Palladium-Catalysed Alkene Difunctionalisation in the Synthesis of Heterocycles

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A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

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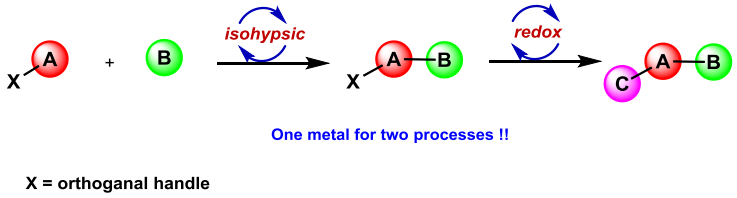
Abstract

The opening chapter of this thesis is split in two with part one providing a summary of the existing methods for palladium-catalysed oxypalladation reactions resulting in the synthesis of oxygen containing heterocycles. Part two focuses on a niche area of palladium catalysis. Here, palladium-catalysed isohypsic reactions, in which the oxidation state of the palladium does not change throughout the entire catalytic cycle, are described and summarised.

Chapter 2 describes the extension of the heteroallylation reaction to incorporate the synthesis of lactones and the pursuit of an enantioselective oxyallylation reaction. The oxyallylation reaction in the synthesis of lactones was successfully applied to include five- and six- membered lactone rings in good yields, with the first enantioselective oxyallylation reaction being developed. Building upon this work, a copper-mediated oxyallylation reaction was developed. Additionally, a palladium-catalysed arylallylation reaction and C-H−cyclisation reaction were pursued.

Ensuing work, detailed in chapter 3, focused on the development of a novel isohypsic−redox sequence, combining both the palladium-catalysed isohypsic heteroallylation reaction with more traditional redox chemistry. The transformations developed give rise to the synthesis of heterocycles with complex functionality both quickly and efficiently using the one palladium source.



Experimental procedures and data are summarised in Chapter 4.

Contents

Acknowledgements

First and foremost, I would like to extend my thanks to Dr. David France for giving me the opportunity to work in his research group and for all his advice, support and patience over the course of my PhD.

I would also like to extend my thanks to my second supervisor, Dr. Richard Hartley and Dr. Joëlle Prunet for their helpful thoughts and discussions on my research. I would also like to express my thanks to the departmental staff, academic, technical and administrative, for their support. Financial support from the University of Glasgow, WestCHEM and ESPRC is gratefully acknowledged.

Over the years, I have enjoyed my time within the France group and would like to thank the other members. As the “founding father” of the France group I would like to thank Jo Gemmell (née Hewitt) for being an impossible act to follow. A special thank you goes to Lewis Williams, a fellow F.B.I co-founder, for helping me solve the numerous mysteries around the department. David Phillips absolutely must be thanked and it must be noted he is a terrible vegetarian. Until I met David, my research had led me to believe a man could not sustain himself on a diet of square cheese slices on rolls and salt ‘n’ vinegar Golden Wonder crisps, and so I must thank him for proving me wrong. Stuart Ruddell has been a good gym buddy recently and I thank him for making me film him work out. It’s as odd as it sounds and I didn’t enjoy doing it, but I feel I am stronger as a person for coming through the other side. I would also like to thank all the France, Prunet, Clark and Marquez group members past and present.

My friends, over the course of the PhD, made me aware on multiple occasions that through the taxes they pay they support my lifestyle and that I should be forever grateful for my flat, the clothes on my back and the food in my belly. I am truly lucky to have such a magnanimous bunch around me. Without continual reminders to get ‘a real job’ and that I am ‘just a student’, I don’t think I would have had the strength to pull through the PhD experience. The desire to join them in the work force and to pay taxes spurred me on when times were tough.

I am appreciative of all the support and encouragement from my friends, family and loved ones over the years. I couldn’t have done it without you and I am eternally grateful.

I would also like to thank the Watson group from the University of Strathclyde for providing chiral phosphoric acids.

Author's Declaration

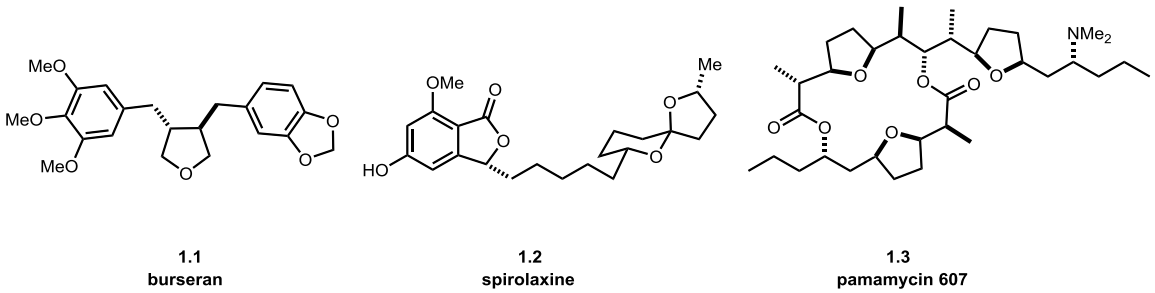
This thesis represents the original work of Craig David Smith unless otherwise explicitly stated in the text. The research was carried out at the University of Glasgow in the Raphael and Henderson Laboratories under the supervision of Dr. David France during the period of October 2012 to March 2016. Portions of the work described herein have been published elsewhere, as below:

Hewitt, J. F. M.; Williams, L.; Aggarwal, P.; Smith, C. D.; France, D. J. *Chem*. *Sci*. **2013**, *4*, 3538–3543.

1. Palladium-Catalysed Functionalisation of Alkenes in the Synthesis of Oxygen-Containing Heterocycles

1.1 Introduction

Oxygen-containing heterocycles are prevalent in natural products and have been studied extensively by organic and medicinal chemists due to their pharmacological and biological activities.[1] In particular, tetrahydrofurans and lactones with five- and six-membered ring sizes are common motifs found in natural product classes such as lignans **1.1**,[2] spiroketals **1.2**[3] and macrocycles **1.3**[4] (Figure 1.1). Due to their biological activity, oxygen-containing natural products continue to play a significant role in the design and development of drugs in the treatment of diseases.[5]



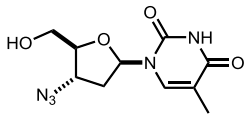
1.1
burseran

1.2
spirolaxine

1.3
pamamycin 607

Figure 1.1: Oxygen-containing natural products

Synthetic tetrahydrofurans have also been shown to exhibit powerful pharmacological activity. Zidovudine **1.4**, is an antiretroviral medication used for the treatment of HIV/AIDS (Figure 1.2).[6] It is currently on the world health organisation's list of essential medicines, which further highlights the importance of oxygen-containing heterocycles.



1.4
zidovudine

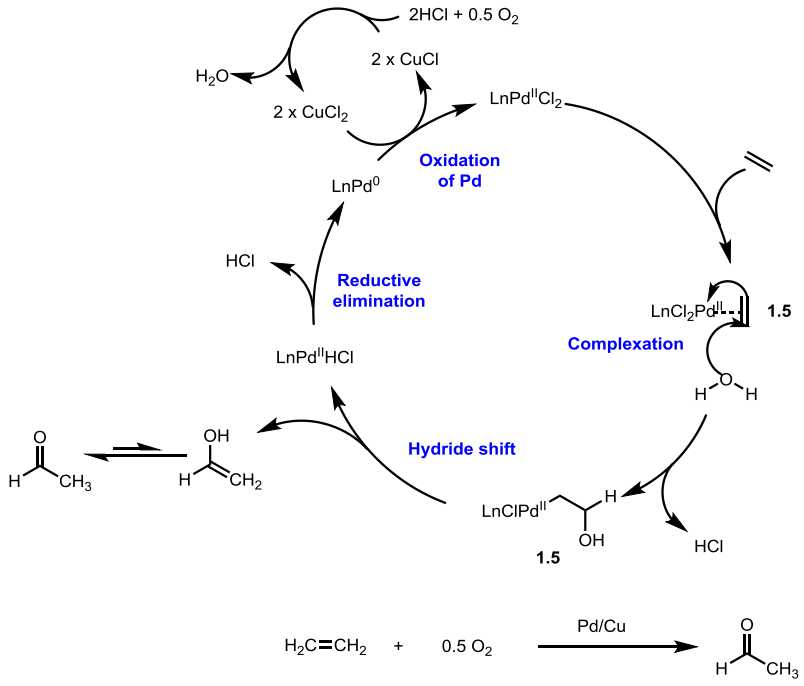
Figure 1.2: Structure of Zidovudine **1.4**

The aforementioned importance of tetrahydrofurans and lactones has resulted in their synthesis being of significant importance. New technologies and methodologies in the construction of oxygen-containing heterocycles are highly sought after. Amongst the most common methods for the construction of oxygen-containing heterocycles are acid catalysed cyclisations, ring-closing metathesis,[7] haloetherification,[8] and hetero-Diels−Alder reactions.[9] Additionally, functionalisation of alkenes by transition metal catalysis has been used to construct oxygen-containing heterocycles. Various metal

catalysts such as Cu,[10] Ag,[11] Pt,[12] Ni[13] and Au[14] have all been employed in the synthesis of oxygen-containing heterocycles, however, by far the most prevalent transition-metal catalyst is Pd.[15]

Over the years, palladium-catalysis has added numerous strings to the organic chemists bow. The importance of this transition-metal to the synthetic chemist was emphasised when the 2010 Nobel Prize in chemistry was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki in recognition to their contribution to the field of palladium-catalysis.

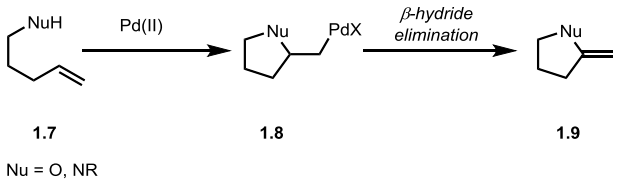
In 1959, Wacker Chemie published a report detailing the reaction for the catalysed aerobic oxidation of ethylene with water to acetaldehyde.[16] The reaction owes its success to the fact that the Pd(II) catalyst could be regenerated by the Cu(II) co-catalyst in the presence of oxygen (Scheme 1.1). The Lewis acid Pd(II) catalyst coordinates to ethylene generating palladium-complex **1.5**. In turn, this reverses the nucleophilicity of the alkene making it electrophilic and activating it for attack from the water molecule. Attack on the alkene forms a Pd(II)-alkyl intermediate with a β-hydroxyl group **1.6**. A hydride shift affords vinyl alcohol, which quickly tautomerises to give acetaldehyde and Pd(0). The Pd(II)-catalyst is regenerated by the oxidation of Pd(0) by $CuCl_2$. The mechanism of the Wacker reaction has been studied considerably and much debate has centred around whether the water or hydroxide attacks from the same face as the Pd(II)-catalyst (*cis*-oxypalladation) or form the opposite face of the Pd(II)-catalyst (*trans*-oxypalladation).[17]



Scheme 1.1: Catalytic cycle of the Wacker reaction

After the success and the development of the Wacker process, it was reported that palladium(II) salts could activate alkenes for nucleophilic attack from a range of

nucleophiles giving rise to new C−O, C−N, and C−C bond formation under oxidative and non-oxidative conditions.[18] As well as intermolecular reactions, Wacker-type cyclisations have also been developed for alkenes bearing a tethered nucleophile (Scheme 1.2).



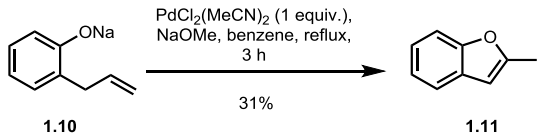
Scheme 1.2: Nucleopalladation in the synthesis of heterocycles

Alkene difunctionalisation *via* palladium-catalysis is the most common method for the construction of oxygen-containing heterocycles using transition metal catalysis.[13] This report will describe the wide range of multiple-bond forming reactions which have been coupled with palladium-catalysed oxycyclisation.

1.2 Oxypalladation of Alkenes

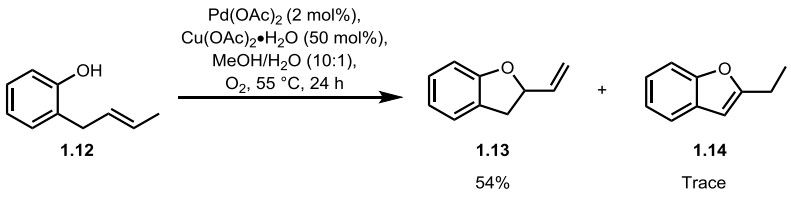
1.2.1 Wacker-type cyclisations

A number of different nucleophiles can attack a double bond that Pd(II) has coordinated to, however, the first part of this review will focus on the intramolecular formation of C−O bonds. In 1973, Hosokawa *et al.* published a report that detailed the first intramolecular oxypalladation reaction using a palladium(II) salt.[19] Herein, the authors reported the cyclisation reaction of the sodium salt of phenol **1.10** using one equivalent of $PdCl_2(MeCN)_2$ onto an unactivated alkene. Oxypalladation onto an unactivated alkene was subsequently followed by β-hydride elimination to give the more thermodynamically stable product 2-methyl benzofuran **1.11** in a 31% yield (Scheme 1.3). Although the yield was low, this was an important discovery in the synthesis of oxygen-containing heterocycles through the use of palladium.



Scheme 1.3: Wacker-type cyclisation of sodium salt of 2-allyl phenol **1.10**

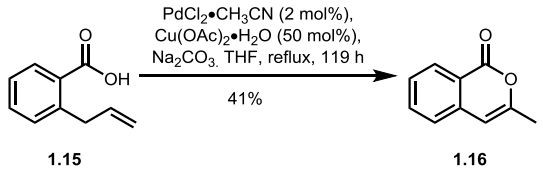
Improving on this methodology, Hosokawa and co-workers published a paper that describes the direct cyclisations of allyl phenol derivatives.[20] By changing the catalyst from $PdCl_2(MeCN)_2$ to $Pd(OAc)_2$ it was found that the sodium salts of phenols were not required. Varying the ratio of substrates such as 2-(but-2'-en-1'-yl)phenol **1.12** to $Pd(OAc)_2$ was found to vary the ratio of products **1.13** to **1.14**. Furthermore, the reaction was made catalytic by employing re-oxidation conditions using $Cu(OAc)_2$−O_2 as the re-oxidant (Scheme 1.4). It was proposed, that under the optimised conditions (Scheme 1.4), that the lack of formation of benzofuran **1.14**, the reaction proceeds through a *cis*-oxypalladation mechanism. Similar Wacker-type cyclisations were also extended to aliphatic alcohols in a paper published by Hosokawa and co-workers in 1976 using a similar catalyst and solvent system as that detailed below.[21]



Scheme 1.4: Wacker-type cyclisation of 2-(but-2'-en-1'-yl)phenol **1.12**

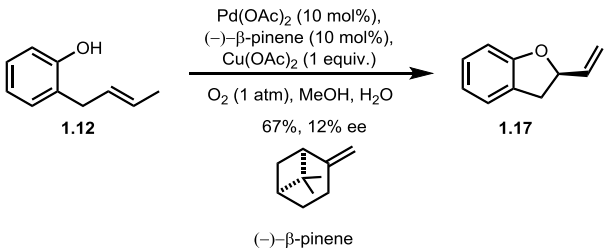
In addition to the synthesis of benzofurans and tetrahydrofurans, Hegedus and co-workers reported the first Pd(II)-cyclisation of allyl benzoic acid substrates in the synthesis of

isocoumarins – a motif often observed in natural products.[22] Through employing $Cu(OAc)_2$−O_2 as the re-oxidant the reaction was made catalytic. A consequence of the catalytic variant was that the reaction time had to be elongated from 3 h to 119 h and the yield dropped from 86% to 41% (Scheme 1.5). It was noted by the authors that the coordination of the carboxylate group prior to attack on the alkene is unknown, and thus, whether *trans*- or *cis*-oxypalladation is taking place is unclear.



Scheme 1.5: Oxypalladation reaction in the synthesis of isocoumarin **1.16**

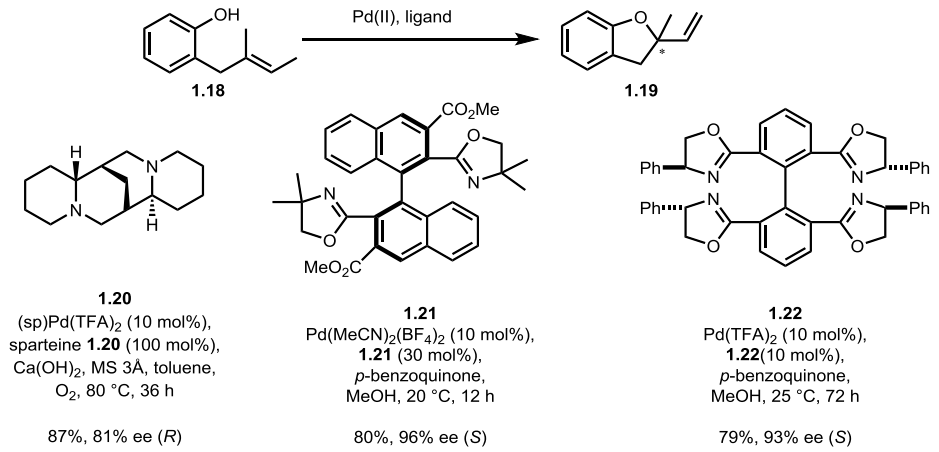
Building on their pioneering work, Hosokawa and co-workers developed an enantioselective Pd(II)-catalysed cyclisation reaction using a catalytic amount of (−)-β-pinene as the chiral ligand achieving a 12% ee (Scheme 1.6). If excess (−)-β-pinene was used, the cyclisation of allyl phenol **1.12** did not occur. This result suggests that coordination of the alkene on the substrate **1.12** is in direct competition with the olefin on the (−)-β-pinene molecule, thus, excess will retard oxidative cyclisation. The difficulty of improving on the 12% ee achieved by Hosokawa and co-workers is emphasised by the duration of no reported advancements. Almost 20 years passed before new reports of enantioselective Pd(II)-catalysed alkene functionalisation began to appear in the literature again.[18c]



Scheme 1.6: Enantioselective cyclisation using a (−)-β-pinene ligand

Since Hosokawa and co-workers seminal work on enantioselective oxypalladation reactions, their initial result has been improved upon. The most common ligand class in the Pd(II)-catalysed oxidative cyclisation reactions are bidentate nitrogen ligands. Stoltz and co-workers found that the natural product (−)-sparteine **1.20** was the most effective ligand in the enantioselective reaction of allyl phenols to benzofuran derivatives, which used O_2 as the re-oxidant (Scheme 1.7).[23] Surprisingly, the extent of asymmetry induced in the synthesis of dihydrobenzofuran **1.19** relied heavily upon which palladium salt was used. Electron donating groups around the aromatic ring caused the yield to drop,

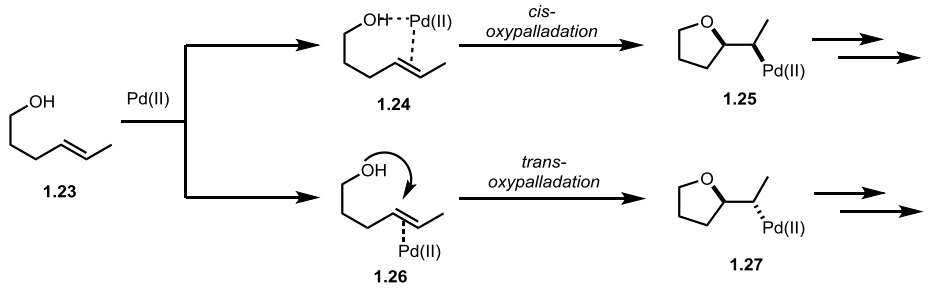
however, the enantioselectivity remained high. Conversely, electron withdrawing substituents around the ring caused the enantioselectivity to fall as low as 20% ee. Hayashi and co-workers developed Boxax ligand **1.21** and achieved an enantioselectivity of 96% ee and a yield of 80%.[24] Zhang *et al.* developed tetraoxazoline ligand **1.22**, which became axially chiral upon chelation with either one or two palladium centres. Interestingly, the enantioselectivites were dependent upon the ratio of ligand to palladium(II) salt and it is proposed that the ratio of mono- and bi-metallic complexes in the reaction mixture has a significant effect on enantioselectivity observed.[25]



Scheme 1.7: Enantioselective Wacker-type cyclisations in the synthesis of benzofuran **1.19**

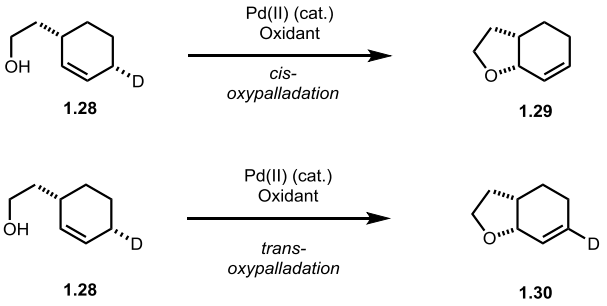
1.2.2 Mechanistic Considerations

The following reactions discussed will have one common first step in the synthesis of oxygen-containing heterocycles: oxypalladation. Oxypalladation is known to occur *via* one of two mechanisms: *cis*- or *trans*-oxypalladation (Scheme 1.8).[18c, 26] *Cis*-oxypalladation is when the palladium(II) catalyst coordinates to both the tethered hydroxyl group and the olefin and nucleophilic attack occurs leading to intermediate **1.25**.[23, 27] Conversely, *trans*-oxypalladation occurs when the palladium(II) catalyst coordinates solely to the alkene and the tethered hydroxyl nucleophile attacks from the opposite side generating intermediate **1.27**. Whether the mechanism proceeds *via cis*- or *trans*-oxypalladation has important implications on the stereochemical outcome of the reaction. In turn, this can have a significant bearing on the development of enantio- and diastereo-selective oxypalladation reactions.[18c]



Scheme 1.8: *Cis*- and *trans*-oxypalladation reactions

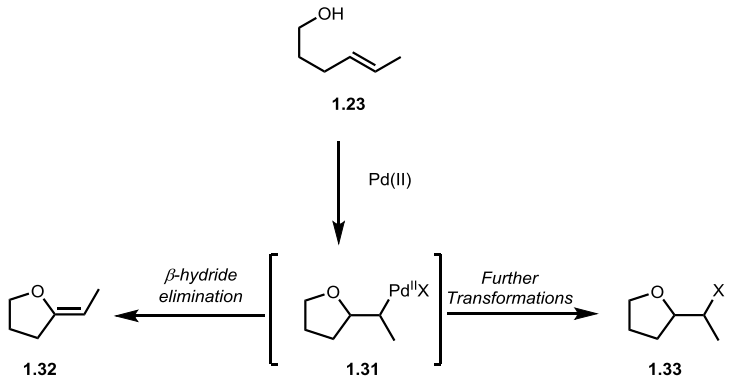
In order to determine whether a *cis*- or *trans*-oxypalladation reaction is taking place, deuterium labelling experiments can be performed (Scheme 1.9). Through analysis of the products **1.29** and **1.30**, whether the reaction proceeds through *cis*- or *trans*-oxypalladation can be deduced by the presence of deuterium in the product.



Scheme 1.9: Deuterium labelling experiments

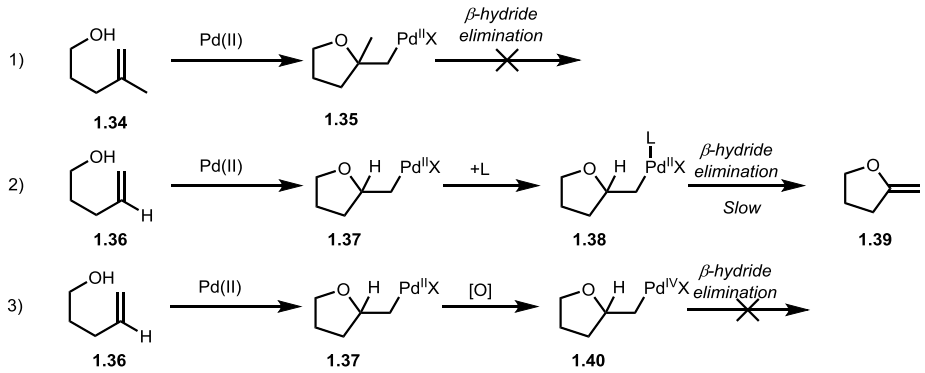
The nature of the mechanism, whether the reaction proceeds through *cis*- or *trans*-oxypalladation, has been studied in depth.[18c] It has been found that small changes in substrate, catalyst and reaction conditions can result in changes to the mechanism.

Another consideration, when developing a second bond forming event, is the rate of β-hydride elimination relative to the other transformation being developed (Scheme 1.10). Generally, β-hydride elimination is an intramolecular process that is fast and can lead to inactive catalysts.



Scheme 1.10: Competing pathways of alkylpalladium(II) intermediates **1.31**

To avoid β-hydride elimination, and promote further transformations, there are 3 main methods to consider (Scheme 1.11). Through the use of *gem*-disubstituted alkene **1.34**, strategy 1 removes β-hydrogens in the intermediate **1.35** and thus cannot undergo β-hydride elimination. Strategy 2 involves stabilising alkylpalladium(II) intermediate **1.38**, thus slowing down the rate of β-hydride elimination. Strategy 3 involves using processes that are more rapid than β-hydride elimination, such as oxidation to Pd(IV) species **1.40** from alkylpalladium(II) intermediate **1.37**, and thus circumventing β-hydride elimination.

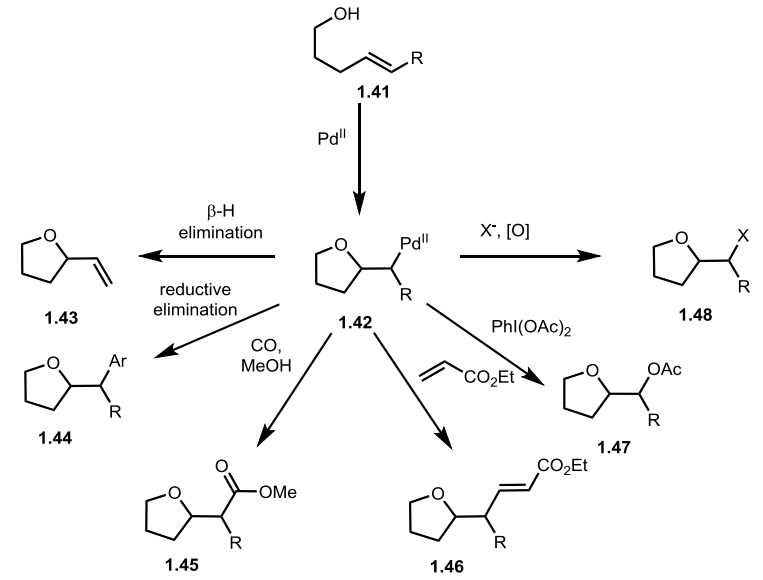


Scheme 1.11: Strategies to circumvent β-hydride elimination

1.3 Alkene Difunctionalisation *via* Wacker-Type Cyclisation

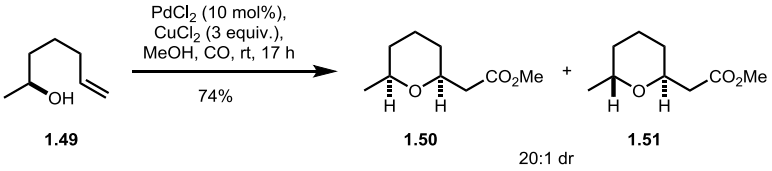
1.3.1 C−O and sp^3−sp^2 C−C Alkene Difunctionalisation

As described previously, oxypalladation followed by β-hydride elimination by palladium-catalysis is one way to synthesise heterocycles. In the aforementioned reaction, functionalisation has taken place at one of the carbons on the alkene. Difunctionalisation occurs when two new bonds are formed over the alkene. The functionalisation steps that are formed after the initial oxypalladation reaction can deliver a wide range of heterocyclic products (Scheme 1.12). The following review will focus on the formation of new C−C bonds which are formed after the initial oxypalladation reaction.



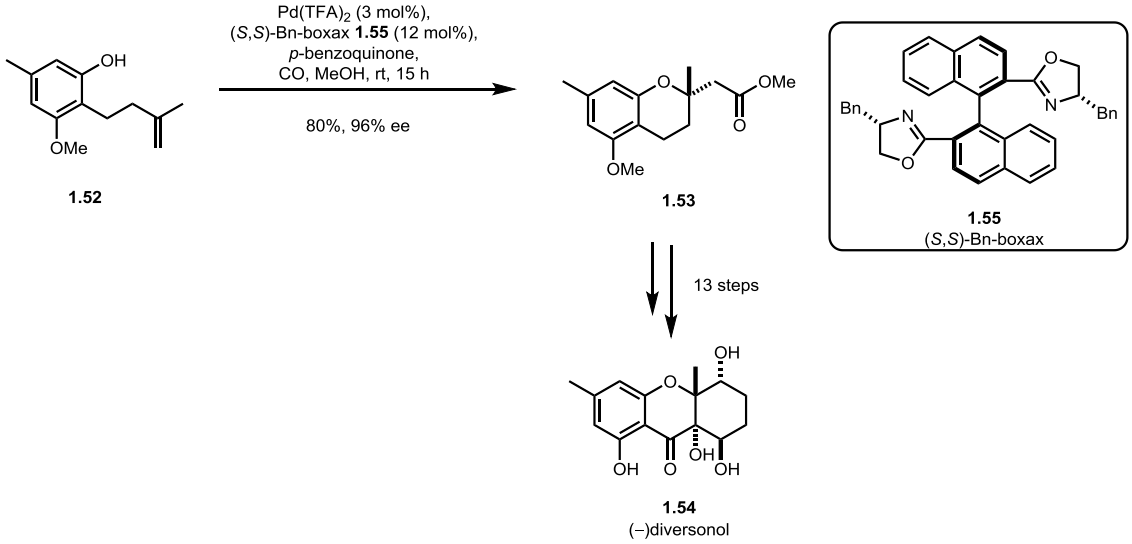
Scheme 1.12: Transformations of the alkylpalladium(II) intermediate **1.42**

In 1984, Semmelhack and co-workers reported a new alkoxylation and subsequent carbonylation in the synthesis of tetrahydrofuran and pyran derivatives.[28] Additionally, the developed methodology was used in the stereoselective synthesis of the methyl ester **1.50** of a glandular secretion from the civet cat (Scheme 1.13). In an atmosphere of carbon monoxide, the alkylpalladium(II) intermediate formed in the heterocyclisation step undergoes a migratory insertion with the carbon monoxide which is subsequently trapped with alcohols to afford esters.



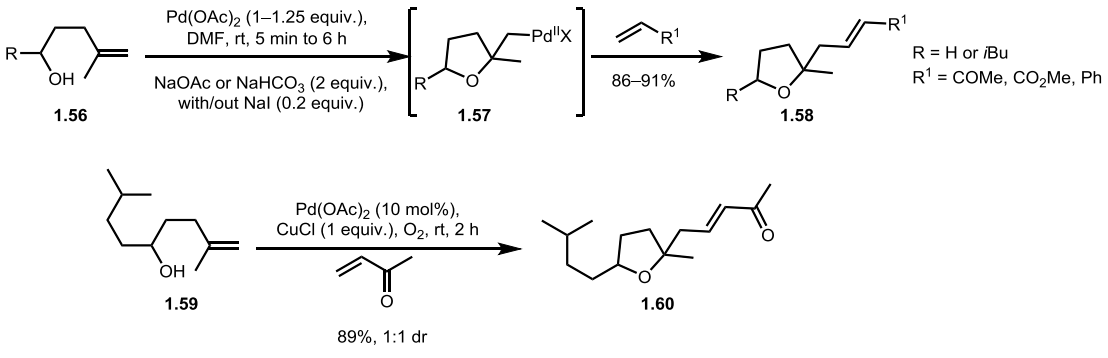
Scheme 1.13: Synthesis of the methyl ester of a glandular secretion civet cat **1.50**

In 2013, using the methodology developed by Semmelhack and co-workers, the Tietze group applied an enantioselective variant in the total synthesis of (−)-diversinol **1.54**.[29] The key step in the total synthesis starts with phenol **1.52** which is cyclised enantioselectively using catalytic amounts of $Pd(TFA)_2$ with the (*S*,*S*) Bn-boxax ligand **1.55**, under an atmosphere of carbon monoxide and using methanol as the solvent (Scheme 1.14). The desired chroman was synthesised in an 80% yield and a 96% ee. A further 13 steps were required to reach the desired (−)-diversinol **1.54**.



Scheme 1.14: Enantioselective oxycarbonylation of **1.52**

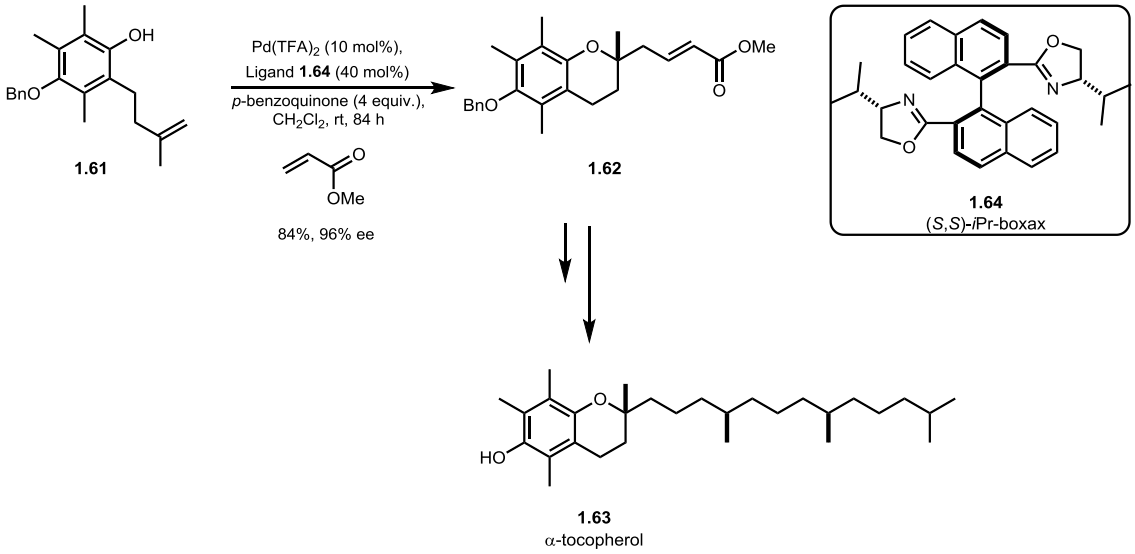
Pd(II)-alkyl intermediates can undergo carbopalladation onto electron deficient alkenes. Semmelhack and co-workers continued their seminal alkene difunctionalisation work by using *gem*-disubstituted hydroxy alkene **1.56** in the presence of palladium(II). Cyclisation, to give alkylpalladium(II) intermediate **1.57** then undergoes carbopalladation on Heck acceptors such as methyl acrylate, styrene and methyl vinyl ketone in the synthesis of tetrahydrofuran derivatives **1.58** (Scheme 1.15).[30] When cyclohexene or hexene were the Heck acceptor, the reaction did not proceed to the desired heterocyclised product. This discovery led the authors to propose that formation of Pd(II)-alkyl intermediate **1.57** is reversible under the reaction conditions. Through the use of CuCl in an O_2 atmosphere the reaction was made catalytic and was used to synthesise tetrahydrofuran product **1.60** in 89% yield (Scheme 1.15). The use of *mono*-substituted alkene starting materials afforded none of the desired heterocyclised products and produced only unwanted side products.



Scheme 1.15: Tandem oxypalladation−vinylation reaction

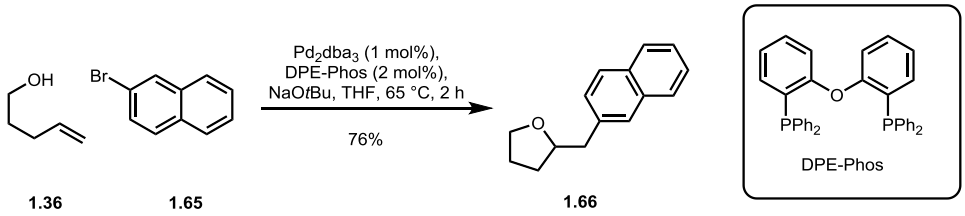
The methodology developed by Semmelhack *et al*. was extended to an enantioselective version of the oxypalladation−vinylation reaction by Tietze and co-workers in the synthesis of α-tocopherol **1.63** (Scheme 1.16).[31] A significant step in the total synthesis was the

cyclisation of *mono*-protected phenol **1.61** using a catalytic amount of $Pd(TFA)_2$ and (*S*,*S*)-*i*Pr-boxax ligand **1.64** afforded chroman **1.62**. The highest yield was 84% with a 96% ee with methyl acrylate as the Heck acceptor.



Scheme 1.16: Enantioselective tandem oxypalladation−vinylation reaction

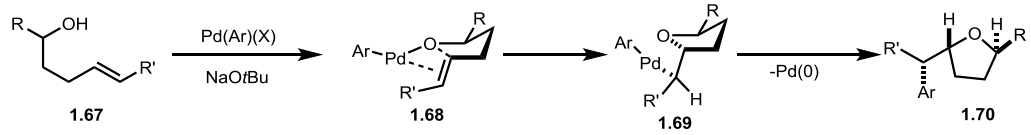
Wolfe *et al.* published reports that describe a new strategy in the heterocyclisation and alkene difunctionalisation class of reactions (Scheme 1.17). [32] Treatment of naphthyl bromide **1.65** with a Pd(0) catalyst and DPE-Phos as the ligand and hydroxy alkene **1.36** generated tetrahydrofuran **1.66**. The reaction worked well with aryl and vinyl bromides; however, the methodology was less successful with *gem*-disubstituted alkenes. The protocol developed was successfully modified and extended to an aminoarylation reaction of alkenes,[33] an intramolecular alternative[34] and in the synthesis of isoxazolidines.[35]



Scheme 1.17: Oxyarylation reaction of hydroxyl alkene **1.36**

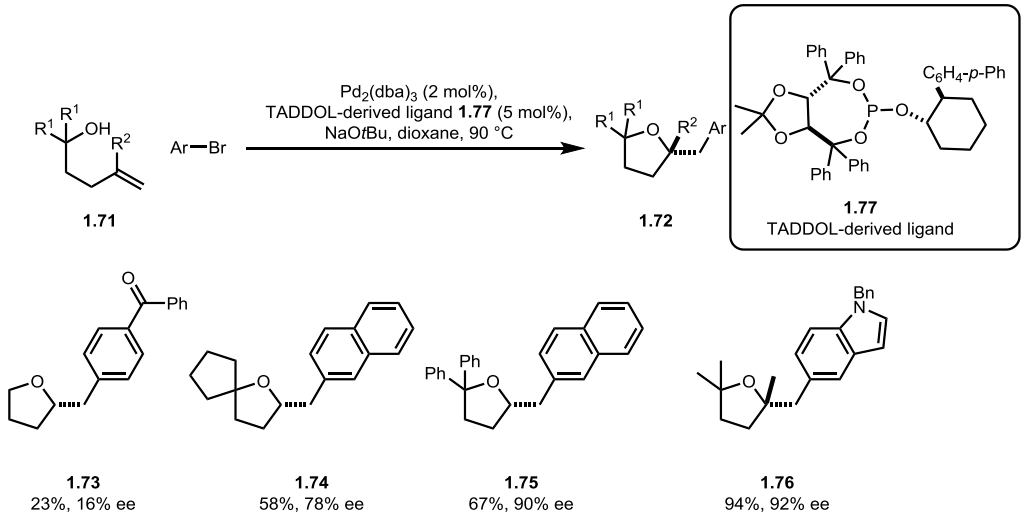
In order to deduce the mechanism for the reaction, Wolfe and co-workers performed deuterium labelling experiments.[36] Experimentation, led to the proposed mechanism below (Scheme 1.18). Oxidative addition of the Pd(0) catalyst into an aryl bromide generates the active palladium(II) catalyst. Reaction of the alcohol **1.67** with NaO*t*Bu and Pd(Ar)(X) would lead to Pd(Ar)(OR) transition state **1.68**. Insertion of the olefin into the Pd−O bond could lead to alkylpalladium(II) intermediate **1.69**. Reductive elimination of species **1.69** would lead to the observed product **1.70**. The mechanistic pathway outlined

below explains the *trans*-tetrahydrofuran stereochemistry of the products observed (Scheme 1.18).



Scheme 1.18: Proposed mechanistic pathway for the oxyarylation of alcohols **1.67**

In 2015, Wolfe and co-workers reported a palladium-catalysed enantioselective oxyarylation reaction of hydroxy alkenes.[37] Through rigorous screening, it was found that $Pd_2(dba)_3$ combined with TADDOL-derived ligand **1.77** provided the best enantioselectivities. In order to obtain good yields and high enantioselectivities, it was required that the nucleophile was a tertiary alcohol, which is shown by the low yields and enantioselectivity observed in tertrahydrofuran **1.73** (Scheme 1.19). *Mono*-substituted alkenes generated a range of substrates, a sample of which can be seen below in products **1.74** and **1.75**. The reaction also proceeded well with *gem*-disubstituted alkenes to yield tetrahydrofuran derivatives such as **1.76** in high yields and high ee's. A limitation of the reaction is that the use of substrates bearing internal alkenes were unreactive under the conditions outlined (Scheme 1.19).

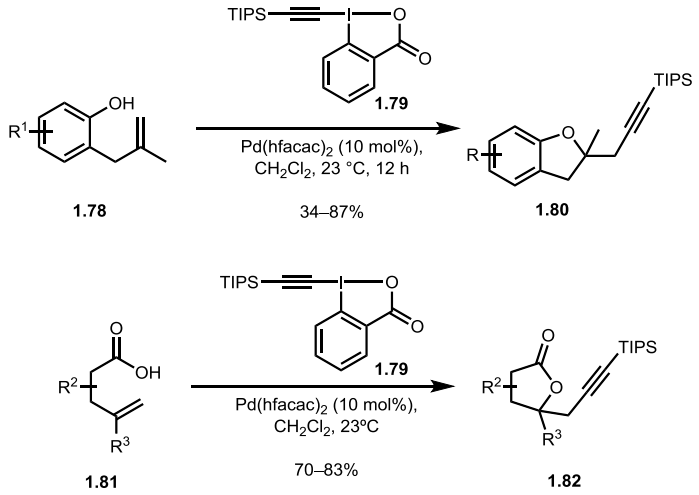


Scheme 1.19: Enantioselective oxyarylation reaction of hydroxyl alkenes

1.3.2 C−O and sp^3−sp C−C Alkene Difunctionalisation

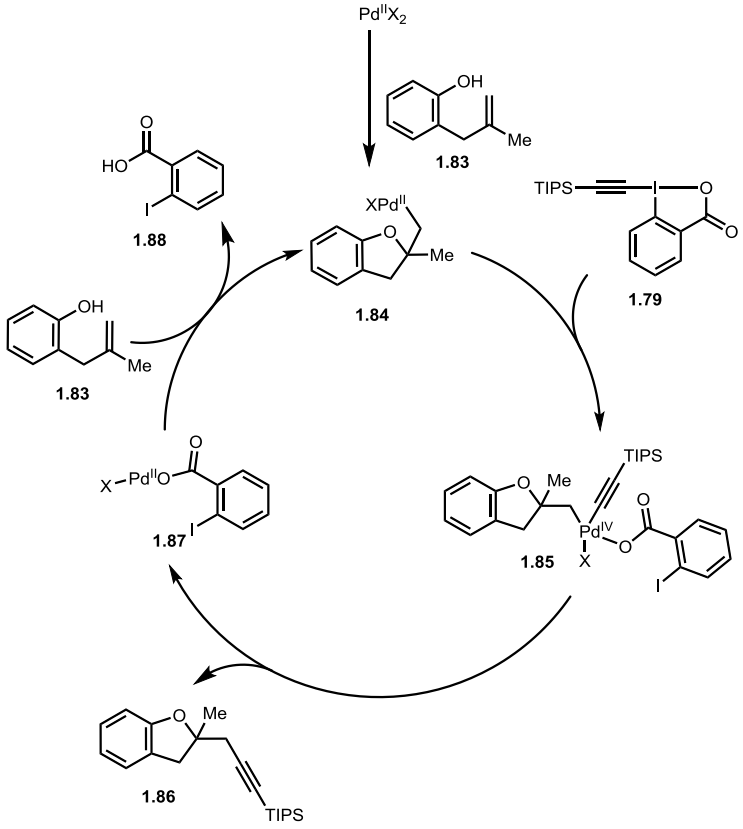
In 2010, Waser *et al.* published an article on the oxyalkynylation reaction of unactivated alkenes with tethered alcohol and carboxylic acid nucleophiles using tri*iso*propylsilyl ethynylbenziodoxolone (TIPS-EBX) reagent **1.79** (Scheme 1.20).[38] Generally, the reaction afforded the heterocyclised products in good yields. One exception was when

there was a methyl substituent *para* to the hydroxyl group, which afforded the dihydrobenzofuran in 34% yield. More electron rich substituents than methyl, around the aromatic ring, did not generate any of the corresponding dihydrobenzofuran. In the synthesis of lactones, more electron rich aryl substituents could be placed around the aromatic ring. Furthermore, oxyalkynylation reaction of aliphatic alcohols was unsuccessful; however, the oxyalkynylation reaction worked well for aliphatic acids. *Mono*-substituted alkenes in the synthesis of lactones performed the oxyalkynylation reaction better than *mono*-subsituted phenols with far superior yields.



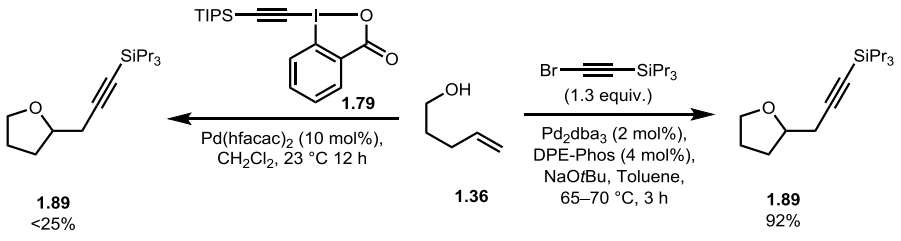
Scheme 1.20: Oxyalkynylation reaction of phenols and carboxylic acids

The hypervalent iodide reagent, TIPS-EBX **1.79**, is a strong oxidant that allows the allows the oxidation of alkylpalladium(II) intermediates to alkylpalladium(IV) intermediates, which is key for this particular oxyalkynylation reaction. The proposed mechanism can be seen below (Scheme 1.21). Oxypalladation of phenol **1.83** by a palladium(II) catalyst will produce alkylpalladium intermediate **1.84**. Oxidative addition into the iodo-alkynylbond of the hypervalent iodide species yields alkylpalladium(IV) intermediate **1.85** which quickly undergoes reductive elimination to afford the dihydrobenzofuran **1.86** and reproduce the palladium(II) catalyst.



Scheme 1.21: Mechanism of oxyalkynylation reaction

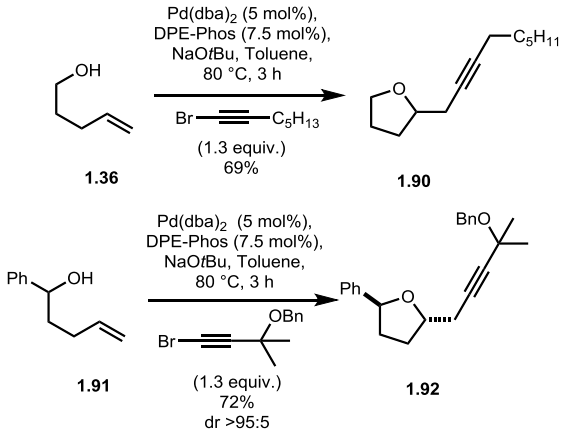
As described above, one major drawback of the oxyalkynylation reaction using the strong oxidant TIPS-EBX **1.79**, was its inability to cyclise aliphatic alcohols in good yields. Using the hypervalent iodine reagent and the conditions developed for the heterocyclisation reaction of phenols, aliphatic hydroxyl alkene **1.36** afforded less than 25% of the desired tetrahydrofuran **1.89** (Scheme 1.22). Through the use of Wolfe-type conditions a highly successful oxyalkynylation reaction was developed by the Waser group. [39] Using a Pd(0) catalyst, tri*iso*propylsilyl ethynyl bromide, the desired tetrahydrofuran product **1.89** was afforded in 92% yield. Secondary alcohols were also tolerated to give tetrahydrofurans in good to excellent diastereoselectivities.



Scheme 1.22: Oxyalkynylation reaction of aliphatic alcohol **1.36**

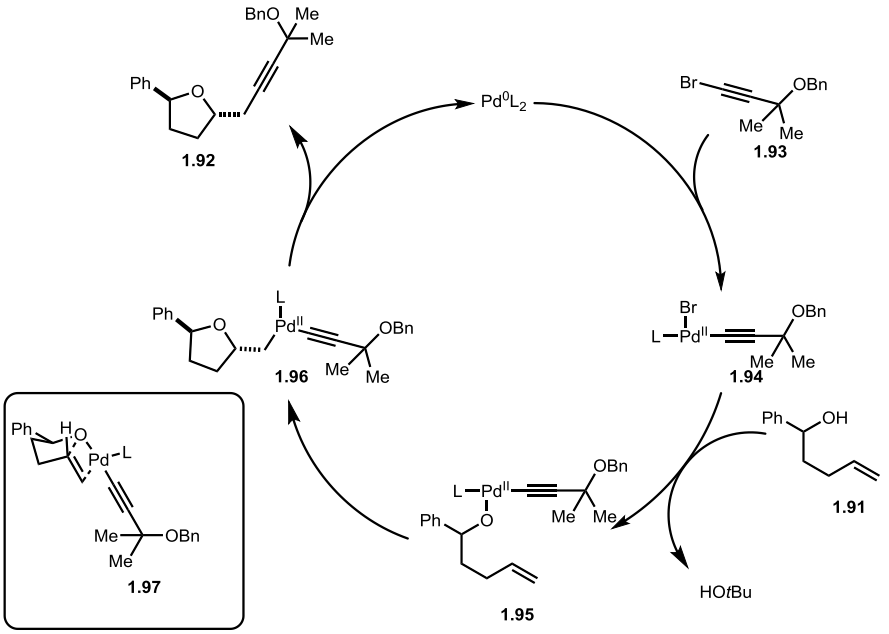
A modification of the reaction conditions allowed the use of bromoacetylenes substituted with aliphatic groups.[40] Changing the palladium catalyst from $Pd_2(dba)_3$ to $Pd(dba)_2$ and altering the catalyst to ligand ratio the reaction proceeded in good yields and excellent

diastereoselectivities (Scheme 1.23). Optimisation of the desired reaction revealed that the choice of base also had an effect on the outcome of the reaction. LiO*t*Bu and KO*t*Bu were screened; however, only traces of the desired product could be detected. The use of NaHMDS gave a modest yield of 24% of tetrahydrofuran **1.90**, indicating that the sodium counter-ion plays a significant role in the reaction.



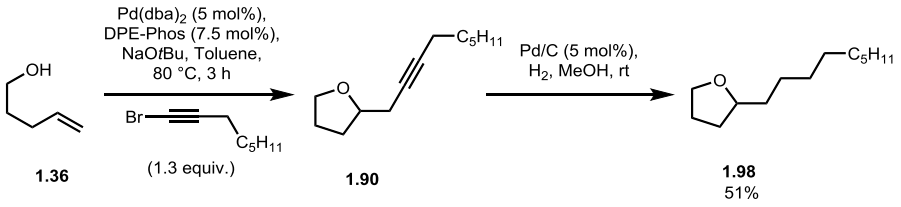
Scheme 1.23: The use of aliphatic bromoacetylenes as electrophiles

While tetrahydrofuran products **1.90** and **1.92** are structurally similar to the previously discussed oxyalkynylation poducts obtained using TIPS-EBX **1.79** (Scheme 1.20), the process is mechanistically different (Scheme 1.24). Similarities exist between the mechanism detailed below and the mechanism described in detail by Wolfe and co-workers (Scheme 1.18). A probable first step is the oxidative addition of the Pd(0) catalyst to alkynyl bromide **1.93** to generate the intermediate **1.94** (Scheme 1.24). Ligand exchange on the Pd(II)-catalyst followed by intramolecular oxypalladation on **1.95** to give palladium(II)-alkyne intermediate **1.96** would be in agreement with the excellent *trans*-diastereoselectivity observed, if the two substituents are in the pseudo-equatorial positions in the transition state **1.97**. Tetrahydrofuran intermediate **1.96** then undergoes reductive elimination to generate the product **1.92**.



Scheme 1.24: Mechanism for the Pd(0)-catalysed oxyalkynylation

The report also described a method for the indirect synthesis of a new C−O and C−C sp^3−sp^3 bond. Waser *et al.* detail a one-pot oxyalkynylation reaction and hydrogenation procedure in the synthesis of 2-alkyl tetrahydrofuran **1.98** (Scheme 1.25).[40] This indirect method for the synthesis for a new C−C sp^3−sp^3 in the oxyalkynylation−hydrogenation reaction in the alkene difunctionalisation requires a new palladium catalyst to be added to the mixture and thus the reaction suffers from a lack of elegance.



Scheme 1.25: Indirect synthesis of C−C sp^3−sp^3 in the oxyalkynylation−hydrogenation reaction

1.3.3 C−O and sp^3−sp^3 C−C Alkene Difunctionalisation

Complexity, in the form of chiral, non-aromatic molecules towards the synthesis of preclinical drug candidates has not been a priority for the pharmaceutical industry. Instead, achiral, aromatic molecules were favoured. High-throughput drug discovery practices tended towards compounds of which analogues could be easily constructed, which often led to high aromatic ring count. However, these practices have been found to have a detrimental effect on clinical success rate.[41]

Highly complex molecules, those with more chiral and sp^3 centres (more saturation), have the opportunity to access more chemical space. There has been a demonstrated correlation between the fraction of sp^3 carbons (Fsp^3) where Fsp^3 = (number of sp^3 hybridised carbons / total carbon count) and the higher clinical trial success rate (Figure 1.3).

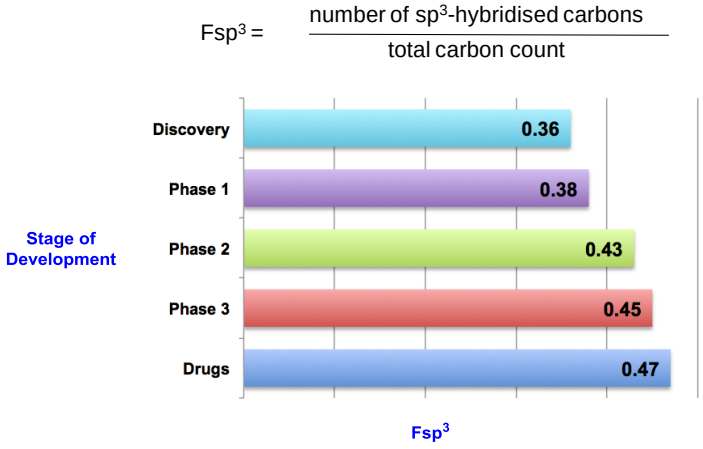
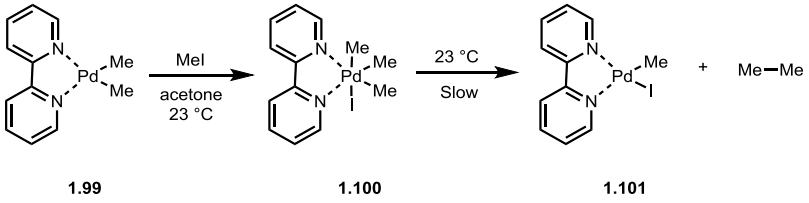


Figure 1.3: Mean Fsp^3 change as development proceeds

At the start of this work, there was no report in the literature of a palladium-catalysed oxypalladation reaction which leads to the construction of a new sp^3−sp^3 carbon−carbon bond. The one-pot oxyalkynylation−hydrogenation procedure described by Waser and co-workers, demonstrates an indirect formation of a new sp^3−sp^3 carbon−carbon bond (Scheme 1.25). It also suffers from low functional group tolerance due to the nature of the aggressive hydrogenation protocol.[40]

In 1986, Canty and co-workers published a procedure which described the synthesis of a palladium-catalysed sp^3−sp^3 carbon−carbon bond. [42] In the presence of methyl iodide, in acetone at room temperature, dimethylpalladium(II)-bipy complex **1.99** produces ethane (Scheme 1.26). It was proposed that the reaction proceeded through an oxidative addition of methyl iodide into dimethylpalladium(II)-bipy complex **1.99** yielding palladium(IV) intermediate **1.100**. Subsequent reductive elimination results in the palladium(II) iodide complex **1.101** and the bubbling of ethane through the reaction

mixture, which was detected by ^{1}H NMR. The work conducted by Canty *et al.* represents the first example of an sp^3–sp^3 carbon–carbon bondformation that proceeds *via* a palladium(IV) intermediate.



1.99 **1.100** **1.101**

Scheme 1.26: Oxidative addition of methyl iodide into a palladium(II) complex

The palladium(IV) intermediate was confirmed by concentration of the reaction mixture which yielded x-ray quality crystals. ^{1}H NMR and crystallographic analysis allowed palladium(IV) complex **1.100** to be fully characterised. Before palladium(IV) intermediate **1.100** was isolated and analysed, palladium(IV) intermediates were proposed by a number of groups working in this area, however they were undetected.[43] The all important crystal structure can be seen below (Figure 1.4). It is worth noting that the palladium(IV) complex **1.100** is more stable than one would presume, and the release of ethane occurs slowly at room temperature.

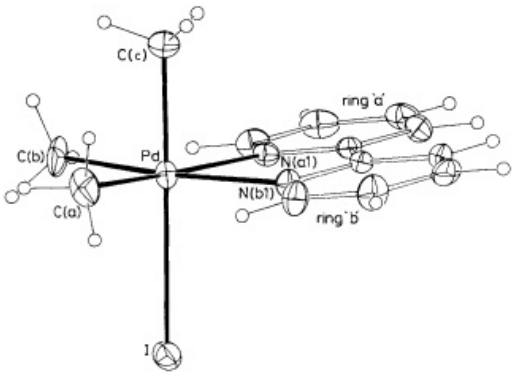
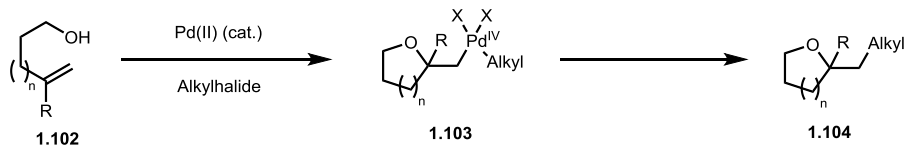


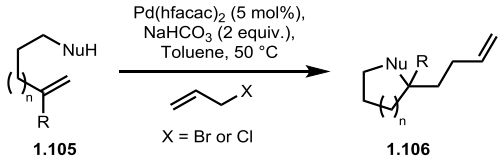
Figure 1.4: X-ray crystal structure of Pd(IV) intermediate **1.100**

Combining the palladium(IV) chemistry in the synthesis of sp^3–sp^3 carbon–carbon bond, developed by Canty and co-workers, and the palladium(II)-catalysed heterocyclisation reaction would not only expand the repertoire, but potentially add finesse in the synthesis of heterocyclic targets (Scheme 1.27). Unfortunately, the palladium-catalysed oxyalkylation reaction has not been developed, and is a large gap in the methodology currently available. Its development would constitute a significant advancement if this reactivity could be harnessed in a heterocyclisation reaction.



Scheme 1.27: Theoretical palladium-catalysed oxyalkylation reaction

However, in the pursuit of the palladium-catalysed oxyalkylation reaction the France group has developed a new palladium(II)-catalysed alkene difunctionalisation reaction of unactivated alkenes with tethered nucleophiles and external electrophiles. The reaction facilitates the formation of oxygen- and nitrogen-containing heterocycles and a new sp^3–sp^3 carbon–carbon bond (Scheme 1.28).[44] Additionally, the terminal alkene can also be used as a handle for further transformations.



Scheme 1.28: Palladium(II)-catalysed oxyallylation reaction

The oxyallylation reaction is a significant advance on the already established methodologies. Until recently, the procedures available in the palladium-catalysed alkene difunctionalisation reactions would involve the formation of a new C–C bond to a new sp- or sp^2-hybridised carbon centre. As mentioned previously, the synthesis of new sp^3–sp^3 carbon–carbon bond is of increasing importance in the synthesis of drug candidates as it has been shown that the Fsp^3 content of a molecule increases with each stage of drug development.

The operationally simple methodology, carried out at ambient atmosphere, was successful with more than 20 oxygen-containing cyclised products. The reaction also shows high functional group tolerance, with strong electron-withdrawing and electron-donating groups placed around the aromatic ring. The synthesis of benzofurans, isobenzofurans, isobenzopyrans and aliphatic furan derivatives proceeded in good yields. A cross-section of substrates can be seen below (Figure 1.5). The synthesis of benzofurans with a halogen around the aromatic ring is of particular significance, as the bromide can be used as a handle for further chemical transformations. Additionally, spirocyclic compounds, a motif often displayed in natural products, were also synthesised under the optimised conditions. Furthermore, the construction of two six-membered lactams was also effective, when a change of base was employed.

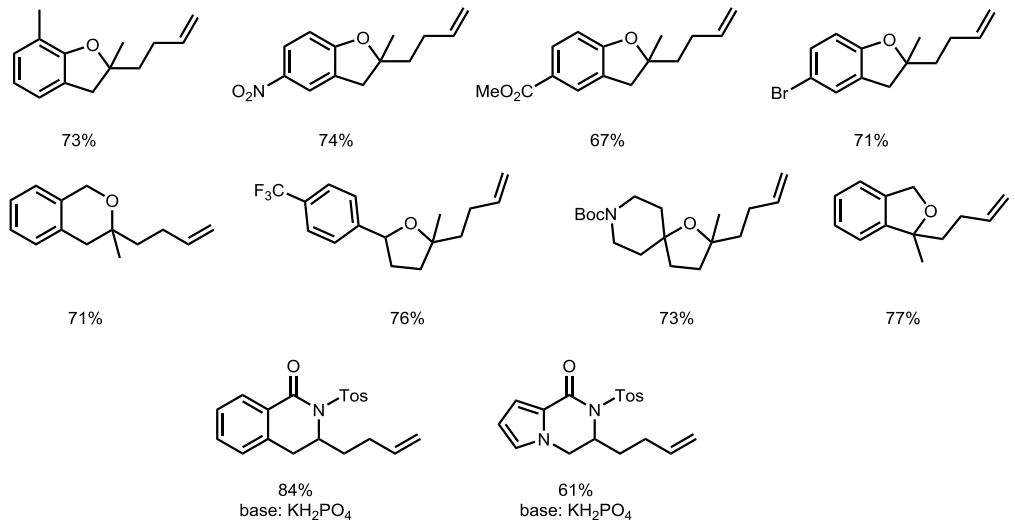
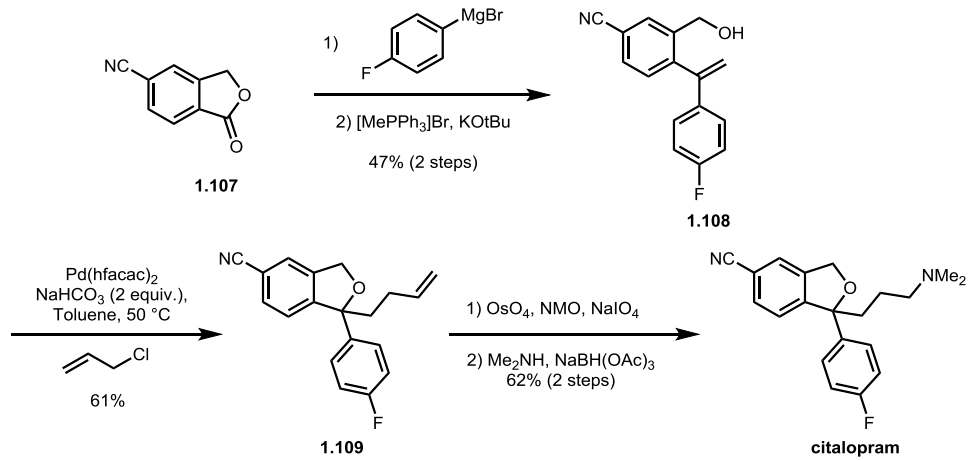


Figure 1.5: Range of nucleoallylation products

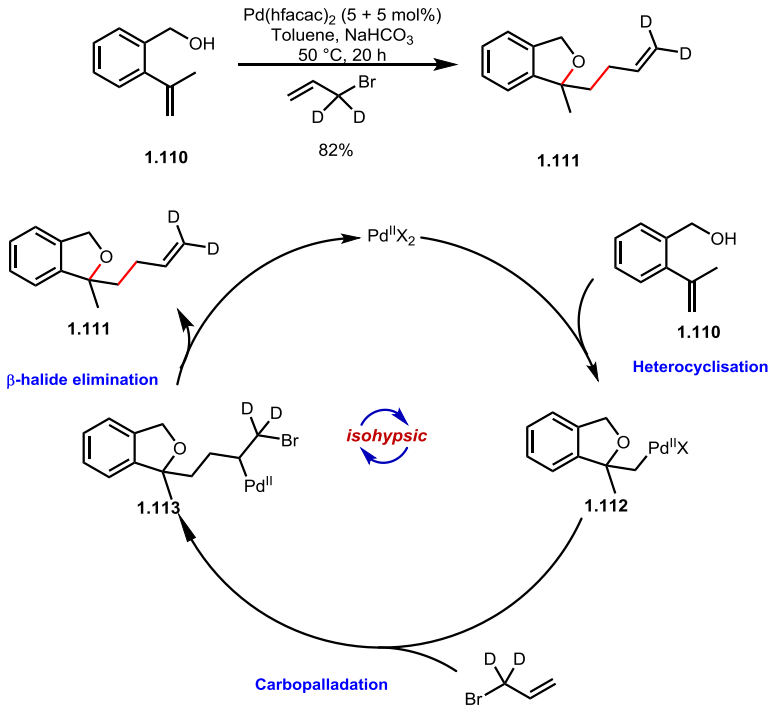
The effectiveness and practicality of the oxyallylation reaction was demonstrated further in the synthesis of citalopram − a widely prescribed selective serotonin reuptake inhibitor (SSRI) for the treatment of depression (Scheme 1.29). Oxyallylation precursor **1.108**, was synthesised in two steps from commercially available cyanophthalide **1.107**. With the desired benzylic alcohol **1.108** in hand, it was subjected to the oxyallylation conditions to give the late stage cyclised intermediate **1.109**. Subsequent dihydroxylation/oxidative cleavage followed by reductive amination gave citalopram in 5 steps.



Scheme 1.29: Synthesis of citalopram

In order to decipher between the various mechanisms possible, a mechanistic study was undertaken by the France group. Treatment of benzylic alcohol **1.110**, with palladium(II) and dideutero-allyl bromide resulted in the chemoselective transformation to isobenzofuran **1.111** as the sole product (Scheme 1.30). The mechanistic experiment allowed the proposal of a somewhat unusual redox-neutral catalytic cycle. The initial oxypalladation of benzylic alcohol **1.110** forms cyclised alkylpalladium(II) intermediate **1.112**. In turn, this intermediate will undergo carbopalladation with the dideutero-allyl

bromide to form a new alkylpalladium(II) intermediate **1.113** which experiences a β-halide elimination to generate isobenzofuran **1.111** as the only product. The palladium(II) catalyst does not change oxidation state throughout the catalytic cycle, a process known as isohypsic.[45]

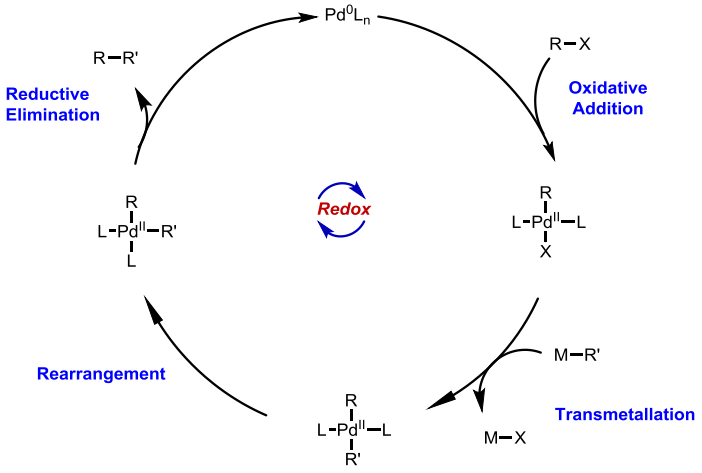


Scheme 1.30: Proposed isohypsic oxyallylation mechanism

1.4 Palladium(II)-Catalysed Isohypsic Reactions

The synthesis of carbon−carbon bonds is of immense importance in organic chemistry. Amongst the most common methods for their construction in the early 20th century were the Grignard,[46] Diels−Alder[47] and the Wittig[48] reactions, all of which won the Nobel prize for their contributions to chemistry. In the last quarter of the 20th century a new class of carbon−carbon bond forming reactions have emerged, which involved transition-metal catalysis. Within this class, the most prominent and most important in organic synthesis is the palladium-catalysed cross-coupling reactions which also won the Nobel prize in 2010. Their influence and utility on the organic chemistry field has been shown on numerous occasions; for example, by playing a major role in the total synthesis of many natural products.[49]

The general mechanism for the cross coupling reactions follows the pathway outlined below (Scheme 1.31). The first step in the cross-coupling reactions is an oxidative addition of R−X to Pd(0) to give an organopalladium(II) compound. In the second step, the organic group R' is transferred to palladium in a process called transmetallation. In this way, the two organic groups are assembled on the same palladium atom *via* palladium-carbon bonds. The palladium(II) intermediate then rearranges in order to allow coupling. In the final step the R' and R groups couple with one another to give a new carbon−carbon single bond and R−R' is released from palladium. In this process Pd(II) is reduced to Pd(0) and therefore the final step is called a reductive elimination.

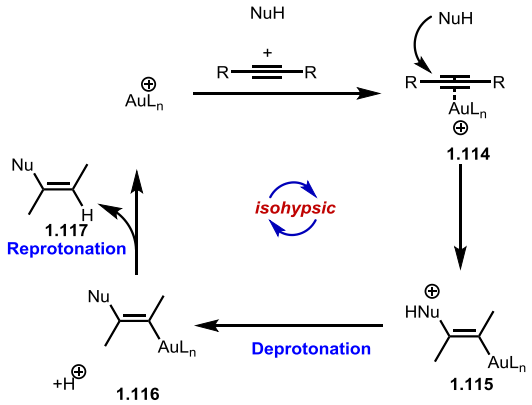


Scheme 1.31: General mechanism in palladium cross coupling reactions

Generally, the oxidation state of palladium-catalysed reactions throughout the catalytic cycle is either Pd(0)/Pd(II), following a redox process. Chemistry can also take place outside the traditional Pd(0)/Pd(II) cycles. More and more processes are emerging that contain proposed catalytic cycles with the palladium centre in higher oxidation states.[50] Reactions, such as the Catellani reaction,[51] have proposed mechanisms which involve

the metal centre change through various oxidation states such as: Pd(0)/Pd(II)/Pd(IV). Other palladium-catalysed high oxidation state reactions, particularly C−H activation, see the metal change between Pd(II)/Pd(IV) oxidation states.[52] There is also a small, but appreciable, class of palladium(II)-catalysed reactions where the oxidation state of the palladium does not change throughout the entirety of the catalytic cycle. The all palladium(II)-catalysed reactions are known as redox-neutral or isohypsic reactions.

As well as palladium, isohypsic reactions are known to occur for a number of transition metals in certain oxidation states such as rhodium,[53] ruthenium,[54] cobalt[55] and gold.[56] The isohypsic nature of a transition metal catalysed reaction is a peculiarity often associated with gold-catalysis. The fundamental reaction pathway of Au(I) catalysis can be seen below, where it activates a C−C triple bond (Scheme 1.32). Coordination to the alkyne forms aurated intermediate **1.114**, which activates the alkyne for nucleophilic attack. Attack from a nucleophile followed by subsequent deprotonation−reprotonation sequence regenerates the active catalyst and the desired product.



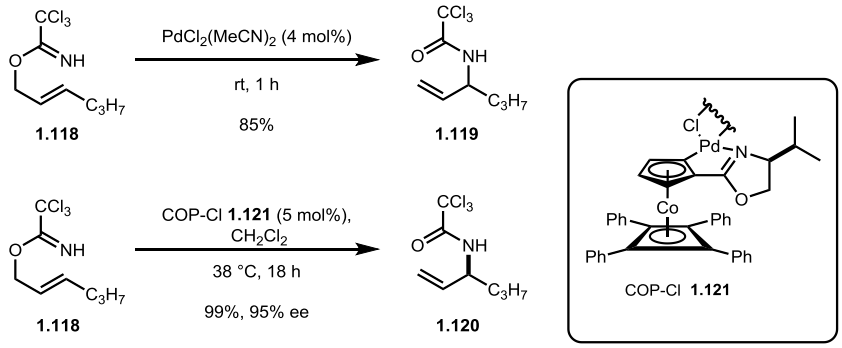
Scheme 1.32: Fundamental reaction pathway of Au(I) catalysis

The following sections will contain a detailed discussion into a number of palladium(II)-catalysed isohypsic catalytic processes, which will lead to the synthesis of new carbon−carbon bonds and carbon−heteroatom bonds.

It must be noted, that this far from exhaustive short review has focused on reactions that involve a proposed formation of a palladium−carbon bond at any point throughout the catalytic cycle. This was a conscious decision, as it allowed the avoidance of reactions in which the palladium(II) species acts as a Lewis acid; for example, a palladium(II)-catalysed aldol reaction.[57]

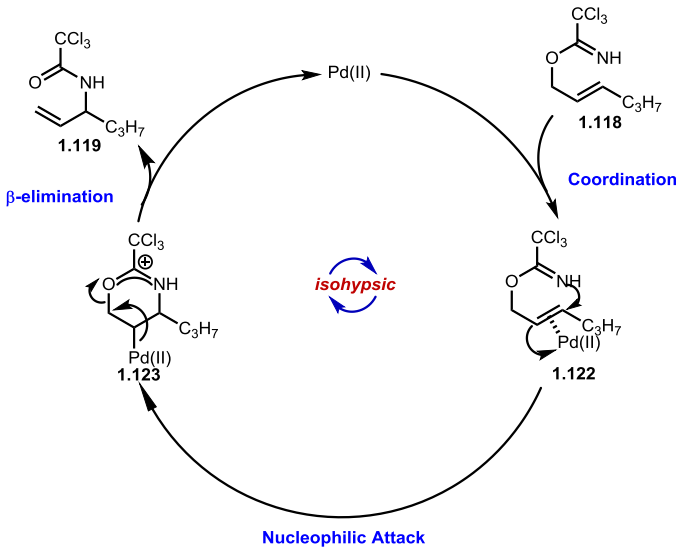
1.4.1 Carbon−Heteroatom Bond Formation

The vast majority of palladium(II)-catalysed isohypsic reactions form new carbon−carbon bonds, however, some reactions do form new carbon−heteroatom bonds. Although palladium(II)-catalysed isohypsic carbon−heteroatom bond forming reactions are even rarer than their carbon−carbon bond forming counterparts among the most famous of all isohypsic reactions is the Overman rearrangement. Here, a new carbon−nitrogen bond is formed in a [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates. Initially developed as a rearrangement that is induced thermally and in the presence of Hg(II) salts, it involves a 1,3 transposition of alcohol and amine functionality.[58] Not long after, a palladium(II)-catalysed variant emerged which required lower temperatures, shorter reaction times, lower catalyst loading and also circumvented the use of Hg(II) and the inherent toxicity of the metal (Scheme 1.33).[59] It wasn't until much later, that Overman and co-workers developed a successful asymmetric variant to the [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates with both high yields and high ee's using COP-Cl **1.121** as the catalyst (Scheme 1.33).[60] The enantioselective Overman rearrangement worked well with (*E*)-alkenes to give (*S*)-allylic trichloroacetamides **1.118**, however, (*Z*)-alkenes were less reactive and gave the corresponding (*R*)-allylic trichloroacetamides in poor yields and moderate enantioselectivities. In order to access the (*R*)-allylic trichloroacetamides the enantiomer of COP-Cl **1.121** must to be prepared and used.



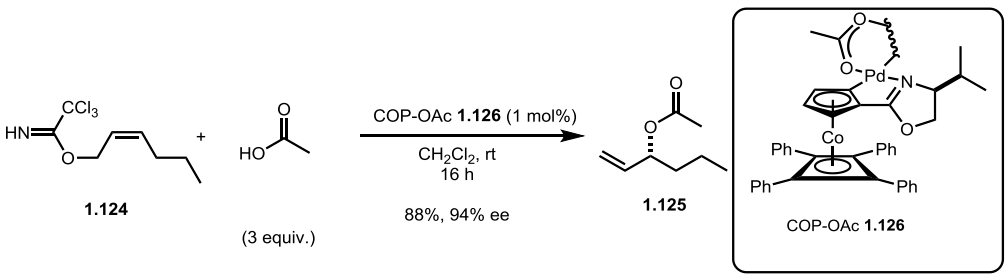
Scheme 1.33: Palladium(II)-catalysed Overman rearrangement of (*E*)-allylic trichloroacetimidates

Extensive mechanistic studies on the palladium(II) catalysed [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates have been conducted by the Overman group.[61] In the cyclisation induced rearrangement mechanism, coordination of palladium(II) to the olefin generates intermediate **1.122** (Scheme 1.34). Subsequently, nitrogen attacks the activated alkene to produce cyclic intermediate **1.123**. Collapse of this intermediate produces the desired allylic trichloroacetamide and releases the palladium(II) catalyst.



Scheme 1.34: Mechanism of the Overman rearrangement

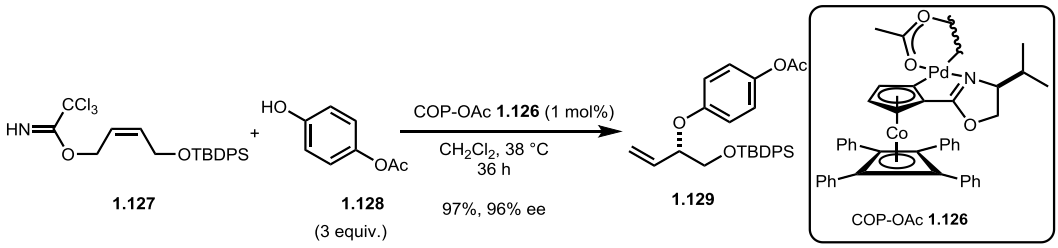
Additionally, Overman *et al.* reported the development of an asymmetric palladium(II)-catalysed synthesis of chiral allylic esters (Scheme 1.35).[62] Prochiral (*Z*)-allylic trichloroacetimidates in the presence of 1 mol% COP-OAc **1.126** at room temperature, react efficiently with carboxylic acids to give the allylic esters in excellent yields and ee's. A range of aliphatic (*Z*)-allylic trichloroacetimidates bearing oxygen containing functional groups worked well under the optimised conditions (Scheme 1.35). Both aromatic and aliphatic carboxylic acids provided the corresponding esters in excellent ee's of 91−99%. Reaction of the (*E*)-stereoisomer of **1.124** under the reaction conditions provided the enantiomer of allylic ester **1.125** in low yield and enantioselectivity (42%, 54% ee).



Scheme 1.35: Synthesis of chiral allylic ester **1.125** using COP-OAc **1.126**

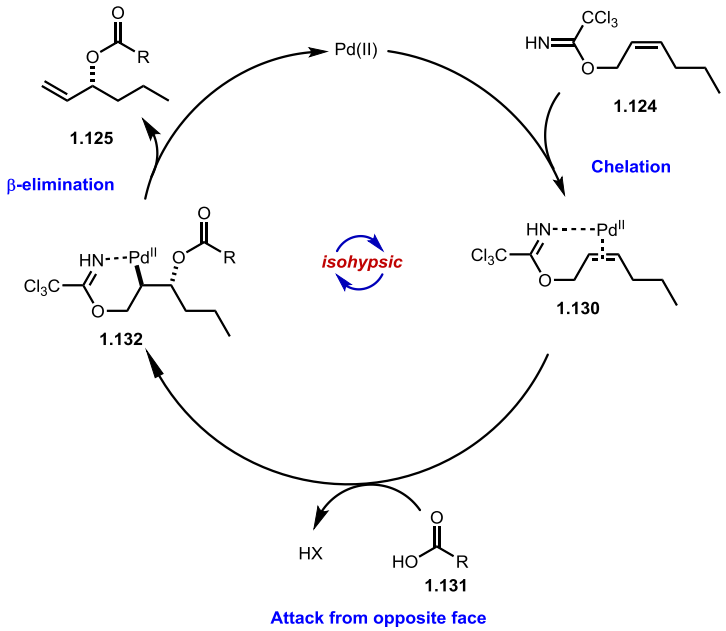
An analogous reaction in the synthesis of chiral allylic ethers was also published by Overman and co-workers, using the same COP-OAc **1.126** catalyst.[63] Herein, it is reported that (*Z*)-allylic trichloroacetimidates provide branched allylic aryl ethers in high yield and enantiopurity under mild reaction conditions (Scheme 1.36). Phenol nucleophiles worked well and could contain electron-donating or mild electron-withdrawing groups with excellent enantioselctivities. Phenols containing strong electron withdrawing groups such as nitro and cyano in various positions around the aromatic ring, either failed to furnish any of the desired product or the corresponding allylic ether was furnished in

moderate enantioselecivity. Reactions of (*E*)-allylic trichloroacetimidates under the optimised reaction conditions, provided low yields.



Scheme 1.36: Synthesis of chiral allylic ether **1.129** using COP-Ac **1.126**

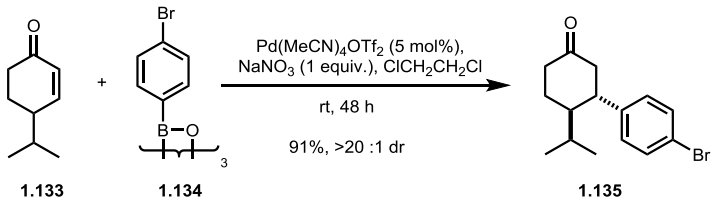
A detailed study into the mechanism of the palladium(II)-catalysed asymmetric synthesis of chiral allylic esters and ethers by the Overman group was reported in the literature.[64] In the overall S_N2'-displacement of (*Z*)-allylic trichloroacetimidates to form chiral allylic esters it was proposed the first step was chelation from the nitrogen and the olefin, which would form palladacycle intermediate **1.130** (Scheme 1.37). This in turn would activate the (*Z*)-alkene for nucleophilic attack from carboxylic acid **1.131**. Deuterium labelling experiments revealed that the attack from the carboxylic acid occurs from the opposite face from the palladium in an anti acyloxypalladation addition sequence and this, in turn, would give alkylpalladium(II) intermediate **1.132**. β-elimination, *via* syn deoxypalladation, would produce the desired chiral allylic ester **1.125** and regenerate the palladium(II) catalyst.



Scheme 1.37: Proposed mechanism of the palladium(II)-catalysed asymmetric synthesis of chiral allylic esters

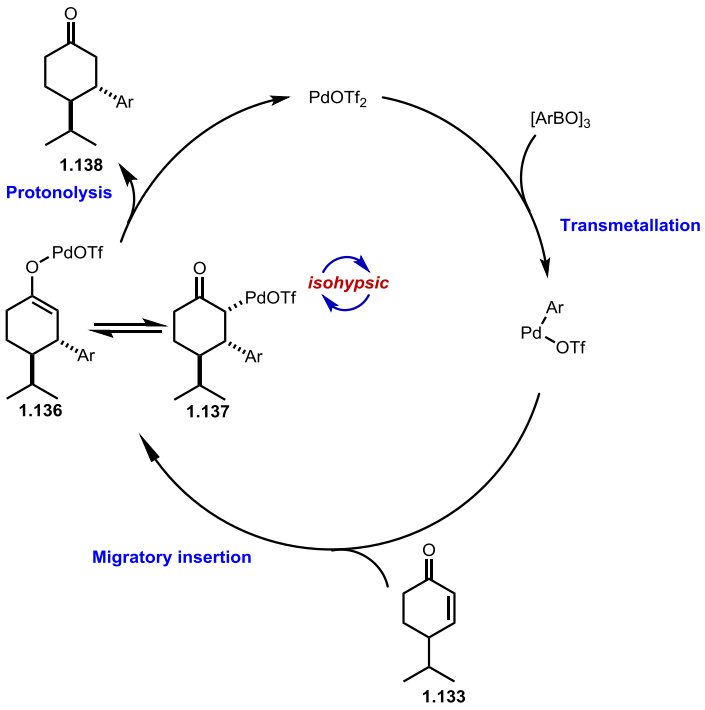
1.4.2 Carbon−Carbon Bond Formation

Palladium(II)-catalysed conjugate additions[65] to enones have emerged as a cheaper alternative to the already established Rh-catalysed[66] procedures. The advantages of using a palladium(II) catalyst extend beyond cost alone, as the reactions can be tolerant of air and moisture. Asymmetric palladium(II)-catalysed Michael-type additions have been developed in recent years.[67] In addition, Lee and co-workers have disclosed a procedure that involves a cationic, ligandless palladium(II) catalyst and a reaction that is highly tolerant of steric hinderance (Scheme 1.38).[68] Initial investigations showed that boroxine was the reactive reagent and not the boronic acid equivalent. The addition of $NaNO_3$ was found to improve the yield through decreasing the formation of side products. The 1,4 conjugate addition of boroxine **1.134** to enone **1.133** proceeds in a high yield and excellent diastereoselectivity, with the reaction below representative of the selectivity observed in the reaction with dr's ranging from 8:1 to >20:1.



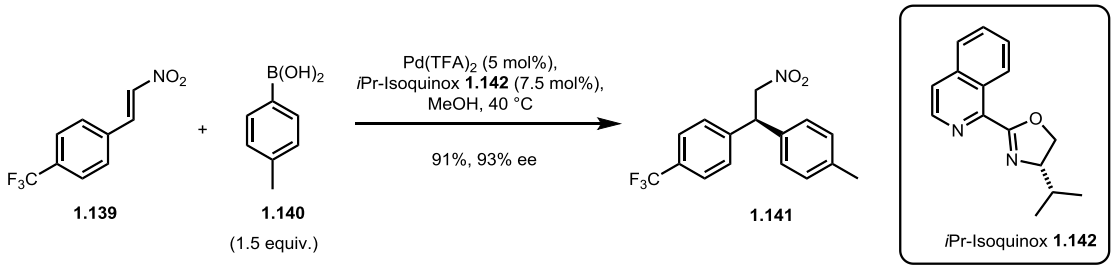
Scheme 1.38: Diastereoselective palladium(II)-catalysed 1,4 conjugate addition

The proposed mechanism for the reaction by Lee *et al.* was outlined in a subsequent paper and can be seen below (Scheme 1.39).[69] Transmetallation of the cationic palladium(II) catalyst with the boroxine species is the first step in the reaction mechanism. Migratory insertion of the alkene into the Pd−C bond, on the opposite face of the bulky alkyl group in the γ-position, would give intermediates **1.136** and **1.137**. Consequent protonolysis would provide the desired the conjugate addition product **1.138** and regenerate the palladium(II) catalyst.



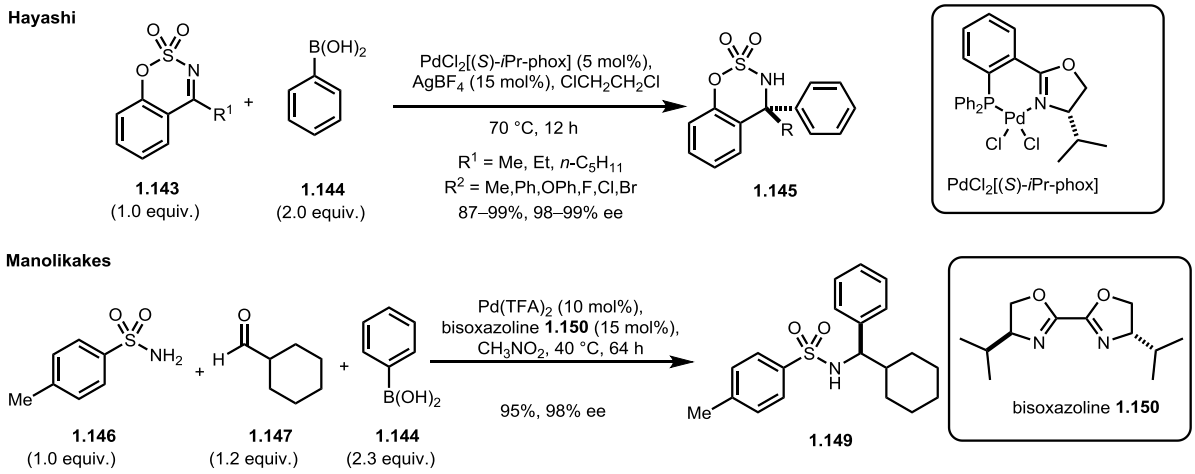
Scheme 1.39: Proposed mechanism of the diastereoselective palladium(II)-catalysed 1,4 conjugate addition

In 2015, an asymmetric Michael-type addition to nitrostyrenes was published by Zhang and co-workers.[70] Herein, it is reported that the addition of boronic acids to nitroalkenes bearing electron-donating and electron-withdrawing groups produced biaryl products such as **1.141** in high enantioselectivities using *i*Pr-isoquinox **1.142** as the ligand to induce asymmetry (Scheme 1.40). The use of aliphatic nitroalkenes failed to return any product. The scope of the arylboronic acids was also explored. Aromatic boronic acids with both electron-donating and electron-withdrawing groups worked well, with high ee's. However, it was found that aromatic boronic acids bearing electron-donating groups performed better; this was attributed to higher nucleophilicity of the more electron-rich aryl group.



Scheme 1.40: Palladium(II)-catalysed asymmetric addition of arylboronic acids to nitrostyrenes

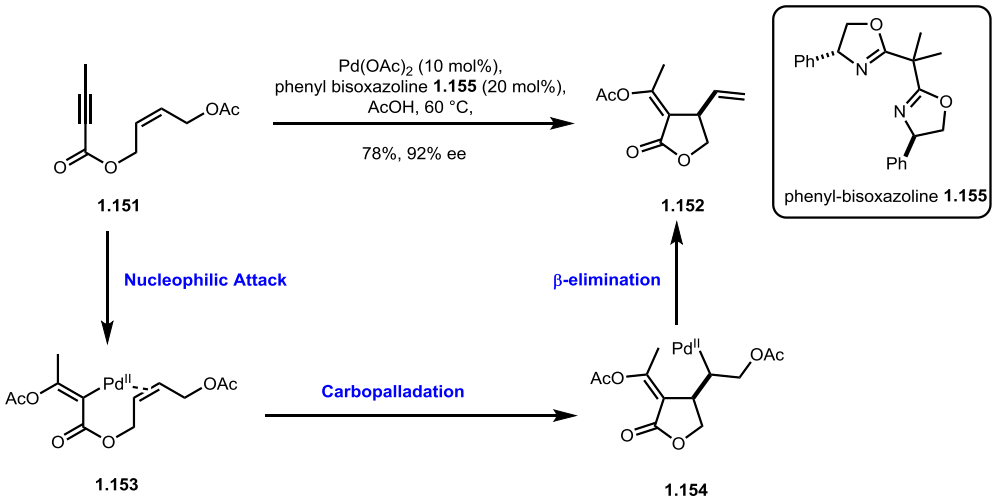
Palladium(II)-catalysed asymmetric 1,2 addition of boronic acids to *N*-sulfonyl imines is known in the literature.[71] Asymmetric arylation of five-membered cyclic *N*-sulfonyl ketimines has been reported by Zhang.[72] Recently, Hayashi and co-workers reported the 1,2 addition of aryl boronic acids to six-membered rings of *N*-sulfonyl ketimines such as **1.143**.[73] Five-membered imines easily undergo arylation but are difficult to cleave to yield the corresponding methylamine. In contrast, six-membered imines are less reactive towards arylation whereas the sulfamidates **1.145** are known to undergo ring opening without loss of enantiopurity. The arylation of ketimines, *via* palladium-catalysis, is not traditionally a facile process and often methodology falls short when ketimines such as **1.143** are used in place of aldimines as substrates. However, as can be seen below, the optimised reaction conditions tolerate various aliphatic groups on the imine and a range of boronic acids (Scheme 1.41). The use of palladium(II)-catalysed boronic acids as nucleophiles has always had one drawback: the use of preformed imines. Manolikakes and co-workers have developed an elegant enantioselective, three-component one-pot synthesis of α-aryl *N*-sulfonamides.[74] An example of the strategy and its success is detailed below (Scheme 1.41).



Scheme 1.41: Palladium(II)-catalysed 1,2 addition of aryl boronic acids to imines

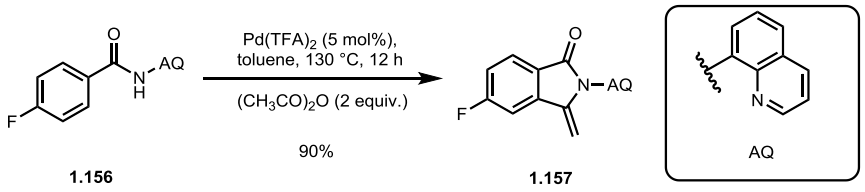
The carbocyclisation of alkynes and alkenes offers a route to rapidly building chemicial compexity quickly from simple starting materials. Lu *et al.* have previously developed the cyclisation of enynes by palladium(II)-catalysis in the synthesis of racemic butyrolactones.[75] An asymmetric palladium(II) variant was developed by Lu and co-workers in the cyclisation of enynes using various catalyst systems, an example of which is outlined below, with acetic acid as the solvent (Scheme 1.42).[76] The proposed mechanism of the reaction involves *trans*-acetoxypalladation of the triple bond, followed by intramolecular carbopalladation onto the alkene. The final step in the mechanism is the β-acetoxy elimination to generate the butyrolactone **1.152** in good yield and

enantioselectivity. In developing the reaction it was found that the bidentate nitrogen ligands used in the reaction inhibit β-hydride elimination and protonolysis.



Scheme 1.42: Palladium(II)-catalysed asymmetric synthesis of butyrolactone **1.152**

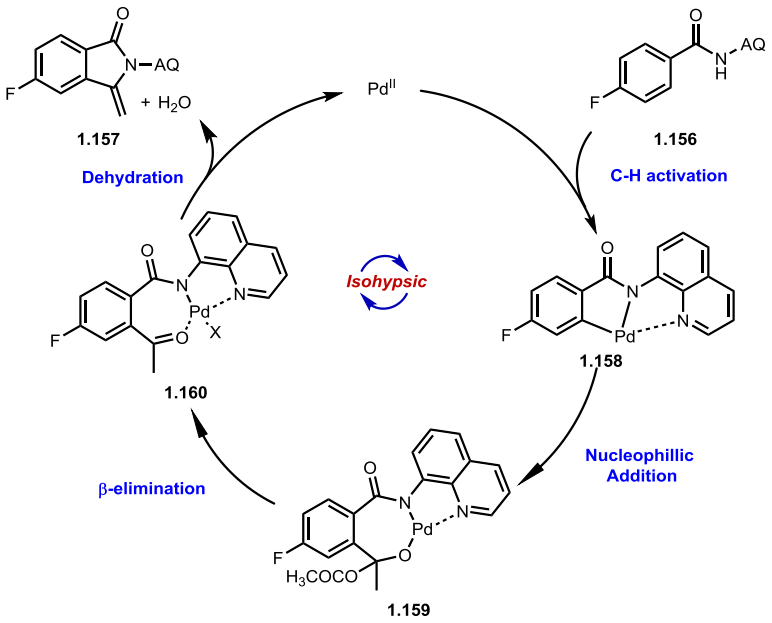
Transition-metal-mediated C−H activation is an important class of chemical reaction in organic chemistry.[77] Aminoquinoline is a common bidentate directing group used to cleave C−H bonds, which is due to a number of advantages: readily available, easily incorporated and removed and can be attached to a wide variety of the carboxylic acid precursors.[78] In 2015, Wei and co-workers published a palladium(II)-catalysed isohypsic C−H functionalisation−cyclisation reaction in the synthesis of isoindolinones using AQ as the chelating auxiliary (Scheme 1.43).[79]



Scheme 1.43: Palladium(II)-catalysed synthesis of isoindolinone **1.157**

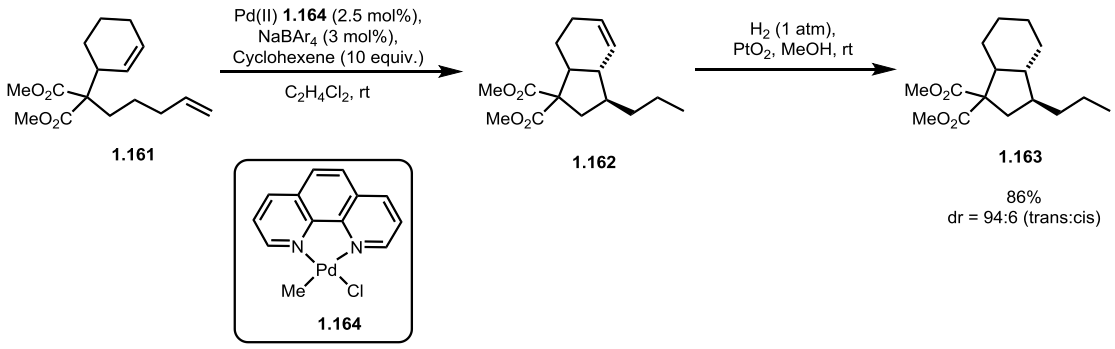
A plausible mechanism, presented by the authors, for the C−H functionalisation−cyclisation reaction has the first step as the palladium(II)-mediated aminoquinoline directed C−H activation (Scheme 1.44). Next, the arylpalladium(II) intermediate **1.158** reacts with an anhydride to form a palladacycle **1.159**. β-acetoxy elimination generates late stage palladium(II) intermediate **1.160**. Intramolecular dehydration furnishes the desired product and regenerates the palladium(II) catalyst in the redox neutral process. Electron-donating and electron-withdrawing groups can be tolerated around the aromatic ring. In order to make the reaction more applicable, a variety of carboxylic acids were used in the reaction as electrophiles, however, the use of

(tBuCO)$_2$O in the reaction mixture was required, as an *in situ* formation of an anhydride was a prerequisite for the reaction to proceed.



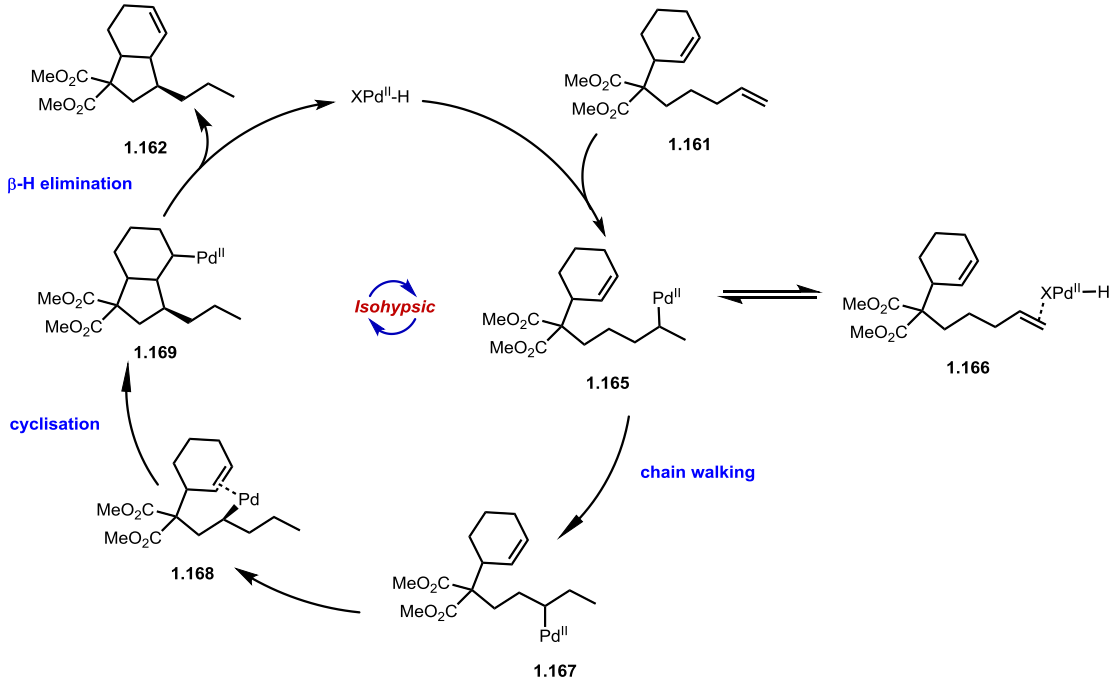
Scheme 1.44: Proposed mechanism of the C−H functionalisation−cyclisation reaction

Transition-metal catalysed chain walking is a process whereby a transition-metal undergoes a rapid β-hydride elimination−reinsertion sequence, gradually moving along the carbon backbone. Often, chain walking is an undesirable side reaction; the need to suppress this process is paramount due to the unwanted isomerisation of alkenes. In 2012, Kochi and co-workers published a paper that utilised this well established process in a palladium(II)-catalysed cycloisomerisation of dienes akin to 1,8 diene **1.161** (Scheme 1.45). It was found that 1,10 phenanthroline palladium(II) catalyst **1.164** was the system best suited for the reaction and generated desired unsaturated bicyclo[4.3.0]nonane **1.162** with the least amount of isomerised side product. Cyclohexene was added to the reaction as it prevented isomerisation in the desired final bicyclo[4.3.0]nonane **1.162**. A number of isomers, albeit in low quantities, of bicyclo[4.3.0]nonane **1.162** was formed. In order to determine the efficiency of the developed reaction the products were hydrogenated using platinum oxide to furnish saturated product **1.163** in excellent diastereoselectivity.



Scheme 1.45: Palladium(II)-catalysed cycloisomerisation of 1,8 diene **1.161**

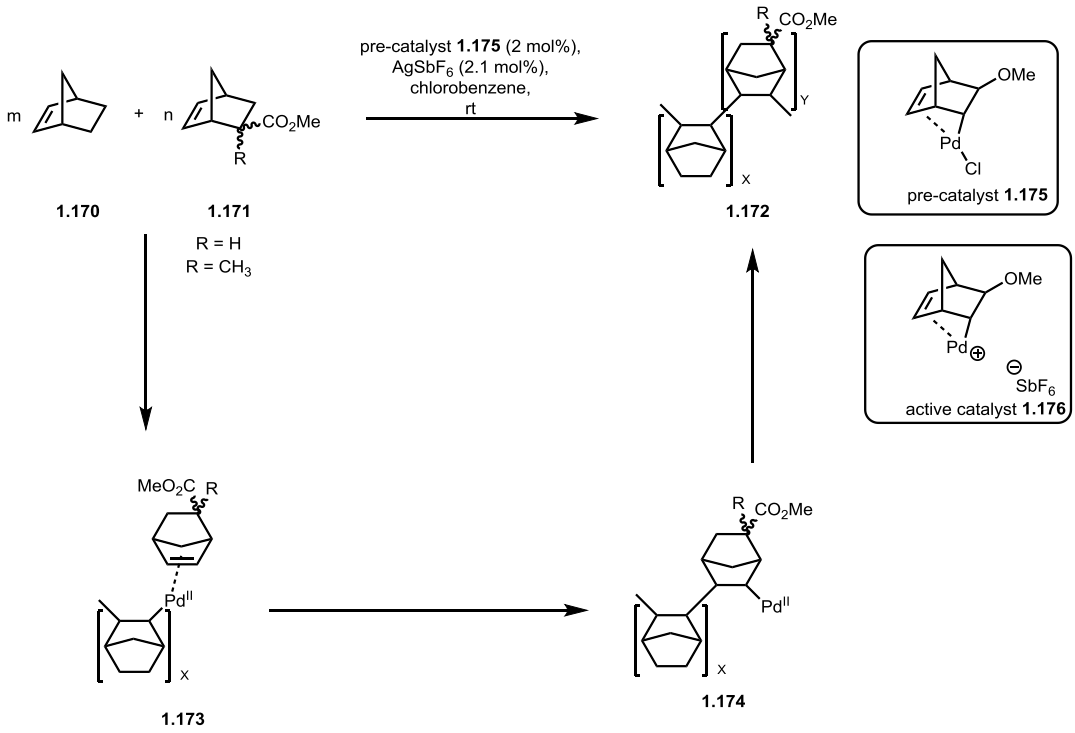
Kochi *et al*. propose the following mechanism for the isohypsic palladium(II)-catalysed cycloisomerisation reaction (Scheme 1.46). The terminal olefin reacts preferentially over the internal, more sterically encumbered olefin and alkylpalladium(II) intermediate **1.165** is formed. Chain walking along the aliphatic spine of the molecule occurs *via* a β-hydride elimination−reinsertion sequence until it reaches the position where it can coordinate to the alkene forming intermediate **1.168**. Alkene insertion into the palladium(II)-alkyl intermediate will form cyclised alkylpalladium(II) **1.169**. Syn β-hydride elimination gives the palladium(II) hydride catalyst and bicyclo[4.3.0]nonane **1.162**.



Scheme 1.46: Mechanism for the isohypsic palladium(II)-catalysed cycloisomerisation reaction

Another well precedented isohypsic process is the palladium(II)-catalysed alkene polymerisation.[80] The self-propagating polymerisation process maintains the metal centre in the +2 oxidation state, *via* an alkylpalladium(II) intermediate undergoing a carbopalladation step on another alkene monomer. This process repeats. Theoretically, if

enough monomer(s) is present this process can go on indefinitely, unless an unwanted side reaction such as β-hydride elimination occurs or an additive is added to prevent polymerisation from occurring. An example of palladium(II)-catalysed vinylic polymerisation of norbornene **1.170** and norbornene carboxylic acid esters **1.171** can be seen below (Scheme 1.47).[81] Using palladium(II) pre-catalyst in the presence of $AgSbF_6$ the active palladium(II) catalyst **1.175** was formed. Chlorobenzene, although an unusual solvent choice, was highly practical as the polymer was soluble in this medium. Norbornene carboxylic acid methyl esters **1.171** were used in varying amounts of exo/endo ratios with the yield of any co-polymerisation reaction not exceeding 46%.



Scheme 1.47: Palladium(II)-catalysed vinylic polymerisation of norbornene **1.170** and norbornene carboxylic acid esters **1.171**

1.5 Summary

Palladium catalysis is an area of research that has seen a surge of activity since it was first developed decades ago. The literature examples outlined in this chapter emphasise the versatility of the metal and illustrate the various transformations that can occur, with catalytic cycles involving various oxidation states: Pd(0), Pd(II) or Pd(IV).

The oxypalladation of alkenes to afford oxygen-containing heterocycles is a well-studied area of research that has seen a recent revitalisation of interest. In addition to the development of asymmetric example of Wacker-type cyclisations, the contributions of Wolfe and Waser groups has seen an expansion in the scope of the C−C bond formation capabilities of these reactions. Recently, the France group have published a report in which a new C−O bond was formed and a new sp^3–sp^3 C−C bond has been constructed. This is a particularly valuable piece of methodology as many natural products and pharmaceuticals contain heterocycles with alkyl chains.

A small, but appreciable, class of palladium(II)-catalysed reactions where the oxidation state of the palladium does not change throughout the entirety of the catalytic cycle are established. More specifically known as an isohypsic reaction. Unique reactivity and transformations are available for all palladium(II) catalytic cycles. Further exploration of isohypsic palladium-catalysed reactions could be of immense use and importance to the synthetic community.

2. Synthetic Approaches Towards the Heterocyclisation of Alkenes

2.1 Oxyallylation Reaction of Unactivated Alkenes

2.1.1 Introduction and Aims

As discussed previously (Chapter 1), oxygen-containing heterocycles are crucial intermediates in organic synthesis and are a common structural motif in natural products and pharmaceutically active compounds. Lactones are a structurally important heterocycle and are a functional group ubiquitously found in many different classes of molecules. Lactone rings are found in antibiotics,[82]enzymes,[83] neurotransmitters,[84] anti-cancer drugs,[85] phytoestrogens, statins (e.g. lovastatin **2.1**),[86] hormones (e.g. aldactone **2.2**), many natural products and building blocks in nature such as ascorbic acid **2.3**, nepetalactone **2.4** and kavain **2.5** (Figure 2.1).

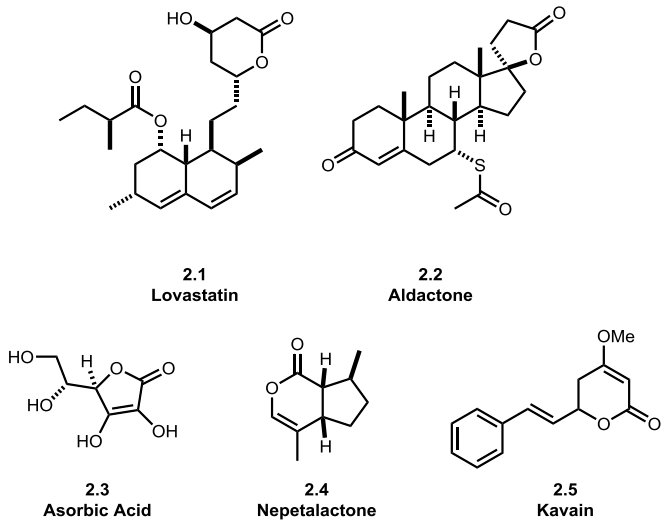
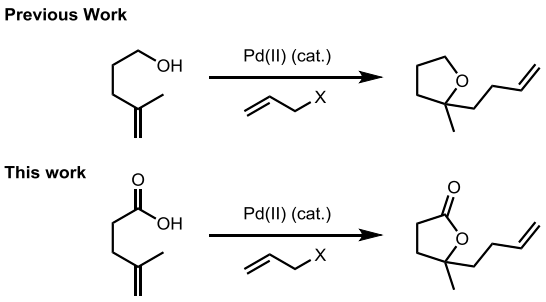


Figure 2.1: Lactone motif in drugs and natural building blocks

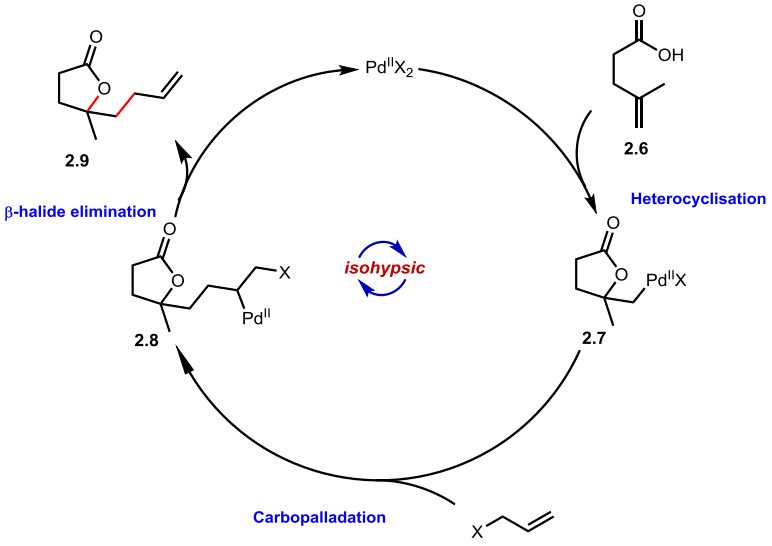
The aim of this project was to extend the scope of the previously optimised oxyallylation methodology to include the synthesis of lactones (Scheme 2.1). The proposed palladium(II)-catalysed heterocyclisation of tethered carboxylic acids onto unactivated alkenes would be followed by allylation using an allylic halide. In theory, this would open up the oxyallylation reaction to a host of potential new intermediates and products and thus significantly expand the already well developed methodology.



Scheme 2.1: Proposed extension of oxyallylation reaction

The proposed reaction would construct a lactone heterocycle and furnish a new sp^3−sp^3 C−C bond in a single step. This would represent a significant advance as it would be the first example of a sp^3−sp^3 C−C bond forming reaction using carboxylic acids as the nucleophile in alkene difunctionalisation reactions. All previous formation of lactones, briefly discussed in Chapter 1, form new sp^3−sp^2 or sp^3−spC−C bonds *via* reactions like oxycarbonylation and oxyalkynylation reactions. Increased Fsp^3 content in drug candidates has been directly linked to the chance of success and is, consequently, a major goal of the pharmaceutical industry (Figure 1.3).

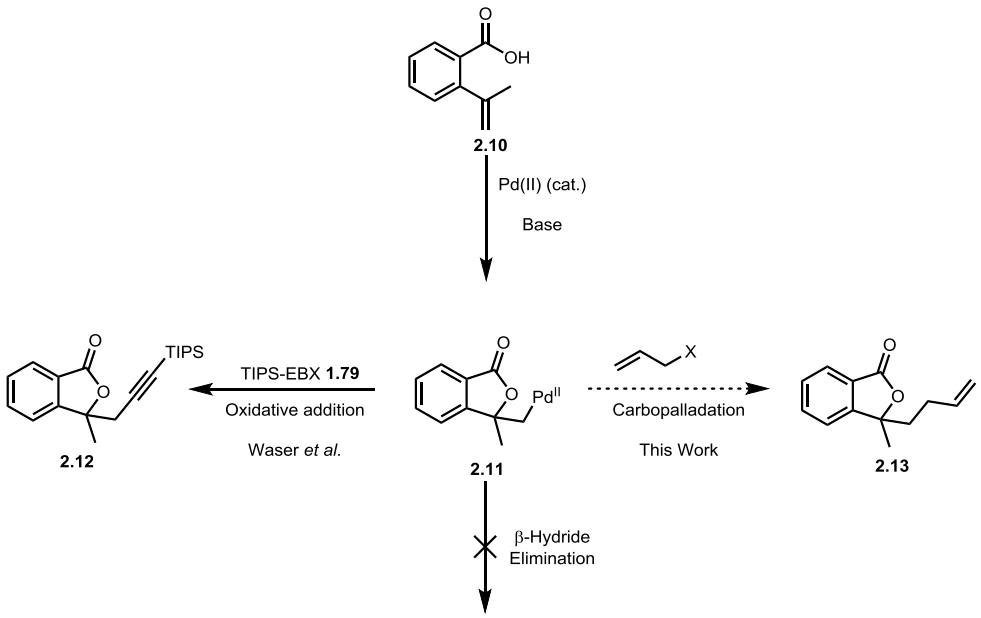
The oxyallylation reaction mechanism for benzylic alcohols was investigated previously within the France group. Although it is known that changing the nucleophile from an alcohol to an acid can impact the *cis*- and *trans*-oxypalladation step, it is postulated that the overall mechanism will essentially have a similar pathway (Scheme 2.2).[18c] The palladium(II) catalyst would activate the alkene on carboxylic acid **2.6**, triggering nucleophilic attack from the acid, forming cyclic alkylpalladium(II) intermediate **2.7**. This will then undergo a carbopalladation reaction on the allyl halide electrophile forming late stage intermediate **2.8**. Subsequent β-halide elimination will garner the desired lactone **2.9** and regenerate the palladium(II) catalyst.



Scheme 2.2: Proposed catalytic cycle

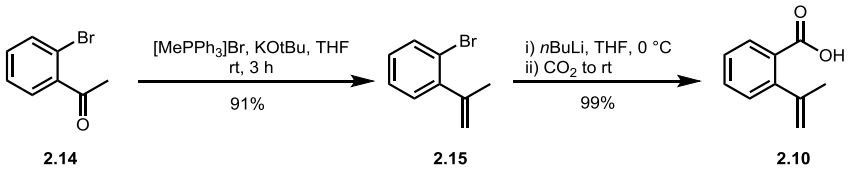
2.1.2 *Gem*-disubstituted Alkene Substrates

The utilisation of carboxylic acids as substrates towards the synthesis of lactones *via* oxypalladation is a well precedented process.[15] In particular, the oxyalkynylation protocol reported by Waser and co-workers in 2010 bears similar reactivity to the desired oxyallylation reaction this project aims to develop (Scheme 2.3).[38] Palladium(II)-alkyl intermediate **2.11** is a common intermediate in each process. Waser and co-workers demonstrated the trapping of alkylpalladium(II) intermediate **2.11** with TIPS-EBX **1.79**, a strong oxidant, to furnish the desired lactone **2.12**. This work aims to trap the alkylpalladium(II) intermediate **2.11** with an allyl halide species in a similar fashion to the previously described oxyallylation reaction of alcohols. β-hydride elimination is a common competing pathway in the oxypalladation reaction of *mono*-substituted alkenes when attempting to difunctionalise the olefin. Due to this, it was prudent to begin the investigation into the oxyallylation reaction in the synthesis of lactones, with *gem*-disubstituted alkene substrates.



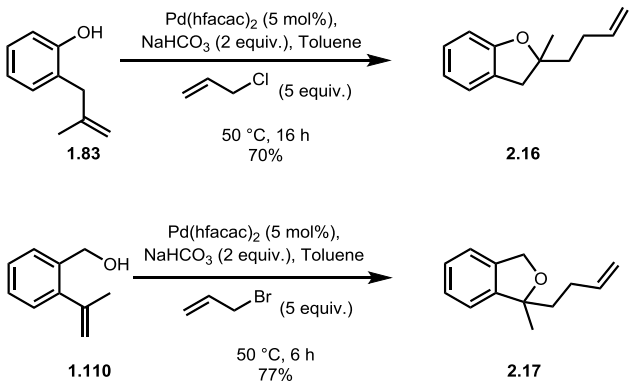
Scheme 2.3: Common reactivity between this work and Waser's oxyalkynylation

The similarity between Waser and co-workers'oxyalkynylation reaction and the desired oxyallylation prompted the use of benzoic acid **2.10**. The first step in the synthesis of benzoic acid **2.10** is the Wittig olefination of *o*-bromoacetophenone **2.14** (Scheme 2.4). Following the procedure of Waser and co-workers,[38] a solution of ketone **2.15** was added to a prepared suspension of methyl triphenylphosphonium bromide and potassium *tert*-butoxide in THF at room temperature, affording alkene **2.15** in 91% yield. Aryl bromide **2.15** then underwent lithium−halogen exchange with *n*BuLi in Et_2O which was subsequently quenched with CO_2 to afford carboxylic acid **2.10**.



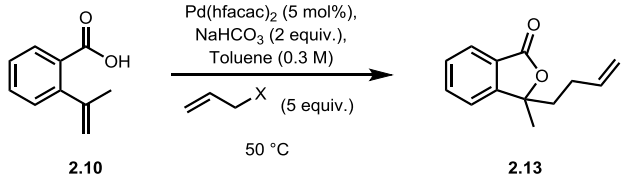
Scheme 2.4: Synthesis of benzoic acid **2.10**

Previous exploration of the oxyallylation reaction of alcohols found that the allyl halide electrophile has an effect on the overall yield and rate of reaction. The reaction of phenol **1.83** required allyl chloride as the electrophile in order to proceed in a good yield of 70% (Scheme 2.5). Conversely, the reaction of benzylic alcohol **1.110** required allyl bromide to proceed well in 77% yield.



Scheme 2.5: Oxyallylation reaction using different allyl halide electrophiles

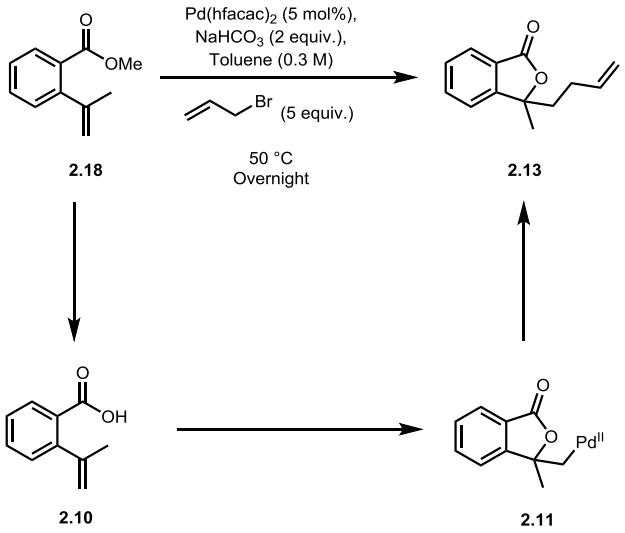
Based on the above experiments, expanding the oxyallylation methodology in the synthesis of lactones began with probing the effect the allyl halide electrophile has on the reaction. Pleasingly, utilising allyl chloride as the electrophile afforded the desired lactone **2.13** in a 37% yield, confirming the theory that the methodology could be expanded to include lactones in the scope of products available (Table 2.1, entry 1). Dramatic improvements were made with a change to allyl bromide increasing the yield to 85% whilst simultaneously shortening the reaction time significantly to 5 h (entry 2). Through these observations, and based on the premise that increasing the leaving group ability would improve the reaction, allyl iodide was tried as the electrophile, however, none of the desired lactone **2.13** was observed. Literature examples have shown acetate to be a good leaving group in palladium-catalysed β-elimination reactions; because of this allyl acetate was selected as the electrophile,however, none of the desired product was afforded (entry 4).[87]



Entry	X	Time (h)	Yield (2.13)
1	Cl	24	37%
2	Br	5	85%
3	I	24	Not Detected
4	OAc	24	Not Detected

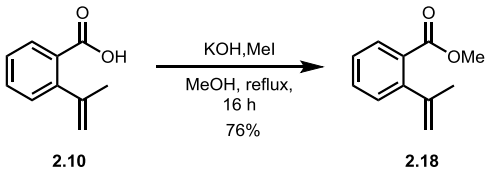
Table 2.1: Varying the allyl electrophile in the synthesis of lactone **2.13**

Investigations into circumventing the need to synthesise acids in the oxyallylation reaction were undertaken (Scheme 2.6). It was proposed, that starting from the ester **2.18**, and subjecting it to the reaction conditions, it would hydrolyse the ester bond *in situ* through the adventitious water, forming the acid **2.10**. This would then undergo the oxyallylation reaction to form the desired lactone **2.13**. In order to synthesise acid substrates, many are made *via* the ester. As a result, the ability to avoid pre-forming the acids would be advantageous and would save a step in the synthesis of various target molecules.



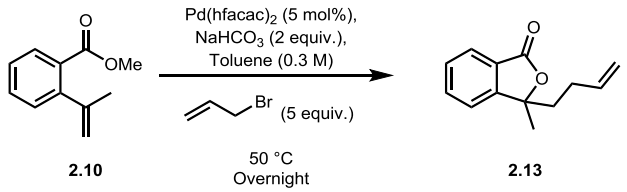
Scheme 2.6: Proposed oxyallylation of esters

As stated above, a common way to synthesise acids is to saponify esters; however, in the synthesis of benzoic methyl ester **2.18** it was easier to methylate benzoic acid **2.10** (Scheme 2.7). The main, practical reason is that sufficient amounts of the benzoic acid had already been synthesised, thus methylating the benzoic acid **2.10** would be a facile reaction.Placing benzoic acid **2.10** in refluxing methanol with potassium hydroxide as base and methyl iodide as electrophile, afforded the desired ester **2.18** in good yield.



Scheme 2.7: Synthesis of benzoic methyl ester **2.18**

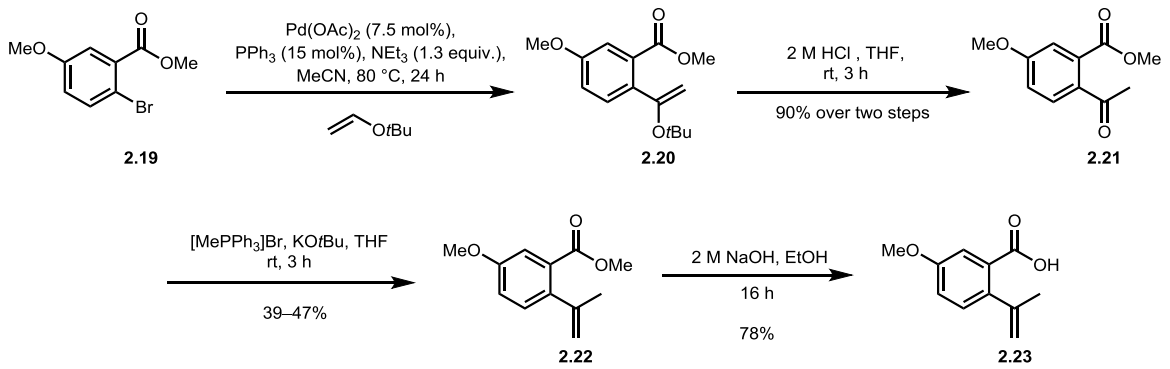
Subjecting the benzoic methyl ester **2.18** to the standard oxyallylation conditions for 24 h resulted in no formation of the desired lactone **2.13** (Table 2.2, entry 1). Increasing the temperature to 75 °C did not improve the result as none of the product was detected (entry 2). In an attempt to force the reaction, the temperature was then increased to 100 °C and left to stir for two days. However, the result was disappointing as no desired lactone **2.13** was formed (entry 3).



Entry	Temperature (°C)	Time (h)	Result 2.10 : 2.13
1	50	24	1.0 : 0.0
2	75	24	1.0 : 0.0
3	100	48	1.0 : 0.0

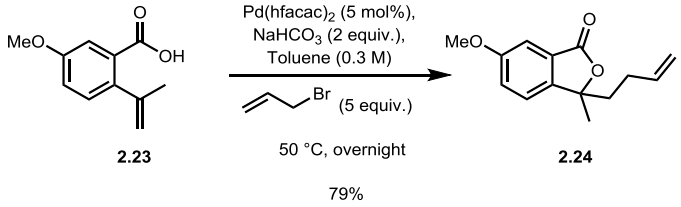
Table 2.2: Attempted oxyallylation reaction using ester starting material

Next, the goal was to analyse the effect different functional groups around the aromatic ring would have on the newly developed oxyallylation reaction. In general, a large number of steps would be required to access aryl substituted analogues of benzoic acid **2.10**. However, one example of a substrate that could be quickly accessed is methoxy-substituted benzoic acid **2.23** (Scheme 2.8). A previous project carried out within the France group had followed the synthesis outlined below and had left a sizeable amount of methoxy-substituted benzoic methyl ester **2.22**.[44] Saponification of methoxy-substituted benzoic methyl ester **2.22** overnight using 2 M aq. NaOH in ethanol resulted in the desired methoxy-substituted benzoic acid **2.23** in 78% yield (Scheme 2.8).



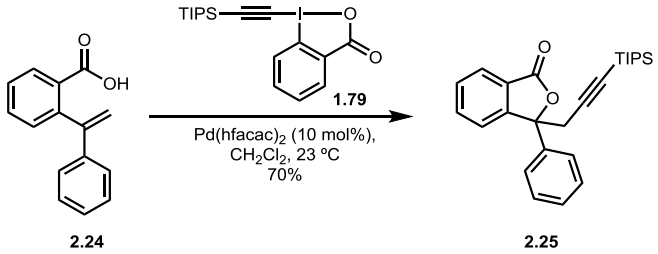
Scheme 2.8: Synthesis of methoxy-substituted benzoic acid **2.23**

Upon treatment of benzoic acid **2.23** with catalytic $Pd(hfacac)_2$, $NaHCO_3$ and allyl bromide in toluene at 50 °C, complete conversion of the starting material was observed after the reaction was left to stir overnight (Scheme 2.9). The desired product **2.24** was obtained in a 79% yield.



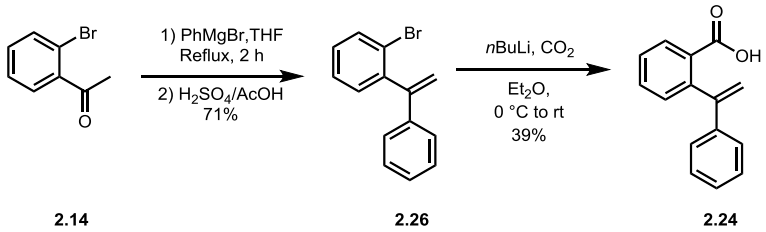
Scheme 2.9: Oxyallylation of methoxy-substituted benzoic acid **2.23**

The heterocyclisation reactions outlined thus far have contained alkenes substituted with a methyl group, and so, the effect of increasing the steric bulk was investigated. Waser and co-workers reported the oxyalkynylation reaction of diphenyl alkene **2.24** with a tethered carboxylic acid nucleophile, affording heterocyclised product **2.27** in a 70% yield (Scheme 2.10).[38]



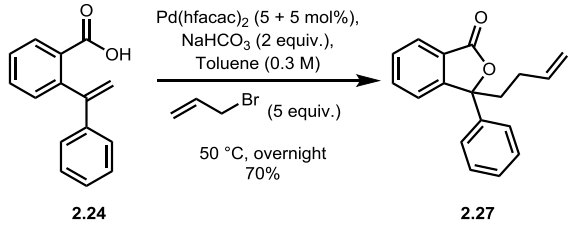
Scheme 2.10: Oxyalkynylation reaction of diaryl alkene **2.24**

Following the procedure outlined by Waser and co-workers,[38] carboxylic acid **2.24** was prepared by Grignard reaction of phenylmagnesium bromide with *o*-bromoacetophenone **2.14** followed by dehydration to afford alkene **2.26**. The bromide **2.26** then underwent lithium−halogen exchange and the aryllithium was subsequently quenched with CO_2 to afford carboxylic acid **2.24** (Scheme 2.11). The product was reported to be unstable under storage.



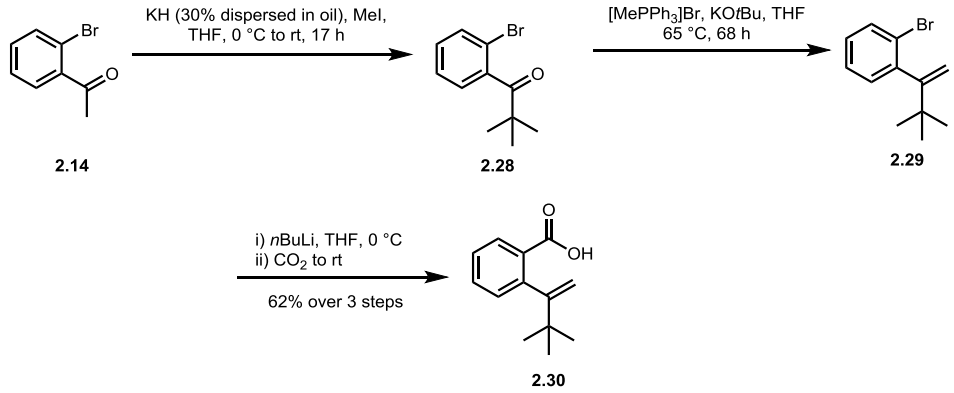
Scheme 2.11: Synthesis of diaryl substrate **2.24**

Reaction of diaryl substrate **2.24** under the standard oxyallylation conditions using allyl bromide gave poor conversion of the starting material, and resulted in a low conversion to the desired lactone **2.27**. Addition of a further 5 mol% of catalyst was required to force the reaction to complete conversion and to obtain the desired lactone **2.27** in a good yield of 70% (Scheme 2.12).



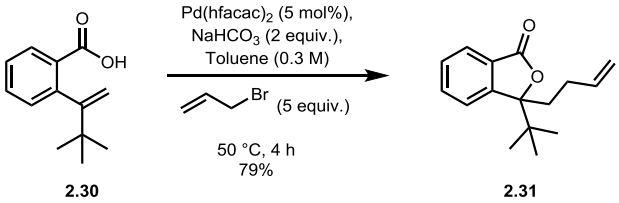
Scheme 2.12: Oxyallylation reaction of diaryl substrate **2.24**

A greater understanding as to whether steric or electronic factors were more influential in the sluggish heterocyclisation of biphenyl substrate **2.24** was required. *tert*-Butyl substituted alkene substrate **2.30** was identified as the substrate that could conceivably answer the aforementioned unknowns. As part of another project within the France group, *tert*-butyl substrate **2.30** was already synthesised.[44] The synthesis of which is outlined below (Scheme 2.13).



Scheme 2.13: Synthesis of *tert*-Butyl substrate **2.30**

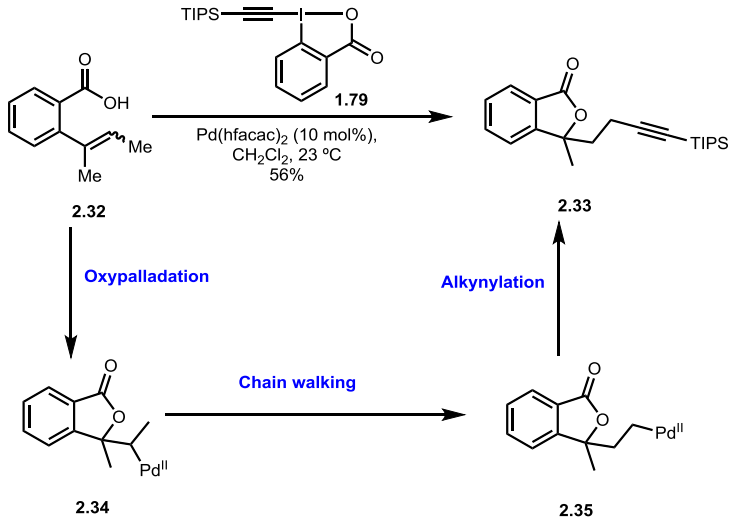
The oxyallylation reaction of *tert*-butyl substrate **2.30** using allyl bromide proceeded well. Using only 5 mol% of catalyst at 50 °C the reaction afforded lactone **2.31** in 79% yield in 4 hours (Scheme 2.14). The improvement in yield, reaction time and catalyst loading suggests that the electronics of the alkene substrate play a more important role in the reaction conversion than sterics.



Scheme 2.14: Oxyallylation of *tert*-butyl substrate **2.30**

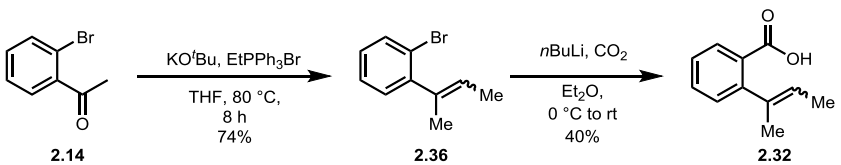
Waser and co-workers demonstrated that the oxyalkynylation reaction can be performed successfully using trisubstituted olefin substrate **2.32**. Benzoic acid **2.32**, when placed under the optimised conditions for the oxyalkynylation reaction, undergoes oxypalladation

to form internal alkylpalladium(II) intermediate **2.34** (Scheme 2.15). This is then followed by a β-hydride elimination−reinsertion sequence which causes the palladium to chain walk generating terminal alkylpalladium(II) intermediate **2.35**. This will then undergo the oxidative addition with TIPS-EBX **1.79** to form a high valent Pd(IV) intermediate followed by reductive elimination to garner the desired lactone in 56% yield.



Scheme 2.15: Oxyalkynylation of **2.32**

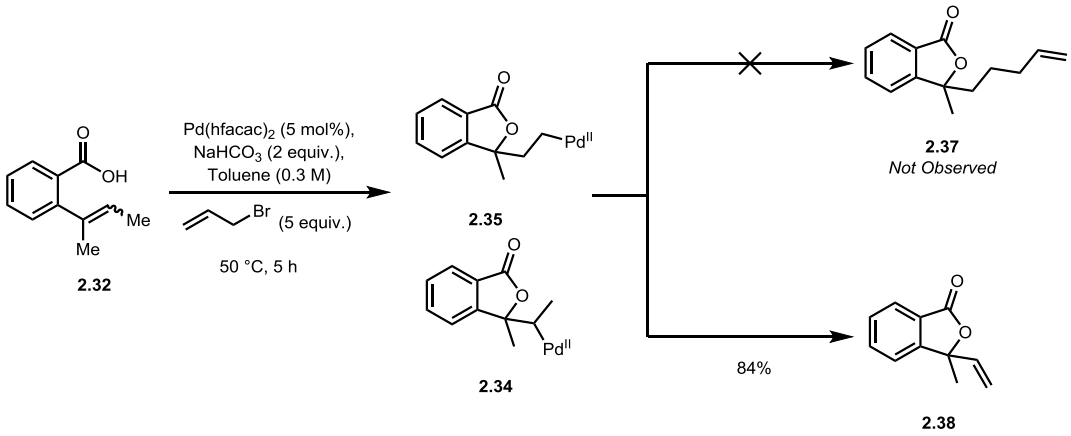
Based on this interesting result, itwas proposed that a similar sequence could be performed using the optimised conditions for the oxyallylation reation. Following the protocol by Waser and co-workers, the synthesis of trisubstituted alkene **2.32** was embarked upon (Scheme 2.16). Initiating the synthesis with a Wittig olefination, *o*-bromoacetophenone **2.14** was added to a prepared suspension of ethyl triphenylphosphonium bromide and potassium *tert*-butoxide in THF 80 °C, affording alkene **2.36** in 74% yield. Aryl bromide **2.36** then underwent lithium−halogen exchange with *n*BuLi in Et_2O and the resulting aryllithium was subsequently quenched with CO_2 to afford carboxylic acid **2.32**.



Scheme 2.16: Synthesis of trisubsituted alkene **2.32**

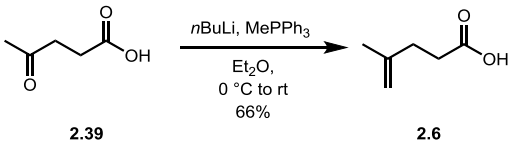
Treatment of trisubstituted alkene **2.32** to the oxyallylation conditions with allyl bromide and 5 mol% of catalyst led to complete conversion of the starting material. However, none of the desired product **2.37** was observed (Scheme 2.17). Instead, the product of β-hydride elimination, lactone **2.38** was formed in an 84% yield. Under the reaction conditions it is proposed that oxypalladation would lead to either terminal alkylpalladium(II)

intermediate **2.35** or internal alkylpalladium(II) intermediate **2.34** which would subsequently undergo β-hydride elimination to generate the unwanted heterocyclised product **2.38**. For trisubstituted alkene substrate **2.32**, it was disappointing that the rate of a β-hydride elimination pathway was greater than the rate of the desired oxyallylation reaction.



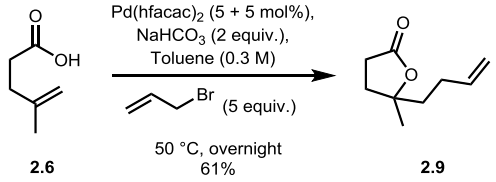
Scheme 2.17: Heterocyclisation of trisubstituted alkene **2.32**

The success of the aromatic alkenes with tethered carboxylic acid nucleophiles prompted the investigation to expand to incorporate aliphatic acids. Here, the aim was to allow aliphatic acids to undergo the oxyallylation reaction in the synthesis of 5-membered lactone rings. Spurred on by the success of Waser and co-workers'palladium-catalysed oxyalkynylation of aliphatic acids it was decided to begin the pursuit with the synthesis of acid **2.6**. The renewable feedstock levulinic acid **2.39** was converted into 4-methylpent-4-enoic acid **2.6** in one step from commercially available starting materials (Scheme 2.18).[38] This was achieved through a Wittig olefination reaction which used both *n*BuLi and methyltriphenylphosphonium bromide to give **2.6** in 66% yield.



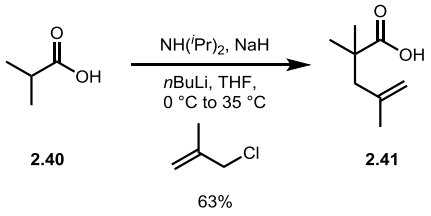
Scheme 2.18: Synthesis of aliphatic substrate **2.6**

With aliphatic substrates now the focus of investigation, 4-methylpent-4-enoic acid **2.6** was treated to the optimised oxyallylation conditions. Through monitoring the reaction, it was noticed that a further 5 mol% of catalyst was required (Scheme 2.19). The reaction afforded the desired aliphatic lactone **2.9** in a modest yield of 61%. The lower yield can be attributed to the free rotation of the linear acid **2.6**, thus obtaining the ideal reactive rotamer was more difficult.



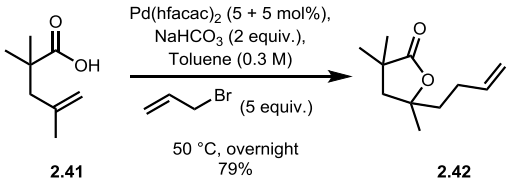
Scheme 2.19: Oxyallylation reaction of aliphatic carboxylic acid **2.6**

Based on this result, it was hypothesised that restricting the free rotation would increase reactivity and thus yield. As a result, *gem*-dimethyl carboxylic acid **2.41** was identified as a suitable substrate to confirm the proposed theory. The *gem*-dimethyl analogue of aliphatic acid **2.6** was synthesised in one step (Scheme 2.20). Isobutyric acid **2.40** was initially treated with sodium hydride and di*iso*propyl amine. The addition of *n*BuLi followed by the addition of methallyl chloride yielded the desired product 2,2,4-trimethylpent-4-enoic acid **2.41** in 63% yield.



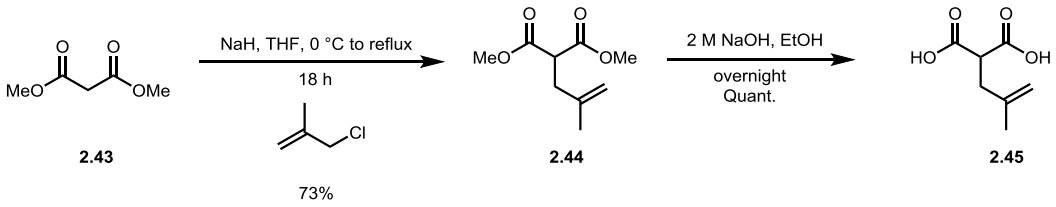
Scheme 2.20: Synthesis of *gem*-dimethyl aliphatic acid **2.41**

As predicted, the yield of the isolated *gem*-dimethyl aliphatic lactone **2.42** increased to 79% (Scheme 2.21). However, the reaction still required an additional 5 mol% of catalyst after 5 hours. The improvement can be attributed to the *gem*-dimethyl effect which is the name given to the acceleration of a cyclisation due to the replacement of hydrogen atoms with methyl groups on a carbon tethering the two reactive centres.[88]



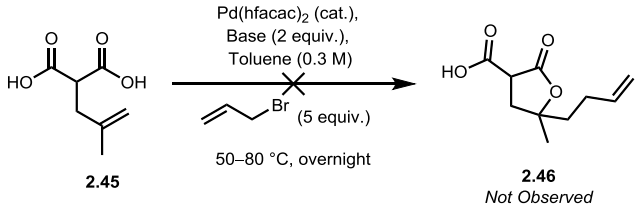
Scheme 2.21: Oxyallylation of acid *gem*-dimethyl aliphatic acid **2.41**

Following a literature procedure, malonic acid **2.45** was synthesised in 2 steps to assess whether the reaction could tolerate an unprotected carboxylic acid that was not involved in the cyclisation.[89] It is possible, that through coordination of the non-participating acid, substrate **2.42** could potentially deactivate the palladium-catalyst. Three equivalents of dimethyl malonate **2.43** was reacted with sodium hydride and one equivalent of methallyl chloride in THF and subsequent reflux to afford malonate **2.44** in 73% yield. Saponification with 2 M aq. NaOH gave the desired diacid **2.45** in quantitative yield.



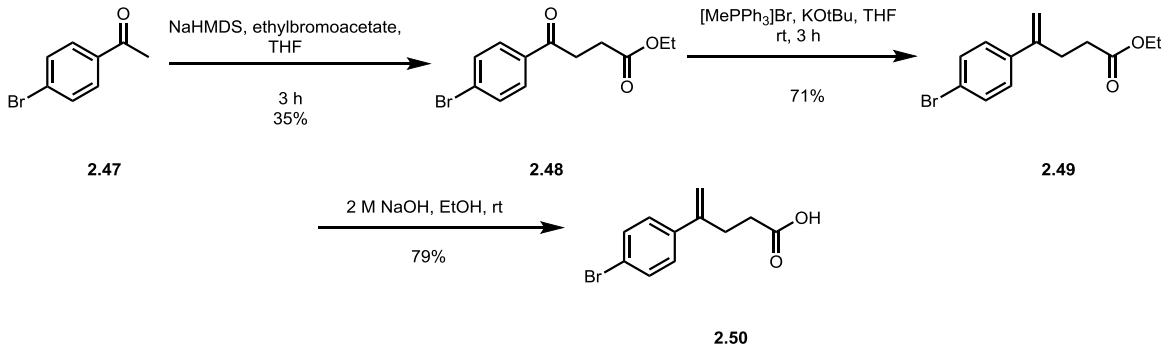
Scheme 2.22: Synthesis of malonic acid **2.45**

Malonic acid **2.45** was placed under the developed oxyallylation reaction condition for the synthesis of lactones; however, it never afforded any of the desired lactone **2.46** (Scheme 2.23). Conditions were then varied, with changes in temperature, base and catalyst loading. Regardless of the parameters changed,none of the desired product was observed *via* ^{1}H NMR analysis. Unfortunately, the main product formed in the reaction was unidentifiable.



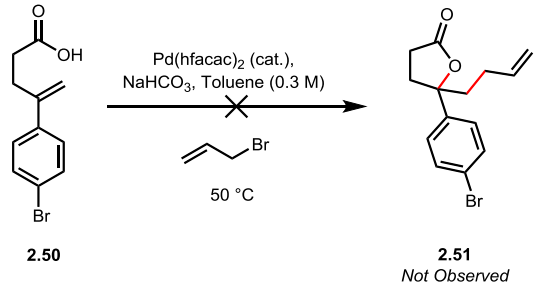
Scheme 2.23: Attempted oxyallylation reaction of malonic acid **2.45**

A further target of the project was to extend the oxyallylation of carboxylic acids to include a substrate with a halogen atom bonded to the molecule. A halogen atom attached to the substrate would be useful, as it can be used as a handle for further transformations. However, problems arose when attempting to devise a synthesis. The main problem was the use of chemistry that involved *n*BuLi or palladium. As can be seen above, this rules out all the benzoic acid substrates. After much deliberation and research, bromo-pentenoic acid **2.50** was identified as a viable substrate, as reactions that could conceivably interact with the halogen, when synthesising **2.50**, were circumvented (Scheme 2.24). The synthesis of acid **2.50** began with a S_N2 reaction of *p*-bromoacetophenone **2.47** on ethylbromoacetate to furnish ester intermediate **2.48**, which subsequently underwent a Wittig olefination to give 4-(bromophenyl)pent-4-enoate **2.49** in a 71% yield. Hydrolysis of the ester to the corresponding acid then resulted in the desired bromo-pentenoic acid **2.50** in a 79% yield.



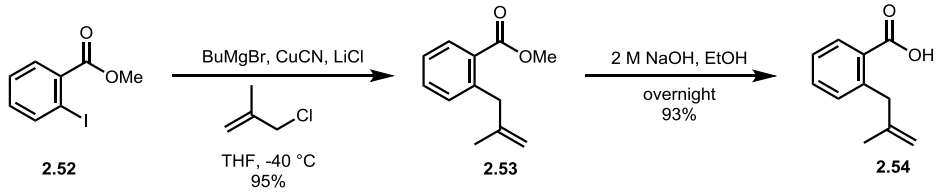
Scheme 2.24: Synthesis of halogen-containing acid **2.50**

Upon treatment of aliphatic acid **2.50** to the optimised oxyallylation reaction, no desired product was observed (Scheme 2.25). Numerous attempts were made by varying the catalyst loading. Starting with 5 mol%, then increasing to 5 + 5 mol% and finally 10 mol% of catalyst loading, resulted in none of the desired lactone **2.51** observed *via* ^{1}H NMR analysis, with only starting material recovered. Two major factors are potentially contributing to the lack of heterocyclisation. Firstly, the phenyl substituent tethered to the alkene of acid **2.50** is withdrawing electrons away from the double bond, and as witnessed with a previous example (Scheme 2.12), has a deleterious effect on the rate and yield. Secondly, as discussed previously, this is complicated by the reactive rotamer effect.[88] Although individually not enough to prevent the oxyallylation reaction, combined they exert a detrimental effect which results in the lack of desired lactone **2.51** being formed.



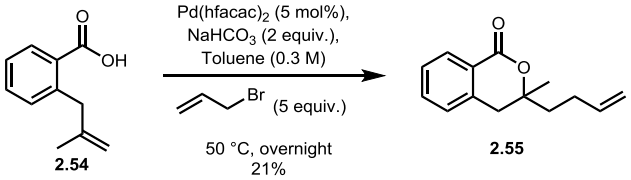
Scheme 2.25: Attempted oxyallylation of bromo-pentenoic acid **2.50**

Efforts were then focused on the construction of 6-membered lactones as it would extend the substrate scope and increase the effectiveness of the oxyallylation reaction even further. With the success in the construction of 5-membered lactones using benzoic acid substrates, it was reasoned that starting from methallylbenzoic acid **2.54** would be prudent. The substrate was synthesised in 2 steps following a literature procedure (Scheme 2.26).[38] Allylation of aryl iodide **2.52** with 2-methallylchloride yielded methallylbenzyl ester **2.53**. Subsequent ester hydrolysis afforded the desired methallylbenzoic acid **2.54**.



Scheme 2.26: Synthesis of methallylbenzoic acid **2.54**

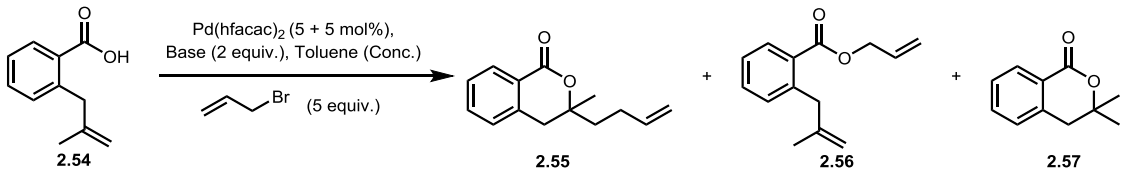
Initial attempts towards the oxyallylation reaction of lactone **2.55** were made using the then optimal conditions, with 5 mol% catalyst in toluene and with allyl bromide as the electophile (Scheme 2.27). Low conversion of starting material resulted in a low yield of 21% of desired lactone **2.55**.



Scheme 2.27: Oxyallylation of methallylbenzoic acid **2.54**

Dissatisfied with result above, improving upon the 21% yield was the priority. In an attempt to improve the yield, the catalyst loading was increased. Starting at 5 mol%, a further 5 mol% was added after 5 h (Table 2.3, entry 1). Incomplete conversion of the methallylbenzoic acid **2.54** was still an issue; however, the yield almost doubled which was encouraging. Increasing the temperature to 80 °C still resulted in a large amount of unreacted starting material **2.54** with the desired lactone **2.55** being formed in equal amounts. Additionally, *O*-allylated side product **2.56** was observed *via* ^{1}H NMR analysis of the crude material. Increasing the concentration did result in more of the desired lactone **2.55**; however, there was still an abundance of benzoic acid **2.54** (entry3). Increasing both the temperature and concentration resulted in equal amounts of starting material **2.54**, desired lactone **2.55** and *O*-allylated side product **2.56** (entry 4). As such a change in strategy to a weaker base was envisioned to improve the ailing reaction,as it would limit formation of the *O*-allylated side product **2.56**. However, this change also brought an unsatisfactoryresult as a large amount of unreacted starting material **2.54** remained and proto-demetallated product **2.57** was the major product (entry 5). In order to improve the conversion an increase in temperature or concentration was employed with KH_2PO_4 kept constant as the base. As before, complete conversion of starting material did not arise when either the temperature or concentration increased (entries 6 and 7). The increase in temperature and concentration resulted in a slight increase of desired product **2.55**, yet also furnished *gem*-dimethyl lactone **2.57** in greater amounts. When both the temperature and concentration are increased simultaneously, sole formation of *gem*-dimethyl lactone **2.57** was observed (entry 8). However, when the temperature is increased further to 100

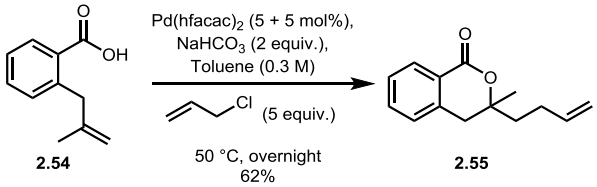
°C the *O*-allylated product **2.56** is formed exclusively (entry 9). Excluding a base from the reaction and varying the temperature was also attempted in the pursuit of ideal conditions; however,the results were not encouraging (entries 10 and 11). Increasing the strength of the base was hypothesised to deprotonate the benzoic acid **2.54**. The carboxylate would be more nucleophilic, resulting in the formation of the desired 6-membered lactone **2.55** (entry 12). The nucleophilicity did increase; however, it resulted in the sole formation of the *O*-allylated compound **2.56**.



Entry	Conc. (M)	Temp. (°C)	Base	Result 2.54 : 2.55 : 2.56 : 2.57
1	0.3	50	$NaHCO_3$	2.0 : 1.0 (41%): 0.0 : 0.0
2	0.3	80	$NaHCO_3$	2.0 : 2.0 : 1.0 : 0.0
3	0.6	50	$NaHCO_3$	1.4 : 1.0 : 0.0 : 0.0
4	0.6	80	$NaHCO_3$	1.0 : 1.0 : 1.0 : 0.0
5	0.3	50	KH_2PO_4	2.0 : 1.0 : 0.0 : 2.4
6	0.3	80	KH_2PO_4	2.5 : 1.0 : 0.0 : 2.5
7	0.6	50	KH_2PO_4	2.0 : 1.0 : 0.0 : 4.0
8	0.6	80	KH_2PO_4	0.0 : 0.0 : 0.0 : 1.0
9	0.3	100	KH_2PO_4	0.0 : 0.0 : 1.0 : 0.0
10	0.3	50	No Base	0.0 : 0.0 : 0.0 : 1.0
11	0.3	80	No Base	0.0 : 1.0: 0.0 : 4.0
12	0.3	50	K_2CO_3	0.0 : 0.0 : 1.0 : 0.0

Table 2.3: Optimisation of oxyallylation reaction for 6-membered lactone ring **2.55**

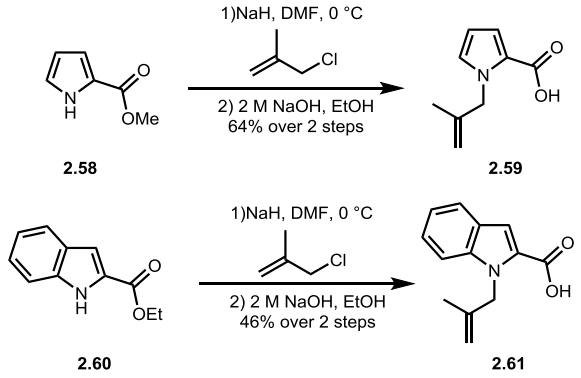
After much screening, optimised conditions were discovered. Simply changing the allyl halide electrophile from allyl bromide to allyl chloride in the presence of toluene, $NaHCO_3$ and $Pd(hfacac)_2$ catalyst (5 + 5 mol%) the reaction afforded the desired 6-membered lactone **2.55** in 62% yield (Scheme 2.28).



Scheme 2.28: Optimised conditions for the synthesis of **2.55**

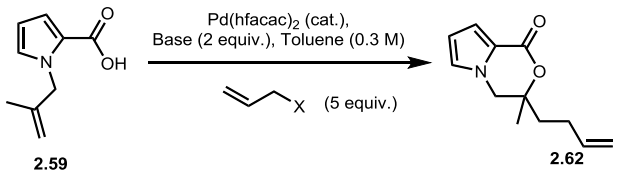
At this juncture, it must be noted that the switching of allyl halide to allyl chloride and its effect on the reaction came as a surprise. Previous oxyallylation experiments had shown that allyl chloride had a deleterious effect on the conversion, rate and yield of reaction. With this new information, substrates that did not heterocyclise or required a higher catalyst loading in order to result in complete conversion of starting material were examined. Substituting allyl bromide for allyl chloride resulted in no improvement in the aforementioned reactions.

Due to their importance in medicinal chemistry, the synthesis of nitrogen-containing substrates amenable to the oxyallylation conditions was the next objective. As such both pyrrole and indole derivatives were chosen. Both pyrrolecarboxylic acid **2.59** and indolecarboxylic acid **2.61** were synthesised in two steps from commercially available starting materials pyrrole methyl ester **2.58** and indole ethyl ester **2.60** (Scheme 2.29). The first step in the synthesis of both substrates is the allylation of the nitrogen atom using methallyl chloride in DMF, with sodium hydride as the base. The intermediates were then saponified by 2 M aq. NaOH, to give the desired pyrrole **2.59** and indole **2.61** in 64% and 46% yields, over two steps.



Scheme 2.29: Synthesis of pyrrole **2.59** and indole **2.61** substrates

Pyrrole **2.59** and indole **2.61** were next subjected to the oxyallylation reaction conditions. More focus was directed towards the pyrrole **2.59** variant (Table 2.4). This was intentional, because the two compounds bear structural similarities; it was assumed conditions that would work for one would work for the other. However, irrespective of the reaction conditions the formation of the desired pyrrole lactone **2.62** was not observed *via* ^{1}H NMR analysis of the crude material. Catalyst loading, base, temperature and electrophile were varied (Table 2.4, entries 1 – 8). Unfortunately, each time the reaction mixture quickly turned black, alluding to the formation of Pd(0).

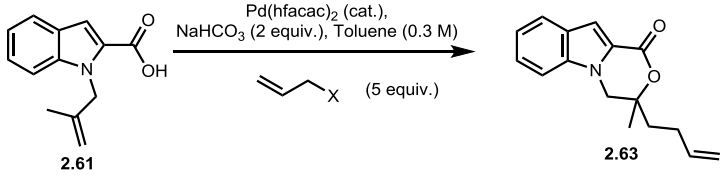


2.59 2.62

Entry	Pd(hfacac)$_2$ (mol%)	X	Base	Temp (°C)	Result 2.59 : 2.62
1	5	Br	$NaHCO_3$	50	1 : 0
2	5	Cl	$NaHCO_3$	50	1 : 0
3	10	Br	$NaHCO_3$	80	1 : 0
4	10	Cl	$NaHCO_3$	80	1 : 0
5	10	Br	KH_2PO_4	50	1 : 0
6	10	Cl	KH_2PO_4	50	1 : 0
7	10	Br	No Base	50	1 : 0
8	10	Cl	No Base	50	1 : 0

Table 2.4: Attempted oxyallylation of pyrrole **2.59**

Reactions on indole **2.61** were run simultaneously (Table 2.5). Again, variables such as catalyst loading, temperature and electrophile were changed, however, were also unsuccessful in synthesising the desired compound **2.63** (Table 2.5, entries 1−4). As with previous results on pyrrole substrate **2.59**, the reaction mixture quickly turned black, hinting at formation of Pd(0) under the reaction conditions.



2.61 2.63

Entry	Pd(hfacac)$_2$ (mol %)	X	Temp (°C)	Result 2.61 : 2.63
1	5	Br	50	1 : 0
2	5	Cl	50	1 : 0
3	10	Br	80	1 : 0
4	10	Cl	80	1 : 0

Table 2.5: Attempted oxyallylation of indole **2.61**

The consequences of the Pd(0) formation allowed other reactions to dominate with the major products an unwanted, complex mixture of *O*-allylated product **2.64** and *O*-allylated products with allyl group on the aromatic ring generating compounds **2.65** and **2.66** (Figure 2.2). Attempts to purify and isolate the allylated products were futile as they elute off the column as one in petroleum ether with an Rf value of 0.8.

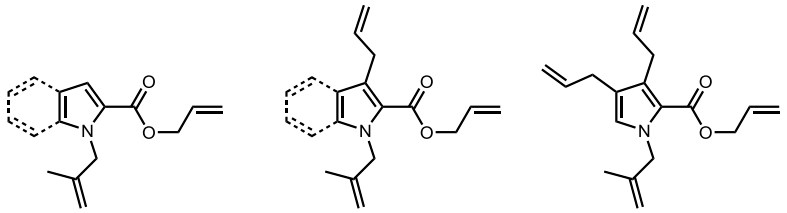
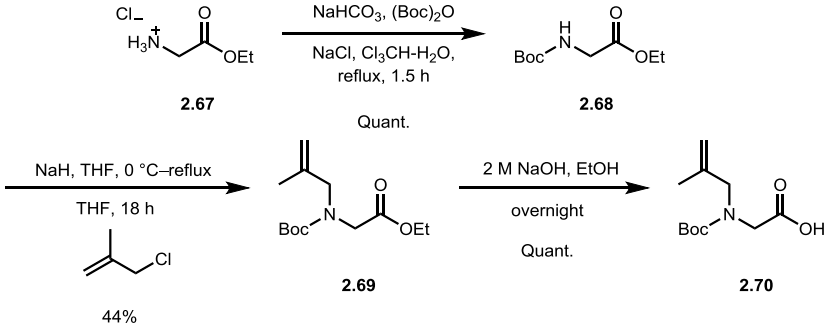


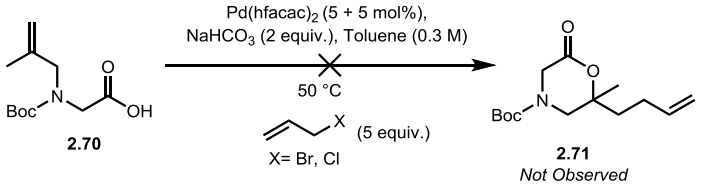
Figure 2.2: Allylated side products

Glycine-derived aliphatic acid **2.70** was chosen because the glycine motifis present in many bioactive molecules and molecules found throughout nature. Substrate **2.70** was synthesised in 3 steps initially starting with the protection of the amine functionality in the presence of Boc anhydride at reflux, which quantitatively yielded the desired Boc-protected amine **2.68** (Scheme 2.30). The second step involved the deprotonation of the nitrogen with sodium hydride in THF followed by the addition of methallyl chloride to give allylated carbamate **2.69**. Saponification with 2 M aq. NaOH to give the desired glycine derived carboxylic acid **2.70** was achieved in quantitative yield. Compound **2.69** exists as two rotamers and as such had to be analysed with high temperature ^{1}H NMR to confirm its synthesis. Compound **2.70** also existed as two rotamers and was also analysed with high temperature ^{1}H NMR to confirm its synthesis.



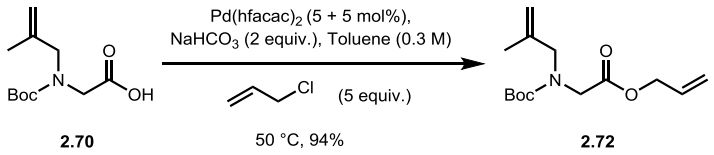
Scheme 2.30: Synthesis of glycine derived substrate **2.70**

With the desired glycine derived carboxylic acid **2.70** at hand, it was then subjected to oxyallylation conditions. Unfortunately, results did not provide any of the desired product **2.71**.Varying the allyl halide electrophile from allyl chloride resulted in no formation of the desired lactone **2.71** (Scheme 2.31).



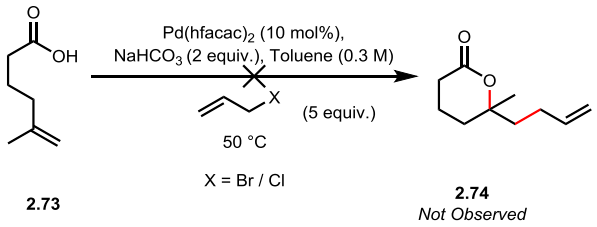
Scheme 2.31: Attempted oxyallylation of glycine derived substrate **2.70**

In the attempted oxyallylation reaction on glycine derived substrate **2.70**, the major product that was formed was the *O*-allylation product **2.72** in a 94% yield (Scheme 2.32). A possible reason for the sole formation of *O*-allylated **2.72** is because of the hybridisation of the nitrogen atom being sp^2 hybridised as opposed to sp^3 hybridised. This increases the bond angle from approximately 109° to 120°, thus keeping the reactive centres further apart. As such it can be determined that *O*-allylation is a more facile reaction than the Pd(II)-induced heterocyclisation. Additionally, product **2.72** is a rotamer and as such its synthesis had to be confirmed by variable temperature ^{1}H NMR.



Scheme 2.32: Formation of side product **2.72**

Based on the success of the palladium(II)-catalysed heterocyclisation of aliphatic acids to form 5-membered lactones, commercially available hexenoic acid **2.73** was selected as a potentially viable substrate to expand the reaction into 6-membered lactones starting from aliphatic acids. Hexenoic acid **2.73** was submitted to the reaction conditions (Scheme 2.33). Unfortunately, the desired product was not observed *via* ^{1}H NMR analysis of the crude mixture and only starting material was recovered. One possible reason for the failure of hexenoic acid **2.73** to cyclise is that it was unable to acquire a reactive conformation.[88] This can be ascribed to the barrier of cyclisation being higher than for the corresponding cyclisation for 5-membered lactones.

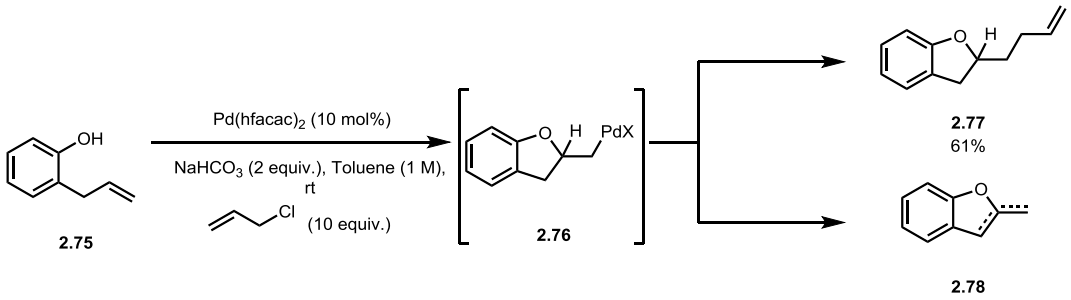


Scheme 2.33: Attempted oxyallylation of hexenoic acid **2.73**

2.1.3 *Mono*-substituted Alkene Substrates

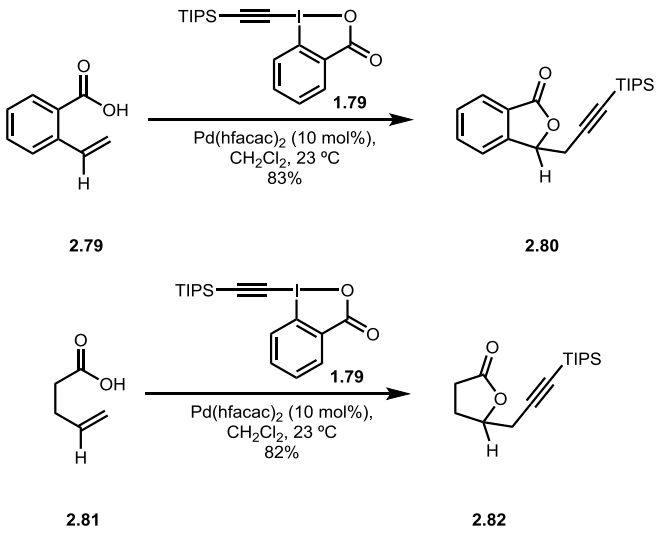
Oxyallylation reactions of unactivated *mono*-substituted alkenes have been previously demonstrated within the France group. Mixed results were obtained with only 2-allyl phenol **2.75** successfully performing the oxyallylation reaction in a synthetically viable yield (Scheme 2.34). A modification of the standard palladium-catalysed oxyallylation conditions were required to circumvent the synthesis of benzofuran **2.78**. Increasing the catalyst loading to 10 mol%, increasing the concentration, doubling the number of

equivalents of allyl chloride and lowering the temperature to room temperature was necessary to furnish the desired benzofuran **2.77** in a 61% yield.



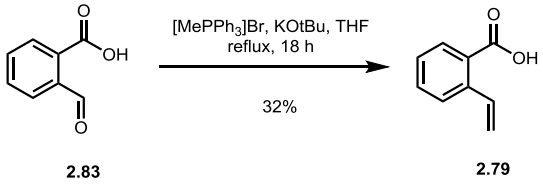
Scheme 2.34: Oxyallylation of 2-allyl phenol **2.75**

Palladium-catalysed reactions of *mono*-substituted alkenoic acids, in comparison to their hydroxyl counterparts, have not been studied as extensively. Early examples include the work of Yoshida[90] and Larock[91] in the synthesis lactones *via* palladium catalysis. Additionally, the previously discussed report on oxyalkynylation from Waser and co-workers reported examples of *mono*-substituted alkenes in good yields (Scheme 2.35).[38]



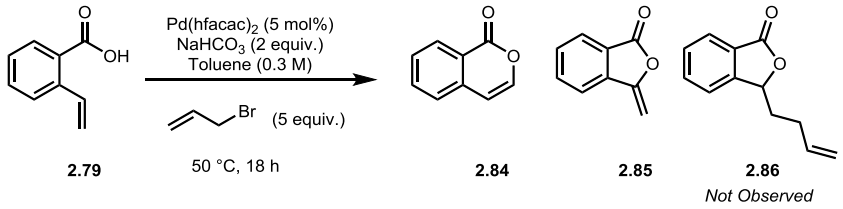
Scheme 2.35: Oxyalkynylation of *mono*-substituted alkenoic acids

The success of benzoic acid substrates in the oxyallylation reaction of *gem*-disubstituted alkenes for the synthesis of 5-membered lactones, prompted the synthesis of 2-vinyl benzoic acid **2.79**. Wittig olefination of aldehyde **2.83** in THF at reflux yielded the desired 2-vinyl benzoic acid **2.79**, albeit in a lowly 32% yield (Scheme 2.36).



Scheme 2.36: Synthesis of 2-vinyl benzoic acid **2.79**

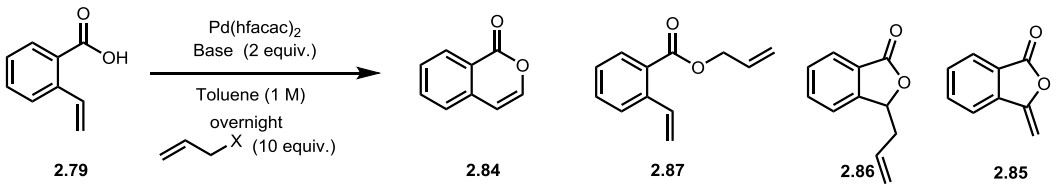
The results of of Waser and co-workers for *mono*-substituted alkenes led to 2-vinyl benzoic acid **2.79** being subjected to the oxyallylation conditions developed for the *gem*-disubstituted analogue. Unfortunately, the reaction never went to full conversion of 2-vinyl benzoic acid **2.79** and none of the desired oxyallylated lactone **2.86** was observed (Scheme 2.37). Analysis of the crude material revealed no formation of compound **2.86** but instead gave unreacted starting material **2.79**, isocoumarin **2.84** and exo-methylene lactone **2.85** in a ratio of 4.7: 1.1: 1.0 respectively.



Scheme 2.37: Attempted oxyallylation of 2-vinyl benzoic acid **2.79**

The analysis of previous palladium-catalysed oxyallylation results indicates that cyclisations to form 5-membered lactones are a more facile process, when compared to the synthesis of the 6-membered lactones. This led to the screening of conditions to optimise the oxyallylation reaction for 2-vinylbenzoic acid **2.79** (Table 2.6). Initially, the conditions employed were similar to those developed for the only successful *mono*-substituted alkene to undergo the Pd(II)-catalysed oxyallylation reaction, with a yield that was acceptable (Scheme 2.34). Catalyst loading was initially lower at 5 mol% (entry 1 and 2); however, desired lactone **2.86** was not detected by analysis of ^{1}H NMR of the crude mixture. As such, the catalyst loading was increased to 10 mol%, yet still no desired product was observed, with only unwanted side products formed(entry 3). However, when the temperature was lowered to room temperature, a small amount of the desired oxyallylated lactone **2.86** was observed *via* analysis of the ^{1}H NMR of the crude mixture (entry 4). The base was also varied in an attempt to limit the synthesis of *O*-allylated compound **2.87**; however, this resulted in the sole formation of isocoumarin **2.84** (entries 5 and 6). When allyl bromide was replaced with allyl chloride a more favourable ratio was observed, but still not ideal (entry 7). The reaction temperature was then decreased to room temperature, however, no desired product formed (entry 8). It should be noted that

all reactions listed below resulted in low conversion of starting material, and as a result, it was more prudent to focus more on the ratio of products formed.

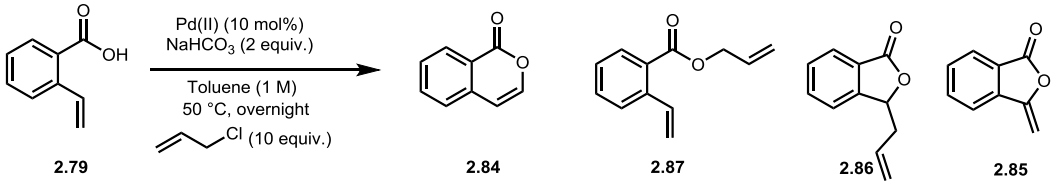


Entry	Base	Temp. (°C)	Catalyst Loading	Allyl X	Ratio 2.84 : 2.87 : 2.86 : 2.85
1	$NaHCO_3$	50	5 mol%	Br (5 equiv.)	1.0 : 1.0 : 0.0 : 0.0
2	$NaHCO_3$	50	5 mol%	Br	2.0 : 1.0 : 0.0 : 0.0
3	$NaHCO_3$	50	10 mol%	Br	1.8 : 1.0 : 0.0 : 1.0
4	$NaHCO_3$	r.t.	10 mol%	Br	2.6: 1.6 : 1.0 : 0.0
5	-	50	10 mol%	Br	1.0 : 0.0 : 0.0 : 0.0
6	KH_2PO_4	50	10 mol%	Br	1.0 : 0.0 : 0.0 : 0.0
7	$NaHCO_3$	50	10 mol%	Cl	1.0 : 3.5 : 1.3 : 0.0
8	$NaHCO_3$	rt	10 mol%	Cl	1.0 : 6.0 : 0.0 : 0.0

NB – No reaction went to complete conversion of starting material and conversion was poor

Table 2.6: Attempted optimisation of oxyallylation reaction for 2-vinyl benzoic acid **2.79**

Simply by swapping allyl bromide with allyl chloride, it was observed that the reaction synthesised less side products (unwanted heterocyclic compounds **2.84** and **2.85**) that involved the formation of Pd(0) and thus could lead to the deactivation of the Pd(II) catalyst, which is required for the isohypsic reaction. With this, it was reasoned that a change in catalyst could conceivably improve the ratio in favour of the desired lactone **2.86**, and improve conversion. As such, screening of the palladium(II) salt used in the reaction was investigated (Table 2.7, entries 1 – 5). Here, it proves that a change away from $Pd(hfacac)_2$ as the catalyst has a deleterious effect on the reaction, and worsens the ratio of desired lactone **2.86** to side products and, as such, no improvements were observed. It should be noted that all reactions listed below resulted in low conversion of starting material, and as a result, it was more prudent to focus more on the ratio of products formed.

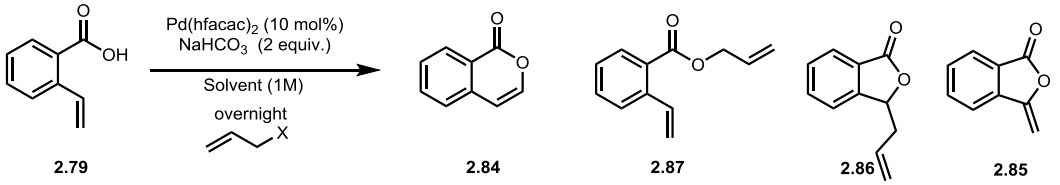


Entry	Catalyst	Ratio **2.84 : 2.87 : 2.86 : 2.85**
1	$Pd(OAc)_2$	4.3 : 3.3 : 1.0 : 4.0
2	$Pd(TFA)_2$	0.0 : 1.0 : 0.0 : 0.0
3	$PdCl_2(C_6H_5CN)_2$	1.0 : 3.0 : 0.0 : 0.0
4	$PdCl_4Na_2$	1.3 : 1.0 : 0.0 : 0.0
5	$PdCl_2$	11 : 3.5 : 1.0 : 0.0

NB – No reaction went to complete conversion of starting material and conversion was poor

Table 2.7: Catalyst screening

With $Pd(hfacac)_2$ as the catalyst, the combination of solvent and allyl halide electrophile was investigated (Table 2.8). When the reaction was performed in dichloromethane at 50 °C, only the isocoumarin product **2.84** was formed (entries 1 and 2). Lowering the temperature to room temperature yielded the desired lactone **2.86** in a reasonable ratio to side products only when allyl bromide is employed as the electrophile (entries 3 and 4), although, still not as favourable as previously observed (Table 2.6, entry 7). Changing the solvent to EtOAc and THF did not improve the ratio, and in each instance favoured the synthesis of side products that led to the formation of Pd(0) (entries 5 – 8). It should be noted that all reactions listed below resulted in low conversion of starting material, and as a result, it was more prudent to focus more on the ratio of products formed.

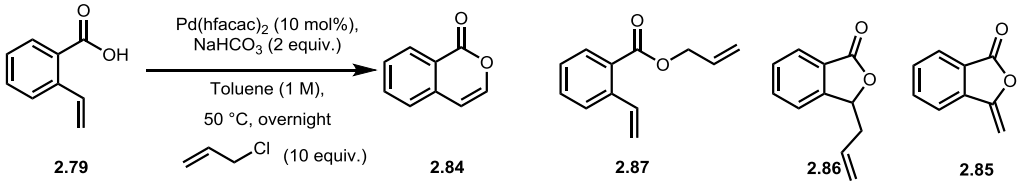


Entry	AllylX	Solvent	Temp. (°C)	Ratio 2.84 : 2.87 : 2.86 : 2.85
1	Cl	CH_2Cl_2	50	1.0 : 0.0 : 0.0 : 0.0
2	Br	CH_2Cl_2	50	1.0 : 0.0 : 0.0 : 0.0
3	Cl	CH_2Cl_2	r.t.	1.0 : 0.0 : 0.0 : 0.0
4	Br	CH_2Cl_2	r.t.	1.2 : 1.6 : 1.0 : 0.0
5	Cl	EtOAc	50	2.3 : 3.6 : 1.0 : 0.0
6	Br	EtOAc	50	4.3 : 1.0 : 0.0 : 0.0
7	Cl	THF	50	2.0 : 1.0 : 0.0 : 3.9
8	Br	THF	50	4.0 : 5.0 : 1.0 : 2.5

NB – No reaction went to complete conversion of starting material

Table 2.8: Effect of varying solvent and allyl halide on reaction

With allyl chloride, toluene and $Pd(hfacac)_2$at 10 mol% catalyst loading seeming to be superior than other possible conditions, it was decided to maintain them as constants. A change in concentration to 0.3 M was first investigated; however, this negated the formation of desired compound **2.86** (Table 2.9, entry 1). The base was also varied; however, this did not improve on the best result obtained previously (entry 2). Variation in the allyl chloride stoichiometry (entries 3 – 5) was also examined, with the use of 20 equivalents marginally improving upon the best previous result. Next, additives were also screened. From the literature, the addition of chloride salts is known to suppress β-hydride elimination in Wacker-type reactions and, thus, should prevent the formation of unwanted lactones **2.84** and **2.85**.[92] The addition of LiCl to the reaction resulted in the sole formation of isocoumarin **2.84**, with none of the desired product observed (entry 7). Other additives like benzoquinone (entry 8) and H_2O were added; however, no improvement was observed, with *O*-allylated side product **2.87** being the main product (entry 9). It should be noted that all reactions listed below resulted in low conversion of starting material, and as a result, it was more prudent to focus more on the ratio of products formed.

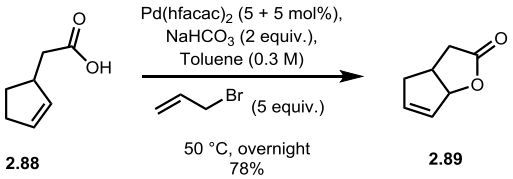


Entry	Additive	Ratio 2.84 : 2.87 : 2.86 : 2.85
1[a]	-	4.4 : 2.0 : 1.0 : 0.0
2[b]	-	1.4 : 6.4 : 2.0 : 1.0
3[c]	-	1.0 : 6.3 : 1.0 : 0.0
4[d]	-	1.0 : 10.0 : 1.3 : 0.0
5[e]	-	1.0 : 5.6 : 2.0 : 0.0
6[f]	-	9.3 : 1.0 : 1.4 : 0.0
7	LiCl (10 equiv.)	1.0 : 0.0 : 0.0 : 0.0
8	BQ (2 equiv.)	1.0 : 0.0 : 0.0 : 0.0
9	H_2O (0.4 mL)	1.3 : 6.0 : 1.0 : 0.0

[a]0.3 M [b] base changed to KH_2PO_4 [c] 20 equiv. of allyl chloride [d] 5 equiv. of allyl chloride [e] no solvent [f] 80 °CNB – No reaction went to complete conversion of starting material

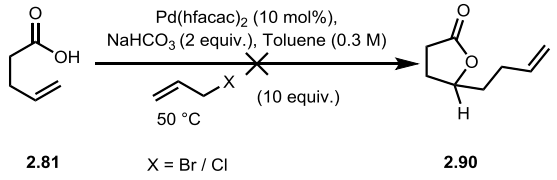
Table 2.9: Attempted optimisation of 2-vinyl benzoic acid **2.79**

Next, the commercially available 2-(cyclopent-2-enyl)acetic acid **2.88** was subjected to the optimised conditions developed for the oxyallylation of *gem*-disubstituted alkenes bearing a tethered carboxylic acid group. However, none of the desired product was isolated. Instead the β-hydride elimination product **2.89** was isolated in 78% yield (Scheme 2.38).



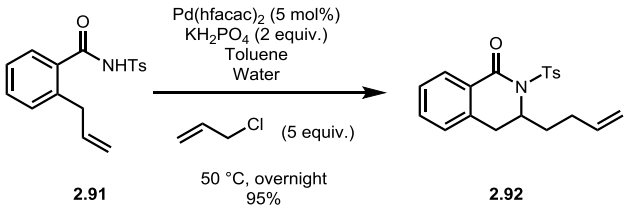
Scheme 2.38: Attempted oxyallylation reaction of cyclopentene carboxylic acid **2.88**

With the above result in hand, it was obvious that oxyallylation reaction of aliphatic acids was not going to be a facile process. As such, commercially available pentenoic acid **2.81** was chosen as a more suitable substrate due to the success of its *gem*-disubstituted analogue in previous studies. Analysing the best results from the previous investigations with *mono*-substituted alkenenoic acids, the investigations began by using reaction conditions from Table 2.6 entry 7, in the hope that an improvement in the ratio would be observed. The allyl halide electrophile was varied from allyl bromide to allyl chloride; however, each reaction only returned starting material (Scheme 2.39).



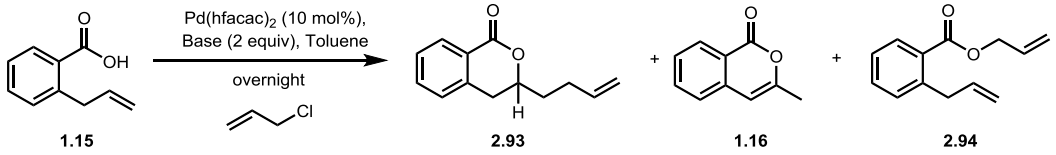
Scheme 2.39: Attempted oxyallylation of aliphatic acid **2.81**

Previous studies within the France group proved to be successful for the aminoallylation of *mono*-substituted alkene substrates. When 2-allyl tosylamide **2.91** was treated with 5 mol% of $Pd(hfacac)_2$ in a biphasic mixture of toluene/H_2O at 50 °C with KH_2PO_4 as the base afforded the desired lactam in an excellent 95% yield (Scheme 2.40).



Scheme 2.40: Aminoallylation reaction of *mono*-substituted alkene **2.91**

The success of the tosylamide **2.91** inspired the study of its carboxylic analogue. Subjecting 2-allylbenzoic acid **1.15** to the standard oxyallylation conditions gave a promising initial result, which was the focus of much optimisation (Table 2.10, entry 1). Varying the concentration resulted ina large amount of starting material **1.15**, with the main palladium-catalysed product the unwanted β-hydride elimination isocoumarin **1.16** (entries 2 and 3). From the literature,[93] it is known that through increasing the halide concentration, the halide can block coordination sites on the palladium which in turn prevents β-hydride elimination. Due to this LiCl and and N(*n*Butyl)$_4$Cl were added, however, the addition of chloride salts appears to retard the synthesis of of desired lactone **2.93**, and instead side products are formed preferentially if at all (entries 4 and 5). As the use of LiCl afforded a small amount of the desired lactone **2.93**, it was decided to increase the equivalents of LiCl and allyl chloride as well as increase the concentration, in order to favour the synthesis of desired oxyallylated lactone **2.93** (entry 6). This did result in complete conversion of 2-allyl benzoic acid **1.15** and a small amount of the desired product **2.93** with none of the unwanted isocoumarin **1.16**. However, the reaction did result in the *O*-allylated side product **2.94** as the predominant product. Varying concentration and temperature resulted in no formation of the oxyallylation product **2.93** (entries 7–10). With the concentration at 0.8 M, changing to a weaker base of KH_2PO_4 resulted in no formation of desired lactone **2.93** and raising the temperature to 80 °C resulted in none of the desired lactone **2.93** (entries 11 and 12).



Entry	Conc.	AllylCl Equiv.	Temp (°C)	Base/ Additive	Result 1.15 : 2.93 : 1.16 : 2.94
1	0.3	5	50	$NaHCO_3$	1.0 : 1.0 : 6.0 : 0.0
2	0.8	5	50	$NaHCO_3$	3.0 : 1.0 : 2.0 : 3.0
3	0.2	5	50	$NaHCO_3$	5.0 : 1.0 : 2.0 : 0.0
4	0.8	5	50	$NaHCO_3$/ LiCl (1 equiv.)	0.0 : 1.0 : 8.0 : 8.0
5	0.8	5	50	$NaHCO_3$/ N(*n*Butyl)$_4$Cl (1 equiv.)	0.0 : 0.0 : 0.0 : 1.0
6	1.0	10	50	$NaHCO_3$/ LiCl (10 equiv.)	0.0 : 1.0 : 0.0 : 4.0
7	1.0	10	50	$NaHCO_3$	0.0 : 0.0 : 1.0 : 0.0
8	No solvent	5	50	$NaHCO_3$	0.0 : 0.0 : 0.0 : 1.0
9	No solvent	5	80	$NaHCO_3$	0.0 : 0.0 : 0.0 : 1.0
10	No solvent	5	rt	$NaHCO_3$	1.0 : 0.0 : 0.0 : 0.0
11	0.8	5	50	KH_2PO_4	5.0 : 0.0 : 1.0 : 0.0
12	0.8	5	80	KH_2PO_4	2.5 : 0.0 : 1.0 : 0.0

Table 2.10: Attempted optimisation of 2-allyl benzoic acid **1.15**

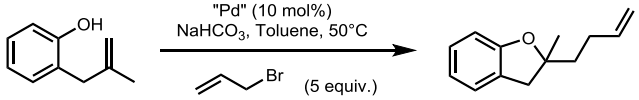
In summary, attempts to extend the oxyallylation reaction to the synthesis of lactones starting from a *mono*-substituted alkene, in good yield, have proved challenging. The desired 5- and 6-membered lactones suffered from poor conversion in some cases, or the predominant reaction pathway forming unwanted side products. Attempts to redirect the reaction pathway towards synthesising the oxyallylated lactone products in a synthetically viable yield have, thus far, remained elusive. Changes in temperature, catalyst, base allyl halide, concentration and the addition of additives have proved unsatisfactory.

2.2 Enantioselective Oxyallylation Reaction of Unactivated Alkenes

2.2.1 *Gem*-disubstituted Alkene Substrates

The ability for chemists to control which enantiomer the reaction performed within the laboratory will produce is highly advantageous. A large number of natural products[94] and pharmaceuticals[95] contain stereogenic centres, which are often enantioselectively placed in the molecule through transition metal chemistry, with the use of chiral ligands.[96]

For the optimised racemic palladium(II)-catalysed oxyallylation reaction, the catalyst employed was palladium(II) hexafluoroacetylacetonate. Early investigations conducted within the France group revealed that varying the $Pd(hfacac)_2$ catalyst in the oxyallylation reaction of alcohols had a detrimental effect on the conversion to the desired oxyallylation product (Table 2.11).[97]



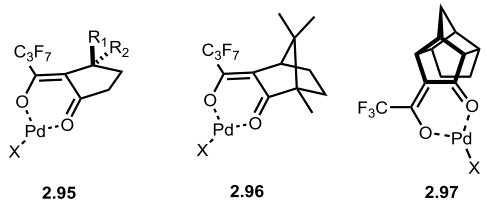
1.83 **2.16**

Entry	"Pd"	Time	Result[a] 1.83 : 2.16
1	$Pd(hfacac)_2$	16 h	0 : 1
2	$Pd(OAc)_2$	22 h	1 : 0.05
3	$Pd(acac)_2$	22 h	1 : 0.1
4	$Pd(TFA)_2$	22 h	1 : 0
5	$PdCl_2$	28 h	1 : 2
6	Pd_2dba_3	18 h	1 : 0

[a]Approximate ratio of **1.83 : 2.16** based on ^{1}H NMR spectroscopy of unpurified reaction mixture

Table 2.11: Previous Pd catalyst screen in the oxyallylation optimisation[97]

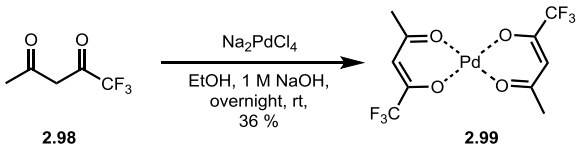
Based on the results above, it was believed that the electronics of the $Pd(hfacac)_2$ play an integral role. In order to make an enantioselective variant of the reaction, it was hypothesised thatchiral catalysts with similar electronics were required (Figure 2.3).[98]



2.95 **2.96** **2.97**

Figure 2.3: Potential Pd(II) chiral catalysts

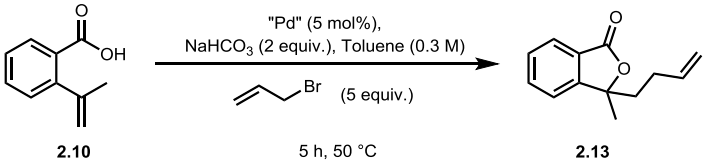
As can be seen above (Figure 2.3), both of the ligands on the palladium(II) centre only have one fluorinated electron-withdrawing group, as opposed to the two on the $Pd(hfacac)_2$ catalyst. Due to the change in electronics, an achiral variant was synthesised in order to test for reactivity in the oxyallylation reaction (Scheme 2.41). Na_2PdCl_4 was added to a solution of dione **2.98** in EtOH and 1 M aq. NaOH and was left to stir overnight at room temperature and afforded the desired palladium(II) trifluoroacetylacetonate catalyst [$Pd(tfacac)_2$] **2.99** in a 36% yield.



2.98 **2.99**

Scheme 2.41: Synthesis of $Pd(tfacac)_2$ **2.99**

The reactivity of $Pd(tfacac)_2$ **2.99** was investigatedwith the benzoic acid substrate **2.10** (Table 2.12, entry 1). Utilising $Pd(tfacac)_2$ successfully resulted in the complete conversion of the starting material to the desired oxyallylated lactone **2.13**. In order to determine whether traces of Na_2PdCl_4 in the newly synthesised $Pd(tfacac)_2$ could catalyse the reaction Na_2PdCl_4 was employed as the catalyst in the oxyallylation reaction (entry 2). Again,this resulted in the complete conversion of starting material. Benzoic acid **2.10** was treated with $Pd(OAc)_2$, $Pd(acac)_2$, $Pd(TFA)_2$ and $PdCl_2$. Irrespective of catalyst employed, it culminated in complete conversion of benzoic acid **2.10** (Table 2.12, entries 3 − 6). Surprised by the reactivity of the benzoic acid substrate **2.10**, when compared to the phenol (Table 2.11), the oxyallylation was attempted with no palladium source in the reaction mixture (entry 7). As expected, no desired lactone was observed *via* ^1H NMR of the crude material.



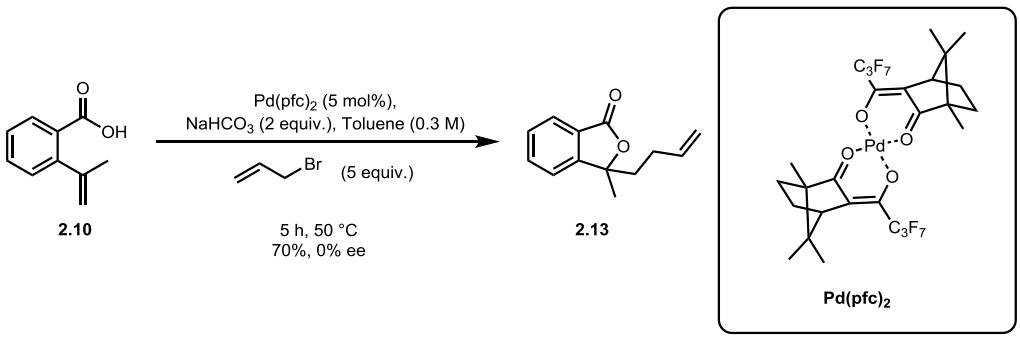
2.10 **2.13**

Entry	"Pd"	Result[a] 2.10 : 2.13
1	$Pd(tfacac)_2$ **2.99**	0 : 1
2	Na_2PdCl_4	0 : 1
3	$Pd(OAc)_2$	0 : 1
4	$Pd(acac)_2$	0 : 1
5	$Pd(TFA)_2$	0 : 1
6	$PdCl_2$	0 : 1
7	No catalyst	1 : 0

[a]Approximate ratio of **2.10 : 2.13** based on ^{1}H NMR spectroscopy of unpurified reaction mixture

Table 2.12: Pd catalyst screen for benzoic acid **2.10**

The high reactivity of the benzoic acid substrate **2.10** in the oxyallylation reaction led to the belief that it would be ideal for developing the enantioselective version. From a previous project within the France group, a palladium(II) perfluoro camphor catalyst [$Pd(pfc)_2$] was synthesised (Scheme 2.43). Due to the similar electronics and the success of both $Pd(hfacac)_2$ and $Pd(tfacac)_2$ catalysts, it was reasoned that $Pd(pfc)_2$ could be employed as a chiral catalyst for the enantioselective oxyallylation reaction. Under standard oxyallylation reaction conditions in the synthesis of lactone **2.13** the reaction proceeded well, yielding the desired lactone in a 70% yield. However, no enantioselectivity was observed (Scheme 2.42).

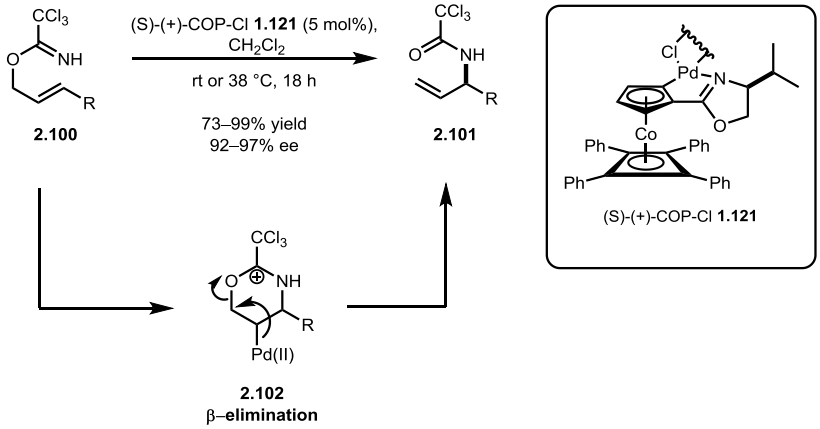


2.10 **2.13**

Scheme 2.42: Attempted enantioselective oxyallylation reaction with $Pd(pfc)_2$ catalyst

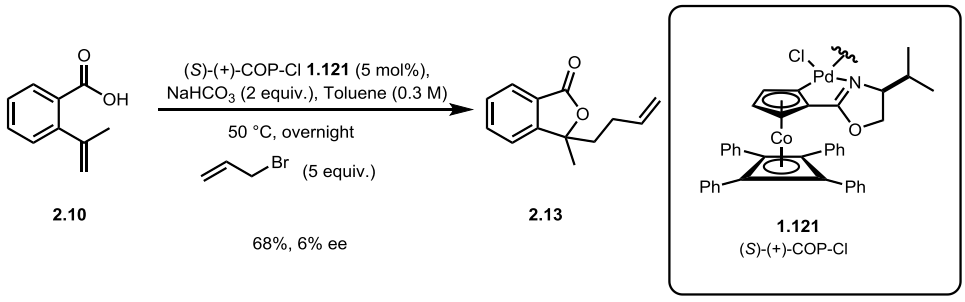
The [3,3]-sigmatropic rearrangement, otherwise known as the Overman rearrangement, of allylic trichloroacetimidates **2.100** by the palladium(II) catalyst (*S*)-(+)-COP-Cl **1.121** exhibits high enantioselectivity and yields (Scheme 2.43). Its relevance to the palladium(II)-catalysed oxyallylation reaction stems from the reaction mechanism, which

also proceeds through an isohypsic mechanism *via* a β-elimination pathway. Additionally, (*S*)-(+)-COP-Cl **1.121** is commercially available making it readily available for testing.



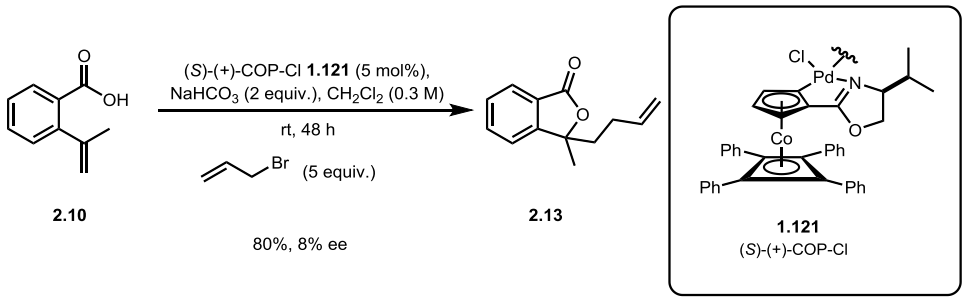
Scheme 2.43: Overman rearrangement with (*S*)-(+)-COP-Cl **1.121**

The mechanistic similarities between the oxyallylation and Overman rearrangement led to the belief (*S*)-(+)-COP Cl **1.121** would be an ideal catalyst for the creation of the enantioselective oxyallylation reaction.[64, 99] The yields when using (*S*)-(+)-COP Cl **1.121** as a catalyst were good; however, the enantioselectivity was poor at a lowly 6% (Scheme 2.44). The temperature of the reaction was decreased to room temperature, however, no conversion of the starting material was observed. Furthermore, (*S*)-(+)-COP-Cl **1.121** was filtered through a silica plug to purify, prior to use; however, no improvement to the enantioselectivity was observed. Although variants of the catalyst are available, where the chloride is replaced with another ligand, their purchase or synthesis was not pursued.[100]



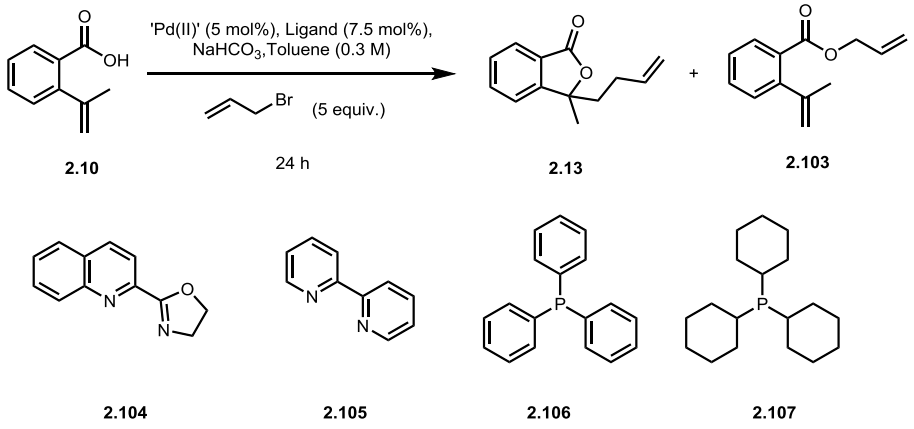
Scheme 2.44: Oxyallylation with (*S*)-(+)-COP-Cl **1.121**

The success of the Overman rearrangement in CH_2Cl_2 at room temperature prompted the enantioselective oxyallylation to be attempted under similar conditions (Scheme 2.45). Varying the solvent and lowering the temperature had a negligible effect on the enantioselectivity, as it was only increased slightly.



Scheme 2.45: Similar conditions to the Overman rearrangement

With the lack of success using palladacycle (*S*)-(+)-COP Cl **1.121**, more traditional routes such as a Pd(II) salt plus ligand were sought. Previous studies conducted within the France group, in the optimisation of the palladium(II)-catalysed oxyallylation of alcohols with ligands, revealed that the presence of nitrogen and phosphine based ligands had a deleterious effect on the conversion of starting material. Hitherto, the effect of ligands on the oxyallylation reaction of carboxylic acids was unknown. With palladium(II) chloride as the catalyst, nitrogen based quinox **2.104** and bipyridine **2.105** ligands were screened (Table 2.13, entries 1 and 2). Mixed results were observed with the quinox ligand **2.104** resulting in formation of the desired product and bipyridine **2.105** retarding the formation of desired lactone **2.13**. The temperature was increased from 50 °C to 80 °C due to low conversion of the starting material; however, this resulted in an increase in the formation of *O*-allylated side product **2.103**. Next, phosphorous based ligands were investigated as they are used ubiquitously in metal-catalysed reactions. Again, mixed results were observed, with triphenylphosphine **2.106** resulting in small formation of the desired product and tricyclohexylphosphine **2.107** retarding the formation of desired lactone **2.13** (entries 3 and 4). The temperature was increased from 50 °C to 80 °C due to low conversion of the starting material; however, this resulted in an increase in the formation of *O*-allylated side product **2.103**. Finally, to determine the effect of catalyst/ligand combination, $Pd(TFA)_2$/Bipyridine **2.105** was investigated. Bipyridine **2.105** was chosen as the ligand as it garnered none of the desired lactone **2.13**. Interestingly, improvements were observed, with some oxyallylated product **2.13** formed. Low conversion again led to the increase in temperature, however, again this resulted in an increase in *O*-allylated side product **2.13** (entry 5).

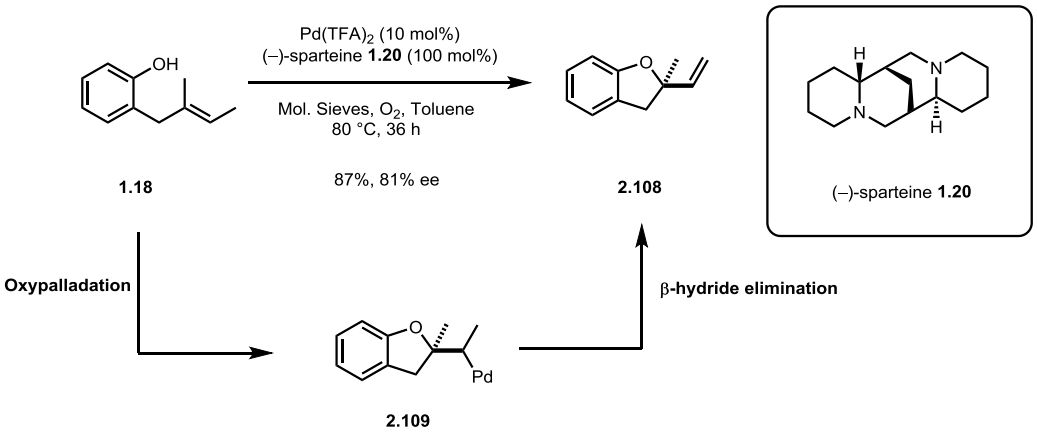


Entry	Pd/ Ligand	Temp. (°C)	Result 2.13 : 2.103
1	$PdCl_2$/Quinox **2.104**	50 then 80	1.0 : 1.3
2	$PdCl_2$/Bipyridine **2.105**	50 then 80	0.0 : 1.0
3	$PdCl_2/PPh_3$ **2.106**	50 then 80	1.0 : 5.6
4	$PdCl_2/PCy_3$ **2.107**	50 then 80	0.0 : 1.0
5	$Pd(TFA)_2$/Bipyridine **2.105**	50 then 80	1.0 : 1.3

[a]Approximate ratio of **2.10 : 2.13** based on ^{1}H NMR spectroscopy of unpurified reaction mixture

Table 2.13: Achiral ligand screen

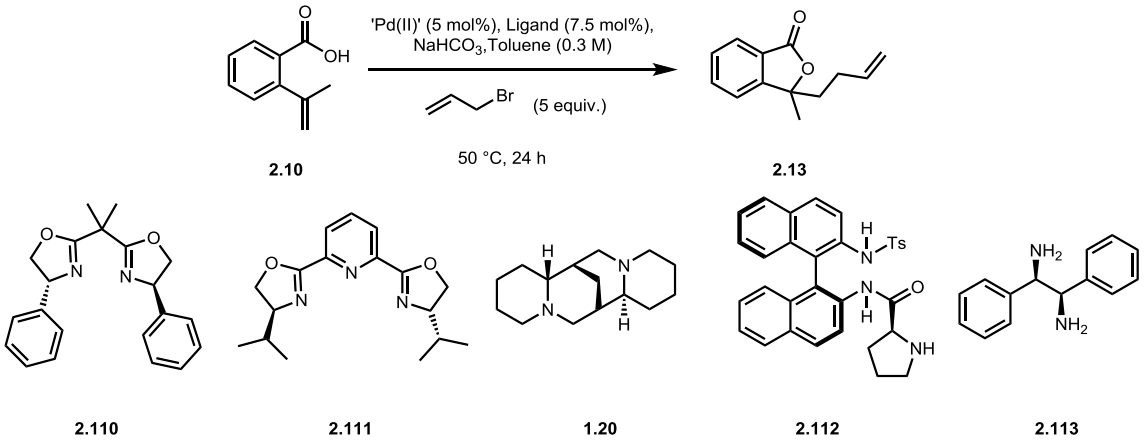
A literature example by Stoltz and co-workers employed conditions remarkably similar to those developed for the oxyallylation reactions, and represents an ideal precedent (Scheme 2.45).[23] Additionally, Stoltz *et al.* reported that a change in palladium salt had a dramatic effect on the enantioselectivity.



Scheme 2.45: Asymmetric oxypalladation reaction using (−)-sparteine **1.20**

Initially, $Pd(TFA)_2$ was chosen as a suitable catalyst to screen ligands with because it catalysed the achiral oxyallylation reaction of benzoic acid **2.10**, with complete consumption of starting material, and is most electronically similar to $Pd(hfacac)_2$.

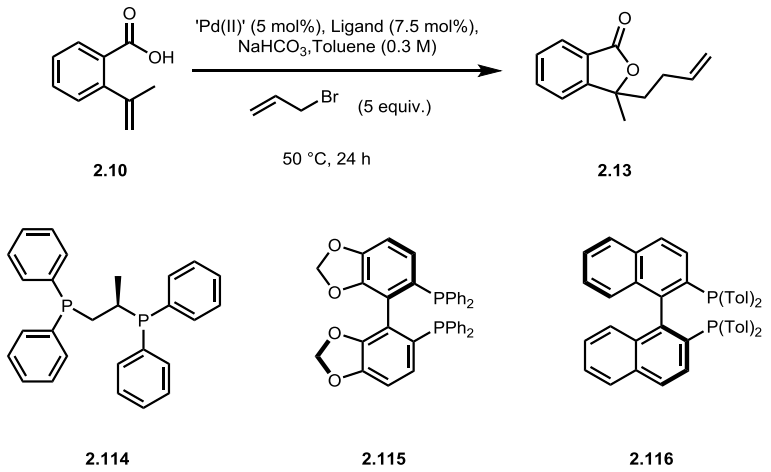
Additionally, it is commonly used in asymmetric oxypalladation reactions as the palladium catalyst.[18c] Many ligands were screened when using benzoic acid **2.13** as the substrate (Table 2.14). The initial bidentate nitrogen ligand screen was relatively unsuccessful. Bisoxazoline **2.110**, pyBOX **2.111** and (−)-sparteine **1.20** all resulted in no conversion to the desired lactone (entries 1 – 3). (*S*)-BINAM **2.112** did result in a 10% yield; however no enantioselectivity was induced by the ligand (entry 4). Because the use of (*S*)-BINAM **2.112** ligand garnered some of the desired lactone **2.13**, a different catalyst was attempted in the hope it would improve the result. A combination of $Pd(OAc)_2$/(*S*)-BINAM **2.112** resulted in an 81% yield of racemic lactone **2.13** (entry 5). The diamine ligand **2.113** afforded enantioenriched product in a 10% ee (entry 6). With this as the best result, the catalyst was then varied to $Pd(OAc)_2$ and $PdCl_2$. However, no product was detected when the catalyst was varied from $Pd(TFA)_2$ (entries 6 and 7).



Entry	Catalyst/Ligand	Result (2.13)
1	$Pd(TFA)_2$/bisoxazoline **2.110**	Not Detected
2	$Pd(TFA)_2$/pyBOX **2.111**	Not Detected
3	$Pd(TFA)_2$/(−)-sparteine **1.20**	Not Detected
4	$Pd(TFA)_2$/(*S*)-BINAM **2.112**	10%, 0% ee
5	$Pd(OAc)_2$/(*S*)-BINAM **2.112**	81%, 0% ee
5	$Pd(TFA)_2$/diamine **2.113**	5%, 10% ee
6	$Pd(OAc)_2$/diamine **2.113**	Not Detected
7	$PdCl_2$/diamine **2.113**	Not Detected

Table 2.14: Bidentatenitrogen ligand screen

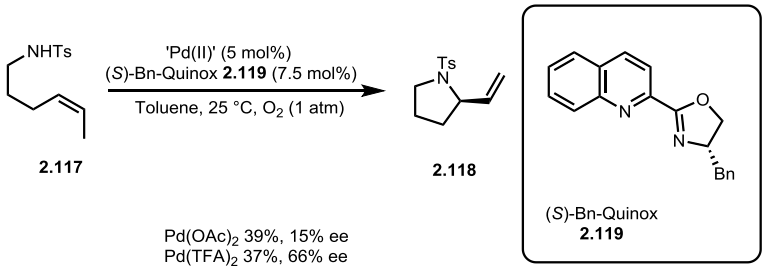
Concurrently, the palladium-catalysed oxyallylation reactions with chiral bidentate phosphine ligands were performed. The addition of dppe **2.114**, and bisphosphine **2.115** resulted in no formation of the desired lactone **2.13** (Table 2.15, entry 1 and 2). Utilising (*S*)-T-BINAP **2.116**, afforded the desired lactone in an 81% yield, albeit as a racemic mixture (entry 3).



Entry	Catalyst/ Ligand	Result (2.13)
1	$Pd(TFA)_2$/ dppe **2.114**	Not Detected
2	$Pd(TFA)_2$/ bisphosphine **2.115**	Not Detected
3	$Pd(TFA)_2$/ (*S*)-T-BINAP **2.116**	81%, 0% ee

Table 2.15: Bidentatephosphine ligand screen

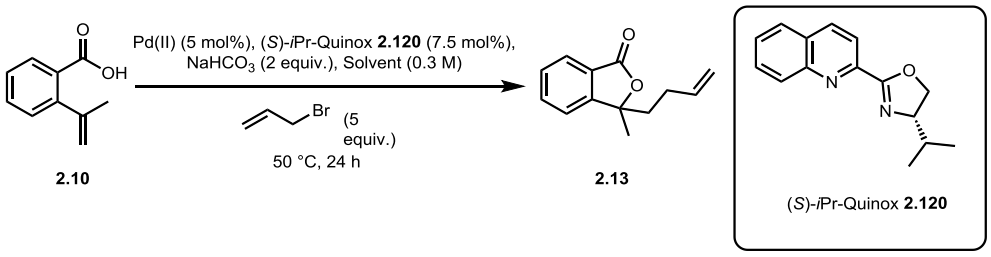
Stahl and co-workers have successfully used quinox ligands in enantioselective aminopalladation reactions with conditions similar to the oxypalladation reaction. Herein, they report that a change in the palladium(II)-catalyst has a dramatic effect on the enantioselectivity (Scheme 2.46). A variant of the ligand seen below was chosen as a ligand to begin screening conditions as it is 1) commercially available and 2) the same ligand class Stahl *et al*. reported as the starting point to developing their aminopalladation reaction enantioselectively.[101]



Scheme 2.46: Aminopalladation with Quinox **2.119** as ligand

Based on the Stahl publications, the catalyst was varied (Table 2.16). Initial investigations provided an encouraging result (Table 2.16, entry 1). Changing the catalyst of the reaction (entries 2 – 6) all yielded the desired product **2.13**. For the most part, no major improvement in the enantioselectivity was observed, with the largest increase being the use of $Pd(OAc)_2$ and the biggest decrease being the use of $PdCl_4Na_2$ as catalyst (entries 4 and 6 respectively). A change of solvent to CH_2Cl_2, resulted in no improvement in enantioselectivity (entries 7 – 10) and in the $Pd(TFA)_2$ and $PdCl_2$ examples, the Pd(II) salts

afforded the racemic product (entries 9 and 10). Finally, the most successful reaction using $Pd(OAc)_2$ as the catalyst was next repeated at room temperature and allowed to stir for 7 days (entry 11). Unfortunately, the decrease in temperature did not result any increase in enantioselectivity or yield.

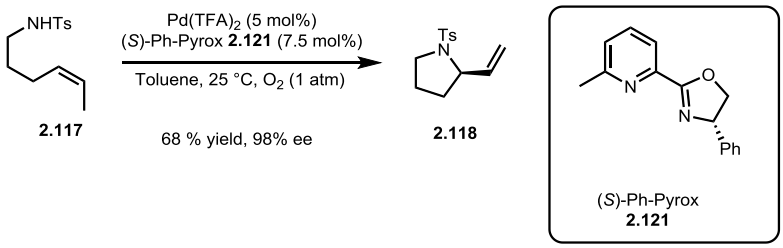


Entry	Catalyst	Solvent	Result (2.13)
1	$Pd(TFA)_2$	Toluene	9%, 9% ee
2	$PdCl_2$	Toluene	21%, 9% ee
3	$Pd(hfacac)_2$	Toluene	3%, 7% ee
4	$Pd(OAc)_2$	Toluene	9%, 18% ee
5	$Pd(O_3STol)_2(MeCN)_2$	Toluene	10%, 11% ee
6	$PdCl_4Na_2$	Toluene	4%, 0% ee
7	$Pd(OAc)_2$	CH_2Cl_2	7%, 18% ee
8	$Pd(O_3STol)_2(MeCN)_2$	CH_2Cl_2	6%, 9% ee
9	$Pd(TFA)_2$	CH_2Cl_2	20%, 0% ee
10	$PdCl_2$	CH_2Cl_2	53%, 0% ee
11*	$Pd(OAc)_2$	Toluene	9%, 16% ee

*r.t. 7 days

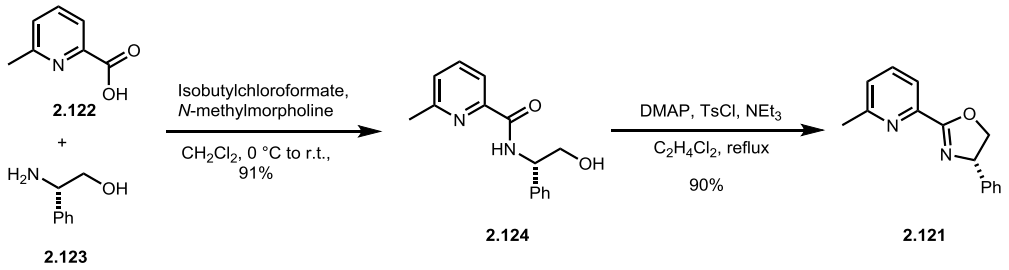
Table 2.16: Oxyallylation reaction with (*S*)-*i*Pr-Quinox ligand **2.120**

Stahl and co-workers also reported a dramatic increase in enantioselecitivity when (*S*)-Ph-Pyrox ligand **2.121** was used in place of a quinox ligand (Scheme 2.47).[101a] Based on the results gathered (Table 2.16) and the precedent set by the Stahl group, it was believed that a change in ligand might give a similar increase in enantioselectivity.



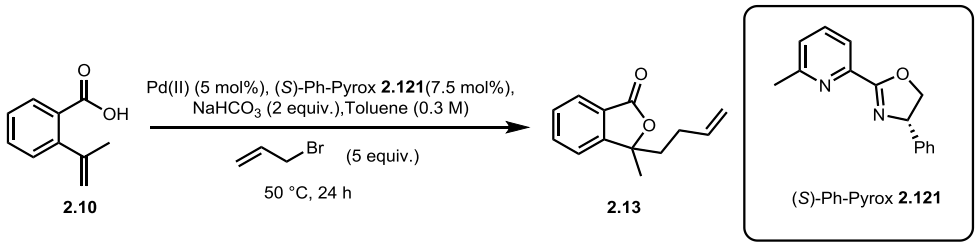
Scheme 2.47: Use of (*S*)-Ph-Pyrox ligand **2.121** in aminopalladation reactions

As the (*S*)-Ph-Pyrox ligand **2.121** is not commercially available, its synthesis was required (Scheme 2.48). The first step was the coupling of picolinic acid **2.122** and (*S*)-(+)-2-phenylglycinol **2.123**, which reacted to yield the amide product **2.124** in 91% yield. Tosylation of the primary alcohol **2.124** induced an intramolecular nucleophilic attack on the now activated alcohol. This resulted in the closing of the oxazoline ring to give (*S*)-Ph-Pyrox **2.121** in a 90% yield.[101a]



Scheme 2.48: Synthesis of (*S*)-Ph-Pyrox **2.121**

With ligand **2.121** in hand, screening of the ligand with palladium(II)-catalysts was subsequently undertaken (Table 2.17). Starting with $Pd(OAc)_2$, which previously gave the best result, using (*S*)-*i*Pr-Quinox **2.120** as the ligand, provided no enantioselectivity (Table 2.17, entry 1). Further screening resulted in lower ee's than was hoped, with $Pd(TFA)_2$ yielding no desired lactone **2.13** (entry 2). Next, $PdCl_2$ and $Pd(O_3STol)_2(MeCN)_2$ when employed as the catalyst gave poor enantioselectivity with 6% ee and 3% ee respectively (entries 3 and 4).

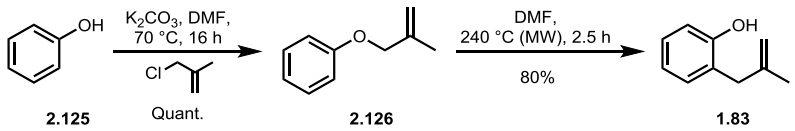


Entry	Catalyst	Result (2.13)
1	$Pd(OAc)_2$	16%, 0% ee
2	$Pd(TFA)_2$	Not detected
3	$PdCl_2$	32%, 6% ee
4	$Pd(O_3STol)_2(MeCN)_2$	15%, 3% ee

Table 2.17: Screening of catalysts with (*S*)-Ph-Pyrox **2.121**

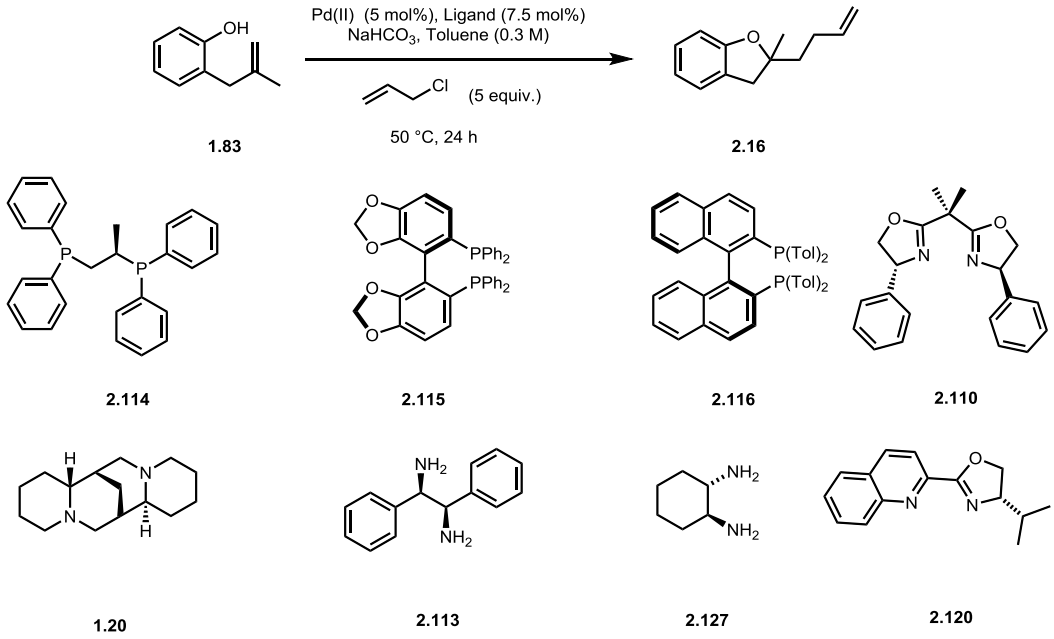
The lack of success with benzoic acid **2.10** led to the investigation of other possible enantioselective oxyallylation reactions. Following a literature procedure, phenol substrate **1.83** was synthesised in two steps by reacting phenol **2.125** with 2-methylallyl chloride, which generates allylated intermediate **2.126** in quantitative yield (Scheme 2.49).[44] Next,

compound **2.126** undergoes a thermally induced Claisen reaction, performed in the microwave, to give 2-(2-methylallyl)phenol **1.83** in 80% yield.



Scheme 2.49: Synthesis of 2-(2-methylallyl)phenol **1.83**

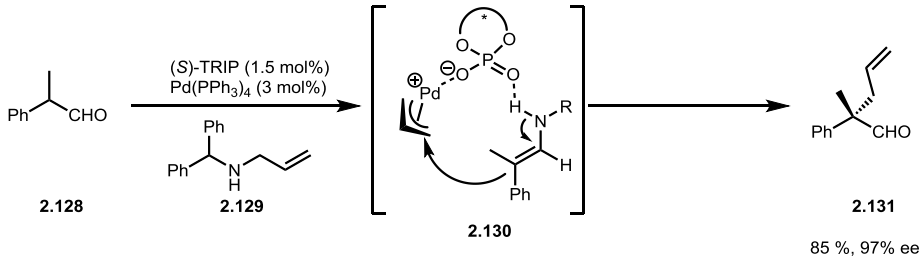
With the substrate synthesised, potential asymmetric heterocyclisation of phenol **1.83** was also examined. $PdCl_2$ was chosen as the catalyst; previous screening experiments performed within the France group showed $PdCl_2$ was the second best catalyst for the racemic oxyallylation reaction, second only to $Pd(hfacac)_2$. Both palladium(II) catalysts ligands were then screened (Table 2.18). Unfortunately, addition of a bidentate phosphine or nitrogen ligand to the reaction, with palladium(II) chloride as the catalyst, resulted in no conversion of starting material and prevented conversion to the desired benzofuran **2.16** (entries 1 – 7). Only the use of (*S*)-*i*Pr-Quinox **2.120** as the ligand afforded any benzofuran **2.16**. Disappointingly, benzofuran **2.16** was a racemic mixture (entry 8). A brief screen using a different Pd(II)-catalyst was undertaken in the hope of improving reactivity and enantioselectivity (entries 8 – 11). As can be seen below, the change of catalyst had no desirable effect on the reaction; no desired benzofuran **2.16** was detected by ^{1}H NMR of the crude mixture.



Entry	Catalyst	Ligand	Result (2.16)
1	$PdCl_2$	dppe **2.114**	Not Detected
2	$PdCl_2$	diphosphine **2.115**	Not Detected
3	$PdCl_2$	(*S*)-T-BINAP **2.116**	Not Detected
4	$PdCl_2$	Bisoxazoline **2.110**	Not Detected
5	$PdCl_2$	(−)-sparteine **1.20**	Not Detected
6	$PdCl_2$	diamine **2.113**	Not Detected
7	$PdCl_2$	cyclohexyl diamine **2.127**	Not Detected
8	$PdCl_2$	(*S*)-*i*Pr-Quinox **2.120**	7%, 0% ee
9	$Pd(hfacac)_2$	Diphosphine **2.115**	Not Detected
10	$Pd(hfacac)_2$	bisoxazoline **2.110**	Not Detected
11	$Pd(hfacac)_2$	(*S*)-*i*Pr-Quinox **2.120**	Not Detected

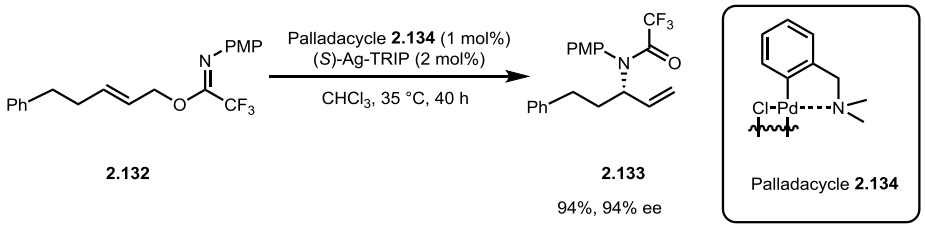
Table 2.18: Ligand screen with phenol **1.83**

Conventional methods of inducing enantioselectivity in the oxyallylation reaction, using chiral ligands co-ordinated to the metal, were proving fruitless. As a result, an alternative method was sought.[102] Recent literature has reported the use of chiral phosphoric acids, which can induce asymmetry through hydrogen bonding. An elegant example is by List and co-workers using chiral phosphoric acids in the Tsuji–Trost reaction (Scheme 2.50).[103] The hypothesis behind the use of a chiral phosphoric acid to induce enantioselectivity was that the reaction in question proceeds through a π-allyl cationic intermediate **2.130**, whereby the phosphate would form the counter-anion. The intermediate **2.130** is proposed to hydrogen bond to the substrate. This assembly resulted in the synthesis of many α-branched aldehydes like **2.131**, forming quaternary centres stereoselectively with high enantioselectivity.



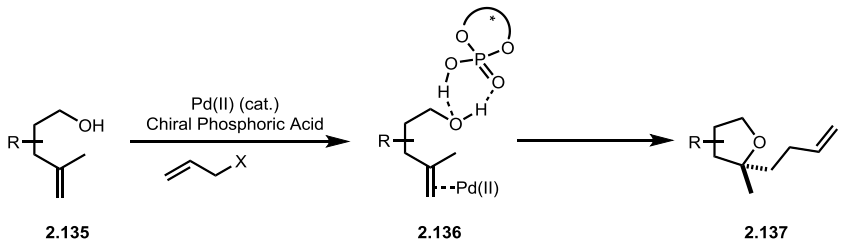
Scheme 2.50: Stereoselective Tsuji–Trost reaction utilising a chiral phosphoric acid

Another elegant example, developed by List and co-workers, is the enantioselective Overman rearrangement (Scheme 2.51).[104] Interestingly, it was discovered (through an X-ray crystal structure of the catalyst) that the chiral phosphate actually acts as a chiral ligand and not a chiral counter-ion. As a chiral ligand it gave excellent yields and enantioselecivities in conjunction with an achiral palladacycle **2.134**.



Scheme 2.51: Chiral phosphoric acids used as chiral ligands

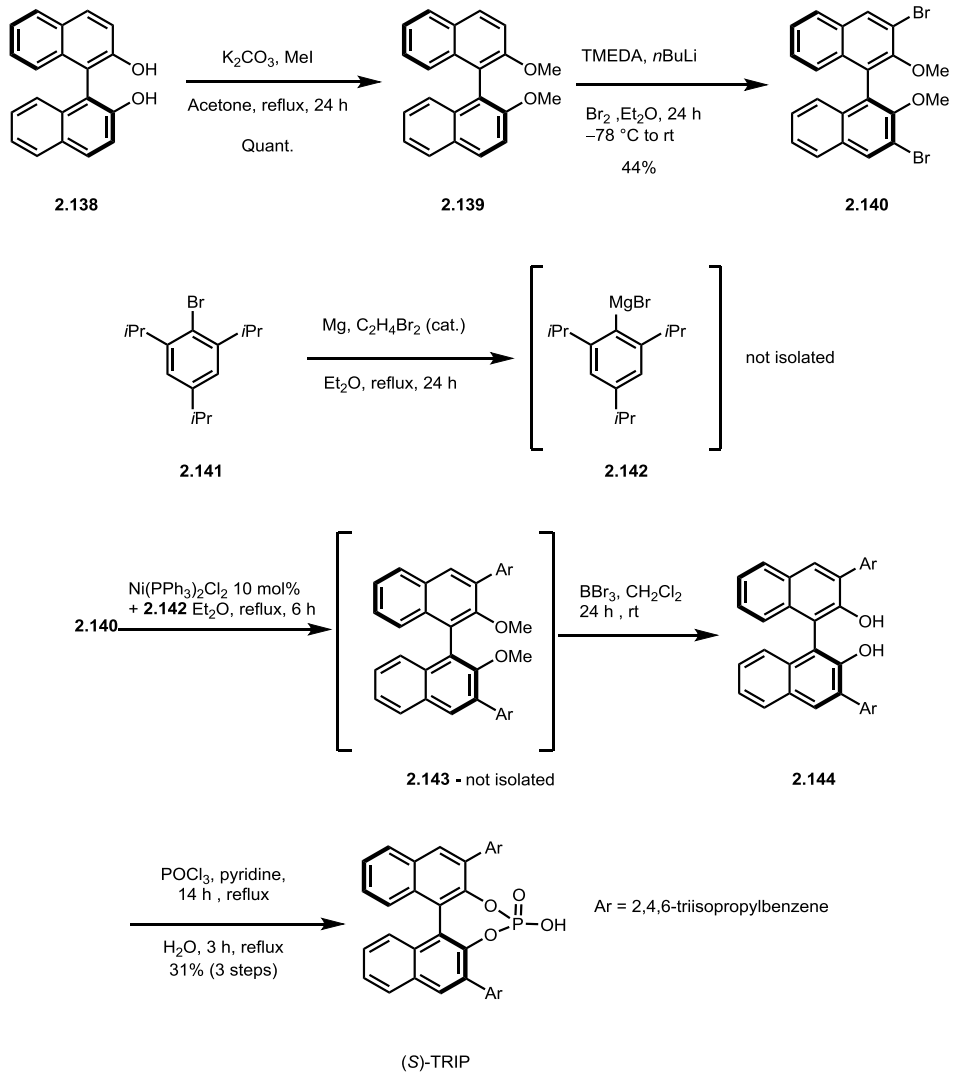
Investigations thus far have revealed that the addition of a ligand to the palladium(II)-catalysed oxyallylation reaction has adverse and unfavourable effects. Based on the reports by List and co-workers and the reports of others,[105] the aim was to develop an asymmetric cooperative catalytic oxyallylation reaction, through the use of chiral phosphoric acids (Scheme 2.52). It is hypothesised that through hydrogen bonding an asymmetric oxypalladation reaction would ensue, leading to an enantioenriched product.



Scheme 2.52: Proposed oxyallylation with chiral phosphoric acids

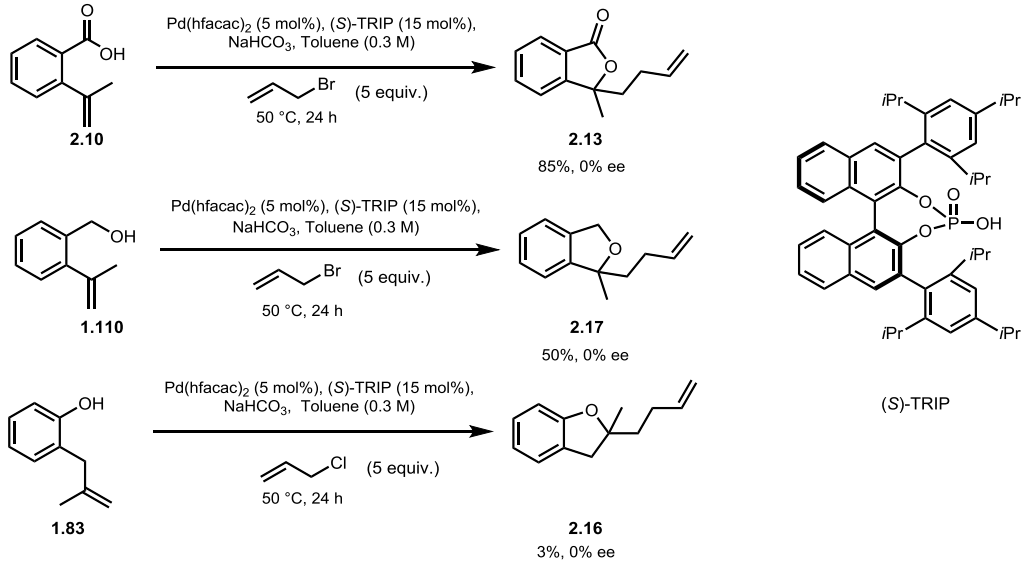
With the potential of chiral phosphoric acids to induce enantioselectivity, the aim was to synthesise the most commonly used chiral phosphoric acid, (*S*)-TRIP.[106] Synthesis began by protection of the BINOL **2.138** with methyl iodide, which gave dimethylated product **2.139** in a quantitative yield (Scheme 2.53). Next, with the addition of *n*BuLi, lithiation occurred ortho to both methoxy groups. With the addition of bromine, compound **2.140**

was synthesised in a modest yield of 44%. The nickel-catalysed Kumada coupling between dibrominated compound **2.140**, and the freshly synthesised Grignard reagent **2.142** proceeded well to afford compound **2.143**, which was not purified and was subjected to the next step. Deprotection of the hydroxyl groups using BBr_3 garnered **2.144**, which again was not purified. The resulting diol **2.144** is then reacted with $POCl_3$ and hydrolysed. The resulting solid is recrystallised from MeCN, which gave (*S*)-TRIP in 31% yield over 3 steps (Scheme 2.53).



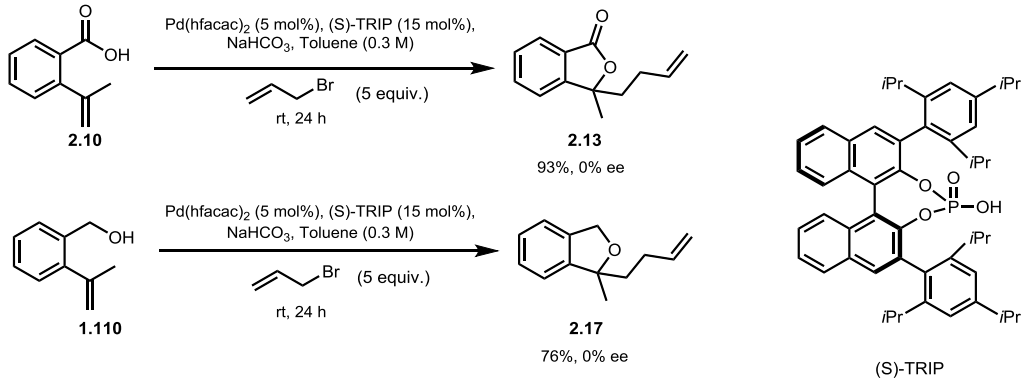
Scheme 2.53: Synthesis of (*S*)-TRIP

With the synthesis of (*S*)-TRIP, the usual substrates were initially subjected to the standard palladium(II)-catalysed oxyallylation reaction conditions for substrates: benzoic acid **2.10**, phenol **1.83** and benzylic alcohol **1.110** (Scheme 2.54). Benzoic acid **2.10** and benzylic alcohol **1.110** both underwent the oxyallylation reaction and generated their respective products in good yields. Conversely, the oxyallylation reaction of phenol **1.83** proceeded poorly, and only gave the benzofuran **2.16** in a 3% yield. All reactions only afforded racemic products with no enantioselectivity was observed.



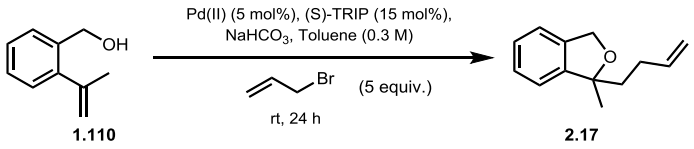
Scheme 2.54: Use of (*S*)-TRIP in oxyallylation reactions at 50 °C

As enantioselectivity was not induced by the phosphoric acid at 50 °C it was decided that the reaction temperature would be decreased to room temperature. Yields for the reaction both increased in the synthesis of lactone **2.10** and isobenzofuran **2.17**. However, enantioselectivity was not induced by (*S*)-TRIP as only racemic mixtures were isolated (Scheme 2.55). It must be noted, that without the use of (*S*)-TRIP both reactions gave poor conversion of their respective starting materials when the reaction is performed at room temperature.



Scheme 2.55: Use of (*S*)-TRIP in oxyallylation reactions at room temperature

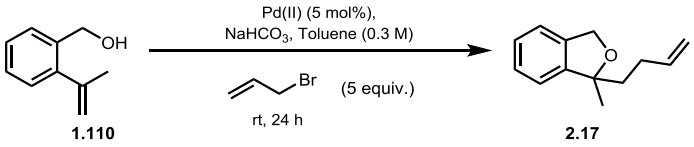
The addition of (*S*)-TRIP with $Pd(hfacac)_2$ does not give any of the the enantioenriched isobenzofuran **2.17**. It was hypothesised that a change in the palladium(II)-catalyst could improve the enantioselectivity, whilst keeping the reaction mixture at room temperature. Unfortunately, with a change in catalyst from the standard $Pd(hfacac)_2$ (Table 2.19, entry 1) to $Pd(OAc)_2$ and $Pd(TFA)_2$, the product **2.17** was still racemic (entries 2 and 3).



Entry	Catalyst	Result (2.17)
1	$Pd(hfacac)_2$	76%, 0% ee
2	$Pd(TFA)_2$	55%, 0% ee
3	$Pd(OAc)_2$	74%, 0% ee

Table 2.19: Catalyst screen with (*S*)-TRIP

Interestingly, when benzylic alcohol **1.110** was reacted with either $Pd(OAc)_2$ or $Pd(TFA)_2$ with no catalytic (*S*)-TRIP in the reaction mixture at room temperature, incomplete conversion of starting material to the desired isobenzofuran **2.17** occurs (Table 2.20, entries 1 and 3). When (*S*)-TRIP was added, complete conversion to the desired isobenzofuran **2.17** is observed *via* ^{1}H NMR of the crude mixture (entries 2 and 4). With these observations, it is clear that the addition of 15 mol% of (*S*)-TRIP, is having a catalytic effect on the reaction and cooperative catalysis is occurring, albeit not enantioselectively. To prove that (*S*)-TRIP is not catalysing the reaction on its own a reaction without palladium was performed, and only returned starting material (entry 5).

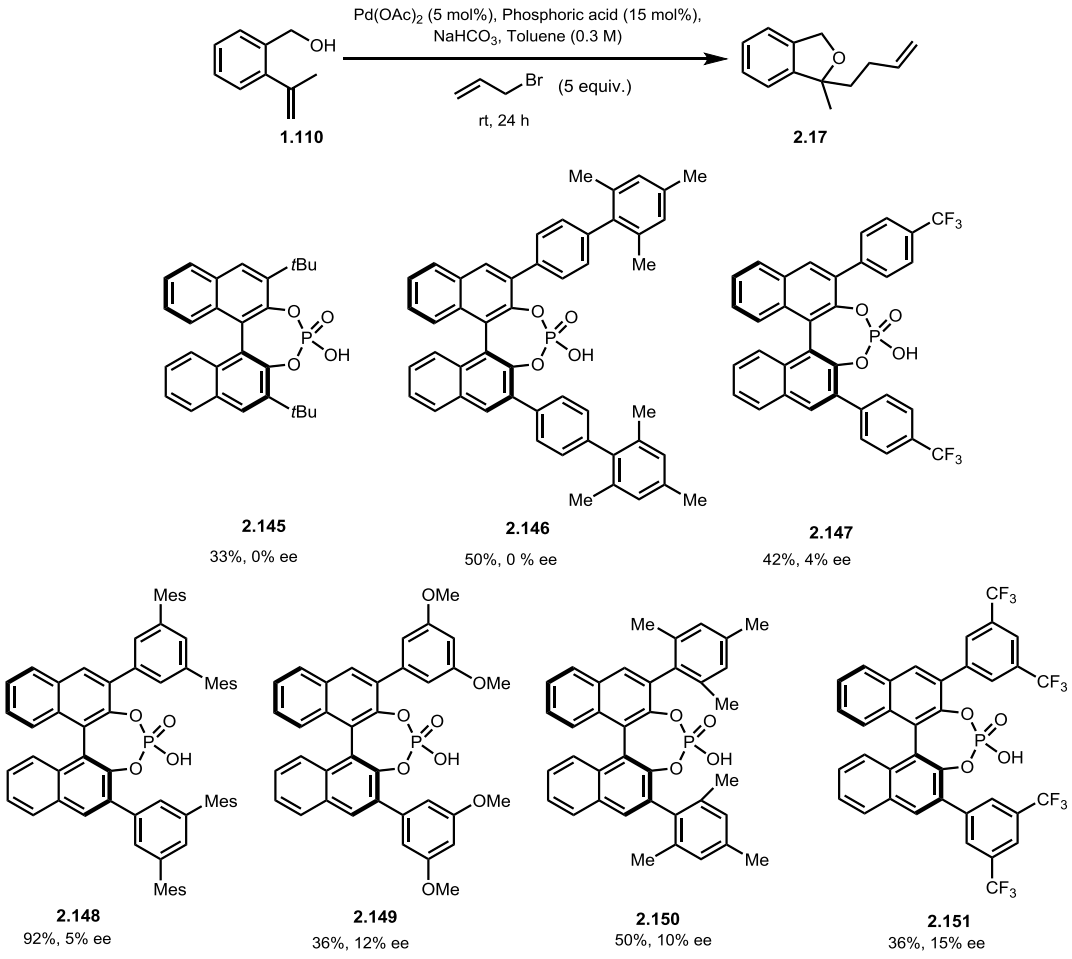


Entry	Catalyst	(*S*)-TRIP (15 mol%)	Result 1.110 : 2.17
1	$Pd(OAc)_2$	None	1 : 1.8
2	$Pd(OAc)_2$	Yes	0 : 1
3	$Pd(TFA)_2$	None	1 : 2
4	$Pd(TFA)_2$	Yes	0 : 1
5	-	Yes	1 : 0

Table 2.20: Effect of (*S*)-TRIP of the conversion of starting material **1.110**

Thus far, very little success in developing a highly enantioselective palladium(II)-catalysed oxyallylation reaction of unactivated alkenes had been achieved. With the evident catalytic effect (*S*)-TRIP was having on the reaction it was deemed worthwhile to screen other chiral phosphoric acids, with different bulky groups in the *ortho*-position (Scheme 2.56). Unfortunately, screening different phosphoric acids did not provide much success. Enantioselectivities varied from 0 – 15%. Large bulky *t*Bu phosphoric acid **2.145** and 4-mesityl benzene **2.146** only provided a racemic mixture of isobenzofuran **2.17**. 4-

Trifluoromethyl benzene **2.147** and 3,5-dimesityl benzene **2.148** gave low ee's of 4% and 5% respectively. Although higher enantioselectivities were achieved by 3,5-dimethoxybenzene **2.149**, 2,4,6-trimethyl benzene **2.150** and 3,5-ditrifluoromethyl benzene **2.151**; however, the enantioselectivities observed were still disappointingly low, with ee's of isobenzofuran **2.17** being 12%, 10% and 15% respectively (Scheme 2.56).

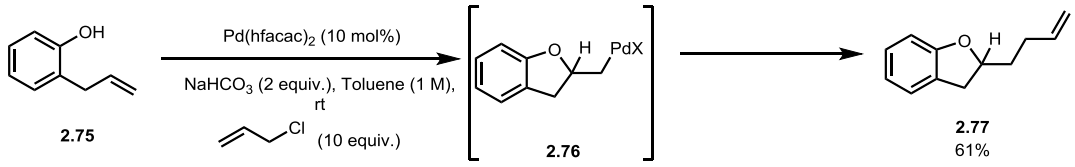


NB- Chiral phosphonic acids kindly donated by the Watson Group, University of Strathclyde

Scheme 2.56: Screening of chiral phosphoric acids

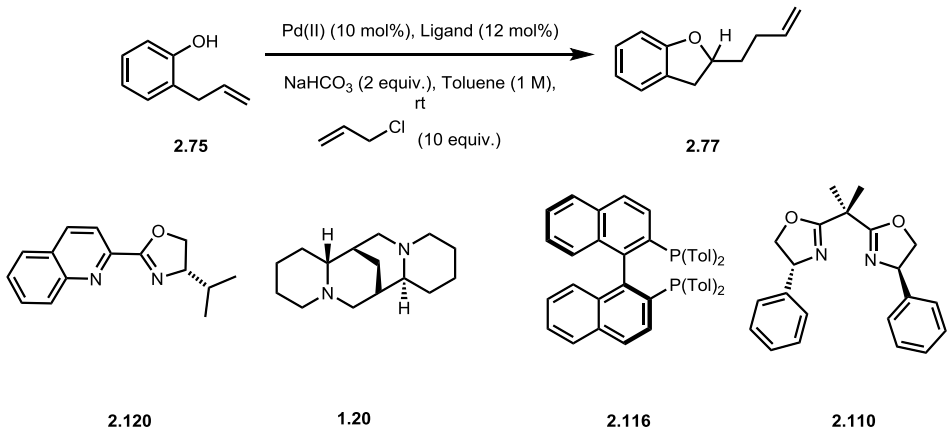
2.2.2 Enantioselective Oxyallylation reaction of *Mono*-substituted Alkenes

The success of the 2-allyl phenol substrate **2.75**, the only *mono*-substituted alkene substrate to undergo the oxyallylation reaction in favourable yields, prompted investigations into the possibility of developing an enantioselective oxyallylation reaction 2-allyl phenol **2.75**. Buoyed by the fact that many asymmetric oxypalladation reactions are known for similar substrates, and actually work better for *mono*-substituted alkenes,it was decided to opt for the traditional ligand plus Pd(II)-catalyst strategy.[18c]



Scheme 2.57: Oxyallylation reaction of 2-allyl phenol **2.75**

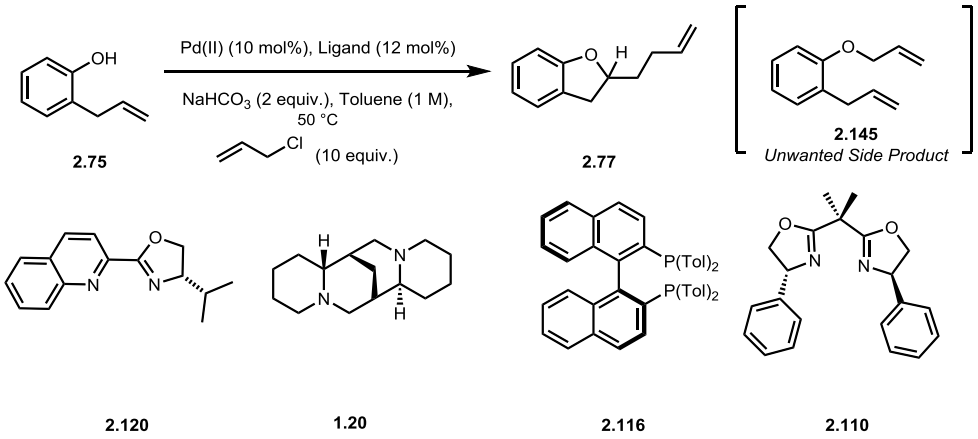
Screening was undertaken with bidentate nitrogen and phosphine ligands such as: (*S*)-*i*Pr-Quinox **2.120**, (–)-sparteine **1.20**, (*S*)-T-BINAP **2.116** and bisoxazoline **2.110** (Table 2.21). The ligands were initially screened against $PdCl_2$, however, no desired product was observed *via* ^{1}H NMR of the crude material (entries 1 – 4). As a result, a change of tactic was employed, in the form of changing the catalyst to $Pd(hfacac)_2$. As before, no product was observed and only starting material was recovered (entries 5 – 8).



Entry	Catalyst/ Ligand	Result 2.75 : 2.77
1	$PdCl_2$/ (*S*)-*i*Pr-Quinox **2.120**	1 : 0
2	$PdCl_2$/ (–)-sparteine **1.20**	1 : 0
3	$PdCl_2$/ (*S*)-T-BINAP **2.116**	1 : 0
4	$PdCl_2$/ bisoxazoline **2.110**	1 : 0
5	$Pd(hfacac)_2$/ (*S*)-*i*Pr-Quinox **2.120**	1 : 0
6	$Pd(hfacac)_2$/ (–)-sparteine **1.20**	1 : 0
7	$Pd(hfacac)_2$/ (*S*)-T-BINAP **2.116**	1 : 0
8	$Pd(hfacac)_2$/ bisoxazoline **2.110**	1 : 0

Table 2.21: Screening of catalyst and ligand at room temperature

The previous reactions were performed at room temperature. However, with no conversion to the desired benzofuran **2.77**, the temperature was increased to 50 °C. The same experiments as before were performed,with the same result (Table 2.22, entries 1 – 8). If the temperature was increased above 50 °C the formation of *O*-allylated side product **2.145** formed preferentially.



Entry	Catalyst/ Ligand	Result 2.75 : 2.77
1	$PdCl_2$/ (*S*)-*i*Pr-Quinox **2.120**	1 : 0
2	$PdCl_2$/ (–)-sparteine **1.20**	1 : 0
3	$PdCl_2$/ (*S*)-T-BINAP **2.116**	1 : 0
4	$PdCl_2$/ bisoxazoline **2.110**	1 : 0
5	$Pd(hfacac)_2$/ (*S*)-*i*Pr-Quinox **2.120**	1 : 0
6	$Pd(hfacac)_2$/ (–)-sparteine **1.20**	1 : 0
7	$Pd(hfacac)_2$/ (*S*)-T-BINAP **2.116**	1 : 0
8	$Pd(hfacac)_2$/ bisoxazoline **2.110**	1 : 0

Table 2.22: Screening of ligands at 50 °C

2.3 Palladium-Catalysed Oxyallylation Conclusions

The oxyallylation project has been divided into three sections: *gem*-disubstituted alkene substrates in the synthesis of lactones, the development of the *mono*-substituted alkene oxyallylation reaction in the synthesis of lactones and the enantioselective oxyallylation reaction. *Gem*-disubstituted substrates undergo the desired heterocyclistaion reaction and could be applied to a range of substrates in good yields (Figure 2.5). Benzoic acids, aliphatic acids, substitution on the aromatic ring as well as large bulky electron donating and electron withdrawing groups on the alkene could all be tolerated under the optimised conditions.

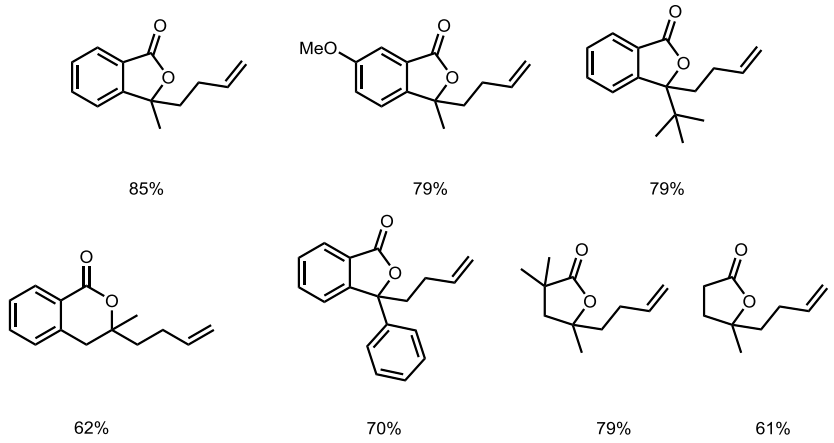


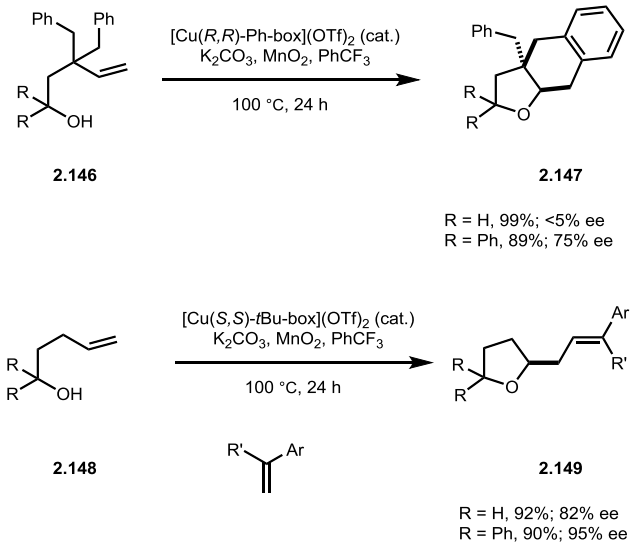
Figure 2.4: Successful oxyallylation reaction substrates in the synthesis of lactones

Attempts to extend the oxyallylation reaction to incorporate lactones from a *mono*-substituted alkene, in good yield, have proved challenging. The desired 5- and 6-membered lactones suffered from poor conversion in some cases, or the predominant reaction pathway forming unwanted side products. Attempts to redirect the reaction pathway towards synthesising the oxyallylated lactone products in a synthetically viable yield have, thus far, remained elusive. Changes in temperature, catalyst, base allyl halide, concentration and the addition of additives have proved unsatisfactory.

Additionally, the oxyallylation reaction has been made enantioselective, the first of its kind for *gem*-disubstituted alkene substrates. However, the enantioselectivities are still low and require further optimisation for it to be synthetically viable. Attempts at developing an enantioselective oxyallylation reaction for *mono*-substituted alkene substrates returned none of the desired product, racemic or enantioenriched.

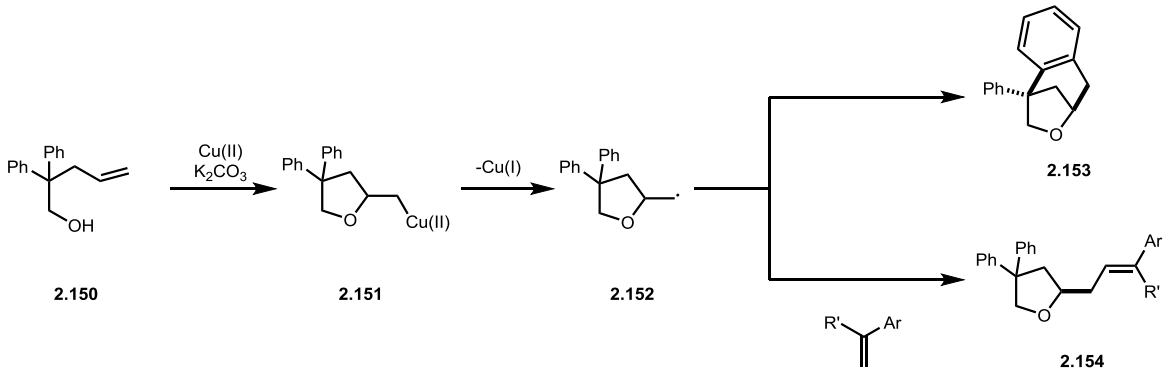
2.4 Copper-Facilitated Oxyallylation Reaction of Unactivated Alkenes

Copper-catalysed oxycyclisations are known in the literature and have given rise to new reactivity and products. Recently, the synthesis of heterocycles has particularly piqued the interest of organic chemists. The low cost of copper salts also helps its appeal and their ability to move between oxidation states of 0 to +3 allows for rich mechanistic possibilities.[107] Copper has an affinity for amines and alcohols as well as π bonds, so makes it an attractive metal in the synthesis of heterocycles. Recent reports by Chemler and co-workers have demonstrated the enantioselective copper(II)-catalysed intramolecular[108] and intermolecular[109] carboetherification reaction of unactivated alkenes (Scheme 2.58). Herein, high yields and high enantioselectivities are reported.



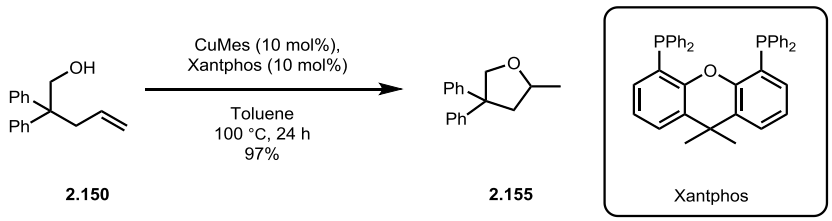
Scheme 2.58: Copper(II)-catalysed carboetherification of unactivated alkenes

The mechanism for each reaction is proposed to follow similar pathways. Oxycupration occurs across the alkene with a concomitant formation of an unstable alkylcopper(II) species **2.151** (Scheme 2.59). This undergoes homolysis to generate a copper(I) side product and a carbon radical **2.152**. In the case of the intramolecular carboetherification reaction, the radical adds to a tethered arene and subsequent re-aromatisation in oxidising conditions provides the desired bicyclic product **2.153**. The intermolecular carboetherification reaction the carbon radical intermediate **2.152** is intercepted by a vinyl arene. Subsequent oxidation results in the desired compound **2.154** (Scheme 2.59).



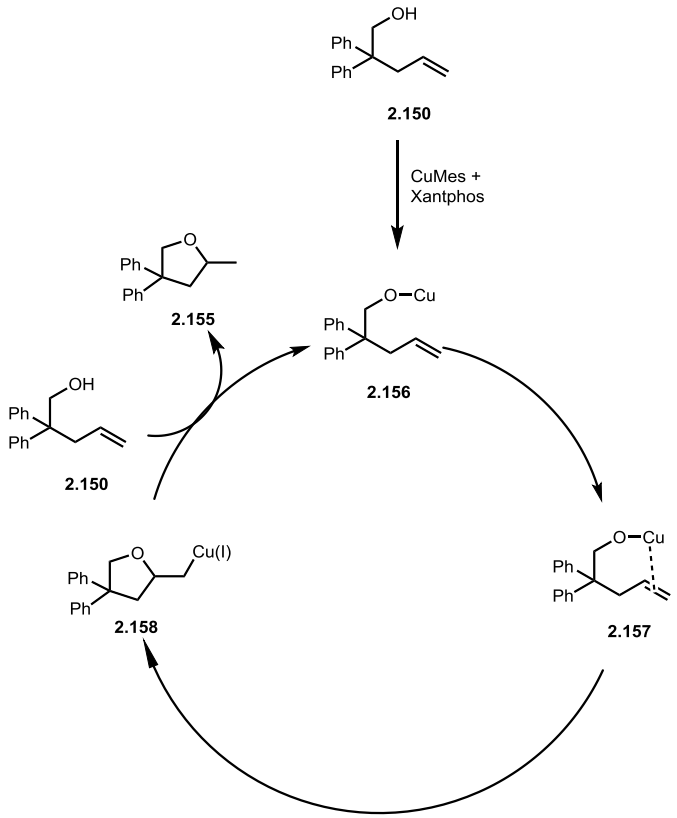
Scheme 2.59: Proposed intra- and intermolecular carboetherification mechanism

In 2015, a copper(I)-catalysed hydroalkoxylation reaction of unactivated alkenes was reported.[110] Starting with aliphatic alcohol **2.150**, the use of CuMes at 10 mol%, Xantphos at 10 mol% in toluene at 100 °C for 24 h generated the desired tetrahydrofuran derivative **2.155** in an excellent 97% yield (Scheme 2.60). Additionally, the authors report that an enantioselective version has been developed – the first of its kind.



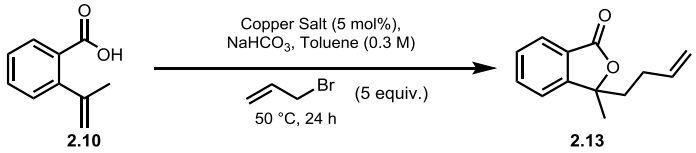
Scheme 2.60: Copper(I)-catalysed intramolecular hydroalkoxylation of unactivated alkenes

It is well known in the literature, that a common way to synthesise copper(I) alkoxides is with mesitylcopper(I) in the presence of an alcohol (Scheme 2.61).[111] Once the Cu−O bond is formed the copper in intermediate **2.156** coordinates to the terminal π bond forming intermediate **2.157**. The insertion of the alkene into the Cu−O bond of the copper(I) alkoxide affords the heterocyclised copper(I) intermediate **2.158**. Finally, protonolysis of the heterocyclised copper(I) intermediate **2.158** affords the desired compound **2.155**.



Scheme 2.61: Proposed catalytic cycle for copper(I)-catalysed intramolecular hydroalkoxylation

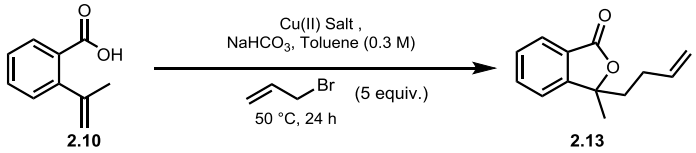
Buchwald and co-workers have employed carboxylic acids in copper-catalysed cyclisation reactions and as such this led to the use of benzoic acid substrate **2.10** in preliminary investigations.[112] Based on the studies described above, a copper-catalysed oxyallylation study was undertaken. The ability of both copper(I) and copper(II) salts to induce heterocyclisation reactions led to a screening of various copper salts (Table 2.23). As a starting point for the copper-catalysed oxyallylation reaction, the conditions utilised were similar to those in the palladium(II)-catalysed oxyallylation reaction. Screening various copper salts proved successful. With the use of $Cu(hfacac)_2$ or $Cu(acac)_2$ at 5 mol% loading, trace amounts of the desired oxyallylation product **2.13** was observed (entries 7 and 8). All other copper salts did not return any of the desired product.



Entry	Copper Salt (5 mol%)	Result (2.13)
1	CuBr	Not Detected
2	CuCN	Not Detected
3	CuI	Not Detected
4	$CuCl_2$	Not Detected
5	$CuBr_2$	Not Detected
6	$Cu(ClO_4)_2$	Not Detected
7	$Cu(hfacac)_2$	Trace
8	$Cu(acac)_2$	Trace
9	$Cu(OAc)_2$	Not Detected
10	$Cu(SO_4)_2$	Not Detected

Table 2.23: Initial copper salt investigation

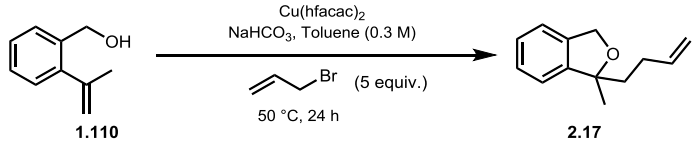
With $Cu(acac)_2$ and $Cu(hfacac)_2$ forming trace amounts of the desired lactone with a catalyst loading of 5 mol% the next step was to increase the loading (Table 2.24). Increasing the copper(II) loading of $Cu(acac)_2$ to 20 mol%, 100 mol% and 300 mol% resulted in no formation of the desired lactone **2.13** (entries 1 – 3). Next, the $Cu(hfacac)_2$ loading was increased to 20 mol%, 100 mol% and 300 mol%; however, each experiment only resulted in trace amounts of the desired lactone **2.13** (entries 4 – 6).



Entry	Copper Salt (mol%)	Result (2.13)
1	$Cu(acac)_2$ (20 mol%)	Not Detected
2	$Cu(acac)_2$ (100 mol%)	Not Detected
3	$Cu(acac)_2$ (300 mol%)	Not Detected
4	$Cu(hfacac)_2$ (20 mol%)	Trace
5	$Cu(hfacac)_2$ (100 mol%)	Trace
6	$Cu(hfacac)_2$ (300 mol%)	Trace

Table 2.24: Increase loading of copper(II) salts

The lack of improvement observed when increasing the copper(II) salt loading led to the screening of $Cu(hfacac)_2$ with benzylic alcohol **1.110** (Table 2.25). Unfortunately, the use of 20 mol%, 100 mol% and 300 mol% loading of $Cu(hfacac)_2$ resulted in no formation of isobenzofuran **2.17** (entries 1 – 3).

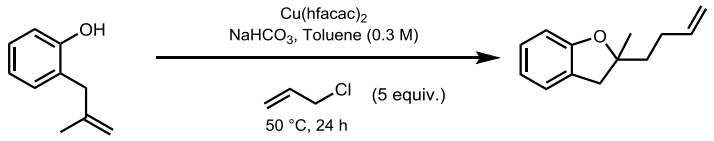


1.110 **2.17**

Entry	$Cu(hfacac)_2$ (mol%)	Result (2.17)
1	20 mol%	Not Detected
2	100 mol%	Not Detected
3	300 mol%	Not Detected

Table 2.25: Screening of $Cu(hfacac)_2$ loading with benzylic alcohol **1.110**

Phenol **1.83** was also screened with various loadings of $Cu(hfacac)_2$ (Table 2.26). At 20 mol% of $Cu(hfacac)_2$ no benzofuran **2.16** was formed (entry 1). However, when the $Cu(hfacac)_2$ loading was increased to 100 mol%, the desired benzofuran **2.16** was observed (entry 2). When the $Cu(hfacac)_2$ loading was increased further to 300 mol% the ratio improved again and afforded the benzofuran **2.16** in a 28% yield (entry 3).

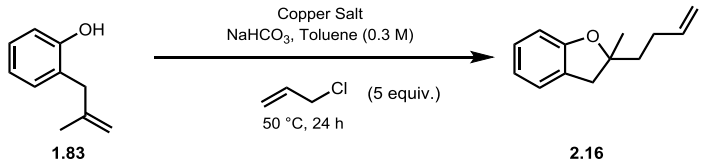


1.83 **2.16**

Entry	$Cu(hfacac)_2$ (mol%)	Result 1.83 : 2.16
1	20 mol%	Not Detected
2	100 mol%	2.0 : 1.0
3	300 mol%	1.2 : 1.0 (28%)

Table 2.26: Screening of $Cu(hfacac)_2$ loading with phenol **1.83**

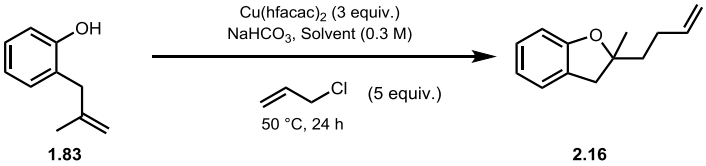
With $Cu(hfacac)_2$ at 300 mol% still returning large amounts of unreacted starting material, other copper salts were screened (Table 2.27). Unfortunately, no desired benzofuran **2.16** was detected, irrespective of copper salt employed (entries 1 – 5).



Entry	Copper Salt (300 mol%)	Result (2.16)
1	CuBr	Not Detected
2	CuI	Not Detected
3	$CuBr_2$	Not Detected
4	$Cu(OAc)_2$	Not Detected
5	$Cu(acac)_2$	Not Detected

Table 2.27: Copper salt screen with phenol substrate **1.83**

With $Cu(hfacac)_2$ as the best copper salt, the solvent applied in the oxyallylation reaction was investigated (Table 2.28). As can be seen below, the use of aprotic, non-polar solvents such as hexane and CH_2Cl_2 favours the $Cu(hfacac)_2$ facilitated oxyallylation reaction of unactivated alkenes (entries 2 and 3). When hexane and CH_2Cl_2 were employed equal amounts of phenol **1.83** and benzofuran **2.16** were observed *via* analysis of the ^{1}H NMR of the crude material.



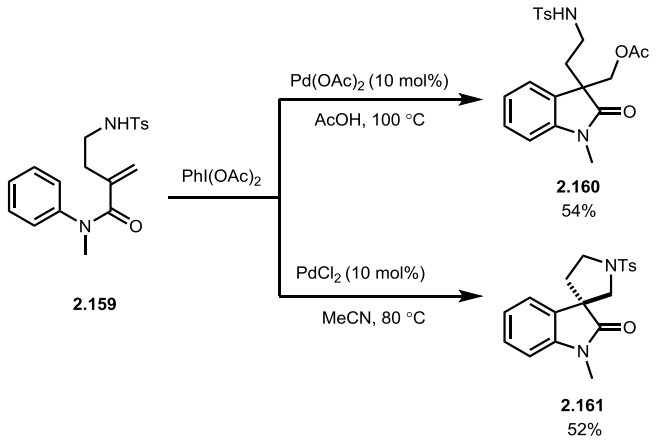
Entry	Solvent (0.3 M)	Result 1.83 : 2.16
1	MeCN	1 : 0
2	CH_2Cl_2	1 : 1
3	Hexane	1 : 1
4	*tert*-Amyl-OH	1 : 0
5	EtOAc	1 : 0
6	THF	1 : 0

Table 2.28: Solvent screen for the $Cu(hfacac)_2$ facilitated oxyallylation reaction

To conclude, the results obtained for phenol substrate **1.83** serve as a promising start. The inability to achieve full conversion even with super stoichiometric metal led to cessation.

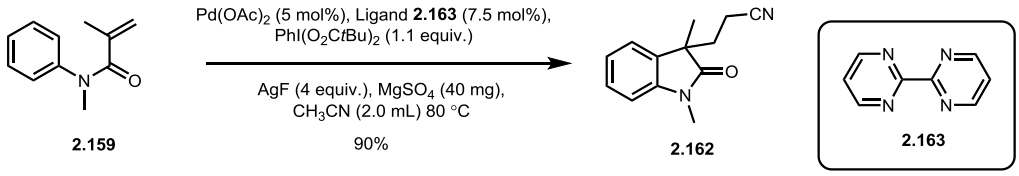
2.5 The Pd(II)-Catalysed Arylallylation of Activated Alkenes

The following section proposes a Pd(II)-catalysed arylallylation reaction of activated alkenes, inspired by recent reports in the literature. In 2010, Zhu and co-workers reported the Pd(II)-catalysed oxidative hetero-functionalisation of acrylanilide derivitives **2.159**, with both C–C and C–X bond formation (Scheme 2.62).[113] With $Pd(OAc)_2$ in acetic acid at 100 °C, it was noted that the carboacetoxylated product **2.160** was formed. A change of conditions with the use of $PdCl_2$ in MeCN at 80 °C resulted in the carboaminated product **2.161**.



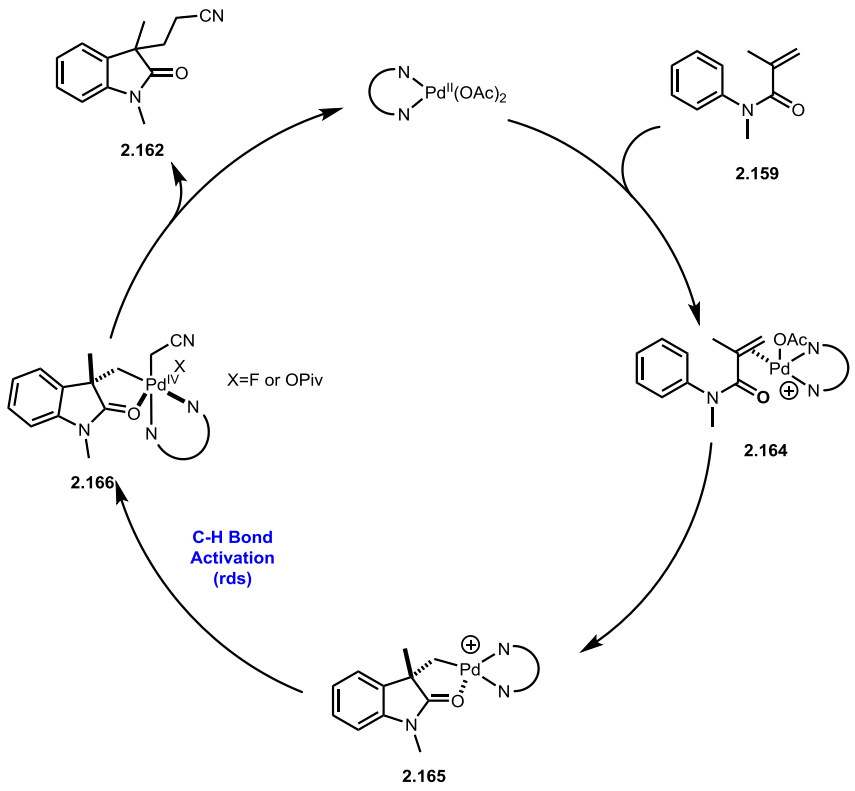
Scheme 2.62: Zhu and co-workers Pd(II)-catalysed synthesis of oxindoles

Palladium(II)-catalysed oxidative dicarbonation of alkenes is a challenging transformation. The Liu group, in 2011, published an intriguing paper where oxindoles **2.162** are synthesised through an oxidative arylalkylation of activated alkenes (Scheme 2.63).[114] In one step, the alkene undergoes a dicarbonation reaction forming a sp^2–sp^3 C–C bond and a sp^3–sp^3 C–C bond.



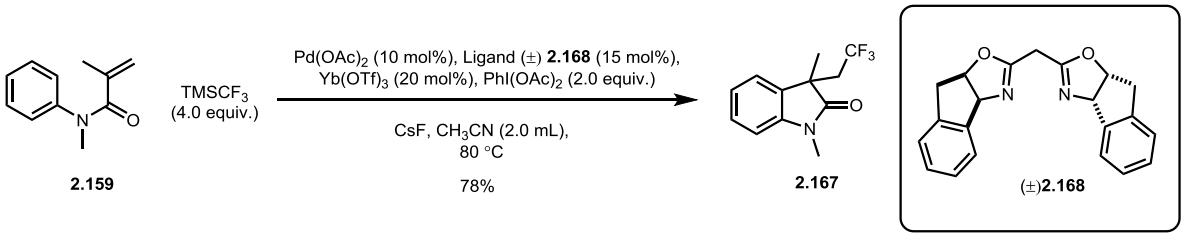
Scheme 2.63: Liu and co-workers Pd(II)-catalysed arylalkylation of activated alkenes

Mechanistic investigations were conducted by Liu and co-workers and based on the evidence gathered the following mechanism was proposed (Scheme 2.64). Co-ordination of the palladium(II) salt to the alkene, followed by nucleophilic attack from the aromatic ring to give complex **2.165**. Sp^3 C–H activation occurs next, which is promoted in the presence of $PhI(OPiv)_2$ and AgF to generate palladium(IV) intermediate **2.166**. Lastly, reductive elimination occurs to give oxindole **2.162** and regenerates the palladium(II) catalyst.



Scheme 2.64: Proposed mechanism for the oxidative arylalkylation of activated alkenes

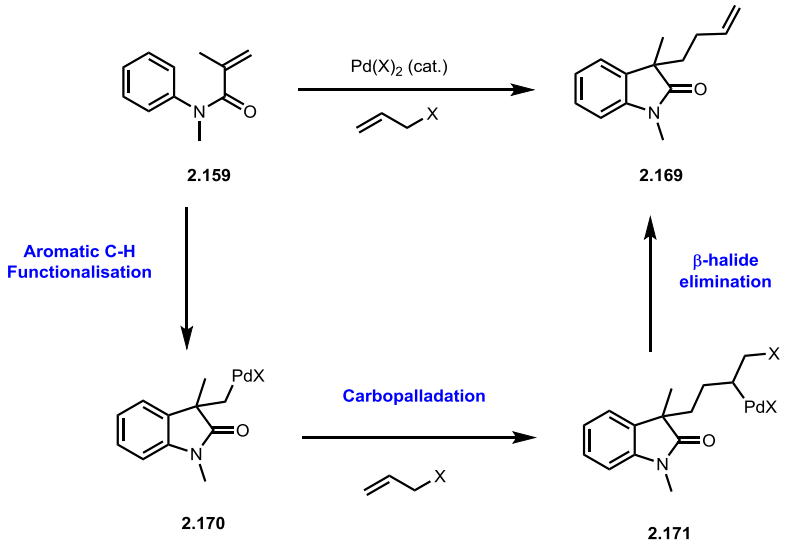
Liu *et al*. also reported the oxidative aryltrifluoromethylation of activated alkenes (Scheme 2.65).[115] Herein, inexpensive trifluoromethylating reagent in $TMSCF_3$ was employed and the development of an efficient way to synthesise CF_3-substituted oxindoles was described. Oxindoles such as **2.167** are biologically active and trifluoromethylating techniques can be of great use (Scheme 2.65). Mechanistic studies indicate that the mechanism for the reaction is similar to that depicted above.



Scheme 2.65: Pd(II)-catalysed aryltrifluoromethylation of activated alkenes

Using the Zhu and Liu papers as the foundation of the work, the aim of the project within the France group was to submit acrylanilide **2.159** to similar palladium(II)-catalysed conditions, involving an electrophilic allyl halide (Scheme 2.66). Hypothetically, the palladium(II)-induced arylpalladation would lead to intermediate **2.170**, which carbopalladates onto the allyl species followed by β-halide elimination to give the oxindole **2.169**. If successful, there will be many advantages to synthesising oxindoles using this methodology:

1) due to the isohypsic mechanism, no oxidants are required
2) the alkene undergoes a dicarbonation reaction forming an sp^2–sp^3 C–C bond and a sp^3–sp^3 C–C bond and, as previously mentioned, is rare in Pd(II)-catalysed alkene difunctionalisation reactions
3) terminal alkene in oxindole product can be used as a handle for further transformations
4) with the C–H functionalisation reaction the prefunctionalisation of the substrate is not required to induce cyclisation.



Scheme 2.66: Proposed methodology for the synthesis of oxindoles

The bioactive nature of oxindoles makes them ideal targets in the synthesis of pharmaceuticals. Success of the project would lead to the synthesis of a potential target, SSRI Amedalin **2.172** (Figure 2.5).[116]

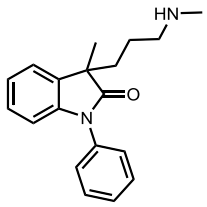
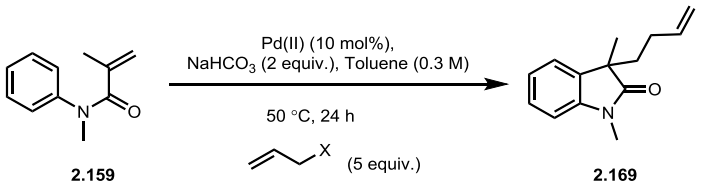


Figure 2.5: SSRI Amedalin **2.172**

Initially, conditions screened were focused on the oxyallylation reaction developed within the France group as the final step in the proposed mechanism, β-halide elimination, is the same. Starting with $Pd(hfacac)_2$ as the catalyst at 50 °C, using either allyl chloride or allyl bromide, resulted in no conversion. As a result, the temperature of the reaction was increased to 100 °C, but no conversion to the desired oxindole **2.169** was observed *via* ^1H NMR analysis of the crude mixture (Table 2.29, entries 1 and 2). In conjunction with the

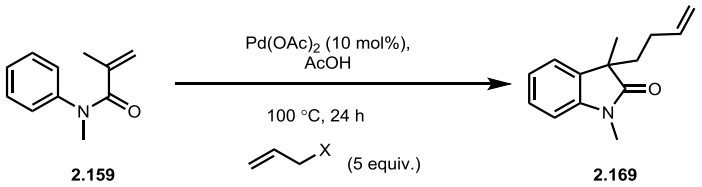
aforementioned experiments, reactions were conducted using the analagous conditions albeit with a change of catalyst to $Pd(O_3STol)_2(MeCN)_2$ (entries 3 and 4). Cationic $Pd(O_3STol)_2(MeCN)_2$ was selected because it is very electrophilic, and according to the mechanisms proposed by Liu *et al*., this feature could prove useful in the arylpalladation step. With this hypothesis, it was disappointing to observe, *via* ^1H NMR analysis of the crude mixture, that there was no conversion to the desired product **2.169**.



Entry	Pd(II) (10 mol%)	Temp. (°C)	Allyl X	Result 2.159 : 2.169
1	$Pd(hfacac)_2$	50 – 100	Br	1 : 0
2	$Pd(hfacac)_2$	50 – 100	Cl	1 : 0
3	$Pd(O_3STol)_2(MeCN)_2$	50 – 100	Br	1 : 0
4	$Pd(O_3STol)_2(MeCN)_2$	50 – 100	Cl	1 : 0

Table 2.29: Initial screening conditions for the attempted synthesis of oxindole **2.169**

The success of Zhu and co-workers carboactetoxylation reaction led us to try conditions analogous to those outlined above. As such, $Pd(OAc)_2$at 10 mol% and acetic acid as the solvent at 100 °C was employed. Initially, the reactions were performed without any additives at 0.1 M; however, this resulted in only unreacted starting material (Table 2.30, entries 1 and 2). The addition of $PhI(OAc)_2$ replicating Zhu's conditions, at 0.1 M concentration, resulted in no conversion to the desired product (entries 3 and 4). Increasing the concentration to 1.0 M, with the addition of $PhI(OAc)_2$, also resulted in none of the desired oxindole **2.169**.

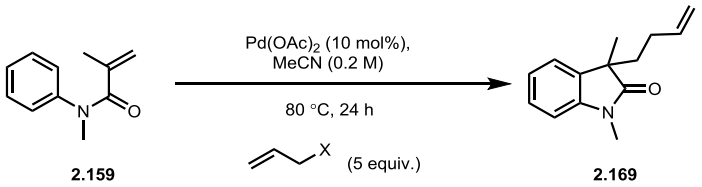


2.159 **2.169**

Entry	Concentration (M)	Allyl X	Additive (equiv.)	Result 2.159 : 2.169
1	0.1	Br	-	1 : 0
2	0.1	Cl	-	1 : 0
3	0.1	Br	$PhI(OAc)_2$ (2)	1 : 0
4	0.1	Cl	$PhI(OAc)_2$ (2)	1 : 0
5	1.0	Br	$PhI(OAc)_2$ (2)	1 : 0
6	1.0	Cl	$PhI(OAc)_2$ (2)	1 : 0

Table 2.30: Attempted arylallylation of activated alkene using Zhu's conditions

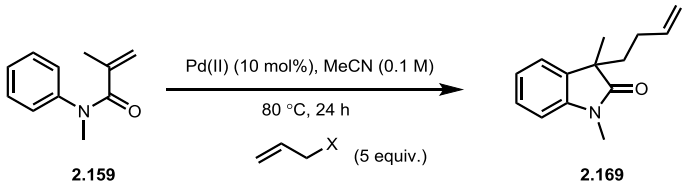
Literature examples show that the palladium-catalysed synthesis of oxindoles were often performed successfully when $Pd(OAc)_2$ was the catalyst and MeCN wasthe solvent and, as such, were kept constant for the following reactions. The reactions listed below, indicate attempts at optimising the arylallylation reaction. The use of various bases, metal salts, ligands and combinations thereof, whilst varying the allyl halide species, garnered none of the desired arylallylated product **2.169**, which was deemed so *via* ^{1}H NMR analysis of the crude material (Table 2.31, entries 1 – 13).



Entry	Allyl X	Additive (Equiv.)	Result 2.159 : 2.169
1	Br	$NaHCO_3$ (2)	1 : 0
2	Cl	$NaHCO_3$ (2)	1 : 0
3	Br	$NaHCO_3$ (2), AgF (4)	1 : 0
4	Cl	$NaHCO_3$ (2), AgF (4)	1 : 0
5	Br	$NaHCO_3$ (2), CsF (4)	1 : 0
6	Cl	$NaHCO_3$ (2), CsF (4)	1 : 0
7	Br	$NaHCO_3$ (4), $AgNO_3$ (4)	1 : 0
8	Cl	$NaHCO_3$ (2), $AgNO_3$ (4)	1 : 0
9	Br	$NaHCO_3$ (2), $AgNO_3$ (4), BiPy (0.12)	1 : 0
10	Br	$NaHCO_3$ (2), AgF (4), BiPy (0.12)	1 : 0
11	Br	$NaHCO_3$ (2), CsF (4), BiPy (0.12)	1 : 0
12	Br	$NaHCO_3$ (2), BiPy (0.12)	1 : 0
13	Br	$NaHCO_3$ (2), CsF (4),$Yb(OTf)_3.xH_2O$ (0.2)	1 : 0

Table 2.31: Attempted optimisation of arylallylation reaction

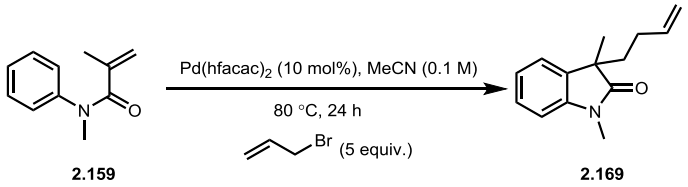
The desired product was eventually observed *via* ^{1}H NMR analysis of the crude mixture (Table 2.32). The result arose when the conditions employed were similar to those used by Zhu and co-workers to synthesise spirooxindole **2.161** (Scheme 2.62). Initially, catalyst $PdCl_2$ was utilised as the Zhu group achieved success using this Pd(II) salt (entries 1 and 2). Unfortunately, no conversion to the desired product was observed and starting material was left unreacted. The catalyst was then varied to $Pd(hfacac)_2$ as it is more electrophilic than its $PdCl_2$ counterpart and previous success was achieved when it was used as the catalyst in the oxyallylation reactions developed within the France group (entries 3 and 4). When allyl bromide was the electrophile, the desired product was observed (entry 3). This result could not be produced with regularity, with the best ratio shown. Attempts at reproducing this result often only returned acrylanilide **2.159**.



Entry	Pd(II) (10 mol%)	Allyl X	Result 2.159 : 2.169
1	$PdCl_2$	Br	1 : 0
2	$PdCl_2$	Cl	1 : 0
3	$Pd(hfacac)_2$	Br	7.7 : 1
4	$Pd(hfacac)_2$	Cl	1 : 0

Table 2.32: Palladium(II)-catalysed arylallylation reaction of activated alkene

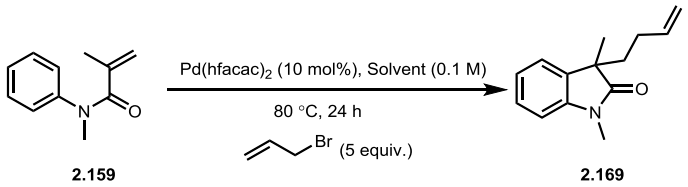
Although encouraging, improvements and consistency were desired. With this, a series of metal salts were added to the reaction in an attempt to improve upon the ratio of starting material to desired oxindole **2.169** (Table 2.33). Unfortunately, no improvements were observed and all reactions only returned starting material (entries 1 – 6).



Entry	Additive (2 equiv.)	Result 2.159 : 2.169
1	KOAc	1 : 0
2	$NaHCO_3$	1 : 0
3	K_2CO_3	1 : 0
4	Cs_2CO_3	1 : 0
5	KH_2CO_3	1 : 0
6	AgOAc	1 : 0

Table 2.33: Effect of metal salts on arylallylation reaction

The lack of improvement observed with the addition of metal salts, prompted an investigation into the change of solvent, with all other conditions remaining constant (Table 2.34). Irrespective of the solvent employed, no desired oxindole **2.169** was observed *via* ^1H analysis of the crude material (entries 1 – 9).

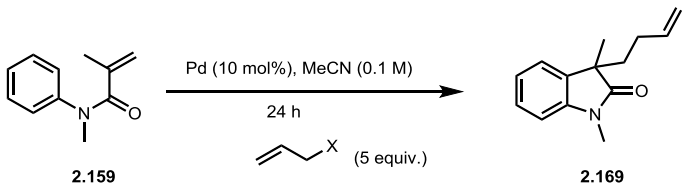


2.159 2.169

Entry	Solvent (0.1 M)	Result 2.159 : 2.169
1	Dioxane	1 : 0
2	*tert*-Amyl-OH	1 : 0
3	Toluene	1 : 0
4	EtOAc	1 : 0
5	THF	1 : 0
6	EtOH	1 : 0
7	TFE	1 : 0
8	CH_2Cl_2	1 : 0
9	$C_2H_4Cl_2$	1 : 0

Table 2.34: Solvent screen for arylallylation reaction

With the addition of metal salts and a change of solvent proving fruitless, a change in catalyst was next investigated (Table 2.35). Irrespective of palladium salt employed at 80 °C, no desired product **2.169** was observed (entries 1 – 7). The lack of success, instigated revisiting the original reaction with $Pd(hfacac)_2$ however with the temperature increased from 80 °C to 100 °C (entry 8). However, none of the desired oxindole **2.169** was observed at the elevated temperature.



2.159 2.169

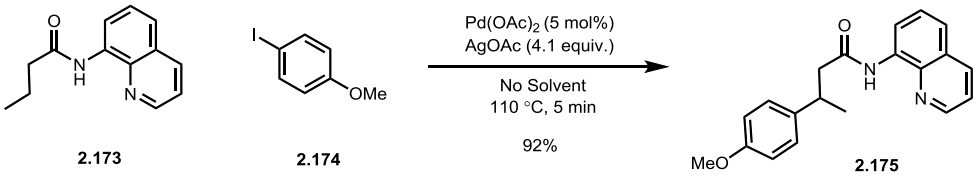
Entry	Pd Catalyst	Allyl X	Temp. (°C)	Result 2.159 : 2.169
1	$Pd(OAc)_2$	Br	80	1 : 0
2	$Pd(OAc)_2$	Cl	80	1 : 0
3	$Pd(TFA)_2$	Br	80	1 : 0
4	$Pd(TFA)_2$	Cl	80	1 : 0
5	$Pd(PPh_3)_4$	Br	80	1 : 0
6	$Pd(dba)_3$	Br	80	1 : 0
7	Pd(allyl)(Cl)	Br	80	1 : 0
8	$Pd(hfacac)_2$	Br	100	1 : 0

Table 2.35: Catalyst screen for arylallylation reaction

In summary, preliminary results prove that arylallylation of activated alkenes can be achieved. However, attempts to improve on the ratio (Table 2.32, entry 3), have remained difficult with reproducibility also an issue.

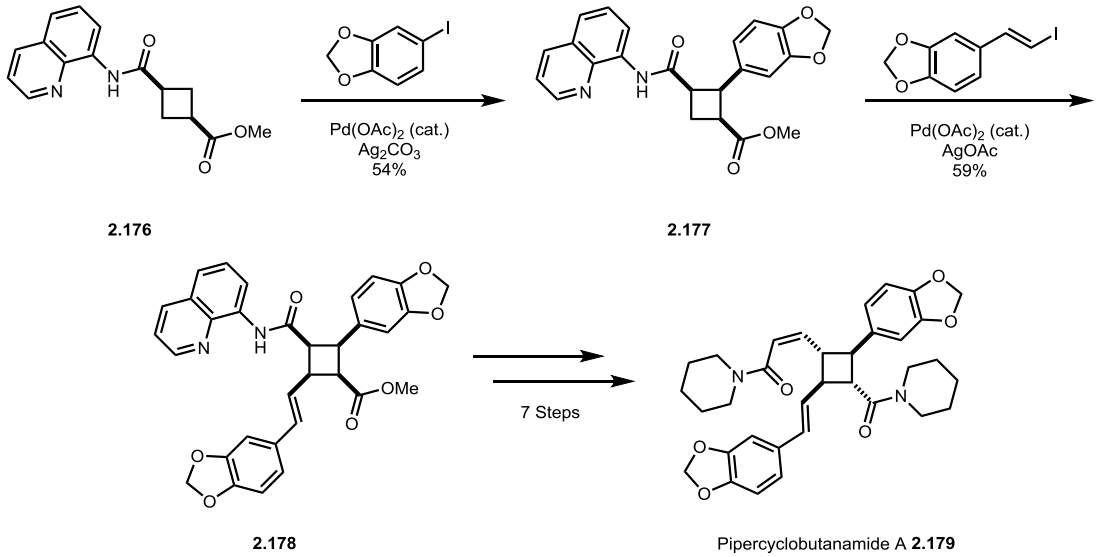
2.6 Sequential sp^3 C–H Activation–Cyclisation Towards the Synthesis of Heterocycles

In 2005, Daugulis and co-workers reported the use of a quinoline directing group in the activation of sp^3 C–H bonds at the β-position.[117] Herein, it was reported that the coupling of amides with aryl iodides in good yields (Scheme 2.67). In this seminal publication, an entire field of palladium-catalysed sp^3 C–H activation using transition metal catalysis was created.



Scheme 2.67: Sp^3 C–H activation–arylation reaction

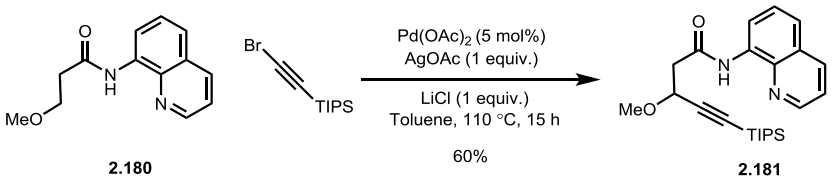
The practicality of palladium-catalysed quinolone-directed sp^3 C–H bond activated methodology in synthesis was epitomised in a report by Baran and co-workers.[118] The synthesis of the proposed structure of Pipercyclobutanamide A **2.179**, included key steps that were performed using quinoline as a directing group (Scheme 2.68).



Scheme 2.68: Pipercyclobutanamide A **2.179**

Since the seminal Daugulis report, numerous publications have been released detailing the use of the quinoline directing group in Pd(II)-catalysed C–H activation reactions.[119] Below, in the coupling of (2-bromoethynyl)tri*iso*propylsilane with amide **2.180** is a coupling reaction that has a significance to the sp^3 C–H activation methodology the France group wishes to develop (Scheme 2.69).[119a] This one example, demonstrates that sp^3 C–H

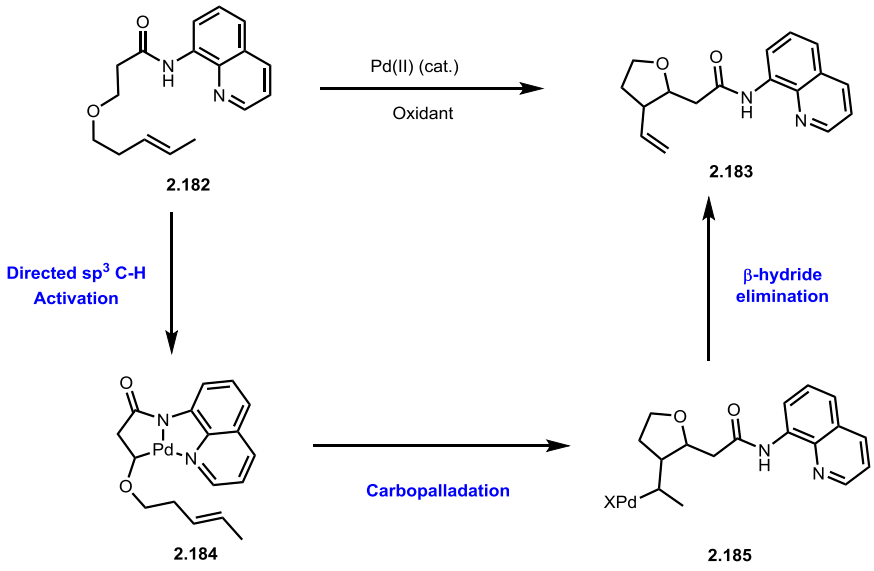
activation, using the quinoline directing group, can occur with an alkoxy group bonded to the β-position of an amide.



2.180 2.181

Scheme 2.69: Sp^3 C–H activation of β-methoxy amide **2.181**

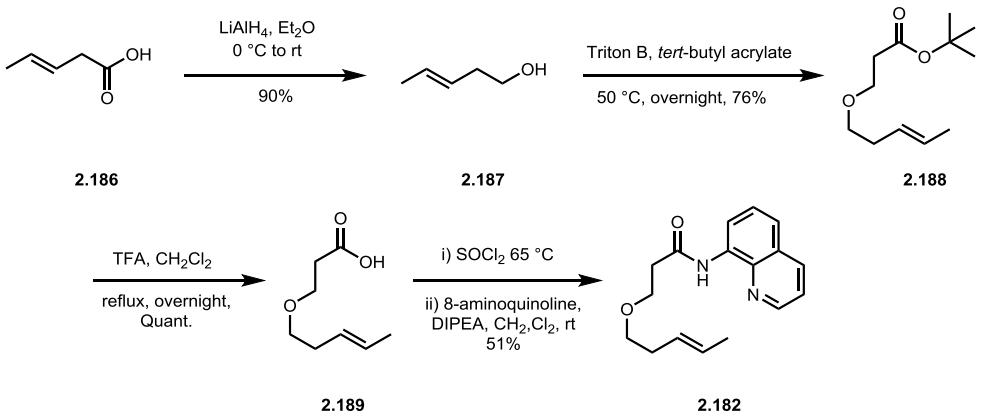
The use of the quinoline directing group in the palladium-catalysed sp^3 C–H activation of β-methoxy amide **2.180** provided the inspiration that heterocycles could be synthesised using the quinolone directing group. The hypothesis: starting with substrate **2.182** and using a Pd(II)-catalyst, sp^3 C–H activation in the β-position would give palladated intermediate **2.184**. Next, the palladacycle intermediate **2.184** would carbopalladate to give 2,3-disubstituted furan intermediate **2.185**. Subsequent β-hydride elimination would yield the desired product **2.183**.



2.182 2.183 2.184 2.185

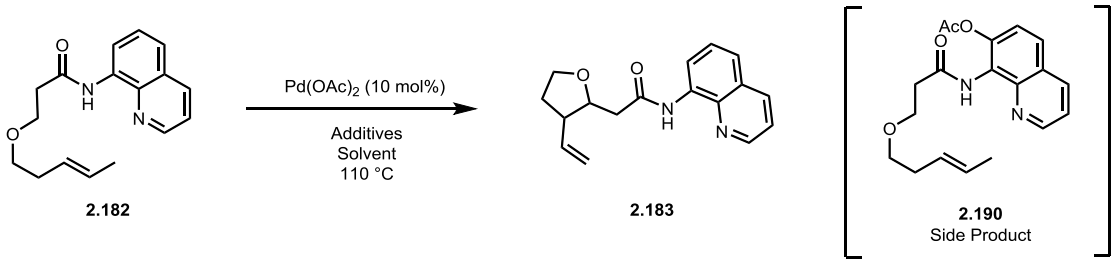
Scheme 2.70: Proposed sp^3 C–H activation–cyclisation methodology

The synthesis of amide **2.182** began with reduction of commercially available pentenoic acid **2.186** to yield pentenol **2.187**, which was used directly without further purification (Scheme 2.71).[120] Coupling of pentenol **2.187** with *tert*-butyl acrylate gave ester intermediate **2.188**.[121] Next, the ester bond was hydrolysed using TFA in CH_2Cl_2.[121] With aliphatic acid **2.189**, the acid chloride was formed *in situ*, which was coupled with 8-aminoquinoline to yield the desired amide **2.182**.[122]



Scheme 2.71: Synthesis of amide **2.182**

Using a number of conditions found in the literature (such as those observed in Scheme 2.69), conditions for the proposed sp^3 C–H activation–cyclisation methodology were screened.[119b] The palladium catalyst, $Pd(OAc)_2$, was constant throughout all the reactions. Additionally, the temperature was kept constant at 110 °C. This was because successful sp^3 C–H activations, using similar substrates to amide **2.182**, were subjected to $Pd(OAc)_2$ and high temperatures. Different solvents and additives were screened that had previously proved successful in other systems (Table 2.36). Screening conditions have proven unsuccessful; no cyclised products have been observed *via* ^{1}H NMR of the crude mixture (entries 1 – 14).The only product observed throughout the initial screening was **2.190**, which is formed by *ortho*-C–H activation.



Entry	Solvent (Conc.)	Additives (equiv.)	Result 2.182 : 2.183
1	Toluene (0.2 M)	AgOAc (1.2), BQ (2)	1: 0
2	Toluene (0.2 M)	AgOAc (1), LiCl (1)	1: 0
3	Toluene (0.2 M)	$Cu(OAc)_2$ (1), Cs_2CO_3 (1)	1: 0
4	Toluene (0.2 M)	AgOAc (1), Cs_2CO_3 (1)	1: 0
5	HFIP (1.0 M)	AgOAc (3)	1: 0
6	*t*BuOH (0.2 M)	AgOAc (1.5)	1: 0
7	*t*BuOH (0.2 M)	Ag_2CO_3(1)	1: 0
8	*t*BuOH (0.2 M)	AgOAc (1), BQ (0.1)	1: 0
9	*t*BuOH (0.2 M)	$AgCO_3$ (1), PivOH (1)	1: 0
10	*t*BuOH (0.2 M)	K_2CO_3 (2.5), PivOH (0.2)	1: 0
11	*t*BuOH (0.2 M)	$AgCO_3$ (1), PivOH (0.2)	1: 0
12	MeOH (0.2 M)	DMP (2)	Decomp.
13	*tert*-Amyl-OH (0.5 M)	K_2CO_3 (3.5), PivOH (0.5)	1: 0[a]
14	Toluene (0.2 M)	$PhI(OAc)_2$ (2.5), AcOH (2)	-[b]

[a]Catalyst used was $Pd(TFA)_2$ (30 mol%) [b]Side product formed

Table 2.36: Attempted optimisation of sp^3 C–H activation–cyclisation methodology

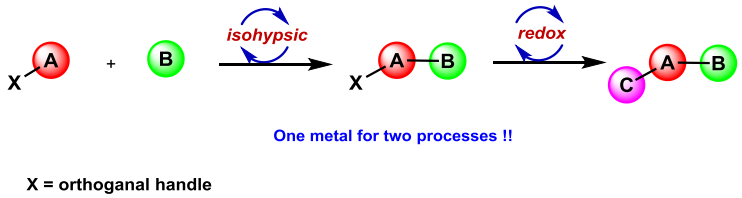
To conclude, preliminary investigations have proved unsuccessful. No cyclic compounds have been detected *via* ^{1}H NMR analysis of the crude material.

3. Palladium-Catalysed Isohypsic−Redox Sequence

3.1 Introduction and Aims

Transition metal catalysis is amongst the most commonly used techniques by organic chemists to construct new bonds. The vast majority of the transition metal catalysed reactions proceed *via* redox transformations, with respect to the metal catalyst. The success of palladium catalysis in recent decades has seen this particular metal become a key method[123] in the synthesis of pharmaceuticals[124] and natural products.[49] Most palladium-catalysed reactions follow a well-known and studied course: oxidative addition, transmetallation and reductive elimination (Scheme 1.31). Here, the palladium centre proceeds through a Pd(0)/Pd(II) cycle. However, a small number of palladium-catalysed reactions occur without changes to the oxidation state of the metal centre, i.e. are redox-neutral or isohypsic, with the palladium in the +2 oxidation state throughout the catalytic cycle (see Chapter 1 for review).

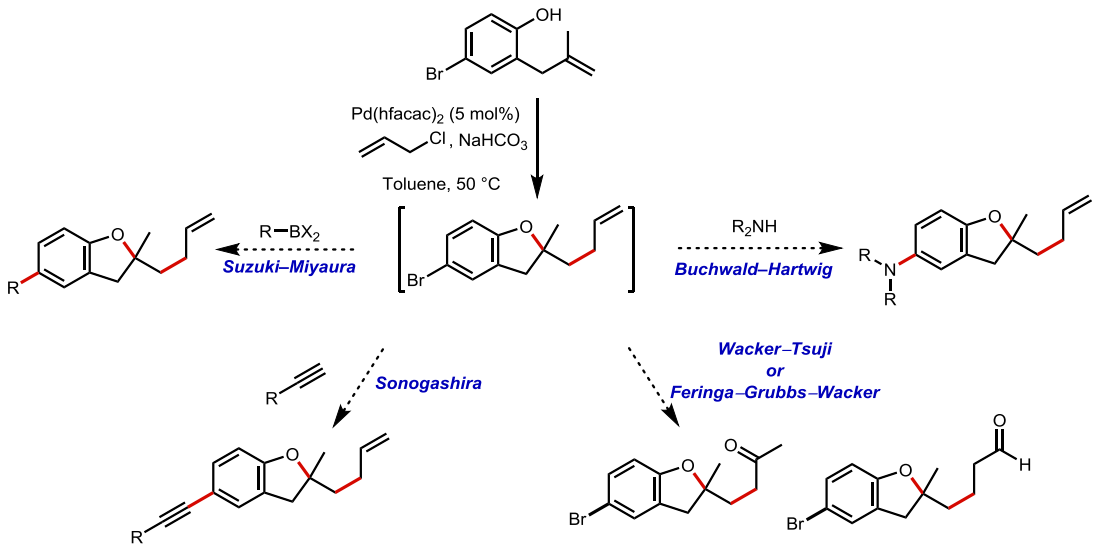
The differences in mechanism between a palladium-catalysed redox reaction and a palladium-catalysed isohypsic reaction allows for orthogonal reactivity. In an isohypsic process, chemical functionality on the molecule will be inert to the palladium(II) catalyst; however, by altering the oxidation state of the metal, through addition of a new reagent, the manipulation of other functional groups can be performed through traditional palladium-catalysed redox chemistry (Scheme 3.1).



Scheme 3.1: Overview of isohypsic−redox sequence

The isohypsic−redox sequence has a number of advantages. Firstly, product diversity through “plug and play” with different palladium-catalysed isohypsic and redox processes. Secondly, molecular complexity can be greatly enhanced through multiple bond forming reactions. Thirdly, one metal catalyses two processes, making the isohypsic−redox sequence efficient and economical. Switching from an isohypsic to a redox manifold is an example of “assisted tandem catalysis”[125] where one metal source can effect two separate catalytic processes. Through the addition of different reagents at specific points, one has the ability to control the change in mechanism. Although the use of an isohypsic−redox sequence has the potential for broad utility across organic chemistry, very seldom has it been used in Pd-catalysis and never in the context of alkene difunctionalisation.[126]

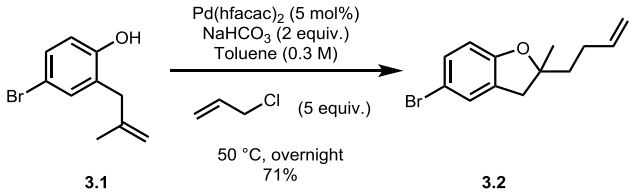
As discussed previously, within the France group the development of an isohypsic palladium(II)-catalysed alkene difunctionalisation reaction that forms a heterocycle with a concomitant sp^3–sp^3 C–C bond. In this chapter, the development of an Isohypsic–Redox Sequence (IRS) based on combining the isohypsic heteroallylation reaction with the more traditional redox chemistry such as: Suzuki–Miyaura, Sonogashira and Buchwald–Hartwig cross coupling reactions as well as the Wacker oxidation and the Feringa–Grubbs–Wacker oxidation (Scheme 3.2).[126c, 127]



Scheme 3.2: Proposed IRS

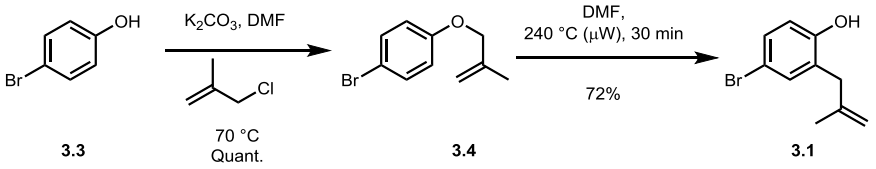
3.2 IRS –The Suzuki–Miyaura Iteration

Identifying a possible substrate that can combine the oxyallylation reaction and one which contains a functional handle that can be used in palladium-catalysed redox reactions was the first priority. Bromophenol **3.1** has successfully performed the oxyallylation reaction to generate the desired bromobenzofuran **3.2** in good yield, with the bromide remaining intact, in the all Pd(II) catalytic process (Scheme 3.3).



Scheme 3.3: Isohypsic oxyallylation reaction with bromide handle

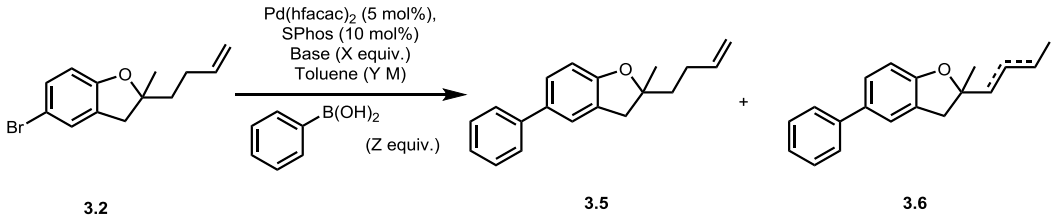
Synthesis of the desired bromophenol **3.2** was undertaken following a procedure established in the group. Allylation of *p*-bromophenol **3.3** in the presence of 3-chloro-2-methylpropene, K_2CO_3 in DMF at 70 °C proceeded in excellent yield to furnish the *O*-allylated product **3.4**. Subjecting the *O*-allylated product **3.4** to microwave radiation at 240 °C for 30 minutes afforded the desired bromophenol **3.1** in a 72% yield (Scheme 3.4).



Scheme 3.4: Synthesis of bromophenol **3.1**

It was deemed prudent to start optimisation for the IRS with the Suzuki−Miyaura reaction. Primarily, this is because it is the most commonly used C−C bond forming reaction used by medicinal chemists.[128] With the isohypsic reaction already optimised, the investigation started from the already heterocyclised bromobenzofuran **3.2**, in order to develop the redox Suzuki−Miyaura cross coupling reaction separately, before combining the two processes. SPhos was chosen as the ligand because it is commonly and successfully used in many Suzuki−Miyaura cross coupling reactions (for the structure, see Table 3.3). The base used in the oxyallylation reaction, $NaHCO_3$, was first used in the Suzuki−Miyaura cross coupling reactions (Table 3.1). Starting at 50 °C the reaction afforded no desired product **3.5**, and only returned starting material (entry 1). The reaction temperature was increased to 80 °C, however, no conversion was observed *via* TLC, and as such the temperature was further increased to 100 °C, yet only returned isomerised material **3.6**, exclusively (entry 2). Employing conditions analogous to those found in the literature,[129] K_3PO_4 was used as the base. Two equivalents of base with 1.5 equivalents of phenyl boronic acid at 50 °C resulted in formation of the isomerised material **3.6** (entry 3). To improve the conversion, the equivalents of base and boronic acid were increased as well as the temperature, and to reduce isomerisation the concentration was decreased, however, unwanted isomerised material **3.6** was the main product, and complete conversion of the starting material was not observed (entry 4). Next, three equivalents of base, phenylboronic acid at 0.5 M at 50 °C for 24 h was tried and resulted in complete conversion of starting material to the unwanted isomerised product **3.6** (entry 5). This result led to the same experimental conditions performed but with a shorter running time (entry 6). The desired Suzuki−Miyaura product **3.5** was observed, however, the starting material was still present. K_3PO_4, phenyl boronic acid and time were all reduced next, with the temperature being increased to 100 °C (entry 7). This resulted in unwanted isomerised product **3.6** and incomplete conversion of the starting material. The conditions were repeated, however, the temperature was reduced to room temperature and the reaction was run for 48 h but only returned starting material (entry 8). Based on the above results, K_3PO_4 and phenyl boronic acid equivalents were increased to 3 apiece, and the reaction was performed at 50 °C for 16 h (entry 9). This resulted in the sole formation of desired Suzuki−Miyaura product **3.5**, with a small amount of starting material. Analagous conditions were employed, however, the reaction was allowed to stir for slightly longer at 19 h in order to allow complete conversion of starting material and also limit the synthesis

of isomerised product **3.6** (entry 10). This resulted in the complete conversion to the desired Suzuki−Miyaura product **3.5**. Similar conditions were explored with the equivalents of K_3PO_4 lowered from 3 to 2 which, again, resulted in the complete conversion to the desired Suzuki−Miyaura product **3.5** (entry 11). Finally, 2 equivalents of base and phenyl boronic acid were utilised, however, this resulted in incomplete conversion to the desired product **3.5** (entry 12). Based on the above, the conditions developed in Table 3.1 entry 11 were employed in the full IRS sequence.



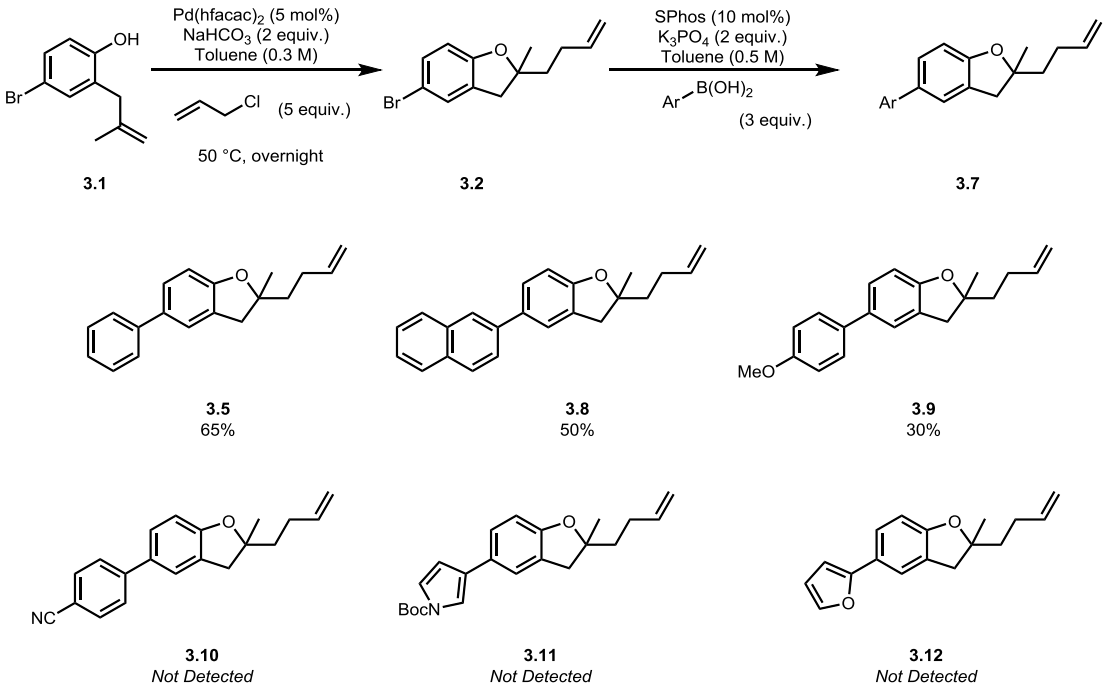
3.2 3.5 3.6

Entry	Base (equiv.)	Toluene (Conc.)	Boronic Acid (equiv.)	Time (h)	Temp. °C	Result 3.2 : 3.5 : 3.6
1	$NaHCO_3$ (2)	0.3 M	1.5	24	50	1.0 : 0.0 : 0.0
2	$NaHCO_3$ (2)	0.3 M	1.5	24	80−100	0.0 : 0.0 : 1.0
3	K_3PO_4 (2)	0.5 M	1.5	24	50	3.3 : 0.0 : 1.0
4	K_3PO_4 (3)	0.3 M	2.0	24	100	1.0 : 0.0 : 2.5
5	K_3PO_4 (3)	0.5 M	3.0	24	50	0.0 : 0.0 : 1.0
6	K_3PO_4 (3)	0.5 M	3.0	5	50	1.0 : 3.4 : 0.0
7	K_3PO_4 (2)	0.5 M	2.0	3.25	100	1.0 : 0.0 : 5.0
8	K_3PO_4 (2)	0.5 M	2.0	48	rt	1.0 : 0.0 : 0.0
9	K_3PO_4 (3)	0.5 M	3.0	16	50	1.0 : 4.2 : 0.0
10	K_3PO_4 (3)	0.5 M	3.0	19	50	0.0 : 1.0 : 0.0
11	**K_3PO_4 (2)**	**0.5 M**	**3.0**	**19**	**50**	**0.0 : 1.0 : 0.0**
12	K_3PO_4 (2)	0.5 M	2.0	19	50	1.0 : 7.0 : 0.0

Table 3.1: Optimisation of Suzuki−Miyaura reaction

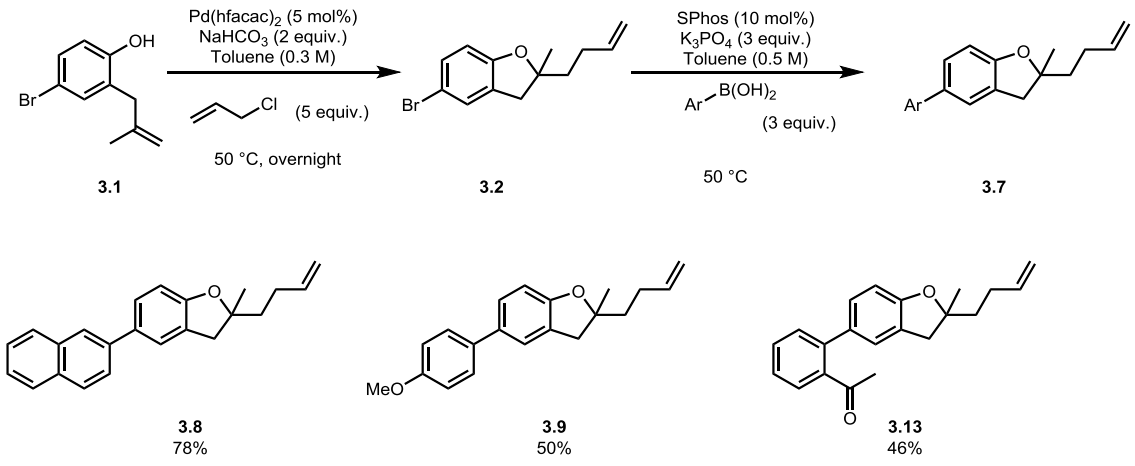
Utilising the previously mentioned optimal conditions, the first palladium-catalysed isohypsic–redox sequence was successfully performed resulting in the desired IRS product **3.5** in a 65% yield overall (Scheme 3.5). It was a relief that the combination of both the isohypsic oxyallylation reaction and the newly optimised Suzuki−Miyaura coupling worked well, with only the reaction time of the Suzuki−Miyaura reaction having to be shortened from 19 h to 16 h. The first step of the sequence, the oxyallylation of phenol **3.1** was performed using a 5 mol% Pd(II) catalyst in presence of base, $NaHCO_3$, and allyl chloride. The reaction proceeded with full conversion to cyclised intermediate **3.2** which was then subjected to a Suzuki−Miyaura coupling with different aromatic boronic acids. As

can be seen below, only the naphthalene derived IRS product **3.8** and 4-methoxy phenylproduct **3.9** derivatives were found. However, compared to the phenyl derivative **3.5**, there was a decrease in the overall yield. Furthermore, the 4-cyano-phenyl **3.10**, 3-pyrrole **3.11** and 2-furanyl **3.12** IRS products were not isolated.



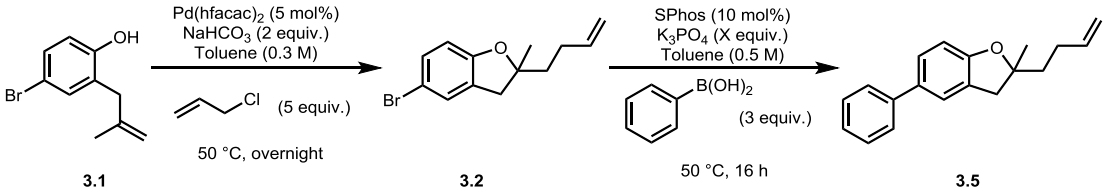
Scheme 3.5: Oxyallylation combined with the Suzuki−Miyaura reaction

In an attempt to improve the yield of the IRS naphthalene **3.8** and phenyl methoxy **3.9** derivatives, the equivalents of the freshly ground K_3PO_4 were increased from 2 to 3. In both cases, the yield increased; therefore, the new overall yield was 78% for the naphthalene **3.8** and 50% for the 4-methoxyphenyl **3.9** compounds (Scheme 3.6).[130] Additionally, 2-acetylphenyl derivative **3.13** worked well with a 46% yield over two steps.



Scheme 3.6: Substrate scope of Suzuki−Miyaura IRS sequence

To ascertain whether three equivalents of K_3PO_4 is the optimal quantity in this case, a study was conducted for the phenyl derivative **3.5**. As can be seen from Table 3.2, entry 3, the highest overall yield was achieved when three equivalents of base were employed. The yield decreased when the equivalents were further increased to four or five (entry 3 or 4).

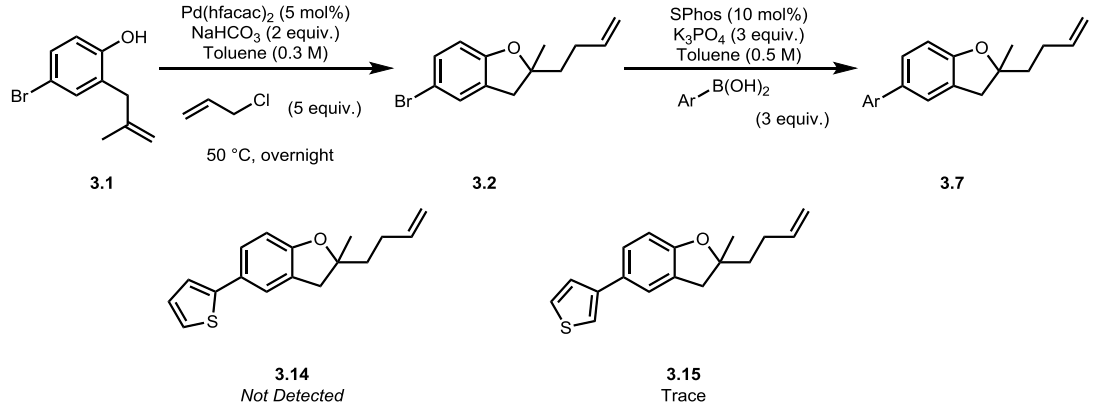


Entry	Equivalents of K_3PO_4	Yield (3.5)
1	2	65%
2	3	68%
3	4	60%
4	5	55%

Table 3.2: Investigation into the equivalents of K_3PO_4

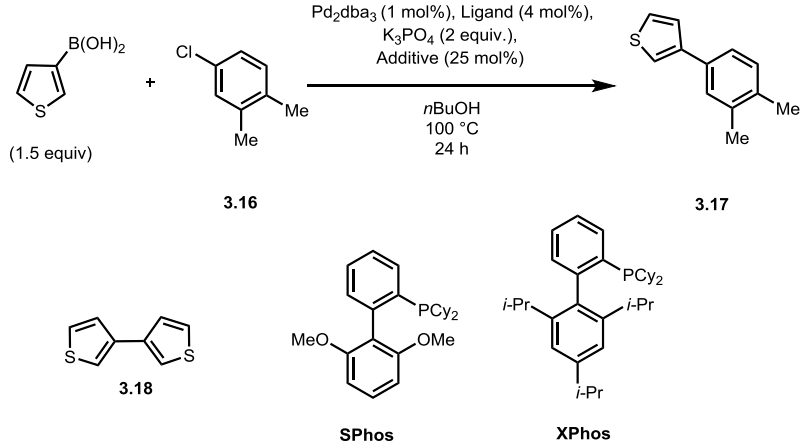
This new optimisation was then further tested when a scale-up for the formation of the desired IRS product **3.5** was performed. Therefore, the reaction was run with 0.2, 0.6 and 1.8 mmols of phenol starting material **3.1**. The overall yields were maintained around 65–68%, ergo, consistency was ensured.

Furthermore, thienyl boronic acids were tested (Scheme 3.7). When 2-thienyl boronic acid was used, no desired IRS product **3.14** formation was observed *via* analysis of the ^{1}H NMR of the crude material. As trace amounts of the 3-thienyl compound **3.15** were observed in the crude NMR, the literature was consulted to determine whether thienyl boronic acids were suitable for the Suzuki−Miyaura reaction.[130]



Scheme 3.7: Thienyl boronic acid screen

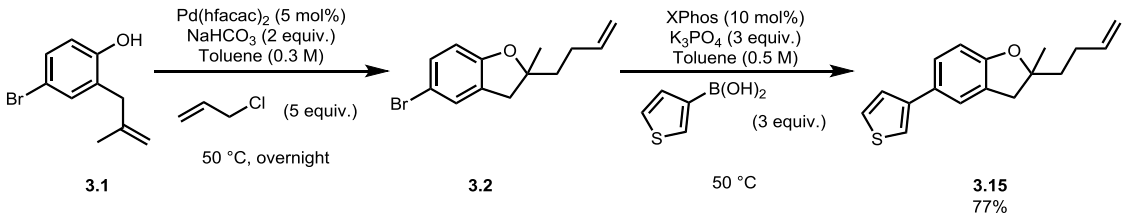
Buchwald and co-workers reported that the formation of the 3,3'-bithiophene **3.18** as a by-product will have a negative effect on the coupling reaction between 3-thienyl boronic acid and aryl chloride **3.16** when SPhos is used as a ligand (Table 3.3, entry 2).[131] Through changing the ligand to XPhos, the formation of the bithiophene **3.18** had no influence on the Suzuki−Miyaura coupling reaction, which proceeded with high yield and conversion (Table 3.3, entry 4).



Entry	Ligand	Additive	Conversion to product 3.17 (%)
1	SPhos	None	93
2	SPhos	**3.18** (25 mol%)	7
3	XPhos	None	100
4	XPhos	**3.18** (25 mol%)	100

Table 3.3: Inhibition by 3,3'-bithiophene **3.18**

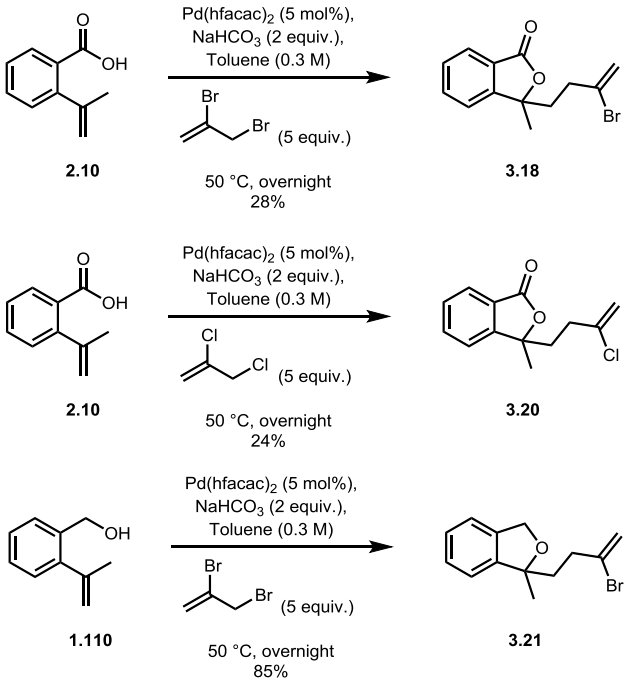
Since the bithiophene **3.18** would be an expected by-product in the synthesis of the IRS product **3.15**, the usual ligand SPhos was exchanged for XPhos and the reaction was performed again (Scheme 3.8). This proved to be successful as the desired compound **3.15** was isolated in a 77% overall yield.



Scheme 3.8: Use of XPhos as ligand

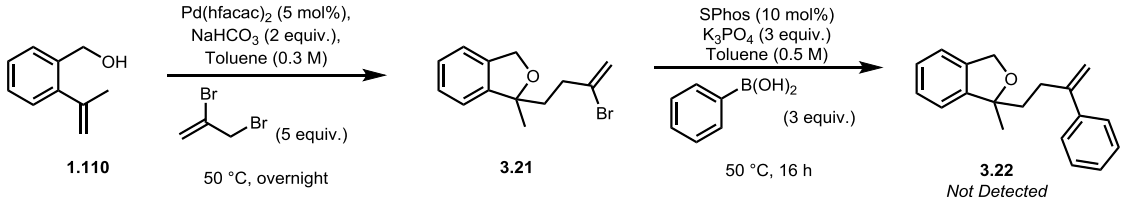
Additionally, other substrates were sought in order to widen the scope of the IRS Suzuki−Miyaura reaction. A halide handle was required and as such both 2,3-dibromopropene and 2,3-dichloropropene were tested with benzoic acid **2.10** and benzylic

alcohol **1.110** (Scheme 3.9). The oxyallylation reaction with 2,3-dibromopropene and 2,3-dichloropropene using benzoic acid **2.10** produced the desired compounds in low yields. However, the oxyallylation reaction using benzylic alcohol **1.110** with 2,3-dibromopropene worked well, garnering the desired isobenzofuran **3.21** in an 85% yield with the bromide handle attached.



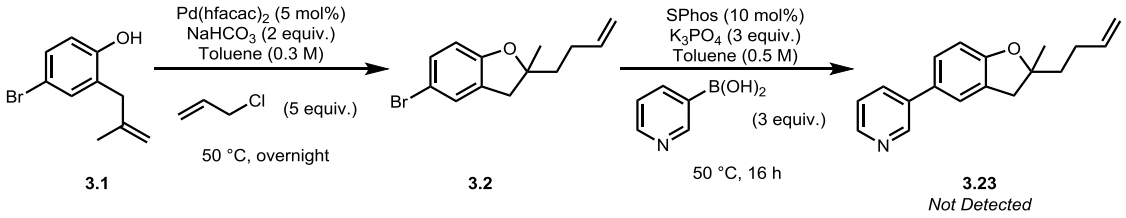
Scheme 3.9: Oxyallylation reaction employing 2,3-dibromopropene and 2,3-dichloropropene

Subjecting benzylic alcohol to optimised IRS for the Suzuki−Miyaura reaction proved unsuccessful, as the desired product was undetected *via* ^{1}H NMR of the crude material (Scheme 3.10).



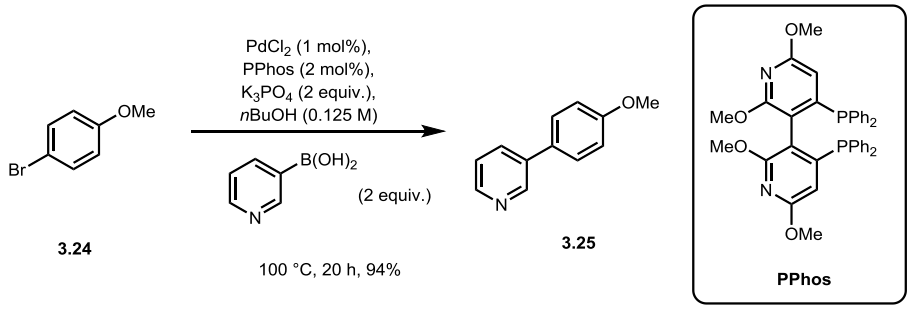
Scheme 3.10: Attempted IRS using benzylic alcohol **1.110**

The pyridine moiety is a prominent component of many pharmaceuticals.[132] Because of its importance, using a pyridinylboronic acid in the Suzuki−Miyaura IRS reaction was desired. However, the reactions pertaining to pyridinylboronic acids have received less attention and are renowned to be difficult coupling partners.[131] Using the previously optimised conditions for 3-pyridinylboronic acid resulted in no formation of the desired IRS product **3.23**, and instead only intermediate **3.2** was isolated (Scheme 3.11).



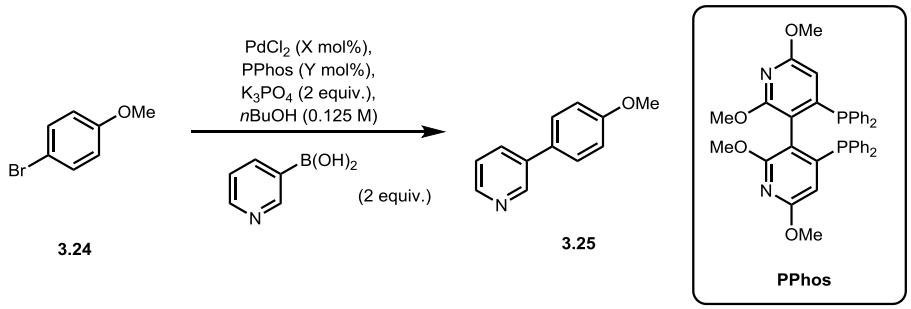
Scheme 3.11: Attemped IRS using 3-pyridinylboronic acid

A search of the literature revealed that a change of solvent and ligand was required.[133] Bromoanisole **3.24** has similar electronics to the oxyallylated intermediate **3.2** that would be generated in the IRS and as such was deemed an ideal precedent (Scheme 3.12).



Scheme 3.12: Suzuki−Miyaura coupling with 3-pyridinylboronic acid[133]

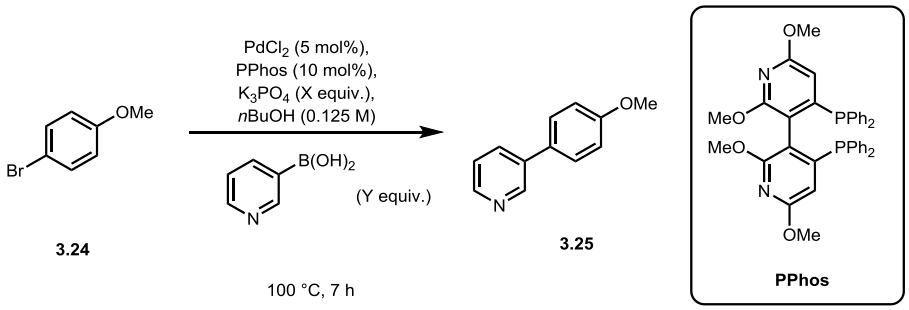
Replicating the above result proved difficult. Applying the conditions outlined in the literature only resulted in starting material (Table 3.4, entry 1). Increasing the catalyst loading and ligand loading resulted in decomposition (entry 2). Decreasing the temperature to 50 °C had no effect on the reaction conversion and only returned starting material (entry 3). Next, the temperature was returned to 100 °C and the time the reaction was performed was investigated (entries 4 – 6). It was found that the reaction time at 8 h produced the best ratio of anisole **3.24** to desired compound **3.25**.



Entry	Catalyst/Ligand Loading	Temperature (°C)	Time (h)	Result 3.24 : 3.25
1	$PdCl_2$ (1 mol%)/ PPhos (2 mol%)	100	20	1.00 : 0.00
2	$PdCl_2$ (5 mol%)/ PPhos (10 mol%)	100	20	Decomp.
3	$PdCl_2$ (5 mol%)/ PPhos (10 mol%)	50	20	1.00 : 0.00
4	$PdCl_2$ (5 mol%)/ PPhos (10 mol%)	100	2	1.00 : 0.53
5	$PdCl_2$ (5 mol%)/ PPhos (10 mol%)	100	5	0.31 : 1.00
6	$PdCl_2$ (5 mol%)/ PPhos (10 mol%)	100	8	0.10 : 1.00

Table 3.4: Towards the optimisation of Suzuki−Miyaura coupling with 3-pyridinylboronic acid

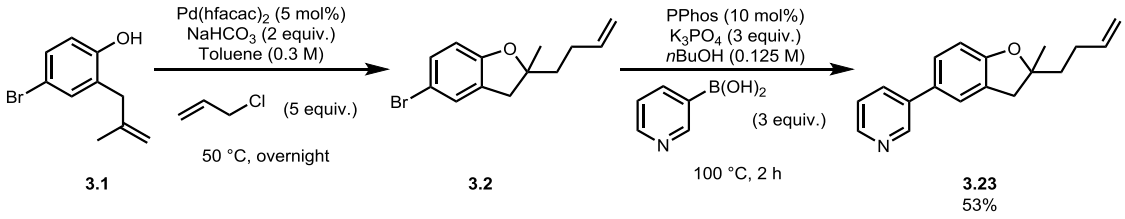
To prevent the reaction running overnight and leading to decomposition, the equivalents of 3-pyridinylboronic acid and base were investigated (Table 3.5). Increasing the equivalents of 3-pyridinylboronic acid to 3 resulted in complete conversion to the desired Suzuki−Miyaura product **3.25** (entry 1). Increasing K_3PO_4 to 3 equivalents resulted in incomplete conversion of the anisole **3.24** (entry 2). Increasing the equivalents of both the 3-pyridinylboronic acid and K_3PO_4 resulted in complete conversion of the starting material to the desired product **3.25** (entry 3). The other IRS Suzuki−Miyaura iterations require 3 equivalents of base and 3 equivalents of boronic acid; thus, for the purposes of consistency, when 3-pyridinylboronic acid was employed three equivalents of each would be used.



Entry	Base (Equiv.)	Boronic Acid (Equiv.)	Result 3.24 : 3.25
1	2	3	0.00 : 1.00
2	3	2	0.11 : 1.00
3	3	3	0.00 : 1.00

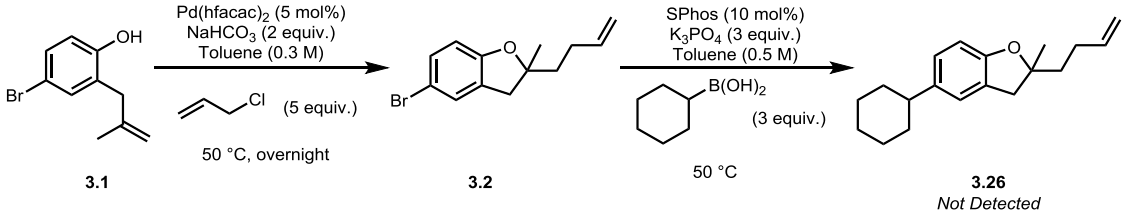
Table 3.5: Varying base and boronic acid equivalents

With the newly developed conditions for the 3-pyridinylboronic acid we sought to incorporate it into full IRS. Gratifyingly, combining both the oxyallylation reaction and the Suzuki−Miyaura reaction using PPhos as the ligand and *n*BuOH at 100 °C worked well to provide the desired IRS compound **3.23** in a 53% yield, with the reaction time shorted to 2 h for the Suzuki−Miyaura coupling (Scheme 3.13).



Scheme 3.13: IRS using 3-pyridinylboronic acid

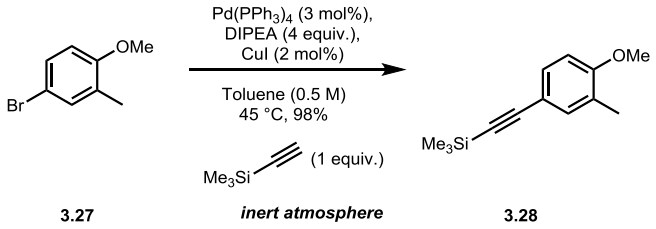
The use of alkyl boronic acids to extend the IRS Suzuki−Miyaura reaction was attempted. Unfortunately, when cyclohexylboronic acid was employed, the desired IRS product **3.26** was not detected and only the bromobenzofuran intermediate **3.2** was observed *via* ^{1}H NMR analysis of the crude material (Scheme 3.14).



Scheme 3.14: Use of cyclohexylboronic acid

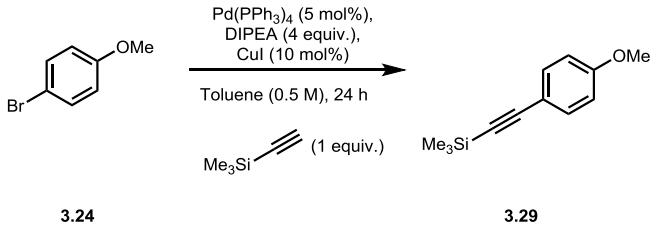
3.3 IRS –The Sonogashira Iteration

The ensuing step in expanding the IRS's available scope was to extend the reaction to incorporate the Sonogashira reaction. Again, this reaction was chosen as it is commonly used by medicinal chemists during the synthesis of bioactive molecules.[128] A patented literature reaction provided a substrate similar in electronics to our own which readily performed the Sonogashira coupling with 2-methyl-4-bromoanisole **3.27** formed in a 98% yield (Scheme 3.15).[134]



Scheme 3.15: Sonogashira reaction of 2-methyl-4-bromoanisole **3.27**

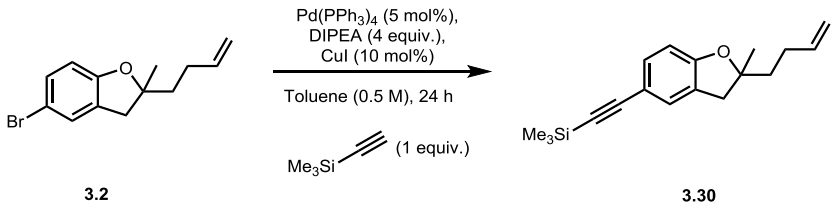
Initial experiments focused on repeating the reaction outlined above (Scheme 3.14). The copper iodide was increased from 4 mol% to 10 mol% loading for the purposes of practical simplicity and the palladium was increased from 3 mol% to 5 mol% catalyst loading in order to replicate the amount of palladium that would be present in the full IRS. Attempts at reproducing the reaction with anisole **3.24** proved difficult (Table 3.6). Starting at 50 °C, the reaction afforded the desired product **3.29**, however, the reaction did not go to complete conversion of starting material (entry 1). Increasing the temperature to both 80 °C and 100 °C had a detrimental effect on the conversion to the desired product **3.29** (entries 2 and 3).



Entry	Temperature (°C)	Result 3.24 : 3.29
1	50	1.8 : 1.0
2	80	10.2 : 1.0
3	100	7.8 : 1.0

Table 3.6: Effect of temperature on Sonogashira reaction

Owing to the lack of success with bromoanisole **3.24**, it was theorised that the Sonogashira reaction would perform better starting from the already heterocyclised bromobenzofuran **3.2**, which is the intermediate produced in the desired IRS. Starting at 50 °C, the reaction afforded poor conversion to the desired product **3.30** (Table 3.7, entry 1). Increasing the temperature to 80 °C, then 100 °C, hindered the conversion to the desired Sonogashira product **3.30** (entries 2 and 3). With this, the reaction temperature was lowered to room temperature, however, this resulted in no conversion to the desired product **3.30**, and only starting material was recovered (entry 4).

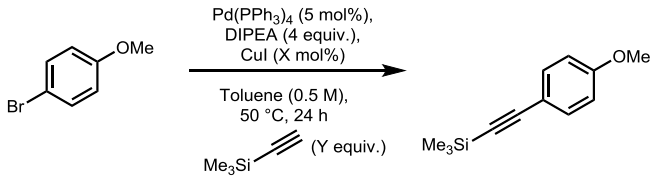


3.2 **3.30**

Entry	Temperature (°C)	Result 3.2 : 3.30
1	50	4.6 : 1.0
2	80	9.9 : 1.0
3	100	9.9 : 1.0
4	rt	1.0 : 0.0

Table 3.7: Sonogashira reaction using bromobenzofuran **3.2**

The equivalents of the alkyne employed were investigated next, in order to facilitate the formation of the desired product **3.29** at 50 °C under air. The equivalents were increased to both 3 and 5 equivalents respectively, with no obvious increase in conversion to the coupled product **3.29** (Table 3.8, entries 1 and 2). The copper iodide loading was decreased to 4 mol%, with the alkyne equivalents returning to 1, which improved the ratio of starting material to desired product **3.29**; however, incomplete conversion was still an issue (entry 3). Increasing the copper iodide loading to 30 mol% and 50 mol% had no drastic increase in the conversion of starting material (entry 4 and 5).

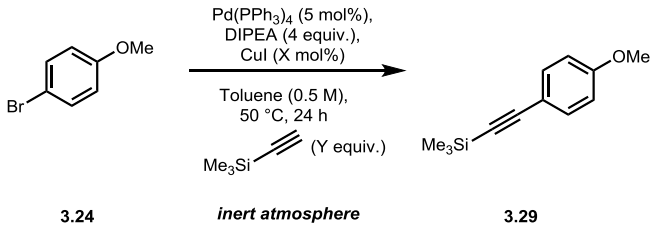


3.24 **3.29**

Entry	CuI (mol%)	Alkyne Equivalents	Results **3.24 : 3.29**
1	10	3	4.6 : 1.0
2	10	5	4.5 : 1.0
3	4	1	2.8 : 1.0
4	30	1	2.3 : 1.0
5	50	1	2.4 : 1.0

Table 3.8: Screening of CuI and Alkyne equivalents under air

Subsequently, the research was directed towards varying the copper iodide loading and the equivalents of alkyne in the reaction under an inert atmosphere. The use of copper iodide at 4 mol% loading with 1 equivalent of alkyne under an inert atmosphere improved the ratio in favour of the desired product **3.29** (Table 3.9, entry 1). The copper iodide loading was then increased to 10 mol% and the alkyne equivalents increased to 3, with the ratio of starting material to product not improving (entry 2). The alkyne equivalents were then increased to 5, however, this had a detrimental effect on the conversion (entry 3). The investigation then focused on increasing the copper iodide loading while utilising 1 equivalent of alkyne. Unfortunately, increasing the loading to 30 mol%, 50 mol%, and 100 mol% had an adverse effect on the conversion of starting material (entries 4−6). Lastly, 10 mol% of copper iodide with 1 equivalent of alkyne added initially, followed by the addition of another equivalent of alkyne 5 hours later, afforded an improved ratio of starting material to desired product up to this point (entry 7).

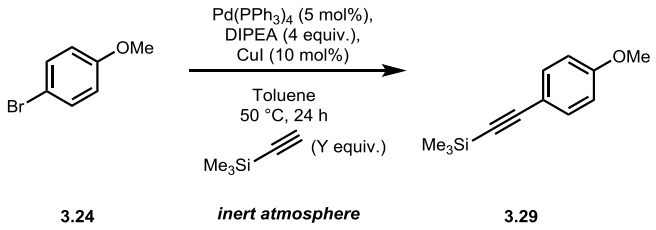


3.24 ***inert atmosphere*** **3.29**

Entry	CuI (mol%)	Alkyne Equivalents	Results **3.24 : 3.29**
1	4	1	0.8 : 1.0
2	10	3	0.9 : 1.0
3	10	5	2.8 : 1.0
4	30	1	2.4 : 1.0
5	50	1	3.8 : 1.0
6	100	1	1.0 : 0.0
7	10	1+1	0.7 : 1.0

Table 3.9: Screening of CuI and Alkyne equivalents in an inert atmosphere

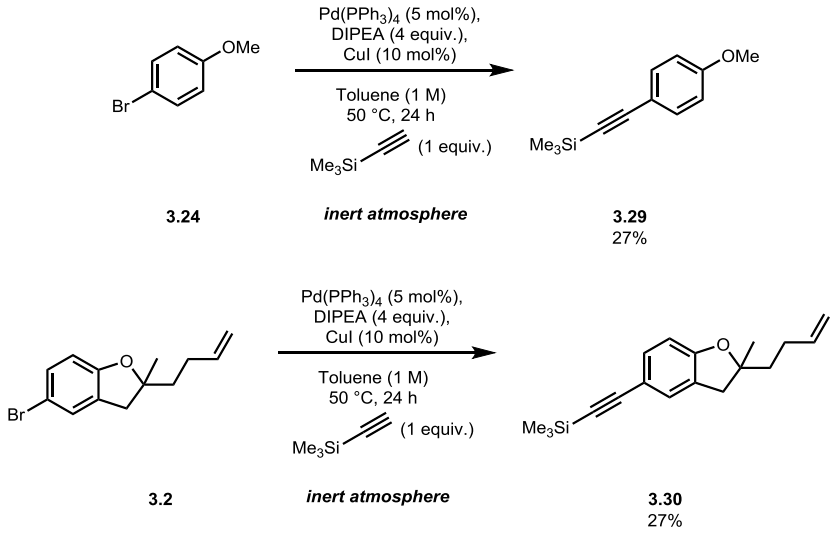
The concentration of the reaction was explored next (Table 3.10). Lowering the concentration to 0.25 M had a negligible effect on the conversion of bromoanisole **3.24** into the Sonogashira product **3.29** (entry 1). Increasing the concentration to 1.0 M afforded a promising ratio of starting material to product (entry 2); however, increasing the concentration further to 2.0 M had a deleterious effect on the conversion (entry 3). Attempting to improve upon the best ratio (entry 1), three equivalents of alkyne were added to the reaction mixture in order to force the conversion; however, this had a negative effect on the conversion (entry 4).



Entry	Concentration (M)	Alkyne Equivalents	Result 3.24 : 3.29
1	0.25	1	0.7 : 1.0
2	1.0	1	0.3 : 1.0
3	2.0	1	0.5 : 1.0
4	1.0	3	0.7 : 1.0

Table 3.10: Concentration effects on the reaction

The best conditions achieved (Table 3.10, entry 2), thus far, were then performed again with bromoanisole **3.24** in order to obtain an isolatable yield (Scheme 3.16). Additionally, the conditions were tested with bromobenzofuran **3.2**, the intermediate that would be generated in the desired IRS. Disappointingly, both bromoanisole **3.24** and bromobenzofuran **3.2** achieved a 27% yield when subjected to the conditions outlined in Table 3.10, entry 2. Currently, the IRS Sonogashira iteration requires more optimisation.

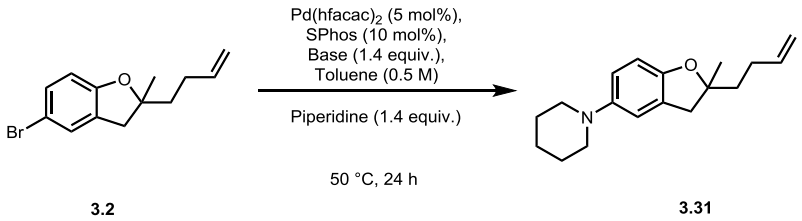


Scheme 3.16: Best conditions developed for the Sonogashira reaction

3.4 IRS –TheBuchwald−Hartwig Iteration

The Buchwald−Hartwig amination is a reaction used widely in the synthesis of pharmaceuticals and natural products.[135] From our previous work with the IRS Suzuki−Miyaura iteration, it was known that the ligand SPhos was also able to promote the Buchwald−Hartwig reaction.[136] The palladium-catalysed study of bromobenzofuran **3.2** with the Buchwald−Hartwig reaction started with a palladium(II) catalyst, SPhos as the

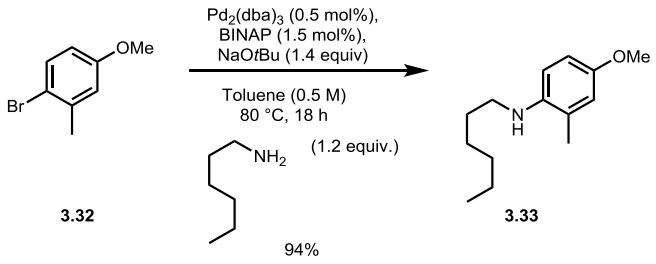
ligand and piperidine as the amine (Table 3.11). The use of NaO*t*Bu or K_3PO_4 as base resulted in returning only starting material (entries 1 and 2). This indicated that the palladium(II) precatalyst was not being reduced to the required palladium(0) catalyst and as such the addition of 10 mol% of phenylboronic acid was used to reduce the catalyst with a combination of the aforementioned bases (entries 3 and 4). Unfortunately, this attempt resulted in no improvement.



Entry	Base/ Addidive (10 mol%)	Result 3.2 : 3.31
1	NaO*t*Bu	1.0 : 0.0
2	K_3PO_4	1.0 : 0.0
3	NaO*t*Bu/ $PhB(OH)_2$	1.0 : 0.0
4	K_3PO_4/ $PhB(OH)_2$	1.0 : 0.0

Table 3.11: Use of SPhos as ligand with base and additive screen

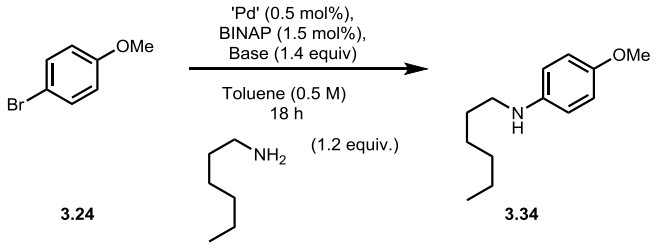
A report by Buchwald and co-workers demonstrated that 3-methyl-4-bromoanisole **3.32** with similar electronics to the benzofuran **3.2** substrate could undergo the Buchwald−Hartwig amination.[137] Through the use of the ligand BINAP, with low catalyst loading at 80 °C in toluene 3-methyl-4-bromoanisole **3.32** underwent the desired Buchwald−Hartwig amination in 94% yield with hexylamine (Scheme 3.17).



Scheme 3.17: Buchwald−Hartwig amination on anisole **3.32**

Replicating the above result was the priority in developing the Buchwald−Hartwig iteration. Using bromoanisole **3.24**, the exact conditions used by Buchwald and co-workers were employed, however, only starting material was recovered (Table 3.12, entry 1). The

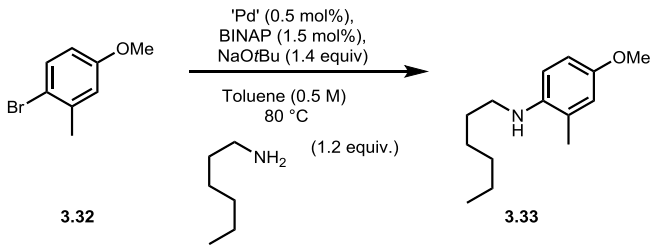
catalyst was changed to $Pd(OAc)_2$ (entry 2), and the base was changed to KO*t*Bu (entry 3), however, no improvement was observed *via* ^{1}H NMR analysis of the crude material. The temperature was increased to 100 °C, which resulted in the synthesis in a trace amount of the desired product **3.34** (entry 4). All reactions below were also performed with distilled amine and purified bases, yet, no improvement was witnessed.



Entry	Pd	Base	Temp (°C)	Result 3.24 : 3.34
1	$Pd_2(dba)_3$	NaO*t*Bu	80	1.0 : 0.0
2	$Pd(OAc)_2$	NaO*t*Bu	80	1.0 : 0.0
3	$Pd_2(dba)_3$	KO*t*Bu	80	1.0 : 0.0
4	$Pd_2(dba)_3$	NaO*t*Bu	100	Trace

Scheme 3.12: Attempted Buchwald−Hartwig amination

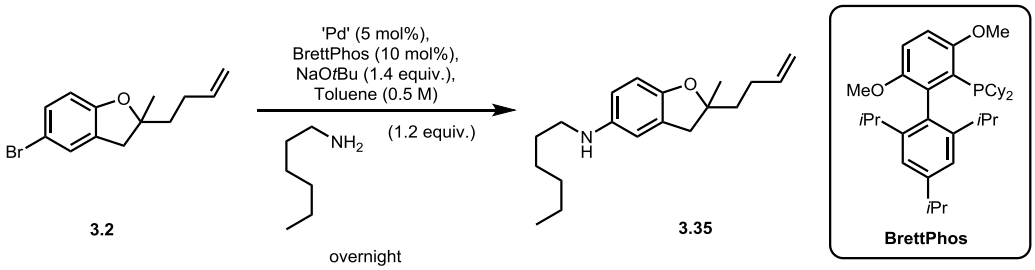
The lack of success with bromoanisole **3.24** prompted a change in substrate to 3-methyl-4-bromoanisole **3.32**. Using the literature conditions, initial results were positive with the Buchwald−Hartwig product being garned in generous amounts after 15 h (Table 3.13, entry 1). Increasing the time to 18 h improved the ratio further (entry 2). The reaction was then attempted starting from a Pd(II) catalyst and was left to react for 72 hours, however, complete conversion of starting material did not occur (entry 3).



Entry	Pd	Time (h)	Result 3.32 : 3.33
1	$Pd_2(dba)_3$	15	1.0 : 3.5
2	$Pd_2(dba)_3$	18	1.0 : 5.1
3	$Pd(hfacac)_2$	72	1.0 : 4.5

Table 3.13: Use of 3-methyl-4-bromoanisole **3.32** as substrate

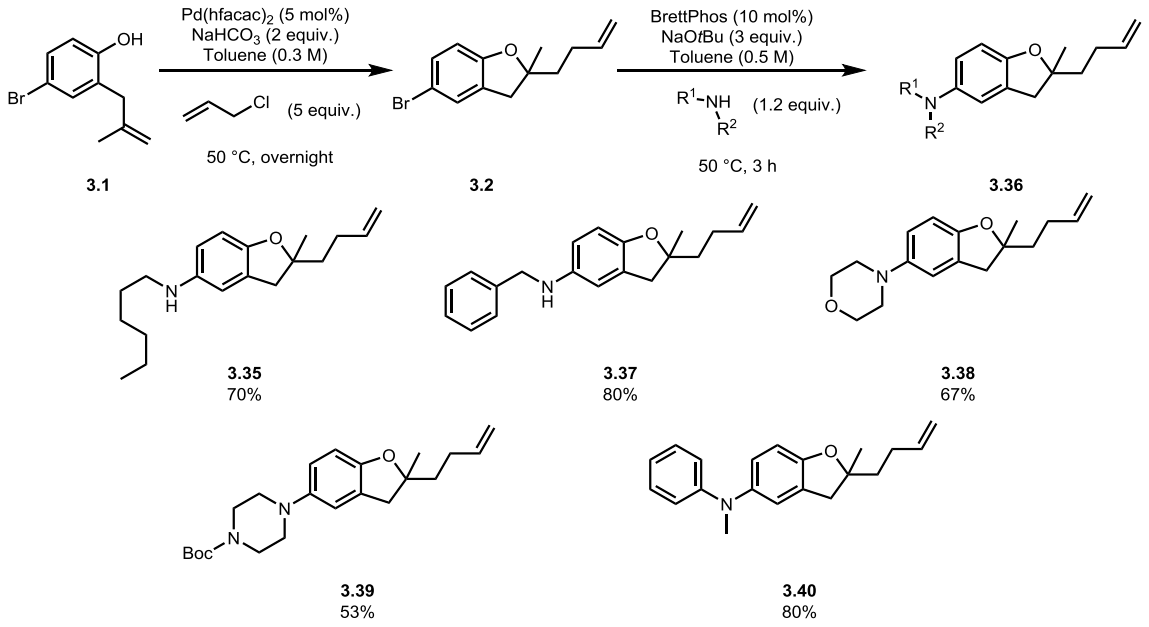
A search of the literature revealed that the ligand in the Buchwald−Hartwig amination is of key importance and that BrettPhos instead of BINAP is more suited to the Buchwald−Hartwig reaction for our substrate.[136, 138] Utilising similar conditions to those previously, albeit with a different ligand, the study of the effect of BrettPhos on our Buchwald−Hartwig amination was initiated (Table 3.14). Irrespective of whether the catalyst was $Pd_2(dba)_3$ or $Pd(hfacac)_2$ at 50 °C or 80 °C the reaction went to complete conversion to the desired Buchwald−Hartwig product **3.35** (entries 1 – 4). In instances where Pd(II) catalysts were employed, the reduction of the palladium(II) was envisaged to occur *via* a β-hydride elimination from a Pd(II)-amine complex.



Entry	Pd	Temp (°C)	Result 3.2 : 3.35
1	$Pd_2(dba)_3$	80	0.0 : 1.0
2	$Pd_2(dba)_3$	50	0.0 : 1.0
3	$Pd(hfacac)_2$	80	0.0 : 1.0
4	$Pd(hfacac)_2$	50	0.0 : 1.0

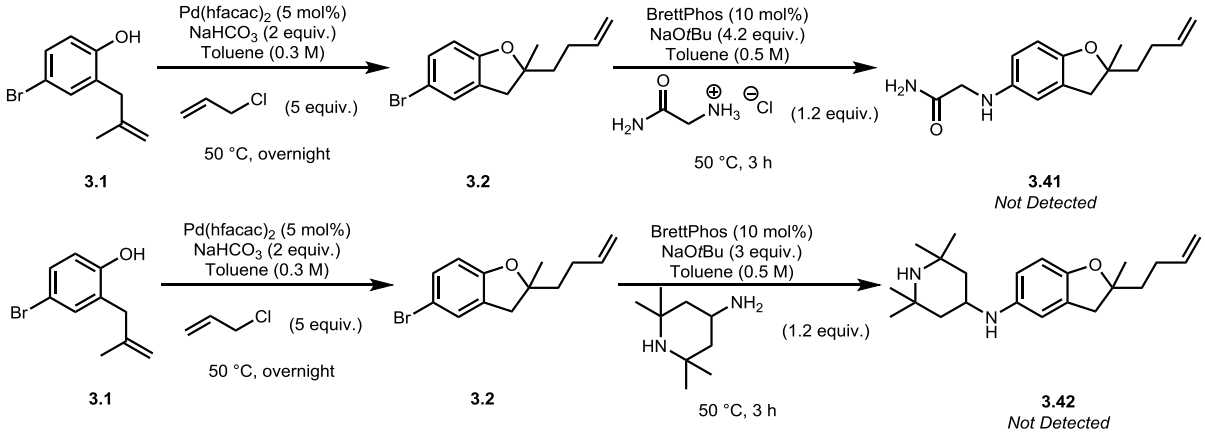
Table 3.14: Effect of BrettPhos on the Buchwald−Hartwig amination

For the full IRS Buchwald−Hartwig iteration it was found that in order for the reaction to proceed to complete conversion, the equivalents of base had to be increased to 3. Additionally, the reaction time for each amine was shortened to 3 hours. As can be seen below, the coupling works well with primary amines, secondary amines and a secondary aniline, with yields ranging from 53% to 83% over the two steps (Scheme 3.18).



Scheme 3.18: Heteroallylation−amination sequence

Not all substrates tested in the IRS Buchwald−Hartwig iteration were successful. The use of an amide hydrochloride salt did not produce the desired product **3.41**, even when the base was increased to 4.2 equivalents to account for the required deprotonation of the amine salt (Scheme 3.19). Analysis, *via* ^{1}H NMR of the crude material, revealed only the bromobenzofuran intermediate **3.2**. Additionally, a diamine was attempted, however, it proved unsuccessful as none of the desired product was detected *via* ^{1}H NMR of the crude material, and only bromobenzofuran intermediate **3.2** was present.

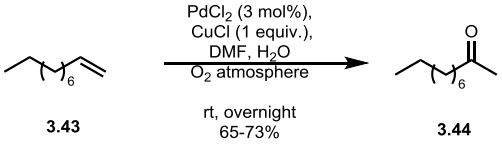


Scheme 3.19: Unsuccessful heteroallylation−amination sequence

3.5 IRS – Wacker−Tsuji Oxidation Iteration

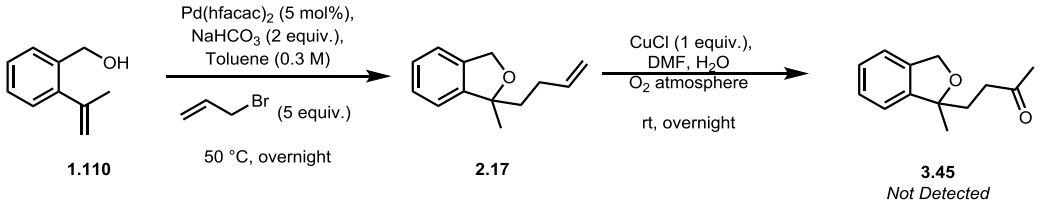
The success of the IRS for the Suzuki−Miyaura and Buchwald−Hartwig iterations, where the bromide handle was successfully engaged with, prompted the investigation for the Wacker−Tsuji oxidation for which the alkene in the isohypsic heteroallylation reaction will

be manipulated further. With this, the literature was consulted for a suitable precedent for the Wacker−Tsuji oxidation. Tsuji and co-workers report that long chain alkene decene **3.43**, when placed in the presence of 3 mol% palladium(II) catalyst with 1 equivalent of copper chloride in a DMF/H_2O mixture under an O_2 atmosphere generates the alkyl ketone **3.44** in good yields after stirring at room temperature overnight (Scheme 3.20).[139]



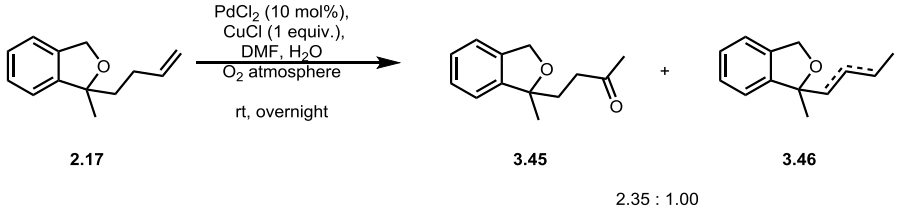
Scheme 3.20: Wacker−Tsuji oxidation of decene **3.43**

The success of the Wacker−Tsuji oxidation over the years, and in particular the conditions outlined above, led to the belief that the procedure would be robust enough to handle the full IRS. As such, benzylic alcohol **1.110** was subjected to the oxyallylation reaction followed by the Wacker−Tsuji oxidation through the addition of 1 equivalent of copper chloride, DMF/H_2O under an O_2 atmosphere (Scheme 3.21). The reaction was left to stir at room temperature overnight; however, none of the desired product **3.45** was observed *via* ^{1}H NMR analysis of the crude material, and only intermediate **2.17** was isolated.



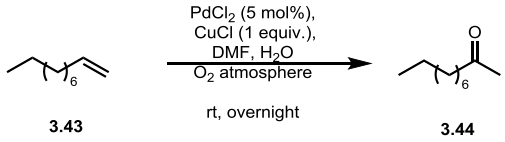
Scheme 3.21: Attemped IRS

Establishing whether it is the conditions that cause the failed Wacker−Tsuji oxidation or the substrate were next explored. Isobenzofuran **2.17** was placed under analogous conditions to those developed by Tsuji and co-workers, albeit with the catalyst loading increased to 10 mol% (Scheme 3.22). The reaction did generate the desired oxidised product **3.45**, however, isomerisation of the alkene was also a problem with considerable amounts of isomerised alkene **3.46** formed. A ratio of 2.35 : 1.00 of desired **3.45** to isomerised isobenzofuran **3.46** was observed.



Scheme 3.22: Wacker−Tsuji oxidation of isobenzofuran **2.17**

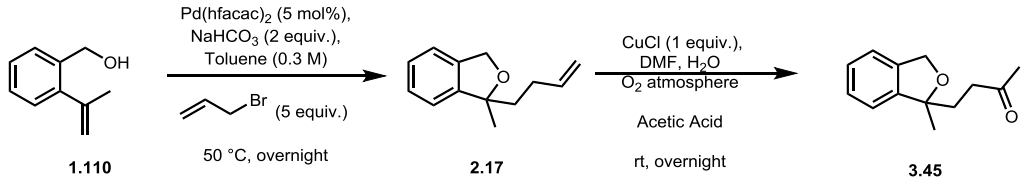
The Wacker−Tsuji oxidation conditions developed by Tsuji and co-workers were next tested on the exact substrate used in their publication, decene **3.43**. The catalyst loading was increased to 5 mol% from the 3 mol% in the report in order to replicate the amount of palladium that would be present in the IRS. Pleasingly, the reaction resulted in complete conversion to the desired oxidised product **3.44** (Table 3.15, entry 1). The isohypsic oxyallylation reaction requires 2 equivalents of $NaHCO_3$. Due to this requirement, the Wacker−Tsuji oxidation was tested with 2 equivalents of $NaHCO_3$, however, this had a detrimental effect on the conversion of decene **3.43** to the desired ketone **3.44** (entry 2).



Entry	Base	Result 3.43 : 3.44
1	No Base	0.0 : 1.0
2	$NaHCO_3$ (2 equiv.)	1.0 : 1.7

Table 3.15: Effect of $NaHCO_3$ on Wacker−Tsuji oxidation

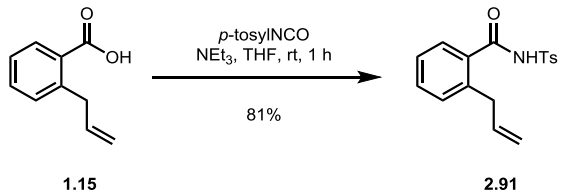
With the presence of base having a deleterious effect on the Wacker−Tsuji oxidation, and with the base being a requirement for the oxyallylation reaction, it was deemed prudent to neutralise the base with addition of acetic acid in the second step (Table 3.16). The use of 2, 4 and 20 equivalents of acetic acid to neutralise $NaHCO_3$ delivered no improvement on the reaction and only returned the intermediate isobenzofuran **2.17** (entries 1 – 3).



Entry	Acetic Acid (equivalents)	Result 2.17 : 3.45
1	2	1.0 : 0.0
2	4	1.0 : 0.0
3	20	1.0 : 0.0

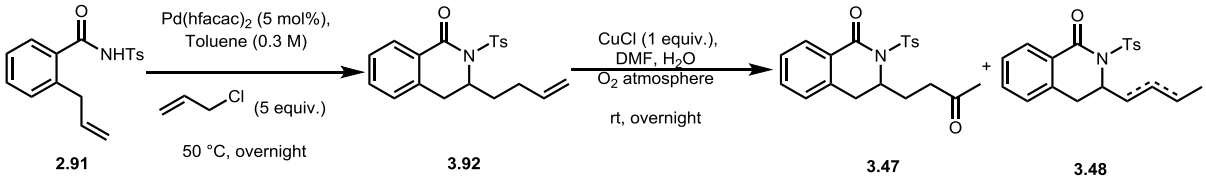
Table 3.16: The use of acetic acid in attempted IRS

With the benzylic alcohol **1.110** proving an unsuccessful substrate for the IRS Wacker−Tsuji oxidation, a change of tactic was undertaken. From previous investigations conducted within the France group, it was already known that tosylamide **2.91** could perform the aminoallylation reaction without the presence of base. Because of this tosylamide **2.91** was synthesised from 2-allylbenzoic acid **1.15** in one step and in good yield following a procedure from Waser and co-workers (Scheme 3.23).[140]



Scheme 3.23: Synthesis of tosylamide **2.91**

Attempting the full IRS for tosylamide **2.91** began with the standard conditions developed from a previous project within the France group, with H_2O as a co-solvent and 2 equivalents of KH_2PO_4.[44] The presence of base proved to hinder the Wacker−Tsuji oxidation with only the cyclised intermediate detected *via* analysis of the ^{1}H NMR of the crude material (Table 3.16, entry 1). Next, the IRS was performed without base which in turn did provide the desired oxidised product **3.47**. However, unreacted alkene **2.92** and isomerised alkene **3.48** were still present in sufficient quantity (entry 2). In light of the results, the reaction was performed with no KH_2PO_4 or water in the aminoallylation reaction. Although the desired ketone **3.47** was garnered, the major product of the reaction was the isomerised alkene (entry 3).

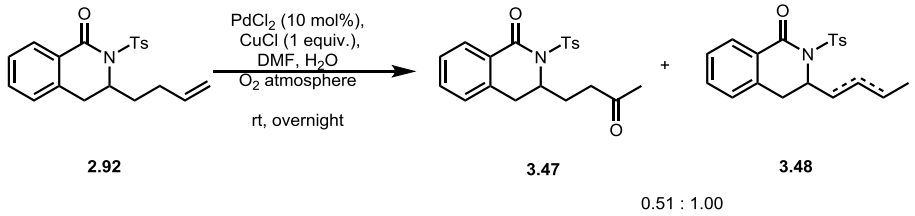


Entry	Base	Additive	Result **2.92 : 3.47 : 3.48**
1	KH_2PO_4 (2 equiv.)	H_2O (co-solvent)	1.0 : 0.0 : 0.0
2	None	H_2O (co-solvent)	1.0 : 1.3 : 0.8
3	None	None	0.0 : 0.5 : 1.0

Table 3.16: Wacker−Tsuji oxidation IRS with tosylamide **2.91**

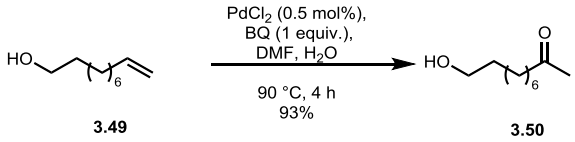
As before, determining whether the intermediate generated in the IRS would undergo the required Wacker−Tsuji oxidation was paramount. The aminocycle **2.92** was subjected to

the conditions developed by Tsuji and co-workers with the exception of the catalyst loading which was increased to 10 mol% (Scheme 3.24). Under the reaction conditions, the desired oxidised tosylamide **3.47** was formed; however, the predominant product of the reaction was the isomerised alkene **3.48**.



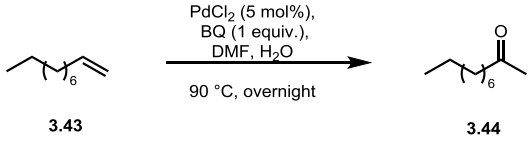
Scheme 3.24: Wacker−Tsuji oxidation starting from aminocycle **2.92**

The lack of success with the Wacker−Tsuji oxidation conditions developed by Tsuji and co-workers for our substrates led to a change in direction. Similar conditions were found to those described above, with the exception being the oxidant was changed from copper chloride to *p*-benzoquinone (Scheme 3.25).[141] Subjecting 10-decenol **3.49** to the oxidising conditions, provided 11-hydroxy-2-undecanone **3.50** in a 93% yield.



Scheme 3.25: Wacker−Tsuji oxidation with *p*-benzoquinone as the oxidant

Subjecting decene **3.43** to the conditions outlined above (Scheme 3.25), resulted in complete conversion to the desired ketone **3.44** (Table 3.17, entry 1). With the presence of base hindering the reaction in the past, the reaction was attempted in the presence of 2 equivalents of $NaHCO_3$ which hindered the formation of the desired ketone **3.44** (entry 2). Adding 4 equivalents of acetic acid did not bear any improvement on the aforementioned reaction (entry 3). Changing from acetic acid to *p*-toluenesulfonic acid, however did result in complete conversion to the desired ketone **3.44** (entry 4). Changing base to KH_2PO_4 and adding 4 equivalents of either acetic acid (entry 5), or 4 equivalents of *p*-toluenesulfonic acid resulted in complete conversion to the desired ketone **3.44** (entry 6).

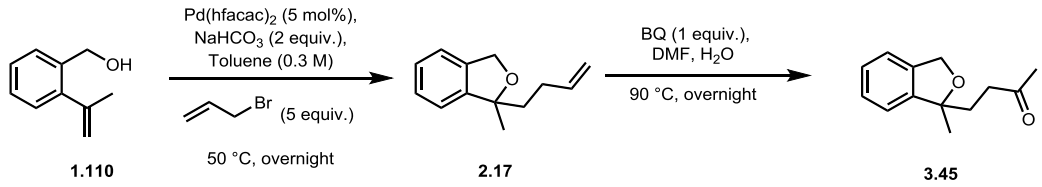


3.43 3.44

Entry	Base (2 equiv.)	Acid (4 equiv.)	Result 3.43 : 3.44
1	None	None	0.0 : 1.0
2	$NaHCO_3$	None	1.0 : 0.3
3	$NaHCO_3$	AcOH	1.0 : 0.2
4	$NaHCO_3$	TsOH	0.0 : 1.0
5	KH_2PO_4	AcOH	0.0 : 1.0
6	KH_2PO_4	TsOH	0.0 : 1.0

Table 3.17: Screening Wacker−Tsuji oxidation with different bases and acids

Benzylic alcohol **1.110** was next subjected to the full IRS for the Wacker−Tsuji oxidation under the new conditions (Table 3.18). When no acid was added to the second step (entry 1), and when 4 equivalents of acetic acid is added to the second step, only intermediate **2.17** can be observed *via* analysis of ^{1}H NMR of the crude material (entry 2). However, with the addition of 4 equivalents of *p*-toluenesulfonic acid to the second step, the reaction garnered the desired ketone **3.45** (entry 3). Moderate conversion was still an issue.



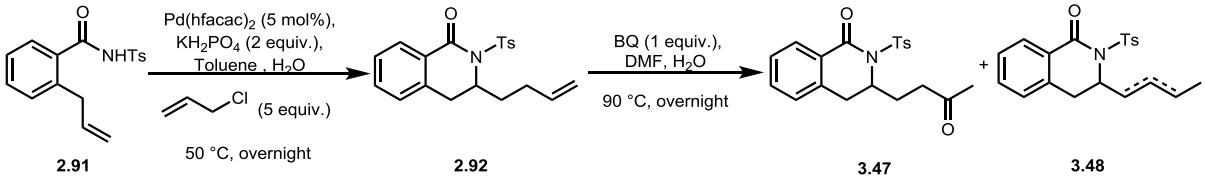
1.110 2.17 3.45

Entry	Acid (4 equiv.)	Result 2.17 : 3.45
1	None	1.00 : 0.00
2	AcOH	1.00 : 0.00
3	TsOH	1.00 : 0.95

Table 3.18: IRS for the Wacker−Tsuji oxidation for benzylic alcohol **1.110**

Uninspiring results with benzylic alcohol **1.106** led the inquiry towards tosylamide **2.91**. Combining both the optimised aminoallylation reaction and the Wacker−Tsuji oxidation garnered none of the desired ketone **3.47** with only the aminocycle **2.92** detected *via* analysis of the ^{1}H NMR of the crude material (Table 3.19, entry 1). Adding 4 equivalents of acetic acid to the Wacker−Tsuji step only resulted in the isomerised alkene **3.48** (entry 2). The addition of 4 equivalents of *p*-toluenesulfonic acid to the second step did generate a

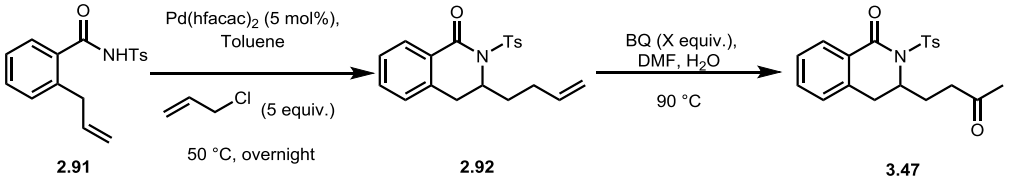
small amount of desired ketone **3.47**, however, unreacted aminocycle **2.92** was by far more prominent (entry 3).



Entry	Acid (4 equiv.)	Results **2.92 : 3.47 : 3.48**
1	None	1.00 : 0.00 : 0.00
2	AcOH	0.00 : 0.00 : 1.00
3	TsOH	1.00 : 0.22 : 0.00

Table 3.19: IRS for the Wacker−Tsuji oxidation for tosylamide **2.91**

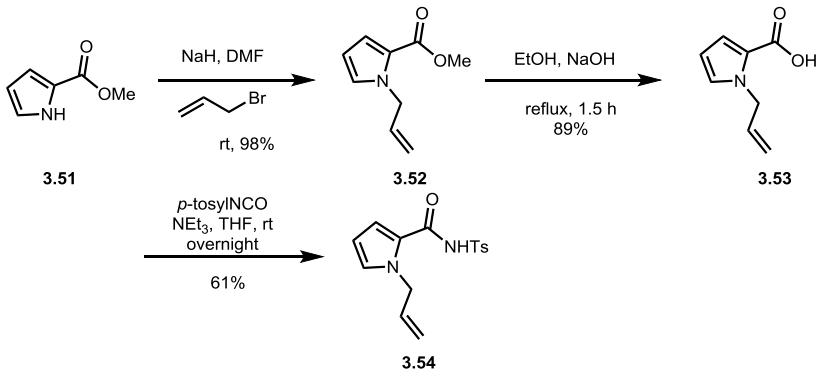
The IRS for the Wacker−Tsuji oxidation thus far proved unsuccessful in the presence of a base and acid. Fortunately, the aminoallylation reaction is known to proceed well without base in the reaction mixture. Initial investigations began with water as the co-solvent in the first step, 1 equivalent of *p*-benzoquinone and the second step performed for 24 hours, which synthesised the desired ketone **3.47**, but unreacted aminocycle **2.92** was still present (Table 3.20, entry 1). Removal of the water as a co-solvent in the first step resulted in an improved ratio; however, unreacted aminocycle **2.92** was still a problem (entry 2). In order to encourage conversion of the aminocycle **2.92** to the desired ketone **3.47**, the equivalents of *p*-benzoquinone were increased to 2.5, and were tested with and without water in the first step of the reaction (entries 3 and 4). Monitoring the reaction *via* TLC analysis revealed complete conversion of the aminocycle **2.92** to the desired ketone **3.47** occurred after 96 hours for both the reactions. Although the addition or exclusion of water in the first step proved successful, the presence of water in the first step appeared make the ^{1}H NMR of the crude material cleaner and for this reason it was selected as the optimal conditions to take the reaction forward. Applying the optimised IRS to obtain a yield resulted in an isolated yield of 54% over the two steps.



Entry	Water (co-solvent)	BQ (Equiv.)	Time (h)	Result 2.92 : 3.47
1	Yes	1	24	1.00 : 1.10
2	No	1	24	1.00 : 2.16
3	Yes	2.5	96	0.00 : 1.00
4	No	2.5	96	0.00 : 1.00 (54%)

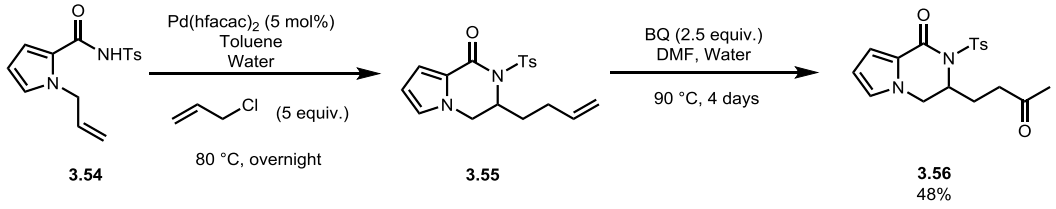
Table 3.20: Optimisation of the IRS for the Wacker−Tsuji oxidation

With optimised conditions having been developed for tosylamide **2.91**, the next goal was to increase the substrate scope for the IRS. It was proposed that pyrrole containing tosylamide **3.54** would be suitable as it too readily underwent the aminoallylation sequence.[44] Pyrrole **3.54** was synthesised in three steps from methyl pyrrole-2-carboxylate **3.51** following a known procedure (Scheme 3.26).[140] Pyrrole **3.51** was subjected to base-promoted allylation conditions to afford *N*-allyl pyrrole **3.52**. The substrate was then complete through ester hydrolysis followed by formation of the tosylamide **3.54** using tosyl isocyanate.



Scheme 3.26: Synthesis of pyrrole **3.54**

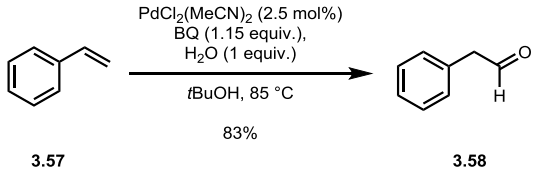
With the pyrrole **3.54** synthesised, there was no guarantee the full IRS sequence would work with this substrate. Subjecting pyrrole **3.54** to the optimised conditions for the IRS for the Wacker−Tsuji oxidation worked well and produced the desired ketone **3.56** in a 48% yield over two steps (Scheme 3.27).



Scheme 3.27: Successful heteroallylation−oxidation sequence for pyrrole **3.54**

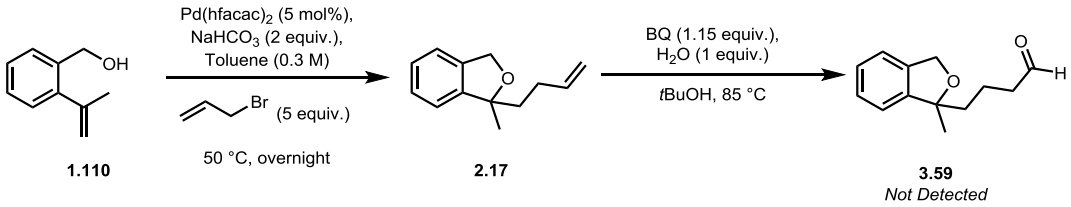
3.6 IRS – Feringa−Grubbs−Wacker Oxidation Iteration

The ability to exert control and oxidise the terminal alkene at the internal position to form the ketone or at the terminal carbon to form the aldehyde is a powerful tool in palladium-catalysis. It is only recently that palladium-catalysed aldehyde selective oxidation of an alkene has been made possible. Early reports by Grubbs and co-workers describe the control to form the aldehyde on styrenyl compounds (Scheme 3.28).[127c] When styrene **3.57** is placed in an environment with a palladium(II) catalyst, stoichiometric *p*-benzoquinone and water, with *t*BuOH as the solvent at 85 °C the desired aldehyde **3.58** is formed in an 83% yield.



Scheme 3.28: Aldehyde selective Wacker oxidation for styrene **3.57**

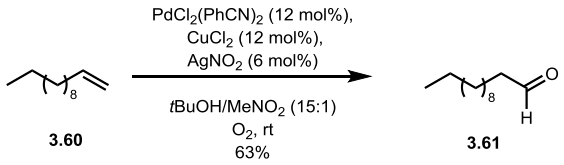
Although only successful for styrenyl compounds, the conditions developed by Grubbs and co-workers, outlined above, were attempted for the full IRS due to the operational simplicity of the procedure. Unsurprisingly, the reaction never yielded any of the desired aldehyde **3.59** and only alkene intermediate **2.17** was isolated (Scheme 3.29).



Scheme 3.29: Attempted full IRS for aldehyde selective Wacker oxidation

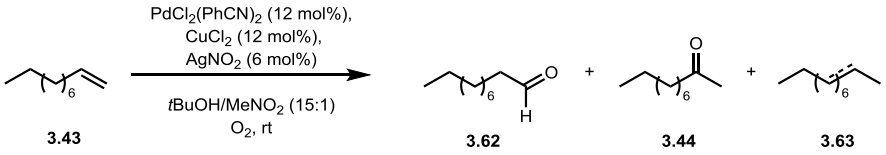
Extensive work on the aldehyde selective Wacker reaction has been performed by Grubbs and co-workers in recent years.[127b, 127f, 142] A relevant paper, by Grubbs and co-workers, reports the aldehyde selective oxidation for unbiased alkenes.[143] In the presence of catalytic $PdCl_2(PhCN)_2$, $CuCl_2$, $AgNO_2$, an O_2 atmosphere and a solvent mixture of

*t*BuOH/$MeNO_2$ (15:1) at room temperature, the alkene dodecene **3.60** is oxidised to the aldehyde **3.61** in a 63% yield (Scheme 3.30).



Scheme 3.30: Aldehyde selective oxidation for unbiased alkenes

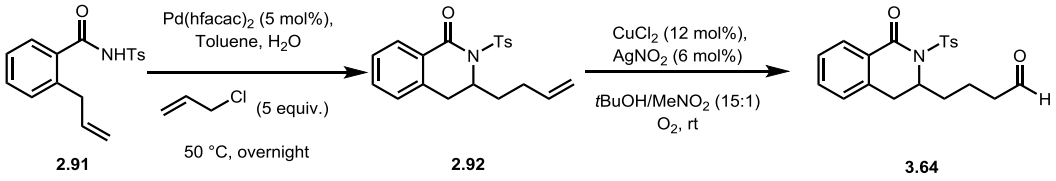
Applying the exact conditions above, to decene **3.43**, resulted in the aldehyde **3.62** being synthesised as the major product with the ketone **3.44** formed in a similar ratio to those observed by Grubbs and co-workers (Table 3.21, entry 1). The addition of 2 equivalents of $NaHCO_3$ (entry 2), and KH_2PO_4 (entry 3) had a negative effect on the conversion and the ratio of desired aldehyde **3.62** to ketone **3.44**. Also both formed prominent amounts of the isomerised alkene **3.63**. The results below, rule out the use of base in the heteroallylation reaction.



Entry	Base (2 equiv.)	Result **3.62 : 3.44 : 3.63**
1	None	1.00 : 0.22 : 0.00
2	$NaHCO_3$	0.12 : 0.37 : 1.00
3	KH_2PO_4	2.30 : 1.70 : 1.00

Table 3.21: Effect of base on the aldehyde selective Wacker reaction

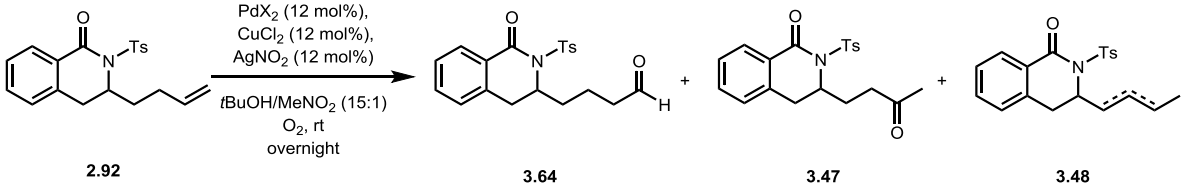
The full IRS – Feringa−Grubbs−Wacker Oxidation was attempted starting from tosylamide **2.91**, with no base present (Table 3.22, entry 1). A small amount of the desired aldehyde **3.64** was observed via analysis of the ^1H NMR of the crude material; however, the major product was the aminocycle **2.92**. The addition of 2 equivalents of KH_2PO_4 resulted in only the aminocycle **2.92** being isolated, with no formation of the desired aldehyde **3.64**.



Entry	Base (2 equiv.)	Result 2.92 : 3.64
1	None	1.00 : 0.07
2	KH_2PO_4	1.00 : 0.00

Table 3.22: Full IRS sequence for tosylamide **2.91**

To determine whether our substrate was suitable under the conditions employed, aminocycle **2.92** was subjected to the conditions developed by Grubbs and co-workers for unbiased alkenes.[143] The $AgNO_2$ loading was increased from 6 mol% to 12 mol% for practical purposes. It was noted by Grubbs and co-workers that the $AgNO_2$ loading at 12 mol% did not have a deleterious effect on the reaction. Applying the standard conditions to tosylamide **2.92**, with $PdCl_2(PhCN)_2$ as the catalyst resulted in complete conversion of the aminocycle **2.92** to oxidised products **3.64** and **3.47** (Table 3.23, entry 1). The change of catalyst to $PdCl_2$ resulted in no conversion with only starting material **2.92** being isolated (entry 2). The use of $Pd(hfacac)_2$ returned only isomerised starting material **3.48** exclusively (entry 3).

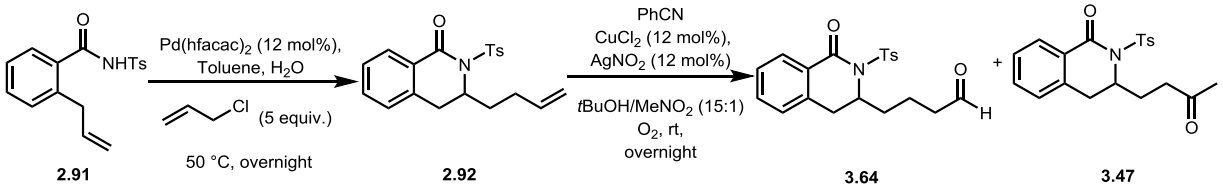


	Pd(II)	Result 2.92 : 3.64 : 3.47 : 3.48
1	$PdCl_2(PhCN)_2$	0.00 : 1.00 : 0.23 : 0.00
2	$PdCl_2$	1.00 : 0.00: 0.00 : 0.00
3	$Pd(hfacac)_2$	0.00 : 0.00: 0.00 : 1.00

Table 3.23: Catalyst screen with aminocycle **2.92**

With the only conceivable difference between the experiments above being the presence of PhCN as a ligand on the catalyst, it was decided that screening the volume of PhCN was a reasonable pursuit (Table 3.24). The addition of 0.5 mL of PhCN to the second step did improve the conversion to oxidised products; however, the intermediate aminocycle **2.92** was still present (entry 1). Addition of 50 µL of PhCN resulted in complete conversion

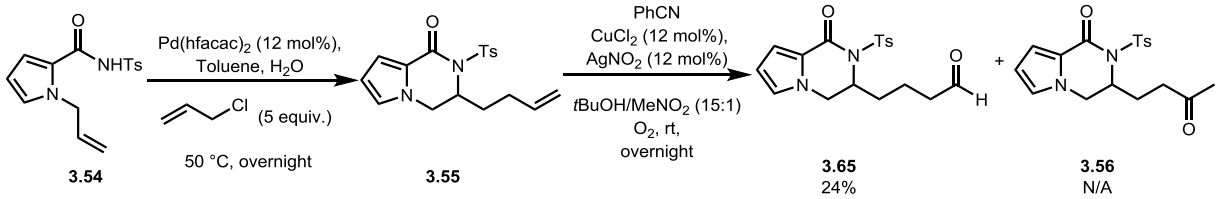
to oxidised aldehyde **3.64** and ketone **3.47**, with the yields being 33% and 19% respectively (entry 2). Interestingly, when 100 µL of PhCN was added to the second step it had a detrimental effect on the conversion to oxidised products with only aminocycle **2.92** being observed *via* ^{1}H NMR analysis of the crude material.



Entry	PhCN	Result
		2.92 : 3.64 : 3.47
1	0.5 mL	0.66 : 1.00 : 0.33
2	50 µL	0.00 : 1.00 (33%) : 0.53 (19%)
3	100 µL	1.00 : 0.00 : 0.00

Table 3.24: Screening with different volumes of PhCN

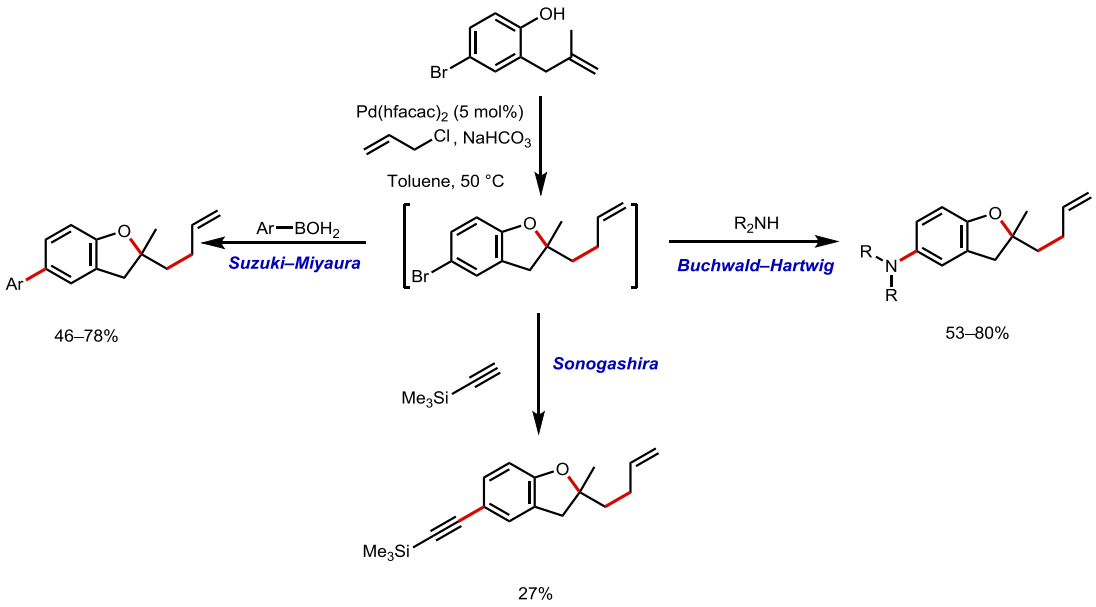
The newly optimised conditions were then tested against the pyrrole substrate **3.54**. The full IRS synthesised the desired aldehyde **3.65** in a 24% yield (Scheme 3.31). Unfortunately, the yield of the ketone **3.56** could not be determined.



Scheme 3.31: Aldehyde selective heteroallylation−oxidation sequence for pyrrole **3.54**

3.7 Conclusions

The successful development of the novel palladium-catalysed IRS that combines the isohypsic heteroallylation reaction with traditional redox chemistry such as the Suzuki−Miyaura, Buchwald−Hartwig and Sonogashira reactions have led to an interesting range of products through the manipulation of a bromide handle (Scheme 3.32). The Suzuki−Miyaura and Buchwald−Hartwig iterations afforded products in good to excellent yields over two steps and effectively generated molecular complexity quickly and efficiently, using one palladium source. The Sonogashira iteration has shown promising results however optimisation is still needed.



Scheme 3.32: IRS summary

It has been demonstrated that the terminal alkene formed in the aminoallylation reaction can be oxidised to either the ketone or the aldehyde. Transformation of the terminal alkene has led to a collection of oxidised products (Figure 3.1). Having control over whether the ketone or aldehyde is formed is highly advantageous for a synthetic chemist, as it provides options for further synthetic processes.

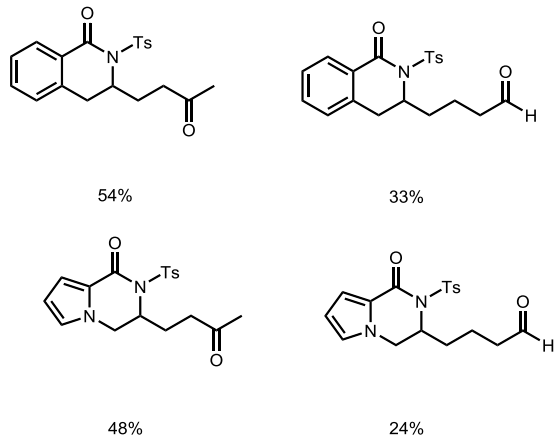


Figure 3.1: Aminoallylation−oxidation products

Future work will be to extend the IRS to other palladium-catalysed isohyspic and redox reactions. This will allow even more molecular complexity to built up quickly and efficiently and complex manifolds to be designed.

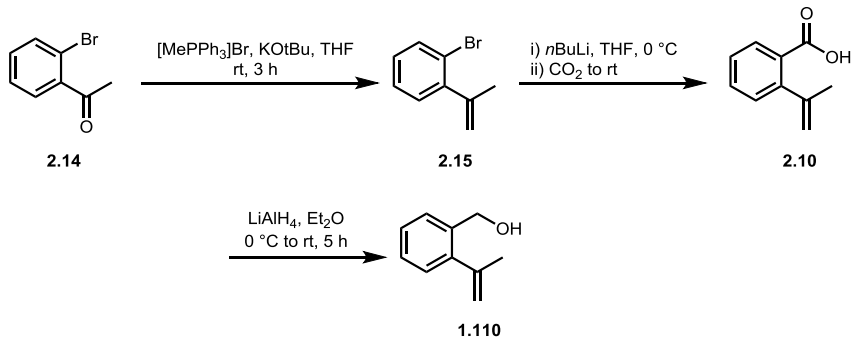
4. Experimental

4.1 General Experimental Information

Reactions involving air-sensitive reagents and dry solvents were performed in glassware that had been dried in an oven (150 °C) or flame-dried prior to use. These reactions were carried out with the exclusion of air using an argon atmosphere. All microwave reactions were carried out using a Biotage Initiator system. NMR spectra were recorded on a Bruker DPX-400 spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) or a Bruker DPX-500 spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz). Chemical shifts are reported in ppm. ^{1}H NMR spectra were recorded with $CDCl_3$ as the solvent using residual $CHCl_3$ (δ = 7.27) as internal standard or C_6D_6 as the solvent using residual C_6D_5H (δ = 7.16), and for ^{13}C NMR spectra the chemical shifts are reported relative to the central resonance of $CDCl_3$ (δ = 77.00) or C_6D_6 (δ = 128.39). Signals in NMR spectra are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), broad (br) or combination of these, which refers to the spin–spin coupling pattern observed. Spin–spin coupling constants reported are uncorrected. Two-dimensional (COSY, HSQC, HMBC, NOESY) NMR spectroscopy was used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra. IR spectra were obtained employing a Shimadzu FTIR-8400 instrument with a Golden Gate™ attachment that uses a type IIa diamond as a single reflection element so that the IR spectrum of the compound (solid or liquid) could be detected directly (thin layer). High resolution mass spectra were recorded under FAB, ESI or CI conditions by the analytical services at the University of Glasgow. Flash column chromatography was performed using forced flow of the indicated solvent system on EMD Geduran® Silica Gel 60 as solid support and HPLC graded solvents as eluant. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60 covered aluminium sheets. TLC plates were developed under UV-light and/or with an acidic ethanolic anisaldehyde solution or a $KMnO_4$-solution. Liquid reagents were distilled prior to use where stated. All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. All HPLC used to determine enantiomeric purity were calibrated with samples of the racemate.

4.2 Experimental Details

(2-(Prop-1'-en-2'-yl)phenyl) methanol (1.110)



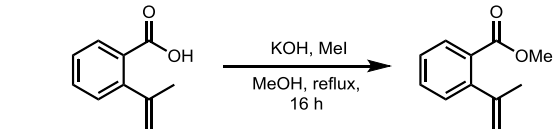
Following a literature procedure,[12] to a stirred suspension of methyl triphenyl-phosphonium bromide (7.2 g, 20 mmol,) in THF (51 mL) was added a solution of potassium *tert*-butoxide (2.3 g, 20 mmol) in THF (21 mL). The resulting bright yellow suspension was stirred at room temperature for 15 minutes then a solution of *o*-bromoacetophenone (**2.14**) (3.4 g, 17 mmol) in THF (34 mL) added dropwise. The resulting suspension was stirred at room temperature for 3 h then sat. aq. NH_4Cl (100 mL) was added. The mixture was extracted with Et_2O (100 mL then 2 x 50 mL) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether) afforded 1-bromo-2-(prop-1'-en-2'-yl)-benzene (**2.15**) as a colourless oil (3.0 g, 91%). Data corresponded to literature values.[144]

Following a literature procedure,[12] to a cooled (0 °C) solution of 1-bromo-2-(prop-1'-en-2'-yl) benzene (**2.15**) (2.1 g, 11 mmol) in Et_2O (21 mL) was added dropwise a solution of *n*-butyllithium (2.1 M in hexanes, 5.3 mL, 11 mmol) under argon. The resulting yellow suspension was stirred for 15 minutes then added dropwise to a flask charged with carbon dioxide pellets (ca. 50 g). The mixture was allowed to warm to room temperature over 2 h then sat. aq. $NaHCO_3$ (100 mL) was added. The mixture was extracted with Et_2O (2 x 50 mL) and the aqueous phase adjusted to pH 1 with 1 M aq. HCl. The aqueous phase was then extracted with Et_2O (3 x 100 mL) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-(prop-1'-en-2'-yl) benzoic acid (**2.10**) as a sticky white solid (1.7 g, 99%). Data corresponded to literature values.[38]

Following a literature procedure,[12] to a cooled (0 °C) suspension of lithium aluminium hydride (0.47 g, 12 mmol) in Et_2O (34 mL) was added dropwise a solution of 2-(prop-1'-en-2'-yl) benzoic acid (**2.10**) (0.78 g, 4.8 mmol) in Et_2O (20 mL). After 5 minutes, the reaction mixture was allowed to warm to room temperature and stirred for 5 h. The mixture was re-cooled to 0 °C and sat. aq. potassium sodium tartrate (25 mL) added slowly. The biphasic mixture was allowed to stir at room temperature for 16 h then extracted with Et_2O (3 x 50 mL). The organic extracts were washed with water (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography

(petroleum ether/EtOAc; 9:1) afforded the title compound (**1.110**) as a colourless oil (0.64 g, 90%). Data corresponded to literature values.[145]

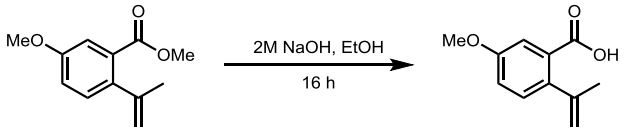
Methyl 2-(prop-1'-en-2'-yl)benzoate (2.18)



2.10 **2.18**

To a solution of 2-(prop-1'-en-2'-yl) benzoic acid (**2.10**) (0.22 g, 1.4 mmol) in MeOH (3.5 mL) was added KOH (95 mg, 1.7 mmol) and methyl iodide (0.67 mL, 11 mmol). The reaction was allowed to stir for 16 h under reflux. The resulting mixture was then quenched with ice water and the organic phase was extracted with chloroform (3 x 5 mL). The crude material was then purified by column chromatography (petroleum ether/EtOAc; 95:5) to afford methyl 2-(prop-1'-en-2'-yl)benzoate (**2.18**) as a colourless oil (0.18 g, 76%). Data corresponded to literature values.[146]

5-methoxy-2-(prop-1'-en-2'-yl)benzoic acid (2.23)

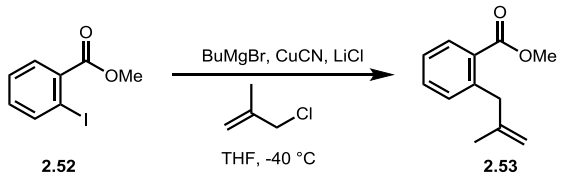


2.22 **2.23**

5-methoxy-2-(prop-1'-en-2'-yl)benzoate (**2.22**) (0.62 g, 3.0 mmol) was dissolved in EtOH (40 mL), and 2 M aq. NaOH (30 mL) added. The mixture was stirred at room temperature for 16 h then EtOH was removed *in vacuo.* The residue was extracted with Et_2O (2 x 30 mL), acidified to pH 3 with 2 M aq. HCl and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 5-methoxy-2-(prop-1'-en-2'-yl)benzoic acid (**2.23**) as a colourless solid (0.45 g, 78%), which was used directly without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47 (1 H, d, *J* = 2.8 Hz, Ar**H**) 7.19, (1 H, d, *J* = 8.3 Hz, Ar**H**), 7.06 (1 H, dd, *J* = 8.2, 2.9 Hz, Ar**H**), 5.13−5.11 (1 H, m, C**H**H), 4.90−4.85 (1 H, m, CH**H**), 3.86 (3 H, s, OC**H$_3$**), 2.12−2.07 (3 H, m, C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 171.8 (**C**=O), 158.3 (**C**), 146.1 (**C**), 138.5 (**C**), 130.8 (Ar**C**H), 128.8 (**C**), 118.9 (Ar**C**H), 115.0 (Ar**C**H), 114.0 (**C**H$_2$), 55.5 (O**C**H$_3$), 24.3 (**C**H$_3$); **IR** (thin film) 2955, 2914, 1693, 1281 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{11}H_{11}O_3$ $[M-H]^-$ *m/z* 191.0714, found *m/z* 191.0711.

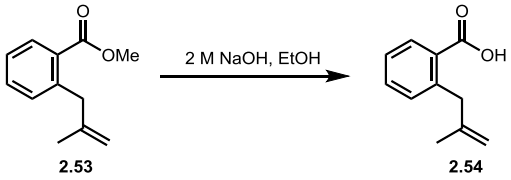
Methyl 2-(2'-methylallyl)benzoate (2.53)



2.52 **2.53**

Following a modification of a reported procedure,[140] to a suspension of magnesium turnings (2.2 g, 92 mmol) and a crystal of iodine in THF (80 mL) was added dropwise bromobutane (9.7 mL, 76 mmol). The mixture was stirred for 15 minutes then cooled to –40 °C before dropwise addition of methyl-2-iodobenzoate (**2.52**) (10 g, 38 mmol) in THF (300 mL). The mixture was stirred at –40 °C for 1.5 h. A freshly prepared solution of LiCl (3.2 g, 76 mmol) and CuCN (3.2 g, 38 mmol) in THF (200 mL) was added and the mixture was stirred for a further 15 minutes, followed by the addition of 3-chloro-2-methylprop-1-ene (15.0 mL, 153 mmol). The mixture was stirred at –40 °C for a further 10 minutes, then warmed to room temperature. The mixture was diluted with EtOAc (200 mL) and filtered over Celite®. The filtrate was washed with 25% aq. NH_4OH (200 mL). The aqueous layer was further extracted with EtOAc (2 x 200 mL), and the combined organic extracts washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc; 95:5), afforded methyl 2-(2'-methylallyl)benzoate (**2.53**) as a yellow oil (6.9 g, 95%). Material was used directly in the next step.[140]

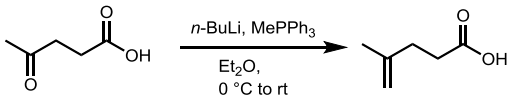
2-(2'-methylallyl)benzoic acid (2.54)



2.53 **2.54**

2-(2'-methylallyl)benzoate (**2.53**) (6.5 g, 34 mmol) was dissolved in EtOH (350 mL), and 2 M aq. NaOH (300 mL) added. The mixture was stirred for at room temperature overnight then EtOH was removed *in vacuo.* The aqueous solution was extracted with Et_2O (2 x 150 mL), acidified to pH 1 with 2 M aq. HCl and extracted with EtOAc (3 x 150 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-(2'-methylallyl)benzoic acid (**2.54**) as a colourless solid (6.1 g, 93%), which was used directly without further purification. Data corresponded to literature values.[89]

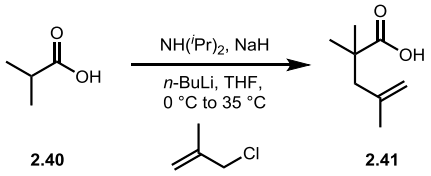
4-methylpent-4-enoic acid (2.6)



2.39 **2.6**

Methyltriphenylphosphonium bromide (3.75 g, 10.5 mmol) was suspended in THF (46 mL). The colourless suspension was cooled to 0 °C and *n*-butyllithium (2.10 M in hexanes, 4.80 mL, 10.5 mmol) was added dropwise. The resulting bright orange solution was stirred at 0 °C for 1 h before the dropwise addition of levulinic acid (**2.39**) (0.410 g, 3.50 mmol). The suspension was allowed to warm to room temperature and stirred overnight. The reaction was then quenched by adding a 1 M aq. HCl solution (10 mL) and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (Petroleum ether/EtOAc; 85:15) to afford 4-methylpent-4-enoic acid (**2.6**) (263 mg, 66%) as a clear yellow oil. Data corresponded to literature values.[38]

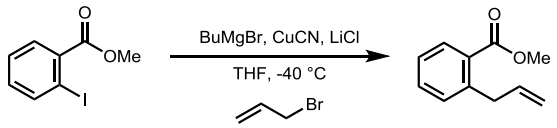
2,2,4-trimethylpent-4-enoic acid (2.41)



2.40 **2.41**

Following a reported procedure,[38] isobutyric acid (**2.40**) (475 mg, 5.39 mmol) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 236 mg, 5.89 mmol) and diisopropylamine (780 µL, 5.50 mmol) in THF (7.50 mL). The resulting suspension was heated at reflux for 20 minutes and then cooled to 0°C for 15 minutes prior to the dropwise addition of *n*-butyllithium (2.20 M in hexanes, 2.50 mL, 5.40 mmol). The resulting suspension was stirred at 0 °C for an additional 15 minutes and then heated to 35 °C for 30 minutes. The suspension was cooled to 0 °C and methallyl chloride (540 µL, 5.50 mmol) was added dropwise to give an off-white suspension which was stirred for 2 h at 35 °C. The suspension was then cooled with an ice-bath and the excess of NaH was quenched with water (10 mL). The organic layer was washed with a 1 M aq. NaOH solution (3 x 20 mL) and the combined aqueous layers were then extracted with Et_2O (20 mL). The aqueous layer was acidified by addition of a 1 M aq. HCl solution until pH 1 and was then extracted with ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo* to afford 2,2,4-trimethylpent-4-enoic acid as a colourless oil (**2.41**) (485 mg, 63%) as a colourless oil. Data corresponded to literature values.[38]

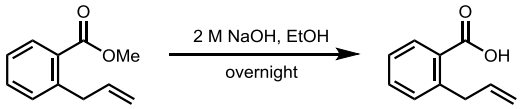
Methyl-2-allyl-benzoate (4.1)



2.52 **4.1**

Following a modification of a reported procedure,[140] to a suspension of magnesium turnings (2.2 g, 92 mmol) and a crystal of iodine in THF (80 mL) was added dropwise bromobutane (9.7 mL, 76 mmol). The mixture was stirred for 15 minutes then cooled to –40 °C before dropwise addition of methyl-2-iodobenzoate (**2.52**) (5.80 mL, 38.0 mmol). The mixture was stirred at –40 °C for 1.5 h. A freshly prepared solution of LiCl (3.2 g, 76 mmol) and CuCN (3.20 g, 38.0 mmol) in THF (200 mL) was added and the mixture was stirred for a further 15 minutes, followed by the addition of allyl bromide (13.0 mL, 153 mmol). The mixture was stirred at –40 °C for a further 10 minutes, then warmed to room temperature. The mixture was diluted with EtOAc (200 mL) and filtered over Celite®. The filtrate was washed with 25% aq. NH_4OH (200 mL). The aqueous layer was further extracted with EtOAc (2 x 200 mL), and the combined organic extracts washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc; 9:1), afforded methyl-2-allyl-benzoate (**4.1**) as a colourless oil (6.39 g, 95%). Data corresponded to literature values.[140]

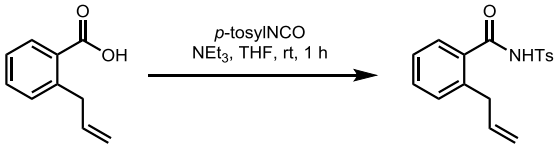
2-allylbenzoic acid (1.15)



4.1 **1.15**

Methyl 2-allylbenzoate (**4.1**) (528 mg, 3.00 mmol) was dissolved in EtOH (10 mL), and 2 M aq. NaOH (10 mL) added. The mixture was stirred for at room temperature overnight then EtOH was removed *in vacuo.* The residue was extracted with Et_2O (2 x 10 mL), acidified to pH 1 with 2 M aq. HCl and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-allylbenzoic acid (**1.15**) as a colourless solid (400 mg, 82%), which was used directly without further purification. Data corresponded to literature values.[140]

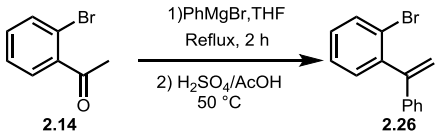
2-allyl-*N*-tosylbenzamide (2.91)



1.15 **2.91**

To a solution of 2-allyl benzoic acid (**1.15**) (2.35 g, 14.5 mmol) in THF (43 mL) was added *p*-tosyl isocyanate (2.20 g, 14.5 mmol). The resulting solution was stirred for 10 minutes then triethylamine (2.02 mL, 14.5 mmol) added dropwise. Gas evolution was observed on addition. After 1 h, the mixture was diluted with EtOAc (50 mL) and washed with 2 M aq. HCl (50 mL) and brine (50 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2) to afford the title compound (**2.91**) as a colourless solid (3.68 g, 81%). Data corresponded to literature values.[140]

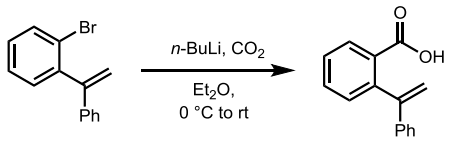
1-bromo-2-(1'-phenylvinyl)benzene (2.96)



2.14 **2.26**

Following a reported procedure,[38] a solution of 2'-bromoacetophenone (**2.14**) (2.00 mL, 15.0 mmol) in THF (2 mL) was added dropwise to a stirred solution of phenylmagnesium bromide in THF (16.6 mL,16.6 mmol). The resulting mixture was heated at reflux for 2 h, then allowed to cool to room temperature and quenched by addition of sat. aq. NH_4Cl (15 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude carbinol. The crude carbinol was treated with a solution of H_2SO_4 in acetic acid (4 mL, 20% v/v) at 50 °C for 5 minutes. The mixture was then poured into an Et_2O/water two-phase system (1:1, 100 mL). The aqueous layer was extracted with diethyl ether (2 x 100 mL) and the combined organic layers were washed with 1 M aq. $NaHCO_3$ (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether) to furnish 1-bromo-2-(1'-phenylvinyl)benzene (**2.26**) (2.75 g , 71%) as a colourless oil. Data corresponded to literature values.[38]

2-(1'-phenylvinyl)benzoic acid (2.24)

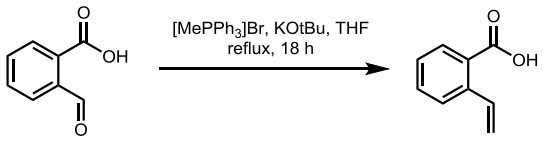


2.26 **2.24**

2-(1'-phenylvinyl)benzene (**2.26**) (1.76 g, 6.80 mmol) was dissolved in Et_2O (15 mL) and the resulting colourless mixture was cooled to 0 °C and stirred for 5 minutes. *n*-butyllithium (2.30 M hexane, 3.10 mL, 7.10 mmol) was added dropwise. After 50 minutes, CO_2 was bubbled through the mixture for 30 minutes upon which the reaction turned yellow. The reaction was then warmed to room temperature and stirred for an additional 2 h. The

reaction was quenched by adding sat. aq. $NaHCO_3$ (20 mL). The aqueous layer was washed with diethyl ether (3 x 20 mL), acidified to pH 1 with 2 M aq. HCl and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*, to afford the product 2-(1-phenylvinyl)benzoic acid (**2.24**) (579 mg, 39%) as a colourless solid. Data corresponded to literature values.[38]

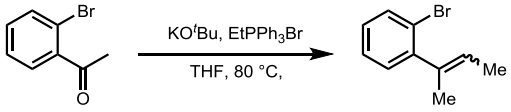
2-vinyl benzoic acid (2.79)



2.83 **2.79**

To a stirred suspension of methyltriphenylphosphonium bromide (19 g, 53 mmol) in THF (80 mL) was added dropwise a solution of potassium *tert*-butoxide (8.8 g, 79 mmol) in THF (40 mL). The resultant yellow solution was stirred for 1.5 h, before the addition of a solution of 2-carboxybenzaldehyde **2.83** (5.0 g, 33 mmol) in THF (20 mL). The solution was warmed to 60 °C and stirred overnight, before cooling and the addition of acetic acid (5.0 mL) and the solution was filtered over Celite®. The filtrate was concentrated *in vacuo*, before being washed with sat. aq. $NaHCO_3$ (3 x 50 mL). The combined aqueous extracts were acidified to pH 1 with 1 M aq. HCl, and the aqueous phase was extracted with Et_2O (3 x 50 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford title compound **2.79** as a colourless solid (1.6 g, 32%). No further purification was required. Data corresponded to literature values.[147]

1-bromo-2-(but-2'-en-2'-yl)benzene (2.36)

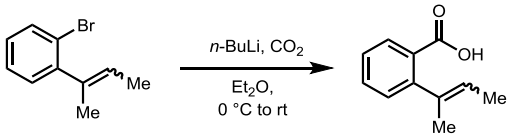


2.14 **2.36**

Following a reported procedure,[38] ethyltriphenylphosphonium bromide (4.40 g, 12.0 mmol) was added to a suspension of potassium *t*-butoxide (1.35 g, 12.0 mmol) in toluene (44 mL). The resulting orange suspension was stirred at 0 °C for 10 minutes, allowed to warm to room temperature and stirred for an additional 1 h. The mixture was cooled to 0 °C and 2'-bromoacetophenone (**2.14**) (0.88 g, 4.4 mmol) was added dropwise. The mixture was heated at reflux for 8 h, then cooled to room temperature and quenched with sat. aq. NH_4Cl (50 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting colourless solid was triturated with hexane (50 mL) and triphenylphosphine oxide was removed by filtration. The filtrate was concentrated *in vacuo* and purified by column chromatography (petroleum ether) to afford bromostyrene (**2.36**)

(684 mg, 74%, mixture of *E* and *Z* isomers) as a colourless oil. Data corresponded to literature values.[38]

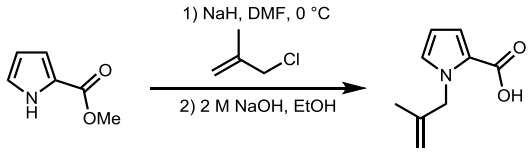
2-(but-2'-en-2'-yl)benzoic acid (2.32)



2.36 **2.32**

n-butyllithium (2.18 M in hexanes, 1.46 mL, 3.20 mmol) was added dropwise to a stirred solution of **2.36** (564 mg, 2.70 mmol) in Et_2O (3.8 mL) at 0 °C. After 15 minutes CO_2 was bubbled through the reaction mixture for 10 minutes. The mixture was then allowed to warm to room temperature and stirred for an additional 2 h. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL). The aqueous layer was washed with Et_2O (3 x 15 mL), then acidified to pH 1 with 2 M aq. HCl and extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford benzoic acid (**2.32**) (190 mg, 40%, mixture of *E* and *Z* isomers) as a colourless solid. Data corresponded to literature values.[38]

1-(2'-methylallyl)pyrrole-2-carboxylic acid (2.59)



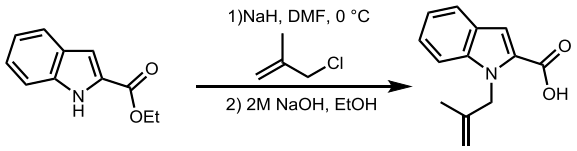
2.58 **2.59**

To a flask containing 60% NaH in mineral oil (480 mg, 12.0 mmol) in DMF (10 mL) was added dropwise a solution of methyl pyrrole-2-carboxylate (**2.58**) (1.00 g, 8.00 mmol) in DMF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 30 minutes before the addition of methallyl chloride (1.30 mL, 13.6 mmol). The mixture was then allowed to warm to room temperature and was stirred for 2 h before quenching with H_2O (20 mL). The aqueous layer was then washed with Et_2O (3 x 30 mL). The combined organic layers were then washed with H_2O (3 x 100 mL) and brine and dried over $MgSO_4$ and concentrated *in vacuo* to afford a crude mixture (1.35 g). The crude mixture was then subsequently dissolved in EtOH (18 mL), and 2 M aq. NaOH (21 mL) added. The mixture was stirred at room temperature overnight then EtOH was removed *in vacuo.* The residue was extracted with Et_2O (2 x 20 mL), acidified to pH 1 with 2 M aq. HCl and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 1-(2'-methylallyl)pyrrole-2-carboxylic acid (**2.59**) as a colourless solid (840 mg, 64% over two steps), which was used directly without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.12 (1 H, dd, *J* = 4.0, 1.8 Hz, Ar**H**), 6.93−6.88 (1 H,

m, Ar**H**), 6.21 (1 H, dd, *J* = 4.0, 2.5 Hz, Ar**H**), 4.89 (2 H, s, NC**H**$_2$), 4.86−4.82 (1 H, m, C=C**H**H), 4.47 (1 H, s, C=CH**H**), 1.72 (3 H, s, C**H**$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 165.5 (**C**=O), 142.2 (**C**), 130.1 (Ar**C**H), 121.2 (**C**), 120.0 (Ar**C**H), 111.1 (Ar**C**H), 108.5 (**C**H$_2$), 53.9 (N**C**H$_2$), 19.9 (**C**H$_3$); **IR** (thin film) 2359, 2342, 1651, 1265 cm^{-1}; **HRMS** (EI) exact mass calculated for $C_9H_{11}NO_2$ $[M]^+$ *m/z* 165.0790 , found *m/z* 165.0791.

1-(2'-methylallyl)indole-2-carboxylic acid (2.61)

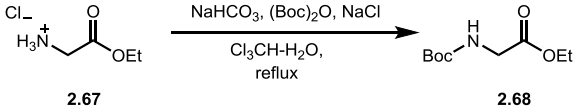


2.60 **2.61**

To a flask containing 60% NaH in mineral oil (320 mg, 8.00 mmol) in DMF (4 mL) was added dropwise a solution of ethyl indole-2-carboxylate (**2.60**) (1.00 g, 5.00 mmol) in DMF (12 mL) at 0 °C. The mixture was stirred at 0 °C for 30 minutes before the addition of methallyl chloride (880 µL, 9.00 mmol). The mixture was then allowed to warm to room temperature and was stirred for 2 h before quenching with H_2O (20 mL). The aqueous layer was then washed with Et_2O (3 x 30 mL). The combined organic layers were then washed with H_2O (3 x 100 mL) and brine and dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude material (940 mg). The intermediate was then subsequently was dissolved in EtOH (20 mL), and 2 M aq. NaOH (20 mL) added. The mixture was stirred at room temperature overnight then EtOH was removed *in vacuo.* The residue was extracted with Et_2O (2 x 20 mL), acidified to pH 1 with 2 M aq. HCl and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 1-(2'-methylallyl)indole-2-carboxylic acid (**2.61**) as a colourless solid (495 mg, 46% over two steps), which was used directly without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76−7.71 (1 H, m, Ar**H**), 7.52 (1 H, s, Ar**H**), 7.39−7.35 (2 H, m, Ar**H**), 7.22−7.15 (1 H, m, Ar**H**), 5.19 (2 H, s, NC**H**$_2$), 4.84−4.79 (1 H, m, C=C**H**H), 4.35 (1 H, s, C=CH**H**), 1.76 (3 H, s, C**H**$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 166.3 (**C**=O), 141.4 (Ar**C**), 140.0 (Ar**C**), 126.3 (**C**), 125.8 (**C**), 125.8 (Ar**C**H), 122.9 (Ar**C**H), 120.8 (Ar**C**H), 112.9 (Ar**C**H), 111.0 (Ar**C**H), 110.6 (**C**H$_2$), 49.9 (**C**H$_2$), 20.1 (**C**H$_3$); **IR** (thin film) 2360, 2332, 1680, 1269 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{13}H_{13}NO_2Na$ $[M+Na]^+$ *m/z* 238.0838, found *m/z* 238.0842.

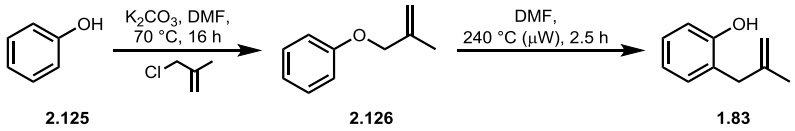
Ethyl 2-(*tert*-butoxycarbonylamino)acetate (2.68)



2.67 **2.68**

Following a literature procedure[148], a solution of sodium hydrogen carbonate (1.20 g, 14.3 mmol) in water (20 mL), a solution of di-*tert*-butyl dicarbonate (**2.67**) (3.12 g, 14.3 mmol) in chloroform (2 mL) and sodium chloride (2.2 g) were added to a stirred suspension of glycine ethyl ester hydrochloride (2.00 g, 14.3 mmol) in chloroform (14 mL). The resulting biphasic mixture was stirred vigorously at reflux for 1.5 h, allowed to cool and the two layers were separated. The aqueous phase was extracted with chloroform (2 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound (**2.68**) (2.91 g, quantitative) as a viscous colourless oil. Data corresponded to literature values.[149]

2-(2'-methylallyl)phenol (1.83)

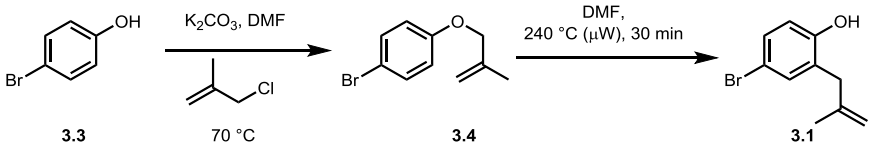


2.125 **2.126** **1.83**

To a stirred suspension of K_2CO_3 (8.8 g, 64 mmol) in DMF (160 mL) was added phenol (**2.125**) (3.0 g, 32 mmol) followed by 3-chloro-2-methyl-1-propene (3.7 mL, 38 mmol). The resulting mixture was heated at 70 °C for 16 h then cooled to room temperature, quenched with water (250 mL) and extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 1-(2'-methylallyloxy)benzene (**2.126**) as a colourless oil (4.7 g, quant.) which was used without any further purification. Data corresponded to literature values.[150]

A solution of 1-(2'-methylallyloxy)benzene (**2.126**) (1.5 g, 10 mmol) in DMF (8.4 mL) under argon was subjected to microwave irradiation at 240 °C for 2.5 h. The resulting mixture was extracted with Et_2O (3 x 50 mL) and the combined organic extracts washed with water (50 mL) then brine (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc; 19:1) afforded the title compound (**1.83**) as a yellow oil (1.2 g, 80%). Data corresponded to literature values.[38]

4-bromo-2-(2'-methylallyl)phenol (3.1)



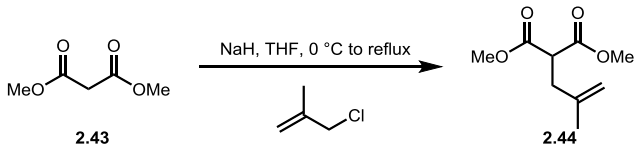
3.3 70 °C **3.4** **3.1**

To a stirred suspension of K_2CO_3 (3.98 g, 28.8 mmol) in DMF (60 mL) was added 4-bromophenol (**3.3**) (2.00 g, 11.6 mmol) followed by 3-chloro-2-methyl-1-propene (1.36 mL, 13.9 mmol). The resulting mixture was heated at 70 °C for 18 h then cooled to room

temperature, quenched with water (25 mL) and extracted with Et_2O (2 x 25 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 1-(2'-methylallyloxy)-4-bromobenzene (**3.4**) as a colourless oil (2.63 g, quant.) which was used without any further purification. Data corresponded to literature values.[38]

A solution of 1-(2'-methylallyloxy)-4-bromobenzene (**3.4**) (2.00 g, 8.81 mmol) in DMF (5.9 mL) under argon was subjected to microwave irradiation at 240 °C for 30 minutes. The resulting mixture was diluted with water (25 mL), extracted with EtOAc (3 x 25 mL) and the combined organic extracts washed with brine (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc, 9:1) afforded the title compound (**3.1**) as a colourless oil (1.43 g, 72%). Data corresponded to literature values.[38]

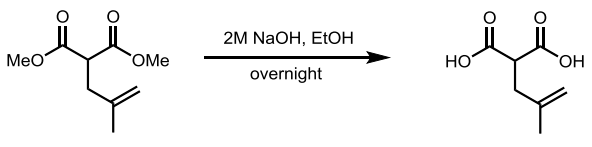
Dimethyl 2-(2'-methylallyl)malonate (2.44)



2.43 **2.44**

Following a modification of the reported procedure,[89] to a cooled (0 °C) suspension of NaH (60% dispersion in mineral oil, 540 mg, 13.5 mmol) in THF (150 mL) was added dropwise dimethyl malonate (**2.43**) (2.0 mL, 18 mmol). Once effervescence had ceased, 3-chloro-2-methyl-1-propene (970 µL, 10.0 mmol) was added then the cooling bath was removed. The mixture was stirred at room temperature for 2 h then heated at reflux for 18 h. After cooling to room temperature, the reaction was quenched by addition of water (50 mL) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc; 95:5) afforded dimethyl 2-(2'-methylallyl)malonate (**2.44**) as a colourless oil (1.35 g, 73%). Data corresponded to literature values.[151]

2-(2'-methylallyl)malonic acid (2.45)

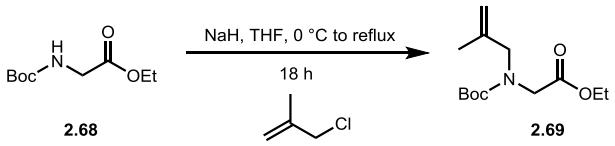


2.44 **2.45**

Dimethyl 2-(2'-methylallyl)malonate (**2.44**) (0.50 g, 2.7 mmol) was dissolved in EtOH (30 mL), and 2 M aq. NaOH (23 mL) added. The mixture was stirred for at room temperature overnight then EtOH was removed *in vacuo.* The residue was extracted with Et_2O (2 x 10

mL), acidified to pH 1 with 2 M aq. HCl and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-(2'-methylallyl)malonic acid (**2.45**) as a colourless solid (0.43 g, quantitative), which was used directly without further purification. Data corresponded to literature values. [152]

Ethyl 2-(*tert*-butoxycarbonylamino)acetate (2.69)



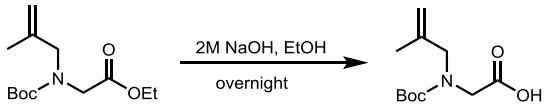
2.68 **2.69**

Following a modified literature procedurefor a related compound,[153] to a 0 °C solution of ethyl 2-(*tert*-butoxycarbonylamino)acetate (**2.68**) (2.43 g, 12.0 mmol) in 30 mL DMF was added allyl bromide (1.80 mL, 18.0 mmol) followed by NaH (60% dispersion in mineral oil, 720 mg, 18.0 mmol). The reaction was maintained at 0 °C for 90 minutes. Sat. aq NH_4Cl and EtOAc were added. The layers were separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether/EtOAc; 95:5) to yield the title compoundas a colourless oil (**2.69**) of a colourless oil (1.37 g, 44%).

^{1}H NMR (400 MHz, C_6D_6, 50 °C due to rotameric mixture) δ (ppm): 4.71 (2 H, br. s, C**H**$_2$), 4.00–3.90 (4 H, m, 2 x C**H**$_2$), 3.87–3.69 (2 H, m, C**H**$_2$), 1.60 (3 H, br. s, C**H**$_3$), 1.42 (9 H, br. s, 3 x C**H**$_3$), 0.94 (3 H, br. s, C**H**$_3$); **IR** (thin film) 2361, 2341, 1737, 1681 cm^{-1}; **HRMS** (CI) exact mass calculated for $C_{13}H_{23}NO_4H$ $[M+H]^+$ *m/z* 258.1705, found *m/z* 258.1703.

^{13}C NMR unavailable due to complex mixture of rotamers.

2-(*tert*-butoxycarbonyl(2'-methylallyl)amino)acetic acid (2.70)



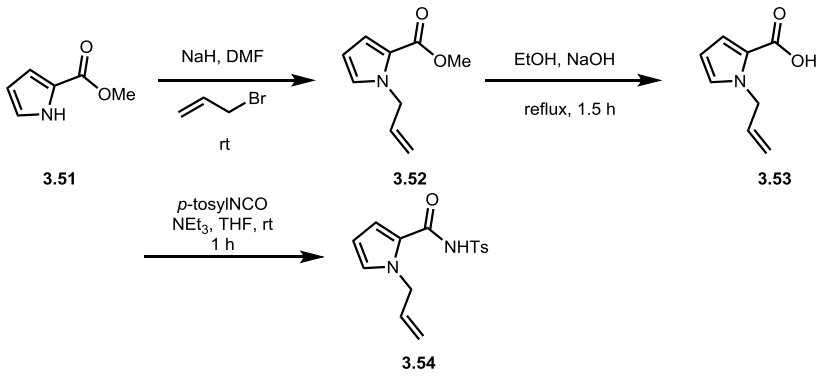
2.69 **2.70**

Ethyl 2-(*tert*-butoxycarbonyl(2'-methylallyl)amino)acetate (**2.69**) (0.40 mg, 1.6 mmol) was dissolved in EtOH (15 mL), and 2 M aq. NaOH (10 mL) was added. The mixture was stirred at room temperature overnight then EtOH was removed *in vacuo.* The residue was extracted with Et_2O (2 x 10 mL), acidified to pH 1 with 2 M aq. HCl and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-(*tert*-butoxycarbonyl(2'-methylallyl)amino)acetic acid (**2.70**) as a colourless solid (0.36 g, quantitative), which was used directly without further purification.

^{1}H NMR (400 MHz, C_6D_6, 50 °C due to rotameric mixture) δ (ppm): 4.74–4.53 (2 H, m, C**H**$_2$), 3.96–3.52 (4 H, m, 2 x C**H**$_2$), 1.53 (3 H, br. s, C**H**$_3$), 1.40 (9 H, br. s, 3 x C**H**$_3$); **IR** (thin film) 2976, 2359, 1697, 1159 cm^{-1}; **HRMS** (CI) exact mass calculated for $C_{11}H_{19}NO_4H$ $[M+H]^+$ *m/z* 230.1392, found *m/z* 230.1400.

^{13}C NMR unavailable due to complex mixture of rotamers.

1-allyl-*N*-tosyl-pyrrole-2-carboxamide (3.54)



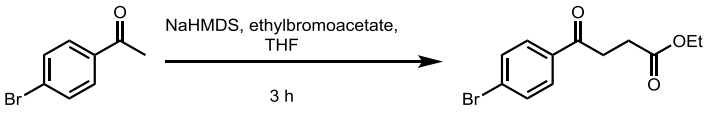
Following a modification of a reported procedure,[140] to a cooled (0 °C) suspension of NaH (60% dispersion in mineral oil, 480 mg, 12 mmol) in DMF (10 mL) was added a solution of methyl-2-pyrrole-carboxylate (**3.51**) (1.0 g, 8.0 mmol) in DMF (2 mL). The resulting mixture was stirred for 20 min at 0 °C, then allyl bromide (1.2 mL, 14 mmol) added dropwise. The mixture was allowed to warm to room temperature, and stirred for 2 h, then quenched by pouring onto ice (30 g). The mixture was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were washed with water (4 x 15 mL), brine (1 x 15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford methyl-1-allyl-pyrrole-2-carboxylate (**3.52**) as a colourless oil (1.3 g, 98%) which was used directly without further purification.

To a solution of methyl-1-allyl-pyrrole-2-carboxylate (**3.52**) (1.30 g, 7.87 mmol) in EtOH (20 mL) was added 1 M aq. NaOH (20 mL). The mixture was refluxed for 1.5 h, then EtOH was removed *in vacuo*. The aqueous phase was washed with EtOAc (3 x 25 mL) then acidified to pH 2 with 4 M aq. HCl and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*, to afford 1-allyl-pyrrole-2-carboxylic acid (**3.53**) as a colourless solid (1.0 g, 89%) which was used directly without further purification.

To a flask charged with 1-allyl-pyrrole-2-carboxylic acid (**3.53**) (0.50 g, 3.3 mmol) in THF (10 mL) was added *p*-tosyl isocyanate (0.77 g, 6.6 mmol). The resulting solution was stirred for 10 minutes then triethylamine (0.50 mL, 3.6 mmol) added dropwise. Gas evolution was observed on addition. After 1 h, the mixture was diluted with EtOAc (50 mL)

and washed with 2 M aq. HCl (50 mL) and brine (50 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2) to afford the title compound (**3.54**) as a colourless solid (0.71 g, 61%). Data corresponded to literature values.[140]

Ethyl 4-(4'-bromophenyl)-4-oxobutanoate (2.48)

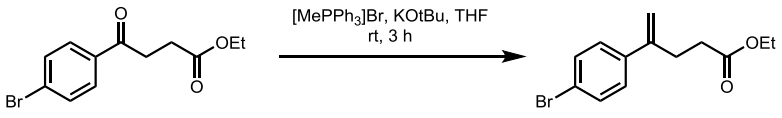


2.47 **2.48**

NaHMDS (7.7 g, 42 mmol) was added to a stirred solution of *p*-bromoacetophenone **2.47** (7.6 g, 38 mmol) in dry THF (100 mL) at −78 °C, under argon, over 20 minutes. To the mixture was added ethyl bromoacetonate (8.9 mL, 80 mmol) in THF (30 mL) over 30 minutes and the temperature was maintained at −78 °C for 35 minutes. The mixture was warmed to −10 °C over 3 h and after this time H_2O (30 mL) was added to the reaction mixture. The solvent was removed by rotary evaporation and the residue was diluted with brine (100 mL). The suspension was extracted with EtOAc (2 x 100 mL). The solution was dried over $MgSO_4$, filtered and concentrated. The crude mixture was then purified by column chromatography (petroleum ether/EtOAc; 95:5) to give the desired product **2.48** as a colourless oil(3.8 g, 35%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.86 (2 H, d, *J* = 8.6 Hz, Ar**H**), 7.62 (2 H, d, *J* = 8.5 Hz, Ar**H**), 4.17 (2 H, q, *J* = 7.1 Hz, C**H$_2$**CH_3), 3.28 (2 H, t, *J* = 6.6 Hz, C**H$_2$**CH_2), 2.76 (2 H, t, *J* = 6.6 Hz, CH_2C**H$_2$**), 1.28 (3 H, t, *J* = 7.1 Hz, CH_2C**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 197.1 (**C**=O), 172.7 (**C**=O), 135.3 (Ar**C**), 131.9 (2 x Ar**C**H), 129.5 (2 x Ar**C**H), 128.4 (Ar**C**), 60.7 (**C**H_2), 33.3 (**C**H_2), 28.2 (**C**H_2), 14.2 (**C**H_3); **IR** (thin film) 1730, 1685, 1585, 1163 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{12}H_{13}O_3Br$ $[M+Na]^+$ *m/z* 306.9946, found *m/z* 306.9944.

Ethyl 4-(4'-bromophenyl)pent-4-enoate (2.49)



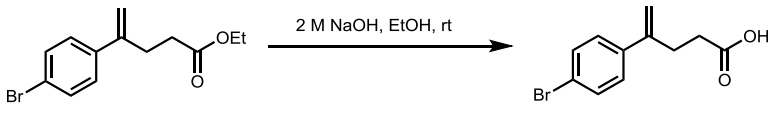
2.48 **2.49**

Following the literature procedure of a related compound,[44] to a stirred suspension of methyl triphenylphosphonium bromide (2.3 g, 6.5 mmol) in THF (13 mL) was added potassium *tert*-butoxide (0.73 g, 6.5 mmol). The resulting bright yellow suspension was

stirred at room temperature for 15 minutes then a solution of **2.48** (1.2 g, 5.4 mmol) in THF (12 mL) was added dropwise. The resulting suspension was stirred at room temperature for 3 h then sat. aq. NH_4Cl (100 mL) was added. The mixture was extracted with Et_2O (100 mL then 2 x 50 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/EtOAc; 98:2) afforded the title compound **2.49** as a colourless oil (1.1 g, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 (2 H, d, *J* = 8.7 Hz, Ar**H**), 7.30–7.25 (2 H, m, Ar**H**), 5.31–5.29 (1 H, m, C=C**H**H), 5.13–5.10 (1 H, m, C=CH**H**), 4.13 (2 H, q, *J* = 6.9 Hz, OC**H$_2$**CH_3), 2.81 (2 H, t, *J* = 7.2 Hz, C**H$_2$**CH_2), 2.49–2.43 (2 H, m, CH_2C**H$_2$**), 1.25 (3 H, t, *J* = 7.2 Hz, OCH_2C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 172.9 (**C**=O), 145.9 (**C**=CH_2), 139.5 (Ar**C**), 131.5 (2 x Ar**C**H), 127.7 (2 x Ar**C**H), 121.5 (Ar**C**), 113.4 (C=**C**H_2), 60.4 (**C**H_2), 33.1 (**C**H_2), 30.3 (**C**H_2), 14.2 (**C**H_3); **IR** (thin film) 1730, 1488, 1154 cm^{-1}; **HRMS** (CI) exact mass calculated for $C_{13}H_{15}O_2BrH$ $[M+H]^+$ *m/z* 283.0334, found *m/z* 283.0331.

4-(4'-bromophenyl)pent-4-enoic acid (2.50)

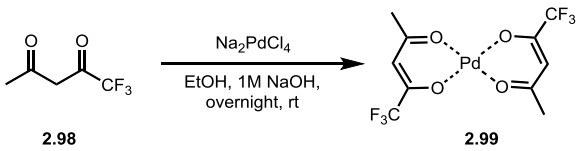


2.49 **2.50**

Following the literature procedure of a related compound,[12] ethyl 4-(4'-bromophenyl)pent-4-enoate (**2.49**) (1.0 g, 3.9 mmol) was dissolved in EtOH (32 mL), and 2 M aq. NaOH (32 mL) was added. The mixture was stirred at room temperature overnight, and then EtOH was removed *in vacuo.* The residue was extracted with Et_2O (2 x 50 mL), acidified to pH 1, with 2 M aq. HCl and extracted with EtOAc (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **2.50** as a colourless solid (0.79 g, 79%), which was used directly without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50–7.44 (2 H, m, Ar**H**), 7.31–7.24 (2 H, m, Ar**H**), 5.33 (1 H, d, *J* = 0.8 Hz, C=CH**H**), 5.14 (1 H, d, *J* = 0.80 Hz, C=C**H**H), 2.82 (2 H, t, *J* = 7.3 Hz, C**H$_2$**CH_2), 2.57–2.50 (2 H, m, CH_2C**H$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 178.4 (**C**=O), 145.5 (Ar**C**), 139.3 (Ar**C**), 131.5 (**C**=CH_2), 127.7 (2 x Ar**C**H), 121.7 (2 x Ar**C**H), 113.6 (C=**C**H_2), 32.6 (**C**H_2), 29.9 (**C**H_2); **IR** (thin film) 2931, 1694, 1336 cm^{-1}; **HRMS** (CI) exact mass calculated for $C_{11}H_{11}O_2BrH$ $[M+H]^+$ *m/z* 255.0021, found *m/z* 255.0019.

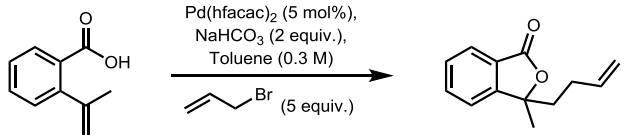
Pd(tfacac)$_2$ (2.99)



2.98 **2.99**

To a solution of 1,1,1-trifluoropentane-2,4-dione (**2.98**) in EtOH (0.36 M) at room temperature, was added a solution of NaOH 50 % aq. MeOH *via* syringe. After the addition of NaOH was complete, Na_2PdCl_4 in H_2O (0.070 M) was added dropwise *via* syringe. The reaction was allowed to stir overnight. The mixture was then washed with CH_2Cl_2 (2 x 10 mL) and the organic layers were then dried over $MgSO_4$ and the solvent was evaporated to yield a brown solid. The amorphous solid was then dissolved in Et_2O and filtered. The solvent was then evaporated to give compound **2.99** as a yellow solid (42 mg, 36%). Data corresponded to literature values.[154]

3-(but-3'-en-1'-yl)-3-methylisobenzofuranone (2.13)

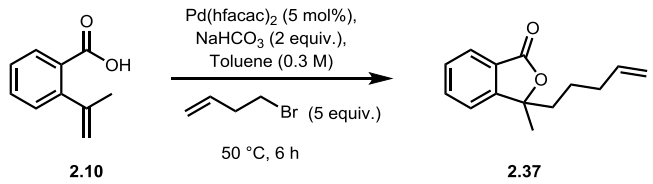


2.10 **2.13**

A 4 mL screw-top glass vial was charged with 2-(prop-1'-en-2'-yl)benzoic acid (**2.10**) (65 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl bromide (0.17 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**2.13**) as a colourless oil (69 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (1 H, dt, *J* = 7.6, 0.9 Hz, Ar**H**), 7.66 (1 H, td, *J* = 7.5, 1.1 Hz, Ar**H**), 7.50 (1 H, td, *J* = 7.5, 0.8 Hz, Ar**H**), 7.36 (1 H, d, *J* = 7.7 Hz, Ar**H**), 5.69 (1 H, ddt, *J* = 16.7, 10.0, 6.3 Hz, C**H**=CH_2), 4.94–4.89 (2 H, m, CH=C**H_2**), 2.15 (1 H, ddd, *J* = 13.6, 11.2, 4.8, C**H**H), 2.10–2.02 (1 H, m, CH**H**), 1.96 (1 H, ddd, *J* = 13.7, 11.0, 4.6 Hz, C**H**H), 1.80–1.73 (1 H, m, CH**H**), 1.65 (3 H, s, C**H_3**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 169.9 (**C**=O), 153.9 (Ar**C**), 137.3 (**C**H=CH_2), 134.2 (Ar**C**), 129.1 (Ar**C**H), 126.5 (Ar**C**H), 126.0 (Ar**C**H), 121.0 (Ar**C**H), 115.2 (CH=**C**H_2), 87.3(**C**CH_3), 39.3 (**C**H_2), 28.0 (**C**H_2), 26.3 (**C**H_3); **IR** (thin film) 1751, 1285, 1030 cm^{-1}; **HRMS** (EI) exact mass calculated for $C_{13}H_{14}O_2$ $[M]^+$ *m/z* 202.0994, found *m/z* 202.0991.

3-methyl-3-(pent-4'-en-1'-yl)isobenzofuranone (2.37)

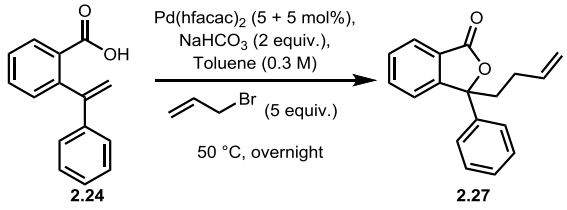


2.10 **2.37**

A 4 mL screw-top glass vial was charged with 2-(prop-1'-en-2'-yl)benzoic acid (**2.10**) (65 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), homoallyl bromide (0.2 mL, 2 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 6 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**2.37**) as a colourless oil (44 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86 (1 H, d, *J* = 7.8 Hz, Ar**H**), 7.69−7.61 (1 H, m, Ar**H**), 7.54−7.46 (1 H, m, Ar**H**), 7.36 (1 H, d, *J* = 7.6 Hz, Ar**H**), 5.67 (1 H, ddt, *J* = 17.1, 10.1, 6.8, C**H**=CH_2), 4.98−4.87 (2 H, m, CH=C**H$_2$**), 2.08−1.95 (3 H, m, CH**H** and C**H$_2$**), 1.92−1.80 (1 H, m, CH**H**CH_2), 1.64 (3 H, s, C**H$_3$**), 1.49−1.32 (1 H, m, C**H**HCH_2), 1.12−0.99 (1 H, m, CH**H**CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 169.9 (**C**=O), 153.8 (Ar**C**), 137.7 (**C**H=CH_2), 134.0 (Ar**C**H), 128.9 (Ar**C**H), 126 (Ar**C**), 125.7 (Ar**C**H), 120.8 (Ar**C**H), 115.0 (CH=C**H$_2$**), 87.5 (**C**CH_3), 39.1 (C**H$_2$**), 33.2 (C**H$_2$**), 25.9 (C**H$_3$**), 22.6 (C**H$_2$**); **IR** (thin film) 2931, 2854, 1750, 1287 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{14}H_{16}O_2Na$ $[M+Na]^+$ *m/z* 239.1043, found *m/z* 239.1041.

3-(but-3'-en-1'-yl)-3-phenylisobenzofuranone (2.27)



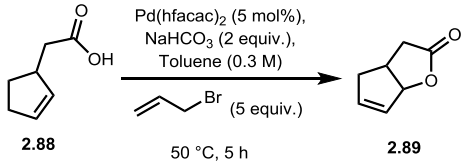
2.24 **2.27**

A 4 mL screw-top glass vial was charged with 2-(1'-phenylvinyl)benzoic acid (**2.24**) (90 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl bromide (0.17 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h then additional $Pd(hfacac)_2$ (10 mg, 0.020 mmol) added. The reaction was heated 50 °C for a further 19 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**2.27**) as a colourless oil (74 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (1 H, d, *J* = 7.6 Hz, Ar**H**), 7.63−7.57 (1 H, m, 1H Ar**H**), 7.50−7.42 (4 H, m, Ar**H**), 7.33−7.27 (2 H, m, Ar**H**), 7.26−7.21 (1 H, m, Ar**H**), 5.65 (1 H, ddt, *J* = 17.2, 10.0, 6.3 Hz, C**H**=CH_2), 4.90−4.80 (2 H, m, CH=C**H$_2$**), 2.55 (1 H, ddd, *J* =

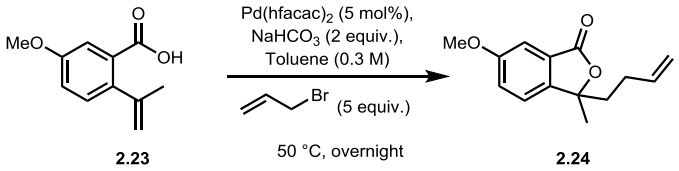
14.0, 11.6, 4.8 Hz, C**H**HCH$_2$), 2.26−2.17 (1 H, m, CH**H**CH$_2$), 2.01−1.91 (1 H, m, CH**H**CH$_2$), 1.88−1.76 (1 H, m, C**H**HCH$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 169.8 (**C**=O), 152.7 (Ar**C**), 140.2 (Ar**C**), 136.9 (**C**H=CH$_2$), 134.3 (Ar**C**H), 129.1 (Ar**C**H), 128.7 (2 x Ar**C**H), 128.1 (Ar**C**H), 125.9 (Ar**C**H), 125.9 (Ar**C**), 124.9 (2 x Ar**C**H), 122.1 (Ar**C**H), 115.1 (CH=**C**H$_2$), 89.7 (**C**Ph), 39.3 (**C**H$_2$), 28.0 (**C**H$_2$); **IR** (thin film) 3055, 2918, 1760, 1259 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{18}H_{16}O_2Na$ $[M+Na]^+$ *m/z* 287.1043, found *m/z* 287.1038.

Bicyclic lactone (2.89)



A 4 mL screw-top glass vial was charged with 2-(cyclopent-2'-en-1'-yl)acetic acid (**2.88**) (48 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl bromide (0.17 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**2.89**) as a colourless oil (39 mg, 78%). Data corresponded to literature values.[155]

3-(but-3'-en-1'-yl)-6-methoxy-3-methylisobenzofuranone (2.24)

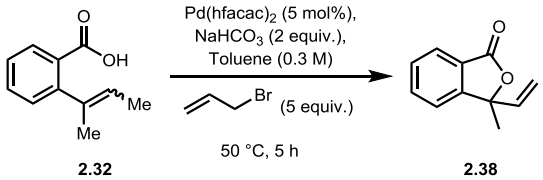


A 4 mL screw-top glass vial was charged with 5-methoxy-2-(prop-1'-en-2'-yl)benzoic acid (**2.23**) (77 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl bromide (0.17 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C overnight. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**2.24**) as a colourless oil (73 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32−7.30 (1 H, m, Ar**H**), 7.29−7.26 (1 H, m, Ar**H**), 7.26−7.22 (1 H, m, Ar**H**), 5.71 (1 H, ddt, *J* = 16.7, 10.0, 6.3 Hz, C**H**=CH$_2$), 4.96−4.88 (2 H, m, CH=C**H$_2$**), 3.88 (3 H, s, OC**H$_3$**), 2.19−2.10 (1 H, m, CH$_2$C**H**H), 2.09−1.99 (1 H, m, CH$_2$CH**H**), 1.98−1.89 (1 H, m, CH$_2$C**H**H), 1.80−1.69 (1 H, m, CH$_2$CH**H**), 1.65 (3 H, s, C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 169.7 (**C**=O), 160.5 (Ar**C**), 146.0 (Ar**C**), 137.1 (**C**H=CH$_2$), 127.4 (Ar**C**), 122.9 (Ar**C**H), 121.8 (Ar**C**H), 115.0 (CH=**C**H$_2$), 107.5 (Ar**C**H), 86.9 (**C**CH$_3$), 55.7 (O**C**H$_3$), 39.0 (**C**H$_2$), 27.8 (**C**H$_2$), 26.2 (**C**H$_3$); **IR** (thin film) 2978, 2930, 2359,

1751 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{14}H_{16}O_3Na$ $[M+Na]^+$ *m/z* 255.0992, found *m/z* 255.0994.

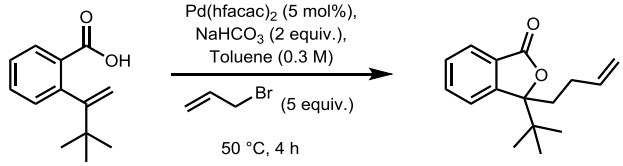
3-methyl-3-vinylisobenzofuranone (2.38)



2.32 **2.38**

A 4 mL screw-top glass vial was charged with 2-(but-2'-en-2'-yl)benzoic acid (**2.32**) (70 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl bromide (0.17 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**2.38**) as a colourless oil (59 mg, 84%). Data corresponded to literature values.[156]

3-(but-3'-en-1'-yl)-3-(*tert*-butyl)isobenzofuranone (2.31)

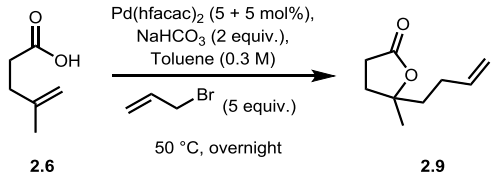


2.30 **2.31**

A 4 mL screw-top glass vial was charged with 2-(3',3'-dimethylbut-1'-en-2'-yl)benzoic acid (**2.30**) (82 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl bromide (0.17 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 4 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**2.31**) as a colourless oil (77 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.88−7.84 (1 H, m, Ar**H**), 7.66−7.61 (1 H, m, Ar**H**), 7.53−7.48 (1 H, m, Ar**H**), 7.44−7.40 (1 H, m, Ar**H**), 5.63 (1 H, ddt, *J* = 16.9, 13.1, 6.4 Hz, C**H**=CH_2), 4.86 (2 H, m, CH=C**H$_2$**), 2.37−2.27 (1 H, m, C**H**HCH_2), 2.14−2.01 (1 H, m, CH**H**CH_2), 1.83−1.69 (1 H,m, C**H**HCH_2), 1.29−1.17 (1 H,m, CH**H**CH_2), 0.99 (9 H, s, C**H$_3$**); **^{13}C NMR** (100 MHz,$CDCl_3$) δ (ppm): 170.6 (**C**=O), 150.6 (Ar**C**), 137.3 (**C**H=CH_2), 133.5 (Ar**C**H), 128.7 (Ar**C**H), 127.4 (Ar**C**C), 125.3 (Ar**C**H), 122.5 (Ar**C**H), 114.9 (CH=**C**H_2), 94.3 (**C**$C(CH_3)_3$), 38.3 (**C**$(CH_3)_3$), 31.5 (**C**H_2), 27.1 (**C**H_2), 25.4 (3 x **C**H_3); **IR** (thin film) 2972, 2249, 1753, 1290 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{16}H_{20}O_2Na$ $[M+Na]^+$ *m/z* 267.1356, found *m/z* 267.1353.

5-(but-3'-en-1'-yl)-5-methyldihydrofuranone (2.9)

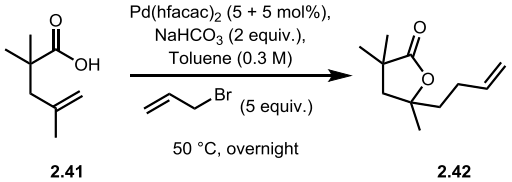


2.6 **2.9**

A 4 mL screw-top glass vial was charged with 4-methylpent-4-enoic acid (**2.6**) (57 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl bromide (0.17 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h then additional $Pd(hfacac)_2$ (10 mg, 0.020 mmol) added. The reaction was heated 50 °C for a further 19 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**2.9**) as a colourless oil (37 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.83 (1 H, ddt, *J* = 16.8, 10.3, 6.4 Hz, C**H**=CH_2), 5.06 (1 H, ddd, *J* = 17.2, 3.4, 1.8 Hz, CH=C**H**H), 5.00 (1 H, ddd, *J* = 10.2, 2.9, 1.3 Hz, CH=CH**H**), 2.70−2.53 (2 H, m, C$\mathbf{H_2}$), 2.22−2.06 (3 H, m, C$\mathbf{H_2}$ and C**H**H), 2.05−1.96 (1 H, m, CH**H**), 1.84−1.69 (2 H, m, C$\mathbf{H_2}$), 1.41 (3 H, s, C$\mathbf{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 176.6 (**C**=O), 137.4 (**C**H=CH_2), 115.1 (CH=**C**H_2), 86.4 (**C**CH_3), 40.1 (**C**H_2), 33.0 (**C**H_2), 29.1 (**C**H_2), 28.1 (**C**H_2), 25.6 (**C**H_3); **IR** (thin film) 2976, 2932, 1761, 1205 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_9H_{14}O_2Na$ $[M+Na]^+$ *m/z* 177.0886, found *m/z* 177.0884.

5-(but-3'-en-1'-yl)-3,3,5-trimethyldihydrofuranone (2.42)



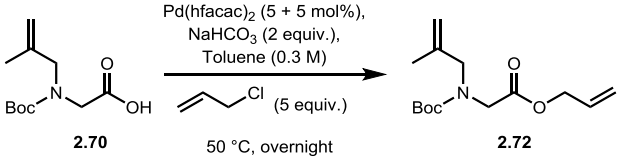
2.41 **2.42**

A 4 mL screw-top glass vial was charged with 2,2,4-trimethylpent-4-enoic acid (**2.41**) (57 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl bromide (0.17 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h then additional $Pd(hfacac)_2$ (10 mg, 0.020 mmol) added. The reaction was heated 50 °C for a further 19 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**2.42**) as a colourless oil (58 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.79 (1 H, ddt, *J* = 16.7, 10.3, 6.5 Hz, C**H**=CH_2), 5.03 (1 H, ddd, *J* = 17.1, 3.3, 1.6 Hz, CH=C**H**H), 4.97 (1 H, ddd, *J* = 10.0, 2.8, 1.1 Hz, CH=CH**H**), 2.18−2.09 (2 H, m, CH_2C$\mathbf{H_2}$), 2.06 (1 H, d, *J* = 13.1 Hz, C$(CH_3)_2$C**H**H), 1.95 (1

H, d, *J* = 13.4 Hz, C(CH$_3$)$_2$CH**H**), 1.78−1.69 (2 H, m, C**H$_2$**CH$_2$), 1.42 (3 H, s, C**H$_3$**), 1.33 (3 H, s, C**H$_3$**), 1.29 (3 H, s, C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 182.1 (**C**=O), 137.5 (**C**H=CH$_2$), 115.0 (CH=**C**H$_2$.), 82.6 (**C**CH$_3$), 47.5 (**C**H$_2$), 41.7 (**C**H$_2$), 40.7 (**C**(CH$_3$)$_2$), 28.1 (**C**H$_2$), 27.8 (**C**H$_3$), 27.5 (**C**H$_3$), 27.4 (**C**H$_3$); **IR** (thin film) 2970, 2360, 1759, 1267 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{11}H_{18}O_2Na$ $[M+Na]^+$ *m/z* 205.1199 , found *m/z* 205.1199.

allyl 2-(*tert*-butoxycarbonyl(2'-methylallyl)amino)acetate (2.72)

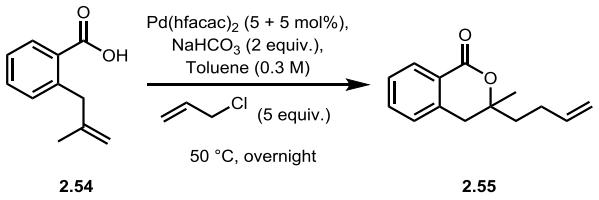


A 4 mL screw-top glass vial was charged with 2-(*tert*-butoxycarbonyl(2'-methylallyl)amino)acetic acid (**2.70**) (92 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl chloride (0.16 mL, 2.0 mmol) and Pd(hfacac)$_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h then additional Pd(hfacac)$_2$ (10 mg, 0.020 mmol) added. The reaction was heated 50 °C for a further 19 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAC; 9:1) to afford the title compound (**2.72**) as a colourless oil (101 mg, 94%).

^{1}H NMR (400 MHz, C_6D_6, 50°C due to rotameric mixture) δ (ppm): 5.68 (1 H, br. s, C**H**), 5.14−4.91 (2 H, m, C**H$_2$**), 4.75−4.66 (2 H, m, C**H$_2$**), 4.41 (2 H, br. s, C**H$_2$**), 3.95 (2 H, br. s, C**H$_2$**), 3.87−3.71 (2 H, m, C**H$_2$**), 1.57 (3 H, br. s, C**H$_3$**), 1.41 (9 H, br. s, 3 x C**H$_3$**); **IR** (thin film) 2361, 1676, 1267 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{14}H_{23}O_4$ $[M+Na]^+$ *m/z* 292.1519, found *m/z* 292.1519.

^{13}C NMR unavailable due to complex mixture of rotamers.

3-(but-3'-en-1'-yl)-3-methylisochromanone (2.55)

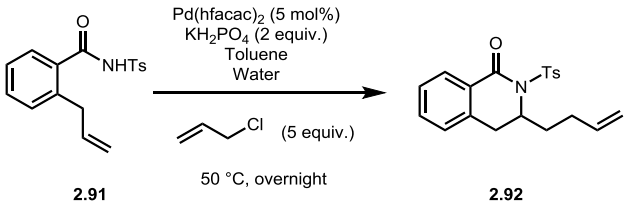


A 4 mL screw-top glass vial was charged with 2-(2'-methylallyl)benzoic acid (**2.54**) (76 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl chloride (0.16 mL, 2.0 mmol) and Pd(hfacac)$_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h then additional Pd(hfacac)$_2$ (10 mg, 0.020 mmol) added. The reaction was heated 50 °C for a further 19 h. The reaction mixture was cooled to room temperature, and subjected

directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**2.55**) as a colourless oil (57 mg, 62%).

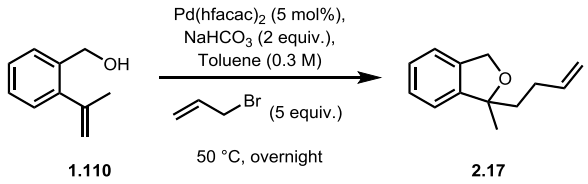
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.13−8.07 (1 H, m, Ar**H**), 7.55 (1 H, dd, *J* = 7.5, 1.3 Hz, Ar**H**), 7.39 (1 H, t, *J* = 7.6 Hz, Ar**H**), 7.23 (1 H, d, *J* = 7.6 Hz, Ar**H**), 5.79 (1 H, ddt, *J* = 16.7, 11.5, 6.6 Hz, C**H**=CH_2), 5.09−4.95 (2 H, m, CH=C**H$_2$**), 3.14 (1 H, d, *J* = 16.3 Hz, C**H**H), 2.96 (1 H, d, *J* = 16.2 Hz, CH**H**), 2.31−2.19 (2 H, m, C**H$_2$**CH_2), 1.93−1.73 (2 H, m, CH_2C**H$_2$**), 1.43 (3 H, s, C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 164.7 (**C**=O), 137.9 (Ar**C**), 137.6 (**C**H=CH_2), 133.8 (Ar**C**H), 130.0 (Ar**C**H), 128.0 (Ar**C**H), 127.4 (Ar**C**H), 124.9 (Ar**C**), 115.0 (CH=**C**H_2), 82.4 (**C**CH_3), 39.6 (**C**H_2), 37.7 (**C**H_2), 28.0 (**C**H_2), 25.0 (**C**H_3); **IR** (thin film) 2939, 2359, 1712 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{14}H_{16}O_2Na$ $[M+Na]^+$ *m/z* 239.1043, found *m/z* 239.1049.

3-(but-3'-en-1'-yl)-2-tosyl-3,4-dihydroisoquinolinone (2.92)



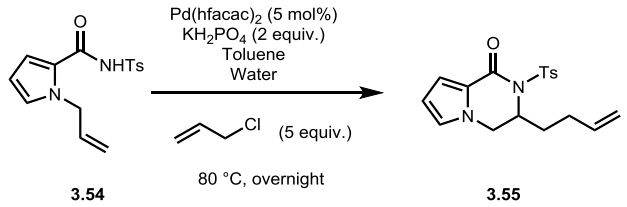
A 4 mL screw-top glass vial was charged with 2-allyl-*N*-tosyl-benzamide (**2.91**) (50 mg, 0.16 mmol), toluene (0.64 mL), H_2O (0.64 mL), KH_2PO_4 (44 mg, 0.32 mmol), allyl chloride (0.070 mL, 0.79 mmol) and $Pd(hfacac)_2$ (4.0 mg, 0.01 mmol). The mixture was heated at 50 °C for 16 h. The mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to yield the title compound as a white powdered solid (**2.92**) (53 mg, 95%). Data corresponded to literature values.[44]

1-(but-3'-en-1'-yl)-1-methyl-1,3-dihydroisobenzofuran (2.17)



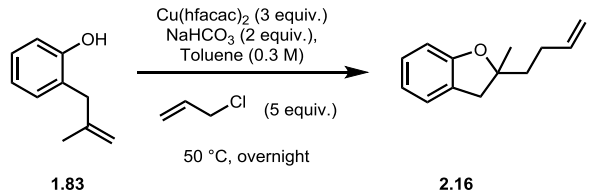
A 4 mL screw-top glass vial was charged with (2-(prop-1'-en-2'-yl)phenyl)methanol (**1.110**) (200 mg, 1.35 mmol), toluene (4.5 mL), $NaHCO_3$ (226 mg, 2.70 mmol), allyl bromide (5.90 mL, 6.75 mmol) and $Pd(hfacac)_2$ (73.0 mg, 0.0675 mmol). The mixture was heated at 50 °C overnight. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/CH_2Cl_2; 1:1) to afford the title compound (**2.17**) as a colourless oil (193 mg, 76%). Data corresponded to literature values.[44]

Pyrrole tosylamide (3.55)



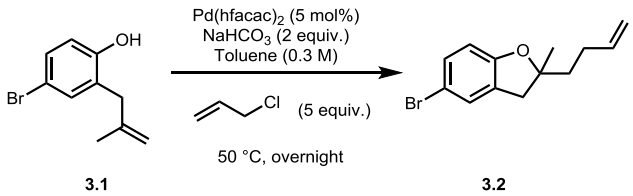
A 4 mL glass screw-top vial was charged with 1-allyl-*N*-tosyl-pyrrole-2-carboxamide (**3.54**) (48 mg, 0.16 mmol), toluene (0.64 mL), H_2O (0.64 mL), KH_2PO_4 (44 mg, 0.32 mmol), allyl chloride (0.07 mL, 0.79 mmol) and $Pd(hfacac)_2$ (4.0 mg, 0.01 mmol). The mixture was heated at 80 °C for 19 h. The mixture was cooled to room temperature, and subjected directly to column chromatography (petroleum ether/EtOAc; 9:1) to yield the title compound (**3.55**) as a white powdered solid (32 mg, 58%). Data corresponded to literature values.[44]

2-(but-3'-en-1'-yl)-2-methyl-2,3-dihydrobenzofuran (2.16)



A 4 mL screw-top glass vial was charged with 2-(2-methylallyl)phenol (**1.83**) (59 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl bromide (0.17 mL, 2.0 mmol) and $Cu(hfacac)_2$ (512 mg, 1.2 mmol). The mixture was heated at 50 °C overnight. The reaction mixture was cooled to room temperature. The reaction was then quenched using a 10% aq. $EDTANa_2$ and the organic layers were separated using Et_2O (3 x 20 mL), dried over $MgSO_4$ and purified with flash chromatography (petroleum ether/CH_2Cl_2; 85:15) to afford the title compound (**2.16**) as a colourless oil (21 mg, 28%). Data corresponded to literature values.[44]

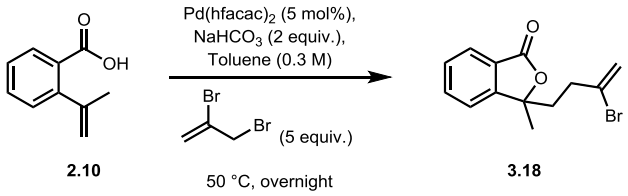
5-bromo-2-(but-3'-en-1'-yl)-2-methyl-2,3-dihydrobenzofuran (3.2)



A 4 mL screw-top glass vial was charged with 4-bromo-2-(2'-methylallyl)phenol (**3.1**) (45 mg, 0.20 mmol), toluene (0.65 mL), $NaHCO_3$ (34 mg, 0.40 mmol), allyl bromide (80 µL,

1.0 mmol) and $Pd(hfacac)_2$ (5.0 mg, 0.010 mmol). The mixture was heated at 50 °C overnight. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/CH_2Cl_2; 85:15) to afford the title compound (**3.2**) as a colourless oil (38 mg, 71%). Data corresponded to literature values.[44]

3-(3'-bromobut-3'-en-1'-yl)-3-methylisobenzofuranone (3.18)

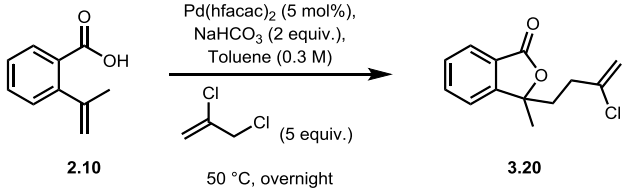


2.10 **3.18**

A 4 mL screw-top glass vial was charged with 2-(prop-1'-en-2'-yl)benzoic acid (**2.10**) (65 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), 2,3-dibromopropene (0.20 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**3.18**) as a colourless oil (31 mg, 28%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.88 (1 H, d, *J* = 7.7 Hz, Ar**H**), 7.69 (1 H, td, *J* = 7.7, 0.8 Hz, Ar**H**), 7.54 (1 H, t, *J* = 7.8 Hz, Ar**H**), 7.42 (1 H, d, *J* = 7.7 Hz, Ar**H**), 5.48−5.46 (1 H, m, CBr=C**H**H), 5.31 (1 H, d, *J* = 1.7 Hz, CBr=CH**H**), 2.49−2.39 (1 H, m, CH_2C**H**H), 2.38−2.30 (1 H, m, CH_2CH**H**), 2.21−2.14 (1 H, m, CH_2C**H**H), 2.09−2.02 (1 H, m, CH_2CH**H**), 1.67 (3 H, s, C**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 169.7 (**C**=O), 153.0 (**C**), 141.0 (**C**), 134.3 (**C**), 132.7 (**C**), 129.2 (Ar**C**H), 125.8 (Ar**C**H), 120.9 (Ar**C**H), 117.3 (Ar**C**H), 86.6 (CBr=**C**H$_2$), 38.2 (**C**H$_2$), 35.7 (**C**H$_2$), 26.3 (**C**H$_3$); **IR** (thin film) 2953, 1759, 1035, 696 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{13}H_{13}O_2BrNa$ $[M+Na]^+$ *m/z* 302.9991, found *m/z* 302.9980.

3-(3'-chlorobut-3'-en-1'-yl)-3-methylisobenzofuranone (3.20)



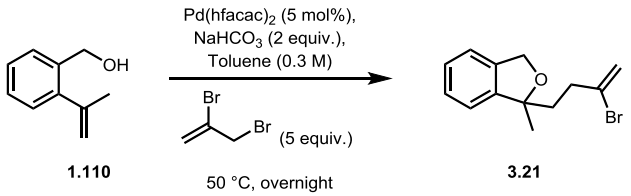
2.10 **3.20**

A 4 mL screw-top glass vial was charged with 2-(prop-1'-en-2'-yl)benzoic acid (**2.10**) (65 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), 2,3-chloropropene (0.19 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**3.20**) as a

colourless oil (23 mg, 24%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.90−7.86 (1 H, m, Ar**H**), 7.69 (1 H, td, *J* = 7.5, 1.1 Hz, Ar**H**), 7.54 (1 H, dd, *J* = 7.7, 0.9 Hz, Ar**H**), 7.43−7.39 (1 H, m, Ar**H**), 5.07 (1 H, d, *J* = 1.4 Hz, CCl=CH**H**), 5.04−5.02 (1 H, m, CCl=C**H**H), 2.40−2.29 (2 H, m, C**H$_2$**CH_2), 2.22−2.15 (1 H, m, CH_2C**H**H), 2.04−1.93 (1 H, m, CH_2CH**H**), 1.67 (3 H, s, C**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 169.7 (**C**=O), 153.0 (**C**), 141.2 (**C**), 137.5 (**C**), 134.3 (Ar**C**H), 129.2 (Ar**C**H), 125.8 (Ar**C**H), 120.9 (Ar**C**H), 112.8 (CH=**C**H_2), 86.7 (**C**CH_3), 37.5 (**C**H_2), 33.5 (**C**H_2), 26.2 (**C**H_3); **IR** (thin film) 2982, 1761, 912, 694 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{13}H_{13}O_2ClNa$ $[M+Na]^+$ *m/z* 259.0496, found *m/z* 259.0490.

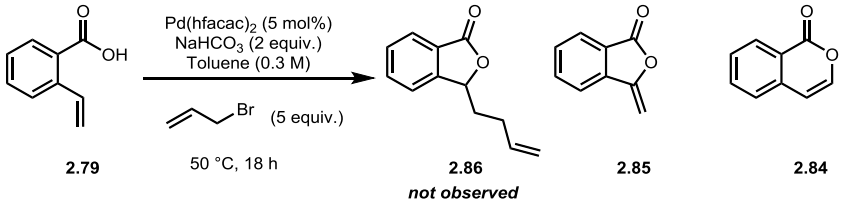
1-(3'-bromobut-3'-en-1'-yl)-1-methyl-1,3-dihydroisobenzofuran (3.21)



A 4 mL screw-top glass vial was charged with (2-(prop-1'-en-2'-yl)phenyl)methanol (**1.110**) (65 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), 2,3-dibromopropene (0.20 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.020 mmol). The mixture was heated at 50 °C for 5 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAc; 9:1) to afford the title compound (**3.20**) as a colourless oil (91 mg, 85%).

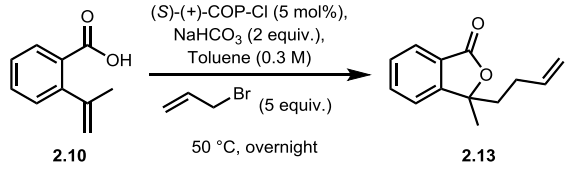
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.32−7.25 (2 H, m, Ar**H**), 7.22−7.18 (1 H, m, Ar**H**), 7.13−7.10 (1 H, m, Ar**H**), 5.51−5.46 (1 H, m, CBr=C**H**H), 5.31 (1 H, d, *J* = 1.3 Hz, CBr=CH**H**), 5.11 (1 H, d, *J* = 12.4 Hz, OC**H**H), 5.06 (1 H, d, *J* = 12.4 Hz, OCH**H**), 2.56−2.49 (1 H, m, C**H**HCH_2), 2.20−2.01 (3 H, m, CH**H**CH_2 and C**H$_2$**), 1.50 (3 H, s, C**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 144.6 (**C**), 138.9 (**C**), 134.6 (**C**), 127.5 (2 x Ar**C**H), 121.0 (Ar**C**H), 120.8 (Ar**C**H), 116.1 (CBr=**C**H_2), 87.6 (**C**CH_3), 71.7 (**C**H_2O), 40.1 (**C**H_2), 36.5 (**C**H_2), 27.6 (**C**H_3); **IR** (thin film) 3026, 2848, 883, 721 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{13}H_{15}OBrNa$ $[M+Na]^+$ *m/z* 289.0198, found *m/z* 289.0192.

Procedure for 2-vinylbenzoic acid subjected to standard Pd-catalysed oxyallylation condition in the synthesis of lactones



A 4 mL screw-top glass vial was charged with 2-vinylbenzoic acid (**2.79**) (59 mg, 0.40 mmol), toluene (1.3 mL), $NaHCO_3$ (67 mg, 0.80 mmol), allyl bromide (0.17 mL, 2.0 mmol) and $Pd(hfacac)_2$ (10 mg, 0.02 mmol). The mixture was heated at 50 °C for 18 h. The reaction mixture was cooled to room temperature and filtered through a cotton wool plug. Analysis of the crude material revealed no formation of compound **2.86** but instead gave unreacted starting material **2.79**, exo-methylene lactone **2.85** and isocoumarin **2.84** in a ratio of 4.3: 0.9: 1.0 respectively. Data corresponded to literature values.[157]

Use of (*S*)-(+)-COP-Cl in Oxyallylation reaction



A 4 mL screw-top glass vial was charged with 2-(prop-1'-en-2'-yl)benzoic acid (**2.10**) (32 mg, 0.20 mmol), toluene (0.65 mL), $NaHCO_3$ (34 mg, 0.40 mmol), allyl bromide (0.90 mL, 1.0 mmol) and (*S*)-(+)-COP-Cl (15 mg, 0.010 mmol). The mixture was heated at 50 °C for 5 h. The reaction mixture was cooled to room temperature, and subjected directly to flash chromatography (petroleum ether/EtOAC; 9:1) to afford the title compound (**2.13**) as a colourless oil (69 mg, 85%). Chiral HPLC (Chiralpak AD-H, 95: 5 *n*-hexane/IPA, 0.5 mL/min, 280 nm) shows that **2.13** was formed in a 6% ee. Data corresponded to compound **2.13**.

General Procedure for Pd-catalysed heteroallylation of mono-substituted alkenes:

A 4 mL screw-top glass vial was charged with Pd(II) (10 mol%), Toluene (0.4 mL), allyl halide (5.0 equiv.), $NaHCO_3$ (2.0 equiv.) and lastly the substrate (1.0 equiv.). The vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a pre-heated aluminium block, and was left to stir overnight. The reaction mixture was cooled to room temperature then purified directly by flash chromatography on silica gel.

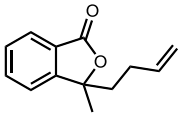
General Procedure for asymmetric Pd-catalysed heteroallylation of unactivated alkenes:

A 4 mL screw-top glass vial was charged with Pd(II) (5 mol%), Ligand (7.5 mol%), Toluene (0.3 M) and the mixture was allowed to stir for 30 minutes at 50 °C. Next, allyl halide (5.0 equiv.), $NaHCO_3$ (2.0 equiv.) and lastly the substrate (1.0 equiv.) was added and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a pre-heated aluminium block and was left to stir

overnight. The reaction mixture was cooled to room temperature then purified directly by flash chromatography on silica gel.

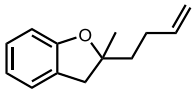
General Procedure for asymmetric Pd-catalysed heteroallylation of unactivated alkenes with chiral phosphoric acids:

A 4 mL screw-top glass vial was charged with Pd(II) (5 mol%), phosphoric acid (15 mol%), Toluene (0.3 M) and $NaHCO_3$ (2.0 equiv.) and the mixture was allowed to stir for 30 minutes at room temperature. Next, allyl halide (5.0 equiv.), and lastly the substrate (1.0 equiv.) were added and the vial was sealed under ambient atmosphere and left to stir overnight at room temperature. The reaction mixture was directly purified by flash chromatography on silica gel.



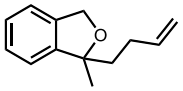
2.13

Chiral HPLC (Chiralpak AD-H, 95: 5 *n*-hexane/IPA, 0.5 mL/min, 280 nm)



2.16

Chiral HPLC (Chiralpak OD-H, 100% *n*-hexane, 0.5 mL/min, 280 nm)

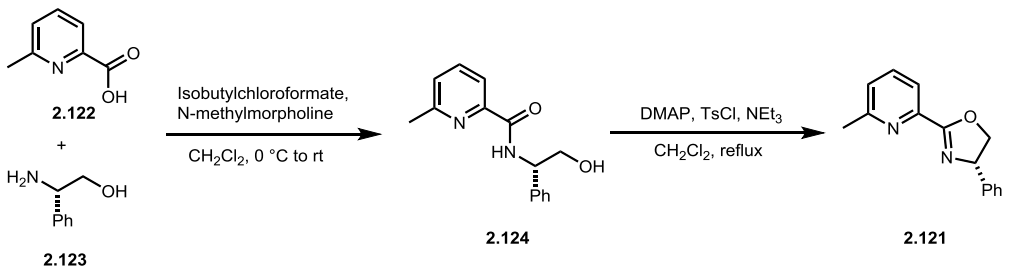


2.17

Chiral HPLC (Chiralpak OD-H, 100% *n*-hexane, 0.5 mL/min, 280 nm)

For ee's please refer toChapter 2.

Synthesis of pyridine-oxazoline ligand (2.121)



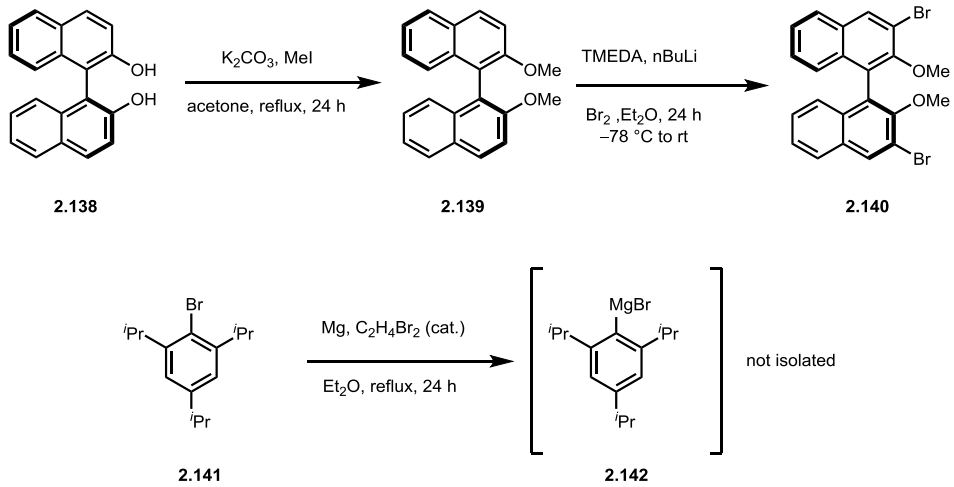
2.122 + **2.123** → **2.124** → **2.121**

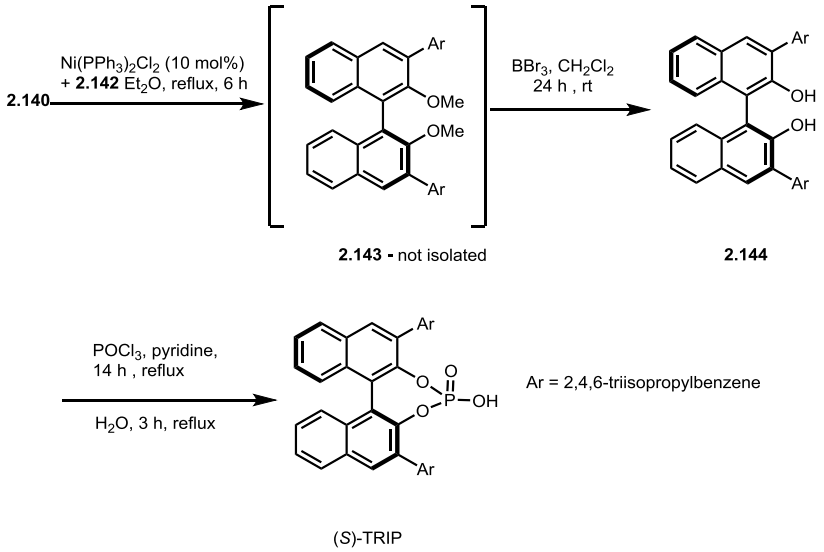
Following a literature procedure,[101a] 6-methylpicolinic acid (**2.122**) (0.70 g, 5.1 mmol) was placed under an atmosphere of argon and dry dichloromethane (50 mL) was added and

the reaction vessel was submerged in a brine ice bath. 4-Methylmorpholine (0.84 mL, 7.7 mmol) was added slowly by syringe and the mixture was stirred for 15 minutes. Isobutylchloroformate (0.77 mL, 5.9 mmol) was added dropwise by syringe and the mixture was stirred for 30 minutes. A solution of (*S*)-phenylglycinol (**2.123**) (0.84 g, 6.2 mmol) in 10 mL of dichloromethane and with additional 4-methylmorpholine (0.64 mL, 5.9 mmol) was added dropwise and the mixture was stirred at reduced temperature for 1 h and then allowed to warm to room temperature and stir overnight (18 h). The reaction mixture was diluted with dichloromethane and washed twice with sat. aq. NH_4Cl, then water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a yellow-pink oil. Purification by flash chromatography (petroleum ether/EtOAc; 1:1) afforded amide (**2.124**) as a clear oil (1.1 g, 91%). Data corresponded to literature values.[101a]

Amide (**2.124**) (1.2 g, 4.6 mmol) was placed under an argon atmosphere and anhydrous 1,2-dichloroethane (45 mL) was added *via* cannula. The rubber septum was quickly removed and DMAP (56 mg, 0.46 mmol) and *p*-toluenesulfonyl chloride (1.3 g, 6.9 mmol) were added. The septum was replaced and triethylamine (2.5 mL, 18 mmol) was added *via* syringe. The mixture was stirred at room temperature for 3 h, then heated at reflux for 15 h during which time the mixture turned dark red. After cooling to room temperature, CH_2Cl_2 was added and the organic layer was washed with sat. aq. $NaHCO_3$, H_2O, brine and dried over $MgSO_4$, filtered and concentrated. The crude mixture was then purified by flash column chromatography (petroleum ether/ EtOAc; 7:3) to give the desired ligand (**2.121**) (0.94 g, 90%) as a yellow oil. Data corresponded to literature values.[101a]

Synthesis of (*S*)-TRIP





(*S*)-2,2'-dimethoxy-1,1'-binaphthyl (2.139)[106]

Following a literature procedure, (*S*)-BINOL (**2.138**) (10.0 g, 34.6 mmol) was placed under an atmosphere of argon. Subsequently, the vessel was charged with acetone (320 mL), upon complete dissolution of BINOL (**2.138**), potassium carbonate (15.8 g, 114 mmol) was added followed by methyl iodide (8.70 mL, 140 mmol). The resulting mixture was heated to reflux for 24 h. After that time the volatile compounds were removed under reduced pressure. The resulting slurry was redissolved in water (180 mL) and stirred for 2 h. The resulting solid is collected, washed with water and dried *in vacuo* furnishing 10.9 g (quant.) of the title compound (**2.139**) as a slightly yellow solid. Data corresponded to literature values.[106]

(*S*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthyl (**2.140**)[106]

Following a literature procedure, dried Et_2O (500 mL) was added, followed by freshly distilled tetramethylethylenediamine (11.5 mL, 77.0 mmol). To the resulting solution, *n*-butyllithium (2.5 M in hexanes, 49 mL, 120 mmol) was added slowly at room temperature *via* syringe, the mixture was allowed to stir for 1 h. Compound **2.139** (11.0 g, 35.0 mmol) was added as a solid at room temperature and the resulting solution was stirred for 3.5 h. After this time, the reaction was cooled to −78 °C and bromine (8.90 mL, 175 mmol) was added dropwise. After complete addition, the cooling bath was removed and the yellowish-brown reaction mixture is allowed to stir for 20 h at room temperature. Sat. aq. Na_2SO_3 (80 mL) was added to the reaction and the mixture was stirred for 1 h. The mixture was extracted with Et_2O (3 x 50 mL), the organic phases were combined, washed with brine (100 mL) and dried over $MgSO_4$, filtered and concentrated. After filtration, the solvent was removed *in vacuo* and the crude mixture was subjected to purification by column chromatography (petroleum ether/EtOAc; 95:5) resulting in a yellowish solid material, which was recrystallised from CH_2Cl_2/hexanes. The mother liquor was subjected

to a second column chromatography and the resulting material was crystallized (same conditions as above). In total, 7.24 g (44%) of the title compound **2.140** was obtained as slightly yellow crystals. Data corresponded to literature values.[106]

(2,4,6-triisopropylphenyl)magnesium bromide (2.142)[106]

Mg (1.3 g, 52 mmol, activated with a spatula tip of iodine) was covered with Et_2O (5 mL), subsequently, 2-bromo-1,3,5-tri*iso*propylbenzene (**2.141**) (7.7 g, 26 mmol) Et_2O (35 mL) and 1,2-dibromoethane (0.1 mL, as activator) were charged in different syringes and added in a manner of maintaining the exothermic Grignard-reaction active. After complete addition of the compounds, the resulting grey suspension was placed in an oil bath and was heated at reflux for 24 h. Data corresponded to literature values.[106]

(1*S*,3*S*)-2,2'-dimethoxy-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl(2.143)[106]

Compound **2.140** (2.3 g, 4.8 mmol) and $Ni(PPh_3)_2Cl_2$ (0.31 g, 0.48 mmol) were placed under an argon atmosphere. Subsequently, Et_2O (25 mL) was added and to the resulting suspension the Grignard-solution **2.142** was added dropwise at room temperature *via* cannula. After complete addition, the resulting mixture was refluxed for 6 h. The resulting brown solution was allowed to cool to room temperature and then further cooled to 0 °C with an ice bath and quenched with 1 M aq. HCl (30 mL). The resulting mixture was extracted with Et_2O (3 x 25 mL), the organic phase is dried over $MgSO_4$, filtered and the solvent is removed *in vacuo*. The resulting slightly yellow solid crude (7.6 g) was subjected to the next step without further purification.

(1*S*, 3*S*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diol (2.144)[106]

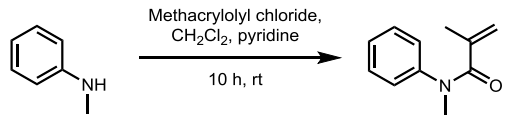
The crude material **2.143** dissolved in 105 mL dry dichloromethane under argon. Subsequently, the solution was cooled with an ice bath followed by slow addition of BBr_3 (1 M in dichloromethane, 29.7 mL, 29.7 mmol). After complete addition, the resulting clear solution was allowed to stir for 24 h at room temperature. Subsequently, water (40 mL) was added to the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL), the combined organic layers are dried over $MgSO_4$, filtered and the solvent was reduced *in vacuo*. Column chromatography (petroleum ether/EtOAc; 99:1) gave compound **2.144** as a yellow oil (2.00 g). Data corresponded to literature values.[106]

(*S*)-TRIP[106]

A flask was charged with **2.144** (2.0 g, 2.9 mmol) and set under argon. Subsequently, pyridine (10 mL) was added, followed by $POCl_3$ (0.80 mL, 8.70 mmol). The resulting mixture was heated at reflux for 14 h. After this time the reaction was allowed to cool to room temperature, followed by addition ofwater (10 mL). The resulting brownish slurry

was heated to reflux and hydrolysed for 3 h. After, the reaction was cooled to room temperature, CH_2Cl_2 (5 mL) was added. The resulting organic phase was thoroughly washed with 1 M aq. HCl (3 x 5 mL). The resulting organic layer was dried over $MgSO_4$, filtered and concentrated. The crude material was recrystallised from MeCN the title compound (*S*)-TRIP as a white solid (1.1 g, 31% over three steps). Data corresponded to literature values.[106]

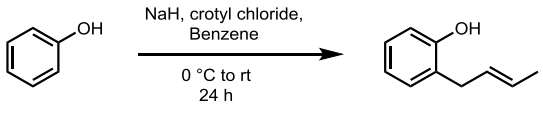
_N_-methyl-_N_-phenylmethacrylamide (2.159)



4.2 **2.159**

Following a modified literature procedure, *N*-Methylaniline (**4.2**) (1.1 mL, 10 mmol) was dissolved in CH_2Cl_2 (130 mL) followed by addition of methacrylolyl chloride (2.9 mL, 30 mmol). Pyridine (1.6 mL, 20 mmol) was then added slowly. After 10 h at room temperature, H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 x 50 mL), once with brine (20 mL) and dried over $MgSO_4$, filtered and concentrated. Solvent evaporation gave the crude anilide as yellow oil. Purification by flash chromatography (CH_2Cl_2/EtOAc; 95:5) to give the title compound **2.159** as a white solid (1.97 g, quant.). Data corresponded to literature values.[158]

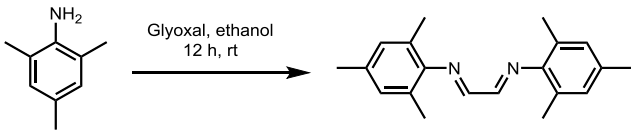
Synthesis of Phenol (1.12)



2.125 **1.12**

To a stirring suspension of NaH (60% in mineral oil, 0.70 g, 18 mmol) in benzene (25 mL) at 0 °C was added a benzene (15 mL) solution of the phenol (**2.125**) (1.5 g, 16 mmol). Crotyl chloride (1.7 mL, 18 mmol) was added to the mixture which was then allowed to warm to room temperature. After 24 h stirring, benzene was removed under reduced pressure and H_2O (50 mL) and petroleum ether (50 mL) were added. The mixture was extracted with 20% aqueous NaOH (3 x 20 mL) and "Claisen's alkali" (20 mL; 6 g KOH in 5 mL H_2O diluted with 25 mL MeOH). The combined alkali extracts were acidified with 6 N H_2SO_4 and extracted with Et_2O (3 x 50 mL). Combination of the organic extracts, which were dried over $MgSO_4$, filtered and concentration *in vacuo* and purification by flash column chromatography on silica gel (petroleum ether/EtOAc; 4:1) provided the *o*-substituted phenol **1.12** as a yellow oil (1.5 g, 65%). Data corresponded to literature values.[23]

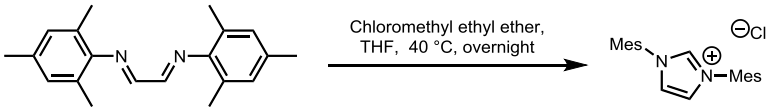
Glyoxal-bis(2,4,6-trimethylphenyl)imine (4.4)



4.3 4.4

Following a modified procedure of Arduengo and co-workers,[159] to a solution of 2,4,6-trimethylaniline **4.3** (12.7 mL, 90.0 mmol) in ethanol (100 mL) were added a mixture of 40% aqueous solution of glyoxal (5.14 mL, 45.0 mmol), and ethanol (100 mL). The mixture was stirred for 16 h at ambient temperature and then for 4 h at 60 °C. Upon addition of water (300 mL), a yellow solid precipitated and was collected by filtration and dried *in vacuo* to yield **4.4** as a yellow crystalline solid (10.6 g, 80%). Data corresponded to literature values.[159]

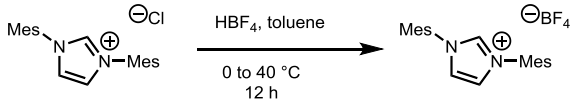
1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride (4.5)



4.4 4.5

Following the procedure of Arduengo and co-workers,[159] to a solution of chloromethylethyl ether (0.72 mL, 7.5 mmol) in THF (5 mL) was added a solution of glyoxal-*bis*(2,4,6-trimethylphenyl)imine **4.4** (2.00 g, 6.85 mmol) in THF (25 mL). The reaction mixture was stirred under argon atmosphere for 5 days. The precipitate was isolated by filtration and washed with fresh THF to yield **4.5** as a pale yellow solid (0.800 g, 34%). Data corresponded to literature values.[159]

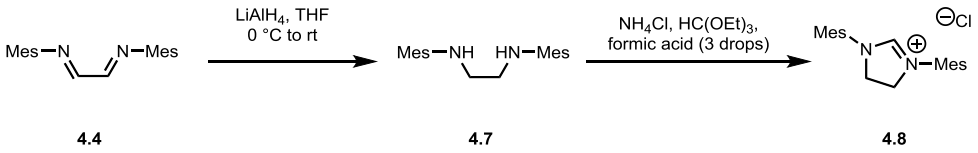
1,3-Bis(2,4,6-trimethylphenyl)imidazolium tetrafluoroborate (4.6)



4.5 4.6

Imidazolium chloride **4.5** (0.61 g, 2.1 mmol) in toluene (4 mL) was cooled to 0 °C. HBF_4 (48 wt. % in H_2O, 0.40 mL, 2.1 mmol), was added dropwise and the mixture was left to stir at room temperature for 30 minutes, followed by heating at 40 °C for 12 h. The solution was allowed to cool to room temperature and was filtered to yield the title compound **4.6** as a yellow solid (0.40 g, 50%). Data corresponded to literature values.[160]

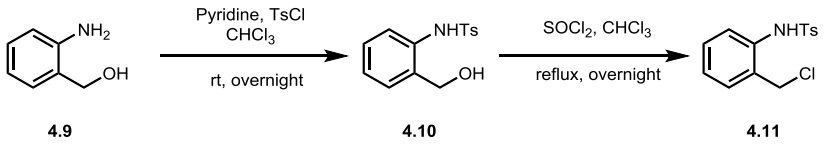
Synthesis of SIMes.HCl (4.8)



Following a literature procedure,[161] ethylenediimine **4.4** (3.00 g, 10.3 mmol) was dissolved in anhydrous THF (100 mL) under an atmosphere of Argon. The solution was cooled to 0 °C and $LiAlH_4$ pellets (0.780 g, 20.6 mmol) were added. The reaction mixture was stirred overnight at room temperature and then poured carefully into an excess of an ice/concentrated HCl mixture. The reaction mixture was basified by using 2 M aq. NaOH and extracted with diethyl ether (3 x 250 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was evaporated *in vacuo* to give the desired product **4.7** as a yellow solid (2.92 g, 97%). Data corresponded to literature values.[161]

Following a literature procedure,[161] diamine **4.7** (2.92 g, 10.0 mmol) and NH_4Cl (0.530 g, 10.0 mmol) was suspended in $HC(OEt)_3$ (5.00 mL, 30.0 mmol) and 3 drops of formic acid was added. The reaction mixture was stirred at 120 °C for 4 h and then poured into water (500 mL). The aqueous phase was washed with diethyl ether (2 x 300 mL) and extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo* to give the imidazolinium salt **4.8** as a white solid (2.90 g, 85%). Data corresponded to literature values.[161]

***N*-(2'-(chloromethyl)phenyl)-4-methylbenzenesulfonamide**

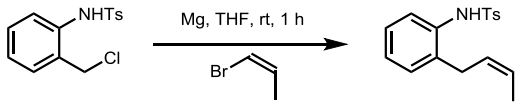


Following a literature procedure,[162] a solution of 2-aminobenzyl alcohol (3.80 g, 13.7 mmol), **4.9** and pyridine (2.35 mL, 29.2 mmol) in dry $CHCl_3$ (90 mL) was treated dropwise with a solution *p*-toluenesulfonyl chloride (5.10 g, 27 mmol) in $CHCl_3$ (25 mL) at room temperature. The reaction mixture was stirred overnight. The volatiles were evaporated and to the resulting residue was added ethyl acetate (50 mL) and sat. aq. NH_4Cl. The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was then recrystallised in *i*PrOH to give *N*-(2'-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide **4.10** as a white solid (5.20 g, 77%). Data corresponded to literature values.[162]

Following a literature procedure,[163] to a solution of thionyl chloride (1.20 mL, 16.5 mmol) in $CHCl_3$ (10 mL), was added a solution of benzyl alcohol **4.10** (3.80 g, 13.7 mmol) in

$CHCl_3$(60 mL) over 1 min. The reaction was heated to 40 °C overnight, cooled to rt, then poured into ice water (30 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (3 x 40 mL). The combined organic layers were washed with brine (30 mL), and dried over $MgSO_4$. Purification by flash column chromatography on silica gel (petroleum ether/EtOAc; 4:1) provided the title compound **4.11** as a white solid (2.5 g, 62%). Data corresponded to literature values.[163]

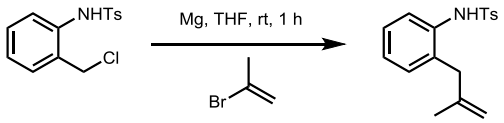
(*Z*)-*N*-(2'-(but-2''-en-1'-yl)phenyl)-4-methylbenzenesulfonamide (4.12)



4.11 **4.12**

Following a literature procedure,[164] to an oven dried flask equipped with a condenser was placed magnesium turnings (0.360 g, 15.0 mmol) and THF (6 mL) in an inert atmosphere. A solution of the *cis*-1-bromo-prop-1-ene (1.28 mL, 15.0 mmol) in 2 mL of THF was introduced slowly into the flask at room temperature with good stirring. After the formation of the Grignard reagent, a solution of *N*-(2'-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **4.11** (1.50 g, 5.00 mmol) in THF (10 mL) was added slowly at room temperature and the mixture was stirred for 1 hour. The excess Grignard reagent was destroyed by adding water and the crude mixture was extracted with ethyl ether (100 mL). The ether solution was then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petroleum ether/EtOAc; 9:1) to give the desired tosyl amide **4.12** as a white solid (249 mg, 17%). Data corresponded to literature values.[165]

4-methyl-*N*-(2'-(2''-methylallyl)phenyl)benzenesulfonamide (4.13)

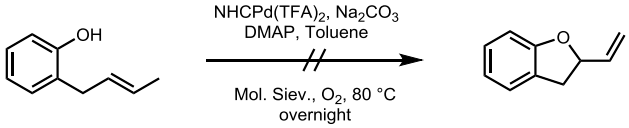


4.11 **4.13**

Following a literature procedure,[164] to an oven dried flask equipped with a condenser was placed magnesium turnings (0.360 g, 15.0 mmol) and THF (6 mL) in an inert atmosphere. A solution of the 2-bromopropene (1.33 mL, 15.0 mmol) in 2 mL of THF was introduced slowly into the flask at room temperature with good stirring. After the formation of the Grignard reagent a solution of *N*-(2'-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **4.11** (1.50 g, 5.00 mmol) in THF (10 mL) was added slowly at room temperature and the mixture was stirred for 1 hour. The excess Grignard reagent was destroyed by adding water and the crude mixture was extracted with ethyl ether (100 mL). The ether solution was then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified

by flash column chromatography (petroleum ether/EtOAc; 9:1) to give the desired tosyl amide **4.13** as a white solid (574 mg, 38%). Data corresponded to literature.[164]

General procedure for Pd-carbene catalysed aerobic intramolecular Wacker-type cyclisation



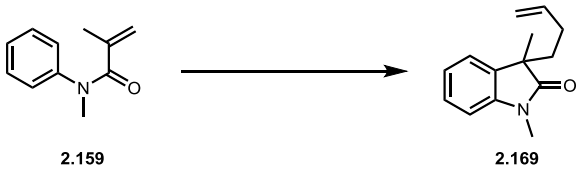
1.12 **1.13**

Following literarture procedures,[166] a solution of freshly prepared carbene (6 mol%) in toluene[167] (0.8 mL) was transferred *via* cannula to a round bottom flask containing a 1 M toluene solution of $Pd(TFA)_2$ (5 mol%) and the resulting mixture was stirred at room temperature for 15 minutes. 4-(*N,N*-Dimethylamino)-pyridine (10.0 mg, 0.080 mmol), sodium carbonate (85 mg, 0.80 mmol) and 3 Å MS (0.50 g) were added under a positive stream of argon and the resulting mixture was stirred for 5 minutes before addition of phenol **1.12** (60 mg, 0.40 mmol) in toluene (0.2 mL). The reaction mixture was submitted to three freeze and thaw cycles employing molecular oxygen. The reaction mixture was heated to 80 °C for 12 hours. After this, the reaction mixture was concentrated under vacuum, and the residue was taken up in dichloromethane, washed with water, dried and evaporated under reduced pressure.

General procedure for Pd-carbene catalysed intramolecular Wacker-type cyclisation−methylation

Following literarture procedures,[166] a solution of freshly prepared carbene[167] (6 mol%) in toluene (0.8 mL) was transferred *via* cannula to a flame-dried round bottom flask containing a 1 M toluene solution of $Pd(TFA)_2$ (5 mol%) and the resulting mixture was stirred at room temperature for 15 minutes. 4-(N,N-Dimethylamino)-pyridine (10 mg, 0.080 mmol), Na_2CO_3 (85 mg, 0.80 mmol), methyl iodide (0.25 mL, 4.0 mmol) and 3 Å MS (0.50 g) were added under a positive stream of argon and the resulting mixture was stirred for 5 minutes before addition of phenol **1.83** (60 mg, 0.40 mmol) in toluene (0.2 mL). The reaction mixture was heated to 80 °C over a period of 12 hours. After this, the reaction mixture was concentrated under vacuum, and the residue was taken up in dichloromethane, washed with water, dried and evaporated under reduced pressure.

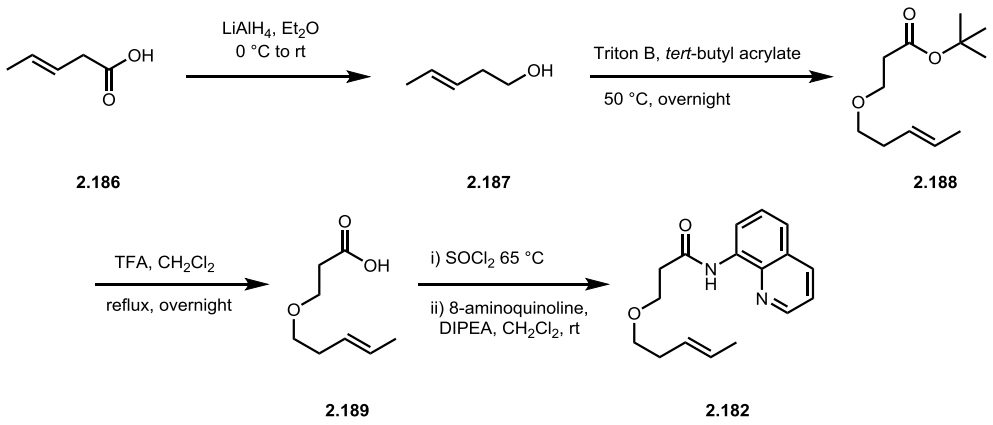
General procedure for Pd-catalysed arylallylation of unactivated alkenes in the synthesis of oxindoles:



2.159 **2.169**

To a solution of anilide **2.159** (35 mg, 0.20 mmol) in Solvent were added Additives, allyl X (2.0 mmol, 5.0 equiv.) and Pd(II) (10 mol%). The reaction mixture was heated and stirred overnight. The reaction was cooled to room temperature and the volatile components were evaporated under reduced pressure. The remaining mixture was partitioned between water and EtOAc and the aqueous layer was extracted with EtOAc. The aqueous layers were then combined and extracted with EtOAc (3 x 10 mL). The organic layers were then dried over $MgSO_4$, filtered and the solvents were evaporated.

Synthesis of Amide 2.182



2.186 **2.187** **2.188** **2.189** **2.182**

To a stirred suspension of $LiAlH_4$ (0.750 g, 19.7 mmol) in diethyl ether (20 mL) cooled to 0 °C was added 3-pentenoic acid (**2.186**) (2.00 mL, 19.7 mmol) in diethyl ether slowly *via* cannula. The reaction was allowed to warm to room temperature and was stirred overnight. Sat. aq. sodium potassium tartrate was added and the reaction was left to stir overnight. The reaction was dried with $MgSO_4$, filtered and carefully concentrated by rotary evaporation to give 3-penten-1ol **2.187** as a colourless oil (1.48 g, 90%). Data corresponded to literature values.[120]

Following a modified literature procedure,[121] to a flask was placed Triton B (40% in methanol, 0.450 mL, 1.40 mmol) and the solvent was removed under reduced pressure. Alcohol **2.187** (1.20 g, 14.0 mmol) was added, followed, after 15 minutes, by *tert*-butyl acrylate (10.30 mL, 70.0 mmol). The reaction was then heated at 50 °C overnight. After completion of the reaction, the resulting solution was filtered over a mixture Celite-silica gel and concentrated under vacuum. The product **2.188** was used without purification for

the next step (3.22 g, 76%).

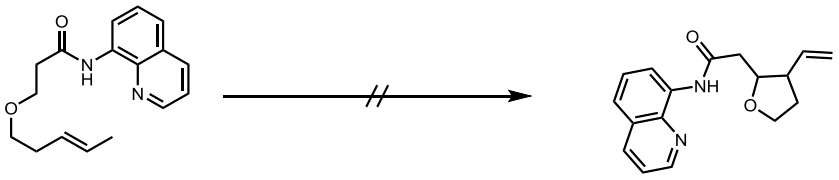
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.56–5.37 (2 H, m, C**H**=C**H**), 3.67 (2 H, t, *J* = 6.5 Hz, OC**H$_2$**), 3.45 (2 H, t, *J* = 6.9 Hz, C**H$_2$**O), 2.49 (2 H, t, *J* = 6.5 Hz, C**H$_2$**COO), 2.29–2.22 (2 H, m, C**H$_2$**CH=CH), 1.67–1.64 (3 H, m, C**H$_3$**), 1.46 (9 H, s, C(C**H$_3$**)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 171.0 (**C**=O), 127.4 (**C**H=CH), 126.8 (CH=**C**H), 80.4 (**C**(CH$_3$)$_3$), 70.9 (**C**H$_2$), 66.4 (**C**H$_2$), 36.4 (**C**H$_2$), 32.9 (**C**H$_2$), 28.1 (C(**C**H$_3$)$_3$), 17.5 (**C**H$_3$); **IR** (thin film) 1730, 1367, 1158 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{12}H_{22}O_3Na$ $[M+Na]^+$ *m/z* 237.1461, found *m/z* 237.1451.

Following a modification of a literature procedure,[121] to a dried flask containing *tert*-butyl ester **2.188** (5.50 g, 25.6 mmol) was added dichloromethane (12 mL) and trifluoroacetic acid (5.80 mL, 76.8 mmol). The mixture was stirred at reflux overnight. After completion of the reaction, the mixture was concentrated *in vacuo* and required no further purification, to yield **2.189** as a yellow oil (4.10 g, quant.).

Following a modified literature procedure,[122] thionyl chloride (89.0 mL, 1.23 mol) was added to a round bottom flask containing acid **2.189** (3.30 g, 18.9 mmol). The mixture was stirred at 65 °C for 1 h in an inert atmosphere. After this time, the volatiles were removed *in vacuo*. To the resulting acid chloride was added CH_2Cl_2 (160 mL), DIPEA (32.7 mL, 189 mmol) and 8-aminoquinoline (1.63 g, 11.3 mmol). The reaction was left to stir overnight at room temperature. The reaction was quenched with H_2O (100 mL) and the organic extracts were separated with CH_2Cl_2. The organic layer was then washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL) and dried over $MgSO_4$, filtered and concentrated. The crude mixture was then purified by flash column chromatography (petroleum ether/EtOAc; 85: 15) to yield the amide **2.182** as a yellow oil (1.65 g, 51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.54–10.50 (1 H, br. s, CON**H**), 8.83–8.79 (2 H, m, Ar**H**), 8.16 (1 H, dd, *J* = 8.3, 1.7 Hz, Ar**H**), 7.57–7.49 (2 H, m, Ar**H**), 7.45 (1 H, dd, *J* = 8.2, 4.2 Hz, Ar**H**), 5.57–5.45 (2 H, m, C**H**=C**H**), 3.87 (2 H, t, *J* = 5.80 Hz, OC**H$_2$**), 3.60 (2 H, t, *J* = 7.1 Hz, C**H$_2$**O), 2.82 (2 H, t, *J* = 5.9 Hz, C**H$_2$**COO), 2.48–2.39 (2 H, m, C**H$_2$**CH=CH), 1.62–1.59 (3 H, m, C**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 170.3 (**C**=O), 148.0 (Ar**C**H), 138.6 (Ar**C**), 136.2 (Ar**C**H), 134.9 (Ar**C**), 127.9 (Ar**C**), 127.3 (2 x **C**H=CH), 127.0 (Ar**C**H), 121.4 (Ar**C**H), 121.4 (Ar**C**H), 116.7 (Ar**C**H), 71.4 (**C**H$_2$), 66.6 (**C**H$_2$), 38.8 (**C**H$_2$), 32.9 (**C**H$_2$), 17.9 (**C**H$_3$); **IR** (thin film) 1684, 1522, 1486, 1109 cm^{-1}; **HRMS** (CI) exact mass calculated for $C_{17}H_{20}O_4N_2H$ $[M+H]^+$ *m/z* 285.1603, found *m/z* 285.1600.

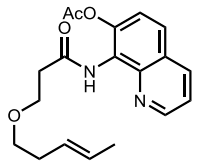
General procedure for sp^3 C−H activation−cyclisation:



2.182 2.183

To a solution of compound **2.182** (57 mg, 0.20 mmol) in Solvent were added Additives, and $Pd(OAc)_2$ (5 mg, 0.02 mmol). The reaction mixture was heated and stirred overnight. The reaction was cooled to room temperature and the volatile solvent was evaporated under reduced pressure.

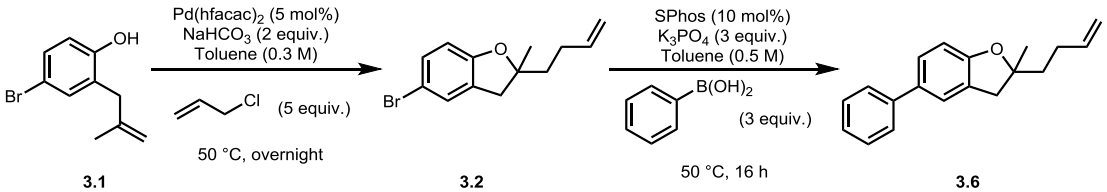
Side product **2.190** was isolated as a yellow oil.



2.190

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.50–10.46 (1 H, br. s, CON**H**), 8.86–8.78 (2 H, m, Ar**H**), 8.17 (1 H, dd, *J* = 10.04, 1.8 Hz, Ar**H**), 7.48 (1 H, dd, *J* = 8.9, 4.1 Hz, Ar**H**), 7.31 (1 H, d, *J* = 8.6 Hz, Ar**H**), 5.56–5.42 (2 H, m, C**H**=C**H**), 3.86 (2 H, t, *J* = 5.8 Hz, OC**H$_2$**), 3.60 (2 H, t, *J* = 6.9 Hz, C**H$_2$**O), 2.81 (2 H, t, *J* = 5.6 Hz, C**H$_2$**COO), 2.45 (3 H, s, C**H$_3$**COO), 1.63–1.59 (5 H, m, C**H$_2$** and C**H$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 170.2 (**C**=O), 169.4 (**C**=O), 148.4 (Ar**C**H), 140.4 (Ar**C**), 138.9 (Ar**C**), 133.2 (Ar**C**), 130.2 (**C**-H), 127.3 (**C**-H), 127.1 (**C**-H), 121.9 (Ar**C**), 121.7 (**C**-H), 119.2 (**C**-H), 116.1 (**C**-H), 71.4 (**C**H_2), 66.6 (**C**H_2), 38.7 (**C**H_2), 32.9 (**C**H_2), 20.9 (**C**H_3COO), 17.9 (**C**H_3); **IR** (thin film) 1768, 1527, 1491, 1196 cm^{-1}; **HRMS** (CI) exact mass calculated for $C_{19}H_{22}O_4N_2H$ $[M+H]^+$ *m/z* 343.1658, found *m/z* 343.1654.

2-(but-3'-en-1'-yl)-2-methyl-5-phenyl-2,3-dihydrobenzofuran (3.6)



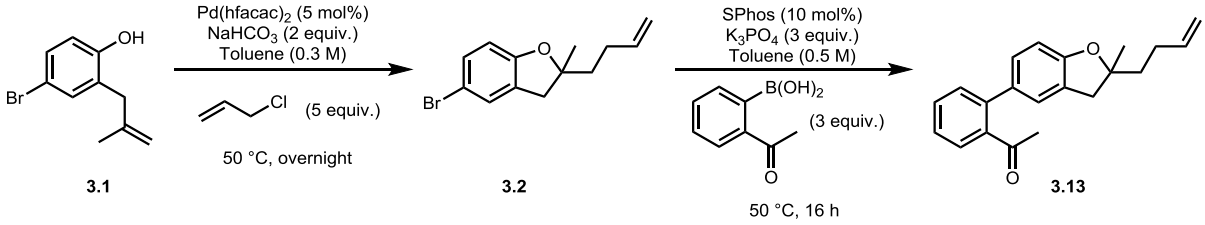
3.1 3.2 3.6

A 4 mL screw-top glass vial was charged with 4-bromo-2-(2'-methylallyl)phenol (**3.1**) (45.0 mg, 0.200 mmol), toluene (0.65 mL), allyl chloride (80.0 µL, 1.00 mmol), $NaHCO_3$ (34.0

mg, 0.400 mmol) and $Pd(hfacac)_2$ (5.00 mg, 0.0100 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block until the substrate had been consumed, as judged by TLC analysis. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added toluene (0.4 mL), SPhos (8.00 mg, 0.0200 mmol), freshly ground K_3PO_4 (127 mg, 0.600 mmol) and phenylboronic acid (73.0 mg, 0.600 mmol) and the vial was sealed under ambient atmosphere. The mixture was then heated at 50 °C for 16 h. The reaction mixture was cooled to room temperature then purified directly by flash chromatography on silica gel (petroleum ether, then petroleum ether/EtOAc; 98:2) to give the title compound **3.6** as a yellow oil (36 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47–7.40 (2 H, m, Ar**H**), 7.35–7.24 (4 H, m, Ar**H**), 7.23–7.16 (1 H, m, Ar**H**), 6.71 (1 H, d, *J* = 8.6 Hz, Ar**H**), 5.91 (1 H, ddt, *J* = 16.8, 10.1, 6.7, C**H**=CH_2), 4.96 (1 H, ddd, *J* = 17.1, 3.4, 1.7 Hz, CH=C**H**H), 4.88 (1 H, ddd, *J* = 10.2, 2.7, 1.7 Hz, CH=CH**H**), 3.09 (1 H, d, *J* = 15.6 Hz, ArC**H**H), 2.91 (1 H, d, *J* = 15.6 Hz, CCH**H**), 2.15–2.09 (2 H, m, C**H$_2$**CH_2), 1.81–1.75 (2 H, m, C**H$_2$**CH_2), 1.40 (3 H, s, C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 158.7 (Ar**C**), 141.5 (Ar**C**), 138.3 (**C**H=CH_2), 133.6 (Ar**C**), 128.7 (2 x Ar**C**H), 127.5 (Ar**C**) , 127.1 (2 x Ar**C**H), 126.7 (Ar**C**H), 126.4 (Ar**C**H), 123.9 (Ar**C**H), 114.6 (CH=**C**H_2), 109.5 (Ar**C**H), 88.9 (O**C**CH_3), 41.3 (**C**H_2), 40.4 (**C**H_2), 28.5 (**C**H_2), 26.5 (**C**H_3); **IR** (thin film) 2976, 2360, 1479, 1265 cm^{-1}; **HRMS** (EI) exact mass calculated for $C_{19}H_{20}O$ $[M]^+$ *m/z* 264.1514, found *m/z* 264.1519.

1-(2-(2'-(but-3''-en-1''-yl)-2'-methyl-2',3'-dihydrobenzofuran-5'-yl)phenyl)ethanone (3.13)

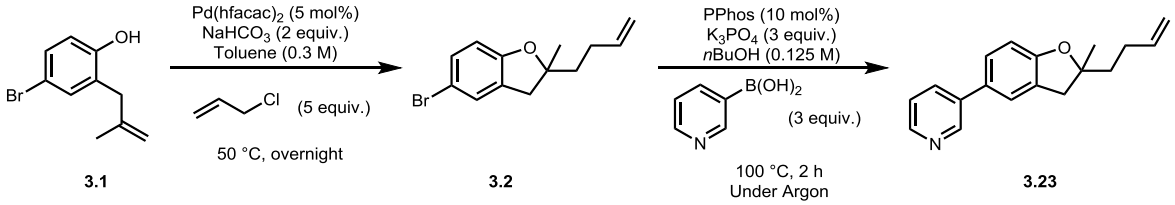


A 4 mL screw-top glass vial was charged with 4-bromo-2-(2'-methylallyl)phenol (**3.1**) (45.0 mg, 0.200 mmol), toluene (0.65 mL), allyl chloride (80.0 µL, 1.00 mmol), $NaHCO_3$ (34.0 mg, 0.400 mmol) and $Pd(hfacac)_2$ (5.00 mg, 0.0100 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block until the substrate had been consumed, as judged by TLC analysis. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added toluene (0.4 mL), SPhos (8.00 mg, 0.0200 mmol), freshly ground K_3PO_4 (127 mg, 0.600 mmol) and (2-acetylphenyl)boronic acid (98.0 mg, 0.600 mmol) and the vial was sealed under ambient

atmosphere. The mixture was then heated at 50 °C for 16 h. The reaction mixture was cooled to room temperature then purified directly by flash chromatography on silica gel (petroleum ether, then petroleum ether/EtOAc; 98:2) to give the title compound **3.13** as a yellow oil (28 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.53–7.46 (2 H, m, Ar**H**), 7.39–7.38 (1 H, m, Ar**H**), 7.37–7.35 (1 H, m, Ar**H**), 7.12–7.05 (2 H, m, Ar**H**), 6.78 (1 H, d, *J* = 8.3 Hz), 5.85 (1 H, ddt, *J* = 16.7, 10.3, 6.3, C**H**=CH_2), 5.05 (1 H, ddd, *J* = 17.1, 3.4, 1.6 Hz, CH=C**H**H), 4.98 (1 H, ddd, *J* = 10.2, 3.0, 1.3 Hz, CH=CH**H**), 3.14 (1 H, d, *J* = 15.7 Hz, CC**H**H), 2.99 (1 H, d, *J* = 15.2 Hz, CCH**H**), 2.25–2.15 (2 H, m, C**H$_2$**CH_2), 2.03 (3 H, s, CO**C**H_3), 1.90–1.84 (2 H, m, CH_2C**H$_2$**), 1.48 (3 H, s, CC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 205.5 (**C**=O), 159.1 (Ar**C**), 140.9 (Ar**C**), 140.6 (Ar**C**), 138.1 (**C**H=CH_2), 132.5 (Ar**C**), 130.5 (Ar**C**H), 130.1 (Ar**C**H), 128.9 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**), 126.8 (Ar**C**H), 125.6 (Ar**C**H), 114.7 (CH=**C**H_2), 109.5 (Ar**C**H), 89.2 (**C**CH_3), 41.0 (**C**H_2), 40.3 (**C**H_2), 30.5 (**C**H_3), 28.4 (**C**H_2), 26.4 (**C**H_3); **IR** (thin film) 2914, 1681, 1275 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{21}H_{22}O_2Na$ $[M+Na]^+$ *m/z* 329.1512, found *m/z* 329.1469.

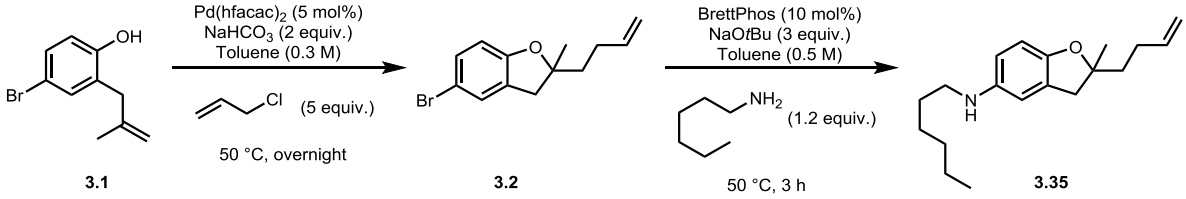
3-(2'-(but-3''-en-1''-yl)-2'-methyl-2',3'-dihydrobenzofuran-5'-yl)pyridine (3.23)



A 4 mL screw-top glass vial was charged with 4-bromo-2-(2'-methylallyl)phenol (**3.1**) (57.0 mg, 0.250 mmol), toluene (0.83 mL), allyl chloride (100 µL, 1.25 mmol), $NaHCO_3$ (42.0 mg, 0.500 mmol) and $Pd(hfacac)_2$ (7.0 mg, 0.0125 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block until the substrate had been consumed, as judged by TLC analysis. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. Following a modified literature procedure,[133] to the vial was added PPhos (16.0 mg, 0.0250 mmol), *n*BuOH (1 mL) and argon was bubbled through the mixture. The reaction was allowed to stir for 5 minutes at room temperature. Freshly ground K_3PO_4 (159 mg, 0.750 mmol), 3-pyridinylboronic acid (92.0 mg, 0.750 mmol) and *n*BuOH (1 mL) were added to the reaction mixture and the vial was sealed under an argon atmosphere. The mixture was then heated to 100 °C for 2 h using the aluminium block. The reaction was allowed to cool to room temperature and quenched with water and the organic layers were extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography on silica gel (petroleum ether/EtOAc; 8:2) to give the title compound **3.23** as a yellow oil (35 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (1 H, br. s, Ar**H**), 8.54 (1 H, br. s, Ar**H**), 7.84−7.76 (1 H, m, Ar**H**), 7.39−7.29 (3 H, m, Ar**H**), 6.83 (1 H, d, *J* = 8.2 Hz, Ar**H**), 5.85 (1 H, ddt, *J* = 16.8, 10.3, 6.4, C**H**=CH_2), 5.05 (1 H, ddd, *J* = 17.1, 3.4, 1.5 Hz, CH=C**H**H), 4.97 (1 H, ddd, *J* = 10.3, 2.9, 1.3 Hz, CH=CH**H**), 3.17 (1 H, d, *J* = 15.7 Hz, OCC**H**H), 3.01 (1 H, d, *J* = 15.7 Hz, OCCH**H**), 2.24−2.16 (2 H, m, C**H$_2$**CH_2), 1.90−1.84 (2 H, m, CH_2C**H$_2$**), 1.49 (3 H, s, C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 159.3 (Ar**C**), 147.9 (Ar**C**H), 147.5 (Ar**C**H), 138.1 (**C**H=CH_2), 133.8 (Ar**C**H), 129.9 (Ar**C**), 128.0 (2 x Ar**C**), 127.3 (2 x Ar**C**H), 123.9 (Ar**C**H), 114.7 (CH=**C**H_2), 109.9 (Ar**C**H), 89.2 (**C**CH_3), 41.1 (**C**H_2), 40.3 (**C**H_2), 28.4 (**C**H_2), 26.4 (**C**H_3); **IR** (thin film) 3074, 2928, 849, 711 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{18}H_{19}NOH$ $[M+H]^+$ *m/z* 266.1539, found *m/z* 266.1532.

2-(but-3'-en-1'-yl)-*N*-hexyl-2-methyl-2,3-dihydrobenzofuran-5-amine (3.35)

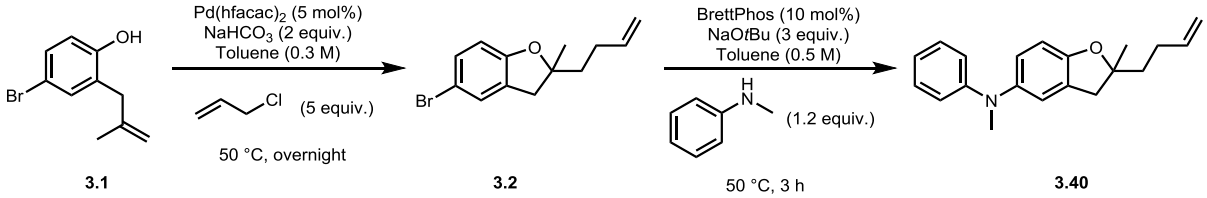


A 4 mL screw-top glass vial was charged with 4-bromo-2-(2'-methylallyl)phenol (**3.1**) (45 mg, 0.20 mmol), toluene (0.65 mL), allyl chloride (80 µL, 1.0 mmol), $NaHCO_3$ (34 mg, 0.40 mmol) and $Pd(hfacac)_2$ (5.0 mg, 0.010 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block until the substrate had been consumed, as judged by TLC analysis. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added BrettPhos (10 mg, 0.020 mmol), NaO*t*Bu (58 mg, 0.60 mmol) and toluene (0.2 mL). The mixture was allowed to stir for 5 minutes at room temperature. Next, toluene (0.2 mL) and hexylamine (30 µL, 0.24 mmol) were added and the vial was sealed under ambient atmosphere. The mixture was then heated at 50 °C for 3 h. The reaction mixture was cooled to room temperature, quenched with water and the organic layers were extracted with Et_2O (3 x 20 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* The crude mixture was then purified by flash chromatography on silica gel (petroleum ether/EtOAc; 95:5) to give the title compound **3.35** as a yellow oil (40 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.59 (1 H, d, *J* = 8.3 Hz, Ar**H**), 6.50 (1 H, s, Ar**H**), 6.44−6.39 (1 H, m, Ar**H**), 5.84 (1 H, ddt, *J* = 16.6, 10.2, 6.4 Hz, C**H**=CH_2), 5.05 (1 H, ddd, *J* = 17.1, 3.4, 1.6 Hz, CH=C**H**H), 4.95 (1 H, ddd, *J* = 10.0, 3.0, 1.1 Hz, CH=CH**H**), 3.07−3.02 (3 H, m, OCC**H**H and C**H$_2$**), 2.88 (1 H, d, *J* = 15.4 Hz, OCCH**H**), 2.21−2.13 (2

H, m, C**H**$_2$), 1.84−1.78 (2 H, m, C**H**$_2$), 1.64−1.56 (2 H, m, C**H**$_2$), 1.44−1.38 (5 H, m, C**H**$_2$ and CC**H**$_3$), 1.35−1.30 (4 H, m, 2 x C**H**$_2$), 0.91 (3 H, t, *J* = 6.9 Hz, CH_2CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 152.1 (Ar**C**), 141.5 (Ar**C**), 138.4 (**C**H=CH_2), 127.7 (Ar**C**), 114.4 (CH=**C**H_2), 113.5 (Ar**C**H), 111.3 (Ar**C**H), 109.4 (Ar**C**H), 87.8 (**C**CH_3), 46.0 (**C**H_2), 41.6 (**C**H_2), 40.3 (**C**H_2), 31.6 (**C**H_2), 29.3 (**C**H_2), 28.4 (**C**H_2), 26.8 (**C**H_2), 26.4 (**C**H_3), 22.6 (**C**H_2), 14.0 (**C**H_3); **IR** (thin film) 2928, 1641, 910, 731 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{19}H_{29}NOBrH$ $[M+H]^+$ *m/z* 288.2322, found *m/z* 288.2309.

2-(but-3'-en-1'-yl)-*N*,2-dimethyl-*N*-phenyl-2,3-dihydrobenzofuran-5-amine (3.40)

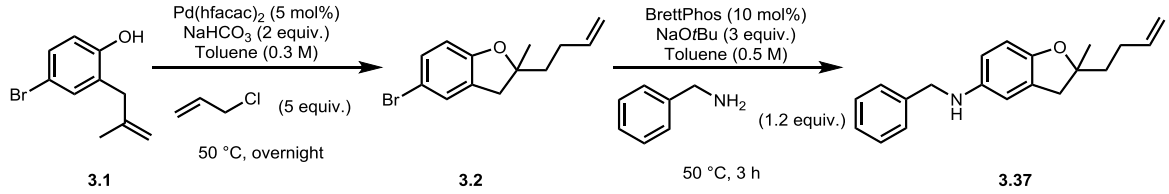


A 4 mL screw-top glass vial was charged with 4-bromo-2-(2'-methylallyl)phenol (**3.1**) (45 mg, 0.20 mmol), toluene (0.65 mL), allyl chloride (80 µL, 1.0 mmol), $NaHCO_3$ (34 mg, 0.40 mmol) and $Pd(hfacac)_2$ (5.0 mg, 0.010 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block until the substrate had been consumed, as judged by TLC analysis. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added BrettPhos (10 mg, 0.020 mmol), NaO*t*Bu (58 mg, 0.60 mmol) and toluene (0.2 mL). The mixture was allowed to stir for 5 minutes at room temperature. Next, toluene (0.2 mL) and *N*-methylaniline (25 mg, 0.24 mmol) were added and the vial was sealed under ambient atmosphere. The mixture was then heated at 50 °C for 3 h. The reaction mixture was cooled to room temperature, quenched with water and the organic layers were extracted with Et_2O (3 x 20 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* The crude mixture was then purified by flash chromatography on silica gel (petroleum ether/EtOAc; 95:5) to give the title compound **3.40** as a yellow oil (47 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.24−7.18 (2 H, m, Ar**H**), 7.00−6.97 (1 H, m, Ar**H**), 6.96−6.91 (1 H, m, Ar**H**), 6.81−6.76 (3 H, m, Ar**H**), 6.73 (1 H, d, *J* = 8.3 Hz, Ar**H**), 5.87 (1 H, ddt, *J* = 17.0, 10.3, 6.4 Hz, C**H**=CH_2), 5.06 (1 H, ddd, *J* = 17.1, 3.4, 1.7 Hz, CH=C**H**H), 4.98 (1 H, ddd, *J* = 10.2, 3.0, 1.7 Hz, CH=CH**H**), 3.26 (3 H, s, NC**H**$_3$), 3.09 (1 H, d, *J* = 15.7 Hz, OCC**H**H), 2.94 (1 H, d, *J* = 15.7 Hz, OCCH**H**), 2.24−2.16 (2 H, m, C**H**$_2$$CH_2$), 1.89−1.82 (2 H, m, CH_2C**H**$_2$), 1.48 (3 H, s, C**H**$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 156.2 (Ar**C**), 149.8 (Ar**C**), 141.6 (Ar**C**), 138.3 (**C**H=CH_2), 128.8 (2 x Ar**C**H), 128.1 (Ar**C**), 125.7 (Ar**C**H), 123.0 (Ar**C**H), 117.9 (Ar**C**H), 115.0 (2 x Ar**C**H), 114.6 (CH=**C**H_2), 109.8 (Ar**C**H), 88.8 (**C**CH_3), 41.3 (**C**H_2), 40.8 (N**C**H_3), 40.3 (**C**H_2), 28.4 (**C**H_2), 26.4 (**C**H_3); **IR** (thin

film) 3068, 914, 729 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{20}H_{23}NOH$ $[M+H]^+$ *m/z* 294.1852, found *m/z* 294.1827.

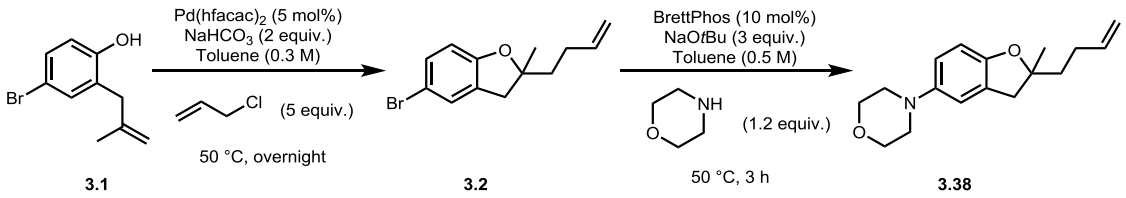
N-benzyl-2-(but-3'-en-1'-yl)-2-methyl-2,3-dihydrobenzofuran-5-amine (3.37)



A 4 mL screw-top glass vial was charged with 4-bromo-2-(2'-methylallyl)phenol (**3.1**) (45 mg, 0.20 mmol), toluene (0.65 mL), allyl chloride (80 µL, 1.0 mmol), $NaHCO_3$ (34 mg, 0.40 mmol) and $Pd(hfacac)_2$ (5.0 mg, 0.010 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block until the substrate had been consumed, as judged by TLC analysis. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added BrettPhos (10 mg, 0.020 mmol), freshly ground NaO*t*Bu (58 mg, 0.60 mmol) and toluene (0.2 mL). The mixture was allowed to stir for 5 minutes at room temperature. Next, toluene (0.2 mL) and benzylamine (26 µL, 0.24 mmol) were added and the vial was sealed under ambient atmosphere. The mixture was then heated at 50 °C for 3 h. The reaction mixture was cooled to room temperature, quenched with water and the organic layers were extracted with Et_2O (3 x 20 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (petroleum ether/EtOAc, 95:5) to give the title compound **3.37** as a yellow oil (49 mg, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.41−7.34 (4 H, m, Ar**H**), 7.31−7.28 (1 H, m, Ar**H**), 6.59 (1 H, d, *J* = 8.5 Hz, Ar**H**), 6.54−6.52 (1 H, m, Ar**H**), 6.47−6.43 (1 H, m, Ar**H**), 5.85 (1 H, ddt, *J* = 17.0, 10.3, 6.4 Hz, C**H**=CH_2), 5.03 (1 H, ddd, *J* = 17.1, 3.3, 1.6 Hz, CH=CH**H**), 4.96 (1 H, ddd, *J* = 10.2, 3.1, 1.4 Hz, CH=CH**H**), 4.27 (2 H, s, C$\mathbf{H_2}$N), 3.69 (1 H, br. s, N**H**), 3.04 (1 H, d, *J* = 15.5 Hz, OCC**H**H), 2.88 (1 H, d, *J* = 15.5 Hz, OCCH**H**), 2.21−2.14 (2 H, m, C$\mathbf{H_2}$$CH_2$), 1.83−1.78 (2 H, m, CH_2C$\mathbf{H_2}$), 1.42 (3 H, s, C$\mathbf{H_3}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 151.7 (Ar**C**), 142.3 (Ar**C**), 139.8 (**C**H=CH_2), 138.4 (Ar**C**), 128.6 (2 x Ar**C**H), 127.7 (Ar**C**), 127.6 (2 x Ar**C**H), 127.1 (Ar**C**H), 114.4 (CH=**C**H_2), 112.6 (Ar**C**H), 110.6 (Ar**C**H), 109.4 (Ar**C**H), 87.7 (**C**CH_3), 49.7 (C$\mathbf{H_2}$), 41.7 (C$\mathbf{H_2}$), 40.3 (C$\mathbf{H_2}$), 28.4 (C$\mathbf{H_2}$), 26.4 (C$\mathbf{H_3}$); **IR** (thin film) 3066, 1492, 1222, 904 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{20}H_{23}NH$ $[M+H]^+$ *m/z* 294.1852, found *m/z* 294.1838.

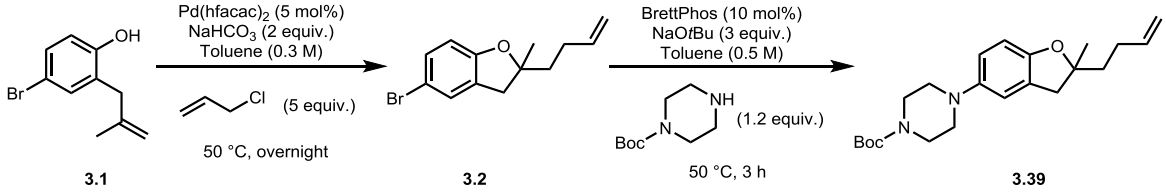
4-(2'-(but-3''-en-1''-yl)-2'-methyl-2',3'-dihydrobenzofuran-5'-yl)morpholine (3.38)



A 4 mL screw-top glass vial was charged with 4-bromo-2-(2'-methylallyl)phenol (**3.1**) (45 mg, 0.20 mmol), toluene (0.65 mL), allyl chloride (80 µL, 1.0 mmol), $NaHCO_3$ (34 mg, 0.40 mmol) and $Pd(hfacac)_2$ (5.0 mg, 0.010 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block until the substrate had been consumed, as judged by TLC analysis. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added BrettPhos (10 mg, 0.020 mmol), NaO*t*Bu (58 mg, 0.60 mmol) and toluene (0.2 mL). The mixture was allowed to stir for 5 minutes at room temperature. Next, toluene (0.2 mL) and morpholine (20 µL, 0.24 mmol) were added and the vial was sealed under ambient atmosphere. The mixture was then heated at 50 °C for 3 h. The reaction mixture was cooled to room temperature, quenched with water and the organic layers were extracted with Et_2O (3 x 20 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (petroleum ether/EtOAc, 85:15) to give the title compound **3.38** as a yellow oil (37 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.83−6.78 (1 H, m, Ar**H**), 6.74−6.69 (1 H, m, Ar**H**), 6.66 (1 H, d, *J* = 8.7 Hz, Ar**H**), 5.84 (1 H, ddt, *J* = 16.7, 10.0, 6.8 Hz, C**H**=CH_2), 5.07−4.99 (1 H, m, CH=C**H**H), 4.98−4.92 (1 H, m, CH=CH**H**), 3.89−3.82 (4 H, m, 2 x C**H$_2$**), 3.08 (1 H, d, *J* = 15.7 Hz, OCC**H**H), 3.05−3.01 (4 H, m, 2 x C**H$_2$**), 2.92 (1 H, d, *J* = 15.7 Hz, OCCH**H**), 2.21−2.12 (2 H, m, C**H$_2$**CH_2), 1.86−1.76 (2 H, m, CH_2C**H$_2$**), 1.43 (3 H, s, C**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 153.8 (Ar**C**), 145.5 (Ar**C**), 138.3 (**C**H=CH_2), 127.6 (Ar**C**), 116.9 (Ar**C**H), 114.9 (Ar**C**H), 114.5 (CH=**C**H_2), 109.3 (Ar**C**H), 88.3 (**C**CH_3), 67.0 (2 x **C**H_2), 51.7 (2 x **C**H_2), 41.6 (**C**H_2), 40.3 (**C**H_2), 28.4 (**C**H_2), 26.4 (**C**H_3); **IR** (thin film) 2962, 1492, 1120, 883 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{17}H_{23}NO_2H$ $[M+H]^+$ *m/z* 274.1802, found *m/z* 274.1792.

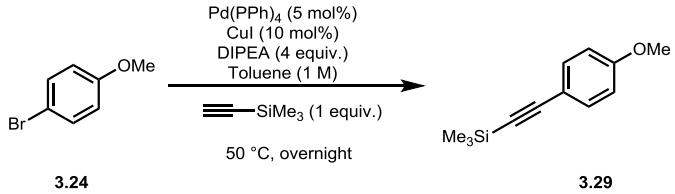
***tert*-butyl 4-(2'-(but-3''-en-1''-yl)-2'-methyl-2',3'-dihydrobenzofuran-5'-yl)piperazine-1-carboxylate (3.39)**



A 4 mL screw-top glass vial was charged with 4-bromo-2-(2'-methylallyl)phenol (**3.1**) (45 mg, 0.20 mmol), toluene (0.65 mL), allyl chloride (80 µL, 1.0 mmol), $NaHCO_3$ (34 mg, 0.40 mmol) and $Pd(hfacac)_2$ (5.0 mg, 0.010 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block until the substrate had been consumed, as judged by TLC analysis. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added BrettPhos (10 mg, 0.020 mmol), NaO*t*Bu (58 mg, 0.60 mmol) and toluene (0.2 mL). The mixture was allowed to stir for 5 minutes at room temperature. Next, toluene (0.2 mL) and *tert*-butyl piperazine-1-carboxylate (40 mg, 0.24 mmol) were added and the vial was sealed under ambient atmosphere. The mixture was then heated at 50 °C for 3 h. The reaction mixture was cooled to room temperature, quenched with water and the organic layers were extracted with Et_2O (3 x 20 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was then purified directly by flash chromatography on silica gel (petroleum ether/EtOAc, 85:15) to give the give the title compound **3.39** as a yellow oil (40 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.83−6.79 (1 H, m, Ar**H**), 6.75−6.69 (1 H, m, Ar**H**), 6.65 (1 H, d, *J* = 8.5 Hz, Ar**H**), 5.83 (1 H, ddt, *J* = 16.8, 10.2, 6.7 Hz, C**H**=CH_2), 5.02 (1 H, dd, *J* = 17.2, 1.5 Hz, CH=C**H**H), 4.95 (1 H, d, *J* = 10.2 Hz, CH=CH**H**), 3.60−3.53 (4 H, m, 2 x C**H$_2$**), 3.05 (1 H, d, *J* = 15.6 Hz, OCC**H**H), 3.00−2.94 (4 H, m, 2 x C**H$_2$**), 2.93 (1 H, d, *J* = 15.4 Hz, OCCH**H**), 2.21−2.10 (2 H, m, C**H$_2$**CH_2), 1.86−1.76 (2 H, m, CH_2C**H$_2$**), 1.49 (9 H, s, C(C**H$_3$**)$_3$), 1.42 (3 H, s, CC**H$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 154.7 (**C**=O), 154.1 (Ar**C**), 145.5 (Ar**C**), 138.3 (**C**H=CH_2), 127.6 (Ar**C**), 117.8 (Ar**C**H), 115.9 (Ar**C**H), 114.5 (CH=**C**H_2), 109.2 (Ar**C**H), 88.4 (**C**CH_3), 79.8 (**C**$(CH_3)_3$), 51.6 (2 x **C**H_2), 44.0 (2 x **C**H_2), 41.6 (**C**H_2), 40.3 (**C**H_2), 28.4 (**C**H_2 and C(**C**$H_3)_3$), 26.4 (CH_3); **IR** (thin film) 3074, 2972, 1693, 910 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{22}H_{32}N_2O_3Na$ $[M+Na]^+$ *m/z* 395.2305, found *m/z* 395.2286.

((4-methoxyphenyl)ethynyl)trimethylsilane (3.29)

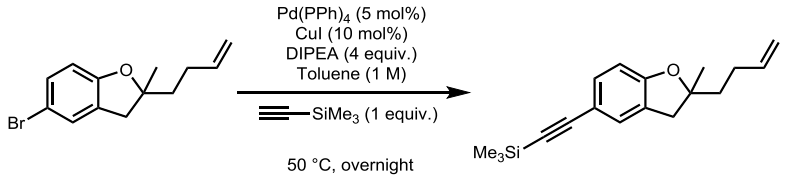


3.24 **3.29**

Following a literature procedure,[134] a solution of 1-bromo-4-methoxybenzene (74 mg, 0.40 mmol) in toluene (0.4 mL) was treated with tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.020 mmol), followed by diisopropylethylamine (0.29 mL, 1.6 mmol), trimethylsilyl acetylene (60 µL, 0.40 mmol) and copper(I) iodide (10 mg, 0.040 mmol). The reaction was heated at 50 °C in an argon atmosphere overnight, cooled to room temperature and the volatiles were removed *in vacuo*. The resultant residue was purified with flash chromatography on silica gel (petroleum ether/CH_2Cl_2; 9:1) to give the title compound (**3.29**) as a yellow oil(22 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (2 H, d, *J* = 8.8 Hz, Ar**H**), 6.83 (2 H, d, *J* = 8.8 Hz, Ar**H**), 3.81 (3 H, s, OC**H$_3$**), 0.25 (9 H, s, Si(C**H$_3$**)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 159.74 (Ar**C**), 133.46 (2 x Ar**C**H), 115.27 (Ar**C**), 113.80 (2 x Ar**C**H), 105.18 (**C**≡C), 92.41 (C≡**C**), 55.26 (OC**H$_3$**), 0.08 (Si(**C**H$_3$)$_3$); **IR** (thin film) 2958, 1458, 854 cm^{-1}; **LRMS** (EI) *m/z* 204.1.

((2-(but-3'-en-1'-yl)-2-methyl-2,3-dihydrobenzofuran-5-yl)ethynyl)trimethylsilane (3.30)



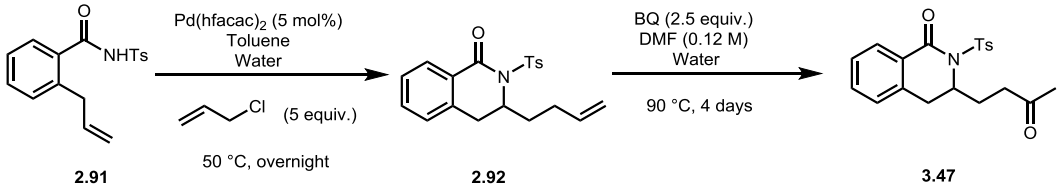
3.2 **3.30**

Following a literature procedure,[134] a solution of 5-bromo-2-(but-3'-enyl)-2-methyl-2,3-dihydrobenzofuran **3.2** (106 mg, 0.40 mmol) in toluene (0.4 mL) was treated with tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.020 mmol), followed by diisopropylethylamine (0.29 mL, 1.6 mmol), trimethylsilyl acetylene (60 µL, 0.40 mmol) and copper(I) iodide (10 mg, 0.040 mmol). The reaction was heated at 50 °C in an argon atmosphere overnight, cooled to room temperature and the volatiles were removed *in vacuo*. The resultant residue was purified with flash chromatography on silica gel (petroleum ether/CH_2Cl_2; 9:1) to give the title compound (**3.30**) as a yellow oil (31 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28−7.22 (2 H, m, Ar**H**), 6.65 (1 H, d, *J* = 8.9 Hz,

Ar**H**), 5.82 (1 H, ddt, *J* = 17.0, 10.3, 6.4 Hz, C**H**=CH_2), 5.03 (1 H, dd, *J* = 17.1, 1.4 Hz, CH=C**H**H), 4.99−4.93 (1 H, m, CH=CH**H**), 3.04 (1 H, d, *J* = 15.7 Hz, OCC**H**H), 2.92 (1 H, d, *J* = 15.7 Hz, OCCH**H**), 2.19−2.10 (2 H, m, CH_2CH_2), 1.85−1.78 (2 H, m, CH_2CH_2), 1.44 (3 H, s, CC**H**$_3$), 0.24 (9 H, s, Si(C**H**$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 159.4 (Ar**C**), 138.1 (**C**H=CH_2), 132.6 (Ar**C**H), 128.8 (Ar**C**H), 127.1 (Ar**C**), 114.7 (CH=**C**H_2), 114.4 (Ar**C**), 109.3 (Ar**C**H), 105.8 (**C**≡C), 91.5 (C≡**C**), 89.3 (**C**CH_3), 40.7 (**C**H_2), 40.3 (**C**H_2), 28.3 (**C**H_2), 26.4 (**C**H_3), 0.1 (Si(**C**H_3)$_3$); **IR** (thin film) 2958, 1247, 1508, 864 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{18}H_{24}OSiNa$ $[M+Na]^+$ *m/z* 307.1489, found *m/z* 307.1453.

3-(3'-oxobutyl)-2-tosyl-3,4-dihydroisoquinolinone (3.47)

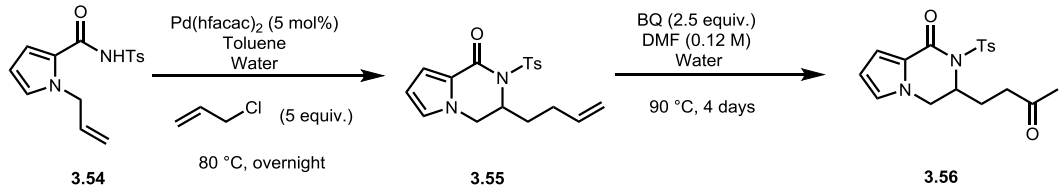


2.91 **2.92** **3.47**

A 4 mL screw-top glass vial was charged with 2-allyl-*N*-tosyl-benzamide (**2.91**) (50 mg, 0.16 mmol), toluene (0.64 mL), H_2O (0.64 mL), allyl chloride (0.070 mL, 0.79 mmol) and Pd(hfacac)$_2$ (4.0 mg, 0.01 mmol). The mixture was heated at 50 °C overnight. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. Following a modification of a literature procedure,[141] to the mixture was added *p*-benzoquinone (43 mg, 0.4 mmol), DMF (0.53 mL) and water (50 µL). The vial was then sealed and heated at 90 °C for four days. The mixture was allowed to cool to room temperature before being poured into water and the organic layers were extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (toluene/Et_2O; 9:1) to give the title compound (**3.47**) as a yellow oil (32 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.99−7.92 (3 H, m, Ar**H**), 7.48 (1 H, td, *J* = 7.4, 1.3 Hz, Ar**H**), 7.34−7.28 (3 H, m, Ar**H**), 7.20 (1 H, d, *J* = 7.5 Hz, Ar**H**), 5.00−4.93 (1 H, m, CH_2C**H**), 3.38 (1 H, dd, *J* = 16.2, 5.5 Hz, C**H**HCH), 2.94 (1 H, dd, *J* = 16.2, 1.9 Hz, CH**H**CH), 2.81 (1 H, dt, *J* = 18.3, 7.7 Hz, C**H**HCH_2), 2.60 (1 H, dt, *J* = 18.3, 6.5 Hz, CH**H**CH_2), 2.41 (3 H, s, C**H**$_3$), 2.18 (3 H, s, C**H**$_3$), 1.89−1.82 (2 H, m, C**H**$_2$$CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 207.6 (**C**=O), 162.6 (**C**=O), 144.8 (Ar**C**), 136.9 (Ar**C**), 136.3 (Ar**C**), 133.7 (Ar**C**H), 129.4 (2 x Ar**C**H), 128.9 (Ar**C**H), 128.8 (2 x Ar**C**H), 128.2 (Ar**C**H), 127.9 (Ar**C**), 127.5 (Ar**C**H), 55.0 (**C**H), 39.8 (**C**H_2), 34.1 (**C**H_2), 30.0 (**C**H_2), 27.7 (**C**H_2), 21.6 (**C**H_3); **IR** (thin film) 2958, 1710, 1685, 736 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{20}H_{21}NO_4SNa$ $[M+Na]^+$ *m/z* 394.1083, found *m/z* 394.1072.

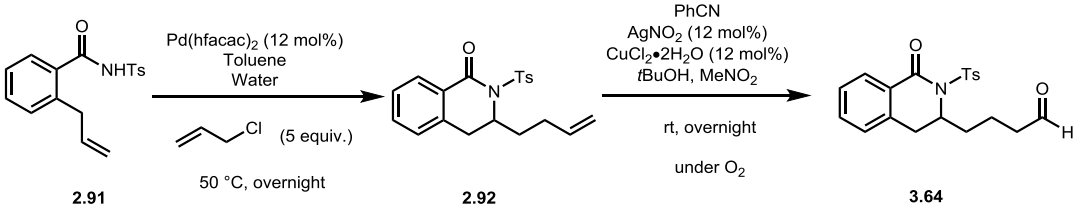
Oxidised pyrrole tosylamide (3.56)



A 4 mL glass screw-top vial was charged with 1-allyl-*N*-tosyl-pyrrole-2-carboxamide (**3.54**) (48 mg, 0.16 mmol), toluene (0.64 mL), H_2O (0.64 mL), allyl chloride (0.07 mL, 0.79 mmol) and $Pd(hfacac)_2$ (4.0 mg, 0.01 mmol). The mixture was heated at 80 °C for 19 h. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. Following a modification of a literature procedure,[141] to the mixture was added *p*-benzoquinone (43 mg, 0.40 mmol), DMF (0.53 mL) and water (50 µL). The vial was then sealed and heated at 90 °C for four days. The mixture was allowed to cool to room temperature before being poured into water and the organic layers were extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (toluene/EtOAc; 8:2) to give the title compound (**3.56**) as a yellow oil (28 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.95 (2 H, d, *J* = 8.4 Hz, Ar**H**), 7.31 (2 H, d, *J* = 8.4 Hz, Ar**H**), 6.97 (1 H, dd, *J* = 4.0, 1.5 Hz, Ar**H**), 6.78−6.75 (1 H, m, Ar**H**), 6.23 (1 H, dd, *J* = 3.9, 2.4 Hz, Ar**H**), 5.01−4.93 (1 H, m, CH_2C**H**), 4.29 (1 H, dd, *J* = 13.2, 4.1 Hz, C**H**HCH), 4.13 (1 H, dd, *J* = 13.2, 1.5 Hz, CH**H**CH), 2.86 (1 H, ddd, *J* = 18.7, 8.3, 6.5 Hz, C**H**HCH_2), 2.59 (1 H, dt, *J* = 18.7, 6.5 Hz, CH**H**CH_2), 2.42 (3 H, s, C**H**$_3$), 2.19 (3 H, s, C**H**$_3$), 2.05−1.93 (1 H, m, C**H**HCH_2), 1.91−1.73 (1 H, m, CH**H**CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 207.5 (**C**=O), 155.8 (**C**=O), 144.9 (Ar**C**), 136.1 (Ar**C**), 129.4 (2 x Ar**C**H), 128.9 (2 x Ar**C**H), 125.3 (Ar**C**H), 122.3 (Ar**C**), 116.9 (Ar**C**H), 111.1 (Ar**C**H), 55.1 (**C**H), 49.0 (**C**H_2), 39.2 (**C**H_2), 30.0 (**C**H_3), 26.9 (**C**H_2), 21.6 (**C**H_3); **IR** (thin film) 3250, 1723, 1674, 731 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{18}H_{20}N_2O_4SNa$ $[M+Na]^+$ *m/z* 383.1036, found *m/z* 383.1032.

4-(1'-oxo-2'-tosyl-1',2',3',4'-tetrahydroisoquinolin-3'-yl)butanal (3.64)

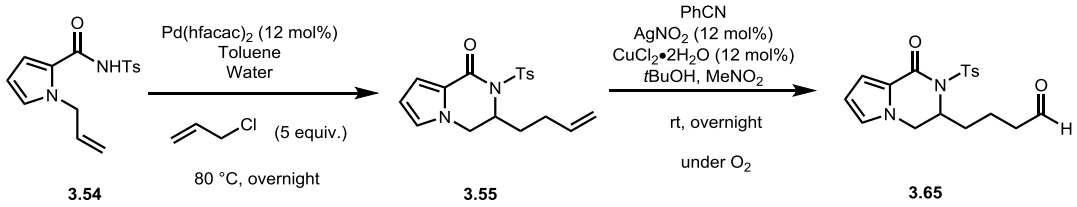


A 4 mL screw-top glass vial was charged with 2-allyl-*N*-tosyl-benzamide (**2.91**) (63 mg, 0.20 mmol), toluene (0.65 mL), H_2O (0.65 mL), allyl chloride (0.080 mL, 1.0 mmol) and

$Pd(hfacac)_2$ (13 mg, 0.024 mmol). The mixture was heated at 50 °C for 16 h. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. Following a modification of a literature procedure,[143] to the vial was added benzonitrile (50 µL, 0.48 mmol), $CuCl_2•2H_2O$ (4.0 mg, 0.024 mmol) and $AgNO_2$ (4.0 mg, 0.024 mmol). The vial was sparged for 45 seconds with oxygen (1 atm balloon) then subsequently *t*BuOH (3 mL), $MeNO_2$ (0.2 mL) were added *via* syringe. The solution was saturated with oxygen by an additional 45 seconds of sparging. The reaction was then allowed to stir at room temperature overnight. Next, the reaction was quenched by addition to water and extracted three times with Et_2O (3 x 20 mL). The combined organic layers were subsequently dried over $MgSO_4$. Immediately prior to NMR analysis trimethoxybenzene (34 mg, 0.2 mmol) was added as an internal standard. The resulting solution was subsequently subjected to ^{1}H NMR analysis to determine yield (33%) of aldehyde (**3.64**) and (19%) ketone (**3.47**). The title compound (**3.64**) was obtained using flash chromatography on silica gel (toluene/EtOAc; 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.74 (1 H, t, *J* = 1.3 Hz, C**H**O), 8.02−7.94 (3 H, m, Ar**H**), 7.49 (1 H, td, *J* = 7.5, 1.3 Hz, Ar**H**), 7.35−7.30 (3 H, m, Ar**H**), 7.21 (1 H, d, *J* = 7.5 Hz, Ar**H**), 5.00−4.89 (1 H, m, CH_2C**H**), 3.37 (1 H, dd, *J* = 16.2, 5.4 Hz, C**H**HCH), 2.98 (1 H, dd, *J* = 16.2, 1.8 Hz, CH**H**CH), 2.50−2.39 (5 H, m, C**H$_2$** and C**H$_3$**),1.81−1.68 (3 H, m C**H**H and C**H$_2$**), 1.64−1.54 (1 H, m, CH**H**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 201.5 (**C**=O), 162.6 (**C**=O), 144.8 (Ar**C**), 136.6 (Ar**C**), 136.5 (Ar**C**), 133.7 (Ar**C**H), 129.3 (2 x Ar**C**H), 128.9 (3 x Ar**C**H), 128.2 (Ar**C**H), 128.0 (Ar**C**), 127.5 (Ar**C**H), 55.3 (**C**H), 43.2 (**C**H_2), 33.1 (**C**H_2), 32.5 (**C**H_2), 21.6 (**C**H_2), 18.8 (**C**H_3); **IR** (thin film) 1722, 1683, 906, 725 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{20}H_{21}NO_4SNa$ $[M+Na]^+$ *m/z* 394.1083, found *m/z* 394.1087.

Oxidised pyrrole tosylamide(3.65)



3.54 **3.55** **3.65**

A 4 mL screw-top glass vial was charged with 1-allyl-*N*-tosyl-pyrrole-2-carboxamide (**3.54**) (61 mg, 0.20 mmol), toluene (0.65 mL), H_2O (0.65 mL), allyl chloride (0.080 mL, 1.0 mmol) and $Pd(hfacac)_2$ (13 mg, 0.024 mmol). The mixture was heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. Following a modification of a literature procedure,[143] to the vial was added benzonitrile (50 µL, 0.48 mmol), $CuCl_2•2H_2O$ (4.0 mg, 0.024 mmol) and $AgNO_2$ (4.0 mg, 0.024 mmol). The vial was sparged for 45 seconds with oxygen (1 atm balloon) then

subsequently *t*BuOH (3 mL), $MeNO_2$ (0.2 mL) were added *via* syringe. The solution was saturated with oxygen by an additional 45 seconds of sparging. The reaction was then allowed to stir at room temperature overnight. Next, the reaction was quenched by addition to water and extracted three times with Et_2O (3 x 20 mL). The combined organic layers were subsequently dried over $MgSO_4$. Immediately prior to NMR analysis trimethoxybenzene (34 mg, 0.2 mmol) was added as an internal standard. The resulting solution was subsequently subjected to ^{1}H NMR analysis to determine yield (24%) of aldehyde (**3.65**). The title compound (**3.65**) was obtained using flash chromatography on silica gel (toluene / EtOAc; 8:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.75 (1 H, t, *J* = 1.1 Hz, C**H**O), 7.99 (2 H, d, *J* = 8.4 Hz, Ar**H**), 7.32 (2 H, d, *J* = 8.4 Hz, Ar**H**), 6.97 (1 H, dd, *J* = 4.0, 1.5 Hz, Ar**H**), 6.79−6.77 (1 H, m, Ar**H**), 6.24 (1 H, dd, *J* = 4.0, 2.4 Hz, Ar**H**), 4.98−4.89 (1 H, m, CH_2C**H**), 4.32 (1 H, dd, *J* = 13.1, 3.8 Hz, C**H**HCH), 4.17 (1 H, dd, *J* = 13.1, 1.4 Hz, CH**H**CH), 2.56−2.47 (2 H, m, C**H$_2$**CH_2), 2.43 (3 H, s, C**H$_3$**), 1.80−1.60 (4 H, m, C**H$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 201.3 (**C**=O), 155.8 (**C**=O), 144.9 (Ar**C**), 136.4 (Ar**C**), 129.4 (2 x Ar**C**H), 129.0 (2 x Ar**C**H), 125.2 (Ar**C**H), 122.4 (Ar**C**), 116.9 (Ar**C**H), 111.1 (Ar**C**H), 55.6 (**C**H), 47.2 (**C**H_2), 43.1 (**C**H_3), 32.1 (**C**H_2), 21.7 (**C**H_3), 18.4 (**C**H_2); **IR** (thin film) 1673, 910, 731 cm^{-1}; **HRMS** (ESI) exact mass calculated for $C_{18}H_{20}N_2O_4SNa$ $[M+Na]^+$ *m/z* 383.1036, found *m/z* 383.1028.

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