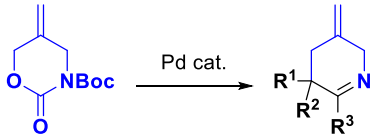
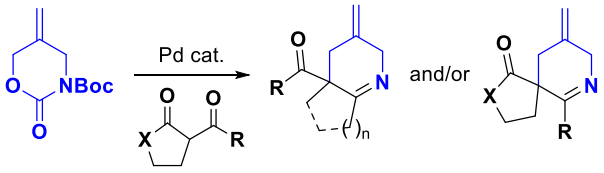
Abstract

A readily-available carbamate serves as a general precursor to a variety of highly functionalised piperidines through a novel Pd-catalysed reaction. This new methodology allows for the synthesis of a variety of complex heterocycles starting with simple, readily available substrates.

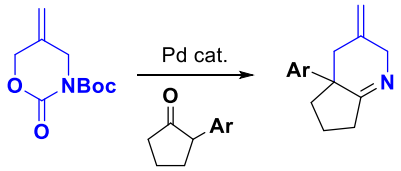


A range of 1,3-dicarbonyl substrates were successfully employed in this strategy to deliver a plethora of piperidine products. Interestingly, the architecture of the final piperidine could be controlled by the choice of 1,3-dicarbonyl employed - acyllactones delivered spirocyclic piperidines, whereas 1,3-ketoesters furnished linearly fused bicyclic piperidines. Unsymmetrical 1,3-diketones proved troublesome in the condensation step and produced a mixture of products resulting from non-regioselective condensation. To avoid this issue, sterically hindered substrates could be employed to allow the regioselective construction of a range of spirocyclic piperidines from 1,3-diketone substrates.

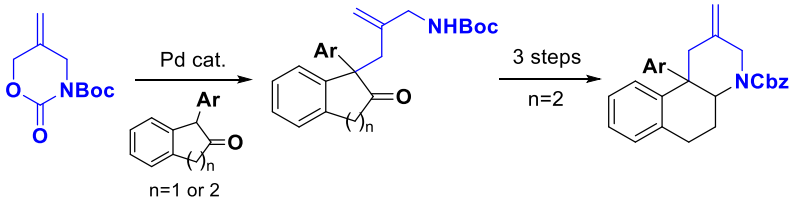


Further studies demonstrated that chiral phosphoramidites were invaluable ligands in promoting the asymmetric variant of this procedure and allowed the enantioselective synthesis of a range of spirocyclic piperidines with excellent enantiomeric purity.

Extension of this methodology to a range of 2-arylketones proved to be efficient, requiring a slight increase in reaction temperature. A range of piperidine rings bearing electron-neutral and electron-deficient aryl rings were synthesised through this method. The inclusion of electron-donating substituents was unsuccessful in this application.



Furthermore, the mild Pd-catalysed allylation of a range of indan-2-ones and 2-tetralones proved to be facile and high-yielding. The reductive amination of the allylated indanone derivatives was found to be more complicated than originally thought, with the formation of a variety of impurities that complicated purification and reduced the yields of isolated products. However, the reductive amination of the tetralone substrates proceeded efficiently, and highly functionalised tricyclic piperidines could be isolated in excellent yields over 4 synthetic steps.



Acknowledgements

"If it was easy, it wouldn't be worth doing"

Joe – Five years ago, you let that fresh-faced 2nd year undergraduate into your lab and now I'm finally leaving, a little wiser and a little less fresh-faced (only a little). It's been a true privilege working with you over the past 5 (or so) years and I can't believe my time here is finally coming to an end. Thank you for your patient guidance, constant support and for all the opportunities you've provided over the years. Thank you for challenging my understanding every step along the way on what's been a fun, frustrating and successful journey. You're a fantastic supervisor and a good friend. I don't think I'll ever be able to listen to P!nk the same way again… All the best for the future, I'm sure our paths will cross again!

Wes(bo) – Not quite sure how I made it this far considering you were my first lab supervisor, but against all the odds, here I am! Thanks for all your help over the last few years. You've always been supportive and provided advice and I'm pleased to be able to call you my friend. I look forward to the next random Friday afternoon phone call, when nobody else will pick up 😉

Steve – The Harrity Lab's very own Yorkshire mascot. Thanks for all the "advice" and the character-building. To be sincere for a second, you've been a great companion, and you've taught me a lot – I wouldn't be half the chemist I am if it weren't for you. But also, you taught me not to care what others think, and I'm certainly a more confident person for that, so thank you. Your factoids will provide me with endless topics when conversations get dull – even the ones that aren't true. You've been a solid source of entertainment and the lab really isn't the same without you. I'm sure Concept (not Peakdale!) are better off for your presence.

Andy – Unlike Steve, thanks for actually being a role model. I've always admired your work ethic and your passion for everything organic chemistry. Wherever you end up, you'll be an asset. I still remember the pep talk you gave me, one evening after many libations in the classy establishment that is Vodka Revs. Words I'll carry with me for the rest of my career (if I have one…!).

Tracy (TMM**B**) – My occasional tea buddy! Thanks for all the sink chats. Like Andy, you've been a superb role model, and I will never forget how trusting you are. As you commented in your acknowledgements, I think a certain comment about a certain market will forever enshrine my memory of our time in the lab!

GuGu! – My little buddy, the lab is much safer without you and your DMDO "bombs" and your OsO_4 everywhere, but it's certainly a lot duller! You livened up any situation. I pray that one day I will reach the title you've been giving me for years – Prof. Allen! ***IF*** that day ever comes, I'll buy you KFC.

Wheatley – Sir, it's been a pleasure. I wish you the best of luck at the Spanish Embassy. I look forward to seeing your name on a low impact journal someday soon

(just kidding…!). You were a great addition to the lab and it's a shame you weren't able to stick around. I know we'll stay in touch!

Chris – Well then young lad, thank you for keeping me company for the past year. If it weren't for you I think I genuinely would have gone insane. Our mindless chats about nothing have provided me with a bit of an escape from the real world, and it's been very welcome. Don't worry – something will work one day, you just need to stop taking so much time off! :P You'll make a monster of a PhD student when you finish – just make sure you take all the opportunities you're given.

Olivieeeer – Monsieur Presidente, the only person left who's been here longer than I have! Thanks for taking me under your wing as a MChem student way back in the day. Also, thank you for being a good friend over the past few years and showing me that being part of a research group isn't just about the chemistry. You're perhaps the most laid-back person I know – "*it's fiiiiiiiiiine*" or "*it's okaaaaay*" spring to mind! Thank you for all the interesting discussions at the whiteboard. I wish you all the best wherever your career takes you.

Matt F – Our trip to Washington was amazing and I'm pleased that it was you sat beside me on those long flights (even if I didn't show it at the time…😉). You've been a great friend and housemate over the years and I'll miss your well-timed sassy comments. Thanks for all the technical chats and the not-so-technical ones too! You're a great chemist, and I know you'll find an amazing postdoc in the US – you just need to find the right person! Good luck with the future – don't be a stranger.

Charlie – The illusive man of mystery. I'll miss your quirks – I doubt I'll ever meet someone quite like you! You've been a fantastic friend. It's been a long time since we've gone and "shot something" but I'm sure a games night is due sometime soon. All the best with the rest of your PhD – stay in touch!

Jenna – Jones group lab manager! Thanks for being there for my rants and raves. Your healthy lifestyle reminded me that I need to eat fruit and veg sometimes too, so thank you for that – otherwise it'd be tuna pasta every night! Thanks for all the games nights, they were great fun and a good way to escape the humdrum of research life. All the best with your final year! Stay in touch!

Júliaaa – Muchas gracias por tu amistad. You were a fantastic lab mate and I miss your constant energy. Thanks for all the charitable donations (I mean drinks) and best of luck with your (not so) new-found job!!!

Sylvestre – Thanks for adopting me in your badminton club, and thank you for being a good friend. I wish you all the best with your post-doc and I hope our paths cross again!

Helena – Well, it's been a hell of a journey, hasn't it! We've had our ups and we've had our downs, but I'll always remember the impromptu curries after getting the bus up the hill! Your obsession with potatoes will live with me forever. All the best at Bayer *putata!*

Prisca – The one with the American accent! Where did the last three years just go? Thanks for your companionship and your knowledge of multi-component reactions 😉.

Jokin – You were only here for a year, but you certainly left a Jokin-sized hole when you left! I really enjoyed my time in the lab when you were around. The baking was especially fun (to eat!). I wish you all the best at Sygnature!

Marie – C'est booooo!!!!! Thanks for tolerating my terrible French. And thanks for not being boring 😉. You're a good lass and I'll miss you being my office neighbour. Thanks for all the biers, keep at it and keep smiling! Harrity group NMR wizard 2017.

"Sensible" Damien – I remember when Damien wasn't so sensible and would end up in SOYO at 3 am on a work night after saying "just one drink". But now you have a job and you're even less sensible (from what I hear!). Thanks for being there over the years, it's always refreshing to see your face. I'll have to come to Nottingham one day and see what all the fuss is about.

Anne-Chloe – The most fierce French person I have ever met! But in a good way! I appreciate your honesty – "*this is a sheeet acknowledgement!"*. Good luck at Concept! I hope The South treats you as well as The North has!

Dr. Matthew Connolly – The man who started it all! Thank you for providing me with the best start anyone could ask for from a PhD (even if it was a challenge to get it published!). Thank you for everything you taught me in the lab when you were still around and thank you for the electronic support over the years. I hope your life in Norway is treating you well and I hope we meet again one day!

Muhannad – I know we never got on as well as we could've, but working alongside you taught me a lot. I sincerely wish you all the best for the future and I hope your research goals come to fruition! "*Five pounds please!*"

Taban – I've never known such a strong woman. You seriously amaze me. I remember when you stepped into the lab and you barely spoke any English – but look at you now! You've worked so incredibly hard to get to where you are now and you deserve every success that comes your way. Best of luck for the future Taban – I'm sure we'll meet again.

Liam Woodhead – I'm pleased Sylvestre left so me and Júlia could share responsibility for you. You were a really good student and I'm pleased you stuck around for a PhD – I'm sure you taught the Haynes lot a thing or two about how to work in a lab 😉

Liam Barber – My first real student! Going through your data for my thesis has reminded me of the good old days when you were around. It wasn't until you left that I realised just how hard you worked in the lab. It wasn't the easiest of projects but you got some really nice results out of it, so thank you so much for all of your efforts. I remember the first time you made a novel compound – you were really excited. It reminded me of why I love science so much - the discovery of new things (no matter how small) is always exciting. Without that intrigue, I wouldn't be where I am now! I

hope the novelty of research will draw you back one day, but until then, all the best wherever your life takes you.

Elliott – Your passion was reinvigorating. At a time when my own work was getting me down, it was so refreshing to see someone so driven and interested in EVERYTHING! Thanks for your work on the project, I know it wasn't easy, but you did really well to get as far as you did. I hope the Aggarwal lab is providing enough work for you to do! And remember, if you ever prick yourself with a needle again, I'll be there 😉

Emma Harwood – The researcher from Rotherham! Thanks for your companionship in the lab. And, of course, thank you for introducing me to Hannah! I owe you a lot for that! I hope your teaching career is as successful as your project was (you got some really nice results!). I KNOW I'll see you around!

David – Thanks for all your work in the lab, you made a fair few nice compounds! Good luck with your PhD, just make sure you shut the front door 😉

George "Polish-name"-Jones – Good luck in the force (if you can call it that, I know "*Hot Fuzz*" would have us think otherwise). Somebody needs to keep them Rotherham folk in check!

The Boys – I know I've not been the best friend over the years. It's hard being so far from everything that's going on. But I know that no matter how much time passes, I can always come back to Colchester and it'll feel like nothing has changed. To have that is incredibly lucky, and I feel very fortunate to call you all my friends. Thanks for all the support over the last few years, I really appreciate it. I'm looking forward to being back for a few months 😊.

The Colemans – I feel truly lucky to have met you all. You're an incredible family and I can't thank you enough for everything you have done for me, from biscuit cake to a personal taxi service. One day I'll pay you all back! I look forward to seeing what the future brings!

Matt and Brad – I could not be more proud of either of you. You're both pursuing careers that you've wanted for ages, and that's success right there! I'm looking forward to finally learning to drive, getting a car, and coming to see you more often. Don't forget there's always a space for you in Cardiff! I love you both dearly.

Mum and Dad – Well, words alone can't possibly describe the debt of gratitude I owe you both for everything you've done for me. I'm sat here writing this after you just left, taking all of my earthly belongings out of Sheffield for the last time, leaving me with just a suitcase and enough clothes for me to submit this thing. I owe you the world, and I look forward to the day I can start to pay you back. You've supported me every step of the way and never once discouraged me from doing anything. You've taught me that, with enough hard work, the world is your oyster – I guess Cardiff will do for now! But with all the hard work, you've reminded me that sometimes it's important to sit back and just enjoy the moment. You're my Mum and Dad, but you're also two of my best friends, and I love you both dearly. From the bottom of my heart – thank you.

Hannah – Don't think for a second you were escaping my soppy messages! You have been amazing over the last 6 months. In such a short span of time, we've shared so much and grown together a lot. Meeting you has been such a fantastic privilege and you've really shaped me as a person. You're ***truly*** incredible and I'm so upset to be leaving Sheffield with you still in it! But, this is just the next adventure in our story, and I can't wait to see what the future has in store for us. I love you more.

I've spent seven years in Sheffield and I've had the utmost privilege to meet so many incredible people, both inside and outside the chemistry department, and to thank everyone individually would certainly annoy my examiner… So, thank you to everyone who has had an impact (however big or small) on my time here. Despite my grievances, Sheffield is a very special "city" and I have a lot of fond memories. It will always be the city where I became who I am today. Whether that's a good or a bad thing, I'll leave with those who know me best!

Table of Contents

Abbreviations

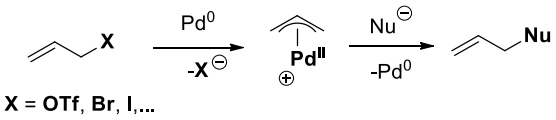
Ac	Acetyl
Ar	Generic aromatic group
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
BINOL	1,1’-Bi-2-naphthol
Bn	Benzyl
Boc	*Tert*-butoxycarbonyl
^{n}Bu	*n*-Butyl
^{t}Bu	*Tert*-butyl
Cbz	Carboxybenzyl
CoA	Coenzyme A
Cp	Cyclopentadienyl
Cy	Cyclopropyl
Δ	Reflux
DABCO	1,4-Diazabicyclo[2.2.0]octane
dba	*Trans*,*trans*-dibenzylideneacetone
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMSO	Dimethylsulfoxide
d.r.	Diastereomer ratio
DYKAT	Dynamic kinetic asymmetric transformation
ee	Enantiomeric excess
e.r.	Enantiomer ratio
ESI	Electrospray Ionisation
Et	Ethyl
et al.	*et alia*
FAB	Fast atom bombardment
FCC	Flash column chromatography
FTIR	Fourier-transform infrared spectroscopy
h	Hours

H-G II	Hoveyda-Grubbs second generation catalyst
HMBC	Heteronuclear multiple bond coherence
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
L	Generic ligand
L*	Generic chiral ligand
LCMS	Liquid chromatography-mass spectrometry
*m*CPBA	*Meta*-chloroperoxybenzoic acid
Me	Methyl
min	Minutes
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Np	Naphthyl
Nu	Generic nucleophile
Ph	Phenyl
PHOX	[2-(diphenylphosphino)phenyl]-2-oxazoline
^{i}Pr	Isopropyl
^{n}Pr	*n*-Propyl
R	Generic carbon-containing group
RCM	Ring-closing metathesis
T	Temperature
t	Time
TBS	*Tert*-butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMM	Trimethylenemethane
TMS	Trimethylsilyl
Ts	4-methylbenzene-1-sulfonyl

1 – Introduction

1.1 – Tsuji-Trost Allylation Reaction

The use of palladium catalysts for the formation of carbon-carbon and carbon-heteroatom bonds has been a pivotal topic in research laboratories for decades. The capacity for palladium to form Pd-π-allyl complexes from allylic electrophiles has enabled the development of the Tsuji-Trost allylation reaction which serves as an archetype of Pd-catalysed processes, allowing the addition of bespoke allyl fragments to a variety of nucleophiles (Scheme 1).[1]



Scheme 1 – General scheme for the Pd-catalysed Tsuji-Trost reaction.

To understand the true nature of these reactions, it is crucial to discuss the nature of the Pd-π-allyl intermediate - a detailed mechanism for their formation and reaction is provided in Figure 1.[2] First, the olefin coordinates to the Pd-metal centre through donation of the electrons in the π-bonding orbital of the alkene into a vacant d-orbital on the metal. Then, through an oxidative insertion, the palladium metal inserts into the C-X bond to deliver the Pd-π-allyl cation. The nucleophile then reacts with the electrophile in a nucleophilic addition process, the nature of which will be discussed in due course. Finally, dissociation of the palladium from the alkene furnishes the product.

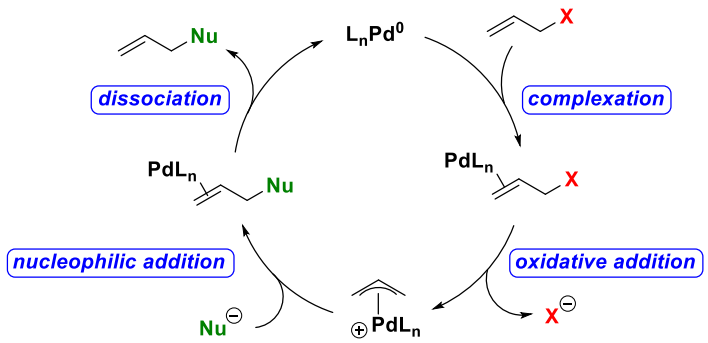


Figure 1 – General catalytic cycle for the Tsuji-Trost reaction.

In the case of substituted allyl acetates, the oxidative addition step occurs with inversion of stereochemistry (Figure 2).[3] The subsequent nucleophilic addition can occur *via* two different mechanisms, dependent on the nature of the nucleophile.[1] "*Soft*" nucleophiles, such as malonates and other stabilised enolates, typically react at the less-substituted, electrophilic carbon terminus of the cation, distal to the palladium (path a). This is considered an *outer-sphere* mechanism, since the palladium is not directly involved with the addition of the nucleophile resulting in net retention of stereochemistry from the starting material. "*Hard"* nucleophiles, such as alkoxides and amides, typically react at the Pd-centre first, followed by reductive elimination to form the C-Nu bond (path b). This constitutes an *inner-sphere* mechanism and results in net inversion of stereochemistry.

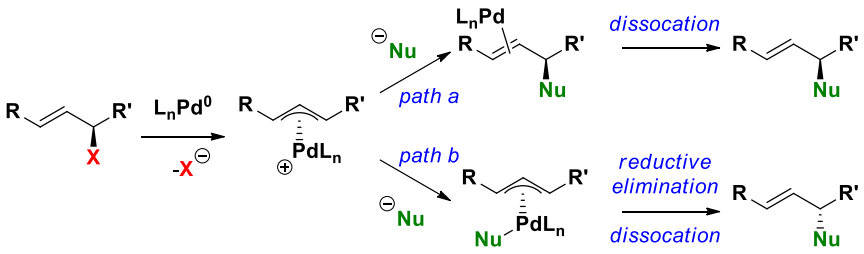


Figure 2 – Stereochemical considerations of the Tsuji-Trost reaction.

1.2 – Asymmetric Allylic Alkylations

Enantioselective allylic alkylations have been described as a special class of asymmetric reaction.[4] This is largely due to the ways in which they differ from most other enantioselective processes: i) there are a variety of mechanisms which account for enantiodiscrimination;[4] ii) they are generally more diverse than other reactions in the fact that they allow a large selection of different bond types to be formed;[4] iii) both reacting partners can be prochiral which allows for the efficient assembly of multiple stereocentres in one process;[5] iv) the asymmetric bond-forming step occurs outside of the coordination sphere of the metal and so distal to the chiral ligands (only in the case of "soft" nucleophiles).[5]

In total, there are five mechanisms for enantiodiscrimination.[4] This section will focus on just one of these mechanisms, which is the facial selectivity of prochiral nucleophile faces (Figure 3).

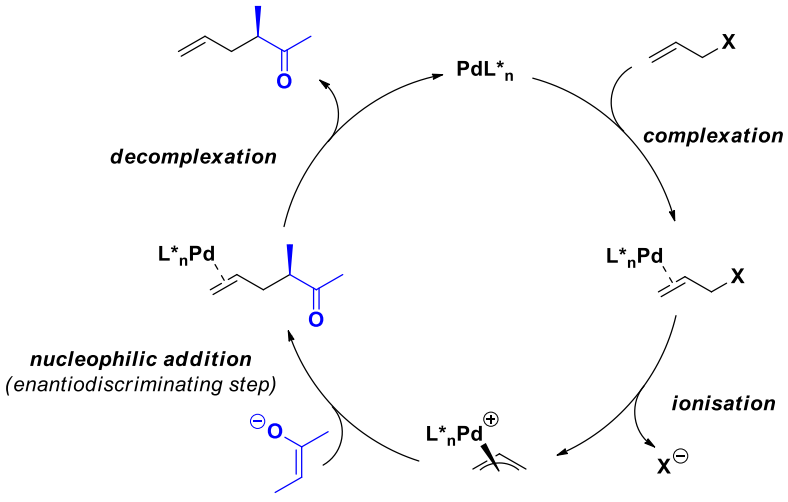


Figure 3 – Discrimination of the faces of a prochiral nucleophile.[4]

This mode of enantiodiscrimination has been described as challenging owing to the difficulty of inducing selectivity.[4] As previously discussed, the difficulty arises from the distal approach of the nucleophile to the metal centre of the palladium-π-allyl complex. Additionally, the use of prochiral nucleophiles in asymmetric allylic alkylations are typically less common than the use of non-prochiral nucleophiles.[6]

To this end, there have been several reports which describe attempts towards this challenging goal. After impressive work on the asymmetric allylation of α-acetamido-β-ketoesters[7] and α-acetamido-β-ketophosphonates,[8] Kuwano and Ito reported the asymmetric allylation of 1,3-diketones which utilised (*R*)-BINAP as the chiral ligand (Figure 4).[9]

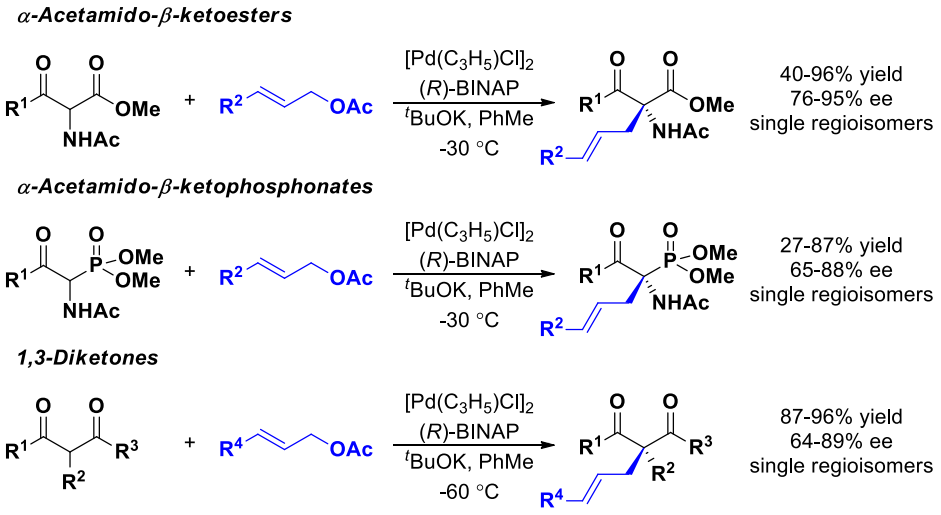
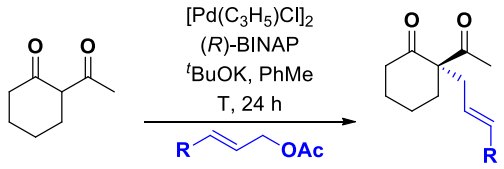


Figure 4 – Kuwano and Ito's palladium-catalysed asymmetric allylation of various 1,3-dicarbonyl compounds.[7–9]

This protocol was found to be applicable to a large variety of allylic acetates. It was found that allyl acetate afforded a 64% ee with 2-acetylcyclohexanone. However, γ-substitution on the allylic acetates increased the selectivity of the reaction, with

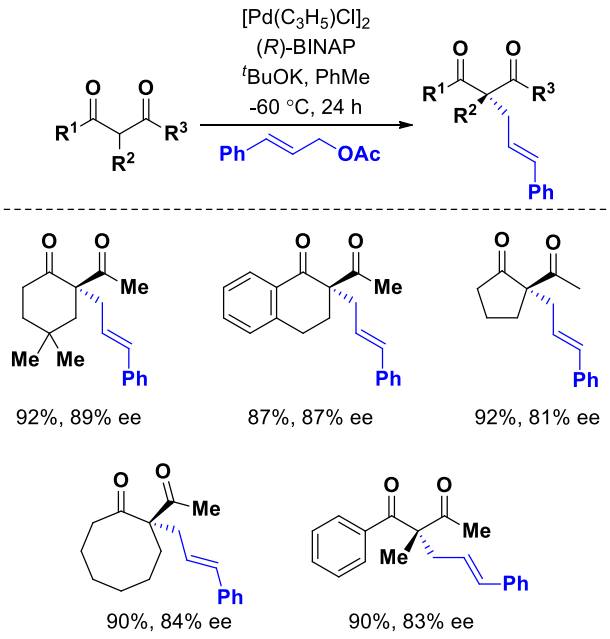
aromatic substituents affording higher enantiomer excesses than aliphatic substituents (Table 1). This clearly demonstrates the difficulty in inducing selectivity in the presence of symmetrical palladium-π-allyl complexes.

Table 1 – Effect of γ-substituent on selectivity in asymmetric allylic alkylation with 1,3-diketones.[9]



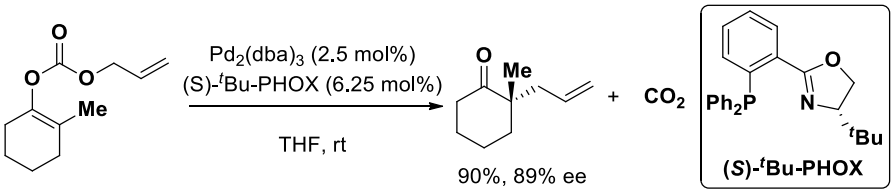
Entry	R	T / °C	Yield / %	ee / %
1	H	-60	82	64
2	^{n}Pr	-30	79	64
3	Cy	-30	65	65
4	Ph	-60	99	85
5	*p*-MeO-C_6H_4	-60	87	83
6	*p*-CF_3-C_6H_4	-60	87	84

A wide range of 1,3-diketones were successfully allylated with cinnamyl acetate with good selectivities, including acyclic diketones. Interestingly, the best selectivity was afforded by 2-acetyl-4,4-dimethylcyclohexanone to give the product in 92% yield and 89% ee (Scheme 2).



Scheme 2 – Scope of 1,3-diketone substrate in enantioselective allylation reaction.[9]

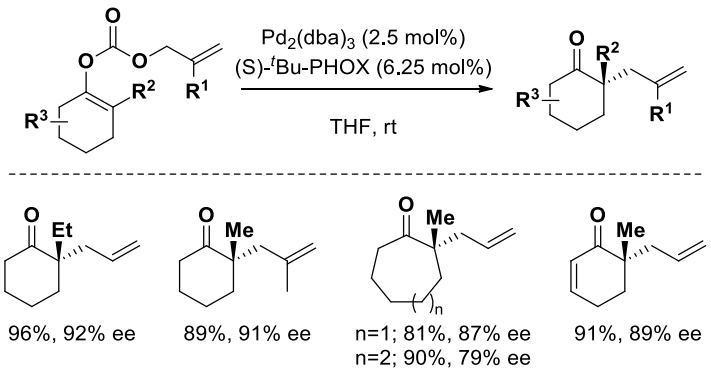
Alternative to an external palladium-allyl source, Stoltz and co-workers devised an asymmetric Carroll rearrangement process, where the allyl group is included in the starting material (Scheme 3).[6] Starting with enol carbonates, introduction of a palladium source and a suitable ligand generates the palladium-π-allyl complex and simultaneously liberates carbon dioxide and the enolate. The enolate can then attack the palladium-π-allyl complex through the carbon to afford the allylation products.



Scheme 3 – Enantioselective allylation using internal source of allyl.[6]

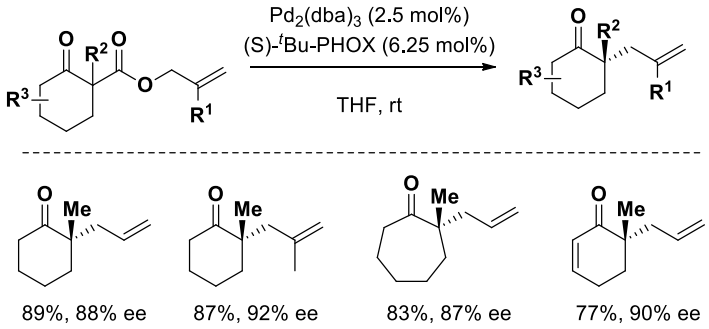
An extensive ligand screen found that the phosphino-oxazoline (PHOX) based ligands generally performed well in this reaction, with (*S*)-^{t}Bu-PHOX giving the best yield and selectivity.

The substrate scope for this reaction was generally limited to 6-membered aliphatic rings with various substitution patterns (Scheme 4). Some larger rings were also subjected to this procedure. Interestingly, inclusion of a methyl group on the central carbon of the allyl moiety afforded a slight increase in selectivity. Another interesting point is that switching the methyl to an ethyl group increased the ee marginally. However, increasing the size of the substituent any further resulted in a drop in yield without much gain in enantioselectivity.



Scheme 4 – Scope of the palladium-catalysed allylation of enol carbonates.[6]

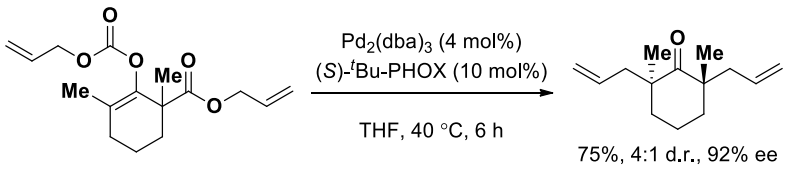
Further to this methodology, the same authors also achieved an enantioselective deracemisation of quaternary carbon stereocentres.[10] This work started with β-ketoester starting materials, but ultimately generated the same products shown in Scheme 4. In this case, treatment with the same catalytic system as before once again formed the palladium-π-allyl system with the liberation of carbon dioxide. However, this time the enolate was generated by an alternative mechanism (Scheme 5).



Scheme 5 – Palladium-catalysed allylation from β-ketoesters.[10]

As can be seen, the enantioselectivities do not benefit from this alternative procedure, and the yields are generally lower than in the previous method. The authors note, however, that this is the first described example of a catalytic enantioselective synthesis of quaternary carbon centres from already existing quaternary carbon stereocentres.

The two described techniques were then combined in an impressive tandem-reaction that afforded a double allylation (Scheme 6).[10]



Scheme 6 - Enantioselective allylation cascade reaction.[10]

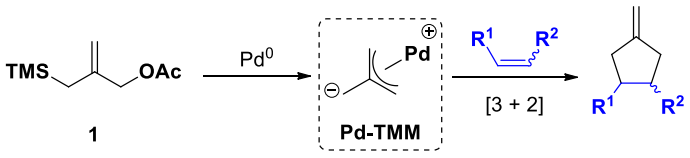
As has been demonstrated, the enantioselective allylation of 1,3-dicarbonyl compounds is a challenging feat to achieve in a highly enantioselective fashion. Clearly, there is still room for improvement in the selectivity of such reactions. Additionally, all of the examples listed in this section introduce an all-carbon containing allyl group, which limits the functionalisation that can be achieved on the products.

1.3 – Generation and Reaction of Pd-Stabilised Zwitterions

The use of dipolar reagents in ring-forming reactions is a powerful methodology as it allows access to a variety of cyclic products with varying ring-sizes and substitution patterns. In this context, Pd-catalysis offers a new approach through the generation of a series of Pd-stabilised zwitterions, which consist of a Pd-π-allyl cation and a stabilised anion.[11] For the purpose of this thesis, the following sections will focus on the application of this technology towards the synthesis of *N*-heterocycles.

1.3.1 – Pd-Stabilized Zwitterions with C-Centred Anions

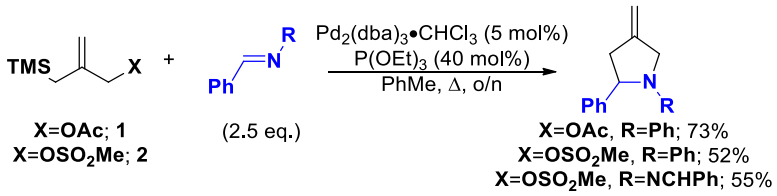
In 1979, Trost and co-workers documented the first catalytic generation of Pd-trimethylenemethane (Pd-TMM).[12] Allylsilane **1** was shown to be a suitable precursor to Pd-TMM which could be generated by employing a suitable source of Pd(0). Additionally, the authors demonstrated its ability to react with electron-deficient alkenes in a [3 + 2] cycloaddition to deliver methylenecyclopentane products (Scheme 7).



Scheme 7 – Reaction of allylsilane **1** with Pd^0 to form Pd-TMM and subsequent [3 + 2] cycloaddition with electron-deficient alkenes.

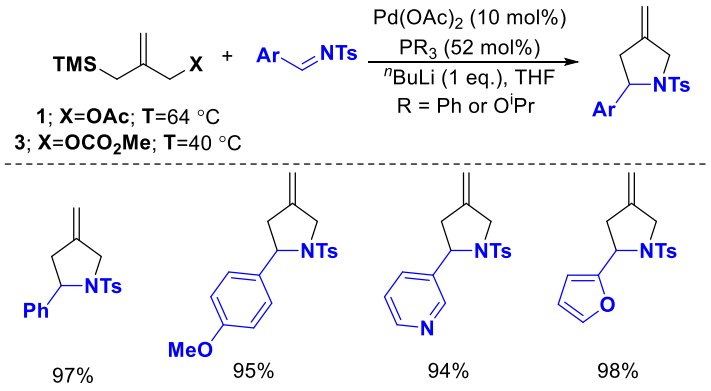
The reaction of Pd-TMM with all-carbon acceptors has been extensively studied and these efforts have been documented elsewhere.[13] But of more relevance to the work presented herein, Pd-TMM has also been shown to be highly useful in the synthesis

of *N*-heterocycles. The first contribution in this area was provided by Jones and Kemmitt who demonstrated that Pd-TMM reacted with a variety of non-enolisable aldimines to deliver pyrrolidine products bearing a highly useful *exo*-methylene unit (Scheme 8).[14] The importance of the electron-rich triethyl phosphite was evident from the lack of reactivity when triphenylphoshine was employed as a ligand. Additionally, allylsilane **2** with a sulfonate leaving group was shown to be a feasible precursor to Pd-TMM.



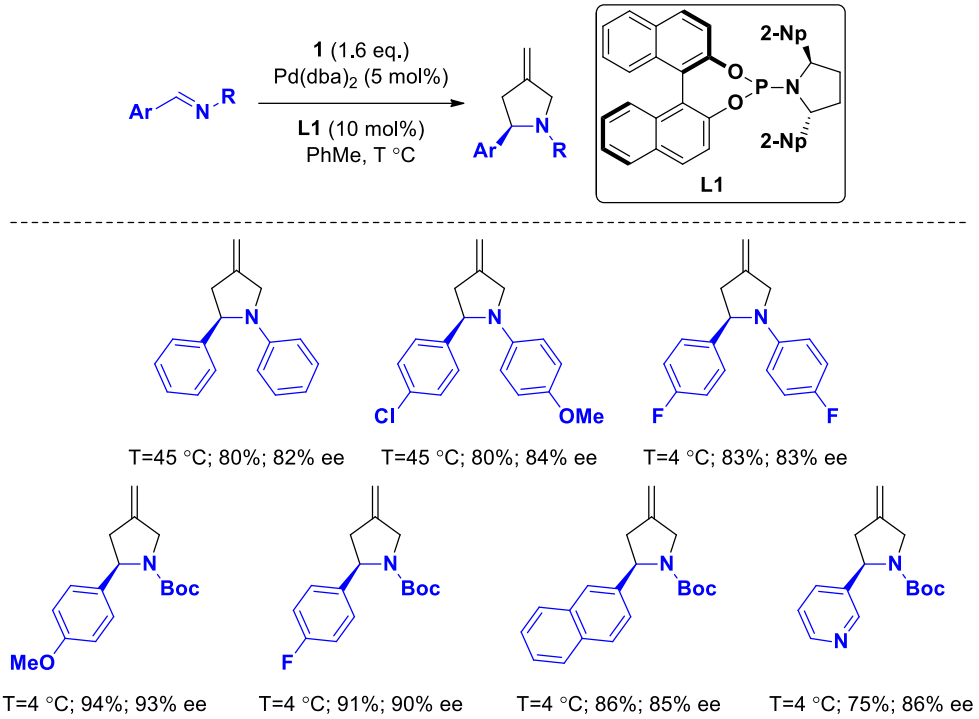
Scheme 8 – Reaction of Pd-TMM with imines to give pyrrolidine products.

The narrow scope of this original publication was later elaborated on by Trost who demonstrated that a variety of other imine substrates could be employed in this strategy (Scheme 9).[15] Notably, the use of an *N*-tosyl protecting group was key, as *N*-alkyl imines seemed to be unreactive in these conditions. This is attributed to the poor electrophilicity of the imine in these cases, and thus the *N*-tosyl group not only serves to protect the amine in the product, but also enhance the reactivity of the imine. Furthermore, a variety of substrates incorporating different electronic nature at the aryl unit could be employed successfully.



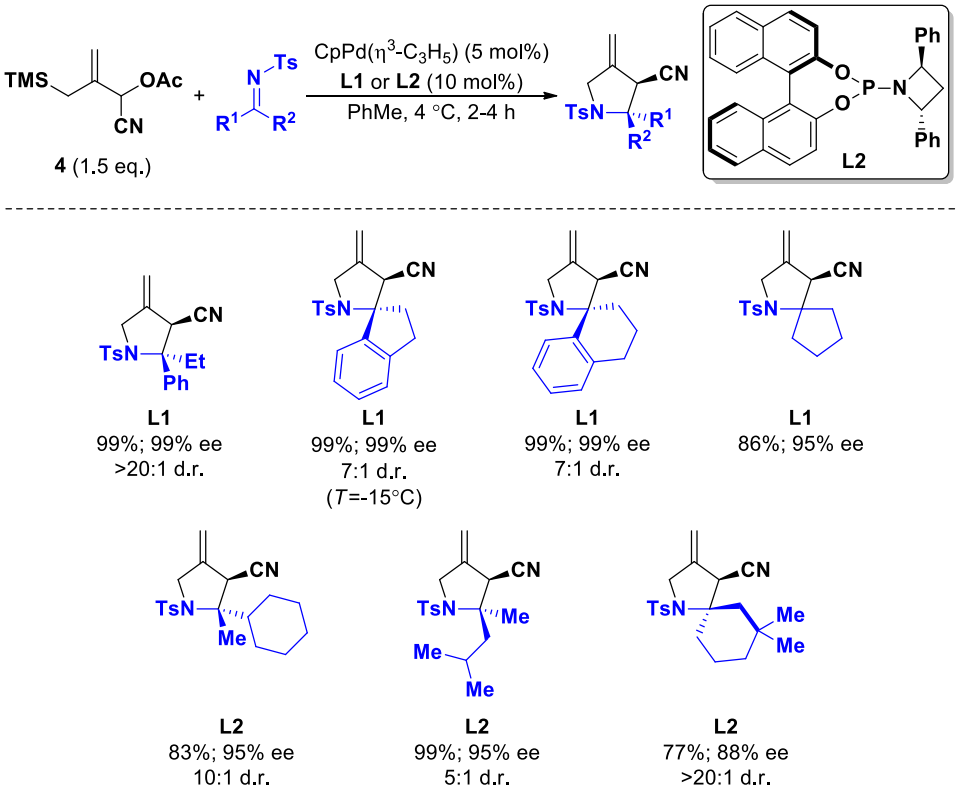
Scheme 9 – The reaction of Pd-TMM with arylimines is not affected by the electronic nature of the aryl unit.

This methodology allows a facile method to install stereocentres in highly functionalised products. Therefore, it is unsurprising that the development of enantioselective methods to synthesise these fragments asymmetrically has received much attention. The first widely successful application of this method was presented by Trost *et al.* in 2007 who demonstrated that chiral phosphoramidites are highly useful for inducing enantioselectivity.[16] Specifically, the ligand **L1** bearing a bis-2-naphthyl substituted pyrrolidine was found to be highly efficient for the asymmetric cycloaddition between Pd-TMM and various arylimine substrates (Scheme 10). Furthermore, both *N*-Boc and *N*-aryl imines could now be employed, demonstrating the enhanced reactivity that these phosphoramidite ligands confer on the Pd-TMM fragment.



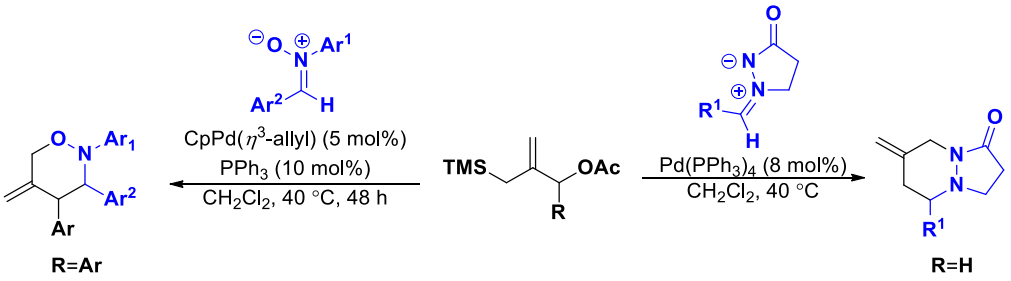
Scheme 10 – Application of **L1** allows the enantioselective synthesis of a variety of pyrrolidine products.

This enhanced reactivity also found application to the cycloaddition of Pd-TMM with the less reactive ketimine substrate class which allowed the synthesis of a range of pyrrolidines containing quaternary stereocentres (Scheme 11).[17] Additionally, whilst arylimines had almost exclusively been used thus far, alkylimines also found use in this procedure. Although tautomerisation of these substrates was problematic when *N*-Boc imines were employed, *N*-tosyl imines were less susceptible to this issue. Furthermore, the cycloaddition process generally proceeded with high diastereoselectivity for most acyclic arylimines (>20:1 d.r.) however, cyclic substrates and alkylimines generally provided lower diastereoselectivities, although with little impact on the enantioselectivity of the major isomer.



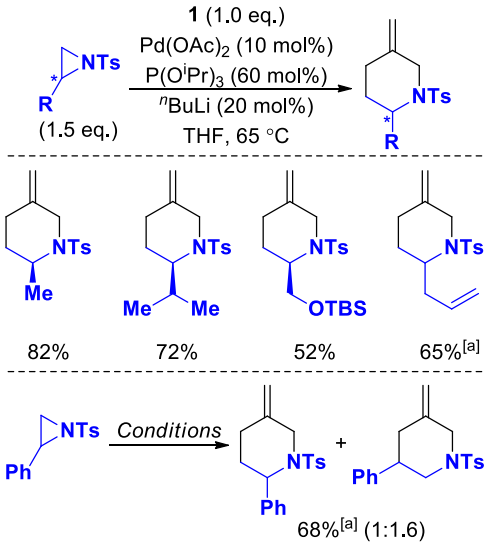
Scheme 11 – Synthesis of pyrrolidines bearing stereogenic quaternary centres.

The employment of Pd-TMM in the synthesis of *N*-heterocycles is not limited to the preparation of pyrrolidine products. It can also react in a [3 + 3] cycloaddition reaction with a number of acceptors to furnish a range of 6-membered heterocycles. For example, the reaction with azomethine imines allows the synthesis of hexahydropyridazine products, and the reaction with nitrones delivers a range of tetrahydro-1,2-oxazines (Scheme 12).[18,19]



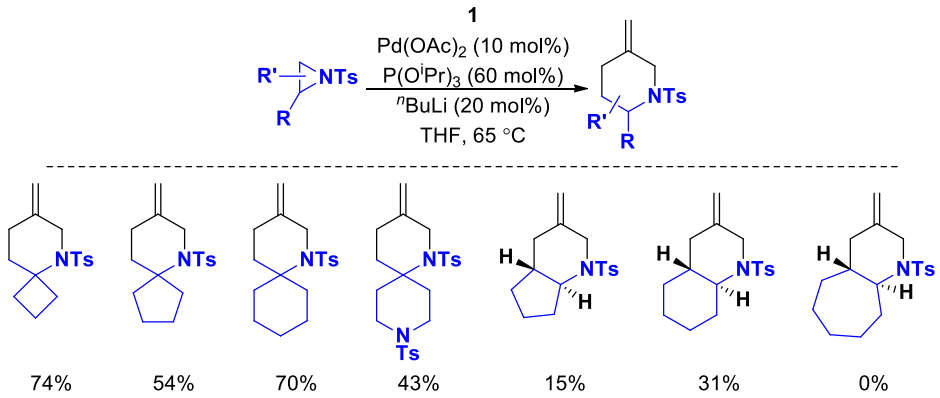
Scheme 12 – [3 + 3] cycloaddition of Pd-TMM with nitrones and azomethine imines.

Furthermore, reaction of Pd-TMM with *N*-tosyl aziridines allows a ring expansion reaction to form a range of piperidine products (Scheme 13).[20] All reactions proceeded with complete regioselectivity, resulting from attack of the Pd-TMM fragment at the least-substituted site of the aziridine. The one exception to this arises through the incorporation of a phenyl unit. In this case, a mixture of products are obtained wherein the Pd-TMM can also attack at the most-substituted side of the aziridine. This presumably arises due to the inherent ability of the phenyl substituent to stabilise the S_N2 transition state.



Scheme 13 – Reaction of Pd-TMM with a variety of 2-substituted aziridines. [a] Performed with racemic aziridine

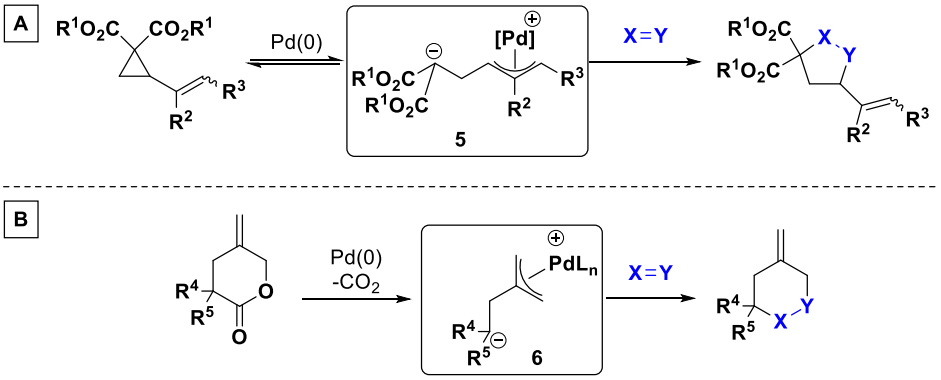
Notably, this represents an enantiospecific process, wherein the chiral information contained in the aziridine starting material is maintained in the product. The synthesis of enantioenriched piperidines through this method is therefore limited to the availability of the enantiopure aziridine. Nevertheless, this procedure is broadly applicable to the synthesis of racemic piperidines bearing quaternary centres (Scheme 14).[21] Employment of 2,2-disubstituted aziridines worked well and a range of spirocyclic piperidine products could be prepared. The reaction with 2,3-disubstituted piperidines proceeded more sluggishly in comparison, a result of the slow addition of Pd-TMM to a trisubstituted carbon centre.



Scheme 14 – [3 + 3] cycloaddition reaction of Pd-TMM with 2,2- and 2,3-disubstituted aziridines.

Other examples of Pd-stabilised zwitterions containing a carbanion include the use of activated cyclopropanes in Pd-catalysed cycloadditions with various heterocumulenes.[22–25] The reactions are proposed to proceed *via* the zwitterion **5** to deliver *N*-heterocyclic products (Scheme 15A). Additionally, Shintani and Hayashi have developed a series of methylenelactones which can react with Pd(0) to generate novel zwitterions **6**.[26–32] These zwitterions were also found to be reactive with a series

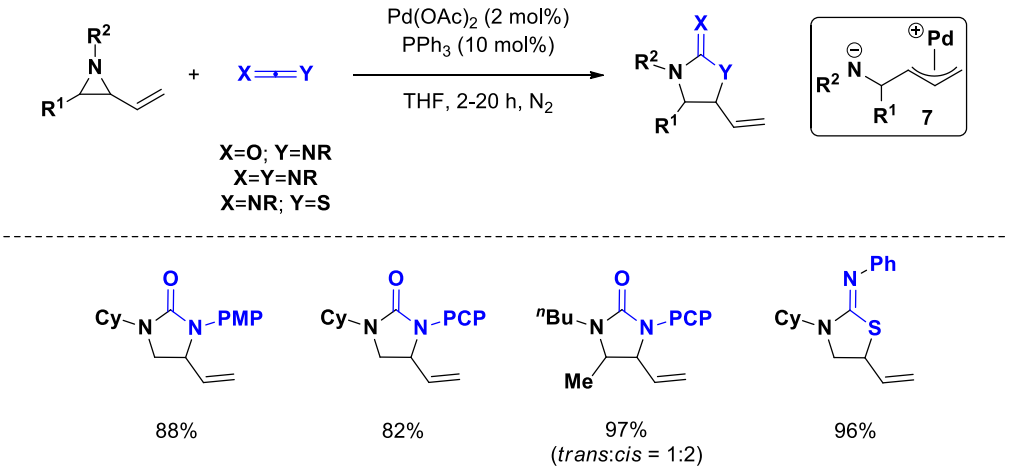
of heterocumulenes to deliver novel *N*-heterocycles with various ring-sizes and substitution patterns (Scheme 15B).



Scheme 15 – (A) Pd-catalysed reaction of vinylcyclopropanes with heterocumulenes *via* **5**. (B) Pd-catalysed reaction of γ-methylidene-δ-valerolactones with heterocumulenes *via* **6**.

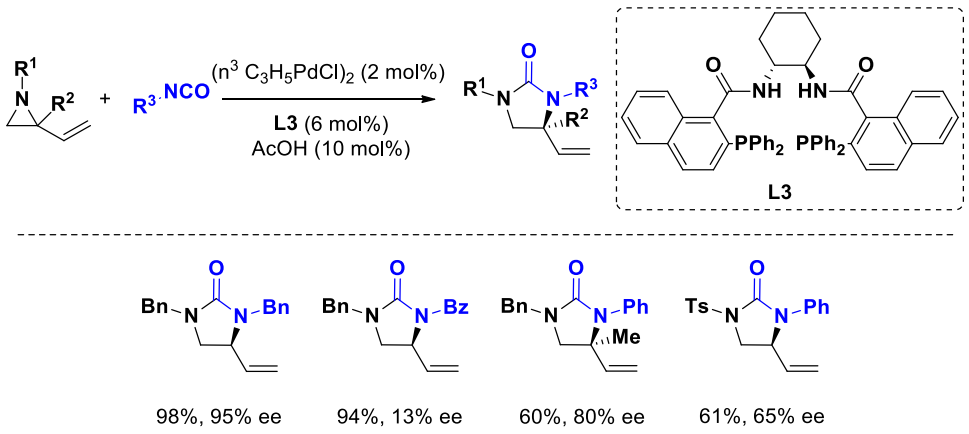
1.3.2 – Pd-Stabilized Zwitterions with *N*-Centred Anions

One of the most commonly employed Pd-stabilised zwitterions to incorporate an amide anion is that derived from the Pd-catalysed ring-opening of vinyl aziridines. The first example of their use in a [3 + 2] cycloaddition came from the Alper laboratories in 2000, when they documented the Pd-catalysed cycloaddition of vinylaziridines with various heterocumulenes.[33] The cycloaddition with isocyanates, carbodiimides and isothiocyanates delivered imidazolidinones, imidazolidineimines, and imidazolidinethiones respectively *via* the proposed zwitterion **7** (Scheme 16). Interestingly, the electronic nature of the isocyanate substrates had little to no effect on the efficiency of the cycloaddition, with a range of electronically distinct *N*-aryl isocyanates undergoing this transformation smoothly. Furthermore, this methodology could be extended to the homologous vinylazetidines and vinylpyrrolidines to deliver 6- and 7-membered ring products respectively.[34–37]



Scheme 16 – Pd-catalysed [3 + 2] cycloaddition of vinylaziridines with heterocumulenes.

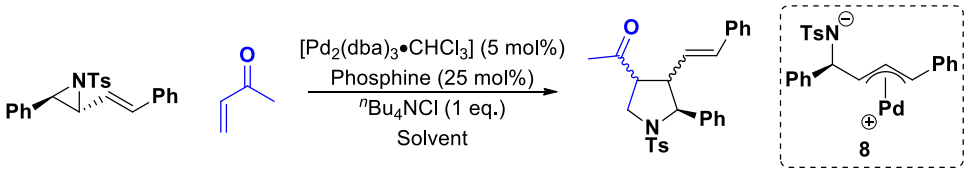
Later, Trost demonstrated that this reaction could also be performed asymmetrically, with the use of **L3**.[38] This allowed the dynamic kinetic asymmetric allylation of heterocumulenes in which racemic vinylaziridines could deliver enantioenriched imidazolidinones (Scheme 17).



Scheme 17 – Pd-catalysed DYKAT of vinylaziridines with isocyanates.

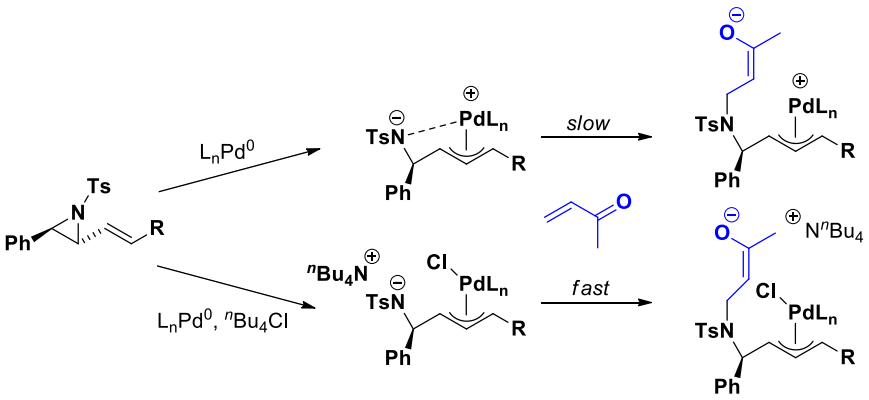
The use of chiral ligands is not necessarily required, however. The laboratories of Aggarwal and others have disclosed highly efficient, asymmetric routes to

vinylaziridines[39,40] through the use of a chiral sulfur ylide. The enantiopure palladium-stabilised zwitterion **8** generated from these enantioenriched substrates could react with an activated Michael acceptor to access chiral pyrrolidine products in an enantioretentive and diastereoselective manner (Scheme 18).[41]



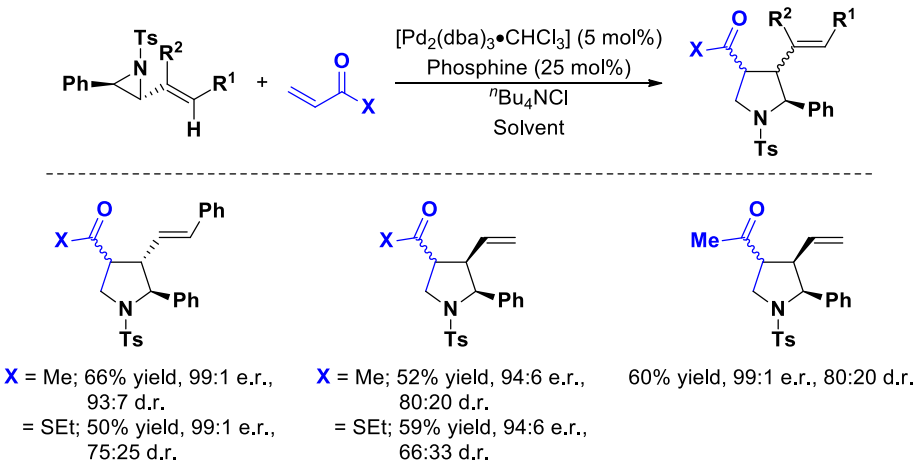
Scheme 18 – Palladium-mediated annulation of vinyl aziridines with Michael acceptors.

Notably, their conditions required the use of tetra-*n*-butylammonium chloride to enable the *in situ* generated amide ion to act as a nucleophile, as the presence of the chloride disrupts the ion-pairing of the amide and the palladium-π-allyl moiety which previously hindered its reactivity (Scheme 19).



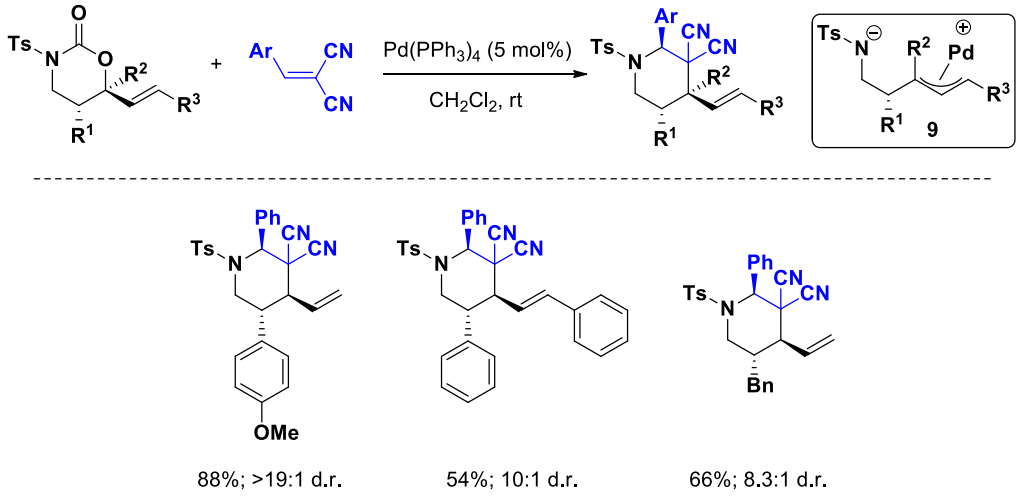
Scheme 19 – Enhanced reactivity with addition of tetra-*n*-butylammonium chloride.

By varying the bulkiness of the phosphine ligand and the polarity of the solvent they afforded good control on the diastereoselectivity with various types of Michael acceptors (Scheme 20).



Scheme 20 – Enantioretentive, diastereoselective annulation of vinyl aziridines with a Michael acceptor

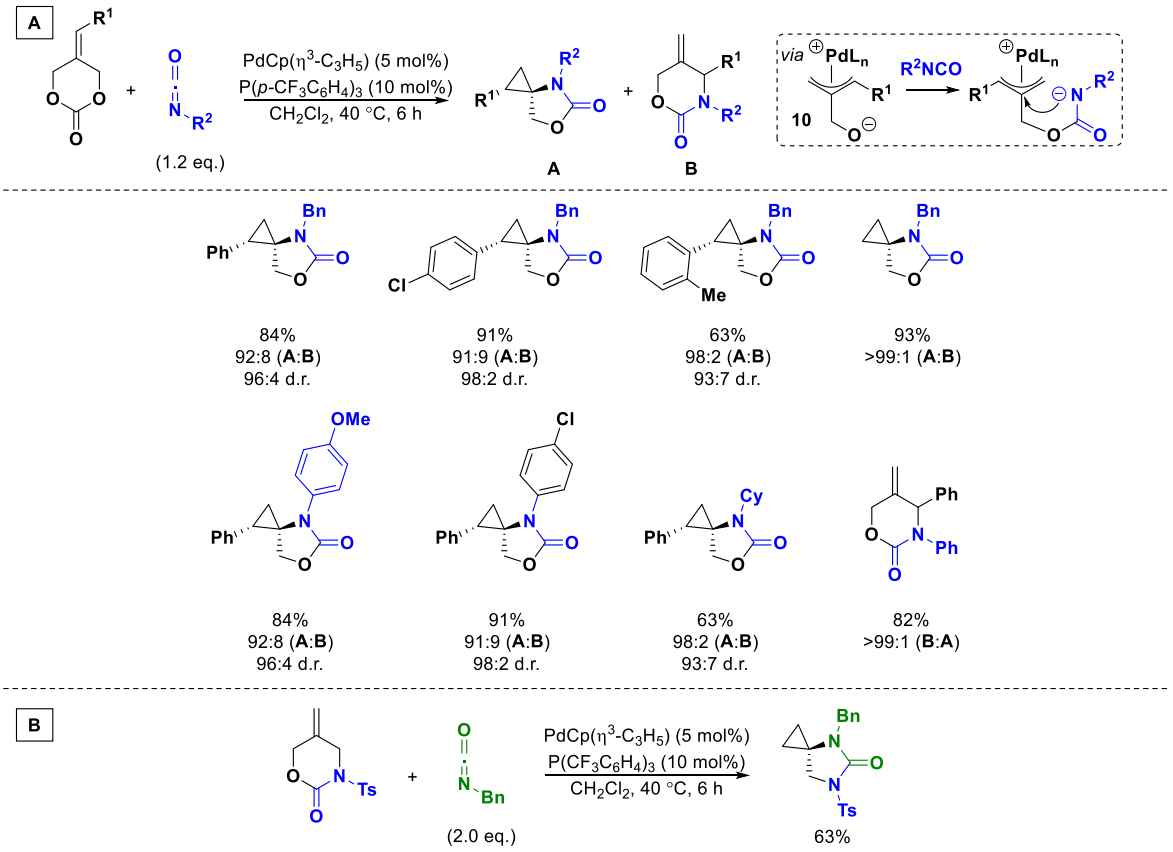
Further examples of Pd-stabilised zwitterions that contain an amide anion come from the Tunge laboratories. 6-Vinyloxazinanones serve as a precursor to the zwitterion **9** which have been shown to react with doubly-activated Michael acceptors to deliver piperidine products (Scheme 21).[42] The reaction proceeds well to give products in generally excellent yields and good diastereoselectivities.



Scheme 21 – Pd-catalysed [4 + 2] cycloaddition of vinyloxazinanones with doubly activated Michael acceptors.

1.3.3 – Pd-Stabilized Zwitterions with *O*-Centred Anions

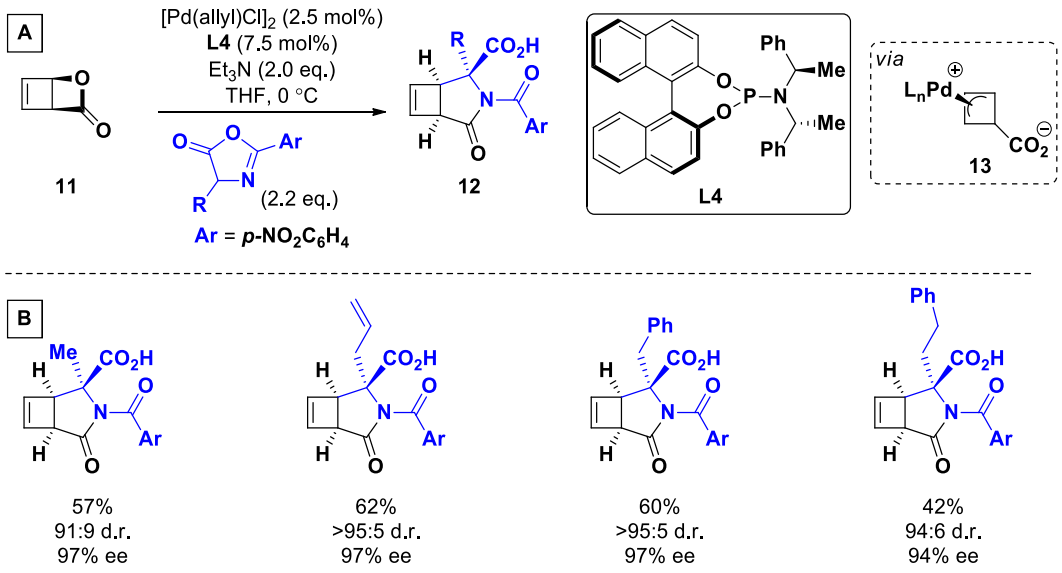
There are relatively fewer examples of Pd-stabilised zwitterions bearing an oxyanion to deliver *N*-heterocycles. However, the examples that do exist lead to some interesting products. For example, Shintani and Hayashi have reported the use of 5-methylenedioxanone to deliver unique *N*-heterocycles in the Pd-catalysed reaction with isocyanates to deliver oxazolidinones containing a spirocyclopropane ring *via* the zwitterion **10** (Scheme 22A).[43] This interesting structure results from the addition of the *in situ* generated amide anion undergoing nucleophilic addition to the central carbon atom of the Pd-π-allyl fragment, followed by reductive elimination to form the cyclopropane.



Scheme 22 – Pd-catalysed [3 + 2] cycloaddition of 5-methylenedioxazinones with isocyanates.

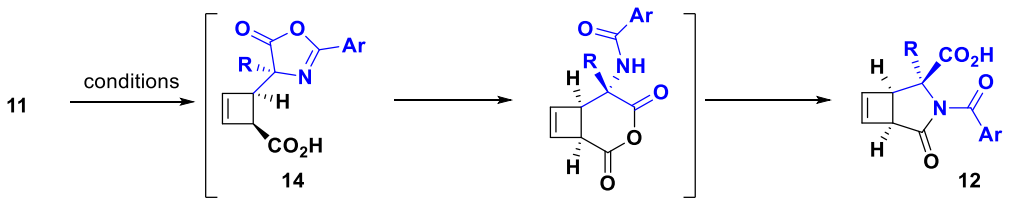
The regioselectivity in this case is directed by the highly electron-withdrawing phosphine ligand which raises the LUMO of the central carbon atom.[28,44] Furthermore, the authors demonstrated the ability of one of the 5-methyleneoxazinanone products to undergo a further Pd-catalysed reaction with benzyl isocyanate to deliver the spirocyclic imidazolidinone in good yield (Scheme 22B).

A further example comes from the Maulide laboratory.[45,46] The reaction between the strained lactone **11** and azlactones under Pd-catalysis generated *cis*-cyclobutene products fused to an imide **12** (Scheme 23). Using the phosphoramidite ligand **L4**, this could be achieved enantioselectively to deliver products with excellent levels of enantiopurity. The zwitterion **13** operates slightly differently in this reaction, as the oxyanion is not directly involved in the ring-forming reaction. Instead, it appears to scavenge the proton from the pronucleophile.



Scheme 23 – Pd-catalysed reaction of strained lactone **11** with azlactones.

The formation of the product **12** is proposed to result from a ring opening of the initial azlactone addition product **14** followed by an unprecedented cyclisation of the amide onto the newly formed anhydride to give the 5-membered lactam fused to a cyclobutene (Scheme 24).

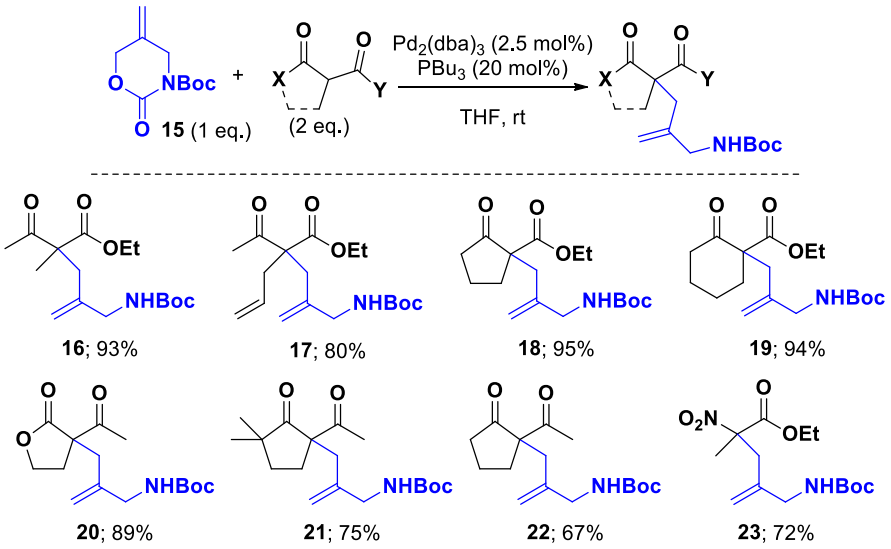


Scheme 24 – Rationale for the formation of product **12**.

In summary, Pd-stabilised zwitterions are a powerful tool for the construction of *N*-heterocycles. A variety of different ring sizes can be accessed bearing a rich variety of substitution patterns and other heteroatoms. Whilst there has been much work in this area, there are still several zwitterionic species which can be envisaged that might prove useful for forming novel heterocyclic scaffolds, or offering more efficient alternatives to already existing pathways.

1.4 – Previous Work

Recent work within the Harrity group has led to the development of a novel conjunctive reagent precursor **15** which allows the allylation of various 1,3-dicarbonyl substrates as displayed in Scheme 25.[47]



Scheme 25 – Initial scope of Pd-catalysed 1,3-dicarbonyl allylation.

Preliminary studies established that the Boc-protected carbamate generally gave higher yields of products than the corresponding Ts-protected carbamate. Application of this novel procedure to various 1,3-dicarbonyl substrates afforded the quaternary carbon containing products in good to excellent yield (Scheme 25). It was found that this methodology was tolerant of a variety of 1,3-dicarbonyl substrates, including acyclic and cyclic β-ketoesters, lactones, 1,3-diketones and even α-nitroesters.

The reaction is proposed to proceed *via* palladium coordination to the olefin of **15**, which activates the allylic oxygen, causing the C-O bond to cleave, thus forming a Pd-π-allyl complex. The carbamate anion **24** can then undergo decarboxylation to

produce the conjunctive reagent **25**. The amide anion is able to deprotonate the dicarbonyl to produce an enolate, which then attacks the Pd-π-allyl system of the protonated conjunctive reagent **26** to form the product (Figure 5).

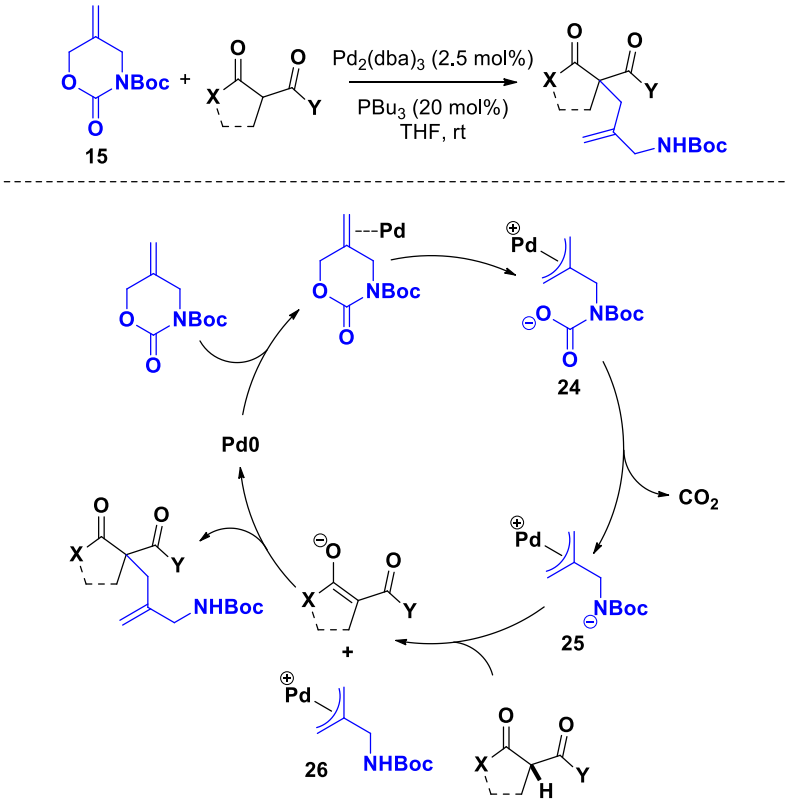
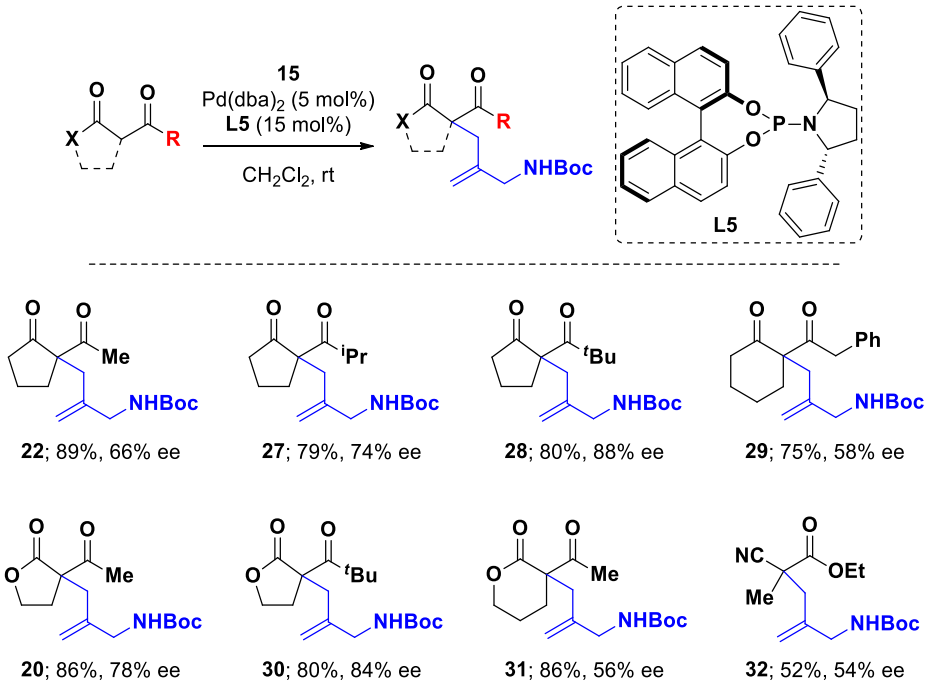


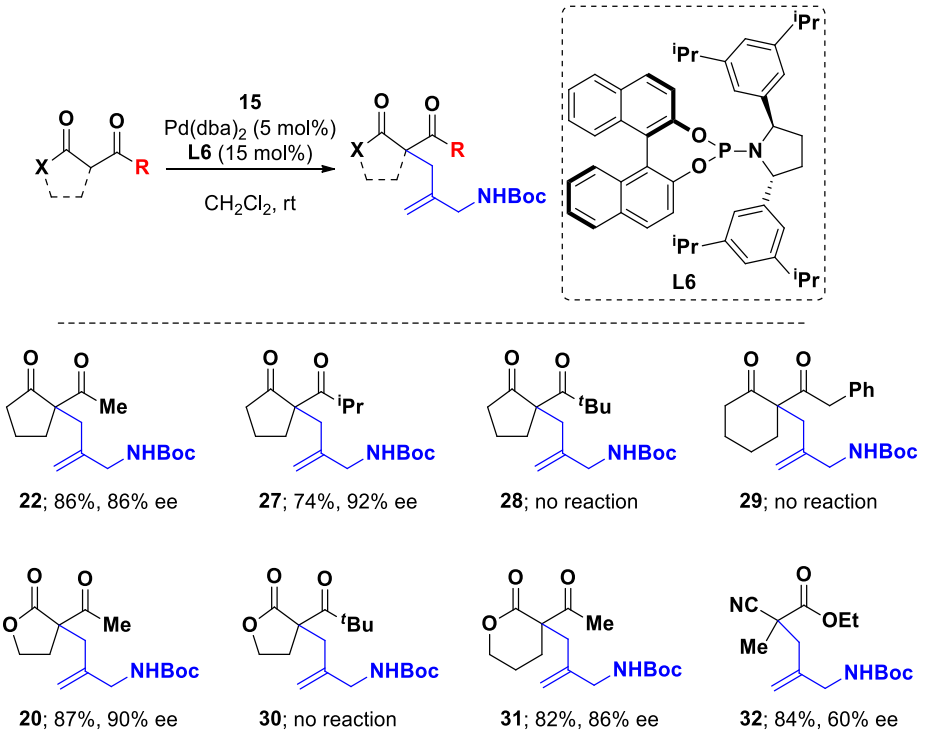
Figure 5 – Reaction scheme and proposed mechanism of palladium-catalysed 1,3-dicarbonyl allylation.

Following success with the racemic allylation reactions, investigations into controlling stereochemistry at the newly formed quaternary carbon began through the use of chiral ligands. After screening various chiral phosphorus-based ligands, and inspired by the work of Trost,[48] it was found that the chiral phosphoramidite ligand **L5** provided the desired products with excellent ee's (Scheme 26). It should be noted, however, that generally only the cyclic substrates gave good selectivities.



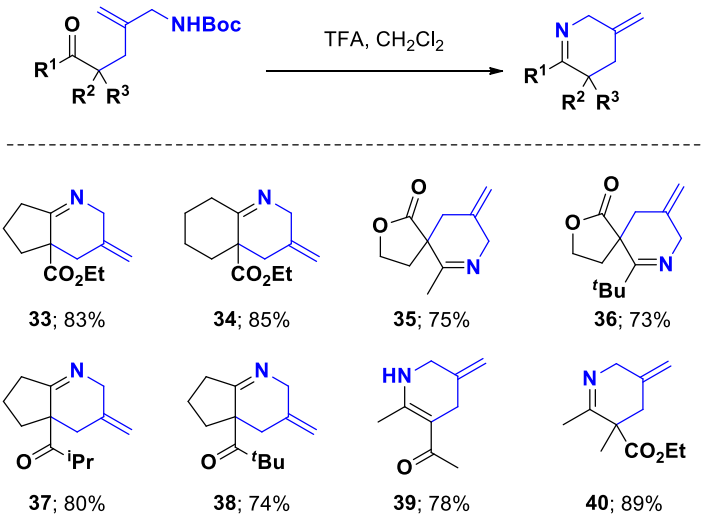
Scheme 26 – Substrate scope for asymmetric Pd-catalysed allylations with **L5.**

Improvements were made to the catalyst system by the instalment of *iso*-propyl groups on the pyrrolidine to give **L6**. Application of this ligand in the asymmetric allylation afforded a significant increase in enantioselectivity for all the substrates with little impact on the yields (Scheme 27). However, due to the increased steric bulk on the ligand, some of the more hindered substrates, such as **28, 29** and **30**, no longer underwent this transformation.



Scheme 27 – Improved selectivities were obtained with **L6**, however the substrate scope was reduced.

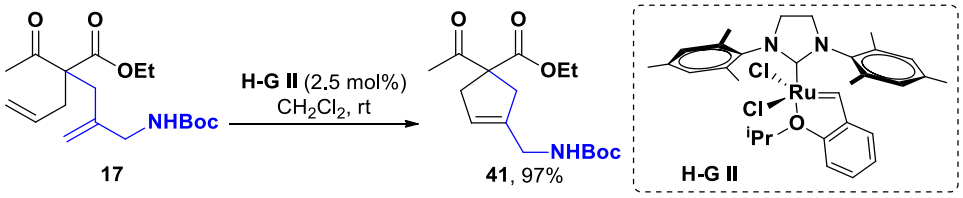
Having established a convenient and efficient methodology to these interesting compounds, focus switched to further functionalisation. Deprotection of the amine, ensued by a condensation reaction, afforded a wide range of piperidine products in excellent yields (Scheme 28).



Scheme 28 – Condensation reaction mediated by TFA to afford various piperidine products.

This procedure exploits the differing reactivities of the various carbonyl components allowing structurally diverse piperidines to be produced.

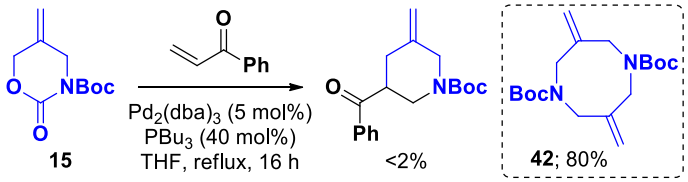
Moreover, the newly generated methylene group also allows further functionalisation. Alkenyl product **17** was subjected to ring-closing metathesis (RCM) conditions using the Hoveyda-Grubbs second generation catalyst to give cyclopentene product **41** in an excellent yield (Scheme 29).



Scheme 29 – Ring-closing methathesis of **17**performed in excellent yield.

One of the initial objectives at the outset of this project was to investigate the propensity of the conjunctive reagent to undergo a [4 + 2] cycloaddition with electron-deficient alkenes in a similar manner to Trost's conjunctive reagent. Unfortunately,

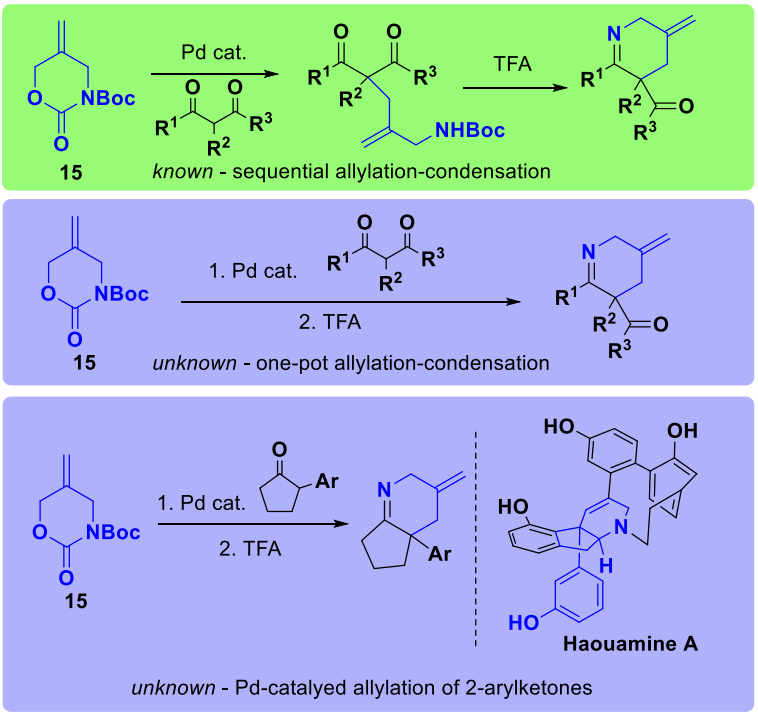
initial attempts in this area did not lead to the desired products (Scheme 30). Instead, the 1,5-diazocine **42** was generated. A repeat of this experiment with the absence of any substrate led to the generation of this by-product in an 80% yield providing indirect evidence for the formation of the dipolar intermediate **25.**



Scheme 30 – Attempted [4 + 2] cycloaddition of **15** with phenyl vinyl ketone.

1.5 – Project Aims

This project aims to elaborate on the previous studies undertaken on the Pd-catalysed allylation of various 1,3-dicarbonyl substrates using the readily-available carbamate **15**. The initial objective will be to investigate the propensity for a one-pot allylation-condensation procedure to provide a facile and direct method for the synthesis of functionalised piperidine products. Additional ligand screening will be undertaken to enhance the enantioselectivities obtained in this reaction. Furthermore, we will study the elaboration of the products to incorporate new functionality in order to demonstrate their applicability and importance.

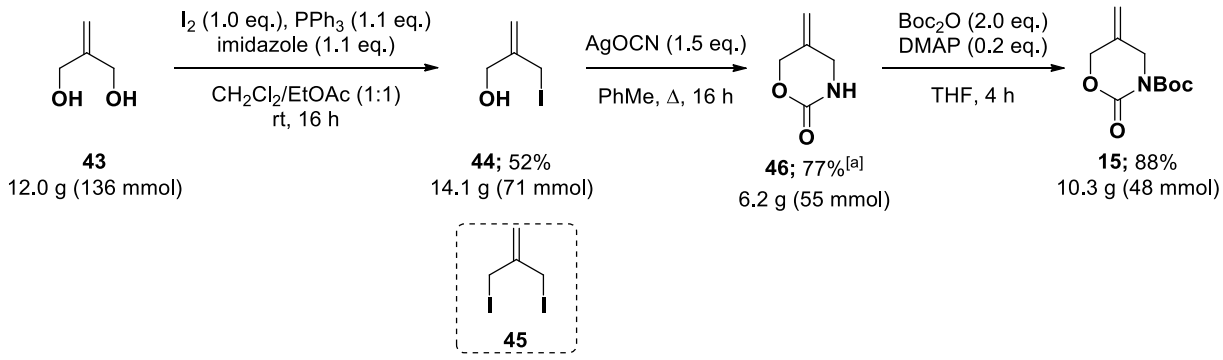


Whilst it is documented that the Pd-catalysed allylation reaction works well for the functionalisation of 1,3-dicarbonyl substrates, further studies will be undertaken to extend this methodology to alternative substrates. In particular, we are interested in whether this technology can be applied to the allylation of a variety of 2-arylketones.

The successful application of this reaction would allow an unprecedented access to highly functionalised piperidine cores which bear some resemblance to the natural product Haouamine A.

2 –Development of a One-Pot Synthesis of Functionalised Piperidines

2.1 – Reaction Development and Optimisation



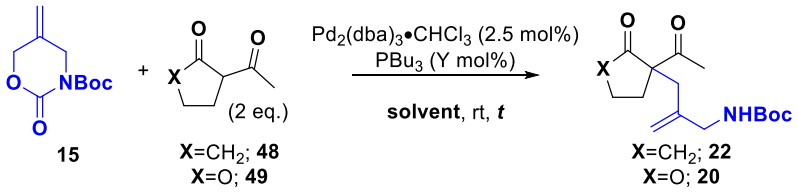
Scheme 31 - Scalable route to conjunctive reagent precursor.[49] [a] Yield of crude material.

Initially, synthesis of the *N*-Boc carbamate **15** was required. Our synthetic sequence towards this compound began with the desymmetrisation of diol **43** through an Appel reaction, followed by treatment with silver cyanate to construct the cyclic carbamate framework.[49] Finally, protection of the *N*-atom with a Boc group afforded the conjunctive reagent precursor (Scheme 31). Notably, we were able to perform this sequence on multigram scale; starting with 12 g (136 mmol) of diol **43** resulted in the production of >10 g of the *N*-Boc carbamate **15** in a respectable 35% yield over 3 steps. The biggest loss of material occurs in the first step. The allyl iodide product **44** is a viable substrate for the Appel reaction, and the diiodinated by-product **45** was observed (Scheme 31 – yield of **45** not quantified). An additional challenging feature of this synthetic sequence is the instability of allyl iodide **44**. Upon elution during chromatographic separation, the colourless fractions containing this material slowly turn to a pink/purple solution, indicating decomposition with the formation of I_2 by-

product (the discolouration disappeared upon addition of $Na_2S_2O_3$). We noted that optimal yields were realised when both the Appel reaction and the construction of the carbamate were performed in the absence of light. Furthermore, we found that Boc protection of **46** resulted in a higher overall yield of **15** from iodide **44** if the intermediate carbamate **46** was not purified by column chromatography, but used directly. We attribute this to retention of some of the carbamate on the silica gel column.

With significant quantities of the carbamate **15** in hand, investigations into the non-enantioselective allylation procedure could begin. The established reaction conditions consisted of 2.5 mol% of $Pd_2(dba)_3$, 20 mol% of tri-*n*-butylphosphine and 2 equivalents of the 1,3-dicarbonyl substrate in THF.[47] However, in our hands, using 2-acetylcyclopentanone as the 1,3-dicarbonyl substrate, conversion of the precursor to allylated product was quite poor (Table 2, entry 1). The ligand loading was both raised and lowered, but the conversion was still below 50% (entries 2 and 3). We repeated the reaction with 20 mol% of tri-*n*-butylphosphine in toluene over a range of different times (entries 4-6), but unfortunately, we observed sub-optimal conversion in all cases. We questioned the purity of **15** and so we tested the reaction with the readily-available *N*-tosyl-protected precursor **47** (entry 7). This too was unsuccessful, even in the presence of an increased loading of palladium catalyst (entry 8). To our surprise however, repetition of the conditions using lactone **48** as the substrate resulted in a 100% conversion and isolation of the product in 40% yield (entry 9).

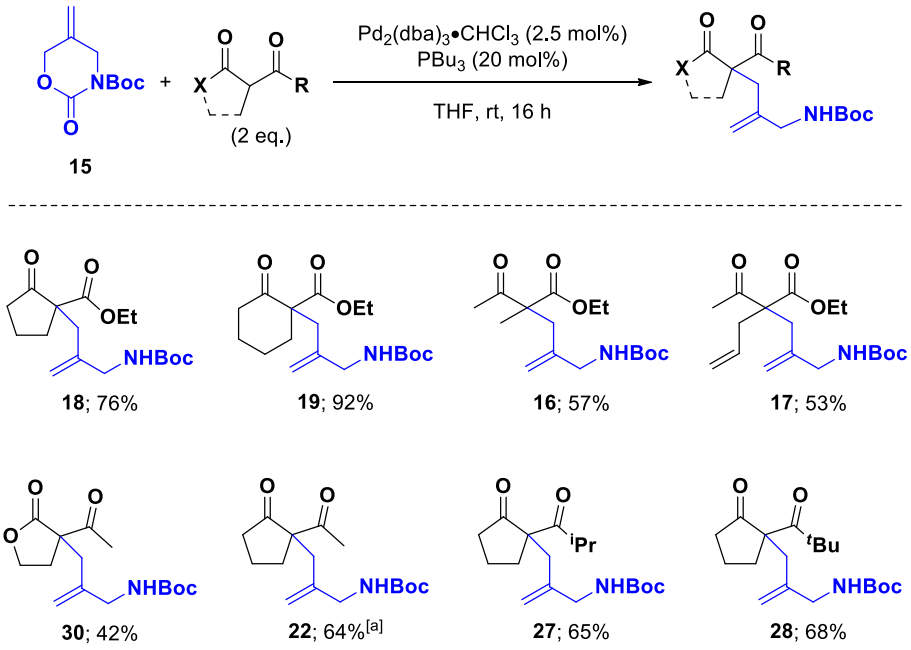
Table 2 - Initial scope of the phosphine catalyst in the allylation reaction.



Entry	Ligand loading / Y mol%	X	Solvent	*t* / h	Conversion[a]
1	20	CH_2	THF	16	38%
2	10	CH_2	THF	16	21%
3	40	CH_2	THF	16	44%
4	20	CH_2	PhMe	16	38%
5	20	CH_2	PhMe	24	64%
6	20	CH_2	PhMe	48	74%
7[c]	20	CH_2	THF	16	20%
8[c],[d]	20	CH_2	THF	16	34%
9	20	O	THF	16	100%; (40% yield)[b]

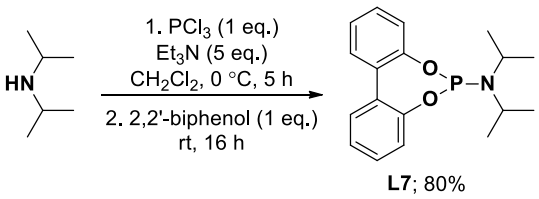
[a] Conversions deduced by integrating relative signals from **15** and product in the crude ^{1}H NMR spectrum; [b] yield of isolated product; [c] reaction performed using tosyl-protected conjunctive reagent precursor **47**; [d] 5 mol% $Pd(dba)_2$ used.

Using the above conditions, we tested various other substrates, to see if similar problems would arise. Representative yields obtained are given in Scheme 32.



Scheme 32 – 1,3-Dicarbonyl substrate scope. [a] Performed using $P(O^iPr)_3$ (20 mol%).

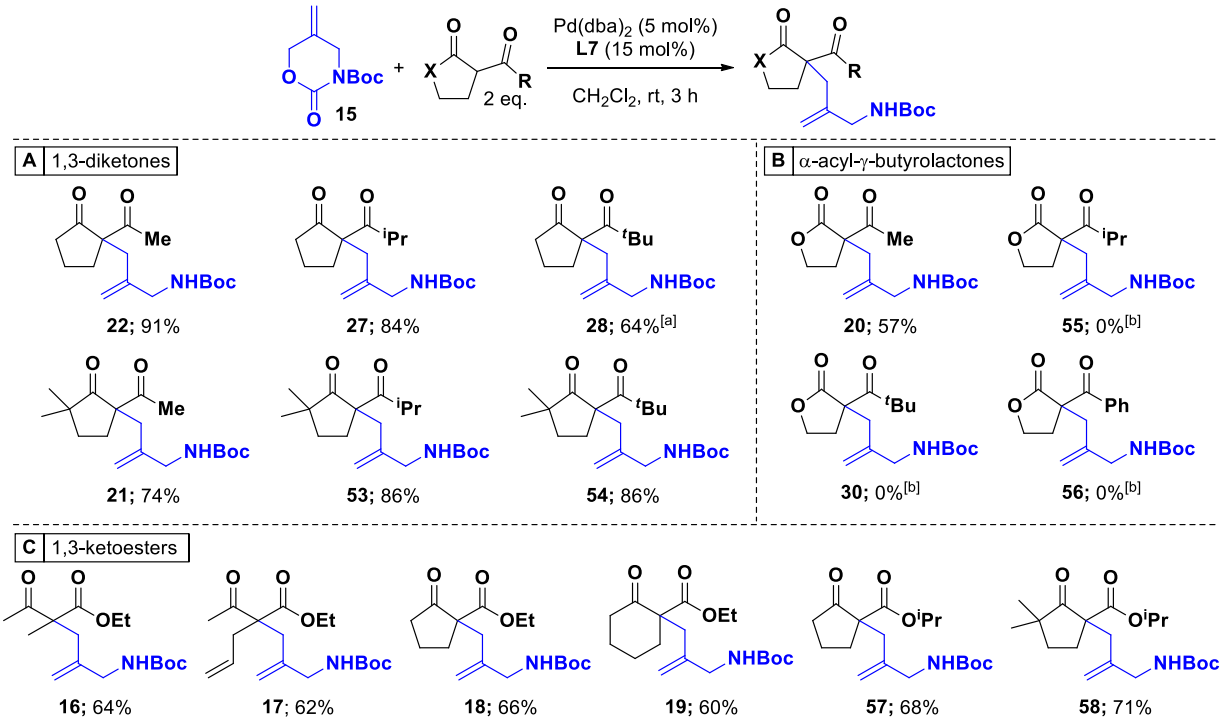
The yields obtained were generally good, but some substrates gave low yields for reasons that were not clear. Additionally, 2-acetylcyclopentanone could be converted to the product **22** in the presence of 20 mol% triisopropyl phosphite. Unfortunately, all of these results were not always reproducible. We attribute this to the sensitivity of the catalyst system. $Pd_2(dba)_3$ is an unstable solid and often requires recrystallization from $CHCl_3$ to yield the adduct, $Pd_2(dba)_3$•$CHCl_3$. Additionally, PBu_3 is readily oxidised to the phosphine oxide in the presence of air, and despite our stringent anaerobic conditions, we believe this was an issue. However, following success with chiral phosphoramidite ligands in the presence of $Pd(dba)_2$, we decided to design an achiral phosphoramidite ligand that we hoped would improve the reaction efficiency. We reasoned that employment of 2,2'-biphenol and a simple achiral amine, such as diisopropylamine, would deliver a suitable catalyst. Fortunately, such a ligand had already been reported in the literature,[50] and **L7** was synthesised in an 80% yield.



Scheme 33 – Synthesis of **L1** from diisopropylamine and 2,2'-biphenol.

Application of this new ligand to the aforementioned allylation reaction allowed the construction of stereogenic quaternary carbon centres in generally excellent yields as detailed in Scheme 34. A range of 1,3-diketones were amenable to this transformation. Interestingly, the steric nature of the pendant ketone group has no detrimental effect on either the conversion or the yield of products **22**, **27** and **28**. We believe that the slightly reduced yield of **28** is an artefact of the purification and does not represent the efficiency of the reaction. This was further confirmed through preparation of the *gem*-dimethyl containing products **21, 53** and **54** in excellent yields which demonstrates that steric hindrance does not affect this transformation. We were particularly impressed with the ability of substrate **52** to deliver product **54** in a 3 hour reaction time. The increased steric nature of **52** led us to believe that the attack of the enolate onto the Pd-π-allyl species would be slow, but fortunately, our suspicions were false and **54** could be isolated in an exemplary 86% yield. Acyllactones could also be subjected to the allylation reaction, with varying results. Interestingly, low yields were consistently obtained for the α-acetyllactone product **20**, albeit they are higher than for the corresponding phosphine ligand system. Unfortunately, although we observed complete conversion in each case, the products **30**, **55** and **56** obtained from other lactone substrates could not be isolated from the crude reaction mixture due to co-elution with other reaction components. However, several acyclic and cyclic ketoesters could be efficiently transformed to the desired products **16**-**19**, **57** and **58** in generally

good yields. Encouragingly, the ring size and steric nature of these substrates had little effect on the efficiency of the reaction.

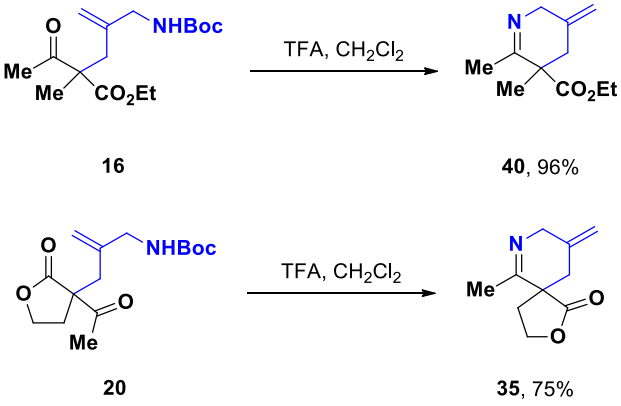


Scheme 34 – Performance of the new racemic ligand **L7**. [a] 4 eq. of substrate **59** were employed; [b] product not isolable.

With a range of allylated products in hand, conversion to the piperidine motifs could now be explored.

2.2 – Development of One-Pot Allylation-Condensation Protocol

Having established **L7** as an efficient and reliable ligand for the allylation reaction, we wished to demonstrate that these products could be further transformed into useful frameworks. Taking a small selection of our allylation products and treating them with TFA, we found that these products could be reliably converted to the piperidine products previously described (Scheme 35).



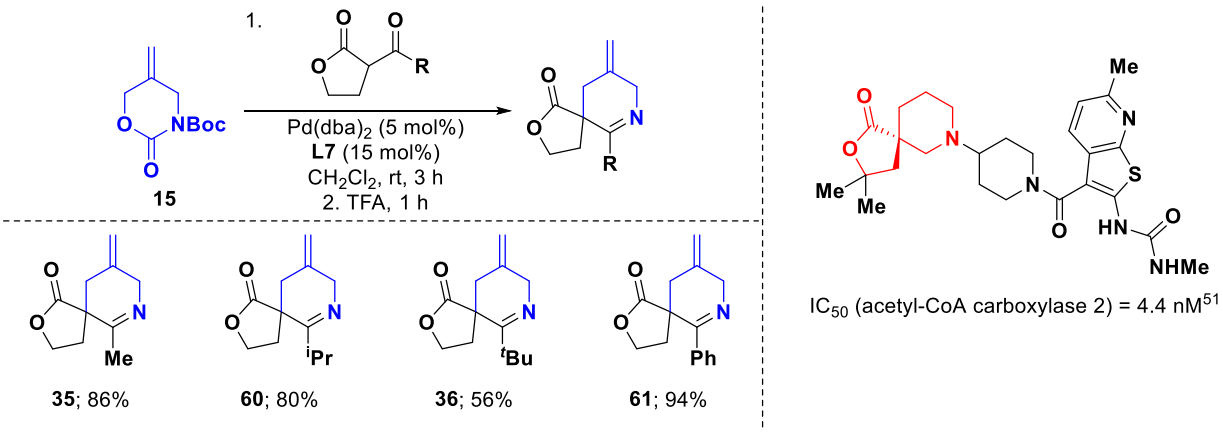
Scheme 35 – TFA-mediated deprotection-condensation to give piperidine products.

We next wondered whether the two-step procedure could be simplified to a one-pot protocol, thereby avoiding isolation and purification of the intermediate allylation products. The following sections describe our progress towards this objective.

2.2.1 – Piperidines from Acyllactones

Since the allylation products **30**, **55** and **56** of the acyllactone substrate class proved to be difficult to isolate, we envisaged that a one-pot allylation-condensation reaction might improve the efficiency of the synthesis of the product piperidines. Pleasingly, the one-pot protocol worked well and we could isolate piperidine products **35**, **36**, **60** and **61** in good to excellent yields. We note that the yield of **36** is low, but we believe this

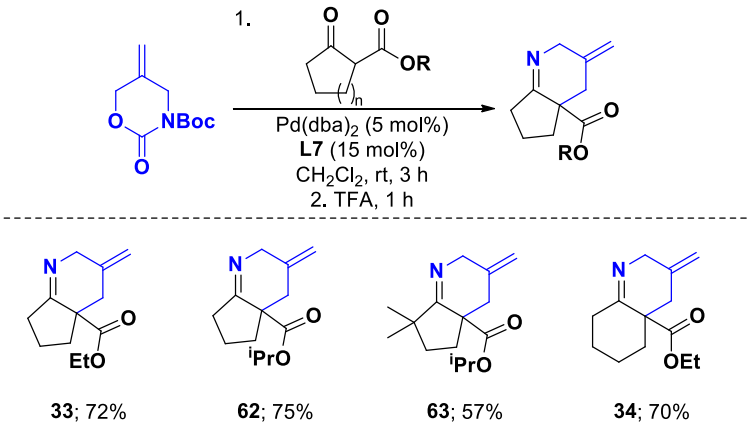
is due to a tricky chromatographic separation, rather than the efficiency of the telescoped reaction conditions. Interestingly, the liberated amine undergoes chemoselective condensation with the pendant ketone to furnish the piperidines as spirocycles. Furthermore, these compounds have potential biological interest, as a recent publication demonstrates that structural analogues exhibit acetyl-CoA carboxylase inhibitory activity when part of a larger molecule.[51]



Scheme 36 – α-Acyl-γ-butyrolactones afford only the spiropiperidine products.

2.2.2 – 1,3-Ketoesters

As expected, 1,3-ketoesters, where the ester is pendant to the cyclic ketone, also perform well in this transformation, affording the linearly fused piperidines in excellent yields. A variety of substrates could be employed, varying the alkyloxy group, the size of the ring, and alpha-substituents on the cyclic ketone without significant change to the yields obtained (Scheme 37).



Scheme 37 – 1,3-Ketoesters furnish linear piperidines.

2.2.3 – 1,3-Diketones

As might be expected, 1,3-diketones pose a more interesting challenge under these conditions, as the condensation step raises a regioselectivity issue because of the presence of two ketones which can both undergo condensation with the amine. In the case of symmetrical 1,3-diketones, this is not an issue and acetylacetone **64** underwent the allylation-condensation procedure to provide piperidine **39** in a 82% yield (Scheme 38A). However, when unsymmetrical 1,3-diketones were subjected to this procedure, a mixture of spiro- and linearly-fused piperidine products were observed (Scheme 38B). Interestingly, there did not appear to be a trend between the steric nature of the pendant ketone and the ratio in which these products were formed.

Fortunately, these isomers were separable by flash column chromatography which allowed them to be characterised individually. Analysis by HMBC NMR spectroscopy allowed us to assign spiro- or linear-structures, based on the interaction of the alkyl chain protons with the corresponding ketone or imine carbon signals (Figure 6, see Appendices 1 and 2 for assignment).

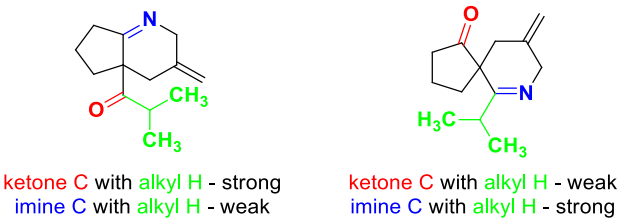
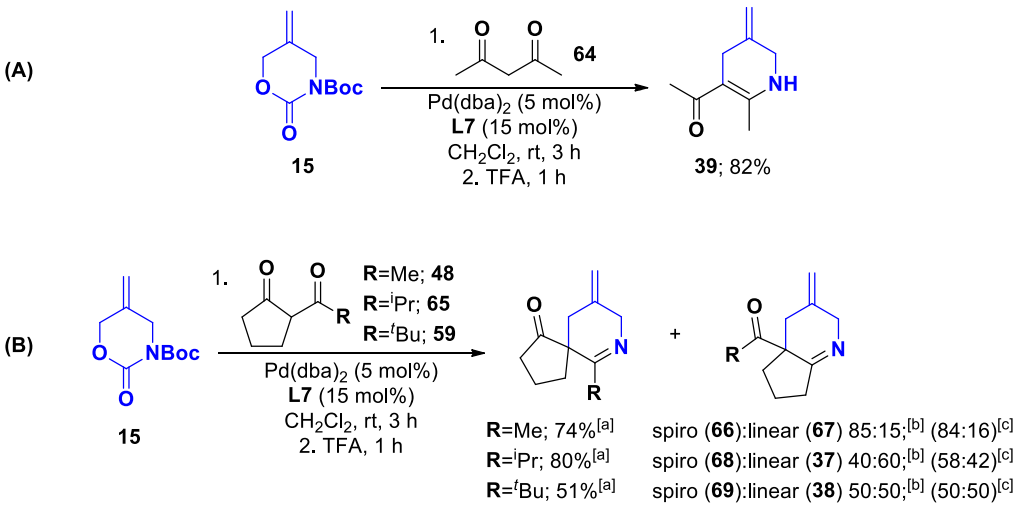


Figure 6 – Assignment of structures based on long-range C-H interactions in HMBC spectra.



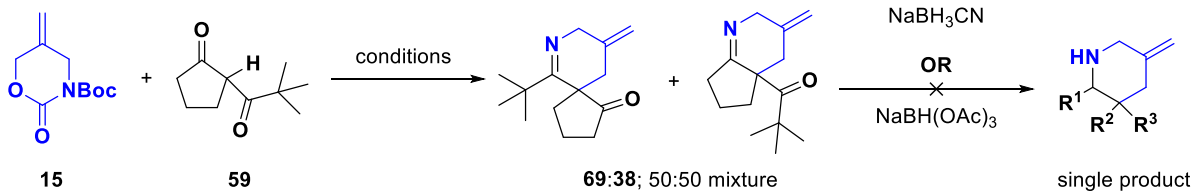
Scheme 38 – 1,3-Diketone annulation reactions (A) symmetrical 1,3-diketone **64** gives a single product (B) unsymmetrical 1,3-diketones give a mixture of spiro- and linear- piperidine isomers. [a] Combined yields of isolated products; [b] ratios of isomers in crude mixtures as determined by 400 MHz ^{1}H NMR spectroscopy; [c] ratios of isolated products.

We also made the interesting observation that neat samples of the spiro- or linear-compounds isomerised back to the original ratios within a few days at room temperature. Based on this observation, we suspect that the ratios displayed above are indicative of the thermodynamic ratio of products from the reaction.

This dynamic behaviour led us to investigate the possibility of converting a mixture of the two isomers to one single product. Specifically, we planned to react one of the isomers selectively over the other under equilibrating conditions. For these studies,

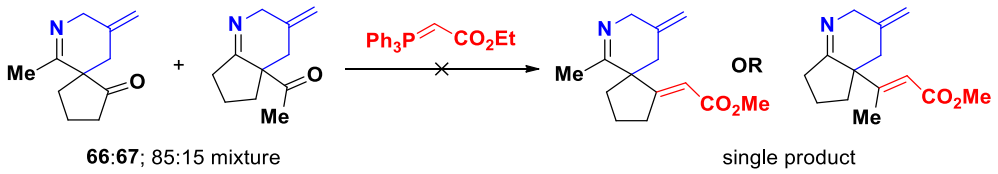
we decided to investigate the reactions of **38** and **69**, since we envisaged that the two isomers would be more chemically distinguishable due to the different steric environments around the carbonyls.

Our initial efforts focussed on reducing one imine selectively over the other using $NaBH(OAc)_3$ or $NaBH_3CN$ (Scheme 39). We attempted this in a variety of ways; the first consisted conducting the allylation procedure followed by treatment of the crude mixture with TFA and the reductant. The other involved treatment of the clean allylation product **28** with TFA to form the mixture of products **38** and **69** followed by treatment with a reductant. However, we saw little conversion of the imines in any of these reactions. In cases where we observed a small amount of conversion, a complex mixture was obtained as determined by ^1H NMR spectroscopy.



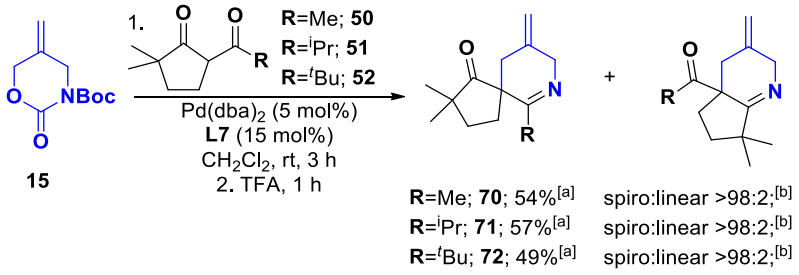
Scheme 39 – Attempted resolution of imines **69** and **38** by reduction.

Another strategy was to differentiate the ketones by performing a Wittig reaction on the less hindered ketone. For this, we opted to test the less sterically hindered ketone **22**. However the two condensation products **66** and **67** proved to be inert to this reaction (Scheme 40).



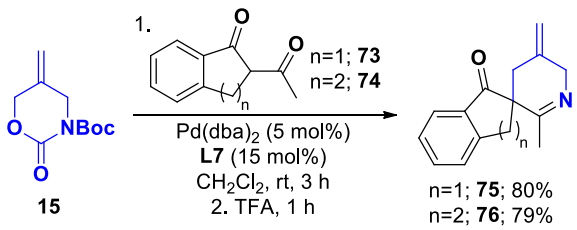
Scheme 40 – Attempted resolution of imines **66** and **67** by Wittig reaction.

Despite this failure, we wanted to show that unsymmetrical 1,3-diketones could be used in this novel methodology to afford single products. Accordingly, we subjected gem-dimethyl substituted diketones **50**-**52** to the tandem allylation-condensation reaction. We were pleased to learn that these afforded only the spiro-piperidine products **70**-**72**, albeit in modest yields (Scheme 41).



Scheme 41 – Regioselective unsymmetrical 1,3-diketone annulation reactions. [a] Yields of isolate product; [b] ratio of products as determined by 400 MHz ^{1}H NMR spectroscopy.

Additionally, fusing an aromatic ring to the cyclic ketones also delivered spirocyclic piperidines selectively, and use of indanone **73** and tetralone **74** afforded the piperidines **75** and **76** respectively as single isomers in excellent yield (Scheme 42).



Scheme 42 – Acetyl-indanone **73** and -tetralone **74** give solely the spiropiperidine products **75** and **76**.

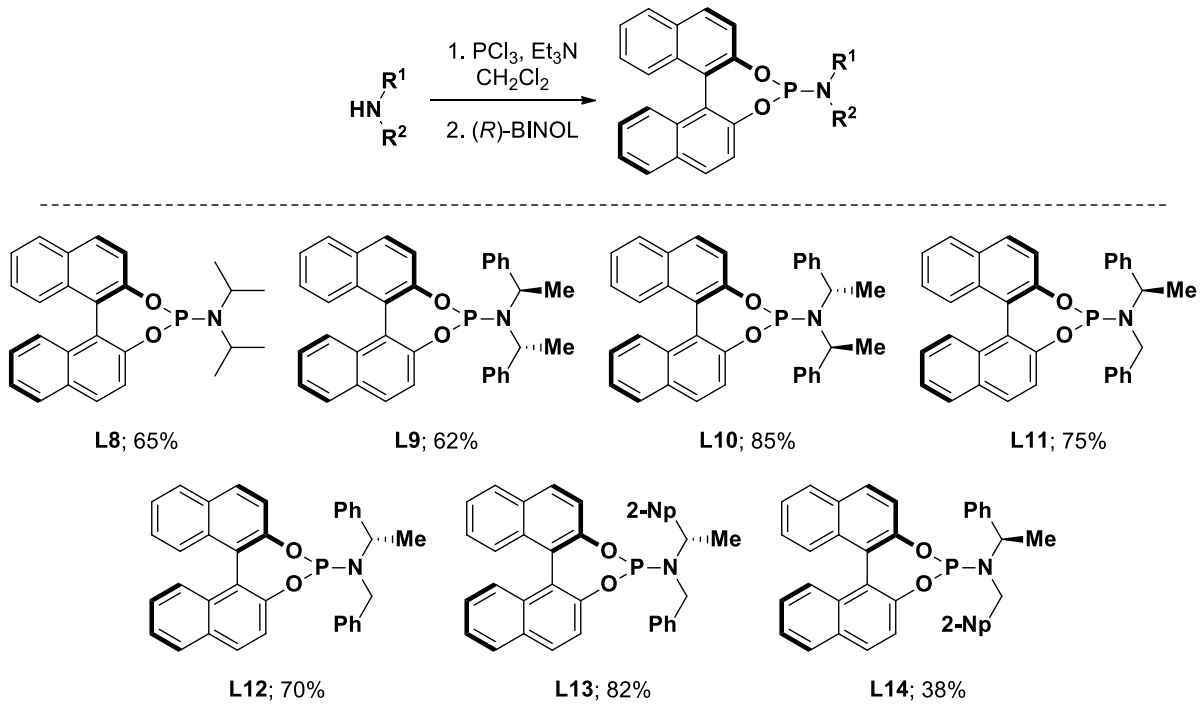
Having established efficient access to a variety of piperidine skeletons, which can be dictated by the type of substrate used, we were interested in the possibility of generating them enantioselectively.

3 – Development of an Asymmetric Catalyst System

3.1 – Ligand Optimisation

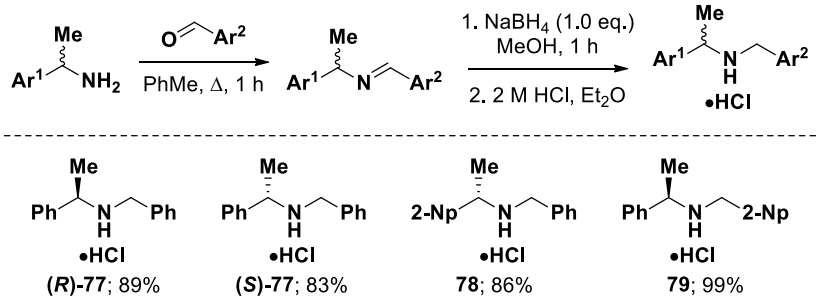
Previous work within the Harrity group highlighted the use of chiral phosphoramidite ligands as a means of controlling the enantioselectivity of the key allylation reaction.[47] The initial results were encouraging and demonstrated that these ligands are efficient both in terms of yield and selectivity. However, the established procedure utilised a pyrrolidine-based phosphoramidite ligand which is difficult to access. Additionally, whilst this ligand provided good selectivities for the allylation of 1,3-diketone substrates, the selectivity for acyllactone substrates was sub-optimal (Scheme 26). For these reasons, we wished to develop conditions that used a more easily accessible ligand in order to improve these selectivities and add synthetic value to this already impressive transformation.

Based on literature precedent, we reasoned that the most attractive phosphoramidites would be those that could be made using commercially available starting materials in a simple and high-yielding procedure. In this context, Trost and co-workers had developed a highly efficient route to phosphoramidites containing an acyclic amine moiety.[52] Following this procedure, we very quickly established a large ligand library (Scheme 43).



Scheme 43 – Synthesis of phosphoramidite ligand library; 2-Np = 2-Naphthyl.

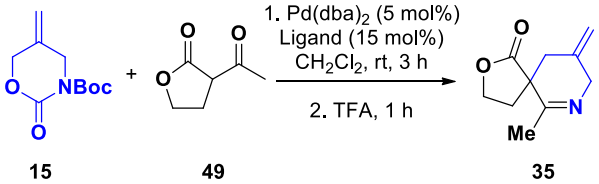
Ligands **L8**, **L9** and **L10** were synthesised using commercially available amines, while all other amines were produced in-house using a simple reductive-amination procedure. This involved the condensation of the commercially available, enantiomerically-pure amine with the appropriate aldehyde, followed by reduction with $NaBH_4$ and trapping the free amine as its hydrochloride salt, which could then be used directly in the ligand synthesis step (Scheme 44).



Scheme 44 – Synthesis of optically active amines.

In order to test the effectiveness of these ligands for the asymmetric allylation step, we decided to investigate the allylation-condensation of lactone **49** as the product enantiomers could easily be separated on chiral HPLC. The results are presented in Table 3.

Table 3 – Ligand screen for the asymmetric allylation-condensation of α-acetyllactone **49** with **15.**



Entry	Ligand	Yield/ %[a]	ee / %[b]
1	**L8**	66	48
2	**L9**	62	78
3	**L10**	75	85
4	**L11**	79	67
5	**L12**	67	58
6	**L13**	72	42
7	**L14**	70	61

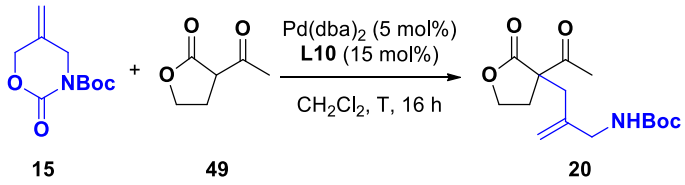
[a] Yield of isolated product; [b] Analysed by chiral HPLC; major enantiomer the same each time.

Using **L8** which employed an achiral amine moiety (Table 4, entry 1), a reasonable selectivity was obtained. With this encouraging result, switching to ligands **L9** and **L10** (entries 2 and 3) provided us with much higher selectivities, much to our delight. Notably, diastereomer **L10** performed better in this reaction than **L9**. At this point we wished to investigate the effects of removing one of the methyl groups from our optimal ligands, and whether increasing the size of the aryl group would increase the selectivity. Removing a methyl to give **L11** and **L12** (entries 4 and 5) appeared to

drastically reduce the selectivity of the allylation step. These results complement the work by Alexakis and co-workers which details the beneficial (or detrimental) effects that minor structural adjustments can have on the selectivity of the reaction.[53] Additionally, switching the phenyl substituent to a 2-naphthyl adjacent to the methyl-substituted carbon (**L13**, entry 6) appears to further reduce the selectivity. Use of **L14** (entry 7) adds evidence to this hypothesis where the benzyl unit has been switched for a 2-naphthylmethyl unit, again resulting in reduced enantioselectivity in the allylation step.

Having found optimal conditions for the asymmetric allylation procedure, we were interested to see if we could perform the reaction at reduced temperature in order to achieve higher selectivities. Benefiting from a highly efficient catalytic system which consistently affords full conversion at room temperature in just 3 hours, we suspected that the catalyst would perform well at low temperatures. Our suspicions were well-founded since at -20 °C, lactone **49** could be allylated in a high yield with an excellent selectivity (Table 4). As demonstrated, lowering the reaction temperature from room temperature down to -20 °C resulted in an increase in selectivity with little effect on the yield of the reaction. Lowering the reaction temperature further did result in a drop in yield, and surprisingly, also a reduction in selectivity.

Table 4 – Asymmetric allylation of lactone **49** at reduced temperature.



15 49 20

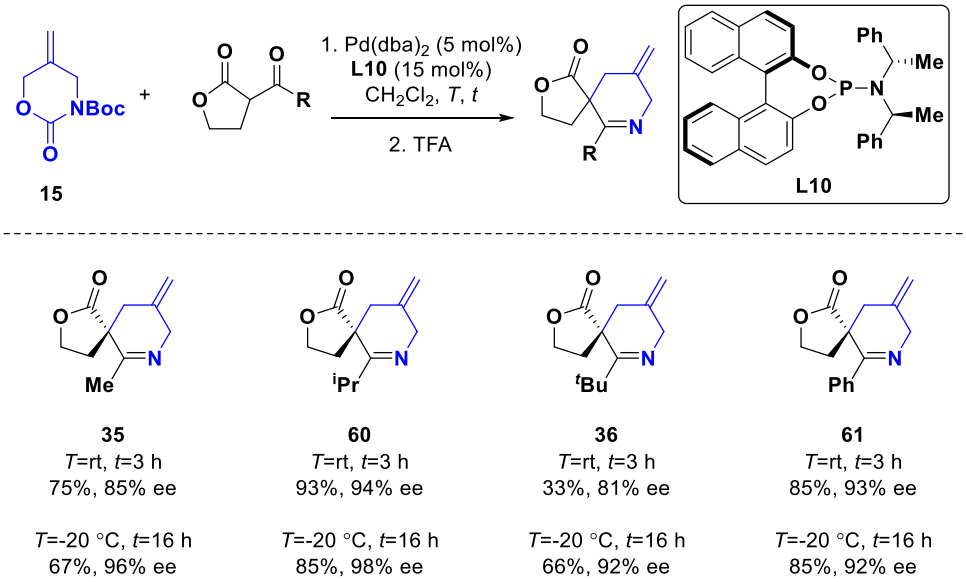
Entry	T / °C[a]	Yield / %[b]	ee / %[c]
1	rt	93	86
2	0	80	90
3	-20	85	94
4	-25	72	93
5	-30	52	87
6	-40	52	89
7	-50	50	87

[a] Reduced temperature achieved using ThermoFisher Haake Immersion Cooler EK90; [b] yield of isolated product; [c] determined using chiral HPLC.

Having developed highly selective conditions for the allylation-condensation of lactone **49**, we extended the study to a variety of other substrates and our results are discussed in the following sections.

3.2 – α-Acyl-γ-Butyrolactone Substrates

Inspired by the impressive selectivity we achieved with lactone **49** in the asymmetric allylation procedure, we explored other α-acyl-γ-butyrolactone substrates. Accordingly, the four lactones **49**, **80**, **81** and **82** were submitted to the asymmetric allylation-condensation procedure both at room temperature and at reduced temperatures. Our results are depicted in Scheme 45. In agreement with our preliminary studies (Table 4), the reactions at -20 °C generally delivered the products with higher enantioselectivities than those that were conducted at room temperature.



Scheme 45 – Asymmetric synthesis of spiropiperidines from acyllactones. Reduced temperature achieved using ThermoFisher Haake Immersion Cooler EK90. Yields of isolated products are reported. Enantioselectivities analysed using chiral HPLC (see "*Experimental Section*" for elution conditions). See Section 3.5 for assignment of absolute configuration.

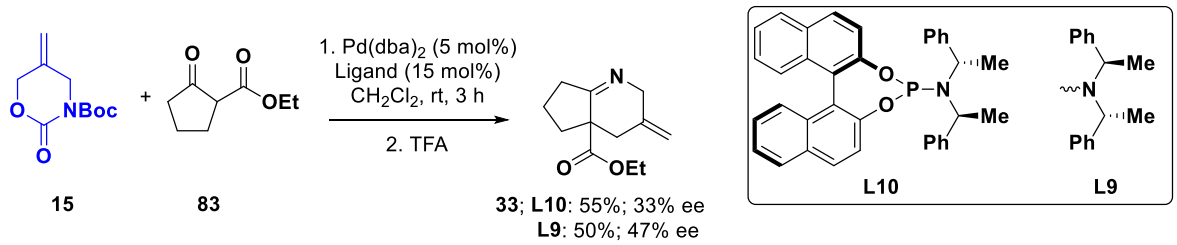
We were surprised to find that spiropiperidine **36** was formed with a lower enantioselectivity than product **60**. This suggests that increasing steric bulk beyond

the isobutyryl group in this position decreases the ability of the chiral palladium catalyst to differentiate between both faces of the enolate nucleophile.

Nevertheless, we were delighted with our results and decided to test these conditions on other 1,3-dicarbonyl substrates to see if they could be generally applied, or if there was an element of substrate specificity.

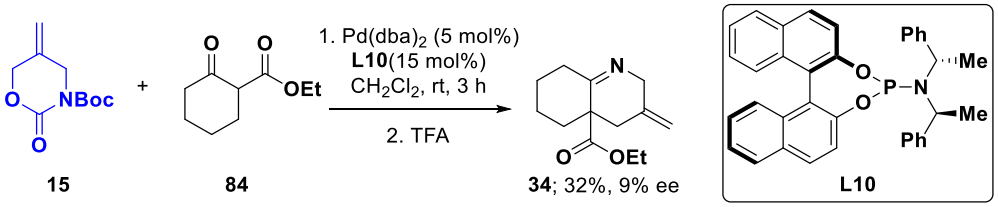
3.3 – 1,3-Ketoester substrates

With our success in subjecting acyllactones to the asymmetric allylation-condensation procedure, we reasoned that the 1,3-ketoester substrates would also perform well in this transformation. We therefore submitted ketoester **83** to the asymmetric allylation procedure. However, we quickly found that this product could not be analysed using chiral HPLC due to the formation of unknown impurities during elution, leading to several indiscernible peaks. However, the condensation product **33** was more amenable to HPLC elution, and we were able to acquire enantiomeric ratios of this compound (Scheme 46).



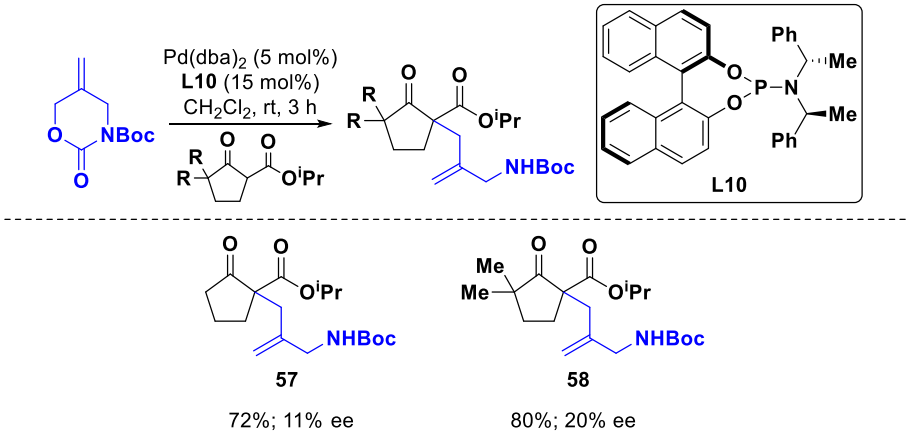
Scheme 46 – Allylation-condensation of 1,3-ketoester substrate **83**.

Interestingly, we found that **L9**, the other diastereomer of ligand **L10**, provided a higher selectivity in the allylation of this substrate, although with reduced selectivities overall as compared to the lactone substrates. We were interested in the effect of ring size on the reaction, and as seen in Scheme 47, although **84** successfully underwent the asymmetric allylation-condensation procedure, the selectivity was markedly decreased. This disappointing result led us to investigate some simple structural alterations that might improve enantioselectivities.



Scheme 47 – Asymmetric allylation-condensation of 1,3-ketoester **84**.

We became interested in the effect of introducing more sterically demanding groups in these substrates and so we performed the asymmetric allylations of bulkier 1,3-ketoesters to furnish products **57** and **58**. This resulted in good yields; however, poor selectivities were once again obtained (Scheme 48).



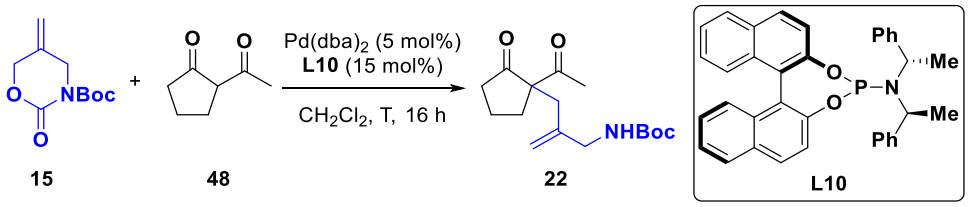
Scheme 48 – Asymmetric allylations of bulky 1,3-ketoesters **85** and **86**.

It should be noted that swapping the ethyl ester for the isopropyl ester allowed us to avoid transesterification issues during HPLC analysis of the allylated products. Surprisingly, we measured a dramatic decrease in enantiomeric ratio when we swapped the ethyl ester for the *iso*-propyl ester. Despite this, adding two methyl groups *alpha* to the carbonyl did have a positive effect on the selectivity of the reaction, increasing the 11% ee to 20% ee.

3.4 – 1,3-Diketone Substrates

We next attempted the allylation of **48** at reduced temperatures (Table 5). Unfortunately, the selectivities obtained in this case were significantly lower than those with the lactone substrates. The asymmetric alkylation of 2-substituted 1,3-diketones has been described as inherently difficult by Kuwano and Ito owing to the steric and electronic similarities of the terminal positions (so called 'pseudo-symmetry').[9]

Table 5 – Effect of temperature variation on the asymmetric allylation of **48** to **22**.



Entry	T / °C[a]	Yield / %[b]	ee / %[c]
1	rt	97	63
2	0	98	71
3	-20	78	76

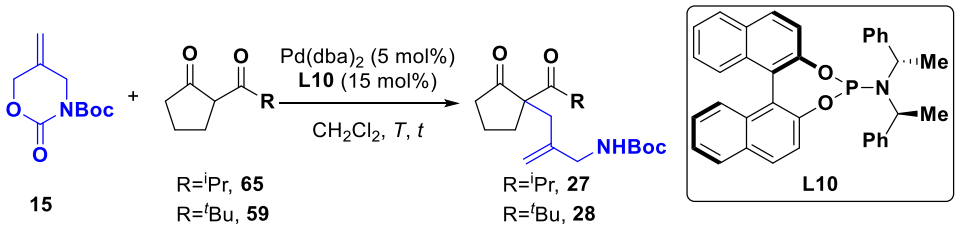
[a] Reduced temperature achieved using ThermoFisher Haake Immersion Cooler EK90; [b] yield of isolated product; [c] analysed using chiral HPLC.

Despite this minor drawback, we were determined to improve on this result and sought bulkier 1,3-diketones. Therefore, the asymmetric allylations of **65** and **59** were performed at reduced temperature (Table 6).

We were interested to find that the allylation of 2-isobutyrylcyclopentanone **65** proceeded with the same selectivity at -20 °C as it did at room temperature. This may indicate that -20 °C is not the optimal temperature for 1,3-diketones; however, further studies to confirm this have not yet been performed. We were surprised to find that 2-

pivaloylcyclopentanone **59** underwent the allylation procedure with reduced selectivity compared to **65**. This result complements our previous observations with the acyllactone substrates and gives further evidence for the decreased compatibility of bulkier substituents in this position to the asymmetric procedure.

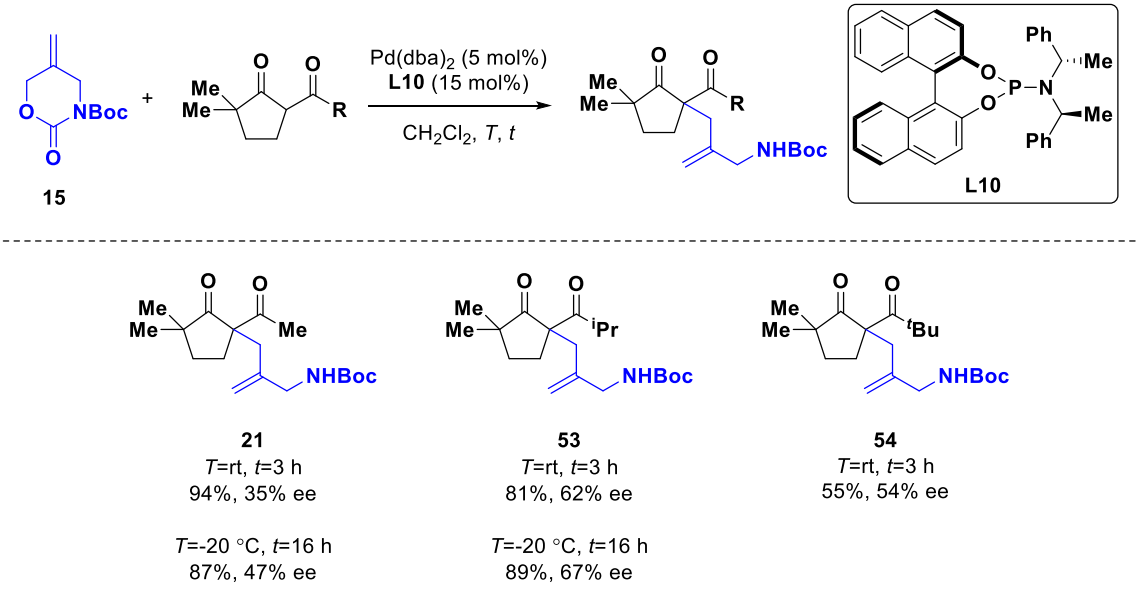
Table 6 – Reduced temperature asymmetric allylations of bulkier 1,3-diketones **65** and **59**.



Entry	R	T / °C[a]	t / h	Yield / %[b]	ee / %[c]
1	^{i}Pr	rt	3	79	79
2	^{i}Pr	-20	16	52	79
3	^{t}Bu	-20	16	63	67

[a] Reduced temperature achieved using ThermoFisher Haake Immersion Cooler EK90; [b] Yield of isolated product; [c] Analysed using chiral HPLC.

Despite the challenges we were presented with at the outset of this study, we feel that the selectivities we have achieved with the 1,3-diketone substrates are very commendable. However, ever keen to achieve higher enantiomeric excesses, we reviewed the substrates and were interested to elucidate the effect of increasing steric bulk on the other side of the cyclic ketone. With this in mind, a range of substrates containing a *gem*-dimethyl group *alpha* to the cyclic carbonyl were subjected to the optimal asymmetric procedure (Scheme 49).



Scheme 49 – Asymmetric allylations of *gem*-dimethylcyclopentanone substrates. Reduced temperature achieved using ThermoFisher Haake Immersion Cooler EK90. Yields of isolated product given.

Unfortunately, these substrates offered poorer selectivities than the parent cyclopentanone substrates. Notably however, 5-isobutyryl-2,2-dimethylcyclopentanone **51** afforded a better selectivity than 5-pivaloyl-2,2-dimethylcyclopentanone **52**, similar to previous results. In fact, **52** performed better than we had expected in the asymmetric allylation, considering the inherent pseudo-symmetry within the molecule. For this reason, we expected the product of the asymmetric allylation to be almost racemic. This result perhaps indicates the ability of the catalyst to distinguish between cyclic and acyclic carbonyl moieties, and to discriminate between the two during the allylation step.

All in all, this new information suggests that increasing the bulk in the 5-position of the cyclopentanone reduces selectivity. This leaves us very little chemical space to explore when designing new 1,3-diketone substrates for the asymmetric allylation.

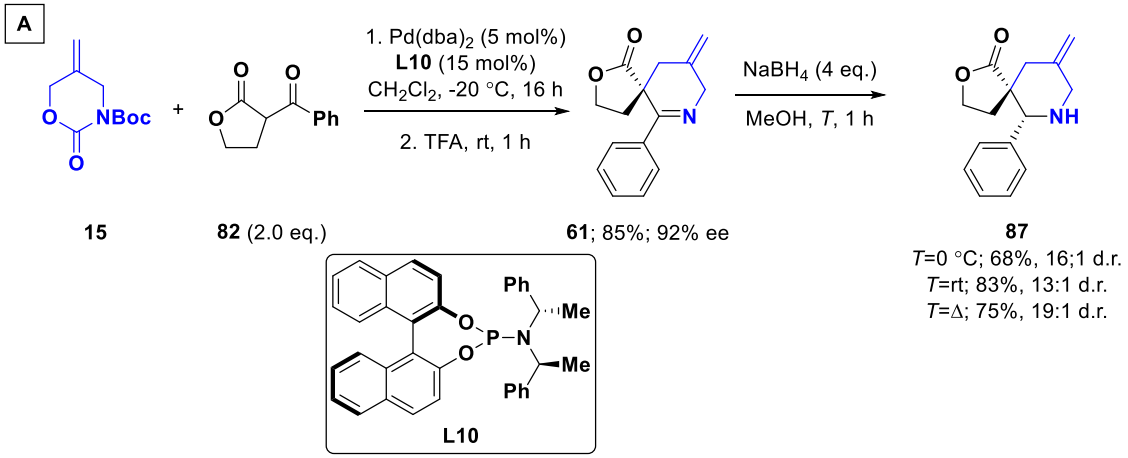
However, previous studies within the group identified that the pyrrolidine-based phosphoramidite ligands **L5** and **L6** were suitable for the asymmetric allylation of the diketone substrates and thus we feel our current catalyst system is complementary.

Indeed, we can conclude that the design of a chiral ligand that can be universally applied to the asymmetric allylation of a wide variety of 1,3-dicarbonyl substrates is yet to be achieved. The large fluctuations in enantioselectivity we found in the different substrate classes using **L10** demonstrates this point. Future work in this area might involve a ligand screen on a much larger scale than we have presented above, with the inclusion of a variety of different ligand classes. Furthermore, a more in-depth knowledge of the mechanism and the shape of the catalyst might be required to aid this effort.

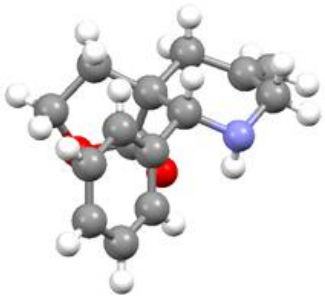
3.5 – Product Functionalisation

In order to further demonstrate the utility of our novel methodology, we wished to demonstrate the ability of the products to undergo further functionalisation. For these studies, we chose to investigate the reactivity of **61**.

Initially, we found that **61** was amenable to a highly diastereoselective reduction of the imine group, providing piperidine **87** in high yield and in excellent diastereoselectivity (Scheme 50). Interestingly, optimisation revealed that the reduction best proceeded in refluxing methanol, as opposed to lower temperatures. In fact, these conditions were employed in an attempt to isolate the minor diastereoisomer, which had been observed in only small amounts at both room temperature and 0 °C. It was therefore surprising to find these higher temperature conditions were more selective. Additionally, we were able to assign both the relative and absolute stereochemistry of this product through X-ray crystallographic structure determination.

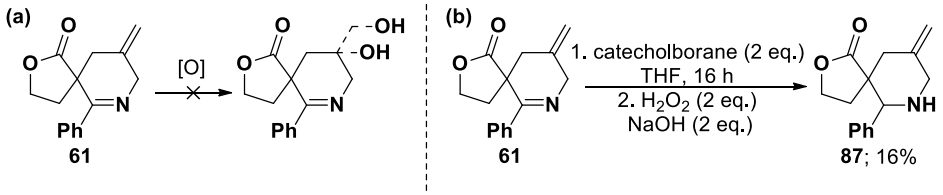


B



Scheme 50 – (A) Diastereoselective reduction of **61** to **87**. (B) Crystal structure of **87** showing relative and absolute stereochemistry. Crystallographic information located in Appendix 5.

Next, we attempted various oxidations of the alkene, such as dihydroxylations using OsO_4/NMO catalyst system, oxidative cleavage with $RuCl_3$, and even hydroboration-oxidation sequences with various borane sources. Unfortunately, in each case, the imine group appeared to complicate the transformation and clean products could not be obtained. In one instance however, hydroboration using catecholborane resulted in imine reduction, albeit in a poor yield (Scheme 51).



Scheme 51 – (a) Various oxidation conditions afforded non-chemoselective reaction at the imine also (b) Hydroboration with catecholborane affords chemoselective reduction at the imine.

Attempts to hydrolyse the lactone were also unsuccessful, which we attribute to the unfavourable formation of a sterically-demanding tetrahedral intermediate adjacent to a quaternary stereocentre (Figure 7).

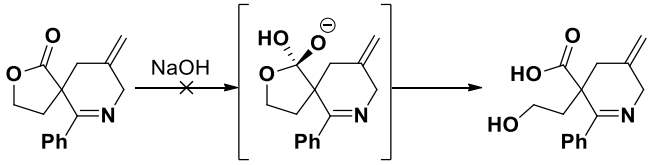
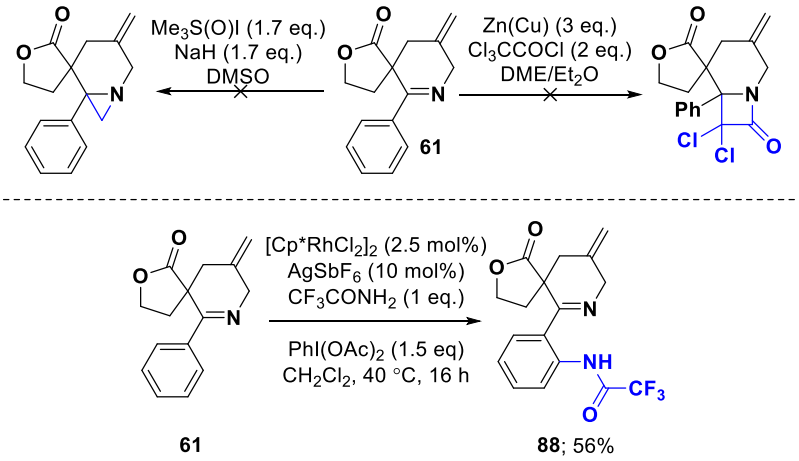


Figure 7 – Possible rationalisation for the unsuccessful saponification of the lactone **61**.

We reasoned that functionalisation of the imine should be facile. Unfortunately, when we tried to oxidise the imine to the oxaziridine, we recovered the starting material. Similar outcomes arose when subjecting the imine to cycloaddition and other annulation conditions (Scheme 52A). This illustrated to us that the imine is unusually stable, a characteristic that is highly desired in directing groups for C-H activation. Our group has previously reported the oxazoline-directed, Rh-catalysed C-H amidation of a variety of aromatic systems,[54–56] and we wondered if these conditions may be applicable to our system, using the imine as a directing group. Much to our delight, subjecting **61** to these conditions allowed us to access **88** in a reasonable 34% yield. Slight modification of the conditions increased this yield to 56% (Scheme 52B). This

result contributes to the small handful of examples which utilise imines as directing groups.

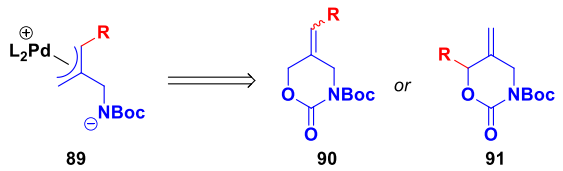


Scheme 52 – (**A**) Attempted cycloadditions of **61**; (**B**) Rh-catalysed C-H amidation of **61**.

4 – Synthesis and Reaction of Prefunctionalised Carbamates

4.1 – Synthesis of Substituted Carbamates

Having established a reliable and robust protocol for the synthesis of functionalised piperidines containing an exocyclic methylene type alkene, we wished to expand the methodology to include substituted carbamates that would deliver more heavily substituted products. As shown in Scheme 1, this chemistry would proceed through an unsymmetrical Pd-π-allyl containing zwitterion **89** (Scheme 53). We envisioned that the unsymmetrical conjunctive reagent **89** could be accessed from one of two starting materials **90** or **91**.



Scheme 53 – New strategy for the synthesis of substituted-alkene-containing piperidines.

The possibility of using **89** to mediate the allylation of 1,3-dicarbonyl substrates raised two important questions. Firstly, would the allylation proceed to generate a tri- or di-substituted alkene containing product? Secondly, what selectivity would be achieved? If the reaction afforded the linear isomer, we could expect a mixture of *E* and *Z* alkene isomers, whereas if it delivered the branched isomer, we might expect a mixture of diastereoisomers. Based on literature precedent,[3] we hypothesised that our Pd-catalysed allylation would afford the linear products, which would result from attack of the enolate at the more accessible terminus of the Pd-π-allyl complex (path a, Figure 8).

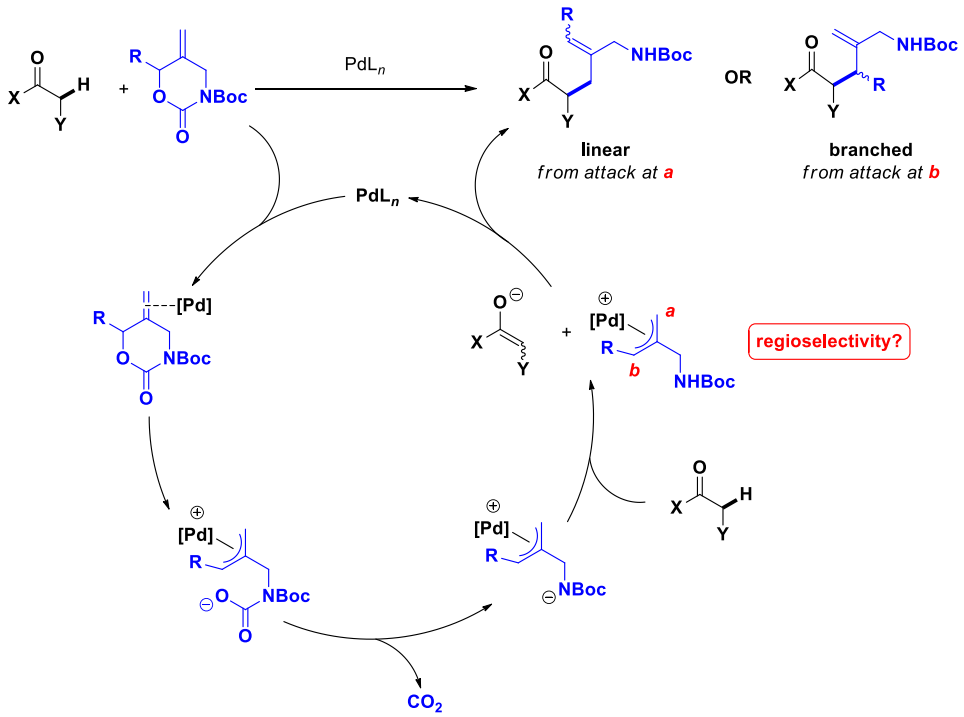
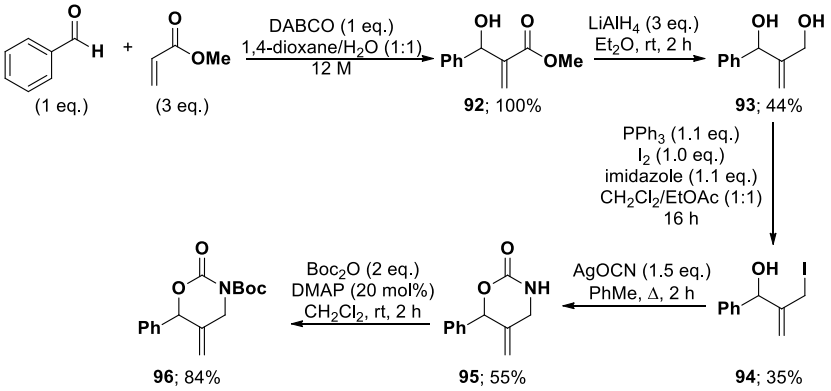


Figure 8 – Proposed mechanistic implications of the employment of an unsymmetrical Pd-π-allyl complex.

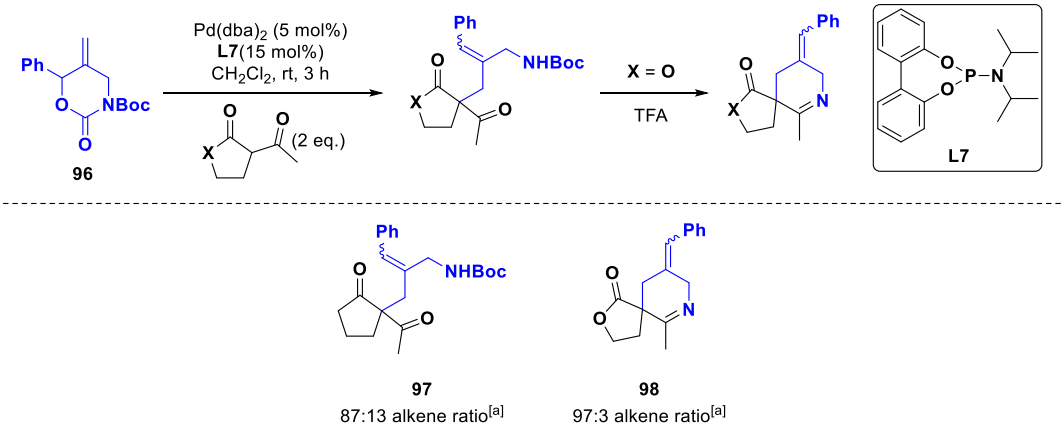
We envisioned that **89** could be accessed using our existing synthesis of **15** (Scheme 31), but starting with a substituted diol. In the event, we chose to access the phenyl-substituted carbamate as we were able to devise a quick route to this compound. Specifically, the Baylis-Hillman reaction of methyl acrylate and benzaldehyde allowed us to form the adduct **92** in quantitative yield (Scheme 54). Reduction of the ester moiety resulted in a moderate yield of the unsymmetrical diol **93**. From **93** our usual strategy was employed, and we were able to access the required carbamate **96**. However, we were disappointed with the overall yield of this route, and we attributed the poor yield of the Appel step to the high reactivity of the iodide, which is most likely light-sensitive and highly electrophilic.



Scheme 54 – Synthesis of phenyl-substituted carbamate **96**.

4.2 – Reaction of Substituted Carbamates

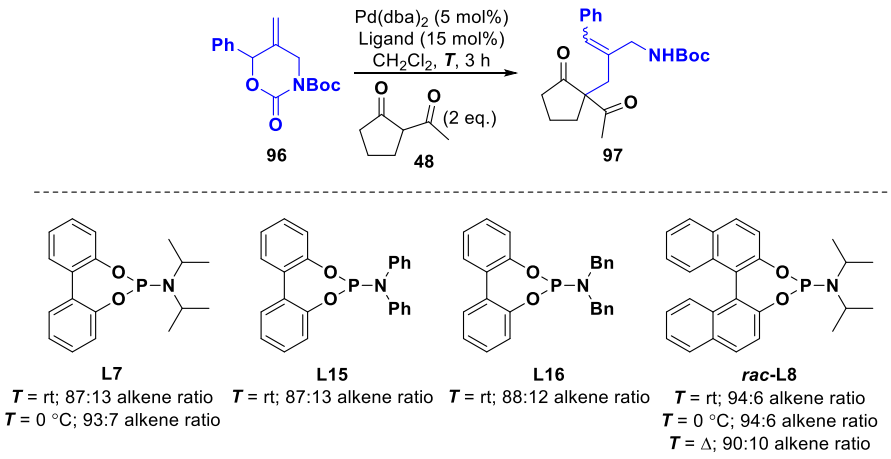
Although low yielding, the route shown in Scheme 54 provided us with a sizable quantity of **96**, and so we next explored its performance in the Pd-catalysed allylation reaction. Subjection of this carbamate to our optimised conditions with a few 1,3-dicarbonyls resulted in the selective formation of the linear isomers, in agreement with our hypothesis, and the products contained a trisubstituted alkene (Scheme 55). Unfortunately, whilst we had formed one alkene isomer in excess, the separation of the two alkenes was difficult, and the products could not be isolated cleanly.



Scheme 55 – Initial application of **96** to the Pd-catalysed allylation of 1,3-dicarbonyl substrates. All alkene ratios assigned by ^{1}H NMR spectroscopy. [a] Major isomer not isolable.

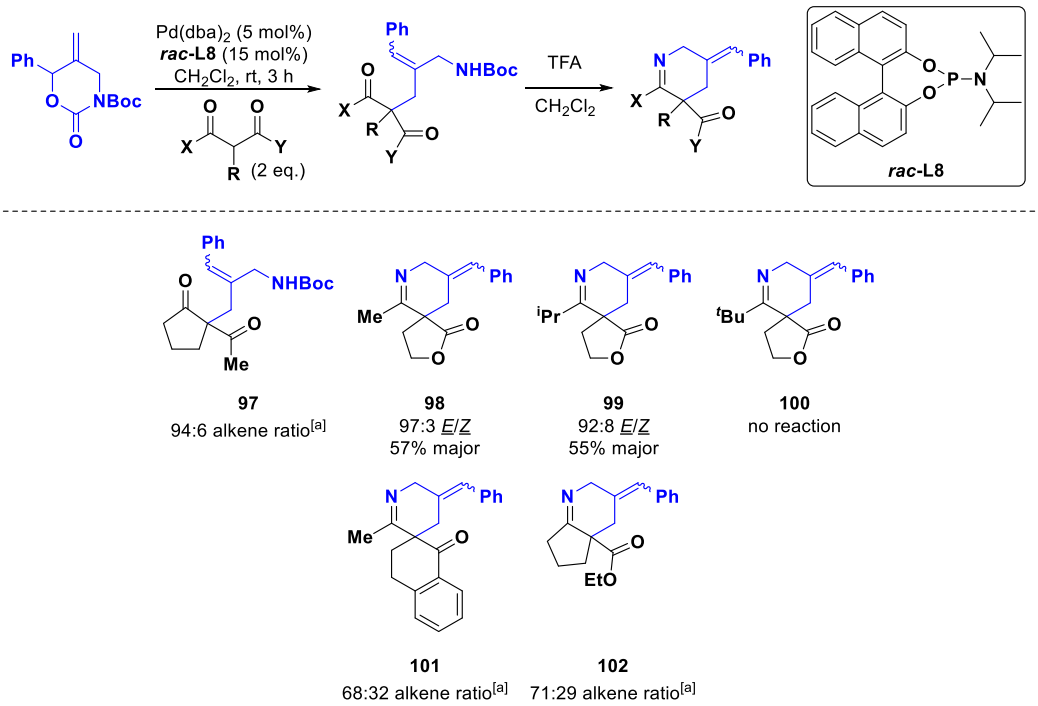
The alkene ratios were promising (the assignment of alkene stereochemistry is discussed later) and we next chose to attain better control of this selectivity through the use of alternative phosphoramidite ligands (Scheme 56). Interestingly, substitution of the isopropyl groups for less bulky substituents had no effect on the alkene ratio, when conducting the reaction at room temperature. To our delight, however, extending the biphenol unit to a binaphthol unit (synthesised with racemic BINOL) improved the

alkene ratio significantly. Further optimisation revealed that changes in the reaction temperature did not seem to have a dramatic effect on the alkene selectivity. For example, conducting the reaction with **L7** at 0 °C led to a marginal increase in selectivity, whereas using ***rac*-L8** at the same temperature resulted in no noticeable difference. However, ***rac*-L8** at reflux had a negative effect on the selectivity. Unfortunately, the issue of alkene separation was persistent, and the major isomer was not isolable.



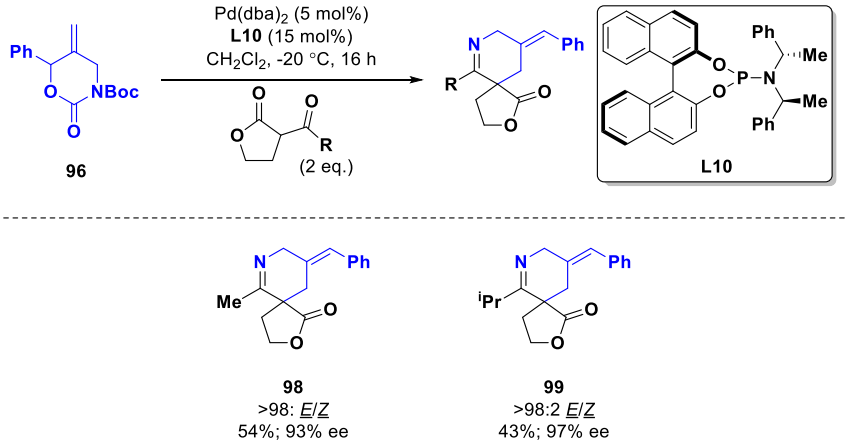
Scheme 56 – Ligand optimisation to control the alkene ratio of allylation products. All alkene ratios assigned by ^{1}H NMR spectroscopy.

A brief scope of this reaction demonstrated that the use of ***rac*-L8** was also suitable for the α-acyl-γ-butyrolactone substrates **49** and **80**, affording the respective piperidine products in moderate yield with good selectivities. The nature of the pendant ketone group seems to have an effect on the alkene selectivity, with the bulkier isopropyl-containing substrate **80** affording a 92:8 ratio compared to the methyl-containing **49** affording a 97:3 ratio. However, switching the substrate to 1,3-ketoester **18** or 2-acetyl-1-tetralone **74** resulted in lower selectivities. It appears then that significant improvement in this area could be achieved through further optimisation of the ligand.



Scheme 57 – Scope of the Pd-catalysed allylation of various 1,3-dicarbonyl substrates with **96**. All alkene ratios assigned by ^{1}H NMR spectroscopy. [a] Major product not isolable.

Furthermore, we demonstrated that this new zwitterion precursor can undergo the asymmetric transformation of the lactone substrates **49** and **80** quite efficiently using our optimised conditions (Scheme 58). Moreover, we only observed one alkene isomer in each case.



Scheme 58 – Enantioselective Pd-catalysed allylation of lactone substrates with **96** and **L10**.

We unambiguously assigned the alkene stereochemistry of compound **99** using nOe experiments which showed a strong interaction between the alkenyl proton and the CH_2 adjacent to the N-atom (Figure 9). The major alkene isomer of **98** was also assigned as *E* on this basis.

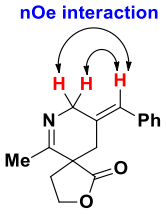


Figure 9 – nOe interaction observed to assign the *E*-alkene stereochemistry. nOe assignment located in Appendix 4.

5 – Activated Ketone Substrates

5.1 – 2-Arylketone Substrates

Having tested a range of 1,3-dicarbonyl-based substrates, we were keen to try the allylation of other activated carbonyl compounds such as α-arylketones. However, we were cognizant that our optimal conditions might not be effective for the enolate forming step in these less acidic substrates (Figure 10).

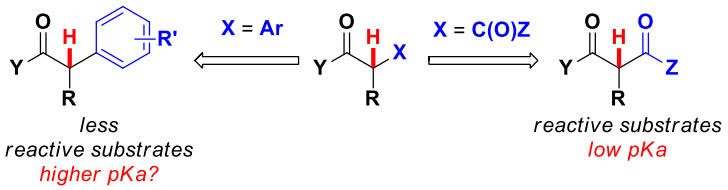
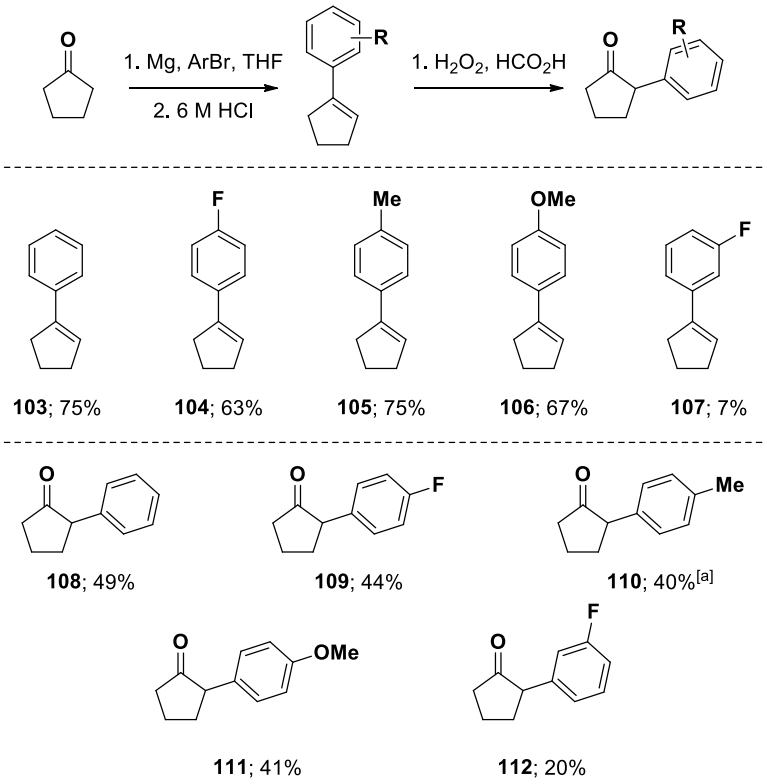


Figure 10 – Comparison of 1,3-dicarbonyl compounds with 2,arylketones.

First, we prepared several 2-arylcyclopentanones with a range of electronic features at the aryl ring. We achieved this through the reaction of aryl Grignard reagents with cyclopentanone, followed by dehydration to afford the alkenes **103**-**107** (Scheme 59). Next, we oxidised the alkenes allowing us to access the 2-arylketone products. We found that the formation of the alkene intermediates was generally efficient, with the exception of the *m*-fluorophenyl analogue **107**. Additionally, we found the need to employ various oxidation conditions, depending on the solubility of the starting alkene. For example, **103** and **104** were found to be soluble in a mixture of water, H_2O_2 and HCO_2H, however **105**, **106** and **107** were not. The use of mCPBA for **105** led to the formation of the required ketone, presumably through formation of the epoxide followed by a Meinwald rearrangement, possibly catalysed by *m*-chlorobenzoic acid. However, the reaction of *p*-anisyl alkene **106** stopped at the epoxide (as evidenced by

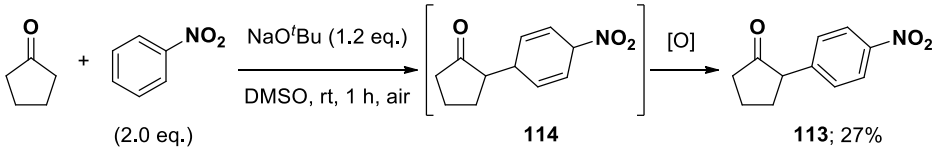
the absence of a carbonyl signal in FTIR spectrum). This led us to revisit the initial oxidation conditions but with the addition of CH_2Cl_2 to mitigate the issue of insolubility. This approach was successful, albeit generating the product in a moderate yield. Additionally, alkene **107** could also be oxidised with these biphasic conditions.



Scheme 59 – Synthesis of a range of 2-arylcyclopentanones. [a] Performed with 2.0 eq. of mCPBA.

We also wanted to access the *p*-nitrophenyl containing **113**, but the method shown in Scheme 59 was unsuccessful in this case, as the formation of the requisite Grignard reagent was unsuccessful. Fortunately, a previous synthesis of **113** existed in the literature, and appeared to be operationally simple. Specifically, it involved the nucleophilic addition of the enolate of cyclopentanone to nitrobenzene, followed by an

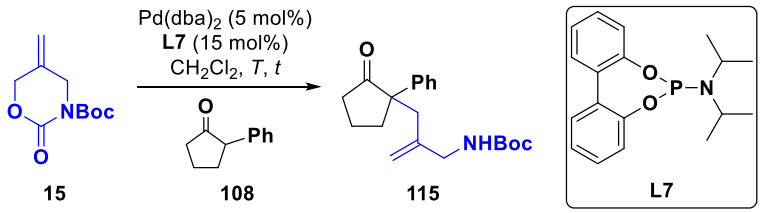
in situ oxidation of the intermediate cyclohexa-1,4-diene **114** (Scheme 60).[57] This procedure allowed us to isolate the required product **113** in 27% yield.



Scheme 60 – Synthesis of *p*-nitrophenyl substituted **113**.

With these substrates in hand, we began to investigate the Pd-catalysed allylation step. As we expected, the allylation of **108** using our previously established conditions was largely unsuccessful, offering a disappointing 50% conversion (Table 7, entry 1). Increasing the reaction time to 19 h had little effect and conversion was increased to only 63% (entry 2). Fortunately, heating the reaction at reflux afforded complete conversion and allowed us to reduce the reaction time to just 3 hours (entries 3 and 4).

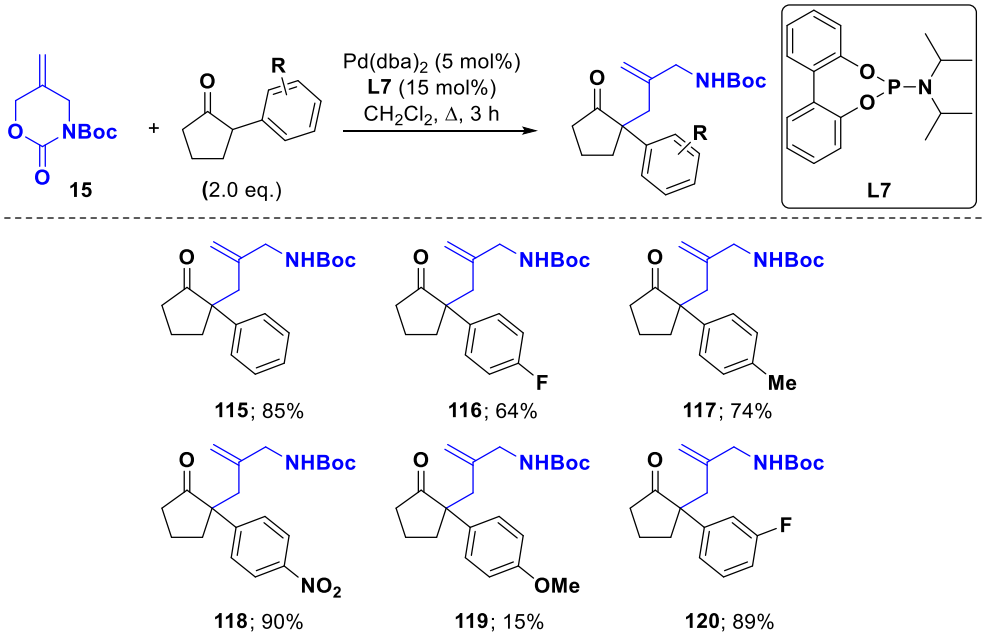
Table 7 – Optimisation of non-enntioselective allylation of 2-phenylcyclopentanone **108**.



Entry	T / °C	t / h	Conversion / %[a]
1	rt	3	50
2	rt	19	63
3	Δ	19	100
4	Δ	3	100

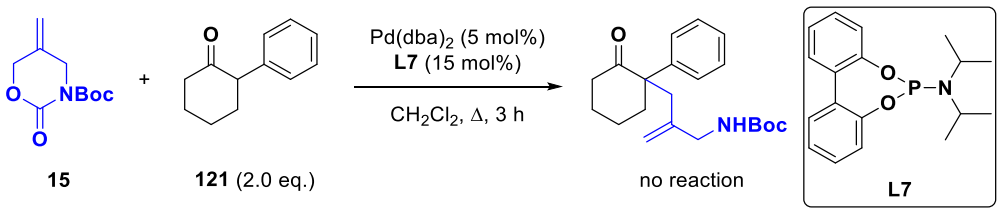
[a] Determined by ^{1}H NMR spectroscopy.

With working conditions in hand, we set out to generate a selection of compounds which allowed us to explore the electronic and steric influence of the aryl unit on the reaction (Scheme 61).



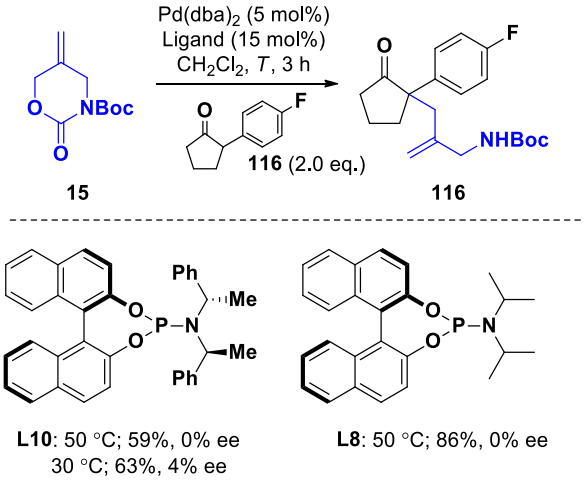
Scheme 61 – Scope of α-arylketone substrates in palladium-catalysed allylation reaction.

As demonstrated, the employment of a variety of electron-withdrawing (**116, 118** and **120**) and electron-neutral (**115** and **117**) substituents allowed the allylation reaction to proceed efficiently, delivering good to excellent yields of products. However, the employment of an electron-donating group, as in **119**, had a deleterious effect on reaction efficiency. We next attempted the allylation in refluxing dichloroethane; however, we observed similarly low levels of conversion and yield. Furthermore, and interestingly, the employment of 2-phenylcyclohexanone **121** was unsuccessful in this reaction (Scheme 62). In this case, we observed no conversion and recovered our starting materials. The underlying reasons for this difference in reactivity are not clear at present.



Scheme 62 – Attempted Pd-catalysed allylation of 2-phenylcyclohexanone **121**.

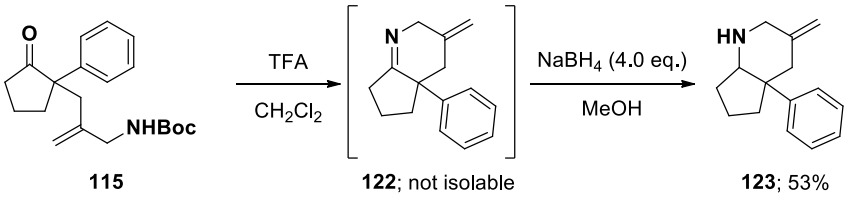
With a reliable racemic reaction in place, we turned our attention to the asymmetric allylation of these substrates (Scheme 63). Unfortunately, our preliminary studies showed little to no enantioenrichment in the products. Switching our optimal ligand **L10** for the less hindered ligand **L8** also resulted in no enantioselectivity. Furthermore, dropping the temperature to 30 °C also had no beneficial effect.



Scheme 63 – Attempts at asymmetric allylation of arylketone substrates.

We anticipated that the allylation products **115**-**120** could be further functionalised to deliver some interesting piperidine products. With this in mind, we stirred **115** in the presence of TFA with the aim of isolating the piperidine **122** (Scheme 64). However, whilst we could clearly see the imine in the crude reaction mixture, we found it to be unstable under a variety of chromatographic conditions. Therefore, we reasoned that

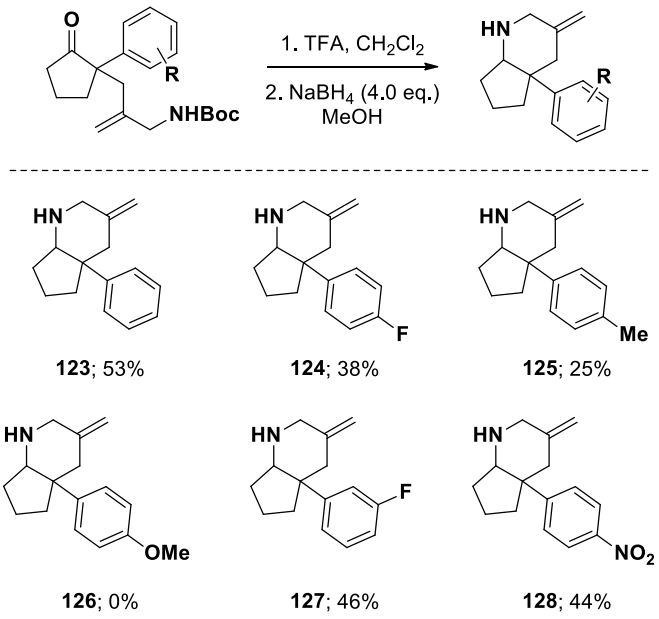
reduction of the imine might enable the isolation of the unprotected piperidine **123**. Dissolving the crude imine **122** in MeOH followed by the addition of 4.0 eq. of $NaBH_4$ allowed us to access **123** in 53% yield as a single diastereoisomer (Scheme 64). Unfortunately, attempts to assign the relative stereochemistry through nOe experiments were unsuccessful, and further work will aim to elucidate this.



115 **122**; not isolable **123**; 53%

Scheme 64 – Attempted isolation of **122** and successful isolation of **123**.

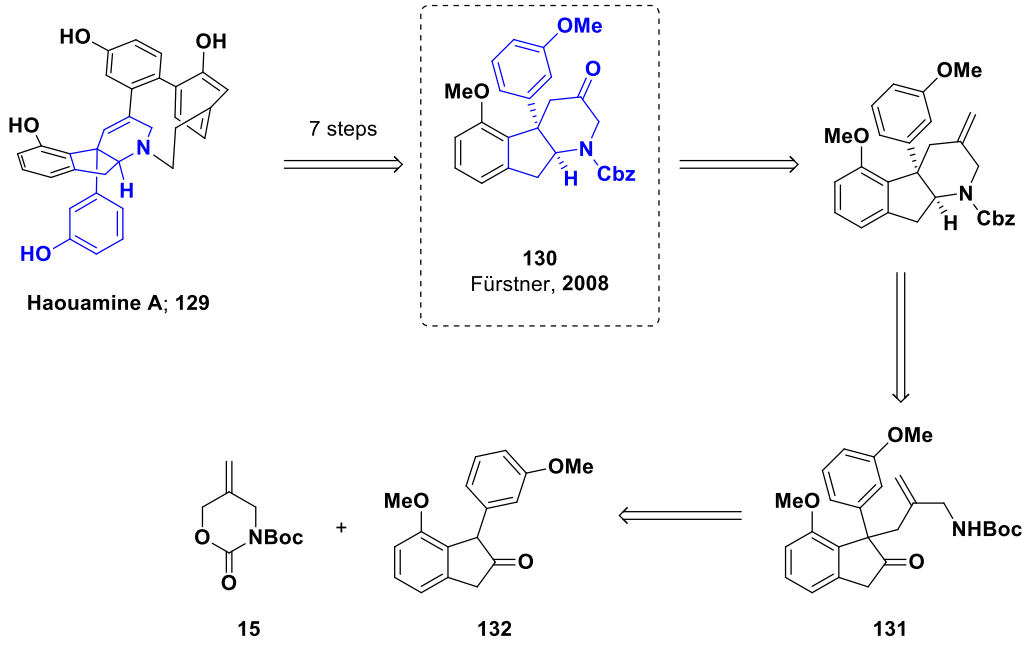
Given this promising result, we extended these conditions to the rest of our family of allylated products and were pleased to find that this methodology was quite general (Scheme 65). Pleasingly, most of our substrates underwent this procedure efficiently, although the products were isolated in only poor to moderate yields. Unfortunately, *p*-anisyl **119** did not afford any product in this reaction as observed in the ^1H NMR spectrum of the crude material. We believe that the low yields generally observed in this reaction are indicative of issues relating to the chromatographic purification of these secondary amine-containing products.



Scheme 65 – Preparation of piperidines **123**-**128** *via* reductive amination of allylated ketones **115**-**120**.

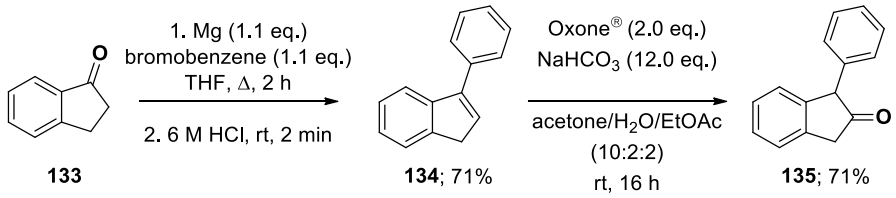
5.2 – Towards Haouamine A: 1-Aryl-2-Indanones

Having confirmed that α-arylketones are effective substrates for the allylation step, we decided to exploit this chemistry in the synthesis of a natural product. Haouamine A **129** seemed a suitable candidate for this purpose, as it contains a piperidine ring fused to cyclopentane ring. Additionally, the piperidine ring bears similar substitution patterns to those contained in our products (Scheme 66). Inspection of previously reported routes to this target, we were pleased to discover a report by Fürstner *et al.* which described the formal total synthesis of **129** *via* the fragment **130**.[58] Retrosynthetic analysis of **130** revealed a concise route to this compound which would allow us to showcase the power of our newly developed methodology (Scheme 66). This would require the Pd-catalysed allylation of electron-rich indanone **132**.



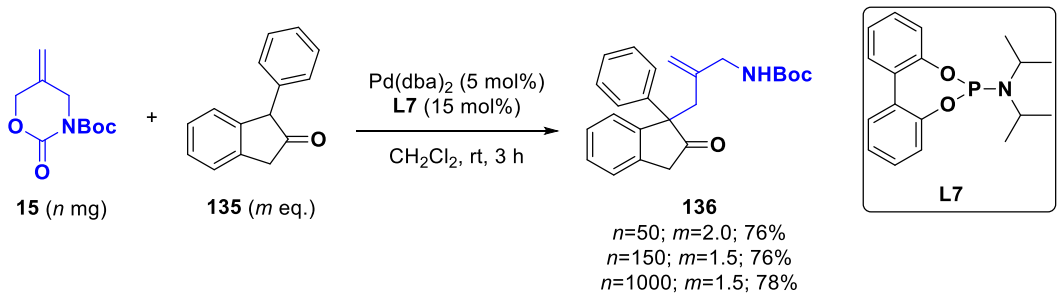
Scheme 66 – Retrosynthetic analysis of Haouamine A **129** through Fürstner's intermediate **130**. Blue highlighted core indicates chemical space previously accessed through our Pd-catalysed methodology.

In order to test the feasibility of our proposed route, we opted to test the Pd-catalysed allylation with a model substrate. We accessed 1-phenyl-2-indanone in a similar fashion to the 2-arylcyclopentanone substrates. Specifically, reaction of phenylmagnesium bromide with 1-indanone **133** followed by acid-promoted condensation accessed the alkene **134**. However, we found that the oxidation of **134** using hydrogen peroxide was inefficient. Instead we found a procedure reported by Ramana and co-workers which used a mixture of Oxone® monopersulfate with $NaHCO_3$.[59] This allowed us to isolate the desired indanone **135** in 71% yield on a ~6 g scale.



Scheme 67 – Synthesis of 1-phenyl-2-indanone **135**.

With the indanone in hand, we discovered that the Pd-catalysed allylation proceeded very efficiently. Our first attempt used our previously established conditions: 5 mol% $Pd(dba)_2$, 15 mol% **L7** and 2 equivalents of the substrate **135** to achieve a 76% yield of allylated product **136** (Scheme 68). We were delighted to find that this substrate underwent selective allylation at the most-substituted alpha-carbon at room temperature to form a stereogenic, quaternary carbon centre. Further experimentation revealed that decreasing the stoichiometry of **135** to 1.5 equivalents afforded the same result (Scheme 68). Moreover, this procedure could be performed on a 1.00 g scale, still employing just 1.5 equivalents of **135**, providing the product in 78% yield.



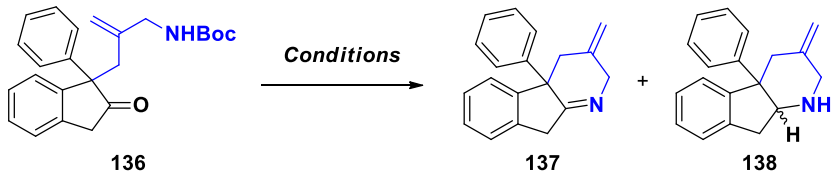
Scheme 68 – Pd-catalysed allylation of **135** with **15** proceeds well on small- and large-scale.

Unfortunately, however, further transformations of this compound proved difficult. Initially we attempted to isolate the imine that resulted from TFA-mediated deprotection and condensation, but we were disappointed to find that the imine appeared to be unstable to a variety of chromatography supports, despite observing the product as the major component in the ^{1}H NMR spectrum of the crude material. As we had experienced this issue previously, we attempted to reduce the imine using $NaBH_4$ (Table 8). We were disappointed to find that our first attempt resulted in a 31% yield of material that was contaminated with various unknown impurities (Table 8, entry 1). Suspecting that the intermediate imine might be unstable during the solvent switch, we investigated the possibility of performing a reductive amination in a one-pot procedure (entries 2 and 4). Interestingly, when we employed $NaBH_3CN$ as the reductant, we only observed the imine **137**. This could indicate that $NaBH_3CN$ was not reactive enough to reduce the imine under these conditions. Unfortunately, this also appeared to be the case if $NaBH_3CN$ was employed in a step-wise fashion (entry 3). The use of $NaBH(OAc)_3$ was also not effective in this transformation, and afforded a complex mixture of products. Additionally, employing $NaBH(OAc)_3$ in a step-wise procedure was also unsuccessful (entry 5). Alternative reductants were sought, and we attempted the use of Hantzsch ester, but we obtained a complex mixture once

again (entry 6). Finally, repeating the conditions from entry 1 afforded a 21% yield of impure product (entry 7), suggesting that this methodology may not be reliably reproduced. We reasoned that we might be able to trap the product as the HCl salt, which would enable a simple filtration to purify the material. Unfortunately, whilst we formed the HCl adduct, we could not isolate it cleanly and the material appeared as a complex mixture.

Given that the conditions employing $NaBH_4$ as reductant consistently led to formation of the desired product, we opted to investigate a number of purification techniques in order to improve the yield and the purity. Importantly, we note that the employment of $NaBH_4$ led to the formation of just one diastereoisomer of the amine product **138**, whereas other methods often led to complex mixtures which may in part be due to the formation of a mixture of diastereomers.

Table 8 – Various attempts to selectively form amine **138**.



136 137 138

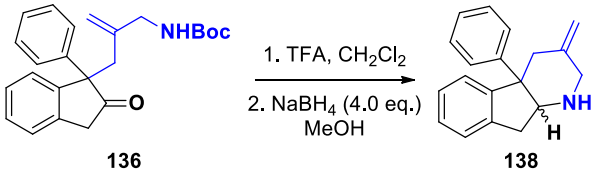
Entry	Conditions	Purification	Result[a]
1	1. TFA, CH_2Cl_2; 2. $NaBH_4$ (4.0 eq.), MeOH	FCC on silica gel	31% **138**[b]
2	TFA, $NaBH_3CN$ (1.2 eq.), CH_2Cl_2	N/A	**137** only
3	1. TFA, CH_2Cl_2; 2. $NaBH_3CN$ (4.0 eq.), MeOH	N/A	**137** only
4	TFA, $NaBH(OAc)_3$ (4.0 eq.), CH_2Cl_2	N/A	Complex mixture
5	1. TFA, CH_2Cl_2; 2. $NaBH(OAc)_3$ (4.0 eq.), MeOH	N/A	Complex mixture
6	TFA, Hantzsch ester (1.5 eq.)[c], CH_2Cl_2	N/A	Complex mixture
7	1. TFA, CH_2Cl_2; 2. $NaBH_4$ (4.0 eq.), MeOH	FCC on silica gel	21% **138**[b]
8	1. TFA, CH_2Cl_2 2. $NaBH_4$ (4.0 eq.), MeOH 3. 2 M HCl in Et_2O	Filter and wash with cold Et_2O	50% **138•HCl**[b]

[a] As determined by ^1H NMR spectroscopy or by chromatographic separation. [b] Product contains unknown impurities. [c] Hantzsch ester = diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. FCC = flash column chromatography.

We believed that the acidic nature of the silica presented an issue during chromatographic separation. The presence of an acidic media likely results in the formation of an ammonium salt which is then retained on the stationary phase and

hence leads to a reduced yield of the product. A common technique to avoid this is the addition of Et_3N to the eluent. Unfortunately, this resulted in just a 17% yield of impure **138** (Table 9, entry 1). Switching to florisil as the stationary phase led to an increase in product yield and purity (entry 2). However, there were still a number of baseline impurities which we struggled to remove and characterisation of these impurities was unsuccessful. Repeating the above conditions but with a slightly slower elution afforded a marginally improved yield (entry 3).

Table 9 – Alternative purifications of **138**.

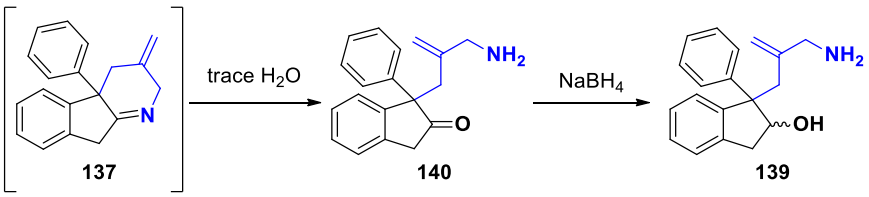


136 138

Entry	Purification	Result
1	FCC on silica gel 1% Et_3N in eluent	17% **138**[a]
2	FCC on florisil	45% **138**[a]
3	FCC on florisil	52% **138**[a]

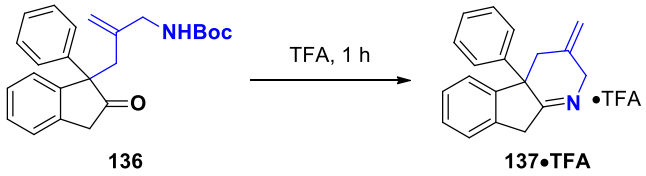
[a] Material contained unknown impurities.

With some success in increasing the yield and purity of the product **138**, we next decided to look more closely at the source of the impurities. Analysis by LCMS revealed the potential formation of the aminoalcohol **139**. Closer inspection of our product mixtures by ^1H NMR spectroscopy revealed some further evidence for the formation of this product. Presumably, this results from hydrolysis of the intermediate imine to give ketone **140** which is subsequently reduced *in situ* to give **139** (Scheme 69).



Scheme 69 – Rationale for the formation of **139**.

Since this impurity would arise from imine hydrolysis, we reasoned that stabilising the imine, perhaps by trapping it as a salt, might allow a more selective reduction. Indeed, **137•TFA** could be isolated simply by stirring **137** in TFA, followed by evaporation of the excess TFA (Scheme 70). The resultant material appeared to be slightly hygroscopic, and as such further manipulations were performed quickly. The reduction of **137•TFA** with $NaBH_4$ in MeOH proceeded in high conversion, however **139** was observed in trace amounts and the purification did not afford clean material. Unfortunately, employment of $NaBH_3CN$ and $NaBH(OAc)_3$ in MeOH or CH_2Cl_2 were unsuccessful, and in each case we observed the formation of unwanted impurities and failed to isolate the product cleanly.



Scheme 70 – Formation of **137•TFA**.

We postulated that the problems arising in this apparently simple transformation could be due to the ring-strain imposed by the unsaturated 5,6-ring system (Figure 11). The 9-carbon bicycle contains 5 unsaturated carbon atoms, which forces the bicycle into a relatively planar conformation. However, the presence of a quaternary carbon centre

at the bridgehead likely destabilises this ideal planarity. Based on this, we reasoned that expanding this bicyclic system by a methylene unit to a 6,6-ring system might ease this ring strain and lead to a less unstable imine, which could result in more selective and clean amine formation.

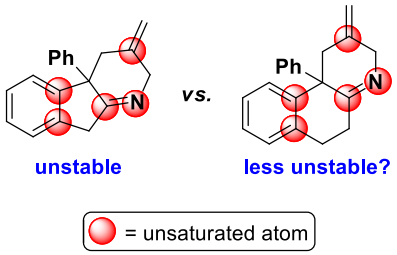
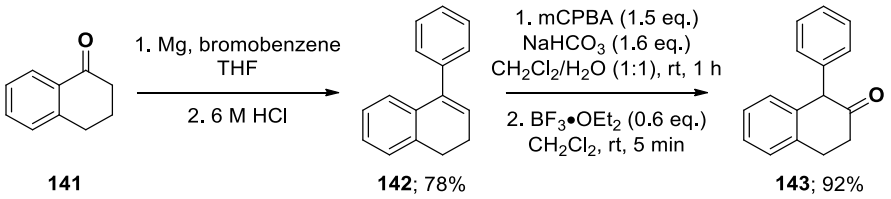


Figure 11 – Proposed stability of 5,6 *versus* 6,6 ring systems.

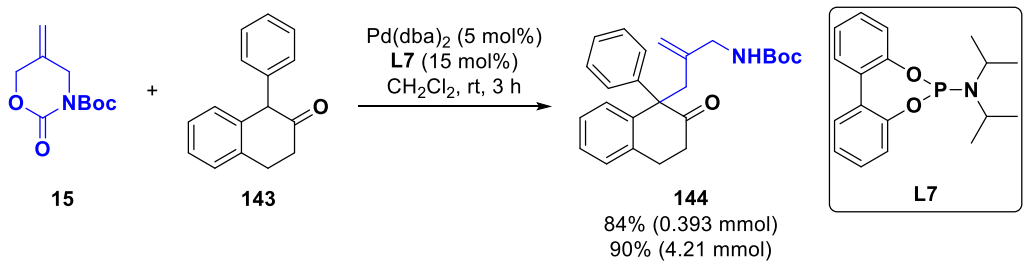
5.3 – 1-Aryl-2-Tetralones

By analogy to the synthesis of the related indanone systems, the reaction of phenylmagnesium bromide with 1-tetralone **141** followed by acid-mediated condensation gave alkene **142** in a 78% yield. Use of Oxone® as oxidant resulted in only 41% yield of tetralone **143**. We also discovered that the product mixture obtained from this reaction often existed as a mixture of ketone and epoxide, despite the authors reporting that the mechanism did not proceed *via* the epoxide.[59] However, we discovered a report by Wills and co-workers that detailed the use of mCPBA for the preparation of 1-aryl-2-tetralones.[60] This entailed the use of mCPBA to prepare the epoxide from **142** followed by a Meinwald rearrangement promoted by ZnI_2 under quite harsh conditions. However we had found an alternative method for the Meinwald step which utilised less harsh conditions and allowed a much faster reaction time (Scheme 71).[61] Through combining these two steps, we could access 1-phenyl-2-tetralone **143** in 92% yield from the alkene.



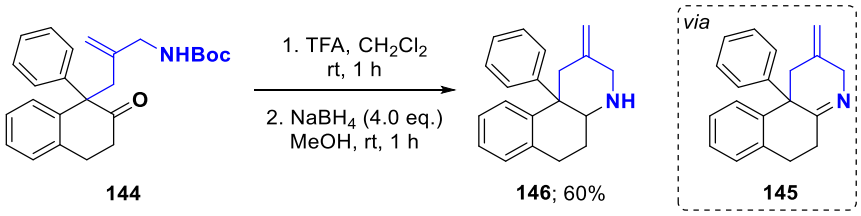
Scheme 71 – Synthesis of 1-phenyl-2-tetralone from 1-tetralone.

With the material in hand, we quickly established that this substrate performed exceptionally well in the Pd-catalysed allylation reaction, providing the product **144** in a 84% yield on a 50 mg scale (Scheme 72). Additionally, using 1.00 g of **15**, a 90% yield of **144** was obtained.



Scheme 72 – Performance of tetralone **143** in the Pd-catalysed allylation reaction.

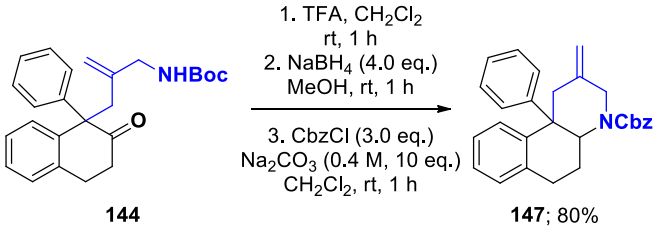
We next stirred **144** in TFA to prepare the imine **145**, which we observed by ^{1}H NMR spectroscopy, followed by reduction with $NaBH_4$ in MeOH. We were delighted to isolate the amine product **146** in 60% yield after column chromatography on silica gel as a single diastereomer (Scheme 73). Although the yield was rather modest, the ^{1}H NMR spectrum of the crude material showed that the reduction proceeded cleanly, with minimal impurities observed.



Scheme 73 – Reductive amination of **144** to furnish amine **146**.

In an effort to improve the overall yield, we submitted the crude reduction product directly to a Cbz-protection reaction, and this allowed us to isolate the Cbz-protected amine **147** as a single diastereomer in 80% yield from allylation product **144** (Scheme 74). We noted that one of the NCH_2 proton signals appeared to be slightly broadened in the ^{1}H NMR spectrum, likely due to rotamer interconversion, but this did not complicate the characterisation. Combining these two yields gives an overall yield of 72% from carbamate **15** and tetralone **143** which is impressive for a 4-step sequence.

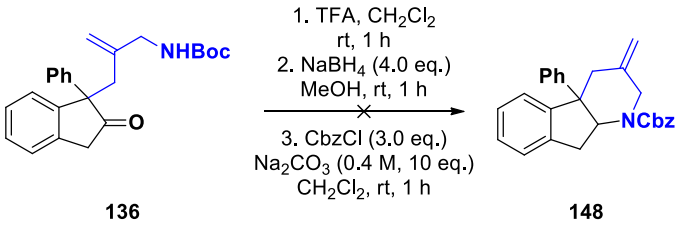
This demonstrates the power of our methodology to deliver highly functionalised, complex products from simple starting materials.



144 **147**; 80%

Scheme 74 – 3-step reductive amination-protection sequence for the synthesis of **147**.

Unfortunately, combining the Pd-catalysed allylation step with the reductive amination-protection sequence into a two-pot procedure afforded only 36% yield of **147**. Furthermore, attempts to extend this methodology to the indanone substrate **136** previously described (Scheme 68) afforded an inseparable, complex mixture of products (Scheme 75). This could be complicated by the presence of Cbz-protected by-products which are difficult to separate from the products.

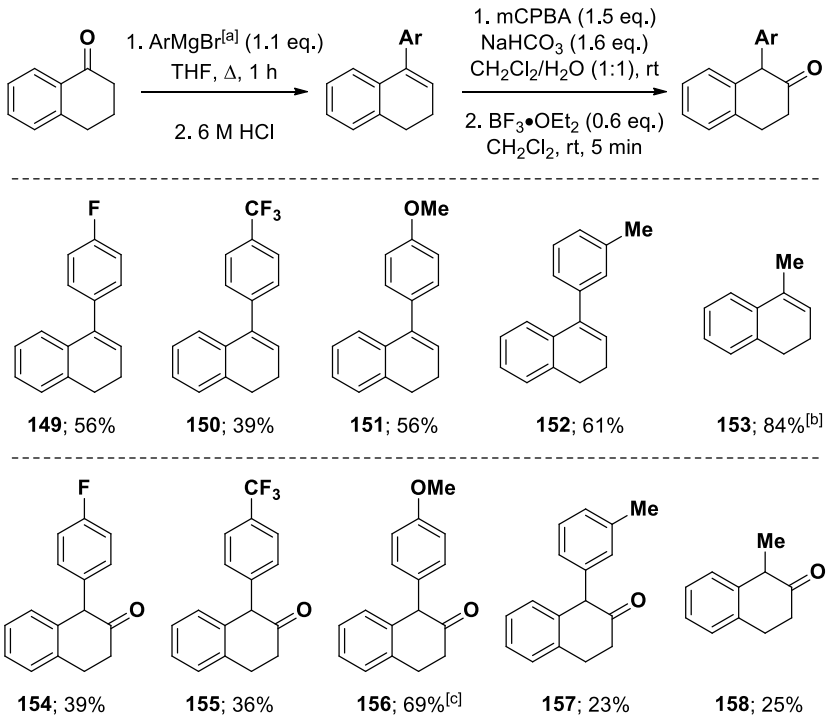


136 **148**

Scheme 75 – Unsuccessful attempt to access **148**.

Naturally, due to the success of this new methodology, we wished to test the scope of this reaction by employing substrates that contained differing steric and electronic environments. We synthesised a range of tetralones using the previously described methodology (Scheme 76). This generally worked well, with the exception of **151**

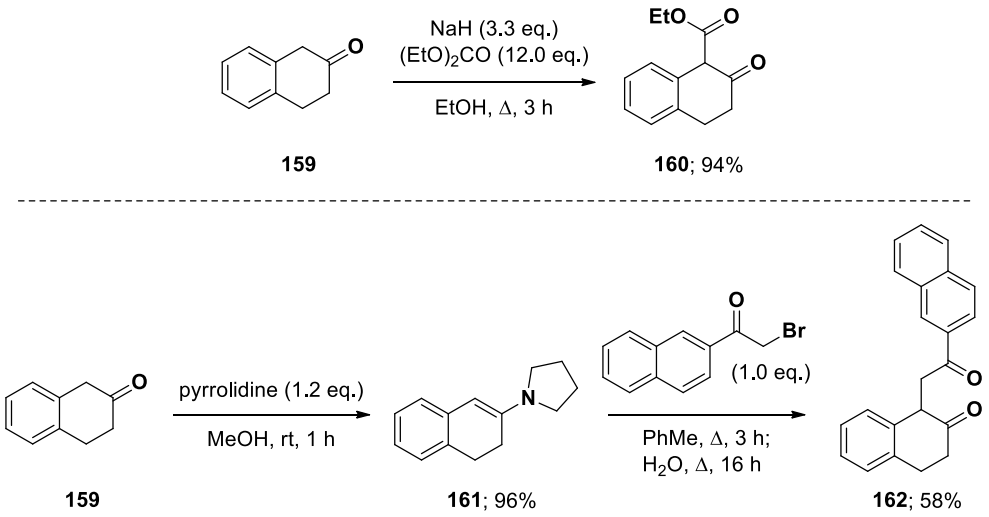
which required an alternative approach. The low yields for the second step are associated with slow and incomplete formation of the epoxide.



Scheme 76 – Synthesis of a range of 1-substituted-2-tetralones. [a] Grignard reagents prepared by stirring Mg (1.2 eq.) in THF with addition of aryl bromide (1.2 eq.) and I_2 used as initiator. [b] Grignard prepared using MeI (1.6 eq.), Mg (1.5 eq.) in Et_2O. [c] Prepared using Oxone (8.0 eq.) and $NaHCO_3$ (40.0 eq.).

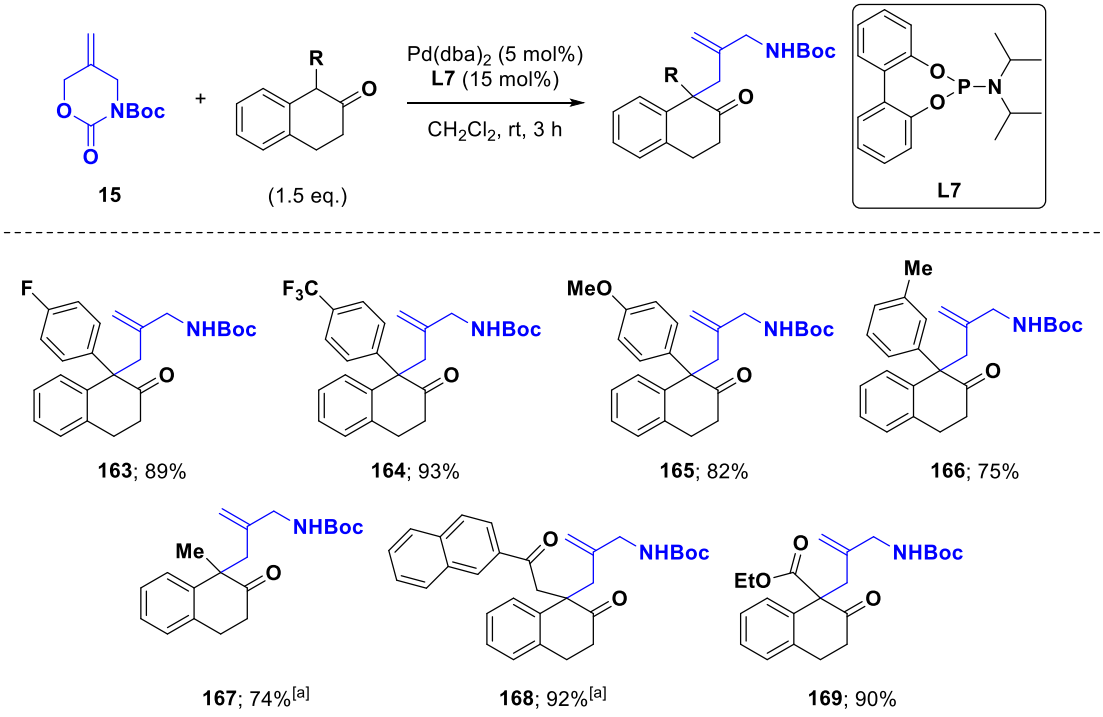
Whilst this procedure allowed us to access a good variety of tetralone substrates, we wished to incorporate other functional groups. Thus, treating 2-tetralone **159** with NaH in the presence of diethyl carbonate allowed access to the 1,3-ketoester **160** in an excellent yield (Scheme 77).[62] Furthermore, we wished to test the ability of 1,4-diketone substrates to undergo this reaction. Stirring **159** with pyrrolidine furnished enamine **161** in near quantitative yield.[63] Treatment of this enamine with a refluxing

solution of 2-(bromoacetyl)naphthalene allowed us to isolate 1,4-diketone **162** (Scheme 77).[64]



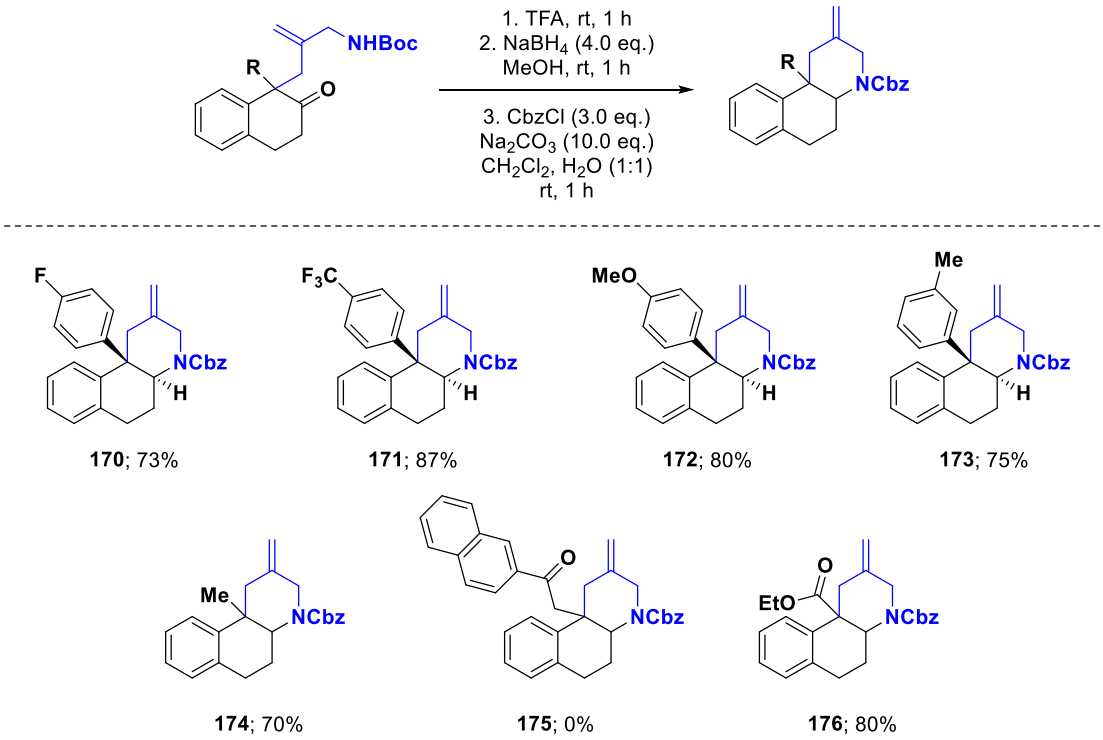
Scheme 77 – Synthesis of other tetralone substrates.

With a selection of substrates in hand, we were in a position to study the Pd-catalysed allylation reaction (Scheme 78). We were pleased to find that all substrates performed exceptionally well in this transformation, providing allylated products **163**-**169** in excellent yields. Given our previous issues with the allylation of electron-rich substrate **111** we were delighted to find that tetralone **156** containing a *p*-anisyl substituent successfully underwent the allylation reaction at room temperature, providing 82% yield of the product **165**. This result suggests that the α-proton in these substrates is significantly more acidic than in the 2-arylcyclopentanone substrates, a property that likely results from the inclusion of a second aromatic ring. Alkyl substituents are also tolerated in this procedure although the reactions did require heating at a slightly elevated temperature. Methyl-substituted tetralone **158** provided 74% yield of **167** and 1,4-diketone **162** underwent selective allylation furnishing 92% yield of **168**. Furthermore, the benzylic 1,3-dicarbonyl **160** provided 90% yield of **169**.



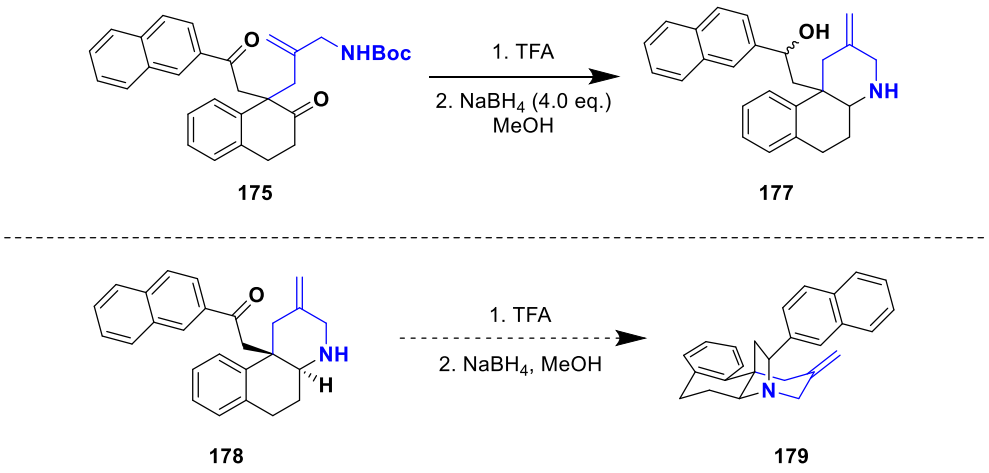
Scheme 78 – Pd-catalysed allylation of 2-tetralone substrates with **15**. [a] Conducted at reflux for 3 h.

Having demonstrated that the Pd-catalysed allylation is widely applicable in the case of tetralone substrates, we set about functionalising these products further to the tricyclic piperidine products. We were pleased to find that all of these products, with the exception of **168**, could be transformed to the Cbz-protected piperidines in generally excellent yields (Scheme 79). The electronic nature of the aryl group does not seem to have an effect on the yield. Additionally, methyl-substituted **167** was tolerated well, providing **174** in 70% yield. As expected, the amine preferentially condenses onto the ketone of **169** to provide the desired product **176** in 80% yield. The relative stereochemistry of the aryl-substituted products is discussed later (Figure 12, p. 103).

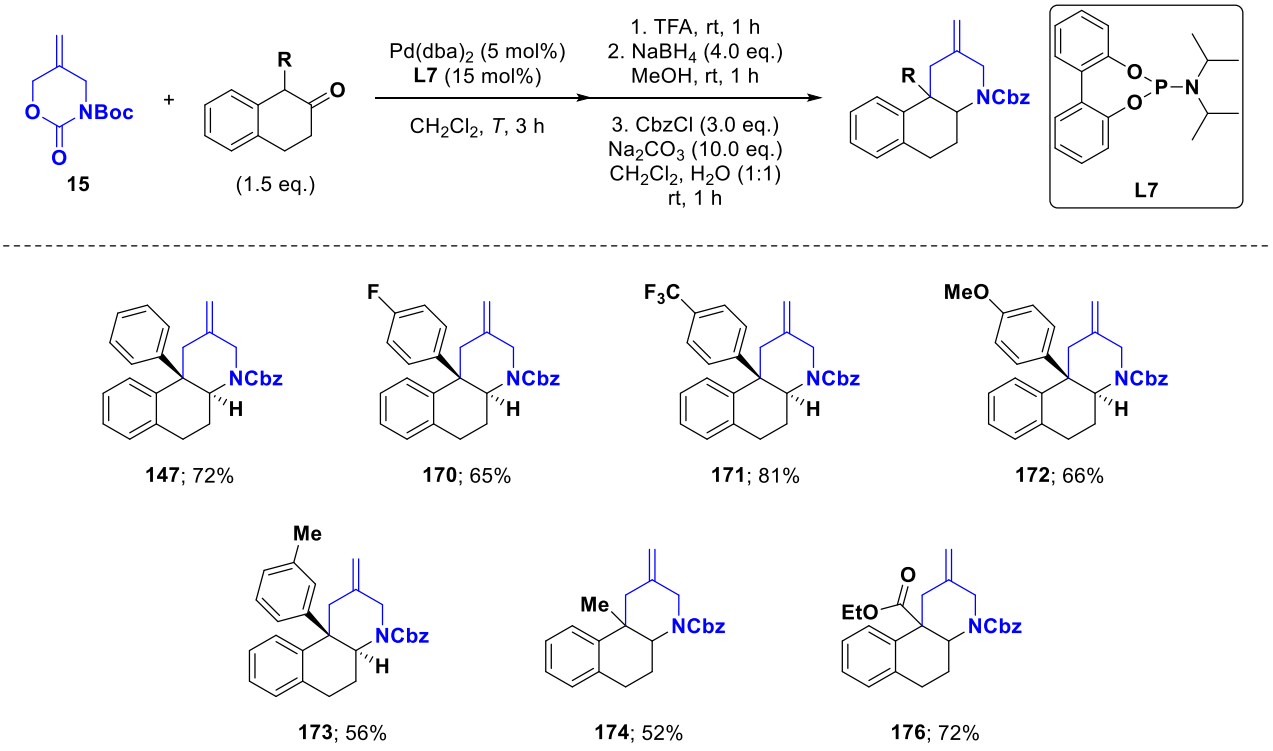


Scheme 79 – Synthesis of Cbz-protected piperidines from allylated tetralones.

We were disappointed that **168** did not undergo the desired transformation smoothly, although this was not entirely unexpected. Whilst we hoped that the amine would regioselectively condense onto the cyclic ketone (6- versus 7-membered ring formation), we overlooked the fact that the ketone would be reduced by $NaBH_4$. This could feasibly provide two different diastereomers of **177** (Scheme 80). Additionally, the newly formed alcohol could also be competitive in the Cbz-protection, affording a complex mixture of compounds. Although we have not yet attempted to do so, we believe that the use of a milder reducing agent would selectively reduce the imine. Additionally, we speculate that, if isolated with *trans*-stereochemistry, stirring the piperidine **178** in TFA, followed by a second reduction step, may well lead to the tetracyclic **179**, which would be a very interesting framework.



Scheme 80 – Proposed fate of substrate **175** under the current reductive amination procedure and hypothetical synthesis of tetracyclic heterocycle **179**.



Scheme 81 – Overall yields of Cbz-protected piperidines from carbamate **15**.

It should be noted that the combined yields of the allylation and reductive amination steps are very respectable for a 4-step sequence yielding such highly functionalised

heterocyclic motifs (Scheme 81). Additionally, all of the steps are operationally simple, requiring little to no heating and the products are easily separable. Furthermore, we have confirmed the relative stereochemistry of the aryl-substituted products through the X-ray crystal structure elucidation of product **172** (Figure 12). This structure clearly shows the relative *trans*-relationship of the aryl substituent with the proton adjacent to the *N*-atom. The stereochemistry of all other aryl-substituted products has been assigned by inference.

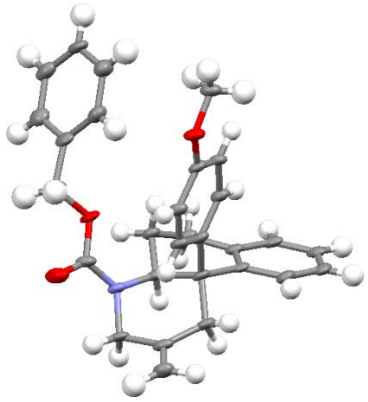
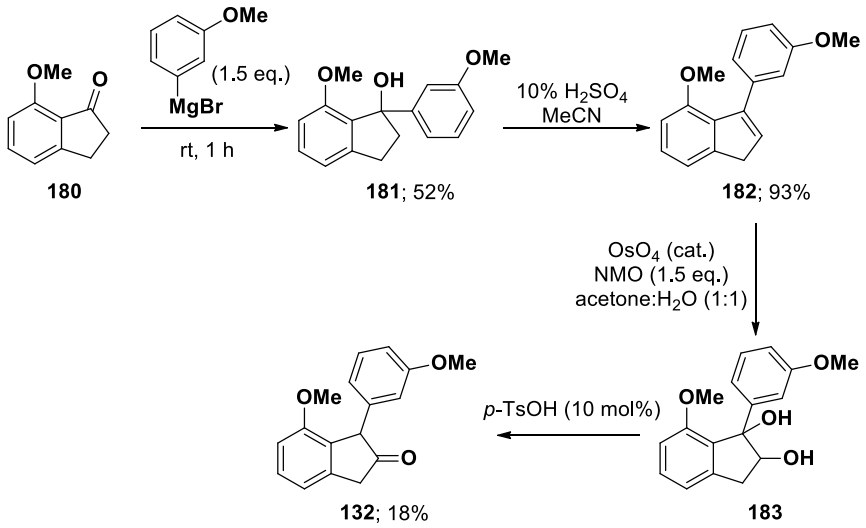


Figure 12 – Crystal structure of **172** showing the relative *trans*-configuration. For crystallographic data see Appendix 6.

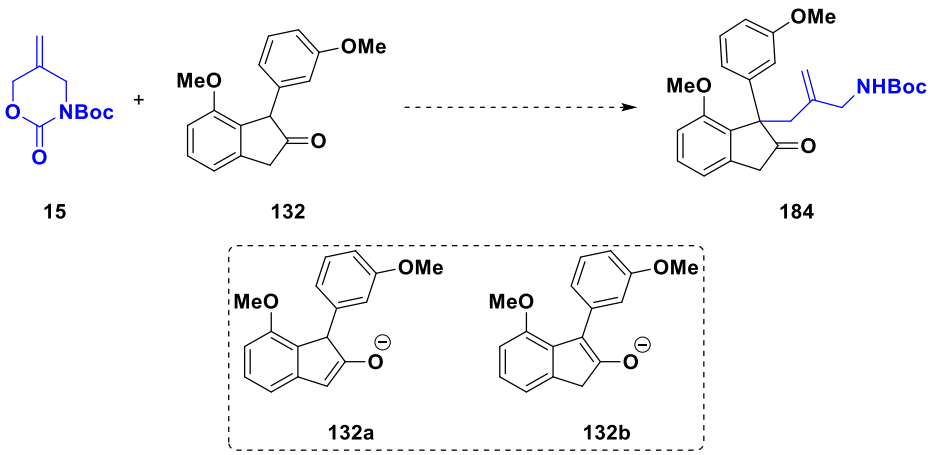
With a robust and reliable procedure in hand, we decided to investigate the application of this synthetically useful methodology towards the synthesis of a natural product. Despite the issues we had previously experienced concerning the reductive amination of allylated indanones, we were keen to revisit the synthesis of the Haouamine A core **130**. We again examined the literature in order to employ a robust method for the required indanone starting material **132** synthesis. Fortunately, Baran and co-workers had previously disclosed this indanone as the starting material for their total synthesis of Haouamine A.[65] Therefore, starting with 7-methoxyindan-1-one **180**, addition of 3-methoxyphenylmagnesium bromide in THF allowed us to isolate the resulting indanol

181 (Scheme 82). Dehydration with H_2SO_4 afforded the indene **182** which was immediately subjected to the dihydroxylation conditions to afford the diol **183**. Finally, dehydration of **183** was achieved by heating this at reflux in the presence of catalytic *p*-TsOH to give indan-2-one **132**. The overall yield of this process was low, but the material obtained was easy to isolate cleanly.



Scheme 82 – Synthesis of indanone **132**.

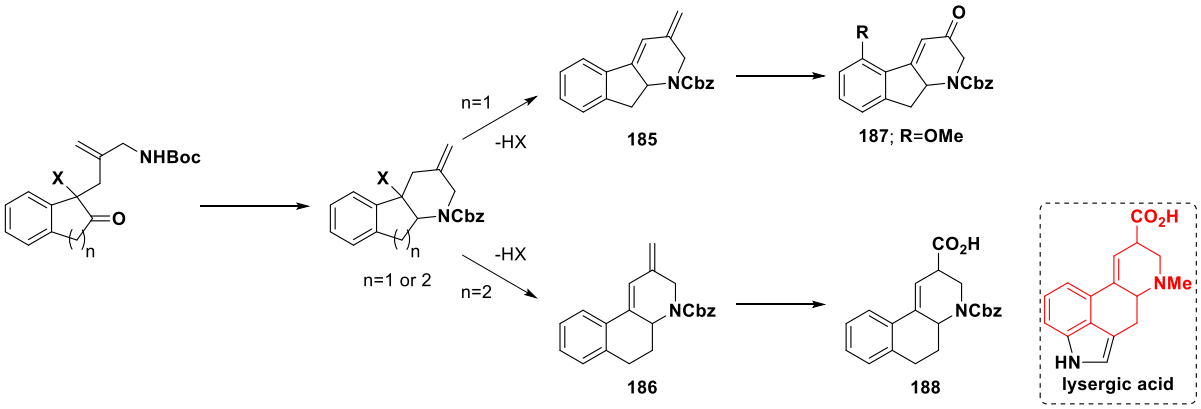
Unfortunately, we were disappointed to find that subjection of this indanone to the Pd-catalysed allylation reaction afforded only trace amounts of the desired product **184** as a component of a complex reaction mixture (Scheme 83). Analysis of mass spectrometry data indicated that there was a significant amount of di-allylated product, and the presence of two mono-allylated products. This suggests that formation of the kinetic enolate **132a** is at least as favourable as formation of the thermodynamic enolate **132b** in our reaction conditions.



Scheme 83 – Attempted Pd-catalysed allylation of **132** gives a complex mixture of products.

In conclusion, we have demonstrated that our newly developed Pd-catalysed allylation reaction can also be applied to the synthesis of polycyclic piperidine products bearing less-activated ketones. The apparent importance of the acidity of the α-proton is evident from the requirement for more forcing conditions in the case of 2-arylcyclopentanone substrates. Additionally, whilst the initial imine products may be unstable, these can readily be converted to the saturated piperidines through a reduction with $NaBH_4$. Expansion to a range of substituted tetralone products proved to be remarkably efficient, providing a range of polycyclic piperidine products in 52-81% overall yields over 4 steps. Whilst the application of this methodology is yet to be uncovered, there are a variety of strategies that can be envisaged to achieve this (Scheme 84). If a suitable leaving group can be incorporated into the indan-2-one and 2-tetralone substrates, then a regioselective elimination could, conceivably, allow access to the cores **185** and **186**. If this could be applied to indanones, then this method would be a viable approach towards the synthesis of Haouamine A, since Fürstner has demonstrated that **187** is a stepping stone towards this goal.[58] Tetralone

core **186** might be further elaborated to allow the synthesis of **188**, which bears some resemblance to lysergic acid, a valuable drug precursor.



Scheme 84 – Proposed strategies to exemplify the chemistry presented in this chapter.

6 – Conclusions and Outlook

In summary, an expedient synthesis of highly functionalised piperidines has been developed. The use of a readily available carbamate **15** under Pd catalysis enables the generation of a Pd-stabilised zwitterion which reacts readily with 1,3-dicarbonyls to afford a range of allylated products. These already highly functionalised products can be further transformed into piperidines through the simple addition of a weak acid. Furthermore, these two processes could be combined into a highly efficient one-pot procedure. Depending on the functionalities that make up the 1,3-dicarbonyl, a range of structurally diverse piperidines can be accessed, some of which possess potential biological interest.

The application of chiral ligands was successfully applied and a range of spirocyclic piperidines can be synthesised in good yields and excellent enantioselectivities. Unfortunately, the universal application of these conditions across a range of substrates was unsuccessful, rendering the process substrate-specific. The identification of a ligand which can be used to synthesise a range of enantioenriched piperidines from a plethora of substrates would be highly desirable, but may require a more in-depth knowledge of the shape of the catalyst and the mode in which the mechanism operates.

Utilisation of a substituted carbamate **96** allows the preparation of piperidine products which contain a trisubstituted alkene. These products can be prepared with high *E*-alkene selectivity and excellent enantioselectivity. Unfortunately, the scope of this procedure at present is limited, and further studies should seek to extend this

methodology to other 1,3-dicarbonyl substrates. These reactions may also offer some insight into the mechanism of the Pd-catalysed allylation reaction.

Successful extension of the racemic procedure to a range of 2-arylketones was also successful. Whilst 2-arylcyclopentanones perform well in the allylation reaction, they appear to be governed by the electron nature of the aryl ring. In particular, electron-rich aromatics reduce the efficiency of this step. Transformation of the allylated products to piperidines required the *in situ* reduction of the initially formed imine with $NaBH_4$. This caused issues with the purification of the piperidine products, and the products were obtained in poor to moderate yields.

Extending the 2-arylcyclopentanone skeleton to 1-phenylindan-2-one was successful and the reaction could be performed on scale without affecting the yield. However, despite extensive efforts in this area, the reductive amination product could not be isolated cleanly or in good yield. A study of the origin of this issue led to the employment of a series of 1-aryl-2-tetralones in this procedure which performed exceptionally well in the allylation reaction. Additionally, the reductive amination of these products was successful, and the piperidines could be isolated as the Cbz-protected amine products in excellent yields. Incorporation of 1-alkyl groups was also successful in this application.

Unfortunately, extension of this methodology to the synthesis of Haouamine A was unsuccessful and an alternative procedure must be sought. This represents the first example of non-selective Pd-catalysed allylation that we have witnessed in these studies.

In the future, it is hoped that this work might allow access to a valuable, pharmaceutically relevant core. An ideal target would be lysergic acid which is a precursor to a vast library of psycho-active drugs.

Furthermore, mechanistic elucidation would be a valuable aid in the discovery of new reactivity. The proposed mechanism in this thesis (Figure 5 – Reaction scheme and proposed mechanism of palladium-catalysed 1,3-dicarbonyl allylation.) relies on the ability of a proposed *N*-centred anion to deprotonate acidic substrates. If this is true, calculation of the pK_a might allow the identification of alternative pronucleophiles that can be incorporated into the allylation reaction.

The seminal work of Alper, Trost, Aggarwal and others has demonstrated that Pd-stabilised zwitterions containing a *N*-centred anion can be utilised in a variety of cycloadditions for the construction of 5- and 6-membered heterocycles (see Section 1.3.2).[33–38,41,42] If our proposed intermediate can participate in such a reaction, this would constitute a one-pot synthesis of 6- or even 7-membered rings. Moreover, it would allow the incorporation of alternative substituents on the final products.

7 – Experimental Section

7.1 – General Considerations

All non-aqueous reactions were conducted in flame-dried glassware under an inert atmosphere of dry nitrogen or argon unless stated otherwise. Diethyl ether, DMF, THF and toluene were dried before use over an alumina column. CH_2Cl_2 was distilled from calcium hydride. Commercially available materials were acquired from Acros, Aldrich, Alfa Aesar, Fluorochem, Fluka, Manchester Organics, Lancaster and Strem Chemicals and were used as supplied, or following purification according to the procedures described by Perrin and Armarego.[66]

Flash column chromatography was carried out according to the method of Still[67] using silica gel 60 Å (0.040-0.063 mm) (Fluorochem) using head pressure by means of a compressed air line. Thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (Merck silica Kieselgel 60 F_{254}). Spots were made visible either by the quenching of UV fluorescence or by staining with a potassium permanganate solution.

^{1}H NMR spectra were recorded on Bruker AVIII HD 400 (400 MHz), Bruker AVI 400 (400 MHz), Bruker AMX-400 (400 MHz) or DPX-400 (400 MHz) supported by an Aspect 3000 data system and referenced to the residual solvent peak ($CDCl_3$: δ 7.26 ppm). Signal positions were recorded in δ ppm with the abbreviations s, d, t, q, br and m denoting singlet, doublet, triplet, quartet, broad and multiplet respectively and combinations of these were used to denote higher order multiplicities. ^{13}C NMR spectra were recorded on a Bruker AVIIIHD-400 (101 MHz) or a Bruker AV1-400 (100

MHz) and were referenced to the residual solvent peak ($CDCl_3$: δ 77.16 ppm). Signal positions were recorded in δ ppm. All signals were recorded as singlets unless otherwise stated. ^{19}F NMR spectra were recorded on the Bruker AVIIIHD-400 (377 MHz) and are uncorrected. ^{31}P NMR spectra were recorded on the Bruker AVIIIHD-400 (162 MHz) and are uncorrected. All NMR chemical shifts are reported in ppm and all coupling constants, *J*, are quoted in Hz.

Infrared spectra were recorded on a Perkin-Elmer Paragon 100 FTIR spectrometer. Spectra were analysed as thin films on an ATR surface or as thin films between KBr plates. The most intense peaks and structurally important peaks are quoted. Absorption maxima (ν_{max}) are recorded in wavenumbers (cm^{-1}).

High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES+) or a MicroMass Prospec operating in FAB (FAB+), EI (EI+) or CI (CI+) mode.

Melting points were obtained using a Gallenkamp melting apparatus and are uncorrected.

“Petrol” refers to the fraction boiling in the range 40-60 °C unless otherwise stated. “Ether” refers to diethyl ether.

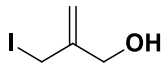
Enantioselectivities were determined by high performance liquid chromatography (HPLC) analysis employing a Gilson HPLC chain with an ABI Analytical Spectroflow 738 UV or SPD-10 Shimadzu UV-vis detector (λ 225 or 256 nm), using a mixture of hexane and propan-2-ol as the mobile phase and Phenomenex Lux 3μ Cellulose-1 or

Phenomenex Lux 3μ Cellulose-2 or Chiralpak-IA as the stationary phase. Mobile phase flow, unless otherwise stated, was 1.0 mL/min.

7.2 – Synthesis of Starting Materials

7.2.1 – Conjunctive Reagent Precursors

2-(Iodomethyl)-prop-2-en-1-ol (44)

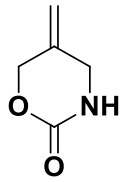


To a stirring solution of 2-methylenepropane-1,3-diol (12.0 g, 136 mmol), triphenylphosphine (39.3 g, 150 mmol) and imidazole (10.2 g, 150 mmol) in a 1:1 mixture of dichloromethane/ethyl acetate (300 mL) at r.t. was added iodine (34.6 g, 136 mmol) portion-wise. The reaction mixture was left to stir for 18 h at r.t. before being diluted in ethyl acetate (100 mL) followed by washing with water (200 mL). The aqueous layer was extracted with ethyl acetate (3 × 25 mL) and the organic layers combined, dried ($MgSO_4$) and concentrated to yield crude material which was purified by flash column chromatography on silica gel (20% ethyl acetate in petroleum ether) to furnish the product as a colourless oil (14.1 g, 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 – 5.33 (m, 1H, C=C$\underline{H_A}$$H_B$), 5.21 – 5.19 (m, 1H, C=C$H_A$$\underline{H_B}$), 4.30 (d, *J* = 5.5 Hz, 2H, OC$\underline{H_2}$), 3.97 (d, *J* = 0.5 Hz, 2H, IC$\underline{H_2}$), 2.10 (t, *J* = 5.5 Hz, 1H, O*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.7, 114.1, 63.7, 5.9.

The data are consistent with those reported in the literature.[49]

5-Methylene-1,3-oxazinan-2-one (46)



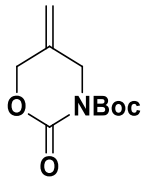
To a stirring solution of 2-(iodomethyl)-prop-2-en-1-ol **44** (10.38 g, 52.3 mmol) in toluene (150 mL) was added silver cyanate (11.8 g, 78.4 mmol) and the resulting mixture heated at reflux for 16 h in the absence of light. Upon completion, the reaction mixture was filtered through a bed of celite with ether (20 mL) and the residue concentrated. Flash column chromatography on silica gel (90% ethyl acetate in petroleum ether) afforded the desired product as white crystals (3.68 g, 62%).

On a separate run, the same procedure was followed, as above, using **44** (14.1 g, 71 mmol), AgOCN (16.0 g, 107 mmol) in toluene (140 mL). The crude material was deemed pure enough and was used without purification (6.19 g, 77%).

m.p. 88-90 °C (lit.[49] 90-91 °C); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.43 (br s, 1H, N*H*), 5.26 (s, 1H, C=C*H*$_A$H$_B$), 5.25 (s, 1H, C=CH$_A$*H*$_B$), 4.70 (s, 2H, OC*H*$_2$), 4.03-3.99 (m, 2H, NC*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.1, 133.2, 113.8, 70.0, 45.3.

The data are consistent with those reported in the literature.[49]

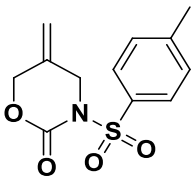
***Tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (15)**



To a stirring solution of 5-methylene-1,3-oxazinan-2-one **46** (6.19 g, 55 mmol) and 4-diethylaminopiperidine (1.23 g, 11 mmol) in CH_2Cl_2 (75 mL) was added a solution of di-*tert*-butyl dicarbonate (23.9 g, 109.3 mmol) in CH_2Cl_2 (25 mL) was added and the reaction mixture left to stir at r.t. for 16 h. Upon completion, the solvent was removed *in vacuo* and the crude residue purified *via* flash column chromatography on silica gel (25% ethyl acetate in petrol) to yield the desired product as a yellow oil which crystallised upon standing in the freezer to an off-white solid (10.3 g, 88%).

m.p.: 35 – 37 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 1791, 1750, 1652, 1266; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.21 – 5.19 (m, 1H, C=C$\underline{H_A}$$H_B$), 5.19 – 5.17 (m, 1H, C=C$H_A$$\underline{H_B}$), 4.64 (s, 2H, OC$\underline{H_2}$), 4.32 – 4.29 (m, 2H, NC$\underline{H_2}$), 1.52 (s, 9H, C(CH_3)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 152.0, 150.9, 134.6, 112.9, 83.9, 69.8, 48.6, 28.0; **HRMS (ESI$^+$)** $C_{10}H_{16}NO_4$ requires $M+H^+$ 214.1079, found 214.1073.

5-Methylene-3-tosyl-1,3-oxazinan-2-one (47)



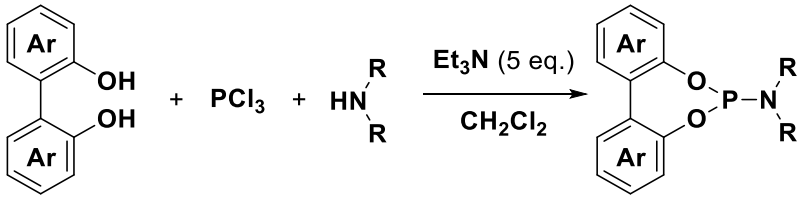
To a stirring solution of 5-methylene-1,3-oxazinan-2-one **46** (505 mg, 4.46 mmol) in THF (20 mL) at -78 °C was added ^{n}BuLi (3.70 mL, 1.82 M in hexanes, 6.69 mmol)

dropwise, followed by careful addition of *p*-tolylsulfonyl chloride (1.70 g, 8.92 mmol) and the mixture left to stir for 10 mins. The cold bath was removed and the mixture allowed to stir at rt for 2 h. The reaction was quenched by the addition of sat. NH_4Cl (20 mL) and water (15 mL) and the organics were extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. Flash colum chromatography on silica gel (20% ethyl acetate in petrol) afforded the product (618 mg, 52%) as a white solid.

m.p.: 105-110 °C; **FTIR ν_{max} (thin film/cm^{-1})** 1724, 1352, 1231, 1173; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.34 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.32 (s, 1H, C=C*H*$_A$H$_B$), 5.30 – 5.25 (m, 1H, C=CH$_A$*H*$_B$), 4.67 (s, 2H, OC*H*$_2$), 4.52 – 4.50 (m, 2H, NC*H*$_2$), 2.44 (s, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 149.6, 145.5, 134.7, 132.6, 129.7, 129.1, 115.3, 70.5, 49.9, 21.8; **HRMS (ESI$^+$)** $C_{12}H_{14}NO_4S$ requires M+H$^+$ 268.0644, found 268.0648.

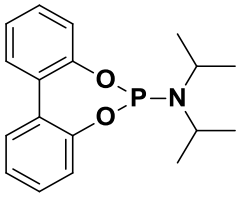
7.2.2 – Phosphoramidite Ligands

General Procedure A – Synthesis of Phosphoramidite Ligands



To a stirring solution of PCl_3 (1 eq.) in CH_2Cl_2 at 0 °C was added triethylamine (5 eq.) drop-wise and the reaction mixture left to stir for 5 minutes. The solution was allowed to warm to room temperature and the amine or amine hydrochloride (1 eq.) was added slowly and the resulting mixture left to stir for 5 hours at rt. (*R*)-BINOL (1 eq.) was added slowly at 0 °C to attenuate the resulting exotherm and the reaction mixture was stirred at rt for 16 h. The solvent was removed *in vacuo* and the crude material purified by flash column chromatography on silica gel to afford the desired phosphoramidite.

N,N-Diisopropyldibenzo[d,f][1,3,2]dioxaphosphepin-6-amine (L7)

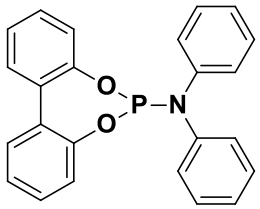


Prepared following General Procedure A using *N,N*-diisopropylamine (500 mg, 4.94 mmol) and 2,2'-biphenol (920 mg, 4.94 mmol). Flash column chromatography on silica gel (20% dichloromethane in petrol) afforded the product as a colourless oil which crystallised upon standing to white crystals (1.25 g, 80%).

m.p.: 78.5 – 81.5 °C (lit.[50] 79 – 80 °C); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (dd, *J* = 7.5, 1.5 Hz, 2H, Ar*H*), 7.33 (td, *J* = 7.5, 1.5 Hz, 2H, Ar*H*), 7.24 – 7.16 (m, 4H, Ar*H*), 3.58 – 3.44 (dhept., *J* = 10.5, 7.0 Hz, 2H, C*H*(Me)$_2$), 1.22 (d, *J* = 7.0 Hz, 12H, CH(C*H*$_3$)$_2$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 152.1 (d, *J* = 5.5 Hz), 131.0 (d, *J* = 3.0 Hz), 129.8, 129.1, 124.3, 122.3, 44.7 (d, *J* = 12.5 Hz), 24.6 (d, *J* = 8.0 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)** δ 152.0.

These data are consistent with those reported in the literature.[50]

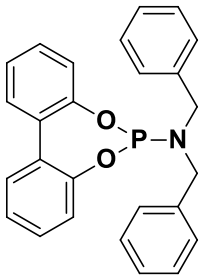
***N*,*N*-Diphenyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (L15)**



Prepared following General Procedure A using diphenylamine (846 mg, 5.0 mmol), 2,2'-biphenol (931 mg, 5.0 mmol), PCl_3 (436 µL, 5.0 mmol) and Et_3N (3.48 mL, 25.0 mmol) in CH_2Cl_2 (10 mL). Flash column chromatography on silica gel (20% dichloromethane in petrol) afforded the product as a white solid (1.59 g, 83%).

m.p.: 136-140 °C (dec.); **FTIR** ν_{max} (thin film/cm^{-1}) 3067, 1592, 1485, 1186, 883; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 (dd, *J* = 7.5, 2.0 Hz, 2H, Ar*H*), 7.29 – 7.14 (m, 12H, Ar*H*), 7.13 – 7.01 (m, 4H, Ar*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.9 (d, *J* = 5.5 Hz), 144.7 (d, *J* = 10.5 Hz), 130.8 (d, *J* = 3.5 Hz), 129.8, 129.1, 128.9, 126.6 (d, *J* = 7.5 Hz), 124.7 (d, *J* = 12.5 Hz), 122.3, 118.0; **^{31}P NMR (162 MHz, $CDCl_3$)** δ 138.2; **HRMS (ESI^{+})** $C_{24}H_{18}NO_2P$ requires M+H^{+} 348.1148, found 348.1153.

***N*,*N*-Dibenzyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (L16)**

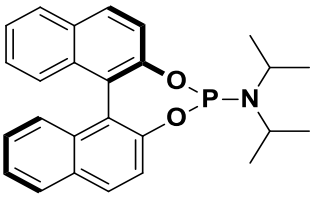


Prepared following General Procedure A using dibenzylamine (986 mg, 5.0 mmol), 2,2'-biphenol (931 mg, 5.0 mmol), PCl_3 (436 µL, 5.0 mmol) and Et_3N (3.48 mL, 25.0 mmol) in CH_2Cl_2 (10 mL). Flash column chromatography on silica gel (20% dichloromethane in petrol) afforded the product as a white solid (1.23 g, 60%).

m.p. 91-95 °C (lit.[68] 89-91 °C); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (dd, *J* = 7.5, 1.5 Hz, 2H, Ar*H*), 7.41 – 7.35 (m, 4H, Ar*H*), 7.36 – 7.29 (m, 8H, Ar*H*), 7.23 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.16 (d, *J* = 8.0 Hz, 2H, Ar*H*), 3.96 (d, *J* = 10.0 Hz, 4H, C*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 151.4 (d, *J* = 5.0 Hz), 138.1, 131.2 (d, *J* = 3.0 Hz), 129.8, 129.4, 128.9, 128.5, 127.4, 124.7, 122.0, 48.3 (d, *J* = 20.5 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)** δ 145.6.

These data are consistent with those reported in the literature.[68]

(11b*R*)-*N*,*N*-Diisopropyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (L8)

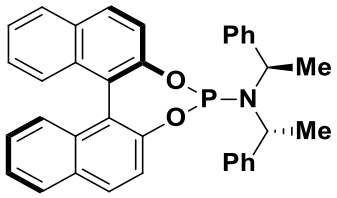


Prepared following General Procedure A using diisopropylamine (122 µL, 1.67 mmol), (*R*)-BINOL (478 mg, 1.67 mmol), PCl_3 (146 µL, 1.67 mmol) and Et_3N (1.16 mL, 8.35 mmol) in CH_2Cl_2 (10 mL). Flash column chromatography on silica gel (20% dichloromethane in petrol) afforded the product as a white solid (236 mg, 65%).

m.p.: 171-175 °C (dec.) (lit. not reported); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.90 (m, 3H, Ar*H*), 7.51 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar*H*), 7.47 – 7.36 (m, 4H, Ar*H*), 7.34 – 7.19 (m, 3H, Ar*H*), 3.46 – 3.30 (dhept., *J* = 11.0, 7.0 Hz, 2H, 2 × C*H*Me$_2$), 1.22 (d, *J* = 7.0 Hz, 6H, 2 × CH(C*H*$_3$)(CH$_3$)), 1.18 (d, *J* = 7.0 Hz, 6H, 2 × CH(CH$_3$)(C*H*$_3$)); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.6 (d, *J* = 7.0 Hz), 150.3, 133.0 (d, *J* = 1.5 Hz), 132.9, 131.4, 130.6, 130.3, 129.5, 128.4, 128.4, 127.3 (2 × C), 126.0, 125.9, 124.7, 124.4, 124.1 (d, *J* = 5.5 Hz), 122.62, 122.55 (d, *J* = 1.5 Hz), 122.0 (d, *J* = 2.0 Hz), 44.9 (d, *J* = 12.5 Hz), 24.6 (d, *J* = 8.5 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)** δ 151.7; **$[\alpha]_D^{23}$** -504.7 (*c* = 0.97, $CHCl_3$) [lit.[69] +591 (*c* = 0.68, $CHCl_3$) for the opposite enantiomer].

These data are consistent with those reported in the literature.[69]

(11b*R*)-N,N-Bis((*R*)-1-phenylethyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (L9)



To a solution of (*R*)-BINOL (5.00 g, 17.46 mmol) in PCl_3 (50 mL) was added NMP (10 µL) and the resulting mixture was heated at reflux for 20 min. The excess PCl_3 was removed under reduced pressure and the resulting yellow foam was dissolved in PhMe (25 mL). The solution was concentrated again under reduced pressure to remove residual PCl_3. The yellow foam thus obtained was dissolved in PhMe to a concentration of 0.73 M to give a solution of (*R*)-BINOL-P-Cl **191**.

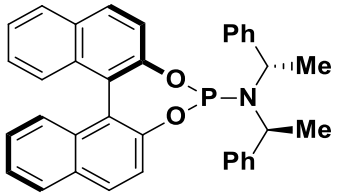
To a solution of (+)-bis((*R*)-1-phenylethyl)amine (870 µL, 3.80 mmol) in THF (18 mL) at -78 °C was added ^{n}BuLi (2.07 mL, 2.02 M, 4.18 mmol) drop-wise and left to stir for 15 minutes before stirring at 0 °C for 5 minutes, and then at -78 °C for an additional 1 hour. A solution of (*R*)-BINOL-P-Cl **191** (7.8 mL, 0.73 M in PhMe, 5.70 mmol) was added dropwise and left to stir for 16 hours. The solvent was removed *in vacuo* and the crude residue purified by flash column chromatography on silica gel (20% dichloromethane in petrol) to afford the product (1.256 g, 62%) as white crystals.

m.p.: 98-101 °C (lit. not reported); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.13 – 7.73 (m, 6H, Ar*H*), 7.70 – 7.25 (m, 14H, Ar*H*), 7.06 – 6.86 (m, 2H, Ar*H*), 4.50 (dq, *J* = 11.0, 7.0 Hz, 2H, C*H*Me), 1.77 (d, *J* = 7.0 Hz, 6H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.6 (d, *J* = 10.0 Hz), 149.9, 143.2, 133.0 (d, *J* = 1.5 Hz), 132.9, 131.5, 130.6, 130.5, 129.7, 128.4,

128.2 (2 × C), 128.1, 127.9, 127.4, 127.3, 126.8, 126.2, 126.0, 124.9, 124.5, 124.3 (d, *J* = 5.5 Hz), 122.7, 122.5 (d, *J* = 2.0 Hz), 121.3 (d, *J* = 2.5 Hz), 54.7 (d, *J* = 10.5 Hz), 23.2 (d, *J* = 12.0 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)** δ 150.5; **$[\alpha]_D^{23}$** -23 (*c* = 0.96, $CHCl_3$) [lit.[70] +11 (*c* = 0.79, $CHCl_3$) for the opposite enantiomer].

These data are consistent with those reported in the literature.[70]

(11b*R*)-*N*,*N*-Bis((*S*)-1-phenylethyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (L10)



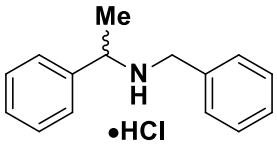
Prepared following General Procedure A using (-)-bis((*S*)-1-phenylethyl)amine (500 mg, 2.22 mmol)), (*R*)-BINOL (635 mg, 2.22 mmol), PCl_3 (194 µL, 2.22 mmol) and triethylamine (1.55 mL, 11.09 mmol). Flash column chromatography on silica gel (20% dichloromethane in petrol) afforded the desired product (1.02 g, 85%) as white crystals.

m.p.: 105 – 110 °C (lit.[71] 102-104 °C); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.93 – 7.88 (m, 2H, Ar*H*), 7.60 (d, *J* = 9.0 Hz, 1H), 7.46 – 7.37 (m, 4H, Ar*H*), 7.32 – 7.20 (m, 3H, Ar*H*), 7.17 – 7.06 (m, 10H, Ar*H*), 4.51 (dq, *J* = 14.0, 7.0 Hz, 2H, 2 × NC*H*), 1.73 (d, *J* = 7.0 Hz, 6H, 2 × CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.2 (d, *J* = 7.5 Hz), 149.7, 143.0, 132.9 (d, *J* = 5.5 Hz), 131.6, 130.6, 130.4, 129.6, 128.5, 128.3, 128.1 (2 × C), 127.9, 127.3 (2 × C), 126.8, 126.1 (2 × C), 124.9, 124.6, 124.2 (d, *J* = 5.5 Hz), 122.6, 122.5 (d, *J* = 1.5 Hz), 121.9 (d, *J* = 2.5 Hz), 52.5 (d, *J* = 12.0

Hz), 22.1 (br); **^{31}P NMR (162 MHz, $CDCl_3$)** δ 145.4; **$[\alpha]_D^{23}$** -436.0 (*c* = 1.00, $CHCl_3$) [lit.[70] -456 (*c* = 0.79, $CHCl_3$)].

These data are consistent with those reported in the literature.[70,71]

_N_-Benzyl-1-phenylethanamine hydrochloride (77)



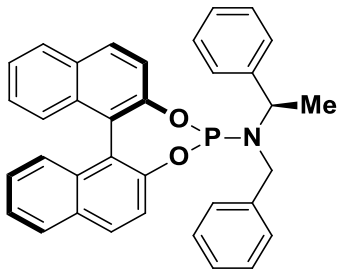
For the (*R*)-amine: To a solution of benzaldehyde (2.00 g, 18.85 mmol) in toluene (20 mL) was added (*R*)-1-phenylethanamine (2.40 mL, 18.85 mmol) and the resulting solution was left to stir for 1 h at reflux. Upon cooling, the solvent was removed and the imine (3.99 g, 100%) was obtained as a colourless oil in quantitative yield. A portion of this imine (2.00 g, 9.56 mmol) was dissolved in MeOH (30 mL). $NaBH_4$ (362 mg, 9.56 mmol) was added and the resulting reaction mixture was left to stir for 1 h. Upon completion, sat. NH_4Cl (30 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting residue was dissolved in Et_2O (30 mL) and HCl (9.56 mL, 2M in Et_2O, 19.12 mmol)) was added dropwise. The resulting suspension was left to stir at rt for 30 min. The white precipitate was filtered, washed with cold Et_2O and dried to afford the product (2.12 g, 89 %) as a white solid.

For the (*S*)-amine: Following the above procedure using benzaldehyde (1.00 g, 9.42 mmol) and (*S*)-1-phenylethanamine (1.20 mL, 9.42 mmol). The imine (2.04 g, 100%) was obtained quanitatively as a colourless oil. A portion of the imine (1.80 g, 8.60

mmol) was subjected to the above conditions with $NaBH_4$ (651 mg, 17.20 mmol). The resultant amine hydrochloride (1.78 g, 83%) was obtained as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (br, 1H, N*H*), 10.28 (br, 1H, N*H*), 7.57 (d, *J* = 7.0 Hz, 2H, Ar*H*), 7.50 – 7.24 (m, 8H, Ar*H*), 4.08 – 3.98 (m, 1H, C*H*Ar), 3.85 (d, *J* = 13.0 Hz, 1H, CH_AH$_B$), 3.65 – 3.53 (m, 1H, CH$_A$$H_B$), 1.78 (d, *J* = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.2, 130.9, 130.2, 129.5, 129.3 (2 × C), 128.9, 128.2, 57.4, 48.5, 20.9; **$[\alpha]_D^{23}$** +50.5 (*c* = 1.07, $CHCl_3$) for (*R*)-amine; -50.6 (*c* = 0.89, $CHCl_3$) for (*S*)-amine.

(11b*R*)-*N*-Benzyl-*N*-((*R*)-1-phenylethyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxa-phosphepin-4-amine (L11)



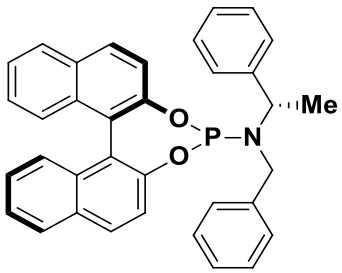
Prepared following General Procedure A using (*R*)-*N*-benzyl-1-phenylethanamine hydrochloride (208 mg, 0.84 mmol), (*R*)-BINOL (241 mg, 0.84 mmol), PCl_3 (73 µL, 0.84 mmol) and Et_3N (585 µL, 4.20 mmol). Flash column chromatography on silica gel (25% dichloromethane in petrol) afforded the product (326 mg, 74%) as white crystals.

m.p. 100-105 °C (lit. not reported); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.94 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.81 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.75 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.66 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.57 – 7.30 (m, 9H, Ar*H*), 7.30 – 7.10 (m, 7H, Ar*H*), 7.04 (d, *J* = 9.0 Hz, 1H, Ar*H*), 4.15 – 4.06 (m, 1H, NC*H*Me), 4.03 (d, *J* = 15.0

Hz, 1H, NC$\underline{H_A}$H$_B$), 3.02 (d, *J* = 15.0 Hz, 1H, NCH$_A$$\underline{H_B}$), 1.79 – 1.64 (m, 3H, C$\underline{H_3}$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 150.3 (d, *J* = 5.0 Hz), 149.8, 143.9, 138.8, 133.0 (d, *J* = 1.0 Hz), 132.6, 131.6, 130.7, 130.4, 130.3, 128.7, 128.6, 128.5, 128.3, 127.6, 127.5 (d, *J* = 1.0 Hz), 127.2, 127.1, 126.2, 126.1, 124.9, 124.3 (d, *J* = 5.0 Hz), 124.6, 122.6 (d, *J* = 1.5 Hz), 122.5 (d, *J* = 1.0 Hz), 121.8, 57.7 (d, *J* = 24.0 Hz), 48.4 (d, *J* = 3.5 Hz), 23.6 (d, *J* = 32.5 Hz); **^{31}P NMR (162 MHz, CDCl$_3$)** δ 141.5; **[α]$_D^{23}$** -215.5 (*c* = 0.97, CHCl$_3$) (lit. not reported).

These data are consistent with those reported in the literature.[72]

(11b*R*)-*N*-Benzyl-*N*-((*S*)-1-phenylethyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (L12)

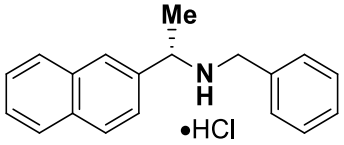


Prepared following General Procedure A using (*S*)-*N*-benzyl-1-phenylethanamine hydrochloride (423 mg, 2.00 mmol), (*R*)-BINOL (573 mg, 2.00 mmol), PCl$_3$ (174 µL, 2.00 mmol) and Et$_3$N (1.39 mL, 10.0 mmol). Flash column chromatography on silica gel (20% dichloromethane in petrol) afford the product (737 mg, 70%) as a white powder.

m.p.: 95 – 99 °C (dec.); **FTIR** ν_{max} (thin film/cm^{-1}) 3059, 3029, 1590, 1506, 1494, 1463, 1327, 1229, 1203, 1070**; ^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.00 (d, *J* = 9.0 Hz, 1H, Ar$\underline{H}$), 7.93 (d, *J* = 8.0 Hz, 1H, Ar$\underline{H}$), 7.81 (d, *J* = 8.0 Hz, 1H, Ar$\underline{H}$), 7.75 (d, *J* = 9.0 Hz, 1H,

Ar*H*), 7.62 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.46 – 7.38 (m, 5H, Ar*H*), 7.38 – 7.30 (m, 4H, Ar*H*), 7.30 – 7.13 (m, 8H, Ar*H*), 4.68 (dq, *J* = 14.0, 7.0 Hz, 1H, NC*H*Me), 3.96 (dd, *J* = 15.5, 4.5 Hz, 1H, NC$H_A$$H_B$), 3.46 (dd, *J* = 15.5, 6.0 Hz, 1H, NC$H_A$$H_B$), 1.39 (d, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.0 (d, *J* = 5.5 Hz), 149.5, 141.9 (d, *J* = 2.5 Hz), 122.3 (d, *J* = 2.5 Hz), 140.7 (d, *J* = 0.5 Hz), 132.9 (d, *J* = 1.0 Hz), 132.7, 131.5, 130.7, 130.4, 130.0, 128.5, 128.4, 128.3, 128.2, 127.4, 127.2, 127.1, 126.9, 126.2, 126.1, 124.9, 124.6, 124.2 (d, *J* = 5.0 Hz), 122.4 (d, *J* = 1.0 Hz), 121.8, 56.0 (d, *J* = 31.0 Hz), 47.2 (d, *J* = 4.5 Hz), 21.0 (d, *J* = 11.5 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)** δ 144.8; **HRMS (ESI$^+$)** $C_{35}H_{29}NO_2P$ requires $M+H^+$ 526.1936, found 526.1930; **$[\alpha]_D^{23}$** -219.6 (*c* = 1.02, $CHCl_3$).

(*S*)-*N*-Benzyl-1-(naphthalen-2-yl)ethanamine hydrochloride (78)

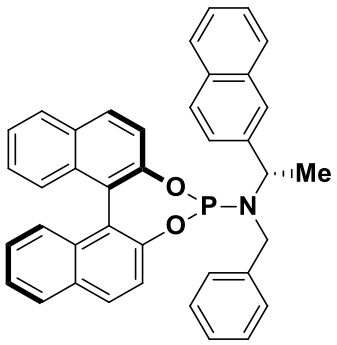


To a solution of benzaldehyde (310 mg, 2.92 mmol) in toluene (4 mL) was added (*S*)-1-(naphthalen-2-yl)ethanamine (500 mg, 2.92 mmol) and the resulting solution was left to stir for 1 h at reflux. Upon cooling, the solvent was removed and the residue was dissolved in MeOH (10 mL). $NaBH_4$ (103 mg, 2.72 mmol) was added and the resulting reaction mixture was left to stir for 1 h. Upon completion, sat. NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting residue was dissolved in Et_2O (11 mL) and HCl (3.00 mL, 2M in Et_2O, 6.00 mmol) was added dropwise. The resulting suspension was left to stir at rt for 30 min. The white

precipitate was filtered, washed with cold Et_2O and dried to afford the product (746 mg, 86%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (br, 1H, N*H*), 10.39 (br, 1H, N*H*), 7.96 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.93 – 7.80 (m, 4H, Ar*H*), 7.56 – 7.50 (m, 2H, Ar*H*), 7.49 – 7.44 (m, 2H, Ar*H*), 7.36 – 7.26 (m, 3H, Ar*H*), 4.28 – 4.17 (m, 1H, C*H*Ar), 3.90 (d, *J* = 13.5 Hz, 1H, CH_AH$_B$), 3.67 – 3.58 (m, 1H, CH$_A$$H_B$), 1.87 (d, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 133.6, 133.5, 133.3, 131.0, 130.2, 129.7, 129.3, 128.9, 128.3, 128.1, 127.9, 127.0, 126.8, 124.9, 57.6, 48.6, 20.9; **[α]$_D^{23}$** -77.5 (*c* = 0.87, $CHCl_3$).

(11b*R*)-*N*-Benzyl-*N*-((*S*)-1-(naphthalen-2-yl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (L13)

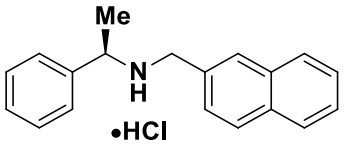


Prepared following General Procedure A using (*S*)-*N*-benzyl-1-(naphthalen-2-yl)ethanamine hydrochloride (260 mg, 0.873 mmol), (*R*)-BINOL (250 mg, 0.873 mmol), PCl_3 (76 µL, 0.873 mmol) and Et_3N (608 µL, 4.365 mmol). Flash column chromatography on silica gel (20% CH_2Cl_2 in petrol) afforded the product (406 mg, 71%) as white crystals.

m.p.: 111-114 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 2922, 1590, 1463, 1229, 948, 820; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.96 – 7.77 (m, 5H, Ar*H*), 7.73

(d, *J* = 9.0 Hz, 2H, Ar*H*), 7.68 – 7.61 (m, 2H, Ar*H*), 7.54 – 7.47 (m, 2H, Ar*H*), 7.45 – 7.38 (m, 1H, Ar*H*), 7.37 – 7.30 (m, 3H, Ar*H*), 7.30 – 7.15 (m, 8H, Ar*H*), 4.82 (dq, *J* = 14.0, 7.0 Hz, 1H, NC*H*Me), 3.98 (dd, *J* = 15.5, 4.5 Hz, 1H, NCH_AH_B), 3.46 (dd, *J* = 15.5, 6.0 Hz, 1H, NCH_AH_B), 1.53 – 1.44 (d, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.1 (d, *J* = 6.0 Hz). 149.5, 140.6, 139.4 (d, *J* = 2.5 Hz), 133.3, 133.0, 132.9, 132.7, 131.6, 130.7, 130.4, 130.1, 128.5, 128.3, 128.2, 128.2, 127.8, 127.2, 127.1, 127.0, 126.9, 126.5, 126.3, 126.2, 126.1, 126.1, 125.0, 124.7, 124.2 (d, *J* = 5.0 Hz), 122.4, 122.3 (d, *J* = 2.0 Hz), 121.8, 56.1 (d, *J* = 31.5 Hz), 47.4 (d, *J* = 4.0 Hz), 21.1 (d, *J* = 11.0 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)** δ 144.8; **HRMS (ESI$^+$)** $C_{39}H_{30}NO_2P$ requires $M+H^+$ 576.2092, found 576.2078; **$[\alpha]_D^{23}$** -155.6 (*c* = 1.29, $CHCl_3$).

(*R*)-*N*-(Naphthalen-2-ylmethyl)-1-phenylethanamine hydrochloride (79)

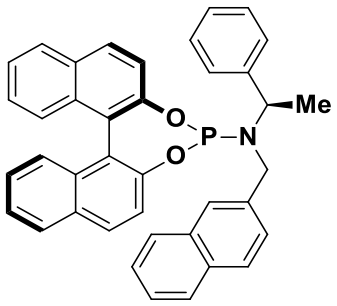


To a solution of 2-naphthaldehyde (1.51 g, 9.67 mmol) in toluene (10 mL) was added (*R*)-1-phenylethanamine (1.23 mL, 9.67 mmol) and the resulting solution was left to stir for 1 h at reflux. Upon cooling, the imine (2.47 g, 98%) was obtained as a white solid. A portion of this imine (1.01 g, 3.89 mmol) was dissolved in MeOH (20 mL). $NaBH_4$ (147 mg, 3.89 mmol) was added and the resulting reaction mixture was left to stir for 1 h. Upon completion, sat. NH_4Cl (20 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting residue was dissolved in Et_2O (20 mL) and HCl (4.00 mL, 2M in Et_2O, 8.00 mmol) was added dropwise. The resulting

suspension was left to stir at rt for 30 min. The resultant white precipitate was filtered, washed with cold Et_2O and dried to afford the product (1.15 g, 99%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (br, 1H, N*H*), 10.36 (br, 1H, N*H*), 7.84 – 7.75 (m, 3H, Ar*H*), 7.71 (dd, *J* = 5.5, 3.0 Hz, 1H, Ar*H*), 7.63 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.55 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.49 – 7.35 (m, 5H, Ar*H*), 4.08 – 3.88 (m, 2H, C*H*Ar, CH_AH_B), 3.76 – 3.63 (m, 1H, CH_AH_B), 1.73 (d, *J* = 6.5 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.2, 133.5, 133.0, 130.7, 129.5, 129.4, 128.8, 128.3, 127.7, 127.6, 127.5, 126.9, 126.6, 57.5, 48.6, 20.8; **$[\alpha]_D^{23}$** +72.2 (*c* = 1.21, $CHCl_3$).

(11b*R*)-*N*-(Naphthalen-2-ylmethyl)-*N*-((*R*)-1-phenylethyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (L14)



Prepared following General Procedure A using (*R*)-*N*-(naphthalen-2-ylmethyl)-1-phenylethanamine hydrochloride (500 mg, 1.68 mmol), (*R*)-BINOL (481 mg, 1.68 mmol), PCl_3 (147 µL, 1.68 mmol) and Et_3N (1.17 mL, 8.40 mmol). Flash column chromatography on silica gel (10% dichloromethane in petrol) afforded the product (364 mg, 38%) as a white solid.

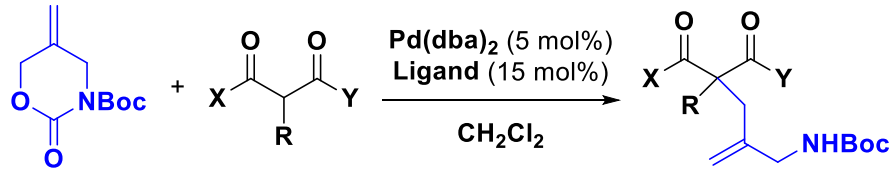
m.p.: 136-142 °C (decomp.) (lit. not reported); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.04 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.95 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.86 – 7.68 (m, 6H, Ar*H*), 7.59 –

7.30 (m, 13H, Ar*H*), 7.30 – 7.16 (m, 2H, Ar*H*), 7.08 (d, *J* = 9.0 Hz, 1H, Ar*H*), 4.20 (d, *J* = 15.0 Hz, 1H, NCH_AH$_B$), 4.11 (dq, *J* = 14.5, 7.0 Hz, 1H, NC*H*Me), 3.21 (dd, *J* = 15.0, 1.0 Hz, 1H, NCH$_A$$H_B$), 1.70 (dd, *J* = 7.0, 4.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 150.4 (d, *J* = 5.0 Hz), 149.8, 143.9, 136.3, 133.3, 133.0, 132.8, 132.7, 131.6, 130.8, 130.4, 130.3, 128.7, 128.5, 128.3, 128.2, 127.7, 127.6 (2 × C), 127.4, 127.3, 127.1, 126.7, 126.2 (2 × C), 126.1, 125.7, 125.0, 124.7, 124.3 (d, *J* = 5.0 Hz), 122.7, 122.5, 121.9, 57.6 (d, *J* = 24.0 Hz), 48.6 (d, *J* = 3.0 Hz), 23.5 (d, *J* = 31.5 Hz); **^{31}P NMR (162 MHz, CDCl$_3$)** δ 141.7; **[α]$_D^{23}$** -213.7 (*c* = 0.88, CHCl$_3$) [lit.[52] -207.8 (*c* = 1.68, CHCl$_3$)].

These data are consistent with those reported in the literature.[52]

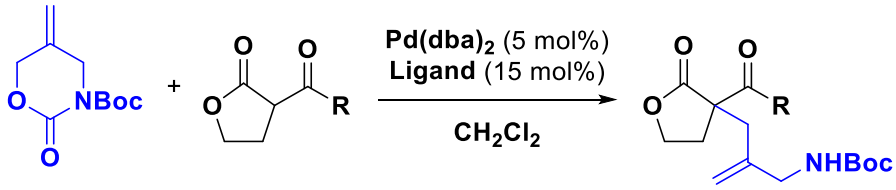
7.3 – 1,3-Dicarbonyl Allylation Products

General Procedure B – Pd-Catalysed Allylation of 1,3-Dicarbonyl Substrates



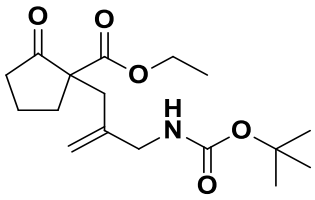
To a flame-dried flask charged with carbamate **15** (1.0 eq.), $Pd(dba)_2$ (5 mol%) and ligand (15 mol%) was added CH_2Cl_2 (0.05 M) and the mixture left to stir for 5 mins. The substrate (2.0 eq.) was added and the reaction mixture was left to stir for 3 h. Removal of the solvent *in vacuo* afforded the crude residue which was purified by flash column chromatography on silica gel to give the title compounds.

General Procedure C – Pd-Catalysed Allylation of α-Acyl-γ-Lactones



Following General Procedure B, but upon completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 and washed with 1 M NaOH. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude residue which was purified by flash column chromatography on silica gel to provide the title compounds.

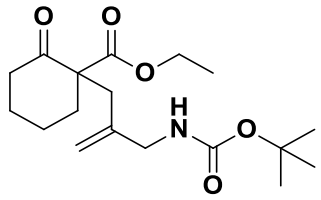
Ethyl 1-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-2-oxocyclopentane-carboxylate (18)



Prepared following General Procedure B using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol) and ethyl 2-oxocyclopentanecarboxylate (69 µL, 0.469 mmol). Flash column chromatography on silica gel (20% ethyl acetate in petrol) afforded the product (50 mg, 66%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3392, 1752, 1716, 1694, 1650; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.05 (d, *J* = 1.0 Hz, 1H, C=C$\underline{H_A}H_B$), 4.86 (d, *J* = 1.0 Hz, 1H, C=C$H_A\underline{H_B}$), 4.80 (br, 1H, N$\underline{H}$), 4.16 (q, *J* = 7.0 Hz, 2H, OC$\underline{H_2}$), 3.64 – 3.55 (m, 2H, NC$\underline{H_2}$), 2.77 (d, *J* = 15.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.63 – 2.49 (m, 1H), 2.49 – 2.20 (m, 2H), 2.33 (d, *J* = 15.0 Hz, 1H, C=C$H_A\underline{H_B}$), 2.10 – 1.83 (m, 3H), 1.44 (s, 9H, C(C$\underline{H_3}$)$_3$), 1.25 (t, *J* = 7.0 Hz, 3H, OCH2C$\underline{H3}$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 214.5, 170.7, 155.8, 142.0, 114.7, 79.3, 61.7, 60.2, 45.6, 37.6, 37.0, 32.3, 28.4, 19.5, 14.0; **HRMS (ESI^+)** $C_{17}H_{27}NO_5$ requires $M+H^+$ 326.1967, found 326.1971.

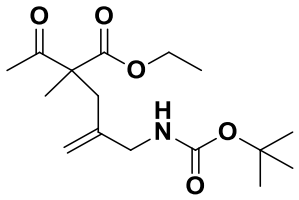
Ethyl 1-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-2-oxocyclohexane-carboxylate (19)



Prepared following General Procedure B using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol) and ethyl 2-oxocyclohexanecarboxylate (75 µL, 0.469 mmol). Flash column chromatography on silica gel (20% ethyl acetate in petrol) afforded the product (48 mg, 60%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3404, 1733, 1711, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.02 (m, 2H, C=C$\underline{H_A}H_B$, N$\underline{H}$), 4.81 (s, 1H, C=C$H_A\underline{H_B}$), 4.23 – 4.10 (m, 2H, OC$\underline{H_2}$), 3.69 – 3.52 (m, 2H, NC$\underline{H_2}$), 2.70 (d, *J* = 14.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.57 – 2.39 (m, 3H), 2.31 (d, *J* = 14.0 Hz, 1H, C=CC$H_A\underline{H_B}$), 2.08 – 1.95 (m, 1H), 1.82 – 1.45 (m, 4H), 1.43 (s, 9H, C(C$\underline{H_3}$)$_3$), 1.25 (t, *J* = 7.0 Hz, 3H, OCH_2C$\underline{H_3}$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 208.3, 171.6, 155.9, 142.3, 115.8, 79.2, 61.7, 61.5, 45.8, 41.4, 38.3, 37.1, 28.6, 27.8, 22.8, 14.2; **HRMS (ESI^+)** $C_{18}H_{29}NO_5$ requires $M+H^+$ 340.2118, found 340.2118.

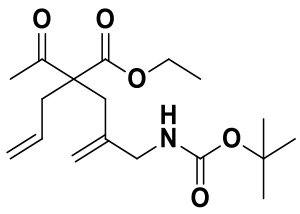
Ethyl 2-acetyl-4-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylpent-4-enoate (16)



Prepared following General Procedure B using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol) and ethyl 2-methylacetoacetate (66 µL, 0.469 mmol). Flash column chromatography on silica gel (15% ethyl acetate in petrol) afforded the product (47 mg, 64%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3398, 1735, 1712, 1648; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.04 (d, *J* = 1.0 Hz, 1H, C=C$\underline{H_A}H_B$), 4.83 (d, *J* = 1.0 Hz, 1H, C=C$H_A\underline{H_B}$), 4.77 (br, 1H, N$\underline{H}$), 4.26 – 4.12 (m, 2H, OC$\underline{H_2}$), 3.57 (m, 2H, NC$\underline{H_2}$), 2.72 (d, *J* = 14.5 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.50 (d, *J* = 14.5 Hz, 1H, C=C$H_A\underline{H_B}$), 2.17 (s, 3H, C(O)C$\underline{H_3}$), 1.43 (s, 9H, C(C$\underline{H_3}$)$_3$), 1.36 (s, 3H, C(O)C(C$\underline{H_3}$)), 1.29 (t, *J* = 7.0 Hz, 3H, $OCH_2C\underline{H_3}$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 205.7, 173.1, 156.1, 142.2, 115.4, 79.7, 61.9, 59.8, 46.1, 38.4, 28.7, 26.5, 19.6, 14.3; **HRMS (ESI^+)** $C_{16}H_{27}NO_5$ requires $M+H^+$ 314.1962, found 314.1959.

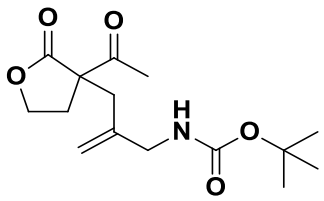
Ethyl 2-acetyl-2-allyl-4-(((*tert*-butoxycarbonyl)amino)methyl)pent-4-enoate (17)



Prepared following General Procedure B using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol) and ethyl 2-acetylpent-4-enoate (80 mg, 0.469 mmol). Flash column chromatography on silica gel (15% ethyl acetate in petrol) afforded the title compound (49 mg, 62%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3395, 1736, 1711, 1650; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.68 – 5.50 (m, 1H, $H_2C{=}C\underline{H}$), 5.13 – 5.02 (m, 3H, $CH{=}C\underline{H_2}$, $C{=}C\underline{H_A}H_B$), 4.84 (d, *J* = 0.5 Hz, 1H, $C{=}CH_A\underline{H_B}$), 4.73 (br, 1H, $N\underline{H}$), 4.26 – 4.12 (m, 2H, $OC\underline{H_2}$), 3.65 – 3.46 (m, 2H, $NC\underline{H_2}$), 2.76 – 2.61 (m, 3H, $C{=}CHC\underline{H_2}$, $C{=}CC\underline{H_A}H_B$), 2.56 (d, *J* = 15.0 Hz, 1H, $C{=}CCH_A\underline{H_B}$), 2.15 (s, 3H, $C(O)C\underline{H_3}$), 1.43 (s, 9H, $C(C\underline{H_3})_3$), 1.26 (t, *J* = 7.0 Hz, 3H, $OCH_2C\underline{H_3}$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 204.8, 172.1, 156.0, 142.1, 132.4, 119.7, 115.3, 79.7, 63.7, 61.9, 46.0, 37.2, 35.9, 28.7, 27.5, 14.3; **HRMS (ESI^+)** $C_{18}H_{29}NO_5$ requires $M+H^+$ 340.2118, found 340.2119.

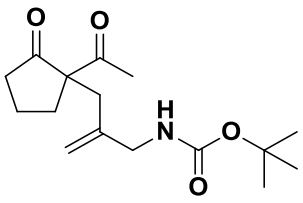
***Tert*-butyl (2-((3-acetyl-2-oxotetrahydrofuran-3-yl)methyl)allyl)carbamate (20)**



Prepared following General Procedure C using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol) and 2-acetyl-γ-butyrolactone (50 µL, 0.469 mmol). Flash column chromatography on silica gel (20% ethyl acetate in petrol) afforded the product (40 mg, 57%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3401, 1766, 1710, 1694, 1653; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.09 (s, 1H, C=C$\underline{H_A}H_B$), 4.82 (s, 1H, C=C$H_A\underline{H_B}$), 4.73 (br, 1H, N$\underline{H}$), 4.32 (td, *J* = 9.0, 3.0 Hz, 1H, OC$\underline{H_A}H_B$), 4.19 (td, *J* = 9.0, 7.0 Hz, 1H, OC$H_A\underline{H_B}$), 3.74 – 3.54 (m, 2H, NC$\underline{H_2}$), 2.98 (ddd, *J* = 13.0, 7.0, 3.0 Hz, 1H, OCH_2C$\underline{H_A}H_B$), 2.86 (d, *J* = 16.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.64 (d, *J* = 16.0 Hz, 1H, C=CC$H_A\underline{H_B}$), 2.35 (s, 3H, C$\underline{H_3}$), 2.24 – 2.10 (m, 1H, OCH_2C$H_A\underline{H_B}$), 1.44 (s, 9H, C(C$\underline{H_3}$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 202.2, 175.5, 155.6, 141.2, 114.5, 79.7, 66.7, 60.9, 45.6, 38.3, 29.4, 28.3, 25.7; **HRMS (ESI^+)** $C_{15}H_{23}NO_5$ requires $M+H^+$ 298.1654, found 298.1661.

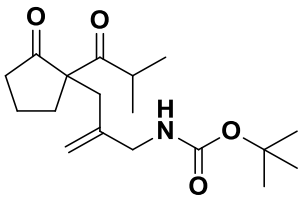
***Tert*-butyl (2-((1-acetyl-2-oxocyclopentyl)methyl)allyl)carbamate (22)**



Prepared following General Procedure B using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol) and 2-acetylcyclopentanone (57 µL, 0.469 mmol). Flash column chromatography on silica gel (20% ethyl acetate in petrol) afforded the product (63 mg, 91%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3372, 1739, 1701, 1658; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.02 (s, 1H, C=C$\underline{H_A}H_B$), 4.77 (s, 1H, C=C$H_A\underline{H_B}$), 4.70 (br, 1H, N$\underline{H}$), 3.70 – 3.42 (m, 2H, NC$\underline{H_2}$), 2.84 – 2.69 (m, 1H), 2.78 (d, *J* = 16.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.42 – 2.20 (m, 2H), 2.38 (d, *J* = 16.0 Hz, 1H, C=CC$H_A\underline{H_B}$), 2.19 (s, 3H, C(O)C$\underline{H_3}$), 1.96 – 1.71 (m, 3H), 1.44 (s, 9H, C(C$\underline{H_3}$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 215.4, 204.1, 155.7, 142.0, 113.5, 79.5, 68.4, 45.8, 38.3, 38.0, 31.0, 28.4, 26.1, 19.4; **HRMS (ESI^+)** $C_{16}H_{25}NO_4$ requires $M+H^+$ 296.1862, found 296.1849.

***Tert*-butyl (2-((1-isobutyryl-2-oxocyclopentyl)methyl)allyl)carbamate (27)**

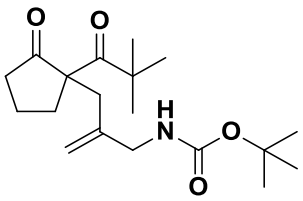


Prepared following General Procedure B using **15** (100 mg, 0.469 mmol), $Pd(dba)_2$ (13 mg, 0.023 mmol), **L7** (22 mg, 0.070 mmol) and 2-isobutyrylcyclopentanone (145

mg, 0.938 mmol). Flash column chromatography on silica gel (20% ethyl acetate in petrol) afforded the product (127 mg, 84%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3444, 1735, 1704, 1655, 1266; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.02 (d, *J* = 1.0 Hz, 1H, C=C$\underline{H_A}$H$_B$), 4.79 (m, 2H, C=CH$_A$$\underline{H_B}$, N$\underline{H}$), 3.62 – 3.42 (m, 2H, NC$\underline{H_2}$), 3.12 (hept, *J* = 6.5 Hz, 1H, C$\underline{H}$Me$_2$), 2.75 – 2.59 (m, 1H), 2.64 (d, *J* = 15.0 Hz, 1H, C=CC$\underline{H_A}$H$_B$), 2.50 (d, *J* = 15.0 Hz, 1H, C=CCH$_A$$\underline{H_B}$), 2.41 – 2.18 (m, 2H), 1.99 – 1.86 (m, 1H), 1.86 – 1.71 (m, 2H), 1.43 (s, 9H, C(C$\underline{H_3}$)$_3$), 1.03 (d, *J* = 6.5 Hz, 3H, CH(C$\underline{H_3}$)(CH$_3$)), 0.91 (d, *J* = 6.5 Hz, 3H, CH(CH$_3$)(C$\underline{H_3}$)); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 216.1, 210.6, 155.8, 142.0, 114.7, 79.4, 68.5, 45.6, 38.1, 37.2, 35.7, 30.7, 28.4, 20.2, 19.5, 19.3; **HRMS (ESI$^+$)** $C_{18}H_{29}NO_4$ requires M+H$^+$ 324.2175, found 324.2173.

***Tert*-butyl (2-((2-oxo-1-pivaloylcyclopentyl)methyl)allyl)carbamate (28)**

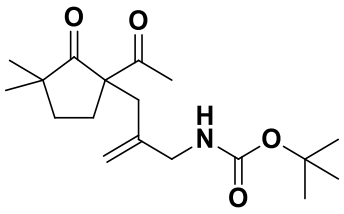


Prepared following General Procedure B using **15** (100 mg, 0.469 mmol), Pd(dba)$_2$ (13 mg, 0.023 mmol), **L7** (22 mg, 0.070 mmol) and 2-pivaloylcyclopentanone (316 mg, 1.876 mmol). Flash column chromatography on silica gel (20% ethyl acetate in petrol) afforded the title compound (102 mg, 64%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3412, 1714, 1684, 1649; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.03 (s, 1H, C=C$\underline{H_A}$H$_B$), 4.88 (br, 1H, N$\underline{H}$), 4.81 (s, 1H, C=CH$_A$$\underline{H_B}$), 3.58 – 3.45 (m, 2H, NC$\underline{H_2}$), 2.76 – 2.56 (m, 2H, C=CC$\underline{H_A}$H$_B$), 2.55 – 2.38 (m, 2H, C=CCH$_A$$\underline{H_B}$), 2.39 – 2.25 (m, 1H), 1.96 – 1.74 (m, 3H), 1.42 (s, 9H, OC(C$\underline{H_3}$)$_3$), 1.17 (s, 9H, C(O)C(C$\underline{H_3}$)$_3$); **^{13}C**

NMR (101 MHz, $CDCl_3$) δ 216.5, 210.8, 155.8, 142.2, 115.5, 79.3, 67.9, 46.5, 45.5, 37.8, 37.4, 33.1, 28.4, 27.6, 19.2; **HRMS (ESI^+)** $C_{19}H_{31}NO_4$ requires $M+H^+$ 338.2326, found 338.2330.

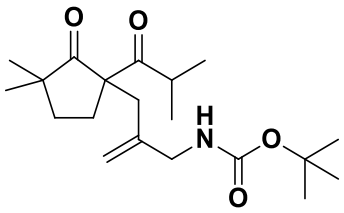
***Tert*-butyl (2-((1-acetyl-3,3-dimethyl-2-oxocyclopentyl)methyl)allyl)carbamate (21)**



Prepared following General Procedure B using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol) and 5-acetyl-2,2-dimethylcyclopentanone (72 mg, 0.469 mmol). Flash column chromatography on silica gel (10% ethyl acetate in petrol) afforded the product (56 mg, 74%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3357, 2969, 1733, 1698, 1659; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.00 (s, 1H, C=C$\underline{H_A}H_B$), 4.76 (s, 1H, C=C$H_A\underline{H_B}$), 4.70 (br, 1H, N$\underline{H}$), 3.63 – 3.53 (m, 2H, NC$\underline{H_2}$), 2.84 – 2.68 (m, 1H), 2.80 (d, *J* = 16.0 Hz, 1H, C=CC$\underline{H_A}H_B$) 2.34 (d, *J* = 16.0 Hz, 1H, C=CC$H_A\underline{H_B}$), 2.19 (s, 3H, C(O)C$\underline{H_3}$), 1.81 – 1.69 (m, 3H), 1.43 (s, 9H, C(C$\underline{H_3}$)$_3$), 1.04 (s, 3H, C(O)C(C$\underline{H_3}$)(CH_3)), 1.00 (s, 3H, C(O)C(CH_3)(C$\underline{H_3}$)); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 219.1, 204.3, 155.9, 142.3, 113.5, 79.7, 68.9, 46.4, 46.0, 39.3, 35.4, 28.5, 27.3, 26.1, 25.0, 24.9; **HRMS (ESI^+)** $C_{18}H_{29}NO_4$ requires $M+Na^+$ 346.1989, found 346.1989.

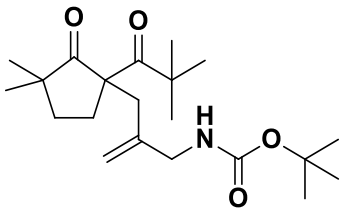
***Tert*-butyl (2-((1-isobutyryl-3,3-dimethyl-2-oxocyclopentyl)methyl)allyl)-carbamate (53)**



Prepared following General Procedure B using **15** (100 mg, 0.469 mmol), $Pd(dba)_2$ (13 mg, 0.023 mmol), **L7** (22 mg, 0.070 mmol) and 5-isobutyryl-2,2-dimethylcyclopentanone (173 mg, 0.938 mmol). Flash column chromatography on silica gel (9% ethyl acetate in petrol) afforded the title compound (141 mg, 86%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3400, 2969, 1730, 1699, 1662; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.03 (s, 1H, C=C$\underline{H_A}H_B$), 4.79 (s, 1H, C=C$H_A\underline{H_B}$), 4.75 (br, 1H, N$\underline{H}$), 3.66 – 3.44 (m, 2H, NC$\underline{H_2}$), 3.24 (hept, J = 6.5 Hz, 1H, C$\underline{H}$(Me)$_2$), 2.76 – 2.62 (m, 1H), 2.67 (d, J = 15.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.50 (d, J = 15.0 Hz, 1H, C=CC$H_A\underline{H_B}$), 1.87 – 1.61 (m, 3H), 1.44 (s, 9H, C(C$\underline{H_3}$)$_3$), 1.06 – 1.01 (m, 9H, C(O)C(C$\underline{H_3}$)(C$\underline{H_3}$), CH(C$\underline{H_3}$)(CH$_3$)), 0.90 (d, J = 6.5 Hz, 3H, CH(CH$_3$)(C$\underline{H_3}$)); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 219.1, 204.3, 155.9, 142.3, 113.5, 79.7, 68.9, 46.4, 46.0, 39.3, 35.4, 28.5, 27.3, 26.2, 25.0, 24.9; **HRMS (ESI^+)** $C_{20}H_{33}NO_4$ requires M+Na^+ 374.2302, found 374.2306.

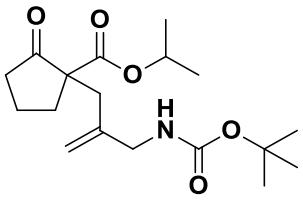
***Tert*-butyl (2-((3,3-dimethyl-2-oxo-1-pivaloylcyclopentyl)methyl)allyl)carbamate (54)**



Prepared following General Procedure B using **15** (150 mg, 0.703 mmol), $Pd(dba)_2$ (20 mg, 0.035 mmol), **L7** (33 mg, 0.106 mmol) and 2,2-dimethyl-5-pivaloylcyclopentanone (276 mg, 1.407 mmol). Flash column chromatography on silica gel (10% ethyl acetate in petrol) gave the product (222 mg, 86%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3386, 2966, 1719, 1684, 1652; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.05 (s, 1H, C=C$\underline{H_A}H_B$), 4.89 – 4.73 (m, 2H, C=C$H_A\underline{H_B}$, N$\underline{H}$), 3.60 – 3.54 (m, 2H, NC$\underline{H_2}$), 2.79 (d, *J* = 15.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.72 – 2.60 (m, 1H), 2.50 (d, *J* = 15.0 Hz, 1H, C=CC$H_A\underline{H_B}$), 1.97 – 1.83 (m, 1H), 1.79 – 1.62 (m, 2H), 1.43 (s, 9H, C(O)C(C$\underline{H_3}$)$_3$), 1.21 (s, 9H, OC(C$\underline{H_3}$)$_3$), 1.11 (s, 3H, C(O)C(C$\underline{H_3}$)(CH_3)), 1.04 (s, 3H, C(O)C(CH_3)(C$\underline{H_3}$)); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 220.1, 211.2, 155.9, 142.4, 115.3, 79.5, 69.2, 46.6, 46.0, 45.6, 37.7, 35.3, 29.4, 28.5, 28.4, 26.0, 25.8; **HRMS (ESI^+)** $C_{21}H_{35}NO_4$ requires $M+Na^+$ 388.2458, found 388.2463.

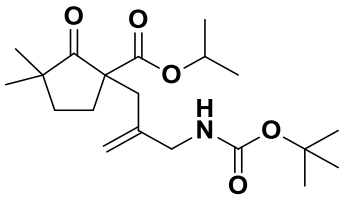
Isopropyl 1-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-2-oxocyclopentane-carboxylate (57)



Prepared following General Procedure B using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (13 mg, 0.035 mmol) and isopropyl 2-oxocyclopentane-carboxylate (80 mg, 0.469 mmol). Flash column chromatography on silica gel (15% ethyl acetate in petrol) afforded the title compound (54 mg, 68%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3386, 2978, 1749, 1706, 1648; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.05 (d, *J* = 1.0 Hz, 1H, C=C$\underline{H_A}H_B$), 4.99 (hept, *J* = 6.5 Hz, 1H, C$\underline{H}Me_2$), 4.86 (d, *J* = 1.0 Hz, 1H, C=C$H_A\underline{H_B}$), 4.82 (br, 1H, N$\underline{H}$), 3.65 – 3.55 (m, 2H, NC$\underline{H_2}$), 2.78 (d, *J* = 15.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.58 – 2.20 (m, 3H), 2.33 (d, *J* = 15.0 Hz, 1H, C=CC$H_A\underline{H_B}$), 2.07 – 1.86 (m, 3H), 1.44 (s, 9H, C(C$\underline{H_3}$)$_3$), 1.22 (d, *J* = 6.5 Hz, 3H, CH(C$\underline{H_3}$)(Me)), 1.21 (d, *J* = 6.5 Hz, 3H, CH(Me)(C$\underline{H_3}$)); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 214.7, 170.5, 155.9, 142.2, 114.8, 79.5, 69.4, 60.3, 45.8, 37.7, 37.0, 32.5, 28.5, 21.8, 21.6, 19.6; **HRMS (ESI$^+$)** $C_{18}H_{29}NO_5$ requires M+Na^+ 362.1943, found 362.1929.

Isopropyl 1-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-3,3-dimethyl-2-oxocyclopentanecarboxylate (58)

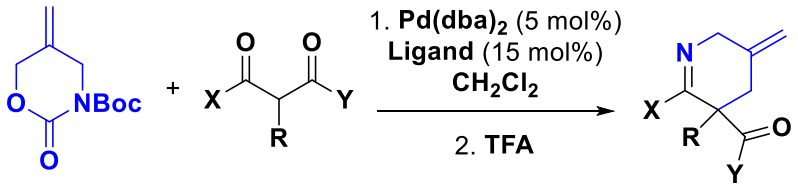


Prepared according to General Procedure B using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol) and isopropyl 3,3-dimethyl-2-oxocyclopentanecarboxylate (93 mg, 0.469 mmol). Flash column chromatography on silica gel (10% ethyl acetate in petrol) gave the product (61 mg, 71%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3386, 2976, 1746, 1710, 1652; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.04 (d, *J* = 1.0 Hz, 1H, C=C$\underline{H_A}H_B$), 4.99 (hept, *J* = 6.5 Hz, 1H, C$\underline{H}Me_2$), 4.87 (br, 1H, N$\underline{H}$), 4.85 (d, *J* = 1.0 Hz, 1H, C=C$H_A\underline{H_B}$), 3.69 – 3.49 (m, 2H, NC$\underline{H_2}$), 2.76 (d, *J* = 15.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.55 – 2.39 (m, 1H), 2.27 (d, *J* = 15.0 Hz, 1H, C=CC$H_A\underline{H_B}$), 2.01 – 1.83 (m, 2H), 1.83 – 1.68 (m, 1H), 1.43 (s, 9H, C(C$\underline{H_3}$)$_3$), 1.22 (d, *J* = 6.5 Hz, 3H, CH(C$\underline{H_3}$)(CH_3)), 1.20 (d, *J* = 6.5 Hz, 3H, CH(CH_3)(C$\underline{H_3}$)), 1.10 (s, 3H, C(O)C(C$\underline{H_3}$)(CH_3)), 1.04 (s, 3H, C(O)C(CH_3)(C$\underline{H_3}$)); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 218.3, 170.7, 155.9, 142.3, 114.9, 79.4, 69.4, 61.0, 45.9, 45.8, 37.5, 35.6, 28.9, 28.5, 25.2, 24.9, 21.8, 21.6; **HRMS (ESI$^+$)** $C_{20}H_{33}NO_5$ requires M+Na^+ 390.2251, found 390.2260.

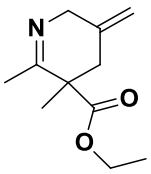
7.4 – 1,3-Dicarbonyl Allylation-Condensation Products

General Procedure D – Tandem Pd-Catalysed Allylation-Condensation of 1,3-Dicarbonyl Substrates



To a flame-dried flask charged with $Pd(dba)_2$ (5 mol%) and ligand (15 mol%) was added CH_2Cl_2 (0.08 M) and the mixture left to stir at rt for 5 mins. A solution of carbamate **15** (1.0 eq.) in CH_2Cl_2 (0.23 M) was added and the reaction mixture left to stir at rt for 3 h. TFA was added and the reaction mixture left to stir for a further 1 h at rt. The reaction was quenched with sat. $NaHCO_3$ and extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel to afford the title compounds.

Ethyl 2,3-dimethyl-5-methylene-3,4,5,6-tetrahydropyridine-3-carboxylate 40)

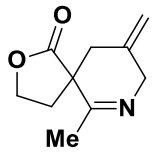


To a solution of ethyl 2-acetyl-4-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylpent-4-enoate **16** (126 mg, 0.402 mmol) in a solution of CH_2Cl_2 (4 mL) was added TFA (1 mL) and the mixture stirred for 1 h. CH_2Cl_2 (10 mL) was added followed by treatment with sat. $NaHCO_3$ (10 mL) and the layers separated. The organics were extracted with

CH_2Cl_2 (2 × 10 mL), combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the clean product (75 mg, 96%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2983, 2937, 1730, 1660; **^{1}H NMR (250 MHz, $CDCl_3$)** δ 4.94 – 4.88 (m, 1H, C=C$\underline{H_A}H_B$), 4.83 – 4.77 (m, 1H, C=C$H_A\underline{H_B}$), 4.24 – 4.17 (m, 2H, NC$\underline{H_2}$); 4.18 (q, *J* = 7.0 Hz, 2H, OC$\underline{H_2}$), 2.78 (d, *J* = 13.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.20 (d, *J* = 13.0 Hz, 1H, C=C$H_A\underline{H_B}$), 1.98 – 1.92 (m, 3H, C(N)C$\underline{H_3}$), 1.32 (s, 3H, C$\underline{H_3}$), 1.26 (t, *J* = 7.0 Hz, 3H, $OCH_2C\underline{H_3}$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.1, 166.8, 139.6, 110.2, 61.4, 55.6, 51.5, 40.4, 23.7, 21.6, 14.3; **HRMS (ESI^+)** $C_{11}H_{17}NO_2$ requires $M+H^+$ 196.1338, found 196.1338.

6-Methyl-9-methylene-2-oxa-7-azaspiro[4.5]dec-6-en-1-one (35)

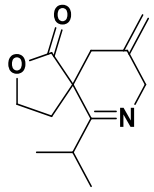


Non-enantioselective Preparation: Prepared following General Procedure D using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), α-acetyl-γ-butyrolactone (50 μL, 0.469 mmol), and TFA (1 mL). Flash column chromatography on silica gel (75% ethyl acetate in petrol) afforded the product (36 mg, 86%) as a colourless oil.

Enantioselective Preparation: Prepared following General Procedure D using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L10** (19 mg, 0.035 mmol), α-acetyl-γ-butyrolactone (50 μL, 0.469 mmol) and TFA (1 mL) and conducted at -20 °C for 16 h. Flash column chromatography (75% ethyl acetate in petrol) afforded the product (26 mg, 62%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2988, 1763, 1659; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.01 (s, 1H, C=C$\underline{H_A}$$H_B$), 4.91 (s, 1H, C=C$H_A$$\underline{H_B}$), 4.43 (td, *J* = 9.0, 3.5 Hz, 1H, OC$\underline{H_A}$$H_B$), 4.37 – 4.26 (m, 2H, OC$H_A$$\underline{H_B}$, NC$\underline{H_A}$$H_B$), 4.20 (d, *J* = 20.0 Hz, 1H, NC$H_A$$\underline{H_B}$), 2.72 (d, *J* = 13.0 Hz, 1H, C=CC$\underline{H_A}$$H_B$), 2.40 – 2.29 (m, 2H, C=CC$H_A$$\underline{H_B}$, OC$H_2C\underline{H_A}$$H_B$), 2.17 (ddd, *J* = 13.5, 7.5, 3.5 Hz, 1H, OCH_2C$H_A$$\underline{H_B}$), 2.05 – 2.00 (m, 3H, C$\underline{H_3}$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.7, 163.6, 138.3, 111.6, 65.5, 55.4, 51.6, 37.1, 32.9, 23.2; **HRMS (ESI^+)** $C_{10}H_{14}NO_2$ requires $M+H^+$ 180.1025, found 180.1024; **$[\alpha]_D^{23}$** +43.5 (*c* = 1.15, $CHCl_3$); **HPLC** (Cellulose 2, hexane:^{i}PrOH 92:8, flow rate 1.0 mL/min, λ = 225 nm, 23 °C) t_R(major) = 31.7, t_R(minor) = 34.9, e.r. = 98:2.

6-Isopropyl-9-methylene-2-oxa-7-azaspiro[4.5]dec-6-en-1-one (60)



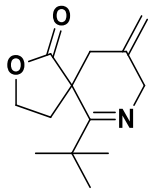
Non-enantioselective Preparation: Prepared following General Procedure D using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), α-isobutyryl-γ-butyrolactone (73 mg, 0.469 mmol) and TFA (1 mL). Flash column chromatography on silica gel (20% ethyl acetate in petrol) afforded the product (39 mg, 80%) as a colourless oil.

Enantioselective Preparation: Prepared following General Procedure D using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L10** (19 mg, 0.035 mmol) and α-isobutyryl-γ-butyrolactone (73 mg, 0.469 mmol) and conducted at -20 °C for 16 h.

Flash column chromatography on silica gel (20% ethyl acetate in petrol) afforded the product (41 mg, 85%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2950, 1761, 1710, 1458, 1375, 1269, 1024, 733; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.01 (d, *J* = 1.0 Hz, 1H, C=C$\underline{H_A}H_B$), 4.90 (d, *J* = 1.0 Hz, 1H, C=C$H_A\underline{H_B}$), 4.43 (td, *J* = 9.0, 3.0 Hz, 1H, OC$\underline{H_A}H_B$), 4.33 (d, *J* = 20.0 Hz, 1H, NC$\underline{H_A}H_B$), 4.31 (ddd, *J* = 13.0, 9.0, 7.5 Hz, 1H, OC$H_A\underline{H_B}$), 4.23 (d, *J* = 20.0 Hz, 1H, NC$H_A\underline{H_B}$), 2.70 (d, *J* = 13.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.41 – 2.27 (m, 3H, C=CC$H_A\underline{H_B}$, $OCH_2C\underline{H_A}H_B$, C$\underline{H}Me_2$), 2.16 (ddd, *J* = 13.0, 7.5, 3.0 Hz, 1H, $OCH_2CH_A\underline{H_B}$), 1.21 (d, *J* = 6.5 Hz, 3H, CH(C$\underline{H_3}$)(CH_3)), 1.12 (d, *J* = 6.5 Hz, 3H, CH(CH_3)(C$\underline{H_3}$)); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.8, 171.4, 139.1, 111.2, 65.4, 55.5, 53.1, 37.6, 35.3, 32.7, 23.3, 22.4; **HRMS (ESI$^+$)** $C_{12}H_{17}NO_2$ requires M+H$^+$ 208.1332, found 208.1331; **$[\alpha]_D^{23}$** -21.0 (*c* = 1.05, $CHCl_3$); **HPLC** (Cellulose-2, hexane:^{i}PrOH 90:10, flow rate 1.2 mL/min, λ = 225 nm, 22 °C) t_R(major) = 8.9, t_R(minor) = 11.0, er = 99:1.

6-(*Tert*-butyl)-9-methylene-2-oxa-7-azaspiro[4.5]dec-6-en-1-one (36)

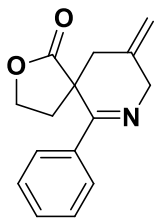


Non-enantioselective Preparation: Prepared following General Procedure D using **15** (100 mg, 0.469 mmol), $Pd(dba)_2$ (13 mg, 0.023 mmol), **L7** (22 mg, 0.070 mmol), α-pivaloyl-γ-butyrolactone (160 mg, 0.938 mmol) and TFA (2 mL). Flash column chromatography on silica gel (5 → 10% ethyl acetate in petrol) afforded the product (58 mg, 56%) as a colourless oil.

Enantioselective Preparation: Prepared following General Procedure D using **15** (150 mg, 0.703 mmol), $Pd(dba)_2$ (20 mg, 0.035 mmol), **L7** (57 mg, 0.106 mmol), α-pivaloyl-γ-butyrolactone (239 mg, 1.407 mmol) and TFA (3 mL) and conducted at -20 °C for 16 h. Flash column chromatography on silica gel (5% → 10% ethyl acetate in petrol) afforded the product (103 mg, 66%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 1765, 1659, 1634 **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.04 – 5.00 (m, 1H, C=C$\underline{H_A}H_B$), 4.93 – 4.84 (m, 1H, C=C$H_A\underline{H_B}$), 4.48 (td, *J* = 9.5, 3.0 Hz, 1H, OC$\underline{H_A}H_B$), 4.43 – 4.21 (m, 3H, OC$H_A\underline{H_B}$, NC$\underline{H_2}$), 2.75 – 2.64 (d, *J* = 13.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.48 – 2.33 (m, 1H, $OCH_2C\underline{H_A}H_B$), 2.26 (d, *J* = 13.0 Hz, 1H, C=C$CH_A\underline{H_B}$), 2.17 (ddd, *J* = 13.5, 8.5, 3.0 Hz, 1H, $OCH_2CH_A\underline{H_B}$), 1.25 (s, 9H, C(C$\underline{H_3}$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.0, 171.5, 139.1, 111.0, 64.9, 55.5, 50.6, 41.4, 40.0, 32.5, 30.5; **HRMS (ESI^+)** $C_{13}H_{19}NO_2$ requires $M+H^+$ 222.1494, found 222.1497; **$[\alpha]_D^{23}$** +38.4 (*c* = 1.12, $CHCl_3$); **HPLC** (Chiralpak-IA, hexane:^{i}PrOH 95:5, flow rate 1.0 mL/min, λ = 225 nm, 22 °C) t_R(major) = 5.7, t_R(minor) = 6.3, er = 96:4.

9-Methylene-6-phenyl-2-oxa-7-azaspiro[4.5]dec-6-en-1-one (61)



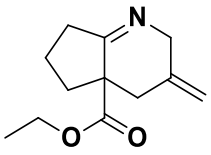
Non-enantioselective Preparation: Prepared following General Procedure D using **15** (500 mg, 2.34 mmol), $Pd(dba)_2$ (67 mg, 0.12 mmol), **L7** (111 mg, 0.35 mmol), α-benzoyl-γ-butyrolactone (892 mg, 4.69 mmol) and TFA (10 mL). Flash column

chromatography on silica gel (30% ethyl acetate in petrol) afforded the product (529 mg, 94%) as off-white crystals.

Enantioselective Preparation: Prepared following General Procedure D using **15** (150 mg, 0.703 mmol), $Pd(dba)_2$ (20 mg, 0.035 mmol), **L10** (57 mg, 0.106 mmol) α-benzoyl-γ-butyrolactone (268 mg, 1.407 mmol) and TFA (3 mL) and conducted at -20 °C for 16 h. Flash column chromatography on silica gel (30% ethyl acetate in petrol) afforded the product (144 mg, 85%) as off-white crystals.

m.p. 92-95 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 2917, 1761, 1626, 1445, 1373, 1176, 1026, 696; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.55 – 7.46 (m, 2H, Ar*H*), 7.41 – 7.31 (m, 3H, Ar*H*), 5.10 (d, *J* = 1.0 Hz, 1H, C=C$H_A$$H_B$), 4.99 (d, *J* = 1.0 Hz, 1H, C=C$H_A$$H_B$), 4.59 (d, *J* = 20.5 Hz, 1H, NC$H_A$$H_B$), 4.49 (d, *J* = 20.5 Hz, 1H, NC$H_A$$H_B$), 4.37 – 4.29 (m, 1H, OC$H_A$$H_B$), 4.25 (td, *J* = 9.0, 4.5 Hz, 1H, OC$H_A$$H_B$), 2.92 (d, *J* = 13.0 Hz, 1H, C=CC$H_A$$H_B$), 2.61 (dt, *J* = 13.5, 9.0 Hz, 1H, OCH_2C$H_A$$H_B$), 2.44 (d, *J* = 13.0 Hz, 1H, C=CC$H_A$$H_B$), 2.26 (ddd, *J* = 13.5, 8.0, 4.5 Hz, 1H, OCH_2C$H_A$$H_B$); **^{13}C NMR (101 MHz, DMSO)** δ 177.7, 162.5, 138.9, 137.7, 129.3, 128.2, 126.9, 111.1, 65.4, 55.3, 50.3, 37.2, 33.0; **HRMS (ESI^+)** $C_{15}H_{15}NO_2$ requires $M+H^+$ 242.1176, found 242.1178; **$[\alpha]_D^{23}$** +31.1 (*c* = 0.45, $CHCl_3$); **HPLC** (Cellulose-2, hexane:^{i}PrOH 90:10, flow rate 1.0 mL/min, λ = 225 nm, 22 °C) t_R (major) = 27.2, t_R(minor) = 45.7, er = 97:3.

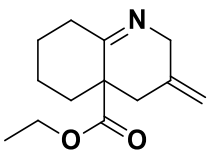
Ethyl 3-methylene-3,4,4a,5,6,7-hexahydro-2H-cyclopenta[b]pyridine-4a-carboxylate (33)



Prepared following General Procedure D using **15** (150 mg, 0.703 mmol), $Pd(dba)_2$ (20 mg, 0.035 mmol), **L7** (33 mg, 0.106 mmol), ethyl 2-oxocyclopentanecarboxylate (208 µL, 1.406 mmol) and TFA (3 mL). Flash column chromatograpy on silica gel (75% ethyl acetate in petrol) afforded the product (105 mg, 72%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 1725, 1679, 1650**;** **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.91 – 4.87 (m, 1H, C=C$\underline{H_A}H_B$), 4.83 (m, 1H, C=C$H_A\underline{H_B}$), 4.40 – 4.30 (m, 1H, NC$\underline{H_A}H_B$), 4.14 – 4.05 (m, 3H, OC$\underline{H_2}$, NC$H_A\underline{H_B}$), 2.97 (d, *J* = 13.5 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.73 – 2.58 (m, 1H), 2.45 – 2.31 (m, 2H), 2.04 (d, *J* = 13.5 Hz, 1H, C=CC$H_A\underline{H_B}$), 1.92 – 1.58 (m, 3H), 1.20 (t, *J* = 7.0 Hz, 3H, $OCH_2C\underline{H_3}$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.8, 173.1, 140.2, 110.1, 61.3, 55.4, 54.6, 38.4, 37.3, 33.6, 20.6, 14.3; **HRMS (ESI^+)** $C_{12}H_{17}NO_2$ requires $M+H^+$ 208.1338, found 208.1333.

Ethyl 3-methylene-2,3,4,4a,5,6,7,8-octahydroquinoline-4a-carboxylate (34)

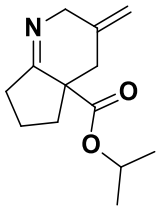


Prepared following General Procedure D using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), ethyl 2-oxocyclohexanecarboxylate (75

μL, 0.469 mmol) and TFA (1 mL). Flash column chromatograpy on silica gel (75% ethyl acetate in petrol) afforded the product (36 mg, 70%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 1727, 1684, 1658; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.85 – 4.81 (m, 1H, C=C$\underline{H_A}$H$_B$), 4.75 – 4.69 (m, 1H, C=CH$_A\underline{H_B}$), 4.25 – 4.07 (m, 4H, NC$\underline{H_2}$, OC$\underline{H_2}$), 2.60 (d, *J* = 13.0 Hz, 1H, C=CC$\underline{H_A}$H$_B$), 2.49 – 2.28 (m, 3H), 2.19 (d, *J* = 13.0 Hz, 1H, C=CCH$_A\underline{H_B}$), 1.93 – 1.83 (m, 1H), 1.74 – 1.63 (m, 1H), 1.57 – 1.34 (m, 3H), 1.22 (t, *J* = 7.0 Hz, 3H, OCH$_2$C$\underline{H_3}$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 173.5, 169.2, 140.2, 109.4, 61.3, 56.1, 53.9, 41.7, 37.9, 37.8, 26.9, 23.2, 14.4; **HRMS (ESI$^+$)** $C_{13}H_{19}NO_2$ requires M+H$^+$ 222.1489, found 222.1489.

Isopropyl 3-methylene-3,4,4a,5,6,7-hexahydro-2H-cyclopenta[b]pyridine-4a-carboxylate (62)

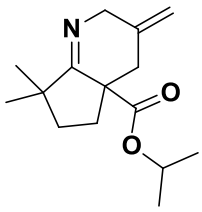


Prepared according to General Procedure D using **15** (150 mg, 0.703 mmol), Pd(dba)$_2$ (20 mg, 0.035 mmol), **L7** (33 mg, 0.106 mmol), isopropyl 2-oxocyclopentanecarboxylate **57** (239 mg, 1.407 mmol) and TFA (3 mL). Flash column chromatography on silica gel (50% ethyl acetate in petrol) afforded the product (117 mg, 75%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2979, 1721, 1680; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.96 (hept, *J* = 6.5 Hz, 1H, C$\underline{H}$Me$_2$), 4.89 (s, 1H, C=C$\underline{H_A}$H$_B$), 4.83 (s, 1H, C=CH$_A\underline{H_B}$), 4.35 (d, *J* = 20.0 Hz, 1H, NC$\underline{H_A}$H$_B$), 4.09 (d, *J* = 20.0 Hz, 1H, NCH$_A\underline{H_B}$), 2.96 (d, *J* = 13.5 Hz, 1H,

C=CC$\underline{H_A}$H$_B$), 2.72 – 2.57 (m, 1H), 2.45 – 2.28 (m, 2H), 2.03 (d, *J* = 13.5 Hz, 1H, C=CH$_A\underline{H_B}$), 1.90 – 1.58 (m, 3H), 1.19 (d, *J* = 6.5 Hz, 3H, C$\underline{H_3}$), 1.17 (d, *J* = 6.5 Hz, 3H, C$\underline{H_3}$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 176.8, 172.5, 140.3, 110.0, 68.7, 55.4, 54.6, 38.5, 37.3, 33.6, 21.8, 21.7, 20.6; **HRMS (ESI$^+$)** $C_{13}H_{19}NO_2$ requires M+H$^+$ 222.1489, found 222.1485.

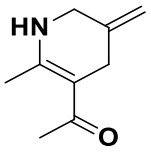
Isopropyl 7,7-dimethyl-3-methylene-3,4,4a,5,6,7-hexahydro-2H-cyclopenta[b]pyridine-4a-carboxylate (63)



Prepared according to General Procedure D using **50** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), isopropyl 3,3-dimethyl-2-oxocyclopentanecarboxylate **58** (93 mg, 0.469 mmol) and TFA (1 mL). Flash column chromatography on silica gel (50% ethyl acetate in petrol) afforded the product (33 mg, 57%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2956, 1723, 1680, 1653; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.96 (sept, *J* = 6.0 Hz, 1H, C$\underline{H}$Me$_2$), 4.89 (s, 1H, C=C$\underline{H_A}$H$_B$), 4.81 (s, 1H, C=CH$_A\underline{H_B}$), 4.40 (d, *J* = 20.0 Hz, 1H, NC$\underline{H_A}$H$_B$), 4.10 (d, *J* = 20.0 Hz, 1H, NCH$_A\underline{H_B}$), 2.93 (d, *J* = 13.5 Hz, 1H, C=CC$\underline{H_A}$H$_B$), 2.40 – 2.25 (m, 1H), 2.03 (d, *J* = 13.5 Hz, 1H, C=CCH$_A\underline{H_B}$), 1.73 – 1.58 (m, 3H), 1.25 – 1.14 (m, 9H, C$\underline{H_3}$, CH(C$\underline{H_3}$)$_2$), 1.12 (s, 3H, C$\underline{H_3}$)); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 182.7, 172.7, 140.4, 109.7, 68.8, 55.5, 55.2, 42.9, 39.5, 37.5, 34.1, 28.0, 27.2, 21.8; **HRMS (ESI$^+$)** $C_{15}H_{23}NO_2$ requires M+H$^+$ 250.1802, found 250.1802.

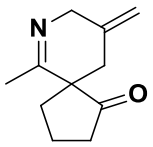
1-(2-Methyl-5-methylene-1,4,5,6-tetrahydropyridin-3-yl)ethanone (39)



Prepared following General Procedure D using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmoll), pentan-2,4-dione (48 µL, 0.469 mmol) and TFA (1 mL). Flash column chromatography on silica gel (75% ethyl acetate in petrol) afforded the product (29 mg, 82%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3452, 1674, 1651; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.06 – 5.01 (m, 1H, C=C$\underline{H_A}$$H_B$), 4.96 – 4.91 (m, 1H, C=C$H_A$$\underline{H_B}$), 4.32 (br, 1H, N$\underline{H}$), 3.75 (s, 2H, NC$\underline{H_2}$), 3.15 (s, 2H, C=CC$\underline{H_2}$), 2.26 (s, 3H, C(O)C$\underline{H_3}$), 2.15 (s, 3H, C$\underline{H_3}$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 195.7, 153.4, 138.7, 110.0, 102.1, 48.0, 32.9, 29.4, 22.9; **HRMS (ESI^+)** $C_9H_{13}NO$ require $M+H^+$ 152.1070, found 152.1071.

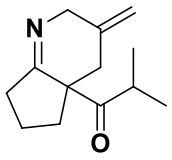
6-Methyl-9-methylene-7-azaspiro[4.5]dec-6-en-1-one (66)



Prepared following General Procedure D using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), 2-acetylcyclopentanone (57 µL, 0.469 mmol) and TFA (1 mL). Flash column chromatography on silica gel (75% ethyl acetate in petrol) afforded the product (28 mg, 68%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2966, 1732, 1655, 1455; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.97 (s, 1H, C=C$\underline{H_A}$H$_B$), 4.84 (s, 1H, C=CH$_A$$\underline{H_B}$), 4.25 (d, *J* = 19.5 Hz, 1H, NC$\underline{H_A}$H$_B$), 4.15 (d, *J* = 19.5 Hz, 1H, NCH$_A$$\underline{H_B}$), 2.51 – 2.27 (m, 3H, C=CC$\underline{H_A}$H$_B$, 2 × C$\underline{H}$), 2.21 – 1.90 (m, 5H, C=CCH$_A$$\underline{H_B}$, 4 × C$\underline{H}$), 1.90 – 1.80 (m, 3H, C$\underline{H_3}$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 218.7, 166.2, 139.4, 110.8, 58.5, 55.5, 39.0, 36.7, 33.7, 23.4, 19.3; **HRMS (ESI$^+$)** $C_{11}H_{15}NO$ requires M+H$^+$ 178.1232, found 178.1235.

2-Methyl-1-(3-methylene-3,4,4a,5,6,7-hexahydro-2*H*-cyclopenta[*b*]pyridin-4a-yl)propan-1-one (37)

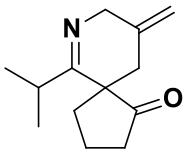


To a solution of *tert*-butyl (2-((1-isobutyryl-2-oxocyclopentyl)methyl)allyl)carbamate **27** (180 mg, 0.557 mmol) in CH_2Cl_2 (12 mL) was added TFA (3 mL) and the mixture stirred for 1 h at rt. The reaction was quenched with sat. $NaHCO_3$ (20 mL) and the products extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the two isomeric products. Flash column chromatography on silica gel (20% then 75% ethyl acetate in petrol) afforded the product (38 mg, 33%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 1703, 1683, 1653; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.90 (s, 1H, C=C$\underline{H_A}$H$_B$), 4.81 (s, 1H, C=CH$_A$$\underline{H_B}$), 4.38 (d, *J* = 20.0, 1H, NC$\underline{H_A}$H$_B$), 4.09 (d, *J* = 20.0, 1H, NCH$_A$$\underline{H_B}$), 2.97 – 2.83 (m, 2H, C=CC$\underline{H_A}$H$_B$, C$\underline{H}$(Me)$_2$), 2.68 – 2.53 (m, 1H), 2.48 – 2.32 (m, 2H), 2.12 (d, *J* = 14.0 Hz, 1H, C=CCH$_A$$\underline{H_B}$), 1.89 – 1.75 (m, 1H), 1.70 – 1.55 (m, 2H), 1.02 (d, *J* = 7.0 Hz, 3H, CH(C$\underline{H_3}$)(Me)), 1.00 (d, *J* = 7.0 Hz, 3H, CH(Me)(C$\underline{H_3}$));

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.4, 177.9, 140.2, 110.2, 61.9, 55.3, 38.2, 36.5, 36.1, 34.0, 20.5, 20.2, 19.9; **HRMS (ESI$^+$)** $C_{13}H_{19}NO$ requires $M+H^+$ 206.1539, found 206.1539; **HMBC** see Appendix 2.

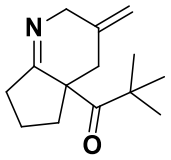
6-Isopropyl-9-methylene-7-azaspiro[4.5]dec-6-en-1-one (37)



To a solution of *tert*-butyl (2-((1-isobutyryl-2-oxocyclopentyl)methyl)allyl)carbamate **27** (180 mg, 0.557 mmol) in CH_2Cl_2 (12 mL) was added TFA (3 mL) and the mixture stirred for 1 h at rt. The reaction was quenched with sat. $NaHCO_3$ (20 mL) and the products extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the two isomeric products. Flash column chromatography on silica gel (20% then 75% ethyl acetate in petrol) afforded the product (53 mg, 46%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2963, 1732, 1701, 1653; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.94 (s, 1H, C=C$\underline{H_A}$H$_B$), 4.80 (s, 1H, C=CH$_A$$\underline{H_B}$), 4.26 (d, *J* = 19.5 Hz, 1H, NC$\underline{H_A}$H$_B$), 4.15 (d, *J* = 19.5 Hz, 1H, NCH$_A$$\underline{H_B}$), 2.50 – 2.29 (m, 3H, C(N)C$\underline{H}$(Me)$_2$, C=CC$\underline{H_A}$H$_B$, C$\underline{H}$), 2.18 – 1.75 (m, 6H, C=CCH$_A$$\underline{H_B}$, 5 × C$\underline{H}$), 1.10 (d, *J* = 6.5 Hz, 3H, CH(C$\underline{H_3}$)(Me)), 1.07 (d, *J* = 6.5 Hz, 3H, CH(Me)(C$\underline{H_3}$)); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 218.9, 173.7, 140.3, 110.4, 60.0, 55.6, 39.2, 37.2, 35.7, 33.4, 23.1, 22.1, 19.3; **HRMS (ESI$^+$)** $C_{13}H_{19}NO$ requires $M+H^+$ 206.1539, found 206.1538; **HMBC** (see Appendix 1).

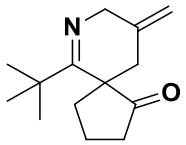
2,2-Dimethyl-1-(3-methylene-3,4,4a,5,6,7-hexahydro-2H-cyclopenta[b]pyridin-4a-yl)propan-1-one (38)



To a stirring solution of carbamate **28** (83 mg, 0.246 mmol) in CH_2Cl_2 (8 mL) was added TFA (2 mL) and the reaction mixture was left to stir at rt for 1 h. A saturated solution of $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography on silica gel (20% → 75% ethyl acetate in petrol) afforded the title compound (16 mg, 30%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 1695, 1673, 1647; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.89 (s, 1H, C=C$\underline{H_A}H_B$), 4.81 (s, 1H, C=C$H_A\underline{H_B}$), 4.34 (d, *J* = 19.5 Hz, 1H, NC$\underline{H_A}H_B$), 3.96 (d, *J* = 19.5 Hz, 1H, NC$H_A\underline{H_B}$), 3.23 (d, *J* = 14.5 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.63 – 2.44 (m, 2H), 2.44 – 2.29 (m, 1H), 2.12 (d, *J* = 14.5 Hz, 1H, C=CC$H_A\underline{H_B}$), 1.87 – 1.51 (m, 3H), 1.24 (s, 9H, C(C$\underline{H_3}$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 213.9, 179.4, 141.0, 109.6, 61.6, 54.6, 45.7, 38.5, 36.3, 34.4, 29.0, 20.9; **HRMS (ESI^+)** $C_{14}H_{21}NO$ requires $M+H^+$ 220.1696, found 220.1698.

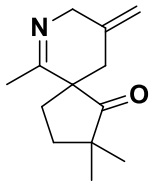
6-(*Tert*-butyl)-9-methylene-7-azaspiro[4.5]dec-6-en-1-one (69)



To a stirring solution of carbamate **28** (83 mg, 0.246 mmol) in CH_2Cl_2 (8 mL) was added TFA (2 mL) and the reaction mixture was left to stir at rt for 1 h. A saturated solution of $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography on silica gel (20% → 75% ethyl acetate in petrol) afforded the title compound (16 mg, 30%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2956, 1731, 1658, 1630; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.96 (s, 1H, C=C$\underline{H_A}$$H_B$), 4.79 (s, 1H, C=C$H_A$$\underline{H_B}$), 4.35 (d, *J* = 20.0 Hz, 1H, NC$\underline{H_A}$$H_B$), 4.23 (d, *J* = 20.0 Hz, 1H, NC$H_A$$\underline{H_B}$), 2.66 – 2.47 (m, 1H), 2.48 – 2.26 (m, 2H, C=CC$\underline{H_A}$$H_B$, C$\underline{H}$), 2.26 – 2.01 (m, 3H, C=CC$H_A$$\underline{H_B}$, 2 × C$\underline{H}$), 2.02 – 1.82 (m, 2H), 1.17 (s, 9H, C(C$\underline{H_3}$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 219.3, 174.3, 140.3, 110.0, 58.5, 55.7, 41.2, 38.8, 37.5, 33.4, 30.8, 18.5; **HRMS (ESI^+)** $C_{14}H_{21}NO$ requires $M+H^+$ 220.1696, found 220.1695.

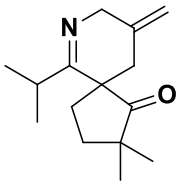
2,2,6-Trimethyl-9-methylene-7-azaspiro[4.5]dec-6-en-1-one (70)



Prepared following General Procedure D using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), 5-acetyl-2,2-dimethylcyclopentanone (72 mg, 0.469 mmol) and TFA (1 mL). Flash column chromatography on silica gel (75% ethyl acetate in petrol) afforded the product (26 mg, 54%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2962, 1733, 1653; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.95 (s, 1H, C=C$\underline{H_A}H_B$), 4.82 (s, 1H, C=C$H_A\underline{H_B}$), 4.26 (d, *J* = 20.0 Hz, 1H, NC$\underline{H_A}H_B$), 4.14 (d, *J* = 20.0 Hz, 1H, NC$H_A\underline{H_B}$), 2.37 (d, *J* = 12.5 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.16 (d, *J* = 12.5 Hz, 1H, C=CC$H_A\underline{H_B}$), 2.07 – 1.95 (m, 1H, C$\underline{H}$), 1.91 – 1.81 (m, 6H, C(N)C$\underline{H_3}$, 3 × C$\underline{H}$), 1.15 (s, 3H, C$\underline{H_3}$), 1.13 (s, 3H, C$\underline{H_3}$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 222.8, 166.0, 139.6, 110.6, 59.3, 55.7, 46.1, 37.5, 35.0, 29.9, 25.7, 24.7, 24.0; **HRMS (ESI^+)** $C_{13}H_{19}NO$ requires $M+H^+$ 206.1539, found 206.1540.

6-Isopropyl-2,2-dimethyl-9-methylene-7-azaspiro[4.5]dec-6-en-1-one (71)

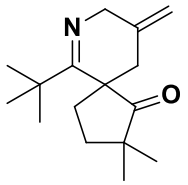


Prepared following General Procedure D using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), 5-isobutyryl-2,2-dimethylcyclopentanone

(85 mg, 0.469 mmol) and TFA (1 mL). Flash column chromatography on silica gel (15% ethyl acetate in petrol) afforded the product (31 mg, 57%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2961, 1730, 1652, 1645; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.94 (s, 1H, C=C$\underline{H_A}$H$_B$), 4.80 (s, 1H, C=CH$_A$$\underline{H_B}$), 4.27 (d, *J* = 19.5 Hz, 1H, NC$\underline{H_A}$H$_B$), 4.16 (d, *J* = 19.5 Hz, 1H, NCH$_A$$\underline{H_B}$), 2.36 (d, *J* = 12.5 Hz, 1H, C=CC$\underline{H_A}$H$_B$), 2.14 (d, *J* = 12.5 Hz, 1H, C=CCH$_A$$\underline{H_B}$), 2.12 – 1.97 (m, 2H, C$\underline{H}Me_2$, C$\underline{H}$), 1.91 – 1.81 (m, 3H), 1.16 (s, 3H, C$\underline{H_3}$), 1.12 (s, 3H, C$\underline{H_3}$), 1.11 (d, *J* = 6.5 Hz, 3H, CH(C$\underline{H_3}$)(Me)), 1.07 (d, *J* = 6.5 Hz, 3H, CH(Me)(C$\underline{H_3}$)); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 222.8, 174.1, 140.2, 110.3, 61.3, 55.6, 46.0, 38.0, 35.9, 35.0, 29.8, 26.1, 24.9, 23.3, 22.1; **HRMS (ESI$^+$)** $C_{15}H_{23}NO$ requires M+H$^+$ 234.1852, found 234.1853.

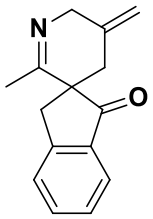
6-(*Tert*-butyl)-2,2-dimethyl-9-methylene-7-azaspiro[4.5]dec-6-en-1-one (72)



To a stirring solution of **54** (222 mg, 0.607 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL) and the reaction mixture was left to stir for 1 h at rt. The reaction was quenched by the addition of sat. $NaHCO_3$ (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (10% ethyl acetate in petrol) to afford the product (86 mg, 57%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 2957, 1729, 1658, 1626; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.91 (s, 1H, C=C$\underline{H_A}$H$_B$), 4.74 (s, 1H, C=CH$_A$$\underline{H_B}$), 4.35 (d, *J* = 20.5 Hz, 1H, NC$\underline{H_A}$H$_B$), 4.22 (d, *J* = 20.5 Hz, 1H, NCH$_A$$\underline{H_B}$), 2.33 (d, *J* = 13.0 Hz, 1H, C=CC$\underline{H_A}$H$_B$), 2.28 – 2.11 (m, 2H, C=CCH$_A$$\underline{H_B}$, C$\underline{H}$), 1.95 – 1.78 (m, 3H), 1.19 (s, 3H, C$\underline{H_3}$), 1.17 – 1.09 (m, 12H, C$\underline{H_3}$, C(C$\underline{H_3}$)$_3$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 222.1, 174.5, 140.2, 109.5, 59.2, 55.3, 44.7, 40.8, 39.4, 34.4, 30.5, 30.2, 28.6, 27.5; **HRMS (ESI$^+$)** $C_{16}H_{25}NO$ requires M+H$^+$ 248.2009, found 248.2009; **HMBC** see Appendix 3.

2'-Methyl-5'-methylene-5',6'-dihydro-4'*H*-spiro[indene-2,3'-pyridin]-1(3*H*)-one (75)

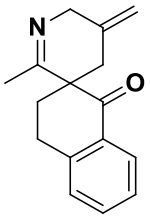


Prepared according to General Procedure D using **15** (50 mg, 0.234 mmol), Pd(dba)$_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol) and **73** (73 mg, 0.469 mmol) and TFA (1 mL). Flash column chromatography on silica gel (50% ethyl acetate in petrol) afforded the product as a colourless oil (42 mg, 80%).

FTIR ν_{max} (thin film/cm^{-1}) 2919, 1705, 1657, 1602**; ^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.82 (d, *J* = 7.5 Hz, 1H, Ar$\underline{H}$), 7.71 – 7.60 (m, 1H, Ar$\underline{H}$), 7.52 – 7.40 (m, 2H, Ar$\underline{H}$), 5.01 – 4.97 (m, 1H, C=C$\underline{H_A}$H$_B$), 4.88 – 4.85 (m, 1H, C=CH$_A$$\underline{H_B}$), 4.41 – 4.30 (m, 1H, NC$\underline{H_A}$H$_B$), 4.24 (d, *J* = 19.5 Hz, 1H, NCH$_A$$\underline{H_B}$), 3.11 (d, *J* = 18.0 Hz, 1H, ArC$\underline{H_A}$H$_B$), 3.04 (d, *J* = 18.0 Hz, 1H, ArCH$_A$$\underline{H_B}$), 2.78 (d, *J* = 13.0 Hz, 1H, C=CC$\underline{H_A}$H$_B$), 2.08 (d, *J* = 13.0 Hz, 1H, C=CCH$_A$$\underline{H_B}$), 1.78 – 1.75 (m, 3H, C$\underline{H_3}$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 206.4, 165.2,

152.6, 140.4, 136.0, 135.7, 128.2, 126.9, 124.9, 110.2, 58.5, 55.9, 39.3, 39.2, 23.2; **HRMS (ESI$^+$)** $C_{15}H_{15}NO$ requires M+H$^+$ 226.1226, found 226.1223.

2'-Methyl-5'-methylene-3,4,5',6'-tetrahydro-1*H*,4'*H*-spiro[naphthalene-2,3'-pyridin]-1-one (76)

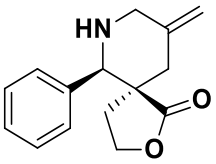


Prepared according to General Procedure D using **15** (50 mg, 0.234 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol) and **74** (88 mg, 0.469 mmol) and TFA (1 mL). Flash column chromatography on silica gel (75% ethyl acetate in petrol) afforded the product as a colourless oil (44 mg, 79%).

FTIR ν_{max} (thin film/cm^{-1}) 2927, 1674, 1655, 1599, 1454, 1224, 926, 905; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.08 (d, *J* = 7.5, 1H, Ar*H*), 7.52 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.35 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.26 (d, *J* = 7.5 Hz, 1H, Ar*H*), 4.98 (s, 1H, C=CH_AH$_B$), 4.80 (d, *J* = 1.0 Hz, 1H, C=CH$_A$$H_B$), 4.33 (dd, *J* = 20.0, 1.5 Hz, 1H, NCH_AH$_B$), 4.22 (dd, *J* = 20.0, 1.0 Hz, 1H, NCH$_A$$H_B$), 3.13 (ddd, *J* = 17.0, 13.5, 4.5 Hz, 1H, CH_AH$_B$), 2.91 – 2.81 (m, 1H, CH$_A$$H_B$), 2.56 (s, 2H, C$H_2$), 2.39 (td, *J* = 13.5, 5.0 Hz, 1H, CH_AH$_B$), 2.07 (ddd, *J* = 13.5, 4.5, 3.0 Hz, 1H, CH$_A$$H_B$), 1.95 – 1.93 (m, 3H, C$H_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 198.1, 167.3, 142.9, 139.6, 134.0, 131.6, 128.9, 128.4, 127.2, 110.5, 55.6, 55.3, 35.9, 30.4, 24.3, 24.1; **HRMS (ESI$^+$)** $C_{16}H_{17}NO$ requires M+H$^+$ 240.1383, found 240.1384.

7.5 – Functionalisation Products

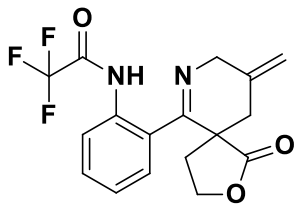
(5S,6R)-9-methylene-6-phenyl-2-oxa-7-azaspiro[4.5]decan-1-one (87)



To a refluxing solution of **61** (50 mg, 0.207 mmol) in MeOH (10 mL) was added $NaBH_4$ (31 mg, 0.829 mmol) and the mixture was left to stir at reflux for 1 h. Upon cooling to room temperature, sat. NH_4Cl (10 mL) was added and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (100% ethyl acetate) to afford the product (42 mg, 83%) as a single diastereoisomer as a white solid. Recrystallisation by slow evaporation of DMF afforded the product as colourless cubes.

m.p.: 158.3 °C (decomp.); **FTIR** ν_{max} (thin film/cm^{-1}) 3230, 2768, 1764, 1659; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37 – 7.27 (m, 5H, Ar*H*), 4.96 (s, 1H, C=C$H_A$$H_B$), 4.82 (s, 1H, C=C$H_A$$H_B$), 3.97 (td, *J* = 9.0, 5.0 Hz, 1H, OC$H_A$$H_B$), 3.80 (s, 1H, NC*H*), 3.71 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 3.43 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 3.12 – 3.03 (m, 1H, OC$H_A$$H_B$), 2.66 (d, *J* = 14.0 Hz, 1H, C=CC$H_A$$H_B$), 2.51 (d, *J* = 14.0 Hz, 1H, C=CC$H_A$$H_B$), 2.27 – 2.16 (m, 1H, OCH_2C$H_A$$H_B$), 2.03 – 1.90 (m, 1H, OCH_2C$H_A$$H_B$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.3, 141.5, 139.0, 129.0, 128.5, 127.7, 111.0, 68.0, 64.7, 53.2, 47.7, 43.2, 34.3; **HRMS (ESI^+)** $C_{15}H_{17}NO_2$ requires $M+H^+$ 244.1332, found 244.1333; **X-ray** see Appendix 5.

2,2,2-Trifluoro-*N*-(2-(9-methylene-1-oxo-7-azaspiro[4.5]dec-6-en-6-yl)phenyl)acetamide (88)

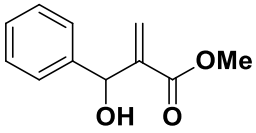


To a flame-dried flask charged with **61** (100 mg, 0.414 mmol), trifluoroacetamide (47 mg, 0.414 mmol), $[Cp^*RhCl_2]_2$ (6 mg, 0.010 mmol), $AgSbF_6$ (14 mg, 0.041 mmol) and $PhI(OAc)_2$ (200 mg, 0.622 mmol) was added CH_2Cl_2 (4 mL) and the reaction mixture was stirred at 40 °C for 16 h. Upon cooling to room temperature the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel (0→30% ethyl acetate in petrol) to afford the product (81 mg, 56%) as a pale yellow solid.

m.p.: 150.5 – 151.1 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 2920, 1766, 1715, 1657; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 14.10 (br, 1H, N*H*), 8.59 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar*H*), 7.49 – 7.38 (m, 1H, Ar*H*), 7.32 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.24 – 7.13 (m, 1H, Ar*H*), 5.19 (s, 1H, C=C$H_A$$H_B$), 5.08 (s, 1H, C=C$H_A$$H_B$), 4.71 (d, *J* = 21.0 Hz, 1H, NC$H_A$$H_B$), 4.62 (td, *J* = 9.5, 2.5 Hz, 1H, OC$H_A$$H_B$), 4.56 (d, *J* = 21.0 Hz, 1H, NC$H_A$$H_B$), 4.46 (td, *J* = 9.5, 8.0 Hz, 1H, OC$H_A$$H_B$), 2.85 (d, *J* = 13.0 Hz, 1H, C=CC$H_A$$H_B$), 2.74 (dt, *J* = 13.5, 9.5 Hz, 1H, $OCH_2C$$H_A$$H_B$), 2.51 (d, *J* = 13.0 Hz, 1H, C=CC$H_A$$H_B$), 2.36 (ddd, *J* = 13.5, 8.0, 2.5 Hz, 1H, $OCH_2C$$H_A$$H_B$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.2, 165.5, 155.2 (q, *J* = 37.0 Hz), 137.4, 136.1, 131.2, 127.4, 124.2, 122.4, 122.1, 116.1 (q, *J* = 289.0 Hz), 112.9, 65.2, 54.4, 50.7, 38.4, 33.5; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -76.2; **HRMS (ESI^+)** $C_{17}H_{15}N_2O_3$ requires $M+H^+$ 353.1108, found 353.1106.

7.6 – Synthesis of Substituted Carbamates

Methyl 2-(hydroxy(phenyl)methyl)acrylate (92)

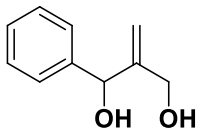


To a flask charged with DABCO (11.22 g, 100 mmol) was added dioxane (4 mL) and water (4 mL). Benzaldehyde (10.20 mL, 100 mmol) was added followed by methyl acrylate (27.02 mL, 300 mmol) and the resulting mixture was left to stir for 3 days. Upon completion, water (100 mL) was added the emulsion was extracted with dichloromethane (3 × 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentraed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (20% ethyl acetate in petrol) to afford the product as a colourless oil (12.09 g, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 4H, Ar*H*), 7.32 – 7.26 (m, 1H, Ar*H*), 6.34 (s, 1H, C=CH_AH$_B$), 5.84 – 5.83 (m, 1H, C=CH$_A$$H_B$), 5.57 (d, *J* = 5.5 Hz, 1H, C*H*OH), 3.73 (s, 3H, CH_3), 2.99 (d, *J* = 5.5 Hz, 1H, CHO*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.9, 142.1, 141.4, 128.6, 128.0, 126.7, 126.4, 73.5, 52.1.

These data are consistent with those reported in the literature.[73]

2-Methylene-1-phenylpropane-1,3-diol (93)

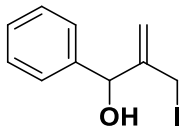


To a flame-dried flask charged with $LiAlH_4$ (11.39 g, 300 mmol) was added Et_2O (600 mL) and the resulting mixture was cooled to -78 °C. A solution of **92** (21.42 g, 100 mmol) in Et_2O (25 mL) was added dropwise and the resulting mixture was left to stir at rt for 16 h. The mixture was cooled to 0 °C and water (100 mL) was added dropwise. The emulsion was diluted with EtOAc (500 mL) and conc. HCl was added dropwise until the emulsion dispersed and the layers were partitioned. The aqueous layer was further extracted with EtOAc (2 × 400 mL) and the organic components were combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (40% ethyl acetate in petrol) to afford the product as a colourless oil (7.97 g, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H, Ar*H*), 5.38 (s, 1H, C*H*OH), 5.25 – 5.23 (m, 2H, C=CH_2), 4.17 (d, *J* = 13.0 Hz, 1H, CH_AH$_B$), 4.07 (d, *J* = 13.0 Hz, 1H, CH$_A$$H_B$), 2.56 (br, 1H, O*H*), 1.80 (br, 1H, O*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 149.5, 141.9, 128.7, 128.0, 126.4, 113.6, 76.5, 64.3.

These data are consistent with those reported in the literature.[74]

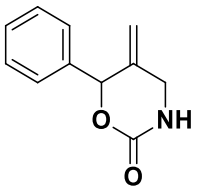
2-(Iodomethyl)-1-phenylprop-2-en-1-ol (94)



To a flask charged with triphenylphosphine (6.02 g, 21.64 mmol) and imidazole was added CH_2Cl_2 (20 mL) and EtOAc (20 mL), followed by **93** (3.23 g, 19.67 mmol). The resulting mixture was cooled to 0 °C and iodine (4.99 g, 19.67 mmol) was added portionwise. The reaction mixture was left to stir at rt in the dark for 16 h, before dilution with CH_2Cl_2 (20 mL) and the addition of water (40 mL). The layers were partitioned and the aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petrol) to afford the product as a colourless oil (1.90 g, 35%)

FTIR ν_{max} (thin film/cm^{-1}) 3369, 3028, 2874, 1492, 1453, 1157, 1023; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.30 (m, 5H, Ar*H*), 5.54 (s, 1H, PhC*H*OH), 5.45 (s, 1H, C=C$H_A$$H_B$), 5.40 (s, 1H, C=C$H_A$$H_B$), 4.00 (d, *J* = 9.5 Hz, 1H, IC$H_A$$H_B$), 3.65 (d, *J* = 9.5 Hz, 1H, IC$H_A$$H_B$), 2.14 (br, 1H, O*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 148.0, 141.4, 128.8, 128.4, 127.0, 114.6, 74.8, 6.2; **HRMS (ESI$^+$)** $C_{10}H_{11}IO$, requires M^+ 273.9849, found 273.9842.

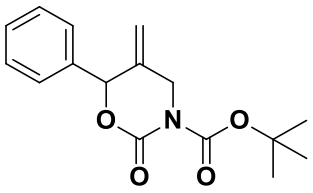
5-Methylene-6-phenyl-1,3-oxazinan-2-one (95)



To a solution of **94** (1.41 g, 5.13 mmol) in toluene (25 mL) was added AgOCN (1.15 g, 769 mmol) and the resulting mixture was left to stir at reflux for 16 h. Upon cooling, the resulting black precipitate was removed by filtration, and washed with cold CH_2Cl_2 (20 mL). The solvent was removed from the filtrate under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (70% ethyl acetate in petrol) to afford the product as a white solid (533 mg, 55%).

m.p.: 142 – 143 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 1697, 1475, 1274, 1102; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.31 (m, 5H, Ar*H*), 6.19 (br, 1H, N*H*), 5.77 (s, 1H, ArC*H*), 5.29 (s, 1H, C=CH_AH$_B$), 5.05 (s, 1H, C=CH$_A$$H_B$), 3.98 (d, *J* = 14.0, Hz, 1H, NCH_AH$_B$), 3.91 (d, *J* = 14.0 Hz, 1H, NCH$_A$$H_B$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.7, 136.9, 136.5, 128.8, 128.6, 126.2, 115.3, 81.2, 44.6; **HRMS (ESI^+)** $C_{11}H_{11}NO_2$ requires $M+H^+$ 190.0863, found 190.0863.

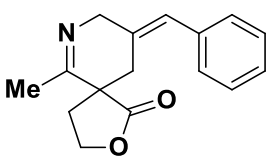
***Tert*-butyl 5-methylene-2-oxo-6-phenyl-1,3-oxazinane-3-carboxylate (96)**



To a flask charged with **95** (533 mg, 2.82 mmol) and DMAP (69 mg, 0.56 mmol) in CH_2Cl_2 (15 mL) was added a solution of Boc_2O (1.23 g, 5.63 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was left to stir for 3 h at rt. Upon completion, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (20% ethyl acetate in petrol) to afford the product as a white solid (783 mg, 96%).

m.p.: 152-156 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 1794, 1727, 1264; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.45 – 7.31 (m, 5H, Ar*H*), 5.76 (s, 1H, PhC*H*), 5.30 – 5.28 (m, 1H, C=CH_AH$_B$), 4.89 – 4.87 (m, 1H, C=CH$_A$$H_B$), 4.44 (d, *J* = 15.0 Hz, 1H, NCH_AH$_B$), 4.26 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$), 1.52 (s, 9H, C(C$H_3$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 151.9, 150.4, 138.3, 135.7, 129.0, 128.8, 126.9, 114.8, 84.1, 81.3, 48.5, 28.1; **HRMS (ESI^+)** $C_{16}H_{19}NO_4$ require $M+H^+$ 312.1206, found 312.1214.

(*E*)-9-Benzylidene-6-methyl-2-oxa-7-azaspiro[4.5]dec-6-en-1-one (98)

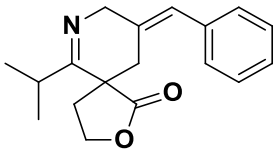


Prepared following General Procedure D using **96** (50 mg, 0.173 mmol), $Pd(dba)_2$ (5 mg, 0.009 mmol), **L10** (14 mg, 0.026 mmol), **49** (44 mg, 0.346 mmol) and TFA (1 mL)

at -20 °C for 16 h. The residue was purified by flash column chromatography on silica gel (75% ethyl acetate in petrol) afforded the product as a white solid (24 mg, 54%).

m.p.: 120 °C (decomp.); **FTIR** ν_{max} (thin film/cm^{-1}) 1761, 1659, 1375, 1171, 1024; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.37 – 7.32 (m, 2H, Ar*H*), 7.29 – 7.23 (m, 1H, Ar*H*), 7.21 – 7.18 (m, 2H, Ar*H*), 6.65 (s, 1H, C=C*H*Ph), 4.52 (d, *J* = 20.0 Hz, 1H, NCH_AH$_B$), 4.29 (d, *J* = 20.0 Hz, 1H, NCH$_A$$H_B$), 4.28 (td, *J* = 9.0, 4.0 Hz, 1H, OCH_AH$_B$), 4.01 (ddd, *J* = 9.0, 8.5, 7.5 Hz, 1H, OCH$_A$$H_B$), 2.98 (d, *J* = 13.5 Hz, 1H, C=CCH_AH$_B$), 2.68 (d, *J* = 13.5 Hz, 1H, C=CCH$_A$$H_B$), 2.27 (dt, *J* = 13.5, 8.5 Hz, 1H, OCH$_2$CH_AH$_B$), 2.06 – 2.02 (m, 3H, CH_3), 1.96 (ddd, *J* = 13.5, 7.5, 4.0 Hz, 1H, OCH$_2$CH$_A$$H_B$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 177.6, 163.9, 136.1, 131.7, 128.9, 128.7, 127.2, 126.5, 65.6, 57.0, 51.3, 32.8, 31.5, 23.2; **HRMS (ESI$^+$)** $C_{16}H_{17}NO_2$ requires M+H$^+$ 256.1332, found 256.1337; **[α]$_D^{23}$** +154.9 (*c* = 0.36, $CHCl_3$); **HPLC** (Cellulose-2, hexane:^{i}PrOH 80:20, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R (major) = 12.8, t_R(minor) = 18.5, er = 97:3.

(*E*)-9-Benzylidene-6-isopropyl-2-oxa-7-azaspiro[4.5]dec-6-en-1-one (99)

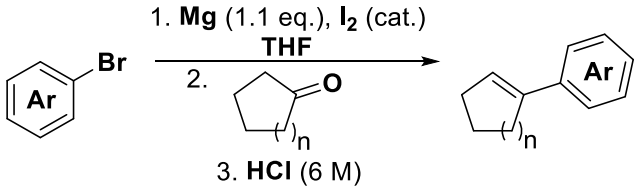


Prepared following General Procedure D using **96** (50 mg, 0.173 mmol), Pd(dba)$_2$ (5 mg, 0.009 mmol), **L10** (14 mg, 0.026 mmol), **80** (54 mg, 0.346 mmol) and TFA (1 mL) at -20 °C for 16 h. The residue was purified by flash column chromatography on silica gel (15% ethyl acetate in petrol) afforded the product as a white solid (21 mg, 43%).

m.p.: 130 °C (decomp.); **FTIR** ν_{max} (thin film/cm^{-1}) 2974, 1766, 1660, 1173, 1027; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.37 – 7.31 (m, 2H, Ar*H*), 7.28 – 7.17 (m, 3H, Ar*H*), 6.65 (s, 1H, C=C*H*Ph), 4.55 (d, *J* = 20.0 Hz, 1H, NCH_AH$_B$), 4.36 – 4.23 (m, 2H, NCH$_A$$H_B$, OC$H_AH_B$), 3.98 (td, *J* = 9.0, 7.5 Hz, 1H, OCH$_A$$H_B$), 2.97 (d, *J* = 13.5 Hz, 1H, C=CCH_AH$_B$), 2.67 (d, *J* = 13.5 Hz, 1H, C=CCH$_A$$H_B$), 2.41 – 2.22 (m, 2H, C*H*(CH$_3$)$_2$, OCH$_2$CH_AH$_B$), 1.96 (ddd, *J* = 13.5, 7.5, 3.5 Hz, 1H, OCH$_2$CH$_A$$H_B$), 1.22 (d, *J* = 6.5 Hz, 3H, CH(CH_3)(CH$_3$)), 1.14 (d, *J* = 6.5 Hz, 3H, CH(CH$_3$)(CH_3)); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 177.8, 171.9, 136.2, 132.3, 128.9, 128.7, 127.2, 126.3, 65.5, 57.1, 52.6, 35.1, 32.8, 32.1, 23.1, 22.2; **HRMS (ESI$^+$)** $C_{18}H_{21}NO_2$ requires M+H$^+$ 284.1645, found 284.1651; **[α]$_D^{23}$** +91.2 (*c* = 0.34, CHCl$_3$); **HPLC** (Cellulose-2, hexane:^{i}PrOH 90:10, flow rate 1.0 mL/min, λ = 254 nm, 22 °C) t_R (major) = 8.4, t_R(minor) = 15.8, er = 98.5:1.5; **nOe** see Appendix 4.

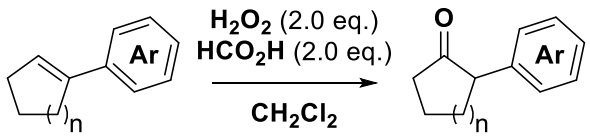
7.7 – Synthesis of Aryl Ketone Substrates

General Procedure E – Addition of Aryl Grignards to Cyclic Ketones



To a flame-dried flask charged with a stirrer bar and flame-dried magnesium (1.1 eq.) was added I_2 (one crystal) and THF (1.0 M with respect to aryl bromide). To this stirring solution was added the requisite aryl bromide (1.0 eq.) and the reaction mixture left to stir for 5 min at rt, followed by heating at reflux for 1 h. Upon cooling, the cyclic ketone was added either neat, or as a solution in THF and the resulting mixture heated at reflux for an addition 1.5 h. Upon cooling, the reaction mixture was added to an ice-water mix, usually accompanied by formation of a precipitate. To this mixture was added HCl (6.0 M in H_2O) and extracted with ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude residue was purified as specified below.

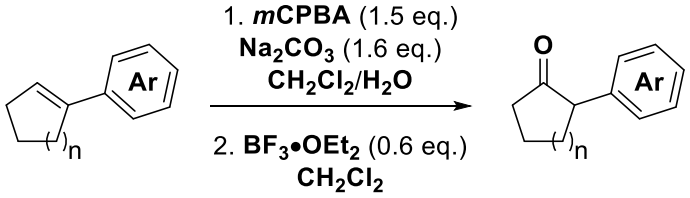
General Procedure F – Wacker-type Oxidation of Alkenes with H_2O_2/HCO_2H



To a flask containing H_2O_2 (2.0 eq., 30% w/v) was added HCO_2H (2.0 eq.) and the mixture was stirred at 40 °C for 10 min at rt. The solution was added to a flask containing the alkene substrate either neat or as a solution in CH_2Cl_2 and the resulting

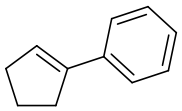
mixture was stirred at rt for 16 h. The mixture was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The layers were partitioned and the aqueous layer was further extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified as specified below.

General Procedure G – Epoxidation-Meinwald Rearrangement of Alkenes



To a solution of mCPBA (1.5 eq.) in CH_2Cl_2:H_2O (1:1, 0.125 M with respect to alkene) was added Na_2CO_3 (1.6 eq.) and the resulting mixture left to stir for 20 min. Alkene (1.0 eq.) was added as a solution in CH_2Cl_2 and the resulting mixture monitored by TLC. Upon completion, the layers were separated and the organics were extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was taken up in CH_2Cl_2 (0.18 M) and was added BF_3•OEt_2 (0.6 eq.) dropwise. The resulting solution was stirred for 5 min before the addition of sat. $NaHCO_3$. The organics were extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified as specified below.

Cyclopent-1-en-1-ylbenzene (103)

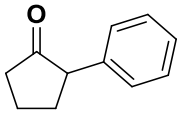


Prepared following General Procedure E using Mg (768 mg, 31.59 mmol), bromobenzene (3.30 mL, 31.59 mmol) and cyclopentanone (2.56 mL, 28.72 mmol) in THF (30 mL). Purification by flash column chromatography (100% petrol on silica gel) afforded the product (3.10 g, 74%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H, Ar*H*), 7.36 – 7.29 (m, 2H, Ar*H*), 7.26 – 7.19 (m, 1H, Ar*H*), 6.24 – 6.16 (m, 1H, C=C*H*), 2.79 – 2.68 (m, 2H, C=CC*H*$_2$), 2.59 – 2.50 (m, 2H, C=CC*H*$_2$), 2.09 – 1.99 (m, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 142.6, 137.0, 128.4, 127.0, 126.2, 125.7, 33.5, 33.3, 23.5.

These data are consistent with those reported in the literature.[75]

2-Phenylcyclopentanone (108)

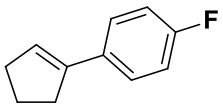


Prepared following General Procedure F using **103** (1.41 g, 9.76 mmol), H_2O_2 (2.21 mL, 19.53 mmol) and HCO_2H (737 µL, 19.53 mmol). Purification by flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product as a colourless oil (761 mg, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H, Ar*H*), 7.29 – 7.22 (m, 1H, Ar*H*), 7.22 – 7.17 (m, 2H, Ar*H*), 3.33 (dd, *J* = 11.0, 9.0 Hz, 1H, C*H*Ar), 2.56 – 2.43 (m, 2H, 2 × C*H*), 2.36 – 2.24 (m, 1H, C*H*), 2.22 – 2.07 (m, 2H, 2 × C*H*), 2.01 – 1.86 (m, 1H, C*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 218.0, 138.4, 128.5, 128.1, 126.8, 55.2, 38.4, 31.7, 20.8.

These data are consistent with those reported in the literature.[76]

1-(Cyclopent-1-en-1-yl)-4-fluorobenzene (104)

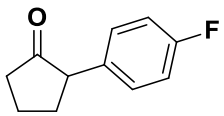


Prepared following General Procedure E using Mg (695 mg, 28.59 mmol), 1-bromo-4-fluorobenzene (3.13 mL, 28.59 mmol) and cyclopentanone (2.30 mL, 26.00 mmol) in THF (30 mL). Purification by flash column chromatography (100% petrol on silica gel) afforded the product (2.63 g, 63%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H, Ar*H*), 7.03 – 6.96 (m, 2H, Ar*H*), 6.15 – 6.07 (m, 1H, C=C*H*), 2.72 – 2.65 (m, 2H CH_2), 2.56 – 2.49 (m, 2H, CH_2), 2.07 – 1.97 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.0 (d, *J* = 245.5 Hz), 141.6, 133.2 (d, *J* = 3.0 Hz), 127.2 (d, *J* = 8.0 Hz), 125.9 (d, *J* = 1.5 Hz), 115.2 (d, *J* = 21.5 Hz), 33.5 (2 × C), 23.5; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -115.7 (m).

These data are consistent with those reported in the literature.[77]

2-(4-Fluorophenyl)cyclopentanone (109)

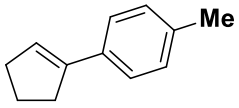


Prepared following General Procedure F using **104** (1.44 g, 8.86 mmol), H_2O_2 (2.00 mL, 17.72 mmol) and HCO_2H (669 µL, 17.72 mmol). Purification by flash column chromatography (15% ethyl acetate in petrol on silica gel) afforded the product as a colourless oil (701 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 2H, Ar*H*), 7.05 – 6.98 (m, 2H, Ar*H*), 3.30 (dd, *J* = 11.5, 8.5 Hz, 1H, C*H*Ar), 2.55 – 2.43 (m, 2H, 2 × C*H*), 2.34 – 2.22 (m, 1H, C*H*), 2.21 – 2.11 (m, 1H, C*H*), 2.11 – 2.01 (m, 1H, C*H*), 2.00 – 1.88 (m, 1H, C*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 217.9, 161.9 (d, *J* = 245.0 Hz), 134.1 (d, *J* = 3.0 Hz), 129.7 (d, *J* = 8.0 Hz), 115.5 (d, *J* = 21.5 Hz), 54.6, 38.3, 31.8, 20.8; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -116.1 (m).

These data are consistent with those reported in the literature.[76]

1-(Cyclopent-1-en-1-yl)-4-methylbenzene (105)

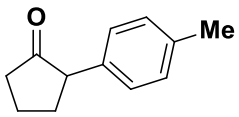


Prepared following General Procedure E using Mg (714 mg, 29.37 mmol), 1-bromo-4-methylbenzene (3.60 mL, 29.37 mmol) and cyclopentanone (2.35 mL, 26.70 mmol) in THF (30 mL). Purification by flash column chromatography (100% petrol on silica gel) afforded the product (3.17 g, 75%) as a white solid.

m.p.: 36-38 °C (lit. not reported); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.34 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.12 (d, *J* = 8.0 Hz, 2H, Ar*H*), 6.16 – 6.11 (m, 1H, C=C*H*), 2.73 – 2.66 (m, 2H, CH_2), 2.56 – 2.49 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.06 – 1.97 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 142.4, 136.6, 134.2, 129.1, 125.6, 125.2, 33.4 (2 × C), 23.5, 21.3.

These data are consistent with those reported in the literature.[78]

2-(*p*-Tolyl)cyclopentanone (110)

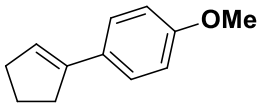


Prepared according to General Procedure G using **105** (2.00 g, 12.64 mmol) and mCPBA (3.27 g, 18.46 mmol) in CH_2Cl_2 (50 mL). Purification by flash column chromatography (5% diethyl ether in petrol on silica gel) afforded the products as a colourless oil (872 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.11 (d, *J* = 8.0 Hz, 2H, Ar*H*), 3.31 (dd, *J* = 11.0, 8.5 Hz, 1H, C*H*Ar), 2.56 – 2.43 (m, 2H, 2 × C*H*), 2.36 (s, 3H, CH_3), 2.34 – 2.24 (m, 1H, C*H*), 2.24 – 2.06 (m, 2H, 2 × C*H*), 2.02 – 1.87 (m, 1H, C*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 218.5, 136.7, 135.5, 129.5, 128.1, 55.2, 38.5, 31.9, 21.2, 21.0.

These data are consistent with those reported in the literature.[76]

1-(Cyclopent-1-en-1-yl)-4-methoxybenzene (106)

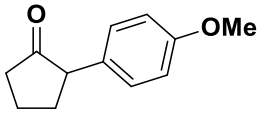


Prepared following General Procedure E using Mg (650 mg, 26.74 mmol), 1-bromo-4-methoxybenzene (3.36 mL, 26.74 mmol) and cyclopentanone (2.15 mL, 24.31 mmol) in THF (30 mL). Purification by flash column chromatography (100% petrol on silica gel) afforded the product (3.14 g, 67%) as a white solid.

m.p.: 79-82 °C (lit. 83-84 °C); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.34 (m, 2H, Ar*H*), 6.87 – 6.83 (m, 2H, Ar*H*), 6.07 – 6.03 (m, 1H, C=C*H*), 3.81 (s, 3H, OC*H*$_3$), 2.71 – 2.64 (m, 2H, C*H*$_2$), 2.55 – 2.48 (m, 2H, C*H*$_2$), 2.05 – 1.96 (m, 2H, C*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 158.7, 141.9, 129.9, 126.8, 124.1, 113.8, 55.4, 33.5, 33.4, 23.5.

These data are consistent with those reported in the literature.[78]

2-(4-Methoxyphenyl)cyclopentanone (111)



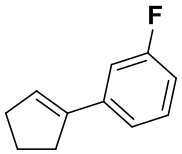
Prepared according to General Procedure F using **106** (2.33 g, 13.35 mmol), H_2O_2 (3.00 mL, 26.70 mmol) and formic acid (1.50 mL, 26.70 mmol) in CH_2Cl_2 (10 mL). Purification by flash column chromatography (20% ethyl acetate in petrol on silica gel) afforded the product as a white solid (1.04 g, 41%).

m.p.: 49-51 °C (lit. not reported); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.11 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.88 (d, *J* = 9.0 Hz, 2H, Ar*H*), 3.79 (s, 3H, OC*H*$_3$), 3.27 (dd, *J* = 11.0, 8.5 Hz, 1H,

C*H*Ar), 2.54 – 2.40 (m, 2H, 2 × C*H*), 2.34 – 2.21 (m, 1H, C*H*), 2.21 – 2.01 (m, 2H, 2 × C*H*), 1.99 – 1.85 (m, 1H, C*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 218.6, 158.6, 130.6, 129.2, 114.2, 55.4, 54.7, 38.4, 31.9, 20.9.

These data are consistent with those reported in the literature.[76]

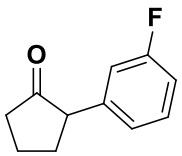
1-(Cyclopent-1-en-1-yl)-3-fluorobenzene (107)



Prepared following General Procedure E using Mg (650 mg, 26.74 mmol), 1-bromo-3-fluorobenzene (3.36 mL, 26.74 mmol) and cyclopentanone (2.15 mL, 24.31 mmol) in THF (30 mL). Purification by flash column chromatography (100% petrol on silica gel) afforded the product (306 mg, 7%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 2H, Ar*H*), 7.17 – 7.10 (m, 1H, Ar*H*), 6.99 – 6.88 (m, 1H, Ar*H*), 6.27 – 6.20 (m, 1H, C=C*H*), 2.75 – 2.66 (m, 2H, CH_2), 2.60 – 2.50 (m, 2H, CH_2), 2.12 – 1.97 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.0 (d, *J* = 244.5 Hz), 141.6 (d, *J* = 2.5 Hz), 139.2 (d, *J* = 7.5 Hz), 129.6 (d, *J* = 8.5 Hz), 127.7, 121.2 (d, *J* = 2.5 Hz), 113.5 (d, *J* = 21.5 Hz), 112.4 (d, *J* = 21.5 Hz), 33.4, 33.2, 23.3; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -114.0.

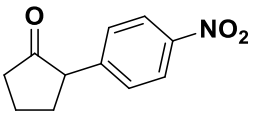
2-(3-Fluorophenyl)cyclopentanone (112)



Prepared according to General Procedure F using **107** (306 mg, 1.89 mmol), H_2O_2 (427 µL, 3.77 mmol) and formic acid (142 µL, 3.77mmol) in CH_2Cl_2 (10 mL). Purification by flash column chromatography (20% diethyl ether in petrol on silica gel) afforded the product as a colourless oil (69 mg, 20%).

FTIR ν_{max} (thin film/cm^{-1}) 2966, 1742, 1615, 1588; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37 – 7.22 (m, 1H, Ar*H*), 7.01 – 6.88 (m, 3H, Ar*H*), 3.33 (dd, *J* = 11.0, 9.0 Hz, 1H, C*H*Ar), 2.59 – 2.41 (m, 2H, 2 × C*H*), 2.37 – 2.23 (m, 1H, C*H*), 2.23 – 2.03 (m, 2H, 2 × C*H*), 2.03 – 1.85 (m, 1H, C*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 217.3, 163.1 (d, *J* = 246.0 Hz), 140.8 (d, *J* = 7.0 Hz), 130.1 (d, *J* = 8.5 Hz), 124.0 (d, *J* = 3.0 Hz), 115.2 (d, *J* = 22.0 Hz), 114.0 (d, *J* = 21.0 Hz), 55.0, 38.5, 31.6, 20.9; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -113.1; **HRMS (ESI$^+$)** $C_{11}H_{11}FO$ requires $M+H^+$ 179.0867, found 179.0868.

2-(4-Nitrophenyl)cyclopentanone (113)



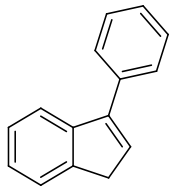
To a stirring solution of nitrobenzene (3.08 mL, 30 mmol) and cyclopentanone (1.33 mL, 15 mmol) in DMSO (75 mL) was added NaO^{t}Bu (1.73 g, 18 mmol) and the resulting mixture was left to stir at rt for 1 h under an atmosphere of air. Upon completion, sat. NH_4Cl (30 mL) was added and the aqueous layer was extracted with

EtOAc (3 × 25 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (20% ethyl acetate in petrol on silica gel) afforded the product as a red-orange oil (758 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.38 (d, *J* = 9.0 Hz, 2H, Ar*H*), 3.45 (dd, *J* = 11.5, 8.5 Hz, 1H, C*H*Ar), 2.63 – 2.48 (m, 2H, 2 × C*H*), 2.39 – 2.08 (m, 3H, 3 × C*H*), 2.06 – 1.91 (m, 1H, C*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 216.1, 147.1, 145.8, 129.2, 123.9, 55.2, 38.4, 31.3, 20.9.

These data are consistent with those reported in the literature.[57]

3-Phenyl-1H-indene (134)



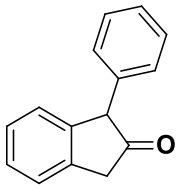
Prepared following General Procedure E using Mg (1.12 g, 46.19 mmol), bromobenzene (4.92 mL, 46.19 mmol) and 1-indanone (5.55 g, 41.99 mmol) in Et_2O (45 mL). Purification by flash column chromatography (100% petrol on silica gel) afforded the product (6.29 g, 71%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 3H, Ar*H*), 7.55 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.47 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.42 – 7.30 (m, 2H, Ar*H*), 7.27 (td, *J* = 7.5, 1.0 Hz, 1H, Ar*H*), 6.60 (t, *J* = 2.0 Hz, 1H, C=C*H*), 3.53 (d, *J* = 2.0 Hz, 2H, C*H*$_2$); **^{13}C NMR (101**

MHz, $CDCl_3$) δ 145.3, 144.9, 144.1, 136.3, 131.1, 128.7, 127.9, 127.7, 126.3, 125.0, 124.3, 120.5, 38.3.

These data are consistent with those reported in the literature.[79]

1-Phenyl-1*H*-inden-2(3*H*)-one (135)

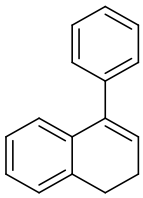


To a solution of **134** (6.29 g, 32.70 mmol) in acetone/H_2O/EtOAc (400 mL, 10/2/2) was added $NaHCO_3$ (33.00 g, 392.6 mmol). To the resulting suspension was added OXONE® monopersulfate (20.10 g, 65.40 mmol) portion-wise and the resulting mixture was left to stir at rt for 16 h. Water (400 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product as a yellow oil (4.87 g, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 6H, Ar*H*), 7.23 – 7.17 (m, 1H, Ar*H*), 7.15 – 7.08 (m, 2H, Ar*H*), 4.69 (s, 1H, C*H*Ar), 3.68 (s, 2H, ArC*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 214.1, 141.4, 138.2, 137.4, 128.9, 128.6, 128.1, 128.0, 127.5, 126.2, 125.0, 59.9, 43.1.

These data are consistent with those reported in the literature.[80]

4-Phenyl-1,2-dihydronaphthalene (142)

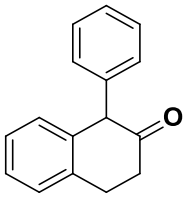


Prepared following General Procedure E using Mg (1.34 g, 55.0 mmol), bromobenzene (5.78 mL, 55.0 mmol) and 1-tetralone (6.65 mL, 50.0 mmol) in THF (50 mL). Purification by flash column chromatography (100% petrol on silica gel) afforded the product as a colourless oil (8.00 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H, Ar*H*), 7.23 – 7.20 (m, 1H, Ar*H*), 7.17 (td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.12 (td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.02 (d, *J* = 7.5 Hz, 1H, Ar*H*), 6.10 (t, *J* = 4.5 Hz, 1H, C=C*H*), 2.87 (t, *J* = 8.0 Hz, 2H, ArCH_2), 2.46 – 2.39 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 140.9, 140.0, 136.9, 135.2, 128.9, 128.4, 127.8, 127.7, 127.2, 127.1, 126.3, 125.6, 28.4, 23.7.

These data are consistent with those reported in the literature.[79]

1-Phenyl-3,4-dihydronaphthalen-2(1*H*)-one (143)



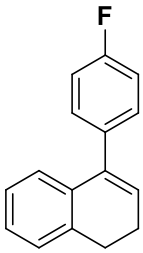
Prepared according to General Procedure G using **142** (7.40 g, 35.90 mmol), mCPBA (9.30 g, 53.8 mmol), $NaHCO_3$ (4.80 g, 57.4 mmol) and BF_3•OEt_2 (2.70 mL, 21.5 mmol).

Purification by flash column chromatography (5→10% ethyl acetate in petrol on silica gel) afforded the product as a yellow oil (7.32 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 6H), 7.14 – 7.05 (m, 2H), 7.02 (d, *J* = 7.3 Hz, 1H), 4.76 (s, 1H), 3.17 – 2.99 (m, 2H), 2.73 (dt, *J* = 16.9, 6.4 Hz, 1H), 2.64 – 2.54 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 209.7, 137.7, 137.1, 136.6, 129.7, 128.8, 128.8, 128.1, 127.5, 127.4, 127.3, 60.0, 37.1, 28.3.

These data are consistent with those reported in the literature.[80]

4-(4-Fluorophenyl)-1,2-dihydronaphthalene (149)

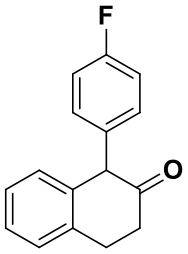


Prepared according to General Procedure E using Mg (183 mg, 7.52 mmol), 1-bromo-4-fluorobenzene (826 µL, 7.52 mmol) and 1-tetralone (910 µL, 6.84 mmol) in THF (7 mL). Purification by flash column chromatography (100% petrol on silica gel) afforded the product as a colourless oil (941 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H, Ar*H*), 7.23 – 7.15 (m, 2H, Ar*H*), 7.15 – 7.03 (m, 3H, Ar*H*), 6.97 (d, *J* = 7.5 Hz, 1H, Ar*H*), 6.07 (t, *J* = 4.5 Hz, 1H, C=C*H*), 2.86 (t, *J* = 8.0 Hz, 2H, ArCH_2), 2.46 – 2.36 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.2 (d, *J* = 245.5 Hz), 139.1, 136.9, 136.9 (d, *J* = 3.5 Hz), 135.1, 130.4 (d, *J* = 8.0 Hz), 127.9, 127.8, 127.3, 126.4, 125.4, 115.2 (d, *J* = 21.0 Hz), 28.4, 23.6; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -115.7 (m).

These data are consistent with those reported in the literature.[81]

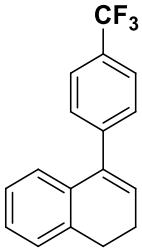
1-(4-Fluorophenyl)-3,4-dihydronaphthalen-2(1*H*)-one (154)



Prepared according to General Procedure G using **149** (941 mg, 4.20 mmol), mCPBA (1.09 g, 6.29 mmol), $NaHCO_3$ (564 mg, 6.71 mmol) and BF_3•OEt_2 (311 µL, 2.52 mmol). Purification by flash column chromatography (5% ethyl acetate in petrol on silica gel) afforded the product as a yellow oil (396 mg, 39%).

FTIR ν_{max} (thin film/cm^{-1}) 2910, 1718, 1602, 1505, 1226; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.31 – 7.20 (m, 3H, Ar*H*), 7.09 – 6.95 (m, 5H, Ar*H*), 4.73 (s, 1H, C*H*Ar), 3.17 – 3.01 (m, 2H, ArCH_2), 2.75 – 2.56 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 209.6, 162.2 (d, *J* = 246.0 Hz), 137.0, 136.4, 133.3 (d, *J* = 3.0 Hz), 130.5 (d, *J* = 8.0 Hz), 129.5, 128.1, 127.6, 127.4, 115.7 (d, *J* = 21.5 Hz), 59.1, 37.1, 28.2; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -115.5 (m); **HRMS (ESI^+)** $C_{16}H_{13}FO$ requires M^+ 240.0945, found 240.0947.

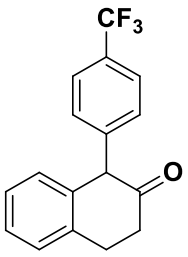
4-(4-(Trifluoromethyl)phenyl)-1,2-dihydronaphthalene (150)



Prepared according to General Procedure E using Mg (201 mg, 8.27 mmol), 1-bromo-4-(trifluoromethyl)benzene (1.16 mL, 8.27 mmol) and 1-tetralone (1.00 mL, 7.52 mmol) in THF (9 mL). Purification by flash column chromatography (100% petrol on silica gel) afforded the product as a colourless oil (886 mg, 39%).

FTIR ν_{max} (thin film/cm^{-1}) 2937, 2831, 1324, 1124; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.47 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.24 – 7.21 (m, 1H, Ar*H*), 7.19 (td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.12 (td, *J* = 7.5, 2.0 Hz, 1H, Ar*H*), 6.93 (dd, *J* = 7.5, 15 Hz, 1H, Ar*H*), 6.13 (t, *J* = 4.5 Hz, 1H, C=C*H*), 2.87 (t, *J* = 8.0 Hz, 2H, ArCH_2), 2.48 – 2.38 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 144.6, 139.1, 136.9, 134.6, 132.2, 129.4 (q, *J* = 32.5 Hz), 129.2, 129.1, 127.9, 127.8, 127.5, 126.5, 125.3 (m, 2 × C), 124.5 (q, *J* = 272.0 Hz), 28.3, 23.7; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -62.4; **HRMS (ESI$^+$)** $C_{17}H_{13}F_3$ requires M+H$^+$ 274.0964, found 274.0965.

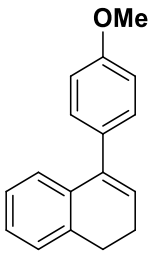
1-(4-(Trifluoromethyl)phenyl)-3,4-dihydronaphthalen-2(1*H*)-one (155)



Prepared according to General Procedure G using **150** (872 mg, 3.18 mmol), mCPBA (823 mg, 4.77 mmol), $NaHCO_3$ (427 mg, 5.09 mmol) and BF_3•OEt_2 (235 µL, 1.91 mmol). Purification by flash column chromatography (40% dichloromethane in petrol on silica gel) afforded the product as an amorphous yellow solid (330 mg, 36%).

FTIR ν_{max} (thin film/cm^{-1}) 2951, 1719, 1617, 1327, 1124; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.34 – 7.20 (m, 5H, Ar*H*), 6.95 (d, *J* = 7.5 Hz, 1H, Ar*H*), 4.82 (s, 1H, C*H*Ar), 3.18 – 3.03 (m, 2H, ArCH_2), 2.77 – 2.59 (m, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 208.8, 141.7, 137.0, 135.8, 129.7, (q, *J* = 32.5 Hz), 129.5, 129.4, 128.2, 127.8, 127.5, 125.8 (q, *J* = 3.5 Hz), 124.2 (q, *J* = 272.0 Hz), 59.6, 37.4, 28.2; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -62.6; **HRMS (ESI^+)** $C_{17}H_{13}F_3O$ requires $M+H^+$ 291.0991, found 291.0995.

4-(4-Methoxyphenyl)-1,2-dihydronaphthalene (151)

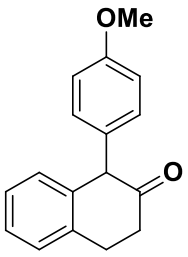


Prepared according to General Procedure E using Mg (201 mg, 8.27 mmol), 4-bromoanisole (1.04 mL, 8.27 mmol) and 1-tetralone (1.00 mL, 7.52 mmol) in THF (9 mL). Purification by flash column chromatography (20% dichloromethane in petrol on silica gel) afforded the product as a white solid (1.09 g, 56%).

m.p.: 42-45 °C (lit. not reported); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 – 7.27 (m, 2H, Ar*H*), 7.23 – 7.09 (m, 3H, Ar*H*), 7.03 (d, *J* = 7.5 Hz, 1H, Ar*H*), 6.95 – 6.89 (m, 2H, Ar*H*), 6.06 (t, *J* = 4.5 Hz, 1H, C=C*H*), 3.85 (s, 3H, OCH_3), 2.85 (t, *J* = 8.0 Hz, 2H, ArCH_2), 2.40 (td, *J* = 8.0, 4.5 Hz, 2H, CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 158.9, 139.4, 137.0, 135.4, 133.3, 129.9, 127.7, 127.1, 127.0, 126.3, 125.5, 113.8, 55.4, 28.5, 23.6.

These data are consistent with those reported in the literature.[82]

1-(4-Methoxyphenyl)-3,4-dihydronaphthalen-2(1*H*)-one (156)



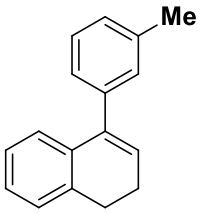
To a stirring solution of $NaHCO_3$ (7.11 g, 84.63 mmol) in H_2O (35 mL) was added OXONE® monopersulfate (5.20 g, 16.93 mmol) portion-wise and the resulting mixture was stirred for 10 minutes. A solution of **151** (500 mg, 2.12 mmol) in acetone (28 mL) was added dropwise and the resulting solution was left to stir for 2.5 h. Water (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was taken up in CH_2Cl_2 (12 mL) and stirred at rt. BF_3•OEt_2 (157 µL, 1.27 mmol) was added and the resulting mixture was stirred at rt for 5 min. Brine solution (20 mL) was added, followed by sat. $NaHCO_3$ (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography (5→10% ethyl acetate in petrol on silica gel) afforded the product as a colourless oil which crystallises upon standing to give a white solid (367 mg, 69%).

m.p.: 79-81 °C (lit. not reported); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.30 – 7.20 (m, 3H, Ar*H*), 7.05 – 6.97 (m, 3H, Ar*H*), 6.88 – 6.80 (m, 2H, Ar*H*), 4.70 (s, 1H, C*H*Ar), 3.78 (s, 3H, OCH_3), 3.17 – 3.07 (m, 1H, ArCH_AH_B), 3.02 (dt, *J* = 15.5, 6.5 Hz, 1H, ArCH_AH_B), 2.71 (dt, *J* = 17.0, 6.5 Hz, 1H, CH_AH_B), 2.57 (ddd, *J* = 17.0, 7.5, 6.5 Hz, 1H, CH_AH_B);

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.8, 158.8, 137.0, 136.8, 129.8, 129.6, 127.9, 127.3, 127.2, 114.2, 59.1, 55.3, 36.9, 28.2.

These data are consistent with those reported in the literature.[60]

4-(*m*-Tolyl)-1,2-dihydronaphthalene (152)

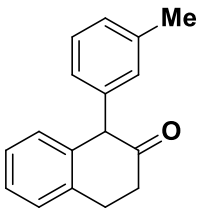


Prepared according to General Procedure E using Mg (201 mg, 8.27 mmol), 1-bromo-3-methylbenzene (1.00 mL, 8.27 mmol) and 1-tetralone (1.00 mL, 7.52 mmol) in THF (9 mL). Purification by flash column chromatography (100% petrol on silica gel) afforded the product as a colourless oil (1.01 g, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.22 – 7.08 (m, 6H, Ar*H*), 7.04 – 6.99 (m, 1H, Ar*H*), 6.08 (t, *J* = 4.5 Hz, 1H, C=C*H*), 2.86 (t, *J* = 8.0 Hz, 2H, ArCH_2), 2.44 – 2.39 (m, 2H, CH_2), 2.38 (s, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 140.9, 140.1, 137.9, 136.9, 135.3, 129.6, 128.2, 128.0, 127.7, 127.6, 127.1, 126.3, 126.0, 125.6, 28.5, 23.7, 21.6.

These data are consistent with those reported in the literature.[81]

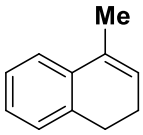
1-(*m*-Tolyl)-3,4-dihydronaphthalen-2(1*H*)-one (157)



Prepared according to General Procedure G using **152** (988 mg, 4.48 mmol), mCPBA (1.55 g, 8.97 mmol), $NaHCO_3$ (791 mg, 9.42 mmol) and BF_3•OEt_2 (332 µL, 2.69 mmol). Purification by flash column chromatography (30→50% dichloromethane in petrol on silica gel) afforded the product as an amorphous yellow oil (240 mg, 23%).

FTIR ν_{max} (thin film/cm^{-1}) 2915, 1717, 1603, 1487; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.31 – 7.14 (m, 4H, Ar*H*), 7.07 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.02 (d, *J* = 7.5 Hz, 1H, Ar*H*), 6.95 (s, 1H, Ar*H*), 6.85 (d, *J* = 7.5 Hz, 1H, Ar*H*), 4.72 (s, 1H, C*H*Ar), 3.19 – 3.09 (m, 1H, ArC$H_A$$H_B$), 3.03 (dt, *J* = 15.5, 6.5 Hz, 1H, ArC$H_A$$H_B$), 2.74 (dt, *J* = 17.0, 6.5 Hz, 1H, C$H_A$$H_B$), 2.63 – 2.53 (m, 1H, C$H_A$$H_B$), 2.31 (s, 3H, C$H_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 209.9, 138.5, 137.7, 137.1, 136.7, 129.8, 129.5, 128.7, 128.2, 128.0, 127.4, 127.3, 125.8, 59.9, 37.2, 28.4, 21.6; **HRMS (ESI$^+$)** $C_{17}H_{16}O$ requires M^+ 236.1196, found 236.1199.

4-Methyl-1,2-dihydronaphthalene (153)



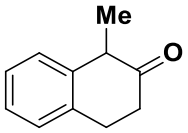
A round-bottomed flask was charged with Mg (274 mg, 11.28 mmol), fitted with a condenser and flame-dried under a high vacuum. The reaction vessel was back-filled

with an atmosphere of nitrogen. A crystal of iodine was added followed by Et_2O (7.5 mL). Iodomethane (749 µL, 12.03 mmol) was added dropwise as to maintain a gentle reflux and the resulting mixture was left to stir for a further 20 min at rt. 1-Tetralone (1.00 mL, 7.52 mmol) was added dropwise and the resulting mixture was left to stir for an addition 1h at rt. Upon completion, HCl (4.5 mL, 3 M, 13.54 mmol) was added and the resulting mixture was left to stir at rt for 1 h. The resulting mixture was extracted with Et_2O (3 × 15 mL) and the combined organics were washed with sat. $NaHCO_3$ (20 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (100% petrol on silica gel) afforded the product as a colourless oil (909 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.11 (m, 4H, Ar*H*), 5.88 – 5.84 (m, 1H, C=C*H*), 2.81 – 2.73 (m, 2H, ArC*H*$_2$), 2.31 – 2.21 (m, 2H, C*H*$_2$), 2.07 (app. dd, *J* = 3.5, 1.5 Hz, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.4, 136.0, 132.3, 127.5, 126.8, 126.5, 125.5, 122.9, 28.5, 23.3, 19.4.

These data are consistent with those in the literature.[82]

1-Methyl-3,4-dihydronaphthalen-2(1*H*)-one (158)

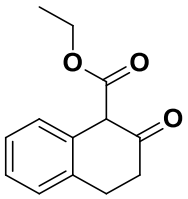


Prepared according to General Procedure G using **153** (875 mg, 6.07 mmol), mCPBA (2.09 g, 12.14 mmol), $NaHCO_3$ (1.07 g, 12.74 mmol) and BF_3•OEt_2 (449 µL, 3.64 mmol). Purification by flash column chromatography (3→7% ethyl acetate in petrol on silica gel) afforded the product as an amorphous yellow oil (246 mg, 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 4H, Ar*H*), 3.54 (q, *J* = 7.0 Hz, 1H, C*H*Me), 3.18 – 3.02 (m, 2H, ArCH_2), 2.64 (dt, *J* = 17.5, 6.0 Hz, 1H, CH_AH$_B$), 2.50 (ddd, *J* = 17.5, 9.0, 6.0 Hz, 1H, CH$_A$$H_B$), 1.49 (d, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 212.5, 138.1, 136.9, 127.6, 127.2, 126.8, 126.2, 47.6, 37.3, 28.1, 14.3.

These data are consistent with those reported previously.[80]

Ethyl 2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (160)



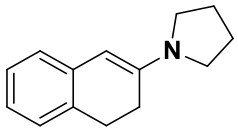
To a flame-dried flask charged with NaH (667 mg, 60% w/w dispersion in mineral oil, 16.67 mmol) was added diethyl carbonate (7.27 mL, 60 mmol). 2-Tetralone (661 µL, 5 mmol) was added dropwise, followed by EtOH (0.1 mL) and the resulting mixture was heated at reflux for 3 h. Upon completion, sat. NH_4Cl (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (30% dichloromethane in petrol on silica gel) afforded the product as a colourless oil (1.02 g, 94%).

Appears to reside as the enol form: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 13.43 (s, 1H, O*H*), 7.73 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.22 – 7.16 (m, 1H, Ar*H*), 7.15 – 7.11 (m, 1H, Ar*H*), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H, Ar*H*), 4.40 (q, *J* = 7.0 Hz, 2H, OCH_2CH$_3$), 2.86 – 2.79 (m, 2H, ArCH_2), 2.58 – 2.51 (m, 2H, CH_2), 1.42 (t, *J* = 7.0 Hz, 3H, OCH$_2$CH_3); **^{13}C NMR (101**

MHz, $CDCl_3$) δ 178.5, 172.2, 133.4, 131.7, 127.3, 126.5, 126.0, 125.1, 100.1, 61.2, 29.7, 27.9, 14.4.

These data are consistent with those reported in the literature.[83]

1-(3,4-Dihydronaphthalen-2-yl)pyrrolidine (161)

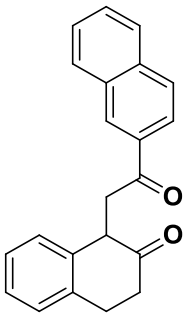


To a solution of 1-tetralone (1.98 mL, 15 mmol) in MeOH (30 mL) was added pyrrolidine (1.48 mL, 18 mmol) and the resulting mixture was left to stir at rt for 1 h. The resulting precipitate was filtered and washed with cold methanol to yield the product as a brown solid (2.88 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 6.96 (m, 2H, Ar*H*), 6.89 – 6.78 (m, 2H, Ar*H*), 5.14 (s, 1H, C=C*H*), 3.34 – 3.21 (m, 4H, N(C*H*$_2$)$_2$), 2.90 – 2.77 (m, 2H, ArC*H*$_2$), 2.54 – 2.42 (m, 2H, ArCH$_2$C*H*$_2$), 1.98 – 1.88 (m, 4H, N(CH$_2$C*H*$_2$)$_2$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.6, 138.3, 130.2, 126.7 (2 × C), 122.9, 121.8, 93.3, 47.5, 28.8, 26.4, 25.3.

These data are consistent with those reported in the literature.[63]

1-(2-(Naphthalen-2-yl)-2-oxoethyl)-3,4-dihydronaphthalen-2(1*H*)-one (162)

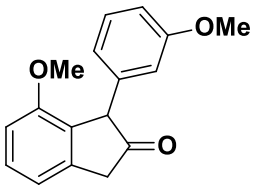


To a refluxing solution of enamine **161** (2.09 g, 10.48 mmol) in PhMe (8 mL) was added dropwise a solution of 2-(bromoacetyl)naphthalene (2.61 g, 10.48 mmol) in PhMe (5 mL). The resulting mixture was left to stir at reflux for 3 h. Water (13 mL) was added and the resulting solution was left to stir at reflux for 16 h. Upon cooling, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was recrystallised from boiling EtOH to afford the product as brown crystals (1.91 g, 58%).

m.p.: 130-134 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 2910, 1713, 1678, 1627, 1184, 1124; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.59 (s, 1H, Ar*H*), 8.07 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 7.98 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.90 (t, *J* = 8.5 Hz, 2H, Ar*H*), 7.65 – 7.53 (m, 2H, Ar*H*), 7.29 – 7.16 (m, 3H, Ar*H*), 7.15 – 7.08 (m, 1H, Ar*H*), 4.29 (t, *J* = 5.5 Hz, 1H, ArC*H*C(O)), 4.05 (dd, *J* = 17.5, 5.5 Hz, 1H, NpC(O)C$H_A$$H_B$), 3.77 (dd, *J* = 17.5, 5.5 Hz, 1H, NpC(O)C$H_A$$H_B$), 3.27 – 3.20 (m, 2H, ArCH_2), 2.85 – 2.74 (m, 1H, C$H_A$$H_B$), 2.65 – 2.52 (m, 1H, C$H_A$$H_B$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 210.6, 197.5, 137.5, 136.0, 135.8, 134.1, 132.6, 130.0, 129.7, 128.6, 128.6, 127.9, 127.9, 127.0, 126.9, 126.9, 125.7,

124.0, 48.3, 37.6, 37.4, 28.4; **HRMS (ESI$^+$)** $C_{22}H_{18}O_2$ requires M+H$^+$ 315.1380, found 315.1383.

7-Methoxy-1-(3-methoxyphenyl)-1*H*-inden-2(3*H*)-one (132)



A flask containing Mg (52 mg, 2.16 mmol) was flame-dried under vacuum and back-filled with an atmosphere of N_2. To this flask was added THF (3.5 mL) followed by 3-bromoanisole (273 µL, 2.16 mmol) and the resulting mixture was heated at reflux for 1 h. Upon cooling to 0 °C, a solution of 7-methoxyindanone (250 mg, 1.54 mmol) in THF (3.5 mL) was added dropwise and the resulting mixture was allowed to stir at rt for 1 h. Ether (10 mL) was added followed by sat. NH_4Cl (10 mL) and the layers were partitioned. The aqueous layer was further extracted with ether (2 × 10 mL) and the organic layers were combined, dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (20% ethyl acetate in petrol) to afford the tertiary alcohol **181** (216 mg, 0.799 mmol, 52%). The product was immediately taken up in MeCN (2 mL). A solution of H_2SO_4 (0.18 mL, 10% in water) and the mixture was stirred at 60 °C for 1 h and then at rt for 16 h. The mixture was diluted with EtOAc (5 mL) and washed with brine (5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the alkene **182** (188 mg, 0.745 mmol, 93%). This material was immediately dissolved in an acetone:H_2O mix (2.4 mL, 9:1). NMO (131 mg, 1.118 mmol) was added followed by OsO_4 (1 crystal) and the reaction mixture was left to stir at rt for 7 h. A solution of sat.

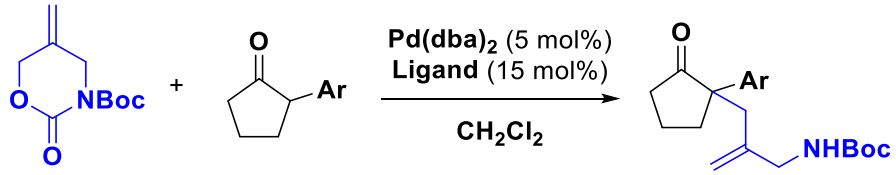
$Na_2S_2O_5$ (5 mL) was added and the resulting mixture was left to stir for 16 h at rt. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered and concentrated and the residue was dissolved in PhMe (2.5 mL). *p*-TSA (14 mg, 0.075 mmol) was added and the reaction mixture was stirred at reflux for 6 h. Upon cooling, the mixture was diluted with CH_2Cl_2 (5 mL) and washed with sat. $NaHCO_3$ (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL) and the organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product as a white solid (75 mg, 0.280 mmol, 18% overall).

m.p.: 102-105 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.34 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.19 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.00 (d, *J* = 7.5 Hz, 1H, Ar*H*), 6.83 (d, *J* = 8.5 Hz, 1H, Ar*H*), 6.80 – 6.75 (m, 1H, Ar*H*), 6.71 – 6.66 (m, 2H, Ar*H*), 4.63 (s, 1H, C*H*Ar), 3.77 (s, 3H, OCH_3), 3.69 (d, *J* = 22.5 Hz, 1H, ArCH_AH$_B$), 3.69 (s, 3H, OCH_3), 3.53 (d, *J* = 22.5 Hz, 1H, ArCH$_A$$H_B$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 213.4, 159.9, 156.8, 139.2, 139.0, 129.6, 129.6, 128.7, 120.0, 117.1, 113.6, 112.3, 109.7, 57.5, 55.5, 55.3, 43.0.

These data are consistent with those reported in the literature.[65]

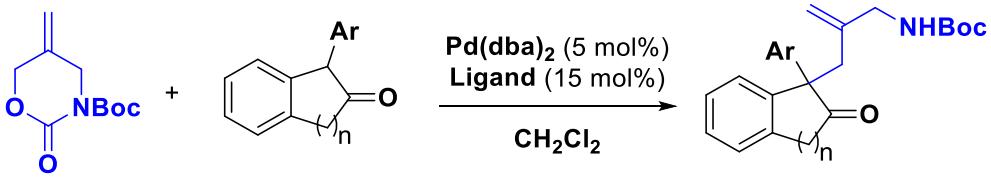
7.8 – Palladium-Catalysed Allylation of Arylketone Substrates

General Procedure H – Palladium-Catalysed Allylation of 2-Arylcyclopentanone Substrates



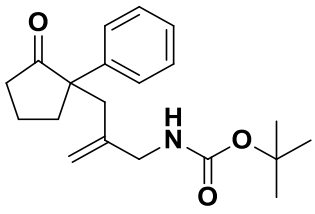
To a flame dried-flask charged with $Pd(dba)_2$ (5 mol%), **L7** (15 mol%), **15** (1.0 eq.) and 2-arylcyclopentanone (2.0 eq.) was added CH_2Cl_2 [0.06 M] and the resulting mixture was left to stir at reflux for 3 h. The solvent was removed *in vacuo* and the resulting material was purified as specified below.

General Procedure J – Palladium-Catalysed Allylation of Indanone and Tetralone Substrates



To a flame-dried flask charged with $Pd(dba)_2$ (5 mol%), **L7** (15 mol%), and **15** (1.0 eq.) was added CH_2Cl_2 [0.1 M] and the resulting mixture was left to stir at rt for 5 min. The corresponding indanone or tetralone (1.5 eq.) was then added either neat or as a solution in CH_2Cl_2 (1 mL) and the resulting mixture was left to stir at rt for 3 h. The solvent was removed *in vacuo* and the resulting material was purified as specified below.

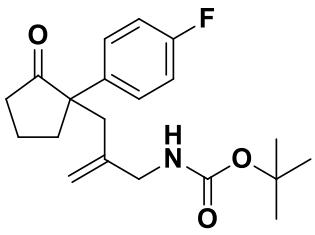
***Tert*-butyl (2-((2-oxo-1-phenylcyclopentyl)methyl)allyl)carbamate (115)**



Prepared according to General Procedure H using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **108** (75 mg, 0.469 mmol). Purification by flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product (65 mg, 85%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3352, 2975, 1754, 1713, 1646, 1510; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.38 (m, 2H, Ar*H*), 7.36 – 7.29 (m, 2H, Ar*H*), 7.28 – 7.20 (m, 1H, Ar*H*), 4.95 – 4.88 (m, 1H, C=C$H_A$$H_B$), 4.68 (s, 1H, C=C$H_A$$H_B$), 4.48 (br, 1H, N*H*), 3.40 – 3.28 (m, 1H, NC$H_A$$H_B$), 3.28 – 3.16 (m, 1H, NC$H_A$$H_B$), 2.70 – 2.62 (m, 1H), 2.59 (d, *J* = 14.0 Hz, 1H, C=CC$H_A$$H_B$), 2.47 (d, *J* = 14.0 Hz, 1H, C=CC$H_A$$H_B$), 2.38 – 2.16 (m, 2H), 2.14 – 2.01 (m, 1H), 2.01 – 1.88 (m, 1H), 1.88 – 1.70 (m, 1H), 1.42 (s, 9H, C(CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 219.2, 155.8, 142.9, 138.9, 128.8, 127.2, 127.1, 114.6, 79.4, 57.0, 45.9, 42.8, 37.2, 33.1, 28.5, 18.6; **MS (ESI^+)** 352 ($M+Na^+$, 100%); **HRMS (ESI^+)** $C_{20}H_{27}NO_3$ requires $M+H^+$ 352.1883, found 352.1872.

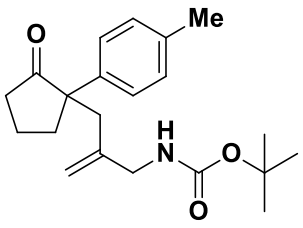
***Tert*-butyl (2-((1-(4-fluorophenyl)-2-oxocyclopentyl)methyl)allyl)carbamate (116)**



Prepared according to General Procedure H using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **109** (84 mg, 0.469 mmol). Purification by flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product (52 mg, 64%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3359, 2975, 1732, 1709, 1653, 1508, 1165; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.33 (m, 2H, Ar$\underline{H}$), 7.08 – 6.94 (m, 2H, Ar$\underline{H}$), 4.92 (s, 1H, C=C$\underline{H_A}H_B$), 4.64 (s, 1H, C=C$H_A\underline{H_B}$), 4.49 (br, 1H, N$\underline{H}$), 3.45 – 3.31 (m, 1H, NC$\underline{H_A}H_B$), 3.31 – 3.19 (m, 1H, NC$H_A\underline{H_B}$), 2.59 – 2.63 (m, 1H), 2.55 (d, *J* = 14.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.44 (d, *J* = 14.0 Hz, 1H, C=CC$H_A\underline{H_B}$), 2.37 – 2.18 (m, 2H), 2.18 – 2.02 (m, 1H), 2.02 – 1.88 (m, 1H), 1.86 – 1.69 (m, 1H), 1.42 (s, 9H, C(C$\underline{H_3}$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 219.0, 162.0 (d, $^1J_{C\text{-}F}$ = 247.0 Hz), 155.8, 142.7, 134.6, 128.8 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 114.7, 79.5, 56.3, 45.9, 42.8, 37.2, 33.4, 28.5, 18.6; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -115.6; **HRMS (ESI^+)** $C_{20}H_{26}FNO_3$ requires $M+Na^+$ 370.1789, found 370.1796.

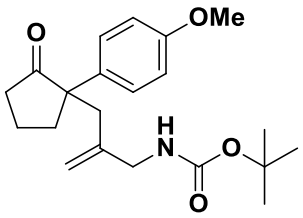
***Tert*-butyl (2-((2-oxo-1-(*p*-tolyl)cyclopentyl)methyl)allyl)carbamate (117)**



Prepared according to General Procedure H using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **110** (82 mg, 0.469 mmol). Purification by flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product (59 mg, 74%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3357, 2973, 1734, 1704, 1511, 1167; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.13 (d, *J* = 8.0 Hz, 2H, Ar*H*), 4.93 – 4.89 (m, 1H, C=C$H_A$$H_B$), 4.69 (s, 1H, C=C$H_A$$H_B$), 4.44 – 5.02 (m, 1H, N*H*), 3.35 (dd, *J* = 16.0, 6.0 Hz, 1H, NC$H_A$$H_B$), 3.24 (dd, *J* = 16.0, 5.5 Hz, 1H, NC$H_A$$H_B$), 2.60 – 2.66 (m, 1H), 2.57 (d, *J* = 14.0 Hz, 1H, C=CC$H_A$$H_B$), 2.45 (d, *J* = 14.0 Hz, 1H, C=CC$H_A$$H_B$), 2.31 (s, 3H, C$H_3$), 2.30 – 2.15 (m, 2H), 2.10 – 1.99 (m, 1H), 1.99 – 1.88 (m, 1H), 1.86 – 1.72 (m, 1H), 1.42 (s, 9H, C(CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 219.3, 155.9, 143.0, 136.9, 135.8, 129.5, 127.0, 114.5, 79.4, 56.6, 45.9, 42.7, 37.1, 33.1, 28.5, 21.1, 18.6; **HRMS (ESI^+)** $C_{21}H_{29}NO_3$ requires $M+H^+$ 344.2220, found 344.2222.

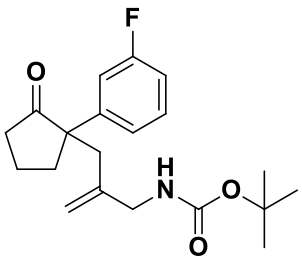
***Tert*-butyl (2-((1-(4-methoxyphenyl)-2-oxocyclopentyl)methyl)allyl)carbamate (119)**



Prepared according to General Procedure H using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **111** (89 mg, 0.469 mmol). Purification by flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product (13 mg, 15%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3376, 2974, 1713, 1511, 1251, 1167; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.35 – 7.28 (m, 2H, Ar*H*), 6.89 – 6.83 (m, 2H, Ar*H*), 4.93 – 4.89 (m, 1H, C=C*H*$_A$H$_B$), 4.70 – 4.64 (m, 1H, C=CH$_A$*H*$_B$), 4.47 (br, 1H, N*H*), 3.79 (s, 3H, OC*H*$_3$), 3.39 – 3.18 (m, 2H, NC*H*$_2$), 2.66 – 2.59 (m, 1H), 2.57 (d, *J* = 14.0 Hz, 1H, C=CC*H*$_A$H$_B$), 2.43 (d, *J* = 14.0 Hz, 1H, C=CCH$_A$*H*$_B$), 2.36 – 2.16 (m, 2H), 2.11 – 1.99 (m, 1H), 1.99 – 1.88 (m, 1H), 1.87 – 1.72 (m, 1H), 1.42 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 219.3, 158.7, 155.9, 143.0, 130.6, 128.2, 114.4, 114.1, 79.4, 56.2, 55.4, 45.9, 42.8, 37.1, 33.3, 28.5, 18.5; **HRMS (ESI^+)** $C_{21}H_{29}NO_4$ requires $M+H^+$ 360.2169, found 360.2173.

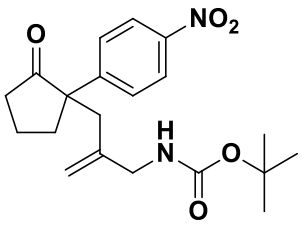
***Tert*-butyl (2-((1-(3-fluorophenyl)-2-oxocyclopentyl)methyl)allyl)carbamate (120)**



Prepared according to General Procedure H using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **112** (69 mg, 0.381 mmol). Purification by flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product (72 mg, 89%) as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3363, 2976, 1701, 1611, 1247, 1164; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.34 – 7.27 (m, 1H, Ar*H*), 7.21 – 7.11 (m, 2H, Ar*H*), 6.97 – 6.90 (m, 1H, Ar*H*), 4.93 (s, 1H, C=C$H_A$$H_B$), 4.66 (s, 1H, C=C$H_A$$H_B$), 4.50 (br, 1H, N*H*), 3.39 (dd, *J* = 16.0, 5.5 Hz, 1H, NC$H_A$$H_B$), 3.27 (dd, *J* = 16.0, 4.5 Hz, 1H, NC$H_A$$H_B$), 2.66 – 2.59 (m, 1H), 2.56 (d, *J* = 14.0 Hz, 1H, C=CC$H_A$$H_B$), 2.46 (d, *J* = 14.0 Hz, 1H, C=CC$H_A$$H_B$), 2.37 – 2.20 (m, 2H), 2.19 – 2.05 (m, 1H), 2.04 – 1.91 (m, 1H), 1.89 – 1.73 (m, 1H), 1.42 (s, 9H, C(CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 218.6, 163.2 (d, *J* = 246.0 Hz), 155.8, 142.5, 141.9 (d, *J* = 7.0 Hz), 130.1 (d, *J* = 8.0 Hz), 122.7 (d, *J* = 2.5 Hz), 114.9, 114.3 (d, *J* = 22.5 Hz), 114.2 (d, *J* = 21.0 Hz), 79.5, 56.8, 45.9, 42.6, 37.3, 33.3, 28.5, 18.6; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -112.2 (m); **HRMS (ESI^+)** $C_{20}H_{26}FNO_3$ requires $M+H^+$ 370.1789, found 370.1793.

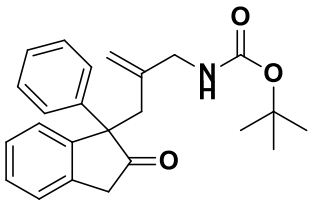
***Tert*-butyl (2-((1-(4-nitrophenyl)-2-oxocyclopentyl)methyl)allyl)carbamate (118)**



Prepared according to General Procedure H using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **113** (89 mg, 0.469 mmol). Purification by flash column chromatography (30% ethyl acetate in petrol on silica gel) afforded the product (79 mg, 90%) as an orange oil.

FTIR ν_{max} (thin film/cm^{-1}) 2978, 1706, 1520, 1347, 1163, 905; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.18 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.62 (d, *J* = 9.0 Hz, 2H, Ar*H*), 4.93 (s, 1H, C=CH_AH_B), 4.60 (s, 1H, C=CH_AH_B), 4.51 (br, 1H, N*H*), 3.48 – 3.37 (m, 1H, NCH_AH_B), 3.37 – 3.25 (m, 1H, NCH_AH_B), 2.76 – 2.64 (m, 1H), 2.60 (d, *J* = 14.5 Hz, 1H, C=CCH_AH_B), 2.50 (d, *J* = 14.5 Hz, 1H, C=CCH_AH_B), 2.39 – 2.29 (m, 2H), 2.28 – 2.13 (m, 1H), 2.10 – 1.95 (m, 1H), 1.91 – 1.69 (m, 1H), 1.42 (s, 9H, C(CH_3)$_3$); **^{13}C NMR ($CDCl_3$)** δ 217.9, 155.8, 147.0 (2 × C), 142.0, 128.2, 123.8, 115.4, 79.7, 57.2, 45.9, 42.6, 37.3, 33.4, 28.5, 18.8 (missing 1 × C); **HRMS (ESI^+)** $C_{20}H_{26}N_2O_5$ requires $M+H^+$ 397.1734, found 397.1736.

***Tert*-butyl (2-((2-oxo-1-phenyl-2,3-dihydro-1*H*-inden-1-yl)methyl)allyl)carbamate (136)**

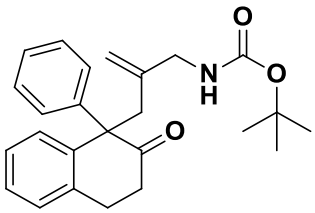


Prepared according to General Procedure J using $Pd(dba)_2$ (20 mg, 0.035 mmol), **L7** (33 mg, 0.106 mmol), **15** (150 mg, 0.703 mmol) and **135** (293 mg, 1.407 mmol). Purification by flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product (230 mg, 87%) as a colourless solid.

Also prepared on a larger scale using $Pd(dba)_2$ (135 mg, 0.234 mmol), **L7** (222 mg, 0.703 mmol), **15** (1.00 g, 4.690 mmol) and **135** (1.47 g, 7.030 mmol). Purified as above to give 1.375 g of product (78%).

m.p.: 95-97 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 3363, 2978, 1749, 1712, 1496, 1249, 1169; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 – 7.17 (m, 9H, Ar*H*), 4.87 (s, 1H, C=C$H_A$$H_B$), 4.65 (s, 1H, C=C$H_A$$H_B$), 4.50 (s, 1H, N*H*), 3.59 (d, *J* = 22.5 Hz, 1H, NC$H_A$$H_B$), 3.46 (d, *J* = 22.5 Hz, 1H, NC$H_A$$H_B$), 3.40 – 3.29 (m, 2H, C=CC$H_A$$H_B$, ArC$H_A$$H_B$), 3.12 (dd, *J* = 16.0, 5.5 Hz, 1H, ArC$H_A$$H_B$), 2.82 (d, *J* = 14.0 Hz, 1H, C=CC$H_A$$H_B$), 1.41 (s, 9H, C(C$H_3$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 216.4, 155.7, 143.4, 142.3, 141.4, 136.9, 128.7, 128.2, 127.8, 127.3, 127.1, 126.7, 125.1, 115.5, 79.3, 63.0, 46.1, 42.8, 41.6, 28.5; **HRMS (ESI$^+$)** $C_{24}H_{27}NO_3$ requires M+Na^+ 400.1883, found 400.1890.

***Tert*-butyl (2-((2-oxo-1-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)allyl)-carbamate (144)**

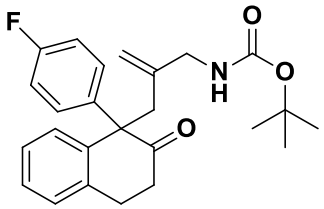


Prepared according to General Procedure J using $Pd(dba)_2$ (13 mg, 0.023 mmol), **L7** (22 mg, 0.070 mmol), **15** (100 mg, 0.469 mmol) and **143** (156 mg, 0.703 mmol). Purification by flash column chromatography (15% ethyl acetate in petrol on silica gel) afforded the product (154 mg, 84%) as an amorphous yellow solid.

Also prepared on a larger scale using $Pd(dba)_2$ (135 mg, 0.234 mmol), **L7** (222 mg, 0.703 mmol), **15** (1.00 g, 4.690 mmol) and **143** (1.56 g, 7.030 mmol). Purified as above to give 1.649 g of product (90%).

FTIR ν_{max} (thin film/cm^{-1}) 3372, 2977, 2927, 1713, 1505, 1445, 1366, 1170; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.36 – 7.17 (m, 7H, Ar*H*), 7.17 – 7.08 (m, 2H, Ar*H*), 4.87 (s, 1H, C=C*H*$_A$H$_B$), 4.66 (br, 1H, N*H*), 4.47 (s, 1H, C=CH$_A$*H*$_B$), 3.71 (d, *J* = 15.0 Hz, 1H, C=CC*H*$_A$H$_B$), 3.44 (br, 1H, NC*H*$_A$H$_B$), 3.24 (br, 1H, NCH$_A$*H*$_B$), 3.06 – 2.77 (m, 3H), 2.70 (d, *J* = 15.0 Hz, 1H, C=CCH$_A$*H*$_B$), 2.63 – 2.49 (m, 1H), 1.44 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 210.4, 155.8, 143.0, 142.6, 139.2, 137.3, 129.8, 128.5, 128.1, 127.7, 127.1 (2 × C), 126.9, 114.8, 79.2, 61.0, 46.3, 41.2, 37.5, 28.4, 28.1; **HRMS (ESI$^+$)** $C_{25}H_{29}NO_3$ requires M+Na^+ 414.2040, found 414.2050.

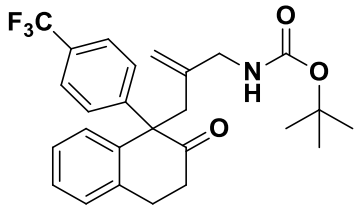
***Tert*-butyl (2-((1-(4-fluorophenyl)-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)-methyl)allyl)carbamate (163)**



Prepared following General Procedure J using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **154** (85 mg, 0.352 mmol). Purification by flash column chromatography (15% ethyl acetate in petrol on silica gel) afforded the product (85 mg, 89%), as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3378, 2977, 2930, 1713, 1506, 1366, 1236, 1165; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.34 – 7.21 (m, 3H, Ar*H*), 7.21 – 7.13 (m, 1H, Ar*H*), 7.14 – 7.04 (m, 2H, Ar*H*), 7.00 – 6.89 (m, 2H, Ar*H*), 4.87 (s, 1H, C=C$H_A$$H_B$), 4.62 (br, 1H, N*H*), 4.46 (s, 1H, C=C$H_A$$H_B$), 3.67 (d, *J* = 15.0 Hz, 1H, C=CC$H_A$$H_B$), 3.45 – 3.34 (m, 1H, NC$H_A$$H_B$), 3.25 – 3.17 (m, 1H, NC$H_A$$H_B$), 3.05 – 2.85 (m, 2H), 2.79 (ddd, *J* = 15.5, 9.0, 6.0 Hz, 1H), 2.68 (d, *J* = 15.0 Hz, 1H, C=CC$H_A$$H_B$), 2.52 (ddd, *J* = 15.5, 6.5, 5.5 Hz, 1H), 1.44 (s, 9H, C(CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 210.4, 161.9 (d, *J* = 247.0 Hz), 155.9, 142.6, 139.1, 138.9 (d, *J* = 3.0 Hz), 137.3, 129.8, 129.5 (d, *J* = 8.0 Hz), 128.4, 127.4, 127.1, 115.4 (d, *J* = 21.0 Hz), 115.0, 79.4, 60.5, 46.4, 41.6, 37.6, 28.5, 28.1; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -115.6; **HRMS (ESI^+)** $C_{25}H_{28}FNO_3$ requires $M+Na^+$ 432.1945, found 432.1955.

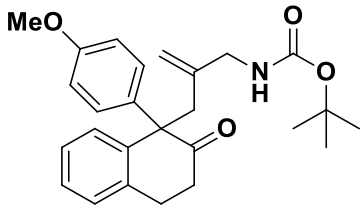
***Tert*-butyl (2-((2-oxo-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)allyl)carbamate (164)**



Prepared following General Procedure J using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **155** (102 mg, 0.352 mmol). Purification by flash column chromatography (15% ethyl acetate in petrol on silica gel) afforded the product (100 mg, 93%), as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3377, 2977, 1714, 1506, 1327, 1167, 1124; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.34 – 7.20 (m, 5H, Ar*H*), 7.16 – 7.09 (m, 1H, Ar*H*), 4.87 (s, 1H, C=C$H_A$$H_B$), 4.58 (br, 1H, N*H*), 4.46 (s, 1H, C=C$H_A$$H_B$), 3.68 (d, *J* = 15.0 Hz, 1H, C=CC$H_A$$H_B$), 3.45 – 3.33 (m, 1H, NC$H_A$$H_B$), 3.26 – 3.15 (m, 1H, NC$H_A$$H_B$), 3.05 – 2.95 (m, 1H), 2.89 (dt, *J* = 16.0, 6.5 Hz, 1H), 2.77 (ddd, *J* = 15.0, 9.0, 6.0 Hz, 1H), 2.68 (d, *J* = 15.0 Hz, 1H, C=CC$H_A$$H_B$), 2.57 (ddd, *J* = 16.0, 6.5, 5.5 Hz, 1H), 1.41 (s, 9H, C(CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 210.0, 155.9, 147.2, 142.3, 138.7, 137.3, 129.8, 129.5 (q, *J* = 32.5 Hz), 128.5, 128.3, 127.6, 127.2, 125.5 (q, *J* = 3.5 Hz), 124.1 (q, *J* = 272.0 Hz), 115.2, 79.4, 61.0, 46.4, 41.5, 37.8, 28.5, 28.0; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -62.6; **HRMS (ESI^+)** $C_{26}H_{28}F_3NO_3$ requires $M+Na^+$ 482.1913, found 482.1928.

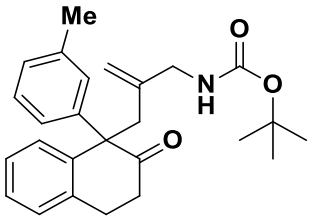
***Tert*-butyl (2-((1-(4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)allyl)carbamate (165)**



Prepared following General Procedure J using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **156** (89 mg, 0.352 mmol). Purification by flash column chromatography (15% ethyl acetate in petrol on silica gel) afforded the product (81 mg, 82%), as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3389, 2975, 1702, 1507, 1249, 1163; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.31 – 7.12 (m, 4H, Ar*H*), 7.04 – 6.96 (m, 2H, Ar*H*), 6.81 – 6.71 (m, 2H, Ar*H*), 4.83 (s, 1H, C=C$H_A$$H_B$), 4.63 (br, 1H, N*H*), 4.43 (s, 1H, C=C$H_A$$H_B$), 3.75 (s, 3H, OC$H_3$), 3.66 (d, *J* = 15.0 Hz, 1H, C=CC$H_A$$H_B$), 3.47 – 3.35 (m, 1H, NC$H_A$$H_B$), 3.27 – 3.17 (m, 1H, NC$H_A$$H_B$), 3.02 – 2.84 (m, 2H), 2.78 (ddd, *J* = 15.5, 9.0, 6.0 Hz, 1H), 2.65 (d, *J* = 15.0 Hz, 1H, C=CC$H_A$$H_B$), 2.50 (dt, *J* = 15.5, 6.0 Hz, 1H), 1.42 (s, 9H, C(CH_3)$_3$)**; ^{13}C NMR (101 MHz, $CDCl_3$)** δ 210.6, 158.7, 155.9, 142.8, 139.5, 137.4, 135.1, 129.8, 129.0, 128.2, 127.1, 126.9, 114.8, 114.0, 79.3, 60.4, 55.4, 46.5, 41.4, 37.5, 28.5, 28.2; **HRMS (ESI^+)** $C_{26}H_{31}NO_4$ requires $M+Na^+$ 444.2145, found 444.2151.

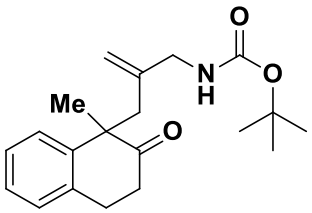
***Tert*-butyl (2-((2-oxo-1-(*m*-tolyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)allyl)-carbamate (166)**



Prepared following General Procedure J using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **157** (83 mg, 0.352 mmol). Purification by flash column chromatography (15% ethyl acetate in petrol on silica gel) afforded the product (71 mg, 75%), as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3375, 2976, 2928, 1703, 1504, 1365, 1246, 1164, 909; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29 – 7.19 (m, 3H, Ar*H*), 7.19 – 7.14 (m, 1H, Ar*H*), 7.11 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.01 (d, *J* = 7.5 Hz, 1H, Ar*H*), 6.95 (s, 1H, Ar*H*), 6.83 (d, *J* = 8.0 Hz, 1H, Ar*H*), 4.84 (s, 1H, C=CH_AH_B), 4.62 (br, 1H, N*H*), 4.44 (s, 1H, C=CH_AH_B), 3.67 (d, *J* = 15.0 Hz, 1H, C=CCH_AH_B), 3.47 – 3.36 (m, 1H, NCH_AH_B), 3.26 – 3.17 (m, 1H, NCH_AH_B), 3.01 – 2.85 (m, 2H), 2.81 (ddd, *J* = 15.5, 9.0, 6.0 Hz, 1H), 2.67 (d, *J* = 15.0 Hz, 1H, C=CCH_AH_B), 2.57 – 2.46 (m, 1H), 2.27 (s, 3H, C*H*$_3$), 1.42 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 210.6, 155.9, 143.1, 142.7, 139.4, 138.3, 137.3, 129.9, 128.5, 128.3, 128.2, 128.0, 127.1, 126.9, 125.0, 114.9, 79.3, 61.1, 46.5, 41.4, 37.7, 28.5, 28.2, 21.7; **HRMS (ESI$^+$)** $C_{26}H_{31}NO_3$ requires M+Na^+ 428.2196, found 428.2206.

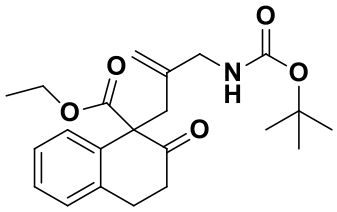
***Tert*-butyl (2-((1-methyl-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)allyl)-carbamate (167)**



Prepared following General Procedure J using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **158** (56 mg, 0.352 mmol) and heating at reflux for 3 h. Purification by flash column chromatography (10→15% ethyl acetate in petrol on silica gel) afforded the product (57 mg, 74%), as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3377, 2975, 1708, 1513, 1453, 1366, 1248, 1169; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.31 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.29 – 7.23 (m, 1H, Ar*H*), 7.20 (td, *J* = 7.0, 1.5 Hz, 1H, Ar*H*), 7.18 – 7.14 (m, 1H, Ar*H*), 4.83 – 4.81 (m, 1H, C=CH_AH_B), 4.53 – 4.51 (m, 1H, C=CH_AH_B), 4.46 (br, 1H, N*H*), 3.32 – 3.22 (m, 1H, NCH_AH_B), 3.19 – 2.95 (m, 3H, NCH_AH_B, 2 × C*H*), 2.90 (d, *J* = 14.0 Hz, 1H, C=CCH_AH_B), 2.76 – 2.58 (m, 2H), 2.41 (d, *J* = 14.0 Hz, 1H, C=CCH_AH_B), 1.45 (s, 3H, CH_3), 1.41 (s, 9H, C(CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 214.3, 155.8, 142.8, 141.5, 135.9, 128.4, 127.2, 127.0, 126.8, 114.6, 79.3, 52.1, 46.1, 43.4, 38.3, 28.5, 28.3, 27.9; **HRMS (ESI$^+$)** $C_{20}H_{27}NO_3$ requires M+Na^+ 352.1883, found 352.1890.

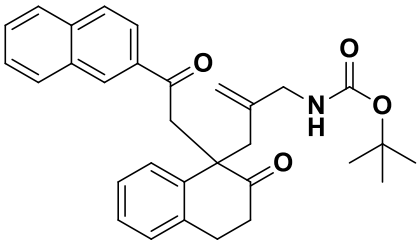
Ethyl 1-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-2-oxo-1,2,3,4-tetrahydro-naphthalene-1-carboxylate (169)



Prepared following General Procedure J using $Pd(dba)_2$ (7 mg, 0.012 mmol), **L7** (11 mg, 0.035 mmol), **15** (50 mg, 0.234 mmol) and **160** (77 mg, 0.352 mmol). Purification by flash column chromatography (15% ethyl acetate in petrol on silica gel) afforded the product (82 mg, 90%), as a colourless oil.

FTIR ν_{max} (thin film/cm^{-1}) 3405, 2979, 1740, 1713, 1510, 1366, 1242, 1215, 1169; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 – 7.17 (m, 4H, Ar*H*), 4.87 – 4.81 (m, 1H, C=C*H*$_A$H$_B$), 4.55 (s, 1H, C=CH$_A$*H*$_B$), 4.51 (br, 1H, N*H*), 4.11 (dq, *J* = 11.0, 7.0 Hz, 1H, OC*H*$_A$H$_B$CH$_3$), 4.05 (dq, *J* = 11.0, 7.0 Hz, 1H, OCH$_A$*H*$_B$CH$_3$), 3.26 – 3.18 (m, 1H, NC*H*$_A$H$_B$), 3.23 (d, *J* = 14.0 Hz, 1H, C=CC*H*$_A$H$_B$), 3.13 – 3.00 (m, 3H, NCH$_A$*H*$_B$, 2 × C*H*), 2.93 – 2.80 (m, 2H, C=CCH$_A$*H*$_B$, C*H*), 2.71 – 2.59 (m, 1H), 1.39 (s, 9H, C(C*H*$_3$)$_3$), 1.10 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 208.5, 171.0, 155.7, 141.6, 136.3, 136.2, 128.8, 127.8, 127.4, 127.2, 115.6, 79.3, 63.1, 62.0, 45.9, 40.1, 39.3, 28.5, 27.8, 13.9; **HRMS (ESI$^+$)** $C_{22}H_{29}NO_5$ requires M+Na^+ 410.1938, found 410.1948.

***Tert*-butyl (2-((1-(2-(naphthalen-2-yl)-2-oxoethyl)-2-oxo-1,2,3,4-tetrahydro-naphthalen-1-yl)methyl)allyl)carbamate (168)**

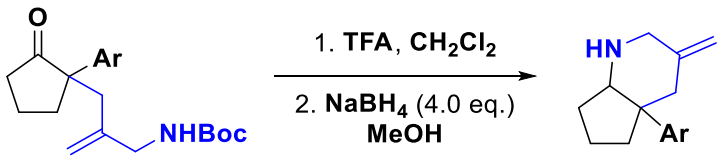


Prepared following General Procedure J using $Pd(dba)_2$ (61 mg, 0.11 mmol), **L7** (100 mg, 0.32 mmol), **15** (452 mg, 2.12 mmol) and **162** (1.00 g, 3.18 mmol) and heating at reflux for 3 h. Purification by flash column chromatography (20→25% ethyl acetate in petrol on silica gel) afforded the product (946 mg, 92%), as a colourless oil.

m.p.: 70-73 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 3400, 2976, 1699, 1682, 1509, 1366, 1249, 1171; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.46 (s, 1H, Ar*H*), 7.96 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.92 – 7.77 (m, 3H, Ar*H*), 7.63 – 7.49 (m, 2H, Ar*H*), 7.24 – 7.07 (m, 4H, Ar*H*), 5.02 (s, 1H, C=CH_AH_B), 4.77 (s, 1H, C=CH_AH_B), 4.39 (br, 1H, N*H*), 4.19 – 4.09 (m, 2H), 3.52 – 3.37 (m, 1H), 3.22 – 2.99 (m, 4H), 2.78 – 2.64 (m, 2H, C=CCH_AH_B, C*H*), 2.58 (d, *J* = 13.0 Hz, 1H, C=CCH_AH_B), 1.42 (s 9H, C(CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 213.4, 196.7, 155.8, 142.2, 139.6, 136.8, 135.7, 133.8, 132.6, 129.9, 129.7, 128.8, 128.6, 128.5, 127.9, 126.9, 126.8 (2 ×C), 125.7, 123.8, 116.0, 79.5, 52.8, 49.2, 45.7, 45.5, 39.1, 28.5 (2 X C); **HRMS (ESI^+)** $C_{31}H_{33}NO_4$ requires $M+Na^+$ 506.2302, found 506.2315.

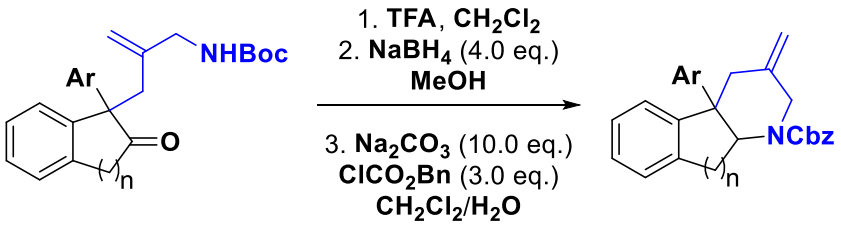
7.9 – Synthesis of Aryl-substituted Piperidines

General Procedure K – Conversion of Arylcyclopentanone Products to Piperidines



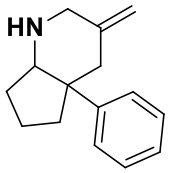
To a solution of substrate (1.0 eq.) in CH_2Cl_2 was added TFA and the resulting mixture was left to stir for 1 h at rt. The mixture was diluted with CH_2Cl_2 and sat. $NaHCO_3$ was added. The layers were partitioned and the aqueous layer was further extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was taken up in MeOH, $NaBH_4$ (4.0 eq.) was added and the mixture was left to stir at rt for 1 h. The mixture was diluted with CH_2Cl_2 and sat. NH_4Cl was added. The layers were partitioned and the aqueous layer was further extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General Procedure L – Conversion of Indanone and Tetralone Products to Piperidines



Prepared as in General Procedure K, but the crude reduction product was taken up in CH_2Cl_2 and added to a solution of Na_2CO_3 (10.0 eq.) in H_2O [0.4 M] and the resulting mixture was stirred for 10 min. Benzyl chloroformate was added (3.0 eq.) and the resulting mixture was stirred at rt for 1 h. The resulting mixture was diluted with CH_2Cl_2 and sat. $NaHCO_3$ was added. The layers were partitioned and the aqueous layer was further extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure.

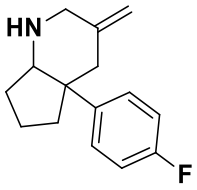
3-Methylene-4a-phenyloctahydro-1*H*-cyclopenta[*b*]pyridine (123)



Prepared according to General Procedure K using **115** (186 mg, 0.565 mmol), TFA (3 mL) and $NaBH_4$ (85 mg, 2.26 mmol). Purification by flash column chromatography (100% ethyl acetate on silica gel) afforded the product as a pale yellow oil (64 mg, 53%).

FTIR ν_{max} (thin film/cm^{-1}) 3065, 2956, 1655; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.59 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.32 – 7.22 (m, 2H, Ar*H*), 7.17 (t, *J* = 7.5 Hz, 1H, Ar*H*), 4.75 – 4.68 (m, 1H, C=C*H*$_A$H$_B$), 4.55 – 4.48 (m, 1H, C=CH$_A$*H*$_B$), 3.62 (d, *J* = 13.5 Hz, 1H, NC*H*$_A$H$_B$), 3.50 (d, *J* = 13.5 Hz, 1H, NCH$_A$*H*$_B$), 2.98 (dd, *J* = 11.5, 8.0 Hz, 1H, NC*H*), 2.92 (d, *J* = 13.5 Hz, 1H, C=CC*H*$_A$H$_B$), 2.35 (dd, *J* = 13.5, 1.0 Hz, 1H, C=CCH$_A$*H*$_B$), 2.30 (br, 1H, N*H*), 2.21 – 2.08 (m, 1H), 1.98 – 1.85 (m, 1H), 1.84 – 1.69 (m, 1H), 1.69 – 1.51 (m, 3H); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 144.3, 143.7, 128.8, 127.9, 125.7, 110.9, 67.8, 54.2, 49.2, 48.7, 39.0, 27.0, 20.3; **HRMS (ESI$^+$)** $C_{15}H_{19}N$ requires M+H$^+$ 214.1591, found 214.1591.

4a-(4-Fluorophenyl)-3-methyleneoctahydro-1*H*-cyclopenta[*b*]pyridine (124)

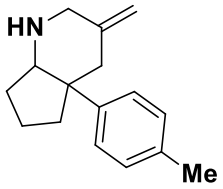


Prepared according to General Procedure K using **116** (139 mg, 0.400 mmol), TFA (3 mL) and $NaBH_4$ (61 mg, 1.600 mmol). Purification by flash column chromatography (100% ethyl acetate on silica gel) afforded the product as a pale yellow oil (35 mg, 38%).

FTIR ν_{max} (thin film/cm^{-1}) 3079, 2955, 1655, 1507, 1222, 835; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.67 – 7.58 (m, 2H, Ar*H*), 6.99 – 6.89 (m, 2H, Ar*H*), 4.73 – 4.70 (m, 1H, C=C*H*$_A$H$_B$), 4.49 (d, *J* = 1.5 Hz, 1H, C=CH$_A$*H*$_B$), 3.60 (d, *J* = 13.5 Hz, 1H, NC*H*$_A$H$_B$), 3.47 (dd, *J* = 13.5, 1.5 Hz, 1H, NCH$_A$*H*$_B$), 2.95 (dd, *J* = 11.5, 8.0 Hz, 1H, NC*H*), 2.81 (d, *J* = 13.5 Hz, 1H, C=CC*H*$_A$H$_B$), 2.33 (dd, *J* = 13.5, 1.5 Hz, 1H, C=CCH$_A$*H*$_B$), 2.16 –

2.06 (m, 1H), 1.92 – 1.82 (m, 1H), 1.81 – 1.67 (m, 2H), 1.65 – 1.46 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 160.9 (d, *J* = 244.5 Hz), 143.5, 140.1 (d, *J* = 3.5 Hz), 130.5 (d, *J* = 7.5 Hz), 114.4 (d, *J* = 20.5 Hz), 111.0, 67.9, 54.4, 49.4, 48.4, 39.0, 26.9, 20.2; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -118.0 (m); **HRMS (ESI$^+$)** $C_{15}H_{18}FN$ requires $M+H^+$ 232.1496, found 232.1499.

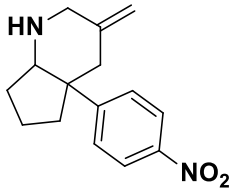
3-Methylene-4a-(*p*-tolyl)octahydro-1*H*-cyclopenta[*b*]pyridine (125)



Prepared according to General Procedure K using **117** (24 mg, 0.070 mmol), TFA (1 mL) and $NaBH_4$ (11 mg, 0.280 mmol). Purification by flash column chromatography (100% ethyl acetate on silica gel) afforded the product as a pale yellow oil (4 mg, 25%).

FTIR ν_{max} (thin film/cm^{-1}) 2956, 1514, 1446, 908, 731; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.09 (d, *J* = 8.0 Hz, 2H, Ar*H*), 4.72 (d, *J* = 2.0 Hz, 1H, C=CH_AH$_B$), 4.54 (d, *J* = 1.5 Hz, 1H, C=CH$_A$$H_B$), 3.60 (d, *J* = 14.0 Hz, 1H, NCH_AH$_B$), 3.49 (dd, *J* = 14.0, 1.5 Hz, 1H, NCH$_A$$H_B$), 2.99 – 2.88 (m, 2H, NC*H*, C=CCH_AH$_B$), 2.38 – 2.25 (m, 4H, C=CCH$_A$$H_B$, C$H_3$), 2.17 – 2.07 (m, 1H), 1.95 – 1.69 (m, 3H), 1.65 – 1.45 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 144.1, 141.1, 135.1, 128.6 (2 × C), 110.7, 67.9, 54.3, 49.1, 48.3, 38.9, 27.1, 21.0, 20.3; **HRMS (ESI$^+$)** $C_{16}H_{21}N$ requires $M+H^+$ 228.1747, found 228.1746.

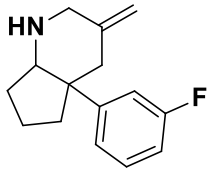
3-Methylene-4a-(4-nitrophenyl)octahydro-1*H*-cyclopenta[*b*]pyridine (128)



Prepared according to General Procedure K using **118** (79 mg, 0.212 mmol), TFA (1 mL) and $NaBH_4$ (32 mg, 0.848 mmol). Purification by flash column chromatography (100% ethyl acetate on silica gel) afforded the product as a pale yellow oil (24 mg, 44%).

FTIR ν_{max} (thin film/cm^{-1}) 3338, 2958, 1595, 1512, 1343, 855; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.13 – 8.06 (m, 2H, Ar*H*), 8.01 – 7.94 (m, 2H, Ar*H*), 4.69 (d, *J* = 1.5 Hz, 1H, C=C$H_A$$H_B$), 4.41 (d, *J* = 1.5 Hz, 1H, C=C$H_A$$H_B$), 3.59 (d, *J* = 12.5 Hz, 1H, NC$H_A$$H_B$), 3.46 (dd, *J* = 12.5, 1.5 Hz, 1H, NC$H_A$$H_B$), 3.04 (dd, *J* = 12.0, 8.0 Hz, 1H, NC*H*), 2.76 (d, *J* = 13.0 Hz, 1H, C=CC$H_A$$H_B$), 2.36 (dd, *J* = 13.0, 1.5 Hz, 1H, C=CC$H_A$$H_B$), 2.17 (dd, *J* = 12.0, 8.0 Hz, 1H), 1.98 – 1.86 (m, 1H), 1.83 – 1.57 (m, 4H), 1.53 – 1.39 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 153.3, 145.8, 142.3, 130.3, 122.6, 111.8, 67.8, 54.2, 49.9, 49.5, 39.0, 26.7, 20.2; **HRMS (ESI$^+$)** $C_{15}H_{18}N_2O_2$ requires $M+H^+$ 259.1441, found 259.1444.

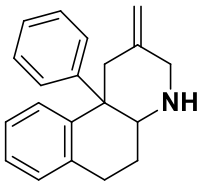
4a-(3-Fluorophenyl)-3-methyleneoctahydro-1*H*-cyclopenta[*b*]pyridine (127)



Prepared according to General Procedure K using **120** (72 mg, 0.208 mmol), TFA (1 mL) and $NaBH_4$ (31 mg, 0.832 mmol). Purification by flash column chromatography (100% ethyl acetate on silica gel) afforded the product as a pale yellow oil (22 mg, 46%).

FTIR ν_{max} (thin film/cm^{-1}) 3073, 2959, 1613, 1583, 1259, 899; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.51 – 7.43 (m, 1H, Ar*H*), 7.39 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.22 (td, *J* = 8.0, 6.5 Hz, 1H, Ar*H*), 6.85 (td, *J* = 8.0, 2.0 Hz, 1H, Ar*H*), 4.72 (d, *J* = 1.5 Hz, 1H, C=CH_AH$_B$), 4.51 (d, *J* = 1.5 Hz, 1H, C=CH$_A$$H_B$), 3.61 (d, *J* = 13.5 Hz, 1H, NCH_AH$_B$), 3.47 (dd, *J* = 13.5, 1.5 Hz, 1H, NCH$_A$$H_B$), 2.96 (dd, *J* = 11.5, 8.0 Hz, 1H, NC*H*), 2.82 (d, *J* = 13.5 Hz, 1H, C=CCH_AH$_B$), 2.33 (dd, *J* = 13.5, 1.5 Hz, 1H, C=CCH$_A$$H_B$), 2.17 – 2.08 (m, 1H), 1.93 – 1.82 (m, 1H), 1.81 – 1.66 (m, 2H), 1.66 – 1.49 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.5 (d, *J* = 243.0 Hz), 147.4 (d, *J* = 7.0 Hz), 143.4, 128.9 (d, *J* = 8.0 Hz), 124.5 (d, *J* = 2.5 Hz), 116.3 (d, *J* = 22.0 Hz), 112.5 (d, *J* = 21.0 Hz), 111.1, 67.8, 54.3, 49.2, 48.9, 38.9, 26.9, 20.2; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -113.6 (m); **HRMS (ESI^+)** $C_{15}H_{18}FN$ requires $M+H^+$ 232.1496, found 232.1501.

2-Methylene-10b-phenyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (146)

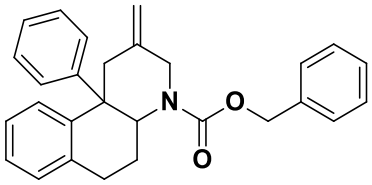


To a flame-dried flask charged with **144** (109 mg, 0.278 mmol) was added TFA (1 mL) and the mixture was left to stir for 1 h at rt. The mixture was diluted with CH_2Cl_2 (10 mL) and sat. $NaHCO_3$ (10 mL) was added. The layers were partitioned and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was dissolved in MeOH (1 mL) and was added $NaBH_4$ (42 mg, 1.114 mmol). The resulting mixture was left to stir at rt for 1 h. A saturated solution of aq. NH_4Cl (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (80% ethyl acetate in petrol on silica gel) afforded the product as a pale yellow oil (46 mg, 60%).

FTIR ν_{max} (thin film/cm^{-1}) 3064, 2939, 1599, 1494, 1443; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29 – 7.11 (m, 9H, Ar*H*), 5.00 – 4.93 (m, 2H, C=C*H*$_2$), 3.81 (d, *J* = 14.5 Hz, 1H, NC*H*$_A$H$_B$), 3.61 (dd, *J* = 14.5, 1.5 Hz, 1H, NCH$_A$*H*$_B$), 3.42 (d, *J* = 14.5 Hz, 1H, C=CC*H*$_A$H$_B$), 3.17 – 2.91 (m, 3H, NC*H*, 2 × C*H*), 2.77 (dd, *J* = 14.5, 2.0 Hz, 1H, C=CCH$_A$*H*$_B$), 1.79 – 1.65 (m, 2H), 1.56 – 1.41 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.4, 145.2, 144.6, 136.5, 130.5, 128.9, 127.4, 126.5 (2 × C), 126.3, 126.1, 109.9,

61.3, 53.4, 46.2, 45.2, 29.1, 25.5; **HRMS (ESI$^+$)** $C_{20}H_{21}N$ requires M+H$^+$ 276.1747, found 276.1750.

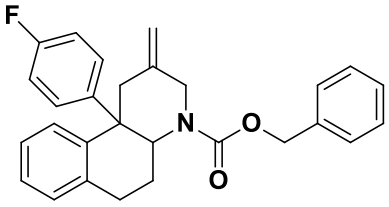
Benzyl 2-methylene-10b-phenyl-1,2,3,5,6,10b-hexahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (147)



Prepared according to General Procedure L using **144** (108 mg, 0.276 mmol), TFA (1 mL), $NaBH_4$ (42 mg, 1.103 mmol), Na_2CO_3 (293 mg, 2.76 mmol) and benzyl chloroformate (118 µL, 0.828 mmol). Purification by flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product as a white solid (90 mg, 80%).

m.p.: 123-128 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 2947, 1687, 1473, 1251; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29 – 7.22 (m, 3H, Ar*H*), 7.22 – 7.09 (m, 8H, Ar*H*), 7.07 (d, *J* = 7.5 Hz, 1H, Ar*H*), 6.98 (br, 2H, Ar*H*), 5.16 – 5.12 (m, 2H, C=CH_2), 5.04 (d, *J* = 15.0 Hz, 1H, NCH_AH$_B$), 4.80 (d, *J* = 12.5 Hz, 1H, OCH_AH$_B$), 4.25 (br, 1H, OCH$_A$$H_B$), 3.73 (dd, *J* = 15.0, 1.0 Hz, 1H, NCH$_A$$H_B$), 3.61 (dd, *J* = 12.5, 2.0 Hz, 1H, NC*H*), 3.49 (d, *J* = 15.0 Hz, 1H, C=CCH_AH$_B$), 3.05 – 2.98 (m, 2H), 2.75 (dd, *J* = 15.0, 1.5 Hz, 1H, C=CCH$_A$$H_B$), 2.44 – 2.29 (m, 1H), 2.15 – 2.04 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.8, 145.7, 144.1, 142.3, 136.6, 135.6, 130.4, 128.9, 128.3, 128.0, 127.9, 127.8, 127.2, 126.8, 126.6, 126.4, 111.9, 66.7, 65.1, 54.5, 47.3, 46.8, 31.5, 24.8; **HRMS (ESI$^+$)** $C_{28}H_{27}NO_2$ requires M+H$^+$ 410.2115, found 410.2119.

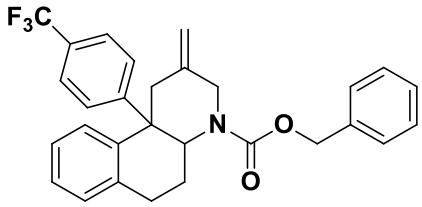
Benzyl 10b-(4-fluorophenyl)-2-methylene-1,2,3,5,6,10b-hexahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (170)



Prepared according to General Procedure L using **163** (78 mg, 0.190 mmol), TFA (1 mL), $NaBH_4$ (29 mg, 0.762 mmol), Na_2CO_3 (202 mg, 1.905 mmol) and benzyl chloroformate (83 µL, 0.578 mmol). Purification by flash column chromatography (10→15% ethyl acetate in petrol on silica gel) afforded the product as a colourless oil (59 mg, 73%).

FTIR ν_{max} (thin film/cm^{-1}) 2886, 1686, 1509, 1252, 1216; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.30 – 7.24 (m, 3H, Ar*H*), 7.23 – 7.07 (m, 5H, Ar*H*), 7.07 – 7.00 (m, 3H, Ar*H*), 6.78 – 6.70 (m, 2H, Ar*H*), 5.16 – 5.10 (m, 2H, C=CH_2), 5.03 (d, *J* = 15.0 Hz, 1H, NCH_AH$_B$), 4.83 (d, *J* = 12.0 Hz, 1H, OCH_AH$_B$), 4.39 (br, 1H, OCH$_A$$H_B$), 3.72 (dd, *J* = 15.0, 1.5 Hz, 1H, NCH$_A$$H_B$), 3.58 (dd, *J* = 12.5, 2.0 Hz, 1H, NC*H*), 3.43 (d, *J* = 15.0 Hz, 1H, C=CCH_AH$_B$), 3.05 – 2.97 (m, 2H), 2.74 (dd, *J* = 15.0, 1.5 Hz, 1H, C=CCH$_A$$H_B$), 2.38 – 2.24 (m, 1H), 2.17 – 2.07 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.4 (d, *J* = 246.0 Hz), 155.6, 143.8, 142.1, 141.4 (d, *J* = 3.0 Hz), 136.5, 135.4, 131.9 (d, *J* = 7.5 Hz), 129.0, 128.4, 128.1, 127.9, 127.8, 126.9, 126.8, 113.9 (d, *J* = 20.5 Hz), 112.2, 66.8, 65.1, 54.4, 46.9, 46.8, 31.5, 24.7; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -116.8 (m); **HRMS (ESI$^+$)** $C_{28}H_{26}FNO_2$ requires M+H^+ 428.2020, found 428.2025.

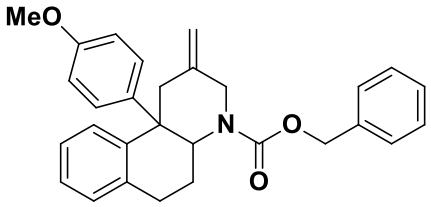
Benzyl 2-methylene-10b-(4-(trifluoromethyl)phenyl)-1,2,3,5,6,10b-hexahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (171)



Prepared according to General Procedure L using **164** (53 mg, 0.115 mmol), TFA (2 mL), $NaBH_4$ (27 mg, 0.723 mmol), Na_2CO_3 (191 mg, 1.806 mmol) and benzyl chloroformate (77 µL, 0.542 mmol). Purification by flash column chromatography (10→15% ethyl acetate in petrol on silica gel) afforded the product as a colourless oil (48 mg, 87%).

FTIR ν_{max} (thin film/cm^{-1}) 2946, 1687, 1473, 1327, 1250, 1117; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.12 (m, 10H, Ar*H*), 7.05 – 6.93 (m, 3H, Ar*H*), 5.19 – 5.12 (m, 2H, C=CH_2), 5.05 (d, *J* = 15.0 Hz, 1H, NCH_AH$_B$), 4.83 (d, *J* = 12.0 Hz, 1H, OCH_AH$_B$), 4.21 (br, 1H, OCH$_A$$H_B$), 3.74 (dd, *J* = 15.0, 1.5 Hz, 1H, NCH$_A$$H_B$), 3.63 (dd, *J* = 12.5, 2.5 Hz, 1H, NC*H*), 3.46 (d, *J* = 15.0 Hz, 1H, C=CCH_AH$_B$), 3.05 – 2.99 (m, 2H), 2.77 (dd, *J* = 15.0, 1.5 Hz, 1H, C=CCH$_A$$H_B$), 2.36 – 2.21 (m, 1H), 2.17 – 2.07 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.5, 149.8, 143.2, 141.8, 137.7, 136.3, 135.5, 130.7, 129.1, 128.40 (q, *J* = 32.5 Hz), 128.37, 128.0 (2 × C), 127.7, 127.0, 124.4 (q, *J* = 272.0 Hz), 124.0 (q, *J* = 3.5 Hz), 112.5, 66.9, 65.0, 54.4, 47.4, 46.6, 31.4, 24.7; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -62.4; **HRMS (ESI$^+$)** $C_{29}H_{26}F_3NO_2$ requires M+H$^+$ 478.1988, found 478.1994.

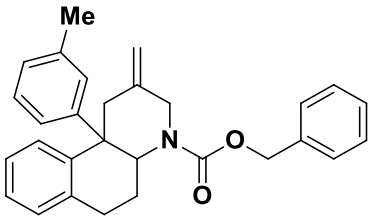
Benzyl 10b-(4-methoxyphenyl)-2-methylene-1,2,3,5,6,10b-hexahydrobenzo[*i*]quinoline-4(4a*H*)-carboxylate (172)



Prepared according to General Procedure L using **165** (76 mg, 0.180 mmol), TFA (2 mL), $NaBH_4$ (27 mg, 0.721 mmol), Na_2CO_3 (191 mg, 1.806 mmol) and benzyl chloroformate (77 µL, 0.541 mmol). Purification by flash column chromatography (10→15% ethyl acetate in petrol on silica gel) afforded the product as a white solid (63 mg, 80%).

m.p.: 139-141 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 2944, 1685, 1511, 1473, 1251**; ^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 – 7.22 (m, 3H, Ar*H*), 7.22 – 7.12 (m, 3H, Ar*H*), 7.12 – 6.97 (m, 5H, Ar*H*), 6.66 (d, *J* = 9.0 Hz, 2H, Ar*H*), 5.17 – 5.10 (m, 2H, C=CH_2), 5.04 (d, *J* = 14.5 Hz, 1H, NCH_AH$_B$), 4.84 (d, *J* = 12.5 Hz, 1H, OCH_AH$_B$), 4.35 (br, 1H, OCH$_A$$H_B$), 3.75 – 3.66 (m, 4H, NCH$_A$$H_B$, OC$H_3$), 3.58 (dd, *J* = 12.5, 2.0 Hz, 1H, NC*H*), 3.45 (d, *J* = 15.0 Hz, 1H, C=CCH_AH$_B$), 3.04 – 2.96 (m, 2H), 2.73 (dd, *J* = 15.0, 1.5 Hz, 1H, C=CCH$_A$$H_B$), 2.41 – 2.26 (m, 1H), 2.15 – 2.05 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 157.9, 155.8, 144.2, 142.4, 137.8, 136.6, 135.4, 131.4, 128.9, 128.3, 128.0, 127.9, 127.8, 126.7, 126.5, 112.6, 111.9, 66.8, 65.2, 55.2, 54.4, 46.9, 46.7, 31.5, 24.8; **HRMS (ESI$^+$)** $C_{29}H_{29}NO_3$ requires M+H$^+$ 440.2220, found 440.2231 **X-ray** see Appendix 6.

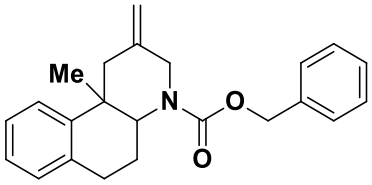
Benzyl 2-methylene-10b-(*m*-tolyl)-1,2,3,5,6,10b-hexahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (173)



Prepared according to General Procedure L using **166** (69 mg, 0.170 mmol), TFA (2 mL), $NaBH_4$ (26 mg, 0.681 mmol), Na_2CO_3 (180 mg, 1.701 mmol) and benzyl chloroformate (73 µL, 0.510 mmol). Purification by flash column chromatography (10% ethyl acetate in petrol on silica gel) afforded the product as a white solid (54 mg, 75%).

m.p.: 149-151 °C; **FTIR** ν_{max} (thin film/cm^{-1}) 2922, 1686, 1473, 1252; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.27 – 7.22 (m, 4H, Ar*H*), 7.20 – 7.11 (m, 3H, Ar*H*), 7.09 – 6.90 (m, 6H, Ar*H*), 5.15 – 5.10 (m, 2H, C=C*H*$_2$), 5.03 (d, *J* = 15.0 Hz, 1H, NC*H*$_A$H$_B$), 4.78 (d, *J* = 12.5 Hz, 1H, OC*H*$_A$H$_B$), 4.25 (br, 1H, OCH$_A$*H*$_B$), 3.71 (dd, *J* = 15.0, 1.5 Hz, 1H, NCH$_A$*H*$_B$), 3.58 (dd, *J* = 12.5, 2.0 Hz, 1H, NC*H*), 3.47 (d, *J* = 15.0 Hz, 1H, C=CC*H*$_A$H$_B$), 3.05 – 2.95 (m, 2H), 2.73 (dd, *J* = 15.0, 1.5 Hz, 1H, C=CCH$_A$*H*$_B$), 2.41 – 2.25 (m, 1H), 2.16 (s, 3H, C*H*$_3$), 2.11 – 2.03 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.9 (br), 145.7, 144.1, 142.5, 136.6 (2 × C), 135.5, 131.3, 128.9, 128.3, 128.0, 127.9, 127.8, 127.4, 127.2, 127.1, 126.7, 126.6, 111.8, 66.8, 65.1, 54.5, 47.3, 46.9, 31.6, 24.8, 21.7; **HRMS (ESI$^+$)** $C_{29}H_{29}NO_2$ requires M+H$^+$ 424.2271, found 424.2278.

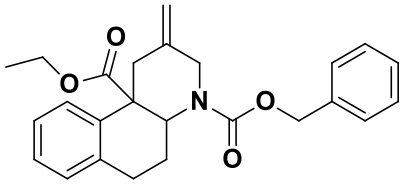
Benzyl 10b-methyl-2-methylene-1,2,3,5,6,10b-hexahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (174)



Prepared according to General Procedure L using **167** (57 mg, 0.173 mmol), TFA (2 mL), $NaBH_4$ (26 mg, 0.692 mmol), Na_2CO_3 (183 mg, 1.73 mmol) and benzyl chloroformate (74 µL, 0.519 mmol). Purification by flash column chromatography (10 ethyl acetate in petrol on silica gel) afforded the product as a colourless oil (42 mg, 70%).

FTIR ν_{max} (thin film/cm^{-1}) 2933, 1688, 1465, 1241, 1203; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.27 (m, 5H, Ar*H*), 7.28 – 7.23 (m, 1H, Ar*H*), 7.18 (td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.13 (td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.10 – 7.05 (m, 1H, Ar*H*), 5.16 – 5.08 (m, 2H, C=C*H*$_2$), 4.99 (br, 1H, OC*H*$_A$H$_B$), 4.93 (br, 1H, OCH$_A$*H*$_B$), 4.78 (dd, *J* = 14.0, 1.0 Hz, 1H, NC*H*$_A$H$_B$), 3.42 (d, *J* = 14.0 Hz, 1H, NCH$_A$*H*$_B$), 3.40 (dd, *J* = 12.5, 2.5 Hz, 1H, NC*H*), 2.96 – 2.86 (m, 2H), 2.82 (d, *J* = 13.5 Hz, 1H, C=CC*H*$_A$H$_B$), 2.67 – 2.51 (m, 1H), 2.37 – 2.26 (m, 1H), 2.26 (d, *J* = 13.5 Hz, 1H, C=CCH$_A$*H*$_B$), 1.14 (s, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.7, 144.4, 140.7, 137.0, 135.0, 129.2, 129.1, 128.6, 128.0, 126.3, 126.2 (2 × C), 113.1, 66.9, 65.5, 54.5, 47.9, 41.3, 31.6, 25.2, 22.7; **HRMS (ESI$^+$)** $C_{23}H_{25}NO_2$ requires $M+H^+$ 348.1958, found 348.1958.

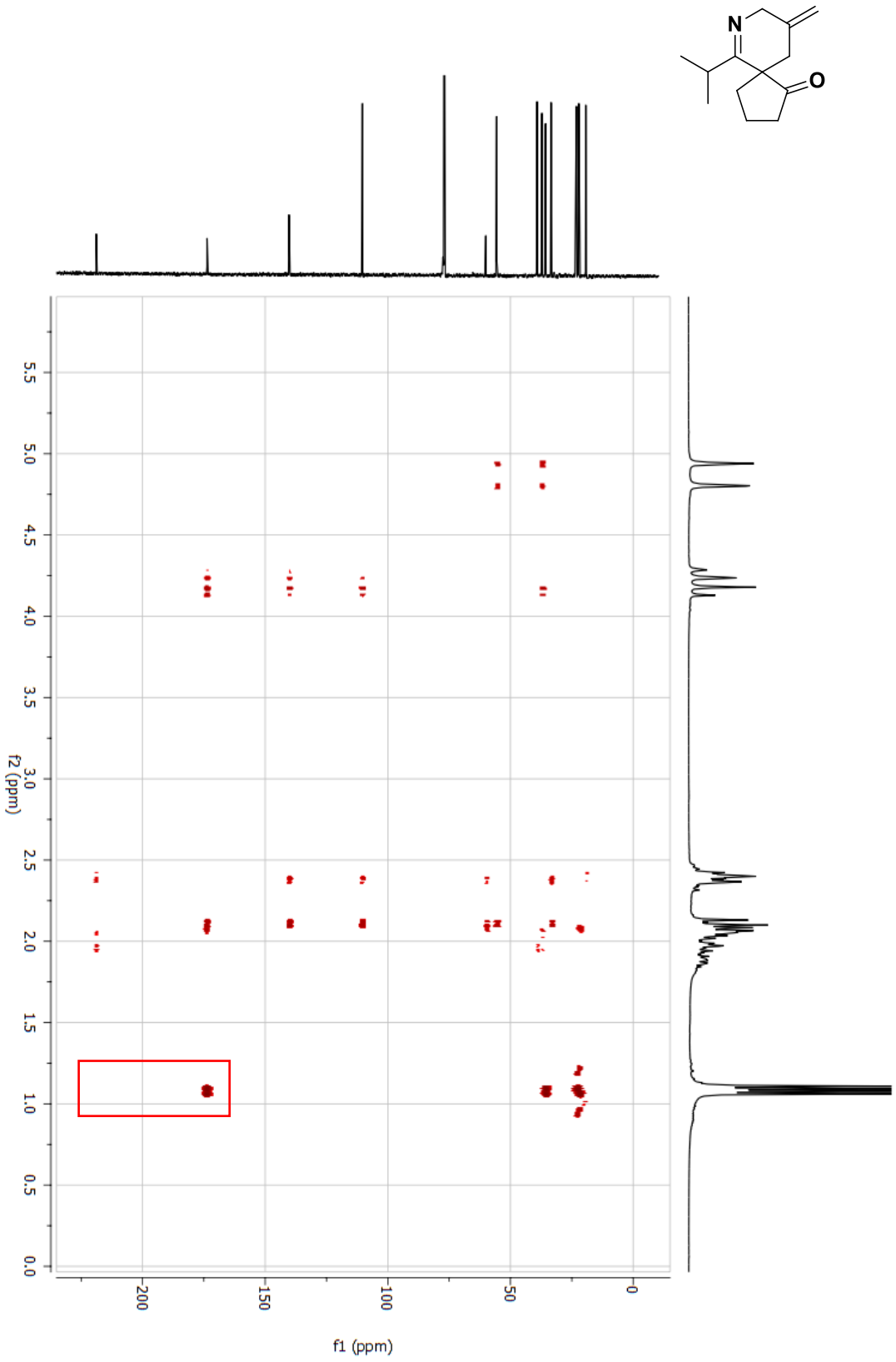
4-Benzyl 10b-ethyl 2-methylene-1,2,3,5,6,10b-hexahydrobenzo[*f*]quinoline-4,10b(4a*H*)-dicarboxylate (176)

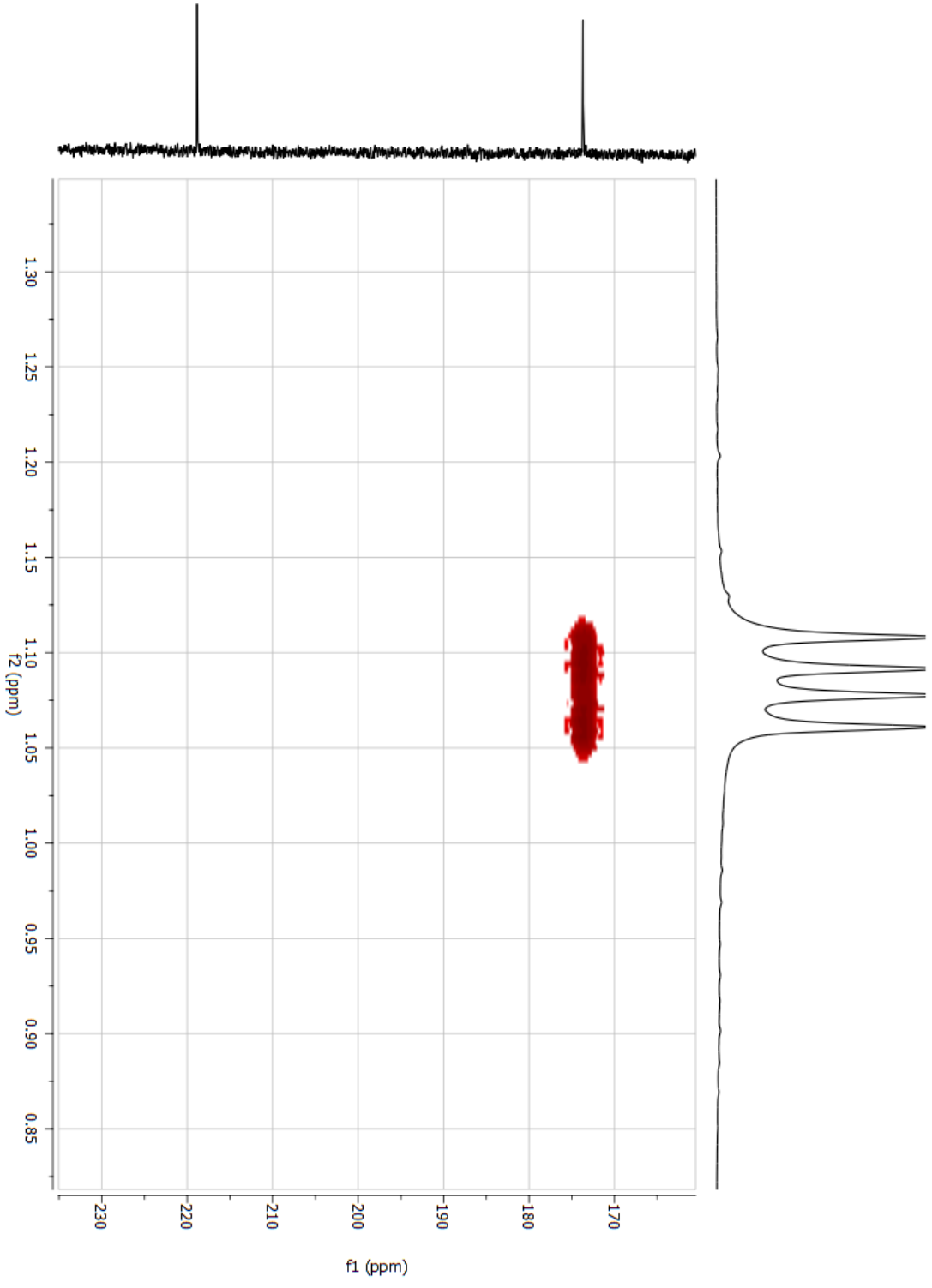


Prepared according to General Procedure L using **169** (80 mg, 0.206 mmol), TFA (2 mL), $NaBH_4$ (31 mg, 0.826 mmol), Na_2CO_3 (219 mg, 2.06 mmol) and benzyl chloroformate (89 µL, 0.619 mmol). Purification by flash column chromatography (10→15% ethyl acetate in petrol on silica gel) afforded the product as a pale yellow oil (67 mg, 80%).

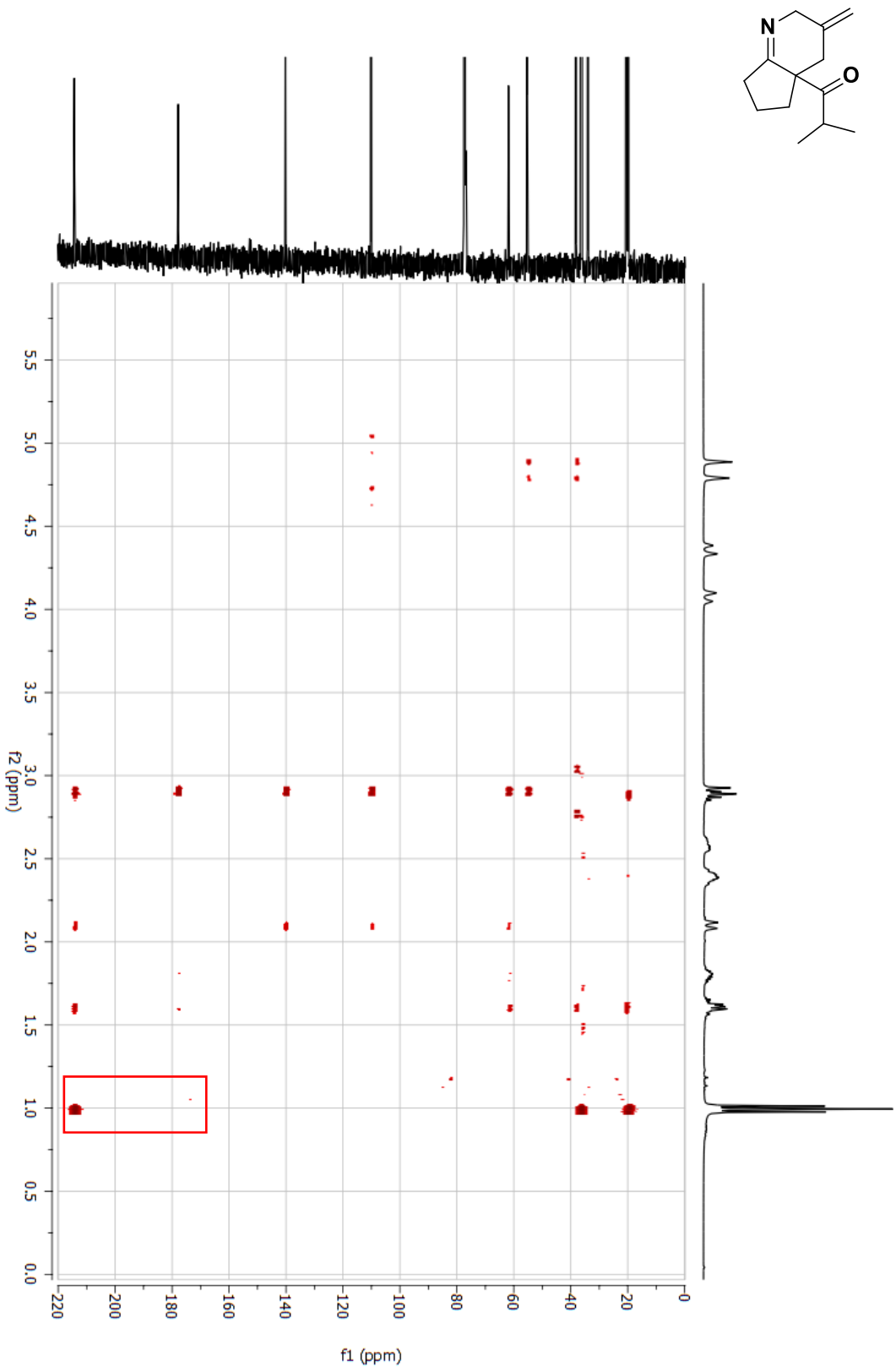
FTIR ν_{max} (thin film/cm^{-1}) 2982, 1717, 1467, 1359, 1223; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.27 (m, 6H, Ar*H*), 7.21 – 7.09 (m, 3H, Ar*H*), 5.14 (d, *J* = 12.5 Hz, 1H, OC*H*$_A$H$_B$), 5.07 (d, *J* = 12.5 Hz, 1H, OCH$_A$*H*$_B$), 5.02 – 4.93 (m, 2H, C=C*H*$_2$), 4.75 (d, *J* = 14.5 Hz, 1H, NC*H*$_A$H$_B$), 3.94 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 3.59 (dd, *J* = 14.5, 0.5 Hz, 1H, NCH$_A$*H*$_B$), 3.50 (d, *J* = 14.5 Hz, 1H, C=CC*H*$_A$H$_B$), 3.49 (dd, *J* = 12.5, 3.0 Hz, 1H, NC*H*), 3.20 – 3.07 (m, 1H), 3.05 – 2.97 (m, 1H), 2.97 – 2.85 (m, 1H), 2.44 – 2.35 (m, 1H), 2.28 (d, *J* = 14.5 Hz, 1H, C=CCH$_A$*H*$_B$), 1.06 (t, *J* = 7.0 Hz, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.7, 155.0, 140.2, 137.9, 137.0, 136.0, 129.5, 128.6, 128.0 (2 × C), 127.3, 126.8, 126.3, 112.4, 67.0, 64.3, 61.2, 53.7, 51.2, 44.5, 31.0, 25.1, 14.0; **HMRS (ESI$^+$)** $C_{25}H_{27}NO_4$ requires M+H$^+$ 406.2013, found 406.2016.

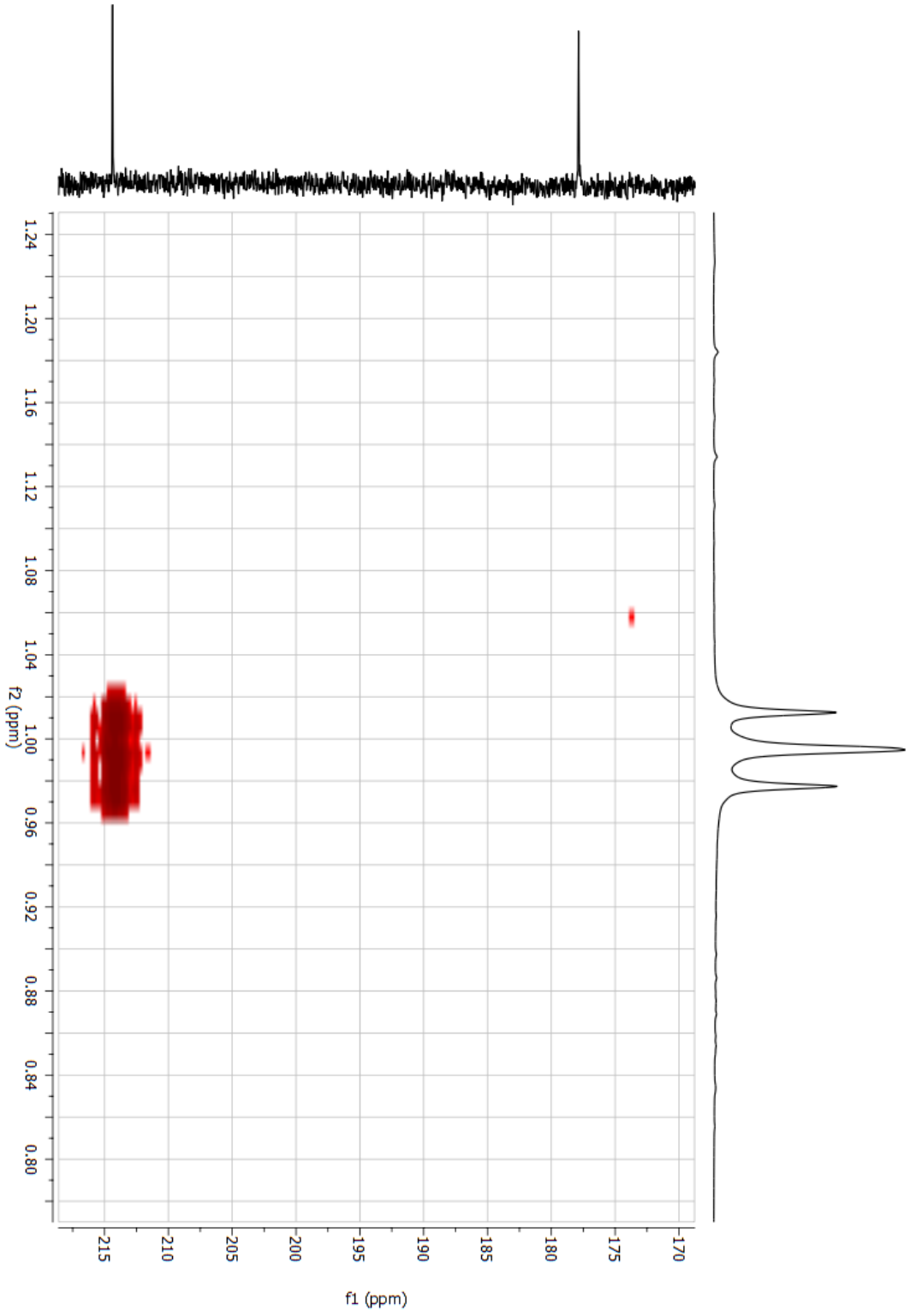
Appendix 1 – HMBC Spectrum of 68



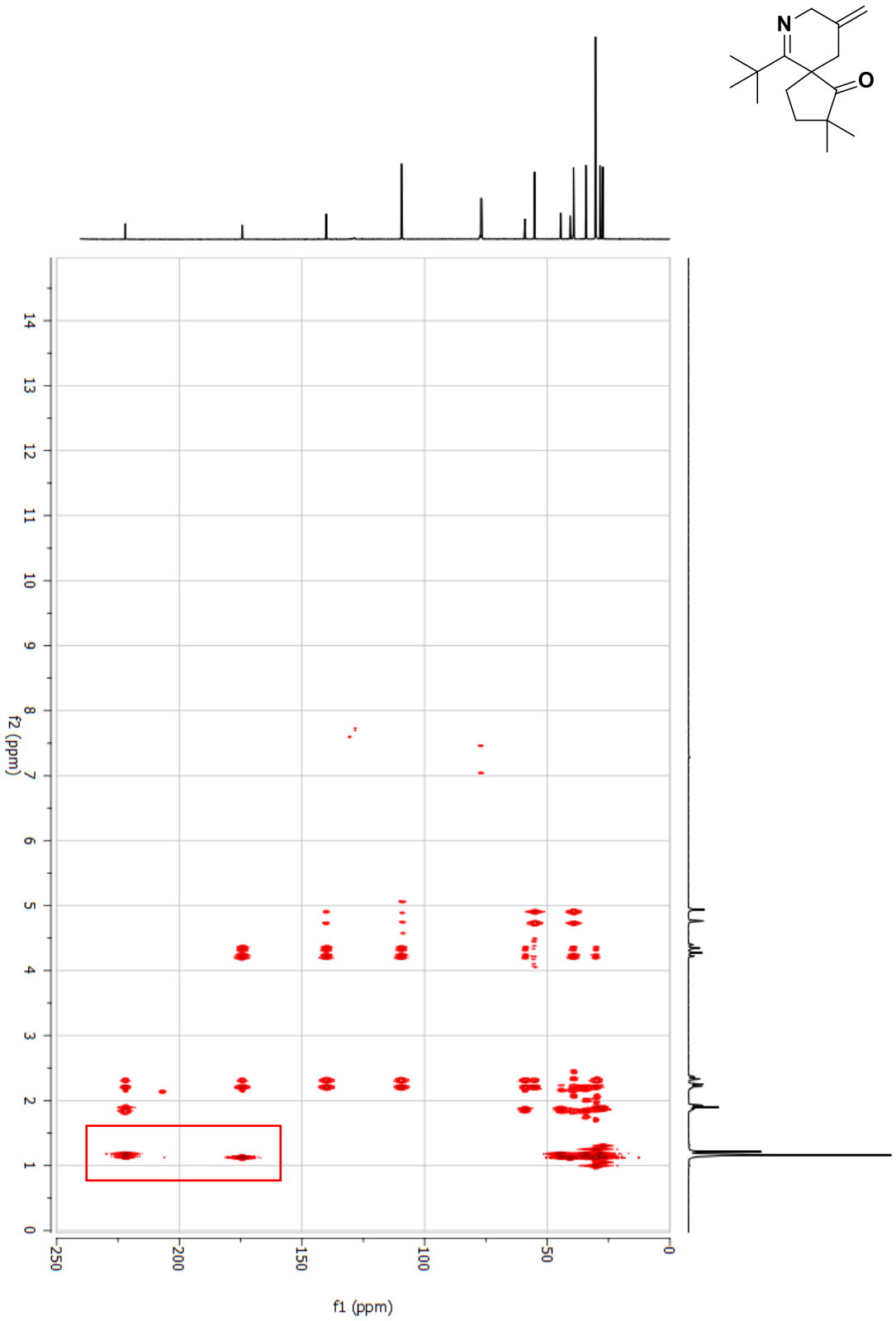

1.30
1.25
1.20
1.15
1.10
1.05
1.00
0.95
0.90
0.85
f2 (ppm)
230
220
210
200
190
180
170
f1 (ppm)

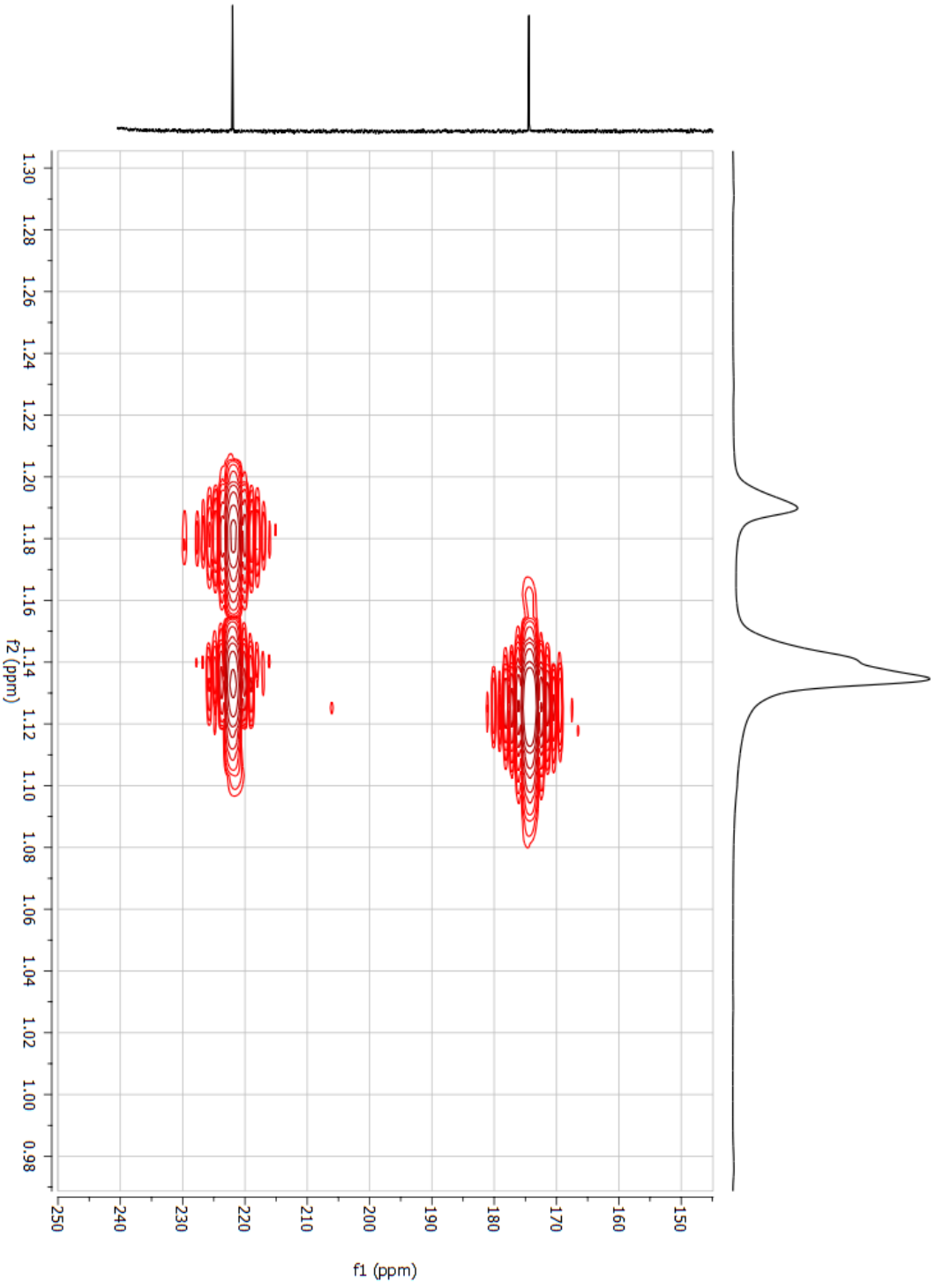
Appendix 2 – HMBC Spectrum of 37



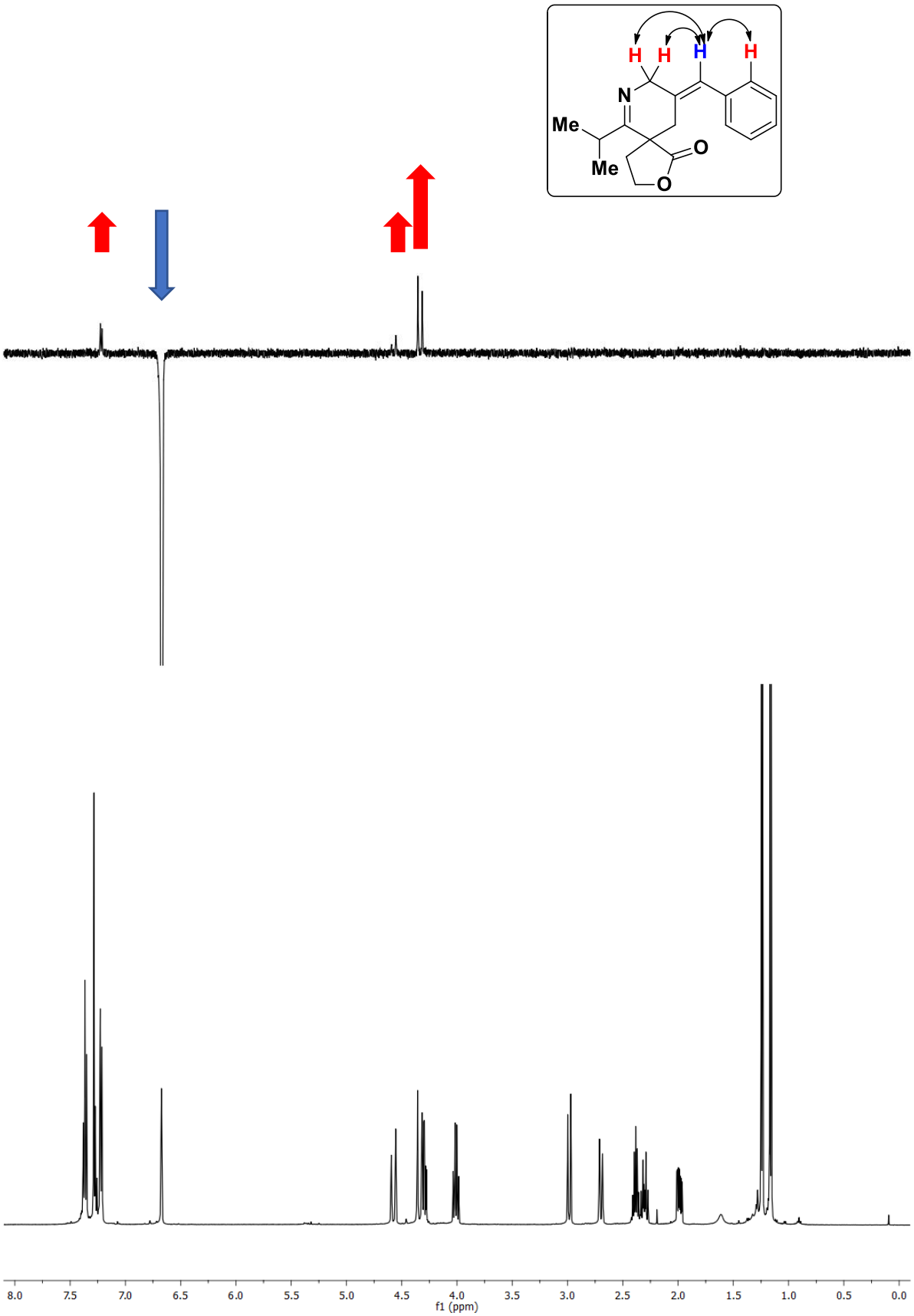

1.24
1.20
1.16
1.12
1.08
1.04
1.00
0.96
0.92
0.88
0.84
0.80
f2 (ppm)
215
210
205
200
195
190
185
180
175
170
f1 (ppm)

Appendix 3 – HMBC Spectrum of 72




f2 (ppm)
1.30
1.28
1.26
1.24
1.22
1.20
1.18
1.16
1.14
1.12
1.10
1.08
1.06
1.04
1.02
1.00
0.98
250
240
230
220
210
200
190
180
170
160
150
f1 (ppm)

Appendix 4 – nOe Spectrum of 99



Appendix 5 – Crystal Structure of 87

See folder “Appendix_5_Crystal_structure_of_87” on attached CD-ROM

Appendix 6 – Crystal Structure of 172

See folder “Appendix_6_Crystal_structure_of_172” on attached CD-ROM

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