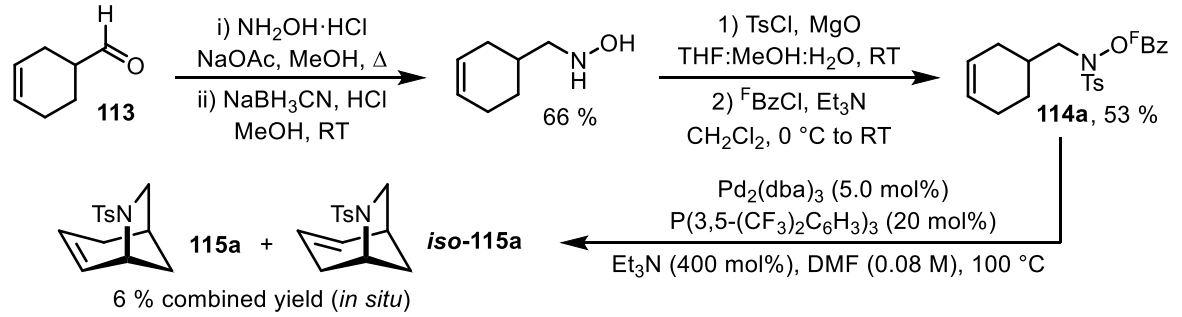
The formation of *p*-toluenesulfonamide is likely the result of an elimination of ^{F}BzOH from **103a**, either through β-hydride elimination or *via* an E2 mechanism, followed by hydrolysis of the resulting imine (**111**), possibly upon workup (Scheme 38). Aldehyde **112** was not observed, although this may have been removed with DMF when the reaction mixture was concentrated *in vacuo*. While the obvious explanation for the elimination would be to invoke β-hydride elimination from intermediate **107**, *p*-toluenesulfonamide was still observed when **103a** was heated with Et_3N in DMF, indicating the E2 pathway is feasible.



*Scheme 38 – Proposed mechanisms for the formation of p-toluenesulfonamide in the cyclisation of **103a**.*

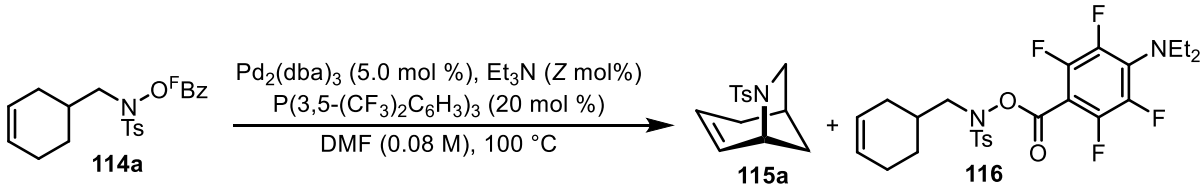
At this stage, further substrates were prepared and evaluated, and substrate **114a** was synthesised in four steps from aldehyde **113** (Scheme 39). The transannular cyclisation of **114a** represented a good challenge for the aza-Heck methodology, as examples of this type of reaction were, at the time, rarely seen with aza-Wacker and aza-Heck chemistry. A low yield was initially obtained in the cyclisation of **114a**, so further optimisation was undertaken on this substrate.

[XIII] Under certain conditions, palladium catalysts have been shown to generate nitrogen-centred radicals.[120] The possibility of the aza-Heck cyclisation proceeding through radical **110** is discussed later (Section 2.5).



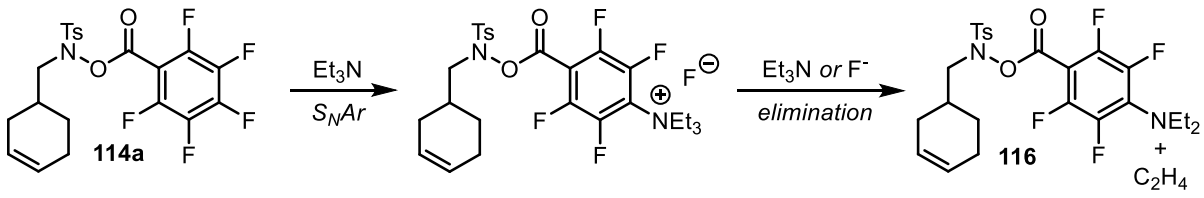
*Scheme 39 – Synthesis and palladium(0)-catalysed cyclisation of substrate **114a**.*

Lowering the equivalents of Et_3N used in the cyclisation of **114a** resulted in an increase in the combined yield of **115a** and ***iso*-115a** (Table 1). The observation of side product **116** (Table 1, entry 2), as well as the previously noted instability of these substrates to elimination (Scheme 38), provides an explanation for this trend. Side product **116** possibly forms by an S_NAr/elimination reaction between the pentafluorobenzoyl group of **114a** and Et_3N (Scheme 40). Not only is **116** less likely to successfully engage in an aza-Heck reaction but the release of proton and fluoride ions could also lead to inhibition of the catalytic cycle.[XIV] An interesting observation in the cyclisation of **114a** is that the majority of the



Entry	*Z*	*yield* (**115a** + ***iso*-115a**)	*yield* (**116**)
1	400	6 %	*not determined*
2	200	(21 %)	(23 %)
3	100	28 %	*not determined*
4	50	32 %	*not determined*

*Table 1 – Optimisation of the equivalents of base in the palladium(0)-catalysed cyclisation of substrate **114a**. Yields were determined by ^1H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses.*

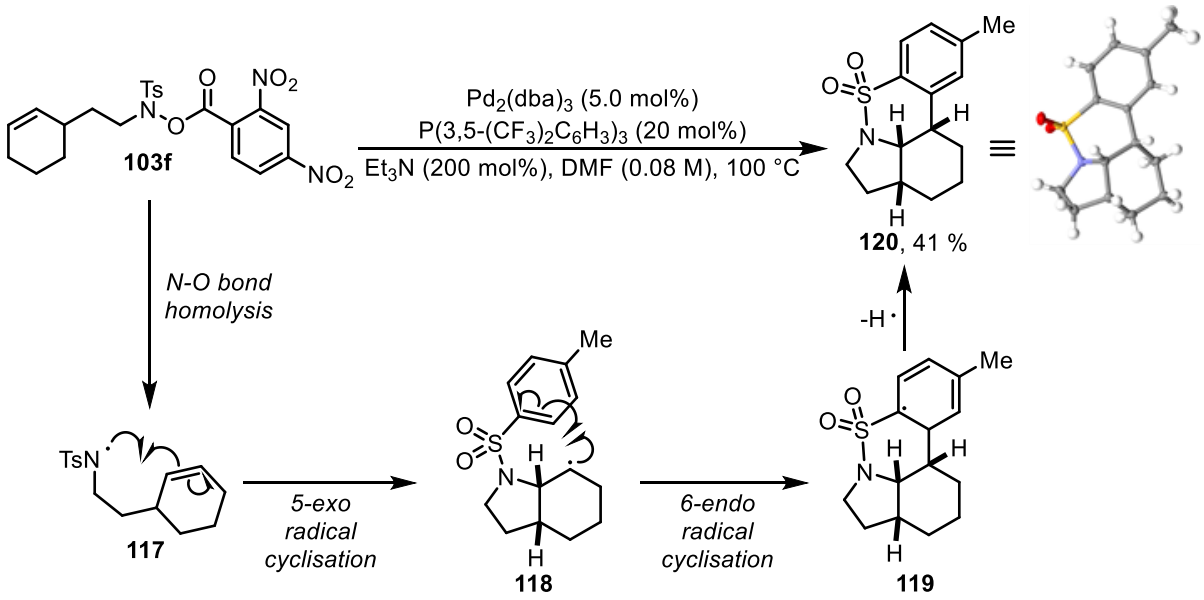


*Scheme 40 – Proposed mechanism for the formation of S_NAr/elimination product **116**.*

[XIV] A higher concentration of hydrogen ions in the reaction mixture could promote protodepalladation (Scheme 37). While protons are also released at the end of the catalytic cycle, these do not persist in the reaction mixture (Section 2.5). The reaction is proposed to proceed through a cationic palladium intermediate (Scheme 77, Section 2.5), which fluoride ions could inhibit access to.

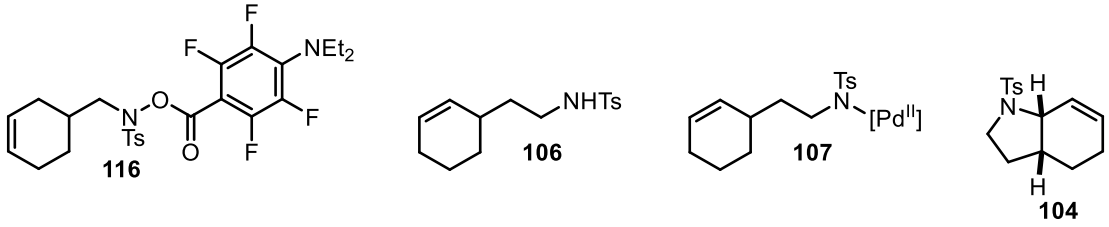
product is in the form of ***iso*-115a** as opposed to **115a**. This kind of isomerisation is somewhat similar to that observed in the 1,2-aminoarylation reaction of **36** (Scheme 11, Section 1.3).[38]

With the observation that the O^FBz leaving group leads to unwanted side reactions, substrates activated with other groups were synthesised (*vide infra*). One of these, 2,4-dinitrobenzoyl-activated **103f** (Scheme 42, Section 2.3.3), generated tetracycle **120** when subjected to the aza-Heck reaction conditions (Scheme 41). Tetracycle **120** appears to result from a radical cascade reaction; homolysis of the N–O bond, either initiated thermally or by palladium(0),[120] generates nitrogen-centred radical **117**, which engages in a 5-*exo* cyclisation to give alkyl radical **118**. A second radical cyclisation onto the arene of the tosyl group leads to **119**, from which loss of a hydrogen atom would afford **120**. Chemler has reported similar copper-catalysed radical cascades.[121,122] The observation of this side product suggests that protodepalladation to **106** is unlikely to proceed *via* a nitrogen-centred radical intermediate (Scheme 37), as the ease with which this radical cascade occurs suggests that **120** would be observed in significant quantities if this were the case.



*Scheme 41 – Observation of radical product **120** in the cyclisation of **103f**.*

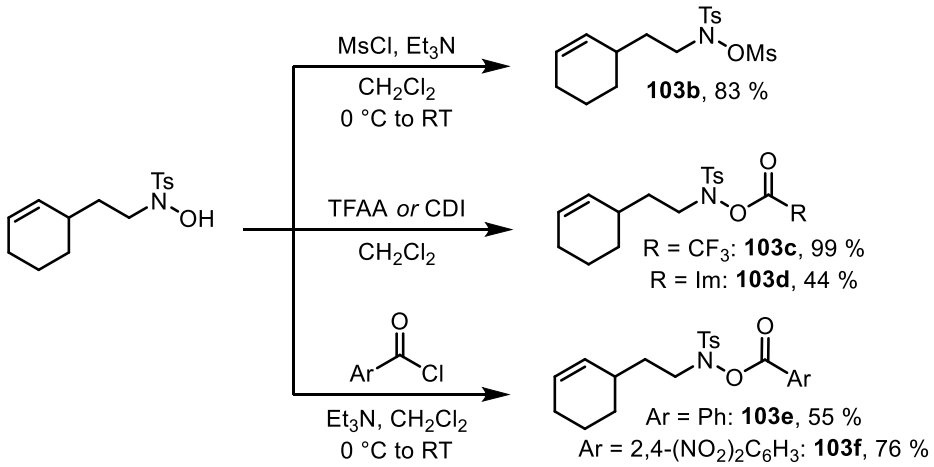
As side products *p*-toluenesulfonamide, **116** and **120** result from the decomposition of substrates **103** and **114a** (Scheme 38, Scheme 40 and Scheme 41, respectively), it is feasible that their formation could be supressed by optimisation of the reaction conditions, for example, by reducing base equivalents or by preventing radical formation. However, **106** forms from **107** (Scheme 37), which is a necessary



intermediate in the pathway to desired product **104** (Scheme 36b). Because of this, it was considered much harder to prevent formation of **106**; in the case of most cyclisations, analogous protodepalladation products were the major side products observed, and this product tends to predominate in reactions which proceed in poor yield.

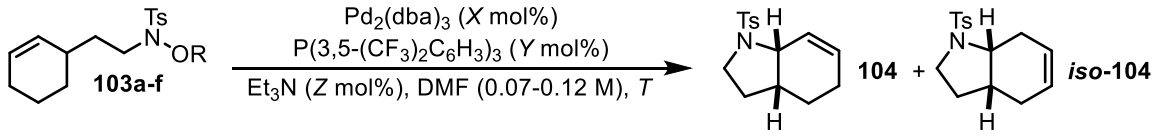
2.3.3 Optimisation

At this stage, the efficacy of a number of different activating groups was investigated, and substrates **103b-f** were synthesised (Scheme 42). Substrates **103b**, **103e** and **103f** were prepared without incident; however, **103c** and **103d** were both highly susceptible to hydrolysis and could not be stored for a significant length of time.



*Scheme 42 – Synthesis of substrates **103b-f**.*

Optimisation was continued using substrates **103a-f** (Table 2). It was found that reducing the temperature from 120 to 80 °C led to a doubling of yield to 34 % in the case of **103a** (Table 2, entry 2); by comparison, mesyl-activated substrate **103b** cyclised in only 4 % yield under the same conditions (Table 2, entry 3). Increasing the precatalyst loading to 5.0 mol% and decreasing the equivalents of Et_3N from 4 to 2 resulted in a 60 % yield from **103a** and a 46 % yield from **103c** (Table 2, entries 4 and 5). While these results are broadly comparable, the instability of **103c** made its continued use impractical. Substrates **103d-f** did not afford significant yields of **104** (Table 2, entries 6, 7 and 10), although **103f** underwent radical cyclisation to form **120** (Scheme 41, Section 2.3.2). By increasing the temperature to 100 °C and further decreasing the equivalents of Et_3N, a yield of 82 % with substrate **103a** was achieved (Table 2, entry 9). However, this result varied considerably upon subsequent repeats.



R = ^{F}Bz: **a** | R = Ms: **b** | R = C(O)CF_3: **c**
R = C(O)Im: **d** | R = Bz: **e** | R = C(O)-2,4-$(NO_2)_2C_6H_3$: **f**

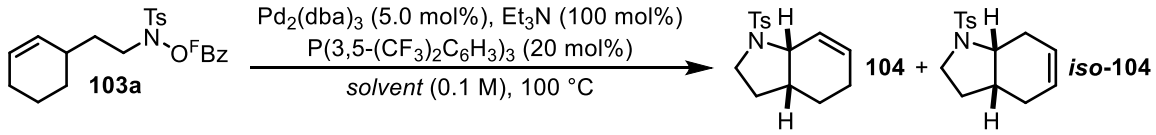
Entry	substrate	*T*	*X*	*Y*	*Z*	*yield* (**104** + ***iso*-104**)
1	**103a**	120 °C	3.75	15	400	(15 %)
2	**103a**	80 °C	3.75	15	400	34 %
3	**103b**	80 °C	3.75	15	400	4 %
4	**103a**	80 °C	5.0	20	200	60 %
5	**103c**	80 °C	5.0	20	200	46 %
6	**103e**	120 °C	5.0	20	200	15 %
7	**103f**	100 °C	5.0	20	200	6 %
8	**103a**	100 °C	5.0	20	200	64 %
9	**103a**	100 °C	5.0	20	100	(82 %)
10	**103d**	100 °C	5.0	20	100	*not observed*

*Table 2 – Optimisation of the palladium(0)-catalysed cyclisation of substrates **103a-f**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses.*

Attempts to overcome this irreproducibility were unsuccessful; it was considered that the source of the problem might be the use of DMF,[XV] and a solvent screen was embarked upon (Table 3). Polar aprotic solvents similar to DMF, such as NMP and DMA, did not lead to high-yielding cyclisations (Table 3, entries 1 and 2). By contrast, medium polarity solvents such as THF, 1,2-DME and EtOAc were far more effective, with **104** being produced in 55-65 % yield with complete selectivity over ***iso*-104** (Table 3, entries 3-5). When MeCN was used, a yield of 76 % was achieved, although at the expense of selectivity (Table 3, entry 6). Other nitrile-based solvents were trialled (Table 3, entries 7 and 8), and *n*-BuCN proved to be optimal when taking both yield and selectivity into account. Increasing the reaction temperature to 110 °C led to a significant increase in yield, with **104** and ***iso*-104** being isolated in 85 % combined yield and a ratio of 25:1 (Table 3, entry 10); crucially, this result did not vary significantly upon repeating.

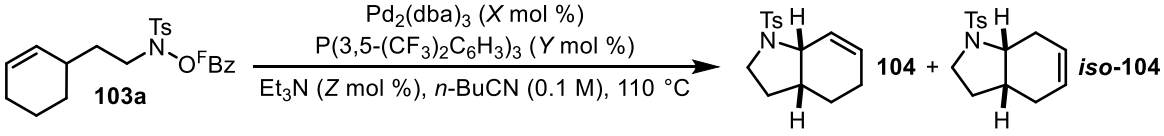
With a suitable solvent identified, the effects of varying the phosphine ligand were investigated. A screen of monodentate ligands revealed P(3,5-$(CF_3)_2C_6H_3)_3$ to be optimal (Table 21, Appendix). The majority of ligands employed provided a poor yield of **104**, and bidentate ligands proved to be especially ineffective, with none delivering a yield of greater than 25 % (Table 22, Appendix).

[XV] This was based on anecdotal evidence suggesting reproducibility problems are commonly observed with DMF.



Entry	*solvent*	*yield* (**104** + ***iso*-104**)	**104**:***iso*-104**
1	NMP	21 %	1:0
2	DMA	28 %	1:0
3	THF	62 %	1:0
4	1,2-DME	65 %	1:0
5	EtOAc	55 %	1:0
6	MeCN	76 %	3:1
7	PhCN	62 %	17:1
8	*n*-BuCN	77 %	24:1
9	PhMe	43 %	1:0
10	*n*-BuCN (110 °C)	(85 %)	25:1

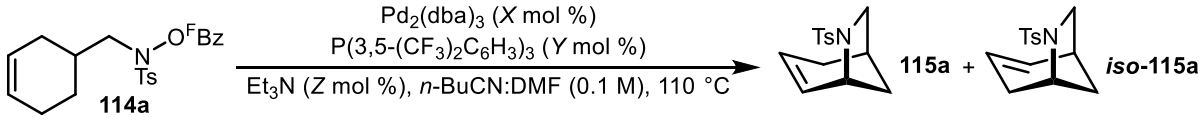
*Table 3 – Solvent screen for the palladium(0)-catalysed cyclisation of substrate **103a**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard.*



Entry	*X*	*Y*	*Z*	*yield* (**104** + ***iso*-104**)
1	5.0	20	100	(85 %)
2	3.75	15	100	77 %
3	3.75	18.8	100	81 %
4	2.5	10	100	57 %
5	2.5	12.5	50	(83 %)
6	1.25	5.0	100	52 %
7	1.25	6.25	50	60 %

*Table 4 – Optimisation of precatalyst and ligand loading for the cyclisation of substrate **103a**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses.*

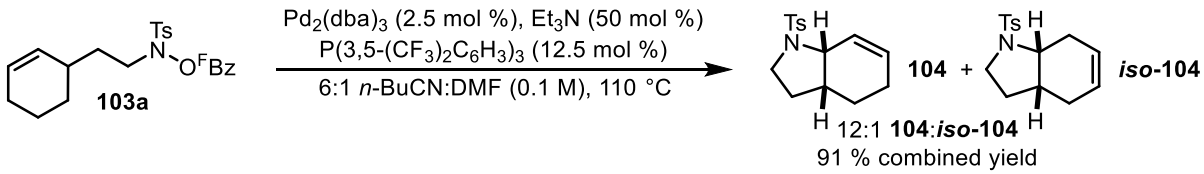
Having achieved a good yield for the cyclisation of **103a** following optimisation of solvent and ligand, the effect of lowering the catalyst loading was examined (Table 4). Significant drops in yield occurred with each 1.25 mol% decrease in palladium precatalyst (Table 4, entries 2, 4 and 6). However, increasing the palladium to ligand ratio to 1:2.5 negated this effect for all but the lowest precatalyst loadings (Table 4, entries 3, 5 and 7).



Entry	*n*-BuCN:DMF	*X*	*Y*	*Z*	*yield* (**115a** + ***iso*-115a**)	**115a**:***iso*-115a**
1	1:0	2.5	12.5	50	33 %	3:5
2	1:0	3.75	18.8	25	41 %	3:5
3	1:0	5.0	25.0	25	53 %	3:5
4	1:1	5.0	25.0	25	47 %	1:2
5	6:1	5.0	25.0	25	(63 %)	2:5

*Table 5 – Final optimisation of the palladium(0)-catalysed cyclisation of substrate **114a**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses.*

The optimised conditions from Table 4 were applied to the challenging substrate **114a**, but the results were still disappointing (Table 5, entry 1). Previously, when the cyclisation was run in DMF, a ratio of 1:4 **115a** to ***iso*-115a** was obtained; by switching to *n*-BuCN this increased to 3:5, which is in line with the trend observed with **103a**. In contrast to substrate **103a**, higher catalyst loadings resulted in increased yield (Table 4, entries 1, 3 and 5 *vs.* Table 5, entries 1-3). In an attempt to fine-tune the solvent polarity, mixtures of *n*-BuCN and DMF were used, and a 6:1 mixture was found to afford a 63 % yield and 2:5 ratio of **115a** to ***iso*-115a** (Table 5, entry 5). This solvent combination was also trialled for the cyclisation of **103a** and provided a 91 % yield and 12:1 ratio of **104** to ***iso*-104** (Scheme 43). In general, the mixture of *n*-BuCN and DMF was more effective as solvent than *n*-BuCN alone. However, this was not the case for all substrates, and both systems were trialled in subsequent studies.

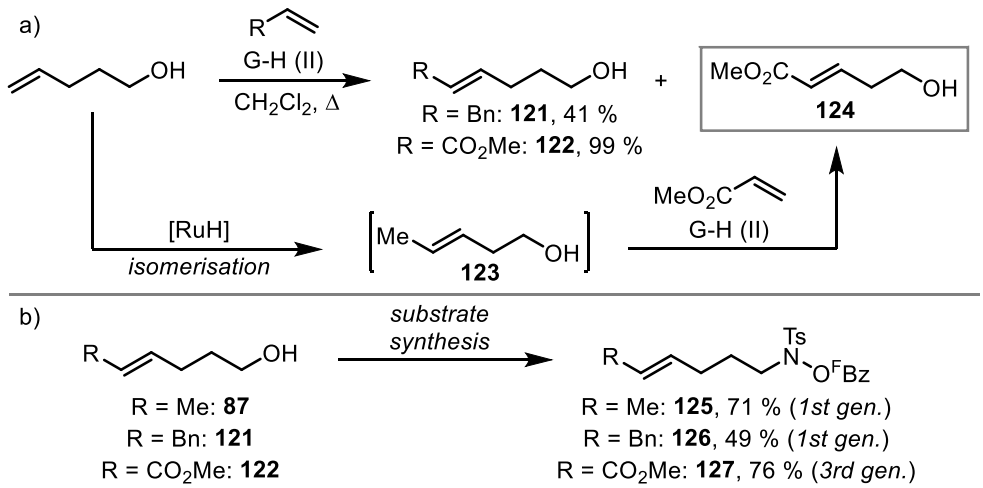


*Scheme 43 – Final conditions for the palladium(0)-catalysed cyclisation applied to substrate **103a**.*

2.4 Substrate scope for the aza-Heck cyclisation

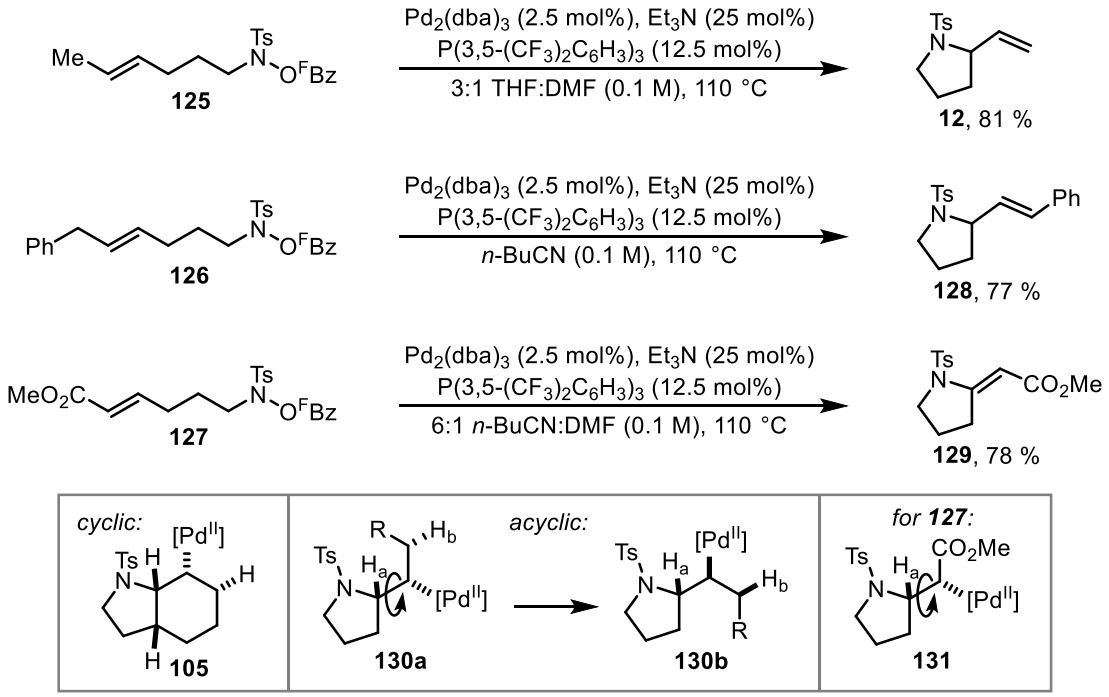
2.4.1 Aza-Heck cyclisations involving 1,2-disubstituted alkenes

With optimised conditions in hand, the substrate scope of the sulfonamide-based aza-Heck reaction was examined, and substrates **125**, **126** and **127**, containing acyclic 1,2-disubstituted alkenes, were synthesised (Scheme 44). Alcohols **121** and **122** were prepared in one step from pent-4-en-1-ol *via* alkene cross-metathesis (Scheme 44a). In the case of **122**, some optimisation was required to eliminate chain-shortened impurity **124**, which may result from competing cross-metathesis of **123**, itself likely formed by ruthenium hydride-mediated isomerisation of pent-4-en-1-ol.[123] Benzoquinone has been used as an additive in order to supress this type of isomerisation,[124] although in this case it was found that simply lowering the catalyst loading to 1 mol% completely prevented formation of **124**. Alcohols **87**, **121** and **122** were converted to substrates **125**, **126** and **127** using the 1st and 3rd generation routes (Scheme 44b).



*Scheme 44 – a) Synthesis of alcohols **121** and **122**, and proposed explanation for the formation of **124** in the synthesis of **122**. b) Synthesis of substrates **125**, **126** and **127**. – G-H (II) = Grubbs-Hoveyda 2nd generation catalyst.*

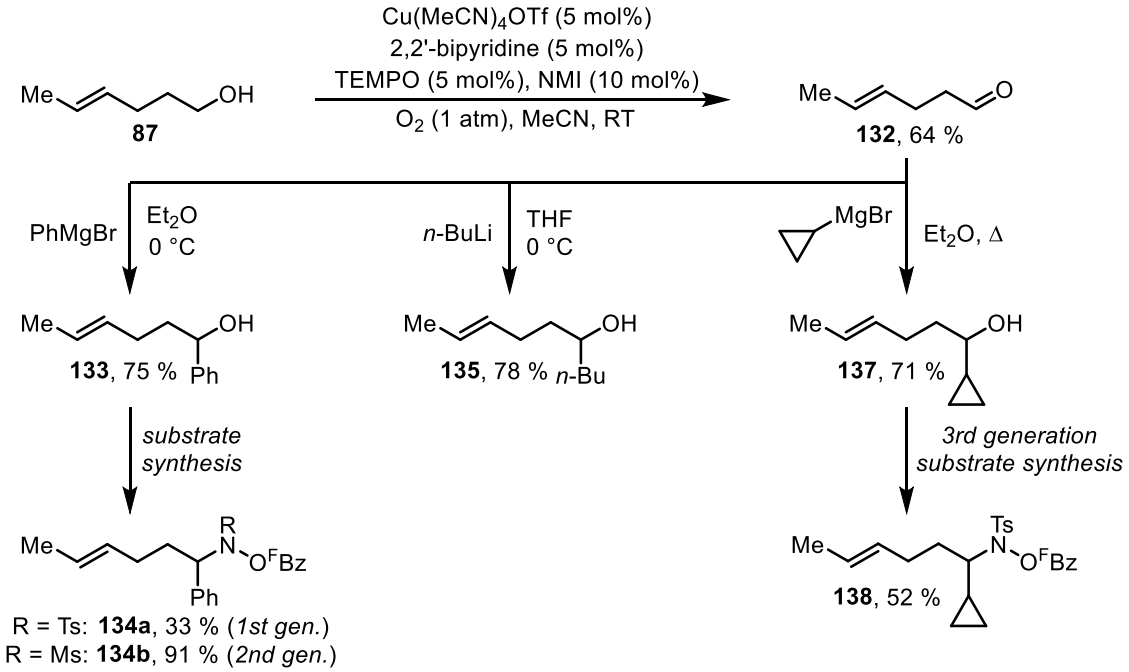
When substrates **125**, **126** and **127** were subjected to the aza-Heck conditions, products **12**, **128** and **129** were isolated in good yields (Scheme 45). Although complete selectivity for **12** and **128** was observed, substrates **125** and **126** could have, in theory, afforded enamine products. In contrast to intermediate **105**, **130a** can undergo C–C bond rotation to **130b**, such that β-hydride elimination is possible *via* H_a or H_b. In the case of substrate **127**, there is no H_b atom in intermediate **131**, so bond rotation has to occur before β-hydride elimination is possible; this accounts for the switch in alkene geometry observed between **127** and **129**. The successful cyclisation of a substrate containing an electron-deficient alkene, such as **127**, is also notable, as similar substrates are unlikely to be suitable for aza-Wacker cyclisations due to competing conjugate addition.



*Scheme 45 – Palladium(0)-catalysed cyclisation of substrates **125**, **126** and **127**.*

2.4.2 Aza-Heck cyclisations of systems with substitution α to nitrogen

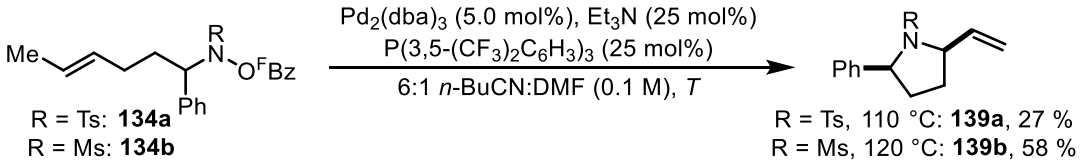
Next, the effects of substitution in the α-position were examined. To this end, substrates **134**, **136** and **138** were prepared (Scheme 46). Copper(I)/TEMPO-catalysed oxidation of alcohol **87** afforded aldehyde **132**,[125] which was reacted with suitable organometallic nucleophiles to afford alcohols **133**, **135** and **137**. Substrates **134**, **136** and **138** were then synthesised from alcohols **133**, **135** and **137**. As



*Scheme 46 – Synthesis of substrates **134a**, **134b**, **136** and **138**.*

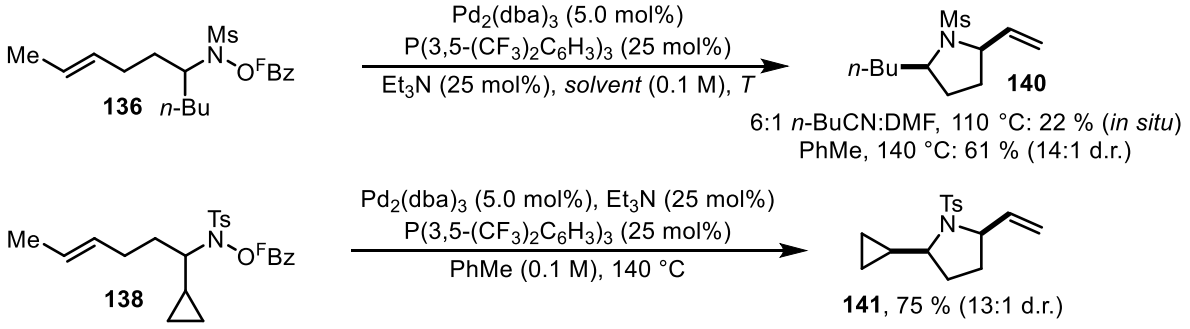
noted previously (Scheme 29, Section 2.2.2), the deprotection step in the first-generation route was poorly yielding, and **134a** was isolated in only 33 % overall yield.

The cyclisation of substrate **134a** was disappointing, with **139a** obtained in 27 % yield, albeit as a single diastereomer (Scheme 47). The reaction proceeded slowly, and significant substrate decomposition was observed along with **139a**; it is possible that the N–O bond of **134a** is too hindered for efficient oxidative addition. A short period of optimisation of reaction temperature and ligand failed to improve the result significantly. It was thought that a substrate with a less sterically hindered N–O bond might lead to a higher yielding cyclisation. In order to test this hypothesis, mesyl-protected substrate **134b** was prepared *via* the second-generation route (Scheme 46). As hoped, when submitted to the aza-Heck cyclisation conditions, substrate **134b** performed significantly better than **134a**, with **139b** isolated in 58 % yield (Scheme 47).



*Scheme 47 – Palladium(0)-catalysed cyclisation of substrates **134a** and **134b**.*

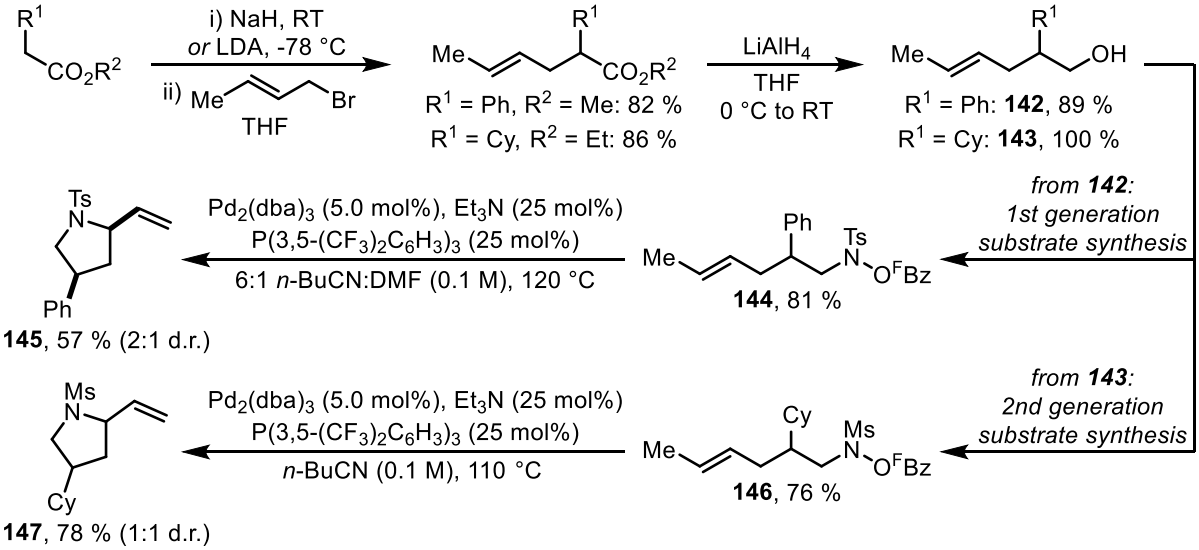
Although changing to the mesyl-protecting group improved the yield for phenyl-substituted system **134b**, the yield of the cyclisation was still disappointing in the case of *n*-butyl-substituted substrate **136** (Scheme 48). Further optimisation was undertaken with this substrate, and it was found that conducting the reaction at higher temperature in toluene was key to achieving a good yield of **140**. Under these conditions, the cyclisation of tosyl-protected substrate **138** was also successful, and **141** was obtained in 75 % yield (Scheme 48).



*Scheme 48 – Palladium(0)-catalysed cyclisation of substrates **136** and **138**.*

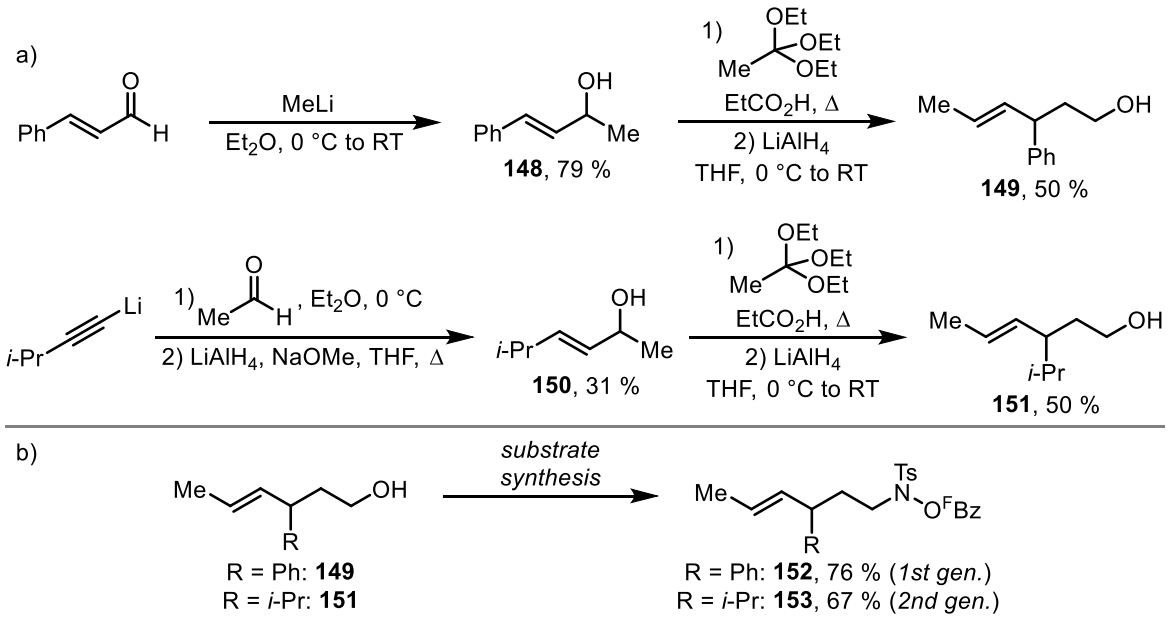
2.4.3 Aza-Heck cyclisations of systems with substitution β to nitrogen

Attention was then turned to substrates containing β-substitution (Scheme 49). Synthesis of substrates **144** and **146** proceeded from alcohols **142** and **143**, which were prepared in two steps *via* alkylation of substituted acetates, followed by reduction. Cyclisation of β-phenyl-system **144** progressed with moderate diastereoselectivity and yield, favouring the *cis*-diastereomer. The *N*-mesyl-protected substrate **146** provided a higher yield of target **147**, although this was formed with no diastereoselectivity, despite incorporating a larger cyclohexyl substituent.



*Scheme 49 – Synthesis and palladium(0)-catalysed cyclisation of substrates **144** and **146**.*

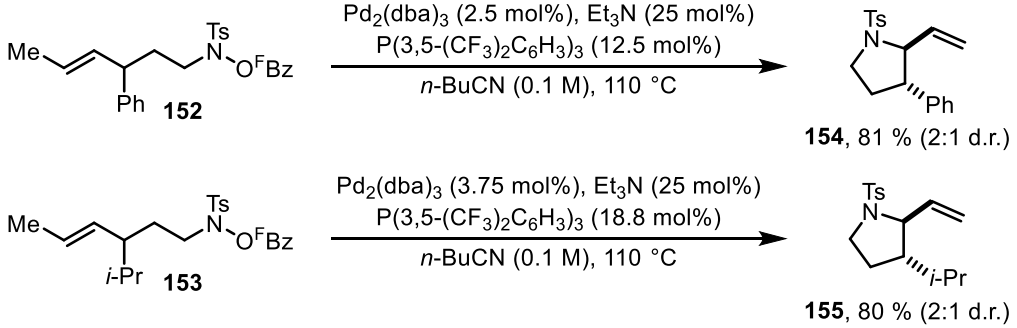
2.4.4 Aza-Heck cyclisations of systems with substitution γ to nitrogen



*Scheme 50 – a) Synthesis of alcohols **149** and **151**. b) Synthesis of substrates **152** and **153**.*

While poor diastereoselectivities were obtained in the cyclisations of substrates with β-substitution (Scheme 49), it was hoped that moving the substituent closer to the alkene would lead to a greater steric influence in the cyclisation step and hence result in higher diastereoselectivity. γ-Substituted-δ,ε-unsaturated alcohols **149** and **151** were prepared by a Johnson-Claisen/reduction sequence from easily accessible allylic alcohols **148** and **150** (Scheme 50a). Substrates **152** and **153** – bearing phenyl and *i*-propyl substituents, respectively – were synthesised from the corresponding alcohols **149** and **151** (Scheme 50b).

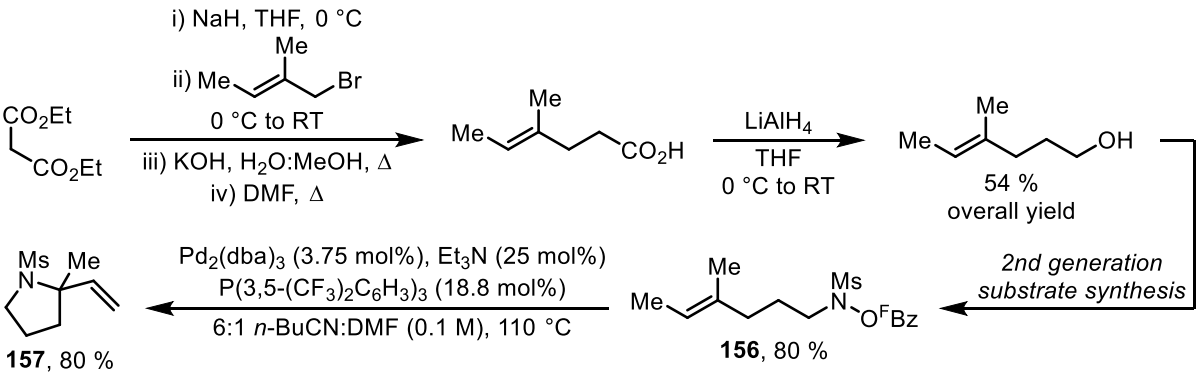
Unfortunately, although substrate **152** afforded an 81 % yield of product **154**, the diastereoselectivity achieved was disappointing (Scheme 51). When exposed to the aza-Heck conditions, substrate **153** provided essentially the same result as **152**, despite the presence of the slightly larger *i*-propyl group (Scheme 51).



*Scheme 51 – Palladium(0)-catalysed cyclisation of substrates **152** and **153**.*

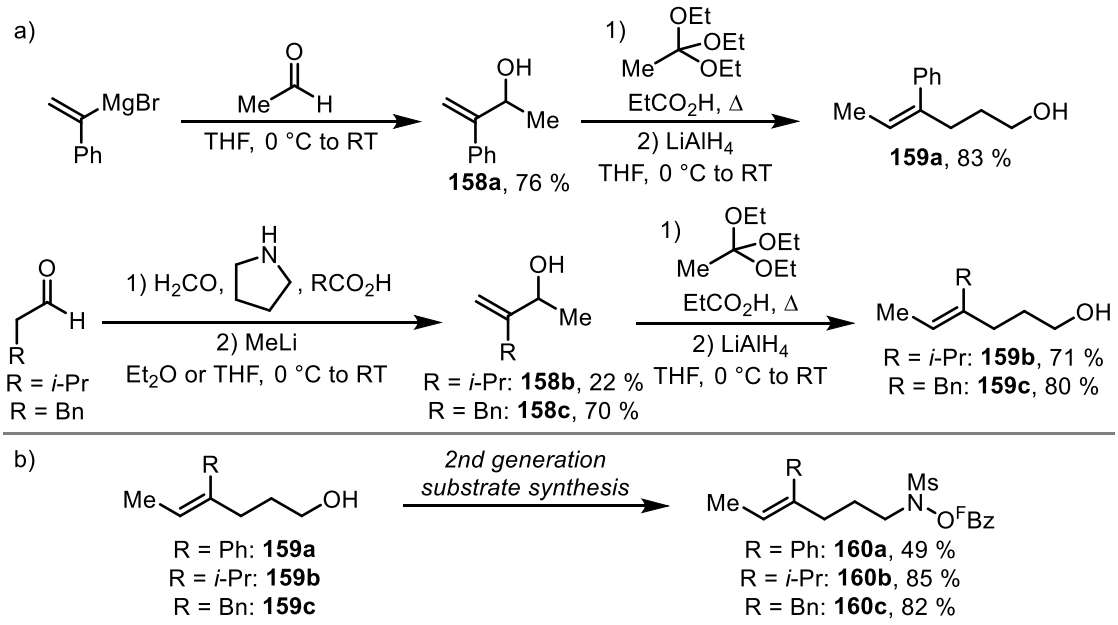
2.4.5 Aza-Heck cyclisations involving trisubstituted alkenes

The use of trisubstituted alkenes in the aza-Heck reaction was examined; as mentioned previously, these kinds of substrates are relatively rare in aza-Wacker reactions (Section 1.2.5). A relatively simple substrate (**156**) was targeted initially (Scheme 52). Substrate **156** was prepared *via* an alkylation/ decarboxylation/reduction strategy starting from diethyl malonate, followed by the second-generation substrate synthesis route. When employed in the aza-Heck cyclisation, **156** afforded an 80 % yield of **157** (Scheme 52).



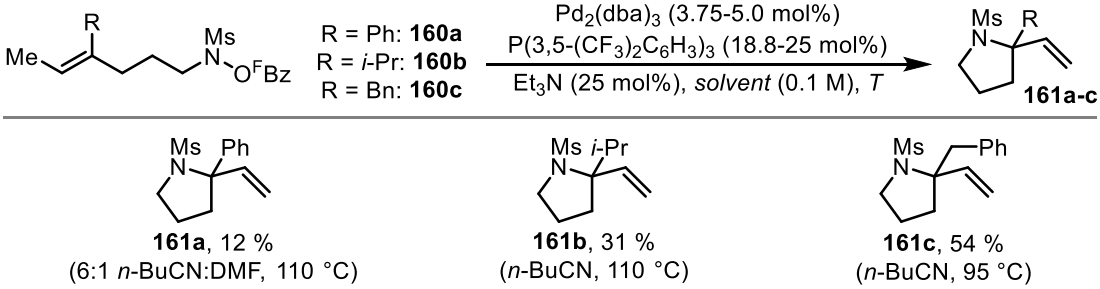
*Scheme 52 – Synthesis and palladium(0)-catalysed cyclisation of substrate **156**.*

Having demonstrated the tolerance of methyl-substituted alkenes with substrate **156**, substrates containing larger substituents were evaluated. The alcohols required for this were prepared by Johnson-Claisen reactions of allylic alcohols **158a-c**, followed by reduction to afford **159a-c** (Scheme 53a). From these alcohols, substrates **160a-c** were synthesised using the second-generation route (Scheme 53b).



*Scheme 53 – a) Synthesis of alcohols **159a-c**. b) Synthesis of substrates **160a-c**.*

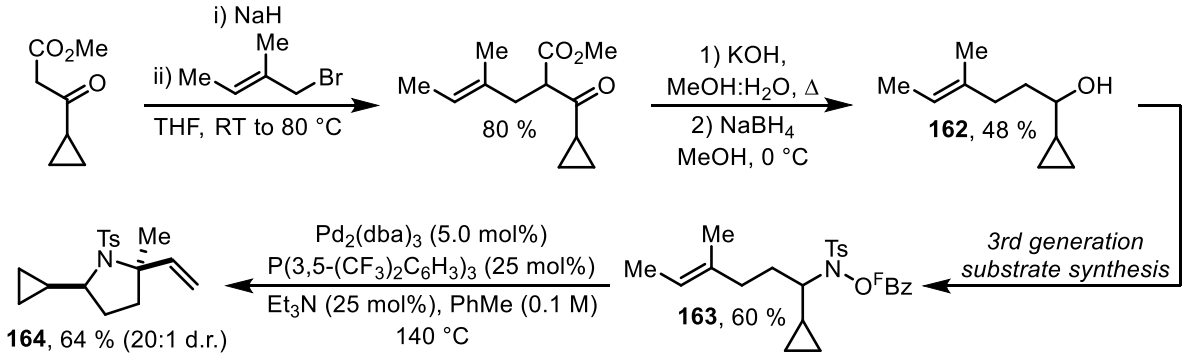
Unfortunately, when substrates **160a-c** were trialled in the aza-Heck reaction, products **161a-c** were obtained in disappointing yields (Scheme 54). Phenyl-substituted system **160a** afforded **161a** in a poor yield, even compared with the 31 % yield of **161b** obtained with *i*-propyl-substituted **160b**. This difference is potentially due to the electronic effect of conjugation of the alkene with the phenyl group. Although a modest yield of 54 % was achieved with benzyl-substituted substrate **160c**, it is clear that sterically encumbered trisubstituted alkenes constitute a limitation of this methodology.



*Scheme 54 – Palladium(0)-catalysed cyclisation of substrates **160a-c**.*

A substrate containing both α-substitution and a trisubstituted alkene (**163**) was prepared and evaluated in the aza-Heck reaction (Scheme 55). By using the conditions developed for substrates **136** and **138** (Scheme 48, Section 2.4.2), a 64 % yield of **164** was obtained from the cyclisation of **163**. As was

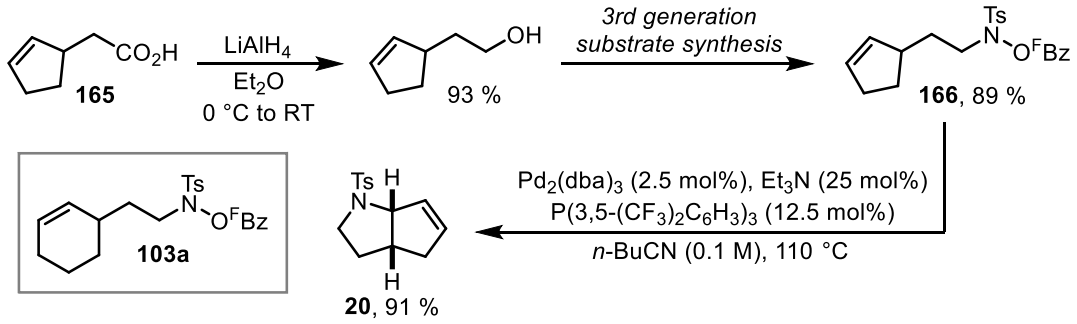
typically observed with other α-substituted systems (Section 2.4.2), **164** was formed with excellent diastereoselectivity.



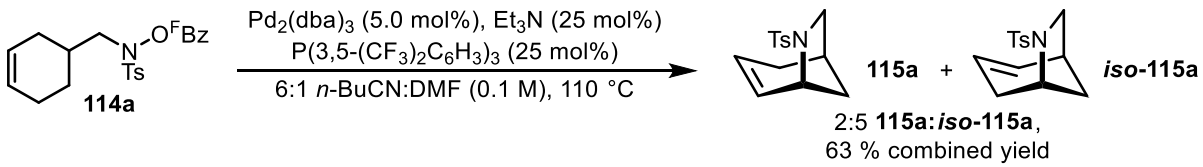
*Scheme 55 – Synthesis and palladium(0)-catalysed cyclisation of substrate **163**.*

2.4.6 Aza-Heck cyclisations to generate bicyclic systems

As an excellent result was achieved with cyclohexenyl substrate **103a** (Scheme 43, Section 2.3.3), further cyclisations that afford bicyclic products were targeted, and cyclopentenyl substrate **166** was prepared from carboxylic acid **165** (Scheme 56). The yield of the cyclisation of **166** was the same as that for **103a** but proceeded with far better selectivity, to generate **20** as a single alkene isomer (Scheme 56). The fact that **20** can be prepared in just three steps from commercially available carboxylic acid **165** demonstrates the power of the combined Mitsunobu/aza-Heck cyclisation sequence.



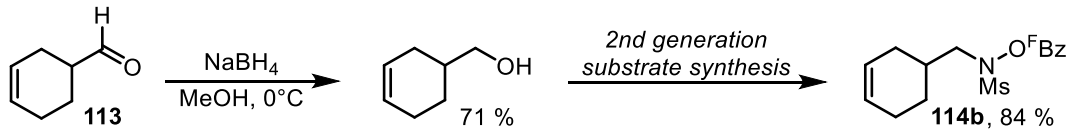
*Scheme 56 – Synthesis and palladium(0)-catalysed cyclisation of substrate **166**.*



*Scheme 57 – Palladium(0)-catalysed cyclisation of substrate **114a**.*

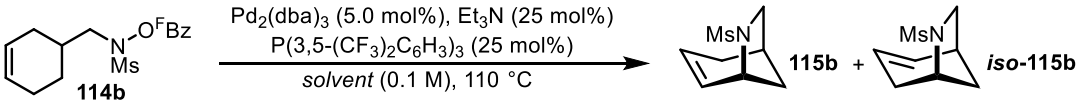
The transannular cyclisation of substrate **114a** was investigated previously (Table 1, Section 2.3.2 and Table 5, Section 2.3.3), and although the yield of the transformation was improved to 63 %, a significant amount of isomerisation of **115a** to ***iso*-115a** was observed (Scheme 57). This system was revisited with

the *N*-mesyl analogue **114b** (Scheme 58). As a higher yield was observed in the reaction of α-substituted *N*-mesyl substrate **134b** compared to its *N*-tosyl analogue **134a** (Scheme 47, Section 2.4.2), it was hoped that **114b** would lead to a higher yielding cyclisation, which could then be optimised to improve product selectivity.



*Scheme 58 – Synthesis of substrate **114b**.*

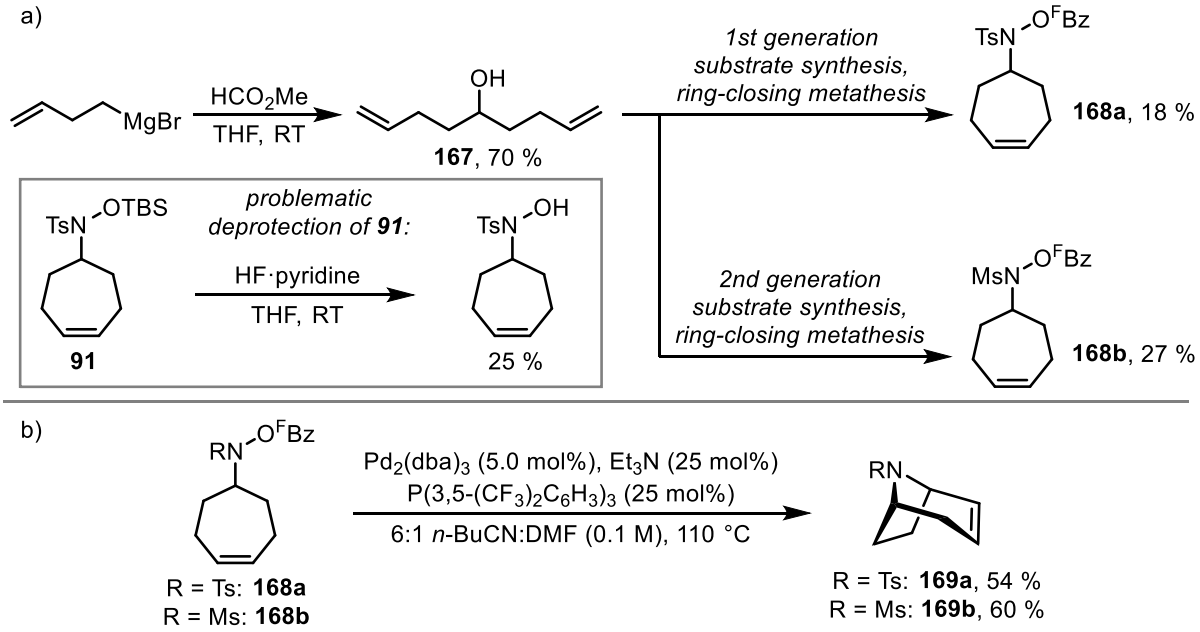
Under identical conditions to those used for *N*-tosyl substrate **114a**, *N*-mesyl substrate **114b** provided a higher yield and greater selectivity for desired product **115** (Table 6, entry 1 *vs.* Scheme 57), with the major product being **115b** rather than ***iso*-115b**. Further improvements in yield and selectivity were observed when *n*-BuCN was used as a solvent alone (Table 6, entry 2), instead of as a mixture with DMF (Table 6, entry 1). Using THF as the reaction solvent resulted in complete selectivity for **115b**, although in a significantly lower yield (Table 6, entry 3). A 1:1 mixture of *n*-BuCN and THF was found to provide the optimal combination of yield and selectivity, with **115b** being isolated in 76 % yield as a single alkene isomer (Table 6, entry 4).



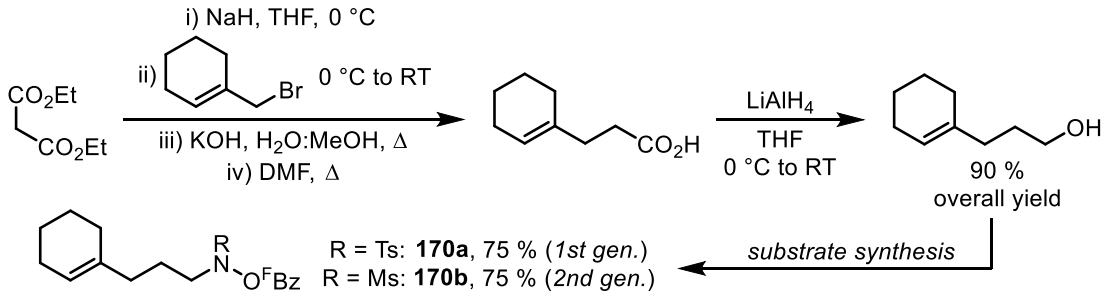
Entry	*solvent*	*yield* (**115b** + ***iso*-115b**)	**115b**:***iso*-115b**
1	6:1 *n*-BuCN:DMF	(79 %)	3:2
2	*n*-BuCN	83 %	4:1
3	THF	71 %	1:0
4	1:1 *n*-BuCN:THF	(76 %)	1:0

*Table 6 – Solvent screen for the palladium(0)-catalysed cyclisation of substrate **114b**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses.*

Following the success achieved in the cyclisation of **114b**, further transannular aza-Heck processes were investigated. To this end, substrates **168a** and **168b** were prepared (Scheme 59a). Addition of two equivalents of but-3-en-1-ylmagnesium bromide to methyl formate afforded alcohol **167**, which was then converted to **168a** and **168b** *via* ring-closing metathesis. The synthesis of substrate **168a** is another example of the limitation of the first-generation route, with the deprotection of **91** proceeding in poor yield. When evaluated in the aza-Heck reaction, **168b** cyclised in a slightly higher yield than **168a** under identical conditions, and **169b** was isolated in 60 % yield (Scheme 59b).

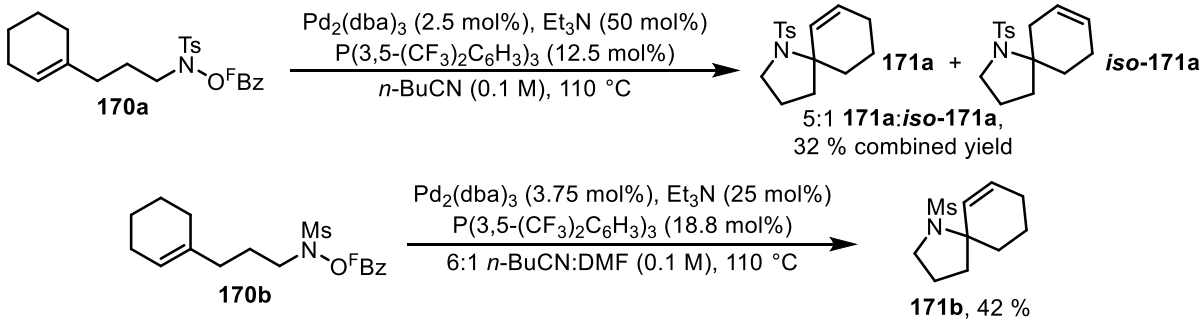


*Scheme 59 – a) Synthesis of substrates **168a** and **168b**. b) Palladium(0)-catalysed cyclisation of substrates **168a** and **168b**.*



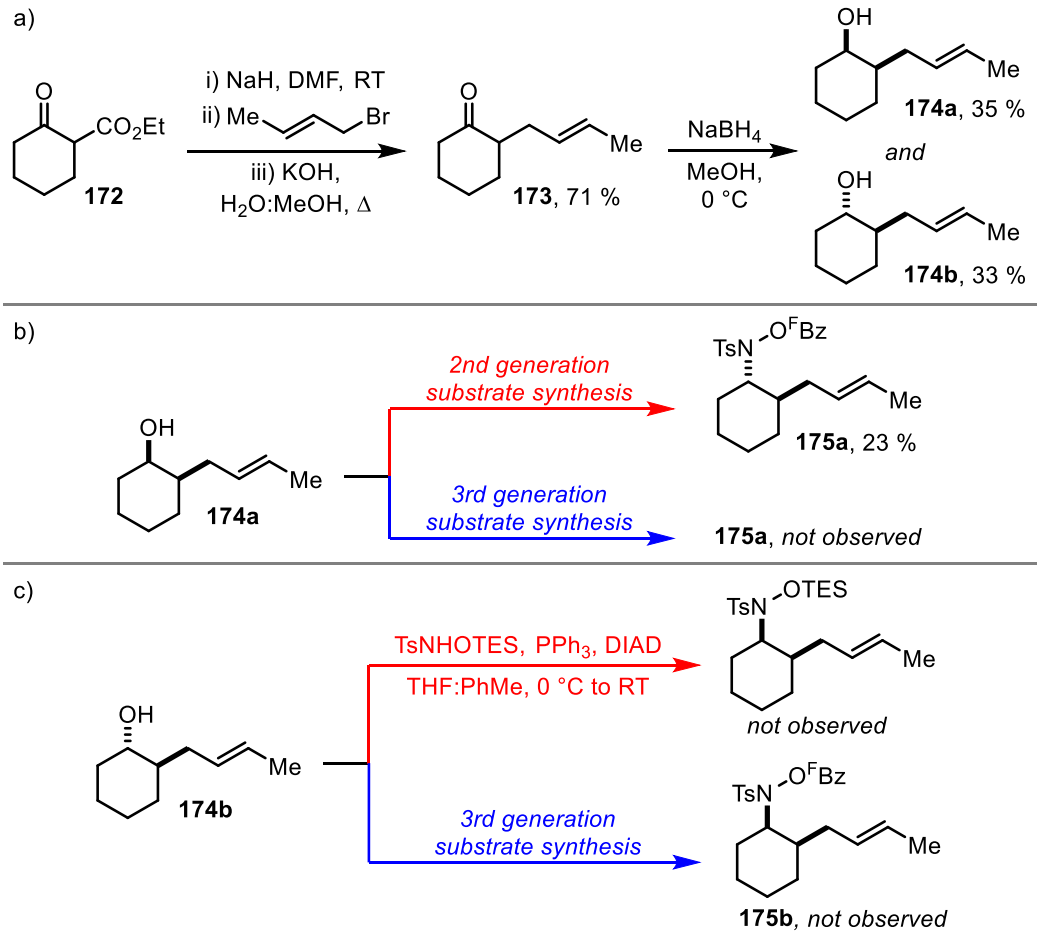
*Scheme 60 – Synthesis of substrates **170a** and **170b**.*

The possibility of C–N bond-forming spirocyclisation was also investigated, and substrate **170** was prepared *via* a route similar to that for **156** (Scheme 52, Section 2.4.5). As with **168**, both *N*-tosyl- and *N*-mesyl-protected systems **170a** and **170b**, respectively, were prepared (Scheme 60). When employed in the aza-Heck cyclisation, substrate **170b** performed significantly better than **170a** (Scheme 61), with **171b** isolated in 42 % yield and without the isomerisation observed for **171a**/***iso*-171a**. While the yield of **171b** was disappointing, it is broadly in line with the results obtained using other trisubstituted alkenes (Section 2.4.5).



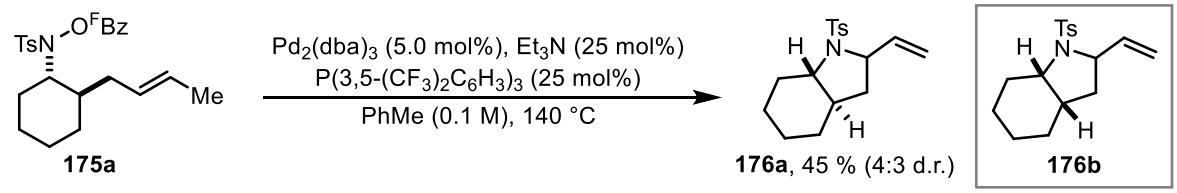
*Scheme 61 – Palladium(0)-catalysed cyclisation of substrates **170a** and **170b**.*

Cyclic substrates **175a** and **175b** were targeted in the hope that the preorganisation contained in their structures would lead to high-yielding and highly diastereoselective cyclisations. The synthesis of these substrates began with the preparation of ketone **173** by alkylation of β-keto ester **172**, followed by decarboxylation. Reduction of **173** ($NaBH_4$) afforded a 1:1 separable mixture of diastereomeric alcohols **174a** and **174b** (Scheme 62a). Both **174a** and **174b** were poorly tolerated in the Mitsunobu reactions, and attempts to synthesise **175a** directly *via* the third-generation route, using $TsNHO^FBz$, were completely unsuccessful (Scheme 62b). The second-generation route, using TsNHOTES, provided an overall yield of 23 %, with the Mitsunobu step proceeding in 39 % yield. The relative stereochemistry of **175a** was determined by X-ray diffraction, and the relative stereochemistry of alcohols **174a** and **174b** was assigned on the assumption that the Mitsunobu step proceeded with inversion. In the case of alcohol **174b**, neither route resulted in the formation of **175b** (Scheme 62c). The failure of the Mitsunobu reactions with alcohols **174a** and **174b** is likely due to steric hindrance, with **174b** performing worse than **174a** because the nucleophile has to approach the activated substrate on the same face of the cyclohexane ring as the butenyl substituent.



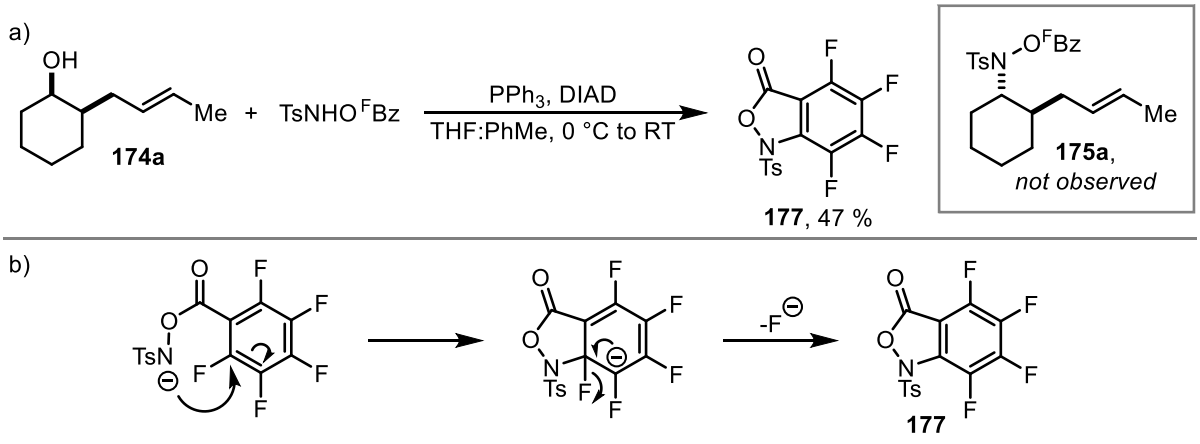
*Scheme 62 – a) Synthesis of alcohols **174a** and **174b**. b) Synthesis of substrate **175a**. c) Attempted synthesis of substrate **175b**.*

Aza-Heck cyclisation of **175a** under the standard conditions provided a low yield of **176a**. As observed for α-substituted substrates (Section 2.4.2), slightly better results were achieved in toluene at 140 °C (Scheme 63). In contrast to the results obtained with α-substituted substrates, **176a** was formed with essentially no diastereoselectivity. It is possible that the *trans* relationship of the α- and β-substituents leads to a reduction in the diastereoselectivity, as, when considered on their own, each substituent exerts a preference for a different diastereomer. It was disappointing that **175b** could not be prepared, as there is a good chance that it would have cyclised in higher yield and possibly with high diastereoselectivity; Szabó has reported palladium-catalysed oxidative cyclisations of sulfonamides onto allyl silanes and achieved a significantly higher yield of **176b** compared to its *trans*-ring junction isomer **176a**.[126] Although, as the two proceed through very different mechanisms, it may not be possible to extrapolate those results to the aza-Heck reaction.



*Scheme 63 – Palladium(0)-catalysed cyclisation of substrate **175a**.*

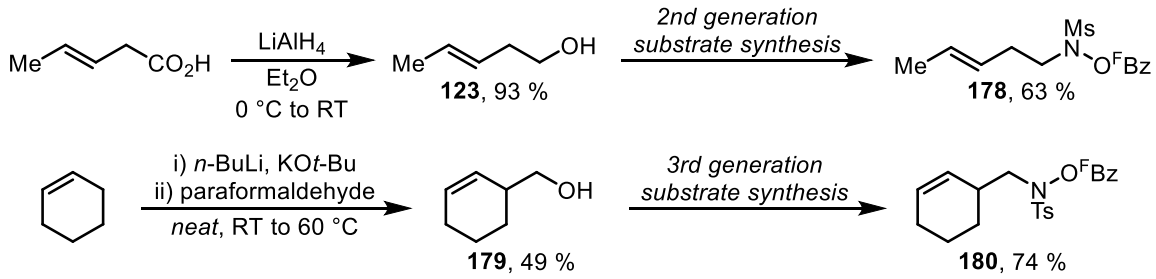
As mentioned previously, attempts to synthesise substrate **175a** directly using the third-generation route failed. However, purification of the reaction mixture led to the isolation of a significant amount of degradation product **177** (Scheme 64a); the structure of which was confirmed by X-ray diffraction. This product is likely formed *via* an intramolecular S_NAr reaction (Scheme 64b). This is seemingly an unfavourable reaction, as **177** is not observed in significant amounts in other Mitsunobu processes; in those cases, the intermolecular reaction appears to outcompete the intramolecular decomposition. For alcohol **174a**, the rate of the desired reaction is presumably so slow that TsNHO^{F}Bz simply decomposes and formation of **177** predominates.



*Scheme 64 – a) Observation of TsNHO^{F}Bz degradation product **177** in an unsuccessful Mitsunobu reaction. b) Proposed mechanism for the formation of **177**.*

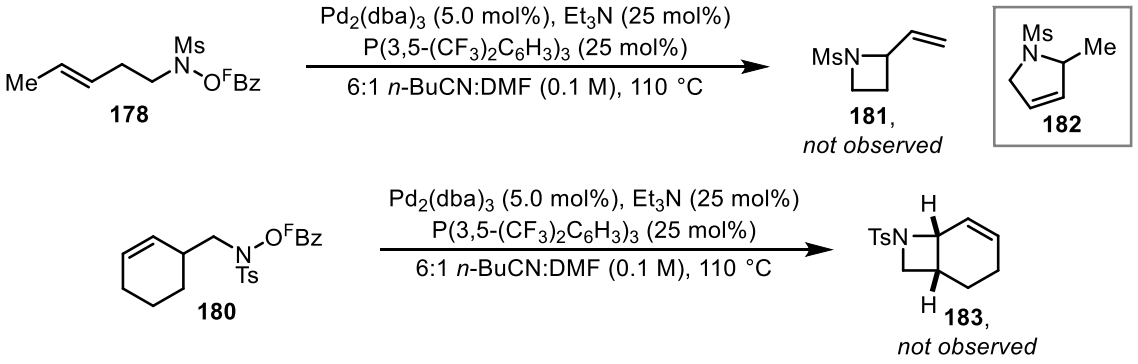
2.4.7 Attempted cyclisations to form 4-membered rings

Having established the effectiveness of the aza-Heck reaction for preparing substituted pyrrolidines, the synthesis of products containing other ring sizes was attempted. The possibility of forming azetidines was especially attractive, as this is something which is not typically possible with aza-Wacker methodologies. Although cyclisation to form 4-membered rings is much slower than for 5-membered rings,[127-129] Heck reactions and related Heck-type processes which generate cyclobutanes have been reported.[130-132] The homoallylic alcohols **123** and **179** required for 4-ring substrates could each be synthesised in one step; *N*-mesyl substrate **178** was prepared from **123**, and *N*-tosyl substrate **180** was prepared from **179** (Scheme 65).



*Scheme 65 – Synthesis of substrates **178** and **180**.*

Vinyl azetidine **181** was not observed when **178** was subjected to the aza-Heck conditions (Scheme 66), nor was the product of 5-*endo* cyclisation (**182**). Despite the fact that disubstituted cyclic alkenes have been shown to be excellent partners in the aza-Heck reaction (Scheme 43, Section 2.3.3 and Scheme 56, Section 2.4.6), substrate **180** did not cyclise to afford **183** (Scheme 66). The azetidine ring system could simply be too strained to form in this manner, especially considering the fact that aminopalladation is likely to be reversible.[133] It is also possible that, even if formed, the vinyl azetidine products decompose under the reaction conditions, as similar systems undergo ring opening under related conditions.[134]

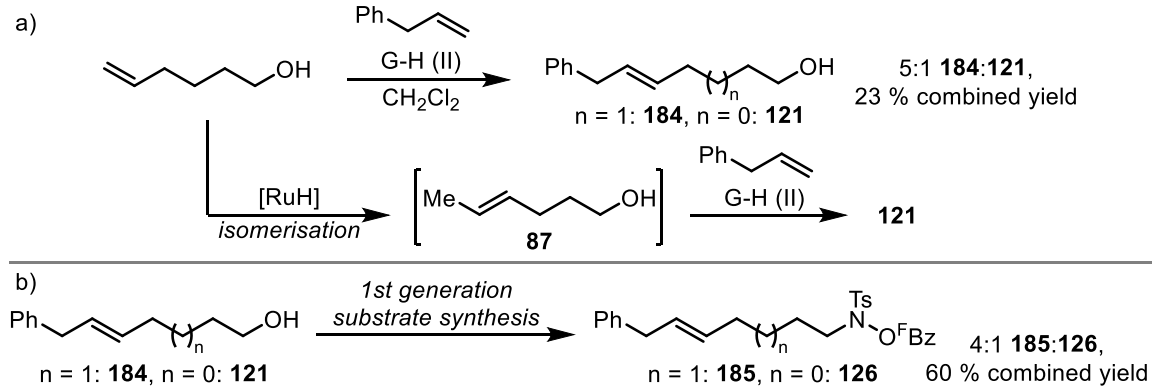


*Scheme 66 – Attempted cyclisation of substrates **178** and **180**.*

2.4.8 Aza-Heck cyclisations to form 6-membered rings

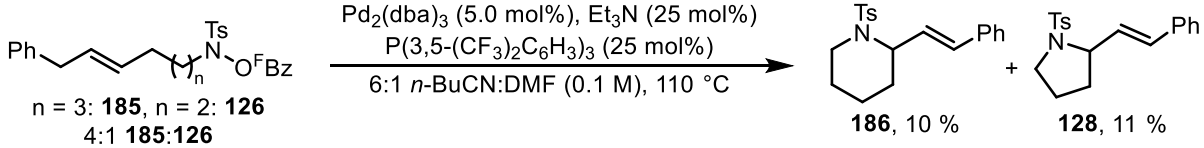
Although attempts to form 4-membered rings were not successful, analogous 6-*exo* cyclisations were investigated. The prevalence of the piperidine unit in natural products[135] and pharmaceuticals[1] makes them an attractive target. Six-*exo* cyclisations were considered a more realistic possibility than 4-*exo* cyclisations, as there is far less ring strain in piperidines compared to azetidines.

Substrate **185** was prepared in a similar manner to **126** (Scheme 44, Section, 2.4.1). However, as was initially observed with alcohol **122** (Scheme 44a, Section 2.4.1), a significant amount of chain-shortened impurity **121** was produced in the synthesis of alcohol **184** (Scheme 67a). It was not possible to separate **184** from **121**, nor was it possible to separate the analogous compounds at any stage of the substrate synthesis. Hence, **185** was isolated as a 4:1 mixture with **126** (Scheme 67b).



*Scheme 67 – a) Synthesis of alcohol **184** and proposed explanation for the formation of **121**. b) Synthesis of substrate **185**. – G-H (II) = Grubbs-Hoveyda 2nd generation catalyst.*

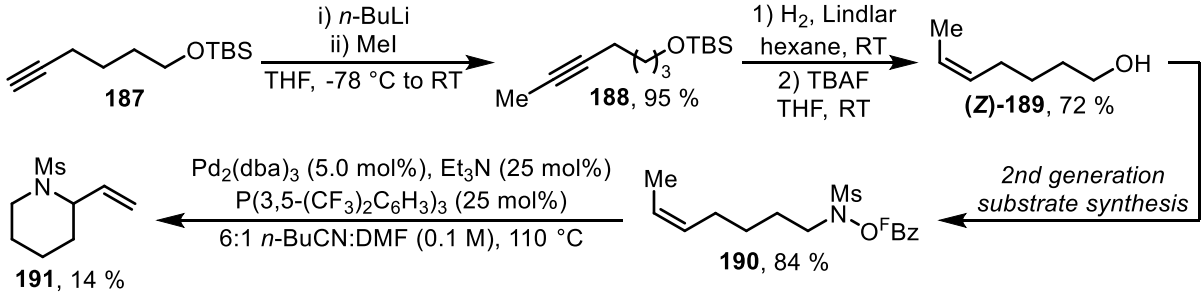
The mixture of **185** and **126** was subjected to the aza-Heck cyclisation conditions; at this stage, the two products could be separated, and a similar amount of piperidine **186** (arising from **185**) was isolated as pyrrolidine **128** (arising from **126**) (Scheme 68). Even taking into account the impurity of the substrate, the yield of **186** was disappointing, so further substrates were prepared.



*Scheme 68 – Palladium(0)-catalysed cyclisation of substrate **185**.*

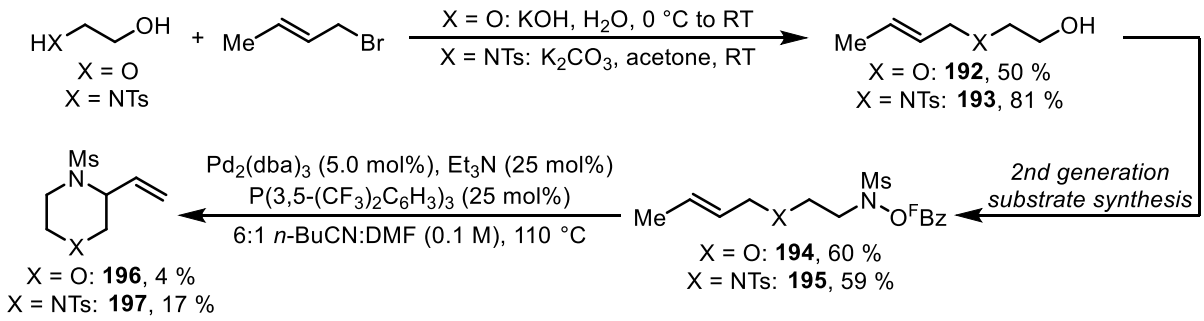
Based on the observation that *N*-mesyl protected substrates generally cyclise in higher yields than the corresponding *N*-tosyl variants (Section 2.4.2, Section 2.4.3 and Section 2.4.6), substrate **190** was targeted (Scheme 69). Alcohol **189** was prepared by methylation of alkyne **187**, followed by reduction and deprotection. Conversion of **189** to substrate **190** was then achieved *via* the second-generation route.

Subjecting **190** to the aza-Heck conditions provided **191** in only 14 % yield (Scheme 69). Although this is a slight improvement compared to **185**, the yield is still too low to be synthetically useful.



*Scheme 69 – Synthesis and palladium(0)-catalysed cyclisation of substrate **190**.*

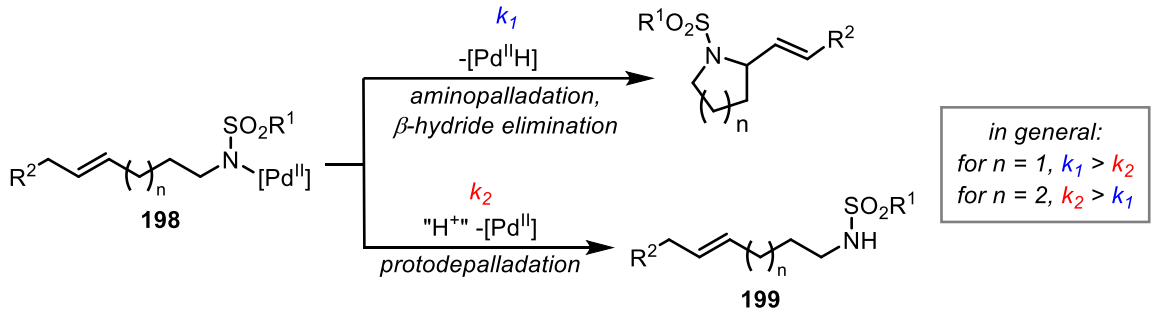
Substrates containing heteroatoms in the tether were prepared (**194** and **195** in Scheme 70). The heteroatom provides a useful synthetic handle and allows for easier preparation of alcohols **192** and **193** compared to **(*Z*)-189**. Furthermore, in a previous report on aza-Wacker cyclisations that form 6-membered rings, the vast majority of products are either morpholines or piperazines,[61] suggesting these kinds of substrates might be effective in the related aza-Heck reaction. However, as found with previous 6-ring substrates, aza-Heck cyclisation of **194** and **195** provided products **196** and **197** in disappointing yields (Scheme 70).



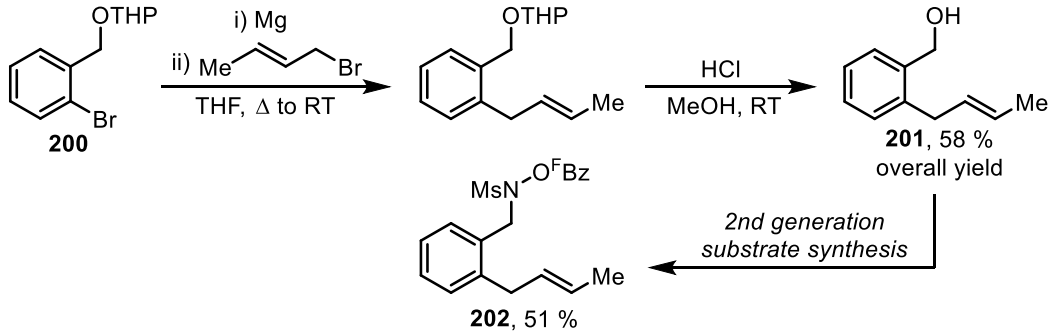
*Scheme 70 – Synthesis and palladium(0)-catalysed cyclisation of substrates **194** and **195**.*

In the majority of cases, the yield-determining step in the cyclisation appears to be aminopalladation of the alkene from intermediate **198** (Scheme 71), with protodepalladation being the major competing pathway to afford side product **199**. This hypothesis is based on the observation that, although other side products have been observed in some cases (Section 2.3.2), protodepalladation product **199** is the most commonly observed side product. The rate of the cyclisation step (k_1) from **198** will be highly dependent on the nature of the tethered alkene; however, the protodepalladation reaction (k_2) is unlikely to be significantly affected by this. From the yields achieved in 5-*exo* cyclisations it is apparent the rates of these two reactions are finely balanced; moving to homologated systems lowers the rate of cyclisation sufficiently such that protodepalladation becomes favoured. Based on this observation, it was thought that introducing a conformational bias into the substrates might increase the rate of cyclisation and

hence lead to improved yields. With this in mind, alcohol **201** was prepared *via* methallylation of the Grignard reagent formed from **200**, followed by *O*-THP deprotection (Scheme 72). Alcohol **201** was then converted to substrate **202** using the second-generation route.

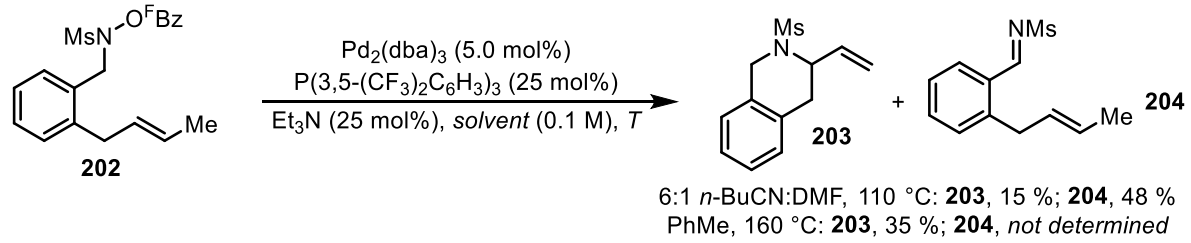


Scheme 71 – Proposed explanation for the low yields observed in cyclisations of 6-ring substrates compared to 5-ring substrates.



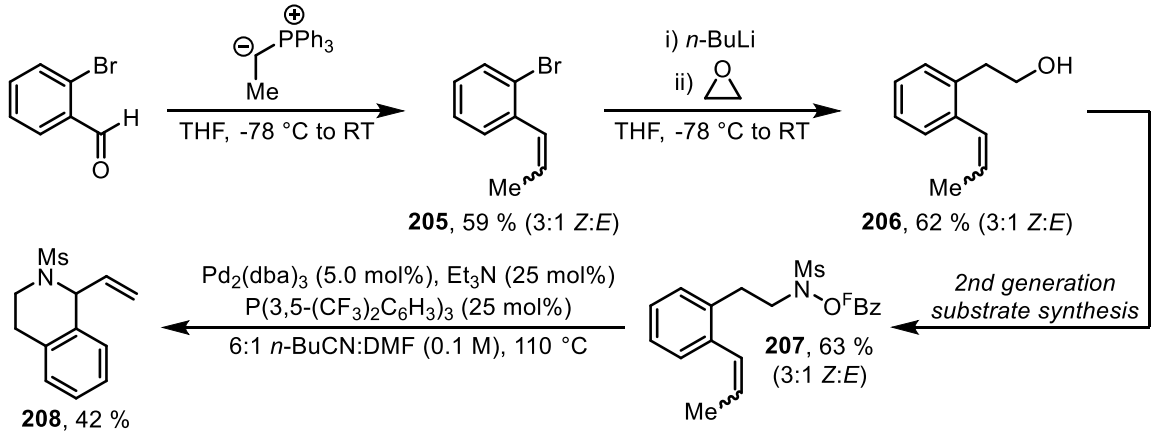
*Scheme 72 – Synthesis of substrate **202**.*

When substrate **202** was employed in the aza-Heck cyclisation using the standard conditions, **203** was obtained in 15 % yield (Scheme 73). While this result is similar to the other 6-ring substrates, the major side product was elimination product **204**, rather than protodepalladation product. The acidification of the C–H bonds α to nitrogen by the adjacent aromatic ring likely makes elimination more facile than in other substrates. Optimisation studies revealed that using toluene as the solvent at 160 °C could provide **203** in 35 % yield. Presumably, the rate of elimination is reduced when the reaction is conducted in an apolar solvent, and this would account for the increased yield.



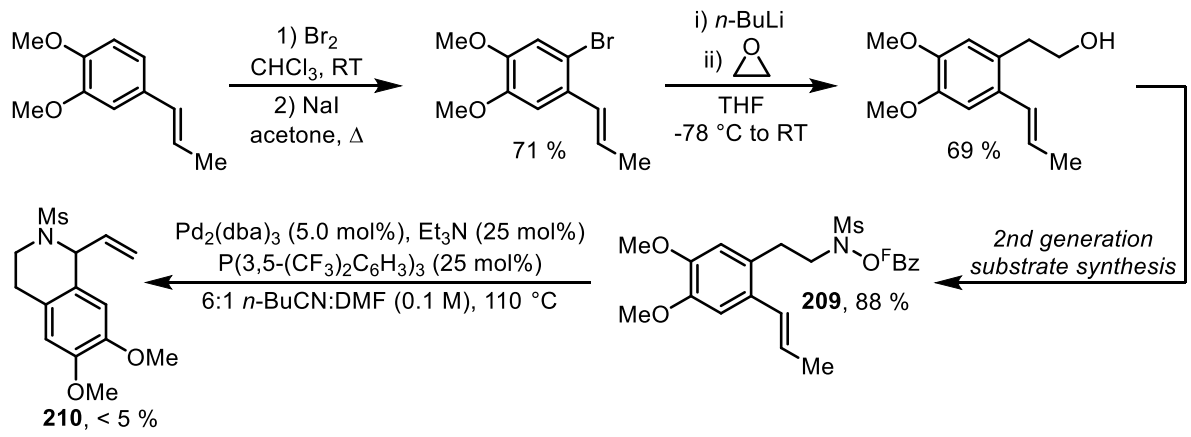
*Scheme 73 – Palladium(0)-catalysed cyclisation of substrate **202**.*

By removing the benzylic activation present in **202**, elimination might be disfavoured. Accordingly, the isomeric substrate **207** was prepared and evaluated in the aza-Heck cyclisation (Scheme 74). Reaction of the aryl lithium species derived from **205** with ethylene oxide afforded alcohol **206**, and **207** was then synthesised from **206** using the second-generation route. When exposed to the aza-Heck conditions, **207** cyclised in moderate yield.



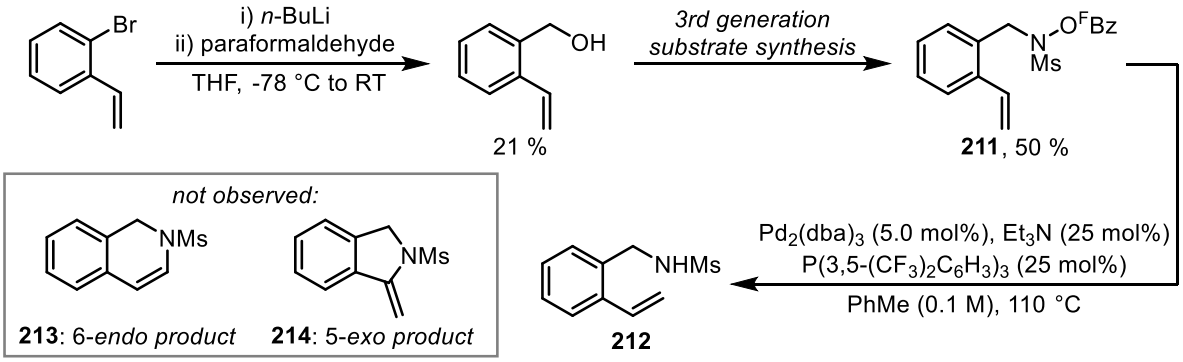
*Scheme 74 – Synthesis and palladium(0)-catalysed cyclisation of substrate **207**.*

While substrate **207** was relatively successful, further improvements to the yield of the 6-*exo* cyclisation were sought. It was considered that a more electron-rich alkene might result in a more efficient reaction, as the alkene is formally the nucleophilic component. To investigate this hypothesis, substrate **209**, bearing electron-donating methoxy groups on the arene, was synthesised (Scheme 75). However, when **209** was subjected to the aza-Heck reaction conditions, a negligible amount of **210** was observed in the ^{1}H NMR spectrum of the crude material (Scheme 75). The poor result in the case of **209** could be attributed to a number of factors: it is possible that the hypothesis is wrong, and electron-rich alkenes are actually less suitable partners in the aza-Heck reaction. Alternatively, the fact that **209** contains an (*E*)-alkene compared to the (*Z*)-alkene in **207** could have been responsible for the low yield observed. Finally, the electron-rich styrene in **209** could have been too unstable to tolerate the reaction conditions, and the substrate may have simply decomposed.



*Scheme 75 – Synthesis and attempted cyclisation of substrate **209**.*

A further styrenyl substrate was prepared (**211** in Scheme 76), and although it was hoped that it would undergo 6-*endo* cyclisation to afford **213**, the generation of 5-*exo* product **214** was also considered likely. As long as the enamine products were sufficiently stable to hydrolysis, either **214** or **213** would have been good additions to the scope of cyclisations to form 5- or 6-membered rings, respectively. In the event, neither the *endo*- (**213**) nor the *exo*-product (**214**) was formed when **211** was exposed to the aza-Heck conditions, and only protodepalladation product **212** was observed in the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 76).



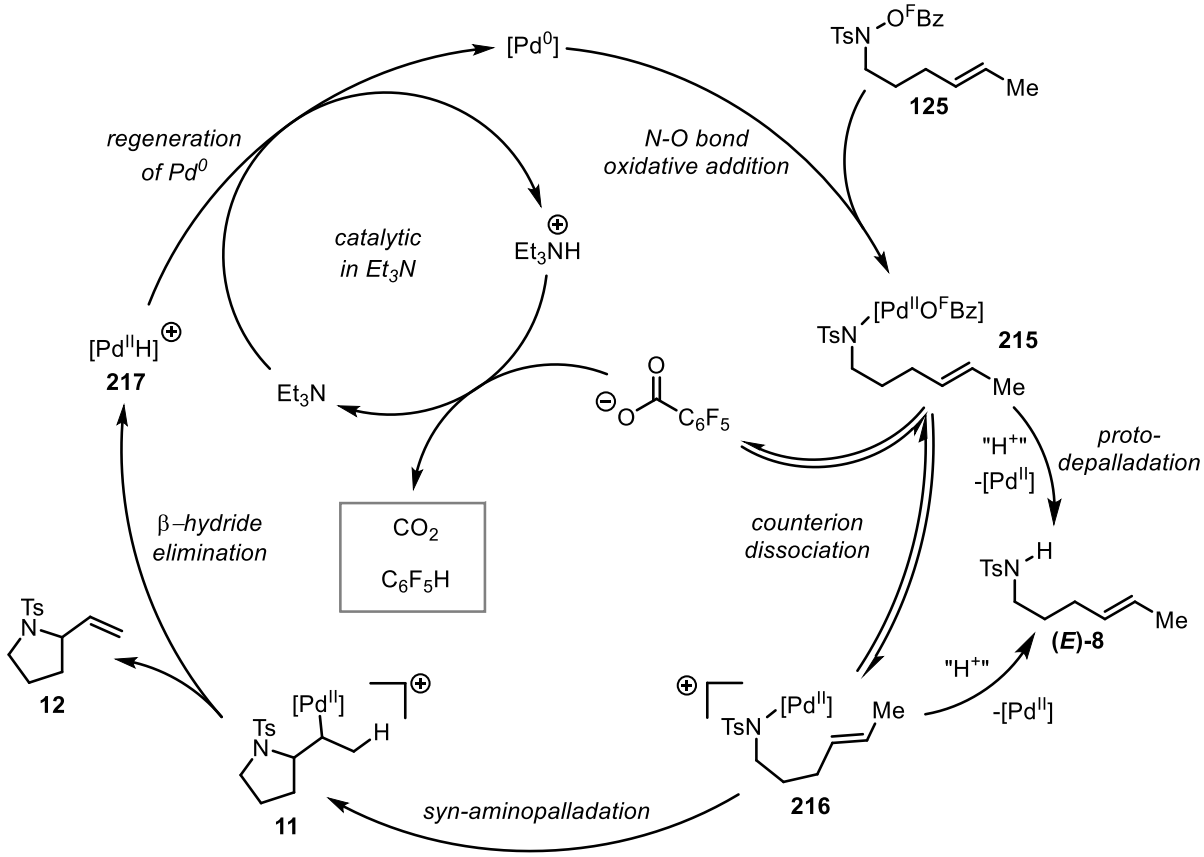
*Scheme 76 – Synthesis and attempted cyclisation of substrate **210**.*

Despite extensive efforts to form 6-membered rings using the aza-Heck cyclisation, this remains a significant limitation of the sulfonamide-based methodology, even taking into account the modest success obtained with **202** and **207** (Scheme 73 and Scheme 74). As will be seen in Chapter 3, this problem was solved with the development of a carbamate-based aza-Heck reaction.

2.5 Mechanistic investigations

A detailed mechanism for the sulfonamide-based aza-Heck cyclisation presented in this chapter is given in Scheme 77. This mechanism is based partly on work carried out on the *O*-pentafluorobenzoyl oxime ester system previously reported by our group[104] and partly on observations obtained during the work detailed in this chapter. In the first step of the catalytic cycle, substrate **125** undergoes oxidative addition with a palladium(0) complex, likely to be $Pd^0[P(3,5\text{-}(CF_3)_2C_6H_3)_3]_2$, to afford neutral intermediate **215**, which lies in equilibrium with cationic complex **216**. *syn*-Aminopalladation from **216** generates intermediate **11**, and **11** then undergoes β-hydride elimination to release product **12** and palladium(II) hydride species **217**. Base-mediated reductive elimination regenerates palladium(0) from **217** and closes the catalytic cycle. It is likely to be complex **216** from which *syn*-aminopalladation proceeds to afford **11**, based on the observation that addition of excess pentafluorobenzoate inhibits the cyclisation of oxime ester-based systems.[104] While protodepalladation (to afford **(*E*)-8**) could conceivably occur from either **215** or **216**, it has been suggested that, at least for the oxime ester-based system, protodepalladation predominantly occurs from a neutral complex analogous to **215**.[104] Throughout the

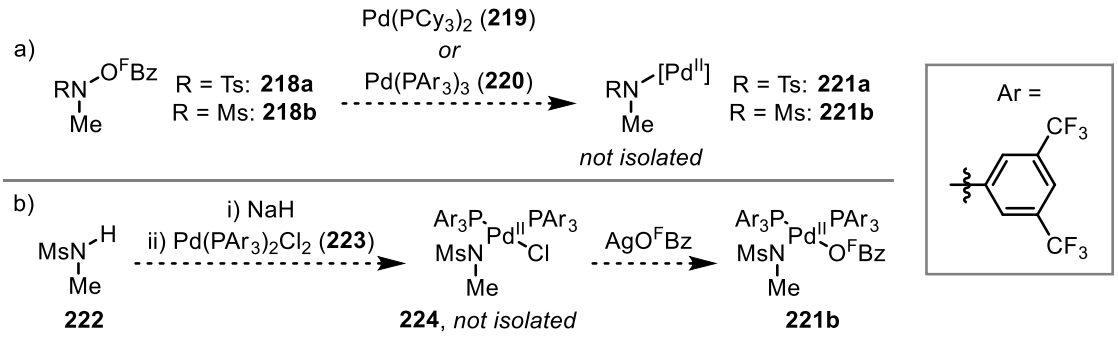
examination of the scope of this reaction, substoichiometric quantities of Et_3N have been used; based on the assumption that one equivalent of $^{F}BzOH$ is produced as a by-product of this reaction, this might seem to be insufficient. However, as previously reported,[104] the triethylammonium salt of pentafluorobenzoate decomposes *via* a surprisingly facile protodecarboxylation reaction to afford C_6F_5H and CO_2; the observation of C_6F_5H in crude reaction mixtures by ^{19}F NMR spectroscopy confirms that this decomposition is operative in the case of the sulfonamide-based reaction. The protodecarboxylation reaction clears pentafluorobenzoate, which would otherwise inhibit subsequent turnovers, from the reaction mixture and regenerates Et_3N, allowing catalytic quantities of the base to be used.



Scheme 77 – Proposed catalytic cycle for the sulfonamide-based aza-Heck reaction.

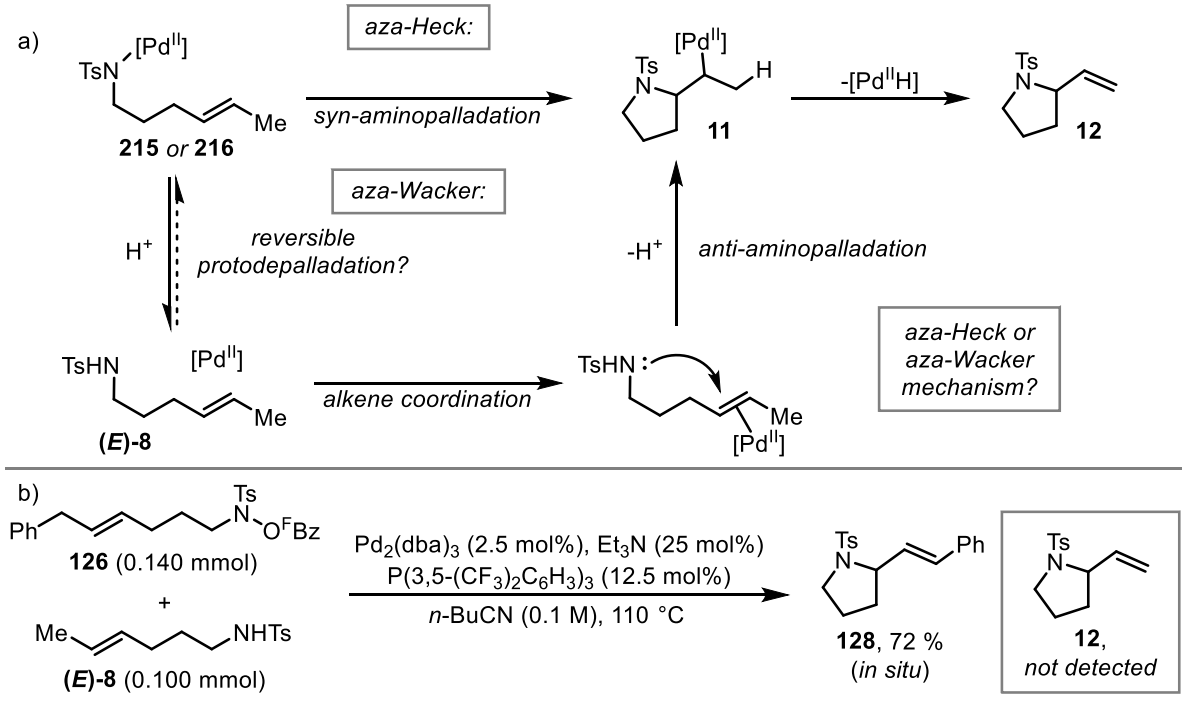
Hartwig[136] and Stahl[137] have confirmed the oxidative addition step in palladium-catalysed reactions of oxime esters by crystallising the resulting iminopalladium(II) products. Inspired by this work, attempts were made to isolate the products of oxidative addition by reacting substrates **218a** and **218b** (*see the experimental section*) with stoichiometric equivalents of palladium(0) complexes (Scheme 78a). These substrates cannot undergo cyclisation, as they lack a pendant alkene, and, in theory, complexes **221a** and **221b** could be isolated if stable enough. However, this was not possible, despite numerous attempts using the palladium(0) complexes **219** and **220**; analysis of the ^{31}P NMR spectra of these reactions showed that complex mixtures were forming in each case. In order to identify **221b** in these reaction mixtures, the synthesis of an authentic sample was undertaken (Scheme 78b). Unfortunately, in spite of

there being some literature precedence for similar transformations,[133] in this case, reaction of the sodium salt of **222** with palladium(II) complex **223** failed to generate target complex **224**.



*Scheme 78 – a) Attempted isolation of oxidative addition products **221a** and **221b**. b) Attempted synthesis of an authentic sample of **221b**.*

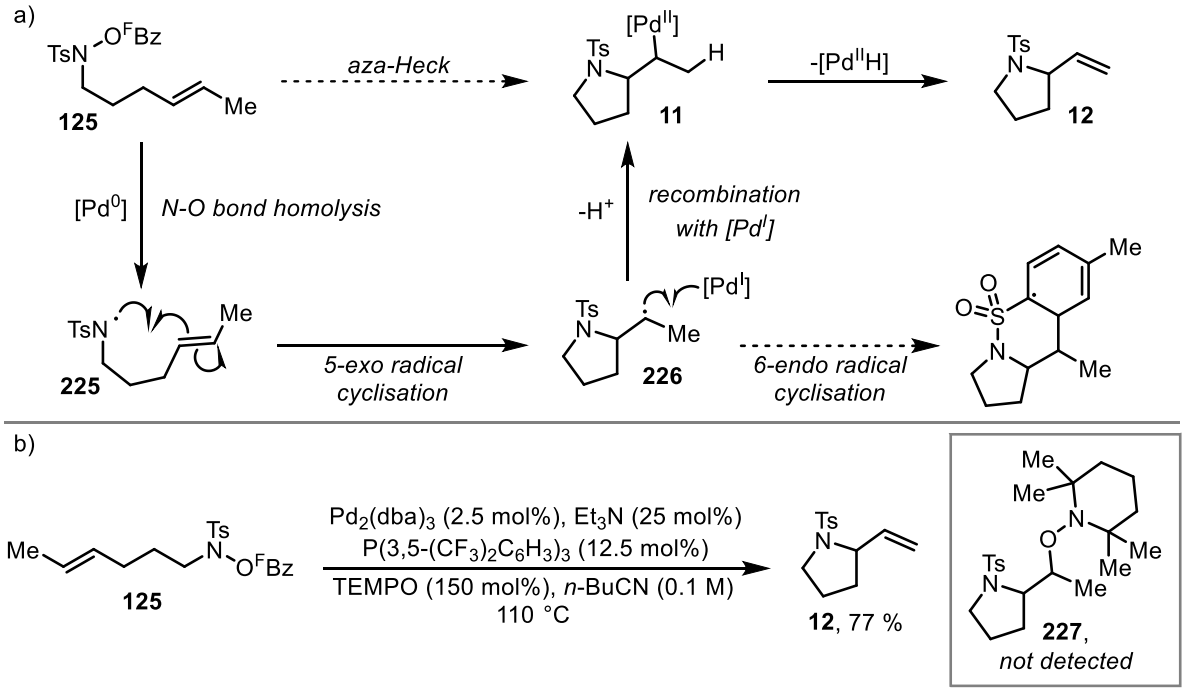
Despite there being good evidence for many elements of the catalytic cycle presented in Scheme 77, there are a number of possibilities for the route taken in going from **125** to **11**. One possibility is that **11** is formed *via* aza-Wacker cyclisation of protodepalladation product **(*E*)-8** (Scheme 79a); in this case, rather than being an aza-Heck reaction, it would be more accurate to describe it as an aza-Wacker reaction using an N–O bond as the terminal oxidant. A simple experiment to determine whether or not the cyclisation proceeds, even in part, through an aza-Wacker mechanism is to conduct a cross-over experiment in the presence of an NH sufonamide. To this end, **(*E*)-8** was prepared (*see the experimental section*) and subjected to the aza-Heck conditions in the presence of **126** (Scheme 79b). Cyclisation to afford **128** was observed in a similar yield to the reaction without **(*E*)-8** (Scheme 45, Section 2.4.1), and



*Scheme 79 – a) Comparison of aza-Heck and aza-Wacker mechanisms for the formation of **11**. b) Palladium(0)-catalysed cyclisation of substrate **126** in the presence of **(E)-8**.*

12 was not observed. This result rules out an aza-Wacker mechanism and also implies that the reverse of protodepalladation does not occur readily, at least in reactions which proceed in good yield.

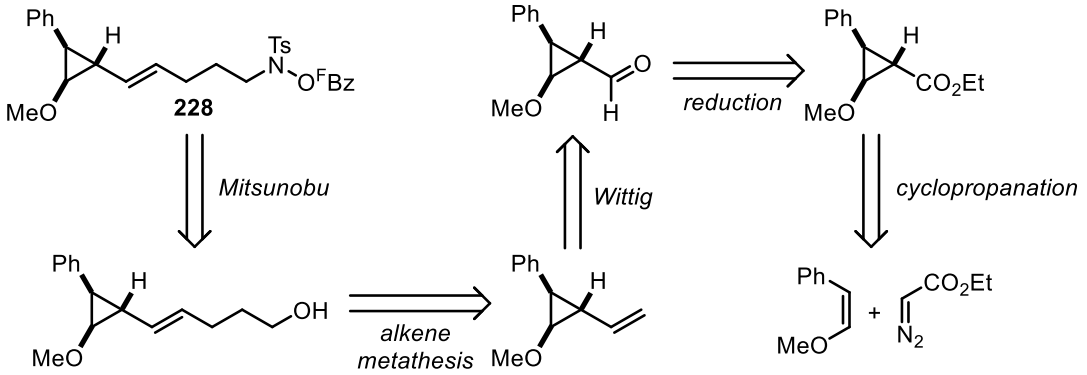
The formation of **11** through a radical pathway is also possible (Scheme 80a). In this scenario, palladium(0)-mediated N–O bond homolysis of **125** generates intermediate **225**, which undergoes radical cyclisation to afford **226**. Carbon radical **226** then recombines with a palladium(I) species to produce key intermediate **11**.[XVI] Previous work from within the group has demonstrated that palladium(0) systems can lead to the generation of nitrogen radicals from oxime esters,[120] although this required electron-donating ligands, as opposed to the electron-withdrawing ligands used for aza-Heck cyclisations. A radical-based mechanism is also considered unlikely as carbon radicals similar to **226** undergo cyclisation onto the arene of the tosyl group fairly readily (Scheme 41, Section 2.3.2). Furthermore, when the cyclisation of **125** was conducted in the presence of TEMPO, trapping product **227** was not observed (Scheme 80b). However, in order to completely rule out a radical pathway, an experiment was carried out using a substrate bearing a radical probe (**228**).[139,140]



*Scheme 80 – a) Comparison of aza-Heck and radical mechanisms for the formation of **11**. b) Palladium(0)-catalysed cyclisation of substrate **125** in the presence of TEMPO.*

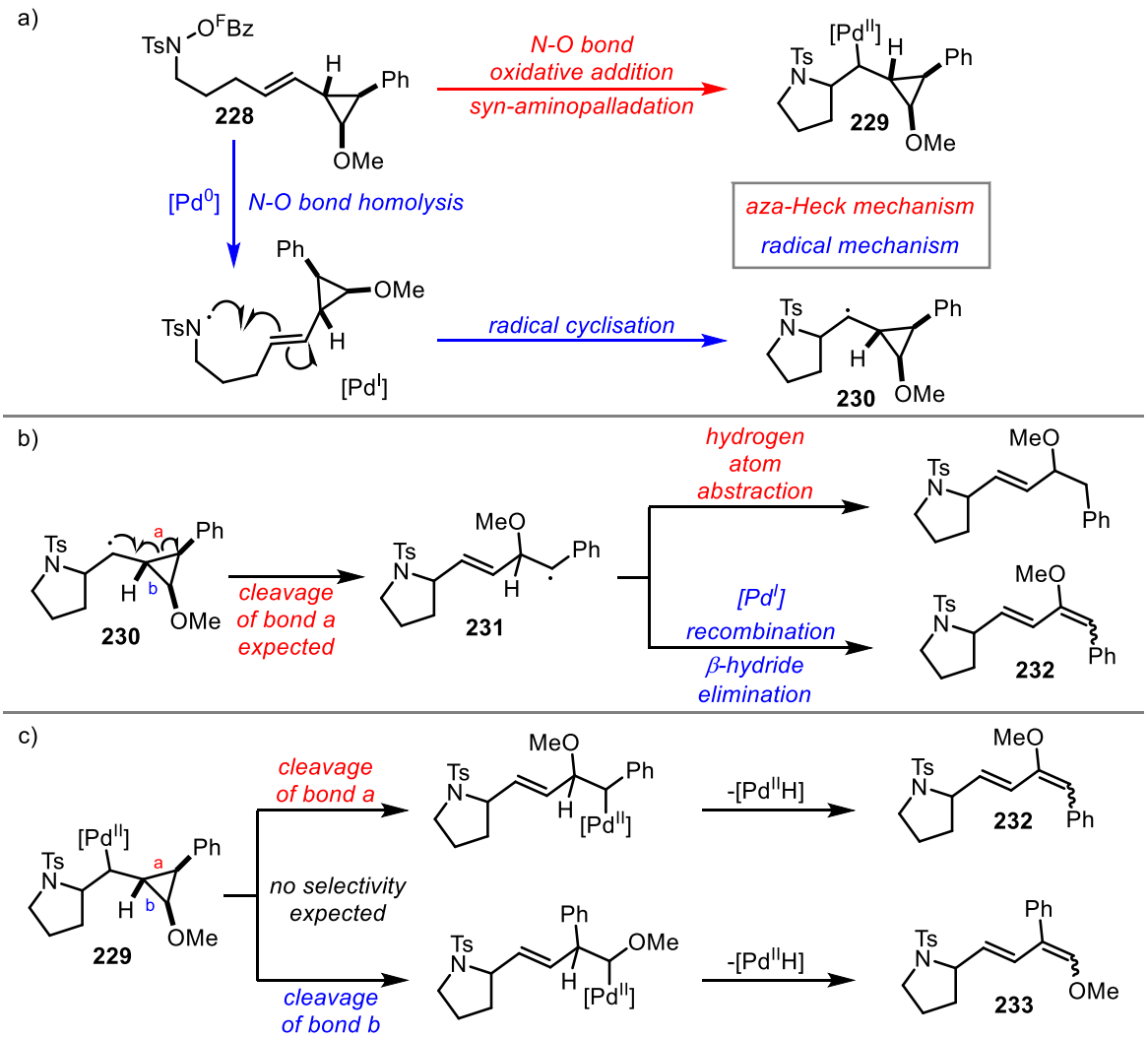
Substrate **228** was prepared by the route detailed in Scheme 81.[XVII] The trisubstituted cyclopropane of **228** enables differentiation of cyclopropane ring opening proceeding *via* radical or β-carbon elimination mechanisms (Scheme 82).[120] In the case of a radical mechanism, intermediate **230** would be unstable

[XVI] An analogous mechanism has been shown to be operative in a copper-catalysed aza-Heck-like cyclisation of oxime esters.[138]
[XVII] Substrate **228** was prepared by Dr Xiaofeng Ma (University of Bristol).



*Scheme 81 – Retrosynthesis of substrate **228**.*

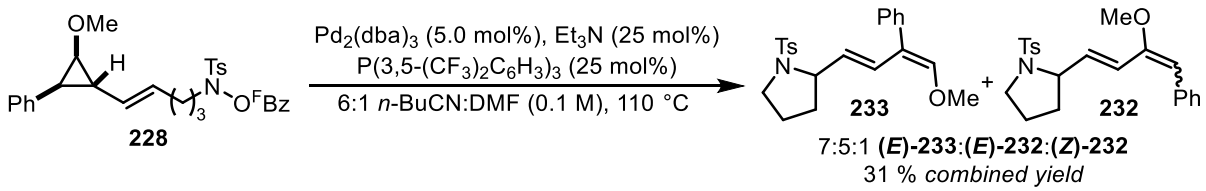
due to the presence of the carbon radical adjacent to the cyclopropane ring. Cleavage of bond A in **230** would be expected to afford **231** selectively, where the radical is stabilised by the phenyl group (Scheme 82b). Previous work has shown that in radical cyclisations, intermediates analogous to **231** can abstract a hydrogen atom from another species in the reaction mixture.[120] However, in order for the



*Scheme 82 – a) Formation of intermediates **229** and **230** in aza-Heck and radical cyclisations, respectively. b) Expected products from a radical cyclisation of substrate **228**. c) Expected products from an aza-Heck cyclisation of substrate **228**.*

mechanism to be consistent with the observed generation of aza-Heck products, **231** would have to recombine with palladium(I) and undergo β-hydride elimination to afford **232**. Similar to intermediate **230**, organopalladium(II) intermediate **229** is also unstable to cyclopropane opening, although the β-carbon elimination step occurs with essentially no selectivity for cleavage of either bond A or bond B (Scheme 82c).[120]

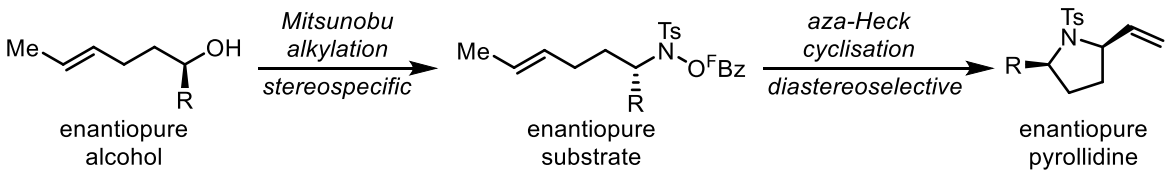
When substrate **228** was exposed to the reaction conditions, a yield of 31 % of **232** and **233** was obtained in an approximately 1:1 ratio (Scheme 83). The lack of selectivity observed in the cyclopropane cleavage indicates that the mechanism does not proceed *via* radical intermediate **230**, and these results are consistent with those obtained in the aza-Heck cyclisation of oxime esters.[120]



*Scheme 83 – Palladium(0)-catalysed cyclisation of substrate **228**.*

2.6 Conclusions

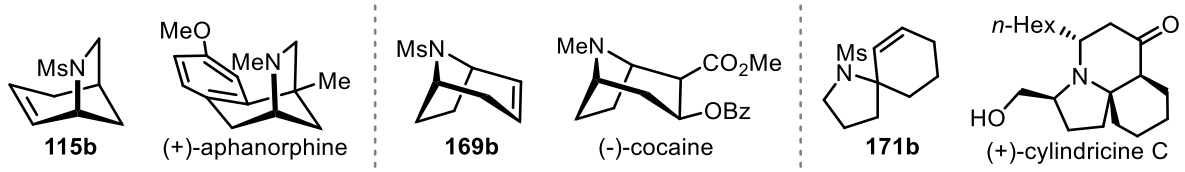
The development of a novel aza-Heck reaction based on *N*-acyloxysulfonamide substrates was successfully achieved; at the time, this was only the second class of aza-Heck reaction reported. The scope of the cyclisation to form simple pyrrolidines is comparable to that available with aza-Wacker cyclisations. However, in addition to the previously mentioned improvements with respect to safety and efficiency associated with an aza-Heck approach (Section 2.1), substrate synthesis is generally more facile compared to aza-Wacker substrates, with substrates being available in one step, rather than two, from the requisite alcohol.[XVIII] Furthermore, successful examples of transannular cyclisations affording complex bicyclic ring systems were demonstrated (**115** and **169**, Section 2.4.6), these kinds of products had not been prepared using either aza-Wacker or aza-Heck processes previously.



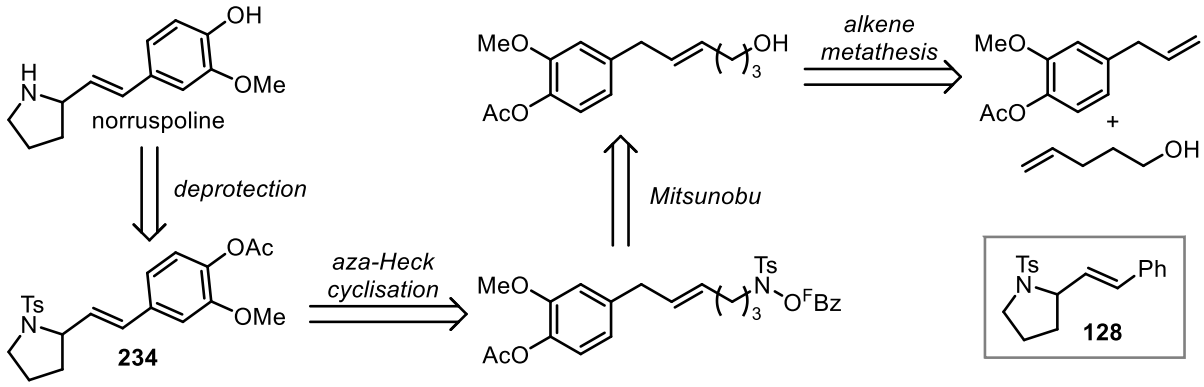
Scheme 84 – Proposed access to enantiopure 2,5-disubstituted pyrrolidines in two steps from enantiopure alcohols.

[XVIII] Aza-Wacker substrates cannot typically be prepared directly from the corresponding alcohol because primary sulfonamides do not participate in Mitsunobu reactions.[141]

As the Mitsunobu reactions to prepare the aza-Heck substrates are enantiospecific (Scheme 33c, Section 2.2.3), and the aza-Heck cyclisations proceed with high levels of diastereoselectivity for α-substituted systems (Section 2.4.2), the preparation of enantiopure 2,5-disubstituted pyrrolidines should be possible from the corresponding enantiopure alcohols (Scheme 84). This could prove beneficial for the application of this methodology to the synthesis of targets containing defined stereocentres.



The bicyclic nitrogen heterocycles presented in Section 2.4.6 are commonly found in the core structures of natural products, for example aphanorphine,[10,11] cocaine[16] and cylindricine C[9] (products **115b**, **169b** and **171b**, respectively). Whereas it is unlikely that **115b** and **171b** could be easily elaborated into aphanorphine or cylindricine C, conversion of **169b** to the *N*-Boc analogue would constitute a formal synthesis of cocaine.[16,142] A comparatively simpler total synthesis is potentially possible for norruspoline[13] (Scheme 85), as global deprotection of **234**, analogous to **128** (Section 2.4.1), would afford the natural product.



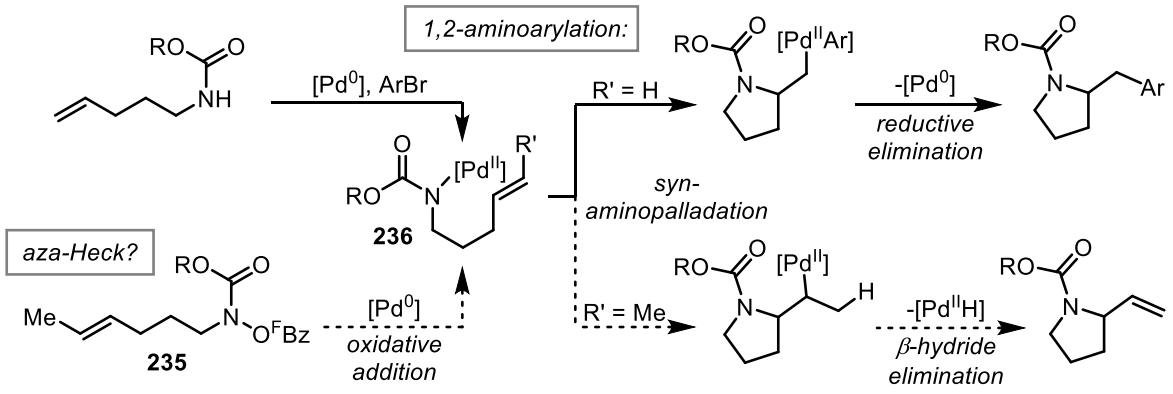
Scheme 85 – Proposed total synthesis of norruspoline.[13]

Chapter 3 - Aza-Heck reactions of *N*-acyloxycarbamates

The contents of this chapter have been communicated: Hazelden, I. R.; Carmona, R. C.; Langer, T.; Pringle, P. G.; Bower, J. F. *Angew. Chem. Int. Ed.* **2018**, *57*, 5124-5128. Parts of this chapter have been reproduced from the aforementioned publication.

3.1 Introduction

A major drawback to the sulfonamide-based reaction described in the previous chapter is the difficulty associated with the deprotection of the products. It is generally possible to remove *N*-tosyl groups under reductive conditions, although removal of *N*-mesyl groups is harder.[XIX] Comparatively, carbamate protecting groups are a far more flexible alternative. Wolfe has reported a number of 1,2-aminoarylation processes that involve the cyclisation of carbamate-based substrates (Section 1.3). These reactions are proposed to proceed through *syn*-aminopalladation of intermediate **236**. Consequently, aza-Heck cyclisation of substrate **235** ought to be possible, as long as access to **236** can be achieved through oxidative addition (Scheme 86). Despite this, the development of aza-Heck reactions of carbamate-protected substrates proved more difficult than the sulfonamide-based reaction (*vide infra*).



Scheme 86 – Proposed aza-Heck reactions of carbamate-based substrates.

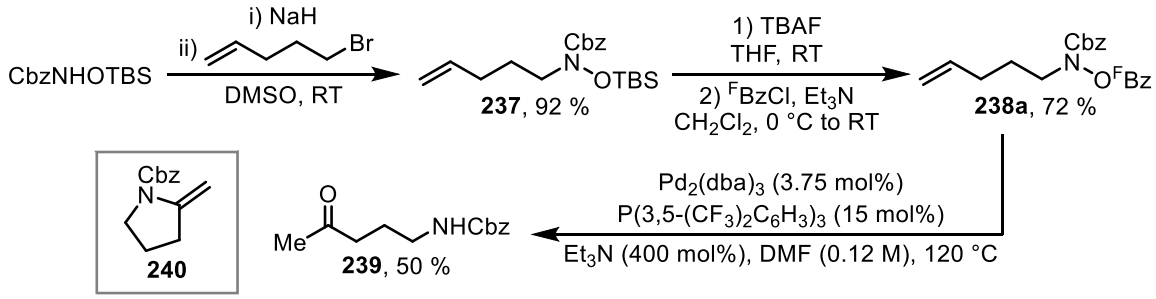
3.2 Development of *N*-acyloxycarbamate-based aza-Heck reactions

3.2.1 Reaction discovery

During the early stages of the development of the sulfonamide-based aza-Heck reaction (Chapter 2), the use of other *N*-protecting groups was investigated. To this end, simple *N*-Cbz system **238a** was prepared (Scheme 87). In contrast to the synthesis of *N*-tosyl-protected substrates, TBAF can be used

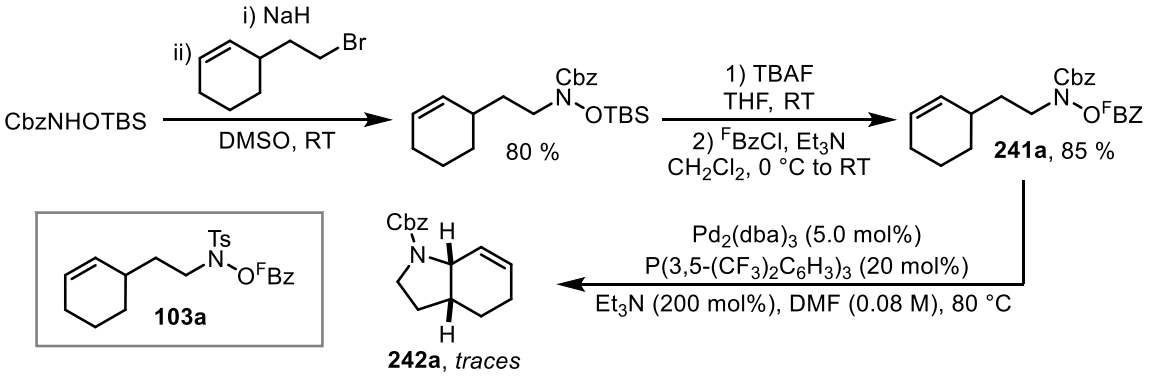
[XIX] The book *Protective Groups in Organic Synthesis* contains over 20 times as many references for *N*-tosyl removal than *N*-mesyl removal.[116]

to effect *O*-TBS cleavage of **237**, as elimination of the carbamate protecting group is not possible from the resulting *O*-anion (*cf.* Scheme 24c, Section 2.2.1). When subjected to conditions previously identified as effective for promoting aza-Heck cyclisation of oxime esters,[101] **238a** provided ketone **239** in 50 % yield, most likely *via* hydrolysis of the initial aza-Heck cyclisation product **240**. Compared to the attempted cyclisation of analogous *N*-tosyl substrate **79** (Scheme 35, Section 2.3.1), the yield of ketone **239** was lower, indicating that the desired reaction proceeds less efficiently.



*Scheme 87 – Synthesis and attempted cyclisation of substrate **238a**.*

Although *N*-tosyl system **79** generated a more promising result than that achieved with **238a**, the feasibility of a carbamate-based aza-Heck process was examined further. Substrate **241a**, which is analogous to **103a**, was prepared for this purpose (Scheme 88). The cyclisation of **241a** was evaluated under conditions effective for the cyclisation of **103a**; however, a negligible amount of target **242a** was observed (Scheme 88, *cf.* 60 % with **103a**, Table 2, entry 4, Section 2.3.3). With only limited success forthcoming from *N*-carbamate-protected substrates, the development of the sulfonamide-based cyclisation was therefore prioritised.

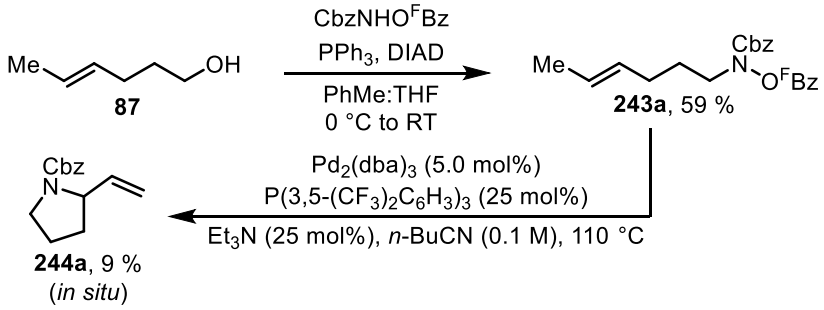


*Scheme 88 – Synthesis and attempted cyclisation of substrate **241a**.*

Following the completion of the work detailed in Chapter 2, it was decided to re-examine other protecting groups due to the limitations of the sulfonamide-based reaction. As some indication of the feasibility of the cyclisation of *N*-Cbz-protected substrates had been observed (Scheme 87), this class of reaction was revisited. Substrate **243a** was prepared by Mitsunobu alkylation of CbzNHO^{F}Bz[XX] and

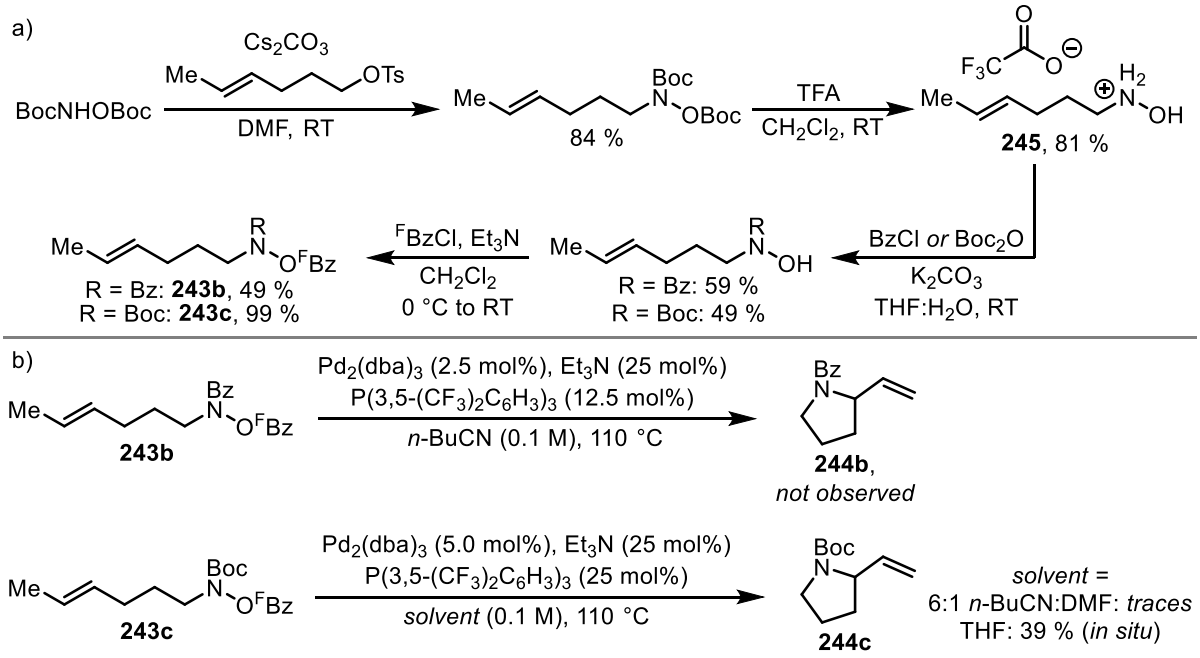
[XX] CbzNHO^{F}Bz was prepared by Dr Xiaofeng Ma (University of Bristol) according to a reported procedure.[117]

trialled in the aza-Heck reaction (Scheme 89). Under reaction conditions found to be optimal for the sulfonamide-based system (Section 2.3.3), substrate **243a** afforded a poor yield of the pyrrolidine **244a**. With disappointing results obtained with substrates bearing an *N*-Cbz group, attention turned to other protecting groups.



*Scheme 89 – Synthesis and palladium(0)-catalysed cyclisation of substrate **243a**, using conditions optimised for the sulfonamide-based aza-Heck reaction.*

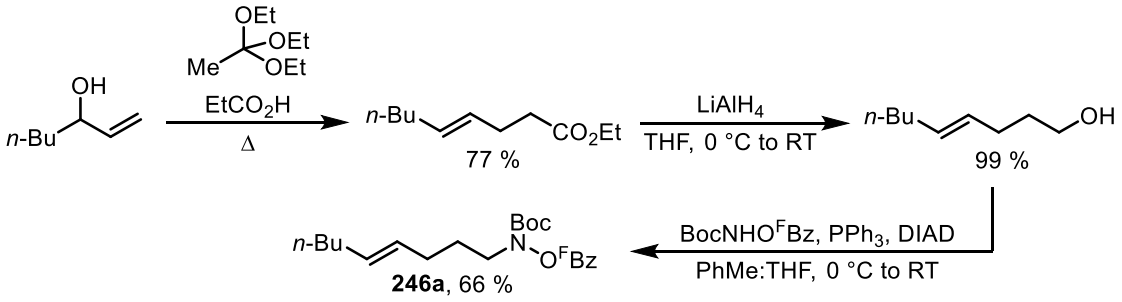
In order to assess the viability of further *N*-protecting groups, common precursor **245** was prepared (Scheme 90a). From **245**, substrates containing an *N*-benzoyl (**243b**) and an *N*-Boc (**243c**) group were synthesised. With these substrates in hand, aza-Heck cyclisation was attempted (Scheme 90b). When **243b** was submitted to the previously optimised conditions (Section 2.3.3), it appeared to be relatively unreactive, and product **244b** was not obtained. In contrast, substrate **243c** did generate **244c**, and a brief solvent screen identified that THF led to a substantially improved yield (39 %). However, **244c** could not be successfully purified, and the isolated yield did not match that determined by ^{1}H NMR analysis of the crude mixture.



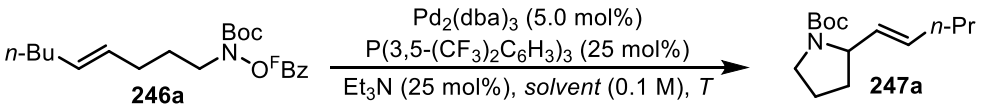
*Scheme 90 – a) Synthesis of substrates **243b** and **243c**. b) Attempted cyclisation of substrates **243b** and **243c**.*

3.2.2 Optimisation

Purification of **244c** was likely complicated by its volatility;[143] consequently, a substrate of higher molecular mass was targeted, and *n*-butyl system **246a** was prepared (Scheme 91). Optimisation of the cyclisation of **246a** initiated with a solvent screen (Table 7), which demonstrated that the reaction is viable in a wide range of solvent polarities (Table 7, entries 1-3 and 5), and identified THF as being optimal (Table 7, entry 2). The effects of reaction temperature were less pronounced (Table 7, entries 7-12), with the best result being achieved at 130 °C (Table 7, entry 10).



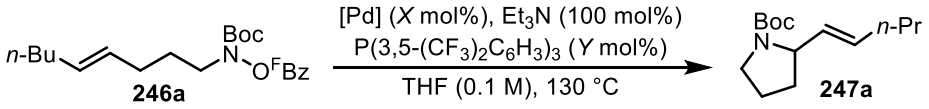
*Scheme 91 – Synthesis of substrate **246a**.*



Entry	*solvent*	*temperature*	*yield*
1	*n*-BuCN	110 °C	56 %
2	THF	110 °C	63 %
3	DMF	110 °C	46 %
4	MeCN	110 °C	17 %
5	dioxane	110 °C	58 %
6	$(CF_3)_2CHOH$	110 °C	*not observed*
7	THF	95 °C	59 %
8	THF	110 °C	63 %
9	THF	125 °C	63 %
10	THF	130 °C	64 %
11	THF	140 °C	64 %
12	THF	150 °C	60 %

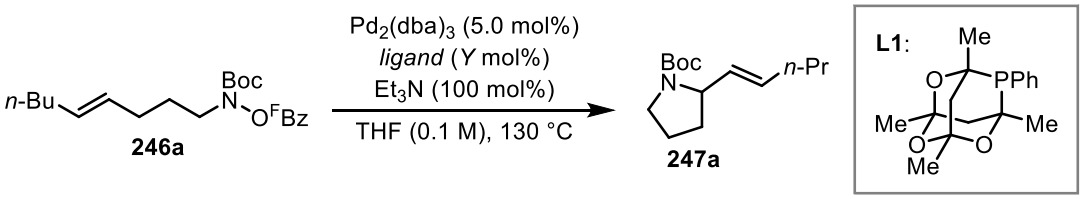
*Table 7 – Optimisation of solvent and temperature in the palladium(0)-catalysed cyclisation of substrate **246a**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard.*

Following optimisation of solvent and temperature, a screen of palladium sources was undertaken (Table 8), which confirmed $Pd_2(dba)_3$ as the optimal precatalyst (Table 8, entry 1). While $Pd(OAc)_2$ gave a comparable yield of **247a** (Table 8, entry 4), $Pd[P(3,5\text{-}(CF_3)_2C_6H_3)_3]_2Cl_2$ failed to generate any product (Table 8, entry 3). This is potentially due to the presence of chloride ions preventing access to the cationic intermediate (analogous to **216**) as proposed in the mechanism presented in Scheme 77 (Section 2.5).



Entry	[Pd]	*X*	*Y*	*yield*
1	$Pd_2(dba)_3$	5.0	25	65 %
2	$Pd[P(3,5\text{-}(CF_3)_2C_6H_3)_3]_3$	10	*none*	49 %
3	$Pd[P(3,5\text{-}(CF_3)_2C_6H_3)_3]_2Cl_2$	10	*none*	*not observed*
4	$Pd(OAc)_2$	10	25	59 %

*Table 8 – Optimisation of palladium source in the cyclisation of substrate **246a**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard.*

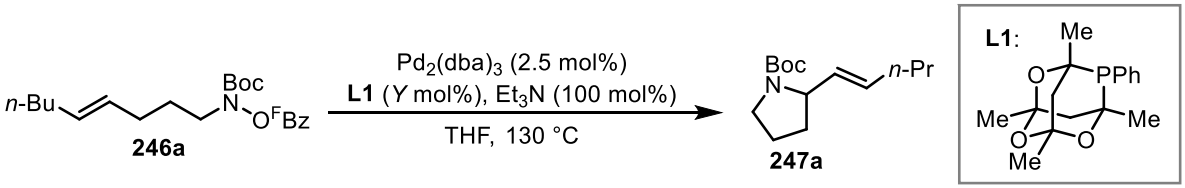


Entry	*ligand*	*Y*	*yield*
1	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	25	65 %
2	PPh_3	25	62 %
3	$AsPh_3$	25	*not observed*
4	$P(4\text{-}(CN)C_6H_4)_3$	25	74 %
5	$P(4\text{-}(CF_3)C_6H_4)_3$	25	(75 %)
6	$P(4\text{-}(F)C_6H_4)_3$	25	(75 %)
7	$P(3,4,5\text{-}(F)_3C_6H_4)_3$	25	72 %
8	$P(C_6F_5)_3$	25	*not observed*
9	**L1**	25	82 %
10	dppb	10	19 %

*Table 9 – Ligand screen for the palladium(0)-catalysed cyclisation of substrate **246a**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses.*

Next, the effects of varying the phosphine ligand were examined (Table 9). In comparison to the sulfonamide-based aza-Heck reaction (Section 2.3.3), a greater number of ligands were found to be effective for the cyclisation of **246a**. The electron-deficient and sterically hindered trioxaphosphaadamantane ligand **L1** (cone angle: 202°,[144] compared to PPh_3: 145° and P*t*-Bu_3: 182°)[145] provided the best result (Table 9, entry 9). Although electron-deficient phosphine ligands were most effective in the cyclisation (Table 9, entries 4-7 and 9), a yield of 62 % of **247a** could be achieved with PPh_3 (Table 9, entry 2). Similar to what was observed in the sulfonamide-based reaction (Section 2.3.3), bidentate ligands, *e.g.* dppb, failed to provide significant yields of **247a** (Table 9, entry 10).

Having optimised the other parameters, the precatalyst loading was lowered to 2.5 mol%, and the effects of concentration and ligand loading were examined (Table 10). Higher concentrations led to better results (Table 10, entries 1-4), although the use of concentrations higher than 1.0 M was not considered practical due to the small scale at which the reactions were carried out on. Finally, it was found that a yield of 85 % of **247a** could be achieved by increasing the ligand to palladium ratio from 2:1 to 3:1 (Table 10, entry 6).



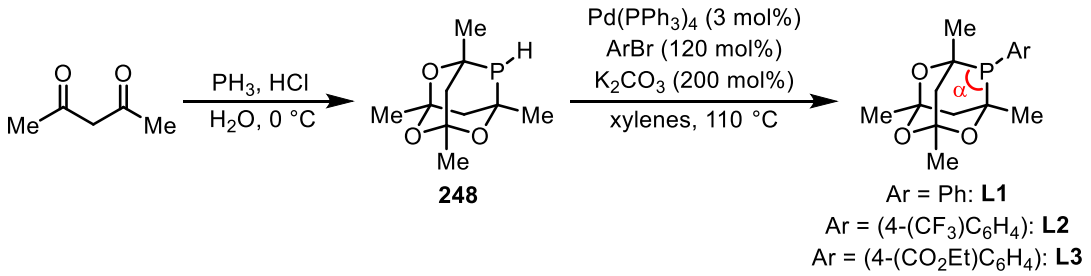
Entry	*concentration*	*Y*	*yield*
1	0.1 M	10	72 %
2	0.2 M	10	78 %
3	0.4 M	10	80 %
4	1.0 M	10	80 %
5	0.4 M	12.5	81 %
6	0.4 M	15	(85 %)

*Table 10 – Optimisation of concentration and palladium to ligand ratio in the cyclisation of substrate **246a**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses.*

3.2.3 Properties of trioxaphosphaadamantane ligands

Although phosphine ligands containing alkyl substituents are typically considered to be electron-rich compared to those with aryl substituents, the properties of trioxaphosphaadamantane ligands, such as **L1**, are closer to those of phosphonites.[144] The electron-deficient nature of these ligands is proposed to be due to two factors: firstly, the constrained C-P-C angle ($\alpha \approx 90°$ in **L1**)[144] increases the π-acidity

of the phosphorous atom. By fixing the σ*-orbitals in an orientation where there is good overlap with the metal d-orbitals, backdonation from the metal centre is facilitated.[146] Secondly, the electron-withdrawing inductive effect of the oxygen atoms is likely to reduce electron density on the phosphorous atom.[144]



*Scheme 92 – Synthesis of **L1** and analogues from **248** through palladium(0)-catalysed coupling with aryl bromides.*[XXI]

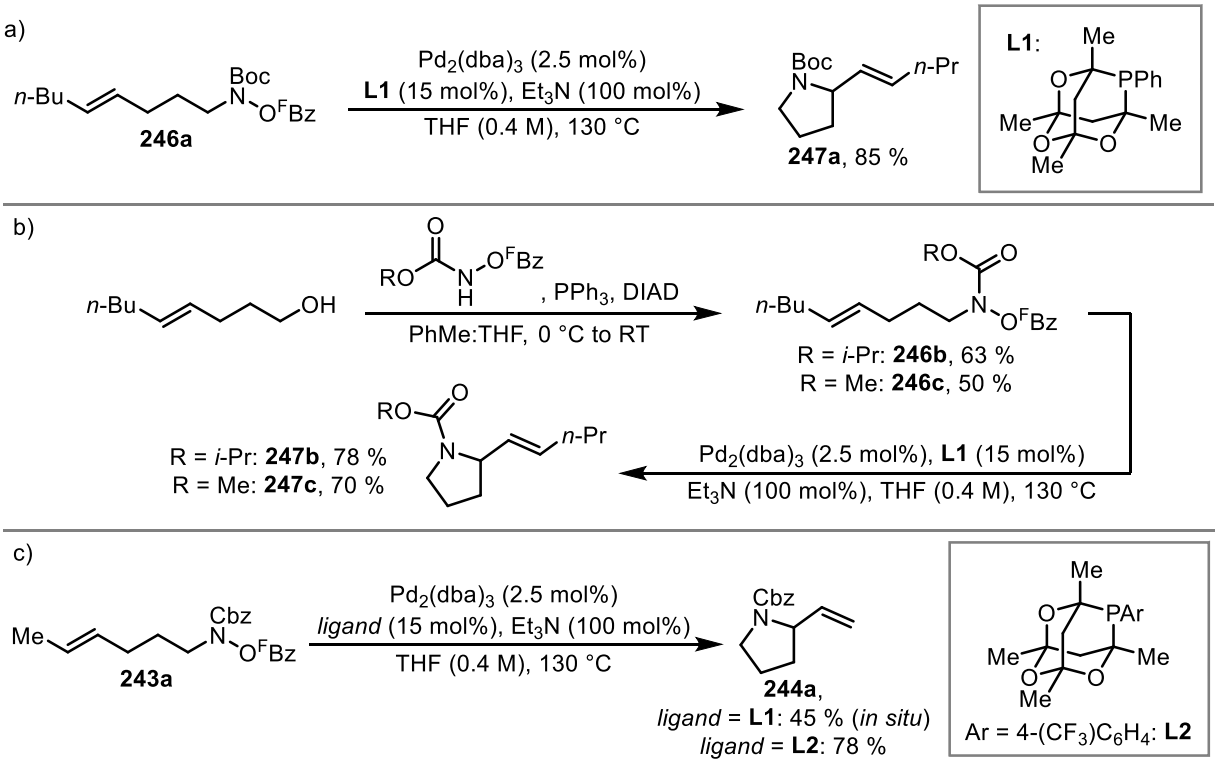
Ligand **L1** is commercially available but can be prepared in one step by condensation of $PhPH_2$ with acetylacetone.[148] Alternatively, condensation of acetylacetone with PH_3 affords the unsubstituted ligand precursor **248** (Scheme 92).[147] Derivatives of **L1** can then be synthesised from **248**[XXI] by coupling with aryl bromides;[149] in this manner, a number of analogues were prepared.[XXII] When used in aza-Heck reactions, ligands **L1**, **L2** and **L3** were found to be the most effective (*vide infra*).

3.3 Substrate scope for 5-*exo* aza-Heck cyclisations

3.3.1 Scope of the carbamate protecting group in the aza-Heck reaction

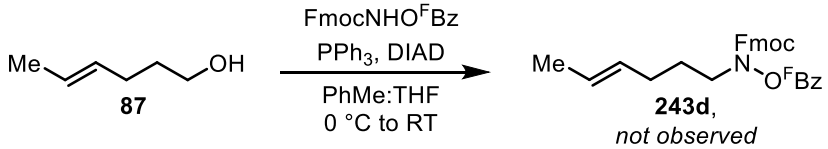
In order to assess the scope of the protecting group, substrates containing *i*-propyl (**246b**) and methyl carbamates (**246c**) were synthesised (Scheme 93b). The cyclisation yield of **246a-c** decreased with decreasing steric bulk of the alkyl group (R in **246**); pyrrolidines **247b** and **247c** were generated in 78 % and 70 % yield, respectively (Scheme 93b), compared to 85 % for **247a** (Scheme 93a). Previously, cyclisations of *N*-Cbz systems were found to proceed in disappointing yields (Section 3.2.1). Despite this, the cyclisation of substrate **243a** was re-examined using the improved conditions (Scheme 93c). While the yield of **244a** was only 45 % using **L1**, a good result was achieved with **L2** in place of **L1**.

[XXI] Phosphine **248** was prepared by Charly Faradji (University of Bristol) according to a literature procedure.[147]
[XXII] Full details are provided in the experimental section.



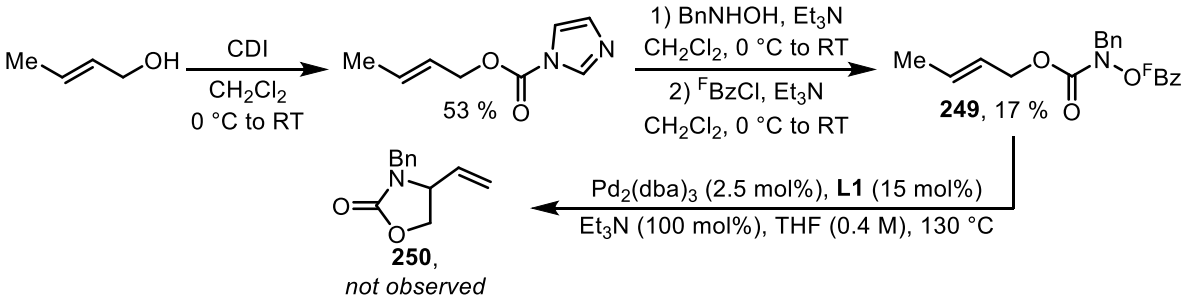
*Scheme 93 – a) Optimised conditions for the palladium(0)-catalysed cyclisation applied to substrate **246a**. b) Synthesis and palladium(0)-catalysed cyclisation of substrates **246b** and **246c**. c) Palladium(0)-catalysed cyclisation of substrate **243a**.*

The cyclisation of *N*-Fmoc system **243d** was also targeted, as this would provide products that could be deprotected under basic conditions, adding another element of orthogonality to the protecting groups suitable for the aza-Heck reaction. Unfortunately, **243d** could not be prepared (Scheme 94), potentially due to the *N*-Fmoc group being unstable under the basic conditions of the Mitsunobu reaction.



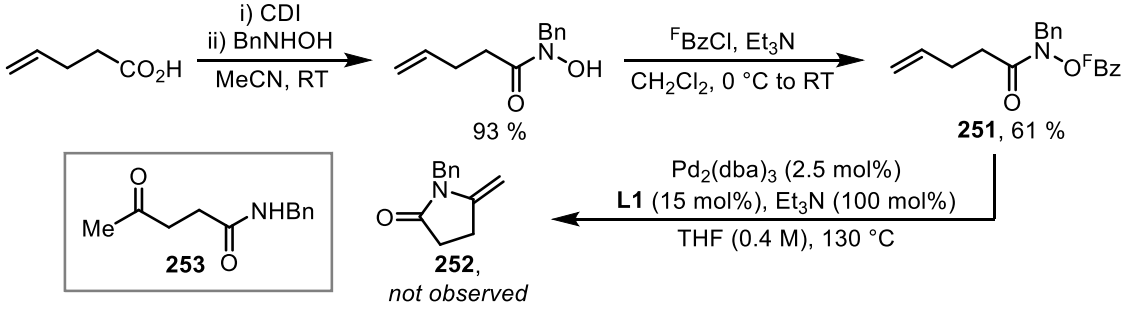
*Scheme 94 – Attempted synthesis of substrate **243d**.*

The possibility of using alkenyl carbamates was investigated with substrate **249** (Scheme 95). However, desired product **250** was not observed when **249** was subjected to the aza-Heck cyclisation conditions. It is conceivable that π-allyl formation competes with oxidative addition into the N–O bond of **249**, as the former process typically occurs at lower temperatures.[150-152]



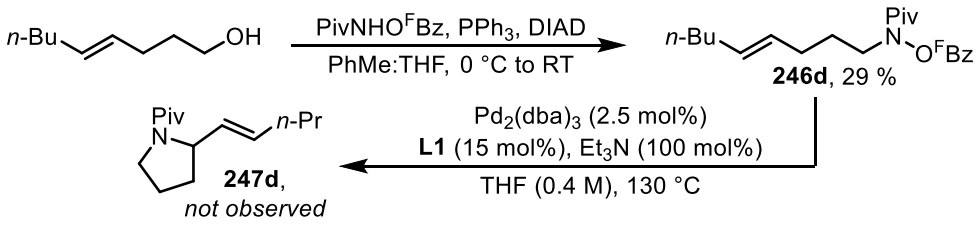
*Scheme 95 – Synthesis and attempted cyclisation of substrate **249**.*

Although *N*-benzoyl-protected substrate **243b** did not participate in the aza-Heck cyclisation under the previously used conditions (Scheme 90b, Section 3.2.1), it was hoped that amide-based substrates would be tolerated following optimisation of the reaction. Substrate **251**, similar to **249** but containing an all-carbon tether, was prepared by sequential *N*- and *O*-acylation of BnNHOH (Scheme 96). However, when **251** was exposed to the aza-Heck conditions, neither lactam **252** nor its hydrolysis product **253** were observed. Watson subsequently reported aza-Heck cyclisations which generate products similar to **252**, but in those reactions, substitution on nitrogen was not tolerated and activation by an *O*-phenyl group was required (Section 1.5.1).[109]



*Scheme 96 – Synthesis and attempted cyclisation of substrate **251**.*

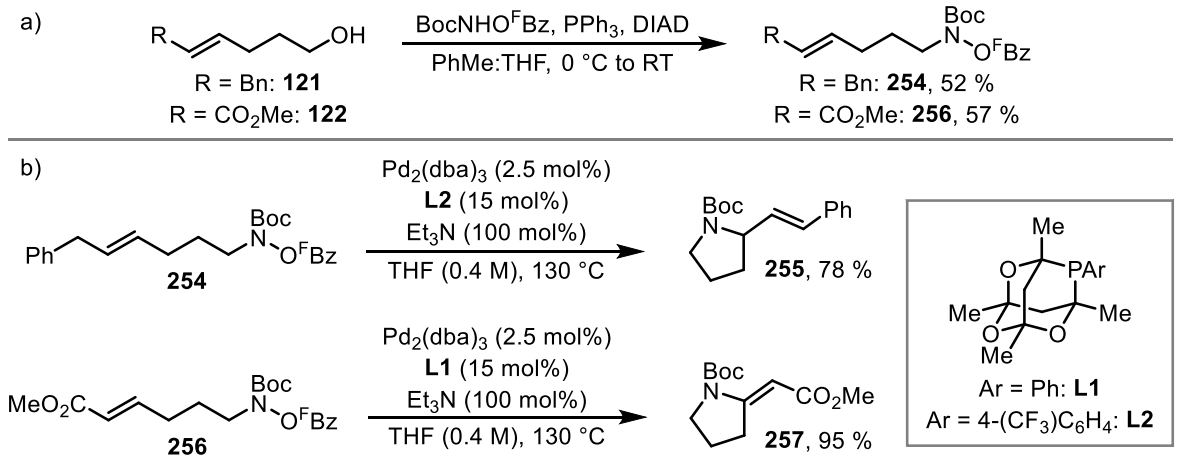
Despite the failure with **251**, the possibility of using *N*-acyloxyamides in the aza-Heck reaction was investigated further. With the observation that protecting groups with greater steric bulk result in higher yielding cyclisations (Scheme 93), *N*-pivaloyl substrate **246d** was prepared and evaluated in the aza-Heck reaction (Scheme 97); unfortunately, target pyrrolidine **247d** was not observed.



*Scheme 97 – Synthesis and attempted cyclisation of substrate **246d**.*

3.3.2 Aza-Heck cyclisations involving 1,2-disubstituted alkenes

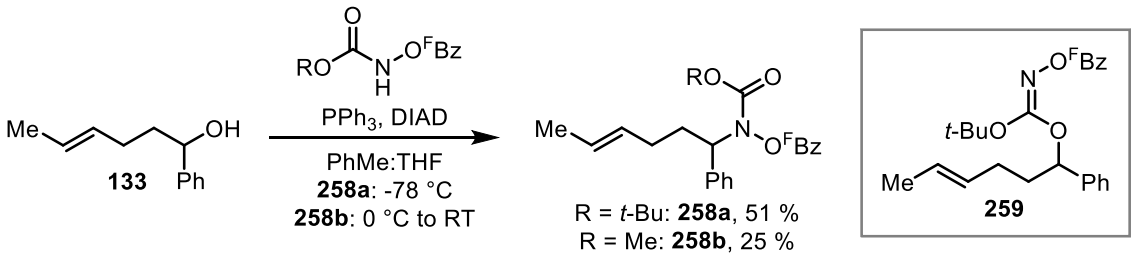
With **243a** and **246a-c** demonstrating the tolerance of methyl and *n*-butyl groups, respectively (Scheme 93, Section 3.3.1), further substrates containing 1,2-disubstituted alkenes were prepared from alcohols **121** and **122** (Scheme 98a). When employed in the aza-Heck cyclisation, **254** performed similarly to the analogous *N*-tosyl substrate **126** (Scheme 98b, *cf.* Scheme 45, Section 2.4.1). In contrast, **256** performed far better, with **257** isolated in 95 % yield (Scheme 98b, *cf.* Scheme 45, Section 2.4.1).



*Scheme 98 – a) Synthesis of substrates **254** and **256**. b) Palladium(0)-catalysed cyclisation of substrates **254** and **256**.*

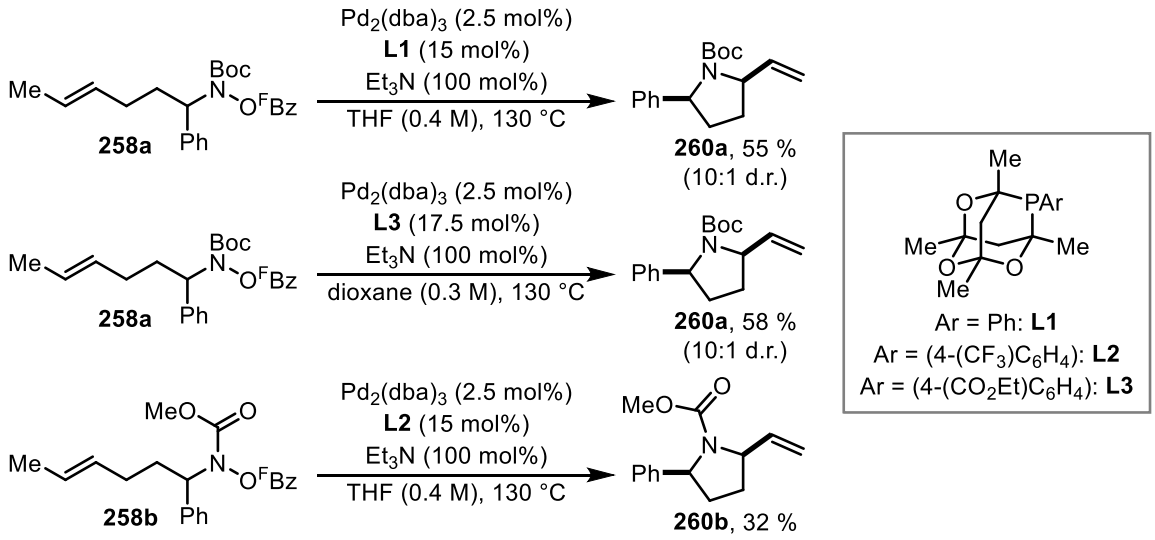
3.3.3 Aza-Heck cyclisations of systems with substitution α, β and γ to nitrogen

Next, the effects of substitution at the α-, β-, and γ-positions of substrates were investigated. The synthesis of carbamate-protected substrate **258a**, containing an α-phenyl substituent, was not straightforward. Initial attempts at Mitsunobu alkylation of **133** with BocNHO^{F}Bz afforded an inseparable mixture of **258a** and another component, suspected to be **259** (Scheme 99). Side product **259** likely arises from competing *O*-alkylation of the anion of BocNHO^{F}Bz. By conducting the reaction at -78 °C, an increased the ratio of **258a** to **259** was obtained, and washing the resulting mixture with acetic acid removed residual **259**. It is conceivable that analogous *O*-alkylated products are also produced in the synthesis of other substrates but are separable from the corresponding *N*-alkylation product; this could partially explain the modest yields typically achieved in the synthesis of substrates in this chapter.



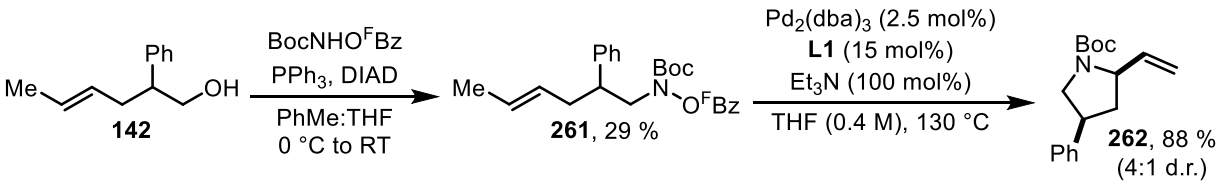
*Scheme 99 – Synthesis of substrates **258a** and **258b**.*

When substrate **258a** was employed in the aza-Heck cyclisation, pyrrolidine **260a** was isolated in only 55 % yield (Scheme 100). By using modified conditions developed subsequently (Section 3.4.2), a slightly improved yield of **260a** was achieved. Reduced yields in cyclisations involving α-substitution were also observed in the sulfonamide-based aza-Heck reaction (Section 2.4.2). In that case, better results were achieved with a smaller protecting group (Scheme 47, Section 2.4.2). However, in the carbamate-based reaction, methyl carbamate substrate **258b** provided a lower yield of **260b** than *N*-Boc system **258a** (Scheme 100).



*Scheme 100 – Palladium(0)-catalysed cyclisation of substrates **258a** and **258b**.*

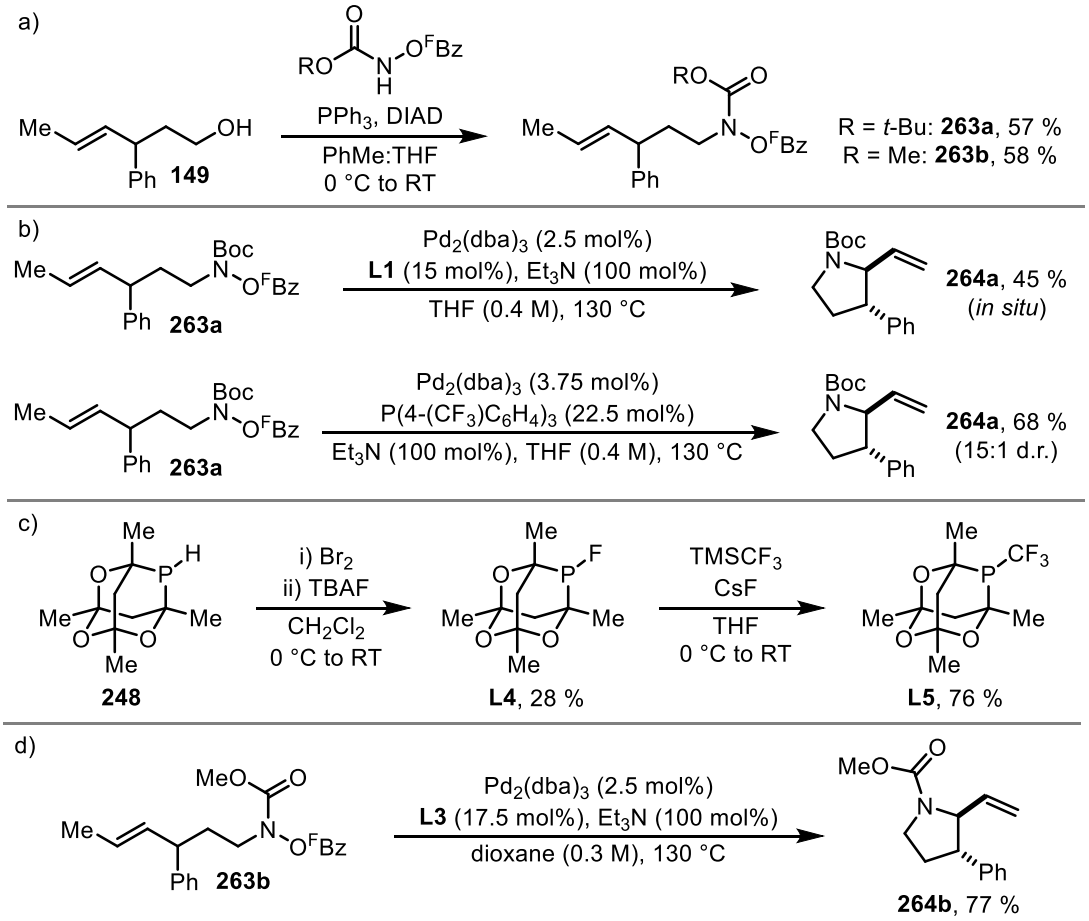
Following this, substrate **261**, which contains substitution at the β-position, was prepared from alcohol **142** (Scheme 101). A low yield was obtained in the Mitsunobu alkylation of **142**, which was typical for alcohols containing β-substitution (*vide infra*), and this constitutes a limitation of the Mitsunobu reaction with carbamate reagents. Substrate **261** cyclised in excellent yield and with acceptable diastereoselectivity (Scheme 101); this is a marked improvement over the results from the sulfonamide-based reaction (Scheme 49, Section 2.4.3).



*Scheme 101 – Synthesis and palladium(0)-catalysed cyclisation of substrate **261**.*

Substitution at the γ-position was then investigated with substrate **263a**, prepared from alcohol **149** (Scheme 102a). Although the use of ligand **L1** led to a poor yield of **264a** (Scheme 102b), P(4-(CF_3)C_6H_4)$_3$ provided a better result (68 %): this might reflect the sterically hindered alkene of **263a** interacting better with a less bulky catalytic system. This observation led to the synthesis of ligands **L4**

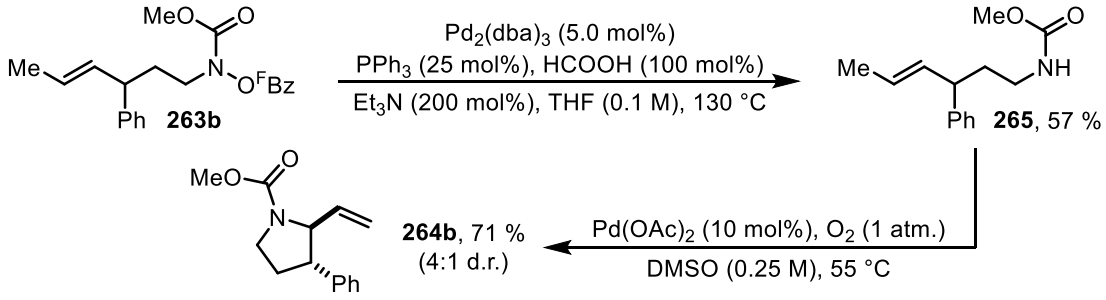
and **L5** (Scheme 102c); however, when used in the aza-Heck cyclisation, **L4** and **L5** failed to improve the yield of **264a**. Ultimately, methyl carbamate substrate **263b** provided the best result, and **264b** was isolated in 77 % yield (Scheme 102d).



*Scheme 102 – a) Synthesis of substrates **263a** and **263b**. b) Palladium(0)-catalysed cyclisation of substrate **263a**. c) Synthesis of ligands **L4** and **L5** from **248**. d) Palladium(0)-catalysed cyclisation of substrate **263b**.*

In order to provide a comparison between the diastereoselectivities achievable in an aza-Heck process *versus* an aza-Wacker process, aza-Wacker substrate **265** was prepared, and its cyclisation was studied (Scheme 103). As mentioned previously (Section 2.6), a major advantage of the aza-Heck reaction is that the substrates can be synthesised in one step from the corresponding alcohol. The difficulty in accessing aza-Wacker substrates is further demonstrated by the fact that is far simpler to prepare **265** from **263b**, by adding formic acid to the aza-Heck reaction conditions, than it would be to prepare it by another route. With **265** in hand, two sets of aza-Wacker conditions were evaluated. Using a procedure reported by Andersson,[26] the cyclisation of **265** to **264b** proceeded in 71 % yield and 4:1 d.r. (Scheme 103). Under conditions reported by Stahl,[55] **264b** was formed in only 37 % yield and 4:3 d.r., based on

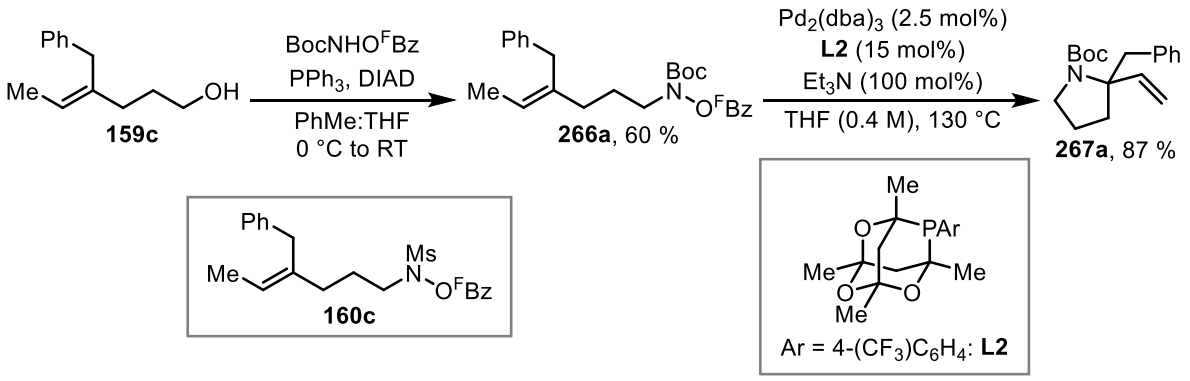
^{1}H NMR analysis of the crude mixture. Both of these results compare unfavourably to the 77 % yield and greater than 20:1 d.r. achieved in the aza-Heck cyclisation (Scheme 102d).



*Scheme 103 – Synthesis and aza-Wacker cyclisation of substrate **265**.*

3.3.4 Aza-Heck cyclisations involving trisubstituted alkenes

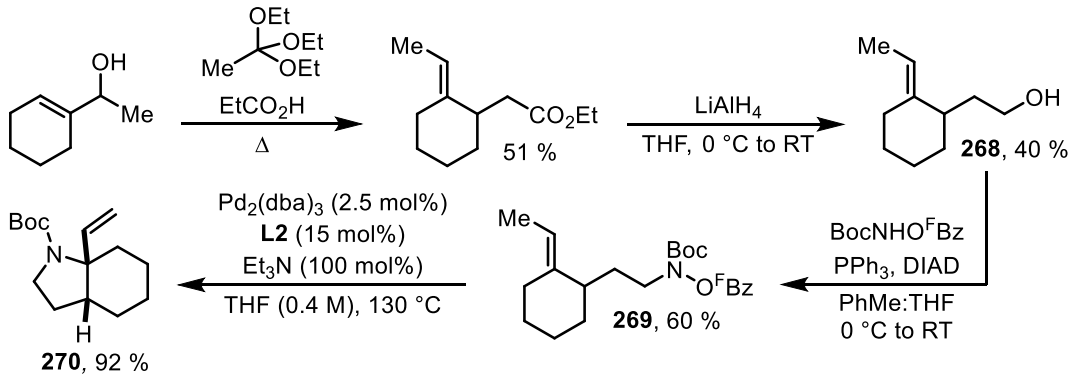
Trisubstituted alkenes constituted a significant limitation of the sulfonamide-based aza-Heck reaction (Section 2.4.5). The highest yield achieved with a substrate bearing a substituent larger than a methyl group was 54 % for **160c** (Scheme 54, Section 2.4.5). To assess this element of substrate scope for the carbamate-based reaction, substrate **266a** was prepared (Scheme 104). When employed in the aza-Heck cyclisation, **266a** afforded an 87 % yield of **267a**, a considerable improvement over its *N*-mesyl analogue **160c**.



*Scheme 104 – Synthesis and palladium(0)-catalysed cyclisation of substrate **266a**.*

With the successful cyclisation of substrate **266a** demonstrating the tolerance of trisubstituted alkenes, further examples were sought, and a substrate containing an exocyclic trisubstituted alkene (**269**) was synthesised from alcohol **268** (Scheme 105). Similarly to **266a**, when submitted to the aza-Heck reaction conditions, **269** afforded an excellent yield of **270**.

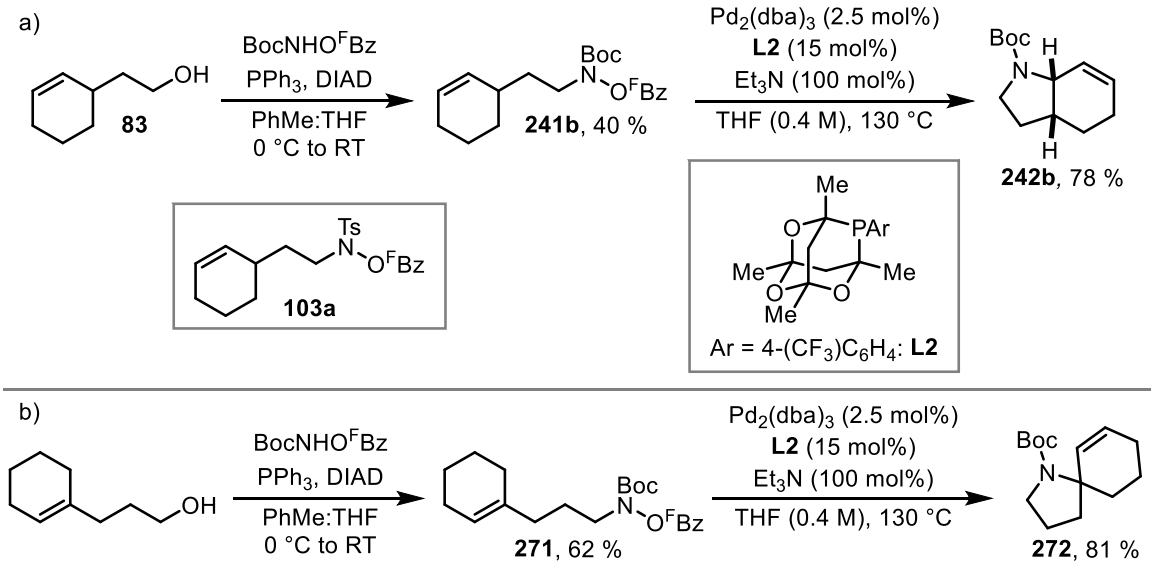
As the alkene acts as the formal nucleophile in the aza-Heck cyclisation, one might expect electron-rich trisubstituted alkenes to be more effective partners than disubstituted alkenes, and this is consistent with the results obtained in this section. The fact that this was not observed for sulfonamide-based processes gives an indication that there is a greater steric influence in those cases.



*Scheme 105 – Synthesis and palladium(0)-catalysed cyclisation of substrate **269**.*

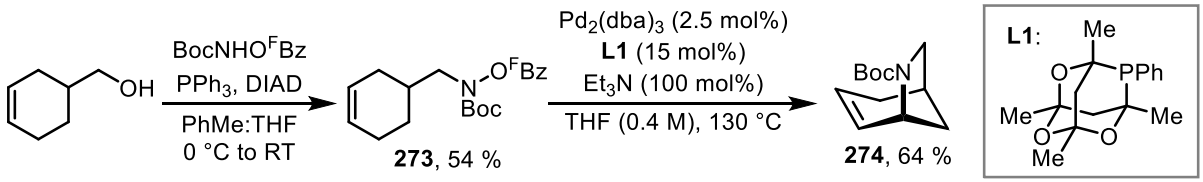
3.3.5 Aza-Heck cyclisations to generate bicyclic systems

Previously, excellent results had been achieved in cyclisations of *N*-acyloxysulfonamides containing cyclic alkenes (Section 2.4.6). This is potentially due to the fact that optimisation of the sulfonamide-based reaction was undertaken on substrate **103a** (Section 2.3.3). This class of cyclisation was also investigated with carbamate systems, starting with substrate **241b** (Scheme 106a). When employed in the aza-Heck reaction, **241b** provided a 78 % yield of **242b**. While this is a good result, it is considerably lower than the yield obtained from **103a** (Scheme 43, Section 2.3.3), although in the case of **241b** no isomerisation of the alkene of **242b** was observed. In contrast to **241b**, **271** performed significantly better in the cyclisation than its *N*-mesyl analogue **170b** (Scheme 106b, *cf.* Scheme 61, Section 2.4.6). This is in keeping with the observation from the previous section that trisubstituted alkenes are tolerated far better in the carbamate-based reaction.



*Scheme 106 – a) Synthesis and palladium(0)-catalysed cyclisation of substrate **241b**. b) Synthesis and palladium(0)-catalysed cyclisation of substrate **271**.*

Next, a transannular cyclisation was investigated with substrate **273** (Scheme 107). Under the aza-Heck cyclisation conditions, **273** afforded a 64 % yield of **274**. Although *N*-acyloxysulfonamide substrates containing 1,2-disubstituted cyclic alkenes provide higher yields of product than the analogous carbamate-based substrates (Scheme 106a *vs.* Scheme 43, Section 2.3.3 and Scheme 107 *vs.* Table 6, entry 3, Section 2.4.6), this is the only area of substrate scope for which this is the case.



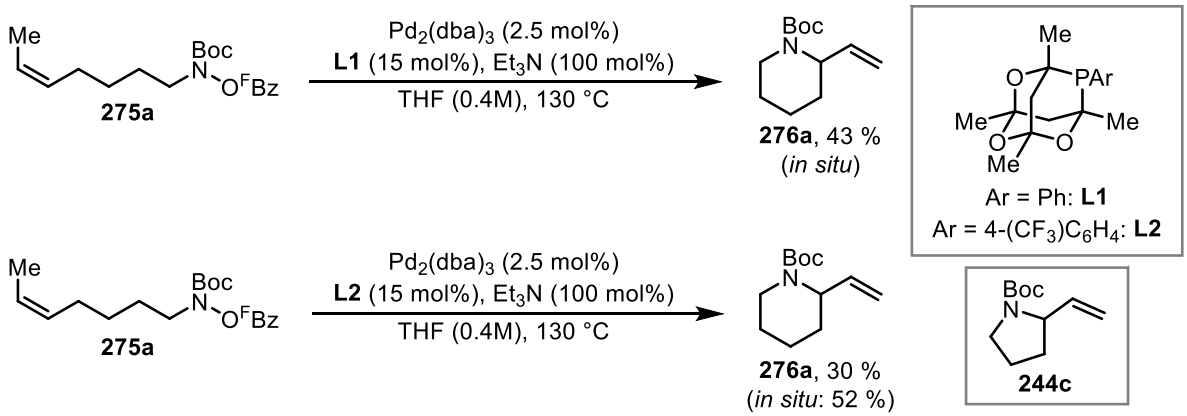
*Scheme 107 – Synthesis and palladium(0)-catalysed cyclisation of substrate **273**.*

3.4 Aza-Heck cyclisations to form 6-membered rings

3.4.1 Initial results

Despite considerable efforts, efficient 6-*exo* cyclisations of sulfonamide-based substrates could not be achieved (Section 2.4.8). Unbiased substrates performed particularly poorly, with 17 % being the highest yield achieved for a substrate lacking a benzo-fused tether. In the course of examining the scope of 5-*exo* aza-Heck cyclisations, carbamate-based substrates were found to provide better results than the analogous sulfonamide-based substrate in almost every area, and it was hoped that this improvement would extend to cyclisations to form 6-membered rings.

Under the previously optimised conditions using **L1**, substrate **275a** (*see the experimental section*) afforded a 43 % yield of **276a** (Scheme 108), which is much higher than for any non-biased sulfonamide-based substrate. By using **L2** as the ligand, the yield (^{1}H NMR) increased to 52 %, although the isolated yield was only 30 %; as the mass of **276a** is similar to **244c** (Scheme 90b, Section 3.2.1),

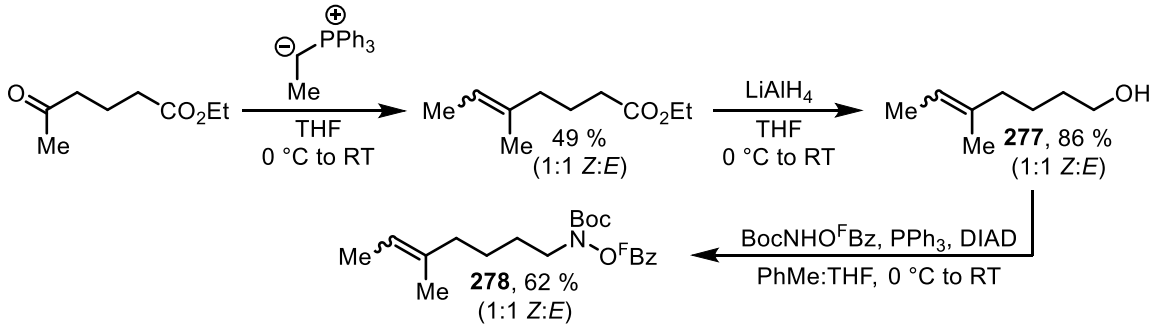


*Scheme 108 – Palladium(0)-catalysed cyclisation of substrate **275a**.*

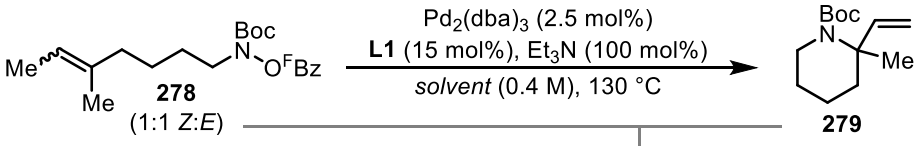
the lower isolated yield might be due to the volatility of **276a**. For continued optimisation, a substrate which is both heavier and easier to prepare on scale was sought, as **275a** requires five steps to synthesise.

3.4.2 Optimisation of the 6-*exo* aza-Heck cyclisation

Substrate **278** was viewed as a more practical choice for the optimisation of the 6-*exo* aza-Heck cyclisation, as alcohol **277** could be prepared in only two steps (Scheme 109). From **277**, substrate **278** was prepared as a 1:1 mixture of (*E*)- and (*Z*)-isomers. Optimisation of the cyclisation of **278** initiated with a brief solvent screen (Table 11), which revealed that dioxane resulted in the highest yield of **279** (Table 11, entry 6).



*Scheme 109 – Synthesis of substrate **278**.*

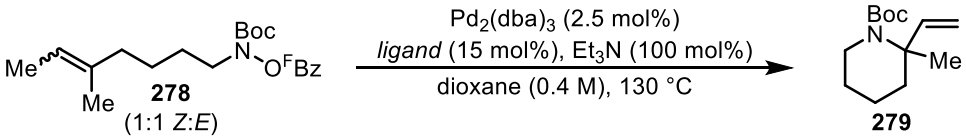


Entry	*solvent*	*yield*
1	THF	17 %
2	*n*-BuCN	6 %
3	EtOAc	16 %
4	PhMe	17 %
5	1,2-DME	15 %
6	dioxane	19 %

*Table 11 – Solvent screen for the palladium(0)-catalysed cyclisation of substrate **278**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard.*

A ligand screen was then embarked upon (Table 12). After identifying that triarylphosphines were generally ineffective at catalysing the reaction (Table 12, entries 1-4), additional derivatives of **L1** were prepared using the route outlined in Scheme 92 (Section 3.2.3). Replacing the phenyl group of **L1** with an electron-poor arene led to improved yields of **279** (Table 12, entries 6-10), with **L9** affording the

highest yield (31 %) (Table 12, entry 10). The use of unsubstituted **248**[XXIII] or phosphinite **L10**[XXIV] failed to provide significant yields of **279** (Table 12, entries 11 and 12). Ultimately, optimisation of the key parameters in the cyclisation of **278** failed to improve the yield of **279** to an acceptable value, and isolation of **279** suffered the same problems as **244c** and **276** (Scheme 110). Consequently, further investigations with this substrate were not deemed worthwhile.



Entry	*ligand*	*yield*
1	PPh_3	5 %
2	$P(4\text{-}(F)C_6H_4)_3$	11 %
3	$P(4\text{-}(CF_3)C_6H_4)_3$	8 %
4	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	2 %
5	**L1**	19 %
6	**L2**	27 %
7	**L6**	21 %
8	**L7**	24 %
9	**L8**	20 %
10	**L9**	31 %
11	**L10**	*not observed*
12	**248**	9 %

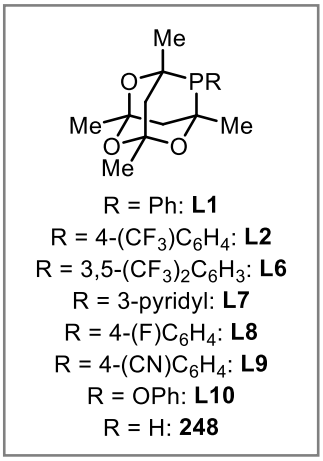
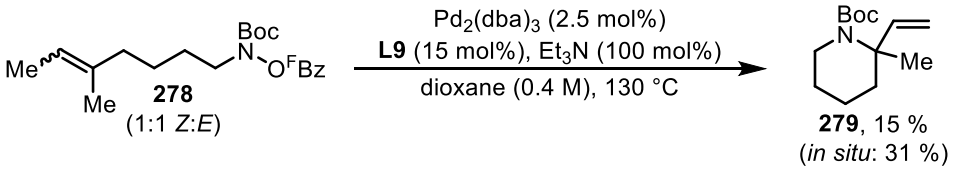
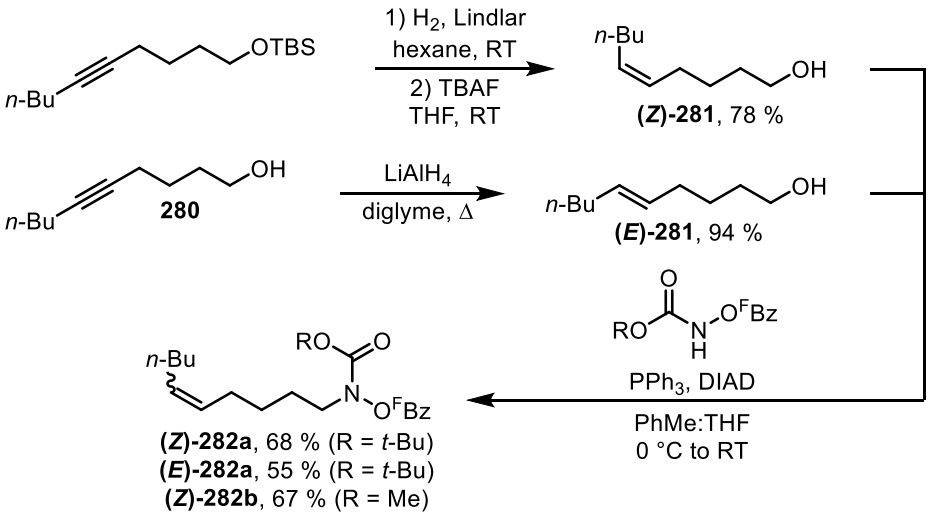


*Table 12 – Ligand screen for the palladium(0)-catalysed cyclisation of substrate **278**. Yields were determined by ^1H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard.*[XXIII,XXIV,XXV]



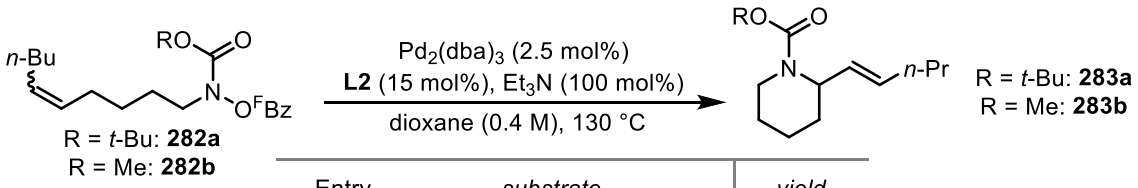
*Scheme 110 – Palladium(0)-catalysed cyclisation of substrate **278**.*

[XXIII] Phosphine **248** was prepared by Charly Faradji (University of Bristol) according to a literature procedure.[147]
[XXIV] Phosphinite **L10** was prepared according to a literature procedure,[153] as opposed to in the manner outlined in Scheme 92 (Section 3.2.3).
[XXV] Ligand **L7** was prepared by Timothy Shuttleworth (University of Bristol) according to a reported procedure.[154]



*Scheme 111 – Synthesis of substrates **(Z)-282a**, **(E)-282a** and **(Z)-282b**.*

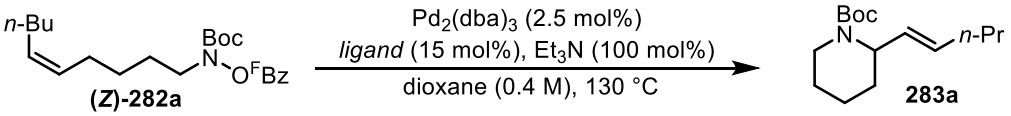
For the continued examination of the 6-*exo* cyclisation, substrate **282** was targeted, and the effects of alkene geometry and protecting group were investigated. From commercially available alkynol **280**, alcohol **281** can be synthesised as either the (*Z*)- or the (*E*)-isomer by reduction with either hydrogen/Lindlar catalyst or $LiAlH_4$, respectively (Scheme 111). From **281**, *N*-Boc (**(*Z*)-282a** and **(*E*)-282a**) and methyl carbamate (**(*Z*)-282b**) systems were prepared. When the three substrates were evaluated in the aza-Heck cyclisation (Table 13), **(*Z*)-282a** provided the highest yield of **283** (Table 13, entry 1) and was hence taken forward for further optimisation.



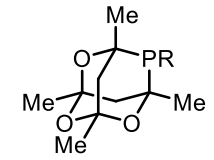
Entry	*substrate*	*yield*
1	**(*Z*)-282a**	49 %
2	**(*E*)-282a**	40 %
3	**(*Z*)-282b**	21 %

*Table 13 – Comparison of the cyclisation of substrates **(Z)-282a**, **(E)-282a** and **(Z)-282b**. Yields were determined by ^1H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard.*

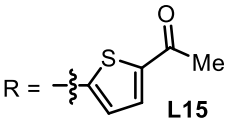
The use of **L1** analogues led to substantial improvements in the cyclisation of **278** (Table 12), so more analogues were prepared and assayed with substrate **(*Z*)-282a** (Table 14). As before, the best results were obtained with ligands bearing electron-poor arenes (Table 14, entries 2, 3, 6 and 9), although beyond a certain point, decreasing the electron density on the arene further leads to lower yields (Table 14, entries 7, 12 and 13). In the case of **(*Z*)-282a**, ligand **L9**, which was optimal for **278**, resulted in the same yield of **283a** as **L1** (Table 14, entries 1 and 6).



Entry	*ligand*	*yield*
1	**L1**	46 %
2	**L2**	49 %
3	**L3**	50 %
4	**L4**	16 %
5	**L5**	10 %
6	**L9**	46 %
7	**L11**	39 %
8	**L12**	42 %
9	**L13**	47 %
10	**L14**	26 %
11	**L15**	18 %
12	**L16**	35 %
13	**L17**	13 %
14	**L18**	27 %

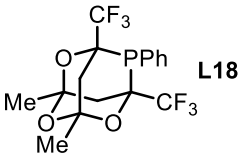


R = Ph: **L1**
R = 4-$(CF_3)C_6H_4$: **L2**
R = 4-$(CO_2Et)C_6H_4$: **L3**
R = F: **L4**
R = CF_3: **L5**
R = 4-$(CN)C_6H_4$: **L9**
R = 3,4,5-$(F)_3C_6H_2$: **L11**
R = 4-$(OMe)C_6H_4$: **L12**
R = 4-$(C(O)Me)C_6H_4$: **L13**
R = 2-thiophenyl: **L14**



L15

R = 4-$(NO_2)C_6H_4$: **L16**
R = 4-$(SO_2NH_2)C_6H_4$: **L17**

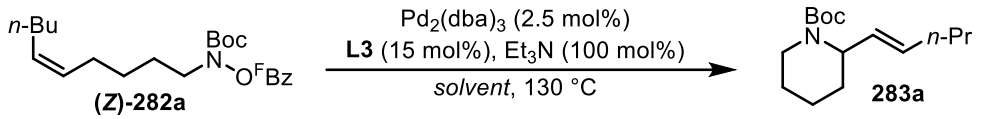


L18

*Table 14 – Ligand screen for the palladium(0)-catalysed cyclisation of substrate **(Z)-282a**. Yields were determined by ^1H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard.*[XXVI]

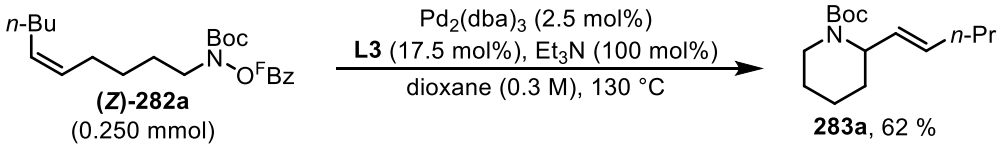
Having identified **L3** as the optimal ligand for the cyclisation of **(*Z*)-282a** (Table 14), the choice of reaction solvent was re-examined, including less commonly utilised solvents (Table 15). The majority of these resulted in poor yields of **283a** (Table 15, entries 2-5 and 8), and none of them were more effective than dioxane (Table 15, entry 1). Fine-tuning of the reaction concentration led to a small increase in yield of **283a** (Table 15, entry 10). Finally, conducting the reaction on a larger scale (0.250 mmol *vs.* 0.105 mmol) and with a slightly higher loading of **L3** provided a 62 % yield of **283a** (Scheme 112).

[XXVI] Ligand **L12** was prepared by Rafaela Carmona *via* the route outlined in Scheme 92 (Section 3.2.3). Phosphine **L18** was not prepared in the manner outlined in Scheme 92 (Section 3.2.3).



Entry	*solvent*	*concentration*	*yield*
1	dioxane	0.4 M	50 %
2	acetone	0.4 M	5 %
3	$MeNO_2$	0.4 M	*not observed*
4	CH_2Cl_2	0.4 M	*not observed*
5	1,2-DCE	0.4 M	12 %
6	$PhCF_3$	0.4 M	47 %
7	MTBE	0.4 M	34 %
8	diglyme	0.4 M	25 %
9	dioxane	0.2 M	51 %
10	dioxane	0.3 M	52 %
11	dioxane	0.5 M	43 %

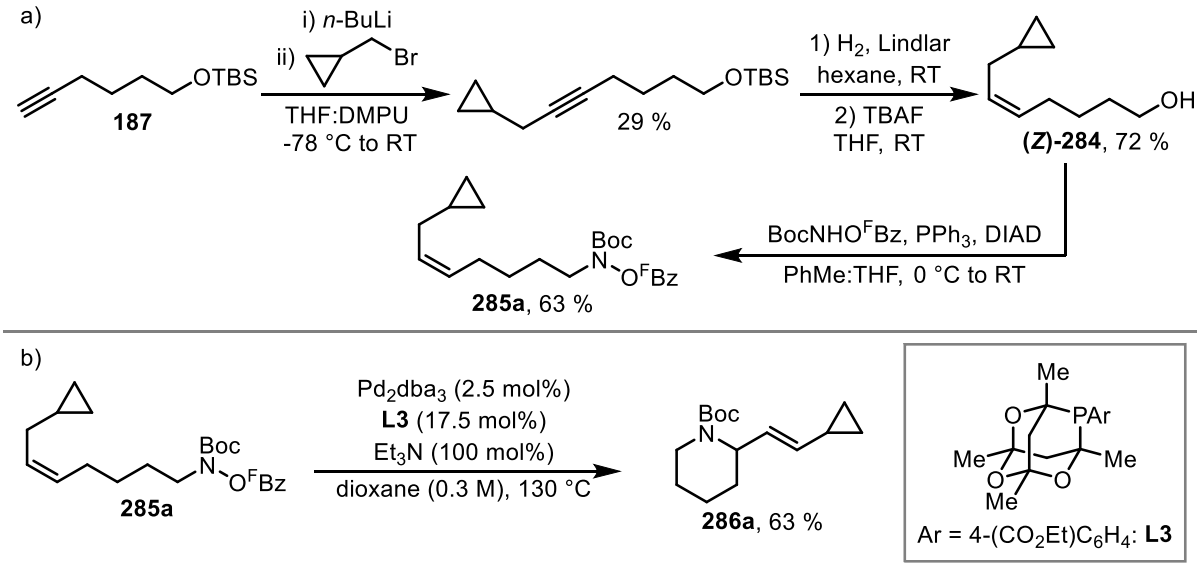
*Table 15 – Optimisation of solvent and concentration in the palladium(0)-catalysed cyclisation of substrate **282a**. Yields were determined by ^1H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard.*



*Scheme 112 – Final conditions applied to the palladium(0)-cyclisation of substrate **(Z)-282a**.*

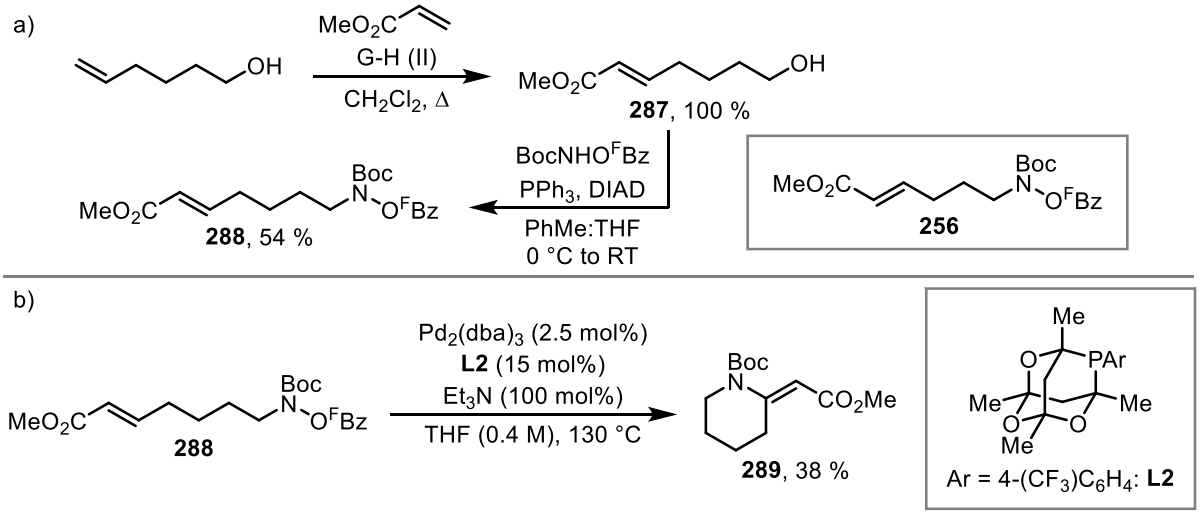
3.4.3 Aza-Heck cyclisations of substrates lacking biasing factors

In order to examine the scope of the 6-*exo* cyclisation, substrate **285a** was prepared from alcohol **(*Z*)-284** (Scheme 113a). When **285a** was exposed the newly optimised conditions, piperidine **286a** was generated in 63 % yield (Scheme 113b), an almost identical result to that obtained with **(*Z*)-282a** (Scheme 112). While cyclopropyl substituents have been shown to be tolerated in the sulfonamide-based reaction (Section 2.4.2 and Section 2.4.5), the achievement is more impressive in the case of **285a**, as product **286a** contains a vinyl cyclopropane moiety, and these have been shown to be reactive towards palladium complexes.[155]



*Scheme 113 – a) Synthesis of substrate **285a**. b) Palladium(0)-catalysed cyclisation of substrate **285a**.*

Following the excellent result achieved with 5-ring acrylate substrate **256** (Scheme 98, Section 3.3.2), the analogous 6-ring substrate **288** was synthesised (Scheme 114a). As observed previously (Section 2.4.1), methyl acrylate proved an excellent partner in the alkene cross-metathesis reaction, and alcohol **287** was obtained in quantitative yield. Unfortunately, substrate **288** provided only a modest yield of cyclised product, with **289** formed in 38 % yield (Scheme 114b).

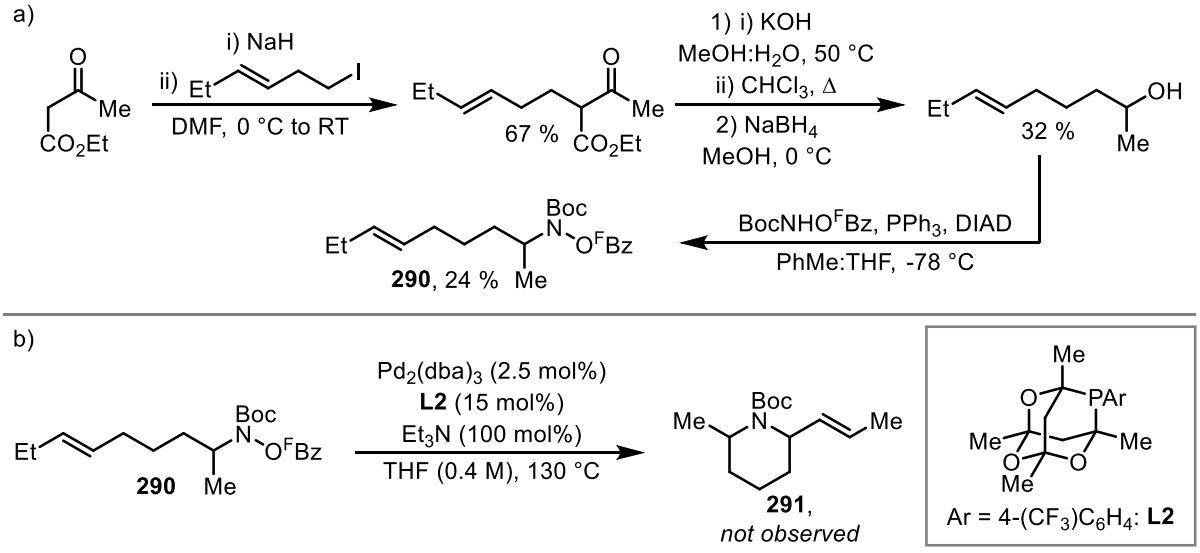


*Scheme 114 – a) Synthesis of substrate **288**. b) Palladium(0)-catalysed cyclisation of substrate **288**.*

3.4.4 Aza-Heck cyclisations of systems with substitution α and β to nitrogen

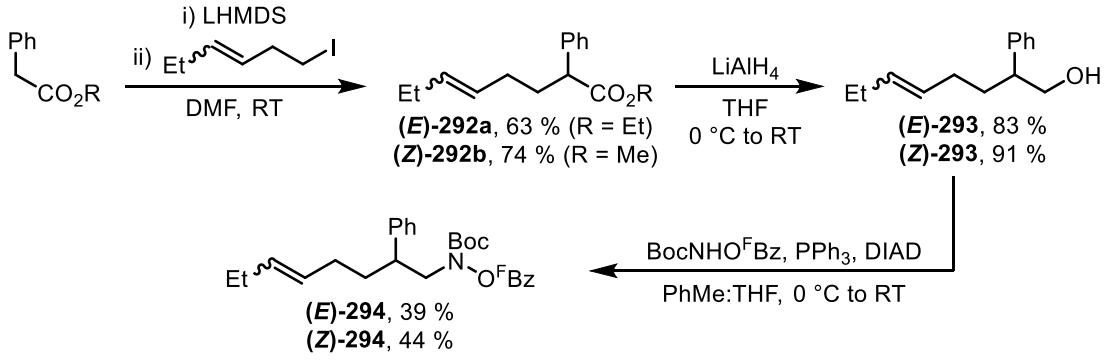
The influence of substitution at the α-position was then investigated with substrate **290** (Scheme 115a). As with **258a** (Section 3.3.3), the Mitsunobu reaction to form **290** was conducted at -78 °C, and the impure product required washing with AcOH to remove the suspected *O*-alkylated side product. When

290 was submitted to the aza-Heck conditions, target **291** was not observed, with protodepalladation predominating (Scheme 115b).



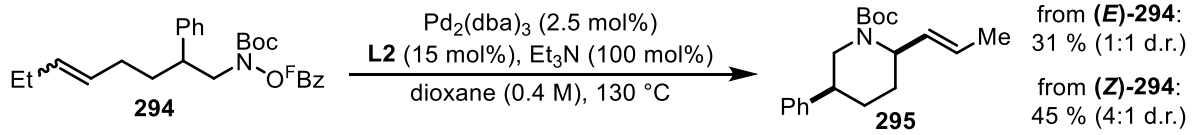
*Scheme 115 – a) Synthesis of substrate **290**. b) Attempted cyclisation of substrate **290**.*

In 5-*exo* cyclisations, better results were achieved with substrates containing β-substitution than those with substitution in the α-position (Section 3.3.3). Based on this observation, β-substituted 6-ring substrate **294** was synthesised. In order to investigate the effect of alkene configuration, both the (*E*)- and (*Z*)-isomers of ester **292** were prepared, starting from either (*E*)- or (*Z*)-hex-3-en-1-yl iodide, respectively. Reduction ($LiAlH_4$) of **292** afforded alcohols **(*E*)-293** and **(*Z*)-293**, which were then converted into substrates **(*E*)-294** and **(*Z*)-294** (Scheme 116).



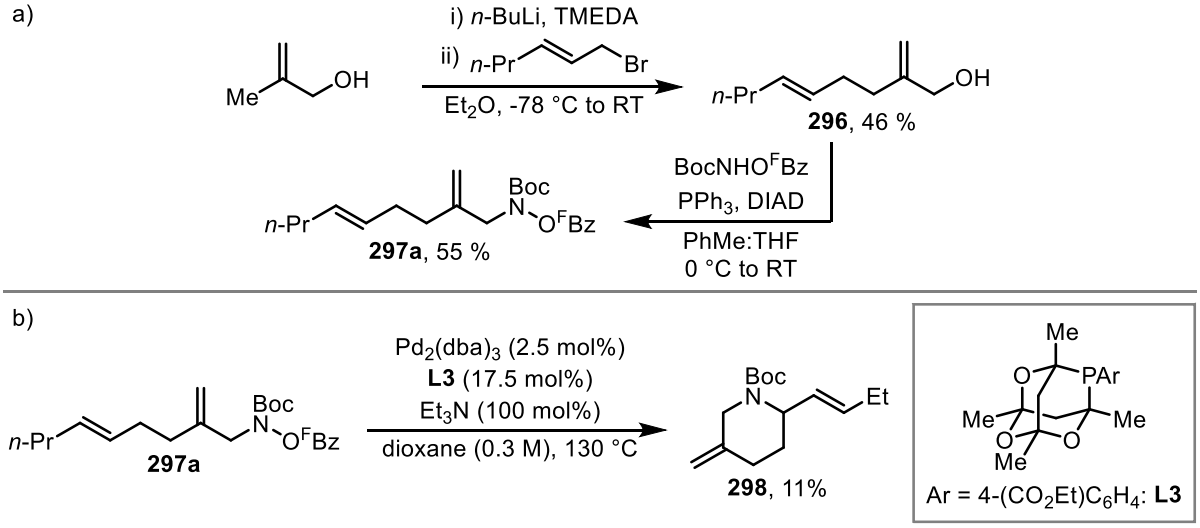
*Scheme 116 – Synthesis of substrates **(Z)-294** and **(E)-294**.*

When employed in the aza-Heck reaction, **(*E*)-294** afforded **295** in 31 % yield, compared to 45 % yield with **(*Z*)-294** (Scheme 117). The improved performance of the substrate containing a (*Z*)-alkene is consistent with the results obtained with **282a** (Table 13, Section 3.4.2). There was a more significant difference between the two substrates in terms of diastereoselectivity; while the (*E*)-isomer cyclised with no diastereoselectivity, **(*Z*)-294** generated **295** with a 4:1 preference for the *cis* diastereomer.



*Scheme 117 – Palladium(0)-catalysed cyclisation of substrates **(E)-294** and **(Z)-294**.*

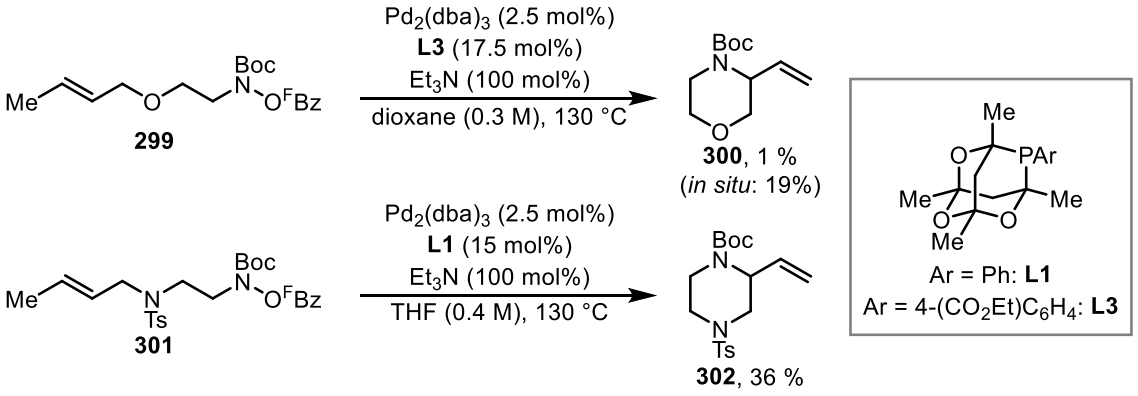
The effects of substitution with an *exo*-methylene group were examined with substrate **297a**, which was prepared from alcohol **296** (Scheme 118a). When submitted to the aza-Heck conditions, substrate **297a** afforded **298** in only 11 % yield (Scheme 118b). The reason for this disappointing result is not clear. One possibility is that the *exo*-methylene group acidifies the α-hydrogen atoms of **297a**, favouring elimination in a similar manner to **202** (Scheme 73, Section 2.4.8). Alternatively, the presence of an sp^2 carbon atom in the tether of **297a** might exert a conformational bias against cyclisation.



*Scheme 118 – a) Synthesis of substrate **297a**. b) Palladium(0)-catalysed cyclisation of substrate **297a**.*

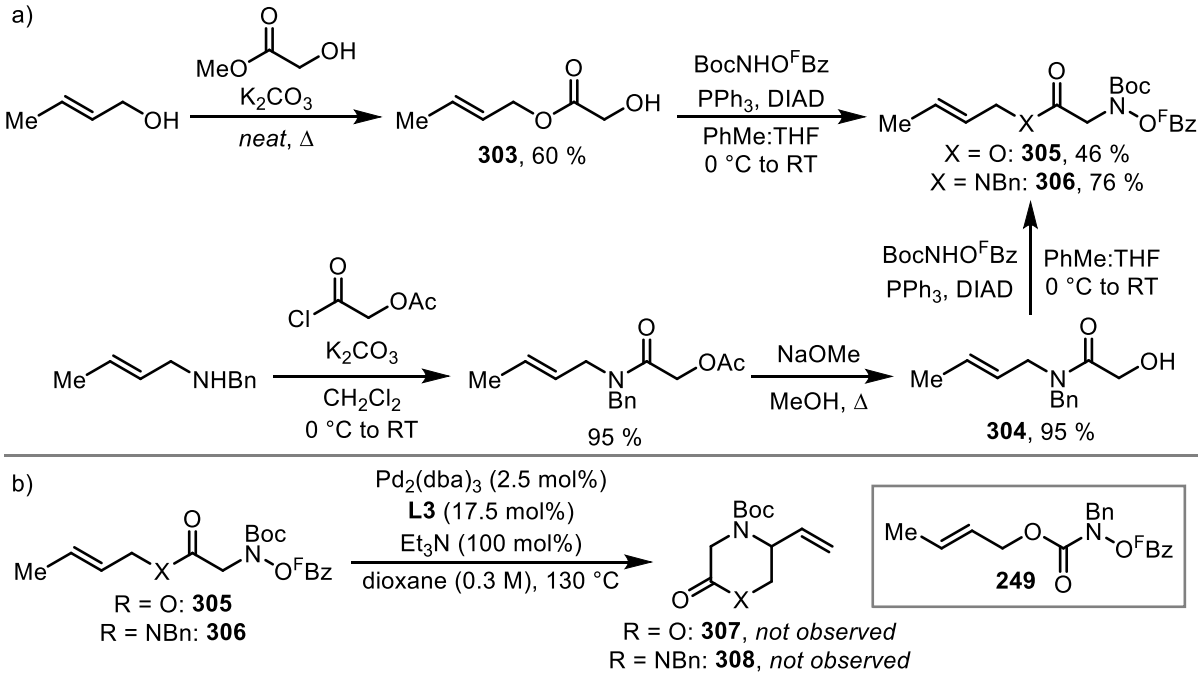
3.4.5 Aza-Heck cyclisations of systems with heteroatom-based tethers

The possibility of forming piperazines and morpholines was investigated with substrates **299** and **301** (*see the experimental section*), respectively. While the analogous *N*-mesyl systems **194** and **195** performed poorly in the aza-Heck cyclisation (Scheme 70, Section 2.4.8), it was hoped that **299** and **301** would fare better, as the carbamate-based reaction has greater tolerance for the formation of 6-membered rings. However, both substrates cyclised in relatively low yield (Scheme 119). Similar to what was observed with the analogous *N*-mesyl substrates, substrate **301** performed significantly better than substrate **299**.



*Scheme 119 – Palladium(0)-catalysed cyclisation of substrates **299** and **301**.*

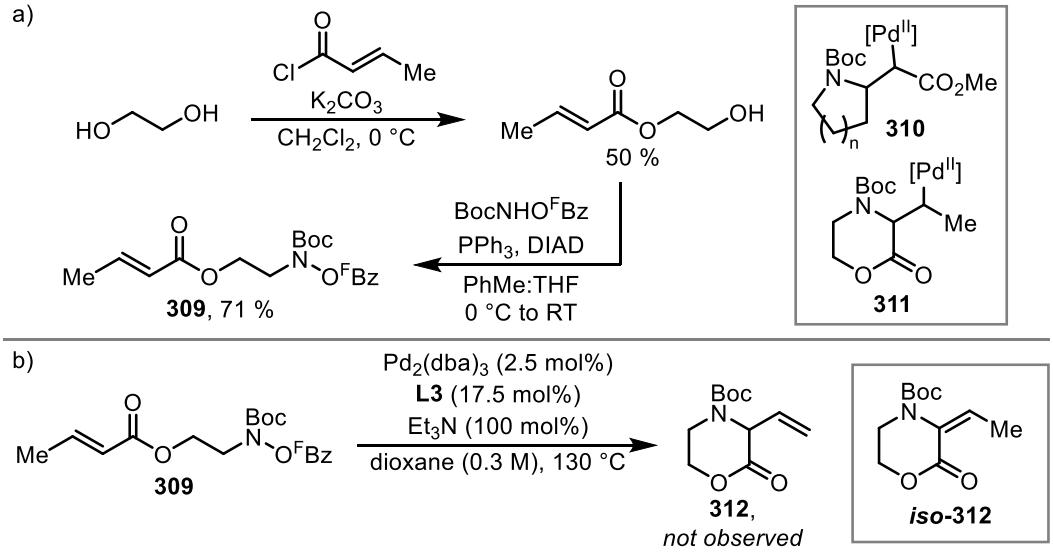
Following this, the formation of other kinds of heterocycles was investigated. To this end, further substrates, containing an ester (**305**) and an amide (**306**) tether, were prepared from alcohols **303** and **304** (Scheme 120a). Unfortunately, when exposed to the aza-Heck reaction conditions, neither **305** nor **306** generated the corresponding target (Scheme 120b). The cyclisation of substrate **305** was potentially hindered by competing π-allyl formation, as was proposed for substrate **249** (Section 3.3.1).



*Scheme 120 – a) Synthesis of substrates **305** and **306**. b) Attempted cyclisation of substrates **305** and **306**.*

Previous work established that aza-Heck cyclisations onto acrylates proceeded in excellent yield for 5-*exo* cyclisations (Section 3.3.2) and moderate yield for 6-*exo* cyclisations (Section 3.4.3); both of these examples involve a migratory insertion in the direction of the acrylate carbonyl, to give an intermediate where palladium is α to the carbonyl (**310**). The feasibility of the inverse scenario, where migratory insertion affords an intermediate with palladium β to the carbonyl (**311**), was assessed with

substrate **309** (Scheme 121). This kind of cyclisation is evidently a more difficult process, and neither desired product **312** nor ***iso*-312** were observed following the attempted aza-Heck reaction.



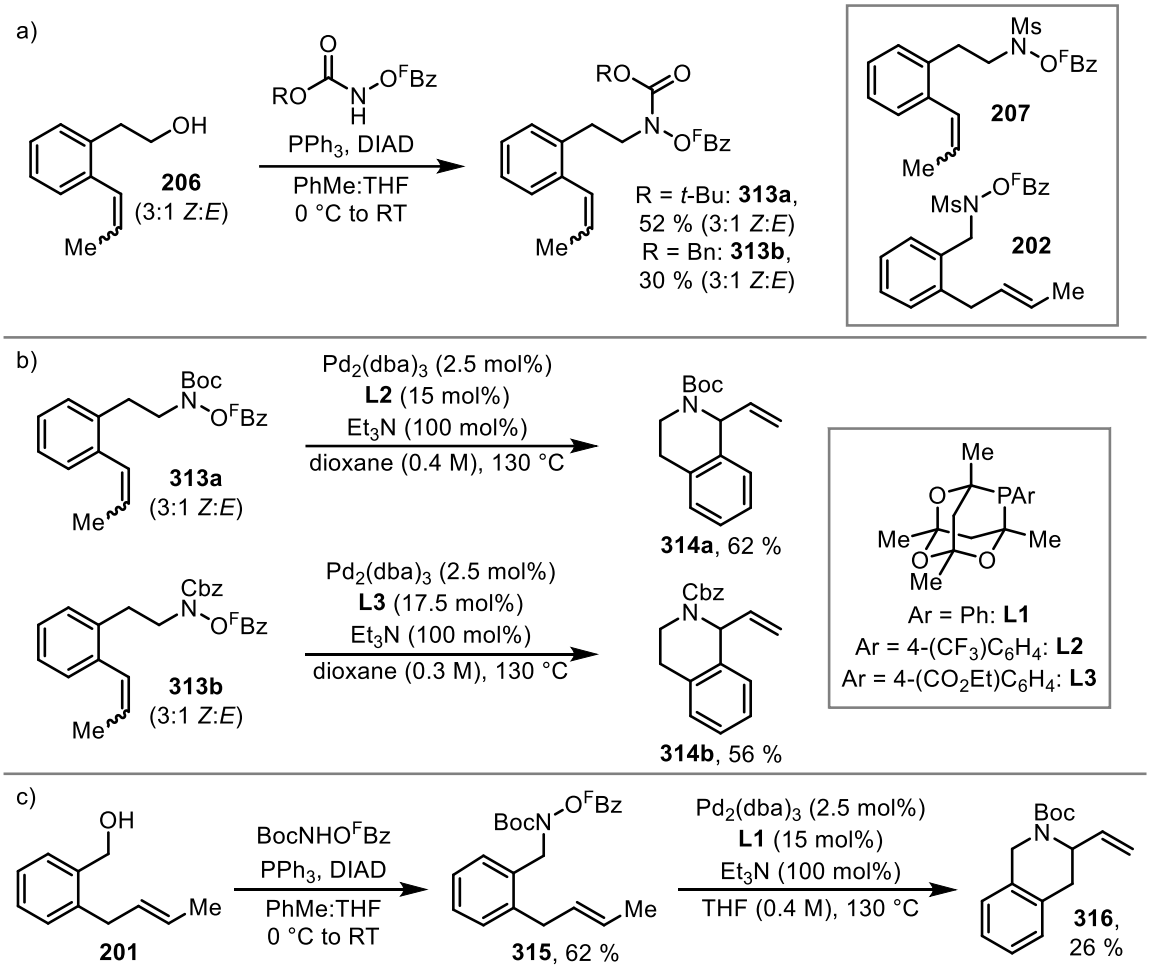
*Scheme 121 – a) Synthesis of substrate **309**. b) Attempted cyclisation of substrate **309**.*

3.4.6 Aza-Heck cyclisations of conformationally biased systems containing 1,2-disubstituted alkenes

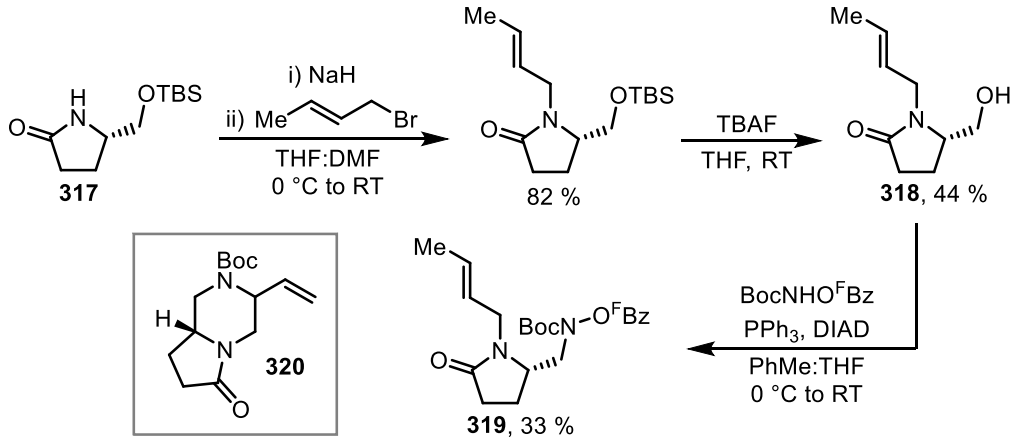
In the sulfonamide-based aza-Heck reaction, benzo-fused styrenyl substrate **207** produced the best result achieved with a 6-ring substrate, cyclising in 42 % yield (Scheme 74, Section 2.4.8). In order to provide a comparison for the carbamate-based reaction, the *N*-Boc and *N*-Cbz analogues of **207** were prepared (**313a** and **313b**, respectively, Scheme 122a). Both **313a** and **313b** afforded **314** in significantly higher yield than **207** (Scheme 122b), with **313a** performing slightly better than **313b**. Substrate **202** also provided a relatively good result for the sulfonamide-based reaction (Scheme 73, Section 2.4.8); however, the analogous *N*-Boc substrate **315** produced only a 26 % yield of **316** (Scheme 122c).

Following the success of benzo-fused substrates **313a** and **313b** (Scheme 122), substrates fused with other heterocycles were targeted. Pyrrolidone-fused system **319** was synthesised from alcohol **318**, which was prepared through alkylation of (*S*)-pyroglutaminol derivative **317**, followed by deprotection (Scheme 123). Substrate **319** proved difficult to purify; its high polarity led to coelution with by-products of the Mitsunobu reaction. When **319** was employed in the aza-Heck cyclisation, a small amount of desired product **320** (less than 20 %) appeared to form.[XXVII] However, purification of the aza-Heck reaction mixture was problematic, and a pure sample of **320** could not be isolated.

[XXVII] By ^{1}H NMR analysis of the crude reaction mixture.



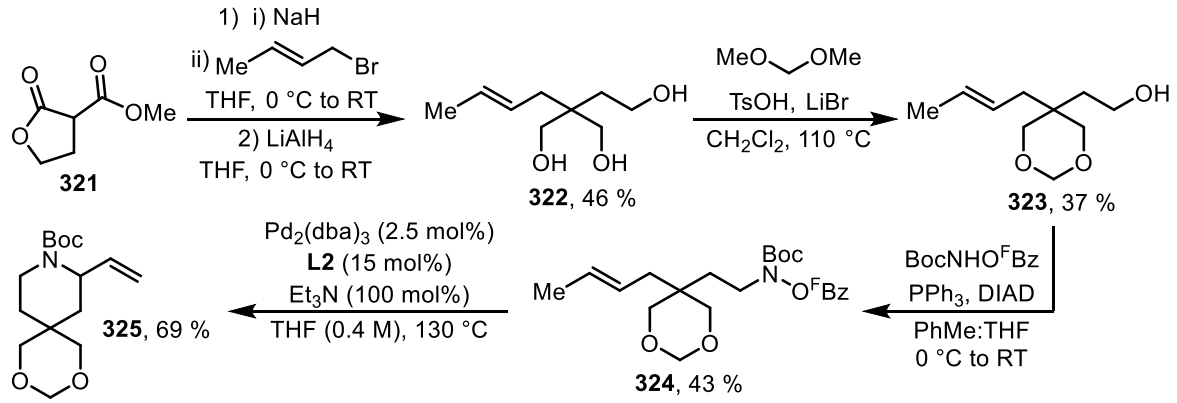
*Scheme 122 – a) Synthesis of substrates **313a** and **313b**. b) Palladium(0)-catalysed cyclisation of substrates **313a** and **313b**. c) Synthesis and palladium(0)-catalysed cyclisation of substrate **315**.*



*Scheme 123 – Synthesis of substrate **319**.*

Presumably, benzo-fused substrates increase rates of cyclisations by fixing four atoms of the forming ring into one plane. Bringing the Pd–N bond in close proximity to the alkene partner entropically favours the cyclisation through preorganisation. Rates of cyclisations can also be increased by the introduction of *gem*-dialkyl groups into the tether.[156] In order to exploit this effect, an appropriate

substrate (**324**) was prepared (Scheme 124). The synthesis of **324** began with alkylation of malonate derivative **321**, followed by reduction to afford triol **322**. Protection of **322** proceeded selectively to provide the 6-ring acetal in **323**. Alcohol **323** was then converted into **324**, which, when exposed to the aza-Heck reaction conditions, afforded product **325** in 69 % yield (Scheme 124).



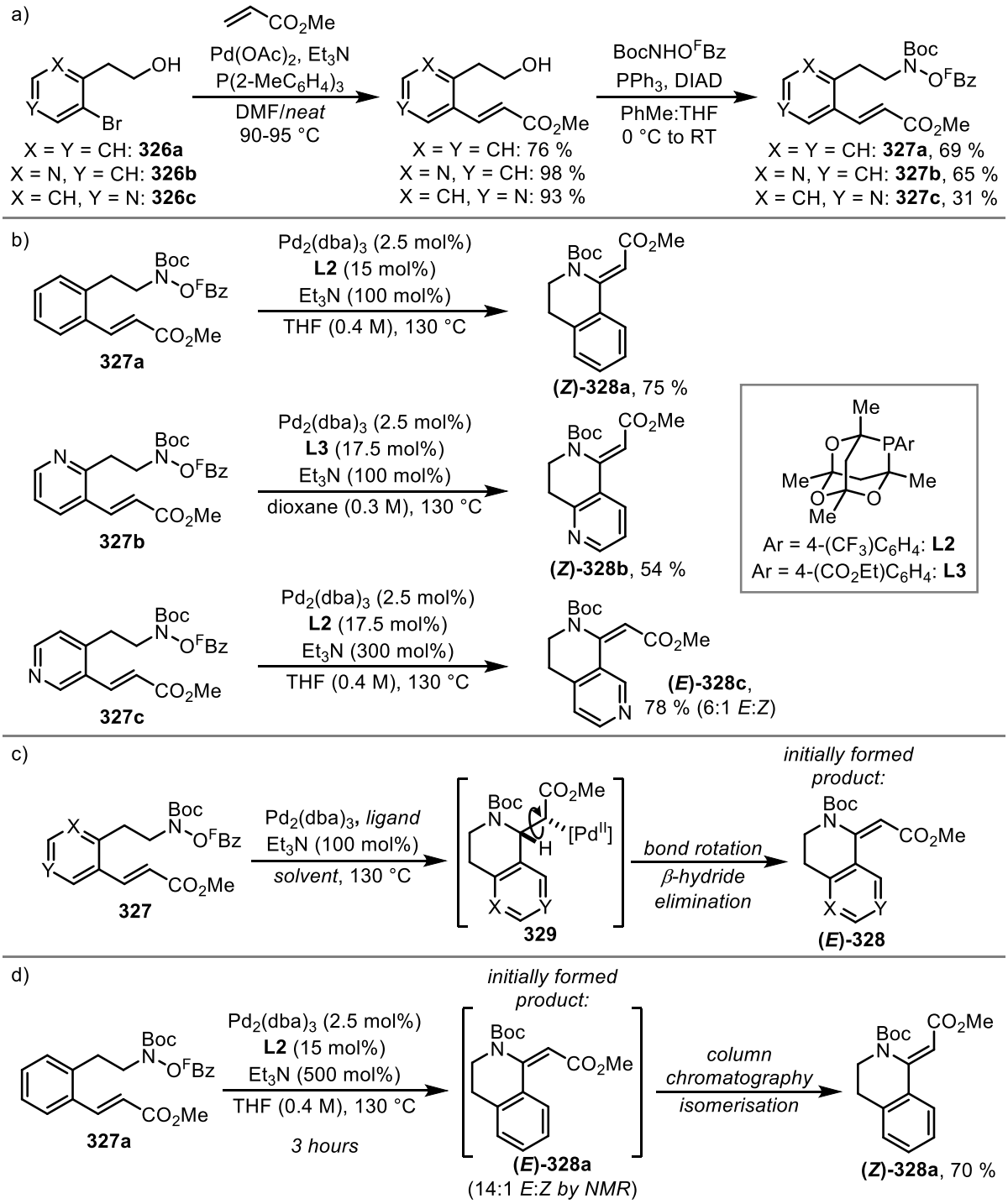
*Scheme 124 – Synthesis and palladium(0)-catalysed cyclisation of substrate **324**.*

3.4.7 Aza-Heck cyclisations of conformationally biased systems containing acrylates

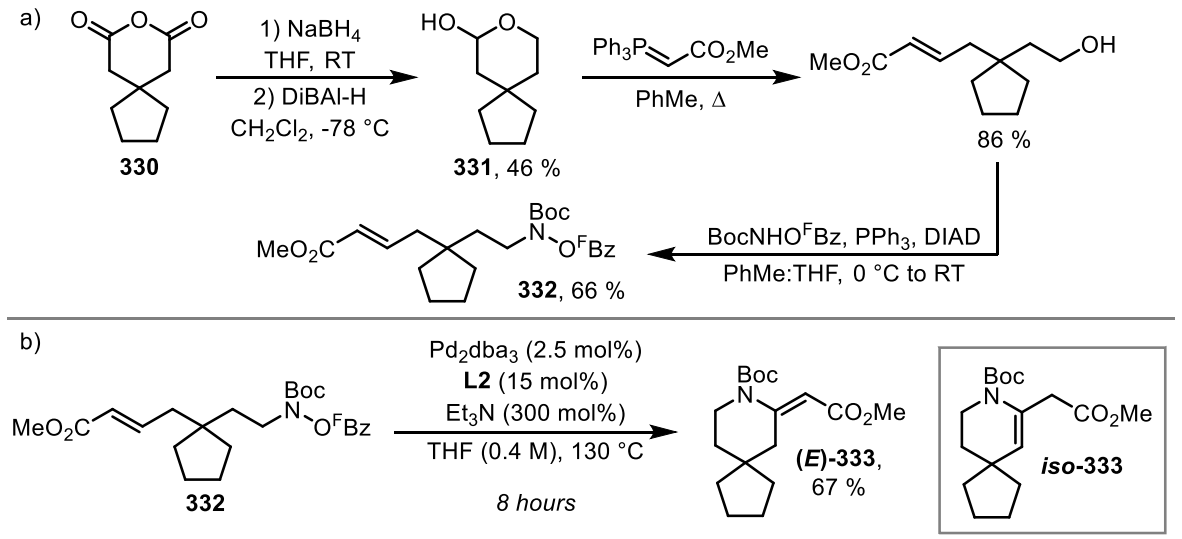
As good results were achieved in the aza-Heck reaction using conformationally biased substrates (Section 3.4.6), the cyclisation of related substrates containing acrylates was investigated. Acrylates are excellent partners in the standard Mizoroki-Heck reaction; consequently, benzo-fused 6-ring substrates **327a-c** were easily prepared starting from aryl bromides **326a-c** (Scheme 125a). Good yields were generally obtained in the cyclisation of **327a-c** (Scheme 125b). Interestingly, the products obtained from **327a** and **327b** contained alkenes with (*Z*)-geometry. Because aminopalladation and β-hydride elimination both procced in a *syn* manner, this cannot be the initially formed isomer (Scheme 125c). *syn*-Aminopalladation of the *trans* acrylate in **327** leads to intermediate **329**, where palladium and hydrogen are on opposite faces; therefore, bond rotation is required before the substituents are in the correct orientation for β-hydride elimination. Isomerisation, potentially acid-mediated, of the (*E*)- to the (*Z*)-isomer is responsible for the observed geometry of products **328a** and **328b**. When the cyclisation of **327a** was run to partial completion (3 *vs.* 24 hours) with a higher loading of base, the major product was determined to be **(*E*)-328a** by ^{1}H NMR analysis (Scheme 125d). However, isomerisation to **(*Z*)-328a** occurs so readily that it was not possible to isolate **(*E*)-328a**.

An acrylate substrate similar to **324** (Scheme 124, Section 3.4.6) was prepared by reduction of anhydride **330** and Wittig reaction of resulting hemiacetal **331**, followed by Mitsunobu alkylation to afford **332** (Scheme 126a). When exposed to the aza-Heck cyclisation conditions, substrate **332** afforded **(*E*)-333** in 67 % yield (Scheme 126b). Slightly modified conditions (a shorter reaction time

and higher loading of base) were used in the cyclisation of **332** to prevent formation of tautomeric enamine ***iso*-333**.



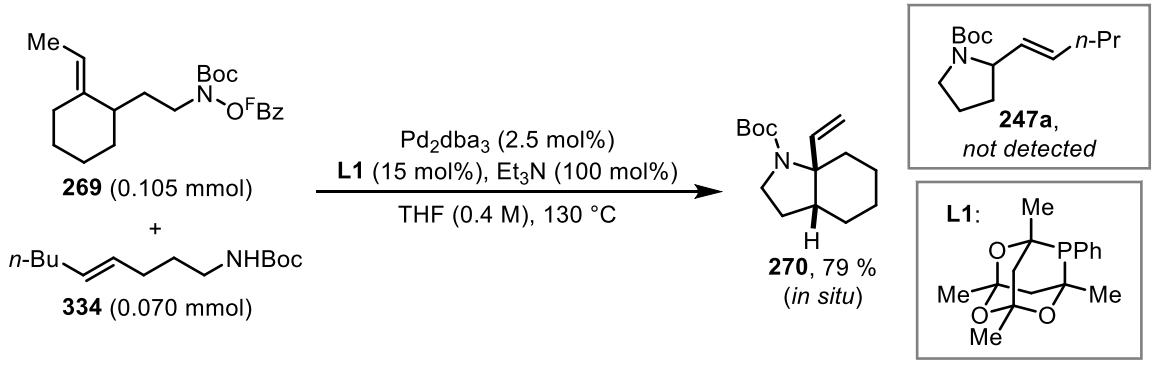
*Scheme 125 – a) Synthesis of substrates **327a-c**. b) Palladium(0)-catalysed cyclisation of substrates **327a-c**. c) Rationale for the geometry of initially formed product **(E)-328** in the cyclisation of substrate **327**. d) Observation of **(E)-328a** as the initially formed product in the cyclisation of substrate **327a**.*



*Scheme 126 – a) Synthesis of substrate **332**. b) Palladium(0)-catalysed cyclisation of substrate **332**.*

3.5 Mechanistic investigations

The aza-Heck reaction detailed in this chapter is presumed to proceed *via* a similar mechanism to the sulfonamide-based reaction in the previous chapter (Scheme 77, Section 2.5); however, the carbamate-based reaction appears to be considerably more efficient. One possibility for this could be the occurrence of a background aza-Wacker reaction which converts NH carbamate side products, such as **334**, into desired products, such as **247a**.[XXVIII] In order to investigate whether this is the case, a crossover experiment akin to the one detailed in Scheme 79b (Section 2.5) was carried out. When the cyclisation of **269** was conducted in the presence of **334** (*see the experimental section*), a good yield of aza-Heck product **270** was achieved, and aza-Wacker product **247a** was not detected (Scheme 127), indicating that the latter process is not operative.

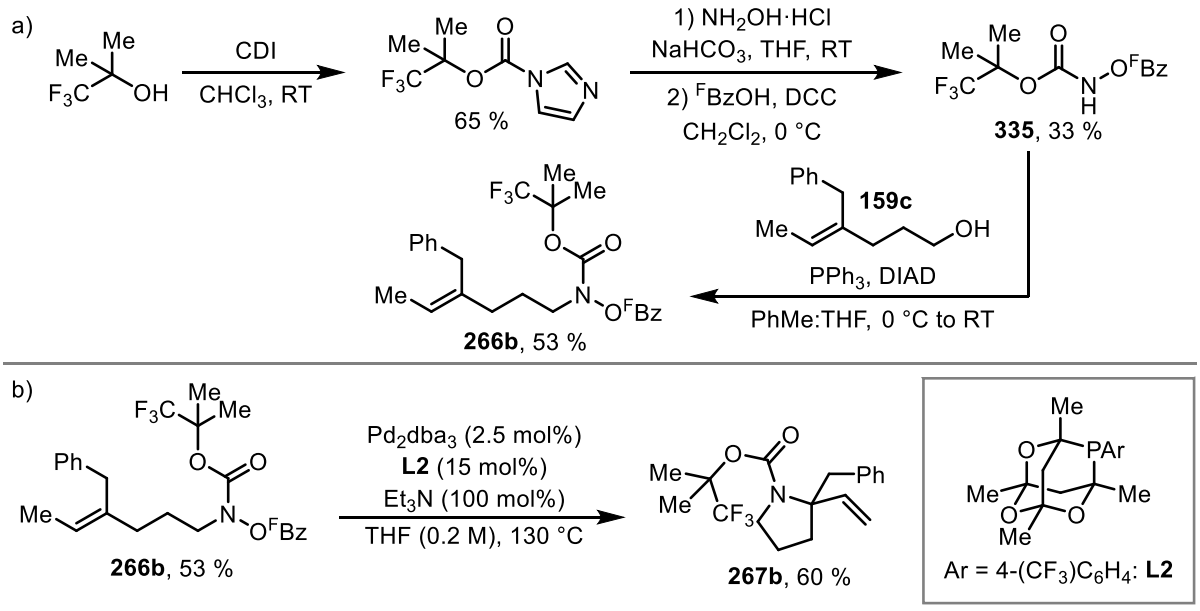


*Scheme 127 – Palladium(0)-catalysed cyclisation of substrate **269** in the presence of **334**.*

[XXVIII] Through a mechanism analogous to that proposed in Scheme 79a (Section 2.5).

Because the reactions are conducted in sealed tubes, it was not possible to follow them by sampling methods (*e.g.*, TLC or GC). The standard use of a 24-hour reaction time was based on the observation that, in the majority of cases, no starting material remains after this time. Without monitoring, it is difficult to observe certain processes that might have implications for successful reaction development. There exist a number of phenomena which could lead to an unusual reaction profile. For instance, there could be an induction period, during which significant starting material decomposition occurs. There is also the possibility of product decomposition, as *N*-Boc groups are known to be thermally unstable.[157,158] This could mean longer reaction times are not only unnecessary but also detrimental to high yields. In order to gain more insight into the reaction, an attempt was made to obtain an accurate reaction profile. As techniques which require sampling of the reaction mixture were not appropriate, alternatives which rely on spectroscopy, such as monitoring by NMR, were a logical choice.

The trifluoromethyl analogue (**266b**) of substrate **266a** (Scheme 104, Section 3.3.4) was prepared from reagent **335** (Scheme 128a). The CF_3 unit provides a fluorine-label for ^{19}F NMR spectroscopy. The cyclisation of **266b** to **267b** (Scheme 128b) was carried out inside an NMR spectrometer and monitored for 24 hours, with spectra obtained every 20 minutes.[XXIX] In the event, the ^{19}F resonances of the trifluoromethyl group of **266b**, **267b** and other species in the reaction mixture were too similar to use for quantification.[XXX] Nevertheless, through the use of solvent suppression, ^{1}H NMR spectroscopy could be used to monitor the build-up of **267b**. Furthermore, the formation of pentafluorobenzene and consumption of **266b**, identified by its pentafluorobenzoyl group, could also be monitored.



*Scheme 128 – a) Synthesis of fluorine-labelled substrate **266b**. b) Palladium(0)-catalysed cyclisation of substrate **266b**.*

[XXIX] Dr David Whittaker and Dr Michael Nunn (both AstraZeneca) set up the NMR spectrometer for reaction monitoring.

[XXX] The situation was potentially complicated by the fact that, at room temperature at least, the ^{19}F NMR spectrum of **267b** consists of two resonances due to the presence of a pair of rotamers.

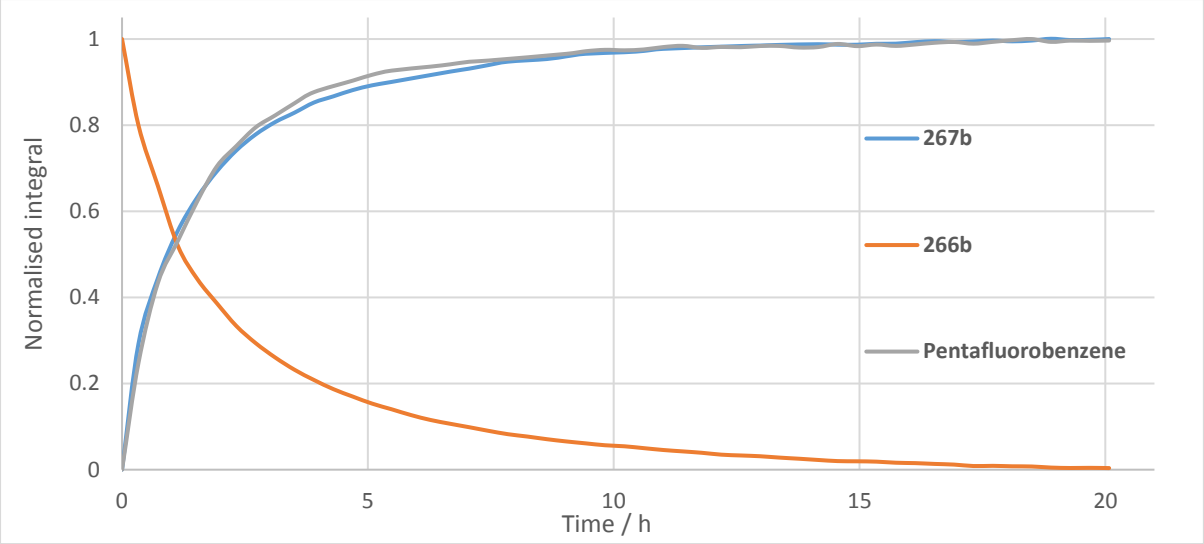


*Figure 3 – Reaction profile for the palladium(0)-catalysed cyclisation of substrate **266b**.*[XXXI]

The reaction profile of the cyclisation of **266b** is presented in Figure 3. Initially, the reaction proceeds rapidly; around 60 % of the final yield of **267b** is formed after 2 hours, and 90 % is achieved after 5 hours. The 24-hour reaction time is justified because the formation of **267b** continues until around 16 hours, and no significant product decomposition is observed following this. Protodecarboxylation of pentafluorobenzoate to pentafluorobenzene has been shown to be extremely facile.[104] This was also the case for the carbamate-based aza-Heck reaction, as formation of pentafluorobenzene was closely aligned to generation of **267b**, and pentafluorobenzoate was not observed in significant quantities.

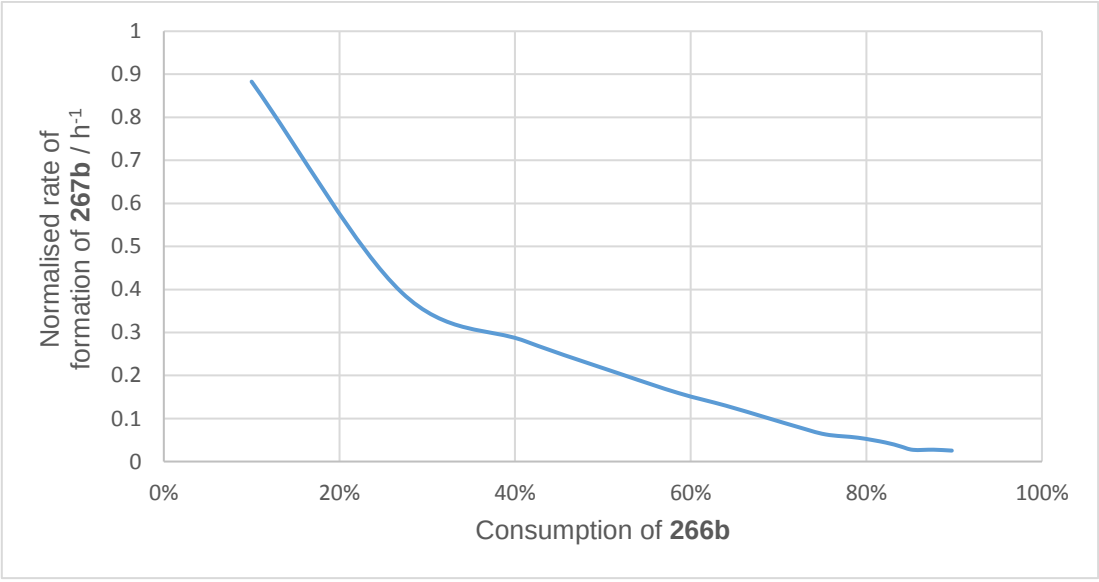
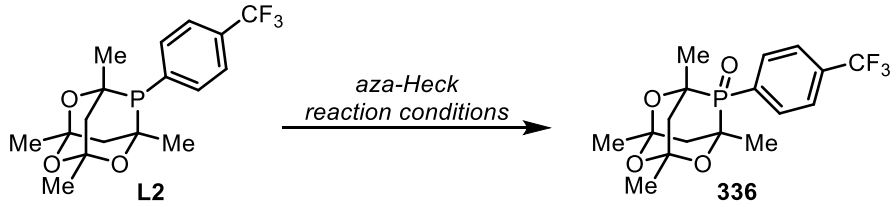


*Figure 4 – Graph of the rate of formation of **267b** vs. consumption of **266b**. Units of rate: 1 h^{-1} = final yield of **267b** formed in 1 hour.*

[XXXI] The Y-axis of Figure 3 corresponds to $\frac{[\mathbf{266b}]_t}{[\mathbf{266b}]_0}$ for the starting material and to $\frac{[product]_t}{[product]_\infty}$ for the products.

Assuming catalyst decomposition does not occur, the reaction would be expected to follow simple pseudo-first-order kinetics, where at any moment the rate of the reaction is proportional to the amount of starting material remaining. However, as can be seen from Figure 4, this was not the case, and proportionally much higher rates were observed at low conversion. Deactivation of the catalyst is likely to be responsible for this. As the reaction proceeds, the concentration of catalyst decreases; hence, the rate of reaction also decreases, even accounting for the lower concentration of **266b**.

The loss of significant quantities of phosphine ligand to oxidation could be responsible for catalyst deactivation, and the corresponding oxide of the ligand (*e.g.* **336**) was commonly observed at the end of the catalytic reactions (Scheme 129). There are a number of possible explanations for this, each with distinct implications. One possibility is that the oxidation occurs rapidly upon mixing the reagents and solvents but then halts. If this is the case, then the presence of peroxides in the ethereal solvents used in the reaction could be responsible. Alternatively, imperfectly sealed reaction vessels could allow sufficient oxygen into the reaction mixture to cause oxidation of the ligand; in this case, the *P*-oxide would build up at a fairly steady rate. Finally, oxidation may not occur under the reaction conditions and might simply be a result of exposing the crude reaction mixtures to air. Of these, the second scenario is most likely to cause the pattern of catalyst deactivation observed in the reaction monitoring.



Scheme 129 – Ligand oxidation under aza-Heck reaction conditions.

By monitoring the ^{31}P NMR spectrum of the mixture as the reaction progressed, the oxidation of the ligand could be followed. As can be seen from Figure 5, the oxidation of **L2** is rapid, with around 90 % of the final amount of **336** being formed after 20 minutes. However, the oxidation of **L2** halted at around 20 % conversion, consistent with a solvent- or reagent-mediated oxidation. This result appears to rule out ligand oxidation as being primarily responsible for catalyst decomposition. It is likely that relatively high ligand to palladium ratios are, at least in part, effective in the aza-Heck reaction as they counteract the effect of ligand oxidation.

Figure 6 shows how the ^{31}P resonance for **L2** varies with time. At the start of the reaction, the peak is very broad and shifted downfield relative to the free ligand, likely as a result of reversible coordination to palladium. As the reaction progresses, the **L2** peak sharpens and moves upfield. This could indicate loss of palladium from the reaction mixture, as lower quantities of palladium in solution would cause the **L2** peak to more closely resemble that of the free ligand. Consistent with this, a black or metallic residue was typically found on the inside of the reaction vessels at the end of the reactions. From the

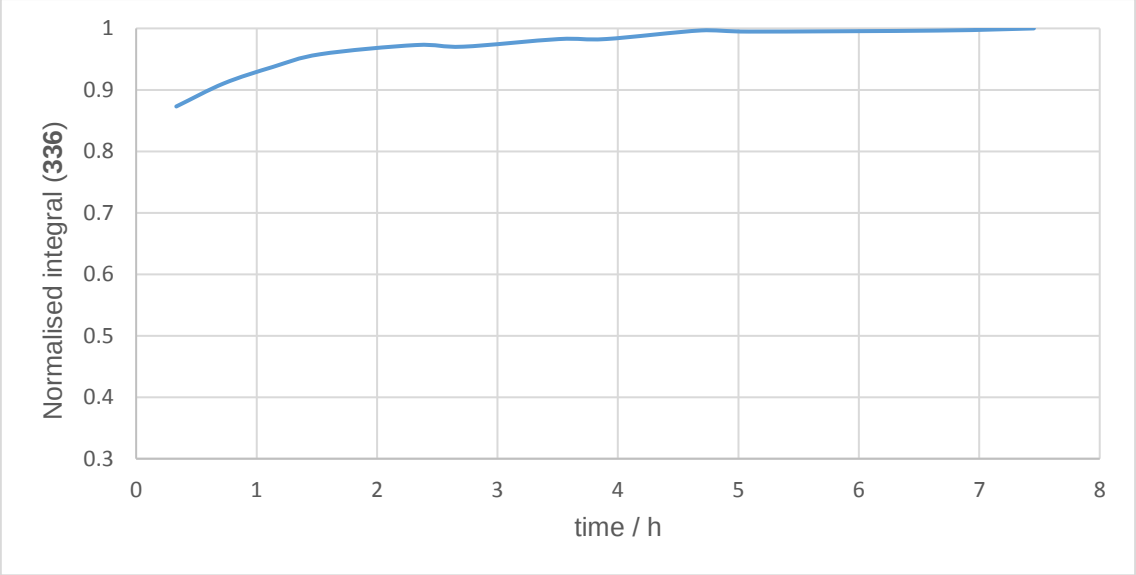


*Figure 5 – Reaction profile for the oxidation of **L2** to **336** in the palladium(0)-catalysed cyclisation of **266b**.*[XXXII]

results in Figure 5 and Figure 6, it appears catalyst deactivation occurs simply due to the instability of the palladium catalyst to aggregation and deposition, rather than as a result of oxidative loss of the phosphine ligand.

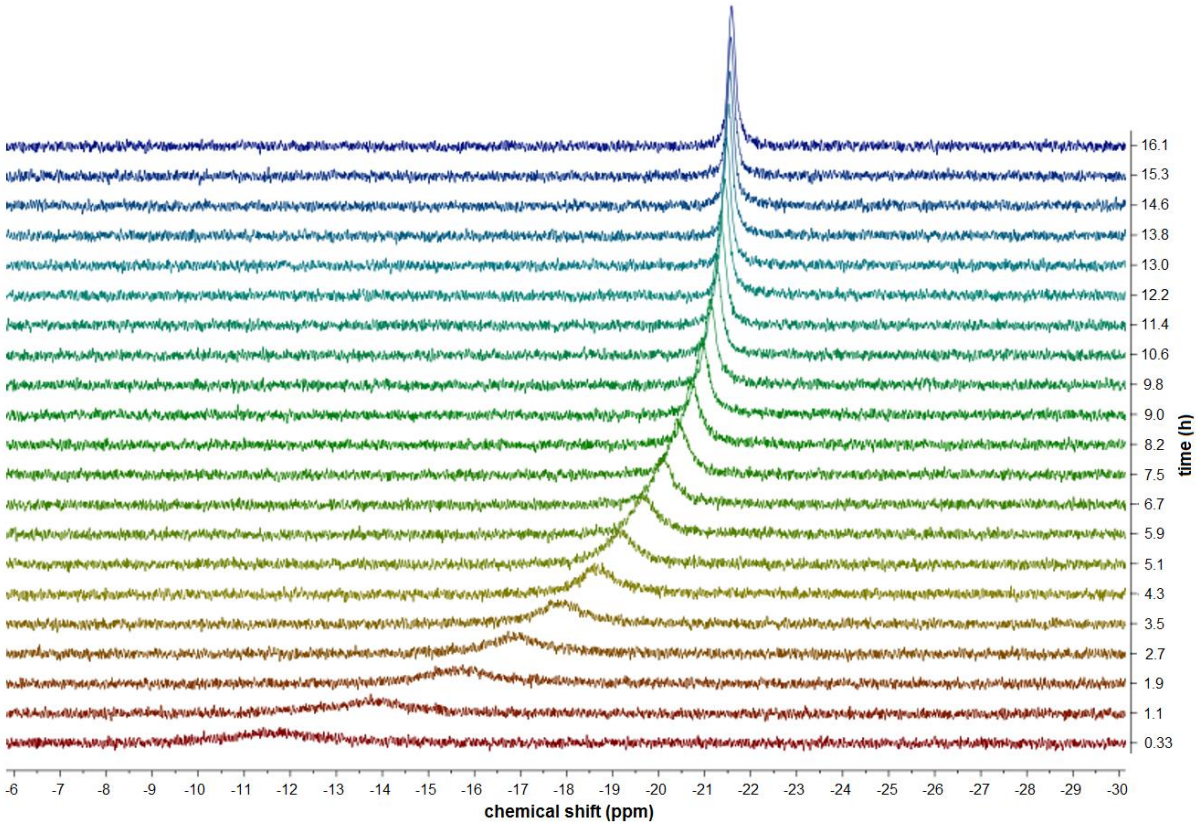


*Figure 6 – Variance of the ^{31}P resonance of **L2** during the cyclisation of **266b**.*

[XXXII] The Y-axis of Figure 6 corresponds to $\frac{[\mathbf{336}]_t}{[\mathbf{336}]_\infty}$.

3.6 Conclusions

The application of the aza-Heck reaction described in Chapter 2 to carbamate-protected substrates was successfully achieved. As well as providing products of greater synthetic value, the substrate scope of the carbamate variant was better in almost every regard compared to sulfonamide-based systems. Additionally, much greater levels of diastereoselectivity were generally observed in cyclisations to afford pyrrolidines containing substitution in the α-, β- and γ-positions (Section 3.3.3 *vs*. Section 2.4.2, Section 2.4.3 and Section 2.4.4). Excellent yields were obtained with substrates containing trisubstituted alkenes (Section 3.3.4), which were a limitation in the sulfonamide-based reaction (Section 2.4.5). Another limitation of the previous methodology, poor yields in 6-*exo* cyclisations, was overcome by switching to carbamate-protected substrates (Section 3.4). The success of unbiased 6-ring substrates **282a** and **285** (Scheme 112, Section 3.4.2 and Scheme 113b, Section 3.4.3) is particularly impressive; while aza-Heck cyclisations to form 6-membered rings had been reported previously,[90,109] good yields had only been achieved with benzo-fused substrates.[XXXIII]

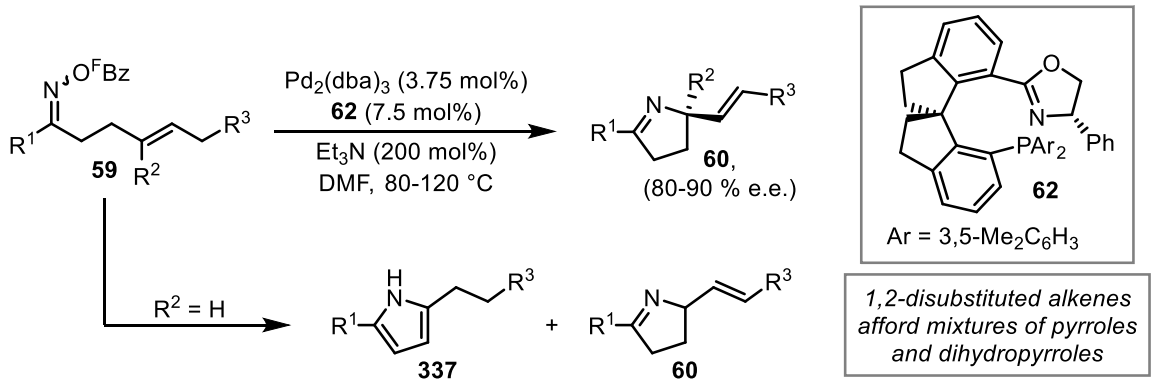
[XXXIII] Excluding one example of pyridine synthesis which proceeds through an unusual 6-*endo* cyclisation.[90]

Chapter 4 - An enantioselective aza-Heck reaction

4.1 Introduction

The aza-Heck reactions of *N*-acyloxysulfonamide (Chapter 2) and *N*-acyloxycarbamate substrates (Chapter 3) have provided powerful methods for the construction of 5- and 6-membered *N*-heterocycles. As these structures are ubiquitous in natural products[135,159-162] and pharmaceutical agents,[1] frequently with defined C–N stereocentres, an enantioselective variant of these cyclisations would be highly valuable.

Although enantioselective processes involving the *syn*-aminopalladation of alkenes had been demonstrated previously, such as the 1,2-aminoarylation reactions developed by Wolfe (Section 1.3),[80,86] the only example of an enantioselective aza-Heck reaction in the literature was recently reported by our group.[103] This methodology used a catalytic system of palladium(0) and P,N-based ligand **62** to convert oxime ester substrates (**59**) into enantioenriched dihydropyrroles (**60**) (Scheme 18, Section 1.4.2 and Scheme 130). The reaction tolerated substrates containing sterically demanding alkenes, allowing the enantioselective formation of highly congested C–N bonds. However, in addition to the general limitations of the Narasaka-Heck reaction (Section 1.4.2), systems with 1,2-disubstituted alkenes were not suitable for the enantioselective cyclisation. This is due to competing formation of pyrrole **337** limiting the yield of dihydropyrrole product **60** (Scheme 130).[103] Furthermore, the enantioselectivies achieved were somewhat low (80-90 % e.e.).



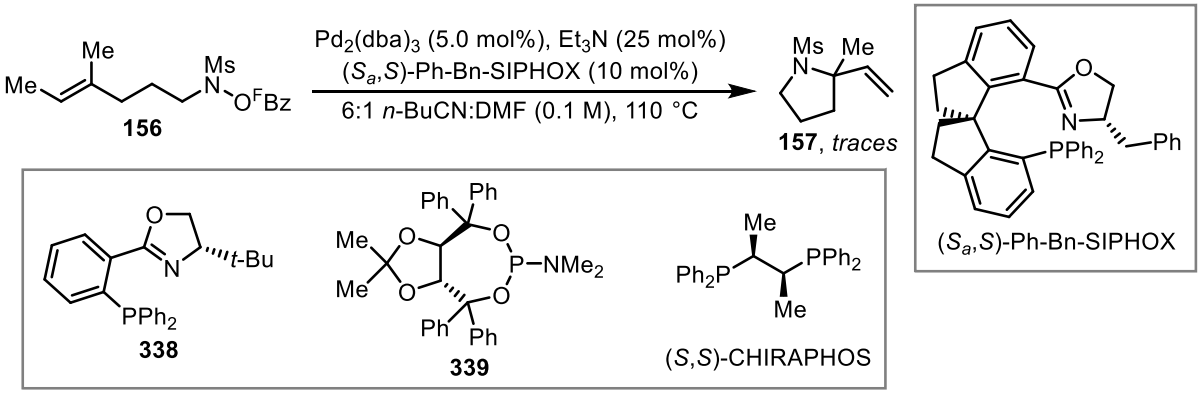
Scheme 130 – Palladium(0)-catalysed enantioselective Narasaka-Heck reaction.[103]

The key challenge for the development of further enantioselective aza-Heck reactions was the identification of ligand systems which not only provide high levels of enantioinduction but also result in efficient cyclisations. In order to achieve this, the use of chiral ligands in the aza-Heck reactions detailed in Chapters 2 and 3 was investigated.

4.2 Investigations into enantioselective aza-Heck cyclisations of *N*-acyloxysulfonamide substrates

Initial work focused on the development of an enantioselective aza-Heck reaction of sulfonamide-based substrates. Substrate **156** was identified as an ideal candidate to conduct a chiral ligand screen on, as the alkene substitution pattern contained in **156** was effective in the enantioselective cyclisation of oxime esters reported by our group (Scheme 130).[103] Additionally, the product of the reaction is sufficiently volatile to allow for analysis by chiral phase GC. When the optimal commercially available ligand for the enantioselective cyclisation of oxime esters, (S_a,*S*)-Ph-Bn-SIPHOX,[103] was used with substrate **156**, a negligible yield of **157** was obtained (Scheme 131). Nine further chiral ligands (such as **338**, **339** and (*S*,*S*)-CHIRAPHOS) were screened for the cyclisation of **156**; however, formation of significant quantities of **157** was not observed with any of the ligands employed.

The application of the aza-Heck reaction of *N*-acyloxysulfonamides to enantioselective cyclisations appeared to be hindered by its restrictive ligand requirements. During optimisation of that reaction (Section 2.3.3), few ligands were found to provide comparable yields to those obtained using $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (Table 21 and Table 22, Appendix). A similar problem was encountered in the development of the enantioselective Narasaka-Heck reaction, although to a lesser extent.[103]

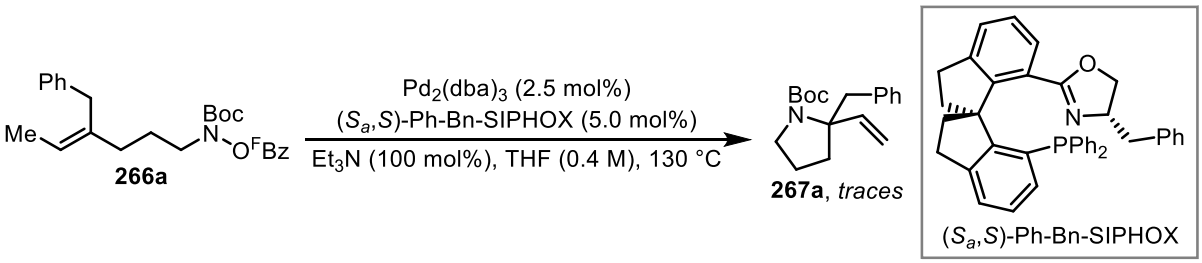


*Scheme 131 – Attempted enantioselective aza-Heck cyclisation of substrate **156**.*

4.3 Enantioselective aza-Heck cyclisations of *N*-acyl- and *N*-sulfonyl-oxycarbamate substrates

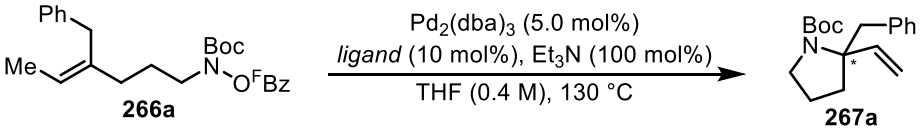
4.3.1 Reaction discovery

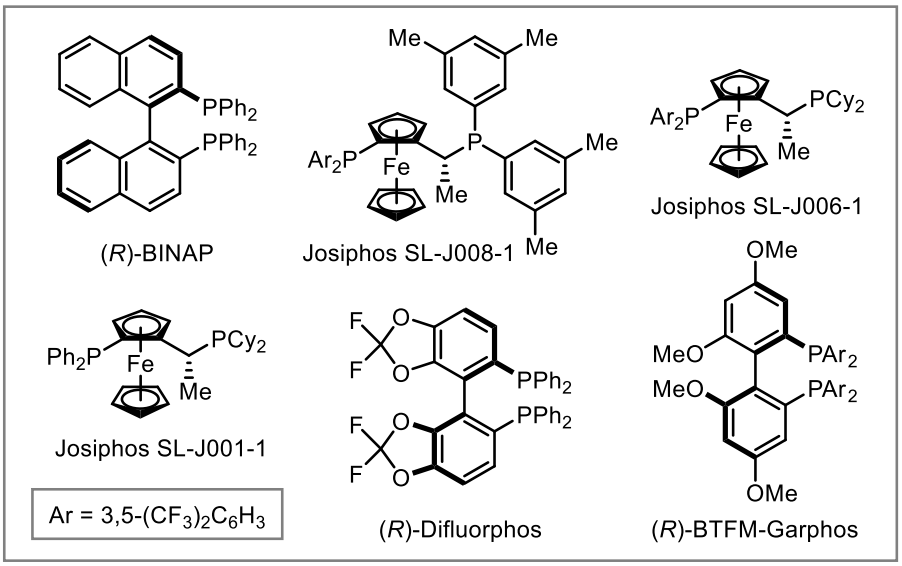
The carbamate-based aza-Heck reaction described in the preceding chapter exhibited far better ligand tolerance, as well as wider substrate scope, than the sulfonamide-based reaction outlined in Chapter 2. Consequently, it was anticipated that the former reaction would prove more amenable to the development of a highly asymmetric protocol. Substrate **266a** was selected for an initial ligand screen; the incorporation of a phenyl group makes **267a** detectable by UV spectroscopy, which renders it suitable for analysis by chiral phase SFC. Due to the thermal instability of *N*-Boc groups,[157,158] chiral phase GC was not considered suitable for the determination of enantiomeric excess.



*Scheme 132 – Attempted enantioselective aza-Heck cyclisation of substrate **266a**.*

As observed with substrate **156** (Scheme 131), (*S*$_a$,*S*)-Ph-Bn-SIPHOX proved ineffective at promoting the cyclisation of **266a** (Scheme 132). More promising results were achieved using other bidentate ligands, and the best of these are presented in Table 16. Some reactivity was observed using Josiphos ligands (Table 16, entries 2-4), albeit with no enantioselectivity. Biaryl ligands generated similar yields of **267a** to Josiphos ligands but with measurable, although modest, enantioselectivity (Table 16, entries 1, 5 and 6).



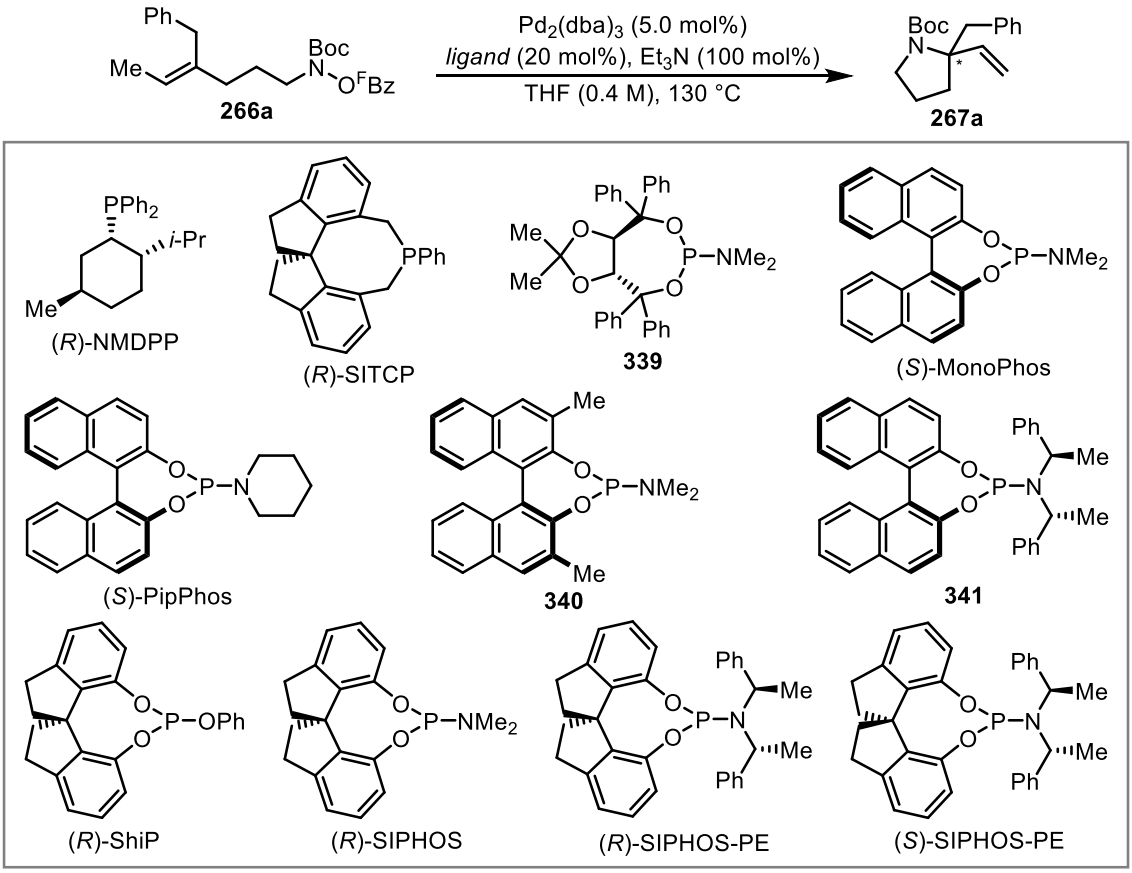


Entry	*ligand*	*yield*	*e.e.*
1	(*R*)-BINAP	24 %	28 %
2	Josiphos SL-J008-1	18 %	*none*
3	Josiphos SL-J006-1	41 %	*none*
4	Josiphos SL-J001-1	26 %	6 %
5	(*R*)-Difluorphos	19 %	27 %
6	(*R*)-BTFM-Garphos	40 %	22 %

*Table 16 – Bidentate ligand screen for the enantioselective aza-Heck cyclisation of substrate **266a**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard.*

With only minor progress being made towards the enantioselective cyclisation of **266a** using bidentate ligands (Table 16), chiral monodentate ligands were assayed (Table 17). Achiral monodentate ligands have previously been found to be more effective than bidentate ligands in aza-Heck reactions (Table 21 and Table 22, Appendix and Table 9, Section 3.2.2), and higher yields were also obtained with chiral monodentate ligands in the enantioselective cyclisation. While a promising result (58 % yield, 27 % e.e.) was achieved using (*R*)-SITCP (Table 17, entry 2), similar ligands were not evaluated due to a lack of availability. Chiral phosphoramidites are comparatively more accessible, and a number of these were employed in the reaction (Table 17, entries 3-7 and 9-11). SPINOL-based ligand (*R*)-SIPHOS-PE provided the best result accomplished thus far, both in terms of yield and enantioselectivity (Table 17, entry 10). Following this, it was found that (*S*)-SIPHOS-PE, the

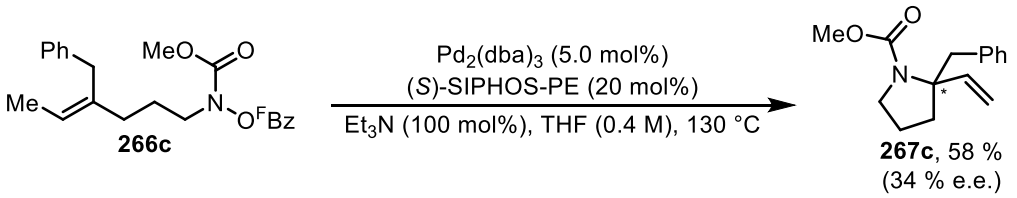
diastereomer of (*R*)-SIPHOS-PE, provided a far greater level of enantiomeric induction, with **267a** isolated in 74 % yield and 61 % e.e. (Table 17, entry 11).



Entry	*ligand*	*yield*	*e.e.*
1	(*S*)-NMDPP	55 %	11 %
2	(*R*)-SITCP	58 %	27 %
3	**339**	62 %	*none*
4	(*S*)-MonoPhos	59 %	22 %
5	(*S*)-PipPhos	68 %	8 %
6	**340**	52 %	*none*
7	**341**	60 %	22 %
8	(*R*)-ShiP	64 %	33 %
9	(*R*)-SIPHOS	64 %	6 %
10	(*R*)-SIPHOS-PE	70 %	37 %
11	(*S*)-SIPHOS-PE	(74 %)	61 %

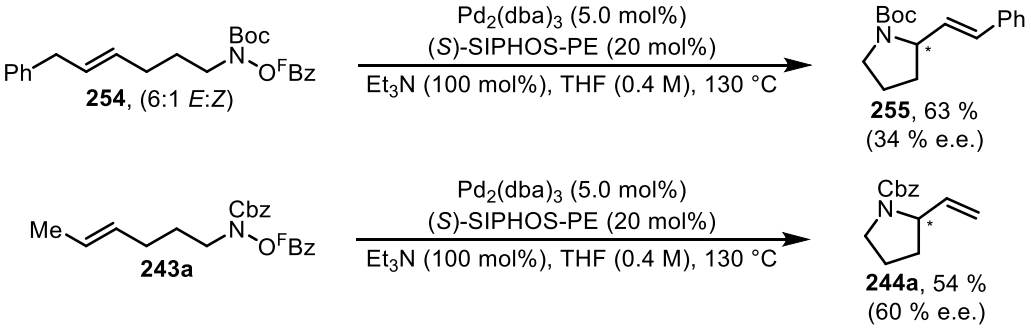
*Table 17 – Monodentate ligand screen for the enantioselective aza-Heck cyclisation of substrate **266a**. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses.*

Having identified a promising ligand for the enantioselective aza-Heck reaction, the effects of the protecting group and alkene substitution pattern were examined. To this end, the cyclisation of methyl carbamate substrate **266c** (*see the experimental section*) was assessed. Under identical conditions to the cyclisation of **266a** (Table 17, entry 11), a comparable yield of **267c** was achieved from **266c** (Scheme 133), but the product was formed with substantially lower e.e. than **267a** (34 % *vs.* 61 % e.e.), indicating that the protecting group has an influence on product enantioselectivity.



*Scheme 133 – Synthesis and enantioselective aza-Heck cyclisation of substrate **266c**.*

Substrates **254** and **243a**, both containing a 1,2-disubstituted alkene, were also evaluated in the enantioselective aza-Heck reaction. Substrate **254** cyclised in good yield but with only 34 % e.e. (Scheme 134). The fact that **254** was prepared as a 6:1 mixture of alkene isomers might explain the low enantioselectivity observed in the cyclisation step. While alkene geometry has only a limited effect on cyclisations to afford racemic products (Table 13, Section 3.4.2), it was established later that it has a more pronounced effect on enantioselective cyclisations (Section 4.3.2). In contrast to **254**, substrate **243a** generated **244a** with 60 % e.e. (Scheme 134), thus demonstrating that substrates containing 1,2-disubstituted alkenes are viable in the enantioselective aza-Heck reaction. This element of substrate scope was not tolerated in the previously reported oxime ester-based enantioselective cyclisation (Scheme 130, Section 4.1).[103]

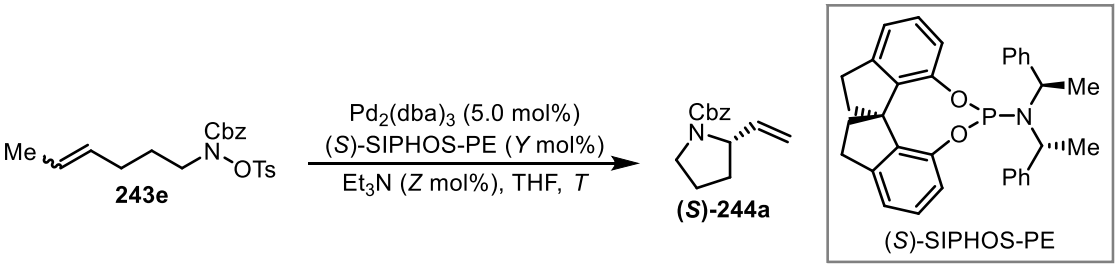


*Scheme 134 – Enantioselective aza-Heck cyclisation of substrates **254** and **243a**.*

4.3.2 Optimisation of the carbamate-based enantioselective aza-Heck reaction

Following the discovery that (*S*)-SIPHOS-PE is an effective ligand for achieving moderate levels of enantioselectivity in the aza-Heck cyclisation, continued optimisation of the reaction was undertaken by Dr Xiaofeng Ma. The results presented in this section are not detailed in the experimental.

The use of tosyl-activated substrate **243e** in the enantioselective aza-Heck cyclisation led to a significantly more efficient cyclisation, with **244a** generated in quantitative yield (Table 18, entry 1), compared to 54 % yield from O^FBz-activated **243a** (Scheme 134). Although similar enantioselectivities were obtained with **243a** and **243e** under the same conditions, the increased reactivity of **243e** allowed the cyclisation to proceed at lower temperatures, where **244a** was formed with greater e.e. (Table 18, entries 2-5). Finally, conducting the reaction at higher dilution provided a modest increase in enantioselectivity (Table 18, entry 7). The enantioselective cyclisation was found to display a significant preference for substrates containing 1,2-disubstituted akenes with (*E*)-geometry, and **(*Z*)-243e** cyclised with significantly diminished yield and enantioselectivity relative to **(*E*)-243e** (Table 18, entry 8). It is interesting to note that a relatively low ligand to palladium ratio of 1.2:1 provides comparable results to those achieved with a 2:1 ratio, potentially indicating that only one molecule of ligand is bound to palladium in the active catalyst. This is in contrast to the aza-Heck reactions of *N*-acyloxysulfonamides and *N*-acyloxycarbamates (Chapters 2 and 3, respectively), which both used ligand to palladium ratios of greater than 2.5:1.



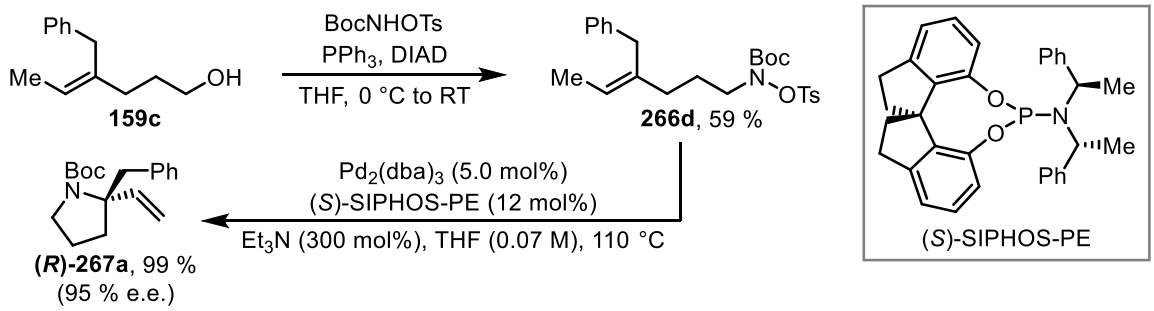
Entry	*substrate*	*temperature*	*concentration*	*Y*	*Z*	*yield*	*e.e.*
1	**(*E*)-243e**	130 °C	0.4 M	20	100	99 %	66 %
2	**(*E*)-243e**	130 °C	0.4 M	12	100	66 %	66 %
3	**(*E*)-243e**	110 °C	0.4 M	12	100	99 %	80 %
4	**(*E*)-243e**	90 °C	0.4 M	12	100	99 %	80 %
5	**(*E*)-243e**	70 °C	0.4 M	12	100	85 %	80 %
6	**(*E*)-243e**	50 °C	0.4 M	12	100	78 %	72 %
7	**(*E*)-243e**	110 °C	0.07 M	12	300	93 %	82 %
8	**(*Z*)-243e**	110 °C	0.07 M	12	300	56 %	42 %

*Table 18 – Optimisation of the enantioselective aza-Heck cyclisation of substrate **243e**.*[XXXIV] *– Results obtained by Dr Xiaofeng Ma.*

[XXXIV] The absolute configuration of **(*S*)-244a** was assigned by comparison of its specific rotation to a literature value.[163]

4.3.3 Enantioselective aza-Heck cyclisations involving trisubstituted alkenes

With a substantial improvement achieved in the enantioselective cyclisation of a substrate containing a 1,2-disubstituted alkene (**243e**), the reactions of substrates containing trisubstituted alkenes were re-examined. Having identified that the use of a tosyl activating group is beneficial for the enantioselective aza-Heck reaction (Table 18), substrate **266d** was prepared. When trialled with the newly optimised conditions, **266d** produced a considerably better result than O^{F}Bz system **266a**, and **(*R*)-267a** was generated in quantitative yield and with 95 % e.e. (Scheme 135, *cf.* Table 17, entry 11, Section 4.3.1).[XXXV]

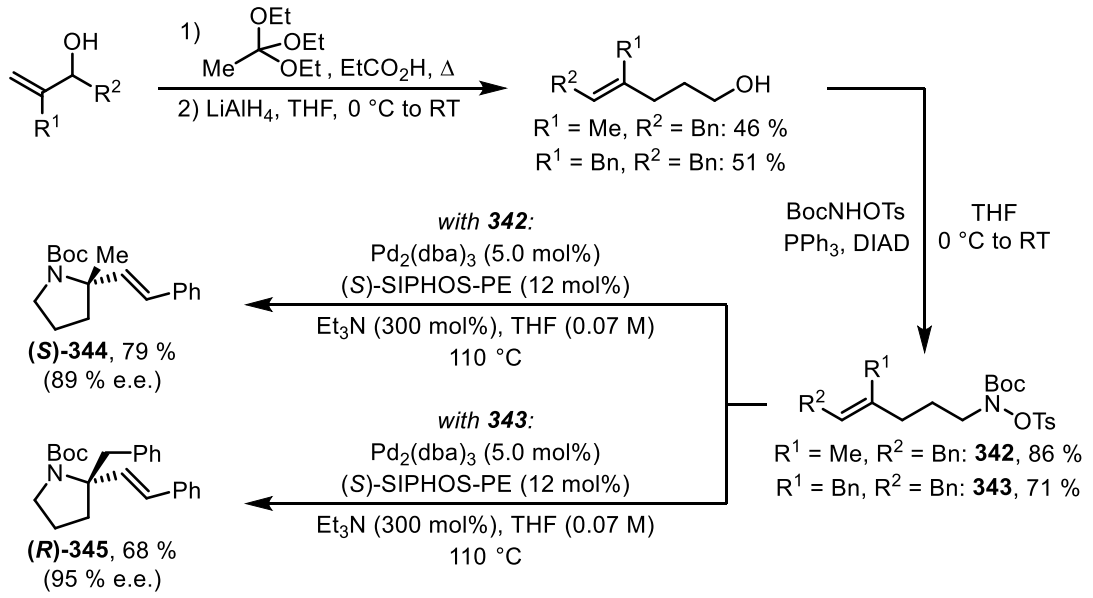


*Scheme 135 – Synthesis and enantioselective aza-Heck cyclisation of substrate **266d**.*[XXXVI]

Following the excellent result obtained with substrate **266d**, the effects of different alkene substitution patterns were investigated. Pleasingly, substrate **342**, which contains a less sterically demanding methyl substituent at R^1, cyclised to afford **(*S*)-344** in 79 % yield and with 89 % e.e. (Scheme 136). While this was a good result, **(*S*)-344** was formed in lower enantiopurity than the 95 % e.e. achieved for **(*R*)-267a**. As alkene substitution differs in two places between **342** and **266d**, it was not possible to identify which change caused the lower enantioselectivity observed with **342** from those results alone. In order to determine this, substrate **343** was prepared and used in the enantioselective aza-Heck reaction (Scheme 136). Pyrrolidine **(*R*)-345** was formed with 95 % e.e., the same as **267a** (Scheme 135); this suggests that for trisubstituted alkenes, the substituent proximal to nitrogen is key to determining enantioselectivity, with larger groups resulting in higher levels of enantioselectivity.

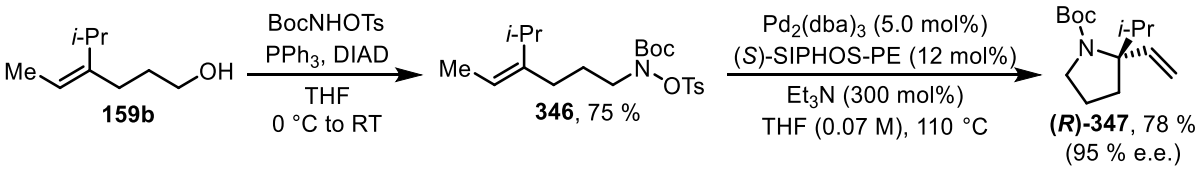
[XXXV] The absolute configuration of **(*R*)-267a** was determined by X-ray diffraction analysis of a brosyl derivative. This was carried out by Dr Xiaofeng Ma (University of Bristol) and hence is not detailed in the experimental section. The absolute configurations of the other products contained in this section were assigned by analogy to **(*R*)-267a**.

[XXXVI] BocNHOTs was prepared by Joshua Farndon (University of Bristol) according to a literature procedure.[164]



*Scheme 136 – Synthesis and enantioselective aza-Heck cyclisation of substrates **342** and **343**.*

Although substrate **343** contains a highly congested alkene, all of the substituents are primary. To examine the tolerance of secondary substituents, a substrate (**346**) containing an *i*-propyl group was synthesised (Scheme 137). When **346** was exposed to the enantioselective aza-Heck conditions, **(*R*)-347** was formed in good yield and with 95 % e.e. (Scheme 137). The result achieved with **346** demonstrates the power of this methodology: sterically congested tertiary C–N bonds can be formed with excellent enantioselectivity, and the further derivatisation of products is trivial due to the ease of *N*-Boc removal.

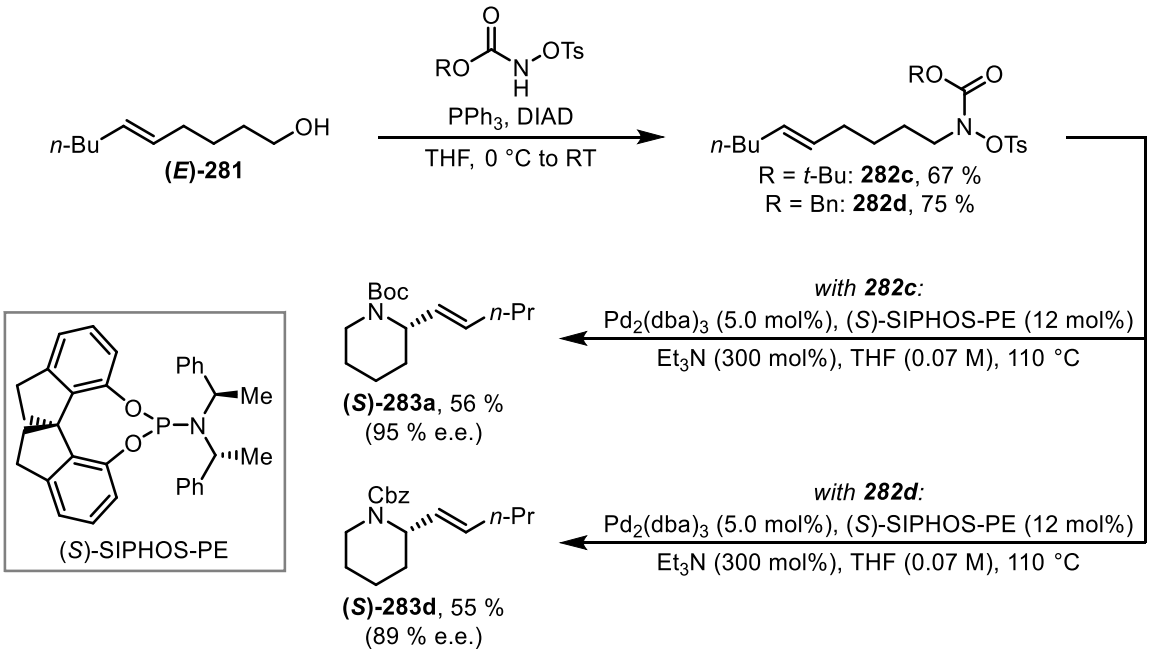


*Scheme 137 – Synthesis and enantioselective aza-Heck cyclisation of substrate **346**.*

4.3.4 Enantioselective aza-Heck cyclisations to form 6-membered rings

The enantioselective aza-Heck reaction was then applied to the synthesis of piperidines. With previous systems, aza-Heck cyclisations to form products containing 6-membered rings were found to be considerably more challenging than those that form 5-membered rings, although good yields were achieved with carbamate-based substrates (Section 3.4). Reactions of *N*-tosyloxycarbamates proceeded with significantly greater efficiency than the analogous $O^{F}Bz$-activated substrates in the synthesis of pyrrolidines (*cf.* Table 18, Section 4.3.2 with Scheme 93c, Section 3.3.1, and Scheme 135, Section 4.3.3 with Scheme 104, Section 3.3.4), and it was hoped that this increase in efficiency would also be observed for piperidine-forming cyclisations. Substrates **282c** and **282d** were prepared from **(*E*)-281** (Scheme 138). While the two substrates cyclised in almost identical yield (56 % *vs.* 55 %), the

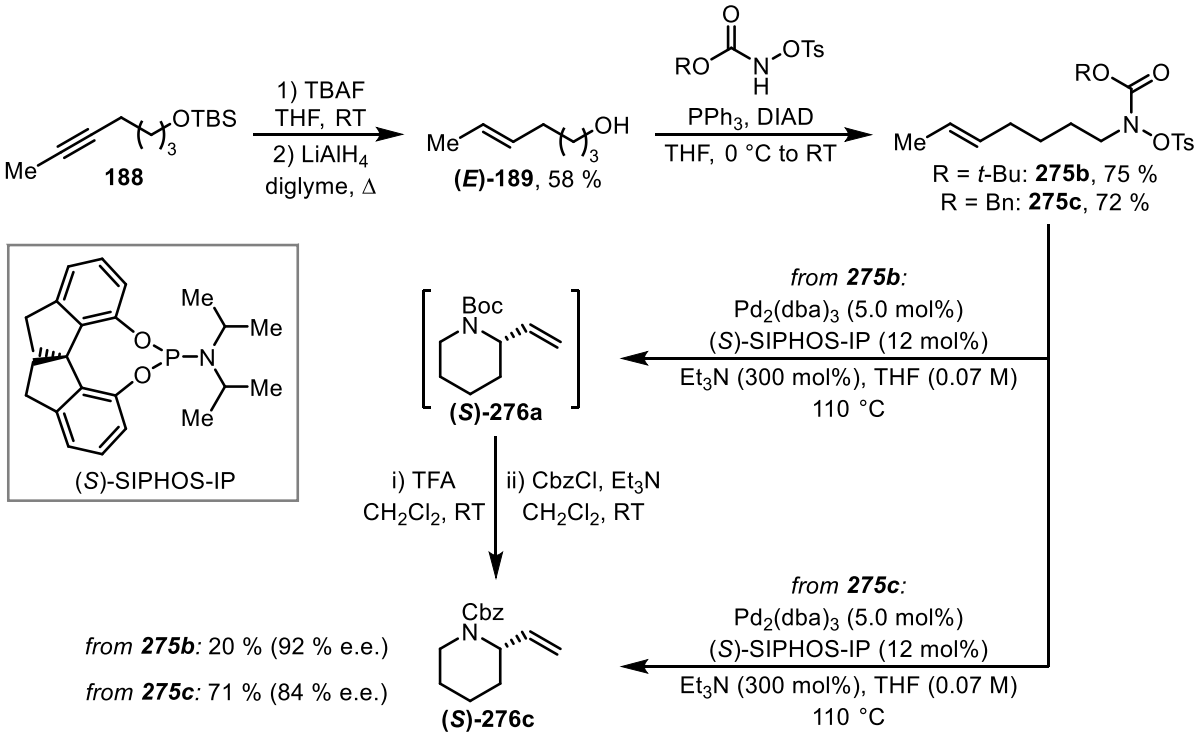
N-Boc-protected substrate **282c** provided **(*S*)-283** with higher enantioselectivity (95 % *vs*. 89 % e.e., Scheme 138).



*Scheme 138 – Synthesis and enantioselective aza-Heck cyclisation of substrates **282c** and **282d**.*[XXXVII]

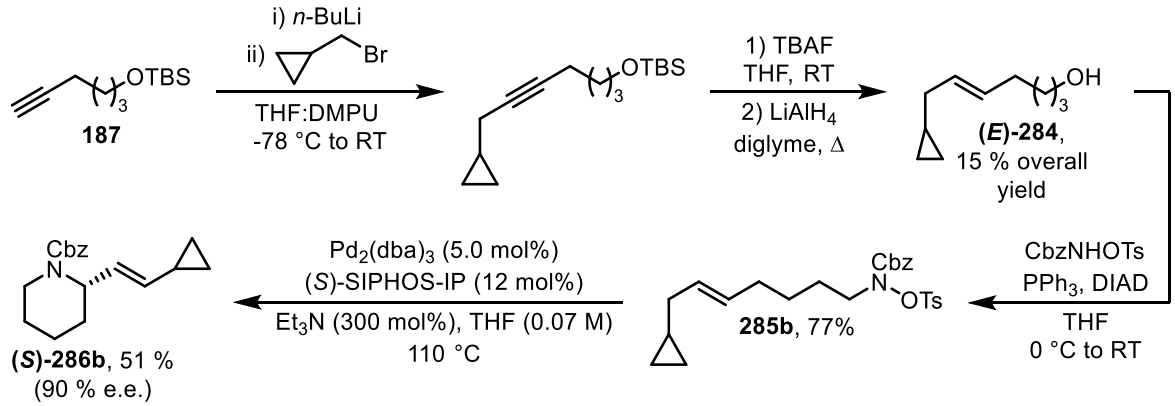
Next, the effects of the alkene substituent were investigated, and a substrate (**275**) containing an alkene with methyl, as opposed to *n*-butyl, substitution was targeted. Both the *N*-Boc- and the *N*-Cbz-protected variants (**275b** and **275c**, respectively) were prepared from alcohol **(*E*)-189** (Scheme 139). When employed in the enantioselective aza-Heck reaction using (*S*)-SIPHOS-PE, substrate **275c** cyclised in low yield; however, the use of the related but less sterically demanding ligand (*S*)-SIPHOS-IP[XXXVIII] led to a good yield of **(*S*)-276c**,[XXXIX] albeit in lower enantioselectivity than observed with (*S*)-SIPHOS-PE (Scheme 139, *cf.* **283d** in Scheme 138). As higher e.e. values are typically obtained with *N*-Boc-protected substrates, the cyclisation of **275b** was also investigated. Due to the problems previously encountered in the isolation of **276a** (Scheme 108, Section 3.4.1), **(*S*)-276a** was converted directly into the *N*-Cbz analogue **(*S*)-276c**, as this was necessary for the determination of enantiomeric excess. However, despite significantly higher enantioselectivity achieved in the reaction of **275b**, **(*S*)-276c** was isolated in only 20 % overall yield (Scheme 139).

[XXXVII] CbzNHOTs was prepared by Dr Xiaofeng Ma (University of Bristol) according to a literature procedure.[164]
[XXXVIII] (*S*)-SIPHOS-IP was prepared by Dr Xiaofeng Ma (University of Bristol) using an adaptation of a literature procedure.[165]
[XXXIX] The absolute configuration of **(*S*)-276c** was assigned by comparison of its specific rotation to a literature value.[166] The absolute configurations of the other products contained in this section were assigned by analogy to **(*S*)-276c**.



*Scheme 139 – Synthesis and enantioselective aza-Heck cyclisation of substrates **275b** and **275c**.*[XXXVIII]

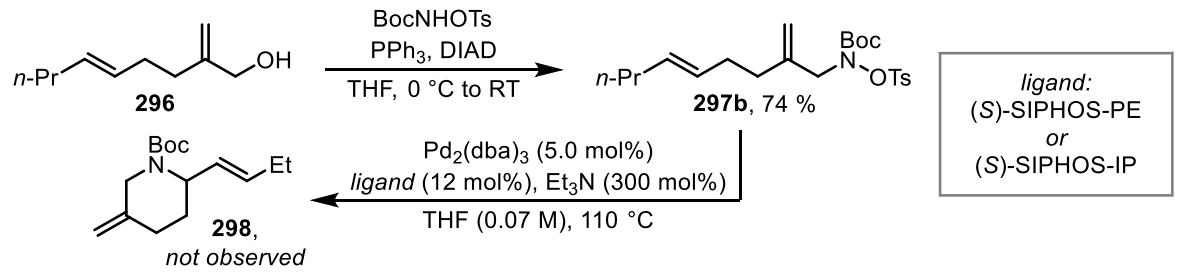
In cyclisations to afford racemic products, cyclopropyl substrate **285a** was found to provide a similar result to **(*Z*)-282a** (Scheme 112, Section 3.4.2 and Scheme 113b, Section 3.4.3). Because of this, **285** was considered a good candidate for the enantioselective aza-Heck cyclisation, and alcohol **(*E*)-284** was converted into substrate **285b** (Scheme 140). Substrate **285b** cyclised to afford **(*S*)-286b** in 51 % yield and with 90 % e.e., a comparable result to that achieved with **282d** (Scheme 138).



*Scheme 140 – Synthesis and enantioselective aza-Heck cyclisation of substrate **285b**.*

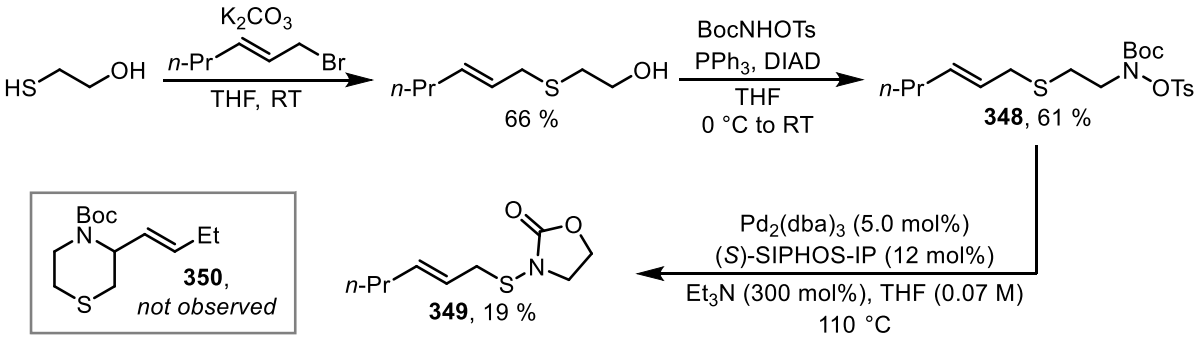
Substrate **297b**, which is analogous to O^{F}Bz-activated substrate **297a** (Scheme 118, Section 3.4.4), was synthesised (Scheme 141). It was hoped that **297** would provide a better result in the enantioselective aza-Heck reaction than it did in the cyclisation to afford racemic products, as there is a preference for substrates containing (*E*)-alkenes in the former (Section 4.3.2), compared to a preference for (*Z*)-alkenes

in the latter (Table 13, Section 3.4.2). Unfortunately, this was not the case, and when **297b** was exposed to the reaction conditions, **298** was not observed (Scheme 141).



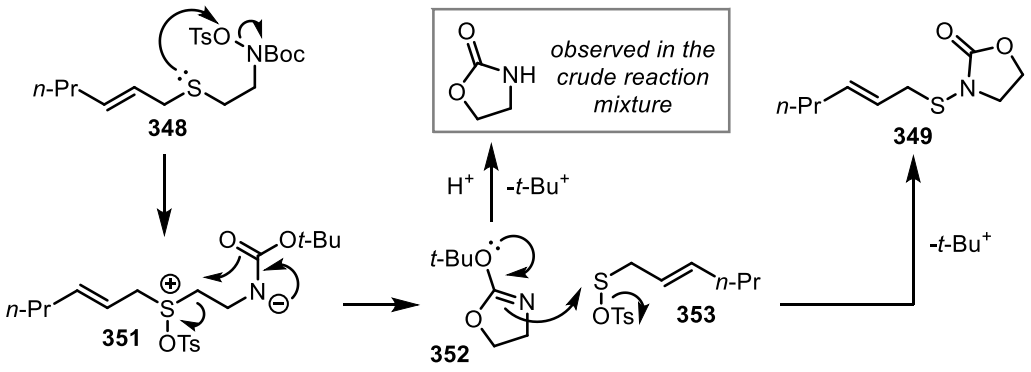
*Scheme 141 – Synthesis and attempted enantioselective aza-Heck cyclisation of substrate **297b**.*

In order to continue assessing the scope of the enantioselective cyclisation, further substrates were sought. While a variety of 6-ring substrates had previously been prepared (Section 3.4), many of these were deemed unsuitable for use in the enantioselective reaction, as they either cyclised in negligible yields or generated achiral products. This led to the examination of a previously untested class of substrate, and **348**, containing a sulfur-based tether, was prepared (Scheme 142). When **348** was employed in the enantioselective aza-Heck cyclisation, target **350** was not observed, and side product **349** was isolated in 19 % yield (Scheme 142).



*Scheme 142 – Synthesis and attempted enantioselective aza-Heck cyclisation of substrate **348**.*

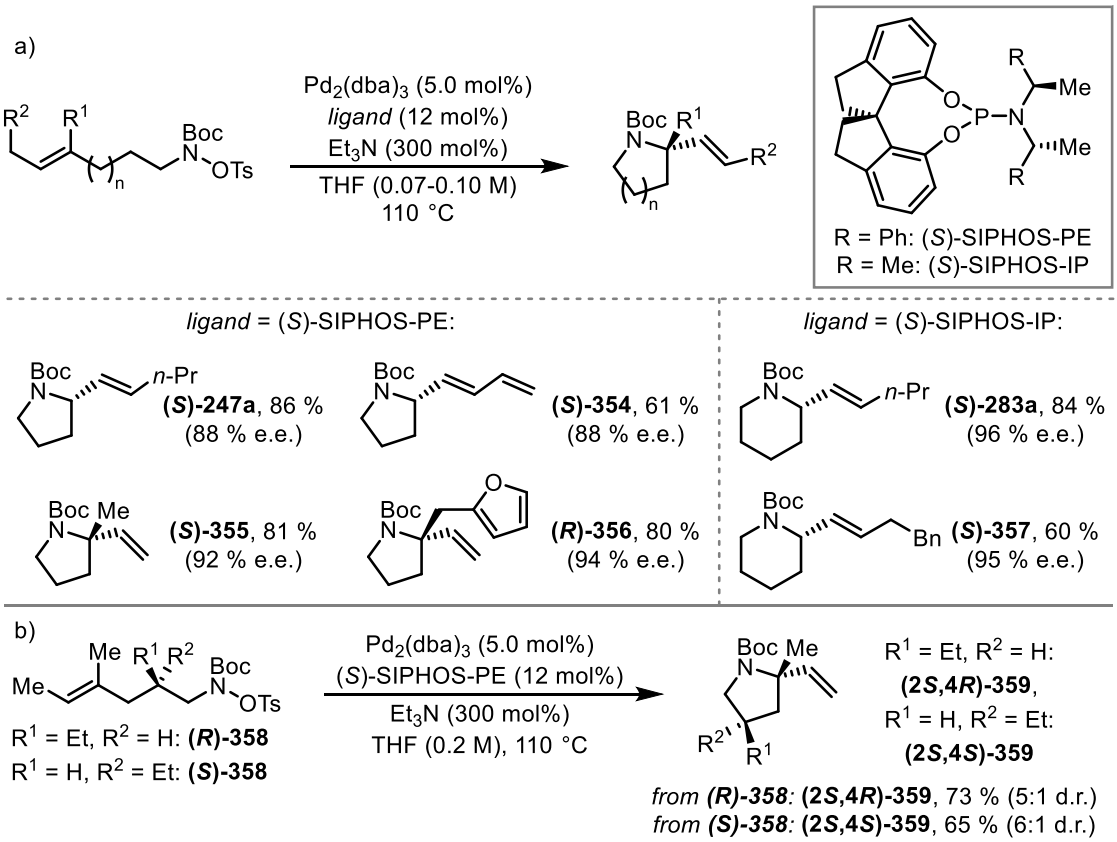
The proposed mechanism for the formation of **349** is outlined in Scheme 143. Intramolecular oxidation of the sulfur atom in **348** affords betaine **351**, which undergoes ring closure to form **352** and expel *O*-tosyl sulfanol derivative **353**. Nucleophilic attack of **352** on **353**, followed by loss of a *t*-Bu cation, provides **349**. Acid-catalysed cleavage of the *t*-Bu group of **352** evidently occurs as well, as oxazolidine-2-one was observed in the crude reaction mixture by ^{1}H NMR spectroscopy. The observation that substrate **348** is unstable to the enantioselective aza-Heck conditions likely explains the absence of desired thiomorpholine **350**.



*Scheme 143 – Proposed mechanism for the formation of side product **349** from substrate **348**.*

4.3.5 Further evaluation of the substrate scope for the enantioselective aza-Heck reaction

Continued exemplification of the enantioselective aza-Heck reaction was undertaken by Dr Xiaofeng Ma, and selected results are presented in Scheme 144. These results are not detailed in the experimental section.



*Scheme 144 – a) Further enantioselective aza-Heck cyclisations of N-sulfonyloxycarbamate substrates. b) Catalyst-controlled diastereoselectivity in the enantioselective aza-Heck cyclisation of substrate **358**. – Results obtained by Dr Xiaofeng Ma.*

The enantioselective aza-Heck cyclisation allowed the synthesis of pyrrolidines from substrates containing 1,2-disubstituted alkenes (**(*S*)-247a** and **(*S*)-354**), although slightly lower enantioselectivities were observed in this kind of process. Additional examples of substrates containing trisubstituted alkenes were demonstrated (**(*S*)-355** and **(*R*)-356**), and improvements were made to the yields obtained

in cyclisations to form piperidines (**(*S*)-283a** and **(*S*)-357**). Using substrate **358**, containing a defined stereocentre in the β-position, good diastereoselectivities could be achieved with catalyst control (Scheme 144b).

4.4 Conclusions

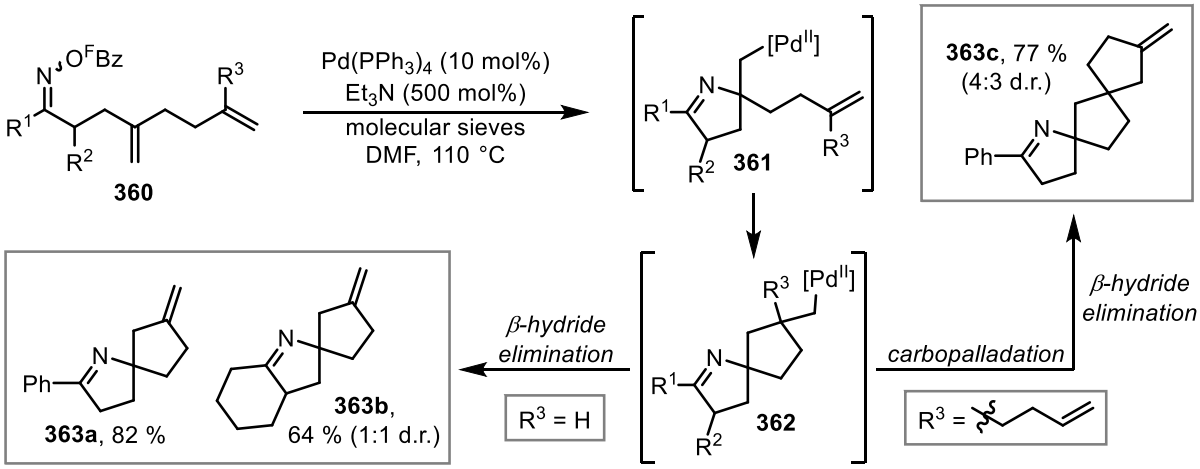
The carbamate-based aza-Heck reaction outlined in Chapter 3 has been successfully adapted into a highly asymmetric variant. The developed reaction constituted an effective method for preparing enantiopure pyrrolidines and piperidines, and tolerated systems containing both 1,2-disubstituted and trisubstituted alkenes. A manuscript based on the work presented in this chapter is currently being prepared for submission.

The methodology presented in this chapter is a far more versatile alternative to previously reported aza-Wacker cyclisations,[43,167,168] as the latter are currently limited to forming 5-membered rings and often make use of tosyl protecting groups. Furthermore, the substrate scope of enantioselective aza-Wacker processes is either limited with respect to alkene partner or restricted to specific substrate classes, *e.g.* benzo-fused systems. By comparison, the combination of the ring size and alkene substitution tolerance of the enantioselective aza-Heck cyclisation, along with the synthetic flexibility of the products, far surpasses what is possible with enantioselective aza-Wacker cyclisations.

Chapter 5 - Aza-Heck cascade reactions

5.1 Introduction

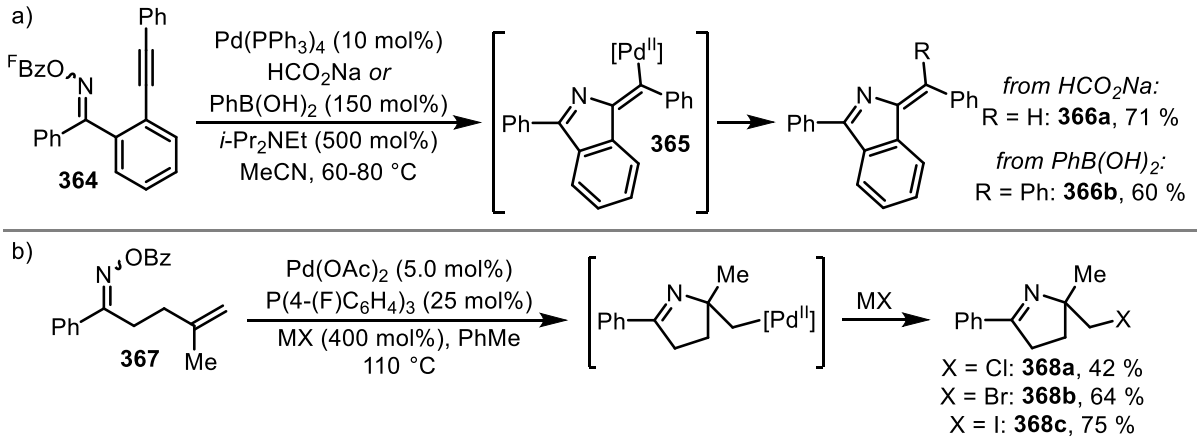
The initiation mode of the Narasaka-Heck reaction has previously been applied to a variety of aza-Heck cascade processes. Shortly after publishing his seminal report on aza-Heck reactions, Narasaka disclosed an aza-Heck/Heck cyclisation cascade of oxime esters (Scheme 145).[169] Here, oxidative addition of **360** and aminopalladation of the pendant alkene provides intermediate **361**, which cannot undergo β-hydride elimination. Instead, carbopalladation of the second olefin occurs to afford **362**, which releases spirocyclic imine **363** through β-hydride elimination. This strategy can also be adapted to form three rings, as demonstrated by the formation of tricyclic imine **363c**. In this case, a further carbopalladation step occurs from intermediate **362**.



Scheme 145 – Palladium(0)-catalysed aza-Heck/Heck cyclisations using the Narasaka-Heck initiation mode.[169]

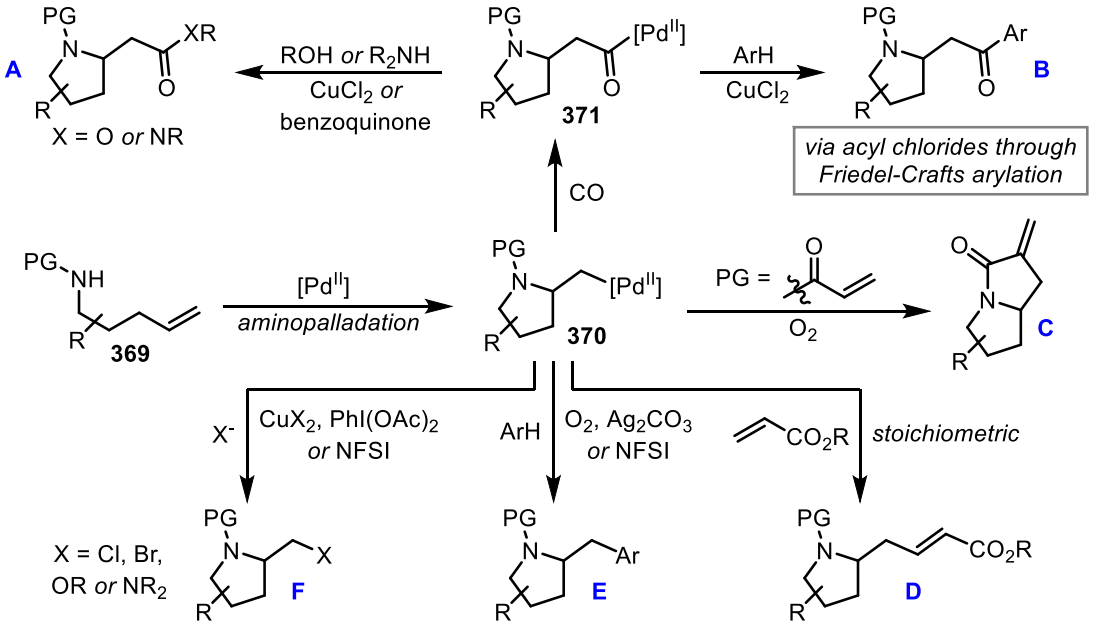
Oxime esters have also been used in partially intermolecular aza-Heck cascade reactions. Nucleophilic trapping of organopalladium(II) intermediate **365**, generated by cyclisation of alkynyl substrate **364**, was demonstrated by Kitamura (Scheme 146a).[170] A number of related processes, involving cyclisations on to alkenes, were then reported by our group (Scheme 19, Section 1.4.2).[104] 1,2-Iminohalogenation reactions have also been achieved using halides as the exogenous nucleophile (Scheme 146b).[171]

In addition to these redox-neutral transformations, cascade processes based on aza-Wacker cyclisations have been developed. Scheme 147 contains an overview of 1,2-aminofunctionalisation reactions that proceed through intermediate **370**, which is generated by aminopalladation of the alkene of **369**. All of these transformations feature nucleophilic interception of **370**, so they require an oxidant to be rendered catalytic. Redox-neutral 1,2-aminofunctionalisation reactions where the exogenous component is electrophilic have been discussed previously (Section 1.3). Insertion of CO into the Pd–C bond of **370** affords acylpalladium(II) intermediate **371**, which can be trapped with oxygen- or nitrogen-based



*Scheme 146 – a) Palladium(0)-catalysed 1,2-iminofunctionalisation of alkynyl substrate **364**.[170] b) Palladium(0)-catalysed 1,2-iminohalogenisation of alkenyl substrate **367**.[171]*

nucleophiles (**A**, Scheme 147). This can be achieved in either an intermolecular[41] or an intramolecular[172-174] manner. Alternatively, arylation of **371** is possible (**B**, Scheme 147), although this proceeds through a Friedel-Crafts reaction of an initially formed acyl chloride species.[105] With substrates incorporating a second olefin in a suitable position, intramolecular aza-Wacker/Heck cascade reactions are feasible (**C**, Scheme 147).[175-177] These are essentially oxidative variations of the process outlined in Scheme 145. Hegedus demonstrated an intermolecular aza-Wacker/Heck reaction (**D**, Scheme 147), although this was stoichiometric in palladium.[178] Aza-Wacker/C–H activation cascades have also been used to achieve 1,2-aminoarylation (**E**, Scheme 147), and these have been applied in both intramolecular[179,180] and intermolecular[181] settings. The latter requires the strong fluorine-based oxidant NFSI and proceeds through a palladium(II)/palladium(IV) mechanism.[181,182] Similar kinds



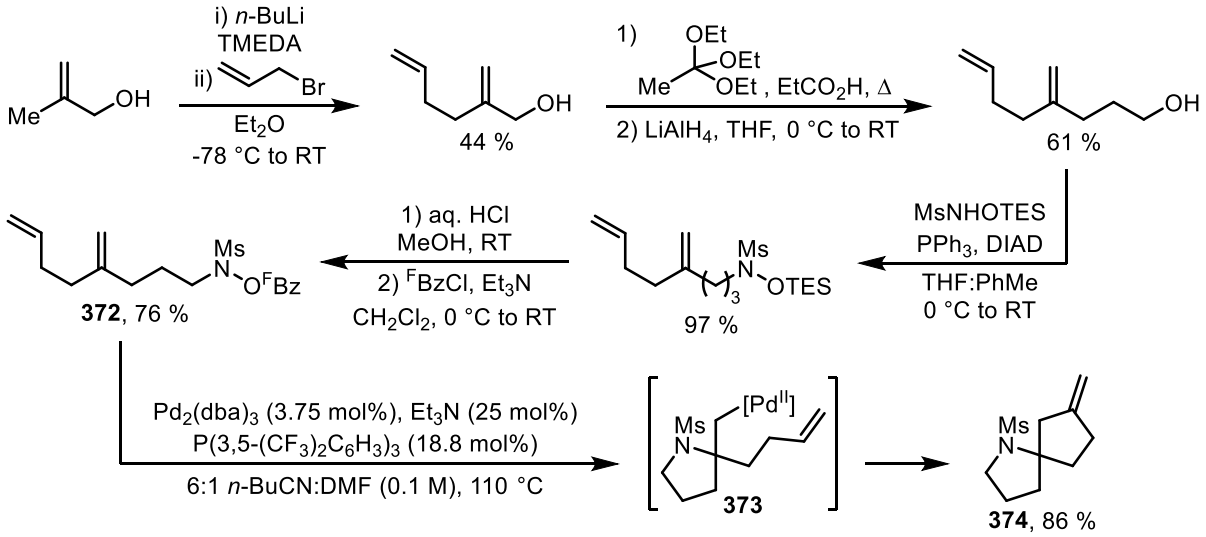
*Scheme 147 – Overview of oxidative 1,2-aminofunctionalisation reactions that proceed via intermediate **370**.*

of mechanisms have been proposed in other 1,2-aminofunctionalisation processes, such as aminohalogenation,[183] aminoacetoxylation,[184] aminoalkoxylation[185] and diamination[186,187] (**F**, Scheme 147). Access to palladium(IV) intermediates in these transformations is key, as this facilitates reductive elimination steps that would be difficult from a palladium(II) species.

The aza-Heck reactions outlined in Chapters 2 and 3 proceed through intermediates analogous to **370**, but as these are accessed from an electrophilic nitrogen source, nucleophilic interception would be an overall redox-neutral transformation. As discussed previously, processes that use internal oxidants possess several advantages over those that employ external oxidants (Section 2.1). Furthermore, good scope with respect to alkene partner and tolerance for the formation of both 5- and 6-membered rings have been demonstrated in aza-Heck reactions (Chapter 3), and these properties might be transferable to related cascade reactions. A number of alkene 1,2-aminofunctionalisation reactions were investigated to establish the feasibility of cascade processes utilising the N–O bond donors detailed in Chapters 2 and 3, and the results of this work are described in this chapter.

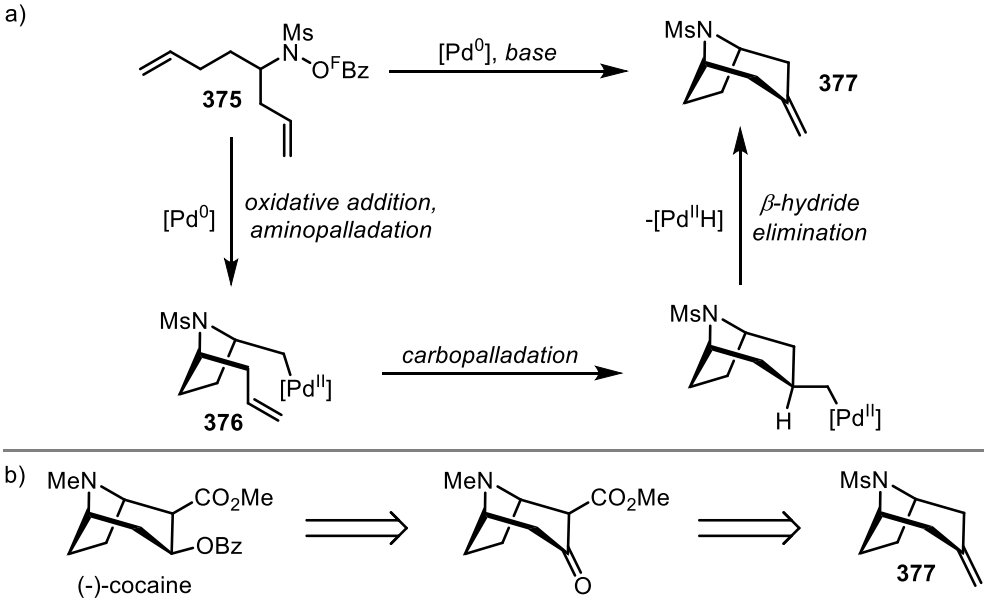
5.2 Aza-Heck/Heck cascades

The examination of cascade processes from *N*-acyloxy-sulfonamide and -carbamate substrates initiated with an aza-Heck/Heck cascade that was inspired by the reactions demonstrated by Narasaka (Scheme 145, Section 5.1).[169] *N*-Mesyl dienyl substrate **372** was prepared and evaluated in the aza-Heck/Heck cyclisation (Scheme 148). Substrate **372** afforded spirocyclic product **374** in excellent yield, demonstrating the possibility of intercepting **373** with a second alkene.



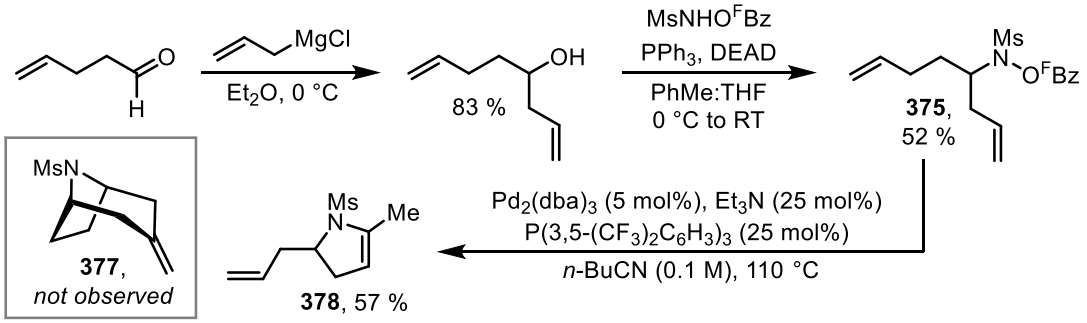
*Scheme 148 – Synthesis and palladium(0)-catalysed aza-Heck/Heck cyclisation of substrate **372**.*

As intermediate **373** does not contain any hydrogen atoms β to palladium, the likelihood of competing reaction pathways occurring is limited. Consequently, substrate **372** is ideal for aza-Heck/Heck cascade reactions. A comparatively more ambitious substrate was targeted in the form of **375**. It was hoped that **375** would cyclise to afford **377** (Scheme 149a), which could potentially be elaborated into cocaine[16] (Scheme 149b). Following the initial cyclisation of **375**, intermediate **376** might either be intercepted by the second pendant alkene or undergo β-hydride elimination. It was hoped that the former process would occur preferentially because β-hydride elimination in the direction of the C–N bond was disfavoured in earlier studies (Section 2.4.1), likely due to the steric influence of the *N*-protecting group.

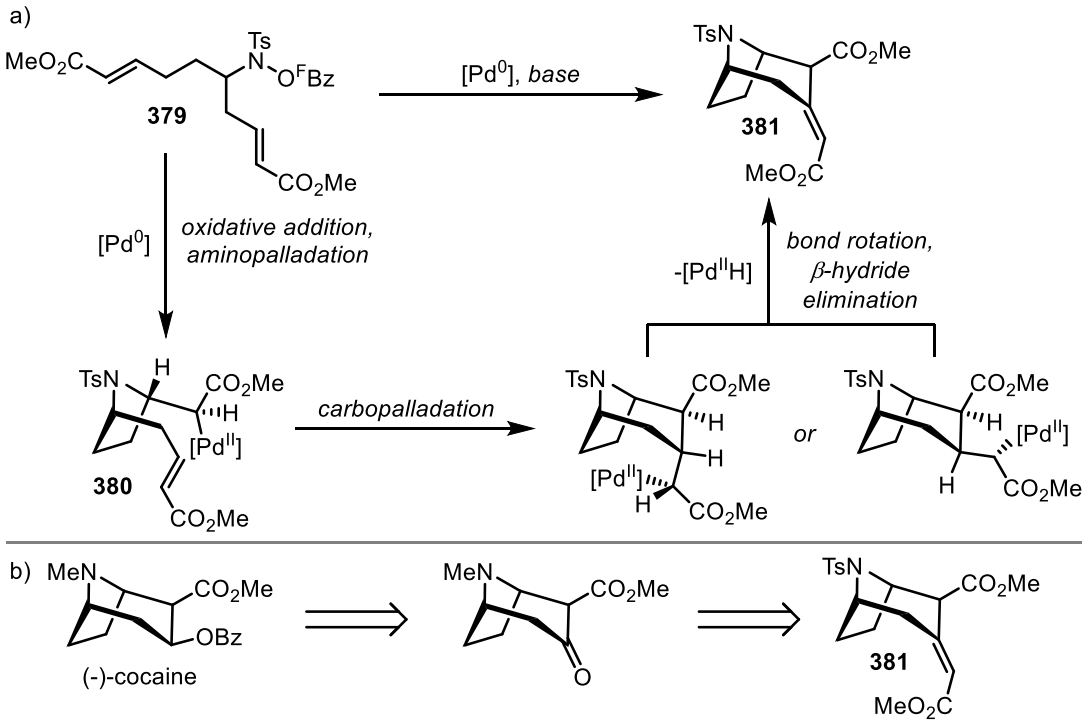


*Scheme 149 – a) Proposed aza-Heck/Heck cyclisation of substrate **375**. b) Retrosynthetic analysis of cocaine[16] to product **377**.*

Substrate **375** was prepared in two steps from pent-5-enal (Scheme 150). However, **375** did not engage in the desired aza-Heck/Heck cascade reaction, and isomerised aza-Heck product **378** was produced instead (Scheme 150). The formation of **378** indicates that β-hydride elimination at the stage of **376** occurs more readily than carbopalladation of the second olefin.

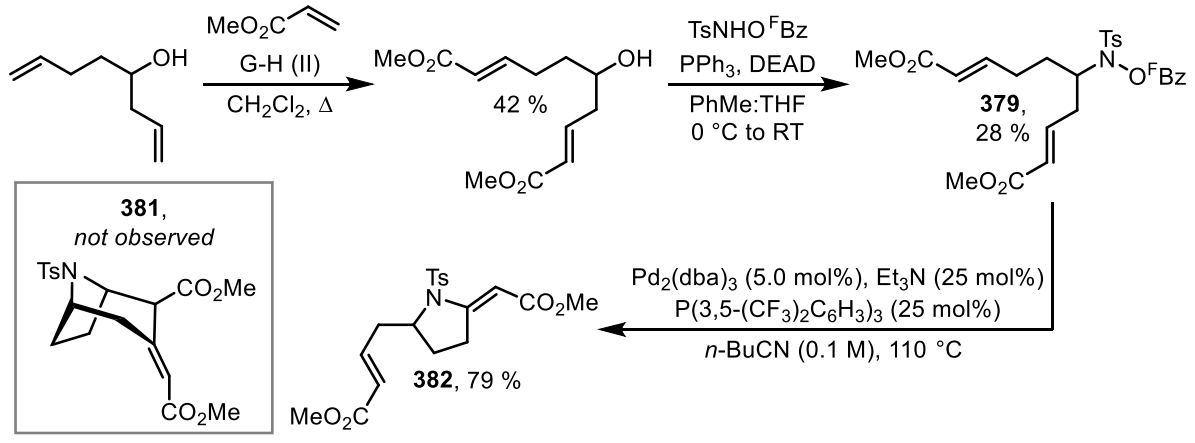


*Scheme 150 – Synthesis and attempted aza-Heck/Heck cyclisation of substrate **375**.*



*Scheme 151 – a) Proposed aza-Heck/Heck cyclisation of substrate **379**. b) Retrosynthetic analysis of cocaine to product **381**.*

Although substrate **375** was unsuccessful at generating the bicyclic scaffold of cocaine, an analogous acrylate substrate (**379**) was considered (Scheme 151a). In this case, organopalladium(II) intermediate **380** might be stabilised by the presence of the adjacent ester group. Furthermore, product **381** could be easier to convert into cocaine as the ester functionality would not need to be introduced (Scheme 151b). Substrate **379** was prepared and trialled in the cascade reaction (Scheme 152). As with substrate **375**, this resulted in the aza-Heck product (**382**, 79 % yield), and **381** was not observed.

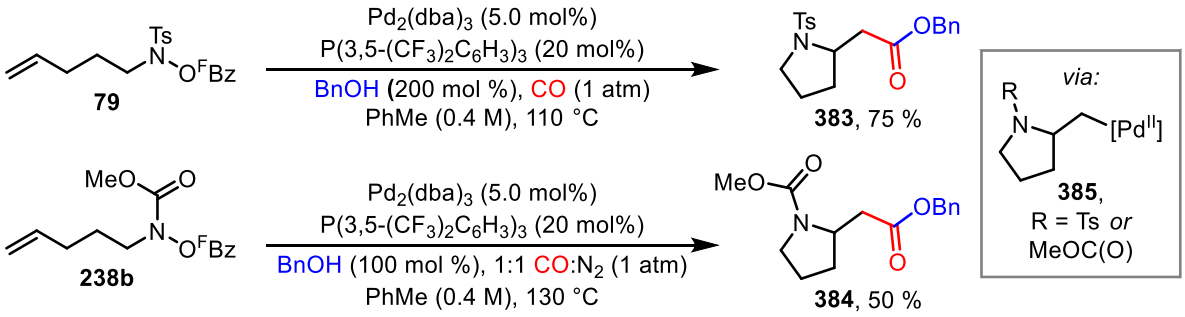


*Scheme 152 – Synthesis and attempted aza-Heck/Heck cyclisation of substrate **379**.*

5.3 Intermolecular 1,2-aminocarboxylation cascades

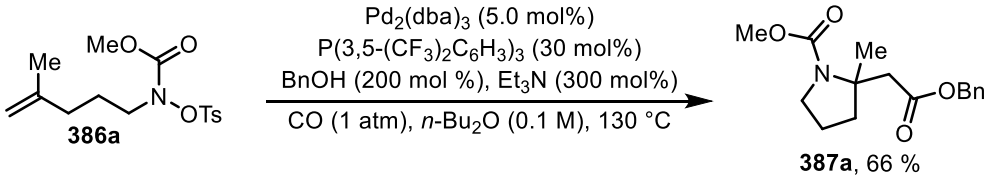
5.3.1 Initial results

The results in this section were obtained by Rafaela Carmona and Ben Jones and hence are not detailed in the experimental section.



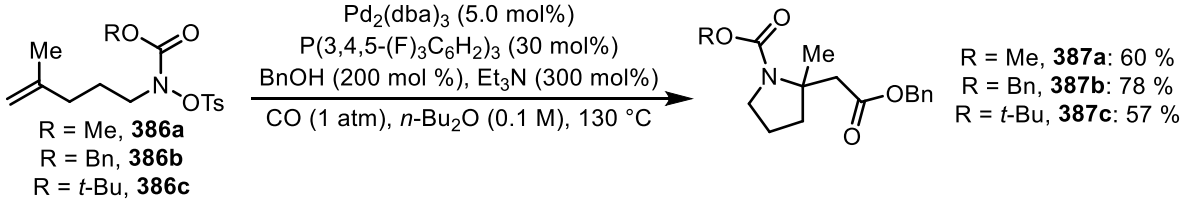
*Scheme 153 – Palladium(0)-catalysed 1,2-aminocarboxylation of **79** and **238b**.*

The possibility of developing 1,2-aminocarboxylation cascades was examined through the interception of intermediate **385** with carbon monoxide and benzyl alcohol. The desired transformation was achieved with sulfonamide- and carbamate-based substrates (**79** and **238b**, respectively, in Scheme 153). Interestingly, the reaction tolerated terminal alkenes, indicating that trapping of **385** is sufficiently fast to outcompete β-hydride elimination;[XL] this is in contrast to previous cases where it was found that elimination outcompeted intramolecular carbopalladation (Scheme 150 and Scheme 152).



*Scheme 154 – Palladium(0)-catalysed 1,2-aminocarboxylation of **386a**.*

The use of tosyl-activated substrate **386a** led to an improvement in the carbamate-based 1,2-aminocarboxylation cascade (Scheme 154), and this allowed substrates containing 1,1-disubstituted alkenes to participate in the reaction. Good protecting group tolerance was observed, with substrates **386a-c** all participating in the aminocarboxylative cyclisation in high yields (Scheme 155).

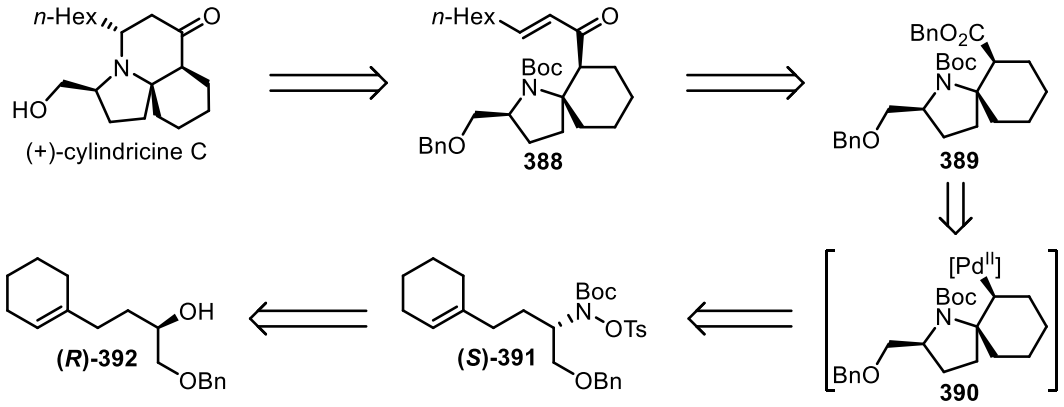


*Scheme 155 – Palladium(0)-catalysed aminocarboxylation of **386a-c**.*

[XL] Similar observations have been made previously in related palladium(0)-catalysed processes.[104,188]

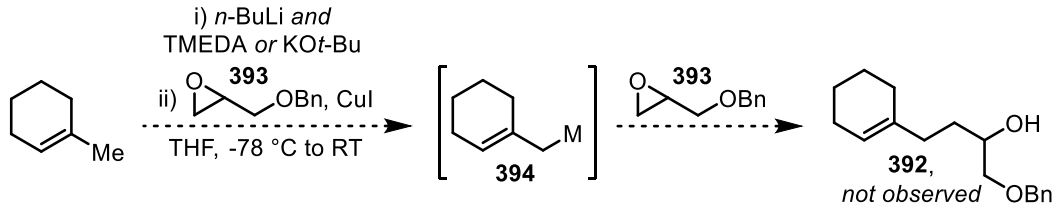
5.3.2 Studies towards the synthesis of (+)-cylindricine C

The application of the 1,2-aminocarboxylation cascade detailed in the previous section to enantiopure substrate **(*S*)-391** was viewed as a route to (+)-cylindricine C,[9] *via* β-amino acid derivative **389** (Scheme 156). Conversion of **389** to enone **388**, followed by deprotection would, in theory, afford the natural product. However, the transformation of **(*S*)-391** into **389** was considered ambitious, and the possibility of β-hydride elimination outcompeting intermolecular trapping was recognised.



*Scheme 156 – Retrosynthetic analysis of (+)-cylindricine C[9] to alcohol **(R)-392**.*

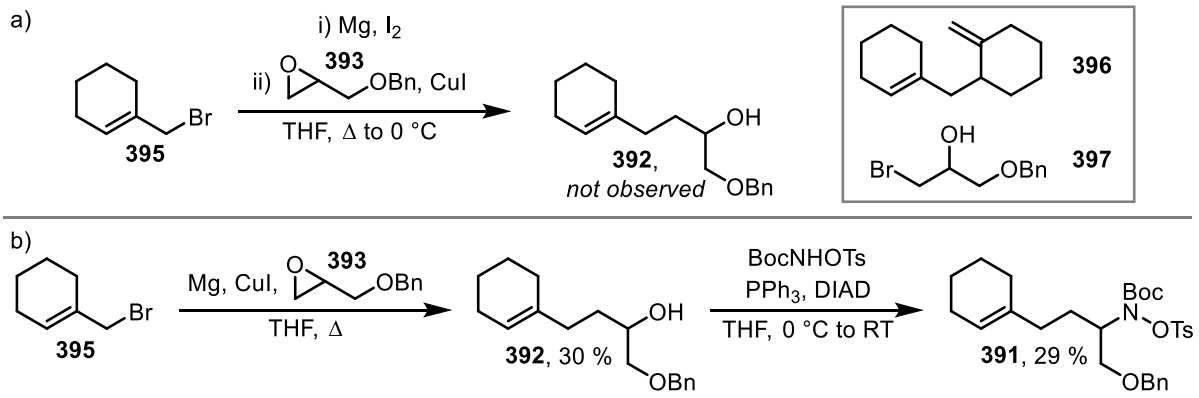
In order to assess the viability of the proposed 1,2-aminocarboxylation cascade, alcohol **392** was synthesised. The reaction of organometallic nucleophile **394** with epoxide **393** was envisaged as a strategy to achieve this. Due to the availability of enantiopure **393**, the possibility of preparing enantioenriched **392** using this route was thought likely. Access to **394** through deprotonation of 1-methylcyclohex-1-ene was considered the most direct approach; unfortunately, this was not successful, despite multiple sets of conditions being trialled (Scheme 157).



*Scheme 157 – Attempted synthesis of alcohol **392** from 1-methylcyclohex-1-ene.*

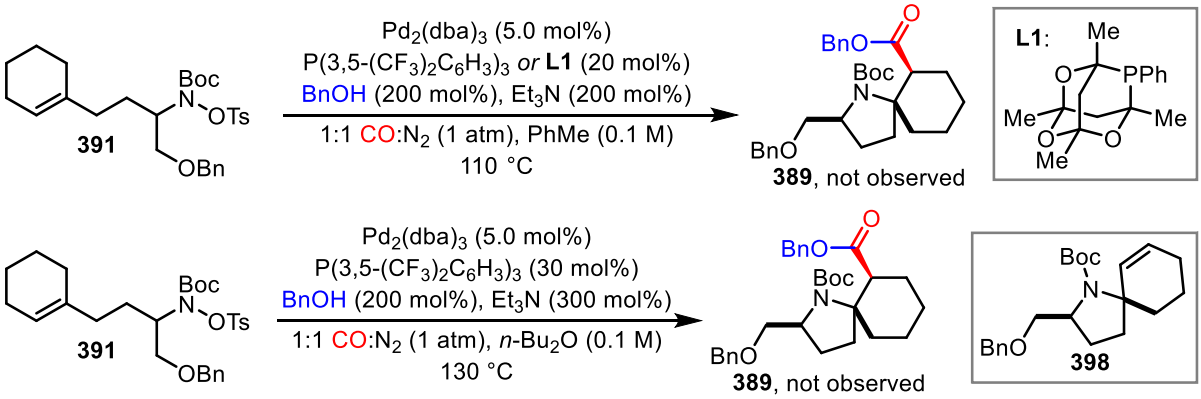
Following the failure of the previous reaction, potentially due to difficulties in the deprotonation step, formation of **394** from bromide **395** was considered as an alternative. However, attempts to react **393** with a preformed Grignard reagent (M = MgBr in **394**) were not successful (Scheme 158a). In this case, hydrocarbon **396** and bromide **397** were observed. This is most likely the result of a reaction between **394** and **395** to afford **396**, with the $MgBr_2$ by-product then leading to ring-opening of epoxide **393** to form **397**. This kind of phenomenon has been observed previously: formation of allylic Grignard reagents is known to be problematic due to competing homocoupling.[189,190] By conducting the Grignard

formation in the presence of **393**, a modest yield of alcohol **392** was achieved, which was then converted into substrate **391** (Scheme 158b).



*Scheme 158 – Attempted synthesis of alcohol **392**. b) Synthesis of substrate **391**.*

When submitted to the 1,2-aminocarboxylation reaction conditions (Section 5.3.1), **391** did not afford desired product **389** (Scheme 159). Competitive β-hydride elimination from **390** (Scheme 156) did not appear to be the problem, as **398** was not observed either, and **391** simply appeared to be unreactive to the conditions employed. Following these disappointing results, investigations with this substrate were suspended.



*Scheme 159 – Attempted 1,2-aminocarboxylation of **391**.*

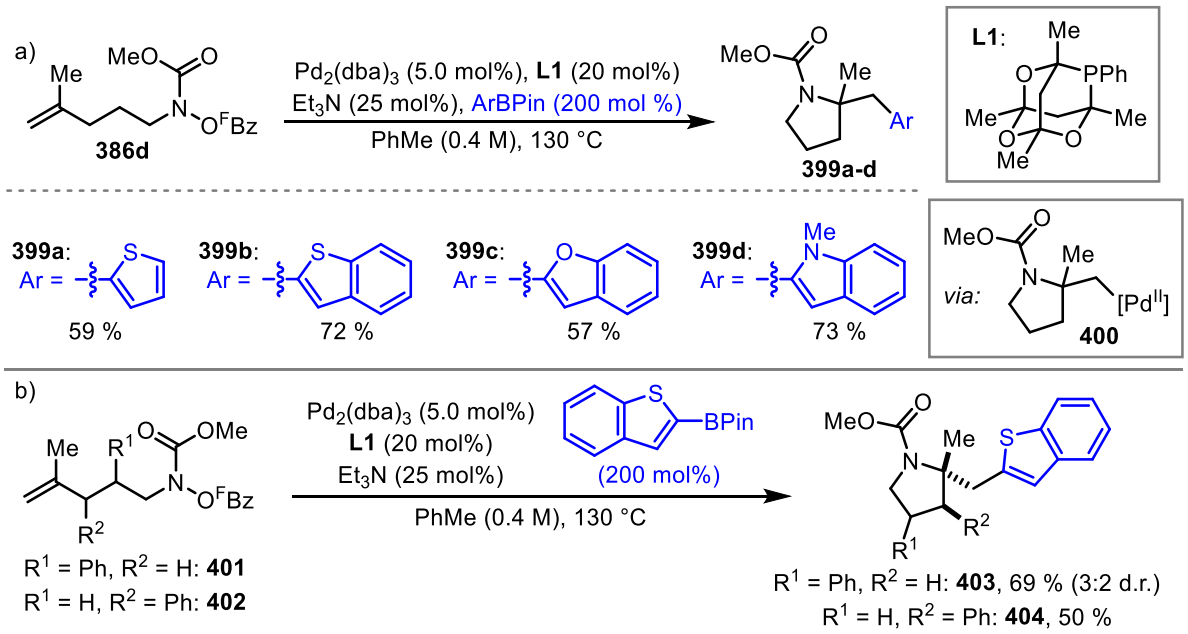
The lack of reactivity observed with substrate **391** could have been a result of the sterically hindered nature of the N–O bond of **391** inhibiting oxidative addition; previously, this problem has been solved with the use of substrates containing smaller protecting groups (Section 2.4.2). Furthermore, methyl carbamate and *N*-Cbz systems **386a** and **386b** were found to provide better results in the 1,2-aminocarboxylation reaction than *N*-Boc substrate **386c** (Scheme 154 and Scheme 155, Section 5.3.1). Consequently, it was considered that analogous substrates containing smaller protecting groups might be more suitable for this transformation. However, due to time constraints, it was not possible to investigate the 1,2-aminocarboxylation cascade with other systems, although this is likely to be the focus of future studies within the group.

5.4 Intermolecular 1,2-amino-arylation and -borylation cascades

5.4.1 Intermolecular 1,2-aminoarylation using boronic esters

The previous sections detailed the development and attempted application of a carbonylative alkene 1,2-aminofunctionalisation reaction. In addition to this, related non-carbonylative processes have also been examined. Of key relevance are studies conducted by Rafaela Carmona that aimed to achieve 1,2-aminoarylation of alkenes. The results in this section are not detailed in the experimental section, but the experimental procedures and characterisation data can be found in the supporting information of reference 108.

It was found that by trapping intermediate **400** with aryl boronic esters, 1,2-aminoarylation of the alkene in **386d** was possible. The best results were obtained using electron-rich, heteroaromatic pinacol boronic esters (Scheme 160a). The reaction tolerated substitution in the β- and γ-positions (Scheme 160b), and 2,2,4-trisubstituted pyrrolidine **403** was generated in good yield from **401**, albeit with negligible diastereoselectivity, whereas γ-phenyl system **402** afforded **404** as a single diastereomer but in a lower yield of 50 %.

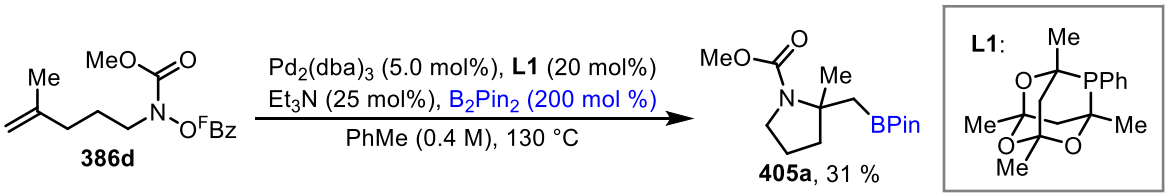


*Scheme 160 – a) Palladium(0)-catalysed 1,2-aminoarylation of **386d**. b) Palladium(0)-catalysed 1,2-aminoarylation of **401** and **402**.*

5.4.2 Extension to intermolecular 1,2-aminoborylation using diboron reagents

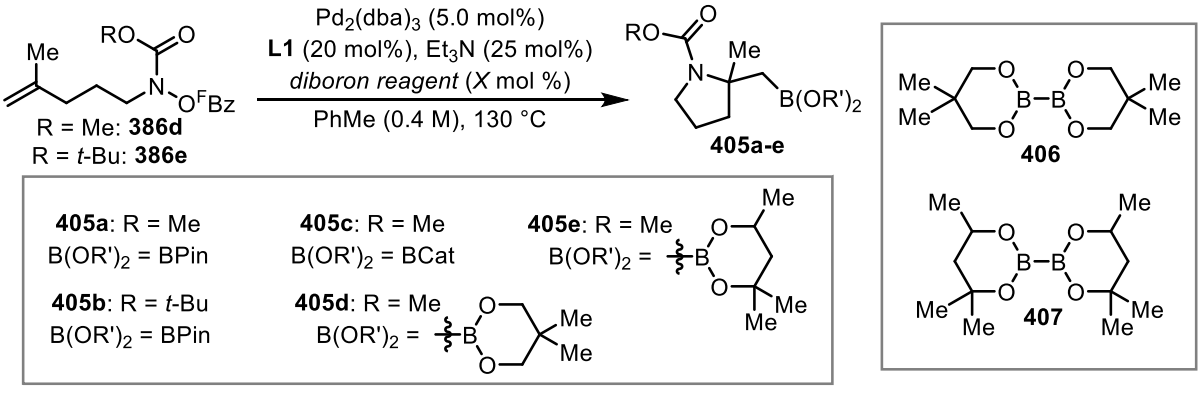
Given the synthetic versatility of boronic esters[191,192] and the ubiquity of nitrogen heterocycles (Section 1.1), a 1,2-aminoborylation cascade would likely be a desirable transformation. Moderating the reactivity of organopalladium(II) intermediate **400** (Scheme 160a) by conversion to a boronic ester (such as **405a**) would potentially allow a wider range of reactions, which might otherwise be unavailable

to **400**, to proceed from **405a**. The feasibility of the 1,2-aminoborylation reaction was examined under conditions found to be effective for 1,2-aminoarylation (Section 5.4.1), with bis(pinacolato)diboron (B_2Pin_2) used in place of the aryl boronic ester (Scheme 161). The initial result was promising, and **405a** was isolated in 31 % yield.



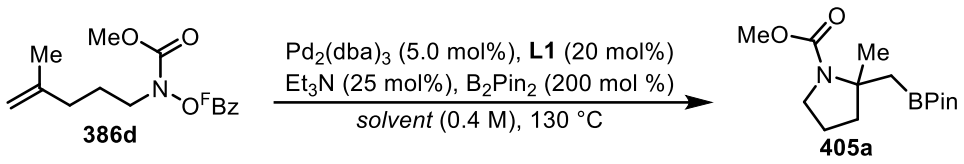
*Scheme 161 – Palladium(0)-catalysed 1,2-aminoborylation of **386d**.*

Optimisation of this reaction was undertaken, initially focusing on *N*-protecting group and the nature of the diboron compound (Table 19). Substrate **386e** (*see the experimental section*), the *N*-Boc-protected analogue of **386d**, was unsuitable for the desired transformation (Table 19, entry 3). The use of B_2Pin_2 proved to be essential, with other diboron compounds not providing significant quantities of **405** (Table 19, entries 4-6). From here, the reaction solvent was examined (Table 20), and *n*-Bu_2O was found to provide the highest yield of **405a** (39 %) (Table 20, entry 8). Following this, a ligand screen was conducted (Table 23, Appendix), and the reaction temperature and base equivalents were varied (Table 24, Appendix). However, optimisation of these parameters did not result in an improved yield of **405a**.



Entry	*substrate*	*diboron reagent*	*X*	*yield*
1	**386d**	B_2Pin_2	200	31 %
2	**386d**	B_2Pin_2	400	26 %
3	**386e**	B_2Pin_2	200	*not determined*
4	**386d**	B_2Cat_2	200	*not determined*
5	**386d**	**406**	200	*not determined*
6	**386d**	**407**	200	*not determined*

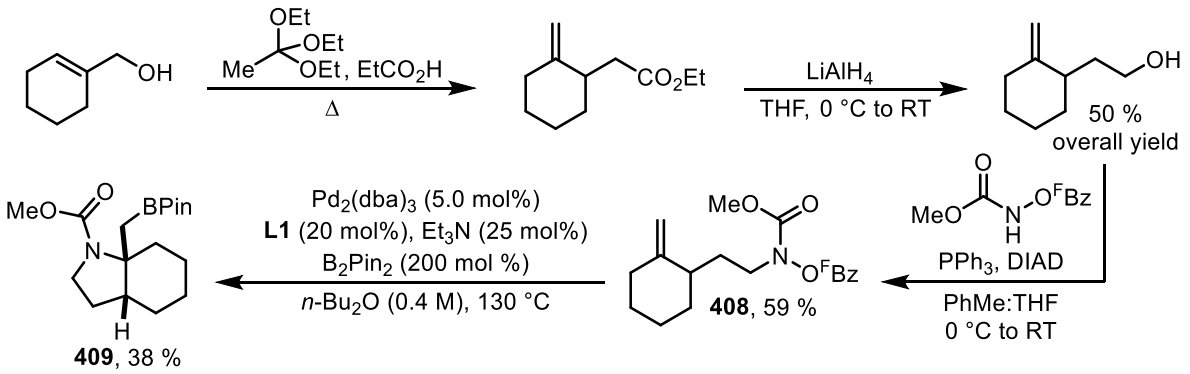
*Table 19 – Optimisation of the palladium(0)-catalysed 1,2-aminoborylation of **386d** and **386e**.*



Entry	*solvent*	*yield*
1	PhMe	31 %
2	THF	*not determined*
3	dioxane	*not determined*
4	*n*-BuCN	*not determined*
5	1,2-DME	32 %
6	CPME	36 %
7	mesitylene	37 %
8	*n*-Bu_2O	39 %

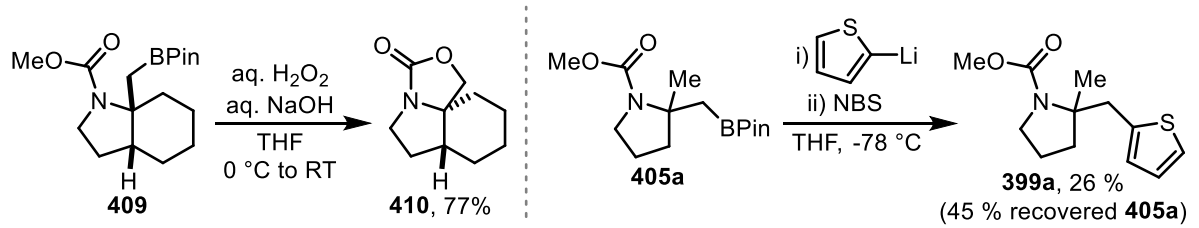
*Table 20 – Solvent screen for the palladium(0)-catalysed 1,2-aminoborylation of **386d**.*

Due to time constraints, further optimisation of the reaction was not undertaken, although the suitability of other systems for the 1,2-aminoborylation cascade was examined. A substrate containing an exocyclic methylene group (**408**) was prepared and submitted to the 1,2-aminoborylation conditions (Scheme 162). The result achieved with **408** was similar to that achieved with **386d** (Table 20, entry 8), and **409** was isolated in 38 % yield.



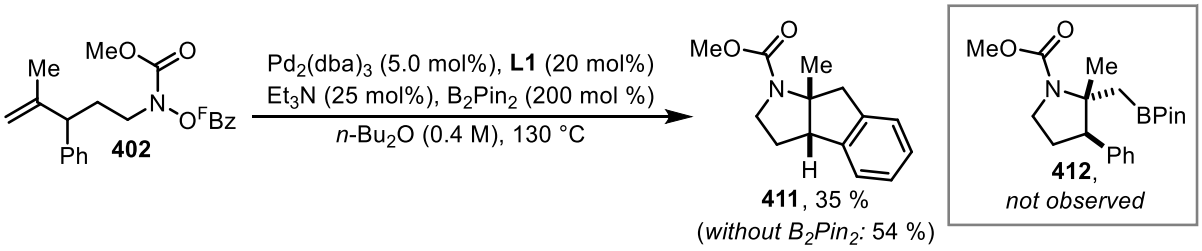
*Scheme 162 – Synthesis and palladium(0)-catalysed 1,2-aminoborylation of **408**.*

Derivatisation of the 1,2-aminoborylation products can be achieved (Scheme 163). Oxidation (H_2O_2) of **409** under basic conditions led to spontaneous cyclisation onto the protecting group, delivering tricyclic carbamate **410** in 77 % yield. An initial attempt at coupling **405a** with 2-thiophenyl lithium, following a procedure reported by Aggarwal,[193] demonstrated the feasibility of the desired transformation.



*Scheme 163 – Derivatisation of 1,2-aminoborylation products **409** and **405a***

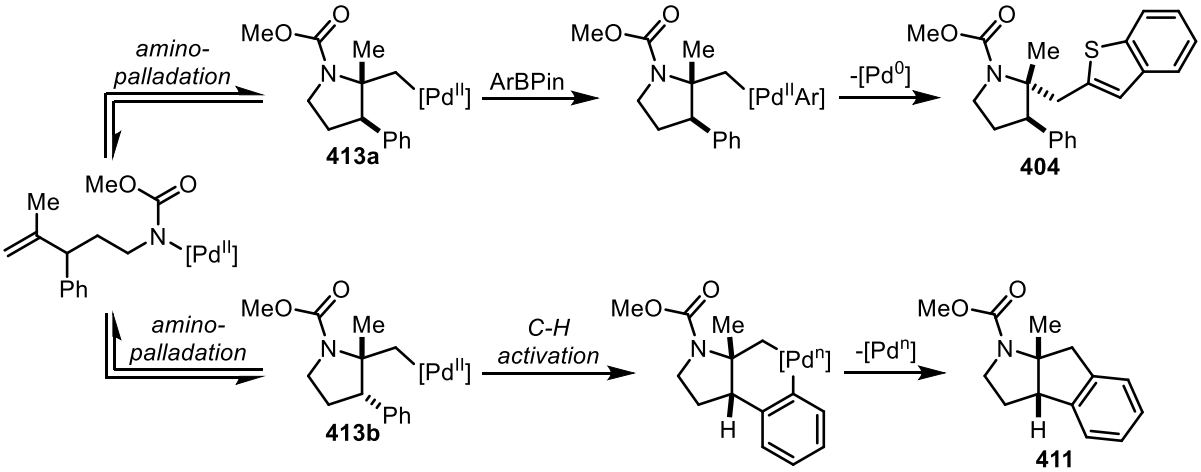
When substrate **402**[XLI] was employed in the 1,2-aminoborylation reaction, desired product **412** was not observed (Scheme 164). Instead, intramolecular aminoarylation product **411** was isolated in 35 % yield. B_2Pin_2 was determined to be unnecessary for the formation of **411**, as an improved yield was achieved in its absence.



*Scheme 164 – Observation of 1,2-aminoarylation product **411** in the attempted 1,2-aminoborylation of **408**.*

Interestingly, the relative stereochemistry of **411**, the product of intramolecular aminoarylation, is opposite to that observed in **404**, the product of intermolecular aminoarylation (Scheme 160b, Section 5.4.1).[XLII] The stereochemistry of **404** mirrors that observed in the products of the aza-Heck reaction (Scheme 102, Section 3.3.3). Products **404** and **411** presumably arise from diastereomeric intermediates **413a** and **413b**, respectively (Scheme 165). It is conceivable that **413a** and **413b** lie in equilibrium, as aminopalladation has been shown to be reversible in similar contexts.[133] However, given the similarity of the two sets of conditions (*cf.* Scheme 160b, Section 5.4.1 and Scheme 164), it is unlikely that **413a** is favoured in one reaction and **413b** in the other. Intermolecular trapping of **413** with a boron-based nucleophile is presumably possible from either diastereomer, although this evidently proceeds preferentially from **413a**. This may be due to there being a greater equilibrium concentration of **413a**, or because transmetalation from **413a** is more facile than from **413b**, or a combination of these two factors. In the attempted 1,2-aminoborylation of **402**, the selectivity for **411** could be a result of transmetalation with B_2Pin_2 being considerably slower than with ArBPin, leading to intramolecular arylation becoming the major reaction pathway.

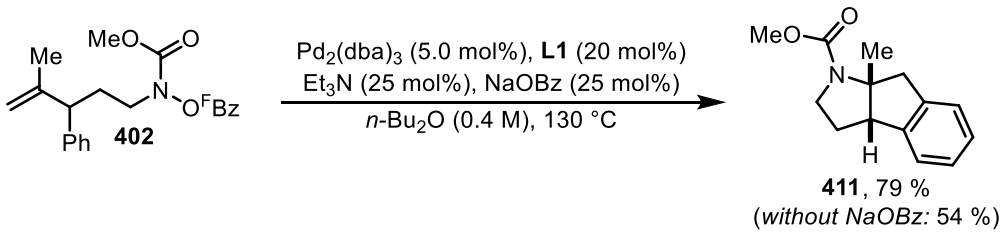
[XLI] Substrate **402** was prepared by Rafaela Carmona (University of Bristol) according to a reported procedure.[108]
[XLII] The stereochemistry of both products was determined by NOE analysis. For details of **404**, see the supporting information of reference 108. For details of **411**, see the experimental section.



*Scheme 165 – Proposed mechanism for the formation of products **404** and **411**.*

5.5 Conclusions

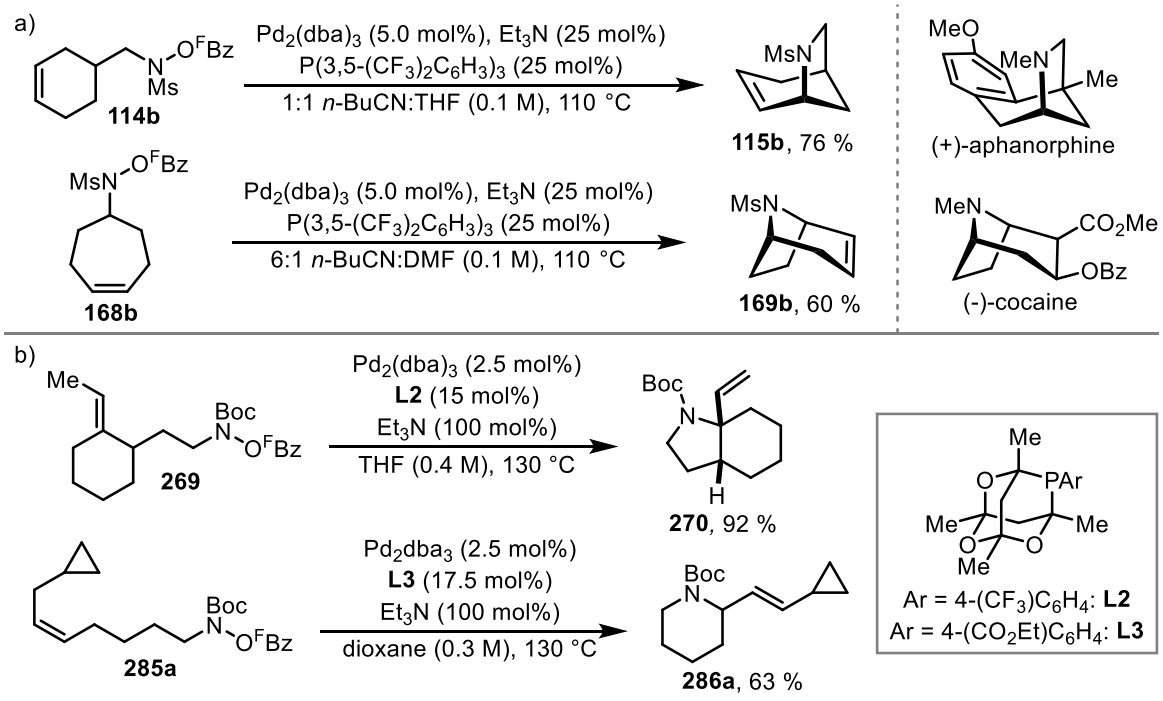
The aza-Heck initiation modes developed in Chapters 2 and 3 have been applied to aza-Heck/Heck cyclisations (Section 5.2) and 1,2-aminoborylation reactions (Section 5.4.2). Additionally, through the work of Rafaela Carmona and Ben Jones, partially intermolecular 1,2-amino-carboxylation and -arylation reactions were demonstrated (Sections 5.3.1 and 5.4.1, respectively). In the course of developing the 1,2-aminoborylation reaction, an interesting intramolecular aza-Heck/C–H activation cascade was observed (Scheme 164, Section 5.4.2), and further work in this area is being undertaken by Ben Jones. In an initial result, it was found that addition of sodium benzoate to the reaction conditions led to a significant increase in the yield of **411** (Scheme 166), suggesting that the C–H activation step may be proceeding *via* a concerted metalation-deprotonation step.[194,195] Work to assess the substrate scope of this transformation is currently ongoing.



*Scheme 166 – Improved conditions for the palladium(0)-catalysed intramolecular 1,2-aminoarylation of substrate **402**. – Results obtained by Ben Jones.*

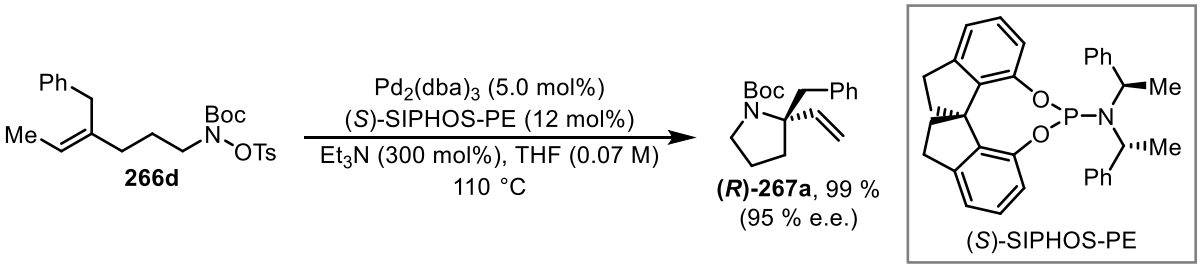
Chapter 6 - Overall summary and conclusions

In summary, two novel classes of aza-Heck reactions have been discovered and developed into practical methodologies. The first of these, based on cyclisations of *N*-acyloxysulfonamides (Chapter 2), was only the second reported class of aza-Heck reaction, after the Narasaka-Heck process (Section 1.4). This reaction proved especially suited to the synthesis of bicyclic nitrogen heterocycles that are commonly found in the core structures of natural products, such as aphanorphine[10,11] or cocaine[16] (**115b** and **169b**, respectively, in Scheme 167a). A carbamate-based aza-Heck reaction (Chapter 3) was subsequently found to be a substantially more efficient process than the *N*-acyloxysulfonamide variant (Chapter 2). Excellent yields of 1,1-disubstituted pyrrolidines (such as **270** in Scheme 167b) could be obtained from substrates containing trisubstituted alkenes. This is an element of substrate scope that was challenging for the sulfonamide-based reaction (Section 2.4.5) and is generally also not well tolerated in aza-Wacker cyclisations (Section 1.2.5). Additionally, good yields in the cyclisations of non-biased 6-*exo* aza-Heck cyclisations were demonstrated for the first time (**286a** in Scheme 167b). The timeline presented in Figure 2 (Section 1.5) indicates that this is a still-growing area of research.



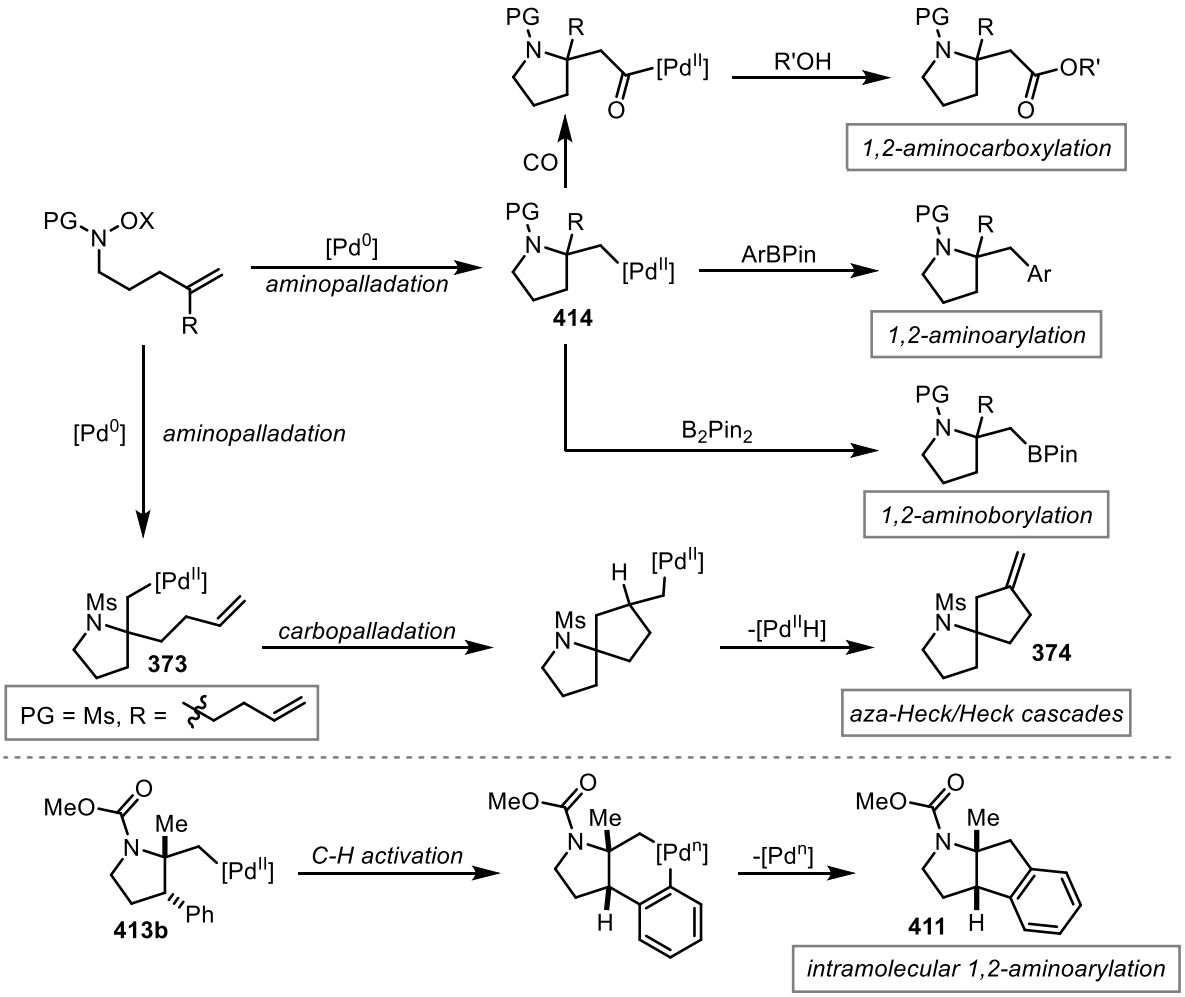
Scheme 167 – a) Aza-Heck cyclisations of N-acyloxysulfonamides. b) Aza-Heck cyclisations of N-acyloxycarbamates.

The aza-Heck reaction of carbamate-based substrates (Chapter 3) was then elaborated into a highly asymmetric variant (Scheme 168 and Chapter 4). This process exhibited impressive generality: the reaction tolerated substrates containing a diverse range of alkenes, and both 5- and 6-*exo* cyclisations proceeded in good yields and with high enantioselectivities. Furthermore, this reaction used substrates activated with tosyl groups, which are preferable both in terms of cost and atom economy over the O^{F}Bz-activated alternatives used in Chapters 2 and 3.



*Scheme 168 – Enantioselective aza-Heck cyclisation of N-sulfonyloxycarbamate **266d**.*

The application of these novel classes of N–O bond donor to a number of aza-Heck cascade reactions was also demonstrated (Scheme 169 and Chapter 5). 1,2-Amino-carboxylation and -arylation processes were developed by Rafaela Carmona and Ben Jones through the trapping of intermediate **414** with exogenous nucleophiles. This was then extended to alkene 1,2-aminoborylation processes, using diboron compounds as the nucleophilic component. In cases where **414** contains a suitably placed alkene (such as **373**), a second Heck-type cyclisation can occur, as demonstrated with spirocyclic pyrrolidine **374**. Furthermore, intermediate **413b** can also be intercepted intramolecularly by an arene, leading to 1,2-aminoarylation product **411**.



*Scheme 169 – 1,2-Aminofunctionalisation cascades proceeding from intermediates **414**, **373** and **413b**.*

– The 1,2-amino-carboxylation and -arylation variants were developed by Rafaela Carmona and Ben Jones.

Chapter 7 - Experimental

7.1 General experimental details

Unless stated, all materials were purchased from commercial sources (Acros, Aldrich, Alfa Aesar, Fluorochem and Strem) and used without any further treatment. Catalytic reactions were carried out in Young-type re-sealable tubes. Anhydrous solvents were obtained by distillation using standard procedures or by passage through drying columns supplied by Anhydrous Engineering Ltd. High-boiling solvents were removed from the reaction crudes employing rotary evaporators connected to high-vacuum pumps. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40-63 μm, 230-400 mesh). Petrol refers to the fraction of petroleum ether boiling in the 40-60 °C range. Thin layer chromatography was performed using aluminium backed $60F_{254}$ silica plates. Visualisation was achieved by UV fluorescence or a basic $KMnO_4$ solution and heat. Proton nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz or 500 MHz as stated. ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz as stated. ^{19}F NMR spectra were recorded at 283 MHz. Chemical shifts (δ) are given in parts per million (ppm). Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), heptets (hept), multiplets (m) and broad (br). Coupling constants (J) are quoted to the nearest 0.5 Hz. All assignments of NMR spectra were based on 2D NMR data (COSY, HSQC and HMBC). In situ yields were determined by employing 1,3,5-trimethoxybenzene as internal standard. Mass spectra were obtained by the University of Bristol mass spectrometry service and were recorded using a Brüker Daltonics FT-ICR-MS Apex 4e 7.0T FT-MS (ESI^+ mode), a Shimadzu GCMS QP2010+ (EI^+ mode) or a Bruker ultrafleXtreme II TOF/TOF (MALDI, using a colloidal graphite matrix). Infrared spectra were recorded on a Perkin Elmer Spectrum Two FTIR spectrometer as thin films or solids compressed on a diamond plate. Melting points were determined using a Stuart SMP30 melting point apparatus and are reported uncorrected. Specific rotation values were measured using a Bellingham & Stanley ADP440+ polarimeter. Chiral SFC was performed on an Agilent 1260 Infinity SFC Control Module system equipped with a quaternary pump, diode array detector and column thermostat under the conditions specified. Enantiomeric excess was determined by integration of chromatogram peaks. The ordering of compounds generally reflects the order they appear in the main text; however, synthetic sequences have been grouped together for clarity. The numbering of compound structures does not necessarily reflect the numbering contained in the systematic names.

7.2 General procedures

General procedure A: Alkylation of TsNHOTBS or CbzNHOTBS

A solution of hydroxylamine-derived pronucleophile (1.0 eq.) and NaH (60 % in mineral oil, 1.05 eq.). in anhydrous DMSO (*approx.* 5 mL/mmol) was stirred at room temperature for 1 hour before addition of alkyl bromide (1.2 eq.). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was poured into brine and extracted with EtOAc (*approx.* 3 × 5 mL/mmol). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by FCC.

General procedure B: *O*-TBS deprotection using HF·pyridine

To a solution of *N*-alkyl-*N*-((*tert*-butyldimethylsilyl)oxy)sulfonamide (1.0 eq.) in anhydrous THF (*approx.* 10 mL/mmol) was added HF·pyridine (70 % HF, 5.0 ml/g). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was quenched with an aqueous solution (*approx.* 8 mL/mmol) of K_2CO_3 (3 g/mL of HF·pyridine) and extracted with CH_2Cl_2 (*approx.* 3 × 10 mL/mmol). The combined organic phases were washed with 1.0 M aqueous HCl (*approx.* 20 mL/mmol), dried over Na_2SO_4, filtered through a plug of silica and concentrated *in vacuo* to afford the product, which was used without further purification (unless otherwise noted).

General procedure C: Acylation with pentafluorobenzoyl chloride

To a solution of *N*,*N*-disubstituted hydroxylamine (1.0 eq.) in anhydrous CH_2Cl_2 (*approx.* 7.5 mL/mmol) at 0°C was added ^{F}BzCl (1.5 eq.) followed by Et_3N (2.0 eq.). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the excess acid chloride was quenched with MeOH (*approx.* 2 mL/mmol), followed by addition of saturated aqueous $NaHCO_3$ (*approx.* 7.5 mL/mmol). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (*approx.* 2 × 10 mL/mmol). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by FCC.

General procedure D: Palladium-catalysed aza-Heck cyclisation

A flame-dried re-sealable tube, fitted with a magnetic stirrer, was charged with cyclisation substrate (1.0 eq.), $Pd_2(dba)_3$ and phosphine ligand. The tube was fitted with a rubber septum and purged with nitrogen before solvent and Et_3N were added *via* syringe. The tube was sealed and heated at the specified temperature for the time noted. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude mixture was purified by FCC.

General procedure E: Mitsunobu alkylation employing silyl-protected *N*-hydroxysulfonamides

To a solution of PPh_3 (2.0 eq.) in anhydrous THF:PhMe (1:1, 10 mL/mmol) at 0 °C was added DIAD (1.5 eq.). The reaction mixture was stirred at 0 °C for 15 minutes before addition of alcohol (*equivalents specified*), and then a further 30 minutes before addition of hydroxylamine-derived pronucleophile (1.0 eq.) as a solution in anhydrous THF (1 mL/mmol). The reaction mixture was stirred at room temperature for the time noted before being concentrated *in vacuo* and loaded directly onto silica gel for purification by FCC.

General procedure F: *O*-TES deprotection with HCl

To a solution of *N*-alkyl-*N*-((triethylsilyl)oxy)sulfonamide (1.0 eq.) in MeOH (*approx.* 10 mL/mmol) was added 12 M aqueous HCl (1 mL/mmol). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (*approx.* 10 mL/mmol) and extracted with CH_2Cl_2 (*approx.* 3 × 10 mL/mmol). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by FCC (unless otherwise noted). *In cases where the starting material was poorly soluble in MeOH, small quantities of CH_2Cl_2 were added in order to solubilise it.*

General procedure G: Pentafluorobenzoylation of *N*-hydroxycarbamates or *N*-hydroxyamides

To a suspension of *N*-hydroxycarbamate or *N*-hydroxyamide (1.0 eq.) and ^{F}BzOH (1.0 eq.) in CH_2Cl_2 (*approx.* 10 mL/mmol) at 0 °C was added a solution of DCC (1.1 eq.) in CH_2Cl_2 (*approx.* 5 mL/mmol) dropwise. The reaction mixture was stirred at room temperature for the time noted before filtration. The filtrate was concentrated *in vacuo*, and the crude mixture was purified by FCC.

General procedure H: Alkylation and decarboxylation of diethyl malonate

To a suspension of NaH (60 % in mineral oil, 2.0 eq.) in anhydrous THF (*approx.* 3 mL/mmol) at 0 °C was added diethyl malonate (2.0 eq.) dropwise. The reaction mixture was stirred at 0 °C for 1 hour before dropwise addition of allylic bromide (1.0 eq.). The reaction mixture was warmed to room temperature and monitored by TLC. Upon completion, the reaction mixture was poured into a solution of KOH (12 eq.) in water (*approx.* 1.5 mL/mmol) and MeOH (*approx.* 1.5 mL/mmol) and stirred for 30 minutes at room temperature. The reaction mixture was acidified with 12 M aqueous HCl (20 eq.), concentrated to an aqueous solution and extracted with EtOAc (*approx.* 3 × 5 mL/mmol). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture of malonic acids was dissolved in DMF (*approx.* 2 mL/mmol) and heated at reflux for 3 hours before being concentrated *in vacuo* to afford the product, which was used without further purification.

General procedure I: Reduction of carboxylic acids or esters

To a solution of carboxylic acid or ester (1.0 eq.) in anhydrous THF or Et_2O (*approx.* 2.5 mL/mmol) at 0 °C was added $LiAlH_4$ (*equivalents specified*) dropwise. The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was cooled to 0 °C before addition of water (1 mL/g of $LiAlH_4$), 15 % aqueous NaOH (1 mL/g of $LiAlH_4$) and a final portion of water (3 mL/g of $LiAlH_4$). The reaction mixture was stirred at room temperature for around 15 minutes before being dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the product, which was used without further purification (unless otherwise noted).

General procedure J: Bromination of alcohols

To a solution of alcohol (1.0 eq.) in Et_2O (*approx.* 5 mL/mmol) at 0 °C was added PBr_3 (0.50 eq.). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was poured into an aqueous solution of K_2CO_3 (1.0 eq.). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (*approx.* 2 × 4 mL/mmol). The Et_2O phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford the product, which was used without further purification (unless other noted).

General procedure K: Mitsunobu alkylation employing DEAD to prepare *N*-acyloxysulfonamides

To a solution of alcohol (1.0 eq.), hydroxylamine-derived pronucleophile (1.5 eq.) and PPh_3 (2.0 eq.) in anhydrous PhMe:THF (3:1, 8 mL/mmol) at 0 °C was added a solution of DEAD (2.0 eq.) in anhydrous PhMe (2 mL/mmol) dropwise. The reaction mixture was stirred at room temperature for the time noted before being concentrated *in vacuo* and loaded directly onto silica gel for purification by FCC.

General procedure L: Johnson-Claisen rearrangement

A solution of propionic acid (0.20 eq.) in triethyl orthoacetate (10 eq.) was heated at 110 °C for 1 hour before addition of allylic alcohol (1.0 eq.). The reaction mixture heated at reflux for the time noted before being cooled to room temperature and concentrated *in vacuo*. The crude mixture was purified by FCC.

General procedure M: TBAF deprotection

To a solution of silyl ether (1.0 eq.) in THF (*approx.* 5 mL/mmol) was added TBAF (1.0 M in THF, *equivalents specified*). The reaction mixture was stirred at room temperature for the time noted before being concentrated *in vacuo*, dissolved in Et_2O (*approx.* 10 mL/mmol) and washed with water (*approx.* 5 mL/mmol) followed by brine (*approx.* 5 mL/mmol). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by FCC (unless otherwise noted).

General procedure N: Mitsunobu alkylation employing DIAD to prepare *N*-acyloxysulfonamides

To a solution of alcohol (1.0 eq.), hydroxylamine-derived pronucleophile (1.3 eq.) and PPh_3 (2.0 eq.) in anhydrous THF:PhMe (2:1, 30 mL/mmol) at 0 °C was added a solution of DIAD (1.5 eq.) in anhydrous PhMe (10 mL/mmol) dropwise. The reaction mixture was stirred at room temperature for the time noted before being concentrated *in vacuo* and loaded directly onto silica gel for purification by FCC.

General procedure O: Mitsunobu alkylation to prepare *N*-acyloxycarbamates

To a solution of alcohol (1.0 eq.), hydroxylamine-derived pronucleophile (1.3 eq.) and PPh_3 (1.5 eq.) in anhydrous THF:PhMe (3:1, 8 mL/mmol) at 0 °C was added a solution of DIAD (1.5 eq.) in anhydrous PhMe (2 mL/mmol) dropwise. The reaction mixture was stirred at room temperature for the time noted before being concentrated *in vacuo* and loaded directly onto silica gel for purification by FCC.

General procedure P: Synthesis of trioxaphosphaadamantane ligands

The following is an adaptation of a literature procedure.[149] A suspension of 1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane (**248**)[XLIII] (1.0 eq.), $Pd(PPh_3)_4$ (3 mol%), aryl bromide (1.2 eq.) and K_2CO_3 (2.0 eq.) in anhydrous xylenes (5 mL/mmol, argon sparged) was heated at 110 °C for the time noted. The reaction mixture was cooled to room temperature before being filtered through silica and rinsed with Et_2O. The filtrate was concentrated *in vacuo*, and the crude product was purified by FCC.

General procedure Q: *N*-Boc deprotection

A solution of carbamate in TFA (2 mL) and CH_2Cl_2 (2 mL) was stirred at room temperature for 1 hour before being concentrated *in vacuo* to afford the product.

General procedure R: Mitsunobu alkylation to prepare *N*-sulfonyloxycarbamates

To a solution of alcohol (1.0 eq.), hydroxylamine-derived pronucleophile (1.0 eq.) and PPh_3 (1.2 eq.) in anhydrous THF (2.5 mL/mmol) at 0 °C was added DIAD (1.1 eq.) dropwise. The reaction mixture was stirred at room temperature for the time noted before being concentrated *in vacuo* and loaded directly onto silica gel for purification by FCC.

General procedure S: Palladium-catalysed aminoborylation cascade reaction

A flame-dried re-sealable tube, fitted with a magnetic stirrer, was charged with cyclisation substrate (1.0 eq.), $Pd_2(dba)_3$, phosphine ligand and B_2Pin_2. The tube was fitted with a rubber septum and purged with nitrogen before solvent and Et_3N were added *via* syringe. The tube was sealed and heated at the specified temperature for 48 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude mixture was purified by FCC.

[XLIII] Phosphine **248** was prepared by Charly Faradji (University of Bristol) according to a literature procedure.[147]

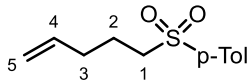
7.3 Experimental procedures for the studies in Chapter 2

N-Hydroxy-4-toluenesulfonamide

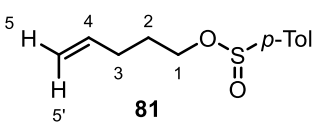
TsNHOH

This compound was prepared according to a literature procedure.[196] To a solution of $NH_2OH{\cdot}HCl$ (1.50 g, 21.6 mmol) in MeOH (9 mL) and water (6 mL) was added MgO (760 mg, 18.9 mmol). The reaction mixture was stirred at room temperature for 10 minutes before addition of a solution of TsCl (1.80 g, 9.44 mmol) in THF (30 mL) followed by another portion of MgO (380 mg, 9.43 mmol). The reaction mixture was stirred for 1 hour before being filtered and concentrated *in vacuo*. FCC (gradient elution: 4:1 – 3:1 – 1:1 hexane:EtOAc) afforded TsNHOH (1.09 g, 62 %) as a colourless crystalline solid. m.p. 136-137 °C (Et_2O:hexane) [Lit., 129-130 °C (C_6H_6:Et_2O)][197]. ν_{max} / cm^{-1}: (*solid*) 3376 (br s), 3220 (s), 1595 (m), 1387 (m), 1318 (s), 1303 (s), 1291 (m), 1156 (s), 1089 (s), 1005 (m). δ_H (500 MHz, CD_3CN) 7.76 (2H, d, *J* = 8.5 Hz), 7.72 (1H, d, *J* = 3.5 Hz), 7.41 (2H, d, *J* = 8.5 Hz), 7.35 (2H, d, *J* = 3.5 Hz), 2.43 (3H, s). δ_C (126 MHz, CD_3CN) 144.9, 133.8, 129.6, 128.5, 20.6. HRMS: (ESI^+) Calculated for $C_7H_9NNaO_3S$: 210.0195. Found $[M+Na]^+$: 210.0186. *The spectroscopic properties were consistent with the data available in the literature.*[197]

p-(Pent-4-en-1-ylsulfonyl)toluene (80) and pent-4-en-1-yl p-tolylsulfinate (81)



80



81

To a solution of TsNHOH (*vide supra*, 250 mg, 0.130 mmol) in anhydrous DMSO (4 mL) was added NaH (60 % in mineral oil, 52.0 mg, 1.30 mmol). The reaction mixture was stirred at room temperature for 1.5 hours before addition of 5-bromo-1-pentene (0.16 mL, 1.30 mmol). The reaction mixture was stirred at room temperature for 1 hour before being poured into an icy solution of brine (50 mL) and extracted with Et_2O (3 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 9:1 – 4:1 hexane:EtOAc) afforded sulfinyl ester **81** (34.0 mg, 12 %) as a colourless oil and sulfone **80** (124 mg, 42 %) as a colourless oil. *Spectroscopic data for **80**:* ν_{max} / cm^{-1}: (*film*) 2923 (s), 2853 (s), 1642 (m), 1598 (m), 1463 (m), 1378 (m), 1136 (s). δ_H (500 MHz, $CDCl_3$) 7.81 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.38 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.70 (1H, ddt, *J* = 16.0, 11.0, 6.5 Hz, C**4**-<u>H</u>), 5.04 – 5.03 (1H, m, C**5**-<u>H</u>), 5.02 – 4.99 (1H, m, C**5**-<u>H</u>'), 3.11 – 3.06 (2H, m, C**1**-$\underline{H}_2$), 2.48 (3H, s, Ts C$\underline{H}_3$), 2.15 (2H, tddd, *J* = 7.0, 6.5, 1.5, 1.5 Hz, C**3**-$\underline{H}_2$), 1.87 – 1.80 (2H, m, C**2**-$\underline{H}_2$). δ_C (126 MHz, $CDCl_3$) 144.8 (Ar<u>C</u>), 136.5 (C**4**), 136.4 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 116.6 (C**5**), 55.8 (C**1**), 32.2 (C**3**), 22.0 (C**2**), 21.8 (Ts <u>C</u>H_3). HRMS: (ESI^+) Calculated for $C_{12}H_{17}O_2S$: 225.0949. Found $[M+H]^+$: 225.0944.

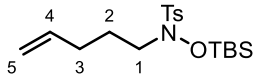
*Spectroscopic data for **81**:* ν_{max} / cm^{-1}: (*film*) 3077 (m), 2980 (m), 2923 (m), 1641 (m), 1597 (m), 1455 (m), 1405 (m), 1313 (s), 1287 (s). δ_H (500 MHz, $CDCl_3$) 7.59 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.34 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.74 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, C**4**-<u>H</u>), 5.00 (1H, ddt, *J* = 17.0, 2.0, 1.5 Hz, C**5**-<u>H</u>'), 4.96 (1H, ddt, *J* = 10.0, 2.0, 1.5 Hz, C**5**-<u>H</u>), 4.04 (1H, dt, *J* = 10.0, 6.5 Hz, C**1**-<u>H</u>), 3.62 (dt, *J* = 10.0, 6.5 Hz, C**1**-<u>H</u>'), 2.43 (3H, s, Tol C<u>H</u>$_3$), 2.10 (2H, tddd, *J* = 8.0, 6.5, 1.5, 1.5 Hz, C**3**-<u>H</u>$_2$), 1.72 (2H, tdd, *J* = 8.0, 6.5, 6.5 Hz, C**2**-<u>H</u>$_2$). δ_C (126 MHz, $CDCl_3$) 142.8 (Ar<u>C</u>), 141.9 (Ar<u>C</u>), 137.4 (C**4**), 129.8 (Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 115.5 (C**5**), 64.0 (C**1**), 29.9 (C**3**), 29.1 (C**2**), 21.7 (Tol <u>C</u>H$_3$). HRMS: (ESI^+) Calculated for $C_{12}H_{17}O_2S$: 225.0949. Found $[M+H]^+$: 225.0942.

_N_-((_tert_-Butyldimethylsilyl)oxy)-4-toluenesulfonamide

TsNHOTBS

To a suspension of TsNHOH (5.00 g, 26.7 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C was added TBSCl (6.00 g, 40.1 mmol) followed by Et_3N (5.6 mL, 40.1 mmol). The reaction mixture stirred at room temperature for 14 hours before addition of water (200 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic phases were washed with brine (200 mL), dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 3:1 hexane:EtOAc) afforded TsNHOTBS (7.20 g, 89 %) as a colourless crystalline solid. *An alternative one-pot procedure[113] failed to provide TsNHOTBS in reliable yield.* ν_{max} / cm^{-1}: (*solid*) 3194 (m), 2928 (m), 1598 (m), 1327 (m), 1252 (m), 1162 (m), 1014 (s). δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* = 8.5 Hz), 7.33 (2H, d, *J* = 8.5 Hz), 6.50 (1H, s), 2.45 (3H, s), 0.88 (9H, s), 0.17 (6H, s). δ_C (101 MHz, $CDCl_3$) 144.7, 133.1, 129.5, 128.9, 25.8, 21.7, 17.9, -5.4. HRMS: (ESI^+) Calculated for $C_{13}H_{24}NO_3SSi$: 302.1246. Found $[M+H]^+$: 302.1228. *The spectroscopic properties were consistent with the data available in the literature.[113]*

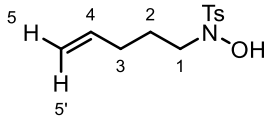
_N_-((_tert_-Butyldimethylsilyl)oxy)-_N_-(pent-4-en-1-yl)-4-toluenesulfonamide (82)



<u>General procedure A:</u> TsNHOTBS (*vide supra*, 2.71 g, 9.00 mmol) was employed with 5-bromopent-1-ene. FCC (eluent: 19:1 hexane:EtOAc) afforded **82** (2.36 g, 97 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2930 (m), 2858 (m), 1598 (m), 1463 (m), 1356 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.74 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, C**4**-<u>H</u>), 5.03 – 4.94 (2H, m, C**5**-<u>H</u>$_2$), 2.91 (2H, t, *J* = 7.5 Hz, C**1**-<u>H</u>$_2$), 2.45 (3H, s, Ts C<u>H</u>$_3$), 2.09 – 2.02 (2H, m, C**3**-<u>H</u>$_2$), 1.65 (2H, tt, *J* = 7.5, 7.5 Hz, C**2**-<u>H</u>$_2$), 0.92 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.29 (6H, s, Si(C<u>H</u>$_3$)$_2$). δ_C (101 MHz, $CDCl_3$) 144.5 (Ar<u>C</u>), 137.4 (C**4**), 130.0 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H),

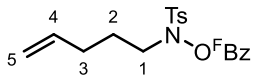
115.3 (C**5**), 55.4 (C**1**), 31.0 (C**3**), 26.1 (C**2**), 26.0 (SiC($\underline{C}H_3)_3$), 21.6 (Ts $\underline{C}H_3$), 18.3 (Si$\underline{C}(CH_3)_3$), -4.2 (Si($\underline{C}H_3)_2$). HRMS: (ESI^+) Calculated for $C_{18}H_{32}NO_3SSi$: 370.1867. Found $[M+H]^+$: 370.1866.

***N*-Hydroxy-*N*-(pent-4-en-1-yl)-4-toluenesulfonamide (78)**



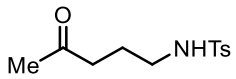
General procedure B: Compound **82** (500 mg, 1.35 mmol) was employed. Compound **78** (340 mg, 99 %) was isolated as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3369 (br s), 2925 (m), 2853 (m), 1641 (m), 1597 (m), 1440 (m), 1331 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* = 8.5 Hz, 2 × ArC$\underline{H}$), 7.36 (2H, d, *J* = 8.5 Hz, 2 × ArC$\underline{H}$), 6.27 (1H, s, O$\underline{H}$), 5.78 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, C**4**-$\underline{H}$), 5.03 (1H, ddt, *J* = 17.0, 1.5, 1.5 Hz, C**5**-$\underline{H}$'), 4.98 (1H, ddt, *J* = 10.0, 1.5, 1.5 Hz, C**5**-$\underline{H}$), 2.92 (2H, t, *J* = 7.0 Hz, C**1**-$\underline{H}_2$), 2.46 (3H, s, Ts C$\underline{H}_3$), 2.16 – 2.09 (2H, m, C**3**-$\underline{H}_2$), 1.71 (2H, tt, *J* = 7.0, 7.0 Hz, C**2**-$\underline{H}_2$). δ_C (101 MHz, $CDCl_3$) 144.9 (Ar$\underline{C}$), 137.5 (C**4**), 129.6 (Ar$\underline{C}$H), 129.5 (Ar$\underline{C}$H), 129.4 (Ar$\underline{C}$), 115.4 (C**5**), 51.9 (C**1**), 30.6 (C**3**), 25.9 (C**2**), 21.7 (Ts $\underline{C}H_3$). HRMS: (ESI^+) Calculated for $C_{12}H_{17}NNaO_3S$: 278.0821. Found $[M+Na]^+$: 278.0821.

***N*-(Pent-4-en-1-yl)-*N*-((pentafluorobenzoyl)oxy)-4-toluenesulfonamide (79)**



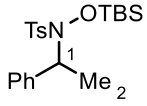
General procedure C: Compound **78** (330 mg, 1.29 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **79** (570 mg, 98 %) as a colourless crystalline solid. m.p. 89-90 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*solid*) 2927 (m), 1787 (s), 1654 (m), 1595 (m), 1505 (s), 1367 (s), 1170 (s). δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* = 8.0 Hz, 2 × ArC$\underline{H}$), 7.38 (2H, d, *J* = 8.0 Hz, 2 × ArC$\underline{H}$), 5.75 (ddt, *J* = 17.0, 10.0, 7.0 Hz, C**4**-$\underline{H}$), 5.07 – 4.97 (2H, m, C**5**-$\underline{H}_2$), 3.23 (2H, br s, C**1**-$\underline{H}_2$), 2.47 (3H, s, Ts C$\underline{H}_3$), 2.20 (2H, dt, *J* = 7.0, 7.0 Hz, C**3**-$\underline{H}_2$), 1.67 (tt, *J* = 7.0, 7.0 Hz, C**2**-$\underline{H}_2$). δ_C (126 MHz, $CDCl_3$) 156.5 (^{F}Bz $\underline{C}$=O), 146.0 (Ar$\underline{C}$), 137.0 (C**4**), 130.2 (Ar$\underline{C}$), 130.0 (Ar$\underline{C}$H), 129.8 (Ar$\underline{C}$H), 116.1 (C**5**), 52.1 (C**1**), 30.5 (C**3**), 25.9 (C**2**), 21.9 (Ts $\underline{C}H_3$). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.1 (2F, m), -146.0 (1F, tt, *J* = 21.0, 5.5 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{19}H_{17}F_5NO_4S$: 450.0793. Found $[M+H]^+$: 450.0794.

***N*-(4-Oxopentyl)-4-toluenesulfonamide (102)**



General procedure D: Conditions: 3.75 mol% $Pd_2(dba)_3$; 15 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 200 mol% Et_3N; DMF (0.11 M); 120 °C; 2 hours. Substrate **79** (50.0 mg, 0.111 mmol) was employed. FCC (gradient elution: 19:1 – 9:1 – 4:1 – 0:1 hexane:EtOAc) afforded **102** (23.0 mg, 81 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3278 (br s), 2925 (m), 1709 (s), 1598 (m), 1423 (m), 1324 (s), 1155 (s). δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 8.5 Hz), 4.83 (1H, t, *J* = 6.5 Hz), 2.93 (2H, dt, *J* = 6.5, 6.5 Hz), 2.50 (2H, t, *J* = 6.5 Hz), 2.41 (3H, s), 2.11 (3H, s), 1.72 (2H, tt, *J* = 6.5, 6.5 Hz). δ_C (101 MHz, $CDCl_3$) 208.5, 143.6, 137.0, 129.9, 127.2, 42.7, 40.3, 30.2, 23.4, 21.6. HRMS: (ESI^+) Calculated for $C_{12}H_{18}NO_3S$: 256.1002. Found $[M+H]^+$: 256.1003. *The spectroscopic properties were consistent with the data available in the literature.*[198]

***N*-(1-Phenylethyl)-*N*-((*tert*-butyldimethylsilyl)oxy)-4-toluenesulfonamide (93)**



General procedure E: TsNHOTBS (*vide supra*, 1.20 g, 3.98 mmol) was employed with 1-phenylethanol (1.5 eq.). The reaction time was 24 hours. FCC (eluent: 1:1 hexane:PhMe) afforded **93** (1.31 g, 81 %) as a colourless crystalline solid. m.p. 133-134 °C (CH_2Cl_2:hexane, *plates*). ν_{max} / cm^{-1}: (*solid*) 2963 (m), 2858 (m), 1596 (m), 1349 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.40 – 7.34 (2H, m, 2 × ArC<u>H</u>), 7.31 – 7.19 (5H, m, 5 × ArC<u>H</u>), 4.98 (1H, q, *J* = 7.0 Hz, C**1**-<u>H</u>), 2.44 (3H, s, Ts C<u>H</u>$_3$), 1.00 (3H, d, *J* = 7.0 Hz, C**2**-<u>H</u>$_3$), 0.87 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.24 (3H, s, SiC<u>H</u>$_3$), -0.41 (3H, s, Si(C<u>H</u>$_3$)'). δ_C (101 MHz, $CDCl_3$) 144.2 (Ar<u>C</u>), 140.5 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 129.3 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 60.0 (C**1**), 26.1 (SiC(<u>C</u>H$_3$)$_3$), 21.6 (Ts C<u>H</u>$_3$), 18.5 (Si<u>C</u>(CH$_3$)$_3$), 13.0 (C**2**), -4.4 (Si<u>C</u>H$_3$), -4.9 (Si(<u>C</u>H$_3$)'). HRMS: (ESI^+) Calculated for $C_{21}H_{31}NNaO_3SSi$: 428.1686. Found $[M+Na]^+$: 428.1673.

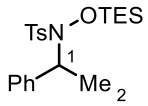
***N*-((Triethylsilyl)oxy)-4-toluenesulfonamide**

TsNHOTES

To a suspension of TsNHOH (*vide supra*, 5.00 g, 26.7 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C was added TESCl (6.70 mL, 40.0 mmol) followed by Et_3N (5.60 mL, 40.2 mmol). The reaction mixture was stirred at room temperature for 19 hours before addition of brine (150 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic

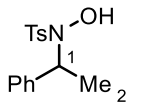
phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 3:1 hexane:EtOAc) afforded TsNHOTES (7.02 g, 87 %) as a colourless crystalline solid, which was stored in a glovebox to prevent hydrolysis. ν_{max} / cm^{-1}: (*solid*) 3196 (s), 2954 (m), 2914 (m), 2878 (m), 1597 (m). δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.34 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 6.45 (1H, s N<u>H</u>), 2.45 (3H, s, Ts C<u>H</u>$_3$), 0.96 (9H, t, *J* = 8.0 Hz, Si($CH_2C\underline{H}_3$)$_3$), 0.71 (6H, q, *J* = 8.0 Hz, Si($C\underline{H}_2CH_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 144.9 (Ar<u>C</u>), 133.3 (Ar<u>C</u>), 129.7 (Ar<u>C</u>H), 129.0 (Ar<u>C</u>H), 21.8 (Ts C<u>H</u>$_3$), 6.7 (Si($CH_2\underline{C}H_3$)$_3$), 4.1 (Si($\underline{C}H_2CH_3$)$_3$). HRMS: (ESI^+) Calculated for $C_{13}H_{23}NNaO_3SSi$: 324.1060. Found $[M+Na]^+$: 324.1060.

***N*-(1-Phenylethyl)-*N*-((triethylsilyl)oxy)-4-toluenesulfonamide (96)**



<u>General procedure E:</u> TsNHOTES (*vide supra*, 600 mg, 1.99 mmol) was employed with 1-phenylethanol (1.5 eq.). The reaction time was 20 hours. FCC (gradient elution: 1:1 – 2:3 hexane:PhMe) afforded **96** (724 mg, 90 %) as a colourless crystalline solid. m.p. 104-105 °C (CH_2Cl_2:hexane, *plates*). ν_{max} / cm^{-1}: (*solid*) 2958 (m), 2877 (m), 1597 (m), 1352 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.35 – 7.28 (2H, m, 2 × ArC<u>H</u>), 7.28 – 7.18 (5H, m, 5 × ArC<u>H</u>), 4.87 (1H, q, *J* = 7.0 Hz, C**1**-<u>H</u>), 2.42 (3H, s, Ts C<u>H</u>$_3$), 1.08 (3H, d, *J* = 7.0 Hz, C**2**-<u>H</u>$_3$), 0.89 (9H, t, *J* = 8.0 Hz, Si($CH_2C\underline{H}_3$)$_3$), 0.65 – 0.45 (6H, m, Si($C\underline{H}_2CH_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 144.2 (Ar<u>C</u>), 140.4 (Ar<u>C</u>), 133.2 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 129.3 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 60.7 (C**1**), 21.8 (Ts <u>C</u>H$_3$), 14.3 (C**2**), 7.0 (Si($CH_2\underline{C}H_3$)$_3$), 4.9 (Si($\underline{C}H_2CH_3$)$_3$). HRMS: (ESI^+) Calculated for $C_{21}H_{31}NNaO_3SSi$: 428.1686. Found $[M+Na]^+$: 428.1685.

***N*-(1-Phenylethyl)-*N*-hydroxy-4-toluenesulfonamide (94)**



<u>General procedure F:</u> Compound **96** (75.0 mg, 0.185 mmol) was employed. Compound **94** (52.1 mg, 97 %) was isolated as a colourless crystalline solid, which required no further purification. ν_{max} / cm^{-1}: (*solid*) 3314 (br s), 2983 (m), 1597 (m), 1332 (s), 1154 (s). δ_H (400 MHz, $CDCl_3$) 7.69 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.36 – 7.29 (2H, m, 2 × ArC<u>H</u>), 7.25 – 7.15 (5H, m, 5 × ArC<u>H</u>), 6.49 (1H, br s, O<u>H</u>), 4.95 (1H, q, *J* = 7.0 Hz, C**1**-<u>H</u>), 2.40 (3H, s, Ts C<u>H</u>$_3$), 1.35 (3H, d, *J* = 7.0 Hz, C**2**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 144.4 (Ar<u>C</u>), 140.1 (Ar<u>C</u>), 132.9 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 60.1 (C**1**), 21.7 (Ts <u>C</u>H$_3$), 17.0 (C**2**). HRMS: (ESI^+) Calculated for $C_{15}H_{17}NNaO_3S$: 314.0821. Found $[M+Na]^+$: 314.0828.

N-Hydroxymethanesulfonamide

MsNHOH

This compound was prepared according to a literature procedure.[196] To a solution of $NH_2OH{\cdot}HCl$ (13.9 g, 200 mmol) in MeOH (60 mL) and water (40 mL) was added MgO (6.93 g, 172 mmol). The reaction mixture was stirred at room temperature for 20 minutes before addition of a solution of MsCl (6.7 mL, 86.0 mmol) in THF (600 mL) followed by another portion of MgO (3.47 g, 86.0 mmol). The reaction mixture was stirred at room temperature for 2.5 hours before being filtered through celite and concentrated *in vacuo* to afford MsNHOH (9.38 g, 98 %) as a colourless crystalline solid, which was used without further purification. ν_{max} / cm^{-1}: (*solid*) 3373 (br s), 3253 (s), 3036 (m), 1302 (s), 1154 (s). δ_H (400 MHz, CD_3CN) 7.45 (2H, m, NH and OH), 2.95 (3H, s, Ms CH_3). δ_C (101 MHz, CD_3CN) 36.0 (Ms CH_3). HRMS: (ESI^+) Calculated for CH_5NNaO_3S: 133.9882. Found $[M+Na]^+$: 133.9888.

N-((Triethylsilyl)oxy)methanesulfonamide

MsNHOTES

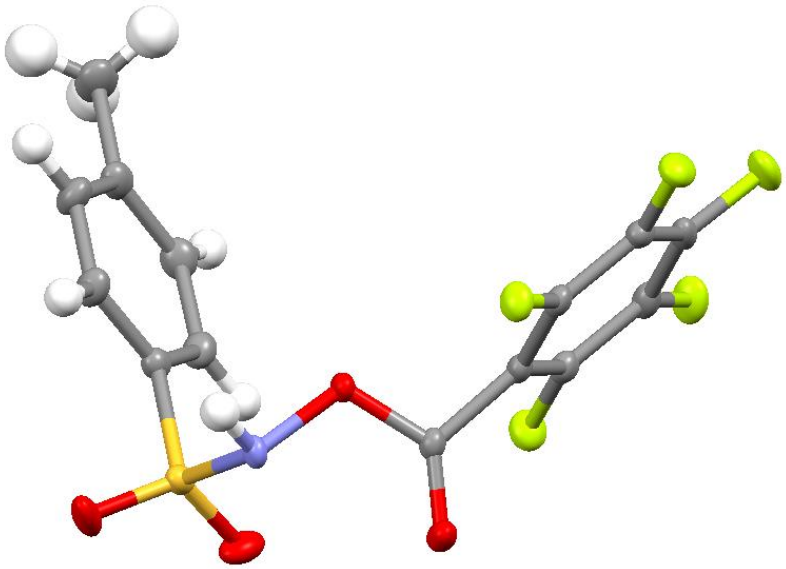
To a suspension of MsNHOH (*vide supra*, 1.33 g, 12.0 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C was added TESCl (2.61 mL, 15.6 mmol) followed by Et_3N (2.17 mL, 15.6 mmol). The reaction mixture was stirred at room temperature for 19 hours before addition of water (25 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 6:1 – 5:1 – 4:1 hexane:EtOAc) afforded MsNHOTES (2.24 g, 83 %) as a colourless oil, which was stored in a glovebox to prevent hydrolysis. ν_{max} / cm^{-1}: (*film*) 3209 (br s), 2957 (s), 2879 (s), 1320 (s), 1160 (s). δ_H (400 MHz, $CDCl_3$) 6.67 (1H, s, NH), 3.05 (3H, s, Ms CH_3), 0.99 (9H, t, J = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.74 (6H, q, J = 8.0 Hz, $Si(CH_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 35.9 (Ms CH_3), 6.6 ($Si(CH_2CH_3)_3$), 4.0 ($Si(CH_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_7H_{19}NNaO_3SSi$: 248.0747. Found $[M+Na]^+$: 248.0746.

N-((Pentafluorobenzoyl)oxy)-4-toluenesulfonamide

TsNHO^{F}Bz

General procedure G: TsNHOH (*vide supra*, 9.36 g, 50.0 mmol) was employed. The reaction time was 19 hours. FCC (gradient elution: 4:1 – 3:1 hexane:EtOAc) afforded TsNHO^{F}Bz (13.9 g, 73 %) as a colourless crystalline solid. m.p. 102-104 °C (CH_2Cl_2:hexane, *needles*). ν_{max} / cm^{-1}: (*solid*) 3189 (br s), 1781 (s), 1653 (s), 1597 (m), 1500 (s), 1163 (s). δ_H (400 MHz, $CDCl_3$) 9.01 (1H, s, NH), 7.85 (2H, d, J = 8.5 Hz, 2 × ArCH), 7.36 (2H, d, J = 8.5 Hz, 2 × ArCH), 2.45 (3H, s, Ts CH_3). δ_C (101 MHz,

$CDCl_3$) 158.0 (C=O), 146.4 (ArC), 132.2 (ArC), 130.2 (ArCH), 129.1 (ArCH), 21.9 (Ts CH_3). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity*. δ_F (377 MHz, $CDCl_3$) -134.7 – -134.8 (2F, m), -144.1 (1F, tt, *J* = 21.0, 6.5 Hz), -158.7 – -158.8 (2F, m). HRMS: (ESI^+) Calculated for $C_{14}H_8F_5NNaO_4$: 403.9986. Found $[M+Na]^+$: 403.9992.



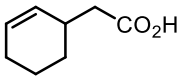
ORTEP view of TsNHO^{F}Bz.

_N_-((Pentafluorobenzoyl)oxy)methanesulfonamide

MsNHO^{F}Bz

General procedure G: MsNHOH (*vide supra*, 2.22 g, 20.0 mmol) was employed. The reaction time was 20 hours. FCC (eluent: 3:1 hexane:EtOAc) afforded MsNHO^{F}Bz (1.93 g, 32 %) as a colourless crystalline solid. m.p. 135-136 °C (Et_2O:hexane, *cubes*). ν_{max} / cm^{-1}: (*solid*) 3151 (s), 2940 (m), 1759 (s), 1653 (m), 1500 (s), 1324 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 8.72 (1H, br s, NH), 3.20 (3H, d, *J* = 1.0 Hz, Ms CH_3). δ_C (101 MHz, $CDCl_3$) 39.3 (Ms CH_3). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity*. δ_F (377 MHz, $CDCl_3$) -134.5 – -134.6 (2F, m), -143.5 (1F, tt, *J* = 21.0, 6.5 Hz), -158.4 – -158.6 (2F, m). HRMS: (ESI^+) Calculated for $C_8H_4F_5NNaO_4S$: 327.9673. Found $[M+Na]^+$: 327.9676.

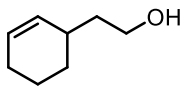
2-(Cyclohex-2-en-1-yl)acetic acid



General procedure H: 3-Bromocyclohexene (6.90 mL, 60.0 mmol) was employed. The title compound (6.23 g, 74 %) was isolated as an orange oil, which was used without further purification. ν_{max} / cm^{-1}: (*film*) 3020 (m), 2927 (m), 1703 (s), 1289 (s). δ_H (400 MHz, $CDCl_3$) 11.28 (1H, br s), 5.72

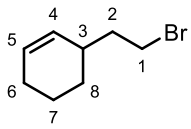
(1H, dtd, *J* = 10.0, 3.5, 2.0 Hz), 5.56 (1H, dtd, *J* = 10.0, 2.5, 2.0 Hz), 2.59 (1H, m), 2.36 (1H, dd, *J* = 15.5, 7.0 Hz), 2.29 (1H, dd, *J* = 15.5, 8.0 Hz), 1.98 (2H, dddd, *J* = 10.5, 5.5, 3.0, 2.5 Hz), 1.90 – 1.81 (1H, m), 1.75 – 1.66 (1H, m), 1.61 – 1.50 (1H, m), 1.30 (1H, dddd, *J* = 13.5, 11.0, 8.5, 3.0 Hz). δ_C (101 MHz, $CDCl_3$) 179.6, 129.9, 128.5, 40.7, 32.1, 28.8, 25.1, 21.0. *The spectroscopic properties were consistent with the data available in the literature.*[199]

2-(Cyclohex-2-en-1-yl)ethan-1-ol (83)



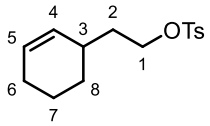
General procedure I: The preceding carboxylic acid (6.20 g, 44.0 mmol) was employed, using anhydrous THF as solvent and 1.7 eq. $LiAlH_4$ (1.0 M in THF). The crude product was filtered through a short plug of silica to afford **83** (4.85 g, 87 %) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 5.68 (1H, dtd, *J* = 10.0, 3.5, 2.5 Hz), 5.57 (1H, ddt, *J* = 10.0, 2.5, 2.0 Hz), 3.77 – 3.67 (2H, m), 2.28 – 2.17 (1H, m), 1.97 (2H, dddd, *J* = 10.5, 5.5, 3.5, 2.0 Hz), 1.80 (1H, dtd, *J* = 12.0, 5.5, 2.5 Hz), 1.76 – 1.67 (1H, m), 1.67 – 1.50 (3H, m), 1.50 (1H, s), 1.25 (1H, dddd, *J* = 12.5, 11.0, 8.5, 2.5 Hz). δ_C (101 MHz, $CDCl_3$) 131.6, 127.4, 60.9, 39.2, 31.9, 29.1, 25.3, 21.4. HRMS: (ESI^+) Calculated for $C_8H_{14}NaO$: 149.0937. Found $[M+Na]^+$: 149.0932. *The spectroscopic properties were consistent with the data available in the literature.*[200]

3-(2-Bromoethyl)cyclohex-1-ene



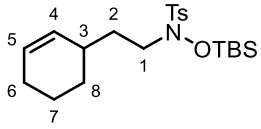
General procedure J: Alcohol **83** (6.40 g, 50.8 mmol) was employed. FCC (eluent: 29:1 hexane:EtOAc) afforded the title compound (2.50 g, 26 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.72 (1H, ddt, *J* = 10.0, 3.5, 3.5 Hz), 5.54 (1H, ddt, *J* = 10.0, 2.5, 2.5 Hz), 3.52 – 3.41 (2H, m), 2.35 – 2.25 (1H, m), 2.01 – 1.95 (2H, m), 1.90 (1H, ddd, *J* = 14.0, 7.0, 7.0 Hz), 1.86 – 1.76 (2H, m), 1.76 – 1.66 (1H, m), 1.60 – 1.49 (1H, m), 1.22 (1H, dddd, *J* = 13.0, 11.0, 8.5, 3.0 Hz). δ_C (101 MHz, $CDCl_3$) 130.2, 127.9, 39.2, 33.8, 31.7, 28.3, 25.2, 21.1. *m/z* (EI^+) 189 and 187 ($[M]^+$, 30 and 30 %), 97 (100 %), 81 and 79 ($[Br]^+$, 74 and 77 %). *The spectroscopic properties were consistent with the data available in the literature.*[201]

2-(Cyclohex-2-en-1-yl)ethan-1-yl tosylate (84)



To a solution of alcohol **83** (3.95 g, 31.3 mmol) and Et_3N (7.00 mL, 50.2 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added TsCl (9.24 g, 48.5 mmol) in two roughly equal portions. The reaction mixture was stirred at room temperature for 22 hours before addition of saturated aqueous $NaHCO_3$ (100 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 9:1 petrol:EtOAc) afforded **84** (8.43 g, 96 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3017 (m), 2927 (m), 1598 (m), 1448 (m), 1361 (s), 1176 (s). δ_H (500 MHz, $CDCl_3$) 7.80 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.35 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.66 (1H, dtd, *J* = 10.0, 4.0, 3.5 Hz, C**5**-<u>H</u>), 5.42 (1H, ddt, *J* = 10.0, 2.5, 2.5 Hz, C**4**-<u>H</u>), 4.10 (2H, t, *J* = 6.5 Hz, C**1**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.17 (1H, m, C**3**-<u>H</u>), 1.94 (2H, dddd, *J* = 5.5, 5.5, 4.0, 2.5 Hz, C**6**-<u>H_2</u>), 1.74 – 1.54 (4H, m, C**2**-<u>H_2</u> C**7**-<u>H</u> and C**8**-<u>H</u>), 1.52 – 1.42 (1H, m, C**7**-<u>H</u>'), 1.18 – 1.11 (1H, m, C**8**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 144.7 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 130.1 (C**4**), 129.8 (Ar<u>C</u>H), 128.0 (C**5**), 127.9 (Ar<u>C</u>H), 68.6 (C**1**), 35.0 (C**2**), 31.4 (C**3**), 28.5 (C**8**), 25.1 (C**6**), 21.6 (Ts C<u>H_3</u>), 21.0 (C**7**). HRMS: (ESI^+) Calculated for $C_{15}H_{20}NaO_3S$: 303.1025. Found $[M+Na]^+$: 303.1025.

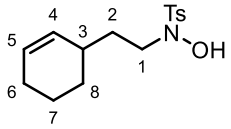
***N*-((*tert*-Butyldimethylsilyl)oxy)-*N*-(2-(cyclohex-2-en-1-yl)ethyl)-4-toluenesulfonamide (85)**



<u>General procedure A:</u> TsNHOTBS (*vide supra*, 2.71 g, 9.00 mmol) was employed with 3-(2-bromoethyl)cyclohex-1-ene (*vide supra*). FCC (eluent: 14:1 hexane:EtOAc) afforded **85** (2.51 g, 57 %) as a colourless oil that solidified upon standing. *Alternative synthesis adapted from a literature procedure:*[113]A solution of TsNHOTBS (2.35 g, 7.79 mmol), tosylate **84** (1.82 g, 6.49 mmol) and Cs_2CO_3 (3.81 g, 11.7 mmol) in DMF (40 mL) was stirred at room temperature for 17 hours before addition of saturated aqueous NH_4Cl (50 mL) and water (50 mL). The reaction mixture was extracted with EtOAc (3 × 80 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 29:1 – 19:1 hexane:EtOAc) afforded **85** (1.95 g, 75 %) as a colourless oil that solidified upon standing. ν_{max} / cm^{-1}: (*solid*) 3021 (m), 2928 (s), 2858 (m), 1597 (m), 1351 (s), 1164 (s). δ_H (500 MHz, $CDCl_3$) 7.73 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.67 (1H, ddt, *J* = 10.0, 3.5, 3.5 Hz, C**5**-<u>H</u>), 5.47 (1H, ddt, *J* = 10.0, 2.0, 2.0 Hz, C**4**-<u>H</u>), 3.04 – 2.89 (2H, m, C**1**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.12 – 2.04 (1H, m, C**3**-<u>H</u>), 1.98 – 1.92 (2H, m, C**6**-<u>H_2</u>), 1.78 – 1.71 (1H, m, C**8**-<u>H</u>), 1.71 – 1.58 (2H, m, C**2**-<u>H</u> and C**7**-<u>H</u>), 1.54 – 1.44 (2H, m, C**2**-<u>H</u>' and C**7**-<u>H</u>'), 1.16 (1H,

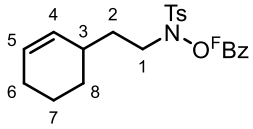
dddd, *J* = 12.5, 11.0, 8.5, 2.5 Hz, C**8**-H'), 0.92 (9H, s, SiC(CH_3)$_3$), 0.30 (3H, s, SiCH_3), 0.29 (3H, s, Si(CH_3)'). δ_C (101 MHz, $CDCl_3$) 144.4 (ArC), 130.8 (C**4**), 130.0 (ArCH), 129.9 (ArCH), 129.2 (ArC), 127.7 (C**5**), 53.9 (C**1**), 33.3 (C**2**), 32.9 (C**3**), 28.7 (C**8**), 26.0 (SiC(CH_3)$_3$), 25.2 (C**6**), 21.6 (Ts CH_3), 21.2 (C**7**), 18.3 (SiC(CH_3)$_3$), 2 × -4.2 (SiCH_3 and Si(CH_3)'). HRMS: (ESI$^+$) Calculated for $C_{21}H_{36}NO_3SSi$: 410.2180. Found $[M+H]^+$: 410.2197.

***N*-(2-(Cyclohex-2-en-1-yl)ethyl)-*N*-hydroxy-4-toluenesulfonamide**



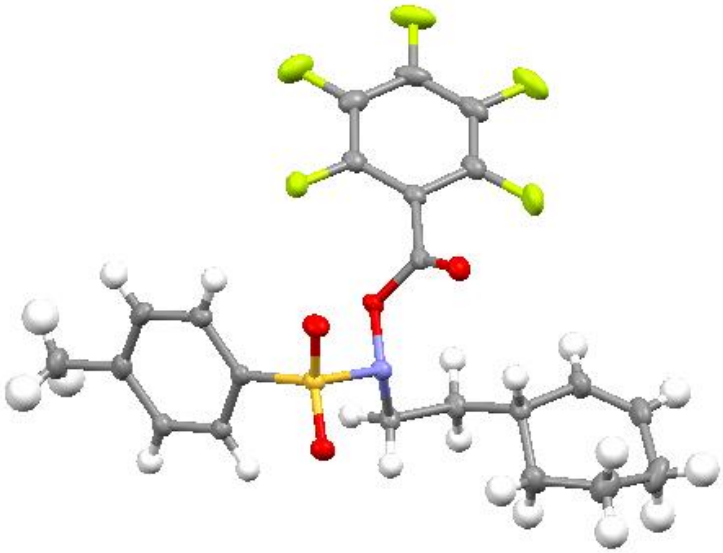
General procedure B: Compound **85** (2.10 g, 5.13 mmol) was employed. The title compound (1.31 g, 87 %) was isolated as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3356 (br s), 2921 (m), 1597 (m), 1437 (m), 1330 (s), 1163 (s). δ_H (500 MHz, $CDCl_3$) 7.80 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 7.39 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 6.28 (1H, s, OH), 5.73 – 5.67 (1H, m, C**5**-H), 5.57 – 5.52 (1H, m, C**4**-H), 3.07 – 2.93 (2H, m, C**1**-H_2), 2.48 (3H, s, Ts CH_3), 2.21 (1H, dddd, *J* = 11.5, 5.5, 5.5, 2.5 Hz, C**3**-H), 1.98 (2H, dddd, *J* = 6.5, 4.5, 3.0, 1.5 Hz, C**6**-H_2), 1.86 – 1.78 (1H, m, C**8**-H), 1.73 – 1.64 (2H, m, C**2**-H and C**7**-H), 1.59 – 1.46 (2H, m, C**2**-H' and C**7**-H'), 1.22 (1H, dddd, *J* = 12.5, 11.5, 8.5, 3.0 Hz, C**8**-H'). δ_C (126 MHz, $CDCl_3$) 144.9 (ArC), 130.9 (C**4**), 129.7 (ArCH), 129.6 (ArCH), 129.4 (ArC), 127.7 (C**5**), 50.3 (C**1**), 33.0 (C**2**), 32.5 (C**3**), 28.7 (C**8**), 25.2 (C**6**), 21.7 (Ts CH_3), 21.2 (C**7**). HRMS: (ESI$^+$) Calculated for $C_{15}H_{21}NNaO_3S$: 318.1134. Found $[M+Na]^+$: 318.1123.

***N*-(2-(Cyclohex-2-en-1-yl)ethyl)-*N*-((pentafluorobenzoyl)oxy)-4-toluenesulfonamide (103a)**



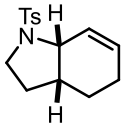
General procedure C: *N*-2-(Cyclohex-2-en-1-yl)ethyl-*N*-hydroxy-4-toluenesulfonamide (*vide supra*, 900 mg, 3.05 mmol) was employed. FCC (gradient elution: 19:1 – 12:1 hexane:EtOAc) afforded **103a** (1.33 g, 89 %) as a colourless crystalline solid. m.p. 81-82 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*solid*) 2988 (m), 2929 (m), 1790 (s), 1654 (m), 1596 (m), 1503 (s), 1170 (s). δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 7.38 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 5.67 (1H, dtd, *J* = 10.0, 3.5, 2.5 Hz, C**5**-H), 5.46 (1H, ddt, *J* = 10.0, 2.5, 2.5 Hz, C**4**-H), 3.26 (2H, br s, C**1**-H_2), 2.46 (3H, s, Ts CH_3), 2.29 (1H, ddddd, *J* = 13.5, 8.5, 5.5, 2.5, 2.5 Hz, C**3**-H), 1.94 (2H, dddd, *J* = 7.0, 5.0, 3.5, 2.5 Hz, C**6**-H_2), 1.83 – 1.73 (1H, m, C**8**-H), 1.72 – 1.44 (4H, m, C**2**-H_2 and C**7**-H_2), 1.29 – 1.13 (1H, m, C**8**-H'). δ_C (101 MHz, $CDCl_3$) 156.4 (^{F}Bz C=O), 145.9 (ArC), 130.3 (C**4**), 2 × 129.9 (ArC and ArCH), 129.5 (ArCH), 127.9 (C**5**), 50.6 (C**1**), 32.8 (C**2**), 32.2 (C**3**), 28.5 (C**8**), 25.1 (C**6**), 21.7 (Ts CH_3), 21.1 (C**7**).

The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity. δ_F (377 MHz, $CDCl_3$) -136.0 – -136.2 (2F, m), -146.2 (1F, tt, *J* = 21.0, 5.5 Hz), -159.0 – -159.2 (2F, m). HRMS: (ESI^+) Calculated for $C_{22}H_{20}F_5NNaO_4S$: 512.0925. Found $[M+Na]^+$: 512.0902.

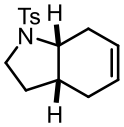


*ORTEP view of **103a**.*

(3a*R,7a*S**)-1-Tosyl-2,3,3a,4,5,7a-hexahydro-1*H*-indole (104) and (*iso*-104)**



104

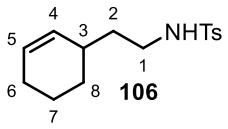


***iso*-104**

General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 12.5 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 50 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 17 hours. Substrate **103a** (68.5 mg, 0.140 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **104** and ***iso*-104** (35.4 mg, 91 %, 12:1 mixture of **104** and ***iso*-104**) as a pale-yellow oil. *Spectroscopic data for **104**:* ν_{max} / cm^{-1}: (*film*) 3031 (m), 2923 (m), 1598 (m), 1450 (m), 1338 (s), 1157 (s). δ_H (500 MHz, $CDCl_3$) 7.73 (2H, d, *J* = 8.0 Hz), 7.30 (2H, d, *J* = 8.0 Hz), 5.83 (1H, dddd, *J* = 10.5, 2.5, 2.5, 2.5 Hz), 5.80 – 5.72 (1H, m), 3.99 (1H, dd, *J* = 5.5, 2.5 Hz), 3.47 (1H, ddd, *J* = 10.0, 7.5, 4.0 Hz), 3.16 (1H, ddd, *J* = 10.0, 7.5, 7.5 Hz), 2.42 (3H, s), 2.04 – 1.95 (2H, m), 1.95 – 1.87 (1H, m), 1.76 (1H, dddd, *J* = 12.0, 8.0, 7.5, 7.5 Hz), 1.71 – 1.51 (3H, m). δ_C (126 MHz, $CDCl_3$) 143.3, 135.1, 129.7, 128.4, 127.7, 127.6, 57.6, 47.4, 36.6, 27.8, 23.0, 21.6, 21.0. HRMS: (ESI^+) Calculated for $C_{15}H_{20}NO_2S$: 278.1209. Found $[M+H]^+$: 278.1207. *The spectroscopic properties were consistent with the data available in the literature.*[26] *Characteristic signals for **iso-104** (obtained from 1D TOCSY):* δ_H (500 MHz, $CDCl_3$) 5.63 – 5.60 (m), 3.70 (ddd, *J* = 7.5, 7.5, 7.5 Hz),

3.50 – 3.45 (m), 3.12 (ddd, *J* = 10.0, 10.0, 7.5 Hz), 2.53 – 2.45 (m), 2.31 – 2.22 (m), 2.14 – 2.05 (m), 1.97 – 1.91 (m), 1.91 – 1.84 (m), 1.84 – 1.77 (m), 1.76 – 1.69 (m).

***N*-(2-(Cyclohex-2-en-1-yl)ethyl)-*p*-tolylsulfonamide (106) and *p*-toluenesulfonamide**



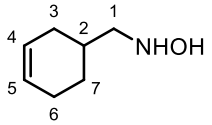
$TsNH_2$

General procedure D: Conditions: 3.75 mol% $Pd_2(dba)_3$; 15 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 400 mol% Et_3N; DMF (0.12 M); 120 °C; 2 hours. Substrate **103a** (59.2 mg, 0.121 mmol) was employed. FCC (gradient elution: 49:1 – 19:1 – 0:1 PhMe:EtOAc) afforded **104** and ***iso*-104** (5.0 mg, 15 %, 5:1 **104**:***iso*-104**) as a pale-yellow oil, **106** (8.1 mg, 24 %) as a colourless oil and *p*-toluenesulfonamide (11.4 mg, 55 %) as a colourless crystalline solid. *Spectroscopic data for **106**:* ν_{max} / cm^{-1}: (*film*) 3278 (s), 2921 (s), 1599 (m), 1424 (s), 1308 (s), 1280 (s), 1147 (s). δ_H (500 MHz, $CDCl_3$) 7.75 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.31 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.66 (1H, ddt, *J* = 10.0, 3.5, 3.5 Hz, C**5**-<u>H</u>), 5.42 (1H, ddt, *J* = 10.0, 2.5, 2.5 Hz, C**4**-<u>H</u>), 4.33 (1H, t, *J* = 6.5 Hz, N<u>H</u>), 3.00 (2H, ddd, *J* = 8.0, 6.5, 6.5 Hz, C**1**-<u>H_2</u>), 2.43 (3H, s, Ts C<u>H_3</u>), 2.12 – 2.04 (1H, m, C**3**-<u>H</u>), 1.97 – 1.90 (2H, m, C**6**-<u>H_2</u>), 1.72 – 1.37 (5H, m, C**2**-<u>H_2</u>, C**7**-<u>H_2</u> and C**8**-<u>H</u>), 1.18 – 1.09 (1H, m, C**8**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 143.5 (Ar<u>C</u>), 137.1 (Ar<u>C</u>), 130.6 (C**4**), 129.9 (Ar<u>C</u>H), 128.1 (C**5**), 127.3 (Ar<u>C</u>H), 41.2 (C**1**), 36.0 (C**2**), 32.6 (C**3**), 28.7 (C**8**), 25.3 (C**6**), 21.7 (Ts <u>C</u>H_3), 21.3 (C**7**). HRMS: (ESI^+) Calculated for $C_{15}H_{22}NO_2S$: 280.1366. Found $[M+H]^+$: 280.1359. *The ^1H spectrum was consistent with the data available in the literature.*[202]

Spectroscopic data for p-toluenesulfonamide: δ_H (500 MHz, $CDCl_3$) 7.81 (2H, d, *J* = 8.0 Hz), 7.32 (2H, d, *J* = 8.0 Hz), 4.78 (2H, br s), 2.43 (3H, s). δ_C (126 MHz, $CDCl_3$) 143.8, 139.2, 129.9, 126.6, 21.7. HRMS: (ESI^+) Calculated for $C_7H_9NNaO_2S$: 194.0246. Found $[M+Na]^+$: 194.0245. *The spectroscopic properties were consistent with the data available in the literature.*[203]

*Characterisation data for **104** has been provided earlier.*

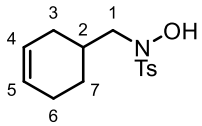
***N*-(Cyclohex-3-en-1-ylmethyl)hydroxylamine**



To a solution of 3-cyclohexene-1-carboxaldehyde (**113**) (2.00 g, 18.2 mmol) in MeOH (50 mL) was added $NH_2OH{\cdot}HCl$ (1.90 g, 27.3 mmol) and NaOAc (2.20 g, 26.8 mmol). The reaction mixture was heated at reflux for 2 hours, then cooled to room temperature before addition of $NaBH_3CN$ (2.26 g, 36.0 mmol) and a small amount of methyl orange. To the resulting suspension was added a pre-mixed

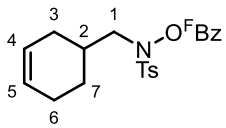
solution of MeOH:AcCl (3:1) dropwise at such a rate as to keep the solution pink. After 30 minutes the reaction mixture was concentrated *in vacuo*. The crude product was dissolved in water (100 mL), made basic with NaOH and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 1:1 hexane:EtOAc) afforded the title compound (1.52 g, 66 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 6.09 (2H, br s), 5.71 – 5.60 (2H, m), 2.86 (2H, dd, *J* = 6.5, 2.0 Hz), 2.14 (1H, dddd, *J* = 17.5, 5.0, 3.0, 1.5 Hz), 2.08 – 2.01 (2H, m), 1.97 – 1.84 (1H, m), 1.83 – 1.66 (2H, m), 1.27 (1H, ddt, *J* = 13.0, 11.0, 8.0 Hz). δ_C (101 MHz, $CDCl_3$) 127.2, 126.0, 59.7, 31.3, 30.0, 27.0, 24.8. HRMS: (ESI^+) Calculated for $C_7H_{14}NO$: 128.1075. Found $[M+H]^+$: 128.1061. *The spectroscopic properties were consistent with the data available in the literature*.[204]

***N*-(Cyclohex-3-en-1-ylmethyl)-*N*-hydroxy-4-toluenesulfonamide**



To a solution of the preceding compound (250 mg, 1.97 mmol) in MeOH (3 mL) and water (2 mL) was added MgO (40.0 mg, 0.993 mmol). The reaction mixture was stirred at room temperature for 10 minutes before addition of a solution of TsCl (380 mg, 1.99 mmol) in THF (15 mL), followed by another portion of MgO (120 mg, 2.98 mmol). The suspension was stirred at room temperature for 2 hours before being filtered and concentrated *in vacuo*. FCC (eluent: 6:1 hexane:EtOAc) afforded the title compound (403 mg, 71 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3351 (br s), 2913 (m), 1596 (m), 1442 (m), 1329 (s), 1163 (s). δ_H (500 MHz, $CDCl_3$) 7.81 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.39 (2H, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 6.41 (1H, br s, O<u>H</u>), 5.75 – 5.63 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 2.92 – 2.75 (2H, m, C**1**-<u>H_2</u>), 2.49 (3H, s, Ts C<u>H_3</u>), 2.21 – 2.14 (1H, m, C**3**-<u>H</u>), 2.10 – 1.99 (3H, m, C**2**-<u>H</u> and C**6**-<u>H_2</u>), 1.87 – 1.73 (2H, m, C**3**-<u>H</u>' and C**7**-<u>H</u>), 1.36 (1H, dtd, *J* = 13.0, 9.5, 6.0 Hz, C**7**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 144.9 (Ar<u>C</u>), 129.6 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>), 127.1 (C**5**), 125.6 (C**4**), 57.6 (C**1**), 31.0 (C**2**), 29.3 (C**3**), 26.1 (C**7**), 24.3 (C**6**), 21.7 (Ts <u>C</u>H_3). HRMS: (ESI^+) Calculated for $C_{14}H_{20}NO_3S$: 282.1158. Found $[M+H]^+$: 282.1147.

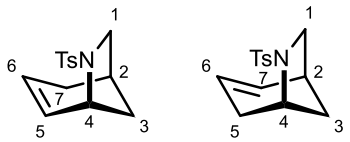
***N*-(Cyclohex-3-en-1-ylmethyl)-*N*-((pentafluorobenzoyl)oxy)-4-toluenesulfonamide (114a)**



<u>General procedure C:</u> The preceding compound (560 mg, 2.00 mmol) was employed. FCC (gradient elution: 19:1 – 9:1 hexane:EtOAc) afforded **114a** (700 mg, 74 %) as a colourless crystalline solid. m.p. 101-102 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*solid*) 2901 (m), 1789 (s), 1656 (m), 1595 (m), 1505 (s),

1168 (s). δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.38 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.70 – 5.58 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 3.22 – 2.93 (2H, m, C**1**-<u>H_2</u>), 2.46 (3H, s, Ts C<u>H_3</u>), 2.28 – 2.14 (1H, m, C**3**-<u>H</u>), 2.11 – 1.86 (3H, m, C**6**-<u>H_2</u> and C**7**-<u>H</u>), 1.83 – 1.72 (2H, m, C**2**-<u>H</u> and C**3**-<u>H</u>'), 1.43 – 1.31 (1H, m, C**7**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 156.3 (<u>C</u>=O), 145.8 (Ar<u>C</u>), 130.0 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 127.1 (C**5**), 125.2 (C**4**), 57.7 (C**1**), 31.3 (C**2**), 29.1 (C**3**), 25.8 (C**7**), 24.0 (C**6**), 21.7 (Ts <u>C</u>H_3). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -135.9 (2F, m), -146.0 (1F, tt, *J* = 21.0, 5.5 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{21}H_{19}F_5NO_4S$: 476.0949. Found $[M+H]^+$: 476.0955.

6-Tosyl-6-azabicyclo[3.2.1]oct-3-ene (115a) and 6-tosyl-6-azabicyclo[3.2.1]oct-2-ene (*iso*-115a)

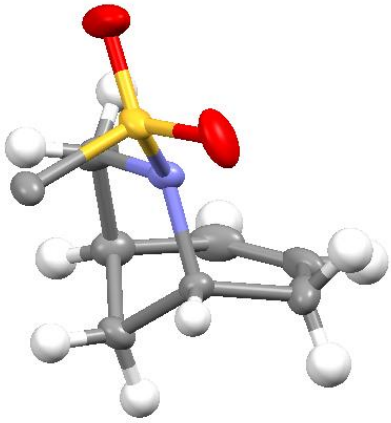


115a ***iso*-115a**

<u>General procedure D:</u> Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 34 hours. Substrate **114a** (65.0 mg, 0.137 mmol) was employed. FCC (eluent: 29:1 PhMe:EtOAc) afforded ***iso*-115a** (15.0 mg, 42 %) as a colourless crystalline solid and **115a** (7.7 mg, 21 %, 4:1 mixture of **115a** and ***iso*-115a**) as a colourless crystalline solid. *Spectroscopic data for **115a**:* ν_{max} / cm^{-1}: (*film*) 3033 (m), 2950 (m), 2883 (m), 1597 (m), 1338 (s), 1154 (s). δ_H (500 MHz, $CDCl_3$) 7.71 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.28 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.99 – 5.91 (1H, m, C**5**-<u>H</u>), 5.54 – 5.50 (1H, m, C**6**-<u>H</u>), 4.21 (dd, *J* = 5.5, 5.0 Hz, C**4**-<u>H</u>), 3.54 – 3.46 (1H, m, C**1**-<u>H</u>), 3.16 (1H, d, *J* = 10.0 Hz, C**1**-<u>H</u>'), 2.58 – 2.51 (1H, m, C**2**-<u>H</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 2.37 (1H, dddd, *J* = 18.5, 4.5, 2.5, 2.5 Hz, C**7**-<u>H</u>), 2.00 (1H, dddd, *J* = 18.5, 4.0, 2.0, 2.0 Hz, C**7**-<u>H</u>'), 1.62 (1H, d, *J* = 11.0 Hz, C**3**-<u>H</u>), 1.40 (1H, ddd, *J* = 11.0, 5.0, 5.0 Hz, C**3**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 143.2 (Ar<u>C</u>), 136.3 (Ar<u>C</u>), 130.2 (C**5**), 129.7 (Ar<u>C</u>H), 127.7 (C**6**), 127.6 (Ar<u>C</u>H), 54.6 (C**4**), 54.1 (C**1**), 35.0 (C**7**), 33.9 (C**3**), 33.5 (C**2**), 21.7 (Ts <u>C</u>H_3). HRMS: (ESI^+) Calculated for $C_{14}H_{17}NNaO_2S$: 286.0872. Found $[M+Na]^+$: 286.0869.

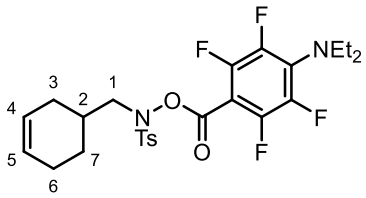
*Characterisation data for **iso-115a**:* m.p. 114-115 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*solid*) 2966 (m), 2873 (m), 1597 (m), 1335 (s), 1053 (s). δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.29 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.93 (1H, ddd, *J* = 8.5, 8.5, 1.5 Hz, C**7**-<u>H</u>), 5.54 – 5.48 (1H, m, C**6**-<u>H</u>), 4.22 (1H, d, *J* = 5.5 Hz, C**4**-<u>H</u>), 3.52 (1H, dd, *J* = 8.5, 1.5 Hz, C**1**-<u>H</u>), 3.12 (1H, dd, *J* = 8.5, 4.5 Hz, C**1**-<u>H</u>'), 2.58 – 2.53 (1H, m, C**2**-<u>H</u>), 2.44 – 2.34 (4H, m, C**5**-<u>H</u> and Ts C<u>H_3</u>), 2.27 (1H, dd, *J* = 18.5, 3.0 Hz, C**5**-<u>H</u>'), 1.69 (1H, d, *J* = 10.5 Hz, C**3**-<u>H</u>), 1.35 (ddd, *J* = 10.5, 5.5, 5.0 Hz, C**3**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 143.2 (Ar<u>C</u>), 136.1 (Ar<u>C</u>), 131.4 (C**7**), 129.7 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 125.5 (C**6**), 57.3 (C**4**),

56.9 (C**1**), 36.2 (C**5**), 34.5 (C**2**), 33.8 (C**3**), 21.7 (Ts $\underline{C}H_3$). HRMS: (ESI^+) Calculated for $C_{14}H_{17}NNaO_2S$: 286.0872. Found $[M+Na]^+$: 286.0866.

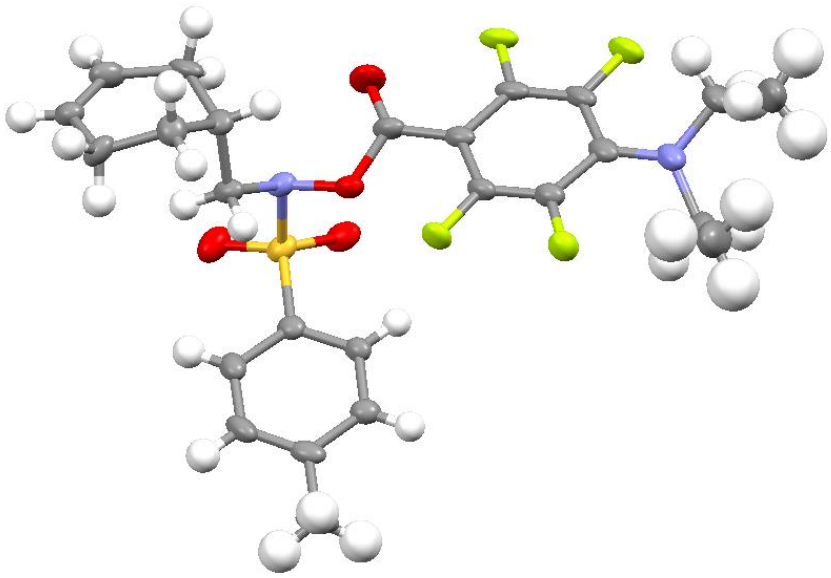


*ORTEP view of **iso-115a** (the arene of the tosyl group has been omitted for clarity).*

***N*-(Cyclohex-3-en-1-ylmethyl)-*N*-((4-(diethylamino)-2,3,5,6-tetrafluorobenzoyl)oxy)-4-toluenesulfonamide (116)**

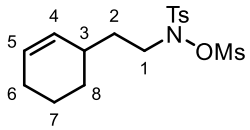


General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 20 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 200 mol% Et_3N; DMF (0.08 M); 100 °C; 11 hours. Substrate **114a** (40.0 mg, 841 µmol) was employed. FCC (gradient elution: 19:1 – 14:1 – 9:1 hexane:EtOAc) afforded **116** (10.4 mg, 23 %) as a colourless crystalline solid, ***iso*-115a** (3.3 mg, 15 %) as a colourless crystalline solid and **115a** (1.3 mg, 6 %) as a colourless crystalline solid. *Characterisation data for **116**:* m.p. 122-123 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*solid*) 2926 (m), 2854 (m), 1763 (s), 1634 (s), 1487 (s), 1360 (s), 1171 (s). δ_H (500 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.0 Hz, 2 × ArC$\underline{H}$), 7.31 (2H, d, *J* = 8.0 Hz, 2 × ArC$\underline{H}$), 5.66 – 5.49 (2H, m, C**4**-$\underline{H}$ and C**5**-$\underline{H}$), 3.28 (4H, q, *J* = 7.0 Hz, $N(C\underline{H}_2CH_3)_2$), 3.12 – 2.86 (2H, m, C**1**-$\underline{H}_2$), 2.40 (3H, s, Ts $C\underline{H}_3$), 2.33 – 2.17 (1H, m, C**3**-$\underline{H}$), 2.11 – 1.89 (3H, m, C**6**-$\underline{H}_2$ and C**7**-$\underline{H}$), 1.84 – 1.72 (2H, m, C**2**-$\underline{H}$ and C**3**-$\underline{H}$'), 1.42 – 1.33 (1H, m, C**7**-$\underline{H}$') 1.09 (6H, t, *J* = 7.0 Hz, $N(CH_2C\underline{H}_3)_2$). δ_C (126 MHz, $CDCl_3$) 157.4 (C=O), 145.6 (Ar$\underline{C}$), 130.6 (Ar$\underline{C}$), 129.9 (Ar$\underline{C}$H), 129.8 (Ar$\underline{C}$H), 127.2 (C**5**), 125.5 (C**4**), 57.9 (C**1**), 46.9 ($N(\underline{C}H_2CH_3)_2$), 31.4 (C**2**), 29.4 (C**3**), 26.1 (C**7**), 24.3 (C**6**), 21.9 (Ts $\underline{C}H_3$), 13.8 ($N(CH_2\underline{C}H_3)_2$). *The ^{13}C signals corresponding to the fluorinated arene could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -137.9 – -138.0 (2F, m), -150.4 – -150.5 (2F, m). HRMS: (ESI^+) Calculated for $C_{25}H_{28}F_4N_2NaO_4S$: 551.1598. Found $[M+Na]^+$: 551.1586. *Characterisation data for **115a** and **iso-115a** has been provided earlier.*



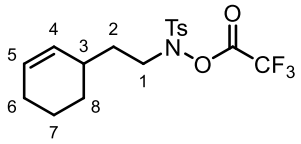
*ORTEP view of **116**.*

_N_-2-(Cyclohex-2-en-1-yl)ethyl-_N_-((mesyl)oxy)-4-toluenesulfonamide (103b)



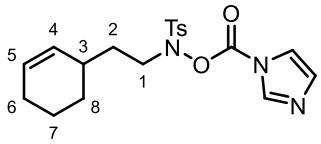
To a solution of *N*-2-(cyclohex-2-en-1-yl)ethyl-*N*-hydroxy-4-toluenesulfonamide (*vide supra*, 630 mg, 2.13 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C was added MsCl (325 μL, 4.19 mmol) followed by Et_3N (0.59 mL, 4.23 mmol). The reaction mixture was stirred at room temperature for 16 hours before addition of MeOH (15 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 49:1 PhMe:EtOAc) afforded **103b** (660 mg, 83 %) as a colourless crystalline solid. m.p. 101-102 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*solid*) 2921 (m), 1598 (m), 1451 (m), 1373 (s), 1355 (s), 1175 (s). δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.41 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.68 (1H, ddt, *J* = 10.0, 3.5, 3.0 Hz, C**5**-<u>H</u>), 5.51 – 5.46 (1H, m, C**4**-<u>H</u>), 3.37 (3H, s, Ms C<u>H</u>$_3$), 3.23 (2H, br s, C**1**-<u>H</u>$_2$). 2.49 (3H, s, Ts C<u>H</u>$_3$), 2.21 – 2.13 (1H, m, C**3**-<u>H</u>), 1.94 (2H, ddd, *J* = 5.5, 5.5, 3.0 Hz, C**6**-<u>H</u>$_2$), 1.82 – 1.61 (4H, m, C**2**-<u>H</u>$_2$, C**7**-<u>H</u> and C**8**-<u>H</u>), 1.57 – 1.44 (1H, m, C**7**-<u>H</u>'), 1.28 – 1.13 (1H, m, C**8**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 146.4 (Ar<u>C</u>), 130.6 (C**4**), 130.2 (Ar<u>C</u>H), 129.9 (Ar<u>C</u>H), 129.3 (Ar<u>C</u>), 128.0 (C**5**), 54.4 (C**1**), 37.9 (Ms <u>C</u>H$_3$), 33.2 (C**2**), 32.7 (C**3**), 28.7 (C**8**), 25.3 (C**6**), 21.9 (Ts <u>C</u>H$_3$), 21.3 (C**7**). HRMS: (ESI^+) Calculated for $C_{16}H_{23}NNaO_5S_2$: 396.0910. Found $[M+Na]^+$: 396.0924.

***N*-2-(Cyclohex-2-en-1-yl)ethyl-*N*-(trifluoroacetyloxy)-4-toluenesulfonamide (103c)**



N-2-(Cyclohex-2-en-1-yl)ethyl-*N*-hydroxy-4-toluenesulfonamide (*vide supra*, 200 mg, 0.677 mmol) was dissolved in trifluoroacetic anhydride (1.0 mL) and stirred for one hour before being concentrated *in vacuo* and analysed by ^{1}H NMR. These steps were repeated until complete conversion was achieved. Substrate **103c** (263 mg, 99 %) was isolated as an amorphous orange solid. *This compound was employed in the catalytic reactions immediately due to its instability to hydrolysis.* ν_{max} / cm^{-1}: (*solid*) 3024 (m), 2926 (m), 1820 (s), 1597 (m), 1371 (s), 1220 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.42 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.70 (1H, ddt, *J* = 10.0, 3.5, 3.0 Hz, C**5**-<u>H</u>), 5.46 (1H, ddt, *J* = 10.0, 2.5, 2.5 Hz, C**4**-<u>H</u>), 3.23 (2H, br s, C**1**-<u>H</u>$_2$), 2.49 (3H, s, Ts C<u>H</u>$_3$), 2.30 – 2.19 (1H, m, C**3**-<u>H</u>), 1.96 (2H, m, C**6**-<u>H</u>$_2$), 1.81 – 1.73 (1H, m, C**8**-<u>H</u>), 1.72 – 1.64 (1H, m, C**7**-<u>H</u>), 1.60 – 1.41 (3H, m, C**2**-<u>H</u>$_2$ and C**7**-<u>H</u>'), 1.18 (1H, dddd, *J* = 13.0, 10.5, 8.0, 2.5 Hz, C**8**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 146.3 (Ar<u>C</u>), 130.1 (Ar<u>C</u>H), 130.0 (C**4**), 129.6 (Ar<u>C</u>H), 129.0 (Ar<u>C</u>), 128.2 (C**5**), 50.8 (C**1**), 32.7 (C**2**), 32.2 (C**3**), 28.5 (C**8**), 25.1 (C**6**), 21.8 (Ts <u>C</u>H$_3$), 21.0 (C**7**). *The ^{13}C signals corresponding to the trifluoroacetyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -73.2 (3F, s). HRMS: (ESI$^+$) Calculated for $C_{17}H_{20}F_3NNaO_4S$: 414.0957. Found $[M+Na]^+$: 414.0965.

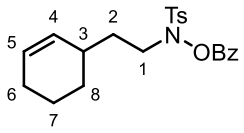
***N*-((1*H*-Imidazole-1-carbonyl)oxy)-*N*-(2-(cyclohex-2-en-1-yl)ethyl)-4-toluenesulfonamide (103d)**



To a solution of carbonyl diimidazole (82.2 mg, 0.507 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 °C was added a solution of *N*-2-(cyclohex-2-en-1-yl)ethyl-*N*-hydroxy-4-toluenesulfonamide (*vide supra*, 150 mg, 0.507 mmol) in anhydrous CH_2Cl_2 (4 mL) dropwise. The reaction mixture was stirred at room temperature for 2.5 hours before being concentrated *in vacuo*, dissolved in Et_2O (30 mL) and washed with water (4 × 25 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 1:1 hexane:EtOAc) afforded **103d** (88.0 mg, 44 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3129 (m), 3021 (m), 2922 (m), 1792 (s), 1597 (m), 1358 (s), 1163 (s). δ_H (400 MHz, $CDCl_3$) 8.02 (1H, dd, *J* = 1.0, 1.0 Hz, ArC<u>H</u>), 7.76 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.40 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.33 (1H, dd, *J* = 1.5, 1.0 Hz, ArC<u>H</u>), 7.09 (1H, dd, *J* = 1.5, 1.0 Hz, ArC<u>H</u>), 5.70 – 5.60 (1H, m, C**5**-<u>H</u>), 5.44 (1H, ddt, *J* = 10.0, 2.5, 2.5 Hz, C**4**-<u>H</u>), 3.28 (2H, br s, C**1**-<u>H</u>$_2$), 2.46 (3H, s, Ts C<u>H</u>$_3$), 2.27 (1H, ddddd, *J* = 11.0, 8.5, 6.0, 5.5, 2.5 Hz, C**3**-<u>H</u>), 1.97 – 1.86 (2H, m, C**6**-<u>H</u>$_2$), 1.75 (1H,

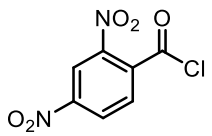
dddd, *J* = 12.5, 8.5, 6.0, 3.0 Hz, C**8**-H), 1.70 – 1.56 (2H, m, C**2**-H and C**7**-H), 1.56 – 1.41 (2H, m, C**2**-H' and C**7**-H'), 1.16 (1H, dddd, *J* = 12.5, 11.0, 8.5, 3.0 Hz, C**8**-H'). δ_C (101 MHz, $CDCl_3$) 146.7 (C=O or ArC), 146.4 (C=O or ArC), 136.9 (ArCH), 131.3 (ArCH), 130.2 (ArCH), 130.1 (C**4**), 129.5 (ArCH), 129.4 (ArC), 128.1 (C**5**), 117.1 (ArCH), 50.9 (C**1**), 32.8 (C**2**), 32.2 (C**3**), 28.5 (C**8**), 25.1 (C**6**), 21.7 (Ts CH_3), 21.0 (C**7**). HRMS: (ESI$^+$) Calculated for $C_{19}H_{24}N_3O_4S$: 390.1482. Found $[M+H]^+$: 390.1482.

_N_-(Benzoyloxy)-_N_-(2-(cyclohex-2-en-1-yl)ethyl)-4-toluenesulfonamide (103e)



To a solution of *N*-2-(cyclohex-2-en-1-yl)ethyl-*N*-hydroxy-4-toluenesulfonamide (*vide supra*, 100 mg, 0.339 mmol) in anhydrous CH_2Cl_2 (7 mL) at 0 °C was added BzCl (48 µL, 0.407 mmol) followed by Et_3N (0.10 mL, 0.717 mmol). The reaction mixture was stirred at room temperature for 22 hours before addition of saturated aqueous $NaHCO_3$ (20 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 39:1 PhMe:EtOAc) afforded **103e** (75.0 mg, 55 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2926 (m), 2857 (m), 1768 (s), 1598 (m), 1451 (m), 1363 (s), 1233 (s), 1170 (s). δ_H (400 MHz, $CDCl_3$) 7.99 – 7.92 (2H, m, 2 × ArCH), 7.82 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 7.65 – 7.59 (1H, m, ArCH), 7.51 – 7.42 (2H, m, 2 × ArCH), 7.38 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 5.65 (1H, dtd, *J* = 10.0, 3.5, 2.5 Hz, C**5**-H), 5.50 – 5.44 (1H, m, C**4**-H), 3.32 (2H, s, C**1**-H_2), 2.47 (3H, s, Ts CH_3), 2.35 – 2.23 (1H, m, C**3**-H), 1.93 (2H, dddd, *J* = 5.5, 5.5, 3.5, 2.5 Hz, C**6**-H_2), 1.77 (1H, dddd, *J* = 12.5, 6.0, 6.0, 2.5 Hz, C**8**-H), 1.71 – 1.44 (4H, m, C**2**-H_2 and C**7**-H_2), 1.18 (1H, dddd, *J* = 12.5, 11.0, 8.5, 3.0 Hz, C**8**-H'). δ_C (101 MHz, $CDCl_3$) 163.4 (C=O), 145.5 (ArC), 133.9 (ArCH), 130.6 (ArC or C**4**), 130.4 (ArC or C**4**), 2 × 129.8 (2 × ArCH), 129.5 (ArCH), 128.7 (ArCH), 127.7 (C**5**), 127.3 (ArC), 50.6 (C**1**), 32.9 (C**2**), 32.4 (C**3**), 28.6 (C**8**), 25.2 (C**6**), 21.7 (Ts CH_3), 21.1 (C**7**). HRMS: (ESI$^+$) Calculated for $C_{22}H_{26}NO_4S$: 400.1577. Found $[M+H]^+$: 400.1593.

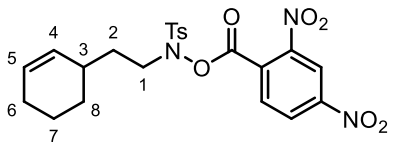
2,4-Dinitrobenzoyl chloride



To a solution of 2,4-dinitrobenzoic acid (2.00 g, 9.43 mmol) in anhydrous PhMe (10 mL) was added thionyl chloride (1.03 mL, 14.1 mmol). The reaction mixture was heated at reflux for 16 hours before being concentrated *in vacuo* to afford the title compound (2.12 g, 98 %) as an amorphous orange solid, which was used without further purification. ν_{max} / cm^{-1}: (*solid*) 3099 (m), 2882 (m), 1781 (s), 1720 (s),

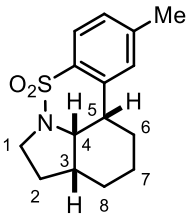
1600 (m), 1531 (s), 1343 (s). δ_H (400 MHz, $CDCl_3$) 8.98 (1H, d, *J* = 2.0 Hz, ArC<u>H</u>), 8.65 (1H, dd, *J* = 8.5, 2.0 Hz, ArC<u>H</u>), 7.90 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>). δ_C (126 MHz, $CDCl_3$) 164.5 (<u>C</u>=O), 149.3 (Ar<u>C</u>), 145.3 (Ar<u>C</u>), 137.1 (Ar<u>C</u>), 129.5 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 120.5 (Ar<u>C</u>H). *m/z* (EI^+) 195 ($[M\text{-}Cl]^+$, 100 %), 91 (75 %).

***N*-(2-(Cyclohex-2-en-1-yl)ethyl)-*N*-((2,4-dinitrobenzoyl)oxy)-4-toluenesulfonamide (103f)**

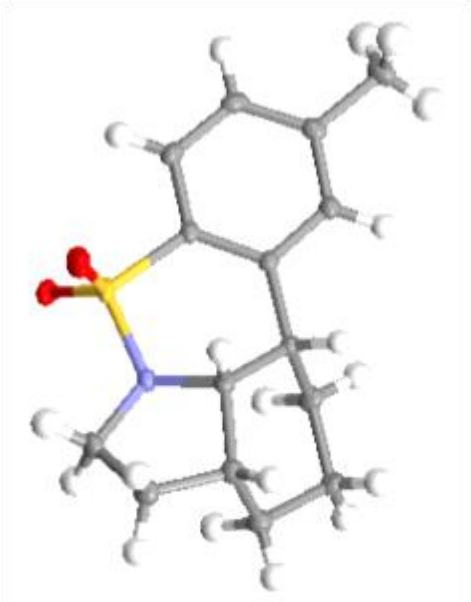


To a reaction vessel charged with *N*-2-(cyclohex-2-en-1-yl)ethyl-*N*-hydroxy-4-toluenesulfonamide (*vide supra*, 150 mg, 0.508 mmol) and 2,4-dinitrobenzoyl chloride (141 mg, 0.612 mmol) in an ice bath was added anhydrous CH_2Cl_2 (5 mL) followed by Et_3N (0.14 mL, 1.02 mmol). The reaction mixture was stirred at room temperature for two hours before addition of saturated aqueous $NaHCO_3$ (10 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 9:1 hexane: EtOAc) afforded **103f** (190 mg, 76 %) as a green crystalline solid. m.p. 118-119 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*solid*) 3115 (m), 2926 (m), 1785 (s), 1603 (m), 1538 (s), 1347 (s). δ_H (400 MHz, $CDCl_3$) 8.96 (1H, d, *J* = 2.0 Hz, ArC<u>H</u>), 8.64 (1H, dd, *J* = 8.5, 2.0 Hz, ArC<u>H</u>), 8.01 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 7.71 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.35 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.69 (1H, ddt, *J* = 10.0, 3.0, 3.0 Hz, C**5**-<u>H</u>), 5.53 (1H, ddt, *J* = 10.0, 2.0, 2.0 Hz, C**4**-<u>H</u>), 3.22 (2H, br s, C**1**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.40 – 2.31 (1H, m, C**3**-<u>H</u>), 1.99 – 1.93 (2H, m, C**6**-<u>H_2</u>), 1.84 – 1.75 (2H, m, C**2**-<u>H</u> and C**8**-<u>H</u>), 1.74 – 1.64 (2H, m, C**2**-<u>H</u>' and C**7**-<u>H</u>), 1.59 – 1.48 (1H, m, C**7**-<u>H</u>'), 1.27 – 1.17 (1H, m, C**8**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 161.9 (<u>C</u>=O), 149.2 (Ar<u>C</u>), 146.5 (Ar<u>C</u>), 146.0 (Ar<u>C</u>), 131.7 (Ar<u>C</u>), 131.3 (Ar<u>C</u>H), 130.5 (C**4**), 130.1 (Ar<u>C</u>H), 130.0 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 127.9 (C**5**), 120.0 (Ar<u>C</u>H), 51.0 (C**1**), 32.6 (C**2**), 32.2 (C**3**), 28.5 (C**8**), 25.2 (C**6**), 21.8 (Ts <u>C</u>H_3), 21.1 (C**7**). HRMS: (ESI^+) Calculated for $C_{22}H_{23}N_3NaO_8S$: 512.1098. Found $[M+Na]^+$: 512.1097.

(3a*R*,3a^1*S***,11b*S***)-10-Methyl-1,2,3,3a,3a^1,4,5,11b-octahydrobenzo[5,6][1,2]thiazino[4,3,2-*hi*]-indole 7,7-dioxide (120)**

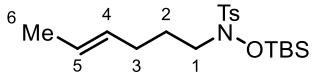


General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 20 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 200 mol% Et_3N; DMF (0.08 M); 100 °C; 2.5 hours. Substrate **103f** (40.0 mg, 818 µmol) was employed. FCC (gradient elution: 19:1 – 14:1 – 9:1 – 4:1 hexane:EtOAc) afforded **104** (0.9 mg, 4 %) as a pale-yellow oil and **120** (9.3 mg, 41 %) as a colourless crystalline solid. *Characterisation data for **120**:* m.p. 202-204 °C (CH_2Cl_2:hexane). ν_{max} / cm^{-1}: (*solid*) 2934 (m), 2852 (m), 1605 (m), 1444 (m), 1283 (s), 1140 (s). δ_H (500 MHz, $CDCl_3$) 7.78 (1H, d, *J* = 8.0 Hz, ArC<u>H</u>), 7.19 (1H, dd, *J* = 8.0, 1.5 Hz, ArC<u>H</u>), 7.06 (1H, d, *J* = 1.5 Hz, ArC<u>H</u>), 3.95 (1H, dd, *J* = 4.0, 4.0 Hz, C**4**-<u>H</u>), 3.86 (1H, ddd, *J* = 10.5, 10.5, 1.5 Hz, C**1**-<u>H</u>), 3.42 (1H, ddd, *J* = 10.5, 10.5, 7.5 Hz, C**1**-<u>H</u>'), 2.94 (1H, ddd, *J* = 12.5, 4.5, 4.0 Hz, C**5**-<u>H</u>), 2.42 – 2.34 (4H, m, C**3**-<u>H</u> and Ar C<u>H</u>$_3$), 2.02 (1H, dddd, *J* = 13.0, 10.5, 10.5, 6.0 Hz, C**2**-<u>H</u>), 1.82 – 1.66 (4H, m, C**2**-<u>H</u>', C**6**-<u>H</u>, C**7**-<u>H</u> and C**8**-<u>H</u>), 1.64 – 1.55 (1H, m, C**6**-<u>H</u>'), 1.41 (1H, ddddd, *J* = 13.0, 13.0, 13.0, 3.0, 3.0 Hz, C**7**-<u>H</u>'), 1.30 – 1.21 (1H, m, C**8**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 142.7 (Ar<u>C</u>), 140.5 (Ar<u>C</u>), 134.0 (Ar<u>C</u>), 129.7 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 124.0 (Ar<u>C</u>H), 61.1 (C**4**), 41.4 (C**1**), 40.1 (C**5**), 39.2 (C**3**), 30.0 (C**6**), 29.8 (C**2**), 26.5 (C**8**), 24.5 (C**7**), 21.6 (Ar <u>C</u>H$_3$). HRMS: (ESI^+) Calculated for $C_{15}H_{20}NO_2S$: 278.1209. Found $[M+H]^+$: 278.1209. *Characterisation data for **104** has been provided earlier*.



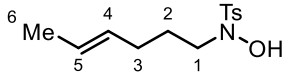
*ORTEP view of **120**.*

(*E*)-*N*-((*tert*-Butyldimethylsilyl)oxy)-*N*-(hex-4-en-1-yl)-4-toluenesulfonamide (88)



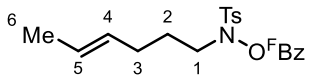
General procedure E: TsNHOTBS (*vide supra*, 603 mg, 2.00 mmol) was employed with (*E*)-hex-4-en-1-ol (**87**) (1.5 eq.). The reaction time was 17 hours. FCC (eluent: 1:1 hexane:PhMe) afforded **88** (700 mg, 91 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2930 (m), 2858 (m), 1598 (m), 1463 (m), 1356 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.32 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.45 – 5.28 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 2.88 (2H, t, *J* = 7.5 Hz, C**1**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 1.96 (2H, dt, *J* = 7.5, 7.0 Hz, C**3**-<u>H_2</u>), 1.64 – 1.55 (5H, m, C**2**-<u>H_2</u> and C**6**-<u>H_3</u>), 0.91 (9H, s, SiC(C<u>H_3</u>)$_3$), 0.28 (6H, s, Si(C<u>H_3</u>)$_2$). δ_C (101 MHz, $CDCl_3$) 144.6 (Ar<u>C</u>), 130.2 (Ar<u>C</u>), 2 × 130.0 (Ar<u>C</u>H and C**4**), 129.3 (Ar<u>C</u>H), 126.0 (C**5**), 55.6 (C**1**), 30.0 (C**3**), 26.9 (C**2**), 26.2 (SiC(<u>C</u>H_3)$_3$), 21.8 (Ts <u>C</u>H_3), 18.4 (Si<u>C</u>(CH_3)$_3$) 18.0 (C**6**), -4.1 (Si(<u>C</u>H_3)$_2$). HRMS: (ESI^+) Calculated for $C_{19}H_{34}NO_3SSi$: 384.2023. Found $[M+H]^+$: 384.2024.

(*E*)-*N*-(Hex-4-en-1-yl)-*N*-hydroxy-4-toluenesulfonamide



General procedure B: Compound **88** (630 mg, 1.63 mmol) was employed. The title compound (400 mg, 91 %) was isolated as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3356 (br s), 2941 (m), 2854 (m), 1596 (m), 1453 (m), 1330 (s), 1162 (s). δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.35 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 6.17 (1H, s, O<u>H</u>), 5.49 – 5.32 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 2.89 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.03 (2H, dt, *J* = 7.0, 7.0 Hz, C**3**-<u>H_2</u>), 1.70 – 1.57 (5H, m, C**2**-<u>H_2</u> and C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 145.0 (Ar<u>C</u>), 130.1 (C**4**), 129.8 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>), 126.1 (C**5**), 52.1 (C**1**), 29.6 (C**3**), 26.7 (C**2**), 21.8 (Ts <u>C</u>H_3), 18.1 (C**6**). HRMS: (ESI^+) Calculated for $C_{13}H_{20}NO_3S$: 270.1158. Found $[M+H]^+$: 270.1148.

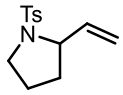
(*E*)-*N*-(Hex-4-en-1-yl)-*N*-((pentafluorobenzoyl)oxy)-4-toluenesulfonamide (125)



General procedure C: The preceding compound (380 mg, 1.41 mmol) was employed. FCC (eluent: 14:1 hexane:EtOAc) afforded **125** (560 mg, 86 %, 11:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless crystalline solid. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*solid*) 2936 (m), 1787 (s), 1652 (m), 1597 (m), 1504 (s), 1170 (s). δ_H (500 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.37 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.44 (1H, dqt, *J* = 15.0, 6.0, 1.5 Hz, C**5**-<u>H</u>), 5.34 (1H, dtq, *J* = 15.0, 7.0,

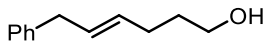
1.5 Hz, C**4**-H), 3.21 (2H, br s, C**1**-H_2), 2.46 (3H, s, Ts CH_3), 2.11 (2H, dtd, *J* = 7.0, 7.0, 1.5 Hz, C**3**-H_2), 1.65 – 1.59 (5H, m, C**2**-H_2 and C**6**-H_3). δ_C (126 MHz, $CDCl_3$) 156.3 (C=O), 145.8 (ArC), 130.1 (ArC), 129.8 (ArCH), 129.6 (ArCH), 129.3 (C**4**), 126.5 (C**5**), 52.0 (C**1**), 29.2 (C**3**), 26.4 (C**2**), 21.7 (Ts CH_3), 17.9 (C**6**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.0 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.5 Hz), -158.9 – -159.1 (2F, m). *Characteristic signals for the (Z)-isomer (obtained from 1D TOCSY):* δ_H (500 MHz, $CDCl_3$) 5.53 – 5.46 (m), 5.35 – 5.25 (m), 3.20 (s), 2.19 (dt, *J* = 7.5, 7.5 Hz), 1.66 – 1.58 (m). HRMS: (ESI^+) Calculated for $C_{20}H_{18}F_5NNaO_4S$: 486.0769. Found $[M+Na]^+$: 486.0760.

1-Tosyl-2-vinylpyrrolidine (12)



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 12.5 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 3:1 THF:DMF (0.1 M); 110 °C; 8 hours. Substrate **125** (65.0 mg, 0.140 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **12** (28.4 mg, 81 %) as a colourless crystalline solid. m.p. 69-70 °C (Et_2O:hexane) [Lit., 70 °C (*no recrystallisation solvent quoted*)][205]. ν_{max} / cm^{-1}: (*solid*) 2986 (m), 2884 (m), 1595 (m), 1460 (m), 1335 (s), 1154 (s). δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, *J* = 8.0 Hz), 7.30 (2H, d, *J* = 8.0 Hz), 5.80 (1H, ddd, *J* = 17.0, 10.0, 6.0 Hz), 5.27 (1H, ddd, *J* = 17.0, 1.5, 1.5 Hz), 5.11 (1H, ddd, *J* = 10.0, 1.5, 1.5 Hz), 4.13 (1H, ddddd, *J* = 6.0, 6.0, 6.0, 1.5, 1.5 Hz), 3.44 (1H, ddd, *J* = 10.0, 7.0, 4.5 Hz), 3.23 (1H, ddd, *J* = 10.0, 7.5, 7.5 Hz), 2.42 (3H, s), 1.87 – 1.73 (1H, m), 1.73 – 1.55 (3H, m). δ_C (101 MHz, $CDCl_3$) 143.4, 138.8, 135.3, 129.7, 127.6, 115.4, 62.0, 48.9, 32.4, 23.9, 21.6. *m/z* (ESI^+) 274 ($[M+Na]^+$, 100 %), 252 ($[M+H]^+$, 20 %). *The spectroscopic properties were consistent with the data available in the literature.*[205]

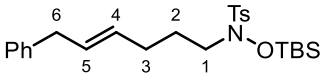
(*E*)-6-Phenylhex-4-en-1-ol (121)



To a solution of Grubbs-Hoveyda 2nd generation catalyst (62.7 mg, 0.100 mmol) in anhydrous CH_2Cl_2 (120 mL, sparged with argon) was added 4-penten-1-ol (1.03 mL, 10.0 mmol) and allyl benzene (13.2 mL, 100 mmol). The reaction mixture was heated at reflux for 14 hours before being concentrated *in vacuo*. FCC (eluent: 5:1 PhMe:EtOAc) afforded **121** (835 mg, 47 %, 6:1 mixture of (*E*)- and (*Z*)-isomers) as a light-brown oil (the colouration was due to the presence of trace amounts of Ru-impurities). *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*film*) 3381 (br s), 3027 (m), 2933 (m), 1693 (m), 1600 (m), 1452 (m), 1052 (s). δ_H (400 MHz, $CDCl_3$) 7.36 – 7.28 (2H, m), 7.25 – 7.18 (3H, m), 5.65 (1H, dt, *J* = 15.0, 6.5 Hz), 5.55 (1H, dt, *J* = 15.0, 7.0 Hz), 3.66 (2H, t, *J* = 6.5 Hz),

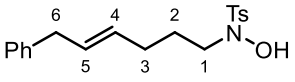
3.37 (2H, d, *J* = 6.5 Hz), 2.14 (2H, dt, *J* = 7.0, 6.5 Hz), 1.96 (1H, br s), 1.71 – 1.63 (2H, m). δ_C (101 MHz, $CDCl_3$) 140.9, 131.1, 129.6, 128.5, 128.4, 125.6, 62.4, 39.1, 32.4, 28.8. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 3.45 (2H, d, *J* = 7.0 Hz), 2.28 (1H, dt, *J* = 7.0, 7.0 Hz). *The spectroscopic properties were consistent with the data available in the literature.*[206,207]

(*E*)-*N*-(6-Phenylhex-4-en-1-yl)-*N*-((*tert*-butyldimethylsilyl)oxy)-4-toluenesulfonamide



General procedure E: TsNHOTBS (*vide supra*, 1.00 g, 3.32 mmol) was employed with alcohol **121** (1.3 eq.). The reaction time was 20 hours. FCC (eluent: 1:1 hexane:PhMe) afforded the title compound (1.28 g, 84 %, 6:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2955 (m), 2930 (m), 2858 (m), 1598 (m), 1355 (s), 1168 (s). *Spectroscopic data for the major (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.34 – 7.25 (4H, m, 4 × ArC<u>H</u>), 7.23 – 7.12 (3H, m, 3 × ArC<u>H</u>), 5.57 (1H, dtt, *J* = 14.5, 6.5, 1.5 Hz, C**5**-<u>H</u>), 5.48 – 5.39 (1H, m, C**4**-<u>H</u>), 3.32 (2H, d, *J* = 6.5 Hz, C**6**-<u>H_2</u>), 2.93 – 2.87 (2H, m, C**1**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.04 (2H, br td, *J* = 7.0, 6.5 Hz, C**3**-<u>H_2</u>), 1.64 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>), 0.92 (9H, s, SiC(C<u>H_3</u>)$_3$), 0.29 (6H, s, Si(C<u>H_3</u>)$_2$). δ_C (101 MHz, $CDCl_3$) 144.4 (Ar<u>C</u>), 140.7 (Ar<u>C</u>), 130.3 (C**4**), 2 × 130.0 (C**5** and Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 2 × 128.4 (2 × Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 55.4 (C**1**), 39.0 (C**6**), 29.8 (C**3**), 26.7 (C**2**), 26.0 (SiC(<u>C</u>H_3)$_3$), 21.6 (Ts <u>C</u>H_3), 18.3 (Si<u>C</u>(CH$_3$)$_3$), -4.2 (Si(<u>C</u>H_3)$_2$). HRMS: (ESI^+) Calculated for $C_{25}H_{38}NO_3SSi$: 460.2336. Found $[M+H]^+$: 460.2335. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 3.37 (2H, d, *J* = 7.5 Hz), 2.16 (2H, dt, *J* = 7.5, 7.5 Hz).

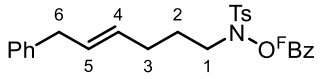
(*E*)-*N*-(6-Phenylhex-4-en-1-yl)-*N*-hydroxy-4-toluenesulfonamide



General procedure B: The preceding compound (1.28 g, 2.78 mmol) was employed. The title compound (685 mg, 71 %, 6:1 mixture of (*E*)- and (*Z*)-isomers) was isolated as a colourless oil. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*film*) 3385 (br s), 3026 (m), 2923 (s), 1597 (m), 1342 (s), 1166 (s). δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.31 – 7.24 (2H, m, 2 × ArC<u>H</u>), 7.21 – 7.14 (3H, m, 3 × ArC<u>H</u>), 6.70 (1H, br s, O<u>H</u>), 5.60 (1H, dtt, *J* = 14.5, 6.5, 1.0 Hz, C**5**-<u>H</u>), 5.51 – 5.42 (1H, m, C**4**-<u>H</u>), 3.32 (2H, d, *J* = 6.5 Hz, C**6**-<u>H_2</u>), 2.91 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.11 (2H, br dt, *J* = 6.5, 6.5 Hz, C**3**-<u>H_2</u>), 1.70 (2H, tt, *J* = 7.0, 6.5 Hz, C**2**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 144.8 (Ar<u>C</u>), 140.8 (Ar<u>C</u>), 130.4 (C**5**), 130.0 (C**4**), 129.7 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 129.4 (Ar<u>C</u>), 128.4 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 52.0 (C**1**), 39.0 (C**6**), 29.4 (C**3**), 26.4 (C**2**), 21.7 (Ts <u>C</u>H_3). HRMS: (ESI^+) Calculated for $C_{19}H_{23}NNaO_3S$:

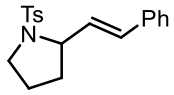
368.1291. Found $[M+Na]^+$: 368.1284. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 3.39 (2H, d, *J* = 7.0 Hz), 2.24 (2H, dt, *J* = 7.5, 7.5 Hz).

(*E*)-*N*-(6-Phenylhex-4-en-1-yl)-*N*-(pentafluorobenzoyloxy)-4-toluenesulfonamide (126)



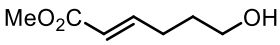
General procedure C: The preceding compound (650 mg, 1.88 mmol) was employed. FCC (eluent: 14:1 hexane:EtOAc) afforded **126** (832 mg, 82 %, 7:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless crystalline solid. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*solid*) 2970 (m), 2920 (m), 1784 (s), 1655 (m), 1598 (m), 1494 (s), 1167 (s). δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.35 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.30 – 7.23 (2H, m, 2 × ArC<u>H</u>), 7.21 – 7.13 (3H, m, 3 × ArC<u>H</u>), 5.60 (1H, dt, *J* = 15.0, 6.5 Hz, C**5**-<u>H</u>), 5.43 (1H, dt, *J* = 15.0, 7.0 Hz, C**4**-<u>H</u>), 3.31 (2H, d, *J* = 6.5 Hz, C**6**-<u>H_2</u>), 3.20 (2H, br s, C**1**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.17 (2H, dt, *J* = 7.0, 7.0 Hz, C**3**-<u>H_2</u>), 1.65 (2H, tt, *J* = 7.0, 7.0 Hz, C**2**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 146.0 (Ar<u>C</u>), 140.8 (Ar<u>C</u>), 130.8 (C**5**), 130.2 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 129.9 (C**4**), 129.7 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 52.2 (C**1**), 39.1 (C**6**), 29.3 (C**3**), 26.5 (C**2**), 21.9 (Ts <u>C</u>H_3). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.0 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.5 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{26}H_{22}F_5NNaO_4S$: 562.1082. Found $[M+Na]^+$: 562.1072. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 3.40 (2H, d, *J* = 7.5 Hz), 2.32 (2H, dt, *J* = 7.0, 7.0 Hz).

(*E*)-2-Styryl-1-tosylpyrrolidine (128)



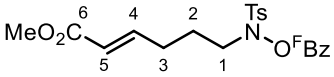
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 12.5 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; *n*-BuCN (0.1 M); 110 °C; 15 hours. Substrate **126** (75.5 mg, 0.140 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **128** (35.4 mg, 77 %) as a pale-yellow oil. δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* = 8.0 Hz), 7.33 – 7.18 (7H, m), 6.54 (1H, d, *J* = 16.0 Hz), 6.04 (1H, dd, *J* = 16.0, 6.5 Hz), 4.34 (1H, ddd, *J* = 7.0, 6.5, 4.5 Hz), 3.48 (1H, ddd, *J* = 10.0, 7.0, 4.5 Hz), 3.34 (1H, ddd, *J* = 10.0, 7.0, 7.0 Hz), 2.39 (3H, s), 1.94 – 1.79 (2H, m), 1.77 – 1.65 (2H, m). δ_C (101 MHz, $CDCl_3$) 143.3, 136.7, 135.7, 130.7, 130.1, 129.7, 128.6, 127.7, 127.6, 126.6, 61.8, 48.8, 32.9, 24.1, 21.6. *The spectroscopic properties were consistent with the data available in the literature.*[208]

Methyl (*E*)-6-hydroxyhex-2-enoate (122)



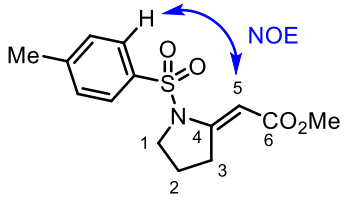
To a solution of Grubbs-Hoveyda 2nd generation catalyst (15.7 mg, 25.0 μmol) in anhydrous CH_2Cl_2 (40 mL, argon sparged) was added methyl acrylate (2.25 mL, 25.0 mmol) and pent-4-en-1-ol (0.26 mL, 2.50 mmol). The reaction mixture was heated at reflux for 15 hours before being concentrated *in vacuo*. FCC (eluent: 2:1 hexane:EtOAc) afforded **122** (357 mg, 99 %) as a light-brown oil (the colouration was due to the presence of trace amounts of Ru-impurities). ν_{max} / cm^{-1}: (*film*) 3417 (br s), 2950 (m), 1720 (s), 1656 (s), 1436 (s), 1272 (s). δ_H (400 MHz, $CDCl_3$) 6.98 (1H, dt, *J* = 15.5, 7.0 Hz), 5.85 (1H, dt, *J* = 15.5, 1.5 Hz), 3.72 (3H, s), 3.67 (2H, t, *J* = 6.5 Hz), 2.30 (2H, dtd, *J* = 7.0, 7.0, 1.5 Hz), 1.77 – 1.68 (2H, m), 1.51 (1H, br s). δ_C (101 MHz, $CDCl_3$) 167.2, 148.9, 121.4, 62.1, 51.6, 31.0, 28.7. *The spectroscopic properties were consistent with the data available in the literature.*[209]

Methyl (*E*)-6-((*N*-(pentafluorobenzoyloxy)-4-tolyl)sulfonamido)hex-2-enoate (127)



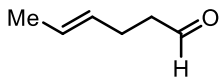
General procedure K: Alcohol **122** (115 mg, 0.800 mmol) was employed with $TsNHO^FBz$ (*vide supra*). The reaction time was 16 hours. FCC (eluent: 49:1 PhMe:EtOAc) afforded **127** (310 mg, 76 %) as a colourless crystalline solid. m.p. 118-119 °C (CH_2Cl_2:hexane, *needles*). ν_{max} / cm^{-1}: (*solid*) 2953 (m), 1790 (s), 1706 (s), 1595 (m), 1501 (s), 1168 (s). δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.38 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 6.90 (1H, dt, *J* = 15.5, 7.0 Hz, C**4**-<u>H</u>), 5.85 (1H, dt, *J* = 15.5, 1.5 Hz, C**5**-<u>H</u>), 3.72 (3H, s, OC<u>H</u>$_3$), 3.24 (2H, br s, C**1**-<u>H</u>$_2$), 2.47 (3H, s, Ts C<u>H</u>$_3$), 2.42 (2H, tdd, *J* = 7.5, 7.0, 1.5 Hz, C**3**-<u>H</u>$_2$), 1.72 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H</u>$_2$). δ_C (101 MHz, $CDCl_3$) 166.8 (C**6**), 147.2 (C**4**), 146.0 (Ar<u>C</u>), 2 × 129.9 (Ar<u>C</u> and Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 122.1 (C**5**), 51.8 (C**1**), 51.5 (O<u>C</u>H$_3$), 28.8 (C**3**), 25.0 (C**2**), 21.7 (Ts <u>C</u>H$_3$). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -136.0 (2F, m), -145.7 (1F, tt, *J* = 20.5, 5.0 Hz), -158.7 – -159.0 (2F, m). HRMS: (ESI^+) Calculated for $C_{21}H_{18}F_5NNaO_6S$: 530.0667. Found $[M+Na]^+$: 530.0662.

Methyl (*E*)-2-(1-tosylpyrrolidin-2-ylidene)acetate (129)



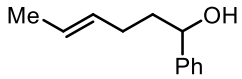
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 12.5 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 15 hours. Substrate **127** (71.0 mg, 0.140 mmol) was employed. FCC (gradient elution: 3:1 – 2:1 hexane:EtOAc) afforded **129** (32.4 mg, 78 %) as a pale-yellow oil. *The product was assigned as the (E)-isomer based on the observed NOE correlation between the C**5** and the aromatic protons.* ν_{max} / cm^{-1}: (*film*) 2950 (m), 1707 (s), 1620 (s), 1346 (s), 1129 (s). δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.32 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 6.03 (1H, t, *J* = 2.0 Hz, C**5**-<u>H</u>), 3.76 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 3.64 (3H, s, OC<u>H_3</u>), 3.03 (2H, td, *J* = 7.5, 2.0 Hz, C**3**-<u>H_2</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 1.88 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 168.3 (C**6**), 156.9 (C**4**), 145.0 (Ar<u>C</u>), 134.3 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 94.9 (C**5**), 51.6 (C**1**), 51.0 (O<u>C</u>H_3), 32.4 (C**3**), 21.7 (Ts <u>C</u>H_3), 21.3 (C**2**). HRMS: (ESI^+) Calculated for $C_{14}H_{17}NNaO_4S$: 318.0770. Found $[M+Na]^+$: 318.0780.

(*E*)-Hex-4-enal (132)



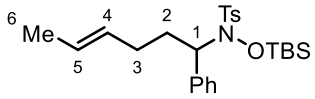
This compound was prepared according to a literature procedure.[125] A solution of (*E*)-hex-4-en-1-ol (**87**) (6.01 g, 60.0 mmol), $(MeCN)_4CuOTf$ (1.13 g, 3.00 mmol), 2,2'-bipyridine (469 mg, 3.00 mmol), TEMPO (469 mg, 3.00 mmol) and *N*-methylimidazole (0.48 mL, 6.00 mmol) in MeCN (250 mL) was stirred at room temperature under an atmosphere of O_2 (balloon pressure) for 5 hours. The reaction mixture was poured into water (400 mL) and extracted with pentane (4 × 200 mL). The combined organic phases were washed with brine (300 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford **132** (3.78 g, 64 %) as an orange oil, which was used without further purification. δ_H (400 MHz, $CDCl_3$) 9.77 (1H, t, *J* = 1.5 Hz), 5.57 – 5.36 (2H, m), 2.52 – 2.47 (2H, m), 2.33 (2H, dt, *J* = 7.0, 7.0 Hz), 1.65 (3H, dd, *J* = 6.0, 1.0 Hz). δ_C (101 MHz, $CDCl_3$) 202.3, 128.8, 126.3, 43.4, 25.1, 17.8. *The spectroscopic properties were consistent with the data available in the literature.*[125]

(*E*)-1-Phenylhex-4-en-1-ol (133)



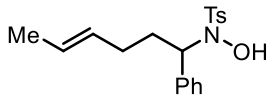
To a solution of phenylmagnesium bromide (16.0 mmol) in anhydrous Et_2O (26 mL) at 0 °C was added a solution of aldehyde **132** (*vide supra*, 981 mg, 10.0 mmol) in anhydrous Et_2O (5 mL). The reaction mixture was stirred at 0 °C for 2 hours before addition of saturated aqueous NH_4Cl (15 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 7:1 hexane:EtOAc) afforded **133** (1.33 g, 75 %) as a pale-yellow oil. δ_H (400 MHz, $CDCl_3$) 7.37 – 7.32 (4H, m), 7.31 – 7.24 (1H, m), 5.52 – 5.39 (2H, m), 4.68 (1H, ddd, *J* = 7.5, 5.5, 3.5 Hz), 2.17 – 1.99 (2H, m), 1.98 – 1.94 (1H, m), 1.91 – 1.71 (2H, m), 1.67 – 1.63 (3H, m). δ_C (101 MHz, $CDCl_3$) 144.8, 130.7, 128.6, 127.6, 126.0, 125.7, 74.2, 38.9, 29.1, 18.1. HRMS: (ESI^+) Calculated for $C_{12}H_{16}NaO$: 199.1093. Found $[M+Na]^+$: 199.1087. *The spectroscopic properties were consistent with the data available in the literature.*[210]

***N*-(1-Phenylhex-4-en-1-yl)-*N*-((*tert*-butyldimethylsilyl)oxy)-4-toluenesulfonamide (92)**



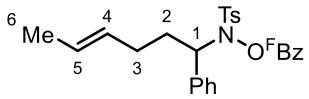
This compound was synthesised by a route starting with alkylation of ethyl benzoylacetate with technical grade crotyl bromide. Because of this, the product contains a significant amount of the (Z)-isomer as an impurity. **General procedure E:** TsNHOTBS (*vide supra*, 800 mg, 2.65 mmol) was employed with alcohol **133** (1.3 eq.). The reaction time was 15 hours. FCC (eluent: 1:1 hexane:PhMe) afforded **92** (1.09 g, 89 %, 5:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless oil. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*film*) 2930 (m), 2858 (m), 1598 (m), 1453 (m), 1360 (s), 1167 (s). δ_H (400 MHz, $CDCl_3$) 7.60 – 7.55 (2H, m, 2 × ArC<u>H</u>), 7.24 – 7.19 (2H, m, 2 × ArC<u>H</u>), 7.16 – 7.12 (5H, m, 5 × ArC<u>H</u>), 5.30 – 5.10 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 4.68 (1H, dd, *J* = 10.0, 4.0 Hz, C**1**-<u>H</u>), 2.38 (3H, s, Ts C<u>H</u>$_3$), 1.93 – 1.80 (2H, m, C**3**-<u>H</u>$_2$), 1.76 – 1.64 (1H, m, C**2**-<u>H</u>), 1.62 – 1.58 (3H, m, C**6**-<u>H</u>$_3$), 1.49 – 1.40 (1H, m, C**2**-<u>H</u>'), 0.93 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.28 (3H, s, SiC<u>H</u>$_3$), -0.07 (3H, s, Si(C<u>H</u>$_3$)'). δ_C (101 MHz, $CDCl_3$) 143.9 (Ar<u>C</u>), 137.6 (Ar<u>C</u>), 133.4 (Ar<u>C</u>), 130.0 (C**4**), 129.3 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 125.9 (C**5**), 65.6 (C**1**), 2 × 29.8 (C**2** and C**3**), 26.5 (SiC(<u>C</u>H$_3$)$_3$), 21.7 (Ts <u>C</u>H$_3$), 18.8 (Si<u>C</u>(CH$_3$)$_3$), 18.1 (C**6**), -3.9 (Si<u>C</u>H$_3$), -4.3 (Si(<u>C</u>H$_3$)'). HRMS: (ESI^+) Calculated for $C_{25}H_{37}NNaO_3SSi$: 482.2156. Found $[M+Na]^+$: 482.2135. *Characteristic signals for the minor (Z)-isomer (obtained from 1D TOCSY):* δ_H (500 MHz, $CDCl_3$) 5.44 – 5.39 (m), 5.20 – 5.13 (m), 4.72 (dd, *J* = 10.0, 4.0 Hz), 1.93 – 1.79 (m), 1.41 (dd, *J* = 7.0, 1.5 Hz).

***N*-(1-Phenylhex-4-en-1-yl)-*N*-hydroxy-4-toluenesulfonamide**

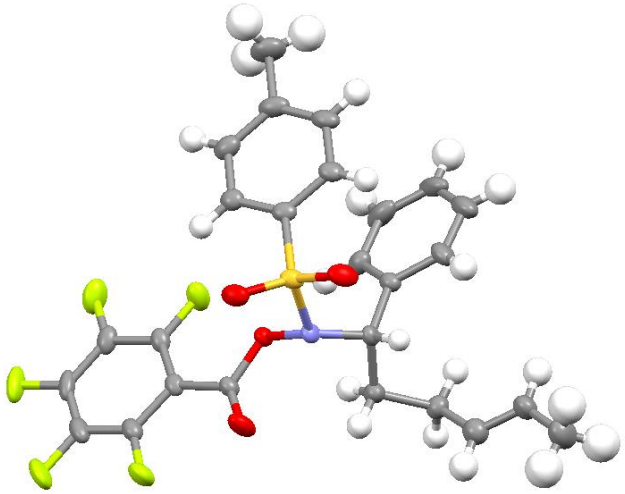


General procedure B: Compound **92** (1.07 g, 2.33 mmol) was employed. FCC (gradient elution: 9:1 – 4:1 hexane:EtOAc) was required to separate deprotected product from unconsumed **92** (490 mg recovered, 46 %) and afforded the title compound (360 mg, 45 %) as a colourless crystalline solid. *This compound was used in the following step with minimal delay due to concerns about its stability.* δ_H (400 MHz, $CDCl_3$) 7.53 (2H, d, *J* = 8.0 Hz), 7.22 – 7.18 (2H, m), 7.16 – 7.04 (5H, m), 5.87 (1H, s), 5.49 – 5.29 (2H, m), 4.83 – 4.76 (1H, m), 2.34 (3H, s), 2.01 – 1.83 (3H, m), 1.65 – 1.55 (4H, m).

***N*-(1-Phenylhex-4-en-1-yl)-*N*-(pentafluorobenzoyloxy)-4-toluenesulfonamide (134a)**

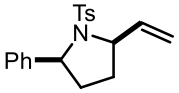


General procedure C: The preceding compound (350 mg, 1.01 mmol) was employed. FCC (gradient elution: 24:1 – 14:1 hexane:EtOAc) afforded **134a** (452 mg, 83 %, *presumed mixture of (E) and (Z)-isomers*) as a colourless crystalline solid. *The determination of the ratio of (E) and (Z)-isomers for this compound was not possible due to the broad nature of the ^1H and ^{13}C spectra.* ν_{max} / cm^{-1}: (*solid*) 2972 (m), 1783 (s), 1651 (m), 1598 (m), 1493 (s), 1165 (s). δ_H (500 MHz, $CDCl_3$) 7.85 – 7.56 (2H, m, 2 × ArC<u>H</u>), 7.37 – 7.11 (7H, m, 7 × ArC<u>H</u>), 5.55 – 5.24 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 5.03 – 4.92 (1H, m, C**1**-<u>H</u>), 2.42 (3H, br s, Ts C<u>H_3</u>), 2.30 – 1.84 (4H, m, C**2**-<u>H_2</u> and C**3**-<u>H_2</u>), 1.65 (3H, d, *J* = 5.0 Hz, C**6**-<u>H_3</u>). δ_C (126 MHz, $CDCl_3$) 156.5 (<u>C</u>=O), 145.2 (Ar<u>C</u>), 136.3 (Ar<u>C</u>), 132.6 (Ar<u>C</u>), 129.4 (C**4**), 129.2 (Ar<u>C</u>H), 2 × 128.7 (2 × Ar<u>C</u>H), 2 × 128.3 (2 × Ar<u>C</u>H), 126.5 (C**5**), 65.9 (C**1**), 33.5 (C**2**), 28.9 (C**3**), 21.7 (Ts <u>C</u>H_3), 17.9 (C**6**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* HRMS: (ESI^+) Calculated for $C_{26}H_{22}F_5NNaO_4S$: 562.1082. Found $[M+Na]^+$: 562.1071.



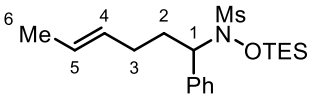
*ORTEP view of **134a**.*

(2*R,5*S**)-2-Phenyl-1-tosyl-5-vinylpyrrolidine (139a)**



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 49 hours. Substrate **134a** (75.5 mg, 0.140 mmol) was employed. FCC (gradient elution: 14:1 – 9:1 – 4:1 hexane:EtOAc) afforded **139a** (12.6 mg, 27 %) as a colourless crystalline solid. m.p. 76-77 °C (CH_2Cl_2:petrol) [Lit., 79 °C (Et_2O:petrol)].[211] δ_H (400 MHz, $CDCl_3$) 7.63 (2H, d, *J* = 8.0 Hz), 7.36 – 7.20 (7H, m), 6.00 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz), 5.33 (1H, d, *J* = 17.0 Hz), 5.19 (1H, d, *J* = 10.5 Hz), 4.82 (1H, dd, *J* = 6.5, 6.5 Hz), 4.33 (1H, ddd, *J* = 6.5, 6.5, 6.5 Hz), 2.41 (3H, s), 2.04 – 1.93 (1H, m) 1.91 – 1.83 (1H, m), 1.82 – 1.71 (2H, m). δ_C (101 MHz, $CDCl_3$) 143.2, 142.4, 139.0, 135.6, 129.4, 128.2, 127.7, 127.1, 126.5, 116.1, 65.0, 63.6, 34.5, 30.9, 21.5. *The spectroscopic properties were consistent with the data available in the literature.*[212]

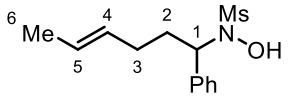
(*E*)-*N*-(1-Phenylhex-4-en-1-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide



General procedure E: MsNHOTES (*vide supra*, 676 mg, 3.00 mmol) was employed with alcohol **133** (*vide supra*, 1.1 eq.). The reaction time was 14 hours. FCC (gradient elution: 1:4:0 – 0:19:1 hexane:PhMe:EtOAc) afforded the title compound (1.15 g, 100 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2956 (m), 2878 (m), 1455 (m), 1349 (s), 1162 (s). δ_H (400 MHz, $CDCl_3$) 7.45 – 7.39 (2H, m, 2 × ArC<u>H</u>), 7.38 – 7.32 (3H, m, 3 × ArC<u>H</u>), 5.41 – 5.32 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 4.66 (1H, t, *J* = 7.5 Hz, C**1**-<u>H</u>), 2.10 – 2.03 (5H, m, C**2**-<u>H_2</u> and Ms C<u>H_3</u>), 1.99 – 1.83 (2H, m, C**3**-<u>H_2</u>), 1.64 (3H,

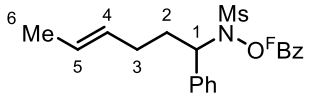
d, *J* = 4.0 Hz, C**6**-H$_3$), 1.05 (9H, t, *J* = 8.0 Hz, Si(CH$_2$CH$_3$)$_3$), 0.96 – 0.79 (6H, m, Si(CH$_2$CH$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 136.0 (ArC), 129.8 (ArCH), 129.6 (C**4**), 128.5 (ArCH), 128.4 (ArCH), 126.2 (C**5**), 66.3 (C**1**), 33.6 (Ms CH$_3$), 33.1 (C**2**), 29.2 (C**3**), 17.9 (C**6**), 6.9 (Si(CH$_2$CH$_3$)$_3$), 5.1 (Si(CH$_2$CH$_3$)$_3$). HRMS: (ESI$^+$) Calculated for $C_{19}H_{33}NNaO_3SSi$: 406.1843. Found [M+Na]$^+$: 406.1861.

(*E*)-*N*-(1-Phenylhex-4-en-1-yl)-*N*-hydroxymethanesulfonamide



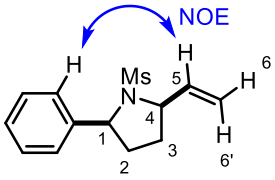
General procedure F: The preceding compound (953 mg, 2.48 mmol) was employed. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (652 mg, 98 %) as a colourless oil. ν_{max} / cm^{-1}: (*solid*) 3345 (br s), 2937 (m), 1494 (m), 1316 (s), 1156 (s). δ_H (400 MHz, $CDCl_3$) 7.49 – 7.43 (2H, m, 2 × ArCH), 7.39 – 7.32 (3H, m, 3 × ArCH), 7.27 (1H, br s, OH), 5.49 – 5.37 (2H, m, C**4**-H and C**5**-H), 4.73 (1H, dd, *J* = 7.5, 7.5 Hz, C**1**-H), 2.24 – 2.16 (4H, m, C**2**-H and Ms CH$_3$), 2.09 – 2.01 (2H, m, C**3**-H$_2$), 2.01 – 1.90 (1H, m, C**2**-H'), 1.65 (3H, d, *J* = 4.0 Hz, C**6**-H$_3$). δ_C (101 MHz, $CDCl_3$) 136.6 (ArC), 129.8 (C**4**), 129.3 (ArCH), 2 × 128.6 (2 × ArCH), 126.2 (C**5**), 64.3 (C**1**), 34.2 (Ms CH$_3$), 32.6 (C**2**), 29.1 (C**3**), 17.8 (C**6**). HRMS: (ESI$^+$) Calculated for $C_{13}H_{19}NNaO_3S$: 292.0978. Found [M+Na]$^+$: 292.0970.

(*E*)-*N*-(1-Phenylhex-4-en-1-yl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (134b)



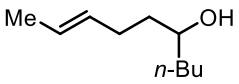
General procedure C: The preceding compound (600 mg, 2.23 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **134b** (965 mg, 93 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3030 (m), 2945 (m), 1775 (s), 1651 (m), 1502 (s), 1367 (s), 1165 (s). δ_H (500 MHz, $CDCl_3$) 7.38 (5H, s, 5 × ArCH), 5.45 – 5.32 (2H, m, C**4**-H and C**5**-H), 5.02 (1H, dd, *J* = 8.5, 6.0 Hz, C**1**-H), 2.38 – 2.18 (4H, m, C**2**-H and Ms CH$_3$), 2.07 – 1.88 (3H, m, C**2**-H' and C**3**-H$_2$), 1.64 (3H, d, *J* = 5.0 Hz, C**6**-H$_3$). δ_C (126 MHz, $CDCl_3$) 156.6 (C=O), 135.8 (ArC), 129.4 (ArCH), 129.3 (C**4**), 129.2 (ArCH), 129.0 (ArCH), 127.0 (C**5**), 66.0 (C**1**), 36.8 (Ms CH$_3$), 32.8 (C**2**), 29.0 (C**3**), 18.1 (C**6**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (283 MHz, $CDCl_3$) -135.5 – -135.7 (2F, m), -144.9 – -145.2 (1F, m), -158.4 – -158.7 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{20}H_{18}F_5NNaO_4S$: 486.0769. Found [M+Na]$^+$: 486.0756.

(2*R,5*S**)-1-Mesyl-2-phenyl-5-vinylpyrrolidine (139b)**



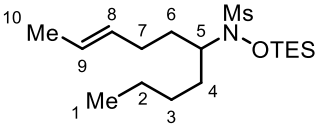
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 120 °C; 19 hours. Substrate **134b** (64.9 mg, 0.140 mmol) was employed. FCC (gradient elution: 10:1 – 5:1 – 2:1 hexane:EtOAc) afforded **139b** (20.4 mg, 58 %) as a pale-yellow oil. *The product was assigned as the cis diastereomer based on the observed NOE correlation between the C5 and the aryl protons.* ν_{max} / cm^{-1}: (*film*) 3029 (m), 2934 (m), 1451 (m), 1328 (s), 1145 (s). δ_H (400 MHz, $CDCl_3$) 7.41 – 7.32 (4H, m, 4 × ArC<u>H</u>), 7.31 – 7.26 (1H, m, ArC<u>H</u>), 6.02 (1H, ddd, *J* = 17.0, 10.0, 7.0 Hz, C**5**-<u>H</u>), 5.40 (1H, ddd, *J* = 17.0, 1.0, 1.0 Hz, C**6**-<u>H</u>'), 5.27 (1H, ddd, *J* = 10.0, 1.0, 1.0 Hz, C**6**-<u>H</u>), 5.00 (1H, dd, *J* = 7.0, 7.0 Hz, C**1**-<u>H</u>), 4.59 (1H, br ddd, *J* = 7.5, 7.0, 7.0 Hz, C**4**-<u>H</u>), 2.66 (3H, s, Ms C<u>H</u>$_3$), 2.40 – 2.30 (1H, m, C**2**-<u>H</u>), 2.17 (1H, dddd, *J* = 12.0, 7.5, 7.5, 6.0 Hz, C**3**-<u>H</u>), 2.01 (1H, dddd, *J* = 12.5, 7.0, 6.0, 6.0 Hz, C**2**-<u>H</u>'), 1.95 – 1.86 (1H, m, C**3**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 142.2 (Ar<u>C</u>), 138.7 (C**5**), 128.7 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 117.2 (C**6**), 64.7 (C**1**), 63.3 (C**4**), 41.3 (Ms <u>C</u>H$_3$), 35.1 (C**2**), 31.5 (C**3**). HRMS: (ESI^+) Calculated for $C_{13}H_{17}NNaO_2S$: 274.0872. Found $[M+Na]^+$: 274.0868.

(*E*)-Dec-8-en-5-ol (135)



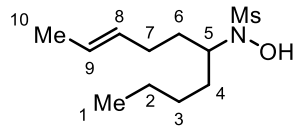
To a solution of *n*-BuLi (1.55 M in hexane, 10.0 mL, 15.5 mmol) in anhydrous THF (30 mL) at 0 °C was added a solution of aldehyde **132** (1.40 g, 14.3 mmol) in anhydrous THF (5 mL) dropwise. The reaction mixture was stirred for 1 hour before addition of saturated aqueous NH_4Cl (25 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford **135** (1.75 g, 78 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3344 (br s), 2930 (s), 2858 (s), 1482 (s), 964 (s). δ_H (400 MHz, $CDCl_3$) 5.52 – 5.40 (2H, m), 3.65 – 3.57 (1H, m), 2.21 – 2.01 (2H, m), 1.65 (3H, d, *J* = 4.5 Hz), 1.59 – 1.24 (9H, m), 0.91 (3H, t, *J* = 7.0 Hz). δ_C (101 MHz, $CDCl_3$) 131.1, 125.3, 71.6, 37.2, 37.1, 28.9, 27.8, 22.7, 17.9, 14.1. *The spectroscopic properties were consistent with the data available in the literature.*[213]

(*E*)-*N*-(Dec-8-en-5-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide



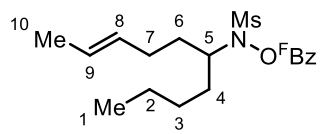
General procedure E: MsNHOTES (676 mg, 3.00 mmol) was employed with alcohol **135** (1.1 eq.). The reaction time was 17 hours. FCC (eluent: PhMe) afforded the title compound (828 mg, 76 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2956 (m), 2877 (m), 1458 (m), 1347 (s), 1163 (s). δ_H (400 MHz, $CDCl_3$) 5.52 – 5.34 (2H, m, C**8**-H and C**9**-H), 3.49 (1H, tt, *J* = 6.5, 6.5 Hz, C**5**-H), 2.88 (3H, s, Ms CH_3), 2.13 – 2.02 (2H, m, C**7**-H_2), 1.73 – 1.26 (11H, m, C**2**-H_2, C**3**-H_2, C**4**-H_2, C**6**-H_2 and C**10**-H_3), 0.99 (9H, t, *J* = 7.5 Hz, $Si(CH_2CH_3)_3$), 0.91 (3H, t, *J* = 7.0 Hz, C**1**-H_3), 0.78 (6H, q, *J* = 7.5 Hz, $Si(CH_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 130.3 (C**8**), 126.1 (C**9**), 63.4 (C**5**), 34.8 (Ms CH_3), 31.7 (C**6**), 31.4 (C**4**), 30.1 (**C7**), 29.3 (C**3**), 22.8 (C**2**), 18.1 (C**10**), 14.2 (C**1**), 6.9 ($Si(CH_2CH_3)_3$), 5.1 ($Si(CH_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{17}H_{37}NNaO_3SSi$: 386.2156. Found $[M+Na]^+$: 386.2156.

(*E*)-*N*-(Dec-8-en-5-yl)-*N*-hydroxymethanesulfonamide



General procedure F: The preceding compound (793 mg, 2.18 mmol) was employed. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (511 mg, 94 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3367 (br s), 2956 (m), 1453 (m), 1320 (s), 1157 (s). δ_H (400 MHz, $CDCl_3$) 6.47 (1H, br s, OH), 5.51 – 5.35 (2H, m, C**8**-H and C**9**-H), 3.69 (1H, tt, *J* = 7.0, 7.0 Hz, C**5**-H), 3.00 (3H, s, Ms CH_3), 2.16 – 1.98 (2H, m, C**7**-H_2), 1.66 – 1.54 (7H, m, C**4**-H_2, C**6**-H_2 and C**10**-H_3), 1.42 – 1.24 (4H, m, C**2**-H_2 and C**3**-H_2), 0.90 (3H, t, *J* = 7.0 Hz, C**1**-H_3). δ_C (101 MHz, $CDCl_3$) 130.3 (C**8**), 126.0 (C**9**), 60.2 (C**5**), 36.6 (Ms CH_3), 30.9 (C**6**), 30.6 (C**4**), 29.5 (C**7**), 28.7 (C**3**), 22.7 (C**2**), 18.1 (C**10**), 14.1 (C**1**). HRMS: (ESI^+) Calculated for $C_{11}H_{23}NNaO_3S$: 272.1291. Found $[M+Na]^+$: 272.1287.

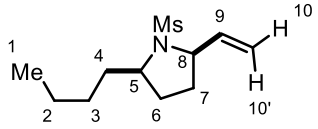
(*E*)-*N*-Dec-8-en-5-yl-*N*-((pentafluorobenzoyl)oxy)methanesulfonamide (136)



General procedure C: The preceding compound (479 mg, 1.92 mmol) was employed. FCC (eluent: 14:1 hexane:EtOAc) afforded **136** (775 mg, 91 %) as a colourless crystalline solid. m.p. 42-43 °C (Et_2O:hexane, *needles*). ν_{max} / cm^{-1}: (*solid*) 2944 (m), 1784 (s), 1651 (m), 1496 (s), 1160 (s). δ_H (400 MHz, $CDCl_3$) 5.54 – 5.44 (1H, m, C**9**-H), 5.43 – 5.34 (1H, m, C**8**-H), 3.98 (1H, tt, *J* = 6.5,

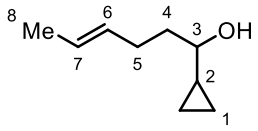
6.5 Hz, C**5**-H), 3.09 (3H, s, Ms CH$_3$), 2.30 – 2.07 (2H, m, C**7**-H$_2$), 1.75 – 1.23 (11H, m, C**2**-H$_2$, C**3**-H$_2$, C**4**-H$_2$, C**6**-H$_2$ and C**10**-H$_3$), 0.91 (3H, t, *J* = 7.0 Hz, C**1**-H$_3$). δ_C (101 MHz, $CDCl_3$) 129.9 (C**8**), 126.4 (C**9**), 62.3 (C**5**), 40.0 (Ms CH$_3$), 31.8 (C**6**), 31.5 (C**4**), 29.5 (C**7**), 28.7 (C**2** or C**3**), 22.6 (C**2** or C**3**), 18.1 (C**10**), 14.0 (C**1**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.1 (2F, m), -145.4 (1F, tt, *J* = 21.0, 5.5 Hz), -158.6 – -158.8 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{18}H_{22}F_5NNaO_4S$: 466.1082. Found $[M+Na]^+$: 466.1070.

(2*R,5*R**)-2-Butyl-1-mesyl-5-vinylpyrrolidine (140)**



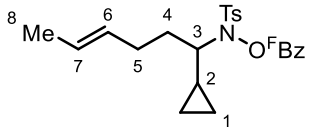
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% P(3,5-$(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; PhMe (0.1 M); 140 °C; 20 hours. Substrate **136** (62.1 mg, 0.140 mmol) was employed. FCC (eluent: 5:1 hexane:EtOAc) afforded **140** (19.9 mg, 61 %, 14:1 ratio of *cis* and *trans* diastereomers) as a pale-yellow oil. *The major product was assigned as the cis diastereomer based on analogy to compounds **139a**, **139b** and **141**. No NOE was observed between the C**5** and the C**9** protons. Spectroscopic data for the major cis diastereomer:* ν_{max} / cm^{-1}: (*film*) 2932 (m), 1331 (s), 1148 (s). δ_H (400 MHz, $CDCl_3$) 5.79 (1H, ddd, *J* = 17.0, 10.0, 6.5 Hz, C**9**-H), 5.30 (1H, ddd, *J* = 17.0, 1.5, 1.5 Hz, C**10**-H'), 5.14 (1H, ddd, *J* = 10.0, 1.5, 1.5 Hz, C**10**-H), 4.29 – 4.23 (1H, m, C**8**-H), 3.81 (1H, dddd, *J* = 9.5, 7.0, 5.0, 5.0 Hz, C**5**-H), 2.84 (3H, s, Ms CH$_3$), 2.10 – 1.93 (2H, m, C**6**-H and C**7**-H), 1.92 – 1.76 (2H, m, C**4**-H and C**7**-H'), 1.72 – 1.62 (1H, m, C**6**-H'), 1.47 – 1.22 (5H, m, C**2**-H$_2$, C**3**-H$_2$ and C**4**-H'), 0.90 (3H, t, *J* = 7.0 Hz, C**1**-H$_3$). δ_C (101 MHz, $CDCl_3$) 139.4 (C**9**), 116.1 (C**10**), 62.9 (C**8**), 61.8 (C**5**), 38.8 (Ms CH$_3$), 36.5 (C**4**), 31.7 (C**7**), 30.2 (C**6**), 28.7 (C**2** or C**3**), 22.7 (C**2** or C**3**), 14.2 (C**1**). HRMS: (ESI$^+$) Calculated for $C_{11}H_{21}NNaO_2S$: 254.1185. Found $[M+Na]^+$: 254.1173. *^{1}H NMR data for the minor trans diastereomer:* δ_H (500 MHz, $CDCl_3$) 5.79 (1H, ddd, *J* = 17.0, 10.0, 8.5 Hz), 5.31 (1H, ddd, *J* = 17.0, 1.0, 1.0 Hz), 5.18 (1H, ddd, *J* = 10.0, 1.0, 1.0 Hz), 4.30 (1H, br dd, *J* = 8.5, 8.5 Hz), 3.74 – 3.68 (1H, m), 2.86 (3H, s), 2.26 – 2.18 (1H, m), 2.11 – 1.95 (2H, m), 1.80 (1H, dddd, *J* = 12.5, 6.5, 1.5, 1.5 Hz), 1.70 (1H, dddd, *J* = 12.5, 6.5, 1.5, 1.5 Hz), 1.48 – 1.39 (1H, m), 1.38 – 1.19 (5H, m), 0.90 (3H, t, *J* = 7.0 Hz).

(*E*)-1-Cyclopropylhex-4-en-1-ol (137)



To a suspension of magnesium turnings (413 mg, 17.0 mmol), activated with a few crystals of iodine, in anhydrous Et_2O (15 mL) was added bromocyclopropane (1.28 mL, 16.0 mmol) before being diluted with Et_2O (20 mL). The reaction mixture was heated at reflux for 2 hours, then cooled to room temperature before addition of a solution of aldehyde **132** (981 mg, 10.0 mmol) in anhydrous Et_2O (10 mL). The reaction mixture was heated at reflux for 15 hours before addition of saturated aqueous NH_4Cl (30 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 5:1 – 3:1 pentane:Et_2O) afforded **137** (993 mg, 71 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3362 (m), 3080 (m), 2924 (s), 1435 (s), 1042 (s). δ_H (400 MHz, $CDCl_3$) 5.51 – 5.38 (2H, m, C**6**-H and C**7**-H), 2.91 – 2.82 (1H, m, C**3**-H), 2.22 – 2.04 (2H, m, C**5**-H_2), 1.69 – 1.61 (5H, m, C**4**-H_2 and C**8**-H_3), 1.56 (1H, br s, OH), 0.89 (1H, dtt, *J* = 8.5, 8.5, 5.0 Hz, C**2**-H), 0.56 – 0.45 (2H, m, 2 × C**1**-H), 0.31 – 0.16 (2H, m, 2 × C**1**-H'). δ_C (101 MHz, $CDCl_3$) 131.2 (C**6**), 125.3 (C**7**), 76.5 (C**3**), 37.1 (C**4**), 29.0 (C**5**), 2 × 18.1 (C**2** and C**8**), 2.8 (C**1**), 2.6 (C**1**'). HRMS: (EI^+) Calculated for C_9H_{14}: 122.1096. Found $[M\text{-}H_2O]^+$: 122.1100.

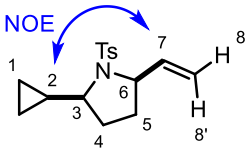
(*E*)-*N*-1-Cyclopropylhex-4-en-1-yl-*N*-(pentafluorobenzoyloxy)-4-toluenesulfonamide (138)



General procedure K: Alcohol **137** (140 mg, 1.00 mmol) was employed with $TsNHO^FBz$ (*vide supra*). The reaction time was 18 hours. FCC (eluent: 1:1 hexane:PhMe) afforded **138** (261 mg, 52 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2929 (m), 1786 (s), 1653 (m), 1598 (m), 1498 (s), 1325 (s), 1165 (s). δ_H (500 MHz, $CDCl_3$) 7.85 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 7.35 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 5.53 – 5.43 (1H, m, C**7**-H), 5.42 – 5.32 (1H, m, C**6**-H), 3.53 – 3.33 (1H, m, C**3**-H), 2.47 (3H, s, Ts CH_3), 2.38 – 2.14 (2H, m, C**5**-H_2), 1.80 – 1.64 (5H, m, C**4**-H_2 and C**8**-H_3), 1.05 (1H, br s, C**2**-H), 0.67 (1H, br s, C**1**-H), 0.63 – 0.54 (2H, m, C**1**-H' and C**1**'-H'), 0.34 (1H, br s, C**1**'-H). δ_C (126 MHz, $CDCl_3$) 156.4 (C=O), 145.6 (ArC), 133.5 (ArC), 130.2 (C**6**), 129.8 (ArCH), 129.5 (ArCH), 126.1 (C**7**), 67.3 (C**3**), 32.8 (C**4**), 29.4 (C**5**), 21.9 (Ts CH_3), 18.1 (C**8**), 13.0 (C**2**), 2 × 5.8 (C**1** and C**1**'). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak*

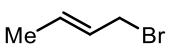
intensity. δ_F (377 MHz, $CDCl_3$) -136.3 – -136.5 (2F, m), -146.3 (1F, tt, *J* = 21.0, 5.0 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{23}H_{22}F_5NNaO_4S$: 526.1082. Found $[M+Na]^+$: 526.1087.

(2*R,5*S**)-2-Cyclopropyl-1-tosyl-5-vinylpyrrolidine (141)**



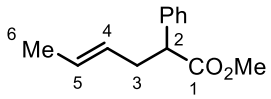
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; PhMe (0.1 M); 140 °C; 15 hours. Substrate **138** (76.3 mg, 0.152 mmol, *added as a solution in PhMe*) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **141** (33.2 mg, 75 %, 13:1 mixture of *cis* and *trans* diastereomers) as a colourless crystalline solid. *The major product was assigned as the cis diastereomer based on the observed NOE correlation between the C2 and the C7 protons. Spectroscopic data for the major cis diastereomer:* ν_{max} / cm^{-1}: (*film*) 3007 (m), 2967 (m), 1598 (m), 1494 (m), 1344 (s), 1158 (s). δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.27 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.86 (1H, ddd, *J* = 17.0, 10.5, 6.0 Hz, C**7**-<u>H</u>), 5.29 (1H, ddd, *J* = 17.0, 1.5, 1.5 Hz, C**8**-<u>H</u>'), 5.10 (1H, ddd, *J* = 10.5, 1.5, 1.5 Hz, C**8**-<u>H</u>), 4.17 – 4.10 (1H, m, C**6**-<u>H</u>), 3.26 (1H, ddd, *J* = 8.0, 8.0, 4.0 Hz, C**3**-<u>H</u>), 2.41 (3H, s, Ts C<u>H</u>$_3$), 1.78 – 1.71 (2H, m, C**5**-<u>H</u>$_2$), 1.70 – 1.61 (1H, m, C**4**-<u>H</u>), 1.57 – 1.46 (1H, m, C**4**-<u>H</u>'), 0.96 (1H, dddt, *J* = 8.0, 8.0, 8.0, 5.0 Hz, C**2**-<u>H</u>), 0.62 – 0.49 (2H, m, C**1**-<u>H</u>$_2$), 0.48 – 0.39 (1H, m, C**1**'-<u>H</u>), 0.25 – 0.17 (1H, m, C**1**'-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 143.1 (Ar<u>C</u>), 139.5 (C**7**), 136.2 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 115.4 (C**8**), 65.9 (C**3**), 63.3 (C**6**), 31.2 (C**5**), 30.3 (C**4**), 21.5 (Ts <u>C</u>H$_3$), 16.9 (C**2**), 4.7 (C**1**), 2.8 (C**1**'). HRMS: (ESI^+) Calculated for $C_{16}H_{22}NO_2S$: 292.1366. Found $[M+H]^+$: 292.1376. *Characteristic signals for the minor trans diastereomer:* δ_H (400 MHz, $CDCl_3$) 5.77 (1H, ddd, *J* = 17.0, 10.0, 7.5 Hz), 5.20 (1H, ddd, *J* = 17.0, 1.0, 1.0 Hz), 5.06 (1H, ddd, *J* = 10.0, 1.0, 1.0 Hz), 4.42 (1H, dd, *J* = 7.5, 7.5 Hz).

Crotyl bromide



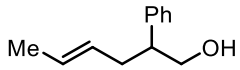
General procedure J: (*E*)-But-2-en-1-ol (21.6 g, 300 mmol) was employed. The title compound (24.2 g, 60 %) was isolated as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.87 – 5.65 (2H, m), 3.94 (2H, d, *J* = 7.0 Hz), 1.74 (3H, d, *J* = 6.0 Hz). δ_C (101 MHz, $CDCl_3$) 131.6, 127.7, 33.6, 17.8. *The spectroscopic properties were consistent with the data available in the literature.*[214]

Methyl (*E*)-2-phenylhex-4-enoate



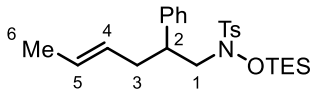
To a suspension of NaH (60 % in mineral oil, 852 mg, 21.3 mmol) in anhydrous THF (25 mL) and DMF (25 mL) was added methyl phenylacetate (3.00 mL, 21.3 mmol). The reaction mixture was stirred at room temperature for 1.5 hours before addition of crotyl bromide (*vide supra*, 1.46 mL, 14.2 mmol). The reaction mixture was stirred for two hours before addition of brine (50 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (3 × 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 39:1 hexane:EtOAc) afforded the title compound (2.38 g, 82 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3029 (m), 2951 (m), 1734 (s), 1435 (s), 1160 (s). δ_H (400 MHz, $CDCl_3$) 7.35 – 7.28 (4H, m, 4 × ArC<u>H</u>), 7.28 – 7.23 (1H, m, ArC<u>H</u>), 5.50 (1H, dqdd, *J* = 15.0, 6.5, 1.5, 1.0 Hz, C**5**-<u>H</u>), 5.40 – 5.28 (1H, m, C**4**-<u>H</u>), 3.65 (3H, s, OC<u>H</u>$_3$), 3.59 (1H, dd, *J* = 8.5, 6.5 Hz, C**2**-<u>H</u>), 2.81 – 2.71 (1H, m, C**3**-<u>H</u>), 2.48 – 2.39 (1H, m, C**3**-<u>H</u>'), 1.61 (3H, dd, *J* = 6.5, 1.5 Hz, C**6**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 174.0 (C**1**), 138.8 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 127.7 (C**4**), 127.6 (C**5**), 127.2 (Ar<u>C</u>H), 52.0 (C**2**), 51.9 (O<u>C</u>H$_3$), 36.6 (C**3**), 17.9 (C**6**). HRMS: (ESI^+) Calculated for $C_{13}H_{16}NaO_2$: 227.1043. Found $[M+Na]^+$: 227.1044.

(*E*)-2-Phenylhex-4-en-1-ol (142)



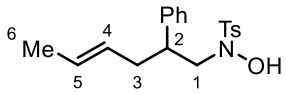
<u>General procedure I:</u> The preceding ester (2.05 g, 10.0 mmol) was employed, using anhydrous THF as the solvent and 0.6 eq. $LiAlH_4$ (1.0 M in THF). Alcohol **142** (1.57 g, 89 %) was isolated as a colourless oil. δ_H (500 MHz, $CDCl_3$) 7.35 – 7.31 (2H, m), 7.26 – 7.20 (3H, m), 5.46 (1H, dqdd, *J* = 15.0, 6.5, 1.0, 1.0 Hz), 5.35 (1H, dddq, *J* = 15.0, 7.5, 6.0, 1.5 Hz), 3.80 (1H, dd, *J* = 11.0, 5.5 Hz), 3.73 (1H, dd, *J* = 11.0, 7.5 Hz), 2.84 (1H, dddd, *J* = 7.5, 7.5, 7.5, 5.5 Hz), 2.40 (1H, ddddq, *J* = 14.0, 7.5, 7.5, 1.0, 1.0 Hz), 2.37 – 2.27 (1H, m), 1.61 (3H, dddd, *J* = 6.5, 1.5, 1.5, 1.0 Hz), 1.36 (1H, br s). δ_C (126 MHz, $CDCl_3$) 142.4, 128.9, 128.8, 128.2, 127.1, 126.9, 67.1, 48.7, 35.7, 18.1. *The spectroscopic properties were consistent with the data available in the literature.*[215]

(*E*)-*N*-(2-Phenylhex-4-en-1-yl)-*N*-((triethylsilyl)oxy)-4-toluenesulfonamide



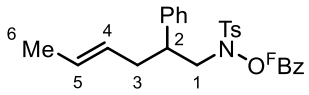
General procedure E: TsNHOTES (*vide supra*, 603 mg, 2.00 mmol) was employed with alcohol **142** (1.3 eq.). The reaction time was 22 hours. FCC (gradient elution: 2:3 – 0:1 hexane:PhMe) afforded the title compound (831 mg, 90 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2957 (s), 2913 (s), 2878 (s), 1598 (m), 1357 (s), 1167 (s). δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.33 – 7.27 (4H, m, 4 × ArC<u>H</u>), 7.23 – 7.17 (1H, m ArC<u>H</u>), 7.14 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.39 (1H, dq, *J* = 15.0, 6.5 Hz, C**5**-<u>H</u>), 5.28 – 5.18 (1H, m, C**4**-<u>H</u>), 3.26 (1H, dd, *J* = 13.0, 8.5 Hz, C**1**-<u>H</u>), 3.05 – 2.96 (1H, m, C**2**-<u>H</u>), 2.80 (1H, dd, *J* = 13.0, 6.5 Hz, C**1**-<u>H</u>'), 2.61 – 2.52 (1H, m, C**3**-<u>H</u>), 2.42 (3H, s, Ts C<u>H</u>$_3$), 2.35 – 2.25 (1H, m, C**3**-<u>H</u>'), 1.57 (3H, d, *J* = 6.5 Hz, C**6**-<u>H</u>$_3$), 0.99 (9H, t, *J* = 7.5 Hz, Si($CH_2C\underline{H}_3$)$_3$), 0.76 (6H, q, *J* = 7.5 Hz, Si($C\underline{H}_2CH_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 144.6 (Ar<u>C</u>), 142.3 (Ar<u>C</u>), 130.1 (ArC<u>H</u>), 129.7 (ArC), 129.4 (ArC<u>H</u>), 128.5 (ArC<u>H</u>), 2 × 128.2 (ArC<u>H</u> and C**4**), 127.4 (C**5**), 126.7 (ArC<u>H</u>), 61.2 (C**1**), 43.2 (C**2**), 37.2 (C**3**), 21.8 (Ts <u>C</u>H$_3$), 18.1 (C**6**), 7.0 (Si($CH_2\underline{C}H_3$)$_3$), 5.1 (Si($\underline{C}H_2CH_3$)$_3$). HRMS: (ESI^+) Calculated for $C_{25}H_{37}NNaO_3SSi$: 482.2156. Found $[M+Na]^+$: 482.2155.

(*E*)-*N*-(2-Phenylhex-4-en-1-yl)-*N*-hydroxy-4-toluenesulfonamide



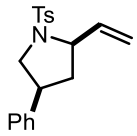
General procedure F: The preceding compound (790 mg, 1.72 mmol) was employed. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (576 mg, 97 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3360 (br s), 2919 (m), 1598 (m), 1335 (s), 1164 (s). δ_H (500 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.36 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.34 – 7.29 (2H, m, 2 × ArC<u>H</u>), 7.26 – 7.21 (1H, m, ArC<u>H</u>), 7.19 – 7.15 (2H, m, 2 × ArC<u>H</u>), 5.46 – 5.37 (1H, m, C**5**-<u>H</u>), 5.25 (1H, dddq, *J* = 15.5, 8.0, 6.5, 1.5 Hz, C**4**-<u>H</u>), 3.25 – 3.20 (1H, m, C**1**-<u>H</u>), 3.07 – 2.98 (2H, m, C**1**-<u>H</u>' and C**2**-<u>H</u>), 2.54 – 2.47 (1H, m, C**3**-<u>H</u>), 2.46 (3H, s, Ts C<u>H</u>$_3$), 2.38 – 2.30 (1H, m, C**3**-<u>H</u>'), 1.60 – 1.56 (3H, m, C**6**-<u>H</u>$_3$). δ_C (126 MHz, $CDCl_3$) 144.9 (Ar<u>C</u>), 142.0 (Ar<u>C</u>), 129.7 (Ar<u>C</u>), 2 × 129.6 (2 × Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 2 × 128.0 (C**4** and Ar<u>C</u>H), 127.3 (C**5**), 126.7 (Ar<u>C</u>H), 57.1 (C**1**), 43.4 (C**2**), 36.8 (C**3**), 21.7 (Ts <u>C</u>H$_3$), 17.9 (C**6**). HRMS: (ESI^+) Calculated for $C_{19}H_{24}NO_3S$: 346.1471. Found $[M+H]^+$: 346.1467.

(*E*)-*N*-(2-Phenylhex-4-en-1-yl)-*N*-(pentafluorobenzoyloxy)-4-toluenesulfonamide (144)



General procedure C: The preceding compound (554 mg, 1.60 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **144** (800 mg, 93 %) as a colourless crystalline solid. m.p. 68-70 °C (Et_2O:hexane, *cubes*). ν_{max} / cm^{-1}: (*film*) 2919 (m), 1785 (s), 1652 (m), 1597 (m), 1496 (s), 1168 (s). δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.36 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.25 – 7.19 (2H, m, 2 × ArC<u>H</u>), 7.15 – 7.06 (3H, m, 3 × ArC<u>H</u>), 5.43 (1H, dq, *J* = 15.0, 6.5 Hz, C**5**-<u>H</u>), 5.25 – 5.15 (1H, m, C**4**-<u>H</u>), 3.75 – 3.64 (1H, m, C**1**-<u>H</u>), 3.21 – 3.03 (1H, m, C**1**-<u>H</u>'), 2.87 – 2.82 (1H, m, C**2**-<u>H</u>), 2.71 – 2.61 (1H, m, C**3**-<u>H</u>), 2.46 (3H, s, Ts C<u>H</u>$_3$), 2.41 – 2.31 (1H, m, C**3**-<u>H</u>'), 1.57 (3H, dd, *J* = 6.5, 1.5 Hz, C**6**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 145.8 (Ar<u>C</u>), 141.3 (Ar<u>C</u>), 130.1 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 127.9 (C**5**), 127.8 (Ar<u>C</u>H), 127.4 (C**4**), 126.6 (Ar<u>C</u>H), 57.1 (C**1**), 44.0 (C**2**), 36.7 (C**3**), 21.7 (Ts <u>C</u>H$_3$), 17.9 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (283 MHz, $CDCl_3$) -135.2 – -135.4 (2F, m), -146.0 (1F, tt, *J* = 21.0, 5.5 Hz), -159.1 – -159.4 (2F, m). HRMS: (ESI^+) Calculated for $C_{26}H_{22}F_5NNaO_4S$: 562.1082. Found $[M+Na]^+$: 562.1060.

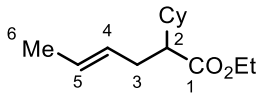
(2*R,4*S**)-4-Phenyl-1-tosyl-2-vinylpyrrolidine (145)**



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 120 °C; 20 hours. Substrate **144** (75.5 mg, 0.140 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **145** (26.3 mg, 57 %, 2:1 mixture of *cis* and *trans* diastereomers) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*film*) 2973 (m), 1643 (m), 1598 (m), 1495 (m), 1345 (s), 1159 (s). *^1H and ^{13}C NMR data for the major cis diastereomer:* δ_H (400 MHz, $CDCl_3$) 7.79 – 7.74 (2H, m), 7.38 – 7.18 (5H, m), 7.15 – 7.09 (2H, m), 6.01 – 5.85 (1H, m), 5.28 (1H, ddd, *J* = 17.0, 1.0, 1.0 Hz), 5.15 (1H, ddd, *J* = 10.5, 1.0, 1.0 Hz), 4.15 (1H, br ddd, *J* = 9.5, 7.0, 7.0 Hz), 3.95 – 3.84 (1H, m), 3.50 – 3.33 (1H, m), 2.85 (1H, dddd, *J* = 11.0, 11.0, 7.0, 7.0 Hz), 2.46 (3H, s), 2.44 – 2.34 (1H, m), 1.94 – 1.78 (1H, m). δ_C (101 MHz, $CDCl_3$) 143.5, 139.6, 138.9, 135.5, 129.7, 128.7, 127.6, 127.1, 127.0, 115.7, 63.2, 55.2, 43.0, 40.9, 21.6. *^1H and ^{13}C NMR data for the minor trans diastereomer:* δ_H (400 MHz, $CDCl_3$) 7.79 – 7.75 (2H, m), 7.37 – 7.19 (5H, m), 7.06 – 7.03 (2H, m), 5.99 – 5.86 (1H, m), 5.40 (1H, ddd, *J* = 17.0, 1.5, 1.5 Hz), 5.22 (1H, ddd, *J* = 10.0, 1.5, 1.5 Hz), 4.42 (1H, ddddd, *J* = 7.0, 7.0, 1.5, 1.5, 1.5 Hz), 3.95 – 3.83 (1H, m), 3.51 – 3.33 (1H, m), 3.14 (1H, dd, *J* =

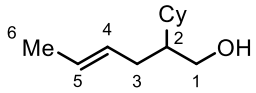
10.0, 10.0 Hz), 2.46 (3H, s), 2.03 (1H, ddd, *J* = 12.5, 6.0, 1.5 Hz), 1.95 – 1.79 (1H, m). δ_C (101 MHz, $CDCl_3$) 143.5, 139.8, 138.5, 134.8, 129.7, 128.6, 127.6, 2 × 127.0, 115.7, 61.6, 54.7, 41.7, 38.8, 21.6. *The spectroscopic properties were consistent with the data available in the literature.*[211]

Ethyl (*E*)-2-cyclohexylhex-4-enoate



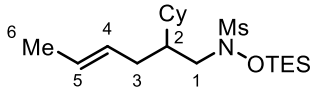
To a solution of *i*-Pr_2NH (1.46 mL, 10.5 mmol) in anhydrous THF (40 mL) at 0 °C was added *n*-BuLi (1.51 M in hexane, 7.00 mL, 10.6 mmol). The reaction mixture was stirred at 0 °C for 30 minutes, then cooled to -78 °C before addition of ethyl 2-cyclohexylacetate (1.80 mL, 10.0 mmol) dropwise. The reaction mixture was stirred at -78 °C for 30 minutes before addition of crotyl bromide (*vide supra*, 1.08 mL, 10.5 mmol). The reaction mixture was stirred at room temperature for 2 hours before addition of saturated aqueous NH_4Cl (30 mL). The resulting phases were separated, and the aqueous phase was extracted with EtOAc (2 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 29:1 hexane:EtOAc) afforded the title compound (1.93 g, 86 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2925 (s), 2853 (s), 1731 (s), 1448 (s), 1157 (s). δ_H (400 MHz, $CDCl_3$) 5.49 – 5.40 (1H, m, C**5**-H), 5.33 (1H, dtq, *J* = 15.0, 6.5, 1.5 Hz, C**4**-H), 4.11 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 2.25 – 2.12 (3H, m, C**2**-H and C**3**-H_2), 1.83 – 1.57 (8H, m, C**6**-H_3 and 5 × Cy CH), 1.56 – 1.45 (1H, m, Cy CH), 1.23 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.29 – 0.86 (5H, m, 5 × Cy CH). δ_C (101 MHz, $CDCl_3$) 175.3 (C**1**), 128.4 (C**4**), 126.8 (C**5**), 59.7 (OCH_2CH_3), 52.3 (C**2**), 39.8 (Cy CH), 32.6 (C**3**), 30.9 (Cy CH), 30.6 (Cy CH), 26.4 (Cy CH), 26.3 (Cy CH), 26.2 (Cy CH), 17.9 (C**6**), 14.4 (OCH_2CH_3). HRMS: (ESI^+) Calculated for $C_{14}H_{24}NaO_2$: 247.1669. Found $[M+Na]^+$: 247.1668.

(*E*)-2-Cyclohexylhex-4-en-1-ol (143)



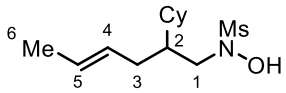
General procedure I: The preceding ester (1.85 g, 8.25 mmol) was employed, using anhydrous THF as the solvent and 0.8 eq. $LiAlH_4$ (1.0 M in THF). Alcohol **143** (1.50 g, 100 %) was isolated as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3335 (br s), 2921 (s), 2851 (s), 1448 (s), 1040 (s). δ_H (400 MHz, $CDCl_3$) 5.54 – 5.38 (2H, m, C**4**-H and C**5**-H), 3.67 – 3.55 (2H, m, C**1**-H_2), 2.17 – 2.09 (1H, m, C**3**-H), 2.03 – 1.92 (1H, m, C**3**-H'), 1.77 – 1.60 (8H, m, C**6**-H_3 and 5 × Cy CH), 1.47 – 1.34 (3H, m, C**2**-H, Cy CH and OH), 1.29 – 0.96 (5H, m, 5 × Cy CH). δ_C (101 MHz, $CDCl_3$) 130.4 (C**4**), 126.3 (C**5**), 63.8 (C**1**), 46.3 (C**2**), 38.4 (Cy CH), 31.9 (C**3**), 30.3 (Cy CH), 30.1 (Cy CH), 2 × 26.8 (2 × Cy CH), 26.7 (Cy CH), 18.0 (C**6**). HRMS: (ESI^+) Calculated for $C_{12}H_{22}NaO$: 205.1563. Found $[M+Na]^+$: 205.1568.

(*E*)-*N*-(2-Cyclohexylhex-4-en-1-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide



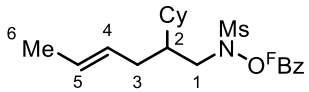
General procedure E: MsNHOTES (*vide supra*, 902 mg, 4.00 mmol) was employed with alcohol **143** (1.1 eq.). The reaction time was 15 hours. FCC (eluent: PhMe) afforded the title compound (1.45 g, 93 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2921 (s), 2877 (s), 2845 (s), 1449 (s), 1347 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 5.49 – 5.40 (1H, m, C**5**-H), 5.34 (1H, dddq, *J* = 15.0, 7.0, 5.5, 1.5 Hz, C**4**-H), 3.10 (1H, dd, *J* = 13.0, 6.5 Hz, C**1**-H), 3.00 (1H, dd, *J* = 13.0, 7.0 Hz, C**1**-H'), 2.84 (3H, s, Ms CH_3), 2.14 – 2.05 (1H, m, C**3**-H), 2.03 – 1.93 (1H, m, C**3**-H'), 1.80 – 1.52 (10H, m, C**2**-H, C**6**-H_3 and 6 × Cy CH), 1.30 – 1.02 (5H, m, 5 × Cy CH), 0.99 (9H, t, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.77 (6H, q, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 129.2 (C**4**), 126.9 (C**5**), 56.8 (C**1**), 41.0 (C**2**), 37.7 (Cy CH), 31.7 (C**3**), 29.9 (Ms CH_3), 29.7 (Cy CH), 28.9 (Cy CH), 26.8 (Cy CH), 2 × 26.7 (2 × Cy CH), 18.0 (C**6**), 6.8 ($Si(CH_2CH_3)_3$), 5.0 ($Si(CH_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{19}H_{40}NO_3SSi$: 390.2493. Found $[M+H]^+$: 390.2492.

(*E*)-*N*-(2-Cyclohexylhex-4-en-1-yl)-*N*-hydroxymethanesulfonamide



General procedure F: The preceding compound (1.39 g, 3.57 mmol) was employed. FCC (eluent: 6:1 hexane:EtOAc) afforded the title compound (951 mg, 97 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3368 (br s), 2924 (s), 2852 (s), 1449 (m), 1342 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 6.47 (1H, br s, OH), 5.51 – 5.33 (2H, m, C**4**-H and C**5**-H), 3.12 (1H, dd, *J* = 12.5, 6.5 Hz, C**1**-H), 3.04 (1H, dd, *J* = 12.5, 7.5 Hz, C**1**-H'), 2.91 (3H, s, Ms CH_3), 2.17 – 2.08 (1H, m, C**3**-H), 2.01 (1H, ddd, *J* = 14.0, 7.0, 7.0 Hz, C**3**-H'), 1.79 – 1.57 (9H, m, C**2**-H, C**6**-H_3 and 5 × Cy CH), 1.57 – 1.47 (1H, m, Cy CH), 1.29 – 0.98 (5H, m, 5 × Cy CH). δ_C (101 MHz, $CDCl_3$) 129.5 (C**4**), 126.9 (C**5**), 53.7 (C**1**), 41.0 (C**2**), 38.3 (Cy CH), 32.0 (C**3**), 31.0 (Ms CH_3), 29.9 (Cy CH), 29.5 (Cy CH), 3 × 26.9 (3 × Cy CH), 18.2 (C**6**). HRMS: (ESI^+) Calculated for $C_{13}H_{25}NNaO_3S$: 298.1447. Found $[M+Na]^+$: 248.1441.

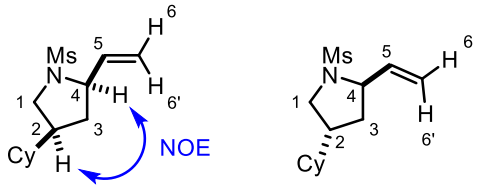
(*E*)-*N*-(2-Cyclohexylhex-4-en-1-yl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (146)



General procedure C: The preceding compound (909 mg, 3.30 mmol) was employed. FCC (gradient elution: 12:1 – 9:1 – 8:1 hexane:EtOAc) afforded **146** (1.33 g, 86 %) as a colourless crystalline solid.

m.p. 73-75 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*solid*) 2926 (m), 1791 (s), 1654 (m), 1504 (s), 1360 (s), 1162 (s). δ_H (500 MHz, $CDCl_3$) 5.51 – 5.43 (1H, m, C**5**-H), 5.32 (1H, dddq, *J* = 15.0, 8.5, 7.0, 1.5 Hz, C**4**-H), 3.46 – 3.24 (2H, m, C**1**-H_2), 3.03 (3H, s, Ms CH_3), 2.25 – 2.04 (2H, m, C**3**-H_2), 1.78 – 1.71 (2H, m, 2 × Cy CH), 1.70 – 1.57 (7H, m, C**6**-H_3 and 4 × Cy CH), 1.51 – 1.44 (1H, m, C**2**-H), 1.32 – 1.20 (2H, m, 2 × Cy CH), 1.16 – 1.08 (1H, m, Cy CH), 1.08 – 0.98 (2H, m, 2 × Cy CH). δ_C (101 MHz, $CDCl_3$) 128.6 (C**4**), 127.5 (C**5**), 53.3 (C**1**), 41.4 (C**2**), 37.6 (Cy CH), 34.2 (Ms CH_3), 31.4 (C**3**), 29.7 (Cy CH), 26.7 (Cy CH), 3 × 26.6 (3 × Cy CH), 18.0 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -136.1 (2F, m), -145.5 (1F, tt, *J* = 21.0, 5.0 Hz), -158.7 – -158.9 (2F, m). HRMS: (ESI^+) Calculated for $C_{20}H_{24}F_5NNaO_4S$: 492.1238. Found $[M+Na]^+$: 492.1230.

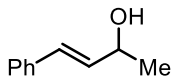
4-Cyclohexyl-1-mesyl-2-vinylpyrrolidine (147)



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; *n*-BuCN (0.1 M); 110 °C; 20 hours. Substrate **146** (65.7 mg, 0.140 mmol) was employed. FCC (gradient elution: 9:1 – 6:1 – 3:1 hexane:EtOAc) afforded **147** (28.1 mg, 78 %, 1:1 mixture of *cis* and *trans* diastereomers) as a colourless crystalline solid. *The relative stereochemistry of the cis diastereomer was assigned based on the observed NOE correlation between the C**2** and the C**4** protons. Spectroscopic data for both diastereomers:* ν_{max} / cm^{-1}: (*film*) 2922 (s), 2851 (m), 1449 (m), 1331 (s), 1150 (s). *The ^1H signals were assigned as being from either the cis or the trans diastereomer based on 1D TOCSY analysis. The ^1H and ^{13}C signals corresponding to the cyclohexyl group could not be assigned to either diastereomer.* δ_H (400 MHz, $CDCl_3$) 5.85 – 5.70 (1H, m, *cis* and *trans*: C**5**-H), 5.26 (0.5H, ddd, *J* = 17.0, 1.5, 1.5 Hz, *trans*: C**6**-H'), 5.25 (0.5H, ddd, *J* = 17.0, 1.0, 1.0 Hz, *cis*: C**6**-H'), 5.16 – 5.10 (1H, m, *cis* and *trans*: C**6**-H), 4.36 – 4.20 (0.5H, m, *trans*: C**4**-H), 4.16 (0.5H, br ddd, *J* = 9.5, 7.5, 7.0 Hz, *cis*: C**4**-H), 3.79 (0.5H, dd, *J* = 10.5, 7.5 Hz, *cis*: C**1**-H), 3.54 (0.5H, dd, *J* = 9.0, 7.5 Hz, *trans*: C**1**-H), 3.00 (0.5H, dd, *J* = 9.5, 9.0 Hz, *trans*: C**1**-H'), 2.94 (0.5H, dd, *J* = 10.5, 10.5 Hz, *cis*: C**1**-H'), 2.83 (3H, s, *cis* and *trans*: Ms CH_3), 2.31 (0.5H, ddd, *J* = 13.0, 7.0, 6.5 Hz, *cis*: C**3**-H), 2.10 – 1.97 (0.5H, m, *trans*: C**2**-H), 1.90 – 1.79 (1H, m, *cis*: C**2**-H and *trans* C**3**-H), 1.75 – 1.55 (5.5H, m, 5 × Cy CH and *trans*: C**3**-H'), 1.40 (0.5H, ddd, *J* = 13.0, 12.0, 9.5 Hz, *cis*: C**3**-H'), 1.29 – 1.06 (4H, m, 4 × Cy CH), 1.04 – 0.86 (2H, m, 2 × Cy CH). δ_C (101 MHz, $CDCl_3$) 138.9 (*cis*: C**5**), 138.3 (*trans*: C**5**), 116.4 (*cis*: C**6**), 115.8 (*trans*: C**6**), 63.0 (*cis*: C**4**), 61.6 (*trans*: C**4**), 52.8 (*cis*: C**1**), 52.4 (*trans*: C**1**), 44.7 (*cis*: C**2**), 43.1 (*trans*: C**2**), 41.5 (Cy CH), 41.3 (Cy CH), 38.7 (*cis*: C**3**), 38.6 (*cis* or *trans*: Ms CH_3), 37.3 (*cis* or *trans*: Ms CH_3), 36.6 (*trans*: C**3**), 32.0 (Cy CH), 31.9 (Cy CH), 31.6 (Cy CH), 31.5 (Cy CH), 2 × 26.2

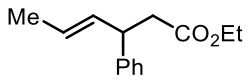
(2 × Cy CH), 4 × 25.9 (4 × Cy CH). HRMS: (ESI^+) Calculated for $C_{13}H_{23}NNaO_2S$: 280.1342. Found $[M+Na]^+$: 280.1344.

(*E*)-4-Phenylbut-3-en-2-ol (148)



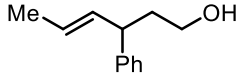
To a solution of cinnamaldehyde (10.0 g, 75.6 mmol) in anhydrous Et_2O (250 mL) at 0 °C was added MeLi (1.6 M in Et_2O, 56.7 mL, 90.7 mmol). The reaction mixture was stirred for 2 hours at room temperature before addition of water (10 mL) followed by saturated aqueous NH_4Cl (150 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 4:1 hexane:EtOAc) afforded **148** (8.87 g, 79 %) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 7.39 – 7.34 (2H, m), 7.33 – 7.28 (2H, m), 7.26 – 7.20 (1H, m), 6.55 (1H, br d, *J* = 16.0 Hz), 6.25 (1H, dd, *J* = 16.0, 6.5 Hz), 4.47 (1H, dqd, *J* = 6.5, 6.5, 1.0 Hz), 2.16 (1H, br s), 1.36 (3H, d, *J* = 6.5 Hz). δ_C (101 MHz, $CDCl_3$) 136.8, 133.7, 129.4, 128.6, 127.7, 126.5, 68.9, 23.5. *The spectroscopic properties were consistent with the data available in the literature.*[216]

Ethyl (*E*)-3-phenylhex-4-enoate



General procedure L: Allylic alcohol **148** (1.39 g, 9.38 mmol) was employed. The reaction time was 15 hours. FCC (eluent: 49:1 hexane:EtOAc) afforded the title compound (1.61 g, 79 %) as a colourless oil. δ_H (500 MHz, $CDCl_3$) 7.32 – 7.27 (2H, m), 7.22 – 7.18 (3H, m), 5.60 (1H, ddq, *J* = 15.0, 7.5, 1.5 Hz), 5.50 (1H, dqd, *J* = 15.0, 6.5, 1.0 Hz), 4.10 – 4.04 (2H, m), 3.81 (1H, br dt, *J* = 7.5, 7.5 Hz), 2.72 – 2.67 (2H, m), 1.66 (3H, ddd, *J* = 6.5, 1.5, 1.0 Hz), 1.17 (3H, t, *J* = 7.0 Hz). δ_C (126 MHz, $CDCl_3$) 172.1, 143.5, 133.3, 128.6, 127.6, 126.6, 125.8, 60.4, 45.1, 41.2, 18.1, 14.3. *The spectroscopic properties were consistent with the data available in the literature.*[217]

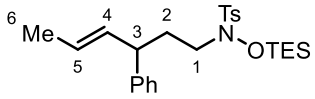
(*E*)-3-Phenylhex-4-en-1-ol (149)



General procedure I: The preceding ester (1.61 g, 7.34 mmol) was employed, using anhydrous THF as the solvent and 0.8 eq. $LiAlH_4$ (1.0 M in THF). FCC (eluent: 3:1 hexane:EtOAc) afforded **149** (821 mg, 63 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.33 – 7.28 (2H, m), 7.23 – 7.17 (3H, m),

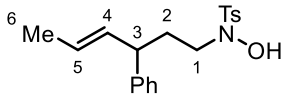
5.60 (1H, ddq, *J* = 15.0, 8.0, 1.5 Hz), 5.56 – 5.46 (1H, m), 3.67 – 3.57 (2H, m), 3.41 (1H, br dt, *J* = 8.0, 8.0 Hz), 2.00 – 1.90 (2H, m), 1.68 (3H, ddd, *J* = 5.5, 1.5, 1.0 Hz), 1.42 (1H, br s). δ_C (101 MHz, $CDCl_3$) 144.8, 134.8, 128.7, 127.6, 126.3, 125.3, 61.3, 45.6, 38.8, 18.1. *The spectroscopic properties were consistent with the data available in the literature.*[218]

(*E*)-*N*-(3-Phenylhex-4-en-1-yl)-*N*-((triethylsilyl)oxy)-4-toluenesulfonamide



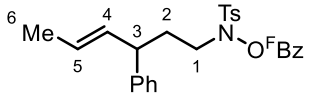
General procedure E: TsNHOTES (*vide supra*, 407 mg, 1.35 mmol) was employed with alcohol **149** (1.1 eq.). The reaction time was 22 hours. FCC (gradient elution: 2:3 – 0:1 hexane:PhMe) afforded the title compound (590 mg, 95 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2956 (s), 2877 (s), 1598 (m), 1357 (s), 1168 (s). δ_H (400 MHz, $CDCl_3$) 7.66 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.34 – 7.27 (4H, m, 4 × ArC<u>H</u>), 7.22 – 7.17 (1H, m, ArC<u>H</u>), 7.16 – 7.13 (2H, m, 2 × ArC<u>H</u>), 5.55 – 5.41 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 3.20 (1H, td, *J* = 7.5, 7.0 Hz, C**3**-<u>H</u>), 2.91 (1H, dt, *J* = 13.5, 7.5 Hz, C**1**-<u>H</u>), 2.80 (1H, dt, *J* = 13.5, 7.5 Hz, C**1**-<u>H</u>'), 2.44 (3H, s, Ts C<u>H</u>$_3$), 1.97 (2H, ddd, *J* = 7.5, 7.5, 7.5 Hz, C**2**-<u>H</u>$_2$), 1.66 (3H, d, *J* = 5.0 Hz, C**6**-<u>H</u>$_3$), 1.00 (9H, t, *J* = 8.0 Hz, Si($CH_2C\underline{H}_3$)$_3$), 0.79 (6H, q, *J* = 8.0 Hz, Si($C\underline{H}_2CH_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 144.4 (Ar<u>C</u>), 144.0 (Ar<u>C</u>), 134.0 (C**4**), 129.9 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>), 129.2 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 125.5 (C**5**), 54.4 (C**1**), 46.4 (C**3**), 32.9 (C**2**), 21.6 (Ts <u>C</u>H$_3$), 17.9 (C**6**), 6.8 (Si($CH_2\underline{C}H_3$)$_3$), 4.8 (Si($\underline{C}H_2CH_3$)$_3$). HRMS: (ESI^+) Calculated for $C_{25}H_{38}NO_3SSi$: 460.2336. Found $[M+H]^+$: 460.2329.

(*E*)-*N*-(3-Phenylhex-4-en-1-yl)-*N*-hydroxy-4-toluenesulfonamide



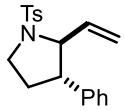
General procedure F: The preceding compound (547 mg, 1.19 mmol) was employed. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (387 mg, 94 %) as a colourless gum. ν_{max} / cm^{-1}: (*film*) 3382 (br s), 2972 (s), 2918 (s), 1597 (m), 1341 (s), 1167 (s). δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.37 – 7.26 (4H, m, 4 × ArC<u>H</u>), 7.23 – 7.16 (3H, m, 3 × ArC<u>H</u>), 6.62 (1H, br s, O<u>H</u>), 5.58 – 5.46 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 3.39 (1H, dt, *J* = 7.0, 7.0 Hz, C**3**-<u>H</u>), 2.96 – 2.85 (2H, m, C**1**-<u>H</u>$_2$), 2.46 (3H, s, Ts C<u>H</u>$_3$), 2.00 (2H, dt, *J* = 7.0, 7.0 Hz, C**2**-<u>H</u>$_2$), 1.67 (3H, d, *J* = 5.0 Hz, C**6**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 144.9 (Ar<u>C</u>), 144.4 (Ar<u>C</u>), 133.9 (C**4**), 129.8 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 125.9 (C**5**), 50.9 (C**1**), 45.9 (C**3**), 32.7 (C**2**), 21.7 (Ts <u>C</u>H$_3$), 18.0 (C**6**). HRMS: (ESI^+) Calculated for $C_{19}H_{24}NO_3S$: 346.1471. Found $[M+H]^+$: 346.1469.

(*E*)-*N*-3-Phenylhex-4-en-1-yl-*N*-((pentafluorobenzoyl)oxy)-4-toluenesulfonamide (152)



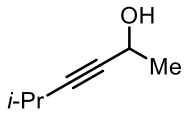
General procedure C: The preceding compound (354 mg, 1.02 mmol) was employed. FCC (eluent: 7:1 hexane:EtOAc) afforded **152** (470 mg, 85 %) as a colourless crystalline solid. m.p. 121-122 °C (Et_2O:hexane, *cubes*). ν_{max} / cm^{-1}: (*solid*) 2907 (m), 1780 (s), 1656 (m), 1596 (m), 1505 (s), 1171 (s). δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.36 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.32 – 7.25 (2H, m, 2 × ArC<u>H</u>), 7.21 – 7.15 (3H, m, 3 × ArC<u>H</u>), 5.59 – 5.46 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 3.53 (1H, dt, *J* = 7.0, 6.5 Hz, C**3**-<u>H</u>), 3.18 (2H, br s, C**1**-<u>H_2</u>), 2.46 (3H, s, Ts C<u>H_3</u>), 1.89 (2H, td, *J* = 7.0, 6.5 Hz, C**2**-<u>H_2</u>), 1.66 (3H, d, *J* = 4.5 Hz, C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 146.0 (Ar<u>C</u>), 144.0 (Ar<u>C</u>), 133.3 (C**4**), 130.2 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 2 × 126.5 (Ar<u>C</u>H and C**5**), 50.9 (C**1**), 45.6 (C**3**), 33.0 (C**2**), 21.9 (Ts <u>C</u>H_3), 18.1 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (283 MHz, $CDCl_3$) -135.7 – -136.0 (2F, m), -146.0 (1F, tt, *J* = 21.0, 5.0 Hz), -158.8 – -159.2 (2F, m). HRMS: (ESI^+) Calculated for $C_{26}H_{22}F_5NNaO_4S$: 562.1082. Found $[M+Na]^+$: 562.1077.

(2*R,3*R**)-3-Phenyl-1-tosyl-2-vinylpyrrolidine (154)**



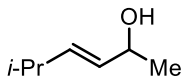
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 12.5 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; *n*-BuCN (0.1 M); 110 °C; 16 hours. Substrate **152** (75.5 mg, 0.140 mmol) was employed. FCC (gradient elution: 9:1 – 4:1 hexane:EtOAc) afforded **154** (37.2 mg, 81 %, 2:1 mixture of *trans* and *cis* diastereomers) as a colourless oil. *Spectroscopic data for the major trans diastereomer:* ν_{max} / cm^{-1}: (*film*) 3029 (m), 2979 (m), 1598 (m), 1345 (s), 1159 (s). δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* = 8.0 Hz), 7.38 – 7.16 (5H, m), 6.95 – 6.89 (2H, m), 5.86 (1H, ddd, *J* = 17.0, 10.5, 7.0 Hz), 5.08 (1H, d, *J* = 10.5 Hz), 5.06 (1H, d, *J* = 17.0 Hz), 3.97 (1H, dd, *J* = 7.0, 7.0 Hz), 3.74 – 3.63 (1H, m), 3.53 (1H, ddd, *J* = 11.0, 9.0, 6.5 Hz), 3.07 (1H, ddd, *J* = 9.5, 7.0, 7.0 Hz), 2.47 (3H, s), 2.18 – 2.01 (1H, m), 1.76 – 1.59 (1H, m). δ_C (101 MHz, $CDCl_3$) 143.4, 140.1, 137.6, 135.4, 129.6, 128.5, 127.6, 127.4, 127.0, 116.2, 69.5, 52.0, 48.6, 32.3, 21.6. *The spectroscopic properties were consistent with the data available in the literature.*[211] *Characteristic signals for the minor cis diastereomer:* δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* = 8.0 Hz), 5.38 – 5.24 (2H, m), 4.52 (1H, dd, *J* = 8.0, 4.5 Hz), 3.35 (1H, ddd, *J* = 10.0, 10.0, 7.0 Hz), 2.31 – 2.20 (1H, m).

5-Methylhex-3-yn-2-ol



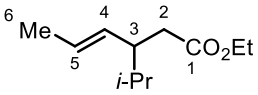
This compound was prepared according to a literature procedure.[219] To a solution of 3-methylbut-1-yne (5.31 mL, 52.0 mmol) in anhydrous Et_2O (30 mL) at 0 °C was added *n*-BuLi (1.55 M in hexane, 28.4 mL, 44.0 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 minutes before addition of acetaldehyde (2.24 mL, 40.0 mmol), then stirred for a further 2 hours at 0 °C before addition of saturated aqueous NH_4Cl (40 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 3:1 hexane:Et_2O) afforded the title compound (1.74 g, 39 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3334 (br s), 2971 (s), 2934 (s), 2873 (s), 1320 (s), 1046 (s). δ_H (400 MHz, $CDCl_3$) 4.50 (1H, br q, *J* = 6.5 Hz), 2.55 (1H, hept d, *J* = 7.0, 2.0 Hz), 2.02 (1H, br s), 1.40 (3H, d, *J* = 6.5 Hz), 1.14 (6H, d, *J* = 7.0 Hz). δ_C (101 MHz, $CDCl_3$) 90.0, 81.4, 58.5, 24.7, 22.9, 20.4. *The spectroscopic properties were consistent with the data available in the literature.*[220]

(*E*)-5-Methylhex-3-en-2-ol (150)



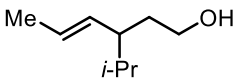
This compound was prepared according to a literature procedure.[221] A solution of the preceding compound (1.50 g, 13.4 mmol), NaOMe (1.16 g, 21.4 mmol) and $LiAlH_4$ (1.0 M in THF, 16.0 mL, 16.0 mmol) in anhydrous THF (9 mL) was heated at reflux for 4 hours. The reaction mixture was cooled to 0 °C before addition of water (1 mL), 4.0 M aqueous NaOH (1 mL) and water (3 mL). The reaction mixture was stirred at room temperature for 15 minutes before filtration through celite and elution with CH_2Cl_2. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo* to afford **150** (1.23 g, 80 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3338 (br s), 2961 (s), 2870 (s), 1464 (s), 1365 (m), 1056 (s). δ_H (400 MHz, $CDCl_3$) 5.58 (1H, ddd, *J* = 15.5, 6.5, 1.0 Hz), 5.44 (1H, ddd, *J* = 15.5, 6.5, 1.0 Hz), 4.23 (1H, dqd, *J* = 6.5, 6.5, 1.0 Hz), 2.25 (1H, hept dd, *J* = 6.5, 6.5, 1.0 Hz), 1.69 (1H, br s), 1.23 (3H, d, *J* = 6.5 Hz), 0.97 (6H, d, *J* = 6.5 Hz). δ_C (101 MHz, $CDCl_3$) 137.9, 131.1, 68.9, 30.5, 23.4, 2 × 22.2. *The spectroscopic properties were consistent with the data available in the literature.*[222]

Ethyl (*E*)-3-isopropylhex-4-enoate



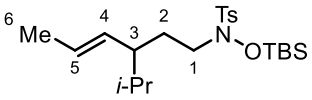
General procedure L: Allylic alcohol **150** (1.14 g, 10.0 mmol) was employed. The reaction time was 15 hours. FCC (eluent: 39:1 hexane:EtOAc) afforded the title compound (1.11 g, 60 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2960 (s), 2874 (m), 1735 (s), 1465 (m), 1369 (s), 1173 (s), 1036 (s). δ_H (400 MHz, $CDCl_3$) 5.41 (1H, dq, *J* = 15.5, 6.5 Hz, C**5**-H), 5.23 (1H, ddq, *J* = 15.5, 8.5, 1.5 Hz, C**4**-H), 4.08 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 2.37 (1H, dd, *J* = 13.0, 5.0 Hz, C**2**-H), 2.34 – 2.26 (1H, m, C**3**-H), 2.19 (1H, dd, *J* = 13.0, 9.0 Hz, C**2**-H'), 1.63 (3H, dd, *J* = 6.5, 1.5 Hz, C**6**-H_3), 1.61 – 1.53 (1H, m, $CH(CH_3)_2$), 1.21 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.86 (3H, d, *J* = 7.0 Hz, $CH(CH_3)(CH_3)$'), 0.82 (3H, d, *J* = 7.0 Hz, $CH(CH_3)(CH_3)$'). δ_C (101 MHz, $CDCl_3$) 173.3 (C**1**), 131.4 (C**4**), 126.7 (C**5**), 60.2 (OCH_2CH_3), 45.9 (C**3**), 38.3 (C**2**), 31.8 ($CH(CH_3)_2$), 20.5 ($CH(CH_3)(CH_3)$'), 19.0 ($CH(CH_3)(CH_3)$'), 18.1 (C**6**), 14.4 (OCH_2CH_3). HRMS: (ESI^+) Calculated for $C_{11}H_{20}NaO_2$: 207.1356. Found $[M+Na]^+$: 207.1347.

(*E*)-3-Isopropylhex-4-en-1-ol (151)



General procedure I: The preceding ester (1.04 g, 5.64 mmol) was employed, using anhydrous Et_2O as the solvent and 0.8 eq. $LiAlH_4$ (1.0 M in Et_2O). FCC (gradient elution: 5:1 – 2:1 hexane:Et_2O) afforded **151** (675 mg, 84 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.41 (1H, dq, *J* = 15.5, 6.5 Hz), 5.21 (1H, ddq, *J* = 15.5, 9.5, 1.5 Hz), 3.68 – 3.53 (2H, m), 1.92 – 1.81 (1H, m), 1.72 – 1.61 (1H, m), 1.67 (3H, dd, *J* = 6.5, 1.5 Hz), 1.58 – 1.39 (3H, m), 0.86 (3H, d, *J* = 7.0 Hz), 0.82 (3H, d, *J* = 7.0 Hz). δ_C (101 MHz, $CDCl_3$) 133.0, 126.3, 61.9, 46.3, 35.3, 32.2, 20.5, 18.9, 17.9. *The spectroscopic properties were consistent with the data available in the literature.*[218]

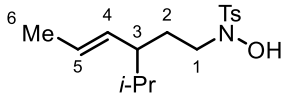
(*E*)-*N*-(3-Isopropylhex-4-en-1-yl)-*N*-((*tert*-butyldimethylsilyl)oxy)-4-toluenesulfonamide



General procedure E: TsNHOTBS (*vide supra*, 905 mg, 3.00 mmol) was employed with alcohol **151** (1.1 eq.). The reaction time was 15 hours. FCC (eluent: 1:4 hexane:PhMe) afforded the title compound (1.25 g, 98 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2957 (s), 2930 (s), 2859 (s), 1598 (m), 1472 (m), 1358 (s), 1170 (s). δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 7.33 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 5.30 (1H, dq, *J* = 15.5, 6.5 Hz, C**5**-H), 5.08 (1H, ddq, *J* = 15.5, 8.5, 1.5 Hz, C**4**-H), 2.94

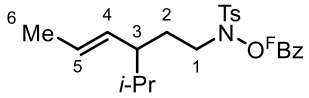
(1H, ddd, *J* = 13.0, 11.0, 4.5 Hz, C**1**-H), 2.79 (1H, ddd, *J* = 13.0, 10.5, 5.0 Hz, C**1**-H'), 2.45 (3H, s, Ts CH_3), 1.72 – 1.59 (5H, m, C**2**-H, C**3**-H and C**6**-H_3), 1.54 – 1.34 (2H, m, C**2**-H' and $CH(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 0.80 (3H, d, *J* = 6.5 Hz, $CH(CH_3)(CH_3)$'), 0.77 (3H, d, *J* = 7.0 Hz, $CH(CH_3)(CH_3)$'), 0.28 (6H, s, $Si(CH_3)_2$). δ_C (101 MHz, $CDCl_3$) 144.5 (ArC), 132.2 (C**4**), 130.4 (ArC), 130.0 (ArCH), 129.3 (ArCH), 126.9 (C**5**), 55.2 (C**1**), 47.4 (C**3**), 32.2 ($CH(CH_3)_2$), 29.6 (C**2**), 26.2 ($SiC(CH_3)_3$), 21.8 (Ts CH_3), 20.6 ($CH(CH_3)(CH_3)$'), 19.1 ($CH(CH_3)(CH_3)$'), 18.3 ($SiC(CH_3)_3$), 18.1 (C**6**), -4.1 ($Si(CH_3)_2$). HRMS: (ESI^+) Calculated for $C_{22}H_{40}NO_3SSi$: 426.2493. Found $[M+H]^+$: 426.2477.

(*E*)-*N*-(3-Isopropylhex-4-en-1-yl)-*N*-hydroxy-4-toluenesulfonamide



General procedure B: The preceding compound (1.16 g, 2.72 mmol) was employed. FCC (eluent: 5:1 hexane:EtOAc) afforded the title compound (791 mg, 93 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3380 (br s), 2959 (s), 2872 (s), 1598 (m), 1439 (m), 1341 (s), 1167 (s). δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 7.36 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 6.38 (1H, s, OH), 5.38 (1H, dq, *J* = 15.5, 6.5 Hz, C**5**-H), 5.12 (1H, ddq, *J* = 15.5, 9.5, 1.5 Hz, C**4**-H), 2.92 (1H, ddd, *J* = 12.5, 8.5, 7.0 Hz, C**1**-H), 2.82 (1H, ddd, *J* = 12.5, 8.5, 5.0 Hz, C**1**-H'), 2.45 (3H, s, Ts CH_3), 1.87 – 1.71 (2H, m, C**2**-H and C**3**-H), 1.65 (3H, dd, *J* = 6.5, 1.5 Hz, C**6**-H_3), 1.60 – 1.38 (2H, m, C**2**-H' and $CH(CH_3)_2$), 0.84 (3H, d, *J* = 6.5 Hz, $CH(CH_3)(CH_3)$'), 0.80 (3H, d, *J* = 7.0 Hz, $CH(CH_3)(CH_3)$'). δ_C (101 MHz, $CDCl_3$) 144.9 (ArC), 132.1 (C**4**), 129.8 (ArCH), 129.7 (ArC), 129.6 (ArCH), 127.1 (C**5**), 51.5 (C**1**), 46.6 (C**3**), 32.1 ($CH(CH_3)_2$), 29.3 (C**2**), 21.8 (Ts CH_3), 20.7 ($CH(CH_3)(CH_3)$'), 19.1 ($CH(CH_3)(CH_3)$'), 18.2 (C**6**). HRMS: (ESI^+) Calculated for $C_{16}H_{25}NNaO_3S$: 334.1447. Found $[M+Na]^+$: 334.1445.

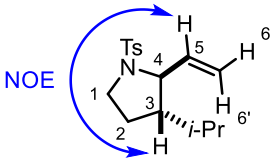
(*E*)-*N*-(3-Isopropylhex-4-en-1-yl)-*N*-(pentafluorobenzoyloxy)-4-toluenesulfonamide (153)



General procedure C: The preceding compound (722 mg, 2.32 mmol) was employed. FCC (eluent: 12:1 hexane:EtOAc) afforded **153** (869 mg, 74 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2961 (m), 1786 (s), 1652 (m), 1597 (m), 1498 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 7.37 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 5.40 (1H, dq, *J* = 15.5, 6.5 Hz, C**5**-H), 5.14 – 5.04 (1H, m, C**4**-H), 3.38 – 3.02 (2H, m, C**1**-H_2), 2.47 (3H, s, Ts CH_3), 1.99 – 1.86 (1H, m, C**3**-H), 1.72 – 1.61 (1H, m, C**2**-H), 1.66 (3H, dd, *J* = 6.5, 1.5 Hz, C**6**-H_3), 1.54 – 1.36 (2H, m, C**2**-H' and $CH(CH_3)_2$), 0.83 (3H, d, *J* = 7.0 Hz, $CH(CH_3)(CH_3)$'), 0.80 (3H, d, *J* = 7.0 Hz, $CH(CH_3)(CH_3)$'). δ_C (101 MHz, $CDCl_3$) 145.7 (ArC), 131.5 (C**4**), 130.2 (ArC), 129.8 (ArCH), 129.6 (ArCH), 127.6 (C**5**), 51.4 (C**1**), 46.3 (C**3**), 32.0

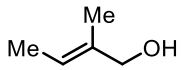
(C<u>H</u>(CH$_3$)$_2$), 28.9 (C**2**), 21.7 (Ts C<u>H</u>$_3$), 20.4 (CH(C<u>H</u>$_3$)(CH$_3$)'), 19.0 (CH(CH$_3$)(C<u>H</u>$_3$)'), 18.0 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.1 – -136.3 (2F, m), -146.3 (1F, tt, *J* = 21.0, 5.0 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{23}H_{24}F_5NNaO_4S$: 528.1238. Found [M+Na]$^+$: 528.1229.

(2*R,3*R**)-3-Isopropyl-1-tosyl-2-vinylpyrrolidine (155)**



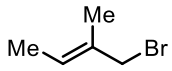
General procedure D: Conditions: 3.75 mol% $Pd_2(dba)_3$; 18.8 mol% P(3,5-$(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; *n*-BuCN (0.1 M); 110 °C; 16 hours. Substrate **153** (70.2 mg, 0.139 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **155** (32.6 mg, 80 %, 2:1 mixture of *trans* and *cis* diastereomers) as a pale-yellow oil. *The major diastereomer was assigned as trans based on the observed NOE correlation between the C**3** and the C**5** protons. The minor diastereomer was assigned as cis based on the observed NOE correlation between the C**6**-H' and isopropyl CH$_3$ protons.* ν_{max} / cm^{-1}: (*film*) 2960 (m), 1598 (m), 1451 (m), 1344 (s), 1161 (s). *^{1}H and ^{13}C NMR data for the major trans diastereomer:* δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.28 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.75 (1H, ddd, *J* = 17.0, 10.5, 7.0 Hz, C**5**-<u>H</u>), 5.24 (1H, dd, *J* = 17.0, 1.0 Hz, C**6**-<u>H</u>'), 5.10 (1H, dd, *J* = 10.5, 1.0 Hz, C**6**-<u>H</u>), 3.81 (1H, dd, *J* = 7.0, 6.5 Hz, C**4**-<u>H</u>), 3.47 – 3.39 (1H, m, C**1**-<u>H</u>), 3.31 (1H, ddd, *J* = 10.5, 8.0, 6.5 Hz, C**1**-<u>H</u>'), 2.41 (3H, s, Ts C<u>H</u>$_3$), 1.73 (1H, ddd, *J* = 11.5, 6.5, 6.0 Hz, C**2**-<u>H</u>), 1.68 – 1.60 (1H, m, C**3**-<u>H</u>), 1.33 – 1.17 (2H, m, C**2**-<u>H</u>' and C<u>H</u>(CH$_3$)$_2$), 0.81 (3H, d, *J* = 6.5 Hz, CH(C<u>H</u>$_3$)(CH$_3$)'), 0.67 (3H, d, *J* = 6.5 Hz, CH(CH$_3$)(C<u>H</u>$_3$)'). δ_C (101 MHz, $CDCl_3$) 143.2 (Ar<u>C</u>), 139.1 (C**5**), 135.7 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 115.5 (C**6**), 65.5 (C**4**), 52.5 (C**3**), 48.0 (C**1**), 28.5 (<u>C</u>H(CH$_3$)$_2$), 26.7 (C**2**), 21.7 (Ts <u>C</u>H$_3$), 21.5 (CH(<u>C</u>H$_3$)(CH$_3$)'), 19.0 (CH(CH$_3$)(<u>C</u>H$_3$)'). *^{1}H and ^{13}C NMR data for the minor cis diastereomer:* δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.28 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.67 (1H, ddd, *J* = 17.0, 10.0, 7.0 Hz, C**5**-<u>H</u>), 5.36 – 5.29 (1H, m, C**6**-<u>H</u>'), 5.19 (1H, d, *J* = 10.5 Hz, C**6**-<u>H</u>), 4.31 (1H, dd, *J* = 7.0, 7.0 Hz, C**4**-<u>H</u>), 3.46 – 3.39 (1H, m, C**1**-<u>H</u>), 3.15 (1H, ddd, *J* = 11.0, 10.0, 6.5 Hz, C**1**-<u>H</u>'), 2.41 (3H, s, Ts C<u>H</u>$_3$), 1.88 (1H, ddd, *J* = 12.0, 6.5, 6.0 Hz, C**2**-<u>H</u>), 1.53 (1H, ddd, *J* = 12.0, 11.0, 8.5 Hz, C**2**-<u>H</u>'), 1.43 – 1.32 (2H, m, C**3**-<u>H</u> and C<u>H</u>(CH$_3$)$_2$), 0.85 (3H, d, *J* = 6.0 Hz, CH(C<u>H</u>$_3$)(CH$_3$)'), 0.81 (3H, d, *J* = 6.5 Hz, CH(CH$_3$)(C<u>H</u>$_3$)'). δ_C (101 MHz, $CDCl_3$) 143.0 (Ar<u>C</u>), 135.8 (Ar<u>C</u>), 133.8 (C**5**), 129.4 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 117.8 (C**6**), 63.9 (C**4**), 51.3 (C**3**), 47.1 (C**1**), 28.0 (C**2**), 27.9 (<u>C</u>H(CH$_3$)$_2$), 21.5 (Ts <u>C</u>H$_3$), 2 × 21.4 (CH(C<u>H</u>$_3$)(CH$_3$)' and CH(CH$_3$)(C<u>H</u>$_3$)'). HRMS: (ESI$^+$) Calculated for $C_{16}H_{24}NO_2S$: 294.1522. Found [M+H]$^+$: 294.1526.

(*E*)-2-Methylbut-2-en-1-ol



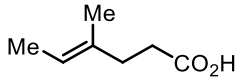
General procedure I: (*E*)-2-Methylbut-2-enoic acid (15.0 g, 150 mmol) was employed, using anhydrous Et_2O as the solvent and 1.1 eq. $LiAlH_4$ (1.0 M in Et_2O). The title compound (10.8 g, 84 %) was isolated as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.48 (1H, qq, *J* = 6.5, 1.5 Hz), 3.98 (2H, s), 1.66 (3H, br s), 1.61 (3H, dq, *J* = 6.5, 1.0 Hz), 1.52 (1H, br s). δ_C (101 MHz, $CDCl_3$) 135.6, 120.7, 69.1, 13.5, 13.2. *The spectroscopic properties were consistent with the data available in the literature.*[223]

(*E*)-1-Bromo-2-methylbut-2-ene



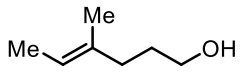
General procedure J: The preceding alcohol (10.4 g, 121 mmol) was employed. The title compound (11.6 g, 63 %) was isolated as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.73 – 5.65 (1H, m), 3.98 (2H, br s), 1.75 (3H, dq, *J* = 1.0, 1.0 Hz), 1.63 (3H, dq, *J* = 7.0, 1.0 Hz). δ_C (101 MHz, $CDCl_3$) 132.8, 126.0, 42.0, 14.5, 14.0. *The spectroscopic properties were consistent with the data available in the literature.*[101]

(*E*)-4-Methylhex-4-enoic acid



General procedure H: (*E*)-1-Bromo-2-methylbut-2-ene (*vide supra*, 1.18 ml, 10.0 mmol) was employed. The crude product was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$) 5.29 – 5.19 (1H, m), 2.47 – 2.40 (2H, m), 2.30 (2H, t, *J* = 7.5 Hz), 1.61 (3H, t, *J* = 1.0 Hz), 1.58 – 1.53 (3H, m). δ_C (101 MHz, $CDCl_3$) 178.8, 133.9, 119.5, 34.5, 33.0, 15.7, 13.5. *The spectroscopic properties were consistent with the data available in the literature*.[224]

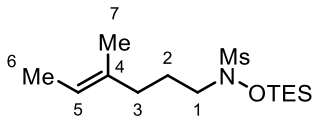
(*E*)-4-Methylhex-4-en-1-ol



General procedure I: The preceding crude carboxylic acid was employed, using anhydrous Et_2O as the solvent and 2.0 eq. $LiAlH_4$ (1.0 M in Et_2O). FCC (eluent: 4:1 pentane:Et_2O) afforded the title compound (618 mg, 54 % over two steps) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3327 (br s), 2936 (s),

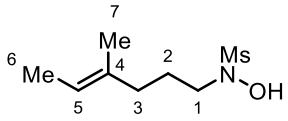
2863 (s), 1444 (s), 1381 (s), 1059 (s). δ_H (400 MHz, $CDCl_3$) 5.28 – 5.22 (1H, m), 3.63 (2H, t, *J* = 6.5 Hz), 2.09 – 2.03 (2H, m), 1.71 – 1.63 (2H, m), 1.61 (3H, t, *J* = 1.0 Hz), 1.57 (3H, br d, *J* = 6.5 Hz), 1.34 (1H, br s). δ_C (101 MHz, $CDCl_3$) 135.6, 119.0, 63.1, 36.1, 30.9, 15.7, 13.5. *The spectroscopic properties were consistent with the data available in the literature*.[225]

(*E*)-*N*-(4-Methylhex-4-en-1-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide



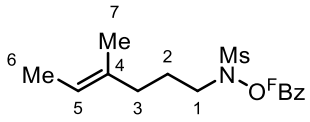
General procedure E: MsNHOTES (*vide supra*, 676 mg, 3.00 mmol) was employed with the preceding alcohol (1.1 eq.). The reaction time was 14 hours. FCC (eluent: 12:1 hexane:EtOAc) afforded the title compound (897 mg, 93 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2956 (s), 2913 (s), 2878 (s), 1350 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 5.22 (1H, q, *J* = 6.5 Hz, C**5**-H), 3.18 – 3.10 (2H, m, C**1**-H_2), 2.85 (3H, s, Ms CH_3), 2.03 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 1.77 (2H, tt, *J* = 8.0, 7.5 Hz, C**2**-H_2), 1.60 (3H, br s, C**7**-H_3), 1.58 (3H, dq, *J* = 6.5, 1.0 Hz, C**6**-H_3), 1.00 (9H, t, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.78 (6H, q, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 134.2 (C**4**), 119.4 (C**5**), 55.3 (C**1**), 36.7 (C**3**), 30.4 (Ms CH$_3$), 25.2 (C**2**), 15.5 (C**7**), 13.4 (C**6**), 6.7 ($Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{14}H_{31}NNaO_3SSi$: 344.1686. Found $[M+Na]^+$: 344.1690.

(*E*)-*N*-(4-Methylhex-4-en-1-yl)-*N*-hydroxymethanesulfonamide



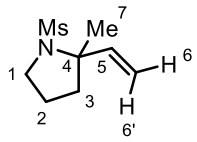
General procedure F: The preceding compound (859 mg, 2.67 mmol) was employed. FCC (eluent: 3:1 hexane:EtOAc) afforded the title compound (546 mg, 99 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*solid*) 3351 (br s), 2973 (m), 2938 (m), 2863 (m), 1324 (s), 1148 (s). δ_H (400 MHz, $CDCl_3$) 6.80 (1H, br s, OH), 5.24 (1H, qq, *J* = 6.5, 1.5 Hz, C**5**-H), 3.17 – 3.12 (2H, m, C**1**-H_2), 2.92 (3H, s, Ms CH_3), 2.10 – 2.03 (2H, m, C**3**-H_2), 1.80 (2H, tt, *J* = 7.5, 7.5 Hz, C**2**-H_2), 1.60 (3H, br s, C**7**-H_3), 1.57 (3H, dq, *J* = 6.5, 1.0 Hz, C**6**-H_3). δ_C (101 MHz, $CDCl_3$) 134.4 (C**4**), 119.4 (C**5**), 52.0 (C**1**), 36.3 (C**3**), 30.9 (Ms CH$_3$), 25.0 (C**2**), 15.4 (C**7**), 13.4 (C**6**). HRMS: (ESI^+) Calculated for $C_8H_{17}NNaO_3S$: 230.0821. Found $[M+Na]^+$: 230.0811.

(*E*)-*N*-4-Methylhex-4-en-1-yl-*N*-(pentafluorobenzoyloxy)methanesulfonamide (156)



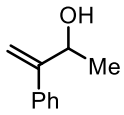
General procedure C: The preceding compound (509 mg, 2.46 mmol) was employed. FCC (gradient elution: 6:1 – 3:1 hexane:EtOAc) afforded **156** (859 mg, 87 %) as a colourless crystalline solid. m.p. 67-68 °C (Et_2O:hexane, *plates*). ν_{max} / cm^{-1}: (*solid*) 2936 (m), 1780 (s), 1653 (m), 1502 (s), 1354 (s), 1163 (s). δ_H (400 MHz, $CDCl_3$) 5.26 (1H, q, *J* = 6.5 Hz, C**5**-H), 3.43 (2H, br s, C**1**-H_2), 3.04 (3H, s, Ms CH_3), 2.15 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 1.78 (2H, tt, *J* = 7.5, 7.5 Hz, C**2**-H_2), 1.61 – 1.56 (6H, m, C**6**-H_3 and C**7**-H_3). δ_C (101 MHz, $CDCl_3$) 133.9 (C**4**), 120.2 (C**5**), 52.2 (C**1**), 36.3 (C**3**), 34.5 (Ms CH$_3$), 25.1 (C**2**), 15.5 (C**7**), 13.5 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -135.9 (2F, m), -145.3 (1F, tt, *J* = 21.0, 5.5 Hz), -158.8 – -159.0 (2F, m). HRMS: (ESI^+) Calculated for $C_{15}H_{16}F_5NNaO_4S$: 424.0612. Found $[M+Na]^+$: 424.0610.

2-Methyl-1-mesyl-2-vinylpyrrolidine (157)



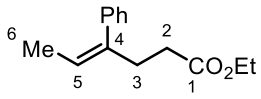
General procedure D: Conditions: 3.75 mol% $Pd_2(dba)_3$; 18.8 mol% P(3,5-$(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 16 hours. Substrate **156** (56.7 mg, 0.140 mmol) was employed. FCC (eluent: 10:1 PhMe:EtOAc) afforded **157** (21.3 mg, 80 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2976 (m), 2928 (m), 1330 (s), 1148 (s). δ_H (400 MHz, $CDCl_3$) 5.98 (1H, dd, *J* = 17.5, 10.5 Hz, C**5**-H), 5.24 (1H, dd, *J* = 17.5, 0.5 Hz, C**6**-H'), 5.15 (1H, dd, *J* = 10.5, 0.5 Hz, C**6**-H), 3.53 – 3.44 (2H, m, C**1**-H_2), 2.86 (3H, s, Ms CH_3), 2.04 – 1.97 (1H, m, C**3**-H), 1.94 – 1.81 (3H, m, C**2**-H_2 and C**3**-H'), 1.57 (3H, s, C**7**-H_3). δ_C (101 MHz, $CDCl_3$) 142.1 (C**5**), 114.0 (C**6**), 67.0 (C**4**), 49.5 (C**1**), 41.7 (C**3**), 39.7 (Ms CH$_3$), 25.1 (C**7**), 22.4 (C**2**). HRMS: (ESI^+) Calculated for $C_8H_{15}NNaO_2S$: 212.0716. Found $[M+Na]^+$: 212.0714.

3-Phenylbut-3-en-2-ol (158a)



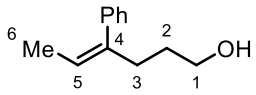
This compound was prepared according to a literature procedure.[226] To a suspension of magnesium turnings (401 mg, 16.5 mmol), activated with a crystal of iodine, in anhydrous THF (35 mL) was added (1-bromovinyl)benzene (1.95 mL, 15.0 mmol). The reaction mixture was heated at reflux for 1 hour, then cooled to 0 °C before addition of acetaldehyde (1.26 mL, 22.5 mmol) dropwise. The reaction mixture was stirred at room temperature for 1.5 hours before addition of saturated aqueous NH_4Cl (100 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 80 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 5:1 hexane:EtOAc) afforded **158a** (1.68 g, 76 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3368 (br s), 3057 (m), 2976 (s), 1493 (s), 1070 (s). δ_H (400 MHz, $CDCl_3$) 7.43 – 7.28 (5H, m), 5.38 (1H, dd, *J* = 1.0, 1.0 Hz), 5.29 (1H, dd, *J* = 1.0, 1.0 Hz), 4.83 (1H, qdd, *J* = 6.5, 1.0, 1.0 Hz), 1.91 (1H, br s), 1.33 (3H, d, *J* = 6.5 Hz). δ_C (101 MHz, $CDCl_3$) 153.1, 139.9, 128.4, 127.6, 126.8, 111.6, 69.5, 22.6. *The spectroscopic properties were consistent with the data available in the literature*.[226]

Ethyl (*Z*)-4-phenylhex-4-enoate



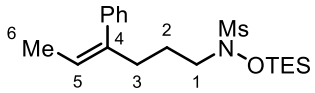
General procedure L: Allylic alcohol **158a** (1.48 g, 10.0 mmol) was employed. The reaction time was 15 hours. FCC (eluent: 29:1 hexane:EtOAc) afforded the title compound (1.85 g, 85 %, 11:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless oil. *Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*film*) 2980 (m), 2935 (m), 1732 (s), 1152 (s). δ_H (400 MHz, $CDCl_3$) 7.37 – 7.29 (2H, m, 2 × ArC**H**), 7.27 – 7.22 (1H, m, ArC**H**), 7.17 – 7.13 (2H, m, 2 × ArC**H**), 5.60 (1H, qt, *J* = 7.0, 1.0 Hz, C**5**-**H**), 4.08 (2H, q, *J* = 7.0 Hz, OC$\underline{H}_2$CH$_3$), 2.70 – 2.64 (2H, m, C**3**-$\underline{H}_2$), 2.33 – 2.28 (2H, m, C**2**-$\underline{H}_2$), 1.55 (3H, dt, *J* = 7.0, 1.0 Hz, C**6**-$\underline{H}_3$), 1.22 (3H, t, *J* = 7.0 Hz, OCH$_2$C$\underline{H}_3$). δ_C (101 MHz, $CDCl_3$) 173.3 (C**1**), 140.1 (Ar**C**), 140.0 (C**4**), 128.6 (Ar**C**H), 128.1 (Ar**C**H), 126.6 (Ar**C**H), 122.2 (C**5**), 60.2 (O**C**H$_2$CH$_3$), 34.4 (C**3**), 33.4 (C**2**), 14.6 (C**6**), 14.2 (OCH$_2$**C**H$_3$). HRMS: (ESI^+) Calculated for $C_{14}H_{18}NaO_2$: 241.1199. Found $[M+Na]^+$: 241.1198. *The minor isomer was assigned as E based on the observed NOE correlation between the C**3** and the C**6** protons. Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 5.78 (1H, q, *J* = 7.0 Hz), 2.88 – 2.82 (2H, m), 1.82 (3H, d, *J* = 7.0 Hz).

(*Z*)-4-Phenylhex-4-en-1-ol (159a)



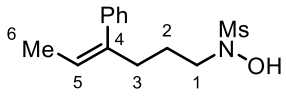
General procedure I: The preceding ester (1.80 g, 8.25 mmol) was employed, using anhydrous THF as the solvent and 0.8 eq. $LiAlH_4$ (1.0 M in THF). Alcohol **159a** (1.42 g, 98 %, 11:1 mixture of (*Z*)- and (*E*)-isomers) was isolated as a colourless oil. *Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*film*) 3326 (br s), 2936 (s), 2859 (s), 1440 (s), 1054 (s). δ_H (400 MHz, $CDCl_3$) 7.37 – 7.31 (2H, m, 2 × ArC<u>H</u>), 7.27 – 7.21 (1H, m, ArC<u>H</u>), 7.18 – 7.13 (2H, m, 2 × ArC<u>H</u>), 5.59 (1H, qt, *J* = 7.0, 1.5 Hz, C**5**-<u>H</u>), 3.61 (2H, t, *J* = 6.5 Hz, C**1**-<u>H_2</u>), 2.46 – 2.40 (2H, m, C**3**-<u>H_2</u>), 1.61 – 1.53 (5H, m, C**2**-<u>H_2</u> and C**6**-<u>H_3</u>), 1.33 (1H, br s, O<u>H</u>). δ_C (101 MHz, $CDCl_3$) 141.0 (Ar<u>C</u>), 140.7 (C**4**), 128.5 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 126.5 (Ar<u>C</u>H), 121.6 (C**5**), 62.5 (C**1**), 35.4 (C**3**), 31.2 (C**2**), 14.7 (C**6**). HRMS: (ESI^+) Calculated for $C_{12}H_{16}NaO$: 199.1093. Found $[M+Na]^+$: 199.1100. *Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 5.79 (1H, q, *J* = 7.0 Hz), 2.64 – 2.58 (2H, m), 1.82 (3H, d, *J* = 7.0 Hz).

(*Z*)-*N*-(4-Phenylhex-4-en-1-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide



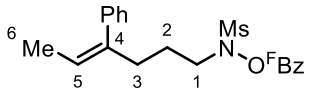
General procedure E: MsNHOTES (*vide supra*, 902 mg, 4.00 mmol) was employed with alcohol **159a** (1.1 eq.). The reaction time was 16 hours. FCC (gradient elution: 1:0 – 9:1 PhMe:EtOAc) afforded the title compound (1.40 g, 91 %, 11:1 mixture of (*Z*)- and (*E*)-isomers) as a pale-orange oil. *Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*film*) 2955 (m), 2913 (m), 2877 (m), 1349 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 7.38 – 7.29 (2H, m, 2 × ArC<u>H</u>), 7.27 – 7.22 (1H, m, ArC<u>H</u>), 7.16 – 7.12 (2H, m, 2 × ArC<u>H</u>), 5.58 (1H, qt, *J* = 6.5, 1.0 Hz, C**5**-<u>H</u>), 3.18 – 3.12 (2H, m, C**1**-<u>H_2</u>), 2.81 (3H, s, Ms C<u>H_3</u>), 2.46 – 2.37 (2H, m, C**3**-<u>H_2</u>), 1.65 (2H, tt, *J* = 7.5, 7.5 Hz, C**2**-<u>H_2</u>), 1.56 (3H, d, *J* = 6.5 Hz, C**6**-<u>H_3</u>), 0.93 (9H, t, *J* = 8.0 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.69 (6H, q, *J* = 8.0 Hz, $Si(C\underline{H}_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 2 × 140.3 (Ar<u>C</u> and C**4**), 128.5 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 122.2 (C**5**), 55.1 (C**1**), 36.4 (C**3**), 30.3 (Ms <u>C</u>H_3), 25.6 (C**2**), 14.6 (C**6**), 6.7 ($Si(CH_2\underline{C}H_3)_3$), 4.7 ($Si(\underline{C}H_2CH_3)_3$). HRMS: ($ESI^+$) Calculated for $C_{19}H_{34}NO_3SSi$: 384.2023. Found $[M+H]^+$: 384.2026. *Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 5.78 (1H, q, *J* = 7.0 Hz), 2.57 (2H, t, *J* = 7.5 Hz), 1.81 (3H, d, *J* = 7.0 Hz).

(*Z*)-*N*-(4-Phenylhex-4-en-1-yl)-*N*-hydroxymethanesulfonamide



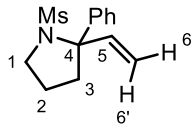
General procedure F: The preceding compound (1.23 g, 3.21 mmol) was employed. FCC (eluent: 3:1 hexane:EtOAc) afforded the title compound (573 mg, 66 %, 11:1 mixture of (*Z*)- and (*E*)-isomers) as a pale-red oil. *Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*film*) 3379 (br s), 3021 (m), 2935 (m), 1337 (s), 1163 (s). δ_H (400 MHz, $CDCl_3$) 7.37 – 7.30 (2H, m, 2 × ArC<u>H</u>), 7.28 – 7.21 (1H, m, ArC<u>H</u>), 7.18 – 7.12 (2H, m, 2 × ArC<u>H</u>), 6.55 (1H, br s, O<u>H</u>), 5.60 (1H, q, *J* = 7.0 Hz, C**5**-<u>H</u>), 3.15 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 2.89 (3H, s, Ms C<u>H_3</u>), 2.49 – 2.42 (2H, m, C**3**-<u>H_2</u>), 1.69 (2H, tt, *J* = 7.0, 7.0 Hz, C**2**-<u>H_2</u>), 1.57 (3H, dt, *J* = 7.0, 1.0 Hz, C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 140.5 (Ar<u>C</u>), 140.2 (C**4**), 128.5 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 126.5 (Ar<u>C</u>H), 122.4 (C**5**), 51.7 (C**1**), 35.8 (C**3**), 30.8 (Ms <u>C</u>H_3), 25.2 (C**2**), 14.7 (C**6**). HRMS: (ESI^+) Calculated for $C_{13}H_{19}NNaO_3S$: 292.0978. Found $[M+Na]^+$: 292.0974. *Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 6.60 (1H, br s), 5.79 (1H, q, *J* = 7.0 Hz), 2.63 (2H, t, *J* = 7.5 Hz), 1.81 (3H, d, *J* = 7.0 Hz).

(*Z*)-*N*-(4-Phenylhex-4-en-1-yl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (160a)



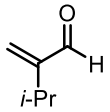
General procedure C: The preceding compound (563 mg, 2.09 mmol) was employed. FCC (eluent: 5:1 hexane:EtOAc) afforded **160a** (786 mg, 81 %, 12:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless crystalline solid. *Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*solid*) 2979 (m), 2933 (m), 1787 (s), 1655 (m), 1504 (s), 1324 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 7.33 – 7.27 (2H, m, 2 × ArC<u>H</u>), 7.23 – 7.18 (1H, m, ArC<u>H</u>), 7.16 – 7.12 (2H, m, 2 × ArC<u>H</u>), 5.63 (1H, qt, *J* = 7.0, 1.0 Hz, C**5**-<u>H</u>), 3.43 (2H, br s, C**1**-<u>H_2</u>), 3.01 (3H, s, Ms C<u>H_3</u>), 2.55 (2H, br t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 1.64 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>), 1.57 (3H, dt, *J* = 7.0, 1.0 Hz, C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 140.0 (Ar<u>C</u>), 139.6 (C**4**), 128.5 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 126.5 (Ar<u>C</u>H), 123.0 (C**5**), 51.7 (C**1**), 35.6 (C**3**), 34.3 (Ms <u>C</u>H_3), 25.0 (C**2**), 14.7 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.7 – -135.8 (2F, m), -145.3 (1F, tt, *J* = 20.5, 5.5 Hz), -158.8 – -159.0 (2F, m). HRMS: (ESI^+) Calculated for $C_{20}H_{18}F_5NNaO_4S$: 486.0769. Found $[M+Na]^+$: 486.0761. *Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 5.81 (1H, q, *J* = 6.5 Hz), 2.75 (2H, t, *J* = 7.5 Hz), 1.84 (3H, d, *J* = 7.0 Hz).

1-Mesyl-2-phenyl-2-vinylpyrrolidine (161a)



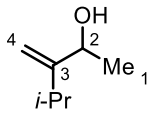
General procedure D: Conditions: 3.75 mol% $Pd_2(dba)_3$; 18.8 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 15 hours. Substrate **160a** (64.9 mg, 0.140 mmol) was employed. FCC (gradient elution: 14:1 – 9:1 – 7:1 – 4:1 – 3:1 – 2:1 hexane:EtOAc) afforded **161a** (4.1 mg, 12 %) as a pale-orange oil. ν_{max} / cm^{-1}: (*film*) 2926 (m), 1447 (m), 1334 (s), 1149 (s). δ_H (500 MHz, $CDCl_3$) 7.50 – 7.45 (2H, m, 2 × ArC<u>H</u>), 7.38 – 7.34 (2H, m, 2 × ArC<u>H</u>), 7.30 – 7.26 (1H, m, ArC<u>H</u>), 6.50 (1H, dd, *J* = 17.5, 10.5 Hz, C**5**-<u>H</u>), 5.49 (1H, dd, *J* = 17.5, 0.5 Hz, C**6**-<u>H</u>'), 5.47 (1H, dd, *J* = 10.5, 0.5 Hz, C**6**-<u>H</u>), 3.77 (1H, ddd, *J* = 8.5, 8.0, 4.5 Hz, C**1**-<u>H</u>), 3.57 (1H, ddd, *J* = 9.5, 8.0, 7.5 Hz, C**1**-<u>H</u>'), 2.81 (3H, s, Ms C<u>H</u>$_3$), 2.44 (1H, ddd, *J* = 12.5, 9.5, 6.5 Hz, C**3**-<u>H</u>), 2.27 – 2.18 (1H, m, C**3**-<u>H</u>'), 1.99 – 1.89 (1H, m, C**2**-<u>H</u>), 1.89 – 1.79 (1H, m, C**2**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 143.6 (Ar<u>C</u>), 139.4 (C**5**), 128.1 (ArC<u>H</u>), 127.2 (ArC<u>H</u>), 126.8 (ArC<u>H</u>), 116.5 (C**6**), 73.0 (C**4**), 49.9 (C**1**), 41.0 (C**3**), 39.3 (Ms <u>C</u>H_3), 22.0 (C**2**). HRMS: (ESI^+) Calculated for $C_{13}H_{17}NNaO_2S$: 274.0872. Found $[M+Na]^+$: 274.0880.

3-Methyl-2-methylenebutanal



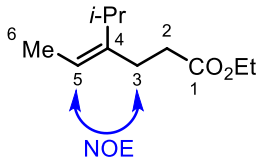
This compound was prepared according to a literature procedure.[227] A solution of 3-methylbutanal (16.1 mL, 150 mmol), aqueous formaldehyde (12.3 M, 12.2 mL, 150 mmol), pyrrolidine (1.25 mL, 15.0 mmol) and propionic acid (1.12 mL, 15.0 mmol) in *i*-PrOH (15 mL) was heated to 45 °C for 5 hours. The reaction mixture was cooled to room temperature before addition of saturated aqueous $NaHCO_3$ (100 mL) and extraction with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Distillation failed to separate completely the desired enal from *i*-PrOH. FCC (eluent: 14:1 pentane:Et_2O) afforded the title compound (4.00 g, 27 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 9.52 (1H, s), 6.23 (1H, d, *J* = 1.0 Hz), 5.94 (1H, s), 2.79 (1H, hept d, *J* = 7.0, 1.0 Hz), 1.07 (6H, d, *J* = 7.0 Hz). δ_C (101 MHz, $CDCl_3$) 194.6, 156.4, 132.1, 26.1, 21.3. *The spectroscopic properties were consistent with the data available in the literature*.[227]

4-Methyl-3-methylenepentan-2-ol (158b)



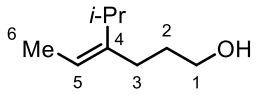
To a solution of MeLi (1.6 M in Et_2O, 16.0 mL, 25.6 mmol) in anhydrous Et_2O (40 mL) at 0 °C was added a solution of the preceding aldehyde (3.00 g, 30.6 mmol) in anhydrous Et_2O (10 mL). The reaction mixture was stirred at 0 °C for 1 hour before addition of water (5 mL) and saturated aqueous NH_4Cl (40 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford **158b** (2.86 g, 82 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3345 (br s), 2962 (s), 1647 (m), 1460 (m), 1098 (s). δ_H (400 MHz, $CDCl_3$) 5.05 (1H, dd, *J* = 1.0, 1.0 Hz, C**4**-H), 4.86 (1H, d, *J* = 1.0 Hz, C**4**-H'), 4.28 (1H, q, *J* = 6.5 Hz, C**2**-H), 2.30 (1H, qqd, *J* = 7.0, 7.0, 1.0 Hz, CH$(CH_3)_2$), 1.58 (1H, br s, OH), 1.29 (3H, d, *J* = 6.5 Hz, C**1**-H_3), 1.08 (3H, d, *J* = 7.0 Hz, CHC$H_3(CH_3)$'), 1.05 (3H, d, *J* = 7.0 Hz, $CHCH_3$(CH_3)'). δ_C (101 MHz, $CDCl_3$) 160.4 (C**3**), 105.8 (C**4**), 70.0 (C**2**), 30.2 (CH$(CH_3)_2$), 23.1 ($CHCH_3$(CH_3)'), 22.8 (C**1**), 22.6 ($CHCH_3(CH_3)$'). HRMS: (ESI^+) Calculated for $C_7H_{14}NaO$: 137.0937. Found $[M+Na]^+$: 137.0934.

Ethyl (*Z*)-4-isopropylhex-4-enoate



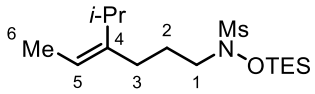
General procedure L: Allylic alcohol **158b** (2.28 g, 20.0 mmol) was employed. The reaction time was 13 hours. FCC (eluent: 19:1 hexane:Et_2O) afforded the title compound (2.60 g, 71 %, 11:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless oil. *The major product was assigned as the (Z)-isomer based on the observed NOE correlation between the C**3** and the C**5** protons. Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*film*) 2962 (s), 2872 (s), 1736 (s), 1155 (s). δ_H (400 MHz, $CDCl_3$) 5.09 (1H, q, *J* = 7.0 Hz, C**5**-H), 4.12 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 2.85 (1H, hept, *J* = 7.0 Hz, CH$(CH_3)_2$), 2.44 – 2.37 (2H, m, C**2**-H_2), 2.28 – 2.22 (2H, m, C**3**-H_2), 1.59 (3H, dt, *J* = 7.0, 1.5 Hz, C**6**-H_3), 1.25 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.98 (6H, d, *J* = 7.0 Hz, CH(C$H_3)_2$). δ_C (101 MHz, $CDCl_3$) 173.7 (C**1**), 143.4 (C**4**), 116.9 (C**5**), 60.2 (OCH_2CH_3), 33.8 (C**2**), 28.4 (CH$(CH_3)_2$), 26.0 (C**3**), 20.8 (CH(C$H_3)_2$), 14.2 (OCH_2CH_3), 12.7 (C**6**). HRMS: (ESI^+) Calculated for $C_{11}H_{20}NaO_2$: 207.1356. Found $[M+Na]^+$: 207.1353. *Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 5.27 (1H, q, *J* = 7.0 Hz), 2.35 – 2.32 (4H, m).

(*Z*)-4-Isopropylhex-4-en-1-ol (159b)



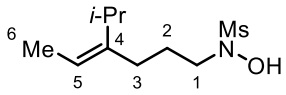
General procedure I: The preceding ester (1.20 g, 6.51 mmol) was employed, using anhydrous Et_2O as the solvent and 0.8 eq. $LiAlH_4$ (1.0 M in Et_2O). Alcohol **159b** (922 mg, 100 %, 11:1 mixture of (*Z*)- and (*E*)-isomers) was isolated as a colourless oil. *Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*film*) 3327 (br s), 2959 (s), 1465 (m), 1056 (s). δ_H (400 MHz, $CDCl_3$) 5.14 (1H, q, *J* = 7.0 Hz, C**5**-H), 3.64 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.84 (1H, hept, *J* = 7.0 Hz, CH$(CH_3)_2$), 2.01 – 1.94 (2H, m, C**3**-H_2), 1.66 (2H, tt, *J* = 7.5, 6.5 Hz, C**2**-H_2), 1.59 (3H, dt, *J* = 7.0, 1.5 Hz, C**6**-H_3), 0.97 (6H, d, *J* = 7.0 Hz, CH$(CH_3)_2$). δ_C (101 MHz, $CDCl_3$) 144.4 (C**4**), 117.0 (C**5**), 63.1 (C**1**), 32.1 (C**2**), 28.5 (CH$(CH_3)_2$), 27.5 (C**3**), 20.9 (CH$(CH_3)_2$), 12.7 (C**6**). HRMS: (EI^+) Calculated for $C_9H_{18}O$: 142.1358. Found $[M]^+$: 142.1358. *Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 5.24 (1H, q, *J* = 7.0 Hz), 2.12 – 2.05 (2H, m).

(*Z*)-*N*-(4-Isopropylhex-4-en-1-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide



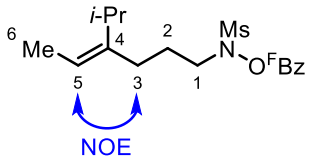
General procedure E: MsNHOTES (*vide supra*, 676 mg, 3.00 mmol) was employed with alcohol **159b** (1.1 eq.). The reaction time was 14 hours. FCC (eluent: 1:4 hexane:PhMe) afforded the title compound (942 mg, 90 %, 12:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless oil. *Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*film*) 2958 (s), 2877 (s), 1460 (m), 1350 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 5.12 (1H, qt, *J* = 7.0, 1.5 Hz, C**5**-H), 3.22 – 3.16 (2H, m, C**1**-H_2), 2.91 – 2.78 (1H, m, CH$(CH_3)_2$), 2.85 (3H, s, Ms CH_3), 2.00 – 1.92 (2H, m, C**3**-H_2), 1.78 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2), 1.60 (3H, dt, *J* = 7.0, 1.5 Hz, C**6**-H_3), 1.01 – 0.95 (15H, m, CH$(CH_3)_2$ and Si$(CH_2CH_3)_3$), 0.77 (6H, q, *J* = 8.0 Hz, Si$(CH_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 143.5 (C**4**), 117.2 (C**5**), 55.6 (C**1**), 30.3 (Ms CH_3), 2 × 28.4 (C**3** and CH$(CH_3)_2$), 26.2 (C**2**), 20.8 (CH$(CH_3)_2$), 12.8 (C**6**), 6.7 (Si$(CH_2CH_3)_3$), 4.8 (Si$(CH_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{16}H_{36}NO_3SSi$: 350.2180. Found $[M+H]^+$: 350.2171. *Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 5.27 (1H, q, *J* = 6.5 Hz), 2.08 – 2.02 (2H, m).

(*Z*)-*N*-(4-Isopropylhex-4-en-1-yl)-*N*-hydroxymethanesulfonamide



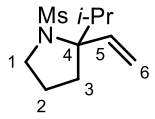
General procedure F: The preceding compound (932 mg, 2.67 mmol) was employed. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (621 mg, 99 %, 13:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless oil. *Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*film*) 3380 (br s), 2960 (s), 2870 (m), 1464 (m), 1334 (s), 1160 (s). δ_H (400 MHz, $CDCl_3$) 6.66 (1H, br s, O<u>H</u>), 5.15 (1H, qt, *J* = 7.0, 1.5 Hz, C**5**-<u>H</u>), 3.22 – 3.16 (2H, m, C**1**-<u>H_2</u>), 2.92 (3H, s, Ms C<u>H_3</u>), 2.84 (1H, hept, *J* = 7.0 Hz, C<u>H</u>$(CH_3)_2$), 2.05 – 1.97 (2H, m, C**3**-<u>H_2</u>), 1.86 – 1.77 (2H, m, C**2**-<u>H_2</u>), 1.60 (3H, dt, *J* = 7.0, 1.5 Hz, C**6**-<u>H_3</u>), 0.98 (6H, d, *J* = 7.0 Hz, CH(C<u>H_3</u>)$_2$). δ_C (101 MHz, $CDCl_3$) 143.7 (C**4**), 117.4 (C**5**), 52.3 (C**1**), 30.8 (Ms <u>C</u>H_3), 28.5 (<u>C</u>H$(CH_3)_2$), 28.1 (C**3**), 26.2 (C**2**), 20.9 (CH(<u>C</u>H_3)$_2$), 12.8 (C**6**). HRMS: (ESI^+) Calculated for $C_{10}H_{21}NNaO_3S$: 258.1134. Found $[M+Na]^+$: 258.1134. *Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 5.26 (1H, q, *J* = 7.0 Hz), 2.15 – 2.08 (2H, m).

(*Z*)-*N*-(4-Isopropylhex-4-en-1-yl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (160b)



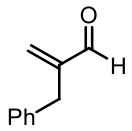
General procedure C: The preceding compound (564 mg, 2.40 mmol) was employed. FCC (gradient elution: 9:1 – 5:1 hexane:EtOAc) afforded **160b** (975 mg, 95 %, 11:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless crystalline solid. *The major product was assigned as the (Z)-isomer based on the observed NOE correlation between the C**3** and the C**5** protons. Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*solid*) 3032 (m), 2962 (m), 2873 (m), 1790 (s), 1657 (m), 1505 (s), 1358 (s), 1167 (s). δ_H (400 MHz, $CDCl_3$) 5.14 (1H, q, *J* = 7.0 Hz, C**5**-<u>H</u>), 3.53 – 3.42 (2H, m, C**1**-<u>H_2</u>), 3.04 (3H, s, Ms C<u>H_3</u>), 2.84 (1H, hept, *J* = 7.0 Hz, C<u>H</u>$(CH_3)_2$), 2.09 (2H, br t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 1.79 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>), 1.60 (3H, dt, *J* = 7.0, 1.5 Hz, C**6**-<u>H_3</u>), 0.97 (6H, d, *J* = 7.0 Hz, CH(C<u>H_3</u>)$_2$). δ_C (101 MHz, $CDCl_3$) 143.2 (C**4**), 117.9 (C**5**), 52.4 (C**1**), 34.3 (Ms <u>C</u>H_3), 28.4 (<u>C</u>H$(CH_3)_2$), 28.0 (C**3**), 26.2 (C**2**), 20.8 (CH(<u>C</u>H_3)$_2$), 12.7 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.1 (2F, m), -145.4 (1F, tt, *J* = 21.0, 5.5 Hz), -158.8 – -159.0 (2F, m). HRMS: (ESI^+) Calculated for $C_{17}H_{20}F_5NNaO_4S$: 452.0925. Found $[M+Na]^+$: 452.0947. *Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 5.29 (1H, q, *J* = 7.0 Hz), 2.23 – 2.16 (2H, m).

2-Isopropyl-1-mesyl-2-vinylpyrrolidine (161b)



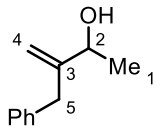
General procedure D: Conditions: 3.75 mol% $Pd_2(dba)_3$; 18.8 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; *n*-BuCN (0.1 M); 110 °C; 14 hours. Substrate **160b** (60.1 mg, 0.140 mmol) was employed. FCC (gradient elution: 5:1 – 4:1 – 3:1 hexane:EtOAc) afforded **161b** (9.5 mg, 31 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2963 (m), 1468 (m), 1331 (s), 1141 (s). δ_H (400 MHz, $CDCl_3$) 6.12 (1H, dd, *J* = 17.5, 11.0 Hz, C**5**-H), 5.28 – 5.22 (2H, m, C**6**-H_2), 3.45 – 3.33 (2H, m, C**1**-H_2), 2.82 (3H, s, Ms CH_3), 2.55 (1H, qq, *J* = 7.0, 6.5 Hz, $CH(CH_3)_2$), 1.97 – 1.90 (2H, m, C**3**-H_2), 1.89 – 1.79 (2H, m, C**2**-H_2), 1.02 (3H, d, *J* = 6.5 Hz, $CH(CH_3)(CH_3)$'), 0.80 (3H, d, *J* = 7.0 Hz, $CH(CH_3)(CH_3)$'). δ_C (101 MHz, $CDCl_3$) 139.6 (C**5**), 114.9 (C**6**), 73.8 (C**4**), 50.1 (C**1**), 38.7 (Ms CH_3), 34.2 ($CH(CH_3)_2$), 29.3 (C**3**), 23.3 (C**2**), 18.3 ($CH(CH_3)(CH_3)$'), 16.7 ($CH(CH_3)(CH_3)$'). HRMS: (ESI^+) Calculated for $C_{10}H_{19}NNaO_2S$: 240.1029. Found $[M+Na]^+$: 240.1022.

2-Benzylacrylaldehyde



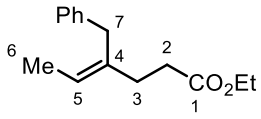
This compound was prepared according to a literature procedure.[228] A solution of 3-phenylpropanal (3.93 mL, 29.8 mL), aqueous formaldehyde (12.3 M, 2.42 mL, 29.8 mmol), pyrrolidine (0.25 mL, 2.98 mmol) and 4-(dimethylamino)benzoic acid (492 mg, 2.98 mmol) in anhydrous CH_2Cl_2 (30 mL) was heated at reflux for 1.5 hours. The reaction mixture was cooled to room temperature before addition of saturated aqueous $NaHCO_3$ (20 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 12:1 hexane:EtOAc) afforded the title compound (3.16 g, 73 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3063 (m), 3029 (m), 2918 (br m), 2827 (br m), 1688 (s), 1496 (s), 1454 (s). δ_H (400 MHz, $CDCl_3$) 9.61 (1H, s), 7.34 – 7.28 (2H, m), 7.25 – 7.22 (1H, m), 7.22 – 7.16 (2H, m), 6.11 (1H, td, *J* = 1.5, 1.0 Hz), 6.07 (1H, dt, *J* = 1.0, 1.0 Hz), 3.58 – 3.57 (2H, m). δ_C (101 MHz, $CDCl_3$) 194.1, 149.8, 138.2, 135.3, 129.3, 128.7, 126.6, 34.3. *The spectroscopic properties were consistent with the data available in the literature.*[228]

3-Benzylbut-3-en-2-ol (158c)



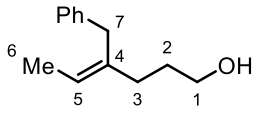
To a solution of MeLi (1.6 M in Et_2O, 16.0 mL, 25.6 mmol) in anhydrous THF (20 mL) at 0 °C was added a solution of the preceding aldehyde (2.50 g, 17.1 mmol) in anhydrous THF (15 mL) dropwise. The reaction mixture was stirred at room temperature for 1 hour before addition of saturated aqueous NH_4Cl (50 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford **158c** (2.67 g, 96 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3349 (br s), 3027 (m), 2975 (m), 1647 (m), 1453 (m), 1070 (s). δ_H (400 MHz, $CDCl_3$) 7.33 – 7.27 (2H, m, 2 × ArC<u>H</u>), 7.24 – 7.19 (3H, m, 3 × ArC<u>H</u>), 5.16 – 5.14 (1H, m, C**4**-<u>H</u>), 4.75 (1H, d, *J* = 1.5 Hz, C**4**-<u>H</u>'), 4.26 (1H, q, *J* = 6.5 Hz, C**2**-<u>H</u>), 3.48 (1H, d, *J* = 15.5 Hz, C**5**-<u>H</u>), 3.36 (1H, d, *J* = 15.5 Hz, C**5**-<u>H</u>'), 1.52 (1H, br s, O<u>H</u>), 1.31 (3H, d, *J* = 6.5 Hz, C**1**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 152.7 (C**3**), 139.5 (Ar<u>C</u>), 129.3 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 111.0 (C**4**), 70.3 (C**2**), 39.1 (C**5**), 22.4 (C**1**). HRMS: (ESI^+) Calculated for $C_{11}H_{14}NaO$: 185.0939. Found $[M+Na]^+$: 185.0941.

Ethyl (*Z*)-4-benzylhex-4-enoate



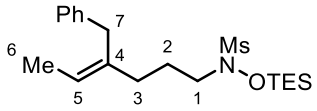
<u>General procedure L:</u> Allylic alcohol **158c** (2.43 g, 15.0 mmol) was employed. The reaction time was 15 hours. FCC (eluent: 29:1 hexane:EtOAc) afforded the title compound (2.98 g, 86 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3027 (m), 2980 (m), 1732 (s), 1602 (m), 1494 (m), 1452 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 7.30 – 7.24 (2H, m, 2 × ArC<u>H</u>), 7.21 – 7.13 (3H, m, 3 × ArC<u>H</u>), 5.45 (1H, q, *J* = 6.5 Hz, C**5**-<u>H</u>), 4.09 (2H, q, *J* = 7.0 Hz, OC<u>H_2</u>CH_3), 3.42 (2H, s, C**7**-<u>H_2</u>), 2.39 – 2.31 (2H, m, C**2**-<u>H_2</u>), 2.29 – 2.23 (2H, m, C**3**-<u>H_2</u>), 1.72 (3H, d, *J* = 6.5 Hz, C**6**-<u>H_3</u>), 1.22 (3H, t, *J* = 7.0 Hz, OCH_2C<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 173.5 (C**1**), 140.0 (Ar<u>C</u>), 137.0 (C**4**), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 121.1 (C**5**), 60.3 (O<u>C</u>H_2CH_3), 35.8 (C**7**), 33.2 (C**2**), 31.9 (C**3**), 14.4 (OCH_2<u>C</u>H_3), 13.8 (C**6**). HRMS: (ESI^+) Calculated for $C_{15}H_{20}NaO_2$: 255.1356. Found $[M+Na]^+$: 255.1354.

(*Z*)-4-Benzylhex-en-1-ol (159c)



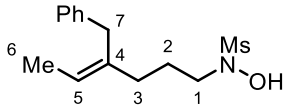
General procedure I: The preceding ester (8.03 g, 34.6 mmol) was employed, using anhydrous THF as the solvent and 0.8 eq. $LiAlH_4$ (1.0 M in THF). FCC (eluent: 4:1 hexane:EtOAc) afforded **159c** (6.12 g, 93 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3330 (br s), 3026 (m), 2929 (m), 1601 (m), 1452 (m), 1055 (s). δ_H (400 MHz, $CDCl_3$) 7.33 – 7.24 (2H, m, 2 × ArC<u>H</u>), 7.22 – 7.12 (3H, m, 3 × ArC<u>H</u>), 5.46 (1H, q, *J* = 7.0 Hz, C**5**-<u>H</u>), 3.58 (2H, t, *J* = 6.5 Hz, C**1**-<u>H_2</u>), 3.42 (2H, s, C**7**-<u>H_2</u>), 2.02 – 1.97 (2H, m, C**3**-<u>H_2</u>), 1.73 (3H, d, *J* = 7.0 Hz, C**6**-<u>H_3</u>), 1.68 – 1.60 (2H, m, C**2**-<u>H_2</u>), 1.35 (1H, br s, O<u>H</u>). δ_C (101 MHz, $CDCl_3$) 140.3 (Ar<u>C</u>), 138.2 (C**4**), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 120.7 (C**5**), 62.9 (C**1**), 35.7 (C**7**), 32.9 (C**3**), 31.0 (C**2**), 13.8 (C**6**). HRMS: (ESI^+) Calculated for $C_{13}H_{18}NaO$: 213.1250. Found $[M+Na]^+$: 213.1248.

(*Z*)-*N*-(4-Benzylhex-4-en-1-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide



General procedure E: MsNHOTES (*vide supra*, 676 mg, 3.00 mmol) was employed with alcohol **159c** (1.1 eq.). The reaction time was 16 hours. FCC (eluent: PhMe) afforded the title compound (1.10 g, 92 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2955 (m), 2877 (m), 1494 (m), 1454 (m), 1350 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 7.30 – 7.24 (2H, m, 2 × ArC<u>H</u>), 7.21 – 7.13 (3H, m, 3 × ArC<u>H</u>), 5.45 (1H, q, *J* = 7.0 Hz, C**5**-<u>H</u>), 3.40 (2H, s, C**7**-<u>H_2</u>), 3.12 – 3.06 (2H, m, C**1**-<u>H_2</u>), 2.81 (3H, s, Ms C<u>H_3</u>), 2.00 – 1.94 (2H, m, C**3**-<u>H_2</u>), 1.77 – 1.67 (5H, m, C**2**-<u>H_2</u> and C**6**-<u>H_3</u>), 0.97 (9H, t, *J* = 8.0 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.73 (6H, q, *J* = 8.0 Hz, $Si(C\underline{H}_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 139.9 (Ar<u>C</u>), 137.1 (C**4**), 2 × 128.4 (2 × Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 121.2 (C**5**), 55.3 (C**1**), 35.6 (C**7**), 33.9 (C**3**), 30.4 (Ms <u>C</u>H_3), 25.3 (C**2**), 13.7 (C**6**), 6.7 ($Si(CH_2\underline{C}H_3)_3$), 4.8 ($Si(\underline{C}H_2CH_3)_3$). HRMS: ($ESI^+$) Calculated for $C_{20}H_{35}NNaO_3SSi$: 420.1999. Found $[M+Na]^+$: 420.2013.

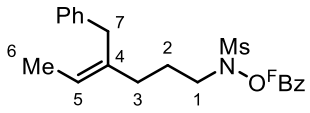
(*Z*)-*N*-(4-Benzylhex-4-en-1-yl)-*N*-hydroxymethanesulfonamide



General procedure F: The preceding compound (1.07 g, 2.69 mmol) was employed. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (732 mg, 96 %) as a colourless crystalline solid.

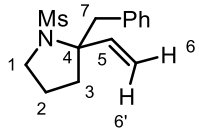
ν_{max} / cm^{-1}: (*solid*) 3304 (br s), 2931 (m), 1493 (m), 1447 (m), 1324 (s), 1152 (s). δ_H (400 MHz, $CDCl_3$) 7.30 – 7.25 (2H, m, 2 × ArC<u>H</u>), 7.21 – 7.14 (3H, m, 3 × ArC<u>H</u>), 6.41 (1H, br s, O<u>H</u>), 5.46 (1H, qt, *J* = 7.0, 1.5 Hz, C**5**-<u>H</u>), 3.41 (2H, s, C**7**-<u>H_2</u>), 3.12 – 3.06 (2H, m, C**1**-<u>H_2</u>), 2.87 (3H, s, Ms C<u>H_3</u>), 2.05 – 1.98 (2H, m, C**3**-<u>H_2</u>), 1.79 – 1.70 (5H, m, C**2**-<u>H_2</u> and C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 140.0 (Ar<u>C</u>), 137.2 (C**4**), 128.5 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 121.2 (C**5**), 51.9 (C**1**), 35.6 (C**7**), 33.3 (C**3**), 30.9 (Ms <u>C</u>H_3), 25.1 (C**2**), 13.7 (C**6**). HRMS: (ESI^+) Calculated for $C_{14}H_{21}NNaO_3S$: 306.1134. Found $[M+Na]^+$: 306.1133.

(*Z*)-*N*-4-Benzylhex-en-1-yl-*N*-(pentafluorobenzoyloxy)methanesulfonamide (160c)



<u>General procedure C:</u> The preceding compound (704 mg, 2.50 mmol) was employed. FCC (gradient elution: 7:1 – 6:1 hexane:EtOAc) afforded **160c** (1.11 g, 93 %) as a colourless crystalline solid. m.p. 82-83 °C (Et_2O:hexane, *needles*). ν_{max} / cm^{-1}: (*solid*) 3028 (m), 2934 (m), 1780 (s), 1655 (m), 1597 (m), 1499 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 7.27 – 7.22 (2H, m, 2 × ArC<u>H</u>), 7.18 – 7.13 (3H, m, 3 × ArC<u>H</u>), 5.48 (1H, q, *J* = 7.0 Hz, C**5**-<u>H</u>), 3.43 – 3.33 (4H, m, C**1**-<u>H_2</u> and C**7**-<u>H_2</u>), 3.00 (3H, s, Ms C<u>H_3</u>), 2.10 (2H, t, *J* = 7.0 Hz, C**3**-<u>H_2</u>), 1.77 – 1.68 (5H, m, C**2**-<u>H_2</u> and C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 140.0 (Ar<u>C</u>), 136.8 (C**4**), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 122.0 (C**5**), 52.2 (C**1**), 35.7 (C**7**), 34.5 (Ms <u>C</u>H_3), 33.5 (C**3**), 25.2 (C**2**), 13.9 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.7 – -135.9 (2F, m), -145.3 (1F, tt, *J* = 20.5, 5.5 Hz), -158.7 – -158.9 (2F, m). HRMS: (ESI^+) Calculated for $C_{21}H_{20}F_5NNaO_4S$: 500.0925. Found $[M+Na]^+$: 500.0919.

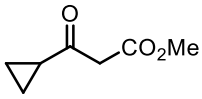
2-Benzyl-1-mesyl-2-vinylpyrrolidine (161c)



<u>General procedure D:</u> Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; *n*-BuCN (0.1 M); 95 °C; 16 hours. Substrate **160c** (66.8 mg, 0.140 mmol) was employed. FCC (gradient elution: 5:1 – 3:1 hexane:EtOAc) afforded **161c** (19.9 mg, 54 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3027 (m), 2978 (m), 1602 (m), 1496 (m), 1318 (s), 1144 (s). δ_H (500 MHz, $CDCl_3$) 7.32 – 7.27 (4H, m, 4 × ArC<u>H</u>), 7.25 – 7.21 (1H, m, ArC<u>H</u>), 6.24 (1H, dd, *J* = 17.5, 11.0 Hz, C**5**-<u>H</u>), 5.27 (1H, dd, *J* = 11.0, 0.5 Hz, C**6**-<u>H</u>), 5.26 (1H, dd, *J* = 17.5, 0.5 Hz, C**6**-<u>H</u>'), 3.40 (1H, d, *J* = 13.5 Hz, C**7**-<u>H</u>), 3.35 – 3.26 (2H, m, C**1**-<u>H_2</u>), 3.06 (1H, d, *J* = 13.5 Hz, C**7**-<u>H</u>'), 2.90 (3H, s, Ms C<u>H_3</u>), 2.05 (1H, ddd, *J* = 13.0, 7.0,

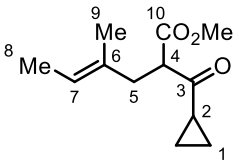
6.5 Hz, C**3**-H), 1.93 (1H, ddd, *J* = 13.0, 7.0, 7.0 Hz, C**3**-H'), 1.71 – 1.62 (1H, m, C**2**-H), 1.34 (1H, dddd, *J* = 14.0, 12.5, 7.0, 7.0 Hz, C**2**-H'). δ_C (126 MHz, $CDCl_3$) 140.3 (C**5**), 137.3 (ArC), 131.1 (ArCH), 128.2 (ArCH), 126.7 (ArCH), 115.5 (C**6**), 70.1 (C**4**), 49.9 (C**1**), 44.7 (C**7**), 39.4 (Ms CH_3), 36.4 (C**3**), 22.4 (C**2**). HRMS: (ESI$^+$) Calculated for $C_{14}H_{19}NNaO_2S$: 288.1029. Found $[M+Na]^+$: 288.1017.

Methyl 3-cyclopropyl-3-oxopropanoate



This compound was prepared according to a literature procedure.[101] To a suspension of NaH (60 % in mineral oil, 2.88 g, 72.0 mmol) and dimethyl carbonate (5.05 mL, 60.0 mmol) in anhydrous THF (50 mL) was added cyclopropyl methyl ketone (5.94 mL, 60.0 mmol) over around 20 minutes. The reaction mixture was heated at reflux for 2 hours before being cooled to room temperature, concentrated *in vacuo*, dissolved in 0.5 M aqueous HCl (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (4.88 g, 57 %) as an orange oil. ν_{max} / cm^{-1}: (*film*) 3013 (m), 2956 (s), 1743 (s), 1699 (s), 1385 (s), 1074 (s). δ_H (400 MHz, $CDCl_3$) 3.74 (3H, s), 3.58 (2H, s), 2.03 (1H, tt, *J* = 8.0, 4.5 Hz), 1.13 – 1.09 (2H, m), 0.99 – 0.93 (2H, m). δ_C (101 MHz, $CDCl_3$) 202.7, 167.7, 52.3, 49.7, 20.8, 11.8. *The spectroscopic properties were consistent with the data available in the literature.*[101]

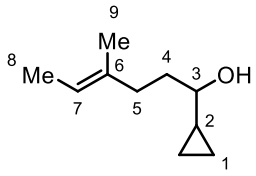
Methyl (*E*)-2-(cyclopropanecarbonyl)-4-methylhex-4-enoate



To a suspension of NaH (60 % in mineral oil, 720 mg, 18.0 mmol) in anhydrous DMF (35 mL) was added the preceding compound (2.31 mL, 18.0 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 hour before addition of (*E*)-1-bromo-2-methylbut-2-ene (*vide supra*, 1.42 mL, 12.0 mmol) and then heated at 80 °C for 13 hours. The reaction mixture was cooled to room temperature before addition of saturated aqueous NH_4Cl (50 mL) and extraction with Et_2O (3 × 50 mL). The organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 19:1 – 14:1 hexane:EtOAc) afforded the title compound (2.01 g, 80 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2954 (m), 1740 (s), 1701 (s), 1436 (s), 1382 (s), 1160 (s). δ_H (400 MHz, $CDCl_3$) 5.26 (1H, qq, *J* = 7.0, 1.5 Hz, C**7**-H), 3.77 (1H, t, *J* = 7.5 Hz, C**4**-H), 3.72 (3H, s, OCH_3), 2.61 – 2.54 (2H, m, C**5**-H_2), 2.05 (1H, tt, *J* = 8.0, 4.5 Hz, C**2**-H), 1.61 (3H, br s, C**9**-H_3), 1.55 (3H, dq, *J* = 7.0, 1.0 Hz, C**8**-H_3), 1.08 –

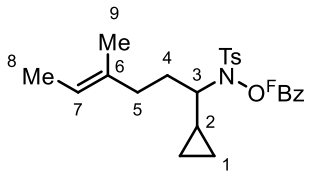
1.03 (2H, m, 2 × C**1**-H), 0.95 – 0.88 (2H, m, 2 × C**1**-H'). δ_C (101 MHz, $CDCl_3$) 205.1 (C**3**), 170.2 (C**10**), 131.6 (C**6**), 121.4 (C**7**), 58.6 (C**4**), 52.3 (OCH_3), 38.0 (C**5**), 19.7 (C**2**), 15.5 (C**9**), 13.5 (C**8**), 11.8 (C**1**), 11.6 (C**1**'). HRMS: (ESI^+) Calculated for $C_{12}H_{18}NaO_3$: 233.1148. Found $[M+Na]^+$: 233.1151.

(*E*)-1-Cyclopropyl-4-methylhex-4-en-1-ol (162)



To a solution of the preceding compound (1.94 g, 9.23 mmol) in MeOH (25 mL) and water (15 mL) was added KOH (2.07 g, 36.9 mmol). The reaction mixture was stirred at room temperature for 40 minutes before addition of 2.0 M aqueous HCl (25 mL) and extraction with Et_2O (3 × 70 mL). The organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was dissolved in EtOAc (30 mL) and heated at reflux for 3 hours before being concentrated *in vacuo*. The resulting oil was dissolved in MeOH (20 mL) and cooled to 0 °C before addition of $NaBH_4$ (349 mg, 9.23 mmol). The reaction mixture was stirred at 0 °C for 2 hours before addition of 1.0 M aqueous HCl (20 mL) and extraction with Et_2O (3 × 40 mL). The organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 5:2 pentane:Et_2O) afforded **162** (688 mg, 48 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3360 (br s), 3080 (m), 2918 (m), 1432 (m), 1019 (s). δ_H (400 MHz, $CDCl_3$) 5.24 (1H, qq, *J* = 6.5, 1.0 Hz, C**7**-H), 2.84 (1H, ddd, *J* = 8.5, 7.5, 5.0 Hz, C**3**-H), 2.20 – 2.00 (2H, m, C**5**-H_2), 1.73 – 1.65 (2H, m, C**4**-H_2), 1.63 (1H, br s, OH), 1.60 (3H, br s, C**9**-H_3), 1.56 (3H, dq, *J* = 6.5, 1.0 Hz, C**8**-H_3), 0.89 (1H, dtt, *J* = 8.5, 8.5, 5.0 Hz, C**2**-H), 0.55 – 0.44 (2H, m, 2 × C**1**-H), 0.29 – 0.16 (2H, m, 2 × C**1**-H'). δ_C (101 MHz, $CDCl_3$) 135.7 (C**6**), 118.5 (C**7**), 76.6 (C**3**), 35.8 (C**4**), 35.3 (C**5**), 17.9 (C**9**), 15.6 (C**8**), 13.3 (C**2**), 2.7 (C**1**), 2.5 (C**1**'). HRMS: (ESI^+) Calculated for $C_{10}H_{18}NaO$: 177.1250. Found $[M+Na]^+$: 177.1246.

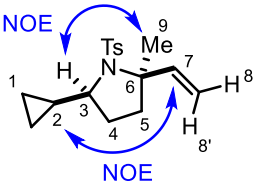
(*E*)-*N*-(1-Cyclopropyl-4-methylhex-4-en-1-yl)-*N*-(pentafluorobenzoyloxy)-4-toluenesulfonamide (163)



General procedure K: Alcohol **162** (540 mg, 3.50 mmol) was employed with $TsNHO^FBz$ (*vide supra*). The reaction time was 15 hours. FCC (gradient elution: 49:1 – 24:1 hexane:EtOAc) afforded **163** (1.09 g, 60 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2926 (m), 1786 (s), 1653 (m), 1598 (m), 1497 (s),

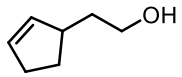
1164 (s). δ_H (500 MHz, $CDCl_3$) 7.86 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.35 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.25 (1H, br s, C**7**-<u>H</u>), 3.50 – 3.28 (1H, m, C**3**-<u>H</u>), 2.47 (3H, s, Ts C<u>H</u>$_3$), 2.39 – 2.13 (2H, m, C**5**-<u>H</u>$_2$), 1.85 – 1.69 (2H, m, C**4**-<u>H</u>$_2$), 1.63 – 1.54 (6H, m, C**8**-<u>H</u>$_3$ and C**9**-<u>H</u>$_3$), 1.18 – 0.95 (1H, m, C**2**-<u>H</u>), 0.72 – 0.55 (3H, m, C**1**-<u>H</u> and C**1**'-<u>H</u>$_2$), 0.33 (1H, br s, C**1**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 156.2 (<u>C</u>=O), 145.4 (Ar<u>C</u>), 134.7 (C**6**), 133.4 (Ar<u>C</u>), 129.6 (Ar<u>C</u>H), 129.3 (Ar<u>C</u>H), 119.3 (C**7**), 67.4 (C**3**), 36.3 (C**5**), 31.2 (C**4**), 21.7 (Ts <u>C</u>H$_3$), 15.5 (C**9**), 13.4 (C**8**), 12.8 (C**2**), 5.7 (C**1**'), 4.8 (C**1**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.3 – -136.5 (2F, m), -146.4 (1F, tt, *J* = 21.0, 5.0 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{24}H_{24}F_5NNaO_4S$: 540.1238. Found $[M+Na]^+$: 540.1232.

(2*R,5*S**)-5-Cyclopropyl-2-methyl-1-tosyl-2-vinylpyrrolidine (164)**



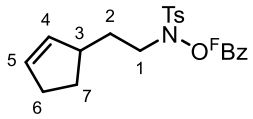
<u>General procedure D:</u> Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; PhMe (0.1 M); 140 °C; 14 hours. Substrate **163** (79.6 mg, 0.154 mmol, *added as a solution in PhMe*) was employed. FCC (*two times*, first eluent: 19:1 hexane:EtOAc; second eluent: 99:1 PhMe:EtOAc) afforded **164** (30.1 mg, 64 %, 20:1 mixture of diastereomers) as a pale-yellow oil. m.p. 94-97 °C (CH_2Cl_2:petrol, *tabular*). *The relative stereochemistry of the major diastereomer was assigned based on the observed NOE correlation between the C**2** and the C**7** protons, as well as the correlation between the C**3** and the C**9** protons. Spectroscopic data for the major diastereomer:* ν_{max} / cm^{-1}: (*film*) 3084 (m), 2972 (m), 1599 (m), 1496 (m), 1327 (s), 1151 (s). δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.22 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 6.10 (1H, dd, *J* = 17.5, 10.5 Hz, C**7**-<u>H</u>), 5.23 (1H, dd, *J* = 17.5, 1.0 Hz, C**8**-<u>H</u>'), 5.08 (1H, dd, *J* = 10.5, 1.0 Hz, C**8**-<u>H</u>), 3.33 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, C**3**-<u>H</u>), 2.39 (3H, s, Ts C<u>H</u>$_3$), 2.15 (1H, ddd, *J* = 12.5, 12.0, 6.5 Hz, C**5**-H), 2.01 (1H, dddd, *J* = 12.5, 12.5, 8.5, 7.0 Hz, C**4**-<u>H</u>), 1.77 – 1.66 (2H, m, C**4**-<u>H</u>' and C**5**-<u>H</u>'), 1.55 (3H, s, C**9**-<u>H</u>$_3$), 0.90 (1H, ddddd, *J* = 8.5, 8.5, 8.5, 5.0, 5.0 Hz, C**2**-<u>H</u>), 0.53 – 0.46 (1H, m, C**1**-<u>H</u>), 0.44 – 0.32 (2H, m, C**1**-<u>H</u>' and C**1**'-<u>H</u>), 0.09 – 0.00 (1H, m, C**1**'-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 145.1 (C**7**), 142.4 (Ar<u>C</u>), 140.7 (Ar<u>C</u>), 129.1 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 112.9 (C**8**), 69.0 (C**6**), 66.7 (C**3**), 40.1 (C**5**), 29.6 (C**4**), 24.4 (C**9**), 21.6 (Ts <u>C</u>H$_3$), 17.1 (C**2**), 7.2 (C**1**), 2.8 (C**1**'). HRMS: (ESI^+) Calculated for $C_{17}H_{23}NNaO_2S$: 328.1342. Found $[M+Na]^+$: 328.1353. *Characteristic signals for the minor diastereomer:* δ_H (500 MHz, $CDCl_3$) 5.91 (1H, dd, *J* = 17.5, 11.0 Hz), 5.17 (1H, dd, *J* = 17.5, 1.0 Hz), 5.02 (1H, dd, *J* = 11.0, 1.0 Hz).

2-(Cyclopent-2-en-1-yl)ethan-1-ol



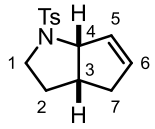
General procedure I: 2-Cyclopentene-1-acetic acid (**165**) (806 mg, 6.81 mmol) was employed, using anhydrous Et_2O as the solvent and 2.0 eq. $LiAlH_4$ (1.0 M in Et_2O). The title compound (713 mg, 93 %) was isolated as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3327 (br s), 3051 (m), 2928 (s), 2851 (s), 1614 (m), 1057 (s). δ_H (400 MHz, $CDCl_3$) 5.74 (1H, ddt, *J* = 6.0, 2.0, 2.0 Hz), 5.69 (1H, ddt, *J* = 6.0, 2.0, 2.0 Hz), 3.76 – 3.64 (2H, m), 2.82 – 2.72 (1H, m), 2.41 – 2.22 (2H, m), 2.12 – 2.02 (1H, m), 1.70 (1H, ddt, *J* = 13.5, 6.5, 6.5 Hz), 1.62 – 1.52 (1H, m), 1.49 – 1.36 (2H, m). δ_C (101 MHz, $CDCl_3$) 134.6, 130.7, 61.8, 42.1, 38.9, 31.9, 29.8. *The spectroscopic properties were consistent with the data available in the literature.*[229]

***N*-2-(Cyclopent-2-en-1-yl)ethyl-*N*-(pentafluorobenzoyloxy)-4-toluenesulfonamide (166)**



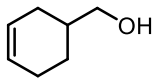
General procedure K: The preceding alcohol (135 mg, 1.20 mmol) was employed with $TsNHO^FBz$ (*vide supra*). The reaction time was 20 hours. FCC (gradient elution: 4:1 – 1:0 hexane:PhMe) afforded **166** (506 mg, 89 %) as a colourless crystalline solid. m.p. 95-96 °C (Et_2O:hexane, *needles*). ν_{max} / cm^{-1}: (*solid*) 3056 (m), 2936 (m), 1792 (s), 1655 (m), 1595 (m), 1504 (s), 1167 (s). δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.38 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.74 (1H, ddt, *J* = 5.5, 2.0, 2.0 Hz, C**5**-<u>H</u>), 5.61 (1H, ddt, *J* = 5.5, 2.0, 2.0 Hz, C**4**-<u>H</u>), 3.26 (2H, br s, C**1**-<u>H_2</u>), 2.88 – 2.76 (1H, m, C**3**-<u>H</u>), 2.47 (3H, s, Ts C<u>H_3</u>), 2.39 – 2.21 (2H, m, C**6**-<u>H_2</u>), 2.06 (1H, dtd, *J* = 13.0, 8.5, 5.0 Hz, C**7**-<u>H</u>), 1.70 (1H, ddt, *J* = 13.5, 7.0, 7.0 Hz, C**2**-<u>H</u>), 1.63 – 1.55 (1H, m, C**2**-<u>H</u>'), 1.37 (1H, ddt, *J* = 13.0, 9.0, 6.5 Hz, C**7**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 146.0 (Ar<u>C</u>), 133.7 (C**4**), 131.6 (C**5**), 130.2 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 51.5 (C**1**), 42.7 (C**3**), 32.8 (C**2**), 32.0 (C**6**), 29.7 (C**7**), 21.9 (Ts <u>C</u>H_3). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.0 – -136.1 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.0 Hz), -159.0 – -159.2 (2F, m). HRMS: (ESI^+) Calculated for $C_{21}H_{18}F_5NNaO_4S$: 498.0769. Found $[M+Na]^+$: 498.0786.

(3a*R,6a*S**)-1-Tosyl-1,2,3,3a,4,6a-hexahydrocyclopenta[*b*]pyrrole (20)**



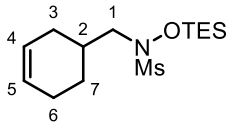
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 12.5 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; *n*-BuCN (0.1 M); 110 °C; 17 hours. Substrate **166** (66.5 mg, 0.140 mmol) was employed. FCC (gradient elution: 9:1 – 4:1 hexane:EtOAc) afforded **20** (33.7 mg, 91 %) as a colourless crystalline solid. m.p. 66-67 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*solid*) 2865 (m), 1596 (m), 1339 (s), 1155 (s). δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.31 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.83 – 5.79 (1H, m, C**5**-<u>H</u>), 5.76 – 5.71 (1H, m, C**6**-<u>H</u>), 4.55 (1H, dd, *J* = 8.0, 2.0 Hz, C**4**-<u>H</u>), 3.36 (1H, ddd, *J* = 9.5, 7.0, 4.5 Hz, C**1**-<u>H</u>), 3.10 – 3.02 (1H, m, C**1**-<u>H</u>'), 2.61 (1H, ddddd, *J* = 8.0, 8.0, 8.0, 7.5, 2.0 Hz, C**3**-<u>H</u>), 2.53 – 2.44 (1H, m, C**7**-<u>H</u>), 2.42 (3H, s, Ts C<u>H</u>$_3$), 2.10 (1H, ddd, *J* = 17.0, 2.0, 2.0 Hz, C**7**-<u>H</u>'), 1.88 – 1.79 (1H, m, C**2**-<u>H</u>), 1.51 (1H, dddd, *J* = 12.5, 7.5, 7.5, 7.0 Hz, C**2**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 143.4 (Ar<u>C</u>), 134.9 (Ar<u>C</u>), 132.0 (C**6**), 131.4 (C**5**), 129.7 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 70.2 (C**4**), 48.4 (C**1**), 40.0 (C**3**), 38.1 (C**7**), 32.5 (C**2**), 21.6 (Ts <u>C</u>H$_3$). HRMS: (ESI^+) Calculated for $C_{14}H_{17}NNaO_2S$: 286.0872. Found $[M+Na]^+$: 286.0873.

Cyclohex-3-en-1-ylmethanol



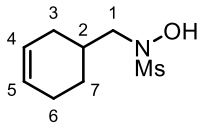
To a solution of 3-cyclohexene-1-carboxaldehyde (**113**) (11.0 g, 100 mmol) in MeOH (150 mL) at 0 °C was added $NaBH_4$ (1.51 g, 40.0 mmol). The reaction mixture was stirred at 0 °C for 1 hour before addition of water (100 mL) and extraction with Et_2O (3 × 150 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 3:1 – 1:1 pentane:Et_2O) afforded the title compound (8.00 g, 71 %) as a pale-yellow oil. δ_H (400 MHz, $CDCl_3$) 5.70 – 5.62 (2H, m), 3.56 – 3.46 (2H, m), 2.14 – 2.02 (3H, m), 1.86 – 1.67 (4H, m), 1.32 – 1.20 (1H, m). δ_C (101 MHz, $CDCl_3$) 127.2, 126.0, 67.9, 36.4, 28.2, 25.3, 24.7. *The spectroscopic properties were consistent with the data available in the literature.*[230]

***N*-(Cyclohex-3-en-1-ylmethyl)-*N*-((triethylsilyl)oxy)methanesulfonamide**



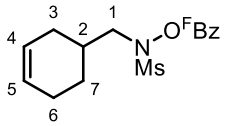
General procedure E: MsNHOTES (*vide supra*, 1.35 g, 6.00 mmol) was employed with the preceding alcohol (1.3 eq.). The reaction time was 16 hours. FCC (eluent: 10:1 hexane:EtOAc) afforded the title compound (1.88 g, 98 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2956 (m), 2913 (m), 2878 (m), 1351 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 5.74 – 5.62 (2H, m, C**4**-H and C**5**-H), 3.11 (1H, dd, *J* = 13.0, 7.5 Hz, C**1**-H), 3.04 (1H, dd, *J* = 13.0, 6.5 Hz, C**1**-H'), 2.85 (3H, s, Ms CH_3), 2.22 – 2.14 (1H, m, C**3**-H), 2.11 – 2.03 (2H, m, C**6**-H_2), 2.03 – 1.95 (1H, m, C**2**-H), 1.94 – 1.85 (1H, m, C**7**-H), 1.80 – 1.68 (1H, m, C**3**-H'), 1.37 – 1.26 (1H, m, C**7**-H'), 0.99 (9H, t, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.78 (6H, q, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 127.2 (C**5**), 125.4 (C**4**), 61.3 (C**1**), 31.4 (C**2**), 29.9 (Ms CH_3), 29.6 (C**3**), 26.4 (C**7**), 24.2 (C**6**), 6.7 ($Si(CH_2CH_3)_3$), 4.9 ($Si(CH_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{14}H_{29}NNaO_3SSi$: 342.1530. Found $[M+Na]^+$: 342.1533.

***N*-(Cyclohex-3-en-1-ylmethyl)-*N*-hydroxymethanesulfonamide**



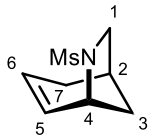
General procedure F: The preceding compound (1.78 g, 5.57 mmol) was employed. FCC (gradient elution: 4:1 – 3:1 hexane:EtOAc) afforded the title compound (1.03 g, 90 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3332 (br s), 3027 (m), 2919 (m), 2840 (m), 1438 (s), 1328 (s), 1147 (s). δ_H (400 MHz, $CDCl_3$) 6.86 (1H, br s, OH), 5.73 – 5.62 (2H, m, C**4**-H and C**5**-H), 3.13 (1H, dd, *J* = 12.5, 7.0 Hz, C**1**-H), 3.07 (1H, dd, *J* = 12.5, 7.0 Hz, C**1**-H'), 2.93 (3H, s, Ms CH_3), 2.25 – 2.16 (1H, m, C**3**-H), 2.15 – 2.01 (3H, m, C**2**-H and C**6**-H_2), 1.91 – 1.73 (2H, m, C**3**-H' and C**7**-H), 1.36 (1H, dddd, *J* = 13.0, 10.5, 8.5, 7.0 Hz, C**7**-H'). δ_C (101 MHz, $CDCl_3$) 127.1 (C**5**), 125.4 (C**4**), 57.5 (C**1**), 31.5 (C**2**), 30.7 (Ms CH_3), 29.2 (C**3**), 26.0 (C**7**), 24.2 (C**6**). HRMS: (ESI^+) Calculated for $C_8H_{15}NNaO_3S$: 228.0665. Found $[M+Na]^+$: 228.0660.

***N*-(Cyclohex-3-en-1-ylmethyl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (114b)**

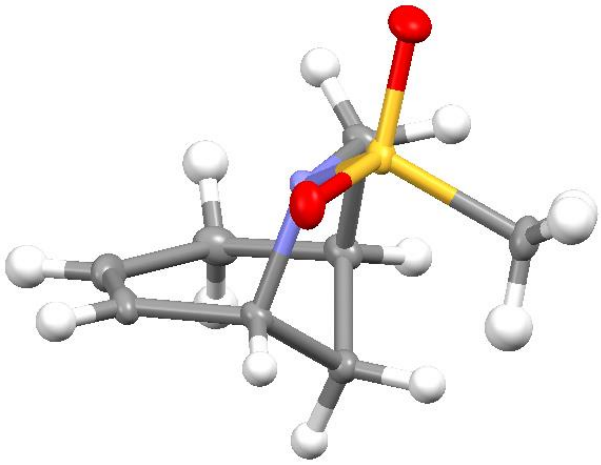


General procedure C: The preceding compound (1.00 g, 4.87 mmol) was employed. FCC (gradient elution: 4:1 – 3:1 hexane:EtOAc) afforded **114b** (1.85 g, 95 %) as a colourless crystalline solid. m.p. 109-110 °C (CH_2Cl_2:hexane, *needles*). ν_{max} / cm^{-1}: (*solid*) 3029 (m), 2917 (m), 1782 (s), 1653 (s), 1505 (s), 1353 (s), 1162 (s). δ_H (400 MHz, $CDCl_3$) 5.73 – 5.62 (2H, m, C**4**-H and C**5**-H), 3.45 – 3.28 (2H, m, C**1**-H_2), 3.04 (3H, s, Ms CH_3), 2.36 – 2.24 (1H, m, C**3**-H), 2.16 – 2.02 (2H, m, C**6**-H_2), 2.02 – 1.79 (3H, m, C**2**-H, C**3**-H' and C**7**-H), 1.50 – 1.38 (1H, m, C**7**-H'). δ_C (101 MHz, $CDCl_3$) 156.4 (C=O), 127.3 (C**5**), 125.2 (C**4**), 57.7 (C**1**), 34.2 (Ms CH_3), 31.6 (C**2**), 29.2 (C**3**), 25.9 (C**7**), 24.1 (C**6**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity*. δ_F (377 MHz, $CDCl_3$) -135.7 – -135.9 (2F, m), -145.3 (1F, tt, *J* = 21.0, 5.5 Hz), -158.8 – -159.0 (2F, m). HRMS: (ESI^+) Calculated for $C_{15}H_{14}F_5NNaO_4S$: 422.0456. Found $[M+Na]^+$: 422.0455.

6-Mesyl-6-azabicyclo[3.2.1]oct-3-ene (115b)

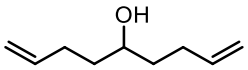


General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 1:1 *n*-BuCN:THF (0.1 M); 110 °C, 17 hours. Substrate **114b** (55.9 mg, 0.140 mmol) was employed. FCC (eluent: 9:1 PhMe:EtOAc) afforded **115b** (19.9 mg, 76 %) as a colourless crystalline solid. m.p. 61-62 °C (Et_2O:hexane, *cubes*). ν_{max} / cm^{-1}: (*solid*) 3034 (m), 2967 (m), 1312 (s), 1133 (s). δ_H (400 MHz, $CDCl_3$) 6.06 (1H, dddd, *J* = 10.5, 5.5, 2.0, 1.0 Hz, C**5**-H), 5.73 – 5.68 (1H, m, C**6**-H), 4.17 (1H, ddd, *J* = 5.5, 5.0, 1.0 Hz, C**4**-H), 3.64 – 3.59 (1H, m, C**1**-H), 3.09 (1H, d, *J* = 10.0 Hz, C**1**-H'), 2.81 (3H, s, Ms CH_3), 2.72 – 2.67 (1H, m, C**2**-H), 2.55 – 2.47 (1H, m, C**7**-H), 2.16 – 2.09 (1H, m, C**7**-H'), 1.95 (1H, ddd, *J* = 11.0, 5.0, 5.0 Hz, C**3**-H), 1.83 (1H, ddd, *J* = 11.0, 1.0, 1.0 Hz, C**3**-H'). δ_C (101 MHz, $CDCl_3$) 129.8 (C**5**), 128.5 (C**6**), 54.1 (C**1**), 54.0 (C**4**), 37.7 (Ms CH_3), 35.6 (C**7**), 34.7 (C**3**), 33.4 (C**2**). HRMS: (ESI^+) Calculated for $C_8H_{13}NNaO_2S$: 210.0559. Found $[M+Na]^+$: 210.0561.



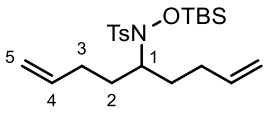
*ORTEP view of **115b**.*

Non-1,8-dien-5-ol (167)



This compound was prepared according to a literature procedure.[231] To a suspension of magnesium turnings (1.22 g, 50.0 mmol), activated with a few crystals of iodine, in anhydrous THF (50 mL) was added 4-bromobut-1-ene (5.10 mL, 50.0 mmol) dropwise at such a rate as to maintain a gentle reflux. The reaction mixture was stirred for 1 hour before dropwise addition of methyl formate (1.54 mL, 25.0 mmol) and then stirred for a further 4 hours at room temperature before addition of saturated aqueous NH_4Cl (30 mL) and extraction with EtOAc (3 × 70 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 20:1 – 2:1 hexane:EtOAc) afforded alcohol **167** (2.47 g, 70 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3344 (br s), 3078 (m), 2931 (m), 1641 (m), 1449 (m). δ_H (400 MHz, $CDCl_3$) 5.83 (2H, ddt, *J* = 17.0, 10.0, 6.5 Hz), 5.04 (2H, ddt, *J* = 17.0, 1.5, 1.5 Hz), 4.96 (2H, ddt, *J* = 10.0, 1.5, 1.5 Hz), 3.65 (1H, tt, *J* = 7.5, 4.5 Hz), 2.25 – 2.06 (4H, m), 1.91 (1H, s), 1.62 – 1.46 (4H, m). δ_C (101 MHz, $CDCl_3$) 138.6, 114.8, 71.0, 36.5, 30.1. *The spectroscopic properties were consistent with the data available in the literature.*[231]

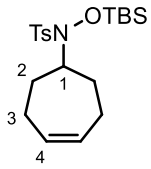
***N*-((*tert*-Butyldimethylsilyl)oxy)-*N*-(nona-1,8-dien-5-yl)-4-toluenesulfonamide**



General procedure E: TsNHOTBS (*vide supra*, 1.00 g, 3.33 mmol) was employed with alcohol **167** (1.5 eq.). The reaction time was 19 hours. FCC (eluent: 1:1 hexane:PhMe) afforded the title compound (1.40 g, 100 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2930 (m), 2859 (m), 1641 (m), 1598 (m), 1355 (s), 1170 (s). δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.31 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>),

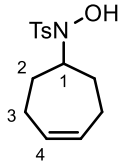
5.61 (2H, ddt, *J* = 18.5, 9.5, 7.0 Hz, 2 × C**4**-H), 4.94 – 4.91 (2H, m, 2 × C**5**-H), 4.92 – 4.86 (2H, m, 2 × C**5**-H'), 3.50 (1H, tt, *J* = 6.5, 6.5 Hz, C**1**-H), 2.43 (3H, s, Ts CH_3), 1.98 (4H, ddddd, *J* = 7.0, 4.0, 4.0, 1.0, 1.0 Hz, 2 × C**3**-H_2), 1.33 – 1.23 (2H, m, 2 × C**2**-H), 1.19 – 1.08 (2H, 2 × C**2**-H'), 0.94 (9H, s, $SiC(CH_3)_3$), 0.31 (6H, s, $Si(CH_3)_2$). δ_C (101 MHz, $CDCl_3$) 144.5 (ArC), 137.9 (C**4**), 133.5 (ArC), 129.5 (ArCH), 129.2 (ArCH), 115.0 (C**5**), 62.7 (C**1**), 31.2 (C**3**), 30.4 (C**2**), 26.3 ($SiC(CH_3)_3$), 21.7 (Ts CH_3), 18.9 ($SiC(CH_3)_3$), -4.0 ($Si(CH_3)_2$). HRMS: (ESI^+) Calculated for $C_{22}H_{38}NO_3SSi$: 424.2336. Found $[M+H]^+$: 424.2326.

***N*-((*tert*-Butyldimethylsilyl)oxy)-*N*-(cyclohept-4-en-1-yl)-4-toluenesulfonamide (91)**



To a reaction vessel charged with Grubbs-Hoveyda 2nd generation catalyst (18.2 mg, 29.0 μmol) was added a solution of the preceding compound (1.23 g, 2.90 mmol) in anhydrous CH_2Cl_2 (200 mL, argon sparged). The reaction mixture was heated at reflux for 4 hours before being cooled to room temperature, partially concentrated *in vacuo* and filtered through a plug of silica, eluting with CH_2Cl_2. The filtrate was concentrated *in vacuo* to afford **91** (1.07 g, 93 %) as a pale-green oil (the colouration was due to the presence of trace amounts of Ru-impurities). m.p. 92-93 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*film*) 3023 (m), 2932 (m), 2856 (m), 1596 (m), 1470 (m), 1446 (m), 1349 (s), 1163 (s). δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 7.31 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 5.71 – 5.67 (2H, m, 2 × C**4**-H), 3.67 (1H, tt, *J* = 11.0, 3.0 Hz, C**1**-H), 2.44 (3H, s, Ts CH_3), 2.12 – 2.02 (2H, m, 2 × C**3**-H), 1.86 – 1.76 (2H, m, 2 × C**3**-H'), 1.54 – 1.45 (2H, m, 2 × C**2**-H), 1.31 (2H, ddd, *J* = 13.5, 11.0, 2.0 Hz, 2 × C**2**-H'), 0.94 (9H, s, $SiC(CH_3)_3$), 0.30 (6H, s, $Si(CH_3)_2$). δ_C (101 MHz, $CDCl_3$) 144.4 (ArC), 133.7 (ArC), 131.6 (C**4**), 129.5 (ArCH), 129.2 (ArCH), 67.7 (C**1**), 31.4 (C**2**), 26.3 ($SiC(CH_3)_3$), 25.7 (C**3**), 21.8 (Ts CH_3), 18.8 ($SiC(CH_3)_3$), -4.0 ($Si(CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{20}H_{34}NO_3SSi$: 396.2023. Found $[M+H]^+$: 396.2026.

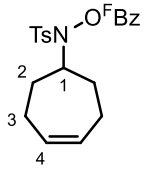
***N*-(Cyclohept-4-en-1-yl)-*N*-hydroxy-4-toluenesulfonamide**



General procedure B: Compound **91** (1.07 g, 2.71 mmol) was employed. FCC (gradient elution: 19:1 – 7:1 hexane:EtOAc) was required to separate deprotected product from unconsumed **91** (242 mg

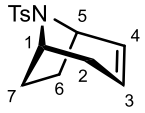
recovered, 23 %) and afforded the title compound (185 mg, 25 %) as a pale-yellow crystalline solid. *This compound was used in the following step with minimal delay due to concerns about its stability.* δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* = 8.5 Hz), 7.33 (2H, d, *J* = 8.5 Hz), 5.97 (1H, s), 5.70 (2H, dt, *J* = 4.5, 2.0 Hz), 3.90 (1H, tt, *J* = 10.0, 4.0 Hz), 2.45 (3H, s), 2.22 – 2.13 (2H, m), 2.01 – 1.90 (2H, m), 1.73 – 1.64 (2H, m), 1.63 – 1.55 (2H, m).

_N_-(Cyclohept-4-en-1-yl)-_N_-((pentafluorobenzoyl)oxy)-4-toluenesulfonamide (168a)



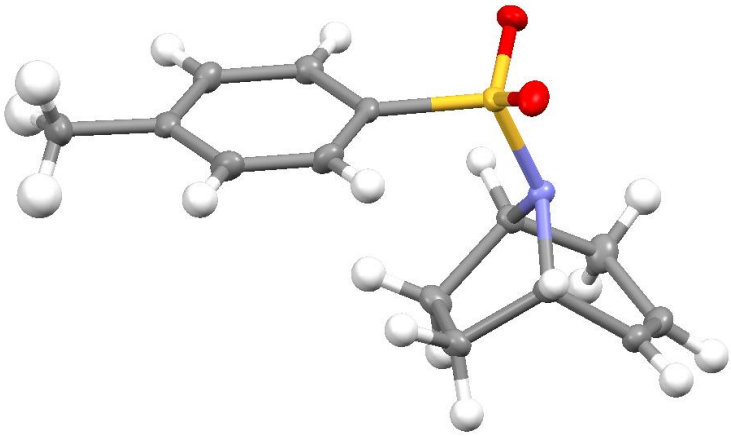
General procedure C: The preceding compound (169 mg, 0.601 mmol) was employed. FCC (eluent: 14:1 hexane:EtOAc) afforded **168a** (224 mg, 78 %) as a colourless crystalline solid. m.p. 110-111 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*film*) 2942 (m), 1785 (s), 1652 (m), 1597 (m), 1496 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.33 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.75 (2H, ddd, *J* = 4.5, 2.0, 2.0 Hz, 2 × C**4**-<u>H</u>), 4.19 (1H, tt, *J* = 10.5, 3.5 Hz, C**1**-<u>H</u>), 2.44 (3H, s, Ts C<u>H</u>$_3$), 2.19 (2H, br s, 2 × C**3**-<u>H</u>), 2.02 (4H, br s, 2 × C**2**-<u>H</u> and 2 × C**3**-<u>H</u>'), 1.56 – 1.46 (2H, m, 2 × C**2**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 156.6 (<u>C</u>=O), 145.6 (Ar<u>C</u>), 133.1 (Ar<u>C</u>), 131.5 (C**4**), 129.8 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 65.6 (C**1**), 2 × 24.9 (C**2** and C**3**), 21.7 (Ts <u>C</u>H$_3$). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -136.0 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.0 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{21}H_{19}F_5NO_4S$: 476.0949. Found $[M+H]^+$: 476.0928.

8-Tosyl-8-azabicyclo[3.2.1]oct-2-ene (169a)



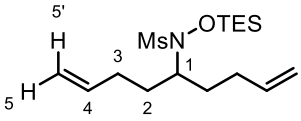
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 37 hours. Substrate **168a** (66.6 mg, 0.140 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **169a** (19.9 mg, 54 %) as a pale-yellow crystalline solid. m.p. 105-107 °C (CH_2Cl_2:petrol). ν_{max} / cm^{-1}: (*solid*) 2953 (m), 2883 (m), 1597 (m), 1450 (m), 1330 (s), 1149 (s). δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.25 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.89 (1H, dddd, *J* = 9.5, 4.0, 4.0, 2.0 Hz, C**4**-<u>H</u>), 5.44 – 5.38 (1H, m, C**3**-<u>H</u>), 4.32 – 4.27 (2H, m, C**1**-<u>H</u> and C**5**-<u>H</u>), 2.65 – 2.57 (1H, m, C**2**-<u>H</u>), 2.41 (3H, s, Ts C<u>H</u>$_3$), 1.94 (1H, dddd, *J* = 9.5, 8.0, 6.0, 5.5 Hz, C**7**-<u>H</u>), 1.88 – 1.80 (2H, m, C**2**-<u>H</u>' and C**6**-<u>H</u>), 1.69 (1H, dddd, *J* = 12.0, 11.5, 6.0, 6.0 Hz, C**6**-<u>H</u>'), 1.58

(1H, dddd, *J* = 12.0, 9.5, 3.5, 3.5 Hz, C**7**-H'). δ_C (101 MHz, $CDCl_3$) 143.3 (ArC), 137.6 (ArC), 131.4 (C**4**), 129.6 (ArCH), 127.6 (ArCH), 123.8 (C**3**), 55.9 (C**5**), 55.6 (C**1**), 36.1 (C**2**), 35.6 (C**6**), 30.2 (C**7**), 21.7 (Ts CH_3). HRMS: (ESI$^+$) Calculated for $C_{14}H_{17}NNaO_2S$: 286.0872. Found $[M+Na]^+$: 286.0863.



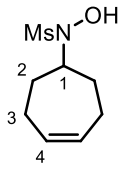
*ORTEP view of compound **169a**.*

***N*-(Nona-1,8-dien-5-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide**



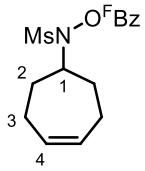
General procedure E: MsNHOTES (*vide supra*, 676 mg, 3.00 mmol) was employed with alcohol **167** (1.1 eq.). The reaction time was 16 hours. FCC (gradient elution: 1:4 – 0:1 hexane:PhMe) afforded the title compound (858 mg, 82 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3078 (m), 2956 (s), 2878 (s), 1641 (m), 1458 (m), 1415 (m), 1348 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 5.80 (2H, ddt, *J* = 17.0, 10.0, 6.5 Hz, 2 × C**4**-H), 5.05 (2H, ddt, *J* = 17.0, 2.0, 1.5 Hz, 2 × C**5**-H'), 5.00 (2H, ddt, *J* = 10.0, 2.0, 1.0 Hz, 2 × C**5**-H), 3.55 (1H, tt, *J* = 6.5, 6.5 Hz, C**1**-H), 2.89 (3H, s, Ms CH_3), 2.20 – 2.12 (4H, m, 2 × C**3**-H_2), 1.73 (2H, dddd, *J* = 13.5, 8.5, 7.0, 6.5 Hz, 2 × C**2**-H), 1.64 – 1.54 (2H, m, 2 × C**2**-H'), 0.99 (9H, t, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.78 (6H, q, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 137.5 (C**4**), 115.5 (C**5**), 62.4 (C**1**), 34.7 (Ms CH_3), 30.9 (C**3**), 30.7 (C**2**), 6.8 ($Si(CH_2CH_3)_3$), 5.0 ($Si(CH_2CH_3)_3$). HRMS: (ESI$^+$) Calculated for $C_{16}H_{33}NNaO_3SSi$: 370.1843. Found $[M+Na]^+$: 370.1840.

***N*-(Cyclohept-4-en-1-yl)-*N*-hydroxymethanesulfonamide**



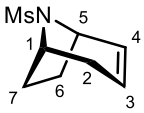
To a solution of the preceding compound (728 mg, 2.09 mmol) in anhydrous CH_2Cl_2 (80 mL, argon sparged) was added Grubbs-Hoveyda 2nd generation catalyst (13.1 mg, 20.9 μmol). The reaction mixture was stirred at room temperature for 3 days before addition of MeOH (40 mL) and 12 M aqueous HCl (8 mL). The reaction mixture was stirred for 1 hour before addition of saturated aqueous Na_2CO_3 (50 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (156 mg, 36 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3317 (br s), 3037 (m), 2948 (m), 2848 (m), 1446 (m), 1317 (s), 1152 (s). δ_H (400 MHz, $CDCl_3$) 6.10 (1H, s, O<u>H</u>), 5.83 – 5.74 (2H, m, 2 × C**4**-<u>H</u>), 3.92 (1H, tt, *J* = 10.0, 4.0 Hz C**1**-<u>H</u>), 3.02 (3H, s, Ms C<u>H</u>$_3$), 2.35 – 2.25 (2H, m, 2 × C**3**-<u>H</u>), 2.12 – 2.02 (2H, m, 2 × C**3**-<u>H</u>'), 2.02 – 1.93 (2H, m, 2 × C**2**-<u>H</u>), 1.84 – 1.73 (2H, m, 2 × C**2**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 131.6 (C**4**), 63.4 (C**1**), 36.7 (Ms <u>C</u>H$_3$), 30.4 (C**2**), 24.9 (C**3**). HRMS: (ESI$^+$) Calculated for $C_8H_{15}NNaO_3S$: 228.0665. Found $[M+Na]^+$: 228.0661.

***N*-(Cyclohept-4-en-1-yl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (168b)**

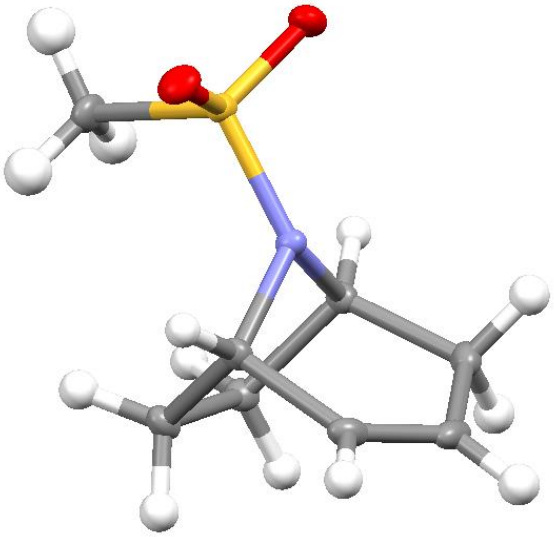


<u>General procedure C:</u> The preceding compound (147 mg, 0.716 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **168b** (261 mg, 91 %) as a colourless crystalline solid. m.p. 78-79 °C (CH_2Cl_2:hexane, *plates*). ν_{max} / cm^{-1}: (*solid*) 2939 (m), 2845 (m), 1768 (s), 1651 (s), 1591 (s), 1157 (s). δ_H (500 MHz, $CDCl_3$) 5.83 – 5.79 (2H, m, 2 × C**4**-<u>H</u>), 4.20 (1H, tt, *J* = 10.5, 3.5 Hz, C**1**-<u>H</u>), 3.09 (3H, s, Ms C<u>H</u>$_3$), 2.32 – 2.24 (2H, m, 2 × C**3**-<u>H</u>), 2.21 – 2.14 (2H, m, 2 × C**2**-<u>H</u>), 2.12 – 2.04 (2H, m, 2 × C**3**-<u>H</u>'), 1.69 – 1.59 (2H, m, 2 × C**2**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 157.3 (<u>C</u>=O), 131.6 (C**4**), 65.6 (C**1**), 39.7 (Ms <u>C</u>H$_3$), 31.0 (C**3**), 24.8 (C**2**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -136.0 (2F, m), -145.2 (1F, tt, *J* = 21.0, 5.5 Hz), -158.5 – -158.7 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{15}H_{14}F_5NNaO_4S$: 422.0456. Found $[M+Na]^+$: 422.0459.

8-Mesyl-8-azabicyclo[3.2.1]oct-2-ene (169b)

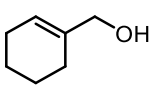


General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 16 hours. Substrate **168b** (55.9 mg, 0.140 mmol) was employed. FCC (gradient elution: 5:1 – 4:1 – 3:1 hexane:EtOAc) afforded **169b** (15.6 mg, 60 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3046 (m), 2958 (m), 2926 (m), 1458 (m), 1321 (s), 1137 (s). δ_H (400 MHz, $CDCl_3$) 5.99 (1H, dddd, *J* = 9.5, 5.5, 2.0, 2.0 Hz, C**4**-H), 5.62 – 5.56 (1H, m, C**3**-H), 4.33 – 4.25 (2H, m, C**1**-H and C**5**-H), 2.93 (3H, s, Ms CH_3), 2.77 – 2.67 (1H, m, C**2**-H), 2.31 – 2.20 (1H, m, C**7**-H), 2.13 – 1.90 (3H, m, C**2**-H' and C**6**-H_2), 1.77 – 1.67 (1H, m, C**7**-H'). δ_C (101 MHz, $CDCl_3$) 131.5 (C**4**), 124.1 (C**3**), 55.6 (C**1** or C**5**), 55.5 (C**1** or C**5**), 40.9 (Ms CH_3), 36.1 (C**6**), 35.6 (C**2**), 30.8 (C**7**). HRMS: (ESI^+) Calculated for $C_8H_{14}NO_2S$: 188.0740. Found $[M+H]^+$: 188.0744.



*ORTEP view of **169b**.*

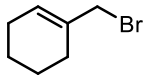
Cyclohex-1-en-1-ylmethanol



To a solution of methyl 1-cyclohexene-1-carboxylate (5.00 g, 35.6 mmol) in anhydrous CH_2Cl_2 (100 mL) at -78 °C was added DiBAl-H (1.0 M in CH_2Cl_2, 78.0 mL, 78.0 mmol). The reaction mixture was stirred at -78 °C for 2 hours before addition of MeOH (70 mL) and saturated aqueous Rochelle salt (70 mL). The mixture was warmed to room temperature and stirred for 15 hours before the resulting phases were separated, and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with brine (100 mL) followed by saturated aqueous Rochelle

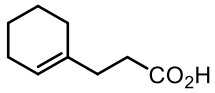
salt (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 8:1 – 4:1 hexane:EtOAc) afforded the title compound (3.98 g, 100 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3307 (br s), 2924 (s), 2857 (s), 2835 (s), 1437 (s), 1004 (s). δ_H (400 MHz, $CDCl_3$) 5.68 – 5.65 (1H, m), 3.96 (2H, s), 2.05 – 1.97 (4H, m), 1.68 – 1.54 (4H, m), 1.52 (1H, s). δ_C (101 MHz, $CDCl_3$) 137.7, 123.1, 67.8, 25.7, 25.0, 22.7, 22.6. *The spectroscopic properties were consistent with the data available in the literature.*[101]

1-(Bromomethyl)cyclohex-1-ene



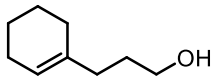
General procedure J: The preceding alcohol (3.50 g, 31.1 mmol) was employed to afford the title compound (4.26 g, 78 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.88 – 5.85 (1H, m), 3.93 (2H, s), 2.14 – 2.09 (2H, m), 2.06 – 1.99 (2H, m), 1.70 – 1.62 (2H, m), 1.60 – 1.52 (2H, m). δ_C (101 MHz, $CDCl_3$) 134.6, 128.1, 39.8, 26.3, 25.4, 22.4, 21.8. *m/z* (EI^+) 176 and 174 ($[M]^+$, 52 and 53 %), 95 ($[M\text{-}Br]^+$, 100 %), 84 (80 %). *The spectroscopic properties were consistent with the data available in the literature.*[101]

3-(Cyclohex-1-en-yl)propanoic acid



General procedure H: The preceding allylic bromide (1.36 mL, 10.0 mmol) was employed. The crude product was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$) 5.51 – 5.39 (1H, m), 2.48 – 2.43 (2H, m), 2.25 (2H, t, *J* = 8.0 Hz), 2.00 – 1.88 (4H, m), 1.65 – 1.58 (2H, m), 1.57 – 1.50 (2H, m). δ_C (101 MHz, $CDCl_3$) 178.5, 135.7, 121.7, 32.6, 32.3, 28.2, 25.1, 22.8, 22.3. *The spectroscopic properties were consistent with the data available in the literature.*[232]

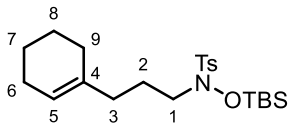
3-(Cyclohex-1-en-yl)propan-1-ol



General procedure I: The preceding crude carboxylic acid was employed, using anhydrous THF as the solvent and 1.5 eq. $LiAlH_4$ (1.0 M in Et_2O). FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (1.26 g, 90 % over two steps) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3326 (br s), 2923 (s), 2834 (s), 1438 (m), 1058 (s). δ_H (400 MHz, $CDCl_3$) 5.44 – 5.40 (1H, m), 3.61 (2H, t, *J* = 6.5 Hz), 2.02 – 1.88 (6H, m), 1.74 (1H, s), 1.69 – 1.48 (6H, m). δ_C (101 MHz, $CDCl_3$) 137.5, 121.4, 63.0, 34.5, 30.6,

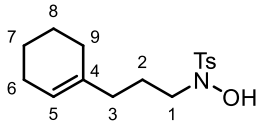
28.3, 25.3, 23.1, 22.6. *The spectroscopic properties were consistent with the data available in the literature.*[232]

***N*-(3-(Cyclohex-1-en-1-yl)propyl)-*N*-((*tert*-butyldimethylsilyl)oxy)-4-toluenesulfonamide**



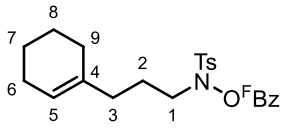
General procedure E: TsNHOTBS (*vide supra*, 1.00 g, 3.32 mmol) was employed with 3-(cyclohex-1-en-yl)propan-1-ol (*vide supra*, 1.3 eq.). The reaction time was 14 hours. FCC (eluent: 1:1 hexane:PhMe) afforded the title compound (1.40 g, 100 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2928 (m), 2857 (m), 1598 (m), 1462 (m), 1357 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.32 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.36 – 5.32 (1H, m, C**5**-<u>H</u>), 2.89 – 2.83 (2H, m, C**1**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 1.99 – 1.81 (6H, m, C**3**-<u>H_2</u>, C**6**-<u>H_2</u> and C**9**-<u>H_2</u>), 1.69 – 1.45 (6H, m, C**2**-<u>H_2</u>, C**7**-<u>H_2</u> and C**8**-<u>H_2</u>), 0.91 (9H, s, SiC(C<u>H_3</u>)$_3$), 0.28 (6H, s, Si(C<u>H_3</u>)$_2$). δ_C (101 MHz, $CDCl_3$) 144.4 (Ar<u>C</u>), 136.4 (C**4**), 130.0 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 121.6 (C**5**), 55.8 (C**1**), 35.2 (C**3**), 28.2 (C**9**), 26.0 (SiC(<u>C</u>H_3)$_3$), 25.2 (C**6**), 25.0 (C**2**), 22.9 (C**8**), 22.5 (C**7**), 21.6 (Ts <u>C</u>H_3), 18.2 (Si<u>C</u>(CH_3)$_3$), -4.2 (Si(<u>C</u>H_3)$_2$). HRMS: (ESI^+) Calculated for $C_{22}H_{37}NNaO_3SSi$: 446.2156. Found $[M+Na]^+$: 446.2149.

***N*-(3-(Cyclohex-1-en-1-yl)propyl)-*N*-hydroxy-4-toluenesulfonamide**



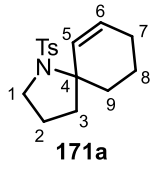
General procedure B: The preceding compound (1.34 g, 3.16 mmol) was employed. The title compound (796 mg, 81 %) was isolated as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3352 (br s), 2919 (s), 1598 (m), 1334 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.35 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 6.22 (1H, br s, O<u>H</u>), 5.41 – 5.36 (1H, m, C**5**-<u>H</u>), 2.88 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.00 – 1.92 (4H, m, C**3**-<u>H_2</u> and C**6**-<u>H_2</u>), 1.90 – 1.83 (2H, m, C**9**-<u>H_2</u>), 1.70 (2H, tt, *J* = 7.0, 7.0 Hz, C**2**-<u>H_2</u>), 1.62 – 1.48 (4H, m, C**7**-<u>H_2</u> and C**8**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 144.8 (Ar<u>C</u>), 136.6 (C**4**), 129.7 (Ar<u>C</u>H), 2 × 129.5 (Ar<u>C</u> and Ar<u>C</u>H), 121.6 (C**5**), 52.3 (C**1**), 34.8 (C**3**), 28.2 (C**9**), 25.2 (C**6**), 24.7 (C**2**), 22.9 (C**8**), 22.5 (C**7**), 21.6 (Ts <u>C</u>H_3). HRMS: (ESI^+) Calculated for $C_{16}H_{23}NNaO_3S$: 332.1291. Found $[M+Na]^+$: 332.1291.

***N*-(3-(Cyclohex-1-en-1-yl)propyl)-*N*-(pentafluorobenzoyloxy)-4-toluenesulfonamide (170a)**

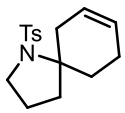


General procedure C: The preceding compound (785 mg, 2.54 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **170a** (1.18 g, 92 %) as a colourless crystalline solid. m.p. 71-72 °C (Et_2O:hexane, *needles*). ν_{max} / cm^{-1}: (*solid*) 2930 (m), 2833 (m), 1788 (s), 1651 (m), 1595 (m), 1502 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.37 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.39 – 5.35 (1H, m, C**5**-<u>H</u>), 3.18 (2H, br s, C**1**-<u>H_2</u>), 2.46 (3H, s, Ts C<u>H_3</u>), 2.03 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 1.98 – 1.91 (2H, m, C**6**-<u>H_2</u>), 1.88 – 1.81 (2H, m, C**9**-<u>H_2</u>), 1.66 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>), 1.61 – 1.45 (4H, m, C**7**-<u>H_2</u> and C**8**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 145.8 (Ar<u>C</u>), 136.0 (C**4**), 130.1 (Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 122.1 (C**5**), 52.3 (C**1**), 34.6 (C**3**), 28.0 (C**9**), 25.2 (C**6**), 24.6 (C**2**), 22.9 (C**8**), 22.4 (C**7**), 21.7 (Ts <u>C</u>H_3). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.0 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.0 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{23}H_{22}F_5NNaO_4S$: 526.1082. Found $[M+Na]^+$: 526.1071.

1-Tosyl-1-azaspiro[4.5]dec-6-ene (171a) and *iso*-171a



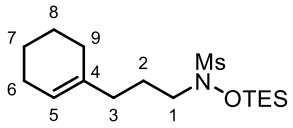
171a



***iso*-171a**

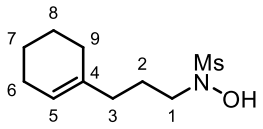
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 12.5 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 50 mol% Et_3N; *n*-BuCN (0.1 M); 110 °C; 15 hours. Substrate **170a** (70.5 mg, 0.140 mmol) was employed. FCC (gradient elution: 14:1 – 9:1 – 4:1 hexane:EtOAc) afforded **171a** and ***iso*-171a** (13.2 mg, 32 %, 5:1 mixture of **171a** and ***iso*-171a**) as a pale-yellow crystalline solid. *Spectroscopic data for **171a**:* ν_{max} / cm^{-1}: (*film*) 2926 (m), 1599 (m), 1447 (m), 1334 (s), 1154 (s). δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.25 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.77 – 5.69 (1H, m, C**6**-<u>H</u>), 5.41 – 5.36 (1H, m, C**5**-<u>H</u>), 3.55 (1H, ddd, *J* = 9.5, 6.0, 2.5 Hz, C**1**-<u>H</u>), 3.27 (1H, ddd, *J* = 9.5, 9.0, 7.0 Hz, C**1**-<u>H</u>'), 2.47 – 2.37 (4H, m, C**9**-<u>H</u> and Ts C<u>H_3</u>), 2.18 – 2.07 (1H, m, C**7**-<u>H</u>), 1.99 – 1.64 (7H, m, C**2**-<u>H_2</u>, C**3**-<u>H_2</u>, C**7**-<u>H</u>', C**8**-<u>H</u> and C**9**-<u>H</u>'), 1.56 – 1.44 (1H, m, C**8**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 142.5 (Ar<u>C</u>), 138.7 (Ar<u>C</u>), 131.8 (C**5**), 129.2 (Ar<u>C</u>H), 128.3 (C**6**), 127.4 (Ar<u>C</u>H), 67.3 (C**4**), 49.1 (C**1**), 40.8 (C**3**), 34.7 (C**9**), 24.3 (C**7**), 22.8 (C**2**), 21.7 (C**8**), 21.5 (Ts <u>C</u>H_3). HRMS: (ESI^+) Calculated for $C_{16}H_{21}NNaO_2S$: 314.1185. Found $[M+Na]^+$: 314.1188. *Characteristic signals for **iso-171a**:* δ_H (400 MHz, $CDCl_3$) 5.61 – 5.51 (2H, m), 3.02 – 2.94 (1H, m), 2.54 (1H, td, *J* = 12.0, 6.0 Hz).

***N*-(3-(Cyclohex-1-en-1-yl)propyl)-*N*-((triethylsilyl)oxy)methanesulfonamide**



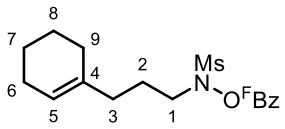
General procedure E: MsNHOTES (*vide supra*, 564 mg, 2.50 mmol) was employed with 3-(cyclohex-1-en-yl)propan-1-ol (*vide supra*, 1.1 eq.). The reaction time was 19 hours. FCC (gradient elution: 1:4 – 0:1 hexane:PhMe) afforded the title compound (776 mg, 89 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2935 (s), 2878 (s), 1351 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 5.43 – 5.40 (1H, m, C**5**-H), 3.18 – 3.13 (2H, m, C**1**-H_2), 2.86 (3H, s, Ms CH_3), 2.02 – 1.95 (4H, m, C**3**-H_2 and C**6**-H_2), 1.94 – 1.87 (2H, m, C**9**-H_2), 1.77 (2H, tt, *J* = 7.5, 7.5 Hz, C**2**-H_2), 1.66 – 1.59 (2H, m, C**8**-H_2), 1.59 – 1.51 (2H, m, C**7**-H_2), 1.00 (9H, t, *J* = 8.0 Hz, Si(CH_2CH_3)$_3$), 0.78 (6H, q, *J* = 8.0 Hz, Si(CH_2CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 136.2 (C**4**), 121.8 (C**5**), 55.4 (C**1**), 35.1 (C**3**), 30.4 (Ms CH_3), 28.2 (C**9**), 25.2 (C**6**), 25.0 (C**2**), 22.9 (C**8**), 22.5 (C**7**), 6.7 (Si(CH_2CH_3)$_3$), 4.8 (Si(CH_2CH_3)$_3$). HRMS: (ESI^+) Calculated for $C_{16}H_{33}NNaO_3SSi$: 370.1843. Found $[M+Na]^+$: 370.1859.

***N*-(3-(Cyclohex-1-en-1-yl)propyl)-*N*-hydroxymethanesulfonamide**



General procedure F: The preceding compound (712 mg, 2.05 mmol) was employed. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (475 mg, 99 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3352 (br s), 2926 (s), 2834 (m), 1436 (m), 1326 (s), 1146 (s). δ_H (400 MHz, $CDCl_3$) 6.58 (1H, br s, OH), 5.46 – 5.42 (1H, m, C**5**-H), 3.17 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 2.93 (3H, s, Ms CH_3), 2.06 – 1.96 (4H, m, C**3**-H_2 and C**6**-H_2), 1.95 – 1.89 (2H, m, C**9**-H_2), 1.81 (2H, tt, *J* = 7.0, 7.0 Hz, C**2**-H_2), 1.66 – 1.59 (2H, m, C**8**-H_2), 1.59 – 1.51 (2H, m, C**7**-H_2). δ_C (101 MHz, $CDCl_3$) 136.4 (C**4**), 121.8 (C**5**), 52.1 (C**1**), 34.7 (C**3**), 30.9 (Ms CH_3), 28.2 (C**9**), 25.2 (C**6**), 24.8 (C**2**), 22.9 (C**8**), 22.5 (C**7**). HRMS: (ESI^+) Calculated for $C_{10}H_{19}NNaO_3S$: 256.0978. Found $[M+Na]^+$: 256.0977.

***N*-3-(Cyclohex-1-en-yl)propyl-*N*-(pentafluorobenzoyloxy)methanesulfonamide (170b)**



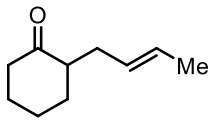
General procedure C: The preceding compound (442 mg, 1.89 mmol) was employed. FCC (eluent: 6:1 hexane:EtOAc) afforded **170b** (685 mg, 85 %) as a colourless crystalline solid. m.p. 98-99 °C

(Et_2O:hexane, *needles*). ν_{max} / cm^{-1}: (*solid*) 3023 (m), 2932 (m), 1779 (s), 1653 (m), 1501 (s), 1323 (s), 1162 (s). δ_H (400 MHz, $CDCl_3$) 5.46 – 5.41 (1H, m, C**5**-H), 3.45 (2H, br t, *J* = 7.0 Hz, C**1**-H_2), 3.04 (3H, s, Ms CH_3), 2.10 (2H, t, *J* = 7.5 Hz, C**3**-H_2), 2.01 – 1.94 (2H, m, C**6**-H_2), 1.92 – 1.87 (2H, m, C**9**-H_2), 1.78 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2), 1.65 – 1.58 (2H, m, C**7**-H_2), 1.58 – 1.50 (2H, m, C**8**-H_2). δ_C (101 MHz, $CDCl_3$) 136.0 (C**4**), 122.5 (C**5**), 52.3 (C**1**), 34.7 (C**3**), 34.6 (Ms CH_3), 28.2 (C**9**), 25.3 (C**6**), 24.9 (C**2**), 23.0 (C**8**), 22.6 (C**7**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -136.0 (2F, m), -145.3 (1F, tt, *J* = 21.0, 5.5 Hz), -158.7 – -158.9 (2F, m). HRMS: (ESI^+) Calculated for $C_{17}H_{18}F_5NNaO_4S$: 450.0769. Found $[M+Na]^+$: 450.0769.

1-Mesyl-1-azaspiro[4.5]dec-6-ene (171b)

General procedure D: Conditions: 3.75 mol% $Pd_2(dba)_3$; 18.8 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 16 hours. Substrate **170b** (59.8 mg, 0.140 mmol) was employed. FCC (eluent: 29:1 PhMe:acetone) afforded **171b** (12.8 mg, 42 %) as a yellow crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3023 (m), 2929 (m), 1447 (m), 1317 (s), 1143 (s). δ_H (400 MHz, $CDCl_3$) 5.82 (1H, ddd, *J* = 10.0, 5.5, 2.5 Hz, C**6**-H), 5.62 – 5.57 (1H, m, C**5**-H), 3.57 (1H, ddd, *J* = 10.5, 6.0, 3.5 Hz, C**1**-H), 3.42 – 3.34 (1H, m, C**1**-H'), 2.89 (3H, s, Ms CH_3), 2.35 (1H, ddd, *J* = 13.0, 13.0, 3.5 Hz, C**9**-H), 2.09 (1H, dddd, *J* = 16.5, 11.0, 5.5, 2.5 Hz, C**7**-H), 2.02 – 1.78 (6H, m, C**2**-H_2, C**3**-H_2, C**7**-H' and C**8**-H), 1.77 – 1.68 (1H, m, C**9**-H'), 1.58 – 1.47 (1H, m, C**8**-H'). δ_C (101 MHz, $CDCl_3$) 131.5 (C**5**), 129.2 (C**6**), 66.6 (C**4**), 49.2 (C**1**), 41.1 (C**3**), 40.0 (Ms CH_3), 34.4 (C**9**), 24.3 (C**7**), 22.6 (C**2**), 21.6 (C**8**). HRMS: (ESI^+) Calculated for $C_{10}H_{17}NNaO_2S$: 238.0872. Found $[M+Na]^+$: 238.0878.

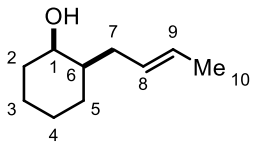
(*E*)-2-(But-2-en-1-yl)cyclohexan-1-one (173)



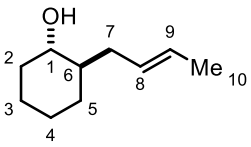
To a suspension of NaH (60 % in mineral oil, 1.05 g, 26.3 mmol) in anhydrous DMF (60 mL) was added ethyl 2-oxocyclohexanecarboxylate (**172**) (4.00 mL, 25.0 mmol). The reaction mixture was stirred at room temperature for 1 hour before addition of crotyl bromide (*vide supra*, 3.10 mL, 30.1 mmol.). The reaction mixture was stirred for 26 hours before addition of water (100 mL) and extraction with Et_2O (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was dissolved in MeOH (60 mL) and water (60 mL); KOH

(20.0 g, 356 mmol) was added to this solution, which was then heated at reflux for 2 hours. The reaction mixture was cooled to room temperature before addition of brine (100 mL) and extraction with Et_2O (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 9:1 hexane:Et_2O) afforded **173** (2.71 g, 71 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2933 (s), 2859 (m), 1708 (s), 1448 (m), 1126 (m). δ_H (400 MHz, $CDCl_3$) 5.53 – 5.31 (2H, m), 2.49 – 2.35 (2H, m), 2.33 – 2.23 (2H, m), 2.15 – 1.99 (2H, m), 1.95 – 1.80 (2H, m), 1.73 – 1.57 (5H, m), 1.41 – 1.28 (1H, m). δ_C (101 MHz, $CDCl_3$) 213.1, 128.9, 126.9, 50.9, 42.2, 33.5, 32.7, 28.1, 25.0, 18.1. *The data available in the literature is for a mixture of the (E) and (Z)-isomers.*[233] *The spectroscopic properties of **173** were consistent with those provided for the (E)-isomer, with the exception of one signal in the* ^{13}C *spectrum which appears to have been misassigned to the (Z)-isomer.*

(1*R,2*R**)-2-((*E*)-But-2-en-1-yl)cyclohexan-1-ol (174a) and (1*R**,2*S**)-2-((*E*)-But-2-en-1-yl)-cyclohexan-1-ol (174b)**



174a



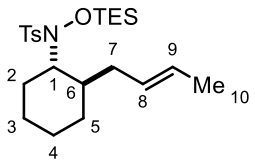
174b

To a solution of ketone **173** (1.52 g, 10.0 mmol) in MeOH (50 mL) at 0 °C was added $NaBH_4$ (378 mg, 10.0 mmol). The reaction mixture was stirred at 0 °C for 2 hours before addition of 1.0 M aqueous HCl (50 mL) and extraction with Et_2O (3 × 50 mL). The Et_2O extracts were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 11:1 hexane:EtOAc) afforded **174a** (534 mg, 35 %) as a colourless oil and **174b** (509 mg, 33 %) as a colourless oil. *Spectroscopic data for **174a**:* ν_{max} / cm^{-1}: (*film*) 3401 (br s), 2956 (s), 1448 (m). δ_H (400 MHz, $CDCl_3$) 5.52 – 5.37 (2H, m, C**8**-H and C**9**-H), 3.90 – 3.85 (1H, m, C**1**-H), 2.12 – 2.02 (1H, m, C**7**-H), 1.99 – 1.90 (1H, m, C**7**-H'), 1.82 – 1.72 (1H, m, C**2**-H), 1.68 – 1.61 (4H, m, C**4**-H and C**10**-H_3), 1.62 – 1.55 (1H, m, C**3**-H), 1.53 – 1.42 (5H, m, C**2**-H', C**3**-H', C**5**-H, C**6**-H and OH), 1.42 – 1.35 (1H, m, C**5**-H'), 1.32 – 1.23 (1H, m, C**4**-H'). δ_C (101 MHz, $CDCl_3$) 129.7 (C**8**), 126.2 (C**9**), 69.1 (C**1**), 41.6 (C**6**), 35.4 (C**7**), 33.0 (C**2**), 26.4 (C**5**), 25.2 (C**4**), 20.5 (C**3**), 17.9 (C**10**). HRMS: (ESI^+) Calculated for $C_{10}H_{18}NaO$: 177.1250. Found $[M+Na]^+$: 177.1251.

*Spectroscopic data for **174b**:* ν_{max} / cm^{-1}: (*film*) 3338 (br s), 2923 (s), 2855 (s), 1448 (s), 1063 (s). δ_H (500 MHz, $CDCl_3$) 5.51 – 5.48 (2H, m, C**8**-H and C**9**-H), 3.27 (1H, ddd, *J* = 9.5, 9.5, 4.5 Hz, C**1**-H), 2.38 – 2.31 (1H, m, C**7**-H), 2.00 – 1.90 (2H, m, C**2**-H and C**7**-H'), 1.80 (1H, br s, OH), 1.79 – 1.71 (2H, m, C**3**-H and C**5**-H), 1.69 – 1.61 (4H, m, C**4**-H and C**10**-H_3), 1.34 – 1.12 (4H, m, C**2**-H', C**3**-H', C**4**-H' and C**6**-H), 0.99 – 0.89 (1H, m, C**5**-H'). δ_C (101 MHz, $CDCl_3$) 129.8 (C**8**), 126.5 (C**9**), 74.8 (C**1**), 45.2

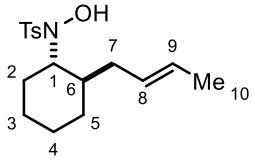
(C**6**), 36.3 (C**7**), 35.4 (C**2**), 30.5 (C**5**), 25.6 (C**4**), 24.9 (C**3**), 17.9 (C**10**). HRMS: (ESI$^+$) Calculated for $C_{10}H_{18}NaO$: 177.1250. Found $[M+Na]^+$: 177.1242.

***N*-((1*R**,2*S**)-2-((*E*)-But-2-en-1-yl)cyclohexyl)-*N*-(triethylsilyl)oxy)-4-toluenesulfonamide**



General procedure E: TsNHOTES (*vide supra*, 603 mg, 2.00 mmol) was employed with alcohol **174a** (1.3 eq.). The reaction time was 25 hours. FCC (gradient elution: 1:4 – 0:1 hexane:PhMe) afforded the title compound (338 mg, 39 %) as a colourless crystalline solid. m.p. 91-93 °C (Et_2O:hexane, *plates*). ν_{max} / cm^{-1}: (*solid*) 2936 (m), 2876 (m), 1597 (m), 1450 (m), 1345 (s), 1166 (s). δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.30 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.50 – 5.33 (2H, m, C**8**-<u>H</u> and C**9**-<u>H</u>), 3.24 (1H, ddd, *J* = 11.5, 11.5, 3.5 Hz, C**1**-<u>H</u>), 2.72 – 2.63 (1H, m, C**7**-<u>H</u>), 2.44 (3H, s, Ts C<u>H</u>$_3$), 1.96 – 1.87 (1H, m, C**5**-<u>H</u>), 1.80 – 1.70 (1H, m, C**7**-<u>H</u>'), 1.69 – 1.64 (3H, m, C**10**-<u>H</u>$_3$), 1.58 – 1.52 (1H, m, C**4**-<u>H</u>), 1.50 – 1.43 (1H, m, C**3**-<u>H</u>), 1.41 – 1.31 (1H, m, C**6**-<u>H</u>), 1.26 – 1.13 (1H, m, C**2**-<u>H</u>), 1.08 – 1.00 (9H, m, Si(CH$_2$C<u>H</u>$_3$)$_3$), 0.99 – 0.74 (9H, m, C**3**-<u>H</u>', C**4**-<u>H</u>', C**5**-<u>H</u>' and Si(C<u>H</u>$_2$CH$_3$)$_3$), 0.72 – 0.61 (1H, m, C**2**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 144.1 (Ar<u>C</u>), 133.8 (Ar<u>C</u>), 129.3 (Ar<u>C</u>H), 129.1 (C**9**), 129.0 (Ar<u>C</u>H), 126.6 (C**8**), 66.3 (C**1**), 40.7 (C**6**), 36.3 (C**7**), 31.9 (C**5**), 26.2 (C**2**), 25.6 (C**3**), 25.5 (C**4**), 21.6 (Ts <u>C</u>H$_3$), 18.1 (C**10**), 6.9 (Si(CH$_2$<u>C</u>H$_3$)$_3$), 5.1 (Si(<u>C</u>H$_2$CH$_3$)$_3$). HRMS: (ESI$^+$) Calculated for $C_{23}H_{39}NNaO_3SSi$: 460.2314. Found $[M+Na]^+$: 460.2314.

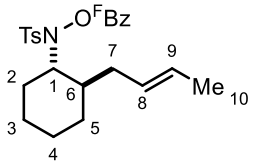
***N*-((1*R**,2*S**)-2-((*E*)-But-2-en-1-yl)cyclohexyl)-*N*-hydroxy-4-toluenesulfonamide**



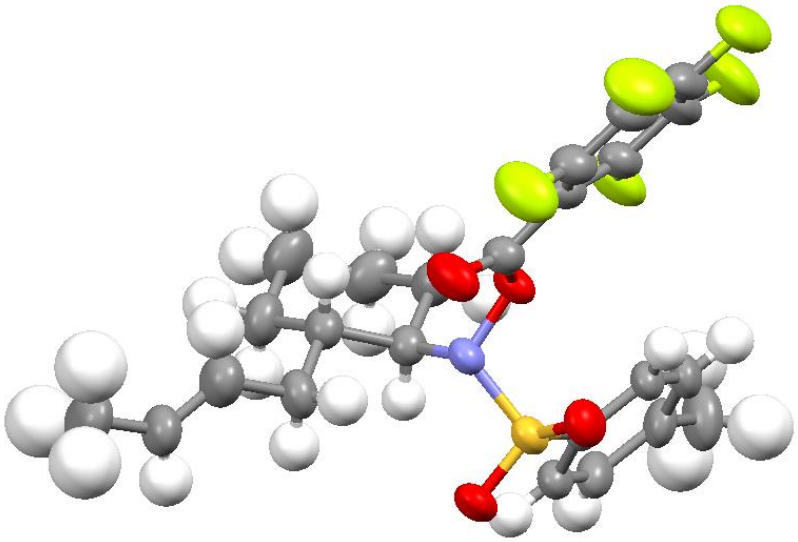
General procedure F: The preceding compound (321 mg, 0.733 mmol) was employed. FCC (eluent: 6:1 hexane:EtOAc) afforded the title compound (209 mg, 88 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3316 (br s), 2919 (m), 2856 (m), 1599 (m), 1332 (s), 1161 (s). δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.31 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.91 (1H, br s, O<u>H</u>), 5.49 – 5.36 (2H, m, C**8**-<u>H</u> and C**9**-<u>H</u>), 3.49 (1H, ddd, *J* = 11.0, 11.0, 4.0 Hz, C**1**-<u>H</u>), 2.44 (3H, s, Ts C<u>H</u>$_3$), 2.42 – 2.35 (1H, m, C**7**-<u>H</u>), 1.95 – 1.80 (2H, m, C**5**-<u>H</u> and C**7**-<u>H</u>'), (3H, d, *J* = 4.0 Hz, C**10**-<u>H</u>$_3$), 1.62 – 1.55 (2H, m, C**3**-<u>H</u> and C**4**-<u>H</u>), 1.55 – 1.47 (1H, m, C**6**-<u>H</u>), 1.45 – 1.33 (1H, m, C**2**-<u>H</u>), 1.28 – 1.20 (1H, m, C**2**-<u>H</u>'), 1.18 – 0.97 (3H, m, C**3**-<u>H</u>', C**4**-<u>H</u>' and C**5**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 144.2 (Ar<u>C</u>), 134.7 (Ar<u>C</u>), 129.5 (Ar<u>C</u>H), 129.0 (C**9**), 128.7 (Ar<u>C</u>H), 126.8 (C**8**), 63.7 (C**1**), 39.9 (C**6**), 35.9 (C**7**), 31.7 (C**5**), 26.2

(C**2**), 25.5 (C**3**), 25.3 (C**4**), 21.6 (Ts CH_3), 18.0 (C**10**). HRMS: (ESI$^+$) Calculated for $C_{17}H_{25}NNaO_3S$: 346.1447. Found [M+Na]$^+$: 346.1446.

***N*-((1*R**,2*S**)-2-((*E*)-But-2-en-1-yl)cyclohexyl)-*N*-(pentafluorobenzoyloxy)-4-toluenesulfonamide (175a)**

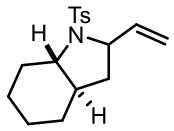


General procedure C: The preceding compound (208 mg, 0.643 mmol) was employed. FCC (eluent: 19:1 hexane:EtOAc) afforded **175a** (227 mg, 68 %) as a colourless crystalline solid. m.p. 108-109 °C (CH_2Cl_2:petrol, *cubes*). ν_{max} / cm^{-1}: (*solid*) 2930 (m), 1773 (s), 1651 (m), 1595 (m), 1493 (s), 1170 (s). δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* = 8.0 Hz, 2 × ArC**H**), 7.33 (2H, d, *J* = 8.0 Hz, 2 × ArC**H**), 5.45 (1H, dq, *J* = 15.0, 6.5 Hz, C**9**-**H**), 5.38 – 5.28 (1H, m, C**8**-**H**), 3.76 (1H, ddd, *J* = 11.0, 11.0, 6.5 Hz, C**1**-**H**), 2.82 – 2.70 (1H, m, C**7**-**H**), 2.45 (3H, s, Ts CH_3), 1.99 – 1.87 (2H, m, C**5**-**H** and C**7**-**H**'), 1.80 – 1.46 (7H, m, C**2**-H_2, C**3**-**H**, C**4**-**H** and C**10**-H_3), 1.34 – 1.15 (2H, m, C**3**-**H**' and C**6**-**H**), 1.13 – 0.94 (2H, m, C**4**-**H**' and C**5**-**H**'). δ_C (101 MHz, $CDCl_3$) 156.3 (**C**=O), 145.5 (Ar**C**), 133.2 (Ar**C**), 129.7 (Ar**C**H), 129.2 (Ar**C**H), 128.5 (C**9**), 127.1 (C**8**), 64.7 (C**1**), 40.5 (C**6**), 35.6 (C**7**), 31.5 (C**5**), 27.7 (C**2**), 25.5 (C**3**), 25.2 (C**4**), 21.7 (Ts **C**H_3), 18.0 (C**10**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.1 (2F, m), -146.2 (1F, tt, *J* = 21.5, 5.0 Hz), -159.0 – -159.1 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{24}H_{24}F_5NNaO_4S$: 540.1238. Found [M+Na]$^+$: 540.1223.



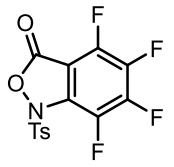
*ORTEP view of **175a**.*

(3a*R,7a*S**)-1-Tosyl-2-vinyloctahydro-1*H*-indole (176a)**



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; PhMe (0.1 M); 140 °C; 17 hours. Substrate **175a** (72.5 mg, 0.140 mmol) was employed. FCC (gradient elution: 29:1 – 19:1 – 14:1 – 9:1 – 3:1 hexane:EtOAc) afforded **176a** (19.4 mg, 45 %, 4:3 mixture of diastereomers) as a pale-yellow oil. *Spectroscopic data for both diastereomers:* δ_H (400 MHz, $CDCl_3$) 7.71 – 7.66 (2H, m), 7.31 (1.2H, d, *J* = 8.5 Hz), 7.26 – 7.23 (0.8H, m), 5.85 (0.6H, ddd, *J* = 17.0, 10.5, 5.0 Hz), 5.64 (0.4H, ddd, *J* = 17.0, 10.0, 8.0 Hz), 5.34 (0.6H, ddd, *J* = 17.0, 1.5, 1.5 Hz), 5.20 (0.4H, ddd, *J* = 17.0, 1.0, 1.0 Hz), 5.13 (0.6H, ddd, *J* = 10.5, 1.5, 1.5 Hz), 5.04 (0.4H, ddd, *J* = 10.0, 1.0, 1.0 Hz), 4.39 (0.4H, br dt, *J* = 8.0, 8.0 Hz), 4.27 – 4.20 (0.6H, m), 2.76 (0.4H, ddd, *J* = 11.5, 10.5, 3.5 Hz), 2.56 – 2.45 (1.6H, m), 2.43 (1.8H, s), 2.41 (1.2H, s), 2.22 – 2.14 (0.4H, m), 1.88 – 1.53 (4.2H, m), 1.50 – 0.9 (5.4H, m). δ_C (101 MHz, $CDCl_3$) 143.2, 142.5, 2 × 139.6, 139.3, 134.6, 129.5, 129.3, 127.7, 127.2, 115.4, 115.1, 66.8, 65.4, 63.3, 61.8, 45.5, 42.8, 38.0, 35.8, 32.6, 30.9, 29.9, 29.6, 25.3, 25.2, 24.9, 24.7, 2 × 21.5. *The spectroscopic properties were consistent with the data available in the literature.*[126]

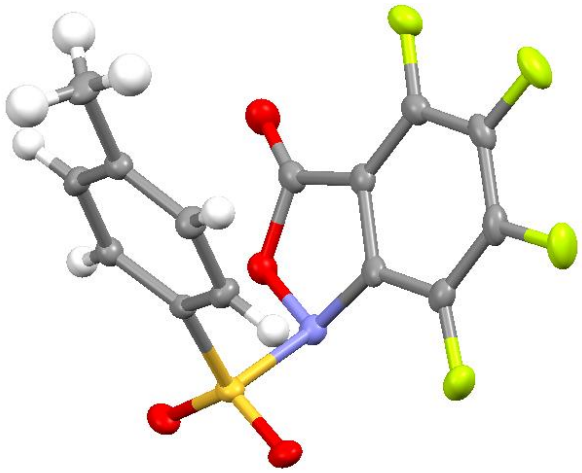
4,5,6,7-Tetrafluoro-1-tosylbenzo[*c*]isoxazol-3(1*H*)-one (177)



General procedure K: Alcohol **174a** (*vide supra*, 242 mg, 1.57 mmol) was employed with $TsNHO^FBz$ (*vide supra*). The reaction time was 14 hours. FCC (gradient elution: 3:1 – 1:1 hexane:PhMe) afforded **177** (345 mg, 47 %) as a colourless crystalline solid. Desired product **175a** was not observed.

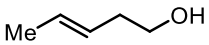
*An alternative procedure was devised to prepare **177**:* To a suspension of NaH (60 % in mineral oil, 105 mg, 2.62 mmol) in anhydrous DMF (30 mL) was added a solution of $TsNHO^FBz$ (*vide supra*, 1.00 g, 2.62 mmol) in anhydrous THF (30 mL) dropwise. The reaction mixture was stirred at room temperature for 16 hours before addition of brine (60 mL) and extraction with Et_2O (3 × 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 9:1 hexane:EtOAc) afforded **177** (419 mg, 44 %) as a colourless crystalline solid. m.p. 144-145 °C (CH_2Cl_2:hexane, *cubes*). ν_{max} / cm^{-1}: (*solid*) 1816 (s), 1594 (m), 1533 (s), 1499 (s), 1184 (s). δ_H (400 MHz, $CDCl_3$) 7.75 – 7.69 (2H, m, 2 × ArC<u>H</u>), 7.38 – 7.33 (2H, m, 2 × ArC<u>H</u>), 2.46 (3H, s,

Ts C$\underline{H}_3$). δ_C (101 MHz, $CDCl_3$) 148.3 (Ar$\underline{C}$), 130.5 (Ar$\underline{C}$H), 130.0 (Ar$\underline{C}$H), 127.6 (Ar$\underline{C}$), 22.0 (Ts $\underline{C}H_3$). *The ^{13}C signals corresponding to the carbonyl and fluorinated arene groups could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.7 – -136.9 (1F, m), -137.8 (1F, ddd, *J* = 19.0, 19.0, 9.5 Hz), -140.6 (1F, ddd, *J* = 20.0, 19.0, 3.5 Hz), -151.4 – -151.6 (1F, m). HRMS: (ESI^+) Calculated for $C_{14}H_7F_4NNaO_4S$: 383.9924. Found $[M+Na]^+$: 383.9916.



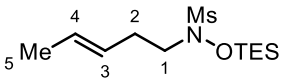
*ORTEP view of **177**.*

(*E*)-Pent-3-en-1-ol (123)



General procedure I: (*E*)-Pent-3-enoic acid (5.00 g, 49.9 mmol) was employed, using anhydrous Et_2O as the solvent and 2.0 eq. $LiAlH_4$ (1.0 M in Et_2O). Alcohol **123** (3.98 g, 93 %) was isolated as a pale-yellow oil. δ_H (400 MHz, $CDCl_3$) 5.55 (1H, dqt, *J* = 15.5, 6.5, 1.5 Hz), 5.39 (1H, dtq, *J* = 15.5, 6.5, 1.5 Hz), 3.60 (2H, t, *J* = 6.5 Hz), 2.23 (2H, dtdq, *J* = 6.5, 6.5, 1.5, 1.5 Hz), 1.74 (1H, br s), 1.67 (3H, ddt, *J* = 6.5, 1.5, 1.5 Hz). δ_C (101 MHz, $CDCl_3$) 128.6, 127.2, 62.1, 36.1, 18.1. *The spectroscopic properties were consistent with the data available in the literature*.[234]

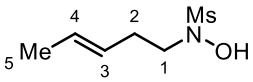
(*E*)-*N*-(Pent-3-en-1-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide



General procedure E: MsNHOTES (*vide supra*, 564 mg, 2.50 mmol) was employed with alcohol **123** (1.3 eq.). The reaction time was 15 hours. FCC (eluent: 1:4 hexane:PhMe) afforded the title compound (1.73 g, 98 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2957 (m), 2878 (m), 1457 (m), 1351 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 5.55 (1H, dqt, *J* = 15.0, 6.5, 1.5 Hz, C**4**-$\underline{H}$), 5.38 (1H, dtq, *J* = 15.0, 7.0, 1.5 Hz, C**3**-$\underline{H}$), 3.23 – 3.16 (2H, m, C**1**-$\underline{H}_2$), 2.85 (3H, s, Ms C$\underline{H}_3$), 2.39 – 2.31 (2H, m, C**2**-$\underline{H}_2$), 1.66 (3H, dq, *J* = 6.5, 1.5 Hz, C**5**-$\underline{H}_3$), 0.99 (9H, t, *J* = 8.0 Hz, Si($CH_2C\underline{H}_3$)$_3$), 0.77 (6H, q, *J* = 8.0 Hz, Si($C\underline{H}_2CH_3$)$_3$).

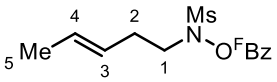
δ_C (101 MHz, $CDCl_3$) 128.1 (C**4**), 126.9 (C**3**), 55.7 (C**1**), 30.6 (C**2**), 30.5 (Ms $\underline{C}H_3$), 18.1 (C**5**), 6.8 (Si($CH_2\underline{C}H_3)_3$), 4.9 (Si($\underline{C}H_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{12}H_{27}NNaO_3SSi$: 316.1373. Found $[M+Na]^+$: 316.1371.

(*E*)-*N*-Hydroxy-*N*-(pent-3-en-1-yl)methanesulfonamide



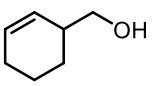
General procedure F: The preceding compound (1.71 g, 5.83 mmol) was employed. FCC (eluent: 3:1 hexane:EtOAc) afforded the title compound (735 mg, 70 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3384 (br s), 2919 (m), 1438 (m), 1334 (s), 1162 (s). δ_H (400 MHz, $CDCl_3$) 7.08 (1H, s, O$\underline{H}$), 5.55 (1H, dqt, *J* = 15.0, 6.5, 1.5 Hz, C**4**-$\underline{H}$), 5.41 (1H, dtq, *J* = 15.0, 7.5, 1.5 Hz, C**3**-$\underline{H}$), 3.19 (2H, t, *J* = 7.0 Hz, C**1**-$\underline{H}_2$), 2.92 (3H, s, Ms C$\underline{H}_3$), 2.37 (2H, dtt, *J* = 7.5, 7.0, 1.5 Hz, C**2**-$\underline{H}_2$), 1.65 (3H, dq, *J* = 6.5, 1.5 Hz, C**5**-$\underline{H}_3$). δ_C (101 MHz, $CDCl_3$) 128.0 (C**4**), 126.9 (C**3**), 52.5 (C**1**), 31.0 (Ms $\underline{C}H_3$), 30.3 (C**2**), 18.1 (C**5**). HRMS: (ESI^+) Calculated for $C_6H_{13}NNaO_3S$: 202.0508. Found $[M+Na]^+$: 202.0515.

(*E*)-*N*-(Pent-3-en-1-yl)-*N*-((pentafluorobenzoyl)oxy)methanesulfonamide (178)



General procedure C: The preceding compound (705 mg, 3.93 mmol) was employed. FCC (gradient elution: 6:1 – 4:1 hexane:EtOAc) afforded **178** (1.35 g, 92 %) as a colourless crystalline solid. m.p. 80-81 °C (CH_2Cl_2:petrol, *fibres*). ν_{max} / cm^{-1}: (*solid*) 3024 (m), 2940 (m), 1787 (s), 1655 (m), 1504 (s), 1348 (s) 1161 (s). δ_H (400 MHz, $CDCl_3$) 5.62 – 5.52 (1H, m, C**4**-$\underline{H}$), 5.47 – 5.38 (1H, m, C**3**-$\underline{H}$), 3.54 – 3.43 (2H, m, C**1**-$\underline{H}_2$), 3.04 (3H, s, Ms C$\underline{H}_3$), 2.39 (2H, dt, *J* = 7.0, 7.0 Hz, C**2**-$\underline{H}_2$), 1.64 (3H, ddt, *J* = 6.5, 1.5, 1.5 Hz, C**5**-$\underline{H}_3$). δ_C (101 MHz, $CDCl_3$) 128.9 (C**4**), 125.9 (C**3**), 52.7 (C**1**), 34.5 (Ms $\underline{C}H_3$), 30.4 (C**2**), 18.0 (C**5**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -135.9 (2F, m), -145.3 (1F, tt, *J* = 21.0, 5.5 Hz), -158.8 – -159.0 (2F, m). HRMS: (ESI^+) Calculated for $C_{13}H_{12}F_5NNaO_4S$: 396.0299. Found $[M+Na]^+$: 396.0308.

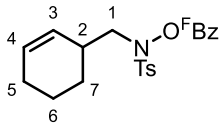
Cyclohex-2-en-1-ylmethanol (179)



This compound was prepared according to a literature procedure.[235] To a suspension of KO*t*-Bu (9.43 g, 84.0 mmol) in cyclohexene (50 mL, argon sparged) was added *n*-BuLi (1.55 M in hexane, 58.0 mL,

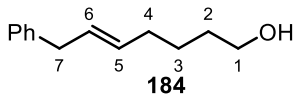
89.9 mmol). The reaction mixture was stirred at room temperature for 15 hours then heated to 60 °C before addition of paraformaldehyde (2.88 g, 96.0 mmol). The reaction mixture was stirred at 60 °C for 2 hours before being cooled to room temperature, addition of saturated aqueous NH_4Cl (200 mL) and extraction with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 3:2 hexane:Et_2O) afforded **179** (4.58 g, 49 %) as a pale-yellow oil. δ_H (400 MHz, $CDCl_3$) 5.85 – 5.78 (1H, m), 5.62 – 5.55 (1H, m), 3.53 (2H, d, *J* = 6.0 Hz), 2.37 – 2.24 (1H, m), 2.04 – 1.93 (2H, m), 1.83 – 1.68 (2H, m), 1.61 – 1.47 (2H, m), 1.45 – 1.33 (1H, m). δ_C (101 MHz, $CDCl_3$) 129.8, 127.8, 67.2, 38.4, 25.6, 25.4, 21.1. *The spectroscopic properties were consistent with the data available in the literature.*[235]

***N*-(Cyclohex-2-en-1-ylmethyl)-*N*-((pentafluorobenzoyl)oxy)-4-toluenesulfonamide (180)**

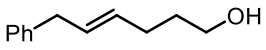


General procedure K: Alcohol **179** (28.0 mg, 0.250 mmol) was employed with $TsNHO^FBz$ (*vide supra*). The reaction time was 21 hours. FCC (eluent: 3:7 hexane:PhMe) afforded **180** (88.5 mg, 74 %) as a colourless crystalline solid. m.p. 123-125 °C (CH_2Cl_2:petrol, *hexagonal*). ν_{max} / cm^{-1}: (*solid*) 2934 (m), 1780 (s), 1653 (m), 1597 (m), 1496 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* = 8.0 Hz, 2 × ArC**H**), 7.39 (2H, d, *J* = 8.0 Hz, 2 × ArC**H**), 5.77 (1H, dtd, *J* = 10.0, 3.5, 3.0 Hz, C**4**-**H**), 5.58 (1H, br s, C**3**-**H**), 3.08 (2H, br s, C**1**-H_2), 2.47 (3H, s, Ts CH_3), 2.29 (1H, br s, C**2**-**H**), 1.98 (2H, br s, C**5**-H_2), 1.92 – 1.81 (1H, m, C**7**-**H**), 1.78 – 1.66 (1H, m, C**6**-**H**), 1.57 – 1.49 (2H, m, C**6**-**H**' and C**7**-**H**'). δ_C (101 MHz, $CDCl_3$) 146.0 (Ar**C**), 130.3 (Ar**C**), 2 × 130.0 (C**4** and Ar**C**H), 129.7 (Ar**C**H), 127.2 (C**3**), 57.6 (C**1**), 33.2 (C**2**), 26.5 (C**7**), 25.2 (C**5**), 21.9 (Ts **C**H_3), 20.7 (C**6**). δ_F (377 MHz, $CDCl_3$) -135.7 – -135.9 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.0 Hz), -159.1 – -159.3 (2F, m). HRMS: (ESI^+) Calculated for $C_{21}H_{18}F_5NNaO_4S$: 498.0769. Found $[M+Na]^+$: 498.0773.

(*E*)-7-Phenylhept-5-en-1-ol (184) and (*E*)-6-Phenylhex-4-en-1-ol (121)



184

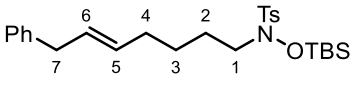


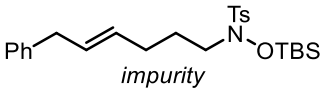
121

*The synthesis of this compound produced material containing a significant impurity of chain-shortened alcohol **121**. It was not possible to separate **184** and **121**; consequently, subsequent compounds in this sequence were all produced with the analogous impurity.* To a solution of Grubbs-Hoveyda 2nd generation catalyst (62.5 mg, 99.8 μmol) in anhydrous CH_2Cl_2 (80 mL, argon sparged) was added hex-5-en-1-ol (1.20 mL, 9.98 mmol) and allyl benzene (8.00 mL, 60.4 mmol). The reaction mixture was stirred at room temperature for 4 days before being concentrated *in vacuo*. FCC (eluent:

7:1 PhMe:EtOAc) afforded **184** (430 mg, 23 %, 5:1 mixture of **184** and **121**) as a light-brown oil (the colouration was due to the presence of trace amounts of Ru-impurities). *Spectroscopic data for **184**:* ν_{max} / cm^{-1}: (*film*) 3335 (br s), 3026 (m), 2927 (s), 1603 (m), 1453 (s), 1055 (s). δ_H (400 MHz, $CDCl_3$) 7.34 – 7.26 (2H, m, 2 × ArC<u>H</u>), 7.22 – 7.15 (3H, m, 3 × ArC<u>H</u>), 5.66 – 5.45 (2H, m, C**5**-<u>H</u> and C**6**-<u>H</u>), 3.64 (2H, t, *J* = 6.5 Hz, C**1**-<u>H_2</u>), 3.33 (2H, d, *J* = 6.5 Hz, C**7**-<u>H_2</u>), 2.06 (2H, tdd, *J* = 7.5, 6.0, 1.0 Hz, C**4**-<u>H_2</u>), 1.63 – 1.53 (2H, m, C**2**-<u>H_2</u>), 1.50 – 1.41 (2H, m, C**3**-<u>H_2</u>), 1.40 (1H, br s, O<u>H</u>). δ_C (101 MHz, $CDCl_3$) 141.0 (Ar<u>C</u>), 131.5 (C**5**), 129.2 (C**6**), 128.5 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 62.8 (C**1**), 39.0 (C**7**), 2 × 32.2 (C**2** and C**4**), 25.6 (C**3**). HRMS: (EI^+) Calculated for $C_{13}H_{18}O$: 190.1358. Found $[M]^+$: 190.1353. *Characteristic signals for **121**:* δ_H (400 MHz, $CDCl_3$) 2.14 (2H, dt, *J* = 7.0, 6.5 Hz). δ_C (101 MHz, $CDCl_3$) 62.4, 28.8.

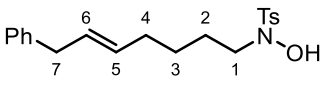
(*E*)-*N*-(7-Phenylhept-5-en-1-yl)-*N*-((*tert*-butyldimethylsilyl)oxy)-4-toluenesulfonamide

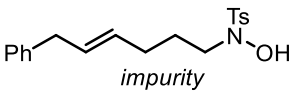




<u>General procedure E:</u> TsNHOTBS (*vide supra*, 645 mg, 2.14 mmol) was employed with alcohol **184** (1.1 eq.). The reaction time was 16 hours. FCC (eluent: 3:5 hexane:PhMe) afforded the title compound (946 mg, 93 %, undetermined mixture of the title compound and chain-shortened impurity) as a colourless oil. *Spectroscopic data for the title compound:* ν_{max} / cm^{-1}: (*film*) 2929 (s), 2858 (s), 1598 (m), 1356 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.37 – 7.25 (4H, m, 4 × ArC<u>H</u>), 7.21 – 7.13 (3H, m, 3 × ArC<u>H</u>), 5.62 – 5.50 (1H, m, C**6**-<u>H</u>), 5.49 – 5.38 (1H, m, C**5**-<u>H</u>), 3.31 (2H, d, *J* = 6.5 Hz, C**7**-<u>H_2</u>), 2.88 (2H, t, *J* = 7.5 Hz, C**1**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.01 (2H, dt, *J* = 7.0, 7.0 Hz, C**4**-<u>H_2</u>), 1.61 – 1.51 (2H, m, C**2**-<u>H_2</u>), 1.37 (2H, tt, *J* = 7.5, 7.0 Hz, C**3**-<u>H_2</u>), 0.92 (9H, s, SiC(C<u>H_3</u>)$_3$), 0.29 (6H, s, Si(C<u>H_3</u>)$_2$). δ_C (101 MHz, $CDCl_3$) 144.4 (Ar<u>C</u>), 140.8 (Ar<u>C</u>), 131.1 (C**5**), 130.0 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.4 (C**6**), 129.2 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 55.9 (C**1**), 39.0 (C**7**), 32.0 (C**4**), 26.8 (C**3**), 26.6 (C**2**), 26.0 (SiC(<u>C</u>H_3)$_3$), 21.6 (Ts <u>C</u>H_3), 18.3 (Si<u>C</u>$(CH_3)_3$), -4.2 (Si(<u>C</u>H_3)$_2$). HRMS: (ESI^+) Calculated for $C_{26}H_{39}NNaO_3SSi$: 496.2312. Found $[M+Na]^+$: 496.2303. *Characteristic signals for the chain-shortened impurity:* δ_C (101 MHz, $CDCl_3$) 130.3, 29.8, 26.7.

(*E*)-*N*-(7-Phenylhept-5-en-1-yl)-*N*-hydroxy-4-toluenesulfonamide

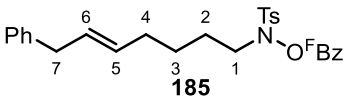




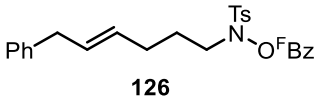
<u>General procedure B:</u> The preceding compound (897 mg, 1.89 mmol) was employed. The title compound (608 mg, 89 %, 8:1 mixture of the title compound and chain-shortened impurity) was

isolated as a colourless oil. *Spectroscopic data for the title compound:* ν_{max} / cm^{-1}: (*film*) 3382 (s), 3027 (m), 2924 (s), 1598 (m), 1340 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.35 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.29 – 7.24 (2H, m, 2 × ArC<u>H</u>), 7.20 – 7.14 (3H, m, 3 × ArC<u>H</u>), 6.80 (1H, br s, O<u>H</u>), 5.62 – 5.52 (1H, m, C**6**-<u>H</u>), 5.52 – 5.42 (1H, m, C**5**-<u>H</u>), 3.31 (2H, d, *J* = 6.5 Hz, C**7**-<u>H_2</u>), 2.90 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.04 (2H, dt, *J* = 7.0, 6.5 Hz, C**4**-<u>H_2</u>), 1.63 (2H, tt, *J* = 7.0, 7.0 Hz, C**2**-<u>H_2</u>), 1.45 (2H, tt, *J* = 7.0, 6.5 Hz, C**3**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 144.8 (Ar<u>C</u>), 140.9 (Ar<u>C</u>), 131.3 (C**5**), 129.7 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 129.4 (Ar<u>C</u>), 129.3 (C**6**), 128.5 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 52.4 (C**1**), 39.0 (C**7**), 32.0 (C**4**), 26.4 (C**3**), 26.1 (C**2**), 21.7 (Ts <u>C</u>H_3). HRMS: (ESI^+) Calculated for $C_{20}H_{26}NO_3S$: 360.1628. Found $[M+H]^+$: 360.1636. *Characteristic signals for the chain-shortened impurity:* δ_H (400 MHz, $CDCl_3$) 2.11 (2H, dt, *J* = 6.5, 6.5 Hz). δ_C (101 MHz, $CDCl_3$) 52.0, 29.4.

(*E*)-*N*-(7-Phenylhept-5-en-1-yl)-*N*-(pentafluorobenzoyloxy)-4-toluenesulfonamide (185) and 126



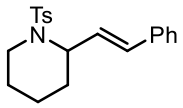
185



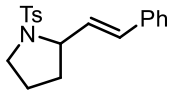
126

<u>General procedure C:</u> The preceding compound (562 mg, 1.56 mmol) was employed. FCC (eluent: 19:1 hexane:EtOAc) afforded **185** (627 mg, 73 %, 4:1 mixture of **185** and **126**) as a colourless crystalline solid. *Spectroscopic data for **185**:* ν_{max} / cm^{-1}: (*solid*) 2919 (m), 1775 (s), 1651 (m), 1594 (m), 1493 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.37 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.28 – 7.23 (2H, m, 2 × ArC<u>H</u>), 7.18 – 7.12 (3H, m, 3 × ArC<u>H</u>), 5.55 (1H, dt, *J* = 15.0, 6.5 Hz, C**6**-<u>H</u>), 5.44 (1H, dt, *J* = 15.0, 7.0 Hz, C**5**-<u>H</u>), 3.30 (2H, d, *J* = 6.5 Hz, C**7**-<u>H_2</u>), 3.20 (2H, br s, C**1**-<u>H_2</u>), 2.46 (3H, s, Ts C<u>H_3</u>), 2.03 (2H, dt, *J* = 7.0, 6.5 Hz, C**4**-<u>H_2</u>), 1.66 – 1.46 (4H, m, C**2**-<u>H_2</u> and C**3**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 145.8 (Ar<u>C</u>), 140.8 (Ar<u>C</u>), 130.9 (C**5**), 130.0 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 2 × 129.6 (C**6** and Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 52.5 (C**1**), 38.9 (C**7**), 31.8 (C**4**), 2 × 26.1 (C**2** and C**3**), 21.7 (Ts <u>C</u>H_3). δ_F (377 MHz, $CDCl_3$) -135.9 – -136.1 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.5 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{27}H_{24}F_5NNaO_4S$: 576.1238. Found $[M+Na]^+$: 576.1234. *Characteristic signals for **126**:* δ_H (400 MHz, $CDCl_3$) 2.17 (2H, dt, *J* = 7.0, 7.0 Hz). δ_C (101 MHz, $CDCl_3$) 29.3, 26.5.

(*E*)-2-Styryl-1-tosylpiperidine (186) and 128



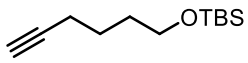
186



128

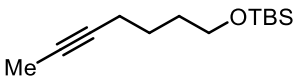
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 20 hours. Substrate **185** (77.5 mg, 0.140 mmol) was employed. FCC (gradient elution: 9:1 – 4:1 hexane:EtOAc) afforded **186** (4.7 mg, 10 %) as a pale-yellow oil and **128** (5.0 mg, 11 %) as a pale-yellow oil. *Spectroscopic data for **186**:* δ_H (500 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 8.5 Hz), 7.30 – 7.28 (2H, m), 7.26 – 7.16 (5H, m), 6.42 (1H, dd, *J* = 16.0, 1.5 Hz), 6.00 (1H, dd, *J* = 16.0, 6.5 Hz), 4.80 – 4.73 (1H, m), 3.80 – 3.75 (1H, m), 3.09 – 2.99 (1H, m), 2.37 (3H, s), 1.84 – 1.76 (2H, m), 1.69 – 1.49 (4H, m). δ_C (126 MHz, $CDCl_3$) 142.9, 137.5, 136.6, 132.2, 129.4, 128.5, 127.6, 127.5, 126.4, 126.3, 55.1, 42.0, 30.7, 25.2, 21.4, 19.3. *The spectroscopic properties were consistent with the data available in the literature*.[236] *Characterisation data for **128** has been provided earlier.*

***tert*-Butyl(hex-5-yn-1-yloxy)dimethylsilane (187)**



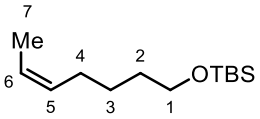
This compound was prepared according to a literature procedure.[237] To a solution of TBSCl (16.6 g, 110 mmol), Et_3N (16.7 mL, 120 mmol) and DMAP (611 mg, 5.00 mmol) in anhydrous CH_2Cl_2 (120 mL) at 0 °C was added hex-5-yn-1-ol (11.0 mL, 100 mmol). The reaction mixture was stirred at room temperature for 23 hours before being poured into saturated aqueous NH_4Cl (150 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Distillation (b.p.: 58 °C, 2 mbar) afforded **187** (19.8 g, 93 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3314 (m), 2930 (s), 2858 (s), 2120 (m), 1472 (m), 1254 (s), 1104 (s). δ_H (400 MHz, $CDCl_3$) 3.62 (2H, t, *J* = 6.0 Hz), 2.20 (2H, td, *J* = 7.0, 2.5 Hz), 1.92 (1H, t, *J* = 2.5 Hz), 1.67 – 1.52 (4H, m), 0.88 (9H, s), 0.03 (6H, s). δ_C (101 MHz, $CDCl_3$) 84.7, 68.4, 62.7, 32.0, 26.1, 25.1, 18.5, 18.4, -5.2. HRMS: (ESI^+) Calculated for $C_{12}H_{24}NaOSi$: 235.1489. Found $[M+Na]^+$: 235.1479. *The spectroscopic properties were consistent with the data available in the literature*.[238]

***tert*-Butyl(hept-5-yn-1-yloxy)dimethylsilane (188)**



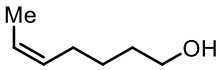
This compound was prepared according to a literature procedure.[239] To a solution of alkyne **187** (4.00 g, 18.8 mmol) in anhydrous THF (40 mL) at -78 °C was added *n*-BuLi (1.60 M in hexane, 12.4 mL, 19.8 mmol). The reaction mixture was stirred at -78 °C for 2 hours before addition of MeI (1.53 mL, 24.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for a further 20 hours before addition of saturated aqueous NH_4Cl (50 mL) and extraction with Et_2O (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Distillation (b.p.: 78-79 °C, 2 mbar) afforded **188** (4.06 g, 95 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.62 (2H, t, *J* = 6.5 Hz), 2.18 – 2.11 (2H, m), 1.77 (3H, t, *J* = 2.5 Hz), 1.64 – 1.57 (2H, m), 1.57 – 1.47 (2H, m), 0.89 (9H, s), 0.05 (6H, s). δ_C (101 MHz, $CDCl_3$) 79.1, 75.5, 62.7, 32.0, 26.0, 25.4, 18.5, 18.3, 3.4, -5.3. *The spectroscopic properties were consistent with the data available in the literature*.[239]

(*Z*)-*tert*-Butyl(hept-5-en-1-yloxy)dimethylsilane



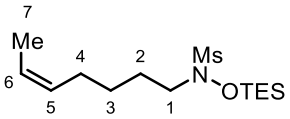
A solution of alkyne **188** (2.00 g, 8.83 mmol), Lindlar catalyst (94.1 mg, 44.2 μmol) and a few drops of quinoline in anhydrous hexane (30 mL) was stirred under an atmosphere of H_2 (balloon pressure) for 1 hour. The reaction mixture was filtered through celite, and the filter cake was rinsed with CH_2Cl_2 (25 mL). The filtrate was washed with 1.0 M aqueous HCl (30 mL) and concentrated *in vacuo* to afford the title compound (1.71 g, 85 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3014 (m), 2929 (s), 2858 (s), 1472 (m), 1254 (s), 1099 (s). δ_H (400 MHz, $CDCl_3$) 5.49 – 5.33 (2H, m, C**5**-H and C**6**-H), 3.61 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.05 (2H, dt, *J* = 7.5, 7.5 Hz, C**4**-H_2), 1.60 (3H, dd, *J* = 6.0, 1.0 Hz, C**7**-H_3), 1.57 – 1.49 (2H, m, C**2**-H_2), 1.44 – 1.35 (2H, m, C**3**-H_2), 0.90 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$). δ_C (101 MHz, $CDCl_3$) 130.6 (C**5**), 123.8 (C**6**), 63.1 (C**1**), 32.5 (C**2**), 26.6 (C**4**), 26.0 (SiC(CH_3)$_3$), 25.8 (C**3**), 18.4 (SiC(CH_3)$_3$), 12.7 (C**7**), -5.3 (Si(CH_3)$_2$). HRMS: (ESI^+) Calculated for $C_{13}H_{28}NaOSi$: 251.1802. Found $[M+Na]^+$: 251.1799.

(*Z*)-Hept-5-en-1-ol ((*Z*)-189)



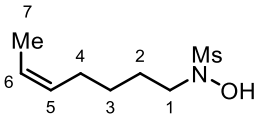
General procedure M: The preceding silyl ether (1.63 g, 7.14 mmol) was employed with 1.5 eq. TBAF. The reaction time was 3 hours. FCC (eluent: 2:1 hexane:Et_2O) afforded **(*Z*)-189** (695 mg, 85 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3326 (br s), 3013 (m), 2933 (s), 1441 (m), 1056 (s). δ_H (400 MHz, $CDCl_3$) 5.48 – 5.39 (1H, m), 5.40 – 5.31 (1H, m), 3.62 (2H, t, *J* = 6.5 Hz), 2.09 – 2.00 (2H, m), 1.63 – 1.53 (5H, m), 1.51 (1H, s), 1.45 – 1.36 (2H, m). δ_C (101 MHz, $CDCl_3$) 130.3, 124.1, 62.9, 32.3, 26.5, 25.6, 12.7. *The spectroscopic properties were consistent with the data available in the literature.*[240]

(*Z*)-*N*-(Hept-5-en-1-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide



General procedure E: MsNHOTES (*vide supra*, 676 mg, 3.00 mmol) was employed with alcohol **(*Z*)-189** (1.1 eq.). The reaction time was 15 hours. FCC (eluent: PhMe) afforded the title compound (915 mg, 95 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3014 (m), 2955 (s), 2877 (s), 1459 (m), 1350 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 5.47 (1H, dqt, *J* = 10.5, 6.5, 1.5 Hz, C**6**-H), 5.36 (1H, dtq, *J* = 10.5, 7.0, 1.5 Hz, C**5**-H), 3.21 – 3.14 (2H, m, C**1**-H_2), 2.84 (3H, s, Ms CH_3), 2.07 (2H, br td, *J* = 7.5, 7.0 Hz, C**4**-H_2), 1.71 – 1.63 (2H, m, C**2**-H_2), 1.60 (3H, ddt, *J* = 6.5, 1.5, 1.0 Hz, C**7**-H_3), 1.41 (2H, tt, *J* = 7.5, 7.5 Hz, C**3**-H_2), 0.99 (9H, t, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.77 (6H, q, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 129.8 (C**5**), 124.5 (C**6**), 55.5 (C**1**), 30.3 (Ms CH_3), 2 × 26.7 (C**2** and C**3**), 26.3 (C**4**), 12.7 (C**7**), 6.7 ($Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{14}H_{32}NO_3SSi$: 322.1867. Found $[M+H]^+$: 322.1871.

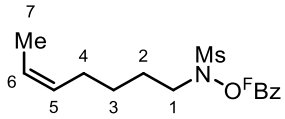
(*Z*)-*N*-(Hept-5-en-1-yl)-*N*-hydroxymethanesulfonamide



General procedure F: The preceding compound (874 mg, 2.72 mmol) was employed. FCC (eluent: 3:1 hexane:EtOAc) afforded the title compound (561 mg, 99 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3379 (br s), 3014 (m), 2934 (m), 1440 (m), 1334 (s), 1160 (s). δ_H (400 MHz, $CDCl_3$) 6.97 (1H, s, OH), 5.46 (1H, dq, *J* = 10.5, 6.5 Hz, C**6**-H), 5.36 (1H, dt, *J* = 10.5, 7.0 Hz, C**5**-H), 3.18 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 2.91 (3H, s, Ms CH_3), 2.07 (2H, td, *J* = 7.5, 7.0 Hz, C**4**-H_2), 1.70 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2),

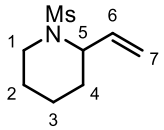
1.60 (3H, d, *J* = 6.5 Hz, C**7**-$\underline{H}_3$), 1.45 (2H, tt, *J* = 7.5, 7.5 Hz, C**3**-$\underline{H}_2$). δ_C (101 MHz, $CDCl_3$) 130.1 (C**5**), 124.5 (C**6**), 52.4 (C**1**), 31.0 (Ms $\underline{C}H_3$), 2 × 26.5 (C**2** and C**3**), 26.4 (C**4**), 12.9 (C**7**). HRMS: (ESI^+) Calculated for $C_8H_{17}NNaO_3S$: 230.0821. Found $[M+Na]^+$: 230.0811.

(*Z*)-*N*-(Hept-5-en-1-yl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (190)



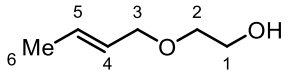
General procedure C: The preceding compound (529 mg, 2.55 mmol) was employed. FCC (eluent: 5:1 hexane:EtOAc) afforded **190** (915 mg, 89 %) as a colourless crystalline solid. m.p. 43-44 °C (Et_2O:hexane, *needles*). δ_H (400 MHz, $CDCl_3$) 5.53 – 5.40 (1H, m, C**6**-$\underline{H}$), 5.35 (1H, dtq, *J* = 10.5, 7.0, 1.5 Hz, C**5**-$\underline{H}$), 3.53 – 3.41 (2H, m, C**1**-$\underline{H}_2$), 3.03 (3H, s, Ms C$\underline{H}_3$), 2.08 (2H, td, *J* = 7.5, 7.0 Hz, C**4**-$\underline{H}_2$), 1.69 (2H, tt, *J* = 8.0, 7.0 Hz, C**2**-$\underline{H}_2$), 1.61 – 1.49 (5H, m, C**3**-$\underline{H}_2$ and C**7**-$\underline{H}_3$). δ_C (101 MHz, $CDCl_3$) 156.3 ($\underline{C}$=O), 129.5 (C**5**), 124.7 (C**6**), 52.3 (C**1**), 34.3 (Ms $\underline{C}H_3$), 26.2 (C**2**), 2 × 26.1 (C**3** and C**4**), 12.7 (C**7**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.0 (2F, m), -145.3 (1F, tt, *J* = 21.0, 5.5 Hz), -158.7 – -158.9 (2F, m). HRMS: (ESI^+) Calculated for $C_{15}H_{16}F_5NNaO_4S$: 424.0612. Found $[M+Na]^+$: 424.0599.

1-Mesyl-2-vinylpiperidine (191)



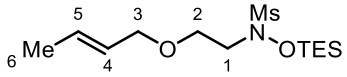
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 14 hours. Substrate **190** (56.2 mg, 0.140 mmol) was employed. FCC (gradient elution: 4:1 – 3:1 – 2:1 hexane:EtOAc) afforded **191** (3.7 mg, 14 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2933 (s), 2857 (m), 1446 (m), 1324 (s), 1146 (s). δ_H (500 MHz, $CDCl_3$) 6.06 (1H, ddd, *J* = 17.0, 10.5, 7.0 Hz, C**6**-$\underline{H}$), 5.36 – 5.29 (2H, m, C**7**-$\underline{H}_2$), 4.59 – 4.52 (1H, m, C**5**-$\underline{H}$), 3.72 – 3.66 (1H, m, C**1**-$\underline{H}$), 3.04 (1H, ddd, *J* = 12.5, 12.5, 3.0 Hz, C**1**-$\underline{H}$'), 1.91 – 1.51 (6H, m, C**2**-$\underline{H}_2$, C**3**-$\underline{H}_2$ and C**4**-$\underline{H}_2$). δ_C (126 MHz, $CDCl_3$) 134.7 (C**6**), 118.1 (C**7**), 55.4 (C**5**), 41.4 (C**1**), 39.0 (Ms $\underline{C}H_3$), 30.4 (C**4**), 25.5 (C**2**), 19.0 (C**3**). HRMS: (ESI^+) Calculated for $C_8H_{15}NNaO_2S$: 212.0716. Found $[M+Na]^+$: 212.0725.

(*E*)-2-(But-2-en-1-yloxy)ethan-1-ol (192)



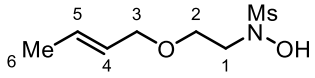
To a solution of ethylene glycol (7.76 g, 125 mmol) and KOH (2.81 g, 50.0 mmol) in water (20 mL) at 0 °C was added crotyl bromide (*vide supra*, 2.57 mL, 25.0 mmol). The resulting suspension was stirred at room temperature for 18 hours before addition of 1.0 M aqueous HCl (50 mL) and extraction with Et_2O (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 2:3 hexane:Et_2O) afforded **192** (1.44 g, 50 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) (br s), 2858 (m), 1450 (m), 1053 (s). δ_H (400 MHz, $CDCl_3$) 5.77 – 5.66 (1H, m, C**5**-H), 5.62 – 5.51 (1H, m, C**4**-H), 3.94 (2H, d, *J* = 6.5 Hz, C**3**-H_2), 3.73 – 3.68 (2H, m, C**1**-H_2), 3.54 – 3.48 (2H, m, C**2**-H_2), 2.26 (1H, br s, OH), 1.70 (3H, d, *J* = 6.5 Hz, C**6**-H_3). δ_C (101 MHz, $CDCl_3$) 129.9 (C**5**), 127.3 (C**4**), 71.8 (C**3**), 71.0 (C**2**), 61.8 (C**1**), 17.7 (C**6**). HRMS: (ESI^+) Calculated for $C_6H_{12}NaO_2$: 139.0730. Found $[M+Na]^+$: 139.0724.

(*E*)-*N*-(2-(But-2-en-1-yloxy)ethyl)-*N*-((triethylsilyl)oxy)methanesulfonamide



General procedure E: MsNHOTES (*vide supra*, 1.13 g, 5.00 mmol) was employed with alcohol **192** (1.1 eq.). The reaction time was 19 hours. FCC (eluent: 19:1 PhMe:Et_2O) afforded the title compound (1.12 g, 69 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2955 (m), 2877 (m), 1458 (m), 1350 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 5.79 – 5.65 (1H, m, C**5**-H), 5.55 (1H, dtq, *J* = 15.0, 6.5, 1.5 Hz, C**4**-H), 3.92 (2H, dq, *J* = 6.5, 1.0 Hz, C**3**-H_2), 3.64 (2H, t, *J* = 6.0 Hz, C**2**-H_2), 3.43 (2H, t, *J* = 6.0 Hz, C**1**-H_2), 2.90 (3H, s, Ms CH_3), 1.71 (3H, br d, *J* = 6.5 Hz, C**6**-H_3), 0.98 (9H, t, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.78 (6H, q, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 130.0 (C**5**), 127.1 (C**4**), 71.6 (C**3**), 65.8 (C**2**), 54.8 (C**1**), 30.8 (Ms CH_3), 17.7 (C**6**), 6.7 ($Si(CH_2CH_3)_3$), 4.6 ($Si(CH_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{13}H_{29}NNaO_4SSi$: 346.1479. Found $[M+Na]^+$: 346.1492.

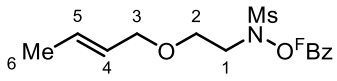
(*E*)-*N*-(2-(But-2-en-1-yloxy)ethyl)-*N*-hydroxymethanesulfonamide



General procedure F: The preceding compound (1.09 g, 3.37 mmol) was employed. FCC (eluent: 2:1 hexane:EtOAc) afforded the title compound (702 mg, 100 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3368 (br s), 2918 (m), 1449 (m), 1335 (s), 1162 (s). δ_H (400 MHz, $CDCl_3$) 7.81 (1H, br s, OH), 5.79 – 5.65 (1H, m, C**5**-H), 5.61 – 5.48 (1H, m, C**4**-H), 3.96 (2H, dq, *J* = 6.5, 1.0 Hz, C**3**-H_2), 3.70 (2H, t, *J* =

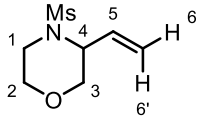
5.5 Hz, C**2**-H$_2$), 3.40 (2H, t, *J* = 5.5 Hz, C**1**-H$_2$), 2.95 (3H, s, Ms CH$_3$), 1.70 (3H, br d, *J* = 6.5 Hz, C**6**-H$_3$). δ_C (101 MHz, $CDCl_3$) 130.5 (C**5**), 126.8 (C**4**), 71.6 (C**3**), 65.9 (C**2**), 51.5 (C**1**), 31.9 (Ms CH$_3$), 17.7 (C**6**). HRMS: (ESI$^+$) Calculated for $C_7H_{15}NNaO_4S$: 232.0614. Found $[M+Na]^+$: 232.0619.

(*E*)-*N*-(2-(But-2-en-1-yloxy)ethyl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (194)



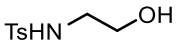
General procedure C: The preceding compound (650 mg, 3.11 mmol) was employed. FCC (eluent: 3:1 hexane:EtOAc) afforded **194** (1.07 g, 85 %) as a colourless crystalline solid. m.p. 67-68 °C (Et_2O:hexane). ν_{max} / cm^{-1}: (*solid*) 3021 (m), 2939 (m), 1789 (s), 1652 (m), 1503 (s), 1365 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 5.65 (1H, dqt, *J* = 15.5, 6.5, 1.0 Hz, C**5**-H), 5.49 – 5.40 (1H, m, C**4**-H), 3.86 (2H, ddq, *J* = 6.5, 1.0, 1.0 Hz, C**3**-H$_2$), 3.76 – 3.71 (2H, m, C**2**-H$_2$), 3.70 – 3.65 (2H, m, C**1**-H$_2$), 3.06 (3H, s, Ms CH$_3$), 1.64 (3H, ddt, *J* = 6.5, 1.5, 1.0 Hz, C**6**-H$_3$). δ_C (101 MHz, $CDCl_3$) 130.3 (C**5**), 126.8 (C**4**), 72.1 (C**3**), 67.2 (C**2**), 52.1 (C**1**), 34.6 (Ms CH$_3$), 17.7 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.2 – -135.3 (2F, m), -145.4 (1F, tt, *J* = 21.0, 6.0 Hz), -159.1 – -159.3 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{14}H_{14}F_5NNaO_5S$: 426.0405. Found $[M+Na]^+$: 426.0412.

4-Mesyl-3-vinylmorpholine (196)



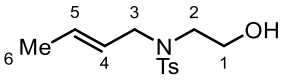
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% P(3,5-$(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 15 hours. Substrate **194** (56.5 mg, 0.140 mmol) was employed. FCC (gradient elution: 7:2 – 3:1 – 5:2 – 1:1 hexane:EtOAc) afforded **196** (1.2 mg, 4 %) as an orange oil. ν_{max} / cm^{-1}: (*film*) 2925 (m), 1455 (m), 1325 (s), 1151 (s). δ_H (500 MHz, $CDCl_3$) 6.26 (1H, ddd, *J* = 17.5, 10.5, 8.5 Hz, C**5**-H), 5.45 (1H, ddd, *J* = 17.5, 1.0, 1.0 Hz, C**6**-H'), 5.41 (1H, ddd, *J* = 10.5, 1.0, 1.0 Hz, C**6**-H), 4.25 – 4.21 (1H, m, C**4**-H), 3.97 (1H, ddd, *J* = 11.5, 3.5, 2.0 Hz, C**2**-H), 3.88 (1H, dd, *J* = 11.5, 2.0 Hz, C**3**-H), 3.81 (1H, dd, *J* = 11.5, 3.0 Hz, C**3**-H'), 3.68 (1H, ddd, *J* = 11.5, 11.5, 3.0 Hz, C**2**-H'), 3.48 (1H, ddd, *J* = 12.5, 3.0, 2.0 Hz, C**1**-H), 3.30 (1H, ddd, *J* = 12.5, 11.5, 3.5 Hz, C**1**-H'), 2.84 (3H, s, Ms CH$_3$). δ_C (126 MHz, $CDCl_3$) 132.5 (C**5**), 120.0 (C**6**), 71.2 (C**3**), 66.8 (C**2**), 56.4 (C**4**), 41.4 (C**1**), 38.2 (Ms CH$_3$). HRMS: (ESI$^+$) Calculated for $C_7H_{13}NNaO_3S$: 214.0508. Found $[M+Na]^+$: 214.0511.

N-(2-Hydroxyethyl)-4-toluenesulfonamide



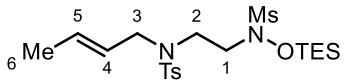
This compound was prepared according to a literature procedure.[241] To a solution of ethanolamine (6.02 mL, 100 mmol) and TsCl (21.0 g, 110 mmol) in anhydrous CH_2Cl_2 (250 mL) at 0 °C was added Et_3N (15.3 mL, 110 mmol) dropwise. The reaction mixture was stirred at room temperature for 19 hours before dilution with CH_2Cl_2 (100 mL) and addition of water (150 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 2:1 – 1:1 – 1:2 hexane:EtOAc) afforded the title compound (15.2 g, 71 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3559 (br s), 3262 (br s), 2935 (m), 2882 (m), 1597 (m), 1310 (s), 1151 (s), 1066 (s). δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* = 8.0 Hz), 7.30 (2H, d, *J* = 8.0 Hz), 5.42 (1H, t, *J* = 6.0 Hz), 3.67 (2H, dt, *J* = 5.5, 5.0 Hz), 3.06 (2H, dt, *J* = 6.0, 5.0 Hz), 2.61 (1H, t, *J* = 5.5 Hz), 2.41 (3H, s). δ_C (101 MHz, $CDCl_3$) 143.6, 136.5, 129.8, 127.1, 61.3, 45.2, 21.5. HRMS: (ESI^+) Calculated for $C_9H_{13}NNaO_3S$: 238.0508. Found $[M+Na]^+$: 238.0499. *The spectroscopic properties were consistent with the data available in the literature*.[242]

(*E*)-*N*-(But-2-en-1-yl)-*N*-(2-hydroxyethyl)-4-toluenesulfonamide (193)



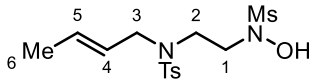
A solution of the preceding compound (2.15 g, 10.0 mmol), K_2CO_3 (2.07 g, 15.0 mmol) and crotyl bromide (*vide supra*, 1.54 mL, 15.0 mmol) in acetone (20 mL) was stirred at room temperature for 30 hours before being concentrated *in vacuo*. FCC (gradient elution: 2:1 – 3:2 – 1:1 hexane:EtOAc) afforded **193** (2.19 g, 81 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3520 (br s), 2920 (m), 1598 (m), 1330 (s), 1153 (s). δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.30 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.60 (1H, dqt, *J* = 15.0, 6.5, 1.0 Hz, C**5**-<u>H</u>), 5.29 (1H, dtq, *J* = 15.0, 6.5, 1.5 Hz, C**4**-<u>H</u>), 3.77 (2H, br d, *J* = 6.5 Hz, C**3**-<u>H_2</u>), 3.71 (2H, t, *J* = 5.5 Hz, C**1**-<u>H_2</u>), 3.21 (2H, t, *J* = 5.5 Hz, C**2**-<u>H_2</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 2.17 (1H, br s, O<u>H</u>), 1.64 (3H, br d, *J* = 6.5 Hz, C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 143.5 (Ar<u>C</u>), 136.3 (Ar<u>C</u>), 131.0 (C**5**), 129.7 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 125.6 (C**4**), 61.1 (C**1**), 51.5 (C**3**), 49.5 (C**2**), 21.5 (Ts <u>C</u>H_3), 17.6 (C**6**). HRMS: (ESI^+) Calculated for $C_{13}H_{19}NNaO_3S$: 292.0978. Found $[M+Na]^+$: 292.0990.

(*E*)-*N*-(But-2-en-1-yl)-*N*-(2-(*N*-((triethylsilyl)oxy)methylsulfonamido)ethyl)-4-toluenesulfonamide



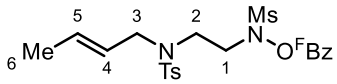
General procedure E: MsNHOTES (*vide supra*, 1.13 g, 5.00 mmol) was employed with alcohol **193** (1.1 eq.). The reaction time was 18 hours. FCC (gradient elution: 1:0 – 19:1 – 9:1 PhMe:Et_2O) afforded the title compound (2.15 g, 90 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2957 (m), 2878 (m), 1599 (m), 1350 (s), 1159 (s). δ_H (400 MHz, $CDCl_3$) 7.67 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.30 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.62 (1H, dq, *J* = 15.0, 7.0 Hz, C**5**-<u>H</u>), 5.28 (1H, dt, *J* = 15.0, 7.0 Hz, C**4**-<u>H</u>), 3.71 (2H, d, *J* = 7.0 Hz, C**3**-<u>H_2</u>), 3.44 – 3.37 (2H, m, C**1**-<u>H_2</u>), 3.35 – 3.27 (2H, m, C**2**-<u>H_2</u>), 2.86 (3H, s, Ms C<u>H_3</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 1.65 (3H, d, *J* = 7.0 Hz, C**6**-<u>H_3</u>), 0.99 (9H, t, *J* = 8.0 Hz, Si(CH_2C<u>H_3</u>)$_3$), 0.75 (6H, q, *J* = 8.0 Hz, Si(C<u>H_2</u>CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 143.5 (Ar<u>C</u>), 136.1 (Ar<u>C</u>), 131.6 (C**5**), 129.7 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 125.2 (C**4**), 55.1 (C**1**), 51.6 (C**3**), 45.0 (C**2**), 30.4 (Ms <u>C</u>H_3), 21.5 (Ts <u>C</u>H_3), 17.7 (C**6**), 6.7 (Si(CH_2<u>C</u>H_3)$_3$), 4.5 (Si(<u>C</u>H_2CH_3)$_3$). HRMS: (ESI^+) Calculated for $C_{20}H_{37}N_2O_5S_2Si$: 477.1908. Found $[M+H]^+$: 477.1901.

(*E*)-*N*-(But-2-en-1-yl)-*N*-(2-(*N*-hydroxymethylsulfonamido)ethyl)-4-toluenesulfonamide



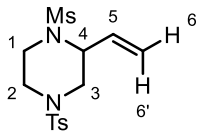
General procedure F: The preceding compound (2.05 g, 4.30 mmol) was employed. FCC (eluent: 2:1 hexane:EtOAc) afforded the title compound (1.51 g, 97 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3389 (br s), 3027 (m), 2939 (m), 1599 (m), 1341 (s), 1155 (s). δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.31 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.02 (1H, br s, O<u>H</u>), 5.62 (1H, dq, *J* = 15.0, 6.5 Hz, C**5**-<u>H</u>), 5.27 (1H, dt, *J* = 15.0, 7.0 Hz, C**4**-<u>H</u>), 3.76 (2H, d, *J* = 7.0 Hz, C**3**-<u>H_2</u>), 3.45 (2H, t, *J* = 5.5 Hz, C**2**-<u>H_2</u>), 3.34 (2H, t, *J* = 5.5 Hz, C**1**-<u>H_2</u>), 3.00 (3H, s, Ms C<u>H_3</u>), 2.43 (3H, s, Ts C<u>H_3</u>), 1.64 (3H, d, *J* = 6.5 Hz, C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 143.6 (Ar<u>C</u>), 136.7 (Ar<u>C</u>), 131.4 (C**5**), 129.8 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 125.1 (C**4**), 50.1 (C**3**), 49.1 (C**1**), 43.2 (C**2**), 33.1 (Ms <u>C</u>H_3), 21.5 (Ts <u>C</u>H_3), 17.6 (C**6**). HRMS: (ESI^+) Calculated for $C_{14}H_{22}N_2NaO_5S_2$: 385.0862. Found $[M+Na]^+$: 385.0860.

(*E*)-*N*-(But-2-en-1-yl)-*N*-(2-(*N*-(pentafluorobenzoyloxy)methylsulfonamido)ethyl)-4-toluenesulfonamide (195)



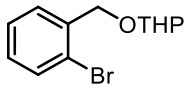
General procedure C: The preceding compound (1.47 g, 4.06 mmol) was employed. FCC (gradient elution: 3:1 – 2:1 hexane:EtOAc) afforded **195** (1.57 g, 69 %) as a colourless crystalline solid. m.p. 109-110 °C (CH_2Cl_2:hexane, *needles*). ν_{max} / cm^{-1}: (*solid*) 3018 (m), 2946 (m), 1785 (s), 1655 (m), 1599 (m), 1503 (s), 1361 (s), 1158 (s). δ_H (400 MHz, $CDCl_3$) 7.66 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.30 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.62 (1H, dq, *J* = 15.0, 6.5 Hz, C**5**-<u>H</u>), 5.26 (1H, dtq, *J* = 15.0, 7.0, 1.5 Hz, C**4**-<u>H</u>), 3.78 – 3.68 (4H, m, C**1**-<u>H_2</u> and C**3**-<u>H_2</u>), 3.40 – 3.33 (2H, m, C**2**-<u>H_2</u>), 3.06 (3H, s, Ms C<u>H_3</u>), 2.42 (3H, s, Ts C<u>H_3</u>), 1.62 (3H, dd, *J* = 6.5, 1.5 Hz, C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 143.8 (Ar<u>C</u>), 135.8 (Ar<u>C</u>), 132.0 (C**5**), 129.8 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 124.9 (C**4**), 52.5 (C**1**), 51.7 (C**3**), 44.5 (C**2**), 34.6 (Ms <u>C</u>H_3), 21.5 (Ts <u>C</u>H_3), 17.6 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.5 – -135.6 (2F, m), -144.6 (1F, tt, *J* = 21.0, 6.0 Hz), -158.5 – -158.7 (2F, m). HRMS: (ESI^+) Calculated for $C_{21}H_{21}F_5N_2NaO_6S_2$: 579.0653. Found $[M+Na]^+$: 579.0649.

1-Mesyl-4-tosyl-2-vinylpiperazine



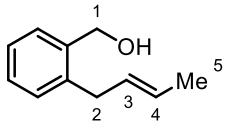
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 16 hours. Substrate **195** (77.9 mg, 0.140 mmol) was employed. FCC (gradient elution: 4:1 – 3:1 – 2:1 – 1:1 hexane:EtOAc) afforded **197** (8.4 mg, 17 %) as a yellow oil. ν_{max} / cm^{-1}: (*film*) 2927 (m), 1598 (m), 1454 (m), 1338 (s), 1163 (s). δ_H (500 MHz, $CDCl_3$) 7.63 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.37 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 6.21 (1H, ddd, *J* = 17.5, 10.5, 8.0 Hz, C**5**-<u>H</u>), 5.49 (1H, ddd, *J* = 17.5, 1.0, 1.0 Hz, C**6**-<u>H</u>'), 5.45 (1H, ddd, *J* = 10.5, 1.0, 1.0 Hz, C**6**-<u>H</u>), 4.50 – 4.46 (1H, m, C**4**-<u>H</u>), 3.80 – 3.73 (2H, m, C**2**-<u>H</u> and C**3**-<u>H</u>), 3.70 – 3.65 (1H, m, C**1**-<u>H</u>), 3.36 – 3.27 (1H, m, C**1**-<u>H</u>'), 2.82 (3H, s, Ms C<u>H_3</u>), 2.63 (1H, dd, *J* = 11.5, 3.5 Hz, C**3**-<u>H</u>'), 2.49 – 2.45 (4H, m, C**2**-<u>H</u>' and Ts C<u>H_3</u>). δ_C (126 MHz, $CDCl_3$) 144.3 (Ar<u>C</u>), 132.1 (Ar<u>C</u>), 131.9 (C**5**), 129.9 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 120.8 (C**6**), 55.3 (C**4**), 50.4 (C**3**), 46.1 (C**2**), 40.6 (C**1**), 39.0 (Ms <u>C</u>H_3), 21.6 (Ts <u>C</u>H_3). HRMS: (ESI^+) Calculated for $C_{14}H_{20}N_2NaO_4S_2$: 367.0757. Found $[M+Na]^+$: 367.0761.

2-((2-Bromobenzyl)oxy)tetrahydro-2*H*-pyran (200)



This compound was prepared according to a literature procedure.[243] To a solution of 2-bromobenzyl alcohol (9.00 g, 48.1 mmol) and 3,4-dihydropyran (5.26 g, 62.5 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added $TsOH{\cdot}H_2O$ (183 mg, 0.962 mmol). The reaction mixture was stirred at room temperature for 8 hours before addition of 5 % aqueous K_2CO_3 (100 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 14:1 hexane:EtOAc) afforded **200** (8.98 g, 69 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2941 (m), 1569 (m), 1440 (m), 1200 (m), 1124 (s), 1022 (s). δ_H (400 MHz, $CDCl_3$) 7.56 – 7.49 (2H, m), 7.34 – 7.28 (1H, m), 7.17 – 7.11 (1H, m), 4.83 (1H, d, *J* = 13.5 Hz), 4.78 (1H, dd, *J* = 3.5, 3.5 Hz), 4.58 (1H, d, *J* = 13.5 Hz), 3.93 (1H, ddd, *J* = 11.5, 8.5, 3.0 Hz), 3.61 – 3.53 (1H, m), 1.97 – 1.83 (1H, m), 1.83 – 1.67 (2H, m), 1.67 – 1.49 (3H, m). δ_C (101 MHz, $CDCl_3$) 137.8, 132.5, 129.0, 128.7, 127.3, 122.7, 98.4, 68.5, 62.2, 30.5, 25.4, 19.3. *The spectroscopic properties were consistent with the data available in the literature*.[243]

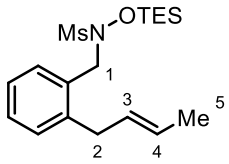
(*E*)-(2-(But-2-en-1-yl)phenyl)methanol (201)



This compound was prepared according to a literature procedure.[244] To a suspension of magnesium turnings (493 mg, 20.3 mmol), activated with a crystal of iodine, in anhydrous THF (5 mL) was added a solution of bromide **200** (5.00 g, 18.4 mmol) in anhydrous THF (15 mL) at such a rate as to maintain a gentle reflux. The reaction mixture was stirred for 45 minutes before addition of crotyl bromide (*vide supra*, 2.45 mL, 23.9 mmol). The reaction mixture was stirred at room temperature for 19 hours before addition of saturated aqueous NH_4Cl (35 mL) and Et_2O (80 mL). The resulting phases were separated, and the organic phase was washed with water (40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was dissolved in MeOH (10 mL) and 1.0 M aqueous HCl (10 mL) and stirred at room temperature for 5 hours before being concentrated to an aqueous solution. The reaction mixture was dissolved in Et_2O (150 mL) then washed with 5 % aqueous $NaHCO_3$ (2 × 50 mL), water (50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 19:1 PhMe:EtOAc) afforded **201** (1.74 g, 58 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3317 (br s), 3022 (m), 2916 (m), 2855 (m), 1489 (m), 1452 (s), 1004 (s). δ_H (400 MHz, $CDCl_3$) 7.40 – 7.36 (1H, m, ArC<u>H</u>), 7.29 – 7.18 (3H, m, 3 × ArC<u>H</u>), 5.65 – 5.56 (1H, m, C**3**-<u>H</u>), 5.45 (1H, dqt, *J* = 15.5, 6.5, 1.5 Hz, C**4**-<u>H</u>), 4.70 (2H, s, C**1**-<u>H_2</u>), 3.40 (2H, ddq, *J* = 6.5, 1.5, 1.5 Hz, C**2**-<u>H_2</u>), 1.67 (3H, ddt, *J* = 6.5, 1.5,

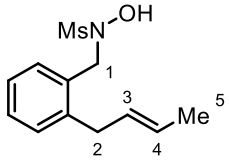
1.5 Hz, C**5**-H$_3$). δ_C (101 MHz, $CDCl_3$) 138.8 (ArC), 138.5 (ArC), 130.0 (C**3**), 129.7 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 2 × 126.5 (C**4** and ArCH), 63.2 (C**1**), 35.6 (C**2**), 17.9 (C**5**). HRMS: (ESI^+) Calculated for $C_{11}H_{14}NaO$: 185.0937. Found $[M+Na]^+$: 185.0939. *The ^{1}H NMR and IR spectra were consistent with the data available in the literature; however, the ^{13}C NMR spectrum differed in the aromatic region.*[244] *The data presented here is supported by HSQC analysis.*

(*E*)-*N*-(2-(But-2-en-1-yl)benzyl)-*N*-((triethylsilyl)oxy)methanesulfonamide



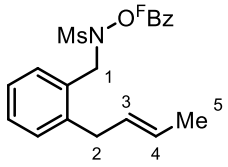
General procedure E: MsNHOTES (*vide supra*, 1.13 g, 5.00 mmol) was employed with alcohol **201** (1.1 eq.). The reaction time was 15 hours. FCC (eluent: 1:4 hexane:PhMe) afforded the title compound (1.62 g, 88 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3025 (m), 2955 (s), 2877 (s), 1492 (m), 1456 (s), 1349 (s), 1165 (s). δ_H (400 MHz, $CDCl_3$) 7.34 – 7.16 (4H, m, 4 × ArCH), 5.54 (1H, dtq, *J* = 15.0, 6.5, 1.5 Hz, C**3**-H), 5.46 (1H, dqt, *J* = 15.0, 6.0, 1.0 Hz, C**4**-H), 4.32 (2H, s, C**1**-H$_2$), 3.49 (2H, br d, *J* = 6.5 Hz, C**2**-H$_2$), 2.94 (3H, s, Ms CH$_3$), 1.66 (3H, ddt, *J* = 6.0, 1.5, 1.5 Hz, C**5**-H$_3$), 0.79 (9H, t, *J* = 8.0 Hz, Si(CH_2CH_3)$_3$), 0.35 (6H, q, *J* = 8.0 Hz, Si(CH_2CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 141.0 (ArC), 2 × 132.1 (ArC and ArCH), 129.8 (ArCH), 129.2 (C**3**), 128.9 (ArCH), 126.7 (C**4**), 126.0 (ArCH), 56.9 (C**1**), 35.4 (C**2**), 30.1 (Ms CH$_3$), 17.9 (C**5**), 6.6 (Si(CH_2CH_3)$_3$), 4.3 (Si(CH_2CH_3)$_3$). HRMS: (ESI^+) Calculated for $C_{18}H_{31}NNaO_3SSi$: 392.1686. Found $[M+Na]^+$: 392.1689.

(*E*)-*N*-(2-(But-2-en-1-yl)benzyl)-*N*-hydroxymethanesulfonamide



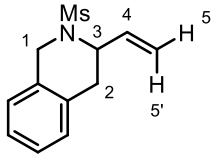
General procedure F: The preceding compound (1.55 g, 4.19 mmol) was employed. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (959 mg, 90 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3342 (br s), 3031 (m), 2963 (m), 1491 (m), 1448 (s), 1329 (s), 1152 (s). δ_H (400 MHz, $CDCl_3$) 7.36 – 7.17 (4H, m, 4 × ArCH), 6.05 (1H, br s, OH), 5.56 (1H, dtq, *J* = 15.0, 6.5, 1.5 Hz, C**3**-H), 5.45 (1H, dqt, *J* = 15.0, 6.0, 1.5 Hz, C**4**-H), 4.36 (2H, s, C**1**-H$_2$), 3.44 (2H, br d, *J* = 6.5 Hz, C**2**-H$_2$), 3.00 (3H, s, Ms CH$_3$), 1.66 (3H, ddt, *J* = 6.0, 1.5, 1.5 Hz, C**5**-H$_3$). δ_C (101 MHz, $CDCl_3$) 140.4 (ArC), 132.0 (ArC), 131.1 (ArCH), 130.0 (ArCH), 129.3 (C**3**), 128.7 (ArCH), 126.7 (C**4**), 126.2 (ArCH), 53.8 (C**1**), 35.4 (C**2**), 31.6 (Ms CH$_3$), 17.9 (C**5**). HRMS: (ESI^+) Calculated for $C_{12}H_{17}NNaO_3S$: 278.0821. Found $[M+Na]^+$: 278.0823.

(*E*)-*N*-(2-(But-2-en-1-yl)benzyl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (202)

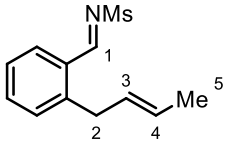


General procedure C: The preceding compound (949 mg, 3.72 mmol) was employed. FCC (eluent: 29:1 hexane:EtOAc) afforded **202** (1.09 g, 65 %) as a colourless crystalline solid. m.p. 122-123 °C (CH_2Cl_2:hexane, *needles*). ν_{max} / cm^{-1}: (*solid*) 3028 (m), 1790 (s), 1654 (m), 1509 (s), 1348 (s), 1159 (s). δ_H (400 MHz, $CDCl_3$) 7.32 – 7.21 (3H, m, 3 × ArC<u>H</u>), 7.17 – 7.12 (1H, m, ArC<u>H</u>), 5.59 (1H, dtq, *J* = 15.5, 6.0, 1.5 Hz, C**3**-<u>H</u>), 5.50 (1H, dqt, *J* = 15.5, 6.0, 1.0 Hz, C**4**-<u>H</u>), 4.63 (2H, br s, C**1**-<u>H_2</u>), 3.57 (2H, br d, *J* = 6.0 Hz, C**2**-<u>H_2</u>), 3.12 (3H, s, Ms C<u>H_3</u>), 1.67 (3H, ddt, *J* = 6.0, 1.5, 1.5 Hz, C**5**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 141.2 (Ar<u>C</u>), 130.9 (Ar<u>C</u>H), 130.2 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>), 129.3 (Ar<u>C</u>H), 129.0 (C**3**), 126.9 (C**4**), 126.2 (Ar<u>C</u>H), 53.9 (C**1**), 35.4 (C**2**), 34.8 (Ms <u>C</u>H_3), 17.9 (C**5**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.7 – -135.8 (2F, m), -145.6 (1F, tt, *J* = 21.0, 5.5 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{19}H_{16}F_5NNaO_4S$: 472.0162. Found $[M+Na]^+$: 472.0604.

2-Mesyl-3-vinyl-1,2,3,4-tetrahydroisoquinoline (203) and *N*-(2-((*E*)-But-2-en-1-yl)benzylidene)-methanesulfonamide (204)



203



204

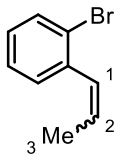
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; PhMe (0.1 M); 160 °C; 15 hours. Substrate **202** (62.9 mg, 0.140 mmol) was employed. FCC (gradient elution: 6:1 – 4:1 – 3:1 hexane:EtOAc) afforded **203** (11.5 mg, 35 %) as a pale-yellow oil.

*The standard conditions afforded a reduced yield of **203**, along with a considerable amount of side product **204**:* **General procedure D:** Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 17 hours. Substrate **202** (62.9 mg, 0.140 mmol) was employed. FCC (gradient elution: 5:1 – 3:1 – 2:1 – 1:1 hexane:EtOAc) afforded **204** (16.0 mg, 48 %) as a colourless oil and **203** (5.0 mg, 15 %) as a pale-yellow oil. *Spectroscopic data for **203**:* ν_{max} / cm^{-1}: (*film*) 2929 (m), 1455 (m), 1325 (s), 1151 (s). δ_H (400 MHz, $CDCl_3$) 7.24 – 7.19 (2H, m, 2 × ArC<u>H</u>), 7.18 – 7.14 (1H, m, ArC<u>H</u>), 7.12 – 7.08 (1H, m, ArC<u>H</u>), 5.83 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz, C**4**-<u>H</u>), 5.32 (1H, ddd, *J* = 17.0, 1.5, 1.5 Hz, C**5**-<u>H</u>'), 5.21 (1H, ddd, *J* = 10.5, 1.5, 1.5 Hz, C**5**-<u>H</u>), 4.79

– 4.73 (1H, m, C**3**-H), 4.67 (1H, d, *J* = 16.0 Hz, C**1**-H), 4.30 (1H, d, *J* = 16.0 Hz, C**1**-H'), 3.27 (1H, dd, *J* = 16.0, 6.0 Hz, C**2**-H), 2.88 – 2.79 (4H, m, C**2**-H' and Ms CH_3). δ_C (101 MHz, $CDCl_3$) 135.1 (C**4**), 132.0 (ArC), 131.5 (ArC), 129.2 (ArCH), 127.2 (ArCH), 126.6 (ArCH), 126.0 (ArCH), 118.4 (C**5**), 54.0 (C**3**), 43.6 (C**1**), 38.4 (Ms CH_3), 33.5 (C**2**). HRMS: (ESI^+) Calculated for $C_{12}H_{15}NNaO_2S$: 260.0716. Found $[M+Na]^+$: 260.0711.

*Spectroscopic data for **204**:* δ_H (400 MHz, $CDCl_3$) 9.35 (1H, s, C**1**-H), 8.11 (1H, dd, *J* = 8.0, 1.5 Hz, ArCH), 7.59 – 7.53 (1H, m, ArCH), 7.38 – 7.28 (2H, m, 2 × ArCH), 5.58 (1H, dtq, *J* = 15.5, 6.0, 1.5 Hz, C**3**-H), 5.43 (1H, dqt, *J* = 15.5, 6.5, 1.5 Hz, C**4**-H), 3.64 (2H, br d, *J* = 6.0 Hz, C**2**-H_2), 3.12 (3H, s, Ms CH_3), 1.66 (3H, ddt, *J* = 6.5, 1.5, 1.5 Hz, C**5**-H_3). δ_C (101 MHz, $CDCl_3$) 170.1 (C**1**), 145.1 (ArC), 135.0 (ArCH), 130.9 (ArCH), 130.0 (ArC), 129.9 (ArCH), 129.3 (C**3**), 127.8 (C**4**), 127.0 (ArCH), 40.3 (Ms CH_3), 35.9 (C**2**), 17.9 (C**5**). HRMS: (ESI^+) Calculated for $C_{12}H_{16}NO_2S$: 238.0896. Found $[M+H]^+$: 238.0901.

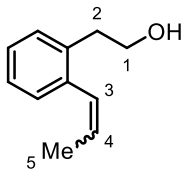
1-Bromo-2-(prop-1-en-1-yl)benzene (205)



This compound was prepared according to a literature procedure.[245] To a suspension of ethyltriphenylphosphonium iodide (25.1 g, 60.0 mmol) in anhydrous THF (400 mL) at -78 °C was added *n*-BuLi (1.55 M in hexane, 38.7 mL, 60.0 mmol). The reaction mixture was stirred at room temperature for 2 hours, then cooled to -78 °C before addition of 2-bromobenzaldehyde (5.84 mL, 50.0 mmol). The reaction mixture was stirred at -78 °C for 4 hours and then at room temperature for a further 20 hours. The reaction mixture was cooled to -40 °C before addition of water (75 mL) and extraction with Et_2O (3 × 200 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 40:1 pentane:Et_2O) afforded **205** (5.82 g, 59 %, 3:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3022 (m), 2913 (m), 1467 (s), 1431 (s). 1023 (s). *^{1}H and ^{13}C NMR data for the major (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.61 – 7.56 (1H, m, ArCH), 7.33 – 7.21 (2H, m, 2 × ArCH), 7.14 – 7.07 (1H, m, ArCH), 6.49 (1H, dq, *J* = 11.5, 2.0 Hz, C**1**-H), 5.90 (1H, dq, *J* = 11.5, 7.0 Hz, C**2**-H), 1.79 (3H, dd, *J* = 7.0, 2.0 Hz, C**3**-H_3). δ_C (101 MHz, $CDCl_3$) 137.5 (ArC), 132.7 (ArCH), 130.8 (ArCH), 129.5 (C**1**), 128.3 (ArCH), 128.2 (C**2**), 126.9 (ArCH), 124.2 (ArC), 14.5 (C**3**). *^{1}H and ^{13}C NMR data for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.54 – 7.50 (1H, m, ArCH), 7.49 – 7.45 (1H, m, ArCH), 7.32 – 7.21 (1H, m, ArCH), 7.08 – 7.02 (1H, m, ArCH), 6.74 (1H, dq, *J* = 15.5, 2.0 Hz, C**1**-H), 6.19 (1H, dq, *J* = 15.5, 6.5 Hz, C**2**-H), 1.93 (3H, dd, *J* = 6.5, 2.0 Hz, C**3**-H_3). δ_C (101 MHz, $CDCl_3$) 137.8 (ArC), 132.9 (ArCH), 130.0 (C**1**), 129.0 (C**2**), 128.2 (ArCH), 127.5

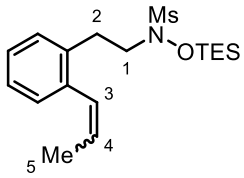
(ArC<u>H</u>), 126.9 (ArC<u>H</u>), 123.1 (Ar<u>C</u>), 18.8 (C**3**). HRMS: (EI$^+$) Calculated for C_9H_9Br: 195.9888. Found $[M]^+$: 195.9986.

2-(2-(Prop-1-en-1-yl)phenyl)ethan-1-ol (206)



To a solution of the bromide **205** (2.96 g, 15.0 mmol) in anhydrous THF (40 mL) at -78 °C was added *n*-BuLi (1.55 M in hexane, 10.6 mL, 16.5 mmol). The reaction mixture was stirred at -78 °C for 2 hours before addition of ethylene oxide (*approx.* 3 M in THF, 7.5 mL, 22.5 mmol). The reaction mixture was stirred at room temperature for 18 hours before addition of saturated aqueous NH_4Cl (30 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 3:1 hexane:EtOAc) afforded **206** (1.50 g, 62 %, 3:1 mixture of (*Z*)- and (*E*)-isomers) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3322 (br s), 3017 (m), 2937 (m), 2876 (m), 1484 (s), 1446 (s), 1041 (s). *^{1}H and ^{13}C NMR data for the major (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.25 – 7.15 (4H, m, 4 × ArC<u>H</u>), 6.55 (1H, dq, *J* = 11.5, 2.0 Hz, C**3**-<u>H</u>), 5.86 (1H, dq, *J* = 11.5, 7.0 Hz, C**4**-<u>H</u>), 3.78 (2H, t, *J* = 7.0 Hz, C**1**-<u>H</u>$_2$), 2.88 (2H, t, *J* = 7.0 Hz, C**2**-<u>H</u>$_2$), 1.73 (3H, dd, *J* = 7.0, 2.0 Hz, C**5**-<u>H</u>$_3$), 1.46 (1H, br s, O<u>H</u>). δ_C (101 MHz, $CDCl_3$) 136.9 (Ar<u>C</u>), 136.6 (Ar<u>C</u>), 2 × 130.0 (2 × Ar<u>C</u>H), 128.7 (C**3**), 127.8 (C**4**), 127.1 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 63.1 (C**1**), 36.9 (C**2**), 14.4 (C**5**). *^{1}H and ^{13}C NMR data for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.46 – 7.41 (1H, m, ArC<u>H</u>), 7.25 – 7.15 (3H, m, 3 × ArC<u>H</u>), 6.66 (1H, dq, *J* = 15.5, 2.0 Hz, C**3**-<u>H</u>), 6.12 (1H, dq, *J* = 15.5, 6.5 Hz, C**4**-<u>H</u>), 3.82 (2H, t, *J* = 7.0 Hz, C**1**-<u>H</u>$_2$), 2.96 (2H, t, *J* = 7.0 Hz, C**2**-<u>H</u>$_2$), 1.91 (3H, dd, *J* = 6.5, 2.0 Hz, C**5**-<u>H</u>$_3$), 1.46 (1H, br s, O<u>H</u>). δ_C (101 MHz, $CDCl_3$) 137.5 (Ar<u>C</u>), 135.0 (Ar<u>C</u>), 130.3 (Ar<u>C</u>H), 128.5 (C**3**), 128.0 (C**4**), 127.1 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 63.3 (C**1**), 36.9 (C**2**), 18.9 (C**5**). HRMS: (ESI$^+$) Calculated for $C_{11}H_{14}NaO$: 185.0937. Found $[M+Na]^+$: 185.0930.

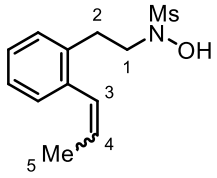
***N*-(2-(Prop-1-en-1-yl)phenethyl)-*N*-((triethylsilyl)oxy)methanesulfonamide**



<u>General procedure E:</u> MsNHOTES (*vide supra*, 902 mg, 4.00 mmol) was employed with alcohol **206** (1.3 eq.). The reaction time was 16 hours. FCC (eluent: PhMe) afforded the title compound (1.11 g,

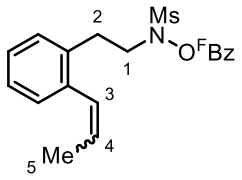
75 %, 3:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2956 (m), 2877 (m), 1458 (m), 1351 (s), 1164 (s). *^{1}H and ^{13}C NMR data for the major (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.24 – 7.13 (4H, m, 4 × ArC<u>H</u>), 6.52 (1H, dq, *J* = 11.5, 1.5 Hz, C**3**-<u>H</u>), 5.89 (1H, dq, *J* = 11.5, 7.0 Hz, C**4**-<u>H</u>), 3.37 – 3.30 (2H, m, C**1**-<u>H_2</u>), 3.01 – 2.96 (2H, m, C**2**-<u>H_2</u>), 2.86 (3H, s, Ms C<u>H_3</u>), 1.73 (3H, dd, *J* = 7.0, 1.5 Hz, C**5**-<u>H_3</u>), 1.06 – 0.99 (9H, m, Si($CH_2C\underline{H}_3)_3$), 0.85 – 0.77 (6H, m, Si($C\underline{H}_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 136.5 (Ar<u>C</u>), 136.1 (Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 128.1 (C**4**), 128.0 (C**3**), 127.2 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 56.0 (C**1**), 31.6 (C**2**), 30.6 (Ms <u>C</u>H_3), 14.3 (C**5**), 6.7 (Si($CH_2\underline{C}H_3)_3$), 4.8 (Si($\underline{C}H_2CH_3)_3$). *^{1}H and ^{13}C NMR data for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.44 – 7.39 (1H, m, ArC<u>H</u>), 7.24 – 7.13 (3H, m, 3 × ArC<u>H</u>), 6.64 (1H, dq, *J* = 15.5, 2.0 Hz, C**3**-<u>H</u>), 6.14 (1H, dq, *J* = 15.5, 6.5 Hz, C**4**-<u>H</u>), 3.37 – 3.30 (2H, m, C**1**-<u>H_2</u>), 3.09 – 3.04 (2H, m, C**2**-<u>H_2</u>), 2.87 (3H, s, Ms C<u>H_3</u>), 1.92 (3H, dd, *J* = 6.5, 2.0 Hz, C**5**-<u>H_3</u>), 1.06 – 0.99 (9H, m, Si($CH_2C\underline{H}_3)_3$), 0.85 – 0.77 (6H, m, Si($C\underline{H}_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 137.1 (Ar<u>C</u>), 134.6 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 128.4 (C**3**), 127.9 (C**4**), 127.2 (Ar<u>C</u>H), 127.1 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 56.0 (C**1**), 31.6 (C**2**), 30.5 (Ms <u>C</u>H_3), 18.8 (C**5**), 6.7 (Si($CH_2\underline{C}H_3)_3$), 4.8 (Si($\underline{C}H_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{18}H_{32}NO_3SSi$: 370.1867. Found $[M+H]^+$: 388.1866.

***N*-(2-(Prop-1-en-1-yl)phenethyl)-*N*-hydroxy-methanesulfonamide**



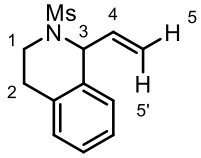
<u>General procedure F:</u> The preceding compound (1.08 g, 2.92 mmol) was employed. FCC (eluent: 3:1 hexane:EtOAc) afforded the title compound (697 mg, 93 %, 3:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3381 (br s), 3019 (m), 2936 (m), 1333 (s), 1160 (s). *^{1}H and ^{13}C NMR data for the major (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.25 – 7.15 (4H, m, 4 × ArC<u>H</u>), 6.72 (1H, br s, O<u>H</u>), 6.55 (1H, dq, *J* = 11.5, 2.0 Hz, C**3**-<u>H</u>), 5.89 (1H, dq, *J* = 11.5, 7.0 Hz, C**4**-<u>H</u>), 3.39 – 3.33 (2H, m, C**1**-<u>H_2</u>), 3.04 – 2.98 (2H, m, C**2**-<u>H_2</u>), 2.90 (3H, s, Ms C<u>H_3</u>), 1.73 (3H, dd, *J* = 7.0, 2.0 Hz, C**5**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 136.6 (Ar<u>C</u>), 136.1 (Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 128.3 (C**3**), 128.1 (C**4**), 127.2 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 52.8 (C**1**), 31.2 (C**2**), 31.1 (Ms <u>C</u>H_3), 14.3 (C**5**). *^{1}H and ^{13}C NMR data for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.44 – 7.40 (1H, m, ArC<u>H</u>), 7.25 – 7.15 (3H, m, 3 × ArC<u>H</u>), 6.80 (1H, s, O<u>H</u>), 6.65 (1H, dq, *J* = 15.5, 2.0 Hz, C**3**-<u>H</u>), 6.15 (1H, dq, *J* = 15.5, 6.5 Hz, C**4**-<u>H</u>), 3.41 – 3.33 (2H, m, C**1**-<u>H_2</u>), 3.12 – 3.06 (2H, m, C**2**-<u>H_2</u>), 2.91 (3H, s, Ms C<u>H_3</u>), 1.92 (3H, dd, *J* = 6.5, 2.0 Hz, C**5**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 137.1 (Ar<u>C</u>), 134.5 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 128.4 (C**4**), 128.0 (C**3**), 2 × 127.1 (2 × Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 53.1 (C**1**), 2 × 31.1 (C**2** and Ms <u>C</u>H_3), 18.8 (C**5**). HRMS: (ESI^+) Calculated for $C_{12}H_{17}NNaO_3S$: 278.0821. Found $[M+Na]^+$: 278.0822.

***N*-(2-(Prop-1-en-1-yl)phenethyl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (207)**



General procedure C: The preceding compound (659 mg, 2.45 mmol) was employed. FCC (gradient elution: 10:1 – 4:1 – 3:1 hexane:EtOAc) afforded **207** (1.00 g, 91 %, 3:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3024 (m), 2943 (m), 1787 (s), 1653 (m), 1498 (s), 1165 (s). *^{1}H and ^{13}C NMR data for the major (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.26 – 7.10 (4H, m, 4 × ArC<u>H</u>), 6.49 (1H, dq, *J* = 11.5, 2.0 Hz, C**3**-<u>H</u>), 5.86 (1H, dq, *J* = 11.5, 7.0 Hz, C**4**-<u>H</u>), 3.66 – 3.58 (2H, m, C**1**-<u>H_2</u>), 3.05 – 3.02 (2H, m, C**2**-<u>H_2</u>), 3.00 (3H, s, Ms C<u>H_3</u>), 1.69 (3H, dd, *J* = 7.0, 2.0 Hz, C**5**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 136.6 (Ar<u>C</u>), 135.1 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>H), 128.4 (C**4**), 127.8 (C**3**), 127.2 (Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 52.7 (C**1**), 34.7 (Ms <u>C</u>H_3), 31.4 (C**2**), 14.3 (C**5**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity. ^{1}H and ^{13}C NMR data for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.41 – 7.37 (1H, m, ArC<u>H</u>), 7.24 – 7.13 (3H, m, 3 × ArC<u>H</u>), 6.59 (1H, dq, *J* = 15.5, 2.0 Hz, C**3**-<u>H</u>), 6.13 (1H, dq, *J* = 15.5, 6.5 Hz, C**4**-<u>H</u>), 3.67 – 3.57 (2H, m, C**1**-<u>H_2</u>), 3.13 – 3.08 (2H, m, C**2**-<u>H_2</u>), 3.02 (3H, s, Ms C<u>H_3</u>), 1.89 (3H, dd, *J* = 6.5, 2.0 Hz, C**5**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 137.2 (Ar<u>C</u>), 133.5 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 128.9 (C**4**), 127.6 (C**3**), 127.4 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 53.1 (C**1**), 34.7 (Ms <u>C</u>H_3), 31.2 (C**2**), 18.7 (C**5**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity. ^{19}F NMR signals for both isomers:* δ_F (377 MHz, $CDCl_3$) -135.6 – -135.8 (2F, m), -144.9 – -145.2 (1F, m), -158.6 – -158.8 (2F, m). HRMS: (ESI^+) Calculated for $C_{19}H_{16}F_5NNaO_4S$: 472.0612. Found $[M+Na]^+$: 472.0614.

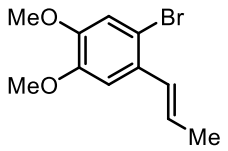
2-Mesyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline (208)



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 19 hours. Substrate **207** (62.9 mg, 0.140 mmol) was employed. FCC (gradient elution: 9:1 – 7:1 – 4:1 – 2:1 hexane:EtOAc) afforded **208** (14.1 mg, 42 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3022 (m), 2931 (m), 1492 (m), 1452 (m), 1327 (s), 1151 (s). δ_H (500 MHz, $CDCl_3$) 7.22 – 7.18 (2H, m, 2 × ArC<u>H</u>), 7.17 – 7.13 (1H, m, ArC<u>H</u>), 7.12 – 7.08 (1H, m, ArC<u>H</u>), 6.02 (1H, ddd, *J* = 17.0, 10.0, 6.5 Hz, C**4**-<u>H</u>), 5.40 (1H, br d, *J* = 6.5 Hz, C**3**-<u>H</u>), 5.28 (1H, ddd, *J* = 10.0, 1.5,

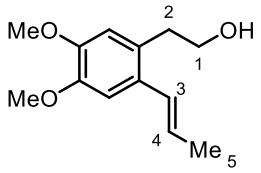
1.5 Hz, C**5**-H), 5.21 (1H, ddd, *J* = 17.0, 1.5, 1.5 Hz, C**5**-H'), 3.91 (1H, ddd, *J* = 13.5, 6.5, 2.5 Hz, C**1**-H), 3.37 (1H, ddd, *J* = 13.5, 11.5, 4.5 Hz, C**1**-H'), 3.07 (1H, ddd, *J* = 16.5, 11.5, 6.5 Hz, C**2**-H), 2.83 (3H, s, Ms CH$_3$), 2.79 (1H, ddd, *J* = 16.5, 4.5, 2.5 Hz, C**2**-H'). δ_C (126 MHz, $CDCl_3$) 136.8 (C**4**), 133.7 (ArC), 133.3 (ArC), 129.2 (ArCH), 128.0 (ArCH), 127.3 (ArCH), 126.4 (ArCH), 118.1 (C**5**), 58.2 (C**3**), 39.7 (Ms CH$_3$), 39.2 (C**1**), 28.2 (C**2**). HRMS: (ESI^+) Calculated for $C_{12}H_{15}NNaO_2S$: 260.0716. Found $[M+Na]^+$: 260.0716.

(*E*)-1-Bromo-4,5-dimethoxy-2-(prop-1-en-1-yl)benzene



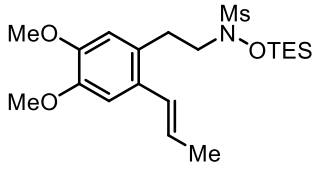
This compound was prepared according to a literature procedure.[246] To a solution of methyl isoeugenol (4.46 g, 25.0 mmol) in $CHCl_3$ (125 mL) was added a solution of Br_2 (2.81 mL, 55.0 mmol) in $CHCl_3$ (12.5 mL) over around 15 minutes. The reaction mixture was stirred at room temperature for 2.5 hours before addition of water (100 mL) and separation of the resulting phases. The organic phase was washed with 10 % aqueous Na_2SO_3 (50 mL), 10 % aqueous Na_2CO_3 (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was dissolved in acetone (250 mL) before addition of NaI (15.0 g, 100 mL). The reaction mixture was heated at reflux for 2 hours before being cooled to room temperature and concentrated *in vacuo*. The crude material was dissolved in hexane (150 mL) and water (100 mL); the resulting phases were separated, and the aqueous phase was extracted with (2 × 60 mL). The combined organic phases were washed with 10 % aqueous Na_2SO_3 (2 × 100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 7:1 hexane:EtOAc) afforded a red oil which was dissolved in Et_2O (70 mL) and washed with 10 % aqueous Na_2SO_3 (2 × 50 mL), 10 % aqueous Na_2CO_3 (50 mL) and water (2 × 50 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (4.59 g, 71 %) as a cream-coloured gum. δ_H (400 MHz, $CDCl_3$) 6.96 (1H, s), 6.95 (1H, s), 6.63 (1H, dq, *J* = 15.5, 1.5 Hz), 6.06 (1H, dq, *J* = 15.5, 6.5 Hz), 3.86 (3H, s), 3.83 (3H, s), 1.89 (3H, dd, *J* = 6.5, 1.5 Hz). δ_C (101 MHz, $CDCl_3$) 148.7, 148.5, 129.9, 129.6, 126.9, 115.3, 113.3, 109.0, 56.2, 56.0, 18.6. *The spectroscopic properties were consistent with the data available in the literature*.[246]

(*E*)-2-(4,5-Dimethoxy-2-(prop-1-en-1-yl)phenyl)ethan-1-ol



To a solution of the preceding bromide (2.82 g, 11.0 mmol) in anhydrous THF (30 mL) at -78 °C was added *n*-BuLi (1.55 M in hexane, 14.2 mL, 22.0 mmol). The reaction mixture was stirred at room temperature for 2 hours, then cooled to -78 °C before addition of ethylene oxide (*approx.* 3 M in THF, 5.5 mL, 16.5 mmol). The reaction mixture was stirred at room temperature for 14 hours before addition of saturated aqueous NH_4Cl (20 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 3:1 hexane:EtOAc) afforded the title compound (1.69 g, 69 %, 11:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless crystalline solid. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*solid*) 3263 (br s), 2947 (m), 2832 (m), 1606 (m), 1506 (s), 1212 (s), 1034 (s). δ_H (400 MHz, $CDCl_3$) 6.94 (1H, s, ArC<u>H</u>), 6.66 (1H, s, ArC<u>H</u>), 6.58 (1H, dq, *J* = 15.5, 1.5 Hz, C**3**-<u>H</u>), 6.02 (1H, dq, *J* = 15.5, 6.5 Hz, C**4**-<u>H</u>), 3.87 (3H, s, OC<u>H</u>$_3$), 3.85 (3H, s, OC<u>H</u>$_3$), 3.77 (2H, t, *J* = 7.0 Hz, C**1**-<u>H</u>$_2$), 2.88 (2H, t, *J* = 7.0 Hz, C**2**-<u>H</u>$_2$), 1.88 (3H, dd, *J* = 6.5, 1.5 Hz, C**5**-<u>H</u>$_3$), 1.60 (1H, br s, O<u>H</u>). δ_C (101 MHz, $CDCl_3$) 148.2 (Ar<u>C</u>), 147.8 (Ar<u>C</u>), 129.7 (Ar<u>C</u>), 128.1 (C**3**), 127.5 (Ar<u>C</u>), 126.0 (C**4**), 113.3 (Ar<u>C</u>H), 109.2 (Ar<u>C</u>H), 63.5 (C**1**), 2 × 56.0 (2 × O<u>C</u>H$_3$), 36.1 (C**2**), 18.8 (C**5**). HRMS: (ESI^+) Calculated for $C_{13}H_{18}NaO_3$: 245.1148. Found $[M+Na]^+$: 245.1154. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 6.73 (2H, s, 2 × ArC<u>H</u>), 6.48 (1H, dq, *J* = 11.0, 2.0 Hz, C**3**-<u>H</u>), 5.78 (1H, dq, *J* = 11.0, 7.0 Hz, C**4**-<u>H</u>), 2.80 (2H, t, *J* = 7.0 Hz, C**2**-<u>H</u>$_2$), 1.73 (3H, dd, *J* = 7.0, 2.0 Hz, C**5**-<u>H</u>$_3$).

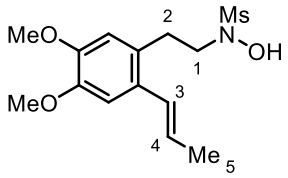
(*E*)-*N*-(4,5-Dimethoxy-2-(prop-1-en-1-yl)phenethyl)-*N*-((triethylsilyl)oxy)methanesulfonamide



<u>General procedure E:</u> MsNHOTES (*vide supra*, 564 mg, 2.50 mmol) was employed with the preceding alcohol (1.2 eq.). The reaction time was 22 hours. FCC (gradient elution: 49:1 – 39:1 – 19:1 PhMe:EtOAc) afforded the title compound (1.04 g, 97 %, 11:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless oil. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*film*) 2956 (m), 2878 (m), 1607 (m), 1512 (s), 1349 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 6.93 (1H, s, ArC<u>H</u>), 6.66 (1H, s, ArC<u>H</u>), 6.55 (1H, dq, *J* = 15.5, 1.5 Hz, C**3**-<u>H</u>), 6.05 (1H, dq, *J* = 15.5, 6.5 Hz, C**4**-<u>H</u>), 3.88 (3H, s, OC<u>H</u>$_3$), 3.86 (3H, s, OC<u>H</u>$_3$), 3.36 – 3.28 (2H, m, C**1**-<u>H</u>$_2$), 3.04 – 2.96 (2H, m, C**2**-<u>H</u>$_2$), 2.87 (3H, s, Ms C<u>H</u>$_3$), 1.90 (3H, dd, *J* = 6.5, 1.5 Hz, C**5**-<u>H</u>$_3$), 1.03 (9H, t, *J* = 8.0 Hz, Si(CH_2C<u>H</u>$_3$)$_3$), 0.81 (6H, q, *J* = 8.0 Hz,

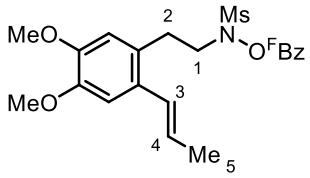
$Si(C\underline{H}_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 148.4 (Ar$\underline{C}$), 148.1 (Ar$\underline{C}$), 129.5 (Ar$\underline{C}$H), 127.7 (C**3**), 127.1 (Ar$\underline{C}$H), 126.6 (C**4**), 113.0 (Ar$\underline{C}$), 109.1 (Ar$\underline{C}$), 56.7 (C**1**), 2 × 56.1 (2 × O$\underline{C}H_3$), 31.3 (C**2**), 30.7 (Ms $\underline{C}H_3$), 18.8 (C**5**), 6.9 ($Si(CH_2\underline{C}H_3)_3$), 4.9 ($Si(\underline{C}H_2CH_3)_3$). HRMS: ($ESI^+$) Calculated for $C_{20}H_{35}NNaO_5SSi$: 452.1897. Found $[M+Na]^+$: 452.1891. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 6.73 (2H, s, 2 × ArC$\underline{H}$), 6.46 (1H, dq, *J* = 11.5, 2.0 Hz, C**3**-$\underline{H}$), 5.83 (1H, dq, *J* = 11.5, 7.0 Hz, C**4**-$\underline{H}$), 1.75 (3H, dd, *J* = 7.0, 2.0 Hz, C**5**-$\underline{H}_3$).

(*E*)-*N*-(4,5-Dimethoxy-2-(prop-1-en-1-yl)phenethyl)-*N*-hydroxymethanesulfonamide



General procedure F: The preceding compound (1.02 g, 2.37 mmol) was employed. FCC (gradient elution: 2:1 – 3:2 hexane:EtOAc) afforded the title compound (700 mg, 94 %, 11:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless crystalline solid. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*solid*) 3378 (br s), 3031 (m), 2940 (m), 1607 (m), 1508 (s), 1345 (s), 1161 (s). δ_H (400 MHz, $CDCl_3$) 6.94 (1H, s, ArC$\underline{H}$), 6.68 (1H, s, ArC$\underline{H}$), 6.62 (1H, s, O$\underline{H}$), 6.57 (1H, dq, *J* = 15.5, 2.0 Hz, C**3**-$\underline{H}$), 6.05 (1H, dq, *J* = 15.5, 6.5 Hz, C**4**-$\underline{H}$), 3.88 (3H, s, OC$\underline{H}_3$), 3.87 (3H, s, OC$\underline{H}_3$), 3.39 – 3.32 (2H, m, C**1**-$\underline{H}_2$), 3.06 – 3.00 (2H, m, C**2**-$\underline{H}_2$), 2.91 (3H, s, Ms C$\underline{H}_3$), 1.90 (3H, dd, *J* = 6.5, 2.0 Hz, C**5**-$\underline{H}_3$). δ_C (101 MHz, $CDCl_3$) 148.3 (Ar$\underline{C}$), 148.1 (Ar$\underline{C}$), 129.6 (Ar$\underline{C}$H), 127.8 (C**3**), 127.1 (Ar$\underline{C}$H), 126.6 (C**4**), 113.0 (Ar$\underline{C}$), 109.2 (Ar$\underline{C}$), 56.2 (O$\underline{C}H_3$), 56.0 (O$\underline{C}H_3$), 53.4 (C**1**), 31.3 (Ms $\underline{C}H_3$), 30.9 (C**2**), 18.9 (C**5**). HRMS: (ESI^+) Calculated for $C_{14}H_{21}NNaO_5S$: 338.1033. Found $[M+Na]^+$: 338.1030. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 6.75 (1H, s, ArC$\underline{H}$), 6.73 (1H, s, ArC$\underline{H}$), 6.49 (1H, dq, *J* = 11.5, 2.0 Hz, C**3**-$\underline{H}$), 5.84 (1H, dq, *J* = 11.5, 7.0 Hz, C**4**-$\underline{H}$), 1.75 (3H, dd, *J* = 7.0, 2.0 Hz, C**5**-$\underline{H}_3$).

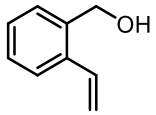
(*E*)-*N*-(4,5-Dimethoxy-2-(prop-1-en-1-yl)phenethyl)-*N*-((pentafluorobenzoyl)oxy)methane-sulfonamide (209)



General procedure C: The preceding compound (683 mg, 2.17 mmol) was employed. FCC (gradient elution: 2:1 – 1:4 hexane:EtOAc) afforded **209** (1.07 g, 97 %, 12:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless crystalline solid. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*solid*) 3021 (m), 2932 (m), 1778 (s), 1649 (m), 1495 (s), 1354 (s), 1161 (s). δ_H (400 MHz, $CDCl_3$) 6.91 (1H, s, ArC$\underline{H}$),

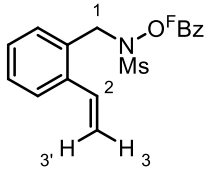
6.67 (1H, s, ArC<u>H</u>), 6.51 (1H, dq, *J* = 15.5, 1.5 Hz, C**3**-<u>H</u>), 6.04 (1H, dq, *J* = 15.5, 6.5 Hz, **C4**-<u>H</u>), 3.87 (6H, s, 2 × OC<u>H</u>$_3$), 3.62 (2H, t, *J* = 8.0 Hz, C**1**-<u>H</u>$_2$), 3.07 – 3.00 (5H, m, C**2**-<u>H</u>$_2$ and Ms C<u>H</u>$_3$), 1.88 (3H, dd, *J* = 6.5, 1.5 Hz, C**5**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 2 × 148.3 (2 × Ar<u>C</u>), 129.6 (Ar<u>C</u>H), 127.5 (C**3**), 127.0 (C**4**), 126.1 (Ar<u>C</u>H), 113.1 (Ar<u>C</u>), 109.3 (Ar<u>C</u>), 56.1 (O<u>C</u>H$_3$), 56.0 (O<u>C</u>H$_3$), 53.4 (C**1**), 34.9 (Ms <u>C</u>H$_3$), 31.0 (C**2**), 18.7 (C**5**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.6 – -135.7 (2F, m), -144.9 (1F, tt, *J* = 21.0, 5.5 Hz), -158.6 – -158.8 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{21}H_{20}F_5NNaO_6S$: 532.0824. Found $[M+Na]^+$: 532.0809. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 6.76 (1H, s, ArC<u>H</u>), 6.70 (1H, s, ArC<u>H</u>), 6.43 (1H, dq, *J* = 11.0, 1.5 Hz, C**3**-<u>H</u>), 5.81 (1H, dq, *J* = 11.0, 7.0 Hz, C**4**-<u>H</u>), 1.72 (3H, dd, *J* = 7.0, 2.0 Hz, C**5**-<u>H</u>$_3$).

(2-Vinylphenyl)methanol



To a solution of 2-bromostyrene (1.25 mL, 10.0 mmol) in anhydrous THF (30 mL) at -78 °C was added *n*-BuLi (1.55 M in hexane, 7.10 mL, 11.0 mmol). The reaction mixture was stirred at -78 °C for 1.5 hours before addition of paraformaldehyde (450 mg, 15.0 mmol). The reaction mixture was stirred at room temperature for 5 hours before addition of saturated aqueous NH_4Cl (20 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 4:1 hexane:EtOAc) afforded the title compound (279 mg, 21 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3317 (br s), 2885 (m), 1627 (m), 1414 (m), 1003 (s). δ_H (500 MHz, $CDCl_3$) 7.54 (1H, dd, *J* = 7.0, 1.5 Hz), 7.37 (1H, dd, *J* = 7.0, 2.0 Hz), 7.33 – 7.26 (2H, m), 7.06 (1H, dd, *J* = 17.5, 11.0 Hz), 5.71 (1H, dd, *J* = 17.5, 1.5 Hz), 5.36 (1H, dd, *J* = 11.0, 1.5 Hz), 4.77 (2H, s), 1.58 (1H, br s). δ_C (126 MHz, $CDCl_3$) 137.7, 136.8, 133.9, 128.5, 128.4, 128.1, 126.1, 116.7, 63.6. *The spectroscopic properties were consistent with the data available in the literature.*[247]

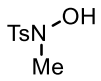
***N*-((Pentafluorobenzoyl)oxy)-*N*-(2-vinylbenzyl)methanesulfonamide (211)**



<u>General procedure N:</u> The preceding alcohol (268 mg, 2.00 mmol) was employed with MsNHO^{F}Bz (*vide supra*, 507 mg, 1.66 mmol). The reaction time was 15 hours. FCC (eluent: PhMe) afforded

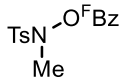
211 (347 mg, 50 %) as a colourless crystalline solid. m.p. 137-138 °C (CH_2Cl_2:petrol, *fibres*). ν_{max} / cm^{-1}: (*solid*) 3027 (m), 1788 (s), 1653 (m), 1497 (s), 1357 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 7.55 (1H, ddd, *J* = 8.0, 1.0, 1.0 Hz, ArC<u>H</u>), 7.35 (1H, ddd, *J* = 8.0, 7.5, 1.5 Hz, ArC<u>H</u>), 7.31 – 7.15 (3H, m, 2 × ArC<u>H</u> and C**2**-<u>H</u>), 5.70 (1H, dd, *J* = 17.5, 1.5 Hz, C**3**-<u>H</u>'), 5.41 (1H, dd, *J* = 11.0, 1.5 Hz, C**3**-<u>H</u>), 4.68 (2H, br s, C**1**-<u>H_2</u>), 3.13 (3H, s, Ms C<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 138.9 (Ar<u>C</u>), 133.6 (C**2**), 131.1 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>), 127.9 (Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 117.6 (C**3**), 53.9 (C**1**), 35.3 (Ms <u>C</u>H_3). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.6 – -135.8 (2F, m), -145.5 (1F, tt, *J* = 21.0, 5.5 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{17}H_{12}F_5NNaO_4S$: 444.0299. Found $[M+Na]^+$: 444.0297.

_N_-Methyl-_N_-hydroxy-4-toluenesulfonamide



A suspension of MeNHOH·HCl (7.18 g, 86.0 mmol) and MgO (3.01 g, 74.8 mmol) in MeOH (27 mL) and water (18 mL) was stirred at room temperature for 10 minutes. To the suspension was added TsCl (7.13 g, 37.4 mmol) in THF (300 mL) followed by MgO (1.51 g, 37.4 mmol). The reaction mixture was stirred for 4 hours before being filtered through celite. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 2:1 hexane:EtOAc) afforded the title compound (6.18 g, 82 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3383 (br s), 2933 (m), 1594 (s), 1336 (s), 1161 (s). δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.37 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 6.75 (1H, s, O<u>H</u>), 2.82 (3H, s, NC<u>H_3</u>), 2.45 (3H, s, Ts C<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 145.1 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>), 40.4 (N<u>C</u>H_3), 21.7 (Ts <u>C</u>H_3). HRMS: (ESI^+) Calculated for $C_8H_{12}NO_3S$: 202.0532. Found $[M+H]^+$: 202.0538.

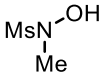
_N_-Methyl-_N_-((pentafluorobenzoyl)oxy)-4-toluenesulfonamide (218a)



<u>General procedure C:</u> The preceding compound (1.01 g, 5.00 mmol) was employed. FCC (eluent: 4:1 hexane:EtOAc) afforded **218a** (1.76 g, 89 %) as a colourless crystalline solid. m.p. 128-129 °C (CH_2Cl_2:hexane, *plates*). ν_{max} / cm^{-1}: (*film*) 2988 (m), 2935 (m), 1781 (s), 1652 (s), 1597 (m), 1497 (s), 1162 (s). δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.39 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 3.08 (3H, s, NC<u>H_3</u>), 2.47 (3H, s, Ts C<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 146.0 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>), 40.1 (N<u>C</u>H_3), 21.7 (Ts <u>C</u>H_3). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz,

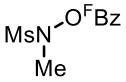
$CDCl_3$) -135.7 – -135.8 (2F, m), -145.8 (1F, tt, *J* = 21.0, 5.0 Hz), -159.0 – -159.2 (2F, m). HRMS: (ESI^+) Calculated for $C_{15}H_{10}F_5NNaO_4S$: 418.0143. Found $[M+Na]^+$: 418.0131.

_N_-Methyl-_N_-hydroxymethanesulfonamide



A suspension of MeNHOH·HCl (5.07 g, 60.7 mmol) and MgO (2.13 g, 52.8 mmol) in MeOH (18 mL) and water (12 mL) was stirred at room temperature for 10 minutes. To the suspension was added MsCl (2.04 mL, 26.4 mmol) in THF (200 mL) followed by MgO (1.06 g, 26.4 mmol). The reaction mixture was stirred at room temperature for 3 hours before being filtered through celite. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 3:2 hexane:EtOAc) afforded the title compound (2.86 g, 87 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3376 (br s), 2937 (m), 2851 (m), 1439 (s), 1318 (s), 1149 (s). δ_H (400 MHz, $CDCl_3$) 7.03 (1H, br s, O<u>H</u>), 3.04 (3H, s, NC<u>H</u>$_3$), 2.93 (3H, s, Ms C<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 40.3 (N<u>C</u>H$_3$), 30.0 (Ms <u>C</u>H$_3$). HRMS: (ESI^+) Calculated for $C_2H_7NNaO_3S$: 148.0039. Found $[M+Na]^+$: 148.0035.

_N_-Methyl-_N_-((pentafluorobenzoyl)oxy)methanesulfonamide (218b)



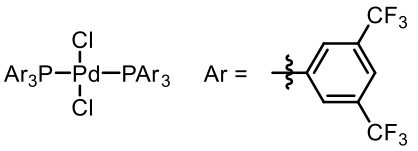
<u>General procedure C:</u> The preceding compound (1.00 g, 7.99 mmol) was employed. FCC (eluent: 2:1 hexane:EtOAc) afforded **218b** (1.93 g, 76 %) as a colourless crystalline solid. m.p. 139-140 °C (CH_2Cl_2:hexane, *plates*). ν_{max} / cm^{-1}: (*solid*) 2945 (m), 1782 (s), 1655 (m), 1498 (s), 1361 (s), 1159 (s). δ_H (400 MHz, $CDCl_3$) 3.30 (3H, s, NC<u>H</u>$_3$), 3.07 (3H, s, Ms C<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 39.5 (N<u>C</u>H$_3$), 33.7 (Ms <u>C</u>H$_3$). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.7 – -135.8 (2F, m), -144.9 (1F, tt, *J* = 21.0, 6.0 Hz), -158.6 – -158.8 (2F, m). HRMS: (ESI^+) Calculated for $C_9H_6F_5NNaO_4S$: 341.9830. Found $[M+Na]^+$: 341.9837.

_N_-Methylmethanesulfonamide (222)

To a solution of $MeNH_2$ (33 % in EtOH, 20 mL, 212 mmol) in EtOH (5 mL) at 0 °C was added MsCl (3.30 mL, 42.4 mmol) dropwise. The reaction mixture was stirred at room temperature for 9 hours before being concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (20 mL), filtered and the filtrate was concentrated *in vacuo*. FCC (gradient elution: 1:1 – 2:3 hexane:EtOAc) afforded **222**

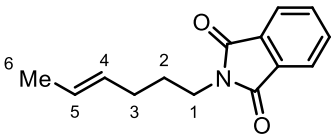
(3.46 g, 75 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 4.65 (1H, br s), 2.93 (3H, s), 2.80 (3H, d, J = 5.5 Hz). δ_C (101 MHz, $CDCl_3$) 38.7, 29.4. *The spectroscopic properties were consistent with the data available in the literature.*[248]

Palladium(II) bis(tris(3,5-bis(trifluoromethyl)phenyl)phosphine) dichloride (223)



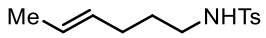
This compound was prepared according to a literature procedure.[249] To a reaction vessel charged with $(MeCN)_2PdCl_2$ (259 mg, 1.00 mmol) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (1.34 g, 2.00 mmol) was added anhydrous CH_2Cl_2 (75 mL, argon sparged). The reaction mixture was stirred at room temperature for 15 hours before being concentrated *in vacuo*. The crude material was suspended in PhMe and filtered to afford **223** (1.09 g, 72 %) as a yellow crystalline solid. δ_H (400 MHz, $CDCl_3$) 8.11 (6H, s), 8.08 – 8.03 (12H, m). δ_P (162 MHz, $CDCl_3$) 25.5 (s). δ_F (377 MHz, $CDCl_3$) -63.2 (s). *The spectroscopic properties were consistent with the data available in the literature.*[249]

(*E*)-2-(Hex-4-en-1-yl)isoindoline-1,3-dione



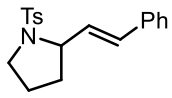
To a solution of phthalimide (2.21 g, 15.0 mmol) and PPh_3 (5.25 g, 20.0 mmol) in anhydrous PhMe (70 mL) at 0 °C was added DIAD (3.94 mL, 20.0 mmol). The reaction mixture was stirred at 0 °C for 1 hour before addition of a solution of (*E*)-hex-4-en-1-ol (**87**) (1.00 g, 10.0 mmol) in anhydrous THF (30 mL). The reaction mixture was stirred at room temperature for 16 hours before being concentrated *in vacuo*. FCC (eluent: 7:1 hexane:EtOAc) afforded the title compound (2.21 g, 96 %) as a colourless crystalline solid. m.p. 53-55 °C (CH_2Cl_2:petrol, *hexagonal*). ν_{max} / cm^{-1}: (*solid*) 3028 (m), 2937 (m), 1696 (s), 1396 (s). δ_H (400 MHz, $CDCl_3$) 7.81 (2H, dd, J = 5.5, 3.0 Hz, 2 × ArC<u>H</u>), 7.68 (2H, dd, J = 5.5, 3.0 Hz, 2 × ArC<u>H</u>), 5.49 – 5.34 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 3.69 – 3.63 (2H, m, C**1**-<u>H_2</u>), 2.05 – 1.98 (2H, m, C**3**-<u>H_2</u>), 1.72 (2H, tt, J = 7.5, 7.5 Hz, C**2**-<u>H_2</u>), 1.60 – 1.56 (3H, m, C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 168.5 (<u>C</u>=O), 133.9 (Ar<u>C</u>H), 132.3 (Ar<u>C</u>), 129.9 (C**4**), 125.9 (C**5**), 123.2 (Ar<u>C</u>H), 37.8 (C**1**), 30.0 (C**3**), 28.3 (C**2**), 18.0 (C**6**). HRMS: (ESI^+) Calculated for $C_{14}H_{15}NNaO_2$: 252.0995. Found $[M+Na]^+$: 252.1000.

(*E*)-*N*-(Hex-4-en-1-yl)-4-toluenesulfonamide ((*E*)-8)



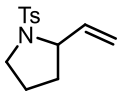
A solution of the preceding compound (1.61 g, 7.00 mmol) and 55 % aqueous hydrazine (0.79 mL, 14.0 mmol) in EtOH (20 mL) was heated at reflux for 1 hour. The reaction mixture was cooled to room temperature, filtered and the filter cake was rinsed with CH_2Cl_2 (80 mL). To the filtrate was added TsCl (1.33 g, 7.00 mmol) and Et_3N (3.00 mL, 21.5 mmol). The reaction mixture was stirred at room temperature for 5 hours before addition of 1.0 M aqueous HCl (50 mL) and separation of the resulting phases. The organic phase was washed with 1.0 M aqueous K_2CO_3 (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 4:1 hexane:EtOAc) afforded **(*E*)-8** (792 mg, 45 %) as a colourless oil. δ_H (500 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* = 8.0 Hz), 5.44 – 5.36 (1H, m), 5.31 (1H, dtd, *J* = 15.0, 7.0, 1.5 Hz), 4.34 (1H, t, *J* = 6.5 Hz), 2.96 (2H, td, *J* = 7.0, 6.5 Hz), 2.45 (3H, s), 1.98 (2H, dtt, *J* = 7.0, 7.0, 1.0 Hz), 1.63 (3H, dd, *J* = 6.0, 1.5 Hz), 1.53 (2H, tt, *J* = 7.0, 7.0 Hz). δ_C (126 MHz, $CDCl_3$) 143.5, 137.1, 2 × 129.8, 127.3, 126.4, 42.8, 29.6, 29.4, 21.7, 18.0. *The ^{1}H NMR spectrum was consistent with the data available in the literature for both the (E)- and the (Z)-isomer.[105] The ^{13}C NMR spectrum was consistent with the data corresponding to the (Z)-isomer, although only one resonance is reported around 129.8 ppm.[105] Based on the observed coupling constant between the alkene protons of **8**, it appears that NMR data for the (E)-isomer has been reported for the (Z)-isomer, and vice versa.*

(*E*)-2-Styryl-1-tosylpyrrolidine



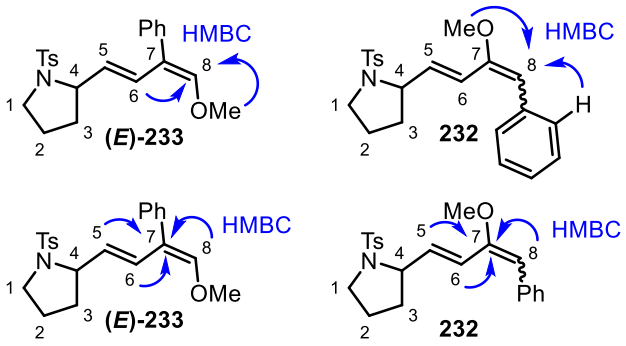
*In the following experiment, a mixture of aza-Heck (**126**) and aza-Wacker (**(E)-8**) substrates were submitted to the reaction conditions. The fact that only **126** afforded cyclised product is consistent with an aza-Heck mechanism (Section 2.5).* **General procedure D:** Conditions: 2.5 mol% $Pd_2(dba)_3$; 12.5 mol% P(3,5-$(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; *n*-BuCN (0.1 M); 110 °C; 18 hours. Substrates **126** (*vide supra*, 75.5 mg, 0.140 mmol) and **(*E*)-8** (25.3 mg, 0.100 mmol) were employed. From analysis of the ^{1}H NMR spectrum of the crude reaction mixture, the yield of **128** was determined to be 72 % and no aza-Wacker product (**12**) was observed. *Characterisation data for **128** has been provided earlier.*

1-Tosyl-2-vinylpyrrolidine



The following reaction was conducted in the presence of TEMPO. **General procedure D:** Conditions: 2.5 mol% $Pd_2(dba)_3$; 12.5 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 150 mol% TEMPO; *n*-BuCN (0.1 M); 110 °C; 16 hours. Substrate **125** (65.0 mg, 0.140 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **12** (27.0 mg, 77 %) as a colourless crystalline solid. *No products derived from TEMPO-trapping of radical intermediates were observed. Characterisation data for **12** has been provided earlier.*

2-((1*E*)-4-Methoxy-3-phenylbuta-1,3-dien-1-yl)-1-tosylpyrrolidine ((*E*)-233) and 2-((1*E*)-3-methoxy-4-phenylbuta-1,3-dien-1-yl)-1-tosylpyrrolidine ((*E*)-232)



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 25 hours. Substrate **228** (126 mg, 0.212 mmol, *added as a solution in n-BuCN*) was employed. FCC (gradient elution: 99:1 – 74:1 PhMe:EtOAc) afforded **233** and **232** (25.3 mg, 31 %, 7:5:1 mixture of **(*E*)-233**, **(*E*)-232** and (***Z*)-232**) as a pale-yellow oil. *The relative stereochemistry of **(E)-233** and **(E)-232** was assigned by analogy to the related dihydropyrrole products.*[120] ν_{max} / cm^{-1}: (*film*) 2932 (m), 1731 (m), 1598 (m), 1492 (m), 1343 (s), 1156 (s). *^1H and ^{13}C NMR data for **(E)-233** (A) and **(E)-232** (B):* δ_H (500 MHz, $CDCl_3$) 7.72 (1.2H, d, *J* = 8.0 Hz, A: 2 × ArC<u>H</u>), 7.69 (0.8H, d, *J* = 8.0 Hz, B: 2 × ArC<u>H</u>), 7.37 – 7.18 (7H, m, A and B: 7 × ArC<u>H</u>), 6.75 (0.6H, dd, *J* = 16.0, 1.0 Hz, A: C**6**-<u>H</u>), 6.49 (0.4H, dd, *J* = 15.5, 1.0 Hz, B: C**6**-<u>H</u>), 6.13 (0.4H, dd, *J* = 15.5, 6.5 Hz, B: C**5**-<u>H</u>), 6.04 (0.6H, s, A: C**8**-<u>H</u>), 5.80 (0.4H, s, B: C**8**-<u>H</u>), 5.42 (0.6H, dd, *J* = 16.0, 7.5 Hz, A: C**5**-<u>H</u>), 4.25 – 4.17 (1H, m, A and B: C**4**-<u>H</u>), 3.74 (1.8H, s, A: OC<u>H</u>$_3$), 3.72 (1.2H, s, B: OC<u>H</u>$_3$), 3.43 – 3.22 (2H, m, A and B: C**1**-<u>H</u>$_2$), 2.42 (1.8H, s, A: Ts C<u>H</u>$_3$), 2.41 (1.2H, s, B: Ts C<u>H</u>$_3$), 1.85 – 1.59 (4H, m, A and B: C**2**-<u>H</u>$_2$ and C**3**-<u>H</u>$_2$). δ_C (126 MHz, $CDCl_3$) 153.4 (B: C**7**), 147.1 (A: C**8**), 143.1 (B: Ar<u>C</u>), 142.9 (A: Ar<u>C</u>), 137.7 (A: Ar<u>C</u>), 136.6 (B: Ar<u>C</u>), 135.7 (A: Ar<u>C</u>), 135.3 (B: Ar<u>C</u>), 132.4 (B: C**5**), 130.2 (A: C**5**), 2 × 129.5 (A and B: Ar<u>C</u>H), 129.4 (B: Ar<u>C</u>H), 129.3 (A: Ar<u>C</u>H), 128.2 (B: Ar<u>C</u>H), 128.1 (A:

ArCH), 2 × 127.5 (A and B: ArCH), 126.7 (A: ArCH), 125.8 (B: ArCH), 124.8 (A: C**6**), 123.6 (B: C**6**), 119.2 (A: C**7**), 103.8 (B: C**8**), 62.4 (A: C**4**), 61.4 (B: C**4**), 60.3 (A: OCH_3), 54.8 (B: OCH_3), 2 × 48.7 (A and B: C**1**), 33.2 (A: C**3**), 32.8 (B: C**3**), 2 × 24.0 (A and B: C**2**), 2 × 21.50 (A and B: Ts CH_3). HRMS: (ESI$^+$) Calculated for $C_{22}H_{26}NO_3S$: 384.1628. Found $[M+H]^+$: 384.1622. *Characteristic ^1H and ^{13}C NMR signals for **(Z)-232**:* δ_H (500 MHz, $CDCl_3$) 5.94 (1H, dd, *J* = 15.5, 6.5 Hz, C**5**-H), 5.84 (1H, s, C**8**-H), 3.64 (3H, s, OCH_3). δ_C (126 MHz, $CDCl_3$) 131.1 (C**5**), 117.0 (C**8**), 58.5 (OCH_3).

7.4 Experimental procedures for the studies in Chapter 3

Benzyl hydroxycarbamate

CbzNHOH

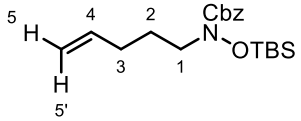
This compound was prepared according to a literature procedure.[250] A solution of $NH_2OH{\cdot}HCl$ (10.0 g, 144 mmol) and K_2CO_3 (19.9 g, 144 mmol) in water (100 mL) and Et_2O (200 mL) was stirred at room temperature for 1 hour then cooled to 0 °C before addition of CbzCl (13.7 mL, 96.0 mmol). The reaction mixture was stirred at room temperature for 1 hour before the phases were separated, and the aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (16.0 g, 100 %) as a colourless crystalline solid. m.p. 71-72 °C (Et_2O:hexane) [Lit., 62-63 °C (no recrystallisation solvent quoted)][250]. ν_{max} / cm^{-1}: (*solid*) 3365 (br s), 3297 (s), 3061 (m), 2978 (m), 1699 (s), 1495 (s), 1272 (s), 1111 (s). δ_H (500 MHz, CD_3CN) 7.97 (1H, br s), 7.40 – 7.32 (5H, m), 6.70 (1H, br s), 5.11 (2H, s). δ_C (126 MHz, CD_3CN) 159.1, 137.7, 129.5, 129.1, 128.9, 67.4. HRMS: (ESI^+) Calculated for $C_8H_9NNaO_3$: 190.0475. Found $[M+Na]^+$: 190.0474. *The spectroscopic properties were consistent with the data available in the literature.*[250]

Benzyl ((*tert*-butyldimethylsilyl)oxy)carbamate

CbzNHOTBS

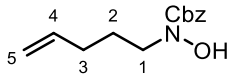
This compound was prepared according to a literature procedure.[251] To a solution of the preceding compound (15.7 g, 94.0 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C was added Et_3N (13.1 mL, 94.0 mmol) followed by TBSCl (14.2 g, 94.0 mmol) in three roughly equal portions. The reaction mixture was stirred at room temperature for 1.5 hours before addition of water (80 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 14:1 hexane:EtOAc) afforded CbzNHOTBS (25.8 g, 98 %) as a colourless low-melting solid. ν_{max} / cm^{-1}: (*film*) 3273 (br s), 2930 (m), 2858 (m), 1731 (s), 1463 (s), 1251 (s), 1101 (s). δ_H (400 MHz, $CDCl_3$) 7.38 – 7.30 (5H, m), 6.93 (1H, s), 5.17 (2H, s), 0.94 (9H, s), 0.16 (6H, s). δ_C (101 MHz, $CDCl_3$) 158.7, 135.8, 128.7, 2 × 128.5, 67.8, 26.0, 18.2, -5.6. HRMS: (ESI^+) Calculated for $C_{14}H_{24}NO_3Si$: 282.1520. Found $[M+H]^+$: 282.1518. *The spectroscopic properties were consistent with the data available in the literature.*[252]

Benzyl ((*tert*-butyldimethylsilyl)oxy)(pent-4-en-1-yl)carbamate (237)



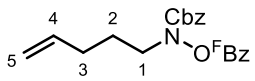
General procedure A: CbzNHOTBS (*vide supra*, 2.81 g, 10.0 mmol) was employed with 5-bromopent-1-ene. FCC (gradient elution: 24:1 – 9:1 hexane:EtOAc) afforded **237** (3.20 g, 92 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2930 (m), 2858 (m), 1704 (s), 1251 (s). δ_H (400 MHz, $CDCl_3$) 7.40 – 7.29 (5H, m, 5 × ArC<u>H</u>), 5.78 (1H, ddt, *J* = 17.0, 10.5, 6.5 Hz, C**4**-<u>H</u>), 5.15 (2H, s, OC<u>H_2</u>Ph), 5.01 (1H, ddt, *J* = 17.0, 2.0, 1.5 Hz, C**5**-<u>H</u>'), 4.96 (1H, ddt, *J* = 10.5, 2.0, 1.5 Hz, C**5**-<u>H</u>), 3.49 (2H, t, *J* = 7.5 Hz, C**1**-<u>H_2</u>), 2.04 (2H, tddd, *J* = 7.0, 6.5, 1.5, 1.5 Hz, C**3**-<u>H_2</u>), 1.75 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>), 0.91 (9H, s, SiC(C<u>H_3</u>)$_3$), 0.10 (6H, s, Si(C<u>H_3</u>)$_2$). δ_C (101 MHz, $CDCl_3$) 158.5 (<u>C</u>=O), 137.9 (C**4**), 136.2 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 115.1 (C**5**), 67.9 (O<u>C</u>H_2Ph), 52.1 (C**1**), 30.9 (C**3**), 25.9 (SiC(<u>C</u>H_3)$_3$), 25.3 (C**2**), 18.0 (Si<u>C</u>(CH$_3$)$_3$), -5.0 (Si(<u>C</u>H_3)$_2$). HRMS: (ESI^+) Calculated for $C_{19}H_{31}NNaO_3Si$: 372.1965. Found $[M+Na]^+$: 372.1973.

Benzyl hydroxy(pent-4-en-1-yl)carbamate



General procedure M: Compound **237** (3.20 g, 9.15 mmol) was employed with 2.0 eq. TBAF. The reaction time was 4 hours. FCC (gradient elution: 3:1 – 2:1 hexane:EtOAc) afforded the title compound (1.78 g, 83 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3257 (br s), 3068 (m), 2936 (m), 1697 (s), 1455 (s), 1210 (s). δ_H (400 MHz, $CDCl_3$) 7.39 – 7.30 (5H, m, 5 × ArC<u>H</u>), 6.82 (1H, s, O<u>H</u>), 5.79 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, C**4**-<u>H</u>), 5.17 (2H, s, OC<u>H_2</u>Ph), 5.04 – 4.94 (2H, m, C**5**-<u>H_2</u>), 3.56 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 2.07 (2H, tddd, *J* = 7.0, 6.5, 1.5, 1.5 Hz, C**3**-<u>H_2</u>), 1.74 (2H, tt, *J* = 7.0, 7.0 Hz, C**2**-<u>H_2</u>). δ_C (126 MHz, $CDCl_3$) 157.5 (<u>C</u>=O), 137.9 (C**4**), 136.1 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 115.3 (C**5**), 68.1 (O<u>C</u>H_2Ph), 49.8 (C**1**), 30.7 (C**3**), 26.2 (C**2**). HRMS: (ESI^+) Calculated for $C_{13}H_{17}NNaO_3$: 258.1101. Found $[M+Na]^+$: 258.1094.

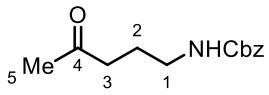
Benzyl pent-4-en-1-yl((pentafluorobenzoyl)oxy)carbamate (238a)



General procedure C: The preceding compound (1.53 g, 6.51 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **238a** (2.42 g, 87 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3070 (m), 2943 (m), 1784 (s), 1727 (s), 1652 (m), 1498 (s), 1174 (s). δ_H (400 MHz, $CDCl_3$) 7.41 – 7.29 (5H, m,

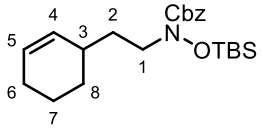
5 × ArC<u>H</u>), 5.78 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, C**4**-<u>H</u>), 5.22 (2H, s, OC<u>H</u>$_2$Ph), 4.97 (2H, m, C**5**-<u>H</u>$_2$), 3.76 (2H, t, *J* = 7.0 Hz, C**1**-<u>H</u>$_2$), 2.14 (2H, tddd, *J* = 7.0, 6.5, 1.5, 1.5 Hz, C**3**-<u>H</u>$_2$), 1.75 (2H, tt, *J* = 7.0, 7.0 Hz, C**2**-<u>H</u>$_2$). δ_C (126 MHz, $CDCl_3$) 157.4 (^{F}Bz <u>C</u>=O), 155.5 (Cbz <u>C</u>=O), 137.3 (C**4**), 135.3 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 115.7 (C**5**), 68.9 (O<u>C</u>H$_2$Ph), 50.7 (C**1**), 30.5 (C**3**), 26.1 (C**2**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.1 (2F, m), -146.0 (1F, tt, *J* = 21.0, 5.5 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{20}H_{16}F_5NNaO_4$: 452.0892. Found $[M+Na]^+$: 452.0884.

Benzyl (4-oxopentyl)carbamate (239)



<u>General procedure D:</u> Conditions: 3.75 mol% $Pd_2(dba)_3$; 15 mol% P(3,5-$(CF_3)_2C_6H_3)_3$; 200 mol% Et_3N; DMF (0.12 M); 120 °C; 2 hours. Substrate **238a** (51.0 mg, 0.119 mmol) was employed. FCC (gradient elution: 9:1 – 1:1 hexane:EtOAc) afforded **239** (14.0 mg, 50 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3340 (br, s), 3034 (m), 2938 (m), 1697 (s), 1528 (s), 1244 (s). δ_H (500 MHz, $CDCl_3$) 7.38 – 7.29 (5H, m, 5 × Ar<u>C</u>H), 5.09 (2H, s, OC<u>H</u>$_2$Ph), 4.86 (1H, br s, N<u>H</u>), 3.20 (2H, dt, *J* = 6.5, 6.5 Hz, C**1**-<u>H</u>$_2$), 2.48 (2H, t, *J* = 7.0 Hz, C**3**-<u>H</u>$_2$), 2.13 (3H, s, C**5**-<u>H</u>$_3$), 1.78 (2H, tt, *J* = 7.0, 6.5 Hz, C**2**-<u>H</u>$_2$). δ_C (126 MHz, $CDCl_3$) 208.4 (C**4**), 156.6 (Cbz <u>C</u>=O), 136.7 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 66.8 (O<u>C</u>H$_2$Ph), 40.8 (C**3**), 40.6 (C**1**), 30.1 (C**5**), 24.0 (C**2**). HRMS: (ESI$^+$) Calculated for $C_{13}H_{17}NNaO_3$: 258.1101. Found $[M+Na]^+$: 258.1096.

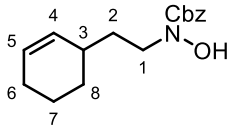
Benzyl ((*tert*-butyldimethylsilyl)oxy)(2-(cyclohex-2-en-1-yl)ethyl)carbamate



<u>General procedure A:</u> CbzNHOTBS (*vide supra*, 2.25 g, 8.00 mmol) was employed with 3-(2-bromoethyl)cyclohex-1-ene (Section 7.3). FCC (eluent: 39:1 hexane:EtOAc) afforded the title compound (2.50 g, 80 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2929 (s), 2858 (m), 1705 (s), 1250 (s). δ_H (400 MHz, $CDCl_3$) 7.39 – 7.28 (5H, m, 5 × Ar<u>C</u>H), 5.69 – 5.64 (1H, m, C**5**-<u>H</u>), 5.53 (1H, ddt, *J* = 10.0, 2.5, 2.5 Hz, C**4**-<u>H</u>), 5.15 (2H, s, OC<u>H</u>$_2$Ph), 3.53 (2H, t, *J* = 7.5 Hz, C**1**-<u>H</u>$_2$), 2.11 – 2.03 (1H, m, C**3**-<u>H</u>), 1.99 – 1.92 (2H, m, C**6**-<u>H</u>$_2$), 1.81 – 1.43 (5H, m, C**2**-<u>H</u>$_2$ C**7**-<u>H</u>$_2$ and C**8**-<u>H</u>), 1.28 – 1.16 (1H, m, C**8**-<u>H</u>'), 0.92 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.11 (6H, s, Si(C<u>H</u>$_3$)$_2$). δ_C (101 MHz, $CDCl_3$) 158.3 (<u>C</u>=O), 136.0 (Ar<u>C</u>), 131.1 (C**4**), 128.4 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 127.4 (C**5**), 67.7 (O<u>C</u>H$_2$Ph), 50.4 (C**1**),

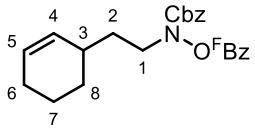
32.8 (C**3**), 32.2 (C**2**), 28.8 (C**8**), 25.7 (SiC($\underline{C}H_3)_3$), 25.2 (C**6**), 21.3 (C**7**), 17.9 (Si$\underline{C}(CH_3)_3$), -5.1 (Si($\underline{C}H_3)_2$). HRMS: (ESI^+) Calculated for $C_{22}H_{36}NO_3Si$: 390.2459. Found $[M+H]^+$: 390.2459.

Benzyl (2-(cyclohex-2-en-1-yl)ethyl)(hydroxy)carbamate



General procedure M: The preceding compound (2.50 g, 6.42 mmol) was employed with 2.0 eq. TBAF. The reaction time was 14 hours. The title compound (1.66 g, 94 %) was isolated as a pale-yellow oil, which was used without further purification. ν_{max} / cm^{-1}: (*film*) 3257 (br s), 3017 (m), 2926 (m), 1697 (s), 1453 (s), 1112 (s). δ_H (500 MHz, $CDCl_3$) 7.43 – 7.30 (5H, m, 5 × ArC$\underline{H}$), 6.35 (1H, br s, O$\underline{H}$), 5.69 (1H, ddt, *J* = 10.0, 3.0, 3.0 Hz, C**5**-$\underline{H}$), 5.57 (1H, ddt, *J* = 10.0, 2.5, 2.5 Hz, C**4**-$\underline{H}$), 5.18 (2H, s, OC$\underline{H}_2$Ph), 3.63 (2H, dd, *J* = 7.0, 7.0 Hz, C**1**-$\underline{H}_2$), 2.18 – 2.09 (1H, m, C**3**-$\underline{H}$), 2.01 – 1.95 (2H, m, C**6**-$\underline{H}_2$), 1.80 (1H, dddd, *J* = 12.5, 6.0, 6.0, 3.0 Hz, C**8**-$\underline{H}$), 1.76 – 1.67 (2H, m, C**2**-$\underline{H}$ and C**7**-$\underline{H}$), 1.65 – 1.57 (1H, m, C**2**-$\underline{H}$'), 1.54 – 1.42 (1H, m, C**7**-$\underline{H}$'), 1.28 – 1.20 (1H, m, C**8**-$\underline{H}$'). δ_C (126 MHz, $CDCl_3$) 157.5 ($\underline{C}$=O), 136.1 (Ar$\underline{C}$), 131.2 (C**4**), 128.6 (Ar$\underline{C}$H), 128.4 (Ar$\underline{C}$H), 128.1 (Ar$\underline{C}$H), 127.5 (C**5**), 68.0 (O$\underline{C}H_2$Ph), 48.3 (C**1**), 33.2 (C**2**), 32.5 (C**3**), 28.8 (C**8**), 25.3 (C**6**), 21.4 (C**7**). HRMS: (ESI^+) Calculated for $C_{16}H_{21}NNaO_3$: 298.1414. Found $[M+Na]^+$: 298.1409.

Benzyl (2-(cyclohex-2-en-1-yl)ethyl)((pentafluorobenzoyl)oxy)carbamate (241)



General procedure C: The preceding compound (130 mg, 0.472 mmol) was employed. FCC (eluent: 14:1 hexane:EtOAc) afforded **241** (200 mg, 90 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3019 (m), 2930 (m), 1785 (s), 1726 (s), 1652 (m), 1498 (s), 1171 (s). δ_H (400 MHz, $CDCl_3$) 7.39 – 7.30 (5H, m, 5 × ArC$\underline{H}$), 5.71 (1H, dtd, *J* = 10.0, 3.5, 2.5 Hz, C**5**-$\underline{H}$), 5.55 (1H, ddt, *J* = 10.0, 2.0, 2.0 Hz, C**4**-$\underline{H}$), 5.23 (2H, s, OC$\underline{H}_2$Ph), 3.83 (2H, dd, *J* = 7.5, 7.5 Hz, C**1**-$\underline{H}_2$), 2.21 (1H, dddddd, *J* = 11.0, 6.0, 5.5, 3.5, 2.5, 2.0 Hz, C**3**-$\underline{H}$), 2.02 – 1.94 (2H, m, C**6**-$\underline{H}_2$), 1.82 (1H, dddd, *J* = 12.5, 6.0, 6.0, 3.0 Hz, C**8**-$\underline{H}$), 1.78 – 1.60 (3H, m, C**2**-$\underline{H}_2$ and C**7**-$\underline{H}$), 1.59 – 1.47 (1H, m, C**7**-$\underline{H}$'), 1.25 (1H, dddd, *J* = 12.5, 11.0, 8.5, 3.0 Hz, C**8**-$\underline{H}$'). δ_C (101 MHz, $CDCl_3$) 157.3 (^{F}Bz $\underline{C}$=O), 155.4 (Cbz $\underline{C}$=O), 135.3 (Ar$\underline{C}$), 130.6 (C**4**), 128.6 (Ar$\underline{C}$H), 128.5 (Ar$\underline{C}$H), 128.2 (Ar$\underline{C}$H), 127.9 (C**5**), 68.8 (O$\underline{C}H_2$Ph), 49.2 (C**1**), 33.1 (C**2**), 32.4 (C**3**), 28.7 (C**8**), 25.3 (C**6**), 21.3 (C**7**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.0 (2F, m),

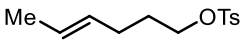
-146.0 (1F, tt, *J* = 21.0, 5.0 Hz), -159.1 – -159.3 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{23}H_{20}F_5NNaO_4$: 492.1210. Found $[M+Na]^+$: 492.1200.

tert-Butyl ((*tert*-butoxycarbonyl)oxy)carbamate

BocNHOBoc

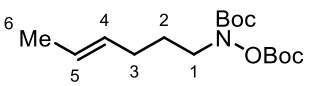
This compound was prepared according to a literature procedure.[253] To a solution of $NH_2OH{\cdot}HCl$ (8.00 g, 115 mmol) and Na_2CO_3 (15.9 g, 150 mmol) in water (70 mL) at 35 °C was added Boc_2O (55.6 mL, 242 mmol) in six roughly equal portions over around 2.5 hours. The reaction mixture was stirred for 30 minutes at 35 °C and then a further 16 hours at room temperature before being extracted with PhMe (4 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford BocNHOBoc (24.9 g, 93 %) as a colourless crystalline solid. m.p. 66-67 °C (CH_2Cl_2:petrol, *plates*) [Lit., 66-69 °C (petrol)].[254] δ_H (400 MHz, $CDCl_3$) 7.51 (1H, s), 1.53 (9H, s), 1.50 (9H, s). δ_C (101 MHz, $CDCl_3$) 155.8, 153.7, 85.6, 83.4, 28.2, 27.7. *The spectroscopic properties were consistent with the data available in the literature*.[255]

(*E*)-Hex-4-en-1-yl 4-toluenesulfonate



To a solution of (*E*)-4-hexen-1-ol (**87**) (2.50 g, 25.0 mmol) in anhydrous CH_2Cl_2 (40 mL) at 0 °C was added TsCl (6.20 g, 32.5 mmol) and pyridine (2.22 mL, 27.5 mmol). The reaction mixture was stirred at room temperature for 2 days before addition of 1.0 M aqueous HCl (30 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 9:1 hexane:EtOAc) afforded the title compound (4.86 g, 76 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.0 Hz), 7.34 (2H, d, *J* = 8.0 Hz), 5.40 – 5.20 (2H, m), 4.01 (2H, t, *J* = 6.5 Hz), 2.45 (3H, s), 1.99 (2H, br dt, *J* = 7.5, 7.0 Hz), 1.68 (2H, tt, *J* = 7.0, 6.5 Hz), 1.58 (3H, ddt, *J* = 5.5, 1.5, 1.5 Hz). δ_C (101 MHz, $CDCl_3$) 144.8, 133.3, 129.9, 129.2, 128.1, 126.6, 70.0, 28.7, 28.3, 21.8, 18.0. *The spectroscopic properties were consistent with the data available in the literature*.[256]

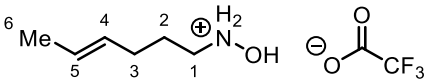
tert-Butyl (*E*)-((*tert*-butoxycarbonyl)oxy)(hex-4-en-1-yl)carbamate



To a solution of BocNHOBoc (*vide supra*, 3.92 g, 16.8 mmol) and the preceding tosylate (3.56 g, 14.0 mmol) in DMF (120 mL) was added Cs_2CO_3 (6.84 g, 21.0 mmol). The reaction mixture was stirred at room temperature for 17 hours before addition of brine (100 mL) and water (50 mL). The reaction

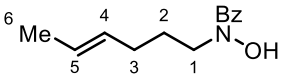
mixture was extracted with Et_2O (4 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 24:1 hexane:EtOAc) afforded the title compound (3.72 g, 84 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2981 (m), 1782 (s), 1716 (s), 1456 (m), 1369 (s), 1251 (s), 1149 (s). δ_H (400 MHz, $CDCl_3$) 5.50 – 5.32 (2H, m, C**4**-H and C**5**-H), 3.56 (2H, br s, C**1**-H_2), 2.03 (2H, dt, *J* = 7.0, 6.5 Hz, C**3**-H_2), 1.70 – 1.60 (5H, m, C**2**-H_2 and C**6**-H_3), 1.53 (9H, s, OC(CH_3)$_3$), 1.47 (9H, s, OC(CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 155.0 (C=O), 152.5 (C=O), 130.3 (C**5**), 125.9 (C**4**), 84.8 (OC(CH_3)$_3$), 82.3 (OC(CH_3)$_3$), 49.8 (C**1**), 29.7 (C**3**), 28.3 (OC(CH_3)$_3$), 27.8 (OC(CH_3)$_3$), 27.0 (C**2**), 18.1 (C**6**). HRMS: (ESI^+) Calculated for $C_{16}H_{29}NNaO_5$: 338.1938. Found $[M+Na]^+$: 338.1954.

(*E*)-*N*-(Hex-4-en-1-yl)hydroxylammonium trifluoroacetate (245)



The preceding compound (2.86 g, 9.01 mmol) was dissolved in TFA (10 mL) and left to stand for 4 hours before being concentrated *in vacuo* to afford **245** (1.67 g, 81 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 2848 (m), 1678 (s), 1656 (s), 1600 (s), 1447 (s), 1184 (s), 1146 (s). δ_H (400 MHz, $CDCl_3$) 11.27 – 9.98 (1H, br s, OH), 9.25 – 7.90 (2H, br s, NH_2), 5.50 (1H, dqt, *J* = 15.0, 6.5, 1.5 Hz, C**5**-H), 5.41 – 5.28 (1H, m, C**4**-H), 3.24 – 3.19 (2H, m, C**1**-H_2), 2.09 (2H, br dt, *J* = 7.0, 7.0 Hz, C**3**-H_2), 1.81 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2), 1.65 (3H, dq, *J* = 6.5, 1.5 Hz, C**6**-H_3). δ_C (101 MHz, $CDCl_3$) 128.5 (C**4**), 127.8 (C**5**), 51.0 (C**1**), 29.3 (C**3**), 23.2 (C**2**), 18.0 (C**6**). *The ^{13}C signals corresponding to the trifluoroacetate counterion could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -75.6 (3F). HRMS: (ESI^+) Calculated for $C_6H_{14}NO$: 116.1070. Found $[M–F_3CCO_2]^+$: 116.1067.

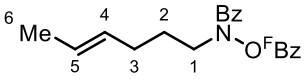
(*E*)-*N*-(Hex-4-en-1-yl)-*N*-hydroxybenzamide



To a solution of **245** (200 mg, 0.873 mmol) and K_2CO_3 (156 mg, 1.13 mmol) in THF (2 mL) and H_2O (2 mL) at 0 °C was added a solution of BzCl (0.12 mL, 1.05 mmol) in THF (1 mL). The reaction mixture was stirred at room temperature for 3.5 hours before addition of water (10 mL) and extraction with Et_2O (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 9:1 – 4:1 – 1:1 hexane:EtOAc) afforded the title compound (112 mg, 59 %) as an orange oil. ν_{max} / cm^{-1}: (*film*) 3163 (br s), 2934 (m), 1691 (m), 1598 (s), 1450 (s). δ_H (400 MHz, $CDCl_3$) 9.19 – 7.89 (1H, br s, OH), 7.52 – 7.39 (5H, m, 5 × ArCH), 5.38 – 5.22 (2H, m, C**4**-H and C**5**-H), 3.63 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 1.94 (2H, br td, *J* = 7.0, 6.5 Hz, C**3**-H_2), 1.79 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2), 1.56 (3H, ddt, *J* = 6.0, 1.5, 1.0 Hz, C**6**-H_3). δ_C (101 MHz, $CDCl_3$) 167.0 (C=O),

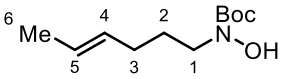
132.6 (ArC), 130.9 (ArCH), 129.7 (C**4**), 128.6 (ArCH), 127.9 (ArCH), 126.2 (C**5**), 50.3 (C**1**), 29.3 (C**3**), 27.3 (C**2**), 18.0 (C**6**). HRMS: (ESI$^+$) Calculated for $C_{13}H_{18}NO_2$: 220.1332. Found $[M+H]^+$: 220.1334.

(*E*)-*N*-(Hex-4-en-1-yl)-*N*-((pentafluorobenzoyl)oxy)benzamide (243b)



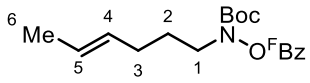
General procedure C: The preceding compound (111 mg, 0.506 mmol) was employed. FCC (*two times*, first eluent: 14:1 hexane:EtOAc; second eluent, gradient elution: 1:9 – 0:1 hexane:PhMe) afforded **243b** (102 mg, 49 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2936 (m), 1779 (s), 1680 (s), 1498 (s), 1173 (s). δ_H (400 MHz, $CDCl_3$) 7.62 – 7.58 (2H, m, 2 × ArCH), 7.51 – 7.45 (1H, m, ArCH), 7.43 – 7.38 (2H, m, 2 × ArCH), 5.49 – 5.31 (2H, m, C**4**-H and C**5**-H), 3.83 (2H, t, *J* = 7.5 Hz, C**1**-H_2), 2.07 (2H, br dt, *J* = 7.0, 7.0 Hz, C**3**-H_2), 1.80 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2), 1.61 (3H, ddt, *J* = 6.0, 1.0, 1.0 Hz, C**6**-H_3). δ_C (101 MHz, $CDCl_3$) 170.6 (Bz C=O), 157.3 (^{F}Bz C=O), 133.2 (ArC), 131.5 (ArCH), 129.6 (C**4**), 128.5 (ArCH), 128.0 (ArCH), 126.5 (C**5**), 50.8 (C**1**), 29.5 (C**3**), 27.0 (C**2**), 18.0 (C**6**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.7 – -136.0 (2F, m), -145.6 (1F, t, *J* = 22.0 Hz), -158.8 – -159.3 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{20}H_{16}F_5NNaO_3$: 436.0943. Found $[M+Na]^+$: 436.0938.

***tert*-Butyl (*E*)-hex-4-en-1-yl(hydroxy)carbamate**



To a solution of **245** (2.08 g, 9.08 mmol) and K_2CO_3 (627 mg, 4.54 mmol) in THF (10 mL) and H_2O (10 mL) at 0 °C was added a solution of Boc_2O (2.18 g, 10.0 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for 3 hours before being concentrated to an aqueous solution. The reaction mixture was suspended in CH_2Cl_2 (50 mL) and washed with water (2 × 30 mL) followed by brine (30 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 8:1 – 6:1 – 4:1 hexane:EtOAc) afforded the title compound (951 mg, 49 %) as an orange oil. ν_{max} / cm^{-1}: (*film*) 3226 (br s), 2934 (m), 1690 (s), 1367 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 7.10 – 6.56 (1H, m, OH), 5.51 – 5.36 (2H, m, C**4**-H and C**5**-H), 3.52 – 3.42 (2H, m, C**1**-H_2), 2.00 (1H, dt, *J* = 6.5, 6.0 Hz, C**3**-H_2), 1.72 – 1.61 (5H, m, C**2**-H_2 and C**6**-H_3), 1.48 (9H, s, OC(CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 157.1 (C=O), 130.5 (C**4**), 125.7 (C**5**), 81.8 (OC(CH_3)$_3$), 49.6 (C**1**), 29.6 (C**3**), 28.5 (OC(CH_3)$_3$), 26.9 (C**2**), 18.1 (C**6**). HRMS: (ESI$^+$) Calculated for $C_{11}H_{21}NNaO_3$: 238.1414. Found $[M+Na]^+$: 238.1411.

***tert*-Butyl (*E*)-hex-4-en-1-yl((pentafluorobenzoyl)oxy)carbamate (243c)**



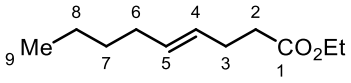
General procedure C: The preceding compound (918 mg, 4.26 mmol) was employed. FCC (eluent: 29:1 hexane:EtOAc) afforded **243c** (1.82 g, 99 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2982 (m), 2938 (m), 1783 (s), 1721 (s), 1653 (m), 1504 (s), 1155 (s). δ_H (400 MHz, $CDCl_3$) 5.51 – 5.35 (2H, m, C**4**-H and C**5**-H), 3.69 – 3.63 (2H, m, C**1**-H_2), 2.06 (2H, dt, *J* = 7.5, 6.5 Hz, C**3**-H_2), 1.73 – 1.62 (5H, m, C**2**-H_2 and C**6**-H_3), 1.49 (9H, s, OC(CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 157.5 (^{F}Bz C=O), 154.7 (Boc C=O), 129.9 (C**4**), 126.2 (C**5**), 83.3 (OC(CH_3)$_3$), 50.6 (C**1**), 29.5 (C**3**), 28.2 (OC(CH_3)$_3$), 26.8 (C**2**), 18.0 (C**6**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.4 – -136.6 (2F, m), -146.7 (1F, tt, *J* = 21.0, 5.0 Hz), -159.3 – -159.6 (2F, m). HRMS: (ESI^+) Calculated for $C_{18}H_{20}F_5NNaO_4$: 432.1205. Found $[M+Na]^+$: 432.1212.

***tert*-Butyl ((pentafluorobenzoyl)oxy)carbamate**

BocNHO^{F}Bz

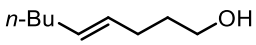
This compound was prepared according to a literature procedure.[164] To a solution of BocNHOH (6.66 g, 50.0 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added ^{F}BzCl (6.90 mL, 50.0 mmol) followed by Et_3N (7.00 mL, 50.0 mmol). The reaction mixture was stirred at room temperature for 3 hours before addition of water (100 mmol). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (70 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 9:1 hexane:EtOAc) afforded BocNHO^{F}Bz (14.7 g, 90 %) as a colourless crystalline solid. m.p. 72-74 °C (CH_2Cl_2:petrol, *cubes*). ν_{max} / cm^{-1}: (*solid*) 3270 (br s), 2996 (m), 1779 (s), 1719 (s), 1654 (s), 1505 (s), 1152 (s). δ_H (301 MHz, $CDCl_3$) 8.10 (1H, s, NH), 1.52 (9H, s, OC(CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 154.9 (Boc C=O), 84.4 (OC(CH_3)$_3$), 28.1 (OC(CH_3)$_3$). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (283 MHz, $CDCl_3$) -135.3 – -135.5 (2F, m), -145.5 (1F, tt, *J* = 21.0, 5.5 Hz), -159.1 – -159.4 (2F, m). HRMS: (ESI^+) Calculated for $C_{12}H_{10}F_5NNaO_4$: 350.0422. Found $[M+Na]^+$: 350.0433. *The spectroscopic properties were consistent with the data available in the literature.*[164]

Ethyl (*E*)-non-4-enoate



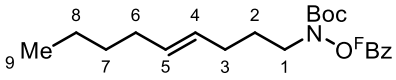
General procedure L: Hept-1-en-3-ol (5.71 g, 50.0 mmol) was employed. The reaction time was 14 hours. FCC (eluent: 49:1 hexane:EtOAc) afforded the title compound (7.10 g, 77 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2959 (m), 2927 (m), 1735 (s), 1446 (m), 1150 (s). δ_H (400 MHz, $CDCl_3$) 5.51 – 5.33 (2H, m, C**4**-H and C**5**-H), 4.12 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 2.38 – 2.26 (4H, m, C**2**-H_2 and C**3**-H_2), 1.97 (2H, dt, *J* = 6.5, 6.5 Hz, C**6**-H_2), 1.35 – 1.26 (4H, m, C**7**-H_2 and C**8**-H_2), 1.25 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.90 – 0.85 (3H, m, C**9**-H_3). δ_C (101 MHz, $CDCl_3$) 173.3 (C**1**), 131.9 (C**5**), 128.0 (C**4**), 60.3 (OCH_2CH_3), 34.5 (C**2**), 32.3 (C**6**), 31.7 (C**7**), 28.1 (C**3**), 22.2 (C**8**), 14.4 (OCH_2CH_3), 14.0 (C**9**). HRMS: (ESI^+) Calculated for $C_{11}H_{20}NaO_2$: 207.1356. Found $[M+Na]^+$: 207.1354.

(*E*)-Non-4-en-1-ol



General procedure I: The preceding ester (7.10 g, 38.5 mmol) was employed, using anhydrous Et_2O as solvent and 0.8 eq. $LiAlH_4$ (1.0 M in Et_2O). The title compound (5.42 g, 99 %) was isolated as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.49 – 5.36 (2H, m), 3.65 (2H, t, *J* = 6.5 Hz), 2.07 (2H, dt, *J* = 7.0, 7.0 Hz), 1.98 (2H, dt, *J* = 6.0, 6.0 Hz), 1.63 (2H, tt, *J* = 7.0, 6.5 Hz), 1.39 – 1.23 (5H, m), 0.88 (3H, t, *J* = 7.0 Hz). δ_C (101 MHz, $CDCl_3$) 131.4, 129.5, 62.7, 32.6, 32.4, 31.9, 29.1, 22.3, 14.1. *The spectroscopic properties were consistent with the data available in the literature*.[257]

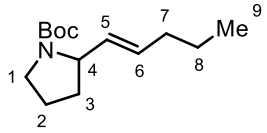
***tert*-Butyl (*E*)-non-4-en-1-yl((pentafluorobenzoyl)oxy)carbamate (246a)**



General procedure O: (*E*)-Non-4-en-1-ol (*vide supra*, 213 mg, 1.50 mmol) was employed with $BocNHO^FBz$ (*vide supra*). The reaction time was 23 hours. FCC (eluent: 1:1 petrol:PhMe) afforded **246a** (450 mg, 66 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2931 (m), 1784 (s), 1722 (s), 1652 (m), 1505 (s), 1154 (s). δ_H (400 MHz, $CDCl_3$) 5.51 – 5.34 (2H, m, C**4**-H and C**5**-H), 3.69 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 2.09 (2H, td, *J* = 7.5, 7.0 Hz, C**3**-H_2), 2.00 (2H, dt, *J* = 8.0, 6.0 Hz, C**6**-H_2), 1.72 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2), 1.52 (9H, s, $OC(CH_3)_3$), 1.39 – 1.26 (4H, m, C**7**-H_2 and C**8**-H_2), 0.94 – 0.87 (3H, m, C**9**-H_3). δ_C (101 MHz, $CDCl_3$) 154.6 (Boc C=O), 131.7 (C**5**), 128.5 (C**4**), 83.2 ($OC(CH_3)_3$), 50.5 (C**1**), 32.2 (C**6**), 31.7 (C**7**), 29.4 (C**3**), 28.0 ($OC(CH_3)_3$), 26.8 (C**2**), 22.2 (C**8**), 13.9 (C**9**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.*

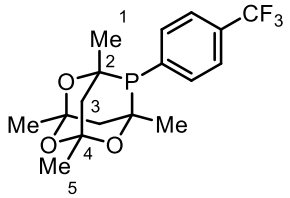
δ_F (377 MHz, $CDCl_3$) -136.4 – -136.7 (2F, m), -146.7 (1F, tt, *J* = 21.0, 5.0 Hz), -159.4 – -159.6 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{21}H_{26}F_5NNaO_4$: 474.1674. Found $[M+Na]^+$: 474.1658.

***tert*-Butyl (*E*)-2-(pent-1-en-1-yl)pyrrolidine-1-carboxylate (247a)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **246a** (47.4 mg, 0.105 mmol) was employed. FCC (gradient elution: 39:1 – 19:1 PhMe:EtOAc) afforded **247a** (21.4 mg, 85 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2964 (m), 2928 (m), 1692 (s), 1389 (s), 1167 (s). δ_H (400 MHz, $CDCl_3$) 5.52 – 5.37 (1H, m, C**6**-H), 5.37 – 5.22 (1H, m, C**5**-H), 4.38 – 4.10 (1H, m, C**4**-H), 3.46 – 3.23 (2H, m, C**1**-H_2), 2.01 – 1.92 (3H, m, C**3**-H and C**7**-H_2), 1.89 – 1.74 (2H, m, C**2**-H_2), 1.65 (1H, dddd, *J* = 12.5, 6.0, 3.0, 3.0 Hz, C**3**-H'), 1.46 – 1.31 (11H, m, C**8**-H_2 and OC(CH_3)$_3$), 0.88 (3H, t, *J* = 7.5 Hz, C**9**-H_3). δ_C (101 MHz, $CDCl_3$) 154.8 (C=O), 130.8 (C**5**), 130.2 (C**6**), 79.0 (OC(CH_3)$_3$), 58.7 (C**4**), 46.2 (C**1**), 34.4 (C**7**), 32.6 (C**3**), 28.7 (OC(CH_3)$_3$), 23.0 (C**2**), 22.6 (C**8**), 13.8 (C**9**). HRMS: (ESI$^+$) Calculated for $C_{14}H_{25}NNaO_2$: 262.1777. Found $[M+Na]^+$: 262.1776.

1,3,5,7-Tetramethyl-8-(4-(trifluoromethyl)phenyl)-2,4,6-trioxa-8-phosphaadamantane (L2)

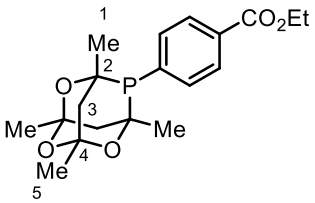


General procedure P: 1,3,5,7-Tetramethyl-2,4,6-trioxa-8-phosphaadamantane (**248**)[XLIV] (1.30 g, 6.00 mmol) was employed with 1-bromo-4-(trifluoromethyl)benzene (0.70 mL, 5.00 mmol). The reaction time was 20 hours. FCC (gradient elution: 1:9 – 0:1 hexane:PhMe) afforded **L2** (1.34 g, 74 %) as a colourless crystalline solid. m.p. 132-133 °C (CH_2Cl_2:petrol, *plates*). ν_{max} / cm^{-1}: (*solid*) 3005 (m), 2920 (m), 1606 (m), 1322 (s), 1119 (s). δ_H (400 MHz, $CDCl_3$) 7.96 (2H, ddq, *J* = 8.5, 7.5, 1.0 Hz, 2 × ArCH), 7.61 (2H, dq, *J* = 7.5, 1.0 Hz, 2 × ArCH), 2.06 (1H, dd, *J* = 13.5, 7.5 Hz, C**3**-H), 1.94 (1H, dd, *J* = 24.5, 13.5 Hz, C**3**-H'), 1.66 (1H, d, *J* = 13.5 Hz, C**3'**-H), 1.52 (3H, d, *J* = 13.0 Hz, C**1**-H_3), 1.50 (1H, dd, *J* = 13.5, 4.0 Hz, C**3'**-H'), 2 × 1.42 (3H, s, C**5**-H_3 and 3H, s, C**5'**-H_3), 1.26 (3H, d, *J* = 13.0 Hz, C**1'**-H_3). δ_C (101 MHz, $CDCl_3$) 139.2 (d, *J* = 31.0 Hz, ArC), 135.2 (d, *J* = 19.5 Hz, ArCH), 131.3 (q, *J* = 32.5 Hz, ArC), 124.9 (dq, *J* = 7.5, 3.5 Hz, ArCH), 96.8 (C**4**), 96.1 (C**4'**), 73.3 (d, *J* = 22.5 Hz, C**2**),

[XLIV] Phosphine **248** was prepared by Charly Faradji (University of Bristol) according to a literature procedure.[147]

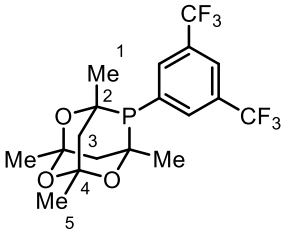
73.1 (d, *J* = 8.0 Hz, C**2'**), 45.1 (d, *J* = 17.5 Hz, C**3**), 36.3 (d, *J* = 2.0 Hz, C**3'**), 28.0 (C**5'**), 27.7 (C**5**), 27.4 (d, *J* = 22.0 Hz, C**1'**), 26.8 (d, *J* = 11.0 Hz, C**1**). *The ^{13}C signal corresponding to the trifluoromethyl group could not be resolved due to its weak intensity*. δ_F (377 MHz, $CDCl_3$) -63.0 (3F). δ_P (162 MHz, $CDCl_3$) -25.0. HRMS: (ESI^+) Calculated for $C_{17}H_{21}F_3O_3P$: 361.1175. Found $[M+H]^+$: 361.1174.

Ethyl 4-(1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantan-8-yl)benzoate (L3)



General procedure P: The reaction was conducted on a 2.00 mmol scale and employed ethyl 4-bromobenzoate. The reaction time was 16 hours. FCC (eluent: 39:1 pentane:acetone) afforded **L3** (636 mg, 87 %) as a colourless crystalline solid. m.p. 114-116 °C (CH_2Cl_2:petrol, *cubes*). ν_{max} / cm^{-1}: (*solid*) 2985 (m), 2917 (m), 1715 (s), 1596 (m), 1371 (s), 1262 (s). δ_H (400 MHz, $CDCl_3$) 8.02 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.91 (2H, dd, *J* = 8.0, 7.0 Hz, 2 × ArC<u>H</u>), 4.39 (2H, q, *J* = 7.0 Hz, OC<u>H</u>$_2$CH$_3$), 2.06 (1H, dd, *J* = 13.5, 7.5 Hz, C**3**-<u>H</u>), 1.94 (1H, dd, *J* = 24.5, 13.5 Hz, C**3**-<u>H</u>'), 1.67 (1H, d, *J* = 13.5 Hz, C**3'**-<u>H</u>), 1.53 (3H, d, *J* = 13.0 Hz, C**1**-<u>H</u>$_3$), 1.47 (1H, dd, *J* = 13.5, 4.0 Hz, C**3'**-<u>H</u>'), 1.43 – 1.37 (9H, m, C**5**-<u>H</u>$_3$, C**5'**-<u>H</u>$_3$ and OCH$_2$C<u>H</u>$_3$), 1.25 (3H, d, *J* = 13.0 Hz, C**1'**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 166.5 (<u>C</u>=O), 140.3 (d, *J* = 30.5 Hz, Ar<u>C</u>), 135.0 (d, *J* = 19.5 Hz, Ar<u>C</u>H), 131.3 (Ar<u>C</u>), 129.2 (d, *J* = 7.0 Hz, Ar<u>C</u>H), 97.0 (C**4**), 96.2 (C**4'**), 2 × 73.4 (d, *J* = 22.0 Hz, C**2** and d, *J* = 8.0 Hz, C**2'**), 61.3 (O<u>C</u>H$_2$CH$_3$), 45.3 (d, *J* = 17.5 Hz, C**3**), 36.5 (d, *J* = 2.0 Hz, C**3'**), 28.1 (C**5'**), 27.9 (C**5**), 27.6 (d, *J* = 21.5 Hz, C**1'**), 27.0 (d, *J* = 11.0 Hz, C**1**), 14.5 (OCH$_2$<u>C</u>H$_3$). δ_P (162 MHz, $CDCl_3$) -24.6. HRMS: (ESI^+) Calculated for $C_{19}H_{25}NaO_5P$: 387.1332. Found $[M+Na]^+$: 387.1333.

8-(3,5-Bis(trifluoromethyl)phenyl)-1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane (L6)

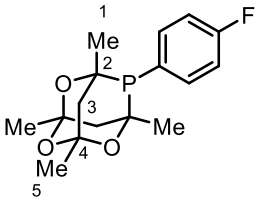


General procedure P: 1,3,5,7-Tetramethyl-2,4,6-trioxa-8-phosphaadamantane (**248**)[XLV] (1.30 g, 6.00 mmol) was employed with 1-bromo-3,5-bis(trifluoromethyl)benzene (0.88 mL, 5.00 mmol). The reaction time was 20 hours. FCC (eluent: 1:9 hexane:PhMe) afforded **L6** (891 mg, 42 %) as a colourless

[XLV] Phosphine **248** was prepared by Charly Faradji (University of Bristol) according to a literature procedure.[147]

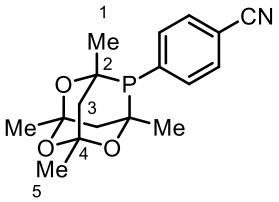
crystalline solid. m.p. 133-134 °C (CH_2Cl_2:petrol, *needles*). ν_{max} / cm^{-1}: (*solid*) 2980 (m), 2940 (m), 1615 (m), 1357 (s), 1276 (s), 1124 (s). δ_H (400 MHz, $CDCl_3$) 8.33 (2H, br d, *J* = 6.0 Hz, 2 × ArC<u>H</u>), 7.88 (1H, br s, ArC<u>H</u>), 2.05 (1H, dd, *J* = 13.5, 8.0 Hz, C**3**-<u>H</u>), 1.96 (1H, dd, *J* = 24.5, 13.5 Hz, C**3**-<u>H</u>'), 1.55 – 1.53 (2H, m, C**3'**-<u>H_2</u>), 1.51 (3H, d, *J* = 13.0 Hz, C**1**-<u>H_3</u>), 1.43 (3H, s, C**5**-<u>H_3</u>), 1.41 (3H, s, C**5'**-<u>H_3</u>), 1.26 (3H, d, *J* = 13.5 Hz, C**1'**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 138.4 (d, *J* = 35.5 Hz, Ar<u>C</u>), 135.1 (d, *J* = 19.5 Hz, Ar<u>C</u>H), 131.6 (d, *J* = 33.5 Hz, Ar<u>C</u>), 123.3 (Ar<u>C</u>H), 97.1 (C**4**), 96.2 (C**4'**), 73.4 (d, *J* = 22.0 Hz, C**2**), 73.2 (d, *J* = 8.0 Hz, C**2'**), 45.1 (d, *J* = 17.5 Hz, C**3**), 36.3 (C**3'**), 28.0 (C**5'**), 27.8 (C**5**), 27.5 (d, *J* = 22.0 Hz, C**1**), 26.9 (d, *J* = 11.0 Hz, C**1'**). *The ^{13}C signal corresponding to the trifluoromethyl groups could not be resolved due to its weak intensity.* δ_F (377 MHz, $CDCl_3$) -63.0 (6F). δ_P (162 MHz, $CDCl_3$) -26.2. HRMS: (ESI^+) Calculated for $C_{18}H_{20}F_6O_3P$: 429.1049. Found $[M+H]^+$: 429.1031.

8-(4-Fluorophenyl)-1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane (L8)



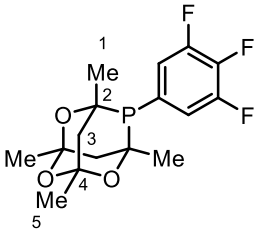
<u>General procedure P:</u> The reaction was conducted on a 2.00 mmol scale and employed 1-bromo-4-fluorobenzene. The reaction time was 20 hours. FCC (*two times:* first, gradient elution: 12:1 – 6:1 – 2:1 hexane:EtOAc; second, gradient elution: 1:4 – 0:1 hexane:PhMe) afforded **L8** (178 mg, 29 %) as a colourless crystalline solid. m.p. 103-104 °C (CH_2Cl_2:petrol, *tabular*). ν_{max} / cm^{-1}: (*solid*) 2924 (m), 1587 (s), 1494 (s), 1379 (s), 1160 (s). δ_H (400 MHz, $CDCl_3$) 7.85 – 7.78 (2H, m, 2 × ArC<u>H</u>), 7.10 – 7.04 (2H, m, 2 × ArC<u>H</u>), 2.05 (1H, dd, *J* = 13.0, 7.0 Hz, C**3**-<u>H</u>), 1.93 (1H, dd, *J* = 25.0, 13.0 Hz, C**3**-<u>H</u>'), 1.73 (1H, d, *J* = 13.5 Hz, C**3'**-<u>H</u>), 1.57 – 1.47 (1H, m, C**3'**-<u>H</u>'), 1.49 (3H, d, *J* = 13.0 Hz, C**1**-<u>H_3</u>), 1.42 (3H, s, C**5**-<u>H_3</u>), 1.41 (3H, s, C**5'**-<u>H_3</u>), 1.23 (3H, d, *J* = 13.0 Hz, C**1'**-<u>H_3</u>). δ_C (126 MHz, $CDCl_3$) 163.9 (d, *J* = 250.0 Hz, Ar<u>C</u>F), 137.2 (dd, *J* = 21.0, 8.0 Hz, Ar<u>C</u>H), 129.5 (dd, *J* = 27.5, 3.5 Hz, Ar<u>C</u>), 115.8 (dd, *J* = 20.5, 8.0 Hz, Ar<u>C</u>H), 97.0 (C**4**), 96.2 (C**4'**), 73.5 (d, *J* = 21.5 Hz, C**2**), 73.1 (d, *J* = 7.5 Hz, C**2'**), 45.5 (d, *J* = 17.5 Hz, C**3**), 36.2 (d, *J* = 2.0 Hz, C**3'**), 28.2 (C**5'**), 27.9 (C**5**), 27.5 (d, *J* = 22.0 Hz, C**1'**), 26.9 (d, *J* = 11.5 Hz, C**1**). δ_F (377 MHz, $CDCl_3$) -110.9 (1F, d, *J* = 3.0 Hz). δ_P (162 MHz, $CDCl_3$) -25.7. HRMS: (ESI^+) Calculated for $C_{16}H_{21}FO_3P$: 311.1207. Found $[M+H]^+$: 311.1216.

4-(-1,3,5,7-Tetramethyl-2,4,6-trioxa-8-phosphaadamantan-8-yl)benzonitrile (L9)



General procedure P: The reaction was conducted on a 2.00 mmol scale and employed 4-bromobenzonitrile. The reaction time was 19 hours. FCC (gradient elution: 14:1 – 9:1 hexane:EtOAc) afforded **L9** (133 mg, 21 %) as a colourless crystalline solid. m.p. 185-187 °C (CH_2Cl_2:petrol, *equant*). ν_{max} / cm^{-1}: (*solid*) 2973 (m), 2914 (m), 2227 (m), 1593 (m), 1381 (s), 1184 (s). δ_H (500 MHz, $CDCl_3$) 7.96 (2H, dd, *J* = 8.0, 6.5 Hz, 2 × ArC<u>H</u>), 7.64 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 2.04 (1H, dd, *J* = 13.5, 7.5 Hz, C**3**-<u>H</u>), 1.95 (1H, dd, *J* = 25.0, 13.5 Hz, C**3**-<u>H</u>'), 1.60 (1H, d, *J* = 13.5 Hz, C**3'**-<u>H</u>), 1.54 – 1.48 (4H, m, C**1**-<u>H</u>$_3$ and C**3'**-<u>H</u>'), 1.42 (3H, s, C**5**-<u>H</u>$_3$), 1.41 (3H, s, C**5'**-<u>H</u>$_3$), 1.26 (3H, d, *J* = 13.0 Hz, C**1'**-<u>H</u>$_3$). δ_C (126 MHz, $CDCl_3$) 141.2 (d, *J* = 33.5 Hz, Ar<u>C</u>), 135.5 (d, *J* = 19.5 Hz, Ar<u>C</u>H), 131.7 (d, *J* = 7.0 Hz, Ar<u>C</u>H), 118.6 (Ar<u>C</u>), 113.2 (<u>C</u>≡N), 97.0 (C**4**), 96.2 (C**4'**), 2 × 73.4 (d, *J* = 22.5 Hz, C**2** and d, *J* = 8.0 Hz, C**2'**), 45.1 (d, *J* = 17.5 Hz, C**3**), 36.5 (d, *J* = 2.0 Hz, C**3'**), 28.1 (C**5'**), 27.8 (C**5**), 27.6 (d, *J* = 22.0 Hz, C**1'**), 26.9 (d, *J* = 11.5 Hz, C**1**). δ_P (162 MHz, $CDCl_3$) -24.4. HRMS: (ESI^+) Calculated for $C_{17}H_{20}NNaO_3P$: 340.1073. Found $[M+Na]^+$: 340.1082.

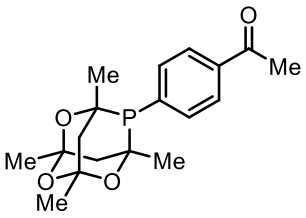
1,3,5,7-Tetramethyl-8-(3,4,5-trifluorophenyl)-2,4,6-trioxa-8-phosphaadamantane (L11)



General procedure P: The reaction was conducted on a 2.00 mmol scale and employed 1-bromo-3,4,5-trifluorobenzene. The reaction time was 20 hours. FCC (*two times:* first, gradient elution: 39:1 – 19:1 – 9:1 hexane:EtOAc; second, gradient elution: 1:9 – 0:1 hexane:PhMe) afforded **L11** (223 mg, 32 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3086 (m), 2934 (m), 1607 (s), 1518 (s), 1214 (s), 1039 (s). δ_H (400 MHz, $CDCl_3$) 7.50 (2H, dt, *J* = 8.0, 6.5 Hz, 2 × ArC<u>H</u>), 2.01 (1H, dd, *J* = 13.5, 8.0 Hz, C**3**-<u>H</u>), 1.93 (1H, dd, *J* = 24.5, 13.5 Hz, C**3**-<u>H</u>'), 1.68 (1H, d, *J* = 13.5 Hz, C**3'**-<u>H</u>), 1.55 – 1.50 (1H, m, C**3'**-<u>H</u>'), 1.47 (3H, d, *J* = 13.0 Hz, C**1**-<u>H</u>$_3$), 1.42 (3H, s, C**5**-<u>H</u>$_3$), 1.41 (3H, s, C**5'**-<u>H</u>$_3$), 1.25 (3H, d, *J* = 13.0 Hz, C**1'**-<u>H</u>$_3$). δ_C (126 MHz, $CDCl_3$) 151.1 (br d, *J* = 253.5 Hz, Ar<u>C</u>F), 140.8 (br d, *J* = 255.5 Hz, Ar<u>C</u>F), 130.7 (d, *J* = 39.0 Hz, Ar<u>C</u>), 119.0 (d, *J* = 21.0 Hz, Ar<u>C</u>H), 97.0 (C**4**), 96.2 (C**4'**), 73.4 (d, *J* = 2.0 Hz, C**2**), 73.1 (d, *J* = 8.0 Hz, C**2'**), 45.2 (d, *J* = 17.5 Hz, C**3**), 36.3 (d, *J* = 2.0 Hz, C**3'**), 28.1 (C**5'**),

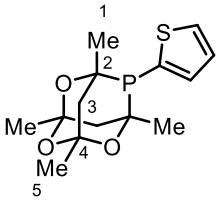
27.8 (C**5**), 27.6 (d, *J* = 22.0 Hz, C**1'**), 26.8 (d, *J* = 11.0 Hz, C**1**). δ_F (377 MHz, $CDCl_3$) -133.3 (2F, d, *J* = 20.5 Hz), -157.8 (1F, t, *J* = 20.5 Hz). δ_P (162 MHz, $CDCl_3$) -24.5. HRMS: (ESI^+) Calculated for $C_{16}H_{19}F_3O_3P$: 347.1018. Found $[M+H]^+$: 347.1024.

1,3,5,7-Tetramethyl-8-(4-acetylphenyl)-2,4,6-trioxa-8-phosphaadamantane (L13)



General procedure P: The reaction was conducted on a 2.00 mmol scale and employed 4-bromoacetophenone. The reaction time was 14 hours. FCC (gradient elution: 29:1 – 19:1 PhMe:EtOAc) afforded **L13** (527 mg, 79 %) as a colourless crystalline solid. m.p. 108-111 °C (CH_2Cl_2:petrol, *tabular*) [Lit., 107.5-110.5 °C (*No recrystallisation solvent quoted*)].[149] δ_H (400 MHz, $CDCl_3$) 7.97 – 7.90 (4H, m), 2.61 (3H, s), 2.05 (1H, dd, *J* = 13.5, 7.0 Hz), 1.94 (1H, dd, *J* = 24.5, 13.5 Hz), 1.66 (1H, d, *J* = 13.5 Hz), 1.53 (3H, d, *J* = 12.5 Hz), 1.48 (1H, dd, *J* = 13.5, 4.5 Hz), 1.42 (3H, s), 1.41 (3H, s), 1.26 (3H, d, *J* = 13.0 Hz). δ_C (101 MHz, $CDCl_3$) 198.0, 140.8 (d, *J* = 31.0 Hz), 137.6, 135.2 (d, *J* = 19.5 Hz), 127.9 (d, *J* = 7.0 Hz), 97.0, 96.2, 2 × 73.4 (d, *J* = 22.0 Hz and d, *J* = 8.0 Hz), 45.3 (d, *J* = 17.0 Hz), 36.6 (d, *J* = 2.0 Hz), 28.1, 27.9, 27.6 (d, *J* = 22.0 Hz), 27.0 (d, *J* = 11.5 Hz), 26.8. δ_P (162 MHz, $CDCl_3$) -24.6. *The spectroscopic properties were consistent with the data available in the literature.*[149]

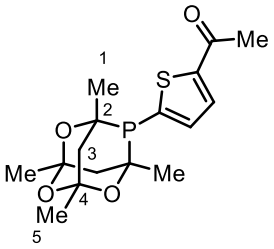
1,3,5,7-Tetramethyl-8-(thiophen-2-yl)-2,4,6-trioxa-8-phosphaadamantane (L14)



General procedure P: The reaction was conducted on a 2.00 mmol scale and employed 2-bromothiophene. The reaction time was 17 hours. FCC (eluent: PhMe) afforded **L14** (323 mg, 54 %) as a colourless crystalline solid. m.p. 92-94 °C (CH_2Cl_2:petrol, *plates*). ν_{max} / cm^{-1}: (*solid*) 3100 (m), 2962 (m), 2911 (m), 1450 (m), 1380 (s), 1343 (s), 1212 (s). δ_H (400 MHz, $CDCl_3$) 7.64 (1H, dd, *J* = 5.0, 1.0 Hz, ArC<u>H</u>), 7.53 (1H, ddd, *J* = 7.0, 3.5, 1.0 Hz, ArC<u>H</u>), 7.13 (1H, ddd, *J* = 5.0, 3.5, 1.5 Hz, ArC<u>H</u>), 2.11 (1H, d, *J* = 13.5 Hz, C**3'**-<u>H</u>), 2.05 (1H, dd, *J* = 13.0, 7.5 Hz, C**3**-<u>H</u>), 1.96 (1H, dd, *J* = 25.0, 13.0 Hz, C**3**-<u>H</u>'), 1.54 (1H, dd, *J* = 13.5, 4.5 Hz, C**3'**-<u>H</u>'), 1.45 (3H, s, C**5**-<u>H_3</u>), 1.42 (3H, s, C**5'**-<u>H_3</u>), 1.40 (3H, d, *J* = 13.0 Hz, C**1**-<u>H_3</u>), 1.26 (3H, d, *J* = 14.0 Hz, C**1'**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 139.2 (d, *J* = 29.5 Hz,

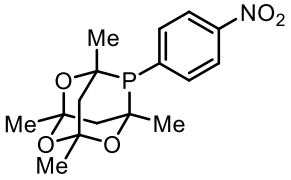
ArCH), 132.9 (ArCH), 132.0 (d, *J* = 45.5 Hz, ArC), 127.5 (d, *J* = 9.5 Hz, ArCH), 97.0 (C**4**), 96.4 (C**4'**), 2 × 73.2 (d, *J* = 18.0 Hz, C**2** and d, *J* = 7.0 Hz, C**2'**), 45.0 (d, *J* = 18.0 Hz, C**3**), 37.0 (d, *J* = 2.0 Hz, C**3'**), 28.1 (C**5'**), 27.9 (C**5**), 27.7 (d, *J* = 23.5 Hz, C**1'**), 27.1 (d, *J* = 11.0 Hz, C**1**). δ_P (162 MHz, $CDCl_3$) -34.3. HRMS: (ESI^+) Calculated for $C_{14}H_{20}O_3PS$: 299.0865. Found $[M+H]^+$: 299.0874.

1,3,5,7-Tetramethyl-8-(5-acetylthiophen-2-yl)-2,4,6-trioxa-8-phosphaadamantane (L15)



General procedure P: The reaction was conducted on a 2.00 mmol scale and employed 2-acetyl-5-bromothiophene. The reaction time was 22 hours. FCC (gradient elution: 99:1 – 49:1 PhMe:acetone) afforded **L15** (377 mg, 55 %) as a colourless crystalline solid. m.p. 104-105 °C (CH_2Cl_2:petrol, *tabular*). ν_{max} / cm^{-1}: (*solid*) 2969 (m), 2915 (m), 1662 (s), 1514 (m), 1213 (s). δ_H (400 MHz, $CDCl_3$) 7.66 (1H, dd, *J* = 4.0, 1.0 Hz, ArCH), 7.50 (1H, dd, *J* = 6.5, 4.0 Hz, ArCH), 2.56 (3H, s, C(O)CH_3), 2.06 – 1.90 (3H, m, C**3**-H_2 and C**3'**-H), 1.56 (1H, dd, *J* = 13.5, 4.5 Hz, C**3'**-H'), 1.45 (3H, s, C**5**-H_3), 1.43 (3H, d, *J* = 13.0 Hz, C**1**-H_3), 1.41 (3H, s, C**5'**-H_3), 1.29 (3H, d, *J* = 14.0 Hz, C**1'**-H_3). δ_C (101 MHz, $CDCl_3$) 190.4 (C(O)CH_3), 150.0 (ArC), 142.3 (d, *J* = 51.0 Hz, ArC), 138.9 (d, *J* = 28.0 Hz, ArCH), 132.0 (d, *J* = 8.5 Hz, ArCH), 96.9 (C**4**), 96.2 (C**4'**), 73.2 (d, *J* = 8.0 Hz, C**2'**), 72.9 (d, *J* = 19.0 Hz, C**2**), 44.5 (d, *J* = 17.5 Hz, C**3**), 36.8 (d, *J* = 2.0 Hz, C**3'**), 27.9 (C**5'**), 27.7 (C**5**), 27.6 (d, *J* = 23.0 Hz, C**1'**), 27.2 (C(O)CH_3), 27.0 (d, *J* = 11.0 Hz, C**1**). δ_P (162 MHz, $CDCl_3$) -32.4. HRMS: (ESI^+) Calculated for $C_{16}H_{22}O_4PS$: 341.071. Found $[M+H]^+$: 341.0980.

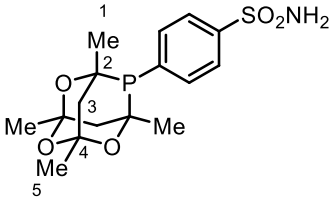
1,3,5,7-Tetramethyl-8-(4-nitrophenyl)-2,4,6-trioxa-8-phosphaadamantane (L16)



General procedure P: The reaction was conducted on a 2.00 mmol scale and employed 1-bromo-4-nitrobenzene. The reaction time was 40 hours. FCC (gradient elution: 29:1 – 19:1 hexane:acetone) afforded **L16** (257 mg, 38 %) as a pale-yellow crystalline solid. m.p. 168-170 °C (CH_2Cl_2:petrol, *plates*). ν_{max} / cm^{-1}: (*solid*) 3099 (m), 2969 (m), 1593 (s), 1517 (s), 1344 (s). δ_H (400 MHz, $CDCl_3$) 8.22 – 8.17 (2H, m), 8.06 – 7.99 (2H, m), 2.05 (1H, dd, *J* = 13.5, 7.5 Hz), 1.96 (1H, dd, *J* = 24.5, 13.5 Hz), 1.59 (1H, d, *J* = 13.5 Hz), 1.53 (3H, d, *J* = 13.0 Hz), 1.51 (1H, dd, *J* = 13.5,

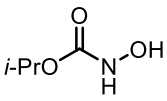
4.0 Hz), 2 × 1.42 (2 × 3H, s), 1.28 (3H, d, *J* = 13.0 Hz). δ_C (101 MHz, $CDCl_3$) 148.6, 143.7 (d, *J* = 34.0 Hz), 135.9 (d, *J* = 19.5 Hz), 123.1 (d, *J* = 7.0 Hz), 97.0, 96.3, 73.5 (d, *J* = 8.5 Hz), 73.4 (d, *J* = 22.0 Hz), 45.1 (d, *J* = 17.5 Hz), 36.6 (d, *J* = 2.0 Hz), 28.1, 27.8, 27.6 (d, *J* = 21.5 Hz), 27.0 (d, *J* = 11.0 Hz). δ_P (162 MHz, $CDCl_3$) -24.8. HRMS: (ESI^+) Calculated for $C_{16}H_{21}NO_5P$: 338.1152. Found $[M+H]^+$: 338.1154. *The spectroscopic properties were consistent with the data available in the literature.*[258]

1,3,5,7-Tetramethyl-2,4,6-trioxa-8-phosphaadamantan-8-yl)benzenesulfonamide (L17)



General procedure P: The reaction was conducted on a 2.00 mmol scale and employed 4-bromobenzenesulfonamide. The reaction time was 21 hours. FCC (*two times:* first, gradient elution: 7:3 – 6:4 – 0:1 hexane:EtOAc; second eluent: 2:1 PhMe:EtOAc) afforded **L17** (302 mg, 41 %) as a pale-yellow crystalline solid. m.p. 225-226 °C (acetone:petrol, *cubes*). ν_{max} / cm^{-1}: (*solid*) 3366 (br s), 3251 (br s), 2966 (m), 1557 (m), 1349 (s), 1167 (s). δ_H (400 MHz, CD_3CN) 8.02 – 7.97 (2H, m, 2 × ArC<u>H</u>), 7.88 – 7.84 (2H, m, 2 × ArC<u>H</u>), 5.73 (2H, br s, N<u>H</u>$_2$), 2.03 (1H, dd, *J* = 13.5, 7.0 Hz, C**3**-<u>H</u>), 1.89 (1H, dd, *J* = 25.0, 13.5 Hz, C**3**-<u>H</u>'), 1.64 (1H, d, *J* = 13.5 Hz, C**3'**-<u>H</u>), 1.47 (3H, d, *J* = 13.0 Hz, C**1**-<u>H</u>$_3$), 1.45 (1H, dd, *J* = 13.5, 4.0 Hz, C**3'**-<u>H</u>'), 1.35 (3H, s, C**5'**-<u>H</u>$_3$), 1.33 (3H, s, C**5**-<u>H</u>$_3$), 1.20 (3H, d, *J* = 13.0 Hz, C**1'**-<u>H</u>$_3$) δ_C (126 MHz, $CDCl_3$) 145.0 (Ar<u>C</u>), 140.7 (d, *J* = 31.5 Hz, Ar<u>C</u>), 136.4 (d, *J* = 20.0 Hz, Ar<u>C</u>H), 126.6 (d, *J* = 7.0 Hz, Ar<u>C</u>H), 97.7 (C**4**), 97.0 (C**4'**), 74.0 (d, *J* = 22.0 Hz, C**2**), 73.9 (d, *J* = 8.0 Hz, C**2'**), 45.8 (d, *J* = 17.5 Hz, C**3**), 36.9 (d, *J* = 2.0 Hz, C**3'**), 28.1 (C**5'**), 28.0 (C**5**), 27.8 (d, *J* = 22.0 Hz, C**1'**), 27.0 (d, *J* = 11.5 Hz, C**1**). δ_P (162 MHz, $CDCl_3$) -25.0. HRMS: (ESI^+) Calculated for $C_{16}H_{22}NNaO_5PS$: 394.0849. Found $[M+Na]^+$: 394.0856.

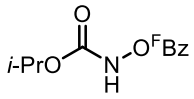
Isopropyl *N*-hydroxycarbamate



To a suspension of $NH_2OH{\cdot}HCl$ (5.00 g, 72.0 mmol) and K_2CO_3 (8.29 g, 60.0 mmol) in THF (120 mL) at 0 °C was added a solution of isopropyl chloroformate (1.0 M in PhMe, 60.0 mL, 60.0 mmol) dropwise over around 30 minutes. The reaction mixture was stirred at room temperature for 48 hours before being filtered; the filtrate was then concentrated *in vacuo*. FCC (eluent: 1:1 hexane:EtOAc) afforded the title compound (2.18 g, 31 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*film*)

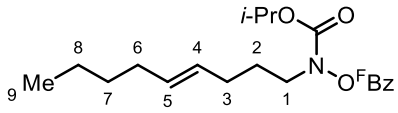
3290 (br s), 2984 (m), 2934 (m), 1704 (s), 1267 (s), 1103 (s). δ_H (400 MHz, $CDCl_3$) 7.28 – 7.11 (2H, m, NH and OH), 4.99 (1H, hept, *J* = 6.5 Hz, OCH(CH_3)$_2$), 1.26 (6H, d, *J* = 6.5 Hz, OCH(CH_3)$_2$). δ_C (101 MHz, $CDCl_3$) 159.4 (C=O), 70.5 (OCH(CH_3)$_2$), 22.1 (OCH(CH_3)$_2$). HRMS: (ESI$^+$) Calculated for $C_4H_9NNaO_3$: 142.0475. Found [M+Na]$^+$: 142.0478.

Isopropyl ((pentafluorobenzoyl)oxy)carbamate



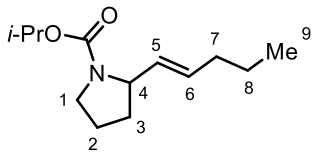
General procedure G: The preceding compound (2.00 g, 16.8 mmol) was employed. The reaction time was 18 hours. FCC (eluent: 9:1 hexane:EtOAc) afforded *i*-PrO(CO)NHO^{F}Bz (3.86 g, 73 %) as a colourless crystalline solid. m.p. 54-55 °C (CH_2Cl_2:petrol, *columnar*). ν_{max} / cm^{-1}: (*solid*) 3230 (br s), 2988 (m), 1776 (s), 1717 (s), 1654 (m), 1489 (s), 1191 (s). δ_H (400 MHz, $CDCl_3$) 8.22 (1H, s, NH), 5.05 (1H, hept, *J* = 6.5 Hz, OCH(CH_3)$_2$), 1.30 (6H, d, *J* = 6.5 Hz, OCH(CH_3)$_2$). δ_C (101 MHz, $CDCl_3$) 155.5 (*i*-PrO–C=O), 71.9 (OCH(CH_3)$_2$), 21.7 (OCH(CH_3)$_2$). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.3 – -135.5 (2F, m), -145.3 (1F, tt, *J* = 21.0, 6.0 Hz), -159.1 – -159.2 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{11}H_8F_5NNaO_4$: 336.0266. Found [M+Na]$^+$: 336.0281.

Isopropyl (*E*)-non-4-en-1-yl((pentafluorobenzoyl)oxy)carbamate (246b)



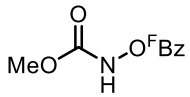
General procedure O: (*E*)-Non-4-en-1-ol (*vide supra*, 284 mg, 2.00 mmol) was employed with *i*-PrO(CO)NHO^{F}Bz (*vide supra*). The reaction time was 15 hours. FCC (gradient elution: 2:3 – 1:4 hexane:PhMe) afforded **246b** (550 mg, 63 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2931 (m), 1786 (s), 1724 (s), 1652 (m), 1505 (s), 1326 (s), 1172 (s). δ_H (400 MHz, $CDCl_3$) 5.49 – 5.32 (2H, m, C**4**-H and C**5**-H), 5.01 (1H, hept, *J* = 6.5 Hz, OCH(CH_3)$_2$), 3.73 – 3.67 (2H, m, C**1**-H$_2$), 2.11 – 2.03 (2H, m, C**3**-H$_2$), 2.02 – 1.94 (2H, m, C**6**-H$_2$), 1.70 (2H, tt, *J* = 7.5, 7.5 Hz, C**2**-H$_2$), 1.34 – 1.28 (4H, m, C**7**-H$_2$ and C**8**-H$_2$), 1.28 (6H, d, *J* = 6.5 Hz, OCH(CH_3)$_2$), 0.90 – 0.86 (3H, m, C**9**-H$_3$). δ_C (101 MHz, $CDCl_3$) 157.4 (^{F}Bz C=O), 155.4 (*i*-PrO–C=O), 132.0 (C**5**), 128.5 (C**4**), 71.4 (OCH(CH_3)$_2$), 50.6 (C**1**), 32.4 (C**6**), 31.8 (C**7**), 29.5 (C**3**), 26.9 (C**2**), 22.3 (C**8**), 22.0 (OCH(CH_3)$_2$), 14.1 (C**9**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.3 – -136.7 (2F, m), -146.5 (1F, tt, *J* = 21.0, 5.0 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{20}H_{24}F_5NNaO_4$: 460.1518. Found [M+Na]$^+$: 460.1512.

Isopropyl (*E*)-2-(pent-1-en-1-yl)pyrrolidine-1-carboxylate (247b)



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **246b** (45.9 mg, 0.105 mmol) was employed. FCC (gradient elution: 29:1 – 19:1 PhMe:EtOAc) afforded **247b** (18.5 mg, 78 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2959 (m), 2928 (m), 1697 (s), 1403 (s), 1113 (s). δ_H (500 MHz, $CDCl_3$) 5.59 – 5.42 (1H, m, C**6**-H), 5.41 – 5.26 (1H, m, C**5**-H), 4.92 (1H, hept, *J* = 6.5 Hz, OCH$(CH_3)_2$), 4.42 – 4.20 (1H, m, C**4**-H), 3.53 – 3.29 (2H, m, C**1**-H_2), 2.04 – 1.96 (3H, m, C**3**-H and C**7**-H_2), 1.92 – 1.79 (2H, m, C**2**-H_2), 1.73 – 1.67 (1H, m, C**3**-H'), 1.39 (2H, tq, *J* = 7.5, 7.5 Hz, C**8**-H_2), 1.27 – 1.18 (6H, m, OCH(CH_3)$_2$), 0.90 (3H, t, *J* = 7.5 Hz, C**9**-H_3). δ_C (126 MHz, $CDCl_3$) 155.0 (C=O), 2 × 130.4 (C**5** and C**6**), 67.8 (OCH$(CH_3)_2$), 58.5 (C**4**), 46.2 (C**1**), 34.2 (C**7**), 32.4 (C**3**), 22.9 (C**2**), 2 × 22.4 (C**8** and OCH(CH_3)(CH_3)'), 22.3 (OCH(CH_3)(CH_3)'), 13.6 (C**9**). HRMS: (ESI^+) Calculated for $C_{13}H_{23}NNaO_2$: 248.1621. Found $[M+Na]^+$: 248.1626.

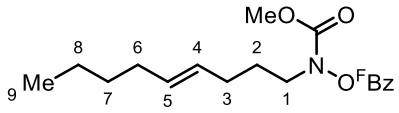
Methyl ((pentafluorobenzoyl)oxy)carbamate



To a solution of methyl *N*-hydroxycarbamate[XLVI] (4.55 g, 50.0 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added ^{F}BzCl (6.90 mL, 50.0 mmol) followed by Et_3N (7.00 mL, 50.0 mmol). The reaction mixture was stirred at room temperature for 5 hours before addition of water (100 mmol). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (70 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 4:1 hexane:EtOAc) afforded MeO(CO)NHO^{F}Bz (12.2 g, 86 %) as a colourless crystalline solid. m.p. 46-47 °C (CH_2Cl_2:petrol, *prisms*). ν_{max} / cm^{-1}: (*solid*) 3220 (br s), 2971 (m), 1794 (s), 1737 (s), 1654 (m), 1503 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 8.34 (1H, s, NH), 3.87 (3H, s, OCH_3). δ_C (101 MHz, $CDCl_3$) 156.5 (MeO–C=O), 54.1 (OCH_3). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.2 – -135.4 (2F, m), -145.2 (1F, tt, *J* = 21.0, 6.0 Hz), -159.2 – -159.4 (1F, m). HRMS: (ESI^+) Calculated for $C_9H_4F_5NNaO_4$: 307.9953. Found $[M+Na]^+$: 307.9964.

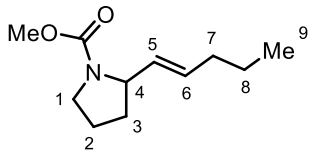
[XLVI] Methyl *N*-hydroxycarbamate was prepared by Rafaela Carmona (University of Bristol) according to a reported procedure.[108]

Methyl (*E*)-non-4-en-1-yl((pentafluorobenzoyl)oxy)carbamate (246c)



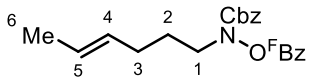
General procedure O: (*E*)-Non-4-en-1-ol (*vide supra*, 284 mg, 2.00 mmol) was employed with MeO(CO)NHO^{F}Bz (*vide supra*). The reaction time was 15 hours. FCC (*two times*, first eluent: 1:4 hexane:PhMe; second eluent: 24:1 hexane:EtOAc) afforded **246c** (413 mg, 50 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2930 (m), 1786 (s), 1730 (s), 1652 (m), 1498 (s), 1326 (s), 1172 (s). δ_H (400 MHz, $CDCl_3$) 5.48 – 5.31 (2H, m, C**4**-H and C**5**-H), 3.81 (3H, s, OCH_3), 3.74 – 3.69 (2H, m, C**1**-H_2), 2.07 (2H, dt, *J* = 7.0, 7.0 Hz, C**3**-H_2), 2.01 – 1.94 (2H, m, C**6**-H_2), 1.71 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2), 1.35 – 1.26 (4H, m, C**7**-H_2 and C**8**-H_2), 0.91 – 0.85 (3H, m, C**9**-H_3). δ_C (101 MHz, $CDCl_3$) 157.4 (^{F}Bz C=O), 156.2 (MeO–C=O), 132.0 (C**5**), 128.5 (C**4**), 54.0 (OCH_3), 50.9 (C**1**), 32.4 (C**6**), 31.8 (C**7**), 29.5 (C**3**), 26.8 (C**2**), 22.3 (C**8**), 14.1 (C**9**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.1 (2F, m), -146.1 (1F, tt, *J* = 20.5, 5.0 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{18}H_{20}F_5NNaO_4$: 432.1205. Found $[M+Na]^+$: 432.1209.

Methyl (*E*)-2-(pent-1-en-1-yl)pyrrolidine-1-carboxylate (247c)



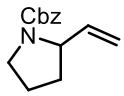
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **246c** (43.0 mg, 0.105 mmol) was employed. FCC (eluent: 19:1 PhMe:EtOAc) afforded **247c** (14.6 mg, 70 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2956 (m), 2873 (m), 1699 (s), 1447 (s), 1381 (s). *The ^{1}H and ^{13}C NMR spectra were acquired at high temperature:* δ_H (500 MHz, CD_3CN, 65 °C) 5.57 – 5.48 (1H, m, C**6**-H), 5.43 (1H, ddt, *J* = 15.0, 6.0, 1.0 Hz, C**5**-H), 4.33 – 4.26 (1H, m, C**4**-H), 3.64 (3H, s, OCH_3), 3.42 – 3.37 (2H, m, C**1**-H_2), 2.08 – 1.99 (3H, m, C**3**-H and C**7**-H_2), 1.95 – 1.80 (2H, m, C**2**-H_2), 1.71 (1H, dddd, *J* = 12.0, 6.5, 4.0, 3.0 Hz, C**3**-H'), 1.43 (2H, tq, *J* = 7.5, 7.5 Hz, C**8**-H_2), 0.93 (3H, t, *J* = 7.5 Hz, C**9**-H_3). δ_C (126 MHz, CD_3CN, 65 °C) 155.1 (C=O), 130.9 (C**5**), 129.9 (C**6**), 58.6 (C**4**), 51.2 (OCH_3), 46.2 (C**1**), 33.8 (C**7**), 31.8 (C**3**), 22.9 (C**2**), 22.2 (C**8**), 12.7 (C**9**). HRMS: (ESI$^+$) Calculated for $C_{11}H_{19}NNaO_2$: 220.1308. Found $[M+Na]^+$: 220.1303.

Benzyl (*E*)-hex-4-en-1-yl((pentafluorobenzoyl)oxy)carbamate (243a)



General procedure O: (*E*)-Hex-4-en-1-ol (**87**) (0.33 mL, 2.80 mmol) was employed with CbzNHO^{F}Bz.[XLVII] The reaction time was 16 hours. FCC (eluent: 2:3 hexane:PhMe) afforded **243a** (734 mg, 59 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2940 (m), 1786 (s), 1730 (s), 1653 (m), 1500 (s), 1175 (s). δ_H (400 MHz, $CDCl_3$) 7.39 – 7.30 (5H, m, 5 × ArC<u>H</u>), 5.50 – 5.33 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 5.22 (2H, s, OC<u>H</u>$_2$Ph), 3.75 (2H, t, *J* = 7.0 Hz, C**1**-<u>H</u>$_2$), 2.06 (2H, td, *J* = 7.5, 6.5 Hz, C**3**-<u>H</u>$_2$), 1.71 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H</u>$_2$), 1.63 (3H, dq, *J* = 6.0, 1.0 Hz, C**6**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 155.5 (Cbz <u>C</u>=O), 135.4 (Ar<u>C</u>), 129.7 (C**4**), 128.7 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 126.3 (C**5**), 68.9 (O<u>C</u>H$_2$Ph), 50.8 (C**1**), 29.4 (C**3**), 26.8 (C**2**), 18.0 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -136.1 (2F, m), -145.9 – -146.1 (1F, m), -159.2 – -159.4 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{21}H_{18}F_5NNaO_4$: 466.1048. Found $[M+Na]^+$: 466.1050.

Benzyl 2-vinylpyrrolidine-1-carboxylate (244a)



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **243a** (46.6 mg, 0.105 mmol) was employed. FCC (eluent: 29:1 PhMe:EtOAc) afforded **244a** (18.9 mg, 78 %) as a colourless oil. δ_H (500 MHz, $CDCl_3$) 7.41 – 7.27 (5H, m), 5.83 – 5.70 (1H, m), 5.19 – 4.98 (4H, m), 4.46 – 4.35 (1H, m), 3.53 – 3.39 (2H, m), 2.08 – 1.96 (1H, m), 1.94 – 1.79 (2H, m), 1.78 – 1.67 (1H, m). *This compound exists as an approximately 1:1 mixture of rotamers; this results in the doubling up of several signals in the ^{13}C spectrum.* δ_C (126 MHz, $CDCl_3$) 155.1 and 154.8, 138.5 and 138.0, 137.1, 128.4 and 128.3, 127.8, 127.7, 114.3 and 114.1, 66.6, 59.5 and 59.0, 46.7 and 46.4, 32.0 and 31.2, 23.5 and 22.6. *The spectroscopic properties were consistent with the data available in the literature.*[163]

(9*H*-Fluoren-9-yl)methyl hydroxycarbamate

FmocNHOH

This compound was prepared according to a literature procedure.[259] To a solution of $NH_2OH{\cdot}HCl$ (2.08 g, 30.0 mmol) and $NaHCO_3$ (5.54 g, 66.0 mmol) in water (100 mL) at 0 °C was added a solution

[XLVII] CbzNHO^{F}Bz was prepared by Dr Xiaofeng Ma (University of Bristol) according to a reported procedure.[117]

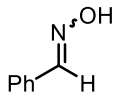
of Fmoc *N*-hydroxysuccinimide ester (10.1 g, 30.0 mmol) in EtOAc (100 mL) dropwise. The reaction mixture was stirred at room temperature for 5 hours before the phases were separated. The organic phase was washed with saturated aqueous $NaHSO_4$ (50 mL), brine (50 mL) and concentrated *in vacuo*. FCC (gradient elution: 3:2 – 1:1 – 2:3 – 0:1 hexane:EtOAc) afforded the title compound (5.92 g, 77 %) as a colourless crystalline solid. m.p. 167-168 °C (acetone:petrol, *fibres*) [Lit., 164.5-167.5 °C (hexane)].[260] δ_H (400 MHz, DMSO-*d*6) 9.76 (1H, s), 8.78 (1H, s), 7.89 (1H, d, *J* = 7.5 Hz), 7.69 (2H, br d, *J* = 7.5 Hz), 7.42 (1H, dd, *J* = 7.5, 7.5 Hz), 7.33 (2H, ddd, *J* = 7.5, 7.5, 1.0 Hz), 4.33 (2H, d, *J* = 7.5 Hz), 4.23 (1H, t, *J* = 7.5 Hz). δ_C (101 MHz, DMSO-*d*6) 157.6, 143.7, 140.7, 127.7, 127.1, 125.2, 120.1, 65.6, 46.6. *The spectroscopic properties were consistent with the data available in the literature.*[261]

(9*H*-Fluoren-9-yl)methyl ((pentafluorobenzoyl)oxy)carbamate

$FmocNHO^FBz$

General procedure G: The preceding compound (5.87 g, 23.0 mmol) was employed. The reaction time was 20 hours. FCC (gradient elution: 4:1 – 3:1 – 0:1 hexane:EtOAc) afforded impure material which was recrystallised from EtOAc:hexane to afford the title compound (2.58 g, 25 %) as a colourless crystalline solid. m.p. 179-180 °C (*fibres*). ν_{max} / cm^{-1}: (*solid*) 3190 (br m), 2949 (m), 1783 (s), 1728 (s), 1655 (m), 1500 (s), 1180 (s). δ_H (400 MHz, $CDCl_3$) 8.27 (1H, br s, NH), 7.75 (2H, dd, *J* = 7.5, 1.0 Hz, 2 × ArCH), 7.61 – 7.55 (2H, m, 2 × ArCH), 7.43 – 7.37 (2H, m, 2 × ArCH), 7.32 (2H, ddd, *J* = 7.5, 7.5, 1.0 Hz, 2 × ArCH), 4.60 (2H, d, *J* = 6.5 Hz, OCH_2CHR_2), 4.28 (1H, t, *J* = 6.5 Hz, OCH_2CHR_2). δ_C (101 MHz, $CDCl_3$) 155.8 (Fmoc C=O), 143.1 (ArC), 141.5 (ArC), 128.1 (ArCH), 127.4 (ArCH), 125.1 (ArCH), 120.2 (ArCH), 68.9 (OCH_2CHR_2), 46.9 (OCH_2CHR_2). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -134.6 – -134.8 (2F, m), -144.7 (1F, tt, *J* = 21.0, 6.0 Hz), -158.9 – -159.1 (2F, m). HRMS: (ESI^+) Calculated for $C_{22}H_{12}F_5NNaO_4$: 472.0579. Found $[M+Na]^+$: 472.0597.

Benzaldehyde oxime



A solution of benzaldehyde (20.0 g, 188 mmol), NaOAc (23.0 g, 280 mmol) and $NH_2OH{\cdot}HCl$ (19.5 g, 280 mmol) in MeOH (300 mL) was heated at reflux for 2 hours. The reaction mixture was cooled to room temperature, diluted with brine (400 mL) and extracted with EtOAc (2 × 500 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (22.6 g, 99 %) as a colourless crystalline solid. δ_H (400 MHz, $CDCl_3$) 8.65 – 8.22 (1H, br s), 8.17 (1H, s), 7.62

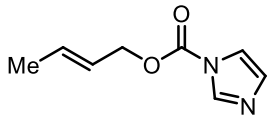
– 7.54 (2H, m), 7.42 – 7.36 (3H, m). δ_C (126 MHz, $CDCl_3$) 150.5, 132.0, 130.20, 128.9, 127.2. *The spectroscopic properties were consistent with the data available in the literature*.[262]

_N_-Benzylhydroxylamine

BnNHOH

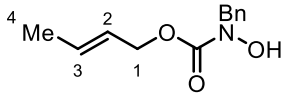
To a suspension of the preceding oxime (5.00 g, 41.3 mmol), $NaBH_3CN$ (5.71 g, 90.9 mmol) and a small amount of methyl orange in MeOH (40 mL) was added a pre-mixed solution of MeOH:AcCl (3:1) dropwise at such a rate as to keep the solution pink. After 1 hour the reaction mixture was concentrated *in vacuo*. The crude product was dissolved in water (200 mL), made basic with NaOH and extracted with CH_2Cl_2 (6 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford BnNHOH (3.50 g, 69 %) as a colourless crystalline solid. δ_H (400 MHz, $CDCl_3$) 7.41 – 7.23 (5H, m), 6.63 – 5.04 (2H, br s), 4.00 (2H, s). δ_C (101 MHz, CD_3CN) 139.7, 129.8, 129.2, 128.0, 58.6. HRMS: (ESI^+) Calculated for $C_7H_{10}NO$: 124.0757. Found $[M+H]^+$: 124.0761. *The spectroscopic properties were consistent with the data available in the literature*.[263]

(*E*)-But-2-en-1-yl 1*H*-imidazole-1-carboxylate



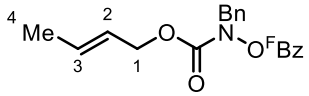
This compound was prepared according to a literature procedure.[264] To a solution of carbonyl diimidazole (4.86 g, 30.0 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C was added (*E*)-but-2-en-1-ol (1.71 mL, 20.0 mmol) dropwise. The reaction mixture was stirred at room temperature for 19 hours before being washed with water (2 × 40 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (1.77 g, 53 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2945 (m), 1755 (s), 1472 (m), 1396 (s), 1236 (s). δ_H (400 MHz, $CDCl_3$) 8.13 (1H, dd, *J* = 1.0, 1.0 Hz), 7.42 (1H, dd, *J* = 1.5, 1.0 Hz), 7.06 (1H, dd, *J* = 1.5, 1.0 Hz), 5.95 (1H, dqt, *J* = 15.5, 6.5, 1.0 Hz), 5.73 – 5.64 (1H, m), 4.82 (2H, br d, *J* = 7.0 Hz), 1.77 (3H, ddt, *J* = 6.5, 2.0, 1.0 Hz). δ_C (101 MHz, $CDCl_3$) 148.7, 137.3, 134.3, 130.7, 123.6, 117.3, 69.0, 18.0. *The spectroscopic properties were consistent with the data available in the literature.*[264]

(*E*)-But-2-en-1-yl benzyl(hydroxy)carbamate



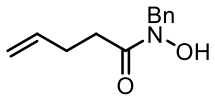
To a solution of the preceding compound (332 mg, 2.00 mmol) and BnNHOH (*vide supra*, 369 mg, 3.00 mmol) in anhydrous CH_2Cl_2 (10 mL) was added Et_3N (0.42 mL, 3.00 mmol). The reaction mixture was stirred at room temperature for 8 hours before being diluted with CH_2Cl_2 (10 mL), then washed with 1.0 M aqueous HCl (15 mL) followed by brine (15 mL). The organic phase was concentrated *in vacuo*. FCC (gradient elution: 5:1 – 3:1 hexane:EtOAc) afforded the title compound (112 mg, 25 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3287 (br s), 3032 (m), 2919 (m), 1699 (s), 1453 (s), 1237 (s), 1101 (s). δ_H (400 MHz, $CDCl_3$) 7.38 – 7.27 (5H, m, 5 × ArC<u>H</u>), 6.33 – 6.11 (1H, br s, O<u>H</u>), 5.87 – 5.76 (1H, m, C**3**-<u>H</u>), 5.67 – 5.55 (1H, m, C**2**-<u>H</u>), 4.70 (2H, s, NC<u>H</u>$_2$Ph), 4.60 (2H, d, *J* = 6.5 Hz, C**1**-<u>H</u>$_2$), 1.73 (3H, d, *J* = 6.5 Hz, C**4**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 157.4 (<u>C</u>=O), 136.1 (Ar<u>C</u>), 132.0 (C**3**), 128.7 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 125.2 (C**2**), 67.4 (C**1**), 54.3 (N<u>C</u>H$_2$Ph), 17.9 (C**4**). HRMS: (ESI^+) Calculated for $C_{12}H_{15}NNaO_3$: 244.0944. Found $[M+Na]^+$: 244.0943.

(*E*)-But-2-en-1-yl benzyl((pentafluorobenzoyl)oxy)carbamate (249)



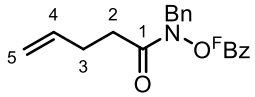
<u>General procedure C:</u> The preceding compound (107 mg, 0.484 mmol) was employed. FCC (eluent: 14:1 hexane:EtOAc) afforded **249** (139 mg, 69 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2945 (m), 1789 (s), 1725 (s), 1655 (m), 1504 (s), 1324 (s), 1172 (s). δ_H (400 MHz, $CDCl_3$) 7.38 – 7.28 (5H, m, 5 × ArC<u>H</u>), 5.82 (1H, dqt, *J* = 15.5, 6.5, 1.5 Hz, C**3**-<u>H</u>), 5.59 (1H, dtq, *J* = 15.5, 6.5, 1.5 Hz, C**2**-<u>H</u>), 4.89 (2H, s, NC<u>H</u>$_2$Ph), 4.66 (2H, br d, *J* = 6.5 Hz, C**1**-<u>H</u>$_2$), 1.73 (3H, ddt, *J* = 6.5, 1.5, 1.5 Hz, C**4**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 155.6 (Carbamate <u>C</u>=O), 134.6 (Ar<u>C</u>), 132.5 (C**3**), 2 × 128.7 (2 × Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 124.5 (C**2**), 68.2 (C**1**), 55.1 (N<u>C</u>H$_2$Ph), 17.9 (C**4**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity*. δ_F (377 MHz, $CDCl_3$) -135.9 – -136.1 (2F, m), -146.3 (1F, tt, *J* = 21.0, 5.0 Hz), -159.3 – -159.5 (2F, m). HRMS: (ESI^+) Calculated for $C_{19}H_{14}F_5NNaO_4$: 438.0735. Found $[M+Na]^+$: 438.0739.

***N*-Benzyl-*N*-hydroxypent-4-enamide**



A solution of pent-4-enoic acid (0.35 mL, 3.40 mmol) and carbonyl diimidazole (827 mg, 5.10 mmol) in anhydrous MeCN (20 mL) was stirred at room temperature for 6 hours before addition of BnNHOH (*vide supra*, 628 mg, 5.10 mmol). The reaction mixture was stirred for a further 16 hours before being concentrated *in vacuo*, dissolved in Et_2O (50 mL) and washed with 4.0 M aqueous NaOH (2 × 50 mL) and water (50 mL). The combined organic phases were dried and concentrated *in vacuo* to afford the title compound (650 mg, 93 %) as a colourless oil, which was used without further purification. δ_H (500 MHz, $CDCl_3$) 8.98 – 8.27 (1H, br s), 7.38 – 7.21 (5H, m), 5.88 – 5.72 (1H, m), 5.04 (1H, d, *J* = 17.5 Hz), 4.99 (1H, br d, *J* = 9.5 Hz), 4.85 – 4.73 (2H, m), 2.64 – 2.30 (4H, m). HRMS: (ESI^+) Calculated for $C_{12}H_{15}NNaO_2$: 228.0995. Found $[M+Na]^+$: 228.0993. *The spectroscopic properties were consistent with the data available in the literature.*[265]

***N*-Benzyl-*N*-((pentafluorobenzoyl)oxy)pent-4-enamide (251)**



General procedure C: The preceding compound (300 mg, 1.47 mmol) was employed. FCC (*two times*, first eluent: 29:1 PhMe:EtOAc; second eluent: 19:1 hexane:EtOAc) afforded **251** (360 mg, 61 %) as a colourless crystalline solid. *This compound exists as an approximately 4:1 mixture of rotamers A and B.* m.p. 31-32 °C (CH_2Cl_2:petrol, *fibres*). ν_{max} / cm^{-1}: (*solid*) 3070 (m), 2927 (m), 1797 (s), 1673 (s), 1500 (s). δ_H (500 MHz, $CDCl_3$) 7.41 – 7.18 (5H, m, A and B: 5 × ArC<u>H</u>), 5.83 – 5.65 (0.2H, m, B: C**4**-<u>H</u>), 5.57 – 5.42 (0.8H, m, A: C**4**-<u>H</u>), 5.13 – 4.84 (3.6H, m, A: C**5**-<u>H_2</u> and NC<u>H_2</u>Ph; B: C**5**-<u>H_2</u>), 4.74 (0.4H, br s, B: NC<u>H_2</u>Ph), 2.54 (0.4H, br s, B: C**2**-<u>H_2</u>), 2.40 (0.4H, br s, B: C**3**-<u>H_2</u>), 2.24 – 2.18 (1.6H, m, A: C**2**-<u>H_2</u>), 2.17 – 2.10 (1.6H, m, A: C**3**-<u>H_2</u>). δ_C (126 MHz, $CDCl_3$) 170.1 (A and B: C**1**), 158.6 (A and B: ^{F}Bz <u>C</u>=O), 143.6 (d, *J* = 254.0 Hz, A and B: Ar<u>C</u>F), 142.5 (d, *J* = 262.5 Hz, A and B: Ar<u>C</u>F), 137.6 (d, *J* = 251.5 Hz, A and B: Ar<u>C</u>F), 134.9 (A and B: C**4**), 133.7 (A and B: Ar<u>C</u>), 128.9 (A and B: Ar<u>C</u>H), 2 × 128.6 (A and B: 2 × Ar<u>C</u>H), 116.4 (A and B: C**5**), 109.6 (A and B: Ar<u>C</u>), 55.5 (B: N<u>C</u>H_2Ph), 51.9 (A: N<u>C</u>H_2Ph), 30.7 (A and B: C**2**), 28.0 (A and B: C**3**). δ_F (377 MHz, $CDCl_3$) -138.4 (0.4F, br s), -138.8 – -139.2 (1.6F, m), -149.4 (0.2F, br s), -150.6 (0.8F, t, *J* = 20.5 Hz), -158.9 (0.4F, br s), -160.0 – -160.4 (1.6F, m). HRMS: (ESI^+) Calculated for $C_{19}H_{15}F_5NO_3$: 400.0967. Found $[M+H]^+$: 400.0972.

N-Hydroxypivalamide

PivNHOH

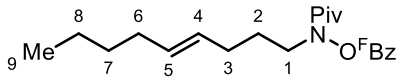
To a suspension of $NH_2OH{\cdot}HCl$ (3.47 g, 50.0 mmol), K_2CO_3 (6.91 g, 50.0 mmol) and PivCl (6.22 mL, 50.5 mmol) in Et_2O (30 mL) was added water (24 mL) dropwise. The reaction mixture was stirred at room temperature for 3 hours before the phases were separated, and the aqueous phase was extracted with EtOAc (30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 3:7 – 0:1 hexane:EtOAc) afforded the title compound (741 mg, 13 %) as a colourless crystalline solid. *This compound decomposed at around 154 °C during melting point analysis.* δ_H (400 MHz, $CDCl_3$) 8.32 (1H, br s), 7.73 (1H, br s), 1.22 (9H, s). δ_C (126 MHz, $CDCl_3$) 176.5, 37.6, 27.0. *The spectroscopic properties were consistent with the data available in the literature.*[266,267]

N-((Pentafluorobenzoyl)oxy)pivalamide

PivNHO^{F}Bz

General procedure G: The preceding compound (682 mg, 5.82 mmol) was employed. The reaction time was 13 hours. FCC (eluent: 4:1 hexane:EtOAc) afforded PivNHO^{F}Bz (1.30 g, 72 %) as a colourless crystalline solid. m.p. 141-142 °C (CH_2Cl_2:petrol, *needles*). ν_{max} / cm^{-1}: (*solid*) 3217 (br s), 2977 (m), 1780 (s), 1669 (s), 1505 (s). δ_H (400 MHz, $CDCl_3$) 9.14 (1H, s, NH), 1.33 (9H, s, C(CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 177.0 (Piv C=O), 39.0 (C(CH_3)$_3$), 27.3 (C(CH_3)$_3$). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -134.9 – -135.0 (2F, m), -145.1 (1F, tt, J = 21.0, 6.0 Hz), -159.1 – -159.3 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{12}H_{10}F_5NNaO_3$: 334.0473. Found $[M+Na]^+$: 334.0491.

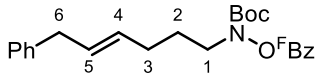
(*E*)-*N*-(Non-4-en-1-yl)-*N*-((pentafluorobenzoyl)oxy)pivalamide (246d)



General procedure O: (*E*)-Non-4-en-1-ol (*vide supra*, 284 mg, 2.00 mmol) was employed with PivNHO^{F}Bz (*vide supra*). The reaction time was 18 hours. FCC (gradient elution: 1:1 – 3:7 hexane:PhMe) afforded **246d** (255 mg, 29 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2961 (m), 2931 (m), 1767 (s), 1616 (m), 1499 (s), 1199 (s). δ_H (400 MHz, $CDCl_3$) 5.48 – 5.29 (2H, m, C**4**-H and C**5**-H), 4.36 (2H, t, J = 6.5 Hz, C**1**-H$_2$), 2.08 (2H, tdd, J = 7.5, 6.0, 1.0 Hz, C**3**-H$_2$), 1.96 (2H, td, J = 6.5, 6.0 Hz, C**6**-H$_2$), 1.72 (2H, tt, J = 7.5, 6.5 Hz, C**2**-H$_2$), 1.33 – 1.26 (4H, m, C**7**-H$_2$ and C**8**-H$_2$), 1.23 (9H, s, C(CH_3)$_3$), 0.90 – 0.85 (3H, m, C**9**-H$_3$). δ_C (101 MHz, $CDCl_3$) 169.2 (Piv C=O), 132.0 (C**5**), 128.4 (C**4**), 73.7 (C**1**), 38.0 (C(CH_3)$_3$), 32.3 (C**6**), 31.8 (C**7**), 30.1 (C**2**), 28.6 (C**3**), 27.6 (C(CH_3)$_3$), 22.3

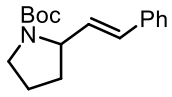
(C**8**), 14.0 (C**9**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -137.5 – -137.7 (2F, m), -148.1 (1F, t, *J* = 20.5 Hz), -159.7 – -159.9 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{21}H_{27}F_5NO_3$: 436.1906. Found $[M+H]^+$: 436.1935.

***tert*-Butyl (*E*)-(6-phenylhex-4-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (254)**



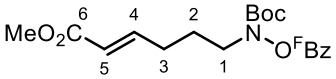
General procedure O: Alcohol **121** (Section 7.3, 824 mg, 4.67 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 16 hours. FCC (eluent: 1:4 hexane:PhMe) afforded **254** (1.18 g, 52 %, 6:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless oil. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*film*) 2938 (m), 1784 (s), 1722 (s), 1653 (m), 1506 (s), 1327 (s), 1154 (s). δ_H (400 MHz, $CDCl_3$) 7.30 – 7.25 (2H, m, 2 × ArC<u>H</u>), 7.21 – 7.15 (3H, m, 3 × ArC<u>H</u>), 5.66 – 5.57 (1H, m, C**5**-<u>H</u>), 5.54 – 5.45 (1H, m, C**4**-<u>H</u>), 3.68 (2H, t, *J* = 7.0 Hz, C**1**-<u>H</u>$_2$), 3.33 (2H, d, *J* = 6.5 Hz, C**6**-<u>H</u>$_2$), 2.12 (2H, dt, *J* = 7.5, 7.5 Hz, C**3**-<u>H</u>$_2$), 1.73 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H</u>$_2$), 1.49 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 154.7 (Boc <u>C</u>=O), 140.9 (Ar<u>C</u>), 130.4 (C**4**), 130.2 (C**5**), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 83.4 (O<u>C</u>(CH$_3$)$_3$), 50.6 (C**1**), 39.1 (C**6**), 29.5 (C**3**), 28.2 (OC(<u>C</u>H$_3$)), 26.8 (C**2**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.4 – -136.7 (2F, m), -146.7 (1F, tt, *J* = 21.0, 5.0 Hz), -159.3 – -159.5 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{24}H_{24}F_5NNaO_4$: 508.1518. Found $[M+Na]^+$: 508.1525. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 3.40 (2H, d, *J* = 7.5 Hz), 2.26 (2H, dt, *J* = 7.0, 7.0 Hz).

***tert*-Butyl (*E*)-2-styrylpyrrolidine-1-carboxylate (255)**



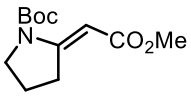
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra)*; 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **254** (51.0 mg, 0.105 mmol) was employed. FCC (gradient elution: 99:1 – 49:1 – 24:1 PhMe:EtOAc) afforded **255** (22.3 mg, 78 %) as a colourless crystalline solid. m.p. 81-88 °C (CH_2Cl_2:petrol, *equant*) [Lit., 96-98 °C (*No recrystallisation solvent quoted*)].[268] δ_H (400 MHz, $CDCl_3$) 7.38 – 7.27 (4H, m), 7.25 – 7.16 (1H, m), 6.40 (1H, br d, *J* = 15.5 Hz), 6.18 – 6.01 (1H, m), 4.61 – 4.30 (1H, m), 3.46 (2H, br s), 2.16 – 2.01 (1H, m), 1.99 – 1.73 (3H, m), 1.43 (9H, s). δ_C (126 MHz, $CDCl_3$) 154.8, 137.2, 130.9, 129.5, 128.6, 127.4, 126.4, 79.3, 59.1, 46.4, 32.7, 28.7, 23.2. *The spectroscopic properties were consistent with the data available in the literature.*[268]

Methyl (*E*)-6-((*tert*-butoxycarbonyl)((pentafluorobenzoyl)oxy)amino)hex-2-enoate (256)



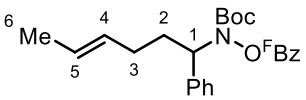
General procedure O: Alcohol **122** (Section 7.3, 214 mg, 1.48 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 16 hours. FCC (eluent: 49:1 PhMe:EtOAc) afforded **256** (381 mg, 57 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2952 (m), 1782 (s), 1721 (s), 1654 (m), 1504 (s), 1151 (s). δ_H (400 MHz, $CDCl_3$) 6.95 (1H, dt, *J* = 15.5, 7.0 Hz, C**4**-H), 5.85 (1H, dt, *J* = 15.5, 1.5 Hz, C**5**-H), 3.73 – 3.68 (5H, m, C**1**-H$_2$ and OCH$_3$), 2.32 (2H, tdd, *J* = 7.5, 7.0, 1.5 Hz, C**3**-H$_2$), 1.80 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H$_2$), 1.49 (9H, s, OC(CH$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 167.0 (C**6**), 154.6 (Boc C=O), 147.8 (C**4**), 121.9 (C**5**), 83.7 (OC(CH$_3$)$_3$), 51.6 (OCH$_3$), 50.2 (C**1**), 29.1 (C**3**), 28.1 (OC(CH$_3$)$_3$), 25.6 (C**2**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.2 – -136.6 (2F, m), -146.2 (1F, tt, *J* = 20.0, 4.5 Hz), -159.0 – -159.4 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{19}H_{20}F_5NNaO_6$: 476.1103. Found [M+Na]$^+$: 476.1114.

***tert*-Butyl (*E*)-2-(2-methoxy-2-oxoethylidene)pyrrolidine-1-carboxylate (257)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **256** (47.6 mg, 0.105 mmol) was employed. FCC (eluent: 9:1 hexane:EtOAc) afforded **257** (24.0 mg, 95 %) as a colourless crystalline solid. δ_H (400 MHz, $CDCl_3$) 6.44 (1H, t, *J* = 2.0 Hz), 3.68 – 3.63 (5H, m), 3.17 (2H, td, *J* = 7.5, 2.0 Hz), 1.87 (2H, tt, *J* = 7.5, 7.5 Hz), 1.51 (9H, s). δ_C (101 MHz, $CDCl_3$) 169.5, 157.8, 152.1, 95.7, 82.2, 50.8, 49.9, 32.1, 28.3, 21.1. *m/z* (ESI$^+$) 264 ([M+Na]$^+$, 100 %), 164 ([M-(*t*-BuO–C=O)+H+Na]$^+$, 22 %). *The spectroscopic properties were consistent with the data available in the literature.*[269]

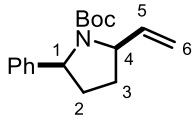
***tert*-Butyl (*E*)-(1-phenylhex-4-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (258a)**



General procedure O: Alcohol **133** (Section 7.3, 176 mg, 1.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*), and the reaction was performed at -78 °C. The reaction time was 18 hours. FCC (eluent: 2:3 hexane:PhMe) afforded impure material which was dissolved in Et_2O (15 mL) and

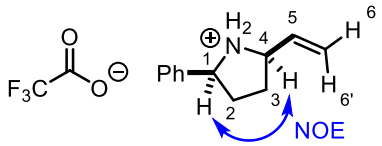
washed with 10 % aqueous AcOH (2 × 10 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 19:1 hexane:EtOAc) afforded **258a** (248 mg, 51 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2981 (m), 1787 (s), 1720 (s), 1652 (m), 1506 (s), 1326 (s), 1158 (s). δ_H (500 MHz, $CDCl_3$) 7.43 – 7.37 (2H, m, 2 × ArC<u>H</u>), 7.37 – 7.29 (3H, m, 3 × ArC<u>H</u>), 5.52 – 5.40 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 5.38 – 5.21 (1H, m, C**1**-<u>H</u>), 2.23 – 2.04 (3H, m, C**2**-<u>H</u> and C**3**-<u>H_2</u>), 1.99 (1H, br s, C**2**-<u>H</u>'), 1.68 (2H, d, *J* = 4.5 Hz, C**6**-<u>H_3</u>), 1.56 – 1.36 (9H, br s, OC($C\underline{H}_3$)$_3$). δ_C (126 MHz, $CDCl_3$) 157.0 (^{F}Bz <u>C</u>=O), 154.4 (Boc <u>C</u>=O), 145.4 (d, *J* = 261.0 Hz, Ar<u>C</u>F), 143.7 (d, *J* = 261.0 Hz, Ar<u>C</u>F), 138.8 (Ar<u>C</u>), 137.8 (d, *J* = 255.0 Hz, Ar<u>C</u>F), 129.7 (C**4**), 128.4 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 126.3 (C**5**), 106.1 (Ar<u>C</u>), 83.5 (O<u>C</u>(CH_3)$_3$), 63.1 (C**1**), 31.5 (C**2**), 29.2 (C**3**), 28.0 (OC(<u>C</u>H_3)$_3$), 17.9 (C**6**). δ_F (377 MHz, $CDCl_3$) -136.0 – -136.7 (2F, m), -147.0 (1F, tt, *J* = 21.0, 5.0 Hz), -159.2 – -159.9 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{24}H_{24}F_5NNaO_4$: 508.1518. Found $[M+Na]^+$: 508.1516.

***tert*-Butyl (2*R**,5*S**)-2-phenyl-5-vinylpyrrolidine-1-carboxylate (260a)**



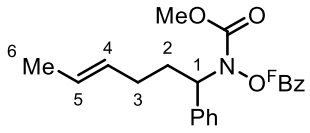
<u>General procedure D:</u> Conditions: 2.5 mol% $Pd_2(dba)_3$; 17.5 mol% ligand **L3** (*vide supra*); 100 mol% Et_3N; dioxane (0.3 M); 130 °C; 24 hours. Substrate **258a** (51.0 mg, 0.105 mmol) was employed. FCC (*two times*, first eluent: 59:1 petrol:acetone; second eluent: 99:1 PhMe:EtOAc) afforded **260a** (16.6 mg, 58 %, 10:1 mixture of *cis* and *trans* diastereomers) as a colourless oil. *It was not possible to determine the relative stereochemistry of **260a** by NOE analysis. The removal of the Boc group was necessary to obtain satisfactory data; details of this are given below. Spectroscopic data for the major cis diastereomer:* ν_{max} / cm^{-1}: (*film*) 2974 (m), 1693 (s), 1380 (s), 1165 (s). δ_H (500 MHz, $CDCl_3$) 7.34 – 7.27 (2H, m, 2 × ArC<u>H</u>), 7.27 – 7.24 (2H, m, 2 × ArC<u>H</u>), 7.23 – 7.18 (1H, m, ArC<u>H</u>), 6.13 – 5.93 (1H, m, C**5**-<u>H</u>), 5.34 – 5.14 (2H, m, C**6**-<u>H_2</u>), 4.93 – 4.70 (1H, m, C**1**-<u>H</u>), 4.55 – 4.34 (1H, m, C**4**-<u>H</u>), 2.26 (1H, dddd, *J* = 12.5, 6.5, 6.0, 6.0 Hz, C**2**-<u>H</u>), 2.06 (1H, dddd, *J* = 12.0, 8.0, 7.5, 6.5 Hz, C**3**-<u>H</u>), 1.88 (1H, dddd, *J* = 12.5, 7.5, 6.5, 6.5 Hz, C**2**-<u>H</u>'), 1.84 – 1.75 (1H, m, C**3**-<u>H</u>'), 1.47 – 1.10 (9H, m, OC($C\underline{H}_3$)$_3$). δ_C (126 MHz, $CDCl_3$) 155.1 (<u>C</u>=O), 144.6 (Ar<u>C</u>), 139.5 (C**5**), 128.3 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 115.3 (C**6**), 79.6 (O<u>C</u>(CH_3)$_3$), 63.1 (C**1**), 61.2 (C**4**), 34.9 (C**2**), 30.7 (C**3**), 28.4 (OC(<u>C</u>H_3)$_3$). HRMS: (ESI$^+$) Calculated for $C_{17}H_{23}NNaO_2$: 296.1621. Found $[M+Na]^+$: 296.1630. *Characteristic signals for the minor trans diastereomer:* δ_H (500 MHz, $CDCl_3$) 5.91 – 5.78 (1H, m), 2.37 (1H, dddd, *J* = 13.5, 11.5, 6.0, 5.5 Hz), 2.18 (1H, dddd, *J* = 13.0, 8.5, 6.0, 6.0 Hz).

(2*R,5*S**)-2-Phenyl-5-vinylpyrrolidin-1-ium trifluoroacetate**



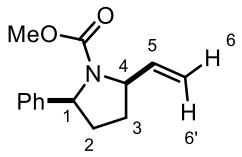
General procedure Q: Pyrrolidine **260a** (15.7 mg, 57.4 μmol) was employed to afford the title compound (15.7 mg, 95 %, 14:1 mixture of *cis* and *trans* diastereomers) as a pale-yellow crystalline solid. *The major product was assigned as the cis diastereomer based on the observed NOE correlation between the C**1** and the C**4** protons. Spectroscopic data for the major cis diastereomer:* ν_{max} / cm^{-1}: (*film*) 2924 (m), 1666 (s), 1432 (s), 1130 (s). δ_H (500 MHz, $CDCl_3$) 10.52 (1H, br s, NH), 8.71 (1H, br s, NH'), 7.37 – 7.27 (5H, m, 5 × ArCH), 5.72 (1H, ddd, *J* = 17.0, 10.5, 8.0 Hz, C**5**-H), 5.19 (1H, d, *J* = 17.0 Hz, C**6**-H'), 4.99 (1H, d, *J* = 10.5 Hz, C**6**-H), 4.57 – 4.48 (1H, m, C**1**-H), 4.10 – 3.99 (1H, m, C**4**-H), 2.45 – 2.24 (3H, m, C**2**-H_2 and C**3**-H), 2.16 – 2.09 (1H, m, C**3**-H'). δ_C (101 MHz, $CDCl_3$) 133.9 (ArC), 131.7 (C**5**), 129.3 (ArCH), 128.9 (ArCH), 127.7 (ArCH), 121.4 (C**6**), 63.1 (C**1**), 62.7 (C**4**), 29.9 (C**2**), 29.2 (C**3**). *The ^{13}C signals corresponding to the trifluoroacetate counterion could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -75.8 (3F, s). HRMS: (ESI^+) Calculated for $C_{12}H_{16}N$: 174.1277. Found $[M–F_3CCO_2]^+$: 174.1280. *Characteristic signals for the minor trans diastereomer:* δ_H (500 MHz, $CDCl_3$) 9.87 (1H, br s), 9.17 (1H, br s), 5.11 (1H, d, *J* = 10.5 Hz), 4.22 – 4.13 (1H, m).

Methyl (*E*)-(1-phenylhex-4-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (258b)



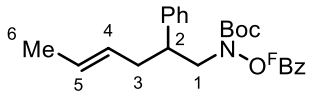
General procedure O: Alcohol **133** (Section 7.3, 438 mg, 2.50 mmol) was employed with MeOC(O)NHO^{F}Bz (*vide supra*). The reaction time was 23 hours. FCC (gradient elution: 2:3 – 1:4 hexane:PhMe) afforded **258b** (278 mg, 25 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3032 (m), 2959 (m), 1787 (s), 1732 (s) 1652 (m), 1497 (s), 1172 (s). δ_H (500 MHz, $CDCl_3$) 7.44 – 7.29 (5H, m, 5 × ArCH), 5.56 – 5.38 (2H, m, C**4**-H and C**5**-H), 5.33 (1H, br s, C**1**-H), 3.80 (3H, s, OCH_3), 2.25 – 1.95 (4H, m, C**2**-H_2 and C**3**-H_2), 1.68 (3H, d, *J* = 4.5 Hz, C**6**-H_3). δ_C (126 MHz, $CDCl_3$) 156.0 (MeO–C=O), 138.4 (ArC), 129.7 (C**4**), 128.7 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 126.6 (C**5**), 63.4 (C**1**), 54.1 (OCH_3), 31.4 (C**2**), 29.3 (C**3**), 18.1 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.6 – -136.5 (2F, m), -146.5 (1F, tt, *J* = 21.0, 5.0 Hz), -159.0 – -159.8 (2F, m). HRMS: (ESI^+) Calculated for $C_{21}H_{18}F_5NNaO_4$: 466.1048. Found $[M+Na]^+$: 466.1049.

Methyl (2*R,5*S**)-2-phenyl-5-vinylpyrrolidine-1-carboxylate (260b)**



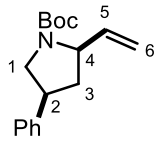
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15.0 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **258b** (46.6 mg, 0.105 mmol) was employed. FCC (*two times*, first eluent: 29:1 PhMe:EtOAc; second eluent: 19:1 petrol:acetone) afforded **260b** (7.7 mg, 32 %) as a colourless oil. *The relative stereochemistry of **260b** was assigned by analogy to **260a**, as it was not possible to determine by NOE analysis.* ν_{max} / cm^{-1}: (*film*) 3029 (m), 2952 (m), 1699 (s), 1445 (s), 1372 (s). δ_H (500 MHz, $CDCl_3$) 7.38 – 7.21 (5H, m, 5 × ArC<u>H</u>), 6.02 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz, C**5**-<u>H</u>), 5.33 (1H, br d, *J* = 17.0 Hz, C**6**-<u>H</u>'), 5.22 (1H, br d, *J* = 10.5 Hz, C**6**-<u>H</u>), 4.96 (1H, dd, *J* = 7.5, 6.0 Hz, C**1**-<u>H</u>), 4.51 (1H, br ddd, *J* = 7.5, 7.0, 6.5 Hz, C**4**-<u>H</u>), 3.62 (3H, br s, OC<u>H</u>$_3$), 2.31 (1H, dddd, *J* = 12.5, 7.5, 7.0, 7.0 Hz, C**2**-<u>H</u>), 2.10 (1H, dddd, *J* = 12.5, 7.0, 7.0, 6.5 Hz, C**3**-<u>H</u>), 1.95 (1H, dddd, *J* = 12.5, 7.0, 6.5, 6.0 Hz, C**2**-<u>H</u>'), 1.88 – 1.79 (1H, m, C**3**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 156.6 (<u>C</u>=O), 143.6 (Ar<u>C</u>), 139.1 (C**5**), 128.4 (Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 115.8 (C**6**), 62.9 (C**1**), 61.6 (C**4**), 52.5 (O<u>C</u>H$_3$), 34.4 (C**2**), 30.5 (C**3**). HRMS: (ESI^+) Calculated for $C_{14}H_{18}NO_2$: 232.1332. Found $[M+H]^+$: 232.1334.

***tert*-Butyl (*E*)-(2-phenylhex-4-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (261)**



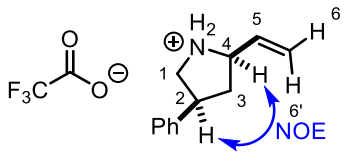
General procedure O: Alcohol **142** (Section 7.3, 441 mg, 2.50 mmol) was employed with $BocNHO^FBz$ (*vide supra*). The reaction time was 15 hours. FCC (*two times*, first eluent: 2:3 hexane:PhMe; second eluent: 29:1 hexane:EtOAc) afforded **261** (353 mg, 29 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3026 (m), 2981 (m), 1783 (s), 1721 (s), 1652 (m), 1497 (s), 1153 (s). δ_H (400 MHz, $CDCl_3$) 7.30 – 7.24 (2H, m, 2 × ArC<u>H</u>), 7.22 – 7.13 (3H, m, 3 × ArC<u>H</u>), 5.49 – 5.38 (1H, m, C**5**-<u>H</u>), 5.32 – 5.22 (1H, m, C**4**-<u>H</u>), 3.97 (1H, dd, *J* = 15.0, 7.0 Hz, C**1**-<u>H</u>), 3.84 (1H, dd, *J* = 15.0, 8.0 Hz, C**1**-<u>H</u>'), 3.00 (1H, dtd, *J* = 8.0, 7.5, 7.0 Hz, C**2**-<u>H</u>), 2.50 – 2.31 (2H, m, C**3**-<u>H</u>$_2$), 1.57 (3H, dd, *J* = 6.5, 1.5 Hz, C**6**-<u>H</u>$_3$), 1.39 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 157.1 (^{F}Bz <u>C</u>=O), 154.0 (Boc <u>C</u>=O), 141.9 (Ar<u>C</u>), 128.3 (Ar<u>C</u>H), 2 × 128.0 (C**4** and Ar<u>C</u>H), 127.4 (C**5**), 126.5 (Ar<u>C</u>H), 83.1 (O<u>C</u>(CH$_3$)$_3$), 55.6 (C**1**), 44.1 (C**2**), 36.5 (C**3**), 27.9 (OC(<u>C</u>H$_3$)$_3$), 17.9 (C**6**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.0 – -136.4 (2F, m), -146.6 (1F, tt, *J* = 21.0, 5.0 Hz), -159.5 – -159.7 (2F, m). HRMS: (ESI^+) Calculated for $C_{24}H_{24}F_5NNaO_4$: 508.1518. Found $[M+Na]^+$: 508.1514.

***tert*-Butyl (2*R**,4*S**)-4-phenyl-2-vinylpyrrolidine-1-carboxylate (262)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **261** (51.0 mg, 0.105 mmol) was employed. FCC (gradient elution: 12:1 – 9:1 hexane:EtOAc) afforded **262** (25.3 mg, 88 %, 4:1 mixture of *cis* and *trans* diastereomers) as a pale-yellow oil. *It was not possible to determine the relative stereochemistry of **262** by NOE analysis. The removal of the Boc group was necessary to obtain satisfactory data, details of this are given below. Spectroscopic data for the major cis diastereomer:* ν_{max} / cm^{-1}: (*film*) 2975 (m), 2928 (m), 1689 (s), 1390 (s), 1164 (s). δ_H (500 MHz, $CDCl_3$) 7.38 – 7.32 (2H, m, 2 × ArC<u>H</u>), 7.28 – 7.24 (3H, m, 3 × ArC<u>H</u>), 5.96 – 5.73 (1H, m, C**5**-<u>H</u>), 5.29 – 5.04 (2H, m, C**6**-<u>H_2</u>), 4.42 – 4.24 (1H, m, C**4**-<u>H</u>), 4.20 – 3.94 (1H, m, C**1**-<u>H</u>), 3.34 – 3.25 (2H, m, C**1**-<u>H</u>' and C**2**-<u>H</u>), 2.59 – 2.48 (1H, m, C**3**-<u>H</u>), 1.88 (1H, ddd, *J* = 12.0, 11.0, 11.0 Hz, C**3**-<u>H</u>'), 1.48 (9H, s, OC($C\underline{H}_3$)$_3$). *Although not observable in the ^1H spectrum, from the ^{13}C spectrum it is apparent that this compound exists as an approximately 3:2 mixture of rotamers A and B.* δ_C (126 MHz, $CDCl_3$) 154.9 (A: <u>C</u>=O), 154.6 (B: <u>C</u>=O), 140.6 (A and B: Ar<u>C</u>), 140.2 (A: C**5**), 139.7 (B: C**5**), 128.7 (A and B: Ar<u>C</u>H), 127.3 (A and B: Ar<u>C</u>H), 127.0 (A and B: Ar<u>C</u>H), 114.4 (A and B: C**6**), 79.7 (A and B: O<u>C</u>(CH_3)$_3$), 60.5 (A and B: C**4**), 53.8 (B: C**1**), 52.9 (A: C**1**), 43.3 (B: C**2**), 42.8 (A: C**2**), 41.1 (A: C**3**), 40.7 (B: C**3**), 28.6 (A and B: OC(<u>C</u>H_3)$_3$). HRMS: (ESI^+) Calculated for $C_{17}H_{23}NNaO_2$: 296.1621. Found $[M+Na]^+$: 296.1632. *Characteristic signals for the minor trans diastereomer:* δ_H (500 MHz, $CDCl_3$) 3.93 – 3.80 (1H, m), 2.26 – 2.17 (1H, m), 2.13 – 2.04 (1H, m).

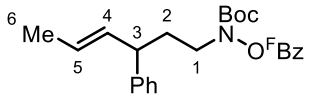
(2*R,4*S**)-4-Phenyl-2-vinylpyrrolidin-1-ium trifluoroacetate**



General procedure Q: Pyrrolidine **262** (25.3 mg, 92.5 μmol) was employed to afford the title compound (24.9 mg, 94 %, 4:1 mixture of *cis* and *trans* diastereomers) as an orange oil. *The major product was assigned as the cis diastereomer based on the observed NOE correlation between the C**2** and the C**4** protons. Spectroscopic data for the major cis diastereomer:* ν_{max} / cm^{-1}: (*film*) 3404 (br s), 2979 (m), 1668 (s), 1429 (m), 1129 (s). δ_H (400 MHz, $CDCl_3$) 10.01 (1H, br s, N<u>H</u>), 9.45 (1H, br s, N<u>H</u>'), 7.38 – 7.31 (2H, m, 2 × ArC<u>H</u>), 7.31 – 7.22 (3H, m, 3 × ArC<u>H</u>), 6.00 (1H, ddd, *J* = 17.5, 10.5, 8.0 Hz, C**5**-<u>H</u>), 5.46 (1H, d, *J* = 17.5 Hz, C**6**-<u>H</u>'), 5.36 (1H, d, *J* = 10.5 Hz, C**6**-<u>H</u>), 4.26 – 4.11 (1H, m,

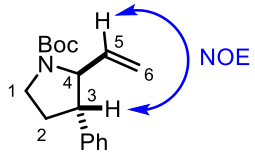
C**4**-H), 3.80 – 3.65 (1H, m, C**1**-H), 3.64 – 3.50 (1H, m, C**2**-H), 3.40 – 3.22 (1H, m, C**1**-H'), 2.50 (1H, ddd, *J* = 12.5, 6.0, 6.0 Hz, C**3**-H), 2.10 (1H, ddd, *J* = 12.5, 12.0, 12.0 Hz, C**3**-H'). δ_C (101 MHz, $CDCl_3$) 138.1 (ArC), 131.7 (C**5**), 129.0 (ArCH), 127.7 (ArCH), 127.1 (ArCH), 122.1 (C**6**), 62.8 (C**4**), 50.6 (C**1**), 43.7 (C**2**), 39.3 (C**3**). *The ^{13}C signals corresponding to the trifluoroacetate counterion could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -75.6 (3F, s). HRMS: (ESI^+) Calculated for $C_{12}H_{16}N$: 174.1277. Found $[M–F_3CCO_2]^+$: 174.1281. *Characteristic signals for the minor trans diastereomer:* δ_H (400 MHz, $CDCl_3$) 10.13 (1H, br s), 9.34 (1H, br s), 5.44 (1H, d, *J* = 17.0 Hz), 4.41 – 4.29 (1H, m), 2.41 – 2.26 (2H, m). δ_C (101 MHz, $CDCl_3$) 61.6, 51.1, 42.2, 38.3.

***tert*-Butyl (*E*)-(3-phenylhex-4-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (263a)**



General procedure O: Alcohol **149** (Section 7.3, 353 mg, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 15 hours. FCC (eluent: 2:3 hexane:PhMe) afforded **263a** (554 mg, 57 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3028 (m), 2981 (m), 1782 (s), 1722 (s), 1652 (m), 1504 (s), 1326 (s), 1152 (s). δ_H (400 MHz, $CDCl_3$) 7.32 – 7.27 (2H, m, 2 × ArCH), 7.21 – 7.16 (3H, m, 3 × ArCH), 5.60 – 5.45 (2H, m, C**4**-H and C**5**-H), 3.72 – 3.55 (2H, m, C**1**-H_2), 3.34 (1H, dt, *J* = 7.5, 7.5 Hz, C**3**-H), 2.01 (2H, dt, *J* = 7.5, 7.5 Hz, C**2**-H_2), 1.67 (3H, d, *J* = 5.5 Hz, C**6**-H_3), 1.47 (9H, s, OC(CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 154.5 (Boc C=O), 144.0 (ArC), 133.8 (C**4**), 128.6 (ArCH), 127.4 (ArCH), 126.3 (ArCH), 125.7 (C**5**), 83.3 (OC(CH_3)$_3$), 49.5 (C**1**), 45.9 (C**3**), 32.8 (C**2**), 28.0 (OC(CH_3)$_3$), 17.9 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.2 – -136.6 (2F, m), -146.5 (1F, tt, *J* = 21.0, 5.5 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI^+) Calculated for $C_{24}H_{24}F_5NNaO_4$: 508.1518. Found $[M+Na]^+$: 508.1512.

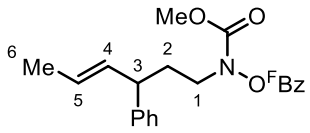
***tert*-Butyl (2*R**,3*R**)-3-phenyl-2-vinylpyrrolidine-1-carboxylate (264a)**



General procedure D: Conditions: 3.75 mol% $Pd_2(dba)_3$; 22.5 mol% P(4-(CF_3)C_6H_4)$_3$; 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **263a** (51.0 mg, 0.105 mmol) was employed. FCC (eluent: 74:1 PhMe:EtOAc) afforded **264a** (19.5 mg, 68 %, 15:1 mixture of *trans* and *cis* diastereomers) as a pale-yellow oil. *The major product was assigned as the trans diastereomer based on the observed NOE correlation between the C**3** and the C**5** protons. This compound exists as an approximately 3:2*

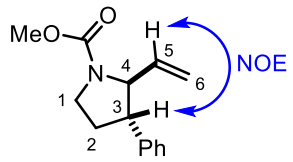
mixture of rotamers A and B. Spectroscopic data for the major trans diastereomer: ν_{max} / cm^{-1}: (*film*) 3029 (m), 2975 (m), 1691 (s), 1454 (m), 1390 (s), 1165 (s). δ_H (500 MHz, $CDCl_3$) 7.35 – 7.27 (2H, m, A and B: 2 × ArC<u>H</u>), 7.25 – 7.18 (3H, m, A and B: 3 × ArC<u>H</u>), 5.79 (1H, s, A and B: C**5**-<u>H</u>), 5.13 – 4.88 (2H, m, A and B: C**6**-<u>H_2</u>), 4.35 (0.4H, br s, B: C**4**-<u>H</u>), 4.20 (0.6H, br s, A: C**4**-<u>H</u>), 3.79 – 3.58 (1H, m, A and B: C**1**-<u>H</u>), 3.48 – 3.39 (1H, m, A and B: C**1**-<u>H</u>'), 3.13 – 3.01 (1H, m, A and B: C**3**-<u>H</u>), 2.29 – 2.18 (1H, m, A and B: C**2**-<u>H</u>), 2.00 – 1.87 (1H, m, A and B: C**2**-<u>H</u>'), 1.45 (9H, s, A and B: OC($C\underline{H}_3$)$_3$). δ_C (126 MHz, $CDCl_3$) 154.7 (A and B: <u>C</u>=O), 142.1 (A and B: Ar<u>C</u>), 138.7 (A: C**5**), 138.2 (B: C**5**), 128.7 (A and B: Ar<u>C</u>H), 127.4 (A and B: Ar<u>C</u>H), 126.9 (A and B: Ar<u>C</u>H), 114.7 (A and B: C**6**), 79.6 (A and B: O<u>C</u>(CH_3)$_3$), 66.6 (A: C**4**), 66.0 (B: C**4**), 51.5 (A: C**3**), 50.7 (B: C**3**), 45.9 (A and B: C**1**), 32.3 (B: C**2**), 31.6 (A: C**2**), 28.6 (A and B: OC(<u>C</u>H_3)$_3$). HRMS: (ESI^+) Calculated for $C_{17}H_{23}NNaO_2$: 296.1621. Found $[M+Na]^+$: 296.1629. *Characteristic signals for the minor cis diastereomer:* δ_H (500 MHz, $CDCl_3$) 5.37 – 5.25 (1H, m, A and B: C**5**-<u>H</u>), 4.72 – 4.66 (0.4H, m, B: C**4**-<u>H</u>), 4.54 (0.6H, dd, *J* = 6.5, 6.5 Hz, A: C**4**-<u>H</u>), 2.14 – 2.06 (1H, m, A and B: C**2**-<u>H</u>').

Methyl (*E*)-(3-phenylhex-4-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (263b)



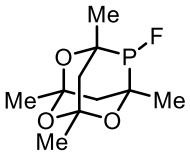
<u>General procedure O:</u> Alcohol **149** (Section 7.3, 353 mg, 2.00 mmol) was employed with MeO(CO)NHO^{F}Bz (*vide supra*). The reaction time was 16 hours. FCC (*two times*, first eluent: 1:4 petrol:PhMe; second eluent: 19:1 petrol:acetone) afforded **263b** (514 mg, 58 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3030 (m), 2959 (m), 1784 (s), 1731 (s), 1652 (m), 1497 (s), 1173 (s). δ_H (400 MHz, $CDCl_3$) 7.32 – 7.27 (2H, m, 2 × ArC<u>H</u>), 7.22 – 7.16 (3H, m, 3 × ArC<u>H</u>), 5.60 – 5.44 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 3.79 (3H, s, OC<u>H_3</u>), 3.75 – 3.61 (2H, m, C**1**-<u>H_2</u>), 3.35 (1H, dt, *J* = 7.5, 7.5 Hz, C**3**-<u>H</u>), 2.02 (2H, dt, *J* = 7.5, 7.5 Hz, C**2**-<u>H_2</u>), 1.67 (3H, dd, *J* = 5.5, 1.0 Hz, C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 156.2 (MeO–<u>C</u>=O), 144.1 (Ar<u>C</u>), 133.8 (C**4**), 128.7 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 126.5 (Ar<u>C</u>H), 126.0 (C**5**), 54.1 (O<u>C</u>H_3), 49.9 (C**1**), 46.1 (C**3**), 32.9 (C**2**), 18.1 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.1 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.5 Hz), -159.2 – -159.5 (2F, m). HRMS: (ESI^+) Calculated for $C_{21}H_{18}F_5NNaO_4$: 466.1048. Found $[M+Na]^+$: 466.1049.

Methyl (2*R,3*R**)-3-phenyl-2-vinylpyrrolidine-1-carboxylate (264b)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 17.5 mol% ligand **L3** (*vide supra*); 100 mol% Et_3N; dioxane (0.3 M); 130 °C; 24 hours. Substrate **263b** (46.6 mg, 0.105 mmol) was employed. FCC (eluent: 7:1 petrol:EtOAc) afforded **264b** (18.8 mg, 77 %) as a colourless oil. *The product was assigned as the trans diastereomer based on the observed NOE correlation between the C**3** and the C**5** protons.* ν_{max} / cm^{-1}: (*film*) 3030 (m), 2953 (m), 1701 (s), 1448 (s), 1383 (s). δ_H (500 MHz, $CDCl_3$) 7.34 – 7.30 (2H, m, 2 × ArC<u>H</u>), 7.26 – 7.22 (1H, m, ArC<u>H</u>), 7.22 – 7.18 (2H, m, 2 × ArC<u>H</u>), 5.83 (1H, ddd, *J* = 17.0, 10.5, 6.0 Hz, C**5**-<u>H</u>), 5.17 – 4.94 (2H, m, C**6**-<u>H</u>$_2$), 4.45 – 4.25 (1H, m, C**4**-<u>H</u>), 3.84 – 3.64 (4H, m, C**1**-<u>H</u> and OC<u>H</u>$_3$), 3.56 – 3.44 (1H, m, C**1**-<u>H</u>'), 3.13 (1H, ddd, *J* = 6.5, 6.5, 6.5 Hz, C**3**-<u>H</u>), 2.27 (1H, dddd, *J* = 13.5, 6.5, 6.5, 6.5 Hz, C**2**-<u>H</u>), 1.98 (1H, dddd, *J* = 13.5, 7.0, 7.0, 6.5 Hz, C**2**-<u>H</u>'). *This compound exists as an approximately 1:1 mixture of rotamers; this results in in the doubling up of several signals in the carbon spectrum.* δ_C (126 MHz, $CDCl_3$) 155.9 and 155.6 (<u>C</u>=O), 142.1 and 141.9 (Ar<u>C</u>), 138.2 and 137.7 (C**5**), 128.8 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 115.4 and 114.7 (C**6**), 66.3 (C**4**), 52.5 (O<u>C</u>H$_3$), 51.2 and 50.4 (C**3**), 46.3 and 46.0 (C**1**), 32.3 and 31.4 (C**2**). HRMS: (ESI^+) Calculated for $C_{14}H_{18}NO_2$: 232.1332. Found $[M+H]^+$: 232.1332.

8-Fluoro-1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane (L4)

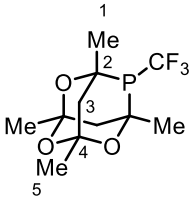


To a solution of 1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane (**248**)[XLVIII] (1.08 g, 5.00 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C was added Br_2 (0.28 mL, 5.50 mmol). The reaction mixture was stirred at room temperature for 7 hours before addition of TBAF (1.0 M in THF, 12.5 mL, 12.5 mmol). The reaction mixture was stirred at room temperature for 2 hours before being diluted with Et_2O (150 mL) and washed with brine (2 × 70 mL), followed by saturated aqueous Na_2SO_3 (70 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 19:1 petrol:EtOAc) afforded **L4** (330 mg, 28 %) as a colourless crystalline solid. δ_H (400 MHz, $CDCl_3$) 1.93 (1H, dd, *J* = 13.5, 5.0 Hz), 1.88 – 1.84 (1H, m), 1.82 (1H, d, *J* = 3.5 Hz), 1.61 (1H, ddd, *J* = 13.5, 5.5, 4.0 Hz), 1.45 (3H, d, *J* = 9.0 Hz), 1.42 (3H, d, *J* = 9.5 Hz), 1.40 (3H, s), 1.36 (3H, s). δ_F (377 MHz, $CDCl_3$) -210.4

[XLVIII] Phosphine **248** was prepared by Charly Faradji (University of Bristol) according to a literature procedure.[147]

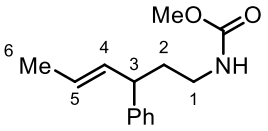
(1F, d, *J* = 903.0 Hz). δ_P (162 MHz, $CDCl_3$) 124.1 (d, *J* = 903.0 Hz). *The spectroscopic properties were consistent with the data available in the literature.*[270]

1,3,5,7-Tetramethyl-8-(trifluoromethyl)-2,4,6-trioxa-8-phosphaadamantane (L5)



To a suspension of **L4** (100 mg, 0.427 mmol) and CsF (13.0 mg, 85.4 µmol) in anhydrous THF (4 mL, argon sparged) at 0 °C was added $TMSCF_3$ (0.19 mL, 1.28 mmol). The reaction mixture was stirred at room temperature for 5 hours before being filtered through celite and concentrated *in vacuo*. FCC (eluent: 24:1 pentane:Et_2O) afforded **L5** (92.2 mg, 76 %) as a colourless crystalline solid. m.p. 77-78 °C (CH_2Cl_2:petrol, *tabular*). ν_{max} / cm^{-1}: (*solid*) 2998 (m), 1449 (m), 1380 (s), 1213 (s), 1077 (s). δ_H (400 MHz, $CDCl_3$) 1.97 – 1.82 (3H, m, C**3**-$\underline{H}_2$ and C**3'**-$\underline{H}$), 1.76 (1H, dd, *J* = 13.5, 5.0 Hz, C**3'**-$\underline{H}$'), 1.53 (3H, d, *J* = 12.5 Hz, C**1**-$\underline{H}_3$), 1.51 (3H, d, *J* = 13.5 Hz, C**1'**-$\underline{H}_3$), 1.39 (3H, s, C**5**-$\underline{H}_3$), 1.38 (3H, s, C**5'**-$\underline{H}_3$). δ_C (101 MHz, $CDCl_3$) 96.8 (C**4**), 95.9 (C**4'**), 72.5 (C**2**), 72.1 (C**2'**), 44.7 (d, *J* = 17.5 Hz, C**3**), 38.3 (C**3'**), 28.7 (d, *J* = 21.0 Hz, C**1'**), 27.7 (C**5'**), 27.5 (C**5**), 26.9 (d, *J* = 10.5 Hz, C**1**). *The ^{13}C signal corresponding to the trifluoromethyl group could not be resolved due to its weak intensity.* δ_F (377 MHz, $CDCl_3$) -48.6 (3F, d, *J* = 62.0 Hz). δ_P (162 MHz, $CDCl_3$) -20.0 (q, *J* = 62.0 Hz). HRMS: (ESI^+) Calculated for $C_{11}H_{16}F_3NaO_4P$: 323.0631. Found $[M+O+Na]^+$: 323.0645. *The apparent ease with which **L5** undergoes oxidation in solution meant it was not possible to obtain HRMS data for the unoxidised ligand.*

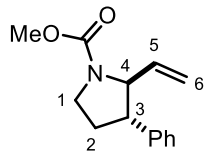
Methyl (*E*)-(3-phenylhex-4-en-1-yl)carbamate (265)



*This compound was prepared from **263b** by modification of **General procedure D**. Formic acid was included to effect reduction of the N–O bond of **263b**.* **General procedure D:** Conditions: 5 mol% $Pd_2(dba)_3$; 25 mol% PPh_3; 200 mol% Et_3N; 100 mol% HCO_2H; THF (0.1 M); 110 °C; 24 hours. Substrate **263b** (295 mg, 0.665 mmol) was employed. FCC (eluent: 5:1 petrol:EtOAc) afforded **265** (88.0 mg, 57 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3333 (br s), 3026 (m), 2938 (m), 1697 (s), 1528 (s), 1251 (s). δ_H (400 MHz, $CDCl_3$) 7.34 – 7.25 (2H, m, 2 × ArC$\underline{H}$), 7.24 – 7.14 (3H, m, 3 × ArC$\underline{H}$), 5.59 – 5.43 (2H, m, C**4**-$\underline{H}$ and C**5**-$\underline{H}$), 4.59 (1H, br s, N$\underline{H}$), 3.65 (3H, s, OC$\underline{H}_3$), 3.25 (1H, dt, *J* = 7.5, 7.5 Hz, C**3**-$\underline{H}$), 3.21 – 3.03 (2H, m, C**1**-$\underline{H}_2$), 1.93 – 1.83 (2H, m, C**2**-$\underline{H}_2$), 1.66 (3H, d, *J* = 6.0 Hz,

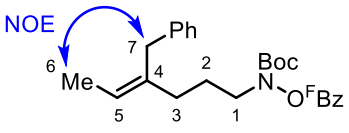
C**6**-H$_3$). δ_C (101 MHz, $CDCl_3$) 157.1 (MeO–C=O), 144.4 (ArC), 134.3 (C**4**), 128.7 (ArCH), 127.5 (ArCH), 126.4 (ArCH), 125.5 (C**5**), 52.1 (OCH_3), 46.7 (C**3**), 39.7 (C**1**), 36.1 (C**2**), 18.1 (C**6**). HRMS: (ESI$^+$) Calculated for $C_{14}H_{19}NNaO_2$: 256.1320. Found $[M+Na]^+$: 256.1313.

Methyl (2*R,3*R**)-3-phenyl-2-vinylpyrrolidine-1-carboxylate (264b)**



This compound was prepared using an adaptation of a literature procedure.[26] A solution of **265** (23.3 mg, 0.100 mmol) and $Pd(OAc)_2$ (2.2 mg, 10.0 μmol) in DMSO (0.4 mL) was stirred under an atmosphere of O_2 (balloon pressure) at 55 °C for 24 hours. The reaction mixture was diluted with Et_2O (5 mL) and washed with water (3 × 5 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 9:1 petrol:EtOAc) afforded **264b** (16.5 mg, 71 %, 4:1 mixture of *trans* and *cis* diastereomers) as a colourless oil. *Conditions reported by Stahl ($Pd(OAc)_2$ (5 mol%); pyridine (10 mol%); O_2 (balloon pressure); xylene (0.1 M); heated at 80 °C for 24 hours)[55] for the aza-Wacker cyclisation of carbamates provided **264b** in 37 % yield and approximately 4:3 d.r. (trans:cis) based on ^{1}H NMR analysis of the crude reaction mixture. Characterisation data for the major diastereomer of **264b** has been provided earlier. ^{1}H NMR signals for the minor cis diastereomer were obtained from 1D TOCSY analysis of the mixture of trans and cis diastereomers. The minor diastereomer exists as an approximately 1:1 mixture of rotamers; this results in the doubling of several signals in the ^{1}H and ^{13}C NMR spectra. Characteristic signals for the minor cis diastereomer:* δ_H (400 MHz, $CDCl_3$) 5.35 – 5.30 (1H, m, C**5**-H), 5.04 (1H, d, *J* = 12.5 Hz, C**6**-H), 4.97 (1H, d, *J* = 16.0 Hz, C**6**-H'), 4.77 – 4.70 and 4.67 – 4.60 (2 × 0.5H, m, C**4**-H), 3.72 – 3.61 (2H, m, C**1**-H_2), 3.59 – 3.45 (1H, m, C**3**-H), 2.36 – 2.22 (1H, m, C**2**-H), 2.17 – 2.08 (1H, m, C**2**-H'). δ_C (126 MHz, $CDCl_3$) 134.7 and 134.2 (C**5**), 116.1 and 115.8 (C**6**), 62.9 and 62.5 (C**4**), 48.0 and 47.2 (C**3**), 45.7 and 45.5 (C**1**), 27.0 and 25.9 (C**2**).

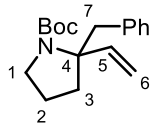
***tert*-Butyl (*Z*)-(4-benzylhex-4-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (266a)**



General procedure O: Alcohol **159c** (Section 7.3, 860 mg, 4.52 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 16 hours. FCC (eluent: 3:7 hexane:PhMe) afforded **266a** (1.35 g, 60 %) as a colourless oil. *The product was assigned as the (Z)-isomer based on the observed NOE correlation between the C**6** and the C**7** protons.* ν_{max} / cm^{-1}: (*film*) 3030 (m), 2935 (m), 1783 (s), 1721 (s), 1653 (m), 1505 (s), 1326 (s), 1150 (s). δ_H (400 MHz, $CDCl_3$) 7.26 – 7.21 (2H, m,

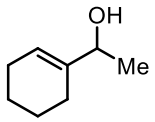
2 × ArC<u>H</u>), 7.17 – 7.12 (3H, m, 3 × ArC<u>H</u>), 5.44 (1H, q, *J* = 7.0 Hz, C**5**-<u>H</u>), 3.59 (2H, t, *J* = 7.0 Hz, C**1**-<u>H</u>$_2$), 3.39 (2H, s, C**7**-<u>H</u>$_2$), 1.98 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 1.74 – 1.65 (5H, m, C**2**-<u>H</u>$_2$ and C**6**-<u>H</u>$_3$), 1.46 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 154.5 (Boc <u>C</u>=O), 140.0 (Ar<u>C</u>), 137.2 (C**4**), 128.4 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 121.1 (C**5**), 83.2 (O<u>C</u>(CH$_3$)$_3$), 50.6 (C**1**), 35.5 (C**7**), 33.4 (C**3**), 28.0 (OC(<u>C</u>H$_3$)$_3$), 25.1 (C**2**), 13.7 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.3 – -136.5 (2F, m), -146.6 (1F, tt, *J* = 21.0, 5.5 Hz), -159.3 – -159.5 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{25}H_{26}F_5NNaO_4$: 522.1674. Found $[M+Na]^+$: 522.1666.

***tert*-Butyl 2-benzyl-2-vinylpyrrolidine-1-carboxylate (267a)**



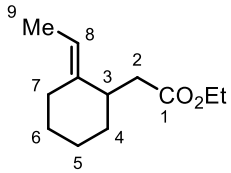
<u>General procedure D:</u> Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **266a** (52.4 mg, 0.105 mmol) was employed. FCC (eluent: 39:1 hexane:EtOAc) afforded **267a** (26.3 mg, 87 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2974 (m), 1686 (s), 1381 (s), 1168 (s). *This compound exists as an approximately 1:1 mixture of rotamers A and B.* δ_H (400 MHz, $CDCl_3$) 7.31 – 7.13 (5H, m, A and B: 5 × ArC<u>H</u>), 6.10 (0.5H, dd, *J* = 17.5, 10.5 Hz, A: C**5**-<u>H</u>), 5.99 (0.5H, dd, *J* = 17.5, 10.5 Hz, B: C**5**-<u>H</u>), 5.12 – 4.96 (2H, m, A and B: C**6**-<u>H</u>$_2$), 3.67 (0.5H, d, *J* = 13.5 Hz, B: C**7**-<u>H</u>), 3.55 – 3.46 (1H, m, A: C**1**-<u>H</u> and C**7**-<u>H</u>), 3.40 (0.5H, ddd, *J* = 11.5, 8.0, 4.0 Hz, B: C**1**-<u>H</u>), 3.06 (0.5H, ddd, *J* = 11.0, 7.5, 7.5 Hz, A: C**1**-<u>H</u>'), 3.01 – 2.82 (1.5H, m, A: C**7**-<u>H</u>'; B: C**1**-<u>H</u>' and C**7**-<u>H</u>'), 2.04 – 1.92 (1H, m, A and B: C**3**-<u>H</u>), 1.80 – 1.70 (1H, m, A and B: C**3**-<u>H</u>'), 1.60 – 1.48 (10H, m, A and B: C**2**-<u>H</u> and OC(C<u>H</u>$_3$)$_3$), 1.26 – 1.08 (1H, m, A and B: C**2**-<u>H</u>'). δ_C (101 MHz, $CDCl_3$) 154.5 (B: <u>C</u>=O), 153.8 (A: <u>C</u>=O), 143.5 (B: C**5**), 142.5 (A: C**5**), 138.2 (A: Ar<u>C</u>), 138.1 (B: Ar<u>C</u>), 131.0 (B: Ar<u>C</u>H), 130.7 (A: Ar<u>C</u>H), 128.3 (A: Ar<u>C</u>H), 128.0 (B: Ar<u>C</u>H), 126.5 (B: Ar<u>C</u>H), 126.3 (A: Ar<u>C</u>H), 112.0 (B: C**6**), 111.7 (A: C**6**), 79.9 (B: O<u>C</u>(CH$_3$)$_3$), 79.0 (A: O<u>C</u>(CH$_3$)$_3$), 67.3 (B: C**4**), 66.8 (A: C**4**), 2 × 48.8 (A and B: C**1**), 42.3 (A: C**7**), 41.5 (B: C**7**), 37.9 (A: C**3**), 36.3 (B: C**3**), 28.8 (A and B: OC(<u>C</u>H$_3$)$_3$), 21.4 (B: C**2**), 21.0 (A: C**2**). HRMS: (ESI$^+$) Calculated for $C_{18}H_{25}NNaO_2$: 310.1778. Found $[M+Na]^+$: 310.1788.

1-(Cyclohex-1-en-1-yl)ethan-1-ol



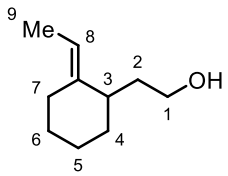
General procedure I: 1-Acetyl-1-cyclohexene (5.14 mL, 40.0 mmol) was employed, using anhydrous Et_2O as solvent and 0.5 eq. $LiAlH_4$ (1.0 M in Et_2O). The title compound (3.98 g, 79 %) was isolated as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.68 – 5.60 (1H, m), 4.20 – 4.10 (1H, m), 2.09 – 1.90 (4H, m), 1.69 – 1.47 (5H, m), 1.24 (3H, d, *J* = 6.5 Hz). δ_C (101 MHz, $CDCl_3$) 141.4, 121.6, 72.3, 25.0, 23.8, 22.8, 22.7, 21.6. *The spectroscopic properties were consistent with the data available in the literature*.[271]

Ethyl (*E*)-2-(2-ethylidenecyclohexyl)acetate



General procedure L: The preceding allylic alcohol (2.52 g, 20.0 mmol) was employed. The reaction time was 19 hours. FCC (eluent: 49:1 hexane:EtOAc) afforded the title compound (1.99 g, 51 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.10 (1H, q, *J* = 6.5 Hz, C**9**-H), 4.16 – 4.06 (2H, m, OCH_2CH_3), 2.59 – 2.48 (2H, m, C**2**-H and C**3**-H), 2.36 – 2.24 (2H, m, C**2**-H' and C**7**-H), 2.04 – 1.93 (1H, m, C**7**-H'), 1.75 – 1.39 (8H, m, C**4**-H, C**5**-H_2, C**6**-H_2 and C**10**-H_3), 1.32 – 1.19 (4H, m, C**4**-H' and OCH_2CH_3). δ_C (101 MHz, $CDCl_3$) 173.2 (C**1**), 141.2 (C**8**), 114.2 (C**9**), 60.1 (OCH_2CH_3), 41.0 (C**3**), 38.0 (C**2**), 33.8 (C**4**), 27.6 (C**6**), 26.8 (C**7**), 24.4 (C**5**), 14.3 (OCH_2CH_3), 12.6 (C**10**). *The spectroscopic properties were consistent with the data available in the literature,*[272] *although the* ^{1}*H NMR spectrum is incorrectly assigned. The assignment provided here is supported by 2D NMR data.*

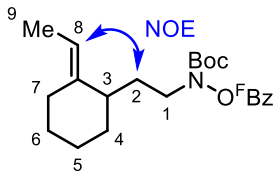
(*E*)-2-(2-Ethylidenecyclohexyl)ethan-1-ol (268)



General procedure I: The preceding ester (1.98 g, 10.1 mmol) was employed, using anhydrous THF as solvent and 0.8 eq. $LiAlH_4$ (1.0 M in THF). FCC (eluent: 4:1 hexane:EtOAc) afforded **268** (627 mg, 40 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3323 (br s), 2922 (s), 2854 (m), 1446 (m), 1053 (s). δ_H (400 MHz, $CDCl_3$) 5.18 (1H, q, *J* = 6.5 Hz, C**9**-H), 3.62 (2H, dd, *J* = 6.5, 6.5 Hz, C**1**-H_2), 2.24 – 2.04

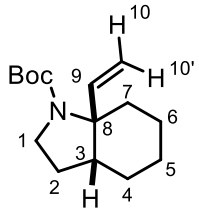
(3H, m, C**3**-H and C**7**-H$_2$), 1.90 (1H, ddt, *J* = 13.5, 9.0, 6.5 Hz, C**2**-H), 1.70 – 1.32 (10H, m, C**2**-H', C**4**-H$_2$, C**5**-H$_2$, C**6**-H$_2$ and C**10**-H$_3$). δ_C (101 MHz, $CDCl_3$) 142.4 (C**8**), 115.0 (C**9**), 61.9 (C**1**), 41.4 (C**3**), 34.8 (C**2**), 33.9 (C**4**), 27.8 (C**6**), 25.7 (C**7**), 23.3 (C**5**), 12.6 (C**10**). HRMS: (ESI$^+$) Calculated for $C_{10}H_{18}NaO$: 177.1250. Found $[M+Na]^+$: 177.1248.

***tert*-Butyl (*E*)-(2-(2-ethylidenecyclohexyl)ethyl)((pentafluorobenzoyl)oxy)carbamate (269)**



General procedure O: Alcohol **268** (309 mg, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 14 hours. FCC (eluent: 1:1 hexane:PhMe) afforded **269** (555 mg, 60 %) as a colourless oil. *The product was assigned as the (E)-isomer based on the observed NOE correlation between the C**2** and the C**9** protons.* ν_{max} / cm^{-1}: (*film*) 2929 (m), 1785 (s), 1723 (s), 1653 (m), 1507 (s), 1156 (s). δ_H (400 MHz, $CDCl_3$) 5.15 (1H, q, *J* = 6.5 Hz, C**9**-H), 3.62 (2H, dd, *J* = 7.5, 7.5 Hz, C**1**-H$_2$), 2.18 – 2.05 (3H, m, C**3**-H and C**7**-H$_2$), 1.93 (1H, ddt, *J* = 13.5, 8.0, 7.5 Hz, C**2**-H), 1.72 – 1.34 (19H, m, C**2**-H', C**4**-H$_2$, C**5**-H$_2$, C**6**-H$_2$, C**10**-H$_3$ and OC(CH$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 154.7 (Boc C=O), 141.2 (C**8**), 115.5 (C**9**), 83.3 (OC(CH$_3$)$_3$), 50.0 (C**1**), 41.9 (C**3**), 33.9 (C**4**), 29.0 (C**2**), 28.2 (OC(CH$_3$)$_3$), 27.9 (C**6**), 26.0 (C**7**), 23.7 (C**5**), 12.8 (C**10**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.4 – -136.6 (2F, m), -146.7 (1F, tt, *J* = 21.0, 5.5 Hz), -159.2 – -159.5 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{22}H_{26}F_5NNaO_4$: 486.1674. Found $[M+Na]^+$: 486.1681.

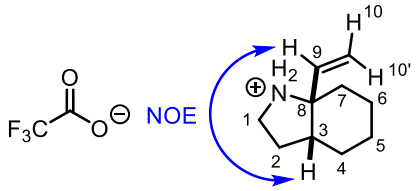
***tert*-Butyl (3a*R**,7a*S**)-7a-vinyloctahydro-1*H*-indole-1-carboxylate (270)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **269** (48.7 mg, 0.105 mmol) was employed. FCC (eluent: 79:1 pentane:acetone) afforded **270** (24.2 mg, 92 %) as a colourless oil. *It was not possible to determine the relative stereochemistry of **270** by NOE analysis. The removal of the Boc group was necessary to obtain satisfactory data, details of this are given below. This compound exists as an approximately 3:2 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 2928 (m), 1682 (s), 1364 (s).

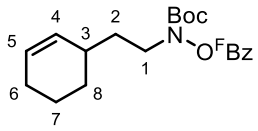
δ_H (500 MHz, $CDCl_3$) 5.83 – 5.69 (1H, m, A and B: C**9**-H), 5.10 – 5.03 (1H, m, A and B: C**10**-H), 4.99 (1H, d, *J* = 17.5 Hz, A and B: C**10**-H'), 3.63 – 3.47 (1H, m, A and B: C**1**-H), 3.46 – 3.34 (1H, m, A and B: C**1**-H'), 2.53 – 2.43 (0.4H, m, B: C**7**-H), 2.13 – 2.04 (0.6H, m, A: C**7**-H), 1.99 – 1.85 (1H, m, A and B: C**3**-H), 1.84 – 1.67 (2H, m, A and B: C**2**-H and C**7**-H'), 1.62 – 1.26 (16H, m, A and B: C**2**-H', C**4**-H_2, C**5**-H_2, C**6**-H_2 and OC(CH_3)$_3$). δ_C (126 MHz, $CDCl_3$) 155.3 (A: C=O), 154.2 (B: C=O), 143.0 (A: C**9**), 142.6 (B: C**9**), 112.7 (A: C**10**), 112.5 (B: C**10**), 79.4 (A: O**C**(CH_3)$_3$), 78.7 (B: O**C**(CH_3)$_3$), 66.2 (B: C**8**), 65.4 (A: C**8**), 46.6 (B: C**1**), 46.5 (A: C**1**), 44.8 (A: C**3**), 43.4 (B: C**3**), 32.0 (A: C**7**), 31.3 (B: C**7**), 28.8 (B: OC(CH_3)$_3$), 28.7 (A: OC(CH_3)$_3$), 27.1 (B: C**4**), 26.7 (B: C**2**), 26.6 (A: C**4**), 26.2 (A: C**2**), 23.8 (B: C**5**), 23.2 (A: C**5**), 22.1 (A: C**6**), 22.0 (B: C**6**). HRMS: (ESI^+) Calculated for $C_{15}H_{25}NNaO_2$: 275.1778. Found $[M+Na]^+$: 274.1776.

(3a*R,7a*S**)-7a-Vinyloctahydro-1*H*-indol-1-ium trifluoroacetate**



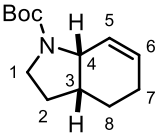
General procedure Q: Pyrrolidine **270** (13.0 mg, 51.7 μmol) was employed to afford the title compound (13.5 mg, 98 %) as a colourless oil. *The relative stereochemistry of the product was assigned based on the observed NOE correlation between the C**3** and the C**9** protons.* ν_{max} / cm^{-1}: (*film*) 3418 (br s), 2941 (m), 1670 (s), 1425 (m), 1201 (s). δ_H (400 MHz, $CDCl_3$) 9.45 (1H, br s, NH), 9.19 (1H, br s, NH'), 5.94 (1H, dd, *J* = 17.5, 11.0 Hz, C**9**-H), 5.50 (1H, d, *J* = 17.5 Hz, C**10**-H'), 5.44 (1H, d, *J* = 11.0 Hz, C**10**-H), 3.45 – 3.31 (2H, m, C**1**-H_2), 2.44 (1H, dddd, *J* = 8.5, 8.5, 4.0, 4.0 Hz, C**3**-H), 2.13 – 2.02 (2H, m, C**2**-H_2), 1.93 (1H, ddd, *J* = 13.0, 3.5, 3.5 Hz, C**7**-H), 1.74 – 1.55 (4H, m, C**4**-H_2, C**6**-H and C**7**-H'), 1.52 – 1.42 (2H, m, C**5**-H_2), 1.41 – 1.27 (1H, m, C**6**-H'). δ_C (101 MHz, $CDCl_3$) 136.1 (C**9**), 120.0 (C**10**), 67.5 (C**8**), 41.9 (C**1**), 41.0 (C**3**), 28.9 (C**7**), 26.5 (C**2**), 24.2 (C**4**), 21.7 (C**6**), 20.0 (C**5**). *The ^{13}C signals corresponding to the trifluoroacetate counterion could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -75.6 (3F, s). HRMS: (ESI^+) Calculated for $C_8H_{12}N$: 152.1434. Found $[M–F_3CCO_2]^+$: 152.1435.

***tert*-Butyl (2-(cyclohex-2-en-1-yl)ethyl)((pentafluorobenzoyl)oxy)carbamate (241b)**



General procedure O: Alcohol **83** (Section 7.3, 240 mg, 1.90 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 16 hours. FCC (eluent: 2:3 hexane:PhMe) afforded **241b** (334 mg, 40 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2932 (m), 1783 (s), 1721 (s), 1652 (m), 1504 (s), 1154 (s). δ_H (400 MHz, $CDCl_3$) 5.69 (1H, dtd, *J* = 10.0, 3.5, 2.5 Hz, C**5**-H), 5.54 (1H, ddt, *J* = 10.0, 2.5, 2.5 Hz, C**4**-H), 3.73 (2H, t, *J* = 7.5 Hz, C**1**-H$_2$), 2.22 – 2.13 (1H, m, C**3**-H), 1.99 – 1.93 (2H, m, C**6**-H$_2$), 1.81 (1H, dddd, *J* = 12.5, 6.0, 6.0, 3.0 Hz, C**8**-H), 1.75 – 1.50 (4H, m, C**2**-H$_2$ and C**7**-H$_2$), 1.48 (9H, s, OC(CH$_3$)$_3$), 1.24 (1H, dddd, *J* = 12.5, 11.0, 8.5, 3.0 Hz, C**8**-H'). δ_C (101 MHz, $CDCl_3$) 154.7 (Boc C=O), 130.8 (C**4**), 127.9 (C**5**), 83.4 (OC(CH$_3$)$_3$), 49.0 (C**1**), 33.2 (C**2**), 32.6 (C**3**), 28.8 (C**8**), 28.2 (OC(CH$_3$)$_3$), 25.4 (C**6**), 21.4 (C**7**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.4 – -136.6 (2F, m), -146.6 (1F, tt, *J* = 21.0, 4.5 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{20}H_{22}F_5NNaO_4$: 458.1361. Found $[M+Na]^+$: 458.1350.

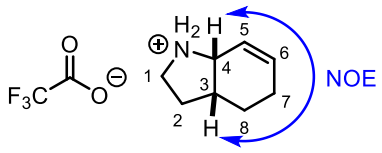
***tert*-Butyl (3a*R**,7a*S**)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (242b)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **243b** (45.7 mg, 0.105 mmol) was employed. FCC (eluent: 59:1 pentane:acetone) afforded **242b** (18.2 mg, 78 %) as a colourless oil. *The Boc group of **242b** was removed to confirm that the presence of two sets of signals are due to the presence of two rotamers rather than two alkene isomers, details of this are given below. This compound exists as an approximately 3:2 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 2925 (m), 1690 (s), 1388 (s), 1114 (s). δ_H (500 MHz, $CDCl_3$) 5.92 (0.4H, br d, *J* = 10.5 Hz, B: C**5**-H), 5.77 (0.6H, br d, *J* = 10.5 Hz, A: C**5**-H), 5.75 – 5.69 (1H, m, A and B: C**6**-H), 4.23 (0.4H, br s, B: C**4**-H), 4.13 (0.6H, br s, A: C**4**-H), 3.49 – 3.27 (2H, m, A and B: C**1**-H$_2$), 2.39 (1H, br s, A and B: C**3**-H), 2.10 – 1.92 (2H, m, A and B: C**7**-H$_2$), 1.85 – 1.72 (3H, m, A and B: C**2**-H$_2$ and C**8**-H), 1.71 – 1.63 (1H, m, A and B: C**8**-H'), 1.49 (5.4H, s, A: OC(CH$_3$)$_3$), 1.48 (3.6H, s, B: OC(CH$_3$)$_3$). δ_C (126 MHz, $CDCl_3$) 154.8 (A and B: C=O), 127.6 (A: C**6**), 127.3 (B: C**6**), 127.0 (A: C**5**), 126.7 (B: C**5**), 79.2 (A: OC(CH$_3$)$_3$), 79.0 (B: OC(CH$_3$)$_3$), 55.1 (A: C**4**), 54.9 (B: C**4**), 45.4 (B: C**1**), 45.0 (A: C**1**), 36.6 (A: C**3**), 35.8 (B: C**3**), 28.7 (A and B: OC(CH$_3$)$_3$), 27.3

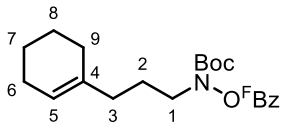
(B: C**2**), 26.5 (A: C**2**), 22.8 (A and B: C**8**), 2 × 20.9 (A and B: C**7**). HRMS: (ESI$^+$) Calculated for $C_{13}H_{21}NNaO_2$: 246.1465. Found $[M+Na]^+$: 246.1470.

(3a*R,7a*S**)-2,3,3a,4,5,7a-Hexahydro-1*H*-indol-1-ium trifluoroacetate**



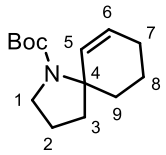
General procedure Q: Pyrrolidine **242b** (12.3 mg, 55.1 μmol) was employed to afford the title compound (12.4 mg, 95 %) as a pale-yellow oil. *The product was assigned as the cis diastereomer based on the observed NOE correlation between the C**3** and the C**4** protons.* ν_{max} / cm^{-1}: (*film*) 3425 (br s), 2936 (m), 1673 (s), 1429 (m), 1201 (s). δ_H (400 MHz, $CDCl_3$) 10.07 (1H, br s, NH), 8.98 (1H, br s, NH'), 6.16 – 6.10 (1H, m, C**6**-H), 5.75 (1H, dddd, *J* = 10.5, 4.0, 2.0, 2.0 Hz, C**5**-H), 3.96 (1H, br s, C**4**-H), 3.38 (1H, br s, C**1**-H), 3.28 (1H, br s, C**1**-H'), 2.55 – 2.41 (1H, m, C**3**-H), 2.24 – 2.11 (2H, m, C**2**-H and C**7**-H), 2.08 – 1.93 (1H, m, C**7**-H'), 1.86 (1H, dddd, *J* = 13.5, 8.5, 5.5, 5.5 Hz, C**2**-H'), 1.76 (1H, dddd, *J* = 13.5, 5.0, 5.0, 5.0 Hz, C**8**-H), 1.58 (1H, dddd, *J* = 13.5, 10.0, 8.0, 5.5 Hz, C**8**-H'). δ_C (101 MHz, $CDCl_3$) 135.3 (C**6**), 120.3 (C**5**), 56.3 (C**4**), 43.0 (C**1**), 35.1 (C**3**), 28.5 (C**2**), 22.8 (C**8**), 22.6 (C**7**). *The ^{13}C signals corresponding to the trifluoroacetate counterion could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -75.7 (3F, s). HRMS: (ESI$^+$) Calculated for $C_8H_{14}N$: 124.1121. Found $[M–F_3CCO_2]^+$: 124.1120.

***tert*-Butyl (3-(cyclohex-1-en-1-yl)propyl)((pentafluorobenzoyl)oxy)carbamate (271)**



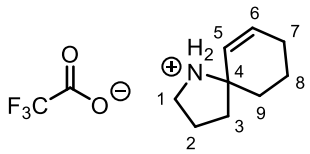
General procedure O: 3-(Cyclohex-1-en-1-yl)propan-1-ol (Section 7.3, 280 mg, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 16 hours. FCC (gradient elution: 3:7 – 0:1 hexane:PhMe) afforded **271** (561 mg, 62 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2932 (m), 1783 (s), 1721 (s), 1652 (m), 1505 (s), 1326 (s), 1150 (s). δ_H (400 MHz, $CDCl_3$) 5.44 – 5.39 (1H, m, C**5**-H), 3.64 (2H, t, *J* = 7.5 Hz, C**1**-H_2), 2.03 – 1.94 (4H, m, C**3**-H_2 and C**6**-H_2), 1.93 – 1.87 (2H, m, C**9**-H_2), 1.74 (2H, tt, *J* = 7.5, 7.5 Hz, C**2**-H_2), 1.65 – 1.58 (2H, m, C**8**-H_2), 1.57 – 1.51 (2H, m, C**7**-H_2), 1.49 (9H, s, OC(CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 154.7 (Boc C=O), 136.5 (C**4**), 121.9 (C**5**), 83.3 (O$C(CH_3)_3$), 50.9 (C**1**), 34.9 (C**3**), 28.3 (C**9**), 28.2 (OC(CH_3)$_3$), 25.4 (C**6**), 24.9 (C**2**), 23.1 (C**8**), 22.6 (C**7**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.4 – -136.8 (2F, m), -146.7 (1F, tt, *J* = 21.0, 5.0 Hz), -159.4 – -159.6 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{21}H_{24}F_5NNaO_4$: 472.1518. Found $[M+Na]^+$: 472.1514.

***tert*-Butyl 1-azaspiro[4.5]dec-6-ene-1-carboxylate (272)**



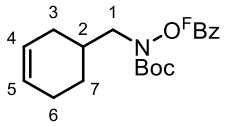
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **271** (47.2 mg, 0.105 mmol) was employed. FCC (eluent: 39:1 PhMe:EtOAc) afforded **272** (20.3 mg, 81 %) as a colourless oil. *The Boc group of **272** was removed to confirm that the presence of two sets of signals is due to the presence of two rotamers, rather than two alkene isomers. Details of this are given below. This compound exists as an approximately 13:7 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 2969 (m), 2927 (m), 1683 (s), 1380 (s), 1159 (s). δ_H (500 MHz, $CDCl_3$) 5.79 – 5.70 (0.35H, m, B: C**5**-H), 5.68 – 5.60 (0.65H, m, A: C**5**-H), 5.51 (0.35H, br d, *J* = 10.0 Hz, B: C**6**-H), 5.41 (0.65H, br d, *J* = 10.0 Hz, A: C**6**-H), 3.61 – 3.45 (1H, m, A and B: C**1**-H), 3.43 – 3.31 (1H, m, A and B: C**1**-H'), 2.39 – 2.27 (0.35H, m, B: C**9**-H), 2.22 – 2.09 (1H, m, A: C**9**-H and B: C**7**-H), 2.00 – 1.88 (2.65H, m, A: C**3**-H and C**7**-H_2, B: C**3**-H and C**7**-H'), 1.84 – 1.71 (4H, m, A and B: C**2**-H_2, C**3**-H' and C**8**-H), 1.65 – 1.50 (2H, m, A and B: C**8**-H' and C**9**-H'), 1.45 (9H, s, A and B: $OC(CH_3)_3$). δ_C (126 MHz, $CDCl_3$) 154.6 (A: C=O), 153.3 (B: C=O), 134.7 (A: C**6**), 134.1 (B: C**6**), 126.6 (B: C**5**), 126.0 (A: C**5**), 79.2 (A: $OC(CH_3)_3$), 78.8 (B: $OC(CH_3)_3$), 62.3 (A and B: C**4**), 47.9 (B: C**1**), 47.6 (A: C**1**), 40.1 (A: C**3**), 39.3 (B: C**3**), 32.1 (A: C**9**), 30.9 (B: C**9**), 28.8 (B: $OC(CH_3)_3$), 28.5 (A: $OC(CH_3)_3$), 24.5 (A: C**7**), 24.2 (B: C**7**), 22.5 (B: C**2**), 22.0 (A: C**2**), 21.9 (A: C**8**), 21.6 (B: C**8**). HRMS: (ESI^+) Calculated for $C_{14}H_{23}NNaO_2$: 260.1621. Found $[M+Na]^+$: 260.1626.

1-Azaspiro[4.5]dec-6-en-1-ium trifluoroacetate



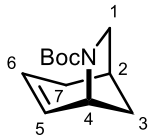
General procedure Q: Pyrrolidine **272** (17.3 mg, 72.9 μmol) was employed to afford the title compound (17.7 mg, 97 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3422 (br s), 2946 (m), 1671 (s), 1431 (m), 1201 (s). δ_H (400 MHz, $CDCl_3$) 9.25 (2H, br s, NH_2), 6.00 (1H, dt, *J* = 10.0, 4.0 Hz, C**6**-H), 5.70 (1H, d, *J* = 10.0 Hz, C**5**-H), 3.44 – 3.24 (2H, m, C**1**-H_2), 2.17 – 1.89 (7H, m, C**2**-H_2, C**3**-H_2, C**7**-H_2 and C**9**-H), 1.85 – 1.61 (3H, m, C**8**-H_2 and C**9**-H'). δ_C (101 MHz, $CDCl_3$) 134.0 (C**6**), 126.0 (C**5**), 65.6 (C**4**), 44.0 (C**1**), 37.6 (C**3**), 31.8 (C**9**), 24.6 (C**7**), 22.8 (C**2**), 19.5 (C**8**). *The ^{13}C signals corresponding to the trifluoroacetate counterion could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -75.6 (3F, s). HRMS: (ESI^+) Calculated for $C_9H_{16}N$: 138.1277. Found $[M–F_3CCO_2]^+$: 138.1283.

***tert*-Butyl (cyclohex-3-en-1-ylmethyl)((pentafluorobenzoyl)oxy)carbamate (273)**



General procedure O: Cyclohex-3-en-1-ylmethanol (Section 7.3, 224 mg, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 21 hours. FCC (eluent: 2:3 hexane:PhMe) afforded **273** (451 mg, 54 %) as a low-melting solid. ν_{max} / cm^{-1}: (*film*) 3026 (m), 2920 (m), 1784 (s), 1720 (s), 1652 (m), 1504 (s), 1326 (s), 1152 (s). δ_H (400 MHz, $CDCl_3$) 5.72 – 5.61 (2H, m, C**4**-H and C**5**-H), 3.68 – 3.55 (2H, m, C**1**-H$_2$), 2.21 – 2.11 (1H, m, C**3**-H), 2.11 – 2.02 (2H, m, C**6**-H$_2$), 2.02 – 1.92 (1H, m, C**2**-H), 1.88 – 1.73 (2H, m, C**3**-H' and C**7**-H), 1.49 (9H, s, OC(CH$_3$)$_3$), 1.39 – 1.27 (1H, m, C**7**-H'). δ_C (101 MHz, $CDCl_3$) 154.7 (Boc C=O), 127.2 (C**5**), 125.6 (C**4**), 83.3 (OC(CH$_3$)$_3$), 56.3 (C**1**), 32.1 (C**2**), 29.2 (C**3**), 28.2 (OC(CH$_3$)$_3$), 26.1 (C**7**), 24.5 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.2 – -136.6 (2F, m), -146.5 (1F, tt, *J* = 21.0, 5.0 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{19}H_{20}F_5NNaO_4$: 444.1205. Found $[M+Na]^+$: 444.1207.

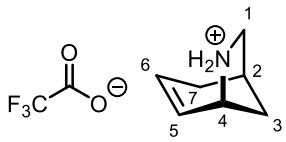
***tert*-Butyl (1*R**,5*R**)-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylate (274)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **273** (44.2 mg, 0.105 mmol) was employed. FCC (eluent: 49:1 PhMe:EtOAc) afforded **274** (14.0 mg, 64 %) as a pale-yellow oil. *The Boc group of **274** was removed to confirm that the presence of two sets of signals are due to the presence of two rotamers rather than two alkene isomers, details of this are given below. This compound exists as an approximately 3:2 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 2928 (m), 1690 (s), 1397 (s), 1099 (s). δ_H (400 MHz, $CDCl_3$) 6.18 (0.4H, dd, *J* = 8.0, 7.0 Hz, B: C**5**-H), 6.07 (0.6H, dd, *J* = 7.5, 7.5 Hz, A: C**5**-H), 5.60 – 5.51 (1H, m, A and B: C**6**-H), 4.26 – 4.20 (0.4H, m, B: C**4**-H), 4.13 – 4.06 (0.6H, m, A: C**4**-H), 3.56 – 3.46 (1H, m, A and B: C**1**-H), 3.22 (0.6H, br d, *J* = 11.0 Hz, A: C**1**-H'), 3.14 (0.4H, br d, *J* = 11.0 Hz, B: C**1**-H'), 2.57 – 2.42 (2H, m, A and B: C**2**-H and C**7**-H), 2.09 (1H, br d, *J* = 18.0 Hz, A and B: C**7**-H'), 1.90 – 1.77 (1H, m, A and B: C**3**-H), 1.73 (1H, br d, *J* = 10.5 Hz, A and B: C**3**-H'), 1.45 (9H, s, A and B: OC(CH$_3$)$_3$). δ_C (126 MHz, $CDCl_3$) 154.2 (A: C=O), 153.8 (B: C=O), 131.7 (B: C**5**), 131.4 (A: C**5**), 127.4 (A: C**6**), 127.1 (B: C**6**), 79.0 (A and B: OC(CH$_3$)$_3$), 53.1 (B: C**1**), 52.9 (A: C**1**), 51.6 (A: C**4**), 50.8 (B: C**4**), 2 × 35.4 (A and B: C**7**), 34.5 (A:

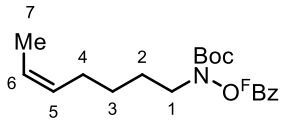
C**3**), 34.0 (B: C**3**), 33.2 (B: C**2**), 32.4 (A: C**2**), 28.7 (A and B: OC(CH_3)$_3$). HRMS: (ESI$^+$) Calculated for $C_{12}H_{19}NNaO_2$: 232.1308. Found [M+Na]$^+$: 232.1315.

(1*R,5*R**)-6-Azabicyclo[3.2.1]oct-3-en-6-ium trifluoroacetate**



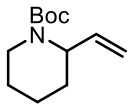
General procedure Q: Pyrrolidine **274** (4.8 mg, 22.9 μmol) was employed to afford the title compound (4.5 mg, 88 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3415 (br s), 2981 (m), 1674 (s), 1430 (m), 1201 (s). δ_H (500 MHz, $CDCl_3$) 9.64 (1H, br s, NH), 9.34 (1H, br s, NH'), 5.99 – 5.92 (1H, m, C**5**-H), 5.92 – 5.86 (1H, m, C**6**-H), 4.12 – 4.02 (1H, m, C**4**-H), 3.57 – 3.46 (1H, m, C**1**-H), 3.27 – 3.18 (1H, m, C**1**-H'), 2.78 – 2.69 (1H, m, C**2**-H), 2.56 (1H, br d, *J* = 19.0 Hz, C**7**-H), 2.19 (1H, br d, *J* = 19.0 Hz, C**7**-H'), 2.11 – 2.05 (1H, m, C**3**-H), 1.96 (1H, d, *J* = 12.0 Hz, C**3**-H'). δ_C (126 MHz, $CDCl_3$) 132.2 (C**6**), 125.7 (C**5**), 52.6 (C**4**), 50.4 (C**1**), 35.3 (C**7**), 32.8 (C**3**), 32.5 (C**2**). *The ^{13}C signals corresponding to the trifluoroacetate counterion could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -75.6 (3F, s). HRMS: (ESI$^+$) Calculated for $C_7H_{12}N$: 110.0964. Found [M–F_3CCO_2]$^+$: 110.0969.

***tert*-Butyl (*Z*)-hept-5-en-1-yl((pentafluorobenzoyl)oxy)carbamate (275a)**



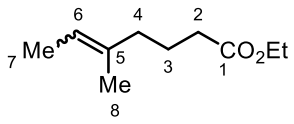
General procedure O: Alcohol **(*Z*)-189** (Section 7.3, 228 mg, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 18 hours. FCC (eluent: 1:4 hexane:PhMe) afforded **275a** (520 mg, 61 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2936 (m), 1783 (s), 1721 (s), 1652 (m), 1505 (s), 1153 (s). δ_H (400 MHz, $CDCl_3$) 5.50 – 5.41 (1H, m, C**6**-H), 5.42 – 5.29 (1H, m, C**5**-H), 3.68 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 2.07 (2H, dt, *J* = 7.5, 7.5 Hz, C**4**-H_2), 1.65 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2), 1.60 (3H, d, *J* = 6.5 Hz, C**7**-H_3), 1.49 (9H, s, OC(CH_3)$_3$), 1.44 (2H, tt, *J* = 7.5, 7.5 Hz, C**3**-H_2). δ_C (101 MHz, $CDCl_3$) 154.8 (Boc C=O), 130.1 (C**5**), 124.5 (C**6**), 83.4 (OC(CH$_3$)$_3$), 51.0 (C**1**), 28.2 (OC(CH_3)$_3$), 26.6 (C**2**), 2 × 26.5 (C**3** and C**4**), 12.9 (C**7**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.4 – -136.6 (2F, m), -146.6 (1F, tt, *J* = 20.5, 5.5 Hz), -159.3 – -159.5 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{19}H_{22}F_5NNaO_4$: 446.1361. Found [M+Na]$^+$: 446.1367.

***tert*-Butyl 2-vinylpiperidine-1-carboxylate (276a)**



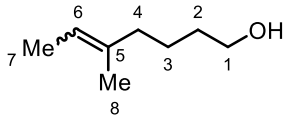
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; dioxane (0.4 M); 130 °C; 24 hours. Substrate **275a** (102 mg, 0.240 mmol) was employed. FCC (*two times*, first eluent: 79:1 pentane:acetone; second, gradient elution: 1:0:0 – 0:1:0 – 0:0:1 PhMe:pentane:Et_2O) afforded **276a** (15.0 mg, 30 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.75 (1H, ddd, *J* = 17.5, 10.5, 4.0 Hz), 5.17 (1H, ddd, *J* = 10.5, 1.5, 1.5 Hz), 5.03 (1H, ddd, *J* = 17.5, 1.5, 1.0 Hz), 4.78 (1H, br s), 3.94 (1H, br d, *J* = 13.0 Hz), 2.82 (1H, ddd, *J* = 13.0, 13.0, 3.0 Hz), 1.78 – 1.32 (6H, m), 1.45 (9H, s). δ_C (101 MHz, $CDCl_3$) 155.6, 137.0, 115.6, 79.4, 52.6, 39.8, 29.1, 28.6, 25.7, 19.6. *The spectroscopic properties were consistent with the data available in the literature.*[273]

Ethyl 5-methylhept-5-enoate



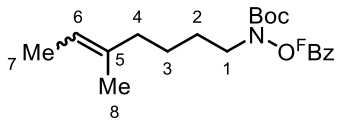
To a suspension of ethyltriphenylphosphonium bromide (6.68 g, 18.0 mmol) in anhydrous THF (140 mL) at 0 °C was added KHMDS (1.0 M in THF, 18.0 mL, 18.0 mmol). The reaction mixture was stirred at 0 °C for 1 hour before addition of ethyl 4-acetylbutyrate (1.92 mL, 50.0 mmol). The reaction mixture was stirred at room temperature for 23 hours before addition of acetone (10 mL). The reaction mixture was filtered through silica, eluted with Et_2O, and the filtrate was concentrated *in vacuo*. FCC (gradient elution: 29:1 – 19:1 hexane:Et_2O) afforded the title compound (1.00 g, 49 %, 1.2:1 mixture of alkene isomers A and B) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2933 (m), 1734 (s), 1447 (m), 1147 (s). δ_H (400 MHz, $CDCl_3$) 5.27 – 5.17 (1H, m, A and B: C**6**-H), 4.12 (1.1H, q, *J* = 7.0 Hz, A: OC$H_2$$CH_3$), 4.11 (0.9H, q, *J* = 7.0 Hz, B: OC$H_2$$CH_3$), 2.27 (1.1H, t, *J* = 7.5 Hz, A: C**2**-H_2), 2.24 (0.9H, t, *J* = 7.5 Hz, B: C**2**-H_2), 2.06 (1.1H, t, *J* = 7.5 Hz, A: C**4**-H_2), 1.99 (0.9H, t, *J* = 7.5 Hz, B: C**4**-H_2), 1.71 (2H, tt, *J* = 7.5, 7.5 Hz, A and B: C**3**-H_2), 1.67 – 1.65 (1.65H, m, A: C**8**-H_3), 1.59 – 1.52 (4.35H, m, A: C**7**-H_3; B: C**7**-H_3 and C**8**-H_3), 2 × 1.25 (1.65H, t, *J* = 7.0 Hz, A: OCH_2CH_3 and 1.35H, t, *J* = 7.0 Hz, B: OCH_2CH_3). δ_C (101 MHz, $CDCl_3$) 174.0 (B: C**1**), 173.9 (A: C**1**), 135.1 (A: C**5**), 134.9 (B: C**5**), 120.1 (A: C**6**), 119.4 (B: C**6**), 2 × 60.3 (A and B: O$CH_2$$CH_3$), 39.1 (B: C**4**), 34.0 (A: C**2**), 33.9 (B: C**2**), 30.7 (A: C**4**), 23.3 (A: C**8**), 23.2 (B: C**3**), 23.1 (A: C**3**), 15.5 (B: C**8**), 2 × 14.4 (A and B: OCH_2CH_3), 13.5 (B: C**7**), 13.4 (A: C**7**). HRMS: (ESI^+) Calculated for $C_{10}H_{18}NaO_2$: 193.1199. Found $[M+Na]^+$: 193.1189.

5-Methylhept-5-en-1-ol (277)



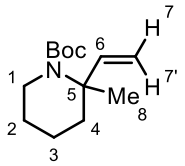
General procedure I: The preceding ester (935 mg, 5.49 mmol) was employed, using anhydrous Et_2O as the solvent and 0.8 eq. $LiAlH_4$ (1.0 M in Et_2O). Alcohol **277** (607 mg, 86 %, 1.2:1 mixture of alkene isomers A and B) was isolated as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3326 (br s), 2932 (m), 2861 (m), 1452 (m), 1056 (s). δ_H (400 MHz, $CDCl_3$) 5.25 – 5.17 (1H, m, A and B: C**6**-H), 3.65 (2H, dt, *J* = 6.0, 6.0 Hz, A and B: C**1**-H_2), 2.05 (1.1H, t, *J* = 7.5 Hz, A: C**4**-H), 2.00 (0.9H, t, *J* = 7.5 Hz, B: C**4**-H), 1.68 – 1.65 (1.65H, m, A: C**8**-H_3), 1.61 – 1.40 (8.35H, m, A: C**2**-H_2, C**3**-H_2 and C**7**-H_3, B: C**2**-H_2, C**3**-H_2, C**7**-H_3 and C**8**-H_3), 1.32 (1H, br s, A and B: OH). δ_C (101 MHz, $CDCl_3$) 135.9 (A: C**5**), 135.7 (B: C**5**), 119.3 (A: C**6**), 118.7 (B: C**6**), 2 × 63.1 (A and B: C**1**), 39.5 (B: C**4**), 32.7 (A: C**2**), 32.5 (B: C**2**), 31.2 (A: C**4**), 24.1 (B: C**3**), 24.0 (A: C**3**), 23.4 (A: C**8**), 15.6 (B: C**8**), 13.5 (B: C**7**), 13.4 (A: C**7**). HRMS: ($MALDI^-$) Calculated for $C_8H_{16}ClO$: 163.0895. Found $[M+Cl]^-$: 163.0891.

***tert*-Butyl (5-methylhept-5-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (278)**



General procedure O: Alcohol **277** (573 mg, 4.47 mmol) was employed with $BocNHO^FBz$ (*vide supra*). The reaction time was 7 hours. FCC (eluent: 3:7 hexane:PhMe) afforded **278** (1.22 g, 62 %, 1.2:1 mixture of alkene isomers A and B) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2935 (m), 1783 (s), 1721 (s), 1652 (m), 1505 (s), 1151 (s). δ_H (400 MHz, $CDCl_3$) 5.25 – 5.16 (1H, m, A and B: C**6**-H), 3.71 – 3.64 (2H, m, A and B: C**1**-H_2), 2.05 (1.1H, t, *J* = 7.5 Hz, A: C**4**-H_2), 2.00 (0.9H, t, *J* = 7.5 Hz, B: C**4**-H_2), 1.68 – 1.52 (8H, m, A and B: C**2**-H_2, C**7**-H_3 and C**8**-H_3), 1.52 – 1.41 (11H, m, A and B: C**3**-H_2 and $OC(CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 2 × 154.8 (A and B: C=O), 135.6 (A: C**5**), 135.3 (B: C**5**), 119.5 (A: C**6**), 118.9 (B: C**6**), 83.4 (A: $OC(CH_3)_3$), 83.3 (B: $OC(CH_3)_3$), 2 × 51.0 (A and B: C**1**), 39.2 (B: C**4**), 30.9 (A: C**4**), 2 × 28.2 (A and B: $OC(CH_3)_3$), 26.8 (A: C**2**), 26.5 (B: C**2**), 24.8 (B: C**3**), 24.7 (A: C**3**), 23.4 (A: C**8**), 15.5 (B: C**8**), 2 × 13.4 (A and B: C**7**). *The ^{13}C signals corresponding to the pentafluorobenzoate group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.4 – -136.8 (2F, m), -146.7 – -146.8 (1F, m), -159.4 – -159.6 (2F, m). HRMS: (ESI^+) Calculated for $C_{20}H_{24}F_5NNaO_4$: 460.1518. Found $[M+Na]^+$: 460.1513.

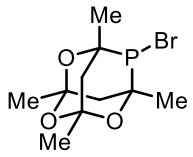
***tert*-Butyl 2-methyl-2-vinylpiperidine-1-carboxylate (279)**



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 20 mol% ligand **L6** (*vide supra*); 100 mol% Et_3N; dioxane (0.4 M); 130 °C; 24 hours. Substrate **278** (45.9 mg, 0.105 mmol) was employed. FCC (eluent: 69:1 pentane:acetone) afforded a 5:1 mixture of **279** and 1,3,5-trimethoxybenzene (4.0 mg, 15 % yield of **279**) as a colourless oil. *Spectroscopic data for **279**:* ν_{max} / cm^{-1}: (*film*) 2931 (m), 1684 (s), 1604 (m), 1456 (m), 1365 (s), 1152 (s). δ_H (500 MHz, $CDCl_3$) 5.99 (1H, dd, *J* = 17.5, 11.0 Hz, C**6**-H), 4.90 (1H, dd, *J* = 11.0, 1.0 Hz, C**7**-H), 4.89 (1H, dd, *J* = 17.5, 1.0 Hz, C**7**-H'), 3.65 – 3.59 (1H, m, C**1**-H), 3.28 – 3.22 (1H, m, C**1**-H'), 1.67 – 1.45 (6H, m, C**2**-H_2, C**3**-H_2 and C**4**-H_2), 1.44 (3H, s, C**8**-H_3), 1.42 (9H, s, OC(CH_3)$_3$). δ_C (126 MHz, $CDCl_3$) 156.4 (C=O), 147.0 (C**6**), 108.7 (C**7**), 79.8 (OC(CH_3)$_3$), 58.4 (C**5**), 41.6 (C**1**), 39.2 (C**4**), 28.6 (OC(CH_3)$_3$), 24.3 (C**2**), 22.4 (C**8**), 19.1 (C**3**). HRMS: (ESI^+) Calculated for $C_{13}H_{23}NNaO_2$: 248.1621. Found $[M+Na]^+$: 248.1631.

^{1}H and ^{13}C NMR data for 1,3,5-trimethoxybenzene: δ_H (500 MHz, $CDCl_3$) 6.09 (3H, s), 3.77 (9H, s). δ_C (126 MHz, $CDCl_3$) 161.7, 93.1, 55.5.

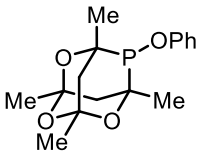
8-Bromo-1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane



This compound was prepared according to a literature procedure.[153] To a solution of 1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane (**248**)[XLIX] (649 mg, 3.00 mmol) in anhydrous CH_2Cl_2 (18 mL, argon sparged) at 0 °C was added a solution of Br_2 (0.17 mL, 3.30 mmol) in anhydrous CH_2Cl_2 (12 mL, argon sparged) dropwise. The reaction mixture was stirred at 0 °C for 30 minutes, then at room temperature for a further 15 hours before being concentrated *in vacuo* to afford the title compound (860 mg, 97 %) as an orange crystalline solid. δ_H (400 MHz, $CDCl_3$) 2.43 (1H, d, *J* = 13.5 Hz), 2.07 (1H, s), 2.02 (1H, d, *J* = 9.5 Hz), 1.63 (1H, dd, *J* = 13.5, 4.5 Hz), 1.43 (3H, d, *J* = 1.5 Hz), 1.42 (3H, s), 1.40 (3H, d, *J* = 1.0 Hz), 1.38 (3H, s). δ_C (101 MHz, $CDCl_3$) 96.8 (d, *J* = 2.0 Hz), 96.0, 74.1 (d, *J* = 27.0 Hz), 73.0 (d, *J* = 42.0 Hz), 44.0 (d, *J* = 19.5 Hz), 35.1, 27.8, 27.3 (d, *J* = 2.0 Hz), 27.2 (d, *J* = 8.0 Hz), 27.0 (d, *J* = 3.5 Hz). δ_P (162 MHz, $CDCl_3$) 52.2. *The spectroscopic properties were consistent with the data available in the literature.*[153]

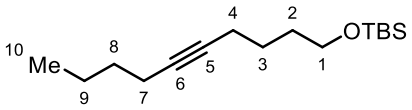
[XLIX] Phosphine **248** was prepared by Charly Faradji (University of Bristol) according to a literature procedure.[147]

1,3,5,7-Tetramethyl-8-phenoxy-2,4,6-trioxa-8-phosphaadamantane (L10)



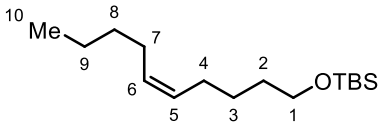
This compound was prepared according to a literature procedure.[153] To a solution of the preceding compound (590 mg, 2.00 mmol) in anhydrous THF (15 mL) at 0 °C was added a solution, prepared at 0 °C, of PhOH (188 mg, 2.00 mmol) and *n*-BuLi (1.6 M in hexane, 1.25 mL, 2.00 mmol) in anhydrous THF (5 mL) dropwise over around 15 minutes. The reaction mixture was stirred at room temperature for 15 hours before being filtered through silica and eluted with CH_2Cl_2. The filtrate was concentrated *in vacuo*. FCC (gradient elution: 1:4 – 0:1 hexane:PhMe) afforded **L10** (230 mg, 37 %) as a colourless crystalline solid. m.p. 85-87 °C (CH_2Cl_2:petrol, *globular*). δ_H (400 MHz, $CDCl_3$) 7.32 – 7.26 (2H, m), 7.12 – 7.07 (2H, m), 7.04 (1H, tt, *J* = 7.5, 1.0 Hz), 2.26 (1H, d, *J* = 13.0 Hz), 1.94 (1H, s), 1.90 (1H, d, *J* = 8.5 Hz), 1.62 (1H, dd, *J* = 13.0, 5.5 Hz), 1.46 (3H, s), 1.44 (3H, d, *J* = 13.0 Hz), 2 × 1.39 (3H, s and 3H, d, *J* = 13.5 Hz). δ_C (101 MHz, $CDCl_3$) 157.8, 129.7, 123.0, 119.1 (d, *J* = 9.5 Hz), 96.3, 96.0, 74.8 (d, *J* = 26.5 Hz), 73.4 (d, *J* = 12.0 Hz), 43.3 (d, *J* = 18.0 Hz), 35.4, 28.0, 27.5, 27.4 (d, *J* = 23.0 Hz), 25.9 (d, *J* = 13.0 Hz). δ_P (162 MHz, $CDCl_3$) 78.7. *The spectroscopic properties were consistent with the data available in the literature.*[153]

***tert*-Butyl(dec-5-yn-1-yloxy)dimethylsilane**



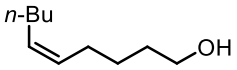
To a solution of dec-5-yn-1-ol (**280**) (771 mg, 5.00 mmol), Et_3N (0.84 mL, 6.00 mmol) and DMAP (30.5 mg, 0.250 mmol) in CH_2Cl_2 at 0 °C was added TBSCl (829 mg, 5.50 mmol). The reaction mixture was stirred at room temperature for 16 hours before addition of saturated aqueous NH_4Cl (15 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 79:1 petrol:EtOAc) afforded the title compound (1.13 g, 84 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2954 (m), 2930 (m), 2858 (m), 1463 (m), 1254 (m), 1103 (s). δ_H (400 MHz, $CDCl_3$) 3.62 (2H, t, *J* = 6.5 Hz, C**1**-$\underline{H}_2$), 2.19 – 2.10 (4H, m, C**4**-$\underline{H}_2$ and C**7**-$\underline{H}_2$), 1.65 – 1.34 (8H, m, C**2**-$\underline{H}_2$, C**3**-$\underline{H}_2$, C**8**-$\underline{H}_2$ and C**9**-$\underline{H}_2$), 0.93 – 0.86 (12H, m, C**10**-$\underline{H}_3$ and $SiC(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2$). δ_C (101 MHz, $CDCl_3$) 80.5 (C**6**), 80.1 (C**5**), 63.0 (C**1**), 32.2 (C**2**), 31.4 (C**8**), 26.1 ($SiC(\underline{C}H_3)_3$), 25.7 (C**3**), 22.1 (C**9**), 18.7 (C**4**), 18.6 (C**7**), 18.5 ($Si\underline{C}(CH_3)_3$), 13.8 (C**10**), -5.1 ($Si(\underline{C}H_3)_2$). HRMS: (ESI^+) Calculated for $C_{16}H_{32}NaOSi$: 291.2115. Found $[M+Na]^+$: 291.2111.

(*Z*)-*tert*-Butyl(dec-5-en-1-yloxy)dimethylsilane



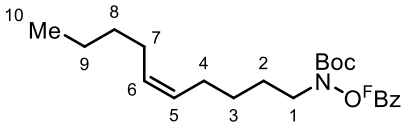
A solution of the preceding alkyne (1.00 g, 3.72 mmol), Lindlar catalyst (39.6 mg, 18.6 μmol) and quinoline (4.5 μL, 37.2 μmol) in petrol (25 mL) was stirred under an atmosphere of H_2 (balloon pressure) for 2 hours. The reaction mixture was filtered through celite, and the filter cake was washed with petrol (25 mL). The filtrate was washed with 1.0 M aqueous HCl, dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (983 mg, 98 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2955 (m), 2928 (m), 2857 (m), 1463 (m), 1254 (m), 1100 (s). δ_H (400 MHz, $CDCl_3$) 5.41 – 5.30 (2H, m, C**5**-H and C**6**-H), 3.61 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.09 – 1.98 (4H, m, C**4**-H_2 and C**7**-H_2), 1.59 – 1.48 (2H, m, C**2**-H_2), 1.42 – 1.27 (6H, m, C**3**-H_2, C**8**-H_2 and C**9**-H_2), 0.94 – 0.86 (12H, m, C**10**-H_3 and $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$). δ_C (101 MHz, $CDCl_3$) 130.2 (C**6**), 129.8 (C**5**), 63.3 (C**1**), 32.7 (C**2**), 32.1 (C**8**), 2 × 27.1 (C**4** and C**7**), 2 × 26.1 (C**3** and $SiC(CH_3)_3$), 22.5 (C**9**), 18.5 ($SiC(CH_3)_3$), 14.2 (C**10**), -5.1 ($Si(CH_3)_2$). HRMS: (ESI^+) Calculated for $C_{16}H_{34}NaOSi$: 293.2271. Found $[M+Na]^+$: 293.2276.

(*Z*)-Dec-5-en-1-ol ((*Z*)-281)



General procedure M: The preceding silyl ether (991 mg, 3.66 mmol) was employed with 1.5 eq. TBAF. The reaction time was 2.5 hours. FCC (eluent: 4:1 hexane:EtOAc) afforded **(*Z*)-281** (460 mg, 80 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.42 – 5.28 (2H, m), 3.63 (2H, t, *J* = 6.5 Hz), 2.09 – 1.98 (4H, m), 1.62 – 1.52 (3H, m), 1.41 (2H, tt, *J* = 7.5, 6.5 Hz), 1.34 – 1.26 (4H, m), 0.92 – 0.86 (3H, m). δ_C (101 MHz, $CDCl_3$) 130.5, 129.4, 63.0, 32.5, 32.0, 27.1, 27.0, 26.0, 22.5, 14.1. *The spectroscopic properties were consistent with the data available in the literature*.[274,275]

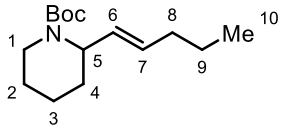
***tert*-Butyl (*Z*)-dec-5-en-1-yl((pentafluorobenzoyl)oxy)carbamate ((*Z*)-282a)**



General procedure O: Alcohol **(*Z*)-281** (932 mg, 5.96 mmol) was employed with $BocNHO^FBz$ (*vide supra*). The reaction time was 16 hours. FCC (eluent: 2:3 hexane:PhMe) afforded **(*Z*)-282a** (1.89 g, 68 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2932 (m), 1784 (s), 1721 (s), 1652 (m), 1505 (s), 1153 (s). δ_H (400 MHz, $CDCl_3$) 5.42 – 5.28 (2H, m, C**5**-H and C**6**-H), 3.68 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 2.11 –

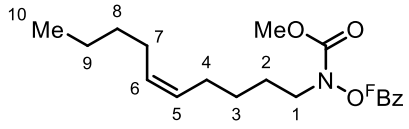
1.97 (4H, m, C**4**-H$_2$ and C**7**-H$_2$), 1.65 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H$_2$), 1.49 (9H, s, OC(CH$_3$)$_3$), 1.47 – 1.38 (2H, m, C**3**-H$_2$), 1.34 – 1.26 (4H, m, C**8**-H$_2$ and C**9**-H$_2$), 0.92 – 0.85 (3H, m, C**10**-H$_3$). δ_C (101 MHz, $CDCl_3$) 154.7 (Boc C=O), 130.7 (C**6**), 129.1 (C**5**), 83.3 (OC(CH$_3$)$_3$), 51.0 (C**1**), 32.0 (C**8**), 28.2 (OC(CH$_3$)$_3$), 27.1 (C**7**), 26.8 (C**4**), 26.7 (C**3**), 26.6 (C**2**), 22.5 (C**9**), 14.1 (C**10**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.5 – -136.8 (2F, m), -146.7 (1F, tt, *J* = 21.0, 5.0 Hz), -159.4 – -159.7 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{22}H_{28}F_5NNaO_4$: 488.1831. Found $[M+Na]^+$: 488.1831.

***tert*-Butyl (*E*)-2-(pent-1-en-1-yl)piperidine-1-carboxylate (283a)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 17.5 mol% ligand **L3** (*vide supra*); 100 mol% Et_3N; dioxane (0.3 M); 130 °C; 24 hours. Substrate **(*Z*)-282a** (116 mg, 0.250 mmol) was employed. FCC (eluent: 39:1 petrol:EtOAc) afforded **283a** (39.4 mg, 62 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2932 (m), 2861 (m), 1693 (s), 1408 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 5.49 – 5.34 (2H, m, C**6**-H and C**7**-H), 4.72 (1H, br s, C**5**-H), 3.91 (1H, dd, *J* = 13.5, 4.0 Hz, C**1**-H), 2.81 (1H, ddd, *J* = 13.5, 13.0, 3.0 Hz, C**1**-H'), 2.00 (2H, td, *J* = 7.0, 6.0 Hz, C**8**-H$_2$), 1.69 – 1.29 (17H, m, C**2**-H$_2$, C**3**-H$_2$, C**4**-H$_2$, C**9**-H$_2$ and OC(CH$_3$)$_3$), 0.88 (3H, t, *J* = 7.5 Hz, C**10**-H$_3$). δ_C (101 MHz, $CDCl_3$) 155.5 (Boc C=O), 131.7 (C**7**), 128.4 (C**6**), 79.2 (OC(CH$_3$)$_3$), 52.0 (C**5**), 39.7 (C**1**), 34.6 (C**8**), 29.6 (C**4**), 28.6 (OC(CH$_3$)$_3$), 25.7 (C**2**), 22.6 (C**9**), 19.6 (C**3**), 13.7 (C**10**). HRMS: (ESI$^+$) Calculated for $C_{15}H_{27}NNaO_2$: 276.1934. Found $[M+Na]^+$: 276.1948.

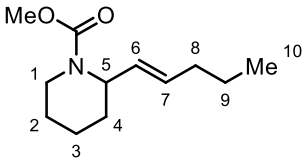
Methyl (*Z*)-dec-5-en-1-yl((pentafluorobenzoyl)oxy)carbamate ((*Z*)-282b)



General procedure O: Alcohol **(*Z*)-281** (195 mg, 1.25 mmol) was employed with MeOC(O)NHO^{F}Bz (*vide supra*). The reaction time was 15 hours. FCC (eluent: 1:9 hexane:PhMe) afforded **(*Z*)-282b** (352 mg, 67 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2931 (m), 1786 (s), 1729 (s), 1652 (m), 1505 (s), 1170 (s). δ_H (400 MHz, $CDCl_3$) 5.42 – 5.28 (2H, m, C**5**-H and C**6**-H), 3.81 (3H, s, OCH$_3$), 3.73 (2H, t, *J* = 7.0 Hz, C**1**-H$_2$), 2.11 – 1.93 (4H, m, C**4**-H$_2$ and C**7**-H$_2$), 1.66 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H$_2$), 1.43 (2H, tt, *J* = 7.5, 7.5 Hz, C**3**-H$_2$), 1.37 – 1.24 (4H, m, C**8**-H$_2$ and C**9**-H$_2$), 0.93 – 0.83 (3H, m, C**10**-H$_3$). δ_C (101 MHz, $CDCl_3$) 156.2 (Boc C=O), 130.8 (C**6**), 129.0 (C**5**), 54.1 (OCH$_3$), 51.3 (C**1**), 32.0 (C**8**), 27.1 (C**7**), 26.8 (C**4**), 2 × 26.6 (C**2** and C**3**), 22.5 (C**9**), 14.1 (C**10**). *The ^{13}C signals corresponding to*

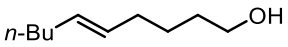
the pentafluorobenzoyl group could not be resolved due to their weak intensity. δ_F (377 MHz, $CDCl_3$) -136.0 – -136.2 (2F, m), -146.2 (1F, tt, *J* = 21.0, 5.5 Hz), -159.3 – -159.5 (2F, m). HRMS: (ESI^+) Calculated for $C_{19}H_{22}F_5NNaO_4$: 446.1361. Found $[M+Na]^+$: 446.1362.

Methyl (*E*)-2-(pent-1-en-1-yl)piperidine-1-carboxylate (283b)



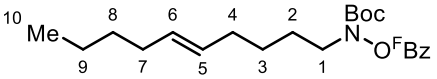
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 17.5 mol% ligand **L3** (*vide supra*); 100 mol% Et_3N; dioxane (0.3 M); 130 °C; 24 hours. Substrate **(*Z*)-282b** (106 mg, 0.250 mmol) was employed. FCC (*two times*, first eluent: 29:1 petrol:acetone; second eluent: 149:1 PhMe:acetone) afforded **283b** (17.4 mg, 33 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2933 (m), 2861 (m), 1699 (s), 1444 (s), 1261 (s). δ_H (400 MHz, $CDCl_3$) 5.48 (1H, dtd, *J* = 15.5, 7.0, 1.5 Hz, C**7**-H), 5.39 (1H, dd, *J* = 15.5, 4.5 Hz, C**6**-H), 4.78 (1H, br s, C**5**-H), 3.96 (1H, br d, *J* = 13.5 Hz, C**1**-H), 3.68 (3H, s, OCH_3), 2.88 (1H, ddd, *J* = 13.5, 13.0, 3.0 Hz, C**1**-H'), 2.00 (2H, td, *J* = 7.5, 7.0 Hz, C**8**-H_2), 1.74 – 1.48 (5H, m, C**2**-H, C**3**-H_2 and C**4**-H_2), 1.46 – 1.31 (3H, m, C**2**-H' and C**9**-H_2), 0.88 (3H, t, *J* = 7.5 Hz, C**10**-H_3). δ_C (101 MHz, $CDCl_3$) 156.5 (C=O), 132.2 (C**7**), 128.2 (C**6**), 52.6 (OCH_3), 52.1 (C**5**), 40.1 (C**1**), 34.6 (C**8**), 29.6 (C**4**), 25.8 (C**2**), 22.5 (C**9**), 19.6 (C**3**), 13.8 (C**10**). HRMS: (ESI^+) Calculated for $C_{12}H_{22}NO_2$: 212.1645. Found $[M+H]^+$: 212.1645.

(*E*)-Dec-5-en-1-ol ((*E*)-281)



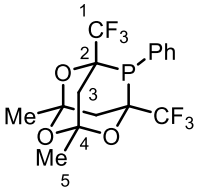
A suspension of dec-5-yn-1-ol (**280**) (1.79 mL, 10.0 mmol) and $LiAlH_4$ (2.28 g, 60.0 mmol) in anhydrous diglyme (70 mL) was heated at reflux for 14 hours before being cooled to 0 °C and diluted with Et_2O (40 mL). The reaction mixture was quenched slowly with water (2.3 mL), 4.0 M aqueous NaOH (2.3 mL) and a further portion of water (6.9 mL). The reaction mixture was stirred at room temperature for 20 minutes before being dried over Na_2SO_4, filtered and concentrated *in vacuo* to remove Et_2O. The crude mixture was dissolved in petrol (200 mL) and washed with water (3 × 200 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford **(*E*)-281** (1.47 g, 94 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.46 – 5.33 (2H, m), 3.64 (2H, t, *J* = 6.5 Hz), 2.06 – 1.91 (4H, m), 1.57 (2H, tt, *J* = 7.0, 6.5 Hz), 1.41 (2H, tt, *J* = 7.0, 7.0 Hz), 1.36 – 1.24 (4H, m), 0.91 – 0.85 (3H, m). δ_C (101 MHz, $CDCl_3$) 131.0, 129.9, 63.1, 3 × 32.4, 32.4, 31.9, 25.9, 22.3, 14.1. *The spectroscopic properties were consistent with the data available in the literature*.[276,277]

***tert*-Butyl (*E*)-dec-5-en-1-yl((pentafluorobenzoyl)oxy)carbamate ((*E*)-282a)**



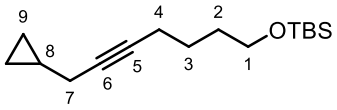
General procedure O: Alcohol **(*E*)-281** (185 mg, 1.18 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 13 hours. FCC (gradient elution: 2:3 – 1:4 hexane:PhMe) afforded **(*E*)-282a** (300 mg, 55 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2931 (m), 1784 (s), 1721 (s), 1652 (m), 1505 (s), 1153 (s). δ_H (400 MHz, $CDCl_3$) 5.46 – 5.30 (2H, m, C**5**-H and C**6**-H), 3.67 (2H, t, *J* = 7.0 Hz, C**1**-H_2), 2.05 – 1.92 (4H, m, C**4**-H_2 and C**7**-H_2), 1.63 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2), 1.49 (9H, s, OC(CH_3)$_3$), 1.42 (2H, tt, *J* = 7.5, 7.5 Hz, C**3**-H_2), 1.36 – 1.23 (4H, m, C**8**-H_2 and C**9**-H_2), 0.90 – 0.83 (3H, m, C**10**-H_3). δ_C (101 MHz, $CDCl_3$) 154.8 (Boc C=O), 131.3 (C**6**), 129.5 (C**5**), 83.3 (OC(CH_3)$_3$), 51.0 (C**1**), 32.4 (C**7**), 32.2 (C**4**), 31.9 (C**8**), 28.2 (OC(CH_3)$_3$), 26.5 (C**3**), 26.4 (C**2**), 22.3 (C**9**), 14.1 (C**10**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.5 – -136.7 (2F, m), -146.7 – -146.8 (1F, m), -159.4 – -159.6 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{22}H_{28}F_5NNaO_4$: 488.1831. Found [M+Na]$^+$: 488.1850.

3,5-Dimethyl-8-phenyl-1,7-bis(trifluoromethyl)-2,4,6-trioxa-8-phosphaadamantane (L18)



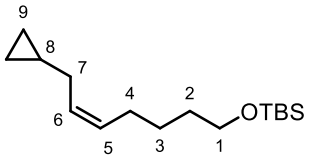
To a solution of 1,1,1-trifluoro-2,4-pentanedione (1.82 mL, 15.0 mmol) in 5.0 M aqueous HCl (10 mL, argon sparged) was added $PhPH_2$ (0.55 mL, 5.00 mmol) dropwise over around 10 minutes. The reaction mixture was stirred at room temperature for 2 days before being diluted with Et_2O (60 mL) and washed with water (2 × 20 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 14:1 petrol:Et_2O) afforded **L18** (156 mg, 8 %) as a colourless crystalline solid. m.p. 94-95 °C (Et_2O:petrol, *needles*). ν_{max} / cm^{-1}: (*solid*) 2994 (m), 2944 (m), 1438 (m), 1384 (m), 1277 (s), 1166 (s). δ_H (400 MHz, $CDCl_3$) 7.91 – 7.82 (2H, m, 2 × ArCH), 7.49 – 7.43 (1H, m, ArCH), 7.42 – 7.35 (2H, m, 2 × ArCH), 2.34 (1H, dd, *J* = 21.0, 13.0 Hz, C**3**-H), 2.32 (1H, d, *J* = 13.5 Hz, C**3'**-H), 2.21 (1H, dd, *J* = 13.0, 7.5 Hz, C**3**-H'), 1.97 (1H, dd, *J* = 13.5, 2.0 Hz, C**3'**-H'), 1.60 (3H, s, C**5'**-H_3), 1.54 (3H, s, C**5**-H_3). δ_C (101 MHz, $CDCl_3$) 135.9 (ArCH), 131.2 (ArCH), 130.6 (d, *J* = 29.0 Hz, ArC), 128.4 (d, *J* = 9.0 Hz, ArCH), 97.3 (C**4**), 96.8 (C**4'**), 36.7 (dq, *J* = 13.5, 2.0 Hz, C**3**), 28.5 (C**3'**), 27.8 (C**5'**), 27.3 (C**5**). *The ^{13}C signals corresponding to C**1** and C**2** could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -77.5 (3F, d, *J* = 15.0 Hz), -79.3 (3F, d, *J* = 16.5 Hz). δ_P (162 MHz, $CDCl_3$) -38.9 (qq, *J* = 16.5, 15.0 Hz). HRMS: (ESI$^+$) Calculated for $C_{16}H_{16}F_6O_3P$: 401.0736. Found [M+H]$^+$: 401.0734.

***tert*-Butyl((7-cyclopropylhept-5-yn-1-yl)oxy)dimethylsilane**



To a solution of alkyne **187** (Section 7.3, 4.25 g, 20.0 mmol) in anhydrous THF (30 mL) and anhydrous DMPU (30 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 8.4 mL, 21.0 mmol). The reaction mixture was stirred at -78 °C for 1.5 hours, then warmed to 0 °C before addition of cyclopropylmethyl bromide (2.52 mL, 26.0 mmol). The reaction mixture was stirred at room temperature for 14 hours before addition of saturated aqueous NH_4Cl (50 mL), brine (50 mL) and Et_2O (100 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 19:1 – 9:1 – 4:1 petrol:PhMe) provided impure material, which was distilled (b.p. 110 °C, 2 mbar) to afford the title compound (1.56 g, 29 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2929 (m), 2857 (m), 1472 (m), 1254 (s), 1104 (s). δ_H (400 MHz, $CDCl_3$) 3.62 (2H, t, *J* = 6.0 Hz, C**1**-$\underline{H}_2$), 2.23 – 2.13 (4H, m, C**4**-$\underline{H}_2$ and C**7**-$\underline{H}_2$), 1.66 – 1.47 (4H, m, C**2**-$\underline{H}_2$ and C**3**-$\underline{H}_2$), 0.92 – 0.85 (1H, m, C**8**-$\underline{H}$), 0.89 (9H, s, SiC($C\underline{H}_3)_3$), 0.48 – 0.40 (2H, m, 2 × C**9**-$\underline{H}$), 0.21 (2H, ddd, *J* = 6.0, 4.5, 4.5 Hz, 2 × C**9**-$\underline{H}$'), 0.05 (6H, s, Si($C\underline{H}_3)_2$). δ_C (101 MHz, $CDCl_3$) 80.5 (C**5**), 78.6 (C**6**), 62.9 (C**1**), 32.1 (C**2**), 26.1 (SiC($\underline{C}H_3)_3$), 25.7 (C**3**), 23.1 (C**7**), 18.7 (C**4**), 18.5 (Si$\underline{C}(CH_3)_3$), 9.8 (C**8**), 3.9 (C**9**), -5.1 (Si($\underline{C}H_3)_2$). HRMS: (MALDI$^-$) Calculated for $C_{16}H_{29}OSi$: 265.1993. Found $[M\text{-}H]^-$: 266.1999.

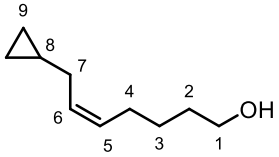
(*Z*)-*tert*-Butyl((7-cyclopropylhept-5-en-1-yl)oxy)dimethylsilane



A solution of the preceding alkyne (1.33 g, 5.00 mmol), Lindlar catalyst (53.2 mg, 25.0 μmol) and quinoline (6.0 μL, 50.0 μmol) in hexane (25 mL) was stirred under an atmosphere of H_2 (balloon pressure) for 3 hours. The reaction mixture was filtered through celite, and the filter cake was rinsed with CH_2Cl_2 (30 mL). The filtrate was concentrated *in vacuo*. FCC (eluent: 24:1 petrol:PhMe) afforded the title compound (1.04 g, 77 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3077 (m), 3006 (m), 2929 (m), 2857 (m), 1472 (m), 1254 (s), 1100 (s). δ_H (400 MHz, $CDCl_3$) 5.51 – 5.33 (2H, m, C**5**-$\underline{H}$ and C**6**-$\underline{H}$), 3.61 (2H, t, *J* = 6.5 Hz, C**1**-$\underline{H}_2$), 2.03 (2H, dt, *J* = 7.5, 7.5 Hz, C**4**-$\underline{H}_2$), 1.96 (2H, dd, *J* = 7.0, 7.0 Hz, C**7**-$\underline{H}_2$), 1.59 – 1.47 (2H, m, C**2**-$\underline{H}_2$), 1.38 (2H, tt, *J* = 7.5, 7.5 Hz, C**3**-$\underline{H}_2$), 0.89 (9H, s, SiC($C\underline{H}_3)_3$), 0.76 – 0.65 (1H, m, C**8**-$\underline{H}$), 0.44 – 0.38 (2H, m, 2 × C**9**-$\underline{H}$), 0.09 – 0.02 (8H, m, 2 × C**9**-$\underline{H}$' and Si($C\underline{H}_3)_2$). δ_C (101 MHz, $CDCl_3$) 130.0 (C**5**), 129.0 (C**6**), 63.3 (C**1**), 32.6 (C**2**), 32.0 (C**7**), 27.2 (C**4**), 26.2 (C**3**),

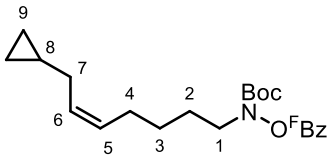
26.1 (SiC($\underline{C}$H$_3$)$_3$), 18.5 (Si$\underline{C}$(CH$_3$)$_3$), 11.1 (C**8**), 4.2 (C**9**), -5.1 (Si($\underline{C}$H$_3$)$_2$). HRMS: (ESI$^+$) Calculated for $C_{16}H_{33}OSi$: 269.2295. Found [M+H]$^+$: 269.2292.

(*Z*)-7-Cyclopropylhept-5-en-1-ol ((*Z*)-284)



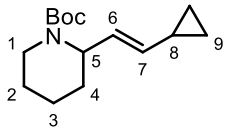
General procedure M: The preceding silyl ether (943 mg, 3.51 mmol) was employed with 1.7 eq. TBAF. The reaction time was 2.5 hours. FCC (eluent: 3:2 petrol:Et$_2$O) afforded **(*Z*)-284** (510 mg, 94 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3328 (br s), 3076 (m), 3005 (m), 2932 (s), 1458 (m), 1427 (m), 1043 (s). δ_H (400 MHz, $CDCl_3$) 5.47 (1H, dtt, *J* = 11.0, 7.0, 1.5 Hz, C**6**-$\underline{H}$), 5.42 – 5.33 (1H, m, C**5**-$\underline{H}$), 3.64 (2H, t, *J* = 6.5 Hz, C**1**-$\underline{H}_2$), 2.05 (2H, br dt, *J* = 7.5, 7.5 Hz, C**4**-$\underline{H}_2$), 1.96 (2H, dd, *J* = 7.0, 7.0 Hz, C**7**-$\underline{H}_2$), 1.63 – 1.52 (2H, m, C**2**-$\underline{H}_2$), 1.46 – 1.36 (2H, m, C**3**-$\underline{H}_2$), 0.77 – 0.64 (1H, m, C**8**-$\underline{H}$), 0.45 – 0.37 (2H, m, 2 × C**9**-$\underline{H}$), 0.09 – 0.03 (2H, m, 2 × C**9**-$\underline{H}$'). δ_C (101 MHz, $CDCl_3$) 129.7 (C**5**), 129.3 (C**6**), 63.1 (C**1**), 32.5 (C**2**), 32.0 (C**7**), 27.1 (C**4**), 26.0 (C**3**), 11.1 (C**8**), 4.2 (C**9**). HRMS: (ESI$^+$) Calculated for $C_{10}H_{18}NaO$: 177.1250. Found [M+Na]$^+$: 177.1238.

***tert*-Butyl (*Z*)-(7-Cyclopropylhept-5-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (285a)**



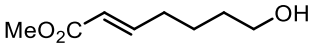
General procedure O: Alcohol **(*Z*)-284** (309 mg, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*)**.** The reaction time was 15 hours. FCC (eluent: 1:1 petrol:PhMe) afforded **285a** (586 mg, 63 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3078 (m), 3006 (m), 2936 (m), 1783 (s), 1721 (s), 1652 (m), 1505 (s), 1153 (s). δ_H (400 MHz, $CDCl_3$) 5.52 – 5.43 (1H, m, C**6**-$\underline{H}$), 5.40 – 5.32 (1H, m, C**5**-$\underline{H}$), 3.67 (2H, t, *J* = 7.0 Hz, C**1**-$\underline{H}_2$), 2.06 (2H, dt, *J* = 7.0, 7.0 Hz, C**4**-$\underline{H}_2$), 1.95 (2H, dd, *J* = 7.0, 7.0 Hz, C**7**-$\underline{H}_2$), 1.64 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-$\underline{H}_2$), 1.49 (9H, s, OC(C$\underline{H}_3$)$_3$), 1.43 (2H, tt, *J* = 7.5, 7.0 Hz, C**3**-$\underline{H}_2$), 0.75 – 0.64 (1H, m, C**8**-$\underline{H}$), 0.44 – 0.37 (2H, m, 2 × C**9**-$\underline{H}$), 0.08 – 0.02 (2H, m, 2 × C**9**-$\underline{H}$'). δ_C (101 MHz, $CDCl_3$) 154.7 (Boc $\underline{C}$=O), 129.5 (C**6**), 129.3 (C**5**), 83.4 (O$\underline{C}$(CH$_3$)$_3$), 50.9 (C**1**), 31.9 (C**7**), 28.2 (OC($\underline{C}$H$_3$)$_3$), 26.9 (C**4**), 26.7 (C**3**), 26.6 (C**2**), 11.0 (C**8**), 4.2 (C**9**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.4 – -136.8 (2F, m), -146.7 (1F, tt, *J* = 21.0, 5.0 Hz), -159.4 – -159.6 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{22}H_{26}F_5NNaO_4$: 486.1674. Found [M+Na]$^+$: 486.1669.

***tert*-Butyl (*E*)-2-(2-cyclopropylvinyl)piperidine-1-carboxylate (286a)**



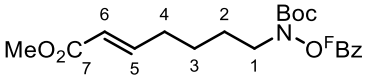
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 17.5 mol% ligand **L3** (*vide supra*); 100 mol% Et_3N; dioxane (0.3 M); 130 °C; 24 hours. Substrate **285a** (116 mg, 0.250 mmol) was employed. FCC (gradient elution: 119:1 – 99:1 petrol:acetone) afforded **286a** (39.4 mg, 63 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2933 (m), 1689 (s), 1408 (s), 1159 (s). δ_H (400 MHz, $CDCl_3$) 5.50 (1H, dd, *J* = 15.5, 5.0 Hz, C**6**-H), 4.98 (1H, ddd, *J* = 15.5, 8.5, 1.5 Hz, C**7**-H), 4.76 – 4.66 (1H, m, C**5**-H), 3.94 – 3.85 (1H, m, C**1**-H), 2.81 (1H, ddd, *J* = 13.0, 13.0, 3.0 Hz, C**1**-H'), 1.70 – 1.30 (16H, m, C**2**-H_2, C**3**-H_2, C**4**-H_2, C**8**-H and OC(CH_3)$_3$), 0.72 – 0.64 (2H, m, 2 × C**9**-H), 0.37 – 0.27 (2H, m, 2 × C**9**-H'). δ_C (101 MHz, $CDCl_3$) 155.5 (C=O), 135.7 (C**7**), 125.8 (C**6**), 79.2 (O*C*(CH_3)$_3$), 52.0 (C**5**), 39.7 (C**1**), 29.6 (C**4**), 28.6 (OC(*C*H_3)$_3$), 25.7 (C**2**), 19.6 (C**3**), 13.7 (C**8**), 6.7 (C**9**). HRMS: (ESI^+) Calculated for $C_{15}H_{25}NNaO_2$: 274.1778. Found $[M+Na]^+$: 274.1785.

Methyl (*E*)-7-hydroxyhept-2-enoate (287)



To a solution of Hoveyda-Grubbs 2nd generation catalyst (31.3 mg, 50.0 μmol) in anhydrous CH_2Cl_2 (60 mL, argon sparged) was added methyl acrylate (4.50 mL, 50.0 mmol) and hex-5-en-1-ol (0.60 mL, 5.00 mmol). The reaction mixture was heated at reflux for 16 hours before being concentrated *in vacuo*. FCC (eluent: 3:2 hexane:EtOAc) afforded **287** (790 mg, 100 %) as a light-brown oil (the colouration was due to the presence of trace amounts of Ru-impurities). δ_H (400 MHz, $CDCl_3$) 6.95 (1H, dt, *J* = 15.5, 7.0 Hz), 5.82 (1H, dt, *J* = 15.5, 1.5 Hz), 3.71 (3H, s), 3.65 – 3.60 (2H, m), 2.25 – 2.19 (2H, m), 1.84 (1H, br s), 1.73 – 1.48 (4H, m). δ_C (101 MHz, $CDCl_3$) 167.3, 149.3, 121.3, 62.6, 51.6, 32.2, 32.0, 24.4. *The spectroscopic properties were consistent with the data available in the literature*.[278]

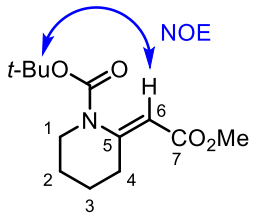
Methyl (*E*)-7-((*tert*-butoxycarbonyl)((pentafluorobenzoyl)oxy)amino)hept-2-enoate (288)



General procedure O: Alcohol **287** (316 mg, 2.00 mmol) was employed with $BocNHO^FBz$ (*vide supra*). The reaction time was 14 hours. FCC (eluent: 49:1 PhMe:EtOAc) afforded **288** (506 mg, 54 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2942 (m), 1782 (s), 1721 (s), 1654 (m), 1504 (s), 1150 (s). δ_H (400 MHz, $CDCl_3$) 6.94 (1H, dt, *J* = 15.5, 7.0 Hz, C**5**-H), 5.83 (1H, dt, *J* = 15.5, 1.5 Hz, C**6**-H), 3.72

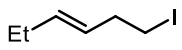
(3H, s, OC<u>H</u>$_3$), 3.69 (2H, t, *J* = 7.0 Hz, C**1**-<u>H</u>$_2$), 2.25 (2H, tdd, *J* = 7.5, 7.0, 1.5 Hz, C**4**-<u>H</u>$_2$), 1.71 – 1.61 (2H, m, C**2**-<u>H</u>$_2$), 1.61 – 1.51 (2H, m, C**3**-<u>H</u>$_2$), 1.49 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 167.1 (C**7**), 154.7 (Boc <u>C</u>=O), 148.8 (C**5**), 121.6 (C**6**), 83.5 (O<u>C</u>(CH$_3$)$_3$), 51.6 (O<u>C</u>H$_3$), 50.6 (C**1**), 31.7 (C**4**), 28.2 (OC(<u>C</u>H$_3$)$_3$), 26.5 (C**2**), 25.0 (C**3**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.4 – -136.7 (2F, m), -146.4 (1F, tt, *J* = 21.0, 5.0 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{20}H_{22}F_5NNaO_6$: 490.1259. Found $[M+Na]^+$: 490.1265.

tert-Butyl (_E_)-2-(2-methoxy-2-oxoethylidene)piperidine-1-carboxylate (289)



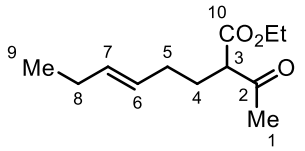
<u>General procedure D:</u> Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **288** (49.1 mg, 0.105 mmol) was employed. FCC (eluent: 79:1 PhMe:EtOAc) afforded **289** (10.3 mg, 38 %) as a colourless oil. *The product was assigned as the (E)-isomer based on the observed NOE correlation between the C**6** and the t-Bu protons.* ν_{max} / cm^{-1}: (*film*) 2947 (m), 1698 (s), 1633 (m), 1367 (s), 1132 (s). δ_H (400 MHz, $CDCl_3$) 5.95 (1H, s, C**6**-<u>H</u>), 3.68 (3H, s, OC<u>H</u>$_3$), 3.62 – 3.57 (2H, m, C**1**-<u>H</u>$_2$), 3.01 – 2.92 (2H, m, C**4**-<u>H</u>$_2$), 1.74 – 1.66 (4H, m, C**2**-<u>H</u>$_2$ and C**3**-<u>H</u>$_2$), 1.47 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 168.1 (C**7**), 156.3 (C**5**), 153.5 (Boc <u>C</u>=O), 110.0 (C**6**), 81.4 (O<u>C</u>(CH$_3$)$_3$), 51.1 (O<u>C</u>H$_3$), 46.1 (C**1**), 28.4 (OC(<u>C</u>H$_3$)$_3$), 27.3 (C**4**), 24.1 (C**2**), 22.9 (C**3**). HRMS: (ESI$^+$) Calculated for $C_{13}H_{21}NNaO_4$: 278.1363. Found $[M+Na]^+$: 278.1369.

(_E_)-1-Iodohex-3-ene



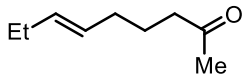
To a solution of PPh_3 (31.5 g, 120 mmol) and imidazole (8.17 g, 120 mmol) in CH_2Cl_2 (125 mL) at 0 °C was added I_2 (30.5 g, 120 mmol) in 9 roughly equal portions over around 30 minutes before addition of (*E*)-hex-3-en-1-ol (12.3 mL, 100 mmol) dropwise. The reaction mixture was stirred at room temperature for 3 hours before being concentrated *in vacuo*, filtered through silica and eluted with pentane. The filtrate was concentrated *in vacuo* to afford the title compound (18.6 g, 89 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.57 (1H, dt, *J* = 15.0, 7.0 Hz), 5.35 (1H, dt, *J* = 15.0, 6.5 Hz), 3.14 (2H, t, *J* = 7.5 Hz), 2.54 (2H, td, *J* = 7.5, 6.5 Hz), 2.01 (2H, qd, *J* = 7.5, 7.0 Hz), 0.98 (3H, t, *J* = 7.5 Hz). δ_C (101 MHz, $CDCl_3$) 135.2, 127.4, 36.9, 25.7, 13.8, 6.3. *The spectroscopic properties were consistent with the data available in the literature*.[279]

Ethyl (*E*)-2-acetyloct-5-enoate



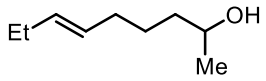
To a suspension of NaH (60 % in mineral oil, 596 mg, 14.9 mmol) in anhydrous DMF (25 mL) at 0 °C was added ethyl acetoacetate (2.00 mL, 14.9 mmol). The reaction mixture was stirred at room temperature for 1 hour before addition of a solution of the preceding iodide (2.09 g, 9.93 mmol) in anhydrous DMF (5 mL). The reaction mixture was stirred at room temperature for 16 hours before addition of saturated aqueous NH_4Cl (30 mL) and extraction with Et_2O (3 × 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 29:1 – 19:1 – 14:1 hexane:EtOAc) afforded the title compound (1.42 g, 67 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2963 (m), 1738 (s), 1714 (s), 1447 (m), 1149 (s). δ_H (400 MHz, $CDCl_3$) 5.52 – 5.42 (1H, m, C**7**-H), 5.32 (1H, dtt, *J* = 15.0, 6.5, 1.5 Hz, C**6**-H), 4.18 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.42 (1H, t, *J* = 7.0 Hz, C**3**-H), 2.21 (3H, s, C**1**-H_3), 2.08 – 1.83 (6H, m, C**4**-H_2, C**5**-H_2 and C**8**-H_2), 1.26 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.95 (3H, t, *J* = 7.5 Hz, C**9**-H_3). δ_C (101 MHz, $CDCl_3$) 203.4 (C**2**), 170.0 (C**10**), 133.9 (C**6**), 127.3 (C**7**), 61.4 (OCH_2CH_3), 59.1 (C**3**), 30.3 (C**5**), 29.1 (C**1**), 28.0 (C**4**), 25.7 (C**8**), 14.2 (OCH_2CH_3), 13.9 (C**9**). HRMS: (ESI^+) Calculated for $C_{12}H_{21}O_3$: 213.1485. Found $[M+H]^+$: 213.1490.

(*E*)-Non-6-en-2-one



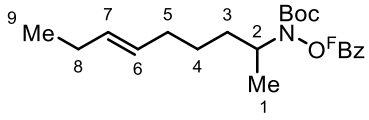
A solution of the preceding compound (1.31 g, 6.17 mmol) and KOH (1.39 g, 24.2 mmol) in MeOH (20 mL) and water (15 mL) was heated at 50 °C for 2 hours before addition of 12.0 M aqueous HCl (2.58 mL, 30.9 mmol). The reaction mixture was cooled to room temperature before being concentrated *in vacuo* to remove MeOH and extracted with Et_2O (3 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was dissolved in $CHCl_3$ (20 mL) and heated at reflux for 3 hours before being concentrated *in vacuo* to afford the title compound (333 mg, 38 %) as a pale-yellow oil. δ_H (400 MHz, $CDCl_3$) 5.51 – 5.41 (1H, m), 5.38 – 5.29 (1H, m), 2.41 (2H, t, *J* = 7.5 Hz), 2.13 (3H, s), 2.03 – 1.93 (4H, m), 1.63 (2H, tt, *J* = 7.5 Hz), 0.96 (3H, t, *J* = 7.5 Hz). δ_C (101 MHz, $CDCl_3$) 209.4, 133.2, 128.3, 43.1, 32.0, 30.1, 25.7, 23.7, 14.1. *The spectroscopic properties were consistent with the data available in the literature*.[280]

(*E*)-Non-6-en-2-ol



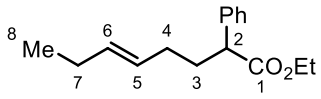
A solution of the preceding ketone (223 mg, 1.59 mmol) and $NaBH_4$ (90.4 mg, 2.39 mmol) in MeOH (15 mL) was stirred at 0 °C for 4 hours before being concentrated *in vacuo*. The reaction mixture was dissolved in 1.0 M aqueous HCl (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 3:1 – 2:1 pentane:Et_2O) afforded the title compound (192 mg, 85 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.51 – 5.32 (2H, m), 3.80 (1H, tq, *J* = 6.0, 6.0 Hz), 2.05 – 1.94 (4H, m), 1.51 – 1.29 (5H, m), 1.21 – 1.14 (3H, m), 0.96 (3H, t, *J* = 7.5 Hz). δ_C (101 MHz, $CDCl_3$) 132.5, 129.0, 68.2, 39.0, 32.6, 25.9, 25.7, 23.6, 14.1. *The spectroscopic properties were consistent with the data available in the literature*.[280]

***tert*-Butyl (*E*)-non-6-en-2-yl((pentafluorobenzoyl)oxy)carbamate (290)**



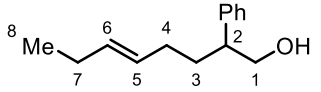
General procedure O: The preceding alcohol (183 mg, 1.29 mmol) was employed with BocNHO^{F}Bz (*vide supra*), and the reaction was performed at -78 °C. The reaction time was 23 hours. FCC (eluent: 1:9 hexane:PhMe) afforded impure material which was dissolved in Et_2O (30 mL) and washed with 10 % aqueous AcOH (3 × 15 mL). The Et_2O phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 19:1 hexane:EtOAc) afforded **290** (137 mg, 24 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2978 (m), 2935 (m), 1785 (s), 1717 (s), 1652 (m), 1504 (s), 1181 (s). δ_H (500 MHz, $CDCl_3$) 5.44 (1H, dt, *J* = 15.0, 6.0 Hz, C**7**-H), 5.40 – 5.29 (1H, m, C**6**-H), 4.43 – 4.18 (1H, m, C**2**-H), 2.03 – 1.93 (4H, m, C**5**-H_2 and C**8**-H_2), 1.66 – 1.32 (4H, m, C**3**-H_2 and C**4**-H_2), 1.49 (9H, s, OC(CH_3)$_3$), 1.20 (3H, d, *J* = 6.5 Hz, C**1**-H_3), 0.94 (3H, t, *J* = 7.5 Hz, C**9**-H_3). δ_C (126 MHz, $CDCl_3$) 157.2 (^{F}Bz C=O), 154.7 (Boc C=O), 145.5 (d, *J* = 256.0 Hz, ArCF), 143.8 (d, *J* = 261.0 Hz, ArCF), 137.9 (d, *J* = 253.0 Hz, ArCF), 132.7 (C**7**), 128.7 (C**6**), 106.4 (ArC), 83.3 (OC(CH_3)$_3$), 56.3 (C**2**), 33.1 (C**3**), 32.3 (C**5**), 28.2 (OC(CH_3)$_3$), 26.3 (C**4**), 25.7 (C**8**), 17.6 (C**1**), 14.0 (C**9**). δ_F (377 MHz, $CDCl_3$) -136.3 – -137.1 (2F, m), -146.9 – -147.4 (1F, m), -159.5 – -159.8 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{21}H_{26}F_5NNaO_4$: 474.1674. Found $[M+Na]^+$: 474.1677.

Ethyl (*E*)-2-phenyloct-5-enoate ((*E*)-292a)



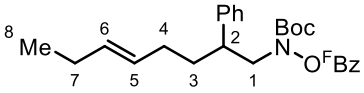
To a solution of LHMDS (1.0 M in THF, 20.0 mL, 20.0 mmol) in anhydrous DMF (40 mL) was added ethyl phenylacetate (3.18 mL, 20.0 mmol). The reaction mixture was stirred at room temperature for 1 hour before addition of a solution of (*E*)-1-iodohex-3-ene (*vide supra*, 5.04 g, 24.0 mmol) in anhydrous DMF (10 mL). The reaction mixture was stirred at room temperature for 17 hours before being concentrated *in vacuo* to remove THF, poured into water (150 mL) and extracted with Et_2O (3 × 80 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 49:1 hexane:EtOAc) afforded **(*E*)-292a** (3.09 g, 63 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3030 (m), 2961 (m), 1731 (s), 1602 (m), 1454 (m), 1153 (s). δ_H (400 MHz, $CDCl_3$) 7.35 – 7.21 (5H, m, 5 × ArC<u>H</u>), 5.48 – 5.30 (2H, m, C**5**-<u>H</u> and C**6**-<u>H</u>), 4.19 – 4.02 (2H, m, OC<u>H</u>$_2$CH$_3$), 3.54 (1H, dd, *J* = 7.5, 7.0 Hz, C**2**-<u>H</u>), 2.13 (1H, ddt, *J* = 13.0, 7.5, 7.5 Hz, C**3**-<u>H</u>), 2.04 – 1.91 (4H, m, C**4**-<u>H</u>$_2$ and C**7**-<u>H</u>$_2$), 1.89 – 1.75 (1H, m, C**3**-<u>H</u>'), 1.20 (3H, t, *J* = 7.0 Hz, OCH$_2$C<u>H</u>$_3$), 0.96 (3H, t, *J* = 7.5 Hz, C**8**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 174.2 (C**1**), 139.4 (Ar<u>C</u>), 133.3 (C**6**), 128.7 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 127.9 (C**5**), 127.2 (Ar<u>C</u>H), 60.8 (O<u>C</u>H$_2$CH$_3$), 51.1 (C**2**), 33.4 (C**3**), 30.5 (C**4**), 25.7 (C**7**), 14.3 (OCH$_2$<u>C</u>H$_3$), 14.0 (C**8**). HRMS: (ESI^+) Calculated for $C_{16}H_{23}O_2$: 247.1693. Found $[M+H]^+$: 247.1698.

(*E*)-2-Phenyloct-5-en-1-ol ((*E*)-293)



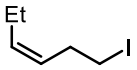
<u>General procedure I:</u> Ester **(*E*)-292a** (2.97 g, 12.1 mmol) was employed, using anhydrous THF as solvent and 0.8 eq. $LiAlH_4$ (1.0 M in THF). Alcohol **(*E*)-293** (2.04 g, 83 %) was isolated as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3343 (br s), 3027 (m), 2924 (m), 1602 (m), 1453 (m), 1029 (s). δ_H (400 MHz, $CDCl_3$) 7.36 – 7.29 (2H, m, 2 × ArC<u>H</u>), 7.26 – 7.18 (3H, m, 3 × ArC<u>H</u>), 5.43 – 5.29 (2H, m, C**5**-<u>H</u> and C**6**-<u>H</u>), 3.78 – 3.68 (2H, m, C**1**-<u>H</u>$_2$), 2.80 (1H, dddd, *J* = 9.5, 7.5, 5.5, 5.5 Hz, C**2**-<u>H</u>), 2.01 – 1.82 (4H, m, C**4**-<u>H</u>$_2$ and C**7**-<u>H</u>$_2$), 1.75 (1H, dddd, *J* = 13.5, 9.0, 6.5, 5.5 Hz, C**3**-<u>H</u>), 1.64 (1H, dddd, *J* = 13.5, 9.5, 8.5, 6.0 Hz, C**3**-<u>H</u>'), 1.30 (1H, br s, O<u>H</u>), 0.95 (3H, t, *J* = 7.5 Hz, C**8**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 142.3 (Ar<u>C</u>), 132.7 (C**6**), 128.8 (Ar<u>C</u>H), 128.6 (C**5**), 128.3 (Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 67.7 (C**1**), 48.1 (C**2**), 32.0 (C**3**), 30.3 (C**4**), 25.7 (C**7**), 14.1 (C**8**). HRMS: (ESI^+) Calculated for $C_{14}H_{20}NaO$: 227.1406. Found $[M+Na]^+$: 227.1415.

***tert*-Butyl (*E*)-(2-phenyloct-5-en-1-yl)((pentafluorobenzoyl)oxy)carbamate ((*E*)-294)**



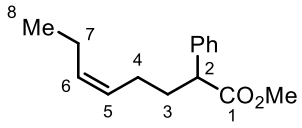
General procedure O: Alcohol **(*E*)-293** (613 mg, 3.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 15 hours. FCC (eluent: 1:1 hexane:PhMe) afforded **(*E*)-294** (606 mg, 39 %) as a colourless crystalline solid. m.p. 60-63 °C (CH_2Cl_2:petrol, *needles*). ν_{max} / cm^{-1}: (*solid*) 2932 (m), 1779 (s) 1719 (s), 1649 (m), 1495 (s), 1156 (s). δ_H (400 MHz, $CDCl_3$) 7.30 – 7.24 (2H, m, 2 × ArC<u>H</u>), 7.20 – 7.15 (3H, m, 3 × ArC<u>H</u>), 5.41 – 5.25 (2H, m, C**5**-<u>H</u> and C**6**-<u>H</u>), 3.92 (1H, dd, *J* = 14.5, 7.0 Hz, C**1**-<u>H</u>), 3.83 (1H, dd, *J* = 14.5, 7.5 Hz, C**1**-<u>H</u>'), 3.03 – 2.94 (1H, m, C**2**-<u>H</u>), 2.00 – 1.76 (5H, m, C**3**-<u>H</u>, C**4**-<u>H</u>$_2$ and C**7**-<u>H</u>$_2$), 1.75 – 1.64 (1H, m, C**3**-<u>H</u>'), 1.39 (9H, s, OC(C<u>H</u>$_3$)$_3$), 0.92 (3H, t, *J* = 7.5 Hz, C**8**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 154.3 (Boc <u>C</u>=O), 141.9 (Ar<u>C</u>), 132.9 (C**6**), 128.6 (Ar<u>C</u>H), 128.4 (C**5**), 128.2 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 83.3 (O<u>C</u>(CH$_3$)$_3$), 56.6 (C**1**), 43.4 (C**2**), 33.0 (C**3**), 30.1 (C**4**), 28.1 (OC(<u>C</u>H$_3$)$_3$), 25.7 (C**7**), 14.0 (C**8**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.1 – -136.5 (2F, m), -146.5 – -146.7 (1F, m), -159.4 – -159.7 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{26}H_{28}F_5NNaO_4$: 536.1831. Found $[M+Na]^+$: 536.1825.

(*Z*)-1-Iodohex-3-ene



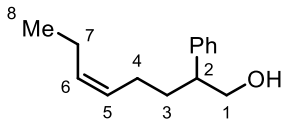
To a solution of PPh_3 (13.3 g, 50.8 mmol) and imidazole (3.46 g, 50.8 mmol) in CH_2Cl_2 (50 mL) was added I_2 (12.9 g, 50.8 mmol) in 5 roughly equal portions over around 10 minutes before addition of (*Z*)-hex-3-en-1-ol (5.00 mL, 42.3 mmol) dropwise. The reaction mixture was stirred at room temperature for 3 hours before being concentrated *in vacuo*, filtered through silica and eluted with pentane. The filtrate was concentrated *in vacuo* to afford the title compound (7.72 g, 87 %) as a pale-red oil. δ_H (500 MHz, $CDCl_3$) 5.53 (1H, dtt, *J* = 10.5, 7.5, 1.5 Hz), 5.34 – 5.24 (1H, m), 3.14 (2H, t, *J* = 7.5 Hz), 2.63 (2H, dtdt, *J* = 7.5, 7.5, 1.5, 0.5 Hz), 2.09 – 1.99 (2H, m), 0.98 (3H, t, *J* = 7.5 Hz). δ_C (126 MHz, $CDCl_3$) 134.4, 127.3, 31.6, 20.9, 14.3, 5.8. *The spectroscopic properties were consistent with the data available in the literature*.[279]

Methyl (*Z*)-2-phenyloct-5-enoate ((*Z*)-292b)



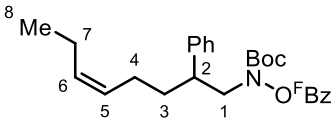
To a solution of methyl phenylacetate (2.82 mL, 20.0 mmol) in anhydrous DMF (40 mL) was added LHMDS (1.0 M in THF, 20.0 mL, 20.0 mmol). The reaction mixture was stirred at room temperature for 45 minutes before addition of a solution of the preceding iodide (5.04 g, 24.0 mmol) in anhydrous DMF (10 mL). The reaction mixture was stirred at room temperature for 18 hours before being concentrated *in vacuo* to remove THF, poured into water (150 mL) and extracted with MTBE (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 49:1 hexane:EtOAc) afforded **(*Z*)-292b** (3.43 g, 74 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3006 (m), 2969 (m), 1734 (s), 1602 (m), 1454 (m), 1156 (s). δ_H (400 MHz, $CDCl_3$) 7.35 – 7.22 (5H, m, 5 × ArC<u>H</u>), 5.44 – 5.36 (1H, m, C**6**-<u>H</u>), 5.34 – 5.25 (1H, m, C**5**-<u>H</u>), 3.65 (3H, s, OC<u>H</u>$_3$), 3.58 (1H, dd, *J* = 8.0, 7.5 Hz, C**2**-<u>H</u>), 2.22 – 2.06 (1H, m, C**3**-<u>H</u>), 2.04 – 1.91 (4H, m, C**4**-<u>H</u>$_2$ and C**7**-<u>H</u>$_2$), 1.83 (1H, ddt, *J* = 14.5, 7.5, 7.5 Hz, C**3**-<u>H</u>'), 0.93 (3H, t, *J* = 7.5 Hz, C**8**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 174.6 (C**1**), 139.2 (Ar<u>C</u>), 133.0 (C**6**), 128.7 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 127.8 (C**5**), 127.3 (Ar<u>C</u>H), 52.0 (O<u>C</u>H$_3$), 51.0 (C**2**), 33.5 (C**3**), 25.1 (C**4**), 20.6 (C**7**), 14.4 (C**8**). HRMS: (ESI^+) Calculated for $C_{15}H_{21}O_2$: 233.1536. Found $[M+H]^+$: 233.1538.

(*Z*)-2-Phenyloct-5-en-1-ol ((*Z*)-293)



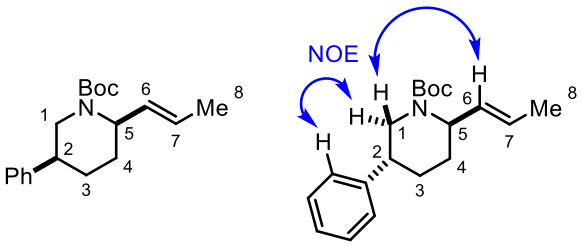
<u>General procedure I:</u> Ester **(*Z*)-292b** (3.25 g, 14.0 mmol) was employed, using anhydrous THF as solvent and 0.8 eq. $LiAlH_4$ (1.0 M in THF). Alcohol **(*Z*)-293** (2.61 g, 91 %) was isolated as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3339 (br s), 3004 (m), 2931 (s), 1602 (m), 1453 (m), 1026 (s). δ_H (400 MHz, $CDCl_3$) 7.36 – 7.31 (2H, m, 2 × ArC<u>H</u>), 7.27 – 7.19 (3H, m, 3 × ArC<u>H</u>), 5.39 – 5.25 (2H, m, C**5**-<u>H</u> and C**6**-<u>H</u>), 3.79 – 3.68 (2H, m, C**1**-<u>H</u>$_2$), 2.81 (1H, dddd, *J* = 9.5, 7.5, 5.5, 5.5 Hz, C**2**-<u>H</u>), 1.98 – 1.85 (4H, m, C**4**-<u>H</u>$_2$ and C**7**-<u>H</u>$_2$), 1.80 – 1.60 (2H, m, C**3**-<u>H</u>$_2$), 1.32 (1H, br s, O<u>H</u>), 0.90 (3H, t, *J* = 7.5 Hz, C**8**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 142.2 (Ar<u>C</u>), 132.3 (C**6**), 128.8 (Ar<u>C</u>H), 128.6 (C**5**), 128.3 (Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 67.7 (C**1**), 48.3 (C**2**), 32.1 (C**3**), 24.9 (C**4**), 20.6 (C**7**), 14.4 (C**8**). HRMS: (ESI^+) Calculated for $C_{14}H_{20}NaO$: 227.1406. Found $[M+Na]^+$: 227.1402.

***tert*-Butyl (*Z*)-(2-phenyloct-5-en-1-yl)((pentafluorobenzoyl)oxy)carbamate ((*Z*)-294)**



General procedure O: Alcohol **(*Z*)-293** (1.02 g, 5.00 mmol) was employed with Boc$NHO^{F}Bz$ (*vide supra*). The reaction time was 20 hours. FCC (gradient elution: 1:1 – 2:3 hexane:PhMe) afforded **(*Z*)-294** (1.12 g, 44 %) as a colourless crystalline solid. m.p. 44-46 °C (Et_2O:petrol, *fibres*). ν_{max} / cm^{-1}: (*solid*) 2935 (m), 1795 (s), 1723 (s), 1652 (m), 1501 (s), 1151 (s). δ_H (400 MHz, $CDCl_3$) 7.31 – 7.25 (2H, m, 2 × ArC**H**), 7.21 – 7.15 (3H, m, 3 × ArC**H**), 5.37 – 5.19 (2H, m, C**5**-**H** and C**6**-**H**), 3.93 (1H, dd, *J* = 15.0, 7.5 Hz, C**1**-**H**), 3.83 (1H, dd, *J* = 15.0, 7.5 Hz, C**1**-**H**'), 3.05 – 2.92 (1H, m, C**2**-**H**), 1.94 – 1.79 (5H, m, C**3**-**H**, C**4**-H_2 and C**7**-H_2), 1.75 – 1.65 (1H, m, C**3**-**H**'), 1.40 (9H, s, OC(CH_3)$_3$), 0.88 (3H, t, *J* = 7.5 Hz, C**8**-H_3). δ_C (101 MHz, $CDCl_3$) 154.2 (Boc **C**=O), 141.8 (Ar**C**), 132.4 (C**6**), 128.6 (Ar**C**H), 128.3 (C**5**), 128.2 (Ar**C**H), 126.8 (Ar**C**H), 83.3 (O**C**(CH_3)$_3$), 56.6 (C**1**), 43.6 (C**2**), 33.2 (C**3**), 28.1 (OC(**C**H_3)$_3$), 24.8 (C**4**), 20.6 (C**7**), 14.4 (C**8**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.1 – -136.5 (2F, m), -146.6 (1F, tt, *J* = 21.0, 5.0 Hz), -159.5 – -159.6 (2F, m). HRMS: (ESI^+) Calculated for $C_{26}H_{28}F_5NNaO_4$: 536.1831. Found $[M+Na]^+$: 536.1827.

***tert*-Butyl (*E*)-5-phenyl-2-(prop-1-en-1-yl)piperidine-1-carboxylate (295)**

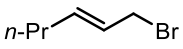


General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; dioxane (0.4 M); 130 °C; 24 hours. Substrate **(*Z*)-294** (53.9 mg, 0.105 mmol) was employed. FCC (*two times*, first eluent: PhMe; second eluent: 49:1 petrol:acetone) afforded **295** (14.2 mg, 45 %, 4:1 mixture of *cis* and *trans* diastereomers) as a colourless oil.

*Alternative procedure starting from **(E)-294**:* **General procedure D:** Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; dioxane (0.4 M); 130 °C; 24 hours. Substrate **(*E*)-294** (53.9 mg, 0.105 mmol) was employed. FCC (*two times*, first eluent: 49:1 petrol:acetone; second, gradient elution: 1:9 – 0:1 petrol:PhMe) afforded **295** (9.8 mg, 31 %, 1:1 mixture *cis* and *trans* diastereomers) as a colourless oil. *The trans diastereomer was assigned as such based on the following NOE correlations: one C**1** proton to the aryl protons, the other C**1** proton to the C**6** proton. Neither C**1***

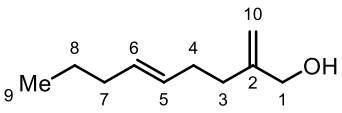
*proton had an NOE correlation to both the C**6** and the aryl protons.* ν_{max} / cm^{-1}: (*film*) 2975 (m), 2932 (m), 1689 (s), 1411 (m), 1161 (s). *The cis diastereomer exists as an approximately 1:1 mixture of rotamers which results in the doubling of several signals in the ^{1}H and ^{13}C NMR spectra. Data for the cis diastereomer:* δ_H (500 MHz, $CDCl_3$) 7.35 – 7.16 (5H, m, 5 × ArC<u>H</u>), 5.59 – 5.46 (2H, m, C**6**-<u>H</u> and C**7**-<u>H</u>), 4.92 and 4.75 (2 × 0.5H, br s, C**5**-<u>H</u>), 4.14 and 3.98 (2 × 0.5H, br s, C**1**-<u>H</u>), 2.94 and 2.82 (2 × 0.5H, br s, C**1**-<u>H</u>'), 2.65 (1H, br s, C**2**-<u>H</u>), 1.88 – 1.69 (7H, m, C**3**-$\underline{H}_2$, C**4**-$\underline{H}_2$ and C**8**-$\underline{H}_3$), 1.51 – 1.42 (9H, m, OC($C\underline{H}_3$)$_3$). δ_C (126 MHz, $CDCl_3$) 155.5 (<u>C</u>=O), 143.9 (Ar<u>C</u>), 129.3 (C**6**), 128.6 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 126.9 (C**7**), 126.3 (Ar<u>C</u>H), 79.6 (O<u>C</u>(CH_3)$_3$), 52.0 and 50.6 (C**5**), 46.5 and 45.4 (C**1**), 43.2 and 42.6 (C**2**), 29.7 and 29.5 (C**3**), 28.6 (OC($\underline{C}H_3$)$_3$), 27.2 and 26.7 (C**4**), 18.1 (C**8**). *^{1}H and ^{13}C NMR data for the trans diastereomer:* δ_H (500 MHz, $CDCl_3$) 7.35 – 7.16 (5H, m, 5 × ArC<u>H</u>), 5.59 – 5.46 (2H, m, C**6**-<u>H</u> and C**7**-<u>H</u>), 4.69 – 4.64 (1H, m, C**5**-<u>H</u>), 4.28 (1H, br d, *J* = 14.0 Hz, C**1**-<u>H</u>), 3.34 (1H, dd, *J* = 14.0, 4.5 Hz, C**1**-<u>H</u>'), 3.00 – 2.96 (1H, m, C**2**-<u>H</u>), 2.06 (1H, dddd, *J* = 13.0, 13.0, 5.0, 3.5 Hz, C**3**-<u>H</u>), 1.88 – 1.69 (5H, m, C**3**-<u>H</u>', C**4**-<u>H</u> and C**8**-$\underline{H}_3$), 1.51 – 1.42 (10H, m, C**4**-<u>H</u>' and OC($C\underline{H}_3$)$_3$). δ_C (126 MHz, $CDCl_3$) 155.5 (<u>C</u>=O), 143.9 (Ar<u>C</u>), 129.7 (C**6**), 128.3 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 126.7 (C**7**), 126.0 (Ar<u>C</u>H), 79.6 (O<u>C</u>(CH_3)$_3$), 52.3 (C**5**), 42.8 (C**1**), 37.7 (C**2**), 28.6 (OC($\underline{C}H_3$)$_3$), 26.0 (C**3**), 24.9 (C**4**), 18.0 (C**8**). HRMS: (ESI^+) Calculated for $C_{19}H_{28}NO_2$: 302.2115. Found $[M+H]^+$: 302.2108.

(*E*)-1-Bromohex-2-ene



<u>General procedure J:</u> (*E*)-Hex-2-en-1-ol (5.01 g, 50.0 mmol) was employed. The title compound (6.51 g, 80 %) was isolated as a colourless oil. δ_H (400 MHz, $CDCl_3$) 5.82 – 5.63 (2H, m), 3.95 (2H, d, *J* = 7.5 Hz), 2.04 (2H, dt, *J* = 7.0, 7.0 Hz), 1.41 (2H, qt, *J* = 7.5, 7.0 Hz), 0.90 (3H, t, *J* = 7.5 Hz). δ_C (101 MHz, $CDCl_3$) 136.6, 126.6, 34.2, 33.7, 22.1, 13.7. *The spectroscopic properties were consistent with the data available in the literature*.[102]

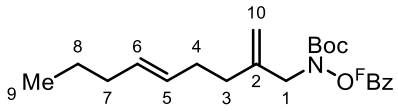
(*E*)-2-Methylenenon-5-en-1-ol (296)



A solution of TMEDA (9.4 mL, 62.5 mmol) and *n*-BuLi (1.55 M in hexane, 40.0 mL, 62.0 mmol) in anhydrous Et_2O (90 mL) was stirred at 0 °C for 20 minutes. The reaction mixture was cooled to -78 °C before addition of 2-methylprop-2-en-1-ol (2.63 mL, 31.3 mmol) dropwise. The reaction mixture was stirred at room temperature for 22 hours, then cooled to -78 °C before addition of a solution of the preceding bromide (4.08 g, 25.0 mmol) in anhydrous Et_2O (10 mL) dropwise. The reaction mixture was stirred at -78 °C for 4 hours, then at room temperature for a further 6 hours before addition of saturated

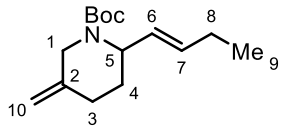
aqueous NH_4Cl (100 mL). The resulting phases were separated, and the organic phase was washed with 1.0 M aqueous HCl (100 mL) followed by brine (100 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 4:1 petrol:Et_2O) afforded **296** (1.77 g, 46 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3326 (br s), 2926 (m), 1713 (m), 1653 (m), 1454 (m). δ_H (400 MHz, $CDCl_3$) 5.48 – 5.34 (2H, m, C**5**-H and C**6**-H), 5.02 (1H, s, C**10**-H), 4.87 (1H, s, C**10**-H'), 4.07 (2H, s, C**1**-H_2), 2.20 – 2.07 (4H, m, C**3**-H_2 and C**4**-H_2), 1.95 (2H, td, *J* = 7.0, 6.0 Hz, C**7**-H_2), 1.61 (1H, br s, OH), 1.35 (2H, qt, *J* = 7.5, 7.0 Hz, C**8**-H_2), 0.88 (3H, t, *J* = 7.5 Hz, C**9**-H_3). δ_C (101 MHz, $CDCl_3$) 148.8 (C**2**), 131.0 (C**6**), 129.6 (C**5**), 109.6 (C**10**), 66.1 (C**1**), 34.8 (C**7**), 33.2 (C**3**), 31.0 (C**4**), 22.8 (C**8**), 13.8 (C**9**). HRMS: (MALDI$^+$) Calculated for $C_{10}H_{19}O$: 155.1430. Found $[M+H]^+$: 155.1435.

***tert*-Butyl (*E*)-(2-methylenenon-5-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (297a)**



General procedure O: Alcohol **296** (309 mg, 2.00 mmol) was employed with BocNHO^FBz (*vide supra*). The reaction time was 15 hours. FCC (eluent: 2:3 petrol:PhMe) afforded **297a** (512 mg, 55 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2932 (m), 1785 (s), 1722 (s), 1652 (m), 1505 (s), 1153 (s). δ_H (400 MHz, $CDCl_3$) 5.48 – 5.34 (2H, m, C**5**-H and C**6**-H), 4.99 (1H, s, C**10**-H), 4.94 (1H, s, C**10**-H'), 4.24 (2H, s, C**1**-H_2), 2.19 – 2.14 (4H, m, C**3**-H_2 and C**4**-H_2), 1.94 (2H, td, *J* = 7.0, 6.0 Hz, C**7**-H_2), 1.50 (9H, s, OC(CH_3)$_3$), 1.35 (2H, qt, *J* = 7.5, 7.0 Hz, C**8**-H_2), 0.87 (3H, t, *J* = 7.5 Hz, C**9**-H_3). δ_C (101 MHz, $CDCl_3$) 154.6 (Boc C=O), 142.9 (C**2**), 131.0 (C**6**), 129.4 (C**5**), 114.2 (C**10**), 83.6 (OC(CH_3)$_3$), 55.8 (C**1**), 34.8 (C**7**), 33.4 (C**3**), 30.6 (C**4**), 28.2 (OC(CH_3)$_3$), 22.8 (C**8**), 13.8 (C**9**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.2 – -136.4 (2F, m), -146.8 (1F, tt, *J* = 21.0, 5.0 Hz), -159.5 – -159.7 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{22}H_{26}F_5NNaO_4$: 486.1674. Found $[M+Na]^+$: 486.1672.

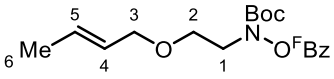
***tert*-Butyl (*E*)-2-(but-1-en-1-yl)-5-methylenepiperidine-1-carboxylate (298)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 17.5 mol% ligand **L3** (*vide supra*); 100 mol% Et_3N; dioxane (0.3 M); 130 °C; 24 hours. Substrate **297a** (48.7 mg, 0.105 mmol) was employed. FCC (*two times*, first eluent: 49:1 petrol:acetone; second eluent: PhMe) afforded **298** (3.0 mg, 11 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2963 (m), 2928 (m), 1694 (s), 1365 (s), 1172 (s). δ_H (500 MHz, $CDCl_3$) 5.63 – 5.54 (1H, m, C**7**-H), 5.47 – 5.40 (1H, m, C**6**-H), 4.82 (1H, s, C**10**-H), 4.77 (1H, br s, C**5**-H), 4.74

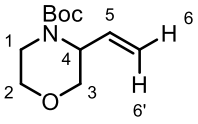
(1H, s, C**10**-H'), 4.33 (1H, d, *J* = 14.5 Hz, C**1**-H), 3.53 (1H, d, *J* = 14.5 Hz, C**1**-H'), 2.32 (1H, ddd, *J* = 13.0, 9.5, 4.5 Hz, C**3**-H), 2.23 – 2.15 (1H, m, C**3**-H'), 2.09 (2H, qd, *J* = 7.5, 7.0 Hz, C**8**-H_2), 1.82 – 1.75 (2H, m, C**4**-H_2), 1.48 (9H, s, OC(CH_3)$_3$), 1.01 (3H, t, *J* = 7.5 Hz, C**9**-H_3). δ_C (126 MHz, $CDCl_3$) 155.3 (C=O), 143.5 (C**2**), 133.9 (C**7**), 126.8 (C**6**), 109.2 (C**10**), 79.6 (OC(CH_3)$_3$), 51.9 (C**5**), 46.0 (C**1**), 30.2 (C**4**), 28.6 (OC(CH_3)$_3$), 28.3 (C**3**), 25.6 (C**8**), 13.9 (C**9**). HRMS: (ESI^+) Calculated for $C_{15}H_{25}NNaO_2$: 274.1778. Found $[M+Na]^+$: 274.1784.

***tert*-Butyl (*E*)-(2-(but-2-en-1-yloxy)ethyl)((pentafluorobenzoyl)oxy)carbamate (299)**



General procedure O: Alcohol **192** (Section 7.3, 339 mg, 2.92 mmol) was employed with BocNHO^FBz (*vide supra*). The reaction time was 16 hours. FCC (gradient elution: 1:0 – 49:1 PhMe:EtOAc) afforded **299** (881 mg, 71 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2981 (m), 2864 (m), 1783 (s) 1722 (s), 1652 (m), 1499 (s). δ_H (400 MHz, $CDCl_3$) 5.73 – 5.63 (1H, m, C**5**-H), 5.58 – 5.44 (1H, m, C**4**-H), 3.93 – 3.85 (4H, m, C**1**-H_2 and C**3**-H_2), 3.63 (2H, t, *J* = 5.5 Hz, C**2**-H_2), 1.67 (3H, ddt, *J* = 6.5, 1.5, 1.0 Hz, C**6**-H_3), 1.49 (9H, s, OC(CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 154.7 (Boc C=O), 129.9 (C**5**), 127.4 (C**4**), 83.5 (OC(CH_3)$_3$), 71.9 (C**3**), 66.4 (C**2**), 50.6 (C**1**), 28.2 (OC(CH_3)$_3$), 17.8 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.0 – -136.3 (2F, m), -146.5 (1F, tt, *J* = 21.0, 5.0 Hz), -159.4 – -159.6 (2F, m). HRMS: (ESI^+) Calculated for $C_{18}H_{20}F_5NNaO_5$: 448.1154. Found $[M+Na]^+$: 448.1160.

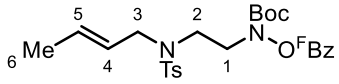
***tert*-Butyl 3-vinylmorpholine-4-carboxylate (300)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 17.5 mol% ligand **L3** (*vide supra*); 100 mol% Et_3N; dioxane (0.3 M); 130 °C; 24 hours. Substrate **299** (44.7 mg, 0.105 mmol) was employed. FCC (*two times*, first, gradient elution: 29:1 – 19:1 PhMe:EtOAc; second eluent: 19:1 petrol:acetone) afforded **300** (0.3 mg, 1 %) as a colourless oil. *The yield determined by ^1H analysis of the crude reaction mixture was 19 %.* ν_{max} / cm^{-1}: (*film*) 2967 (m), 2925 (m), 1697 (s), 1393 (s), 1171 (s). δ_H (500 MHz, $CDCl_3$) 5.94 (1H, ddd, *J* = 17.5, 10.5, 5.5 Hz, C**5**-H), 5.26 (1H, ddd, *J* = 10.5, 1.5, 1.5 Hz, C**6**-H), 5.19 (1H, ddd, *J* = 17.5, 1.5, 1.5 Hz, C**6**-H'), 4.43 (1H, br s, C**4**-H), 3.90 (1H, d, *J* = 11.5 Hz, C**3**-H), 3.85 (1H, dd, *J* = 11.5, 4.0 Hz, C**2**-H), 3.75 – 3.68 (1H, m, C**1**-H), 3.65 (1H, dd, *J* = 11.5, 3.5 Hz, C**3**-H'), 3.48 (1H, ddd, *J* = 12.5, 11.5, 3.0 Hz, C**2**-H'), 3.17 (1H, ddd, *J* = 13.0, 12.5, 4.0 Hz, C**1**-H'), 1.46 (9H, s, OC(CH_3)$_3$). δ_C (126 MHz, $CDCl_3$) 155.1 (C=O), 134.7 (C**5**), 117.2 (C**6**), 80.2 (OC(CH_3)$_3$), 69.8 (C**3**),

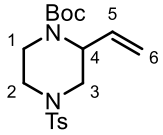
67.1 (C**2**), 53.4 (C**4**), 39.9 (C**1**), 28.5 (OC(CH_3)$_3$). HRMS: (ESI$^+$) Calculated for $C_{11}H_{19}NNaO_3$: 236.1257. Found [M+Na]$^+$: 236.1259.

***tert*-Butyl (*E*)-(2-((*N*-(but-2-en-1-yl)-4-methylphenyl)sulfonamido)ethyl)((pentafluorobenzoyl)-oxy)carbamate (301)**



General procedure O: Alcohol **193** (Section 7.3, 288 mg, 1.07 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 16 hours. FCC (*two times*, first eluent: 19:1 PhMe:EtOAc; second eluent: 9:1 hexane:EtOAc) afforded **301** (256 mg, 41 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2980 (m), 1782 (s), 1727 (s), 1653 (m), 1598 (m), 1499 (s), 1326 (s), 1152 (s). δ_H (400 MHz, $CDCl_3$) 7.68 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.29 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.60 (1H, dqt, *J* = 15.5, 6.5, 1.5 Hz, C**5**-<u>H</u>), 5.33 – 5.20 (1H, m, C**4**-<u>H</u>), 3.91 – 3.83 (2H, m, C**1**-<u>H</u>$_2$), 3.76 (2H, br d, *J* = 7.0 Hz, C**3**-<u>H</u>$_2$), 3.36 – 3.31 (2H, m, C**2**-<u>H</u>$_2$), 2.42 (3H, s, Ts C<u>H</u>$_3$), 1.62 (3H, ddt, *J* = 6.5, 1.5, 1.5 Hz, C**6**-<u>H</u>$_3$), 1.49 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 154.1 (Boc <u>C</u>=O), 143.5 (Ar<u>C</u>), 136.8 (Ar<u>C</u>), 131.4 (C**5**), 129.8 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 125.4 (C**4**), 83.9 (O<u>C</u>(CH$_3$)$_3$), 51.2 (C**3**), 50.4 (C**1**), 44.0 (C**2**), 28.1 (OC(<u>C</u>H$_3$)$_3$), 21.6 (Ts <u>C</u>H$_3$), 17.8 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoate group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.1 – -136.3 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.0 Hz), -159.2 – -159.5 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{25}H_{27}F_5N_2NaO_6S$: 601.1402. Found [M+Na]$^+$: 601.1383.

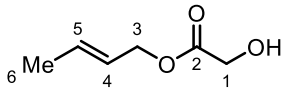
***tert*-Butyl 4-tosyl-2-vinylpiperazine-1-carboxylate (302)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **301** (60.7 mg, 0.105 mmol) was employed. FCC (gradient elution: 39:1 – 19:1 PhMe:EtOAc) afforded **302** (13.8 mg, 36 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2979 (m), 2926 (m), 1693 (s), 1597 (m), 1455 (m), 1164 (s). δ_H (500 MHz, $CDCl_3$) 7.62 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.33 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.88 (1H, ddd, *J* = 17.5, 10.5, 5.0 Hz, C**5**-<u>H</u>), 5.31 – 5.24 (2H, m, C**6**-<u>H</u>$_2$), 4.69 (1H, br s, C**4**-<u>H</u>), 3.91 (1H, d, *J* = 13.0 Hz, C**1**-<u>H</u>), 3.77 (1H, ddd, *J* = 11.5, 2.5, 2.0 Hz, C**3**-<u>H</u>), 3.65 (1H, dddd, *J* = 11.5, 3.5, 2.0, 2.0 Hz, C**2**-<u>H</u>), 3.15 (1H, ddd, *J* = 13.0, 12.5, 3.5 Hz, C**1**-<u>H</u>'), 2.46 – 2.41 (4H, m, C**3**-<u>H</u>' and Ts C<u>H</u>$_3$), 2.25 (1H, ddd, *J* = 12.5, 11.5, 2.5 Hz, C**2**-<u>H</u>'), 1.41 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (126 MHz, $CDCl_3$) 154.5 (<u>C</u>=O), 144.0 (Ar<u>C</u>), 134.0 (C**5**), 132.5 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 118.2 (C**6**), 80.6

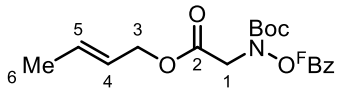
(O<u>C</u>(CH$_3$)$_3$), 52.1 (C**4**), 48.8 (C**3**), 46.1 (C**2**), 38.9 (C**1**), 28.4 (OC(<u>C</u>H$_3$)$_3$), 21.7 (Ts <u>C</u>H$_3$). HRMS: (ESI$^+$) Calculated for $C_{18}H_{26}N_2NaO_4S$: 389.1505. Found [M+Na]$^+$: 389.1509.

(*E*)-But-2-en-1-yl 2-hydroxyacetate (303)



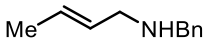
A mixture of methyl glycolate (3.60 g, 40.0 mmol), K_2CO_3 (276 mg, 2.00 mmol) and (*E*)-but-2-en-1-ol (34 mL, 400 mmol) was heated at reflux under a Dean-Stark apparatus for 1.5 hours before being cooled to room temperature. FCC (eluent: 5:2 petrol:EtOAc) afforded **303** (3.11 g, 60 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3449 (br s), 2948 (m), 1737 (s), 1197 (s), 1090 (s). δ_H (400 MHz, $CDCl_3$) 5.90 – 5.75 (1H, m, C**5**-<u>H</u>), 5.58 (1H, dtq, *J* = 15.0, 6.5, 2.0 Hz, C**4**-<u>H</u>), 4.61 (2H, ddq, *J* = 6.5, 1.5, 1.0 Hz, C**3**-<u>H</u>$_2$), 4.15 (2H, s, C**1**-<u>H</u>$_2$), 2.47 (1H, br s, O<u>H</u>), 1.72 (3H, ddt, *J* = 6.5, 2.0, 1.0 Hz, C**6**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 173.3 (C**2**), 132.7 (C**5**), 124.4 (C**4**), 66.3 (C**3**), 60.8 (C**1**), 17.9 (C**6**). HRMS: (ESI$^+$) Calculated for $C_6H_{10}NaO_3$: 153.0522. Found [M+Na]$^+$: 153.0530.

(*E*)-But-2-en-1-yl *N*-(*tert*-butoxycarbonyl)-*N*-((pentafluorobenzoyl)oxy)glycinate (305)



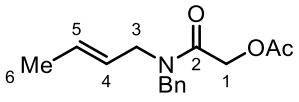
<u>General procedure O:</u> Alcohol **303** (260 mg, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 22 hours. FCC (*two times*, first, gradient elution: 2:8 – 1:9 petrol:PhMe; second eluent: 14:1 petrol:EtOAc) afforded **305** (404 mg, 46 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2982 (m), 1786 (s), 1756 (s), 1730 (s), 1652 (m), 1499 (s), 1151 (s). δ_H (400 MHz, $CDCl_3$) 5.82 (1H, dqt, *J* = 15.0, 6.5, 1.0 Hz, C**5**-<u>H</u>), 5.58 (1H, dtq, *J* = 15.0, 6.5, 1.5 Hz, C**4**-<u>H</u>), 4.61 (2H, ddq, *J* = 6.5, 1.0, 1.0 Hz, C**3**-<u>H</u>$_2$), 4.39 (2H, s, C**1**-<u>H</u>$_2$), 1.72 (3H, ddt, *J* = 6.5, 1.5, 1.0 Hz, C**6**-<u>H</u>$_3$), 1.51 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 167.3 (C**2**), 154.7 (Boc <u>C</u>=O), 132.6 (C**5**), 124.4 (C**4**), 84.5 (O<u>C</u>(CH$_3$)$_3$), 66.5 (C**3**), 52.7 (C**1**), 28.0 (OC(<u>C</u>H$_3$)$_3$), 17.9 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.1 – -136.6 (2F, m), -146.4 (1F, tt, *J* = 21.0, 5.0 Hz), -159.4 – -159.6 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{18}H_{18}F_5NNaO_6$: 462.0946. Found [M+Na]$^+$: 462.0963.

(*E*)-*N*-Benzylbut-2-en-1-amine



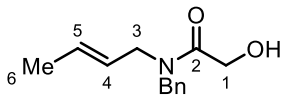
This compound was prepared according to a literature procedure.[281] A suspension of crotyl bromide (Section 7.3, 2.06 mL, 20.0 mmol) and K_2CO_3 (3.46 g, 15.0 mmol) in $BnNH_2$ (10.9 mL, 100 mmol) was heated at 70 °C for 16 hours. The reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL) and washed with water (2 × 40 mL) followed by brine (40 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 30:20:1 petrol:EtOAc:Et_3N) afforded the title compound (2.43 g, 75 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.34 – 7.30 (4H, m), 7.27 – 7.21 (1H, m), 5.67 – 5.51 (2H, m), 3.78 (2H, s), 3.21 (2H, d, *J* = 5.5 Hz), 1.69 (3H, d, *J* = 5.5 Hz), 1.32 (1H, br s). δ_C (101 MHz, $CDCl_3$) 140.6, 129.6, 128.5, 128.3, 127.5, 127.0, 53.5, 51.3, 18.0. *The spectroscopic properties were consistent with the data available in the literature*.[282]

(*E*)-2-(Benzyl(but-2-en-1-yl)amino)-2-oxoethyl acetate



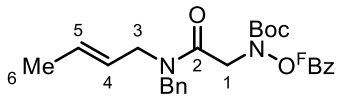
To a suspension of the preceding amine (1.64 g, 10.0 mmol) and K_2CO_3 (1.38 g, 10.0 mol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C was added acetoxyacetyl chloride (1.29 mL, 12.0 mmol) dropwise. The reaction mixture was stirred at room temperature for 5 hours before addition of water (30 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 2:1 petrol:EtOAc) afforded the title compound (2.49 g, 95 %) as a colourless oil. *This compound exists as an approximately 8:5 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 3031 (m), 2940 (m), 1747 (s), 1662 (s), 1449 (s), 1211 (s). δ_H (400 MHz, $CDCl_3$) 7.39 – 7.17 (5H, m, A and B: 5 × ArC<u>H</u>), 5.69 – 5.49 (1H, m, A and B: C**5**-<u>H</u>), 5.47 – 5.28 (1H, m, A and B: C**4**-<u>H</u>), 4.77 (1.2H, s, A: C**1**-<u>H_2</u>), 4.71 (0.8H, s, B: C**1**-<u>H_2</u>), 4.58 (1.2H, s, A: NC<u>H_2</u>Ph), 4.43 (0.8H, s, B: NC<u>H_2</u>Ph), 3.94 (0.8H, d, *J* = 6.5 Hz, B: C**3**-<u>H_2</u>), 3.68 (1.2H, d, *J* = 5.5 Hz, A: C**3**-<u>H_2</u>), 2.20 (1.8H, s, A: Ac C<u>H_3</u>), 2.14 (1.2H, s, B: Ac C<u>H_3</u>), 1.71 (1.8H, d, *J* = 6.5 Hz, A: C**6**-<u>H_3</u>), 1.67 (1.2H, d, *J* = 6.5 Hz, C**6**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 2 × 170.8 (A and B: Ac <u>C</u>=O), 166.9 (A: C**2**), 166.8 (B: C**2**), 137.1 (A: Ar<u>C</u>), 136.0 (B: Ar<u>C</u>), 130.1 (B: C**5**), 129.4 (A: C**5**), 129.1 (B: Ar<u>C</u>H), 128.7 (A: Ar<u>C</u>H), 128.5 (A: Ar<u>C</u>H), 127.9 (B: Ar<u>C</u>H), 127.6 (A: Ar<u>C</u>H), 126.5 (B: Ar<u>C</u>H), 125.2 (B: C**4**), 124.7 (A: C**4**), 61.7 (B: C**1**), 61.5 (A: C**1**), 49.0 (B: N<u>C</u>H_2Ph), 48.6 (A: N<u>C</u>H_2Ph), 47.8 (B: C**3**), 47.6 (A: C**3**), 20.8 (A: Ac <u>C</u>H_3), 20.7 (B: Ac <u>C</u>H_3), 2 × 17.8 (A and B: C**6**). HRMS: (ESI^+) Calculated for $C_{15}H_{20}NO_3$: 262.1438. Found $[M+H]^+$: 262.1447.

(*E*)-*N*-Benzyl-*N*-(but-2-en-1-yl)-2-hydroxyacetamide (304)



A solution of the preceding compound (2.36 g, 9.03 mmol) and NaOMe (488 mg, 9.03 mmol) in MeOH (20 mL) was heated at reflux for 6 hours before being cooled to room temperature and concentrated *in vacuo*. The crude mixture was dissolved in saturated aqueous NH_4Cl (20 mL) and brine (20 mL) before being extracted with EtOAc (3 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford **304** (1.89 g, 95 %) as a colourless oil. *This compound exists as an approximately 5:3 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 3415 (br s), 3030 (m), 2918 (m), 1642 (s), 1397 (s), 1078 (s). δ_H (400 MHz, $CDCl_3$) 7.38 – 7.20 (4.4H, m, A: 4 × ArC<u>H</u>; B: 5 × ArC<u>H</u>), 7.16 – 7.10 (0.6H, m, A: ArC<u>H</u>), 5.63 – 5.51 (1H, m, A and B: C**5**-<u>H</u>), 5.46 – 5.36 (0.4H, m, B: C**4**-<u>H</u>), 5.35 – 5.25 (0.6H, m, A: C**4**-<u>H</u>), 4.62 (1.2H, s, A: NC<u>H</u>$_2$Ph), 4.32 (0.8H, s, B: NC<u>H</u>$_2$Ph), 4.22 (1.2H, d, *J* = 4.5 Hz, A: C**1**-<u>H</u>$_2$), 4.20 (0.8H, d, *J* = 4.0 Hz, B: C**1**-<u>H</u>$_2$), 3.98 (0.8H, d, *J* = 6.5 Hz, B: C**3**-<u>H</u>$_2$), 3.70 – 3.61 (1H, m, A and B: O<u>H</u>), 3.59 (1.2H, d, *J* = 6.0 Hz, A: C**3**-<u>H</u>$_2$), 1.74 – 1.66 (3H, m, A and B: C**6**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 172.0 (A: C**2**), 171.9 (B: C**2**), 136.8 (A: Ar<u>C</u>), 135.6 (B: Ar<u>C</u>), 130.4 (B: C**5**), 129.9 (A: C**5**), 129.2 (B: Ar<u>C</u>H), 128.8 (A: Ar<u>C</u>H), 128.4 (A: Ar<u>C</u>H), 128.0 (B: Ar<u>C</u>H), 127.8 (B: Ar<u>C</u>H), 126.6 (A: Ar<u>C</u>H), 124.9 (B: C**4**), 124.4 (A: C**4**), 60.1 (B: C**1**), 60.0 (A: C**1**), 48.7 (A: N<u>C</u>H$_2$Ph), 48.1 (B: N<u>C</u>H$_2$Ph), 47.7 (B: C**3**), 46.8 (A: C**3**), 2 × 17.8 (A and B: C**6**). HRMS: (ESI^+) Calculated for $C_{13}H_{18}NO_2$: 220.1332. Found $[M+H]^+$: 220.1322.

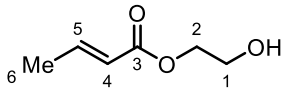
***tert*-Butyl (*E*)-(2-(benzyl(but-2-en-1-yl)amino)-2-oxoethyl)((pentafluorobenzoyl)oxy)carbamate (306)**



<u>General procedure O:</u> Alcohol **304** (439 mg, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 19 hours. FCC (gradient elution: 1:0 – 99:1 – 49:1 PhMe:EtOAc) afforded **306** (802 mg, 76 %) as a colourless crystalline solid. *This compound exists as an approximately 5:3 mixture of rotamers A and B.* m.p. 118-119 °C (acetone:petrol, *fibres*). ν_{max} / cm^{-1}: (*solid*) 2987 (m), 1794 (s), 1738 (s), 1654 (s), 1500 (s), 1152 (s). δ_H (400 MHz, $CDCl_3$) 7.39 – 7.13 (5H, m, A and B: 5 × ArC<u>H</u>), 5.65 – 5.48 (1H, m, A and B: C**5**-<u>H</u>), 5.46 – 5.27 (1H, m, A and B: C**4**-<u>H</u>), 4.59 (1.2H, s, A: NC<u>H</u>$_2$Ph), 4.50 (1.2H, s, A: C**1**-<u>H</u>$_2$), 4.44 (1.6H, s, B: C**1**-<u>H</u>$_2$ and NC<u>H</u>$_2$Ph), 3.98 (0.8H, d, *J* = 6.5 Hz, B: C**3**-<u>H</u>$_2$), 3.70 (1.2H, d, *J* = 5.5 Hz, A: C**3**-<u>H</u>$_2$), 1.70 (1.8H, d, *J* = 6.5 Hz, A: C**6**-<u>H</u>$_3$), 1.67 (1.2H, d, *J* = 6.5 Hz, B: C**6**-<u>H</u>$_3$), 1.53 (5.4H, s, A: OC(C<u>H</u>$_3$)$_3$), 1.51 (3.6H, s, B: OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 166.2 (A: C**2**), 166.1 (B: C**2**), 155.6 (A and B: Boc <u>C</u>=O), 137.1 (A: Ar<u>C</u>), 136.0 (B: Ar<u>C</u>), 130.2 (B:

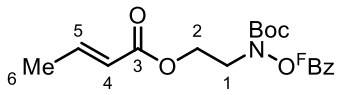
C**5**), 2 × 129.2 (A: C**5**; B: Ar<u>C</u>H), 128.7 (A: Ar<u>C</u>H), 128.5 (A: Ar<u>C</u>H), 128.0 (B: Ar<u>C</u>H), 127.7 (B: Ar<u>C</u>H), 126.3 (A: Ar<u>C</u>H), 125.3 (B: C**4**), 124.7 (A: C**4**), 84.0 (A and B: O<u>C</u>(CH$_3$)$_3$), 53.1 (A and B: C**1**), 49.0 (B: N<u>C</u>H$_2$Ph), 48.9 (A: N<u>C</u>H$_2$Ph), 48.0 (B: C**3**), 47.9 (A: C**3**), 28.1 (A and B: OC(<u>C</u>H$_3$)$_3$), 17.8 (B: C**6**), 17.7 (A: C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, CDCl$_3$) -136.4 – -137.2 (2F, m), -146.8 – -147.1 (1F, m), -159.6 – -159.9 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{25}H_{25}F_5N_2NaO_5$: 551.1576. Found [M+Na]$^+$: 551.1569.

2-Hydroxyethyl (*E*)-but-2-enoate



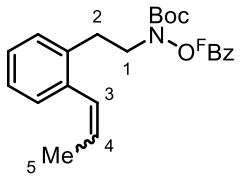
To a suspension of ethylene glycol (4.18 mL, 75.0 mmol) and K_2CO_3 (2.07 g, 15.0 mol) in CH_2Cl_2 (40 mL) at 0 °C was added crotonoyl chloride (1.44 mL, 15.0 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 hour before being diluted with EtOAc (80 mL) and washed with brine (40 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 2:3 – 2:5 petrol:Et$_2$O) afforded the title compound (980 mg, 50 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3416 (br s), 2950 (m), 1703 (s), 1656 (s), 1444 (m), 1181 (s). δ_H (400 MHz, CDCl$_3$) 7.00 (1H, dq, *J* = 15.5, 7.0 Hz, C**5**-<u>H</u>), 5.86 (1H, dq, *J* = 15.5, 1.5 Hz, C**4**-<u>H</u>), 4.26 – 4.22 (2H, m, C**2**-<u>H</u>$_2$), 3.85 – 3.80 (2H, m, C**1**-<u>H</u>$_2$), 2.31 (1H, br s, O<u>H</u>), 1.87 (3H, dd, *J* = 7.0, 1.5 Hz, C**6**-<u>H</u>$_3$). δ_C (101 MHz, CDCl$_3$) 167.0 (C**3**), 145.7 (C**5**), 122.3 (C**4**), 66.0 (C**2**), 61.4 (C**1**), 18.1 (C**6**). HRMS: (ESI$^+$) Calculated for $C_6H_{10}NO_3$: 153.0522. Found [M+Na]$^+$: 153.0529.

2-((*tert*-Butoxycarbonyl)((pentafluorobenzoyl)oxy)amino)ethyl (*E*)-but-2-enoate (309)



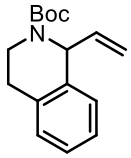
<u>General procedure O:</u> The preceding alcohol (260 mg, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 20 hours. FCC (gradient elution: 1:0 – 49:1 – 19:1 PhMe:EtOAc) afforded **309** (622 mg, 71 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2982 (m), 1784 (s), 1721 (s), 1653 (s), 1499 (s), 1172 (s). δ_H (400 MHz, CDCl$_3$) 6.98 (1H, dq, *J* = 15.5, 7.0 Hz, C**5**-<u>H</u>), 5.81 (1H, dq, *J* = 15.5, 1.5 Hz, C**4**-<u>H</u>), 4.35 (2H, t, *J* = 5.5 Hz, C**2**-<u>H</u>$_2$), 3.98 (2H, t, *J* = 5.5 Hz, C**1**-<u>H</u>$_2$), 1.85 (3H, dd, *J* = 7.0, 1.5 Hz, C**6**-<u>H</u>$_3$), 1.49 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, CDCl$_3$) 166.2 (C**3**), 154.3 (Boc <u>C</u>=O), 145.7 (C**5**), 122.2 (C**4**), 83.9 (O<u>C</u>(CH$_3$)$_3$), 60.5 (C**2**), 49.7 (C**1**), 28.1 (OC(<u>C</u>H$_3$)$_3$), 18.1 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, CDCl$_3$) -136.1 – -136.3 (2F, m), -146.2 (1F, tt, *J* = 21.0, 5.5 Hz), -159.3 – -159.5 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{18}H_{18}F_5NNaO_6$: 462.0946. Found [M+Na]$^+$: 462.0969.

***tert*-Butyl (2-(prop-1-en-1-yl)phenethyl)((pentafluorobenzoyl)oxy)carbamate (313a)**



General procedure O: 2-(2-(Prop-1-en-1-yl)phenyl)ethan-1-ol (Section 7.3, 324 g, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 16 hours. FCC (eluent: 2:3 hexane:PhMe) afforded **313a** (493 mg, 52 %, 3:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3020 (m), 2981 (m), 1783 (s), 1722 (s), 1652 (m), 1499 (s), 1326 (s), 1151 (s). *^{1}H and ^{13}C NMR data for the major (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.24 – 7.12 (4H, m, 4 × ArC<u>H</u>), 6.53 (1H, dq, *J* = 11.5, 2.0 Hz, C**3**-<u>H</u>), 5.86 (1H, dq, *J* = 11.5, 7.0 Hz, C**4**-<u>H</u>), 3.88 – 3.77 (2H, m, C**1**-<u>H</u>$_2$), 3.00 – 2.92 (2H, m, C**2**-<u>H</u>$_2$), 1.71 (3H, dd, *J* = 7.0, 2.0 Hz, C**5**-<u>H</u>$_3$), 1.46 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 154.2 (Boc <u>C</u>=O), 136.6 (Ar<u>C</u>), 136.0 (Ar<u>C</u>), 2 × 129.7 (2 × Ar<u>C</u>H), 2 × 128.0 (C**3** and C**4**), 127.1 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 83.3 (O<u>C</u>(CH$_3$)$_3$), 51.4 (C**1**), 31.1 (C**2**), 28.0 (OC(<u>C</u>H$_3$)$_3$), 14.3 (C**5**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity. ^{1}H and ^{13}C NMR data for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.41 (1H, d, *J* = 7.0 Hz, ArC<u>H</u>), 7.24 – 7.12 (3H, m, 3 × ArC<u>H</u>), 6.64 (1H, dq, *J* = 15.5, 1.5 Hz, C**3**-<u>H</u>), 6.13 (1H, dq, *J* = 15.5, 6.5 Hz, C**4**-<u>H</u>), 3.88 – 3.77 (2H, m, C**1**-<u>H</u>$_2$), 3.07 – 3.00 (2H, m, C**2**-<u>H</u>$_2$), 1.89 (3H, dd, *J* = 6.5, 1.5 Hz, C**5**-<u>H</u>$_3$), 1.46 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 154.2 (Boc <u>C</u>=O), 137.2 (Ar<u>C</u>), 134.4 (Ar<u>C</u>), 130.1 (Ar<u>C</u>H), 128.2 (C**4**), 127.9 (C**3**), 127.1 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 83.3 (O<u>C</u>(CH$_3$)$_3$), 51.7 (C**1**), 30.8 (C**2**), 28.0 (OC(<u>C</u>H$_3$)$_3$), 18.7 (C**5**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity. ^{19}F NMR signals for both isomers:* δ_F (377 MHz, $CDCl_3$) -136.2 – -136.4 (2F, m), -146.2 – -146.5 (1F, m), -159.2 – -159.4 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{23}H_{22}F_5NNaO_4$: 494.1361. Found [M+Na]$^+$: 494.1362.

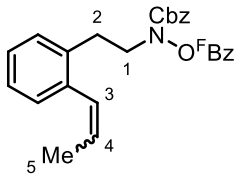
***tert*-Butyl 1-vinyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (314a)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; dioxane (0.4 M); 130 °C; 24 hours. Substrate **313a** (49.5 mg, 0.105 mmol) was employed. FCC (*two times*, first eluent: 79:1 pentane:acetone; second eluent: PhMe) afforded **314a** (16.8 mg, 62 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.20 – 7.11 (4H, m), 5.96 (1H, ddd, *J* = 17.0, 10.0, 5.5 Hz), 5.55 (1H, br s), 5.15 (1H, ddd, *J* = 10.0, 1.5, 1.5 Hz), 5.05 (1H, ddd, *J* = 17.0, 1.5, 1.5 Hz), 4.11 (1H, br s),

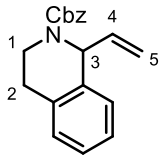
3.21 (1H, br s), 2.98 – 2.83 (1H, m), 2.73 (1H, ddd, *J* = 16.0, 4.0, 4.0 Hz), 1.49 (9H, s). δ_C (126 MHz, $CDCl_3$) 154.9, 137.9, 135.1, 135.0, 129.0, 128.0, 126.8, 126.2, 115.8, 80.0, 57.3, 37.8, 28.9, 28.6. *The spectroscopic properties were consistent with the data available in the literature.*[283]

Benzyl (2-(prop-1-en-1-yl)phenethyl)((pentafluorobenzoyl)oxy)carbamate (313b)



General procedure O: 2-(2-(Prop-1-en-1-yl)phenyl)ethan-1-ol (Section 7.3, 324 mg, 2.00 mmol) was employed with CbzNHO^{F}Bz.[L] The reaction time was 18 hours. FCC (gradient elution: 1:1 – 2:3 hexane:PhMe) afforded **313b** (299 mg, 30 %, 3:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless oil. *Spectroscopic data for the major Z diastereomer:* ν_{max} / cm^{-1}: (*film*) 3022 (m), 2948 (m), 1788 (s), 1734 (s), 1654 (m), 1497 (s), 1171 (s). δ_H (400 MHz, $CDCl_3$) 7.40 – 7.29 (5H, m, 5 × ArC**H**), 7.22 – 7.12 (4H, m, 4 × ArC**H**), 6.48 (1H, dq, *J* = 11.5, 2.0 Hz, C**3**-**H**), 5.79 (1H, dq, *J* = 11.5, 7.0 Hz, C**4**-**H**), 5.17 (2H, s, OC**H**$_2$Ph), 3.91 – 3.86 (2H, m, C**1**-**H**$_2$), 3.00 – 2.93 (2H, m, C**2**-**H**$_2$), 1.67 (3H, dd, *J* = 7.0, 2.0 Hz, C**5**-**H**$_3$). δ_C (101 MHz, $CDCl_3$) 157.3 (^{F}Bz C=O), 155.2 (Cbz **C**=O), 136.8 (Ar**C**), 135.8 (Ar**C**), 135.3 (Ar**C**), 130.0 (Ar**C**H), 129.9 (Ar**C**H), 128.7 (Ar**C**H), 128.6 (Ar**C**H), 128.3 (Ar**C**H), 128.2 (C**4**), 128.1 (C**3**), 127.2 (Ar**C**H), 126.6 (Ar**C**H), 68.9 (O**C**H$_2$Ph), 51.7 (C**1**), 31.3 (C**2**), 14.4 (C**5**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -135.9 (2F, m), -145.9 (1F, tt, *J* = 21.0, 5.0 Hz), -159.1 – -159.3 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{26}H_{20}F_5NNaO_4$: 528.1205. Found $[M+Na]^+$: 528.1181. *Characteristic signals for the minor E diastereomer:* δ_H (400 MHz, $CDCl_3$) 6.60 (1H, dq, *J* = 15.5, 2.0 Hz), 6.08 (1H, dq, *J* = 15.5, 6.5 Hz), 5.16 (2H, s), 3.07 – 3.02 (2H, m), 1.85 (3H, dd, *J* = 6.5, 2.0 Hz). δ_C (101 MHz, $CDCl_3$) 52.0, 31.0, 18.8.

Benzyl 1-vinyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (314b)

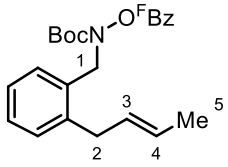


General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 17.5 mol% ligand **L3** (*vide supra*); 100 mol% Et_3N; dioxane (0.4 M); 130 °C; 24 hours. Substrate **313b** (53.1 mg, 0.105 mmol) was employed. FCC (*three times*, first eluent: 24:1 petrol:acetone; second, gradient elution: 1:0 – 99:1 PhMe:EtOAc; third

[L] CbzNHO^{F}Bz was prepared by Dr Xiaofeng Ma (University of Bristol) according to a reported procedure.[117]

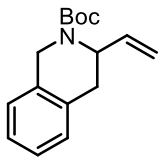
eluent: 14:1 petrol:EtOAc) afforded **314b** (17.2 mg, 56 %) as a colourless oil. *This compound exists as an approximately 1:1 mixture of rotamers; this results in the doubling of several signals in the ^{1}H and ^{13}C NMR spectra.* ν_{max} / cm^{-1}: (*film*) 3030 (m), 2933 (m), 1697 (s), 1425 (s). δ_H (500 MHz, $CDCl_3$) 7.40 – 7.29 (5H, m, 5 × ArC<u>H</u>), 7.21 – 7.09 (4H, m, 4 × ArC<u>H</u>), 5.98 (1H, ddd, *J* = 16.0, 10.0, 5.5 Hz, C**4**-<u>H</u>), 5.73 and 5.64 (2 × 0.5H, br s, C**3**-<u>H</u>), 5.25 – 5.12 (3H, m, C**5**-<u>H</u> and OC<u>H</u>$_2$Ph), 5.06 (1H, br s, C**5**-<u>H</u>'), 4.21 and 4.08 (2 × 0.5H, br s, C**1**-<u>H</u>), 3.37 and 3.29 (2 × 0.5H, br s, C**1**-<u>H</u>'), 2.94 (1H, br s, C**2**-<u>H</u>), 2.78 and 2.74 (2 × 0.5H, dd, *J* = 4.0, 4.0 Hz, C**2**-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 155.5 (<u>C</u>=O), 137.6 (C**4**), 136.9 (Ar<u>C</u>), 134.7 (Ar<u>C</u>), 129.1 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 2 × 128.1 (2 × Ar<u>C</u>H), 2 × 128.0 (2 × Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 116.3 (C**5**), 67.4 (O<u>C</u>H$_2$Ph), 57.0 (C**3**), 39.1 and 38.6 (C**1**), 28.7 (C**2**). HRMS: (ESI^+) Calculated for $C_{19}H_{20}NO_2$: 294.1489. Found $[M+H]^+$: 294.1487.

***tert*-Butyl (*E*)-(2-(but-2-en-1-yl)benzyl)((pentafluorobenzoyl)oxy)carbamate (315)**



<u>General procedure O:</u> Alcohol **201** (Section 7.3, 324 mg, 2.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 15 hours. FCC (gradient elution: 2:3 – 3:7 hexane:PhMe) afforded **315** (589 mg, 62 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2981 (m), 1785 (s), 1721 (s), 1652 (m), 1498 (s), 1152 (s). δ_H (400 MHz, $CDCl_3$) 7.32 – 7.21 (2H, m, 2 × ArC<u>H</u>), 7.21 – 7.14 (2H, m, 2 × ArC<u>H</u>), 5.61 – 5.53 (1H, m, C**3**-<u>H</u>), 5.49 – 5.39 (1H, m, C**4**-<u>H</u>), 4.89 (2H, s, C**1**-<u>H</u>$_2$), 3.42 (2H, br d, *J* = 6.0 Hz, C**2**-<u>H</u>$_2$), 1.66 (3H, ddt, *J* = 6.0, 1.5, 1.5 Hz, C**5**-<u>H</u>$_3$), 1.52 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 154.5 (Boc <u>C</u>=O), 139.8 (Ar<u>C</u>), 132.7 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 129.3 (C**3**), 128.4 (Ar<u>C</u>H), 126.7 (C**4**), 126.4 (Ar<u>C</u>H), 83.7 (O<u>C</u>(CH$_3$)$_3$), 52.3 (C**1**), 35.7 (C**2**), 28.2 (OC(<u>C</u>H$_3$)$_3$), 18.0 (C**5**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.0 – -136.3 (2F, m), -146.6 (1F, tt, *J* = 21.0, 5.0 Hz), -159.3 – -159.6 (2F, m). HRMS: (ESI^+) Calculated for $C_{23}H_{22}F_5NNaO_4$: 494.1361. Found $[M+Na]^+$: 494.1376.

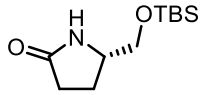
***tert*-Butyl 3-vinyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (316)**



<u>General procedure D:</u> Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **315**

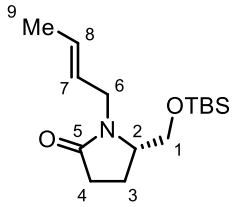
(49.5 mg, 0.105 mmol) was employed. FCC (eluent: 69:1 petrol:acetone) afforded **316** (7.0 mg, 26 %) as a colourless oil. δ_H (500 MHz, $CDCl_3$) 7.20 – 7.07 (4H, m), 5.66 (1H, ddd, *J* = 17.5, 10.5, 5.0 Hz), 5.05 (1H, d, *J* = 17.5 Hz), 5.02 (1H, d, *J* = 10.5 Hz), 5.06 – 4.91 (1H, br s), 4.73 (1H, d, *J* = 16.5 Hz), 4.33 (1H, d, *J* = 16.5 Hz), 3.14 (1H, dd, *J* = 15.5, 5.5 Hz), 2.81 (1H, d, *J* = 15.5 Hz), 1.50 (9H, s). δ_C (126 MHz, $CDCl_3$) 155.2, 137.0, 133.5, 133.1, 128.8, 126.7, 126.4, 126.2, 116.0, 80.1, 52.0, 43.5, 33.4, 28.6. *The spectroscopic properties were consistent with the data available in the literature*.[273]

(*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one (317)



A solution of (*S*)-pyroglutaminol (3.45 g, 30.0 mmol), TBSCl (5.43 g, 36.0 mmol) and imidazole (3.06 g, 45.0 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 5 hours. The reaction mixture was washed with water (3 × 50 mL) followed by brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford **317** (6.84 g, 99 %) as a colourless oil. $[\alpha]_D^{26}$ +44.9 (c = 0.44, $CHCl_3$) [Lit., $[\alpha]_D^{20}$ +44.7 (c = 1.8, $CHCl_3$)].[284] δ_H (400 MHz, $CDCl_3$) 5.99 (1H, br s), 3.79 – 3.68 (1H, m), 3.61 (1H, dd, *J* = 10.0, 4.0 Hz), 3.44 (1H, dd, *J* = 10.0, 7.5 Hz), 2.41 – 2.24 (2H, m), 2.16 (1H, dddd, *J* = 13.0, 9.0, 8.0, 7.0 Hz), 1.73 (1H, dddd, *J* = 13.0, 9.5, 7.5, 5.5 Hz), 0.88 (9H, s), 0.05 (6H, s). δ_C (101 MHz, $CDCl_3$) 178.1, 67.0, 55.9, 29.9, 25.9, 22.9, 18.3, -5.3. *The spectroscopic properties were consistent with the data available in the literature*.[284]

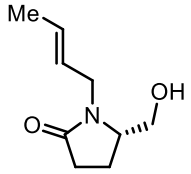
(*S*,*E*)-1-(But-2-en-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one



To a solution of pyrrolidone **317** (3.03 g, 13.2 mmol) in anhydrous THF (30 mL) and anhydrous DMF (15 mL) at 0 °C was added NaH (60 % in mineral oil, 528 mg, 13.2 mmol). The reaction mixture was stirred at room temperature for 2.5 hours, then cooled to 0 °C before addition of crotyl bromide (Section 7.3, 1.48 mL, 14.4 mmol). The reaction mixture was stirred at room temperature for 17 hours before addition of saturated aqueous NH_4Cl (25 mL), brine (25 mL) and extraction with Et_2O (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 3:2 petrol:EtOAc) afforded the title compound (3.05 g, 82 %) as a colourless oil. $[\alpha]_D^{26}$ +28.0 (c = 0.40, CH_2Cl_2). ν_{max} / cm^{-1}: (*film*) 2929 (m), 2857 (m), 1686 (s), 1110 (s). δ_H (400 MHz, $CDCl_3$) 5.69 – 5.53 (1H, m, C**8**-H), 5.42 – 5.29 (1H, m, C**7**-H), 4.22 (1H, dddq, *J* = 15.0, 5.5, 1.5, 1.5 Hz, C**6**-H),

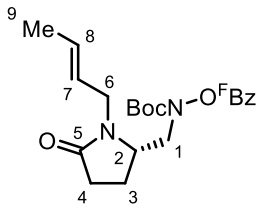
3.69 – 3.54 (3H, m, C**1**-H$_2$ and C**2**-H), 3.49 (1H, br dd, *J* = 15.0, 7.5 Hz, C**6**-H'), 2.45 (1H, ddd, *J* = 16.5, 9.5, 8.0 Hz, C**4**-H), 2.28 (1H, ddd, *J* = 16.5, 10.0, 4.5 Hz, C**4**-H'), 2.05 (1H, dddd, *J* = 13.0, 10.0, 8.0, 8.0 Hz, C**3**-H), 1.91 – 1.82 (1H, m, C**3**-H'), 1.67 (3H, dddd, *J* = 6.5, 1.5, 1.5, 1.0 Hz, C**9**-H$_3$), 0.87 (9H, s, SiC(CH$_3$)$_3$), 0.04 (3H, s, SiCH$_3$), 0.03 (3H, s, Si(CH$_3$)'). δ_C (101 MHz, $CDCl_3$) 175.3 (C**5**), 128.9 (C**8**), 125.9 (C**7**), 63.6 (C**1**), 58.8 (C**2**), 42.9 (C**6**), 30.6 (C**4**), 25.9 (SiC(CH$_3$)$_3$), 21.7 (C**3**), 18.3 (SiC(CH$_3$)$_3$), 17.8 (C**9**), 2 × -5.4 (SiCH$_3$ and Si(CH$_3$)'). HRMS: (ESI$^+$) Calculated for $C_{15}H_{29}NNaO_2Si$: 306.1860. Found $[M+Na]^+$: 306.1873.

(*S*,*E*)-1-(But-2-en-1-yl)-5-(hydroxymethyl)pyrrolidin-2-one (318)



A solution of the preceding silyl ether (2.80 g, 9.88 mmol) and TBAF (1.0 M in THF, 15.0 mL, 15.0 mmol) in THF (30 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo*, dissolved in water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 1:0 - 9:1 EtOAc:MeOH) afforded **318** (731 mg, 44 %) as a colourless oil. $[\alpha]_D^{26}$ +60.6 (c = 0.47, CH_2Cl_2) [Lit., $[\alpha]_D^{20}$ +55.4 (c = 0.52, CH_2Cl_2)].[285] δ_H (400 MHz, $CDCl_3$) 5.71 – 5.58 (1H, m), 5.42 – 5.31 (1H, m), 4.17 (1H, dddq, *J* = 15.0, 5.5, 1.5, 1.5 Hz), 3.81 – 3.75 (1H, m), 3.68 – 3.62 (1H, m), 3.60 – 3.50 (2H, m), 3.05 (1H, br s), 2.46 (1H, ddd, *J* = 16.5, 8.5, 8.5 Hz), 2.35 – 2.21 (1H, m), 2.12 – 1.91 (2H, m), 1.67 (3H, br d, *J* = 6.5 Hz). δ_C (101 MHz, $CDCl_3$) 175.8, 129.6, 125.6, 62.5, 59.0, 42.8, 30.7, 21.1, 17.8. *The spectroscopic properties were consistent with the data available in the literature*.[285]

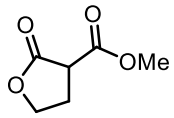
***tert*-Butyl (*S*,*E*)-((1-(but-2-en-1-yl)-5-oxopyrrolidin-2-yl)methyl)((pentafluorobenzoyl)oxy)-carbamate (319)**



General procedure O: Alcohol **318** (508 mg, 3.00 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 22 hours. FCC (*three times*, first eluent: 2:1 PhMe:EtOAc; second, gradient elution: 9:1 – 6:1 – 4:1 PhMe:acetone; third eluent: 9:1 PhMe:MeOH) afforded **319** (472 mg, 33 %) as a pale-yellow oil. $[\alpha]_D^{26}$ +10.6 (c = 0.40, CH_2Cl_2). ν_{max} / cm^{-1}: (*film*) 2980 (m), 2934 (m),

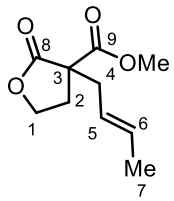
1782 (s), 1690 (s), 1498 (s), 1148 (s). δ_H (400 MHz, $CDCl_3$) 5.70 – 5.58 (1H, m, C**8**-H), 5.40 – 5.30 (1H, m, C**7**-H), 4.32 – 4.23 (1H, m, C**6**-H), 3.91 – 3.80 (2H, m, C**1**-H and C**2**-H), 3.77 – 3.68 (1H, m, C**1**-H'), 3.47 (1H, dd, *J* = 15.0, 8.0 Hz, C**6**-H'), 2.51 (1H, ddd, *J* = 17.5, 9.0, 9.0 Hz, C**4**-H), 2.39 – 2.29 (1H, m, C**4**-H'), 2.23 – 2.11 (1H, m, C**3**-H), 2.05 – 1.95 (1H, m, C**3**-H'), 1.67 (3H, d, *J* = 6.0 Hz, C**9**-H_3), 1.49 (9H, s, OC(CH_3)$_3$). δ_C (101 MHz, $CDCl_3$) 175.0 (C**5**), 154.3 (Boc C=O), 130.0 (C**8**), 125.3 (C**7**), 84.2 (OC(CH_3)$_3$), 55.5 (C**2**), 52.7 (C**1**), 43.0 (C**6**), 29.8 (C**4**), 28.1 (OC(CH_3)$_3$), 22.5 (C**3**), 17.8 (C**9**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.2 – -136.6 (2F, m), -145.6 (1F, tt, *J* = 21.0, 5.5 Hz), -158.8 – -159.1 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{21}H_{24}F_5N_2O_5$: 479.1600. Found $[M+H]^+$: 479.1596.

Methyl 2-oxotetrahydrofuran-3-carboxylate (321)



To a suspension of NaH (60 % in mineral oil, 1.44 g, 36.0 mmol) in dimethyl carbonate (2.53 mL, 30.0 mmol) and anhydrous THF (25 mL) was added γ-butyrolactone (2.31 mL, 30.0 mmol) dropwise. The reaction mixture was heated at reflux for 16 hours before being cooled to room temperature, addition of 0.5 M aqueous HCl (40 mL) and extraction with MTBE (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford **321** (1.97 g, 68 %) as a pale-yellow oil. δ_H (400 MHz, $CDCl_3$) 4.46 (1H, ddd, *J* = 9.0, 8.0, 5.5 Hz), 4.31 (1H, ddd, *J* = 9.0, 7.5, 7.5 Hz), 3.79 (3H, s), 3.56 (1H, dd, *J* = 9.5, 8.0 Hz), 2.66 (1H, dddd, *J* = 13.0, 8.0, 8.0, 7.5 Hz), 2.50 (1H, dddd, *J* = 13.0, 9.5, 7.5, 5.5 Hz). δ_C (101 MHz, $CDCl_3$) 172.4, 168.3, 67.5, 53.2, 45.9, 26.5. *The spectroscopic properties were consistent with the data available in the literature*.[286]

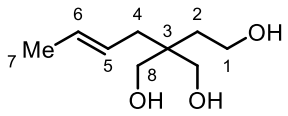
Methyl (*E*)-3-(but-2-en-1-yl)-2-oxotetrahydrofuran-3-carboxylate



To a suspension of NaH (60 % in mineral oil, 1.03 g, 25.7 mmol) in anhydrous THF (50 mL) at 0 °C was added a solution of the preceding compound (3.71 g, 25.7 mmol) in anhydrous THF (15 mL). The reaction mixture was stirred at 0 °C for an hour before addition of crotyl bromide (Section 7.3, 2.91 mL, 28.3 mmol). The reaction mixture was stirred at room temperature for 4 hours before addition of 0.5 M aqueous HCl (100 mL). The resulting phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*.

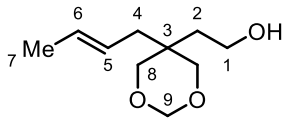
FCC (gradient elution: 6:1 – 2:1) afforded the title compound (3.33 g, 65 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2956 (m), 1771 (s), 1731 (s), 1164 (s), 1025 (s). δ_H (500 MHz, $CDCl_3$) 5.61 (1H, dqdd, *J* = 15.0, 6.5, 1.0 Hz, C**6**-H), 5.31 (1H, dddq, *J* = 15.0, 7.5, 7.0, 1.5 Hz, C**5**-H), 4.36 – 4.26 (2H, m, C**1**-H_2), 3.77 (3H, s, OCH_3), 2.73 – 2.62 (2H, m, C**2**-H and C**4**-H), 2.54 (1H, ddqd, *J* = 14.0, 7.0, 1.5, 1.0 Hz, C**4**-H'), 2.30 (1H, dt, *J* = 13.0, 8.5 Hz, C**2**-H'), 1.67 (3H, dddd, *J* = 6.5, 1.5, 1.5, 1.5 Hz, C**7**-H_3). δ_C (101 MHz, $CDCl_3$) 174.7 (C**8**), 170.2 (C**9**), 131.4 (C**6**), 124.2 (C**5**), 66.3 (C**1**), 54.2 (C**3**), 53.3 (OCH$_3$), 37.2 (C**4**), 31.0 (C**2**), 18.2 (C**7**). HRMS: (ESI^+) Calculated for $C_{10}H_{14}NaO_4$: 221.0784. Found $[M+Na]^+$: 221.0786.

(*E*)-2-(But-2-en-1-yl)-2-(hydroxymethyl)butane-1,4-diol (322)



General procedure I: The preceding compound (3.27 g, 16.5 mmol) was employed, using anhydrous THF as solvent and 2.0 eq. $LiAlH_4$ (1.0 M in THF). Alcohol **322** (2.04 g, 71 %) was isolated as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3317 (br s), 2919 (s), 1439 (m), 1034 (s). δ_H (400 MHz, $CDCl_3$) 5.54 – 5.43 (1H, m, C**6**-H), 5.43 – 5.33 (1H, m, C**5**-H), 3.78 (2H, t, *J* = 5.5 Hz, C**1**-H_2), 3.56 (4H, s, 2 × C**8**-H_2), 2.91 (3H, br s, 3 × OH), 1.95 (2H, d, *J* = 7.0 Hz, C**4**-H_2), 1.72 – 1.64 (5H, m, C**2**-H_2 and C**7**-H_3). δ_C (101 MHz, $CDCl_3$) 129.0 (C**6**), 126.0 (C**5**), 68.1 (C**8**), 58.7 (C**1**), 42.0 (C**3**), 36.4 (C**4**), 35.3 (C**2**), 18.2 (C**7**). HRMS: (ESI^+) Calculated for $C_9H_{18}NaO_3$: 197.1148. Found $[M+Na]^+$: 197.1154.

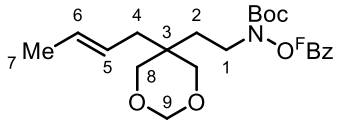
(*E*)-2-(5-(But-2-en-1-yl)-1,3-dioxan-5-yl)ethan-1-ol (323)



This compound was prepared using an adaptation of a literature procedure.[287] A solution of alcohol **322** (375 mg, 2.15 mmol), lithium bromide (37.3 mg, 430 μmol), $TsOH \cdot H_2O$ (40.9 mg, 215 μmol) and dimethoxymethane (0.65 mL, 7.35 mmol) in CH_2Cl_2 (1.1 mL) was stirred at room temperature for 18 hours. The reaction mixture was heated at 110 °C for 10 minutes before being cooled to room temperature; the resulting (solvent-free) material was purified by FCC (gradient elution: 9:1 – 2:1 hexane:EtOAc) to afford **323** (148 mg, 37 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3401 (br s), 2853 (m), 2768 (m), 1452 (m), 1165 (s), 1027 (s). δ_H (500 MHz, $CDCl_3$) 5.50 (1H, dqt, *J* = 15.0, 6.5, 1.0 Hz, C**6**-H), 5.34 (1H, dtq, *J* = 15.0, 7.5, 1.5 Hz, C**5**-H), 4.90 (1H, d, *J* = 6.0 Hz, C**9**-H), 4.73 (1H, d, *J* = 6.0 Hz, C**9**-H'), 3.84 – 3.79 (2H, m, C**1**-H_2), 3.72 (2H, d, *J* = 11.5 Hz, 2 × C**8**-H), 3.59 (2H, d, *J* = 11.5 Hz, 2 × C**8**-H'), 2.38 (1H, br s, OH), 2.01 (2H, br d, *J* = 7.5 Hz, C**4**-H_2), 1.69 – 1.65 (5H, m,

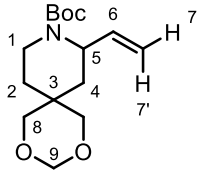
C**2**-H$_2$ and C**7**-H$_3$). δ_C (126 MHz, $CDCl_3$) 129.5 (C**6**), 124.8 (C**5**), 94.1 (C**9**), 75.0 (C**8**), 59.1 (C**1**), 2 × 37.5 (C**2** and C**4**), 35.7 (C**3**), 18.2 (C**7**). HRMS: (ESI^+) Calculated for $C_{10}H_{18}NaO_3$: 209.1148. Found $[M+Na]^+$: 209.1157.

***tert*-Butyl (*E*)-(2-(5-(but-2-en-1-yl)-1,3-dioxan-5-yl)ethyl)((pentafluorobenzoyl)oxy)carbamate (324)**



General procedure O: Alcohol **323** (587 mg, 3.15 mmol) was employed with BocNHO^{F}Bz (*vide supra*). The reaction time was 16 hours. FCC (gradient elution: 1:0 – 19:1 PhMe:EtOAc) afforded **324** (671 mg, 43 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2980 (m), 2851 (m), 2727 (m), 1783 (s), 1721 (s), 1653 (m), 1504 (s), 1149 (s). δ_H (500 MHz, $CDCl_3$) 5.58 – 5.49 (1H, m, C**6**-H), 5.36 (1H, dtq, *J* = 15.0, 7.5, 1.5 Hz, C**5**-H), 4.82 (1H, d, *J* = 6.0 Hz, C**9**-H), 4.77 (1H, d, *J* = 6.0 Hz, C**9**-H'), 3.79 – 3.73 (2H, m, C**1**-H$_2$), 3.64 – 3.56 (4H, m, 2 × C**8**-H$_2$), 2.10 (2H, d, *J* = 7.5 Hz, C**4**-H$_2$), 1.78 – 1.71 (2H, m, C**2**-H$_2$), 1.68 – 1.64 (3H, m, C**7**-H$_3$), 1.50 (9H, s, OC(CH$_3$)$_3$). δ_C (126 MHz, $CDCl_3$) 154.6 (Boc C=O), 129.8 (C**6**), 124.5 (C**5**), 94.4 (C**9**), 83.7 (OC(CH$_3$)$_3$), 74.4 (C**8**), 46.7 (C**1**), 2 × 35.5 (C**3** and C**4**), 29.5 (C**2**), 28.2 (OC(CH$_3$)$_3$), 18.1 (C**7**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (470 MHz, $CDCl_3$) -136.4 – -136.6 (2F, m), -146.4 (1F, tt, *J* = 21.0, 5.0 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI^+) Calculated for $C_{22}H_{26}F_5NNaO_6$: 518.1572. Found $[M+Na]^+$: 518.1574.

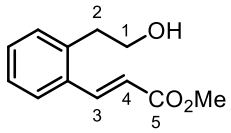
***tert*-Butyl 8-vinyl-2,4-dioxa-9-azaspiro[5.5]undecane-9-carboxylate (325)**



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **324** (52.0 mg, 0.105 mmol) was employed. FCC (eluent: 19:1 petrol:acetone) afforded **325** (20.4 mg, 69 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2977 (m), 2845 (m), 2765 (m), 1688 (s), 1407 (s), 1157 (s). δ_H (400 MHz, $CDCl_3$) 5.72 (1H, ddd, *J* = 17.5, 10.5, 3.5 Hz, C**6**-H), 5.11 (1H, ddd, *J* = 10.5, 2.5, 1.0 Hz, C**7**-H), 4.99 (1H, ddd, *J* = 17.5, 2.5, 1.0 Hz, C**7**-H'), 4.81 (1H, d, *J* = 6.0 Hz, C**9**-H), 4.77 (1H, d, *J* = 6.0 Hz, C**9**-H'), 4.76 – 4.71 (1H, m, C**5**-H), 4.00 – 3.88 (1H, m, C**1**-H), 3.79 (1H, d, *J* = 11.5 Hz, C**8**-H), 3.70 (1H, d, *J* = 11.5 Hz, C**8**-H'), 3.48 (1H, d, *J* = 11.0 Hz, C**8**'-H), 3.41 (1H, d, *J* = 11.0 Hz, C**8**'-H'), 2.95 (1H, ddd, *J* = 13.5, 13.0,

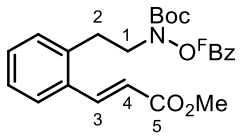
3.0 Hz, C**1**-H'), 1.84 – 1.74 (2H, m, C**2**-H and C**4**-H), 1.53 (1H, dd, *J* = 14.0, 7.0 Hz, C**4**-H'), 1.44 (9H, s, OC(CH_3)$_3$), 1.29 (1H, ddd, *J* = 13.0, 13.0, 5.5 Hz, C**2**-H'). δ_C (101 MHz, $CDCl_3$) 155.4 (C=O), 138.2 (C**6**), 114.0 (C**7**), 94.5 (C**9**), 79.9 (OC(CH_3)$_3$), 77.7 (C**8**'), 73.3 (C**8**), 51.1 (C**5**), 35.5 (C**1**), 33.8 (C**4**), 32.5 (C**3**), 30.0 (C**2**), 28.5 (OC(CH_3)$_3$). HRMS: (ESI^+) Calculated for $C_{15}H_{25}NNaO_4$: 306.1676. Found $[M+Na]^+$: 306.1679.

Methyl (*E*)-3-(2-(2-hydroxyethyl)phenyl)acrylate



This compound was prepared according to a literature procedure.[288] A solution of 2-bromophenethyl alcohol (**326a**) (2.01 g, 10.0 mmol), $Pd(OAc)_2$ (112 mg, 500 μmol), tri(*o*-tolyl)phosphine (304 mg, 1.00 mmol) and methyl acrylate (1.35 mL, 15.0 mmol) in anhydrous Et_3N (7.0 mL) was sparged with argon for five minutes. The reaction mixture was heated at 95 °C in a sealed tube for 19 hours before being filtered through celite. The filter cake was rinsed with EtOAc, and the filtrate was concentrated *in vacuo*. FCC (gradient elution: 2:1 – 3:2 petrol:EtOAc) afforded the title compound (1.57 g, 76 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3406 (br s), 2950 (m), 1698 (s), 1630 (s), 1318 (s), 1170 (s). δ_H (400 MHz, $CDCl_3$) 8.02 (1H, d, *J* = 16.0 Hz, C**3**-H), 7.60 – 7.57 (1H, m, ArCH), 7.37 – 7.31 (1H, m, ArCH), 7.29 – 7.24 (2H, m, 2 × ArCH), 6.38 (1H, d, *J* = 16.0 Hz, C**4**-H), 3.87 – 3.78 (5H, m, C**1**-H_2 and OCH_3), 3.04 (2H, t, *J* = 7.0 Hz, C**2**-H_2), 1.71 – 1.64 (1H, br s, OH). δ_C (101 MHz, $CDCl_3$) 167.5 (C**5**), 142.2 (C**3**), 138.2 (ArC), 133.7 (ArC), 131.0 (ArCH), 130.3 (ArCH), 127.3 (ArCH), 127.0 (ArCH), 119.7 (C**4**), 63.5 (C**1**), 51.9 (OCH_3), 36.6 (C**2**). HRMS: (ESI^+) Calculated for $C_{12}H_{14}NaO_3$: 229.0835. Found $[M+Na]^+$: 229.0845.

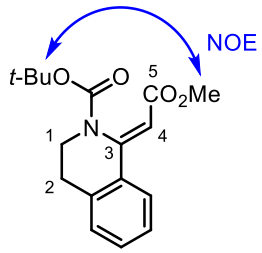
Methyl (*E*)-3-(2-(2-((pentafluorobenzoyloxy)(*tert*-butoxycarbonyl)amino)ethyl)phenyl)acrylate (327a)



General procedure O: The preceding alcohol (619 mg, 3.00 mmol) was employed with $BocNHO^FBz$ (*vide supra*). The reaction time was 16 hours. FCC (gradient elution: 99:1 – 19:1 PhMe:EtOAc) afforded **327a** (1.07 g, 69 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2982 (m), 1783 (s), 1716 (s), 1652 (m), 1634 (m), 1500 (s), 1150 (s). δ_H (400 MHz, $CDCl_3$) 7.97 (1H, d, *J* = 16.0 Hz, C**3**-H), 7.58 – 7.54 (1H, m, ArCH), 7.35 – 7.29 (1H, m, ArCH), 7.29 – 7.23 (2H, m, 2 × ArCH), 6.37 (1H, d, *J* = 16.0 Hz, C**4**-H), 3.87 (2H, t, *J* = 7.5 Hz, C**1**-H_2), 3.77 (3H, s, OCH_3), 3.12 (2H, t, *J* = 7.5 Hz, C**2**-H_2), 1.42 (9H, s,

OC(C$\underline{H}_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 167.0 (C**5**), 154.0 (Boc $\underline{C}$=O), 141.4 (C**3**), 137.3 (Ar$\underline{C}$), 133.5 (Ar$\underline{C}$), 130.7 (Ar$\underline{C}$H), 130.2 (Ar$\underline{C}$H), 127.4 (Ar$\underline{C}$H), 126.8 (Ar$\underline{C}$H), 120.0 (C**4**), 83.4 (O$\underline{C}$(CH$_3$)$_3$), 51.8 (C**1**), 51.6 (O$\underline{C}$H$_3$), 30.6 (C**2**), 27.9 (OC(C$\underline{H}_3$)$_3$). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.1 – -136.4 (2F, m), -146.6 (1F, tt, *J* = 21.0, 5.5 Hz), -159.5 – -159.7 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{24}H_{22}F_5NNaO_6$: 538.1259. Found [M+Na]$^+$: 538.1272.

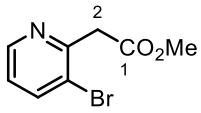
tert-Butyl (*Z*)-1-(2-methoxy-2-oxoethylidene)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate ((*Z*)-328a)



General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **327a** (54.1 mg, 0.105 mmol) was employed. FCC (gradient elution: 49:1 - 19:1 PhMe:EtOAc) afforded **(*Z*)-328a** (23.9 mg, 75 %) as a pale-yellow oil.

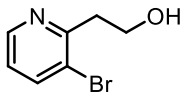
When the cyclisation is run to partial completion: **General procedure D:** Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 500 mol% Et_3N; THF (0.4 M); 130 °C, 3 hours. Substrate **327a** (54.1 mg, 0.105 mmol) was employed. By ^{1}H NMR analysis of the crude product, **328a** was found to be produced as a 14:1 mixture of (*E*)- and (*Z*)-isomers. FCC (eluent: 29:1 PhMe:EtOAc) exclusively afforded **(*Z*)-328a** (22.4 mg, 70 %) as a colourless oil. *The product was assigned as the (Z)-isomer based on the observed NOE correlation between the OMe and the t-Bu protons.* ν_{max} / cm^{-1}: (*film*) 2976 (m), 2929 (m), 1698 (s), 1629 (s), 1149 (s). δ_H (400 MHz, $CDCl_3$) 7.69 – 7.65 (1H, m, ArC$\underline{H}$), 7.33 – 7.20 (2H, m, 2 × ArC$\underline{H}$), 7.18 – 7.14 (1H, m, ArC$\underline{H}$), 6.30 (1H, s, C**4**-$\underline{H}$), 4.24 – 3.54 (2H, br s, C**1**-$\underline{H}_2$), 3.74 (3H, s, OC$\underline{H}_3$), 2.90 (2H, br s, C**2**-$\underline{H}_2$), 1.43 (9H, s, OC(C$\underline{H}_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 166.4 (C**5**), 152.9 (Boc $\underline{C}$=O), 145.8 (C**3**), 136.7 (Ar$\underline{C}$), 131.6 (Ar$\underline{C}$), 129.9 (Ar$\underline{C}$H), 129.3 (Ar$\underline{C}$H), 126.9 (Ar$\underline{C}$H), 124.5 (Ar$\underline{C}$H), 106.9 (C**4**), 81.3 (O$\underline{C}$(CH$_3$)$_3$), 51.4 (O$\underline{C}$H$_3$), 43.5 (C**1**), 29.0 (C**2**), 28.3 (OC(C$\underline{H}_3$)$_3$). HRMS: (ESI$^+$) Calculated for $C_{17}H_{21}NNaO_4$: 326.1363. Found [M+Na]$^+$: 326.1365.

Methyl 2-(3-bromopyridin-2-yl)acetate



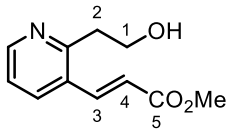
To a solution of LHDMS (0.5 M in THF, 150 mL, 75.0 mmol) was added 3-bromo-2-methylpyridine (2.88 mL, 25.0 mmol) dropwise. The reaction mixture was stirred for 2.5 hours before dropwise addition of dimethyl carbonate (3.37 mL, 40.0 mmol), and then stirred for a further 14 hours before being partially concentrated *in vacuo*. The reaction mixture was partitioned between EtOAc (100 mL) and water (50 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (5.63 g, 98 %) as a red oil, which was used without further purification. ν_{max} / cm^{-1}: (*film*) 2953 (m), 1736 (s), 1574 (m), 1429 (s), 1023 (s). δ_H (400 MHz, $CDCl_3$) 8.49 (1H, dd, *J* = 4.5, 1.5 Hz, ArC<u>H</u>), 7.86 (1H, dd, *J* = 8.0, 1.5 Hz, ArC<u>H</u>), 7.10 (1H, dd, *J* = 8.0, 4.5 Hz, ArC<u>H</u>), 4.06 (2H, s, C**2**-<u>H_2</u>), 3.73 (3H, s, OC<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 170.0 (C**1**), 153.6 (Ar<u>C</u>), 147.9 (Ar<u>C</u>H), 140.3 (Ar<u>C</u>H), 123.6 (Ar<u>C</u>H), 122.0 (Ar<u>C</u>), 52.3 (OC<u>H_3</u>), 43.6 (C**2**). HRMS: (ESI^+) Calculated for $C_8H_9BrNO_2$: 229.9811. Found $[M+H]^+$: 229.9811.

2-(3-Bromopyridin-2-yl)ethan-1-ol (326b)



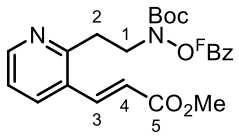
This compound was prepared according to a literature procedure.[289] To a solution of the preceding compound (4.60 g, 20.0 mmol) in anhydrous THF (80 mL) at -78 °C was added DiBAl-H (1.0 M in hexane, 40.0 mL, 40.0 mmol). The reaction mixture was stirred at room temperature for 3 hours before being diluted with Et_2O and cooled to 0 °C. The reaction mixture was quenched slowly with water (1.6 mL), 4.0 M aqueous NaOH (1.6 mL) and a further portion of water (4.0 mL). The reaction mixture was stirred at room temperature for 20 minutes before being dried over Na_2SO_4, filtered and concentrated *in vacuo*. FCC (eluent: 2:3 petrol:EtOAc) afforded **326b** (3.16 g, 78 %) as a red oil. δ_H (500 MHz, $CDCl_3$) 8.45 (1H, dd, *J* = 5.0, 1.5 Hz), 7.86 (1H, dd, *J* = 8.0, 1.5 Hz), 7.07 (1H, ddt, *J* = 8.0, 5.0, 0.5 Hz), 4.08 (2H, t, *J* = 5.5 Hz), 3.16 (2H, td, *J* = 5.5, 0.5 Hz). δ_C (126 MHz, $CDCl_3$) 159.0, 147.2, 140.3, 122.7, 121.8, 60.5, 38.1. *The spectroscopic properties were consistent with the data available in the literature*.[289]

Methyl (*E*)-3-(2-(2-hydroxyethyl)pyridin-3-yl)acrylate



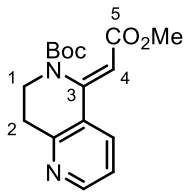
A solution of **326b** (1.21 g, 6.00 mmol), $Pd(OAc)_2$ (67.4 mg, 300 μmol), tri(*o*-tolyl)phosphine (183 mg, 600 μmol), methyl acrylate (0.81 mL, 9.00 mmol) and Et_3N (1.26 mL, 9.00 mmol) in anhydrous DMF (12 mL) was sparged with argon for five minutes. The reaction mixture was heated at 90 °C in a sealed tube for 21 hours before being diluted with brine (25 mL) and extracted with EtOAc (3 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 1:0 – 9:1 EtOAc:MeOH) afforded the title compound (1.22 g, 98 %) as a red crystalline solid. m.p. 70-74 °C (acetone:petrol, *needles*). ν_{max} / cm^{-1}: (*solid*) 3163 (br s), 2855 (m), 1712 (s), 1637 (s), 1169 (s), 1053 (s). δ_H (400 MHz, $CDCl_3$) 8.53 (1H, dd, *J* = 5.0, 2.0 Hz, ArC<u>H</u>), 7.92 (1H, d, *J* = 16.0 Hz, C**3**-<u>H</u>), 7.85 (1H, dd, *J* = 8.0, 2.0 Hz, ArC<u>H</u>), 7.25 (1H, dd, *J* = 8.0, 5.0 Hz, ArC<u>H</u>), 6.40 (1H, d, *J* = 16.0 Hz, C**4**-<u>H</u>), 4.11 (2H, t, *J* = 5.5 Hz, C**1**-<u>H_2</u>), 3.85 (3H, s, OC<u>H_3</u>), 3.17 (2H, t, *J* = 5.5 Hz, C**2**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 166.6 (C**5**), 159.2 (Ar<u>C</u>), 149.6 (Ar<u>C</u>H), 140.0 (C**3**), 134.3 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>), 121.9 (Ar<u>C</u>H), 121.7 (C**4**), 60.8 (C**1**), 51.9 (O<u>C</u>H_3), 35.7 (C**2**). HRMS: (ESI^+) Calculated for $C_{11}H_{13}NNaO_3$: 230.0788. Found $[M+Na]^+$: 230.0797.

Methyl (*E*)-3-(2-(2-((*tert*-butoxycarbonyl)((pentafluorobenzoyl)oxy)amino)ethyl)pyridin-3-yl)-acrylate (327b)

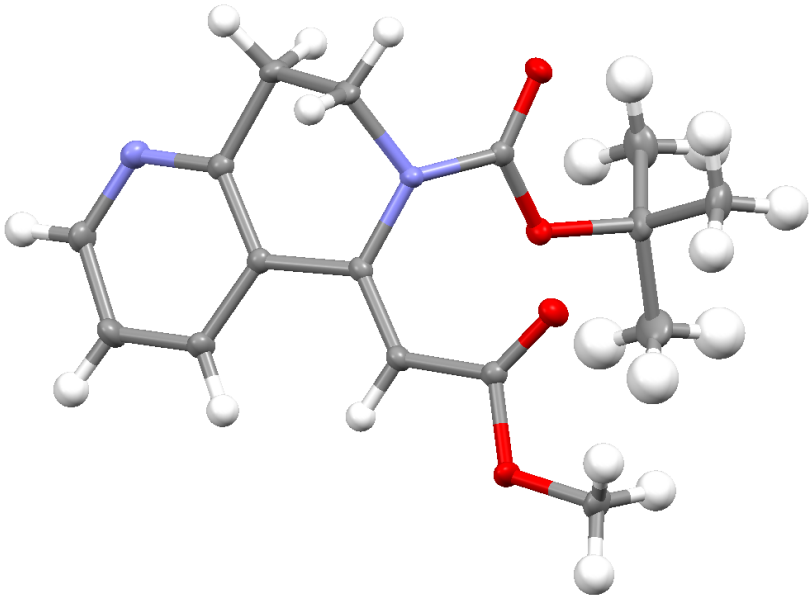


<u>General procedure O:</u> The preceding alcohol (518 mg, 2.50 mmol) was employed with $BocNHO^FBz$ (*vide supra*). The reaction time was 16 hours. FCC (gradient elution: 19:1 – 14:1 – 9:1 PhMe:EtOAc) afforded **327b** (837 mg, 65 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2982 (m), 1782 (s), 1720 (s), 1651 (m), 1501 (s), 1154 (s). δ_H (400 MHz, $CDCl_3$) 8.53 (1H, dd, *J* = 5.0, 2.0 Hz, ArC<u>H</u>), 7.94 (1H, d, *J* = 16.0 Hz, C**3**-<u>H</u>), 7.79 (1H, dd, *J* = 8.0, 2.0 Hz, ArC<u>H</u>), 7.19 (1H, dd, *J* = 8.0, 5.0 Hz, ArC<u>H</u>), 6.36 (1H, d, *J* = 16.0 Hz, C**4**-<u>H</u>), 4.14 (2H, t, *J* = 7.5 Hz, C**1**-<u>H_2</u>), 3.79 (3H, s, OC<u>H_3</u>), 3.30 (2H, t, *J* = 7.5 Hz, C**2**-<u>H_2</u>), 1.45 (9H, s, OC(C<u>H_3</u>)$_3$). δ_C (101 MHz, $CDCl_3$) 166.6 (C**5**), 157.1 (Ar<u>C</u>), 154.2 (Boc <u>C</u>=O), 150.5 (Ar<u>C</u>H), 140.2 (C**3**), 134.3 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>), 122.2 (Ar<u>C</u>H), 122.0 (C**4**), 83.6 (O<u>C</u>$(CH_3)_3$), 51.9 (O<u>C</u>H_3), 50.5 (C**1**), 32.7 (C**2**), 28.1 (OC(<u>C</u>H_3)$_3$). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.9 – -136.4 (2F, m), -146.7 (1F, tt, *J* = 21.0, 5.0 Hz), -159.5 – -159.7 (2F, m). HRMS: (ESI^+) Calculated for $C_{23}H_{22}F_5N_2O_6$: 517.1393. Found $[M+H]^+$: 517.1410.

***tert*-butyl (*Z*)-5-(2-methoxy-2-oxoethylidene)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate ((*Z*)-328b)**

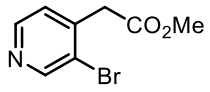


General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 17.5 mol% ligand **L3** (*vide supra*); 100 mol% Et_3N; dioxane (0.3 M); 130 °C; 24 hours. Substrate **327b** (54.2 mg, 0.105 mmol) was employed. FCC (*two times*, first eluent: 3:2 PhMe:EtOAc; second eluent: 14:1 PhMe:acetone) afforded **(*Z*)-328b** (17.2 mg, 54 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*film*) 2976 (m), 1720 (s), 1633 (s), 1150 (s). δ_H (400 MHz, $CDCl_3$) 8.52 (1H, dd, *J* = 5.0, 1.5 Hz, ArC<u>H</u>), 7.96 (1H, dd, *J* = 8.0, 1.5 Hz, ArC<u>H</u>), 7.21 (1H, dd, *J* = 8.0, 5.0 Hz, ArC<u>H</u>), 6.30 (1H, s, C**4**-<u>H</u>), 4.19 – 3.80 (2H, br s, C**1**-$\underline{H}_2$), 3.76 (3H, s, OC$\underline{H}_3$), 3.09 (2H, t, *J* = 6.5 Hz, C**2**-$\underline{H}_2$), 1.45 (9H, s, OC(C$\underline{H}_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 165.8 (C**5**), 156.0 (Ar<u>C</u>), 152.4 (Boc <u>C</u>=O), 150.4 (Ar<u>C</u>H), 143.4 (Ar<u>C</u>), 131.8 (Ar<u>C</u>H), 126.8 (C**3**), 121.9 (Ar<u>C</u>H), 107.7 (C**4**), 81.7 (O<u>C</u>(CH$_3$)$_3$), 51.4 (O<u>C</u>H$_3$), 42.7 (C**1**), 32.2 (C**2**), 28.1 (OC(<u>C</u>H$_3$)$_3$). HRMS: (ESI$^+$) Calculated for $C_{16}H_{20}N_2NaO_4$: 327.1315. Found $[M+Na]^+$: 327.1311.



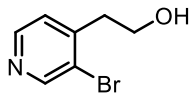
*ORTEP view of **(Z)-328b**.*

Methyl 2-(3-bromopyridin-4-yl)acetate



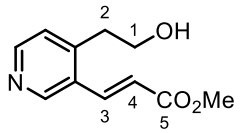
To a solution of LHDMS (0.5 M in THF, 150 mL, 75.0 mmol) was added 3-bromo-4-methylpyridine (2.88 mL, 25.0 mmol) dropwise. The reaction mixture was stirred at room temperature for 1.5 hours before addition of dimethyl carbonate (3.37 mL, 40.0 mmol) dropwise, and then stirred for a further 15 hours before being partially concentrated *in vacuo*. The reaction mixture was partitioned between EtOAc (100 mL) and water (50 mL). The resulting phases were separated, and the aqueous phase was extracted with EtOAc (2 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (5.51 g, 96 %) as a red oil, which was used without further purification. δ_H (400 MHz, $CDCl_3$) 8.71 (1H, s), 8.47 (1H, d, *J* = 5.0 Hz), 7.25 (1H, d, *J* = 5.0 Hz), 3.79 (2H, s), 3.73 (3H, s). δ_C (101 MHz, $CDCl_3$) 169.6, 152.2, 148.5, 142.8, 126.2, 123.6, 52.6, 40.8. *The spectroscopic properties were consistent with the data available in the literature*.[290]

2-(3-Bromopyridin-4-yl)ethan-1-ol (326c)



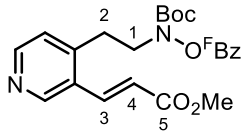
This compound was prepared according to a literature procedure.[289] To a solution of the preceding compound (4.60 g, 20.0 mmol) in anhydrous THF (80 mL) at -78 °C was added DiBAl-H (1.0 M in hexane, 40.0 mL, 40.0 mmol). The reaction mixture was stirred at room temperature for 4 hours before being diluted with Et_2O and cooled to 0 °C. The reaction mixture was quenched slowly with water (1.6 mL), 4.0 M aqueous NaOH (1.6 mL) and a further portion of water (4.0 mL). The reaction mixture was stirred at room temperature for 20 minutes before being dried over Na_2SO_4, filtered and concentrated *in vacuo*. FCC (eluent: 1:4 petrol:EtOAc) afforded **326c** (1.76 g, 44 %) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 8.65 (1H, s), 8.39 (1H, d, *J* = 5.0 Hz), 7.24 (1H, d, *J* = 5.0 Hz), 3.93 (2H, t, *J* = 6.5 Hz), 3.01 (2H, t, *J* = 6.5 Hz), 1.87 (1H, br s). δ_C (101 MHz, $CDCl_3$) 152.0, 148.2, 147.3, 126.2, 123.5, 61.1, 38.6. *The spectroscopic properties were consistent with the data available in the literature*.[289]

Methyl (*E*)-3-(4-(2-hydroxyethyl)pyridin-3-yl)acrylate



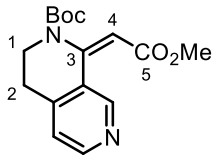
A solution of **326c** (1.21 g, 6.00 mmol), $Pd(OAc)_2$ (67.4 mg, 300 μmol), tri(*o*-tolyl)phosphine (183 mg, 600 μmol), methyl acrylate (0.81 mL, 9.00 mmol) and Et_3N (1.26 mL, 9.00 mmol) in anhydrous DMF (12 mL) was sparged with argon for five minutes. The reaction mixture was heated at 90 °C in a sealed tube for 17 hours before being diluted with brine (25 mL) and extracted with EtOAc (3 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 1:0 – 19:1 EtOAc:MeOH) afforded the title compound (1.16 g, 93 %) as a yellow oil. ν_{max} / cm^{-1}: (*film*) 3356 (br s), 2952 (m), 1717 (s), 1594 (m), 1436 (m), 1318 (s). δ_H (400 MHz, $CDCl_3$) 8.72 (1H, s, ArC<u>H</u>), 8.48 (1H, d, *J* = 5.0 Hz, ArC<u>H</u>), 7.94 (1H, d, *J* = 16.0 Hz, C**3**-<u>H</u>), 7.21 (1H, d, *J* = 5.0 Hz, ArC<u>H</u>), 6.44 (1H, d, *J* = 16.0 Hz, C**4**-<u>H</u>), 3.89 (2H, t, *J* = 6.5 Hz, C**1**-<u>H_2</u>), 3.83 (3H, s, OC<u>H_3</u>), 3.01 (2H, t, *J* = 6.5 Hz, C**2**-<u>H_2</u>), 1.82 (1H, br s, O<u>H</u>). δ_C (101 MHz, $CDCl_3$) 166.9 (C**5**), 150.2 (Ar<u>C</u>H), 147.8 (Ar<u>C</u>H), 147.2 (Ar<u>C</u>), 139.3 (C**3**), 130.2 (Ar<u>C</u>), 125.2 (Ar<u>C</u>H), 121.3 (C**4**), 62.1 (C**1**), 52.1 (O<u>C</u>H_3), 35.9 (C**2**). HRMS: (ESI^+) Calculated for $C_{11}H_{13}NNaO_3$: 230.0788. Found $[M+Na]^+$: 230.0792.

Methyl (*E*)-3-(4-(2-((tert-butoxycarbonyl)((pentafluorobenzoyl)oxy)amino)ethyl)pyridin-3-yl)-acrylate (327c)

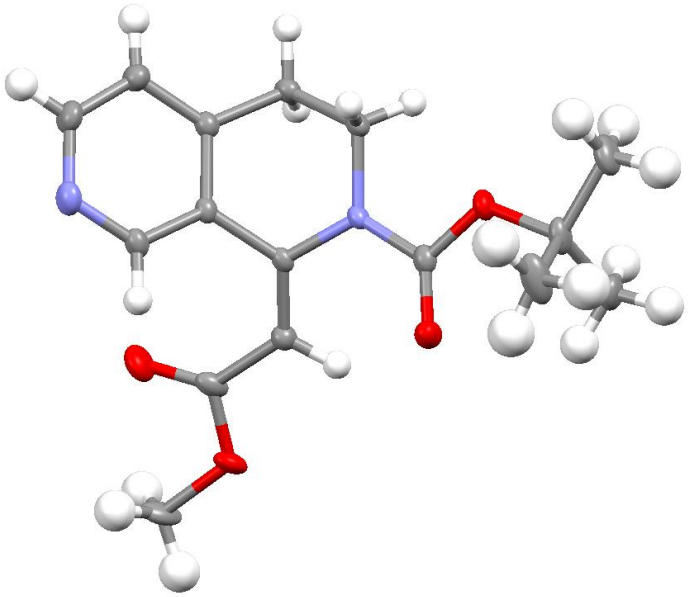


<u>General procedure O:</u> The preceding alcohol (518 mg, 2.50 mmol) was employed with $BocNHO^FBz$ (*vide supra*). The reaction time was 16 hours. FCC (*two times*, first eluent: 39:1 PhMe:Et_3N; second, gradient elution: 5:1 – 5:2 PhMe:EtOAc) afforded **327c** (400 mg, 31 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2983 (m), 1784 (s), 1720 (s), 1653 (m), 1505 (s), 1155 (s). δ_H (400 MHz, $CDCl_3$) 8.74 (1H, s, ArC<u>H</u>), 8.51 (1H, d, *J* = 5.0 Hz, ArC<u>H</u>), 7.90 (1H, d, *J* = 16.0 Hz, C**3**-<u>H</u>), 7.21 (1H, d, *J* = 5.0 Hz, ArC<u>H</u>), 6.45 (1H, d, *J* = 16.0 Hz, C**4**-<u>H</u>), 3.92 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 3.79 (3H, s, OC<u>H_3</u>), 3.10 (2H, t, *J* = 7.0 Hz, C**2**-<u>H_2</u>), 1.41 (9H, s, OC(C<u>H_3</u>)$_3$). δ_C (101 MHz, $CDCl_3$) 166.6 (C**5**), 154.0 (Boc <u>C</u>=O), 150.7 (Ar<u>C</u>H), 148.3 (Ar<u>C</u>H), 145.7 (Ar<u>C</u>), 138.6 (C**3**), 130.1 (Ar<u>C</u>), 125.0 (Ar<u>C</u>H), 122.0 (C**4**), 84.0 (O<u>C</u>$(CH_3)_3$), 52.0 (O<u>C</u>H_3), 50.8 (C**1**), 30.2 (C**2**), 28.0 (OC(<u>C</u>$H_3)_3$). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.2 – -136.5 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.5 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI^+) Calculated for $C_{23}H_{22}F_5N_2O_6$: 517.1393. Found $[M+H]^+$: 517.1391.

***tert*-Butyl (*E*)-1-(2-methoxy-2-oxoethylidene)-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate ((*E*)-328c)**

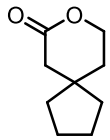


General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 300 mol% Et_3N; THF (0.4 M); 130 °C, 10 hours. Substrate **327c** (54.2 mg, 0.105 mmol) was employed. FCC (*two times*, first, gradient elution: 10:1 – 8:1 PhMe:acetone; second eluent: 19:1 PhMe:MeOH) afforded **(*E*)-328c** (25.0 mg, 78 %, 6:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless crystalline solid. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*film*) 2977 (m), 1707 (s), 1627 (s), 1321 (s), 1139 (s). δ_H (400 MHz, $CDCl_3$) 8.81 (1H, s, ArC<u>H</u>), 8.52 (1H, d, *J* = 5.0 Hz, ArC<u>H</u>), 7.13 (1H, d, *J* = 5.0 Hz, ArC<u>H</u>), 6.61 (1H, s, C**4**-<u>H</u>), 3.67 (3H, s, OC<u>H</u>$_3$), 3.62 (2H, t, *J* = 6.5 Hz, C**1**-<u>H</u>$_2$), 2.83 (2H, t, *J* = 6.5 Hz, C**2**-<u>H</u>$_2$), 1.52 (9H, s, OC(C<u>H</u>$_3$)$_3$). δ_C (126 MHz, $CDCl_3$) 167.2 (C**5**), 153.1 (Boc <u>C</u>=O), 2 × 150.2 (2 × Ar<u>C</u>H), 145.4 (Ar<u>C</u>), 145.1 (C**3**), 128.7 (Ar<u>C</u>), 120.8 (Ar<u>C</u>H), 110.4 (C**4**), 82.4 (O<u>C</u>(CH$_3$)$_3$), 51.5 (O<u>C</u>H$_3$), 43.4 (C**1**), 28.5 (C**2**), 28.4 (OC(<u>C</u>H$_3$)$_3$). HRMS: (ESI$^+$) Calculated for $C_{16}H_{21}N_2O_4$: 305.1496. Found $[M+H]^+$: 305.1504. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 7.10 (1H, d, *J* = 5.0 Hz), 6.40 (1H, s), 3.75 (3H, s), 1.43 (9H, s).



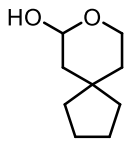
*ORTEP view of **(E)-328c**.*

8-Oxaspiro[4.5]decan-7-one



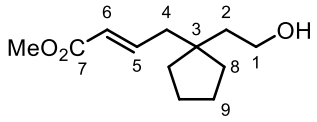
This compound was prepared according to a literature procedure.[291] A solution of 8-oxaspiro[4.5]decane-7,9-dione (**330**) (5.00 g, 29.7 mmol) and $NaBH_4$ (3.37 g, 89.1 mmol) in anhydrous THF (50 mL) was stirred at room temperature for 4 hours, then cooled to 0 °C before addition of 1.0 M aqueous HCl (80 mL). The reaction mixture was extracted with EtOAc (3 × 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 2:1 hexane:EtOAc) afforded the title compound (3.37 g, 74 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 4.36 (2H, t, *J* = 6.0 Hz), 2.41 (2H, s), 1.76 (2H, t, *J* = 6.0 Hz), 1.72 – 1.64 (4H, m), 1.59 – 1.45 (4H, m). δ_C (101 MHz, $CDCl_3$) 171.4, 67.4, 42.5, 40.8, 38.7, 34.4, 23.8. *The spectroscopic properties were consistent with the data available in the literature*.[292]

8-Oxaspiro[4.5]decan-7-ol (331)



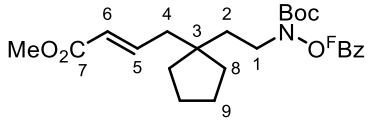
To a solution of the preceding lactone (2.31 g, 15.0 mmol) in anhydrous CH_2Cl_2 (35 mL) at -78 °C was added DiBAl-H (1.0 M in CH_2Cl_2, 16.5 mL, 16.5 mmol). The reaction mixture was stirred at -78 °C for 2.5 hours before being diluted with Et_2O and warmed to 0 °C. The reaction mixture was quenched slowly with water (0.65 mL), 4.0 M aqueous NaOH (0.65 mL) and a further portion of water (1.7 mL). The reaction mixture was stirred at room temperature for 20 minutes before being dried over Na_2SO_4, filtered and concentrated *in vacuo*. FCC (gradient elution: 9:1 – 6:1 PhMe:acetone) afforded **331** (2.02 g, 86 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 4.87 – 4.81 (1H, m), 3.94 (1H, ddd, *J* = 11.5, 4.0, 4.0 Hz), 3.59 (1H, ddd, *J* = 11.5, 10.5, 2.5 Hz), 3.34 – 3.13 (1H, m), 1.74 – 1.28 (12H, m). δ_C (101 MHz, $CDCl_3$) 94.1, 62.4, 44.2, 41.2, 40.9, 36.5, 36.3, 24.3, 23.7. *The spectroscopic properties were consistent with the data available in the literature.*[292]

Methyl (*E*)-4-(1-(2-hydroxyethyl)cyclopentyl)but-2-enoate



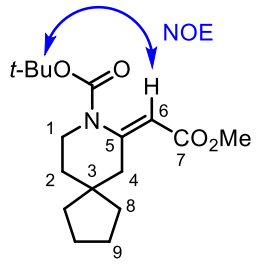
A solution of hemiacetal **331** (1.56 g, 10.0 mmol) and methyl (triphenylphosphoranylidene)acetate (5.02 g, 15.0 mmol) in anhydrous PhMe (50 mL) was heated at reflux for 5 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. FCC (eluent: 4:1 petrol:acetone) afforded the title compound (1.82 g, 86 %, 9:1 mixture of (*E*)- and (*Z*)-isomers) as a colourless oil. *Spectroscopic data for the major (E)-isomer:* ν_{max} / cm^{-1}: (*film*) 3417 (br s), 2948 (m), 1721 (s), 1436 (s), 1166 (s). δ_H (400 MHz, $CDCl_3$) 6.97 (1H, dt, *J* = 15.5, 7.5 Hz, C**5**-H), 5.84 (1H, dt, *J* = 15.5, 1.5 Hz, C**6**-H), 3.72 (3H, s, OCH_3), 3.71 – 3.66 (2H, m, C**1**-H_2), 2.19 (2H, dd, *J* = 7.5, 1.5 Hz, C**4**-H_2), 1.66 – 1.56 (6H, m, C**2**-H_2 and 2 × C**9**-H_2), 1.50 – 1.41 (4H, m, 2 × C**8**-H_2), 1.38 (1H, br s, OH). δ_C (101 MHz, $CDCl_3$) 167.0 (C**7**), 147.2 (C**5**), 123.1 (C**6**), 60.1 (C**1**), 51.6 (OCH_3), 44.5 (C**3**), 41.9 (C**2**), 41.6 (C**4**), 37.8 (C**8**), 24.5 (C**9**). HRMS: (ESI^+) Calculated for $C_{12}H_{20}NaO_3$: 235.1305. Found $[M+Na]^+$: 235.1305. *Characteristic signals for the minor (Z)-isomer:* δ_H (400 MHz, $CDCl_3$) 6.29 (1H, dt, *J* = 11.5, 7.5 Hz), 2.69 (2H, dd, *J* = 7.5, 2.0 Hz). δ_C (101 MHz, $CDCl_3$) 148.2, 120.8, 37.4.

Methyl (*E*)-4-(1-(2-((*tert*-butoxycarbonyl)((pentafluorobenzoyl)oxy)amino)ethyl)cyclopentyl)-but-2-enoate (332)



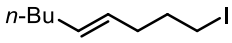
General procedure O: The preceding alcohol (531 mg, 2.50 mmol) was employed with $BocNHO^FBz$ (*vide supra*). The reaction time was 16 hours. FCC (gradient elution: 1:0 – 49:1 PhMe:EtOAc) afforded **332** (859 mg, 66 %) as a colourless oil. *The (E) and (Z)-isomers of **332** were separable by FCC; hence, this compound was isolated as a single alkene isomer.* ν_{max} / cm^{-1}: (film) 2952 (m), 1783 (s), 1722 (s), 1654 (m), 1506 (s), 1158 (s). δ_H (400 MHz, $CDCl_3$) 6.93 (1H, dt, *J* = 15.5, 8.0 Hz, C**5**-H), 5.85 (1H, dt, *J* = 15.5, 1.5 Hz, C**6**-H), 3.71 (3H, s, OCH_3), 3.70 – 3.65 (2H, m, C**1**-H_2), 2.20 (2H, dd, *J* = 8.0, 1.5 Hz, C**4**-H_2), 1.70 – 1.60 (6H, m, C**2**-H_2 and 2 × C**9**-H_2), 1.52 – 1.43 (13H, m, 2 × C**8**-H_2 and $OC(CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 166.8 (C**7**), 154.6 (Boc C=O), 146.3 (C**5**), 123.4 (C**6**), 83.6 ($OC(CH_3)_3$), 51.5 (OCH_3), 47.9 (C**1**), 44.3 (C**3**), 41.1 (C**4**), 37.5 (C**8**), 35.4 (C**2**), 28.2 ($OC(CH_3)_3$), 24.6 (C**9**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.5 – -136.7 (2F, m), -146.7 (1F, tt, *J* = 21.0, 5.0 Hz), -159.4 – -159.5 (2F, m). HRMS: (ESI^+) Calculated for $C_{24}H_{28}F_5NNaO_6$: 544.1729. Found $[M+Na]^+$: 544.1722.

***tert*-Butyl (*E*)-7-(2-methoxy-2-oxoethylidene)-8-azaspiro[4.5]decane-8-caarboxylate ((*E*)-333)**



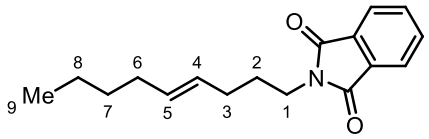
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 300 mol% Et_3N; THF (0.4 M); 130 °C, 8 hours. Substrate **322** (54.8 mg, 0.105 mmol) was employed. FCC (*two times*, first, gradient elution: 1:0 – 149:1 PhMe:acetone; second eluent: 24:1 petrol:acetone) afforded **(*E*)-333** (21.7 mg, 67 %) as a colourless oil. *The product was assigned as the (E)-isomer based on the observed NOE correlation between the C**6** and the t-Bu protons.* ν_{max} / cm^{-1}: (*film*) 2949 (m), 1698 (s), 1365 (s), 1163 (s). δ_H (400 MHz, $CDCl_3$) 5.96 (1H, s, C**6**-H), 3.67 (3H, s, OCH_3), 3.61 – 3.57 (2H, m, C**1**-H_2), 2.87 (2H, s, C**4**-H_2), 1.74 – 1.56 (6H, m, C**2**-H_2 and 2 × C**9**-H_2), 1.55 – 1.44 (11H, m, 2 × C**8**-H and $OC(CH_3)_3$), 1.42 – 1.33 (2H, m, 2 × C**8**-H'). δ_C (101 MHz, $CDCl_3$) 168.0 (C**7**), 155.2 (C**5**), 153.4 (Boc C=O), 111.0 (C**6**), 81.3 ($OC(CH_3)_3$), 51.1 (OCH_3), 44.2 (C**1**), 43.2 (C**3**), 38.5 (C**4**), 38.2 (C**8**), 36.5 (C**2**), 28.4 ($OC(CH_3)_3$), 24.3 (C**9**). HRMS: (ESI^+) Calculated for $C_{17}H_{27}NNaO_4$: 332.1823. Found $[M+Na]^+$: 332.1838.

(*E*)-1-Iodonon-4-ene



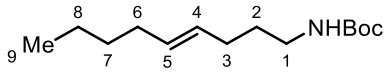
To a solution of PPh_3 (3.15 g, 12.0 mmol) and imidazole (817 mg, 12.0 mmol) in CH_2Cl_2 (15 mL) was added iodine (3.05 g, 12.0 mmol) gradually over around 5 minutes. The reaction mixture was stirred for 30 minutes before addition of (*E*)-non-4-en-1-ol (*vide supra*, 1.42 g, 10.0 mmol). The reaction mixture was stirred at room temperature for 13 hours before being diluted with hexane (25 mL), filtered through silica and eluted with pentane. The filtrate was concentrated *in vacuo*. FCC (eluent: pentane) afforded the title compound (2.40 g, 95 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2955 (m), 2924 (m), 1438 (m), 1219 (m). δ_H (400 MHz, $CDCl_3$) 5.51 (1H, dtt, *J* = 15.0, 7.0, 1.5 Hz), 5.35 (1H, dtt, *J* = 15.0, 7.0, 1.5 Hz), 3.21 (2H, t, *J* = 7.0 Hz), 2.12 (2H, dtd, *J* = 7.0, 7.0, 1.5 Hz), 2.01 (2H, dtd, *J* = 7.0, 7.0, 1.5 Hz), 1.90 (2H, tt, *J* = 7.0, 7.0 Hz), 1.40 – 1.28 (4H, m), 0.94 – 0.88 (3H, m). δ_C (101 MHz, $CDCl_3$) 132.4, 127.8, 2 × 33.3, 32.4, 31.8, 22.3, 14.1, 6.8. *The spectroscopic properties were consistent with the data available in the literature*.[293,294]

(*E*)-2-(Non-4-en-1-yl)isoindoline-1,3-dione



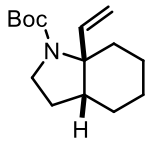
A solution of the preceding iodide (504 mg, 2.00 mmol) and potassium phthalimide (370 mg, 2.00 mmol) in anhydrous DMF (8 mL) was heated at 60 °C for 16 hours. The reaction mixture was cooled to room temperature, diluted with Et_2O (70 mL) and washed with brine (4 × 40 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (523 mg, 96 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2927 (m), 1707 (s), 1394 (s). δ_H (400 MHz, $CDCl_3$) 7.83 (2H, dd, *J* = 5.5, 3.0 Hz, 2 × ArC<u>H</u>), 7.70 (2H, dd, *J* = 5.5, 3.0 Hz, 2 × ArC<u>H</u>), 5.48 – 5.33 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 3.68 (2H, t, *J* = 7.5 Hz, C**1**-<u>H_2</u>), 2.05 (2H, dt, *J* = 7.0, 7.0 Hz, C**3**-<u>H_2</u>), 1.97 – 1.90 (2H, m, C**6**-<u>H_2</u>), 1.74 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>), 1.33 – 1.24 (4H, m, C**7**-<u>H_2</u> and C**8**-<u>H_2</u>), 0.90 – 0.83 (3H, m, C**9**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 168.4 (<u>C</u>=O), 133.8 (Ar<u>C</u>H), 132.2 (Ar<u>C</u>), 131.5 (C**5**), 128.5 (C**4**), 123.1 (Ar<u>C</u>H), 37.7 (C**1**), 32.2 (C**6**), 31.6 (C**7**), 29.9 (C**3**), 28.3 (C**2**), 22.2 (C**8**), 13.9 (C**9**). HRMS: (ESI^+) Calculated for $C_{17}H_{21}NNaO_2$: 294.1464. Found $[M+Na]^+$: 294.1469.

***tert*-Butyl (*E*)-non-4-en-1-ylcarbamate (334)**



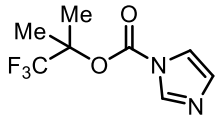
A solution of the preceding compound (505 mg, 1.86 mmol) and hydrazine (55 % aqueous solution, 0.31 mL, 5.58 mmol) in EtOH (10 mL) was heated at reflux for 2.5 hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* and dissolved in CH_2Cl_2 (15 mL) before addition of Boc_2O (0.52 mL, 2.23 mmol) and Et_3N (0.39 mL, 2.79 mmol). The reaction mixture was stirred at room temperature for 16 hours before being concentrated *in vacuo*. FCC (eluent: 9:1 petrol:EtOAc) afforded **334** (332 mg, 74 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3348 (br s), 2927 (m), 1689 (s), 1514 (s), 1169 (s). δ_H (400 MHz, $CDCl_3$) 5.46 – 5.29 (2H, m, C**4**-<u>H</u> and C**5**-<u>H</u>), 4.54 (1H, br s, N<u>H</u>), 3.09 (2H, td, *J* = 7.0, 6.5 Hz, C**1**-<u>H_2</u>), 2.04 – 1.91 (4H, m, C**3**-<u>H_2</u> and C**6**-<u>H_2</u>), 1.52 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>), 1.42 (9H, s, OC(C<u>H_3</u>)$_3$), 1.34 – 1.25 (4H, m, C**7**-<u>H_2</u> and C**8**-<u>H_2</u>), 0.89 – 0.83 (3H, m, C**9**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 156.1 (<u>C</u>=O), 131.5 (C**5**), 129.1 (C**4**), 79.1 (O<u>C</u>(CH$_3$)$_3$), 40.3 (C**1**), 32.4 (C**6**), 31.8 (C**7**), 2 × 30.0 (C**2** and C**3**), 28.6 (OC(<u>C</u>H$_3$)$_3$), 22.3 (C**8**), 14.1 (C**9**). HRMS: (ESI^+) Calculated for $C_{14}H_{27}NNaO_2$: 264.1934. Found $[M+Na]^+$: 264.1942.

***tert*-Butyl (3a*R**,7a*S**)-7a-vinyloctahydro-1*H*-indole-1-carboxylate (270)**



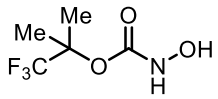
*In the following experiment, a mixture of aza-Heck (**269**) and aza-Wacker (**334**) substrates were submitted to the reaction conditions. The fact that only **269** afforded cyclised product is consistent with an aza-Heck mechanism (Section 3.5).* **General procedure D:** Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrates **269** (*vide supra*, 48.7 mg, 0.105 mmol) and **334** (16.9 mg, 70.0 μmol) were employed. From the ^{1}H NMR spectrum the yield of **270** was determined to be 79 % and no aza-Wacker product (**247a**) was observed. *Characterisation data for **270** has been provided earlier.*

1,1,1-Trifluoro-2-methylpropan-2-yl 1*H*-imidazole-1-carboxylate



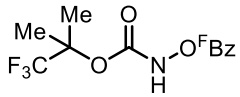
A solution of 1,1,1-trifluoro-2-methylpropan-2-ol (4.92 g, 38.4 mmol) and carbonyl diimidazole (12.5 g, 76.8 mmol) in $CHCl_3$ (80 mL) was stirred at room temperature for 22 hours before addition of water (80 mL). The resulting phases were separated, and the aqueous phase was extracted with $CHCl_3$ (40 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (5.51 g, 65 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3151 (m), 3127 (m), 1759 (s), 1154 (s). δ_H (400 MHz, $CDCl_3$) 8.08 (1H, dd, *J* = 1.0, 1.0 Hz, ArC<u>H</u>), 7.37 (1H, dd, *J* = 1.5, 1.0 Hz, ArC<u>H</u>), 7.07 (1H, dd, *J* = 1.5, 1.0 Hz, ArC<u>H</u>), 1.83 (6H, q, *J* = 1.0 Hz, OC(CF_3)(C<u>H</u>$_3$)$_2$). δ_C (101 MHz, $CDCl_3$) 146.0 (<u>C</u>=O), 137.2 (Ar<u>C</u>H), 131.0 (Ar<u>C</u>H), 124.4 (q, *J* = 282.5 Hz, OC(<u>C</u>F_3)(CH_3)$_2$), 117.2 (Ar<u>C</u>H), 83.7 (q, *J* = 30.5 Hz, O<u>C</u>(CF_3)(CH_3)$_2$), 19.4 (q, *J* = 1.5 Hz, OC(CF_3)(<u>C</u>H_3)$_2$). δ_F (377 MHz, $CDCl_3$) -83.7 (3F, s). HRMS: (ESI$^+$) Calculated for $C_8H_9F_3N_2NaO_2$: 245.0508. Found [M+Na]$^+$: 245.0511.

1,1,1-Trifluoro-2-methylpropan-2-yl hydroxycarbamate



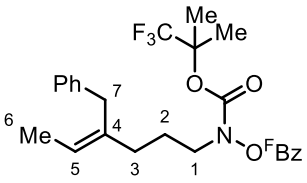
A solution of $NH_2OH{\cdot}HCl$ (3.00 g, 43.2 mmol) and $NaHCO_3$ (5.44 g, 64.8 mmol) in THF (60 mL) and water (60 mL) was stirred at room temperature for 30 minutes before addition of the preceding compound (4.80 g, 21.6 mmol). The reaction mixture was stirred for 20 hours before addition of EtOAc (100 mL) and brine (100 mL). The resulting phases were separated, and the organic phase was concentrated *in vacuo*. The crude material was dissolved in EtOAc (100 mL), washed with water (3 × 40 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (1.77 g, 44 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*film*) 3284 (br s), 2956 (m), 1703 (s), 1132 (s). δ_H (400 MHz, $CDCl_3$) 7.43 – 7.16 (2H, br s, N<u>H</u> and O<u>H</u>), 1.71 (6H, q, *J* = 1.0 Hz, OC(CF_3)(C<u>H</u>$_3$)$_2$). δ_C (101 MHz, $CDCl_3$) 156.7 (<u>C</u>=O), 124.8 (q, *J* = 282.5 Hz, OC(<u>C</u>F_3)(CH_3)$_2$), 81.3 (q, *J* = 30.0 Hz, O<u>C</u>(CF_3)(CH_3)$_2$), 19.7 (q, *J* = 1.5 Hz, OC(CF_3)(<u>C</u>H_3)$_2$). δ_F (377 MHz, $CDCl_3$) -83.8 (3F, s). HRMS: (ESI$^+$) Calculated for $C_5H_8F_3NNaO_3$: 210.0348. Found $[M+Na]^+$: 210.0347.

1,1,1-Trifluoro-2-methylpropan-2-yl ((pentafluorobenzoyl)oxy)carbamate (335)



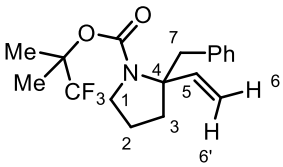
<u>General procedure G:</u> The preceding compound (1.76 g, 9.41 mmol) was employed. The reaction time was 21 hours. FCC (gradient elution: 15:1 – 7:1 hexane:EtOAc) afforded **335** (2.67 g, 74 %) as a colourless crystalline solid. m.p. 87-88 °C (CH_2Cl_2:petrol, *needles*). ν_{max} / cm^{-1}: (*solid*) 3366 (s), 2940 (m), 1782 (s), 1763 (s), 1655 (s), 1498 (s), 1133 (s). δ_H (400 MHz, $CDCl_3$) 8.34 (1H, br s, N<u>H</u>), 1.75 (6H, q, *J* = 1.0 Hz, OC(CF_3)(C<u>H</u>$_3$)$_2$). δ_C (101 MHz, $CDCl_3$) 158.5 (^{F}Bz <u>C</u>=O), 153.1 (Carbamate <u>C</u>=O), 124.3 (q, *J* = 282.5 Hz, OC(<u>C</u>F_3)(CH_3)$_2$), 82.5 (q, *J* = 30.5 Hz, O<u>C</u>(CF_3)(CH_3)$_2$), 19.3 (q, *J* = 1.5 Hz, OC(CF_3)(<u>C</u>H_3)$_2$). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (376 MHz, $CDCl_3$) -83.8 (3F, s), -135.0 – -135.2 (2F, m), -144.8 (1F, tt, *J* = 21.0, 6.0 Hz), -159.0 – -159.2 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{12}H_7F_8NNaO_4$: 404.0140. Found $[M+Na]^+$: 404.0157.

1,1,1-Trifluoro-2-methylpropan-2-yl (*Z*)-(4-benzylhex-4-en-1-yl)((pentafluorobenzoyl)oxy)-carbamate (266b)



General procedure O: Alcohol **159c** (Section 7.3, 381 mg, 2.00 mmol) was employed with **335**. The reaction time was 15 hours. FCC (gradient elution: 3:2 – 3:7 hexane:PhMe) afforded **266b** (587 mg, 53 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2947 (m), 1786 (s), 1731 (s), 1652 (m), 1497 (s), 1166 (s). δ_H (500 MHz, $CDCl_3$) 7.27 – 7.22 (2H, m, 2 × ArC<u>H</u>), 7.19 – 7.12 (3H, m, 3 × ArC<u>H</u>), 5.45 (1H, q, *J* = 7.0 Hz, C**5**-<u>H</u>), 3.62 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 3.39 (2H, s, C**7**-<u>H_2</u>), 1.99 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 1.75 – 1.68 (11H, m, C**2**-<u>H_2</u>, C**6**-<u>H_3</u> and $OC(CF_3)(C\underline{H}_3)_2$). δ_C (126 MHz, $CDCl_3$) 152.1 (Carbamate <u>C</u>=O), 139.7 (Ar<u>C</u>), 136.7 (C**4**), 2 × 128.1 (2 × Ar<u>C</u>H), 125.6 (Ar<u>C</u>H), 121.0 (C**5**), 81.6 (q, *J* = 30.0 Hz, $O\underline{C}(CF_3)(CH_3)_2$), 50.3 (C**1**), 35.2 (C**7**), 33.0 (C**3**), 24.8 (C**2**), 19.0 ($OC(CF_3)(\underline{C}H_3)_2$), 13.4 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl and trifluoromethyl groups could not be resolved due to their weak intensity.* δ_F (470 MHz, $CDCl_3$) -84.0 (3F, s), -135.6 – -135.8 (2F, m), -145.6 (1F, tt, *J* = 21.0, 5.5 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI^+) Calculated for $C_{25}H_{23}F_8NNaO_4$: 576.1392. Found $[M+Na]^+$: 576.1373.

1,1,1-Trifluoro-2-methylpropan-2-yl 2-benzyl-2-vinylpyrrolidine-1-carboxylate (267b)

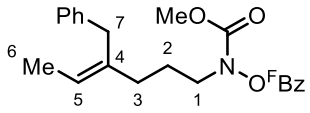


The following reaction was conducted in an NMR spectrometer (without a magnetic stirrer) and the reaction progress was monitored by collecting ^{19}F and solvent-supressed ^1H spectra. **General procedure D:** Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (*vide supra*); 100 mol% Et_3N; THF (0.2 M); 130 °C; 24 hours. Substrate **266b** (58.1 mg, 0.105 mmol) was employed. FCC (*two times*, first eluent: PhMe; second eluent: 59:1 petrol:acetone) afforded **267b** (21.6 mg, 60 %) as a colourless oil. *This compound exists as an approximately 3:2 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 2978 (m), 1701 (s), 1382 (s), 1132 (s). δ_H (400 MHz, $CDCl_3$) 7.31 – 7.19 (3H, m, A and B: 3 × ArC<u>H</u>), 7.19 – 7.11 (2H, m, A and B: 2 × ArC<u>H</u>), 6.07 (0.6H, dd, *J* = 17.5, 10.5 Hz, A: C**5**-<u>H</u>), 5.99 (0.4H, dd, *J* = 17.5, 10.5 Hz, B: C**5**-<u>H</u>), 5.12 (0.6H, d, *J* = 10.5 Hz, A: C**6**-<u>H</u>), 5.08 (0.4H, d, *J* = 10.5 Hz, B: C**6**-<u>H</u>), 5.01 (0.6H, d, *J* = 17.5 Hz, A: C**6**-<u>H</u>'), 4.98 (0.4H, d, *J* = 17.5 Hz, B: C**6**-<u>H</u>'), 3.59 (0.6H, d, *J* = 13.5 Hz, A: C**7**-<u>H</u>), 3.53 (0.4H, ddd, *J* = 12.0, 7.5, 5.0 Hz, B: C**1**-<u>H</u>), 3.44 (0.6H, ddd,

J = 11.5, 8.0, 4.0 Hz, A: C**1**-H), 3.38 (0.4H, d, *J* = 13.5 Hz, B: C**7**-H), 3.10 (0.4H, ddd, *J* = 11.0, 7.5, 7.5 Hz, B: C**1**-H'), 3.01 (0.6H, ddd, *J* = 11.0, 8.0, 7.0 Hz, A: C**1**-H'), 2.98 – 2.90 (1H, m, A and B: C**7**-H'), 2.09 – 1.95 (1H, m, A and B: C**3**-H), 1.84 – 1.70 (7H, m, A and B: C**3**-H' and $OC(CF_3)(CH_3)_2$), 1.64 – 1.51 (1H, m, A and B: C**2**-H), 1.34 – 1.16 (1H, m, A and B: C**2**-H'). δ_C (101 MHz, $CDCl_3$) 152.5 (B: C=O), 151.6 (A: C=O), 142.1 (B: C**5**), 141.5 (A: C**5**), 137.6 (B: ArC), 137.5 (A: ArC), 130.7 (A: ArCH), 130.5 (B: ArCH), 128.2 (B: ArCH), 128.0 (A: ArCH), 126.5 (B: ArCH), 126.4 (A: ArCH), 112.3 (A: C**6**), 112.2 (B: C**6**), 79.8 (q, *J* = 30.0 Hz, B: $OC(CF_3)(CH_3)_2$), 79.3 (q, *J* = 29.0 Hz, A: $OC(CF_3)(CH_3)_2$), 67.7 (A: C**4**), 67.3 (B: C**4**), 49.1 (B: C**1**), 48.8 (A: C**1**), 42.1 (B: C**7**), 41.2 (A: C**7**), 37.7 (B: C**3**), 36.1 (A: C**3**), 21.3 (A: C**2**), 20.9 (B: C**2**), 20.0 (q, *J* = 1.5 Hz, B: $OC(CF_3)(CH_3)(CH_3)$'), 2 × 19.8 (q, *J* = 1.5 Hz, A: $OC(CF_3)(CH_3)(CH_3)$' and q, *J* = 1.5 Hz, A: $OC(CF_3)(CH_3)(CH_3)$'), 19.7 (q, *J* = 1.5 Hz, B: $OC(CF_3)(CH_3)(CH_3)$'). *The ^{13}C signal corresponding to the trifluoromethyl group could not be resolved due to its weak intensity.* δ_F (377 MHz, $CDCl_3$) -82.8 (1.2F, s, B: CF_3), -84.0 (1.8F, s, A: CF_3). HRMS: (ESI^+) Calculated for $C_{18}H_{23}F_3NO_2$: 342.1675. Found $[M+H]^+$: 342.1691.

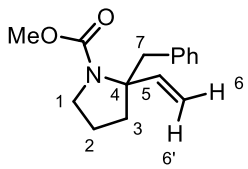
7.5 Experimental procedures for the studies in Chapter 4

Methyl (*Z*)-(4-Benzylhex-4-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (266c)



General procedure O: Alcohol **159c** (Section 7.3, 285 mg, 1.50 mmol) was employed with MeOC(O)NHO^{F}Bz (Section 7.4). The reaction time was 16 hours. FCC (eluent: 1:9 hexane:PhMe) afforded **266c** (387 mg, 56 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2919 (m), 1785 (s), 1729 (s), 1652 (m), 1602 (m), 1496 (s), 1173 (s). δ_H (400 MHz, $CDCl_3$) 7.28 – 7.22 (2H, m, 2 × ArC<u>H</u>), 7.18 – 7.12 (3H, m, 3 × ArC<u>H</u>), 5.45 (1H, q, *J* = 7.0 Hz, C**5**-<u>H</u>), 3.79 (3H, s, OC<u>H</u>$_3$), 3.67 – 3.62 (2H, m, C**1**-<u>H</u>$_2$), 3.40 (2H, s, C**7**-<u>H</u>$_2$), 2.00 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 1.76 – 1.67 (5H, m, C**2**-<u>H</u>$_2$ and C**6**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 156.2 (MeO–<u>C</u>=O), 140.1 (Ar<u>C</u>), 137.2 (C**4**), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 121.3 (C**5**), 54.0 (O<u>C</u>H$_3$), 51.1 (C**1**), 35.6 (C**7**), 33.5 (C**3**), 25.2 (C**2**), 13.8 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.0 – -136.1 (2F, m), -146.2 (1F, tt, *J* = 21.0, 5.5 Hz), -159.3 – -159.5 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{22}H_{21}F_5NO_4$: 458.1385. Found $[M+H]^+$: 458.1387.

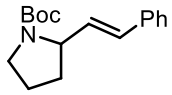
Methyl 2-benzyl-2-vinylpyrrolidine-1-carboxylate (267c)



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 20 mol% (*S*)-SIPHOS-PE; 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **266c** (52.4 mg, 0.105 mmol) was employed. FCC (eluent: 19:1 hexane:EtOAc) afforded **267c** (15.0 mg, 58 %, 34 % e.e.) as a colourless oil. *The following procedure was used to prepare a racemic sample of **267c** for SFC analysis:* **General procedure D:** Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (Section 7.4); 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **266c** (52.4 mg, 0.105 mmol) was employed. FCC (eluent: 19:1 hexane:EtOAc) afforded **267c** (21.7 mg, 84 %) as a colourless oil. *This compound exists as an approximately 2:1 mixture of rotamers A and B.* **SFC conditions:** *column*: CHIRALPACK IC, *elute*: 4.0 % MeOH/CO_2, *detector*: 250 nm, *flow rate*: 1.5 mL/min, *temperature*: 40 °C, *retention times*: (major enantiomer) t_1 = 10.6 min, (minor enantiomer) t_2 = 11.3 min. ν_{max} / cm^{-1}: (*film*) 3027 (m), 2953 (m), 2875 (m), 1693 (s), 1443 (s), 1380 (s). δ_H (400 MHz, $CDCl_3$) 7.33 – 7.06 (5H, m, A and B: 5 × ArC<u>H</u>), 6.13 (0.65H, dd, *J* = 17.5, 10.5 Hz, A: C**5**-<u>H</u>), 6.01 (0.35H, dd, *J* = 17.5, 10.5 Hz, B: C**5**-<u>H</u>),

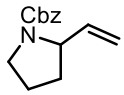
5.11 (0.65H, d, *J* = 10.5 Hz, A: C**6**-H), 5.08 – 4.94 (1.35H, m, A: C**6**-H'; B: C**6**-H_2), 3.78 (1H, s, B: OCH_3), 3.74 (2H, s, A: OCH_3), 3.61 (0.65H, d, *J* = 13.5 Hz, A: C**7**-H), 3.59 – 3.52 (0.35H, m, B: C**1**-H), 3.49 – 3.39 (1H, m, A: C**1**-H; B: C**7**-H), 3.15 – 2.97 (1.65H, m, A: C**1**-H' and C**7**-H'; B: C**1**-H'), 2.89 (0.35H, d, *J* = 13.5 Hz, B: C**7**-H'), 2.06 – 1.91 (1H, m, A and B: C**3**-H), 1.80 – 1.71 (1H, m, A and B: C**3**-H'), 1.64 – 1.52 (1H, m, A and B: C**2**-H), 1.32 – 1.19 (1H, m, A and B: C**2**-H'). δ_C (101 MHz, $CDCl_3$) 155.8 (B: C=O), 154.8 (A: C=O), 142.9 (B: C**5**), 142.0 (A: C**5**), 138.0 (A: ArC), 137.7 (B: ArC), 130.9 (A: ArCH), 130.7 (B: ArCH), 128.3 (B: ArCH), 128.1 (A: ArCH), 126.6 (B: ArCH), 126.4 (A: ArCH), 112.4 (A: C**6**), 112.0 (B: C**6**), 67.7 (A: C**4**), 67.2 (B: C**4**), 52.2 (A and B: OCH_3), 49.4 (B: C**1**), 48.5 (A: C**1**), 42.6 (B: C**7**), 41.5 (A: C**7**), 37.5 (B: C**3**), 36.0 (A: C**3**), 21.7 (A: C**2**), 21.1 (B: C**2**). HRMS: (ESI^+) Calculated for $C_{15}H_{20}NO_2$: 246.1489. Found $[M+H]^+$: 246.1500.

***tert*-Butyl (*E*)-2-styrylpyrrolidine-1-carboxylate (255)**



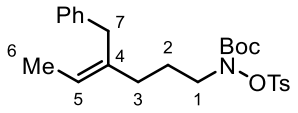
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 20 mol% (*S*)-SIPHOS-PE; 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **254** (Section 7.4, 51.0 mg, 0.105 mmol) was employed. FCC (eluent: 49:1 PhMe:EtOAc) afforded **255** (18.0 mg, 63 %, 34 % e.e.) as a colourless crystalline solid. *The procedure described in Section 7.4 was used to prepare a racemic sample of **255** for SFC analysis.* **SFC conditions:** *column*: CHIRALPACK IC, *elute*: 4.0 % MeOH/CO_2, *detector*: 250 nm, *flow rate*: 1.5 mL/min, *temperature*: 40 °C, *retention times*: (minor enantiomer) t_1 = 11.0 min, (major enantiomer) t_2 = 11.6 min. *Characterisation data for **255** has been provided earlier (Section 7.4).*

Benzyl 2-vinylpyrrolidine-1-carboxylate (244a)



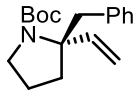
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 20 mol% (*S*)-SIPHOS-PE; 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **243a** (Section 7.4, 46.6 mg, 0.105 mmol) was employed. FCC (eluent: 29:1 PhMe:EtOAc) afforded **244a** (13.2 mg, 54 %, 60 % e.e.) as a pale-yellow oil. *The procedure described in Section 7.4 was used to prepare a racemic sample of **244a** for SFC analysis.* **SFC conditions:** *column*: CHIRALPACK IC, *elute*: 1.5 % MeOH/CO_2, *detector*: 250 nm, *flow rate*: 4.0 mL/min, *temperature*: 40 °C, *retention times*: (*S*) t_1 = 11.6 min, (*R*) t_2 = 12.6 min. *Characterisation data for **244a** has been provided earlier (Section 7.4).*

***tert*-Butyl (*Z*)-(4-benzylhex-4-en-1-yl)(tosyloxy)carbamate (266d)**



General procedure R: Alcohol **159c** (Section 7.3, 571 mg, 3.00 mmol) was employed with BocNHOTs.[LI] The reaction time was 17 hours. FCC (eluent: 1:4 petrol:PhMe) afforded **266d** (812 mg, 59 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2980 (m), 2932 (m), 1721 (s), 1599 (m), 1369 (s), 1179 (s). δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.33 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.29 – 7.23 (2H, m, 2 × ArC<u>H</u>), 7.21 – 7.11 (3H, m, 3 × ArC<u>H</u>), 5.41 (1H, q, *J* = 6.5 Hz, C**5**-<u>H</u>), 3.52 (2H, br s, C**1**-<u>H_2</u>), 3.38 (2H, s, C**7**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 1.87 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 1.76 – 1.63 (5H, m, C**2**-<u>H_2</u> and C**6**-<u>H_3</u>), 1.20 (9H, s, OC(C<u>H_3</u>)$_3$). δ_C (101 MHz, $CDCl_3$) 155.6 (<u>C</u>=O), 145.7 (Ar<u>C</u>), 140.1 (Ar<u>C</u>), 137.3 (C**4**), 131.4 (Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 120.9 (C**5**), 83.2 (O<u>C</u>(CH$_3$)$_3$), 52.9 (C**1**), 35.6 (C**7**), 33.4 (C**3**), 27.7 (OC(<u>C</u>H$_3$)$_3$), 24.0 (C**2**), 21.8 (Ts <u>C</u>H$_3$), 13.8 (C**6**). HRMS: (ESI^+) Calculated for $C_{25}H_{33}NNaO_5S$: 482.1972. Found $[M+Na]^+$: 482.1950.

***tert*-Butyl (*R*)-2-benzyl-2-vinylpyrrolidine-1-carboxylate ((*R*)-267a)**

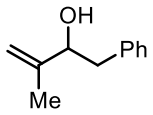


General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 12 mol% (*S*)-SIPHOS-PE; 300 mol% Et_3N; THF (0.07 M); 110 °C; 72 hours. Substrate **266d** (48.3 mg, 0.105 mmol) was employed. FCC (eluent: 39:1 petrol:EtOAc) afforded **(*R*)-267a** (30.0 mg, 99 %, 95 % e.e.) as a colourless oil.

*Alternative procedure starting from O^FBz substrate **267a**:* **General procedure D:** Conditions: 5.0 mol% $Pd_2(dba)_3$; 20 mol% (*S*)-SIPHOS-PE; 100 mol% Et_3N; THF (0.4 M); 130 °C; 24 hours. Substrate **266a** (Section 7.4, 52.4 mg, 0.105 mmol) was employed. FCC (gradient elution: 39:1 – 29:1 petrol:EtOAc) afforded **(*R*)-267a** (22.3 mg, 74 %, 61 % e.e.) as a colourless oil. *The procedure described in Section 7.4 was used to prepare a racemic sample of **267a** for SFC analysis.* **SFC conditions:** *column*: CHIRALPACK IC, *elute*: 1.2 % MeOH/CO_2, *detector*: 250 nm, *flow rate*: 2.0 mL/min, *temperature*: 40 °C, *retention times*: (*R*) t_1 = 10.0 min, (*S*) t_2 = 11.1 min. *For 95 % e.e. material:* $[\alpha]_D^{26}$ +82.2 (c = 0.40, CH_2Cl_2). *Characterisation data for **267a** has been provided earlier (Section 7.4).*

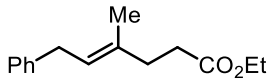
[LI] BocNHOTs was prepared by Joshua Farndon (University of Bristol) according to a literature procedure.[164]

3-Methyl-1-phenylbut-3-en-2-ol



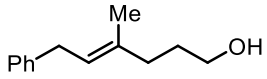
To a suspension of magnesium turnings (875 mg, 36.0 mmol), activated with a few crystals of iodine, in anhydrous Et_2O (30 mL) was added benzyl bromide (3.57 mL, 30.0 mmol). The reaction mixture was heated at reflux for 3 hours, then cooled to 0 °C before addition of methacrolein (3.71 mL, 45.0 mmol). The reaction mixture was stirred at room temperature for 1.5 hours before addition of saturated aqueous NH_4Cl (30 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 7:1 petrol:EtOAc) afforded the title compound (2.80 g, 58 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.34 – 7.29 (2H, m), 7.27 – 7.21 (3H, m), 4.96 (1H, br s), 4.87 (1H, br s), 4.29 (1H, dd, *J* = 8.5, 4.5 Hz), 2.92 (1H, dd, *J* = 13.5, 4.5 Hz), 2.77 (1H, dd, *J* = 13.5, 8.5 Hz), 1.82 (3H, dd, *J* = 1.0, 1.0 Hz), 1.60 (1H, br s). δ_C (101 MHz, $CDCl_3$) 146.9, 138.4, 129.5, 128.6, 126.7, 111.4, 76.7, 42.3, 18.3. *The spectroscopic properties were consistent with the data available in the literature.*[295]

Ethyl (*E*)-4-methyl-6-phenylhex-4-enoate



General procedure L: The preceding allylic alcohol (3.24 g, 20.0 mmol) was employed. The reaction time was 14 hours. FCC (eluent: 39:1 petrol:EtOAc) afforded the title compound (2.56 g, 55 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.31 – 7.24 (2H, m), 7.21 – 7.13 (3H, m), 5.38 (1H, t, *J* = 7.5 Hz), 4.10 (2H, q, *J* = 7.0 Hz), 3.35 (2H, d, *J* = 7.5 Hz), 2.47 – 2.41 (2H, m), 2.40 – 2.33 (2H, m), 1.74 (3H, s), 1.22 (3H, t, *J* = 7.0 Hz). δ_C (101 MHz, $CDCl_3$) 173.5, 141.5, 134.7, 128.5, 128.4, 125.9, 124.0, 60.4, 34.8, 34.3, 33.3, 16.3, 14.4. *The spectroscopic properties were consistent with the data available in the literature.*[296]

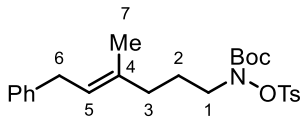
(*E*)-4-Methyl-6-phenylhex-4-en-1-ol



General procedure I: The preceding ester (2.48 g, 10.7 mmol) was employed, using anhydrous Et_2O as solvent and 0.8 eq. $LiAlH_4$ (1.0 M in THF). FCC (eluent: 3:1 petrol:EtOAc) afforded the title compound (1.68 g, 83 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.31 – 7.25 (2H, m), 7.21 – 7.15

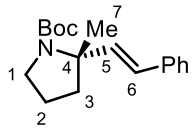
(3H, m), 5.39 (1H, t, *J* = 7.5 Hz), 3.64 (2H, t, *J* = 6.5 Hz), 3.37 (2H, d, *J* = 7.5 Hz), 2.12 (2H, t, *J* = 7.5 Hz), 1.76 – 1.67 (5H, m), 1.52 (1H, br s). δ_C (101 MHz, $CDCl_3$) 141.7, 135.9, 128.5, 128.4, 125.9, 123.6, 62.9, 36.1, 34.4, 30.9, 16.2. *The spectroscopic properties were consistent with the data available in the literature.*[297]

***tert*-Butyl (*E*)-(4-methyl-6-phenylhex-4-en-1-yl)(tosyloxy)carbamate (342)**



General procedure R: The preceding alcohol (571 mg, 3.00 mmol) was employed with BocNHOTs.[LII] The reaction time was 18 hours. FCC (eluent: 1:4 petrol:PhMe) afforded **342** (1.19 g, 86 %) as a colourless crystalline solid. m.p. 69-70 °C (CH_2Cl_2:petrol, *needles*). ν_{max} / cm^{-1}: (*solid*) 2982 (m), 2933 (m), 1751 (s), 1597 (m), 1452 (m), 1364 (s), 1149 (s). δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.31 – 7.27 (2H, m, 2 × ArC<u>H</u>), 7.21 – 7.15 (3H, m, 3 × ArC<u>H</u>), 5.34 (1H, tq, *J* = 7.5, 1.5 Hz, C**5**-<u>H</u>), 3.58 (2H, br s, C**1**-<u>H_2</u>), 3.35 (2H, d, *J* = 7.5 Hz, C**6**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 2.01 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 1.83 – 1.71 (2H, m, C**2**-<u>H_2</u>), 1.70 (3H, br s, C**7**-<u>H_3</u>), 1.22 (9H, s, OC(C<u>H_3</u>)$_3$). δ_C (101 MHz, $CDCl_3$) 155.6 (<u>C</u>=O), 145.8 (Ar<u>C</u>), 141.7 (Ar<u>C</u>), 135.0 (C**4**), 131.5 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 2 × 128.5 (2 × Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 123.9 (C**5**), 83.3 (O<u>C</u>(CH$_3$)$_3$), 53.0 (C**1**), 36.7 (C**3**), 34.4 (C**6**), 27.8 (OC(<u>C</u>H$_3$)$_3$), 24.1 (C**2**), 21.8 (Ts <u>C</u>H$_3$), 16.1 (C**7**). HRMS: (ESI$^+$) Calculated for $C_{25}H_{33}NNaO_5S$: 482.1972. Found $[M+Na]^+$: 482.1955.

***tert*-Butyl (*S*,*E*)-2-methyl-2-styrylpyrrolidine-1-carboxylate ((*S*)-344)**



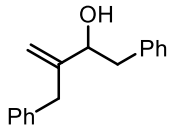
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 12 mol% (*S*)-SIPHOS-PE; 300 mol% Et_3N; THF (0.07 M); 110 °C; 72 hours. Substrate **342** (48.3 mg, 0.105 mmol) was employed. FCC (eluent: 39:1 PhMe:EtOAc) afforded **(*S*)-344** (23.7 mg, 79 %, 89 % e.e.) as a colourless oil.

*The following procedure was used to prepare a racemic sample of **344** for SFC analysis:* **General procedure D:** Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (Section 7.4); 100 mol% Et_3N; THF (0.1 M); 130 °C; 24 hours. Substrate **342** (48.3 mg, 0.105 mmol) was employed. FCC (eluent: 49:1 PhMe:EtOAc) afforded **344** (25.5 mg, 85 %) as a pale-yellow oil. *This compound exists as an approximately 11:4 mixture of rotamers A and B.* **SFC conditions:** *column*: CHIRALPACK IA,

[LII] BocNHOTs was prepared by Joshua Farndon (University of Bristol) according to a literature procedure.[164]

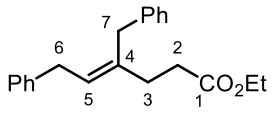
elute: 1.0 % MeOH/CO_2, *detector*: 250 nm, *flow rate*: 1.2 mL/min, *temperature*: 40 °C, *retention times*: (*R*) t_1 = 12.2 min, (*S*) t_2 = 13.0 min. $[\alpha]_D^{26}$ -89.3 (c = 0.40, CH_2Cl_2). ν_{max} / cm^{-1}: (*film*) 2970 (m), 2875 (m), 1682 (s), 1386 (s), 1158 (s). δ_H (400 MHz, $CDCl_3$) 7.39 – 7.27 (4H, m, A and B: 4 × ArC<u>H</u>), 7.25 – 7.16 (1H, m, A and B: ArC<u>H</u>), 6.39 – 6.18 (2H, m, A and B: C**5**-<u>H</u> and C**6**-<u>H</u>), 3.65 – 3.39 (2H, m, A and B: C**1**-<u>H_2</u>), 2.04 – 1.96 (1H, m, A and B: C**3**-<u>H</u>), 1.93 – 1.75 (3H, m, A and B: C**2**-<u>H_2</u> and C**3**-<u>H</u>'), 1.63 (0.8H, br s, B: C**7**-<u>H_3</u>), 1.55 (2.2H, br s, A: C**7**-<u>H_3</u>), 1.47 (2.4H, br s, B: OC($C\underline{H}_3$)$_3$), 1.39 (6.6H, br s, A: OC($C\underline{H}_3$)$_3$). *^{13}C NMR data for rotamer A only:* δ_C (101 MHz, $CDCl_3$) 154.7 (<u>C</u>=O), 137.5 (Ar<u>C</u>), 136.2 (C**5**), 128.7 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 126.7 (C**6**), 126.3 (Ar<u>C</u>H), 79.4 (O<u>C</u>(CH_3)$_3$), 63.1 (C**4**), 48.2 (C**1**), 42.4 (C**3**), 28.6 (OC(<u>C</u>H_3)$_3$), 25.0 (C**7**), 21.8 (C**2**). HRMS: (ESI^+) Calculated for $C_{18}H_{25}NNaO_2$: 310.1777. Found $[M+Na]^+$: 310.1767.

3-Benzyl-1-phenylbut-3-en-2-ol



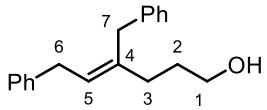
This compound appears to be unstable, potentially to heat. Consequently, it is recommended to use a water bath at room temperature during concentration. To a suspension of magnesium turnings (255 mg, 10.5 mmol), activated with a few crystals of iodine, in anhydrous Et_2O (40 mL) was added benzyl bromide (1.19 mL, 10.0 mmol). The reaction mixture was heated at reflux for 2 hours, then cooled to room temperature before addition of a solution of 2-benzylacrylaldehyde (Section 7.3, 1.46 g, 10.0 mmol) in anhydrous Et_2O (20 mL) dropwise. The reaction mixture was stirred at room temperature for 1 hour before addition of saturated aqueous NH_4Cl (40 mL). The resulting phases were separated, and the aqueous phase extracted with Et_2O (50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (*two times*, first, gradient elution: 7:1 – 5:1 petrol:EtOAc; second eluent: 7:1 petrol:acetone) afforded the title compound (603 mg, 25 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.36 – 7.28 (4H, m), 7.27 – 7.18 (6H, m), 5.18 (1H, ddt, *J* = 1.0, 1.0, 1.0 Hz), 4.83 (1H, td, *J* = 1.5, 1.0 Hz), 4.29 (1H, br dd, *J* = 9.0, 4.0 Hz), 3.52 (1H, br d, *J* = 15.5 Hz), 3.39 (1H, br d, *J* = 15.5 Hz), 2.95 (1H, dd, *J* = 13.5, 4.0 Hz), 2.77 (1H, dd, *J* = 13.5, 9.0 Hz), 1.60 (1H, br s). δ_C (101 MHz, $CDCl_3$) 150.8, 139.4, 138.4, 129.5, 129.4, 2 × 128.6, 126.7, 126.4, 112.4, 75.1, 42.9, 39.5. *The spectroscopic properties were consistent with the data available in the literature.*[298]

Ethyl (*Z*)-4-benzyl-6-phenylhex-4-enoate



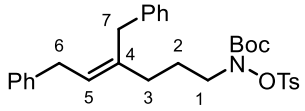
General procedure L: The preceding allylic alcohol (586 mg, 2.46 mmol) was employed. The reaction time was 14 hours. FCC (eluent: 19:1 petrol:EtOAc) afforded the title compound (420 mg, 55 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3027 (m), 2980 (m), 1731 (s), 1602 (m), 1453 (m), 1180 (s). δ_H (400 MHz, $CDCl_3$) 7.33 – 7.24 (4H, m, 4 × ArC<u>H</u>), 7.23 – 7.15 (6H, m, 6 × ArC<u>H</u>), 5.57 (1H, t, *J* = 7.5 Hz, C**5**-<u>H</u>), 4.06 (2H, q, *J* = 7.0 Hz, OC<u>H</u>$_2$CH$_3$), 3.53 (2H, s, C**7**-<u>H</u>$_2$), 3.51 (2H, d, *J* = 7.5 Hz, C**6**-<u>H</u>$_2$), 2.44 – 2.37 (2H, m, C**2**-<u>H</u>$_2$), 2.35 – 2.28 (2H, m, C**3**-<u>H</u>$_2$), 1.19 (3H, t, *J* = 7.0 Hz, OCH$_2$C<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 173.3 (C**1**), 141.2 (Ar<u>C</u>), 139.6 (Ar<u>C</u>), 137.2 (C**4**), 128.7 (Ar<u>C</u>H), 2 × 128.6 (2 × Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 125.8 (C**5**), 60.4 (O<u>C</u>H$_2$CH$_3$), 36.3 (C**7**), 34.4 (C**6**), 33.2 (C**2**), 31.9 (C**3**), 14.3 (OCH$_2$<u>C</u>H$_3$). HRMS: (ESI^+) Calculated for $C_{21}H_{24}NaO_2$: 331.1669. Found $[M+Na]^+$: 331.1683.

(*Z*)-4-Benzyl-6-phenylhex-4-en-1-ol



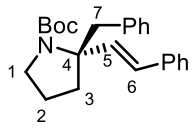
General procedure I: The preceding ester (399 mg, 1.29 mmol) was employed, using anhydrous Et_2O as solvent and 0.8 eq. $LiAlH_4$ (1.0 M in Et_2O). The title compound (330 mg, 96 %) was isolated as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3336 (br s), 3026 (m), 2937 (m), 1601 (m), 1494 (m), 1452 (m). δ_H (400 MHz, $CDCl_3$) 7.33 – 7.25 (4H, m, 4 × ArC<u>H</u>), 7.23 – 7.17 (6H, m, 6 × ArC<u>H</u>), 5.58 (1H, t, *J* = 7.5 Hz, C**5**-<u>H</u>), 3.59 (2H, td, *J* = 6.5, 6.0 Hz, C**1**-<u>H</u>$_2$), 3.54 – 3.50 (4H, m, C**6**-<u>H</u>$_2$ and C**7**-<u>H</u>$_2$), 2.06 (2H, t, *J* = 7.5 Hz, C**3**-<u>H</u>$_2$), 1.68 (2H, tt, *J* = 7.5, 6.5 Hz, C**2**-<u>H</u>$_2$), 1.19 (1H, br s, O<u>H</u>). δ_C (101 MHz, $CDCl_3$) 141.4 (Ar<u>C</u>), 139.9 (Ar<u>C</u>), 138.3 (C**4**), 128.7 (Ar<u>C</u>H), 2 × 128.6 (2 × Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 125.4 (C**5**), 62.9 (C**1**), 36.2 (C**7**), 34.5 (C**6**), 32.9 (C**3**), 31.1 (C**2**). HRMS: (ESI^+) Calculated for $C_{19}H_{22}NaO$: 289.1563. Found $[M+Na]^+$: 289.1557.

***tert*-Butyl (*Z*)-(4-benzyl-6-phenylhex-4-en-1-yl)(tosyloxy)carbamate (343)**



General procedure R: The preceding alcohol (323 mg, 1.21 mmol) was employed with BocNHOTs.[LIII] The reaction time was 15 hours. FCC (gradient elution: 2:8 – 1:9 – 0:1 petrol:PhMe) afforded **343** (457 mg, 71 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3027 (m), 2978 (m), 2935 (m), 1720 (s), 1599 (m), 1369 (s), 1178 (s). δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.36 – 7.26 (6H, m, 6 × ArC<u>H</u>), 7.24 – 7.15 (6H, m, 6 × ArC<u>H</u>), 5.55 (1H, t, *J* = 7.5 Hz, C**5**-<u>H</u>), 3.63 – 3.48 (6H, m, C**1**-<u>H_2</u>, C**6**-<u>H_2</u> and C**7**-<u>H_2</u>), 2.44 (3H, s, Ts C<u>H_3</u>), 1.94 (2H, t, *J* = 7.5 Hz, C**3**-<u>H_2</u>), 1.83 – 1.67 (2H, m, C**2**-<u>H_2</u>), 1.20 (9H, s, OC(C<u>H_3</u>)$_3$). δ_C (101 MHz, $CDCl_3$) 155.6 (<u>C</u>=O), 145.7 (Ar<u>C</u>), 141.3 (Ar<u>C</u>), 139.7 (Ar<u>C</u>), 137.6 (C**4**), 131.4 (Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 2 × 128.6 (2 × Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 125.6 (C**5**), 83.3 (O<u>C</u>(CH$_3$)$_3$), 52.9 (C**1**), 36.0 (C**7**), 34.4 (C**6**), 33.5 (C**3**), 27.7 (OC(<u>C</u>H$_3$)$_3$), 24.1 (C**2**), 21.8 (Ts <u>C</u>H$_3$). HRMS: (ESI^+) Calculated for $C_{31}H_{37}NNaO_5S$: 558.2285. Found $[M+Na]^+$: 558.2280.

***tert*-Butyl (*R*,*E*)-2-benzyl-2-styrylpyrrolidine-1-carboxylate ((*R*)-345)**



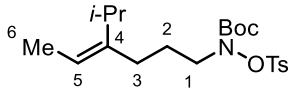
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 12 mol% (*S*)-SIPHOS-PE; 300 mol% Et_3N; THF (0.07 M); 110 °C; 72 hours. Substrate **343** (56.2 mg, 0.105 mmol) was employed. FCC (gradient elution: 149:1 – 99:1 PhMe:EtOAc) afforded **(*R*)-345** (26.0 mg, 68 %, 95 % e.e.) as a colourless oil.

*The following procedure was used to prepare a racemic sample of **345** for SFC analysis:* **General procedure D:** Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (Section 7.4); 100 mol% Et_3N; THF (0.1 M); 130 °C; 24 hours. Substrate **343** (56.2 mg, 0.105 mmol) was employed. FCC (*two times*, first eluent: 29:1 petrol:EtOAc; second eluent: 99:1 PhMe:EtOAc) afforded **345** (28.4 mg, 74 %) as a colourless oil. *This compound exists as an approximately 3:2 mixture of rotamers A and B.* **SFC conditions:** *column*: CHIRALPACK IA, *elute*: 2.0 % MeOH/CO_2, *detector*: 250 nm, *flow rate*: 2.5 mL/min, *temperature*: 40 °C, *retention times*: (*S*) t_1 = 11.6 min, (*R*) t_2 = 12.6 min. $[\alpha]_D^{26}$ -26.5 (c = 0.40, CH_2Cl_2). ν_{max} / cm^{-1}: (*film*) 3032 (m), 2973 (m), 2868 (m), 1676 (s), 1600 (m), 1385 (s). δ_H (400 MHz, $CDCl_3$) 7.41 – 7.16 (10H, m, A and B: 10 × ArC<u>H</u>), 6.58 (0.4H, d, *J* = 16.0 Hz, B: C**5**-<u>H</u>), 6.42 – 6.27 (1.6H, m, A: C**5**-<u>H</u> and C**6**-<u>H</u>; B: C**6**-<u>H</u>), 3.73 (0.4H, d, *J* = 13.5 Hz, B: C**7**-<u>H</u>), 3.64 – 3.56

[LIII] BocNHOTs was prepared by Joshua Farndon (University of Bristol) according to a literature procedure.[164]

(1.2H, m, A: C**1**-H and C**7**-H), 3.47 (0.4H, ddd, *J* = 9.5, 7.5, 4.0 Hz, B: C**1**-H), 3.15 – 2.94 (2H, m, A and B: C**1**-H' and C**7**-H'), 2.14 – 2.02 (1H, m, A and B: C**3**-H), 1.92 – 1.83 (1H, m, A and B: C**3**-H'), 1.66 – 1.57 (1H, m, A and B: C**2**-H), 1.54 (3.6H, s, B: OC(CH_3)$_3$), 1.50 (5.4H, s, A: OC(CH_3)$_3$), 1.35 – 1.29 (0.4H, m, B: C**2**-H'), 1.24 – 1.15 (0.6H, m, A: C**2**-H'). δ_C (101 MHz, $CDCl_3$) 154.5 (A: C=O), 153.8 (B: C=O), 138.1 (B: ArC), 137.9 (A: ArC), 137.5 (B: ArC), 137.3 (A: ArC), 135.6 (A: C**5**), 134.3 (B: C**5**), 131.0 (B: ArCH), 130.7 (A: ArCH), 128.8 (A: ArCH), 2 × 128.5 (B: 2 × ArCH), 128.4 (A: ArCH), 128.1 (B: ArCH), 127.4 (A: ArCH), 127.3 (B: C**6**), 127.1 (A: C**6**), 2 × 126.6 (A and B: ArCH), 2 × 126.3 (A and B: ArCH), 80.0 (A: O$C(CH_3)_3$), 79.0 (B: O$C(CH_3)_3$), 67.3 (B: C**4**), 66.6 (A: C**4**), 2 × 48.8 (A and B: C**1**), 42.8 (A: C**7**), 42.3 (B: C**7**), 38.3 (A: C**3**), 36.4 (B: C**3**), 28.8 (A and B: OC(CH_3)$_3$), 21.6 (B: C**2**), 21.2 (A: C**2**). HRMS: (ESI^+) Calculated for $C_{24}H_{30}NO_2$: 364.2271. Found $[M+H]^+$: 364.2284.

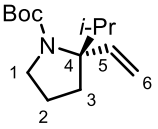
***tert*-Butyl (*Z*)-(4-isopropylhex-4-en-1-yl)(tosyloxy)carbamate (346)**



General procedure R: Alcohol **159b** (Section 7.3, 284 mg, 2.00 mmol) was employed with BocNHOTs.[LIV] The reaction time was 16 hours. FCC (eluent: 1:4 petrol:PhMe) afforded **346** (615 mg, 75 %, 13:1 mixture of (*Z*)- and (*E*)-isomers) as a colourless oil. *Spectroscopic data for the major (Z)-isomer:* ν_{max} / cm^{-1}: (*film*) 2962 (m), 1715 (s), 1597 (m), 1355 (s). δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 7.34 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 5.10 (1H, q, *J* = 7.0 Hz, C**5**-H), 3.60 (2H, br s, C**1**-H_2), 2.82 (1H, hept, *J* = 7.0 Hz, C$H(CH_3)_2$), 2.45 (3H, s, Ts CH_3), 1.87 (2H, br t, *J* = 8.0 Hz, C**3**-H_2), 1.78 – 1.65 (2H, m, C**2**-H_2), 1.59 (3H, dt, *J* = 7.0, 1.5 Hz, C**6**-H_3), 1.23 (9H, s, OC(CH_3)$_3$), 0.95 (6H, d, *J* = 7.0 Hz, CH(CH_3)$_2$). δ_C (101 MHz, $CDCl_3$) 155.6 (C=O), 145.7 (ArC), 143.6 (C**4**), 131.5 (ArC), 129.8 (ArCH), 129.6 (ArCH), 117.3 (C**5**), 83.2 (O$C(CH_3)_3$), 53.2 (C**1**), 28.6 (C$H(CH_3)_2$), 28.2 (C**3**), 27.8 (OC(CH_3)$_3$), 25.1 (C**2**), 21.8 (Ts CH_3), 21.0 (CH(CH_3)$_2$), 12.9 (C**6**). HRMS: (ESI^+) Calculated for $C_{21}H_{33}NNaO_5S$: 434.1972. Found $[M+Na]^+$: 434.1984. *Characteristic signals for the minor (E)-isomer:* δ_H (400 MHz, $CDCl_3$) 5.23 (1H, q, *J* = 7.0 Hz, C**5**-H), 2.23 – 2.13 (1H, m, C$H(CH_3)_2$), 1.97 (2H, t, *J* = 8.0 Hz, C**3**-H_2).

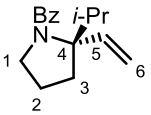
[LIV] BocNHOTs was prepared by Joshua Farndon (University of Bristol) according to a literature procedure.[164]

***tert*-Butyl (*R*)-2-isopropyl-2-vinylpyrrolidine-1-carboxylate ((*R*)-347)**



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 12 mol% (*S*)-SIPHOS-PE; 300 mol% Et_3N; THF (0.07 M); 110 °C; 72 hours. Substrate **346** (43.2 mg, 0.105 mmol) was employed. FCC (eluent: 59:1 PhMe:EtOAc) afforded **(*R*)-347** (19.6 mg, 78 %, 95 % e.e.) as a colourless oil. *It was necessary to convert the protecting group from Boc to Bz in order to determine the e.e. of this compound. Details of this are provided below.* $[\alpha]_D^{26}$ -22.9 (c = 0.40, CH_2Cl_2). *This compound exists as an approximately 1:1 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 2970 (m), 2875 (m), 1686 (s), 1466 (m), 1380 (s). δ_H (400 MHz, $CDCl_3$) 6.16 (0.5H, dd, *J* = 17.5, 10.5 Hz, B: C**5**-H), 6.02 (0.5H, dd, *J* = 17.5, 10.5 Hz, A: C**5**-H), 5.07 – 4.90 (2H, m, A and B: C**6**-H_2), 3.75 – 3.66 (0.5H, m, A: C**1**-H), 3.63 – 3.54 (0.5H, m, B: C**1**-H), 3.26 – 3.12 (1H, m, A and B: C**1**-H'), 2.79 (0.5H, qq, *J* = 7.5, 7.0 Hz, B: C$H(CH_3)_2$), 2.52 (0.5H, qq, *J* = 7.0, 7.0 Hz, A: C$H(CH_3)_2$), 1.89 – 1.61 (4H, m, A and B: C**2**-H_2 and C**3**-H_2), 1.44 (9H, s, A and B: OC(CH_3)$_3$), 0.91 – 0.83 (3H, m, A and B: CH(CH_3)(CH_3)'), 0.83 – 0.74 (3H, m, A and B: CH(CH_3)(CH_3)'). δ_C (101 MHz, $CDCl_3$) 154.5 (A: C=O), 153.5 (B: C=O), 140.4 (A: C**5**), 140.1 (B: C**5**), 112.0 (A: C**6**), 111.9 (B: C**6**), 79.4 (A: OC$(CH_3)_3$), 78.7 (B: OC$(CH_3)_3$), 70.6 (B: C**4**), 70.1 (A: C**4**), 49.3 (B: C**1**), 49.2 (A: C**1**), 32.3 (A: C$H(CH_3)_2$), 31.2 (B: C$H(CH_3)_2$), 30.9 (A: C**3**), 29.5 (B: C**3**), 28.7 (A and B: OC(CH_3)$_3$), 21.7 (B: C**2**), 21.1 (A: C**2**), 18.4 (A: CH(CH_3)(CH_3)'), 18.1 (B: CH(CH_3)(CH_3)'), 16.4 (B: CH(CH_3)(CH_3)'), 16.2 (A: CH(CH_3)(CH_3)'). HRMS: (ESI^+) Calculated for $C_{14}H_{25}NNaO_2$: 262.1777. Found $[M+Na]^+$: 262.1785.

(*R*)-1-Benzoyl-2-isopropyl-2-vinylpyrrolidine

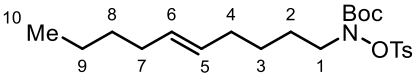


A solution of pyrrolidine **(*R*)-347** (18.4 mg, 76.9 μmol) in TFA (2 mL) and CH_2Cl_2 (2 mL) was stirred at room temperature for 1 hour before being concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (3 mL) before addition of Et_3N (54 μL, 0.385 mmol) and BzCl (27 μL, 0.231 mmol). The reaction mixture was stirred at room temperature for 2.5 hours before being concentrated *in vacuo*. FCC (eluent: 5:1 petrol:EtOAc) afforded the title compound (14.2 mg, 76 %, 95 %) as a colourless oil.

The following procedure was used to prepare a racemic sample of the title compound for SFC analysis:
General procedure D: Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L2** (Section 7.4); 100 mol% Et_3N; THF (0.1 M); 130 °C; 24 hours. Substrate **346** (43.2 mg, 0.105 mmol) was employed. The crude

reaction mixture was dissolved in CH_2Cl_2 (2 mL) and TFA (2 mL) and stirred at room temperature for two hours before being concentrated *in vacuo*. The crude reaction mixture was dissolved in CH_2Cl_2 (3 mL) before addition of Et_3N (73 µL, 0.525 mmol) and BzCl (37 µL, 0.315 mmol). The reaction mixture was stirred at room temperature for 3 hours before being concentrated *in vacuo*. FCC (gradient elution: 7:1 – 4:1 petrol:EtOAc) afforded the title compound (12.8 mg, 50 %) as a colourless oil. **SFC conditions:** *column*: CHIRALPACK IC, *elute*: 4.5 % MeOH/CO_2, *detector*: 250 nm, *flow rate*: 2.5 mL/min, *temperature*: 40 °C, *retention times*: (*R*) t_1 = 15.3 min, (*S*) t_2 = 16.3 min. $[\alpha]_D^{26}$ +4.7 (c = 0.40, CH_2Cl_2). ν_{max} / cm^{-1}: (*film*) 3079 (m), 2957 (m), 2874 (m), 1626 (s), 1400 (s). δ_H (400 MHz, $CDCl_3$) 7.43 – 7.33 (5H, m, 5 × ArC<u>H</u>), 6.45 (1H, dd, *J* = 17.5, 11.0 Hz, C**5**-<u>H</u>), 5.15 (1H, dd, *J* = 11.0, 1.0 Hz, C**6**-<u>H</u>), 5.07 (1H, dd, *J* = 17.5, 1.0 Hz, C**6**-<u>H</u>'), 3.44 – 3.30 (2H, m, C**1**-<u>H_2</u>), 3.11 (1H, qq, *J* = 7.0, 7.0 Hz, C<u>H</u>$(CH_3)_2$), 2.00 – 1.84 (2H, m, C**3**-<u>H_2</u>), 1.83 – 1.65 (2H, m, C**2**-<u>H_2</u>), 0.99 (3H, d, *J* = 7.0 Hz, CH(C<u>H_3</u>)(CH_3)'), 0.93 (3H, d, *J* = 7.0 Hz, CH(CH_3)(C<u>H_3</u>)'). δ_C (101 MHz, $CDCl_3$) 169.1 (<u>C</u>=O), 139.5 (C**5**), 139.2 (Ar<u>C</u>), 129.3 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 112.5 (C**6**), 72.8 (C**4**), 52.9 (C**1**), 30.8 (<u>C</u>H$(CH_3)_2$), 29.6 (C**3**), 22.9 (C**2**), 18.1 (CH(CH_3)(<u>C</u>H_3)'), 16.5 (CH(<u>C</u>H_3)(CH_3)'). HRMS: (ESI^+) Calculated for $C_{16}H_{21}NNaO$: 266.1515. Found $[M+Na]^+$: 266.1509.

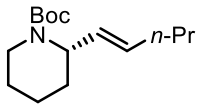
***tert*-Butyl (*E*)-dec-5-en-1-yl(tosyloxy)carbamate (282c)**



<u>General procedure R:</u> Alcohol **(*E*)-281** (Section 7.4, 469 mg, 3.00 mmol) was employed with BocNHOTs.[LV] The reaction time was 16 hours. FCC (*two times*, first, gradient elution: 14:1 – 9:1 petrol:EtOAc; second, gradient elution: 1:3 – 1:4 – 0:1 petrol:PhMe) afforded **282c** (856 mg, 67 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2929 (m), 2860 (m), 1722 (s), 1599 (m), 1369 (s), 1179 (s). δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.34 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.44 – 5.27 (2H, m, C**5**-<u>H</u> and C**6**-<u>H</u>), 3.60 (2H, br s, C**1**-<u>H_2</u>), 2.45 (3H, s, Ts C<u>H_3</u>), 2.00 – 1.92 (4H, m, C**4**-<u>H_2</u> and C**7**-<u>H_2</u>), 1.61 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>), 1.35 – 1.25 (6H, m, C**3**-<u>H_2</u>, C**8**-<u>H_2</u> and C**9**-<u>H_2</u>), 1.22 (9H, s, OC(C<u>H_3</u>)$_3$), 0.88 (3H, t, *J* = 7.0 Hz, C**10**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 155.7 (<u>C</u>=O), 145.7 (Ar<u>C</u>), 131.5 (Ar<u>C</u>), 131.2 (C**5**), 129.9 (Ar<u>C</u>H), 2 × 129.6 (Ar<u>C</u>H and C**6**), 83.2 (O<u>C</u>$(CH_3)_3$), 52.9 (C**1**), 32.4 (C**7**), 32.3 (C**4**), 31.9 (C**8**), 27.8 (OC(<u>C</u>H_3)$_3$), 26.7 (C**3**), 25.4 (C**2**), 22.3 (C**9**), 21.9 (Ts <u>C</u>H_3), 14.1 (C**10**). HRMS: (ESI^+) Calculated for $C_{22}H_{35}NNaO_5S$: 448.2128. Found $[M+Na]^+$: 448.2126.

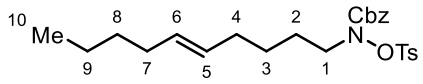
[LV] BocNHOTs was prepared by Joshua Farndon (University of Bristol) according to a literature procedure.[164]

***tert*-Butyl (*S*,*E*)-2-(pent-1-en-1-yl)piperidine-1-carboxylate ((*S*)-283a)**



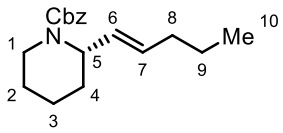
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 12 mol% (*S*)-SIPHOS-PE; 300 mol% Et_3N; THF (0.07 M); 110 °C; 72 hours. Substrate **282c** (44.7 mg, 0.105 mmol) was employed. FCC (eluent: 9:1 petrol:EtOAc) afforded **(*S*)-283a** (14.9 mg, 56 %, 95 % e.e.) as a colourless oil. *It was necessary to convert the protecting group from Boc to Cbz in order to determine the e.e. of this compound (vide infra).* $[\alpha]_D^{23}$ -30.5 (c = 1.13, $CHCl_3$). *Characterisation data for **283a** has been provided earlier (Section 7.4).*

Benzyl (*E*)-dec-5-en-1-yl(tosyloxy)carbamate (282d)



General procedure R: Alcohol **(*E*)-281** (Section 7.4, 250 mg, 1.60 mmol) was employed with CbzNHOTs.[LVI] The reaction time was 19 hours. FCC (eluent: 1:4 petrol:PhMe) afforded **282d** (550 mg, 75 %) as a colourless crystalline solid. m.p. 48-49 °C (CH_2Cl_2:petrol, *needles*). ν_{max} / cm^{-1}: (*solid*) 2935 (m), 1715 (s), 1596 (m), 1496 (m), 1370 (s), 1180 (s). δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.35 – 7.30 (3H, m, 3 × ArC<u>H</u>), 7.20 – 7.12 (4H, m, 4 × ArC<u>H</u>), 5.43 – 5.27 (2H, m, C**5**-<u>H</u> and C**6**-<u>H</u>), 4.90 (2H, s, OC<u>H</u>$_2$Ph), 3.65 (2H, br s, C**1**-<u>H</u>$_2$), 2.39 (3H, s, Ts C<u>H</u>$_3$), 2.01 – 1.91 (4H, m, C**4**-<u>H</u>$_2$ and C**7**-<u>H</u>$_2$), 1.67 – 1.58 (2H, m, C**2**-<u>H</u>$_2$), 1.36 – 1.24 (6H, m, C**3**-<u>H</u>$_2$, C**8**-<u>H</u>$_2$ and C**9**-<u>H</u>$_2$), 0.92 – 0.85 (3H, m, C**10**-<u>H</u>$_3$). δ_C (101 MHz, $CDCl_3$) 156.7 (<u>C</u>=O), 145.8 (Ar<u>C</u>), 135.0 (Ar<u>C</u>), 131.2 (C**5**), 131.0 (Ar<u>C</u>), 2 × 129.6 (2 × Ar<u>C</u>H), 129.4 (C**6**), 2 × 128.5 (2 × Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 68.7 (O<u>C</u>H$_2$Ph), 53.1 (C**1**), 32.4 (C**7**), 32.2 (C**4**), 31.9 (C**8**), 26.6 (C**3**), 25.5 (C**2**), 22.3 (C**9**), 21.9 (Ts <u>C</u>H$_3$), 14.1 (C**10**). HRMS: (ESI^+) Calculated for $C_{25}H_{33}NNaO_5S$: 482.1972. Found $[M+Na]^+$: 492.1951.

Benzyl (*S*,*E*)-2-(pent-1-en-1-yl)piperidine-1-carboxylate ((*S*)-283d)



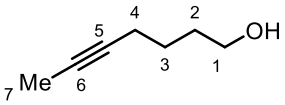
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 12 mol% (*S*)-SIPHOS-PE; 300 mol% Et_3N; THF (0.07 M); 110 °C; 72 hours. Substrate **282d** (48.3 mg, 0.105 mmol) was employed. FCC (*two*

[LVI] CbzNHOTs was prepared by Dr Xiaofeng Ma (University of Bristol) according to a literature procedure.[164]

times, first eluent: 99:1 PhMe:acetone; second eluent: 39:1 petrol:acetone) afforded **(*S*)-283d** (16.7 mg, 55 %, 89 % e.e.) as a colourless oil.

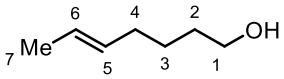
*The following procedure was used to prepare a racemic sample of **283d** for SFC analysis:* A solution of *N*-Boc-protected piperidine **283a** (Section 7.4, 40.9 mg, 0.161 mmol) in TFA (3 mL) and CH_2Cl_2 (3 mL) was stirred at room temperature for 30 minutes before being concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (5 mL) before addition of Et_3N (67 µL, 0.483 mmol) and CbzCl (35 µL, 0.242 mmol). The reaction mixture was stirred at room temperature for 16 hours before being concentrated *in vacuo*. FCC (eluent: 14:1 petrol:EtOAc) afforded **283d** (24.7 mg, 53 %) as a colourless oil. *An analogous procedure was used to convert **(S)-283a** to **(S)-283d**.* **SFC conditions:** *column*: CHIRALPACK IC, *elute*: 1.5 % MeOH/CO_2, *detector*: 250 nm, *flow rate*: 4.0 mL/min, *temperature*: 40 °C, *retention times*: (*S*) t_1 = 6.75 min, (*R*) t_2 = 7.31 min. *For 95 % e.e. material:* $[\alpha]_D^{26}$ -40.5 (c = 0.40, CH_2Cl_2). ν_{max} / cm^{-1}: (*film*) 2933 (m), 2860 (m), 1694 (s), 1418 (s), 1255 (s). δ_H (400 MHz, $CDCl_3$) 7.40 – 7.27 (5H, m, 5 × ArC<u>H</u>), 5.52 – 5.37 (2H, m, C**6**-<u>H</u> and C**7**-<u>H</u>), 5.17 (1H, d, *J* = 12.5 Hz, OC<u>H</u>H'Ph), 5.11 (1H, d, *J* = 12.5 Hz, OCH<u>H</u>'Ph), 4.85 (1H, br s, C**5**-<u>H</u>), 4.02 (1H, br d, *J* = 13.0 Hz, C**1**-<u>H</u>), 2.91 (1H, ddd, *J* = 13.0, 13.0, 3.0 Hz, C**1**-<u>H</u>'), 2.00 (2H, dt, *J* = 7.0, 7.0 Hz, C**8**-<u>H_2</u>), 1.74 – 1.40 (6H, m, C**2**-<u>H_2</u>, C**3**-<u>H_2</u> and C**4**-<u>H_2</u>), 1.38 (2H, qt, *J* = 7.5, 7.0 Hz, C**9**-<u>H_2</u>), 0.88 (2H, t, *J* = 7.5 Hz, C**10**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 155.9 (<u>C</u>=O), 137.2 (Ar<u>C</u>), 132.3 (C**7**), 128.5 (Ar<u>C</u>H), 128.1 (C**6**), 127.9 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 67.0 (O<u>C</u>H_2Ph), 52.3 (C**5**), 40.1 (C**1**), 34.6 (C**8**), 29.6 (C**4**), 25.8 (C**2**), 22.5 (C**9**), 19.5 (C**3**), 13.8 (C**10**). HRMS: (ESI^+) Calculated for $C_{18}H_{26}NO_2$: 288.1958. Found $[M+H]^+$: 288.1965.

Hept-5-yn-1-ol



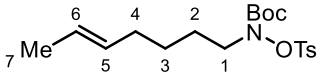
A solution of silyl ether **188** (Section 7.3, 3.92 g, 17.3 mmol) and TBAF (1.0 M in THF, 26.0 mL, 26.0 mmol) in THF (70 mL) was stirred at room temperature for 2 hours before being concentrated *in vacuo*. FCC (gradient elution: 1:0 – 1:1 pentane:Et_2O) afforded the title compound (1.92 g, 99 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.67 (2H, t, *J* = 6.5 Hz), 2.17 (2H, tq, *J* = 7.0, 2.5 Hz), 1.78 (3H, t, *J* = 2.5 Hz), 1.71 – 1.63 (2H, m), 1.60 – 1.51 (2H, m), 1.32 (1H, br s). δ_C (101 MHz, $CDCl_3$) 79.1, 76.0, 62.7, 32.0, 25.4, 18.6, 3.6. *The spectroscopic properties were consistent with the data available in the literature.*[299]

(*E*)-Hept-5-en-1-ol ((*E*)-189)



A suspension of the preceding compound (1.92 g, 17.1 mmol) and $LiAlH_4$ (3.26 g, 86.0 mmol) in anhydrous diglyme (80 mL) was heated at reflux for 16 hours before being cooled to 0 °C and diluted with Et_2O (40 mL). The reaction mixture was quenched slowly with water (3.3 mL), 4.0 M aqueous NaOH (3.3 mL) and a further portion of water (10 mL). The reaction mixture was stirred at room temperature for 20 minutes before being dried over Na_2SO_4, filtered and concentrated *in vacuo* to remove Et_2O. The crude mixture was dissolved in petrol (500 mL) and washed with water (500 mL), the aqueous phase was extracted with Et_2O (150 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was dissolved in Et_2O (300 mL) and washed with water (5 × 200 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford **(*E*)-189** (1.15 g, 59 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3322 (br s), 2932 (m), 1438 (m), 1057 (s). δ_H (400 MHz, $CDCl_3$) 5.48 – 5.36 (2H, m, C**5**-H and C**6**-H), 3.64 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.04 – 1.97 (2H, m, C**4**-H_2), 1.66 – 1.63 (3H, m, C**7**-H_3), 1.61 – 1.52 (2H, m, C**2**-H_2), 1.46 – 1.36 (2H, m, C**3**-H_2), 1.25 (1H, br s, OH). δ_C (101 MHz, $CDCl_3$) 131.2 (C**5**), 125.3 (C**6**), 63.1 (C**1**), 2 × 32.4 (C**2** and C**4**), 25.8 (C**3**), 18.1 (C**7**). HRMS: ($MALDI^-$) Calculated for $C_7H_{13}O$: 113.0972. Found $[M-H]^-$: 113.0977.

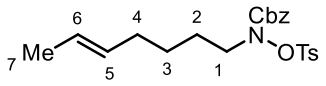
***tert*-Butyl (*E*)-hept-5-en-1-yl(tosyloxy)carbamate (275b)**



General procedure R: Alcohol **(*E*)-189** (228 mg, 2.00 mmol) was employed with BocNHOTs.[LVII] The reaction time was 22 hours. FCC (gradient elution: 7:3 – 1:4 petrol:PhMe) afforded **275b** (579 mg, 75 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2933 (m), 1720 (s), 1598 (m), 1368 (s), 1178 (s). δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 7.34 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 5.46 – 5.31 (2H, m, C**5**-H and C**6**-H), 3.60 (2H, br s, C**1**-H_2), 2.45 (3H, s, Ts CH_3), 1.97 (2H, dt, *J* = 7.0, 7.0 Hz, C**4**-H_2), 1.66 – 1.56 (5H, m, C**2**-H_2 and C**7**-H_3), 1.30 (2H, tt, *J* = 7.5, 7.0 Hz, C**3**-H_2), 1.22 (9H, s, $OC(CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 155.7 (C=O), 145.8 (ArC), 131.5 (ArC), 130.9 (C**5**), 129.9 (ArCH), 129.6 (ArCH), 125.5 (C**6**), 83.2 ($OC(CH_3)_3$), 53.0 (C**1**), 32.2 (C**4**), 27.8 ($OC(CH_3)_3$), 26.6 (C**3**), 25.4 (C**2**), 21.8 (Ts CH_3), 18.0 (C**7**). HRMS: (ESI^+) Calculated for $C_{19}H_{29}NNaO_5S$: 406.1659. Found $[M+Na]^+$: 406.1667.

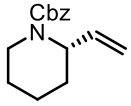
[LVII] BocNHOTs was prepared by Joshua Farndon (University of Bristol) according to a literature procedure.[164]

Benzyl (*E*)-hept-5-en-1-yl(tosyloxy)carbamate (275c)



General procedure R: Alcohol **(*E*)-189** (275 mg, 2.41 mmol) was employed with CbzNHOTs.[LVIII] The reaction time was 20 hours. FCC (gradient elution: 1:4 – 9:1 – 0:1 petrol:PhMe) afforded **275c** (722 mg, 72 %) as a colourless crystalline solid. m.p. 50-52 °C (Et_2O:petrol, *tabular*). ν_{max} / cm^{-1}: (*film*) 2934 (m), 1725 (s), 1597 (m), 1455 (m), 1384 (s), 1178 (s). δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.35 – 7.30 (3H, m, 3 × ArC<u>H</u>), 7.20 – 7.13 (4H, m, 4 × ArC<u>H</u>), 5.45 – 5.30 (2H, m, C**5**-<u>H</u> and C**6**-<u>H</u>), 4.90 (2H, s, OC<u>H_2</u>Ph), 3.64 (2H, br s, C**1**-<u>H_2</u>), 2.40 (3H, s, Ts C<u>H_3</u>), 1.94 (2H, td, *J* = 7.0, 6.5 Hz, C**4**-<u>H_2</u>), 1.67 – 1.57 (5H, m, C**2**-<u>H_2</u> and C**7**-<u>H_3</u>), 1.28 (2H, tt, *J* = 7.5, 7.0 Hz, C**3**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 156.8 (<u>C</u>=O), 145.8 (Ar<u>C</u>), 135.1 (Ar<u>C</u>), 131.1 (Ar<u>C</u>), 130.8 (C**5**), 2 × 129.6 (2 × Ar<u>C</u>H), 2 × 128.6 (2 × Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 125.5 (C**6**), 68.7 (O<u>C</u>H_2Ph), 53.2 (C**1**), 32.2 (C**4**), 26.5 (C**3**), 25.5 (C**2**), 22.0 (Ts <u>C</u>H_3), 18.1 (C**7**). HRMS: (ESI^+) Calculated for $C_{22}H_{27}NNaO_5S$: 440.1502. Found $[M+Na]^+$: 440.1510.

Benzyl (*S*)-2-vinylpiperidine-1-carboxylate ((*S*)-276c)



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 12 mol% (*S*)-SIPHOS-IP;[LIX] 300 mol% Et_3N; THF (0.07 M); 110 °C; 24 hours. Substrate **275c** (43.8 mg, 0.105 mmol) was employed. FCC (eluent: 29:1 petrol:acetone) afforded **(*S*)-276c** (18.3 mg, 71 %, 84 % e.e.) as a colourless oil.

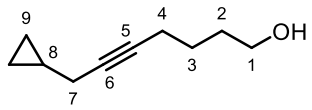
*The following procedure was used to prepare a racemic sample of **276c** for SFC analysis:* **General procedure D:** Conditions: 2.5 mol% $Pd_2(dba)_3$; 15 mol% ligand **L3** (Section 7.4); 200 mol% Et_3N; THF (0.1 M); 130 °C; 24 hours. Substrate **275c** (43.8 mg, 0.105 mmol) was employed. FCC (eluent: 29:1 petrol:acetone) afforded **276c** (8.7 mg, 34 %) as a colourless oil.

*The following procedure started from Boc-protected substrate **275b**. N-Boc piperidine **(S)-276a** was converted to N-Cbz analogue **(S)-276c** without isolation.* **General procedure D:** Conditions: 5.0 mol% $Pd_2(dba)_3$; 12 mol% (*S*)-SIPHOS-IP;[LIX] 300 mol% Et_3N; THF (0.07 M); 110 °C; 24 hours. Substrate **275b** (40.3 mg, 0.105 mmol) was employed. The crude mixture was dissolved in TFA (1 mL) and CH_2Cl_2 (3 mL) and stirred at room temperature for 4 hours before being concentrated *in vacuo*. The

[LVIII] CbzNHOTs was prepared by Dr Xiaofeng Ma (University of Bristol) according to a literature procedure.[164]
[LIX] (*S*)-SIPHOS-IP was prepared by Dr Xiaofeng Ma (University of Bristol) using an adaptation of a literature procedure.[165]

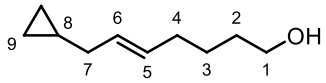
crude mixture was dissolved in CH_2Cl_2 (3 mL) before addition of Et_3N (0.15 mL, 1.08 mmol) and CbzCl (3.0 M in PhMe, 0.18 mL, 0.540 mmol). The reaction mixture was stirred at room temperature for 20 hours before being concentrated *in vacuo*. FCC (*two times*, first eluent: 39:1 petrol:acetone; second eluent: 64:1 PhMe:Et_2O) afforded **(*S*)-276c** (5.2 mg, 20 %, 92 % e.e.) as a colourless oil. **SFC conditions:** *column*: CHIRALPACK IC, *elute*: 1.5 % MeOH/CO_2, *detector*: 210 nm, *flow rate*: 4.0 mL/min, *temperature*: 40 °C, *retention times*: (*S*) t_1 = 6.25 min, (*R*) t_2 = 6.70 min. *For 92 % e.e. material:* $[\alpha]_D^{26}$ -22.0 (c = 0.17, $CHCl_3$) [Lit., $[\alpha]_D^{28}$ -17.5 (c = 0.20, $CHCl_3$)].[166] δ_H (500 MHz, $CDCl_3$) 7.37 – 7.28 (5H, m), 5.78 (1H, ddd, *J* = 17.5, 10.5, 4.0 Hz), 5.20 (1H, ddd, *J* = 10.5, 2.0, 1.5 Hz), 5.17 – 5.11 (2H, m), 5.07 (1H, ddd, *J* = 17.5, 2.0, 1.5 Hz), 4.89 (1H, br s), 4.04 (1H, br d, *J* = 13.0 Hz), 2.92 (1H, ddd, *J* = 13.0, 13.0, 3.0 Hz), 1.80 – 1.37 (6H, m). δ_C (126 MHz, $CDCl_3$) 156.0, 137.1, 136.7, 128.6, 128.0, 127.9, 116.1, 67.1, 52.9, 40.2, 29.1, 25.7, 19.5. *The spectroscopic properties were consistent with the data available in the literature.*[166]

7-Cyclopropylhept-5-yn-1-ol



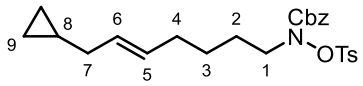
To a solution of alkyne **187** (Section 7.3, 4.25 g, 20.0 mmol) in anhydrous THF (100 mL) and anhydrous DMPU (20 mL) at -78 °C was added *n*-BuLi (1.6 M in hexane, 12.5 mL, 20.0 mmol). The reaction mixture was stirred at -20 °C for 1 hour, then cooled to -78 °C before addition of cyclopropylmethyl bromide (2.52 mL, 26.0 mmol). The reaction mixture was stirred at -78 °C for 1 hour and then at room temperature for 18 hours before addition of saturated aqueous NH_4Cl (50 mL). The reaction mixture was extracted with Et_2O (3 × 50 mL), and the combined organic phases were concentrated *in vacuo*. The crude mixture was dissolved in Et_2O (80 mL) and petrol (80 mL) and then washed with water (4 × 80 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Distillation afforded impure material which was dissolved in THF (30 mL) before addition of TBAF (1.0 M in THF, 27.0 mL, 27.0 mmol). The reaction mixture was stirred at room temperature for 4 hours before being concentrated *in vacuo*, dissolved in Et_2O (100 mL) and washed with water (100 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 9:1 PhMe:EtOAc) afforded the title compound (552 mg, 18 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3331 (br s), 3079 (m), 2937 (m), 2174 (m), 1433 (m), 1057 (m). δ_H (400 MHz, $CDCl_3$) 3.67 (2H, t, *J* = 6.5 Hz, C**1**-$\underline{H}_2$), 2.23 – 2.16 (4H, m, C**4**-$\underline{H}_2$ and C**7**-$\underline{H}_2$), 1.72 – 1.63 (2H, m, C**2**-$\underline{H}_2$), 1.61 – 1.52 (2H, m, C**3**-$\underline{H}_2$), 1.42 (1H, br s, O$\underline{H}$), 0.94 – 0.84 (1H, m, C**8**-$\underline{H}$), 0.48 – 0.37 (2H, m, 2 × C**9**-$\underline{H}$), 0.24 – 0.15 (2H, m, 2 × C**9**-$\underline{H}$'). δ_C (101 MHz, $CDCl_3$) 80.3 (C**5**), 78.9 (C**6**), 62.7 (C**1**), 32.0 (C**2**), 25.5 (C**3**), 23.0 (C**7**), 18.7 (C**4**), 9.8 (C**8**), 3.9 (C**9**). HRMS: (ESI^+) Calculated for $C_{10}H_{16}NaO$: 175.1093. Found $[M+Na]^+$: 175.1095.

(*E*)-7-Cyclopropylhept-5-en-1-ol ((*E*)-284)



A suspension of the preceding compound (512 mg, 3.36 mmol) and $LiAlH_4$ (638 mg, 16.8 mmol) in anhydrous diglyme (16 mL) was heated at reflux for 15 hours before being cooled to 0 °C and diluted with Et_2O (10 mL). The reaction mixture was quenched slowly with water (0.65 mL), 4.0 M aqueous NaOH (0.65 mL) and a further portion of water (2.0 mL). The reaction mixture was stirred at room temperature for 20 minutes before being dried over Na_2SO_4 and filtered. The filtrate was dissolved in Et_2O (70 mL) and washed with water (5 × 100 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford **(*E*)-284** (418 mg, 81 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3326 (br s), 3076 (m), 2931 (m), 1427 (m), 1056 (m). δ_H (400 MHz, $CDCl_3$) 5.53 – 5.40 (2H, m, C**5**-H and C**6**-H), 3.65 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.07 – 2.00 (2H, m, C**4**-H_2), 1.93 – 1.85 (2H, m, C**7**-H_2), 1.62 – 1.54 (2H, m, C**2**-H_2), 1.48 – 1.39 (2H, m, C**3**-H_2), 1.27 (1H, br s, OH), 0.71 (1H, ttt, *J* = 8.0, 6.5, 5.0 Hz, C**8**-H), 0.44 – 0.38 (2H, m, 2 × C**9**-H), 0.07 – 0.01 (2H, m, 2 × C**9**-H'). δ_C (101 MHz, $CDCl_3$) 130.3 (C**5**), 129.8 (C**6**), 63.1 (C**1**), 37.4 (C**7**), 2 × 32.4 (C**2** and C**4**), 25.8 (C**3**), 10.7 (C**8**), 4.2 (C**9**). HRMS: ($MALDI^-$) Calculated for $C_{10}H_{17}O$: 153.1285. Found $[M-H]^-$: 153.1291.

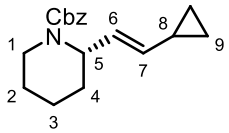
Benzyl (*E*)-(7-cyclopropylhept-5-en-1-yl)(tosyloxy)carbamate (285b)



General procedure R: Alcohol **(*E*)-284** (170 mg, 1.10 mmol) was employed with CbzNHOTs.[LX] The reaction time was 19 hours. FCC (gradient elution: 1:9 – 0:1 petrol:PhMe) afforded **285b** (388 mg, 77 %) as a colourless crystalline solid. m.p. 45-46 °C (CH_2Cl_2:petrol, *needles*). ν_{max} / cm^{-1}: (*film*) 3073 (m), 2927 (m), 1724 (s), 1597 (m), 1456 (m), 1383 (s), 1178 (s). δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 7.35 – 7.30 (3H, m, 3 × ArCH), 7.19 – 7.13 (4H, m, 4 × ArCH), 5.50 – 5.32 (2H, m, C**5**-H and C**6**-H), 4.90 (2H, s, OCH_2Ph), 3.65 (2H, br s, C**1**-H_2), 2.40 (3H, s, Ts CH_3), 1.97 (2H, dt, *J* = 7.0, 7.0 Hz, C**4**-H_2), 1.88 (2H, dd, *J* = 6.5, 6.5 Hz, C**7**-H_2), 1.63 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-H_2), 1.31 (2H, tt, *J* = 7.5, 7.0 Hz, C**3**-H_2), 0.78 – 0.63 (1H, m, C**8**-H), 0.43 – 0.39 (2H, m, 2 × C**9**-H), 0.06 – 0.01 (2H, m, 2 × C**9**-H'). δ_C (101 MHz, $CDCl_3$) 156.8 (C=O), 145.8 (ArC), 135.1 (ArC), 131.1 (ArC), 130.1 (C**6**), 129.8 (C**5**), 2 × 129.6 (2 × ArCH), 2 × 128.6 (2 × ArCH), 128.3 (ArCH), 68.7 (OCH_2Ph), 53.2 (C**1**), 37.4 (C**7**), 32.3 (C**4**), 26.5 (C**3**), 25.5 (C**2**), 21.9 (Ts CH_3), 10.7 (C**8**), 4.2 (C**9**). HRMS: (ESI^+) Calculated for $C_{25}H_{32}NO_5S$: 458.1996. Found $[M+H]^+$: 458.2009.

[LX] CbzNHOTs was prepared by Dr Xiaofeng Ma (University of Bristol) according to a literature procedure.[164]

Benzyl (*S*,*E*)-2-(2-cyclopropylvinyl)piperidine-1-carboxylate ((*S*)-286b)

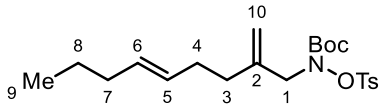


General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 12 mol% (*S*)-SIPHOS-IP;[LXI] 300 mol% Et_3N; THF (0.07 M); 110 °C; 48 hours. Substrate **285b** (48.0 mg, 0.105 mmol) was employed. FCC (*two times*, first eluent: 199:1 PhMe:acetone; second eluent: 39:1 petrol:acetone) afforded **(*S*)-286b** (15.3 mg, 51 %, 90 % e.e.) as a colourless oil.

*The following procedure was used to prepare a racemic sample of **286b** for SFC analysis:* A solution of *N*-Boc-protected piperidine **286a** (Section 7.4, 17.6 mg, 70.0 µmol) in TFA (1 mL) and CH_2Cl_2 (3 mL) was stirred at room temperature for 18 hours before being concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (3 mL) before addition of Et_3N (98 µL, 0.700 mmol) and CbzCl (3.0 M in PhMe, 0.12 mL, 0.350 mmol). The reaction mixture was stirred at room temperature for 4 hours before being concentrated *in vacuo*. FCC (eluent: 65:1 PhMe:Et_2O) afforded **286b** (9.7 mg, 49 %) as a colourless oil. **SFC conditions:** *column*: CHIRALPACK IC, *elute*: 1.5 % MeOH/CO_2, *detector*: 210 nm, *flow rate*: 4.0 mL/min, *temperature*: 40 °C, *retention times*: (*S*) t_1 = 9.89 min, (*R*) t_2 = 10.9 min. $[\alpha]_D^{26}$ -37.4 (c = 0.40, CH_2Cl_2). ν_{max} / cm^{-1}: (*film*) 3004 (m), 2935 (m), 1694 (s), 1419 (s), 1261 (s). δ_H (500 MHz, $CDCl_3$) 7.38 – 7.27 (5H, m, 5 × ArC<u>H</u>), 5.54 (1H, dd, *J* = 15.5, 5.5 Hz, C**6**-<u>H</u>), 5.17 (1H, d, *J* = 12.5 Hz, OC<u>H</u>H'Ph), 5.10 (1H, d, *J* = 12.5 Hz, OCH<u>H</u>'Ph), 5.00 (1H, dd, *J* = 15.5, 9.0 Hz, C**7**-<u>H</u>), 4.86 – 4.80 (1H, m, C**5**-<u>H</u>), 4.01 (1H, br d, *J* = 13.0 Hz, C**1**-<u>H</u>), 2.91 (1H, ddd, *J* = 13.0, 13.0, 3.0 Hz, C**1**-<u>H</u>'), 1.74 – 1.50 (5H, m, C**2**-<u>H</u>, C**3**-<u>H_2</u> and C**4**-<u>H_2</u>), 1.47 – 1.32 (2H, m, C**2**-<u>H</u>' and C**8**-<u>H</u>), 0.72 – 0.64 (2H, m, C**9**-<u>H</u> and C**9**'-<u>H</u>), 0.36 – 0.26 (2H, m, C**9**-<u>H</u>' and C**9**'-<u>H</u>'). δ_C (126 MHz, $CDCl_3$) 155.8 (<u>C</u>=O), 137.3 (Ar<u>C</u>), 136.2 (C**7**), 128.6 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 125.5 (C**6**), 67.0 (O<u>C</u>H_2Ph), 52.3 (C**5**), 40.1 (C**1**), 29.7 (C**4**), 25.7 (C**2**), 19.5 (C**3**), 13.8 (C**8**), 2 × 6.8 (C**9** and C**9**'). HRMS: (ESI^+) Calculated for $C_{18}H_{24}NO_2$: 286.1802. Found $[M+H]^+$: 286.1812.

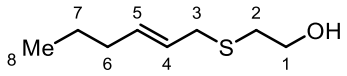
[LXI] (*S*)-SIPHOS-IP was prepared by Dr Xiaofeng Ma (University of Bristol) using an adaptation of a literature procedure.[165]

***tert*-Butyl (*E*)-(2-methylenenon-5-en-1-yl)(tosyloxy)carbamate (297b)**



General procedure R: Alcohol **296** (Section 7.4, 309 mg, 2.00 mmol) was employed with BocNHOTs.[LXII] The reaction time was 14 hours. FCC (eluent: 1:4 petrol:PhMe) afforded **297b** (625 mg, 74 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2958 (m), 2930 (m), 1721 (s), 1598 (m), 1369 (s), 1179 (s). δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 7.35 (2H, d, *J* = 8.5 Hz, 2 × ArC<u>H</u>), 5.45 – 5.31 (2H, m, C**5**-<u>H</u> and C**6**-<u>H</u>), 4.92 (1H, s, C**10**-<u>H</u>), 4.86 (1H, s, C**10**-<u>H</u>'), 4.19 (2H, br s, C**1**-$\underline{H}_2$), 2.45 (3H, s, Ts C$\underline{H}_3$), 2.16 – 2.08 (2H, m, C**4**-$\underline{H}_2$), 2.04 – 1.97 (2H, m, C**3**-$\underline{H}_2$), 1.93 (2H, td, *J* = 7.0, 6.5 Hz, C**7**-$\underline{H}_2$), 1.34 (2H, qt, *J* = 7.5, 7.0 Hz, C**8**-$\underline{H}_2$), 1.23 (9H, s, OC(C$\underline{H}_3$)$_3$), 0.87 (3H, t, *J* = 7.5 Hz, C**9**-$\underline{H}_3$). δ_C (101 MHz, $CDCl_3$) 155.3 (<u>C</u>=O), 145.8 (Ar<u>C</u>), 142.3 (C**2**), 131.5 (Ar<u>C</u>), 131.1 (C**6**), 129.8 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>H), 129.4 (C**5**), 113.4 (C**10**), 83.4 (O<u>C</u>(CH$_3$)$_3$), 56.8 (C**1**), 34.8 (C**7**), 33.9 (C**3**), 30.6 (C**4**), 27.7 (OC(<u>C</u>H$_3$)$_3$), 22.8 (C**8**), 21.9 (Ts <u>C</u>H$_3$), 13.8 (C**9**). HRMS: (ESI^+) Calculated for $C_{22}H_{33}NNaO_5S$: 446.1972. Found $[M+Na]^+$: 446.1978.

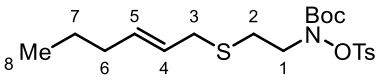
(*E*)-2-(Hex-2-en-1-ylthio)ethan-1-ol



A suspension of (*E*)-1-bromohex-2-ene (Section 7.4, 1.48 mL, 11.0 mmol), 2-mercaptoethanol (0.70 mL, 10.0 mmol) and K_2CO_3 (1.66 g, 12.0 mmol) in anhydrous THF (10 mL) was stirred at room temperature for 6 hours before being filtered and concentrated *in vacuo*. FCC (eluent: 1:1 petrol:Et_2O) afforded the title compound (1.05 g, 66 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3367 (br s), 2957 (m), 2925 (m), 1419 (m), 1045 (s). δ_H (400 MHz, $CDCl_3$) 5.52 (1H, dtt, *J* = 15.5, 6.5, 1.0 Hz, C**5**-<u>H</u>), 5.40 (1H, dtt, *J* = 15.5, 7.0, 1.0 Hz, C**4**-<u>H</u>), 3.69 (2H, t, *J* = 6.0 Hz, C**1**-$\underline{H}_2$), 3.10 (2H, ddt, *J* = 7.0, 1.0, 1.0 Hz, C**3**-$\underline{H}_2$), 2.68 (2H, t, *J* = 6.0 Hz, C**2**-$\underline{H}_2$), 2.14 (1H, br s, O<u>H</u>), 2.01 (2H, br td, *J* = 7.5, 6.5 Hz, C**6**-$\underline{H}_2$), 1.39 (2H, tq, *J* = 7.5, 7.5 Hz, C**7**-$\underline{H}_2$), 0.89 (3H, t, *J* = 7.5 Hz, C**8**-$\underline{H}_3$). δ_C (101 MHz, $CDCl_3$) 134.3 (C**5**), 125.9 (C**4**), 60.3 (C**1**), 34.4 (C**6**), 33.8 (C**2**), 33.5 (C**3**), 22.6 (C**7**), 13.8 (C**8**). HRMS: (ESI^+) Calculated for $C_8H_{16}NaOS$: 183.0814. Found $[M+Na]^+$: 183.0818.

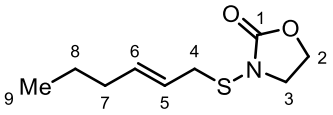
[LXII] BocNHOTs was prepared by Joshua Farndon (University of Bristol) according to a literature procedure.[164]

***tert*-Butyl (*E*)-(2-(hex-2-en-1-ylthio)ethyl)(tosyloxy)carbamate (348)**



General procedure R: The preceding alcohol (321 mg, 2.00 mmol) was employed with BocNHOTs.[LXIII] The reaction time was 24 hours. FCC (gradient elution: 1:4 – 1:9 petrol:PhMe) afforded **348** (522 mg, 61 %) as a colourless crystalline solid. m.p. 69-71 °C (CH_2Cl_2:petrol, *tabular*). ν_{max} / cm^{-1}: (*solid*) 2955 (m), 2927 (m), 1713 (s), 1598 (m), 1443 (m), 1376 (s), 1190 (s). δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 7.35 (2H, d, *J* = 8.0 Hz, 2 × ArC<u>H</u>), 5.56 (1H, dtt, *J* = 14.5, 7.0, 1.0 Hz, C**5**-<u>H</u>), 5.41 – 5.32 (1H, m, C**4**-<u>H</u>), 3.79 (2H, br s, C**1**-<u>H_2</u>), 3.06 (2H, dd, *J* = 7.0, 1.0 Hz, C**3**-<u>H_2</u>), 2.70 (2H, t, *J* = 7.5 Hz, C**2**-<u>H_2</u>), 2.46 (3H, s, Ts C<u>H_3</u>), 2.02 (2H, td, *J* = 7.5, 7.0 Hz, C**6**-<u>H_2</u>), 1.40 (2H, tq, *J* = 7.5, 7.5 Hz, C**7**-<u>H_2</u>), 1.21 (9H, s, OC(C<u>H_3</u>)$_3$), 0.90 (3H, t, *J* = 7.5 Hz, C**8**-<u>H_3</u>). δ_C (101 MHz, $CDCl_3$) 155.3 (<u>C</u>=O), 145.9 (Ar<u>C</u>), 134.6 (C**4**), 131.3 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>H), 125.5 (C**5**), 83.5 (O<u>C</u>(CH$_3$)$_3$), 51.6 (C**1**), 34.5 (C**6**), 33.7 (C**3**), 27.7 (OC(<u>C</u>H$_3$)$_3$), 25.9 (C**2**), 22.6 (C**7**), 21.9 (Ts <u>C</u>H$_3$), 13.8 (C**8**). HRMS: (ESI^+) Calculated for $C_{20}H_{31}NNaO_5S_2$: 452.1536. Found $[M+Na]^+$: 452.1539.

(*E*)-3-(Hex-2-en-1-ylthio)oxazolidin-2-one (349)

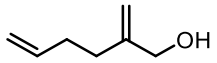


General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 12 mol% (*S*)-SIPHOS-IP;[LXIV] 300 mol% Et_3N; THF (0.07 M); 110 °C; 24 hours. Substrate **348** (45.1 mg, 0.105 mmol) was employed. FCC (eluent: 2:1 pentane:EtOAc) afforded **349** (4.0 mg, 19 %) as a colourless oil. Desired product **350** was not observed. ν_{max} / cm^{-1}: (*film*) 2960 (m), 2926 (m), 1759 (s), 1384 (s), 1208 (s). δ_H (500 MHz, $CDCl_3$) 5.62 (1H, dt, *J* = 15.0, 7.0 Hz, C**6**-<u>H</u>), 5.53 (1H, dt, *J* = 15.0, 7.0 Hz, C**5**-<u>H</u>), 4.29 (2H, dd, *J* = 9.0, 7.0 Hz, C**2**-<u>H_2</u>), 3.76 (2H, dd, *J* = 9.0, 7.0 Hz, C**3**-<u>H_2</u>), 3.45 (2H, d, *J* = 7.0 Hz, C**4**-<u>H_2</u>), 2.02 (2H, td, *J* = 7.5, 7.0 Hz, C**7**-<u>H_2</u>), 1.39 (2H, tq, *J* = 7.5, 7.5 Hz, C**8**-<u>H_2</u>), 0.90 (3H, t, *J* = 7.5 Hz, C**9**-<u>H_3</u>). δ_C (126 MHz, $CDCl_3$) 159.1 (C**1**), 136.4 (C**6**), 123.4 (C**5**), 62.1 (C**2**), 49.7 (C**3**), 40.1 (C**4**), 34.5 (C**7**), 22.3 (C**8**), 13.7 (C**9**). HRMS: (ESI^+) Calculated for $C_9H_{16}NO_2S$: 202.0896. Found $[M+H]^+$: 202.0898.

[LXIII] BocNHOTs was prepared by Joshua Farndon (University of Bristol) according to a literature procedure.[164]
[LXIV] (*S*)-SIPHOS-IP was prepared by Dr Xiaofeng Ma (University of Bristol) using an adaptation of a literature procedure.[165]

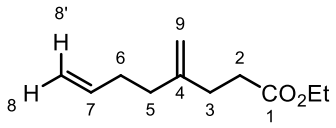
7.6 Experimental procedures for the studies in Chapter 5

2-Methylenehex-5-en-1-ol



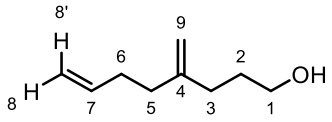
This compound was prepared according to a literature procedure.[300] A solution of TMEDA (24.0 mL, 160 mmol) and *n*-BuLi (1.6 M in hexane, 100 mL, 160 mmol) in anhydrous Et_2O (200 mL) was stirred at 0 °C for 20 minutes. The reaction mixture was cooled to -78 °C before addition of 2-methylprop-2-en-1-ol (6.73 mL, 80.0 mmol) dropwise. The reaction mixture was stirred at room temperature for 19 hours and then cooled to -78 °C before addition of a solution of allyl bromide (5.19 mL, 60.0 mmol) in anhydrous Et_2O (10 mL) dropwise. The reaction mixture was stirred at -78 °C for 2 hours and then at room temperature for a further 6 hours before addition of saturated aqueous NH_4Cl (150 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with water (100 mL), saturated aqueous $CuSO_4$ (2 × 100 mL) and brine (2 × 100 mL) before being dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 2:1 hexane:Et_2O) afforded the title compound (2.99 g, 44 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3319 (br s), 3078 (m), 2921 (s), 1641 (s), 1449 (s), 1022 (s). δ_H (400 MHz, $CDCl_3$) 5.81 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz), 5.03 (1H, br s), 5.02 (1H, ddt, *J* = 17.0, 2.0, 1.5 Hz), 4.96 (1H, ddt, *J* = 10.0, 2.0, 1.0 Hz), 4.87 (1H, br s), 4.05 (2H, s), 2.25 – 2.18 (2H, m), 2.17 – 2.11 (2H, m), 1.94 (1H, br s). δ_C (101 MHz, $CDCl_3$) 148.3, 138.1, 114.8, 109.6, 65.8, 32.2, 31.9. *The spectroscopic properties were consistent with the data available in the literature.*[300,301]

Ethyl 4-methyleneoct-7-enoate



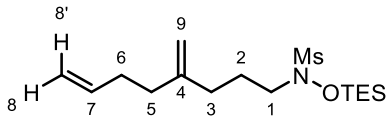
General procedure L: The preceding allylic alcohol (2.24 g, 20.0 mmol) was employed. The reaction time was 16 hours. FCC (eluent: 29:1 hexane:EtOAc) afforded the title compound (2.26 g, 62 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3079 (m), 2981 (s), 2934 (s), 1785 (s), 1643 (s), 1445 (s), 1371 (s), 1154 (s). δ_H (400 MHz, $CDCl_3$) 5.80 (1H, ddt, *J* = 17.0, 10.5, 6.5 Hz, C**7**-H), 5.02 (1H, ddt, *J* = 17.0, 2.0, 1.5 Hz, C**8**-H'), 4.95 (1H, ddt, *J* = 10.5, 2.0, 1.0 Hz, C**8**-H), 4.76 (1H, br s, C**9**-H), 4.74 (1H, br s, C**9**-H'), 4.12 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 2.47 – 2.42 (2H, m, C**2**-H_2), 2.36 – 2.30 (2H, m, C**3**-H_2), 2.23 – 2.16 (2H, m, C**6**-H_2), 2.14 – 2.08 (2H, m, C**5**-H_2), 1.25 (3H, t, *J* = 7.0 Hz, OCH_2CH_3). δ_C (101 MHz, $CDCl_3$) 173.4 (C**1**), 147.5 (C**4**), 138.3 (C**7**), 114.8 (C**8**), 109.7 (C**9**), 60.5 (OCH_2CH_3), 35.7 (C**5**), 32.9 (C**2**), 32.1 (C**6**), 31.1 (C**3**), 14.4 (OCH_2CH_3). HRMS: (ESI^+) Calculated for $C_{11}H_{18}NaO_2$: 205.1199. Found $[M+Na]^+$: 205.1190.

4-Methyleneoct-7-en-1-ol



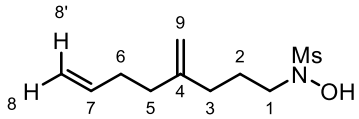
General procedure I: The preceding ester (1.00 g, 5.49 mmol) was employed, using anhydrous Et_2O as the solvent and 0.8 eq. $LiAlH_4$ (1.0 M in Et_2O). The title compound (765 mg, 99 %) was isolated as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3323 (br s), 3078 (m), 2932 (s), 1642 (s), 1442 (s), 1057 (s). δ_H (400 MHz, $CDCl_3$) 5.81 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, C**7**-H), 5.01 (1H, ddt, *J* = 17.0, 1.5, 1.5 Hz, C**8**-H'), 4.97 – 4.92 (1H, m, C**8**-H), 4.76 (1H, br s, C**9**-H), 4.75 (1H, br s, C**9**-H'), 3.64 (2H, t, *J* = 6.5 Hz, C**1**-H_2), 2.23 – 2.15 (2H, m, C**6**-H_2), 2.14 – 2.05 (4H, m, C**3**-H_2 and C**5**-H_2), 1.77 (1H, br s, OH), 1.70 (2H, tt, *J* = 7.5, 6.5 Hz, C**2**-H_2). δ_C (101 MHz, $CDCl_3$) 148.7 (C**4**), 138.5 (C**7**), 114.7 (C**8**), 109.5 (C**9**), 62.7 (C**1**), 35.4 (C**5**), 32.5 (C**3**), 32.1 (C**6**), 30.7 (C**2**). HRMS: (EI^+) Calculated for C_9H_{14}: 122.1096. Found $[M-H_2O]^+$: 122.1091.

***N*-(4-Methyleneoct-7-en-1-yl)-*N*-((triethylsilyl)oxy)methanesulfonamide**



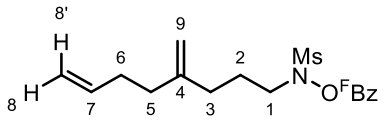
General procedure E: MsNHOTES (Section 7.3, 676 mg, 3.00 mmol) was employed with the preceding alcohol (1.1 eq.). The reaction time was 16 hours. FCC (eluent: PhMe) afforded the title compound (1.01 g, 97 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3078 (m), 2956 (s), 2878 (s), 1642 (m), 1458 (m), 1350 (s), 1164 (s). δ_H (400 MHz, $CDCl_3$) 5.81 (1H, ddt, *J* = 17.0, 10.5, 6.5 Hz, C**7**-H), 5.02 (1H, ddt, *J* = 17.0, 2.0, 1.5 Hz, C**8**-H'), 4.96 (1H, ddt, *J* = 10.5, 2.0, 1.0 Hz, C**8**-H), 4.78 (1H, s, C**9**-H), 4.76 (1H, s, C**9**-H'), 3.18 (2H, t, *J* = 7.5 Hz, C**1**-H_2), 2.85 (3H, s, Ms CH_3), 2.24 – 2.15 (2H, m, C**6**-H_2), 2.14 – 2.04 (4H, m, C**3**-H_2 and C**5**-H_2), 1.81 (2H, tt, *J* = 7.5, 7.5 Hz, C**2**-H_2), 1.00 (9H, t, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.77 (6H, q, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$). δ_C (101 MHz, $CDCl_3$) 147.5 (C**4**), 138.2 (C**7**), 114.6 (C**8**), 110.0 (C**9**), 55.3 (C**1**), 35.3 (C**5**), 33.2 (C**3**), 31.9 (C**6**), 30.3 (Ms CH_3), 25.1 (C**2**), 6.7 ($Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$). HRMS: (ESI^+) Calculated for $C_{16}H_{33}NNaO_3SSi$: 370.1843. Found $[M+Na]^+$: 370.1860.

***N*-(4-Methyleneoct-7-en-1-yl)-*N*-hydroxymethanesulfonamide**



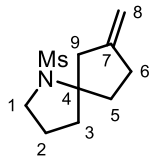
General procedure F: The preceding compound (955 mg, 2.75 mmol) was employed. FCC (eluent: 3:1 hexane:EtOAc) afforded the title compound (639 mg, 100 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3347 (br s), 3078 (m), 2934 (m), 1642 (m), 1445 (m), 1340 (s), 1158 (s). δ_H (400 MHz, $CDCl_3$) 7.32 (1H, br s, O<u>H</u>), 5.81 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, C**7**-<u>H</u>), 5.05 – 4.99 (1H, m, C**8**-<u>H</u>'), 4.97 – 4.93 (1H, m, C**8**-<u>H</u>), 4.77 (2H, s, C**9**-<u>H_2</u>), 3.17 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 2.91 (3H, s, Ms C<u>H_3</u>), 2.23 – 2.15 (2H, m, C**6**-<u>H_2</u>), 2.14 – 2.07 (4H, m, C**3**-<u>H_2</u> and C**5**-<u>H_2</u>), 1.84 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 147.9 (C**4**), 138.4 (C**7**), 114.7 (C**8**), 110.1 (C**9**), 52.2 (C**1**), 35.4 (C**5**), 32.9 (C**3**), 32.1 (C**6**), 31.0 (Ms <u>C</u>H_3), 25.0 (C**2**). HRMS: (ESI^+) Calculated for $C_{10}H_{19}NNaO_3S$: 256.0978. Found $[M+Na]^+$: 256.0974.

***N*-4-Methyleneoct-7-en-1-yl-*N*-(pentafluorobenzoyloxy)methanesulfonamide (372)**



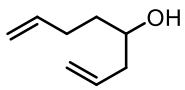
General procedure C: The preceding compound (595 mg, 2.55 mmol) was employed. FCC (eluent: 5:1 hexane:EtOAc) afforded **372** (831 mg, 76 %) as a colourless crystalline solid. ν_{max} / cm^{-1}: (*solid*) 3078 (m), 2940 (s), 1782 (s), 1656 (m), 1500 (s), 1355 (s), 1162 (s). δ_H (400 MHz, $CDCl_3$) 5.81 (1H, ddt, *J* = 17.0, 10.0, 7.0 Hz, C**7**-<u>H</u>), 5.02 (1H, ddt, *J* = 17.0, 2,0, 1.0 Hz, C**8**-<u>H</u>'), 4.96 (1H, ddt, *J* = 10.0, 2.0, 1.0 Hz, C**8**-<u>H</u>), 4.80 (1H, s, C**9**-<u>H</u>), 4.78 (1H, s, C**9**-<u>H</u>'), 3.48 (2H, t, *J* = 7.0 Hz, C**1**-<u>H_2</u>), 3.04 (3H, s, Ms C<u>H_3</u>), 2.20 (4H, m, C**3**-<u>H_2</u> and C**6**-<u>H_2</u>), 2.10 (2H, t, *J* = 7.5 Hz, C**5**-<u>H_2</u>), 1.82 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-<u>H_2</u>). δ_C (101 MHz, $CDCl_3$) 156.4 (<u>C</u>=O), 147.3 (C**4**), 138.3 (C**7**), 114.8 (C**8**), 110.5 (C**9**), 52.2 (C**1**), 35.3 (C**5**), 34.4 (Ms <u>C</u>H_3), 32.7 (C**3**), 32.0 (C**6**), 24.9 (C**2**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -136.0 (2F, m), -145.2 (1F, tt, *J* = 21.0, 5.5 Hz), -158.7 – -158.9 (2F, m). HRMS: (ESI^+) Calculated for $C_{17}H_{18}F_5NNaO_4S$: 450.0769. Found $[M+Na]^+$: 450.0764.

7-Methylene-1-mesyl-1-azaspiro[4.4]nonane (374)



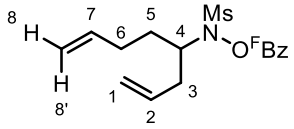
General procedure D: Conditions: 3.75 mol% $Pd_2(dba)_3$; 18.8 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; 6:1 *n*-BuCN:DMF (0.1 M); 110 °C; 16 hours. Substrate **372** (59.8 mg, 0.140 mmol) was employed. FCC (gradient elution: 4:1 – 2:1 hexane:EtOAc) afforded **374** (25.9 mg, 86 %) as a colourless crystalline solid. m.p. 64-66 °C (Et_2O:hexane, *cubes*). ν_{max} / cm^{-1}: (*solid*) 3069 (m), 2930 (m), 1655 (m), 1311 (s), 1143 (s). δ_H (400 MHz, $CDCl_3$) 4.89 – 4.86 (1H, m, C**8**-H), 4.83 – 4.80 (1H, m, C**8**-H'), 3.51 – 3.37 (2H, m, C**1**-H_2), 3.09 (1H, dddd, *J* = 15.5, 3.0, 3.0, 3.0 Hz, C**9**-H), 2.86 (3H, s, Ms CH_3), 2.59 – 2.42 (2H, m, C**5**-H and C**6**-H), 2.27 – 2.16 (2H, m, C**6**-H' and C**9**-H'), 1.90 – 1.74 (4H, m, C**2**-H_2 and C**3**-H_2), 1.65 (1H, ddd, *J* = 10.0, 6.0, 2.0 Hz, C**5**-H'). δ_C (101 MHz, $CDCl_3$) 147.8 (C**7**), 107.4 (C**8**), 72.0 (C**4**), 50.0 (C**1**), 44.4 (C**9**), 40.1 (C**3**), 39.3 (Ms CH_3), 36.3 (C**5**), 29.8 (C**6**), 22.6 (C**2**). HRMS: (ESI^+) Calculated for $C_{10}H_{17}NNaO_2S$: 238.0872. Found $[M+Na]^+$: 238.0878.

Octa-1,7-dien-4-ol



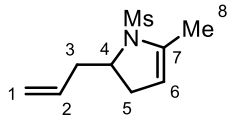
This compound was prepared according to a literature procedure.[302] To a solution of allylmagnesium chloride (2.0 M in THF, 8.33 mL, 16.7 mmol) in anhydrous Et_2O (25 mL) at 0 °C was added pent-4-enal (1.10 mL, 11.1 mmol) dropwise. The reaction mixture was stirred at room temperature for 3 hours before addition of saturated aqueous NH_4Cl (20 mL). The resulting phases were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 4:1 pentane:Et_2O) afforded the title compound (1.16 g, 83 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3357 (br s), 3078 (m), 2933 (m), 1641 (m). δ_H (500 MHz, $CDCl_3$) 5.88 – 5.78 (2H, m), 5.16 – 5.11 (2H, m), 5.05 (1H, ddt, *J* = 17.0, 1.5, 1.5 Hz), 4.97 (1H, ddt, *J* = 10.0, 2.5, 1.5 Hz), 3.67 (1H, dddd, *J* = 7.5, 7.5, 4.5, 4.5 Hz), 2.30 (1H, ddddd, *J* = 13.5, 7.0, 4.5, 1.5, 1.5 Hz), 2.26 – 2.10 (3H, m), 1.66 (1H, br s), 1.60 – 1.52 (2H, m). δ_C (126 MHz, $CDCl_3$) 138.6, 134.8, 118.3, 114.9, 70.3, 42.1, 36.0, 30.2. *The spectroscopic properties were consistent with the data available in the literature.*[303]

***N*-(Octa-1,7-dien-4-yl)-*N*-(pentafluorobenzoyloxy)methanesulfonamide (375)**



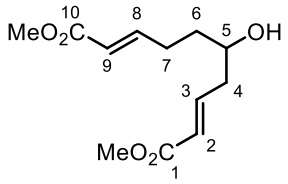
General procedure K: The preceding alcohol (379 mg, 3.00 mmol) was employed with $MsNHO^FBz$ (Section 7.3). The reaction time was 16 hours. FCC (eluent: 24:1 hexane:EtOAc) afforded **375** (651 mg, 52 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3079 (m), 2942 (m), 1784 (s), 1653 (m), 1499 (s), 1420 (m), 1163 (s). δ_H (400 MHz, $CDCl_3$) 5.88 – 5.72 (2H, m, C**2**-H and C**7**-H), 5.16 – 5.09 (2H, m, C**1**-H_2), 5.07 (1H, dddd, *J* = 17.0, 1.5, 1.5, 1.0 Hz, C**8**-H'), 5.01 (1H, dddd, *J* = 10.0, 1.5, 1.5, 1.0 Hz, C**8**-H), 4.14 – 4.04 (1H, m, C**4**-H), 3.12 (3H, s, Ms CH_3), 2.56 (1H, br s, C**3**-H), 2.43 – 2.29 (2H, m, C**3**-H' and C**6**-H), 2.23 (1H, ddddd, *J* = 15.0, 7.5, 7.5, 1.0, 1.0 Hz, C**6**-H'), 1.82 – 1.71 (1H, m, C**5**-H), 1.63 (1H, br s, C**5**-H'). δ_C (126 MHz, $CDCl_3$) 157.2 (C=O), 137.2 (C**7**), 133.9 (C**2**), 118.3 (C**1**), 115.7 (C**8**), 61.5 (C**4**), 40.0 (Ms CH_3), 36.3 (C**3**), 30.5 (C**5**), 30.3 (C**6**). *The aromatic ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -135.8 – -135.9 (2F, m), -145.1 (1F, tt, *J* = 21.0, 5.5 Hz), -158.5 – -158.7 (2F, m). HRMS: (ESI^+) Calculated for $C_{16}H_{16}F_5NNaO_4S$: 436.0612. Found $[M+Na]^+$: 436.0595.

2-Allyl-5-methyl-1-mesyl-2,3-dihydro-1*H*-pyrrole (378)



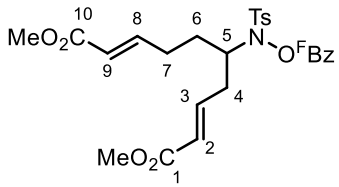
General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; *n*-BuCN (0.1 M); 110 °C; 15 hours. Substrate **375** (60.6 mg, 0.147 mmol, *added as a solution in n-BuCN*) was employed. FCC (gradient elution: 49:1 – 19:1 – 14:1 PhMe:EtOAc) afforded **378** (16.9 mg, 57 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 3078 (m), 2929 (m), 1434 (m), 1337 (s), 1156 (s). δ_H (400 MHz, $CDCl_3$) 5.76 (1H, ddt, *J* = 17.5, 10.5, 7.0 Hz, C**2**-H), 5.14 – 5.06 (2H, m, C**1**-H_2), 4.96 (1H, br s, C**6**-H), 4.22 – 4.14 (1H, m, C**4**-H), 2.85 (3H, s, Ms CH_3), 2.76 – 2.64 (1H, m, C**5**-H), 2.48 – 2.30 (2H, m, C**3**-H_2), 2.21 – 2.11 (1H, m, C**5**-H'), 1.98 (3H, br s, C**8**-H_3). δ_C (101 MHz, $CDCl_3$) 138.8 (C**7**), 133.2 (C**2**), 118.1 (C**1**), 110.7 (C**6**), 61.8 (C**4**), 41.3 (C**3**), 36.6 (Ms CH_3), 32.7 (C**5**), 15.5 (C**8**). HRMS: (ESI^+) Calculated for $C_9H_{15}NNaO_2S$: 224.0716. Found $[M+Na]^+$: 224.0714.

Dimethyl (2*E*,8*E*)-5-hydroxydeca-2,8-dienedioate



To a solution of Grubbs-Hoveyda 2nd generation catalyst (18.8 mg, 30.0 μmol) in anhydrous CH_2Cl_2 (60 mL, argon sparged) was added methyl acrylate (6.75 mL, 75.0 mmol) and octa-1,7-dien-4-ol (*vide supra*, 0.42 mL, 3.00 mmol). The reaction mixture was heated at reflux for 2 days before being concentrated *in vacuo*. FCC (gradient elution: 1:1 – 0:1 hexane:Et_2O) afforded the title compound (303 mg, 42 %) as a light-brown oil (the colouration was due to the presence of trace amounts of Ru-impurities). ν_{max} / cm^{-1}: (*film*) 3441 (br s), 2951 (m), 1717 (s), 1655 (s), 1436 (s), 1271 (s). δ_H (400 MHz, $CDCl_3$) 6.98 – 6.86 (2H, m, C**3**-H and C**8**-H), 5.86 (1H, d, *J* = 15.5 Hz, C**2**-H), 5.80 (1H, d, *J* = 15.5 Hz, C**9**-H), 3.76 – 3.70 (1H, m, C**5**-H), 3.68 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.55 (1H, br s, OH), 2.41 – 2.19 (4H, m, C**4**-H_2 and C**7**-H_2), 1.62 – 1.54 (2H, m, C**6**-H_2). δ_C (101 MHz, $CDCl_3$) 167.1 (C**10**), 166.9 (C**1**), 148.8 (C**8**), 145.3 (C**3**), 123.6 (C**2**), 121.4 (C**9**), 69.6 (C**5**), 51.6 (OCH_3), 51.5 (OCH_3), 40.4 (C**4**), 35.2 (C**6**), 28.4 (C**7**). HRMS: (ESI^+) Calculated for $C_{12}H_{18}NaO_5$: 265.1046. Found $[M+Na]^+$: 265.1055.

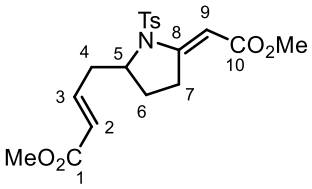
Dimethyl (2*E*,8*E*)-5-((4-methyl-*N*-((pentafluorobenzoyl)oxy)phenyl)sulfonamido)deca-2,8-dienedioate (379)



General procedure K: The preceding alcohol (378 mg, 1.56 mmol) was employed with $TsNHO^FBz$ (Section 7.3). The reaction time was 16 hours. FCC (eluent: 24:1 PhMe:acetone) afforded **379** (265 mg, 28 %) as a colourless crystalline solid. m.p. 94-95 °C (Et_2O, *fibres*). ν_{max} / cm^{-1}: (*film*) 2950 (m), 1786 (s), 1721 (s), 1655 (s), 1497 (s), 1167 (s). δ_H (500 MHz, $CDCl_3$) 7.82 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 7.37 (2H, d, *J* = 8.0 Hz, 2 × ArCH), 6.92 – 6.68 (2H, m, C**3**-H and C**8**-H), 5.86 – 5.70 (2H, m, C**2**-H and C**9**-H), 4.06 (1H, dddd, *J* = 8.5, 8.5, 4.5, 4.5 Hz, C**5**-H), 3.72 (2 × 3H, s, OCH_3), 2.65 (1H, br s, C**7**-H), 2.50 – 2.24 (6H, m, C**4**-H_2, C**7**-H' and Ts CH_3), 1.72 – 1.43 (2H, m, C**6**-H_2). δ_C (126 MHz, $CDCl_3$) 167.0 (C**10**), 166.4 (C**1**), 156.6 (C=O), 147.5 (C**8**), 146.4 (ArC), 146.1 (d, *J* = 260.0 Hz, ArCF), 144.2 (d, *J* = 262.5 Hz, ArCF), 143.6 (C**3**), 138.0 (d, *J* = 258.5 Hz, ArCF), 132.6 (ArC), 130.2 (ArCH), 129.4 (ArCH), 124.3 (C**2**), 122.1 (C**9**), 105.1 (ArC), 60.4 (C**5**), 51.8 (OCH_3), 51.6 (OCH_3), 34.1 (C**4**),

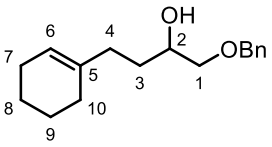
30.4 (C**6**), 28.9 (C**7**), 21.9 (Ts $\underline{C}H_3$). δ_F (377 MHz, $CDCl_3$) -135.7 – -135.9 (2F, m), -145.2 (1F, tt, *J* = 21.0, 5.0 Hz), -158.5 – -158.7 (2F, m). HRMS: (ESI^+) Calculated for $C_{26}H_{24}F_5NNaO_8S$: 628.1035. Found $[M+Na]^+$: 628.1035.

Methyl (*E*)-4-((*E*)-5-(2-methoxy-2-oxoethylidene)-1-tosylpyrrolidin-2-yl)but-2-enoate (382)



General procedure D: Conditions: 5.0 mol% $Pd_2(dba)_3$; 25 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$; 25 mol% Et_3N; *n*-BuCN (0.1 M); 110 °C; 17 hours. Substrate **379** (74.8 mg, 0.140 mmol) was employed. FCC (gradient elution: 3:1 – 2:1 hexane:EtOAc) afforded **382** (43.4 mg, 79 %) as a pale-yellow oil. ν_{max} / cm^{-1}: (*film*) 2950 (m), 1710 (s), 1622 (s), 1437 (m), 1346 (s), 1130 (s). δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* = 8.0 Hz, 2 × ArC$\underline{H}$), 7.31 (2H, d, *J* = 8.0 Hz, 2 × ArC$\underline{H}$), 6.88 (1H, ddd, *J* = 15.5, 8.0, 7.0 Hz, C**3**-$\underline{H}$), 6.00 (1H, dd, *J* = 2.0, 2.0 Hz, C**9**-$\underline{H}$), 5.92 (1H, ddd, *J* = 15.5, 1.5, 1.5 Hz, C**2**-$\underline{H}$), 4.37 (1H, dddd, *J* = 9.5, 7.0, 3.5, 3.5 Hz, C**5**-$\underline{H}$), 3.73 (3H, s, OC$\underline{H}_3$), 3.64 (3H, s, OC$\underline{H}_3$), 3.18 (1H, dddd, *J* = 18.5, 8.5, 4.0, 2.0 Hz, C**7**-$\underline{H}$), 2.95 – 2.81 (2H, m, C**4**-$\underline{H}$ and C**7**-$\underline{H}$'), 2.53 (1H, dddd, *J* = 14.5, 9.5, 8.0, 1.5 Hz, C**4**-$\underline{H}$'), 2.42 (3H, s, Ts C$\underline{H}_3$), 1.79 – 1.68 (2H, m, C**6**-$\underline{H}_2$). δ_C (101 MHz, $CDCl_3$) 168.0 (C**10**), 166.5 (C**1**), 156.3 (C**8**), 145.0 (Ar$\underline{C}$), 143.4 (C**3**), 135.3 (Ar$\underline{C}$), 130.0 (Ar$\underline{C}$H), 127.3 (Ar$\underline{C}$H), 124.5 (C**2**), 96.5 (C**9**), 62.9 (C**5**), 51.7 (O$\underline{C}H_3$), 51.1 (O$\underline{C}H_3$), 38.4 (C**4**), 30.1 (C**7**), 26.2 (C**6**), 21.7 (Ts $\underline{C}H_3$). HRMS: (ESI^+) Calculated for $C_{19}H_{24}NO_6S$: 394.1319. Found $[M+H]^+$: 394.1305.

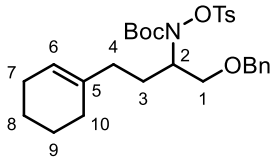
1-(Benzyloxy)-4-(cyclohex-1-en-1-yl)butan-2-ol (392)



To a suspension of magnesium turnings (207 mg, 8.51 mmol), benzyl glycidyl ether (**393**) (0.65 mL, 4.26 mmol) and CuI (81.1 mg, 0.426 mmol) in anhydrous THF (30 mL) was added a solution of 1-(bromomethyl)cyclohex-1-ene (Section 7.3, 1.49 g, 8.51 mmol) in anhydrous THF (15 mL). The reaction mixture was heated at reflux for 3 hours, then cooled to room temperature before addition of saturated aqueous NH_4Cl (50 mL). The reaction mixture was extracted with Et_2O (2 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (gradient elution: 9:1 – 7:1 petrol:EtOAc) afforded **392** (329 mg, 30 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 3436 (br s), 3030 (m), 2922 (m), 1453 (m), 1089 (s). δ_H (400 MHz, $CDCl_3$) 7.38 – 7.27 (5H, m, 5 × ArC$\underline{H}$), 5.41

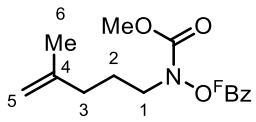
(1H, br s, C**6**-H), 4.56 (2H, s, OCH_2Ph), 3.81 (1H, dddd, *J* = 8.0, 7.5, 5.5, 3.0 Hz, C**2**-H), 3.51 (1H, dd, *J* = 9.5, 3.0 Hz, C**1**-H), 3.34 (1H, dd, *J* = 9.5, 7.5 Hz, C**1**-H'), 2.13 – 1.88 (6H, m, C**4**-H_2, C**7**-H_2 and C**10**-H_2), 1.64 – 1.49 (6H, m, C**3**-H_2, C**8**-H_2 and C**9**-H_2). δ_C (101 MHz, $CDCl_3$) 138.1 (ArC), 137.4 (C**5**), 128.6 (ArCH), 2 × 127.9 (2 × ArCH), 121.4 (C**6**), 74.7 (C**1**), 73.5 (OCH_2Ph), 70.4 (C**2**), 34.0 (C**4**), 31.2 (C**3**), 28.4 (C**10**), 25.3 (C**7**), 23.1 (C**9**), 22.6 (C**8**). HRMS: (ESI^+) Calculated for $C_{17}H_{24}NaO_2$: 283.1669. Found $[M+Na]^+$: 283.1674.

***tert*-Butyl (1-(benzyloxy)-4-(cyclohex-1-en-1-yl)butan-2-yl)(tosyloxy)carbamate (391)**



General procedure R: Alcohol **392** (325 mg, 1.25 mmol) was employed with BocNHOTs.[LXV] The reaction time was 15 hours. FCC (gradient elution: 1:4 – 1:9 – 0:1 petrol:PhMe) afforded **391** (193 mg, 29 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2927 (m), 1723 (s), 1598 (m), 1454 (m), 1369 (s), 1179 (s). δ_H (500 MHz, $CDCl_3$) 7.88 (2H, d, *J* = 8.5 Hz, 2 × ArCH), 7.35 – 7.22 (7H, m, 7 × ArCH), 5.39 (1H, br s, C**6**-H), 4.48 (2H, s, OCH_2Ph), 4.21 (1H, dddd, *J* = 9.0, 8.5, 5.0, 5.0 Hz, C**2**-H), 3.67 (1H, dd, *J* = 9.5, 9.0 Hz, C**1**-H), 3.43 (1H, dd, *J* = 9.5, 5.0 Hz, C**1**-H'), 2.44 (3H, s, Ts CH_3), 2.12 – 1.93 (4H, m, C**4**-H_2 and C**7**-H_2), 1.92 – 1.87 (2H, m, C**10**-H_2), 1.86 – 1.76 (1H, m, C**3**-H), 1.63 – 1.57 (2H, m, C**9**-H_2), 1.57 – 1.40 (3H, m, C**3**-H' and C**8**-H_2), 1.21 (9H, s, OC(CH_3)$_3$). δ_C (126 MHz, $CDCl_3$) 156.8 (C=O), 145.5 (ArC), 138.3 (ArC), 136.8 (C**5**), 132.0 (ArC), 129.9 (ArCH), 129.6 (ArCH), 128.4 (ArCH), 127.8 (ArCH), 127.6 (ArCH), 121.7 (C**6**), 83.2 (OC(CH$_3$)$_3$), 73.1 (OCH_2Ph), 69.5 (C**1**), 63.6 (C**2**), 34.8 (C**4**), 28.4 (C**10**), 27.7 (OC(CH_3)$_3$), 27.2 (C**3**), 25.4 (C**7**), 23.1 (C**9**), 22.7 (C**8**), 21.8 (Ts CH_3). HRMS: (ESI^+) Calculated for $C_{29}H_{39}NNaO_6S$: 552.2390. Found $[M+Na]^+$: 552.2370.

Methyl (4-methylpent-4-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (386d)

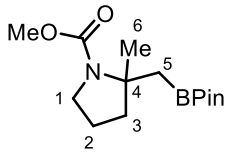


General procedure O: 4-Methylpent-4-en-1-ol (170 mg, 1.70 mmol) was employed with MeOC(O)NHO^{F}Bz (Section 7.4). The reaction time was 20 hours. FCC (*two times*, first, gradient elution: 3:7 – 3:17 petrol:PhMe; second eluent: 14:1 petrol:acetone) afforded **386d** (491 mg, 79 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 4.75 (1H, s), 4.70 (1H, s), 3.81 (3H, s), 3.72 (2H, t, *J* = 7.5 Hz), 2.10 (2H, t, *J* = 7.5 Hz), 1.80 (2H, tt, *J* = 7.5, 7.5 Hz), 1.72 (3H, s). δ_C (101 MHz, $CDCl_3$) 156.2, 144.5,

[LXV] BocNHOTs was prepared by Joshua Farndon (University of Bristol) according to a literature procedure.[164]

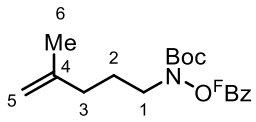
110.9, 54.1, 51.1, 34.5, 24.8, 22.4. *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.0 – -136.3 (2F, m), -146.1 (1F, tt, *J* = 21.0, 5.5 Hz), -159.3 – -159.5 (2F, m). *The spectroscopic properties were consistent with the data available in the literature.*[108]

((1-(Methoxycarbonyl)-2-methylpyrrolidin-2-yl)methyl)boronic acid pinacol ester (405a)



General procedure S: Conditions: 5.0 mol% $Pd_2(dba)_3$; 20 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 25 mol% Et_3N; 200 mol% B_2Pin_2; *n*-Bu_2O (0.4 M); 130 °C; 48 hours. Substrate **386d** (36.7 mg, 0.100 mmol) was employed. FCC (eluent: 5:1 petrol:EtOAc) afforded **405a** (11.1 mg, 39 %) as a pale-yellow oil. *This compound exists as an approximately 5:4 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 2976 (m), 1692 (s), 1445 (s), 1369 (s), 1143 (s). δ_H (500 MHz, $CDCl_3$) 3.68 (1.35H, s, B: OC$\underline{H}_3$), 3.62 (1.65H, s, A: OC$\underline{H}_3$), 3.56 – 3.50 (0.45H, m, B: C**1**-$\underline{H}$), 3.47 – 3.38 (1H, m, A: C**1**-$\underline{H}$; B: C**1**-$\underline{H}$'), 3.37 – 3.30 (0.55H, m, A: C**1**-$\underline{H}$'), 2.11 – 2.03 (0.45H, m, B: C**3**-$\underline{H}$), 1.97 – 1.90 (0.55H, m, A: C**3**-$\underline{H}$), 1.82 – 1.71 (3H, m, A and B: C**2**-$\underline{H}_2$ and C**3**-$\underline{H}$'), 1.69 – 1.48 (2H, m, A and B: C**5**-$\underline{H}_2$), 1.41 (1.65H, s, A: C**6**-$\underline{H}_3$), 1.33 (1.35H, s, B: C**6**-$\underline{H}_3$), 1.22 (6.6H, s, A: OC(C$\underline{H}_3$)$_2$C(C$\underline{H}_3$)$_2$O), 1.21 (5.4H, s, B: OC(C$\underline{H}_3$)$_2$C(C$\underline{H}_3$)$_2$O). δ_C (126 MHz, $CDCl_3$) 155.8 (B: $\underline{C}$=O), 154.5 (A: $\underline{C}$=O), 83.1 (B: O$\underline{C}$(CH$_3$)$_2$$\underline{C}$(CH$_3$)$_2$O), 82.9 (A: O$\underline{C}$(CH$_3$)$_2$$\underline{C}$(CH$_3$)$_2$O), 62.1 (A: C**4**), 61.5 (B: C**4**), 51.9 (B: O$\underline{C}$H$_3$), 51.6 (A: O$\underline{C}$H$_3$), 48.8 (B: C**1**), 47.8 (A: C**1**), 41.7 (B: C**3**), 41.0 (A: C**3**), 27.6 (B: C**6**), 26.6 (A: C**6**), 25.0 (A: OC($\underline{C}$H$_3$)$_2$C($\underline{C}$H$_3$)$_2$O), 24.9 (B: OC($\underline{C}$H$_3$)$_2$C($\underline{C}$H$_3$)$_2$O), 22.5 (A: C**2**), 22.1 (B: C**2**). *The ^{13}C signal corresponding to C**5** could not be resolved due to their weak intensity.* δ_B (128 MHz, $CDCl_3$) 32.8. HRMS: (ESI^+) Calculated for $C_{14}H_{27}BNO_4$: 284.2030. Found $[M+H]^+$: 284.2041.

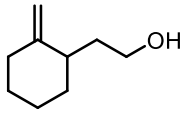
***tert*-Butyl (4-methylpent-4-en-1-yl)((pentafluorobenzoyl)oxy)carbamate (386e)**



General procedure O: 4-Methylpent-4-en-1-ol (200 mg, 2.00 mmol) was employed with BocNHO^FBz (Section 7.4). The reaction time was 21 hours. FCC (gradient elution: 1:1 – 2:3 petrol:PhMe) afforded **386e** (663 mg, 81 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2982 (m), 2938 (m), 1783 (s), 1721 (s), 1652 (m), 1504 (s), 1151 (s). δ_H (400 MHz, $CDCl_3$) 4.74 (1H, s, C**5**-$\underline{H}$), 4.70 (1H, s, C**5**-$\underline{H}$'), 3.68 (2H, t, *J* = 7.0 Hz, C**1**-$\underline{H}_2$), 2.10 (2H, t, *J* = 7.5 Hz, C**3**-$\underline{H}_2$), 1.79 (2H, tt, *J* = 7.5, 7.0 Hz, C**2**-$\underline{H}_2$), 1.73 (3H, s,

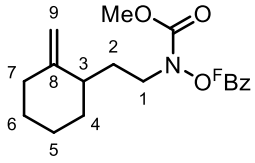
C**6**-$\underline{H}_3$), 1.49 (9H, s, OC(C$\underline{H}_3$)$_3$). δ_C (101 MHz, $CDCl_3$) 154.7 (Boc $\underline{C}$=O), 144.6 (C**4**), 110.8 (C**5**), 83.4 (O$\underline{C}$(CH$_3$)$_3$), 50.8 (C**1**), 34.6 (C**3**), 28.2 (OC($\underline{C}$H$_3$)$_3$), 24.9 (C**2**), 22.4 (C**6**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz, $CDCl_3$) -136.5 – -136.8 (2F, m), -146.7 (1F, tt, *J* = 21.0, 5.0 Hz), -159.3 – -159.6 (2F, m). HRMS: (ESI$^+$) Calculated for $C_{18}H_{20}F_5NNaO_4$: 432.1205. Found $[M+Na]^+$: 432.1194.

2-(2-Methylenecyclohexyl)ethan-1-ol



General procedure L: Cyclohex-1-en-1-ylmethanol (Section 7.3, 2.24 g, 20.0 mmol) was employed. The reaction time was 14 hours. The crude mixture was used in the next step without further purification. **General procedure I:** The preceding crude mixture was employed, using anhydrous THF as solvent and 1.0 eq. $LiAlH_4$ (2.0 M in THF). FCC (gradient elution: 7:3 – 1:1 pentane:Et_2O) afforded the title compound (1.40 g, 50 % over two steps) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 4.67 (1H, s), 4.61 (1H, s), 3.68 (2H, t, *J* = 6.5 Hz), 2.29 – 2.18 (2H, m), 2.09 – 1.99 (1H, m), 1.97 – 1.86 (1H, m), 1.79 – 1.70 (1H, m), 1.70 – 1.60 (1H, m), 1.59 – 1.40 (4H, m), 1.36 – 1.26 (1H, m). δ_C (101 MHz, $CDCl_3$) 152.8, 106.1, 61.7, 40.0, 35.2, 34.6, 34.1, 28.9, 24.0. *The spectroscopic properties were consistent with the data available in the literature.*[304]

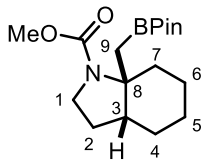
Methyl (2-(2-methylenecyclohexyl)ethyl)((pentafluorobenzoyl)oxy)carbamate (408)



General procedure O: The preceding alcohol (421 mg, 3.00 mmol) was employed with MeOC(O)NHO^{F}Bz (Section 7.4). The reaction time was 22 hours. FCC (*two times*, first, gradient elution: 3:7 – 1:4 petrol:PhMe; second eluent: 24:1 petrol:acetone) afforded **408** (726 mg, 59 %) as a colourless oil. ν_{max} / cm^{-1}: (*film*) 2931 (m), 2857 (m), 1787 (s), 1730 (s), 1651 (m), 1505 (s), 1177 (s). δ_H (400 MHz, $CDCl_3$) 4.70 (1H, s, C**9**-$\underline{H}$), 4.59 (1H, s, C**9**-$\underline{H}$'), 3.81 (3H, s, OC$\underline{H}_3$), 3.74 (2H, dd, *J* = 7.5, 7.5 Hz, C**1**-$\underline{H}_2$), 2.28 – 2.11 (2H, m, C**3**-$\underline{H}$ and C**7**-$\underline{H}$), 2.08 – 1.93 (2H, m, C**2**-$\underline{H}$ and C**7**-$\underline{H}$'), 1.80 – 1.71 (1H, m, C**4**-$\underline{H}$), 1.70 – 1.41 (5H, m, C**2**-$\underline{H}$', C**5**-$\underline{H}_2$ and C**6**-$\underline{H}_2$), 1.36 – 1.25 (1H, m, C**4**-$\underline{H}$'). δ_C (101 MHz, $CDCl_3$) 156.2 (MeO–$\underline{C}$=O), 151.5 (C**8**), 106.5 (C**9**), 54.1 (O$\underline{C}$H$_3$), 50.0 (C**1**), 40.4 (C**3**), 34.6 (C**7**), 34.0 (C**4**), 29.2 (C**2**), 28.8 (C**6**), 24.2 (C**5**). *The ^{13}C signals corresponding to the pentafluorobenzoyl group could not be resolved due to their weak intensity.* δ_F (377 MHz,

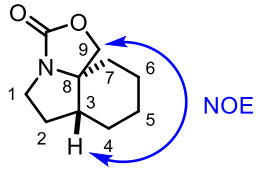
$CDCl_3$) -136.1 – -136.3 (2F, m), -146.2 (1F, tt, *J* = 21.0, 5.5 Hz), -159.2 – -159.4 (2F, m). HRMS: (ESI^+) Calculated for $C_{18}H_{18}F_5NNaO_4$: 430.1048. Found $[M+Na]^+$: 430.1042.

(((3a*R,7aR*)-1-(Methoxycarbonyl)octahydro-7a*H*-indol-7a-yl)methyl)boronic acid pinacol ester (409)**



General procedure S: Conditions: 5.0 mol% $Pd_2(dba)_3$; 20 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 25 mol% Et_3N; 200 mol% B_2Pin_2; *n*-Bu_2O (0.4 M); 130 °C; 48 hours. Substrate **408** (40.7 mg, 0.100 mmol) was employed. FCC (eluent: 7:1 petrol:EtOAc) afforded **409** (12.4 mg, 38 %) as a pale-yellow oil. *This compound exists as an approximately 1:1 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 2926 (m), 1694 (s), 1447 (s), 1370 (s), 1144 (s). δ_H (400 MHz, $CDCl_3$) 3.60 (1.5H, s, B: OC$\underline{H}_3$), 3.55 (1.5H, s, A: OC$\underline{H}_3$), 3.55 – 3.48 (0.5H, m, B: C**1**-$\underline{H}$), 3.45 – 3.37 (0.5H, m, A: C**1**-$\underline{H}$), 3.31 – 3.18 (1H, m, A and B: C**1**-$\underline{H}$'), 2.31 – 2.22 (0.5H, m, B: C**3**-$\underline{H}$), 2.10 – 1.95 (1H, m, A: C**3**-$\underline{H}$ and C**7**-$\underline{H}$), 1.89 – 1.81 (0.5H, m, B: C**7**-$\underline{H}$), 1.78 – 1.04 (23H, m, A and B: C**2**-$\underline{H}_2$, C**4**-$\underline{H}_2$, C**5**-$\underline{H}_2$, C**6**-$\underline{H}_2$, C**7**-$\underline{H}$', C**9**-$\underline{H}_2$ and OC(C$\underline{H}_3$)$_2$C(C$\underline{H}_3$)$_2$O). δ_C (101 MHz, $CDCl_3$) 156.0 (B: $\underline{C}$=O), 154.8 (A: $\underline{C}$=O), 82.9 (B: O$\underline{C}$(CH$_3$)$_2$$\underline{C}$(CH$_3$)$_2$O), 82.7 (A: O$\underline{C}$(CH$_3$)$_2$$\underline{C}$(CH$_3$)$_2$O), 62.9 (A: C**8**), 62.3 (B: C**8**), 51.8 (B: O$\underline{C}$H$_3$), 51.6 (A: O$\underline{C}$H$_3$), 46.7 (B: C**1**), 45.9 (A: C**1**), 43.2 (A: C**3**), 43.1 (B: C**3**), 35.7 (B: C**7**), 34.4 (A: C**7**), 26.8 (A: C**2**), 26.2 (B: C**2**), 25.7 (A: C**4**), 25.4 (B: C**4**), 25.2 (B: OC($\underline{C}$H$_3$)(CH$_3$)'C($\underline{C}$H$_3$)(CH$_3$)'O), 25.0 (A: OC($\underline{C}$H$_3$)(CH$_3$)'C($\underline{C}$H$_3$)(CH$_3$)'O), 24.9 (A: OC(CH$_3$)($\underline{C}$H$_3$)'C(CH$_3$)($\underline{C}$H$_3$)'O), 24.8 (B: OC(CH$_3$)($\underline{C}$H$_3$)'C(CH$_3$)($\underline{C}$H$_3$)'O), 22.8 (B: C**6**), 22.7 (A: C**6**), 21.9 (A: C**5**), 21.4 (B: C**5**). *The ^{13}C signals corresponding to C**9** could not be resolved due to their weak intensity.* δ_B (128 MHz, $CDCl_3$) 32.8. HRMS: (ESI^+) Calculated for $C_{17}H_{31}BNO_4$: 324.2343. Found $[M+H]^+$: 324.2353.

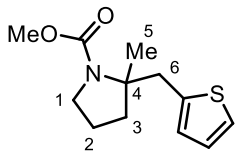
(6a*R,10a*R**)-Hexahydro-1*H*,3*H*,5*H*-oxazolo[4,3-*i*]indol-3-one (410)**



To a solution of boronic ester **409** (38.4 mg, 0.119 mmol) in THF (3 mL) at 0 °C was added mixture of 2.0 M aqueous NaOH (2.0 mL) and 30 % aqueous H_2O_2 (1.0 mL) dropwise over around 10 minutes. The reaction mixture was stirred at room temperature for 24 hours before addition of water (15 mL)

and extraction with Et_2O (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 1:4 petrol:Et_2O) afforded **410** (16.7 mg, 77 %) as a colourless crystalline solid. *The relative stereochemistry of the product was assigned based on the observed NOE correlation between the C**3** and the C**9** protons.* m.p. 58-59 °C (Et_2O:petrol, *globular*). ν_{max} / cm^{-1}: (*film*) 2930 (m), 2862 (m), 1752 (s), 1054 (m). δ_H (400 MHz, $CDCl_3$) 4.27 (1H, d, *J* = 8.5 Hz, C**9**-H), 4.09 (1H, d, *J* = 8.5 Hz, C**9**-H'), 3.62 (1H, ddd, *J* = 12.0, 8.5, 8.5 Hz, C**1**-H), 3.26 (1H, ddd, *J* = 12.0, 7.5, 5.0 Hz, C**1**-H'), 2.07 – 1.91 (3H, m, C**2**-H_2 and C**3**-H), 1.86 – 1.47 (6H, m, C**4**-H_2, C**5**-H, C**6**-H and C**7**-H_2), 1.39 – 1.26 (1H, m, C**5**-H'), 1.04 (1H, ddddd, *J* = 13.5, 13.5, 13.5, 3.5, 3.5 Hz, C**6**-H'). δ_C (101 MHz, $CDCl_3$) 161.5 (C=O), 73.6 (C**9**), 66.4 (C**8**), 44.0 (C**1**), 41.4 (C**3**), 32.1 (C**7**), 28.5 (C**2**), 23.9 (C**4**), 22.9 (C**6**), 19.7 (C**5**). HRMS: (ESI^+) Calculated for $C_{10}H_{16}NO_2$: 182.1176. Found $[M+H]^+$: 182.1177.

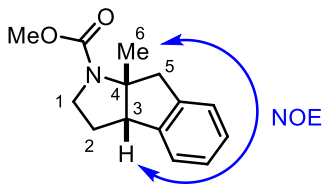
Methyl 2-methyl-2-(thiophen-2-ylmethyl)pyrrolidine-1-carboxylate (399a)



This compound was prepared using an adaptation of a literature procedure.[193] To a solution of thiophene (15 µL, 0.187 mmol) in anhydrous THF (1 mL) at -78 °C was added a solution of *n*-BuLi (1.46 M in hexane, 0.13 mL, 0.187 mmol). The reaction mixture was stirred at room temperature for 1 hour and then cooled to -78 °C before addition of a solution of **405a** (44.2 mg, 0.156 mmol) in anhydrous THF (2 mL). The reaction mixture was stirred at -78 °C for 1 hour before addition of a solution of NBS (33.3 mg, 0.187 mmol) in anhydrous THF (2 mL), then stirred at -78 °C for a further 1 hour before addition of saturated aqueous Na_2SO_3 (2 mL). The reaction mixture was warmed to room temperature before addition of water (10 mL) and extraction with EtOAc (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. FCC (eluent: 24:1 PhMe:EtOAc) afforded **399a** (9.7 mg, 26 %) as a colourless oil. Impure **405a** was also isolated; FCC (5:1 petrol:EtOAc) of this material afforded **405a** (20.0 mg, 45 %). *This compound exists as an approximately 7:3 mixture of rotamers A and B.* δ_H (400 MHz, $CDCl_3$) 7.15 (1H, d, *J* = 5.0 Hz, A and B: ArCH), 6.92 (1H, dd, *J* = 5.0, 3.5 Hz, A and B: ArCH), 6.79 – 6.74 (1H, m, A and B: ArCH), 3.79 (0.9H, s, B: OCH_3), 3.73 – 3.66 (2.8H, m, A: C**5**-H and OCH_3), 3.58 – 3.38 (1.3H, m, A: C**1**-H; B: C**1**-H and C**5**-H), 3.26 – 3.08 (1H, m, A and B: C**1**-H'), 3.07 (0.7H, d, *J* = 14.5 Hz, A: C**5**-H'), 2.99 (0.3H, d, *J* = 14.5 Hz, B: C**5**-H'), 2.11 – 1.98 (1H, m, A and B: C**3**-H), 1.71 – 1.61 (2H, m, A and B: C**2**-H and C**3**-H'), 1.47 (2.1H, s, A: C**6**-H_3), 1.45 – 1.36 (1.9H, m, A: C**2**-H'; B: C**2**-H' and C**6**-H_3). δ_C (126 MHz, $CDCl_3$) 155.6 (B: C=O), 154.7 (A: C=O), 140.5 (A: ArC), 140.0 (B: ArC), 126.9 (A and B: ArCH), 126.6 (B: ArCH), 126.5 (A: ArCH), 124.7 (B: ArCH), 124.4 (A: ArCH), 63.8 (A: C**4**), 63.1 (B: C**4**), 52.2 (B: OCH_3), 52.0 (A:

O<u>C</u>H$_3$), 49.3 (B: C**1**), 48.4 (A: C**1**), 2 × 39.0 (B: C**3** and C**5**), 2 × 37.8 (A: C**3** and C**5**), 26.6 (B: C**6**), 25.5 (A: C**6**), 22.1 (A: C**2**), 21.6 (B: C**2**). *The spectroscopic properties were consistent with the data available in the literature.*[108]

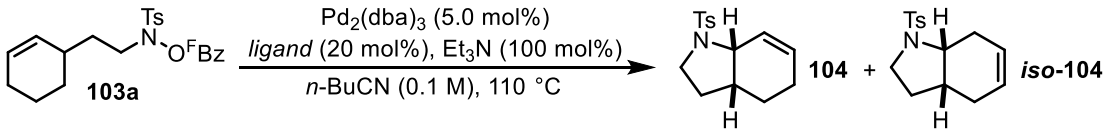
Methyl (3a*R,8a*S**)-8a-methyl-3,3a,8,8a-tetrahydroindeno[2,1-*b*]pyrrole-1(2*H*)-carboxylate (411)**



<u>General procedure D:</u> Conditions: 5.0 mol% $Pd_2(dba)_3$; 20 mol% 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (**L1**); 25 mol% Et_3N; *n*-Bu_2O (0.4 M); 130 °C; 48 hours. Substrate **402**[LXVI] (44.3 mg, 0.100 mmol) was employed. FCC (eluent: 24:1 petrol:acetone) afforded **411** (12.6 mg, 54 %) as a pale-yellow oil. *The product was assigned as the cis diastereomer based on the observed NOE correlation between the C**3** and the C**6** protons. This compound exists as an approximately 2:1 mixture of rotamers A and B.* ν_{max} / cm^{-1}: (*film*) 2955 (m), 1696 (s), 1444 (s), 1371 (s). δ_H (500 MHz, $CDCl_3$) 7.21 – 7.11 (4H, m, A and B: 4 × ArC<u>H</u>), 3.80 (0.65H, d, *J* = 17.0 Hz, A: C**5**-<u>H</u>), 3.75 (1.05H, s, B: OC<u>H</u>$_3$), 3.69 – 3.59 (0.35H, m, B: C**1**-<u>H</u>), 3.62 (1.95H, s, A: OC<u>H</u>$_3$), 3.59 – 3.43 (2H, m, A: C**1**-<u>H</u> and C**3**-<u>H</u>; B: C**5**-<u>H</u> and C**3**-<u>H</u>), 3.18 (0.35H, ddd, *J* = 10.5, 10.0, 6.5 Hz, B: C**1**-<u>H</u>'), 3.06 – 2.96 (1.65H, m, A: C**1**-<u>H</u>' and C**5**-<u>H</u>'; B: C**5**-<u>H</u>'), 2.29 – 2.13 (1H, m, A and B: C**2**-<u>H</u>), 2.13 – 1.96 (1H, m, A and B: C**2**-<u>H</u>'), 1.63 (1.95H, s, A: C**6**-<u>H</u>$_3$), 1.56 (1.05H, s, B: C**6**-<u>H</u>$_3$). δ_C (126 MHz, $CDCl_3$) 155.5 (B: <u>C</u>=O), 154.5 (A: <u>C</u>=O), 143.5 (A: Ar<u>C</u>), 143.4 (B: Ar<u>C</u>), 143.0 (A: Ar<u>C</u>), 142.3 (B: Ar<u>C</u>), 2 × 127.4 (A and B: Ar<u>C</u>H), 126.9 (B: Ar<u>C</u>H), 126.7 (A: Ar<u>C</u>H), 125.1 (A: Ar<u>C</u>H), 125.0 (B: Ar<u>C</u>H), 123.7 (B: Ar<u>C</u>H), 123.6 (A: Ar<u>C</u>H), 71.6 (A: C**4**), 70.8 (B: C**4**), 58.5 (B: C**3**), 57.1 (A: C**3**), 52.3 (B: O<u>C</u>H$_3$), 51.8 (A: O<u>C</u>H$_3$), 48.2 (B: C**1**), 48.0 (A: C**1**), 44.9 (B: C**5**), 43.4 (A: C**5**), 28.3 (A: C**2**), 28.1 (B: C**2**), 25.0 (B: C**6**), 23.7 (A: C**6**). HRMS: (ESI$^+$) Calculated for $C_{14}H_{18}NO_2$: 232.1332. Found [M+H]$^+$: 232.1343.

[LXVI] Substrate **402** was prepared by Rafaela Carmona (University of Bristol) according to a reported procedure.[108]

Appendix



Entry	*ligand*	*yield* (**104** + ***iso*-104**)
1	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	(85 %)
2	PPh_3	51 %
3	$P(C_6F_5)_3$	*not observed*
4	$P(2\text{-}(OMe)C_6H_4)_3$	7 %
5	$P(4\text{-}(CF_3)C_6H_4)_3$	39 %
6	$P(4\text{-}(CN)C_6H_4)_3$	6 %
7	PCy_2Ph	*negligible*
8	PPh_2Me	7 %
9	PBn_3	4 %
10	**L1**	33 %
11	$P(3,5\text{-}Me_2C_6H_3)_3$	43 %

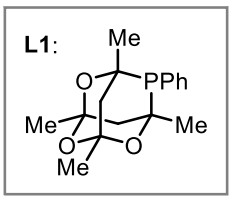
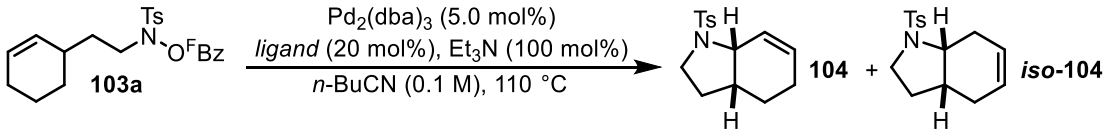


*Table 21 – Monodentate ligand screen for the palladium(0)-catalysed cyclisation of substrate **103a**. Yields were determined by ^1H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses.*



Entry	*n*	Ar	*yield* (**104** + ***iso*-104**)
1	1	C_6F_5	*not observed*
2	2	Ph	20 %
3	2	C_6F_5	*not observed*
4	3	Ph	24 %
5	3	4-$(CF_3)C_6H_4$	22 %
6	3	3,5-$(CF_3)_2C_6H_3$	8 %
7	3	C_6F_5	*not observed*
8	4	Ph	17 %
9	4	3,5-$(CF_3)_2C_6H_3$	8 %
10	4	C_6F_5	*negligible*
11	N/A	*ligand* = xantphos	*not observed*
12	N/A	*ligand* = BINAP	*negligible*

ligand:

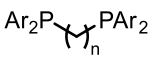
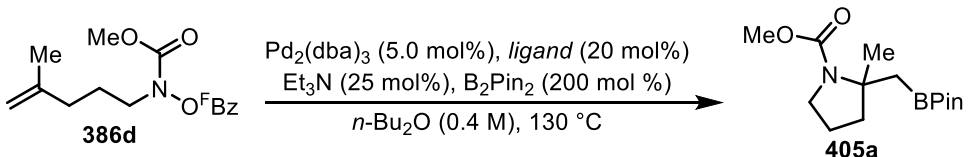


*Table 22 – Bidentate ligand screen for the palladium(0)-catalysed cyclisation of substrate **103**a. Yields were determined by ^{1}H NMR analysis of the crude material vs. 1,3,5-trimethoxybenzene as an internal standard.*



Entry	*ligand*	*yield*
1	**L1**	39 %
2	**L2**	30 %
3	**L3**	26 %
4	**L12**	27 %
5	$P(4\text{-}(CF_3)C_6H_4)_3$	21 %
6	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	37 %
7	$P(3,5\text{-}Me_2C_6H_3)_3$	11 %
8	$P(3,4,5\text{-}(F)_3C_6H_2)_3$	18 %
9	$P(C_6F_5)_3$	*not determined*

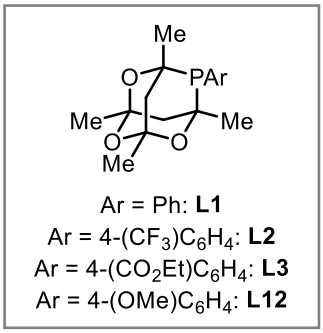
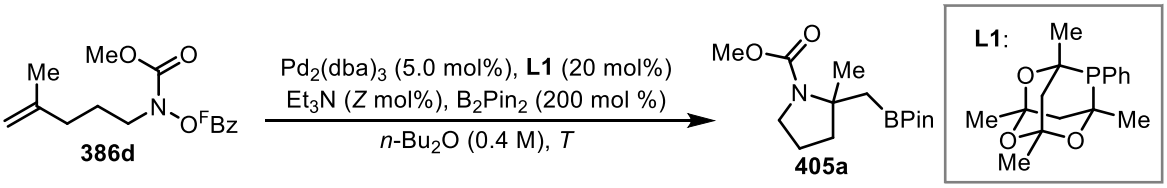


*Table 23 – Ligand screen for the palladium(0)-catalysed 1,2-aminoborylation of **386d**.*



Entry	*temperature*	*Z*	*yield*
1	120 °C	25	29 %
2	130 °C	25	39 %
3	140 °C	25	26 %
4	130 °C	*none*	37 %
5	130 °C	50	39 %
6	130 °C	100	16 %

*Table 24 – Optimisation of temperature and base equivalents in the palladium(0)-catalysed 1,2-aminoborylation of **386d**.*

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