Palladium-Catalysed Synthesis of Highly Functionalised Compounds

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

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November 2017

Abstract

Palladium-catalysis is extremely important in fine chemical synthesis. This thesis looks at the development of new palladium-catalysed carbon–carbon bond formation reactions, with particular attention to forming new bonds to sp^3 carbons.

The opening chapter of this thesis gives an overview of current methods for palladium-catalysed heterocyclisation, and the methods for incorporating further functionalisation into this process, then focuses on the optimisation and expansion of a new palladium-catalysed carboallylation reaction. The reaction mechanism was demonstrated *via* a deuterium-labelling study, confirming that the reaction proceeds through an isohypsic mechanism.

Chapter 2 begins with a summary of palladium-catalysed isohypsic reactions, and the introduction of the isohypsic–redox sequence. New results are presented on the expansion of this isohypsic–redox sequence to include the oxyallylation–Heck-coupling, and work on the aminoallylation–Grubbs–Wacker oxidation.

Chapter 3 commences with an introduction to MIDA boronates, describing their useful properties along with some uses, particularly in step-wise synthesis. The development of a new palladium-catalysed allylation of MIDA boronates is then detailed. Using MIDA boronates to form a new bond to an sp^3 carbon for the first time, this was applicable to a range of allyl halides as well as a large number of MIDA boronates containing a range of functionality. Formation of a new sp^3–sp^3 carbon–carbon bond was explored, as well as an enantioselective allylation. The application of the allylation was demonstrated in the development of a new palladium-catalysed synthesis of Ibuprofen.

Experimental procedures and data are summarised in Chapter 4. An appendix containing NMR spectra for new compounds is attached.

Contents

Acknowledgements

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

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

Thanks to the other members of the France group, past and present. A special thank you goes to Jo Hewitt, Lewis Williams and Craig Smith for their guidance and making the lab a more enjoyable place. Stuart Ruddell and Glen Brodie must also be thanked, and I wish Glen all the best in his relentless quest to sell hoodies. Thanks to Gi Lum Tang for being my first student, and her great work on MIDA boronates. I would also like to thank all the Prunet, Marquez and Clark group members past and present.

Finally, I would like to thank all my friends and family for their support and encouragement over the past years.

Author's Declaration

This thesis represents the original work of David John Phillips unless otherwise explicitly stated in the text. The research was carried out at the University of Glasgow in the Raphael and Henderson Laboratories under the supervision of Dr. David France during the period of October 2013 to May 2017.

Abbreviations

Ac	acetyl
Alk	alkyl
aq.	aqueous
atm.	atmosphere
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
°C	degrees centigrade
cat.	catalytic
CI	chemical ionisation
COP	cobaltocenyloxazoline palladacycle
COSY	correlation spectroscopy
d	doublet
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEA	diethanolamine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide

dppe	diphenylphosphorylethane
dppm	diphenylphosphorylmethane
dppf	diphenylphosphorylferrocene
dppp	diphenylphosphorylpropane
dr	diasteriomeric ratio
ee	enantiomeric excess
EI	electron impact
equiv	equivalents
ESI	electrospray ionisation
Et	ethyl
Et2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
FTIR	Fourier transform infrared spectroscopy
Fur	furyl
g	gram(s)
h	hour(s)
hfacac	hexafluoroacetylacetonate
HMBC	heteronuclear multiple bond correlation
HMDS	bis(trimethylsilyl)amine
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation
Hz	hertz

IR	infrared
J	NMR spectra coupling constant
M	molar
m	multiplet
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram(s)
MHz	megahertz
MIDA	methyliminodiacetic acid
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mol(es)
Ms	methanesulfonyl
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
Ph	phenyl
Pin	pinacol
Piv	pivalyl
PMB	*p*-methoxybenzene
ppm	parts per million

q	quartet
quant.	quantitative
s	singlet
sat.	saturated
rt	room temperature
t	triplet
TBDPSE	tert-Buyldiphenylsilylethyl
Temp	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMG	Tetramethylguanidine
TMS	trimethylsilane
o-tol	*o*-tolyl
Ts	4-toluenesulfonyl
TSE	trimethylsilylethyl
µL	microlitre(s)

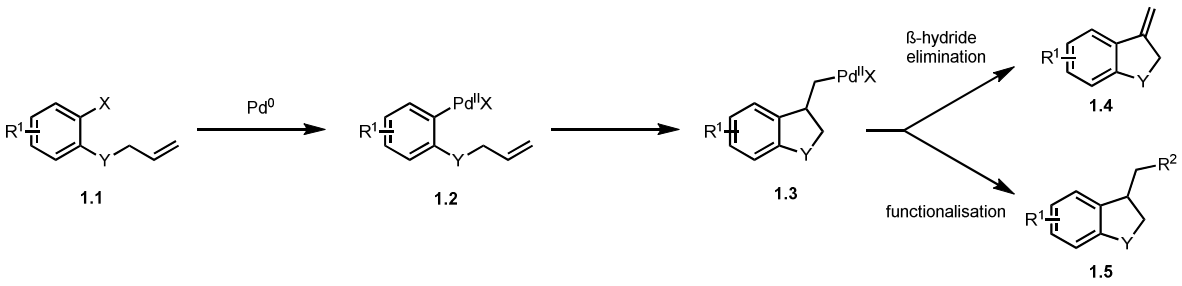
1 Pd-catalysed formation of heterocycles

1.1 Introduction

Palladium catalysis is widely used in formation of heterocycles.[1, 2] It is particularly useful due to the wide range of reactivity available both during cyclisation and further functionalisation. This chapter describes some of the methods used to carry out both heterocyclisation and further functionalisation. After examining various different ways of initiating heterocyclisation, the development of a carboallylation reaction forming a new sp^3–sp^3 carbon–carbon bond is shown.

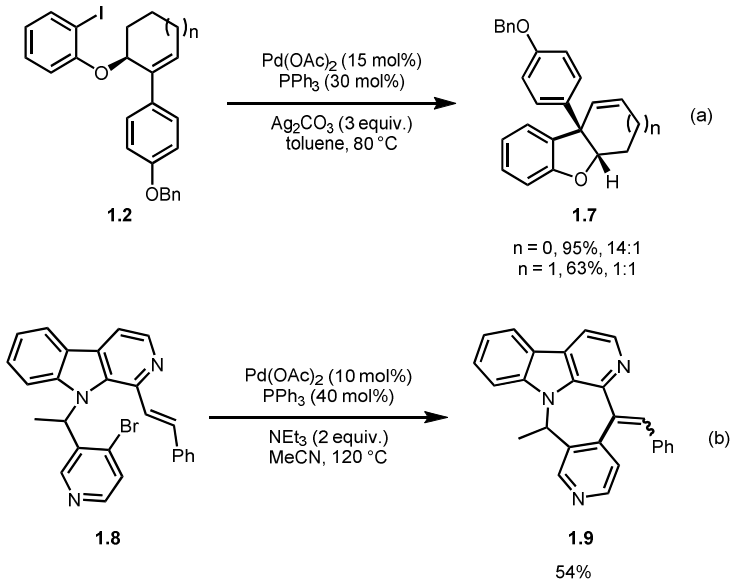
1.1.1 C–X initiated heterocyclisation

Aryl halides provide a widely available source to initiate heterocyclisation. Oxidative addition with a Pd(0) catalyst forms Pd(II) intermediate **1.2** (Scheme 1). After heterocyclisation has occurred, termination can occur via simple β-elimination, or the complex **1.3** can undergo further functionalisation giving access to a large selection of functionally diverse products.



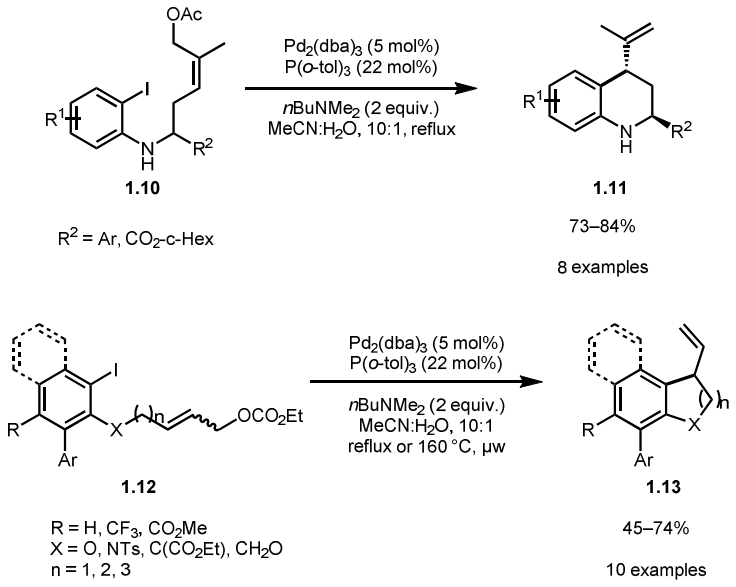
Scheme 1.1: Palladium-catalysed heterocyclisation

The simplest method of termination is ß-hydride elimination. This involves an intramolecular Heck-type reaction to form the desired heterocycles, such as dihydrobenzofurans (Scheme 1.2a).[3, 4] While this is a simple process, it can result in the formation of complex structures such as **1.9**, a key intermediate in the synthesis of maxonine (Scheme 1.2b).



Scheme 1.2: Heterocyclisation via intramolecular Heck-type reaction

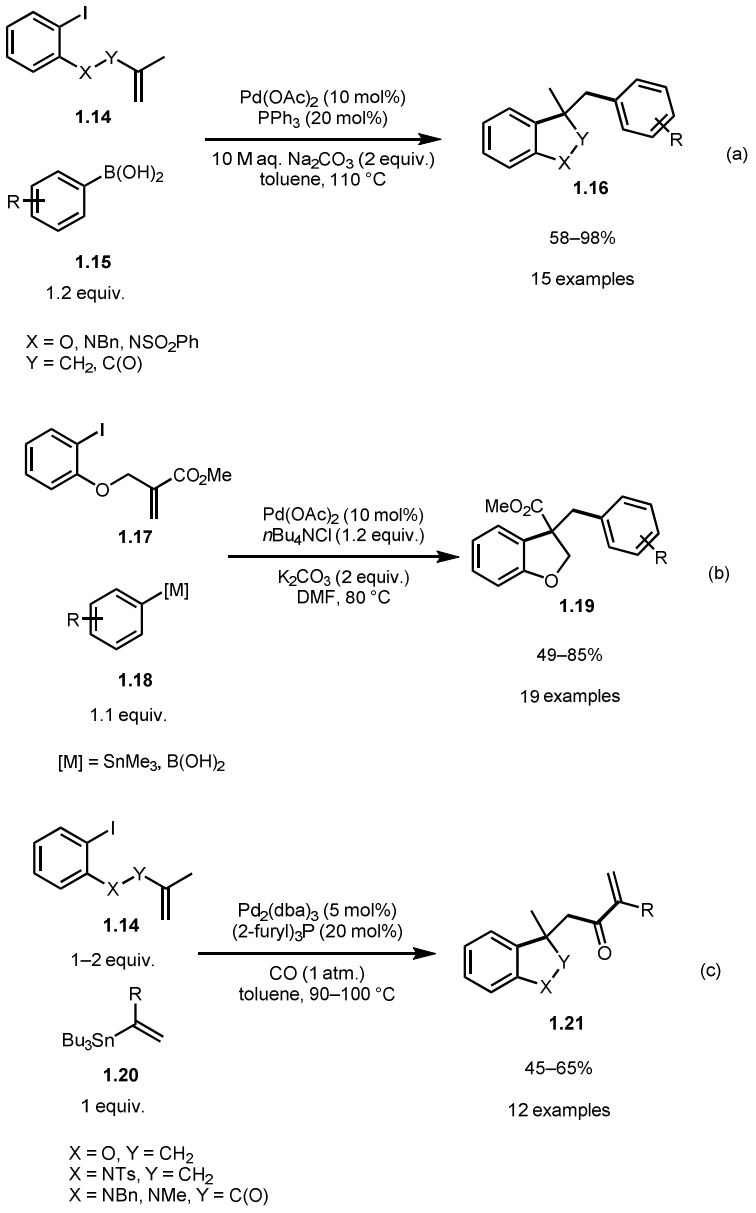
While β-hydride elimination may be more common, other groups can also be eliminated to reform an alkene. Lautens *et al.* showed this with an intramolecular Heck–β-oxygen elimination sequence (Scheme 1.3).[5] This approach proved useful in the synthesis of a range of highly substituted heterocycles including tetrahydroquinolines **1.11** and dihydrobenzofurans **1.13**.



Scheme 1.3: Heterocyclisation followed by β-oxygen elimination

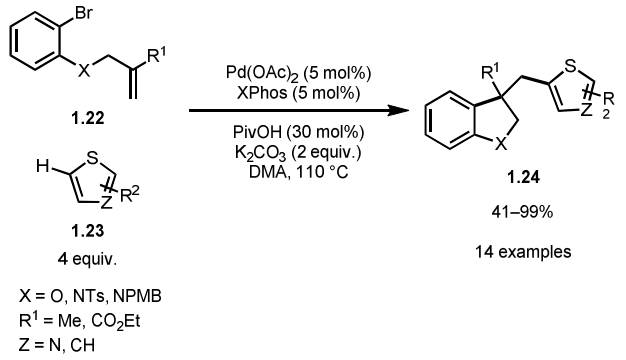
While simple, ß-elimination does not add any extra functionality into the resulting product. If instead Pd(II) intermediate **1.2** (Scheme 1.1) is trapped in some way, a wide range of functionality can be introduced into the newly formed heterocycle. The use of widely available

organometallics such as boronic acids[6-12] and stannanes as traps has been demonstrated by Grigg[13] and Lamaty[14, 15] (Scheme 1.4a, b). After heterocyclisation occurs, the resulting Pd(II) intermediate is trapped via a Suzuki or Stille coupling. Incorporation of CO during the trapping is also possible (Scheme 1.4c).[16] Trapping via Sonogashira coupling has also been shown.[17, 18]



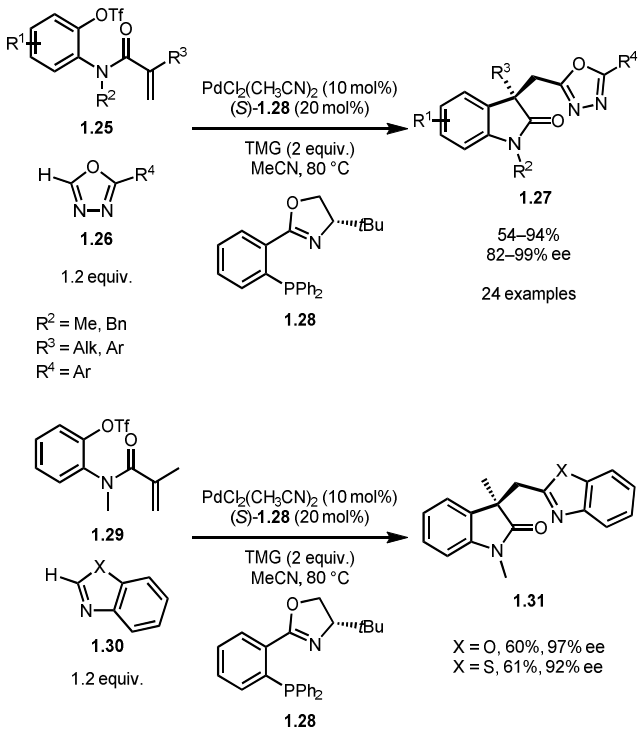
Scheme 1.4: Heterocyclisation terminating with organometallic traps

While the availability of organometallic traps makes them extremely useful, they are inherently atom-inefficient. A more efficient coupling is available by terminating by direct C–H activation.[19-21] Fagnou and co-workers demonstrated the use of C–H activation to trap the Pd(II) intermediate with various sulfur containing heterocycles (Scheme 1.5).[22] This resulted in the formation of a range of heterocycles including dihydrobenzofurans and indolinones **1.24**.



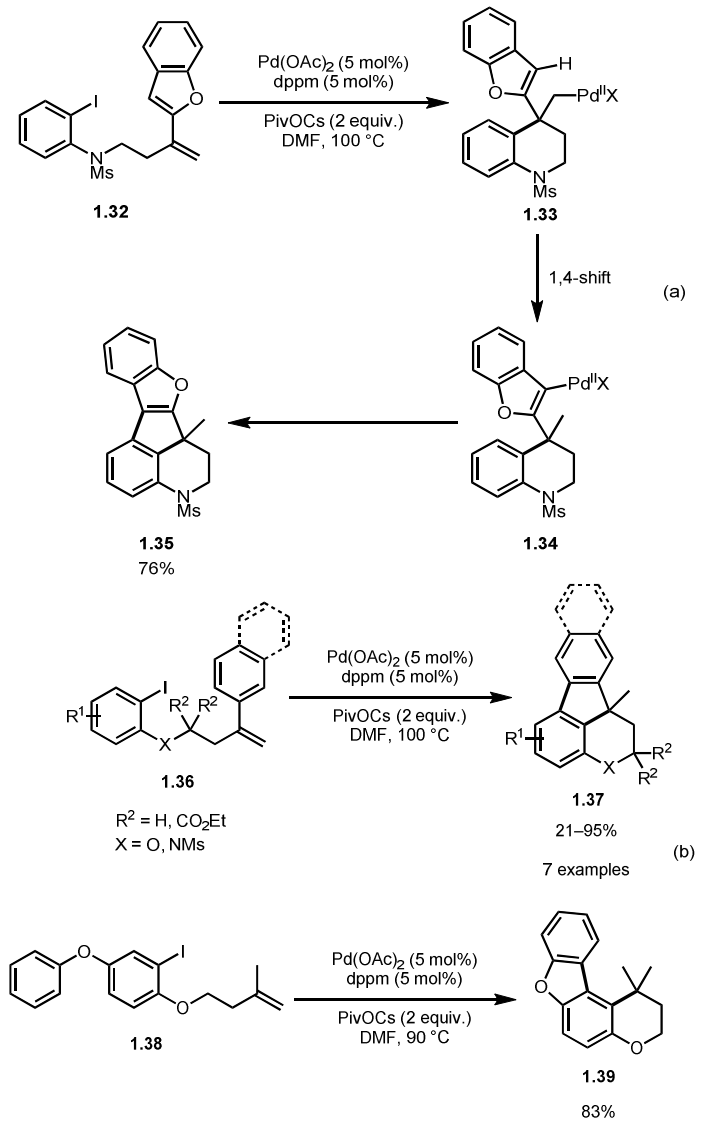
Scheme 1.5: Heterocyclisation terminating by C–H activation

A similar reaction was developed by Zhu *et al.* After formation of the cyclised Pd(II) intermediate, C–H activation was used to trap with 1,3,4-oxadiazoles. By using chiral ligand **1.28**, they were able to form a range of indolinones, achieving good yields and excellent *ee* (Scheme 1.6).[23]



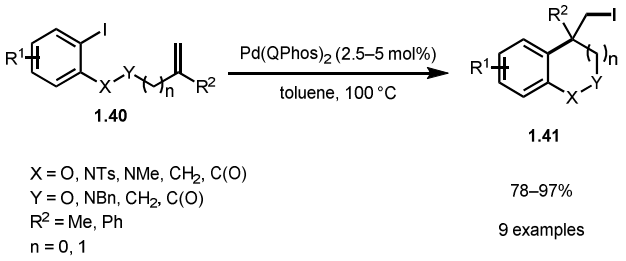
Scheme 1.6: Heterocyclisation terminating by C–H activation

Instead of immediately trapping the Pd(II) intermediate, further transformations can also be carried out. Larock and co-workers showed that after heterocyclisation, **1.33** can undergo a 1,4-shift to give **1.34** (Scheme 1.7).[24] This intermediate can then undergo C–H activation followed by reductive elimination to form a second new ring. This allowed formation of a number of polycyclic compounds.



Scheme 1.7: Heterocyclisation followed by 1,4-shift and another cyclisation

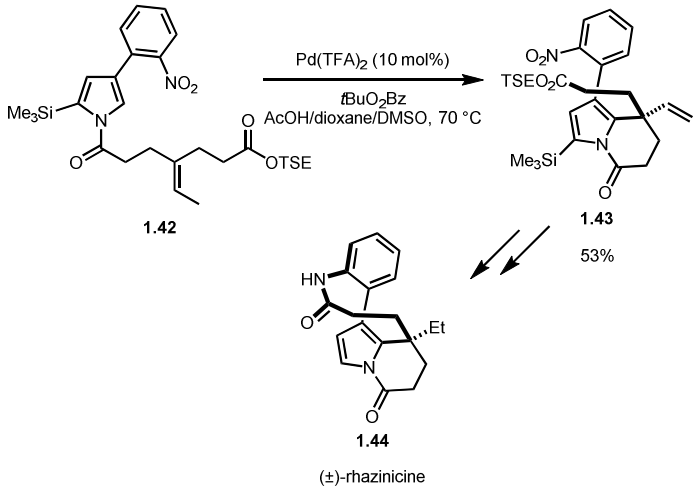
As well as the standard methods of termination, more exotic traps have also been shown to be effective. Lautens *et al.* reported a 100% atom-efficient carboiodination to form a range of heterocycles (Scheme 1.8).[25, 26] This was one of the first examples of reductive elimination to form a C–halogen bond, and leaves an extremely useful functional handle in an otherwise difficult to access position. Other more unusual traps include cyanation,[27, 28] isocyanides[29] and trapping with a Buchwald-Hartwig-type aminocarbonylation.[30]



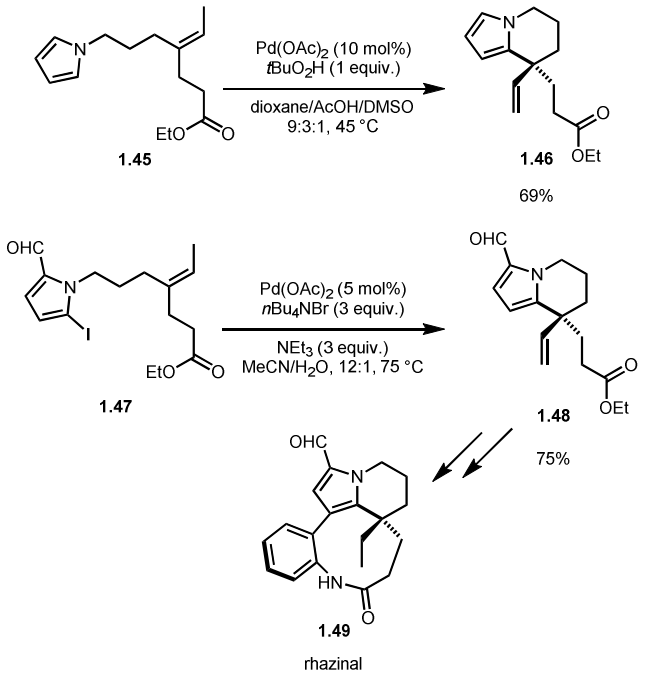
Scheme 1.8: Heterocyclisation terminated by reductive elimination to form C–I bond

1.1.2 C–H activation

As well as providing a method of termination, C–H activation can also provide another route for heterocyclisation itself.[31] The lack of requirement for pre-activation of the reactive site allows for more atom- and step-efficient reactions. It is not without drawbacks, however – generally an external oxidant is required to complete the catalytic cycle. As with C–halogen initiated heterocyclisation, some of the earlier examples of C–H activation initiated heterocyclisation involve carbopalladation of an alkene, followed by β-hydride elimination.[32] Generally requiring electron-rich arenes, reactions of this type have been used by Stoltz[33, 34] and Oestreich[35] to form heterocycles such as benzofurans and indolinones. Also proving useful in total synthesis, this type of heterocyclisation has been used as a key step in the synthesis of (±)-rhazinicine **1.44** (Scheme 1.9) and rhazinal **1.49** (Scheme 1.10) by Gaunt[36] and Trauner[37] respectively.



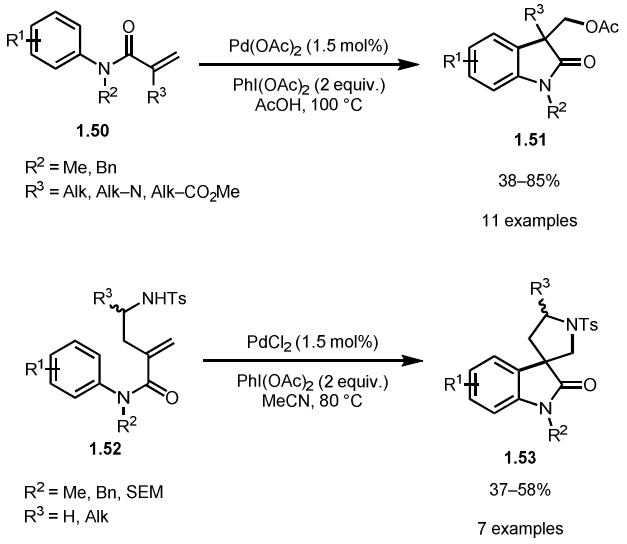
Scheme 1.9: Use of C–H activation initiated heterocyclisation in the synthesis of rhazinicine



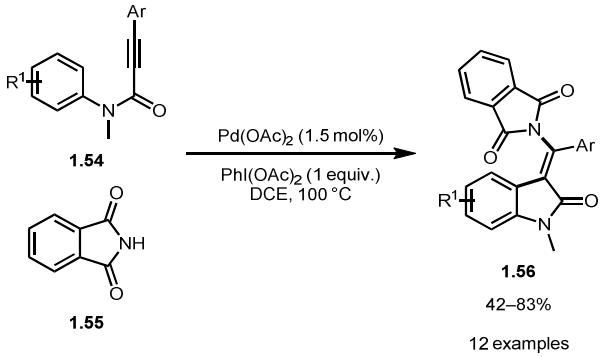
Scheme 1.10: Use of C–H activation initiated heterocyclisation in the synthesis of rhazinal

While all of the previous trapping methods make use of Pd(II), the less common Pd(IV) oxidation state can also be used. Oxidation to Pd(IV) can be achieved by use of a suitable oxidant, often a hypervalent iodine reagent. The C–H activation can occur before or after oxidation.[38]

This type of trapping was used by Zhu and Li, using bisacetoxyiodobenzene as an oxidant. This allowed the introduction of O and N based nucleophiles during the formation of indolinones. These indolinones were generated from alkenes[39] (Scheme 1.11) or alkynes[40] (Scheme 1.12).

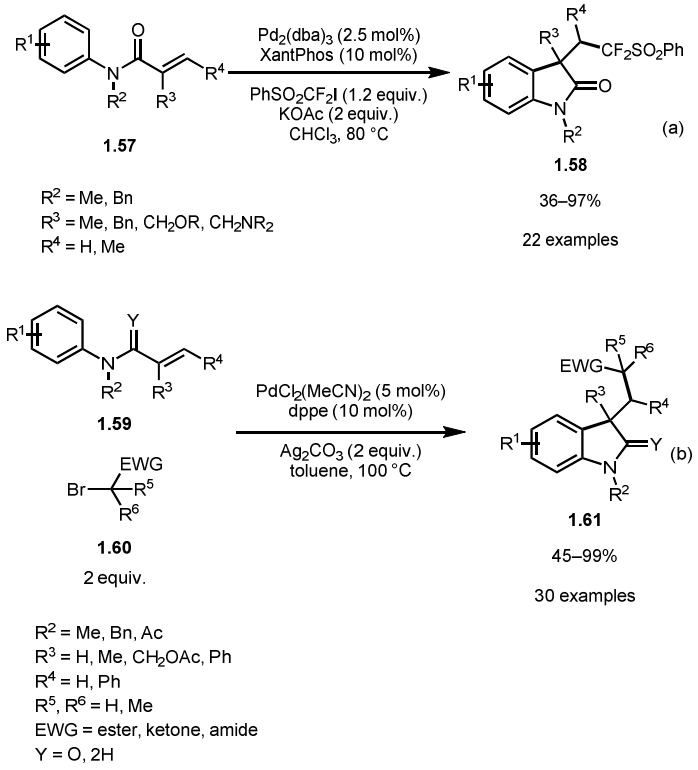


Scheme 1.11: Heterocyclisation terminating with formation of C–Nu bond by Pd(IV)



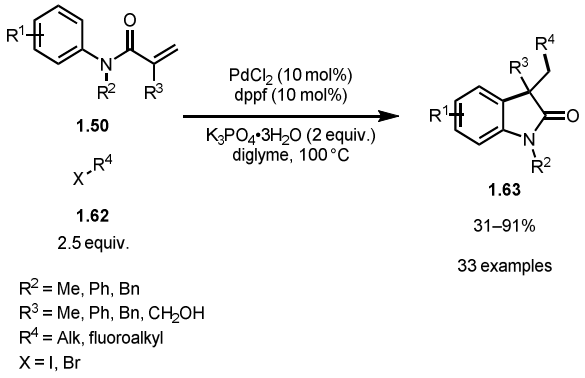
Scheme 1.12: Heterocyclisation terminating with formation of C–N bond by Pd(IV)

As well as through the standard 0–II or a II–IV cycle, heterocyclisation can also occur via a radical process. Wang demonstrated this with a radical heterocyclisation/difluoromethylation process.[41] In their proposed mechanism, $PhSO_2CF_2I$ was reduced by Pd(0), affording Pd(I) and a difluoromethyl radical. Addition of this radical to the activated alkene of the acrylamide generated a further radical. This radical could be trapped by the aromatic ring, with C–H cleavage forming the indolinone (Scheme 1.13a). A similar reaction was reported by Li and co-workers, here, they instead used an electron-deficient alkyl bromide as a radical source (Scheme 1.13b).[42]



Scheme 1.13: Palladium-catalysed radical heterocyclisation

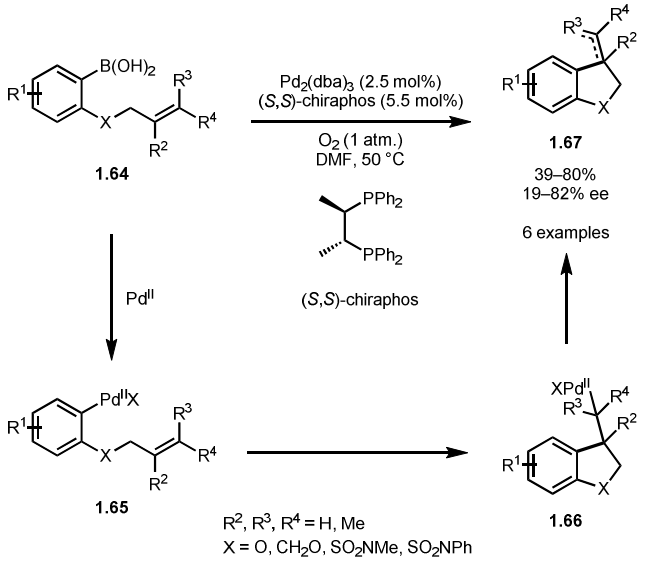
A range of other groups have also been incorporated during heterocyclisation. By changing the order of events, Duan showed the addition of a selection of alkyl and fluoroalkyl halides (Scheme 1.14).[43] First carrying out an oxidative addition with the alkyl halide, carbopalladation of the alkene took place. This Pd(II) intermediate could then undergo C–H activation and reductive elimination to form the indolinone.



Scheme 1.14: Heterocyclisation using alkyl halides

1.1.3 Boron initiated heterocyclisation

While far less common, other initiation methods such as use of arenediazonium salts[44] and boronic acids[45] have been described. Mikami reported an enantioselective synthesis of dihydrobenzofurans and sulfonamides from boronic acids (Scheme 1.15).[46] Beginning with transmetallation of the boronic acid to give **1.65**, carbopalladation gave heterocyclic intermediate **1.66**. Finally, ß-hydride elimination gave **1.67**. Molecular oxygen was used to re-oxidise the palladium catalyst and complete the cycle.

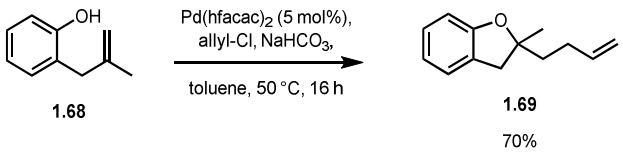


Scheme 1.15: Heterocyclisation initiated by boronic acids

1.1.4 Initial development of a carboallylation reaction

While there are many different termination methods giving access to a range of functionality, there are very few examples involving formation of a new sp^3–sp^3 C–C bond. A recent goal of the pharmaceutical industry has been to increase the proportion of sp^3 hybridised atoms in new drug candidates.[47] This is due to research showing that drugs completing clinical trials have a higher proportion of sp^3 hybridised atoms than those in the earlier stages of testing. For this reason, the ability to form a new sp^3–sp^3 C–C bond as part of the heterocyclisation-functionalisation process would be highly desirable.

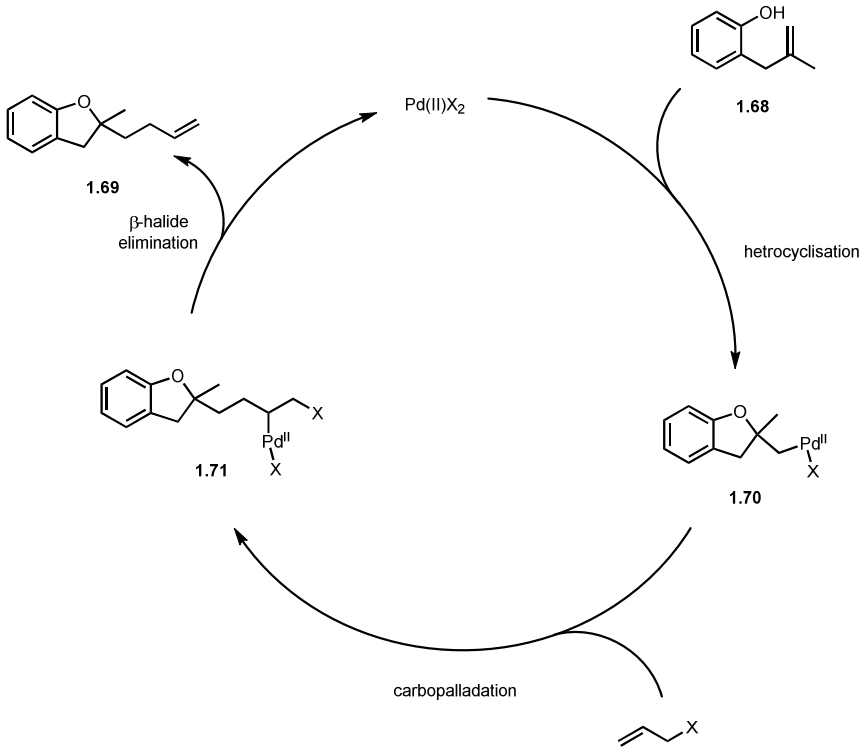
Previous work in the France group led to the development of a palladium-catalysed heteroallylation reaction.[48] As well as forming a new C–Nu bond, this reaction also forms a new sp^3–sp^3 C–C bond. The reaction was carried out on a range of alkenyl alcohols and amines under mild conditions, with no need for an inert atmosphere, forming the corresponding heterocycles, *e.g.* dihydrobenzofuran **1.69** (Scheme 1.16) and other heterocycles. As well as phenols, the methodology was also found to be applicable to cyclisation of benzyl alcohols, aliphatic alcohols, benzoic acid derivatives and tosyl amides.



1.68 **1.69** 70%

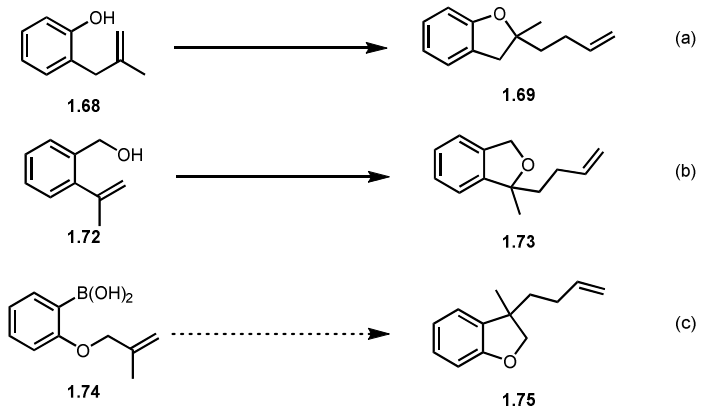
Scheme 1.16: Oxyallylation reaction to form dihydrobenzofurans

The reaction was demonstrated to proceed through an isohypsic Pd(II) catalytic cycle (Scheme 1.17). The first step involved activation of the alkene followed by oxypalladation to give cyclised intermediate **1.70**. The resulting Pd(II) intermediate **1.70** was then trapped by the allyl halide in a carbopalladation to form the new sp^3–sp^3 C–C bond in **1.71**. The final step involved β-halide elimination to give the cyclised product **1.69**. A deuterium labelling study was carried out and the results were consistent with this mechanism.



Scheme 1.17: Mechanism of oxyallylation reaction

As part of a range of heterocycles formed, the oxyallylation reaction allowed formation of dihydrobenzofuran isomers **1.69** and **1.73** (Scheme 1.18a, b). It was proposed that the use of boronic acid **1.74** could lead to a similar reaction to form the structural isomer **1.75** (Scheme 1.18c). As with the oxyallylation reaction, this palladium-catalysed heterocyclisation would result in the formation of a new sp^3–sp^3 C–C bond.

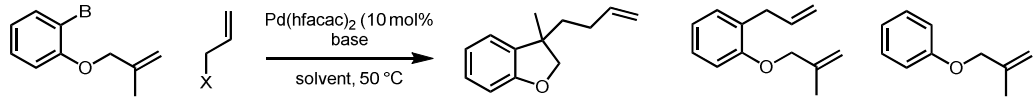


Scheme 1.18: Ways to form 3 different dihydrobenzofuran isomers

Initial studies showed formation of the desired dihydrobenzofuran **1.75**, albeit as the minor component (Table 1.1, entry 1).[49] The major side products were the result of direct coupling **1.76** and the de-boronation product **1.77**. Changing the electrophile from allyl bromide to allyl

chloride improved the rate of reaction and reduced de-boronation, but direct coupling was still the major product (entries 1, 2 and 3). A screen of different catalyst/ligand combinations identified $Pd(hfacac)_2$ as the best catalyst system. Use of solid Na_2CO_3 instead of an aqueous solution improved conversion to the desired dihydrobenzofuran, but also increased formation of de-boronation product (entry 3 vs. entry 4). Organic bases proved ineffective, preferentially forming the direct coupling or de-boronation products (entry 5). After screening of several solvents, dimethoxyethane (DME) gave a good ratio of desired:direct coupling products, with no de-boronation product formed (entry 6). Finally, the boron source was investigated, with potassium trifluoroborate **1.78** providing increased conversion without loss of selectivity (entry 7).

Table 1.1: Initial development of the carboallylation reaction[49]



1.74 1.75 1.76 1.77

Entry	B	X (equiv.)	Base	Solvent	1.74	1.75	1.76	1.77
1	$B(OH)_2$	Br (5)	2 M aq. Na_2CO_3	Toluene	0	0.1	1	1.2
2	$B(OH)_2$	Cl (5)	2 M aq. Na_2CO_3	Toluene	0.2	0.1	1	0.3
3	$B(OH)_2$	Cl (2)	2 M aq. Na_2CO_3	Toluene	0.1	0.3	1	0.7
4	$B(OH)_2$	Cl (2)	Na_2CO_3	Toluene	3.2	6.7	1	10
5	$B(OH)_2$	Cl (2)	NEt_3	Toluene	0.1	0.3	1	3.1
6	$B(OH)_2$	Cl (2)	Na_2CO_3	DME	9.2	3.4	1	0
7	BF_3K	Cl (2)	Na_2CO_3	DME	0	3.5	1	0.2

Product ratio determined by ^1H NMR

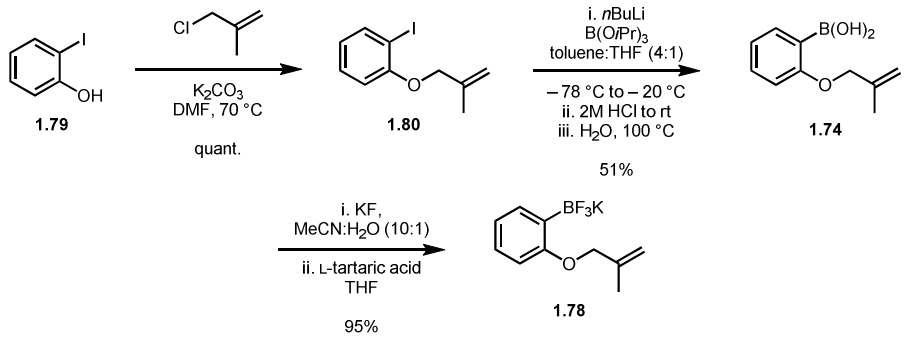
1.2 Results

1.2.1 Optimisation of carboallylation reaction

While the initial optimisation had yielded some improvements in the carboallylation reaction, there were still some issues to overcome. Further optimisation was planned to improve the ratio between the dihydrobenzofuran and direct coupling products and to improve the yield of the reaction.

Synthesis of trifluoroborate

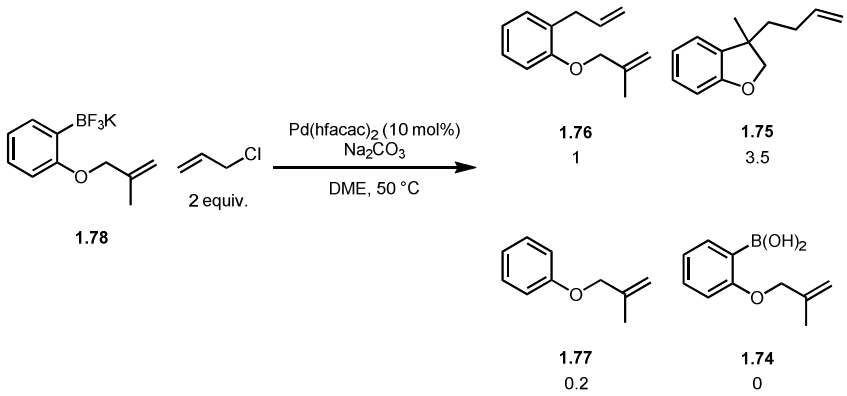
Before further optimisation could occur, synthesis of trifluoroborate **1.78** was required (Scheme 1.19). The synthesis began with the alkylation of 2-iodophenol with methallyl chloride. Stirring in DMF overnight at 70 °C with potassium carbonate gave alkylated aryl iodide **1.80** in a quantitative yield. Iodide **1.80** underwent lithium-halogen exchange upon treatment with *n*BuLi at –78 °C. Addition of triisopropylborate formed the corresponding boronic ester, which was hydrolysed on addition of HCl giving the desired boronic acid **1.74** in a 51% yield. Following a procedure developed by Lloyd-Jones *et al*,[50] boronic acid **1.74** was converted to potassium trifluoroborate **1.78** in 95% yield using KF and L-tartaric acid. This simple procedure avoids the formation of the HF traditionally generated during formation of trifluoroborates.



Scheme 1.19: Synthesis of potassium trifluoroborate **1.78**

Initial attempts at optimisation

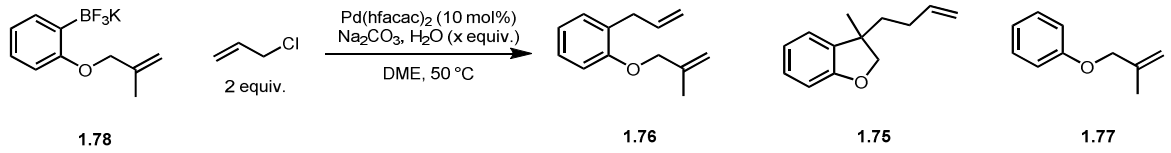
With boronic acid **1.74** and potassium trifluoroborate **1.78** in hand, the carboallylation reaction was subjected to further optimisation in order to suppress formation of the undesired direct coupling **1.76** and de-boronation **1.77** side products (Scheme 1.20). As potassium trifluoroborate **1.78** had been shown to increase conversion compared to using boronic acid **1.74** (Table 1.1), the previously optimised conditions were re-examined (Scheme 1.20).



Scheme 1.20: Product distribution of the carboallylation reaction

Next, the presence of added water was examined (Table 1.2). Some water will be required in the reaction when using potassium trifluoroborate **1.78**, as it must be hydrolysed to the boronic acid before reacting.[51] As the solvent used was technical grade and used as received, it can be expected that it contained some adventitious water. However, adding extra water proved to have a negative effect on selectivity (Table 1.2, entry 1 vs. entry 2). This saw a reduction in the amount of the desired product **1.75**, while there was increased conversion to the direct coupling product **1.76**.

Table 1.2: Effect of water on the carboallylation reaction

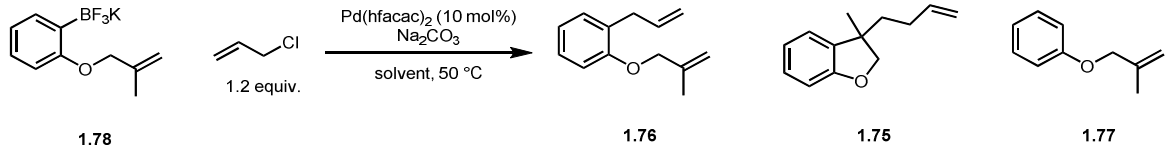


Entry	X (equiv. H_2O)	1.78	1.76	1.75	1.77
1	168	0	1	2.8	0.1
2	0	1.4	1	4.9	0.45

Product ratio determined by ^{1}H NMR

The choice of solvent was again found to be important (Table 1.3). Changing solvent from DME to toluene proved to have a negative effect on the selectivity (entry 1 vs. entry 2). Using toluene, the direct coupling product **1.76** was formed as the major product.

Table 1.3: Effect of solvent on the carboallylation reaction

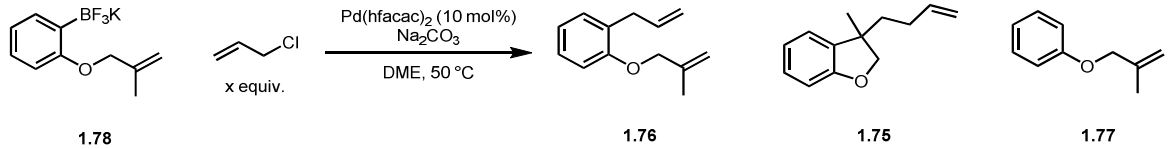


1.78 **1.76** **1.75** **1.77**

Entry	Solvent	1.78	1.76	1.75	1.77
1	DME	0	1	1.4	0.4
2	Toluene	0	1	0.5	0.6

Finally, the number of equivalents of allyl chloride was examined (Table 1.4). This was important to examine as allyl chloride is a key part of the formation of both the desired product and the direct coupling side product. If too much is added then formation of the side product will be faster; however, if too little is added, the formation of the desired product will occur too slowly for an efficient reaction. The previous optimisation had shown that 2 equivalents of allyl chloride provided the best selectivity for the desired carboallylation product **1.75**. Increasing the number of equivalents, it was found that using more than 2 equivalents of allyl chloride had a negative effect on the ratio of desired products (entries 4–7). Using between 1.2 and 2 equivalents also had a negative effect (entries 1–4). The results therefore showed that two equivalents of allyl chloride provided the best ratio of the desired product **1.75** to the two side products **1.76** and **1.77** (Figure 1.1).

Table 1.4: Effect of the number of equivalents of allyl chloride on the carboallylation reaction



1.78 1.76 1.75 1.77

Entry	x	SM	1.76	1.75	1.77
1	1.2	0	1	1.4	0.4
2	1.5	0.25	1	3.6	0.3
3	1.8	0.2	1	3.3	0.25
4	2	1.4	1	4.9	0.45
5	4	0.9	1	2.5	0.2
6	8	0.6	1	1	0.15
7	10	0.35	1	0.7	0.1

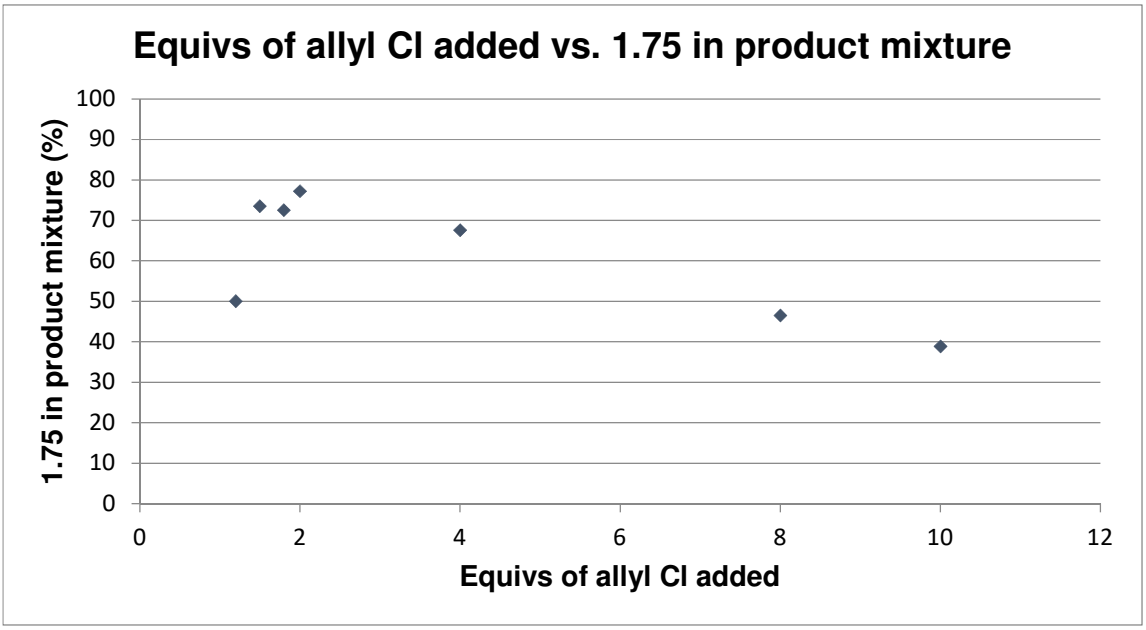
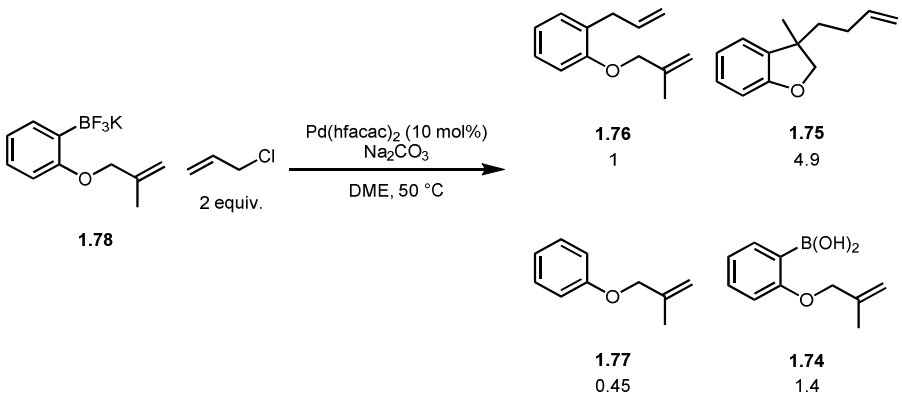


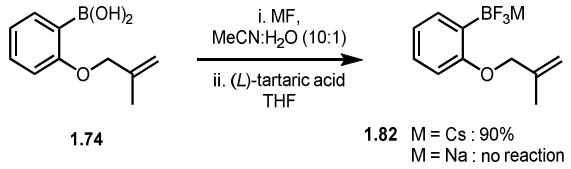
Figure 1.1: Graph of allyl Cl equivs vs. desired product ratio

Overall, the results of the optimisation study showed that using potassium trifluoroborate **1.78** instead of boronic acid **1.74** did not change the previously optimal conditions (Scheme 1.20). As before, these were using $Pd(hfacac)_2$, DME, 2 equivalents of allyl chloride, sodium carbonate and potassium trifluoroborate **1.78** with no added water (Scheme 1.21).



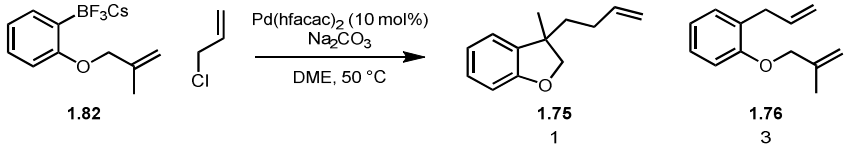
Scheme 1.21: Product distribution of carboallylation reaction

While the potassium trifluoroborate **1.78** had proven to be the best boron source, it is also possible to form other trifluoroborate salts. Following the same procedure used to form the potassium trifluoroborate, the synthesis of the corresponding cesium and sodium trifluoroborates was attempted (Scheme 1.22). Synthesis of the cesium trifluoroborate **1.82** was successful, proceeding in a 90% yield. Unfortunately, synthesis of the sodium trifluoroborate was unsuccessful, with none of the desired product being isolated.



Scheme 1.22: Synthesis of other trifluoroborates

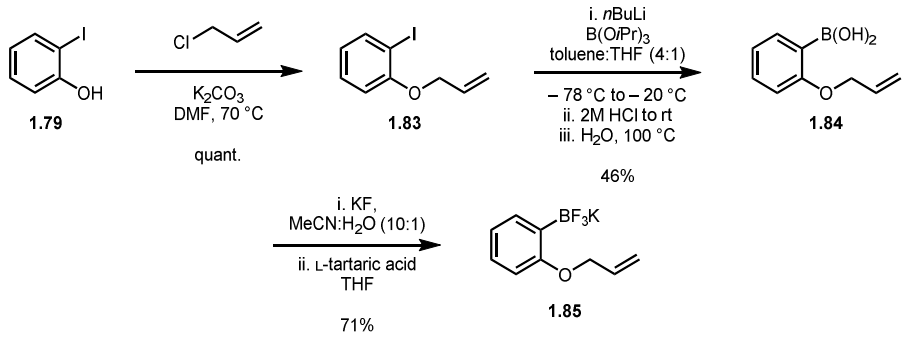
The cesium trifluoroborate **1.82** was then submitted to the optimised reaction conditions (Scheme 1.23). Disappointingly, direct coupling product **1.76** was the major product formed, giving a 3:1 ratio between the direct coupling product and the carboallylation product **1.75**.



Scheme 1.23: Carboallylation of cesium trifluoroborate **1.82**

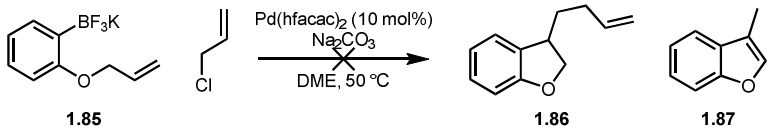
1.2.2 Synthesis and reaction of other substrates

To test the effect of substitution in the *O*-allyl chain, the unsubstituted potassium trifluoroborate **1.85** was formed. Starting with 2-iodophenol **1.79**, an identical procedure was used as for the synthesis of potassium trifluoroborate **1.78** was followed (Scheme 1.24). 2-Iodophenol was treated with allyl chloride and potassium carbonate in DMF at 70 °C overnight. After workup, this gave alkylated aryl iodide **1.83** in a quantitative yield. Aryl iodide **1.83** was then treated with *n*BuLi at –78 °C. Addition of triisopropyl borane followed by hydrolysis of the resulting boronate ester gave boronic acid **1.84** in 46% yield. Finally, treatment of the boronic acid with potassium fluoride and L-tartaric acid afforded potassium trifluoroborate **1.85** in 71% yield.



Scheme 1.24: Synthesis of potassium trifluoroborate **1.85**

Submitting potassium trifluoroborate **1.85** to the optimised carboallylation conditions, none of the desired cyclised product was formed, with a complex mixture of products resulting instead (Scheme 1.25). Interestingly, no formation of benzofuran **1.87** was detected either. This would form as a result of β-hydride elimination and isomerisation after cyclisation had taken place.

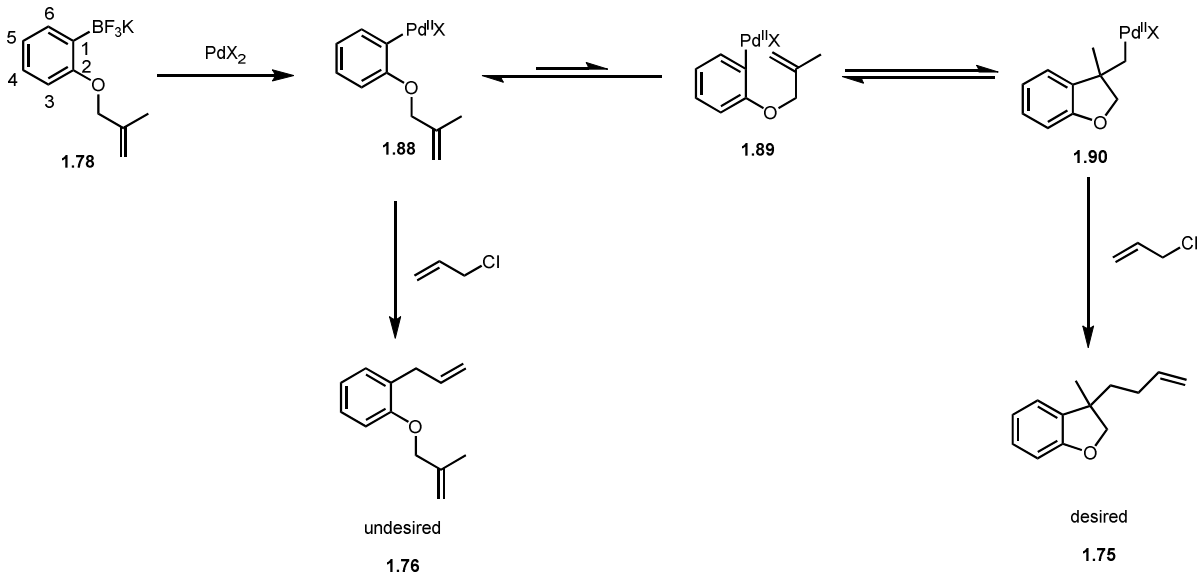


Scheme 1.25: Carboallylation reaction of potassium trifluoroborate **1.85**

Rotomer restriction with methyl substrate

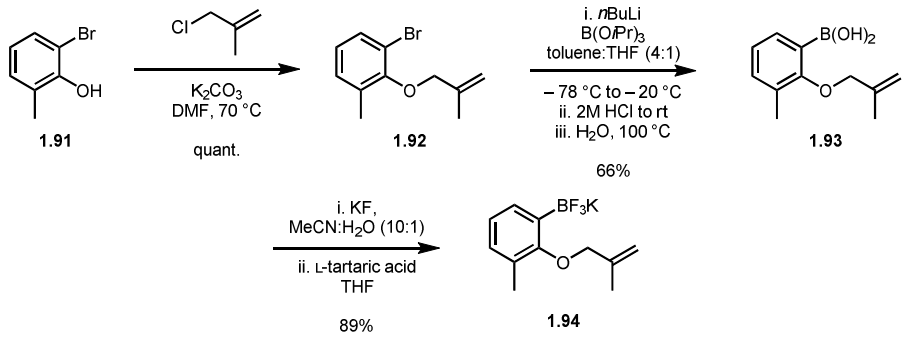
As both the desired **1.75** and direct coupling **1.76** products can form via an isohypsic process, the "reactive rotomer" effect[52] can have an important effect (Scheme 1.26). After transmetallation to form Pd(II) intermediate **1.88**, the proximity of the *O*-methallyl chain determines how easily direct coupling or cyclisation can occur. For cyclisation to occur, the *O*-

methallyl chain must be in close proximity to the Pd(II). As it is less sterically favourable for the *O*-methallyl chain to be close to the Pd(II) (**1.89**), it will likely spend more time at a greater distance (**1.88**). This leaves the Pd(II) intermediate **1.88** more vulnerable to direct coupling. By replacing the hydrogen in the 3-position with another group, it is less favourable for the O-methallyl chain to be oriented towards the 3-position. This should result in the equilibrium being pushed towards **1.89**, therefore favouring cyclisation.



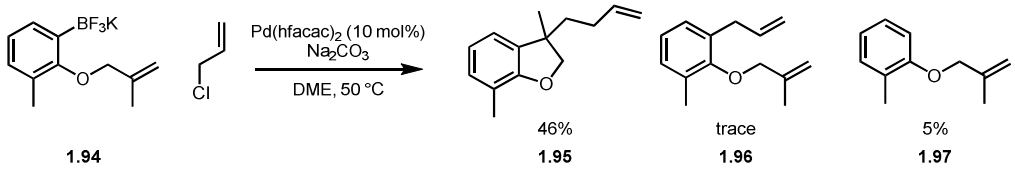
Scheme 1.26: Reactive rotomer effect

In order to test this theory, it was proposed to synthesise **1.94** (Scheme 1.27). While small, the addition of a methyl group in the 3-position should give some insight into whether the reactive rotomer hypothesis is correct. Starting with *o*-bromocresol **1.91**, an identical procedure was used as for the synthesis of potassium trifluoroborate **1.78** was followed. *o*-Bromocresol was treated with methallyl chloride and potassium carbonate in DMF at 70 °C overnight. After workup, this gave alkylated aryl bromide **1.92** in a quantitative yield. Aryl bromide **1.92** was then treated with *n*BuLi at –78 °C, followed by addition of triisopropyl borane. Hydrolysis of the resulting boronate ester gave boronic acid **1.93** in 66% yield. Finally, treatment of the boronic acid with potassium fluoride and L-tartaric acid afforded potassium trifluoroborate **1.94** in 89% yield, 59% overall yield.



Scheme 1.27: Synthesis of potassium trifluoroborate **1.94**

Methyl substituted potassium trifluoroborate **1.94** was then subjected to the optimised carboallylation conditions (Scheme 1.28). Gratifyingly, only a trace of direct coupling product **1.96** was observed, with only 5% of de-boronation product **1.97** observed. Unfortunately, despite complete consumption of starting material, only 46% of carboallylated product **1.95** was formed.



Scheme 1.28: Carboallylation of potassium trifluoroborate **1.94**

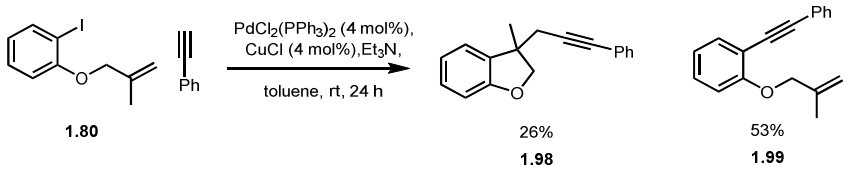
To rule out the possibility of decomposition during purification, the reaction was repeated and a known quantity of 1,3,5-trimethoxybenzene added to the crude reaction mixture. Analysis of the crude mixture by ^{1}H NMR then allowed direct calculation of the yield. This analysis showed a 49% yield of the dihydrobenzofuran product, 6% yield of the de-boronation product and a 2% yield of the direct coupling product. No other significant peaks were identified.

While addition of the methyl group in the 3-position successfully suppressed formation of the direct coupling product, the overall yield of the carboallylation reaction remains low. Despite full conversion and analysis of the product mixture, there is still some material unaccounted for.

1.2.3 Synthesis and reaction of BPin acrylamide

Examples in literature and aim

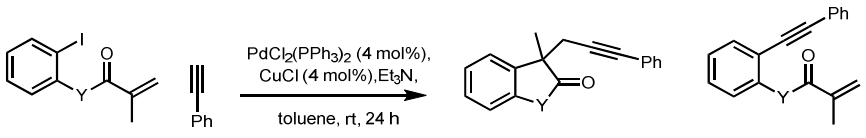
An interesting carboalkynylation reaction from Liu and co-workers was reported.[18] This allowed the formation of a range of heterocycles, including dihydrobenzofurans. The reaction was proposed to follow a similar pathway to our carboallylation reaction. After formation of an aryl Pd(II) intermediate, carbopalladation formed the heterocycle. This Pd(II) intermediate was then trapped in a Sonogashira-type reaction. While Liu's work proceeded through a standard 0–II cycle rather than the isohypsic process proposed for the carboallylation reaction, they also had competition between cyclisation and direct alkynylation (Scheme 1.29).



1.80 — 26% 1.98 — 53% 1.99

Scheme 1.29: Carboalkynylation reaction

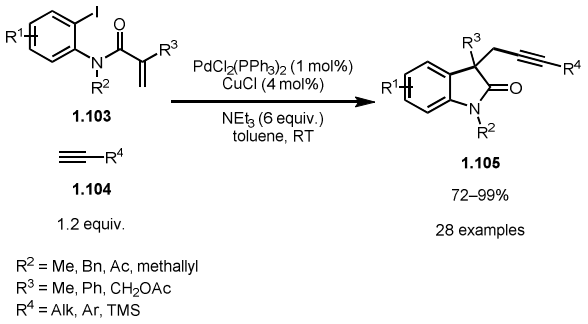
As in our experiments with the methyl-substituted potassium trifluoroborate, Liu found that increasing steric clash between the alkene side-chain and the 3-position favoured cyclisation. In their case, use of an *N*-methylated amide eliminated formation of the direct alkynylation product (Scheme 1.30). This allowed synthesis of 28 products in good to excellent yields (Scheme 1.31).



1.100

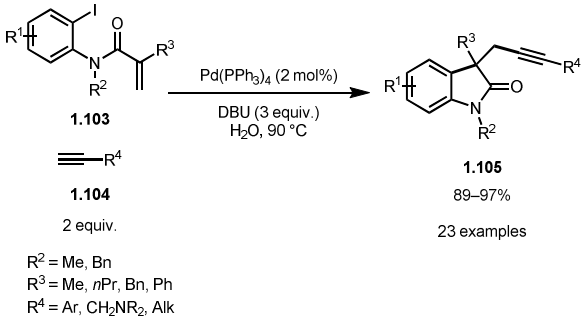
Y = NMe	1	0
Y = O	0	1
	1.101	1.102

Scheme 1.30: Products of carboalkynylation reaction



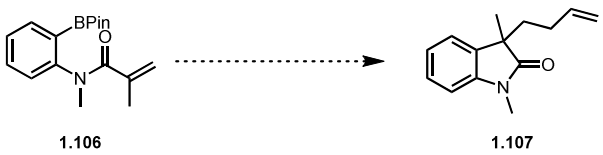
Scheme 1.31: Carboalkynylation reaction using acrylamides **1.103**

A very similar reaction was reported in 2016 by Guo.[17] This carboalkynylation again made use of *N*-substituted acrylamides in the formation of indolinones (Scheme 1.32).



Scheme 1.32: Carboalkynylation reaction using acrylamides **1.103**

With Liu's results in mind, acrylamide **1.106** was proposed as a possible carboallylation precursor (Scheme 1.33). Use of the pinacol boronate ester as a boron source was proposed as the previous syntheses required use of strong base *n*BuLi. This would be unsuitable in this case due to the number potential sites for deprotonation. Use of the pinacol boronate ester avoids this by allowing installation via a palladium-catalysed Miyaura borylation.

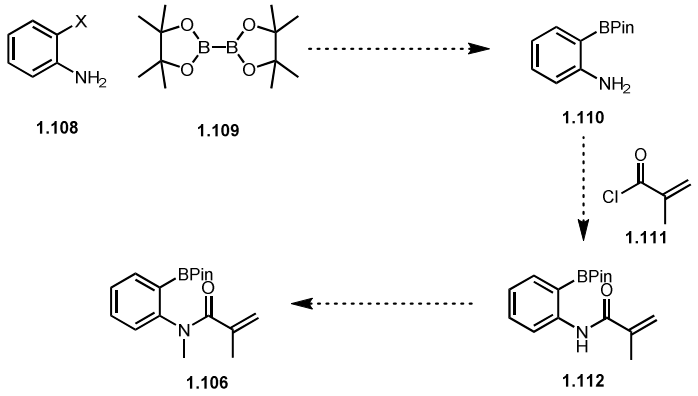


Scheme 1.33: Proposed carboallylation reaction of **1.106**

Synthesis of BPin acrylamide

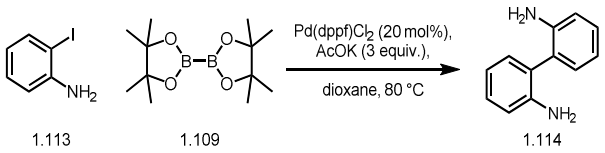
In order to synthesise the BPin acrylamide, the following synthetic route was proposed. Starting with a haloaniline **1.108**, a palladium-catalysed Miyaura borylation would yield pinacol ester **1.110** (Scheme 1.34). This could then be subjected to an amide coupling using

methacryloyl chloride affording acrylamide **1.112**. Finally, methylation with methyl iodide would then give methylated acrylamide **1.106**.



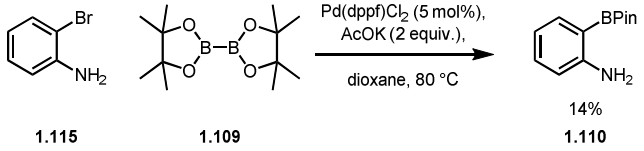
Scheme 1.34: Proposed synthesis of BPin acrylamide **1.106**

Following the planned route, Miyaura borylation was attempted using iodoaniline (Scheme 1.35). Unfortunately, while the starting material was completely consumed, none of the desired pinacol ester was formed. The only product formed during the reaction was dianiline **1.114**.



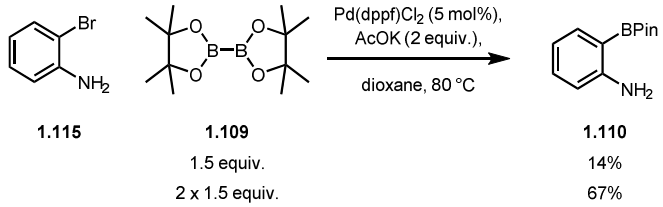
Scheme 1.35: Initial attempt at Miyaura borylation

As iodoaniline was believed to be too reactive, the borylation was instead attempted using the less reactive bromoaniline (Scheme 1.36). This proved more successful, albeit with the desired pinacol ester being formed in just 14% yield – mainly due to low conversion.



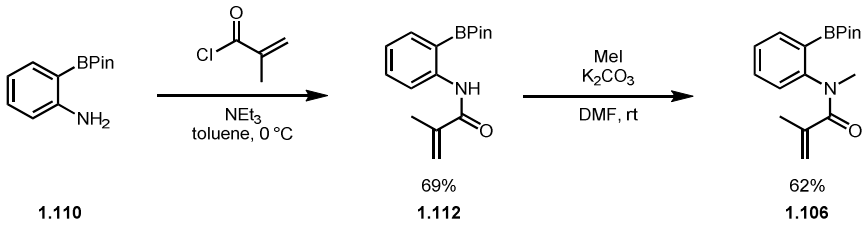
Scheme 1.36: Miyaura borylation using bromoaniline

While the lower reactivity of bromoaniline helped prevent formation of dianiline **1.114**, it had the undesired side effect of significantly reducing conversion. However, addition of a second portion of bis(pinacolato)diboron after 24 h greatly increased conversion, resulting in formation of pinacol ester **1.110** in 67% yield.



Scheme 1.37: Improved Miyaura borylation

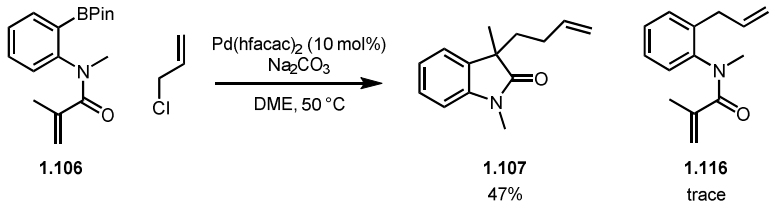
With pinacol ester **1.110** in hand, amidation was attempted (Scheme 1.38). The pinacol ester was treated with methacryloyl chloride and triethylamine in toluene at 0 °C. The reaction proceeded cleanly, giving acrylamide **1.112** in a 69% yield. Acrylamide **1.112** was then methylated using methyl iodide in the presence of potassium carbonate in DMF. This gave acrylamide **1.106** in 62% yield.



Scheme 1.38: Synthesis of BPin acrylamide **1.106**

Reactions of BPin acrylamide and derivatives

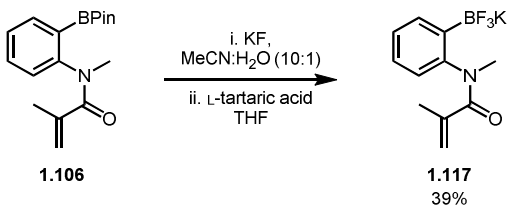
With the synthesis of acrylamide **1.106** successful, it was then subjected to the optimised carboallylation conditions (Scheme 1.39). Pleasingly, indolinone **1.107** was formed in a 47% yield, with only a trace of direct coupling product **1.116** detected. While the conversion to a single product was welcome, the overall yield was still only 47%, comparable to **1.95** (Scheme 1.28).



Scheme 1.39: Carboallylation of BPin acrylamide **1.106**

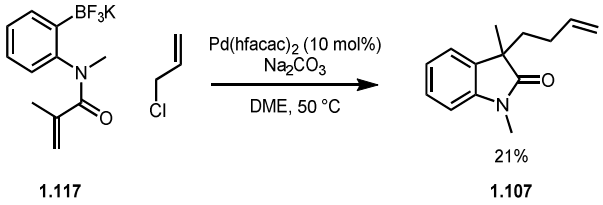
During the synthesis of dihydrobenzofurans, use of potassium trifluoroborates had produced the best results. It was therefore decided to form the potassium trifluoroborate analogue **1.117** (Scheme 1.40). As before, this was carried out following the procedure developed by

Lloyd-Jones and co-workers.[50] Disappointingly, the yield in this case was much poorer than expected. This was likely due to the difficulty in removing the pinacol byproduct.



Scheme 1.40: Synthesis of potassium trifluoroborate **1.117**

The optimised conditions were then applied to potassium trifluoroborate **1.117**. Indolinone **1.107** was formed, but only in 21% yield.



Scheme 1.41: Carboallylation of potassium trifluoroborate **1.117**

As the low yield in the previous cyclisation was thought to be caused by residual pinacol from the formation of the potassium trifluoroborate, a revised synthesis was attempted. This time, the crude mixture was washed repeatedly with Et_2O to remove the pinacol byproduct. This gave two products, one of which was the previously isolated potassium trifluoroborate. The second product also appeared to be a fluoroborate, but was soluble in chlorinated solvents – an unusual property for potassium trifluoroborates. Further NMR and mass spectrometry analysis suggested the product could be difluoroborane **1.118** (Figure 1.2).

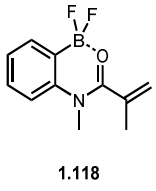
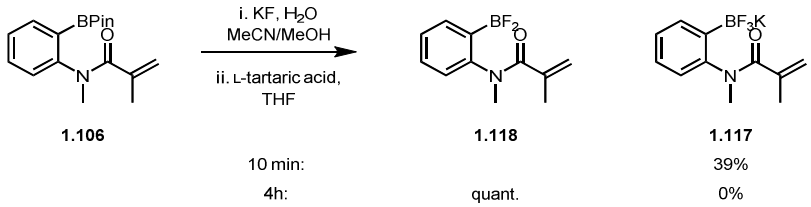


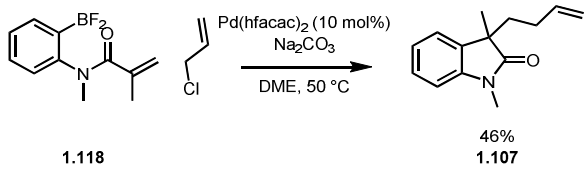
Figure 1.2: Difluoroborane **1.118**

It was found that difluoroborane **1.118** could be formed in a quantitative yield from acrylamide **1.106** under the Lloyd-Jones conditions.[50] Stirring the reaction mixture for four hours rather than working up the reaction immediately afforded the difluoroborane **1.118** rather than the potassium trifluoroborate **1.117** (Scheme 1.42). Examples of similar difluoroboranes were found in the literature,[53-55] often forming in a similar manner.



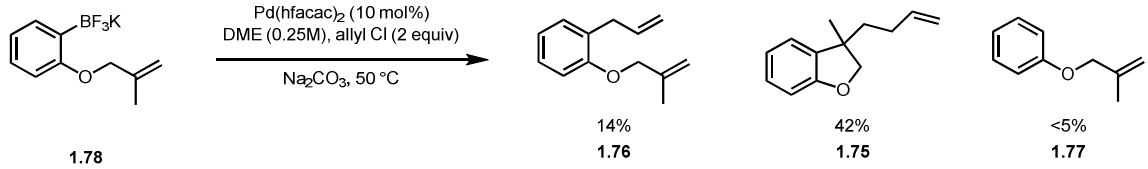
Scheme 1.42: Synthesis of **1.118** and **1.117**

Interestingly, when difluoroborane **1.118** was subjected to the carboallylation conditions, it could successfully be cyclised giving indolinone **1.107** in a moderate yield (Scheme 1.43). As with the other acrylamides, there was no formation of the direct coupling product.



Scheme 1.43: Carboallylation of difluoroborane **1.118**

While the cyclisations of all three acrylamides were successful in forming the desired indolinone, the yields were disappointing. It was, however, unclear as to where the rest of the material was as the ^{1}H NMR of the crude reaction mixture showed no other peaks. This suggests any loss of material occurs during the reaction rather than during purification. These observations are similar to the dihydrobenzofuran forming reactions carried out previously (Scheme 1.44). An investigation was therefore started to try and account for the missing mass.

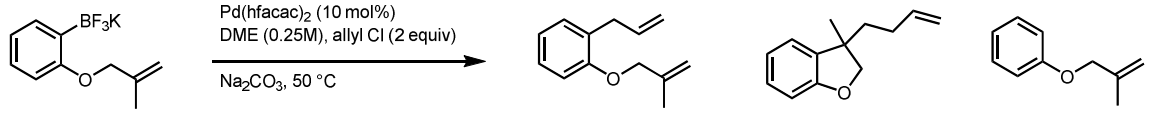


Scheme 1.44: Products resulting from the carboallylation reaction

1.2.4 NMR study of the carboallylation reaction

The carboallylation reaction to form dihydrobenzofuran **1.75** was chosen as the model reaction for this analysis due to the well characterised nature of the known side products, and the availability of the starting material. This reaction gave a moderate yield of the desired dihydrobenzofuran **1.75**, as well as some of the direct coupling product **1.76** and a small amount of de-boronation product **1.77** (Scheme 1.44).

Due to the lack of other major peaks in the ^{1}H NMR of the crude material, the first concern was that some of the material was being lost during purification. To find out if this was the case, a known quantity of 1,3,5-trimethoxybenzene was added to the crude material after workup as an internal standard. A ^{1}H NMR was then taken of this mixture to work out the yield. This showed a similar yield suggesting that purification was not the problem (Scheme 1.45).

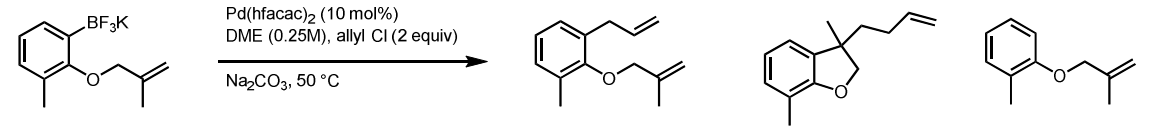


1.78		1.76	1.75	1.77
	isolated	14%	42%	<5%
	internal standard	17%	45%	5%

Scheme 1.45: Yields before and after purification

The next concern was that material was being lost during workup. Changing the workup from filtering through a silica plug to an aqueous workup had little effect on the yield (Scheme 1.46). The aqueous phase was concentrated *in vacuo* and analysed by ^{1}H NMR, but only traces of the previously identified products were detected. As the reaction takes place under basic conditions the aqueous phase was acidified then extracted, but this did not yield any additional material.

Finally, an internal standard was then added to the reaction mixture before workup and a small amount of this mixture analysed by ^{1}H NMR. Examination of the carboallylation using methyl-substituted trifluroborate **1.94** by the different workup methods showed a similar yield suggesting that the material was not lost during any workup process.

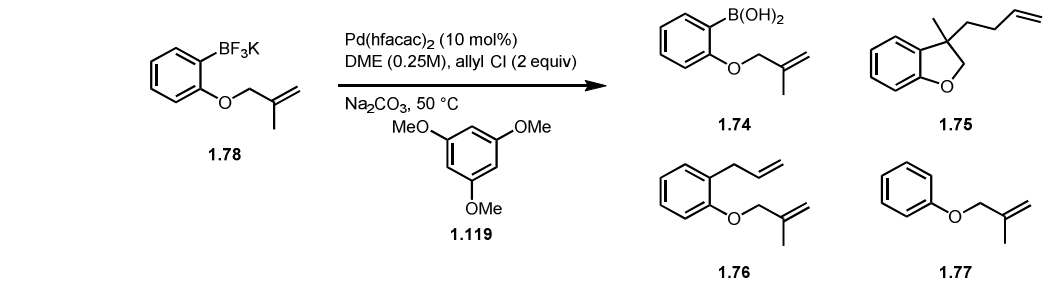


1.94		1.96	1.95	1.97
	silica plug	0%	46%	5%
	aqueous workup	0%	40%	11%

Scheme 1.46: Yields by different workup methods

As loss of material during workup or purification had been ruled out, any loss of material must be occurring during the reaction itself. In an attempt to detect this, the reaction was followed by ^{1}H NMR. The reaction was carried out under the standard conditions, with the addition of

1,3,5-trimethoxybenzene **1.119** as an internal standard. At each time point, a small aliquot of the reaction mixture was removed and concentrated *in vacuo*. This was then analysed by ^{1}H NMR to determine the product distribution. The results showed a rapid consumption of the starting material **1.78**, with some conversion to the intermediate boronic acid **1.74** (Figure 1.3). The desired product was formed, alongside small amounts of the direct coupling and deboronation products. Even after the first time-point, there appeared to be material missing. Integration of the aromatic and alkene regions suggested that some of this missing material was insoluble, and that some contained aromatic protons but no alkene.



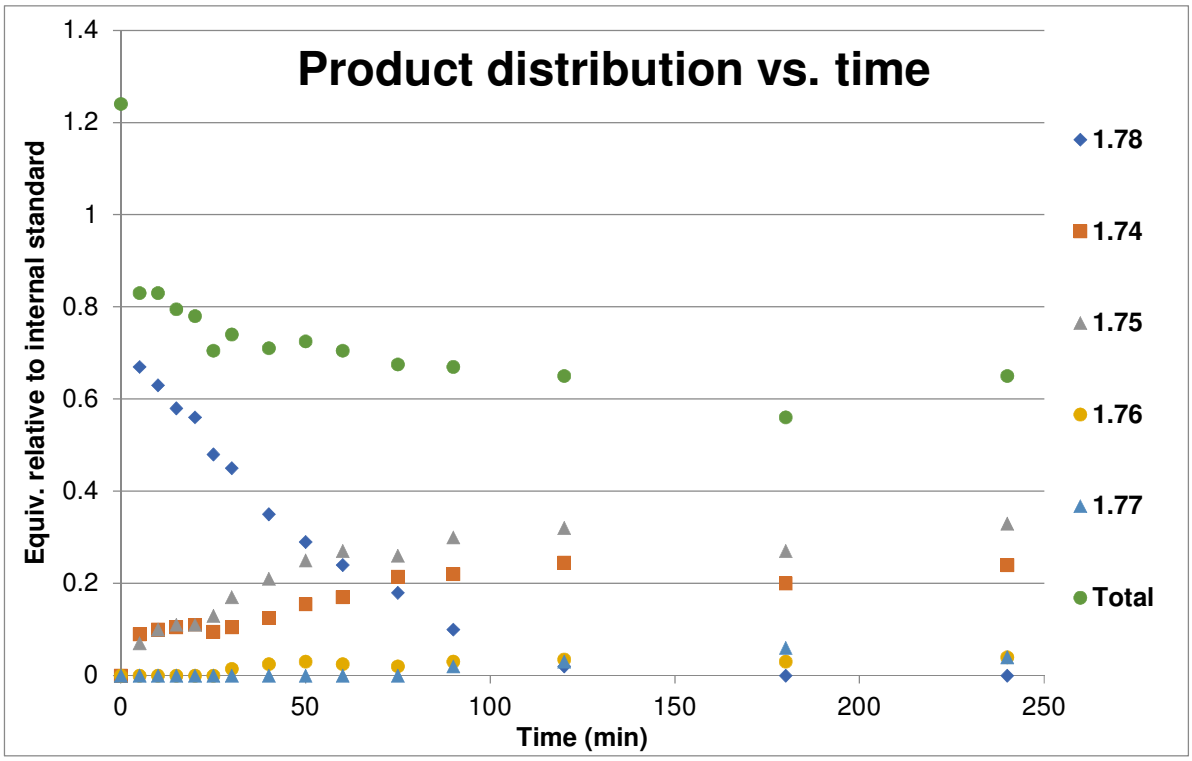


Figure 1.3: Product distribution in the carboallylation reaction over time

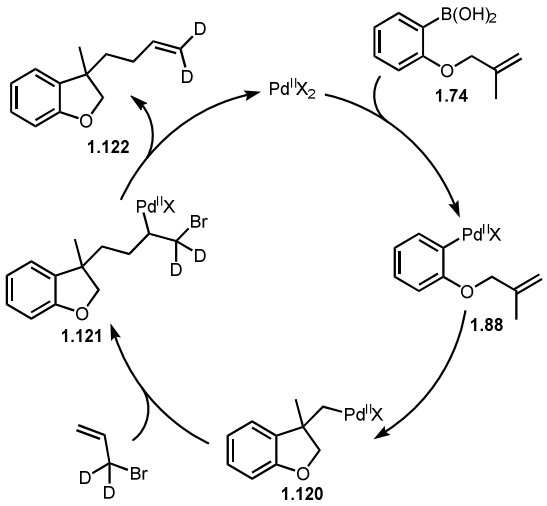
To try and analyse any insoluble material, the reaction was stopped after a short time and the mixture filtered, washing with acetone. The solid material was then collected and dissolved in various solvents for analysis by ^{1}H NMR. The solid was completely or nearly insoluble in all

solvents used apart from D_2O. ^1H NMR analysis showed no significant peaks, suggesting it was likely leftover sodium carbonate.

While the exact pathway for loss of material was not able to be determined, loss of material during purification or workup has been ruled out. Following the reaction by ^1H NMR shows loss of material during the reaction, but no further products could be identified. Attempted analysis of solid material in the reaction mixture showed no organic peaks.

1.2.5 Deuterium labelling study

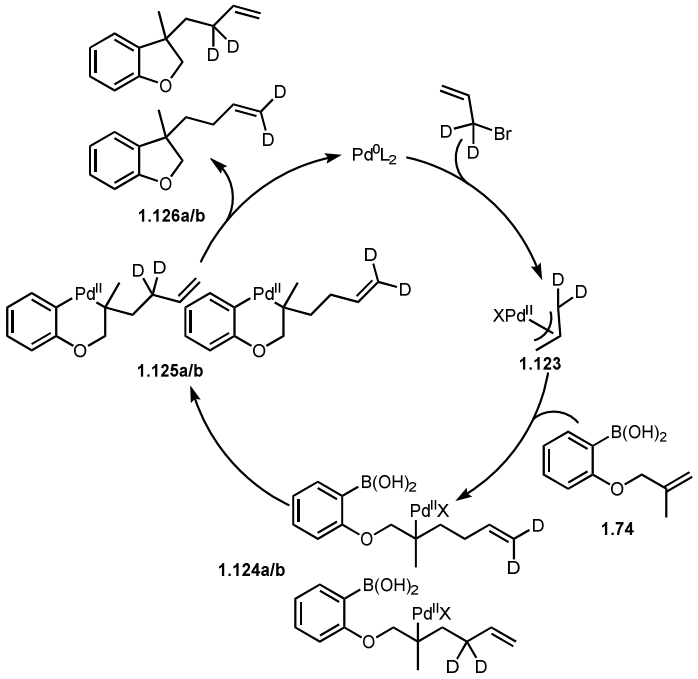
In order to provide a greater insight into the reaction mechanism, a deuterium labelling study was carried out. By replacing the allyl chloride with dideuteroallyl bromide, the product distribution should give a strong indication of the operative mechanism. It was proposed that there were three possible catalytic cycles. Mechanism A is the initially proposed isohypsic mechanism (Scheme 1.47).[48] Beginning with transmetallation of boronic acid **1.74**, Pd(II) intermediate **1.88** is formed. Carbopalladation then forms dihydrobenzofuran **1.120**. A second carbopalladation with dideuteroallyl bromide forms **1.121** which can undergo a ß-halide elimination to give dihydrobenzofuran **1.122** as a single isomer deuterated at the terminal position.



Scheme 1.47: Mechanism A

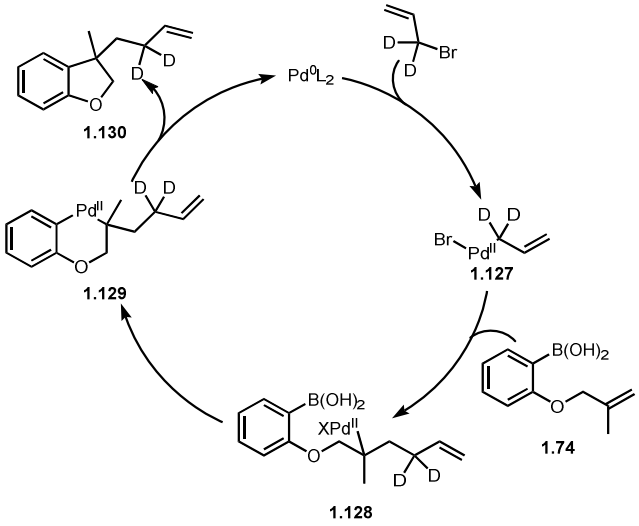
Mechanism B begins with the oxidative addition of dideuteroallyl bromide to Pd(0) to form allyl Pd(II) species **1.123** (Scheme 1.48).[56] Carbopalladation on the *O*-methallyl chain of boronic acid **1.74** forms intermediates **1.124a** and **1.124b** in a 1:1 mixture of the deuterated isomers. Transmetallation of the boronic acid gives rise to the cyclised intermediates **1.125a** and

1.125b. Finally, reductive elimination gives dihydrobenzofuran product **1.126** in a 50:50 mixture of deuterated isomers.



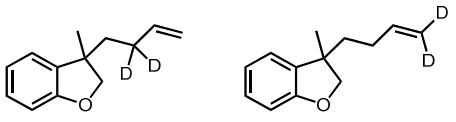
Scheme 1.48: Mechanism B

Mechanism C begins with direct oxidative addition of Pd(0) into the C–Br bond of dideuteroallyl bromide to form Pd(II) species **1.127** (Scheme 1.49).[57] This results in the formation of the η^1-palladium species instead of the η^3-palladium species formed in Mechanism B. As with Mechanism B, carbopalladation on the *O*-methallyl chain of boronic acid **1.74** forms intermediate **1.128**. Transmetallation of the boronic acid gives rise to the cyclised intermediate **1.129**. Finally, reductive elimination gives dihydrobenzofuran product **1.130** as a single isomer of the deuterated product.



Scheme 1.49: Mechanism C

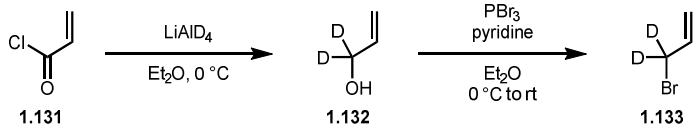
Examining the ratio of the deuterated dihydrobenzofuran product formed should give an insight into the operative mechanism. Mechanism A should give only product **1.122**, Mechanism B a 50:50 ratio and Mechanism C only product **1.130** (Figure 1.4).



	1.130	1.122
A	0	1
B	1	1
C	1	0

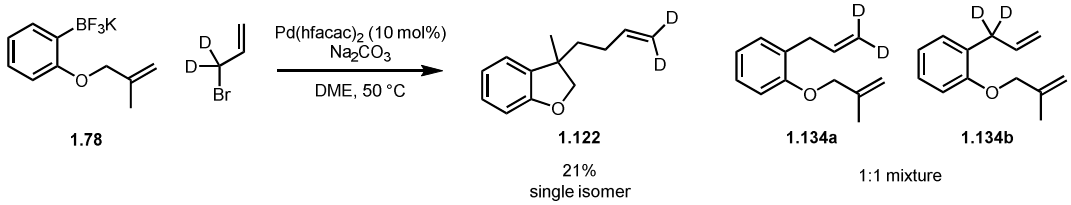
Figure 1.4: Product distribution by Mechanism

Before the mechanism could be tested, synthesis of dideuteroallyl bromide was required. This was done following a literature procedure (Scheme 1.50).[58] Reduction of acrolyl chloride **1.131** with lithium aluminium deuteride at 0 °C in Et_2O gave dideuteroallyl alcohol **1.132** as a solution in Et_2O. Treatment of dideuteroallyl alcohol **1.132** with phosphorous tribromide and pyridine in Et_2O at 0 °C gave dideuteroallyl bromide **1.133**. Distillation gave the desired dideuteroallyl bromide as a solution in diethyl ether. Dideuterioallyl bromide **1.133** was formed as a single deuterated isomer, with none of the other isomer formed by an S_N2' mechanism detected by ^1H NMR.

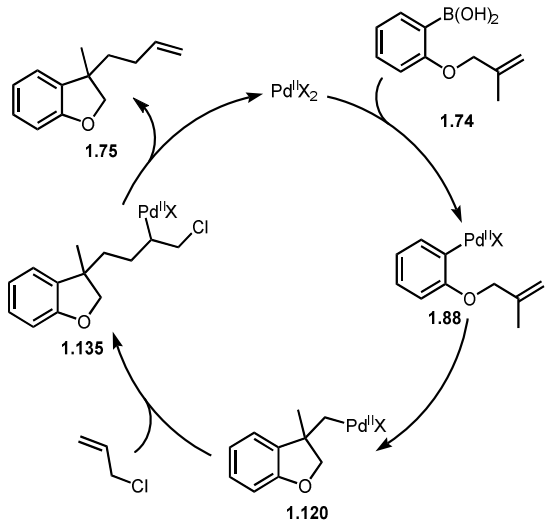


Scheme 1.50: Synthesis of dideuteroallyl bromide **1.133**

With dideuteroallyl bromide **1.133** now available, the carboallylation reaction was carried out (Scheme 1.51). As predicted, dihydrobenzofuran was formed as a single deuterated isomer **1.122**, suggesting mechanism A is operative (Scheme 1.52).

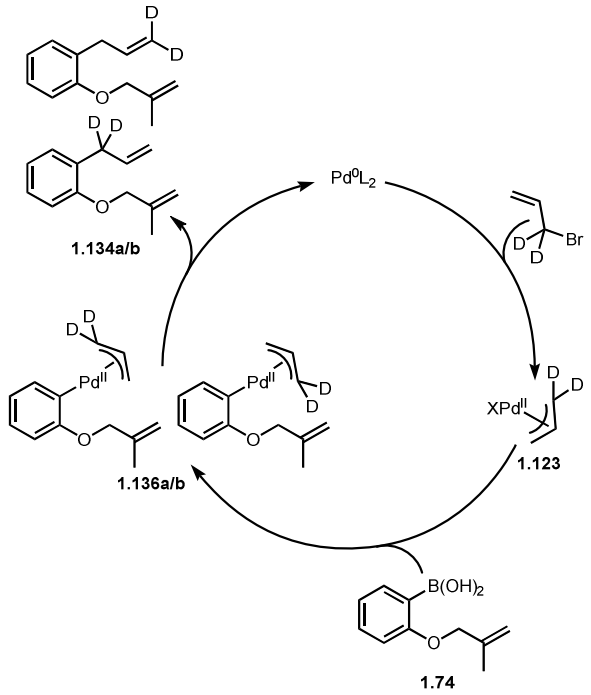


Scheme 1.51: Carboallylation using dideuteroallyl bromide **1.133**



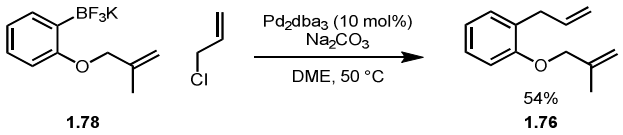
Scheme 1.52: Mechanism of the carboallylation reaction

Interestingly, direct coupling product **1.134a**/**b** was formed as a 50:50 mixture of deuterated isomers. This suggests that mechanism B is responsible for its formation (Scheme 1.53). This is in contrast to earlier theories that both products shared a catalytic cycle, branching after transmetallation to form **1.88**. With formation of the two products in fact involving different mechanisms, new options are opened up in controlling which is formed.



Scheme 1.53: Mechanism for formation of the direct coupling product

As the direct coupling product **1.77** is formed through a Pd(0) mechanism, use of a Pd(0) catalyst should yield only this product, with no dihydrobenzofuran product **1.75** being formed. Swapping $Pd(hfacac)_2$ for Pd_2dba_3 showed that this was indeed the case (Scheme 1.54). ^1H NMR analysis of the crude mixture showed complete conversion to direct coupling product **1.76** in a 54% yield, with no dihydrobenzofuran detected.

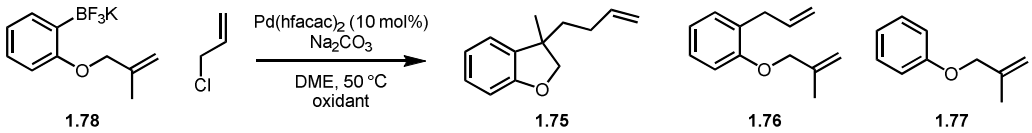


Scheme 1.54: Sole formation of the direct coupling product using Pd(0)

1.2.6 Further optimisation attempts

As the direct coupling product **1.77** is formed by a Pd(0) mechanism, it was proposed that an oxidant could remove any Pd(0) present therefore suppressing formation of **1.77**. To this end, a range of oxidants were screened in the carboallylation reaction (Table 1.5). Initially, standard Pd(0) reoxidants were screened. Benzoquinone proved ineffective, forming only the direct coupling product (entry 1). Use of an oxygen atmosphere, either with (entry 2) or without (entry 3) a copper co-oxidant, mainly saw conversion to the de-boronated product. Silver(I) acetate also saw the de-boronated product formed primarily (entry 5). Use of DDQ saw low conversion, with oxidation of the boronic acid to the alcohol being the major product (entry 4). Use of oxone resulted in the desired dihydrobenzofuran **1.75** being the major product, but significant amounts of the direct coupling product were also formed (entry 6).

Table 1.5: Carboallylation reaction with various oxidant additives



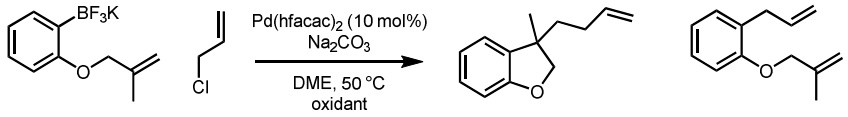
1.78 1.75 1.76 1.77

Entry	Oxidant	Equivalents	1.75	1.76	1.77	Notes
1	Benzoquinone	1	0	1	0	
2	O_2 atm.	-			1	
3	O_2 atm. + $CuCl_2$	1			1	
4	DDQ	1				Boronic acid and alcohol only
5	AgOAc	1			1	
6	Oxone	1	2	1		

Due to the rapid oxidative addition of allyl chloride to any Pd(0) present, an extremely quick oxidant was required. A search of the literature revealed that oxidation of Pd(0) by benzyl chloride occurs extremely rapidly.[59] It induces fast electron transfers forming the corresponding Pd(II) chloride species as well as dibenzyl. As this seemed ideal for our purposes, the carboallylation reaction was carried out using 2 equivalents of benzyl chloride

(Table 1.6, entry 2). Unfortunately, the ratio of carboallylation to direct coupling products was worse than with no oxidant present (entry 1). Increasing the number of equivalents of benzyl chloride to 5 saw an improvement in the ratio, but still slightly worse than with no oxidant (entry 3). The use of 10 equivalents of benzyl chloride saw a further increase in the selectivity, this time giving a better ratio than the base reaction (entry 4). Conversion was, however, slightly lower with the benzyl chloride present. Use of benzyl chloride as a solvent proved to inhibit the desired reaction (entry 5). In this case, the major product was that of direct coupling. This is thought to be due to solubility issues hindering the carboallylation reaction.

Table 1.6: Carboallylation with benzyl chloride as oxidant

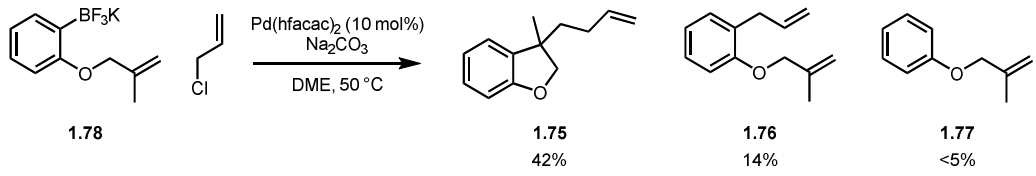


1.78 1.75 1.76

Entry	Oxidant	Equivalents	1.75	1.76
1	None	-	3.3	1
2	Benzyl Cl	2	2.4	1
3	Benzyl Cl	5	3.2	1
4	Benzyl Cl	10	3.7	1
5	Benzyl Cl	Solvent	0	1

1.2.7 Conclusions

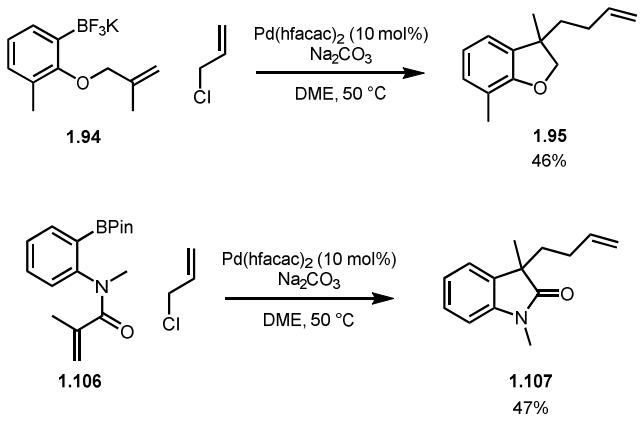
After extensive attempts at optimisation, the optimal carboallylation conditions were shown to be using $Pd(hfacac)_2$, 2 equivalents of allyl chloride, Na_2CO_3, DME as a solvent at 50 °C with no added water (Scheme 1.55). Attempts to improve the overall yield of the reaction proved unsuccessful, with mass recovery studies suggesting that material is lost over the course of the reaction.



1.78 | **1.75** 42% | **1.76** 14% | **1.77** <5%

Scheme 1.55: Carboallylation reaction of potassium trifluoroborate **1.78**

While the direct coupling product was not completely suppressed in the carboallylation reaction of **1.78**, its formation could be decreased by using substrates with restricted rotation. Both methyl substituted potassium trifluoroborate **1.94** and BPin acrylamide **1.106** were successfully cyclised without any formation of the corresponding direct coupling product (Scheme 1.56).



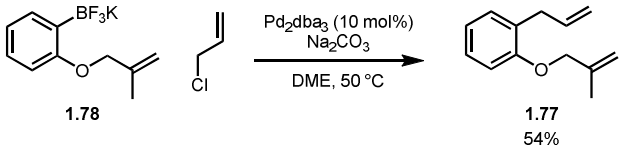
1.94 | **1.95** 46%

1.106 | **1.107** 47%

Scheme 1.56: Carboallylation reaction of other substrates

A deuterium labelling study was carried out using dideuteroallyl bromide. This gave crucial insights into the mechanisms of both the carboallylation product and the direct coupling product. The carboallylation product was confirmed to form via an isohypsic Pd(II) mechanism. Surprisingly, the direct coupling did not use this method, instead forming via a 0–II cycle. The different mechanisms used to form each product could lead to a method for controlling completely which product is formed. This was partially demonstrated with the

ability to form direct coupling product **1.77** as the sole product by using a Pd(0) catalyst (Scheme 1.57).



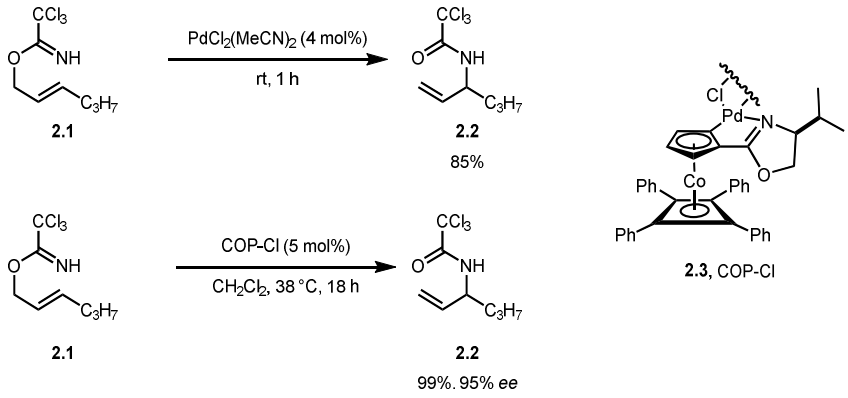
1.78 **1.77**
54%

Scheme 1.57: Sole formation of direct coupling product using Pd(0)

2 Expansion of the Isohypsic–Redox Sequence

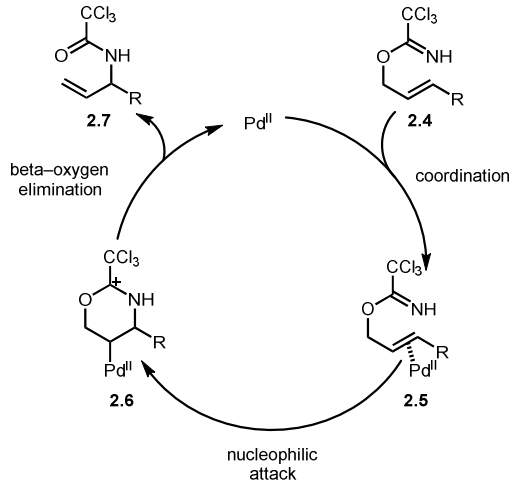
2.1 Introduction

Most palladium-catalysed reactions proceed through a 0–II cycle. Other processes have emerged more recently involving Pd(IV), particularly during C–H activation.[38] There is also a small class of reactions where the oxidation state of the palladium is unchanged throughout the catalytic cycle. These are known as isohypsic reactions, and are also known to occur for rhodium,[60] ruthenium,[61] cobalt[62] and gold.[63] Some examples of palladium-catalysed isohypsic reactions were shown in Chapter 1, with the heteroallylation reaction and the carboallylation reaction (section 1.1.4). Probably the most famous example of a palladium-catalysed isohypsic reaction is the Overman rearrangement. Involving a [3,3]-sigmatropic rearrangement, this leads to formation of a new carbon–nitrogen bond. Initially reported as a thermal rearrangement, requiring the use of mercury salts,[64, 65] the palladium-catalysed version was reported needing lower temperatures and shorter reaction times (Scheme 2.1).[66, 67] Eventually, an asymmetric version was developed, making use of COP-Cl **2.3** as the catalyst (Scheme 2.1).[68]



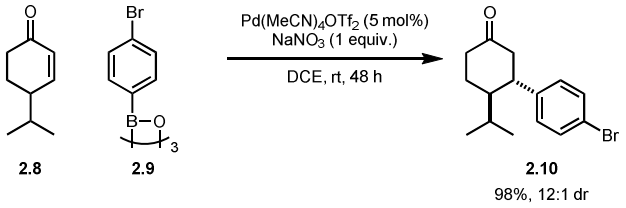
Scheme 2.1: The Overman rearrangement

Extensive studies by Overman *et al.* revealed the operative isohypsic mechanism (Scheme 2.2).[69] Beginning with coordination of the palladium(II) catalyst to the alkene, **2.5** is formed. This species can then undergo nucleophilic attack by the imine, resulting in aminopalladation of the alkene to form cyclised intermediate **2.6**. Finally, β-oxygen elimination gives rise to the product alkene **2.7** as well as releasing the palladium(II) catalyst. As there is no change in the palladium oxidation state, remaining in the 2+ state for the entire catalytic cycle, the Overman rearrangement is indeed isohypsic.



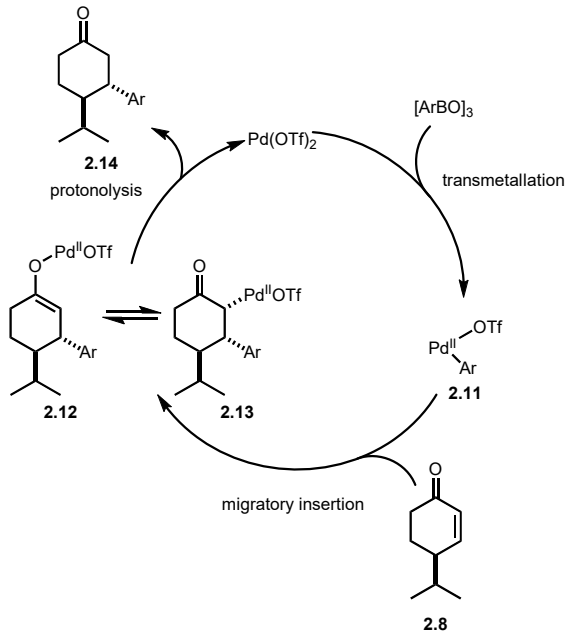
Scheme 2.2: Mechanism of the Overman rearrangement

While rhodium-catalysed conjugate addition to enones is well established,[70] the palladium-catalysed analogue has emerged as a cheaper alternative.[71, 72] Often making use of boronic acids, they can be tolerant of air and moisture. These Michael-type additions can often take place with high diastereoselectivity (Scheme 2.3).[73] Lee and co-workers showed how the 1,4-conjugate addition of boroxine **2.9** to enone **2.8** could occur in high yields with excellent diastereoselectivity.



Scheme 2.3: Michael-type addition of boroxines

In a follow-up paper, Lee *et al.* outlined their proposed mechanism for the transformation (Scheme 2.4).[74] Beginning with transmetallation of the arylboroxine, palladium(II) intermediate **2.11** is formed. Migratory insertion into the alkene **2.8** then takes place, occurring on the opposite face from the bulky alkyl group in the γ-position affording palladium(II) intermediates **2.12** and **2.13**. Subsequent protonolysis will yield the desired conjugate addition product **2.14** as well as regenerating the palladium(II) catalyst.



Scheme 2.4: Mechanism of Michael-type addition of boroxines

2.1.1 Isohypsic–Redox Concept

By exploiting the differences in mechanism between palladium-catalysed isohypsic and redox processes, orthogonal reactivity can be accessed (Figure 2.1). During the isohypsic reaction, some functionality will be inert to the Pd(II) catalyst. When desired, the oxidation state of the metal can be changed, allowing the manipulation of this functionality in a traditional palladium-catalysed redox reaction.

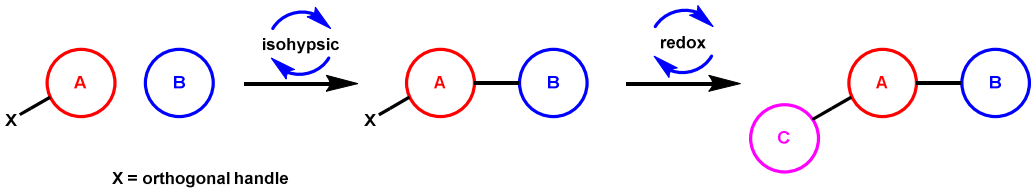
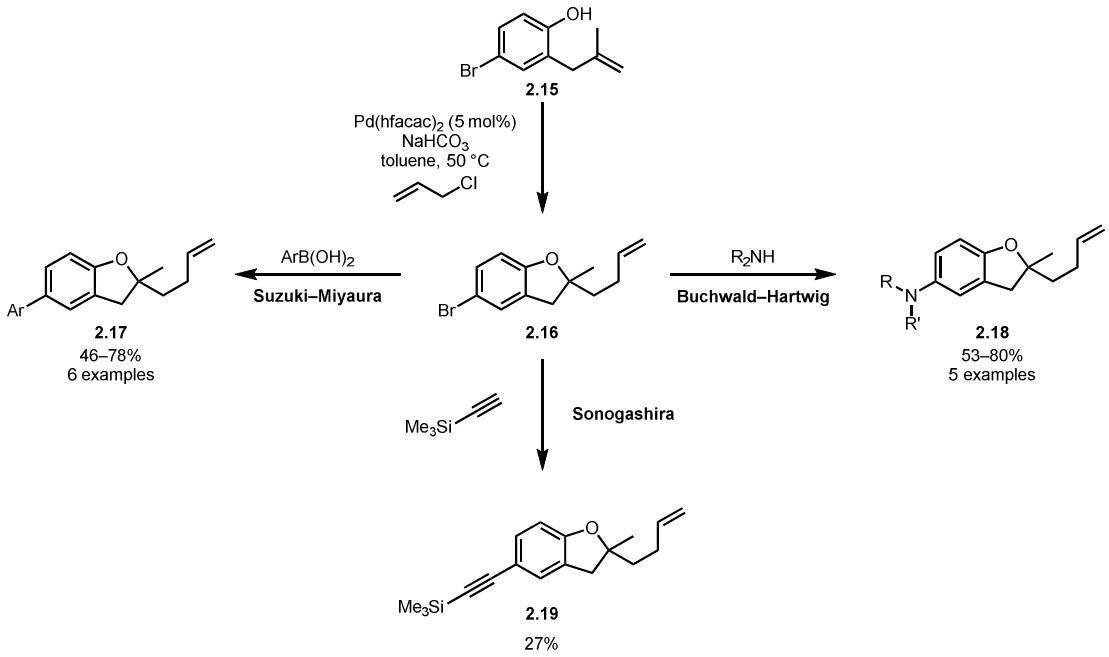


Figure 2.1: Isohypsic–Redox sequence

This combined isohypsic–redox sequence can have a number of advantages. Traditionally, a major limitation of transition-metal catalysis has been the “one reaction–one bond” nature. The ability to form more than one new bond in a single process can allow greatly enhanced molecular complexity. The “plug and play” nature due to the number of known palladium-catalysed isohypsic and redox processes opens up a wide range of product diversity. Finally, by using only a single metal to catalyse two processes, the entire sequence is made more efficient and more economical.

2.1.2 Previous work on Isohypsic–Redox Sequence

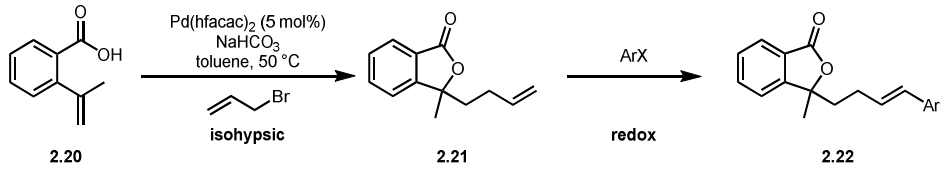
Previous work in the France group saw the development of an Isohypsic–Redox Sequence (Scheme 2.5).[75] By carrying out the an initial isohypsic oxyallylation reaction using phenol **2.15**, benzofuran **2.16** was formed. This contains an aryl bromide, which remains unaffected by the Pd(II) catalyst using in the oxyallylation. By reducing the catalyst to Pd(0), a range of traditional palladium-catalysed redox cross-couplings were able to be carried out. This led to the development of a novel palladium-catalysed process, combining the isohypsic heteroallylation reaction with redox reactions including Suzuki–Miyaura, Buchwald–Hartwig and Sonogashira couplings.



Scheme 2.5: Previously developed isohypsic–redox sequences

2.1.3 Aims

The previously discussed work on the isohypsic–redox sequence has mainly focused on functionalisation at the aryl bromide site (Scheme 2.5). The aim of this work is to expand further functionalisation to the alkene site. This would allow incorporation of reactions such as the Heck-coupling (Scheme 2.6).



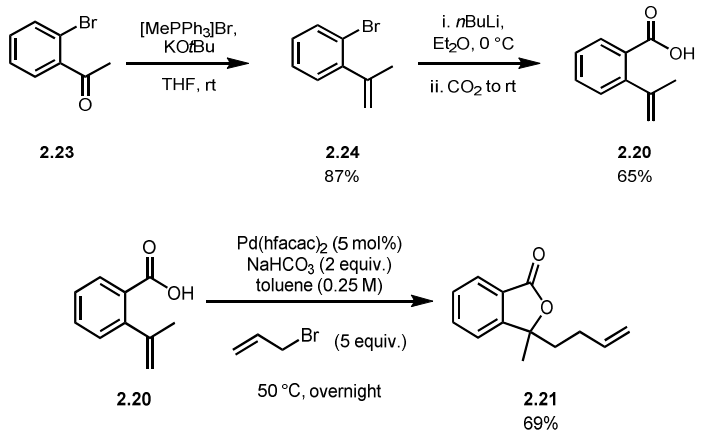
Scheme 2.6: Proposed oxyallylation–Heck-coupling sequence

2.2 Results

2.2.1 Heck reaction

Synthesis of substrate

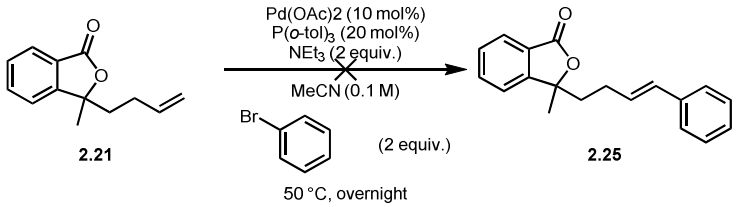
In order to test the oxyallylation–Heck-coupling, it was first required to synthesise alkene **2.21** (Scheme 2.7). Following a known procedure,[48] starting from 2'-bromoacetophenone **2.23**, a Wittig reaction was carried out using methyl triphenylphosphonium bromide and potassium *tert*-butoxide in THF. This formed alkene **2.24** in 87% yield. Treatment with *n*-butyllithium to give lithium–halogen exchange, followed by addition of CO_2 formed acid **2.20** in 65% yield. Finally, the oxyallylation reaction was performed on acid **2.20** to give alkene **2.21** in 69% yield.



Scheme 2.7: Synthesis of **2.21**

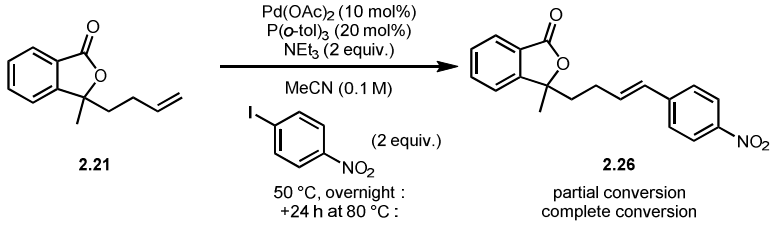
Optimisation of oxyallylation-Heck sequence

The Heck reaction was initially attempted on isolated **2.21** with bromobenzene (Scheme 2.8). Using palladium acetate with tri-*o*-tolylphosphine as a ligand, triethylamine was used both as a base and to help the initial reduction from Pd(II) to Pd(0). Unfortunately, the reaction proved unsuccessful, giving none of the desired product **2.25**.



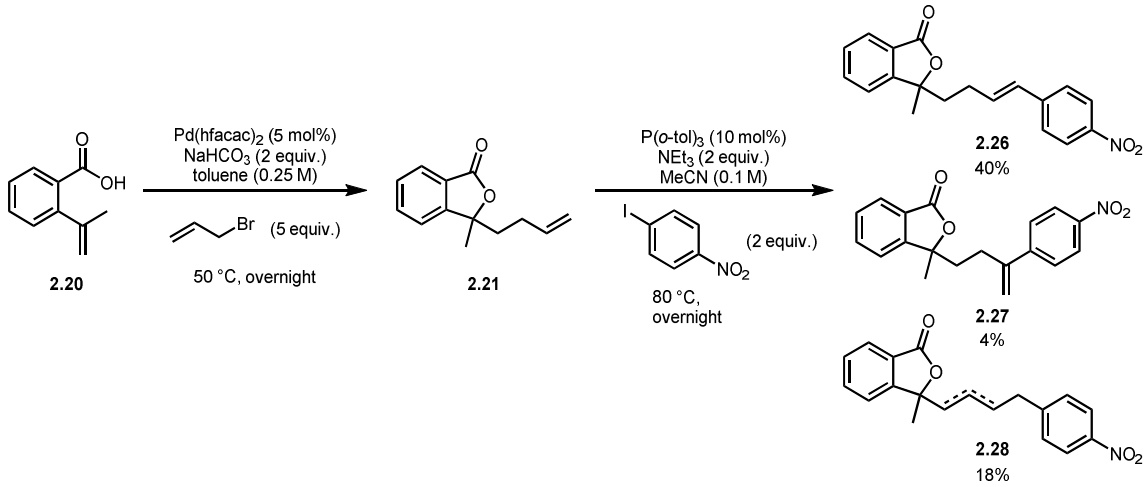
Scheme 2.8: Initial attempt at Heck-coupling

In order to improve the reactivity, bromobenzene was replaced with 4-iodonitrobenzene (Scheme 2.9). Stirring overnight at 50 °C gave some of the desired alkene **2.26**, but significant amount of starting material **2.21** still remained. Stirring for an additional 24 hours at an increased temperature of 80 °C resulted in complete conversion to the desired product.



Scheme 2.9: Heck-coupling using 4-iodonitrobenzene

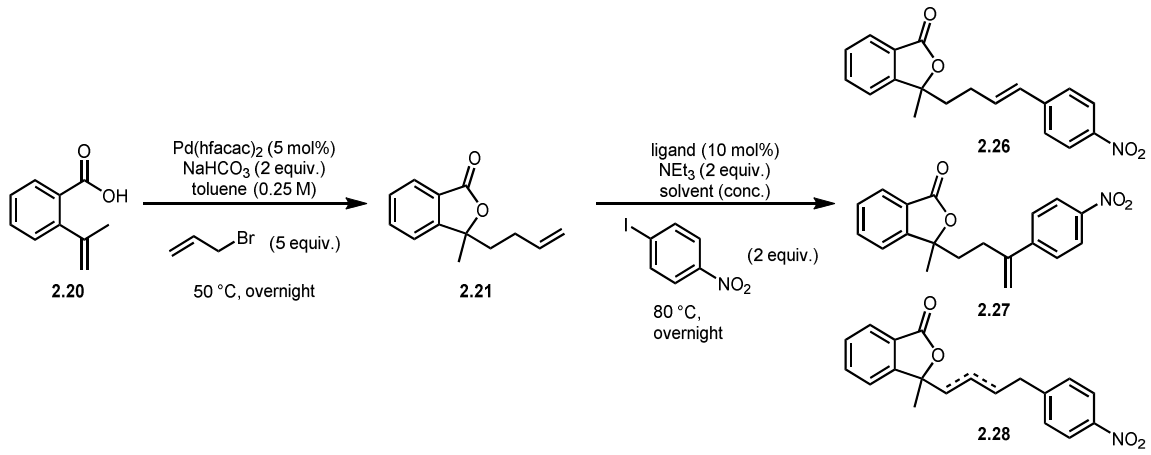
With the Heck reaction providing an initial hit, the combined oxyallylation–Heck procedure was tested (Scheme 2.10). After the oxyallylation under standard conditions was complete, the volatile components were removed *in vacuo*. Tri-*o*-tolylphosphine, acetonitrile and triethylamine were added, followed by 4-iodonitrobenzene. After stirring overnight at 80 °C, the desired Heck product **2.26** was formed in 40% yield along with 4% of the other Heck product **2.27** and 18% of the isomerised products **2.28**.



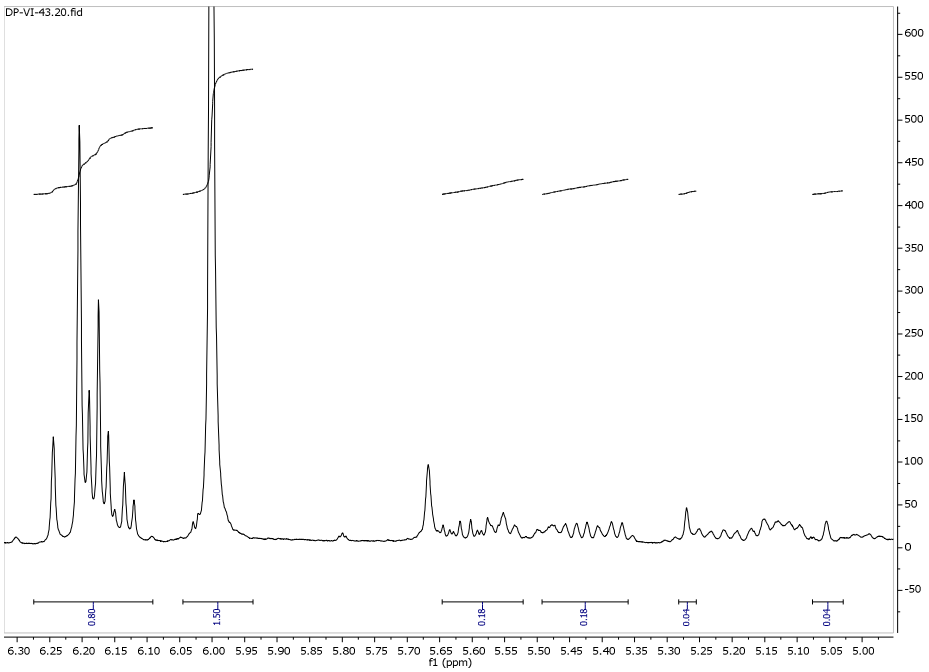
Scheme 2.10: Oxyallylation–Heck-coupling sequence

With the combined oxyallylation–Heck reaction proving successful, a small ligand screen was carried out (Table 2.1). Changing from tri-*o*-tolylphosphine to the Buchwald ligand DavePhos[76, 77] saw a decrease in yield from 40% to 34% mainly due to increased isomerisation when using DavePhos (entries 1 and 2). Use of SPhos saw no change, with **2.26** formed in 40% yield (entry 3). To try and increase the rate of the Heck coupling, the concentration of the second step was increased, but this had no real effect on the yield (entry 4). Use of toluene for both steps, along with an increased temperature in the 2nd step saw no formation of any Heck products, with intermediate **2.21** the only product (entry 5).

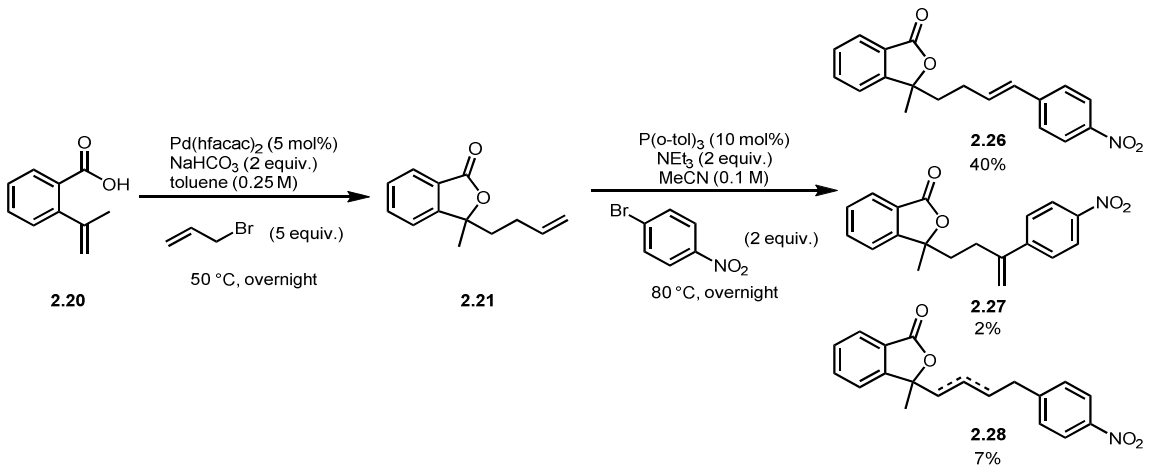
Table 2.1: Optimisation of oxyallylation–Heck-coupling sequence



Entry	Ligand	Solvent	Concentration	2.26	2.27	2.28
1	P(*o*-tol)$_3$	MeCN	0.1 M	40%	4%	18%
2	DavePhos	MeCN	0.1 M	34%	4%	26%
3	SPhos	MeCN	0.1 M	40%	5%	19%
4	SPhos	MeCN	0.25 M	39%	6%	18%
5	SPhos	toluene (110 °C)	0.1 M	0%	0%	0%



Changing from 4-iodonitrobenzene to 4-bromonitrobenzene did not improve the yield, with the desired Heck product **2.26** still formed in 40% yield (Scheme 2.11). However, the formation of both the isomerised product **2.28** and the other Heck product **2.27** were decreased, forming in 7% and 2% yields respectively.



Scheme 2.11: Oxyallylation–Heck-coupling using 4-bromonitrobenzene

Aryl halide screening

Screening was undertaken on a selection of aryl bromides (Figure 2.2). These aryl bromides were chosen as they are part of a GSK reagent set. These are designed to include more challenging, but biologically relevant, functional groups.

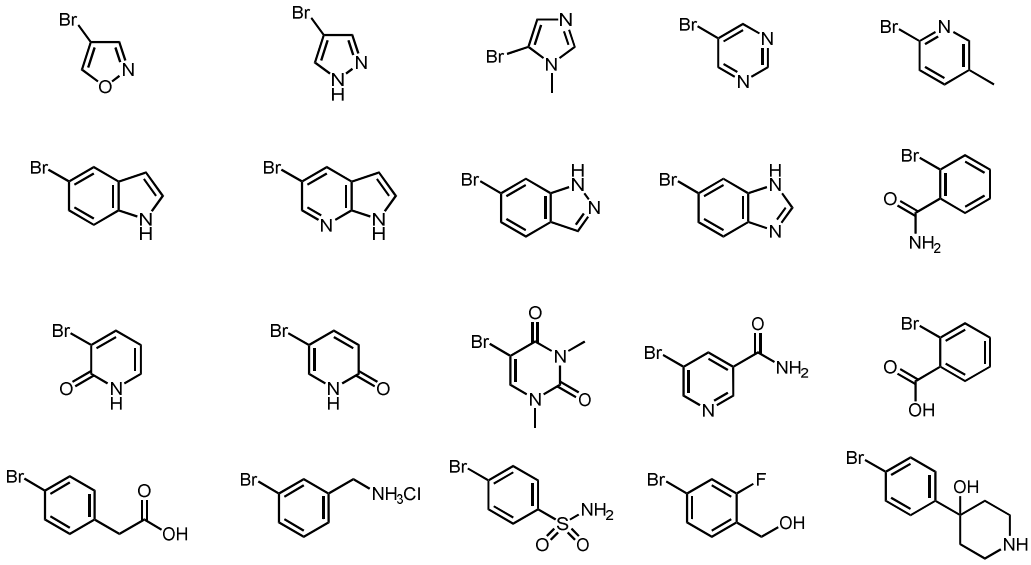


Figure 2.2: Aryl bromides screened

While a lot of the aryl bromides did not undergo Heck-coupling, several did (Figure 2.3). These contained a range of functional groups such as free amines, alcohols, acids and sulfonamides. Addition of a known quantity 1,3,5-trimethoxybenzene allowed calculation of the yield of the combined oxyallylation–Heck reaction by ^{1}H NMR. This showed that for these substrates, the Heck-coupling had proceeded in low to moderate yield.

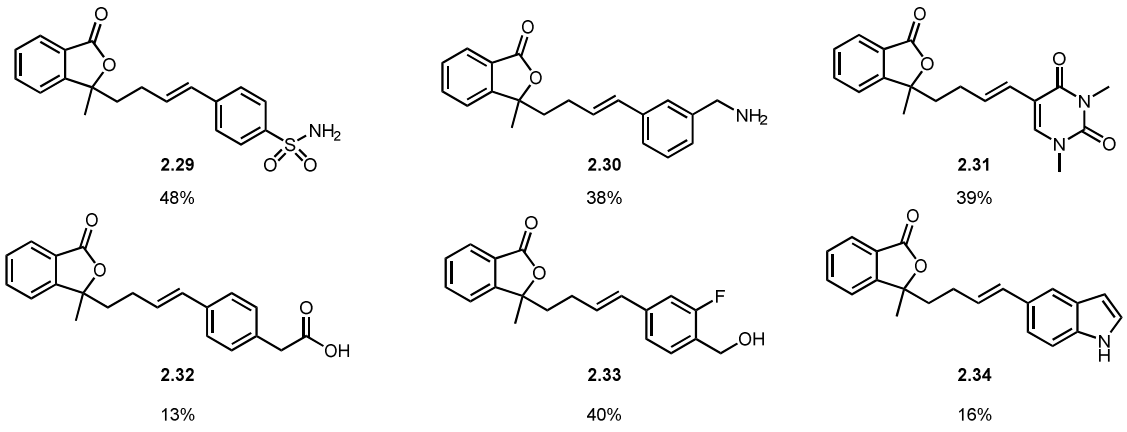
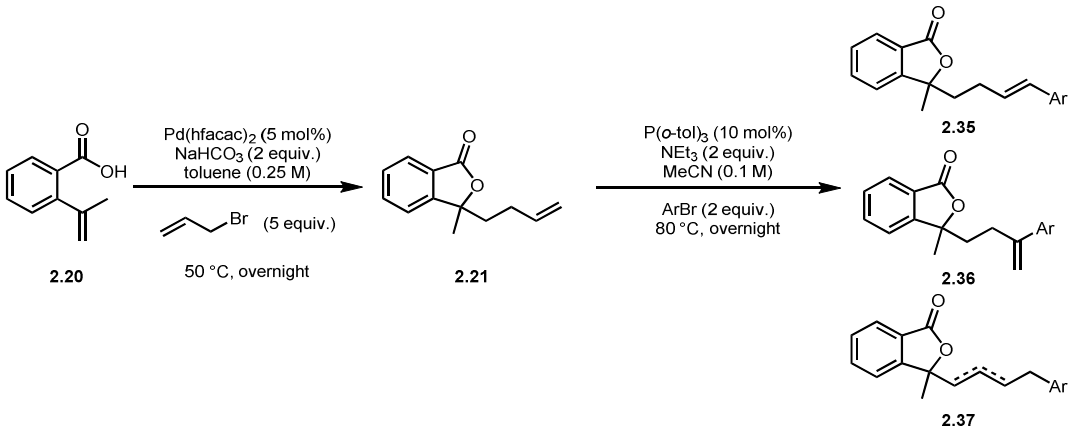


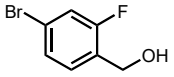
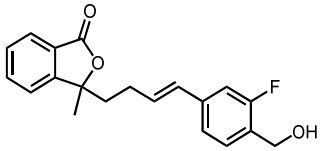
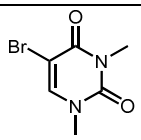
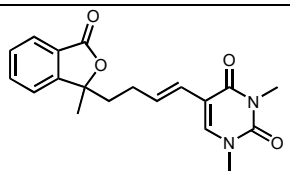
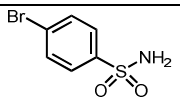
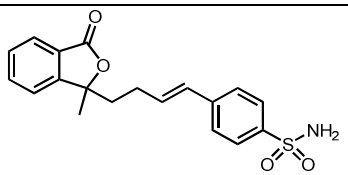
Figure 2.3: Successfully formed products in the oxyallylation–Heck-coupling

Further purification was carried out on **2.29**, **2.31** and **2.33**. This allowed isolation as a mixture of the desired Heck-coupling **2.35**, the branched Heck product **2.36** and the isomerised product **2.37** (Table 2.2). The selectivity for the linear Heck product was high in most cases, though the coupling of 5-bromo-1,3-dimethyluracil did lead to formation of a larger amount of the branched product (entry 2). A similar amount of isomerisation was seen

using 4-bromobenzenesulfonamide as with 4-bromonitrobenzene (entry 3). More isomerisation was seen using 5-bromo-1,3-dimethyluracil and 4-bromo-2-fluorobenzyl alcohol (entries 1 and 2).

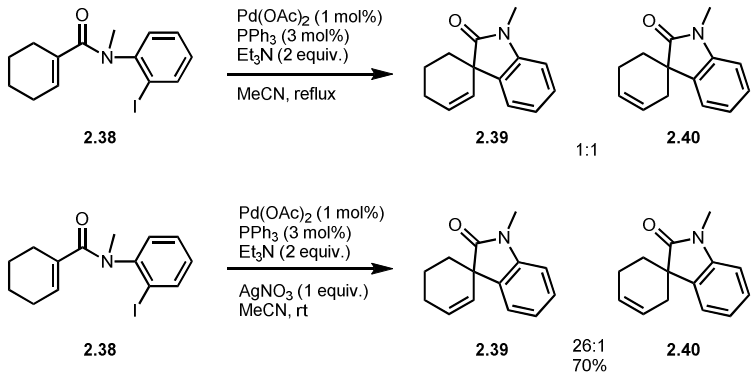
Table 2.2: Product distribution in the oxyallylation–Heck-coupling



Entry	ArBr	Product	2.35	2.36	2.37
1			33%	2%	11%
2			36%	10%	11%
3			44%	4%	8%

While the Heck-coupling generally proceeded with good selectivity between the linear and branched products, isomerisation of the alkene after Heck-coupling is still an issue. This is likely caused by the re-addition and elimination of palladium hydride species after the Heck-coupling has taken place. Overman and co-workers have shown that the addition of silver salts can suppress this type of isomerisation during Heck-couplings (Scheme 2.12).[78] Initial attempts at the cyclisation of tertiary anilide **2.38** resulted in a 1:1 mixture of the desired 3-

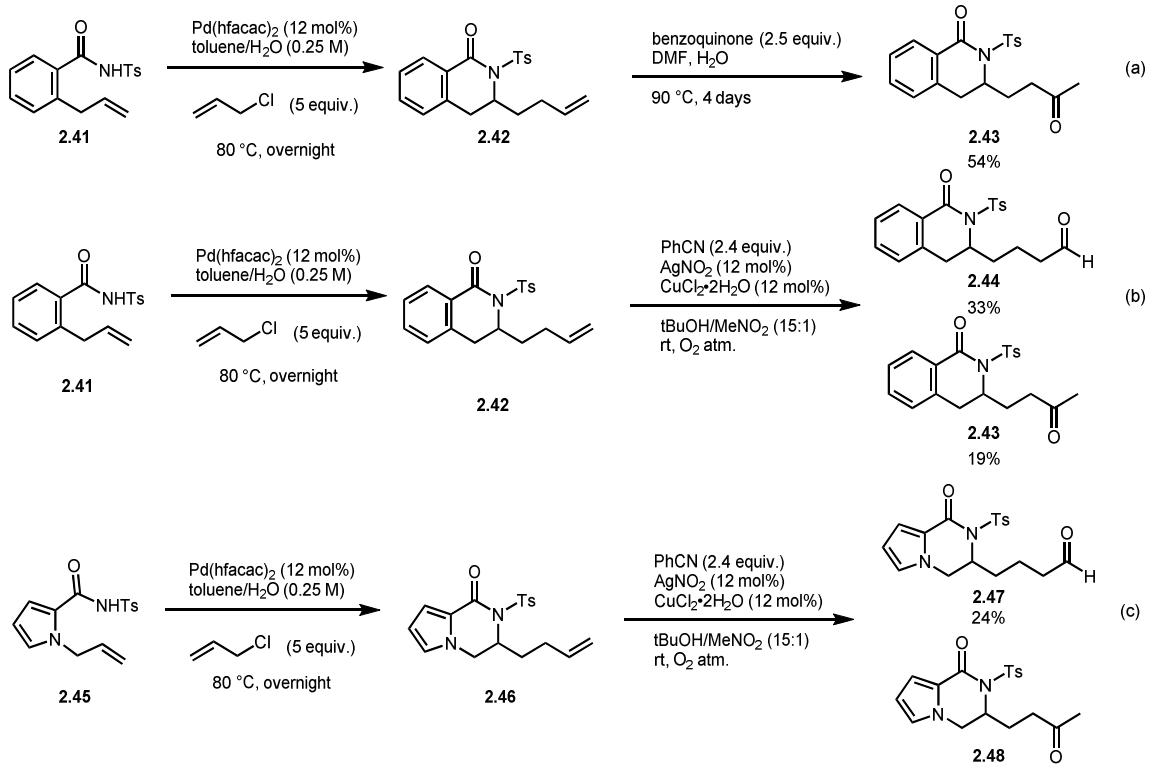
spiro-2-oxindole **2.39** and its alkene regioisomer **2.40**. After screening a range of inorganic salts, it was found that the addition of 1 equivalent of silver nitrate allowed the formation of the desired **2.39** and its regioisomer **2.40** in a 70% yield and a 26:1 ratio. With this information in mind, addition of silver salts could be used during our Heck-couplings to reduce alkene isomerisation – the main side product formed. In some cases, this should give a significant boost to the overall yield.



Scheme 2.12: Use of silver salts to suppress isomerisation in Heck-couplings

2.2.2 Grubbs–Wacker reaction

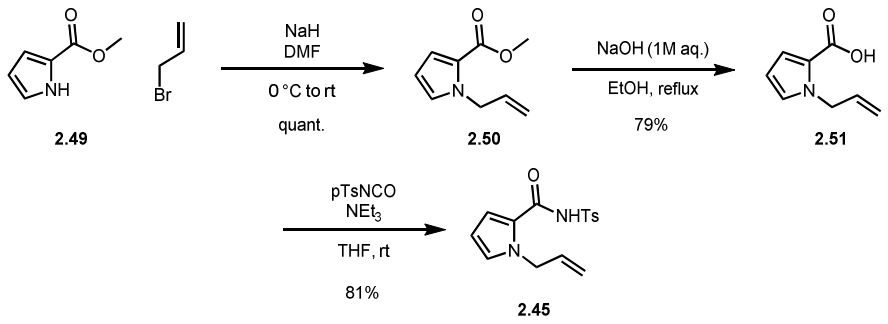
Following the successful development of the oxyallylation–Wacker oxidation in the France group (Scheme 2.13a), work was begun on the oxyallylation–Grubbs–Wacker oxidation as an isohypsic–redox sequence.[75] This resulted in the development of conditions for the formation of aldehyde **2.44** in 33% yield, with ketone **2.43** formed in 19% yield (Scheme 2.13b). When these conditions were applied to **2.45**, aldehyde **2.47** was formed in 24%, with a yield not obtained for ketone **2.48** (Scheme 2.13c). In an attempt to improve the yield and aldehyde/ketone ratios, further optimisation was planned.



Scheme 2.13: Previous work on the aminoallylation–Wacker and –Grubbs–Wacker sequence

Substrate synthesis

The first step was the synthesis of pyrrole **2.45** following a known procedure (Scheme 2.14).[79] Base-promoted allylation of methyl pyrrole-2-carboxylate **2.49** afforded *N*-allyl pyrrole **2.50** in a quantitative yield. Ester hydrolysis to the acid **2.51** allowed formation of the tosylamide **2.45** in 81% yield using tosyl isocyanate.



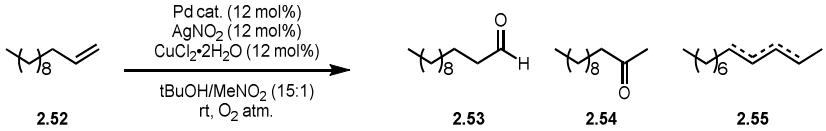
Scheme 2.14: Synthesis of tosylamide **2.45**

Tests with dodecene

Before testing of the Grubbs–Wacker on pyrrole **2.45**, testing was carried out on dodecene **2.52** (Table 2.3). To try and simulate the conditions that would be present in the combined

oxyallylation-Grubbs–Wacker reaction, the oxidation of dodecene was carried out using $Pd(hfacac)_2$ with addition of benzonitrile. Instead of oxidation, this resulted in isomerisation of the alkene, with no oxidised products formed (entry 1). Pre-stirring the catalyst and benzonitrile for 10 minutes before addition of dodecene made no difference, with isomerisation again the only product (entry 2). Use of the pre-formed catalyst $PdCl_2(PhCN)_2$ gave a 1:2 aldehyde:ketone ratio (entry 3). When dried solvents were used, the aldehyde:ketone ratio was increased to 3:1 (entry 4).

Table 2.3: Grubbs–Wacker oxidation of dodecene



Entry	Catalyst	2.52	2.53	2.54	2.55
1	$Pd(hfacac)_2$/PhCN	0	0	0	1
2	$Pd(hfacac)_2$/PhCN	0	0	0	1
3	$PdCl_2(PhCN)_2$	0	1	2	0
4*	$PdCl_2(PhCN)_2$	0	3	1	0

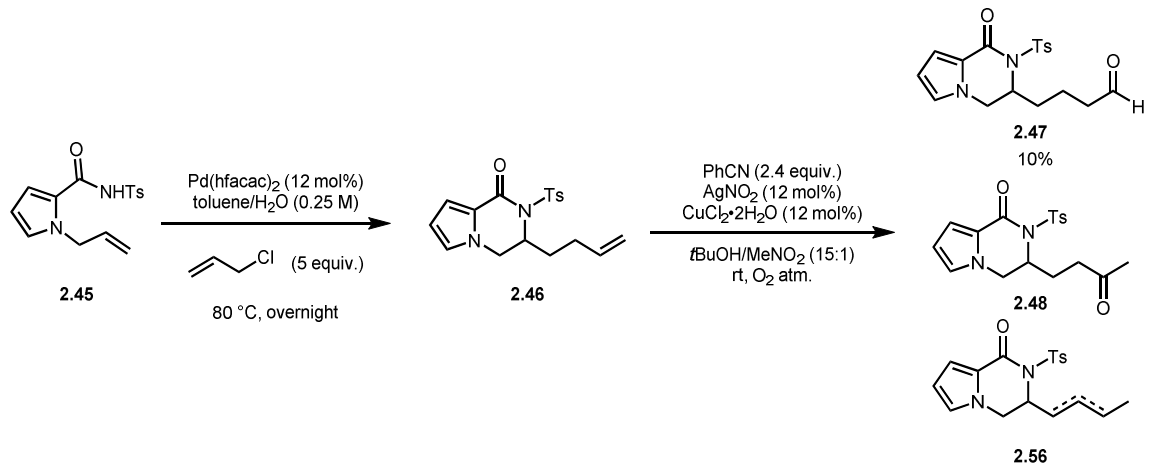
*Using dried solvents

Optimisation with pyrrole substrate

With these results in mind, attention was turned to the combined reaction using pyrrole substrate **2.45** (Table 2.4). After carrying out the aminoallylation, the volatile components were removed *in vacuo*. After addition of benzonitrile, silver nitrite, copper chloride and dry *tert*-butanol/acetonitrile, the reaction mixture was stirred under an oxygen atmosphere at room temperature. This resulted in low conversion of the intermediate to the oxidised products, with aldehyde **2.47** formed in 10% yield, with the amount of ketone formed unable to be determined (entry 1). Isomerisation of the alkene intermediate formed during the aminoallylation was also seen in significant amounts. As water has a negative effect on the aldehyde/ketone selectivity in the Grubbs–Wacker reaction, attempts were made to eliminate it. Addition of molecular sieves during the second step had a negative effect on conversion, with only a small amount of aldehyde formed (entry 2). As complete removal of the water present in the aminoallylation is difficult, this was attempted in the absence of water.

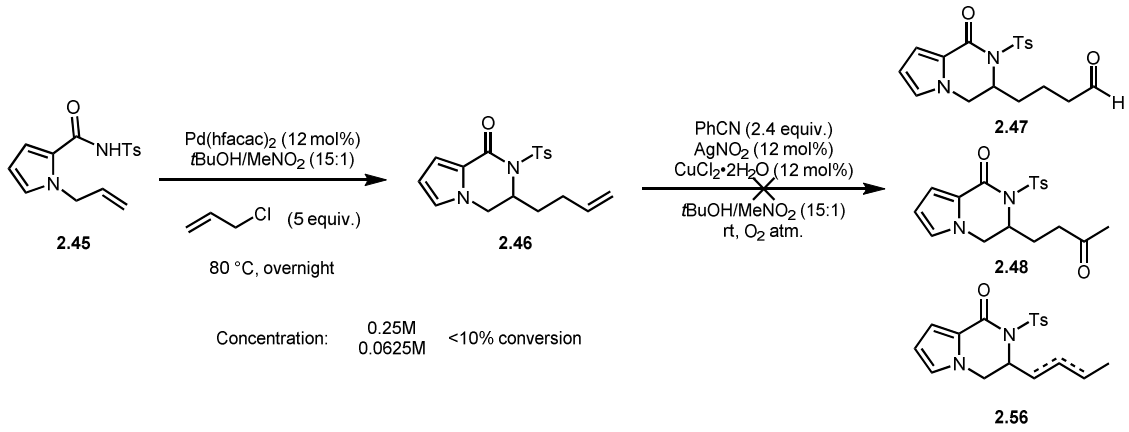
However, this resulted in greatly reduced conversion in the aminoallylation step, rendering this avenue fruitless (entry 3).

Table 2.4: Attempted optimisation of aminoallylation–Grubbs–Wacker



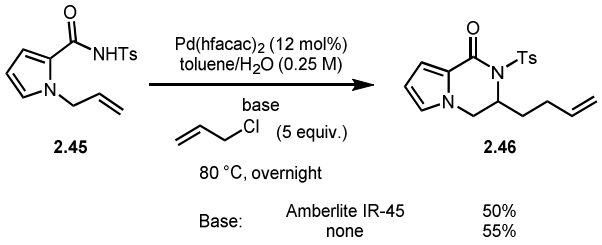
Entry	Change	2.47
1	-	10%
2	Molecular sieves in step 2	<5%
3	No water in step 1	0%, <20% conversion in 1st step

Carrying out the aminoallylation step using *tert*-butanol and nitromethane had a negative effect on conversion (Scheme 2.15). Whether carried out at the standard concentration of 0.25 M, or the lower concentration normally used for the Grubbs–Wacker step, only a small amount of the cyclised intermediate **2.46** was formed, leading to no formation of aldehyde **2.47** in a detectable quantity.



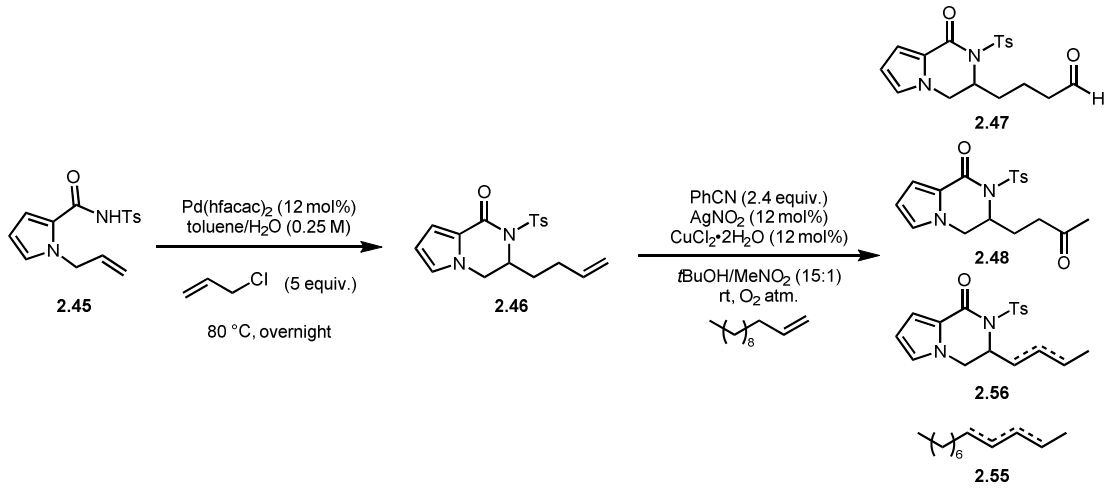
Scheme 2.15: Aminoallylation using tBuOH/$MeNO_2$ as solvent

Previous studies had shown that the presence of an inorganic base such as KH_2PO_4 greatly improved the conversion in the aminoallylation. Unfortunately, the presence of any base also shuts down the Grubbs–Wacker reaction.[75] To solve this, the aminoallylation was attempted using the solid-supported base Amberlite IR-45 (Scheme 2.16). Due to the base being supported on a resin removal should be easy, allowing the Grubbs–Wacker to proceed uninhibited. However, conversion to the cyclised product **2.46** was only 50%, showing no improvement over the base free reaction.



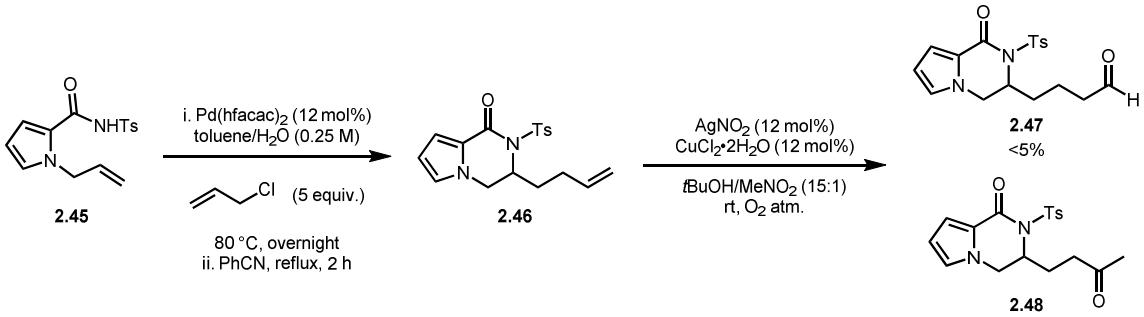
Scheme 2.16: Aminoallylation using solid-supported base

Previous tests on dodecene had shown isomerisation occurring when using $Pd(hfacac)_2$ and benzonitrile as the catalyst system. To check if this was the issue again, the second step of the aminoallylation–Grubbs–Wacker was spiked with one equivalent of dodecene (Scheme 2.17). As well as the normal isomerisation of the pyrrole alkene giving **2.56**, this also resulted in isomerisation of the dodecene to form **2.55**. This suggests that the active $Pd(PhCN)_2$ catalyst is not being formed properly.



Scheme 2.17: Spiking second step with dodecene

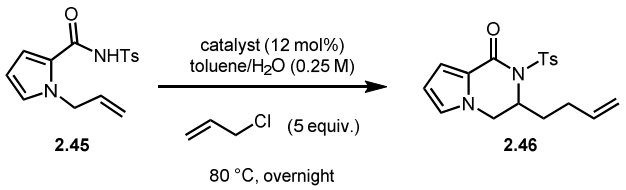
In an attempt to form the active $Pd(PhCN)_2$ catalyst, benzonitrile was added to the reaction mixture after the aminoallylation was complete (Scheme 2.18). This mixture was then refluxed for 2 hours. The Grubbs–Wacker step was then carried out as normal, with the removal of volatiles before addition of the new reagents. While the amount of isomerisation was reduced, the conversion was also reduced. This meant only a small amount of aldehyde **2.47** was formed, with <5% yield.



Scheme 2.18: Attempts to form active catalyst

As the hfacac ligands could be hindering formation of the active Grubbs–Wacker catalyst, the aminoallylation was attempted using alternative catalysts (Table 2.5). Using the pre-formed $PdCl_2(PhCN)_2$ catalyst, conversion was extremely low, with a 9:1 ratio between the starting pyrrole **2.45** and the cyclised product **2.46** (entry 1). Use of palladium chloride was more successful, giving a 1.8:1 ratio (entry 2). Increasing the concentration from 0.25 M to 0.5 M had a negative effect, reducing conversion to just 25% (entry 3). Lowering the concentration to 0.1 M improved conversion slightly, but the starting material was still the major product, with a 1.4:1 ratio (entry 4). Still below 50% conversion, this was not good enough to form a reasonable amount of the oxidised products in the Grubbs–Wacker step.

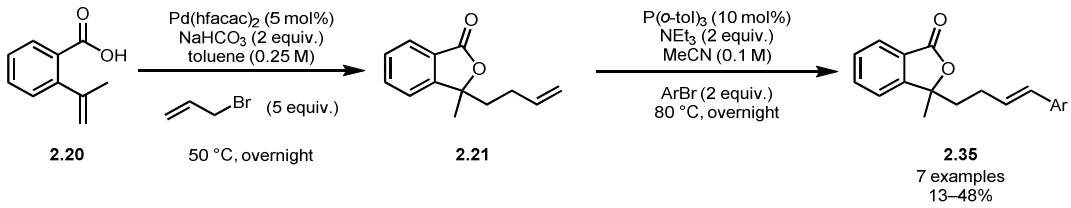
Table 2.5: Screening of aminoallyation with different catalysts



Entry	Catalyst	Concentration	2.45:2.46
1	$PdCl_2(PhCN)_2$	0.25 M	9:1
2	$PdCl_2$	0.25 M	1.8:1
3	$PdCl_2$	0.5 M	3:1
4	$PdCl_2$	0.1 M	1.4:1

2.2.3 Conclusions

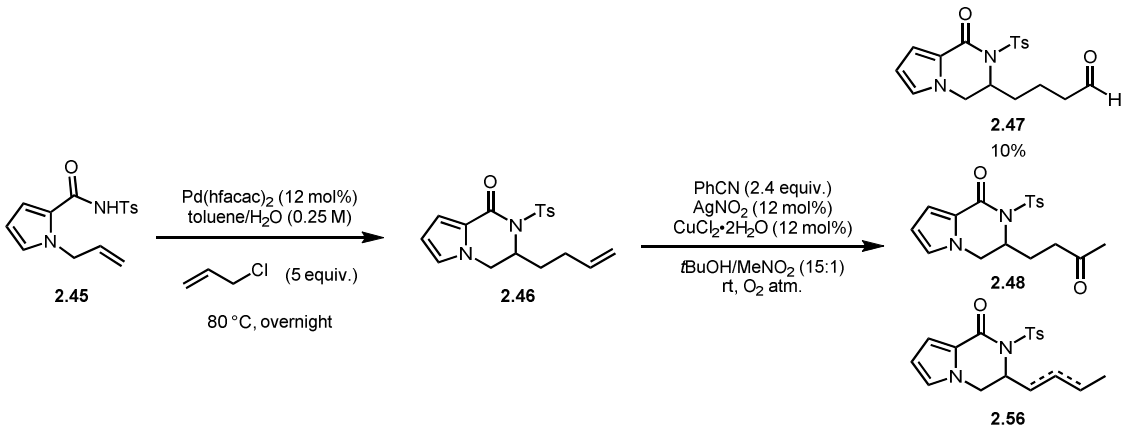
The isohypsic–redox sequence has been successfully expanded to include the Heck-coupling. This resulted in the oxyallylation–Heck-coupling of acid **2.20** with a range of functionally diverse aryl bromides (Scheme 2.19). Some further optimisation is required to suppress isomerisation of the alkene, but this could possibly be achieved through the addition of silver salts, such as silver nitrate, to the Heck-coupling. Overall, the development of this sequence opens up another point of functionalisation after the heteroallylation reaction and adds another tool to the isohypsic–redox sequence.



Scheme 2.19: Oxyallylation–Heck-coupling sequence

While further optimisation of the aminoallylation–Grubbs–Wacker sequence was unsuccessful, crucial insights were gained (Scheme 2.20). One of the main issues was caused by isomerisation of the alkene to form **2.56** instead of oxidation. Competition experiments with dodecene showed that this is likely due to improper formation of the active $Pd(PhCN)_2$ catalyst. Further work to ensure efficient formation of this catalyst could help

suppress alkene isomerisation, boosting the yield of the oxidised products **2.47** and **2.48**. While silver nitrite is present in this reaction, addition of other silver salts could assist in the suppression of this isomerisation.



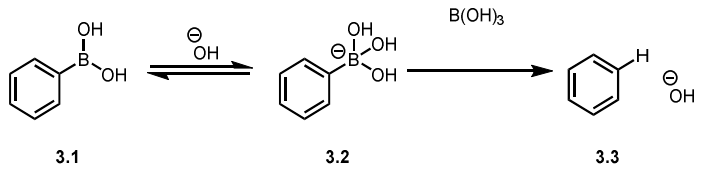
Scheme 2.20: Aminoallylation–Grubbs–Wacker sequence

3 Allylation of MIDA boronates

3.1 Introduction

3.1.1 Background of MIDA boronates

While the utility of boronic acids can hardly be understated, there are still issues surrounding their use in organic synthesis. As has been seen in Chapter 1, they can be prone to undergo undesired side reactions such as protodeboronation, oxidation and polymerisation. Protodeboronation, for example, often occurs in highly acidic or basic aqueous conditions, particularly when ortho-substituted or electron-poor aryl boronic acids are used (Scheme 3.1). Unfortunately, these are precisely the type of conditions used in Suzuki-Miyaura cross-coupling reactions. Some types of boronic acid, e.g. alkyl boronic acids and 2-heteroaromatic boronic acids, are prone to decomposition on storage under air, often to the corresponding alcohol.[80]

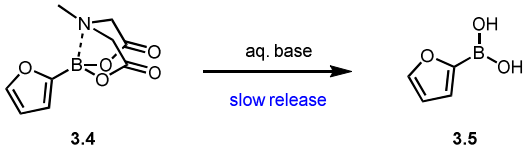


Scheme 3.1: Protodeboronation of boronic acids

Some alternatives to boronic acids have been developed. As seen in Chapter 1, potassium trifluoroborates provide a more stable alternative to boronic acids. Due to the strong B–F bonds and the tetrahedral complex, the undesired side reactions that affect boronic acids are less common. When used in cross-coupling reactions, potassium trifluoroborates provide a slow release of the active boronic acid under aqueous conditions. Some of the drawbacks of potassium trifluoroborates are their low solubility in apolar and chlorinated solvents. They are also generally unstable to column chromatography.

A more recently developed alternative to boronic acids are MIDA boronates.[81] Formation of a dative B–N bond gives a tetrahedral space around boron. As well as the two five-membered rings protecting the boron atom, it has a filled p-orbital, increasing the stability of the boronate ester. This stability means that MIDA boronates are both air and water stable, tolerating neutral or acidic aqueous solutions. MIDA boronates are stable to anhydrous cross-coupling conditions, even when carried out at elevated temperatures. While not tolerant of strong nucleophiles, MIDA boronates are tolerant of other harsh conditions such as triflic acid or Jones reagent.[82] When exposed to aqueous base, MIDA boronates undergo slow release of

the active boronic acids (Scheme 3.2). The speed of this release can be tuned by the temperature and by the base used. As the boronic acid is released slowly over the course of a reaction, it can be used as soon as it is formed. This prevents the boronic acid building-up in the reaction and undergoing the undesired side reactions.



Scheme 3.2: Hydrolysis of MIDA boronates to release boronic acid

Unlike potassium trifluoroborates, MIDA boronates have good solubility in a range of organic solvents. They are also stable to column chromatography, displaying useful properties. By exploiting the solubility of MIDA boronates, they can be purified using "catch and release" chromatography. When run in 1.5% MeOH/Et_2O, the MIDA boronate will remain stationary, while most other organic molecules will elute quickly (Figure 3.1, left). Simply changing the eluent to THF results in rapid elution of the MIDA boronate (Figure 3.1, right).

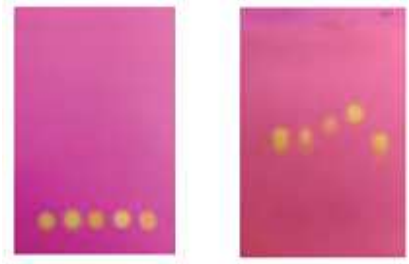
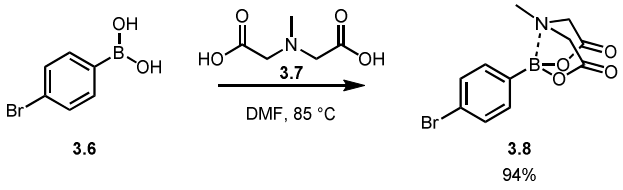


Figure 3.1: TLC of MIDA boronates in 1.5% MeOH/Et_2O (left) and THF (right) [83]

Synthesis of MIDA boronates

A range of methods have been developed for the synthesis of MIDA boronates. This allows formation of MIDA boronates containing a range of different functionalities – if one method fails, another is likely to succeed. Probably the simplest method is the condensation of a boronic acid with MIDA. Initially requiring the use of Dean–Stark conditions and DMSO as co-solvent, this can now often be performed simply by heating the boronic acid in the presence of MIDA in DMF (Scheme 3.3).[84]

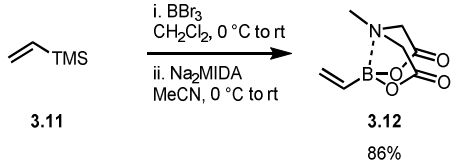


Scheme 3.3: Synthesis of MIDA boronate **3.8**

Other methods do not require an existing boronic acid. Bromoboration of an alkyne with tribromoborane gives the corresponding dibromoborane (Scheme 3.4).[85] Trapping of this dibromoborane with MIDA in the presence of 2,6-lutidine affords the alkenyl MIDA boronate **3.10**.

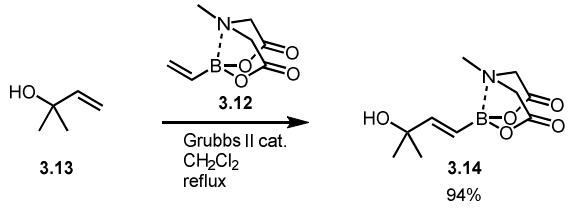
Scheme 3.4: Synthesis of MIDA boronate **3.10**

Organotrimethylsilanes can also be converted into MIDA boronates (Scheme 3.5).[86] After undergoing transmetalltion with tribromoborane, the resulting dibromoborane can be trapped by the disodium salt of MIDA. This approach has been use in the synthesis of vinyl MIDA boronate **3.12**, where other methods had been unsuccessful.



Scheme 3.5: Synthesis of MIDA boronate **3.12**

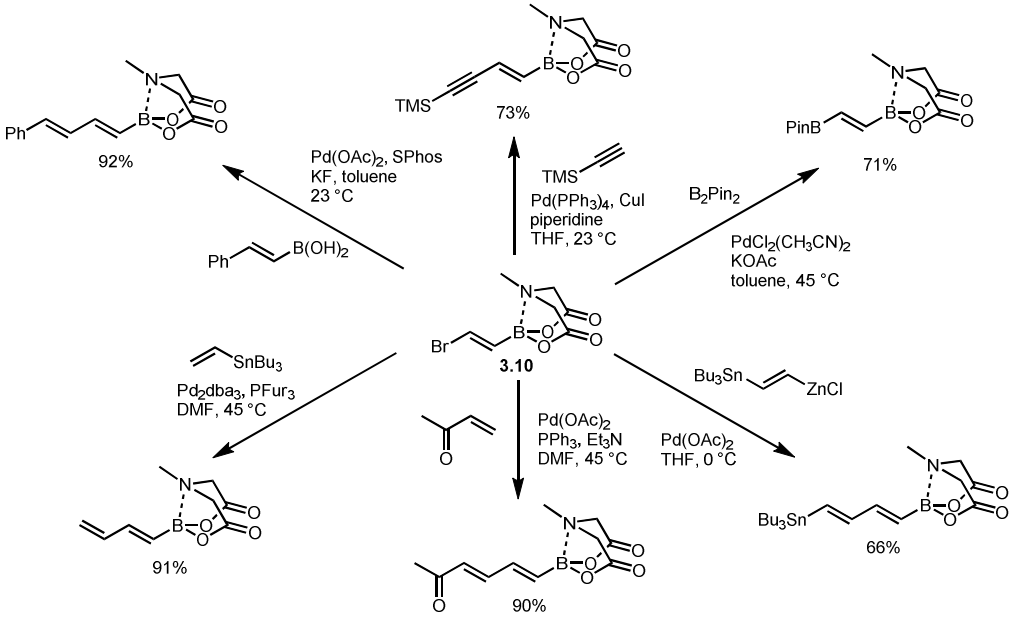
Once formed, vinyl MIDA boronate **3.12** can also be used in the synthesis of a range of other alkenyl MIDA boronates (Scheme 3.6).[86] By carrying out cross-metathesis, a wide range of alkenyl MIDA boronates can be synthesised. This mild approach tolerates a range of functionality and forms the *E* alkene isomer exclusively.



Scheme 3.6: Synthesis of MIDA boronates via cross-metathesis

Use as a boronic acid protecting group

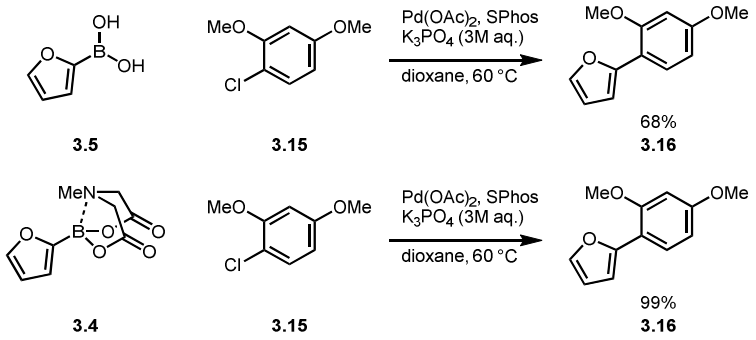
As a result of their stability in the absence of aqueous base, MIDA boronates can effectively be used as protecting groups for boronic acids. They can allow a wide range of cross-coupling reactions to take place while leaving the boronic acid completely untouched. Burke has particularly demonstrated this using bifunctional MIDA boronate **3.10** (Scheme 3.7).[85] Suzuki–Miyaura, Stille and Heck couplings were all carried out without any effect on the MIDA boronate. Further functionalisation was provided by Sonagashira and Negishi couplings and a Miyaura borylation, all yielding a highly useful bifunctionalised molecule.



Scheme 3.7: Cross-coupling reactions carried out in the presence of MIDA boronates

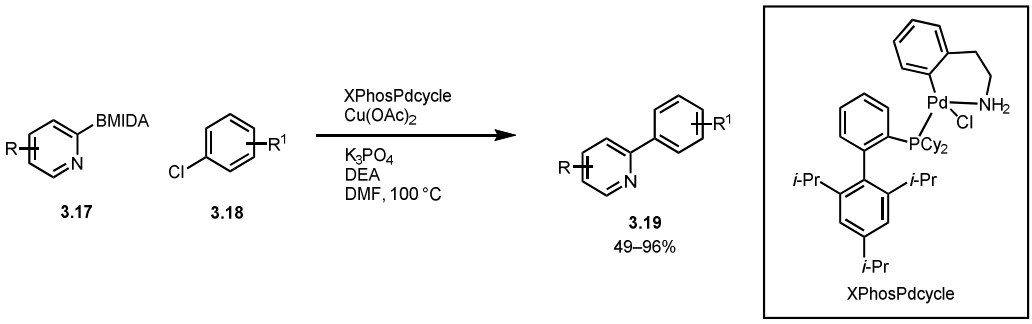
Reactions of MIDA boronates

The ability of MIDA boronates to supress side reactions of boronic acids was demonstrated by Burke in the cross-coupling of furanylboronic acid **3.5** with the particularly deactivated 2,4-dimethoxychlorobenzene **3.15** (Scheme 3.8).[80] By using the furanyl MIDA boronate **3.4**, the yield was improved from 68% to 99%. This is mainly due to the slow release of boronic acid over the course of the reaction preventing build-up of significant amounts of boronic acid. As the boronic acid is not forming in large amounts, the amount lost to any side reactions is greatly decreased.



Scheme 3.8: Difference in yield using MIDA boronate and boronic acid

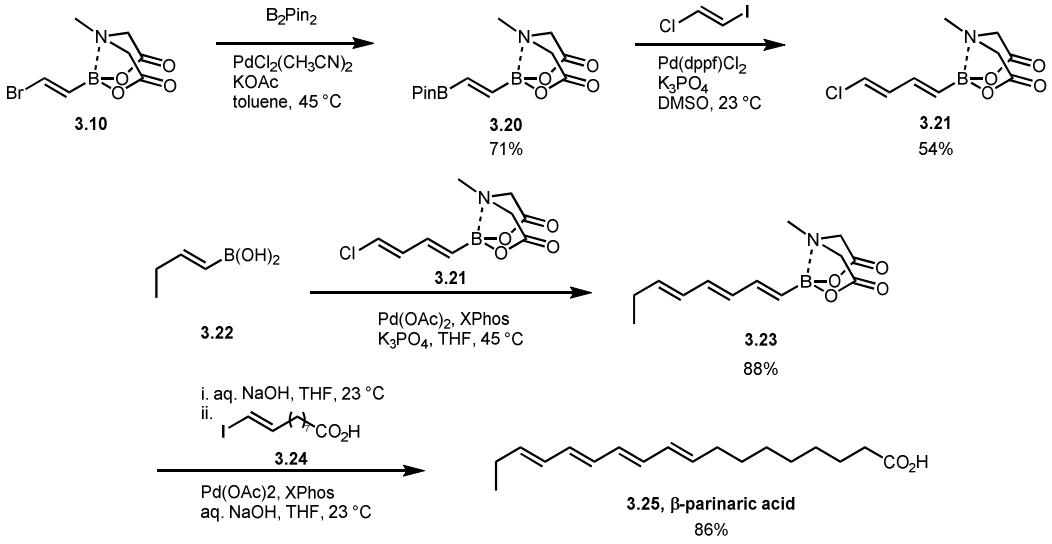
One of the most difficult substrates for cross-coupling reactions is the 2-pyridyl group. This is mainly due to the extreme sensitivity of the 2-pyridyl–boron bond to protodeboronation. Having isolated the 2-pyridyl MIDA boronate and found it to be air-stable, Burke developed conditions to allow its efficient cross-coupling (Scheme 3.9).[87] By making use of a highly active pre-formed catalyst, XPhosPdcycle, the oxidative addition is ensured to take place quickly, increasing the amount of Pd(II) available for transmetallation. This helps reduce the amount of time the free 2-pyridyl boronic acid spends in solution. Addition of copper acetate along with diethanolamine led to formation of a $Cu(DEA)_2$ species. This could then undergo a pre-transmetallation with the 2-pyridyl boronic acid, allowing a faster transmetallation to palladium. Finally, the use of the stable MIDA boronate allowed a slow release of the reactive 2-pyridyl boronic acid. As only a small amount of the free boronic acid was present at any one time, the potential for protodeboronation was greatly decreased. Altogether, these measures allowed the cross-coupling of 2-pyridyl MIDA boronate with over 20 different halides in moderate to excellent yields.



Scheme 3.9: Cross-coupling of 2-pyridyl MIDA boronates

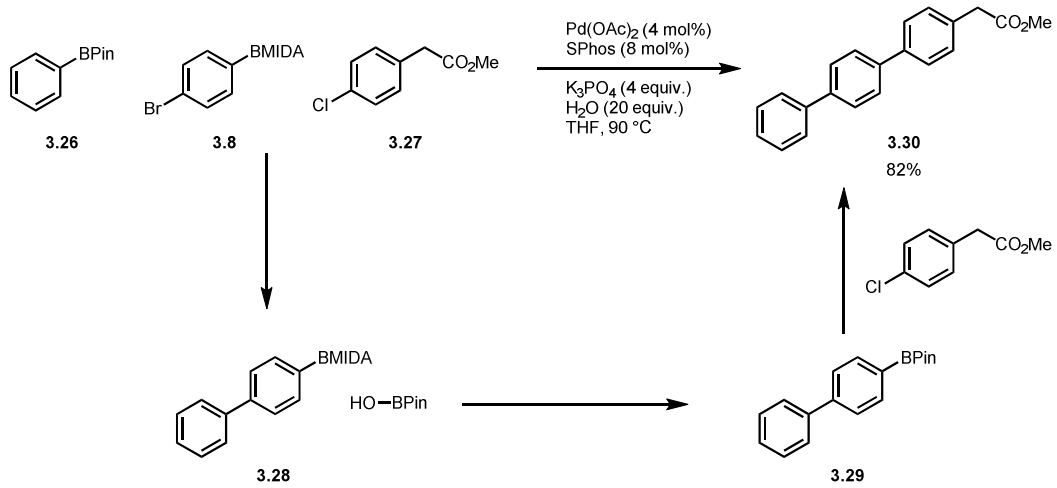
3.1.2 Step-wise/synthesis machine potential

Due to the stability of MIDA boronates to anhydrous cross-coupling and the ability to control the release of the active boronic acid, they can be extremely useful in step-wise synthesis. This ability to carry out iterative cross-coupling has proven particularly useful in the synthesis of complex polyene frameworks.[85] Beginning with alkenyl MIDA boronate **3.10**, installation of the pinacol boronic ester formed bifunctional alkene **3.20** (Scheme 3.10). Selective cross-coupling with (*E*)-1-chloro-2-iodoethylene gave diene **3.21** in 54% yield. Coupling of **3.21** with (*E*)-1-butenylboronic acid **3.22** afforded the all-*trans* trieneyl MIDA boronate **3.23** in 88% yield. Finally, full hydrolysis of the MIDA boronate, followed by cross-coupling with vinyl iodide **3.24** gave the fluorescent probe β-parinaric acid **3.25** in an 86% yield.



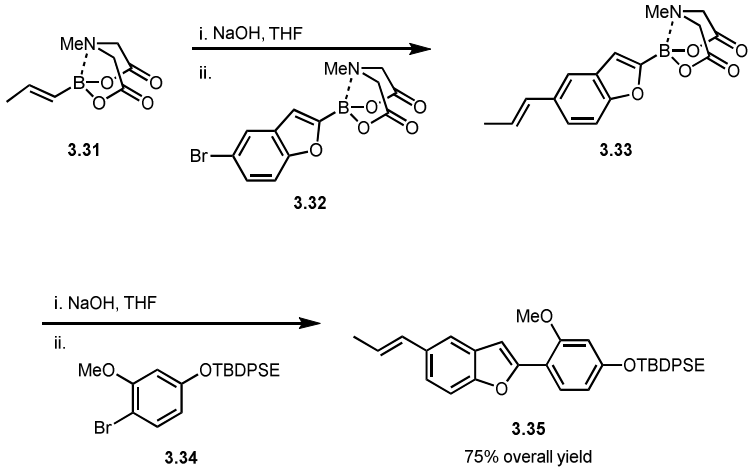
Scheme 3.10: Step-wise synthesis of β-parinaric acid using MIDA boronates

Watson *et al.* reported a tandem chemoselective Suzuki–Miyaura cross-coupling made possible by careful control of the boron species (Scheme 3.11).[88] Careful control of the amount of water and base present allowed conversion of the MIDA boronate into the pinacol borane to only occur after initial chemoselective cross-coupling of the boronate ester **3.26** and aryl bromide **3.8**. Once hydrolysis and conversion of the MIDA boronate **3.28** into the pinacol borane **3.29** had occurred, this allowed a second cross-coupling to form triaryl species **3.30**.



Scheme 3.11: Chemoselective cross-coupling using controlled hydrolysis of MIDA boronates

In 2015, Burke demonstrated the use of MIDA boronates in step-wise synthesis by forming a range of complex natural and bio-active molecules.[83] Synthesis of protected ratanhiaphenol III **3.35**, a PTP1B inhibitor, began with vinyl MIDA boronate **3.31** (Scheme 3.12). After full hydrolysis of the MIDA boronate, the resulting boronic acid was coupled with the MIDA boronate containing aryl halide **3.32**. Due to the anhydrous conditions used, the new MIDA boronate was completely untouched during the reaction. Hydrolysis of the resulting MIDA boronate **3.33** allowed cross-coupling with another aryl halide **3.34** giving the protected ratanhiaphenol III **3.35** in a 75% overall yield.



Scheme 3.12: Step-wise synthesis of **3.35**

By using the ability to control the release of boronic acid, the stability to anhydrous cross-coupling, and the “catch and release” column chromatography properties, Burke designed a deprotection-coupling-purification cycle (Figure 3.2, top). This process could be automated,

with a machine built that was capable of synthesising complex molecules from 14 different classes of small molecule (Figure 3.2, bottom).

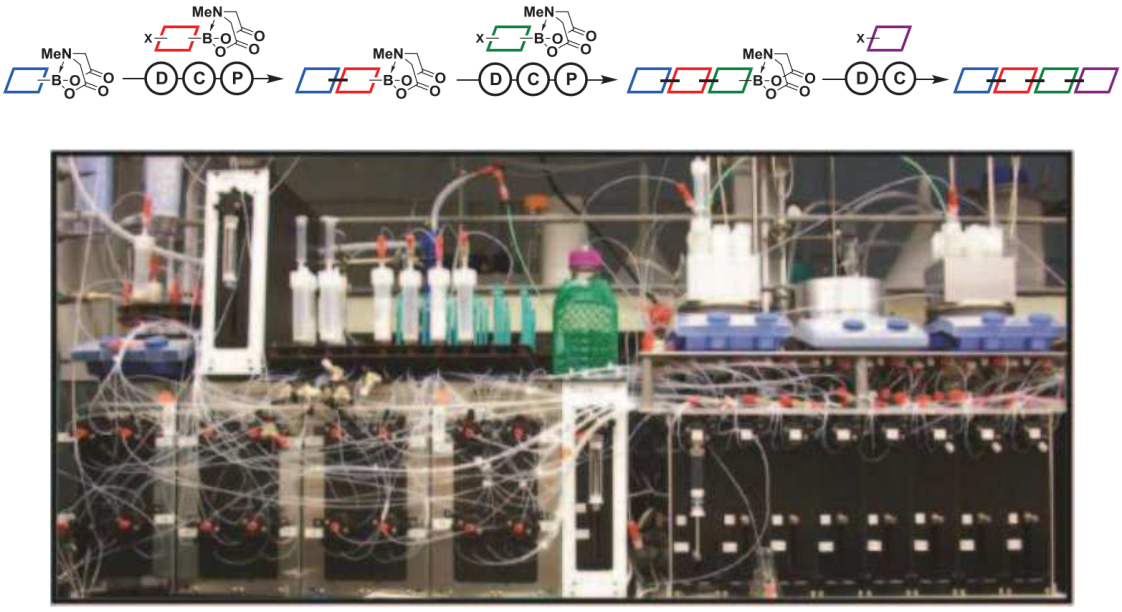
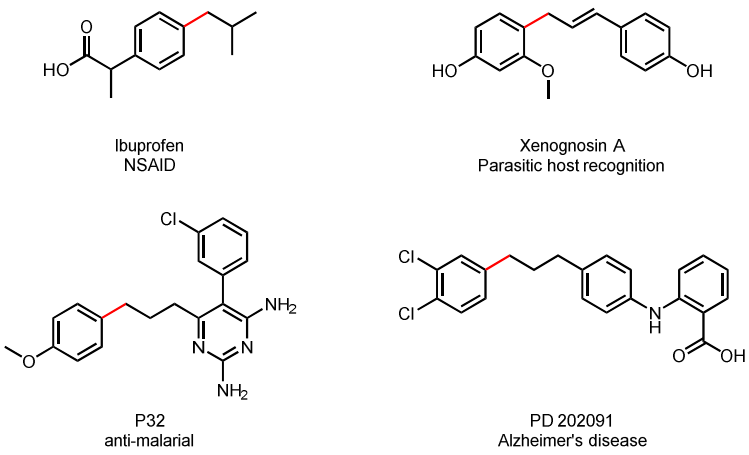


Figure 3.2: Use of MIDA boronates in the synthesis machine[83]

3.2 Results

3.2.1 Development of MIDA allylation reaction

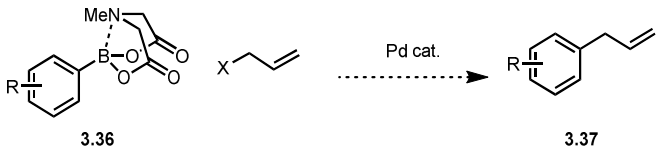
While the previous examples are wide-ranging, there is one clear omission. None of these reactions form a new bond to an sp^3 carbon. This is something that Burke himself has described as "particularly critical to realizing this potential".[82] By developing a reaction that takes the utility of MIDA boronates and combines it with formation of new bonds to sp^3 carbons, we could develop an extremely useful process. There are many bio-active or drug molecules which contain this aryl–sp^3 carbon functionality that could not be accessed using existing aryl MIDA boronate chemistry (Scheme 3.13).



Scheme 3.13: Compounds containing aryl–sp^3 C–C bonds

Initial optimisation

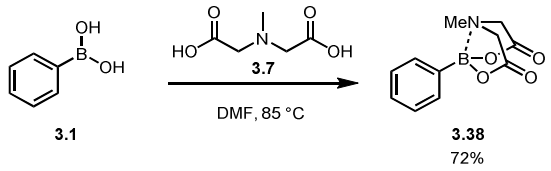
The proposed reaction would take a MIDA boronate **3.36** and couple it with an allyl halide in the presence of a palladium catalyst (Scheme 3.14). This should generate the corresponding allylaryl species **3.37** containing a new bond to an sp^3 carbon.



Scheme 3.14: Proposed allylation of MIDA boronates

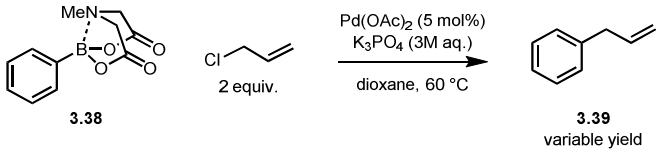
The obvious starting point was with phenyl MIDA boronate **3.38**. This was synthesised by stirring phenyl boronic acid **3.1** with MIDA in DMF at 85 °C (Scheme 3.15). After aqueous workup, phenyl MIDA boronate was separated from any residual phenyl boronic acid by

stirring the solid in Et_2O. After stirring for an hour, the pure MIDA boronate **3.38** was collected by filtration resulting in a 72% yield.



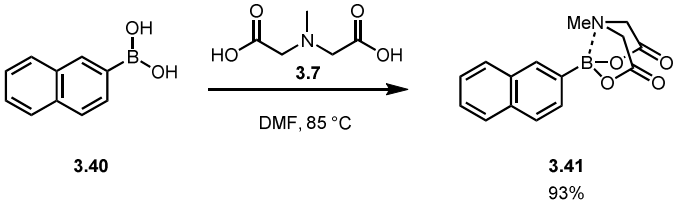
Scheme 3.15: Synthesis of MIDA boronate **3.38**

With phenyl MIDA boronate in hand, the allylation was attempted using Burke's standard conditions (Scheme 3.16). While allyl benzene **3.39** was being formed, it was found to be evaporating during concentration.



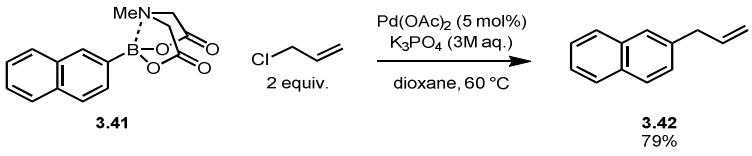
Scheme 3.16: Allylation of **3.38**

To avoid this problem, a heavier MIDA boronate was chosen. As allyl naphthalene should have a high enough boiling point, naphthyl MIDA boronate was synthesised (Scheme 3.17). Using the same procedure used in the synthesis of phenyl MIDA boronate, naphthyl MIDA boronate **3.41** was formed in a 93% yield.



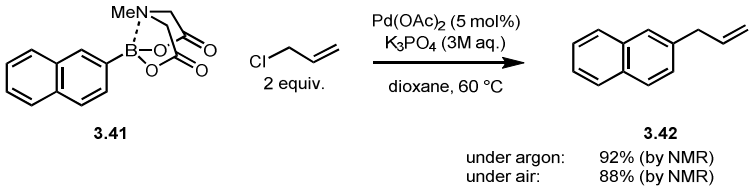
Scheme 3.17: Synthesis of MIDA boronate **3.41**

The allylation conditions were then applied to naphthyl MIDA boronate **3.41** (Scheme 3.18). Pleasingly, this resulted in the formation of allyl naphthalene **3.42** in a 79% isolated yield.



Scheme 3.18: Allylation of **3.41**

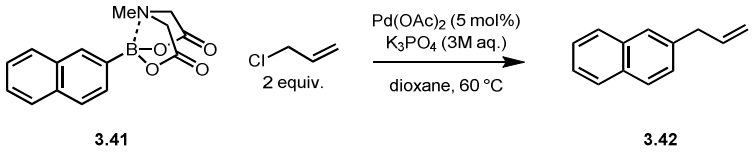
With the allylation working successfully, the reaction conditions were examined to see which parameters were required. In Burke's work, the reactions were carried out under an argon atmosphere. When the allylation was instead carried out under air, there was found to be little difference in yield (92% vs. 88%) (Scheme 3.19). For operational ease, it was decided to carry out future reactions under air.



Scheme 3.19: Allylation under air and argon

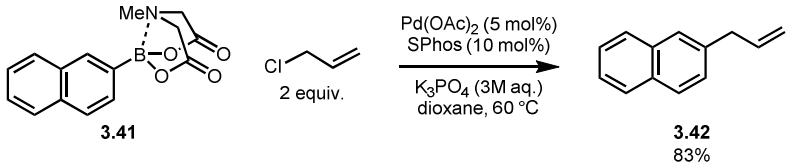
Next, the amount of base required in the reaction was examined. Not surprisingly, decreasing the amount of base present had a negative effect on the yield (Table 3.1). This is likely due to the importance of the base in both hydrolysing the MIDA boronate and facilitating the allylation reaction.

Table 3.1: Effect of number of equivalents of base on allylation



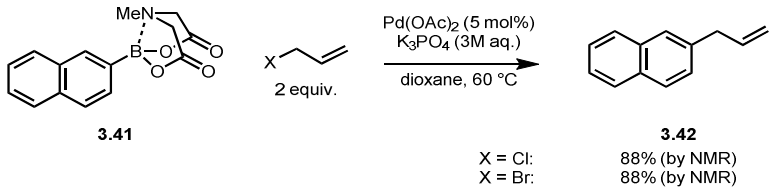
Entry	Equivalents of Base	Yield of 3.42
1	2	35%
2	4	72%
3	7.5	88%

In Burke's reactions, he made use of phosphine ligand SPhos. Carrying out the allylation reaction using SPhos showed a small reduction in yield, but the ligand was still tolerated (Scheme 3.20). This is positive as it leaves open the possibility of using a chiral phosphine ligand to carry out an enantioselective allylation.



Scheme 3.20: Use of ligand in the allylation

Finally, the effect of the allyl halide used was examined. Both the previously used allyl chloride and allyl bromide were found to be effective, with both achieving allylation in an 88% yield (Scheme 3.21).

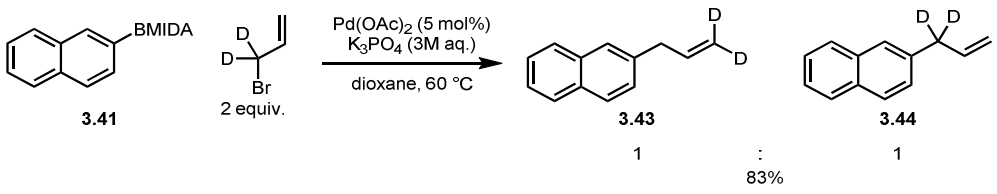


Scheme 3.21: Effect of allyl halide source in the allylation

3.2.2 Deuterium labelling study

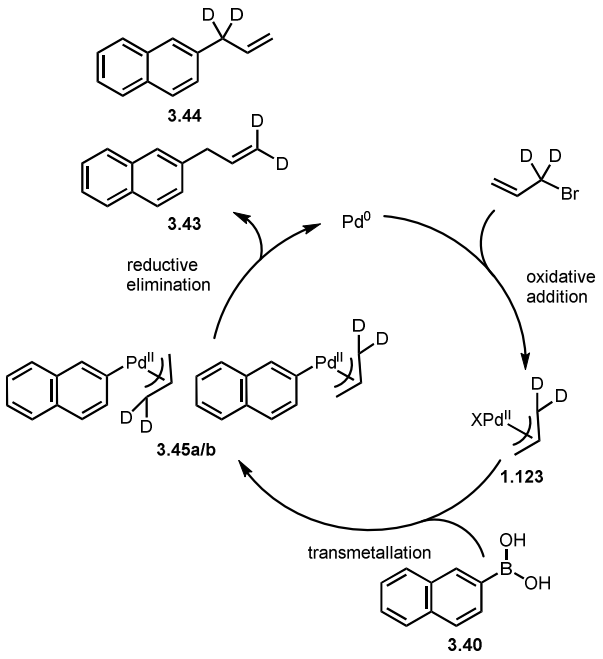
In order to determine the mechanism of the allylation, a deuterium labelling study was carried out using dideuterioallyl bromide. As with the carboallylation reaction and the direct coupling side product (see section 1.2.5), there are three potential pathways that the allylation reaction could go through. Examination of the ratio of the deuterated product isomers should determine which pathway is operative.

Using the previously optimised conditions, the allylation reaction was carried out using dideuteroallyl bromide (Scheme 3.22). The allylation was successful giving a 1:1 mixture of deuterated isomers, in an 83% overall yield.



Scheme 3.22: Allylation using dideuteroallyl bromide

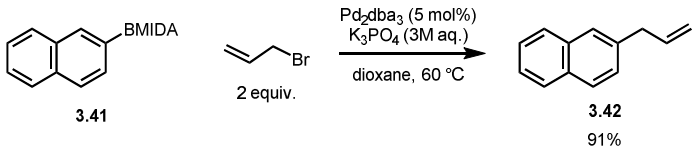
Having carried out the deuterium labelling study, an operative mechanism could be proposed consistent with the results. Beginning with Pd(0), oxidative addition of the allyl halide forms π-allyl Pd(II) species **1.123** (Scheme 3.23). Transmetallation of the boronic acid gives Pd(II) species **3.45a**/**b**. This can then undergo reductive elimination to give the allylated products **3.43** and **3.44**.



Scheme 3.23: Proposed mechanism of the allylation

As the reaction proceeds through a 0–II cycle, addition of a Pd(0) catalyst could help improve the yield. When a Pd(II) catalyst such as palladium acetate is used, it must first be reduced to Pd(0). A common way for this to occur is through the double transmetallation/reductive elimination of boronic acids. As the MIDA boronate is the limiting reagent in our allylation reaction, any boronic acid that is consumed during this process will have a negative effect on the yield. Indeed, during further investigations, some of the binaphthyl product of this process was detected by ^{1}H NMR.

Replacement of palladium acetate with Pd(0) catalyst Pd_2dba_3 had the desired effect (Scheme 3.24). In this case, the allylation was successfully carried out in a 91% yield – a modest improvement on the 88% yield achieved when using palladium acetate. With the mechanism of the reaction confirmed, and the optimised conditions for the allylation found, attention was turned to the scope of the allylation reaction.

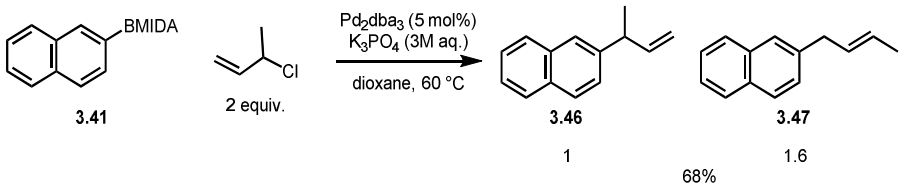


Scheme 3.24: Allylation using a Pd(0) catalyst

3.2.3 Examination of substrate scope

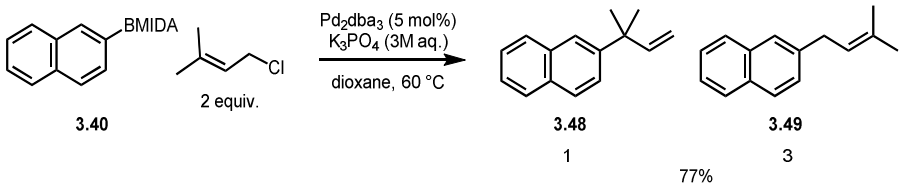
Allyl halide scope

First, the use of different allyl halides was examined. Use of 1-methallyl chloride was successful (Scheme 3.25). The reaction proceeded in a 68% yield, giving a 1:1.6 ratio of the two possible product isomers. This is consistent with the reaction mechanism with reductive elimination being slightly favoured on the less hindered side.



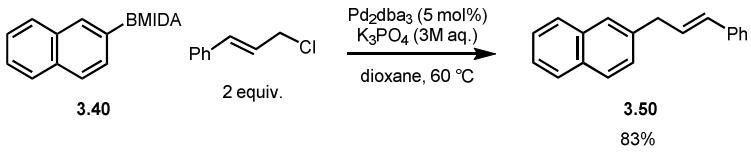
Scheme 3.25: Allylation with 1-methallyl chloride

Prenyl chloride was also a viable substrate for the allylation reaction, giving a 77% yield (Scheme 3.26). Unsurprisingly, the ratio was even higher at 1:3, reflecting the increased steric bulk of the extra methyl group.



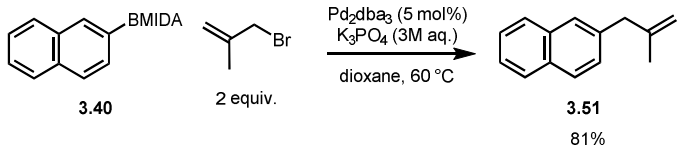
Scheme 3.26: Allylation with prenyl chloride

Use of cinnamyl chloride was also successful (Scheme 3.27). Here, the allylation occurred in an 83% yield. Due to the size of the phenyl group giving complete selectivity during the reductive elimination, only the terminal product isomer was formed.



Scheme 3.27: Allylation with cinnamyl chloride

Finally, the use of 2-methallyl bromide was also shown to be viable (Scheme 3.28). In this case, the symmetry of the π-allyl complex means only a single product isomer is possible. This was formed in an 81% yield.

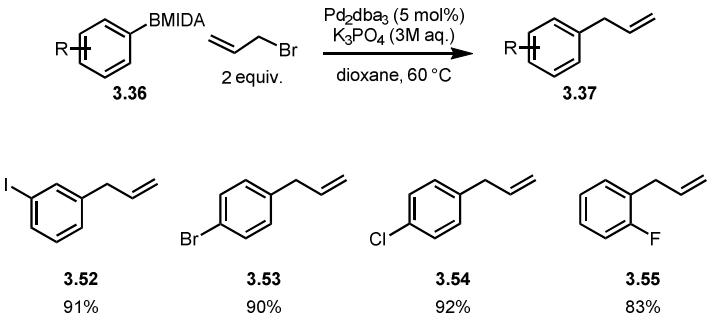


Scheme 3.28: Allylation with 2-methallyl bromide

MIDA boronate scope

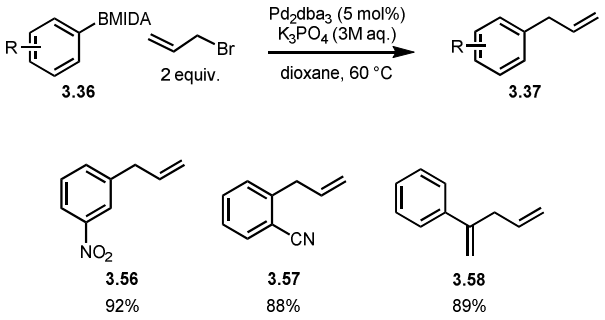
Having examined the scope of allyl halides, attention was then turned to the MIDA boronate scope. The wide range of commercially available MIDA boronates meant that a range of functionality could be examined.

First, a range of aryl halide containing MIDA boronates were examined (Scheme 3.29). These are potentially challenging due to the potential for oxidative addition into the aryl halide bond. This could lead to undesired side reactions such as cross-coupling between the aryl halide and MIDA boronate, and possible polymerisation if this process continued. Pleasingly, this was not an issue and none of these possible side products were detected. Even in the case containing an aryl iodine, usually excellent for carrying out oxidative addition, only the desired allylated product was formed in a 91% yield. The lack of reaction at the aryl halide sites is thought to be due to the extremely rapid oxidative addition of the allyl halide to any Pd(0) present. As an excess of allyl bromide is used in these reactions, there is never a sufficient enough concentration of Pd(0) exposed to the aryl halide leaving no possibility for oxidative addition to occur. Another advantage of these reactions is that the aryl halide, while unreactive during the allylation reaction, provides a useful functional handle that could be used to carry out further transformations.



Scheme 3.29: Allylation with aryl halide containing MIDA boronates

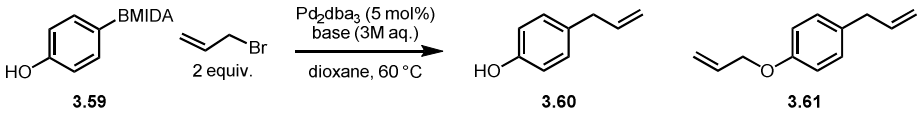
The allylation reaction is also successful when applied to MIDA boronates with electron withdrawing groups present (Scheme 3.30). Both nitro and cyano groups were tolerated, achieving 92% and 88% yields respectively. While aryl MIDA boronates have been the focus so far, the allylation of vinyl MIDA boronate to form **3.58** also occurs in an excellent yield.



Scheme 3.30: Allylation of different MIDA boronates

The next MIDA boronate examined was 4-hydroxyphenyl MIDA boronate **3.59**. Using the standard allylation conditions, the product was not the expected 4-hydroxyallylbenzene **3.60**, but the doubly allylated **3.61** (Table 3.2, entry 1). This is likely due to the strong base used in the reaction. Deprotonation of the phenol will assist in the alkylation by allyl bromide. By using the weak base potassium phosphate monobasic, this deprotonation should be prevented. This was indeed the case, with none of the doubly allylated product being detected (entry 2). Unfortunately, as the base is also required for hydrolysis of the MIDA boronate, conversion was greatly reduced with only 15% of the desired 4-hydroxyallylbenzene **3.60** being formed. When a slightly stronger base, sodium hydrogen carbonate, was used, the conversion was improved giving the desired product in 28% yield while still supressing formation of the undesired doubly allylated product (entry 3).

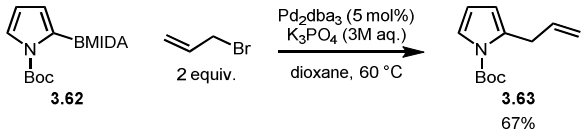
Table 3.2: Effect of base on allylation of **3.59**



3.59 **3.60** **3.61**

Entry	Base	3.60	3.61
1	K_3PO_4	0%	Major product
2	KH_2PO_4	15%	Not observed
3	$NaHCO_3$	28%	Not observed

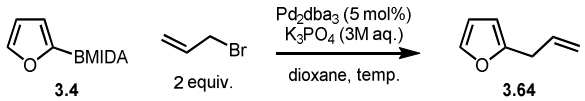
Attention was then turned to heterocyclic MIDA boronates. Allylation of *N*-Boc pyrrole MIDA boronate **3.62** proceeded well under the standard conditions. The desired *N*-Boc 2-allylpyrrole **3.63** was formed in a 67% yield (Scheme 3.31).



3.62 **3.63** 67%

Scheme 3.31: Allylation of **3.62**

The allylation of furanyl MIDA boronate **3.4** proved more challenging. Under the standard conditions, only 31% of the desired allylfuran **3.64** was formed (Scheme 3.32). Examination of the crude material showed that a significant amount of de-boronation to form furan was occurring. To slow the hydrolysis of the MIDA boronate, and therefore reduce the amount of boronic acid building up in the reaction, the temperature was reduced. This did improve the conversion to the desired allylfuran **3.64**, increasing the yield to 45%.



3.4 **3.64**

60 °C 31%

RT 45%

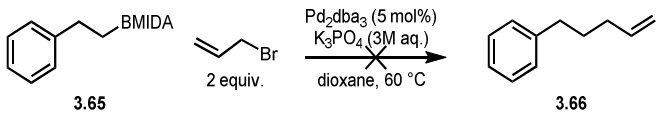
Scheme 3.32: Allylation of **3.4**

3.2.4 Attempts at sp^3 allylation

With the allylation reaction being successfully applied to a range of MIDA boronates and allyl halides, so far, the bonds formed have been sp^2–sp^3 C–C bonds. If the methodology could be expanded to allow formation of sp^3–sp^3 C–C bonds, it would open up new areas of synthetic utility.

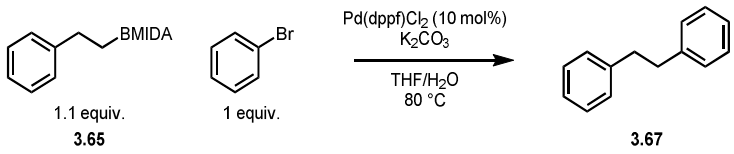
Initial attempts

The standard allylation conditions were applied to phenylethyl MIDA boronate **3.65**. Unfortunately, none of the desired phenylpentene **3.66** was formed (Scheme 3.33). Use of different palladium catalysts, $Pd(dppf)Cl_2$ and $Pd(PPh_3)_4$, also proved ineffective, with only hydrolysis of the MIDA boronate occurring.



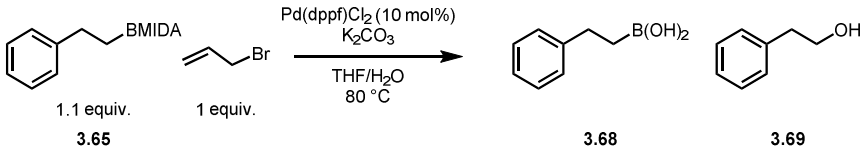
Scheme 3.33: Attempted sp^3–sp^3 allylation

To diagnose the problem, the literature was searched for examples using phenylethyl MIDA boronate. A cross-coupling developed by Yudin[89] was found (Scheme 3.34). In their case, bromobenzene was coupled with phenylethyl MIDA boronate using $Pd(dppf)Cl_2$. While the solvent and base used are different, the conditions are reasonably similar.



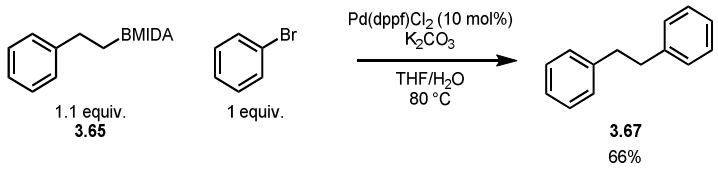
Scheme 3.34: Cross-coupling of sp^3 MIDA boronate **3.65** with bromobenzene

Yudin's conditions were then applied to the allylation (Scheme 3.35). None of the desired product was detected, instead the major products detected were unreacted boronic acid **3.68** and the alcohol **3.69** resulting from oxidation of the boronic acid.



Scheme 3.35: Attempted allylation using Yudin conditions

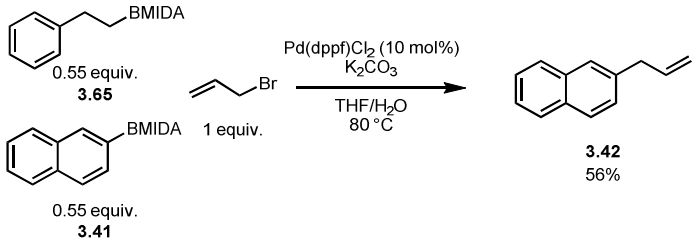
To check that there were no issues with the MIDA boronate, or any of the other reagents being used, the literature reaction reported by Yudin was carried out (Scheme 3.36). The reaction was successful, and diphenylethane **3.67** was formed in 66% yield.



Scheme 3.36: Confirmation that control reaction works

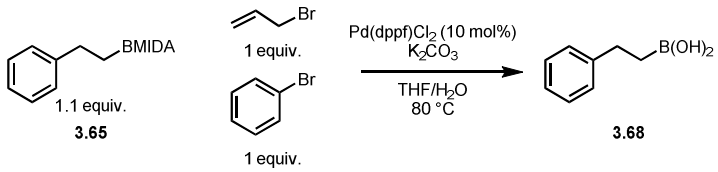
Competition reaction

To determine where in the catalytic cycle the reaction was failing, a series of competition reactions were carried out. The first point of potential failure was during oxidative addition. If this step does not happen, none of the other steps in the cycle can. To test this, naphthyl MIDA boronate **3.41** was added to the reaction (Scheme 3.37). If the allylnaphthylene product is formed, then the oxidative addition must be happening. This was indeed the case, with allylnaphthalene **3.42** being formed in 56% yield. The problem, therefore, is not with the oxidative addition stage.



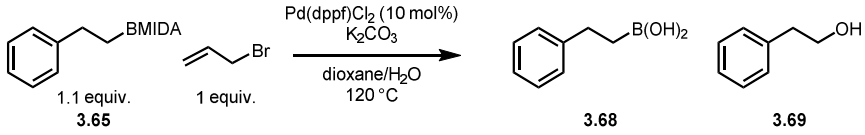
Scheme 3.37: Competition reaction between sp^3 and sp^2 MIDA boronate

The next competition reaction saw the addition of both allyl bromide and bromobenzene (Scheme 3.38). In this case, neither the allylated product or diphenylethane were formed. Instead, the major product was unreacted boronic acid **3.68**. This is not unexpected given that the oxidative addition of allyl bromide was found to be much faster than that of aryl halides. It also suggests that the problem may be occurring at the transmetallation or reductive elimination stages, as the boronic acid is clearly formed but is not being used to form the desired product.



Scheme 3.38: Competition reaction between allyl bromide and bromobenzene

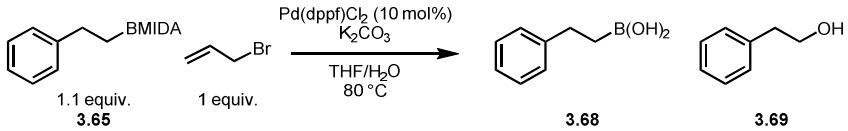
In an attempt to help the transmetallation and reductive elimination, more forcing reaction conditions were attempted. Changing the solvent to dioxane allowed testing of higher temperatures. Running the reaction at 120 °C saw no improvement – the only products were still unreacted boronic acid **3.68** and the corresponding alcohol **3.69** (Scheme 3.39).



Scheme 3.39: Attempted allylation at increased temperature

Next, the concentration was varied. Due to the biphasic nature of the reaction, this was done both by keeping the THF:H_2O ratio constant and by keeping the amount of H_2O constant. Increasing the concentration from 0.1 M to 0.5 M, both with and without a constant THF:H_2O ratio, saw little change (Table 3.3, entries 2 and 3). The major product was again the boronic acid and corresponding alcohol. Further increasing the concentration to 1 M did provoke a change (entries 4 and 5). In these cases, styrene was now also formed in appreciable amounts. This could be as a result of β-hydride elimination after the transmetallation has occurred.

Table 3.3: Effect of concentration of allylation

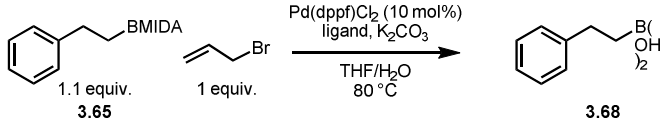


Entry	Concentration	THF:H_2O ratio	Products
1	0.1 M	5:1	**3.68**/**3.69**
2	0.5 M	5:1	**3.68**/**3.69**
3	0.5 M	2.5:1	**3.68**/**3.69**
4	1 M	5:1*	**3.68**/**3.69**+Styrene
5	1 M	1:2	**3.68**/**3.69**+Styrene

*aqueous layer saturated with K_2CO_3

If β-hydride elimination is the cause of the styrene formation, use of ligands could help prevent it and encourage formation of the desired allylated product. Screening of a range of ligands was therefore undertaken (Table 3.4). The first ligands examined were phosphine ligands. Using either BrettPhos or SPhos saw no improvement, with styrene still being formed (entries 2 and 3). Interestingly, use of SPhos at 0.1 M also saw formation of styrene, something that was not observed in the ligand-free reaction at this concentration (entry 4).

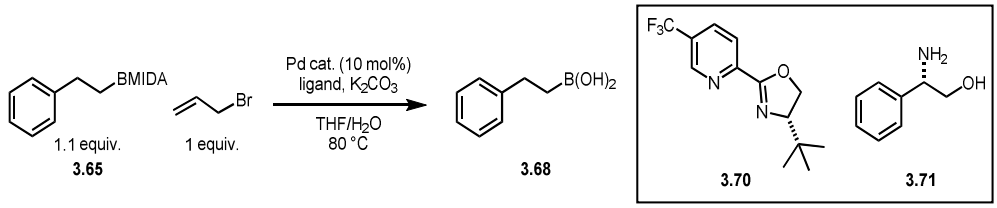
Table 3.4: Effect of ligand on allylation



Entry	Concentration	Ligand	Products
1	1 M	-	**3.68**/Styrene, 10:1
2	1 M	BrettPhos	**3.68**/Styrene, 20:1
3	1 M	SPhos	**3.68**/Styrene, 7:1
4	0.1 M	SPhos	**3.68**/Styrene, 4:1

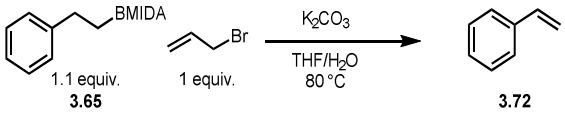
Use of other catalyst/ligand systems was then examined (Table 3.5). Pd(quinox)Cl_2 was ineffective, with styrene again being formed alongside the unreacted boronic acid (entry 1). Pyridinyl oxazoline ligand **3.70** and amino alcohol **3.71** were used in combination with palladium acetate. Again, styrene was formed in these reactions (entries 2 and 3).

Table 3.5: Effect of ligand on allylation



Entry	Concentration	Catalyst/Ligand	Products
1	1 M	Pd(quinox)Cl_2	**3.68** + trace Styrene
2	1 M	$Pd(OAc)_2$/**3.70**	**3.68**/Styrene, 10:1
3	1 M	$Pd(OAc)_2$/**3.71**	**3.68**/ Styrene, 20:1

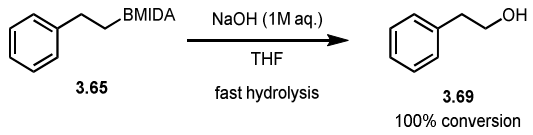
As no catalyst/ligand combination seems to have any effect on the formation of styrene, the palladium-free reaction was run (Scheme 3.40). Interestingly, styrene **3.72** was also formed during this reaction. This suggests that styrene formation is at least not solely caused by β-hydride elimination after transmetallation, but by the increased concentration. In this case, it is maybe due to elimination of the alcohol formed by oxidation of the boronic acid.



Scheme 3.40: Formation of styrene in palladium-free allylation

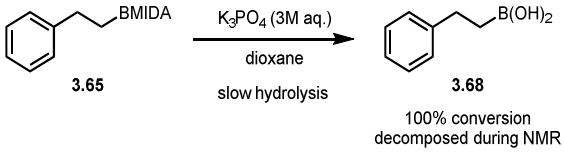
Tests using boronic acid

To remove the requirements for MIDA boronate hydrolysis, it was decided to try the allylation reaction directly on the boronic acid. To this end, the MIDA boronate was fully hydrolysed to the boronic acid using Burke's "fast hydrolysis" conditions.[83] This was unsuccessful, instead yielding the corresponding alcohol **3.69** (Scheme 3.41).



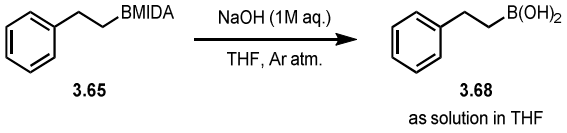
Scheme 3.41: Fast hydrolysis of MIDA boronate **3.65**

As the fast hydrolysis conditions led to formation of the alcohol, the "slow hydrolysis" conditions were applied instead (Scheme 3.42). This time, some of the boronic acid **3.68** was formed successfully. Unfortunately, it decomposed to the alcohol upon standing in an NMR tube.



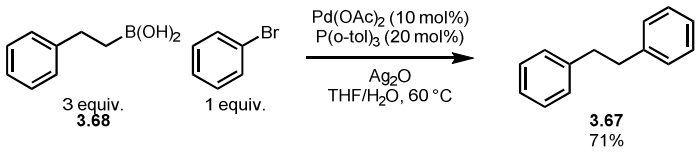
Scheme 3.42: Slow hydrolysis of MIDA boronate **3.65**

To try and prevent formation of the alcohol, oxygen was excluded from the reaction (Scheme 3.43). Again, using the "fast hydrolysis" conditions, the MIDA boronate was converted to the boronic acid. With the reaction carried out under an argon atmosphere, care was taken to avoid introduction of oxygen during the workup. After separation, the boronic acid **3.68** was partially concentrated under a flow of argon, and used as a solution in THF.



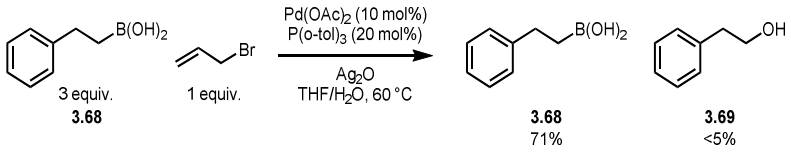
Scheme 3.43: Hydrolysis of MIDA boronate **3.65** under argon atm.

To ensure the sp^3–sp^2 reaction was still working with the boronic acid, a control reaction was carried out using bromobenzene (Scheme 3.44). This was successful, with diphenylethane **3.67** being formed in a 71% yield.



Scheme 3.44: Control reaction with boronic acid

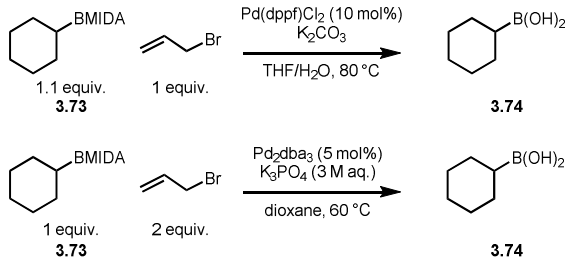
These conditions were then applied using allyl bromide (Scheme 3.45). Once again, the allylation did not occur. Analysis of the reaction mixture showed mainly unreacted boronic acid **3.68**, along with a small amount of alcohol **3.69**.



Scheme 3.45: Attempted allylation using boronic acid **3.68**

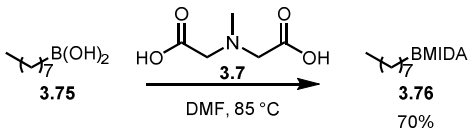
Other sp^3 substrates

As the allylation of phenylethyl MIDA boronate had not been possible, attention was turned to other potential sp^3–sp^3 C–C bond forming targets. Allylation was next attempted on the commercially available cyclohexyl MIDA boronate **3.73** (Scheme 3.46). Under Yudin's conditions, none of the desired product was detected, with mainly cyclohexyl boronic acid **3.74** remaining. Under the standard allylation conditions, the boronic acid **3.74** was again the main product. A trace amount of an unidentified allylated product was detected by ^{1}H NMR, but it was not possible to isolate this species for further identification.



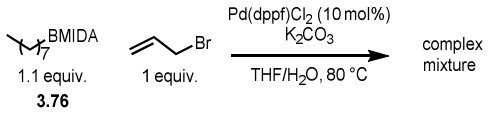
Scheme 3.46: Attempted allylation of cyclohexyl MIDA boronate

The next candidate was octyl MIDA boronate **3.76**. This was synthesised from octyl boronic acid **3.75** in a 70% yield using the standard conditions (Scheme 3.47).



Scheme 3.47: Synthesis of octyl MIDA boronate

With the MIDA boronate **3.76** in hand, it was submitted to the allylation conditions (Scheme 3.48). This resulted in a complex mixture of products, with no clear sign of the desired alkene product by ^{1}H NMR. Further analysis by mass spectrometry found no evidence that the desired alkene had been formed.

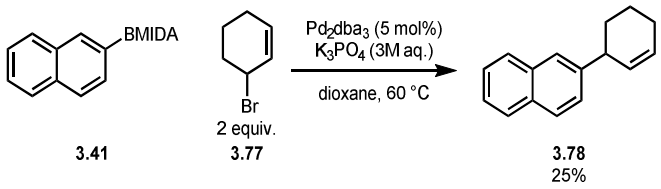


Scheme 3.48: Attempted allylation of octyl MIDA boronate

3.2.5 Attempts at enantioselective allylation

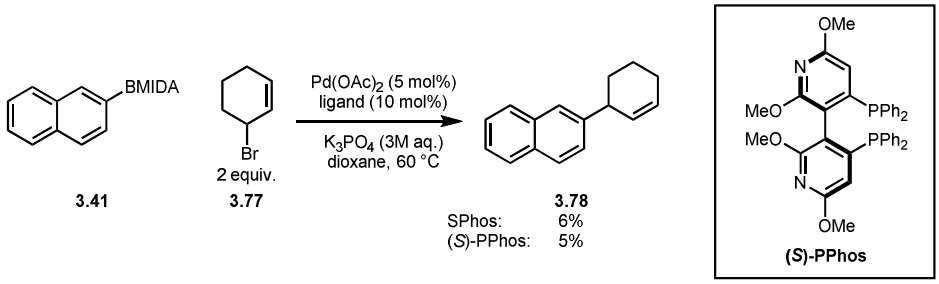
Returning to sp^2–sp^3 couplings, investigations were carried out into whether an enantioselective version of the allylation reaction could be developed. By making use of a chiral ligand, it may be possible to control the selectivity during reductive elimination, leading to formation of a single enantiomer.

In order to test this, 3-bromocyclohex-1-ene **3.77** was chosen as the allyl halide partner. After submission to the allylation conditions, the allylated product **3.78** was formed in 25% yield (Scheme 3.49). The lower yield could be due to the use of a more sterically bulky allyl halide.



Scheme 3.49: Allylation using 3-bromocyclohex-1-ene

Next, the reaction was carried out using different phosphine ligands (Scheme 3.50). As SPhos had previously been shown to be tolerated by the allylation reaction, it was tested first. While there had been little effect on the yield when using allyl bromide, here, the yield dropped to just 6%. This was due to greatly reduced conversion. The next ligand tested was chiral phosphine ligand (*S*)-PPhos. The yield in this case was 5%. While the yield was disappointing, the product was analysed by chiral HPLC to see whether any enantioselectivity had been conferred by the ligand. Unfortunately, the analysis showed that the allylated product **3.78** was racemic. This could be due to the bulkiness of both the allyl bromide and the ligand inhibiting the reaction. The allylation could then occur via any unligated palladium present explaining why there was no enantioselectivity during the product formation.

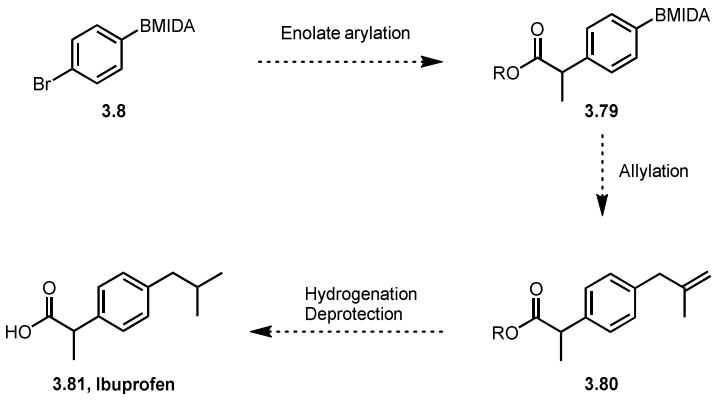


Scheme 3.50: Attempted enantioselective allylation

3.2.6 Synthesis of Ibuprofen

Aim

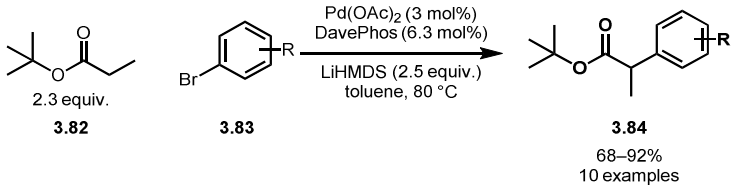
To show the utility of the allylation reaction on a more complex system, a synthesis of Ibuprofen **3.81** was designed, featuring an allylation of a MIDA boronate as a key step (Scheme 3.51). Beginning with 4-bromophenyl MIDA boronate **3.8**, a palladium-catalysed enolate arylation would give MIDA boronate **3.79**. This would undergo allylation with 2-methallyl bromide to give the allylated ester **3.80**. Finally, a palladium-catalysed hydrogenation and deprotection would give Ibuprofen **3.81**. As well as using the allylation reaction as the key step, this process could potentially be carried out using a single palladium catalyst for all 3 steps.



Scheme 3.51: Proposed synthesis of Ibuprofen

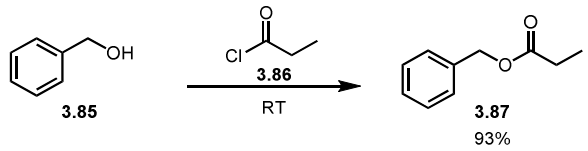
Enolate arylation

A search of the literature revealed a palladium-catalysed enolate arylation developed by Buchwald (Scheme 3.52).[90] Using palladium acetate with DavePhos as a ligand, he was able to carry out the enolate arylation on a range of aryl bromides. The choice of LiHMDS as a base proved key to avoiding formation of the diarylated ester, or the product of Claisen condensation.



Scheme 3.52: Enolate arylations carried out by Buchwald

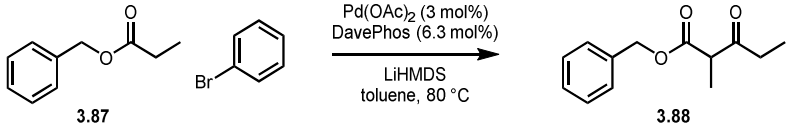
While in Buchwald's case, the *tert*-butyl ester **3.84** was used, we attempted to see if the benzyl ester could also be used. If this was possible, it should allow both the planned hydrogenation and deprotection to occur at the same time. Benzyl propionate **3.87** was formed in a 93% yield by stirring benzyl alcohol and propionyl chloride neat (Scheme 3.53).



Scheme 3.53: Synthesis of benzyl propionate

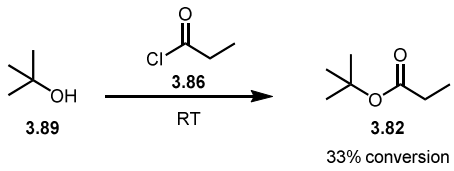
Before testing on the MIDA boronate, the enolate arylation was carried out on bromobenzene (Table 3.6). Rather than the desired α-aryl ester, the product was instead the result of Claisen condensation **3.88**. In an attempt to suppress formation of the Claisen condensation product, the ester addition was carried out at –20 °C instead but again, the Claisen condensation product was formed. To try and speed the reaction of the bromobenzene with the enolate, addition was carried out at room temperature. This was also unsuccessful, leading only to formation of the Claisen condensation product **3.88**.

Table 3.6: Attempted enolate arylation using benzyl propionate



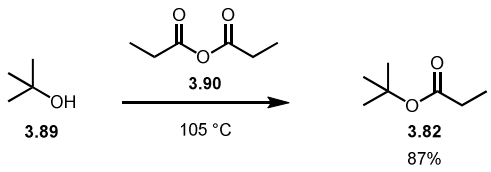
Entry	Enolate formation temp.	Result
1	–10 °C	Full conversion to **3.88**
2	–20 °C	Full conversion to **3.88**
3	RT	Full conversion to **3.88**

As the enolate arylation with the benzyl ester was proving fruitless, use of the *tert*-butyl ester **3.82** was planned instead. Using the same conditions as those used in the formation of benzyl propionate, *tert*-butyl propionate **3.82** was formed (Scheme 3.54). In this case however, the reaction did not go to completion, and the volatility of the product made purification difficult.



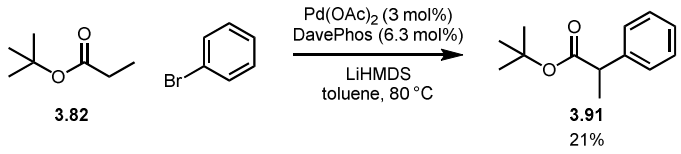
Scheme 3.54: Synthesis of tert-butyl propionate

Alternative conditions were therefore sought. Reaction of *tert*-butyl alcohol with propionic anhydride at 105 °C proved the best conditions (Scheme 3.55). Careful washing of the reaction mixture with 1 M aq. NaOH allowed the collection of *tert*-butyl propionate **3.82** in 87% yield.



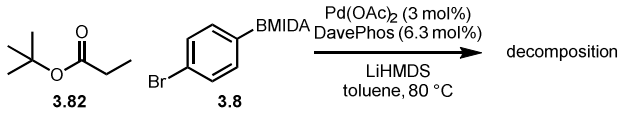
Scheme 3.55: Synthesis of tert-butyl propionate

With *tert*-butyl propionate available, the reaction was again tested on bromobenzene (Scheme 3.56). This time, the enolate arylation was successful, giving the α-aryl ester **3.91** in 21% yield.



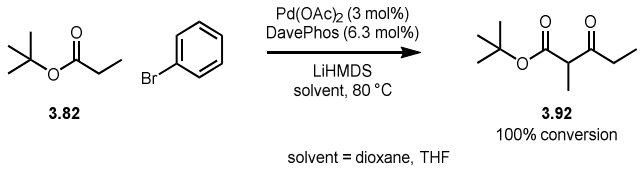
Scheme 3.56: Enolate arylation using tert-butyl propionate and bromobenzene

The enolate arylation was next attempted on 4-bromophenyl MIDA boronate **3.8** (Scheme 3.57). In this case, none of the desired α-aryl ester was formed, with decomposition of the MIDA boronate instead. This could be due to the low solubility of the MIDA boronate in toluene.



Scheme 3.57: Attempted enolate arylation of MIDA boronate **3.8**

To address the solubility of the MIDA boronate **3.8**, the enolate arylation was tested using alternative solvents (Scheme 3.58). Using dioxane, the enolate formation had to be carried out at room temperature due to the relatively high melting point of dioxane. This led only to formation of the Claisen condensation product **3.92**. Next, THF was tested. This allowed formation of the enolate at –10 °C, but once again, the only product was that of Claisen condensation **3.92**.

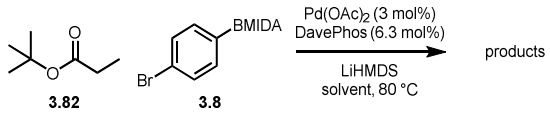


Scheme 3.58: Attempted enolate arylation using different solvents

As none of the single solvents tested seemed viable for both suppressing the formation of the Claisen condensation product and providing the required solubility for the MIDA boronate, solvent mixtures were examined (Table 3.7). A 1:1 mixture of toluene and dioxane lead to decomposition of the MIDA boronate **3.8** and formation of the Claisen condensation product **3.92** (entry 2). Swapping dioxane for THF prevented complete decomposition of the MIDA boronate, only resulting in hydrolysis to the boronic acid. The Claisen condensation product

3.92 was also formed (entry 3). Use of dimethoxyethane also led to hydrolysis of the MIDA boronate and formation of the Claisen condensation product (entry 4). It appears that while the Claisen condensation product **3.92** does not immediately form when using mixed solvent systems, the unreactiveness of the MIDA boronate leads to its formation over time.

Table 3.7: Effect of different solvents on enolate arylation



3.82 3.8

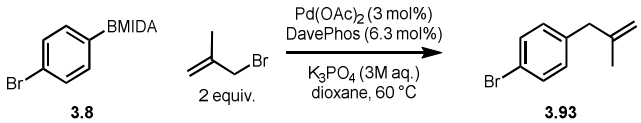
Entry	Solvent	Result[a]
1	Toluene	Decomposition
2	Toluene:Dioxane, 1:1	Claisen + decomposition
3	Toluene:THF, 1:1	Claisen + boronic acid
4	DME	Claisen + boronic acid

a). Full conversion of **3.82** and **3.8**

Revised step order

As the enolate arylation of the MIDA boronate **3.8** was proving unsuccessful, it was decided to reverse the order of the first two steps. First, the MIDA boronate would be allylated using 2-methallyl bromide. The allylated product would then undergo enolate arylation to afford the α-aryl ester. This should avoid the solubility issues faced during the enolate arylation, and avoid the need for an alternative solvent leading to formation of the Claisen condensation product **3.92**.

As there was potential to use a single palladium catalyst for all steps, the allylation of 4-bromophenyl MIDA boronate **3.8** was undertaken using palladium acetate and DavePhos (Scheme 3.59). This worked well, giving the allylated product **3.93** in an excellent yield.

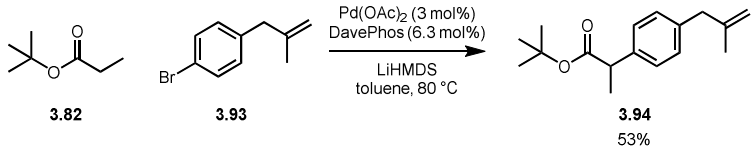


3.8 3.93

94%

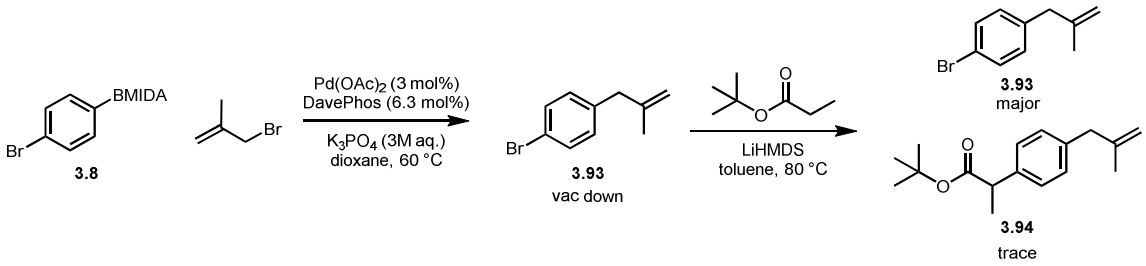
Scheme 3.59: Allylation of MIDA boronate **3.8**

The allylated aryl bromide **3.93** was then submitted to the enolate arylation conditions (Scheme 3.60). Pleasingly, this resulted in formation of the desired α-aryl ester **3.94** in 53% yield. None of the Claisen condensation product **3.92** was formed, and only a trace amount of the diarylated product was detected.



Scheme 3.60: Enolate arylation of **3.93**

With both steps now working, the combined reaction was attempted using a single palladium source. As the allylation requires water, which is likely to be a problem in the enolate arylation, this must first be removed. Before fully combining the reactions, it was decided to carry out the usual aqueous workup then submit the crude material to the enolate arylation conditions without further purification (Scheme 3.61). This resulted in formation of a trace amount of the α-aryl ester **3.94**, however the main product was the allylated intermediate **3.93**.

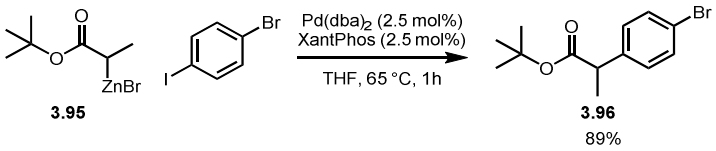


Scheme 3.61: Combined allylation and enolate arylation

Due to the requirement for water in the first step, it is difficult to ensure the second step is completely dry. As even a small amount of residual water will severely hinder the enolate arylation, an alternative was sought in order to return to the initial step order.

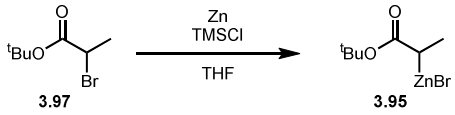
Enolate arylation by Negishi coupling

Examination of the literature revealed an interesting Negishi coupling.[91] After formation of a zinc enolate **3.95** from *tert*-butyl 2-bromopropionate, this could be coupled with an aryl halide giving the corresponding α-aryl ester **3.96** (Scheme 3.62). The use of THF as a solvent could help avoid the solubility issues experienced previously, while the lack of a strong base could help avoid decomposition of the MIDA boronate.



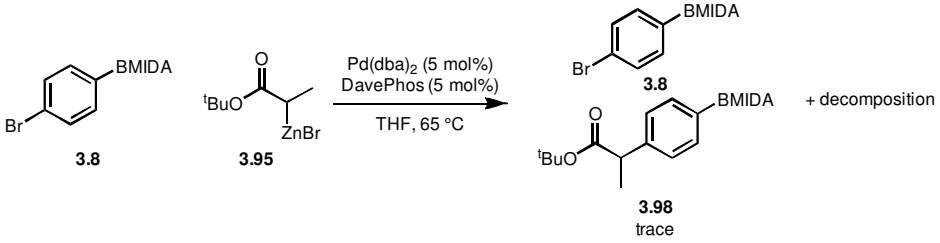
Scheme 3.62: Negishi coupling using zinc enolate **3.95**

Formation of the zinc enolate was carried out by the slow addition of *tert*-butyl 2-bromopropionate **3.97** to zinc metal in THF (Scheme 3.63). This resulted in a highly exothermic reaction. After cooling to room temperature, the freshly prepared zinc enolate **3.95** was used directly as a solution in THF.



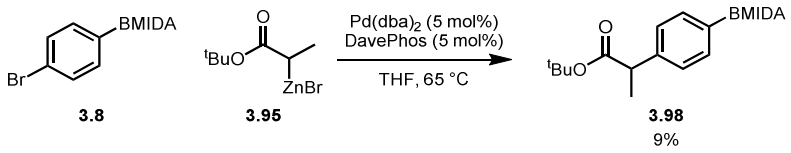
Scheme 3.63: Formation of zinc enolate

The zinc enolate **3.95** was then used in the Negishi coupling with 4-bromophenyl MIDA boronate **3.8** (Scheme 3.64). Pleasingly, this resulted in formation of the desired α-aryl ester **3.98**, albeit only in small amounts. As well as unreacted starting material, a large amount of decomposed material was also produced.



Scheme 3.64: Attempted Negishi coupling using MIDA boronate **3.8**

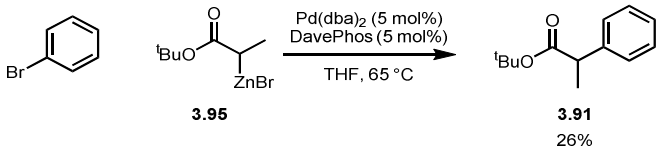
Increasing the number of equivalents of zinc enolate from 1.2 to 2 achieved full conversion of the 4-bromophenyl MIDA boronate **3.8** (Scheme 3.65). The main result of this, however, was increased decomposition with the desired α-aryl ester **3.98** being formed in just 9% yield.



Scheme 3.65: Negishi coupling with increased equivalents of zinc enolate

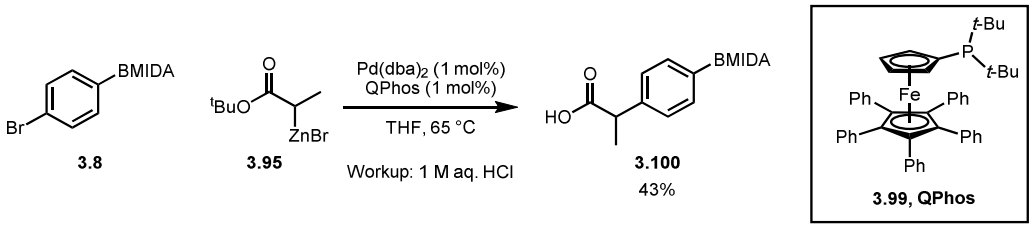
To see whether it was the MIDA boronate that was the problem, the Negishi coupling was tested using bromobenzene (Scheme 3.66). This resulted in formation of the α-aryl ester **3.91**

in 26% yield. While an improvement on the examples using the MIDA boronate, this was still lower than expected.



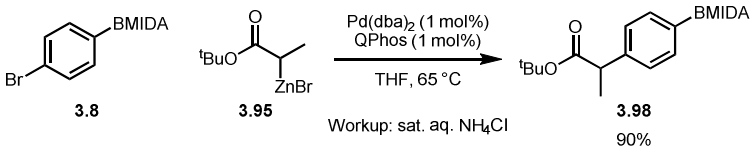
Scheme 3.66: Negishi coupling using bromobenzene

An investigation into the use of ligands revealed that phosphine ligand QPhos is highly active in these types of transformation.[92] By increasing the rate of the reaction, decomposition of the MIDA boronate could be limited or completely prevented. The Negishi coupling was repeated, using QPhos **3.99** as a ligand (Scheme 3.67). The coupling was successful, giving the desired α-aryl ester. During workup, the *tert*-butyl ester was inadvertently hydrolysed, giving the free acid **3.100** in a 43% yield.



Scheme 3.67: Negishi coupling using QPhos as ligand

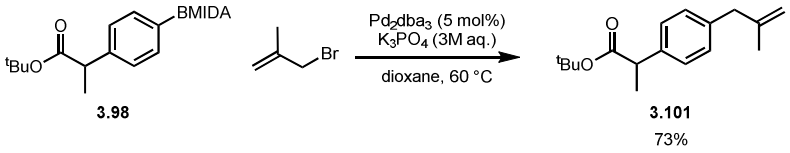
Repeating the reaction, this time with a modified workup, once again resulted in formation of the desired α-aryl ester **3.98** (Scheme 3.68). This time the *tert*-butyl ester remained intact, giving the desired product in a 90% yield. Care had to be taken with the reaction time – after 1.5–2 hours, the reaction was usually complete. If left much longer than this, decomposition of the MIDA boronate would start to occur. However, if the reaction was stopped too early, the mixture of the two MIDA boronates **3.8** and **3.98** proved impossible to separate.



Scheme 3.68: Negishi coupling with alternative workup

Allylation of Ibuprofen MIDA

With the successful formation of the α-aryl ester MIDA boronate **3.98**, the next step was to carry out the allylation. Using the standard conditions and 2-methallyl bromide, formation of allylated ester **3.101** was achieved in 73% yield (Scheme 3.69).

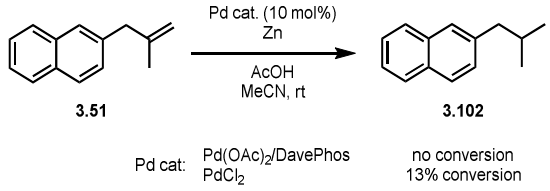


3.98 **3.101** 73%

Scheme 3.69: Allylation of MIDA boronate **3.98**

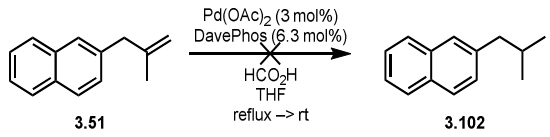
Hydrogenation/deprotection

With both the enolate arylation and the allylation carried out successfully, attention was now turned to the final hydrogenation and deprotection steps. Initially, transfer hydrogenation was explored. Using zinc and acetic acid as a hydrogen source,[93] along with zinc and a palladium catalyst, a small amount of the hydrogenated product **3.102** was formed (Scheme 3.70). Using palladium acetate and DavePhos, no conversion was seen. However, using palladium chloride, a 7:1 ratio between the alkene **3.51** and alkane **3.102** was observed.



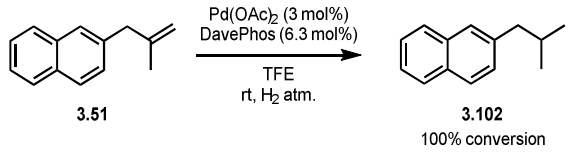
Scheme 3.70: Attempted hydrogenation of **3.51**

Due to the low conversion when using acetic acid, a different procedure was attempted, using formic acid as a hydrogen source (Scheme 3.71).[94] In this case, none of the hydrogenated product was obtained, with the alkene being recovered intact.



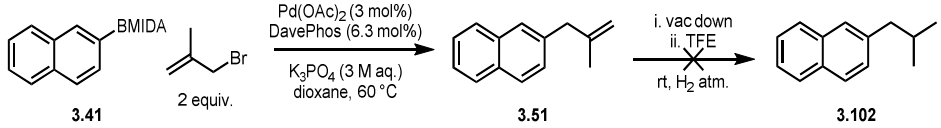
Scheme 3.71: Attempted hydrogenation of **3.51**

As transfer hydrogenation was proving problematic, hydrogenation using molecular hydrogen and a homogenous palladium catalyst was attempted (Scheme 3.72). Carrying out the reaction in trifluoroethanol, using palladium acetate with DavePhos as a catalyst system, full conversion was achieved to the hydrogenated product **3.102**.



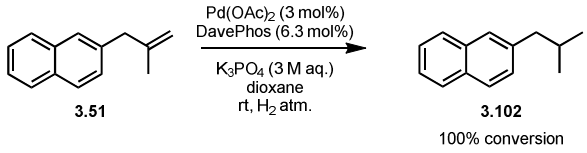
Scheme 3.72: Hydrogenation of **3.51**

Attempting to combine the allylation and hydrogenation, the allylation reaction was carried out on naphthyl MIDA boronate **3.41** (Scheme 3.73). The reaction mixture was then concentrated *in vacuo* before addition of trifluoroethanol and H_2 atmosphere. Disappointingly, none of the hydrogenated product was formed, with only the intermediate alkene **3.51** present after 24 hours.



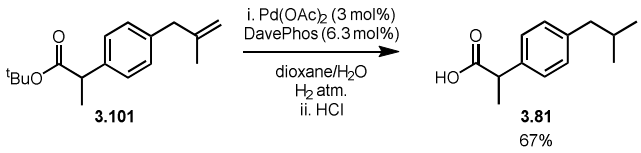
Scheme 3.73: Combined allylation and hydrogenation

In an attempt to help harmonise the conditions, hydrogenation was attempted under the allylation conditions at room temperature, simply with addition of a H_2 atmosphere. Again, testing on methallylnaphthalene **3.51**, the hydrogenation was successful, with full conversion to the alkane achieved (Scheme 3.74).



Scheme 3.74: Hydrogenation under allylation conditions

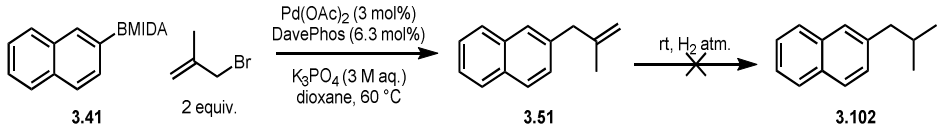
The hydrogenation was then attempted on the α-aryl ester **3.101** (Scheme 3.75). After 16 hours, the H_2 atmosphere was removed and HCl added. After stirring for a further 16 hours, Ibuprofen **3.81** was formed in 67% yield.



Scheme 3.75: Hydrogenation and ester hydrolysis to give Ibuprofen **3.81**

With the synthesis of Ibuprofen **3.81** successfully achieved, attempts were made again to combine the allylation and hydrogenation steps in order to minimise the number of operations

involved (Scheme 3.76). Using the standard allylation conditions, followed by addition of a H_2 atmosphere, hydrogenation was unsuccessful, with the alkene **3.51** remaining present.

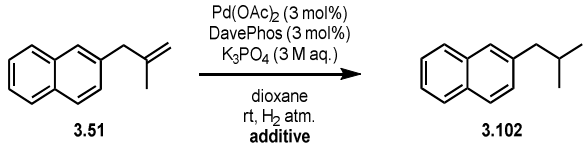


3.41 3.51 3.102

Scheme 3.76: Combined allylation and hydrogenation

As the presence of leftover allyl halide, or MIDA formed after hydrolysis of the MIDA boronate could be inhibiting the hydrogenation, these were submitted as additives (Table 3.8). Neither of these were found to inhibit the hydrogenation, which gave full conversion to the alkane **3.102** in both cases.

Table 3.8: Effect of allyl bromide or MIDA on hydrogenation

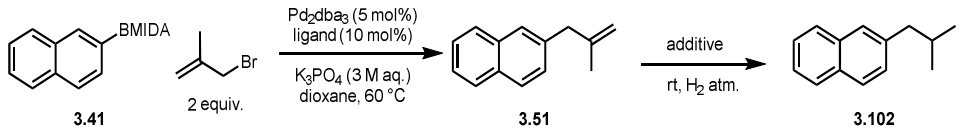


3.51 3.102

Entry	Additive	Result
1	Allyl bromide	Full conversion to **3.102**
2	MIDA	Full conversion to **3.102**

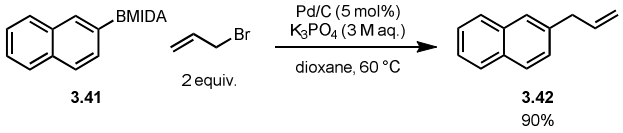
As the presence of leftover allyl halide, or MIDA was not inhibiting the hydrogenation, there could be an issue with the catalyst system being used. A change of catalyst from palladium acetate/DavePhos to Pd_2dba_3 saw no change, with the allylation successfully carried out, but no hydrogenation (Table 3.9, entry 1). Addition of HCl during the hydrogenation step did result in some hydrogenation taking place, but resulted in a complex mixture of products (entry 2). Use of DavePhos as a ligand during the allylation step, and HCl during the hydrogenation saw no conversion to the hydrogenated product, with the alkene remaining (entry 3). Perhaps unsurprisingly, addition of Pd/C to the hydrogenation step resulted in complete conversion to the hydrogenated product (entry 4).

Table 3.9: Effect of ligands and additives on hydrogenation after allylation



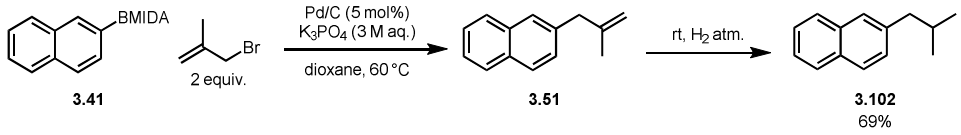
Entry	Ligand	Additive	Result
1	-	-	**3.51**
2	-	HCl	Complex mixture
3	DavePhos	HCl	**3.51**
4	-	Pd/C (5 mol%)	**3.102**

As the hydrogenation had proceeded to completion using Pd/C, the allylation was attempted using this as the catalyst (Scheme 3.77). This proved successful, giving the desired allylated product **3.42** in an excellent 90% yield.



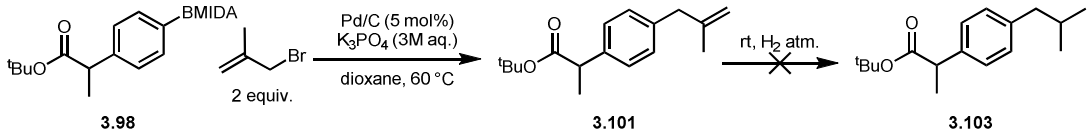
Scheme 3.77: Allylation using Pd/C as catalyst

Having shown that Pd/C could be used to carry out both the allylation and hydrogenation, this was then applied to the combined reaction (Scheme 3.78). This proved to be successful, giving the hydrogenated product **3.102** in 69% yield over the two steps.



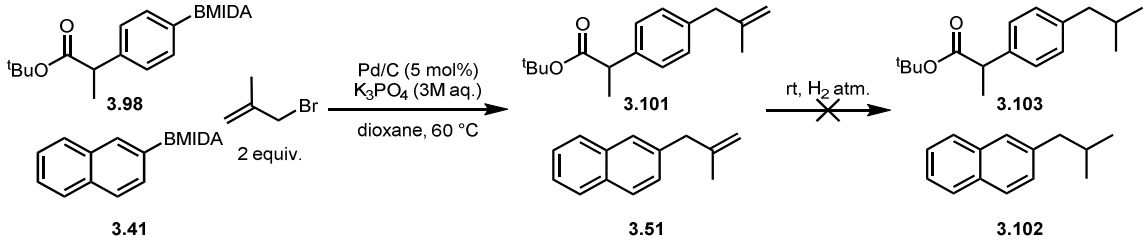
Scheme 3.78: Combined allylation and hydrogenation using Pd/C

With the combined allylation/hydrogenation successfully carried out, it was attempted on the α-aryl ester MIDA boronate **3.95** (Scheme 3.79). In this case, no hydrogenated product was observed after 24 hours. Additional Pd/C was added, and the hydrogenation continued for a further 24 hours, however still only 70% conversion from alkene **3.101** to alkane **3.103** was achieved.



Scheme 3.79: Attempted allylation and hydrogenation of **3.98**

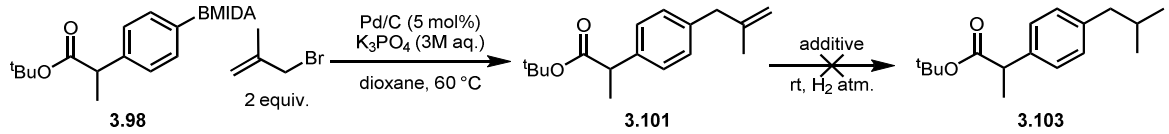
To determine where the problem with the hydrogenation of the α-aryl ester **3.101** was, a competition reaction was setup using naphthyl MIDA boronate **3.41** (Scheme 3.80). As the allylated naphthalene **3.51** had already been shown to be hydrogenated under these conditions, if the hydrogenated product **3.102** is not formed, then it suggests the presence of the α-aryl ester is inhibiting the hydrogenation. Analysis of the product mixture showed that both alkenes had been formed successfully, but neither hydrogenated product was present.



Scheme 3.80: Competition reaction between **3.41** and **3.98**

If the α-aryl ester was indeed inhibiting the hydrogenation, this could be due to formation of a palladium enolate species. Addition of acid during the hydrogenation could help suppress this formation if it is occurring. To that end, the allylation/hydrogenation was carried out with various acid additives included during the hydrogenation step (Table 3.10). Addition of HCl, either 10 or 50 equivalents, saw no hydrogenation product formed, with a small amount of decomposition (entries 1 and 2). Acetic acid saw only the formation of the alkene **3.101**, with no hydrogenation taking place (entry 3). Finally, *p*-toluenesulfonic acid also had no effect, with only the alkene **3.101** and a small amount of decomposition present (entry 4).

Table 3.10: Effect of acid on allylation and hydrogenation of **3.98**



3.98 **3.101** **3.103**

Entry	Additive	Equiv. acid	Result
1	HCl	10	**3.101** + some decomposition
2	HCl	50	**3.101** + some decomposition
3	Acetic acid	50	**3.101**
4	*p*-Toluenesulfonic acid	50	**3.101** + some decomposition

3.2.7 Conclusions

A new allylation reaction of MIDA boronates has been developed, allowing formation of a new bond to an sp^3 carbon for the first time. While attempts at sp^3–sp^3 allylation proved unsuccessful, the allylation was successfully applied to a wide range of MIDA boronates and allyl halide coupling partners (Figure 3.3).

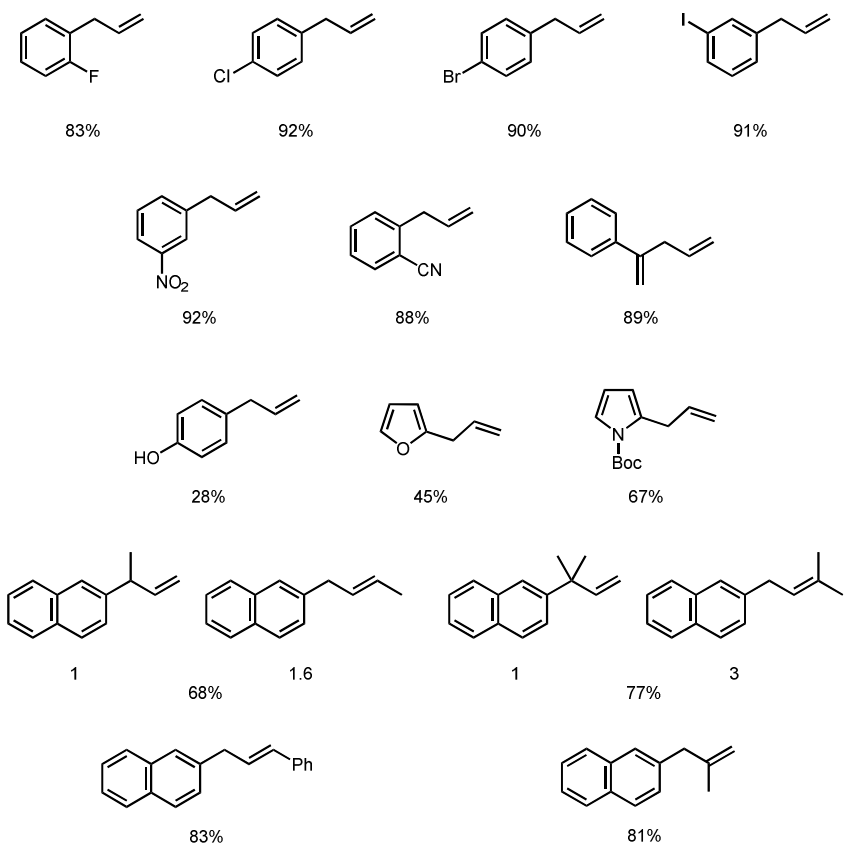
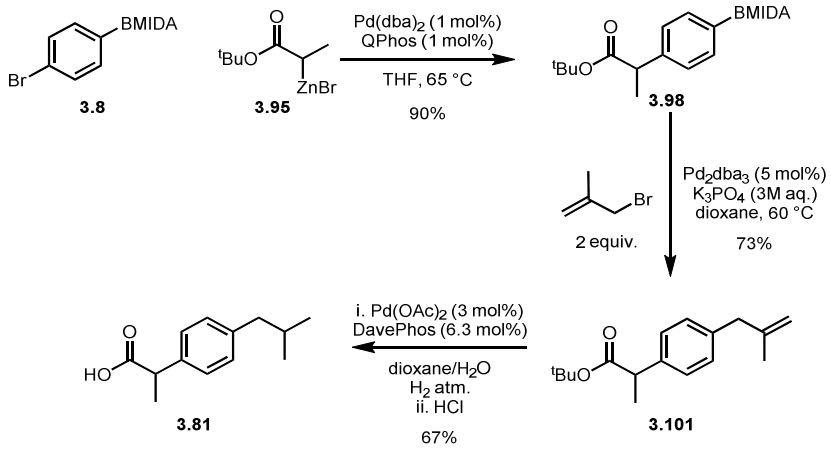


Figure 3.3: Products of MIDA boronate allylation

A deuterium labelling study was carried out, revealing that the reaction proceeds via a π-allyl 0–II cycle. This was able to help explain some of the selectivity observed during the allylation reaction.

The utility of the allylation reaction was demonstrated in its application to a new synthesis of Ibuprofen **3.81**. It was used as the key step in a three-step palladium-catalysed synthesis giving Ibuprofen in a 44% overall yield (Scheme 3.81). By making use of the "catch and release" purification on **3.98**, the synthesis of Ibuprofen can be compatible with automated synthesis.



Scheme 3.81: New palladium-catalysed synthesis of Ibuprofen **3.81**

Summary

In Chapter 1, the carboallylation reaction was further optimised and expanded to include formation of indolinones. It was shown that formation of the undesired direct coupling product could be supressed via substrates with restricted rotation. The isohypsic mechanism was demonstrated by a deuterium-labelling study, with the separate mechanism for direct coupling giving insight into additional routes for further optimisation.

The second chapter detailed the expansion of the isohypsic-redox sequence to include the oxyallylation–Heck-coupling. The two-step procedure was applied to a range of functionally diverse aryl bromides, adding another point of functionalisation after the heteroallylation reaction. Further studies into the aminoallylation–Grubbs–Wacker oxidation were also undertaken, showing the vital role of the catalyst formation in avoiding unwanted isomerisation.

Chapter 3 described the development of a new palladium-catalysed allylation of MIDA boronates. Allowing formation of a new bond to an sp3 carbon, this was applied to a range of MIDA boronate and allyl halide coupling partners. A deuterium-labelling study revealed he operative mechanism, helping explain the observed selectivity. Finally, the allylation was applied as a key step in the development of a new palladium-catalysed synthesis of Ibuprofen.

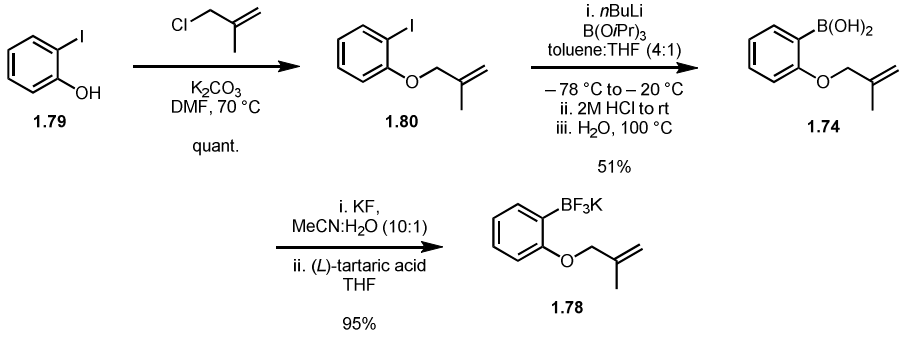
4 Experimental

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 101 MHz) or a Bruker DPX-500 spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 126 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-d6 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), multiplet (m) 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) 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 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

Potassium (2-(2-methylallyloxy)phenyl)trifluoroborate



Following a literature procedure,[25] to a stirred suspension of 2-iodophenol **1.79** (12 g, 52 mmol) and potassium carbonate (14 g, 110 mmol) in DMF (260 mL) was added methallyl chloride (6.1 mL, 63 mmol). The reaction mixture was heated at 70 °C for 16 h then cooled to room temperature, diluted with EtOAc (250 mL) and the phases were separated. The organic phase was washed with water (100 mL) and brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 1-(2-methylallyloxy)-2-iodobenzene **1.80** as a yellow oil (14 g, quant.). Analytical data were in accordance with literature values.[95]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.78 (1H, dd, *J* = 7.7, 1.6 Hz, Ar-H), 7.28 (1H, ddd, *J* = 8.3, 7.4, 1.6 Hz, Ar-H), 6.80 (1H, dd, *J* = 8.3, 1.3 Hz, Ar-H), 6.71 (1H, td, *J* = 7.6, 1.3 Hz, Ar-H), 5.20–5.19 (1H, m, C=C*Ha*), 5.02–5.01 (1H, m, C=C*Hb*), 4.48 (2H, s, OCH_2), 1.86 (3H, d, *J* = 0.5 Hz, CH_3).

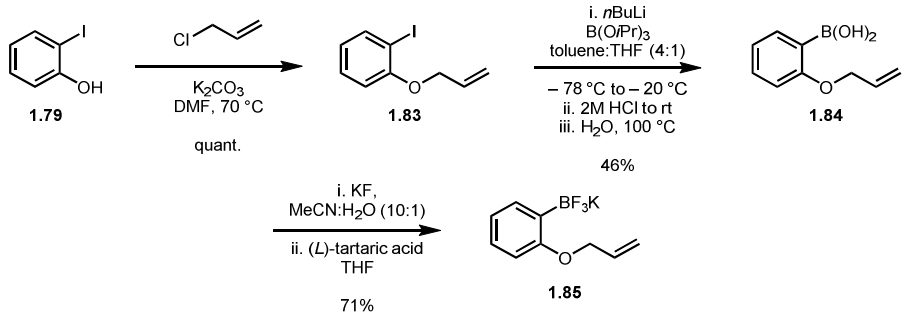
Following a literature procedure,[96] to a stirred solution of 1-(2-methylallyloxy)-2-iodobenzene **1.80** (12 g, 43 mmol) and triisopropyl borate (12 mL, 52 mmol) in toluene:THF (4:1) (160 mL) at –78 °C was added *n*BuLi (26 mL, 52 mmol). The reaction mixture was stirred at –78 °C for 1 h then allowed to warm to –20 °C and quenched with 2M aq. HCl (100 mL). The mixture was allowed to warm to room temperature then extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 9:1 to 4:1) gave a pale yellow solid which was boiled in water for 2 hours. After cooling, the mixture was filtered to give 2-(2-methylallyloxy)phenylboronic acid **1.74** as a pale yellow crystalline solid (4.2 g, 51%). Analytical data were in accordance with literature values.[96]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.86 (1H, dd, *J* = 7.3, 1.7 Hz, Ar-H), 7.42 (1H, ddd, *J* = 8.3, 7.3, 1.7 Hz, Ar-H), 7.04 (1H, t, *J* = 7.3 Hz, Ar-H), 6.90 (1H, d, *J* = 8.3 Hz, Ar-H), 6.17 (2H, s, $B(OH)_2$), 5.08 (2H, d, *J* = 23.8 Hz, $C=CH_2$), 4.55 (2H, s, OCH_2), 1.86 (3H, s, CH_3).

Following a literature procedure,[50] to a stirred solution of 2-(2-methylallyloxy)phenylboronic acid **1.74** (0.50 g, 2.6 mmol) in acetonitrile (11 mL) was added a solution of KF (0.60 g, 10 mmol) in water (1.2 mL). A solution of (*L*)-tartaric acid (0.80 g, 5.3 mmol) in THF (4.0 mL) was then added to the rapidly stirring solution and a white precipitate was observed immediately. The reaction mixture was stirred rapidly for 30 min then the precipitate was removed by filtration, and washed with acetonitrile. The filtrate was concentrated *in vacuo* to give the title compound **1.78** as a fluffy white solid (0.63 g, 95%).

^{1}H NMR (400 MHz, d6-DMSO) δ (ppm): 7.29 (1H, dd, *J* = 7.1, 1.9 Hz, Ar-H), 6.96 (1H, ddd, *J* = 8.0, 7.2, 2.0 Hz, Ar-H), 6.66 (1H, t, *J* = 7.2 Hz, Ar-H), 6.62 (1H, d, *J* = 8.1 Hz, Ar-H), 5.16–5.14 (1H, m, C=*CHa*), 4.85–4.84 (1H, m, C=*CHb*), 4.27 (2H, s, OCH_2), 1.76 (3H, s, CH_3); ^{13}C NMR (125 MHz, DMSO) δ (ppm): 161.6 (C), 142.1 (C), 138.7 (C)*, 133.4 (q, ^3J(C–F) = 3.1 Hz, CH), 126.3 (CH), 119.1 (CH), 110.99 (CH), 110.97 (CH_2), 70.5 (CH_2), 19.3 (CH_3); IR (solid) 1597, 1437, 1209, 1188, 922 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{10}H_{11}F_3OB$ $[M\text{-}K]^-$ *m/z* 214.0897, found *m/z* 214.0858. *detected by HMBC

Potassium (2-(allyloxy)phenyl)trifluoroborate



Following a literature procedure,[25] to a stirred suspension of 2-iodophenol **1.79** (10 g, 46 mmol) and potassium carbonate (13 g, 91 mmol) in DMF (250 mL) was added allyl chloride (4.2 mL, 55 mmol). The reaction mixture was heated at 70 °C for 16 h then cooled to room temperature, diluted with EtOAc (250 mL) and separated. The organic phase was washed with water (100 mL) and brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 1-allyloxy-2-iodobenzene **1.83** as a yellow oil (12 g, quant.). Analytical data were in accordance with literature values.[97]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.78 (1H, dd, *J* = 7.8, 1.6 Hz, Ar-H), 7.30–7.26 (1H, m, Ar-H), 6.81 (1H, dt, *J* = 8.2, 1.3 Hz, Ar-H), 6.73–6.69 (1H, m, Ar-H), 6.11–6.02 (1H, m, *CH*=CH_2), 5.53 (1H, dq, *J* = 17.2, 1.8 Hz, C=*CHa*), 5.32 (1H, dq, *J* = 10.6, 1.6 Hz, C=*CHb*), 4.61–4.59 (2H, m, OCH_2).

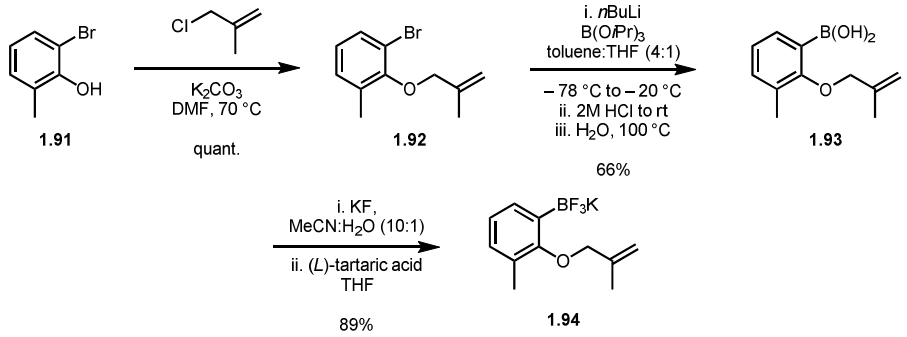
Following a literature procedure,[96] to a stirred solution of 1-allyloxy-2-iodobenzene **1.83** (11 g, 43 mmol) and triisopropyl borate (12 mL, 52 mmol) in toluene:THF (4:1) (160 mL) at –78 °C was added *n*BuLi (26 mL, 52 mmol). The reaction mixture was stirred at –78 °C for 1 h then allowed to warm to –20 °C and quenched with 2M aq. HCl (100 mL). The mixture was allowed to warm to room temperature then extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:EtOAc, 4:1) gave a pale yellow solid which was boiled in water for 2 hours. After cooling, the mixture was filtered to give 2-allyloxyphenylboronic acid **1.84** as a pale yellow crystalline solid (3.5 g, 46%). Analytical data were in accordance with literature values.[98]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.85 (1H, dd, *J* = 7.3, 1.7 Hz, Ar-H), 7.44–7.40 (1H, m, Ar-H), 7.03 (1H, dt, *J* = 7.3, 0.8 Hz, Ar-H), 6.90 (1H, d, *J* = 8.3 Hz, Ar-H), 6.14–6.04 (1H, m, *CH*=CH_2), 5.88 (2H, s, $B(OH)_2$), 5.43 (1H, dq, *J* = 17.2, 1.4 Hz, C=*CHa*), 5.36 (1H, dd, *J* = 10.5, 1.2 Hz, C=*CHb*), 4.64 (2H, td, *J* = 5.6, 1.3 Hz, OCH_2).

Following a literature procedure,[50] to a stirred solution of 2-allyloxyphenylboronic acid **1.84** (3.5 g, 20 mmol) in acetonitrile (79 mL) was added a solution of KF (4.6 g, 79 mmol) in water (7.9 mL). A solution of (*L*)-tartaric acid (6.1 g, 40 mmol) in THF (30 mL) was then added to the rapidly stirring solution and a white precipitate was observed immediately. The reaction mixture was stirred rapidly for 30 min then the precipitate was removed by filtration, and washed with acetonitrile. The filtrate was concentrated *in vacuo* to give the title compound **1.85** as a fluffy white solid (3.4 g, 71%). Analytical data were in accordance with literature values.[96]

^{1}H NMR (500 MHz, DMSO) δ (ppm): 7.30 (1H, dd, *J* = 7.1, 1.7 Hz, Ar-H), 6.98 (1H, td, *J* = 7.9, 1.9 Hz, Ar-H), 6.69 (1H, t, *J* = 7.1 Hz, Ar-H), 6.65 (1H, d, *J* = 8.0 Hz, Ar-H), 6.00 (1H, ddt, *J* = 17.3, 10.6, 4.7 Hz, *CH*=CH$_2$), 5.46 (1H, dq, *J* = 17.3, 2.0 Hz, C=*CHa*), 5.15 (1H, dq, *J* = 10.6, 2.0 Hz, C=*CHb*), 4.41 (2H, dt, *J* = 4.6, 1.8 Hz, OCH$_2$).

Potassium (2-(2-methylallyloxy)-3-methylphenyl)trifluoroborate



Following a literature procedure,[25] to a stirred suspension of 6-bromo-*o*-cresol **1.91** (0.66 mL, 5.4 mmol) and potassium carbonate (1.5 g, 11 mmol) in DMF (30 mL) was added methallyl chloride (0.62 mL, 6.4 mmol). The reaction mixture was heated at 70 °C for 16 h then cooled to room temperature, diluted with EtOAc (30 mL) and separated. The organic phase was washed with water (20 mL) and brine (3 x 20 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give 2-(2-methylallyl)-3-bromotoluene **1.92** as a yellow oil (1.3 g, quant.).

^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.38 (1H, dd, *J* = 8.0, 1.5 Hz, Ar-H), 7.12 (1H, dq, *J* = 7.6, 0.7 Hz, Ar-H), 6.89 (1H, t, *J* = 7.8 Hz, Ar-H), 5.19–5.18 (1H, m, C=*CHa*), 5.02–5.01 (1H, m, C=*CHb*), 4.31 (2H, s, OCH$_2$), 2.33 (3H, s, CH$_3$), 1.93 (3H, d, *J* = 0.4 Hz, CH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 154.4 (C), 141.4 (C), 133.6 (CH), 131.2 (CH), 130.5 (C), 125.3 (CH), 117.7 (C), 113.1 (CH$_2$), 76.2 (CH$_2$), 19.9 (CH$_3$), 16.8 (CH$_3$); IR (thin film) 2920, 1653, 1464, 1452, 1260, 1220 cm^{-1}; HRMS (EI) exact mass calculated for C$_{11}$H$_{13}$OBr [M]+ *m/z* 240.0150, found *m/z* 240.0153.

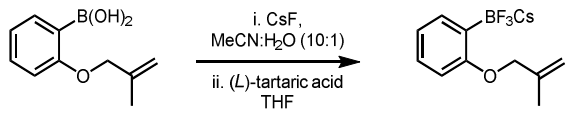
Following a literature procedure,[96] to a stirred solution of 2-(2-methylallyl)-3-bromotoluene **1.92** (0.79 g, 3.3 mmol) and triisopropyl borate (0.90 mL, 3.9 mmol) in toluene:THF (4:1) (14 mL) at –78 °C was added *n*BuLi (1.8 mL, 3.9 mmol). The reaction mixture was stirred at –78 °C for 1 h then allowed to warm to –20 °C and quenched with 2M aq. HCl (10 mL). The mixture was allowed to warm to room temperature then extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:ethyl acetate, 9:1) gave a pale yellow solid which was boiled in water for 2 hours. After cooling, the mixture was filtered to give 2-(2-methylallyloxy)-3-methyl-phenylboronic acid **1.93** as a pale yellow crystalline solid (0.44 g, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (1H, dd, *J* = 7.2, 1.6 Hz, Ar-H), 7.31 (1H, ddt, *J* = 7.5, 1.9, 0.7 Hz, Ar-H), 7.11 (1H, t, *J* = 7.4 Hz, Ar-H), 6.04 (2H, s, $B(OH)_2$), 5.23 (1H, s, C=*CHa*), 5.05 (1H, s, C=*CHb*), 4.23 (2H, s, OCH_2), 2.31 (3H, s, CH_3), 1.89 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 163.1 (C), 140.9 (C), 135.1 (CH), 134.3 (CH), 130.3 (C), 124.8 (CH), 123.0 (C)*, 113.3 (CH_2), 78.0 (CH_2), 19.8 (CH_3), 16.1 (CH_3); IR (thin film) 3412, 2910, 1464, 1435, 1383, 1344, 1084 cm^{-1}; HRMS (CI) exact mass calculated for $C_{11}H_{15}O_3B$ [M]+ *m/z* 206.1229, found *m/z* 206.1232. *detected by HMBC

Following a literature procedure,[50] to a stirred solution of 2-(2-methylallyloxy)-3-methyl-phenylboronic acid **1.93** (0.072 g, 0.35 mmol) in acetonitrile (1.4 mL) was added a solution of KF (0.081 g, 1.4 mmol) in water (0.15 mL). A solution of (*L*)-tartaric acid (0.11 g, 0.72 mmol) in THF (0.53 mL) was then added to the rapidly stirring solution and a white precipitate was observed immediately. The reaction mixture was stirred rapidly for 30 min then the precipitate was removed by filtration, and washed with acetonitrile. The filtrate was concentrated *in vacuo* to give the title compound **1.94** as a fluffy white solid (0.084 g, 89%).

^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.20 (1H, dd, *J* = 7.2, 1.9 Hz, Ar-H), 6.87 (1H, ddd, *J* = 7.2, 2.0, 0.8 Hz, Ar-H), 6.73 (1H, t, *J* = 7.2 Hz, Ar-H), 5.05 (1H, dq, *J* = 2.4, 1.0 Hz, C=*CHa*), 4.83 (1H, dq, *J* = 2.7, 1.3 Hz, C=*CHb*), 4.23 (2H, s, O*CH*$_2$), 2.12 (3H, s, CH_3), 1.78 (3H, dd, *J* = 1.5, 0.8 Hz, CH_3); ^{13}C NMR (125 MHz, DMSO) δ (ppm): 160.6 (C), 143.3 (C), 142.0 (C)*, 132.0 (q, ^3J(C–F) = 3.0 Hz, CH), 128.3 (CH), 128.2 (C), 121.8 (CH), 110.2 (CH_2), 75.5 (CH_2), 19.6 (CH_3), 16.5 (CH_3); IR (solid) 1448, 1192, 993 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{11}H_{13}F_3OB$ [M-K]$^-$ *m/z* 228.1053, found *m/z* 228.1034. *detected by HMBC

Cesium (2-(2-methylallyloxy)phenyl)trifluoroborate

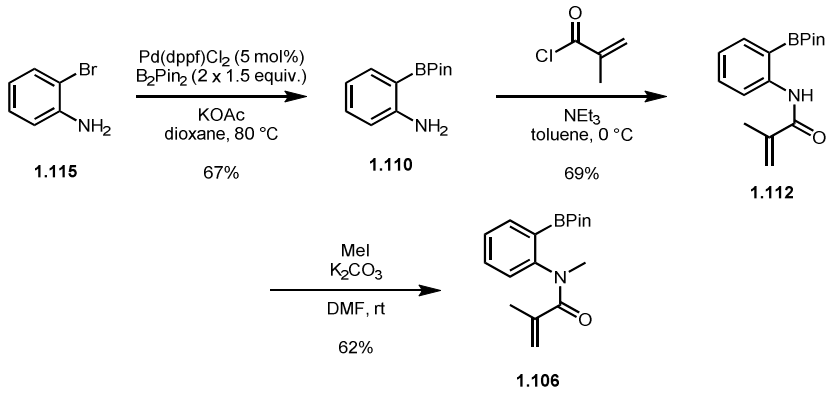


1.74 **1.82**
90%

Following a literature procedure,[50] to a stirred solution of 2-(2-methylallyloxy)phenylboronic acid **1.74** (0.20 g, 1.1 mmol) in acetonitrile (4.2 mL) was added a solution of CsF (0.64 g, 4.2 mmol) in water (0.42 mL). A solution of (*L*)-tartaric acid (0.33 g, 2.2 mmol) in THF (1.7 mL) was then added to the rapidly stirring solution and a white precipitate was observed immediately. The reaction mixture was stirred rapidly for 30 min then the precipitate was removed by filtration, and washed with acetonitrile. The filtrate was concentrated *in vacuo* to give the title compound **1.82** as a fluffy white solid (0.34 g, 90%).

^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.29 (1H, dd, *J* = 7.1, 1.9 Hz, Ar-H), 6.97 (1H, ddd, *J* = 8.0, 7.2, 2.0 Hz, Ar-H), 6.67 (1H, tt, *J* = 7.2, 0.8 Hz, Ar-H), 6.63 (1H, d, *J* = 8.1 Hz, Ar-H), 5.15 (1H, dq, *J* = 2.6, 0.8 Hz, C=*CHa*), 4.85 (1H, dq, *J* = 2.6, 1.4 Hz, C=*CHb*), 4.28 (2H, d, *J* = 1.5 Hz, O*CH*$_2$), 1.77–1.76 (3H, m, CH_3); ^{13}C NMR (100 MHz, DMSO) δ (ppm): 161.6 (C), 142.1 (C), 138.4 (C)*, 133.4 (q, ^{3}J(C–F) = 2.8 Hz, CH), 126.3 (CH), 119.1 (CH), 111.02 (CH), 111.98 (CH_2), 70.5 (CH_2), 19.3 (CH_3); IR (solid) 1597, 1438, 1186, 949 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{10}H_{11}BCsF_3NaO$ $[M+Na]^+$ *m/z* 370.9802, found *m/z* 370.9762. *detected by HMBC

N,2-Dimethyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide



Following a modification of a literature procedure[99], a mixture of bromoaniline **1.115** (0.11 mL, 1.0 mmol) and bis(pinacolato)diboron (0.38 g, 1.5 mmol) in dioxane (4 mL) was sparged with argon for 20 min. Potassium acetate (0.20 g, 2.0 mmol) and $Pd(dppf)Cl_2$ (0.041 g, 0.050 mmol) were added and the reaction mixture was stirred at 80 °C. After 24 h, bis(pinacolato)diboron (0.38 g, 1.5 mmol) was added, and the reaction mixture stirred at 80 °C for a further 24 h. After cooling to room temperature, water (10 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:ethyl acetate, 96:4) afforded 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **1.110** as an orange crystalline solid (0.15 g, 67%). Analytical data were in accordance with literature values.[100]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.61 (1H, dd, *J* = 7.4, 1.5 Hz, Ar-H), 7.21 (1H, m, Ar-H), 6.67 (1H, td, *J* = 7.4, 1.0 Hz, Ar-H), 6.60 (1H, d, *J* = 8.1 Hz, Ar-H), 4.74 (2H, s, NH_2), 1.34 (12H, s, 4xCH_3).

Following a literature procedure,[100] to a stirred solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **1.110** (0.1 g, 0.46 mmol) in toluene (15 mL) at 0 °C was added triethylamine (0.50 mL, 0.46 mmol, 0.90 M) in toluene. A solution of methacryloyl chloride (0.50 mL, 0.46 mmol, 0.9 M) in toluene was added slowly (0.2 mL/min). The reaction mixture was stirred at 0 °C for 20 min then allowed to warm to room temperature. The reaction mixture was washed with water (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:ethyl acetate, 85:15) afforded 2-methyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide **1.112** as a

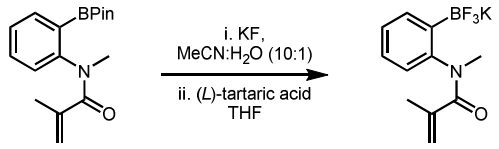
light brown crystalline solid (90 mg, 69%). Analytical data were in accordance with literature values.[100]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.82 (1H, s, N-H), 8.62 (1H, d, *J* = 8.4, Ar-H), 7.78 (1H, dd, *J* = 7.5, 1.6 Hz, Ar-H), 7.47 (1H, td, *J* = 7.9, 1.7 Hz, Ar-H), 7.07 (1H, td, *J* = 7.4, 0.8 Hz, Ar-H), 5.97 (1H, s, C=*CHa*), 5.47 (1H, s, C=*CHb*), 2.10 (3H, s, CH_3), 1.37 (12H, s, 4xCH_3).

Following a literature procedure, to a stirred suspension of 2-methyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide **1.112** (0.73 g, 2.5 mmol) and potassium carbonate (0.40 g, 2.9 mmol) in DMF (41 mL) was added methyl iodide (0.22 mL, 3.6 mmol). The reaction mixture was stirred at room temperature overnight, diluted with EtOAc (100 mL), water (100 mL) and extracted. The organic phase was washed with water (2 x 100 mL) and brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:ethyl acetate, 4:1) afforded the title compound **1.106** as an orange crystalline solid (0.47 g, 62%).

1H NMR (500 MHz, d6-DMSO, 80 °C) δ (ppm): 7.69 (1H, dd, *J* = 7.4, 1.7 Hz, Ar-H), 7.48 (1H, td, *J* = 7.7, 1.7 Hz, Ar-H), 7.31 (1H, td, *J* = 7.4, 1.1 Hz, Ar-H), 7.19 (1H, dd, *J* = 8.0, 1.1 Hz, Ar-H), 4.99 (2H, s, C=CH_2), 3.20 (3H, s, NCH_3), 1.73 (3H, s, CCH_3), 1.29 (12H, s, 4 x CCH_3); 13C NMR (125 MHz, d6-DMSO, 80 °C) δ (ppm): 169.7 (C), 140.3 (C), 136.0 (C), 135.3 (CH), 132.5 (CH), 131.3 (C), 128.6 (CH), 126.2 (CH), 116.8 (CH_2), 82.9 (C), 37.7 (CH_3), 24.2 (CH_3), 19.5 (CH_3); IR (thin film) 2978, 1653, 1352, 1145 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{17}H_{24}BNNaO_3$ $[M+Na]^+$ *m/z* 324.1741, found *m/z* 324.1740.

Potassium 2-methyl-*N*-methyl-*N*-(phenyltrifluoroborate)-2-propenamide

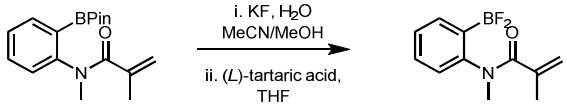


1.106 **1.117** 39%

Following a literature procedure,[50] to a stirred solution of *N*,2-dimethyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide **1.106** (0.10 g, 0.33 mmol) in acetonitrile/methanol (0.67 mL/0.67 mL) was added a solution of potassium fluoride (0.077 g, 1.3 mmol) in water (0.13 mL). A solution of (*L*)-tartaric acid (0.10 g, 0.68 mmol) in THF (0.50 mL) was then added to the rapidly stirring solution and a white precipitate was observed immediately. The reaction mixture was stirred rapidly for 1 h then the precipitate was removed by filtration, and washed with acetonitrile. The filtrate was concentrated *in vacuo* to give a yellow oil. This oil was washed with CH_2Cl_2 to give the title compound **1.117** as a brown solid (0.036 g, 39%).

^{1}H NMR (500 MHz, DMSO) δ (ppm): 7.44–7.42 (1H, m, Ar-H), 7.04–7.00 (2H, m, Ar-H), 6.75–6.73 (1H, m, Ar-H), 4.94 (1H, s, C=C*H*H), 7.74–7.73 (1H, m, C=CH*H*), 3.10 (3H, s, N*CH$_3$*), 1.64 (3H, s, CH_3); ^{13}C NMR (125 MHz, DMSO) δ (ppm): 170.2 (C), 147.3 (C), 140.8 (C), 134.0 (q, ^3J(C-F) = 2.8 Hz, CH), 126.9 (CH), 126.0 (CH), 125.4 (CH), 117.2 (CH_2), 37.1 (CH_3), 20.5 (CH_3).

2-Methyl-*N*-methyl-*N*-(phenyldifluoroborane)-2-propenamide



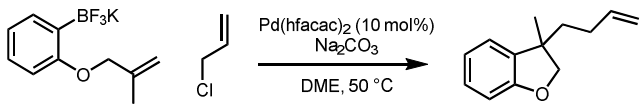
1.106 **1.118** quant.

Following a modification of a literature procedure,[50] to a stirred solution of *N*,2-dimethyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide **1.106** (0.10 g, 0.33 mmol) in acetonitrile/methanol (0.67 mL/0.67 mL) was added a solution of potassium fluoride (0.077 g, 1.3 mmol) in water (0.13 mL). A solution of (*L*)-tartaric acid (0.10 g, 0.68 mmol) in THF (0.50 mL) was then added to the rapidly stirring solution and a white precipitate was observed immediately. The reaction mixture was stirred rapidly for 2 h, at which point TLC analysis showed the presence of starting material. A solution of potassium fluoride (0.077 g, 1.3 mmol) in water (0.13 mL) was added, followed by a solution of (*L*)-tartaric acid (0.10 g,

0.68 mmol) in THF (0.50 mL). The reaction mixture was stirred rapidly for a further 1 h then the precipitate was removed by filtration, and washed with acetonitrile. The filtrate was concentrated *in vacuo* at 50 °C for 1 h to give the title compound **1.118** as a light brown solid (0.075 g, quant.).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.78–7.76 (1H, m, Ar-H), 7.44–7.40 (2H, m, Ar-H), 7.20–7.19 (1H, m, Ar-H), 5.73 (1H, d, *J* = 1.6 Hz, C=C*H*H), 5.55 (1H, d, *J* = 0.9 Hz, C=CH*H*), 3.74 (3H, s, N*CH*$_3$), 2.17 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 170.9 (C), 139.6 (t, ^2J(C-F) = 3.0 Hz, C), 136.7 (C), 132.0 (CH), 128.8 (CH), 128.5 (CH), 123.8 (CH_2), 115.0 (CH), 38.4 (CH_3), 20.0 (CH_3); LRMS (EI) mass calculated for $C_{11}H_{12}BF_2NO$ [M]+ *m/z* 222.1, found *m/z* 222.1.

3-(But-3-en-1-yl)-3-methyl-2,3-dihydrobenzofuran

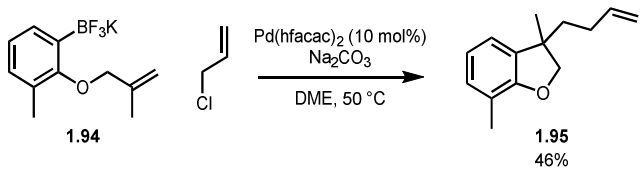


1.78 **1.75**
48%

A 4 mL screw-top glass vial was charged with potassium (2-(2-methylallyloxy)phenyl)trifluoroborate **1.78** (76 mg, 0.30 mmol), $Pd(hfacac)_2$ (16 mg, 0.030 mmol), Na_2CO_3 (64 mg, 0.60 mmol), dimethoxyethane (1.2 mL) and allyl chloride (49 µL, 0.60 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block for 16 hours. Purification by flash chromatography (petroleum ether:dichloromethane, 9:1) afforded the title compound **1.75** as a colourless oil (27 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.15–7.07 (2H, m, Ar-H), 6.88 (1H, td, *J* = 7.4, 1.0 Hz, Ar-H), 6.79 (1H, dt, *J* = 8.0, 0.5 Hz, Ar-H), 5.76 (1H, ddt, *J* = 16.7, 10.2, 6.4 Hz, C*H*=CH_2), 4.98 (1H, dq, *J* = 17.1, 1.7 Hz, CH=C*H*H), 4.94–4.90 (1H, m, CH=CH*H*), 4.37 (1H, d, *J* = 8.7 Hz, O-C*H*H), 4.16 (1H, d, *J* = 8.6 Hz, O-CH*H*), 2.15–2.05 (1H, m, CH_2CH*H*CH=CH_2), 1.92–1.82 (1H, m, CH_2C*H*HCH=CH_2), 1.73–1.68 (2H, m, *CH*$_2$$CH_2$CH=$CH_2$), 1.36 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 159.9 (C), 138.5 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.7 (CH_2), 109.7 (CH), 82.6 (CH_2), 45.3 (C), 40.2 (CH_2), 29.2 (CH_2), 25.7 (CH_3); IR (thin film) 2934, 1365, 1196 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{16}O$ [M]$^+$ *m/z* 188.1201, found *m/z* 188.1203.

3-(But-3-en-1-yl)-3-methyl-7-methyl-2,3-dihydrobenzofuran

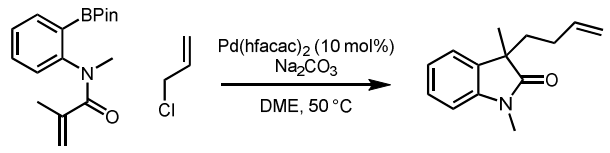


1.94 **1.95** 46%

A 4 mL screw-top glass vial was charged with potassium (2-(2-methylallyloxy)-3-methylphenyl)trifluoroborate **1.94** (220 mg, 0.80 mmol), $Pd(hfacac)_2$ (42 mg, 0.080 mmol), Na_2CO_3 (170 mg, 1.6 mmol), dimethoxyethane (3.2 mL) and allyl chloride (0.13 mL, 1.6 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block for 16 hours. Purification by flash chromatography (petroleum ether:dichloromethane, 9:1) afforded the title compound **1.95** as a colourless oil (74 mg, 46%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.96 (1H, dq, *J* = 7.4, 0.7 Hz, Ar-H), 6.92 (1H, dd, *J* = 7.4, 0.7 Hz, Ar-H), 6.80 (1H, t, *J* = 7.4 Hz, Ar-H), 5.75 (1H, ddt, *J* = 16.8, 10.2, 6.5 Hz, C*H*=CH_2), 4.99 (1H, dq, *J* = 17.1, 1.7 Hz, CH=C*H*H), 4.93–4.91 (1H, m, CH=CH*H*), 4.38 (1H, d, *J* = 8.7 Hz, O-C*H*H), 4.17 (1H, d, *J* = 8.7 Hz, O-CH*H*), 2.22 (3H, s, CH_3), 2.14–2.06 (1H, m, CH_2C*H*HCH=CH_2), 1.91–1.84 (1H, m, CH_2CH*H*CH=CH_2), 1.75–1.65 (2H, m, *C**H*$_2$$CH_2$CH=$CH_2$), 1.35 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 158.0 (C), 138.6 (CH), 134.3 (C), 129.4 (CH), 120.5 (CH), 120.4 (CH), 119.9 (C), 114.6 (CH_2), 82.4 (CH_2), 45.6 (C), 40.2 (CH_2), 29.2 (CH_2), 25.7 (CH_3), 15.2 (CH_3); IR (thin film) 2965, 2922, 1456, 1188 cm^{-1}; HRMS (EI) exact mass calculated for $C_{14}H_{18}O$ [M]+ *m/z* 202.1358, found *m/z* 202.1357.

3-(But-3-en-1-yl)-3-methyl-7-methyl-2,3-dihydrobenzofuran



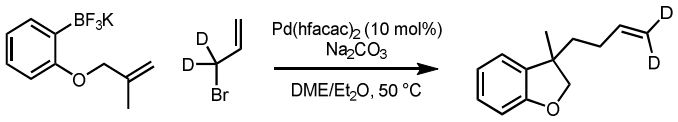
1.106 **1.107** 47%

A 4 mL screw-top glass vial was charged with *N*,2-dimethyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide **1.106** (22 mg, 0.080 mmol), $Pd(hfacac)_2$ (4.2 mg, 0.0080 mmol), Na_2CO_3 (17 mg, 0.16 mmol), dimethoxyethane (0.32 mL) and allyl chloride (13 µL, 0.16 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block for 16

hours. Purification by flash chromatography (petroleum ether:ethyl acetate, 95:5) afforded the title compound **1.107** as a colourless oil (7.5 mg, 47%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.27 (1H, td, *J* = 7.7, 1.2 Hz, Ar-H), 7.17 (1H, dd, *J* = 7.3, 0.7 Hz, Ar-H), 7.07 (1H, td, *J* = 7.5, 0.8 Hz, Ar-H), 6.84 (1H, d, *J* = 7.8 Hz, Ar-H), 5.68–5.60 (1H, m, C*H*=CH_2), 4.843–4.841 (1H, m, CH=C*H*H), 4.82–4.81 (1H, m, CH=CH*H*), 3.20 (3H, s, N-CH_3), 2.05–2.00 (1H, m, CH_2C*H*HCH=CH_2), 1.85–1.79 (1H, m, CH_2CH*H*CH=CH_2), 1.77–1.69 (1H, m, C*H*HCH_2CH=CH_2), 1.66–1.59 (1H, m, CH*H*CH_2CH=CH_2), 1.36 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 180.7 (C), 143.5 (C), 137.9 (CH), 134.0 (C), 127.9 (CH), 122.7 (CH), 122.6 (CH), 114.7 (CH_2), 108.0 (CH), 48.3 (CH_3), 37.7 (CH_2), 29.1 (CH_2), 26.2 (CH_3); IR (thin film) 2974, 2929, 1705, 1614, 1379, 1352 cm^{-1}; HRMS (EI) exact mass calculated for $C_{14}H_{17}ON$ [M]+ *m/z* 215.1310, found *m/z* 215.1311.

3-(4,4-Dideuteriobut-3-en-1-yl)-3-methyl-2,3-dihydrobenzofuran



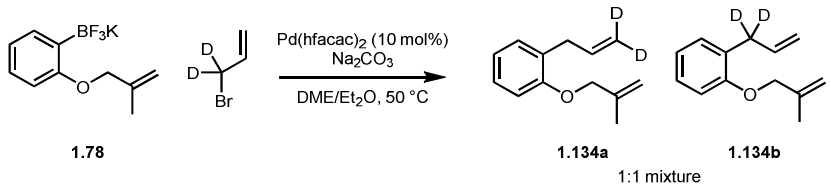
1.78 **1.122**

21%

A 4 mL screw-top glass vial was charged with potassium (2-(2-methylallyloxy)phenyl)trifluoroborate **1.78** (64 mg, 0.25 mmol), $Pd(hfacac)_2$ (13 mg, 0.025 mmol), Na_2CO_3 (53 mg, 0.50 mmol), dimethoxyethane (1.0 mL) and dideuteroallyl bromide[58] (0.37 mL, 1.3 M in Et_2O, 0.50 mmol). and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block for 16 hours. Purification by flash chromatography (petroleum ether:dichloromethane, 9:1) afforded the title compound **1.122** as a colourless oil (8.8 mg, 19%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.13 (1H, ddd, *J* = 8.0, 7.4, 1.5 Hz, Ar-H), 7.08 (1H, ddd, *J* = 7.4, 1.5, 0.6 Hz, Ar-H), 6.88 (1H, td, *J* = 7.4, 1.0 Hz, Ar-H), 6.79 (1H, ddd, *J* = 8.0, 1.0, 0.5 Hz, Ar-H), 5.79–5.73 (1H, m, C*H*=CD_2), 4.38 (1H, d, *J* = 8.7 Hz, O-C*H*H), 4.17 (1H, d, *J* = 8.7 Hz, O-CH*H*), 2.15–2.06 (1H, m, C*H*HCH_2CH=CD_2), 1.92–1.83 (1H, m, CH*H*CH_2CH=CD_2), 1.73–1.69 (2H, m, CH_2*CH_2*CH=CD_2), 1.36 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.7 (C), 138.3 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.0 (t, ^1J(C-D) = 24.1 Hz, CD_2), 109.7 (CH), 82.6 (CH_2), 45.3 (C), 40.2 (CH_2), 29.1 (CH_2), 25.7 (CH_3); IR (thin film) 2926, 2237, 1600, 1481 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{14}D_2O$ [M]$^+$ *m/z* 190.1321, found *m/z* 190.1315.

1-(Dideuterioallyl)-2-((2-methallyl)oxy)benzene



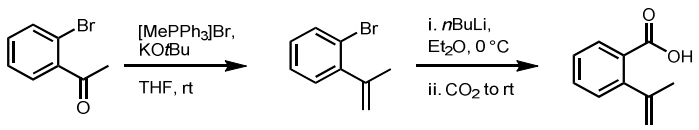
1.78 **1.134a** **1.134b**

1:1 mixture

A 4 mL screw-top glass vial was charged with potassium (2-(2-methylallyloxy)phenyl)trifluoroborate **1.78** (64 mg, 0.25 mmol), $Pd(hfacac)_2$ (13 mg, 0.025 mmol), Na_2CO_3 (53 mg, 0.50 mmol), dimethoxyethane (1.0 mL) and dideuteroallyl bromide[58] (0.37 mL, 1.3 M in Et_2O, 0.50 mmol). and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block for 16 hours. Purification by flash chromatography (petroleum ether:dichloromethane, 9:1) afforded the title compounds in a 1:1 mixture as a colourless oil (1 mg, 1%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.19–7.14 (2H, m, Ar-H), 6.90 (1H, t, *J* = 7.4, Ar-H), 6.83 (1H, d, *J* = 8.1, Ar-H), 6.04–5.97 (1H, m, C*H*=CD_2/C*H*=CH_2), 5.11 (1H, s, OCH_2C=*CHa*), 5.09–5.02 (2H, m, CD_2C=C*H*$_2$), 4.98 (1H, s, OCH_2C=*CHb*), 4.43 (2H, s, OCH_2), 3.43 (2H, d, *J* = 6.6 Hz, C*H*$_2$C=CD_2), 1.84 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.7 (C), 138.3 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.0 (t, ^1J(C-D) = 24.1 Hz, CD_2), 109.7 (CH), 82.6 (CH_2), 45.3 (C), 40.2 (CH_2), 29.1 (CH_2), 25.7 (CH_3); IR (thin film) 2926, 2237, 1600, 1481 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{14}D_2O$ $[M]^+$ *m/z* 190.1321, found *m/z* 190.1315.

2-(Prop-1-en-2-yl)benzoic acid



2.23 **2.24** 87% **2.20** 65%

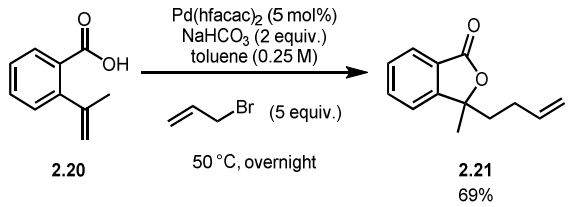
To a stirred suspension of methyl triphenylphosphonium bromide (21 g, 60 mmol) in THF (150 mL) was added a solution of potassium *tert*-butoxide (6.7 g, 60 mmol) in THF (60 mL). The resulting yellow solution was stirred for 15 minutes then a solution of *o*-bromoacetophenone **2.23** (6.7 mL, 50 mmol) in THF (100 mL) was added dropwise. The resulting suspension was stirred at room temperature for 3 h then quenched with sat. aq. NH_4Cl (200 mL). The mixture was extracted with Et_2O (3 x 100 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether) afforded 1-bromo-2-(prop-1-en-2-yl)-benzene **2.24** as a colourless oil (8.20 g, 87%). Analytical data were in accordance with literature values.[101]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.55 (1H, dd, *J* = 8.0, 1.1 Hz, Ar-H), 7.27 (1H, td, *J* = 7.5, 1.2 Hz, Ar-H), 7.19 (1H, dd, *J* = 7.6, 1.8 Hz, Ar-H), 7.11 (1H, td, *J* = 7.7, 1.9 Hz, Ar-H), 5.24–5.22 (1H, m, C=*CHa*), 4.943–4.938 (1H, m, C=*CHb*), 2.104–2.099 (3H, m, CH_3).

To a cooled (0 °C) solution of 1-bromo-2-(prop-1-en-2-yl)-benzene **2.24** (4.0 g, 22 mmol) in Et_2O (42 mL) was added dropwise a solution of *n*-butyllithium (2.1 M in hexanes, 15 mL, 32 mmol). The resulting yellow suspension was stirred for 15 minutes then CO_2 bubbled through the mixture. The mixture was allowed to warm to room temperature over 2 h then quenched with sat. aq. $NaHCO_3$ (100 mL). The mixture was extracted with Et_2O (3 x 50 mL) and the aqueous phase adjusted to pH 1 with 1M aq. HCl. The aqueous phase was then extracted with Et_2O (3 x 100 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound **2.20** as a light yellow solid (2.3 g, 65%). Analytical data were in accordance with literature values.[102]

Melting point: 76–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.95 (1H, dd, *J* = 7.8, 1.1 Hz, Ar-H), 7.50 (1H, td, *J* = 7.5, 1.4 Hz, Ar-H), 7.35 (1H, td, *J* = 7.7, 1.3 Hz, Ar-H), 7.26 (1H, dd, *J* = 7.5, 1.0 Hz, Ar-H), 5.14–5.12 (1H, m, C=*CHa*), 4.90–4.89 (1H, m, C=*CHb*), 2.12 (3H, dd, *J* = 1.4, 0.9 Hz, CH_3).

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

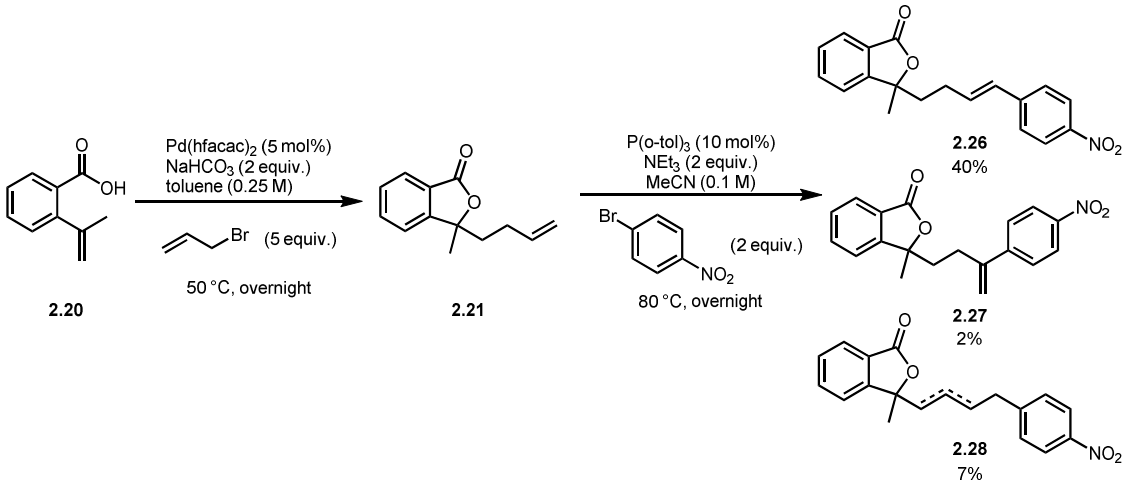


2.20 **2.21** 69%

A 4 mL screw-top glass vial was charged with 2-(prop-1-en-2-yl)benzoic acid **2.20** (54 mg, 0.33 mmol), toluene (1.3 mL), allyl bromide (0.14 mL, 1.7 mmol), $NaHCO_3$ (49 mg, 0.66 mmol) and $Pd(hfacac)_2$ (8.8 mg, 0.017 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block for 16 hours. The reaction mixture was cooled to room temperature and diluted with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:ethyl acetate, 9:1) afforded the title compound **2.21** as a colourless oil (46 mg, 69%). Analytical data were in accordance with literature values.[48]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (1H, dt, *J* = 7.7, 1.0 Hz, Ar-H), 7.65 (1H, td, *J* = 7.5, 1.1 Hz, Ar-H), 7.49 (1H, td, *J* = 7.5, 1.0 Hz, Ar-H), 7.36 (1H, dd, *J* = 7.7, 0.9 Hz, Ar-H), 5.67 (1H, ddt, *J* = 16.8, 10.2, 6.3 Hz, C*H*=CH_2), 4.92–4.88 (1H, m, C=*CHa*), 4.87–4.85 (1H, m, C=*CHb*), 2.13 (1H, ddd, *J* = 13.3, 11.2, 4.1 Hz, $CH_2CHHCH=CH_2$), 2.07–1.98 (1H, m, $CH_2CHHCH=CH_2$), 1.94 (1H, ddd, *J* = 13.4, 11.0, 4.0 Hz, C*H*$HCH_2CH=CH_2$), 1.77–1.67 (1H, m, $CHHCH_2CH=CH_2$), 1.63 (3H, s, CH_3).

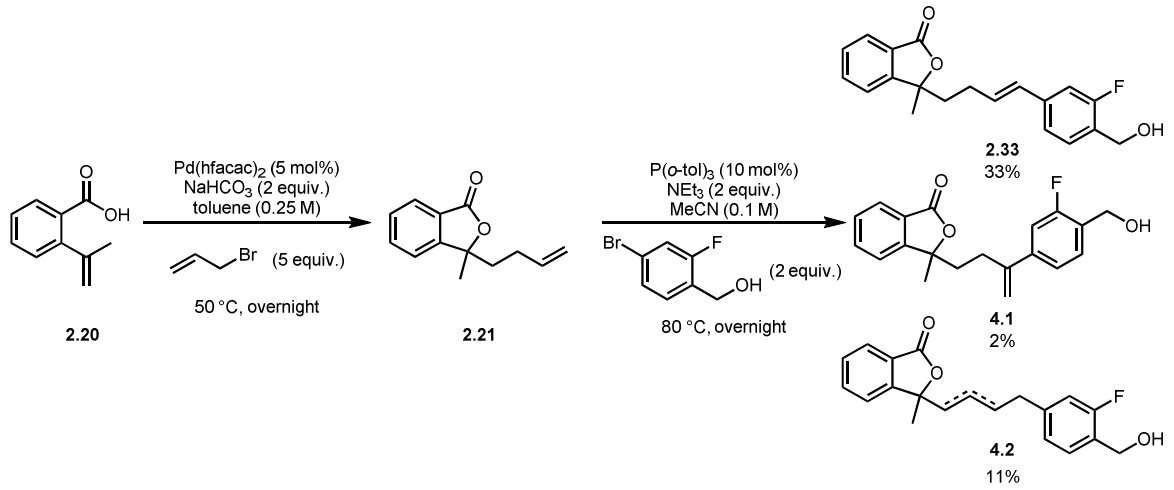
(*E*)-3-Methyl-3-(4-(4-nitrophenyl)but-3-en-1-yl)isobenzofuran-1(*3H*)-one



A 4 mL screw-top glass vial was charged with 2-(prop-1-en-2-yl)benzoic acid **2.20** (32 mg, 0.20 mmol), toluene (0.80 mL), allyl bromide (90 µL, 1.0 mmol), $NaHCO_3$ (30 mg, 0.40 mmol) and $Pd(hfacac)_2$ (5.0 mg, 0.010 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block for 16 hours. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added acetonitrile (2.0 mL), P(*o*-tol)$_3$ (6.0 mg, 0.020 mmol), 4-bromonitrobenzene (81 mg, 0.40 mmol) and triethylamine (60 µL, 0.40 mmol) and the vial was sealed under ambient atmosphere. The mixture was then heated at 80 °C for 16 hours. The reaction mixture was cooled to room temperature and quenched with H_2O (10 mL) then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $NaSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. This oil was then purified by flash chromatography on silica gel (toluene/EtOAc; 98:2) to give the title compound **2.26** as a colourless oil (32 mg, 40% from **2.20** along with minor isomers **2.27** and **2.28**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (2H, dt, *J* = 9.2, 2.0 Hz, Ar-H), 7.87 (1H, dt, *J* = 7.6, 0.8 Hz, Ar-H), 7.68 (1H, td, *J* = 7.6, 1.2 Hz, Ar-H), 7.51 (1H, td, *J* = 7.6, 0.8 Hz, Ar-H), 7.40 (1H, dt, *J* = 7.6, 0.8 Hz, Ar-H), 7.35 (2H, dt, 8.8, 2.0 Hz, Ar-H), 6.30 (1H, d, *J* = 16.0 Hz, HC=C*H*), 6.23 (1H, dt, *J* = 16.0, 6.0 Hz, *H*C=CH), 2.33–2.20 (2H, m, C=CHCH*H*CH*H*), 2.11–1.94 (2H, m, C=CHC*H*HC*H*H), 1.69 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (C), 153.4 (C), 146.7 (C), 143.9 (C), 134.4 (CH), 134.3 (CH), 129.3 (CH), 128.9 (CH), 126.5 (CH), 126.2 (C), 126.0 (CH), 124.0 (CH), 121.0 (CH), 87.2 (C), 39.0 (CH_2), 27.6 (CH_2), 26.5 (CH_3); IR (thin film) 2930, 1755, 1512, 1341, 1031; HRMS (EI) exact mass calculated for $C_{19}H_{17}NO_4$ $[M]^+$ *m/z* 323.1158, found *m/z* 323.1142.

(*E*)-3-(4-(3-Fluoro-4-(hydroxymethyl)phenyl)but-3-en-1-yl)-3-methylisobenzofuran-1(*3H*)-one

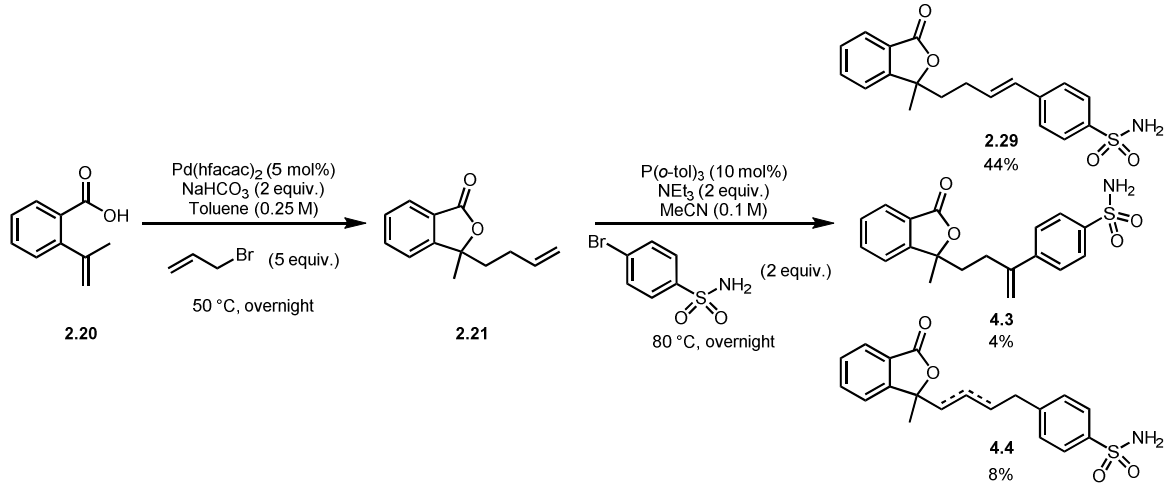


A 4 mL screw-top glass vial was charged with 2-(prop-1-en-2-yl)benzoic acid **2.20** (32 mg, 0.20 mmol), toluene (0.80 mL), allyl bromide (90 µL, 1.0 mmol), $NaHCO_3$ (30 mg, 0.40 mmol) and $Pd(hfacac)_2$ (5.0 mg, 0.010 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block for 16 hours. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added acetonitrile (2.0 mL), P(*o*-tol)$_3$ (6.0 mg, 0.020 mmol), 4-bromo-2-fluorobenzyl alcohol (82 mg, 0.40 mmol) and triethylamine (60 µL, 0.40 mmol) and the vial was sealed under ambient atmosphere. The mixture was then heated at 80 °C for 16 hours. The reaction mixture was cooled to room temperature and quenched with H_2O (10 mL) then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $NaSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. This oil was then purified by flash chromatography on silica gel (toluene/EtOAc; 4:1) to give the title compound **2.33** as a colourless oil (30 mg, 33% from **2.20** along with minor isomers **4.1** and **4.2**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, dt, *J* = 7.6, 1.0 Hz, Ar-H), 7.67 (1H, td, *J* = 7.6, 1.2 Hz, Ar-H), 7.51 (1H, td, *J* = 7.6, 0.8 Hz, Ar-H), 7.39 (1H, dt, *J* = 7.6, 1.0 Hz, Ar-H), 7.29 (1H, t, 7.8 Hz, Ar-H), 7.00 (1H, dd, *J* = 8.0, 1.6 Hz, Ar-H), 6.93 (1H, dd, *J* = 11.4, 1.6 Hz, Ar-H), 6.20 (1H, d, *J* = 16.0 Hz, *H*C=CH), 6.03 (1H, dt, *J* = 16.0, 6.6 Hz, HC=C*H*), 4.70 (2H, d, *J* = 6.0 Hz, C*H*$_2$OH), 2.28–2.16 (2H, m, C=CHCH*H*CH*H*), 2.07–1.99 (1H, m, C=CHC*H*HCHH), 1.92–1.85 (1H, m, C=CHCHHC*H*H), 1.68, (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C), 160.9 (d, ^1J(C-F) = 245.7 Hz, C), 153.6 (C), 139.4 (C), 134.3 (CH), 130.5 (CH), 129.5 (d, ^3J(C-F) = 5.2 Hz, CH), 129.4 (d, ^4J(C-F) = 2.5 Hz, CH), 129.3 (CH), 126.5 (d, ^2J(C-F) = 15.3 Hz, C),

126.2 (C), 126.0 (CH), 122.1 (d, ^{4}J(C-F) = 3.0 Hz, CH), 121.0 (CH), 112.4 (d, ^{2}J(C-F) = 21.9 Hz, CH), 87.3 (C), 59.4 (d, ^{3}J(C-F) = 4.0 Hz, CH_2), 39.3 (CH_2), 27.3 (CH_2), 26.4 (CH_3); IR (thin film) 3410, 2925, 1740, 1287, 1034; HRMS (EI) exact mass calculated for $C_{20}H_{19}FO_3$ $[M]^+$ *m/z* 326.1318, found *m/z* 326.1333.

(*E*)-4-(4-(1-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)but-1-en-1-yl)benzenesulfonamide

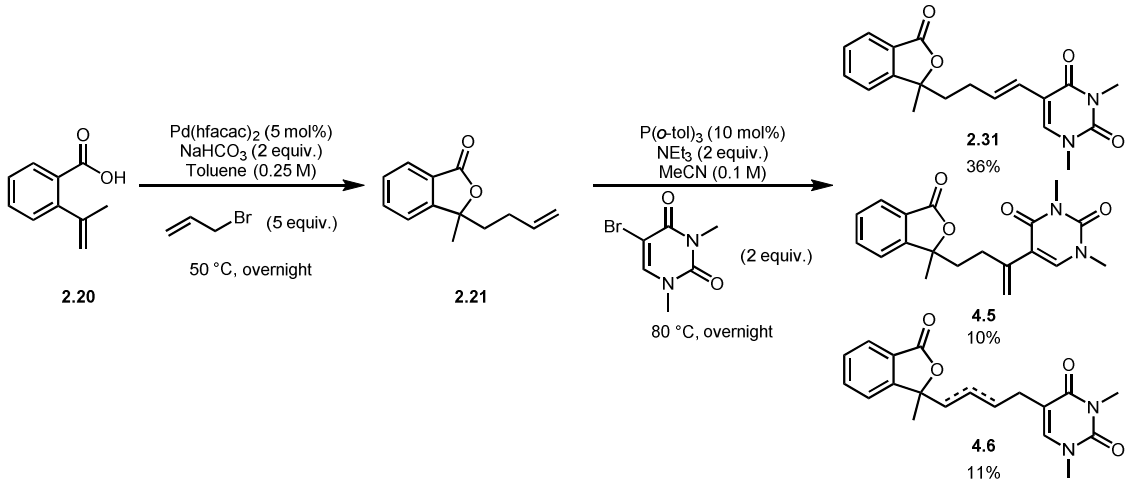


A 4 mL screw-top glass vial was charged with 2-(prop-1-en-2-yl)benzoic acid **2.20** (32 mg, 0.20 mmol), toluene (0.80 mL), allyl bromide (90 µL, 1.0 mmol), $NaHCO_3$ (30 mg, 0.40 mmol) and $Pd(hfacac)_2$ (5.0 mg, 0.010 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block for 16 hours. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added acetonitrile (2.0 mL), P(*o*-tol)$_3$ (6.0 mg, 0.020 mmol), 4-bromobenzenesulfonamide (94 mg, 0.40 mmol) and triethylamine (60 µL, 0.40 mmol) and the vial was sealed under ambient atmosphere. The mixture was then heated at 80 °C for 16 hours. The reaction mixture was cooled to room temperature and quenched with H_2O (10 mL) then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $NaSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. This oil was then purified by flash chromatography on silica gel (toluene/EtOAc; 3:2) to give the title compound **2.29** as a colourless oil (40 mg, 44% from **2.20** along with minor isomers **4.3** and **4.4**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, d, *J* = 7.6 Hz, Ar-H), 7.79 (2H, d, *J* = 8.4 Hz, Ar-H), 7.67 (1H, td, *J* = 7.6, 1.2 Hz, Ar-H), 7.51 (1H, td, *J* = 7.6, 1.2 Hz, Ar-H), 7.40 (1H, d, *J* = 7.6 Hz, Ar-H), 7.32 (2H, d, *J* = 8.8 Hz, Ar-H), 6.24 (1H, d, *J* = 16.0 Hz, *H*C=CH), 6.15 (1H, dt, *J* = 16.0, 6.4 Hz, HC=C*H*), 5.15 (2H, s, NH_2), 2.30–2.16 (2H, m, C=CHCH*H*CH*H*), 2.08–1.89 (2H, m, C=CHC*H*HC*H*H), 1.67 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C), 153.4 (C), 141.9 (C), 140.2 (C), 134.4 (CH), 132.9 (CH), 129.3 (CH), 129.2 (CH), 126.8 (2xCH), 126.5 (2xCH), 126.1 (C), 125.9 (CH), 121.0 (CH), 87.4 (C), 39.0 (CH_2), 27.5 (CH_2), 26.4 (CH_3); IR

(thin film) 3248, 2925, 1740, 137, 1159, 1036; HRMS (EI) exact mass calculated for $C_{19}H_{19}NO_4S$ $[M]^+$ *m/z* 357.1035, found *m/z* 357.1017.

(*E*)-1,3-Dimethyl-5-(4-(1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)but-1-en-1-yl)pyrimidine-2,4(*1H,3H*)-dione

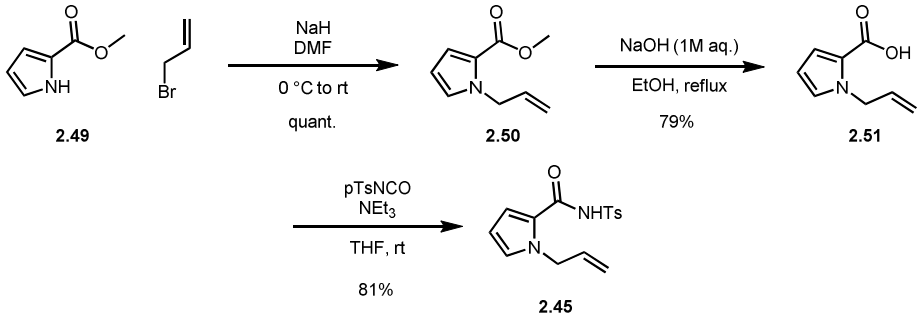


A 4 mL screw-top glass vial was charged with 2-(prop-1-en-2-yl)benzoic acid **2.20** (32 mg, 0.20 mmol), toluene (0.80 mL), allyl bromide (90 µL, 1.0 mmol), $NaHCO_3$ (30.0 mg, 0.400 mmol) and $Pd(hfacac)_2$ (5.0 mg, 0.010 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminium block for 16 hours. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added acetonitrile (2.0 mL), P(*o*-tol)$_3$ (6.0 mg, 0.020 mmol), 5-bromo-1,3-dimethyluracil (88 mg, 0.40 mmol) and triethylamine (60 µL, 0.40 mmol) and the vial was sealed under ambient atmosphere. The mixture was then heated at 80 °C for 16 hours. The reaction mixture was cooled to room temperature and quenched with H_2O (10 mL) then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $NaSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. This oil was then purified by flash chromatography on silica gel (toluene/EtOAc; 3:1) to give the title compound **2.31** as a colourless oil (39 mg, 36% from **2.20** along with minor isomers **4.5** and **4.6**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, dt, *J* = 7.6, 1.0 Hz, Ar-H), 7.67 (1H, td, *J* = 7.6, 1.0 Hz, Ar-H), 7.50 (1H, td, *J* = 7.6, 0.8 Hz, Ar-H), 7.37 (1H, dt, *J* = 7.6, 1.0 Hz, Ar-H), 7.10 (1H, s, C=C*H*), 6.21 (1H, dt, *J* = 15.6, 6.6 Hz, HC=C*H*), 5.96 (1H, d, *J* = 15.6 Hz, *H*C=CH), 3.40 (3H, s, NCH_3), 3.33 (3H, s, NCH_3), 2.24–2.15 (1H, m, C=CHC*H*HCH$_2$), 2.13–2.04 (1H, m, C=CHCH$_2$C*H*H), 2.03–1.95 (1H, m, C=CHCH$_2$CH*H*), 1.91–1.83 (1H, m, C=CHCH*H*CH$_2$), 1.65

(3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C), 162.5 (C), 153.52 (C), 153.50 (C), 138.7 (CH), 134.3 (CH), 130.4 (CH), 129.2 (CH), 126.2 (C), 125.8 (CH), 121.2 (CH), 121.0 (CH), 111.5 (C), 87.5 (C), 39.2 (CH_2), 37.2 (CH_3), 28.1 (CH_3), 27.8 (CH_2), 26.4 (CH_3); IR (thin film) 2928, 1755, 1697, 1647, 1034; HRMS (EI) exact mass calculated for $C_{19}H_{20}N_2O_4$ $[M]^+$ *m/z* 340.1423, found *m/z* 340.1419.

1-Allyl-*N*-tosyl-pyrrole-2-carboxamide



Following a modified literature procedure,[79] to a cooled (0 °C) suspension of NaH (60% dispersion in mineral oil, 0.72 g, 16 mmol) in DMF (15 mL) was added a solution of methyl 2-pyrrole-carboxylate **2.49** (1.5 g, 12 mmol) in DMF (3 mL). The resulting mixture was stirred for 20 minutes at 0 °C, then allyl bromide (1.8 mL, 21 mmol) was added dropwise. The mixture was allowed to warm to room temperature, and stirred for 2 h, then quenched by pouring onto ice (45 g). The mixture was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with H_2O (4 x 25 mL) and brine (2 x 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a brown oil (2.0 g, quant.) which was used without further purification.

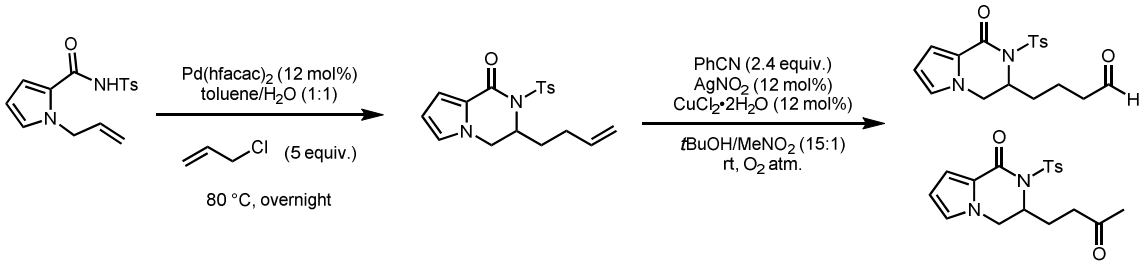
To a solution to methyl 1-allyl-pyrrole-2-carboxylate **2.50** (2.0 g, 12 mmol) in EtOH (28 mL) was added 1 M aq. NaOH (33 mL). The mixture was refluxed for 2h, then EtOH was removed *in vacuo*. The residue was washed with EtOAc (3 x 40 mL) then adjusted to pH 2 with 2 M aq. HCl and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a brown solid (1.4 g, 79%) which was used without further purification.

To a solution of 1-allyl-pyrrole-2-carboxylic acid **2.51** (0.25 g, 1.7 mmol) in THF (5 mL) was added *p*-tosyl isocyanate (0.51 mL, 3.3 mmol). The resulting solution was stirred for 10 minutes then triethylamine (0.25 mL, 1.8 mmol) was added dropwise. Gas evolution was observed on addition. After 1 h, the mixture was diluted with EtOAc (25 mL) and washed with 2 M aq. HCl (25 mL) and brine (25 mL). The organic extracts were dried (Na_2SO_4), filtered

and concentrated *in vacuo*. Purification by flash chromatography (dichloromethane) afforded the title compound **2.45** as a white solid (0.41 g, 81%). Analytical data were in accordance with literature values.[79]

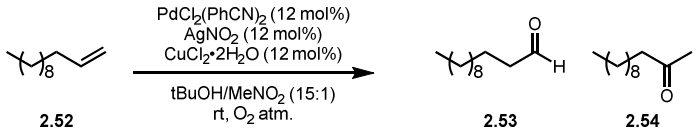
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, s, NH), 8.00 (2H, d, *J* = 8.3 Hz, Ar-H), 7.34 (2H, d, *J* = 8.1 Hz, Ar-H), 6.88 (1H, t, *J* = 2.1 Hz, Ar-H), 6.72 (1H, dd, *J* = 4.1, 1.6 Hz, Ar-H), 6.16 (1H, dd, *J* = 4.1, 2.6 Hz, Ar-H), 5.90 (1H, ddt, *J* = 16.2, 10.8, 5.8 Hz, *CH*=CH_2), 5.09 (1H, dd, *J* = 10.2, 1.4 Hz, CH=*CHa*), 4.96 (1H, dd, *J* = 17.0, 1.6 Hz, CH=*CHb*), 4.85 (2H, d, *J* = 5.8 Hz, CH_2), 2.44 (3H, s, CH_3).

4-(1-Oxo-2-tosyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-3-yl)butanal



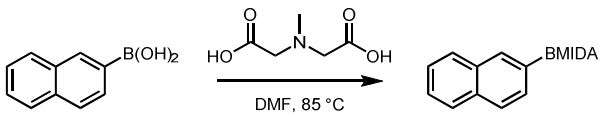
A 4 mL screw-top glass vial was charged with 1-allyl-*N*-tosyl-pyrrole-2-carboxamide (61 mg, 0.20 mmol), toluene (0.32 mL), H_2O (0.32 mL), allyl chloride (80 µL, 1.0 mmol) and $Pd(hfacac)_2$ (13 mg, 0.024 mmol) and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 80 °C by immersion of the entire vial into a preheated aluminium block overnight. The reaction mixture was cooled to room temperature and the volatile components were evaporated *in vacuo*. To the vial was added benzonitrile (50 µL, 0.48 mmol), $CuCl_2$•$2H_2O$ (4.1 mg, 0.024 mmol) and silver nitrite (3.7 mg, 0.024 mmol). The vial was sparged for 2 minutes with O_2. *t*BuOH (3.0 mL) and $MeNO_2$ (0.20 mL) were added and the vial sparged for 2 minutes with O_2. The reaction mixture was then stirred at room temperature under an O_2 atmosphere overnight. The reaction mixture was quenched with water (20 mL) then extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*.

Dodecanal



Following a literature procedure,[103] to a 4 mL vial was added dodecene **2.52** (50 µL, 0.20 mmol), $PdCl_2(PhCN)_2$ (9.2 mg, 0.024 mmol), $CuCl_2•2H_2O$ (4.1 mg, 0.024 mmol) and silver nitrite (3.7 mg, 0.024 mmol). The vial was sparged for 45 seconds with O_2. *t*BuOH (3.0 mL) and $MeNO_2$ (0.20 mL) were added and the vial sparged for a further 45 seconds with O_2. The reaction mixture was then stirred at room temperature under an O_2 atmosphere overnight. The reaction mixture was quenched with water (20 mL) then extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was then analysed by ^1H NMR. Analytical data were in accordance with literature values.[103]

2-Naphthyl boronic acid MIDA ester



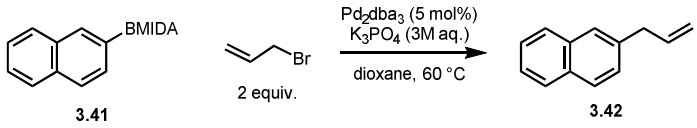
Following a literature procedure, naphthyl boronic acid (0.86 g, 5.0 mmol) and MIDA (0.74 g, 5.0 mmol) were stirred in DMF (15 mL) at 85 °C for 16 h then allowed to cool to room temperature. The reaction mixture was diluted with EtOAc (100 mL) and H_2O (100 mL) then separated. The organic phase was washed with H_2O (50 mL) and brine (3 x 50 mL) then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (diethyl ether:methanol, 98.5:1.5 then THF) gave a yellow oil. Addition of Et_2O formed a white precipitate which was collected by vacuum filtration affording the title compound as a white solid (1.3 g, 93%). Analytical data were in accordance with literature values.[104]

^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.99 (1H, s, Ar-H), 7.94–7.88 (3H, m, Ar-H), 7.57–7.50 (3H, m, Ar-H), 4.38 (2H, d, *J* = 17.2 Hz, 2 x NC*H*H), 4.17 (2H, d, *J* = 17.1 Hz, 2 x NCH*H*), 2.52 (3H, s, NCH_3).

General procedure for allylation of MIDA boronates

A 4 mL screw-top glass vial was charged with boronic acid MIDA ester (0.10 mmol), dioxane (1.25 mL), allyl bromide (0.020 mL, 0.20 mmol) and Pd_2dba_3 (5.2 mg, 0.0050 mmol). A 3 M aq. solution of K_3PO_4 (0.25 mL, 0.75 mmol) was added and the vial sealed under ambient atmosphere. The resulting mixture was heated to 60 °C by immersion of the entire vial into a preheated aluminium block until the substrate had been consumed, as judged by TLC analysis. The reaction mixture was cooled to room temperature, quenched with 1 M aq. NaOH (5 mL) then extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Addition of 1,3,5-trimethoxybenzene (17 mg, 0.10 mmol) allowed determination of the yield by ^{1}H NMR.

2-Allylnaphthalene

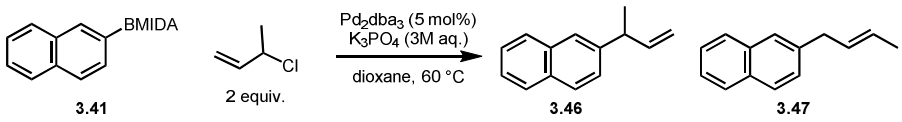


3.41 **3.42** 91%

The general procedure was employed for the allylation of 2-naphthylboronic acid MIDA ester (28 mg, 0.10 mmol). Yield determined by ^{1}H NMR: 91%. Analytical data were in accordance with literature values.[105]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.81 (3H, m, Ar-H), 7.67 (1H, s, Ar-H), 7.51–7.44 (2H, m, Ar-H), 7.37 (1H, dd, *J* = 8.4, 1.8 Hz, Ar-H), 6.10 (1H, ddt, *J* = 16.8, 10.1, 6.7 Hz, *CH*=CH_2), 5.19 (1H, dq, *J* = 10.5, 1.7 Hz, C=*CHa*), 5.17–5.15 (1H, m, C=*CHb*), 3.59 (2H, d, *J* = 6.6 Hz, CH_2).

2-(2-Buten-1-yl)-naphthalene/2-(1-methyl-2-propen-1-yl)-naphthalene

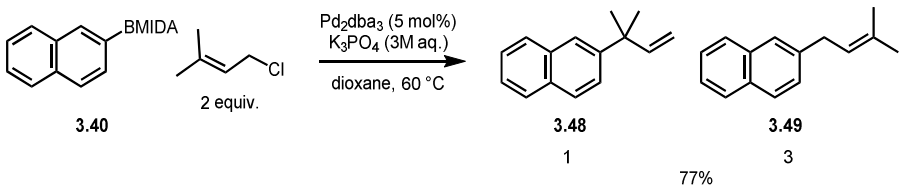


3.41 **3.46** **3.47** 1 1.6 68%

The general procedure was employed for the allylation of 2-naphthylboronic acid MIDA ester (32 mg, 0.10 mmol) using 3-chlorobut-1-ene (0.020 mL, 0.20 mmol). Purification by flash chromatography (petroleum ether) afforded the title compounds as a colourless oil (12.4 mg, 68%, 1.6:1). Analytical data were in accordance with literature values.[106]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.77 (3H, m, Ar-H), 7.66 (1H, s, Ar-H), 7.62 (1H, s, Ar-H), 7.48–7.40 (2H, m, Ar-H), 7.39–7.32 (1H, m, Ar-H), 6.10 (1H, ddd, *J* = 16.9, 10.3, 6.4 Hz, *CH*=CH_2), 5.72–5.54 (2H, m, *CH*=*CH*), 5.14–5.08 (2H, m, CH=*CH_2*), 3.67–3.57 (1H, m, *CH*CH_3), 3.49 (2H, dd, *J* = 6.5, 1.2 Hz, CH_2), 1.73 (3H, dq, *J* = 6.1, 1.4 Hz, CH*CH_3*), 1.47 (3H, d, *J* = 7.0 Hz, CH=CH*CH_3*).

2-(3-Methyl-2-buten-1-yl)-naphthalene/2-(2-methyl-3-buten-2-yl)-naphthalene



3.40 **3.48** **3.49**

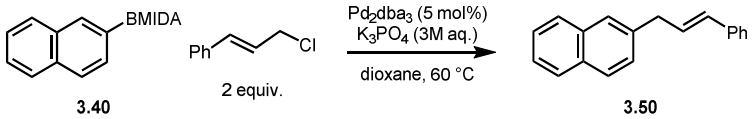
1 3

77%

The general procedure was employed for the allylation of 2-naphthylboronic acid MIDA ester (32 mg, 0.10 mmol) using prenyl chloride (0.020 mL, 0.20 mmol). Purification by flash chromatography (petroleum ether) afforded the title compounds as a colourless oil (15.1 mg, 77%, 3:1). Analytical data were in accordance with literature values.[107]

^{1}H NMR (400 MHz, $CDCl_3$) δ .82 (3H, m, Ar-H), 7.62 (1H, s, Ar-H), 7.52–7.40 (2H, m, Ar-H), 7.34 (1H, dd, *J* = 8.5, 1.8 Hz, Ar-H), 6.12 (1H, dd, *J* = 17.3, 10.7 Hz, *CH*=CH_2), 5.43 (1H, tseptet, *J* = 7.3, 1.4 Hz, *CH*=$C(CH_3)_2$), 5.15–5.10 (2H, m, CH=*CH_2*), 3.52 (2H, d, *J* = 7.3 Hz, CH_2), 1.79 (6H, dd, *J* = 4.4, 1.4 Hz, CH=*$C(CH_3)_2$*), 1.52 (6H, s, 2 x CH_3).

2-(3-Phenyl-2-propen-1-yl)-naphthalene



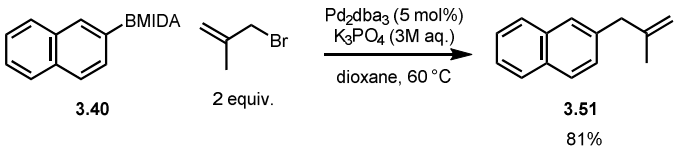
3.40 **3.50**

83%

The general procedure was employed for the allylation of 2-naphthylboronic acid MIDA ester (32 mg, 0.10 mmol) using cinnamyl chloride (0.030 mL, 0.20 mmol). Purification by flash chromatography (petroleum ether) afforded the title compound as a colourless oil (20.2 mg, 83%). Analytical data were in accordance with literature values.[108]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.80 (3H, m, Ar-H), 7.70 (1H, s, Ar-H), 7.50–7.43 (2H, m, Ar-H), 7.41–7.38 (3H, m, Ar-H), 7.34–7.29 (2H, m, Ar-H), 7.25–7.21 (1H, m, Ar-H), 6.53 (1H, d, *J* = 15.8 Hz, CH_2CH=*CH*), 6.45 (1H, dt, *J* = 15.8, 6.3 Hz, CH_2*CH*=CH), 3.73 (2H, d, *J* = 6.2 Hz, *CH_2*CH=CH).

2-(2-Methyl-2-propen-1-yl)-naphthalene

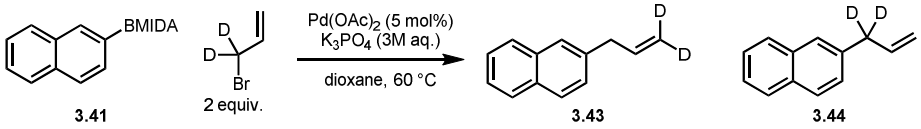


3.40 **3.51** 81%

The general procedure was employed for the allylation of 2-naphthylboronic acid MIDA ester (85 mg, 0.30 mmol) using 2-methylallyl bromide (0.030 mL, 0.30 mmol). Purification by flash chromatography (petroleum ether) afforded the title compound as a colourless oil (47.2 mg, 86%). Analytical data were in accordance with literature values.[106]

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.83–7.78 (3H, m, Ar-H), 7.65 (1H, s, Ar-H), 7.45 (2H, quintet d, *J* = 6.8, 1.5 Hz, Ar-H), 7.35 (1H, dd, *J* = 8.4, 1.7 Hz, Ar-H), 4.88–4.87 (1H, m, C=*CHa*), 4.81–4.80 (1H, m, C=*CHb*), 3.50 (2H, s, CH_2), 1.72 (3H, s, CH_3).

2-(2-Propen-1-yl-*3,3-d$_2$*)-naphthalene/2-(2-propen-1-yl-*1,1-d$_2$*)-naphthalene



3.41 **3.43** : **3.44**

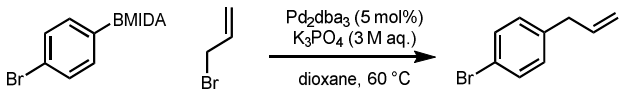
1 1

83%

The general procedure was employed for the allylation of 2-naphthylboronic acid MIDA ester (28 mg, 0.10 mmol) using dideuteroallyl bromide[58] (0.23 mL, 0.89 M in Et_2O, 0.20 mmol). Purification by flash chromatography (petroleum ether) afforded the title compounds as a colourless oil (14.1 mg, 83%, 1:1). Analytical data were in accordance with literature values.[109]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.78 (3H, m, Ar-H), 7.64 (1H, dd, *J* = 1.8, 0.8 Hz, Ar-H), 7.49–7.42 (2H, m, Ar-H), 7.35 (1H, dd, *J* = 8.4, 1.8 Hz, Ar-H), 6.09–6.02 (1H, m, C*H*=CH_2/C*H*=CD_2), 5.16 (0.5H, dd, *J* = 12.0, 2.0 Hz, CH=C*H*H), 5.13 (0.5H, dd, *J* = 5.2, 2.0 Hz, CH=CH*H*), 3.57 (1H, dd, *J* = 6.6, 0.7 Hz, C*H$_2$*CH=CD_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (2 x C), 137.4 (CH), 137.2 (CH), 133.8 (2 x C), 132.3 (2 x C), 128.0 (2 x CH), 127.8 (2 x CH), 127.6 (2 x CH), 127.5 (2 x CH), 126.8 (2 x CH), 126.1 (2 x CH), 125.4 (2 x CH), 116.22 (CH_2), 115.7 (p, ^1J(C-D) = 23.7 Hz, CD_2), 40.4 (CH_2), 39.8 (p, ^1J(C-D) = 19.6 Hz, CD_2); IR (thin film) 3053, 2923, 2113, 1689 cm^{-1}; HRMS (EI) exact mass calculated for $C_{13}H_{10}D_2$ $[M]^+$ *m/z* 170.1059, found *m/z* 170.1080.

4-Allylbromobenzene

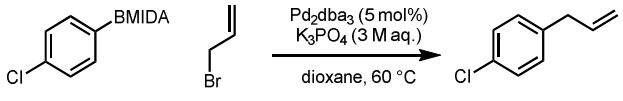


3.53
90%

The general procedure was employed for the allylation of 4-bromophenylboronic acid MIDA ester (31 mg, 0.10 mmol). Yield determined by ^{1}H NMR: 90%. Analytical data were in accordance with literature values.[110]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.39 (2H, m, Ar-H), 7.09–7.04 (2H, m, Ar-H), 5.93 (1H, ddt, *J* = 16.6, 10.4, 6.4 Hz, *CH*=CH_2), 5.11–5.03 (2H, m, CH=*CH*$_2$), 3.34 (2H, d, *J* = 6.6 Hz, CH_2).

4-Allylchlorobenzene

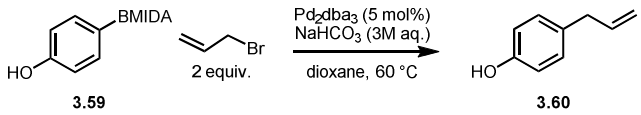


3.54
92%

The general procedure was employed for the allylation of 4-chlorophenylboronic acid MIDA ester (27 mg, 0.10 mmol). Yield determined by ^{1}H NMR: 92%. Analytical data were in accordance with literature values.[110]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (2H, m, Ar-H), 7.14–7.11 (2H, m, Ar-H), 5.94 (1H, ddt, *J* = 17.2, 10.4, 6.8 Hz, *CH*=CH_2), 5.11–5.10 (1H, m, CH=*CHa*), 5.09–5.05 (1H, m, CH=*CHb*), 3.36 (2H, d, *J* = 6.7 Hz, CH_2).

4-Allylphenol

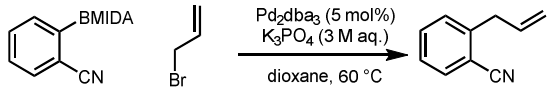


3.59 **3.60**

The general procedure was employed for the allylation of 4-hydroxyphenylboronic acid MIDA ester (31 mg, 0.10 mmol). Yield determined by ^{1}H NMR: 28%. Analytical data were in accordance with literature values.[111]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (2H, d, *J* = 8.4 Hz, Ar-H), 6.78 (2H, d, *J* = 8.5 Hz, Ar-H), 5.95 (1H, ddt, *J* = 16.7, 10.4, 6.7 Hz, *CH*=CH_2), 5.08–5.03 (2H, m, CH=*CH*$_2$), 4.86 (1H, s, OH), 3.32 (2H, d, *J* = 6.7 Hz, CH_2).

2-Allylcyanobenzene

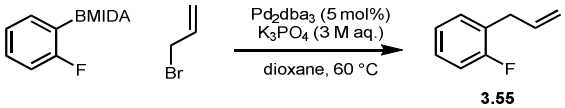


3.57
88%

The general procedure was employed for the allylation of 2-cyanophenylboronic acid MIDA ester (77 mg, 0.30 mmol). Yield determined by ^{1}H NMR: 88%. Analytical data were in accordance with literature values.[112]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, dd, *J* = 7.7, 1.1 Hz, Ar-H), 7.53 (1H, td, *J* = 3.9, 1.4 Hz, Ar-H), 7.36–7.28 (2H, m, Ar-H), 5.95 (1H, ddt, *J* = 16.9, 10.2, 6.6 Hz, *CH*=CH_2), 5.17–5.08 (2H, m, CH=*CH*$_2$), 3.61 (2H, d, *J* = 6.6 Hz, CH_2).

2-Allylfluorobenzene

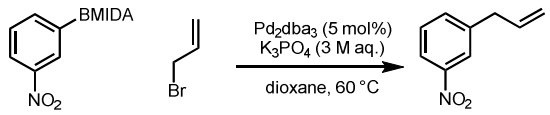


3.55
83%

The general procedure was employed for the allylation of 2-fluorophenylboronic acid MIDA ester (25 mg, 0.10 mmol). Yield determined by ^{1}H NMR: 83%. Analytical data were in accordance with literature values.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.16 (2H, m, Ar-H), 7.09–6.98 (2H, m, Ar-H), 6.01–5.91 (1H, m, *CH*=CH_2), 5.10–5.05 (2H, m, CH=*CH*$_2$), 3.41 (2H, dd, *J* = 6.6, 1.5 Hz, CH_2).

3-Allylnitrobenzene

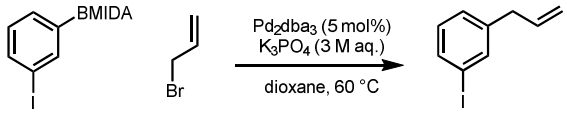


3.56
92%

The general procedure was employed for the allylation of 3-nitrophenylboronic acid MIDA ester (83 mg, 0.30 mmol). Yield determined by ^{1}H NMR: 92%. Analytical data were in accordance with literature values.[113]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.06 (2H, m, Ar-H), 7.54–7.51 (1H, m, Ar-H), 7.46 (1H, ddd, *J* = 7.6, 7.0, 1.6 Hz, Ar-H), 5.96 (1H, ddt, *J* = 16.8, 10.1, 6.7 Hz, *CH*=CH_2), 5.17 (1H, dq, *J* = 10.3, 1.4 Hz, CH=*CHa*), 5.13 (1H, dq, *J* = 17.3, 1.6 Hz, CH=*CHb*), 3.50 (2H, d, *J* = 6.6 Hz, CH_2).

3-Allyliodobenzene

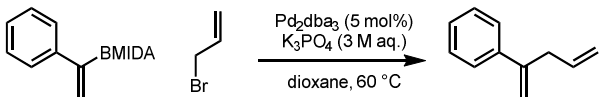


3.52
91%

The general procedure was employed for the allylation of 3-iodophenylboronic acid MIDA ester (36 mg, 0.10 mmol). Yield determined by ^{1}H NMR: 91%. Analytical data were in accordance with literature values.[114]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.53 (2H, m, Ar-H), 7.17–7.14 (1H, m, Ar-H), 7.06–7.00 (1H, m, Ar-H), 5.92 (1H, ddt, *J* = 18.0, 10.7, 6.7 Hz, *CH*=CH_2), 5.13–5.06 (2H, m, CH=*CH*$_2$), 3.33 (2H, d, *J* = 6.6 Hz, CH_2).

2-Phenyl-1,4-pentadiene

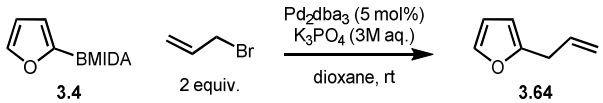


3.58
89%

The general procedure was employed for the allylation of 1-phenylvinylboronic acid MIDA ester (78 mg, 0.30 mmol). Yield determined by ^{1}H NMR: 89%. Analytical data were in accordance with literature values.[115]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.42 (2H, m, Ar-H), 7.36–7.30 (2H, m, Ar-H), 7.30–7.25 (1H, m, Ar-H), 5.91 (1H, ddt, *J* = 17.1, 10.1, 6.6 Hz, *CH*=CH_2), 5.42–5.41 (1H, m, C=*CHa*), 5.16–5.04 (3H, m, C=*CHb*, CH=*CH*$_2$), 3.27–3.25 (2H, m, CH_2).

2-Allylfuran

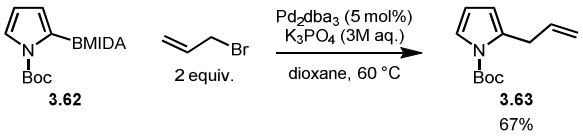


3.4
2 equiv.
3.64
45%

The general procedure was employed for the allylation of 2-furanylboronic acid MIDA ester (22 mg, 0.10 mmol). Yield determined by ^{1}H NMR: 45%. Analytical data were in accordance with literature values.[116]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (1H, d, *J* = 2.4 Hz, Ar-H), 7.32 (1H, d, *J* = 2.8 Hz, Ar-H), 6.29 (1H, d, *J* = 2.8 Hz, Ar-H), 6.02 (1H, d, *J* = 3.1 Hz, Ar-H), 5.97–5.88 (1H, m, *CH*=CH_2), 5.16–5.10 (2H, m, CH=*CH*$_2$), 3.39 (2H, d, *J* = 6.5 Hz, CH_2).

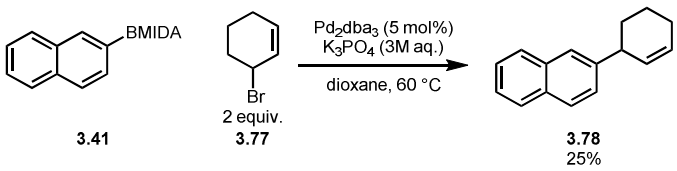
2-Allyl-*N*-Boc pyrrole



The general procedure was employed for the allylation of *N*-Boc-pyrrole-2-boronic acid MIDA ester (32 mg, 0.10 mmol). Yield determined by ^{1}H NMR: 67%. Analytical data were in accordance with literature values.[117]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, dd, *J* = 1.8, 1.5 Hz, Ar-H), 6.09 (1H, t, *J* = 3.3 Hz, Ar-H), 6.02 (1H, ddt, *J* = 16.7, 10.2, 6.4 Hz, *CH*=CH_2), 5.98–5.96 (1H, m, Ar-H), 5.10–5.02 (2H, m, CH=*CH_2*), 3.61 (2H, dd, *J* = 6.3, 1.2 Hz, CH_2), 1.58 (9H, s, $C(CH_3)_3$).

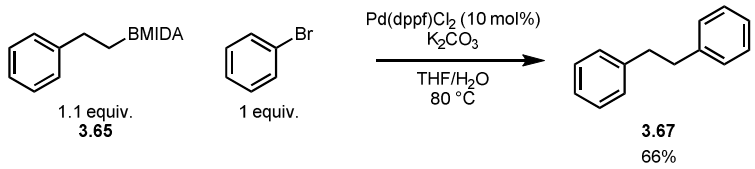
2-(2-Cyclohexen-1-yl)-naphthalene



The general procedure was employed for the allylation of 2-naphthylboronic acid MIDA ester (28 mg, 0.10 mmol) using 3-bromocyclohex-1-ene (0.020 mL, 0.20 mmol). Purification by flash chromatography (petroleum ether) afforded the title compound as a colourless oil (5.3 mg, 25%). Analytical data were in accordance with literature values.[107]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.78 (3H, m, Ar-H), 7.65 (1H, s, Ar-H), 7.47–7.42 (2H, m, Ar-H), 7.38 (1H, dd, *J* = 8.4, 1.8 Hz, Ar-H), 5.97 (1H, dtd, *J* = 9.9, 3.6, 2.3 Hz, *CH*=CH), 5.84–5.79 (1H, m, CH=*CH*), 3.61–3.55 (1H, m, Ar*CH*), 2.17–2.06 (3H, m, CH_2), 1.82–1.75 (1H, m, CH_2), 1.71–1.64 (2H, m, CH_2).

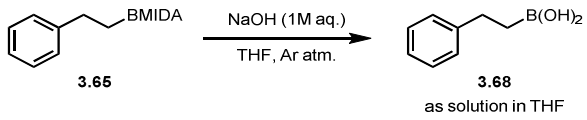
1,2-Diphenylethane



Following a literature procedure,[89] to a 4 mL vial was added phenethylboronic acid MIDA ester (29 mg, 0.11 mmol) and $Pd(dppf)Cl_2$ (8.2 mg, 0.010 mmol). The vial was evacuated and backfilled with argon. THF (1.0 mL) and bromobenzene (11 µL, 0.10 mmol) were added, followed by degassed, distilled H_2O (0.20 mL). The mixture was stirred at room temperature for 5 minutes followed by the addition of K_2CO_3 (83 mg, 0.60 mmol). The vial was sealed with a screw-cap and heated at 80 °C for 72 h by submerging the vial in a pre-heated aluminium block. The reaction mixture was then cooled to room temperature and H_2O (2 mL) added. The aqueous mixture was extracted with Et_2O (3 x 5 mL), then the combined organic extracts dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether) afforded the title compound as a colourless oil (12 mg, 66%). Analytical data were in accordance with literature values.[89]

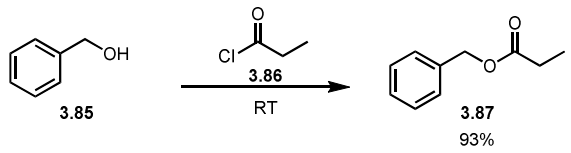
^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (4H, m, Ar-H), 7.23–7.19 (6H, m, Ar-H), 2.94 (4H, s, CH_2).

Phenethylboronic acid



Following a literature procedure,[83] to a solution of phenethylboronic acid MIDA ester (0.13 g, 0.50 mmol) in THF (2.5 mL) was added 1 M aq. NaOH (2.5 mL). The reaction was stirred at room temperature for 20 minutes. After removal of THF *in vacuo*, sat. aq. NH_4Cl (10 mL) was added with vigorous stirring. The mixture was extracted with Et_2O (3 x 5 mL), then the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to ~1 mL. This solution was then transferred to a 7 mL vial, rinsing with THF (1 mL). The vial was sealed with a septum cap and the solution concentrated to ~1 mL under a stream of argon. THF (2 mL) was added and the solution concentrated to ~1.25 mL under a stream of argon. This solution was used directly in the next reaction. Analytical data were in accordance with literature values.[118]

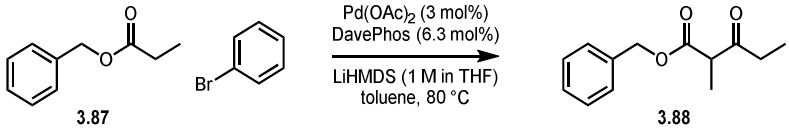
Benzyl propanoate



Following a literature procedure,[119] to a dry flask was added benzyl alcohol (1.6 mL, 15 mmol) and propionyl chloride (1.6 mL, 18 mmol). The neat mixture was stirred at room temperature until the alcohol was consumed, as determined by TLC analysis. The reaction mixture was then dissolved in Et_2O (60 mL), then washed with sat. aq. $NaHCO_3$ (60 mL) and brine (60 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:ethyl acetate, 95:5) afforded the title compound as a colourless oil (2.3 g, 93%). Analytical data were in accordance with literature values.[120]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (5H, m, Ar-H), 5.12 (2H, s, OCH_2), 2.39 (2H, q, J = 7.6 Hz, CH_2CH_3), 1.17 (3H, t, J = 7.6 Hz, CH_2CH_3).

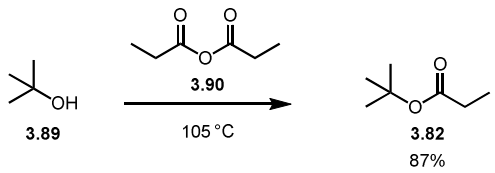
Benzyl 2-methyl-3-oxopentanoate



Following a literature procedure,[90] to an oven dried 7 mL vial fitted with a stir bar was added palladium acetate (5.4 mg, 0.024 mmol) and DavePhos (20 mg, 0.050 mmol). LiHMDS (1 M in THF, 2.0 mL, 2.0 mmol) and toluene (3.2 mL) were added and the mixture was stirred for 10 minutes at room temperature. The mixture was cooled to –10 °C and benzyl propanoate (0.29 mL, 1.8 mmol) was added dropwise. The mixture was stirred for a further 10 minutes at –10 °C then benzyl bromide (90 µL, 0.80 mmol) was added. The reaction mixture was allowed to warm to room temperature, then was stirred at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:ethyl acetate, 99:1) afforded an analytical sample of the title compound as a colourless oil. Analytical data were in accordance with literature values.[121]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (5H, m, Ar-H), 5.17 (2H, s, CH_2O), 3.57 (1H, q, J = 7.1 Hz, $CHCH_3$), 2.62–2.42 (2H, m, CH_2), 1.36 (3H, d, J = 7.2 Hz, $CHCH_3$), 1.26 (3H, t, J = 7.1 Hz, CH_3).

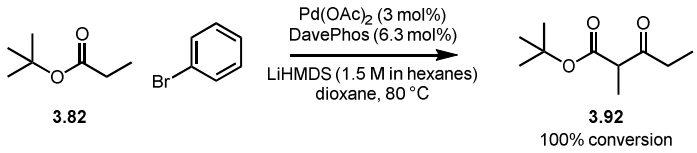
tert-Butyl propanoate



Following a modified literature procedure,[122] to a flask fitted with a stir bar and condenser was added *tert*-butyl alcohol (4.3 mL, 45 mmol) and propionic anhydride (17 mL, 140 mmol). The reaction mixture was stirred at 105 °C overnight. After cooling to room temperature, the mixture was quenched with 1 M aq. NaOH, taking care to avoid a large exotherm by addition in small portions. The mixture was then separated, affording the title compound as a colourless oil (5.9 mL, 87%). Analytical data were in accordance with literature values.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (2H, q, J = 7.5 Hz, CH_2), 1.44 (9H, s, $C(CH_3)_3$), 1.09, (3H, t, J = 7.6 Hz, CH_3).

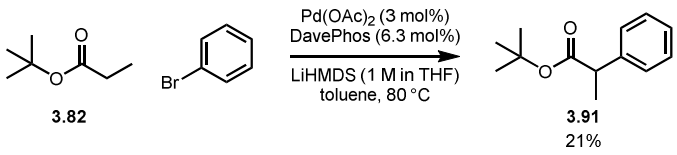
tert-Butyl 2-methyl-3-oxopentanoate



Following a literature procedure,[90] to an oven dried flask fitted with a stir bar and condenser was added palladium acetate (5.4 mg, 0.024 mmol) and DavePhos (20 mg, 0.050 mmol). LiHMDS (1.5 M in hexanes, 1.3 mL, 2.0 mmol) and 1,4-dioxane (3.2 mL) were added and the was mixture stirred for 10 minutes at room temperature, then *tert*-butyl propanoate (0.16 mL, 1.8 mmol) was added dropwise. The mixture was stirred for a further 10 minutes then bromobenzene (90 µL, 0.80 mmol) was added. The reaction mixture was stirred at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:ethyl acetate, 99:1) afforded an analytical sample of the title compound as a colourless oil. Analytical data were in accordance with literature values.[123]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (1H, q, J = 7.1 Hz, *CH*CH_3), 2.66–2.45 (2H, m, CH_2), 1.46 (9H, s, $C(CH_3)_3$), 1.29 (3H, d, J = 7.1 Hz, CH*CH*$_3$), 1.08 (3H, t, J = 7.3 Hz, CH_3).

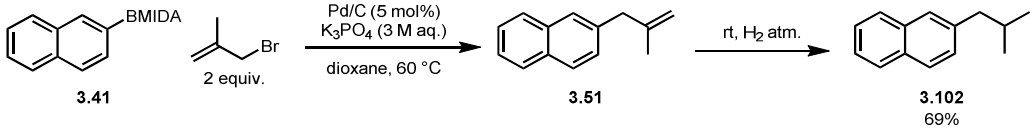
tert-Butyl 2-phenylpropionate



Following a literature procedure,[90] to an oven dried flask fitted with a stir bar and condenser was added palladium acetate (5.4 mg, 0.024 mmol) and DavePhos (20 mg, 0.050 mmol). LiHMDS (1 M in THF, 2.0 mL, 2.0 mmol) and toluene (3.2 mL) were added and the mixture was stirred for 10 minutes at room temperature. The mixture was cooled to –10 °C and benzyl propanoate (0.29 mL, 1.8 mmol) was added dropwise. The mixture was stirred for a further 10 minutes at –10 °C then bromobenzene (90 µL, 0.80 mmol) was added. The reaction mixture was allowed to warm to room temperature, then stirred at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (petroleum ether:ethyl acetate, 99:1) afforded the title compound as a colourless oil (83 mg, 21%). Analytical data were in accordance with literature values.[124]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.18 (5H, m, Ar-H), 3.57 (1H, q, *J* = 7.2 Hz, *CH*CH_3), 1.41 (3H, d, *J* = 7.2 Hz, CH*CH*$_3$), 1.36 (9H, s, $C(CH_3)_3$).

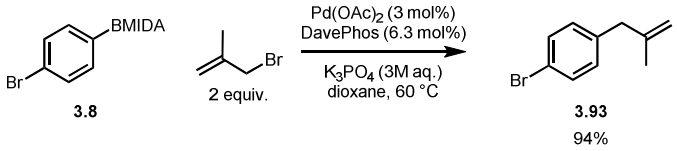
2-(2-Methylpropyl)naphthalene



A 4 mL screw-top glass vial was charged with naphthylboronic acid MIDA ester (28 mg, 0.10 mmol), dioxane (1.25 mL), allyl bromide (0.020 mL, 0.20 mmol) and (10%) Pd/C (5.3 mg, 0.0050 mmol). A 3 M aq. solution of K_3PO_4 (0.25 mL, 0.75 mmol) was added and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 60 °C by immersion of the entire vial into a preheated aluminium block for 16 h. After cooling to room temperature, the vial was evacuated and backfilled with argon, then evacuated and backfilled with H_2. The reaction mixture was stirred at room temperature under H_2 atm. for 16 h. After removal of H_2, the reaction mixture was filtered through celite, then diluted with H_2O (10 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Yield determined by ^{1}H NMR: 69%. Analytical data were in accordance with literature values.[125]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.75 (3H, m, Ar-H), 7.58 (1H, s, Ar-H), 7.46–7.39 (2H, m, Ar-H), 7.31 (1H, dd, *J* = 8.4, 1.7 Hz, Ar-H), 2.64 (2H, d, *J* = 7.2 Hz, CH_2), 1.98 (1H, septet, *J* = 6.8 Hz, C*H*(CH_3)$_2$), 0.94 (6H, d, *J* = 6.6 Hz, 2xCH_3).

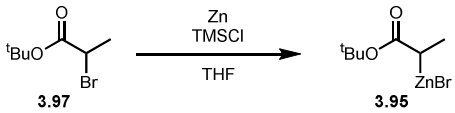
1-Bromo-4-(2-methyl-2-propen-1-yl)-benzene



The general procedure was employed for the allylation of 4-bromophenylboronic acid MIDA ester (0.94 g, 3.0 mmol) using 2-methylallyl bromide (0.60 mL, 6.0 mmol). Purification by flash chromatography (petroleum ether) afforded the title compound as a colourless oil (594 mg, 94%). Analytical data were in accordance with literature values.[126]

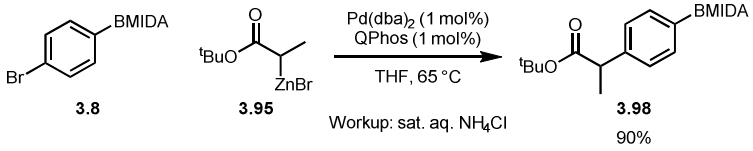
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.40 (2H, m, Ar-H), 7.08–7.05 (2H, m, Ar-H), 4.82 (1H, t, *J* = 1.7 Hz, C=*CHa*), 4.72 (1H, dd, *J* = 2.3, 1.2 Hz, C=*CHb*), 3.27 (2H, s, CH_2), 1.66 (3H, s, CH_3).

tert-Butyl 2-bromozincpropionate



Following a literature procedure,[91] to a dry 2-necked flask with a condenser was added zinc powder (1.2 g, 19 mmol), THF (7.5 mL) and trimethylsilyl chloride (0.080 mL, 0.63 mmol). The mixture was stirred for 15 minutes. A solution of *tert*-butyl 2-bromopropionate (2.10 mL, 12.5 mmol) in THF (17.5 mL) was added over 2–3 minutes with an exotherm observed. Once the mixture returned to room temperature, stirring was discontinued. The solution was used directly in the next step (assumed concentration: 0.23M).

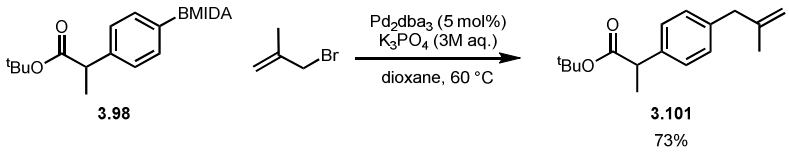
tert-Butyl 2-(4-phenyl boronic acid MIDA ester)propionate



Following a modified literature procedure,[91] to a dry flask charged with a stir bar was added 4-bromophenylboronic acid MIDA ester (0.31 g, 1.0 mmol), $Pd(dba)_2$ (5.8 mg, 0.010 mml), QPhos (7.1 mg, 0.010 mmol) and THF (3.0 mL). The mixture was stirred briefly, then a freshly prepared solution of *tert*-butyl 2-bromozincpropionate in THF (8.7 mL, 2.0 mmol) was added. The reaction mixture was stirred at 65 °C for 1.5 h. After cooling to room temperature, the reaction was quenched with sat. aq. NH_4Cl (10 mL), followed by addition of brine (10 mL). The phases were separated and the organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was adsorbed onto silica gel then purification by flash chromatography (diethyl ether:methanol, 98.5:1.5 then THF) afforded the title compound as a light pink solid (0.32 g, 90%).

^{1}H NMR (400 MHz, d_6-DMSO) δ 7.39 (2H, d, *J* = 8.1 Hz, Ar-H), 7.25 (2H, d, *J* = 8.1 Hz, Ar-H), 4.32 (2H, d, *J* = 17.2 Hz, 2 x NC*H*H), 4.11 (2H, d, *J* = 17.2 Hz, 2 x NCH*H*), 3.64 (1H, q, *J* = 7.1 Hz, C*H*CH_3), 2.49 (3H, s, NCH_3), 1.34 (9H, s, 3 x CCH_3); ^{13}C NMR (100 MHz, d_6-DMSO) δ 174.3 (C), 173.0 (C), 169.3 (C), 141.6 (C), 132.5 (CH), 126.5 (CH), 79.9 (C), 61.8 (CH_2), 47.5 (CH_3), 45.5 (CH), 27.6 (CH_3), 18.5 (CH_3); IR (solid) 2978, 1724, 1713, 1367, 1150 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{18}H_{24}BNNaO_6$ $[M+Na]^+$ *m/z* 384.1589, found *m/z* 384.1575.

tert-Butyl 2-(4-methallylphenyl)propionate

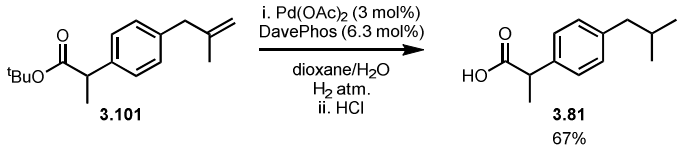


The general procedure was employed for the allylation of *tert*-butyl MIDA (36 mg, 0.10 mmol) using 2-methylallyl bromide (0.020 mL, 0.20 mmol). Yield was determined by ^{1}H NMR: 73%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (2H, d, *J* = 8.1 Hz, Ar-H), 7.13 (2H, d, *J* = 8.1 Hz, Ar-H), 4.81–4.79 (1H, m, C=C*H*H), 4.73–4.71 (1H, m, C=CH*H*), 3.59 (1H, q, *J* = 7.2 Hz, C*H*CH_3), 3.29 (2H, s, Ar-CH_2C), 1.67 (3H, s, CCH_3), 1.44 (3H, d, *J* = 7.2 Hz, CH*CH*$_3$), 1.39 (9H, s, 3 x CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9 (C), 145.2 (C), 139.0 (C), 138.3 (C), 128.9 (CH),

127.3 (CH), 111.6 (CH_2), 80.3 (C), 46.0 (CH), 44.1 (CH_2), 27.8 (CH_3), 21.9 (CH_3), 18.3 (CH_3); IR (thin film) 2978, 2934, 1728, 1452, 1148, 739 cm^{-1}; HRMS (ESI) exact mass calculated for $C_{17}H_{24}NaO_2$ $[M+Na]^+$ *m/z* 283.1669, found *m/z* 283.1666.

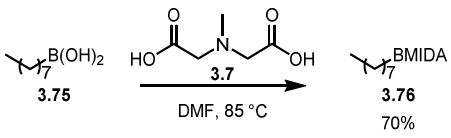
Ibuprofen



A stirred solution of ester (18 mg, 0.069 mmol), palladium acetate (1.1 mg, 0.0050 mmol) and DavePhos (3.9 mg, 0.010 mmol) in dioxane/H_2O (1.25 mL/0.25 mL) under an argon atmosphere was evacuated and backfilled with H_2. The reaction mixture was stirred at room temperature under a H_2 atmosphere for 16 h. The flask was evacuated and backfilled with argon, then conc. HCl (0.60 mL) was added to give an overall concentration of 4 M HCl. The reaction mixture was stirred at room temperature for 16 h then quenched with 2 M aq. NaOH. The mixture was extracted with Et_2O (2 x 10 mL) then the aqueous phase adjusted to pH 1 with 2 M aq. HCl. The aqueous phase was extracted with Et_2O (2 x 10 mL) then the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* affording the title compound as a white solid (9.5 mg, 67%). Analytical data were in accordance with literature values.[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (1H, s, COOH), 7.22 (2H, d, *J* = 7.9 Hz, Ar-H), 7.10 (2H, d, *J* = 7.8 Hz, Ar-H), 3.71 (1H, q, *J* = 7.1 Hz, *CH*CH_3), 2.44 (2H, d, *J* = 7.2 Hz, CH_2), 1.84 (1H, septet, *J* = 6.6 Hz, *CH*$(CH_3)_2$), 1.50 (3H, d, *J* = 7.1 Hz, CH*CH*$_3$), 0.90 (6H, d, *J* = 6.6 Hz, CH*(CH*$_3$*)*$_2$).

Octyl boronic acid MIDA ester



Following a literature procedure, octyl boronic acid (0.32 g, 2.0 mmol) and MIDA (0.29 g, 2.0 mmol) were stirred in DMF (6.0 mL) at 85 °C for 16 h then allowed to cool to room temperature. The reaction mixture was diluted with EtOAc (50 mL) and H_2O (50 mL) then separated. The organic phase was washed with H_2O (2 x 25 mL) and brine (3 x 25 mL) then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Et_2O (50 mL) was added to the residue

and the resulting suspension was stirred at room temperature for 1 h. The precipitate was then collected by vacuum filtration affording the title compound as a white solid (0.38 g, 70%). Analytical data were in accordance with literature values.[83]

^{1}H NMR (400 MHz, d_6-DMSO) δ 4.15 (2H, d, *J* = 17.0 Hz, 2 x NC*H*H), 3.96 (2H, d, *J* = 17.0 Hz, 2 x NCH*H*), 2.82 (3H, s, NCH_3), 1.32–1.24 (12H, m, CH_2), 0.86 (3H, t, *J* = 6.8 Hz, CH_2CH_3), 0.51–0.48 (2H, m, CH_2CH_3)

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