Development of Methodology for the Palladium-Catalysed Synthesis of Oxygen-Containing Heterocycles

Joanne F. M. Hewitt (M. Sci)

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

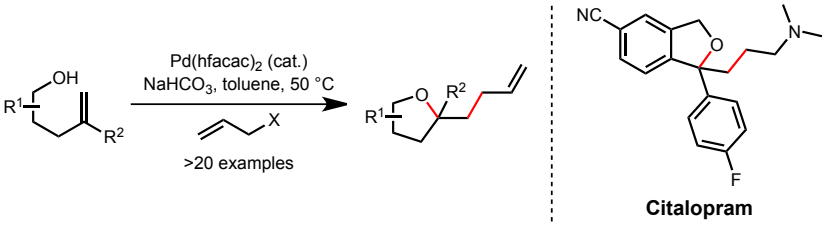
School of Chemistry
College of Science and Engineering
University of Glasgow

April 2014

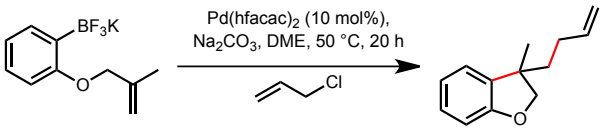
Abstract

The opening chapter of this thesis gives an overview of the existing methods to functionalise palladium(II)-alkyl intermediates resulting from oxy- or carbopalladation of unactivated alkenes, outlining the range of heterocycles which can be formed using this type of methodology. A summary of Pd(IV) species in synthesis and catalysis follows, with a focus on Pd(IV) intermediates arising from oxidative addition of alkyl halides to Pd(II) and those suggested in alkene difunctionalisation reactions.

As the subsequent formation of sp^3–sp^3 C–C bonds from Pd(II)-alkyl intermediates was noted as a limitation of prevailing nucleopalladation methods, the second chapter of this thesis outlines the work towards development of an oxypalladation reaction of hydroxyalkenes, with concomitant formation of an sp^3–sp^3 C–C bond. Allyl halides proved to be competent electrophiles for this transformation. The oxyallylation reaction was successfully applied to a range of hydroxyalkene substrates, with the methodology developed also applied to a 5-step synthesis of anti-depressant citalopram. The oxyallylation reaction constructs heterocycles substituted in the 2-position, forming two new bonds in a single step.



Ensuing work, detailed in Chapter 3, focused on the development of an analogous carboallylation reaction, using aryl boronic acid derivatives. This transformation gives rise to the formation of two new C–C bonds in a single step, including the construction of a fully substituted carbon centre.



Experimental procedures and data are summarised in Chapter 4.

Acknowledgements

I would like to extend my thanks to Dr. David France for giving me the opportunity to work in (and launch!) his research group and for all his advice and support over the course of my PhD.

I am also grateful to my second supervisor, Dr. Andrew Sutherland, and Dr. Joëlle Prunet for their helpful thoughts and discussions on my research. I would like to express my gratitude to the department staff, academic, technical and administrative, for their support.

Many thanks to the France boyz Lewis, Craig and David for their diligent thesis proof reading efforts. I'd also like to thank all the France, Prunet and Marquez group members, past and present, for some truly hilarious moments in the Raphael lab. Particular thanks to Helen, Toni, Pooja, Mhairi and Anna for great chat and keeping the testosterone levels in the lab slightly lower!

Outwith the department: for cocktails, mocktails, Sunday runs and endless cups of tea, the experience wouldn't have been quite the same without the witches Victoria, Leigh and Laura and running buddy Michael. Writing up wouldn't have been half as entertaining without random chat, thesis avoidance and procrastination with Jonathan. For keeping me sane by getting me away from chemistry to explore Scotland and beyond through running, cycling and swimming (and eating good food and cake!), many thanks to Glasgow Triathlon Club, especially the tri girls Hannah, Lexy, Christine, Elizabeth, Caroline and Fiona.

I am appreciative of the endless support and encouragement from my family: my Mum, sister Jennie, brother Iain and all the other Allan nutters.

Financial support from the University of Glasgow, WestCHEM and EPSRC is gratefully acknowledged.

Finally, I'd like to thank Douglas Adams for giving me the answer to the great question of life, the universe and everything.

Author's Declaration

This thesis represents the original work of Joanne Frances Mary Hewitt unless otherwise explicitly stated in the text. The research was carried out at the University of Glasgow in the Raphael Laboratory under the supervision of Dr. David France during the period of October 2010 to September 2013. 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.

Abbreviations

Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
BBN	borabicyclo[3.3.1]nonane
bipy	bipyridine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOXAX	bis(oxazolyl)-binaphthyl
br	broad
BRSM	based on recovered starting material
BSA	bis(trimethylsilyl)acetamide
Bu	butyl
Bz	benzoyl
°C	degrees centigrade
cat.	catalytic
CI	chemical ionisation
conc.	concentration/concentrated
COP	cobaltocenyloxazoline palladacycle
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DCE	dichloroethane
DIBAL-H	di*iso*butylaluminium hydride
DIPEA	di*iso*propyl ethyl amine
dppf	diphenylphosphorylferrocene
dppp	diphenylphosphorylpropane
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dtbpy	di-*tert*-butylpyridine
er	enantiomeric ratio
EI	electron impact
equiv	equivalents

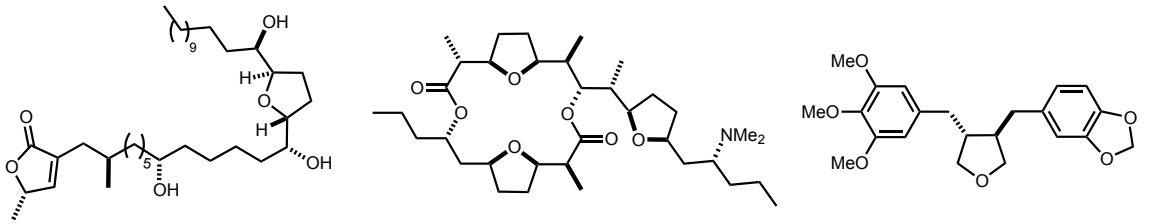
ESI	electrospray ionisation
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
FAB	fast atom bombardment
FTIR	Fourier transform infrared spectroscopy
g	gram(s)
h	hour(s)
hfacac	hexafluoroacetylacetonate
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation
Hz	hertz
IPA	2-propanol
IR	infrared
J	NMR spectra coupling constant
L	ligand
LDA	lithium di*iso*propylamide
M	molar
m	multiplet
mdtbpy	4-methyl-2,6-di-*tert*-butylpyridine
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram(s)
MHz	megahertz
MIDA	methyliminodiacetic acid
min	minute(s)
mL	millilitre(s)
mmHg	millimetres mercury
mmol	millimole(s)
mol	mol(es)
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieves
m/z	mass to charge ratio
NMR	nuclear magnetic resonance

NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methylpyrrolidinone
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
PBQ	*p*-benzoquinone
PG	protecting group
Ph	phenyl
phen	phenanthroline
ppm	parts per million
*i*Pr	*iso*propyl
py	pyridine
q	quartet
quant.	quantitative
s	singlet
sat.	saturated
SERT	serotonin transporter
SET	single electron transfer
sp	sparteine
SPRIX	spiro bis(isoxazoline)
SSRI	selective serotonin reuptake inhibitor
R_f	retention factor
RT	room temperature
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butyl methyl ether
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
Temp	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS-EBX	tri*iso*propylsilyl ethynylbenziodoxolone
TLC	thin layer chromatography
Tf	trifluoromethanesulfonyl
Ts	4-toluenesulfonyl
µL	microlitre(s)
µw	microwave
% wt.	percentage by weight

1. Functionalisation of Alkenes: Synthesis of Oxygen Containing Heterocycles

1.1 Introduction

Heterocyclic architectures are prevalent in natural products and are of particular interest to synthetic and medicinal chemists due to their pharmacological and biological activities.[1] Five- and six-membered oxygen-containing heterocycles are amongst the most commonly found moieties, with the tetrahydrofuran core found in natural product classes including annonaceous acetogenins **1.1**,[2] macrodiolides **1.2**[3] and lignans **1.3**[4] (Figure 1.1). To synthesise heterocycles such as those shown in Figure 1.1, in addition to acid catalysed cyclisations and ring closing metathesis,[5] many of these ring systems are constructed *via* haloetherification of hydroxyalkenes of an appropriate chain length.[6] Although haloetherifications result in the formation of a new C–X bond, which can be elaborated through standard C–C bond formation techniques, methods that allow for ring closure with concomitant formation of a new C–C bond are of great interest.



1.1 acetogenin - annonacin

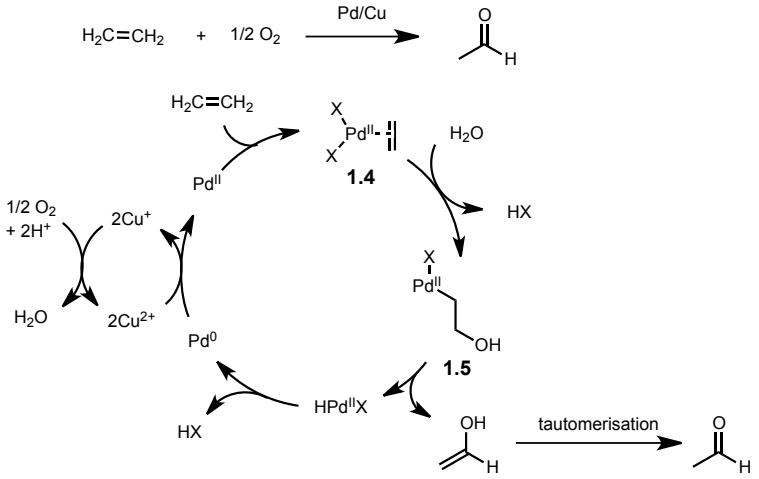
1.2 macrodiolide - pamamycin 607

1.3 lignan - burseran

Figure 1.1: Natural products containing tetrahydrofuran architectures

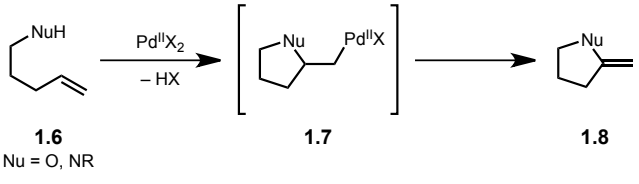
Functionalisation of alkenes by transition metal catalysis is another method that has been used to construct oxygen-containing heterocycles and, although there are examples making use of Cu,[7] Ag,[8] Pt[9] and Au[10] catalysts, the majority of examples reported are catalysed by palladium complexes.[11] Highlighting the significant impact that palladium chemistry has made to the evolution of the chemists' synthetic toolbox, the 2010 Nobel Prize in chemistry was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki in recognition of their contribution. However, whilst the Heck, Negishi and Suzuki reactions result in the construction of only one new C–C bond, many palladium-catalysed reactions are cascade reactions,[12] giving rise to multiple new bonds in a single step. These reactions allow rapid assembly of molecular complexity from comparatively simple starting materials.

In 1959, Wacker Chemie reported the development of an industrial scale palladium-catalysed method for the aerobic oxidation of ethylene to acetaldehyde, where Pd(II) could be regenerated by molecular oxygen in the presence of a copper co-catalyst (Scheme 1.1).[13] Upon coordination of an alkene by Lewis acidic Pd(II), affording a palladium complex such as **1.4** (Scheme 1.1), the traditional nucleophilicity of the alkene is reversed, activating the alkene towards nucleophilic attack. This can proceed *via* attack from an inner sphere coordinated water or hydroxide (*cis*-oxypalladation) or outer sphere water or hydroxide (*trans*-oxypalladation) to form a Pd(II)-alkyl intermediate with a β-hydroxyl group **1.5**. β-hydride elimination affords vinyl alcohol, which tautomerises to give acetaldehyde and Pd(0). The catalytic cycle is completed by Cu/O_2 re-oxidation of Pd(0), produced by reductive elimination of HX from Pd(II). The Wacker reaction has been the subject of considerable study and mechanistic debate since the original report, primarily over whether the reaction proceeds *via cis*- or *trans*-oxypalladation.[14]



Scheme 1.1: Catalytic cycle of Wacker process

Subsequent to the development of the Wacker process, it was reported that Pd(II) could facilitate the addition of a number of different types of nucleophiles to alkenes, giving rise to C–O, C–N and C–C bond formation under oxidative and non-oxidative conditions.[15] In addition to intermolecular procedures, Wacker-type cyclisations have also been developed, in which a palladium(II) complex activates an alkene with a tethered nucleophile, such as **1.6** (Scheme 1.2) towards *intra*molecular nucleophilic attack. The Pd(II)-alkyl intermediate **1.7** produced in these reactions readily undergoes β-hydride elimination to afford heterocycles such as **1.8**.

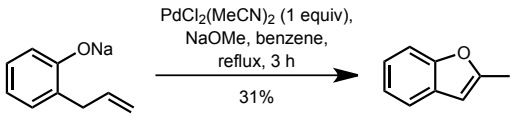


Scheme 1.2: Nucleopalladation–β-hydride elimination of 1.6

1.2 Oxypalladation of Alkenes

1.2.1 Wacker-Type Cyclisations

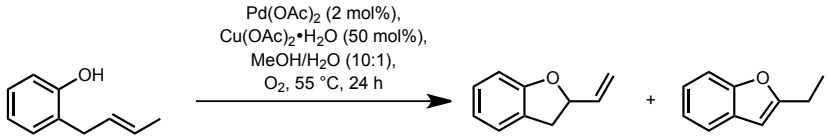
Although a number of different nucleophiles can attack a Pd(II) coordinated alkene, the first part of this review will focus on those forming C–O bonds. In 1973, Hosokawa and co-workers reported the first intramolecular cyclisation of alcohol nucleophiles onto unactivated alkenes (Scheme 1.3).[16] Oxypalladation of the sodium salt of *o*-allylphenol **1.9** with stoichiometric $PdCl_2(MeCN)_2$ followed by β-hydride elimination and isomerisation to the more thermodynamically stable alkene afforded 2-methylbenzofuran **1.10**. Despite the low yield, no starting material was recovered from this cyclisation, only polymeric residue.



1.9 **1.10**

Scheme 1.3: Wacker-type cyclisation of *o*-allyl phenol sodium salt 1.9

Hosokawa and co-workers subsequently reported that use of $Pd(OAc)_2$ as the Pd(II) source allowed the phenols to be used directly (Scheme 1.4).[17] In the cyclisation of disubstituted alkene **1.11**, the authors observed that use of the acetate salt of palladium in place of the chloride salt resulted in the formation of a 1:1 mixture of the direct β-hydride elimination product **1.12** and the isomerised product **1.13**. Resubjecting **1.12** to the reaction conditions did not induce isomerisation to **1.13** so the difference in product composition was concluded to be due to the alteration of Pd salt used. Furthermore, carrying out the reaction under catalytic conditions using $Cu(OAc)_2$–O_2 as the re-oxidant afforded almost complete conversion of **1.11** to **1.12**. These conditions could be applied to the synthesis of a range of substituted benzofurans and dihydrobenzofurans.

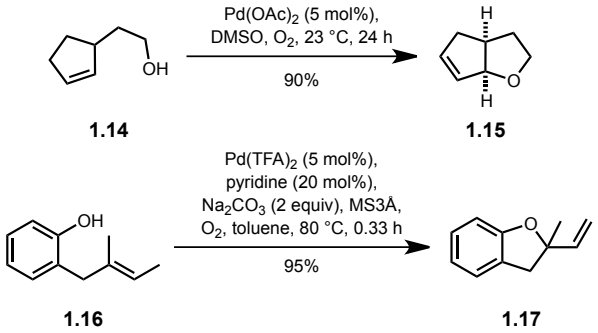


1.11 **1.12** 54% **1.13** trace

Scheme 1.4: Wacker cyclisation of *o*-allyl phenol 1.11

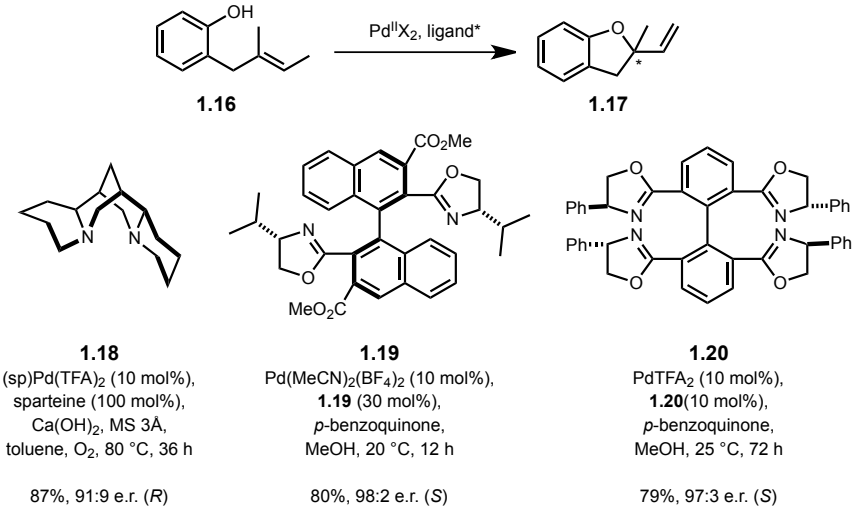
In addition to the cyclisation of phenols, Wacker-type cyclisations have also been used in the reactions of alcohols[18] and carboxylic acids.[19,20] As the terminating step of these processes produces Pd(0), catalyst re-oxidation is an essential feature. Use of copper/oxygen couples introduces a secondary catalytic cycle and use of oxidants such

as *p*-benzoquinone requires the removal of stoichiometric quantities of organic compounds. Bäckvall *et al*.[21] and subsequently Stoltz and co-workers[22] developed procedures utilising O_2–coupled catalysis, which produce water or hydrogen peroxide as the only re-oxidation by-product (Scheme 1.5). These procedures could be successfully applied to both aliphatic alcohols and *o*-allylphenols.



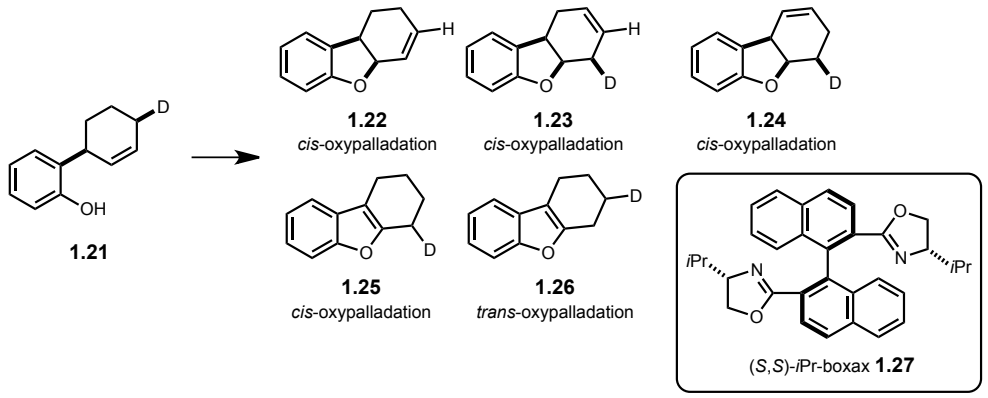
Scheme 1.5: Aerobic Wacker-type cyclisations of alcohols 1.14 and 1.16

Although Hosokawa and co-workers were able to demonstrate low levels of enantioselectivity in Wacker cyclisations using an $[(\eta^3\text{-pinene})PdOAc]_2$ catalyst system (up to 63:37 e.r.),[23] the most effective catalyst systems have employed ligands based on chelating nitrogen ligands (Scheme 1.6). Stoltz and co-workers found the natural product (−)-sparteine **1.18** was the most effective at inducing asymmetry in the heterocyclisation of **1.16**, with benzofuran **1.17** afforded in 87% yield and 91:9 e.r.. Hayashi *et al*. achieved enantioselectivity of 98:2 e.r. in the cyclisation of **1.16** to afford **1.17** in 80% yield using BOXAX ligand **1.19**.[24] However, Zhang and co-workers developed a chelation-induced, axially chiral tetraoxazoline ligand **1.20**, which showed greater generality in the asymmetric heterocyclisation of phenols onto tri-[25] or tetra[26]-substituted alkenes, affording consistently high enantiomeric ratios.



Scheme 1.6: Enantioselective Wacker-type cyclisation of phenol 1.16

Many mechanistic studies have been carried out to investigate the stereochemistry of oxypalladation; however, Hayashi and co-workers elegantly demonstrated that the cyclisation of a single substrate could afford *cis*- or *trans*-oxypalladation, dependent on the reaction conditions (Scheme 1.7).[27] Thus, using catalytic $Pd(MeCN)_4(BF_4)_2$ and (*S*,*S*)-*i*Pr-boxax ligand **1.27**, cyclisation of **1.21** provided only products **1.22**, **1.23**, **1.24** and **1.25**, consistent with *cis*-oxypalladation, as did cyclisation using Hosokawa's $[(\eta^3\text{-pinene})PdOAc]_2$ catalyst system. However, use of a $PdCl_2(MeCN)_2$ catalyst with added LiCl afforded predominantly **1.26**, a product consistent with *trans*-oxypalladation. Although it appears tempting to conclude that higher concentrations of chloride ions leads to *trans*-nucleopalladation, other examples where *cis*-nucleopalladation occurs in the presence of high chloride concentrations exist,[28] indicating that the identity of the substrate can also directly affect the products afforded.



	1.22	1.23	1.24	1.25	1.26
$Pd(MeCN)_4(BF_4)_2$ (5 mol%), (*S*,*S*)-*i*Pr-boxax **1.27** (10 mol%), *p*-benzoquinone, MeOH, 40 °C, 4 h, 78%	16	46	29	9	0
Bis[acetoxy(3,2,10-η^3-pinene)palladium(II) (10 mol%), $Cu(OAc)_2$ (10 mol%), O_2, MeOH, 65 °C, 82%	83	14	3	0	0
$PdCl_2MeCN_2$ (10 mol%), *p*-benzoquinone, Na_2CO_3, **LiCl**, THF, 65 °C, 24 h, 59%	6	5	7	0	82

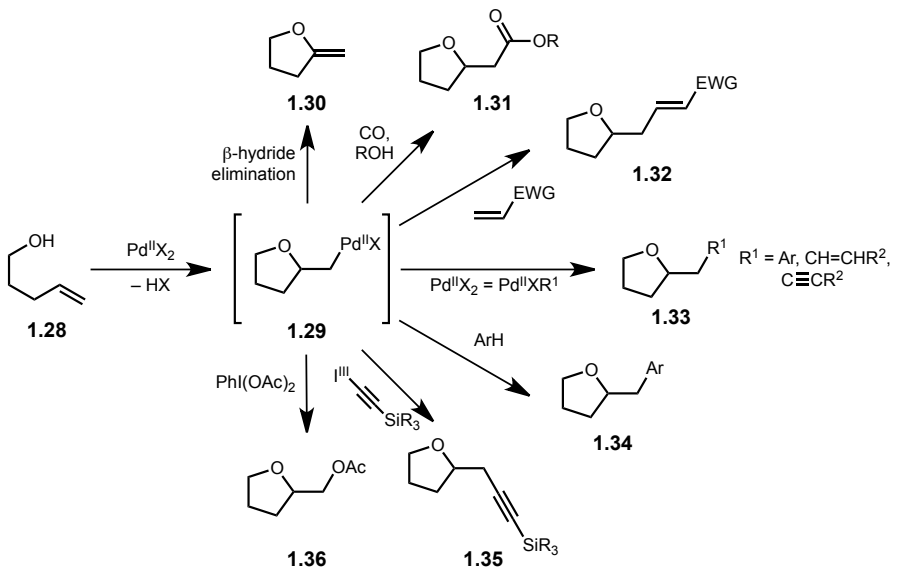
Scheme 1.7: Product distribution of Wacker-type cyclisations of alcohol 1.21

1.2.2 Difunctionalisation *via* Wacker-Type Cyclisations

C–O and sp^3–sp^2 C–C Difunctionalisation

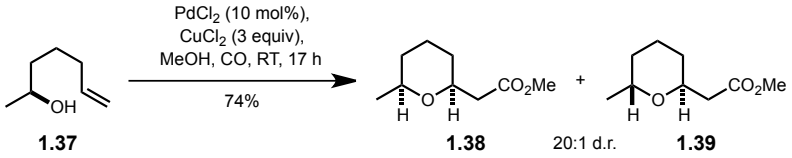
Oxypalladation–β-hydride elimination processes afford heterocycles that have undergone functionalisation at one carbon of the alkene. In order to achieve difunctionalisation, β-hydride elimination must be prevented. This can be achieved either by stabilisation of the Pd(II)-alkyl intermediate, or by interception of the intermediate by a functionalisation step that occurs at an increased rate with respect to β-hydride elimination. These subsequent functionalisation steps can furnish a wide range of heterocyclic products (Scheme 1.8) and will be discussed forthwith. Although the methods detailed herein focus predominantly on those forming new C–C bonds, a variety of methods have been recently

reported in which the Pd(II)-alkyl intermediate is intercepted oxidatively to subsequently form new C–halogen,[29] C–O[30] and C–N bonds.[31]



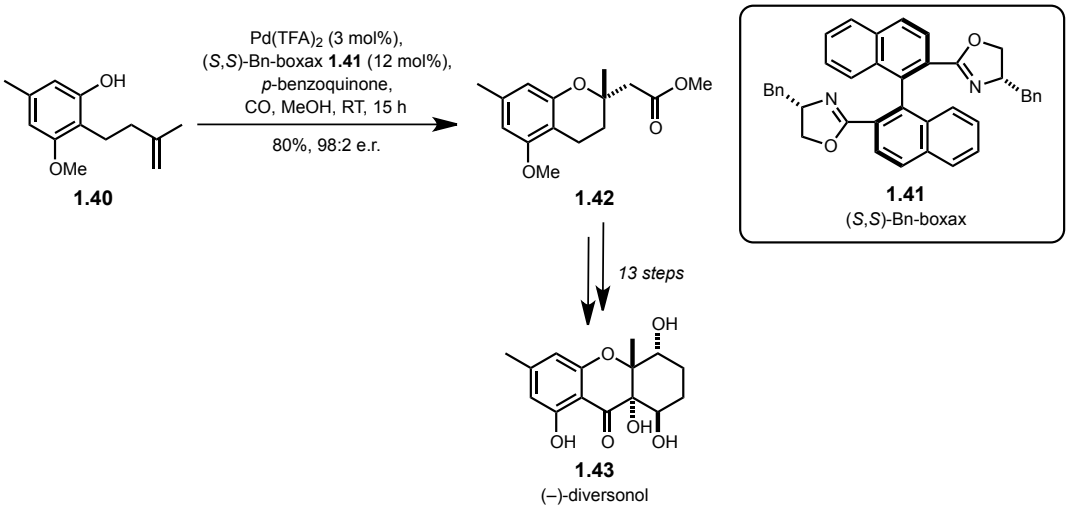
Scheme 1.8: Transformations of the Pd(II)-alkyl intermediate 1.29 produced by oxypalladation of 1.28

Under an atmosphere of carbon monoxide, the Pd(II)-alkyl intermediate formed from a heterocyclisation step can undergo migratory insertion and subsequently be trapped using alcohols to afford esters. This methodology was originally reported by Semmelhack and co-workers in 1984 and was used in a stereoselective synthesis of the methyl ester of a glandular secretion from the civet cat **1.38** (Scheme 1.9).[32] In addition to the synthesis of **1.38**, the authors demonstrated that a range of substitution patterns could be tolerated in the substrate. The formation of 6-membered rings was found to proceed in a highly stereoselective fashion, affording the products as a single diastereomer.



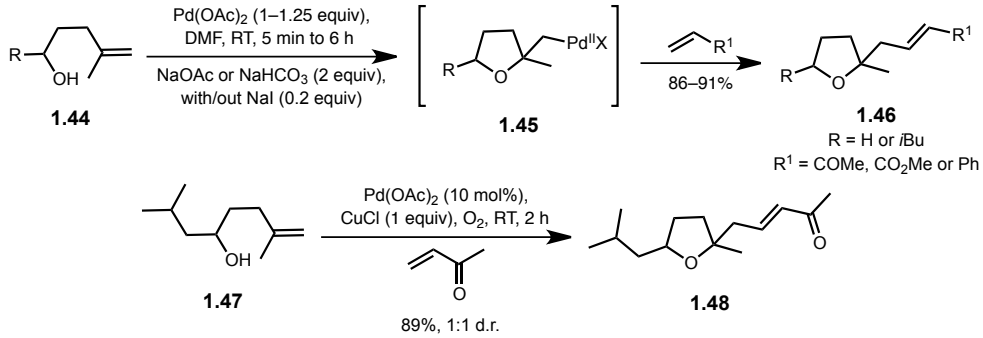
Scheme 1.9: Synthesis of the methyl ester of civet cat secretion 1.38

This oxycarbonylation methodology was employed by the Tietze group as a key step in the enantioselective total synthesis of (–)-diversonol **1.43** (Scheme 1.10).[33] Thus, treatment of phenol **1.40** with catalytic $Pd(TFA)_2$ and (*S*,*S*)-Bn-boxax **1.41** under an atmosphere of CO in methanol afforded chroman product **1.42** in 80% yield and 98:2 e.r.. Here, *p*-benzoquinone was used re-oxidise Pd(0) back to Pd(II). A further 13 steps facilitated the transformation of chroman **1.42** into (–)-diversonol **1.43**.



Scheme 1.10: Enantioselective oxycarbonylation of 1.40 in total synthesis of (–)-diversonol 1.43

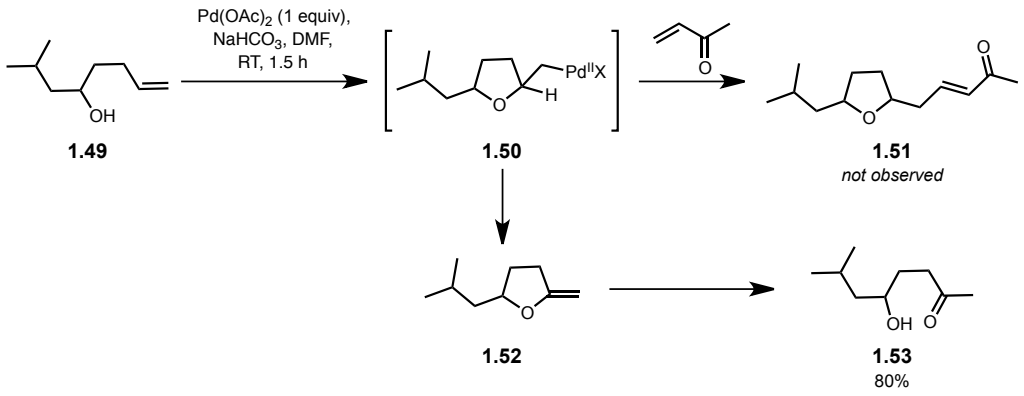
In addition to carbonylation, the Pd(II)-alkyl intermediate can also undergo carbopalladation onto an exogeneous alkene. By employing substrates which were geminally disubstituted on the alkene, Semmelhack and co-workers reported that Pd(II) intermediate **1.45**, formed from heterocyclisation of hydroxyalkene **1.44**, could be intercepted by Heck acceptors such as methyl acrylate, methyl vinyl ketone and styrene to afford heterocycles **1.46** (Scheme 1.11).[34] The reaction was only successful for electronically biased olefins – no detectable oxyvinylation products were obtained where hexene or cyclohexene were employed, with the alcohols recovered in good yield. Importantly, this observation suggests that the formation of palladium intermediate **1.45** is reversible under the reaction conditions. Although these reactions were stoichiometric in palladium, catalysis of the heterocyclisation of alcohol **1.47** was successful when a $CuCl–O_2$ re-oxidation system was employed to afford product **1.48** in 89% yield (Scheme 1.11).



Scheme 1.11: Oxyvinylation of disubstituted alkenes 1.44 and 1.47

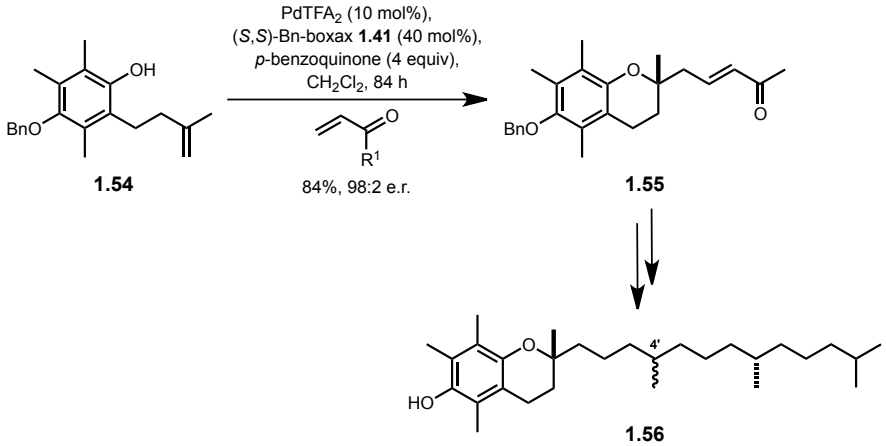
In order to probe whether monosubstituted alkenes could be tolerated in the oxyvinylation reaction, hydroxyalkene **1.49** was reacted under identical conditions to those shown in Scheme 1.11; however, desired product **1.51** was not afforded, with only ketone **1.53** afforded (Scheme 1.12). The authors proposed this product was formed by oxypalladation

of **1.49** to afford Pd(II)-alkyl intermediate **1.50**, which could then undergo β-hydride elimination to afford **1.52** followed by hydrolysis under the work-up procedure to give observed product **1.53**. Thus, unlike the carbonylation example (Scheme 1.9), the rate of carbopalladation of the Pd(II)-alkyl intermediate **1.50** with the alkene is not sufficiently fast to compete with the rate of β-hydride elimination, thus the substrates must be designed such that β-hydride elimination is not a possibility.



Scheme 1.12: Attempted oxyvinylation of monosubstituted alkene 1.49

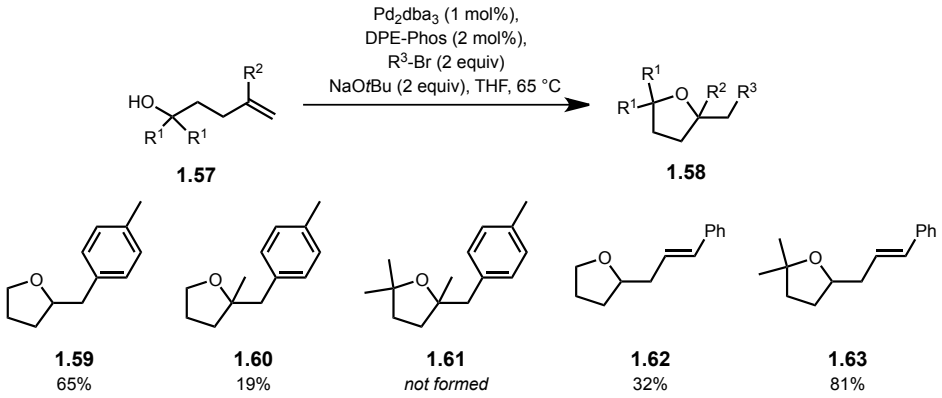
Tietze and co-workers were able to extend this oxyvinylation methodology to an enantioselective synthesis of α-tocopherol, one of the components of vitamin E (Scheme 1.13).[35] Cyclisation of phenol **1.54** using catalytic $Pd(TFA)_2$ and (*S*,*S*)-Bn-Boxax ligand **1.41** afforded chroman **1.55**. The highest enantioselectivity (98:2 e.r.) was obtained where the spectator hydroxyl group was protected by a benzyl group and the alkene trap was methyl vinyl ketone. Further elaboration of this intermediate afforded α-tocopherol as a mixture of epimers at the 4´ position.[36]



Scheme 1.13: Enantioselective oxyvinylation reaction of 1.54 in synthesis of α-tocopherol 1.56

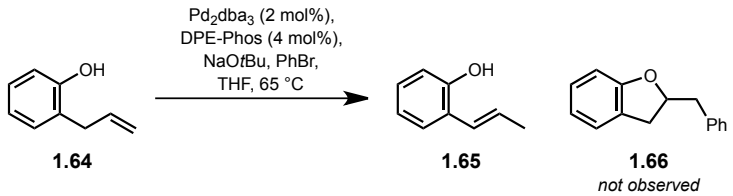
The methodology detailed thus far has made use of Pd(II) salts and relied on subsequent interception of the Pd(II)-alkyl intermediate. Wolfe and co-workers made use of a Pd(0) catalyst source and aryl or alkenyl halides to produce Pd(II) sources *in situ*. These

catalysts were able to effect the oxyarylation or oxyalkenylation of γ-hydroxyalkenes to afford substituted tetrahydrofurans (Scheme 1.14).[37] In contrast to the methodology developed by the groups of Semmelhack and Tietze, monosubstituted alkenes were not only tolerated in these reactions, but performed better. Thus, oxyarylation of 4-pentenol (R^1 = R^2 = H) with 4-bromotoluene afforded a 65% yield of tetrahydrofuran **1.59** whereas the disubstituted alkene (R^1 = H, R^2 = Me) gave only 19% yield of **1.60**. Tertiary alcohol **1.57** (R^1 = R^2 = Me) proved unreactive even when heated to 140 °C in xylenes. During the reaction development, the authors found that use of a chelating bis(phosphine) ligand was essential to suppress competing reduction of the aryl halide.[38] Another common side reaction was the formation of ethers from *O*-arylation or *O*–vinylation. The formation of these side products was most problematic when primary alcohol substrates were employed, hence **1.62** was formed in only 32% yield from 4-pentenol **1.57** (R^1 = R^2 = H) whereas tertiary alcohol **1.57** (R^1 = Me, R^2 = H) gave an 81% yield of **1.63**.



Scheme 1.14: Carboetherification of alkenes 1.57

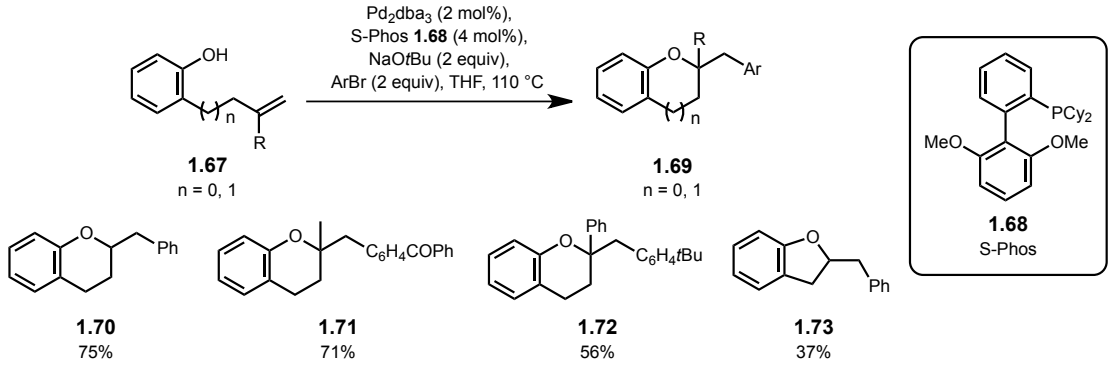
Despite the range of substrates successfully cyclised under the developed conditions, Wolfe and co-workers were unable to effect the formation of 6-membered heterocycles under the optimised conditions. The reaction scope was also limited to aliphatic alcohols where, under the optimised conditions, the attempted cyclisation of *o*-allylphenol **1.64** gave rise to only isomerisation of the alkene to afford **1.65**, with desired product **1.66** not observed (Scheme 1.15).[39]



Scheme 1.15: Attempted carboetherification of *o*-allyl phenol 1.64

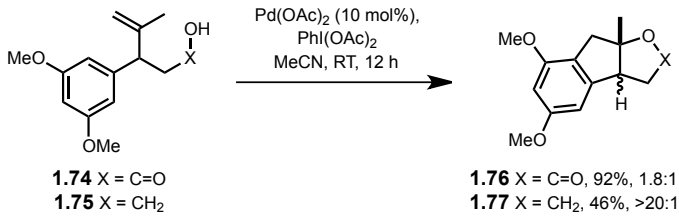
In order to address these limitations, the authors chose to analyse the reaction of phenol **1.67** (n = 1), as this substrate was expected to be less disposed to alkene isomerisation

(Scheme 1.16). Pleasingly, simple alteration of the phosphine ligand from bidentate ligand DPE-Phos to monodentate ligand S-Phos **1.68**, which had shown success in other difficult cyclisation reactions,[40] afforded desired product **1.70** in 75% isolated yield. In contrast to the reactions of linear aliphatic alcohols, the cyclisations of substrates bearing geminally disubstituted alkenes provided synthetically useful yields of chroman heterocycles **1.71** and **1.72**. Substrates with internal alkenes failed to undergo the desired carboetherification reaction, even at temperatures of 140 °C. In addition, although chroman products could be prepared effectively using these modified conditions, benzofuran products remained challenging; **1.73** was formed in only 37% isolated yield.



Scheme 1.16: Carboetherifiation of alkenes 1.67

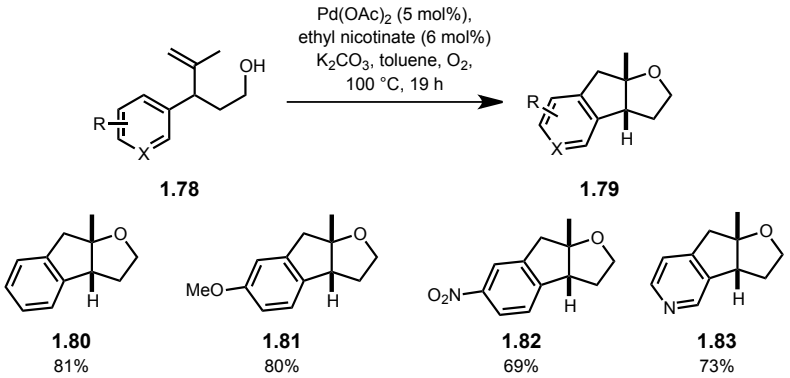
The Stephenson group reported an oxidative alkene difunctionalisation, proposed to proceed *via* a Pd(II)–Pd(IV) cycle, using $PhI(OAc)_2$ as a stoichiometric oxidant (Scheme 1.17). The reaction predominantly employed electron rich or neutral arenes with pendant carboxylic acid groups to afford lactones.[41] Although the cyclisation of primary alcohol **1.75** was demonstrated, tetrahydrofuran **1.77** was isolated in only 46% yield, whereas the corresponding lactone **1.76** was formed in 92% yield.



Scheme 1.17: Oxidative alkene difunctionalisation of 1.74 and 1.75 using $PhI(OAc)_2$

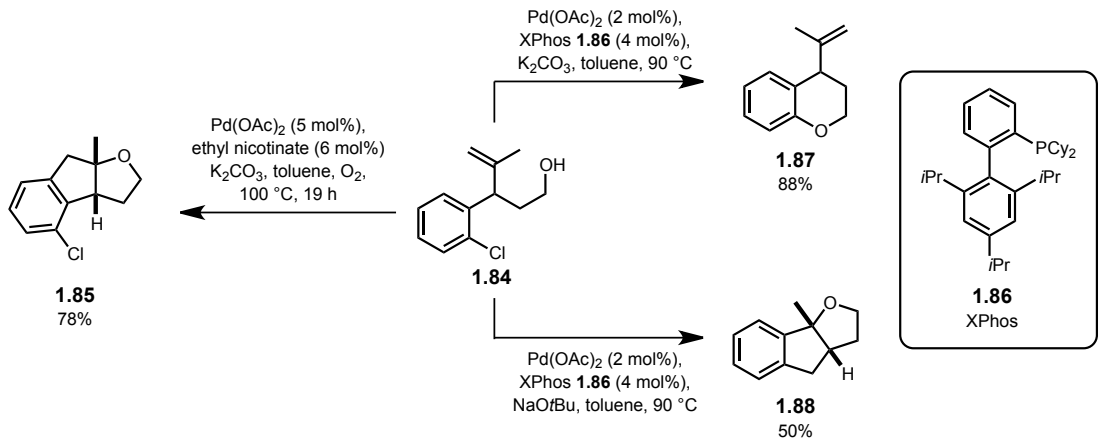
Subsequent to this publication, Buchwald *et al*. reported an oxidative functionalisation of arylhydroxyalkenes **1.78** proceeding *via* oxypalladation–CH functionalisation, affording tricyclic compounds **1.79** in high yields (Scheme 1.18).[42] Oxygen proved to be the most effective oxidant for the desired reaction, with little to no conversion observed using Pd(II)/Cu(II), Pd(II)/Ag(I) or Pd(II)/$PhI(OAc)_2$ combinations. In contrast to the reaction developed by Stephenson and co-workers, the reaction tolerated electron donating and

withdrawing groups on the aromatic ring, in addition to a pyridyl group, which was functionalised regioselectively to afford **1.83**.



Scheme 1.18: Oxidative functionalisation of arylhydroxyalkenes 1.78

Buchwald effectively demonstrated the orthogonality of oxidative palladium(II) chemistry with Pd(0) reactions, illustrated through the reactions of **1.84** (Scheme 1.19): a) under the conditions described in the manuscript, **1.84** undergoes oxypalladation–C–H activation to afford **1.85** with the aryl chloride still intact and no dechlorinated side products observed; b) chroman **1.87** is formed under Pd(0)-catalysed C–O bond forming conditions; c) finally, under carboetherification conditions similar to those developed by Wolfe and co-workers, the alkene undergoes an oxyarylation reaction with the aryl chloride to afford **1.88**. This also demonstrates the versatility of palladium chemistry – that one starting material, under slightly modified conditions, can give rise to three different products.

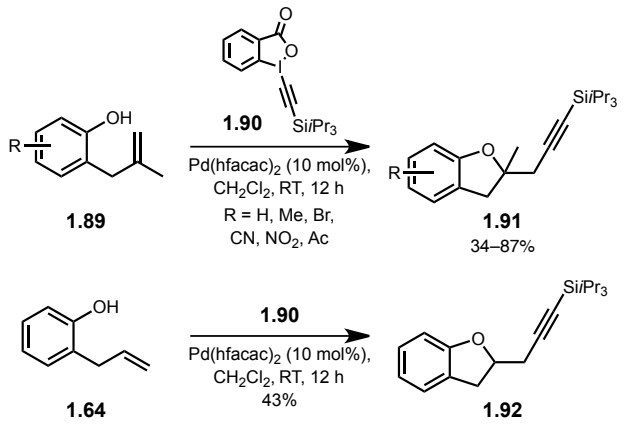


Scheme 1.19: Orthogonality of Pd(II) catalysis with Pd(0) catalysis

C–O and sp^3–sp C–C Difunctionalisation

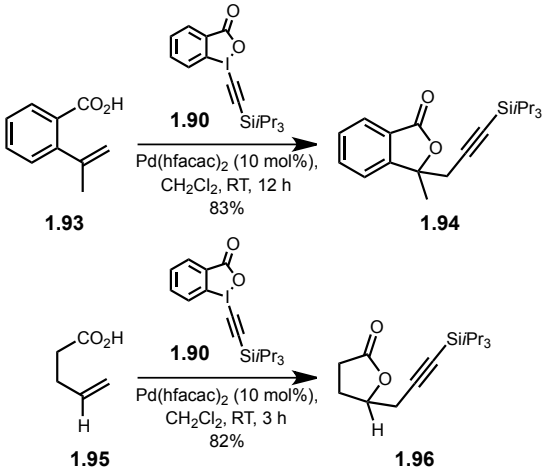
The methodology detailed thus far has demonstrated the variety of ways in which an alkene can be difunctionalised through Wacker-type cyclisations to give rise to a new C–O and C–C bond. However these examples all result in the formation of a new

C–C bond between an sp^3-hybridised and an sp^2-hybridised carbon. In 2010, Waser and co-workers reported that tri*iso*propylsilyl ethynylbenziodoxolone (TIPS-EBX) reagent **1.90** could be used to effect the palladium-catalysed oxyalkynylation of unactivated alkenes **1.89** (Scheme 1.20). [43] These reactions afforded generally excellent yields of heterocyclised products, although only 34% of desired product **1.91** was obtained where the aryl ring was substituted with a methyl group *para* to the hydroxyl group. Substrates containing more electron donating substituents than a methyl group did not provide any of the desired product. Although monosubstituted alkene substrate **1.64** could be heterocyclised to afford desired product **1.92**, the yield was moderate (Scheme 1.20). Complete consumption of starting material **1.64** was observed; however, no side products were formed in sufficient quantity to be isolated and characterised.



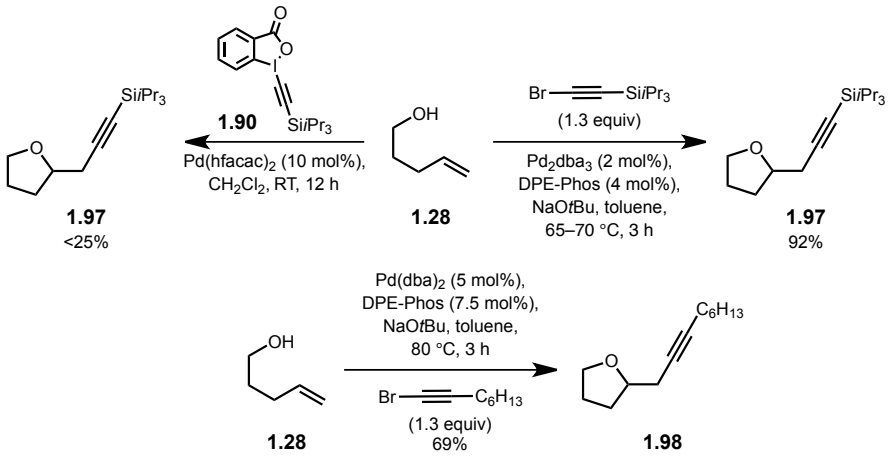
Scheme 1.20: Oxyalkynylation of unactivated alkenes 1.89 and 1.64

The oxyalkynylation reaction using TIPS-EBX could also be applied to the heterocyclisation of benzoic acids to afford lactones (Scheme 1.21). In contrast to the reactions of the phenol substrates, electron rich aryl substitution could be tolerated. In addition to the increased tolerance of aryl substitution, whilst the oxyalkynylation of aliphatic alcohols had proven unsuccessful, aliphatic acids could be employed to afford the desired oxyalkynylation products. The oxyalkynylation of **1.95** to afford lactone **1.96** also demonstrates that monosubstituted alkenes can be tolerated in the reaction of carboxylic acids (Scheme 1.21).



Scheme 1.21: Oxyalkynylation of carboxylic acids 1.93 and 1.95

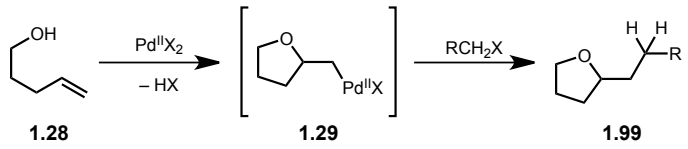
A major limitation of the chemistry developed by Waser and co-workers was its inability to allow access to tetrahydrofuran derivatives; under the standard conditions, cyclisation of 4-pentenol **1.28** afforded less than 25% of desired product **1.97** (Scheme 1.22). However, by recourse to Wolfe-type conditions, using a Pd(0) catalyst and a silyl-protected bromoacetylene, Waser *et al*. were able to afford tetrahydrofuran adduct **1.97** from cyclisation of 4-pentenol **1.28** in 92% yield.[44] A variety of substitution patterns could be tolerated in the oxyalkynylation reaction, including the cyclisation of secondary alcohols to give 2,5-disubstituted tetrahydrofuran products in good to excellent diastereoselectivities (5.7:1 – 19:1 d.r.). By a slight modification of the reaction conditions – use of $Pd(dba)_2$ in place of Pd_2dba_3 and reduction of the Pd/ligand ratio – Waser *et al*. were able to extend this methodology to the use of bromoacetylenes substituted with aliphatic groups to afford products such as **1.98**.[45]



Scheme 1.22: Pd(0)–Pd(II) catalysed oxyalkynylation of aliphatic alcohol 1.28

To summarise, 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 examples of Wacker-type cyclisations, the contributions of

the Wolfe and Waser groups has seen an expansion in the scope of the C–C bond formation capabilities of these reactions. However, it remains a challenge to construct a new sp^3–sp^3 C–C bond from the Pd(II)-alkyl intermediate (Scheme 1.23) and, as many of the oxygen-containing heterocycles found in natural products and biologically active compounds are substituted with saturated alkyl chains, this would be an attractive prospect.

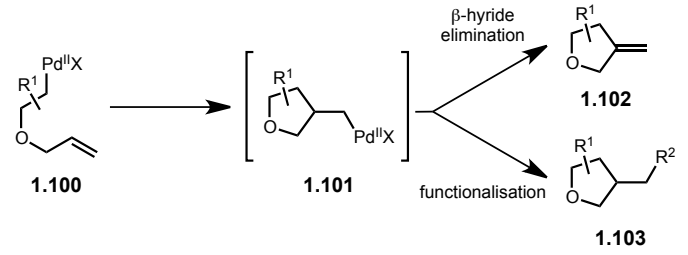


1.28 **1.29** **1.99**

Scheme 1.23: Heterocyclisation of 1.28 with construction of new sp^3–sp^3 C–C bond

1.3 Carbopalladation of Alkenes

In addition to facilitating the addition of oxygen nucleophiles to alkenes, as in the heterocyclisation reactions described in Section 1.2, palladium(II) can also facilitate the addition of carbon nucleophiles to alkenes. However, the problem associated with the development of these reactions is the readiness with which carbanions are oxidised to carbon radicals and so less reactive or masked carbanions must often be used. Many examples of carbocyclisation reactions give rise to the formation of all-carbon rings; however, this type of chemistry can also be used to access heterocycles *via* Pd(II)-catalysed carbopalladation of alkenes containing a heteroatom tether **1.100** (Scheme 1.24).[46] The resulting Pd(II) species **1.101** can then undergo β-hydride elimination, or further functionalisation to afford heterocycles **1.102** and **1.103** (Scheme 1.24).



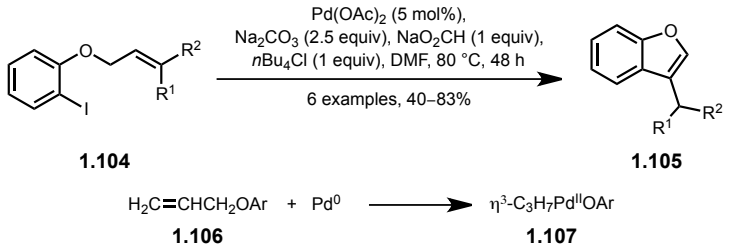
1.100 **1.101** **1.102** **1.103**

Scheme 1.24: Pathways for carbocyclised intermediate 1.101

1.3.1 Carbocyclisation–β-hydride Elimination

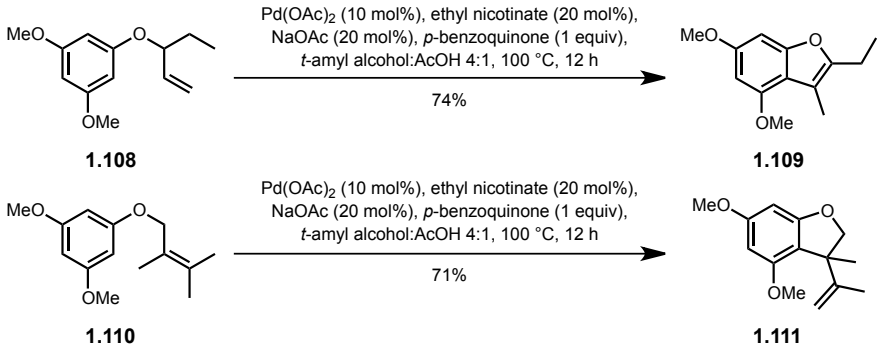
Many methods of constructing heterocycles through carbopalladation are initiated *via* oxidative addition of Pd(0) to an aryl or vinyl halide.[47] Larock and Stinn found that aryl iodides possessing an *ortho O*-allyl group **1.104** could be successfully cyclised using

$Pd(OAc)_2$, Na_2CO_3, nBu$_4$Cl and sodium formate in DMF to afford benzofurans **1.105** (Scheme 1.25).[48] These conditions were similar to those developed for the analogous anilines,[49] however, the addition of one equivalent of sodium formate was found to be beneficial. This was proposed to be due to the reduction of π-allyl Pd(II) side product **1.107**, and so keeping the Pd(0) catalyst active. Consistent with this suggestion, allyl groups with a lower degree of substitution and better aryl leaving groups afforded lower yields.



Scheme 1.25: Pd-catalysed synthesis of benzofurans 1.105 from aryl iodides 1.104

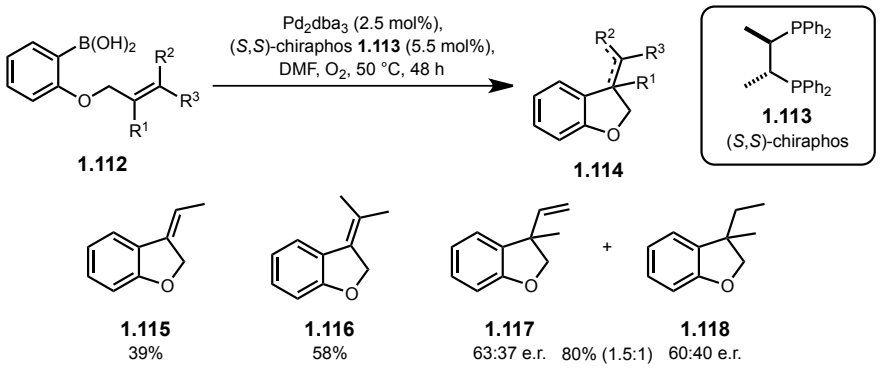
Stoltz and co-workers developed an oxidative synthesis of benzofuran and dihydrobenzofuran derivatives, proceeding *via* direct C–H bond functionalisation of arenes followed by cyclisation onto unactivated alkenes (Scheme 1.26).[50] Although O_2 was a competent oxidant for this transformation, yields were higher using *p*-benzoquinone. Thus, treatment of *O*-aryl ether **1.108** with catalytic $Pd(OAc)_2$, ethyl nicotinate, NaOAc and *p*-benzoquinone afforded the corresponding benzofuran **1.109**. Quaternary carbon-containing dihydrobenzofuran **1.111** could also be successfully synthesised using tetra-substituted alkene **1.110**, where alkene isomerisation is not possible in this product. This chemistry was limited to the cyclisation of highly electron rich arenes and the synthesis of five-membered oxygen heterocycles.



Scheme 1.26: Oxidative CH functionalisation–carbopalladation of alkenes 1.108 and 1.110

In 2007, Akiyama and Mikami reported an oxidative intramolecular cyclisation of boronic acids to afford heterocycles (Scheme 1.27). Although products could be formed in moderate yields using Pd_2dba_3 and chiral ligand (*S*,*S*)-chiraphos **1.113**, often mixtures of oxidative **1.117** and non-oxidative **1.118** products were obtained and the scope of this

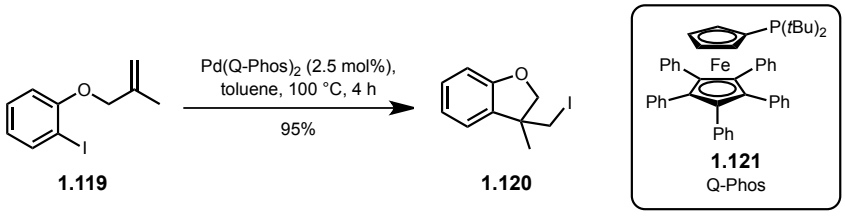
cyclisation proved to be somewhat limited.[51] Oxygen was found to be necessary for this reaction to operate, so the authors proposed that the reaction was initiated by oxidation of Pd(0) to give a Pd(II)-peroxo species.



Scheme 1.27: Carbocyclisation of boronic acids 1.112

1.3.2 Carbocyclisation–C–X Bond Formation

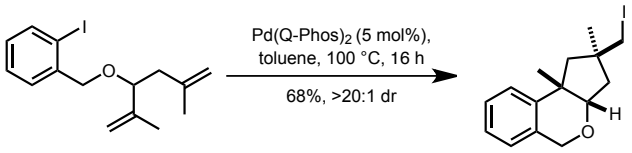
Although a number of examples of carbopalladation of alkenes have been demonstrated, construction of multiple new bonds from a single reaction would constitute a more efficient and rapid method of establishing molecular complexity. In 2011, Lautens and Newman reported an elegant synthesis of heterocycles by Pd-catalysed carboiodination (Scheme 1.28).[52] In these reactions, the iodine from aryl starting material **1.119** is incorporated into product **1.120** *via* C–X bond forming reductive elimination from Pd(II) and consequently no stoichiometric waste is formed in these transformations. A bulky phosphine was required for reactivity and the most effective ligand was found to be Q-Phos **1.121**. A range of products could be afforded in very high yields, although the authors noted that monosubstituted alkenes could not be tolerated, giving alkene isomerisation or Heck-type products under these conditions. The scope of the carboiodination could be subsequently expanded to the cyclisation of aryl bromides, with the iodine containing products still obtained by inclusion of KI.[53]



Scheme 1.28: Carboiodination of alkenes 1.119

Lautens and co-workers also found that polyunsaturated aryl halides such as **1.122** could effectively undergo a domino reaction, giving rise to the formation of two new C–C bonds

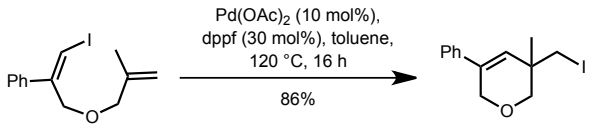
and one C–I bond in a single step (Scheme 1.29). Due to competing intramolecular processes, the carboiodination of **1.122** was not anticipated to be trivial. However, in the example shown, the second carbopalladation step proved sufficiently faster than the C–I bond forming reductive elimination to obtain the desired domino reaction product **1.123** in 68% yield and as a single diastereomer.[53]



1.122 **1.123**

Scheme 1.29: Domino carboiodination reaction of 1.122

Simultaneously with Lautens, Tong and co-workers reported the carboiodination of unactivated alkenes, initiated by oxidative addition into an alkenyl iodide bond (Scheme 1.30).[54] Using catalytic $Pd(OAc)_2$ and dppf as a ligand, the cyclised products could be afforded in generally high yields. Although most of the examples demonstrated the formation of nitrogen-containing heterocycles, one example of the formation of an oxygen-containing heterocycle was given, with product **1.125** afforded in an 86% yield. A *Z*-alkene was found to be necessary for cyclisation and the authors reported that the addition of radical inhibitors such as TEMPO did not affect the alkyl iodide reductive elimination, suggesting that this is not a radical process.



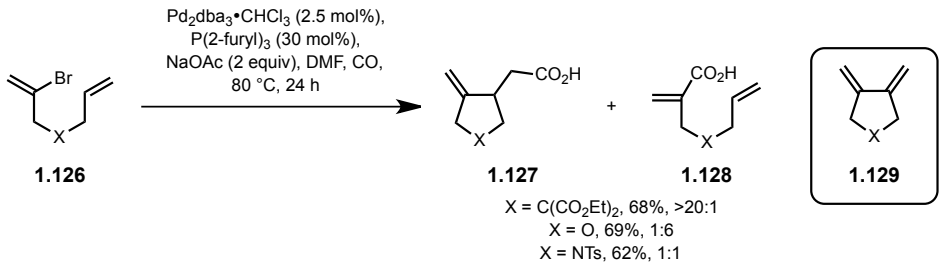
1.124 **1.125**

Scheme 1.30: Carboiodination of vinyl iodide 1.124

1.3.3 Carbocyclisation–C–C Bond Formation

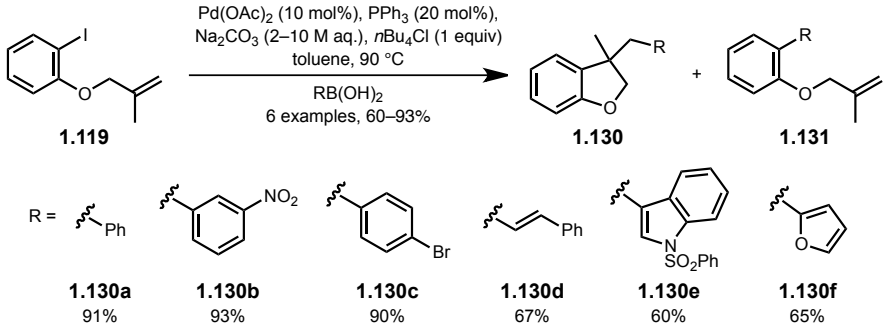
In addition to carbopalladation reactions forming subsequent C–X bonds from the Pd(II)-alkyl intermediate, there are many examples of subsequent C–C bond formation. Aggarwal *et al*. developed a cyclisation–carbonylation of bromodienes to construct carbo- and heterocycles **1.127** (Scheme 1.31).[55] This cascade process proved a significant challenge as, in addition to the product of direct palladium-catalysed carbonylation of the bromoalkene **1.128**, β-hydride elimination from the carbopalladated intermediate to afford **1.129** could also occur. The simple solution of increasing the pressure of CO used could not be employed as this could lead to direct trapping product **1.128**. The authors reasoned that the use of an electron rich phosphine ligand should favour binding of CO to palladium

as CO is a strong π-acceptor. In accordance with their expectations, the authors observed formation of a mixture of products in the absence of a ligand, including diene **1.129**. Highly electron rich alkyl phosphines such as P(*t*Bu)$_3$ lessened formation of diene **1.129** but promoted carbonylation to an extent that direct carbonylation to afford **1.128** competed with carbopalladation. However, aryl phosphines were found to possess the correct balance between the rate of carbopalladation, carbonylation and β-hydride elimination. The ratio of linear:cyclised acids reflected the relative rates of cyclisation for the substrates studied, with the ether linked substrate (X = O) performing most poorly in this respect.



Scheme 1.31: Carbopalladation–carbonylation of alkenes 1.126

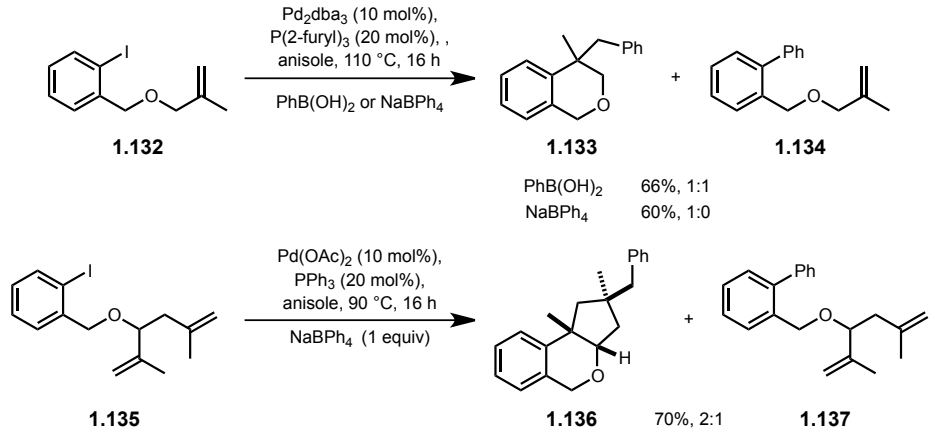
Grigg and co-workers reported the intramolecular cyclisation of Pd(II)-aryl intermediates onto heteroatom tethered alkenes followed by trapping with organoboron species in a so called "cyclisation–anion capture process" to afford dihydrobenzofurans (Scheme 1.32).[56] Analogously to the methodology developed by Aggarwal *et al*., one of the concerns in this process is that the Pd(II)-aryl intermediate will be trapped directly by the organoboron species prior to cyclisation to afford the Suzuki–Miyaura coupling product **1.131**. With aryl boronic acids, the cyclisation–anion capture products **1.130a–c** were the sole products observed; however, lower yields of **1.130d–f** were obtained with alkenyl or heteroaryl boronic acids, where the mass balance was accounted for by formation of direct coupling product **1.131**.



Scheme 1.32: Cyclisation–anion capture of aryl iodide 1.119

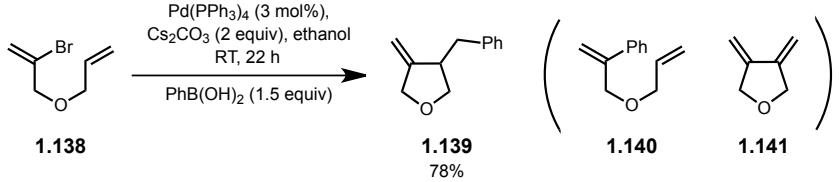
In attempting to extend this methodology to the formation of 6-membered oxacycles, the authors found that desired product **1.133** and direct coupling product **1.134** were formed

in a 1:1 ratio (Scheme 1.33), even using phenyl boronic acid, which had afforded a 91% yield in the formation of dihydrobenzofuran **1.130a** (Scheme 1.32). However, use of tetraphenylborate allowed a 60% yield of desired product **1.133** to be obtained with direct coupling product **1.134** not observed. Grigg and co-workers also reported that a cascade reaction, forming three new C–C bonds in one transformation, could be carried out but afforded a mixture of cyclisation **1.136** and direct coupling **1.137** products in 2:1 ratio.[56] Similar "cyclisation–anion capture" methodology proved successful employing organostannanes in place of organoboranes. [57]



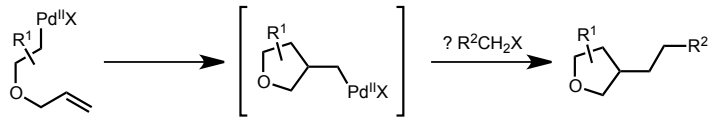
Scheme 1.33: Cyclisation–anion capture of aryl iodides 1.132 and 1.135

Oh *et al*. developed a similar transformation, employing bromodienes as the starting material (Scheme 1.34).[58] As the substrates were similar to those studied by Aggarwal and co-workers, it would be expected that a similar range of side products could be formed from the cyclisation of bromodienes with boronic acids: **1.140**, corresponding to coupling of the alkenyl bromide with the boronic acid; and **1.141**, corresponding to carbopalladation of the alkene followed by β-hydride elimination. The authors observed that a careful balance of the number of equivalents of boronic acid was required – lower concentrations gave rise to greater formation of diene **1.141** and higher concentrations gave rise to greater formation of direct coupling product **1.140**. 1.5 equivalents of boronic acid was found to be optimum and **1.138** could be cyclised using catalytic $Pd(PPh_3)_4$, Cs_2CO_3 and phenyl boronic acid to afford desired product **1.139** in 78% yield.



Scheme 1.34: Cyclisation–anion capture of bromodienes 1.138

This section has presented a range of ways in which heterocycles can be accessed *via* the carbopalladation of alkenes.[46] The majority of these examples involve oxidative addition of an aryl or alkenyl halide to Pd(0), which can then undergo intramolecular carbopalladation. The resulting Pd(II) intermediate can then be participate in a range of transformations to afford substituted heterocycles. One of the remaining challenges in multi-component and multiple bond forming processes, highlighted in some of the carbocyclisations detailed herein, is controlling the sequence of steps to obtain the desired product in a selective fashion. In addition, as with oxypalladation reactions, development of processes that furnish a new sp^3–sp^3 C–C bond remains under-unexplored and would present a beneficial and complementary addition to the scope of existing carbocyclisation transformations (Scheme 1.35).

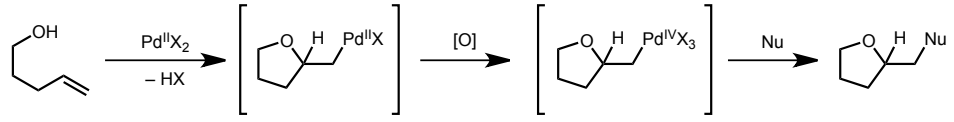


1.100 **1.101** **1.142**

Scheme 1.35: Carbocyclisation of 1.100 with construction of new sp^3–sp^3 C–C bond

1.4 Pd(IV) Chemistry

The construction of sp^3–sp^3 C–C bonds is a difficult transformation to achieve under Pd(0)–Pd(II) catalysis due to the susceptibility of Pd(II)-alkyl species to β-hydride elimination. Recently, catalytic reactions proceeding through a Pd(II)–Pd(IV) cycle have garnered significant interest, with a number of reviews published in this area.[59] This higher oxidation state catalytic cycle has the potential to allow access to new reactivity or give rise to transformations which would have been difficult or impossible using Pd(0)–Pd(II) chemistry. As such, another method for avoiding β-hydride elimination from Pd(II)-alkyl intermediates produced by heterocyclisation reactions is to intercept them *via* oxidation to Pd(IV) (Scheme 1.36).



1.28 **1.29** **1.143** **1.144**

Scheme 1.36: Pd(II)–Pd(IV) catalysed alkene difunctionalisation

In order to develop organic transformations which operate *via* a Pd(II)–Pd(IV) catalytic cycle, palladium must be capable of achieving the required oxidation state at a given stage of the cycle and under given reaction conditions. Pd(IV) complexes have been isolated from oxidative addition of alkyl halides to Pd(II) complexes and are usually

characterised by neutral chelating nitrogen ligands and carbon ligands. Pd(IV) intermediates have also been suggested in various alkene difunctionalisation reactions taking place in the presence of strong oxidants such as hypervalent iodine species.

1.4.1 Pd(IV) Species from Oxidative Addition of Alkyl Halides

Although Pd(IV) complexes had previously been implicated as reaction intermediates,[60] it wasn't until 1986 that Canty and co-workers prepared and isolated a trimethylpalladium iodide Pd(IV) complex with 2,2'-bipyridine (bipy) **1.145** (Scheme 1.37). This complex proved sufficiently stable to be fully characterised by ^{1}H NMR spectroscopy and X-ray crystallography (Figure 1.2).[61]

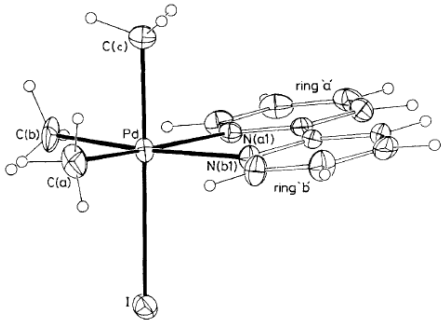
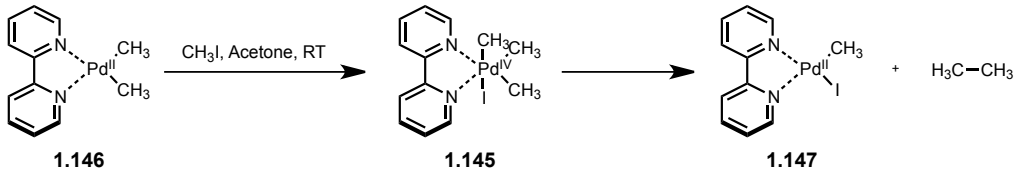


Figure 1.2: X-ray crystal structure of [PdMe$_3$Ibipy] 1.145

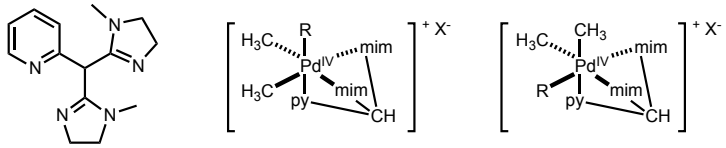
Complex **1.145** was obtained by oxidative addition of MeI to [PdMe$_2$bipy] **1.146** in acetone (Scheme 1.37). X-ray quality crystals were obtained by concentrating the reaction mixture to low volume to give *fac*-[PdMe$_3$Ibipy] **1.145**. The ^{1}H NMR spectrum of **1.145** in deuterated acetone showed slow disappearance of this species and concomitant appearance of the resonances corresponding to ethane and [PdMeIbipy] **1.147**. At 10 °C this reductive elimination took place over several hours but required only 30–40 minutes at ambient temperature. Importantly, this is an example of a reductive elimination from palladium forming a new sp^3–sp^3 C–C bond, under very mild conditions. The solid complex **1.145** was found to be stable at –20 °C but colourised over several days at ambient temperature. Elimination of ethane and conversion to a yellow solid occurred at 100–110 °C, followed by melting (decomposition) at 212–214 °C, consistent with the melting point of [PdMeIbipy] **1.147**.



1.146 **1.145** **1.147**

Scheme 1.37: Oxidative addition of methyl iodide to 1.146 and reductive elimination of ethane

Canty and co-workers subsequently extended this work to the synthesis of ethyl, allyl and benzyl complexes of Pd(IV) (Figure 1.3).[62] In the oxidative addition of ethyl iodide or allyl bromide to Pd(bipy)Me_2, the Pd(IV) complexes were only transiently observed in trace quantities in the ^{1}H NMR spectra prior to C–C bond forming reductive elimination. However, cationic Pd(IV) complexes, prepared by reaction of ethyl iodide, allyl bromide or benzyl bromide with $PdMe_2$((py)$(mim)_2$CH), could be isolated and characterised by ^{1}H NMR spectroscopy as a mixture of isomers **1.149** and **1.150**.



1.148 (py)$(mim)_2$CH

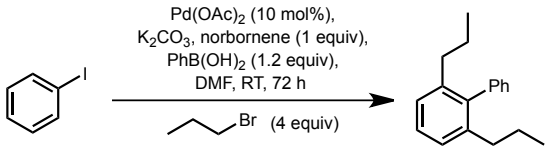
1.149 **1.150**

R = Et, $CH_2CH{=}CH_2$, CH_2Ph

X = Br, I

Figure 1.3: Dimethyl Pd(IV) complexes with 1.148 and ethyl iodide, allyl bromide and benzyl bromide

The work presented by Canty *et al*. showed that palladium(IV) species could be formed by oxidative addition of alkyl halides to Pd(II) under stoichiometric conditions. Catellani and co-workers proposed a Pd(IV) intermediate arising from oxidative addition of alkyl halides to Pd(II) under catalytic conditions in a multi-component *ortho*-dialkylation of aryl iodides (Scheme 1.38). Despite the many components and steps in this reaction, the *ortho*-dialkylation proceeds with a high degree of chemoselectivity at room temperature to give the products in excellent yields. Thus, treatment of phenyl iodide with catalytic $Pd(OAc)_2$, norbornene, propyl bromide, $PhB(OH)_2$ and K_2CO_3 in DMF at room temperature afforded dialkylated biaryl product **1.152** in 90% yield. [63]

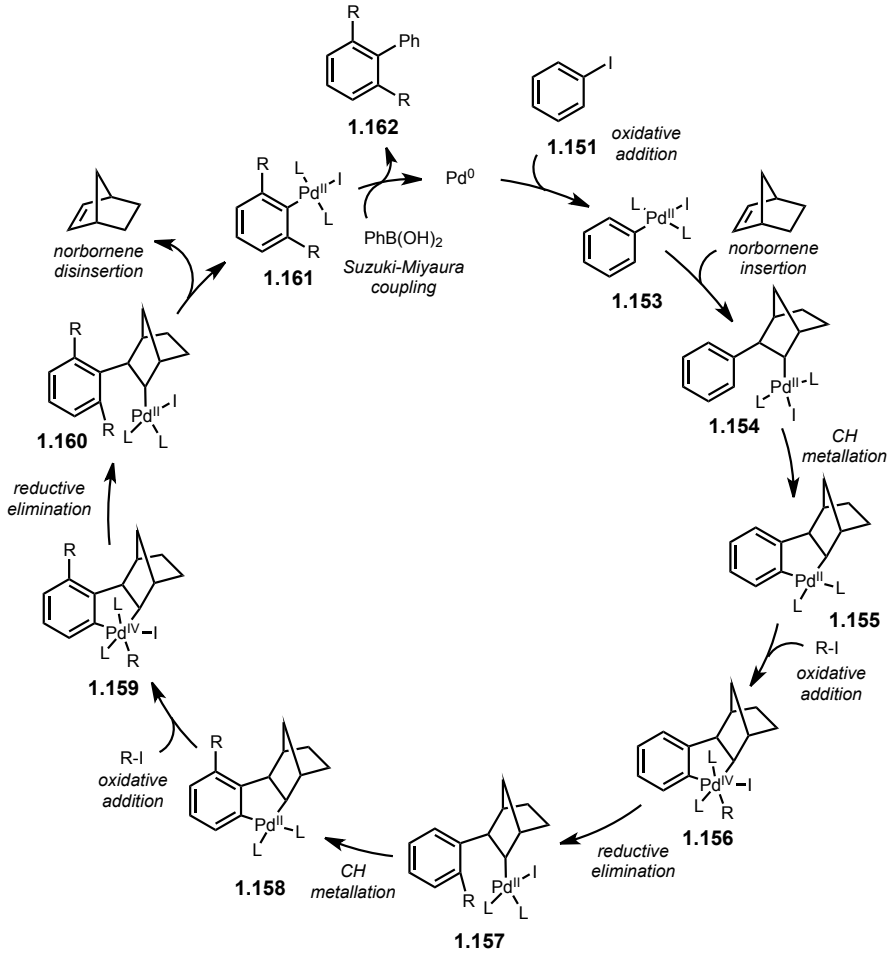


1.151 90% **1.152**

Scheme 1.38: Synthesis of *o,o*-disubstituted biaryls from aryl iodides 1.151

The postulated mechanism of the *ortho*-dialkylation is complex and proceeds through three oxidation states of palladium (Scheme 1.39). Initial oxidative addition of aryl iodide

1.151 to Pd(0) affords aryl palladium(II) intermediate **1.153**, which then undergoes norbornene insertion to afford *cis*,*exo* Pd(II)-alkyl intermediate **1.154**.[64] As β-hydride elimination from this intermediate is not possible, direct CH metallation occurs to afford palladacycle **1.155**. This intermediate can then undergo oxidative addition with an alkyl halide to afford Pd(IV) species **1.156**.[65] C–C bond forming reductive elimination forms the aryl-alkyl bond selectively, and liberates Pd(II)-alkyl species **1.157**, which then undergoes another direct CH metallation and oxidative addition to afford **1.159**. C–C bond forming reductive elimination is followed by norbornene deinsertion, induced by steric repulsion, to afford Pd(II)-aryl intermediate **1.161**. This Pd(II)-aryl intermediate is then intercepted by transmetallation with the boronic acid followed by reductive elimination to afford the product **1.162** and regenerate Pd(0). The norbornene moiety in this reaction can be regarded as co-catalyst as it is regenerated at the end of the catalytic cycle; however, stoichiometric quantities are required to drive this reaction to completion.

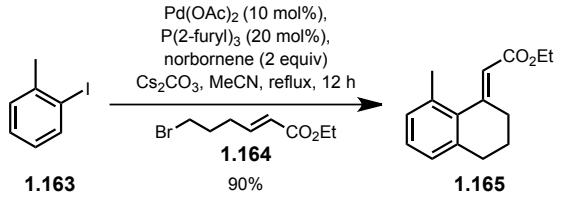


Scheme 1.39: Proposed mechanism of Catellani reaction

Pd(II)-aryl intermediate **1.161** can also be intercepted by other reactions that are well known for the aryl-Pd bond, for example Heck coupling with olefins[66] or Sonogashira reaction with acetylenes.[67] This strategy results in the formation of three new C–C bonds in a domino fashion and is a demonstration of a Pd-catalysed reaction involving oxidative

addition of an alkyl halide to a Pd(II) intermediate.

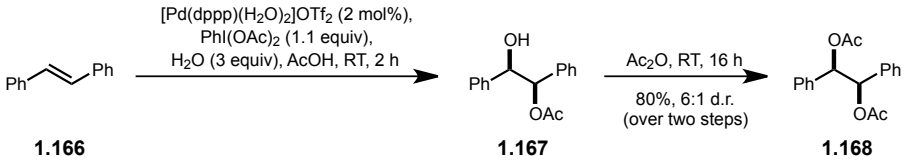
This methodology has been modified and extended to the formation of fused ring systems by Lautens and co-workers (Scheme 1.40).[68] These conditions can be applied to the functionalisation of a variety of iodoaryl substrates such as **1.163** using difunctional alkyl halides containing an alkene acceptor **1.164** to form carbocycles such as **1.165**. Six and seven membered carbocycles can be obtained as single stereoisomers.



Scheme 1.40: Pd-catalysed alkylation–alkenylation of 1.163

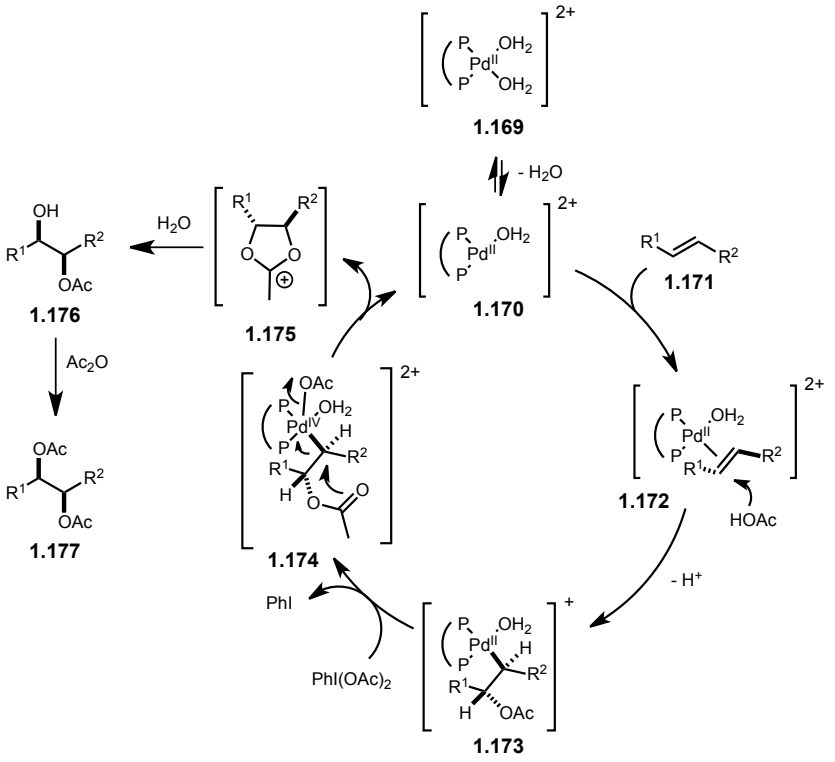
1.4.2 Pd(IV) Species from Stoichiometric Oxidants

Hypervalent iodine reagents have emerged as useful reagents in palladium catalysis, enabling selective metal oxidation of particular palladium intermediates in the catalytic cycle.[69] Using the hypervalent iodine reagent $PhI(OAc)_2$, Song and Dong were able to effect the vicinal oxidation of alkenes with a cationic palladium catalyst in acetic acid (Scheme 1.41).[30] Hydroxyacetate **1.167** was formed selectively in the oxidation of *trans*-stilbene **1.166** in favour of the diacetate, despite the acetic acid medium. However, treatment of the reaction mixture with acetic anhydride allowed diacetate **1.168** to be isolated in excellent yield. The scope of the diacetoxylation was not limited to terminal alkenes or those with an adjacent directing group. Jiang *et al*. subsequently reported a similar transformation, where oxygen was the sole oxidant employed.[70]



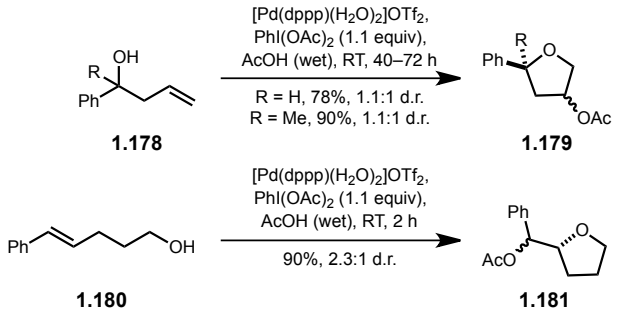
Scheme 1.41: Pd-catalysed vicinal oxidation of alkene 1.166 with $PhI(OAc)_2$

On the basis of isotopic labeling studies and the observed *syn* diastereoselectivity, the authors proposed the mechanism detailed in Scheme 1.42. *Trans*-oxypalladation of alkene **1.171** with cationic Pd(II) complex **1.170** affords organopalladium intermediate **1.173**. Oxidation of Pd(II) complex **1.173** to Pd(IV) complex **1.174** followed by intramolecular cyclisation affords **1.175**, regenerating Pd(II) catalyst **1.170**. Hydrolysis of **1.175** affords the observed *syn*-hydroxyacetate product **1.176**.



Scheme 1.42: Proposed mechanism of Pd-catalysed vicinal oxidation of alkenes 1.171 with $PhI(OAc)_2$

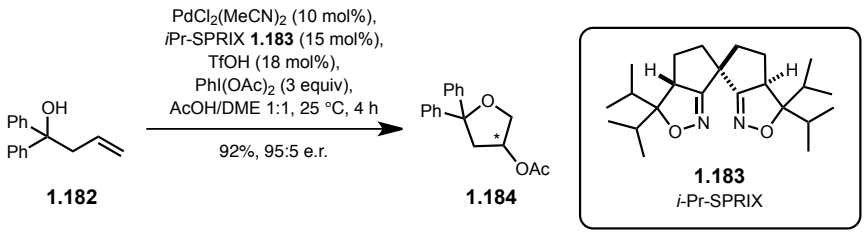
Song and Dong also demonstrated that this methodology could be extended to the synthesis of tetrahydrofurans and lactones using substrates bearing free hydroxyl groups (Scheme 1.43). Homoallylic alcohols **1.178** gave rise to the products of 5-*endo* cyclisation **1.179** and γ-hydroxyalkene **1.180** gave 5-*exo* cyclisation product **1.181** selectively. The products were isolated as mixtures of diastereomers.



Scheme 1.43: Intramolecular Pd-catalysed vicinal oxidation of alkenes 1.178 and 1.180

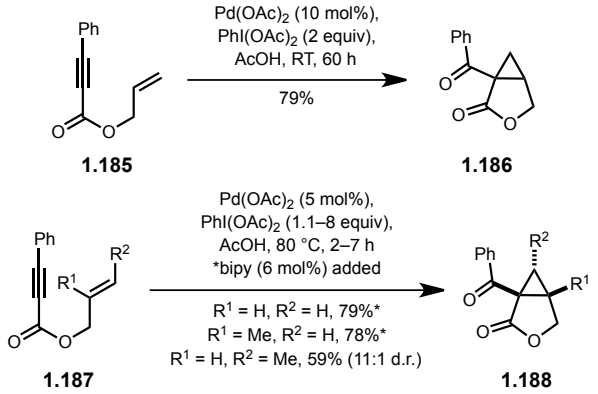
Sasai and co-workers subsequently reported that the cyclisation–acetoxylation transformation developed by Song and Dong could be effected in an asymmetric fashion (Scheme 1.44),[71] a rare example of an enantioselective reaction involving Pd(IV) intermediates. Using catalytic $PdCl_2(MeCN)_2$, *i*Pr-SPRIX **1.183**, triflic acid and $PhI(OAc)_2$, the authors were able to afford generally high enantiomeric ratios of 5-*endo* tetrahydrofuran products **1.184**. In the absence of triflic acid, reactivity and enantioselectivity were significantly lower. Through exclusion and ^1H NMR spectroscopy

experiments, the authors proposed that the anion exchange took place to give PdCl(OTf)(*i*Pr-SPRIX) as the active catalyst.



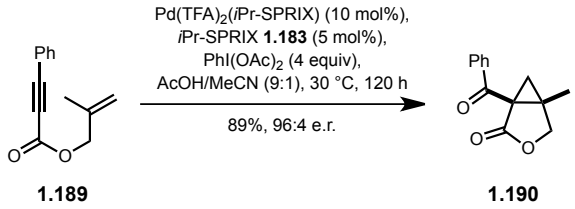
Scheme 1.44: Enantioselective intramolecular Pd-catalysed vicinal oxidation of alkene 1.182

Simultaneously and independently, Tse[72] and Sanford[73] reported a domino reaction of 1,6-enynes proceeding *via* a Pd(II)–Pd(IV) pathway and resulting in the formation of two new C–C bonds and one C=O bond (Scheme 1.45). These reactions are initiated by oxypalladation of the alkyne followed by intramolecular cyclisation. The Pd(II) intermediate is oxidised to Pd(IV), circumventing β-hydride elimination, and undergoes cyclopropanation to give bicyclo[3.1.0]hexanes such as **1.186** and **1.188**. The conditions reported by these groups were similar and scope included variation of the alkyne substitution and the heteroatom tether. Additionally, Sanford *et al*. reported the cyclisation of a number of 1,1- and 1,2-disubstituted alkene examples **1.187**.



Scheme 1.45: Pd-catalysed cyclisation–oxidation of 1,6-enynes 1.185 and 1.187

Sasai and co-workers reported the first example of enantioselective Pd(II)–Pd(IV) catalysis using a Pd(II) catalyst preformed from $Pd(TFA)_2$ and *i*Pr-SPRIX **1.183**, with additional *i*Pr-SPRIX **1.183** added to suppress a background reaction (Scheme 1.46). This catalytic system conferred excellent enantioselectivity in the cyclisation of 1,6-enynes to form bicyclo[3.1.0]hexanes.[74] In applying the *i*Pr-SPRIX **1.183** ligand to a range of oxidative palladium-catalysed reactions, detailed throughout this review, the Sasai group have highlighted the remarkable stability of this ligand to oxidative and acidic conditions.



Scheme 1.46: Enantioselective Pd-catalysed cyclisation–oxidation of 1,6-enyne 1.189

As has been demonstrated through the examples given in this review, transformations involving Pd(IV) intermediates represent a powerful method for the construction of heterocyclic species. Importantly, there are examples where Pd(IV) intermediates have been isolated or implicated as a result of oxidative addition of alkyl halides to Pd(II) complexes or intermediates. C–C bond forming reductive elimination to form a new sp^3–sp^3 bond has also been observed and it would constitute a significant advancement if this reactivity could be harnessed in a heterocyclisation reaction.

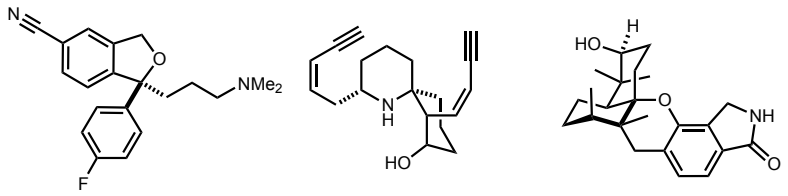
1.5 Summary

Palladium-catalysed alkene functionalisation is an area of research that has seen a recent surge of interest. The literature examples outlined in this chapter demonstrate the variety of methods available to further functionalise Pd(II)-alkyl intermediates resulting from nucleopalladation, providing a wide scope of heterocycles which can be formed using this type of methodology. The construction of multiple bonds in a single process is an attractive goal, reducing waste and the number of synthetic operations required, provided that the sequence of transformations can be controlled. Despite the variety of reported methods to functionalise Pd(II)-alkyl intermediates, the subsequent formation of sp^3–sp^3 C–C bonds is an area which remains challenging and development of reactions of this type would greatly expand the range of products which could be accessed through nucleopalladation chemistry.

2. Synthetic Approaches Towards Heterocyclisation of Unactivated Alkenes

2.1 Introduction and Aims

Heterocycles can be found in a vast array of organic molecules of biological importance, from natural products to pharmaceutical compounds. The examples shown in Figure 2.1 all contain heterocyclic moieties that are α-substituted with a chain of sp^3-hybridised carbons. As described in Chapter 1, new methods of constructing heterocycles that allow for simultaneous functionalisation of the ring with aliphatic side chains would constitute a significant advancement over current methods, which predominantly give rise to functionalisation with sp^2 or sp carbon centres.



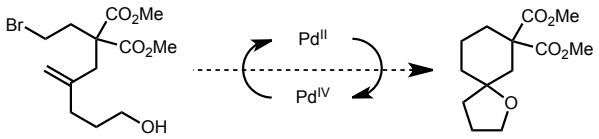
(*S*)-2.1
escitalopram
selective serotonin
reuptake inhibitor

2.2
(–)-histrionicotoxin
nicotinic acetylcholine
receptor inhibitor

2.3
stachyflin
H1N1 influenza
inhibitor

Figure 2.1: Heterocyclic rings in medicinal and natural products

This project initially sought to combine the known affinity of palladium(II) for alkenes with the ability of palladium to undergo oxidative addition with alkyl halides to attain the +4 oxidation state. The proposed reaction (Scheme 2.1) would allow access to spirocycles substituted with a heteroatom at the 2-position from simple alkenes. In addition, the transformation would construct a new bond between two sp^3-hybridised carbon centres, a feat that is difficult in palladium catalysis.[75]

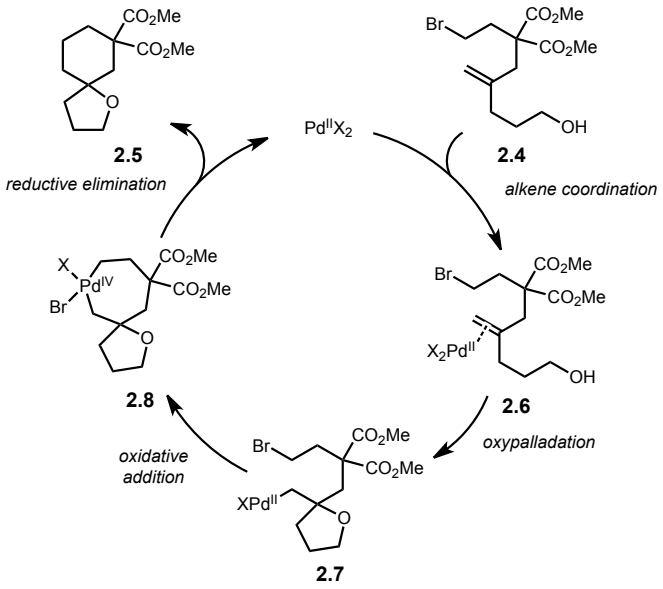


2.4 **2.5**

Scheme 2.1: Proposed Pd-catalysed spirocyclisation

2.1.1 Mechanistic Rationale

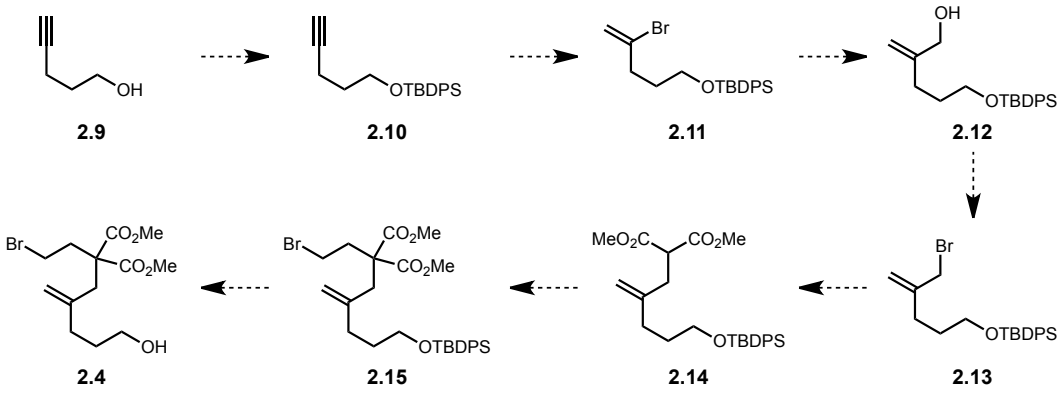
The mechanism for the proposed transformation is shown in Scheme 2.2. The cycle begins with coordination of alkene **2.4** by a palladium(II) species followed by oxypalladation to form heterocycle **2.7** as a σ-alkyl palladium(II) complex. The substrate has been designed such that there are no β-hydrogens available for palladium(II)-alkyl intermediate **2.7** to undergo β-hydride elimination, which would give rise to Wacker-type products. The subsequent oxidative addition should be favoured by the intramolecular nature of the pendant alkyl bromide and by the entropic advantage arising from the *gem*-diester functionality.[76] Thus, oxidative addition of the alkyl bromide would afford Pd(IV) palladacycle **2.8** which should readily undergo reductive elimination to give rise to desired spirocycle **2.5** and regenerate palladium(II).



Scheme 2.2: Proposed mechanism for spirocyclisation

2.1.2 Substrate Design and Synthesis

The synthetic route to **2.4**, the substrate designed to test the heterocyclisation–oxidative addition reaction, is based on a literature route to allylic bromide **2.13** from commercially available 4-pentynol **2.9**, reported by Pattenden and co-workers as an intermediate towards the synthesis of taxanes (Scheme 2.3).[77] Monoalkylation of dimethyl malonate with allylic bromide **2.13** to give **2.14**, followed by a second alkylation with 1,2-dibromoethane, should afford **2.15**. Deprotection of the silyl group should afford bromoalcohol **2.4**.



2.9 **2.10** **2.11** **2.12** **2.13** **2.14** **2.15** **2.4**

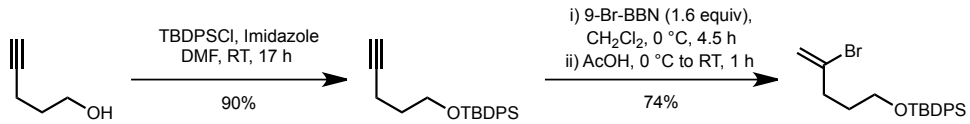
Scheme 2.3: Proposed synthesis of bromoalcohol 2.4

2.2 Attempted Pd(II)–Pd(IV) Catalysed Heterocyclisation

2.2.1 Attempted Heterocyclisation Using Bromoalcohol

Synthesis of Bromoalcohol

The initial work towards the development of a palladium-catalysed heterocyclisation involving a palladium(IV) intermediate began with the synthesis of bromoalcohol **2.4**. Using the Corey protocol,[78] 4-pentynol **2.9** was protected using *tert*-butyldiphenylsilyl chloride and imidazole in DMF to afford protected alcohol **2.10** in 90% yield (Scheme 2.4). Hydrobromination of **2.10** was achieved by treatment of the alkyne with 9-bromo-9-borabicyclo[2.2.2]nonane (9-Br-BBN) followed by protonolysis with acetic acid (Scheme 2.4). Following the procedure reported by Banwell and co-workers,[79] treatment of alkyne **2.10** with 1.2 equivalents of 9-Br-BBN afforded vinyl bromide **2.11** but with incomplete conversion observed. Additionally, the product proved to be difficult to separate from unreacted starting material. Increasing the number of equivalents to 1.4 with a further 0.2 equivalents added after 3.5 h allowed **2.11** to be isolated in a yield of 74%.

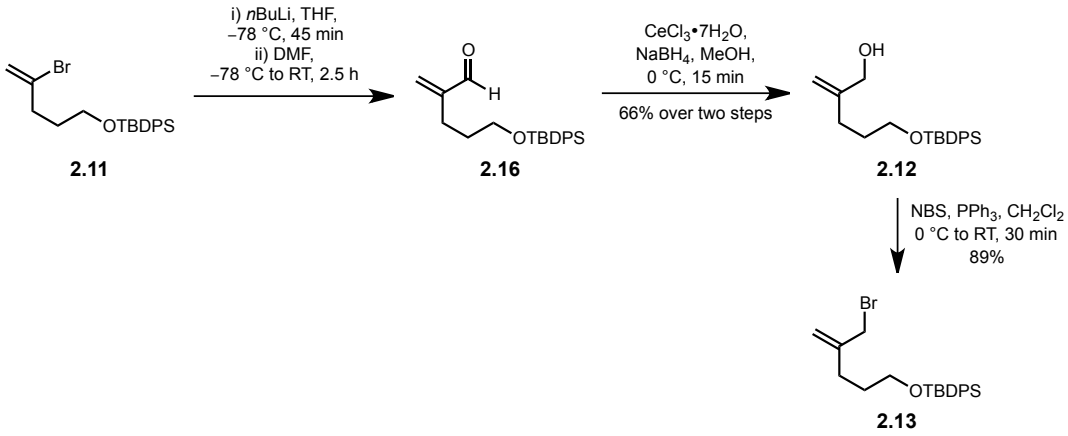


2.9 **2.10** **2.11**

Scheme 2.4: Synthesis of vinyl bromide 2.11

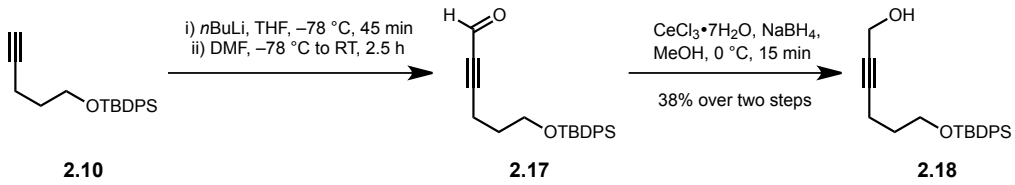
Pattenden and co-workers reported the transformation of vinyl bromide **2.11** to aldehyde **2.16** by lithium–halogen exchange using *t*BuLi in Et_2O at –110 °C, followed by quench with DMF. However, use of *n*BuLi in THF at –78 °C was found to be sufficient to carry out this lithium–halogen exchange, and quenching with DMF afforded aldehyde **2.16** (Scheme 2.5). The crude aldehyde was reduced using Luche reduction conditions to afford allylic alcohol **2.12** in 66% yield over two steps. Treatment of allylic alcohol **2.12** with

triphenylphosphine and *N*-bromosuccinimide (NBS) at 0 °C in dichloromethane afforded the allylic bromide **2.13** in 89% yield (Scheme 2.5).



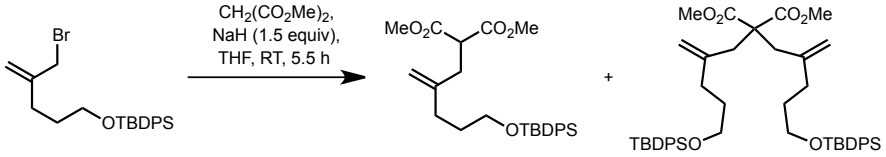
Scheme 2.5: Synthesis of allyl bromide 2.13

The ^{1}H NMR spectrum of the unpurified allylic alcohol **2.12** also indicated the presence of propargyl alcohol **2.18**, which could have been formed by *n*BuLi promoted elimination of HBr from vinyl bromide **2.11** to give alkyne **2.10** (Scheme 2.6). Alkyne **2.10** could then be deprotonated by another equivalent of *n*BuLi and quenched with DMF to form aldehyde **2.17**, which could be reduced under the Luche reduction conditions. The identity of this impurity was confirmed by treatment of alkyne **2.10** under identical conditions, affording propargyl alcohol **2.18** in 38% yield over two steps.



Scheme 2.6: Synthesis of propargyl alcohol 2.18

The monoalkylation of dimethylmalonate with allylic bromide **2.13** proved to be a problematic reaction. Initial attempts to effect the transformation using sodium hydride in DMF afforded the dialkylation product **2.19** (Table 2.1, entry 1). Although lowering the concentration allowed monoalkylated product **2.14** to be obtained preferentially, this result gave variable ratios of mono- to dialkylation (entry 2). It was subsequently found that using an excess of dimethyl malonate (2 equiv) with respect to sodium hydride (1.5 equiv) gave rise to complete conversion to the desired product, with an isolated yield of 70% (entry 3).



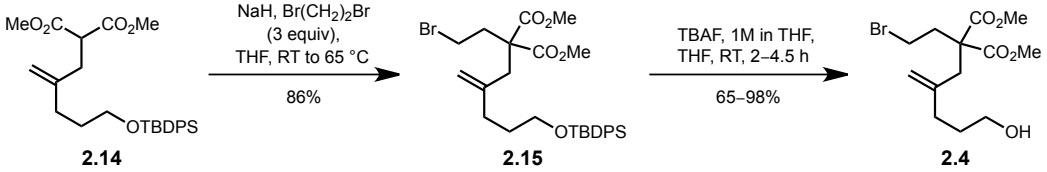
2.13 **2.14** **2.19**

Entry	Malonate (equiv)	Overall conc. [M][a]	Ratio[b] **2.14**	**2.19**	Yield[c] **2.14** (%)
1	1.2	0.1	0	1[d]	0
2	1.2	0.05	variable ratio		64–85
3	2.0	0.05	1	0	70

[a] Concentration of the bromide in the total volume of THF used; [b] Approximate ratio of **2.14** : **2.19** by ^{1}H NMR spectroscopy of unpurified reaction mixture; [c] Isolated yield of pure **2.14**; [d] **2.19** isolated in 80% yield.

Table 2.1: Alkylation of dimethyl malonate with allylic bromide 2.13

Attempts to effect the alkylation of **2.14** with dibromoethane initially suffered from moderate yields (52–67%) due to incomplete conversion of the starting material (Scheme 2.7). However, it was found that carrying out the deprotonation of diester **2.14** at room temperature instead of at 0 °C and increasing the number of equivalents of dibromoethane used from 2 to 3 gave complete conversion and improved the yield of **2.15** to 86%. Deprotection of the TBDPS ether **2.15** to reveal primary alcohol **2.4** was achieved using *tetra*-butylammonium fluoride in THF at room temperature. Yields varied from 65–98%, with longer reaction times giving lower yields. However, no side products were identified as the crude reaction mixtures were concentrated *in vacuo* and subjected directly to flash chromatography.



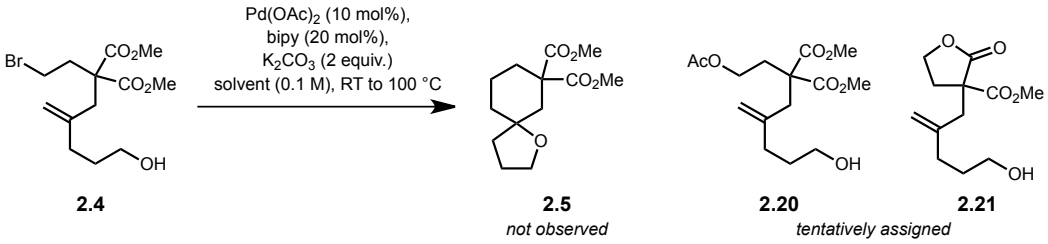
2.14 **2.15** **2.4**

Scheme 2.7: Completion of synthesis of bromoalcohol 2.4

Attempted Heterocyclisation Using Bromoalcohol

With bromoalcohol **2.4** in hand, attempts were made to effect the desired heterocyclisation (Table 2.2). As many of the seminal examples of oxidative addition of alkyl halides to Pd(II) species had made use of chelating nitrogen ligands,[61] investigations began using bipy as a ligand and $Pd(OAc)_2$ as the Pd(II) source. Potassium carbonate was added as a base because this heterocyclisation–oxidative addition, if successful, should produce HBr stoichiometrically. A variety of solvents were investigated with

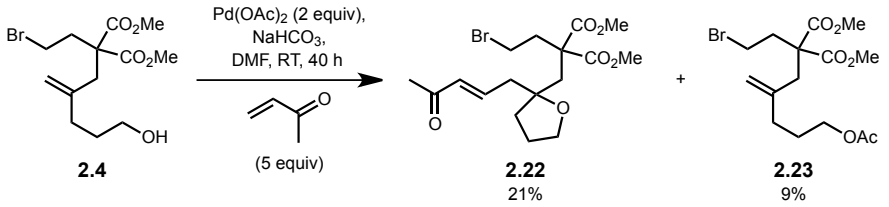
temperatures from ambient to 100 °C, however desired cyclisation product **2.5** was not observed. Non-polar solvents gave unreacted starting material exclusively (Table 2.2, entries 1–2) whereas polar solvents gave a complex mixture of products (entries 3–4). Of these mixtures, only two components could be tentatively identified from ^{1}H NMR and mass spectral analysis: acetate **2.20**, likely formed by nucleophilic displacement of bromide by acetate from the palladium catalyst; and lactone **2.21**, likely formed by base promoted hydrolysis of one of the ester groups followed by intramolecular displacement of bromide to form the lactone.



Entry	Solvent	Temp	Time	Result
1	CH_2Cl_2	RT to 45 °C	23 h	**2.4**
2	Toluene	RT to 80 °C	22 h	**2.4**
3	MeCN	RT to 80 °C	21 h	Complex mixture
4	DMF/DMSO	RT to 100 °C	22 h	Complex mixture

Table 2.2: Attempted heterocyclisation of bromoalcohol 2.4

In order to investigate if bromoalcohol **2.4** was capable of undergoing a heterocyclisation, the material was subjected to the conditions developed by Semmelhack and co-workers,[34] which had induced cyclisation in related systems (Scheme 2.8). This was intended to demonstrate if the problematic step in the heterocyclisation–oxidative addition reaction was the initial oxypalladation or the attempted oxidative addition. Using stoichiometric $Pd(OAc)_2$, $NaHCO_3$ and methyl vinyl ketone in DMF at room temperature, conversion was slow and so an additional equivalent of $Pd(OAc)_2$ was added after 16 h. After stirring for a further 24 h, 21% of expected heterocyclised product **2.22** was isolated. Although a small amount of acetate side product **2.23** was also isolated, the low yield was primarily related to low conversion of the starting material.



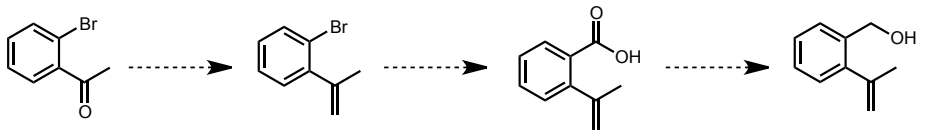
Scheme 2.8: Oxyvinylation of bromoalcohol 2.4

Due to the low conversion observed in the attempted heterocyclisation of bromoalcohol **2.4** under conditions known to be successful for oxypalladation of similar species and the number of steps required to access **2.4**, it was decided to carry out the development of the heterocyclisation–oxidative addition reaction on a simpler and more easily accessible substrate.

2.2.2 Attempted Heterocyclisation Using Benzylic Alcohol

Synthesis of Benzylic Alcohol

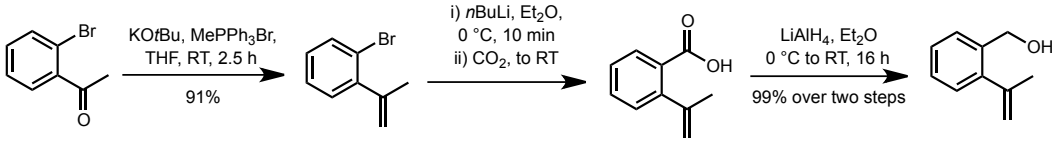
Benzylic alcohol **2.27** (Scheme 2.9), which should be readily prepared in three steps from commercially available *o*-bromoacetophenone, was selected as an alternative substrate to investigate the proposed transformation. Oxypalladation and β-hydride elimination of a similar substrate has been reported by Stoltz and co-workers,[22] suggesting that benzylic alcohol **2.27** should be suited to this investigation. Wittig reaction of *o*-bromoacetophenone **2.24** should give styrene moiety **2.25**. Lithium–halogen exchange, quenching with CO_2, should give benzoic acid **2.26**, which can then be reduced to benzylic alcohol **2.27**.



2.24 **2.25** **2.26** **2.27**

Scheme 2.9: Proposed synthesis of benzylic alcohol 2.27

The first step in the synthesis of benzylic alcohol **2.27** is the Wittig olefination of *o*-bromoacetophenone (Scheme 2.10). Following the procedure of Waser and co-workers,[43] a solution of ketone **2.24** was added to a prepared suspension of methyl triphenylphosphonium bromide and potassium *tert*-butoxide in THF at room temperature, affording alkene **2.25** in 91% yield (Scheme 2.10). Aryl bromide **2.25** underwent lithium–halogen exchange with *n*BuLi in Et_2O, followed by quench with CO_2 to afford carboxylic acid **2.26**. Variable amounts of an unidentified alkyl impurity were found in reactions using 1.2 equivalents of *n*BuLi; however, reducing the number of equivalents to 1.05 was sufficient to obtain clean conversion to **2.26**. The carboxylic acid was reduced with lithium aluminium hydride to afford benzylic alcohol **2.27** in 99% yield over two steps.[22]

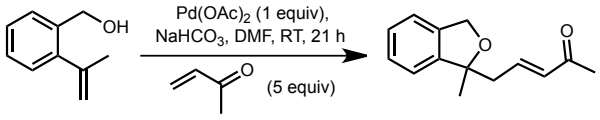


2.24 **2.25** **2.26** **2.27**

Scheme 2.10: Synthesis of benzylic alcohol 2.27

Oxypalladation–Heck of Benzylic Alcohol

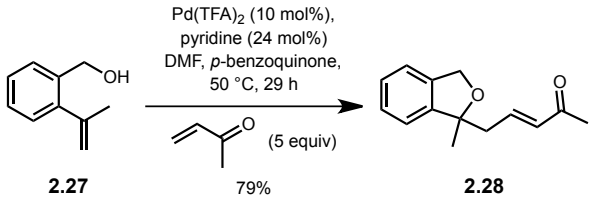
Under Semmelhack's conditions,[34] treatment of benzylic alcohol **2.27** with stoichiometric $Pd(OAc)_2$, $NaHCO_3$ and methyl vinyl ketone in DMF at room temperature for 21 h gave rise to approximately 85% conversion of the starting material with dihydrobenzofuran product **2.28** isolated in a 67% yield (Scheme 2.11).[34] Although incomplete conversion was still observed with this substrate, a greater level of conversion of benzylic alcohol **2.27** than of bromoalcohol **2.4** was observed under these conditions (Section 2.2.1, Scheme 2.8) so **2.27** was considered to be a more suitable substrate for the investigation of the heterocyclisation–oxidative addition. It was postulated that conditions where benzylic alcohol **2.27** could be catalytically converted to dihydrobenzofuran **2.28** could be an appropriate starting point for the development of the desired Pd(II)–Pd(IV) catalysed transformation.



2.27 67% **2.28**

Scheme 2.11: Oxyvinylation of benzylic alcohol 2.27

Wacker-type 5-*exo*-*trig* cyclisations reported in the literature have typically used electron poor catalyst $Pd(TFA)_2$ with a nitrogen-containing ligand and *p*-benzoquinone as a re-oxidant.[22,35] Thus, treatment of benzylic alcohol **2.27** with $Pd(TFA)_2$, pyridine, methyl vinyl ketone and *p*-benzoquinone at 50 °C in DMF afforded the desired product in 79% yield (Scheme 2.12). *p*-Benzoquinone is known to be alkaline sensitive[80] so it was found to be beneficial to carry out the reaction in the absence of an exogenous base.

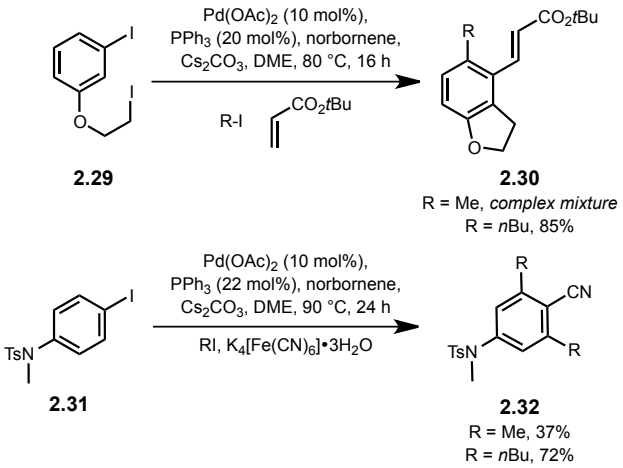


2.27 79% **2.28**

Scheme 2.12: Pd-catalysed oxyvinylation of benzylic alcohol 2.27

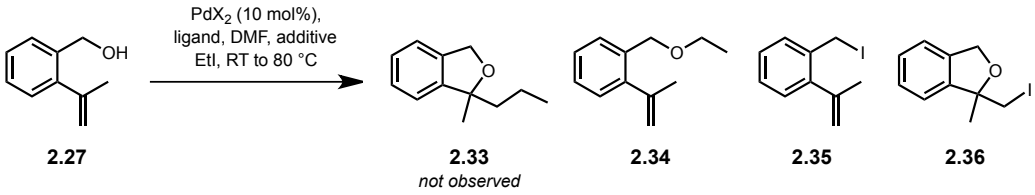
Attempted Oxypalladation–Oxidative Addition of Benzylic Alcohol

In the initial attempts at effecting the desired heterocyclisation–oxidative addition reaction of benzylic alcohol **2.27**, the alkyl halide chosen was ethyl iodide (Table 2.3). Although Canty and co-workers demonstrated oxidative addition of methyl iodide to Pd(II) (Section 1.4, Scheme 1.37), the C–H functionalisation reactions carried out by Catellani *et al*. and subsequently by Lautens *et al*. made use of longer chain alkyl halides, typically butyl iodide (Scheme 2.13). The synthesis of oxacycles **2.30** from substituted phenyl iodides **2.29** proceeded in 85% yield using butyl iodide but afforded a complex mixture of products using methyl iodide.[81] Lautens subsequently reported a single example of the successful use of methyl iodide in the related synthesis of polyfunctionalised aromatic nitrile compounds **2.32**, although use of butyl iodide afforded a significantly higher yield of the desired product (72% *cf*. 37%). The problems encountered upon attempted use of methyl iodide were reported to be due to the high reactivity and volatility of this reagent.



Scheme 2.13: Pd-catalysed ortho dialkylation of aryl iodides 2.29 and 2.31 with alkyl iodides

Replacement of methyl vinyl ketone with ethyl iodide under the conditions shown in Scheme 2.12 afforded a complex mixture of products including ethyl ether **2.34**, iodide **2.35** and iodoetherification product **2.36** (Table 2.3, entry 1). However, despite varying the catalyst (entries 3–4) or ligand (entries 5–6), no conversion to desired product **2.33** was observed. Additives such as $NaHCO_3$ (entry 7) and molecular sieves (entry 8) decreased formation of the side products but the main component from these reactions was unreacted starting material.



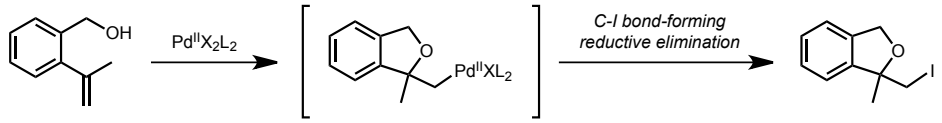
2.27 | **2.33** *not observed* | **2.34** | **2.35** | **2.36**

Entry	PdX_2	Ligand (mol%)	Additive	Time	Result[a]			
					2.27	**2.34**	**2.35**	**2.36**
1	$Pd(TFA)_2$	py (24 mol%)	PBQ	43 h	0	0.5	0.3	0.2
2	$Pd(TFA)_2$	py (24 mol%)	-	67 h	0	0.3	0.5	0.2
3	$Pd(OAc)_2$	py (24 mol%)	-	86 h	0.2	0.4	0.3	0.1
4	$Pd(OAc)_2$	py (24 mol%)	MS 4Å	22 h	1	0	0	0
5	$Pd(TFA)_2$	bipy (12 mol%)	MS 4Å	40 h	0.9	0	0	0.1
6	$Pd(TFA)_2$	phen (12 mol%)	MS 4Å	40 h	1	0	0	0
7	$Pd(TFA)_2$	py (24 mol%)	$NaHCO_3$	59 h	0.6	0.1	0.1	0.2
8	$Pd(TFA)_2$	py (24 mol%)	MS 4Å	62 h	0.6	0.1	0.1	0.2

[a] Approximate ratio of **2.27** : **2.34 : 2.35 : 2.36** by ^{1}H NMR spectroscopy of unpurified reaction mixture

Table 2.3: Attempted heterocyclisation of 2.27 using ethyl iodide trap in DMF

The formation of iodoetherification product **2.36** could arise from an initial oxypalladation of **2.27** to form a palladium(II)-alkyl intermediate (Scheme 2.14). Where X is iodide, carbon–iodine bond-forming reductive elimination, akin to that observed in the carboiodination reactions reported by the Lautens[52,53] and Tong[54] groups, could give rise to the observed product. Iodide ions would be present in the reaction mixture as a result of the formation of **2.34** by alkylation of alcohol **2.27** with ethyl iodide.

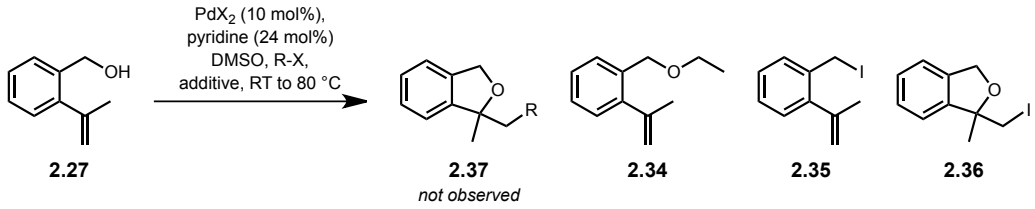


2.27 | **Pd(II)-alkyl intermediate** | **2.36**

Scheme 2.14: Pd-catalysed ortho dialkylation of aryl iodides 2.29 and 2.31 with alkyl iodides

Upon repeating the reaction using $Pd(TFA)_2$, pyridine, *p*-benzoquinone and ethyl iodide using DMSO as a solvent, complete conversion to iodoetherification product **2.36** was observed (Table 2.4, entry 1). Replacing $Pd(TFA)_2$ with $Pd(OAc)_2$ gave the same result (entry 2) and, in the absence of *p*-benzoquinone, **2.36** was still the main product observed (entries 3–4). Use of ethyl triflate or methyl iodide in place of ethyl iodide (entries 5 and 6) gave mostly unreacted starting material, with a small amount of ethyl ether observed using ethyl triflate. Addition of $NaHCO_3$ completely suppressed all side product formation (entry 7). In order to investigate if the formation of iodoetherification product **2.36** was a

Pd-catalysed process, a control reaction was carried out, under otherwise identical conditions to entry 3, but in the absence of $Pd(TFA)_2$. Although **2.36** was still formed under the described conditions (entry 8), conversion was significantly reduced.[82]



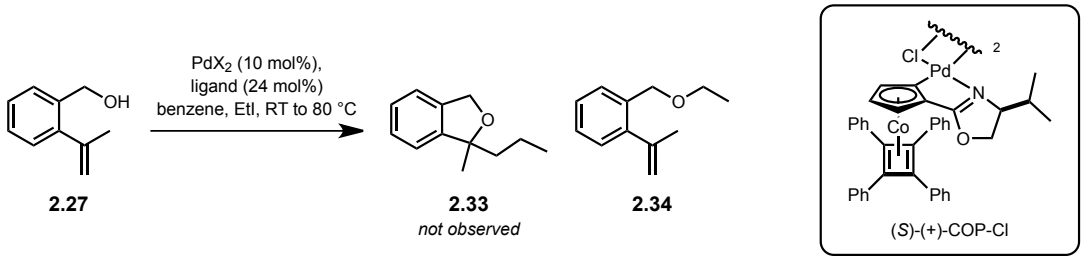
2.27 **2.37** *not observed* **2.34** **2.35** **2.36**

Entry	PdX_2	R-X	Additive	Time	Result[a]			
					2.27	**2.34**	**2.35**	**2.36**
1	$Pd(TFA)_2$	EtI	PBQ	47 h	0	0	0	1 (45%)[b]
2	$Pd(OAc)_2$	EtI	PBQ	41 h	0	0	0	1 (48%)[b]
3	$Pd(TFA)_2$	EtI	-	28 h	0	0	0.2	0.8 (33%)[b]
4	$Pd(OAc)_2$	EtI	-	24 h	0	0	0.2	0.8 (32%)[b]
5	$Pd(TFA)_2$	EtOTf	PBQ	22 h	0.9	0.1	0	0
6	$Pd(TFA)_2$	MeI	-	24 h	1	0	0	0
7	$Pd(TFA)_2$	EtI	$NaHCO_3$	24 h	1	0	0	0
8	-	EtI	-	24 h	0.6	0	0.1	0.3

[a] Approximate ratio of **2.27** : **2.34** : **2.35** : **2.36** by ^{1}H NMR spectroscopy of unpurified reaction mixture; [b] isolated yield of iodoetherification product

Table 2.4: Attempted heterocyclisation of 2.27 using alkyl halide/pseudohalide trap in DMSO

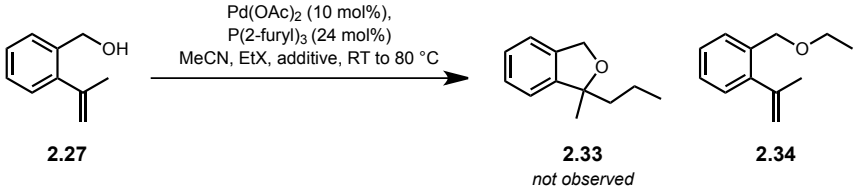
When benzylic alcohol **2.27** was treated with $Pd(TFA)_2$, pyridine and ethyl iodide in benzene, iodoetherification product **2.36** was not observed (Table 2.5, entry 1). However, despite variations in ligand employed (entries 2–3) or inclusion of a base (entry 4), no conversion of starting material was observed. As the examples of alkyl halide oxidative addition to Pd(II) reported by Canty *et al*.[61] and Catellani *et al*.[63] had contained Pd(II) species with two Pd–C bonds, the use of commercially available COP-Cl as the catalyst source was attempted. As this species already contains a Pd–C bond, if this catalyst could promote the oxypalladation step then the Pd(II)-alkyl intermediate would contain two Pd–C bonds. However, use of COP-Cl gave rise to only unreacted starting material (entry 5). It was postulated that addition of a silver salt may facilitate oxidative addition of the ethyl iodide to the Pd(II) species by sequestration of iodide. However, when silver triflate was added to the reaction mixture (entry 6), the sole product observed was the ethyl ether of the starting material. Silver triflate has been used as reagent to promote the etherification of alcohols with alkyl, allyl, benzyl[83] and trityl[84] halides in a non-palladium catalysed process.



Entry	PdX_2	Ligand	Additive	Time	Result
1	$Pd(TFA)_2$	Pyridine	-	24 h	**2.27**
2	$Pd(TFA)_2$	PPh_3	-	44 h	**2.27**
3	$Pd(TFA)_2$	$P(2\text{-furyl})_3$	-	24 h	**2.27**
4	$Pd(TFA)_2$	$P(2\text{-furyl})_3$	K_2CO_3	42 h	**2.27**
5	(*S*)-(+)-COP-Cl	Pyridine	-	44 h	**2.27**
6	$Pd(TFA)_2$	Pyridine	AgOTf	3 h	**2.34**

Table 2.5: Attempted heterocyclisation of 2.27 using ethyl iodide trap in benzene

In their Pd-catalysed synthesis of fused aromatic systems, Lautens and co-workers used a catalyst system based on $Pd(OAc)_2$ and $P(2\text{-furyl})_3$ in acetonitrile.[68] However, when benzylic alcohol **2.27** was treated with this catalyst system in the presence of ethyl iodide, only unreacted starting material was observed (Table 2.6, entry 1). Addition of molecular sieves or potassium carbonate (entries 2–3) also gave unreacted starting material. Where ethyl triflate was used in place of ethyl iodide, desired product **2.33** was not observed, with decomposition of the starting material observed (entry 4). Addition of molecular sieves gave rise to formation of the ethyl ether **2.34** (entry 5) and addition of a base afforded a complex mixture (entry 6).



Entry	EtX	Additive	Time	Result
1	EtI	-	24 h	**2.27**
2	EtI	MS 4Å	24 h	**2.27**
3	EtI	K_2CO_3	24 h	**2.27**
4	EtOTf	-	3 h	decomposition
5	EtOTf	MS 4Å	3 h	**2.34**
6	EtOTf	K_2CO_3	24 h	complex mixture

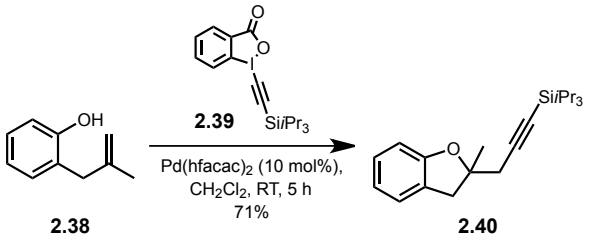
Table 2.6: Heterocyclisation attempts using ethyl iodide or triflate trap in acetonitrile

Although a variety of conditions were employed in the attempted heterocyclisation–alkyl halide trap of benzylic alcohol **2.27**, the desired product was not observed in any reaction attempted. Whilst a large number of the reactions carried out afforded only unreacted starting material, the formation of ethyl ether side product **2.34** and iodoetherification side product **2.36** was also problematic and thus an alternative substrate for investigating this transformation was sought.

2.2.3 Attempted Heterocyclisation Using Phenol

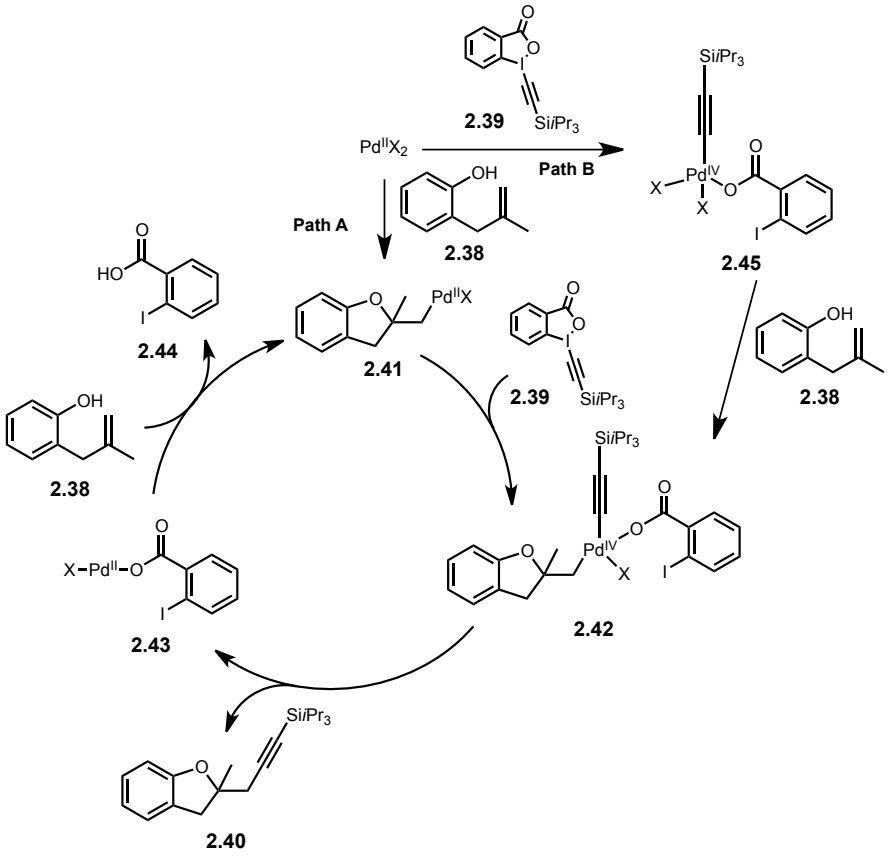
Synthesis and Oxyalkynylation of Phenol

Following the lack of success in effecting the oxypalladation–oxidative addition reaction of benzylic alcohol **2.27**, phenol **2.38** was investigated. As detailed in Chapter 1 (Section 1.1.2, Scheme 1.20), this substrate had demonstrated success in the oxidative functionalisation of alkenes, as reported by Waser *et al*. (Scheme 2.15).[43] Using electrophilic palladium(II) source $Pd(hfacac)_2$, Waser and co-workers reported that phenol **2.38** underwent heterocyclisation followed by trap with TIPS-EBX **2.39** to afford oxyalkynylation product **2.40** in 71% yield.



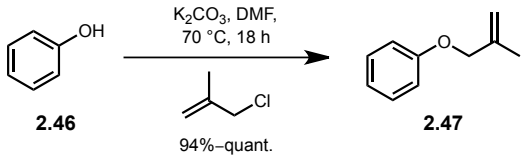
Scheme 2.15: Pd-catalysed oxyalkynylation of 2.38

The oxyalkynylation was proposed to proceed *via* a Pd(IV) intermediate and so **2.38** was considered to be a suitable substrate upon which to carry out further reaction development (Scheme 2.16). The authors suggested that this reaction could proceed *via* two possible mechanisms, where PdX_2 could either: undergo initial alkene coordination and oxypalladation, followed by oxidation of Pd(II)-alkyl intermediate **2.41** to Pd(IV)-alkyl intermediate **2.42** by TIPS-EBX **2.39** (Path A); or be oxidised to Pd(IV) complex **2.45** by TIPS-EBX **2.39** (Path B), followed by alkene coordination and oxypalladation. The authors favoured Path A of their proposed mechanistic options as: oxidation of Pd(II)-alkyl intermediate **2.41** should be easier than oxidation of $Pd^{II}X_2$; electron deficient catalysts proved to be the best for this reaction; and no acceleration of the reaction was observed upon pre-mixing $Pd(hfacac)_2$ and TIPS-EBX **2.39** prior to addition of phenol **2.38**.



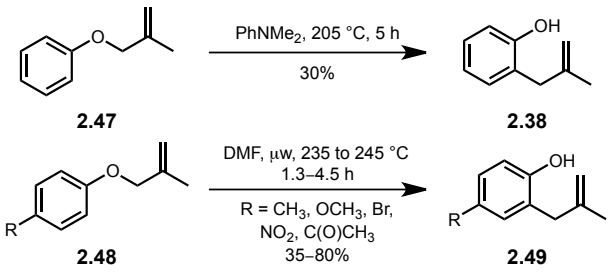
Scheme 2.16: Mechanism of Pd-catalysed oxyalkynylation

Waser and co-workers reported the synthesis of substituted phenol **2.38** in two steps *via* alkylation of phenol **2.46** with 3-chloro-2-methylpropene, followed by a thermal Claisen rearrangement, with a reported yield of ≤41% in the alkylation step by refluxing in acetone.[43] However, according the procedure of Lautens *et al*.,[52] heating at 70 °C in DMF for 18 h, the desired *O*-allyl phenol **2.47** could be afforded in 94% to quantitative yield (Scheme 2.17).



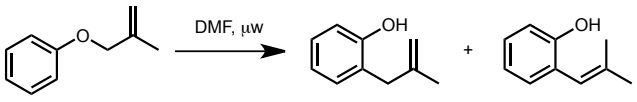
Scheme 2.17: Synthesis of 2.47

Waser and co-workers effected the Claisen rearrangement of *O*-allyl phenol by heating at 205 °C using dimethylaniline for 5 h, giving rearranged product **2.38** in 30% yield (Scheme 2.18). However, the authors used microwave heating for the remaining substituted phenol examples reported in their manuscript.[43] Microwave irradiation allows reactions to be carried out at a higher temperature than the boiling point of the solvent employed and has been shown to accelerate Claisen rearrangements. [85]



Scheme 2.18: Claisen rearrangements of *O*-allyl phenols 2.47 and 2.48

Accordingly, heating *O*-allyl ether **2.47** in DMF at 240 °C using microwave irradiation afforded an 80% yield of the desired rearrangement product after 2.5 h (Table 2.7, entry 1). However, when the Claisen rearrangement was repeated on a larger scale, the instrument recorded high pressures, requiring the reaction to be halted to vent the reaction vessel before further heating. The build up of pressure in these reactions is likely due to decomposition of DMF. The material obtained from this reaction was found to be a 1:0.2 mixture of the desired rearranged product **2.38** and styrene isomer **2.50** (entry 2). Reducing the volume of material charged into the reaction vessel and lowering the reaction temperature to 230 °C suppressed formation of the styrene isomer **2.50** to afford the desired product in excellent yields (entries 3–6).



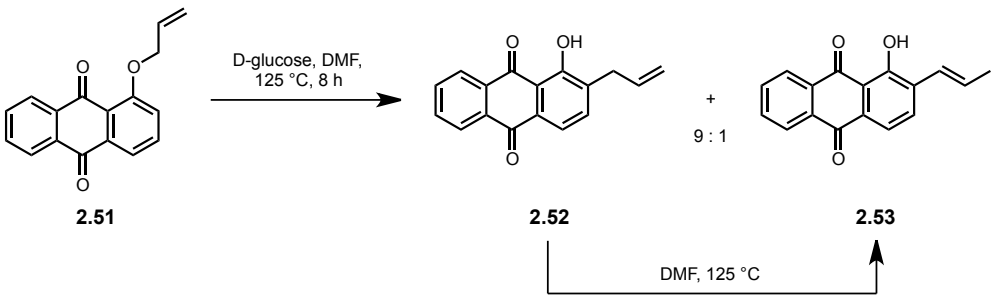
Entry	Solvent Volume	Temp	Time	Ratio [a]			Yield
				2.47	**2.38**	**2.50**	**2.38**
1	6.4 mL	240 °C	2.5 h	0	1	0	80%
2	13 mL	240 °C	0.5 h then 1 h[b]	0	1	0.2	76%
3	6.8 mL	230 °C	2.5 h	0	1	0.03	83%[c]
4	6.8 mL	230 °C	2.5 h	0.1	1	0	
5	5.6 mL	230 °C	2.5 h	0.05	1	0	89%
6	11.2 mL	230 °C	2.5 h	0.04	1	0	92%

[a] Approximate ratio of **2.38** : **2.50** by ^{1}H NMR spectroscopy of unpurified reaction mixture; [b] reaction mixtures exceeded maximum safe pressure on microwave system (22 bar) so were vented then resubjected to heating; [c] material from entries 3 and 4 combined for purification

Table 2.7: Synthesis of phenol 2.38

In the Claisen rearrangement of allyloxy anthraquinones **2.51**, Mal and co-workers found that terminal allyl **2.52** and styrenyl **2.53** products were formed in a 9:1 ratio (Scheme 2.19).[86] When a pure sample of terminal allyl product **2.52** was heated at 125 °C in DMF, styrenyl isomer **2.53** was obtained. This suggested that double bond isomerisation

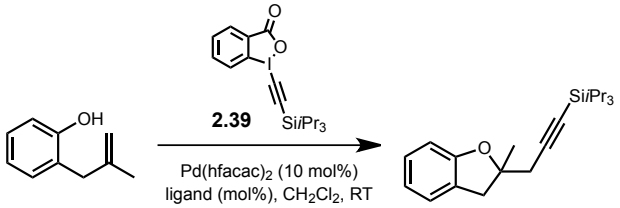
followed completion of the rearrangement reaction. Brower[87] and Walling[88] have both demonstrated that Claisen rearrangements are accelerated by high pressure and so the high pressures recorded during the rearrangement of **2.47** (Table 2.7, entry 2) may have resulted in reaction acceleration and thus greater isomerisation of desired product **2.38** to styrenyl isomer **2.50**.



2.51 **2.52** **2.53**

Scheme 2.19: Claisen rearrangement of allyloxy anthraquinone

Under Waser's conditions,[43] repetition of the oxyalkynylation reaction of phenol **2.38** afforded desired product **2.40** in 76% yield (Table 2.8, entry 1). As it was envisaged that the proposed heterocyclisation–oxidative addition of an alkyl halide may require a ligand and a base to succeed, the tolerance of the oxyalkynylation reaction to the addition of ligands was investigated (Table 2.8). Investigation of these variables would demonstrate the conditions under which oxypalladation of **2.38** definitely occurs. Addition of an excess of 2 equivalents of *N*-methylimidazole,[89] with respect to palladium (Table 2.8, entry 2) gave rise to a sluggish reaction rate and desired product **2.40** was not observed in the case of P(2-furyl)$_3$ (Table 2.8, entry 3).

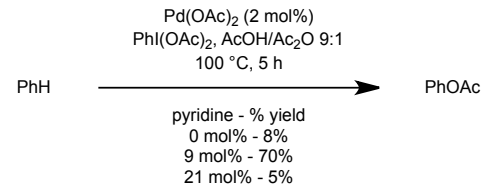


Entry	Ligand	Ligand mol%	Time	Result[a] 2.38	Result[a] 2.40
1	-	-	19 h	0	1 (76%)[b]
2	*N*-methylimidazole	24	19 h	1	1
3	P(2-furyl)$_3$	24	96 h	1	0
4	*N*-methylimidazole	9	5 h	0	1
5	P(2-furyl)$_3$	9	4 h	0	1
6	P*t*Bu$_3$	9	5 h	0	1

[a] Approximate ratio of **2.38** : **2.40** by ^{1}H NMR of unpurified reaction mixture; [b] isolated yield of **2.40**

Table 2.8: Addition of ligands to Pd-catalysed oxyalkynylation of phenol 2.38

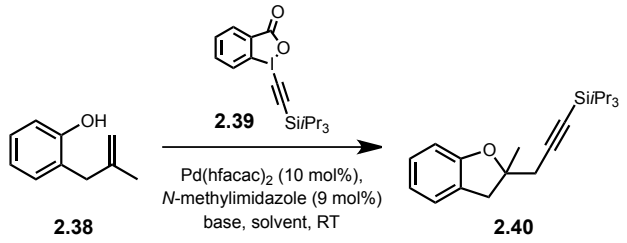
Sanford and co-workers found that the catalyst $Pd(OAc)_2(py)_2$ performed poorly in the Pd(II)–Pd(IV) C–H acetoxylation of benzene when compared with $Pd(OAc)_2$, giving less than 20% conversion to desired product under identical reaction conditions (Scheme 2.20).[90] This was suggested to be due to the lack of vacant coordination sites at the palladium centre. However, reducing the ratio of palladium to pyridine to 1:1 gave a dramatic rate enhancement, with the reaction proceeding to completion 8 times faster than without the ligand present. The optimum palladium/pyridine ratio was found to be 1:0.9. Accordingly, reducing the number of equivalents of *N*-methylimidazole used in the oxyalkynylation of **2.38** to 9 mol% (Table 2.8, entry 4) gave rapid conversion of phenol **2.38** to the heterocyclised product. Using P(2-furyl)$_3$ as a ligand, which had not afforded desired product **2.40** when a 2.4:1 ligand:palladium ratio was used, gave full conversion after 4 h when only 9 mol% was used (Table 2.8, entry 5). P(*t*Bu)$_3$ was also an effective ligand for the oxyalkynylation (Table 2.8, entry 6).



Scheme 2.20: Pd-catalysed acetoxylation of benzene

Although a range of bases could be tolerated in the oxyalkynylation of phenol **2.38** (Table

2.9, entries 1–4), di-*tert*-butylpyridine (dtbpy) (entry 1) and $NaHCO_3$ (entry 2) achieved the greatest conversion of the starting material. The reaction could also be carried out in toluene (entry 5) or acetonitrile (entry 6) but the ^1H NMR spectrum of crude material in these examples showed a number of minor, unidentified, side products.



2.38 **2.40**

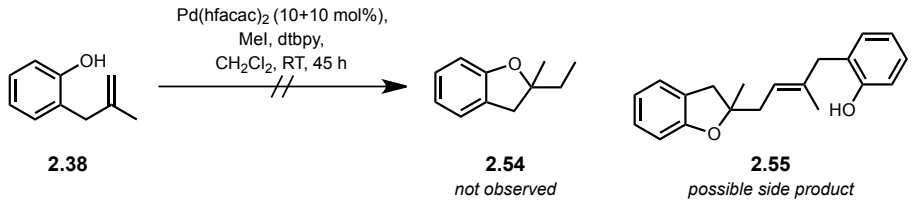
Entry	Base	Solvent	Time	Result[a]	
				2.38	**2.40**
1	dtbpy	CH_2Cl_2	4 h	0	1
2	$NaHCO_3$	CH_2Cl_2	4 h	0	1
3	K_2CO_3	CH_2Cl_2	4 h	0.3	1
4	$NaO_2CC_6H_5$	CH_2Cl_2	4 h	0.4	1
5	-	Toluene	22 h	0	1
6	-	MeCN	16 h	0	1

[a] Approximate ratio of **2.38** : **2.40** based on ^1H NMR spectroscopy of unpurified reaction mixture

Table 2.9: Addition of bases or alternative solvents to Pd-catalysed oxyalkynylation of phenol 2.38

Attempted Oxypalladation–Oxidative Addition of Phenol

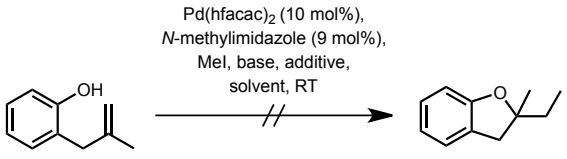
In attempting to effect the oxypalladation–oxidative addition of phenol substrate **2.38**, methyl iodide was chosen in place of ethyl iodide due to its greater reactivity (Scheme 2.21). Treatment of phenol **2.38** with catalytic $Pd(hfacac)_2$, methyl iodide and di-*tert*-butylpyridine in dichloromethane resulted in the formation of a palladium mirror by the time 29 h had elapsed. An additional 10 mol% of $Pd(hfacac)_2$ was added to the reaction mixture; however, desired product **2.54** was not observed after a further 16 h, only unreacted starting material **2.38** and a heterocyclised side product in approximately 9:1 ratio. The heterocyclised side product was tentatively identified as **2.55**, which could potentially be formed by oxypalladation of **2.38** followed by a Heck coupling with another molecule of the starting material. Production of a palladium mirror indicates formation of Pd(0) under these reaction conditions, which would be consistent with oxypalladation–Heck of **2.38** with another molecule of starting material.



2.38 **2.54** *not observed* **2.55** *possible side product*

Scheme 2.21: Attempted heterocyclisation of phenol 2.38 with methyl iodide trap

The successful oxyalkynylation of phenol **2.38** under analogous conditions indicates that Pd(II)-alkyl intermediate **2.41** (Section 2.2.3, Scheme 2.16) is forming; however, the formation of homo-coupled product **2.55** suggests that the Pd(II)-alkyl intermediate is electrophilic. In order to undergo an oxidative addition with methyl iodide, the palladium(II) species must be nucleophilic. In an attempt to increase the nucleophilicity of the Pd(II) species, a range of reactions using *N*-methylimidazole as the ligand were carried out (Table 2.10). However, despite varying the base (entries 1–3), additive (entries 3–4), and reaction temperature, desired product **2.54** was not observed. Starting material remained in all reactions and palladium black was formed in one example (entry 6).



2.38 **2.54** *not observed*

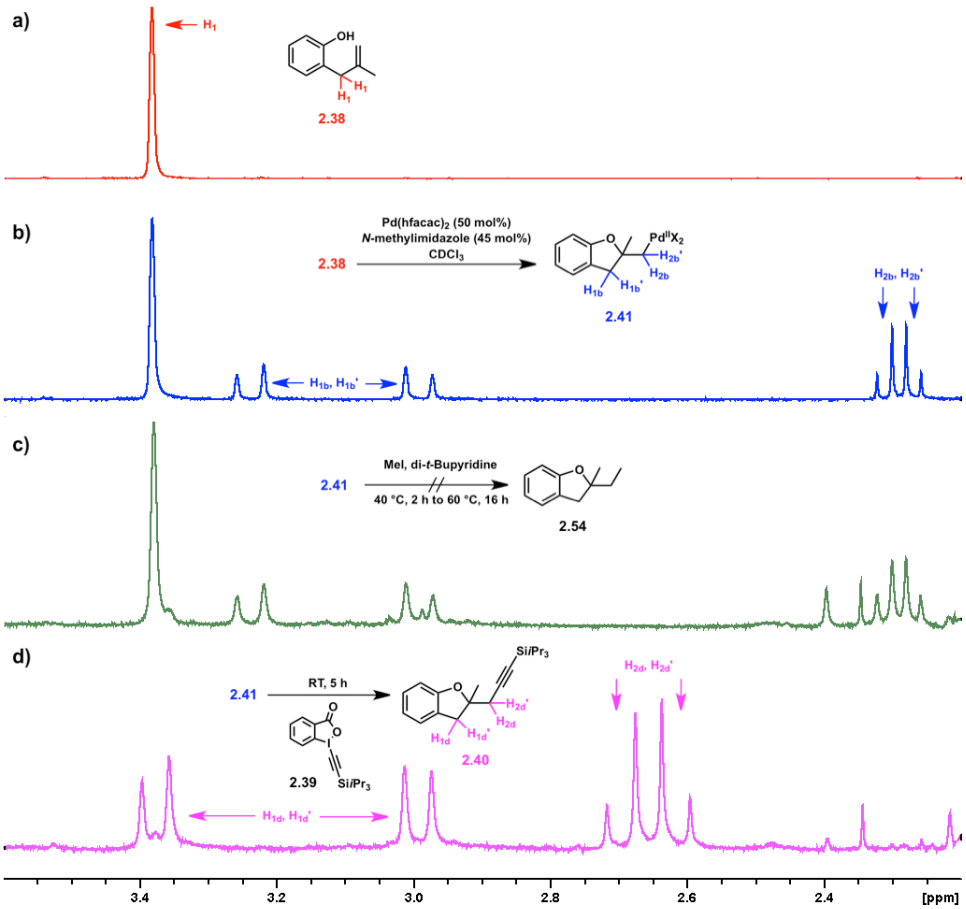
Entry	Base	Additive	Solvent	Temp	Time	Result
1	dtbpy	-	CH_2Cl_2	RT	96 h	**2.38**
2	$NaO_2CC_6H_5$	-	CH_2Cl_2	RT to 45 °C	22 h	**2.38**
3	$NaHCO_3$	LiCl	$CDCl_3$	RT	16 h	**2.38**
4	dtbpy	$AgNO_3$	$CHCl_3$	RT to 60 °C	23 h	**2.38**
5[a]	dtbpy	-	$CDCl_3$	μw 80 °C	1 h	**2.38**
6[a,b]	dtbpy	-	$CDCl_3$	50 °C	18 h	**2.38**

[a] 20% catalyst loading; [b] Reaction precipitated Pd black

Table 2.10: Attempts to heterocyclise phenol 2.38 using alkyl halide trap and *N*-methylimidazole ligand

Conducting reactions in $CDCl_3$ (Table 2.10, entries 3, 5–6) allowed the reactions to be monitored directly by ^{1}H NMR spectroscopy (Figure 2.2). The region from 2.2 to 3.6 ppm in the ^{1}H NMR spectrum of phenol **2.38** in $CDCl_3$ is shown in Figure 2.2a. The signal at 3.4 ppm corresponds to the benzylic position, indicated as H_1. Upon treatment with $Pd(hfacac)_2$ (50 mol%) and *N*-methylimidazole (45 mol%), the ^{1}H NMR spectrum shown in Figure 2.2b was obtained. This spectrum shows the presence of starting material **2.38** was well as signals corresponding to the formation of Pd(II)-alkyl species **2.41**. The

protons H_{1b} and H_{1b}' are diastereotopic and appear as two roofed doublets at 3.2 and 3.0 ppm. Through the course of these studies, this paired doublet signal has been found to be very characteristic for H_{1b} and H_{1b}' in dihydrobenzofuran species. The protons H_{2b} and H_{2b}' are also diastereotopic and appear as two roofed doublets at approximately 2.3 ppm. Upon addition of methyl iodide and di-*tert*-butylpyridine and heating at 40 °C for 2 h then 60 °C for 16 h, the ^{1}H NMR spectrum in Figure 2.2c is obtained. Pd(II)-alkyl species **2.41** is very clearly still present, as is unreacted starting material, but no new heterocyclised components are observed. In order to identify whether the catalytic system was still active after this period, 1.2 equivalents of TIPS-EBX **2.39** was added to the mixture, which was then stirred at room temperature for 5 h to obtain the ^{1}H NMR spectrum in Figure 2.2d. Consumption of starting material **2.38** and Pd(II)-alkyl intermediate **2.41** has occurred to afford the product of oxyalkynylation **2.40**.

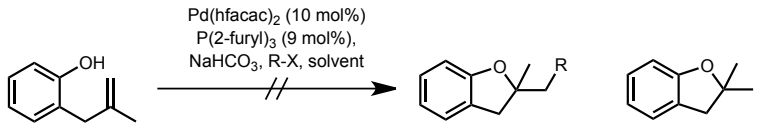


a) ^{1}H NMR spectrum of phenol **2.38**; b) ^{1}H NMR of phenol **2.38** and Pd(II) complex **2.41**; c) ^{1}H NMR spectrum of phenol **2.38** and Pd(II) complex **2.41** after heating with MeI; d) ^{1}H NMR spectrum of oxyalkynylation product **2.40**

Figure 2.2: Monitoring of reaction of 2.38 by ^{1}H NMR spectroscopy, region 2.2–3.6 ppm shown

As *N*-methylimidazole had not proven successful as a ligand in the proposed heterocylisation–oxidative addition of phenol **2.38**, use of P(2-furyl)$_3$ as the ligand was investigated (Table 2.11). However, desired product **2.55** was not observed when

reactions were conducted at room temperature or heated to 60 °C (entries 1 and 2). The heated reaction was monitored by ^{1}H NMR spectroscopy but, although Pd(II)-alkyl intermediate **2.41** was formed, this species persisted even after extended heating with no new heterocyclised moieties observed. Altering the reaction solvent to acetonitrile, as used in many of the Lautens examples,[68] gave rise to precipitation of Pd(0) after 4 h (entry 3). The ^{1}H NMR spectrum of crude material showed only unreacted starting material. Use of ethyl triflate as the trap gave rise to consumption of the starting material after 4 h, along with precipitation of Pd(0), however the ^{1}H NMR spectrum was consistent with the product of protocyclisation **2.56** (entry 4).



2.38 **2.55** *not observed* **2.56**

Entry	R-X	Solvent	Temp	Time	Result
1	MeI	CH_2Cl_2	RT	22 h	**2.38**
2[a]	MeI	$CDCl_3$	RT to 60 °C	72 h	**2.38**
3[b]	MeI	MeCN	RT	4 h	**2.38**
4[b]	EtOTf	CH_2Cl_2	RT	4 h	**2.56**

[a] 50 mol% Pd; [b] Pd black precipitated from reaction

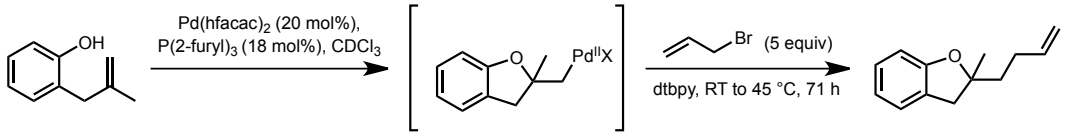
Table 2.11: Attempts to heterocyclise phenol 2.38 using P(2-furyl)$_3$ and alkyl halide/pseudohalide trap

Despite the range of different palladium sources, ligands, bases, solvents and additives employed, the attempted cyclisation of bromoalcohol **2.4** (Section 2.2.1), benzylic alcohol **2.27** (Section 2.2.2) and phenol **2.38** to construct a new C–O and sp^3–sp^3 C–C bond in a single transformation proved ineffective. As it has been demonstrated that these substrates can all undergo the oxypalladation step, it is likely that the problematic step of the heterocyclisation–oxidative addition reaction is the proposed oxidative addition of an alkyl halide to the Pd(II)-alkyl intermediate. As the examples of oxidative addition of an alkyl halide to a Pd(II) species given in Chapter One all featured a Pd(II) species with two carbon ligands[61,63] it could be that a more electron-rich, nucleophilic catalyst than those employed in the reactions detailed above is required for the oxidative addition step. However, it should be noted that the oxypalladation step is initiated by coordination of Lewis acidic palladium to the alkene. As such, for the proposed reaction to be successful, a balance must be sought between an electrophilic palladium(II) species to facilitate the oxypalladation step and a nucleophilic palladium(II) species to undergo the oxidative addition step.

2.3 Oxyallylation of Unactivated Alkenes

2.3.1 Oxyallylation Reaction Development

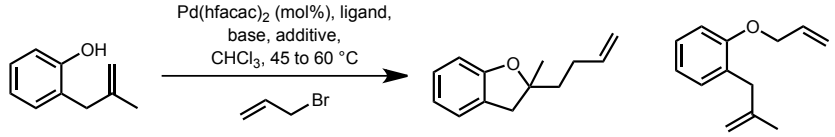
Although the desired heterocyclisation compounds had not been observed thus far, in recognition of the affinity Pd(II) has for alkenes, allyl bromide was employed as a trap (Scheme 2.22). Upon treatment of phenol **2.38** with catalytic $Pd(hfacac)_2$ and $P(2\text{-furyl})_3$ in $CDCl_3$, formation of Pd(II)-alkyl intermediate **2.41** could be observed in the ^1H NMR spectrum. After addition of di-*tert*-butylpyridine and allyl bromide and heating at 45 °C for 5 h, Pd(II)-alkyl intermediate **2.41** was consumed and a new heterocyclised species formed; however, significant starting material still remained. Although starting material still remained after a further 66 h of heating, heterocyclised product **2.57** could be isolated in 22% yield.



2.38 **2.41** **2.57** 22%

Scheme 2.22: Pd-catalysed oxyallylation of phenol 2.38

In intial attempts to optimise the oxyallylation reaction, the effects of ligands, bases and additives were first studied. These reaction mixtures were not purified; conversion was assessed by the ratio of starting material to product. The ^1H NMR spectrum of the crude material obtained from the oxyallylation reaction shown in Scheme 2.22 showed a 1:0.4 ratio of unreacted starting material to desired product (Table 2.12, entry 1). Altering the ligand to *N*-methylimidazole did not afford any further conversion of the starting material (entry 2), however alteration of the base from di-*tert*-butylpyridine to $NaHCO_3$ afforded significant further conversion to the desired product (entry 3). Use of stronger base Cs_2CO_3 gave rise to rapid *O*-allylation to form **2.58** rather than heterocyclisation (entry 5). Addition of a silver salt in an attempt to increase conversion by sequestration of the halide ion suppressed the reactivity in this system (entry 6 *cf*. entry 4). Whilst PPh_3 did not offer any advantage over the use of $P(2\text{-furyl})_3$ (entry 7), use of pyridine gave rise to further conversion (entry 8). The highest levels of conversion were obtained in the absence of a ligand, although this result produced variable ratios of starting material **2.38** to product **2.57** (entry 9).



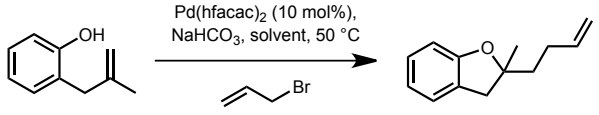
2.38 **2.57** **2.58**

Entry	Pd (mol%)	Ligand[a]	Base	Additive	Time	Result[c] **2.38**	Result[c] **2.57**
1[b]	20	P(2-furyl)$_3$	dtbpy	-	71 h	1	0.4
2[b]	20	*N*-methylimidazole	dtbpy	-	71 h	1	0.3
3	20	P(2-furyl)$_3$	$NaHCO_3$	-	72 h	1	1.7
4	10	P(2-furyl)$_3$	$NaHCO_3$	-	48 h	1	0.4
5	10	P(2-furyl)$_3$	Cs_2CO_3	-	2 h	0	0[d]
6	10	P(2-furyl)$_3$	$NaHCO_3$	$AgNO_3$	48 h	1	0.1
7	10	PPh_3	$NaHCO_3$	-	46 h	1	0.2
8	10	pyridine	$NaHCO_3$	-	46 h	1	0.7
9	10	-	$NaHCO_3$	-	21 h	variable ratio	

[a] Ligand loadings were 0.9 equivalents with respect to Pd; [b] reaction carried out in $CDCl_3$; [c] Approximate ratio of **2.38** : **2.57** based on ^{1}H NMR spectroscopy of unpurified reaction mixture; [d] complete conversion to **2.58**

Table 2.12: Optimisation of ligands and bases in oxyallylation of 2.38

In order to further optimise the oxyallylation reaction, the solvent employed was investigated (Table 2.13). Altering the solvent to DCE (entry 2) gave rise to lower conversion than $CHCl_3$ (entry 1), as did coordinating solvents such as THF, TBME and MeCN (entries 3–5). The lower conversion observed with coordinating solvents is consistent with the detrimental effect of exogenous ligands. However, non-polar solvents such as hexane and toluene gave rise to complete conversion of the starting material, with the desired product obtained in good yield (entries 6 and 7).



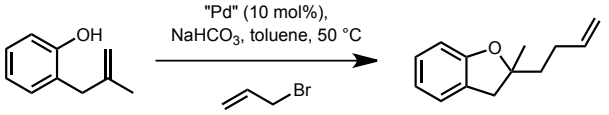
2.38 **2.57**

Entry	Solvent	Time	Result[a]	
			2.38	**2.57**
1	$CHCl_3$	16 h	1.3	1
2	DCE	96 h	2.5	1
3	THF	72 h	2	1
4	TBME	72 h	2	1
5	MeCN	18 h	5	1
6	hexane	8 h	0	1 (70%)
7	toluene	16 h	0	1 (69%)

[a] Approximate ratio of **2.38** : **2.57** based on ^{1}H NMR spectroscopy of unpurified reaction mixture

Table 2.13: Optimisation of solvents in oxyallylation of 2.38

Although $Pd(hfacac)_2$ is commercially available, it is more expensive per mmol than some of the other more commonly used palladium catalysts and so a screen of palladium sources was conducted (Table 2.14). $Pd(OAc)_2$ afforded only low levels of conversion to desired product **2.57**, as did $Pd(acac)_2$ (entries 2–3), which may suggest that a more electrophilic palladium catalyst source gives improved conversion; however, $Pd(TFA)_2$ gave no conversion of **2.38** (entry 4). $PdCl_2$ gave moderate to good conversion to heterocyclised product **2.57**, albeit with unreacted starting material still observed after 28 hours (entry 5). Pd(0) source Pd_2dba_3 was also employed in the oxyallylation reaction but gave only unreacted starting material **2.38** (entry 6). This is particularly noteworthy as it suggests that a Pd(0)–Pd(II) catalytic cycle may not be operating under these conditions.



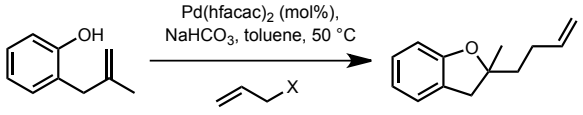
2.38 **2.57**

Entry	"Pd"	Time	Result[a]	
			2.38	**2.57**
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 **2.38** : **2.57** based on ^{1}H NMR spectroscopy of unpurified reaction mixture

Table 2.14: Optimisation of Pd-catalyst source in oxyallylation of 2.38

With the optimal solvent and palladium catalyst in hand, the catalyst loading and the identity of the allyl species were subsequently investigated (Table 2.15). Reducing the loading of $Pd(hfacac)_2$ from 10 mol% to 5 mol% (entry 1 *cf*. entry 2) gave rise to a large reduction in conversion. Under these conditions, the oxyallylation may be proceeding sufficiently slowly for a catalyst deactivation pathway to become more favourable. In fact, when an additional 5 mol% catalyst is added to the reaction mixture after 2 h, the transformation proceeds sufficiently well to afford almost complete conversion of the starting material after a further 20 h (entry 3). Use of allyl chloride as the electrophile gave rise to complete conversion of the starting material after only 6 h (entry 4) and the catalyst loading could be successfully reduced to 5 mol% to give full conversion of **2.38** after slightly longer reaction time (entry 5). Other allyl electrophiles such as allyl iodide, allyl acetate and allyl benzoate gave little to no conversion of starting material (entries 6–8).



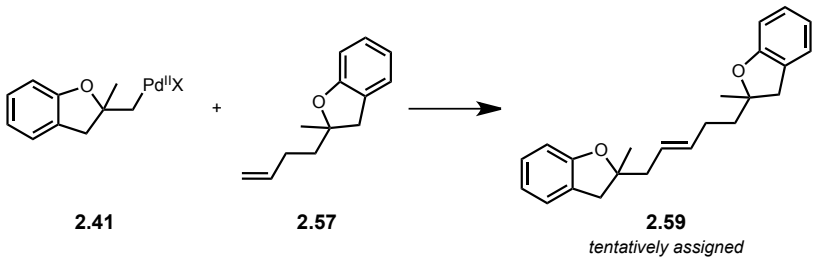
2.38 **2.57**

Entry	Pd mol%	X	Time	Result[a] **2.38**	**2.57**
1	10	Br	16 h	0	1
2	5	Br	26 h	1	0.3
3	5+5	Br	22 h	0.1	1
4	10	Cl	6 h	0	1
5	5	Cl	15 h	0	1
6	10	I	18 h	1	0.2
7	10	OAc	18 h	1	0
8	10	OBz	18 h	1	0

[a] Approximate ratio of **2.38** : **2.57** based on ^{1}H NMR spectroscopy of unpurified reaction mixture;

Table 2.15: Optimisation of Pd-catalyst loading and allyl electrophile in oxyallylation of 2.38

The main identifiable side product from the oxyallylation reaction was pseudo-dimer **2.59**, which could be separated from the desired product by flash chromatography, but could not be obtained in sufficient purity and quantity for full characterisation (Scheme 2.23). This compound is believed to have formed by a Heck reaction of Pd(II)-alkyl intermediate **2.41** with heterocyclisation product **2.57**.

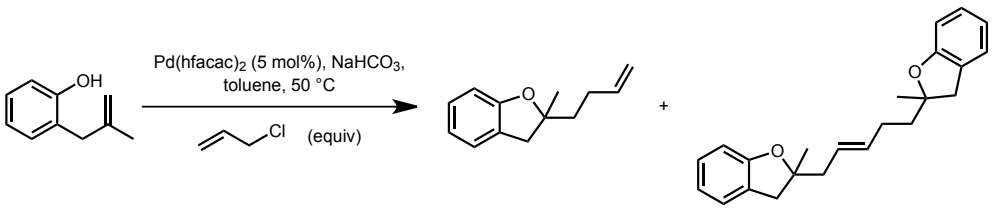


2.41 **2.57** **2.59**
tentatively assigned

Scheme 2.23: Formation of pseudo-dimer side product 2.59

If Pd(II)-alkyl intermediate **2.41** can coordinate either the alkene in the product or that in allyl chloride, then variation of the reaction concentration or the number of equivalents of allyl chloride may result in variation of the ratio of desired product **2.57** to side product **2.59**. Under the standard reaction conditions, using 5 equivalents of allyl chloride in 0.25 M toluene, the reaction proceeded to full conversion after 16 h to give a 1:0.2 mixture of **2.57** to **2.59** (Table 2.16, entry 1), corresponding to a 70% isolated yield of the desired product. Reducing the reaction concentration to 0.06 M improved the ratio of **2.57** to **2.59** to 1:0.1, but the reaction did not go to completion (entry 2). Increasing the concentration of the reaction mixture to 1 M did not give rise to a change in the ratio of **2.57** to **2.59**

(entry 3). Upon reducing the number of equivalents of allyl chloride to 1.2, a small increase in the amount of side product **2.59** formed was observed and the reaction did not go to completion (entry 4). However, increasing the number of equivalents of allyl chloride to 10 equivalents improved the ratio of **2.57** to **2.59** and afforded an isolated yield of **2.57** of 80% (entry 5). Use of 20 equivalents, whilst improving the ratio of **2.57** to **2.59** further, gave rise to only a small increase in isolated yield (entry 6).



2.38 **2.57** **2.59**

Entry	Conc.	Equiv Cl	Time	Result[a]			Yield[b]
				2.38	**2.57**	**2.59**	**2.57**
1	0.25 M	5	16 h	0	1	0.2	70%
2	0.06 M	5	18 h	1.8	1	0.1	-
3	1 M	5	18 h	0	1	0.2	-
4	0.25 M	1.2	40 h	1.8	1	0.3	-
5	0.25 M	10	16 h	0	1	0.1	80%
6	0.25 M	20	16 h	0	1	0.05	82%

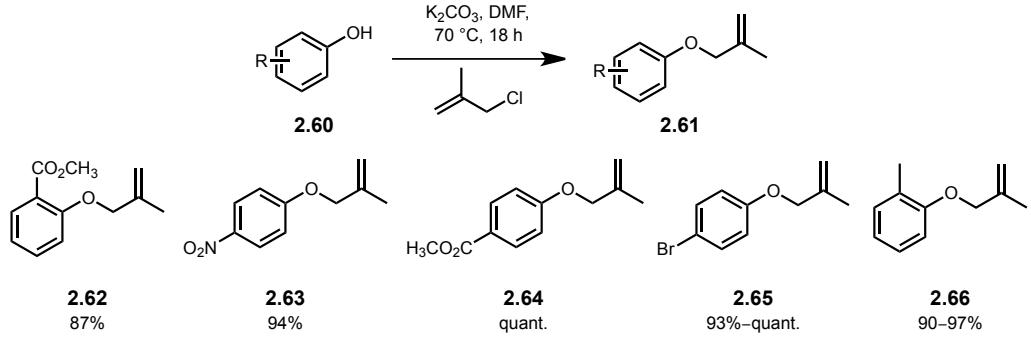
[a] Approximate ratio of **2.38** : **2.57** : **2.59** based on ^{1}H NMR spectroscopy of unpurified reaction mixture; [b] Isolated yield of **2.57**

Table 2.16: Effect of concentration and equivalents of allyl chloride on formation of side product 2.59

2.3.2 Substrate Scope: Phenols

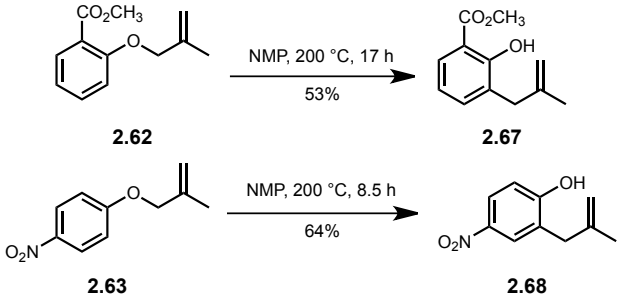
Synthesis of Substrates

With optimised conditions to effect the oxyallylation reaction of phenol **2.38** in hand, the scope of the reaction was subsequently investigated, beginning with the synthesis of a range of substituted phenol substrates. These substrates could be accessed *via* alkylation of the corresponding phenols, followed by a Claisen rearrangement. The alkylation reactions proceeded using K_2CO_3 and 3-chloro-2-methylpropene in DMF at 70 °C in generally excellent yields to afford the *O*-allylphenols **2.62**–**2.66** (Scheme 2.24).



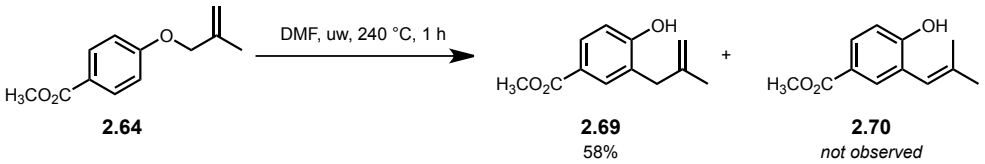
Scheme 2.24: Alkylation of phenols 2.60

Phenol substrates containing an *o*-ester or *p*-nitro group underwent a thermal Claisen rearrangement by heating at 200 °C in NMP to afford phenols **2.67** and **2.68** in 53% and 64% yields, respectively (Scheme 2.25). The remainder of the material was accounted for by unreacted allyl ether.



Scheme 2.25: Claisen rearrangements of *O*-allylphenols 2.62 and 2.63

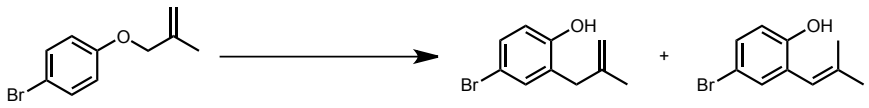
Attempts to effect the rearrangement of *p*-ester substrate **2.64** by conventional heating gave rise to inseparable mixtures of desired product **2.69** and isomerised product **2.70**, despite variations in solvent and temperature. However, by recourse to microwave heating at 240 °C in DMF, clean conversion to substrate **2.69** could be afforded, albeit in a moderate yield of 58% due to partial conversion of the starting material (Scheme 2.26).



Scheme 2.26: Claisen rearrangement of *O*-allyphenol 2.64

Subjecting *p*-bromo substrate **2.65** to conventional heating at 200 °C in NMP resulted in decomposition, with desired product **2.71** not observed (Table 2.17, entry 1). When subjected to microwave irradiation at 245 °C in DMF for 1h 20 minutes, the conditions reported by Waser and co-workers,[43] a mixture of desired product **2.71** and isomerised product **2.72** was obtained (entry 2). Reducing the reaction temperature to 220 °C did not

suppress formation of side product **2.72** (entry 3); however, reducing the reaction time to afford partial conversion of **2.65** gave rise to clean product **2.71** in 70% yield (entry 4).



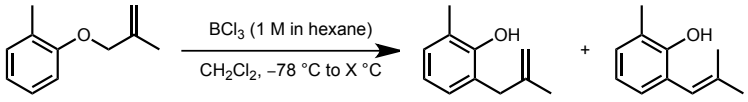
2.65 **2.71** **2.72**

Entry	Heating	Solvent	Temp	Time	Result[a]		
					2.65	**2.71**	**2.72**
1	Conventional	NMP	200 °C	24 h	decomposition		
2	Microwave	DMF	245 °C	1.3 h	0	1	0.3
3	Microwave	DMF	220 °C	2 h	0	1	0.1
4	Microwave	DMF	240 °C	0.5 h	0.3	1 (70%)	0

[a] Approximate ratio of **2.65** : **2.71** : **2.72** based on ^{1}H NMR spectroscopy of unpurified reaction mixture

Table 2.17: Claisen rearrangements of *O*-allylphenol 2.65

The formation of *o*-methyl substrate **2.73** proved to be the most difficult, with conventional heating and microwave heating both affording mixtures of desired product **2.73** and isomerised product **2.74**. However, a Lewis acid-catalysed Claisen rearrangement by BCl_3[91] in CH_2Cl_2 from −78 °C to room temperature afforded desired product **2.73**, containing less than 3% of isomerised side product **2.74** (Table 2.18, entry 1). Maintaining the reaction temperature at −78 °C gave rise to clean product, but poor conversion of the starting material (entry 2). Allowing the reaction mixture to slowly warm to −20 °C prior to quenching afforded a good yield of pure desired product **2.73** (entry 3), although a more prolonged reaction time afforded a lower yield (entry 4).



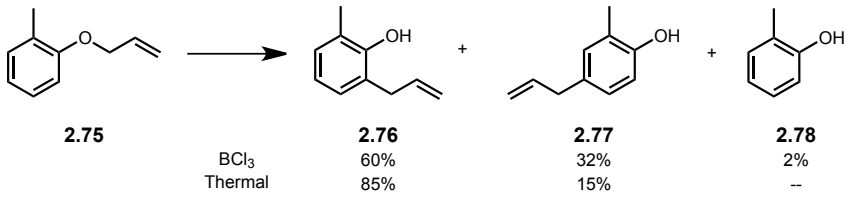
2.66 **2.73** **2.74**

Entry	X °C	Time	Result[a]			Yield[b]
			2.66	**2.73**	**2.74**	**2.73**
1	RT	3.5 h	0	1	0.03	49%
2	−78 °C	6.5 h	1	1	0	-
3	−20 °C	2 h	0	1	0	60%
4	−20 °C	5 h	0	1	0	48%

[a] Approximate ratio of **2.65** : **2.71** : **2.72** based on ^{1}H NMR spectroscopy of unpurified reaction mixture; [b] isolated yield of **2.73**

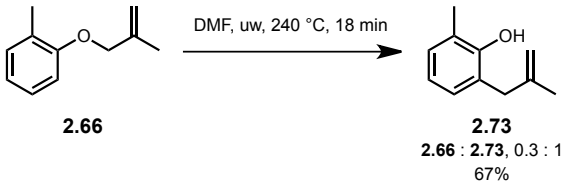
Table 2.18: BCl_3-catalysed Claisen rearrangement of *O*-allylphenol 2.66

Schmid and co-workers reported that the Claisen rearrangements of substrates with an *ortho* substituent formed substantial amounts of *para*-substituted products, consistent with a [3,3]-shift (Scheme 2.27).[92,93] This effect was found to be more pronounced when the Claisen rearrangements were carried out using BCl_3-catalysis. These observations could account for the lower yields of **2.73** observed on prolonged reaction times (Table 2.18, entry 4 *cf*. entry 3).



Scheme 2.27: Claisen rearrangement of *o*-substituted *O*-allylphenol 2.75

In accordance with the observations made during the synthesis of *p*-bromo phenol **2.71**, it was found that *o*-methyl substrate **2.73** could be successfully obtained by microwave heating in DMF by reducing the reaction time to that which gives incomplete conversion of starting material (Scheme 2.28). Thus, after 18 minutes at 240 °C, approximately 75% conversion of **2.66** was achieved, allowing phenol **2.73** to be isolated pure in 67% yield.

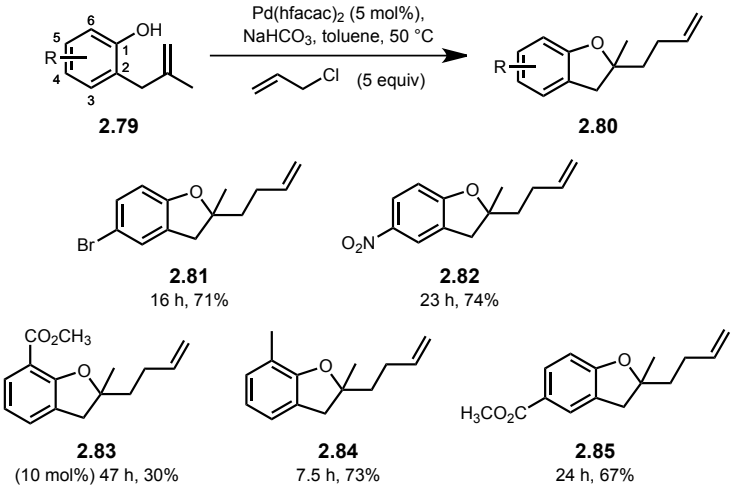


Scheme 2.28: Microwave Claisen rearrangement of *O*-allyphenol 2.66

Cyclisation of Substrates

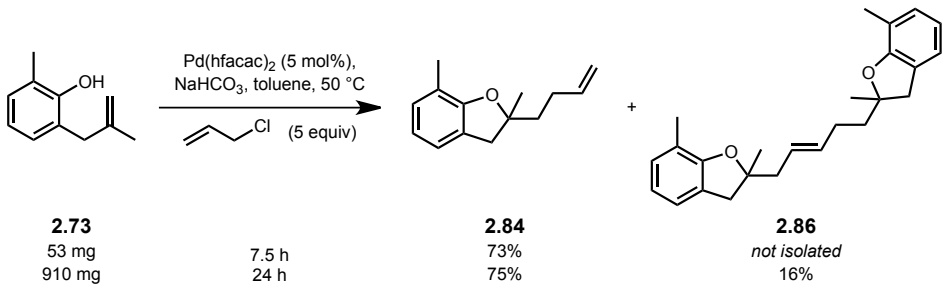
The phenol substrates prepared were treated with 5 mol% $Pd(hfacac)_2$, $NaHCO_3$ and 5 equivalents of allyl chloride in toluene at 50 °C (Scheme 2.29). Thus *p*-bromo and *p*-nitro substituted phenol substrates **2.71** (Table 2.17) and **2.68** (Scheme 2.25) afforded good yields of the dihydrobenzofuran products **2.81** and **2.82**. It is particularly noteworthy that an aryl bromide is tolerated in the oxyallylation reaction – suggesting that Pd(0) may not be an intermediate in this catalytic process. In addition to this, an aryl bromide could function as a handle for a range of orthogonal palladium-catalysed processes. The *o*-ester substrate **2.67** (Scheme 2.25) showed poor conversion after 23 h and so an additional 5 mol% $Pd(hfacac)_2$ was added to the reaction mixture and heating continued for a further 24 h. After this time, significant starting material still remained and desired product **2.83** was obtained in only 30% yield (74% based on recovered starting material). However,

o-methyl substrate **2.73** (Table 2.18) gave clean conversion to desired product **2.84** in 73% yield after 7.5 h, indicating that *ortho* substitution is tolerated. In addition, *p*-ester substrate **2.69** (Scheme 2.26) gave a 67% yield of desired product **2.85** after 24 h, showing that ester functionality is also tolerated. It is possible that the *ortho* substitution of ester substrate **2.67** results in chelation, and thus deactivation, of the palladium catalyst.



Scheme 2.29: Oxyallylation of phenol substrates 2.79

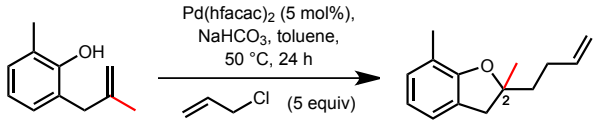
In order to investigate if the oxyallylation reaction could be repeated successfully on larger scale, 910 mg of *o*-methyl substrate **2.73** was treated under the standard conditions with 5 mol% $Pd(hfacac)_2$, $NaHCO_3$ and 5 equivalents of allyl chloride in toluene at 50 °C (Scheme 2.30). Reactions are typically carried out in 1.3 mL of toluene in a 4 mL sealed screw top vial and immersed into a pre-heated metal heating block. As the oxyallylation of **2.73** was scaled approximately 17-fold, a large microwave vial was required contain the reaction mixture. Heating was thus conducted in a pre-heated oil bath. The scaled-up reaction gave a comparable yield, although a prolonged heating period was required for the reaction to attain completion. On this larger scale, pseudo-dimer side product **2.86** could also be isolated in 16% yield and characterised.



Scheme 2.30: Scale up of oxyallylation of 2.73

In order to gain some insight into the progression of the reaction, the conversion of *o*-methyl substrate **2.73** was monitored by ^1H NMR spectroscopy (Scheme 2.31). Small

samples were removed from the reaction mixture at regular time intervals and the aliquots diluted in $CDCl_3$. The conversions recorded are not calibrated to a known standard, but simply represent the ratio of the integration of the ^1H NMR signal corresponding to the methyl substituent of the alkene in **2.73** to the integration of the signal corresponding to 2-Me in product **2.84**.



2.73 **2.84**

Scheme 2.31: Conversion in oxyallylation reaction monitored by ^1H NMR spectroscopy

Figure 2.3 shows a plot of the conversion of **2.73** to **2.84**, where the proportion shown is the division of the integral value by the sum of both integrals. From this plot, it is evident that there is no significant induction period in the oxyallylation of **2.73** and the conversion is fairly constant. That the conversion is fairly constant suggests that the rate of the reaction is independent of the starting material concentration, suggesting that the rate determining step of this transformation is the reaction of the Pd(II)-alkyl intermediate **2.41** with the allyl halide (Scheme 2.22). As the allyl halide is present in a large excess, no significant decrease in conversion is observed as the reaction proceeds.

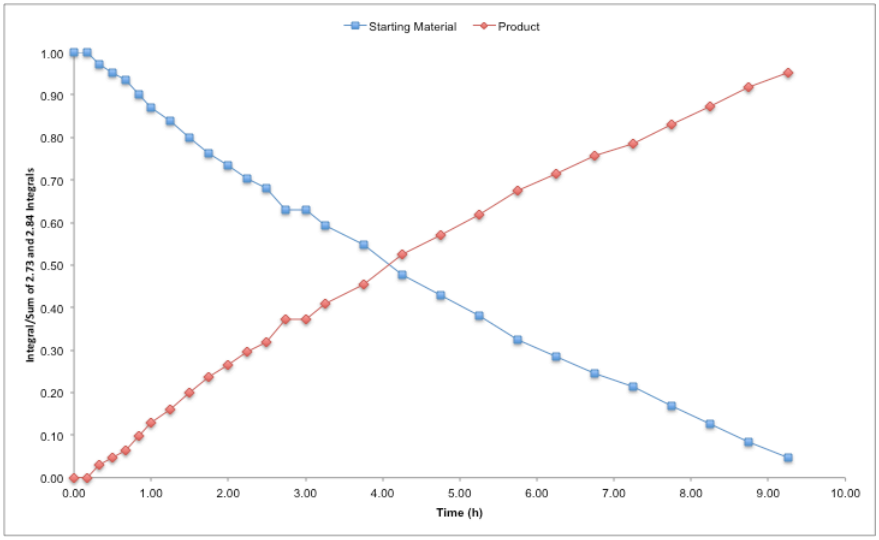
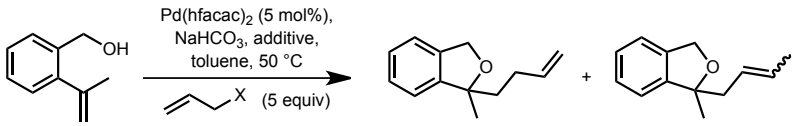


Figure 2.3: Conversion of 2.73 to 2.84 over time

2.3.3 Substrate Scope: Alcohols

Oxyallylation of Benzylic Alcohol

Having demonstrated that the oxyallylation of a range of phenol substrates could be effected, the oxyallylation conditions developed were subsequently applied to non-phenolic alcohols. Treatment of benzylic alcohol **2.27** (Section 2.2.2, Scheme 2.10) under the standard conditions afforded complete conversion of the starting material in 3 h to afford a mixture of desired product **2.87** and a *trans*/*cis* isomeric mixture of internal alkene product **2.88** (Table 2.19, entry 1). Addition of one equivalent of $AgNO_3$ was sufficient to suppress the isomerisation of the terminal alkene into the internal position (entry 2).[94] However, use of allyl bromide in place of allyl chloride, in the absence of exogenous additives, afforded full conversion to the desired product in 77% yield after 6 h, with no isomerisation to **2.88** observed (entry 3).



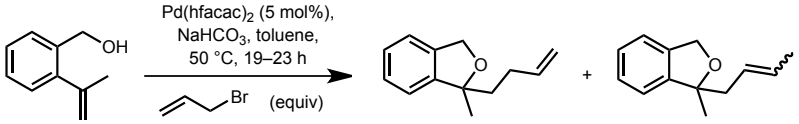
2.27 **2.87** **2.88**

Entry	X	Additive	Time	Ratio[a]		Yield[b]
				2.87	**2.88**	
1	Cl	-	3 h	1	0.5	63%
2	Cl	$AgNO_3$	6 h	1	0	-
3	Br	-	6 h	1	0	77%

[a] Approximate ratio of **2.87** : **2.88** based on ^{1}H NMR spectroscopy of unpurified reaction mixture; [b] total yield of alkene products

Table 2.19: Oxyallylation of 2.27

Although isomerisation of **2.87** was not observed when allyl bromide was employed as the electrophile (Table 2.20, entry 1), upon reducing the number of equivalents of allyl bromide to 3, alkene isomerisation product **2.88** began to be observed (entry 2). Further reduction of the number of equivalents of allyl bromide to 1.2 gave rise to greater formation of alkene isomerisation product **2.88** (entry 3).



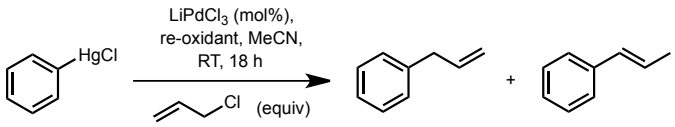
2.27 **2.87** **2.88**

Entry	Equiv Br	Ratio[a]	
		2.87	**2.88**
1	5	1	0
2	3	1	0.3
3	1.2	1	1.1

[a] Approximate ratio of **2.87** : **2.88** based on ^{1}H NMR spectroscopy of unpurified reaction mixture, yields not determined.

Table 2.20: Effect of altering number of equivalents of allyl bromide on formation of 2.88

Heck reported a similar effect in the allylation of arylpalladium salts, prepared *in situ* from arylmercurial salts (Table 2.21).[95] Phenyl mercuric chloride **2.89** was allylated using stoichiometric $LiPdCl_3$ in MeCN with 12 equivalents of allyl chloride to afford complete conversion to terminal olefin product **2.90** (entry 1). However, upon reducing the number of equivalents of allyl chloride to 2, a 1:0.3 mixture of **2.90** to **2.91** was obtained (entry 2). Similarly, using catalytic $LiPdCl_3$ and $CuCl_2$ as a reoxidant, reaction with 4.9 equivalents of allyl chloride afforded clean conversion to terminal alkene **2.90** (entry 3) where 1.2 equivalents gave a small amount of isomerisation to internal alkene **2.91** (entry 4). In the presence of an increased concentration of allyl chloride, the extent to which palladium coordinates the product olefin would be expected to be decreased, which should correspondingly result in a lesser degree of alkene isomerisation.



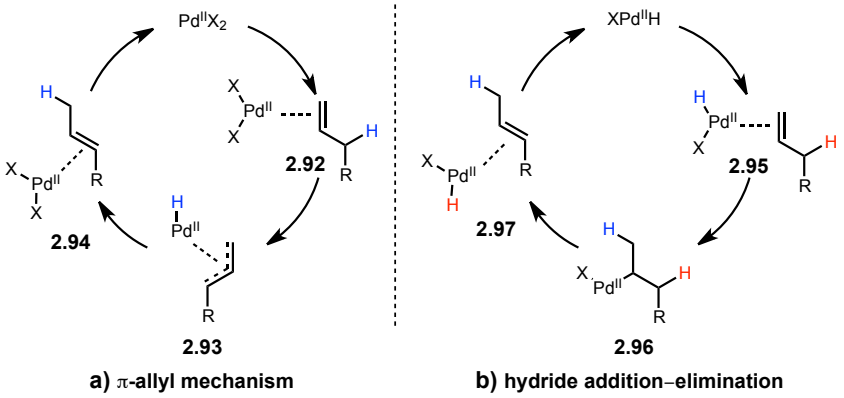
2.89 **2.90** **2.91**

Entry	$LiPdCl_3$ (mol%)	Re-oxidant	Equiv Cl	Result[a]	
				2.90	**2.91**
1	100	-	12	1	0
2	100	-	2	1	0.3
3	9	$CuCl_2$ (100 mol%)	4.9	1	0
4	9	$CuCl_2$ (100 mol%)	1.2	1	0.1

[a] Approximate ratio of **2.90** to **2.91** determined by GC

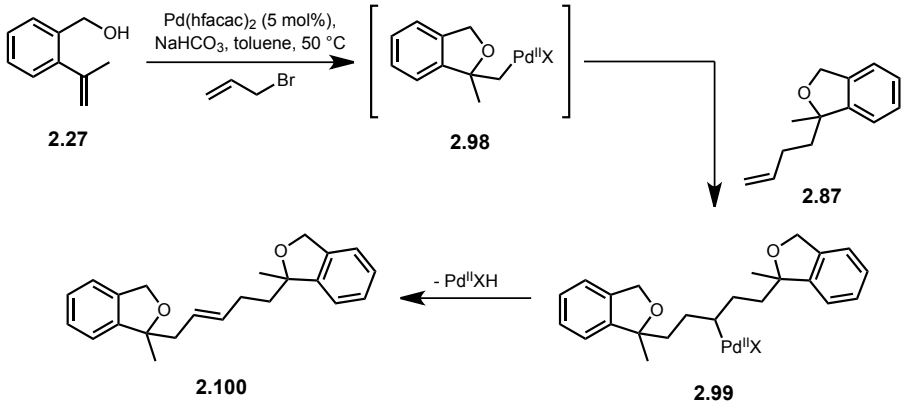
Table 2.21: Effect of altering reaction conditions on isomerisation of 2.90

For Pd-catalysed alkene isomerisation to occur in the oxyallylation reaction, a hydrogen atom must be delivered from palladium to the terminal carbon of the alkene. This palladium-hydride species could either be generated intramolecularly *via* a π-allyl mechanism [96, 97] (Scheme 2.32a) or intermolecularly by hydride addition–elimination (Scheme 2.32b). The π-allyl mechanism involves alkene complexation by a coordinatively unsaturated palladium complex followed by insertion into the allylic C–H bond to form π-allyl palladium hydride species **2.93**. Hydride can then be transferred from the metal to the terminal position by reductive elimination, giving a formal [1,3]-hydride shift. In the hydride addition–elimination sequence, a Pd(II)-hydride species coordinates the alkene then undergoes hydropalladation to afford Pd(II)-alkyl species **2.96**, which then undergoes β-hydride elimination to give the isomerised product.



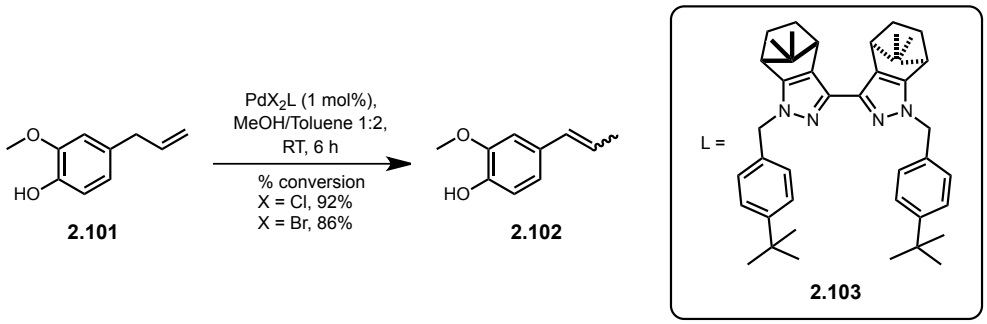
Scheme 2.32: Mechanisms of alkene isomerisation

The operation of a π-allyl mechanism is typically consistent with conditions where formation of a hydrido-Pd complex is unlikely to occur: usually in purified, dry, aprotic solvents and in the absence of a co-catalyst or coordinating ligand.[96,98] Palladium-hydrides can be generated by oxidation of alcohols,[99, 100] however, although not definitive, no aldehyde formation was observed in the ^{1}H NMR spectrum of crude material. However, formation of pseudo-dimeric side product **2.100**, analogous to that observed in the oxyallylation of phenol substrates (Section 2.3.1, Scheme 2.23 and Section 2.3.2, Scheme 2.30), would result in the simultaneous formation of a palladium-hydride species as a result of β-hydride elimination being the terminating step (Scheme 2.33). This could be a source of Pd(II)-hydrido species for the hydride addition–elimination mechanism of alkene isomerisation in the oxyallylation reaction of benzylic alcohol **2.27**.



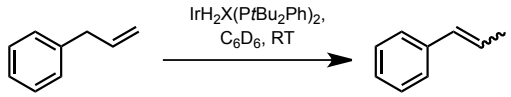
Scheme 2.33: Formation of palladium hydride in formation of side product 2.100

The observation that product alkene isomerisation occurs more readily in the oxyallylation reaction of benzylic alcohol **2.27** where allyl chloride is employed as the electrophile *cf*. allyl bromide (Table 2.19) might be explained by the formation of a more reactive isomerisation catalyst. Trapp and co-workers studied the use of palladium bipyrazoles as catalysts for the isomerisation of allylbenzenes **2.101**.[101] Small differences in the yields were observed when using a catalyst based on pyrazole ligand **2.103** and $PdCl_2$ when compared with $PdBr_2$ catalyst, with slightly lower conversion observed using the bromide catalyst over the same time period (Scheme 2.34). This difference was rationalised as to be due to the lower π-donation ability of bromide as compared to chloride.



Scheme 2.34: Effect of palladium halide source on rate of alkene isomerisation

Caulton and Cooper studied the effect of varying the identity of X in the isomerisation of allyl benzene using $IrH_2X(PtBu_2Ph)_2$ as a the catalyst precursor and, although these reactions were carried out using an iridium system, a pronounced halide effect was reported (Table 2.22).[102] Catalysts with better π-donating ligands, where a low ν (CO) stretching frequency for $RuH(X)(CO)(PtBu_2Ph)_2$ indicates high (σ + π) donation by X, were found to be the most reactive. The rate of isomerisation of **2.90** to **2.91** increased with the alteration of ligand X in the order I < Br < Cl < OH < OCH_2CF_3 < F (Table 2.22, entries 1–6). The authors proposed that the rate-determining step involved a highly unsaturated species, the formation of which would be more favourable in the presence of a π-donating ligand.



2.90 **2.91**

Entry	X	Relative Rate	ν (CO) (cm^{-1})
1	I	1	1908
2	Br	2.5	1906
3	Cl	6.2	1904
4	OH	10.0	1896
5	OCH_2CF_3	35.4	1892
6	F	55.4	1892

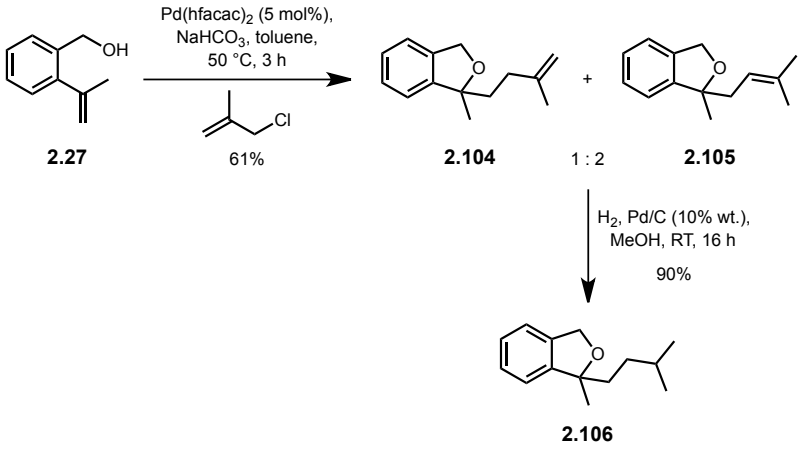
[a] ν (CO) stretching frequencies for RuH(X)(CO)(P*t*Bu$_2$Ph)$_2$

Table 2.22: Effect of halide on rate of alkene isomerisation

These observations suggest that palladium-catalysed alkene isomerisation in the presence of chloride ions may proceed more rapidly than isomerisation in the presence of bromide ions, consistent with the reactivity observed in the oxyallylation of benzylic alcohol **2.27** (Table 2.19).

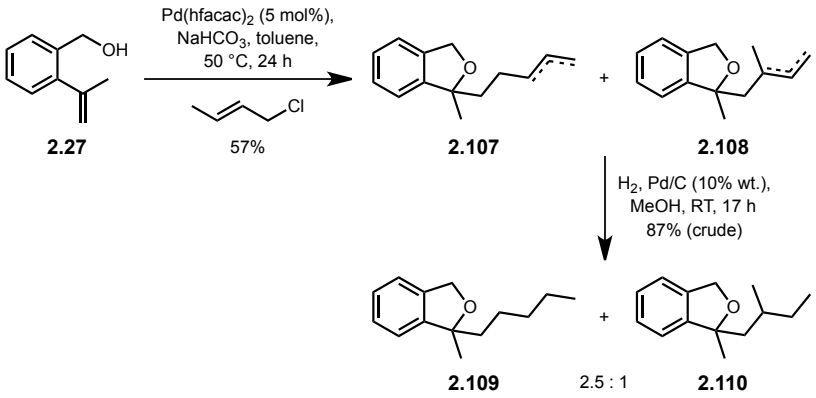
Use of Other Allyl Traps

In addition to unsubstituted allyl electrophiles, a number of other substituted allyl species could be used in the oxyallylation reaction. Treatment of benzylic alcohol **2.27** with catalytic Pd(hfacac)$_2$, $NaHCO_3$ and 3-chloro-2-methylpropene in toluene at 50 °C gave complete conversion of the starting material after three hours to afford the dihydroisobenzofuran product as a mixture of terminal **2.104** and internal **2.105** alkene isomers in a 1:2 ratio (Scheme 2.35). In this example, alkene isomerisation results in the favourable conversion of a disubstituted alkene to a trisubstituted alkene. The mixture of alkene isomers **2.104** and **2.105** could be successfully reduced using H_2 and 10% wt. Pd/C in MeOH to obtain isopentyl substituted isobenzofuran **2.106**, as a single compound, in 90% yield.



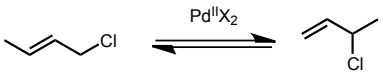
Scheme 2.35: Oxyallylation of 2.27 with 3-chloro-2-methylpropene and hydrogenation of product mixture to 2.106

Where crotyl chloride was used as the allyl electrophile, benzylic alcohol **2.27** was heterocyclised to afford a complex mixture of products **2.107** and **2.108**, consisting of both alkene isomers and regioisomers in 57% yield (Scheme 2.36). Reduction of this product mixture with H_2 and 10% wt. Pd/C allowed the regioisomeric ratio to be established as a 2.5:1 ratio of pentyl to 2-methylbutyl substituted isobenzofurans **2.109** and **2.110**.



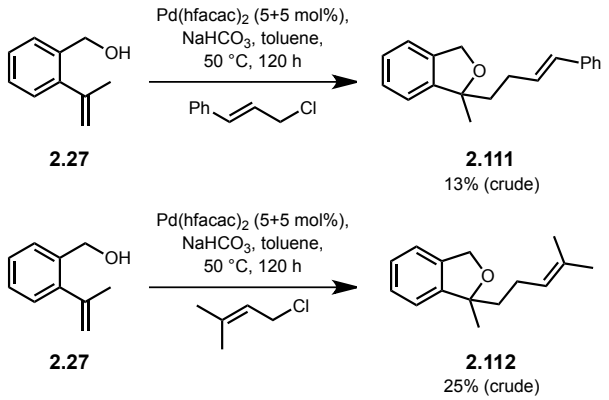
Scheme 2.36: Oxyallylation of 2.27 with crotyl chloride

Heck,[95] and subsequently Bergstorm[103] *et al*., reported that palladium halides are effective catalysts for the rearrangement of allylic halides (Scheme 2.37). Thus, although crotyl chloride is available commercially with only 4% of 3-chlorobutene impurity present, crotyl chloride could be expected to isomerise to 3-chlorobutene under the reaction conditions, giving rise to the regioisomeric mixture observed in the oxyallylation reaction of **2.27** with crotyl chloride.



Scheme 2.37: Isomerisation of crotyl chloride by $Pd^{II}X_2$

Use of more highly substituted allyl electrophiles such as cinammyl chloride or prenyl chloride gave poor conversion of the starting material **2.27**, even after prolonged heating and addition of a further 5 mol% of $Pd(hfacac)_2$ (Scheme 2.38). Although conversion to desired product **2.111** was observed when cinnamyl chloride was used, the reaction was low yielding and the product could not be obtained pure. Similarly, prenyl product **2.112** could be observed but was not obtained in sufficient quantity and purity for full characterisation.

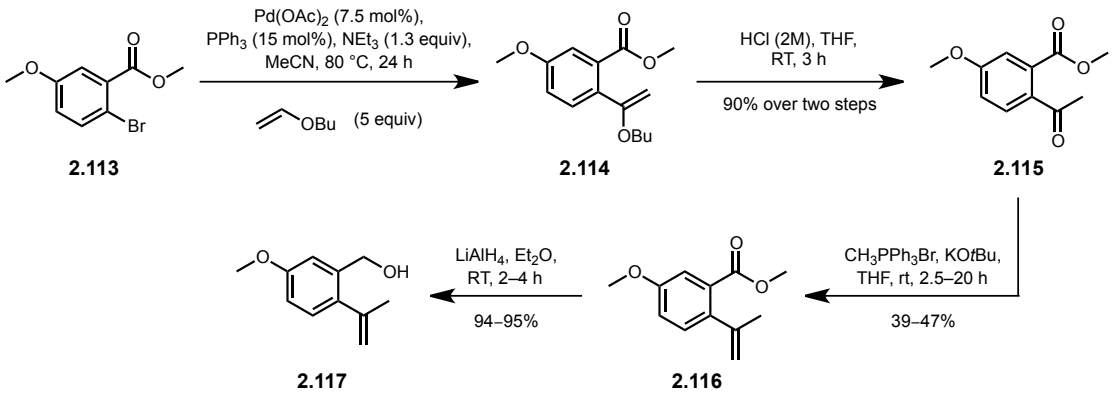


Scheme 2.38: Oxyallylation of 2.27 with cinnamyl and prenyl chloride

Synthesis and Cyclisation of Other Alcohols

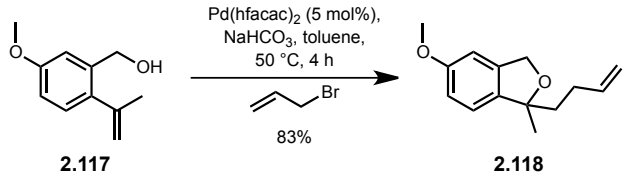
The investigation of the substrate scope of the oxyallylation reaction would ideally employ substrates that could be accessed in a low number of synthetic transformations from commercial materials. In general, a larger number of steps would be required to access analogues of benzylic alcohol **2.27** as compared to analogues of phenol substrate **2.38** in order to investigate the tolerance of the conditions to aryl substituents. However, one example of a substrate that could be quickly accessed is methoxy-substituted benzyl alcohol **2.117** (Scheme 2.39). Commercially available methyl 2-bromo-5-methoxybenzoate **2.113** underwent a Heck reaction with *n*-butylvinyl ether using catalytic $Pd(OAc)_2$, PPh_3 and NEt_3 in MeCN at 80 °C to afford butyl enol ether **2.114**. The crude material obtained from the work up was hydrolysed directly using HCl (2 M aq.) in THF to afford ketone **2.115**.[104] The coupling step proved difficult to follow by TLC as the starting material and product had the same R_f; an initial attempt at this coupling reaction afforded low yields due to poor conversion of starting material **2.113**. However, by extending the reaction time to 24 h, the ketone could be obtained in 90% yield over two steps. Addition of ketone **2.115** to a prepared suspension of methyl triphenylphosphonium bromide and potassium *tert*-butoxide in THF afforded alkene **2.116** in moderate yields. The ^{1}H NMR spectrum of crude material showed approximately 25% unreacted starting material as well

as several other minor components. Reduction of ester **2.116** using $LiAlH_4$ in Et_2O afforded **2.117**.



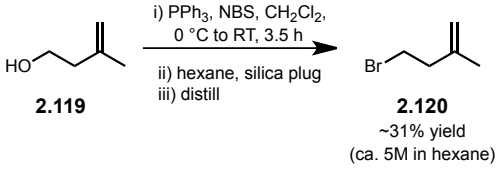
Scheme 2.39: Synthesis of 2.117

Upon treatment of hydroxyalkene **2.117** with catalytic $Pd(hfacac)_2$, $NaHCO_3$ and allyl bromide in toluene at 50 °C, complete conversion of the starting material was observed after 4 h, with desired product **2.118** obtained in 83% yield (Scheme 2.40). This increase in reaction rate *cf*. the oxyallylation of benzylic alcohol **2.27** (Table 2.19), which took 6 h to reach completion, is likely to be due to an increase in the nucleophilicity of the alkene.



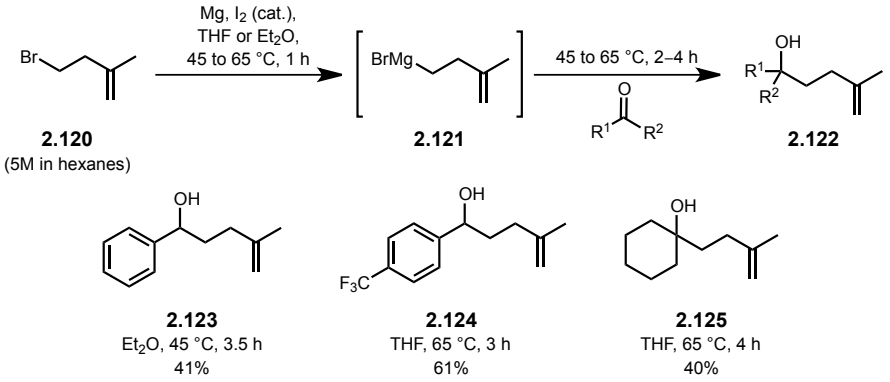
Scheme 2.40: Oxyallylation of 2.117

Akin to the work of Waser and co-workers,[44] a number of substrates could be accessed by treatment of aldehydes or ketones with the Grignard reagent prepared from 4-bromo-2-methylbutene **2.120** (Scheme 2.41) to afford γ-hydroxyalkenes. As bromide **2.120** is not commercially available, it was prepared from 3-methylbut-3-enol **2.119** by reaction with PPh_3 and NBS in CH_2Cl_2. Although the literature precedent followed reported a 75% yield of bromide **2.120**,[105] this reaction proved difficult to reproduce. Initial attempts afforded a mixture of starting material **2.119** and product **2.120** that could not be separated by distillation. In addition to this, bromide **2.120** appeared volatile and was azeotroped by the removal of residual CH_2Cl_2 and hexane when the distillation system was placed under reduced pressure, necessitating a dry ice cooling trap to be applied to the collection flask. Whilst the bromination gave variable results, pure bromide **2.120** was afforded in sufficient quantity and, although this material was obtained as an approximately 5 M solution in residual hexane, this did not prove problematic in the subsequent Grignard reactions.



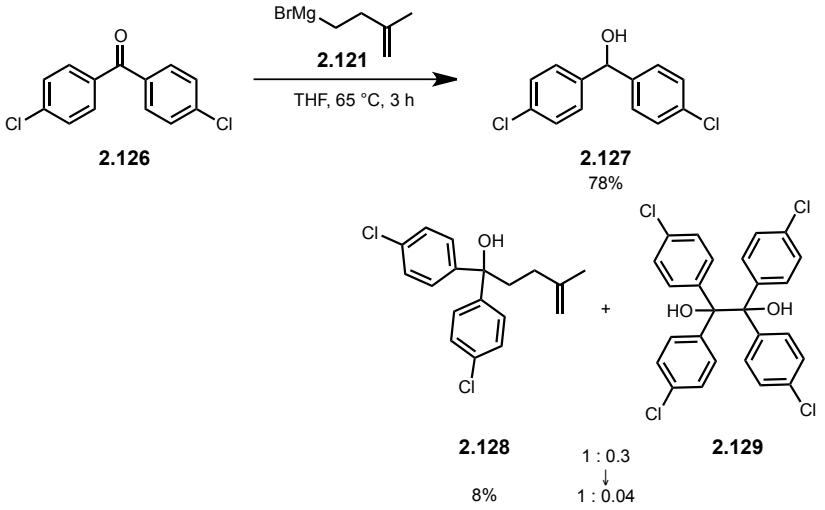
Scheme 2.41: Synthesis of 2.120

Using Waser's conditions,[44] benzaldehyde was added to a mixture of Grignard **2.121** in Et_2O to afford secondary alcohol product **2.123** in 41% yield (Scheme 2.42). The corresponding *p*-trifluoromethyl substrate **2.124** could be formed in 61% yield and tertiary cyclohexanol **2.125** was obtained in 40% yield.



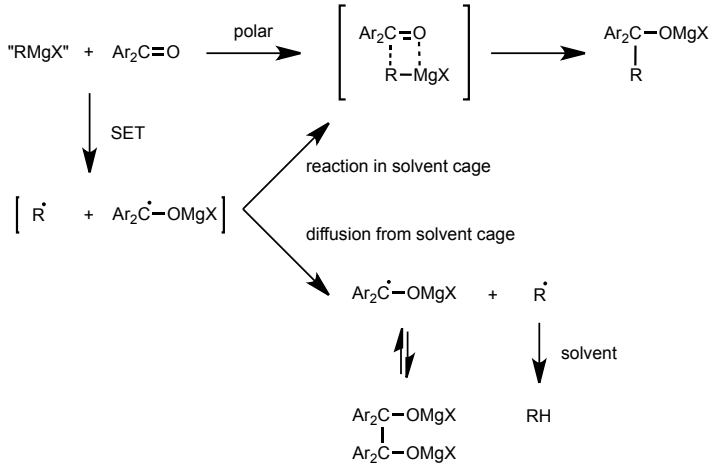
Scheme 2.42: Grignard reactions of 2.121 to form alcohols 2.123–2.125

When 4,4'-dichlorobenzophenone **2.126** was treated with Grignard **2.121**, desired product **2.128** was formed as the minor component of a mixture of compounds (Scheme 2.43). The main component of this mixture was benzhydrol compound **2.127**, isolated in 78% yield. Despite repeated flash chromatography, desired compound **2.128** could not be separated from an impurity tentatively identified as the product of pinacol coupling **2.129**; these compounds were afforded in a 1:0.3 mixture. However, trituration with petroleum ether allowed solid pinacol product **2.129** to be almost completely removed from hydroxyalkene **2.128**, which was an oil. The purity of this species was increased to a 1:0.04 ratio of **2.128**:**2.129** by the trituration.



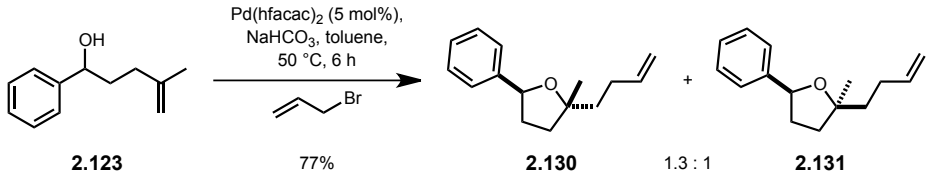
Scheme 2.43: Grignard reaction of 4,4'-dichlorobenzophenone 2.126

The formation of benzhydrol and pinacol side products is a known complication in Grignard reactions, indicative of radical side pathways. Blomberg and Mosher observed the formation of benzopinacol in the Grignard reaction of benzophenone with neopentyl magnesium bromide and, in support of their results, suggested a mechanism by which both polar and single electron transfer (SET) pathways may operate (Scheme 2.44).[106] Ashby and co-workers have studied the conditions giving rise to formation of benzhydrol and pinacol side products in the reaction of benzophenone with methyl magnesium bromide.[107,108,109] The authors found that pinacol side products were formed in greater quantities where the magnesium used to prepare the Grignard reagent was of lower purity, containing small amounts of other transition metals such as iron. Observation of the benzhydrol side product was attributed to formation of approximately 0.2% of a very reactive magnesium hydride species formed during the reaction of bromomethane with magnesium. Ashby *et al*. found that use of an excess of bromomethane relative to magnesium in the preparation of the Grignard reagent suppressed the formation of benzhydrol.



Scheme 2.44: Proposed pathways for Grignard reaction and side product formation

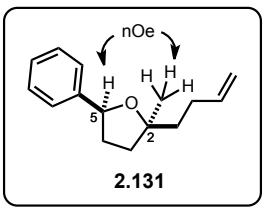
Despite the moderate yields observed in these Grignard reactions (Scheme 2.42, Scheme 2.43), sufficient quantities of hydroxyalkenes **2.123–2.125** and **2.128** were obtained to investigate the use of these substrates in the oxyallylation reaction. Upon reaction of secondary alcohol **2.123** with catalytic $Pd(hfacac)_2$, $NaHCO_3$ and allyl chloride in toluene at 50 °C, formation of two new, less polar species was observed on the TLC. However, although the desired product appeared to have formed, the crude material obtained was a complex mixture of diastereomers **2.130** and **2.131** and alkene isomers of these products. Repetition of the oxyallylation of **2.123** using allyl bromide afforded the desired heterocyclisation product as a 1.3:1 mixture of diastereomers **2.130** and **2.131** in 77% yield (Scheme 2.45). Whilst the reactions of the phenol substrates appear to perform better using allyl chloride as the electrophile (Section 2.3.1, Table 2.15), it was observed that non-phenolic alcohols generally gave alkene isomerisation under these conditions with reactions proceeding much cleaner using allyl bromide. It is possible that, in the reactions of phenol substrates, coordination of the phenol oxygen to palladium reduces coordination of the oxyallylation product alkene, giving rise to significantly less alkene isomerisation using these substrates.



2.123 77% **2.130** 1.3 : 1 **2.131**

Scheme 2.45: Oxyallylation of 2.123

The diastereomeric mixture formed in the oxyallylation of **2.123** could be partially separated by flash chromatography, allowing a pure sample of each diastereomer to be obtained for identification by 2D ^{1}H NMR spectroscopy. Analysis of the spectrum for minor diastereomer **2.131** showed an nOe between the benzylic proton and the protons of the CH_3 group (Figure 2.5). Thus, the minor diastereomer was identified as having the 5-H and the 2-CH_3 group in a *cis* position relative to each other. The major diastereomer **2.130** therefore corresponded to the *trans* isomer.

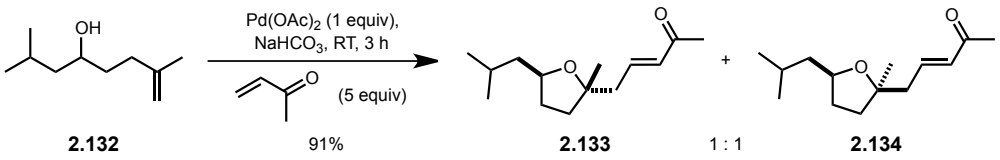


2.131

Figure 2.5: nOe of 2.131 showing assignment of stereochemistry

In the formation of 2,5-disubstituted tetrahydrofurans, Semmelhack and co-workers found that the heterocyclisation of secondary alcohols onto disubstituted alkenes afforded 1:1

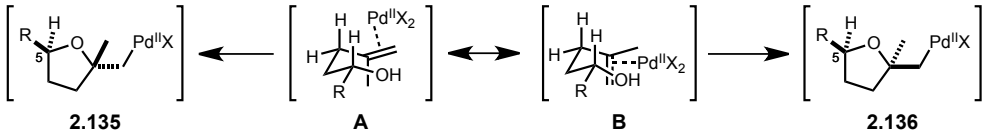
mixtures of the corresponding diastereomeric products (Scheme 2.46). As such, the oxyvinylation of hydroxyalkene **2.132** using stoichiometric $Pd(OAc)_2$, $NaHCO_3$ and methyl vinyl ketone afforded a 1:1 mixture of diastereomers **2.133** and **2.134**.[34] This effect was consistent with observations the authors had made in their study of the alkoxycarbonylation reactions of disubstituted alkenes.[32,110]



2.132 91% **2.133** 1 : 1 **2.134**

Scheme 2.46: Oxyvinylation of 2.132

Semmelhack and co-workers proposed the formation of these products could proceed through chair-like transition states A and B, with the conformations minimising non-bonded (*e.g*. pseudodiaxial) interactions.[32] The folding of the substrate *via* conformation A to form intermediate **2.135**, with the methyl group and the 5-H *trans* relative to each other, was suggested to be no less favourable than the folding of the substrate *via* conformation B to afford the corresponding *cis* intermediate **2.136** (Scheme 2.47). However, Goldsmith and Liotta proposed that the formation of cyclic ethers should be geometrically more feasible from transition state A, giving *trans* product **2.135**, than transition state B and that stereoselectivity in these types of reactions is likely to be dependent on the steric demands of reversibly formed palladium intermediates.[111] These observations could be consistent with the near equal formation of diastereomeric products in the oxyallylation reaction of **2.123** (Scheme 2.45), with a slight preference shown for the formation of "*trans*" product.

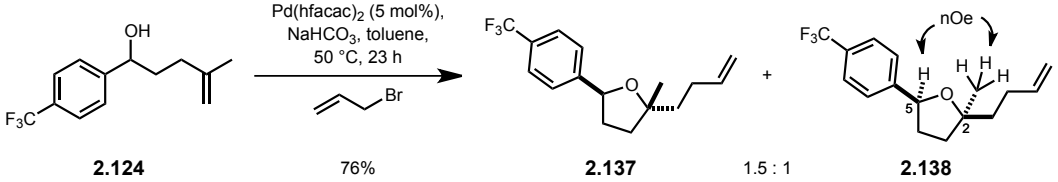


2.135 **A** **B** **2.136**

Scheme 2.47: Proposed transition states in heterocyclisation of 2.132

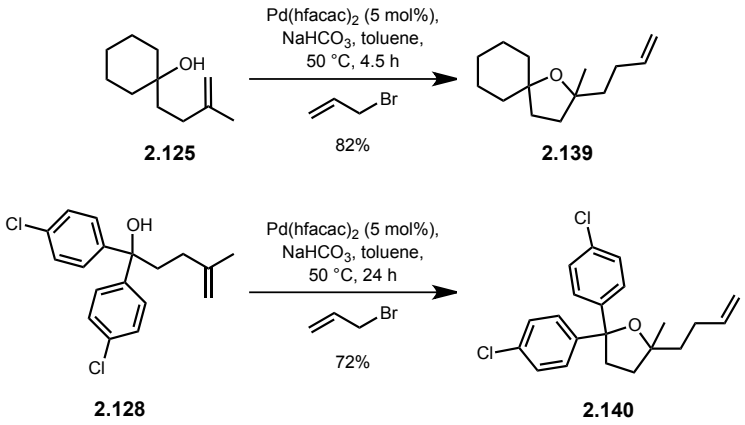
Upon treatment of *p*-trifluoromethyl substituted benzylic alcohol **2.124** with catalytic $Pd(hfacac)_2$, $NaHCO_3$ and allyl bromide in toluene, the desired product was afforded in 76% yield as a mixture of diastereomers **2.137** and **2.138**, after 23 h at 50 °C (Scheme 2.48). Analogous yields were thus obtained to the oxyallylation reaction of **2.123** (Scheme 2.45); however, the reaction time was significantly longer. This is likely to be due to decreased nucleophilicity of the hydroxyl group in **2.124** *cf*. **2.123** due to the electron withdrawing nature of the trifluoromethyl group. Diastereomers **2.137** and **2.138** were obtained in a comparable ratio as that observed in the reaction of substrate **2.123** (Scheme 2.45), with a similar preference for the formation of the "*trans*" isomer. As a pure

sample of each diastereomer could be obtained by partial separation by flash chromatography, 2D ^{1}H NMR spectroscopy could be used to identify the two diastereomers. An nOe between the 5-H and the 2-CH_3 group was found for minor *cis* diastereomer **2.138** (Scheme 2.48).



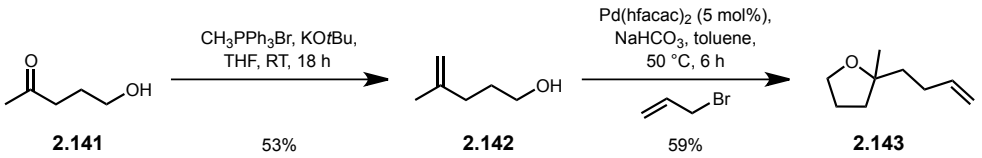
Scheme 2.48: Oxyallylation of 2.124 and assignment of stereochemistry of 2.138

The oxyallylation methodology was successfully applied to the cyclisation of tertiary alcohols **2.125** and **2.128** to form 2,5-tetrasubstituted tetrahydrofurans. Under the standard conditions, spirocycle **2.139** was formed in 82% yield after 4.5 h (Scheme 2.49). The formation of spirocyclic product **2.139** is likely facilitated by the reactive rotamer effect[76] from the cyclohexyl substitution of alcohol **2.125**, giving rise to the observed excellent yield and short reaction time for the oxyallylation of **2.125**. Diaryl tetrahydrofuran **2.140** was formed in 72% yield after 24 h at 50 °C. In addition to demonstrating that tertiary alcohols are tolerated in the oxyallylation reaction, the heterocyclisation of **2.128** also indicates that aryl chlorides can be used, with no depreciation in yields observed. The reaction time of 24 h is similar to that obtained for the *p*-trifluoromethyl susbtrate **2.124** (Scheme 2.48) and, although chlorine is a less strongly electron withdrawing group, it is possible that the diaryl substitution has a compound effect on the nucleophilicity of the hydroxyl group in **2.128**. Although the formation of spirocyclic product **2.139** demonstrates that a tertiary alcohol can be heterocyclised in a relatively short reaction time, the steric bulk around alcohol **2.128** is greater and thus sterics may also be important in the slow reaction of **2.128**.



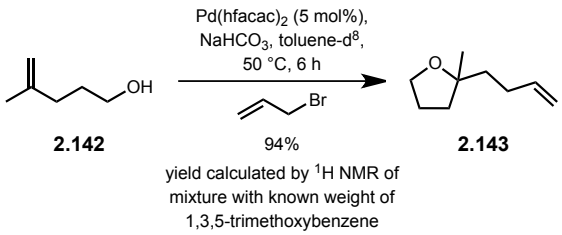
Scheme 2.49: Oxyallylation of tertiary alcohols 2.125 and 2.128

The heterocyclisation of tertiary alcohol **2.125** indicates that the oxyallylation can be used to effect the heterocyclisation of fully aliphatic alcohols; this capability was subsequently extended to simple linear γ-hydroxyalkenes. Linear substrate **2.142** was synthesised from commercial 5-hydroxy-2-pentanone, sold by Sigma Aldrich as a "mixture of monomer and dimer" (Scheme 2.50). Addition of this material to the Wittig reagent prepared from methyl triphenylphosphonium bromide and potassium *tert*-butoxide afforded complete consumption of the starting material mixture. Purification by flash chromatography afforded the desired alkene **2.142** in 53% yield. Under the conditions employed for the benzylic alcohol **2.77** (Section 2.3.3, Table 2.19) *i.e.* heating at 50 °C in toluene with catalytic $Pd(hfacac)_2$, $NaHCO_3$ and allyl bromide, the reaction of linear alcohol **2.142** afforded complete conversion to a new, less polar spot in 6 h by TLC. Although the desired product had formed, product **2.143** proved to be volatile and was obtained in only 59% isolated yield (Scheme 2.50).



Scheme 2.50: Synthesis and oxyallylation of 2.142

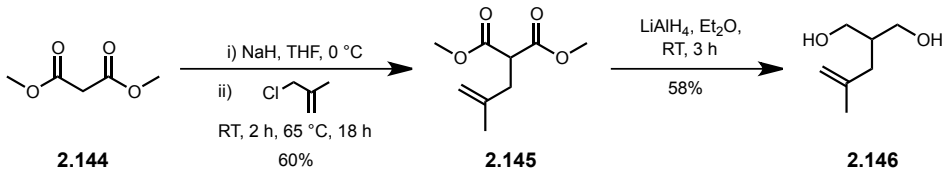
In order to obtain an accurate yield for the cyclisation of **2.142**, taking into account the product volatility, the oxyallylation of **2.142** was repeated on 50% of the standard scale in toluene-d^8, although under otherwise identical conditions (Scheme 2.51). Upon completion of the reaction, the entire reaction mixture was transferred to an NMR tube containing a known mass of 1,3,5-trimethoxybenzene as an internal standard. The yield of **2.143** was calculated to be 94%.



Scheme 2.51: Oxyallylation of 2.142 with yield of 2.143 determined by ^{1}H NMR spectroscopy with internal standard

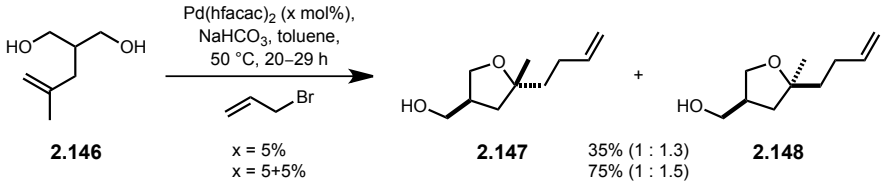
Diol **2.146** (Scheme 2.52) was subsequently prepared to assess whether the reaction conditions could tolerate an unprotected alcohol that was not involved in the cyclisation. Whilst Wacker–Tsuji oxidation of the substrate alcohol to the corresponding aldehyde or ketone was not observed in the cyclisation reactions detailed thus far, as this substrate has a non-participating hydroxyl group, there is potential for oxidation to give rise to the formation of side products and reduction of the active catalyst to Pd(0). Even if alcohol

oxidation does not occur, it is possible that the non-participating hydroxyl group could deactivate the palladium by coordination. *gem*-Diester **2.145** was obtained in 60% yield by treatment of dimethyl malonate **2.144** with sodium hydride in THF and subsequent reflux with 3-chloro-2-methylpropene (Scheme 2.52). The diester **2.145** was then reduced using lithium aluminium hydride to obtain diol **2.146** in 58% yield.



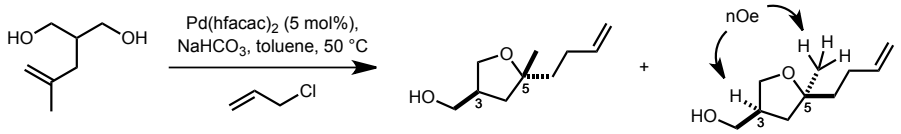
Scheme 2.52: Synthesis of diol 2.146

The rate of cyclisation of diol **2.146** proved to be significantly slower than that of linear alcohol **2.142** (Scheme 2.50), with full conversion not reached after 20 h of heating (Scheme 2.53). Although the desired product could be obtained from the oxyallylation of **2.146**, it was isolated in only 35% yield as a mixture of diastereomers **2.147** and **2.148**. From monitoring the reaction by ^{1}H NMR spectroscopy, the ratio of starting material to products was 1:0.5 after 4 h and 20 h, indicating that conversion of the starting material stalled early in the reaction, suggesting catalyst deactivation. Repeating this reaction, but with an additional 5 mol% of Pd(hfacac)$_2$ added after 23 h and heating for a further 6 h, gave complete conversion of the starting material to afford the product as a mixture of diastereomers **2.147** and **2.148** in 75% yield.



Scheme 2.53: Oxyallylation of diol 2.146 using allyl bromide

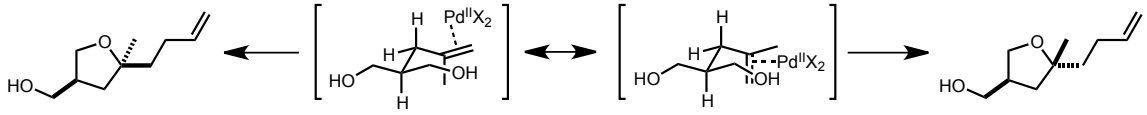
As was observed in the reactions of the phenol substrate **2.38** (Section 2.3.1, Table 2.16), where coordination of the phenol is believed to result in catalyst deactivation when allyl bromide is used as the electrophile, recourse to allyl chloride allowed the heterocyclisation of diol **2.146** to occur using only 5 mol% Pd(hfacac)$_2$ (Scheme 2.54). The inseperable diastereomers **2.147** and **2.148** were afforded in 63% combined yield after only 2.5 h. However, as the 3-H and 5-CH$_3$ signals in the ^{1}H NMR spectrum of the diastereomeric mixture were resolved for the major and minor components, 2D ^{1}H NMR spectroscopy allowed assignment of the stereochemistry. The major diastereomer was identified as the '*cis*' diastereomer **2.148**, by an nOe between the 3-H and 5-CH$_3$.



2.146 2.5 h, 63% **2.147** 1 : 1.4 **2.148**

Scheme 2.54: Oxyallylation of diol 2.146 using allyl chloride and assignment of stereochemistry of 2.147

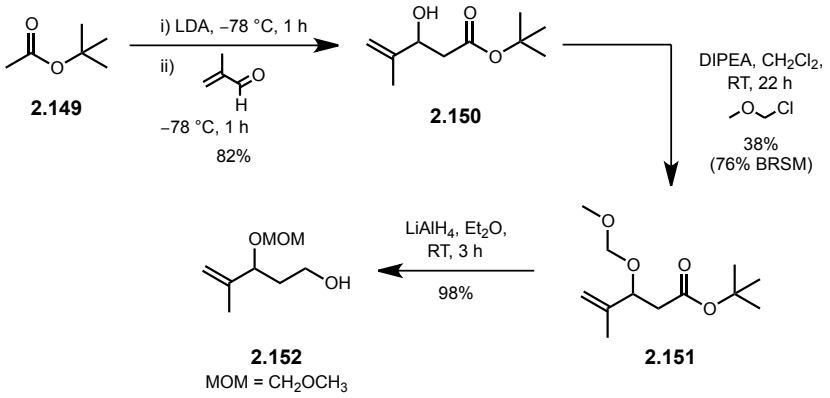
This is the same level of diastereoselection that was observed in the cyclisation of secondary alcohols **2.123** and **2.124** (Schemes 2.44 and 2.47), but with a preference for the opposite diastereomer. Conformers analogous to those shown in Scheme 2.47 could explain this difference in diastereoselectivity; conformers A and B (Scheme 2.55), with the CH_2OH substituent equatorial, will give rise to the formation of products **2.148** and **2.147** respectively. However, a slight preference for reaction through conformer A, as in the cyclisation reactions of **2.123** and **2.124**, gives rise to a slight preference for the formation of **2.148**.



2.148 **A** **B** **2.147**

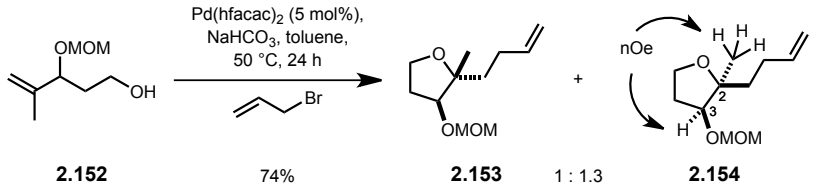
Scheme 2.55: Oxyallylation of diol 2.146 using allyl chloride and assignment of stereochemistry of 2.147

Following on from this result, protected alcohol **2.152** was prepared (Scheme 2.56). This substrate should allow investigation of whether protecting the free hydroxyl functionality reduces the catalyst deactivation observed. In addition to this, use of the acid sensitive methoxymethyl (MOM) protecting group should allow analysis of whether acid sensitive functionality can be tolerated in the oxyallylation reaction, as HX (X = Br or Cl) is produced stoichiometrically in the oxyallylation reaction. Following a reported procedure,[112] *tert*-butyl acetate **2.149** was treated with LDA, followed by methacrolein at −78 °C to afford β-hydroxyester **2.150** (Scheme 2.56). The hydroxyl group of **2.150** was protected with methoxymethyl chloride to give protected alcohol **2.151** in 38% yield, or 76% based on recovered starting material. The low yield in the MOM protection of **2.150** was due to poor conversion and is believed to be due to the quality of the methoxymethyl chloride reagent used. However, as sufficient material was obtained for subsequent transformation, the protection of **2.150** was not further optimised. Reduction of *tert*-butyl ester **2.151** using lithium aluminium hydride afforded the desired γ-hydroxyalkene **2.152** in 98% yield.



Scheme 2.56: Synthesis of MOM substrate 2.152

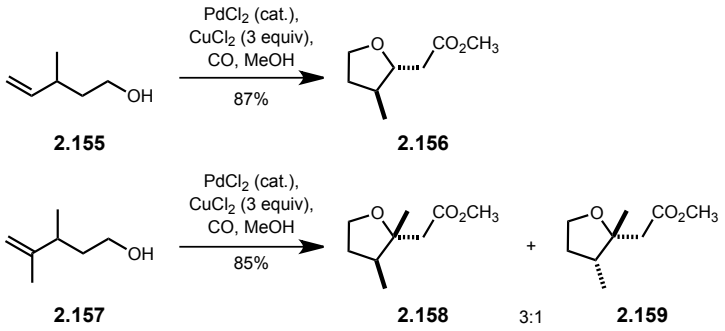
Under the oxyallylation conditions with allyl bromide, near full conversion of monoprotected diol **2.152** was observed after 24 h (Scheme 2.57). This represents a significant decrease in reaction rate when compared to the heterocyclisation of linear alcohol **2.142** (Scheme 2.50), which had reached full conversion after 6 h. However, in contrast with the reaction of unprotected diol **2.146** (Scheme 2.53), no catalyst deactivation was observed in the cyclisation of **2.152** and the desired product could be isolated in 74% yield using only 5 mol% of palladium catalyst. The product was formed as a mixture of diastereomers **2.153** and **2.154**, which could be partially separated by flash chromatography and the pure diastereomers identified by 2D ^{1}H NMR spectroscopy. The major diastereomer **2.154** was identified as the '*cis*' isomer by an nOe between the 3-H and 2-CH_3 group. This is the same selectivity as was observed in the cyclisation of unprotected diol **2.146** (Scheme 2.54).



Scheme 2.57: Oxyallylation of MOM substrate 2.152 and assignment of stereochemistry of 2.154

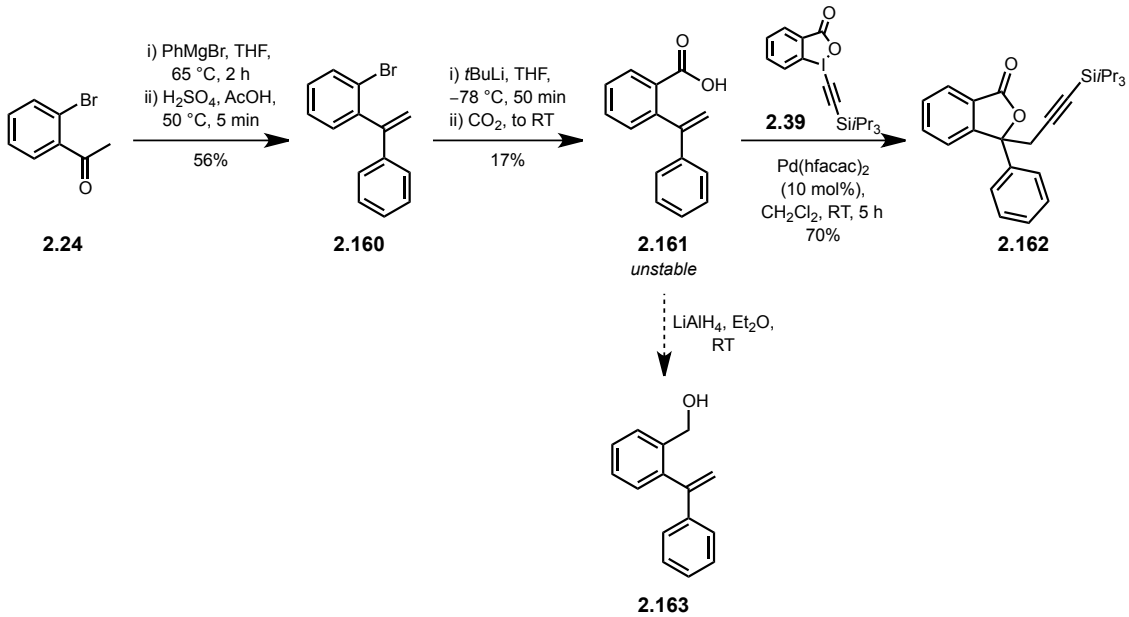
Goldsmith and Liotta found that the alkoxycarbonylation of monosubstituted alkene **2.155** using catalytic $PdCl_2$, $CuCl_2$ and CO in MeOH was highly stereoselective, affording *trans*-2,3-disubstituted tetrahydrofuran **2.156** as a single diastereomer and in excellent yield (Scheme 2.58).[111] However, upon treatment of the analogous *gem*-disubstituted alkene **2.157** under the same conditions, a 3:1 mixture of diastereomers **2.158** and **2.159** was obtained, although with a similar preference for *trans* product **2.158**. On the basis of this precedent, the *trans* product might have been expected to form in the cyclisation of protected diol **2.152** and conformers similar to those shown in Schemes 2.47 and 2.55 would predict the same result. The preferential formation of the *cis* product **2.154** could be

as a result of palladium coordinating the non-participating ether functionality, despite the presence of a protecting group.



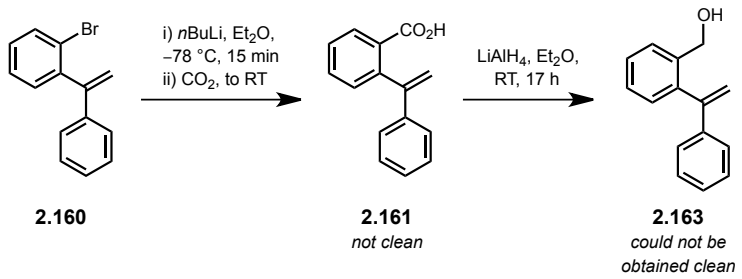
Scheme 2.58: Comparison of diastereoselectivity in alkoxycarbonylation of mono- and disubstituted alkenes 2.155 and 2.157

The heterocyclisations of the substrates outlined thus far have demonstrated the wide functional group tolerance of the oxyallylation reaction developed. However, all of these examples have contained alkenes substituted with a methyl group and so the effect of increasing the steric bulk on the alkene was investigated. Waser and co-workers reported the oxyalkynylation of diphenyl alkene **2.161** with a tethered carboxylic acid group, affording heterocyclised product **2.162** in 70% yield (Scheme 2.59).[43] The authors prepared carboxylic acid **2.161** by Grignard reaction of phenylmagnesium bromide with *o*-bromoacetophenone **2.24** then elimination to afford alkene **2.160**. The bromide **2.160** then underwent lithium–halogen exchange and quench with CO_2 to afford carboxylic acid **2.161** (Scheme 2.59). This species was reported to be unstable upon storage; however, reduction of carboxylic acid **2.161** to the corresponding alcohol **2.163** would afford a suitable substrate for the oxyallylation reaction.



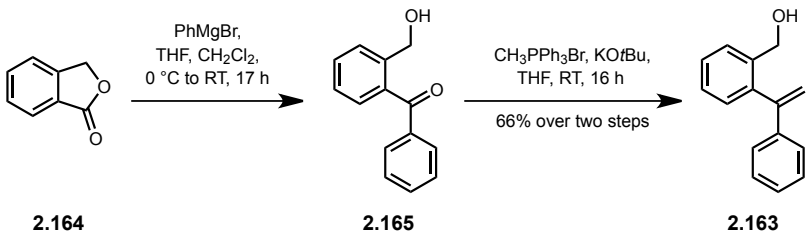
Scheme 2.59: Proposed synthesis of diaryl substrate 2.163

Treatment of bromide **2.160**[113] with *n*BuLi in Et_2O, followed by quench with CO_2, afforded carboxylic acid **2.161**; however, despite acid–base work-up, this material could not be obtained pure (Scheme 2.60). Reduction of acid **2.161** with lithium aluminium hydride afforded the desired alcohol **2.163** that, despite repeated flash chromatography, could not be successfully purified. An alternative route to this material was thus sought.



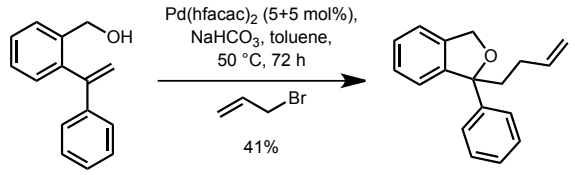
Scheme 2.60: Attempted synthesis of diaryl substrate 2.163

Following a modification of a reported procedure,[114] phthalide **2.164** was treated with phenylmagnesium bromide in a THF–dichloromethane solvent mixture to afford ketone **2.165** (Scheme 2.61). After passing the material through a silica plug, the residue was treated directly with the Wittig reagent prepared from methyl triphenylphosphonium bromide and potassium *tert*-butoxide to afford hydroxyalkene **2.163** in 66% yield over two steps. No inherent instability of hydroxyalkene **2.163** was noted.



Scheme 2.61: Synthesis of diaryl substrate

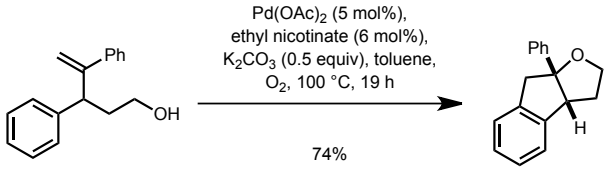
Reaction of diaryl substrate **2.163** under the oxyallylation conditions using allyl bromide gave poor conversion of the starting material, even after heating at 50 °C for up to 72 h and addition of a further 5 mol% catalyst (Scheme 2.62). Although desired product **2.166** was formed, the isolated yield from the oxyallylation of **2.163** was only 41%. A number of other minor components were formed, although they could not be identified and prevented recovery of pure unreacted starting material, which accounted for the remainder of the reaction mixture. Recourse to allyl chloride did not show any improvement in the reaction.



2.163 **2.166**

Scheme 2.62: Oxyallylation of diaryl substrate 2.163

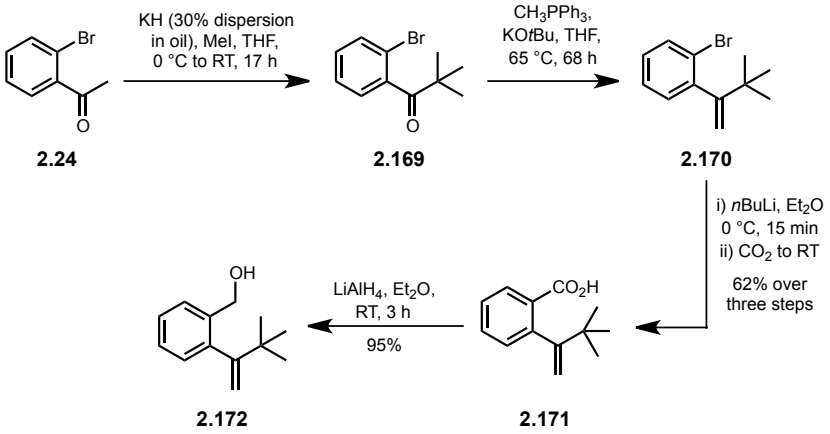
In their oxidative functionalisation of arylhydroxyalkenes, Buchwald and co-workers reported an example employing an aryl-substituted alkene **2.167** (Scheme 2.63). This substrate underwent successful oxypalladation–CH functionalisation using a $Pd(OAc)_2$/ethyl nicotinate catalyst to afford tricycle **2.168** in 74% yield.[42] This suggests that phenyl substitution on the alkene should be tolerated in the oxypalladation reaction. However, in addition to steric effects, the conjugation of two aryl rings with alkene **2.163** may result in decreased coordination to palladium.



2.167 **2.168**

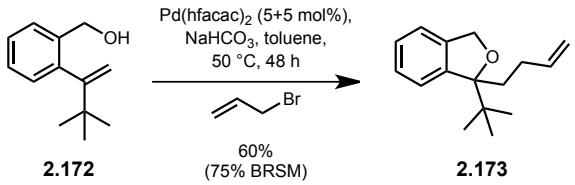
Scheme 2.63: Oxyarylation of aryl alkene 2.167

tert-Butyl substituted alkene substrate **2.172** (Scheme 2.64) was prepared subsequently to allow a greater understanding of whether steric or electronic factors were more influential in the low-yielding cyclisation of **2.163** (Scheme 2.62). Following a modification of a reported procedure,[115] *o*-bromoacetophenone **2.24** was treated with potassium hydride (30% dispersion in oil) and methyl iodide in THF at room temperature (Scheme 2.64). This trialkylation procedure afforded *tert*-butyl ketone **2.169**; however, due to the low polarity of the product, the material could not be separated from residual mineral oil by flash chromatography and so was carried directly into the next step. Wittig olefination with methyl triphenylphosphonium bromide and potassium *tert*-butoxide afforded alkene **2.170**, which remained contaminated with mineral oil residues. Lithium–halogen exchange followed by quench with CO_2 afforded carboxylic acid **2.171**. Acid–base work-up allowed acid **2.171** to be obtained pure and in 62% yield over three steps. Reduction of carboxylic acid **2.171** with lithium aluminium hydride afforded hydroxyalkene **2.172** in 95% yield.



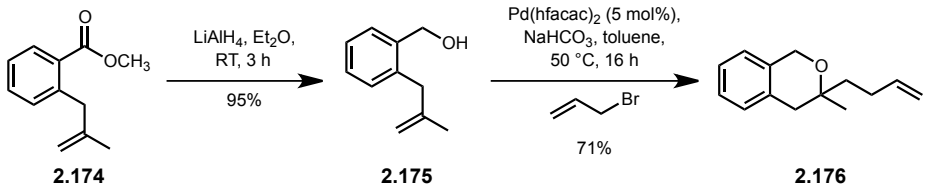
Scheme 2.64: Synthesis of *tert*-butyl substrate 2.172

The oxyallylation reaction of *tert*-butyl substrate **2.172** using allyl bromide did not proceed to full conversion after 48 h of heating and an additional 5 mol% of catalyst added; however, desired product **2.173** was isolated in 60% yield, or 75% based on recovered starting material (Scheme 2.65). This improvement in yield of product **2.173** *cf*. that obtained using phenyl substrate **2.163** (Scheme 2.62) suggests that, although the increase in the steric bulk around the alkene results in a generally more sluggish reaction and incomplete conversion of starting material, the electronics of the alkene in phenyl substrate **2.163** play an important role in the reaction conversion.



Scheme 2.65: Oxyallylation of *tert*-butyl substrate 2.172

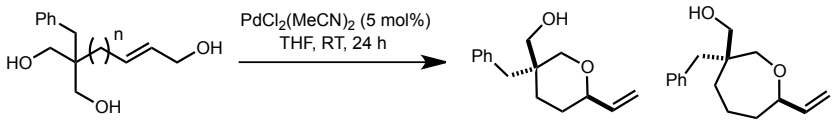
With a range of successful cyclisations to form dihydro- and tetrahydrofuran species, the formation of larger and smaller ring sizes was subsequently investigated. In Wacker-type cyclisations to form oxacycles that are not 5-membered rings, the cyclisation of δ-hydroxyalkenes to form pyran species has been most prevalently reported.[32,35,39] As a substrate for the oxyallylation reaction, the 6-membered ring precursor **2.175** was obtained by simple reduction of ester **2.174**[113] with lithium aluminium hydride to the corresponding alcohol **2.176** in 83% yield (Scheme 2.66). Oxyallylation of **2.175** using allyl bromide afforded dihydropyran product **2.176** in 71% yield after 16 h. The longer reaction time is consistent with the general observation that the formation of 5-membered cycles occurs faster than the formation of 6-membered cycles.



2.174 **2.175** **2.176**

Scheme 2.66: Synthesis and oxyallylation of 2.175

Having demonstrated that the oxyallylation of hydroxyalkenes could afford 6-membered heterocycles, the extension of this methodology to the synthesis of larger heterocycles was investigated. Sinou and co-workers reported the Pd(II) catalysed cyclisation of bis(hydroxymethyl)allylic alcohols to afford a range of tetrahydrofuran products.[116] However, this methodology could also be successfully extended to the synthesis of 6-membered and 7-membered cyclic ethers **2.178** and **2.179** (Scheme 2.67). Similar to related work reported by Uenishi *et al*.,[117] the authors propose the reaction proceeds *via* initial coordination of Pd(II) to the alkene and allylic hydroxyl group, *syn* intramolecular oxypalladation followed by *syn* Pd(OH)Cl elimination to give the observed products.



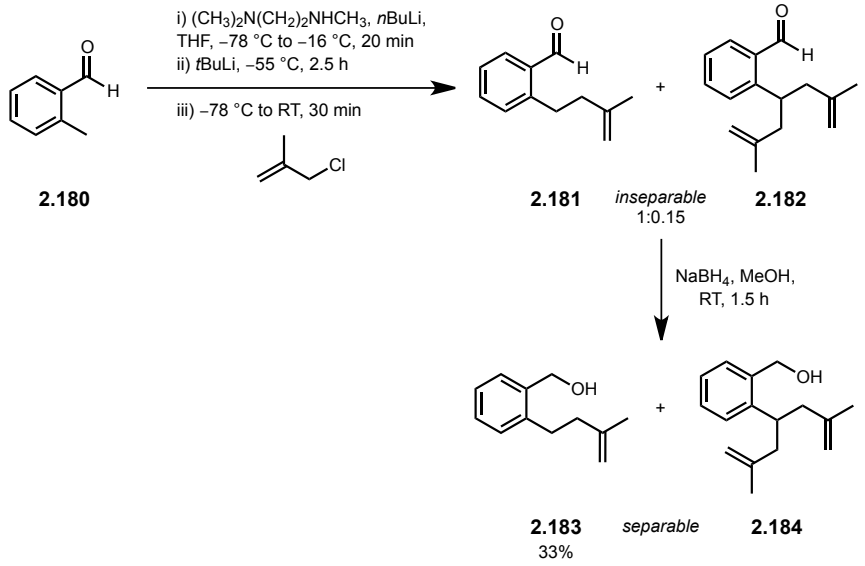
2.177

2.178
n = 2
72% *dr* 1.3:1

2.179
n = 3
89% *dr* 1.3:1

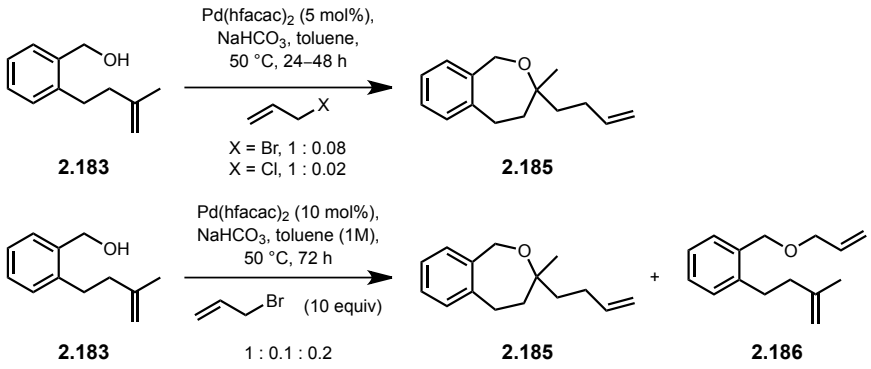
Scheme 2.67: Synthesis of 6- and 7-membered heterocycles 2.178 and 2.179 by oxypalladation

In order to investigate if seven-membered rings could be formed using the oxyallylation procedure, substrate **2.183** was chosen as it is a homologue of hydroxyalkene **2.175** and could be easily accessed by reduction of literature reported aldehyde **2.181** (Scheme 2.68). Following a reported procedure,[118] *o*-tolualdehyde **2.180** was treated with *n*BuLi and *N*,*N*,*N*-trimethylethylenediamine, followed by *t*BuLi then 3-chloro-2-methylpropene. However, these conditions afforded an inseparable mixture of mono- and di-alkylation aldehyde products, **2.181** and **2.182** respectively (Scheme 2.68). Following reduction with $NaBH_4$ in MeOH, the mono- and di-alkylated species could be successfully separated, giving heterocyclisation precursor **2.183** in 33% yield over two steps.



Scheme 2.68: Synthesis of 2.183

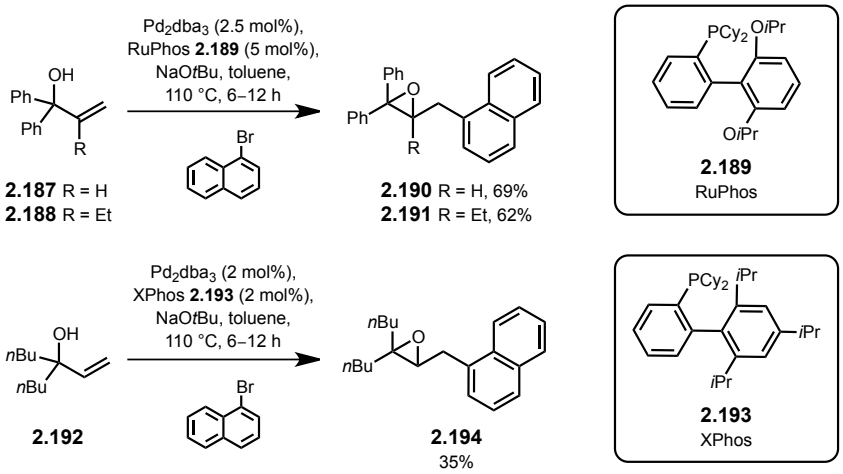
When **2.183** was subjected to the oxyallylation conditions using allyl bromide, the ^{1}H NMR spectrum of crude material suggested formation of a heterocyclised product containing an allyl group (Scheme 2.69). However, the main component of the reaction mixture corresponded to unreacted starting material **2.183**, with less than 10% of conversion to desired product **2.185** observed. A variety of minor, unidentified side products were also formed. Alteration of the electrophile to allyl chloride, and increasing the reaction time or temperature were ineffective in increasing conversion. Similarly, carrying out the reaction with a larger catalyst loading and at higher concentration did not increase conversion but appeared to result in formation of *O*-allyl side product **2.186**.



Scheme 2.69: Attempted oxyallylation of 2.183

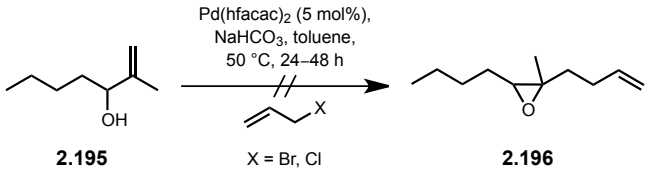
Having investigated the oxyallylation of hydroxyalkenes to form heterocycles with greater than 5 atoms, the synthesis of smaller ring sizes was subsequently explored. In 2009, Oshima and Yorimitsu reported the carboetherification of allylic alcohols to form epoxides using a Pd(0) catalyst and aryl and alkenyl bromides and chlorides (Scheme 2.70).[119] Diphenyl allylic alcohol **2.187** could be successfully heterocyclised with catalytic Pd_2dba_3, RuPhos **2.189** and 1-bromonaphthalene to afford epoxide **2.190** in 69% yield.

Monosubstituted alkenes were not required for reactivity and the tetrasubstituted epoxide **2.191** could be afforded from ethyl substituted alkene **2.188** in 62% yield. However, the bulky diphenyl substitution on the allylic alcohol appeared to be important to obtain good reactivity, where the di-*n*-butyl substituted allylic alcohol **2.192** afforded only 35% yield of epoxide **2.194** under further optimised conditions.



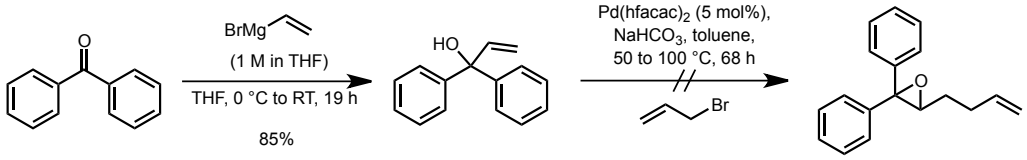
Scheme 2.70: Pd-catalysed carboetherification of allylic alcohols

As allylic alcohol **2.195** was commercially available, the oxyallylation of this substrate was first attempted. However, despite extended heating and attempting the reaction using either allyl chloride or allyl bromide as the electrophile, oxyallylation product **2.196** was not observed (Scheme 2.71). In fact, unreacted starting material was the only species observed, with no side products detected by TLC or ^{1}H NMR spectroscopy of the reaction mixture.



Scheme 2.71: Attempted oxyallylation of allylic alcohol 2.195

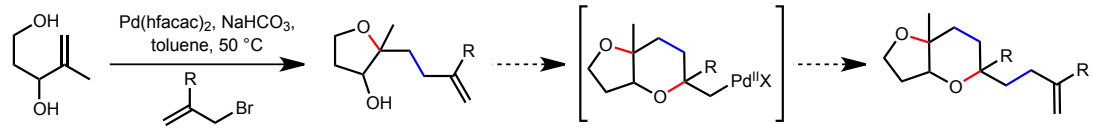
On the basis of the precedent detailed above, where bulky substitution was required adjacent to the alcohol to increase the rate of cyclisation (Scheme 2.67), substrate **2.187** was synthesised (Scheme 2.72). Following a reported procedure, treatment of benzophenone **2.197** with vinylmagnesium bromide afforded allylic alcohol **2.187** in 85% yield. [120] The oxyallylation of allylic alcohol **2.187** was attempted using catalytic $Pd(hfacac)_2$, $NaHCO_3$ and allyl bromide in toluene, heating from 50 to 100 °C for up to 68 hours; however, desired product **2.198** was not observed in these reactions and unreacted starting material remained the sole observed species.



2.197 **2.187** **2.198**

Scheme 2.72: Synthesis and attempted oxyallylation of 2.177

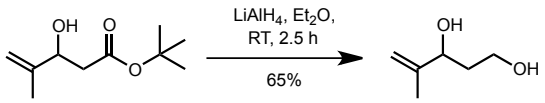
As discussed in Chapter 1, the construction of multiple bonds in a single transformation is an attractive goal, reducing waste and the number of synthetic operations required. It was postulated that the oxyallylation product of a substrate containing an additional unprotected hydroxyl group, such as **2.200** (Scheme 2.73), would be appropriately substituted to undergo a second oxyallylation reaction to afford bicyclic ethers such as **2.203**. Use of 3-bromo-2-methylpropene as the allyl trap (R = Me), should avoid any complicating side products which could arise from β-hydride elimination from Pd(II) intermediate **2.202** where R = H. This cyclisation would construct two new C–O and two new C–C bonds in a single transformation from one molecule of hydroxyalkene **2.200** and two molecules of the allyl bromide and is an example of a cascade reaction: the first oxyallylation must occur to set up the second oxyallylation.



2.200 **2.201** **2.202** **2.203**

Scheme 2.73: Proposed cascade oxyallylation reaction of 2.200

Diol substrate **2.200** could be easily accessed from intermediate **2.150**, obtained in the preparation of the MOM protected substrate **2.152** (Scheme 2.56). Reduction of *tert*-butyl ester **2.150** using lithium aluminium hydride in Et_2O afforded diol substrate **2.200** in 65% yield (Scheme 2.74).

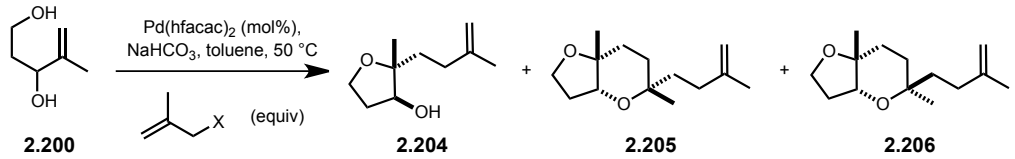


2.150 **2.200**

Scheme 2.74: Synthesis of diol 2.200

Upon treatment of diol **2.200** with 5 mol% $Pd(hfacac)_2$, $NaHCO_3$ and 5 equivalents of 3-bromo-2-methylpropene in toluene at 50 °C, the formation of several new species could be observed by TLC after 24 h (Table 2.23). However, unreacted starting material still remained and so an additional 5 mol% of $Pd(hfacac)_2$ and a further three equivalents of 3-bromo-2-methylpropene were added to the reaction mixture. The reaction mixture was

heated for a further 24 h, after which starting material still remained. Flash chromatography of the reaction mixture afforded three isolated products in a total yield of 35%: tetrahydrofuran **2.204** with the butenyl group and the hydroxyl group in a *trans* position relative to each other; *cis*-fused furopyran **2.205** with both methyl groups on the concave face; and *cis*-fused furopyran **2.206** with the methyl groups on opposite faces (entry 1). Alteration of the allyl species to the corresponding chloride and increasing the number of equivalents improved the total yield slightly to 44% (entry 2) but addition of a total of 15 mol% catalyst further increased the total yield to 62% (entry 3) and gave rise to full conversion of the starting material. Use of 20 equivalents of chloride allowed a similar yield and conversion to be obtained with only 10 mol% catalyst (entry 4).



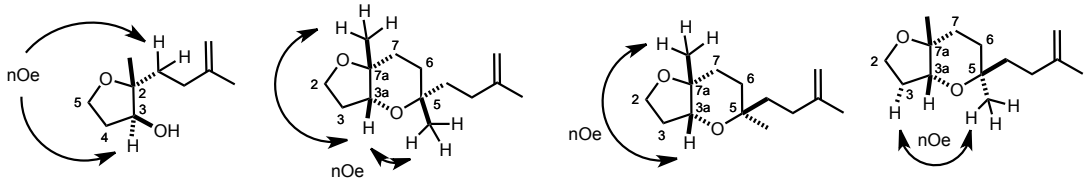
2.200 **2.204** **2.205** **2.206**

Entry	Pd	X	Equiv	Time	Result[a]			Total Yield[b]
	mol%		X		**2.204**	**2.205**	**2.206**	
1	5+5	Br	5+3	51 h	21%	7%	7%	35%
2	10	Cl	10	24 h	24%	13%	7%	44%
3	10+5	Cl	10	48 h	27%	15%	20%	62%
4	10	Cl	20	48 h	28%	18%	18%	64%

[a] Isolated yield of **2.204**, **2.205** and **2.206**; [b] sum of the yields of **2.204**, **2.205** and **2.206**

Table 2.23: Cascade oxyallylation of 2.200

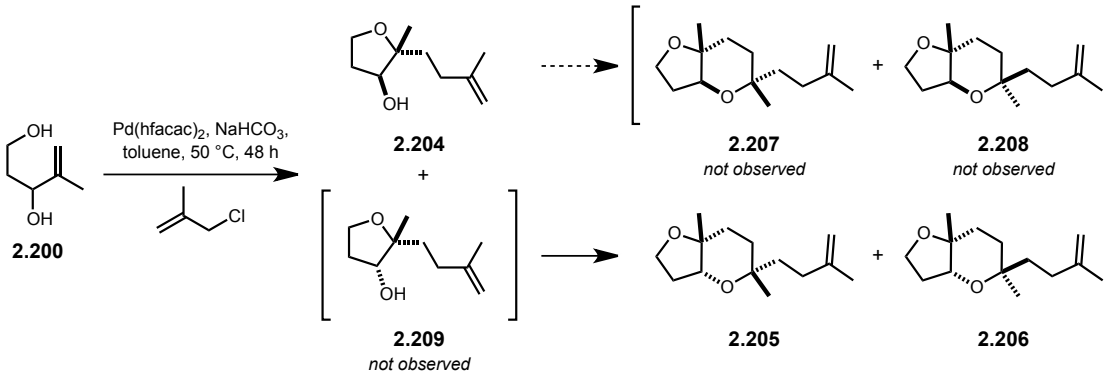
In the reactions which achieved full conversion (Table 2.23, entries 3 and 4), the *cis* reaction products are formed in a slight preference to the *trans* products in an approximate ratio of 1.3:1, consistent with the diastereomeric ratio observed in the oxyallylation of the corresponding MOM protected substrate **2.152** (Scheme 2.57). The product structures were assigned using 2D ^{1}H NMR spectroscopy (Scheme 2.75). Tetrahydrofuran **2.204** showed an nOe between 3-H and the CH_2 on the 2-butenyl group, indicating a *trans* stereochemistry between the butenyl group and the hydroxyl group. Furopyran **2.205** showed an nOe between the 3a-H and the 7a-CH_3, indicating the rings were *cis*-fused. An additional nOe between the 3a-H and the 5-CH_3 indicated that the two methyls were on the same face of the molecule. Furopyran **2.206** also showed an nOe between the 3a-H and the 7a-CH_3, indicating *cis*-fusion but an nOe between the 3-H and the 5-CH_3 indicated that this species was diastereomeric with **2.205** at the 5-position.



2.204 **2.205** **2.206**

Scheme 2.75: Assignment of the stereochemistry of 2.204–2.206 by nOe

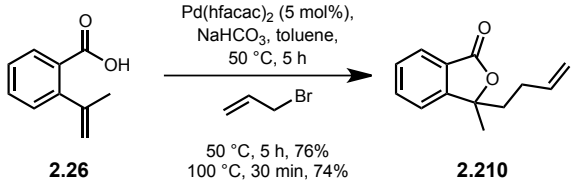
The formation of the observed products **2.204**, **2.205** and **2.206** is consistent with the proposed cascade cyclisation reaction (Scheme 2.73). Oxyallylation of diol **2.200** with 3-chloro-2-methylpropene would afford a mixture of tetrahydrofuran isomers **2.204** and **2.209** (Scheme 2.76). Both isomers could undergo a further oxyallylation reaction; however, *trans*-fused furopyran products **2.207** and **2.208** were not observed. Conversely, the tetrahydrofuran **2.209** was not observed, instead this product undergoes further oxyallylation to afford diastereomeric furopyran products **2.205** and **2.206**. Although this cascade cyclisation affords mixtures of products in a moderate overall yield, it demonstrates the ability of this methodology to rapidly construct complex architectures from simple starting materials.



2.200 **2.204** + **2.209** *not observed* **2.207** *not observed* **2.208** *not observed* **2.205** **2.206**

Scheme 2.76: Possible products from oxyallylation/cascade oxyallylation of 2.200

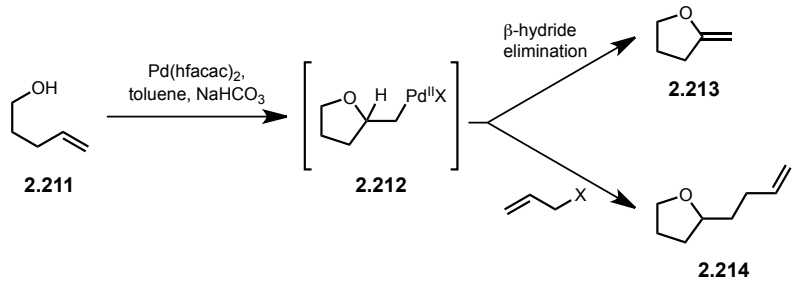
In the oxyallylation examples discussed thus far, the nucleophile participating in the heterocyclisation step is an alcohol. Waser and co-workers demonstrated the successful heterocyclisation of a range of carboxylic acid substrates in their reported oxyalkynylation reaction (Section 1.2, Scheme 1.21).[43] As carboxylic acid **2.26** is an intermediate in the synthesis of benzylic alcohol **2.27** (Section 2.2.2, Scheme 2.10), this substrate was readily available to investigate if the oxyallylation conditions could be applied to the heterocyclisation of carboxylic acids to obtain lactone products. Upon treatment of **2.26** with catalytic $Pd(hfacac)_2$, $NaHCO_3$ and allyl bromide in toluene at 50 °C, complete conversion to the desired lactone product resulted, affording **2.210** in 76% yield (Scheme 2.77). This oxyallylation of **2.26** could achieve full conversion in only 30 minutes by heating the reaction at 100 °C, with no depreciation in the yield of product obtained.



Scheme 2.77: Oxyallylation of carboxylic acid 2.26

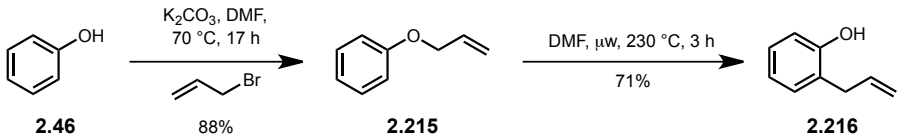
2.3.4 Reaction Limitations: Oxyallylation of Monosubstituted Alkenes

As has been discussed, the Pd(II)-alkyl intermediate **2.212** produced by oxypalladation of an alkene can readily undergo β-hydride elimination, affording products such as **2.213** (Scheme 2.78). In the examples discussed thus far, β-hydride elimination has been prevented by employing substrates which would not have a β-hydrogen in the Pd(II)-alkyl intermediate. In order to expand the generality of the oxyallylation reaction, it would be beneficial if the oxyallylation reaction could allow access to products such as **2.214**, derived from a heterocyclisation reaction onto a monosubstituted alkene.



Scheme 2.78: Pathways for heterocyclisation of monosubstituted alkene 2.211

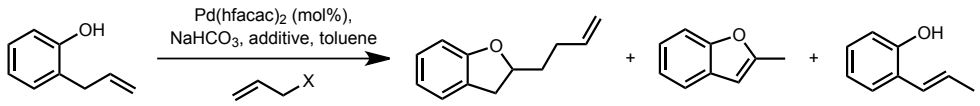
In order to assess whether the oxyallylation methodology could be extended to substrates with monosubstituted alkenes, *o*-allyl phenol **2.216** was synthesised (Scheme 2.79). Phenol **2.46** was alkylated with allyl bromide and potassium carbonate at 70 °C in DMF to afford allyl phenyl ether **2.215** in 88% yield. This was followed by a Claisen rearrangement using microwave irradiation at 230 °C for 3 h to afford *o*-allyl phenol **2.216** in 71% yield.



Scheme 2.79: Synthesis of *o*-allyl phenol 2.216

When *o*-allyl phenol **2.216** was treated with 5 mol% $Pd(hfacac)_2$, $NaHCO_3$ and allyl bromide in toluene at 50 °C, consumption of the starting material occurred in 2 h (Table 2.24). However, desired product **2.217** was not observed and the main component of the reaction mixture proved to be 2-methylbenzofuran **2.218** (entry 1). Despite lowering the

reaction temperature to ambient, formation of side product **2.218** was not suppressed nor was oxyallylation product **2.217** observed (entry 2). Chloride additives can be used to suppress β-hydride elimination,[121,122,123] however, addition of lithium chloride still afforded 2-methylbenzofuran **2.218**, albeit at a reduced rate (entry 3). Changing the electrophile to allyl chloride gave 2-methylbenzofuran **2.218** preferentially however some conversion to oxyallylation product **2.217** was observed (entry 4). Lowering the reaction temperature to ambient gave an improved ratio of oxyallylation product **2.217** to 2-methylbenzofuran **2.218**, but with a significant proportion of unreacted starting material (entry 5). The desired oxyallylation product **2.217** could be isolated in 19% yield. *trans*-β-Methylstyrene **2.219** was formed as a minor side product in all of these reactions (entries 1–5).



2.216 **2.217** **2.218** **2.219**

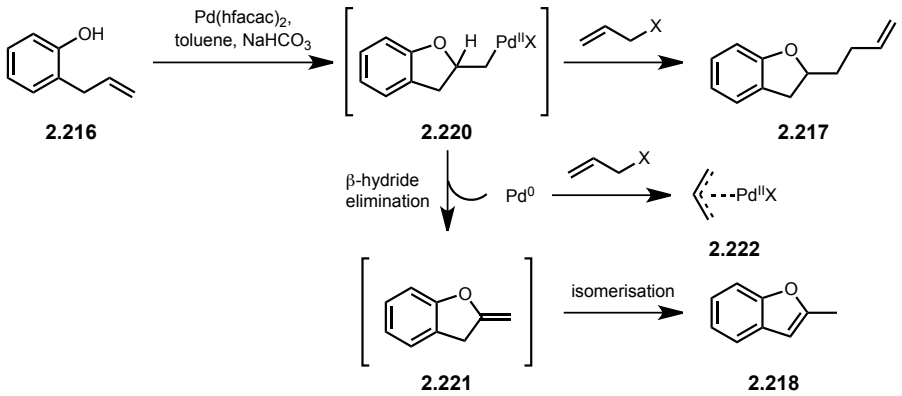
Entry	Pd mol%	X	Additive	Temp	Time	Result[a] **2.216**	**2.217**	**2.218**	**2.219**
1	5	Br	-	50 °C	2 h	0.3	0	1	0.2
2	5	Br	-	RT	20 h	0.3	0	1	0.3
3	5	Br	LiCl[b]	50 °C	30 h	0	0	1	0.3
4	5+5	Cl	-	50 °C	27 h	0	0.3	1	0.3
5	10	Cl	-	RT	72 h	2	1.8[c]	1	0.6

[a] Approximate ratio of **2.216** : **2.217** : **2.218** : **2.219** by ^{1}H NMR of unpurified reaction mixture; [b] 1.2 equiv; [c] 19% isolated yield

Table 2.24: Initial optimisation of oxyallylation of 2.216

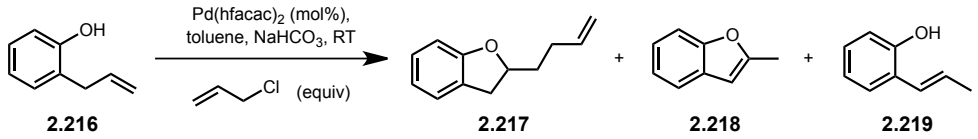
Under the oxyallylation conditions, phenol substrate **2.216** undergoes oxypalladation to afford Pd(II)-alkyl intermediate **2.220** (Scheme 2.80). In the desired transformation, this species would be trapped with the allyl electrophile to give oxyallylation product **2.217**. However, as Pd(II)-alkyl intermediate **2.220** has a β-hydrogen, β-hydride elimination could instead occur to afford **2.221**, which is not observed but instead undergoes isomerisation to the thermodynamically more stable 2-methylbenzofuran **2.218**. The formation of 2-methylbenzofuran **2.218** as a side product should produce Pd(0), suggesting that this species could only be formed in quantities corresponding to the catalyst loading. However, as 2-methylbenzofuran **2.218** was the main observed product (Table 2.24, entries 1–4), Pd(0) must have been re-oxidised to Pd(II) in order for catalysis to continue. This could occur by: re-oxidation with molecular oxygen; or oxidative addition of Pd(0) to

allyl halide to produce a Pd(II)-allyl species **2.222** (Scheme 2.80), which could then carry out further oxypalladation–β-hydride elimination.



Scheme 2.80: Formation of side product 2.218 in oxyallylation of 2.216

The preferential formation of 2-methylbenzofuran **2.218** over oxyallylation product **2.217** indicates that β-hydride elimination is occurring faster than the reaction of Pd(II)-alkyl intermediate **2.220** with the allyl electrophile. In order to increase the rate of the latter step relative to β-hydride elimination, the reaction was carried out at a higher concentration (Table 2.25). Using 5 mol% $Pd(hfacac)_2$, this gave an improved ratio of 1:0.1 of the oxyallylation product to the β-hydride elimination product, affording desired product **2.217** in 37% yield, although with substantial unreacted starting material still present (Table 2.25, entry 1). Increasing the number of equivalents of allyl chloride from 5 to 10 was also effective in suppressing the formation of 2-methylbenzofuran **2.218** (entry 2). Carrying out the oxyallylation reaction with 10 mol% $Pd(hfacac)_2$ and 10 equivalents of allyl chloride in 1 M toluene afforded nearly complete conversion of the starting material after stirring at room temperature for 144 h (entry 3). Desired product **2.217** could be isolated in 61% yield. Further increasing the number of equivalents of allyl chloride used to 20 gave lower conversion, presumably due to the effective decrease in the reaction concentration (entry 4). Carrying out the reaction neat in 10 equivalents of allyl chloride (entry 5) also gave lower conversion over the same time period. The reaction volume in this case was very low and it is possible that, as the mixture contains a heterogeneous base, improper mixing gave rise to lower conversion.



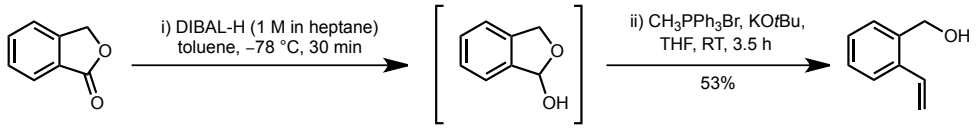
2.216 **2.217** **2.218** **2.219**

Entry	Pd (mol%)	Conc. toluene	Equiv Cl	Time	Result[a]			
					2.216	**2.217**	**2.218**	**2.219**
1	5	1 M	5	144 h	3.5	1 (37%)[b]	0.1	0.1
2	5	0.25 M	10	120 h	3	1	0.3	0.1
3	10	1 M	10	144 h	0.1	1 (61%)[b]	0.2	0.1
4	10	1 M	20	144 h	0.4	1	0.2	0.1
5	10	neat	10	120 h	1.7	1	0.2	0.2

[a] Approximate ratio of **2.216** : **2.217** : **2.218** : **2.219** by ^{1}H NMR of unpurified reaction mixture; [b] isolated yield of **2.217**

Table 2.25: Optimisation of the oxyallylation of 2.216

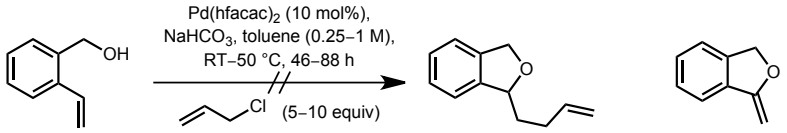
With conditions successfully optimised to effect the oxyallylation of *o*-allyl phenol **2.216**, the application of this methodology to the heterocyclisation of other monosubstituted alkene substrates was investigated. As the corresponding disubstituted alkene **2.27** (Section 2.3.3, Table 2.19) had shown excellent reactivity in the oxyallylation reaction, benzylic alcohol **2.224** was prepared (Scheme 2.81). Substrate **2.224** was prepared by DIBAL-H reduction of phthalide **2.164** to lactol **2.223** followed by a Wittig olefination. This procedure afforded **2.224** in 53% yield.[124]



2.164 **2.223** **2.224**

Scheme 2.81: Synthesis of 2.224

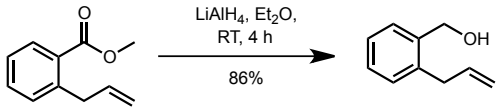
Although, in the disubstituted alkene cyclisations reported, benzylic alcohol substrate **2.27** (Section 2.3.3, Table 2.19) had shown greater reactivity than phenol substrate **2.38** (Section 2.3.1, Table 2.15), hydroxyalkene **2.224** proved unreactive under a range of oxyallylation conditions (Scheme 2.82). Increasing the concentration of the reaction medium, employing a range of temperatures, and use of a larger excess of allyl electrophile were all unsuccessful approaches to carry out the oxyallylation of **2.224**. This substrate appeared to be completely unreactive under this range of conditions, giving unreacted starting material in every case. The product of oxypalladation–β-hydride elimination **2.226** was also not observed, suggesting that this substrate did not undergo the initial oxypalladation reaction. It is possible that this substrate is unable to adopt the correct conformation to undergo oxypalladation.



2.224 | **2.225** *not observed* | **2.226** *not observed*

Scheme 2.82: Attempted oxyallylation of 2.224

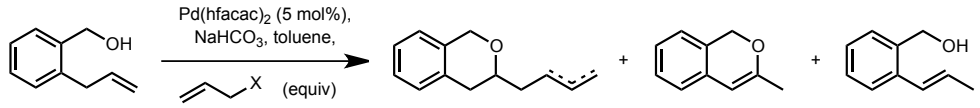
As γ-hydroxyalkene **2.224** had shown no reactivity in the oxyallylation reaction, δ-hydroxyalkene **2.228** was prepared (Scheme 2.83); cyclisation of substrate **2.228** would afford a dihydropyran product rather than a dihydrofuran product and the alkene in this substrate is not conjugated with the aromatic system. The substrate was prepared by lithium aluminium hydride reduction of ester **2.227**[113] to afford the desired product in 86% yield.



2.227 | **2.228**

Scheme 2.83: Synthesis of 2.228

Under the standard oxyallylation conditions using allyl chloride, complete consumption of hydroxyalkene **2.228** was observed to afford a 1:0.2 mixture of the product of β-hydride elimination–isomerisation **2.230** and the alkene isomer of starting material **2.231** (Table 2.26, entry 1). Desired product **2.229** was not observed using these conditions at 50 °C or at room temperature (entry 2). By employing the conditions optimised for the oxyallylation of *o*-allyl phenol **2.216** (Table 2.25, entry 3), using 10 equivalents of allyl chloride and carrying out the reaction 1 M in toluene, a 1:1 mixture of desired product **2.229** to β-hydride elimination product **2.230** could be afforded (entry 3). The oxyallylation product **2.229** was afforded in a 31% yield, albeit contaminated with alkene isomers of the product. Recourse to allyl bromide in an attempt to suppress alkene isomerisation (entry 4) afforded complete conversion to β-hydride elimination product **2.230**.



2.228 **2.229** **2.230** **2.231**

Entry	X	Equiv X	Conc. toluene	Temp	Time	Result[a] 2.228	2.229	2.230	2.231
1	Cl	5	0.25 M	50 °C	2 h	0	0	1	0.2
2	Cl	5	0.25 M	RT	6 h	0	0	1	0.1
3	Cl	10	1 M	RT	24 h	0	1 (31%)[b]	1	0
4	Br	10	1 M	RT	19 h	0	0	1	0

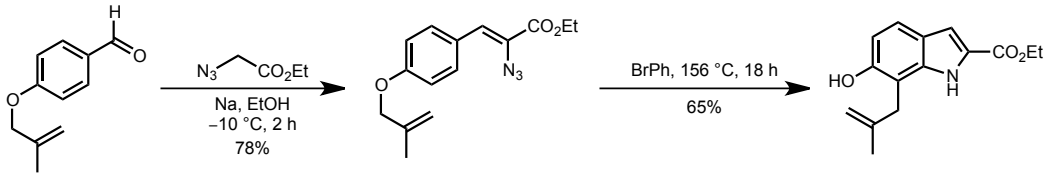
[a] Approximate ratio of **2.228** : **2.229** : **2.230** : **2.231** by ^{1}H NMR of unpurified reaction mixture; [b] Yield after flash chromatography, material isolated was mixture of aprroximately 1:0.4 of terminal to internal alkenes

Table 2.26: Oxyallylation of 2.228

Although conditions were found which successfully effected the oxyallylation of *o*-allyl phenol substrate **2.216**, these conditions did not prove as effective when applied to the heterocyclisation of other substrates. Oxypalladation of monosubstituted alkenes thus remains a challenge in this methodology.

2.3.5 Reaction Limitations: Nitrogen-Containing Substrates

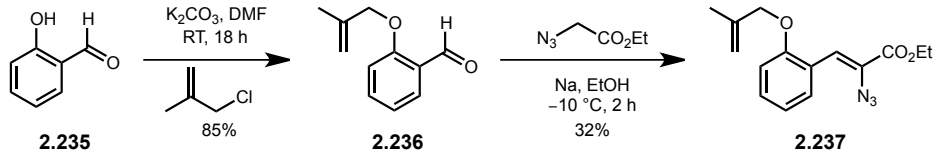
Nitrogen containing structures are prevalent in natural products and the ability to construct these species using the developed oxyallylation reaction would be beneficial. As indole is a commonly found moiety in bioactive compounds, the investigation of the heterocyclisation of nitrogen-containing substrates commenced with the design of an indole substrate. Moody reported a convenient method for the regioselective one-pot ring closure–Claisen rearrangement of allyloxyazidocinnamates **2.233** to afford substituted hydroxyindoles **2.234** (Scheme 2.84).[125] The allyloxyazidocinnamates **2.233** were formed in excellent yield by reaction of the corresponding allyloxybenzaldehyde **2.232** with sodium ethoxide and ethyl azidoacetate. The allyloxyazidocinnamate **2.233** could then undergo a Hemetsberger–Knittel indole formation and Claisen rearrangement in bromobenzene to give hydroxyindole **2.234** in 65% yield.



2.232 **2.233** **2.234**

Scheme 2.84: Synthesis of hydroxyindole 2.234

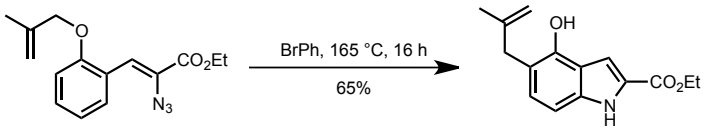
Alkylation of salicylaldehyde **2.235** with 3-chloro-2-methylpropene and potassium carbonate in DMF at room temperature afforded aldehyde **2.236** in 85% yield (Scheme 2.85).[118] Following the procedure reported by Moody, addition of a solution of aldehyde **2.236** and ethyl azidoacetate to freshly prepared sodium ethoxide afforded a 32% yield of the azidocinnamate product **2.237**. The low yield observed in this condensation reaction is attributable to partial conversion of the starting material and the difficulty in purifying the product **2.237**, which required repeated flash chromatography and trituration in order to be obtained pure.



2.235 **2.236** **2.237**

Scheme 2.85: Synthesis of 2.237

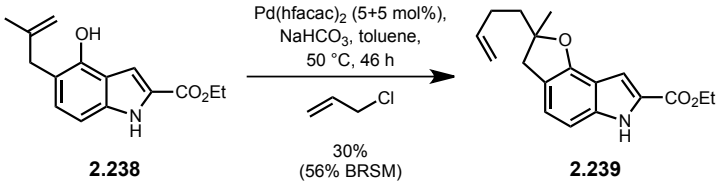
Despite the low yielding condensation reaction, sufficient allyloxyazidocinnamate **2.237** had been obtained to attempt the one-pot Hemetsberger–Knittel reaction–Claisen rearrangement (Scheme 2.86). The high boiling point of bromobenzene (156 °C) made the solvent difficult to remove and so the reaction mixture was subjected directly to flash chromatography to afford a 65% yield of hydroxyindole **2.238**.



2.237 **2.238**

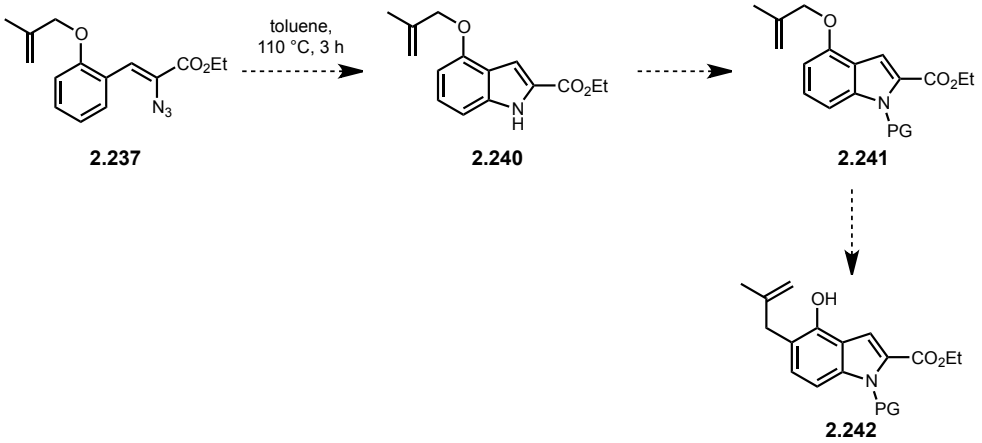
Scheme 2.86: Hemetsberger–Knittel–Claisen rearrangement of 2.237

Upon treatment of hydroxyindole substrate **2.238** with 5 mol% $Pd(hfacac)_2$, $NaHCO_3$ and allyl chloride in toluene at 50 °C, a small amount of conversion to a new, less polar species could be observed by TLC (Scheme 2.87). However, conversion remained low after 22 h and so an additional 5 mol% $Pd(hfacac)_2$ was added to the reaction mixture. After a further 24 h of heating, unreacted starting material still remained so the reaction was halted. Conversion to the desired product had occurred, with the furanoindole oxyallylation product **2.239** isolated in 30% yield (56% based on recovered starting material). Although a full recovery of starting material **2.238** was not achieved, the reaction itself was clean, with low conversion accounting for the low yield observed. As the investigation of the substrate scope has already demonstrated that the oxyallylation reaction tolerates ester groups and substitution *ortho* to the reacting phenol group (Section 2.3.2, Scheme 2.29), this low reactivity is likely to be due to the presence of the indole nitrogen.



Scheme 2.87: Oxyallylation of 2.238

In order to probe whether this effect was due to coordination of the indole nitrogen, an *N*-protected analogue of indole **2.238** was desired. As Moody and co-workers had demonstrated that the Hemetsberger-Knittel reaction could be effected in toluene at 110 °C without accompanying Claisen rearrangement,[125] it was envisaged that synthesis of **2.240** may allow protection of the indole nitrogen to afford **2.241** prior to effecting the Claisen rearrangement (Scheme 2.88). However, in attempting to prepare additional allyloxyazidocinnamate **2.237** to carry out this synthetic sequence, the condensation reaction of the aldehyde with ethyl azidoacetate was found to be irreproducible and led only to decomposition.

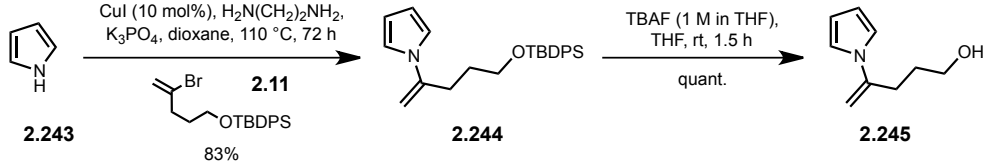


Scheme 2.88: Proposed synthesis of *N*-protected indole substrate 2.242

As protected indole substrate **2.242** could not be accessed through the route detailed in Scheme 2.88, selective nitrogen-protection *versus* oxygen protection in hydroxyindole **2.238** was investigated. However, although a number of strategies exist for the protection of indole nitrogen in the presence of a phenolic hydroxyl group *via* double protection, mono-deprotection methods,[126] attempts to carry out this kind of transformation led to mixtures of inseparable products and so this strategy was abandoned.

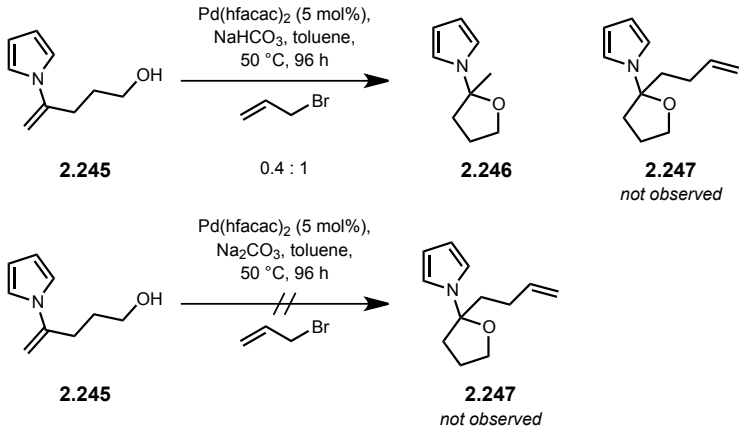
As the oxyallylation of hydroxyindole substrate **2.238** had proven low yielding (Scheme 2.87), the synthesis and heterocyclisation of an alternative substrate containing a nitrogen heterocycle was investigated. Pyrrole is a moiety that is also prevalent in biologically active compounds and has low basicity due to the delocalisation of the nitrogen lone pair

into the aromatic ring. Padwa and co-workers reported a copper-catalysed coupling method for the synthesis of *N*-alkenylindoles as intermediates for alkaloid synthesis.[127] Using this methodology, vinyl bromide **2.11** (Section 2.2.1, Scheme 2.4) could be coupled with pyrrole to afford *N*-alkenyl pyrrole **2.244** in 83% yield (Scheme 2.89). Deprotection of the silyl group of **2.244** gave a quantitative yield of hydroxyalkene **2.245**.



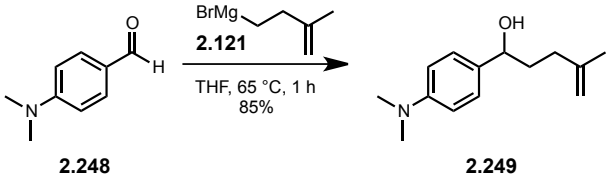
Scheme 2.89: Synthesis of 2.245

When subjected to the standard oxyallylation conditions with allyl bromide, the reaction of **2.245** showed unreacted starting material, even after an extended heating period (Scheme 2.90). The ^{1}H NMR spectrum of the crude material did not show any allylated products, but appear to have formed protocyclisation product **2.246**. In order to investigate if this side product could be suppressed, a stronger base was used. Although formation of protocyclisation product **2.246** was suppressed when $NaHCO_3$ was replaced with Na_2CO_3, under otherwise identical conditions, oxyallylation product **2.247** was not formed and unreacted starting material remained the only component of the reaction mixture.



Scheme 2.90: Attempted oxyallylation of 2.245

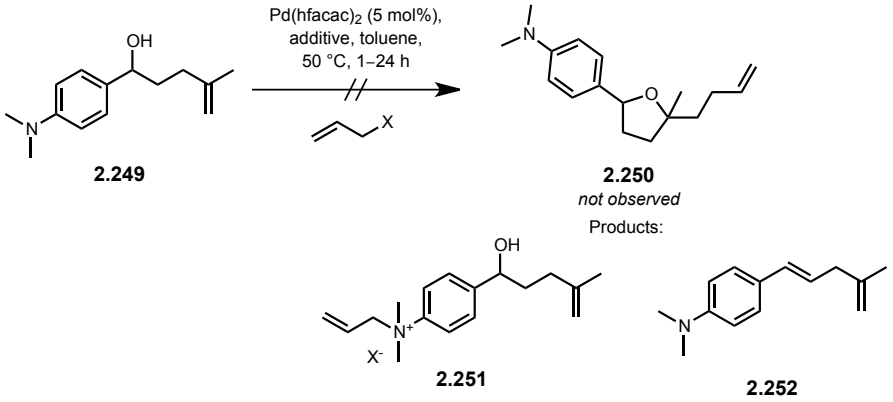
As the oxyallylation of nitrogen heterocycle-containing substrates had proven mostly unsuccessful (Schemes 2.85 and 2.88), the synthesis and heterocyclisation of aniline substrates was explored. Tertiary amine **2.249** could be easily accessed in one step by a Grignard reaction analogously to the preparation of secondary and tertiary alcohol substrates **2.123–2.125** and **2.128** detailed earlier (Schemes 2.41 and 2.42). Treatment of 4-dimethylaminobenzaldehyde **2.248** with Grignard **2.121** in THF afforded the secondary alcohol **2.249** in excellent yield (Scheme 2.91).



2.248 **2.249**

Scheme 2.91: Synthesis of 2.249

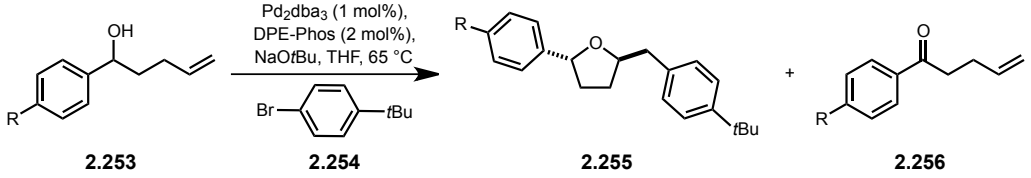
When substrate **2.249** was subjected to the oxyallylation conditions with allyl bromide, the reaction mixture formed a sticky gum on the walls of the vessel (Table 2.27). The gum was found to be quite insoluble and a dichloromethane/methanol solvent mixture was required for dissolution. The ^{1}H NMR spectrum of the crude material contained signals corresponding to an allyl group, but was not consistent with heterocyclisation product **2.250**, due to a lack of aliphatic signals consistent with the tetrahydrofuran moiety, observed in the analogous oxyallylations of **2.123** and **2.124** (Schemes 2.44 and 2.47). Based on this observation, the insolubility of this material in toluene and the observation that the species had a baseline R_f by TLC, it is believed that the allyl quaternary ammonium salt **2.251** formed in the attempted oxyallylation of **2.249** (entry 1). In the absence of a base, decomposition was observed (entry 2). The reaction was repeated in the absence of a base but with one equivalent of trifluoroacetic acid added in the hope that protonation of the nitrogen would allow the oxyallylation reaction to proceed. However, rapid consumption of starting material **2.249** occurred under these conditions to afford elimination product **2.252** (entry 3). Alteration of the electrophile to allyl chloride also afforded elimination product **2.252** (entry 4).



Entry	X	Additive	Time	Result
1	Br	$NaHCO_3$	25 h	**2.251**
2	Br	-	2 h	decomposition
3	Br	TFA (1 equiv)	1 h	**2.252**
4	Cl	-	24 h	**2.252**

Table 2.27: Attempted oxyallylation of 2.249

Wolfe and co-workers were able to carry out the carboetherification of similar substrates **2.253** using a Pd(II) catalyst produced from oxidative addition of aryl bromide **2.254** to Pd(0) (Table 2.28).[37] However, the authors found that, as the electron donating ability of the *para* substituent R increased (entry 2 *cf*. entries 3 and 4), the isolated yield of desired product **2.255** decreased and ketone side product **2.256** was observed in greater proportions. These results indicate that, as well as chelation effects, inductive effects can also have an impact on yields in oxypalladation reactions.



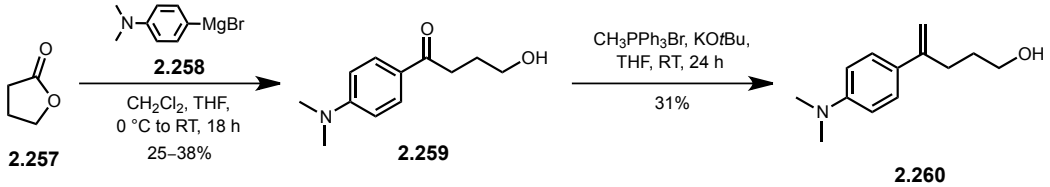
2.253 **2.254** **2.255** **2.256**

Entry	R	Yield[a]	Ratio[b]	
			2.255	**2.256**
1	CF_3	64%	20	1
2	H	69%	20	1
3	OMe	58%	5	1
4	NMe_2	35%	3	1

[a] Isolated yield of **2.255**; [b] Ratio of isolated yield of **2.255** to **2.256**

Table 2.28: Effect of aryl substitution on carboetherification of alcohols 2.253

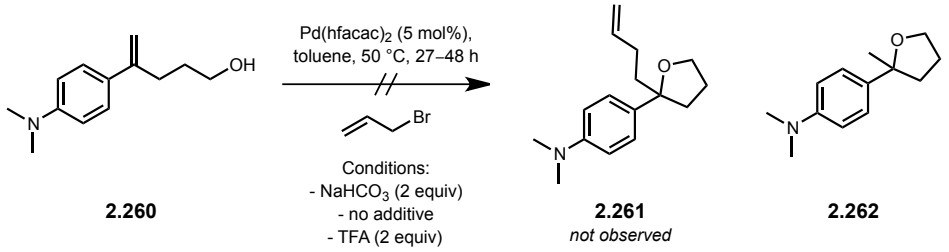
In order to circumvent the formation of side products such as elimination product **2.252**, observed in the attempted oxyallylation of **2.249** (Table 2.27), a substrate such as **2.260** was sought (Scheme 2.92); this substrate should be less susceptible to elimination of the hydroxyl group. Butyrolactone **2.257** was treated with 4-dimethylaminophenylmagnesium bromide **2.258** in a dichloromethane:THF solvent mixture. This afforded desired ketone **2.259** in relatively low yields, but gave sufficient material for the subsequent Wittig olefination, affording alkene **2.260** in 31% yield. Both products in this synthetic sequence proved very difficult to purify, requiring repeated flash chromatography to obtain clean material. Substrate **2.260** proved to be slightly unstable, with new impurities observed in the second purification that had not been present subsequent to the first purification.



2.257 **2.259** **2.260**

Scheme 2.92: Synthesis of 2.260

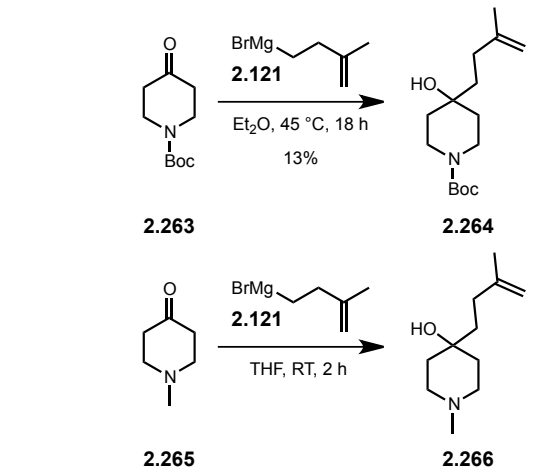
Under the standard oxyallylation conditions using allyl bromide, reaction of **2.260** gave rise to complete consumption of the starting material, however formation of desired product **2.261** was not observed (Scheme 2.93). Instead, a complex mixture of components was obtained. When carrying out the reaction in the absence of an exogenous base, protocyclisation product **2.262** was found to be the main component of the reaction mixture, along with a number of other minor impurities. In an attempt to protonate the tertiary amine to allow the oxyallylation reaction to occur, the reaction was carried out in the absence of a base but with 2 equivalents of TFA added. Consumption of the starting material was observed giving rise to formation of a complex mixture, with no allylated components observed.



2.260 **2.261** *not observed* **2.262**

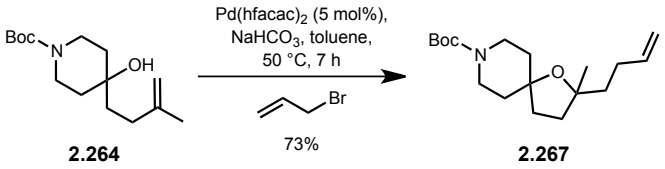
Scheme 2.93: Attempted oxyallylation of 2.260

Although little success was achieved in the oxyallylation of amine-containing substrates, all of the examples described have featured aniline or heteroaromatic nitrogen groups. Aliphatic amine containing substrates could be very easily accessed by treatment of piperidinones with Grignard **2.121** (Scheme 2.94) in an analogous fashion to several of the substrates already discussed (Schemes 2.41, 2.42 and 2.89). Preparation of *N*-Boc and *N*-methyl substrates **2.264** and **2.266** *via* this method then reaction under the oxyallylation conditions should allow a direct comparison of the effect of the basicity of the nitrogen on the reactivity. Due to the problems encountered during the preparation of 4-bromo-2-methylbutene (Scheme 2.41), Grignard **2.121** was prepared from an impure batch of the corresponding bromide and the resulting Grignard reaction with 1-Boc-4-piperidone **2.263** was low yielding, although pure product **2.264** could be afforded (Scheme 2.94). Whilst desired product **2.266** was formed in the analogous reaction of Grignard **2.121** with 1-methyl-4-piperidone **2.265**, the material could not be obtained pure.



Scheme 2.94: Synthesis of 2.264 and 2.266

The *N*-Boc substrate **2.264** showed excellent reactivity when subjected to the standard oxyallylation conditions using allyl bromide, affording expected product **2.267** in 73% yield after 7 hours (Scheme 2.95). When compared with the reaction of substrate **2.125**, in which *N*-Boc is replaced with a methylene group (Scheme 2.49), the reaction of **2.264** proceeds in a slightly lower yield and longer reaction time, suggesting that the *N*-Boc group may still be having some effect on the reactivity. However, the successful cyclisation of an amine-containing substrate using this methodology expands the scope of the oxyallylation reaction.

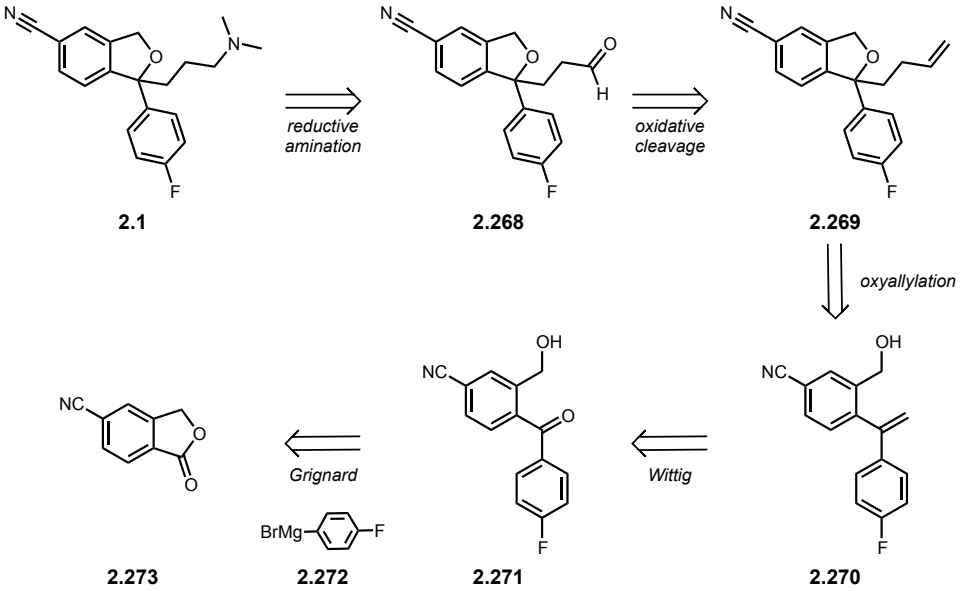


Scheme 2.95: Oxyallylation of 2.264

As expected from the greater reactivity of the oxyallylation reaction in the absence of coordinating ligands or solvents, the inclusion of basic nitrogen-containing moieties in the substrates proved to be detrimental to activity. Most of the amine-containing substrates analysed did not show formation of the desired product, with the exception of hydroxyindole substrate **2.238** and *N*-Boc protected substrate **2.264**. Whilst it is useful to note that functionalisation of nitrogen moieties with deactivating protecting groups allows the oxyallylation reaction to proceed, protection and deprotection steps elongates chemical syntheses, where the shortest possible strategy is desired.

2.4 Synthesis of Citalopram

In order to demonstrate the use of the developed methodology in an applied context, it was anticipated that selective serotonin reuptake inhibitor (SSRI) citalopram **2.1** could be accessed using the oxyallylation methodology developed (Scheme 2.96). The dimethylamino functional group of citalopram **2.1** could be introduced by reductive amination of aldehyde **2.268**, which in turn could be obtained by oxidative cleavage of terminal alkene **2.269**. Dihydroisobenzofuran **2.269** would be the product of the key step of this synthesis: the oxyallylation of hydroxyalkene **2.270**. Hydroxyalkene **2.270** could be obtained by Wittig olefination of ketone **2.271**, which in turn could be formed *via* Grignard reaction of 5-cyanophthalide **2.273** with 4-fluorophenylmagnesium bromide **2.272**.[114]

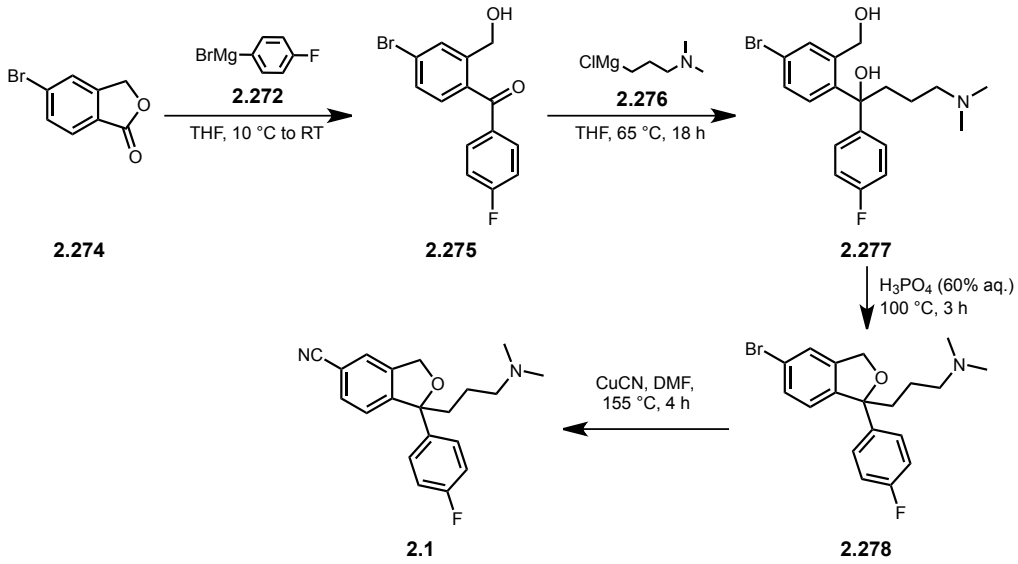


Scheme 2.96: Proposed synthetic route to citalopram 2.1

2.4.1 Selected Literature Syntheses of Citalopram and Escitalopram

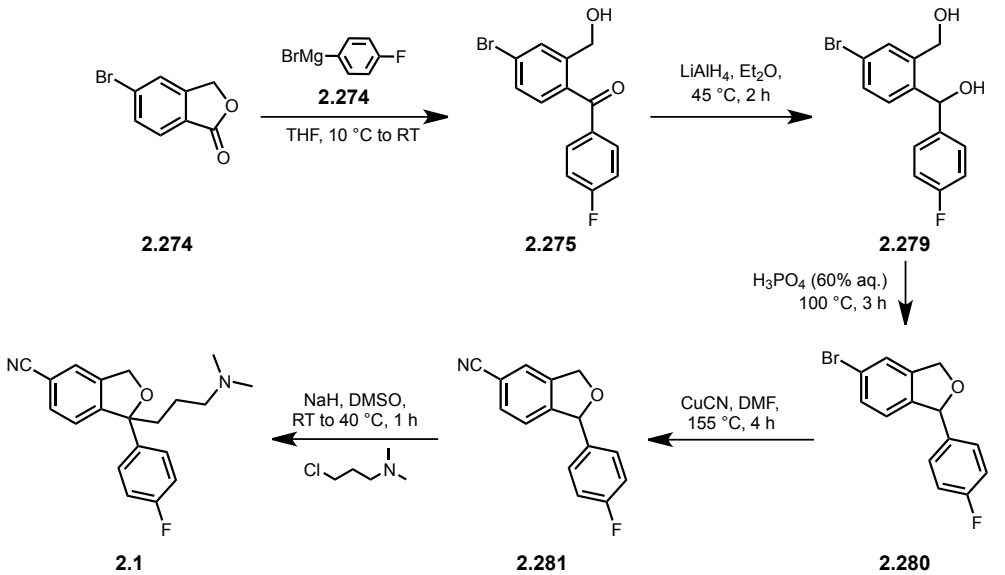
Citalopram **2.1** was first reported by Lundbeck in 1979 as having selective potentiating effects on the concentrations of tryptophan and 5-hydroxytryptophan.[128] SSRIs are used clinically to treat anxiety and depression and operate by reducing reuptake of serotonin from the synapse to the presynaptic cell terminal by the serotonin transporter (SERT).[129] Citalopram **2.1** binds to SERT with high affinity and selectivity relative to other monoamine transporters.[130] The Lundbeck patent detailed two strategies for accessing citalopram **2.1** and its analogues: two sequential Grignard reactions to introduce the 4-fluorophenyl and dimethylaminopropyl substituents followed by ring closure (Scheme 2.97); or a Grignard reaction to introduce the 4-fluorophenyl substituent, ring closure of the dihydrofuran followed by alkylation to introduce the dimethylaminopropyl group (Scheme 2.98). In the

former strategy, 5-bromophthalide **2.274** was treated with 4-fluorophenylmagnesium bromide **2.272** to afford ketone **2.275** (Scheme 2.97). Ketone **2.275** was then treated with 3-(dimethylamino)propylmagnesium chloride **2.276** to afford diol **2.277**, which undergoes ring closure in phosphoric acid to give dihydroisobenzofuran **2.278**. Treatment of **2.278** with copper cyanide in DMF at 155 °C introduces the nitrile group to form citalopram **2.1**.



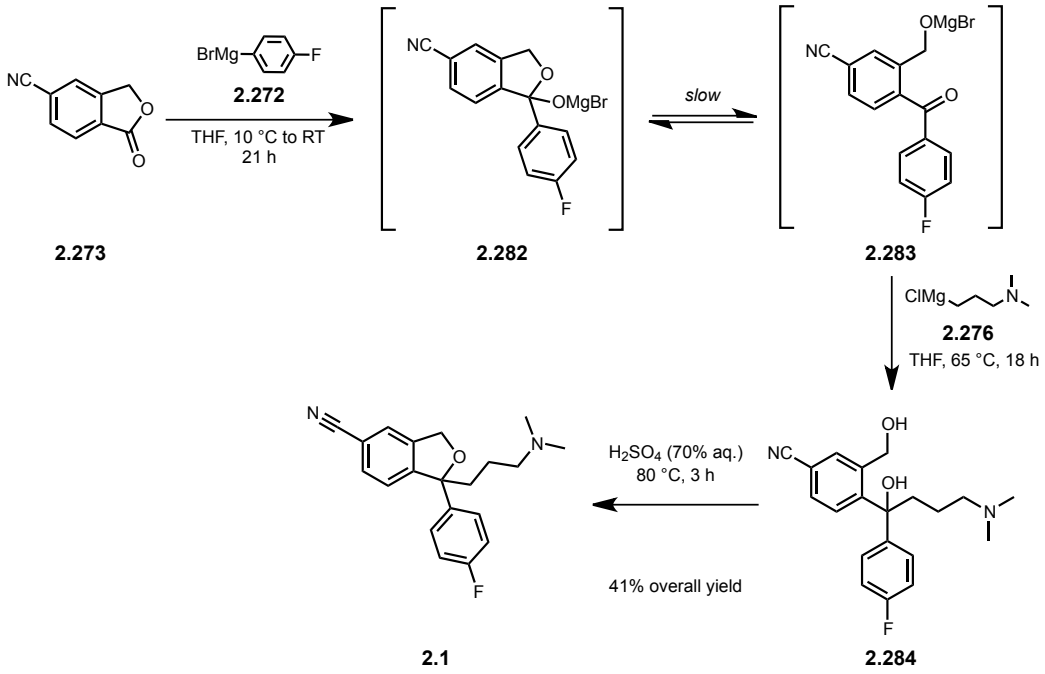
Scheme 2.97: Sequential Grignard strategy to synthesis citalopram 2.1

Alternatively, following Grignard reaction of 5-bromophthalide **2.274** with **2.272**, ketone **2.275** was reduced with lithium aluminium hydride to afford diol **2.279** (Scheme 2.98). Diol **2.279** was then cyclised in phosphoric acid to afford dihydroisobenzofuran **2.280** followed by introduction of the cyano group using CuCN in DMF. Alkylation of **2.281** with sodium hydride and dimethylaminopropyl chloride affords citalopram **2.1**.



Scheme 2.98: Grignard–Alkylation strategy to synthesise citalopram 2.1

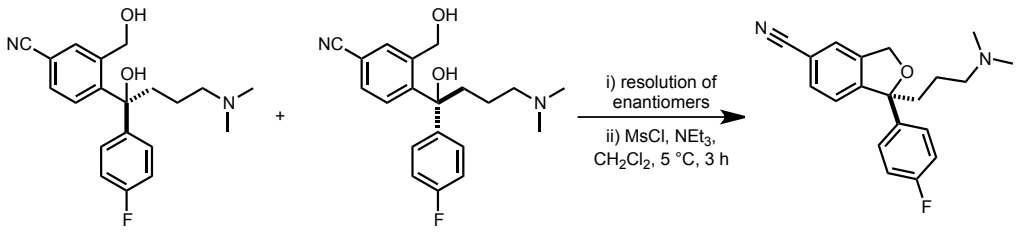
Lundbeck found these routes to be problematic in the scale up and production of citalopram **2.1**, so developed a shorter route to access the compound (Scheme 2.99).[131] The nitrile group had originally been installed at a later stage in the synthesis due to anticipated side reactions between the nitrile group and Grignard reagents **2.272** and **2.276**, or the strong acid employed in the synthesis. However, it was found that 5-cyanophthalide **2.273** could be reacted directly with 4-fluorophenylmagnesium bromide **2.272**, with the Grignard reagent added over a period of 3 hours. After standing overnight, the reaction mixture was treated with 3-(dimethylamino)propylmagnesium chloride **2.276** to afford diol **2.284**. Although this material can be isolated and purified, crude diol **2.284** can also be used directly in the ring closure in sulfuric acid. This sequence proved to be robust on technical scale and afforded pure citalopram **2.1** in just three steps and in 41% overall yield.



Scheme 2.99: Improved synthesis of citalopram 2.1

Lundbeck were unable to achieve resolution of the enantiomers of citalopram **2.1** by crystallisation of diastereomeric salts.[132] However, it was found that enantiomeric diols **(*S*)-2.284** and **(*R*)-2.284** could be separated by: reaction with an enantiomerically pure acid derivative (acid chloride, anhydride or labile ester), followed by separation of the diastereomeric esters by HPLC or fractional crystallisation; or stereoselective crystallisation with an enantiomerically pure acid. Stereoselective ring closure of the pure enantiomers using mesyl chloride and triethylamine afforded the individual enantiomers, upon which (*S*)-(+)-citalopram **(*S*)-2.1** was found to be >50-fold more active than (*R*)-(–)-citalopram **(*R*)-2.1** (Scheme 2.100). Chromatographic separation of the enantiomers of citalopram **2.1** or intermediate diol **2.284** to afford (*S*)-(+)-citalopram **(*S*)-2.1**, also known

as escitalopram, could also be achieved using a chiral stationary phase such as Chiralpak™ AD or Chiralcel™ OD.[133]



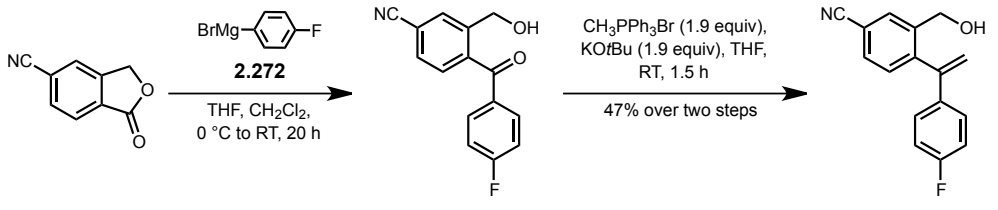
(*S*)-2.284 **(*R*)-2.284** **(*S*)-2.1**

Scheme 2.100: Resolution of enantiomers of 2.284 in synthesis of escitalopram (*S*)-2.1

These methods of preparing enantiomerically pure escitalopram **(*S*)-2.1** make use of chiral pool reagents or chromatographic methods that are likely to add considerable expense to the synthesis. In addition to this, as escitalopram **(*S*)-2.1** is prepared by separation of a racemate, 50% of the material formed during the synthesis corresponds to the undesired enantiomer. Use of a synthetic method that establishes the stereochemistry of the chiral centre in an enantioselective fashion would constitute a significant improvement.

2.4.2 Synthesis of Citalopram *via* an Oxyallylation Reaction

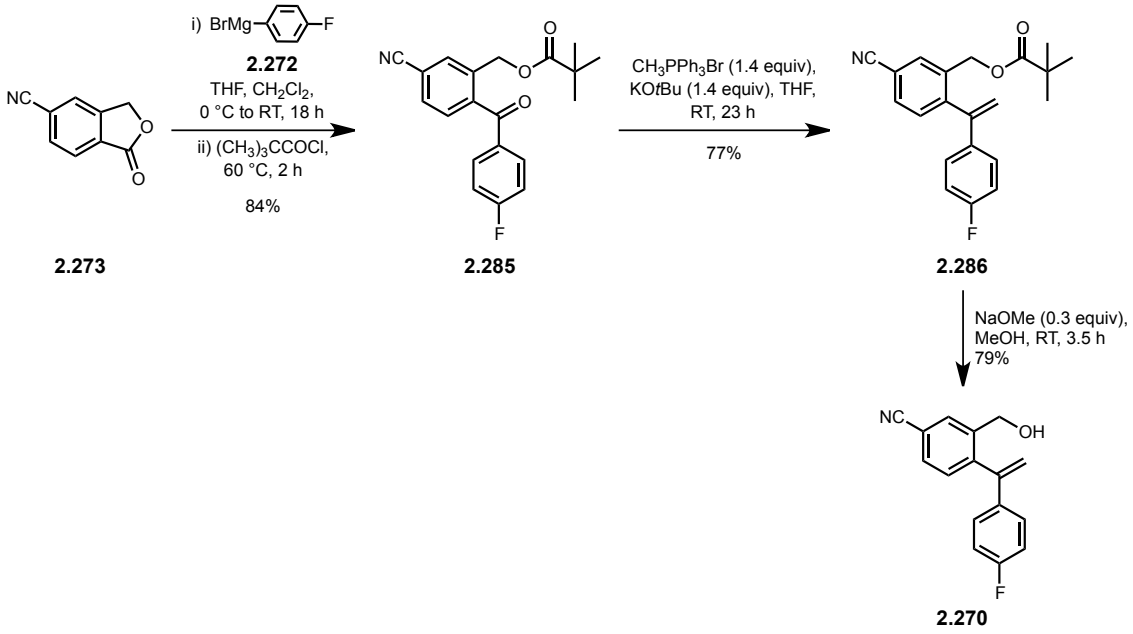
Following a modification of a reported procedure,[114] in which **2.271** is isolated as the pivaloyl ester, 5-cyanophthalide **2.273** was treated with 4-fluorophenylmagnesium bromide **2.272** to afford ketone **2.271** (Scheme 2.101). This material proved difficult to purify and characterise, presumably due to formation of the corresponding lactol. However, carrying out the Wittig reaction on unpurified material was unsuccessful, so **2.271** underwent minimal purification by filtration through a short silica plug and the resulting crude material was used directly in the Wittig reaction. Addition of ketone **2.271** to a prepared suspension of 1.9 equivalents of methyl triphenylphosphonium bromide and potassium *tert*-butoxide afforded heterocyclisation precursor **2.270** in 47% over two steps, albeit with a small amount (<5%) of an unidentified, inseparable impurity.



2.273 **2.271** **2.270**

Scheme 2.101: Synthesis of 2.270

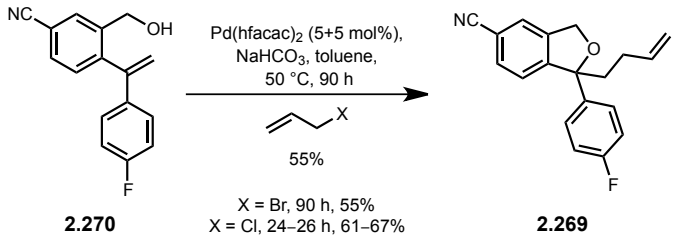
The source of this impurity, which appeared to contain an allyl component, could have been from the use of excess methyl triphenylphosphonium bromide; however, an excess of Wittig reagent was required in order to achieve full conversion of ketone **2.271**. Use of the literature procedure[114] to form the pivaloyl ester of ketone **2.285** was thus explored (Scheme 2.102). Treatment of 5-cyanophthalide **2.273** with 4-fluorophenylmagnesium bromide **2.272** was carried out as before; however, after stirring at room temperature for 16 h, pivaloyl chloride was added to the reaction mixture and the mixture heated to 60 °C for 2 h. This two-step procedure afforded pivaloyl ester **2.285** in 84% yield. The Wittig reaction with methyl triphenylphosphonium bromide and potassium *tert*-butoxide afforded alkene **2.286** in 77% yield and the pivaloyl ester could be subsequently deprotected using catalytic sodium methoxide in 79% yield to afford hydroxyalkene **2.270**. This sequence, although one step longer and similar yielding overall to the two-step sequence (Scheme 2.101), did afford material of greater purity.



Scheme 2.102: Synthesis of 2.270 *via* pivaloyl ester 2.285

With hydroxyalkene **2.270** in hand, the key step of the synthesis of citalopram **2.1** was attempted. Upon subjecting hydroxyalkene **2.270** to the oxyallylation conditions using allyl bromide, the reaction showed slow conversion of the starting material to a less polar component (Scheme 2.1030). An additional 5 mol% of $Pd(hfacac)_2$ was added after 16 h and the reaction showed significant further conversion over the following 6 h; however, starting material still remained after 90 h. Purification of the reaction mixture afforded desired heterocyclised product **2.269** in 55% yield. Altering the electrophile to allyl chloride gave rise to improved conversion and higher yield than when allyl bromide was used, although 10 mol% $Pd(hfacac)_2$ was still required to achieve significant

conversion and a small amount of starting material (<10%) still remained. Oxyallylation product **2.269** could be isolated in 61–67% yield.

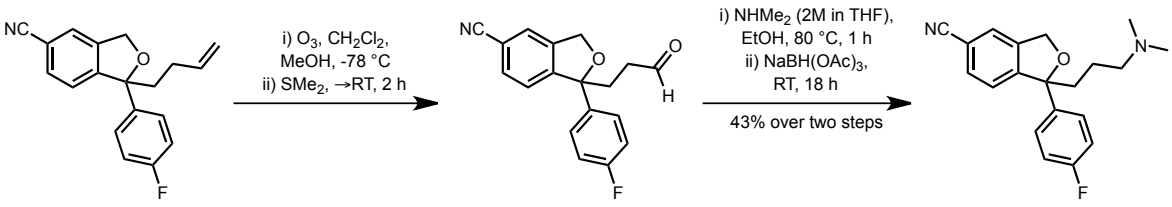


2.270 **2.269**

Scheme 2.103: Oxyallylation of 2.270 with allyl chloride

Hydroxyalkene **2.270** shows improved reactivity compared with the reactions of diaryl alkene **2.163** detailed earlier (Section 2.3.3, Scheme 2.62). It is possible that the nucleophilicity or coordinating ability of the alkene in **2.270** is affected by the presence of the presence of a fluorine on the aromatic ring.

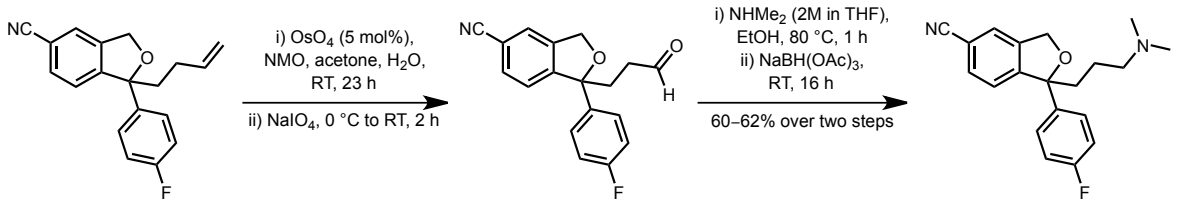
Having successfully applied the oxyallylation reaction to the synthesis of **2.269**, the final steps of the synthesis of citalopram **2.1** were to carry out an oxidative cleavage of alkene **2.269** to afford the corresponding aldehyde **2.268**, followed by a reductive amination (Scheme 2.104). Oxidative cleavage of **2.269** was achieved by ozonolysis, followed by reductive work-up using dimethyl sulfide. The crude aldehyde **2.268** was treated with dimethylamine in ethanol at 80 °C for 1 h to form the imine, followed by reduction at room temperature using sodium tri(acetoxy)borohydride to give citalopram **2.1** in 43% over two steps from alkene **2.269**.



2.269 **2.268** **2.1**

Scheme 2.104: Synthesis of citalopram from 2.269 by ozonolysis–reductive amination

Alternatively, aldehyde **2.268** could be accessed by dihydroxylation of the alkene using Upjohn conditions with osmium tetroxide and *N*-methylmorpholine *N*-oxide, followed by Lemieux–Johnson oxidative cleavage using sodium periodate (Scheme 2.105). Treatment of the crude aldehyde **2.268** with dimethylamine in ethanol at 80 °C, followed by reduction of the imine with sodium tri(acetoxy)borohydride, afforded citalopram **2.1** in 60–62% over the two steps.



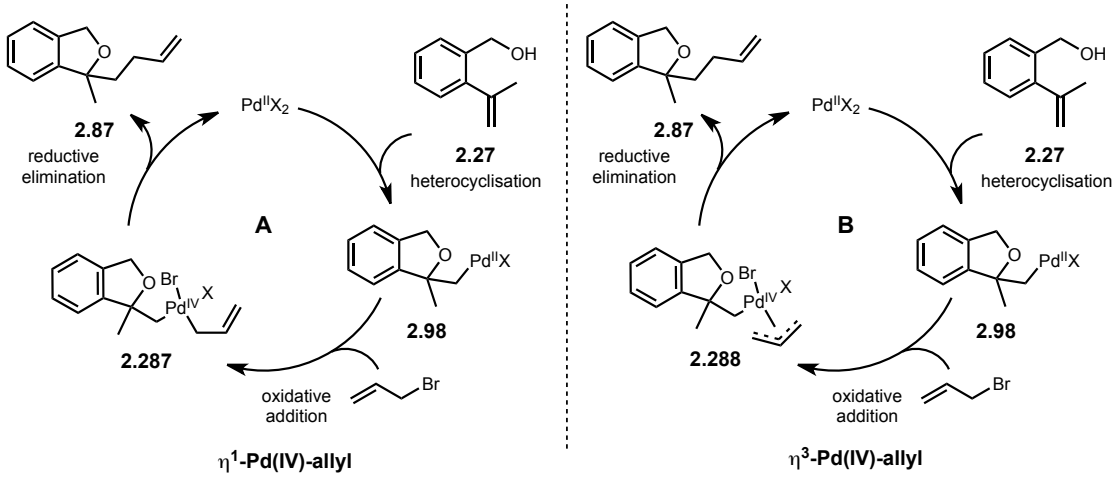
2.269 **2.268** **2.1**

Scheme 2.105: Synthesis of citalopram from 2.269 by dihydroxylation–oxidative cleavage–reductive amination

The synthesis of citalopram using the oxyallylation procedure developed demonstrates that this methodology can be used to synthesise biologically active molecules, allowing access to complex structures in relatively few steps. In addition to this, it demonstrates that the methodology can tolerate a nitrile group, which could potentially coordinate and deactivate the catalyst. If the oxyallylation methodology could be rendered asymmetric by the inclusion of a chiral ligand, then escitalopram **(*S*)-2.1** could feasibly be accessed enantioselectively by this synthetic route.

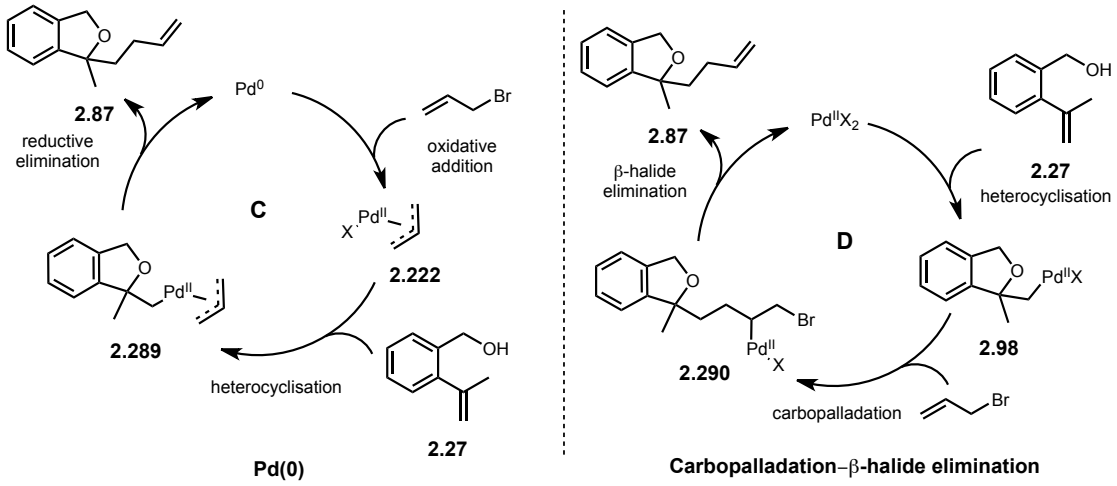
2.5 Oxyallylation Reaction Mechanism

At the beginning of this research program, the aim was to develop a heterocyclisation reaction that would construct a new C–O and C–C sp^3–sp^3 bond in a single transformation. Although no other alkyl halides proved successful as reagents in the heterocyclisation, allyl halides proved to be very successful electrophiles in the heterocyclisation reaction developed. In order to fully understand the scope and limitations of the oxyallylation reaction, a greater understanding of the mechanism is required. According to the original hypothesis, hydroxyalkene **2.27** would undergo heterocyclisation to afford Pd(II)-alkyl intermediate **2.98**. This Pd(II)-alkyl intermediate **2.98** could then undergo an oxidative addition with allyl bromide[62] to afford either η^1-Pd(IV)-allyl intermediate **2.287** (Scheme 2.106, mechanism **A**) or η^3-Pd(IV)-allyl intermediate **2.288** (Scheme 2.106, mechanism **B**). Reductive elimination would furnish observed product **2.87** and regenerate Pd(II).



Scheme 2.106: Possible mechanisms of oxyallylation reaction *via* a Pd(IV) intermediate

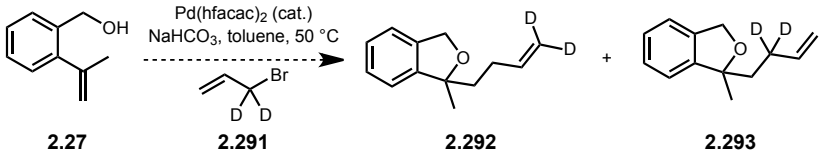
However, alternative mechanisms are plausible. If Pd(0) is produced under the reaction conditions, then oxidative addition of allyl bromide would afford Pd(II)-allyl species **2.222**. This Pd(II)-allyl species **2.222** could then catalyse the heterocyclisation reaction and subsequent reductive elimination would give observed product **2.87** (Scheme 2.107, mechanism **C**). Alternatively, if hydroxyalkene **2.27** undergoes heterocyclisation with Pd(II) to give Pd(II)-alkyl intermediate **2.98**, this species could then undergo a carbopalladation reaction with allyl bromide to give Pd(II) intermediate **2.290**, followed by a β-halide elimination[134] to afford observed product **2.87** (Scheme 2.107, mechanism **D**). The latter mechanism is redox-neutral – palladium stays in the +2 oxidation state throughout the catalytic cycle.



Scheme 2.107: Possible mechanisms of oxyallylation reaction *via* Pd(0) or β-halide elimination

It was anticipated that carrying out the oxyallylation reaction of benzylic alcohol **2.27** with deuterium labeled allyl bromide **2.291** would assist in distinguishing between the possible mechanisms (Table 2.29). If the reaction was proceeding *via* η^1-allyl-Pd(IV) intermediate **2.287** (mechanism **A**), di-deutero allyl compound **2.293** would be expected to be the sole

observed product (entry 1). If the reaction was proceeding *via* η^3-allyl-Pd^{IV} intermediate **2.288** (mechanism **B**), then di-deutero vinyl compound **2.292** and di-deutero allyl compound **2.293** would be expected to be formed in an approximately equal ratio (entry 2). The same result would be expected if a Pd(0)–Pd(II) catalytic cycle were operating (entry 3). If the reaction was proceeding through a carbopalladation–β-halide elimination mechanism, sole formation of di-deutero vinyl compound **2.292** would be expected to be the observed result (entry 4).

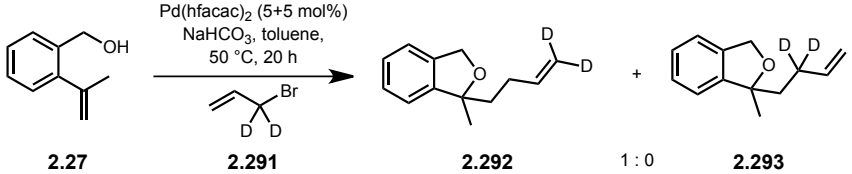


2.27 **2.291** **2.292** **2.293**

Entry	Mechanism	Expected Result	
		2.292	**2.293**
1	η^1-allyl-Pd^{IV} (**A**)	0	1
2	η^3-allyl-Pd^{IV} (**B**)	1	1
3	Pd(0) (**C**)	1	1
4	β-halide elimination (**D**)	1	0

Table 2.29: Expected product distribution from oxyallylation of 2.27 with d^2-allyl bromide 2.291 for possible mechanisms

As part of ongoing research into the oxyallylation transformation, a co-worker, Lewis Williams, investigated the outcome of the experiment depicted in Table 2.29.[113] Upon treatment of benzylic alcohol **2.27** with catalytic $Pd(hfacac)_2$, $NaHCO_3$ and di-deutero allyl bromide **2.291** in toluene at 50 °C, complete conversion of the starting material was observed after 20 h (Scheme 2.108). Di-deutero vinyl compound **2.292** was the sole isolated product, obtained in 82%. The formation of **2.292** preferentially is consistent with only proposed mechanism **D**, where the reaction is proposed to proceed *via* carbopalladation–β-halide elimination.



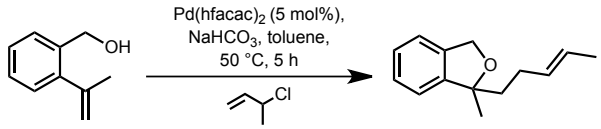
2.27 **2.291** **2.292** 82% 1 : 0 **2.293** *not observed*

Scheme 2.108: Oxyallylation of 2.27 with d^2-allyl bromide 2.291

This mechanistic suggestion is consistent with the observation that the heterocyclisation reaction developed was successful for allyl electrophiles but not for other alkyl halides,

indicating that an alkene is required in the electrophile for reactivity. In addition to this, the observation that reactivity is very low when using Pd(0) source Pd_2dba_3 and the tolerance of the reaction conditions for aryl bromides suggests that Pd(0) intermediates may not be involved in the oxyallylation reaction.

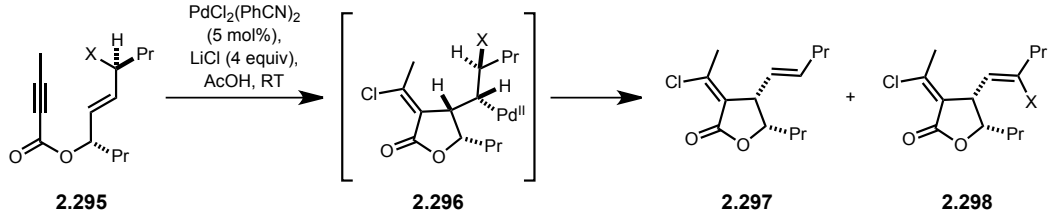
In related work, a co-worker, Lewis Williams, also demonstrated that benzylic alcohol **2.27** undergoes oxyallylation with 3-chloro-1-butene to give the internal alkene product **2.294** as a single regioisomer (Scheme 2.109).[135] The formation of this product is also consistent with the proposed carbopalladation–β-halide elimination mechanism. The observation that **2.294** was formed preferentially in the oxyallylation reaction of **2.27** with crotyl chloride (Scheme 2.36) suggests that crotyl chloride undergoes isomerisation to 3-chloro-1-butene under the reaction conditions (Scheme 2.37), which can then undergo the oxyallylation reaction.



2.27 69% **2.294**

Scheme 2.109: Oxyallylation of 2.27 with d^2-allyl bromide 2.291

Although β-hydride elimination is more frequently discussed in the literature, β-halide elimination is a phenomenon that was originally suggested by Heck in his reported allylation of arylpalladium salts (Section 2.3.3, Table 2.21)[95] and has been proposed in many other systems.[134] Lu and Zhu carried out a study of the relative β-leaving abilities of various leaving groups in the palladium-catalysed cyclisation of alkenyl alkynoates (Table 2.30).[136] The cyclisation of alkenyl alkynoate **2.295** using catalytic $PdCl_2(PhCN)_2$ proceeds *via* Pd(II) intermediate **2.296**. Pd-X elimination from this intermediate would afford product **2.297**, with heteroatom substituted products **2.298** expected where Pd-H elimination occurs. Comparison of the product ratios allowed an evaluation of the relative β-leaving abilities of the groups studied. Where the leaving group was chloride (Table 2.30, entry 1), the cyclisation proceeded rapidly to give the β-chloro elimination product **2.297** in excellent yield and as the sole observed product. Under similar conditions but where X = OAc as the leaving group, **2.297** was still the sole observed product, although the reaction was markedly slower (entry 2), proceeding to completion in 60 h *cf*. 3 h.



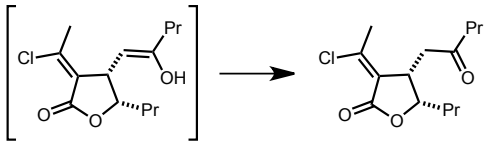
2.295 **2.296** **2.297** **2.298**

Entry	X	Time	Yield[a]	
			2.297	**2.298**
1	Cl	3 h	85%	0
2	OAc	60 h	91%	0
3	OH	60 h	23%	51

[a] Isolated yield of **2.297** or **2.298**

Table 2.30: Comparison of relative β-elimination rates of chloride, acetate, hydroxyl and hydride in cyclisation of alkenyl alkynoates 2.295

Where the leaving group was a hydroxyl group, the reaction was slow and showed preferential formation of product **2.300** (Table 2.30, entry 3 and Scheme 2.110), arising from β-hydride elimination from Pd(II) intermediate **2.296** (Table 2.30), followed by tautomerisation of enol **2.299** to ketone **2.300**. From these results, it was concluded that the elimination of palladium and a good leaving group such as chloride or acetate was faster than β-hydride elimination but that β-hydroxy elimination proceeds at a similar rate to β-hydride elimination.

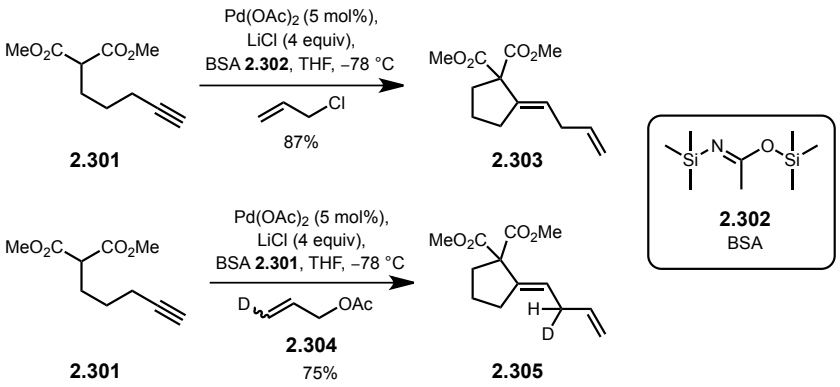


2.299
not observed

2.300
observed product

Scheme 2.110: Tautomerisation of β-hydride elimination product 2.298

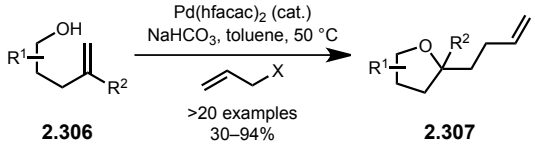
Lu and Liu developed a carboallylation of alkynes that was proposed to proceed *via* a similar mechanism to the oxyallylation reaction reported herein, involving β-heteroatom elimination as the terminating step (Scheme 2.111).[137] Treatment of substituted diester **2.301** with $Pd(OAc)_2$, lithium chloride, BSA **2.302** and allyl chloride afforded carbocycle **2.303** in 87% yield. Allyl acetate was also a competent electrophile in the carboallylation reaction and, in order to investigate the reaction mechanism, diester **2.301** was reacted using 3-deuterioallyl acetate **2.304** as the electrophile. Carbocycle **2.305** was isolated as the sole regioisomeric product in 75% yield, consistent with a carbopalladation–β-heteroatom elimination mechanism.



Scheme 2.111: Pd-catalysed carboallylation of alkyne 2.301

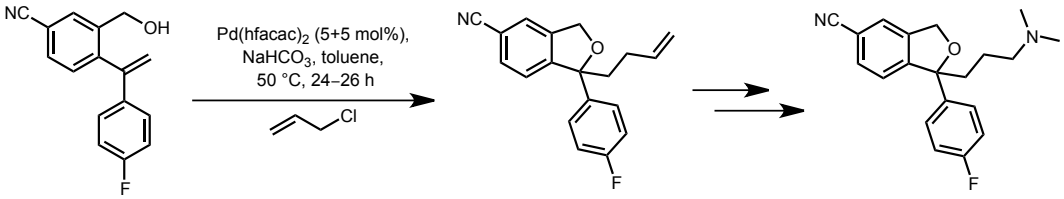
2.6 Conclusions

Through the course of this research, new methodology has been developed to synthesise heterocycles substituted in the 2-position, constructing a new C–O and C–C sp^3–sp^3 bond in a single step. Allyl halides proved to be competent electrophiles for the oxypalladation reaction developed, and optimisation of the oxyallylation transformation gave rise to the operationally simple conditions of heating the substrate with commercially available palladium(II) catalyst $Pd(hfacac)_2$, inorganic base $NaHCO_3$ and an allyl halide in toluene (Scheme 2.112). These reactions could be carried out using technical grade solvent, under air and did not require an exogenous ligand. The developed reaction was successfully applied to a range of hydroxyalkene substrates **2.306**, with greater than 20 examples reported; heterocycles **2.307** were afforded in 30% to 94% yields. Whilst a range of substitution patterns could be tolerated in these reactions, the major limitations of the oxyallylation reaction proved to be difficulty in achieving the oxyallylation of monosubstituted alkenes and substrates containing basic nitrogen moieties.



Scheme 2.112: Oxyallylation of hydroxyalkenes 2.306

Once optimised, the methodology developed was successfully applied to a 5-step synthesis of a widely prescribed SSRI, citalopram **2.1** (Scheme 2.113). The synthesis of citalopram **2.1** indicated that biologically active molecules could be successfully synthesised using the oxyallylation chemistry developed.



2.270 **2.269** **2.1**

Scheme 2.113: Synthesis of citalopram 2.1 using oxyallylation methodology

2.7 Future Work

Although the development of the oxyallylation reaction described herein has been successfully applied to a wide range of substrates bearing different substitution patterns, future work to address the limitations of this transformation, in particular the lack of tolerance for basic nitrogen-containing substrates, would be beneficial. The successful oxyallylation of an *N*-Boc containing substrate suggests that methods that attenuate the basicity of nitrogen in these substrates may improve the reactivity of the oxyallylation reaction. As protection–deprotection strategies add additional steps to a synthetic sequence, it would be desirable to devise a strategy for *in situ* protection of the nitrogen moiety during the oxyallylation reaction *e.g.* as an *N*-oxide or using an *N*-silyl group.

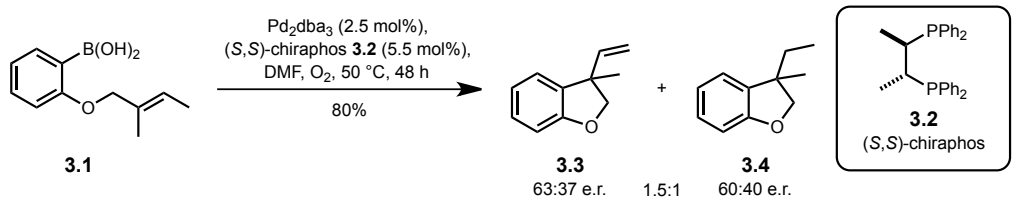
The oxyallylation of a carboxylic acid substrate demonstrates that expansion of the scope of the oxyallylation reaction to the synthesis of a variety of lactone products should be possible. Furthermore, the prevalence of aminopalladation and carbopalladation transformations in the literature[15] suggests that these nucleophiles may also be suitable avenues for exploration.

It would constitute a significant improvement in the synthesis of citalopram **2.1** if the dihydrobenzofuran could be constructed in an enantioselective fashion. However, the development of an asymmetric oxyallylation reaction could prove challenging due to the noted reduction in reactivity in the presence of coordinating moieties. Finding a suitable chiral catalyst that affords enantioselectivity whilst affording appreciable conversion of the starting material would be a significant development.

3. Synthetic Approaches Towards Carbocyclisation of Unactivated Alkenes

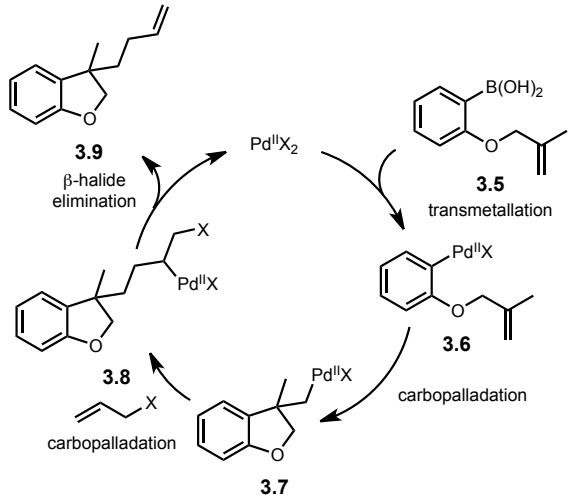
3.1 Introduction and Aims

As discussed in Chapter 1, in addition to facilitating the addition of oxygen nucleophiles to alkenes, Pd(II) can also promote the addition of carbon nucleophiles to alkenes by carbopalladation. This method could still be used to access heterocycles *via* carbopalladation of substrates containing an alkene and a heteroatom tether. Whilst the majority of the examples of carbopalladation detailed in Section 1.3 were initiated by oxidative addition of Pd(0) to an aryl or alkenyl halide to obtain the Pd(II) species, organopalladium(II) intermediates can also be accessed by transmetallation of an organoboron species. As outlined in Section 1.3 (Scheme 1.27), Mikami reported an oxidative intramolecular palladium-catalysed cyclisation of boronic acids onto unactivated alkenes to afford heterocycles (Scheme 3.1).



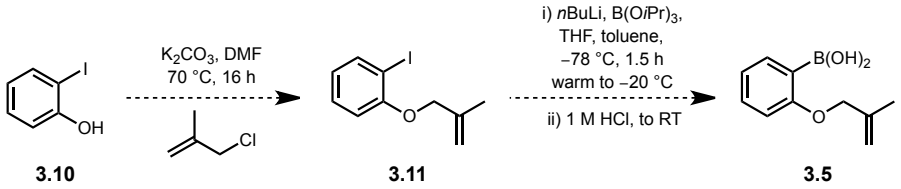
Scheme 3.1: Carbocyclisation of boronic acid

Based on this report and following the development of the oxyallylation reaction, it was proposed that boronic acid **3.5** could undergo transmetallation with Pd(II) to afford arylpalladium(II) intermediate **3.6** (Scheme 3.2). Intramolecular carbopalladation of the pendant alkene would give rise to construction of benzofuran **3.7** as a Pd(II)-alkyl intermediate. Carbopalladation with an allyl halide would afford Pd(II) intermediate **3.8** and subsequent β-halide elimination would afford benzofuran **3.9**. This carboallylation constructs two new C–C bonds in a single step. The proposed product **3.9** is a structural isomer of oxyallylation products dihydrobenzofuran **2.57** (Section 2.3.1, Scheme 2.22) and dihydroisobenzofuran **2.87** (Section 2.3.3, Table 2.19). Dihydrobenzofuran **3.9** has the fully substituted carbon centre adjacent to a methylene rather than oxygen and so products of this type would have a complimentary substitution pattern to the products of the oxyallylation reaction.



Scheme 3.2: Mechanism of proposed transformation of boronic acid 3.5

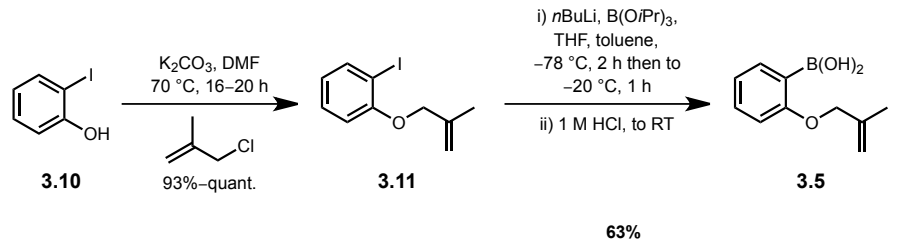
The literature route to access known boronic acid **3.5** proceeds *via* alkylation of 2-iodophenol with 3-chloro-2-methylpropene followed by lithium–halogen exchange with *n*BuLi and quench with tri*iso*propylborate (Scheme 3.3).[138]



Scheme 3.3: Synthetic route to boronic acid 3.5

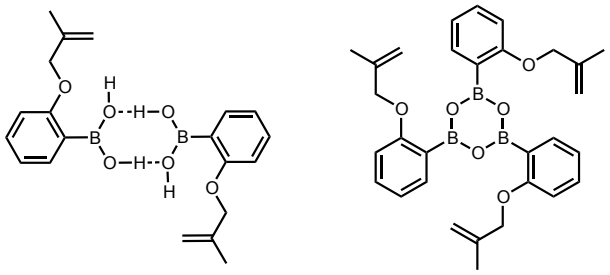
3.2 Synthesis and Reactions of Boronic Acid

In order to investigate the carbocyclisation of boronic acids onto unactivated alkenes, boronic acid substrate **3.5** was first prepared (Scheme 3.4). 2-Iodophenol **3.10** was alkylated with 3-chloro-2-methylpropene using potassium carbonate in DMF at 70 °C, affording *O*-allyl product **3.11** in 93% to quantitative yield.[52] Following a procedure reported by Baran and co-workers,[138] treatment of aryl iodide **3.11** with *n*BuLi in the presence of tri*iso*propylborate at −78 °C to −20 °C, followed by quenching of the reaction with 1 M HCl afforded boronic acid **3.5**.



Scheme 3.4: Synthesis of boronic acid 3.5

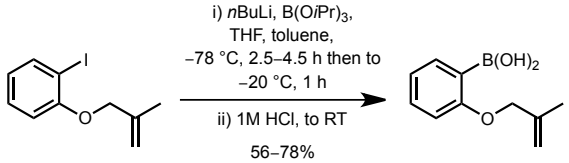
However, the ^{1}H NMR spectrum of **3.5** after flash chromatography indicated the presence of major impurities, despite TLC analysis indicating a single component. Boronic acids are known to form dimers or undergo dehydration to form trimeric boroxines (Scheme 3.5), which can be differentiated from the boronic acid by ^{1}H NMR spectroscopy.[139] It is possible that the boronic acid prepared underwent dehydration whilst the chromatographic fractions corresponding to **3.5** were concentrated *in vacuo*. However, it was found that pure boronic acid **3.5** could be obtained by boiling the sample in water. Whilst the material was too insoluble in water to undergo recrystallisation, this procedure afforded a mixture of glassy and crystalline material that was a single component by ^{1}H and ^{13}C NMR spectroscopy and was consistent with the literature data for the boronic acid **3.5**.[138]



3.12 **3.13**

Scheme 3.5: Dimeric and boroxine structures of boronic acid 3.5

Upon repeating the lithium–halogen exchange reaction to obtain boronic acid **3.5**, the material obtained from flash chromatography of the crude reaction mixture was treated directly under the conditions described above, *i.e.* boiling in water, to obtain pure boronic acid **3.5** in 56–78% yield (Scheme 3.6).

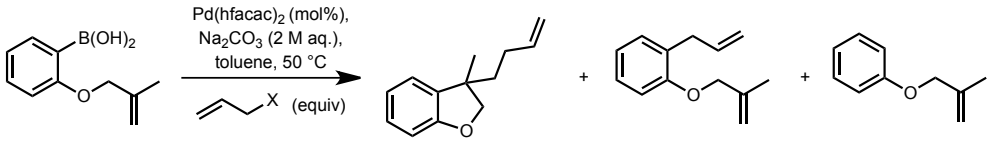


3.11 **3.5**

Scheme 3.6: Synthesis of boronic acid 3.5 with improved purification

With the boronic acid **3.5** in hand, screening of conditions that could be used to effect the carboallylation was commenced (Table 3.1). The conditions selected initially were based on those developed for the oxyallylation of alcohols (Section 2.3.3, Table 2.19), using $Pd(hfacac)_2$ as the catalyst, toluene as the solvent and allyl bromide. The base was altered from $NaHCO_3$, used in the oxyallylation reaction, to Na_2CO_3 (2 M aq.), as this is a base typically employed in Suzuki–Miyaura coupling reactions. Upon heating the reaction mixture at 50 °C for 17 h, complete consumption of starting material **3.5** was observed (Table 3.1, entry 1). However, although desired product **3.9** was observed, it was formed only as a minor component, with the product of direct coupling of allyl bromide **3.14** and

the de-boronation product **3.15** the main observed components. Altering the electrophile to allyl chloride (entry 2) increased the rate of reaction and decreased the formation of de-boronation side product **3.15** but direct coupling **3.14** remained the main product formed. In an attempt to favour intramolecular carbopalladation to form the desired product **3.9**, over intermolecular carbopalladation to form direct coupling product **3.14**, the number of equivalents of allyl chloride used was reduced to 2 (entry 3). An improved ratio of **3.9**:**3.14** was observed, although the proportion of deboronation product **3.15** increased under these conditions. Further reduction of the number of equivalents of allyl chloride to 1.1 did not show any significant advantage (entry 4). Interestingly, formation of the direct coupling product **3.14** was still observed in the absence of palladium, although full conversion of starting material **3.5** was not observed even after 144 hours of heating (entry 5). No reaction was observed in the absence of a base (entry 6).



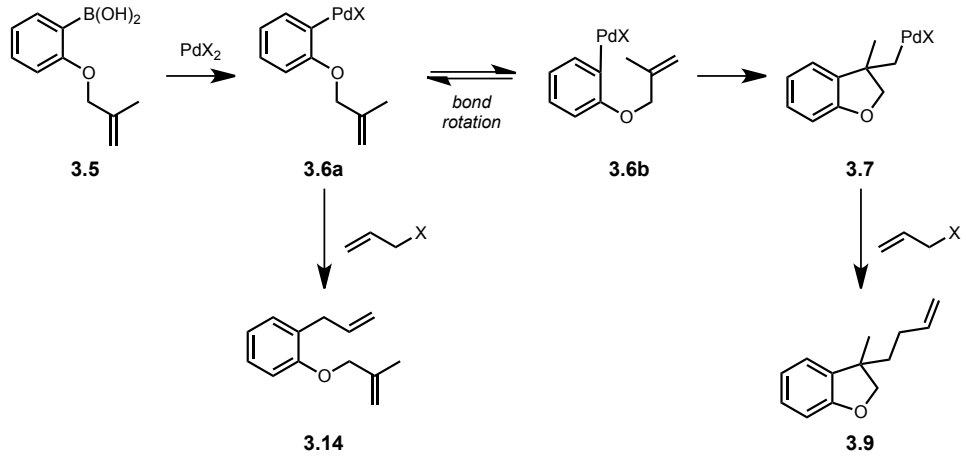
3.5 **3.9** **3.14** **3.15**

Entry	Pd (mol%)	Base (equiv)	X	Equiv X	Time	Ratio[a] **3.5**	**3.9**	**3.14**	**3.15**
1	10	2	Br	5	17 h	0	0.1	1	1.2
2	10	2	Cl	5	2.5 h	0.2	0.1	1	0.3
3	10	2	Cl	2	4 h	0.1	0.3	1	0.7
4	10	2	Cl	1.1	23 h	0	0.4	1	0.9
5	0	2	Cl	2	144 h	0.1	0	1	0.5
6	0	0	Cl	2	23 h	1	0	0	0.2

[a] Approximate ratio of **3.5** : **3.9** : **3.14** : **3.15** by ^{1}H NMR of unpurified reaction mixture

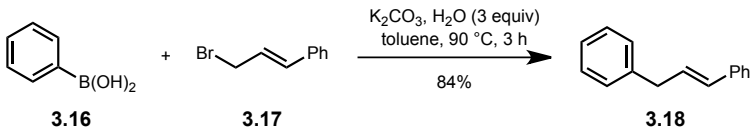
Table 3.1: Initial investigation of carboallylation of 3.5

Following transmetallation of boronic acid **3.5** with PdX_2, arylpalladium(II) species **3.6** would then be expected to undergo fast intramolecular carbopalladation to afford **3.7** (Scheme 3.2), which could then undergo carbopalladation–β-halide elimination with the allyl halide to afford desired product **3.9** (Scheme 3.7). However, arylpalladium(II) intermediate **3.6** would have to adopt conformation **3.6b** in order to undergo the intramolecular carbopalladation, whereas **3.6** in any conformer is already appropriately functionalised to react directly with the allyl halide to give side product **3.14**. As the allyl halide is present in excess, this side reaction can occur readily.



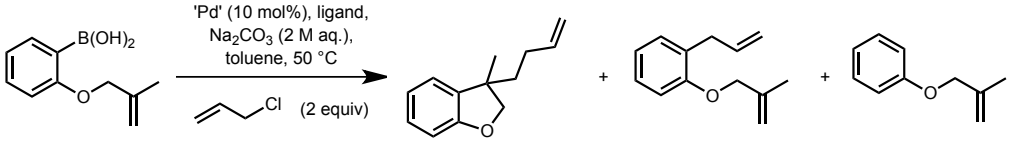
Scheme 3.7: Formation of side product 3.14 in carboallylation of boronic acid 3.5

Whilst the formation of direct-coupled side product in the absence of palladium may be surprising, Scrivanti and co-workers reported a method for the catalyst-free coupling of aryl boronic acids with allylic bromides (Scheme 3.8).[140] This procedure made use of potassium carbonate and heating at 90 °C in toluene, affording the coupled products in generally high yields. The authors used purified reagents in order to avoid the presence of trace metals and the transition metal content of the potassium carbonate was considered to be too low to promote the reaction. Addition of $Pd(OAc)_2$, even at very low loadings, gave rise to considerable rate enhancement.



Scheme 3.8: Transition metal free coupling of boronic acid 3.16 with allyl bromide 3.17

The first variable investigated in an attempt to optimise the carboallylation reaction was the palladium source and the presence or absence of an exogeneous ligand (Table 3.2). Addition of triphenylphosphine (entries 2–3) gave rise to preferential formation of direct-coupling side product **3.14**. Addition of triphenylphosphite, whilst not detrimental to the ratio of desired product **3.9** to side product **3.14**, did not offer any significant advantage (entry 4). Use of $PdCl_2$ did not show any improvement in the ratio of **3.9**:**3.14** over $Pd(hfacac)_2$ (entry 5 *cf*. entry 1).



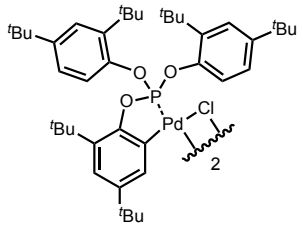
3.5 **3.9** **3.14** **3.15**

Entry	'Pd'	Ligand	Time	Ratio[a]			
				3.5	**3.9**	**3.14**	**3.15**
1	$Pd(hfacac)_2$	-	4 h	0.1	0.3	1	0.7
2	$Pd(hfacac)_2$	PPh_3 (1 equiv)	24 h	0	0	1	0.2
3	$Pd(hfacac)_2$	PPh_3 (2 equiv)	24 h	0.3	0	1	0
4	$Pd(hfacac)_2$	$P(OPh)_3$ (1 equiv)	72 h	0	0.4	1	0.8
5	$PdCl_2$	-	2 h	0	0.2	1	0.1
6	$PdCl_2$dppf	-	24 h	0.3	0	1	0.1
7	$Pd(Oac)_2$	-	2 h	0	0	1	0.2
8	$Pd(TFA)_2$	-	2 h	0	0	1	0.1
9	$Pd(acac)_2$	-	24 h	0	0	1	0.3
10	$Pd(PPh_3)_4$	-	24 h	0.3	0	1	0.1
11	Pd_2dba_3	-	2 h	0	0	1	0
12[b]	**3.19**[c]	-	24 h	0	0.7	1	0.1

[a] Approximate ratio of **3.5** : **3.9** : **3.14** : **3.15** by ^{1}H NMR of unpurified reaction mixture; [b] Crude mixture also contained several unidentified product-related impurities; [c] Structure shown in Figure 3.1

Table 3.2: Effect of palladium source and ligands on outcome of carbopalladation of 3.5

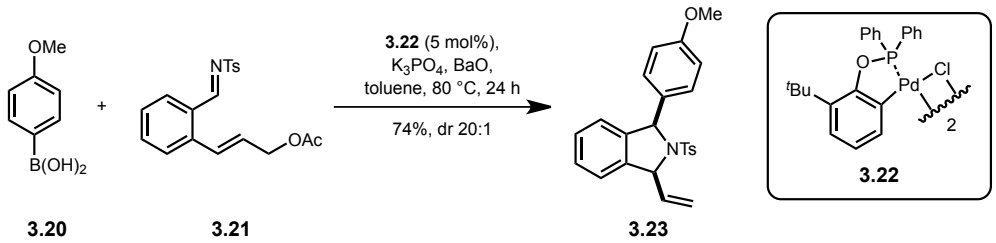
The majority of the other palladium catalysts explored gave preferential conversion of boronic acid **3.5** to direct-coupling side product **3.14** (Table 3.2, entries 6–11). Palladium(II) catalyst **3.19** (Figure 3.1) afforded the best ratio of **3.9**:**3.14** observed thus far of 0.7:1. However, a number of unidentified carbocyclised side products were also observed in the ^{1}H NMR spectrum of crude material, where the formation of a dihydrobenzofuran moiety was characterised by the diastereotopic protons of the dihydrobenzofuran ring, appearing as two doublets in the region of 4.0–4.5 ppm.



3.19

Figure 3.1: Structure of Pd(II) catalyst 3.19

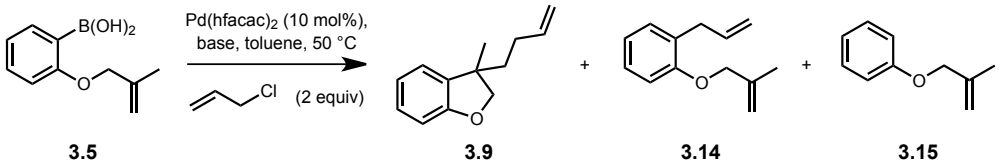
3.19 is a commercially available catalyst, structurally similar to **3.22** (Scheme 3.9), employed by Jarvo and Williams in their palladium-catalysed synthesis of substituted isoindolines **3.23**. [141] The insoindoline formation is believed to be initiated by transmetallation of boronic acid **3.20**, followed by nucleophilic arylation of imine **3.21**, migratory insertion to construct the indoline core then β-acetoxy elimination to afford the observed product **3.23**. Phosphinite palladacycle **3.22**, which had demonstrated success in the arylation of imines,[142] was found to strike an effective balance betwen the electronic requirements of the nucleophilic arylation step and the migratory insertion step due to the π-accepting ability of the phosphonite.



3.20 **3.21** **3.23**

Scheme 3.9: Pd-catalysed synthesis of substituted isoindolines

In order to further optimise the carboallylation reaction of boronic acid **3.5**, alteration of the base was subsequently investigated, with $Pd(hfacac)_2$ remaining the catalyst of choice (Table 3.3). Although use of solid Na_2CO_3 instead of an aqueous solution gave rise to incomplete conversion of starting material **3.5** after 16 h at 50 °C, desired product **3.9** was formed preferentially in a ratio of 6.7:1 with direct-coupled side product **3.14** (entry 2 *cf*. entry 1). However, deboronation side product **3.15** was also formed in significant proportions in this reaction. Under "water-free" conditions, *i.e*. with no additional water added, Na_2CO_3 proved to be the superior base, with NaOH (entry 3) and CsF (entry 4) both affording complete conversion to direct-coupling side product **3.14**. As inorganic bases are likely to be insoluble in the toluene reaction medium, organic bases were investigated. Triethylamine afforded slow conversion of boronic acid **3.4** but gave preferential formation of direct-coupled product **3.14** (entry 5). Use of 4-methyl-2,6-di-*tert*-butylpyridine (mdtbpy) did not afford any allylated products and gave only deboronation product **3.15** after heating at 50 °C for 20 h (entry 6). It should be noted that, whilst the base was not added as an aqueous solution, technical grade solvents were used and efforts were not made to thoroughly dry the reagents, thus it is expected that these reactions contain adventitious water.



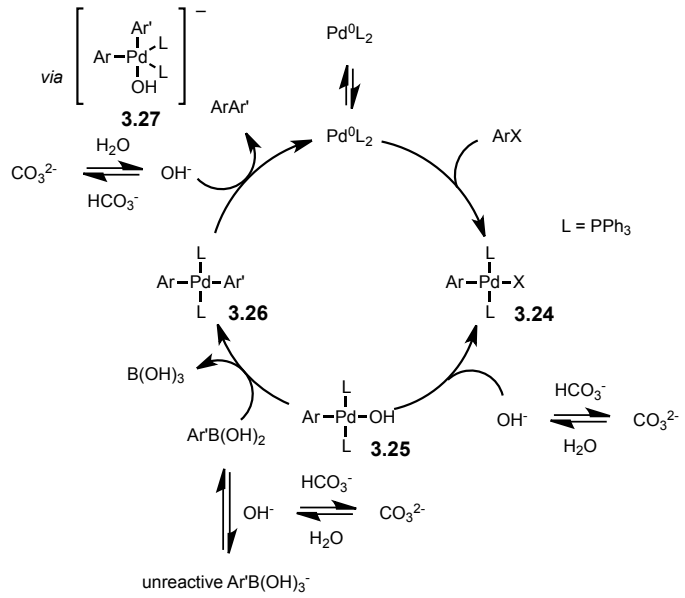
3.5 **3.9** **3.14** **3.15**

Entry	Base	Time	Ratio[a]			
			3.5	**3.9**	**3.14**	**3.15**
1	Na_2CO_3 (2 M aq.)	4 h	0.1	0.3	1	0.7
2	Na_2CO_3	16 h	3.2	6.7	1	10
3	NaOH	2 h	0	0.1	1	0.2
4	CsF	72 h	0	0	1	0.2
5	NEt_3	48 h	0.1	0.3	1	3.1
6	mdtbpy	20 h	1.0	0	0	2.5

[a] Approximate ratio of **3.5** : **3.9** : **3.14** : **3.15** by ^{1}H NMR of unpurified reaction mixture

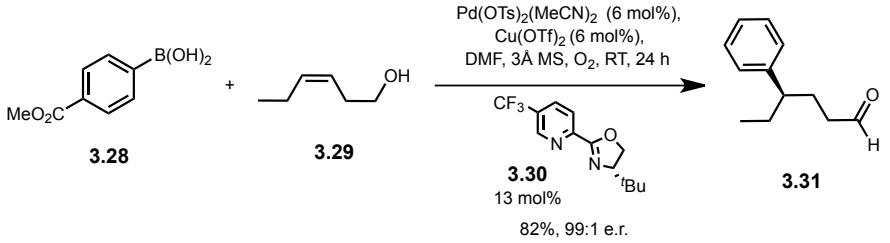
Table 3.3: Effect of altering base on the carboallylation of 3.5

Jutand and co-workers have demonstrated that, when carbonate bases are employed in Suzuki–Miyaura reactions, they operate as a source of hydroxide ions by reaction with water (Scheme 3.10).[143] The liberated hydroxide ions enhance the rate of reaction by forming the active transmetallating oxo-palladium species **3.25** and facilitating reductive elimination *via* diaryl palladium intermediate **3.27**, but also inhibit reactivity by sequestration of the boronic acid as the boronate. By altering the base used during the development of the carboallylation reaction of boronic acid **3.5** to solid form *cf*. an aqueous solution (Table 3.3), the effective concentration of hydroxide ions in the reaction medium may have decreased due to the low solubility of carbonate bases in organic solvents, retarding the rate of reaction. However, Lloyd-Jones and co-workers stated that in a single phase, high pH medium *i.e.* in the absence of biphasic conditions, boronic acids predominantly exist as the trihydroxyboronate,[144] giving rise to greater decomposition to protodeboronation products. Whilst the work of Jutand and co-workers provides insight into the catalytic cycle of Suzuki–Miyaura reactions, the transmetallating species in a Suzuki–Miyaura reaction differs fundamentally from that in the reaction under development as it contains a carbon ligand on palladium. The carboallylation reaction of boronic acid **3.5** under investigation may therefore not have the same response to changes in the nature of the catalyst and the base.



Scheme 3.10: Role of carbonate bases in Suzuki–Miyaura reactions

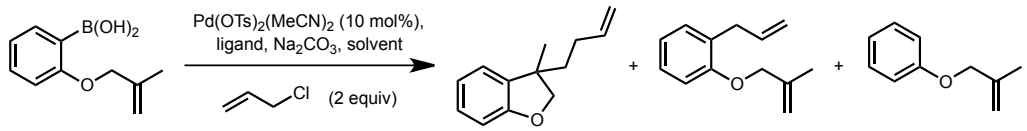
Sigman and co-workers used cationic palladium(II) salt $Pd(OTs)_2(MeCN)_2$ and a chiral pyridine oxazoline ligand **3.30** to catalyse an enantioselective oxidative Heck reaction of boronic acids **3.28** with alkenyl alcohols **3.29** (Scheme 3.11). [145] This reaction is described as a "redox-relay" process, where an iterative β-hydride elimination–migratory insertion sequence gives rise to oxidation of the alcohol to give the observed ketone product **3.31**. Re-oxidation of the catalyst is achieved using $Cu(OTf)_2$ and O_2, with high yields and enantioselectivities of the products afforded.



Scheme 3.11: Oxidative Heck arylation of alkenyl alcohols 3.29

The transformation outlined in Scheme 3.11 represents another example of a reaction where transmetallation of a boronic acid with PdX_2 is the initiating step and so the use of palladium catalyst $Pd(OTs)_2(MeCN)_2$ was investigated in the carboallylation of boronic acid **3.5** (Table 3.4). Boronic acid **3.5** was reacted under a modification of the conditions employed by Sigman and co-workers, using $Pd(OTs)_2(MeCN)_2$ as the Pd(II) source but with achiral bidentate nitrogen ligand bipyridine used in place of pyridine oxazoline ligand **3.30**. Na_2CO_3 was used as a base and 2 equivalents of allyl chloride were added. Heating at 50 to 80 °C in DMF at the reaction concentration employed by Sigman *et al*. afforded slow conversion of boronic acid **3.5** to direct-coupled side product **3.14**, with desired product **3.9** not observed. Incomplete conversion was observed even after 72 h (Table

3.4, entry 1). Recourse to toluene gave lower conversion of **3.5** but still afforded solely the direct-coupled product **3.14** (entry 2). Upon increasing the reaction concentration to 0.25 M, as in the carboallylation reactions already carried out, complete conversion of starting material **3.5** was observed in 24 h (entry 3). Although direct-coupled product **3.14** was formed preferentially, a small amount of desired product **3.9** was formed. However, deboronation of the starting material, **3.15**, was the major product in this reaction. In the absence of an exogeneous ligand full conversion of the starting material **3.5** was achieved in 6 h and an improved ratio of desired product **3.9** to side product **3.14** was obtained (entry 4).



3.5 **3.9** **3.14** **3.15**

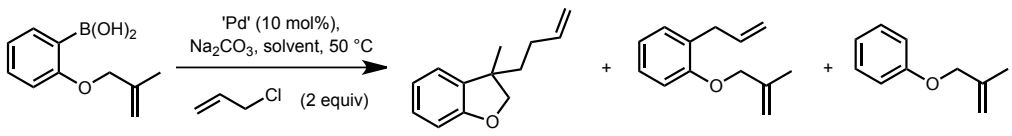
Entry	Ligand	Solvent	Temp	Time	Ratio[a]			
					3.5	**3.9**	**3.14**	**3.15**
1	bipy[b]	DMF (0.09 M)	50 to 80 °C	72 h	0.9	0	1	0
2	bipy[b]	toluene (0.09 M)	50 to 80 °C	72 h	3.1	0	1	0.8
3	bipy[b]	toluene (0.25 M)	50 °C	24 h	0	0.1	1	5.5
4	-	toluene (0.25 M)	50 °C	6 h	0	0.4	1	0.1

[a] Approximate ratio of **3.5** : **3.9** : **3.14** : **3.15** by ^{1}H NMR of unpurified reaction mixture; [b] 2.2 equiv

Table 3.4: Carboallylation of boronic acid 3.5 using $Pd(OTs)_2(MeCN)_2$ catalyst

Although formation of desired product **3.9** was observed using the $Pd(OTs)_2(MeCN)_2$ catalyst system, direct-coupled side product **3.14** was still formed preferentially (Table 3.4, entry 4). Thus, under analogous conditions, $Pd(hfacac)_2$ remains the optimum catalyst source, with a ratio of **3.9**:**3.14** of 6.7:1 afforded (Table 3.3, entry 2). However, as deboronation side product **3.15** is formed in significant quantities in the carboallylation reaction, a screening of solvents was conducted in order to investigate if deboronation could be suppressed (Table 3.5). Upon alteration of the solvent to DMF (entry 2), complete conversion of the boronic acid **3.5** to the direct-coupling product **3.14** was observed. Other Lewis basic, coordinating solvents afforded incomplete conversion of the starting material; however, desired product **3.9** was observed and less protodeboronation than was observed with toluene resulted (entry 1). Use of acetonitrile, THF and TBME all resulted in preferential formation of desired product **3.9** *cf*. direct-coupling product **3.14**, although in a less favourable ratio than reactions conducted in toluene (entries 3– 5 *cf*. entry 1). Of these three reactions, use of THF gave rise to the lowest conversion but with the least protodeboronation **3.15** observed. Use of 2-methyltetrahydrofuran (2-MeTHF)

gave a poorer ratio of **3.9**:**3.14** (entry 7) when compared with THF (entry 4). Use of dimethoxyethane (DME), although giving low conversion, afforded a 3.4:1 ratio of **3.9**:**3.14**, importantly with no protodeboronation observed (entry 8). The Lewis basic nature of dimethoxyethane could be coordinating the Lewis acidic boron, resulting in suppression of the protodeboronation side reaction, but simultaneously attenuating the reactivity of boronic acid **3.5** and giving rise to the low conversion observed. Replacement of $Pd(hfacac)_2$ with phosphonite catalyst **3.19** (Figure 3.1) when the reaction was carried out in DME afforded greater conversion of starting material **3.5**, but with desired product **3.9** and direct-coupling product **3.14** formed in equal ratio (entry 9). Use of $Pd(OTs)_2(MeCN)_2$ as the catalyst source in DME gave near complete conversion of starting material **3.5** and preferential formation of desired product **3.9**, although in a lower ratio than when $Pd(hfacac)_2$ was used in DME (entry 10 *cf*. entry 8). A small amount of protodeboronation side product was observed using the $Pd(OTs)_2(MeCN)_2$ catalyst system in DME.



3.5 **3.9** **3.14** **3.15**

Entry	'Pd'	Solvent	Time	Ratio[a]			
				3.5	**3.9**	**3.14**	**3.15**
1	$Pd(hfacac)_2$	Toluene	16 h	3.2	6.7	1	10
2	$Pd(hfacac)_2$	DMF	18 h	0	0	1	0
3	$Pd(hfacac)_2$	MeCN	24 h	2.4	1.1	1	3.3
4	$Pd(hfacac)_2$	THF	24 h	3.6	1.4	1	0.7
5	$Pd(hfacac)_2$	TBME	20 h	1.5	1.4	1	3.3
6	$Pd(hfacac)_2$	EtOH	44 h	0	0.1	1	0.6
7	$Pd(hfacac)_2$	2-MeTHF	72 h	0.2	0.4	1	0.4
8	$Pd(hfacac)_2$	DME	20 h	9.2	3.4	1	0
9	**3.19**	DME	48 h	1.5	1.0	1	0
10	$Pd(OTs)_2(MeCN)_2$	DME	48 h	0.4	1.8	1	0.4

[a] Approximate ratio of **3.5** : **3.9** : **3.14** : **3.15** by ^1H NMR of unpurified reaction mixture

Table 3.5: Effect of varying solvent and Pd source on carboallylation of 3.5

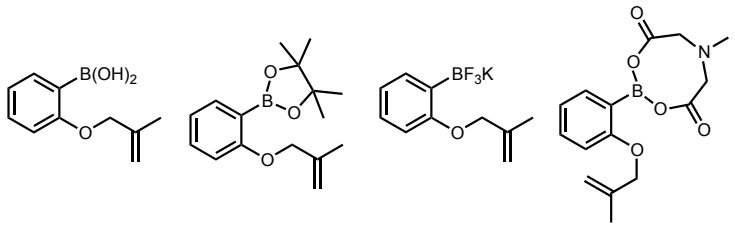
Whilst initial attempts at effecting the carboallylation of boronic acid **3.5** did not afford desired product **3.9**, further experiments revealed that preferential formation of desired product **3.9** could be achieved, albeit at the expense of conversion of the starting material. The modifications to the reaction conditions giving the highest ratios of desired product

3.9 to direct-coupled side product **3.14** are believed to be those that slow down the transmetallation step.

3.3 Synthesis and Reactions of Boronic Acid Derivatives

3.3.1 Synthesis of Boronic Acid Derivatives

Boronic acids are susceptible to a number of side reactions, including: protodeboronation, as observed in the carboallylation reaction under development; oxidation to the corresponding phenol; and oxidative homocoupling. In order to protect boronic acids from deleterious side reactions, a number of boronic acid derivatives have been developed that allow slow release of the boronic acid into the catalytic cycle, keeping the concentration of the free boronic acid in the reaction medium low. This "slow-release strategy" has been recently reviewed and makes use of modifications that reduce the Lewis acidity of boron.[146,147] In order to investigate whether use of this "slow-release strategy" could suppress formation of direct-coupling side product **3.14** and protodeboronation side product **3.15** in the carboallylation of boronic acid **3.5**, a number of boronic acid derivatives of **3.5** were prepared (Scheme 3.12). The pinacol ester **3.32**, potassium trifluoroborate **3.33** and methyliminodiacetic acid (MIDA) boronate **3.34** derivatives were chosen. Whilst the advantages of each of these types of derivatives over the use of boronic acids will be discussed forthwith, their lower reactivity is generally attributed to boron being significantly less Lewis acidic.

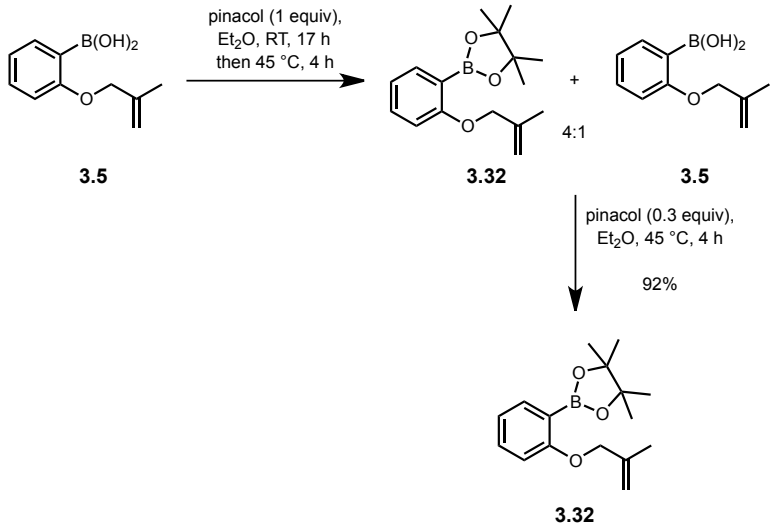


3.5 **3.32** **3.33** **3.34**

Scheme 3.12: Boronic acid 3.5 and derivatives

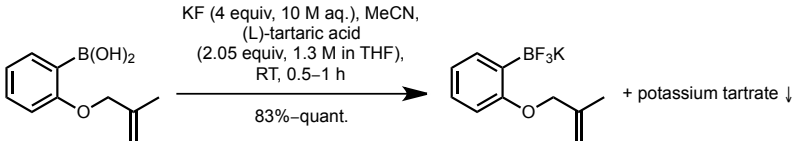
Pinacol esters are one of the most commonly used boronic esters for Suzuki–Miyaura couplings due to their stability and ease of preparation. The σ-donating ability of carbon results in increased conjugation of the oxygen lone pairs into boron centre, giving a reduction in Lewis acidity and thus lower reactivity when compared with the corresponding boronic acid.[147] It is unclear whether boronate esters undergo transmetallation directly or whether partial or complete hydrolysis to the boronic acid occurs prior to transmetallation. In order to prepare pinacol ester derivative **3.32**, boronic acid **3.5** was treated with pinacol in anhydrous Et_2O; however, incomplete conversion was observed after 17 h at ambient

temperature and 4 h at 45 °C (Scheme 3.13).[148] After work-up, the crude material was re-subjected to a further 0.3 equivalents of pinacol in Et_2O at reflux to afford clean and complete conversion to pinacol ester **3.32** in 92% yield.



Scheme 3.13: Synthesis of pinacol ester 3.32

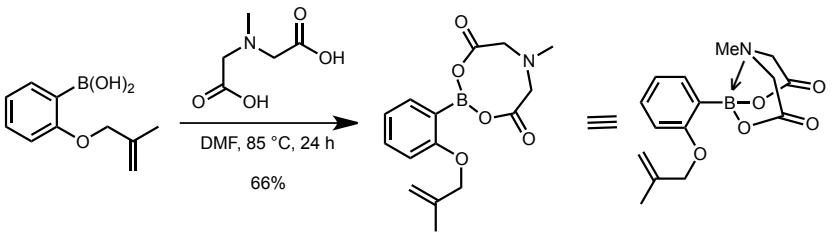
In contrast to pinacol esters, organotrifluoroborates are tetrahedral in geometry and lack Lewis acidicity due to the tetravalent nature of the boron centre. They are typically air-stable, crystalline solids but undergo hydrolysis in aqueous solutions to the corresponding boronic acid, which has been shown to be the active transmetallating species when organotrifluoroborates are used in Suzuki–Miyaura coupling reactions.[149] Generally superior reaction outcomes are afforded using organotrifluoroborates when compared to the corresponding boronic acids due to suppression of the formation of side products.[149] Lloyd-Jones and Lennox developed a method to synthesise organotrifluoroborates from boronic acids using potassium fluoride and tartaric acid.[150] The tartaric acid serves to sequester the KOH liberated by the displacement of OH^- by F^- by precipitation of potassium tartrate from solution. This procedure avoids the use of corrosive HF or KHF_2 in preparing the organotrifluoroborates and, unlike the former procedures, does not result in etching of glassware. Under the conditions reported by Lloyd-Jones and Lennox, treatment of a solution of boronic acid **3.5** in acetonitrile with aqueous KF, followed by a solution of tartaric acid in THF resulted in rapid deposition of a white solid (Scheme 3.14). The solid was removed by filtration and the filtrate concentrated to afford clean potassium trifluoroborate **3.33** in 83%–quantitative yield.



3.5 **3.33**

Scheme 3.14: Synthesis of potassium trifluoroborate 3.33

Burke and co-workers have demonstrated the effectiveness of MIDA boronates in iterative cross-coupling reactions.[151] These species contain two B–O covalent bonds with a dative bond from the Lewis basic lone pair of nitrogen to Lewis acidic boron. This dative bond alters the hybridisation of boron from sp^2 to sp^3 resulting in boron adopting a tetrahedral geometry. MIDA boronates are stable to a range of chemical transformations and to anhydrous Suzuki–Miyaura coupling conditions, but undergo slow hydrolysis in protic or alcoholic solvents. MIDA boronate **3.34** was prepared by the DMSO-free method reported by Grob and co-workers that circumvents the use of Dean-Stark apparatus for azeotropic removal of water produced.[152] Heating boronic acid **3.5** with methyliminodiacetic acid in DMF at 85 °C for 24 h afforded the MIDA boronate **3.34** in 66% yield.



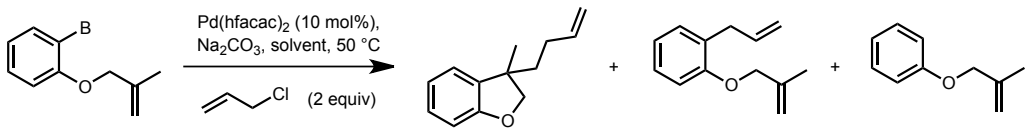
3.5 **3.34** **3.34**

Scheme 3.15: Synthesis of MIDA boronate 3.34

3.3.2 Reactions of Boronic Acid Derivatives

With the boronic acid derivatives **3.32**, **3.33** and **3.34** prepared, their performance in the carboallylation reaction was first compared to that of boronic acid **3.5** in toluene (Table 3.6, entries 1–3). The pinacol ester **3.32** and potassium trifluoroborate **3.33** reagents showed complete conversion of the starting material in 22–24 h (Table 3.6, entries 2 and 3, respectively). A significant reduction in formation of protodeboronation product **3.15** was observed, when compared to the reaction of the boronic acid **3.5** (entry 1), although direct-coupling product **3.14** was formed preferentially. As discussed in Section 3.2 (Table 3.5), the reaction of boronic acid **3.5** in coordinating solvent DME showed incomplete conversion of the starting material and a lower ratio of **3.9**:**3.14** of 3.4:1 when compared with reaction in toluene, but protodeboronation product **3.15** was suppressed completely (Table 3.6, entry 4). In contrast, although protodeboronation **3.15** was still not observed, the reaction of pinacol ester **3.32** in DME afforded complete conversion of the starting

material to an approximately 1:9 ratio of **3.9**:**3.14** (entry 5). The reaction of the organotrifluoroborate **3.33** proved to be the most optimum of those shown in Table 3.6, with complete conversion of the starting material to afford a 3.5:1 ratio of desired product **3.9** to direct-coupling product **3.14** with only a trace of protodeboronation product **3.15** observed (entry 6). Under the same conditions, MIDA boronate ester gave rise to very slow conversion to direct-coupling product **3.14** (entry 7).



3.9 **3.14** **3.15**

Entry	Boron Reagent	Solvent	Time	Ratio[a]			
				SM[b]	**3.9**	**3.14**	**3.15**
1	**3.5**	Toluene	16 h	3.2	6.7	1	10
2	**3.32**	Toluene	22 h	0	0.3	1	0.2
3	**3.33**	Toluene	24 h	0	0.6	1	0.7
4	**3.5**	DME	20 h	9.2	3.4	1	0
5	**3.32**	DME	44 h	0	0.1	1	0
6	**3.33**	DME	20 h	0	3.5	1	0.2
7[c]	**3.34**	DME	48 h	8.8	0	1	0

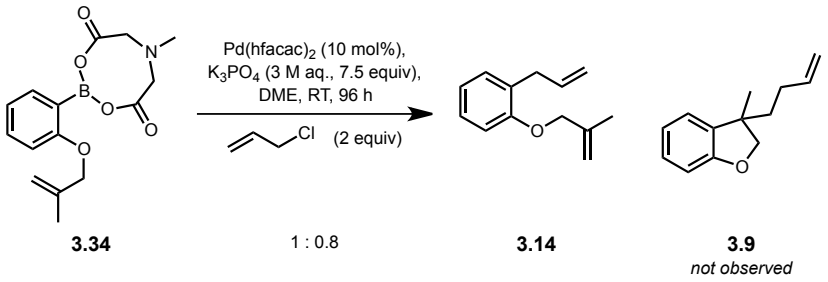
[a] Approximate ratio of **SM** : **3.9** : **3.14** : **3.15** by ^{1}H NMR of unpurified reaction mixture; [b] unreacted starting material; [c] Reaction concentration 0.13 M (all others 0.25 M)

Table 3.6: Effect of altering boron reagent used on carboallylation reaction outcome

As discussed, the slow release of boronic acid from organotrifluoroborate and MIDA boronate derivatives is based on their hydrolytic instability thus, under the "anhydrous" conditions employed in the reactions of Table 3.6, potassium trifluoroborate **3.33** and MIDA boronate **3.34** would be expected to be unreactive. However, as the solvents employed in these transformations were technical grade and used as received, they may be expected to contain adventitious water. Although water is expected to be required for potassium organotrifluoroborates to undergo hydrolysis to the corresponding boronic acids, Lloyd-Jones and co-workers have demonstrated that organotrifluoroborates also undergo acid-catalysed hydrolysis in the absence of a base, mediated by the glassware, albeit in the presence of added water.[144]

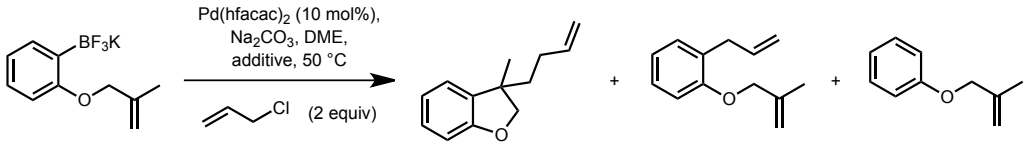
Due to the low reactivity displayed by MIDA boronate **3.34**, this substrate was subsequently subjected to a modification of the conditions reported by Burke and co-workers for the Suzuki–Miyaura coupling of MIDA boronates,[153] in order to investigate if the desired carboallylation product **3.9** could be formed selectively under these conditions

(Scheme 3.16). The authors reported that the boronic acid release rate could be attenuated by variation of the temperature and so, in order to favour slow release, the carboallylation reaction of **3.34** was carried out at room temperature using catalytic $Pd(hfacac)_2$, an excess of aqueous K_3PO_4 and allyl chloride in DME. After 96 h at room temperature, less than 50% conversion of starting material **3.34** had occurred, with sole conversion to the direct-coupling product **3.14** observed.



Scheme 3.16: Attempted carboallylation of MIDA boronate 3.34

As potassium trifluoroborate **3.33** had demonstrated the best ratio of desired product **3.9** to side product **3.14**, whilst also achieving full conversion, reactions of this substrate were investigated further (Table 3.7). In order to investigate the effect of residual water, a sample of DME was stored over 4Å molecular sieves, under argon, 24 h prior to use.[154] Carrying out the reaction under otherwise identical conditions but using dried DME and an argon atmosphere afforded slower conversion of starting material **3.33**, with full conversion still not achieved after 60 h (Table 3.7, entry 2 *cf*. entry 1). The ratio of desired product **3.9** to direct-coupled product **3.14** remained approximately equal. Addition of 3 equivalents of water into a reaction carried out in dry DME under argon afforded complete conversion of the starting material but with a lower ratio of **3.9**:**3.14** (entry 3). Addition of 3 equivalents of IPA gave rise to near complete conversion of **3.33** but with an approximately 1:1 ratio of **3.9**:**3.14** formed (entry 4).[155] Use of technical grade DME but with 4Å molecular sieves added to the reaction mixture afforded a 7.1:1 ratio of desired product **3.9** to direct-coupling product **3.14** with some unreacted starting material (entry 5). However, a number of minor impurities remained in the ^{1}H NMR spectrum of **3.9** after flash chromatography.



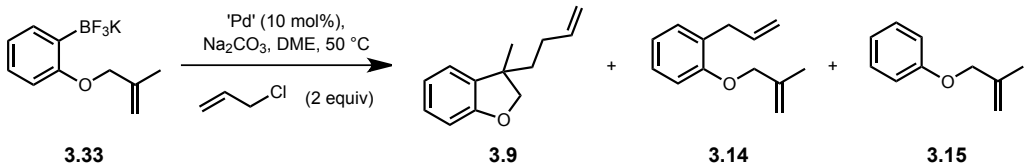
3.33 **3.9** **3.14** **3.15**

Entry	Additive	Time	Ratio[a]			
			3.33	**3.9**	**3.14**	**3.15**
1	-	20 h	0	3.5	1	0.2
2[b]	-	60 h	0.7	3.7	1	0
3[b]	H_2O (3 equiv)	60 h	0	2.5	1	0.2
4[b]	IPA (3 equiv)	60 h	0.3	1.1	1	0
5	4Å MS	60 h	0.9	7.1 (50%)[c]	1	0

[a] Approximate ratio of **3.33** : **3.9** : **3.14** : **3.15** by ^{1}H NMR of unpurified reaction mixture; [b] DME used dried over 4Å molecular sieves for 24 h prior to use. Glassware dried in oven and reaction carried out under argon; [c] Yield of impure **3.9**, material could not be obtained pure.

Table 3.7: Investigation of effect of water/additive quantities on carboallylation of 3.33

A brief investigation of the effect of varying the palladium source on the reaction of organotrifluoroborate **3.33** was subsequently conducted (Table 3.8). Cationic palladium catalyst $Pd(OTs)_2(MeCN)_2$ gave complete conversion of **3.33**, but with protodeboronation product **3.15** observed and a reduced ratio of **3.9**:**3.14** relative to the reaction using $Pd(hfacac)_2$ (entry 2 *cf*. entry 1). Whilst $PdCl_2$ demonstrated a similar ratio of **3.9**:**3.14** to the reaction of $Pd(hfacac)_2$, a lower level of conversion was observed after the same reaction time (entry 3). Use of phosphonite catalyst **3.19** afforded incomplete conversion of the starting material after 48 h and formed direct-coupling product **3.14** in preference to desired product **3.9** (entry 4). $Pd(hfacac)_2$ thus remained the superior catalyst.



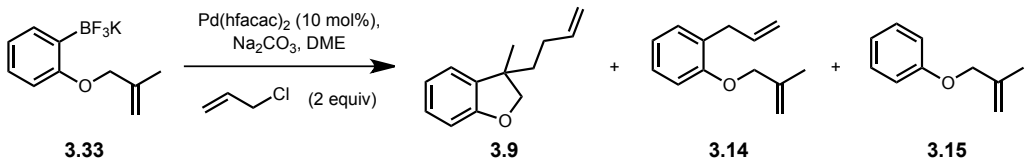
3.33 **3.9** **3.14** **3.15**

Entry	'Pd'	Time	Ratio[a]			
			3.33	**3.9**	**3.14**	**3.15**
1	$Pd(hfacac)_2$	20 h	0	3.5	1	0.2
2	$Pd(OTs)_2(MeCN)_2$	24 h	0	2.6	1	1.0
3	$PdCl_2$	22 h	0.8	3.6	1	0.1
4	**3.19**	48 h	0.4	0.5	1	0.1

[a] Approximate ratio of **3.33** : **3.9** : **3.14** : **3.15** by ^{1}H NMR of unpurified reaction mixture;

Table 3.8: Effect of varying Pd source on carboallylation of 3.33

The effects of concentration and temperature on the reaction of the potassium organotrifluoroborate were next investigated as it is expected that the concentration of the reaction mixture may be important factor in attempting to favour an intramolecular reaction over an intermolecular reaction (Table 3.9). Carrying out the reaction at room temperature afforded a significantly improved ratio of desired product **3.9** to direct-coupling product **3.14**, but at the expense of conversion of the starting material. In addition to this, several minor, unidentified, side products were also formed (entry 2). When the reaction was conducted at lower concentration, *i.e.* 0.13 M *cf*. 0.25 M, the ratio of desired product **3.9** to side product **3.14** approximately doubled, although unreacted starting material was observed (entry 3). Whilst the desired product **3.9** could be isolated in a 51% yield from the carboallylation reaction, this yield is approximately the same as the 48% yield obtained from the reaction carried out at 0.25 M (entry 1). Further reduction of the concentration to 0.05 M increased the ratio of desired product **3.9** to side product **3.14**, but with a greater proportion of unreacted starting material (entry 4). Increasing the temperature of the reaction at the lowest concentration gave rise to nearly complete conversion of starting material **3.33**, but with a lower ratio of desired product **3.9** to side product **3.14** obtained as a result (entry 5).



3.33 **3.9** **3.14** **3.15**

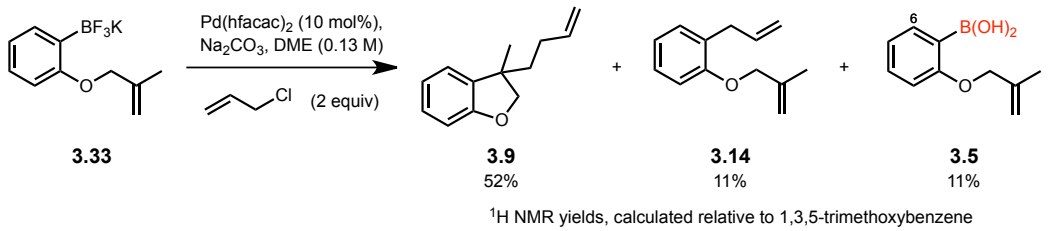
Entry	Conc. DME	Temp	Time	Ratio[a]			
				3.33	**3.9**	**3.14**	**3.15**
1	0.25 M	50 °C	22 h	0	3.5 (48%)[b]	1	0.2
2	0.25 M	RT	24 h	3	8.5	1	0.3
3	0.13 M	50 °C	48 h	1.4	6 (51%)[b]	1	0
4	0.05 M	50 °C	44 h	2.4	7.5	1	0.1
5	0.05 M	90 °C	21 h	0.2	2.4	1	0.3

[a] Approximate ratio of **3.33** : **3.9** : **3.14** : **3.15** by ^{1}H NMR of unpurified reaction mixture; [b] isolated yield of pure **3.9**

Table 3.9: Effect of concentration and temperature on carboallylation of 3.33

The isolated yields from the carboallylation reactions in Table 3.9 were lower than expected from the ratios of desired product **3.9** to side product **3.14**. In order to investigate if this loss of material was occurring on purification or as a result of a decomposition pathway, the reaction conducted at 0.13 M (Table 3.9, entry 3) was repeated and, upon work up, an ^{1}H NMR spectrum of the crude material was recorded with a known mass of an internal standard (1,3,5-trimethoxybenzene) (Scheme 3.17). The

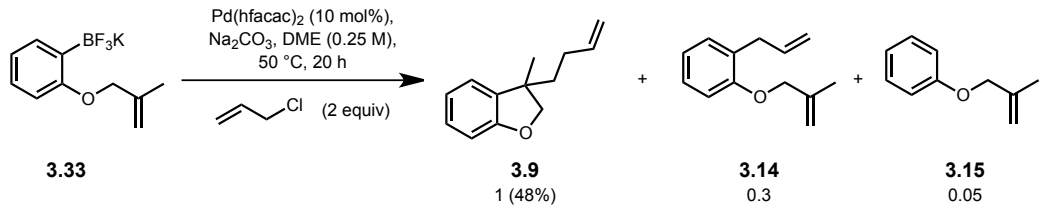
calculated yield of desired product **3.9** from the carboallylation reaction was 52%, which is consistent with the yield isolated. A yield of the direct-coupling product **3.14** of 11% was also calculated, in addition to 11% of an organoboron species believed to be the boronic acid **3.5**. Whilst the identity of the organoboron species was not confirmed, this species was identified as a boronic acid derivative by the chemical shift of the 6-H proton. The observed ^{1}H NMR chemical shift of the 6-H proton in boronic acid is 7.85 ppm, which is consistent with the observed shift of the organoboron species present in the crude reaction mixture.



Scheme 3.17: Calculated yields of carboallylation products from crude reaction mixture

3.4 Conclusions

Following on from the successful development of the oxyallylation reaction, the aim of this research was to develop a palladium-catalysed carboallylation reaction of unactivated alkenes to access heterocycles using arylboron species. Whilst initial attempts at effecting the desired carboallylation reaction gave rise to preferential formation of direct-coupling product **3.14** (Scheme 3.18), subsequent optimisation of the palladium source, solvent and base led to preferential formation of the desired dihydrobenzofuran species **3.9**. Protodeboronation of the starting material was another problematic side reaction; however, formation of this product could be almost completely suppressed by use of the potassium organotrifluoroborate derivative **3.33**.



Scheme 3.18: Optimum conditions for carboallylation of 3.33

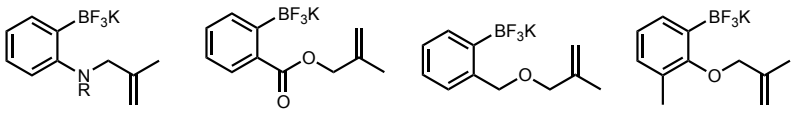
Although the desired carboallylation transformation was achieved, the isolated yield of the desired product **3.9** from this reaction remains moderate, leaving scope for improvement. The carboallylation reaction gives rise to the formation of two new C–C bonds in a single transformation, including the construction of an sp^3–sp^3 bond and forming a fully

substituted carbon centre, and thus constitutes a complementary addition to existing methods of effecting the carbopalladation of unactivated alkenes.

3.5 Future Work

Whilst the yield of the carboallylation product **3.9** afforded in this reaction is not yet comparable to the product yields obtained in the oxyallylation reaction, the moderate yield obtained demonstrates that a transformation of this type, once fully optimised, would represent a very useful method for the construction of heterocycles. Further investigations into the origin of the low isolated yield would be instructive – repeating the reaction on a larger scale may allow any additional minor impurities to be isolated and characterised.

Exploration of a small amount of substrate scope could demonstrate whether the low yield observed in the carboallylation reaction is due to poor choice of substrate for the optimisation process (Scheme 3.19). Substrate **3.35** contains a different heteroatom in the alkene tether and, as described in some of the examples in Section 1.3, this can often have a dramatic effect over the outcome of intra- *versus* intermolecular transformations. Substrates **3.36** and **3.37** would form 6-membered heterocycles and thus are likely to display a different reactivity profile. In addition to this, the electronics of the aryl ring in these susbtrates is different to organotrifluoroborate **3.33** as substrate **3.36** contains an electron withdrawing ester group and substrate **3.37** does not have the oxygen linker directly attached to the aromatic ring. With a methyl group *ortho* to the ether linkage, substrate **3.38** may display greater preference towards formation of the dihydrobenzofuran product due to steric interaction with the methyl group causing a shift in the equilibrium between reacting conformations (as in Scheme 3.7).



3.35 **3.36** **3.37** **3.38**

Scheme 3.19: Possible substrates for carboallylation reaction

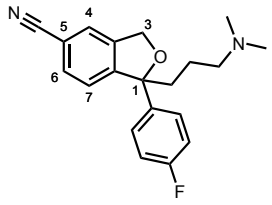
4. Experimental

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 = 7.26) as internal standard or DMSO-d^6 as the solvent using residual DMSO (δ = 2.5) as internal standard. For ^{13}C NMR spectra the chemical shifts are reported relative to the central resonance of $CDCl_3$ (δ = 77.16) or DMSO (δ = 39.52). 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 in 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, EI and CI conditions by the analytical services at the University of Glasgow. Melting points were recorded with a Stuart Scientific SMP1 apparatus. 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 visualised under UV-light and/or developed 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.

4.2 Experimental Details

Citalopram 2.1.

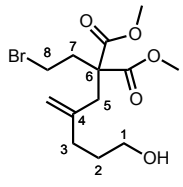


2.1

To a solution of 1-(but-3-enyl)-1-(4-fluorophenyl)-1,3-dihydroiso benzofuran-5-carbonitrile **2.269** (170 mg, 0.57 mmol) in acetone (19 mL) and water (10 mL) was added NMO (330 mg, 2.8 mmol) then OsO_4 (4% wt. in water, 0.18 mL, 0.03 mmol). The resulting mixture was stirred at RT for 23 h then cooled to 0 °C and $NaIO_4$ (290 mg, 1.4 mmol) added. The reaction mixture was allowed to warm to RT and stirred for 2 h then quenched with sat. aq. sodium sulfite (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a yellow oil. The oil was dissolved in EtOH (5.7 mL) and dimethylamine (2.0 M in THF, 0.86 mL, 1.7 mmol) added. The resulting mixture was heated to reflux for 1 h then cooled to RT. $NaBH(OAc)_3$ (160 mg, 0.74 mmol) was then added in one portion and the mixture stirred at RT for 16 h. The reaction mixture was quenched with aq. HCl (1 M, 5 mL) and partitioned between Et_2O (25 mL) and sat. aq. $NaHCO_3$ (25 mL). The aqueous phase was further extracted with Et_2O (2 × 25 mL) and the combined organic extracts washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2:MeOH:NEt_3, 95:4:1) afforded the title compound as a colourless oil (110 mg, 62% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.59 (1H, d, *J* = 7.9 Hz, 6-H), 7.50 (1H, s, 4-H), 7.44–7.41 (2H, m, 2×ArH), 7.40 (1H, d, *J* = 7.9 Hz, 7-H), 7.02–6.98 (2H, m, 2×ArH), 5.20 (1H, d, *J* = 13.0 Hz, 3-H_a), 5.15 (1H, d, *J* = 12.9 Hz, 3-H_b), 2.28–2.11 (10H, m, $CH_2CH_2CH_2N(CH_3)_2$), 1.52–1.43 (1H, m, $CH_aCH_2N(CH_3)_2$), 1.38–1.29 ((1H, m, $CH_bCH_2N(CH_3)_2$). Analytical data observed were in accordance with literature values.[156]

8-Bromo-6,6-bis(methoxycarbonyl)-4-methyleneoctan-1-ol 2.4



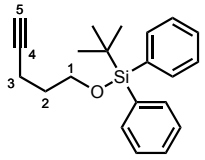
2.4

To a stirred solution of 8-bromo-1-(*tert*-butyldiphenylsilyloxy)-6,6-bis(methoxycarbonyl)-4-methyleneoctane **2.15** (950 mg, 1.7 mmol) in THF (1.8 mL) was added dropwise a solution of tetrabutylammonium fluoride (1 M in THF, 1.8 mL, 1.8 mmol). The reaction mixture was stirred at RT for 2 h then concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1 then 1:1) afforded the title compound **2.4** as a colourless oil (360 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.94 (1H, d, *J* = 1.3 Hz, C=CH_a), 4.80 (1H, s, C=CH_b), 3.74 (6H, s, 2 × OCH_3), 3.62 (2H, t, *J* = 6.3 Hz, 1-H_2), 3.33–3.29 (2H, m, 8-H_2), 2.73 (2H, s, 5-H_2), 2.47–2.43 (2H, m, 7-H_2), 1.97 (2H, t, *J* = 7.6 Hz, 3-H_2), 1.71–1.64 (2H,

m, 2-H_2), 1.49 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.2 (2 × C), 143.5 (C), 115.4 (CH_2), 62.4 (CH_2), 57.4 (C), 52.9 (2 × CH_3), 39.3 (CH_2), 36.5 (CH_2), 32.6 (CH_2), 30.8 (CH_2), 27.3 (CH_2); IR (thin film) 1728, 1204, 1161 cm^{-1}; HRMS (CI/Isobutane) exact mass calculated for $C_{13}H_{21}BrO_5$ $[M]^+$ *m/z* 337.0651, found *m/z* 337.0646.

tert-Butyl(pent-4-ynyloxy)diphenylsilane 2.10

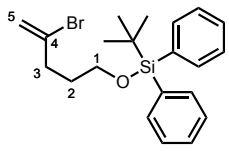


2.10

To a stirred solution of 4-pentynol **2.9** (6.25 g, 74.3 mmol) in DMF (230 mL) was added imidazole (7.59 g, 111 mmol) followed by *tert*-butyldiphenylsilyl chloride (18.6 g, 67.5 mmol). The resulting solution was stirred at RT for 17 h. Water (1000 mL) was added and the reaction mixture extracted with EtOAc (4 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.10** as a colourless oil (19.7 g, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.68–7.67 (4H, m, 4×ArH), 7.45–7.37 (6H, m, 6×ArH), 3.75 (2H, t, *J* = 6.0 Hz, 1-H_2), 2.35 (2H, td, *J* = 7.2, 2.7 Hz, 3-H_2), 1.92 (1H, t, *J* = 2.7 Hz, 5-H), 1.81–1.76 (2H, m, 2-H_2), 1.06 (9H, s, $SiC(CH_3)_3$). Analytical data observed were in accordance with literature values.[77]

(4-Bromopent-4-enyloxy)(*tert*-butyl)diphenylsilane 2.11

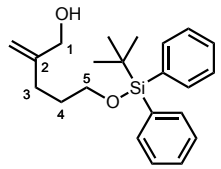


2.11

To a cooled (0 °C) solution of freshly prepared 9-bromo-9-borabicyclo[3.3.1]nonane[157] (4.0 mL, 26 mmol) in CH_2Cl_2 (100 mL) was added dropwise a solution of *tert*-butyl(pent-4-ynyloxy)diphenylsilane **2.10** (6.0 g, 19 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred at 0 °C for 3.5 h, after which additional 9-bromo-9-borabicyclo[3.3.1]nonane (0.57 mL, 3.7 mmol) was added to the reaction mixture. The mixture was stirred at 0 °C for a further 1 h then acetic acid (8.5 mL, 150 mmol) was added. The reaction mixture was allowed to warm to RT and stirred for 45 minutes. The reaction mixture was re-cooled to 0 °C and NaOH (10% aq., 120 mL, 300 mmol) added dropwise. After a further 5 minutes, a 30% aqueous solution of H_2O_2 (30% aq., 19 mL, 150 mmol) was added dropwise, with effervescence observed upon addition. The mixture was allowed to warm to RT over 20 minutes and extracted with petroleum ether (2 × 200 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:Et_2O, 98.5:1.5) afforded the title compound **2.11** as a colourless oil (5.6 g, 74%).

^{1}H NMR (400 MHz) δ (ppm): 7.69–7.67 (4H, m, 4×ArH), 7.46–7.38 (6H, m, 6×ArH), 5.57 (1H, d, *J* = 1.2 Hz, 5-H_a), 5.40 (1H, d, *J* = 1.4 Hz, 5-H_b), 3.71 (2H, t, *J* = 6.1 Hz, 1-H_2), 2.58 (2H, t, *J* = 7.3 Hz, 3-H_2), 1.86–1.80 (2H, m, 2-H_2), 1.08 (9H, s, $SiC(CH_3)_3$). Analytical data observed were in accordance with literature values.[77]

5-(*tert*-Butyldiphenylsilanyloxy)-2-methylenepentan-1-ol 2.12

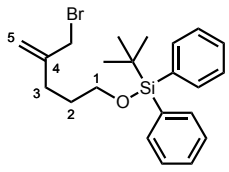


2.12

To a cooled (–78 °C) solution of *n*BuLi (16 mL, 1.8 M in hexanes, 28 mmol) in THF (140 mL) was added dropwise a solution of (4-bromopent-4-enyloxy)(*tert*-butyl)diphenylsilane **2.11** (5.6 g, 14 mmol) in THF (14 mL). After 30 minutes at –78 °C, DMF (11 mL, 140 mmol) was added dropwise and the mixture allowed to warm to RT over 2.5 h. The reaction mixture was partitioned between water (100 mL) and petroleum ether (200 mL). The organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in methanol (35 mL) and the solution cooled to 0 °C. Cerium(III) chloride heptahydrate (5.7 g, 15 mmol) was added to the mixture, followed by portionwise addition of sodium borohydride (580 mg, 15 mmol). The reaction mixture was stirred at 0 °C for 15 minutes then quenched with acetic acid (10% aq., 50 mL). The mixture was extracted with petroleum ether (2 × 100 mL) and the combined organic extracts washed with sat. aq. $NaHCO_3$ (50 mL) then brine (50 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.12** as a colourless oil (3.2 g, 66% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68–7.66 (4H, m, 4×ArH), 7.45–7.36 (6H, m, 6×ArH), 5.01 (1H, d, *J* = 0.7 Hz, C=CH_a), 4.86 (1H, d, *J* = 1.1 Hz, C=CH_b), 4.05 (2H, d, *J* = 6.2 Hz, 1-H_2), 3.69 (2H, t, *J* = 6.3 Hz, 5-H_2), 2.15 (2H, t, *J* = 7.6 Hz, 3-H_2), 1.76–1.69 (2H, m, 4-H_2), 1.41 (1H, t, *J* = 6.2 Hz, OH), 1.05 (9H, s, $SiC(CH_3)_3$). Analytical data observed were in accordance with literature values.[77]

(4-(Bromomethyl)pent-4-enyloxy)(*tert*-butyl)diphenylsilane 2.13

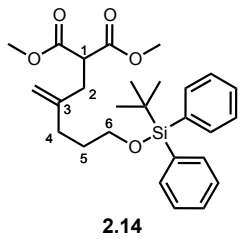


2.13

To a cooled (0 °C) solution of 5-(*tert*-butyldiphenylsilanyloxy)-2-methylenepentan-1-ol **2.12** (3.23 g, 9.11 mmol) and triphenylphosphine (3.11 g, 11.9 mmol) in CH_2Cl_2 (46 mL) was added *N*-bromosuccinimide (2.11 g, 12.0 mmol). The mixture was allowed to warm to RT, by which time it had become a yellow solution. After 30 minutes, the mixture was partitioned between Et_2O (100 mL) and water (100 mL). The organics were washed with sat. aq. $NaHCO_3$ (50 mL), turning purple upon shaking. The organics were further washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) afforded the title compound **2.13** as a colourless oil (3.39 g, 89%).

^{1}H (400 MHz, $CDCl_3$) δ (ppm): 7.71–7.68 (4H, m, 4×ArH), 7.47–7.38 (6H, m, 6×ArH), 5.16 (1H, s, 5-H_a), 4.95 (1H, d, *J* = 1.2 Hz, 5-H_b), 3.95 (2H, s, CH_2Br), 3.71 (2H, t, *J* = 6.3 Hz, 1-H_2), 2.33 (2H, t, *J* = 7.7 Hz, 3-H_2), 1.78–1.71 (2H, m, 2-H_2), 1.08 (9H, s, $SiC(CH_3)_3$). Analytical data observed were in accordance with literature values.[77]

6-(*tert*-Butyldiphenylsilyloxy)-1,1-bis(methoxycarbonyl)-3-methylenehexane 2.14

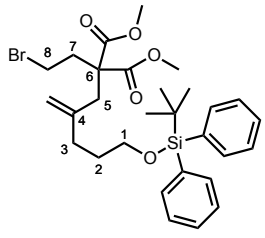


2.14

To a cooled (0 °C) suspension of sodium hydride (60% dispersion in mineral oil, 150 mg, 3.8 mmol) in THF (45 mL) was added dropwise dimethyl malonate (0.57 mL, 5.0 mmol). After 5 minutes, a solution of (4-(bromomethyl)pent-4-enyloxy)(*tert*-butyl)diphenylsilane **2.13** (1.1 g, 2.5 mmol) in THF (2.7 mL) was added dropwise. The mixture was allowed to warm to RT. After 21 h, the mixture was quenched with water (20 mL) and extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 95:5 then 9:1) afforded the title compound **2.14** as a colourless oil (820 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67–7.65 (4H, m, 4 × ArH), 7.44–7.36 (6H, m, 6 × ArH), 4.78 (1H, s, C=CHa), 4.73 (1H, s, C=CH_b), 3.72 (6H, s, 2 × OCH_3), 3.65 (2H, t, *J* = 6.3 Hz, 6-H_2), 3.61 (1H, t, *J* = 7.9 Hz, 1-H), 2.61 (2H, d, *J* = 7.8 Hz, 2-H_2), 2.11 (2H, t, *J* = 7.7 Hz, 4-H_2), 1.72–1.65 (2H, m, 5-H_2), 1.04 (9H, s, $SiC(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 169.7 (2 × C), 145.4 (C), 135.7 (4 × CH), 134.1 (2 × C), 129.7 (2 × CH), 127.8 (4 × CH), 111.3 (CH_2), 63.4 (CH_2), 52.7 (2 × CH_3), 50.4 (CH), 35.0 (CH_2), 32.2 (CH-$_2$), 30.7 (CH_2), 27.0 (3 × CH_3), 19.3 (C); IR (thin film) 1736, 1107 cm^{-1}. HRMS (CI/Isobutane) exact mass calculated for $C_{27}H_{37}O_5Si$ $[M+H]^+$ *m/z* 469.2410, found *m/z* 469.2407.

8-Bromo-1-(*tert*-butyldiphenylsilyloxy)-6-6-bis(methoxycarbonyl)-4-methyleneoctane 2.15



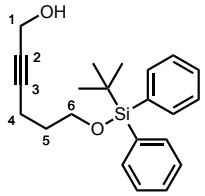
2.15

To a solution of 6-(*tert*-butyldiphenylsilyloxy)-1,1-bis (methoxycarbonyl)-3-methylenehexane **2.14** (1.8 g, 3.8 mmol) in THF (4.8 mL) was added sodium hydride (60% dispersion in mineral oil, 230 mg, 5.7 mmol). After 10 minutes, 1,2-dibromoethane (1.0 mL, 11 mmol) was added dropwise and the resulting solution heated to 65 °C. After 2.5 h, the reaction mixture was cooled to room temperature, quenched by addition of water and the mixture extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.15** as a colourless oil (1.9 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66–7.64 (4H, m, 4 × ArH), 7.45–7.36 (6H, m, 6 × ArH), 4.89 (1H, d, *J* = 1.3 Hz, C=*CHa*), 4.75 (1H, s, C=CH_b), 3.71 (6H, s, 2 × OCH_3), 3.63 (2H, t, *J* = 6.3 Hz, 1-H_2), 3.33–3.29 (2H, m, 8-H_2), 2.70 (2H, s, 5-H_2), 2.47–2.43 (2H, m, 7-H_2), 1.98 (2H, t, *J* = 7.6 Hz, 3-H_2), 1.69–1.62 (2H, m, 2-H_2), 1.04 (9H, s, $SiC(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.2 (2 × C), 143.6 (C), 135.7 (4 × CH), 134.0 (2 × C),

129.7 (2 × CH), 127.8 (4 × CH), 115.0 (CH_2), 63.4 (CH_2), 57.4 (C), 52.8 (2 × CH_3), 39.5 (CH_2), 36.4 (CH_2), 32.7 (CH_2), 30.8 (CH_2), 27.4 (CH_2), 27.0 (3 × CH_3), 19.3 (C); IR (thin film) 1732, 1107 cm^{-1}; HRMS (CI/Isobutane) exact mass calculated for $C_{29}H_{39}BrO_5Si$ $[M]^+$ *m/z* 575.1828, found *m/z* 575.1824.

6-(*tert*-Butyldiphenylsilanyloxy)hex-2-yn-1-ol 2.18

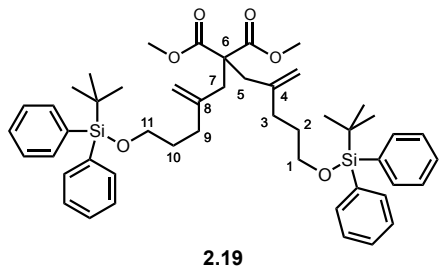


2.18

To a cooled (–78 °C) solution of *tert*-butyl(pent-4-ynyloxy)diphenyl silane **2.10** (200 mg, 0.6 mmol) in THF (6.8 mL) was added dropwise a solution of *n*BuLi (0.35 mL, 2.1 M in hexanes, 0.74 mmol). After 45 minutes at –78 °C, DMF (0.48 mL, 6.2 mmol) was added dropwise and the mixture allowed to warm to RT. The reaction mixture was partitioned between water (20 mL) and Et_2O (20 mL). The organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in methanol (1 mL) and the solution cooled to 0 °C. Cerium chloride heptahydrate (170 mg, 0.46 mmol) was added to the mixture followed by sodium borohydride (17 mg, 0.45 mmol). The reaction mixture was stirred at 0 °C for 15 minutes then quenched with 1 M HCl (2 mL). The mixture was extracted with Et_2O (2 × 15 mL) and the combined organic extracts washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 95:5 then 85:15) afforded the title compound **2.18** as a colourless oil (83 mg, 38% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.69–7.67 (4H, m, 4×Ar), 7.45–7.37 (6H, m, 6×Ar), 4.20 (2H, dt, *J* = 6.1, 2.2 Hz, 1-H_2), 3.74 (2H, t, *J* = 6.0 Hz, 6-H_2), 2.38 (2H, tt, *J* = 7.1, 2.2 Hz, 4-H_2), 1.79–1.74 (2H, m, 5-H_2), 1.44 (1H, t, *J* = 6.1 Hz, OH), 1.06 (9H, s, $SiC(CH_3)_3$). Analytical data observed were in accordance with literature values.[158]

1,11-Di(*tert*-butyldiphenylsilyloxy)-6,6-bis(methoxycarbonyl)-4,8-bis(methylene)undecane 2.19

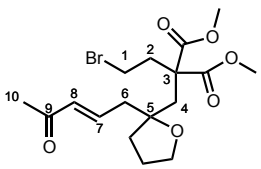


2.19

To a cooled (0 °C) suspension of sodium hydride (60% dispersion in mineral oil, 14 mg, 0.36 mmol) in THF (1.3 mL) was added dropwise a solution of dimethyl malonate (30 µL, 0.29 mmol) in THF (0.3 mL). After 5 minutes, a solution of (4-(bromomethyl)pent-4-enyloxy)(*tert*-butyl)diphenylsilane **2.13** (100 mg, 0.24 mmol) in THF (0.5 mL) was added dropwise. The mixture was allowed to warm to RT. After 24 h, the mixture was quenched with water (10 mL). The mixture was extracted with Et_2O (3 × 10 mL) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 95:5) afforded the title compound **2.19** as a colourless oil (78 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65–7.62 (8H, m, 8 × ArH), 7.41–7.33 (12H, m, 12 × ArH), 4.81 (2H, d, *J* = 1.2 Hz, 2 × C=CH_a), 4.70 (2H, s, 2 × C=CH_b), 3.62–3.59 (10H, m, 2 × OCH_3, 1-H_2, 11-H_2), 2.70 (4H, s, 5-H_2, 7-H_2), 1.99 (4H, t, *J* = 7.6 Hz, 3-H_2, 9-H_2), 1.68–1.61 (4H, m, 2-H_2, 10-H_2), 1.02 (18H, s, 2 × $SiC(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 172.0 (2 × C), 144.6 (2 × C), 135.7 (8 × CH), 134.1 (4 × C), 129.6 (4 × CH), 127.7 (8 × CH), 113.7 (2 × CH_2), 63.5 (2 × CH_2), 57.3 (C), 52.4 (2 × CH_3), 39.0 (2 × CH_2), 33.2 (2 × CH_2), 30.9 (2 × CH_2), 27.0 (6 × CH_3), 19.3 (2 × C); IR (thin film, CH_2Cl_2) 1736, 1107 cm^{-1}; HRMS (FAB) exact mass calculated for $C_{49}H_{64}O_6Si$ $[M]^+$ *m/z* 805.4320, found *m/z* 805.4326.

1-Bromo-3,3-bis(methoxycarbonyl)-5-(tetrahydrofuran-2-yl)dec-7-en-9-one 2.22

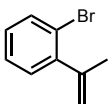


2.22

To a vial pre-charged with palladium(II) acetate (34 mg, 0.15 mmol) and $NaHCO_3$ (25 mg, 0.30 mmol) was added a solution of 8-bromo-6,6-bis(methoxycarbonyl)-4-methyleneoctan-1-ol **2.4** (50 mg, 0.15 mmol) and methyl vinyl ketone (distilled, 0.06 mL, 0.74 mmol) in DMF (0.6 mL). The resulting suspension was stirred at RT for 16 h then further palladium(II) acetate (34 mg, 0.15 mmol) added. The mixture was stirred for a further 24 h then partitioned between water (20 mL) and Et_2O (20 mL) and filtered over Celite®. The organic extracts were washed with water (2 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography afforded the title compound **2.22** as a colourless oil (26 mg, 21%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.74 (1H, dt, *J* = 15.9, 7.4 Hz, 7-H), 6.11 (1H, d, *J* = 16.0 Hz, 8-H), 3.78–3.72 (8H, m, O*C*$H_2$$CH_2CH_2$, 2 × OCH_3), 3.36–3.25 (2H, m, 1-H_2), 2.69 (1H, ddd, *J* = 15.4, 9.6, 4.4 Hz, 2-H_a), 2.58 (1H, ddd, *J* = 15.4, 9.6, 4.4 Hz, 2-H_b), 2.44 (1H, ddd, *J* = 14.5, 7, 1.5 Hz, 6-H_a), 2.37 (1H, ddd, *J* = 14.4, 7.6, 1.1 Hz, 6-H_b), 2.29 (2H, d, *J* = 1.2 Hz, 4-H_2), 2.25 (3H, s, 10-H_3), 1.98–1.89 (1H, m, OCH_2*C*$H_a$$CH_2$), 1.88–1.69 (3H, m, OCH_2*C*H_b*C*H_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 198.3 (C), 171.4 (C), 171.3 (C), 143.4 (CH), 134.2 (CH), 83.1 (C), 68.5 (CH_2), 56.6 (C), 52.9 (CH_3), 52.8 (CH_3), 43.2 (CH_2), 41.4 (CH_2), 37.5 (CH_2), 36.9 (CH_2), 27.7 (CH_2), 27.3 (CH_3), 25.6 (CH_2); IR (thin film) 1732, 1254 cm^{-1}; HRMS (CI/Isobutane) exact mass calculated for $C_{17}H_{25}BrO_6$ $[M]^+$ *m/z* 405.0913, found *m/z* 405.0916.

1-Bromo-2-(prop-1-en-2-yl) benzene 2.25

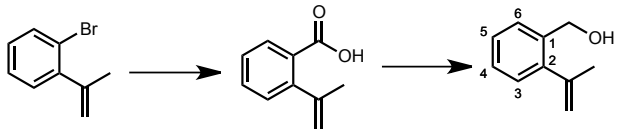


2.25

To a stirred suspension of methyl triphenylphosphonium 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 RT for 15 minutes then a solution of *o*-bromoacetophenone (3.4 g, 17 mmol) in THF (34 mL) added dropwise. The resulting suspension was stirred at RT for 3 h then quenched with sat. aq. NH_4Cl (100 mL). The mixture was extracted with Et_2O (100 mL then 2 × 50

mL) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether) afforded the title compound **2.25** as a colourless oil (3.0 g, 91%). Analytical data observed were in accordance with literature values.[159]

(2-(Prop-1-en-2-yl)phenyl) methanol 2.27

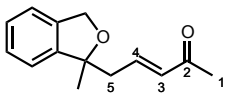


2.25 **2.26** **2.27**

To a cooled (0 °C) solution of 1-bromo-2-(prop-1-en-2-yl) benzene **2.25** (4.48 g, 22.7 mmol) in Et_2O (45 mL) was added dropwise a solution of *n*BuLi (1.49 M in hexanes, 16.0 mL, 23.8 mmol). The resulting yellow suspension was stirred for 15 minutes then added dropwise to a flask charged with CO_2 pellets (*ca*. 50 g). The mixture was allowed to warm to RT over 2 h then quenched with sat. aq. $NaHCO_3$ (100 mL). The mixture was extracted with Et_2O (2 × 50 mL) and the aqueous phase adjusted to pH 1 with aq. HCl (2 M). The aqueous phase was then extracted with Et_2O (3 × 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 **2.26** as a sticky white solid (3.70 g). To a cooled (0 °C) suspension of lithium aluminium hydride (2.26 g, 59.5 mmol) in Et_2O (97 mL) was added dropwise a solution of 2-(prop-1-en-2-yl) benzoic acid **2.26** (3.70 g) in Et_2O (67 mL). After stirring for 5 minutes, the reaction mixture was allowed to warm to RT and stirred for 16 h. The mixture was re-cooled to 0 °C and sat. aq. potassium sodium tartrate (50 mL) added slowly. The biphasic mixture was allowed to stir at RT for 1 h then extracted with Et_2O (100 mL). The organic extracts were washed with water (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.27** as a colourless oil (3.33 g, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.46–7.44 (1H, m, 6-H), 7.31–7.25 (2H, m, 4-H, 5-H), 7.18–7.16 (1H, m, 3-H), 5.25–5.23 (1H, m, C=CH_a), 4.911–4.905 (1H, m, C=CH_b), 4.68 (2H, d, *J* = 6.0 Hz, *C*H_2OH), 2.09–2.08 (3H, m, CH_3), 1.80 (1H, t, *J* = 6.0 Hz, OH). Analytical data observed were in accordance with literature values.[160]

(*E*)-5-(1,3-Dihydro-1-methylisobenzofuran-1-yl)pent-3-en-2-one 2.28



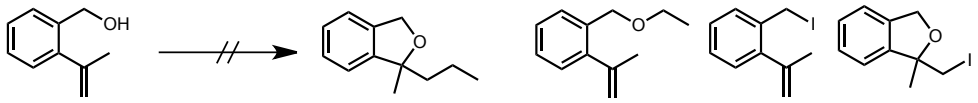
2.28

To a stirred solution of $Pd(TFA)_2$ (10 mg, 0.03 mmol) in DMF (0.41 mL) was added pyridine (0.4 M in DMF, 0.19 mL, 0.07 mmol). The reaction mixture was stirred at RT for 30 minutes then *p*-benzoquinone (101 mg, 0.93 mmol) and a solution of (2-(prop-1-en-2-yl)phenyl)methanol **2.27** (46 mg, 0.31 mmol) and methyl vinyl ketone (0.13 mL, 1.6 mmol) in DMF (0.6 mL) added. The resulting solution was heated at 50 °C for 28 h then cooled to room temperature, 1 M

NH_4Cl (aq., 1 mL) was added and the mixture partitioned between Et_2O (25 mL) and water (25 mL). The organic extracts were washed with water (25 mL), brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) afforded the title compound **2.28** as a colourless oil (53 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.30–7.26 (2H, m, 2 × ArH), 7.22–7.19 (1H, m, ArH), 7.11–7.09 (1H, m, ArH), 6.69 (1H, dt, *J* = 16.0, 7.5 Hz, 4-H), 6.04 (1H, dt, *J* = 16.0 Hz, 1.2Hz, 3-H), 5.10 (1H, d, *J* = 12.4 Hz, CH_aO), 5.05 (1H, d, *J* = 12.4 Hz, CH_bO), 2.72–2.68 (1H, ddd, *J* = 12.6, 6.4, 1.4 Hz, 5-H_a), 2.67–2.63 (1H, ddd, *J* = 13.0, 5.8, 1.3 Hz, 5-H_b), 2.17 (3H, s, CCH_3), 1.51 (3H, s, 1-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 198.5 (C), 144.7 (C), 143.4 (CH), 138.8 (C), 134.2 (CH), 127.9 (CH), 127.7 (CH), 121.3 (CH), 120.9 (CH), 87.6 (C), 71.8 (CH_2), 44.9 (CH_2), 27.2 (CH_3), 26.9 (CH_3); IR (thin film) 1670, 1358, 1254, 1022 cm^{-1}; HRMS (FAB+NaI) exact mass calculated for $C_{14}H_{16}O_2Na$ [M+Na]+ *m/z* 239.1048, found *m/z* 239.1052.

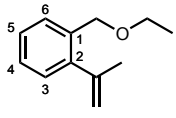
1-(Ethoxymethyl)-2-(prop-1-en-2-yl)benzene 2.34; 1-(Iodomethyl)-2-(prop-1-en-2-yl)benzene 2.35 and 1,3-Dihydro-1-(iodomethyl)-1-methylisobenzofuran 2.36



2.27 **2.33** *not observed* **2.34** **2.35** *components isolated* **2.36**

To a stirred solution of $Pd(TFA)_2$ (10 mg, 0.03 mmol) in DMF (0.41 mL) was added pyridine (0.4 M in DMF, 0.19 mL, 0.07 mmol). The solution turned from brown to yellow upon addition and was stirred at RT for 25 minutes. *p*-Benzoquinone (100 mg, 0.93 mmol) was then added, followed by a solution of (2-(prop-1-en-2-yl)phenyl) methanol **2.27** (45 mg, 0.31 mmol) and ethyl iodide (0.12 mL, 1.6 mmol) in DMF (0.60 mL). The resulting mixture was maintained at RT for 2.5 h, heated at 50 °C for 19 h, then heated at 80 °C for 21 h. The reaction was partitioned between sat. aq. NH_4Cl (25 mL), extracted with Et_2O (25 mL) and filtered over Celite®. The organic extracts were washed with sat. aq. $NaHCO_3$ (25 mL), brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude material indicated a complex mixture of products. Purification by flash chromatography (petroleum ether:CH_2Cl_2, 1:0 to 3:1 to 1:1 to 0:1) allowed several components to be isolated.

1-(Ethoxymethyl)-2-(prop-1-en-2-yl)benzene 2.34

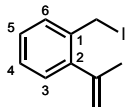


2.34

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.47–7.44 (1H, m, 6-H), 7.29–7.22 (2H, m, 4-H, 5-H), 7.18–7.15 (1H, m, 3-H), 5.21–5.20 (1H, m, C=CH_a), 4.88–4.87 (1H, m, C=CH_b), 4.51 (2H, s, $ArCH_2O$), 3.54 (2H, q, *J* = 8.8 Hz, O*C*$H_2$$CH_3$), 2.07 (3H, m, CCH_3), 1.24 (3H, t, *J* = 8.8 Hz, OCH_2*C*H_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 144.7 (C), 143.6 (C), 135.1 (C), 128.9 (CH), 128.0 (CH),

127.5 (CH), 127.1 (CH), 115.2 (CH_2), 70.5 (CH_2), 65.9 (CH_2), 25.2 (CH_3), 15.4 (CH_3); IR (thin film) 1098, 1083 cm^{-1}; HRMS (CI/Isobutane) exact mass calculated for $C_{12}H_{17}O$ $[M+H]^+$ *m/z* 177.1279, found *m/z* 177.1280.

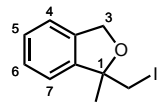
1-(Iodomethyl)-2-(prop-1-en-2-yl)benzene 2.35



2.35

^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.44–7.42 (1H, m, 6-H), 7.24–7.19 (2H, m, 4-H, 5-H), 7.09–7.07 (1H, m, 3-H), 5.29–5.28 (1H, m, C=CH_a), 5.034–5.028 (1H, m, C=CH_b), 4.56 (2H, s, CH_2I), 2.14–2.13 (3H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 144.2 (C), 143.5 (C), 135.7 (C), 130.7 (CH), 128.7 (CH), 128.0 (CH), 127.7 (CH), 115.7 (CH_2), 24.8 (CH_3), 4.6 (CH_2); IR (thin film) 1157 cm^{-1}; LRMS (EI) mass calculated for $C_{10}H_{11}$ $[M-I]^+$ *m/z* 131.2, found *m/z* 131.1.

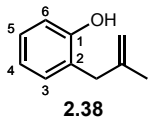
1,3-Dihydro-1-(iodomethyl)-1-methylisobenzofuran 2.36



2.36

^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.34–7.29 (2H, m, 5-H, 6-H), 7.23–7.21 (1H, m, 4-H), 7.18–7.16 (1H, m, 7-H), 5.17 (1H, d, *J* = 12.4 Hz, 3-H_a), 5.08 (1H, d, *J* = 12.4 Hz, 3H_b), 3.54 (1H, d, *J* = 10.5 Hz, CH_a-I), 3.49 (1H, d, *J* = 10.5 Hz, CH_b-I), 1.69 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 143.1 (C), 139.2 (C), 128.3 (CH), 127.7 (CH), 121.32 (CH), 121.29 (CH), 86.2 (C), 72.2 (CH_2), 26.5 (CH_3), 17.5 (CH_2); IR (thin film) 1018 cm^{-1}; HRMS (CI/Isobutane) exact mass calculated for $C_{10}H_{12}OI$ $[M+H]^+$ *m/z* 274.9933, found *m/z* 274.9936.

2-(2-Methylallyl)phenol 2.38

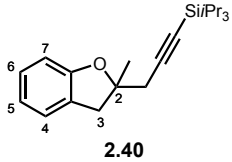


2.38

A solution of 1-(2-methylallyloxy)benzene **2.47** (1.99 g, 13.4 mmol) in DMF (11.2 mL) under argon was subjected to microwave irradiation at 230 °C for 2.5 h. The resulting mixture was extracted with Et_2O (3 × 50 mL) and the combined organic extracts washed with brine (3 × 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 19:1) afforded the title compound **2.38** as a yellow oil (1.84 g, 92%).

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.16 (1H, td, *J* = 7.7, 1.4 Hz, 5-H), 7.11 (1H, d, *J* = 7.4 Hz, 3-H), 6.89 (1H, td, *J* = 7.4, 0.6 Hz, 4-H), 6.84 (1H, d, *J* = 8.0 Hz, 6-H), 5.13 (1H, s, OH), 4.94 (1H, s, C=CH_a), 4.87 (1H, s, C=CH_b), 3.40 (2H, s, CH_2C=CH_2), 1.76 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[43]

Tri*iso*propyl(3-(2-methyl-2,3-dihydrobenzofuran-2-yl)prop-1-yn-1-yl)silane 2.40



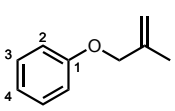
2.40

Following the reported procedure,[43] to a stirred solution of $Pd(hfacac)_2$ (17 mg, 0.03 mmol) in CH_2Cl_2 (3.3 mL) was added a solution of 2-(2-methylallyl)phenol **2.38** (49 mg, 0.33 mmol) and 1-[(tri*iso*propyllsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one[43] (170 mg, 0.40 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at RT for 19 h then

quenched with NH_4Cl (2 mL), extracted with Et_2O (15 mL) and filtered through a plug of cotton wool. The organic extracts were washed with sat. aq. $NaHCO_3$ (15 mL), brine (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:CH_2Cl_2, 49:1 then 9:1) afforded the title compound **2.40** as a yellow oil (82 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.15 (1H, d, *J* = 7.2 Hz, 4-H), 7.10 (1H, t, *J* = 7.6 Hz, 6-H), 6.83 (1H, t, *J* = 7.4 Hz, 5-H), 6.73 (1H, d, *J* = 8.0 Hz, 7-H), 3.39 (1H, d, *J* = 15.6 Hz, 3-H_a), 3.00 (1H, d, *J* = 16.0 Hz, 3-H_b), 2.71 (1H, d, *J* = 16.8 Hz, $CH_aCCSiiPr_3$), 2.63 (1H, d, *J* = 16.4 Hz, $CH_bCCSiiPr_3$), 1.60 (3H, s, 2-CH_3), 1.03 (21 H, Si*i*Pr_3). Analytical data observed were in accordance with literature values.[43]

1-(2-Methylallyloxy)benzene 2.47



2.47

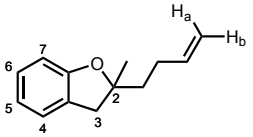
To a stirred suspension of K_2CO_3 (8.8 g, 64 mmol) in DMF (160 mL) was added phenol **2.46** (3.0 g, 32 mmol) followed by 3-chloro-2-methylpropene (3.7 mL, 38 mmol). The resulting mixture was heated at 70 °C for 16 h then cooled to RT, quenched with water (250 mL) and extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.47** as a colourless oil (4.7 g, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.31–7.27 (2H, m, 2×3-H), 6.97–6.93 (3H, m, 2×2-H, 4-H), 5.11 (1H, s, C=CH_a), 5.00 (1H, s, C=CH_b), 4.45 (2H, s, *C*H_2C=CH_2), 1.85 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[43]

General Procedure for Pd-catalysed oxyallylation of unactivated alkenes:

A 4 mL screw-top glass vial was charged with the substrate (1 equiv), toluene (0.25 M), allyl halide (5 equiv), $NaHCO_3$ (2 equiv) and $Pd(hfacac)_2$ (5 mol%) and the vial sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a pre-heated aluminium block until the substrate had been consumed, as judged by TLC analysis or ^{1}H NMR spectroscopy. The reaction mixture was cooled to RT then purified directly by flash chromatography on silica gel.

2-(But-3-enyl)-2,3-dihydro-2-methylbenzofuran 2.57



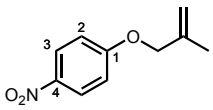
2.57

The general procedure was employed for the heterocyclisation of 2-(2-methylallyl)phenol **2.38** (49 mg, 0.33 mmol) with allyl chloride (0.13 mL, 1.6 mmol) over 16 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 17:3) afforded the title compound **2.57** as a colourless oil (44 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.14–7.09 (2H, m, 4-H, 6-H), 6.81 (1H, t, *J* = 7.4 Hz, 5-H), 6.73 (1H, d, *J* = 8.0 Hz, 7-H), 5.83 (1H, m, *CH*=CH_2), 5.03 (1H, dd, *J* = 17.1, 1.7 Hz,

CH=CH_a), 4.95 (1H, dd, J = 10.2 Hz, 1.4 Hz, CH=CH_b), 3.10 (1H, d, J = 15.6 Hz, 3-H_a), 2.94 (1H, d, J = 15.5 Hz, 3-H_b), 2.20–2.15 (2H, m, $CH_2CH_2CH=CH_2$), 1.85–1.81 (2H, m, $CH_2CH_2CH=CH_2$), 1.44 (3H, s, 2-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 159.1 (C), 138.5 (CH), 128.1 (CH), 127.0 (C), 125.2 (CH), 120.0 (CH), 114.7 (CH_2), 109.5 (CH), 88.4 (C), 41.4 (CH_2), 40.5 (CH_2), 28.6 (CH_2), 26.6 (CH_3); IR (thin film) 1481, 1242 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{17}O$ $[M+H]^+$ *m/z* 189.1279, found *m/z* 189.1283.

1-(2-Methylallyloxy)-4-nitrobenzene 2.63

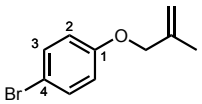


2.63

To a stirred suspension of K_2CO_3 (1.0 g, 7.2 mmol) in DMF (18 mL) was added 4-nitrophenol (0.50 g, 3.6 mmol) followed by 3-chloro-2-methypropene (0.42 mL, 4.3 mmol). The resulting mixture was heated at 70 °C for 17 h then cooled to RT, quenched with water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.63** as a colourless oil (650 mg, 94%), which was used without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.23–8.19 (2H, m, 2×3-H), 7.00–6.96 (2H, m, 2×2-H), 5.11 (1H, s, C=CH_a), 5.05 (1H, s, C=CH_b), 4.54 (2H, s, $CH_2C=CH_2$), 1.84 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[43]

1-(2-Methylallyloxy)-4-bromobenzene 2.65

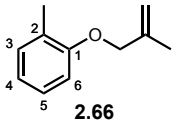


2.65

To a stirred suspension of K_2CO_3 (0.80 g, 5.8 mmol) in DMF (15 mL) was added 4-bromophenol (0.50 g, 2.9 mmol) followed by 3-chloro-2-methylpropene (0.34 mL, 3.5 mmol). The resulting mixture was heated at 70 °C for 18 h then cooled to RT, quenched with water (25 mL) and extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (2 × 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.65** as a colourless oil (660 mg, quant.), which was used without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39–7.35 (2H, m, 2×3-H), 6.83–6.79 (2H, m, 2×2-H), 5.08 (1H, s, C=CH_a), 5.00 (1H, s, C=CH_b), 4.41 (2H, s, $CH_2C=CH_2$), 1.83 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[161]

1-(2-Methylallyloxy)-2-methylbenzene 2.66

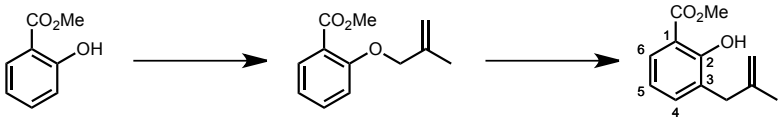


2.66

To a stirred suspension of K_2CO_3 (5.1 g, 37 mmol) in DMF (93 mL) was added *o*-cresol (2.0 g, 19 mmol) followed by 3-chloro-2-methylpropene (2.2 mL, 22 mmol). The resulting mixture was heated at 70 °C for 18 h then cooled to RT, quenched with water (150 mL) and extracted with Et_2O (3 × 75 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.66** as a colourless oil (2.9 g, 97%), which was used without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.17–7.13 (2H, m, 3-H, 5-H), 6.87 (1H, t, *J* = 7.3 Hz, 4-H), 6.82 (1H, d, *J* = 8.3 Hz, 6-H), 5.13 (1H, s, C=CH_a), 5.00 (1H, s, C=CH_b), 4.45 (2H, s, *CH_2*C=CH_2), 2.28 (3H, s, 2-CH_3), 1.86 (3H, s, C(*CH_3*)=CH_2). Analytical data observed were in accordance with literature values.[162]

Methyl 2-hydroxy-3-(2-methylallyl)benzoate 2.67

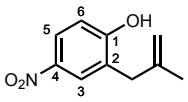


2.62 **2.67**

To a stirred suspension of K_2CO_3 (910 mg, 6.6 mmol) in DMF (17 mL) was added methyl 2-hydroxybenzoate (0.5 g, 3.3 mmol) followed by 3-chloro-2-methylpropene (0.39 mL, 4.0 mmol). The resulting mixture was heated at 70 °C for 17 h then cooled to RT, quenched with water (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (3 × 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford methyl 2-(2-methylallyloxy)benzoate **2.62** as a colourless oil (590 mg, 87%). The material was taken up in NMP (0.9 mL) and transferred to a 4 mL screw top vial then heated under argon at 200 °C for 8.5 h. The mixture was cooled to RT, diluted with brine (25 mL) and extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 39:1) afforded the title compound **2.67** as a colourless oil (310 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.04 (1H, s, OH), 7.73 (1H, dd, *J* = 8.0, 1.6 Hz, 6-H), 7.33 (1H, d, *J* = 7.4 Hz, 4-H), 6.83 (1H, t, *J* = 7.7 Hz, 5-H), 4.82 (1H, s, C=CH_a), 4.66 (1H, s, C=CH_b), 3.94 (3H, s, OCH_3), 3.38 (2H, s, CH_2), 1.75 (3H, s, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 171.1 (C), 160.0 (C), 144.4 (C), 136.5 (CH), 128.3 (C), 128.2 (CH), 118.7 (CH), 112.1 (C), 111.8 (CH_2), 52.4 (CH_3), 37.3 (CH_2), 22.6 (CH_3); IR (thin film) 1599, 1441, 1352, 1072 cm^{-1}; HRMS (CI/Isobutene) exact mass calculated for $C_{12}H_{15}O_3$ $[M+H]^+$ *m/z* 207.1021, found *m/z* 207.1020.

2-(2-Methylallyl)-4-nitrophenol 2.68



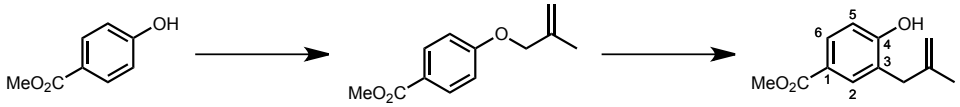
2.68

A solution of 1-(2-methylallyloxy)-4-nitrobenzene **2.63** (650 mg, 3.4 mmol) in NMP (1 mL) under argon was heated at 200 °C for 8.5 h. The mixture was diluted with brine (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (3 × 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.68** as a sticky brown solid (410 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10–8.07 (2H, m, 3-H, 5-H), 6.91 (1H, d, *J* = 8.3 Hz, 6-H), 6.01 (1H, s, OH), 5.03 (1H, s, C=CH_a), 4.93 (1H, s, C=CH_b), 3.46 (2H, s,

$CH_2C{=}CH_2$), 1.77 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[43]

Methyl 4-hydroxy-3-(2-methylallyl)benzoate 2.69

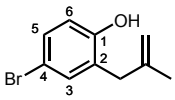


2.64 **2.69**

To a stirred suspension of K_2CO_3 (1.8 g, 13 mmol) in DMF (33 mL) was added methyl 4-hydroxybenzoate (1.0 g, 6.6 mmol) followed by 3-chloro-2-methylpropene (0.77 mL, 7.9 mmol). The resulting mixture was heated at 70 °C for 20 h then cooled to RT, quenched with water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford methyl 4-(2-methylallyloxy)benzoate **2.64** as a colourless oil (1.4 g, quant.), which was used without any further purification. A solution of methyl 4-(2-methylallyloxy)benzoate **2.64** (340 mg, 1.6 mmol) in DMF (1.4 mL) under argon was subjected to microwave irradiation at 240 °C for 1 h. The resulting mixture was diluted with water (25 mL), extracted with EtOAc (3 × 25 mL) and the combined organic extracts washed with brine (3 × 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1 then 4:1) afforded the title compound **2.69** as a white solid (190 mg, 58%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.85 (1H, dd, *J* = 8.4, 2.2 Hz, 6-H), 7.82 (1H, d, *J* = 2.1 Hz, 2-H), 6.85 (1H, d, *J* = 8.4 Hz, 5-H), 5.79 (1H, s, OH), 4.95 (1H, s, $C{=}CH_a$), 4.88 (1H, s, $C{=}CH_b$), 3.88 (3H, s, OCH_3), 3.41 (2H, s, CH_2), 1.73 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 167.2 (C), 159.2 (C), 144.3 (C), 133.1 (CH), 130.3 (CH), 124.8 (C), 122.8 (C), 116.0 (CH), 113.1 (CH_2), 52.1 (CH_3), 39.9 (CH_2), 22.1 (CH_3); IR (thin film) 3302, 1682, 1601, 1424, 1306, 1287, 1123 cm^{-1}; HRMS (EI) exact mass calculated for $C_{12}H_{14}O_3$ $[M]^+$ *m/z* 206.0943, found *m/z* 206.0940.

4-Bromo-2-(2-methylallyl)phenol 2.71

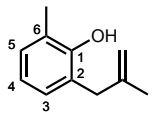


2.71

A solution of 1-(2-methylallyloxy)-4-bromobenzene **2.65** (380 mg, 1.7 mmol) in DMF (1.4 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 × 25 mL) and the combined organic extracts washed with brine (3 × 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.71** as a colourless oil (260 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26–7.22 (2H, m, 3-H, 5-H), 6.73 (1H, d, *J* = 8.4 Hz), 5.15 (1H, s, OH), 4.96 (1H, s, $C{=}CH_a$), 4.88 (1H, s, $C{=}CH_b$), 3.35 (2H, s, $CH_2C{=}CH_2$), 1.75 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[43]

6-Methyl-2-(2-methylallyl)phenol 2.73



2.73

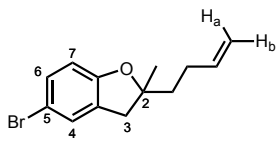
6-methyl-2-(2-methylallyl)phenol **2.73** could be prepared from 1-(2-methylallyloxy)-2-methylbenzene **2.66** by BCl_3-promoted Claisen rearrangement (Procedure A) or by a microwave-promoted Claisen rearrangement (Procedure B).

Procedure A: Following a modification of a reported procedure,[91] to a cooled (–78 °C) solution of 1-(2-methylallyloxy)-2-methylbenzene **2.66** (1.0 g, 6.2 mmol) in CH_2Cl_2 (31 mL) was added dropwise BCl_3 (1 M in hexanes, 6.5 mL, 6.5 mmol). The solution was allowed to warm to –20 °C over 2 h then quenched with water (5 mL) and allowed to warm to RT. The resulting mixture was adjusted to alkaline pH with sat. aq. $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 39:1) afforded the title compound **2.73** as a yellow oil (600 mg, 60%).

Procedure B: A solution of 1-(2-methylallyloxy)-2-methylbenzene **2.66** (900 mg, 5.6 mmol) in DMF (4.6 mL) under argon was subjected to microwave irradiation at 240 °C for 18 minutes. The resulting mixture was diluted with sat. aq. NH_4Cl (25 mL), extracted with Et_2O (3 × 25 mL) and the combined organic extracts washed with brine (2 × 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 39:1) afforded the title compound **2.73** as a colourless oil (600 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.03 (1H, d, *J* = 7.5 Hz, 5-H), 6.94 (1H, d, *J* = 7.2 Hz, 3-H), 6.78 (1H, t, *J* = 7.5 Hz, 4-H), 5.1 (1H, s, OH), 4.94 (1H, s, C=CH_a), 4.89 (1H, s, C=CH_b), 3.39 (2H, s, CH_2), 2.25 (3H, s, CH_3), 1.75 (3H, s, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 153.3 (C), 145.0 (C), 129.6 (CH), 128.8 (CH), 124.8 (C), 124.4 (C), 120.4 (CH), 112.5 (CH_2), 40.5 (CH_2), 22.1 (CH_3), 15.9 (CH_3); IR (thin film) 3499, 1470, 1196 cm^{-1}; HRMS (CI) exact mass calculated for $C_{11}H_{15}O$ $[M+H]^+$ *m/z* 163.1123, found *m/z* 163.1123.

5-Bromo-2-(but-3-enyl)-2,3-dihydro-2-methylbenzofuran 2.81



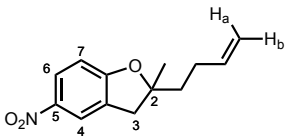
2.81

The general procedure was employed for the heterocyclisation of 4-bromo-2-(2-methylallyl)phenol **2.71** (75 mg, 0.33 mmol) with allyl chloride (0.13 mL, 1.6 mmol) over 16 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 17:3) afforded the title compound **2.81** as a colourless oil (63 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.23–7.22 (1H, m, 4-H), 7.20–7.18 (1H, m, 7-H), 6.60 (1H, d, *J* = 8.4 Hz, 6-H), 5.84–5.78 (1H, m, *CH*=CH_2), 5.03 (1H, dq, *J* = 17.1, 1.7 Hz, CH=*CH*$_a$), 4.96 (1H, ddd, *J* = 10.2, 1.7, 1.2 Hz, CH=*CH*$_b$), 3.08 (1H, d, *J* = 15.8 Hz, 3-H), 2.93 (1H, d, *J* = 15.8 Hz, 3-H), 2.18–2.13 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.83–1.80 (2H, m, *CH*$_2$$CH_2$CH=$CH_2$), 1.43 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 158.3 (C),

138.2 (CH), 130.9 (CH), 129.5 (C), 128.1 (CH), 114.8 (CH_2), 111.7 (C), 111.0 (CH), 89.4 (C), 41.1 (CH_2), 40.3 (CH_2), 28.4 (CH_2), 26.5 (CH_3); IR (thin film) 1472, 1256, 1234 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{15}OBr$ $[M]^+$ *m/z* 266.0306, found *m/z* 266.0307.

2-(But-3-enyl)-2,3-dihydro-2-methyl-5-nitrobenzofuran 2.82

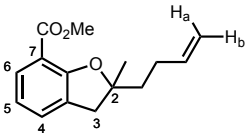


2.82

The general procedure was employed for the heterocyclisation of 2-(2-methylallyl)-4-nitrophenol **2.68** (64 mg, 0.33 mmol) with allyl chloride (0.13 mL, 1.6 mmol) over 23 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 3:1) afforded the title compound **2.82** as a colourless oil (57 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.09 (1H, dd, *J* = 8.8, 2.5 Hz, 6-H), 8.04–8.03 (1H, m, 4-H), 6.75 (1H, d, *J* = 8.9 Hz, 7-H), 5.86–5.78 (1H, m, *CH*=CH_2), 5.05 (1H, dq, *J* = 17.1, 1.6 Hz, CH=*CH*$_a$), 4.98 (1H, dq, *J* = 10.2, 1.4 Hz, CH=*CH*$_b$), 3.16 (1H, d, *J* = 16.0 Hz, 3-H), 3.01 (1H, d, *J* = 16.0 Hz, 3-H), 2.20–2.14 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.88 (2H, t, *J* = 8.2 Hz, *CH*$_2$$CH_2$CH=$CH_2$), 1.49 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 164.6 (C), 142.0 (C), 137.8 (CH), 128.4 (C), 126.0 (CH), 121.7 (CH), 115.2 (CH_2), 109.3 (CH), 92.0 (C), 40.6 (CH_2), 40.5 (CH_2), 28.4 (CH_2), 26.6 (CH_3); IR (thin film) 1595, 1508, 1478, 1331, 1271, 1057 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{15}O_3N$ $[M]^+$ *m/z* 233.1052, found *m/z* 233.1052.

Methyl 2-(but-3-enyl)-2,3-dihydro-2-methylbenzofuran-7-carboxylate 2.83



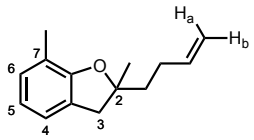
2.83

A 4 mL screw-top glass vial was charged with the methyl 2-hydroxy-3-(2-methylallyl)benzoate **2.67** (68 mg, 0.33 mmol), toluene (1.3 mL), allyl chloride (0.13 mL, 1.6 mmol), $NaHCO_3$ (55 mg, 0.66 mmol) and $Pd(hfacac)_2$ (8.5 mg, 0.02 mmol) and the vial sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a pre-heated aluminium block for 23 h. Additional $Pd(hfacac)_2$ (8.5 mg, 0.02 mmol) was then added and heating continued for a further 24 h. The reaction mixture was cooled to RT then purified directly by flash chromatography (petroleum ether:EtOAc, 19:1) to afford unreacted starting material **2.67** (38 mg, 60%) and the title compound **2.83** as a colourless oil (24 mg, 30%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.26 (1H, ddd, *J* = 7.2, 1.3, 1.2 Hz, 4-H), 7.70 (1H, d, *J* = 8.0 Hz, 6-H), 6.81 (1H, t, *J* = 7.6 Hz, 5-H), 5.89–5.80 (1H, m, *CH*=CH_2), 5.02 (1H, ddd, *J* = 17.1, 3.4, 1.7 Hz, CH=*CH*$_a$), 4.95 (1H, ddd, *J* = 10.2, 3.1, 1.3 Hz, CH=*CH*$_b$), 3.88 (3H, s, OCH_3), 3.08 (1H, d, *J* = 15.7 Hz, 3-H_a), 2.94 (1H, d, *J* = 15.6 Hz, 3-H_b), 2.23–2.17 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.87 (2H, dd, *J* = 9.0, 7.3 Hz, *CH*$_2$$CH_2$CH=$CH_2$), 1.50 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 166.1 (C), 159.9 (C), 138.4 (CH), 129.9 (CH), 129.6 (C), 129.4 (CH), 119.6 (CH), 114.7 (CH_2), 113.2 (C), 90.1 (C), 51.7 (CH_3), 40.9 (CH_2),

40.5 (CH_2), 28.5 (CH_2), 26.5 (CH_3); IR (thin film) 1708, 1448 cm^{-1}; HRMS (EI) exact mass calculated for $C_{15}H_{18}O_3$ $[M]^+$ *m/z* 246.1256, found *m/z* 246.1252.

2-(But-3-enyl)-2,3-dihydro-2,7-dimethylbenzofuran 2.84

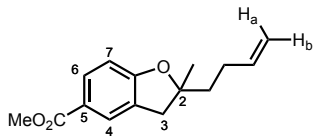


2.84

The general procedure was employed for the heterocyclisation of 2-methyl-6-(2-methylallyl)phenol **2.73** (53 mg, 0.33 mmol) with allyl chloride (0.13 mL, 1.6 mmol) over 7.5 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 9:1) afforded the title compound **2.84** as a colourless oil (49 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.97 (1H, d, *J* = 7.3 Hz, 4-H), 6.93 (1H, d, *J* = 7.5 Hz, 6-H), 6.73 (1H, t, *J* = 7.4 Hz, 5-H), 5.90–5.82 (1H, m, *CH*=CH_2), 5.04 (1H, dq, *J* = 17.1, 1.7 Hz, CH=*CH$_a$*), 4.96 (1H, ddd, *J* = 10.2, 1.8, 1.3 Hz, CH=*CH$_b$*), 3.10 (1H, d, *J* = 15.4 Hz, 3-H_a), 2.96 (1H, d, *J* = 15.4 Hz, 3-H_b), 2.23–2.17 (5H, m, 7-CH_3, CH_2*CH*$_2$CH=CH_2), 1.89–1.80 (2H, m, *CH*$_2$$CH_2CH$=$CH_2$), 1.46 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 157.8 (C), 138.7 (CH), 129.3 (CH), 126.2 (C), 122.5 (CH), 119.8 (CH), 119.7 (C), 114.5 (CH_2), 87.8 (C), 41.9 (CH_2), 40.6 (CH_2), 28.6 (CH_2), 26.7 (CH_3), 15.4 (CH_3); IR (thin film) 1466, 1261 cm^{-1}; HRMS (EI) exact mass calculated for $C_{14}H_{18}O$ $[M]^+$ *m/z* 202.1358, found *m/z* 202.1358.

Methyl 2-(but-3-enyl)-2,3-dihydro-2-methylbenzofuran-5-carboxylate 2.85

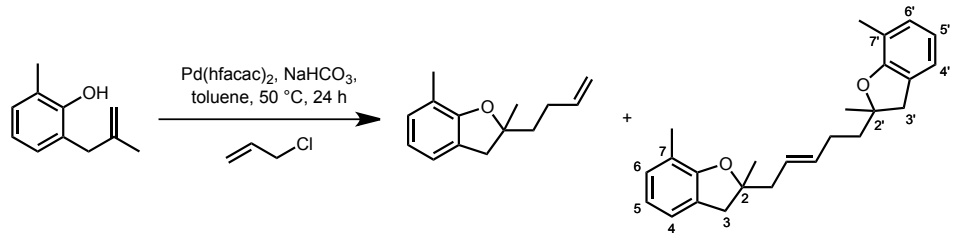


2.85

The general procedure was employed for the heterocyclisation of methyl 4-hydroxy-3-(2-methylallyl)benzoate **2.69** (68 mg, 0.33 mmol) with allyl chloride (0.13 mL, 1.6 mmol) over 24 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 1:1) afforded the title compound **2.85** as a colourless oil (54 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.86 (1H, d, *J* = 8.4, 6-H), 7.83 (1H, s, 4-H), 6.73 (1H, d, *J* = 8.4 Hz, 7-H), 5.86–5.78 (1H, m, *CH*=CH_2), 5.08–5.03 (1H, m, CH=*CH$_a$*), 5.00–4.98 (1H, m, CH=*CH$_b$*), 3.87 (3H, s, OCH_3), 3.11 (1H, d, *J* = 15.7 Hz, 3-H_a), 2.96 (1H, d, *J* = 15.7 Hz, 3-H_b), 2.18–2.13 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.86–1.82 (2H, m, *CH*$_2$$CH_2CH$=$CH_2$), 1.46 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 167.2 (C), 163.2 (C), 138.1 (CH), 131.3 (CH), 127.4 (C), 127.1 (CH), 122.3 (C), 114.9 (CH_2), 109.2 (CH), 90.4 (C), 51.9 (CH_3), 40.7 (CH_2), 40.4 (CH_2), 28.4 (CH_2), 26.6 (CH_3); IR (thin film) 1711, 1271 cm^{-1}; HRMS (CI) exact mass calculated for $C_{15}H_{19}O_3$ $[M+H]^+$ *m/z* 247.1334, found *m/z* 247.1333.

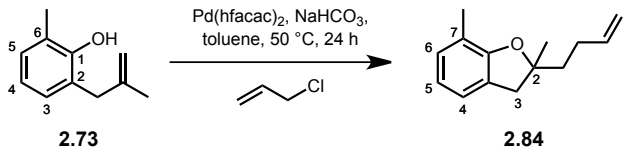
Scale up of cyclisation of 2-methyl-6-(2-methylallyl)phenol 2.73, isolation of (*E*)-2,2'-(pent-2-ene-1,5-diyl)bis(2,7-dimethyl-2,3-dihydrobenzofuran) 2.86



A microwave vial was charged with 2-methyl-6-(2-methylallyl)phenol **2.73** (910 mg, 5.6 mmol), allyl chloride (2.2 mL, 28 mmol), toluene (22 mL), $NaHCO_3$ (940 mg, 11 mmol) and $Pd(hfacac)_2$ (150 mg, 0.3 mmol). The microwave vial was capped and the resulting mixture heated at 50 °C by immersion of the entire vial into a pre-heated oil bath for 24 h. After cooling to room temperature, purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 9:1) afforded the title compound **2.84** as a colourless oil (840 mg, 75%). Analytical data observed was in accordance with that previously obtained. Side product (*E*)-2,2'-(pent-2-ene-1,5-diyl)bis(2,7-dimethyl-2,3-dihydrobenzofuran) **2.86** was also obtained as a pale yellow oil (159 mg, 16%), contaminated with a small amount of unidentified impurity.

2.86: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00–6.94 (4H, m, 4-H, 6-H, 4'-H, 6'-H), 6.78–6.73 (2H, m, 5-H, 5'-H), 5.61–5.55 (1H, m, *CH*=CHCH$_2$CH$_2$), 5.52–5.46 (1H, m, CH=*CH*CH$_2$CH$_2$), 3.12–3.05 (2H, m, 3-H$_a$, 3'-H$_a$), 2.98–2.85 (2H, m, 3-H$_b$, 3'-H$_b$), 2.51–2.42 (2H, m, C*CH$_2$*CH=CH), 2.27–2.13 (8H, m, 7-CH$_3$, 7'-CH$_3$, CH=CH*CH$_2$*CH$_2$), 1.83–1.75 (2H, m, CH=CHCH$_2$*CH$_2$*), 1.47–1.45 (6H, m, 2-CH$_3$, 2'-CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7 (C), 157.6 (C), 134.1 (CH), 129.2 (CH), 129.1 (CH), 126.3 (C), 126.2 (C), 125.1 (CH), 122.5 (2 × CH), 119.80 (CH), 119.76 (CH), 119.6 (C), 119.5 (C), 87.8 (2 × C), 44.4 (CH$_2$), 41.6 (CH$_2$), 41.1 (CH$_2$), 40.9 (CH$_2$), 27.5 (CH$_2$), 26.7 (CH$_3$), 26.6 (CH$_3$), 15.50 (CH$_3$), 15.49 (CH$_3$); IR (thin film) 1466, 1261 cm^{-1}; HRMS (EI) mass calculated for $C_{25}H_{30}O_2Na$ $[M+Na]^+$ *m/z* 362.2246, found *m/z* 362.2248.

^{1}H NMR spectroscopy monitoring of conversion of 2-methyl-6-(2-methylallyl)phenol 2.73 to 2-(but-3-enyl)-2,3-dihydro-2,7-dimethylbenzofuran 2.84



A microwave vial was charged with 2-methyl-6-(2-methylallyl)phenol **2.73** (300 mg, 1.9 mmol), allyl chloride (0.75 mL, 9.3 mmol), toluene (7.4 mL), $NaHCO_3$ (310 mg, 3.7 mmol) and $Pd(hfacac)_2$ (48 mg, 0.09 mmol). The microwave vial was capped and the resulting mixture heated at 50 °C by immersion of the entire vial into a pre-heated oil bath.

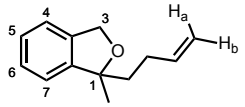
Conversion of starting material **2.73** to product **2.84** was monitored by removal of approximately 0.05 mL of the reaction mixture by syringe and dilution in $CDCl_3$. Using ^1H NMR spectroscopy, the signal at 1.75 ppm corresponding to C=C*CH*$_3$ in **2.73** was integrated relative to the signal at 1.46 ppm corresponding to 2-CH_3 in product **2.84**.

Time (h min)	**2.73**	**2.84**[a]	% Conversion
0h 0 min	1	0	0
0h 10 min	1	0	0
0h 20 min	1	0.03	3
0h 30 min	1	0.05	5
0h 40 min	1	0.07	7
0h 50 min	1	0.11	10
0h 60 min	1	0.15	13
1h 15 min	1	0.19	16
1h 30 min	1	0.25	20
1h 45 min	1	0.31	24
2h 0 min	1	0.36	26
2h 15 min	1	0.42	30
2h 30 min	1	0.47	32
2h 45 min	1	0.59	37
3h 0 min	1	0.59	37
3h 15 min	1	0.69	41
3h 45 min	1	0.83	45
4h 15 min	1	1.10	52
4h 45 min	1	1.33	57
5h 15 min	1	1.63	62
5h 45 min	1	2.08	68
6h 15 min	1	2.51	72
6h 45 min	1	3.10	76
7h 15 min	1	3.66	79
7h 45 min	1	4.93	83
8h 15 min	1	6.89	87
8h 45 min	1	11.07	92
9h 15 min	1	20	95
23h 30 min	0	1	100

[a] Approximate integral value of ^1H NMR spectral peak corresponding to 2-CH_3 in **2.84** *cf.* where the integral value of the signal corresponding to the alkene CH_3 in **2.73** is calibrated to 1.

Table 4.1: Conversion of 2.73 to 2.84

1-(But-3-enyl)-1,3-dihydro-1-methylisobenzofuran 2.87

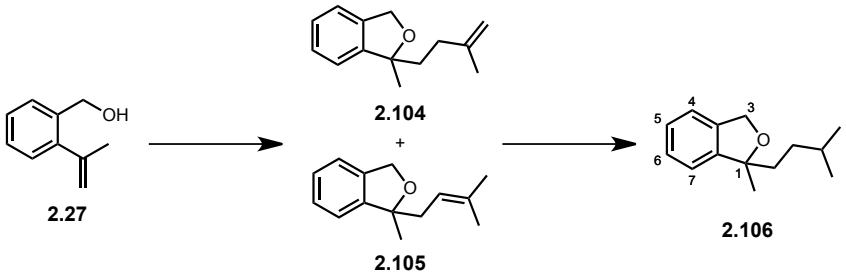


2.87

The general procedure was employed for the heterocyclisation of (2-(prop-1-en-2-yl)phenyl) methanol **2.27** (49 mg, 0.33 mmol) with allyl bromide (0.14 mL, 1.6 mmol) over 6 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 1:1) afforded the title compound **2.87** as a colourless oil (48 mg, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.28–7.24 (2H, m, 5-H, 6-H), 7.19–7.18 (1H, m, 4-H), 7.09–7.08 (1H, m, 7-H), 5.81–5.73 (1H, m, *CH*=CH_2), 5.10 (1H, d, *J* = 12.3 Hz, 3-H_a), 5.06 (1H, d, *J* = 12.3 Hz, 3-H_b), 4.93 (1H, ddt, *J* = 17.1, 1.8, 1.7 Hz, CH=*CH*$_a$), 4.87 (1H, ddt, *J* = 10.2, 1.8, 1.3 Hz, CH=*CH*$_b$), 2.15–2.08 (1H, m, CH_2*CH*$_a$CH=CH_2), 1.94–1.77 (3H, m, *CH*$_2$*CH*$_b$CH=CH_2), 1.48 (3H, s, 1-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 145.4 (C), 139.2 (C), 138.9 (CH), 127.5 (CH), 127.4 (CH), 121.1 (CH), 121.0 (CH), 114.2 (CH_2), 88.3 (C), 71.8 (CH_2), 41.1 (CH_2), 28.6 (CH_2), 27.6 (CH_3); IR (thin film) 1451, 1358, 1026 cm^{-1}; HRMS (CI/Isobutane) exact mass calculated for $C_{13}H_{17}O$ [M+H]+ *m/z* 189.1279, found *m/z* 189.1281.

1-Isopentyl-1-methyl-1,3-dihydroisobenzofuran 2.106



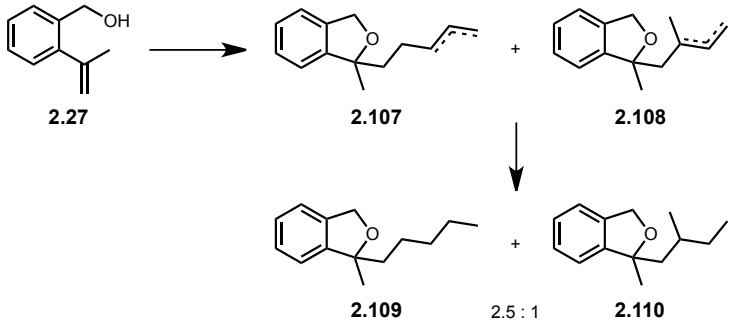
2.27 **2.104** + **2.105** **2.106**

A 4 mL screw-top glass vial was charged with (2-(prop-1-en-2-yl)phenyl) methanol **2.27** (49 mg, 0.33 mmol), toluene (1.3 mL), $NaHCO_3$ (55 mg, 0.66 mmol), $Pd(hfacac)_2$ (8.5 mg, 0.02 mmol) then 3-chloro-2-methyl-1-propene (0.16 mL, 1.7 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 pre-heated aluminium block for 3 h then cooled to room temperature and partitioned between brine (25 mL) and Et_2O (5 mL). The mixture was extracted with Et_2O (2 × 25 mL) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography afforded 1,3-dihydro-1-methyl-1-(3-methylbutenyl)isobenzofuran as a mixture of alkene isomers **2.104** and **2.105** (41 mg, 61%). The mixture was transferred to a flask and Pd/C (10% wt., 4 mg) added. The flask was twice evacuated and backfilled with argon then evacuated and backfilled with H_2. MeOH (2 mL) was added and the resulting mixture stirred at RT for 16 h. The reaction mixture was filtered over Celite®, washing with CH_2Cl_2. The filtrate was concentrated *in vacuo* to afford the title compound **2.106** as a colourless oil (36 mg, 90%).

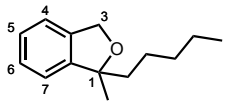
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.28–7.23 (2H, m, 5-H, 6-H), 7.20–7.17 (1H, m, 4-H), 7.09–7.06 (1H, m, 7-H), 5.09 (1H, d, *J* = 12.3 Hz, 3-H_a), 5.05 (1H, d, *J* = 12.3 Hz, 3-H_b),

1.80 (1H, ddd, *J* = 13.3, 11.6, 4.6 Hz, $CH_aCH_2CH(CH_3)_2$), 1.74 (1H, ddd, *J* = 13.3, 11.6, 4.3 Hz, $CH_bCH_2CH(CH_3)_2$), 1.49–1.43 (4H, m, $CH_2CH_2CH(CH_3)_2$, 1-CH_3), 1.31–1.23 (1H, m, $CH_2CH_aCH(CH_3)_2$), 0.90–0.91 (1H, m, $CH_2CH_bCH(CH_3)_2$), 0.83 (6H, t, *J* = 6.4 Hz, $CH_2CH_2CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 145.9 (C), 139.2 (C), 127.3 (CH), 127.2 (CH), 121.01 (CH), 120.0 (CH), 88.5 (C), 71.6 (CH_2), 39.7 (CH_2), 33.0 (CH_2), 28.4 (CH), 27.5 (CH_3), 22.74 (CH_3), 22.66 (CH_3); IR (thin film) 2954, 1459, 1366, 1208 cm^{-1}; HRMS (CI/Isobutane) exact mass calculated for $C_{14}H_{21}O$ $[M+H]^+$ *m/z* 205.1592, found *m/z* 205.1594.

Cyclisation of (2-(prop-1-en-2-yl)phenyl) methanol 2.27 with crotyl chloride



A 4 mL screw-top glass vial was charged with (2-(prop-1-en-2-yl)phenyl) methanol **2.27** (49 mg, 0.33 mmol), toluene (1.3 mL), $NaHCO_3$ (55 mg, 0.66 mmol), $Pd(hfacac)_2$ (8.5 mg, 0.02 mmol) and crotyl chloride (0.16 mL, 1.7 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 pre-heated aluminium block for 24 h then the mixture allowed to cool to RT and subjected directly to flash chromatography (petroleum ether:CH_2Cl_2, 3:1) to afford 1-methyl-1-(pent-4-en-1-yl)-1,3-dihydroisobenzofuran **2.107** and 1-methyl-1-(2-methylbut-3-en-1-yl)-1,3-dihydroisobenzofuran **2.108**, both as a mixture of alkene isomers (38 mg, 57%). The material was transferred to a flask and Pd/C (10% wt., 4 mg) added. The flask was twice evacuated and backfilled with argon then evacuated and backfilled with H_2. MeOH (2 mL) was added and the resulting mixture stirred at RT for 17 h. The reaction mixture was filtered over Celite®, washing with CH_2Cl_2. The filtrate was concentrated *in vacuo* to afford a 2.5:1 mixture of 1-methyl-1-pentyl-1,3-dihydroisobenzofuran **2.109** and 1-methyl-1-(2-methylbutyl)-1,3-dihydroisobenzofuran **2.110** (33 mg, 87%), contaminated with aromatic impurities. A sample of 1-methyl-1-pentyl-1,3-dihydroisobenzofuran **2.109** was separated by flash chromatography (petroleum ether:CH_2Cl_2, 3:1) for analytical purposes. A clean sample of 1-methyl-1-(2-methylbutyl)-1,3-dihydroisobenzofuran **2.110** could not be obtain in sufficient quantity and purity for characterisation.

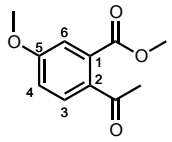


2.109

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.28–7.23 (2H, m, 5-H, 6-H), 7.20–7.18 (1H, m, 4-H), 7.10–7.07 (1H, m, 7-H), 5.10 (1H, d, *J* = 12.3 Hz, 3-H_a), 5.06 (1H, d, *J* = 12.3 Hz, 3-H_b), 1.80 (1H, ddd, *J* = 13.9, 11.8, 5.0 Hz, $CH_aCH_2CH_2CH_2CH_3$), 1.74 (1H, ddd, *J* = 13.9, 11.8, 4.9 Hz,

$CH_bCH_2CH_2CH_2CH_3$), 1.47 (3H, s, 1-CH_3), 1.42–1.33 (1H, m, $CH_2CH_aCH_2CH_2CH_3$), 1.29–1.18 (4H, m, $CH_2CH_2CH_2CH_2CH_3$), 1.11–1.03 (1H, m, $CH_2CH_bCH_2CH_2CH_3$), 0.84 (3H, t, J = 7.0 Hz, $CH_2CH_2CH_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 145.9 (C), 139.2 (C), 127.34 (CH), 127.26 (CH), 121.03 (CH), 121.00 (CH), 88.6 (C), 71.7 (CH_2), 41.9 (CH_2), 32.3 (CH_2), 27.5 (CH_3), 23.8 (CH_2), 22.7 (CH_2), 14.2 (CH_3); IR (thin film) 1030; HRMS (CI) exact mass calculated for $C_{14}H_{21}O$ $[M+H]^+$ *m/z* 205.1592, found *m/z* 205.1587.

Methyl 2-acetyl-5-methoxybenzoate 2.115

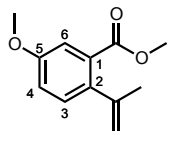


2.115

Following a reported procedure,[104] to a suspension of $Pd(OAc)_2$ (140 mg, 0.62 mmol) and triphenylphosphine (320 mg, 1.2 mmol) in degassed acetonitrile (16 mL) was added *n*butyl vinyl ether (5.3 mL, 41 mmol), triethylamine (1.5 mL, 11 mmol) and methyl 2-bromo-5-methoxybenzoate **2.113** (2.0 g, 8.2 mmol). The resulting mixture was heated at reflux for 24 h then cooled to RT, diluted with water (20 mL) and EtOAc (20 mL) and filtered over Celite®, rinsing with EtOAc (25 mL). The filtrate was concentrated *in vacuo* then dissolved in THF (51 mL) and 10% aq. HCl (51 mL) added. The mixture was stirred at RT for 3 h then concentrated to low volume, poured into sat. aq. $NaHCO_3$ (100 mL) and extracted with 10:1 EtOAc:CH_2Cl_2 (4 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 7:3) afforded the title compound **2.115** as a yellow oil (1.5 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59 (1H, d, J = 8.6 Hz, 3-H), 7.15 (1H, d, J = 2.8 Hz, 6-H), 7.02 (1H, dd, J = 8.6, 2.5 Hz, 4-H), 3.92 (3H, s, CO_2CH_3), 3.88 (3H, s, $ArOCH_3$), 2.53 (3H, s, $COCH_3$). Analytical data observed were in accordance with literature values.[104]

Methyl 5-methoxy-2-(prop-1-en-2-yl)benzoate 2.116



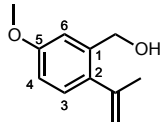
2.116

To a suspension of methyl triphenylphosphonium bromide (710 mg, 2.0 mmol) in THF (4 mL) was added a solution of potassium *tert*-butoxide (220 mg, 2.0 mmol) in THF (2 mL). The resulting bright yellow suspension was stirred at RT for 10 minutes then a solution of methyl 2-acetyl-5-methoxybenzoate **2.115** (350 g, 1.7 mmol) in THF (3.4 mL) added dropwise. The brown suspension was stirred at RT for 2.5 h then quenched with water (5 mL) and sat. aq. NH_4Cl (5 mL) and extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 19:1) afforded the title compound **2.116** as a yellow oil (165 mg, 47%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.29 (1H, d, J = 2.8 Hz, 6-H), 7.16 (1H, d, J = 8.5 Hz, 3-H), 6.98 (1H, dd, J = 8.5 Hz, 2.8 Hz, 4-H), 5.07–5.06 (1H, m, C=CH_a), 4.81–4.80 (1H, m,

C=CH_b), 3.85 (3H, s, CO_2CH_3), 3.83 (3H, s, OCH_3), 2.06–2.05 (3H, m, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.5 (C), 158.6 (C), 146.2 (C), 137.8 (C), 130.8 (C), 130.6 (CH), 117.8 (CH), 114.6 (CH), 113.7 (CH_2), 55.7 (CH_3), 52.1 (CH_3), 24.3 (CH_3); IR (thin film) 1724, 1285, 1244, 1069, 1034 cm^{-1}; HRMS (EI) exact mass calculated for $C_{12}H_{14}O_3$ $[M]^+$ *m/z* 206.0943, found *m/z* 206.0941.

(5-Methoxy-2-(prop-1-en-2-yl)phenyl)methanol 2.117

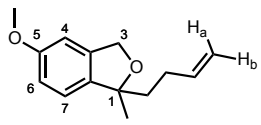


2.117

To a cooled (0 °C) suspension of lithium aluminium hydride (77 mg, 2.0 mmol) in Et_2O (4.0 mL) was added dropwise a solution of methyl 5-methoxy-2-(prop-1-en-2-yl)benzoate **2.116** (160 mg, 0.78 mmol) in Et_2O (2 mL). The cooling bath was removed and the mixture allowed to warm to RT then stirred for 3 h. The mixture was cooled to 0 °C, quenched by dropwise addition of sat. aq. potassium sodium tartrate (10 mL) and stirred for 30 minutes then extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with water (25 mL), brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.117** as a colourless oil (130 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.09 (1H, d, *J* = 8.4 Hz, 3-H), 7.02 (1H, d, *J* = 2.7 Hz, 6-H), 6.80 (1H, dd, *J* = 8.4, 2.7 Hz, 4-H), 5.21–5.20 (1H, m, C=CH_a), 4.87–4.86 (1H, m, C=CH_b), 4.69 (2H, d, *J* = 3.9 Hz, CH_2OH), 3.82 (3H, s, OCH_3), 2.06–2.05 (3H, m, CCH_3), 1.70–1.69 (1H, m, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 159.1 (C), 144.7 (C), 139.1 (C), 135.6 (C), 129.4 (CH), 115.5 (CH_2), 113.5 (CH), 113.3 (CH), 63.4 (CH_3), 55.5 (CH_2), 25.2 (CH_3); IR (thin film) 3343, 1607, 1497, 1288, 1233, 1161 cm^{-1}; HRMS (EI) exact mass calculated for $C_{11}H_{14}O_2$ $[M]^+$ *m/z* 178.0994, found *m/z* 178.0995.

1-(But-3-enyl)-1,3-dihydro-5-methoxy-1-methylisobenzofuran 2.118

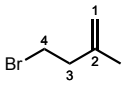


2.118

The general procedure was employed for the heterocyclisation of (5-methoxy-2-(prop-1-en-2-yl)phenyl)methanol **2.117** (59 mg, 0.33 mmol) with allyl bromide (0.14 mL, 1.6 mmol) over 4 h. Purification of the reaction mixture by flash chromatography (petroleum ether:EtOAc, 19:1) afforded the title compound **2.118** as a colourless oil (60 mg, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.93 (1H, d, *J* = 8.3 Hz, 7-H), 6.81 (1H, dd, *J* = 8.3, 2.3 Hz, 6-H), 6.71 (1H, d, *J* = 2.0 Hz, 4-H), 5.82–5.74 (1H, m, *CH*=CH_2), 5.05 (1H, d, *J* = 12.4 Hz, 3-H_a), 5.01 (1H, d, *J* = 12.4 Hz, 3-H_b), 4.96–4.92 (1H, m, CH=CH_a), 4.89–4.86 (1H, m, CH=CH_b), 3.81 (3H, s, OCH_3), 2.16–2.08 (1H, m, CH_2CH_aCH=CH_2), 1.93–1.79 (3H, m, CH_2CH_bCH=CH_2), 1.46 (3H, s, 1-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 159.8 (C), 141.0 (C), 139.1 (CH), 137.9 (C), 121.7 (CH), 114.1 (CH_2), 113.8 (CH), 106.4 (CH), 88.0 (C), 77.6 (CH_2), 55.7 (CH_3), 41.3 (CH_2), 28.7 (CH_2), 27.8 (CH_3); IR (thin film) 1493, 1271, 1150, 1028 cm^{-1}; HRMS (EI) exact mass calculated for $C_{14}H_{18}O_2$ $[M]^+$ *m/z* 218.1307, found *m/z* 218.1310.

4-bromo-2-methyl-1-butene 2.120

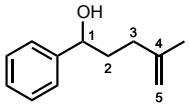


2.120

Following a reported procedure,[105] to a suspension of PPh_3 (29 g, 162 mmol) in CH_2Cl_2 (30 mL) was added 3-methylbut-3-en-1-ol **2.119** (15 mL, 147 mmol). The mixture was cooled to 0 °C then NBS (43 g, 162 mmol) added portionwise. The cooling bath was removed and the thick purple suspension stirred at room temperature for 2.5 h then additional CH_2Cl_2 (3 mL) was added to aid stirring. The mixture was stirred for a further 1 h then hexane (90 mL) added and the mixture filtered through a short plug of silica, rinsing with hexane (60 mL). The filtrate was distilled to remove the solvent then the residue distilled under reduced pressure (90 mmHg) with the collection flask cooled to 0 °C to afford the title compound **2.120**, which was calculated by ^{1}H NMR to be an approximately 1:0.6 mixture with hexane, equivalent to approximately 5 M (9.2 g of which 6.8 g title compound, ~31%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.87 (1H, s, C=CH_a), 4.79 (1H, s, C=CH_b), 3.49 (2H, t, *J* = 7.3 Hz, 4-H_2), 2.59 (2H, t, *J* = 7.3 Hz, 3-H_2), 1.76 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[105]

4-Methyl-1-phenylpent-4-en-1-ol 2.123

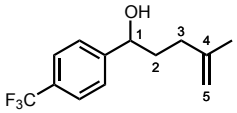


2.123

To a flask charged with magnesium turnings (430 mg, 18 mmol) and a crystal of iodine in Et_2O (17 mL) was added 4-bromo-2-methyl-1-butene **2.120** (5 M in hexanes, 2.0 mL, 10 mmol). The mixture was heated to reflux for 1 h then allowed cooled to RT before dropwise addition of benzaldehyde (0.87 mL, 8.6 mmol). The mixture was heated at reflux for 3.5 h then cooled to RT, poured onto ice and aq. HCl (1 M, 25 mL) added dropwise. The mixture was extracted with Et_2O (2 × 50 mL) and the combined organic extracts washed with sat. aq. $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.123** as a colourless oil (630 mg, 41%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36–7.34 (4H, m, 4 × ArH), 7.30–7.26 (1H, m, ArH), 4.74 (1H, s, 5-H_a), 4.71 (1H, s, 5-H_b), 4.69 (1H, dd, *J* = 7.6 Hz, 5.5Hz, 1-H), 2.18–2.12 (1H, m, 3-H_a), 2.08–2.02 (1H, m, 3-H_b), 1.98–1.82 (3H, m, 2-H_2, OH), 1.73 (3H, s, 4-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 145.6 (C), 144.8 (C), 128.6 (2 × CH), 127.7 (CH), 126.0 (2 × CH), 110.3 (CH_2), 74.4 (CH), 37.0 (CH_2), 34.2 (CH_2), 22.7 (CH_3); IR (thin film) 3353, 1451, 1062, 1017 cm^{-1}; HRMS (CI) exact mass calculated for $C_{12}H_{15}$ [M-OH]$^+$ *m/z* 159.1174, found *m/z* 159.1169.

1-(4-(Trifluoromethyl)phenyl)-4-methylpent-4-en-1-ol 2.124

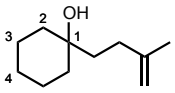


2.124

To a flask charged with magnesium turnings (430 mg, 18 mmol) and a crystal of iodine in THF (17 mL) was added 4-bromo-2-methyl-1-butene **2.120** (5 M in hexanes, 2.0 mL, 10 mmol). The mixture was heated to reflux for 1 h then allowed to cool to RTbefore dropwise addition of 4-(trifluoromethyl)benzaldehyde (1.2 mL, 8.6 mmol). The mixture was heated at reflux for 3 h then cooled to RT, poured onto ice and stirred for 30 minutes before addition of aq. HCl (1 M, 25 mL). The mixture was extracted with Et_2O (2 × 50 mL) and the combined organic extracts washed with sat. aq. $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.124** as a faintly yellow oil (1.3 g, 61%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.61 (2H, d, *J* = 8.1 Hz, 2 × ArH), 7.47 (2H, d, *J* = 8.5 Hz, 2 × ArH), 4.79–4.73 (3H, m, 1-H, 5-H_2), 2.27–2.06 (2H, m, 3-H_2), 2.04–1.82 (3H, m, 2-H_2, OH), 1.75 (3H, s, 4-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.9 (C), 145.3 (C), 130.0 (q, ^2J (C-F) = 32 Hz, C), 126.3 (2 × CH), 125.6 (q, ^3J (C-F) = 3.8 Hz, 2 × CH), 124.4 (q, ^1J (C-F) = 270 Hz, C) 110.7 (CH_2), 73.8 (CH), 37.2 (CH_2), 34.0 (CH_2), 22.5 (CH_3); IR (thin film) 3339, 1323, 1122, 1109, 1067 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{16}OF_3$ $[M+H]^+$ *m/z* 245.1153, found *m/z* 245.1153.

1-(3-Methylbut-3-enyl)cyclohexanol 2.125

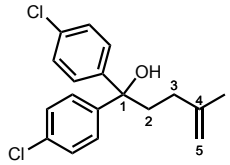


2.125

To a flask charged with magnesium turnings (160 mg, 6.7 mmol) and a crystal of iodine in THF (6.5 mL) was added 4-bromo-2-methyl-1-butene **2.120** (5 M in hexanes, 0.75 mL, 3.8 mmol). The mixture was heated to reflux for 1 h then allowed to cool to RT before dropwise addition of cyclohexanone (0.34 mL, 3.3 mmol). The mixture was heated at reflux for 4 h then cooled to RT and quenched by dropwise addition of aq. HCl (1 M, 5 mL). The mixture was poured into sat. aq. $NaHCO_3$ (25 mL) then extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.125** as a colourless oil (250 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.72 (2H, s, C=CH_2), 2.13–2.09 (2H, m, *C*H_2C=CH_2), 1.76 (3H, s, CH_3), 1.62–1.41 (12H, m, 2×2-H_2, 2×3-H_2, 4-H_2, *C*$H_2$$CH_2$C($CH_3$)=$CH_2$), 1.25 (1H, s, OH). Analytical data observed were in accordance with literature values.[163]

1,1-Bis(4-chlorophenyl)-4-methylpent-4-en-1-ol 2.128

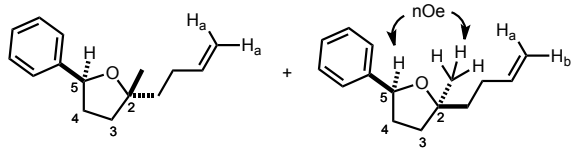


2.128

To a flask charged with magnesium turnings (240 mg, 10 mmol) and a crystal of iodine in THF (17 mL) was added 4-bromo-2-methyl-1-butene **2.120** (5 M in hexanes, 2.0 mL, 10 mmol). The mixture was heated to reflux for 1 h then allowed to cool to RT before portionwise addition of 4,4'-dichlorobenzophenone **2.126** (2.2 g, 8.6 mmol). The mixture was heated at reflux for 3 h then cooled to RT and quenched by dropwise addition of aq. HCl (1 M, 5 mL). The mixture was extracted with Et_2O (3 × 50 mL) and the combined organic extracts washed with sat. aq. $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Iterative purification by flash chromatography (petroleum ether:EtOAc, 17:3 then 19:1) followed by removal of a solid impurity by trituration with petroleum ether afforded the title compound **2.128** as a colourless oil (220 mg, 8%), contaminated with approximately 4% of an unknown impurity.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35–7.32 (4H, m, 4 × ArH), 7.29–7.27 (4H, m, 4 × ArH), 4.74 (1H, s, 5-H_a), 4.69 (1H, s, 5-H_b), 2.40–2.37 (2H, m, 2-H_2), 2.27 (1H, s, OH), 2.00–1.97 (2H, m, 3-H_2), 1.73 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 145.9 (2 × C), 145.1 (C), 133.1 (2 × C), 128.6 (4 × CH), 127.5 (4 × CH), 110.5 (CH_2), 77.9 (C), 39.7 (CH_2), 32.0 (CH_2), 22.8 (CH_3); IR (thin film) 1489, 1093, 1013 cm^{-1}; HRMS (EI) exact mass calculated for $C_{18}H_{18}OCl_2$ $[M]^+$ *m/z* 320.0735, found *m/z* 320.0738.

2-(But-3-enyl)-tetrahydro-2-methyl-5-phenylfuran 2.130 and 2.131



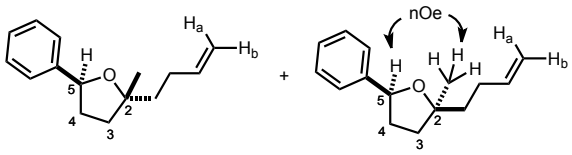
2.130 1.3 : 1 **2.131**

The general procedure was employed for the heterocyclisation of 4-methyl-1-phenylpent-4-en-1-ol **2.123** (49 mg, 0.33 mmol) with allyl bromide (0.14 mL, 1.6 mmol) over 6 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 3:1) afforded a 1.3:1 mixture of diastereomers **2.130** and **2.131** (55 mg, 77%), determined by nOe as shown above. A sample of each diastereomer was separated by flash chromatography (petroleum ether:CH_2Cl_2, 3:1) for analytical purposes.

2.130: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37–7.35 (2H, m, 2 × ArH), 7.34–7.31 (2H, m, 2 × ArH), 7.25–7.22 (1H, m, ArH), 5.93–5.85 (1H, m, *CH*=CH_2), 5.06 (1H, dq, *J* = 17.1, 1.7 Hz, CH=*CH$_a$*), 4.98–4.92 (2H, m, CH=*CH$_b$*, 5-H), 2.33–2.28 (1H, m, 4-H_a), 2.27–2.14 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.98–1.89 (2H, m, 3-H_a, 4-H_b), 1.86–1.82 (1H, m, 3-H_a), 1.79–1.67 (2H, m, *CH*$_2$$CH_2$CH=$CH_2$), 1.36 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 143.8 (C), 139.3 (CH), 128.4 (2 × CH), 127.2 (CH), 126.0 (2 × CH), 114.2 (CH_2), 83.5 (C), 81.1 (CH), 40.9 (CH_2), 37.8 (CH_2), 25.7 (CH_2), 29.2 (CH_2), 27.1 (CH_3); IR (thin film) 1449, 1044, 1020 cm^{-1}; HRMS (EI) exact mass calculated for $C_{15}H_{20}O$ $[M]^+$ *m/z* 216.1514, found *m/z* 216.1519.

2.131: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37–7.35 (2H, m, 2 × ArH), 7.33–7.30 (2H, m, 2 × ArH), 7.25–7.22 (1H, m, ArH), 5.94–5.86 (1H, m, *CH*=CH_2), 5.07 (1H, ddd, *J* = 17.1, 1.8, 1.7 Hz, CH=*CH*$_a$), 4.99–4.96 (2H, m, CH=*CH*$_b$, 5-H), 2.36–2.29 (1H, m, 4-H_a), 2.27–2.21 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.99–1.93 (1H, m, 3-H_a), 1.89–1.70 (4H, m, 3-H_b, 4-H_b, *CH*$_2$$CH_2$CH=$CH_2$), 1.33 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 143.6 (C), 139.4 (CH), 128.4 (2 × CH), 127.3 (CH), 126.0 (2 × CH), 114.3 (CH_2), 83.3 (C), 80.2 (CH), 41.5 (CH_2), 37.6 (CH_2), 35.6 (CH_2), 29.3 (CH_2), 26.3 (CH_3); IR (thin film) 2967, 1045 cm^{-1}; HRMS (EI) exact mass calculated for $C_{15}H_{20}O$ $[M]^+$ *m/z* 216.1514, found *m/z* 216.1510.

2-(But-3-enyl)-5-(4-(trifluoromethyl)phenyl)-tetrahydro-2-methylfuran 2.137 and 2.138



2.130 1.3 : 1 **2.131**

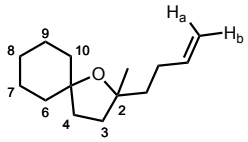
The general procedure was employed for the heterocyclisation of 1-(4-(trifluoromethyl)phenyl)-4-methylpent-4-en-1-ol **2.124** (81 mg, 0.33 mmol) with allyl bromide (0.14 mL, 1.6 mmol) over 23 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 1:1) afforded a 1.5:1 mixture of diastereomers **2.137** and **2.138** (71 mg, 76%), determined by nOe as shown. A sample of each diastereomer was separated by flash chromatography (petroleum ether:CH_2Cl_2, 3:1) for analytical purposes.

2.137: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.58 (2H, d, *J* = 8.2 Hz, 2 × ArH), 7.46 (2H, d, *J* = 8.4 Hz, 2 × ArH), 5.92–5.84 (1H, m, *CH*=CH_2), 5.05 (1H, ddd, *J* = 17.1, 1.8, 1.7 Hz, CH=*CH*$_a$), 5.00–4.94 (2H, m, CH=*CH*$_b$, 5-H), 2.39–2.32 (1H, m, 4-H_a), 2.25–2.14 (2H, m, CH_2*CH*$_2$CH=CH_2), 2.00–1.94 (1H, m, 3-H_a), 1.90–1.81 (2H, m, 3-H_b, 4-H_b), 1.79–1.68 (2H, m, *CH*$_2$$CH_2$CH=$CH_2$), 1.35 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.2 (CH), 139.1 (C), 129.6 (q, ^{2}*J* (C-F) = 32 Hz, C), 126.1 (2 × CH), 125.4 (q, ^{3}*J* (C-F) = 3.7 Hz, 2 × CH), 124.5 (q, ^{1}*J* (C-F) = 272 Hz, C), 114.3 (CH_2), 84.0 (C), 80.3 (CH), 40.8 (CH_2), 37.7 (CH_2), 35.6 (CH_2), 29.1 (CH_2), 27.0 (CH_3); IR (thin film) 1323, 1121, 1065 cm^{-1}; HRMS (CI) exact mass calculated for $C_{16}H_{20}OF_3$ $[M+H]^+$ *m/z* 285.1466, found *m/z* 285.1460.

2.138: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.58 (2H, d, *J* = 8.2 Hz, 2 × ArH), 7.47 (2H, d, *J* = 8.1 Hz, 2 × ArH), 5.93–5.85 (1H, m, *CH*=CH_2), 5.06 (1H, ddd, *J* = 17.2, 1.8, 1.6 Hz, CH=*CH*$_a$), 5.03 (1H, t, *J* = 7.0 Hz, 5-H), 4.99–4.96 (1H, m, CH=*CH*$_b$), 2.42–2.35 (1H, m, 4-H_a), 2.29–2.16 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.98–1.92 (1H, m, 3-H_a), 1.86–1.80 (2H, m, 3-H_b, 4-H_b), 1.78–1.72 (2H, m, *CH*$_2$$CH_2$CH=$CH_2$), 1.33 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 147.9 (CH), 139.1 (C), 129.6 (q, ^{2}*J* (C-F) = 33 Hz, C), 126.1 (2 × CH), 125.4 (q, ^{3}*J* (C-F) = 3.8 Hz, 2 × CH), 124.5 (q, ^{1}*J* (C-F) = 272 Hz, C), 114.4 (CH_2), 83.9 (C), 79.4 (CH), 41.4 (CH_2), 37.5 (CH_2), 35.5 (CH_2), 29.3 (CH_2), 26.3 (CH_3); IR (thin film)

1323, 1121, 1065 cm^{-1}; HRMS (CI) exact mass calculated for $C_{16}H_{20}OF_3$ $[M+H]^+$ *m/z* 285.1466, found *m/z* 285.1467.

2-(But-3-enyl)-2-methyl-1-oxaspiro[4.5]decane 2.139

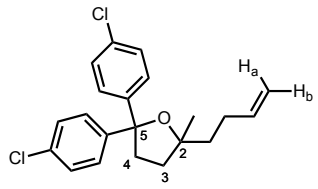


2.139

The general procedure was employed for the heterocyclisation of 1-(3-methylbut-3-enyl)cyclohexanol **2.125** (55 mg, 0.33 mmol) with allyl bromide (0.14 mL, 1.6 mmol) over 4.5 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 1:1) afforded the title compound **2.139** as a colourless oil (57 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.88–5.80 (1H, m, *CH*=CH_2), 5.00 (1H, ddd, *J* = 17.1, 1.9, 1.7 Hz, CH=*CH*$_a$), 4.92–4.89 (1H, m, CH=*CH*$_b$), 2.17–2.04 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.86–1.74 (3H, m, 3-H, 4-H_2), 1.72–1.64 (3H, m, 3-H, 7-H, 9-H), 1.62–1.44 (6H, m, 6-H_2, 10-H_2, *CH*$_2$$CH_2$CH=$CH_2$), 1.43–1.26 (4H, m, 7-H, 8-H_2, 9-H), 1.19 (3H, s, 2-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 139.5 (CH), 113.9 (CH_2), 83.1 (C), 82.2 (C), 41.9 (CH_2), 39.7 (CH_2), 39.1 (CH_2), 36.6 (CH_2), 35.9 (CH_2), 29.3 (CH_2), 27.9 (CH_3), 25.9 (CH_2), 24.29 (CH_2), 24.26 (CH_2); IR (thin film) 2928, 1449 cm^{-1}; HRMS (CI) exact mass calculated for $C_{14}H_{25}O$ $[M+H]^+$ *m/z* 209.1905, found *m/z* 209.1902.

2-(But-3-enyl)-5,5-bis(4-chlorophenyl)-tetrahydro-2-methylfuran 2.140

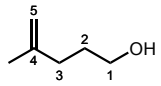


2.140

The general procedure was employed for the heterocyclisation of 1,1-bis(4-chlorophenyl)-4-methylpent-4-en-1-ol **2.128** (50 mg, 0.16 mmol) with allyl bromide (0.08 mL, 0.80 mmol) over 24 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 17:3) afforded the title compound **2.140** as a colourless oil (42 mg, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37–7.34 (4H, m, 4 × ArH), 7.25–7.23 (4H, m, 4 × ArH), 5.85 (1H, m, *CH*=CH_2), 5.00 (1H, ddd, *J* = 17.1, 1.7, 1.6, CH=*CH*$_a$), 4.94–4.92 (1H, m, CH=*CH*$_b$), 2.65–2.56 (2H, m, 4-H_2), 2.24–2.17 (1H, m, CH_2*CH*$_a$CH=CH_2), 2.13–2.05 (1H, m, CH_2*CH*$_b$CH=CH_2), 1.88–1.76 (2H, m, 3-H_2), 1.69–1.63 (1H, m, *CH*$_a$$CH_2$CH=$CH_2$), 1.61–1.54 (1H, m, *CH*$_b$$CH_2$CH=$CH_2$), 1.25 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 146.4 (C), 146.1 (C), 139.0 (CH), 132.60 (C), 132.57 (C), 128.34 (2 × CH), 128.33 (2 × CH), 127.30 (2 × CH), 127.29 (2 × CH), 114.4 (CH_2), 87.2 (C), 84.8 (C), 41.6 (CH_2), 38.8 (CH_2), 37.6 (CH_2), 29.4 (CH_2), 26.6 (CH_3); IR (thin film) 1489, 1090, 1011 cm^{-1}; HRMS (CI) exact mass calculated for $C_{21}H_{23}OCl_2$ $[M+H]^+$ *m/z* 361.1126, found *m/z* 361.1118.

4-Methylpent-4-en-1-ol 2.142

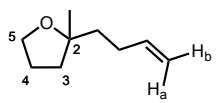


2.142

To a stirred suspension of methyl triphenylphosphonium bromide (4.2 g, 12 mmol) in THF (29 mL) was added a solution of potassium *tert*-butoxide (1.3 g, 12 mmol) in THF (12 mL). The suspension turned bright yellow and was stirred at RT for 15 minutes before addition of a solution of 1-hydroxy-4-pentanone **2.141** (1.0 g, 9.8 mmol) in THF (19 mL). The mixture was stirred at RT for 18 h then quenched with sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated to low volume *in vacuo*. Purification by flash chromatography (CH_2Cl_2:Et_2O, 9:1) afforded the title compound **2.142** as a colourless oil (520 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.74 (1H, s, C=CH_a), 4.73 (1H, s, C=CH_b), 3.68 (2H, q, *J* = 6.1 Hz, 1-H_2), 2.11 (2H, t, *J* = 7.6 Hz, 3-H_2), 1.77–1.70 (5H, m, 2-H_2, CH_3), 1.35–1.32 (1H, m, OH). Analytical data observed were in accordance with literature values.[164]

2-(But-3-enyl)-tetrahydro-2-methylfuran 2.143

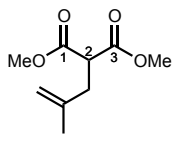


2.143

A 4 mL screw-top glass vial was charged with 4-methylpent-4-en-1-ol **2.142** (19 mg, 0.19 mmol), toluene-d^8 (0.75 mL), allyl bromide (0.08 mL, 0.95 mmol), $NaHCO_3$ (32 mg, 0.38 mmol) and $Pd(hfacac)_2$ (4.9 mg, 0.01 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 pre-heated aluminium block for 6 h then cooled to RT and filtered through cotton wool directly into an NMR tube containing 1,3,5-trimethoxybenzene (17.5 mg), rinsing with further toluene-d^8 (0.75 mL). ^{1}H NMR spectroscopy indicated a 94% yield of the title compound **2.143** (by integration *cf.* 1,3,5-trimethoxybenzene internal standard). A small amount of the volatile oil was purified by flash chromatography ($CHCl_3$) for characterisation.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.88–5.80 (1H, m, *CH*=CH_2), 5.02 (1H, dq, *J* = 17.1, 1.7 Hz, CH=*CH*$_a$), 4.94–4.92 (1H, m, CH=*CH*$_b$), 3.86–3.77 (2H, m, 5-H_2), 2.17–2.05 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.98–1.85 (2H, m, 4-H_2), 1.77–1.71 (1H, m, 3-H_a), 1.67–1.53 (3H, m, 3-H_b, *CH*$_2$$CH_2$CH=$CH_2$), 1.18 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 139.3 (CH), 114.2 (CH_2), 82.5 (C), 67.3 (CH_2), 40.4 (CH_2), 36.9 (CH_2), 29.2 (CH_2), 26.2 (CH_2), 25.8 (CH_3); IR (thin film) 2969, 1047 cm^{-1}; HRMS (CI) exact mass calculated for $C_9H_{17}O$ $[M+H]^+$ *m/z* 141.1279, found *m/z* 141.1275.

Dimethyl 2-(2-methylallyl)malonate 2.145



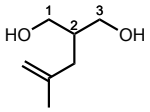
2.145

Following a modification of the reported procedure,[165] to a cooled (0 °C) suspension of sodium hydride (60% dispersion in mineral oil, 180 mg, 4.5 mmol) in THF (57 mL) was added dropwise dimethyl malonate **2.144** (0.69 mL, 6.0 mmol). Once effervescence had ceased, 3-chloro-2-methylpropene (0.32 mL, 3.3 mmol) was added then the cooling bath was removed. The

mixture was stirred at RT for 2 h then heated at reflux for 18 h. After cooling to RT, the reaction mixture was quenched by addition of water (25 mL) and extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.145** as a colourless oil (340 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.80 (1H, s, C=CH_a), 4.73 (1H, s, C=CH_b), 3.74 (6H, s, 2×OCH_3), 3.63 (1H, t, *J* = 7.8 Hz, 2-H), 2.64 (2H, d, *J* = 7.8 Hz, *C*H_2C=CH_2), 1.74 (3H, s, C(*C*H_3)=CH_2). Analytical data observed were in accordance with literature values.[166]

2-(2-Methylallyl)propane-1,3-diol 2.146

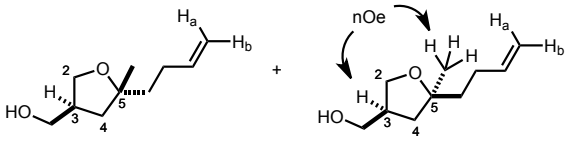


2.146

To a cooled (0 °C) suspension of lithium aluminium hydride (180 mg, 4.7 mmol) in Et_2O (10 mL) was added dropwise a solution of dimethyl 2-(2-methylallyl)malonate **2.145** (330 mg, 1.8 mmol) in Et_2O (3 mL). The cooling bath was removed and the reaction mixture stirred at RT for 3 h. The mixture was re-cooled to 0 °C before dropwise addition of sat. aq. potassium sodium tartrate (10 mL). The resulting mixture was stirred at RT for 18 h. The organics were separated, washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2:EtOAc, 3:2 then 2:3) afforded the title compound **2.146** as a colourless oil (130 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.80 (1H, s, C=CH_a), 3.74 (1H, s, C=CH_b), 3.81–3.64 (4H, m, 1-H_2, 2-H_2), 2.19 (2H, br s, 2×OH), 2.05–1.96 (3H, m, 2-H, *C*H_2C=CH_2), 1.75 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[167]

(5-(But-3-enyl)-tetrahydro-5-methylfuran-3-yl)methanol 2.147 and 2.148



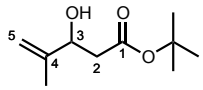
2.147 1 : 1.4 **2.148**

The general procedure was employed for the heterocyclisation of 2-(2-methylallyl)propane-1,3-diol **2.146** (39 mg, 0.30 mmol) with allyl chloride (0.12 mL, 1.5 mmol) over 2.5 h. Purification of the reaction mixture by flash chromatography (petroleum ether:EtOAc, 19:1) afforded the title compound as a colourless oil (32 mg, 63%) and as a 1:1.4 mixture of inseparable diastereomers **2.147** and **2.148**, determined by nOe as shown above.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.85–5.79 (2H, m, **2.147**, **2.148**, *C*H=CH_2), 5.04–5.00 (2H, m, **2.147**, **2.148**, CH=*C*H_a), 4.95–4.92 (2H, m, **2.147**, **2.148**, CH=*C*H_b), 3.99 (1H, dd, *J* = 8.8, 7.4 Hz, **2.148**, *C*HOH), 3.95 (1H, dd *J* = 8.9, 7.3 Hz, **2.147**, *C*HOH), 3.66–3.58 (6H, m, **2.147**, **2.148**, *C*HOH, 2-H_2), 2.63–2.48 (2H, m, **2.147**, **2.148**, 3-H), 2.14–2.04 (4H, m, **2.147**, **2.148**, CH_2*C*H_2CH=CH_2), 1.97 (1H, dd, *J* = 12.7 Hz, **2.147**, OH), 1.84 (1H, dd, *J* = 12.4 Hz, 8.3 Hz, **2.148**, OH), 1.67–1.58 (4H, m, **2.147**, **2.148**, *C*$H_2$$CH_2$CH=C$H_2$), 1.55–

1.38 (4H, m, **2.147**, **2.148**, 4-H_2), 1.25 (3H, m, **2.147**, 5-CH_3), 1.18 (3H, s, **2.148**, 5-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 139.1 (CH, **2.147**), 139.0 (CH, **2.148**), 114.4 (CH_2, **2.148**), 114.3 (CH_2, **2.147**), 83.2 (C, **2.148**), 83.0 (C, **2.147**), 69.6 (CH_2, **2.148**), 69.5 (CH_2, **2.147**), 65.4 (CH_2, **2.147**), 65.3 (CH_2, **2.148**), 42.7 (CH, **2.148**), 42.2 (CH, **2.147**), 41.0 (CH_2, **2.148**), 40.5 (CH_2, **2.147**), 40.2 (CH_2, **2.148**), 39.9 (CH_2, **2.147**), 29.2 (CH_2, **2.148**), 29.0 (CH_2, **2.147**), 26.3 (CH_3, **2.147**), 25.4 (CH_3, **2.148**); IR (thin film) 3377, 2930, 1049, 1022 cm^{-1}; HRMS (CI) exact mass calculated for $C_{10}H_{19}O_2$ $[M+H]^+$ *m/z* 171.1385, found *m/z* 171.1388.

tert-Butyl 3-hydroxy-4-methylpent-4-enoate 2.150

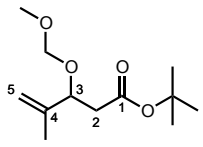


2.150

To a cooled (−78 °C) solution of di*iso*propylamine (4.2 mL, 30 mmol) in THF (25 mL) was added dropwise *n*BuLi (2.2 M in hexanes, 14 mL, 30 mmol). After 10 minutes, a solution of *tert*-butylacetate **2.149** (3.4 mL, 25 mmol) in THF (25 mL) was added dropwise. After 1 h at −78 °C, methacrolein (2.5 mL, 30 mmol) was added, resulting in a pale green solution. After stirring for a further 1 h, the cooling bath was removed and the reaction quenched with sat. aq. NH_4Cl (25 mL) and allowed to warm to RT. The mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.150** as a colourless oil (3.84 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.03 (1H, s, C=CH_a), 4.88 (1H, s, C=CH_b), 4.45–4.41 (1H, m, 3-H), 3.10 (1H, d, *J* = 4.0 Hz, OH), 2.55–2.44 (2H, m, 2-H_2), 1.76 (3H, s, 4-CH_3), 1.47 (9H, s, $C(CH_3)_3$). Analytical data observed were in accordance with literature values.[168]

tert-Butyl 3-(methoxymethoxy)-4-methylpent-4-enoate 2.151



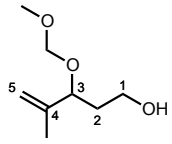
2.151

To a cooled (0 °C) solution of *tert*-butyl 3-hydroxy-4-methylpent-4-enoate **2.150** (1.5 g, 8.1 mmol) in CH_2Cl_2 (16 mL) was added di*iso*propylethylamine (2.8 mL, 16 mmol) followed by methoxymethyl chloride (0.92 mL, 12.1 mmol). The cooling bath was removed and the mixture stirred at RT for 22 h. The reaction was quenched with aq. HCl (1 M, 16 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 97:3 to 19:1) afforded unreacted starting material (750 mg, 50% recovery) and the title compound **2.151** as a colourless oil (710 mg, 38%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.013–5.010 (1H, m, 5-H), 4.95–4.94 (1H, m, 5-H), 4.61 (1H, d, *J* = 6.7 Hz, OCH_aO), 4.51 (1H, d, *J* = 6.1 Hz, OCH_bO), 4.45 (1H, dd, *J* = 8.8, 5.1 Hz, 3-H), 3.36 (3H, s, OCH_3), 2.56 (1H, dd, *J* = 14.8, 8.8 Hz, 2-H), 2.40 (1H, dd, *J* =

14.8, 5.2 Hz, 2-H), 1.69–1.68 (3H, m, 4-CH_3), 1.44 (9H, s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 170.3 (C), 143.0 (C), 114.8 (CH_2), 94.0 (C), 80.7 (CH_2), 76.7 (CH), 55.8 (CH_3), 41.0 (CH_2), 28.2 (3 × CH_3), 17.0 (CH_3); IR (thin film) 1732, 1147 1029 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{12}H_{22}NaO_4$ $[M+Na]^+$ *m/z* 253.1410, found *m/z* 253.1415.

3-(Methoxymethoxy)-4-methylpent-4-en-1-ol 2.152

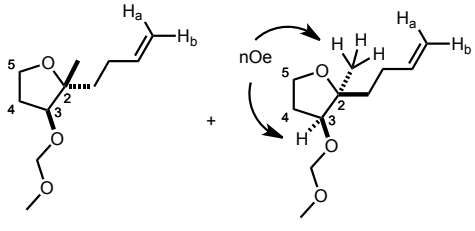


2.152

To a cooled (0 °C) suspension of $LiAlH_4$ (300 mg, 7.9 mmol) in Et_2O (21 mL) was added a solution of *tert*-butyl 3-(methoxymethoxy)-4-methylpent-4-enoate **2.151** (700 mg, 3.0 mmol). The cooling bath was removed and the reaction stirred at RT for 3 h. The reaction mixture was re-cooled to 0 °C and quenched by dropwise addition of sat. aq. potassium sodium tartrate (20 mL). The mixture was stirred at RT for 1 h then extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.152** as a colourless oil (470 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.98–4.97 (1H, m, 5-H_a), 4.95–4.93 (1H, m, 5-H_b), 4.63 (1H, d, *J* = 6.6 Hz, OCH_aO), 4.52 (1H, d, *J* = 6.6 Hz, OCH_bO), 4.23 (1H, dd, *J* = 9.0, 4.5 Hz, 3-H), 3.80–3.72 (2H, m, 1-H_2), 3.40 (3H, s, OCH_3), 2.27 (1H, dd, *J* = 6.2, 5.2 Hz, OH), 1.93–1.87 (1H, m, 2-H_a), 1.80 (1H, m, 2-H_b), 1.690–1.686 (3H, m, 4-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 143.9 (C), 113.9 (CH_2), 94.0 (CH_2), 78.9 (CH), 60.6 (CH_2), 55.9 (CH_3), 36.2 (CH_2), 17.3 (CH_3); IR (thin film) 3408, 1025 cm^{-1}; HRMS (ESI) exact mass calculated for $C_8H_{16}NaO_3$ $[M+Na]^+$ *m/z* 183.0992, found *m/z* 183.0991.

2-(But-3-en-1-yl)-3-(methoxymethoxy)-2-methyltetrahydrofuran 2.153 and 2.154



2.153 1 : 1.3 **2.154**

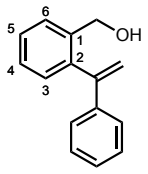
The general procedure was employed for the heterocyclisation of 3-(methoxymethoxy)-4-methylpent-4-en-1-ol **2.152** (53 mg, 0.33 mmol) with allyl bromide (0.14 mL, 1.6 mmol) over 24 h. Purification of the reaction mixture by flash chromatography (petroleum ether:EtOAc, 19:1) afforded a 1:1.3 mixture of diastereomers **2.153** and **2.154** (49 mg, 74%), determined by nOe as shown. A sample of each diastereomer was separated by flash chromatography (petroleum ether:EtOAc) for analytical purposes.

2.153: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.86–5.78 (1H, m, *CH*=CH_2), 5.02 (1H, ddd, *J* = 17.1, 3.4, 1.7 Hz, CH=*CH*$_a$), 4.95–4.92 (1H, m, CH=*CH*$_b$), 4.68 (1H, d, *J* = 6.8 Hz, OCH_aO), 4.62 (1H, d, *J* = 6.8 Hz, OCH_bO), 3.94–3.89 (2H, m, 3-H, 5-H_a), 3.80–3.76 (1H, m, 5-H_b), 3.37 (3H, s, OCH_3), 2.26–2.19 (1H, m, 4-H_a), 2.15–2.10 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.98–1.91 (1H, m, 4-H_b), 1.57–1.53 (2H, m, *CH*$_2$$CH_2$CH=$CH_2$), 1.18

(3H, s, 2-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 139.0 (CH), 114.4 (CH_2), 95.9 (CH_2), 83.4 (C), 81.4 (CH), 64.4 (CH_2), 55.6 (CH_3), 39.1 (CH_2), 32.2 (CH_2), 28.5 (CH_2), 19.6 (CH_3); IR (thin film) 1040 cm^{-1}; HRMS (CI) exact mass calculated for $C_{11}H_{21}O_3$ $[M+H]^+$ *m/z* 201.1491, found *m/z* 201.1491.

2.154: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.90–5.82 (1H, m, *CH*=CH_2), 5.03 (1H, ddd, *J* = 17.1, 3.6, 1.7 Hz, CH=*CH*$_a$), 4.94–4.92 (1H, m, CH=*CH*$_b$), 4.68 (1H, d, *J* = 6.8 Hz, OCH_aO), 4.62 (1H, d, *J* = 6.8 Hz, OCH_bO), 3.93–3.82 (3H, m, 3-H, 5-H_2), 3.37 (3H, s, OCH_3), 2.27–2.20 (1H, m, 4-H_a), 2.19–2.09 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.99–1.93 (1H, m, 4-H_b), 1.72 (1H, ddd, *J* = 13.7, 11.4, 5.4 Hz, *CH*$_a$$CH_2$CH=$CH_2$), 1.62 (1H, ddd, *J* = 13.7, 11.5, 5.4 Hz, *CH*$_b$$CH_2$CH=$CH_2$), 1.16 (3H, s, 2-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 139.5 (CH), 114.1 (CH_2), 96.0 (CH_2), 83.3 (C), 83.0 (CH), 64.4 (CH_2), 55.8 (CH_3), 33.8 (CH_2), 31.9 (CH_2), 28.5 (CH_2), 23.9 (CH_3); IR (thin film) 1035 cm^{-1}; HRMS (CI) exact mass calculated for $C_{11}H_{21}O_3$ $[M+H]^+$ *m/z* 201.1491, found *m/z* 201.1491.

(2-(1-Phenylvinyl)phenyl)methanol 2.163



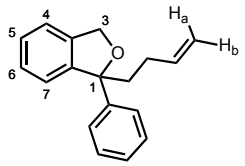
2.163

Following a modification of a reported procedure,[114] to a mixture of magnesium turnings (240 mg, 9.8 mmol) and a crystal of iodine in THF (7.5 mL) was added bromobenzene (0.86 mL, 8.3 mmol). The mixture slowly warmed and refluxed gently at the neck of the flask. After 30 minutes the mixture had cooled to RT and was added by syringe to a cooled (0 °C) suspension of phthalide **2.164** (1.0 g, 7.5 mmol) in CH_2Cl_2 (12 mL). The cooling bath was removed and the mixture allowed to warm to RT then stirred for 17 h. The reaction mixture was quenched with sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was passed through a silica plug (petroleum ether:EtOAc, 3:1) to afford a pale yellow oil. The oil was dissolved in THF (15 mL) and added dropwise to a suspension of methyl triphenylphosphonium bromide (3.2 g, 9.0 mmol) and potassium *tert*-butoxide (1.0 g, 9.0 mmol) in THF (27 mL). The mixture was stirred at RT for 16 h then sat. aq. NH_4Cl (25 mL) added and the mixture extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether:EtOAc, 4:1) afforded the title compound **2.163** as a yellow oil (1.0 g, 66% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.51 (1H, dd, *J* = 7.6, 0.7 Hz, 6-H), 7.40 (1H, td, *J* = 7.5, 1.5 Hz, 5-H), 7.35 (1H, td, *J* = 7.4, 1.2 Hz, 4-H), 7.33–7.27 (6H, m, 3-H, 5 × ArH), 5.82 (1H, d, *J* = 1.3 Hz, C=CH_a), 5.27 (1H, d, *J* = 1.3 Hz, C=CH_b), 4.45 (2H, s, CH_2OH), 1.61 (1H, s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.4 (C), 140.7 (C), 140.6 (C), 138.8 (C), 130.3 (CH), 128.6 (2 × CH), 128.15 (CH), 128.14 (CH), 128.09 (CH), 127.7 (CH),

126.7 (2 × CH), 115.7 (CH_2), 63.2 (CH_2); IR (thin film) 3349, 1026 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{15}H_{14}ONa$ $[M+Na]^+$ *m/z* 233.0937, found *m/z* 233.0926.

1-(But-3-en-1-yl)-1-phenyl-1,3-dihydroisobenzofuran 2.166

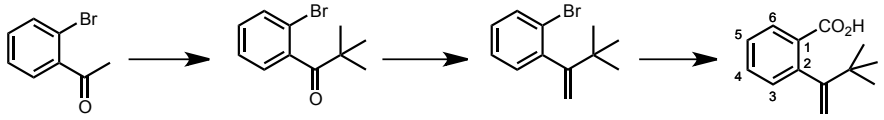


2.166

To a 4 mL screw-topped vial charged with a solution of (2-(1-phenylvinyl)phenyl)methanol **2.163** (69 mg, 0.33 mmol) and allyl bromide (0.14 mL, 1.6 mmol) in toluene (1.3 mL) was added $NaHCO_3$ (55 mg, 0.66 mmol) and $Pd(hfacac)_2$ (17 mg, 0.03 mmol). The vial was sealed under ambient atmosphere and the mixture heated at 50 °C for 72 h then the mixture subjected directly to flash chromatography (petroleum ether:CH_2Cl_2, 4:1) to afford the title compound **2.166** as a colourless oil (34 mg, 41%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.45–7.42 (2H, m, 2 × ArH), 7.26–7.22 (3H, m, 7-H, 2 × ArH), 7.22–7.15 (2H, m, 5-H, 6-H), 7.15–7.10 (2H, m, 4-H, ArH), 5.76–5.68 (1H, m, *CH*=CH_2), 5.10 (1H, d, *J* = 12.4 Hz, 3-H), 5.08 (1H, d, *J* = 12.3 Hz, 3-H), 4.87 (1H, ddd, *J* = 17.1, 3.6, 1.7 Hz, CH=*CH*$_a$), 4.83–4.80 (1H, m, CH=*CH*$_b$), 2.23 (1H, ddd, *J* = 14.0, 11.7, 4.9 Hz, *CH*$_a$$CH_2$CH=$CH_2$), 2.14 (1H, ddd, *J* = 13.9, 11.4, 4.8 Hz, *CH*$_b$$CH_2$CH=$CH_2$), 2.04–1.96 (1H, m, CH_2*CH*$_a$CH=CH_2), 1.90–1.82 (1H, m, CH_2*CH*$_b$CH=CH_2); ^{13}C (125 MHz, $CDCl_3$) δ (ppm): 145.4 (C), 144.2 (C), 139.3 (C), 138.7 (CH), 128.4 (2 × CH), 127.7 (CH), 127.5 (CH), 127.0 (CH), 125.2 (2 × CH), 122.1 (CH), 121.2 (CH), 114.3 (CH_2), 91.2 (C), 72.1 (CH_2), 41.0 (CH_2), 28.7 (CH_2); IR (thin film) 1010 cm^{-1}; HRMS (CI) exact mass calculated for $C_{18}H_{19}O$ $[M+H]^+$ *m/z* 251.1436, found *m/z* 251.1437.

2-(3,3-Dimethylbut-1-en-2-yl)benzoic acid 2.171



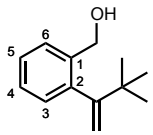
2.24 **2.169** **2.170** **2.171**

Following a modification of a reported procedure,[115] to a cooled (0 °C) suspension of potassium hydride (30% suspension in mineral oil, 2.3 g, 18 mmol) in THF (25 mL) was added *o*-bromoacetophenone **2.24** (1.0 g, 5.0 mmol). After 15 minutes, methyl iodide (1.6 mL, 25 mmol) was added and the mixture stirred at RT for 17 h. The mixture was quenched with sat. aq. NH_4Cl (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 19:1) afforded 1-(2-bromophenyl)-2,2-dimethylpropan-1-one **2.169** as a colourless oil (2.4 g) containing residual mineral oil. The material was taken up in THF (20 mL) then added dropwise to a suspension of methyl triphenylphosphonium bromide (4.3 g, 12 mmol) and potassium *tert*-butoxide (1.4 g, 12 mmol) in THF (36 mL). The resulting mixture was heated at reflux for 68 h then cooled to RT, quenched with sat. aq. NH_4Cl (50 mL) and

extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether) afforded 1-bromo-2-(3,3-dimethylbut-1-en-2-yl)benzene **2.170** as a colourless oil (2.5 g) containing residual mineral oil. The material was taken up in Et_2O (5 mL), cooled to 0 °C and a solution of *n*BuLi (2.0 M in hexanes, 5.4 mL, 11 mmol) added dropwise. The resulting mixture was stirred for 15 minutes then CO_2 bubbled through the mixture for 1.5 h. The reaction was quenched with sat. aq. $NaHCO_3$ (50 mL) and extracted with Et_2O (2 × 50 mL). The aqueous phase was adjusted to pH 1 with aq. HCl (conc.) then extracted with Et_2O (2 × 50 mL). The combined organic extracts from the acidic aqueous layer were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-(3,3-dimethylbut-1-en-2-yl)benzoic acid **2.171** as a pale yellow oil (1.3 g, 62% over three steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.7 (1H, s, OH), 7.99 (1H, dd, *J* = 7.9, 1.2 Hz, 6-H), 7.47 (1H, td, *J* = 7.5, 1.4 Hz, 4-H), 7.35 (1H, td, *J* = 7.6, 1.3 Hz, 5-H), 7.19 (1H, dd, *J* = 7.7, 1.0 Hz, 3-H), 5.30 (1H, d, *J* = 1.1 Hz, C=CH_a), 4.86 (1H, d, *J* = 1.1 Hz, C=CH_b), 1.14 (9H, s, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 173.0 (C), 158.7 (C), 144.9 (C), 131.7 (CH), 130.8 (CH), 130.7 (CH), 129.4 (C), 126.8 (CH), 112.3 (CH_2), 36.8 (C), 30.4 (3 × CH_3); IR (thin film) 3377, 2955, 1694, 1260, 1068 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{16}O_2$ $[M]^+$ *m/z* 204.1150, found *m/z* 204.1151.

(2-(3,3-Dimethylbut-1-en-2-yl)phenyl)methanol 2.172

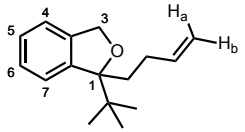


2.172

To a cooled (0 °C) suspension of lithium aluminium hydride (480 mg, 13 mmol) in Et_2O (30 mL) was added dropwise a solution of 2-(3,3-dimethylbut-1-en-2-yl)benzoic acid **2.171** (1.0 g, 4.9 mmol) in Et_2O (5 mL). After 5 minutes, the reaction mixture was allowed to warm to RT and stirred for 3 h. The mixture was re-cooled to 0 °C and sat. aq. potassium sodium tartrate (25 mL) added slowly. The biphasic mixture was stirred at RT for 16 h then extracted with Et_2O (50 mL). The organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.172** as a colourless oil (880 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.50 (1H, d, *J* = 7.0 Hz, 6-H), 7.30 (1H, td, *J* = 7.5, 1.3 Hz, 5-H), 7.22 (1H, td, *J* = 7.5, 1.3 Hz, 4-H), 7.08 (1H, dd, *J* = 7.6, 1.2 Hz, 3-H), 5.34 (1H, d, *J* = 1.5 Hz, C=CH_a), 4.82 (1H, d, *J* = 1.5 Hz, C=CH_b), 4.63 (2H, s, CH_2OH), 1.56–1.54 (1H, m, OH), 1.12 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 157.3 (C), 141.5 (C), 138.8 (C), 129.6 (CH), 128.1 (CH), 127.2 (CH), 126.6 (CH), 113.3 (CH_2), 63.6 (CH_2), 36.7 (C), 30.0 (3 × CH_3); IR (thin film) 3314, 2955, 1481, 1360, 1190 cm^{-1}; HRMS (CI) exact mass calculated for $C_{13}H_{17}$ $[M\text{-}OH]^+$ *m/z* 173.1330, found *m/z* 173.1326.

1-(But-3-en-1-yl)-1-(tert-butyl)-1,3-dihydroisobenzofuran 2.173

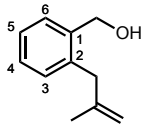


2.173

To a 4 mL screw-topped vial charged with a solution of (2-(3,3-dimethylbut-1-en-2-yl)phenyl)methanol **2.172** (63 mg, 0.33 mmol) and allyl bromide (0.14 mL, 1.6 mmol) in toluene (1.3 mL) was added $NaHCO_3$ (55 mg, 0.66 mmol) and $Pd(hfacac)_2$ (8.5 mg, 0.02 mmol). The vial was sealed under ambient atmosphere and the mixture heated at 50 °C for 24 h then additional $Pd(hfacac)_2$ (8.5 mg, 0.02 mmol) added. Heating was continued for a further 24 h then the mixture allowed to cool to RT and subjected directly to flash chromatography (petroleum ether:CH_2Cl_2, 17:3) to afford unreacted starting material **2.172** (13 mg, 19%) and the title compound **2.173** as a colourless oil (45 mg, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.28–7.22 (2H, m, 5-H, 6-H), 7.17–7.15 (2H, m, 4-H, 7-H), 5.79–5.71 (1H, m, *CH*=CH_2), 5.11 (1H, d, *J* = 12.2 Hz, 3-H_a), 5.06 (1H, d, *J* = 12.2 Hz, 3-H_b), 4.89–4.83 (2H, m, CH=*CH_2*), 2.08–2.03 (1H, m, CH_2*CH_a*CH=CH_2), 1.98–1.88 (2H, m, *$CH_a$$CH_b$*CH=$CH_2$), 1.45–1.37 (1H, m, *$CH_b$*$CH_2$CH=$CH_2$), 0.96 (9H, s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 142.0 (C), 140.9 (C), 139.4 (CH), 127.3 (CH), 126.8 (CH), 123.0 (CH), 120.7 (CH), 113.9 (CH_2), 96.1 (C), 74.0 (CH_2), 40.2 (CH_2), 34.5 (CH_2), 30.1 (C), 25.8 (3 × CH_3); IR (thin film) 2955, 1040 cm^{-1}; HRMS (CI) exact mass calculated for $C_{16}H_{23}O$ $[M+H]^+$ *m/z* 231.1749, found *m/z* 231.1751.

(2-(2-Methylallyl)phenyl)methanol 2.175

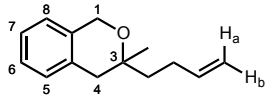


2.175

To a cooled suspension of lithium aluminium hydride (260 mg, 6.8 mmol) in Et_2O (15 mL) was added a solution of methyl 2-(2-methylallyl)benzoate **2.174**[113] (0.50 g, 2.6 mmol) in Et_2O (3.0 mL). The cooling bath was removed and the reaction mixture stirred at RT for 3 h then quenched by dropwise addition of sat. aq. potassium sodium tartrate (25 mL) and stirred for 16 h. The mixture was extracted with Et_2O (2 × 25 mL) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography afforded the title compound **2.175** as a colourless oil (400 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.41–7.39 (1H, m, 6-H), 7.27–7.25 (2H, m, 4-H, 5-H), 7.19–7.18 (1H, m, 3-H), 4.84 (1H, s, C=CH_a), 4.67 (2H, d, *J* = 5.7 Hz, CH_2OH), 4.54 (1H, s, C=CH_b), 3.41 (2H, s, CH_2), 1.86 (1H, t, *J* = 5.9 Hz, OH), 1.76 (3H, s, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 145.8 (C), 139.2 (C), 137.5 (C), 130.7 (CH), 128.6 (CH), 128.0 (CH), 126.9 (CH), 111.9 (CH_2), 63.3 (CH_2), 41.1 (CH_2), 22.9 (CH_3); IR (thin film) 3320, 1445, 1038, 1005 cm^{-1}; HRMS (EI) exact mass calculated for $C_{11}H_{14}O$ $[M]^+$ *m/z* 162.1045, found *m/z* 162.1042.

3-(But-3-enyl)-3,4-dihydro-3-methyl-1H-isochromene 2.176

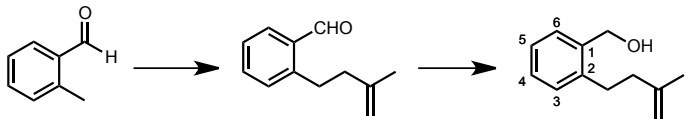


2.176

The general procedure was employed for the heterocyclisation of (2-(2-methylallyl)phenyl)methanol **2.175** (54 mg, 0.33 mmol) with allyl bromide (0.14 mL, 1.6 mmol) over 16 h. Purification of the reaction mixture by flash chromatography (petroleum ether:CH_2Cl_2, 1:1), followed by trituration with petroleum ether to remove a yellow solid afforded the title compound **2.176** as a colourless oil (48 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.18–7.15 (2H, m, 6-H, 7-H), 7.10–7.07 (1H, m, 8-H), 7.03–6.99 (1H, m, 5-H), 5.90–5.82 (1H, m, *CH*=CH_2), 5.05 (1H, ddd, *J* = 17.1, 3.5, 1.7 Hz, CH=*CH*$_a$), 4.96 (1H, ddd, *J* = 10.2, 3.1, 1.3 Hz, CH=*CH*$_b$), 4.80 (1H, d, *J* = 15.5 Hz, 1-H_a), 4.75 (1H, d, *J* = 15.5 Hz, 1-H_b), 2.79 (1H, d, *J* = 16.1 Hz, 4-H_a), 2.66 (1H, d, *J* = 16.1 Hz, 4-H_b), 2.25–2.19 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.75 (1H, ddd, *J* = 13.8, 10.3, 6.1 Hz, *CH*$_a$$CH_2$CH=$CH_2$), 1.61 (1H, ddd, *J* = 13.8, 10.6, 6.4 Hz, *CH*$_b$$CH_2$CH=$CH_2$), 1.25 (3H, s, 3-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 139.0 (CH), 134.4 (C), 133.0 (C), 129.3 (CH), 126.5 (CH), 126.0 (CH), 124.1 (CH), 114.4 (CH_2), 72.7 (C), 63.1 (CH_2), 39.2 (CH_2), 38.8 (CH_2), 28.1 (CH_2), 23.4 (CH_3); IR (thin film) 1454, 1373, 1080 cm^{-1}; HRMS (EI) exact mass calculated for $C_{14}H_{18}O$ $[M]^+$ *m/z* 202.1358, found *m/z* 202.1360.

(2-(3-Methylbut-3-enyl)phenyl)methanol 2.183



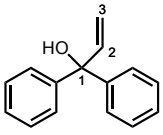
2.180 **2.181** **2.183**

Following a reported procedure,[118] to a cooled (−78 °C) solution of *N*,*N*,*N*′-trimethylethylamine (1.0 mL, 8.9 mmol) in THF (22 mL) was added dropwise *n*BuLi (2.5 M in hexanes, 3.4 mL, 8.5 mmol). The resulting yellow solution was stirred for 20 minutes then *o*-tolualdehyde **2.180** (0.96 mL, 8.3 mmol) added dropwise. The mixture was warmed to −15 °C and stirred for 20 minutes then cooled to −55 °C before dropwise addition of *t*BuLi (1.7 M in pentane, 14.6 mL, 24.9 mmol). The deep red solution was stirred at −55 °C for 2.5 h then cooled to −78 °C and 3-chloro-2-methylpropene (4.1 mL, 50.0 mmol) added rapidly. After 5 minutes, the cooling bath was removed and the mixture allowed to warm to RT, upon which the mixture was stirred for 30 minutes. The reaction was quenched by pouring into aq. HCl (1 M, 50 mL) and stirred for 10 minutes. The mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 19:1) afforded 2-(3-methyl-3-buten-1-yl)-benzaldehyde **2.181** (1.1 g), contaminated with approximately 12% of a side product. The material was taken up in MeOH (4 mL) and added dropwise to a cooled (0 °C) suspension of $NaBH_4$ (950 mg, 25 mmol) in MeOH (12 mL). The cooling bath was removed and the mixture stirred at RT

for 1.5 h. The mixture was quenched with water (5 mL) and concentrated *in vacuo*. The residue was partitioned between EtOAc (25 mL) and water (25 mL) and the organic extracts washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography afforded the title compound **2.183** as a colourless oil (500 mg, 33% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39–7.37 (1H, m, 6-H), 7.27–7.20 (3H, m, 3-H, 4-H, 5-H), 4.77 (4H, m, CH_2OH, C=CH_2), 2.85–2.82 (2H, m, ArCH_2CH_2), 2.33–2.30 (2H, m, ArCH_2CH_2), 1.80 (3H, s, CH_3), 1.49 (1H, br s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 145.6 (C), 140.5 (C), 138.5 (C), 129.5 (CH), 128.4 (CH), 128.1 (CH), 126.4 (CH), 110.5 (CH_2), 63.3 (CH_2), 39.6 (CH_2), 31.0 (CH_2), 22.7 (CH_3); IR (thin film) 3313, 1452, 1003 cm^{-1}; HRMS (CI) exact mass calculated for $C_{12}H_{15}$ [M-OH]$^+$ *m/z* 159.1174, found *m/z* 159.1171.

1,1-diphenylprop-2-en-1-ol 2.187

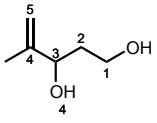


2.187

Following a reported procedure,[169] to a cooled (0 °C) solution of benzophenone **2.197** (1.0 g, 5.5 mmol) in THF (11 mL) was added dropwise vinylmagnesium bromide (1 M in THF, 6.6 mL, 6.6 mmol). After 20 minutes at 0 °C, the mixture was allowed to warm to room temperature and stirred for 18 h. TLC analysis indicated significant unreacted benzophenone so the mixture was re-cooled to 0 °C and additional vinylmagnesium bromide (1 M in THF, 6.6 mL, 6.6 mmol) added dropwise. The mixture was stirred at 0 °C for 20 minutes then allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 19:1) afforded the title compound **2.187** as a colourless oil (980 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42–7.40 (4H, m, 4×ArH), 7.37–7.33 (4H, m, 4×ArH), 7.31–7.27 (2H, m, 2×ArH), 6.54 (1H, dd, *J* = 17.4, 10.3 Hz, 2-H), 5.38–5.33 (2H, m, 3-H_2), 2.29 (1H, s, OH). Analytical data observed were in accordance with literature values.[169]

4-methylpent-4-ene-1,3-diol 2.200

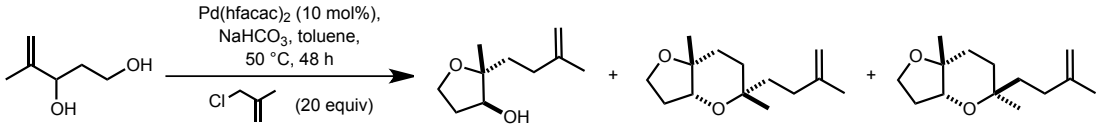


2.200

To a cooled (0 °C) suspension of $LiAlH_4$ (400 mg, 10 mmol) in Et_2O (25 mL) was added a solution of *tert*-butyl 3-hydroxy-4-methylpent-4-enoate **2.150** (750 mg, 4.0 mmol) in Et_2O (4 mL). The cooling bath was removed and the mixture stirred at RT for 2.5 h then the mixture re-cooled to 0 °C and sat. aq. potassium sodium tartrate (15 mL) added dropwise. The cooling bath was removed and the mixture stirred at RT for 1 h then extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.200** as a colourless oil (300 mg, 65%).

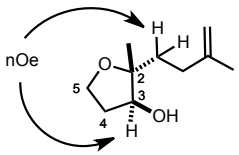
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.04 (1H, s, 5-H_a), 4.89 (1H, s, 5-H_b), 4.33 (1H, m, 3-H), 3.90–3.81 (2H, m, 1-H_2), 2.23–2.20 (2H, m, 2×OH), 1.85–1.81 (2H, 2-H_2), 1.76 (3H, s, 4-CH_3). Analytical data observed were in accordance with literature values.[170]

Cascade oxyallylation of 4-methylpent-4-ene-1,3-diol 2.200: 2-methyl-2-(3-methylbut-3-en-1-yl)tetrahydrofuran-3-ol 2.204; 5,7a-dimethyl-5-(3-methylbut-3-en-1-yl)hexahydro-2*H*-furo[3,2-*b*]pyran 2.205; and 5,7a-dimethyl-5-(3-methylbut-3-en-1-yl)hexahydro-2*H*-furo[3,2-*b*]pyran 2.206



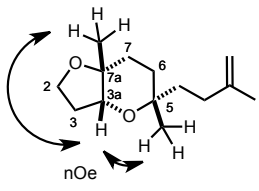
2.199 **2.204** **2.205** **2.206**

A 4 mL screw-top glass vial was charged with 4-methylpent-4-ene-1,3-diol **2.200** (50 mg, 0.43 mmol), toluene (1.7 mL), 3-chloro-2-methylpropene (0.80 mL, 8.6 mmol), $NaHCO_3$ (72 mg, 0.86 mmol) and $Pd(hfacac)_2$ (22 mg, 0.04 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 pre-heated aluminium block for 48 h. The reaction mixture was cooled to RT then purified directly by flash chromatography (petroleum ether:EtOAc, 19:1 then 3:1) to afford 2-methyl-2-(3-methylbut-3-en-1-yl)tetrahydrofuran-3-ol **2.204** (20 mg, 28%), 5,7a-dimethyl-5-(3-methylbut-3-en-1-yl)hexahydro-2*H*-furo[3,2-*b*]pyran **2.205** (17 mg, 18%) and 5,7a-dimethyl-5-(3-methylbut-3-en-1-yl)hexahydro-2*H*-furo[3,2-*b*]pyran **2.206** (17 mg, 18%). The stereochemistry of **2.204**, **2.205** and **2.206** was determined by nOe, as shown below.



2.204

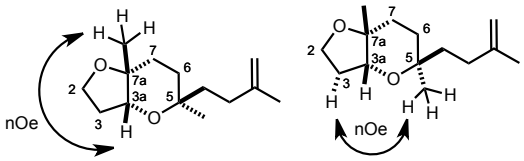
2.204: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.72–4.68 (2H, m, C=CH_2), 4.03–4.01 (1H, m, 3-H), 3.97–3.92 (1H, m, 5-H_a), 3.79–3.75 (1H, m, 5-H_b), 2.34–2.27 (1H, m, 4-H_a), 2.10–2.02 (2H, m, CH_2*CH_2*C(CH_3)=CH_2), 1.93–1.87 (2H, m, 4-H_b, OH), 1.73 (3H, s, C(*CH_3*)=CH_2), 1.58–1.50 (2H, m, *CH_2*CH_2C(CH_3)=CH_2), 1.20 (3H, s, 2-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 146.1 (C), 109.7 (CH_2), 84.4 (C), 77.0 (CH), 64.1 (CH_2), 37.0 (CH_2), 34.9 (CH_2), 32.2 (CH_2), 22.8 (CH_3), 18.8 (CH_3); IR (thin film) 3413, 1095, 1035 cm^{-1}; HRMS (CI) exact mass calculated for $C_{10}H_{19}O_2$ $[M+H]^+$ *m/z* 171.1385, found *m/z* 171.1384.



2.205

2.205: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.68–4.67 (2H, m, C=CH_2), 4.03–3.98 (1H, m, 2-H_a), 3.91–3.88 (2H, m, 2-H_b, 3a-H), 2.25–2.18 (1H, m, 3-H_a), 2.07–2.03 (2H, m, CH_2*CH_2*C(CH_3)=CH_2), 1.88–1.81 (2H, m, 3-H_b, 7-H_a), 1.76–1.67 (5H, m, 6-H_a, 7-H_b, C(*CH_3*)=CH_2), 1.59–1.57 (2H, m, *CH_2*CH_2C(CH_3)=CH_2), 1.22–1.19 (1H, m, 6-H_b), 1.15 (3H, s, 5-CH_3), 1.07 (3H, s, 7a-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 146.6 (C), 109.4 (CH_2), 79.1 (C), 75.6 (CH), 72.7 (C), 65.9 (CH_2), 41.8 (CH_2), 33.6

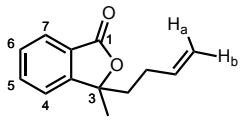
(CH_2), 31.6 (CH_2), 29.54 (CH_2), 29.47 (CH_2), 25.7 (CH_3), 22.9 (CH_3), 20.1 (CH_3); IR (thin film) 1077, 1040 cm^{-1}; HRMS (CI) exact mass calculated for $C_{14}H_{25}O_2$ $[M+H]^+$ *m/z* 225.1855, found *m/z* 225.1860.



2.206

2.206: ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.71–4.70 (2H, m, C=CH_2), 4.05–4.02 (1H, m, 2-H_a), 3.92–3.88 (1H, m, 2-H_b), 3.81 (1H, d, *J* = 4.6 Hz, 3a-H), 2.24–2.17 (1H, m, 3-H_a), 2.01–1.98 (2H, m, $CH_2CH_2C(CH_3)=CH_2$), 1.90–1.85 (1H, ddd, *J* = 13.2, 7.1, 2.4 Hz, 3-H_b), 1.83–1.72 (5H, m, 7-H_a, $CH_aCH_2C(CH_3)=CH_2$), 1.71–1.63 (2H, m, 6-H_a, 7-H_b), 1.54–1.48 (1H, m, $CH_bCH_2C(CH_3)=CH_2$), 1.34–1.28 (1H, m, 6-H_b), 1.14 (3H, s, 5-CH_3), 1.07 (3H, s, 7a-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 146.6 (C), 109.7 (CH_2), 79.5 (C), 75.7 (CH), 73.1 (C), 65.9 (CH_2), 33.6 (CH_2), 32.7 (CH_2), 32.2 (CH_2), 31.2 (CH_2), 29.4 (CH_2), 27.3 (CH_3), 25.5 (CH_3), 23.0 (CH_3); IR (thin film) 1086 cm^{-1}; HRMS (CI) exact mass calculated for $C_{14}H_{25}O_2$ $[M+H]^+$ *m/z* 225.1855, found *m/z* 225.1862.

3-(But-3-enyl)-3-methylisobenzofuran-1(3H)-one 2.210

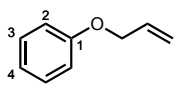


2.210

The general procedure was employed for the heterocyclisation of 2-(prop-1-en-2-yl) benzoic acid **2.26** (54 mg, 0.33 mmol) with allyl bromide (0.14 mL, 1.6 mmol) over 5 h. Purification of the reaction mixture by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.210** as a colourless oil (51 mg, 76%).

^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.87 (1H, dt, *J* = 7.6, 0.9 Hz, 7-H), 7.66 (1H, td, *J* = 7.5, 1.1 Hz, 5-H), 7.50 (1H, td, *J* = 7.5, 0.8 Hz, 6-H), 7.36 (1H, d, *J* = 7.7 Hz, 4-H), 5.74–5.66 (1H, m, CH=CH_2), 4.94–4.89 (2H, m, CH=CH_2), 2.15 (1H, ddd, *J* = 13.6, 11.2, 4.8 Hz, $CH_aCH_2CH=CH_2$), 2.10–2.02 (1H, m, $CHCH_aCH=CH_2$), 1.96 (1H, ddd, *J* = 13.7, 11.0, 4.6 Hz, $CH_bCH_2CH=CH_2$), 1.80–1.73 (1H, m, $CH_2CH_bCH=CH_2$), 1.65 (3H, s, 3-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 169.9 (C), 153.9 (C), 137.3 (CH), 134.2 (CH), 129.1 (CH), 126.5 (C), 126.0 (CH), 121.0 (CH), 115.2 (CH_2), 87.3 (C), 39.3 (CH_2), 28.0 (CH_2), 26.3 (CH_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.

1-(Allyloxy)benzene 2.215



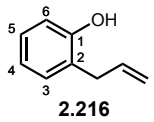
2.215

To a mixture of phenol **2.46** (1.00 g, 10.6 mmol) and K_2CO_3 (2.93 g, 21.2 mmol) in DMF (53 mL) was added allyl bromide (1.10 mL, 12.8 mmol). The resulting mixture was heated at 70 °C for 17 h then quenched with water (50 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*.

Purification by flash chromatography afforded the title compound **2.215** as a colourless oil (1.25 g, 88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.32–7.28 (2H, m, 2×3-H), 6.99–6.94 (3H, m, 2×2-H, 4-H), 6.13–6.05 (1H, m, CH_2CH=CH_2), 5.44 (1H, dd, *J* = 17.3, 1.4 Hz, CH_2CH=CH_a), 5.30 (1H, dd, *J* = 10.4, 1.3 Hz, CH_2CH=CH_b), 4.56 (2H, d, *J* = 5.4 Hz, CH_2CH=CH_2). Analytical data observed was in accordance with literature values.[171]

2-Allylphenol 2.216

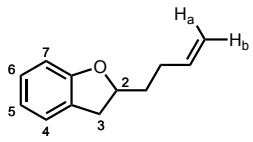


2.216

A solution of 1-(allyloxy)benzene **2.215** (1.25 g, 9.30 mmol) in DMF (7.8 mL) under argon was subjected to microwave irradiation at 230 °C for 3 h. The resulting mixture was extracted with Et_2O (2 × 50 mL) and the combined organic extracts washed brine (2 × 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 19:1) afforded the title compound **2.216** as a yellow oil (1.01 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.17–7.12 (2H, m, 3-H, 5-H), 6.90 (1H, t, *J* = 7.1 Hz, 4-H), 6.38 (1H, d, *J* = 7.9 Hz, 6-H), 5.20–5.18 (1H, m, CH_2CH=CH_2), 5.20–5.18 (1H, m, CH_2CH=CH_a), 5.16–5.15 (1H, m, CH_2CH=CH_b), 4.97–4.92 (1H, m, OH), 3.43 (1H, d, *J* = 6.3 Hz, CH_2CH=CH_2). Analytical data observed was in accordance with literature values.[172]

2-(But-3-enyl)-2,3-dihydrobenzofuran 2.217

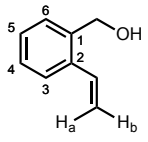


2.217

To a solution of 2-allylphenol **2.216** (200 mg, 1.5 mmol) and allyl chloride (1.2 mL, 15 mmol) in toluene (1.5 mL) was added $NaHCO_3$ (250 mg, 3.0 mmol) and $Pd(hfacac)_2$ (78 mg, 0.15 mmol). The mixture was stirred at RT for 144 h then subjected directly to purification by flash chromatography (petroleum ether:CH_2Cl_2, 9:1) to afford the title compound **2.217** as a colourless oil (160 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.15 (1H, d, *J* = 7.3 Hz, 4-H), 7.10 (1H, t, *J* = 7.7 Hz, 6-H), 6.82 (1H, t, *J* = 7.6 Hz, 5-H), 6.76 (1H, d, *J* = 8.0 Hz, 7-H), 5.91–5.82 (1H, m, CH=CH_2), 5.08 (1H, ddd, *J* = 17.1, 3.3, 1.6 Hz, CH=CH_a), 5.01–4.99 (1H, m, CH=CH_b), 4.81–4.75 (1H, m, 2-H), 3.28 (1H, dd, *J* = 15.4, 7.8 Hz, 3-H), 2.87 (1H, dd, *J* = 15.4, 7.8 Hz, 3-H), 2.32–2.18 (2H, m, CH_2CH_2CH=CH_2), 1.98–1.91 (1H, m, CH_aCH_2CH=CH_2), 1.80–1.73 (1H, m, CH_bCH_2CH=CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 159.6 (C), 137.9 (CH), 128.1 (CH), 127.0 (C), 125.0 (CH), 120.3 (CH), 115.2 (CH_2), 109.4 (CH), 82.7 (CH), 35.6 (CH_2), 35.4 (CH_2), 29.8 (CH_2); IR (thin film) 1598, 1479, 1461, 1230 cm^{-1}; HRMS (EI) exact mass calculated for $C_{12}H_{14}O$ $[M]^+$ *m/z* 174.1045, found *m/z* 174.1042.

(2-Vinylphenyl)methanol 2.224

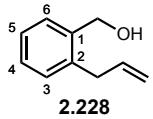


2.224

To a cooled (−78 °C) solution of phthalide **2.164** (1.0 g, 7.5 mmol) in toluene (38 mL) was added dropwise a solution of DIBAL-H (1 M in heptane, 9.0 mL, 9.0 mmol). The mixture was stirred at −78 °C for 30 minutes and then quenched with EtOH (0.3 mL). The mixture was then added by syringe to a prepared suspension of methyl triphenylphosphonium bromide (4.0 g, 11 mmol) and potassium *tert*-butoxide (1.26 g, 11.3 mmol) in THF (40 mL). The mixture was stirred at RT for 2 h then additional methyl triphenylphosphonium bromide (2.0 g, 5.6 mmol) and potassium *tert*-butoxide (630 mg, 5.3 mmol) added. After a further 1.5 h the mixture was quenched with aq. HCl (1 M, 35 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with aq. HCl (1 M, 25 mL), sat. aq. $NaHCO_3$ (25 mL) and brine (25 mL) then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1) afforded the title compound **2.224** as a pale yellow oil (525 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.54 (1H, dd, *J* = 7.4, 1.6 Hz, 6-H), 7.36 (1H, dd, *J* = 7.1, 1.7 Hz, 3-H), 7.33–7.26 (2H, m, 4-H, 5-H), 7.06 (1H, dd, *J* = 17.4, 11 Hz, *CH*=CH_2), 5.71 (1H, dd, *J* = 17.4, 1.3 Hz, CH=*CH*$_a$), 5.36 (1H, dd, *J* = 11.0, 1.3 Hz, CH=*CH*$_b$), 4.76 (2H, d, *J* = 5.8 Hz, *CH*$_2$OH), 1.63 (1H, t, *J* = 5.8 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 137.7 (C), 136.8 (C), 133.9 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 126.1 (CH), 116.7 (CH_2), 63.6 (CH_2); IR (thin film) 3323, 1000 cm^{-1}; HRMS (EI) exact mass calculated for $C_9H_{10}O$ $[M]^+$ *m/z* 134.0732, found *m/z* 134.0735.

(2-Allylphenyl)methanol 2.228

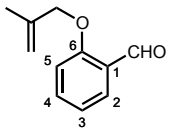


2.228

To a cooled (0 °C) suspension of $LiAlH_4$ (280 mg, 7.4 mmol) in Et_2O (20 mL) was added a solution of methyl 2-allylbenzoate **2.227**[113] (500 mg, 2.8 mmol). The cooling bath was removed and the mixture stirred at RT for 4 h. The mixture was quenched by slow addition of sat. aq. potassium sodium tartrate (25 mL) then stirred at RT for 16 h. The mixture was diluted with Et_2O (25 mL) and the organic extracts washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 17:3) afforded the title compound **2.228** as a pale yellow oil (362 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.23–7.21 (1H, m, 3-H), 7.13–7.03 (3H, m, 4-H, 5-H, 6-H), 5.89–5.80 (1H, m, CH_2*CH*=CH_2), 4.92 (1H, dd, *J* = 10.1, 1.5 Hz, CH_2CH=CH_a), 4.84 (1H, dd, *J* = 17.0, 1.6 Hz, CH_2CH=CH_b), 4.53 (2H, d, *J* = 5.5 Hz, *CH*$_2$CH=CH_2), 3.31 (2H, d, *J* = 6.0 Hz, CH_2OH), 1.67 (1H, t, *J* = 5.8 Hz, OH). Analytical data observed were in accordance with literature values.[173]

2-(2-Methylallyloxy)-benzaldehyde 2.236

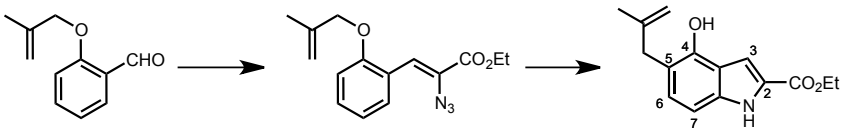


2.236

To a stirred suspension of K_2CO_3 (2.3 g, 16 mmol) in DMF (8.2 mL) was added salicylaldehyde **2.235** (1.0 g, 8.2 mmol) followed by 3-chloro-2-methylpropene (0.96 mL, 9.8 mmol). The resulting mixture was stirred at RT for 18 h then quenched with water (50 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.236** as a yellow oil (1.2 g, 85%), which was used without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.57 (1H, s, C(H)=O), 7.86 (1H, dd, *J* = 7.7, 1.7 Hz, 2-H), 7.54 (1H, td, *J* = 7.8, 1.8 Hz, 4-H), 7.04 (1H, t, *J* = 7.5 Hz, 3-H), 6.99 (1H, d, *J* = 8.4 Hz, 5-H), 5.14 (1H, s, C=CH_a), 5.05 (1H, s, C=CH_b), 4.56 (2H, s, *C*H_2C=CH_2), 1.87 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[174]

Ethyl 4-hydroxy-5-(2-methylallyl)-*1H*-indole-2-carboxylate 2.238



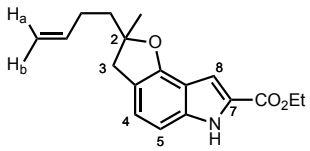
2.236 **2.237** **2.238**

Following a modification of the reported procedure,[125] to a cooled (−10 °C) solution of sodium (640 mg, 28 mmol) in EtOH (21 mL) was added dropwise a solution of 2-(methylallyloxy)-benzaldehyde **2.236** (1.2 g, 6.9 mmol) and ethyl azidoacetate (25% in toluene, 11 g, 28 mmol) in EtOH (5 mL) over 30 minutes. The mixture was stirred at –10 °C for 2 h then allowed to warm to RT and poured into water (130 mL). The resulting mixture was extracted with EtOAc (3 × 50 mL) and the combined organic extracts washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 17:3 to 4:1; re-purified with petroleum ether:Et_2O, 19:1) followed by trituration with petroleum ether afforded (*Z*)-ethyl 3-(2-(2-methylallyloxy)phenyl)-2-azidoacrylate **2.237** as a pale yellow solid (610 mg, 32%). The material was taken up in bromobenzene (26 mL) and heated at reflux for 16 h. After cooling to RT, the mixture was purified directly by flash chromatography (petroleum ether:EtOAc, 9:1 then 4:1) to afford the title compound **2.238** as a lilac coloured solid (350 mg, 65%).

Melting point: 157–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.85 (1H, br s, NH), 7.30 (1H, dd, *J* = 2.1, 0.9 Hz, 3-H), 7.04 (1H, d, *J* = 8.4 Hz, 6-H), 6.94 (1H, dd, *J* = 8.3, 0.8 Hz, 7-H), 5.65 (1H, s, OH), 4.93 (1H, s, C=CH_a), 4.91 (1H, s, C=CH_b), 4.40 (2H, q, *J* = 7.1 Hz, O*C*H_2CH$_3$), 3.46 (2H, s, ArCH_2), 1.75 (3H, s, CCH_3), 1.41 (3H, t, *J* = 7.1 Hz, OCH$_2$*C*H_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 162.1 (C), 149.0 (C), 145.5 (C), 137.8 (C), 129.3 (CH), 126.8 (C), 118.9 (C), 113.6 (C), 112.2 (CH_2), 105.6 (CH), 104.4 (CH), 61.1 (CH_2), 39.8 (CH_2), 22.1 (CH_3), 14.5 (CH_3); IR (thin film) 3316, 1694, 1217 cm^{-1}; HRMS (EI) exact

mass calculated for $C_{15}H_{17}O_3N$ $[M]^+$ *m/z* 259.1208, found *m/z* 259.1211.

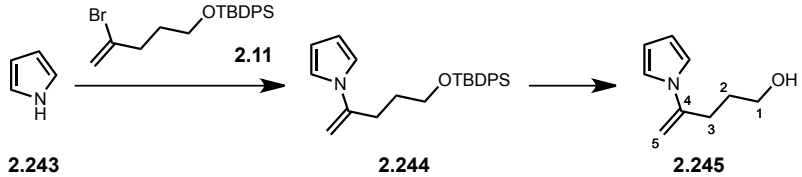
Ethyl 2-(but-3-enyl)-3,6-dihydro-2-methyl-2*H*-furo[2,3-*e*]indole-7-carboxylate 2.239



2.239

A 4 mL screw-top glass vial was charged with ethyl 4-hydroxy-5-(2-methylallyl)-*1H*-indole-2-carboxylate **2.238** (86 mg, 0.33 mmol), toluene (1.3 mL), allyl chloride (0.13 mL, 1.6 mmol), $NaHCO_3$ (55 mg, 0.66 mmol) and $Pd(hfacac)_2$ (8.5 mg, 0.02 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 pre-heated aluminium block for 22 h. Additional $Pd(hfacac)_2$ (8.5 mg, 0.02 mmol) was then added and heating continued for a further 24 h. The reaction mixture was cooled to RT then purified directly by flash chromatography (petroleum ether:EtOAc, 19:1 then 9:1) to afford unreacted starting material (40 mg, 47%) and the title compound **2.239** as an off-white solid (30 mg, 30%). Melting point: 111–113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.01 (1H, s, NH), 7.22–7.23 (1H, m, 8-H), 7.09 (1H, d, *J* = 8.3 Hz, 4-H), 6.90 (1H, dd, *J* = 8.2, 0.7 Hz, 5-H), 5.89–5.82 (1H, m, *CH*=CH_2), 5.03 (1H, ddd, *J* = 17.1, 1.7, 1.6 Hz, CH=*CH*$_a$), 4.95 (1H, dd, *J* = 10.2, 1.6 Hz, CH=*CH*$_b$), 4.40 (2H, q, *J* = 7.1 Hz, O*CH*$_2$$CH_3$), 3.18 (1H, d, 14.6 Hz, 3-H_a), 3.02 (1H, d, *J* = 14.6 Hz, 3-H_b), 2.23–2.17 (2H, m, CH_2*CH*$_2$CH=CH_2), 1.91–1.88 (2H, m, *CH*$_2$$CH_2$CH=$CH_2$), 1.51 (3H, s, 2-$CH_3$), 1.40 (3H, t, *J* = 7.2 Hz, OCH_2*CH*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 162.2 (C), 152.7 (C), 138.8 (C), 138.5 (CH), 127.0 (C), 122.6 (CH), 115.2 (C), 114.6 (CH_2), 114.2 (C), 105.4 (CH), 103.3 (CH), 90.1 (C), 61.0 (CH_2), 41.4 (CH_2), 40.6 (CH_2), 28.5 (CH_2), 26.9 (CH_3), 14.5 (CH_3); IR (thin film) 1740, 1690, 1209 cm^{-1}; HRMS (EI) exact mass calculated for $C_{18}H_{21}O_3N$ $[M]^+$ *m/z* 299.1521, found *m/z* 299.1524.

4-(1*H*-Pyrrol-1-yl)pent-4-en-1-ol 2.245



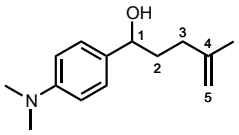
2.243 **2.244** **2.245**

A 5–10 mL microwave vial was charged with K_3PO_4 (1.1 g, 5.0 mmol), dioxane (degassed, 2.5 mL), pyrrole **2.243** (0.21 mL, 3.0 mmol), copper(I) iodide (48 mg, 0.25 mmol), ethylene diamine (2 M in dioxane, 0.25 mL, 0.50 mmol) then a solution of (4-bromopent-4-enyloxy)(*tert*-butyl)diphenylsilane **2.11** (1.0 g, 2.5 mmol) in dioxane (degassed, 1.5 mL). The vial was sealed under argon and heated at 110 °C for 72 h. The mixture was then diluted with EtOAc (5 mL) and filtered over Celite®, rinsing with further EtOAc (25 mL), and the filtrate concentrated *in vacuo*. Purification of the residue by flash chromatography (petroleum ether:CH_2Cl_2, 4:1) afforded the title compound as a colourless oil (800 mg, 83%). The material was taken up in THF (2.3 mL) and TBAF (1 M in THF, 2.3 mL, 2.3

mmol) added. The mixture was stirred at RT for 1.5 h then concentrated under reduced pressure. The residue was subjected directly to flash chromatography (petroleum ether:EtOAc, 1:3 then 2:3) to afford the title compound **2.245** as a yellow oil (310 mg, quant.).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.92 (2H, t, *J* = 2.2 Hz, 2 × ArH), 6.22 (2H, t, *J* = 2.2 Hz, 2 × ArH), 4.97 (1H, s, 5-H_a), 4.64 (1H, s, 5-H_b), 3.69 (2H, q, *J* = 5.5 Hz, 1-H_2), 2.62 (2H, td, *J* = 7.5, 0.7 Hz, 3-H_2), 1.80–1.75 (2H, m, 2-H_2), 1.30 (1H, s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 145.0 (C), 118.7 (2 × CH), 109.7 (2 × CH), 99.6 (CH_2), 62.1 (CH_2), 30.4 (CH_2), 30.3 (CH_2); IR (thin film) 1645, 1481, 1089, 1053 cm^{-1}; HRMS (CI) exact mass calculated for $C_9H_{14}ON$ $[M+H]^+$ *m/z* 152.1075, found *m/z* 152.1080.

1-(4-(Dimethylamino)phenyl)-4-methylpent-4-en-1-ol 2.249

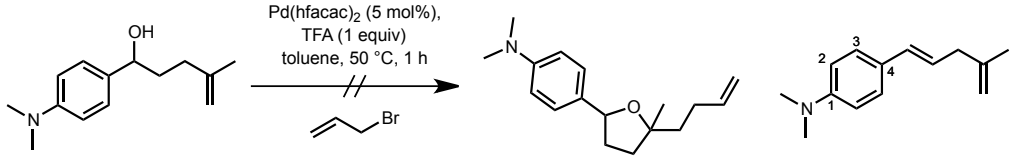


2.249

To a flask charged with magnesium turnings (430 mg, 18 mmol) and a crystal of iodine in THF (17 mL) was added 4-bromo-2-methylbutene **2.120** (5 M in hexanes, 2.0 mL, 10 mmol). The mixture was heated to reflux for 1 h then allowed to cool before portionwise addition of 4-(dimethylamino)benzaldehyde **2.248** (1.3 g, 8.6 mmol). The mixture was heated at reflux for 1 h then cooled to RT, poured onto ice and stirred for 30 minutes before addition of aq. HCl (1 M, 25 mL). The mixture was partitioned between Et_2O (50 mL) and sat. aq. $NaHCO_3$ (100 mL). The aqueous phase was further extracted with Et_2O (50 mL) and the combined organic extracts washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 17:3) afforded the title compound **2.249** as a green oil (1.6 g, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.24–7.22 (2H, m, 2 × ArH), 6.74–6.72 (2H, m, 2 × ArH), 4.73 (1H, s, 5-H_a), 4.72 (1H, s, 5-H_b), 4.59 (1H, t, *J* = 6.4 Hz, 1-H), 2.95 (6H, s, $N(CH_3)_2$), 2.17–2.11 (1H, m, 3-H_a), 2.06–2.00 (1H, m, 3-H_b), 2.00–1.93 (1H, m, 2-Ha), 1.89–1.82 (1H, m, 2-H_b), 1.74 (3H, s, 4-CH_3), 1.65 (1H, s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 150.4 (C), 145.8 (C), 132.6 (C), 127.1 (2 × CH), 112.7 (2 × CH), 110.1 (CH_2), 74.3 (CH), 40.3 (2 × CH_3), 36.7 (CH_2), 34.3 (CH_2), 22.7 (CH_3); IR (thin film) 1614, 1522, 1265 cm^{-1}; HRMS (EI) exact mass calculated for $C_{14}H_{21}ON$ $[M]^+$ *m/z* 219.1623, found *m/z* 219.1627.

Attempted cyclisation of 1-(4-(Dimethylamino)phenyl)-4-methylpent-4-en-1-ol 2.249; isolation of (*E*)-*N*,*N*-dimethyl-4-(4-methylpenta-1,4-dien-1-yl)aniline 2.252

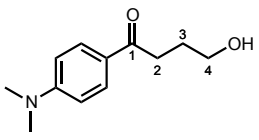


2.249 **2.250** *not observed* **2.252**

A 4 mL screw-top glass vial was charged with 1-(4-(dimethylamino)phenyl)-4-methylpent-4-en-1-ol **2.249** (72 mg, 0.33 mmol), toluene (1.3 mL), allyl bromide (0.14 mL, 1.6 mmol), TFA (25 µL, 0.33 mmol) and $Pd(hfacac)_2$ (8.5 mg, 0.02 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 pre-heated aluminium block for 1 h. The reaction mixture was cooled to RT then partitioned between Et_2O (15 mL) and NaOH (10% aq., 15 mL). The aqueous phase was further extracted with Et_2O (2 x 10 mL) and the combined organic extracts washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:Et_2O, 19:1) afforded (*E*)-*N*,*N*-dimethyl-4-(4-methylpenta-1,4-dien-1-yl)aniline **2.252** as a yellow oil (28 mg, 42%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.26 (2H, d, *J* = 8.8 Hz, 2 × 3-H), 6.68 (2H, d, *J* = 8.3 Hz, 2 × 2-H), 6.33 (1H, d, *J* = 15.8 Hz, Ar*CH*=CH), 6.01 (1H, dt, *J* = 15.7, 7.2 Hz, ArCH=*CH*), 4.77–4.76 (2H, m, C=CH_2), 2.94 (6H, s, N(CH_3)$_2$), 2.87 (2H, d, *J* = 7.1 Hz, CH=CH*CH_2*), 1.76 (3H, s, C(*CH_3*)=CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 150.0 (C), 145.4 (C), 131.3 (CH), 127.1 (2 × CH), 126.5 (C), 124.1 (CH), 112.7 (2 × CH), 110.7 (CH_2), 41.7 (CH_2), 40.8 (2 × CH_3), 22.6 (CH_3); IR (thin film) 1607, 1520, 1348, 1165 cm^{-1}; HRMS (EI) exact mass calculated for $C_{14}H_{19}N$ $[M]^+$ *m/z* 201.1517, found *m/z* 201.1515.

1-((4-Dimethylamino)phenyl)-4-hydroxybutan-1-one 2.259

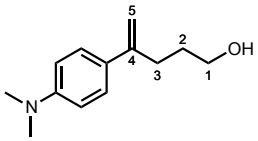


2.259

To mixture of magnesium turnings (160 mg, 6.5 mmol) and a crystal of iodine in THF (4 mL) was added a solution of 4-dimethylaminophenyl bromide (1.1 g, 5.5 mmol) in THF (1.5 mL). The mixture was heated at 60 °C for 1 h then, after cooling to RT, added dropwise to a cooled (0 °C) solution of γ-butyrolactone **2.257** (0.38 mL, 5.0 mmol) in CH_2Cl_2 (8 mL). The cooling bath was removed and the mixture allowed to warm to RT then stirred for 18 h. The reaction mixture was quenched with aq. HCl (1 M, 10 mL), poured into sat. aq. $NaHCO_3$ (50 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 2:3; repurification in petroleum ether:EtOAc, 1:3) afforded the title compound **2.259** (390 mg, 38%).

Melting point: 115–118 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.91–7.89 (2H, m, 2 × ArH), 6.66–6.64 (2H, m, 2 × ArH), 3.73 (2H, q, *J* = 5.8 Hz, 4-H_2), 3.07–3.04 (8H, m, 2-H_2, N(CH_3)$_2$), 2.20 (1H, t, *J* = 5.4 Hz, OH), 2.02–1.97 (2H, m, 3-H_2); ^{13}C NMR (125 MHz, $CDCl_3$) 199.0 (C), 153.6 (C), 130.5 (2 × CH), 124.9 (C), 110.8 (2 × CH), 62.9 (CH_2), 40.2 (2 × CH_3), 35.0 (CH_2), 27.5 (CH_2); IR (thin film) 2360, 1727, 1372, 1256 cm^{-1}; HRMS (EI) exact mass calculated for $C_{12}H_{17}O_2N$ $[M]^+$ *m/z* 207.1259, found *m/z* 207.1261.

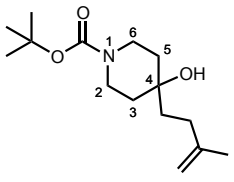
4-(4-(Dimethylamino)phenyl)pent-4-en-1-ol 2.260



2.260

To a suspension of methyl triphenylphosphonium bromide (1.4 g, 4.0 mmol) in THF (8 mL) was added a solution of potassium *tert*-butoxide (450 mg, 4.0 mmol) in THF (4 mL). The mixture was stirred at RT for 10 minutes then a solution of 1-((4-dimethylamino)phenyl)-4-hydroxybutan-1-one **2.259** (390 mg, 1.9 mmol) in THF (4 mL) was added dropwise. The mixture was stirred at RT for 4 h then quenched with water (5 mL) and partitioned between sat. aq. NH_4Cl (25 mL) and Et_2O (25 mL). The aqueous phase was further extracted with Et_2O (25 mL) and the combined organic extracts washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 17:1 then EtOAc, re-purified in petroleum ether:EtOAc, 3:1) afforded the title compound **2.260** (118 mg, 31%).
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35–7.33 (2H, m, 2 × ArH), 6.71–6.69 (2H, m, 2 × ArH), 5.21 (1H, d, *J* = 1.5 Hz, 5-H_a), 4.94 (1H, d, *J* = 1.3 Hz, 5-H_b), 3.67 (2H, q, *J* = 5.6 Hz, 1-H_2), 2.96 (6H, s, N(*CH_3*)$_2$), 2.58 (2H, t, *J* = 7.5 Hz, 3-H_2), 1.76–1.72 (2H, m, 2-H_2), 1.26 (1H, s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 150.2 (C), 147.4 (C), 128.8 (C), 126.9 (2 × CH), 112.4 (2 × CH), 109.4 (CH_2), 62.8 (CH_2), 40.7 (2 x CH_3), 31.6 (CH_2), 31.5 (CH_2); IR (thin film) 1610, 1518, 1346 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{19}ON$ $[M]^+$ *m/z* 205.1467, found *m/z* 205.1469.

***tert*-Butyl-4-hydroxy-4-(3-methylbut-3-en-1-yl)piperidine-1-carboxylate 2.264**

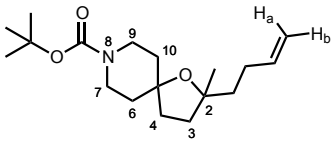


2.264

To a flask charged with magnesium turnings (250 mg, 10.3 mmol) and a crystal of iodine in Et_2O (6 mL) was added 4-bromo-2-methylbutene **2.120** (860 mg, 5.8 mmol). The mixture was heated to reflux for 30 minutes then cooled to 0 °C before dropwise addition of 1-boc-4-piperidone **2.263** (1.0 g, 5.0 mmol) in Et_2O (5 mL). Additional Et_2O (5 mL) was added and the mixture heated at reflux for 18 h then cooled to RT and quenched by dropwise addition of sat. aq. NH_4Cl (50 mL). The aqueous phase was extracted with Et_2O (2 × 50 mL) and the combined organic extracts washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 8:2 to 7:3 then CH_2Cl_2:EtOAc, 93:7) afforded the title compound **2.264** as a pale yellow oil (174 mg, 13%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.73 (1H, s, C=CH_a), 4.72 (1H, s, C=CH_b), 3.80 (2H, s, 2-H, 6-H), 3.16 (2H, s, 2-H, 6-H), 2.12–2.09 (2H, m, $CH_2CH_2C(CH_3)=CH_2$), 1.75 (3H, s, CH_3), 1.63–1.60 (2H, m, $CH_2CH_2C(CH_3)=CH_2$), 1.55–1.53 (4H, m, 3-H_2, 5-H_2), 1.45 (9H, s, $OC(CH_3)_3$), 1.28 (1H, s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 155.0 (C), 146.2 (C), 110.3 (CH_2), 79.5 (C), 70.0 (C), 40.9 (CH_2), 39.9 (2 × CH_2), 36.9 (2 × CH_2), 31.2 (CH_2), 28.6 (3 × CH_3), 22.7 (CH_3); IR (thin film) 3437, 2930, 1694, 1665, 1424, 1366, 1246, 1150 cm^1; HRMS (CI) exact mass calculated for $C_{15}H_{28}O_3N$ $[M+H]^+$ *m/z* 270.2069, found *m/z* 270.2066.

tert-Butyl-2-(but-3-en-1-yl)-2-methyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate 2.267



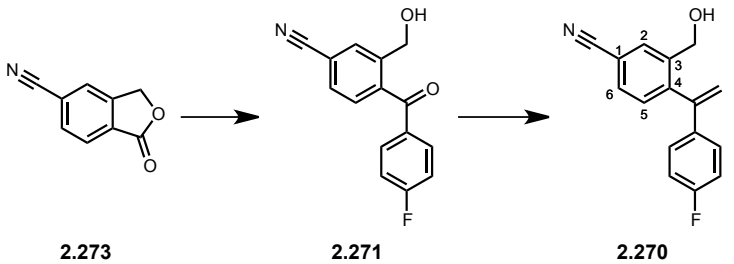
2.267

The general procedure was employed for the heterocyclisation of *tert*-butyl-4-hydroxy-4-(3-methylbut-3-en-1-yl)piperidine-1-carboxylate **2.264** (85 mg, 0.31 mmol) with allyl bromide (0.14 mL, 1.6 mmol) over 7 h. Purification of the reaction mixture by flash chromatography (CH_2Cl_2 then CH_2Cl_2:EtOAc, 9:1) afforded the title compound **2.267** as a colourless oil (70 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.88–5.79 (1H, m, *CH*=CH_2), 5.01 (1H, ddd, *J* = 17.1, 1.8, 1.6 Hz, CH=CH_a), 4.94–4.92 (1H, m, CH=CH_b), 3.46–3.38 (4H, m, 7-H_2, 9-H_2), 2.15–2.05 (2H, m, $CH_2CH_2CH=CH_2$), 1.89–1.71 (4H, m, 3-H_2, 4-H_2), 1.60–1.48 (6H, m, 6-H_2, 10-H_2, $CH_2CH_2CH=CH_2$), 1.45 (9H, s, $C(CH_3)_3$), 1.19 (3H, s, 2-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 155.1 (C), 139.3 (CH), 114.2 (CH_2), 83.0 (C), 80.4 (C), 79.4 (C), 41.8 (CH_2), 41.5 (2 × CH_2), 38.6 (CH_2), 38.1 (CH_2), 36.4 (CH_2), 36.3 (CH_2), 29.3 (CH_2), 28.6 (3 × CH_3), 27.7 (CH_3); IR (thin film) 1692, 1418, 1364, 1244, 1171, 1142 cm^{-1}; HRMS (EI) exact mass calculated for $C_{18}H_{31}O_3N$ $[M]^+$ *m/z* 309.2304, found *m/z* 309.2308.

4-(1-(4-Fluorophenyl)vinyl)-3-(hydroxymethyl)benzonitrile 2.270

Method A



2.273 **2.271** **2.270**

Following a modification of a reported procedure,[114] to mixture of magnesium turnings (200 mg, 8.2 mmol) and a crystal of iodine in THF (7 mL) was added 1-bromo-4-fluorobenzene (0.76 mL, 6.9 mmol). The mixture slowly warmed and refluxed gently at the neck of the flask. After 30 minutes the mixture had cooled to RT and was added by syringe to a cooled (0 °C) suspension of 5-cyanophthalide **2.273** (1.0 g, 6.3 mmol) in

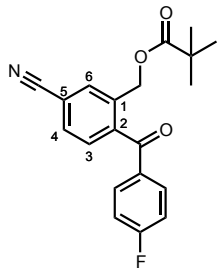
CH_2Cl_2 (10 mL). The cooling bath was removed and the mixture allowed to warm to RT then stirred for 20 h. The reaction mixture was quenched with sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was passed through a silica plug (petroleum ether:EtOAc, 7:3) to afford a yellow oil. The oil was taken up in THF (11 mL) and added dropwise to a prepared suspension of methyl triphenylphosphonium bromide (4.4 g, 12 mmol) and potassium *tert*-butoxide (1.4 g, 12 mmol) in THF (44 mL). The mixture was stirred at RT for 1.5 h then sat. aq. NH_4Cl (25 mL) added and the mixture extracted with Et_2O (50 mL). The organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography afforded the title compound **2.270** as a yellow oil (757 mg, 47% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.88 (1H, d, 2-H), 7.61 (1H, dd, *J* = 7.8, 1.6 Hz, 5-H), 7.33 (1H, d, *J* = 7.8 Hz, 6-H), 7.20–7.16 (2H, m, 2 × ArH), 7.02–6.98 (2H, m, 2 × ArH), 5.79 (1H, s, C=CH_a), 5.23 (1H, s, C=CH_b), 4.45 (2H, d, *J* = 5.8 Hz, *CH_2*OH), 1.78 (1H, t, *J* = 5.8 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 162.9 (d, ^1J (C-F) = 249 Hz, C), 145.9 (C), 144.6 (C), 140.5 (C), 135.5 (d, ^4J (C-F) = 4 Hz, C), 131.14 (CH), 131.12 (CH), 130.8 (CH), 128.3 (d, ^3J (C-F) = 8 Hz, 2 × CH), 118.9 (C), 116.6 (CH_2), 115.9 (d, ^2J (C-F) = 22 Hz, 2 × CH), 112.1 (C), 62.0 (CH_2); IR (thin film) 3439, 2231, 1601, 1507, 1224, 1160 cm^{-1}; HRMS (EI) exact mass calculated for $C_{16}H_{12}ONF$ $[M]^+$ *m/z* 253.0903, found *m/z* 253.0900.

Method B

To a solution of 5-cyano-2-(1-(4-fluorophenyl)vinyl)benzyl pivalate **2.286** (1.4 g, 4.0 mmol) in methanol (6.6 mL) was added sodium methoxide (5.4 M, 0.22 mL, 1.2 mmol). The mixture was stirred at RT for 3.5 h then concentrated *in vacuo*. The residue was partitioned between Et_2O (50 mL) and sat. aq. NH_4Cl (50 mL). The aqueous phase was further extracted with Et_2O (25 mL) and the combined organic extracts washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 4:1) afforded the title compound **2.270** as a colourless oil (0.79 g, 79%). Analytical data observed were in accordance with those previously obtained.

5-Cyano-2-(4-fluorobenzoyl)benzyl pivalate 2.285

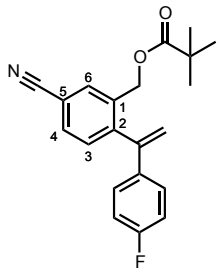


2.285

Following a reported procedure,[114] to mixture of magnesium turnings (200 mg, 8.2 mmol) and a crystal of iodine in THF (7 mL) was added 1-bromo-4-fluorobenzene (0.76 mL, 6.9 mmol). The mixture slowly warmed and refluxed gently at the neck of the flask. After 30 minutes the mixture had cooled to RT and was added by syringe to a cooled (0 °C) suspension of 5-cyanophthalide **2.273** (1.0 g, 6.3 mmol) in CH_2Cl_2 (10 mL). The cooling bath was removed and the mixture allowed to warm to RT then stirred for 18 h. Pivaloyl chloride (0.85 mL, 6.9 mmol) was added and the mixture heated to 60 °C for 2 h. The reaction mixture was poured into a cold (0 °C) solution of sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.285** as a yellow oil (1.8 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85–7.81 (3H, m, 6-H, 2×ArH), 7.72 (1H, dd, *J* = 7.9, 1.4 Hz, 4-H), 7.48 (1H, d, *J* = 7.8 Hz, 3-H), 5.18 (2H, $ArCH_2O$), 1.10 (9H, s, $C(CH_3)_3$). Analytical data observed were in accordance with literature values.[114]

5-Cyano-2-(1-(4-fluorophenyl)vinyl)benzyl pivalate 2.286



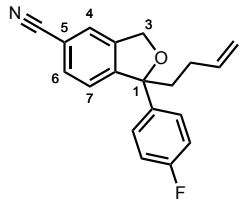
2.286

To a suspension of methyl triphenylphosphonium bromide (2.2 g, 13 mmol) in THF (6 mL) was added a solution of potassium *tert*-butoxide (700 mg, 6.2 mmol) in THF (6 mL), giving rise to a bright yellow suspension. After 15 minutes, a solution of 5-cyano-2-(4-fluorobenzoyl)benzyl pivalate **2.285** (1.8 g, 5.2 mmol) in THF (11 mL) was added. The resulting brown suspension was stirred at RT for 6 h, after which additional methyl triphenylphosphonium bromide (370 mg, 1.04 mmol) and potassium *tert*-butoxide (120 mg, 1.04 mmol) were added. Stirring at RT was continued for a further 17 h then the reaction mixture quenched with water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 19:1) afforded the title compound **2.286** as a colourless oil (1.4 g, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.71 (1H, d, *J* = 1.1 Hz, 6-H), 7.63 (1H, dd, *J* = 7.9, 1.7 Hz, 4-H), 7.35 (1H, d, *J* = 7.9 Hz, 3-H), 7.21–7.17 (2H, m, 2 × ArH), 7.02–6.98 (2H, m, 2 × ArH), 5.82 (1H, s, C=CH_a), 5.24 (1H, s, C=CH_b), 4.90 (2H, s, CH_2OPiv), 1.19 (9H, s, 3 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 178.0 (C), 163.1 (d, ^1J(C-F) = 249 Hz, C), 145.74 (C), 145.67 (C), 136.5 (C), 135.5 (d, ^4J(C-F) = 3.6 Hz, C), 131.9 (CH), 131.6 (CH), 131.1 (CH), 128.5 (d, ^3J(C-F) = 8.1 Hz, 2 × CH), 118.6 (C), 116.8 (CH_2), 115.9 (d, ^2J(C-F) = 21.6 Hz, 2 × CH), 112.4 (C), 63.0 (CH_2), 39.0 (C), 27.3 (3 × CH_3); IR (thin film) 1728,

1508, 1140 cm^{-1}; HRMS (EI) exact mass calculated for $C_{21}H_{20}O_2NF$ $[M]^+$ *m/z* 338.1556, found *m/z* 338.1550.

1-(But-3-enyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile 2.269

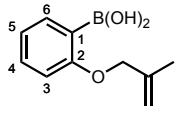


2.269

A 4 mL glass screw-top vial was charged with of 4-(1-(4-fluorophenyl)vinyl)-3-(hydroxymethyl)benzonitrile **2.270** (150 mg, 0.58 mmol)**,** allyl chloride (0.22 mL, 2.7 mmol), toluene (2.2 mL), $NaHCO_3$ (92 mg, 1.1 mmol) and $Pd(hfacac)_2$ (14 mg, 0.03 mmol). The mixture was heated at 50 °C for 8.5 h then additional $Pd(hfacac)_2$ (14 mg, 0.03 mmol) added. Heating was continued for a further 18 h then the mixture allowed to cool to RT and subjected directly to flash chromatography (petroleum ether:CH_2Cl_2, 1:1) to afford the title compound **2.269** as a yellow oil (98 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.60 (1H, d, *J* = 7.8 Hz, 6-H), 7.50 (1H, s, 4-H), 7.44–7.41 (2H, m, 2 × ArH), 7.39 (1H, d, *J* = 7.9 Hz, 7-H), 7.03–7.00 (2H, m, 2 × ArH), 5.81–5.73 (1H, m, CH_2CH_2CH=CH_2), 5.20 (1H, d, *J* = 13.0 Hz, 3-H_a), 5.15 (1H, d, *J* = 13.0 Hz, 3-H_b), 4.96–4.90 (2H, m, CH=CH_2), 2.32–2.26 (1H, m, CH_2CH_aCH=CH_2), 2.22–2.16 (1H, m, CH_2CH_bCH=CH_2), 2.09–2.01 (1H, m, $CH_a$$CH_2$CH=$CH_2$), 1.95–1.88 (1H, m, $CH_b$$CH_2$CH=$CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 162.2 (d, ^1J (C-F) = 247 Hz, C), 149.3 (C), 140.5 (C), 139.6 (d, ^4J (C-F) = 3 Hz, C), 137.9 (CH), 132.0 (CH), 126.9 (d, ^3J (C-F) = 8 Hz, 2 × CH), 125.3 (CH), 122.9 (CH), 118.7 (C), 115.5 (d, ^2J (C-F) = 21 Hz, 2 × CH), 114.8 (CH_2), 111.9 (C), 91.1 (C), 71.4 (CH_2), 40.6 (CH_2), 28.4 (CH_2); IR (thin film) 2231, 1506, 1479, 1225, 1159 cm^{-1}; HRMS (CI) exact mass calculated for $C_{19}H_{17}ONF$ $[M+H]^+$ *m/z* 294.1294, found *m/z* 294.1288.

2-(2-Methylallyloxy)phenylboronic acid 3.5



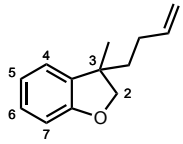
3.5

Following a reported procedure,[138] to a cooled (−78 °C) solution of 1-(2-methylallyloxy)-2-iodobenzene **3.11** (3.5 g, 13 mmol) and B(O*i*Pr)$_3$ (3.5 mL, 15 mmol) in THF (11 mL) was added dropwise *n*BuLi (2.3 M, 6.6 mL, 15 mmol). The mixture was stirred at −78 °C for 2.5 h then allowed to warm to −20 °C over 30 minutes and quenched with aq. HCl (2 M, 30 mL). The mixture was allowed to warm to RT and extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1 to 4:1) followed by recrystallisation from water (quant) afforded the title compound **3.5** as an off-white crystalline solid (1.7 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86 (1H, dd, *J* = 7.2, 1.6 Hz, 6-H), 7.43 (1H, td, *J* = 7.8, 1.8 Hz, 4-H), 7.04 (1H, t, *J* = 7.1 Hz, 5-H), 6.91 (1H, d, *J* = 8.4 Hz, 3-H), 5.97 (2H, s,

$B(OH)_2$), 5.12 (1H, s, C=CH_a), 5.07 (1H, s, C=CH_b), 4.56 (2H, s, CH_2C=CH_2), 1.87 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[138]

3-(But-3-en-1-yl)-3-methyl-2,3-dihydrobenzofuran 3.9

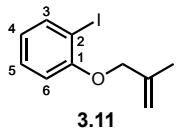


3.9

A 4 mL screw-top glass vial was charged with potassium (2-(2-methylallyloxy)phenyl)trifluoroborate **3.33** (84 mg, 0.33 mmol), DME (2.3 mL), allyl chloride (2.5 M in DME, 0.26 mL, 0.66 mmol), Na_2CO_3 (70 mg, 0.66 mmol) and Pd(hfacac)$_2$ (17 mg, 0.03 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 pre-heated aluminium block for 48 h. The reaction mixture was cooled to RT then filtered through a short silica plug, rinsing with petroleum ether:EtOAc, 9:1. The filtrate was concentrated *in vacuo* then purified by flash chromatography (petroleum ether:CH_2Cl_2, 9:1) to afford 3-(but-3-en-1-yl)-3-methyl-2,3-dihydrobenzofuran **3.9** (32 mg, 51%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.14 (1H, td, *J* = 7.7, 1.4 Hz, 6-H), 7.09 (1H, dd, *J* = 7.4, 1.3 Hz, 4-H), 6.89 (1H, td, *J* = 7.4, 1.0 Hz, 5-H), 6.80 (1H, d, *J* = 8.0 Hz, 7-H), 5.82–5.74 (1H, m, *CH*=CH_2), 5.00 (1H, ddd, *J* = 17.1, 3.4, 1.7 Hz, CH=*CH$_a$*), 4.95–4.92 (1H, m, CH=*CH$_b$*), 4.39 (1H, d, *J* = 8.7 Hz, 2-H_a), 4.18 (1H, d, *J* = 8.7 Hz, 2-H_b), 2.16–2.08 (1H, m, CH_2*CH$_a$*CH=CH_2), 1.93–1.85 (1H, m, CH_2*CH$_b$*CH=CH_2), 1.77–1.68 (2H, m, *CH*$_2$$CH_2$CH=$CH_2$), 1.37 (3H, s, 3-$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 159.7 (C), 138.5 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.6 (CH_2), 109.7 (CH), 82.5 (CH_2), 45.3 (C), 40.2 (CH_2), 29.1 (CH_2), 25.7 (CH_3); IR (thin film) 1480, 1459 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{16}O$ $[M]^+$ *m/z* 188.1201, found *m/z* 188.1202.

1-(2-Methylallyloxy)-2-iodobenzene 3.11



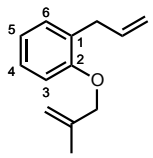
3.11

To a stirred suspension of K_2CO_3 (3.5 g, 26 mmol) in DMF (64 mL) was added 2-iodophenol **3.10** (2.8 g, 13 mmol) followed by 3-chloro-2-methyl-1-propene (1.5 mL, 15 mmol). The resulting mixture was heated at 70 °C for 17 h then cooled to RT, quenched with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **3.11** as a colourless oil (3.6 g, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):7.79 (1H, dd, *J* = 7.7, 2.8 Hz, 3-H), 7.31–7.27 (1H, m, 5-H), 6.81 (1H, dd, *J* = 8.1, 0.8 Hz, 6-H), 6.72 (1H, td, *J* = 7.6, 1.0 Hz, 4-H), 5.21 (1H, s, C=CH_a), 5.03 (1H, s, C=CH_b), 4.49 (2H, s, OCH_2), 1.88 (3H, s, CH_3). Analytical data observed were in accordance with literature values.[175]

1-Allyl-2-((2-methylallyl)oxy)benzene 3.14

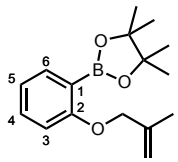
A sample of carboallylation side product 1-allyl-2-((2-methylallyl)oxy)benzene **3.14** was purified for analytical purposes.



3.14

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.19–7.16 (2H, m, 4-H, 6-H), 6.91 (1H, td, *J* = 7.4, 1.0 Hz, 5-H), 6.85 (1H, d, *J* = 8.1 Hz, 3-H), 6.07–5.98 (1H, m, CH_2CH=CH_2), 5.13 (1H, s, C(CH_3)=CH_a), 5.10–5.03 (2H, m, CH_2CH=CH_2), 4.99 (1H, s, C(CH_3)=CH_b), 4.44 (2H, s, OCH_2), 3.44 (2H, d, *J* = 6.7 Hz, CH_2CH=CH_2), 1.85 (3H, s, C(CH_3)=CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 156.4 (C), 141.2 (C), 137.2 (CH), 129.9 (CH), 129.0 (C), 127.3 (CH), 120.7 (CH), 115.5 (CH_2), 112.3 (CH_2), 111.6 (CH), 71.7 (CH_2), 34.6 (CH_2), 19.6 (CH_3); IR (thin film) 1491, 1451, 1238 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{16}O$ $[M]^+$ *m/z* 188.1201, found *m/z* 188.1997.

2-(2-Methylallyloxy)phenylboronic acid pinacol ester 3.32

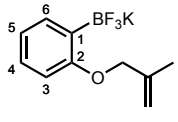


3.32

Following a modification of the reported procedure,[148] a mixture of 2-(2-methylallyloxy)phenylboronic acid **3.5** (500 mg, 2.6 mmol) and pinacol (307 mg, 2.6 mmol) in Et_2O (15 mL) was stirred at RT for 17 h then heated at reflux for 4 h. The mixture was cooled to RT and washed with brine (3 × 25 mL). The organic phase was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The ^{1}H NMR spectrum of the crude material indicated approximately 80% conversion so the residue was taken up Et_2O (15 mL), pinacol (92 mg, 0.8 mmol) added and the mixture refluxed for 16 h. The cooled reaction mixture was washed with water (25 mL), brine (2 × 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **3.32** as a colourless oil (650 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.68 (1H, dd, *J* = 7.3, 1.8 Hz, 6-H), 7.37 (1H, ddd, *J* = 8.8, 6.9, 1.4 Hz, 4-H), 6.94 (1H, td, *J* = 7.3, 0.8 Hz, 5-H), 6.84 (1H, d, *J* = 8.3 Hz, 3-H), 5.34–5.35 (1H, m, C=CH_a), 4.97–4.98 (1H, m, C=CH_b), 4.42 (2H, s, OCH_2), 1.86 (3H, s, CH_3), 1.35 (12H, s, 2 × C(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.4 (C), 141.1 (C), 136.9 (CH), 132.6 (CH), 120.4 (CH), 118.4 (C, observed indirectly by HMBC), 111.9 (CH_2), 111.6 (CH), 83.5 (2 × C), 71.6 (CH_2), 25.1 (4 × CH_3), 19.6 (CH_3); IR (thin film) 1670, 1438, 1300, 1246, 1196, 1142 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{16}H_{23}NaO_3B$ $[M+Na]^+$ *m/z* 296.1669, found *m/z* 296.1664.

Potassium (2-(2-methylallyloxy)phenyl)trifluoroborate 3.33



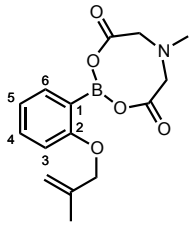
3.33

Following a reported procedure,[150] to a solution of 2-(2-methylallyloxy) phenylboronic acid **3.5** (500 mg, 2.6 mmol) in MeCN (10 mL) was added a solution of KF (600 mg, 10 mmol) in water (1.0 mL). A solution of (*L*)-tartaric acid (800 mg, 5.3 mmol) in THF (4.1 mL) was then added to the rapidly stirring solution and a white precipitate observed immediately. The mixture was stirred rapidly for 30 min then the precipitate removed by filtration, washing with further MeCN (15 mL). The

filtrate was concentrated under reduced pressure to afford the title compound **3.33** as a fluffy white solid (660 mg, quant.).

Melting point: 189–191 °C; ^{1}H NMR (500 MHz, DMSO) δ (ppm): 7.33 (1H, dd, *J* = 7.1, 1.8 Hz, 6-H), 7.00 (1H, td, *J* = 7.6, 1.8 Hz, 4-H), 6.71 (1H, t, *J* = 7.1 Hz, 5-H), 6.66 (1H, d, *J* = 8.1 Hz, 3-H), 5.19–5.18 (1H, m, C=CH_a), 4.89–4.88 (1H, m, C=CH_b), 4.31 (2H, s, OCH_2), 1.80 (3H, s, C(*CH_3*)=CH_2); ^{13}C NMR (125 MHz, DMSO) δ (ppm): 161.6 (C), 142.1 (C), 138.3 (C, observed indirectly by HMBC), 133.4 (q, ^{3}*J*(C-F) = 2.7 Hz, CH), 126.4 (CH), 119.2 (CH), 111..1 (CH_2), 111.0 (CH), 70.5 (CH_2), 19.3 (CH_3); IR (thin film) 1740, 1217 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{10}H_{11}F_3KNaOB$ $[M+Na]^+$ *m/z* 276.0421, found *m/z* 276.0423.

2-(2-Methylallyloxy)phenylboronic acid methyliminodiacetic acid ester 3.34



3.34

Following a modification of the reported procedure,[152] to a solution of 2-(2-methylallyloxy)phenylboronic acid **3.5** (86 mg, 0.50 mmol) in DMF (1.5 mL) was added methylimindodiacetic acid (74 mg, 0.50 mmol). The resulting suspension was heated at 85 °C for 24 h then filtered through an Isolute® Si-Carbonate cartridge (500 mg), rinsing with MeCN. The filtrate was concentrated *in vacuo* then partitioned between EtOAc (15 mL) and water (15 mL). The organic extracts were washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 1:2 then 0:1) afforded the title compound **3.34** as a colourless foam (100 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.69 (1H, d, *J* = 6.8 Hz, 6-H), 7.34 (1H, t, *J* = 7.7 Hz, 4-H), 6.99 (1H, t, *J* = 7.3 Hz, 5-H), 6.87 (1H, d, *J* = 8.4 Hz, 3-H), 5.02 (2H, s, C=CH_2), 4.46 (2H, s, OCH_2), 3.96 (4H, s, *CH_2*N(CH_3)*CH_2*), 2.71 (3H, s, NCH_3), 1.80 (3H, s, C(*CH_3*)=CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.0 (2 × C), 161.7 (C), 141.2 (C), 135.3 (CH), 131.5 (CH), 123.3 (C, observed indirectly by HMBC), 121.5 (CH), 114.3 (CH_2), 111.9 (CH), 72.7 (CH_2), 63.9 (2 × CH_2), 47.5 (CH_3), 19.7 (CH_3); IR (thin film) 1746, 1311, 1208, 1035, 1000 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{15}H_{18}NNaO_5B$ $[M+Na]^+$ *m/z* 325.1207, found *m/z* 325.1195.

5. References

[1] Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed., Wiley-Blackwell, **2010**.

[2] Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat*. *Prod*. *Rep*. **2005**, *22*, 269–303.

[3] Kang, E. J.; Lee, E. *Chem*. *Rev*. **2005**, *105*, 4348–4378.

[4] Saleem, M.; Kim, H. J.; Alic, M. S.; Lee, Y. S. *Nat*. *Prod*. *Rep*. **2005**, *22*, 696–716.

[5] Deiters, A.; Martin, S. F. *Chem*. *Rev*. **2004**, *104*, 2199–2238.

[6] Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261–290.

[7] Evano, G.; Blanchard, N.; Toumi, N. *Chem*. *Rev*. **2008**, *108*, 3054–3131.

[8] a) Weibel, J.-M.; Blanc, A.; Pale, P. *Chem*. *Rev*. **2008**, *108*, 3149–3173. b) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem*. *Rev*. **2008**, *108*, 3174–3198.

[9] Qian, H.; Han, X.; Widenhoefer, R. A. *J*. *Am*. *Chem*. *Soc*. **2004**, *126*, 9536–9537.

[10] Li, Z.; Brouwer, C.; He, C.; *Chem*. *Rev*. **2008**, *108*, 3239–3265.

[11] a) Nakamura, I.; Yamamoto, Y. *Chem*. *Rev*. **2004**, *104*, 2127−2198. b) Zeni, G.; Larock, R. C. *Chem*. *Rev*. **2004**, *104*, 2285–2309.

[12] For reviews, see: a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. b) Nicolaou, K. C.; Chen, J. S. *Chem*. *Soc*. *Rev*. **2009**, *38*, 2993–3009. c) Touré, B. B.; Hall, D. G. *Chem*. *Rev*. **2009**, *109*, 4439–4486.

[13] Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Kojer, H.; Rttinger, R. *Angew*. *Chem*. **1959**, *71*, 176–182.

[14] Keith, J. A.; Henry, P. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9038–9049.

[15] For reviews, see: a) Bäckvall, J.-E. *Acc*. *Chem*. *Res*. **1983**, *16*, 335–342. b) Sigman, M. S.; Jensen, K. H. *Org*. *Biomol*. *Chem*. **2008**, *6*, 4083–4088. c) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem*. *Rev*. **2011**, *111*, 2981–3019.

[16] Hosokawa, T.; Maeda, K.; Koga, K.; Moritani, I. *Tetrahedron Lett*. **1973**, *10*, 739–740.

[17] Hosokawa, T.; Ohkata, H.; Moritani, I. *Bull*. *Chem*. *Soc*. *Jpn*. **1975**, *48*, 1533–1536.

[18] Hosokawa, T.; Hirata, M.; Murahashi, S.-I.; Sonada, A. *Tetrahedron Lett*. **1976**, *21*, 1821–1824.

[19] Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J*. *Org*. *Chem*. **1977**, *42*, 1329–1336.

[20] Larock, R. C.; Hightower, T. R. *J*. *Org*. *Chem*. **1993**, *58*, 5298–5300.

[21] Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett*. **1995**, *36*, 7749–7752.

[22] Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J*. *Am*. *Chem*. *Soc*. **2005**, *127*, 17778–17788.

[23] Hosokawa, T.; Okuda, C.; Murahashi, S.-I. *J*. *Org*. *Chem*. **1985**, *50*, 1282–1287.

[24] Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J*. *Org*. *Chem*. **1999**, *64*, 1620–1625.

[25] Wang, F.; Yang, G.; Zhang, Y. J.; Zhang, W. *Tetrahedron* **2008**, *64*, 9413–9416.

[26] Zhang, Y. J.; Wang, F.; Zhang, W. *J. Org. Chem.* **2007**, *72*, 9208–9213.

[27] Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036–3037.

[28] Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335.

[29] Doroski, T. A.; Cox, M. R.; Morgan, J. B. *Tetrahedron Lett.*, **2009**, *50*, 5162–5164.

[30] Li, Y.; Song, D.; Dong, V. *J. Am. Chem. Soc.* **2008**, *130*, 2962–2964.

[31] Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737–5740.

[32] Bodurow, C.; Semmelhack, M. F. *J. Am. Chem. Soc.* **1984**, *106*, 1496–1498.

[33] Tietze, L. F.; Jackenkroll, S.; Raith, C.; Spiegl, D. A.; Reiner, J. R.; Campos, M. C. O. *Chem. Eur. J.* **2013**, *19*, 4876–4882.

[34] Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, *34*, 7205–7208.

[35] Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257–259.

[36] Tietze, L. F.; Stecker, F.; Zinngrebe, J.; Sommer, K. M. *Chem. Eur. J.* **2006**, *12*, 8770–8776.

[37] Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099–3107.

[38] a) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810–3813. b) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179–4181 and references therein.

[39] Ward, A. F.; Xu, Y.; Wolfe, J. P. *Chem. Commun.* **2012**, *48*, 609–611.

[40] Ward, A. F.; Wolfe, J. P. *Org. Lett.* **2009**, *11*, 2209–2212.

[41] Matsuura, B. S.; Condie, A. G.; Buff, R. C.; Karahalis, G. J.; Stephenson, C. R. J. *Org. Lett.* **2011**, *13*, 6320–6323.

[42] Zhu, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1926–1929.

[43] Nicolai, S.; Erard, S.; Fernández González, D.; Waser, J. *Org. Lett.* **2010**, *12*, 384–387.

[44] Nicolai, S.; Waser, J. *Org. Lett.* **2011**, *13*, 6324–6327.

[45] Nicolai, S.; Sedigh-Zadeh, R.; Waser, J. *J. Org. Chem.* **2013**, *78*, 3783–3801.

[46] Deng, Y.; Perrson, A. K. Å.; Bäckvall, J.-E. *Chem. Eur. J.* **2012**, *18*, 11498–11523.

[47] Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680.

[48] Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1988**, *29*, 4687–4690.

[49] Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291–5294.

[50] Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144–6148.

[51] Akiyama, K.; Mikami, K. *Heterocycles* **2007**, *74*, 827–834.

[52] Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 1778–1780.

[53] Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14916–14919.

[54] Liu, H.; Li, C.; Qiu, D.; Tong, X. *J. Am. Chem. Soc.* **2011**, *133*, 6187–6193.

[55] Aggarwal, V. K.; Davies, P. W.; Moss, W. O. *Chem*. *Commun*. **2002**, 972–973.

[56] Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron*, **1997**, *53*, 11803–11826.

[57] Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron*, **2000**, *56*, 7525–7539.

[58] Oh, C. H.; Sung, H. R.; Park, S. J.; Ahn, K. H. *J. Org*. *Chem*. **2002**, *67*, 7155–7157.

[59] For reviews, see: a) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412–9423. b) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem*. *Soc*. *Rev*. **2010**, *39*, 712–733. c) Sehnal, P. Taylor, R. J. K.; Fairlamb, I. J. S. *Chem*. *Rev*. **2010**, *110*, 824–889. d) Hickman, A. J.; Sanford, M. S. *Nature*, **2012**, *484*, 177–185.

[60] a) Stille, J. K.; Lau, K. S. Y. *J. Am*. *Chem*. *Soc*. **1976**, *98*, 5841–5849. b) Ito, T.; Tsuchiya, H.; Yamamoto, A. *Bull*. *Chem*. *Soc*. *Jpn*. **1977**, *50*, 1319–1327. c) Milstein, D.; Stille, J. K. *J*. *Am*. *Chem*. *Soc*. **1979**, *101*, 4981–4991.

[61] Byers, P. K.; Canty, A. J.; Skelton, B. W.; White, A. H. *J. Chem*. *Soc*. *Chem*. *Commun*. **1986**, 1722–1724.

[62] Byers, P. K.; Canty, A. H. *J. Chem*. *Soc*. *Chem*. *Commun*. **1988**, 639–641.

[63] Catellani, M.; Motti, E.; Minari, M. *Chem*. *Commun*. **2000**, 157–158.

[64] Horino, H.; Arai, M.; Inoue, N. *Tetrahedron Lett*. **1974**, *15*, 647–650.

[65] Catellani, M.; Mann, B. E. *J. Organomet*. *Chem*. **1990**, *390*, 251–255.

[66] Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 119–122.

[67] Motti, E.; Rossetti, M.; Bocelli, G.; Catellani, M. *J. Organomet*. *Chem*. **2004**, *689*, 3741–3749.

[68] Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045–1046.

[69] Deprez, N. R.; Sanford, M. S. *Inorg*. *Chem*. **2007**, *46*, 1924–1935.

[70] Wang, A.; Jiang, H.; Chen, H. *J. Am*. *Chem*. *Soc*. **2009**, *131*, 3846–3847.

[71] Takenaka, K.; Dhage, Y. D.; Sasai, H. *Chem*. *Commun*. **2013**, *49*, 11224–11226.

[72] Tong, X.; Beller, M.; Tse, M. K. *J. Am*. *Chem*. *Soc*. **2007**, *129*, 4906–4907.

[73] Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am*. *Chem*. *Soc*. **2007**, *129*, 5836–5837.

[74] Tsujihara, T.; Takenaka, K.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Am*. *Chem*. *Soc*. **2009**, *131*, 3452–3453.

[75] For reviews, see: a) Luh, T.-Y.; Leung, M.; Wong, K.-T. *Chem*. *Rev*. **2000**, *100*, 3187–3204. b) Cárdenas, D. J. *Angew*. *Chem*., *Int*. *Ed*. **2003**, *42*, 384–387. c) Frisch, A. C.; Beller, M. *Angew*. *Chem*., *Int. Ed*. **2005**, *44*, 674–688. d) Rudolph, A.; Lautens, M. *Angew*. *Chem*., *Int. Ed*. **2009**, *48*, 2656–2670. e) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem*. *Rev*. **2011**, *111*, 1417–1492.

[76] Parrill, A. L.; Dolata, D. P. *J. Mol. Struct. (Theochem)*, **1996**, *370*, 187–202.

[77] Hitchcock, S. A.; Houldsworth, S. J.; Pattenden G.; Pryde, D. C.; Thomson, N. M.; Blake, A. J. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 3181–3206.

[78] Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6192.

[79] Banwell, M. G.; McLeod, M. D.; Riches, A. G. *Aust. J. Chem.* **2004**, *57*, 53–66.

[80] Dodgson, J. W. *J. Chem. Soc., Trans.* **1914**, *105*, 2435–2443.

[81] Pache, S.; Lautens, M. *Org. Lett.* **2003**, *5*, 4827–4830.

[82] Doroski, T. A.; Cox, M. R.; Morgan, J. B. *Tetrahedron Lett.* **2009**, *50*, 5162–5164.

[83] Burk, R. M.; Gac, T. S.; Roof, M. B. *Tetrahedron Lett*, **1994**, *35*, 8111–8112.

[84] Lundquist IV, J. Q.; Satterfield, A. D. Pelletier, J. C. *Org. Lett.* **2006**, *8*, 3915–3918.

[85] Giguere, R. J.; Bray, T. L.; Duncan, S. M. *Tetrahedron Lett.* **1986**, *27*, 4945–4948.

[86] Murty, K. V. S. N.; Pal, R.; Datta, K.; Mal, D. *Synth. Comm.* **1994**, *24*, 1287–1292.

[87] Brower, K. R. *J. Am. Chem. Soc.* **1961**, *83*, 4370–4372.

[88] Walling, C.; Naiman, M. *J. Am. Chem. Soc.* **1962**, *84*, 2628–2632.

[89] Canty, A. J.; Lee, C. V. *Organometallics*, **1982**, *1*, 1063–1066.

[90] Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9409–9412.

[91] Rudolph, J.; Chen, L.; Majumdar, D.; Bullock, W. H.; Burns, M.; Claus, T.; Dela Cruz, F. E.; Daly, M.; Ehrgott, F. J.; Johnson, J. S.; Livingston, J. N.; Schoenleber, R. W.; Shapiro, J.; Yang, L.; Tsutsumi, M.; Ma, X. *J. Med. Chem.* **2007**, *50*, 984–1000.

[92] Borgulya, J.; Madeja, R.; Fahrni, P.; Hansen, H.-J.; Schmid, H.; Barner, R. *Helv. Chim. Acta*, **1973**, *56*, 14–75.

[93] Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205–247.

[94] Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130–4133.

[95] Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5531–5534.

[96] Bingham, D.; Hudson, B.; Webster, D. E.; Wells, P B. *J. Chem. Soc. Dalton Trans.* **1974**, 1521–1524.

[97] Chrisope, D. R.; Beak, P.; Saunders W. H. Jr. *J. Am. Chem. Soc.* **1988**, *110*, 230–238.

[98] Bray, K. L.; Charmant, J. P. H.; Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Eur. J.* **2001**, *7*, 4205–4215.

[99] Moiseev, I. I.; Stromnova, T. A.; Vargaftik, M. N. *J. Mol. Catal. A*, **1994**, *86*, 71–94.

[100] Tsuji, J. *Palladium Reagents and Catalysts – New Perspectives for the 21st Century*, John Wiley & Sons Ltd., Chichester, England, **2004**, 656.

[101] Spallek, M. J.; Stockinger, S.; Goddard, R.; Trapp, O. *Adv. Synth. Catal.*, **2012**, *354*, 1466–1480.

[102] Cooper, A. C.; Caulton, K. G. *Inorg. Chim. Acta*, **1996**, *251*, 41–51.

[103] Bergstrom, D. E.; Ruth, J. L.; Warwick, P. *J. Org. Chem.* **1981**, *46*, 1432–1441.

[104] Mercola, M.; Dawson, M.; Cashman, J. WO Patent 2010/33643, **2010**.

[105] Berkowitz, W. F.; Wu, Y. *J. Org. Chem.* **1997**, *62*, 1536–1539.

[106] Blomberg, C.; Sallinger, R, M.; Mosher, H. S. *J. Org. Chem.*, **1969**, *34*, 2385–2388.

[107] Ashby, E. C.; Walker, F. W.; Neumann, H. M. *Chem. Comm.* **1970**, 330–332.

[108] Ashby, E. C.; Neumann, H. M.; Walker, F. W.; Laemmle, J.; Chao, L.-C. *J. Am. Chem. Soc.* **1972**, *94*, 3330–3337.

[109] Ashby, E. C.; Buhler, J. D. Lopp, I. G.; Wiesemann, T. L.; Bowers, J. S. Jr.; Laemmle, J. T. *J. Am. Chem. Soc.* **1976**, *98*, 6561–6570.

[110] Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure & Appl. Chem.* **1990**, *62*, 2035–2040.

[111] McCormick, M.; Monahan III, R.; Soria, J.; Goldsmith, D.; Liotta, D. *J. Org. Chem.* **1989***, 54*, 4485–4487.

[112] Bauer, M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 2205–2208.

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

[114] Rock, M. H.; Petersen, H.; Ellegaard, P. WO Patent 2000/012044, **2000**.

[115] Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.*, **2010**, *132*, 10706–10716.

[116] Zawisza, A.; Fenêt, B.; Sinou, D. *Eur. J. Org. Chem.* **2007**, 2296–2309.

[117] Uenishi, J.; Vikhe, Y. S.; Kawai, N. *Chem. Asian. J.* **2008**, *3*, 473–484.

[118] Dreis, A. M.; Douglas, C. J. *J. Am. Chem. Soc.* **2009**, *131*, 412–413.

[119] Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052–2053.

[120] Zheng, H.; Lejkowski, M.; Hall, D. G. *Chem. Sci.* **2011**, *2*, 1305–1310.

[121] Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26–47.

[122] Merlic, C. A.; Semmelhack, M. F. *J. Organomet. Chem.* **1990**, *391*, C23–C27.

[123] Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. *Organometallics* **2001**, *20*, 3724–3728.

[124] Boland, W.; Ney, P.; Jaenicke, L. *Synthesis*, **1980**, *12*, 1015–1017.

[125] Moody, C. J. *J. Chem. Soc. Perkin. Trans. 1*, **1984**, 1333–1337.

[126] Heller, S. T.; Schultz, E. E.; Sarpong, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 8304–8308.

[127] Li, H.; Boonnak, N.; Padwa, A. *J. Org. Chem.* **2011**, *76*, 9488–9496.

[128] Bøgesø, K. P.; Toft, A. S. US Patent 4136193, **1979**.

[129] Butler, S. G.; Meegan, M. J. *Curr. Med. Chem.* **2008**, *15*, 1737–1761.

[130] Waugh, J.; Goa, K. L. *CNS Drugs* **2003**, *17*, 343–362.

[131] Bøgesø, K. P. US Patent 4650884, **1987**.

[132] Bøgesø, K. P.; Perregaard, J. EP 0347066 A1, **1989**.

[133] Bech Sommer, M.; Nielsen, O.; Pedersen, H.; Ahmadian, H.; Pedersen, H.; Brøsen, P.; Geiser, F.; Lee, J.; Cox, G.; Dapremont, O.; Steu, C.; Assenza, S. P.; Hariharan, S.; Nair, U. WO Patent 03/006449, **2003**.

[134] Le Bras, J.; Muzart, J. *Tetrahedron* **2012**, *68*, 10065–10113.

[135] Lewis Williams, 2nd Year PhD Report, University of Glasgow, 2013.

[136] Zhu, G.; Lu, X. *Organometallics*, **1995**, *14*, 4899–4904.

[137] Liu, G.; Lu, X. *Tetrahedron Lett*. **2002**, *43*, 6791–6794.

[138] Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. *Org*. *Lett*. **2011**, *13*, 5628–5631.

[139] Fraser, A. W.; Besaw, J. E.; Hull, L. E.; Baird, M. C. *Organometallics* **2012**, *31*, 2470–2475.

[140] Scrivanti, A; Beghetto, V.; Bertoldini, M.; Matteoli, U. *Eur*. *J*. *Org*. *Chem*. **2012**, 264–268.

[141] Williams, F. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *50*, 4459–4463.

[142] He, P.; Lu Y.; Hu, Q.-S. *Tetrahedron Lett*. **2007**, *48*, 5283–5288.

[143] Amatore, C.; Jutand, A.; Le Duc, G. *Chem*. *Eur*. *J*. **2012**, *18*, 6616–6625.

[144] Lennox, A. J. J.; Lloyd-Jones, G. C. *J*. *Am*. *Chem*. *Soc*. **2012**, *134*, 7431–7441.

[145] Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J*. *Am*. *Chem*. *Soc*. **2013**, *135*, 6830–6833.

[146] Lennox, A. J. J.; Lloyd-Jones, G. C. *Isr*. *J*. *Chem*. **2010**, *50*, 664–674.

[147] Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem*. *Soc*. *Rev*. **2014**, *43*, 412–443.

[148] Oehlke, A.; Auer, A. A.; Jahre, I.; Walfort, B.; Rüffer, T. Zoufalá, P.; Lang, H.; Spange, S. *J*. *Org*. *Chem*. **2007**, *72*, 4328–4339.

[149] Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones G. C.; Murray, P. M. *Angew*. *Chem*., *Int*. *Ed*. **2010**, *49*, 5156–5160.

[150] Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 9385–9388.

[151] Gillis, E. P.; Burke, M. D. *J*. *Am*. *Chem*. *Soc*. **2007**, *129*, 6716–6717.

[152] Grob, J. E.; Nunez, J.; Dechantsreiter, M. A.; Hamann, L. G. *J*. *Org*. *Chem*. **2011**, *76*, 4930–4940.

[153] Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J*. *Am*. *Chem*. *Soc*. **2009**, *131*, 6961–6963.

[154] Burfield, D. R.; Lee, K.-H.; Smithers, R. H. *J*. *Org*. *Chem*. **1977**, *42*, 3060–3065.

[155] Barder, T. E.; Buchwald, S. L. *Org*. *Lett*. **2004**, *6*, 2649–2652.

[156] S. P. Thomas, B. M. Partridge, V. K. Aggarwal, *Tetrahedron*, **2011**, *67*, 10082–10088.

[157] 9-Br-BBN was prepared by the reaction of 9-BBN with BBr_3 as outlined in Brown, J. C.; Kulkarni, S. U. *J*. *Organomet*. *Chem*. **1979**, *168*, 281–293 and stored at –18 °C under Ar.

[158] Shapland, P. D. P.; Thomas, E. J. *Tetrahedron*, **2009**, *65*, 4201–4211.

[159] Kim, J.; Li, H. B.; Rosenthal, A. S.; Sang, D.; Shapiro, T. A.; Bachi, M. D.; Posner, G. H. *Tetrahedron*, **2006**, *62*, 4120–4127.

[160] Jiménez-Estrada, M.; Navarro, A.; Flores M. V.; Chilpa, R. R.; Hernández, B.; Anaya, A. L.; Lotina-Hennsen, B. *J*. *Agric*. *Food*. *Chem*. **1996**, *44*, 2839–2841.

[161] Li, F.-N.; Kim, N.-J.; Paek, S.-M.; Kwon, D.-Y.; Park, H.-G.; Suh, Y.-G.; Min, K. H.; Jeong, Y.-S.; Kim, S.-Y.; Park, Y.-H.; Kim, H.-D. *Bioorg*. *Med*. *Chem*. **2009**, *17*, 3557–3567.

[162] Kyoung M. K.; Hyoung R. K.; and Eung K. R. *Heterocycles*, 1993, *36*, 497–505.

[163] Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8559–8568.

[164] Fernández-Mateos, A.; Herrero Teijón, P.; Mateos Burón, L.; Rabanedo Clemente, R.; Rubio Gonazález, R. *J. Org. Chem.*, **2007**, *72*, 9973–9982.

[165] Park, H.; Hong, Y.-L.; Kim, Y. B.; Choi, T.-L. *Org. Lett.*, **2010**, 12, 3442–3445.

[166] Rao Volla, C. M.; Vogel, P.; Dubbaka, S. R. *Tetrahedron*, **2009**, *65*, 504–511.

[167] Yang, C.-G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett.* **2005**, *7*, 4553–4556.

[168] Bulger, P. G.; Moloney, M. G.; Trippier, P. C. *Org. Biomol. Chem.* **2003**, *1*, 3726–3737.

[169] Marion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653–2656.

[170] Breit, B.; Zahn, S. K. *J. Org. Chem.* **2001**, *66*, 4870–4877.

[171] Brimble, M. A.; Flowers, C. L.; Trzoss, M.; Tsang, K. Y. *Tetrahedron*, **2006**, *62*, 5883–5896.

[172] Trivedi, R.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 5650–5652.

[173] Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901–12903.

[174] Miege, F.; Meyer, C.; Cossy, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5932–5937.

[175] Yamane, M.; Kubota, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 331–340.