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By

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Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in September 2011, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification. I confirm that the work submitted is my own, except work which has formed part of jointly-authored publications. The contributions of myself and other authors to this work have been specifically indicated where relevant. I confirm that appropriate credit has been given with the thesis where references has been made to the work of others,

The following chapters contain results reported in the follow publications:

Chapter 1:

1) Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 8309-8313.
2) Hepburn H. B.; Chotsaeng, N.; Luo, Y.; Lam, H. W. *Synthesis*, **2013**, *45*, 2649-2661.

Chapter 2

1) Hepburn, H. B.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 11605-11610.

Acknowledgements

I would like to dedicate this piece of work to my late grandfather, Dr Randolph Webster PhD (1924-2012). His own scientific undertakings and knowledge directly inspired me to undertake my own scientific research and for that, I am eternally grateful.

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Contents

Chapter 2: The Isomerisation of Allylrhodium Intermediates in the Nucleophilic Allylation of Cyclic Imines

Chapter 3: Experimental

List of Abbreviations

Ac	acetyl
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*t*-butyloxycarbonyl
br	broad
calcd	calculated
cat.	catalyst
cod	1,5-cyclooctadiene
d	doublet
d.r.	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalent
g	gram
h	hour
m	multiplet
mg	milligram
min	minute
mL	millilitre
m.p.	melting point
MHz	megahertz
pin	pinacol
q	quartet
rac	racemic
rt	room temperature
s	singlet
t	triplet

Thoroughout this work, “wedges” have been used to indicate stereochemistry at quaternary centres and “blocks” have been used to indicate stereochemistry at tertiary centres

Lay Summary

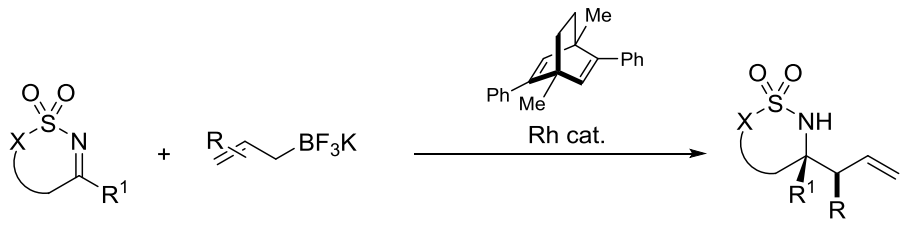
A catalyst is defined as a substance that speeds up a chemical reaction while undergoing no permanent change itself. Such substances are incredibly important in both industrial and academic situations and allow chemical reactions to occur quicker and at milder conditions. These variables are important for minimising both ecological and financial concerns in modern day industrial chemistry

Catalysts come in many forms and the use of a metal catalyst is common in a range of chemical processes. This report describes the use of a catalyst derived from the metal rhodium to allow a new chemical reaction to occur.

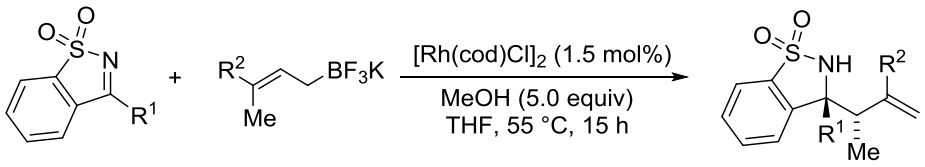
This reaction resulted in the formation of a new carbon-carbon bond and created a new substance in excellent yield and exhibited outstanding control over a range of other chemical parameters. This new reaction was applied to a range of substrates and the resultant products were also converted into chemical substances that feature characteristics found in pharmaceutical products.

Abstract

A highly enantioselective and diastereoselective rhodium-catalysed addition of potassium allyltrifluoroborates to cyclic imines is described within. By utilising rhodium-chiral diene complexes, a wide range of cyclic imines were successfully allylated in high yields and enantioselectivities. Using a variety of more highly substituted allyl reagents, additional stereocentres and further molecular complexity was achieved with good yields, enantioselectivities and diastereoselectivities. Investigations involving isomeric allyl species and deuterated allyl species provided results that gave mechanistic insight, leading to the proposal of a plausible mechanistic pathway and suggested the formation of interconverting allylrhodium intermediates.



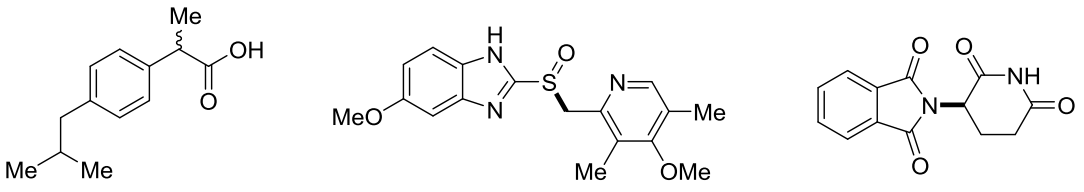
Furthermore, during these investigations, a highly interesting isomerisation of the allylrhodium intermediate was discovered. Such isomerisation led to the *in situ* formation of the more complex allylrhodium intermediates which led to complex products upon allylation with cyclic imines that would be difficult to synthesis *via* other methods. This isomerisation was found to occur for a range of cyclic imines and disubstituted allyltrifluoroborates, proceeding in good yields and diastereomeric ratios. Deuterium studies indicate it is probable that this isomerisation proceeds *via* a 1,4 rhodium migration and a plausible mechanism is proposed explaining both the connectivity of the products and the relative stereochemistry.



Chapter 1: The Rhodium-Catalysed Enantioselective Nucleophilic Allylation of Cyclic Imines

1.0 The Importance of Chirality

Chirality, the symmetry property of a molecule that makes it impossible for it to be superimposed upon its mirror image, is a fundamental principle that underpins many facets of chemistry. With the exception of glycine, proteinogenic amino acids are homochiral, therefore, chirality is often of great importance in biological systems. Protein-protein and protein-small molecule interactions all occur within a chiral environment thus; it is of no surprise that drug molecules that target these proteins often feature chirality in order to improve parameters such as binding strength and selectivity. In 2013, eight of the ten top selling small molecule drugs contained a stereocentre, underlining the importance of chirality.[1] In some drugs, such as ibuprofen (**1**), one enantiomer is found to be the biologically active species. However, enzymes within the body convert the non-active isomer into the active isomer *in vivo* allowing the racemic drug to be administered.[2] However, although the inactive (*R*)-isomer of the proton pump inhibitor omeprazole (**2**) is usually converted to the active (*S*)-isomer *in vivo*, it was discovered that a small demographic of people metabolised the (*R*)-isomer slowly leading to poor and unreliable dose efficiency. Thus, it was prudent to administer enantiopure omeprazole (**2**), called esomeprazole (**3**), to provide higher and safer dose efficiencies (Figure 1.1).[3]



Ibuprofen (**1**) racemic = Omeprazole (**2**) (*S*) = Esomeprazole (**3**) Thalidomide (**4**)

Figure 1.1: Drug molecules featuring stereocentres

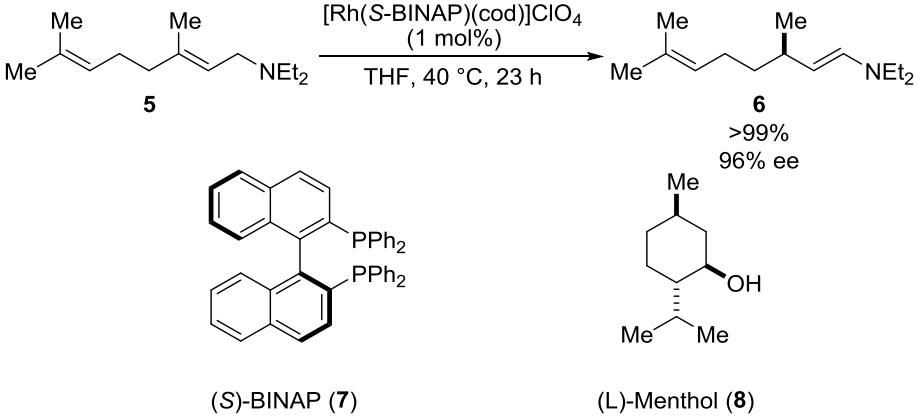
In these highlighted examples, the inactive isomer is non-therapeutic and is converted into the desired theraputic isomer, but this does not always occur. In the case of the infamous morning-sickness drug thalidomide (**4**), the non-therapeutic isomer was not inactive, but operated in a different manner leading to pronounced and often fatal side effects in the babies being carried by the patient.[4] After the problems with thalidomide, drug approval agencies such as the Food and Drug Administration (FDA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) now require substantial analysis and testing of both enantiomers of any new chiral drug molecule.

Given the pronounced and sometimes important biological differences that enantiomers can have, it is of little surprise that considerable time and effort has been expended on the research and development of methodologies that can preferentially form one enantiomer over the other. There are a myriad of methods to realise this goal for a variety of substrates. One of the most important features the complexation of a transition metal with a chiral ligand to act as a chiral catalyst in a range of bond-forming reactions. These complexes form chiral environments where the reaction occurs allowing the product to be formed in a stereoselective manner.

1.1 Rhodium-Based Catalysts

Rhodium is a group 9 transition metal first discovered in 1804[5] that has a range of applications in consumer products such as catalytic converters, electrical contacts and jewellery. It is also an important catalyst in organic chemistry, and rhodium-based catalysts have been shown to be suitable for a range of transformations such as the hydrogenation[6] and hydroformylation[7] of olefins. A range of modern industrial processes employ rhodium as a catalyst, including the Monsanto process for the synthesis of acetic acid,[8] the synthesis of silicon rubbers,[9] and the reduction of benzene.[10] Rhodium is also an excellent catalyst, when complexed to chiral ligands, for asymmetric transformations. It has been used extensively in asymmetric hydrogenations[11] and hydroformylations.[12] A chiral-rhodium/BINAP complex is employed by Takasago, a major international producer of flavours and fragrances, in the synthesis of L-menthol, a process that produces 3000 tonnes of L-menthol

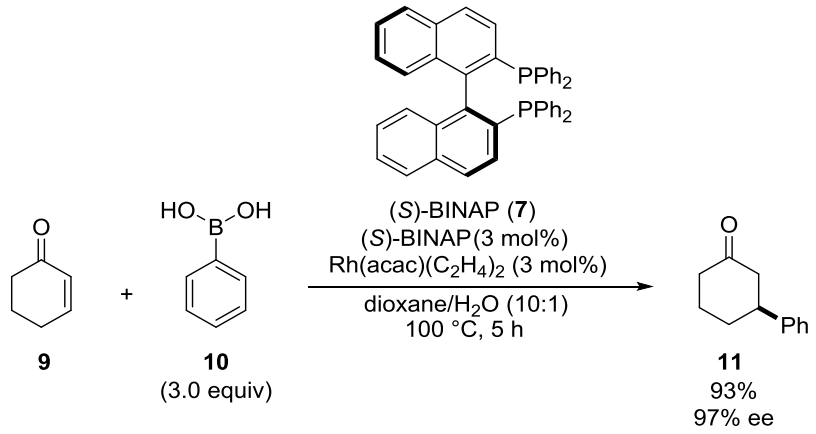
annually.[13] The synthesis proceeds *via* a rhodium-catalysed asymmetric isomerisation of allylic amine **5** into the chiral enamine **6** developed by Noyori (Scheme 1.1).[13]



Scheme 1.1: Rhodium-catalysed asymmetric synthesis of intermediate **6**[13]

1.2 Rhodium-Catalysed Asymmetric 1,4-Addition of Arylboron Reagents

Chiral rhodium catalysts have also been shown to be excellent catalysts for the nucleophilic addition of organoboron reagents to π-electrophiles. The seminal report in this field was published in 1998 by Miyaura and Hayashi (Scheme 1.2).[14] By using a Rh(I) pre-catalyst in conjunction with the chiral bisphosphine (*S*)-BINAP (**7**), it was possible to catalyse the enantioselective addition of phenylboronic acids to 2-cyclohexen-1-one (**9**) in high yields and enantioselectivities.



Scheme 1.2: Seminal report of Rh(I) asymmetric addition of organoboron species[14]

The reaction proceeds *via* the following catalytic cycle (Figure 1.2): The rhodium complexes with the chiral ligand and is then activated by the addition of water to form the active rhodium-hydroxide species **12**, which undergoes transmetallation with phenylboronic acid (**10**) to form arylrhodium intermediate **13**. Studies have shown that in most cases, this step is the turnover limiting step.[15] The intermediate **13** then co-ordinates with the electrophile **9** before undergoing a 1,4-addition to form species **14**. Hydrolysis of **14** liberates the product **11** while regenerating the active catalytic species **12**.

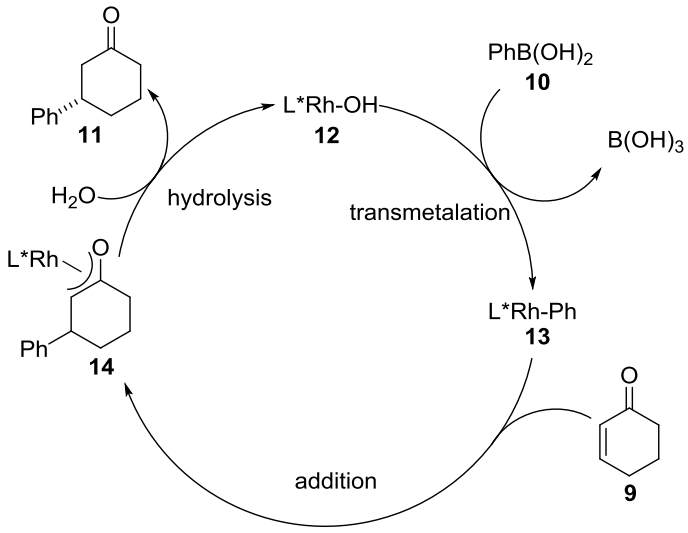


Figure 1.2: Catalytic cycle of Rh(I)-addition of boronic acid

Following this work, a substantial programme of research has been undertaken to develop this class of reactions into a wide ranging and reliable organic transformation that is sometimes known as the Hayashi-Miyaura reaction.[16]

1.2.1 The Use of Bisphosphine Ligands

Chiral bisphosphine ligands such as BINAP (**7**) are very attractive ligands for asymmetric synthesis given that many bisphosphines are commercially available and most are air stable solids. From the original work by Hayashi and Miyaura using (*S*)-BINAP (**7**), a range of similar substrates have been shown to undergo the 1,4-addition of arylboronic acids in good yields and excellent enantioselectivities using

similar catalytic conditions. Suitable electrophiles for conjugate addition include *α,β*-unsaturated esters,[17] lactones,[18] amides,[19] lactams,[20] phosphonates[21] and nitroalkenes.[22]

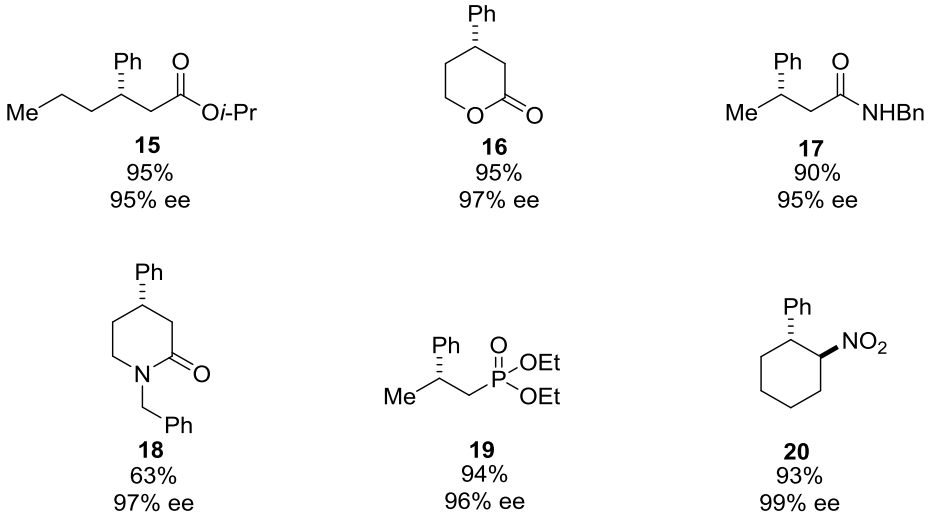
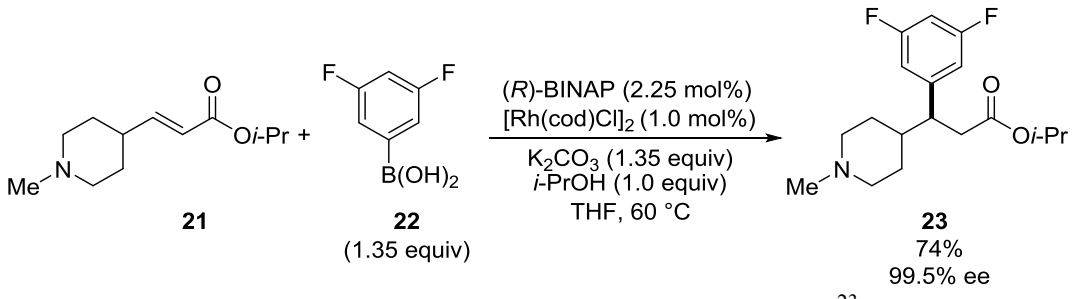


Figure 1.3: Products formed using BINAP[17,18,19,20,21,22]

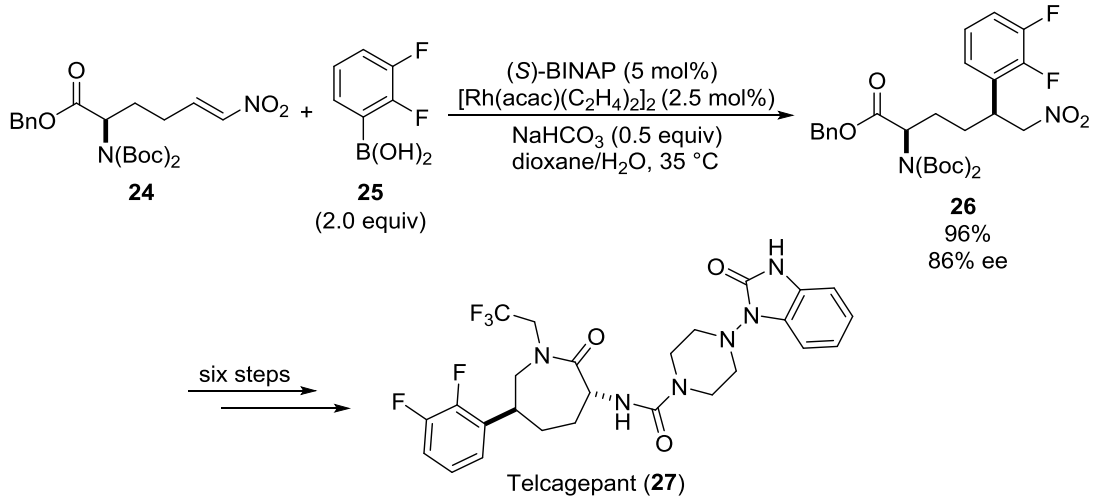
Rhodium(I)-catalysed 1,4-addition of arylboronic acids have also been employed in large scale industrial processes. AstraZeneca reported the rhodium-catalysed addition of 3,5-difluorophenylboronic acid (**22**) to *α,β*-unsaturated ester **21** to give drug target intermediate **23** (Scheme 1.3).[23] The catalytic system consisted of the commercially available pre-catalyst $[Rh(cod)Cl]_2$ and (*R*)-BINAP, resulting in the synthesis of **23** in 74% yield and 99.5% ee on a 25 kg scale.



Scheme 1.3: Large scale synthesis of drug target **23**[23]

An additional asymmetric arylation was employed in the synthesis of 2 kg of the Merck drug Telcagepant (**27**) (Scheme 2.4).[24] Using a catalytic system consisting of

[Rh(acac)(C_2H_4)$_2$]$_2$ and (*S*)-BINAP, 2,3-difluorophenylboronic acid (**25**) was used to arylate nitroalkene **24** to give product **26** in 96% yield and 86% ee. From product **26**, Telcagepant (**27**) can be synthesised in six further steps.

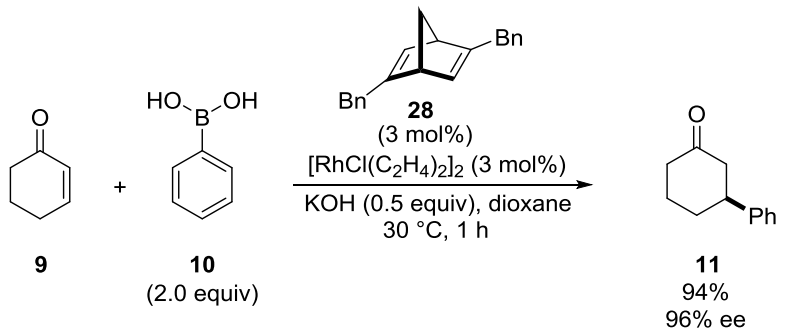


Scheme 1.4: Synthesis of Telcagepant intermediate **26**[24]

These examples illustrate the robustness and reproducibility of rhodium-catalysed asymmetric addition of arylboronic acids on a large scale. However, due to the high cost of rhodium and reasonably high catalytic loading, the only economically feasible way to employ these reactions on an industrial scale is to scavenge and recycle the rhodium catalyst after use.

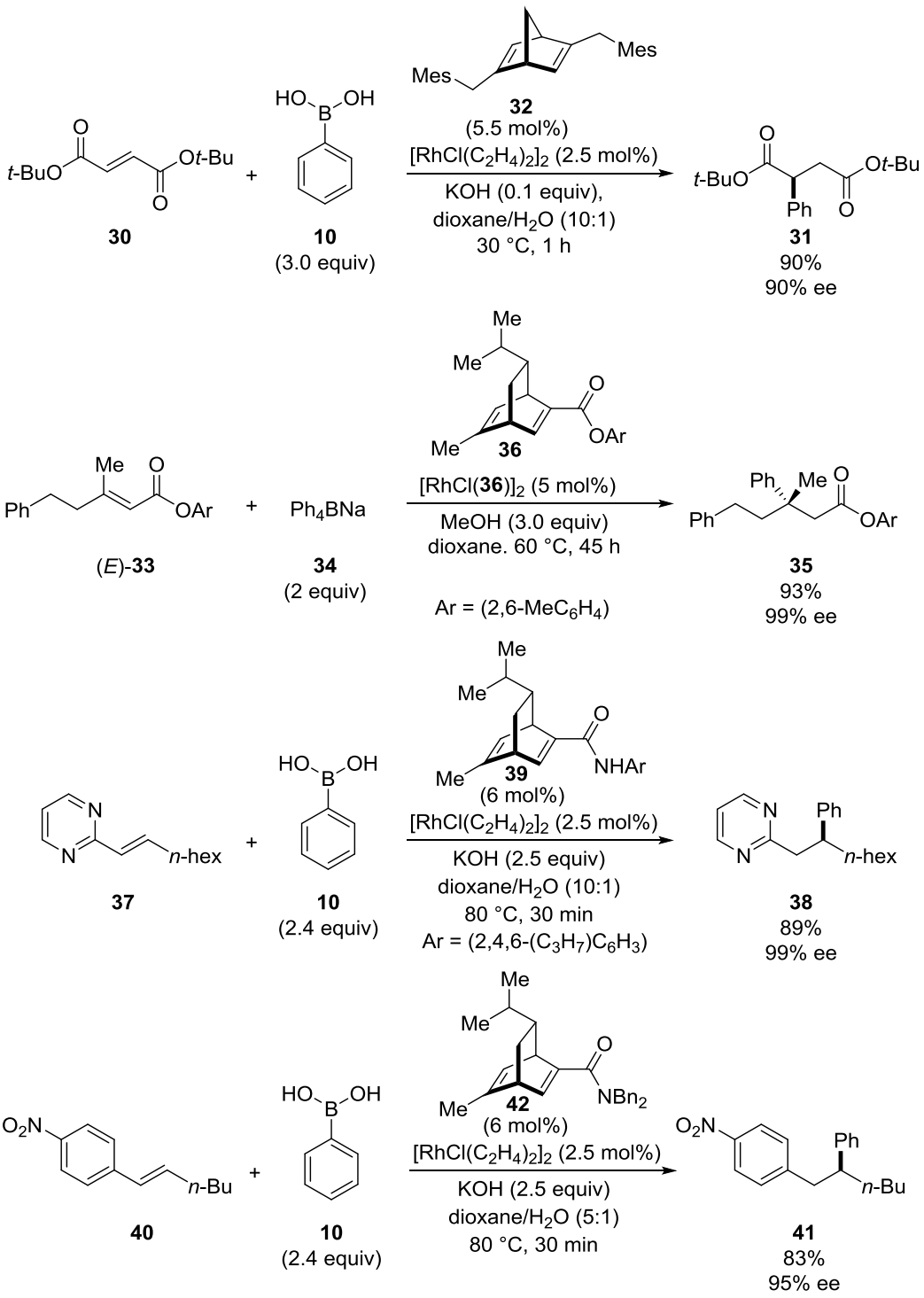
1.2.2 Non-Phosphine Ligands in Rhodium-Catalysed Arylation Reaction

Although bisphosphine ligands work well for a range of substrates, they are not as suitable for certain less reactive species. Also, they often require a large excess of boron reagent, and elevated temperatures. In 2003, the group of Hayashi reported the development of a chiral diene ligand and its use in a rhodium-catalysed arylation reaction (Scheme 1.5).[25] Using 2-cyclohexen-1-one (**9**) as a model substrate, they reported the addition of phenylboronic acid (**10**) in far milder conditions compared to the bisphosphine system and after a reaction time of only 1 hour, the product **11** was isolated in 94% yield and 96% ee.



Scheme 1.5: First report of a chiral diene ligand in rhodium-catalysed arylation[25]

Chiral dienes have rapidly become the optimal ligands for a range of rhodium-catalysed 1,4-additions.[26,27] The ligand **28** first reported by Hayashi and co-workers, features a [2.2.1]-bicyclic backbone, and a range of ligands featuring [2.2.2]-bicyclo,[28] [3.3.2]-bicyclo,[29] [3.3.0]-bicyclo,[30] and [3.3.1]-bicyclo[31] backbones have all been shown to be excellent in these reactions. Chiral dienes have shown to give similar or higher yields and enantioselectivities than bisphosphines as well as operating at milder conditions with shorter reaction times. Chiral dienes also allow the addition of arylboronic acid to a range of further less reactive substrates such as fumarates **30**,[32] di-β-substituted-α,β-unsaturated esters **33**,[33] alkenylheteroarenes **37**,[34,35] and electron deficient alkenylarenes **40**[36] that are not possible with bisphosphine ligated catalysts (Scheme 1.6).



Scheme 1.6: Chiral diene ligands in 1,4-addition[32,33,35,36]

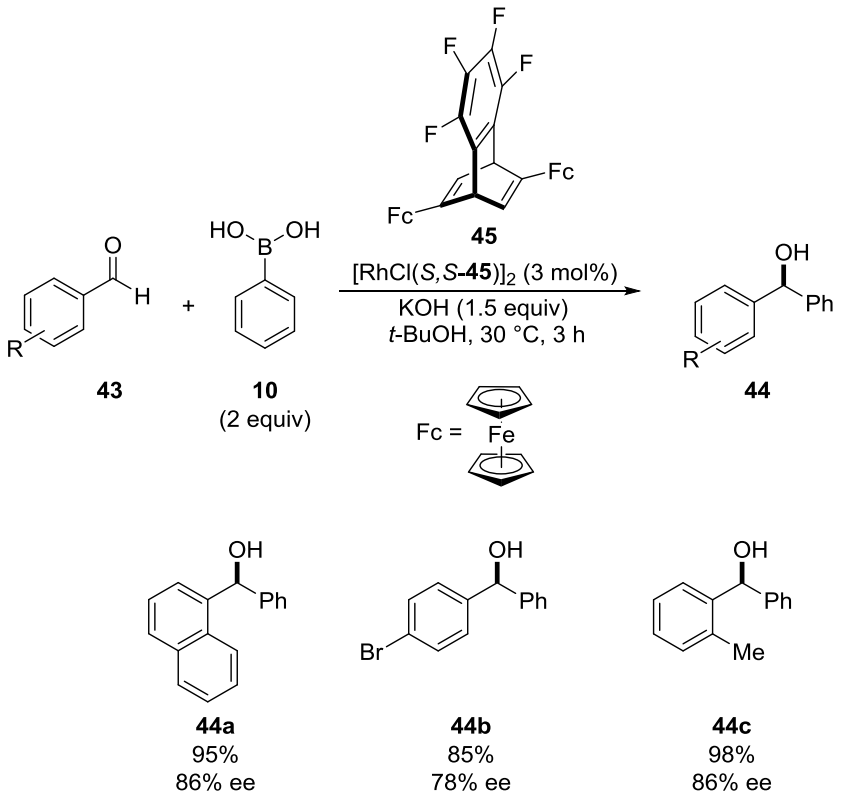
Further ligand classes such as sulfur-olefin, nitrogen-based ligands, mono-phosphine, and hybridisations of the numerous classes have led to a wide array of

ligands that all give excellent results for asymmetric rhodium-catalysed 1,4 conjugate additions.[37]

1.3 Rhodium-Catalysed Asymmetric 1,2-Addition of Arylboron Reagents

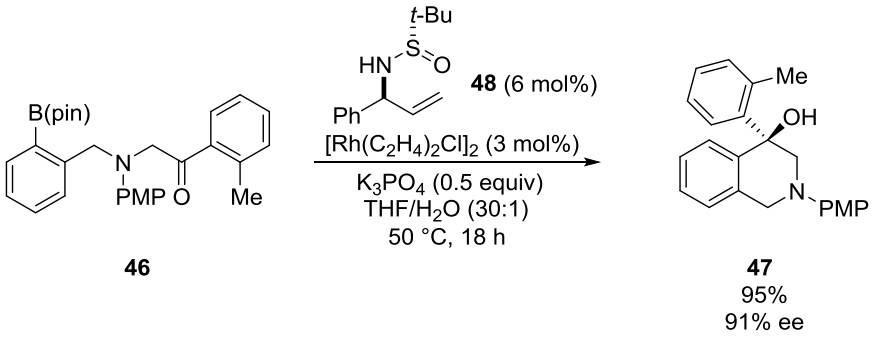
1.3.1 Rhodium-Catalysed Arylation of Carbonyl Compounds

As well as 1,4-addition, it is also possible to achieve 1,2-addition to electrophiles using rhodium catalysis. Early work using bisphosphine ligands found aldehydes to be unsuitable substrates leading to products with poor enantioselectivities. Conversely, ketones were found to be unreactive.[38] However, again chiral dienes were to prove superior, a di-ferrocenyl-barralene chiral diene **45** was found to successfully catalyse the addition of phenylboronic acid to a range of aromatic aldehydes, giving the appropriate alcohols in good yields and %ee (Scheme 1.7).[39]



Scheme 1.7: Enantioselective arylation of aldehydes[39]

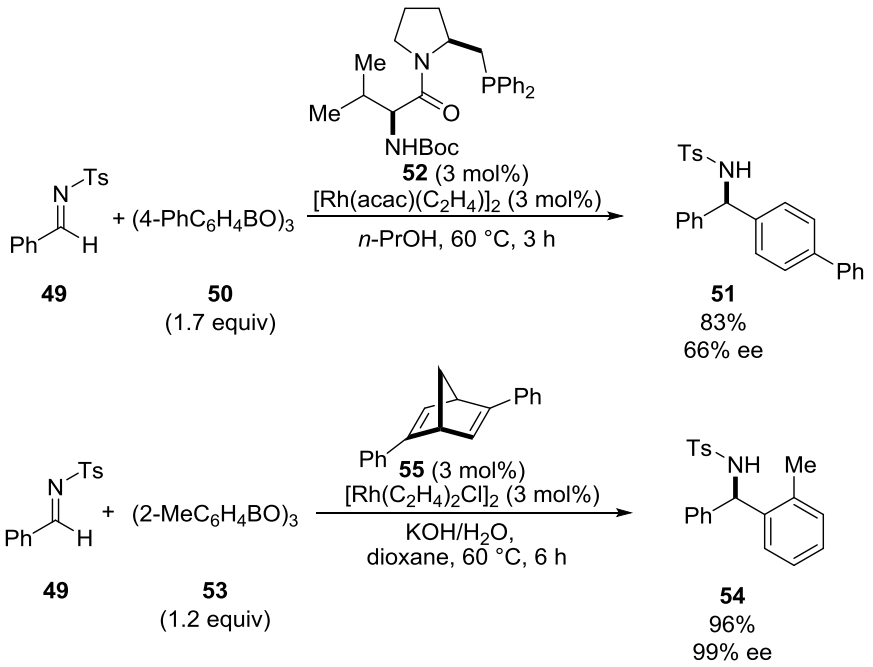
Ketones have been found to only be sufficiently reactive to undergo 1,2-addition if the ketone is activated by an adjacent electron-withdrawing group: trifluoromethyl-ketones,[40] isatins,[41] and ketoesters[42] have all been reported as excellent substrates for 1,2-addition of arylboronic acids. In 2012, the group of Lam reported the intramolecular 1,2-addition of arylboronic esters to unactivated ketones. Using sulfur-olefin chiral ligand **48** along with a rhodium catalyst it was possible to synthesise bicyclic tertiary alcohols in good yields and enantioselectivities (Scheme 1.8).[43] Similar work was reported at the same time by the group of Sarpong.[44] However, despite these advances, the intermolecular rhodium-catalysed 1,2-addition of arylboron species to unactivated ketones remains an unattained goal within rhodium catalysis.



Scheme 1.8: Intramolecular arylation of unactivated ketones[43]

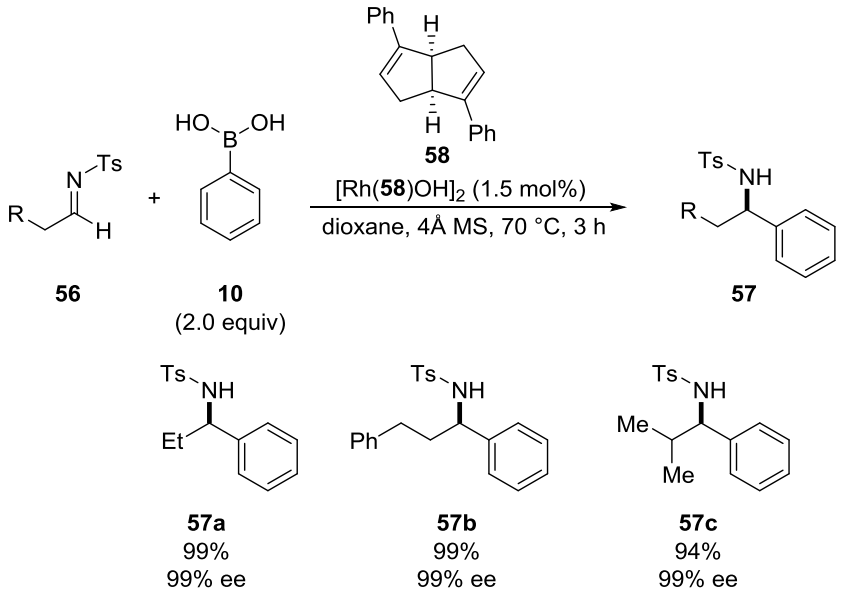
1.3.2 Rhodium-Catalysed Addition to Imines

The enantioselective addition of arylboron species to imines using rhodium catalysis has also been researched extensively. Diarylmethylamines are important biological motifs that feature in many natural products and pharmaceuticals.[45] Early reports into the rhodium-catalysed arylation of aromatic aldimines came from the group of Tomioka in 2004 (Scheme 1.9).[46] Their work focussed on the addition of arylboronic acids to *N*-tosylaldimines **49** using an unusual amidomonophosphane ligand **52** but the enantiomeric excess of product **51** was only moderate. In the same year, Hayashi and co-workers reported a very similar transformation using a bicyclo[2.2.1]octadiene ligand **55**,[47] which provided a similar products in good yield and enantioselectivity (Scheme 1.9).



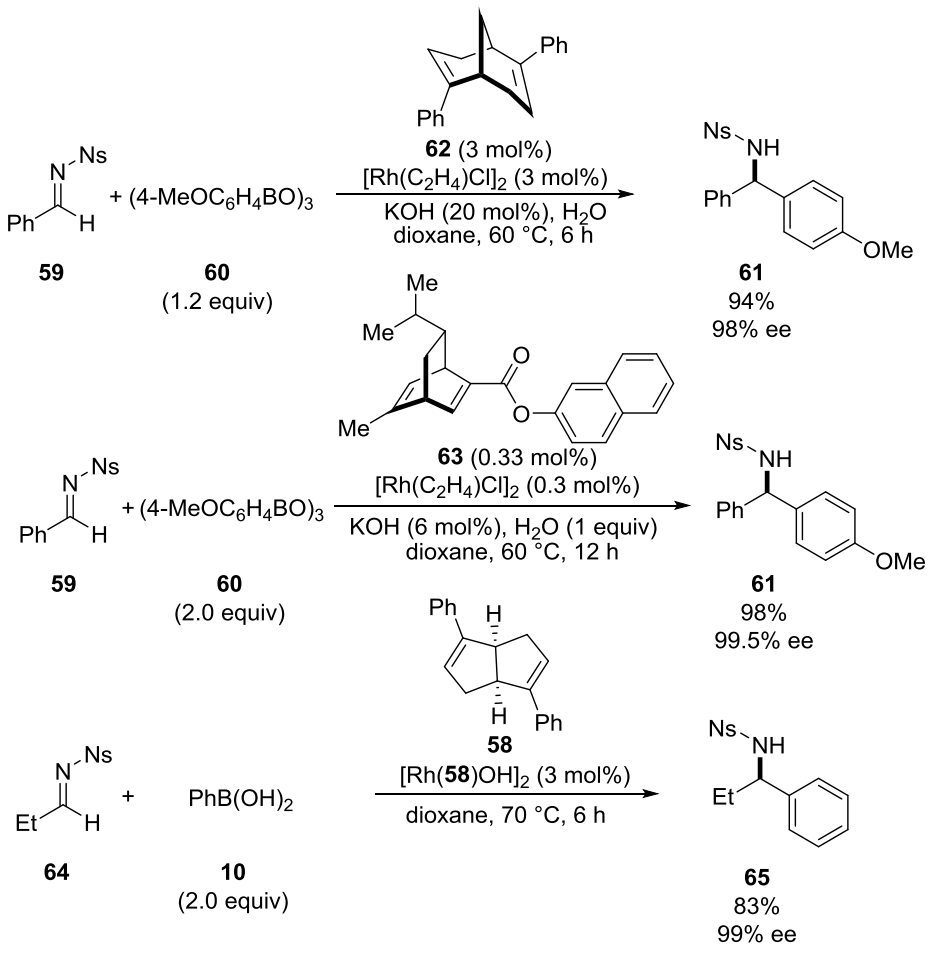
Scheme 1.9: Arylation of tosyl-aldimines[46,47]

Further studies[30] have demonstrated that the electronic nature of both the imine and the boron species has no pronounced effect upon either the yield or the enantioselectivity. However, these methodologies are exclusively limited to aromatic imines; it was found that aliphatic imines were prone to imine-enamine tautomerisation, self-condensation, and other non-productive decomposition pathways. This synthetic challenge was solved in 2011 by Lin and co-workers when his group reported the successful 1,2 arylation of aliphatic *N*-tosylimines (Scheme 1.10).[48] By utilising a pre-formed rhodium-hydroxide catalyst, the known active species, it removed the requirement of an external base, and thus milder conditions could be implemented to preserve the less stable aliphatic imine.



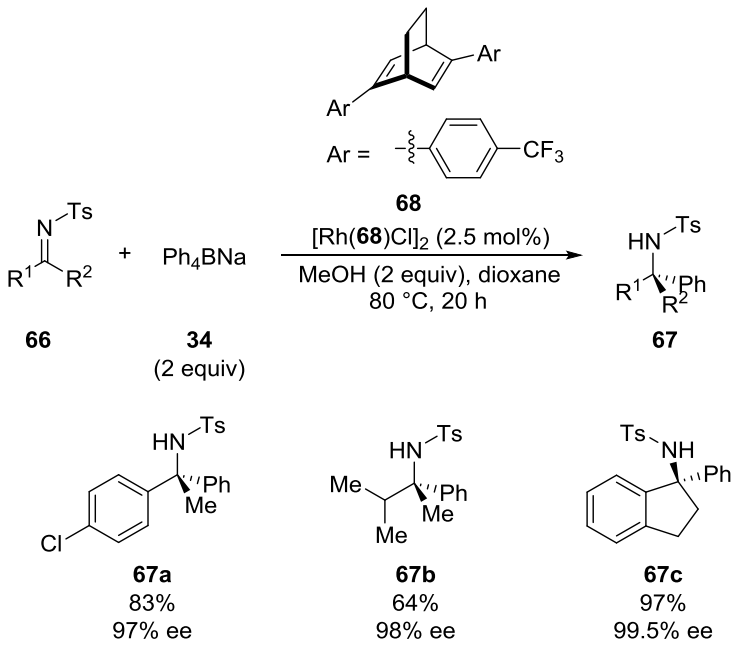
Scheme 1.10: Arylation of aliphatic imines[48]

Accessing enantioenriched diarylmethylamines by the arylation of *N*-tosylimines can be difficult in reality, as the harsh methods of removing the tosyl group tend to either erode enantioselectivity or cause degradation of the product. In order to access diarylmethylamines, methodology using a more labile protecting group was sought. The 4-nitrobenzenesulfonyl (nosyl) group has a similar reactivity profile to the tosyl group, but, it is more readily removed.. Hayashi and co-workers demonstrated that the rhodium-catalysed arylation of *N*-nosylimine could be achieved using a bicyclo[3.3.1]octadiene ligand **62**,[31] or a bicyclo[2.2.2]octadiene ligand **63**,[49] and the group of Lin reported similar transformations using a bicyclo[3.3.0]octadiene ligand **58** (Scheme 1.11).[48] From these resultant nosylamines, diarylmethylamines could be accessed *via* a transamination reaction with no loss of enantioselectivity.



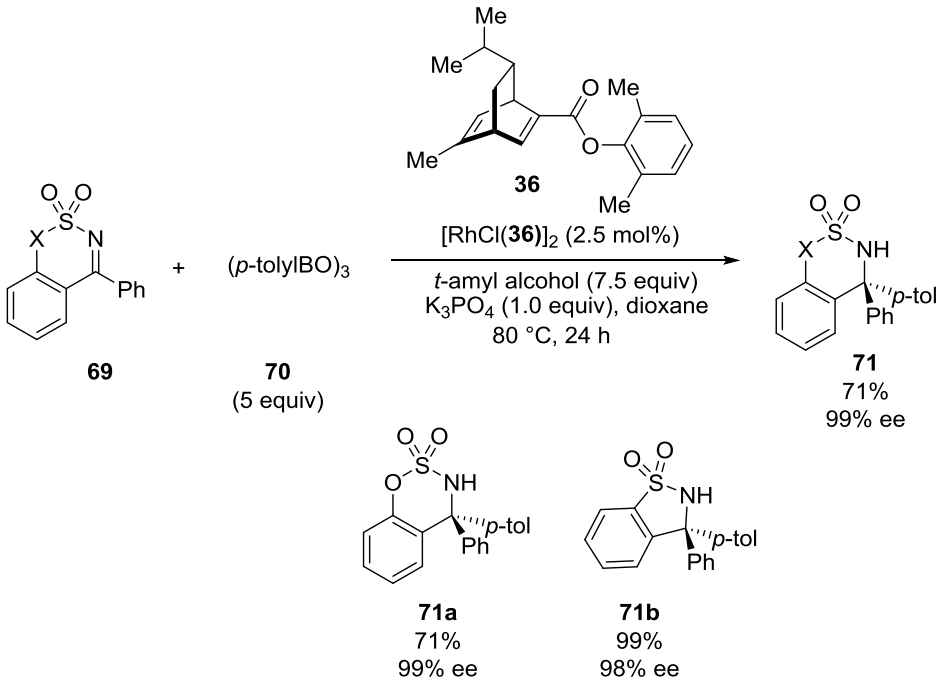
Scheme 1.11: Arylation of *N*-nosylimines[31,49,48]

Similar to the analogous reactions with ketones, ketimines are substantially less reactive species than the corresponding aldimines. However, this synthetic problem, unlike the arylation of ketones, has been surmounted and the rhodium-catalysed arylation of ketimines is a maturing field. Although traditional arylboron species were found to be unreactive, Hayashi reported that by using sodium tetraphenylborate (**34**) it was possible to arylate a range of *N*-tosylketimines **66**, both aromatic and aliphatic, acyclic and cyclic, in good yields and enantioselectivities using bicyclo[2.2.2]octadiene ligand **68** (Scheme 1.12).[50] Unlike the corresponding product resulting from the addition to aldimines, these trisubstituted *N*-tosylamines could be deprotected using lithium in liquid ammonia to give the tertiary amine in high yield with no loss of enantioselectivity.



Scheme 1.12: Arylation of *N*-nosylketimines[50]

Hayashi and co-workers also demonstrated that a chiral rhodium catalyst can differentiate between two very similar sized aromatic groups, leading to the synthesis of enantioenriched triarylamines (Scheme 1.13).[51] This was achieved *via* the arylation of cyclic ketimine **69** with *para*-tolylboroxine **70** using chiral diene **36** to give the product **71** in high yields and good enantioselectivities. Treatment of compound **71** with lithium aluminium hydride removed the cyclic sulfamate bridge to give enantioenriched triarylamines.



Scheme 1.13: Differentiation between two similar sized aryl groups[51]

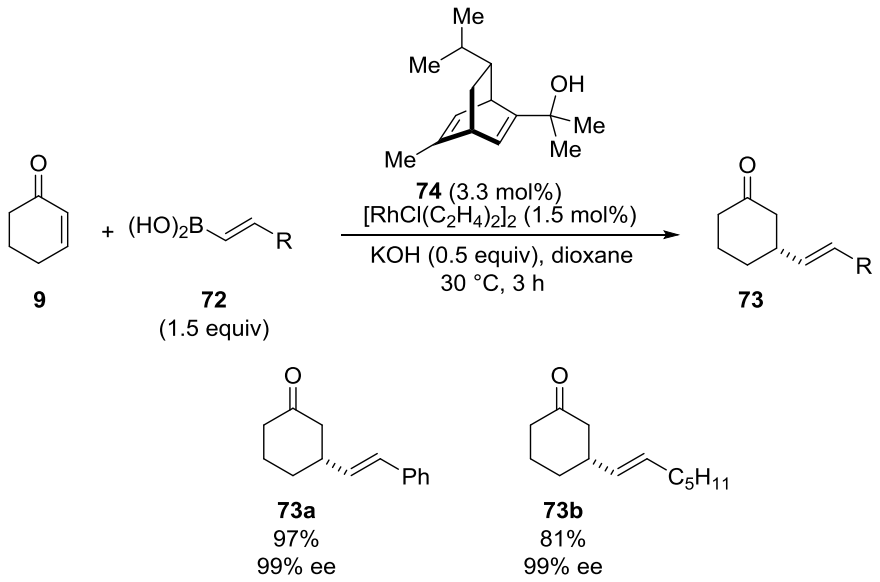
Following the seminal report of enantioselective rhodium-catalysed addition of arylboron species in 1998.[14] A huge amount of time and effort has been expended in the field, resulting in a very mature field. More than 300 publications have illustrated a wide range of suitable electrophiles for both 1,4-addition and 1,2-addition, along with numerous different classes of ligand, each having their own optimal scope and conditions set.[37] Furthermore, large scale industrial processes involving rhodium-catalysed arylations have been disclosed, underpinning the fact that although some challenges remain, rhodium-catalysed arylation reactions are now a very important class of enantioselective transformations.

1.4 Rhodium-Catalysed Asymmetric Alkenylation

The field of rhodium-catalysed addition of organoboron reagents is dominated by the addition of arylboron reagents, but, it is not limited to these reagents and other organoboron reagents have been successfully utilised in these reactions. Alkenylboron species have been shown to work in a similar manner to furnish the enantioenriched alkenylated products.

1.4.1 Rhodium-Catalysed 1,4-Alkenylation Reactions

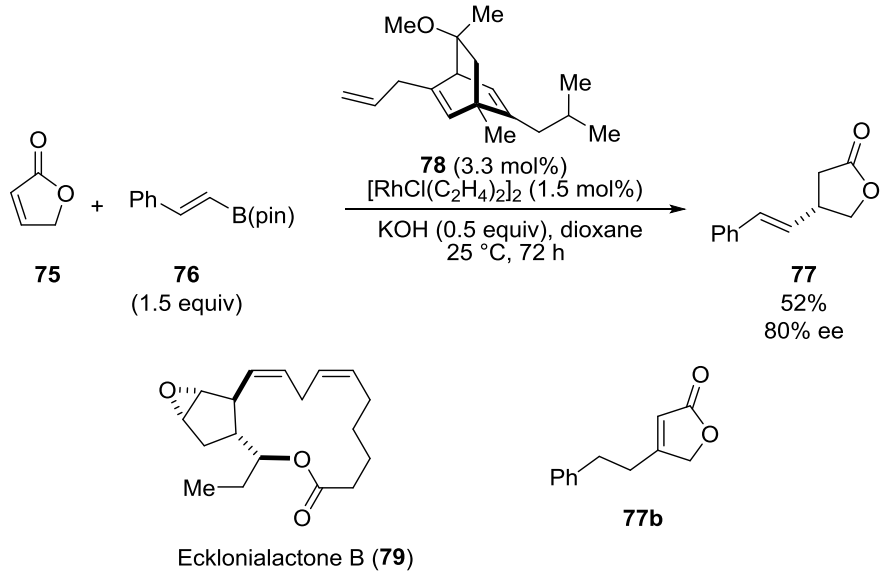
The first reported rhodium-catalysed alkenylation was by Hayashi and Miyuara in 1998.[14] They found that such transformations were limited by lower yields relative to the arylation reaction. In 2008 the group of Hayashi reported that chiral dienes helped address this issue (Scheme 1.14).[52] By utilising bicyclo[2.2.2]octadiene ligand **74** it was possible to add alkenylboronic acids **72** to 2-cyclohexen-1-one (**9**) to form the 1,4-addition adducts **73** in 97% yield and 99% enantiomeric excess with both aromatic **73a** and aliphatic substituents **73b**.



Scheme 1.14: Alkenylation of 2-cyclohexen-1-one (**9**)[52]

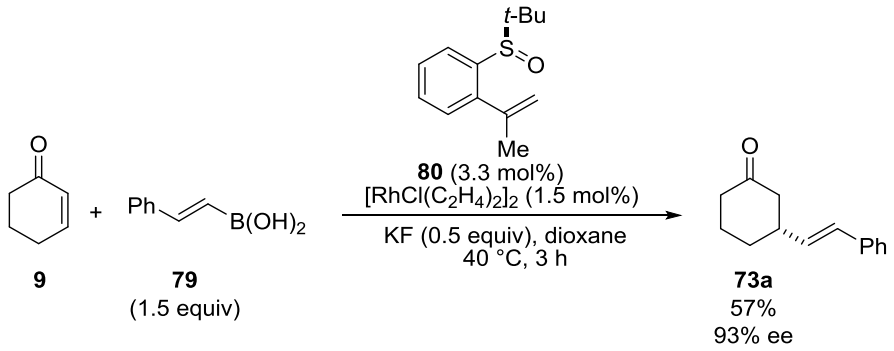
Fürstner and co-workers also reported the successful rhodium-catalysed alkenylation of butenolide **75** with styrylboronic acid pinacol ester (**76**) using

bicyclo[2.2.2]octadiene **78** in their total synthesis of the natural product Ecklonialactone B (**79**) (Scheme 1.15).[53] Higher temperatures (65 °C) were required if bisphosphine ligands were used, but at this elevated temperature the product **77** underwent an isomerisation resulting in the formation of conjugated enone **77b**, destroying the newly formed stereocentre. Fortunately, chiral diene **78** was found to be superior and allowed the reaction to proceed at room temperature to furnish the product without any isomerisation.



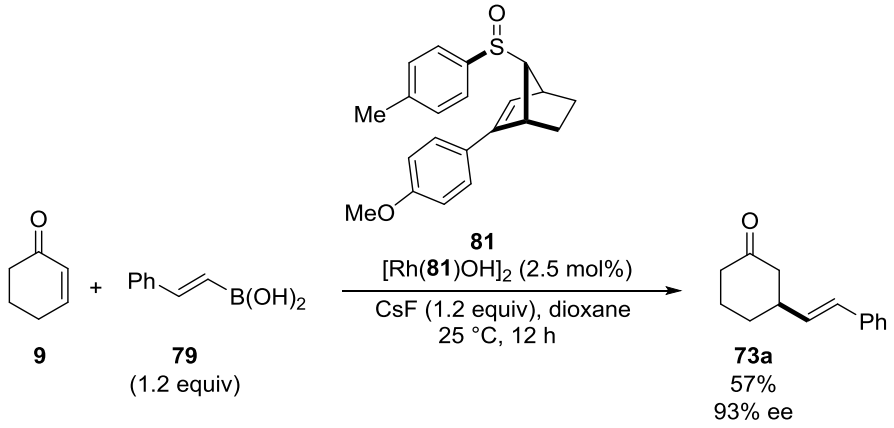
Scheme 1.15: The use of rhodium-catalysed alkenylation in the total synthesis of Ecklonialactone B (**79**)[53]

As well as chiral dienes, other ligands have also been successfully used in rhodium-catalysed alkenylation. Liao and co-workers reported a single example of the alkenylation of 2-cyclohexen-1-one (**9**) using sulfur-olefin ligand **76**; the reaction proceeds to give product **71a** with moderate yield but excellent enantiomeric excess (Scheme 1.16).[54]



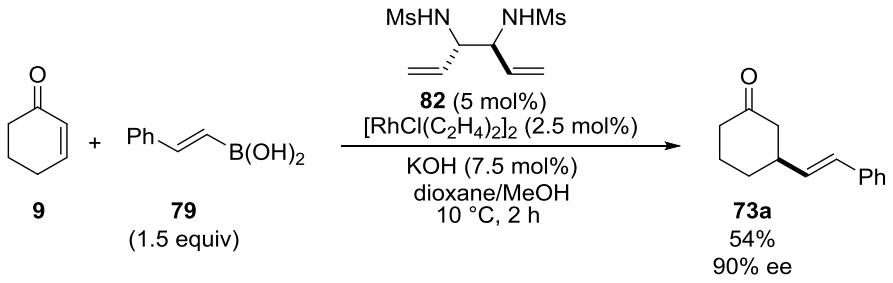
Scheme 1.16: The use of sulfur-olefin ligands in rhodium-catalysed alkenylation[54]

Work by the group of Knochel also demonstrated that hybrid sulfur-olefin ligand **81** could also be used in rhodium-catalysed alkenylation (Scheme 1.17).[16] Again using 2-cyclohexen-1-one (**9**) as a model substrate, the product **73a** was attained in moderate yields and an excellent 93% ee.



Scheme 1.17: Sulfur-olefin ligands in alkenylation[16]

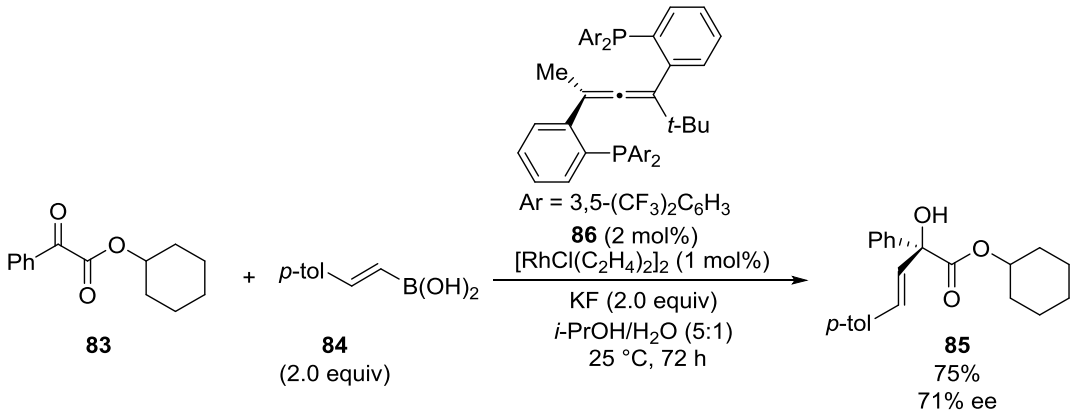
Work by Du and co-workers also demonstrated that a rhodium complex composed of diamine-diene ligands such as **82** can successfully catalyse the alkenylation of 2-cyclohexen-1-one (**9**) providing **73a** in moderate yields and good enantiomeric excess (Scheme 1.18).[55]



Scheme 1.18: Diamine-diene ligand in rhodium-catalysed alkenylation[55]

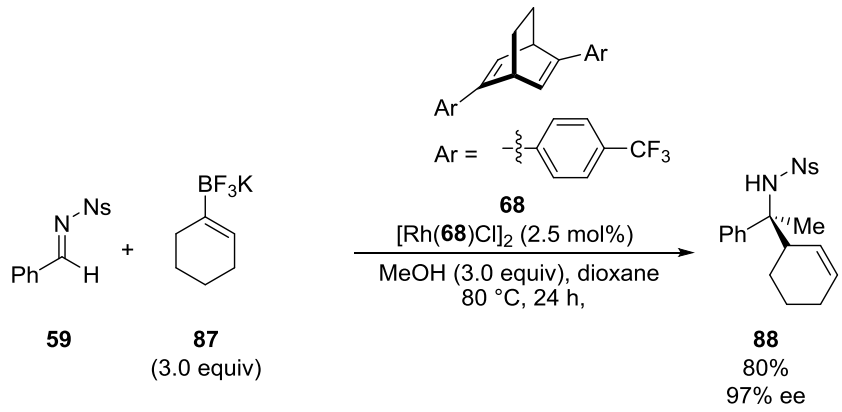
1.4.2 Rhodium-Catalysed 1,2-Alkenylation Reactions

As with arylation, alkenylation is not limited to 1,4-additions, it is also possible for alkenylboron species to undergo 1,2-addition to electrophiles in high yields and high enantiomeric excesses. The alkenylation of carbonyl compounds are somewhat limited. The addition of alkenylboron species to ketoester **83** gave allylic alcohol **85** in only moderate yields and enantiomeric excess (Scheme 1.19).[56]



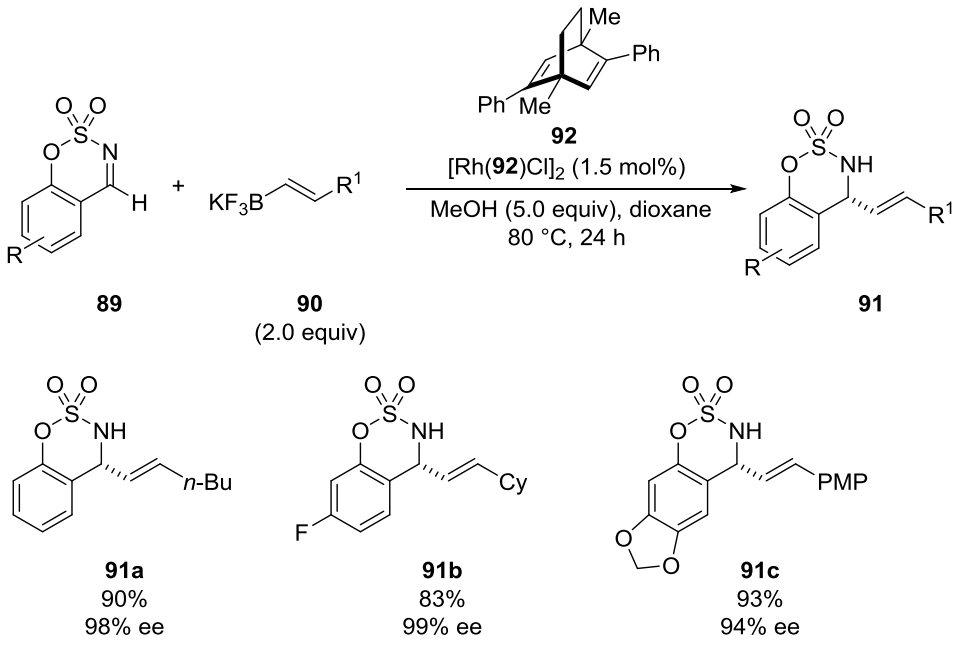
Scheme 1.19: Alkenylation of ketoester **83**[56]

Better results were obtained when using an imine as the electrophile. The group of Hayashi reported a single example of the asymmetric addition of cyclohexenylboron species **87** to *N*-nosylimine **59** using chiral diene **68** (Scheme 1.20).[57] This transformation is limited to the addition of the cyclic alkenyl species and no reports of using this catalytic system to successfully add linear alkenylboron species to imines have been disclosed.



Scheme 1.20: 1,2-Addition of alkenyltrifluoroborates[57]

In 2012 Lam reported the asymmetric addition of linear alkenyltrifluoroborates to a range of cyclic aldimines and cyclic ketimines utilising chiral diene **92** (Scheme 1.21).[58] The addition of alkenyltrifluoroborates **90** to cyclic imine **89** resulted in the formation of the allylic sulfamate **91** in high yields and high enantiomeric excess with a range of substitution tolerated on both the aromatic region of the imine **89** and the alkenyltrifluoroborate salt **90**. Recent work by the groups of Lin[59] and Wu[60] have demonstrated the ability to add alkenyltrifluoroborate salts to acyclic *N*-nosyl and *N*-tosyl aldimines respectively using a rhodium-chiral diene catalytic complex with good yields and enantioselectivities.

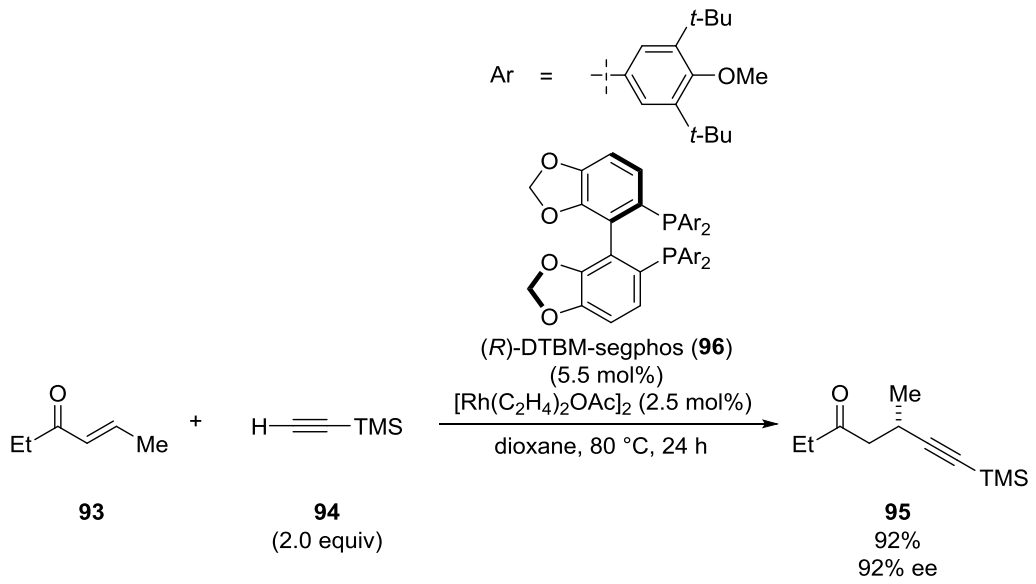


Scheme 1.21: Addition of linear alkenylboron species to cyclic imines[58]

The challenges in rhodium-catalysed alkenylation arise from the lower stability of an alkenylrhodium intermediate compared with an arylrhodium intermediate leading to quicker decomposition pathways such as protodeboration. Although it is not as well-developed as the field of rhodium-catalysed arylation, rhodium-catalysed alkenylation has been reported with a range of different ligands having been shown to catalyst both 1,4-addition and 1,2-addition of alkenylboron species to π-electrophiles.

1.5 Rhodium-Catalysed Alkynylation Reactions

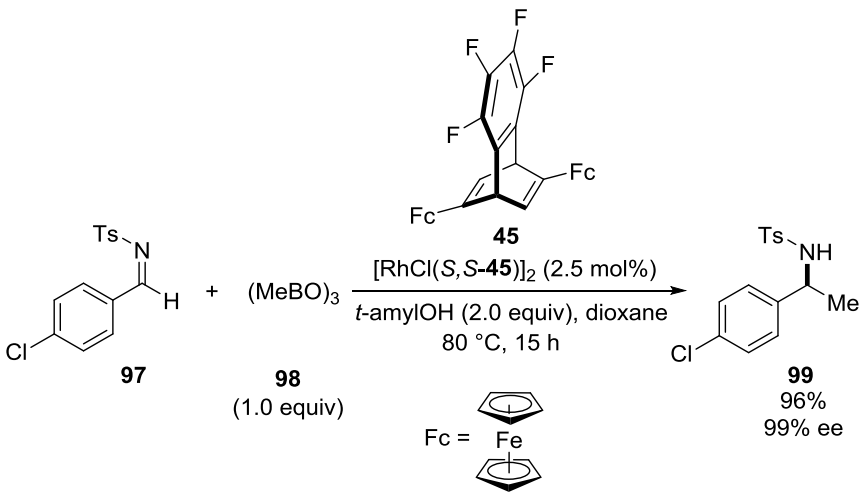
Terminal alkynes are rather different to the previously covered aryl and alkenyl species as they feature a facile terminal proton. Therefore, terminal alkynes can transmetallate readily with rhodium to form alkynylrhodium species without the need for a heteroatomic handle to facilitate the transmetallation. Early research discovered that these alkynylrhodium species tended to have a greater affinity for a second terminal alkyne rather than a π-electrophile, resulting in alkyne dimerisation rather than nucleophilic addition.[61] This dimerisation process can be inhibited by the use of bulky ligands chelated to the rhodium, with the increased steric bulk resulting in a complete shutdown of the dimerisation pathway, allowing the 1,4-addition of the alkyne to enone **93** to occur in excellent yields and enantiomeric excess (Scheme 1.22).[62]



Scheme 1.22: Rhodium-catalysed asymmetric alkynylation[62]

1.6 Rhodium-Catalysed Addition of Alkylboron Reagents

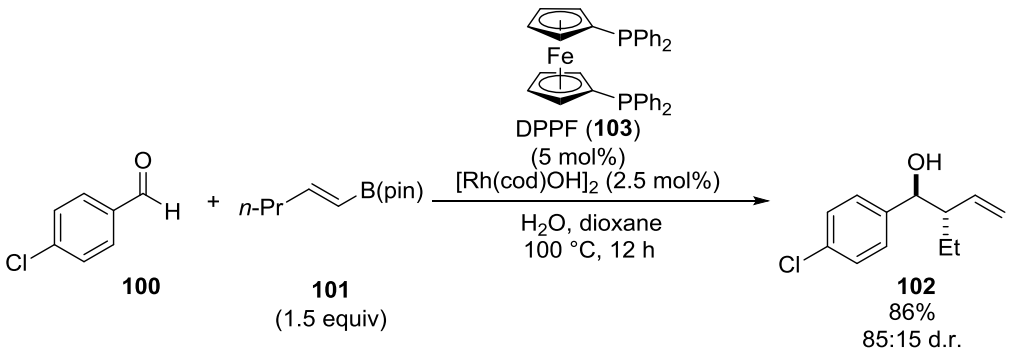
Although alkylboron reagents are commercially available and air-stable, the rhodium-catalysed alkylation reaction is a very underdeveloped field. The main reason for this is the inherent instability of alkylrhodium species: β-hydride elimination usually occurs rapidly leading to an unproductive pathway, thus, only alkyl species that cannot undergo β-hydride elimination have been found generate stable alkylrhodium species. The only reported rhodium-catalysed alkylation is the methylation of *N*-sulfonylimines with the commercially available trimethylboroxine **98**. These reactions proceed smoothly to give high yields and enantiomeric excesses when using a rhodium-chiral diene complex (Scheme 1.23).[63] However, these kinds of transformations can also be realised using rhodium catalysis and dimethyl zinc[64-66] or trimethylaluminium.[67]



Scheme 1.23: Rhodium-catalysed methylation[63]

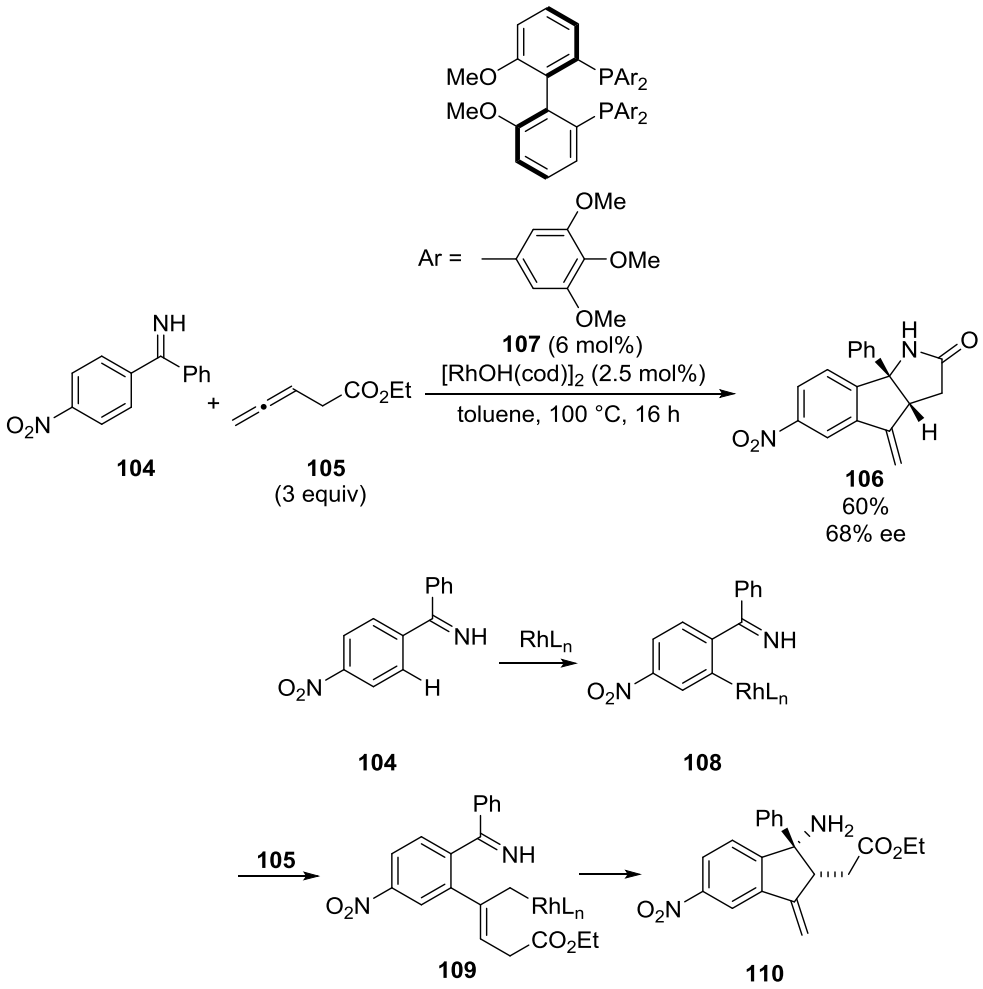
1.7 Rhodium-Catalysed Addition of Allylboron Reagents

The rhodium-catalysed asymmetric addition of organoboron species to π-electrophiles is now a very important organic transformation; a plethora of catalytic systems have been shown to facilitate asymmetric arylation and many examples of asymmetric alkenylation have also been reported. Although far less developed, rhodium-catalysed asymmetric alkynylation and asymmetric methylation are also possible under certain conditions. Conspicuously absent is the corresponding rhodium-catalysed asymmetric nucleophilic allylation, despite the fact that the nucleophilic allylation reaction is a fundamental organic transformation and some allylboron species are commercially available and stable. Some reports have made limited headway into the field; In 2011, Murakami and co-workers reported the *in situ* isomerisation of alkenylboronic esters into allylboronic esters, before the allylation of aldehydes (Scheme 1.24).[68] However, they believe the rhodium catalyst merely initiates the isomerisation, and there is no boron to rhodium transmetallation.. Thus, any chiral ligands complexed with rhodium, would have no effect on the stereochemistry generating step.



Scheme 1.24: Isomerisation of Alkenyl-B(pin) species followed by racemic allylation[68]

The only reported enantioselective Rh(I)-catalysed nucleophilic allylation was from the group of Cramer in 2010 (Scheme 1.25).[69] They reported a C-H functionalisation, followed by addition to an allene to generate an allylrhodium species which then underwent nucleophilic allylation to an imine followed by lactamisation. Although most published examples employed an achiral rhodium catalyst to provide racemic products, by using chiral ligand **107** it was possible to synthesis **106** in 68% ee.

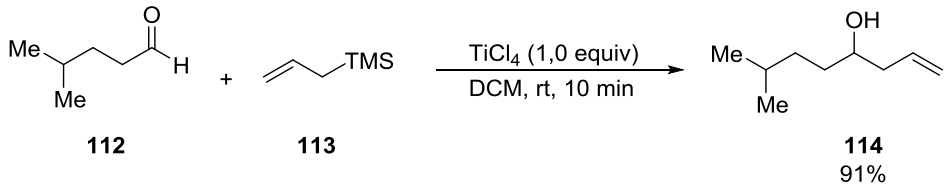


Scheme 1.25: Enantioselective allylation of imines[69]

This work is limited by the need for an adjacent aryl group for C-H functionalisation and an allene to facilitate allylation, resulting in the ability to synthesise a limited range of products and at this point, there were no reports of a simple enantioselective allylation of a π-electrophile using a rhodium(I) catalyst and allylboron species.

2.0 The Nucleophilic Allylation Reaction

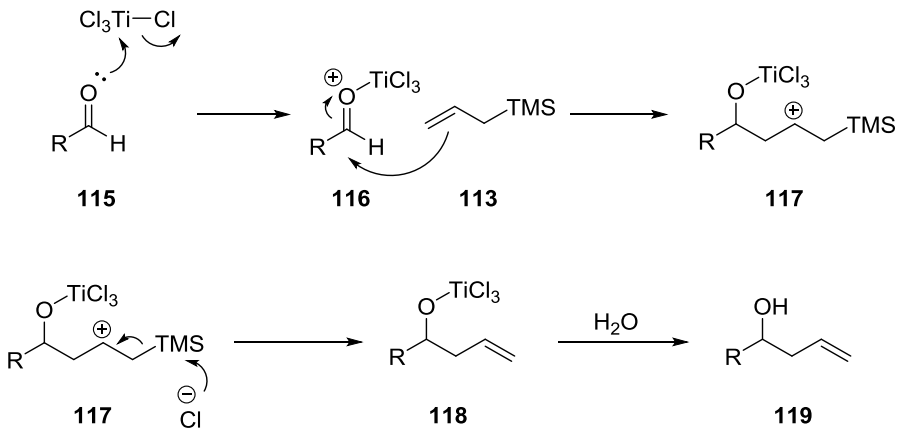
The nucleophilic allylation reaction has been an important transformation in organic chemistry for some time. The allylation of carbonyl compounds and imines allows rapid access to homoallylic alcohols and homoallylic amines. These products are important chemical building blocks and often feature multiple functional handles to enable further derivitisation.[70] An early form of the allylation reaction involved the addition of an allyl halide to an aldehyde in the presence of zinc or magnesium *via* a Barbier-type reaction, but these allyl species are very reactive and tend to be incompatible with many functional groups.[71] Another early allylation reaction was reported by Hosomi and Sakurai in the 1970's, involving the addition of allyltrimethylsilane (**113**) to aldehyde **112** in the presence of a Lewis acid to furnish the resultant homoallylic alcohol **114** in excellent yield (Scheme 2.1).[72]



112 **113** **114**
91%

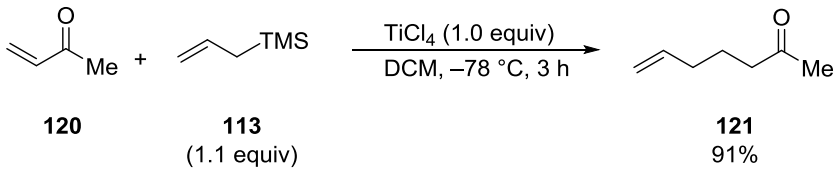
Scheme 2.1: The Hosomi-Sakurai reaction[72]

The Hosomi-Sakurai reaction proceeds *via* the following mechanism: the Lewis acidic titanium coordinates with a lone pair of the oxygen to form an oxonium ion **116**, which is then attacked by the nucleophilic allylsilane **113** to form carbocation **117**. This carbocation is stabilised by the β-silicon effect where the electron density in the $\sigma_{Si\text{-}C}$ bonding orbital is donated into the empty p-orbital of the carbocation. Cleavage of the silyl group reforms the olefin **118** before aqueous work up liberates the homoallylic alcohol **119** (Scheme 2.2).



Scheme 2.2: Mechanism of the Hosomi-Sakurai reaction

Hosomi and Sakurai went on to demonstrate this process could be extended to *α,β*-unsaturated enones which resulted in a 1,4-addition of the allyl group (Scheme 2.3).[73]



Scheme 2.3: 1,4,-Conjugate allylation reaction[73]

From these two important reactions, there has been substantial research into both 1,2- and 1,4-allylations. The suitable substrate scope has been extended substantially and numerous catalytic systems have been employed. Also, diastereoselective and enantioselective reactions have been developed allowing the synthesis of enantioenriched products, along with the application of such methodology in the total synthesis of natural products.[70]

2.1 Asymmetric Nucleophilic Allylation of Carbonyl Compounds

The asymmetric addition of allyl species to carbonyl compounds is a well-developed and mature field of organic chemistry. The field is too vast to concisely summarise within this text but excellent yields and enantioselectivities have been achieved by employed both a variety of allyl reagents and catalytic systems. Allylsilanes have successfully been used with a silver-bisphosphine catalyst[74] as well as Lewis basic

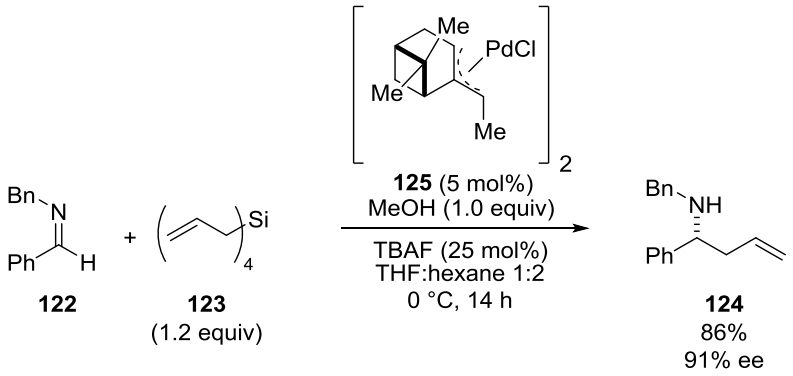
catalysts such as phosphoramidites,[75] phosphane oxides[76] and *N*,*N*-dioxides.[77] Allylstannanes have been successfully used with a diol-titanium catalyst,[78] Cr(III)-salen Lewis acids,[79] indium-PyBox systems,[80] silver-phosphoramidite catalysts,[81] platinum-bisphosphite catalysts,[82] and a proline based organocatalyst.[83] Allylboron species have been employed with tin-diol catalysts,[84] chiral phosphoric acids,[85] copper-lanthanum-bisphosphine,[86] indium-oxazoline,[87] and nickel-phosphoramidites.[88] As well as these examples, a host of other catalytic systems such as iridium-phosphine catalysts[89-99] and ruthenium-phosphine catalysts[100-102] have been successfully employed to furnish enantioenriched homoallylic alcohols.

2.2 Asymmetric Nucleophilic Allylation of Imines

Enantioenriched homoallylic amines are important organic building blocks and can be functionalised into many useful products.[103] Therefore it is no surprise that considerable effort has been expended into the synthesis of these compounds. Allylation reactions of imines can be categorised according to the source of the allyl group; with allylsilanes, allylstannanes, allyl halides and allylboronates being the most-studied allylating agents.

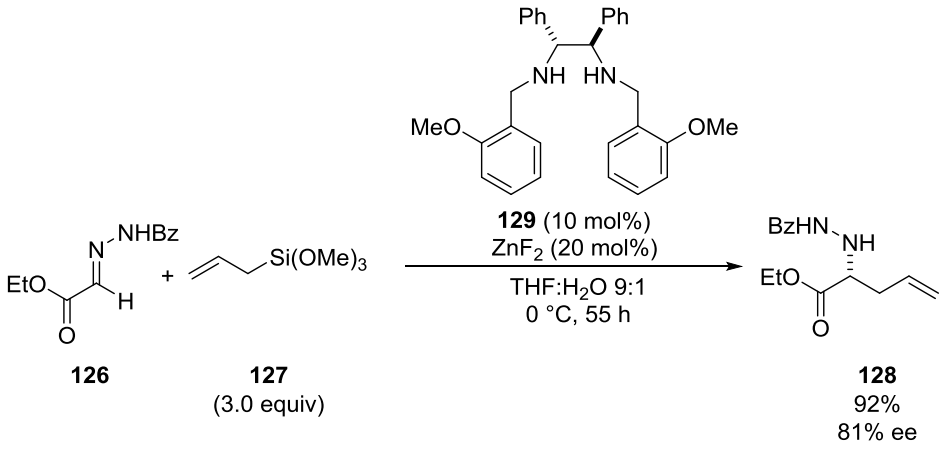
2.2.1 Nucleophilic Allylation of Imines Using Allylsilanes

Like Hosomi and Sakurai,[72] allylsilanes have been utilised by other groups as excellent allylating agents in the enantioselective allylation of imines. An early report of a catalytic enantioselective allylation with allylsilanes came from the laboratory of Yamamoto in 2004 (Scheme 2.4).[104] Their conditions feature tetraallylsilane (**123**), methanol, and tetrabutylammonium fluoride along with chiral palladium catalyst **125**. They proposed the fluoride helps promote the formation of a bis-allyl palladium species which can then undergo nucleophilic addition to the imine. The methanol acts as a proton source to ensure catalytic turnover.



Scheme 2.4: Palladium-catalysed allylation of imines[104]

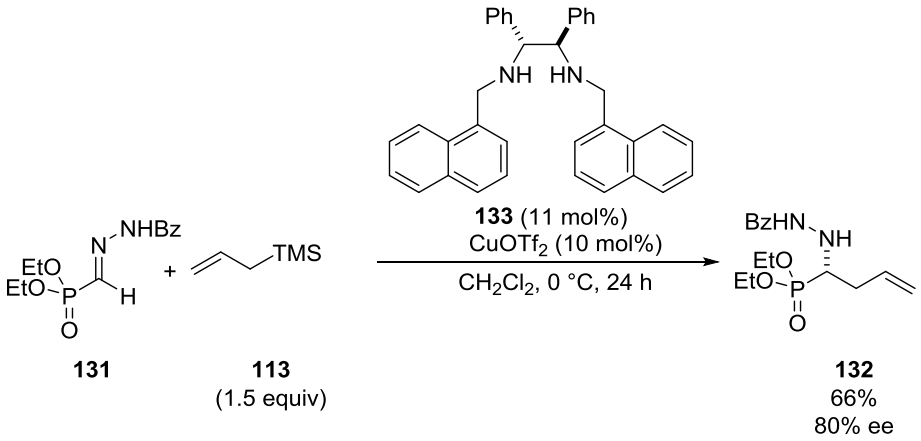
Allylsilanes were also used by the group of Kobayashi in the allylation of hydrazones using ZnF_2 and diamine catalyst **129** (Scheme 2.5).[105] Hydrazones such as **126** have proven to be attractive substrates in the development of allylation reactions. This is due to these substrates being far more hydrolytically stable than other imines. Additionally there are opportunities for many catalysts to undergo two-point binding with the substrates *via* nitrogen and oxygen atoms, allowing greater stereoinduction. They propose the zinc acts as a Lewis acid in the activation of the imine while the fluoride acts as a Lewis base, activating trimethoxallylsilane (**127**) allowing the addition of the allyl group to proceed to give homoallylic amine **128** in good yields and good enantioselectivities.



Scheme 2.5: Zinc-diamine-catalysed allylation of iminoesters[105]

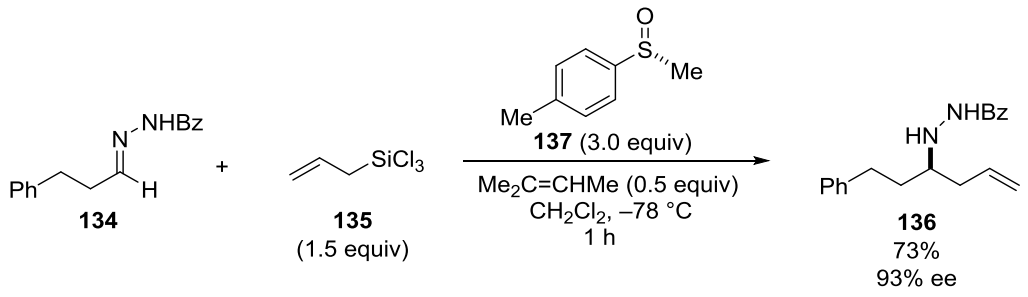
Further work by Kobayashi and co-workers demonstrated that similar iminoesters could be allylated using a copper-diamine catalytic system, and iminophosphonates

were also found to be suitable substrates under the same catalytic conditions leading to the formation of the product **132** in moderate yields and good enantiomeric excess (Scheme 2.6).[106]



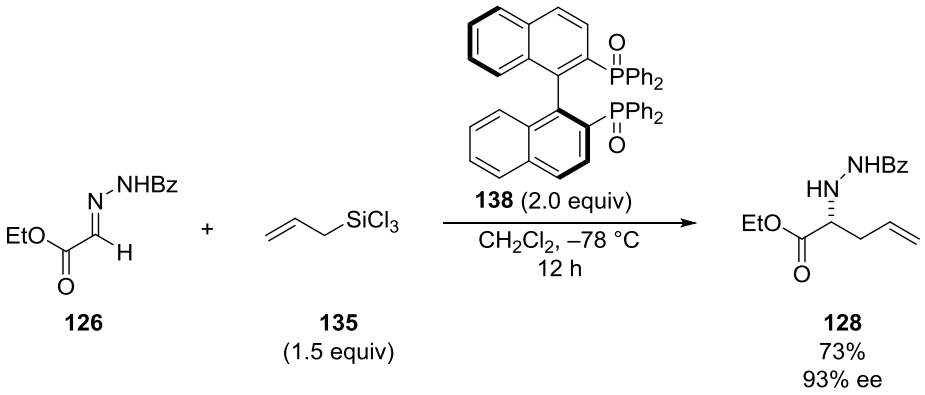
Scheme 2.6: Copper-diamine-catalysed allylation of iminophosphonates[106]

Other allylsilane-based methodologies used allyltrichlorosilane (**135**) as the allylating agent, and in these cases, Lewis basic species were employed (often sulfoxides or *N*-oxides) in order to promote the reaction. In 2003, Kobayashi and co-workers reported the addition of allyltrichlorosilane (**135**) to *N*-benzoylhydrazones promoted by simple chiral sulfoxide **137**. These conditions gave the resulting homoallylic amine **136** in good yields and excellent enantiomeric excesses. These processes are limited by the need of an acid scavenger, in the form of 2-methyl-2-butene to suppress the racemisation of sulfoxide **137** (Scheme 2.7).[107] One problem with this methodology is the superstoichiometric loading of the chiral sulfoxide. Despite this, it was shown that the sulfoxide can be recovered after the reaction in 90% yield with minimal erosion of enantiopurity.



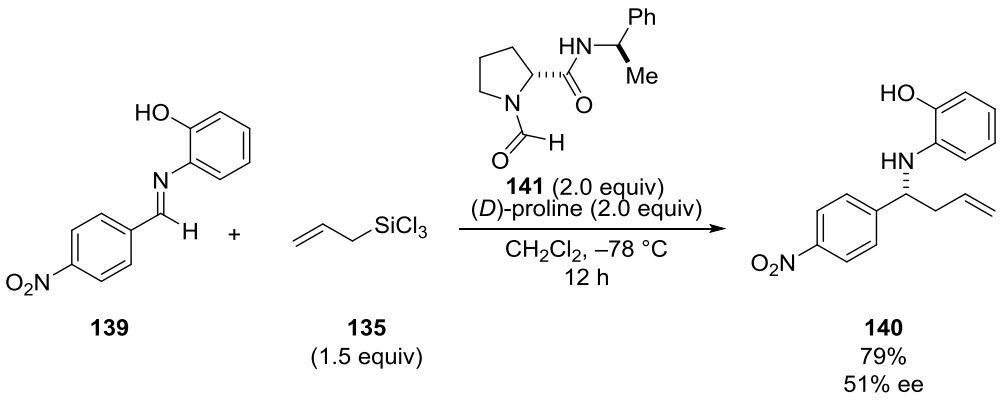
Scheme 2.7: Chiral sulfoxide assisted allylation of *N*-benzoylhydrazones[107]

The chiral sulfoxide functions by coordinating with the allyltrichlorosilane (**135**) to activate this silicon species which then reacts with the electrophile in a stereospecific manner to give an enantioenriched homoallylic amine. Fernandez[108-110] and others[111,112] have advanced this chemistry and demonstrated that a wide range of chiral sulfoxides can successfully promote the allylation of *N*-benzylhydrazones. This field was furthered by Kobayashi using phosphine oxide **138** rather than a sulfoxide additive in the allylation of α-hydrazone esters (Scheme 2.8).[113]. These additives also suffer from requiring superstoichiometric quantities, although they also can be recovered afterward in good yields with no loss of optical purity.



Scheme 2.8: Chiral phosphine oxide-assisted allylation of α-hydrazone esters[113]

The group of Tsogoeva have successfully used other imines such as **139** in enantioselective allylation reaction using amino acid based promoters; however, only moderate enantioselectivities have been achieved using these systems (Scheme 2.9).[114]

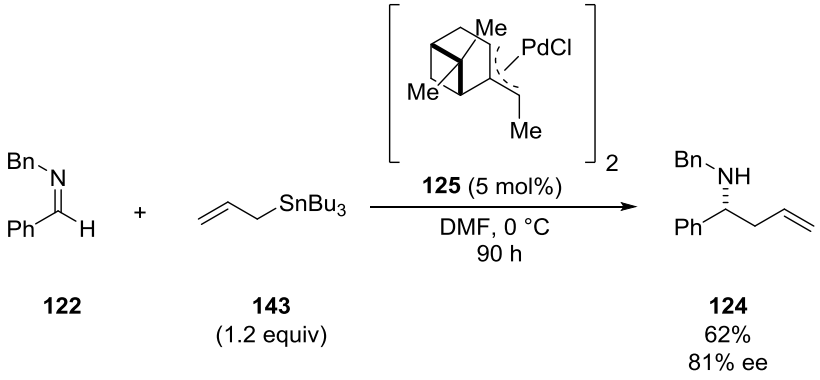


Scheme 2.9: Amino-acid promoted allylation of imines[114]

Although allylsilanes are excellent allylating agents, their performance in asymmetric allylations has been somewhat underwhelming. In order to reliably attain enantiomeric excesses over 90% with a large substrate scope, the electrophile was often limited to hydrazones. However, the requirement of superstoichiometric sulfoxide promoters is the biggest limiting factor, and as a result, currently no truly catalytic process involving the asymmetric addition of allylsilanes to a wide range of imines has been reported.

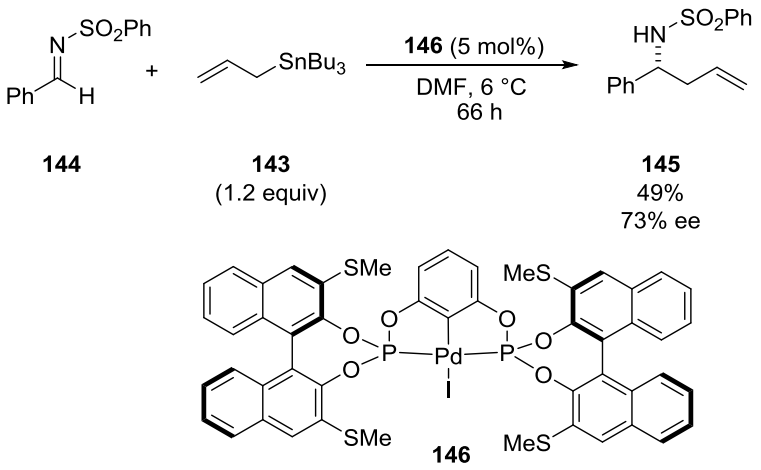
2.2.2 Nucleophilic Allylation of Imines Using Allylstannanes

Allylstannanes have also been investigated and found to be suitable reagents for the enantioselective allylation of imines. The first reported enantioselective addition using allylstannanes was by the group of Yamamoto in 1998. They reported the palladium-catalysed allylation of *N*-benzylimine **122** in moderate yields and good enantioselectivities (Scheme 2.10).[115] They found it was necessary to use chiral π-allylpalladium catalyst **125** in order to attain acceptable enantioselectivities. The corresponding reaction with chiral bisphosphine-palladium species were found to give a racemic product. It was later found that the addition of exactly one equivalent of water helped the reaction become more reliable and reproducible.[116]



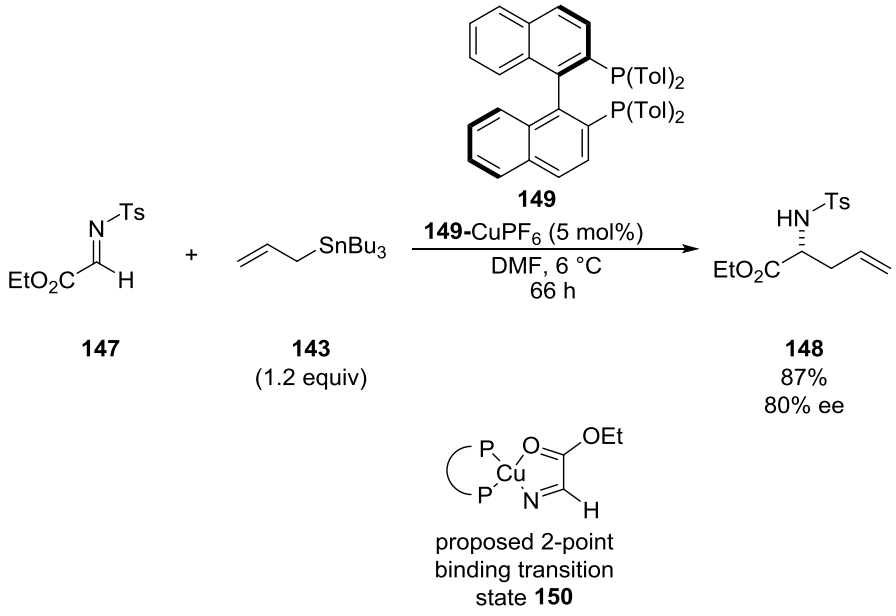
Scheme 2.10: The palladium-catalysed addition of tributylallylstannane[115]

Szabo and co-workers also reported the successful allylation using a chiral palladium catalyst, and in this case they used pincer complex **146** in order to attain moderate to good enantioselectivities with a range of sulfonamide imines (Scheme 2.11).[117]



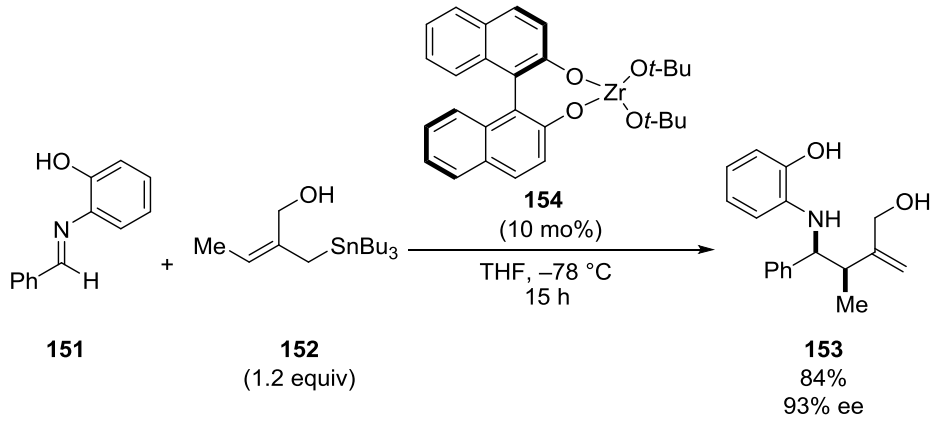
Scheme 2.11:Palladium pincer complexes in the allylation of imines[117]

Other metals were also found to catalyse similar reactions. Jørgensen reported the use of a copper catalyst along with bisphosphine ligands to allylate iminoesters. With the use of allylstannanes it was possible to attain the product **148** in excellent yield and a good enantiomeric excess. (Scheme 2.12).[118] Mechanistically, they proposed a two point binding of the chiral copper species between the nitrogen and oxygen of the ester to form rigid structure **150** that is then attacked preferentially from a single face to induce enantioselectivity.



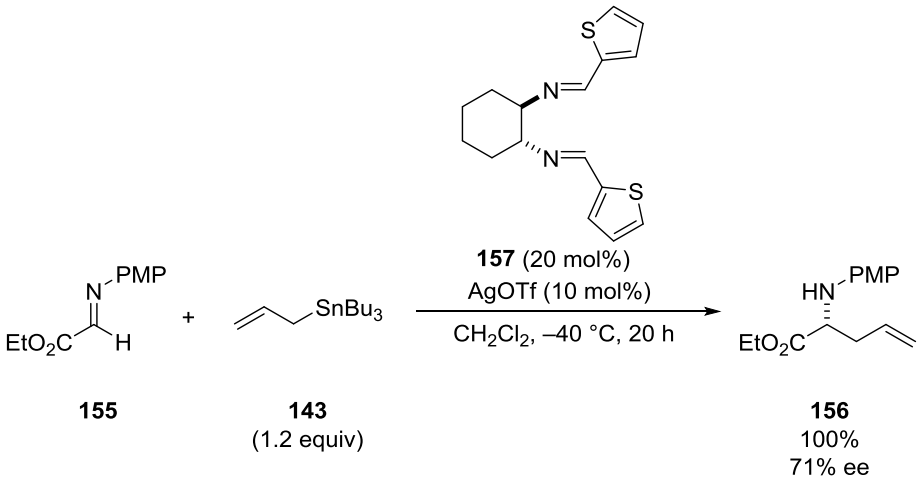
Scheme 2.12: Copper-catalysed allylation of iminoesters[118]

In 2001 Kobayashi developed a zirconium-catalysed enantioselective allylation that provided the products in a higher than 90% ee for the first time. This methodology relied on chiral complex **154** formed from BINOL and Zr(O*t*-Bu)$_4$ to provide the homoallylic amine in greater than 90% ee for a range of aromatic imines (Scheme 2.13).[119] However, this methodology was somewhat limited in substrate scope, and in order to attain these excellent results, imine **151** required the unusual *ortho*-phenol protecting group and an unprotected alcohol in allylstannane **152**. These requirements were rationalised by proposing both alcohol groups coordinated with the zirconium, not only bringing the two substrates close to each other, but also allowing them to combine in a stereoselective manner. If either of the substrates did not feature a free alcohol then the enantiomeric excesses were greatly diminished.



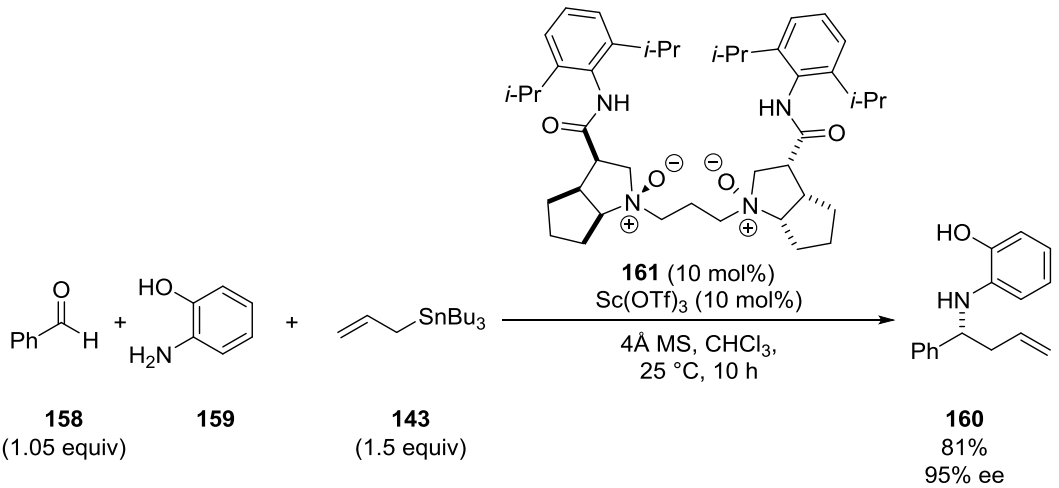
Scheme 2.13: Zirconium-catalysed allylation of imines[119]

Work by the group of Benaglia illustrated the ability of silver to catalyse the allylation of iminoester **155** with allyltributyl stannane (Scheme 2.14).[120] Utilising a silver-chiral diimine catalytic system the homoallylic aminoester products **156** were formed in up to 71% ee. A wide range of chiral backbones were analysed and of these, ligand **157** featuring two thiophene moieties was optimal for the transformation.



Scheme 2.14: Silver-catalysed allylation of iminoesters[120]

In 2008, Feng and co-workers reported a three-component asymmetric allylation involving a scandium complex alongside *N*-oxide ligand **161** (Scheme 2.15).[121] This work featured the *in situ* formation of an imine *via* the condensation of aldehyde **158** and 2-aminophenol (**159**), which can then co-ordinate with the chiral scandium species *via* the phenolic hydroxyl group, before undergoing allylation. Interestingly, subjecting the pre-formed pure aldimine to identical reaction conditions resulted in a drop of enantioselectivity to 80%, illustrating that the *in situ* formation of the imine is important to the reactions. However, the authors did not propose an explanation for this observation.



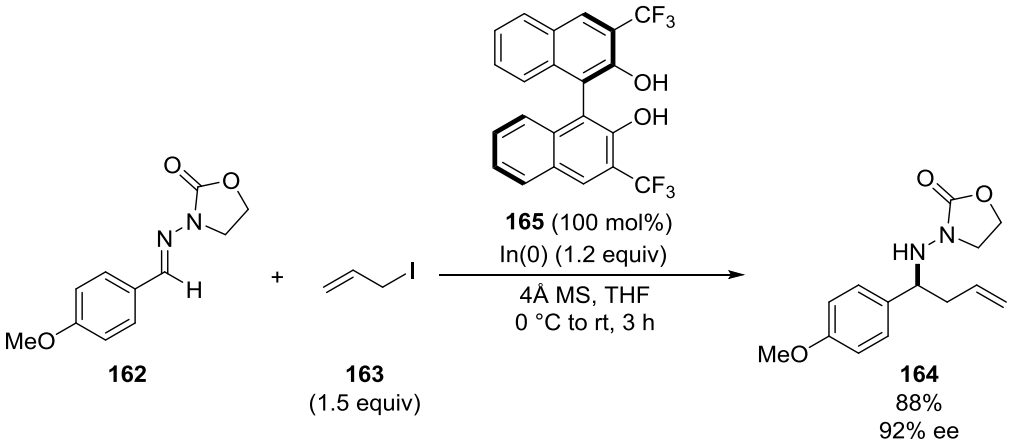
Scheme 2.15: Scandium-catalysed 3-component allylation[121]

Much like allylsilanes, allylstannanes have proven to be effective allylating reagents for amines, but a truly general catalytic asymmetric process has not been reported. For many reported methodologies, enantiomeric excesses were moderate. For other work where enantiomeric excesses were greater 90% have been obtained, a limited scope of both electrophile and nucleophile are required.

2.2.3 Nucleophilic Allylation of Imines using Allyl Halides

Allyl halides are one of the most common sources of the allyl functionality, these commercially available electrophilic substrates can readily transformed into nucleophilic species *via* the formation of Grignard reagents and zincates. However, these highly nucleophilic reagents are often incompatible with various functional groups and there have been no reports of an asymmetric allylation of an imine using such reagents. The stoichiometric formation of other allylmetal species, notably allyl-indium species, is far milder, allowing investigation into asymmetric variants.

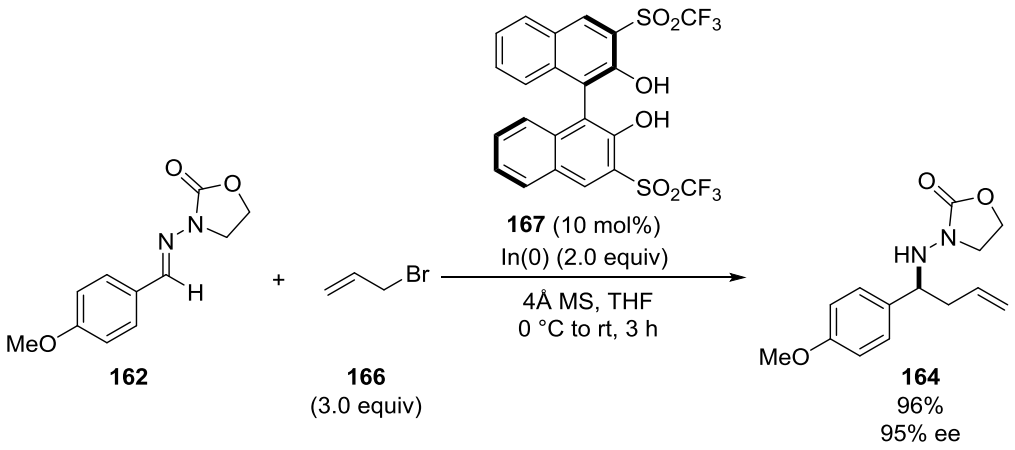
In 2005, Cook and co-workers reported the allylation of hydrazones using allyliodide (**163**) in the presence of indium and a chiral ligand (Scheme 2.16).[122] Unfortunately it was found that the chiral ligand was required in stoichiometric quantities in order to obtain higher enantioselectivities.



Scheme 2.16: Indium-mediated addition of allyliodide[122]

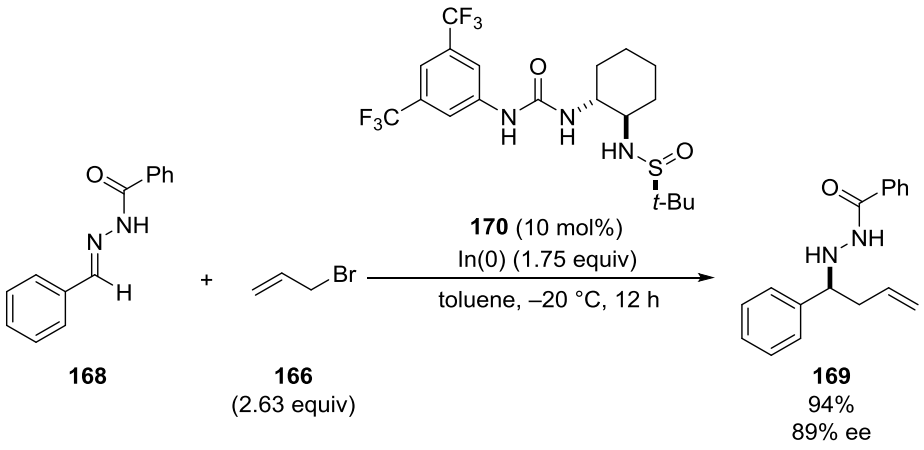
Further studies by Cook and Lloyd-Jones discovered that not only was allylbromide (**166**) a superior allylating agent compared to allyliodide (**163**) but also modifications

at the 3 and 3' positions of the BINOL-based additive allowed for sub-stoichiometric quantities to be used and excellent results were still obtained (Scheme 2.17).[123]



Scheme 2.17: Sub-stoichiometric chiral ligand[123]

Jacobsen reported that chiral urea-based catalysts could also successfully catalyse the asymmetric addition of allylindium species (Scheme 2.18).[124] As well as being able to allylate aromatic hydrazones, the catalytic system was also shown to work for aliphatic hydrazones too. Furthermore, Jacobsen illustrated that the reaction could be conducted on a 10 mmol scale (2.24 g of imine) with minimal reduction of yield and enantioselectivity.



Scheme 2.18: Urea-catalysed allylation of hydrazones[124]

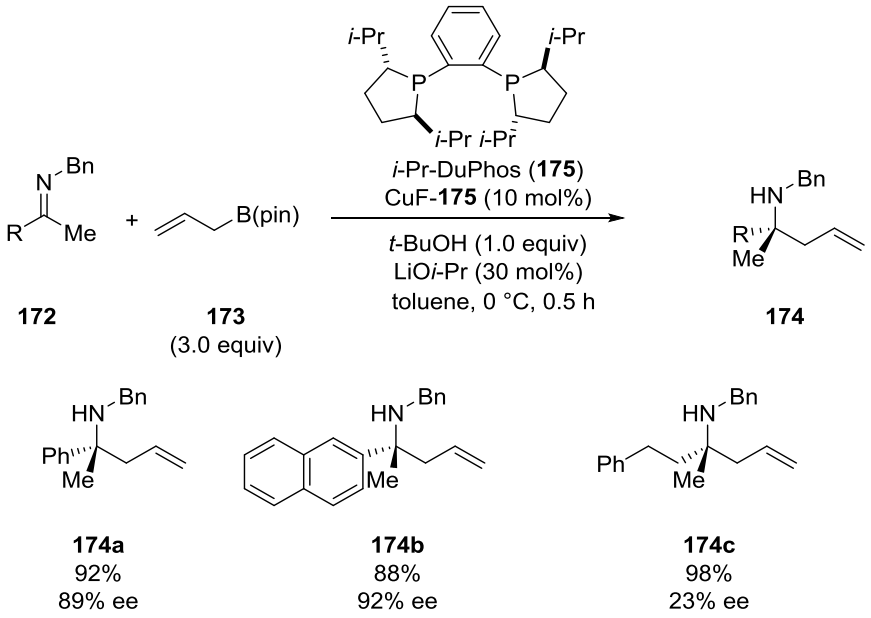
Despite these advances,* the addition of allyl halides is still limited to hydrazones and requires superstoichiometric equivalents of indium metal.

2.2.4 Nucleophilic Allylation of Imines using Allylboron Reagents

Given the difficulty in handling trichloroallylsilanes, the limitations of allyl halides and the toxicity of allylstannanes, research began to focus on alternative allylating reagents, and allylboron reagents became of interest. Organoboron reagents are popular due to their stability in air, ease of handling, functional group tolerance and usually have low toxicity.

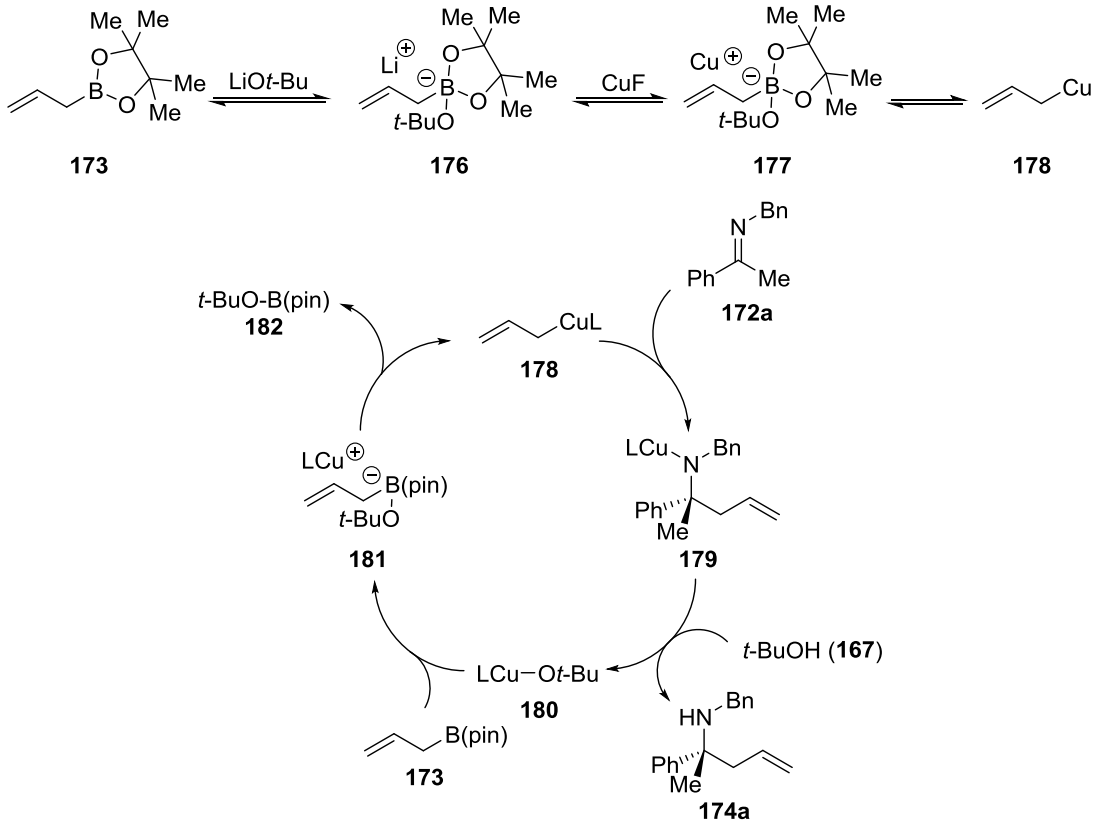
The first reported catalytic enantioselective allylation using an allylboron reagent was in 2006 by the group of Shibasaki (Scheme 2.19).[125,126] Using copper-catalysis and conditions previously developed and applied to the allylation of ketones,[86] it was possible to allylate *N*-benzyl protected ketimines with allylboronic acid pinacol ester (**173**) asymmetrically using the chiral bisphosphine ligand, *i*-Pr-DuPhos (**175**). A range of aromatic ketimines were allylated with good enantioselectivities **174a** and **174b**. However, aliphatic ketimine **174c** gave poor enantioselectivity.

* An Indium-mediated allylation was reported: Kim, J.-S.; Jang, D.O. *J. Am. Chem. Soc.* **2010**, *132*, 12618-12619, however, it was later retracted over concerns about the true structure of the catalyst: Kim, J.-S.; Jang, D.O. *J. Am. Chem. Soc.* **2014**, *136*, 11850-11850.



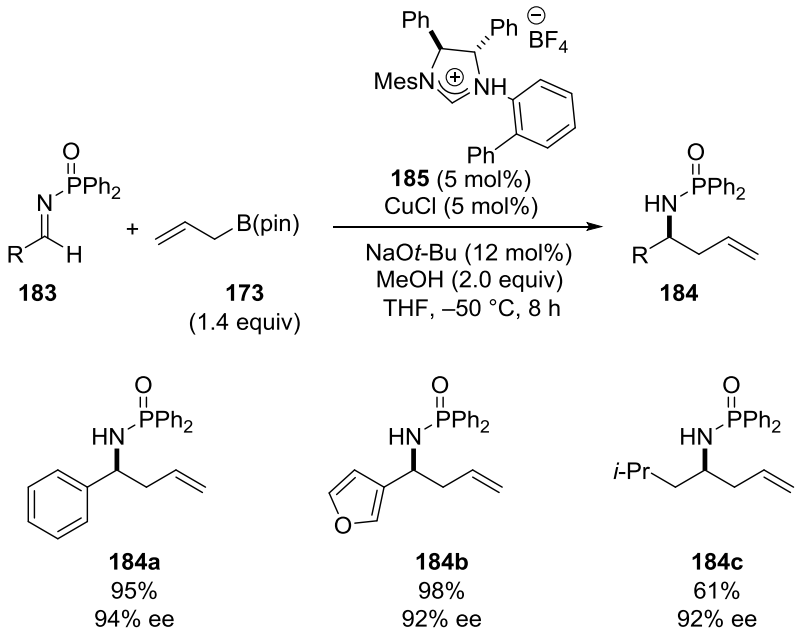
Scheme 2.19: First catalytic enantioselective allylation of imine using allylboron reagents[109,110]

It was demonstrated that 30 mol% of LiO*i*-Pr was essential for the reaction to proceed. Further mechanistic and NMR analysis determined that activation of the boronic ester by the LiO*i*-Pr formed lithium-boronate **176** which, after a cation swap forms **177**, transmetallates with copper to form nucleophilic allylcopper species **178**. Allylcopper species **178** then attacks ketimine **172a** to give homo-allylic amine **174a**. It is believed the LiO*i*-Pr is only used to start the catalytic cycle, and afterwards, *t*-BuOH forms CuO*t*-Bu **180** which also mediates transmetallation and is the main catalytically active copper species (Scheme 2.20).[109,110]



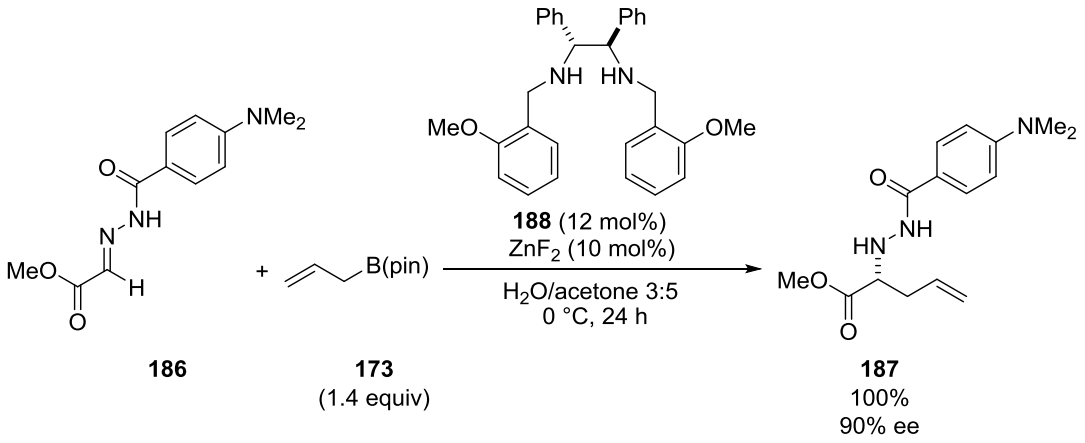
Scheme 2.20: Mechanism of copper-catalysed allylation

The ability of copper to function as a catalyst in allylation reactions was also utilised by Snapper and Hoveyda in 2011 (Scheme 2.21).[127] Using *N*-heterocyclic carbene ligands ligated to copper, it was possible to allylate diphenylphosphinoylimines (DPP-imines) with allylboronic acid pinacol ester **173**. A range of aromatic **184a**, heteroaromatic **184b** and aliphatic **184c** imines were successfully allylated achieving enantiomeric excesses of up to 97%.



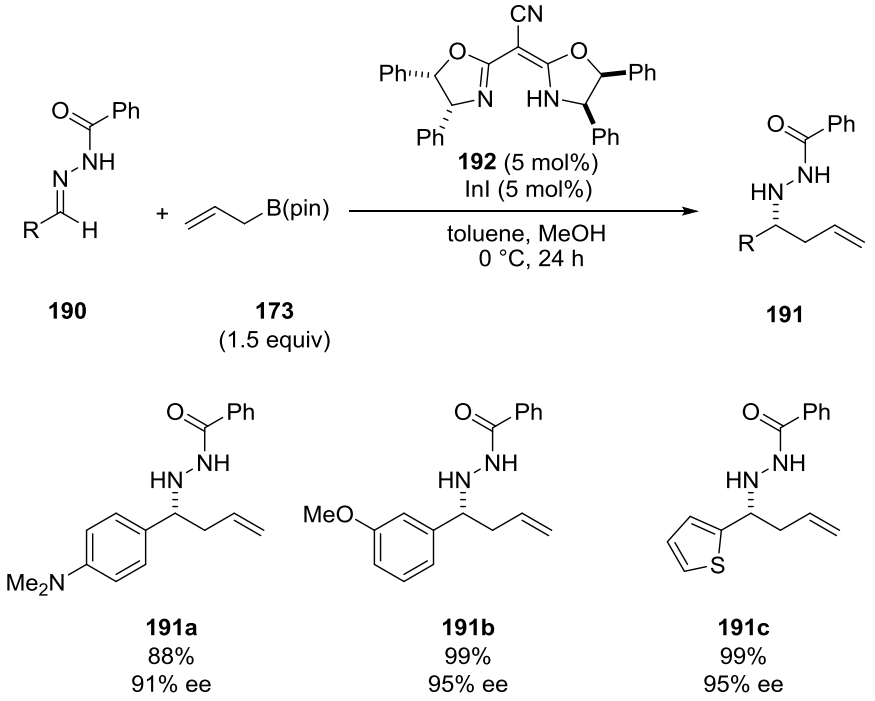
Scheme 2.21: NHC-copper-catalysed allylation of DPP-imines[127]

Other transition metals have also proven to be effective catalysts for allylation of imines with allylboron reagents. Kobayashi reported the zinc-catalysed allylation of hydrazones in aqueous media using a chiral diamine ligand **188**. The allylation proceeded smoothly to give homoallylic amine **187** in quantative yield and 90% ee (Scheme 2.22).[128] Due to the aqueous media, regeneration of the catalyst requires the formation of zinc hydroxide, and attempts to replicate this reaction using $Zn(OH)_2$ rather than ZnF_2 were successful with good yield and very little loss of enantioselectivity.



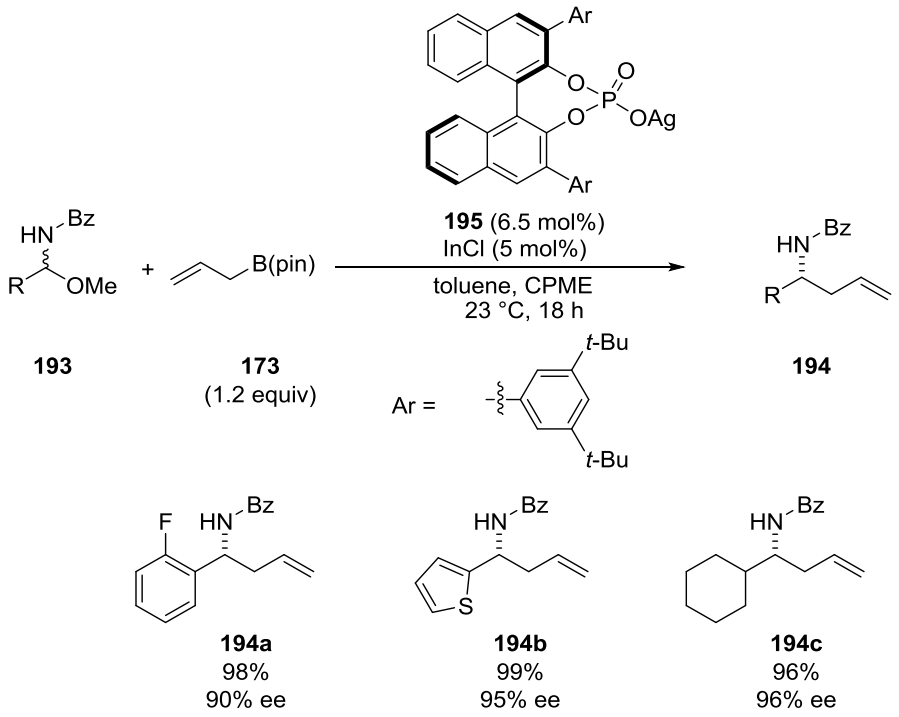
Scheme 2.22: Zinc-catalysed allylation of hydrazones[128]

In 2010, the group of Kobayashi reported the enantioselective indium-catalysed allylation of hydrazones with allylboron species **173** (Scheme 2.23)[129]. Complexation of indium with chiral ligand **192** resulted in formation of a chiral indium species, which then underwent Lewis base promoted transmetallation with **173** to generate a chiral allylindium species, leading to the enantioselective allylation. The methodology was applied to a wide range of aromatic (**191a**, **191b**) and heteroaromatic (**191c**) hydrazones, resulting in high yields and high enantioselectivities throughout.



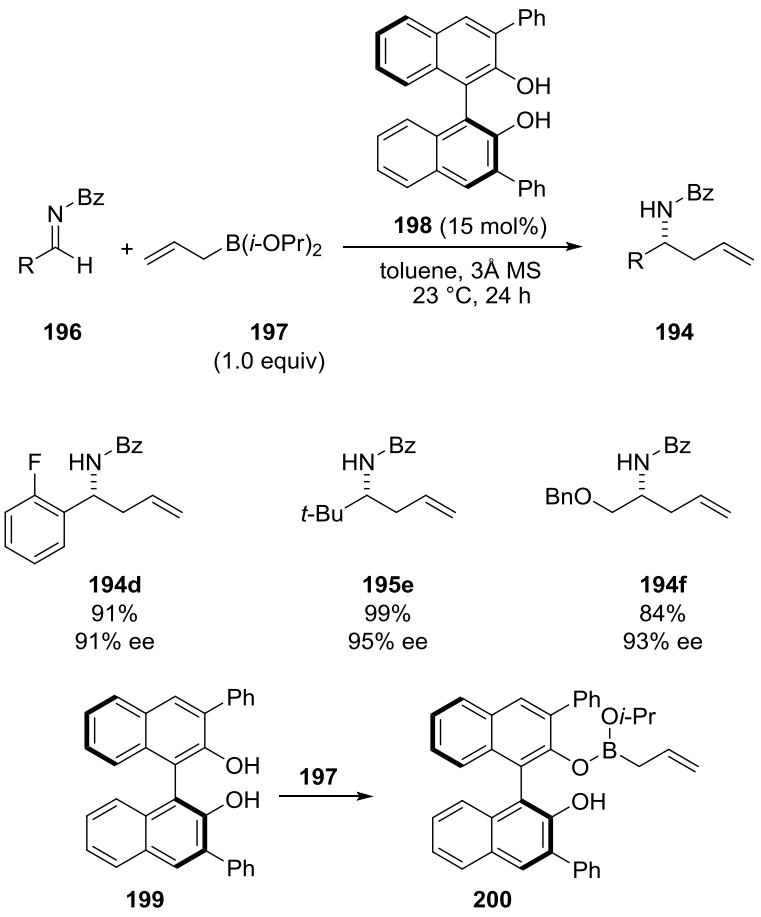
Scheme 2.23: Enantioselective In(I)-catalysed allylation of hydrazones[129]

This work was further extended by the application of indium and a chiral silver counterion in the allylation of aminals (Scheme 2.24).[130] It was shown that using a racemic aminal **193** along with boron reagent **173** it was possible to prepare enantioenriched allylation products such as **194a-c** by using InCl and a chiral silver salt. It is proposed the aminal undergoes loss of methanol to form an imine *in situ* and is co-ordinated to the chiral silver salt. This species then undergoes allylation *via* the addition of allylindium to form the allylated products in comparable yields and enantioselectivities to their previous work.



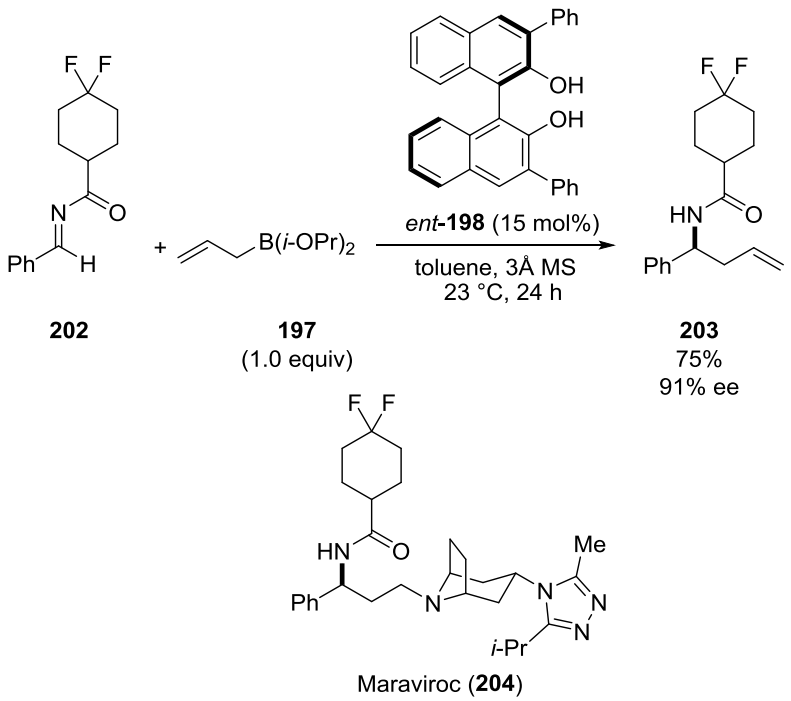
Scheme 2.24: Resolution of racemic aminals using indium catalysis[130]

Although transition metals are often catalysts for asymmetric allylations, organocatalysts have also been utilised. In 2007 Schaus and co-workers reported the allylation of acyl imines using chiral diol catalysis (Scheme 2.25).[131] Using allylboronic acid *iso*-propoxy ester **197** and a chiral BINOL catalyst **198** it was possible to allylate a wide range of aromatic (**194d**) and aliphatic (**194e-f**) acyl imines with excellent yields and enantioselectivities. By utilising the labile *iso*-propoxy ester, it was proposed that transesterification occurred to form chiral boron species **200**, although NMR evidence suggested only one *iso*-propoxy group was lost. Once this chiral allylboron species was formed, allylboration occurred, followed by liberation of the diol to regenerate the catalytic species.



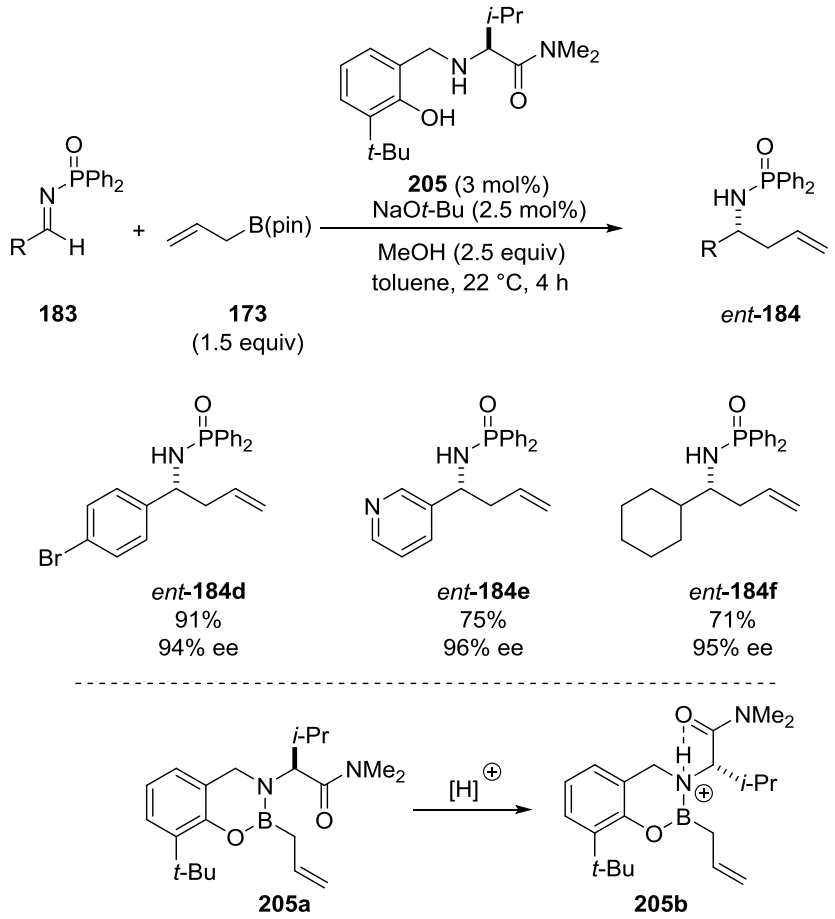
Scheme 2.25: BINOL-catalysed allylation of acyl imines[131]

The group of Schaus illustrated the usefulness of his methodology by applying it in the total synthesis of the anti-HIV-drug Maraviroc (**204**).[131] Following the rapid synthesis of imine **202**, allylation using **197** and catalyst *ent*-**198** resulted in the formation of product **203** in 75% yield and 91% ee. Two further high-yielding steps furnished Maraviroc in only five steps from commercially available materials (Scheme 2.26).



Scheme 2.26: Total synthesis of Maraviroc *via* a enantioselective allylation[131]

In 2013, Snapper and Hoveyda published the allylation of DPP-imines using a simple and versatile organocatalyst **205** (Scheme 2.27).[132] By only employing catalyst **205** and catalytic amounts of NaO*t*-Bu, it was possible to allylate a wide range of DPP-imines in good yields and excellent enantioselectivities. They propose the phenol group and the nitrogen of the catalyst co-ordinates with the boron reagent to form chiral boron reagent **205a**. Protonation of this species leads to intermediate **205b**, featuring an intramolecular hydrogen bond. This hydrogen bond is proposed to increase the Lewis acidity of the boron, and facilitates both imines binding and allyl transfer. Also, the H-bonding forms a more rigid species thus is proposed to improve stereoselectivity.[132]



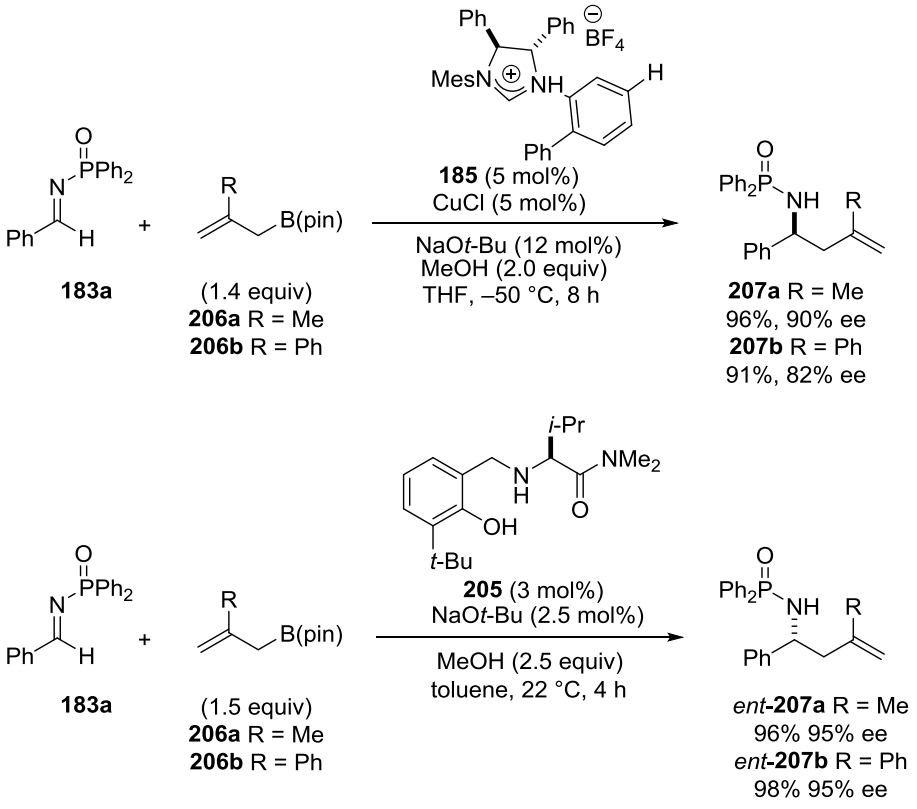
Scheme 2.27: Organocatalysed allylation of DPP imines[132]

2.2.5 Challenges Remaining in the Asymmetric Nucleophilic Allylation of Imines

Despite the considerable research on the asymmetric allylation of imines with allylboron reagents, there are still some outstanding challenges for the chemistry community to address. Similar to additions to ketones, the addition of nucleophiles to ketimines tends to be more difficult than the corresponding addition to aldimines. Additionally, the generation of enantioenriched quaternary centres is still of great interest.[133] Only the publication by Shibasaki in 2006[125] using copper catalysis reported successful additions of allylboron reagents to ketimines to generate quaternary stereocentres. Shibasakai only reported the addition of the simple allyl moiety and made no mention of reactions involving more highly substituted allyl reagents. All subsequent reports have exclusively focussed on the allylation of aldimines, with no reports of corresponding additions to ketimines. Therefore, it is

still potentially useful to develop a methodology that allows the allylation of ketimines, especially when using more highly substituted allyl reagents, which was unprecedented at the commencement of the project.

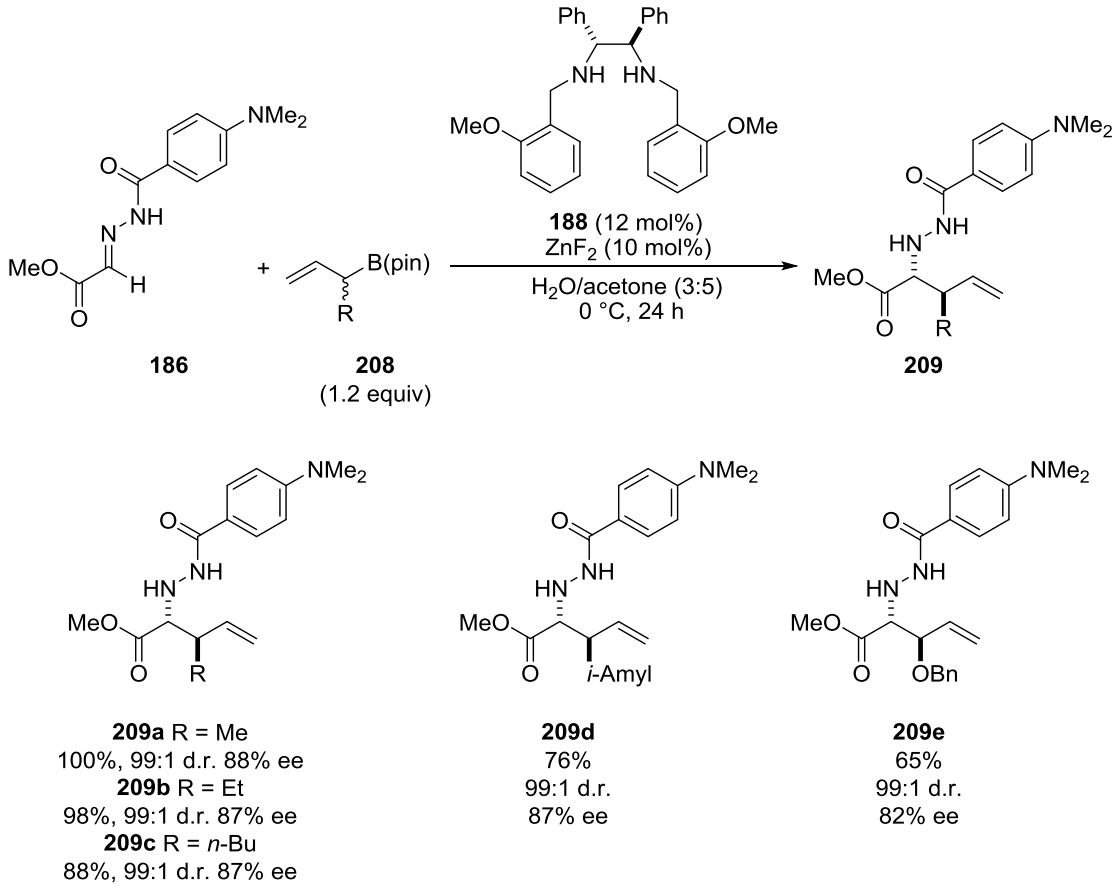
An asymmetric allylation reaction not only aims to synthesise an enantioenriched product, it is also advantageous to rapidly increase molecular complexity during the formation of the new carbon-carbon bond. One possible method for the creation of such complexity involves the use of more highly substituted allylboron reagents to allow the formation of more complex products. The least complicated manner to increase the complexity of the allylboron reagent is to use allyl species **206** with substitution at the *β*-position. In 2011 Snapper and Hoveyda reported the use of both *β*-methyl **206a** and *β*-phenyl **206b** species along with a chiral copper-NHC catalyst **185**t to successfully generate homoallylic amine products **207a-b** with substitution in the 2-position in excellent yields and %ee.[127] This work was successfully repeated 2 years later using organocatalyst **205** as the catalyst (Scheme 2.28).[132]



Scheme 2.28: Addition of *β*-substituted allylboron species[127,132]

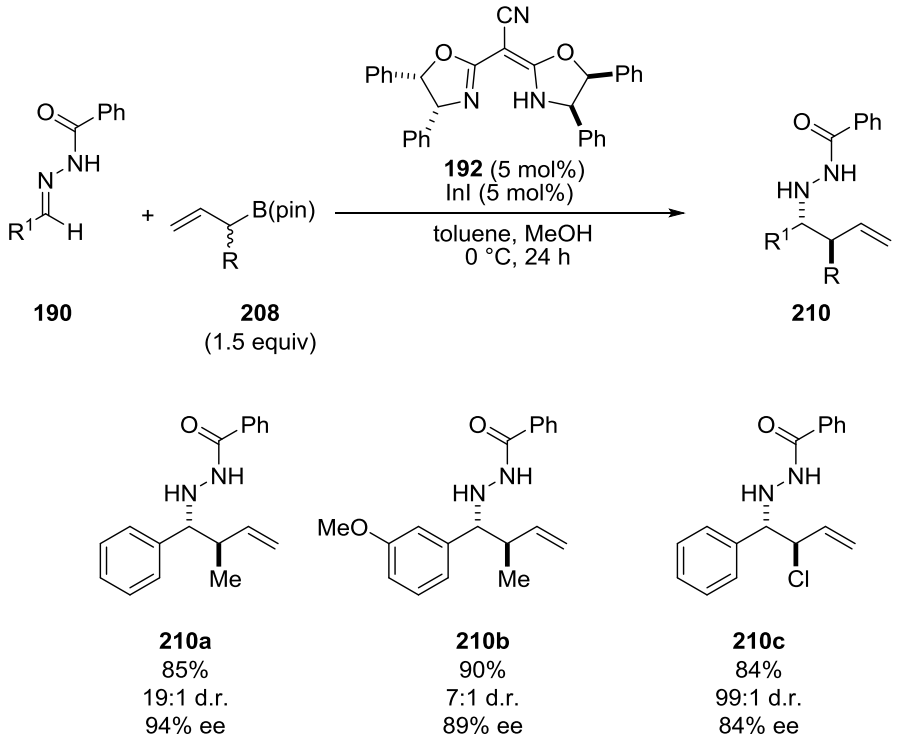
Allylboron species with substitution at the α-position present two further challenges, and firstly if there is only mono-substitution or substitution by two different groups, the boron reagent will have a stereocentre. Whether this allylboron reagent is racemic or enantioenriched may have a pronounced outcome of the stereochemistry of the product. The resultant product may feature an additional stereocentre, and thus the relative stereochemistry as well as the absolute stereochemistry must also be considered.

Kobayashi's work involving a zinc catalyst investigated the addition of racemic α-substituted allylboron species with great success. A range of simple alkyl substituted species **208** furnished the corresponding α-substituted products **209a-c** exclusively as the *anti*-diastereomer and with high enantiomeric excess. Other, branched or more functionalised allylborons also gave similarly excellent results **208d-e** (Scheme 2.29).[128]



Scheme 2.29: Zinc-catalysed addition of α-substituted allyboron species[128]

Kobayashi and co-workers also demonstrated that α-methyl and α-chloro allylboron species were excellent nucleophiles for the indium-catalysed allylation of hydrazones (Scheme 2.30).[129] Both these reagents led to the formation of the α-substituted products **210a-c** in high yields and enantiomeric excesses. The diastereomeric ratios for these reactions were good, but not as impressive as in the zinc-catalysed work.

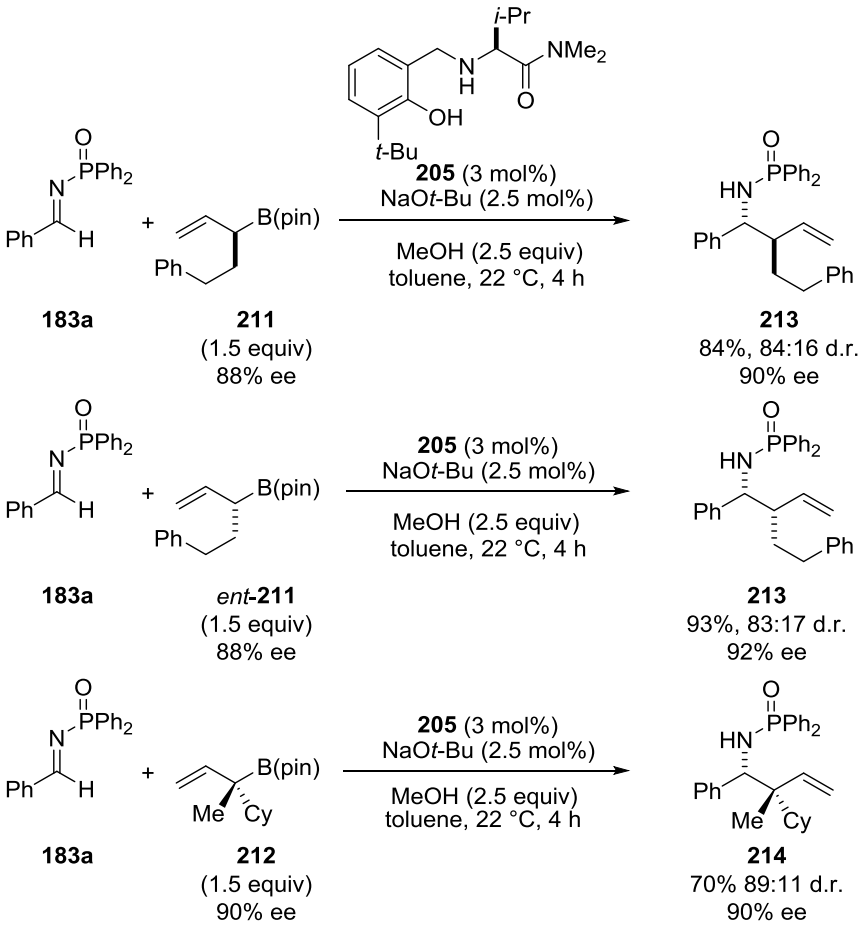


190 **208** (1.5 equiv) **210**

210a	**210b**	**210c**
85%	90%	84%
19:1 d.r.	7:1 d.r.	99:1 d.r.
94% ee	89% ee	84% ee

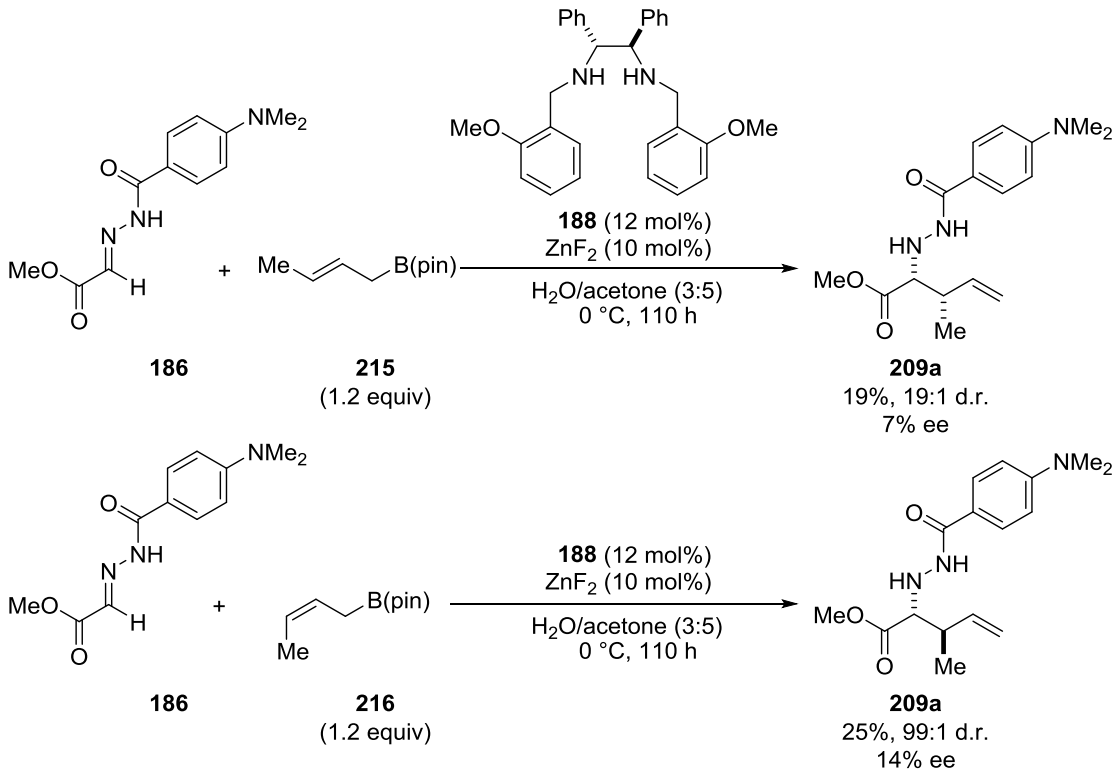
Scheme 2.30: Indium-catalysed addition of α-substituted allyboron species[129]

Hoveyda and Snapper took a different approach in their work, by using an enantioenriched allylboron species, they attempted to investigate whether the chiral catalyst had any effect on the enantioenrichment. Interestingly, a complete inversion of stereochemistry at the α-position with retention was observed, they propose this occurs due to a cyclic transition state during the transfer of the allylboron to catalyst **205** (Scheme 2.31).[132]



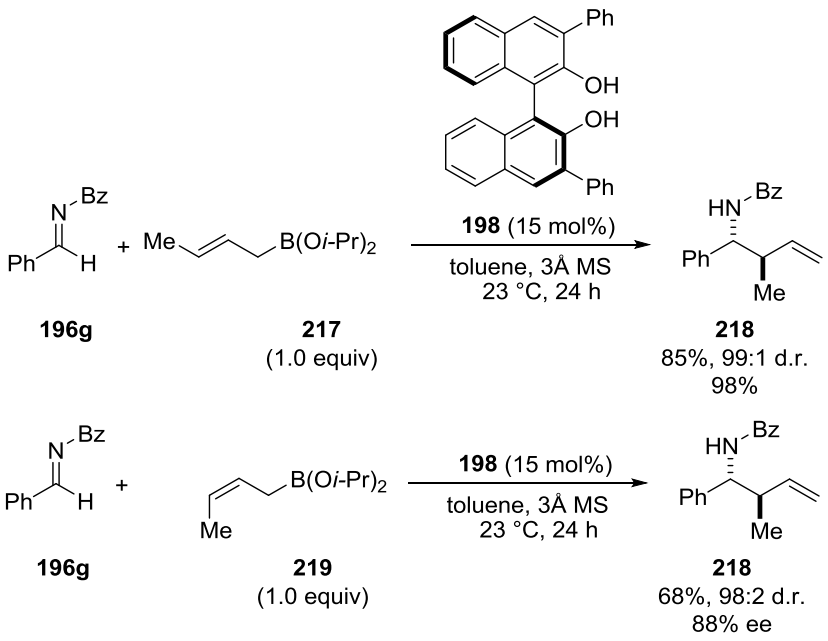
Scheme 2.31: Inversion of enantioenriched allylboron species[132]

Attempts to utilise allyboron reagents that feature γ-substitution have also proved problematic; these types of species pose similar issues with α-substituted allylboron reagents, namely the formation of a second stereocentre and the nature of the olefin, either *cis* or *trans*, can lead to the formation of the opposite *anti*- and *syn*-diastereomers. Kobayashi and co-workers reported such an observation when allylating hydrazone **186a** with (*E*)-crotylboronic ester **215** and (*Z*)-crotylboronic ester **216** (Scheme 2.32).[105] Species **215** gave the *syn*-product **209a** in a diastereomeric ratio of 19:1; however, even after prolonged reaction time only a low yield (19%) was obtained. Even more problematic was that the enantiomeric excess of the major diastereomer was only 7%. Similar results, 25% yield, 14% ee, and 99:1 d.r., was observed with (*Z*)-crotylboronic ester **216**, which gave the opposite *anti*-product as the major diastereomer. The unusually low enantiomeric excess was unexplained.



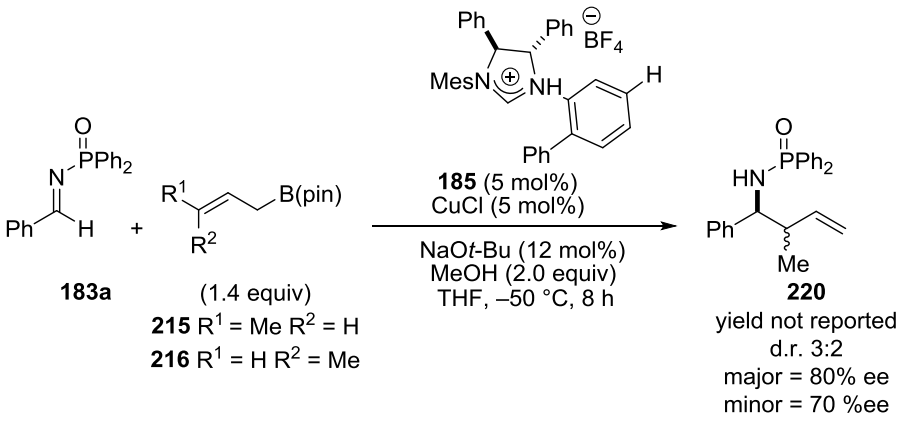
Scheme 2.32: Zinc-catalysed crotylation of hydrazone **186**[105]

Conversely, a completely opposite effect was observed by Schaus and co-workers when performing chiral diol-catalysed allylation of acyl imine **186**. Regardless of whether (*E*)-crotyl species **215** or (*Z*)-crotyl species **216** was used, only the corresponding *anti*-product was recovered in high yield, diastereomeric ratio and enantiomeric excess (Scheme 2.33).[131] This illustrated that under these conditions the stereochemical information contained within the olefin is irrelevant, and the relative stereochemistry was determined *via* another parameter.



Scheme 2.33: Diol-catalysed crotylation of imine **196g**[131]

The groups of Snapper and Hoveyda also reported the asymmetric crotylation of imines under their copper-NHC catalysis conditions (Scheme 2.34).[127] Although the attempted crotylation proceeded smoothly to give enantiomeric excesses of 70% ee and 80% ee, the resultant product only had a diastereomeric ratio of 3:2 and it was not possible to determine which diastereomer was the major diastereomer.

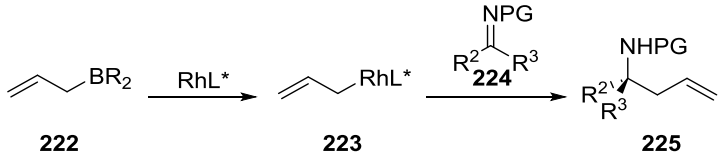


Scheme 2.34: Poorly-diastereoselective crotylation of imine **183a**[127]

Apart from these three examples, there had been no other successful asymmetric crotylations of aldimines using allyboron reagents and no reports at all of the crotylation of ketimines.

3.0 Aims

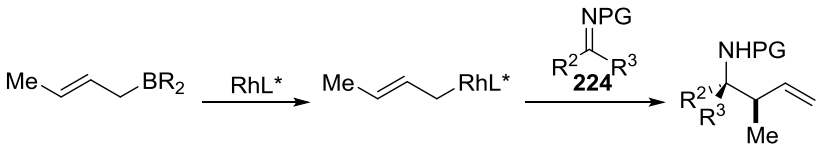
Given the Lam group's experience and expertise in asymmetric rhodium-catalysed transformations[34-36,43] and in allylation reactions,[134] it was envisaged that a rhodium-catalysed asymmetric allylation of imines could be developed to complement the current literature. By combining transmetallation and the nucleophilicity of rhodium(I)-allyl species[135] it was hoped that allylboron species **222** could form chiral allylrhodium species **223** which could then undergo nucleophilic attack on imine **224** to form enantioenriched homoallylic amine **225** (Scheme 3.1).



222 **223** **225**

Scheme 3.1: Proposed rhodium-catalysed asymmetric allylation

It was hoped that not only would a rhodium-catalysed asymmetric allylation be developed, but that challenges remaining in the field that had not been solved using previously reported catalytic systems could also be surmounted. Importantly, the allylation of ketimines, especially allylation involving allyl species with higher degrees of substitution, was a major goal, along with the *anti*- and *syn*- selective crotylation of both aldimines and ketimines using (*E*) and (*Z*) crotyl reagents respectively.



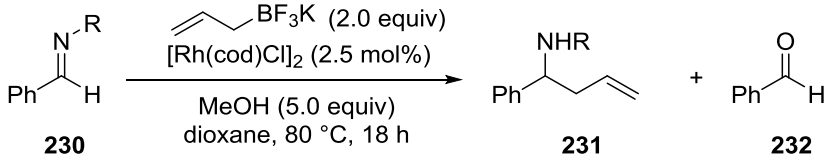
226 **227** **228**

Scheme 3.2: Proposed rhodium-catalysed asymmetric crotylation reactions

4.0 Development and Optimisation of the Racemic Rhodium-Catalysed Addition of Allylboron Species to Cyclic Imines

Our investigations began with attempts to develop the racemic reaction, an achiral rhodium source, $[Rh(cod)Cl]_2$, along with conditions developed within the Lam group for the alkenylation of imines with trifluoroborate salts (dioxane, methanol)[58] were used to screen a range of imine electrophiles (Table 4.1).

Table 4.1: Screening of imines for racemic allylation

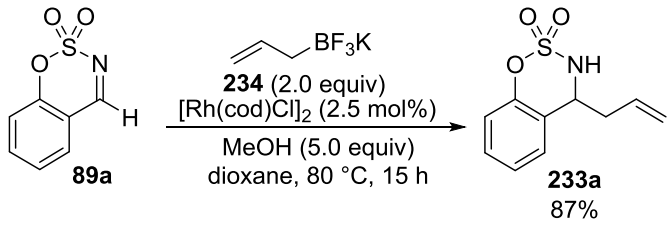


230 **231** **232**

Entry	R	Recovered Starting Material (%)[a]	**231** (%)[a]	**232** (%)[a]
1	Ph	>95	<5	<5
2	$P(O)Ph_2$	>95	<5	<5
3	SO_2NMe_2	85	5	10
4	Ts	60	25	15
5	Ns	42	28	30

[a] Conversion determined by ^{1}H NMR analysis of crude reaction mixture

Unsatisfactory results were obtained using *N*-phenyl or *N*-diphenylphosphinoyl imines, with only starting material recovered from the reaction mixtures (entries 1 and 2). However, with more activated imines such as *N*-SO_2NMe_2, *N*-tosyl, and *N*-nosyl imines, some homoallylic sulfonamide product **231** was observed as well as starting material, and benzaldehyde (**232**) (entries 3,4, and 5). Drawing inspiration from the alkenylation work,[58] the cyclic benzoxathiazine-2,2-dioxide **89a** was also subjected to the reaction conditions. Pleasingly allylation product **233a** was observed in almost quantitative conversion and isolated in 87% yield (Scheme 4.1).

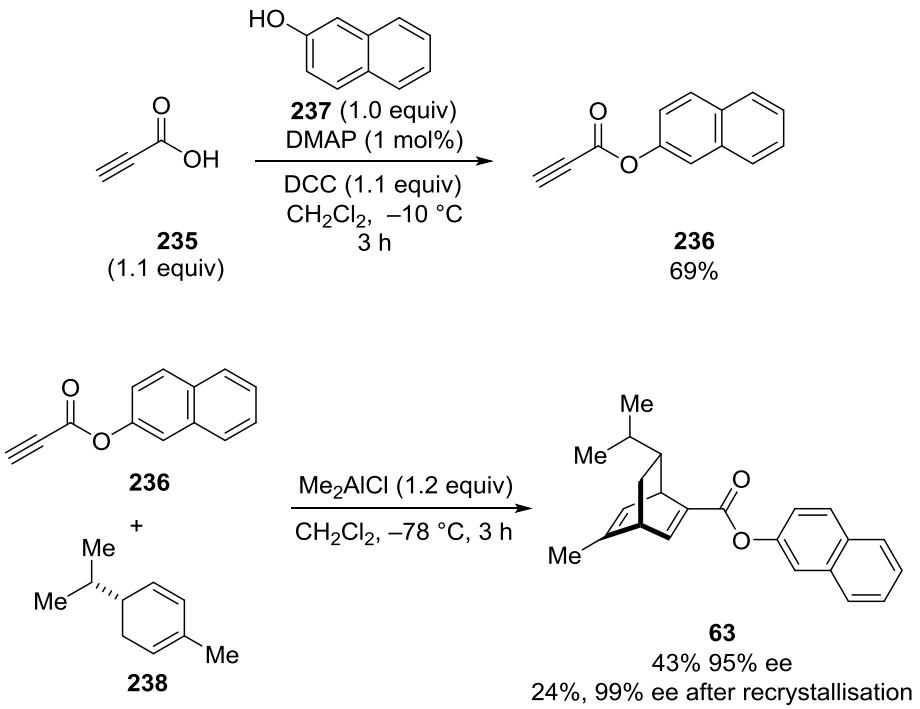


Scheme 4.1: The allylation of the cyclic benzoxathiazine-2,2-dioxide

Having synthesised and isolated the racemic product from the rhodium-catalysed addition of potassium trifluoroborate to benzoxathiazine-2,2-dioxide **89a**, attempts were focussed on investigating whether this process could be made into an enantioselective process.

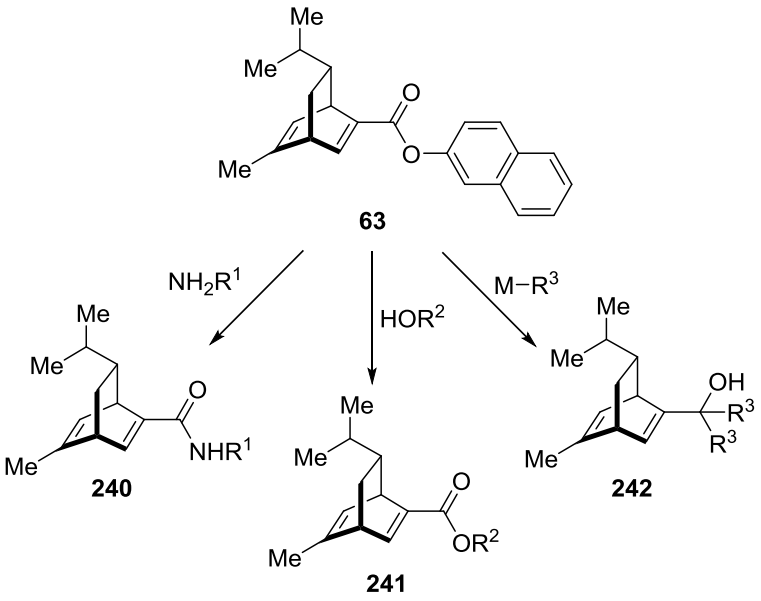
4.1 The Synthesis of Chiral Diene Ligands

The Lam group have a considerable interest in chiral dienes as ligands and have previously had success in enantioselective rhodium-catalysed additions of organoboron reagents using chiral diene ligated rhodium complexes.[34-36,43,58] Therefore, it was hypothesised that chiral dienes may lead to the enantioselective addition of potassium allyltrifluoroborate to cyclic imine **89a**. Although some chiral dienes are commercially available, many are not and it is necessary to synthesise them. One common family of chiral dienes developed by Hayashi are derived from the enantioenriched natural product *α*-phellandrene (**238**).[49] These bicyclo[2.2.2]octadienes are prepared *via* the aluminium-promoted Diels-Alder reaction between *α*-phellandrene (**238**) and the naphthyl ester of propiolic acid (**236**). Following the formation of the bicyclic scaffold, a recrystallisation furnishes (1*R*,4*R*,7*R*)-naphthalen-2-yl-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate (**63**) in greater than 99% ee (Scheme 4.2).



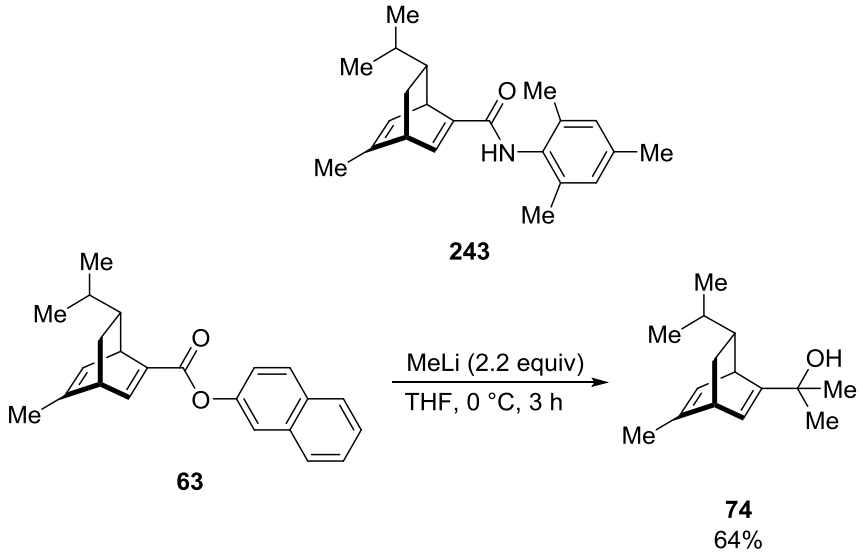
Scheme 4.2: Synthesis of bicyclo[2.2,2]octadiene **63**

From this optically pure scaffold, a range of chiral diene ligands can be synthesised *via* amidation, transesterification, and nucleophilic addition to give dienes featuring amides **240**, esters **241**, and alcohols **242** side-arms (Scheme 4.3).



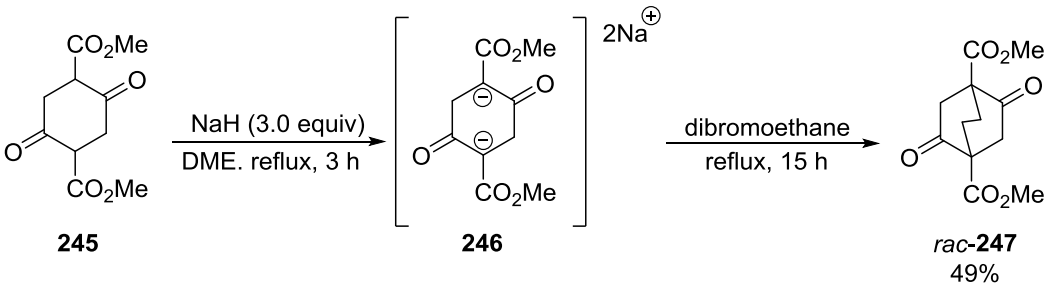
Scheme 4.3: The synthesis of chiral diene derivatives

As well as the naphthyl ester diene **63**, amide diene **243** had previously been synthesised within the Lam group. Diene **74** was prepared from the double addition of methyl lithium to **63** (Scheme 4.4).



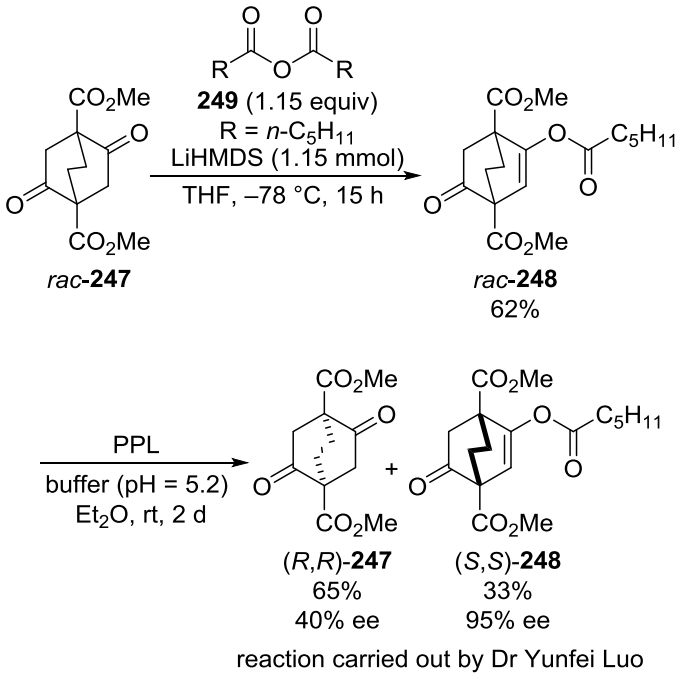
Scheme 4.4: The synthesis of chiral diene **244**

A further diene of interest that was selected for investigation, also featured a bicyclo[2.2.2]octadiene core, with bis-aryl substitution, developed by Luo and Carnell.[136] The synthesis of this chiral diene is somewhat cumbersome, requiring nine steps from commercially available 1,4-di(dimethoxycarbonyl)cyclohexan-2,5-dione (**245**). However, this route involves a chemoenzymatic approach to obtain optically pure material and is therefore is far more appealing than other routes to similar ligands which rely on the separation of enantiomers using chiral HPLC. First, double deprotonation of **245** gave the dianion **246** which was trapped with dibromoethane forming the bicyclic system *rac*-**247** (Scheme 4.5).



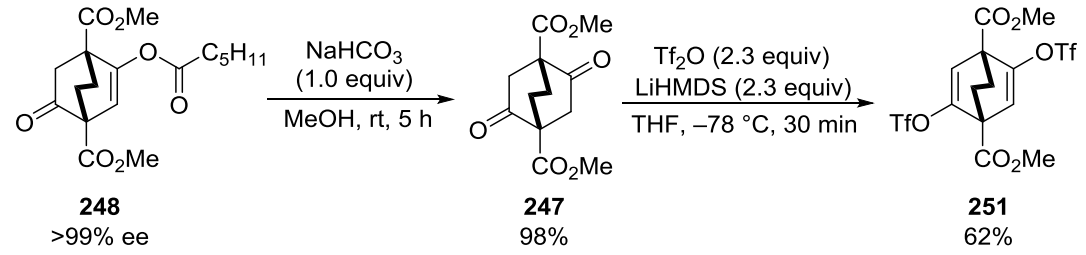
Scheme 4.5: Synthesis of bicyclic system *rac*-**247**

The bicycle **247** was then subjected to mono-enolisation by LiHMDS, followed by trapping with hexanoic anhydride, to give the hexyl enol ester *rac*-**248** (Scheme 4.6). Carnell reported that this enol ester was an excellent substrate for enzyme-catalysed resolution and it was demonstrated that a porcine pancreatic lipase (PPL) selectively cleaved the enol ester of the (*R*,*R*)-species, allowing isolation of the (*R*,*R*)-dione **247** and (*S*,*S*)-enol ether **248**.



Scheme 4.6: Chemoenzymatic resolution of **248**

Recrystallisation of the enantioenriched pure enol ester **248** gave colourless crystals that were found to be racemic, allowing enantiopure material, as measured by HPLC analysis, to be recovered from the mother liquor after two recrystallisations in 25% yield. It is also possible to successfully recrystallise (*R*,*R*)-dione **247** to enantiopurity to enable the synthesis of both enantiomers of the chiral diene. To convert the resulting enantiopure enol ester into the final ligand involved methanolysis of the enol ester to give (*S*,*S*)-dione **247**, followed by bis-triflation to form the bis-alkenyl triflate **251** (Scheme 4.7).



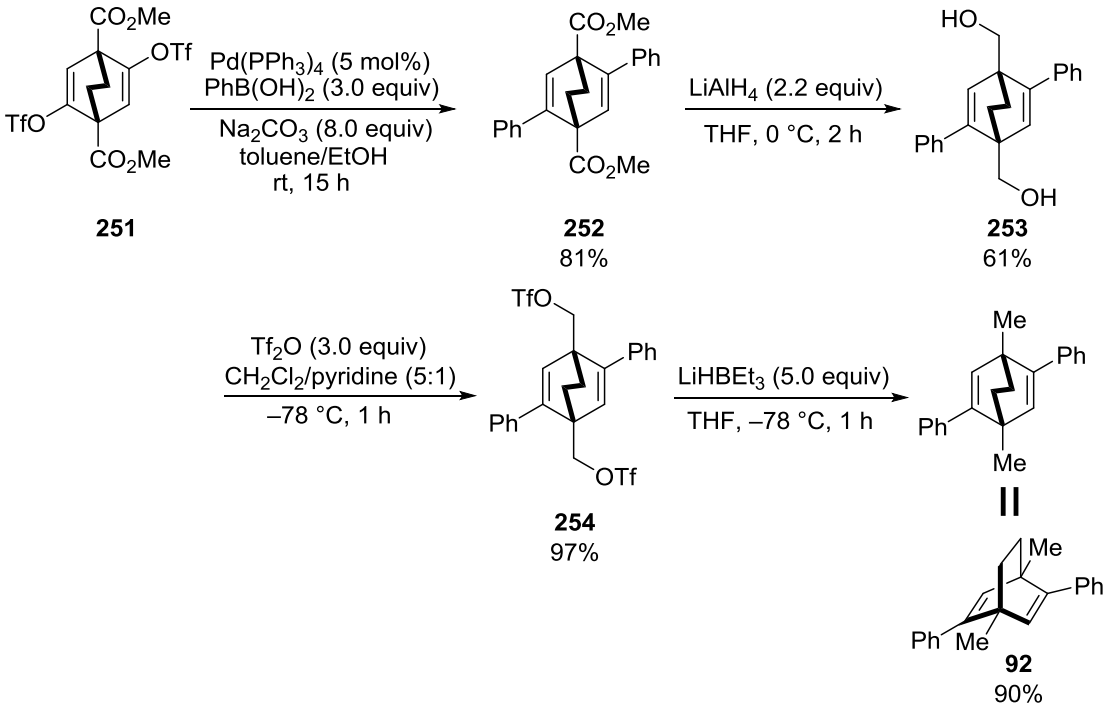
248
>99% ee

247
98%

251
62%

Scheme 4.7: Formation of bis-triflate **251**

Suzuki-Miyaura cross-coupling of **251** with $PhB(OH)_2$ proceeded smoothly to give the bis-aryl diene scaffold **252.** Reduction of the diester utilising $LiAlH_4$ gave the diol **253** in moderate yield, and triflation of the diol with triflic anhydride followed by reduction of the bis-triflate using lithium Super-Hydride® gave chiral diene **92** (Scheme 4.8).



251

252
81%

253
61%

254
97%

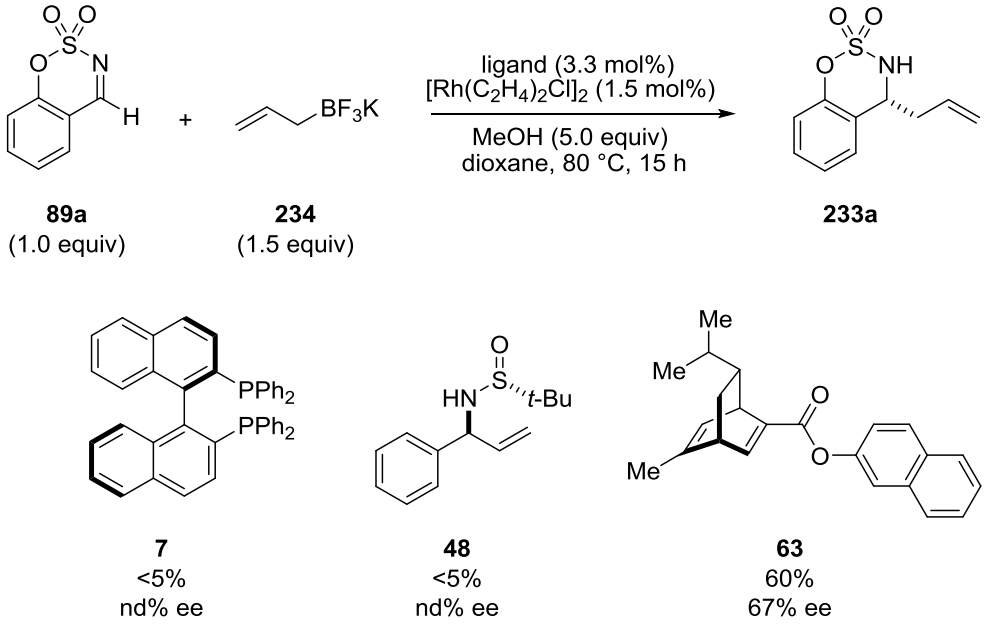
92
90%

Scheme 4.8: Final steps of the synthesis of chiral diene **92**

4.2 Development and Optimisation of the Enantioselective Rhodium-Catalysed Addition of Allyboron Species to Cyclic Imines

Having developed a reproducible and reliable rhodium-catalysed addition of potassium allyltrifluoroborate to cyclic imine **89a** (Scheme 1.21), work was undertaken to investigate whether this reaction could be made enantioselective. A

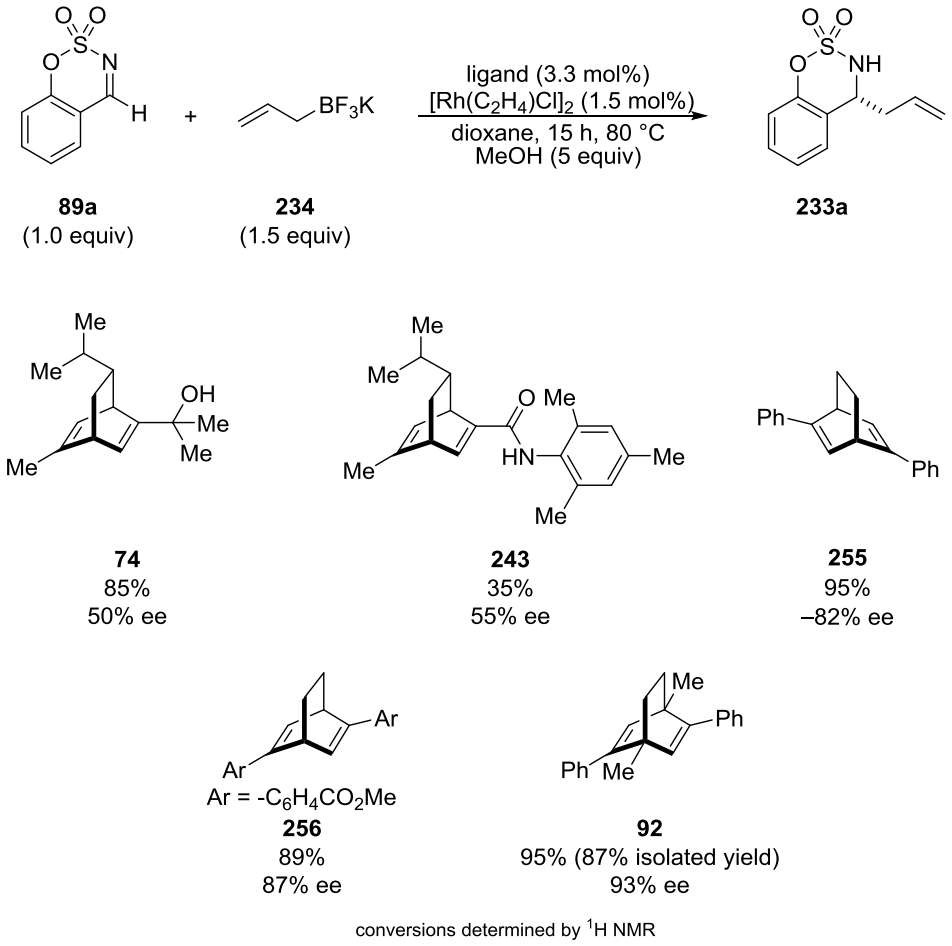
representative ligand from each of the three classes most commonly associated with the enantioselective rhodium-catalysed addition of organoboron species: bisphosphine **7**;[37] sulfur-olefin **48**;[137] and, chiral diene **63**,[27] were screened to investigate which class of ligand may facilitate the reaction (Scheme 4.9). It was found that the bisphosphine ligand (*R*)-BINAP (**7**) led to no formation of the product, as was the case for the sulfur-olefin ligand **48**. However, chiral diene ligand **63** led to the formation of the product in 60% yield with an enantiomeric excess of 67% (Scheme 4.9).



Scheme 4.9: Screening of different ligand classes

Given these results, a programme of screening was undertaken focussing on chiral diene ligands (Scheme 4.10). Chiral diene **74** featuring the same α-phellandrene scaffold as diene **63** but with a hydroxyl side chain had a negative effect on the enantioselectivity (50% ee) but improved the conversion (85%). A related diene **243** featuring an aryl amide side chain was detrimental to both the conversion (35%) and enantioselectivity (55% ee). Varying the structure of the side-arm of chiral diene **63** yielded unimpressive results and other chiral dienes were therefore investigated as potential ligands. The commercially available Ph-bod ligand (**255**), developed by Hayashi,[47] was more successful in catalysing the addition of the allylboron species, giving the product **233a** in excellent conversion (95%) and good enantiomeric excess

(82% ee). A more electron-deficient derivative of Ph-bod **256** further provided high conversions (89%) and increased the enantioselectivity (87% ee). Chiral diene **92**, developed by Carnell, features the main scaffold of Ph-bod but with additional bridgehead methyl groups, and this ligand led to the allylation of benzoxathiazne-2,2-dioxide **89a** in near quantitative conversion, an isolated yield of 87% and an enantiomeric excess of 93% (Scheme 4.10).

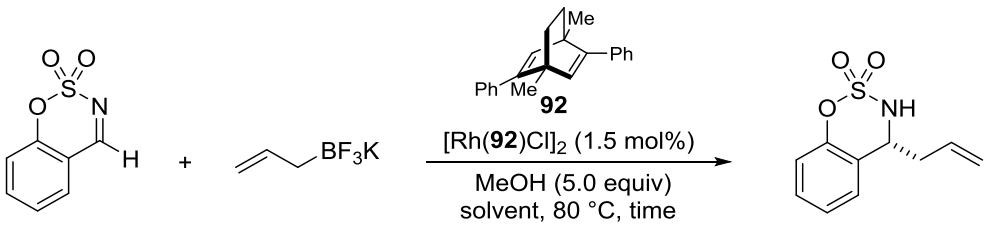


Scheme 4.10: Screening of chiral diene ligands

The screen of chiral diene ligands demonstrated that chiral diene **92** was the best ligand for the addition of potassium allyltrifluoroborate to benzoxathiazine **89a** under the present reaction conditions. Therefore further optimisations of the conditions were undertaken using rhodium-chiral diene **92** complex (Table 4.1). First, the use of two equivalents of allyltrifluoroborate was unnecessary and the loading was successfully reduced to one and a half equivalents without any loss of

conversion (entry 2). Also, analysis of the reaction mixture indicated that the reaction proceeded quite quickly and complete conversion was observed after only three hours (entry 3).

Table 4.1: Optimisation of reaction conditions



89a (1.0 equiv) + **234** (X equiv) → **233a**

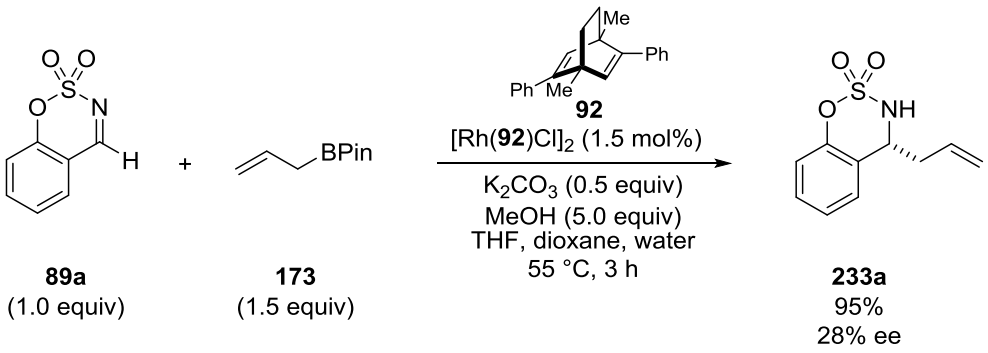
Entry	Equiv. of BF_3K	Solvent	Temp. (°C)	Time (h)	Conversion (%)[a]	ee (%)[b]
1	2	dioxane	80	15	95	93
2	1.5	dioxane	80	15	95	93
3	1.5	dioxane	80	3	94	93
4	1.5	toluene	80	3	95	93
5	1.5	THF	55	3	95	96

[a] Determined by ^1H NMR analysis of crude reaction mixture. [b] Determined by HPLC analysis on a chiral stationary phase.

Changing the solvent to toluene (entry 4) had minimal effect on the reaction; however, employing THF as the solvent (entry 5) resulted in an increase in enantioselectivity to 96%. By using THF as the solvent, the temperature could be reduced to 55 °C and this had no detrimental effect on the yield or enantiomeric excess. Although no systematic studies were employed to analyse the role of the alcohol additive, later reactions showed that ethanol and *iso*-propanol could be used instead of methanol with no negative effect on the yields or enantioselectivity.

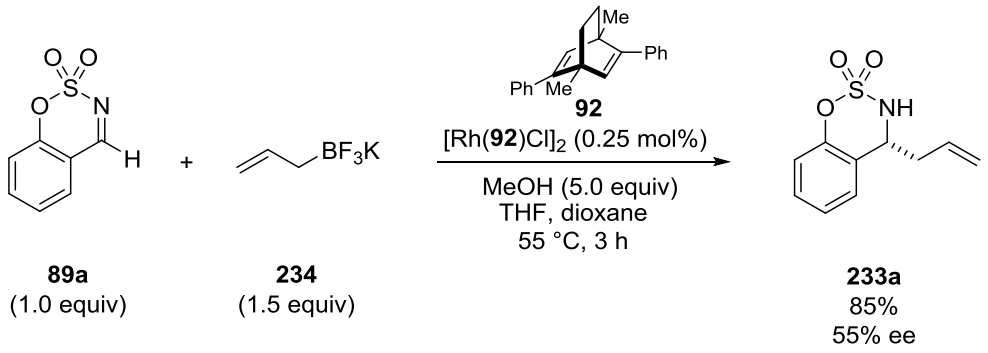
Potassium organotrifluoroborate salts are appealing to use due to their ease of handling and general stability to both air and moisture.[138] Although they were shown to be an excellent nucleophilic source of allyl functionality, they are accessed *via* fluorination of the corresponding boronic acid or ester. Therefore, we wanted to compare their performance in the reaction to avoid an additional synthetic step in the preparation of the starting materials. However, allylboronic acids are unstable to oxygen,[139] only allylboronic acid pinacol ester was analysed as a possible

replacement for potassium allyltrifluoroborate. Thus, employing allylboronic acid pinacol ester (**173**), the reaction proceeded smoothly but furnished the product in only 28% ee (Scheme 4.11).



Scheme 4.11: Test reaction using allylboronic acid pinacol ester

Similarly, it was found that a reduction of the molar percentage of rhodium also led to a decrease in the enantioselectivity. This may also indicate an alternative achiral non-rhodium catalysed pathway becoming a more prominent pathway at lower catalytic loading (Scheme 4.12).



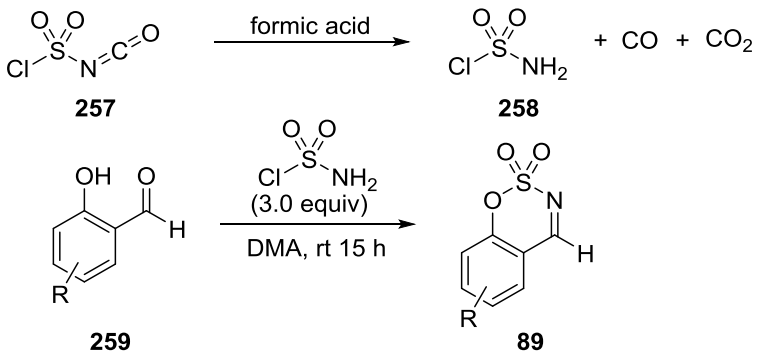
Scheme 4.12: Reaction with lower catalytic loading

These studies demonstrated that the optimal conditions for good yields and enantioselectivities consisted of a cyclic imine, 1.5 equivalents of potassium allyltrifluoroborate, THF as solvent, five equivalents of MeOH as a proton source and rhodium-chiral diene **92** complex in dioxane (dioxane was found to be beneficial to the stability of the catalyst for long term storage, if the catalyst was prepared and kept in a THF solution, it was found to degrade within a month, rendering it useless). This reaction mixture was then heated at 55 °C for three hours to give the resultant

homoallylic sulfonamide in good yields and enantiomeric excesses. With these conditions established, the scope of the reaction with respect to the imine component was investigated.

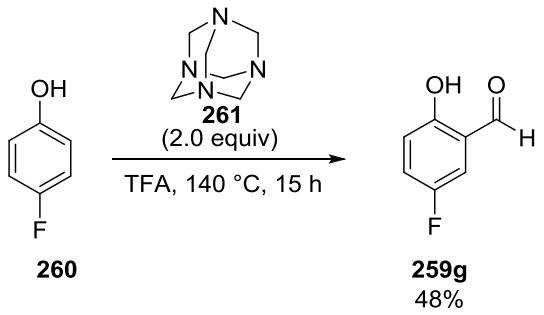
4.3 Preparation of Cyclic Sulfonyl Imines

Having established that cyclic imines were the best type of imine for the rhodium-catalysed addition of allyltrifluoroborates, an array of benzoxathiazine-2,2-dioxides were prepared utilising the conditions described by Du Bois[140] in order to allow investigations into the scope of the electrophile. This protocol involves the *in-situ* generation of sulfamoyl chloride (**258**) from chlorosulfonyl isocyanate (**257**) and formic acid, which then reacts with salicylaldehyde (**259**) to furnish the desired cyclic aldimine **89** (Scheme 4.13).



Scheme 4.13: The preparation of benzoxathiazine-2,2-dioxides

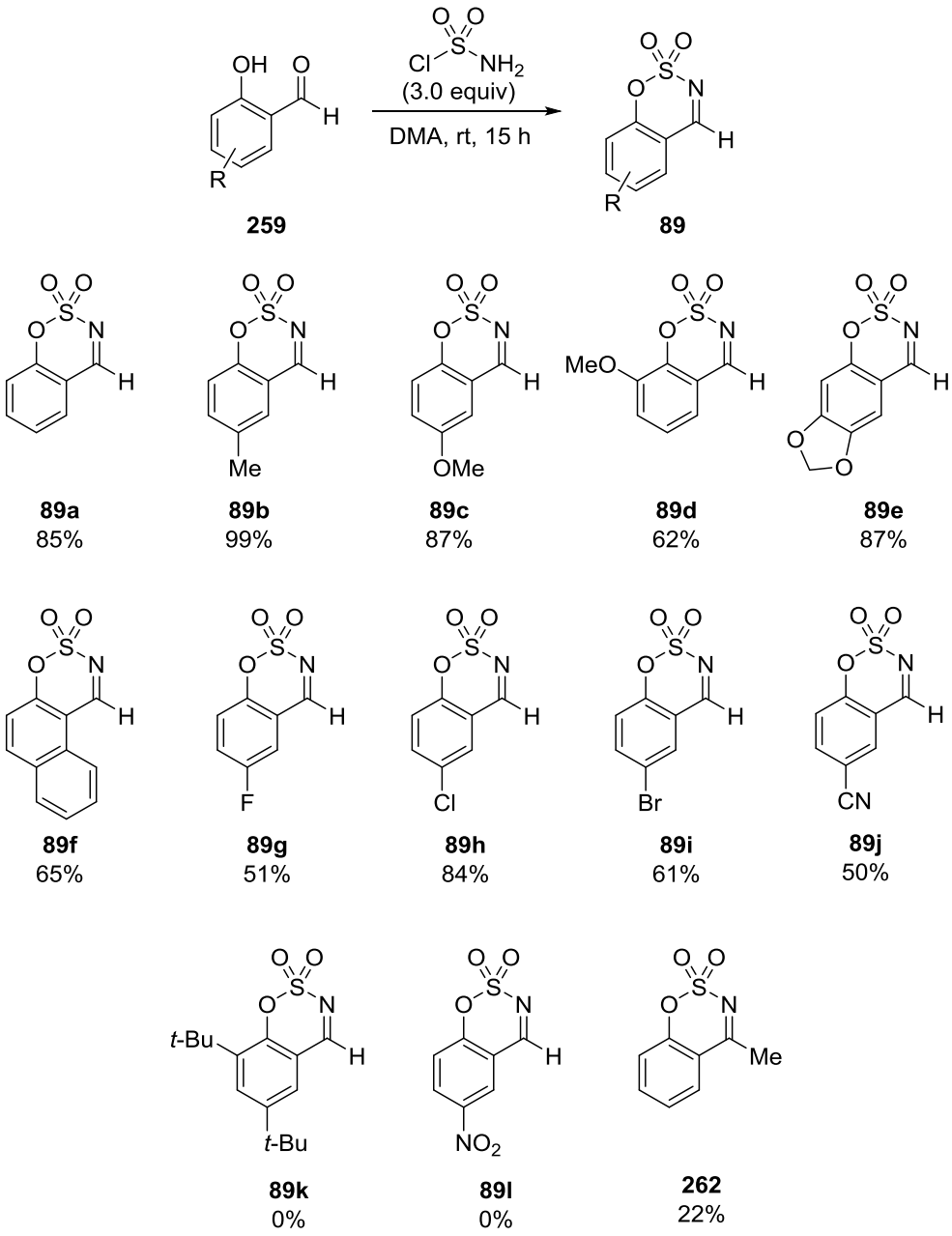
The majority of salicylaldehydes were commercially available, and the non-commercially available 5-fluorosalicylaldehyde (**259g**) was synthesised *via* a Duff reaction between 4-fluorophenol (**260**) and hexamethylenetetramine (**261**) (Scheme 4.14).[141]



260 **259g** 48%

Scheme 4.14: The synthesis of 5-fluorosalicylaldehyde (**259g**)

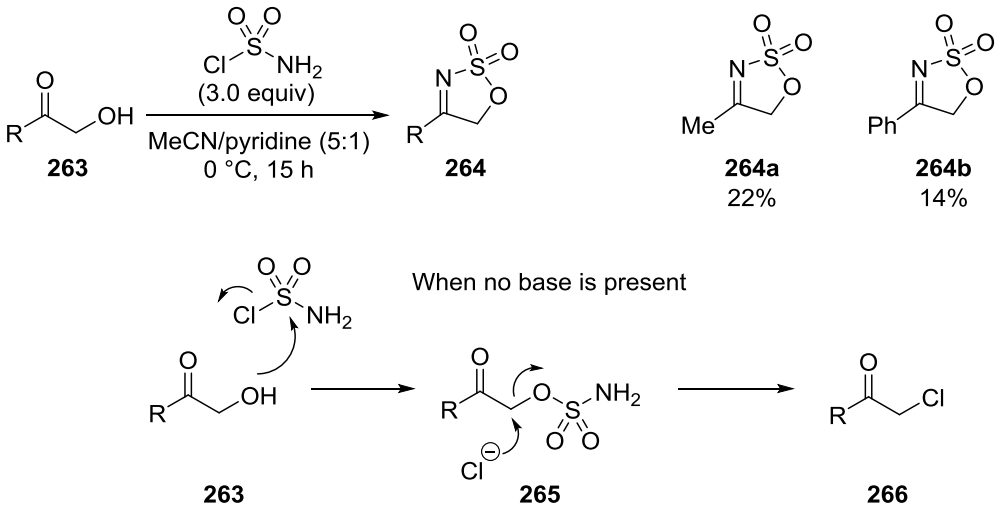
Various salicylaldehydes gave the corresponding aldimine in moderate to good yields, with the exception of the sterically hindered 3,5'-di-*tert*-butylsalicylaldehyde and the highly electron deficient 3-nitrosalicylaldehyde, both of which returned only starting material (Scheme 4.15).



Scheme 4.15: The synthesis of a range of benzoxathiazine-2,2-dioxides

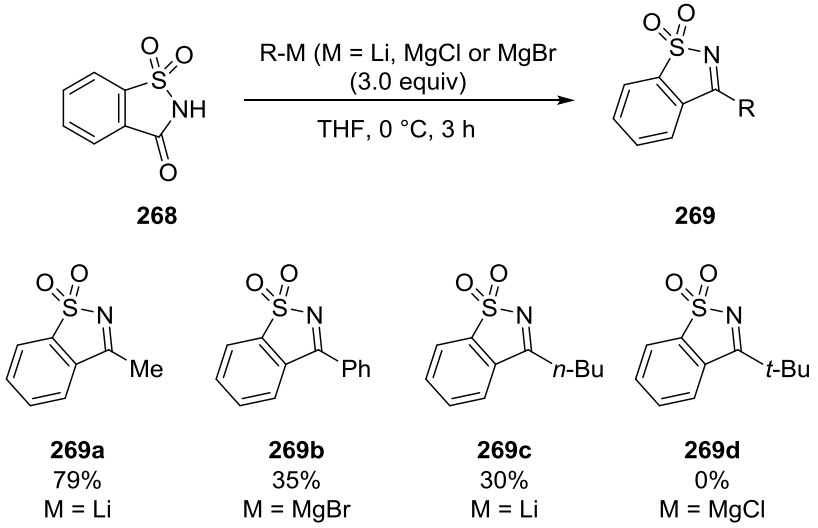
Cyclic sulfamate imines **264a** and **264b** were prepared using a similar method. However, instead of using dimethylformamide, conditions employing acetonitrile and stoichiometric pyridine were preferred. This modification traps the hydrogen chloride released by the nucleophilic attack of the alcohol on the sulfamoyl chloride. If no base is present in order to trap the liberated HCl, the chloride undergoes a nucleophilic attack of the activated oxo-sulfonamide **265** resulting in the exclusive formation of the α-chloro ketone **266**. Any products from the corresponding chloride

S_NAr reaction with the salicylaldehydes were not observed showing that this side reaction was only a problem for alkyl-hydroxyl substrates (Scheme 4.16).



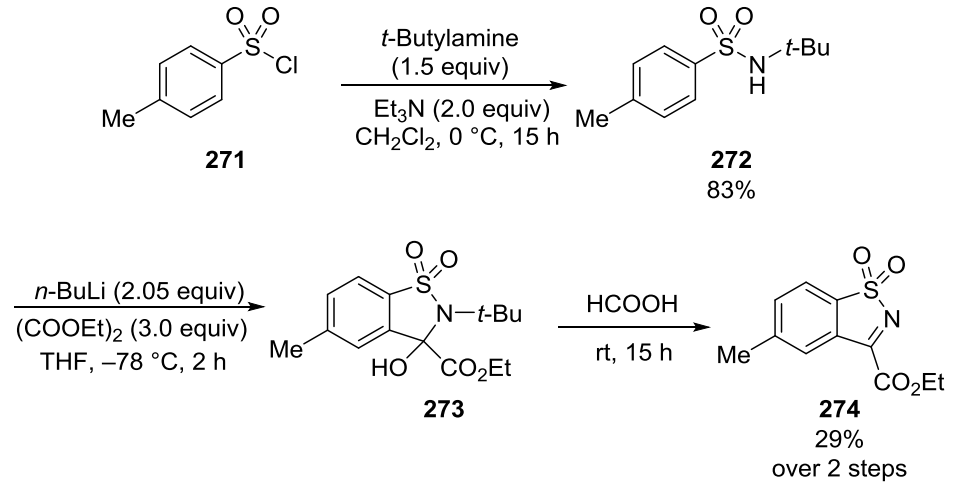
Scheme 4.16: Formation of cyclic imines **264a** and **264b**

To further probe the scope of the cyclic imine, a set of saccharin-derived cyclic ketimines **269** were synthesised by the addition of three equivalents of the desired Grignard reagent to saccharin (**268**)[142] with varying degree of success. Ketimine **269a** and **269c** were formed using the alkyl lithium as the nucleophile instead. However, sterically hindered Grignard reagents such as *tert*-butylmagnesium chloride led to no formation of the product (Scheme 4.17).



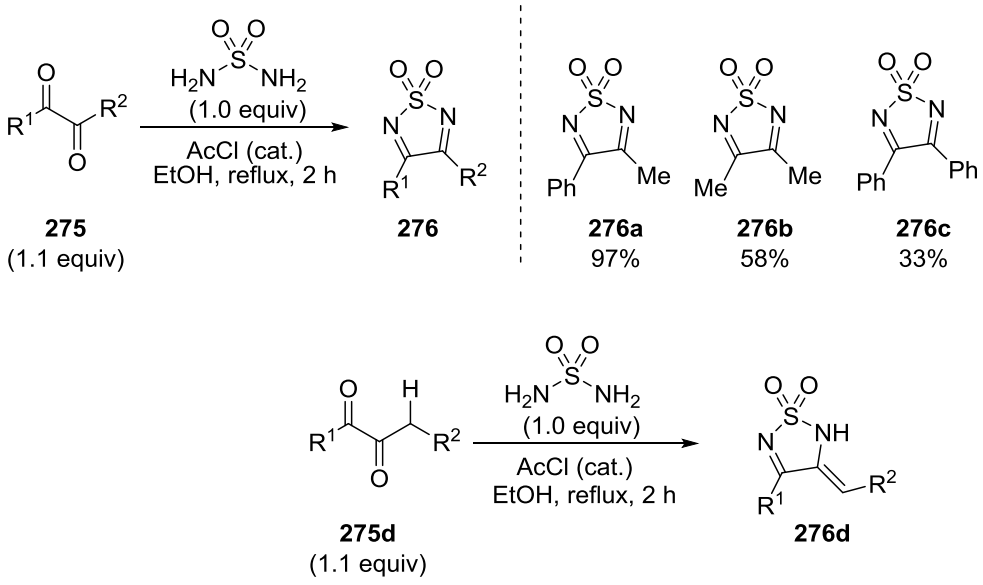
Scheme 4.17: Synthesis of saccharin-based cyclic imines **269a-d**

Similar ketimine **274** was readily synthesised from tosyl chloride (**271**) in 3 steps (Scheme 4.18)



Scheme 4.18: Synthesis of imine **274**

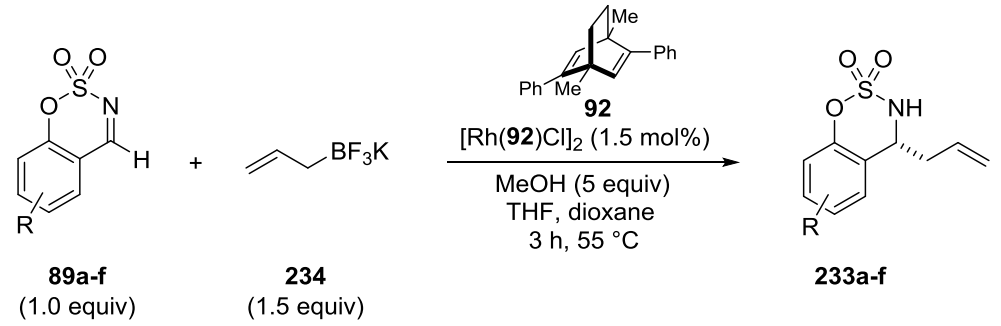
Five-membered 1,2,6-thiadiazine-1,1-dioxide substrates **276a-c** were prepared by the double condensation of the appropriate 1,2-diketone **275** with sulfamide (Scheme 4.19). Unfortunately, only diketones with an adjacent methyl or a phenyl group were successfully converted into the diimine. Diketones which have *β*-hydrogens (**275d)** resulted in the formation of imino-enamines (**276d)** rather than the desired diimine and these products proved difficult to successfully purify and isolate.

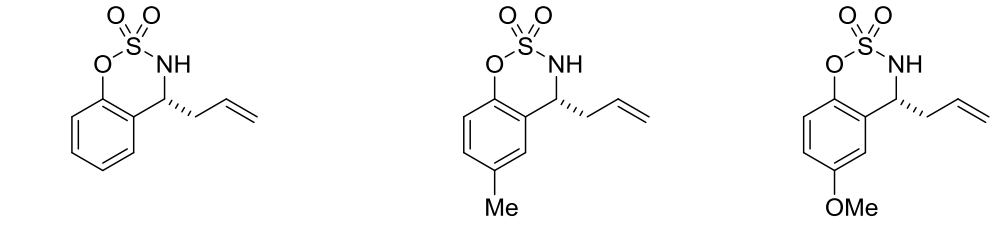


Scheme 4.19: Synthesis of cyclic diimines **276a-c**

4.4 Enantioselective Allylation of Cyclic Imines with Potassium Allyltrifluoroborate

The optimised conditions were then applied to a range of different cyclic imines to further investigate the scope of the newly developed reaction. First, taking benzoxathiazine-2,2-dioxides, electron-neutral imines (**89a**), electron-rich imines (**89b-e**) and sterically hindered imines (**89f**) were all found to give the homoallylic sulfonamide in very good yields and high enantiomeric excess (Scheme 4.20).

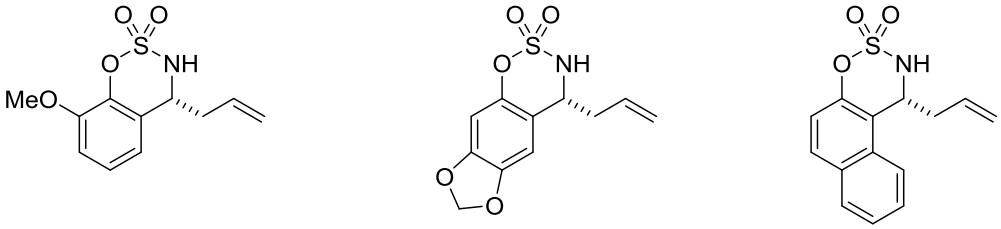




233a
87%
96% ee

233b[a]
93%
97% ee

233c[a]
92%
91% ee



233d[a]
95%
95% ee

233e
94%
98% ee

233f
95%
93% ee

[a] Reaction performed by Dr Yunfei Luo

Scheme 4.20: Allylation of electron-neutral and electron-rich imines

The absolute stereochemistry of sulfonamides **233d** and **233e** were determined by single crystal X-ray diffraction and the stereochemistry of the other products was assigned by analogy (Figure 4.1).

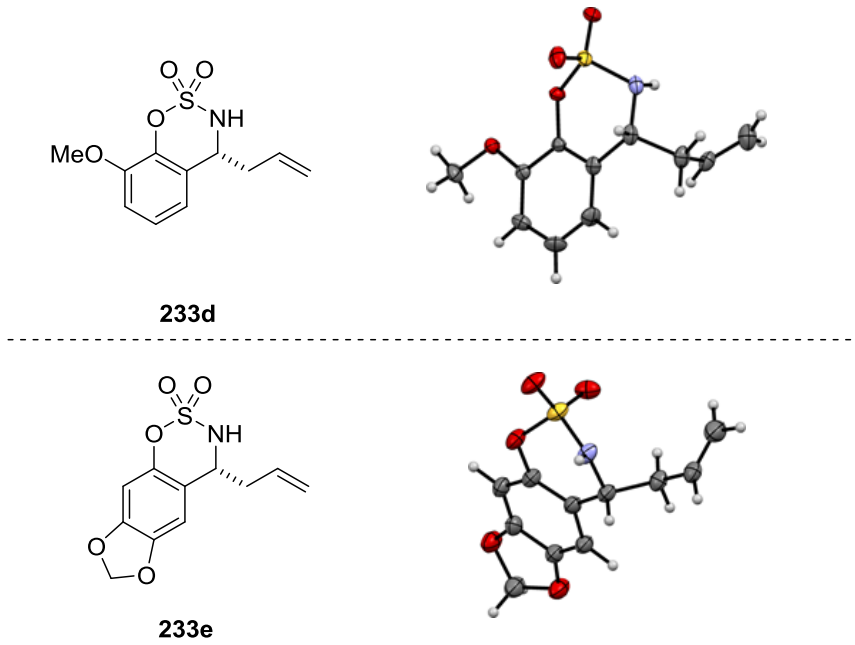
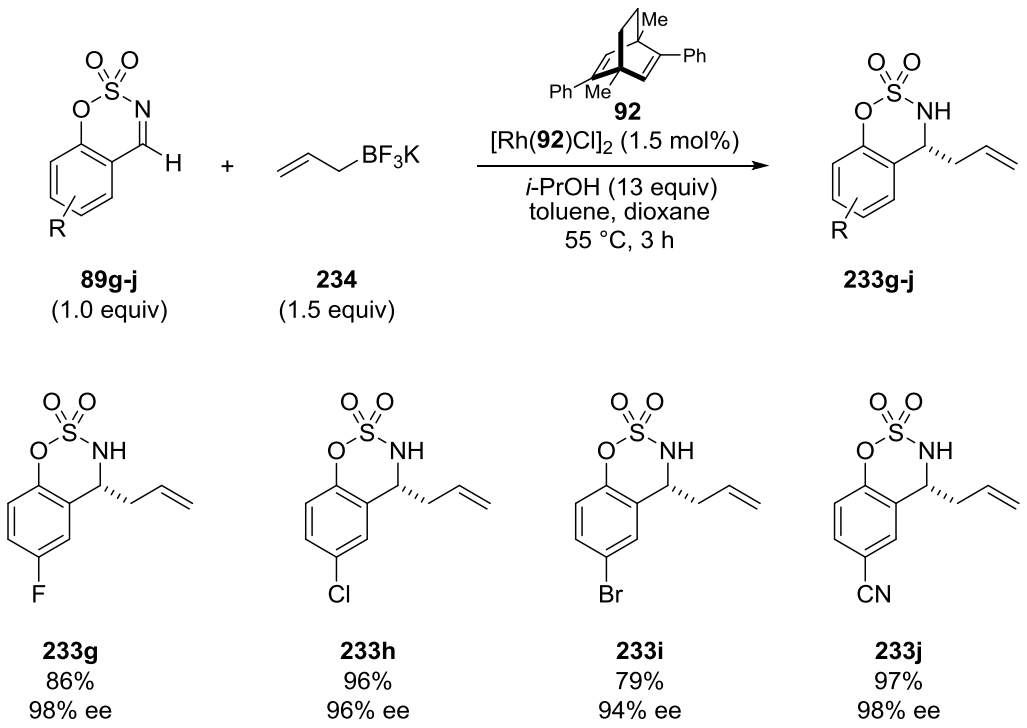


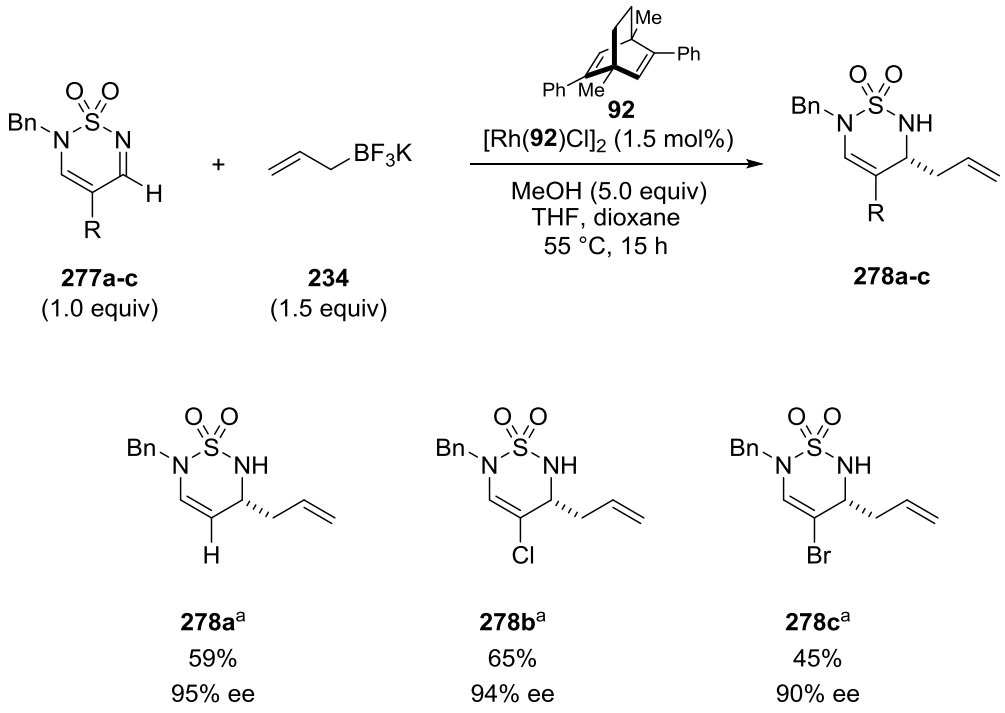
Figure 4.1: X-ray structures of products **233d** and **233e**.

Unfortunately, electron-poor benzoxathiazine-2,2-dioxides did not react so smoothly. It was found that these electron-poor imines gave inconsistent enantiomeric excesses, differing substantially each time the reaction was performed. However, this inconsistency was solved by simply altering the reaction solvent from THF to toluene and changing the alcohol additive from methanol to *iso*-propanol. This led to a reliable and reproducible reaction that provided the products (**233g-j**) in high yields and enantiomeric excesses (Scheme 4.21).



Scheme 4.21: Allylation of electron-poor imines.

Furthermore, cyclic imino-enamines were also good substrates for the allylation, and various 1,2,6-thiadiazine-1,1-dioxides (**277a-c**) underwent allylation to give products **278a-c** in moderate yields but excellent enantioselectivities (Scheme 4.22).



278a[a]
59%
95% ee

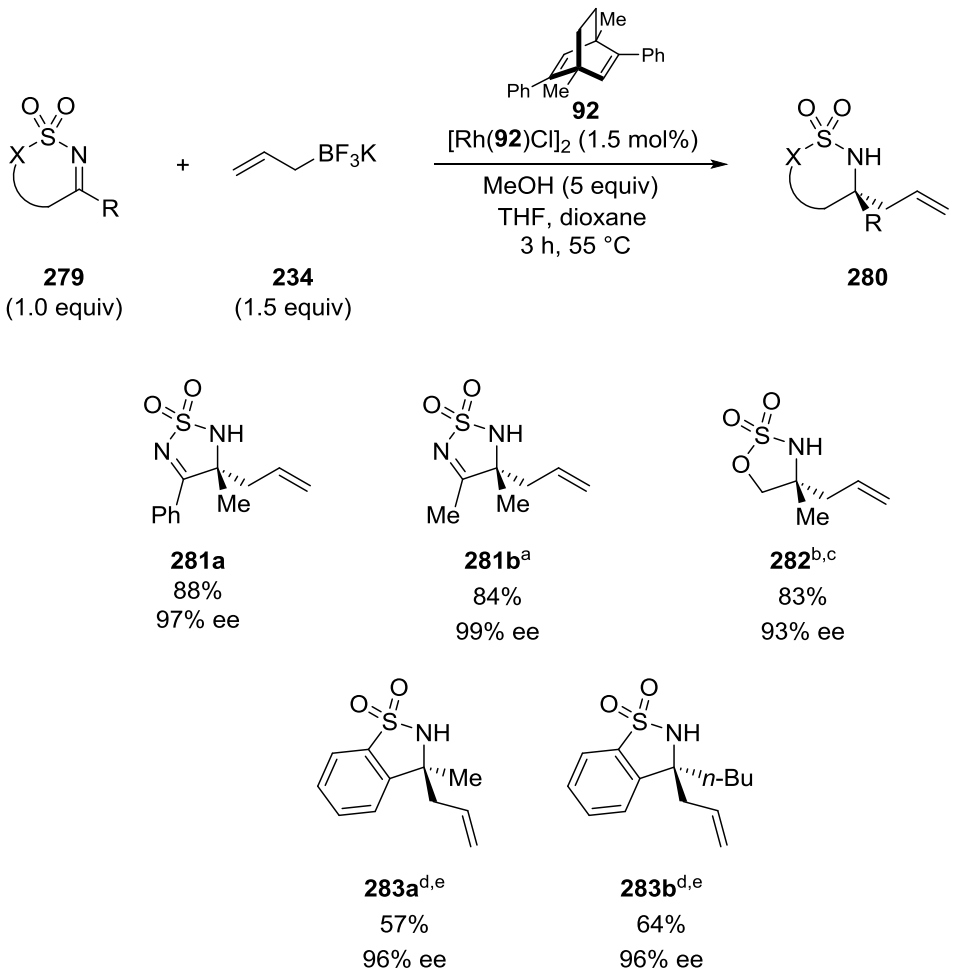
278b[a]
65%
94% ee

278c[a]
45%
90% ee

[a] Reactions performed by Nawasit Chotsaeng

Scheme 4.22: Allylation of 1,2,5-thiadiazine-1,1-dioxides

Having demonstrated that the developed rhodium-catalysed allylation gave excellent results with a range of different cyclic aldimines, the focus of the project was altered to investigate whether the same reaction conditions could be successfully applied to cyclic ketimines as well. As discussed previously (Section 2.0), the enantioselective allylation of ketimines has proven to be somewhat difficult with few reported examples. Pleasingly, when the optimised conditions were applied to various cyclic ketimines, the allylation reaction proceeded smoothly to provide the products, featuring quaternary stereocentres, in moderate to good yields and excellent enantioselectivities. In some cases the reaction time was needed to be increased four to five fold as the reaction had not proceeded to completion within the first three hours (Scheme 4.23).

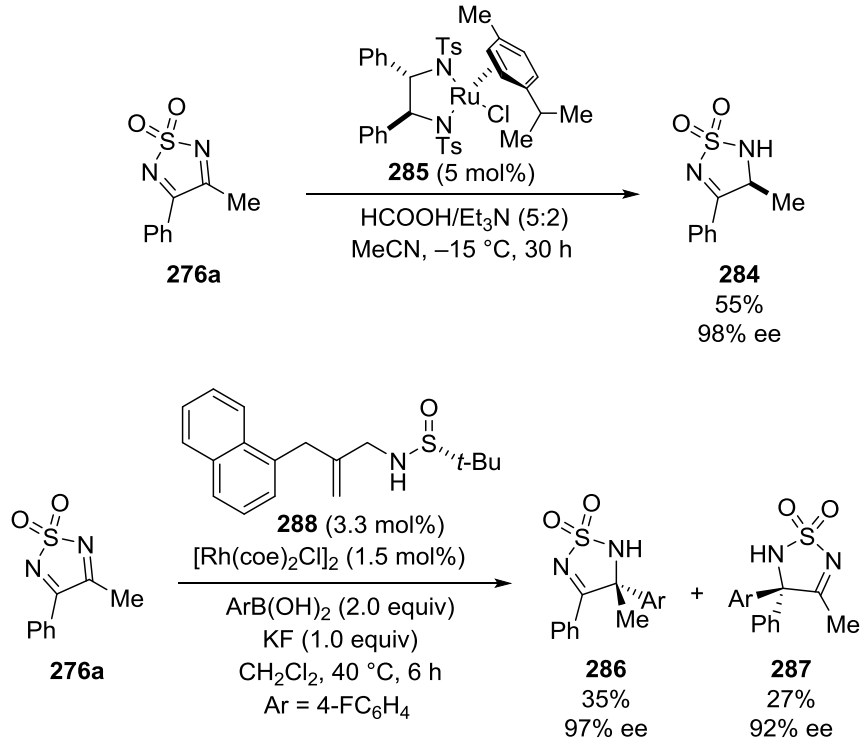


[a] Reaction time = 12 h, [b] Reaction time = 15 h using exclusively dioxane at 80 °C, [c] Reaction performed by Dr Yunfei Luo, [d] Reaction time = 15 h, [e] Using *ent*-**LX**

Scheme 4.23: Allylation of cyclic ketimines

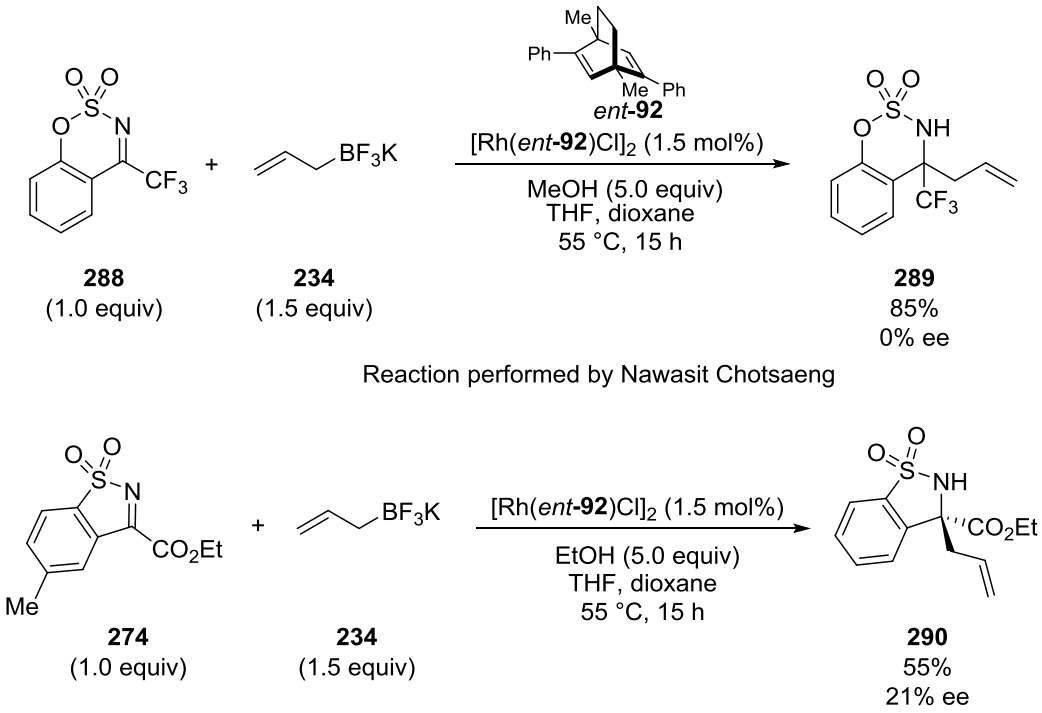
Cyclic diimines **276a** and **276b** were found to give the products **281a** and **281b** in high yields and high enantiomeric excesses. Products **281b** and **282** lacked suitable chromophores required for HPLC analysis, and therefore the enantiomeric excess was determined by HPLC analysis of the *N*-benzylated derivatives. It is interesting to note that for substrates **276a** and **276b**, exclusive mono-allylation was observed; it is speculated that once the addition of one allyl group has occurred, the ring strain of the molecule is relieved, deactivating the second imine functionality. This is especially pertinent for substrate **276b** where the two imines are identical. Furthermore, substrate **276a** only underwent allylation at the alkyl-substituted imine, demonstrating that this imine is appreciably more reactive than the aryl-substituted imine. This observation is in agreement with other reported observations such as the

Ru-catalysed transfer hydrogenation of these substrates (Scheme 4.24).[143] However, it is in contrast to other reports, where addition occurs at either imine, such as the case of Rh-catalysed arylation (Scheme 4.24).[144]



Scheme 4.24: Other reaction using diimine **276a**[143,144]

Cyclic sulfamate **264a** and saccharin derived imines **269a** and **269b** also underwent allylation with moderate to good yields and excellent enantioselectivities. However, not all ketimine substrates were successful as, similar to the aldimine examples, and the reactions with electron-deficient ketimines were poorly enantioselective. Specifically, substrates which featured electron-withdrawing groups adjacent to the imine functionality were especially poor (Scheme 4.25). Substrates **288** and **274** both gave products with good yields but poor-to-non-existent enantiomeric excesses. Modifications to the reaction conditions that improved the enantiomeric excess in the case of electron-poor aldimines had a limited effect in these cases.



288 (1.0 equiv) + **234** (1.5 equiv) → **289** 85% 0% ee

Reaction performed by Nawasit Chotsaeng

274 (1.0 equiv) + **234** (1.5 equiv) → **290** 55% 21% ee

Scheme 4.25: Allylation of electron-deficient ketimines

It is possible that these electron-poor substrates give poor results because they are more electrophilic. Therefore, an alternative pathway, not involving an allylrhodium species, may be becoming more prominent. An alternative pathway may not be unable to impart any enantiodiscrimination upon the product leading to the poor results.

Ketimines bearing additional aryl substituents (**276c**,**264b**, and **269c**) were also unreactive, as was ketimine **262** (Figure 4.2). In those reactions a rapid decolourisation of the reaction mixture occurred within ten minutes. After this point, no product was observed and no further loss of starting material was apparent. One possible explanation for this observation could be the rapid oxidative insertion of rhodium(I) into a C-H bond leading to Rh(III) species **291** akin to reports by Hayashi involving similar substrates and Ir(I) C-H functionalisation.[145,146] Preliminary attempts by others within the Lam group to promote catalytic turnover in this process by adding a suitable electrophile and oxidant proved to be unsuccessful. Thus, it is still not possible to fully explain why these substrates do not lead to allylated products.

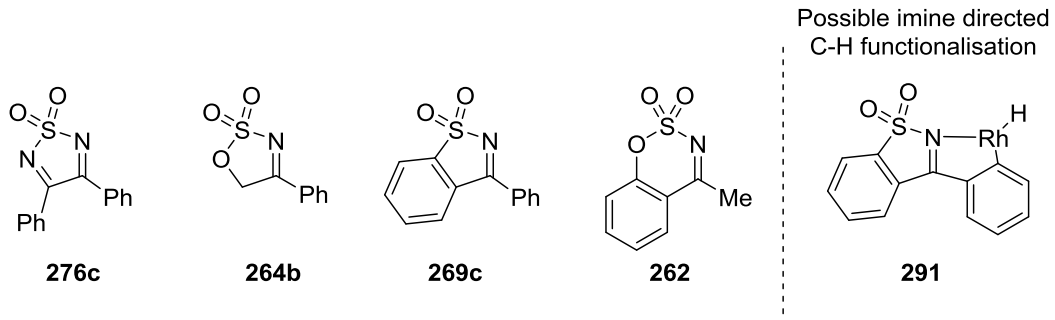
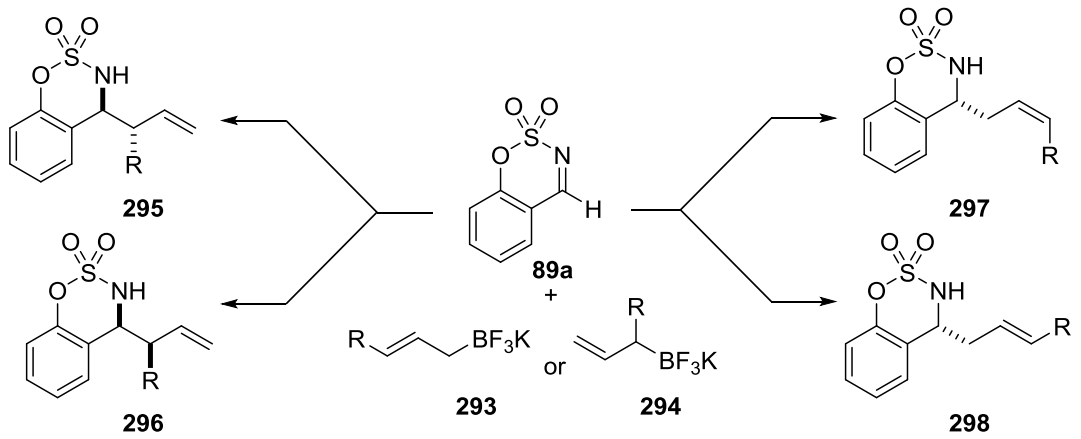


Figure 4.2: Unsuccessful substrates and possible C-H insertion

4.5 Reactions Involving More Highly Substituted Allyboron Reagents

A further under investigated facet of the allylation of imines is the addition of more highly substituted allylboron reagents. As discussed earlier (see Section 2.2.5), many reports either do not address these reactions,[125] exhibit poor results, especially diastereoselectivities,[131] or have only limited examples.[127] It was hoped that the newly developed rhodium-catalysed allylation would be able to tolerate substituted potassium allyltrifluoroborates and give the appropriate products in good yields, diastereoselectivities and enantiomeric excesses.

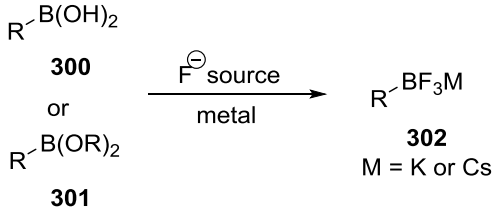
Substitution can be present in the α-, β- or γ-positions of the allyl species. Substitution in the β-position can only furnish one product. However, substitution in the α- or γ-positions could theoretically lead to four different products, i.e. the α-substituted *anti*-product **295**, the α-substituted *syn*-product **296**, the γ-substituted *E*-product **297**, and the γ-substituted *Z*-product **298**. Therefore it would be of interest to investigate these kinds of reagents in order to see if selectivity for any of these products is observed (Scheme 4.26).



Scheme 4.26: Possible isomers from allylation reaction with substituted allyl reagents

4.5.1 Synthesis of More Highly Substituted Allyltrifluoroborate Reagents

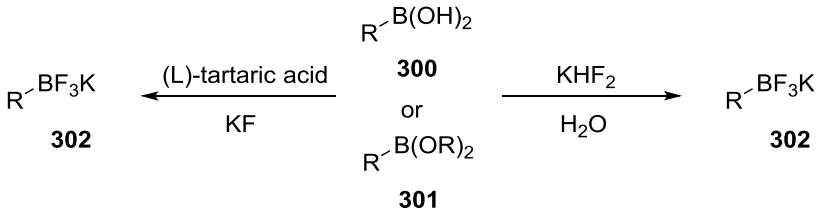
Potassium allyltrifluoroborates are an attractive organoboron reagent due to their stability to air and moisture and their ease of handling. Early reports showed that trifluoroborate salts could be prepared using boron trifluoride and organostannanes.[147] However, this method is rather antiquated today due to the poor yield and toxicity of stannane compounds. Nowadays, the most common route to access trifluoroborate salts *via* the fluorination of the corresponding allylboronic ester (**301**) or acid (**300**) (Scheme 4.27).



Scheme 4.27: Formation of trifluoroborate salts.

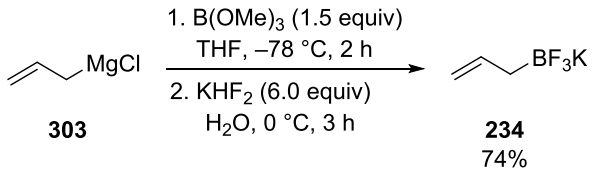
To convert an allylboronic ester into a trifluoroborate, there are two methods; the common method, reported first by Vedejs[148] and popularised by Molander,[149] involves the use of aqueous potassium hydrogen difluoride to generate the trifluoroborate. Alternatively, a recent method reported by Lloyd-Jones[150] uses potassium fluoride in conjunction with tartaric acid to furnish the trifluoroborate (Scheme 4.28). Both methods have their own merits and throughout this work, potassium trifluoroborate salts were prepared using both methods interchangeably

unless a substrate required the use of one method for a particular reason. For crude allylboronic esters, or samples contaminated by metal salts, only the KHF_2 method was successful. This is due to metal salts co-ordinating with the tartaric acid, preventing the generation of fluoride ions. Alternatively, potassium allyltrifluoroborates featuring long alkyl chain required the use of KF/tartaric acid to enable the resultant product to be isolated in high purity.



Scheme 4.28: The method of preparation of trifluoroborate salts

Simple potassium allyltrifluoroborate (**234**) is commercially available; however, it is also cheaply and efficiently prepared from the addition of allylmagneisum chloride (**303**) to trimethylborate to form the allylboronic acid methyl ester which is converted to potassium allyltrifluoroborate (**234**) *in situ* by the addition of aqueous KHF_2 (Scheme 4.29)

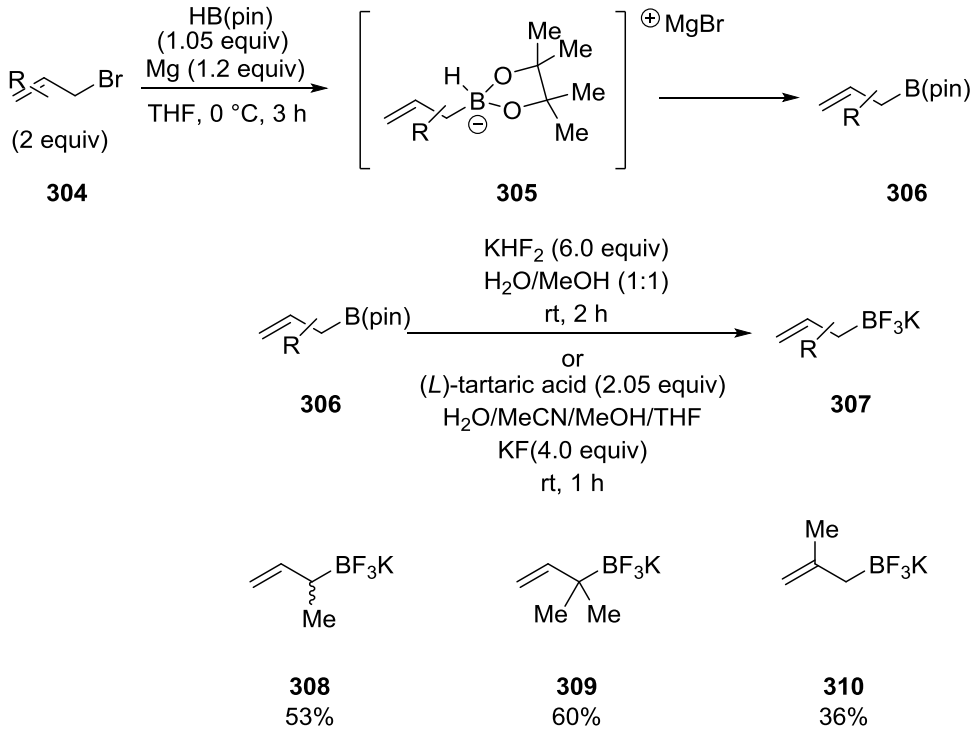


Scheme 4.29: Synthesis of potassium allyltrifluoroborate

More highly substituted potassium allyltrifluoroborates were synthesised *via* different methods depending on the position and degree of substitution required, literature precedent, and availability of starting materials.

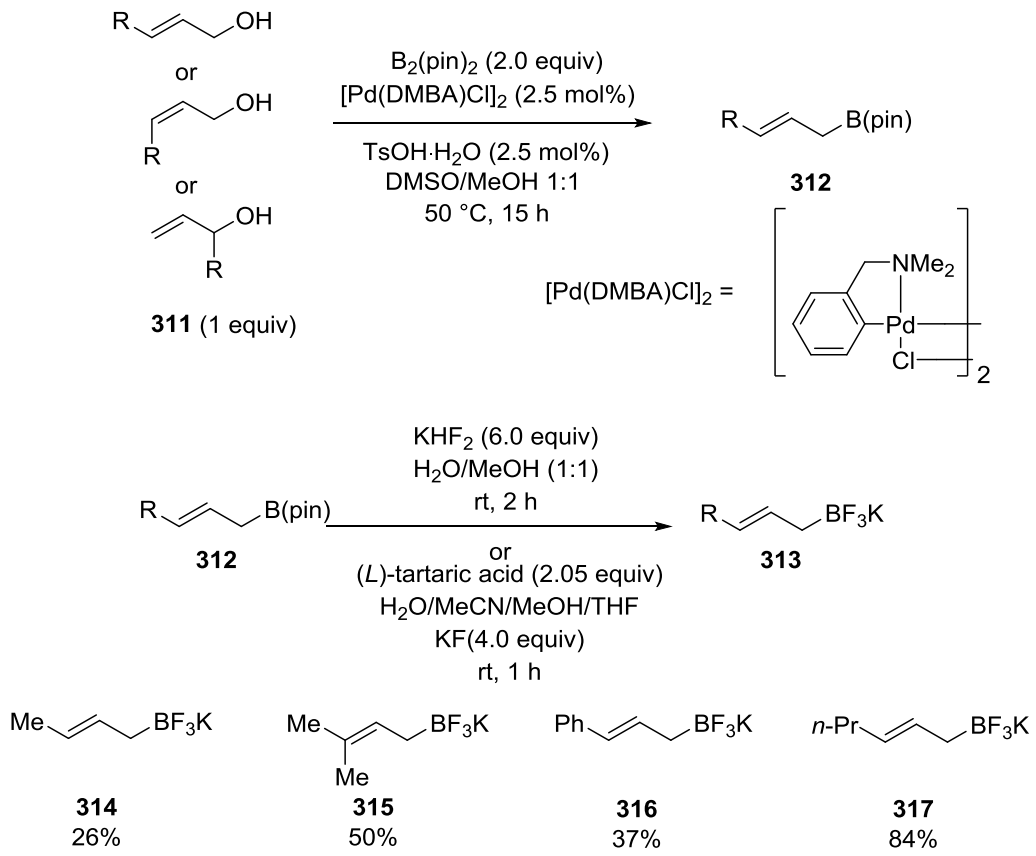
Allyltrifluoroborates that have substitution in either the α- or β-position were prepared according to the methods of Singaram.[151] The allyl bromide is converted into the allyl Grignard reagent by reacting with elemental magnesium. This Grignard reagent reacts with pinacolborane to form dialkoxy allylboronhydride **305** which eliminates hydridomagneisum bromide to form the allylboronic acid pinacol ester

306 which is converted to the potassium allyltrifluoroborate **307** using either KHF_2 or KF/tartaric acid (Scheme 4.30). A small range of α- and β-substituted allyltrifluoroborates were synthesised in this manner.



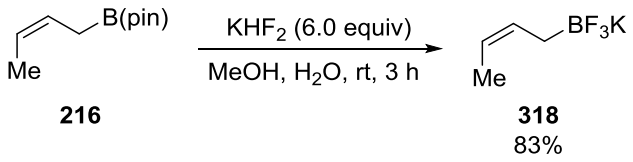
Scheme 4.30: Synthesis of allyboron species *via* Grignard reagent

Allylboron reagents that feature substitution in the γ-position were prepared from the appropriate allylic alcohol using the methods of Szabo.[152] In order to prepare these species, the allylic alcohol underwent a palladium-catalysed borylation with $B_2(pin)_2$ to form the allylboronic acid pinacol ester, which was then converted into the trifluoroborate salt using the aforementioned methods. Due to the preference for π-allylpalladium species to undergo nucleophilic substitution at the least hindered carbon, regioisomeric allyl alcohols could be used, always giving the (*E*)-γ-substituted product (Scheme 4.31).



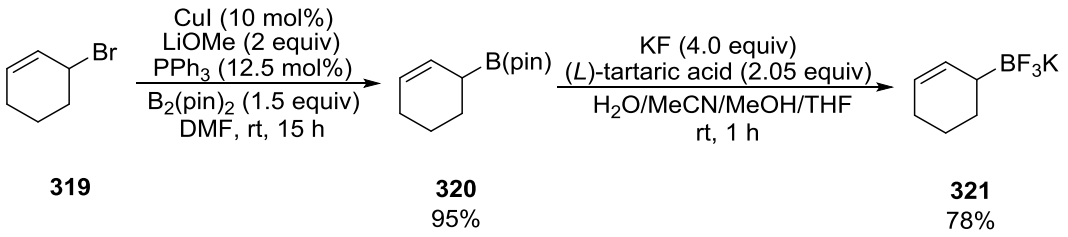
Scheme 4.31: Synthesis of γ-substituted allylboron reagents

Z-Crotylboronic acid pinacol ester **216** is commercially available and was converted into the trifluoroborate **318** using 6 equivalents of potassium hydrogen difluoride (Scheme 4.32).



Scheme 4.32: Conversion of **216** to trifluoroborate **318**

The cyclic potassium cyclohexenyltrifluoroborate **321** required a slightly different route for its preparation, namely the copper-catalysed borylation of 1-bromocyclohex-2-ene (**319**) developed by Marder and co-workers,[153] followed by the conversion of the pinacol ester **320** into trifluoroborate **321** using the method of Lloyd-Jones (Scheme 4.33).[150]

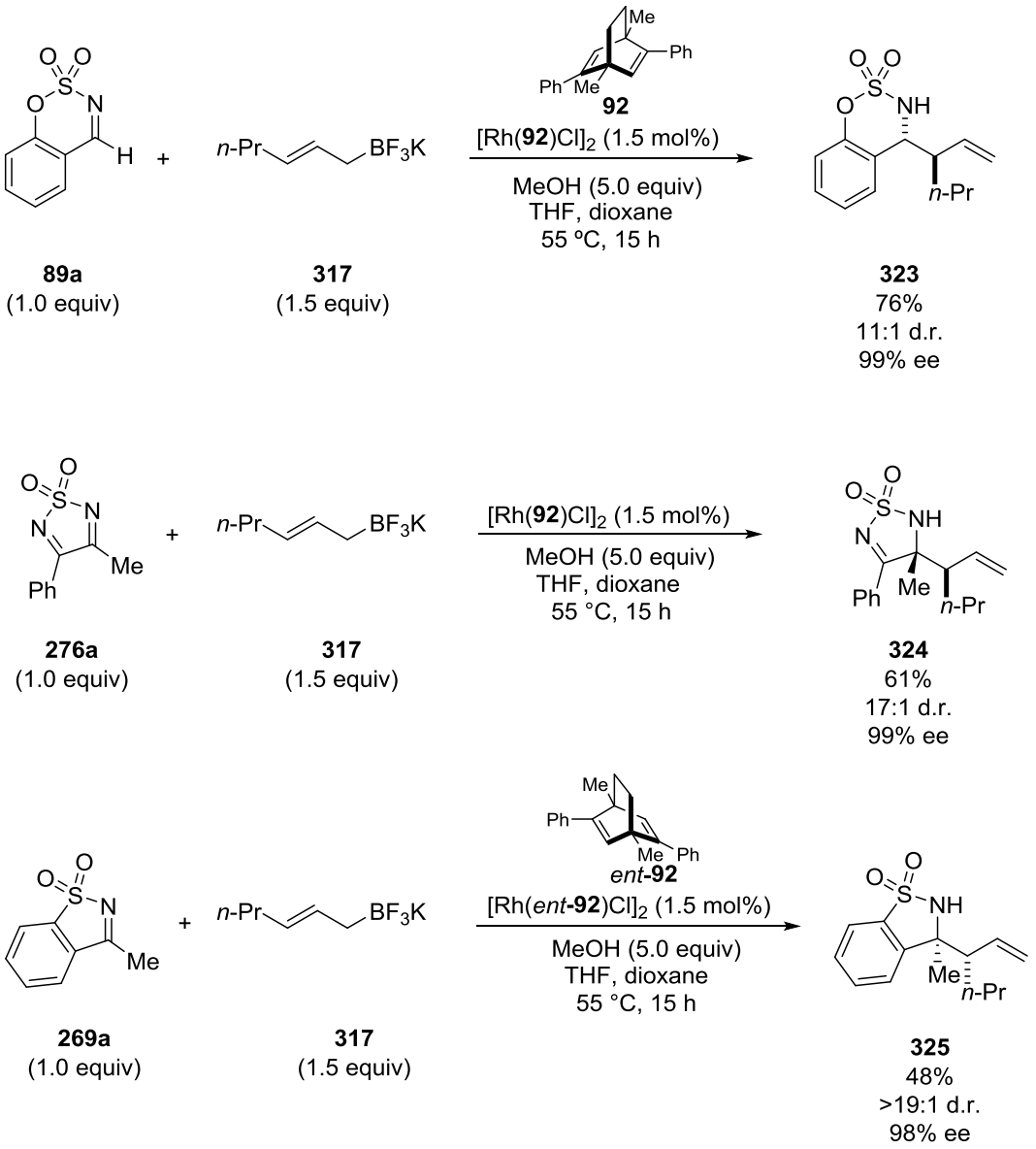


319 **320** 95% **321** 78%

Scheme 4.33: Synthesis of trifluoroborate **321**

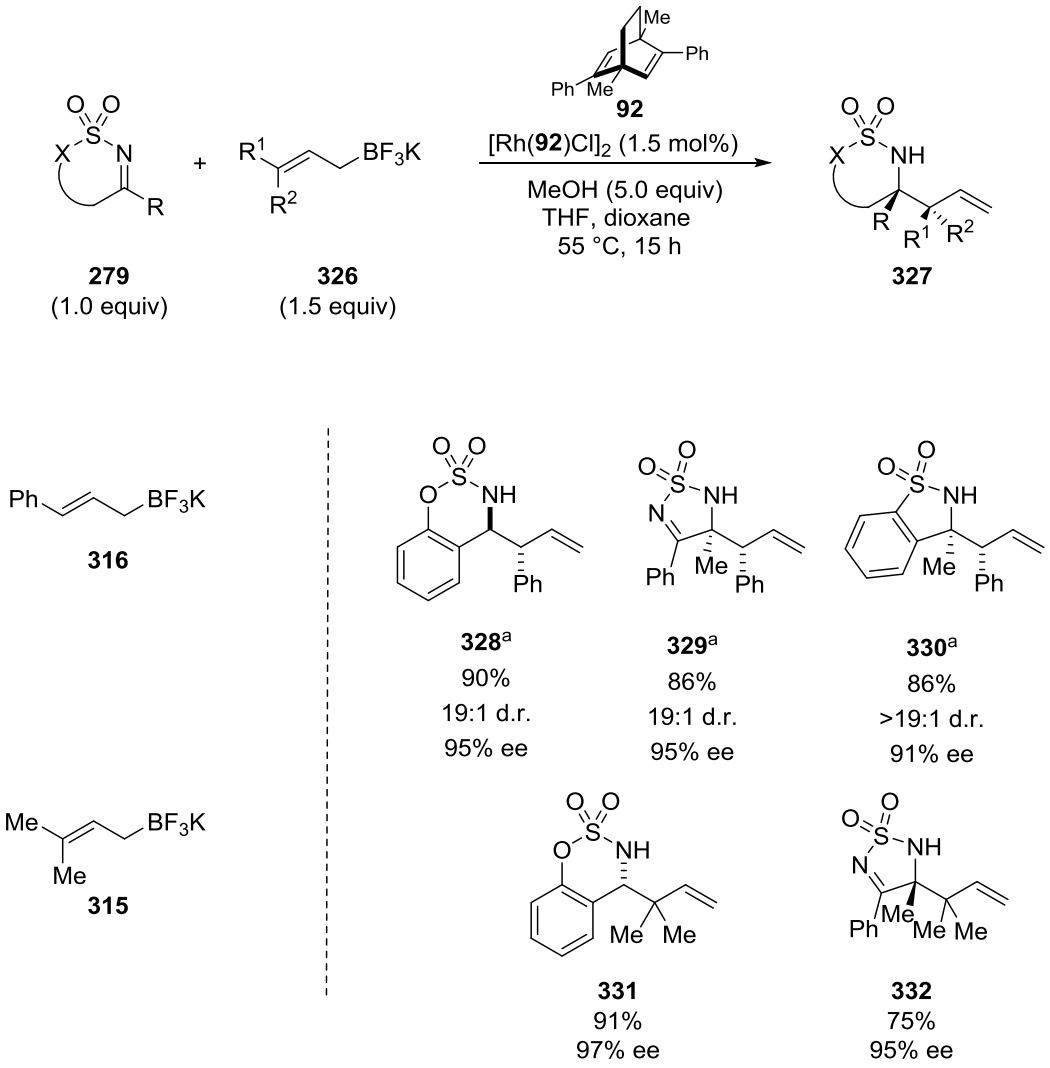
4.5.2 Allylation Reactions Using More Highly Substituted Allylboron Reagents

Following the synthesis of substituted potassium allyltrifluoroborates, it was decided to first investigate the addition of γ-substituted allyl trifluoroborates using aldimine **89a**, ketimine **276a**, and ketimine **269a** as a representative cross-section of the cyclic imines that are known to work with potassium allyltrifluoroborate. Using potassium (*E*)-2-hexen-1-yltrifluoroborate (**317**), and identical conditions to those used previously, albeit with an increase of reaction time to ensure the reaction proceeded to completion, and it was found that only the α-substituted *anti*-product was formed with all three cyclic imines (Scheme 4.34). These results demonstrate that clean allylic transposition occurs, forming the new carbon–carbon bond at the more highly substituted γ-carbon of the allyltrifluoroborate. These results indicate the rhodium-based catalytic system can also exert good diastereomeric control, as well as good enantiomeric control.



Scheme 4.34: Reactions with (*E*)-2-hexen-1-yltrifluoroborate

Other γ-substituted allyltrifluoroborates exhibited similar reactivities. Potassium cinnamyltrifluoroborate (**316**) also exclusively furnished the α-aryl *anti*-product in high yields, diastereomeric ratios and enantiomeric excess for all three cyclic imine substrates. Potassium prenyltrifluoroborate (**315**) gave the α,α-disubstituted product in good yield with aldimine **89a** and ketimine **276a**, illustrating that it is also possible to form quaternary centres adjacent to the stereocentre (Scheme 4.35).

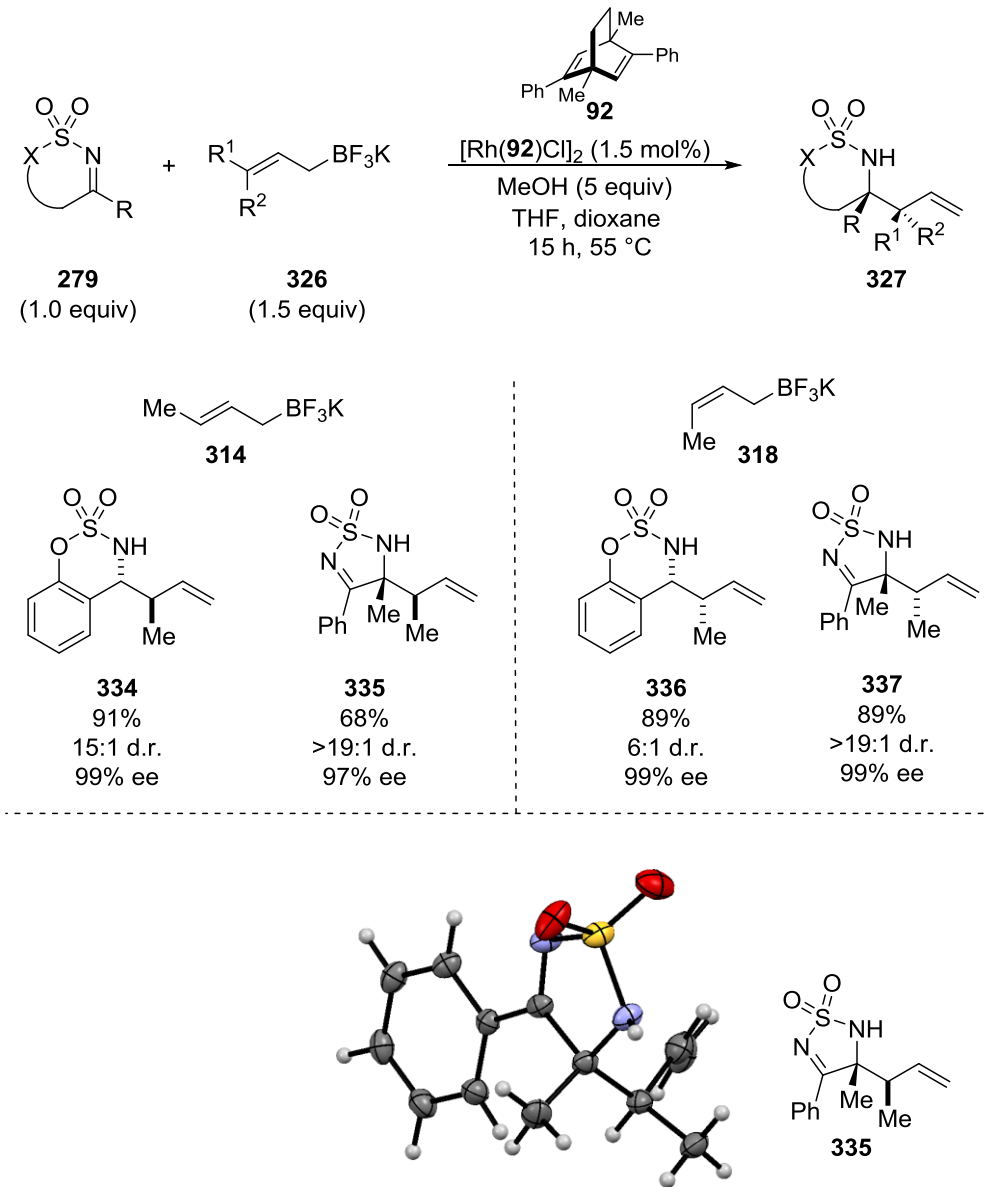


[a] Using *ent*-**92**

Scheme 4.35: Allylation reactions involving cinnamyl- and prenyl- trifluoroborates

Experiments were undertaken to investigate the contribution of the stereochemical information present in the olefin of the allyltrifluoroborate towards the relative stereochemistry. Previous studies have shown it to be somewhat difficult to synthesise the less thermodynamically favourable *syn*-diastereomer (See Section 4.2.5).[131] However, it was found that the rhodium-catalysed addition of allyltrifluoroborates allowed access to both the *anti* and *syn*-products depending on the nature of the starting allyltrifluoroborate. It was found that *E*-crotyltrifluoroborate (**314**) gave exclusively the α-methyl *anti*-product with ketimine **276a** (confirmed by single crystal X-ray diffraction) and the similar product with aldimine **89a** in a d.r. of 15:1. Conversely, *Z*-crotyltrifluoroborate (**318**) gave the

opposite α-methyl *syn*-product as either the major diastereomer (aldimine **89a**) or as the exclusive product (ketimine **276a**) (Scheme 4.26).

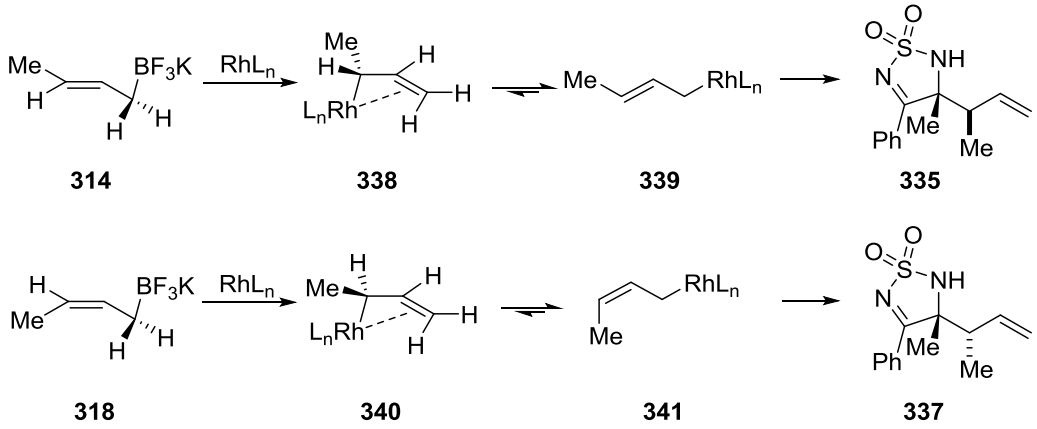


X-ray structure of product **335**

Scheme 4.36: Reactions involving (*E*)- and (*Z*)-allyl species

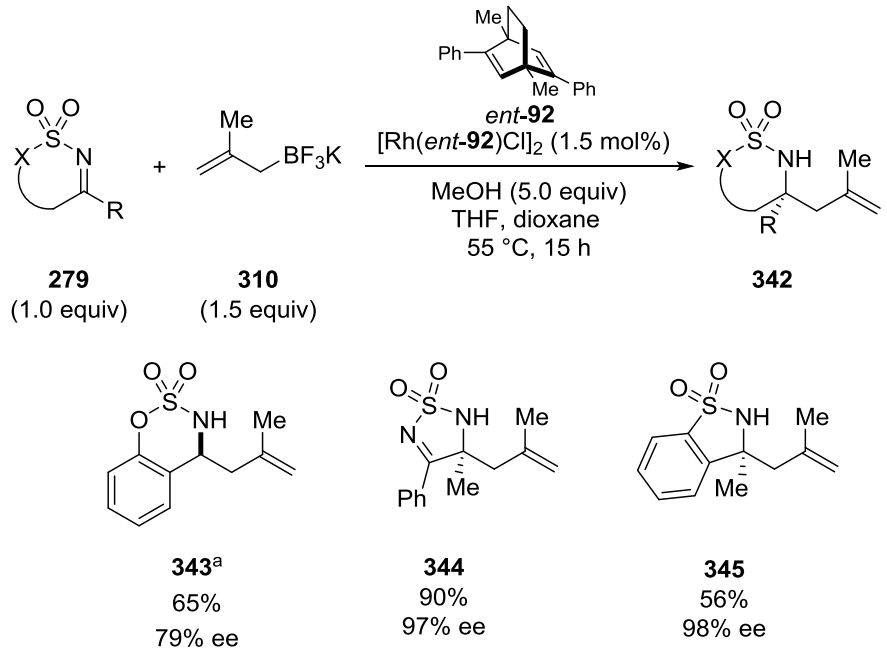
These results indicate that the stereochemical information embedded within the olefin can be transferred into the product of the allylation reaction. The reason for this transfer of stereochemical information is not readily explainable. Transmetallation may occur at the least hindered carbon, leading to the conservation of the stereochemistry. Alternatively, a form of weak bonding interaction between

rhodium and the olefin, forming an intermediate that can transfer *E* and *Z* stereochemistry could be maintaining stereochemistry (Scheme 4.37). Similar proposals were put forward by both Evans and co-workers[154] and the group of Oshima and Yorimitsu.[135]



Scheme 4.37: Proposed mechanism of conserved stereochemistry

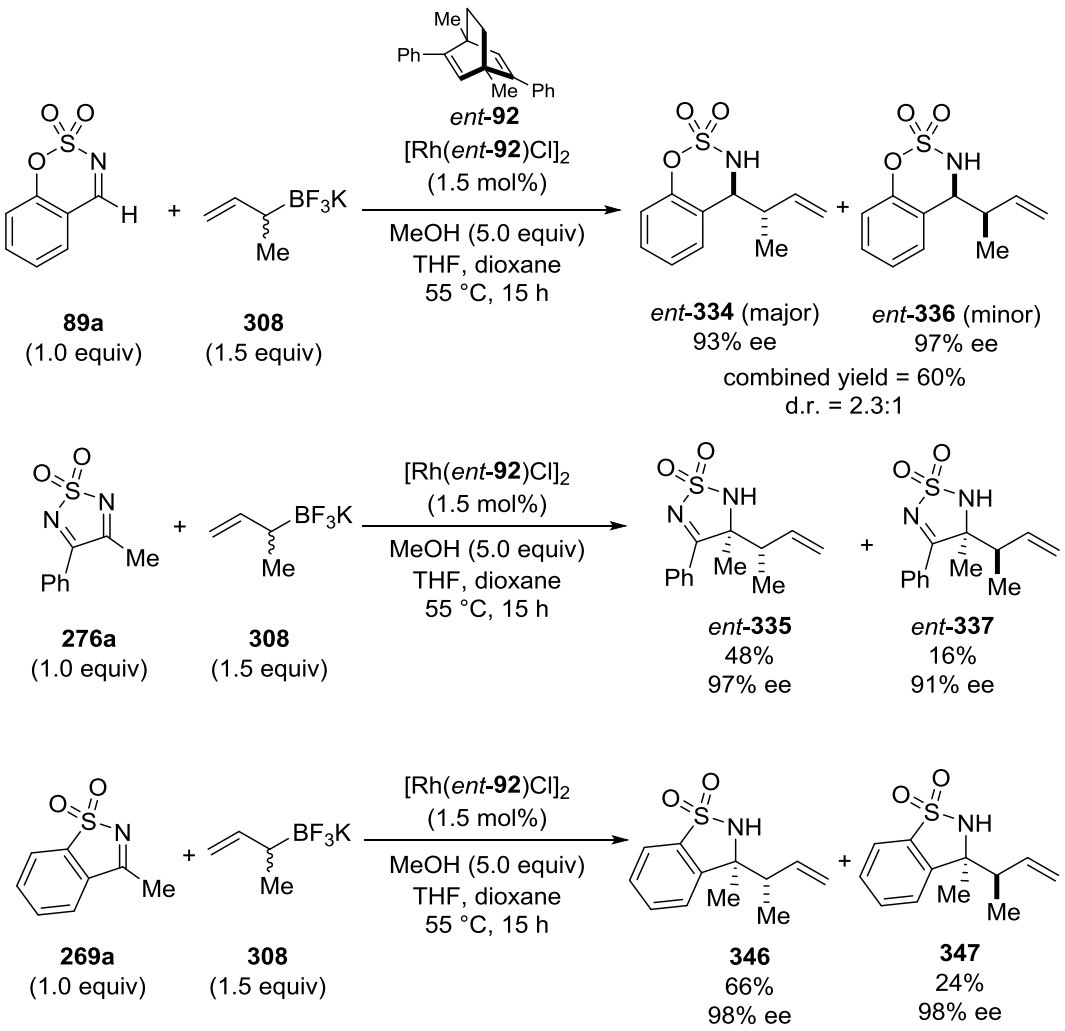
With ketimine **276a** and **269a**, potassium *β*-methylallyltrifluoroborate (**310**) was effective, and the *β*-substituted products were synthesised in moderate to good yields and high enantioselectivities. However, the product derived from aldimine **89a** was found to have only moderate enantioselectivity (50% ee), Altering the conditions to toluene/*i*-PrOH improved the enantiomeric excess to 79% (Scheme 4.38).



[a] Using toluene/*i*-PrOH instead of THF/MeOH

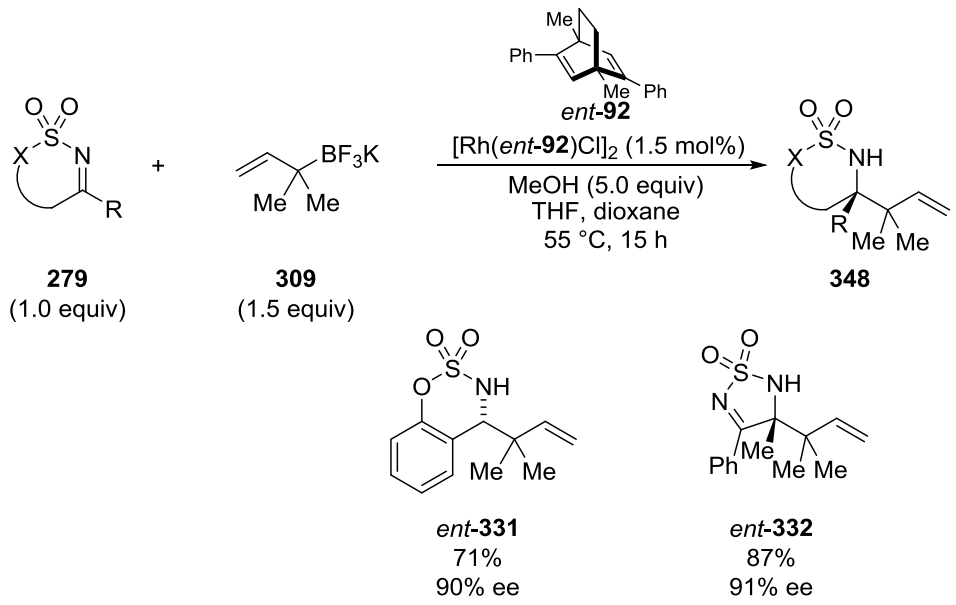
Scheme 4.38: Allylation reactions with *β*-methylallyltrifluoroborate (**310**)

The *α*-substituted allyl species were also reacted successfully. Interestingly, they also gave the identical product to that obtained from *γ*-substituted allyl species. Racemic potassium *α*-methyltrifluoroborate **308** furnished the *α*-substituted product in good yields and enantioselectivities. However, this reagent gave poor diastereomeric ratios for all cyclic imines. In the case of ketimines **276a** and **269a**, it was possible to separate the two diastereomers using chromatography (Scheme 4.39)



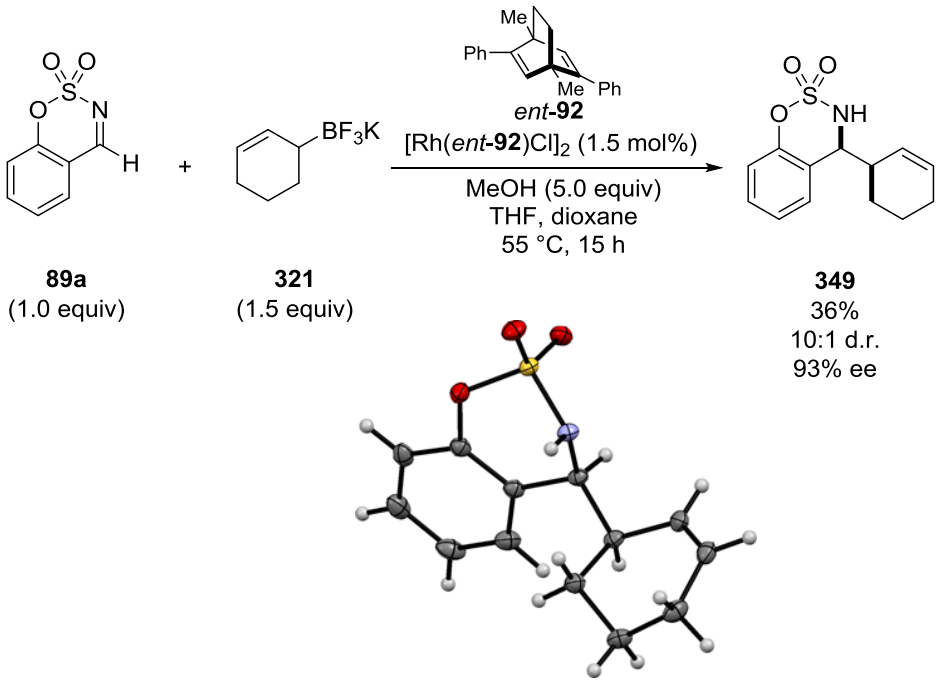
Scheme 4.39: Reactions involving *α*-methylallyltrifluoroborate (**308**)

α,α-Dimethylallyltrifluoroborate (**309**), the isomeric form of prenyltrifluoroborate (**315**), also reacted in a similar manner, giving the same products as the prenyl species (see Scheme 4.35 previously), albeit in a slightly lower enantiomeric excess, (**331** = 97% ee v 90% ee and **332** 95% ee v 91% ee) (Scheme 4.40).



Scheme 4.40 Reactions involving *α*,*α*-dimethylallyltrifluoroborate

Cyclic allyltrifluoroborates were also investigated in the allylation reaction. Unfortunately, with potassium 2-cyclohexen-1-yltrifluorborate (**321**) and ketimine **276a**, no product was observed. However, with the appreciably more reactive aldimine **89a**, the allylation product **349** was isolated in 36% yield but with high diastereomeric ratio and enantiomeric excess. The cyclic trifluoroborate features a *Z* alkene, and therefore it would expected to form the *syn*-diastereomer as the major product and this was confirmed by single crystal X-ray diffraction, further confirming that the stereochemical information contained within the double bond is important in determining which diastereomer is the major product of the reaction (Scheme 4.41).



Scheme 4.41:Reaction involving a cyclic trifluoroborate salt

4.6 Elucidation of the Mechanism

In order to further the understanding of this rhodium-catalysed nucleophilic allylation, consideration of the possible mechanistic pathways was required. Tentatively, three possible mechanisms were identified as being feasible: Pathway 1 involves the rhodium species acting as a chiral Lewis acid, activating imine **352** towards nucleophilic attack; Pathway 2 involves transmetallation between the allylboron reagent and rhodium to form allylrhodium species **353** that cannot interconvert between the two possible σ-haptomers (**353** and **355**). This allylrhodium species **353** then undergoes nucleophilic attack of imine **354**, similar to mechanism proposed for reactions involving indium[129] and zinc;[128] Pathway 3 is similar to pathway 2. However, the resultant allylrhodium species **353** can interconvert between the two possible σ-haptomers (**353** and **355**) before undergoing nucleophilic attack of imine **354** (Figure 4.3).

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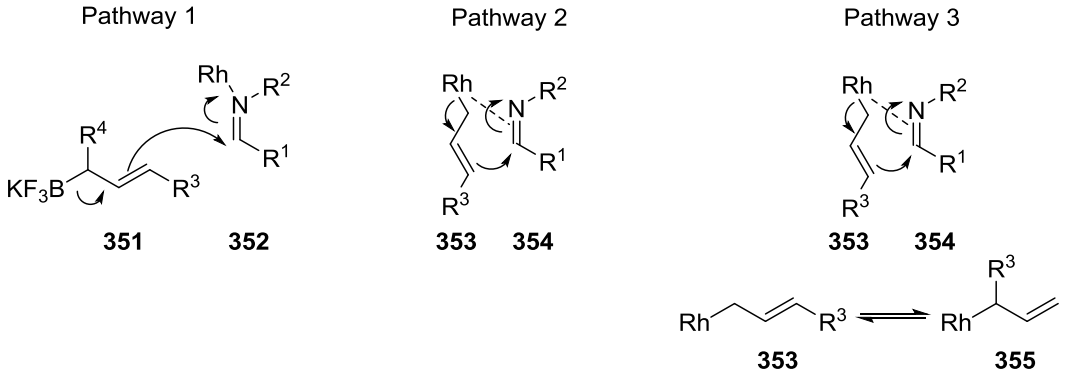
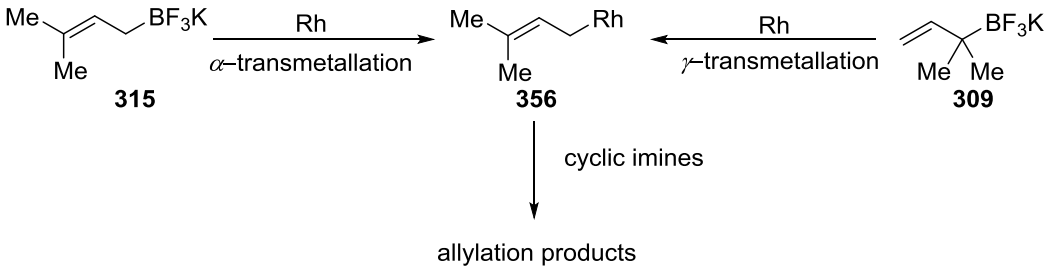


Figure 4.3: Possible mechanistic pathways

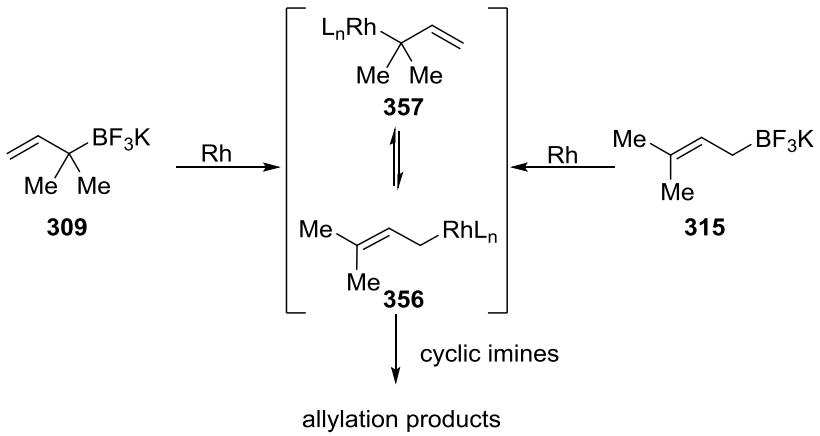
Upon considering these mechanisms, the product isolated from the reactions involving α-substituted allyltrifluoroborates featured α-substitution (see Schemes 4.39 and 4.40), demonstrating that pathway 1 cannot be operative. Under pathway 1, α-substituted allyl species would give the γ-substituted products rather than the isolated α-substituted products. Thus, the two more plausible pathways are pathway 2 and pathway 3. This indicates that transmetallation between the rhodium and the allyltrifluoroborate is likely to occur. The results obtained from the reactions involving the α-substituted allyltrifluoroborates do not help determine whether pathway 2 or 3 is in operation because, in the case of pathway 2, transmetallation may be occurring from the least hindered position, resulting in α-transmetallation in the case of the prenyl species and γ-transmetallation in the case of the α,α-dimethyl species (Scheme 4.40). If this was the case, these two allyl species would furnish the same allylrhodium species which would not be required to undergo isomerisation to give the product (Scheme 4.42).



Scheme 4.42: Possible alternative routes of transmetallation in pathway 2

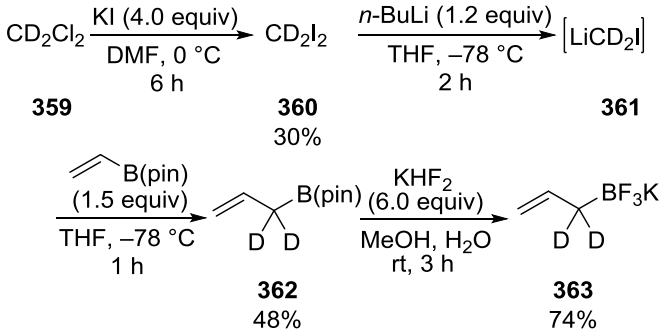
Alternatively, pathway 3 is an option where both allyltrifluoroborates could undergo the same method of transmetallation, leading to the two different allylrhodium σ-

haptomers which could then interconvert. To then only observe a single product, one of the allylrhodium haptomers must be more reactive, leading to the formation of a single allylation product (Scheme 4.43).



Scheme 4.43: The interconversion of allyl-rhodium intermediates in pathway 3

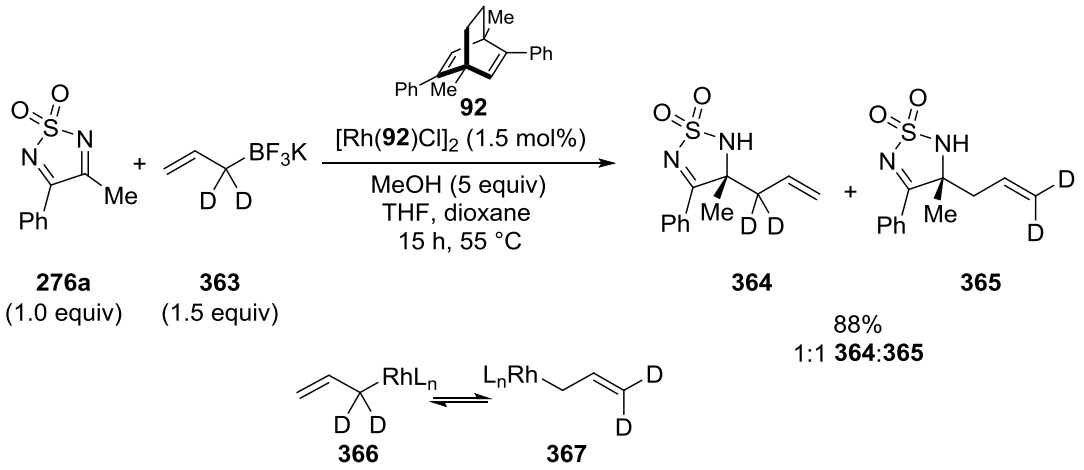
In order to attempt to distinguish between pathway 2 and 3, dideuterated potassium allyltrifluoroborate **363** was synthesised from dideuterated dichloromethane (**359**) (reactions performed by Dr Yunfei Luo). First, halide exchange with potassium iodide gave dideuterodiiodomethane (**360**), lithium-halogen exchange then occurred with *n*-BuLi to give compound **361**. Homologation of this compound with vinylboronic acid pinacol ester (**362**) gave the corresponding *α*,*α*-dideuteroallylboronic acid pinacol ester which was converted into the trifluoroborate **363** using KHF_2 (Scheme 4.44).



All reaction carried out by Dr Yunfei Luo

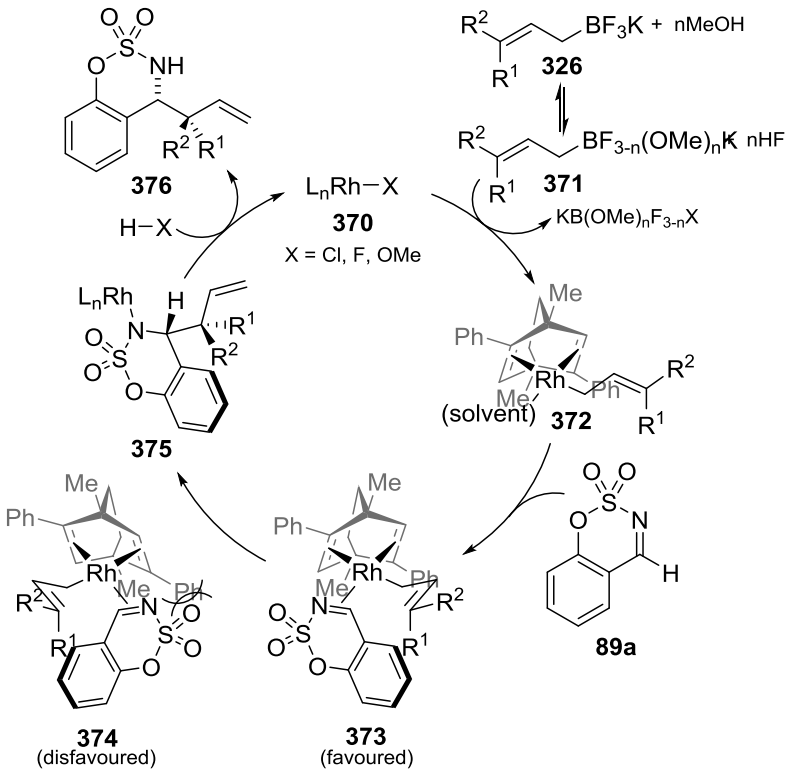
Scheme 4.44: The synthesis of dideuteroallyltrifluoroborate

Substituting the allyltrifluoroborate **234** for its deuterated equivalent **363** in the reaction with ketimine **276a**, resulted in the formation of an exact 1:1 mixture between the α-deutero product **364** and the γ-deutero product **365** (Scheme 4.45). This scrambling of the deuterium label strongly suggests that pathway 3 is in operation and that the allylrhodium species can interconvert post-transmetallation, leading to the observed product distribution. These observations and conclusions are the same as proposed by Jarvo and co-workers for the iridium-catalysed allylation of ketones.[155]



Scheme 4.45: Allylation with deuterated allyl species

It is important to note that even though these results suggest that pathway 3 is in operation and the allylrhodium species can interconvert, it does not show or provide evidence to determine whether the transmetallation occurs *via* α-transmetallation or γ-transmetallation. With the information gathered from the reaction involving more highly substituted allyl species and the deuterium labelling experiments, the following catalytic cycle was proposed (Scheme 4.46).



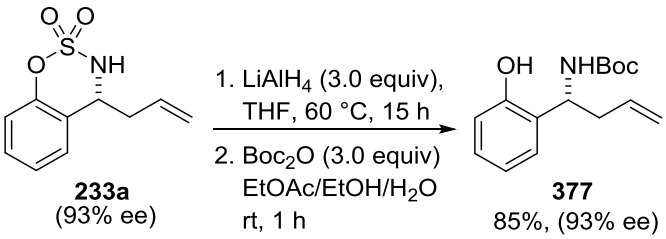
Scheme 4.46: Proposed catalytic cycle

In the presence of methanol, the trifluoroborate **326** undergoes methanolysis to form the mixed fluoro-alkoxide species **371**. This activated species then undergoes transmetallation with the rhodium-diene complex **370** to form allyl-rhodium species **372**. The imine **89a** then co-ordinates with the allylrhodium species forming a six-membered chair-like transition state followed by addition of the allyl group. Release of the product **376** and regeneration of the catalyst, most probably by methanol then occurs. It is proposed that the enantiodiscrimination occurs from the chair-like transition state **373**, the conformer **373** is favoured over conformer **374** to minimise steric clash between the sulfonyl group of the imine and the aryl group of the chiral diene leading to observed stereochemistry of the products.

4.7 Derivatisation of Products

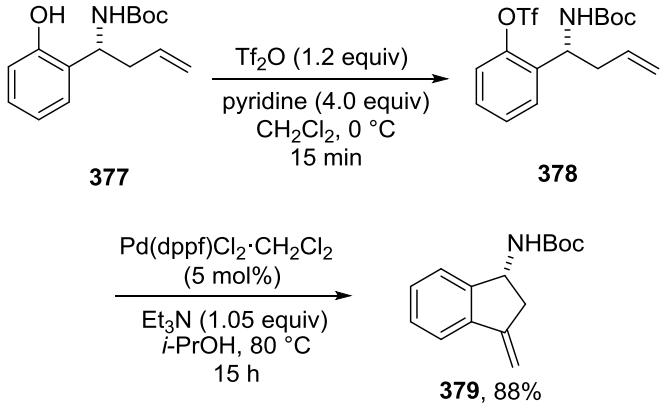
The sulfonyl group not only held the imine in the *Z*-geometry, essential for enantiomeric induction, but also proved to be an excellent functional handle to allow further manipulations of the products. Treating **233a** with lithium aluminium hydride

removed the sulfonyl bridge, and following Boc-protection, amino-phenol **377** was isolated in 85% yield with no loss of enantioselectivity (Scheme 4.47).



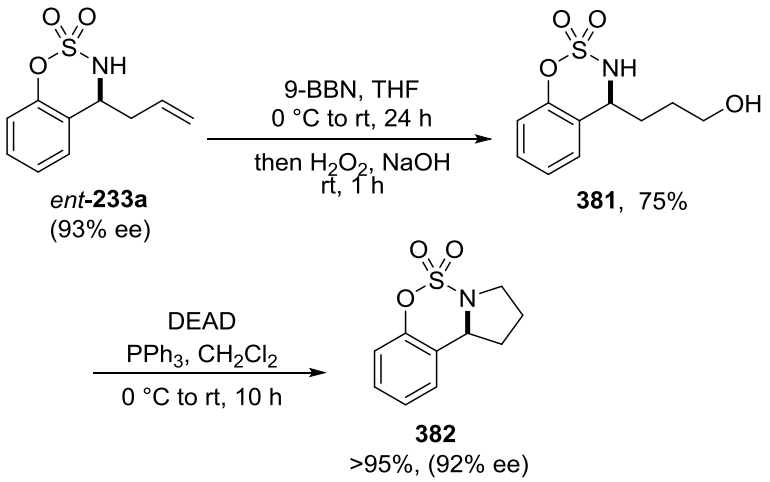
Scheme 4.47: Removal of the sulfonyl group

Triflation of product **377** resulted in the generation of alkenyl-aryltriflate **378** which, when subjected to palladium catalysis, underwent a *5*-exo-*trig* Heck cyclisation to give the bicyclic amine **379** in 88% yield (Scheme 4.48).



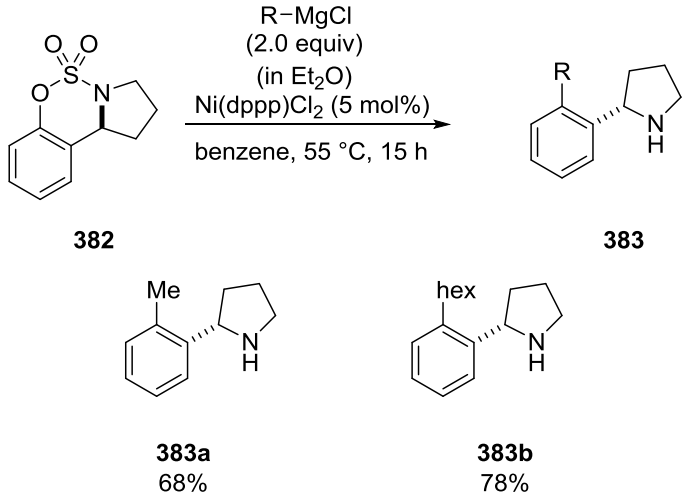
Scheme 4.48: Intramolecular Heck cyclisation

Functionalisation of the olefin within product **233a** was also achieved. A hydroboration/oxidation sequence of *ent*-**233a** furnished the alcohol **381** in good yield, which then underwent Mitsunobu cyclisation to give the tricyclic sulfamate **382** in good yield (Scheme 4.49).



Scheme 4.49: Formation of tricyclic sulfamate **382**

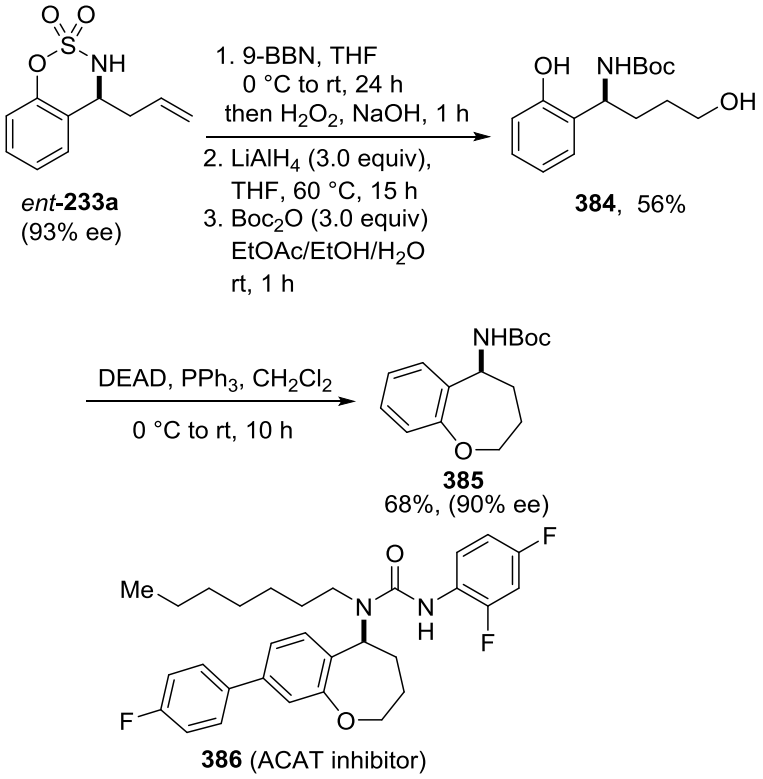
The sulfonyl group can also act as a pseudo-halide, oxidative insertion of transition metals can occur between the carbon and oxygen bond, allowing cross-coupling reactions to be examined. The sulfonyl group in tricyclic sulfamate **382** was shown to be a suitable leaving group for the nickel-catalysed Kumada cross-coupling with alkyl Grignard reagents, a method developed by Du Bois.[156] These cross-coupling reactions proceeded to furnish the enantioenriched 2-arylpyrrolidines in moderate yields (Scheme 4.50).



Scheme 4.50: Cross-coupling of sulfamate and Grignard reagent

Allylation product **233a** also underwent sequential hydroboration/oxidation, sulfonyl removal then Boc-protection to give aminodiol **384** in an overall yield of 56%. This compound then underwent a Mitsunobu cyclisation to give tetrahydrobenzoxepine

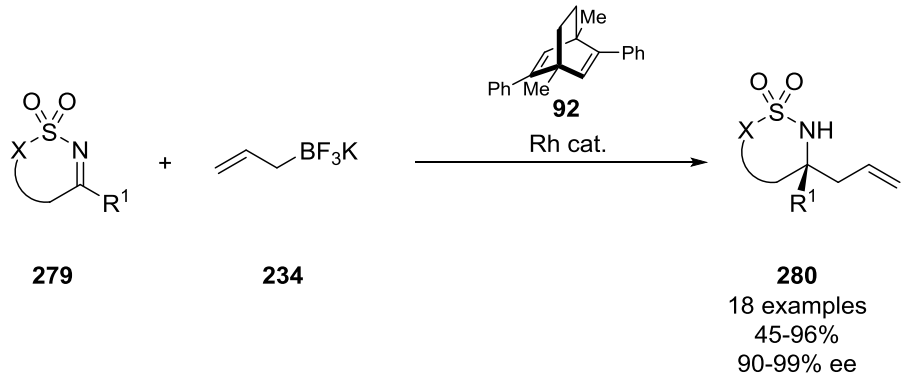
385 in 68% yield and 90% ee. Compounds containing tetrahydrobenzoxepines (**386**) have been shown to be acyl coenzyme A, cholesterol *O*-acyltransferase inhibitors, and useful in the treatment of atherosclerosis (Scheme 4.51).[157]



Scheme 4.51: Synthesis of tetrahydrobenzoxepine **385**

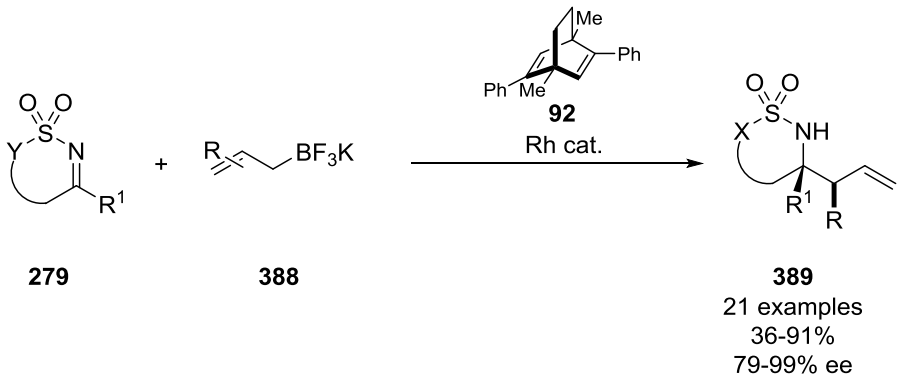
5.0 Conclusions and Future Work

In summary, a new rhodium-catalysed enantioselective nucleophilic allylation of cyclic imines using potassium allyltrifluoroborates has been developed. Using a rhodium-chiral diene complex, a wide range of cyclic aldimines and cyclic ketimines have been shown to be suitable for allylation, and giving the products with good yields and high enantioselectivities (Scheme 5.1).



Scheme 5.1: Rhodium-catalysed enantioselective nucleophilic allylation of cyclic imines

Furthermore, more highly substituted allylboron reagents were excellent allylating agents, leading to a range of products bearing multiple stereocentres in good yields, high diastereomeric ratios and high enantioselectivities (Scheme 5.2).

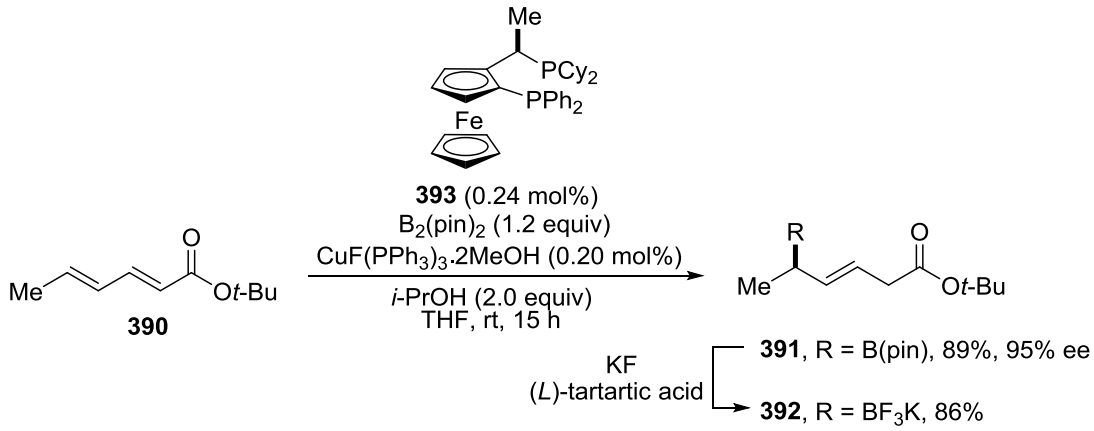


Scheme 5.2: Reactions using more highly substituted allylboron species

Experiments using both deuterated species and isomeric allyltrifluoroborates gave insight to the mechanistic pathway and allowed a possible mechanism to be proposed. Also, the products were further derivatised into small molecules that

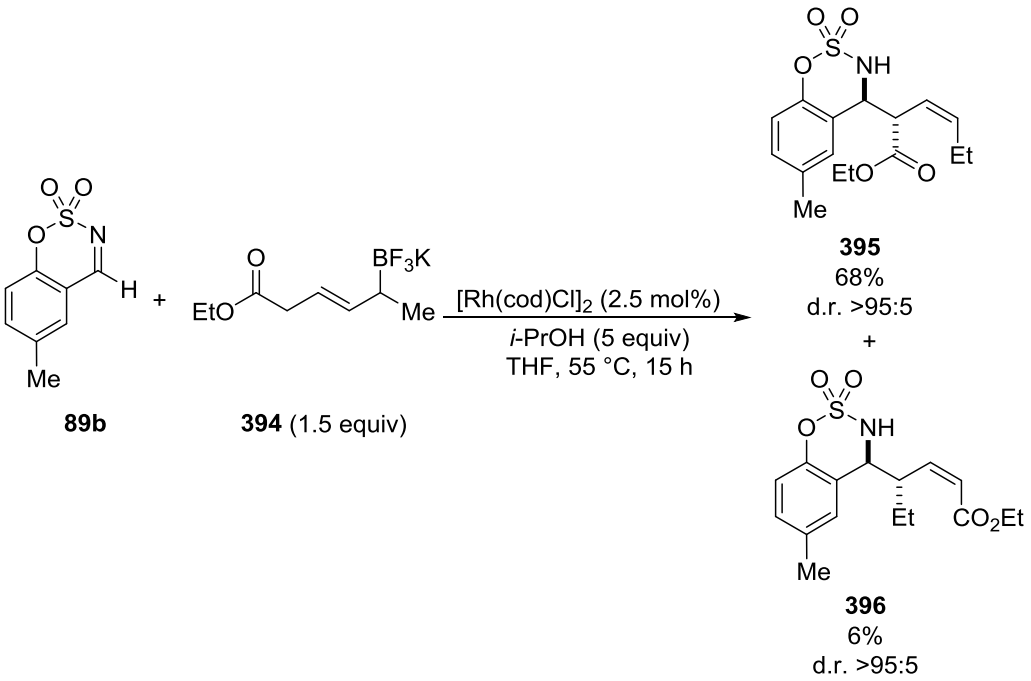
feature key structural motifs that are either useful in organic synthesis or feature in biologically active molecules.

Previously, the Lam group developed an enantioselective 1,6-selective boration of $\alpha,\beta,\gamma,\delta$-dienones **390**. These products featured an allylic boronic ester which was successfully converted into the corresponding trifluoroborate salt **392** (Scheme 5.3).[158]



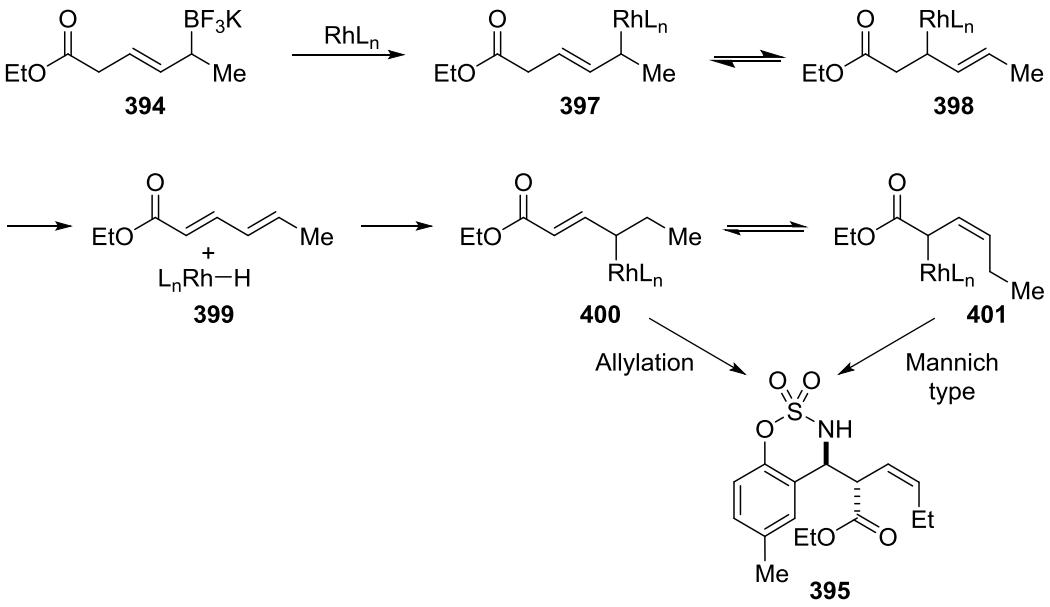
Scheme 5.3: Formation of allylboron species *via* 1,6-boration

Subjecting racemic allylboron species **394**, formed in a similar way, to the reaction conditions developed for the rhodium-catalysed nucleophilic allylation resulted in the formation of two very interesting products, **395** and **396** (Scheme 5.4).[158]



Scheme 5.4: Product recovered after reaction with **394**

The formation of products **395** and **396** indicate an interesting isomerism is occurring post-transmetallation, and both major and minor products are a single observable diastereomer and feature a *cis*-olefin. This isomerisation has been successfully repeated on a range of aldimines and ketimines to give the same product, similarly variation of the trifluoroborate salt also gives the similar isomerisation products. Currently, the proposed mechanism involves a *β*-hydride elimination from allylrhodium species **398** to form diene/rhodium-hydride species **399** Reinsertion of the rhodium-hydride forms allylrhodium species **400** and this species could undergo an allylation reaction to give product **395** (Scheme 5.5).



Scheme 5.5: Proposed mechanism for the formation of **395**

However, it is not currently clear whether the formation of the new carbon-carbon bond between the allyl moiety and the imine occurs *via* a rhodium-catalysed allylation or a rhodium-enolate based Mannich-type addition (Scheme 5.5). Work is undergoing within the Lam group to expand the scope of this reaction, develop an asymmetric version, further understand the mechanism, and to distinguish between the possible pathways.

Chapter 2: The Isomerisation of Allylrhodium Intermediates in the Nucleophilic Allylation of Cyclic Imines

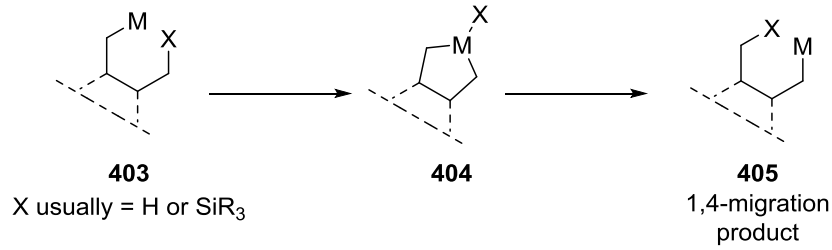
1.0 Transition Metal Catalysis

Transition metals have irrefutably become an essential tool for forming new bonds in modern organic synthesis. These highly versatile metals have proved to be excellent catalysts for a range of reactions including: the formation of carbon–carbon, carbon–hydrogen, carbon–heteroatom bonds, and asymmetric additions.[159] The importance of these reactions is reflected by the fact that no fewer than nine chemists have been awarded the Nobel Prize for work pertaining to transition metal catalysts and their use in organic synthesis: William S. Knowles,[160] Ryoji Noyori,[161] K. Barry Sharpless,[162] Yves Chauvin,[163] Robert H. Grubbs,[164] Richard R. Schrock,[165] Richard F. Heck,[166] Ei-ichi Negishi,[167] and Akira Suzuki.[168] The reactions developed by these chemists and a plethora of other transition metal catalysed transformations are now a fundamental part of both academic and industrial synthetic organic research.

The chemical behaviour of transition metal catalysts can often be defined by four key processes: ligand substitution, oxidative addition/reductive elimination, insertion/elimination, and nucleophilic/electrophilic attacks. However, other processes can also be observed for transition metals, although in a far smaller number of cases. 1,4-Migration is a well-described "non-standard" process, and involves the metal undergoing a 1,4-shift to form an isomeric metal species.[169,170]

1.1 1,4-Migration of Transition Metals

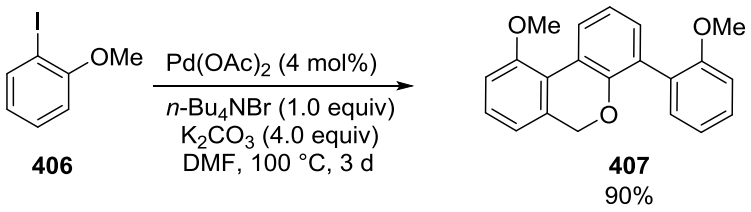
Transition metal 1,4-migration is a reaction pathway where a metal species **403** migrates to a carbon four atoms away. It is thought that this process proceeds through a rapid and reversible C-H insertion/reductive elimination process *via* metallacycle **404** (Scheme 6.1). The insertion process is not limited to C-H bonds, and other atoms such as silicon can also be exchanged.[169,170]



Scheme 6.1: Formal pathway of 1,4-migration

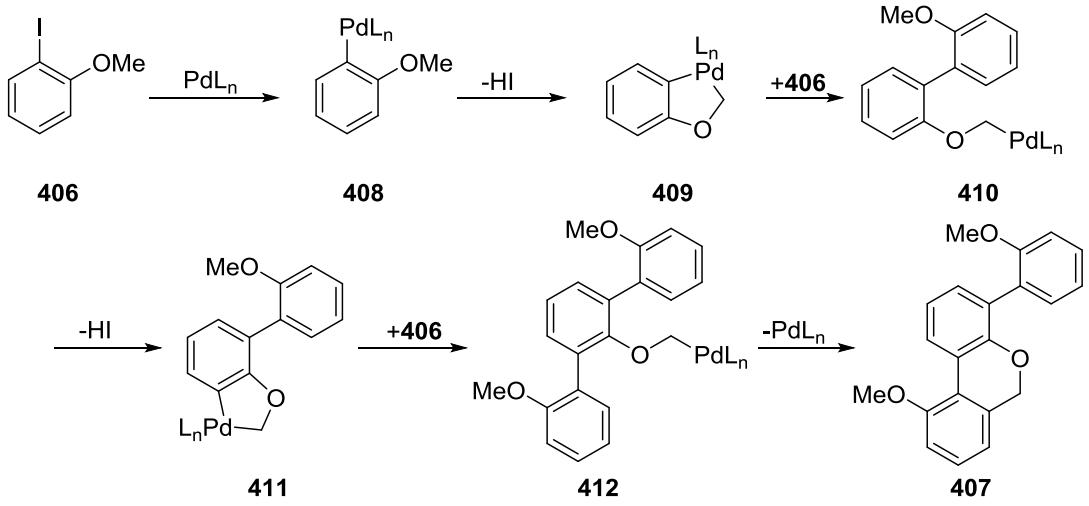
1.2 1,4 Migration of Palladium Species

Although earlier reports observed products that were likely to arise from a 1,4-migration,[171,172] the first proposed 1,4-migration mechanism was by Gerald Dyker in 1992. This report involved a 1,4-palladium migration during the Pd-catalysed trimerisation of *ortho*-iodoanisole (**406**) (Scheme 6.2).[173]



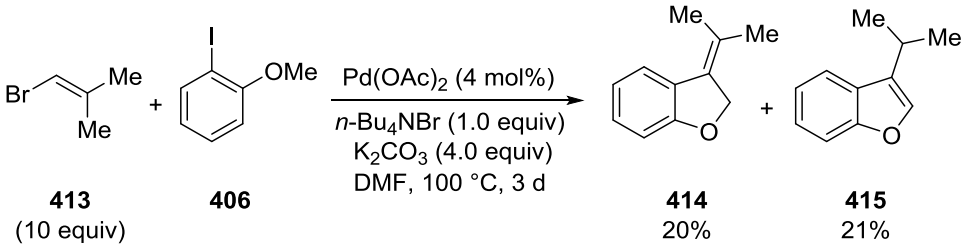
Scheme 6.2: Trimerisation of *ortho*-iodoanisole[173]

Dyker rationalised the formation of such an unusual product by the following mechanism (Scheme 6.3). First, oxidative addition of the aryliodide to palladium occurs to form arylpalladium(II) species **408**. This undergoes cyclometallation by intramolecular 1,4-C-H activation of a methyl proton and forms palladacycle **409**. Further oxidative addition of an additional equivalent of **406** gives rise to a palladium(IV) reactive intermediate which then undergoes a reductive elimination to give **410**. A second cyclometallation forms intermediate **411**, which is then proposed to undergo a second Pd(II)-Pd(IV)-Pd(II) cross-coupling sequence to yield palladium species **412**. A third cyclometallation followed by a reductive-coupling liberates the product **407** and a Pd(0) species.



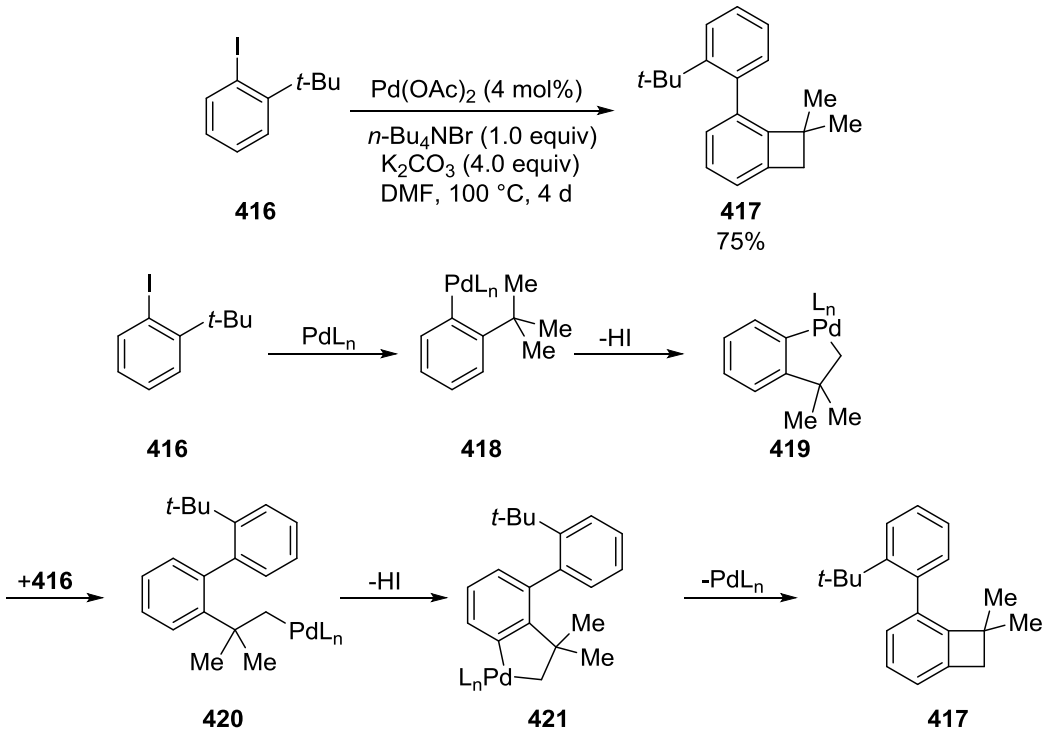
Scheme 6.3: Proposed mechanism of trimerisation involving 1,4-migration[173]

This work is arguably not a true 1,4-migration because the hydrogen in the 4-position does not end up in the 1-position. However, it is the first proposed illustration of palladium being able to migrate within a reactive intermediate. Dyker further extended this work by using alkenyl-bromide species **413** to undergo a cross-coupling with the palladacycle **409** (Scheme 6.4).[174] He recovered a mixture of products, with ether **414** and benzofuran **415** being the main components of the mixture.



Scheme 6.4: Trapping the palladacycle with an alkenyl bromide[174]

Dyker also demonstrated that the 1,4-C-H activation was not limited to a relatively acidic methoxy hydrogen. A far less acidic *tert*-butyl group, was also reported to undergo the transformation (Scheme 6.5).[175] Substrate **416** was found to act in a slightly different manner than iodoanisole (**406**). After C-H activation and cross-coupling, the alkyl-palladium species **420** underwent an additional C-H activation-migration (from a C–sp^3 to a C–sp^2) to form second palladacycle **421**. Reductive elimination from this species gave cyclobutane **417**.



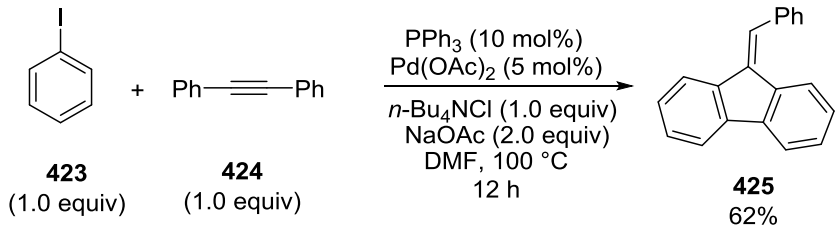
Scheme 6.5: Activation of *tert*-butyl group[175]

Despite these promising reports by Dyker, there were no further reports of 1,4-palladium migrations between the years 1994 and 1999. From 2000 there has been a host of reports on the 1,4-migration of palladium leading to an increasingly mature field. Palladium 1,4-migrations can be split into three main categories with each defined by the nature of the sites of migration: migration of palladium from a C–sp^2 centre to a second C–sp^2 centre, migration of palladium from a C–sp^2 centre to a C–sp^3 centre, and migration of palladium from a C–sp^3 centre to a C–sp^2 centre.

1.2.1 The 1,4-Migration of Palladium from a C–sp^2 Centre to a C–sp^2 Centre

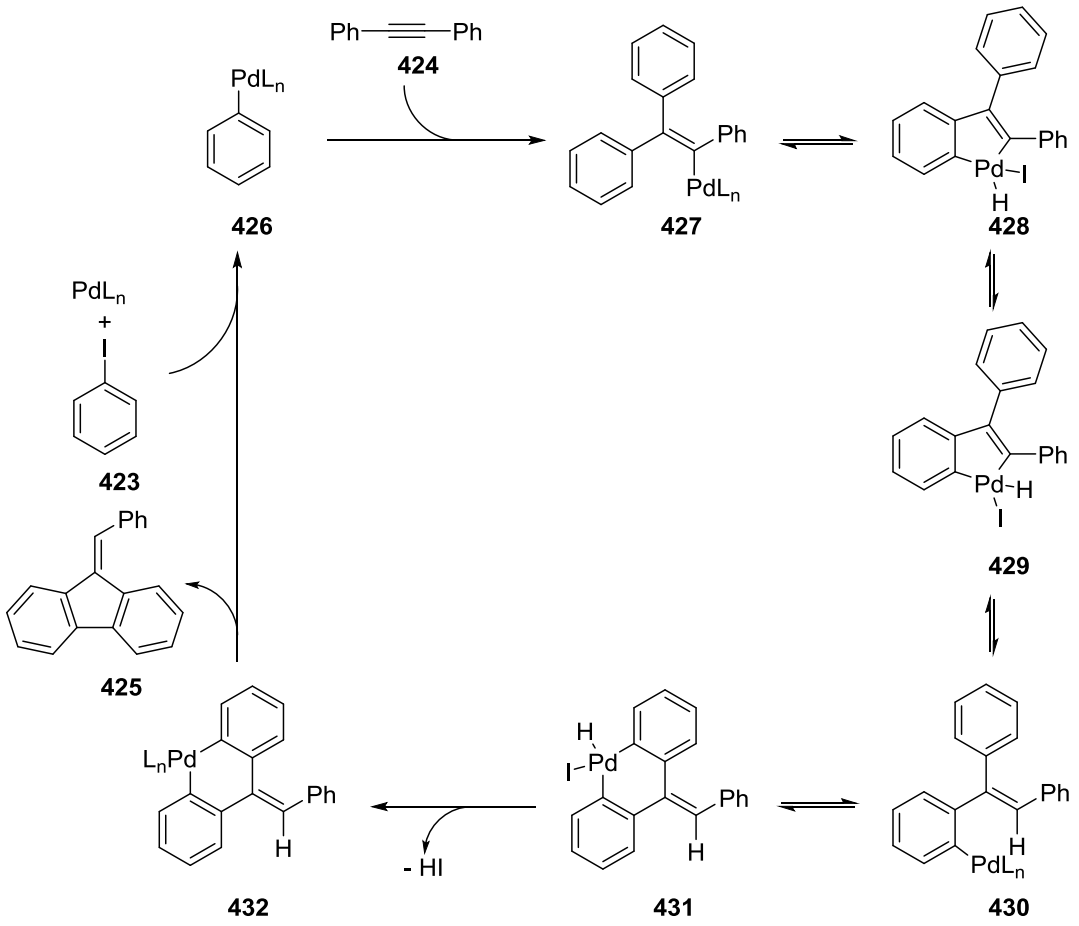
Although Dyker's pioneering work was mainly sp^2–sp^3 migration, most research has been focussed on sp^2–sp^2 1,4-migration. This is due to the stability of C–sp^2-palladium species, the ease of accessing such intermediates, and the usefulness of the products formed. The first report of a sp^2–sp^2 1,4-migration came from the group of Larock in 2000 (Scheme 6.6).[176] They reported that in the presence of palladium, a bisphosphine ligand, base and a chloride source, the reaction between iodobenzene

(**423**) and diphenyl acetylene (**424**) gave fluorene **425**. Screening of reagents and condition optimised this process to give **425** in a 62% yield.[176,177]



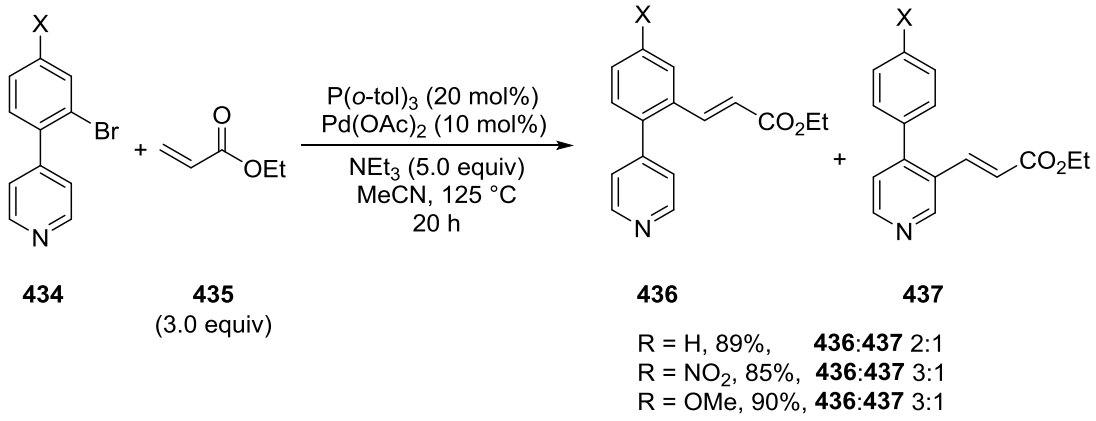
Scheme 6.6: Formation of fluorene **425** *via* 1,4-migration[176,177]

The rationalisation of the formation of fluorene **425** involves a 1,4-migration (Scheme 6.7). Initially, oxidative addition of iodobenzene (**423**) to palladium gives palladium(II) species **426**. Addition of this species across the triple bond of **424** gives triaryl species **427**. Then, a 1,4-migration of palladium *via* a bridged Pd(IV) intermediate **428** gives **430** after isomerisation. Rotation of the aryl-alkenyl bond allows the occurrence of a second C-H activation to form bis-aryl species Pd(IV) species **431**. Reductive eliminations of HI and C-C bond formation gives fluorene (**425**) and regenerated the catalytic species. Larock does acknowledge that rather than proceeding *via* a Pd(IV) species, it may proceed *via* an electrophilic aromatic substitution.[177]



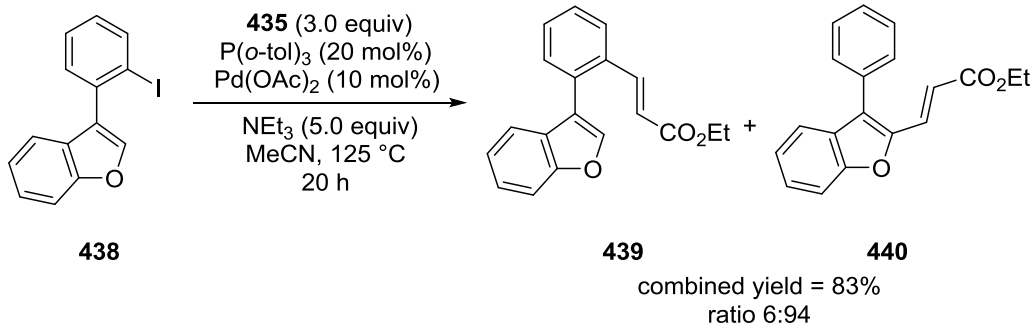
Scheme 6.7: Proposed catalytic cycle by Larock[176,177]

Following the disclosure of an alkenyl to aryl palladium migration, the corresponding aryl to aryl palladium migration was reported around the same time. The groups of both Gallagher[178] and Larock[179] observed similar migratory behaviour. During Gallagher's investigations into the Heck reaction between ethyl acrylate (**435**) and biaryl pyridines **434**, they observed an important minor side product **437** resulting from the palladium 1,4-migration as well as the expected cross-coupling product **436** (Scheme 6.8).[178] Conditions were not optimised to favour the migration product, and no pronounced effect on either yield or ratio between **436** and **437** was found to exist when varying the electronic nature of the substituent.



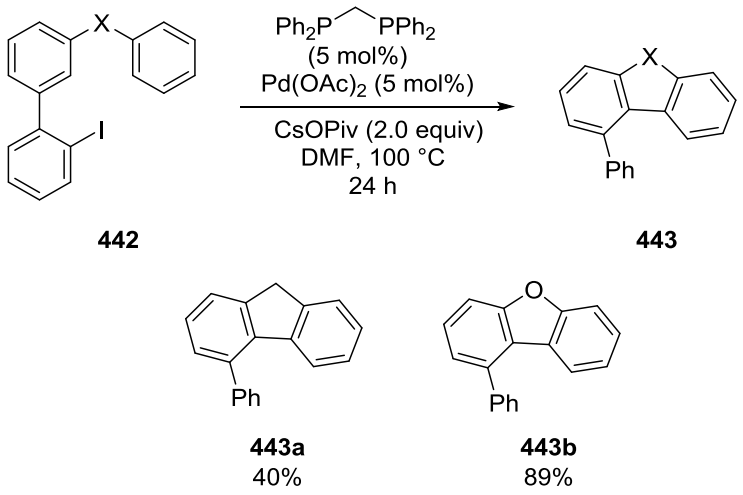
Scheme 6.8: Cross-over Heck reaction[178]

Independently and almost simultaneously, Larock and co-workers disclosed a similar 1,4-migration during the attempted Heck reaction between bis-aryl halides and acrylates (Scheme 6.9).[179] Following attempts at optimising the conditions in favour of a 1,4-migration product, the best ratio attained for a range of standard bis-aryl species was a 1:1 mixture of standard Heck product **436** and migration Heck product **437**. Modifying the substrates, in particular replacing the aryl ring that was to receive the palladium in the migratory process with a benzofuran **438**, resulted in a large increase in selectivity in favour for the migration product **440** and it was possible to isolate the two products in a 94:6 inseparable mixture.



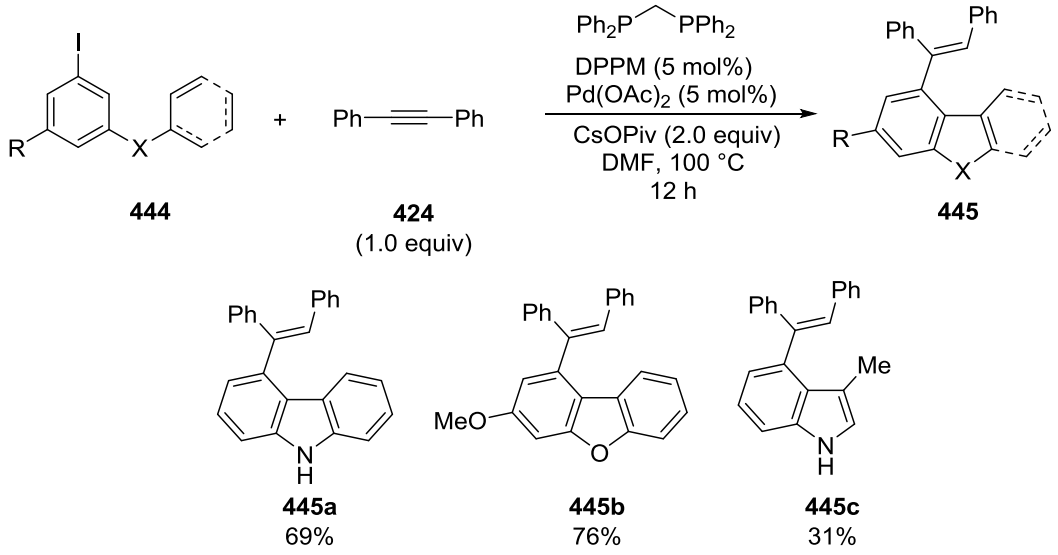
Scheme 6.9: 1,4-Migration to a benzofuran group[179]

Larock and co-workers also reported that similar substrates **442**, with an appended aryl group, underwent a similar 1,4-migration (Scheme 6.10).[180] The resulting intermediate underwent an aryl-aryl cross coupling to give a range of heterocyclic and carbocyclic fused polycycles **443**.



Scheme 6.10: Formation of fused polycycles *via* 1,4-migration[180]

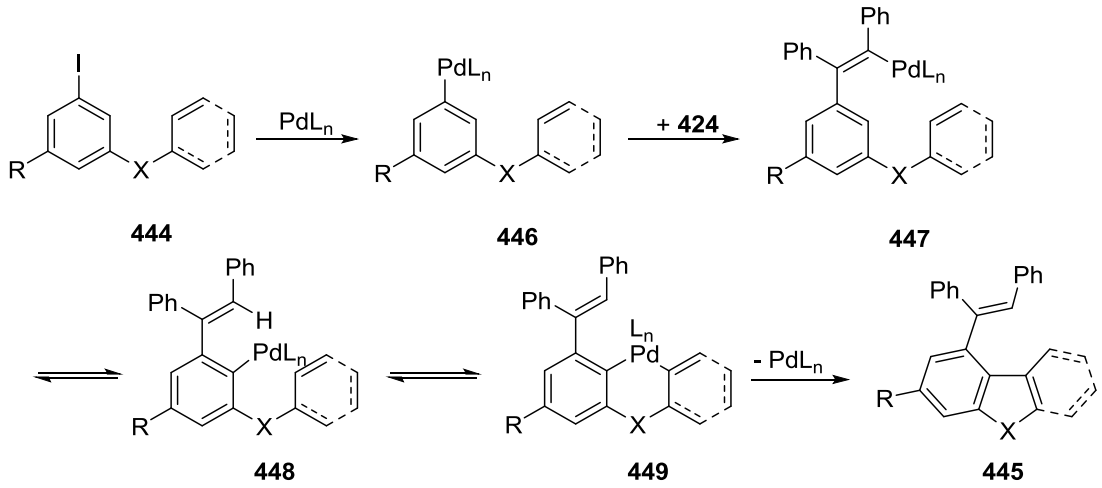
Using the knowledge gained from their previous work, the Larock group successfully designed substrates **444** that they believed would lend themselves to 1,4-migration (Scheme 6.11).[165,166] This was proved correct and the reaction of these substrates led to the synthesis of a range of carbazoles, dibenzofurans and indoles in moderate to high yields.



Scheme 6.11: Formation of carbazoles, dibenzofurans and indoles[165,166]

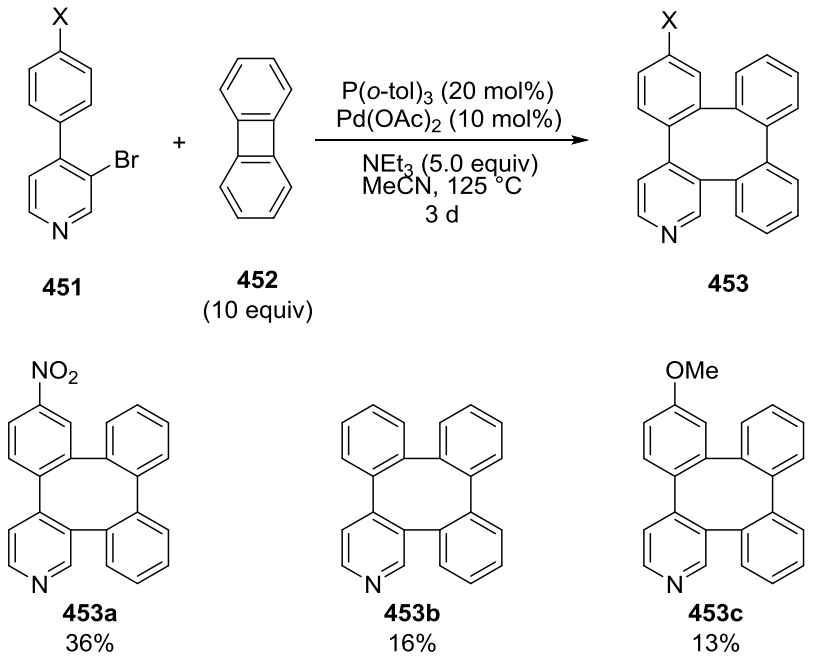
These reactions were proposed to proceed *via* the following mechanism (Scheme 6.12).[181,182] Oxidative addition of aryl iodide **444** to palladium formed arylpalladium species **446**, followed by insertion into the alkyne **424** to give **447**. Following an

alkenyl to aryl 1,4-migration, the resultant palladium species underwent cross-coupling to form the products **445**.



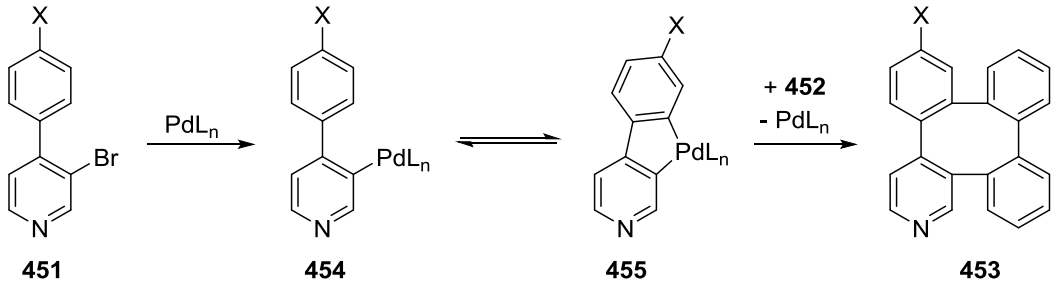
Scheme 6.12: Mechanism of the formation of polycycles[165,166]

Gallagher and co-workers reported the formation of tetraphenylene products **453** using similar biaryl pyridine template **451**. Coupling of biphenylene (**452**) with **451** formed the products in low but appreciable and isolable yields (Scheme 6.13).[183]



Scheme 6.13: Formation of tetraphenylenes *via* 1,4-migration[183]

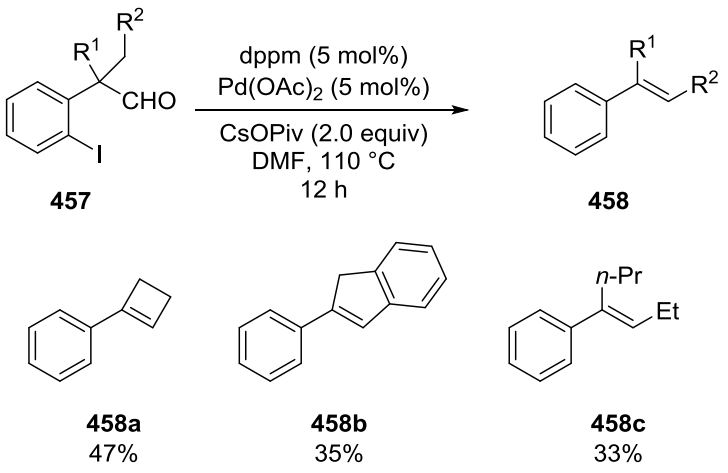
They proposed that following oxidative addition of the aryl bromide **451** to palladium to form species **454**, the palladium undergoes a 1,4-C-H insertion to form palladacycle **455**. This species then undergoes reaction with biphenylene (**452**) to form product **453** (Scheme 6.14).[183]



Scheme 6.14: Reaction between palladacycle **451** and biphenylene **452**[183]

The Larock group performed a thorough and substantial investigation into these sp^2–sp^2 palladium 1,4-migrations in an attempt to gain greater insight of the reaction.[184] 1,4-Migration was evident during a range of Heck and Suzuki-Miyaura reactions, demonstrating that the 1,4-migration can occur under conditions that are amenable to other transformations. Studies showed that the steric and electronic nature of the aryl components can have a pronounced effect upon the degree of migration that occurs. Furthermore, subtle changes in conditions such as altering the base can completely shut down the migration in order to favour a standard reaction pathway. However, following computational and experimental analysis it was not possible to determine whether a Pd(IV) intermediate exists or whether a direct migration occurred.

In 2009 the group of Larock reported the activation of an acyl group resulting in the sp^2–sp^2 migration of palladium from an aryl to an acyl species (Scheme 6.15),[185] leading to the formation of styrene **458** in good yield.

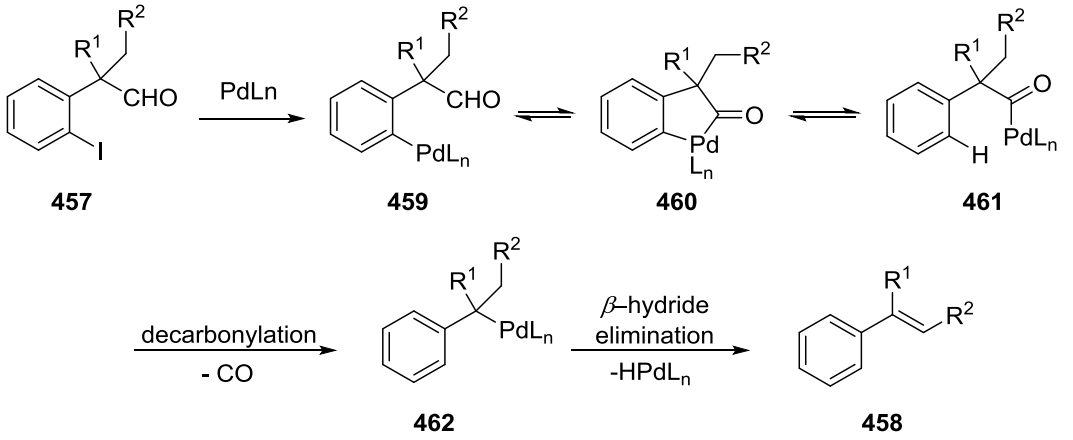


457 **458**

458a 47% **458b** 35% **458c** 33%

Scheme 6.15: Activation of acyl groups *via* 1,4-migration[185]

The mechanism of such a process first involves the oxidative addition of aryl iodide **457** to palladium. A reversible 1,4-palladium migration gives formylpalladium species **460**. Decarbonylation and *β*-hydride elimination gives styrene **458** (Scheme 6.16).[185]

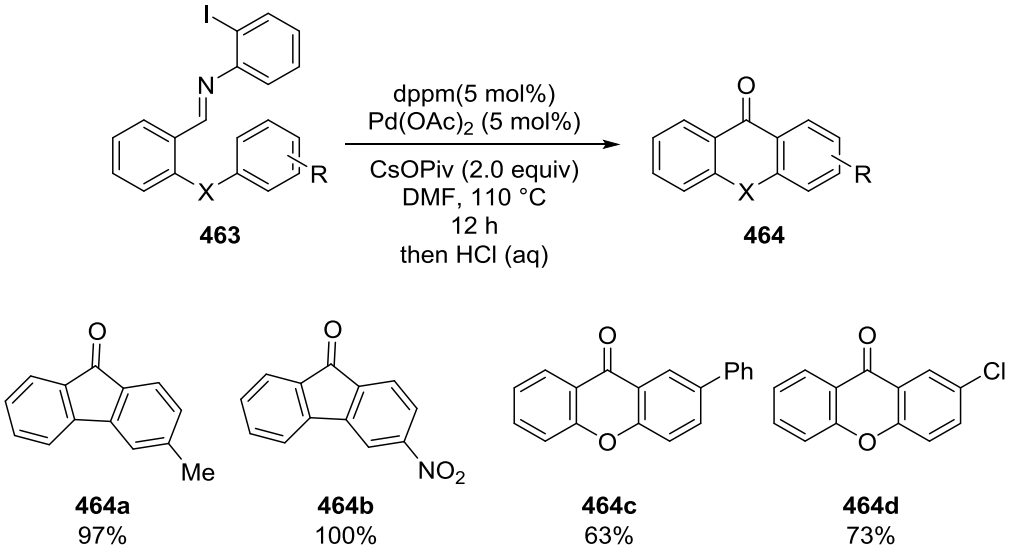


457 **459** **460** **461**

462 **458**

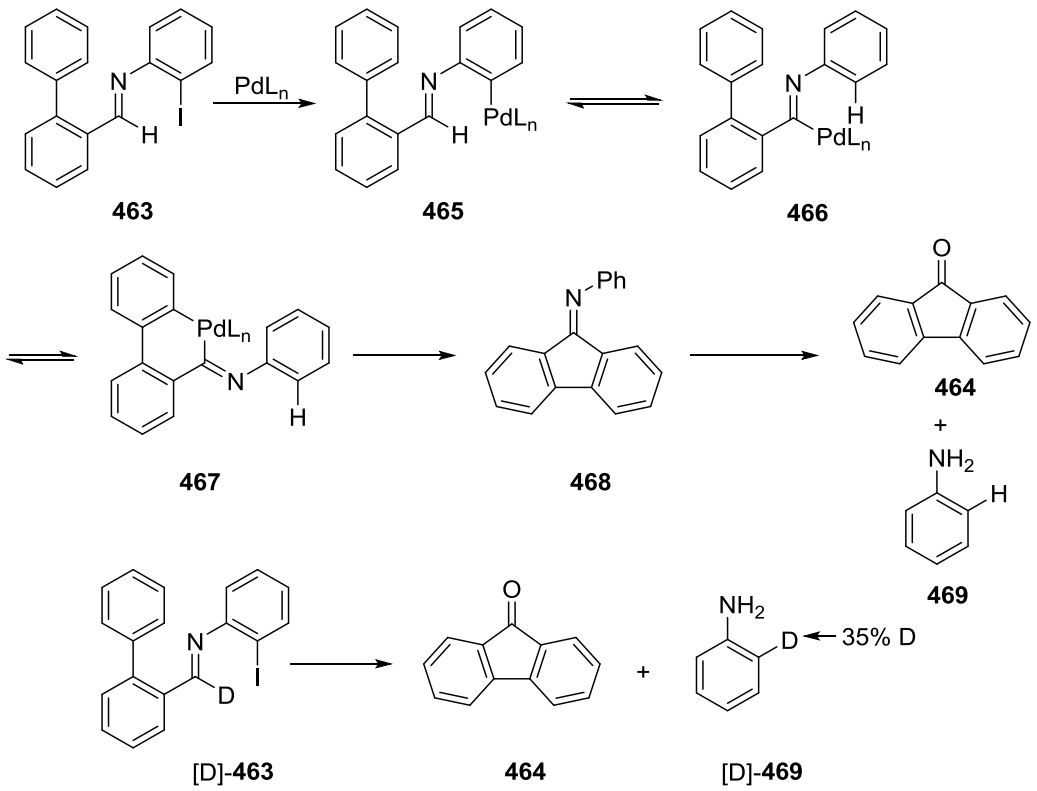
Scheme 6.16: Formation of styrenes by 1,4-migration[185]

The similar activation of an imidyl position was reported by Larock and co-workers (Scheme 6.17).[186] By utilising substrates such as **463**, it was possible to synthesis a range of flavones **464a-b** and xanthones **464c-d** with both electron-donating and electron-withdrawing substituents in good yields.



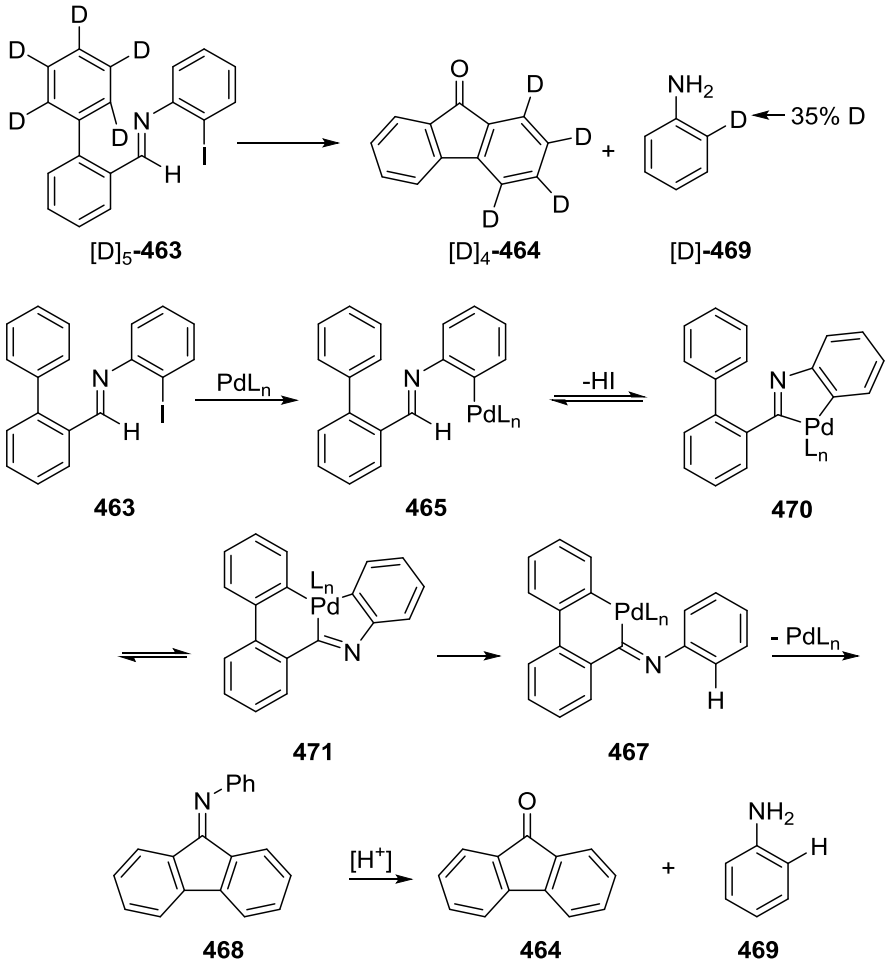
Scheme 6.17: Synthesis of flavones and xanthones *via* 1,4-migration[186]

Mechanistic analysis and deuterium labelling indicated a complex dual mechanism gave these products (Scheme 6.18).[186] The first proposed route involves the oxidative addition of aryl iodide to palladium to form arylpalladium species **465**. 1,4-Palladium migration forms species **466** which can undergo coupling with the aryl ring to form tricyclic species **467**. Following reductive elimination, treatment of **468** with acid hydrolyses the imine to give flavone (**464**) and aniline (**469**). Deuterium labelling of the imino-hydrogen ([D]-**463**) resulted in 35% deuterium incorporation in the aniline product, indicating that this hydrogen does undergo 1,4-migration to the aryl ring.



Scheme 6.18: Proposed mechanism A[186]

However, using pentadeuterated species $[D]_5$-**463** also gave 35% deuterium incorporation in the resultant aniline product. Such an observation is not consistent with the proposed mechanism A, and therefore an additional mechanism was proposed by Larock and co-workers (Scheme 6.19). After oxidative addition and insertion of the palladium to the imino-hydrogen, the hydrogen is lost by the elimination of HI to give palladacycle **470**. This palladacycle undergoes an additional C-H insertion on the aryl ring to form species **471**. At this point, the deuterium label is transferred to the opposite aryl ring. Finally reductive elimination and hydrolysis gave flavone (**464**) and aniline (**469**). Deuterium labelling at both the imino and aromatic positions resulted in the recovery of aniline with 75% deuterium incorporation, indicating that both mechanistic pathways are likely to be in operation.

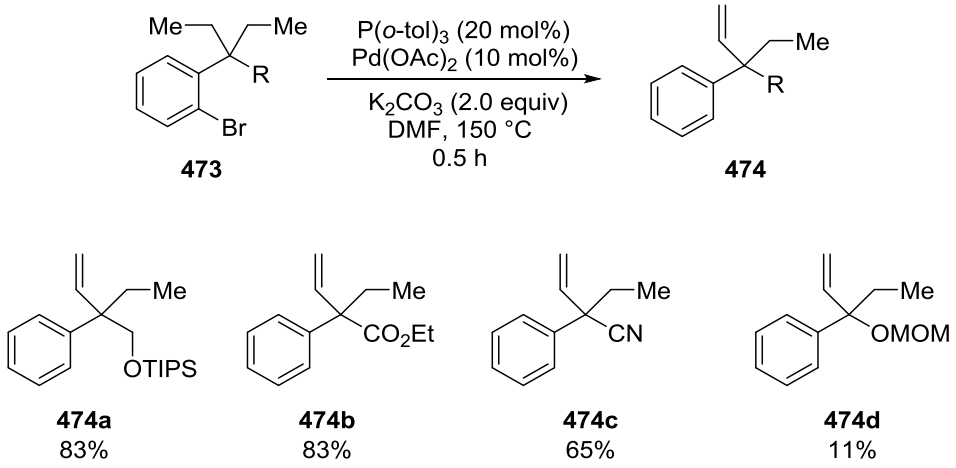


Scheme 6.19: Alternative mechanistic pathway B[186]

1.2.2 The 1,4-Migration of Palladium From a C–sp^2 Centre to a C–sp^3 Centre

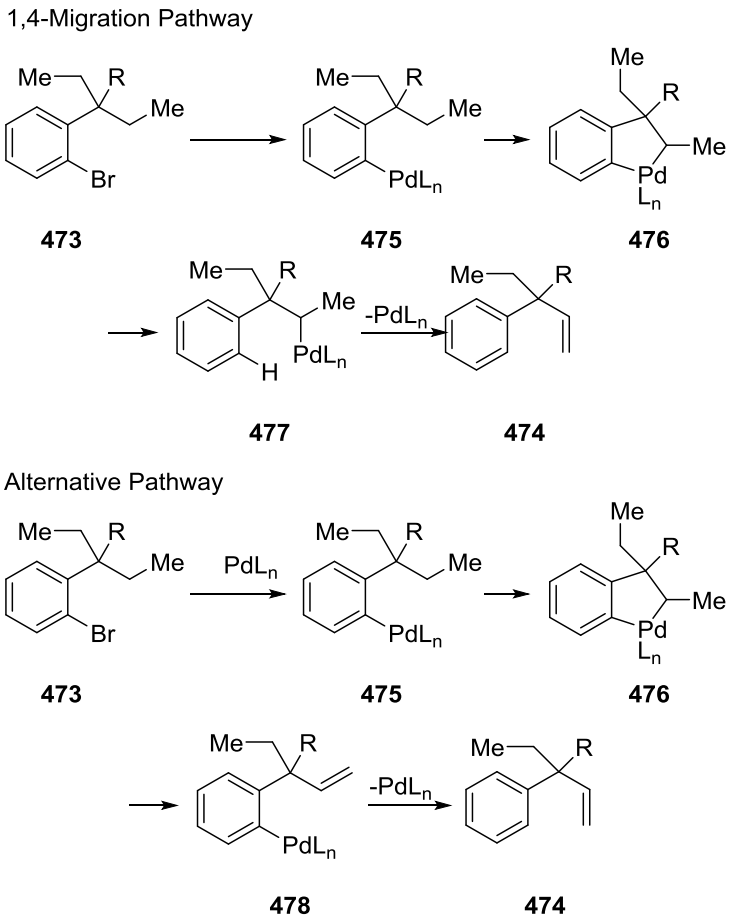
Although sp^2–sp^2 migrations are the most prevalent and well-studied, Dyker's original work was in fact a sp^2–sp^3 migration (Scheme 6.2). These transformations have proven to be less common but some further work has explored their potential in organic synthesis.

In 2003 Baudoin and co-workers reported the formation of alkenes **474** from aryl bromide **473** (Scheme 6.20).[187]



Scheme 6.20: Formation alkenes from aryl bromides[187]

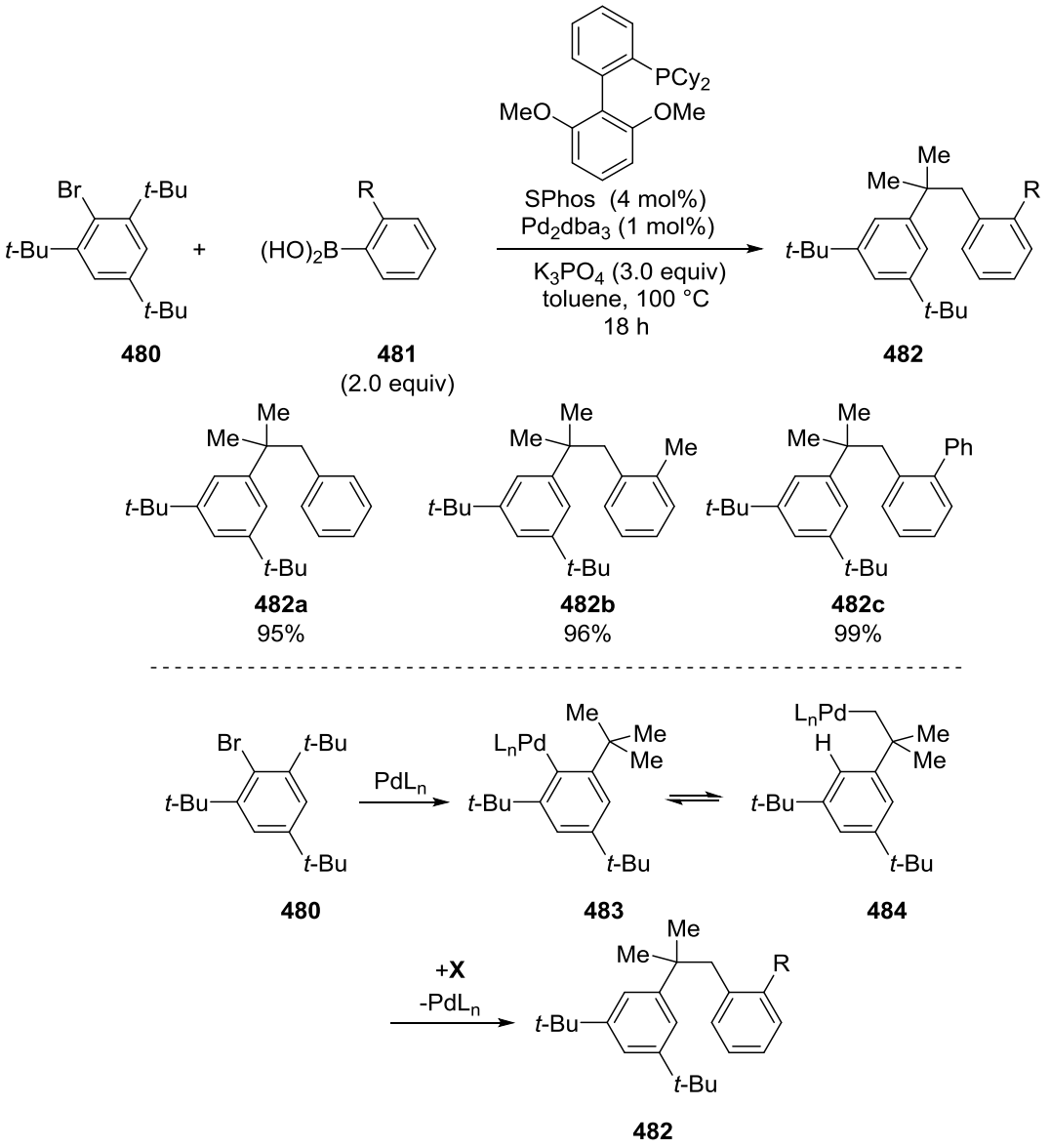
This reaction has been proposed to involve a 1,4-migration between the intermediate arylpalladium **475** and an C–sp^3 centre. Baudoin alternatively proposed a remote C-H functionalisation, leading to palladacycle **476** that underwent β-hydride elimination to give arylpalladium intermediate **478** (Scheme 6.21). [187,188]



Scheme 6.21: Proposed Mechanistic Pathways[187,188]

The 1,4-migration of palladium has also been found unexpectedly while the Buchwald group investigated the efficiency of their mono-phosphine ligands in Suzuki-Miyaura reactions (Scheme 6.22).[189] They increased the steric bulk of the aryl bromide to observe how this effected the catalytic efficiency in the cross coupling reaction. As the steric bulk surrounding the carbon-bromine bond was increased, longer reaction times, higher temperatures, and higher catalytic loadings were found to be necessary in order for good yields to be obtained. However, when 2,4,6-tri-*tert*-butylbromobenzene (**480**) was used, they found complete conversion of starting material to product **482** occurred rapidly with a much lower catalytic loading than other less hindered species had required. Upon NMR analysis of the products, it was found that a simple aryl-aryl Suzuki-Miyaura cross-coupling had not occurred, rather a alkyl-aryl cross-coupling involving a 1,4-palladium migration. They propose the proximity of the *tert*-butyl group and the lower reactivity of the aryl position

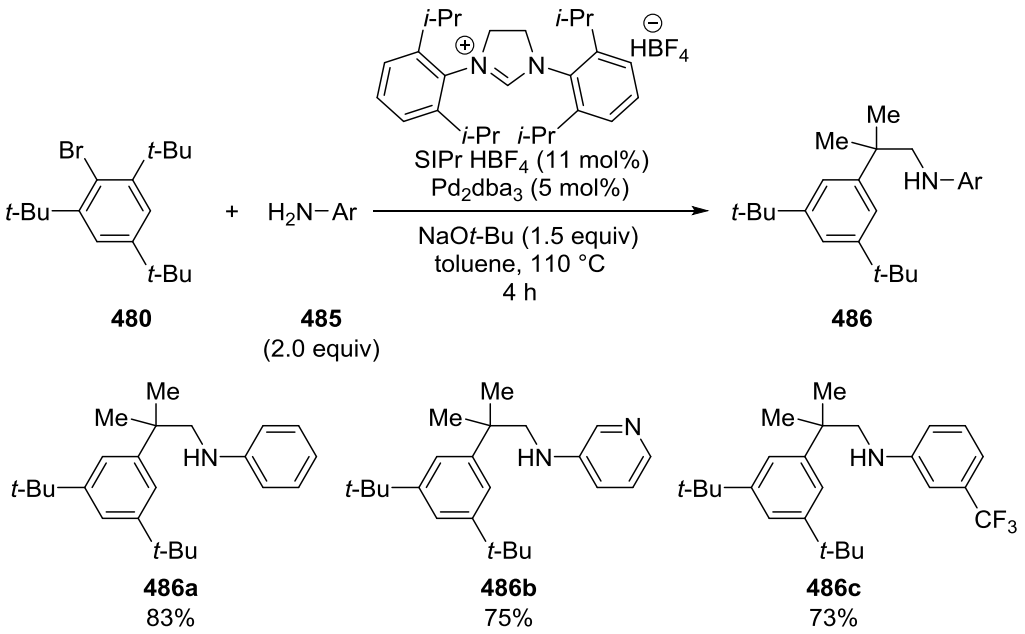
permits a C–sp^2 – C–sp^3 1,4-migration to form primary alkylpalladium species **484**. This intermediate is far less hindered and more reactive, and undergoes cross-coupling with the boronic acid **481** to give the observed products **482**.



Scheme 6.22: Unexpected 1,4-migration during Suzuki-Miyaura reactions[189]

Using the knowledge gained from this unexpected side-reaction, the group of Buchwald then purposely designed a reaction that would benefit from the known 1,4-migration.[190] Using aryl bromide **480** with a palladium-NHC catalyst, it was possible to perform a range of alkyl aminations (Scheme 6.23). As in their previous work, the hindered aryl palladium species underwent a 1,4-migration to form an

alkyl palladium species. Ligand exchange and reductive elimination occurred leading to the formation of amine products **486**.



Scheme 6.23: Intermolecular amination *via* 1,4-migration[190]

Buchwald attempted to quantify the amount of steric hindrance required to promote the 1,4-migration. Replacing an *ortho-tert*-butyl group with a methyl group resulted in exclusive formation of the non-migratory amination product **487**. More sterically hindered alkyl groups exclusively gave the migration amination product **488** and **489**. Replacing the CH_2 groups in a five-membered ring with oxygen, resulted in the formation of non-migratory product **490**, and increasing the ring size and additional methyl groups promoted the migration **491**. Finally, large silyl protecting groups also promoted migration leading to amine product **492** (Figure 6.1).

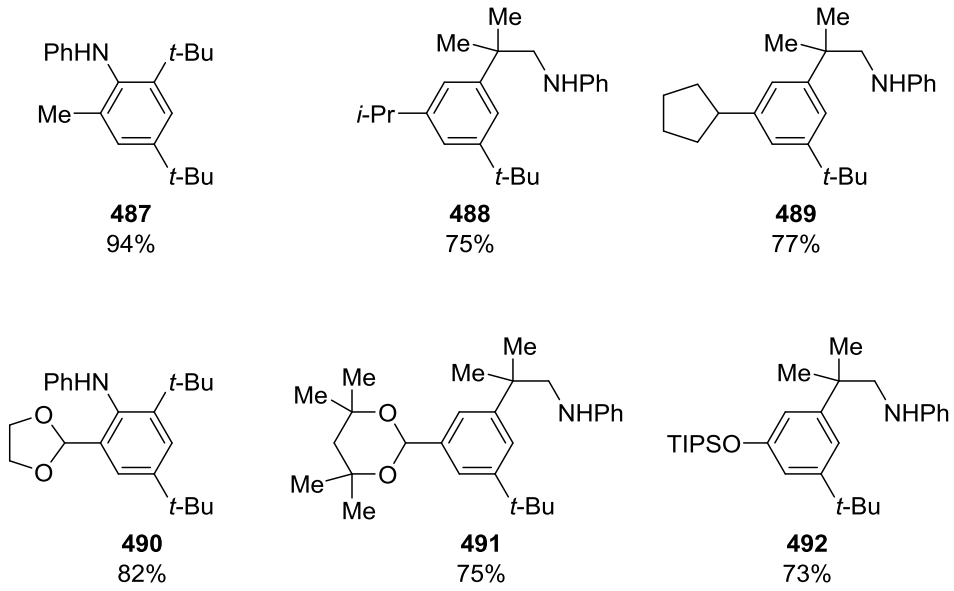
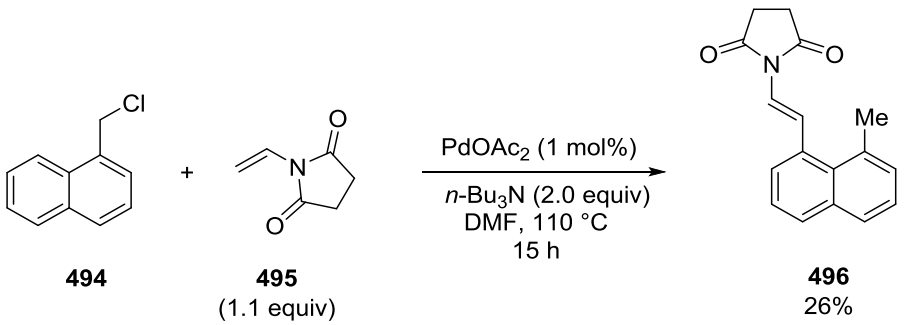


Figure 6.1: Investigations into steric hindrance of aryl substituents[190]

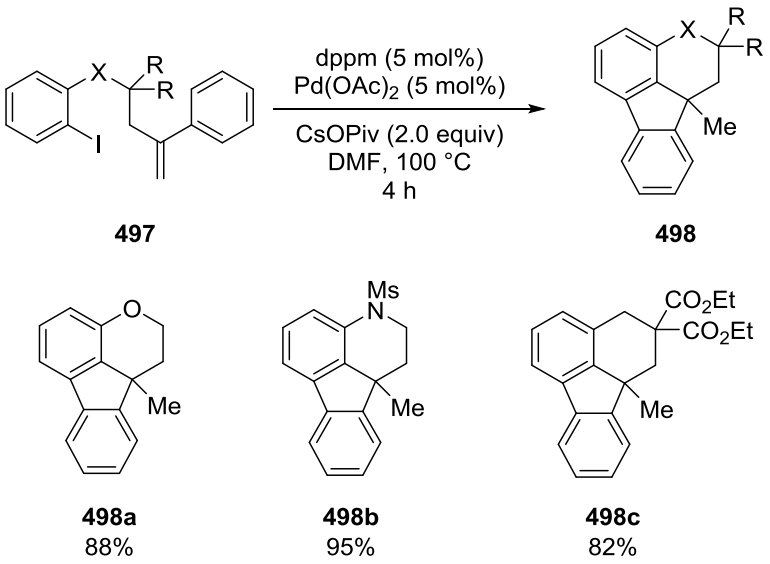
1.2.3 The 1,4-Migration of Palladium From a C–sp^3 Centre to a C–sp^2 Centre

The 1,4-migration of palladium from a sp^3 centre to a sp^2 centre was first reported by Pan and co-workers in 2000. They were attempting to couple *α*-chloromethylnaphthalene (**494**) with a range of alkenes (Scheme 6.24).[191] In most cases the reaction proceeded smoothly, but with alkene **495**, an appreciable amount of enamine **496** was isolated. This product resulted from the 1,4-migration of the intermediate benzylic palladium species to the aryl position prior to cross-coupling.



Scheme 6.24: Side product due to 1,4-migration[191]

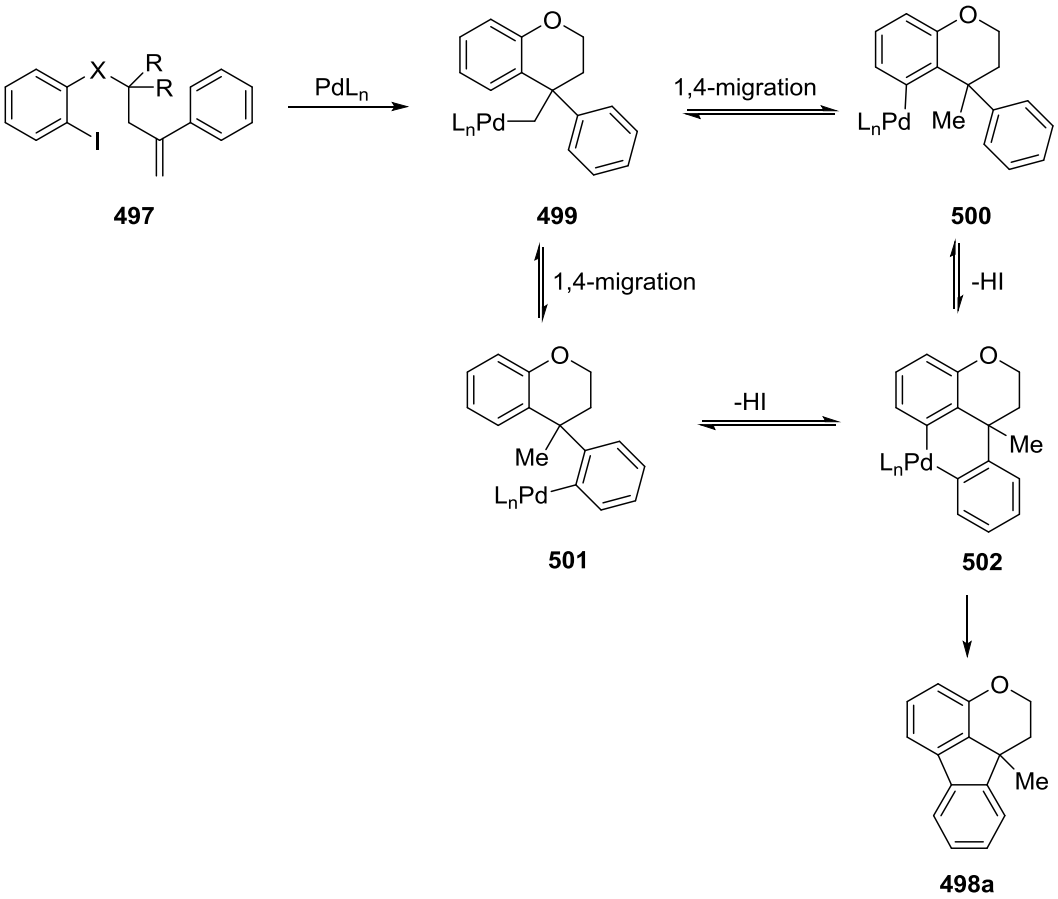
The group of Larock reported an sp^3–sp^2 migration during the synthesis of fused polycycles **498** (Scheme 6.25).[192] A range of polycycles, including heteroatoms **498a-b** and substituents **498c** were successfully synthesised (Scheme 6.25).



Scheme 6.25: Synthesis of fused polycycles[192]

They proposed that the reaction follows a pathway outline in Scheme 6.26. After oxidation addition of **497** to palladium and carbopalladation of the alkene to give **499**, an sp^3–sp^2 1,4-migration occurs to either of the aryl groups **500** or **501**. Subsequently C-H activation and reductive elimination gives product **498**.

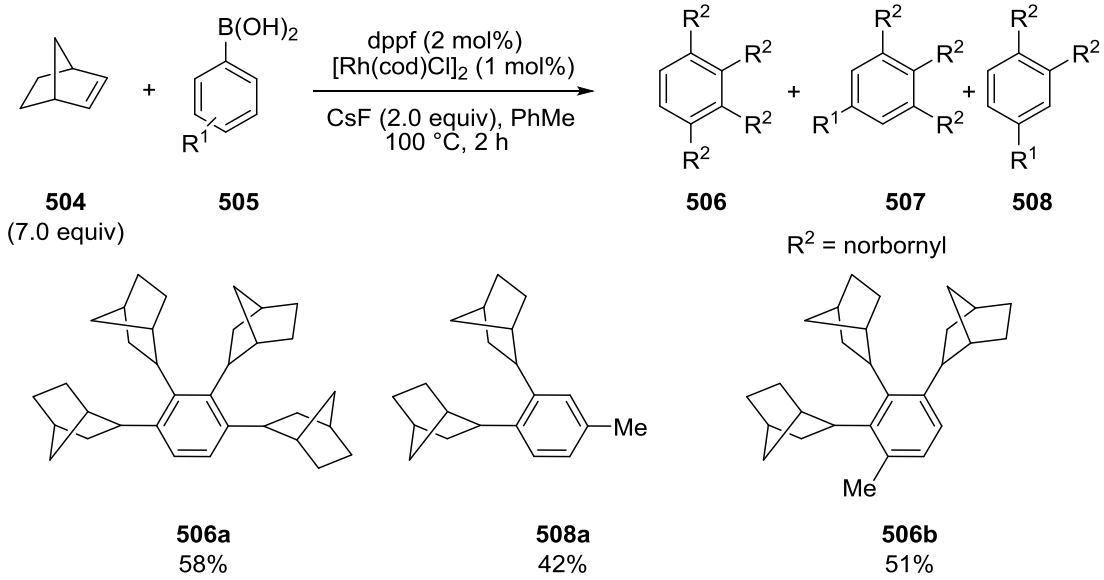
Work along similar lines has been reported by Kim[193] and Zhu,[194] but there are far fewer examples of sp^3–sp^2 1,4-palladium migration compared to the related sp^2–sp^2 and sp^2–sp^3 migrations.



Scheme 6.26: Proposed mechanism of 1,4-migration[192]

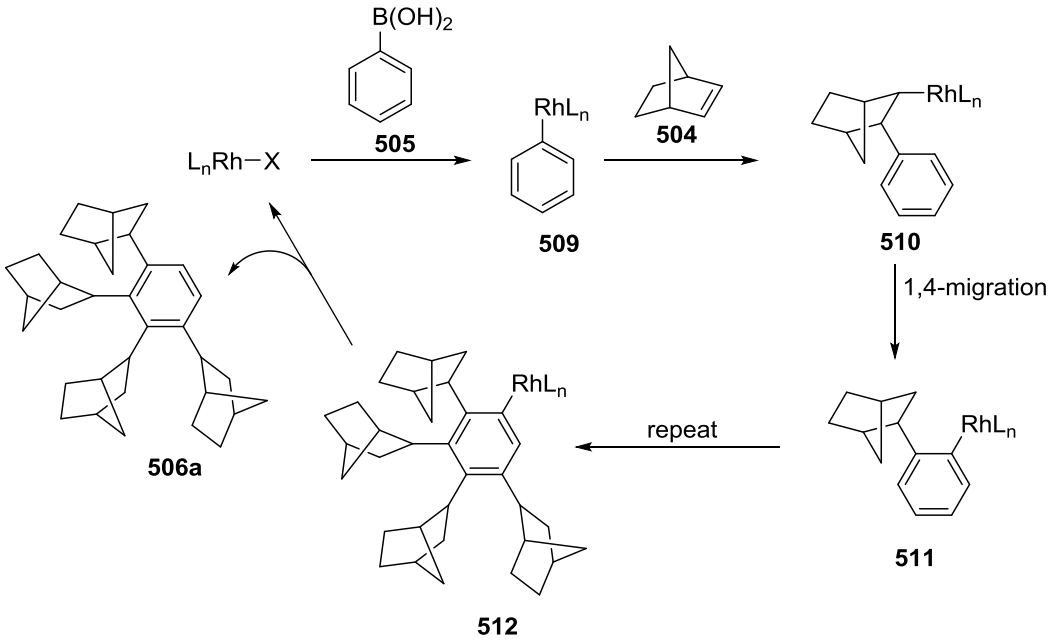
1.3 1,4-Migration of Rhodium Species

The group 9 metal rhodium has also proved quite effective in undergoing 1,4-transition metal migrations. The first rhodium 1,4-migration was reported in 2000 by Miura, during studies on their "merry-go-round" type reactions.[195] They observed that under Rh(I) catalysis the reaction between 2-norbornene (**504**) and arylboronic acids resulted in the formation of aromatic products with multiple norbornyl substitutions (Scheme 6.27). A range of arylboronic acids exhibited this behaviour. When substitution was present on the aromatic ring, the 1,4-migration occurred until *meta* to the substituent. The migration was then found to be unfavourable presumably due to steric hindrance and no further norbornyl moieties were incorporated.



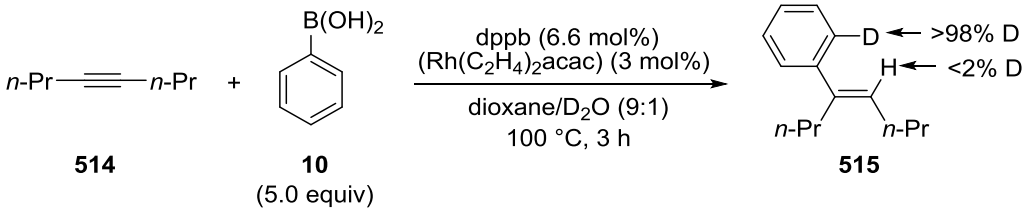
Scheme 6.27: The first reported rhodium 1,4-migration[195]

The proposed catalytic cycle involves first the transmetallation of the arylboronic acid to rhodium giving arylrhodium species **509**. Carborhodation across the olefin forms alkylrhodium species **510**. A 1,4-rhodium migration from the alkylrhodium species back to the aryl group, through an oxidative bridging mechanism, forms arylrhodium species **511**. The carborhodation/1,4-migration process can repeat until protonation liberates the product **506a** and regenerates the rhodium(I) catalyst (Scheme 6.28).



Scheme 6.28: Mechanism of rhodium 1,4-migration[195]

The next report of rhodium 1,4-migration came from the laboratory of Hayashi in 2001 and similar to reports of palladium 1,4-migration, this was an unexpected result.[196] During their investigations into the hydroarylation of alkynes using rhodium catalysts, they employed D_2O in attempt to confirm the role of water in the reaction (Scheme 6.29). However, rather than deuterium being incorporated at the expected alkenyl position, deuterium was in fact incorporated on the adjacent aryl group. These observations demonstrated that rhodium underwent a 1,4-migration from the alkenyl position to the aryl position before undergoing deuteration.

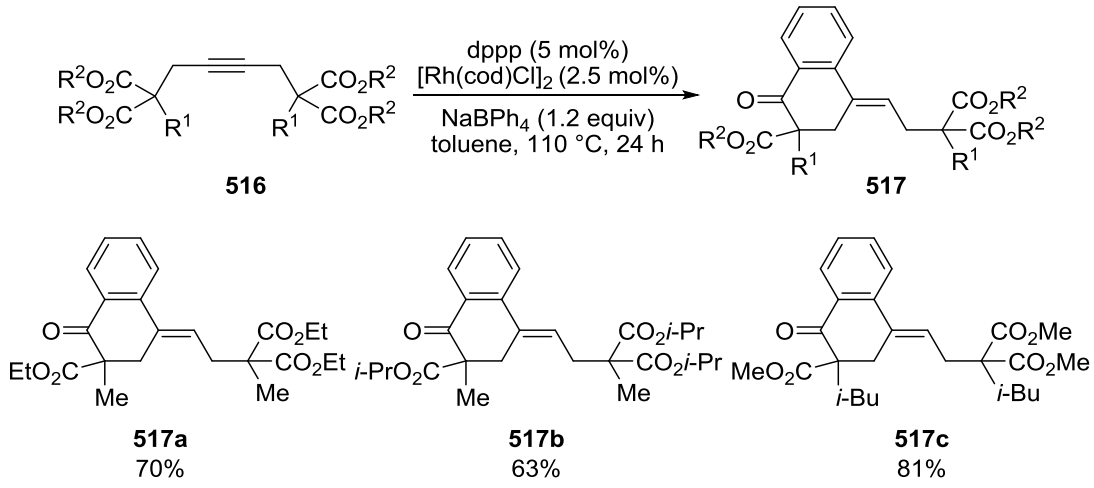


Scheme 6.29: Unexpected deuterium incorporation[196]

Based on these initial findings, a plethora of reactions involving rhodium 1,4-migration have been reported. Similarly to palladium, these can be roughly categorised in accordance to the nature of the carbons that the rhodium migrates from and to: C–sp^2 – C–sp^2, C–sp^3 – C–sp^2, and C–sp^2 – C–sp^3.

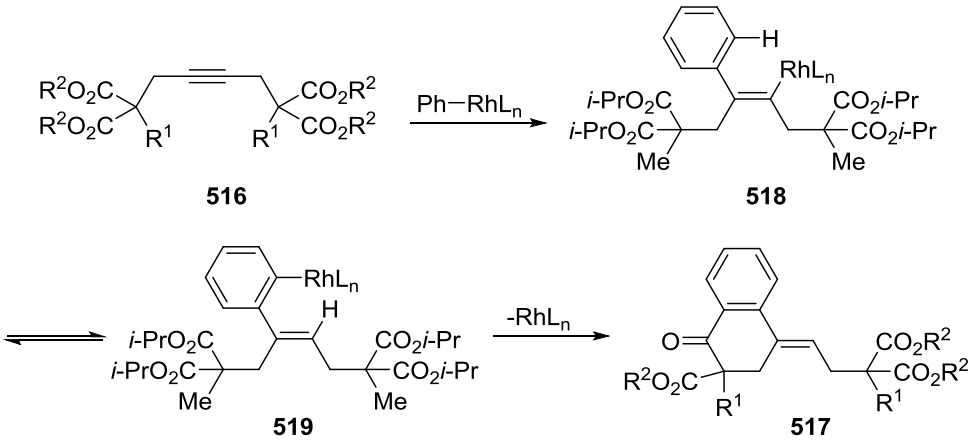
1.3.1 The 1,4-Migration of Rhodium From a C–sp^2 Centre to a C–sp^2 Centre

In 2004 the group of Murakami reported the 1,4-migration of rhodium following the carborhodation of an alkyne (Scheme 6.30).[197] This work relied on the same phenomenon observed by Hayashi, a 1,4-migration from an alkenylrhodium species to form an arylrhodium species. By featuring a substrate **516** that have an appended electrophile, it was possible for this newly formed arylrhodium species to cyclise to form bicyclic ketone **517**.



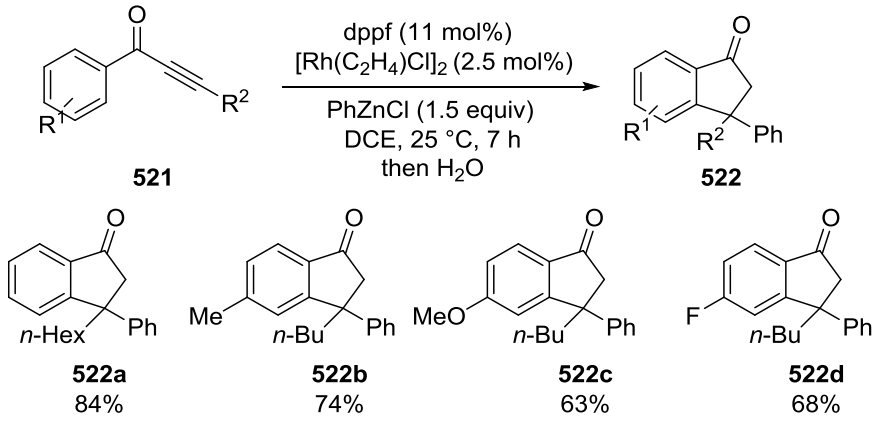
Scheme 6.30: Formation of bicyclic ketones *via* 1,4-migration[197]

The mechanism proposed is outlined in Scheme 6.31. Carborhodation of alkyne **516** results in alkenylrhodium species **518** and 1,4-rhodium migration gives arylrhodium species **519** This nucleophilic arylrhodium species attacks an ester to form cyclic ketone **517** (Scheme 6.31).



Scheme 6.31: The mechanism of the formation of ketone **517**[197]

The concept of the carborhodation of an alkyne to form a alkenylrhodium species amenable to 1,4-migration was utilised further by Hayashi and co-workers (Scheme 6.32).[198] They reported the rhodium-catalysed addition of arylzinc reagents to aromatic alkynyl ketones to give an array of highly substituted indanones **522**.

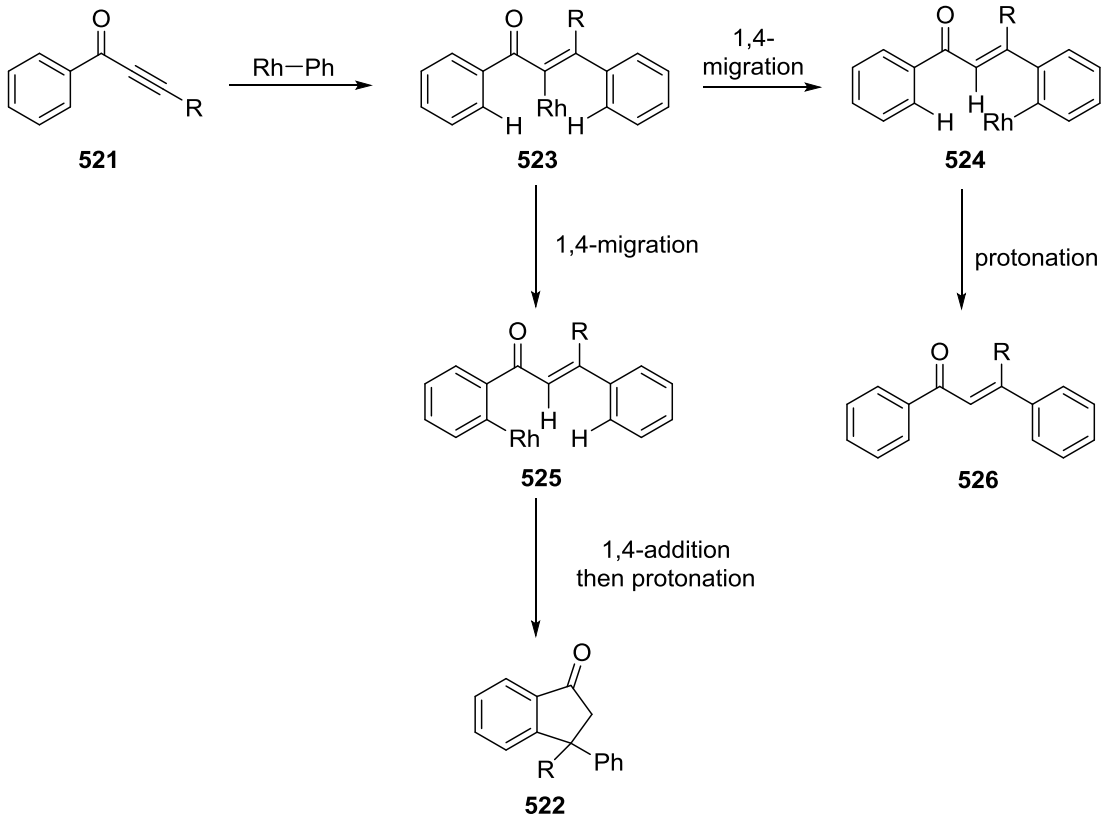


Scheme 6.32: Synthesis of indanones *via* 1,4-migration[198]

The synthesis of indanones **522** is proposed to occur by the mechanism outlined in Scheme 6.33. Initial rhodium-catalysed addition of the arylzinc to alkyne **521** leads to the formation of alkenylrhodium species **523**. From this intermediate there are two possible routes for 1,4-rhodium migration to proceed. If the rhodium migrates to the aryl ring next to the ketone, species **525** is formed, which can then undergo a 1,4-addition to the *α,β*-unsaturated ketone to form indanone **522**. It is also possible for

the rhodium species to undergo a 1,4-migration to the opposite aryl ring to form species **524**, From this species no further intramolecular additions can occur and the rhodium is protonated to form *β*,*β*-disubstituted enone **526**.

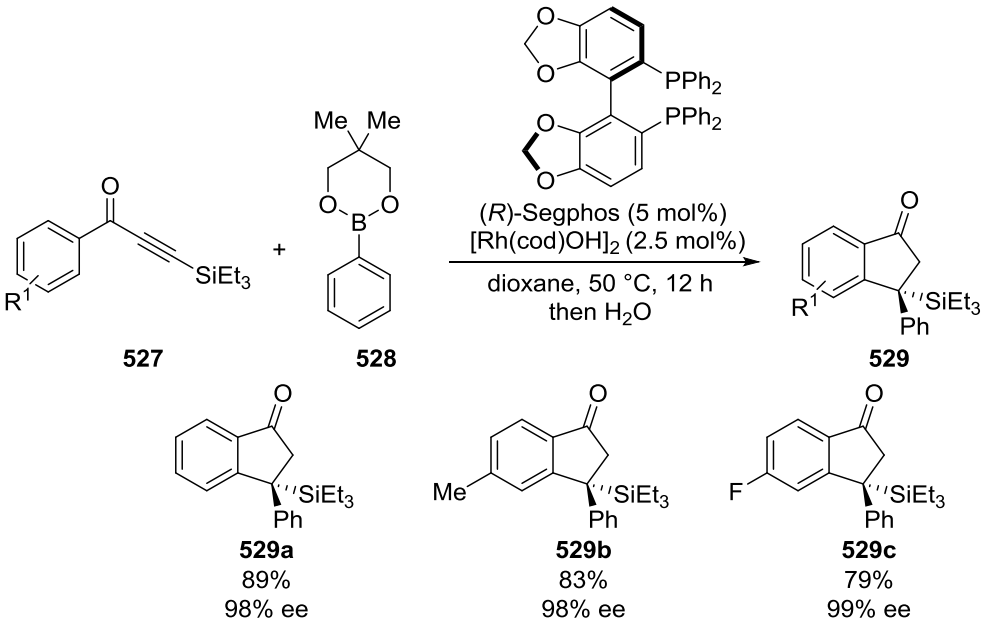
It was found that the nature of the ligand on rhodium had a pronounced effect upon this selectivity, as did the solvent. Using cycloctadiene as a ligand and DCE as a solvent resulted in almost the exclusive formation of **526**. Conversely using diphenylphosphinoferrocene (dppf) using DCE as a solvent resulted in almost the exclusive formation of **522**. Employing dppf but with THF or toluene as the solvent resulted in a complete switch in selectivity in favour of **526**. The reasons for these pronounced changes are currently not clear.



Scheme 6.33: Alternative 1,4-migration pathways[198]

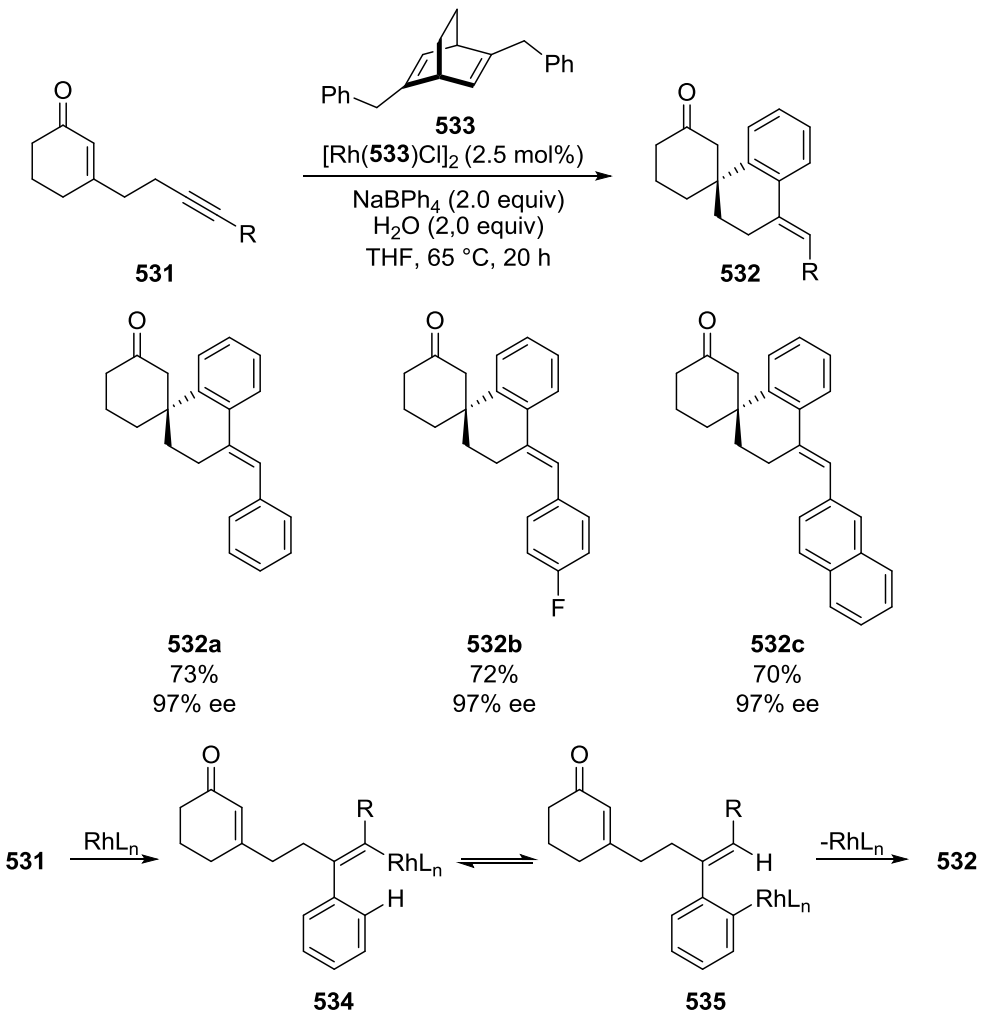
As shown by the proposed mechanism (Scheme 6.33), the stereochemistry of product **522** is determined in the final step, which is an intramolecular 1,4-addition.[14] Unfortunately, efforts to develop an enantioselective process were hindered by two issues. Chiral dienes led to the preferential formation of the achiral **526**. Conversely,

axial chiral phosphines such as BINAP gave good selectivity for indanone **522** but in low conversion. Hayashi found that by using an arylboron species, rather than an arylzinc species, and a silyl-substituted alkyne, the formation of the indanones **529** occurred in good yields when using BINAP-based ligands (Scheme 6.34).[199] After optimisation it was found a range of indanones could be synthesised in high yields and excellent enantiomeric excess using a bisphosphine ligand.



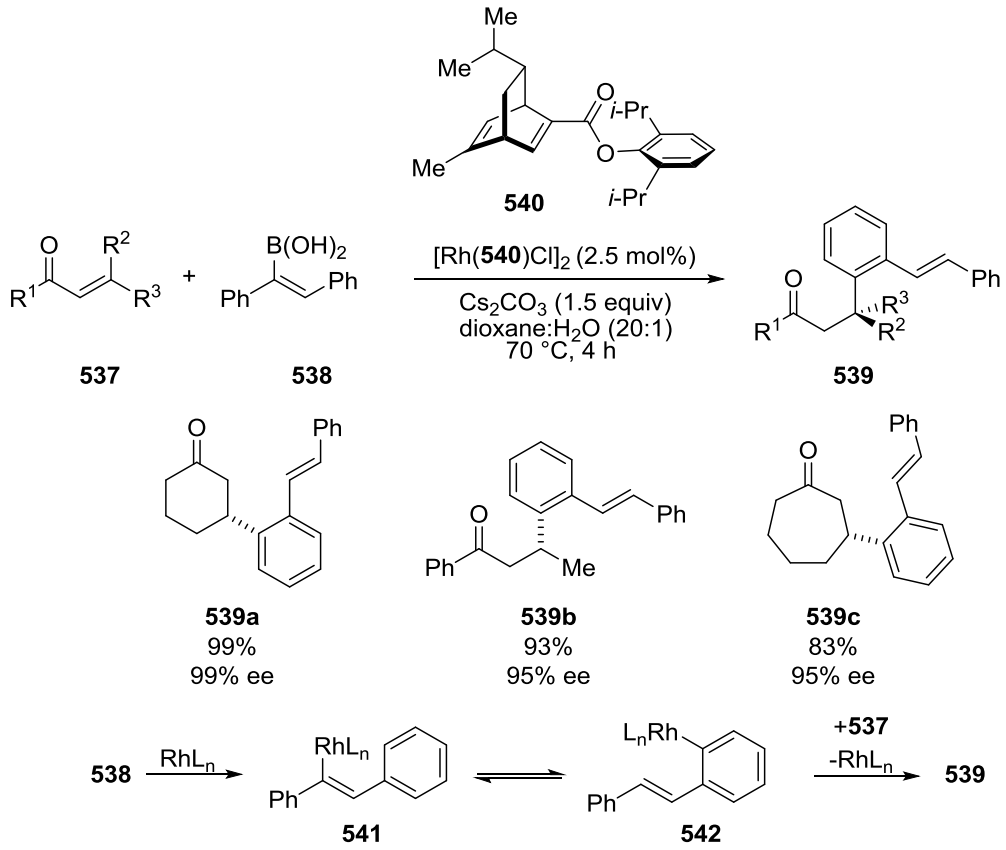
Scheme 6.34: Asymmetric formation of indanones[199]

In 2010, Hayashi and Shintani reported the synthesis of spirocarbocycles **532** following 1,4-rhodium migration (Scheme 6.35).[200] The reaction is proposed to proceed by an initial carborhodation of the alkyne to form an alkenylrhodium species. 1,4-Rhodium migration to the adjacent aryl ring gives new arylrhodium species **535** which undergoes 1,4-addition to the cyclohexenone moiety to furnish the spirocarbocycles **532**. A range of deuterium studies confirmed that a 1,4-migration was indeed occurring and by employing chiral diene **533**, it was possible to synthesise various carbocycles in good yields and excellent enantioselectivities (Scheme 6.35).



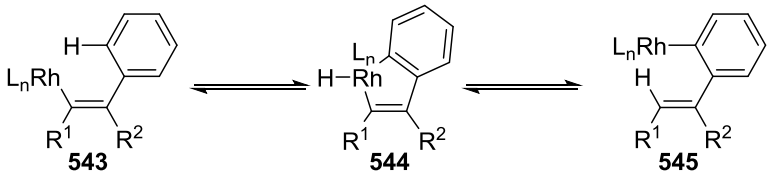
Scheme 6.35: Asymmetric synthesis of carbocycles *via* 1,4-migration[200]

In 2012, Hayashi and Kantchev reported the transmetallation between rhodium and styrylboron species **538** gave access to alkenylrhodium species **541**.[201] Post-transmetallation, the rhodium underwent a 1,4-migration to form arylrhodium species **542** that then underwent an asymmetric 1,4-addition to form product **539** (Scheme 6.36).[202] When employing chiral diene **540**, a range of both cyclic and acyclic enones were tolerated giving the arylation products in high yields and enantiomeric excess.



Scheme 6.36: 1,4-Migration arising from styrylboronic acids[201]

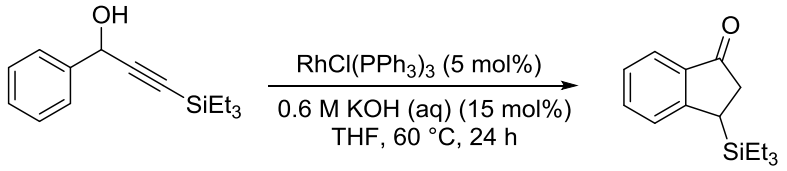
Kantchev performed density functional theory (DFT) calculations to model the 1,4-migration and determined that the 1,4-migration does proceed by a Rh(I)-Rh(III)-Rh(I) oxidative/reductive pathway that includes a Rh(III)-hydride bridged intermediate **544** (Scheme 6.37).[201]



Scheme 6.37: Rh(III)-hydride species predicted by DFT calculations[201]

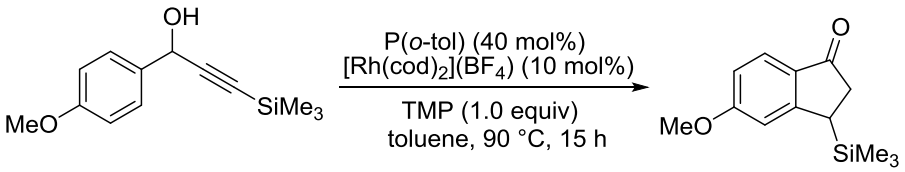
Another process to generate a similar rhodium intermediate in order to facilitate 1,4-migration was reported simultaneously by the groups of Hayashi[203] and Iwasawa (Scheme 6.38).[204]

Hayashi



547 **548** 92%

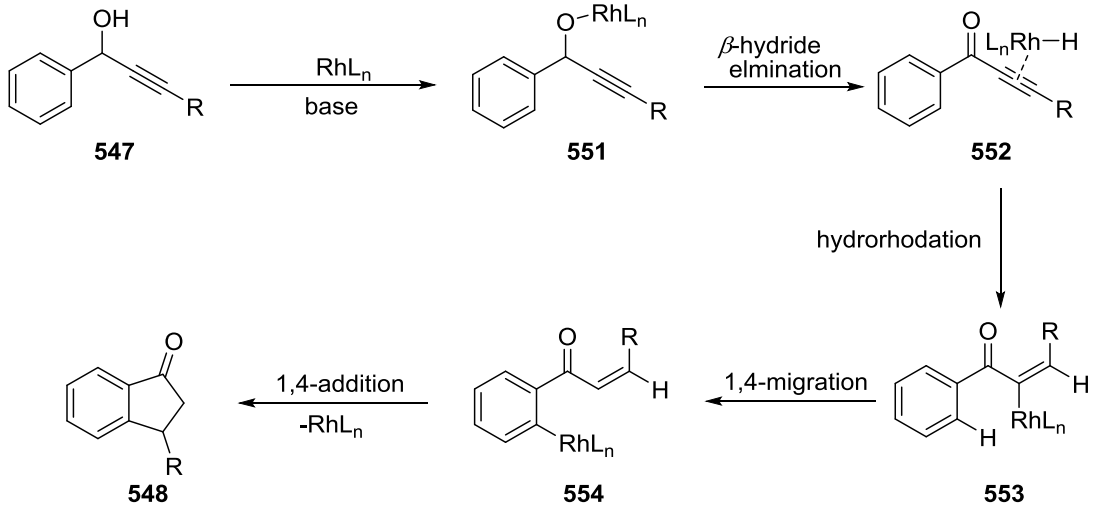
Iwasawa



549 **550** 72%

Scheme 6.38: Synthesis of indanones **548** + **550**[203,204]

This methodology involves the *β*-hydride elimination from alkoxyrhodium species **551** to form rhodium-hydride species **552**. Following intramolecular hydrorhodation of the alkyne to form alkenylrhodium species **553**, 1,4-migration, followed by a 1,4-addition formed indanones **548** (Scheme 6.39).[203]

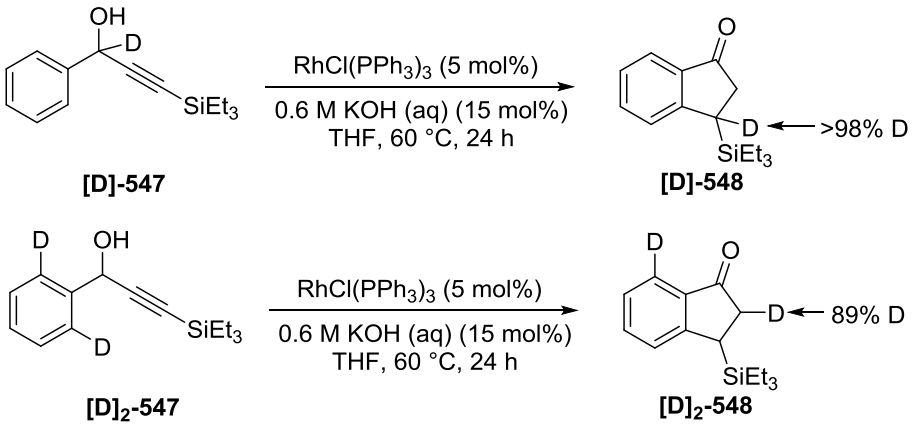


547 **551** **552** **553** **554** **548**

Scheme 6.39: Formation of indanones from propargyl alcohols[203]

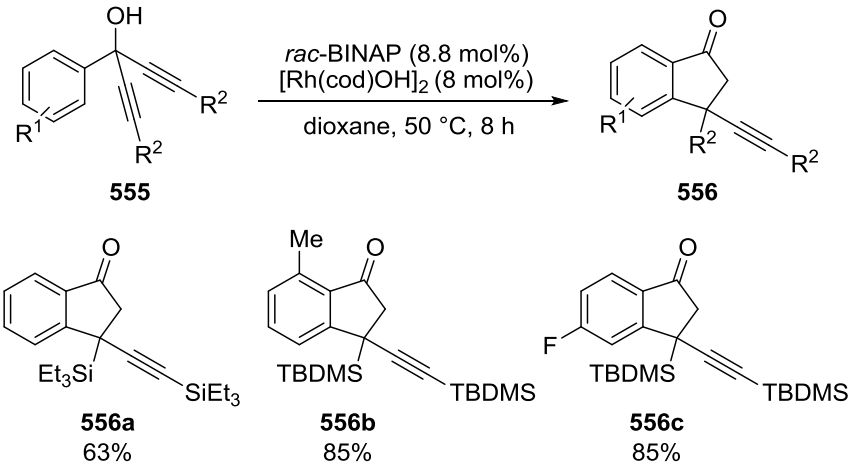
Deuterium labelling experiments demonstrated that: a) The hydrogen proposed to undergo *β*-hydride elimination exclusively transfers to the *β*-position with respect to the carbonyl (>98% D-incorporation), b) A hydrogen from the aromatic ring

transfers to α-position with respect to the carbonyl (89% D-incorporation) thus supporting the proposed mechanism (Scheme 6.40).[203]



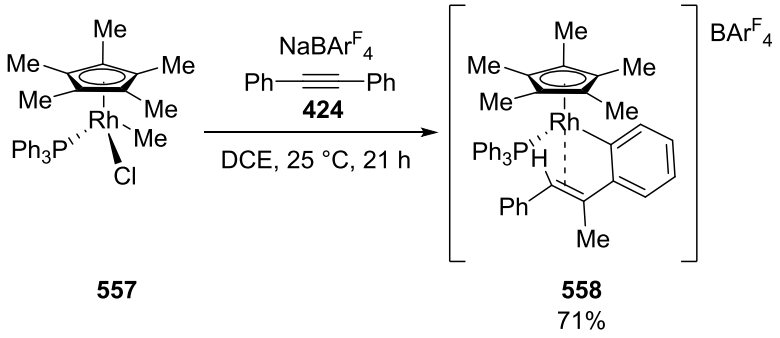
Scheme 6.40: Deuterium incorporation experiments[203]

It was also reported by Hayashi and Shintani that the group that undergoes β-elimination in these reaction is not limited to hydrides (Scheme 6.41).[205] The bis(alkynyl) carbinol **555** underwent β-alkynyl elimination and formed an alkynylrhodium species that underwent a carborhodation forming the alkenylrhodium species. This species underwent 1,4-migration followed by 1,,4-addition to give product **556** in high yields along the same mechanism outlined in Scheme 6.39.



Scheme 6.41: Elimination of alkynyl substituents[205]

As well as Rh(I) sp^2–sp^2 1,4-migrations, Ishii and co-workers reported the corresponding Rh(III) migration.[206,207] Although no successful synthetic methodology has been developed from this observation, the isolation of rhodium complex **558** gave conclusive proof of the migration occurring (Scheme 6.42).

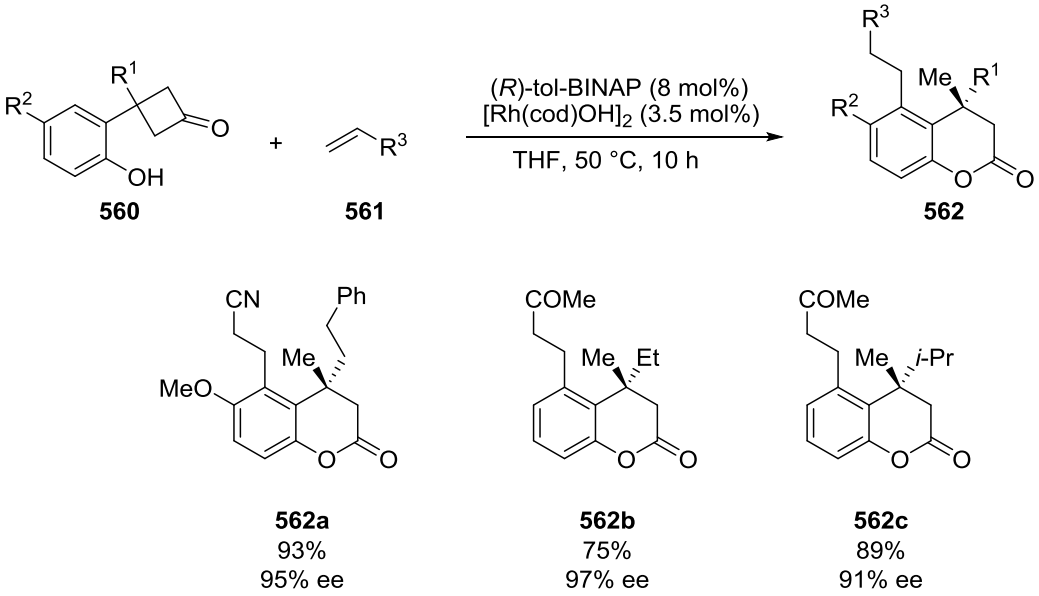


557 **558** 71%

Scheme 6.42: Rh(III) 1,4-migration[206,207]

1.3.2 The 1,4-Migration of Rhodium from a C–sp^3 Centre to a C–sp^2 Centre

The ability of rhodium to migrate from a C–sp^3 centre to a C–sp^2 centre was first reported by Miura and co-workers in 2000 (Scheme 6.27).[195] Following on from the pioneering work, Murakami reported the enantioselective synthesis of coumarins **562** involving a 1,4-rhodium migration (Scheme 6.43).[208]

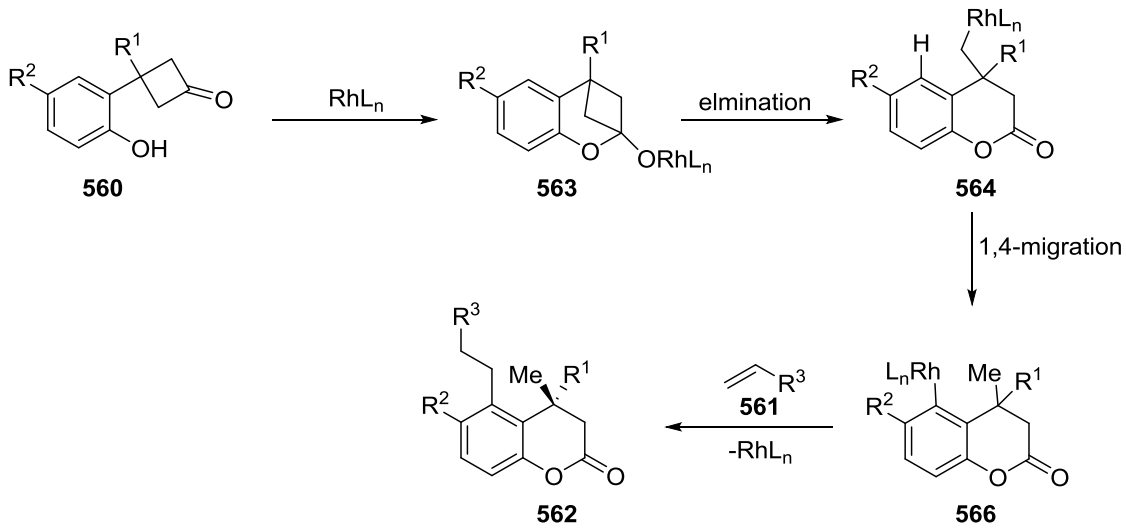


560 **561** **562**

562a 93% 95% ee **562b** 75% 97% ee **562c** 89% 91% ee

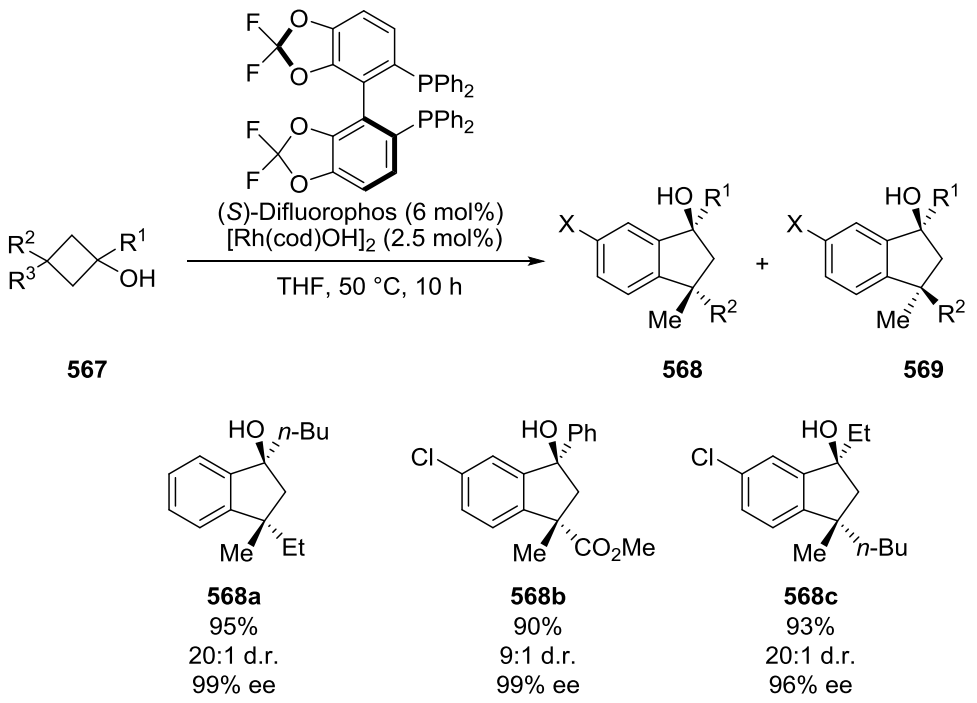
Scheme 6.43: Synthesis of coumarins *via* 1,4-migration[208]

Murakami proposed that the mechanism proceeded as follows:[208] Initial rhodium-promoted acetal formation gives alkoxyrhodium species **563** which can undergo *β*-carbon elimination to give intermediate **564** (Scheme 6.44). This intermediate then undergoes an sp^3 to sp^2 1,4-rhodium migration to form arylrhodium species **565**. Following this, a 1,4-addition of **561** to an electron-deficient olefin gives coumarin **562** in good yield and high enantioselectivity.



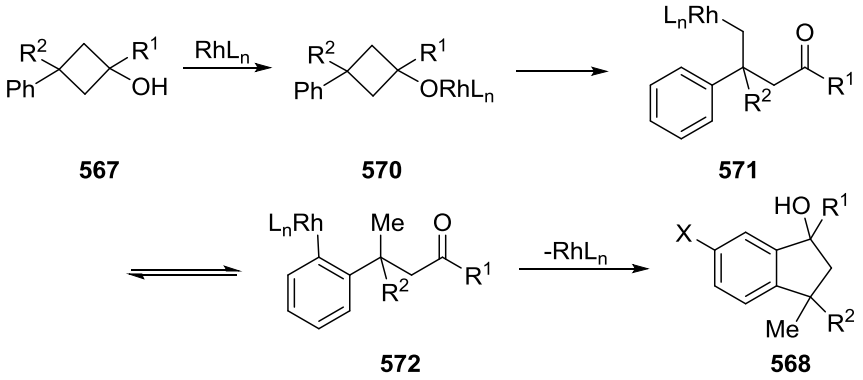
Scheme 6.44: Proposed mechanism of coumarin synthesis[208]

Cyclobutanes and the favourable *β*-carbon elimination (due to their ring strain) have been utilised by the groups of Cramer,[209] Murakami,[210] and Matsuda[211] in 1,4-migration reactions. Originally reported by the group of Cramer, the *β*-carbon elimination/1,4-migration sequence allowed the formation of indanol **568** from cyclobutanol **567** in good yield (Scheme 6.45). By employing a chiral ligand, it is possible to synthesise these molecules in excellent enantiomeric excess as well.



Scheme 6.45: Expansion of cyclobutanols[209]

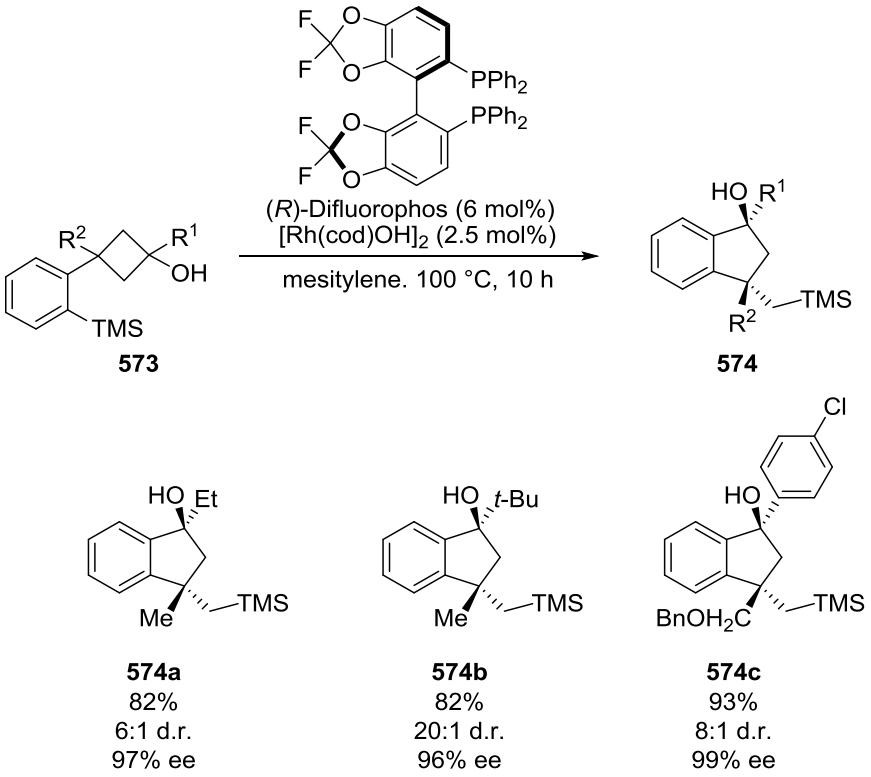
Following coordination of the rhodium to **567**, *β*-carbon elimination gives alkylrhodium **571**. 1,4-Rhodium migration to the adjacent aryl ring gives arylrhodium species **572**. Nucleophilic attack of the ketone by the arylrhodium moiety forms the bicyclic product **568** (Scheme 6.46).



Scheme 6.46: *β*-Carbon elimination followed by 1,4-migration[209]

In the majority of 1,4-migrations, rhodium undergoes a migratory insertion into a carbon-hydrogen bond. In 2010 Cramer reported the migratory insertion of a rhodium species into a carbon-silicon bond, resulting in the 1,4-shift of a silicon

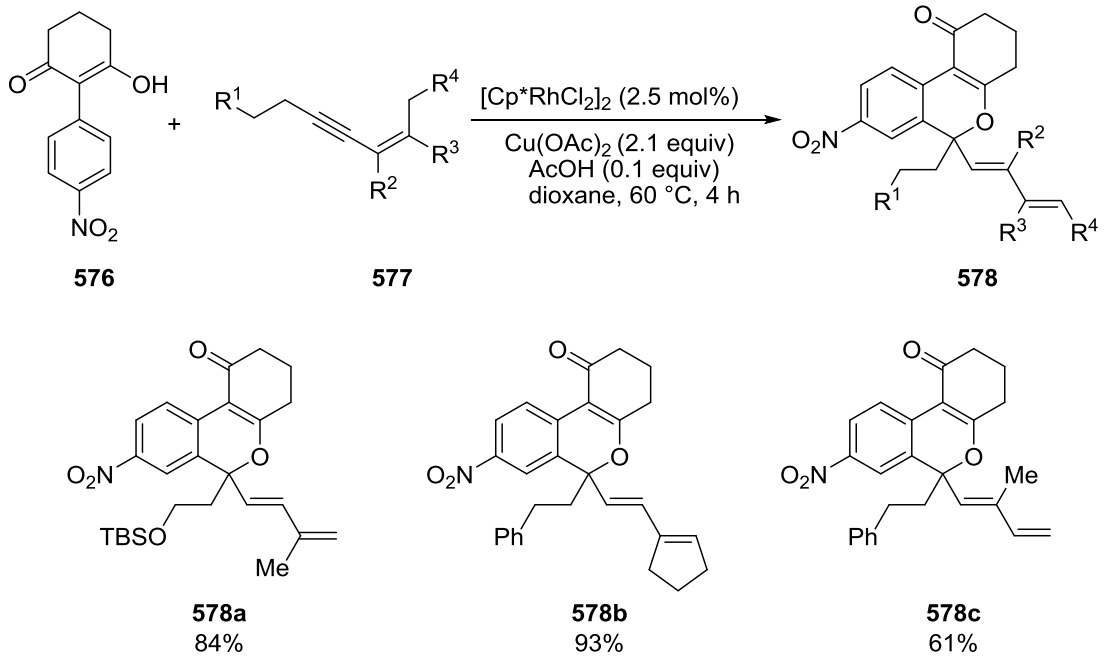
atom (Scheme 6.47).[212] Utilising cyclobutanol substrates that were similar to previously reported work,[209] and by simply replacing the *ortho*-substituent of the aromatic ring with a silyl group, it was possible to synthesise silyl-substituted bicyclic products **574** in high yields and enantiomeric excess. They found that insertion of the rhodium to the C-Si bond was more favoured than insertion into the C-H bond, and under the optimised conditions the C-H insertion pathway was not in operation.



Scheme 6.47: 1,4-Migration of a silyl group[212]

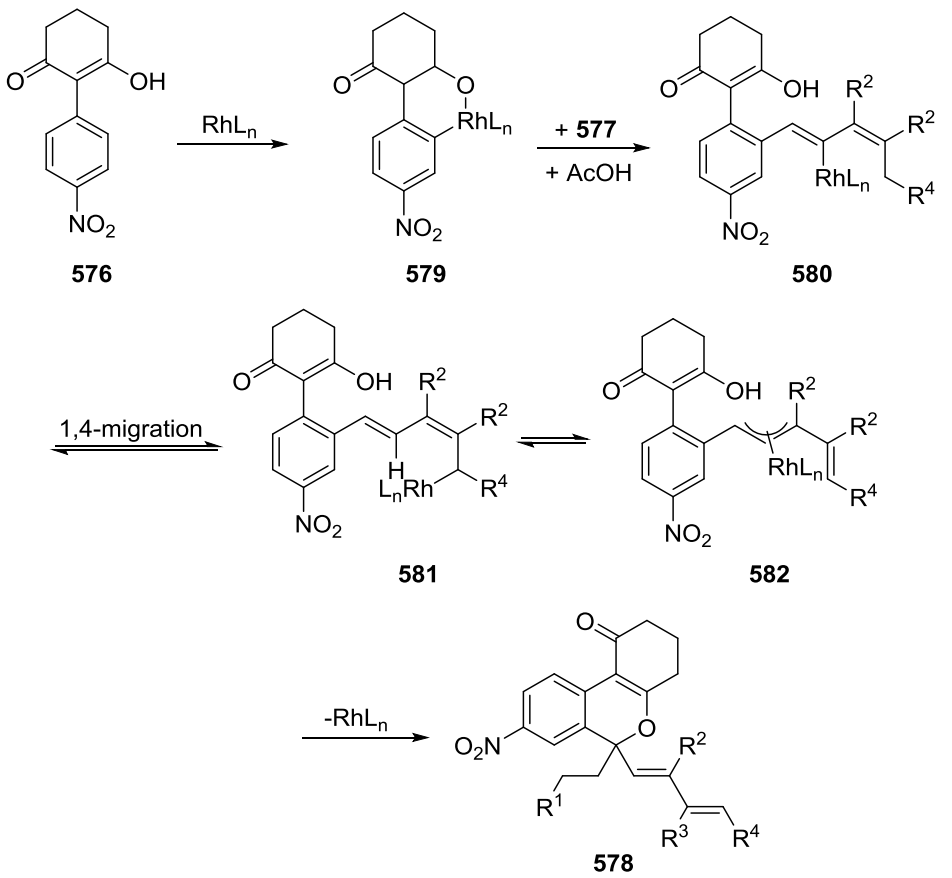
1.3.3 The 1,4-Migration of Rhodium From a C–sp^2 Centre to a C–sp^3 Centre

The first example of a rhodium 1,4-migration from a C–sp^2 centre to a C–sp^3 centre was recently published by the group of Lam.[213] In this work, a Rh(III) species was demonstrated to undergo a 1,4-migration from a C–sp^2 alkenyl position to an allylic C–sp^3 position (Scheme 6.48).



Scheme 6.48: First reported sp^2-sp^3 rhodium 1,4-migration[213]

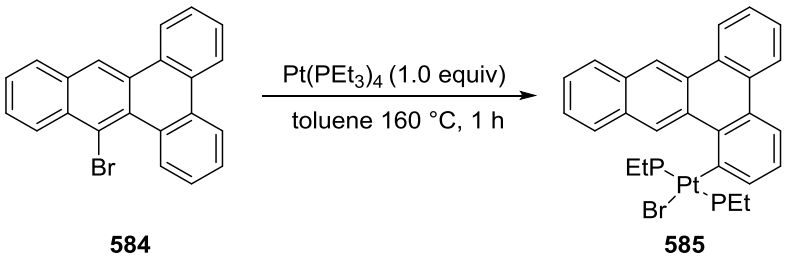
The reaction is thought to proceed by initial directed C–sp^2 C-H functionalisation to form rhodacycle **570**. Insertion of rhodacycle **579** across enyne **577** and acetic acid mediated cleavage of the resultant rhodacycle gives alkenylrhodium species **580**. This species undergoes a 1,4-migration to an allylic C–sp^3 centre forming Rh(III)-allyl species **581**. In contrast to previous examples, this intermediate is an electrophilic Rh(III) species rather than a nucleophilic Rh(I) species and following isomerisation to species **582**, cyclisation gives tricycle **578** (Scheme 6.49).



Scheme 6.49: Proposed mechanism of 1,4-Rh(III) migration[213]

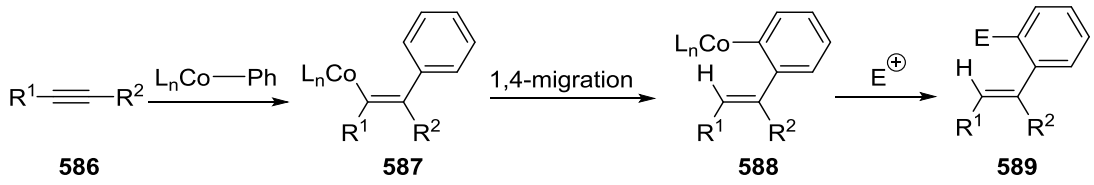
1.4 1,4 Migration of Other Transition Metal Species

As well as palladium and rhodium, other transition metals have also been reported to undergo 1,4-migration. In 2006, the proof of concept of platinum 1,4-migration was published by the group of Sharp.[214] Although only a single example was reported, and no synthetic application has since been described, it is an important example of platinum migration (Scheme 6.50).



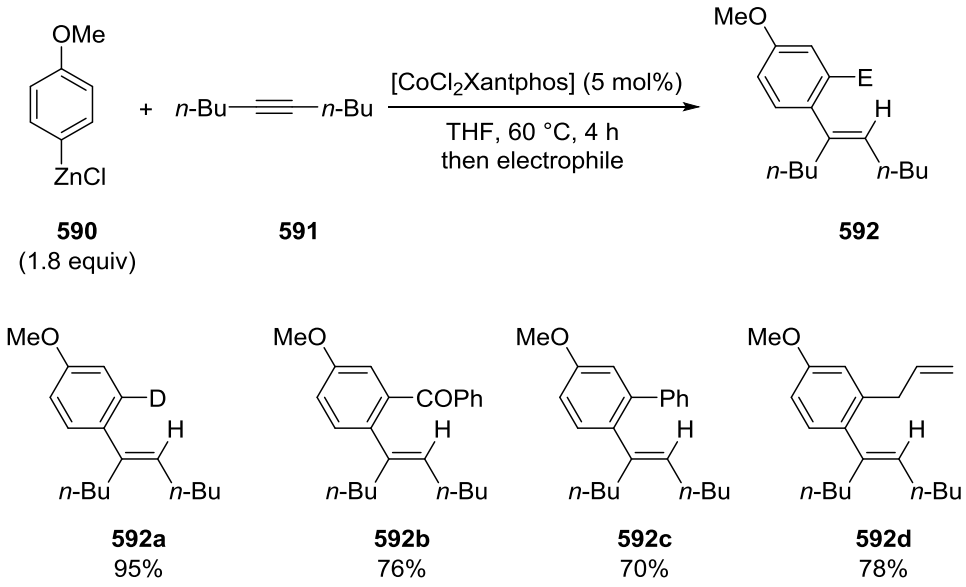
Scheme 6.50: Platinum 1,4-migration[214]

Yoshikai and co-workers reported that cobalt can also undergo 1,4-migration.[215,216] The cobalt-mediated addition arylzinc reagent to alkynes resulted in formation of the cobalt-alkenyl species **587** undergoes 1,4-migration in an analogous fashion to Rh (Scheme 6.51).



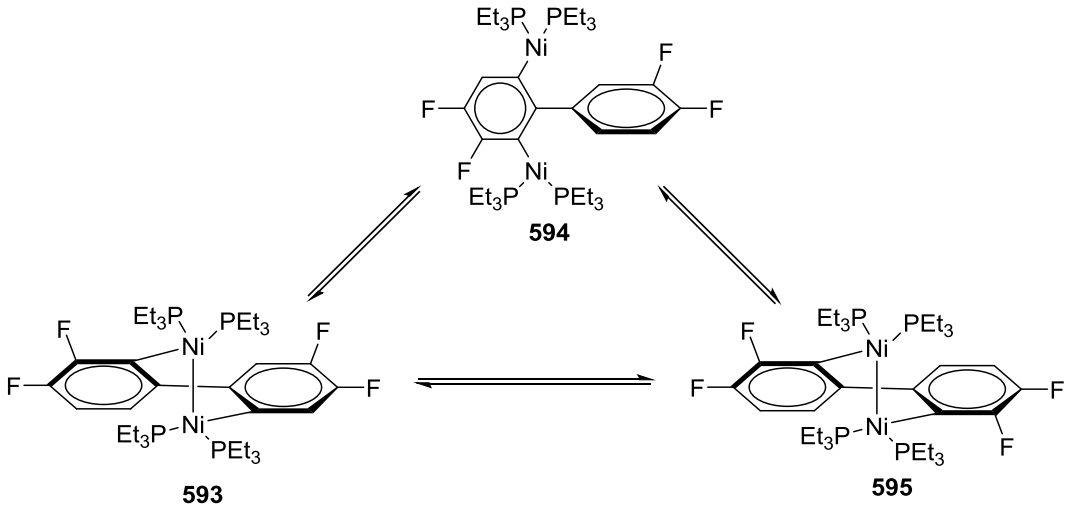
Scheme 6.51: Proposed 1,4-cobalt migration[199,200]

They demonstrated that a similar migration did occur in the case of cobalt and the resultant arylcobalt species **588** could either be quenched or transmetallate to form an arylzinc species that could undergo a range of transformations (Scheme 6.52).



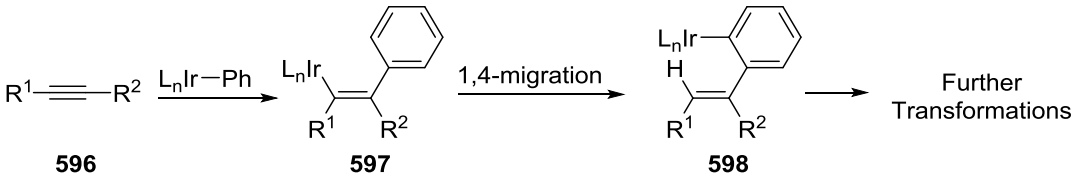
Scheme 6.52: Cobalt 1,4-migration[199,200]

In 2006, Johnson and co-workers demonstrated that nickel can also undergo 1,4-migration. This study utilised stoichiometric nickel but the proof of concept that nickel can behave in this way may lead to future catalytic transformations (Scheme 6.53).[217] They proposed the interconversion between **593** and **595** could only occur *via* intermediate **594** involving a 1,4-migration of the nickel metal.



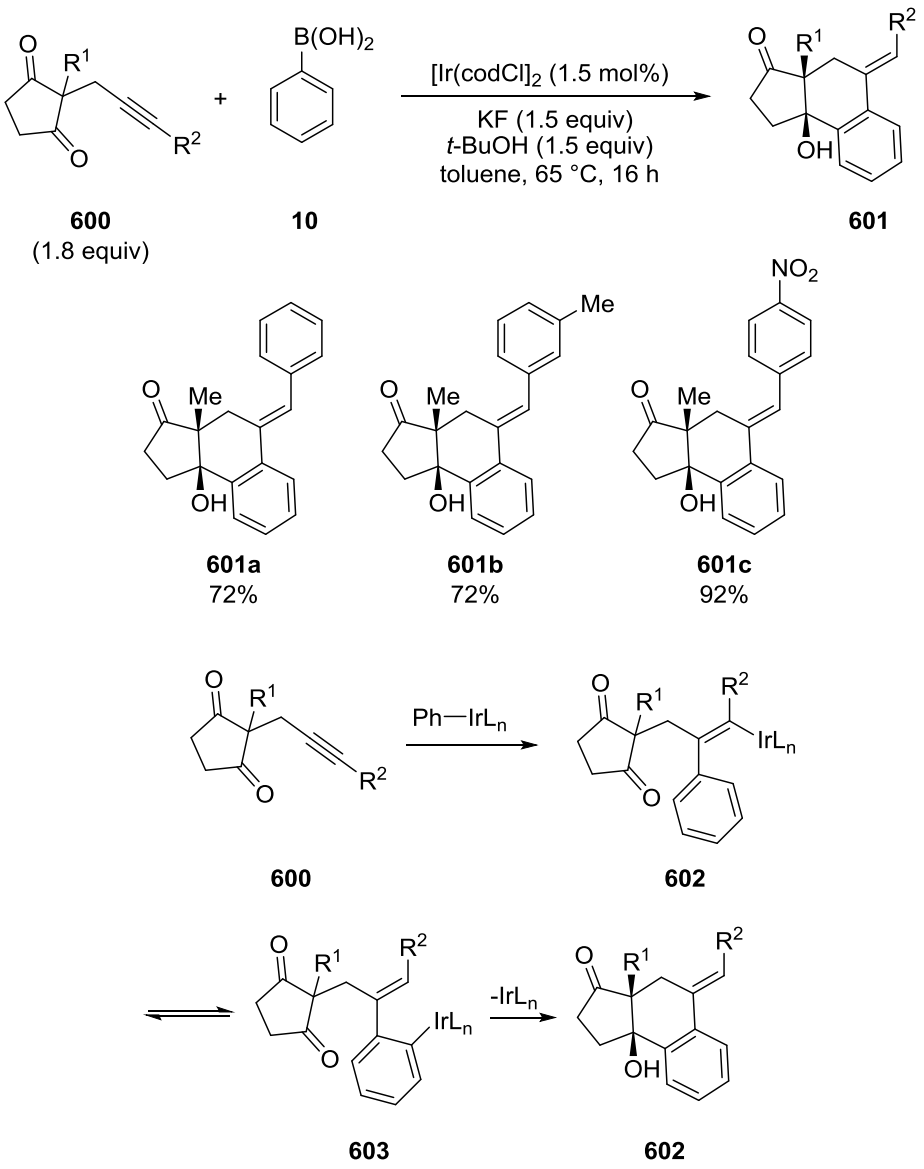
Scheme 6.53: Proposed interconversion of nickel complexes[217]

Recently the group of Lam have reported the 1,4-migration of iridium and its use in the arylative cyclisation of alkynone **600**. In similar fashion to rhodium and cobalt, they proposed that the formation of the analogous alkenyliridium species **597** would lend itself to 1,4-migration (Scheme 6.54).[218]



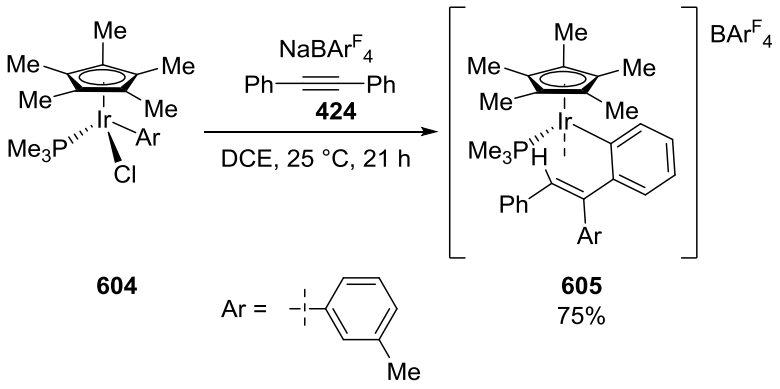
Scheme 6.54: Proposed 1,4-iridium migration

These intermediates were accessed by carboiridation of alkyne **600** with phenylboronic acid (**10**). Following the formation of intermediate **602**, an iridium sp^2–sp^2 1,4-migration occurs to form an aryliridium species **603**. This Ir(I) species **603** then undergoes nucleophilic attack of a pendant ketone by a cyclisation to form bicycles **601** as a single diastereomer in good yield (Scheme 6.55).



Scheme 6.55: Iridium-catalysed arylative cyclisation[218]

Around the same time, Ishii and co-workers reported a Ir(III) migration, analogous to their Rh(III) migration.[206,207] Only the migrated iridium species **605** was isolated and no catalytic activity was investigated, but product **605** demonstrates that Ir(III) can also undergo 1,4-migration (Scheme 6.56).



Scheme 6.56: Ir(III) 1,4-migration[190,191]

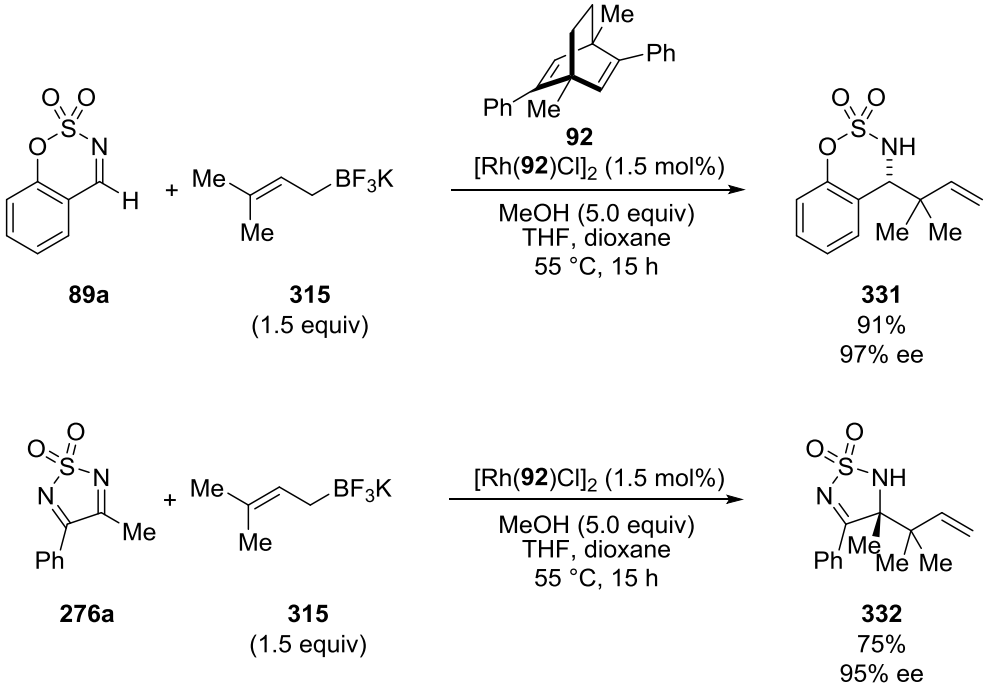
A substantial amount of research has been undertaken investigating the 1,4-migration of transitions metals, both from a mechanistic and synthesis standpoint. The majority of reports involve palladium or rhodium migration, but other metals have also been shown to undergo such a process. A range of sp^2–sp^2, sp^2–sp^3, and sp^3–sp^2 migrations have been reported, as have enantioselective processes. The migratory insertion of a transition metal into a carbon-silicon bond has also been reported. 1,4-Migration is a powerful method of remote C-H functionalisation. The 1,4-migration can lead to the rapid formation complex products in only one step and in some cases give products featuring newly formed stereocentres with high enantioselectivities.

2.0 Aims

During out study of rhodium-catalysed nucleophilic allylations of cyclic imines with potassium allyltrifluoroborates (Chapter 1) we discovered an unexpected product that seemed to be formed by 1,4-rhodium migration. Intrigued by this observation, we aimed to investigate the scope of this process and attempt to prove a 1,4-rhodium migration mechanism was in operation.

3.0 Early Observations of the Isomerisation of Allylrhodium Intermediates

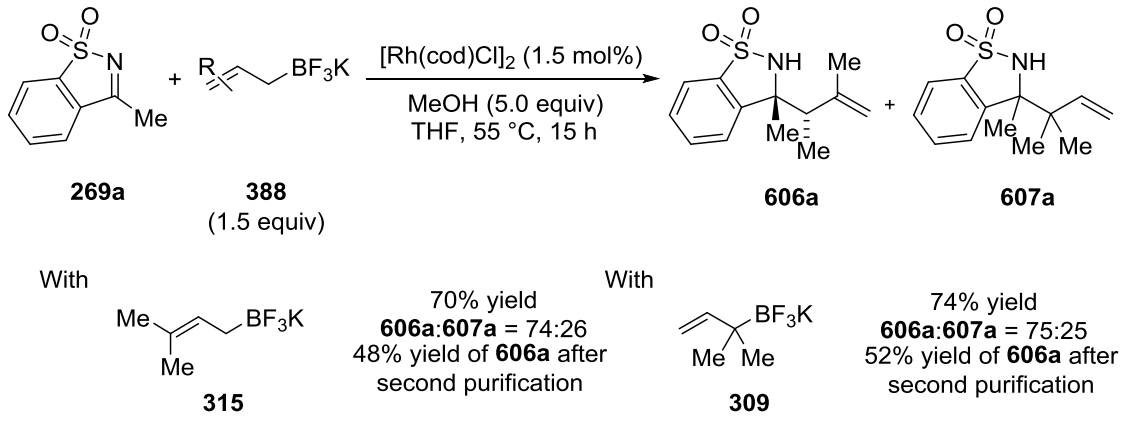
During the development of the rhodium-catalysed enantioselective nucleophilic allylation of cyclic imines (see Section 4.0),[219] reactions utilising more substituted allylboron species were investigated in an attempt to increase the molecular complexity of the resultant products. In particular, potassium prenyltrifluoroborate (**315**) was found to be a suitable allylating agent for aldimine **89a** and ketimine **276a**, exclusively delivering the reverse prenylation products **331** and **332** in good yields and excellent enantioselectivities (Scheme 8.1).



Scheme 8.1: Allylation reactions using prenyltrifluoroborate (**315**)

When the corresponding racemic reaction, using $[Rh(cod)Cl]_2$, with ketimine **269a** was attempted, a mixture of products was observed in ^1H NMR spectrum of the crude reaction mixture and the expected product was only the minor component (Scheme 8.2). Upon further purification and analysis of the isolated material, it was found the major product was in fact homoallylic sulfonamide **606a**. ^1H NMR analysis of the crude reaction mixture demonstrated that the ratio between the major and minor products was 74:26 with the major product observed as a single

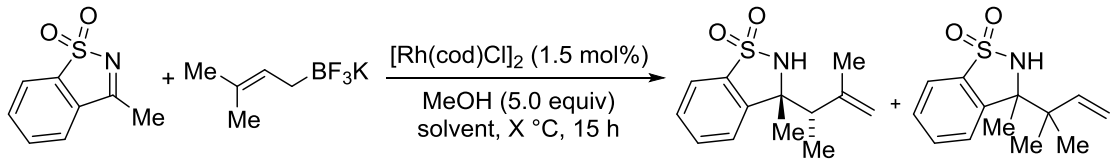
diastereomer. The reaction using isomeric allyl species **309** rather than **315** resulted in formation of the same unexpected product in a similar yield and ratio.



Scheme 8.2: Discovery of unexpected product **606a**

A range of variables were then systematically altered in an attempt to see if the selectivity could be improved in favour of either of the products (Table 8.1). Changes in solvent and an increase in temperature had minimal effect upon both the ratio and conversion (entries 2, and 3). Similarly altering the molarity of the reaction mixture also seemed to have minimal impact (entry 1). Increasing the equivalents of allylboron species **315** had no observed effect (entry 4). However, it was found that running the reaction at room temperature resulted in a large reverse in selectivity in favour of the non-isomerised product (entry 5). This reverse in selectivity might be due to an alternative non-rhodium catalysed pathway being in operation at room temperature as transmetallation may be far slower at this temperature.

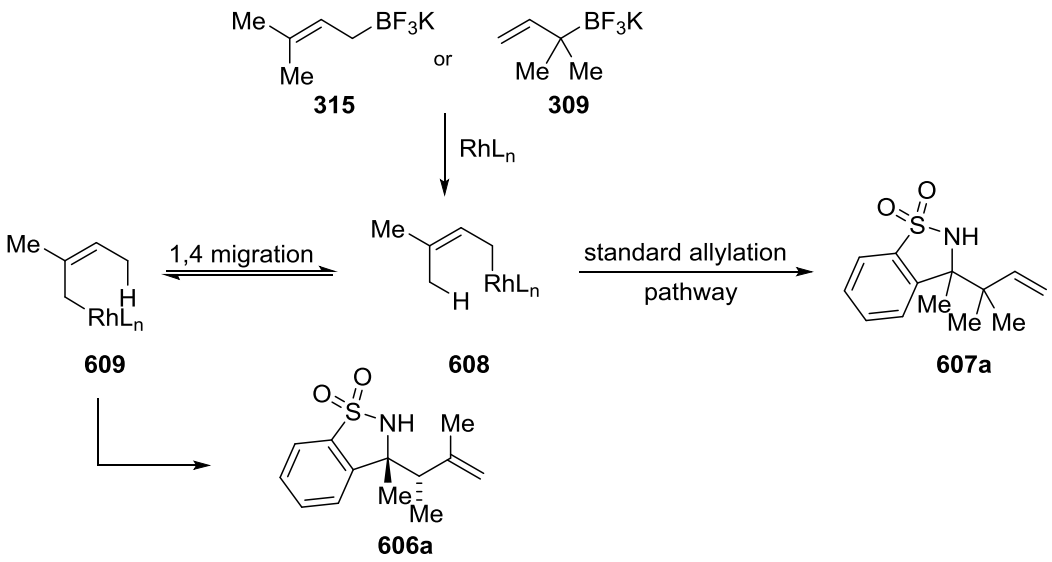
Table 8.1: Attempted Optimisation of Isomerisation



Entry	Solvent	Temperature (°C)	Molarity of **269a**	Equivalents of **315**	Conversion[a]	Ratio of **606a**:**607a**[a]
1	THF	55	0.033	1.5	84	76:24
2	dioxane	80	0.1	1.5	95	69:31
3	toluene	80	0.1	1.5	67	70:30
4	THF	55	0.1	2	86	75:25
5	THF	23	0.1	1.5	65	7:93

[a] Determined by ^{1}H NMR

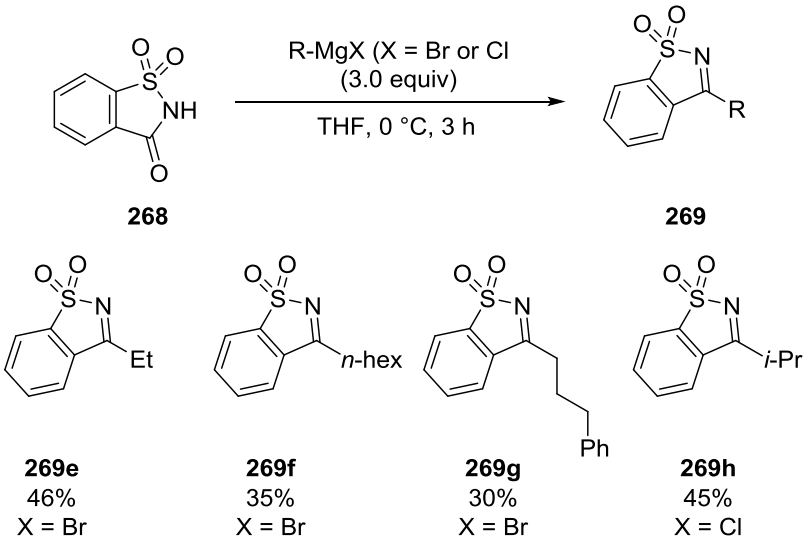
It is proposed that this unexpected product **606a** is formed due to an isomerisation of the allylrhodium intermediate **608**. A mechanism that explains the observed experimental data is shown in Scheme 8.3 and involves transmetallation of the allylboron species to form allylrhodium species **608**. With reactive substrates **89a** and **276a**, the standard allylation pathway proceeds rapidly to the reverse prenylation products **331** and **332**. With the less reactive ketimine **269a**, this pathway may be slower, resulting in an allylic 1,4-migration to give allylrhodium species **609**. This may then undergo a nucleophilic allylation with cyclic imine **269a** to give product **606a**.



Scheme 8.3: Plausible mechanistic pathway

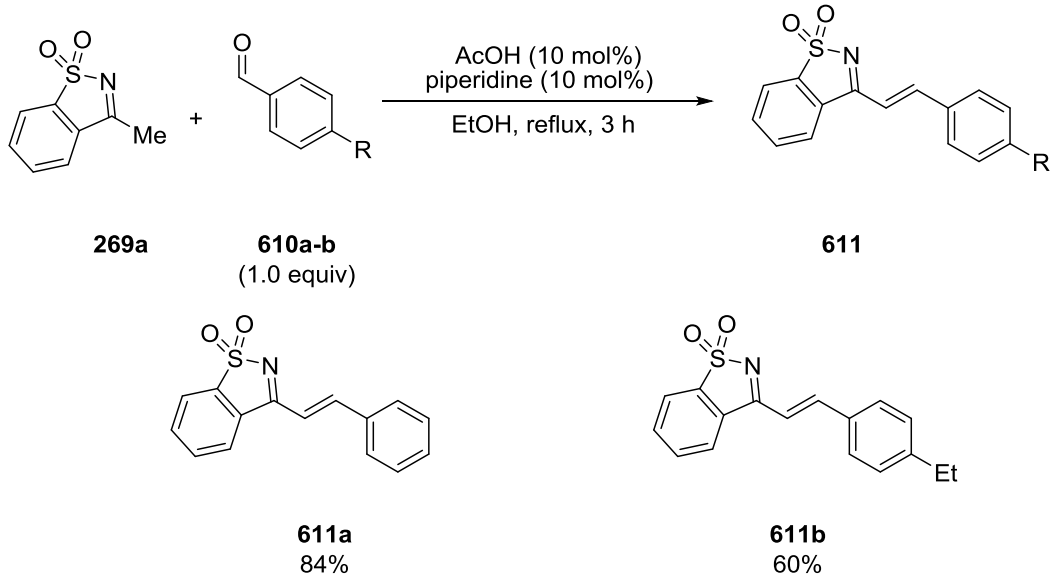
3.1 Synthesis and Reaction of Other Cyclic Ketimines

To further investigate this unusual reactivity, a variety of related cyclic ketimines were prepared. Ketimines **269b** and **269c** had been prepared previously and ketimines **269e-h** were prepared by the addition of the appropriate Grignard reagent to saccharin (**268**) (Scheme 8.4).



Scheme 8.4: Synthesis of ketimines **269e-h**

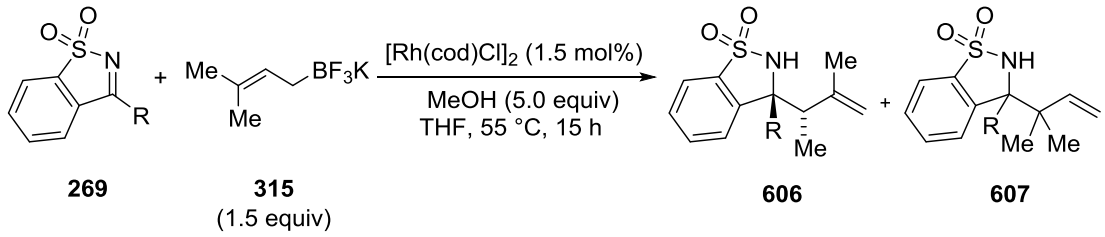
A further two ketimines **611a** and **611b** bearing alkenyl side chains were synthesised by the condensation between ketimine **269a** and the appropriate benzaldehyde (Scheme 8.5).



Scheme 8.5: Synthesising ketimines **611a** and **611b**

The ketimines were then subjected to the allylation reaction conditions to investigate whether any isomerisation products were observed. Pleasingly, for the ketimines similar to **269**a, featuring a simple alkyl chain (**269c**, **269e**, and **269f**), the reaction proceeded smoothly, giving a similar yield and product distribution as observed for **269a**. Also, the isomerised product **606** was formed as a single diastereomer. Ketimine **269g** bearing a $CH_2CH_2CH_2Ph$ side chain also worked well, giving comparable results to the previous examples. Ketimines featuring either an aryl side chain **269b** or a bulky alkyl species, **269h**, were unreactive and only starting material was recovered. α,β-Unsaturated imines **611a** and **611b** reacted well and gave similar product distributions, but, the isomerised product **606** had a much lower diastereomeric ratio (Table 8.2).

Table 8.2: Investigations into ketimine scope

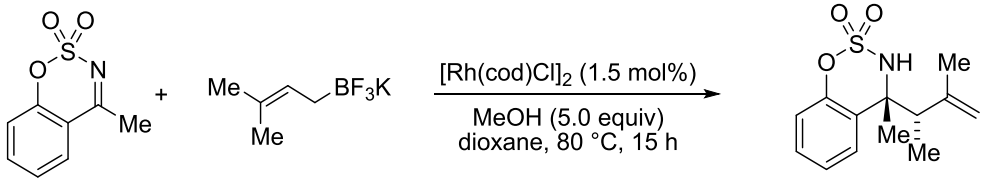


269 **315** (1.5 equiv) **606** **607**

Entry	Ketimine	R	Yield of **606** and **607** (%)[a]	Ratio of **606** and **607**[b]	Yield of **606** (%)[c]	d.r. of **606**[b]
1	**269b**	Phenyl	0	n/a	0	n/a
2	**269c**	*n*-butyl	66	75:25	50	>95:5
3	**269e**	Ethyl	84	76:24	62	>95:5
4	**269f**	*n*-hexyl	91	79:21	61	>95:5
5	**269g**	$(CH_2)_3Ph$	69	76:24	47	>95:5
6	**269h**	*i*-propyl	0	n/a	0	n/a
7	**611a**	CH=CHPh	68	72:28	56	85:15
8	**611b**	CH=CHAr Ar = 4-EtC_6H_4	75	82:18	46	76:24

[a] Yield of an isolated, combined mixture of **606** and **607**. [b] Determined by ^1H NMR analysis. [c] Yield of an isolated pure sample of **606** after second purification.

Less reactive ketimine **262** was a poor electrophile for the reaction, leading to only a 4% conversion. However, the product distribution was exclusively in favour of the rearranged product **612** formed as a single diastereomer (Scheme 8.6).



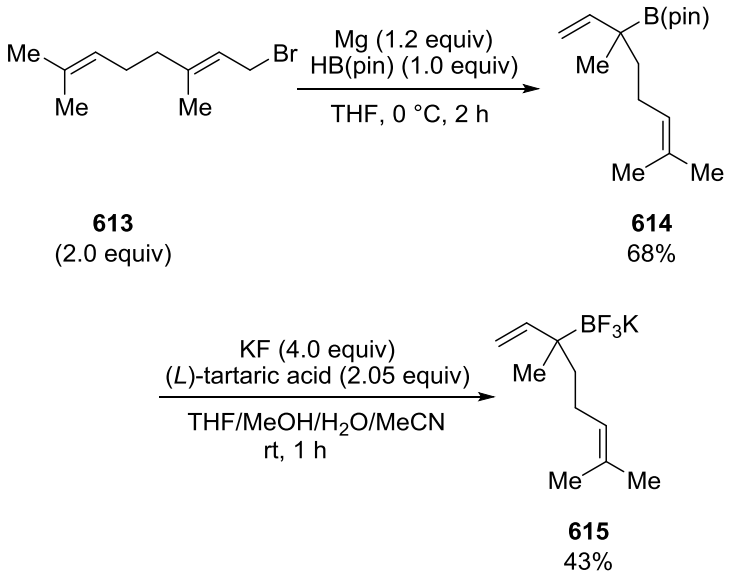
262 **315** (1.5 equiv) **612** 4% conversion d.r. >95:5

Scheme 8.6: Reaction involving ketimine **262**

3.2 Synthesis and Reaction of Other Boron Species

In order to investigate whether the 1,4-migration was limited to prenyltrifluoroborate **315** and its isomer **309**, other trifluoroborate salts were synthesised. Given that previous reactions (see Section 4.5.2) had demonstrated that mono-γ-substituted trifluoroborate salts and mono-γ-substituted trifluoroborate salts do not lead to any isomerisation, a variety of γ,γ-disubstituted trifluoroborate salts and α,α-disubstituted trifluoroborate salts were prepared.

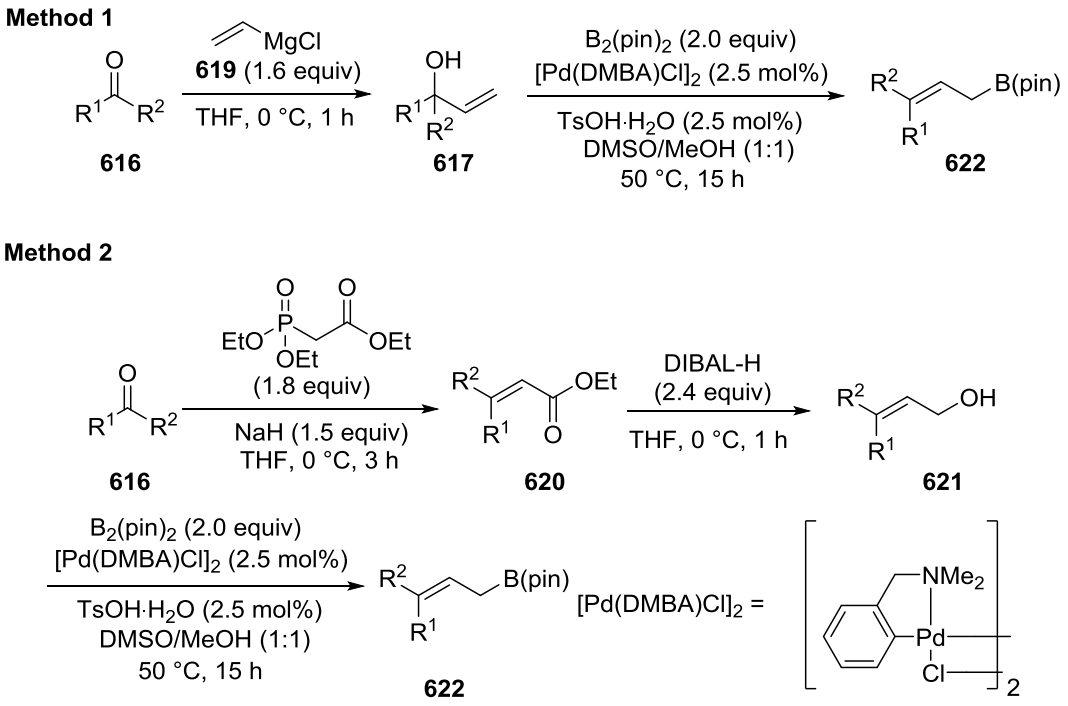
For α-substituted species, the appropriate γ,γ-disubstituted allylbromide was converted into the allyboron species in the presence of magnesium and pinacol borane in accordance to the protocol developed by Singaram.[151] Commercially available geranyl bromide (**613**) was converted in allylboronic acid pinacol ester **614** in good yield, then converted into the corresponding trifluoroborate salt using the method of Lloyd-Jones (Scheme 8.7).[150]



Scheme 8.7: Synthesis of trifluoroborate **615**

For γ,γ-disubstituted species, the appropriate allylic alcohol was converted to allylboron species using a palladium-catalysed borylation reported by Szabo and Aggarwal.[152] The allylic alcohols were synthesised either by a Horner-Wadsworth-Emmons reaction followed by a reduction by di-*iso*-butylaluminium hydride

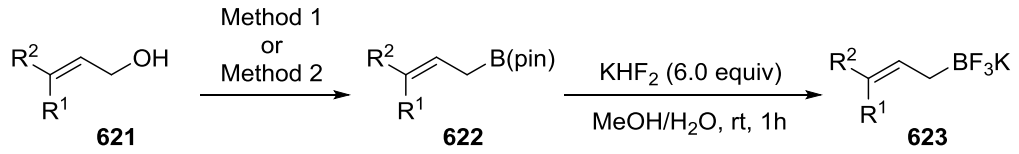
(DIBAL-H), or by the addition of vinylmagnesium chloride (**619**) to the appropriate ketone (Scheme 8.8).



Scheme 8.8: Methods for the formation of allylB(pin)

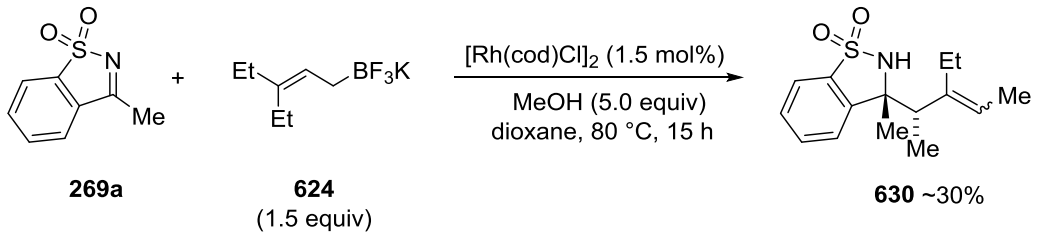
Once the allylboronic acid pinacol esters **622** were synthesised, they were converted into the potassium allyltrifluoroborate through reaction with aqueous potassium hydrogen difluoride. A variety of symmetrical and non-symmetrical allyltrifluoroborates were synthesised in a variety of acceptable yields (Table 8.3).

Table 8.3: Synthesis of disubstituted allyltrifluoroborates



Entry	R^1	R^2	Method for preparation of B(pin)	Compound Number	Overall Yield (%)
1	Et	Et	1	**624**	41
2	Me	CH_2CH_2Ph	1	**625**	11 (100% E)
3	Me	Ph	1	**626**	19 (2.4:1 E:Z)
4	Me	Ph	2	**626**	18 (2.4:1 E:Z)
5	CH_2Ph	CH_2Ph	2	**627**	33
6	$-(CH_2)_6-$	N/A	1	**628**	16

Unfortunately, in the rhodium-catalysed nucleophilic allylation reaction, trifluoroborates **627** and **628** were completely unreactive with ketimine **269a**, exclusively returning starting materials. Allyl species **624** was slightly more reactive, and at 80 °C around 30% of product **630** was isolated. This material was impure and an authentically pure sample of **630** could not be isolated (Scheme 8.9).

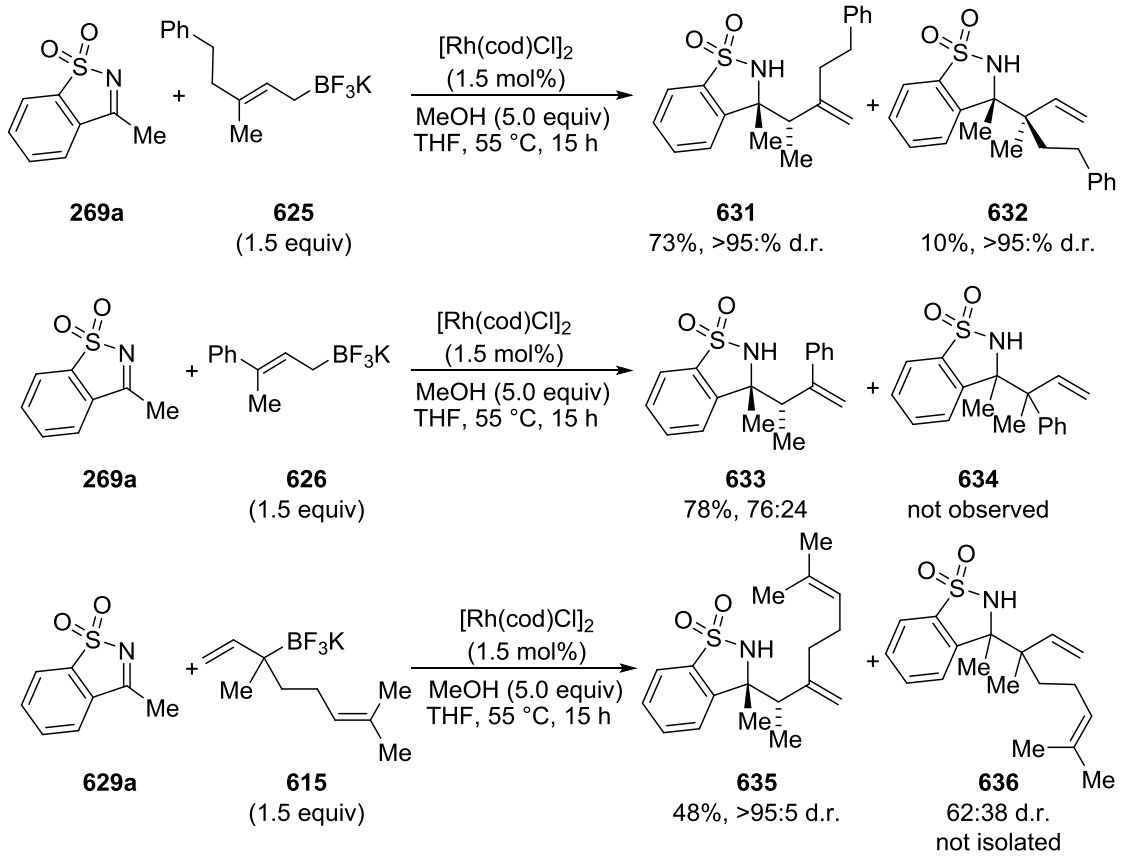


Scheme 8.9: Reaction using reagent **624**

Pleasingly, allyl species bearing methyl groups (**625** and **626**) and the α-substituted species **615** underwent the isomerisation and provided the rearranged product in good yields and selectivities with ketimine **269a** (Scheme 8.10). Allyl species **625** gave the rearranged product **631**, isolated as a single diastereomer, in 73% yield. The non-rearranged product **632** was also obtained in 10% yield as a single diastereomer. Unfortunately, allyl species **626** could not be synthesised as a single isomer and therefore the relative contribution of the E and Z isomers to the product ratio in the reaction could not be quantified. Regardless, the product **633** was formed in a

diastereomeric ratio of 76:24, and interestingly, no non-rearranged product **634** was observed. This suggests that the formation of such a sterically congested centre is not favourable. Finally, species **615** gave the rearranged product **635** in only 48% yield but as a single diastereomer. The non-rearranged product **636** was observed in a 20% yield by ^{1}H NMR but attempts to isolate and characterise **636** were unsuccessful. These results are significant as they demonstrate that further substitution in allyl species are tolerated and that rhodium can migrate to secondary carbons as well as primary carbons

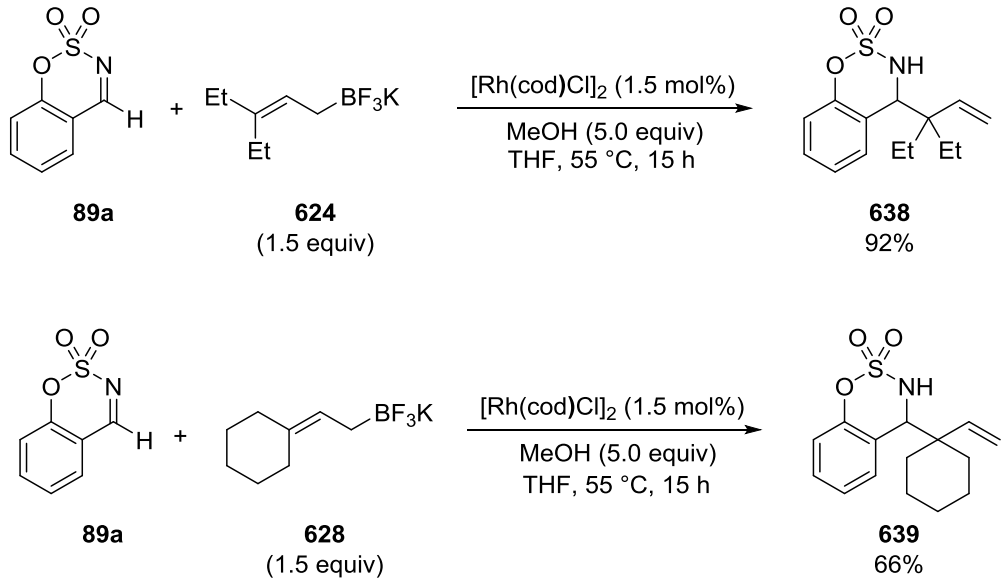
.



Scheme 8.10: Successful reactions involving trifluoroborates

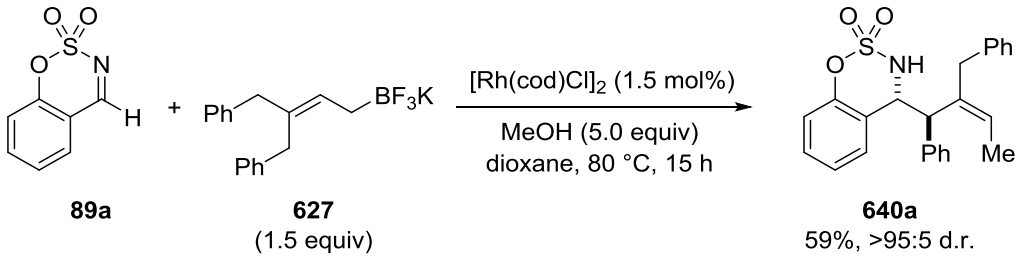
In an attempt to broaden the substrate scope, aldimine **89a** was considered as an electrophile. Aldimine **89a** is more reactive than ketimine **269a**. The reaction of **89a** with allylboron species **315** gave the non-rearranged product **331** exclusively. It was wondered if these less reactive allylboron species could in fact undergo a 1,4-migration before allylating aldimine **89a**. In small scale test reactions, reagents **625**, **626**, and **615** exclusively gave non-rearranged products. Reactions with species **624**

and **628** which were too unreactive to react with ketimine **269a** exclusively gave the non-rearranged products **638** and **639** in good yields (Scheme 8.11).



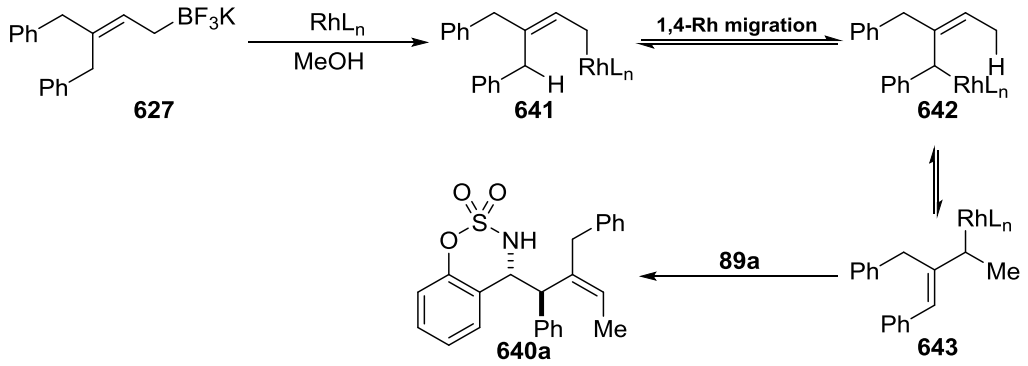
Scheme 8.11: Reactions involving species **624** and **628**

It was believed that in order for the rate of Rh-catalysed allylation of substrate **89a** to be sufficiently low to allow the 1,4-migration to occur, a far more sterically hindered allyl species would be required. Allylboron species **627**, considerably more hindered than any previous species investigated, gave no product with ketimine **269a**. Disappointingly upon subjecting aldimine **89a** to the standard reaction conditions with **627**, only starting material was recovered. However, increasing the temperature to 80 °C and using dioxane rather than THF resulted in the recovery of product **640a** as a single diastereomer in 59% yield (Scheme 8.12).



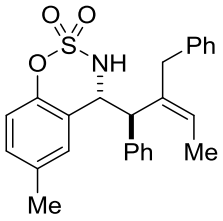
Scheme 8.12: 1,4-Migration of hindered species **627**

A possible explanation for the formation of product **640a** involves a similar 1,4-migration pathway (Scheme 8.13). Following transmetallation between the allyltrifluoroborate **627** and rhodium, allylrhodium species **641** is formed. At this point, a pre-migratory allylation is strongly disfavoured due to the steric hindrance caused by the large benzyl substituents, and instead, a 1,4-migration occurs to give isomerised species **642**. Although the imine **89a** could potentially undergo allylation with species **642**, the product isolated is consistent with the allylation of **89a** by species **643**, which can be formed *via* a 1,3-allylic transposition of the rhodium.

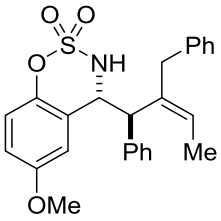


Scheme 8.13: Proposed pathway of formation of **640a**

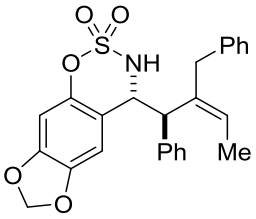
A range of substitutions were tolerated on the aromatic ring of the aldimine to give a range of substituted products in good yields. Each product was isolated as a single diastereomer (Figure 8.1).



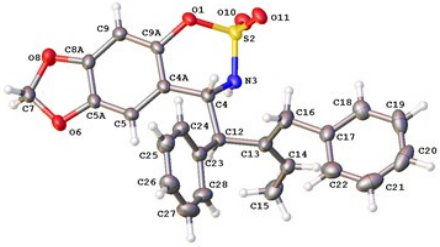
640b
74%, >95:5 d.r.

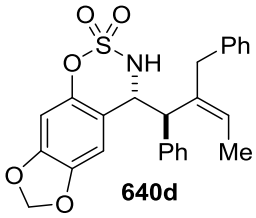


640c
55%, >95:5 d.r.



640d
63%, >95:5 d.r.

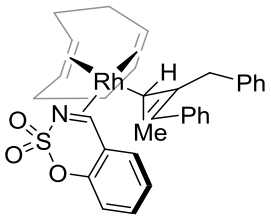




640d

Figure 8.1: Further products bearing substitution

Single crystal X-ray analysis of **640d** determined that the product was the *anti*-diastereomer and the double bond was in a *cis*-configuration, demonstrating that this process controls three different stereochemical elements. If, as with previous rhodium-catalysed allylations (see Section 4.5.2), a chair-like transition state **644** is in operation, the *cis*-configuration of the alkene in the products presumably arises from the methyl group occupying a pseudo-axial position. One possible explanation for the methyl group occupying such a position is in order to reduce steric clash between the methyl group and the cyclooctadiene ligand (Figure 8.2).



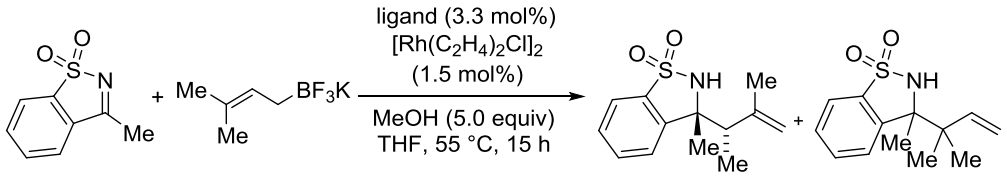
644

Figure 8.2: Possible chair-like transition state

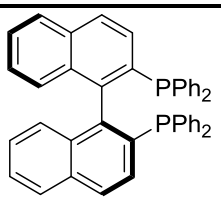
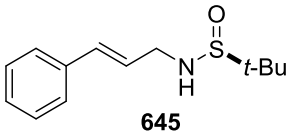
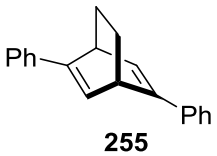
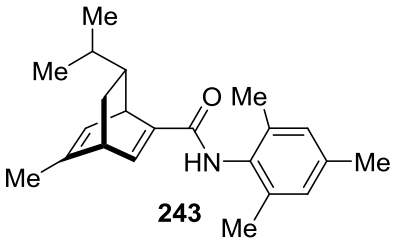
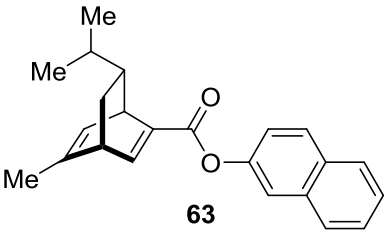
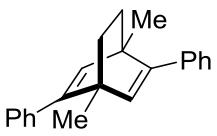
3.3 An Enantioselective Variant of 1,4-Rhodium Migration

Following the discovery of the 1,4-rhodium migration and the excellent results achieved with $[Rh(cod)Cl]_2$ as a precatalyst, work focussed on attempts to develop an enantioselective variant of the process. Given that an achiral diene (cyclooctadiene) worked well, it was proposed that a chiral diene-rhodium complex could also promote the isomerisation and lead to enantioinduction during the allylation (Table 8.4). Early investigations focussed on the allylation of ketimine **269a** with boron species **315**, and somewhat unsurprisingly, bisphosphine ligand **7** and sulfur-olefin ligand **645** led only to recovery of starting material (entries 1 and 2). Chiral diene **255**, Ph-bod, gave a 64:36 ratio in favour of the non-isomerised product (entry 3). This suggests that a **255**-rhodium complex leads to a relatively faster allylation process and a relatively slower 1,4-migration process. Chiral diene **74** gave unsatisfactory results, but naphthyl ester diene **63** and diene **92** both gave the 1,4-migration product **606a** in good conversion, high diastereomeric ratio and excellent enantioselectivity (entries 4 and 5). Although diene **92** gave the highest diastereomeric ratio (>95:5) and enantioselectivity (98%), the conversion was only moderate and the ratio between **606a** and **607a** lower. Therefore, diene **63** was chosen to be the optimal ligand for the enantioselective process due to its high conversion, selectivity, diastereoselectivity and enantioselectivity.

Table 8.4: Screening of Chiral Ligands



269a **315** (1.5 equiv) **606a** **607a**

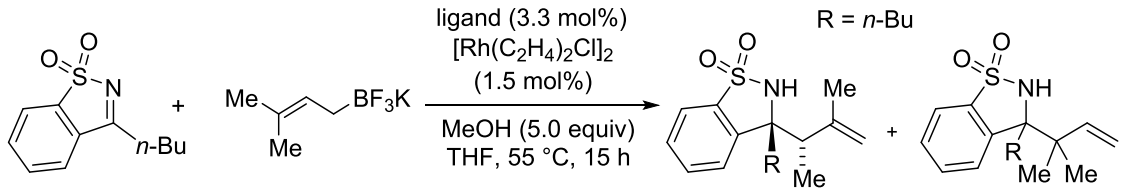
Entry	Ligand	Conversion (%)[a]	Ratio of **606a** and **607a**[a]	d.r. of **606a**[a]	%ee of **606a**[b]
1	 **7**	0	n/a	n/a	n/a
2	 **645**	0	n/a	n/a	n/a
3	 **255**	85	36:64	>95:5	85
4	 **243**	47	55:45	5:1	45
5	 **63**	80	87:13	95:5	97
6	 **92**	65	71:29	95:5	98

[a] Determined by ^{1}H NMR analysis. [b] Determined by HPLC analysis on a chiral stationary phase.

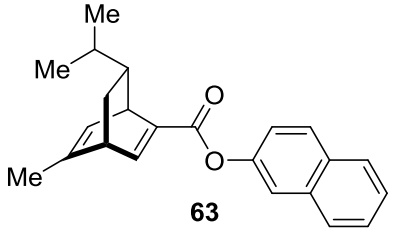
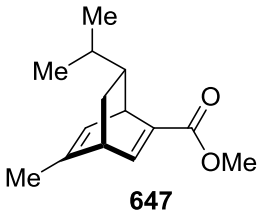
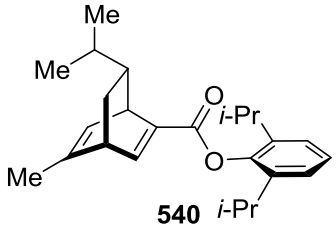
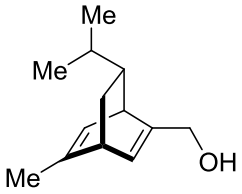
With diene **63** identified as the optimal ligand, further ketimines were examined as electrophiles. Unfortunately, it became apparent that the excellent result achieved with ketimine **369a** was not transferrable to other substrates. Using *n*-butyl ketimine **269c** as a model substrate, rhodium complex formed with chiral diene **63** gave a 68% conversion with isomerised product **606c** formed preferentially in a 9:1 ratio over non-isomerised product **607c**. However, there was almost no diastereoselectivity (d.r. 1.2:1). The erosion of diastereoselectivity is currently unexplained.

A further screen of additional ligands was conducted to investigate if this loss of diastereoselectivity could be remedied (Table 8.5). Methyl ester diene **647** gave good conversion and selectivity, but in fact gave the opposite diastereomer for unknown reasons (entry 2). However, this result was not pursued as an assay could not be developed to determine the enantioselectivity of the product. 2,6-Di*iso*-propylphenyl substituted diene **540** gave unsatisfactory conversion and hydroxy-diene **648** gave poor selectivity between isomerised and non-isomerised products (entries 3 and 4).

Table 8.5: Screening of Chiral Ligands



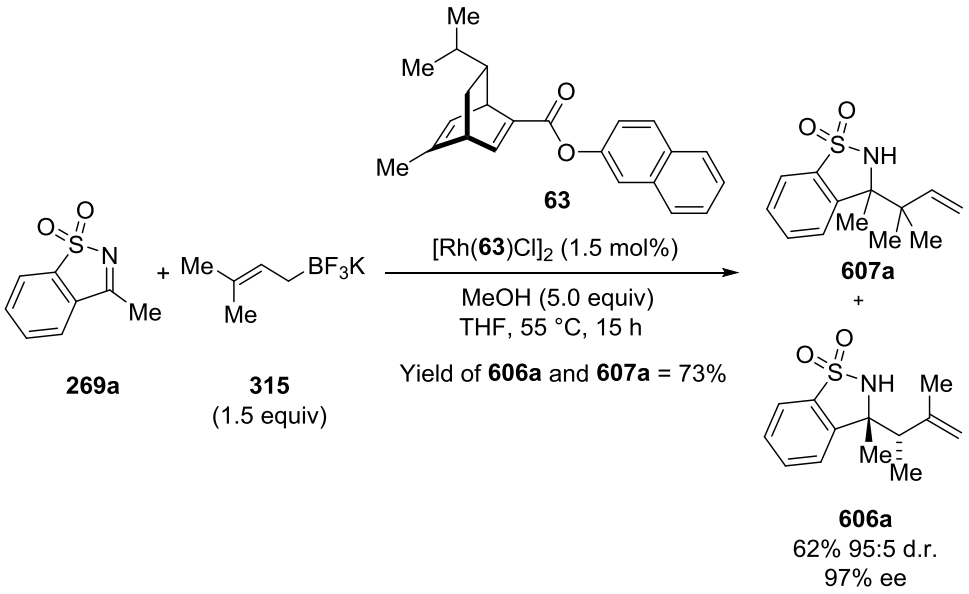
269c **315** (1.5 equiv) **606c** **607c**

Entry	Ligand	Conversion (%)[a]	Ratio of **606c** and **607c**[a]	d.r. of **606c**[a]	ee of **606c** (%)[b]
1	 **63**	68	90:10	1.2:1	92
2	 **647**	71	93:7	1:13	n.d
3	 **540**	34	83:17	5:1	52
4	 **648**	68	64:36	10:1	73

[a] Determined by ^{1}H NMR analysis. [b] Determined by HPLC analysis on a chiral stationary phase.

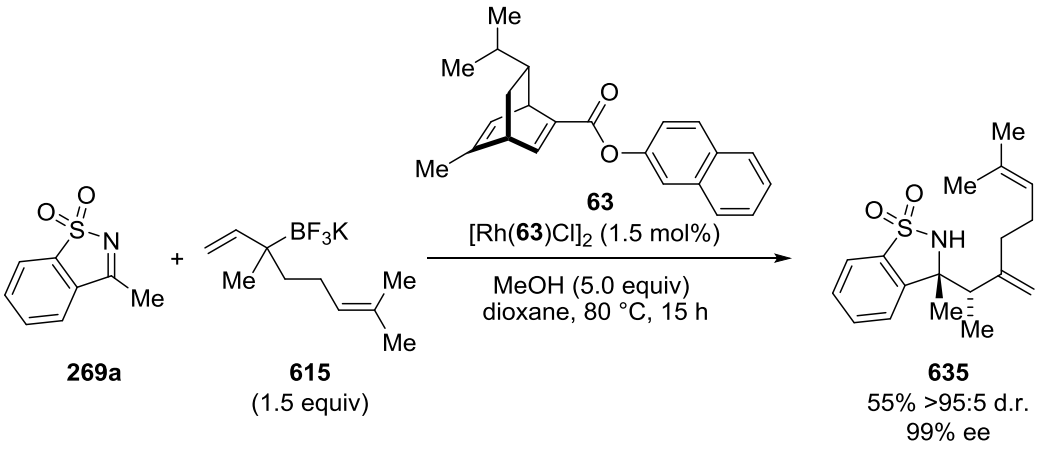
Despite these unsatisfactory results, no further dienes were prepared and tested. The scope of the enantioselective 1,4-migratory allylation is limited to ketimine **269a**

giving product **696a** in good yields, diastereomeric ratio and enantioselectivity (Scheme 8.14).



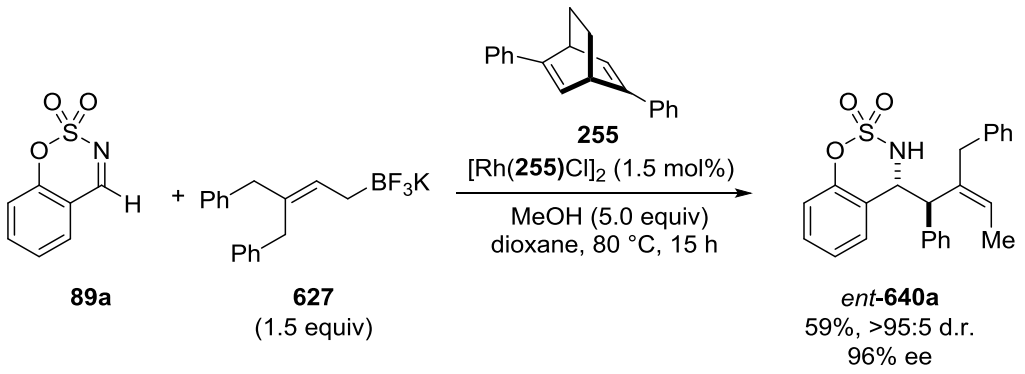
Scheme 8.14: Enantioselective 1,4-migration

Investigations were then focussed on different nucleophiles. Unfortunately, allyboron species **625** and **626** were found to be unreactive using ligand **63**, only returning starting material. Boron species **615** reacted smoothly when employing ligand **62** to exclusively give isomerised product **635** in 55% yield as a single diastereomer and 99% ee (Scheme 8.15).



Scheme 8.15: Enantioselective addition of allylboron **615**

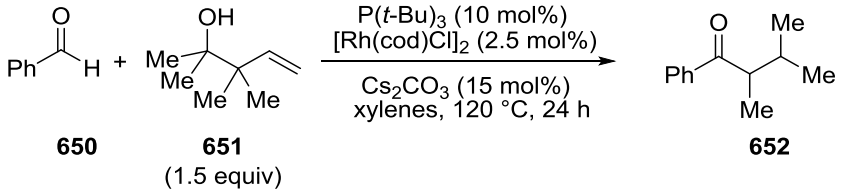
Investigations also took place into the enantioselective addition of allyl species **627** to aldimine **89a**. When naphthyl diene **63** was employed as a ligand, no reaction occurred and starting material was recovered. However, pleasingly, the reaction between **89a** and **627** using Rh-**255** complex gave the isomerisation product *ent*-**640a** in 62% as a single diastereomer and in 96% ee (Scheme 8.16).



Scheme 8.16: Enantioselective addition of allylboron **627**

3.4 Mechanistic Insights

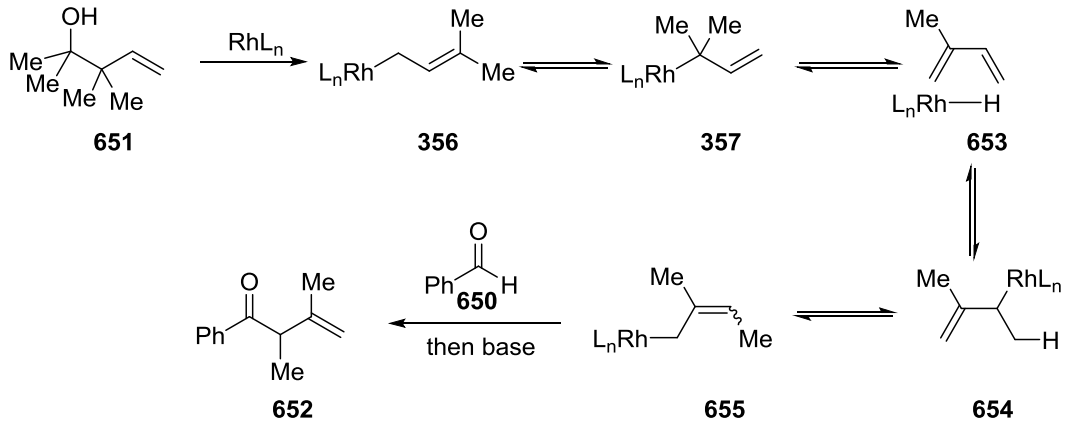
After the discovery of the 1,4-migration of the allylrhodium species, it was uncovered that this was not a new discovery, and in 2006 the group of Yorimitsu and Oshima reported a similar isomerisation during their studies into rhodium-catalysed retro-allylations (Scheme 8.17).[135,220]



Scheme 8.17: Yorimitsu and Oshima's retro-allylation

Yorimitsu and Oshima proposed a different mechanistic pathway than a 1,4-migration (Scheme 8.18).[66] Following retro-allylation, allylrhodium species **356** was formed, and they propose, following allylic-transposition of Rh to give **357**, *β*-hydride elimination occurs to form isoprene/rhodium-hydride complex **653**. Hydrorhodation of the other, less-substituted olefin leads to allylrhodium species

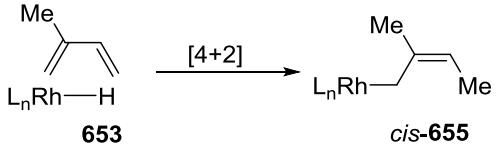
654, and following allylic transposition to **655**. Allylation then isomerisation gives product **652**.



Scheme 8.18: Proposed mechanism by Oshima and Yorimitsu

Although this mechanistic pathway is plausible, some experimental evidence observed suggested this was not the operative mechanism of our migration. Following allylic transposition to species **655**, the olefin will neither be exclusively *cis* or *trans*, and this would suggest that any resulting products would either have low diastereomeric ratio or be the more favourable *anti*-diastereomer (see Section 4.5.2). Despite this, the homoallylic amines products **606** were exclusively the *syn*-isomer, suggesting the intermediate should feature a *cis*-olefin, and this is something that is unlikely in their proposed mechanism.

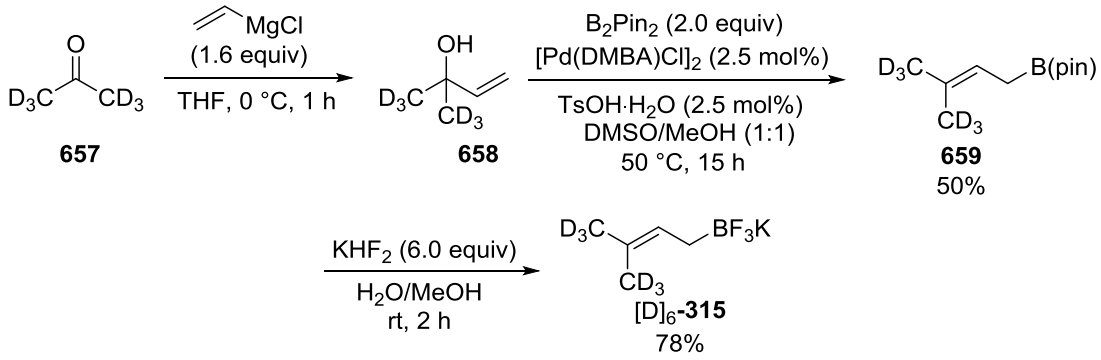
This is not conclusive proof that a *β*-hydride based mechanism is not operative (Scheme 8.19). An alternative mechanism could involve a stereoselective [4+2] addition of Rh-H to give *cis*-**655**. The subsequent allylation of *cis*-**655** would give product **606** with *syn*-selectivity.



Scheme 8.19: Possible [4+2] addition

In order to gain further insight into the mechanism, deuterated $[D]_6$-allyl species **315** was prepared (Scheme 8.20). Starting with $[D]_6$-acetone (**657**), the addition of

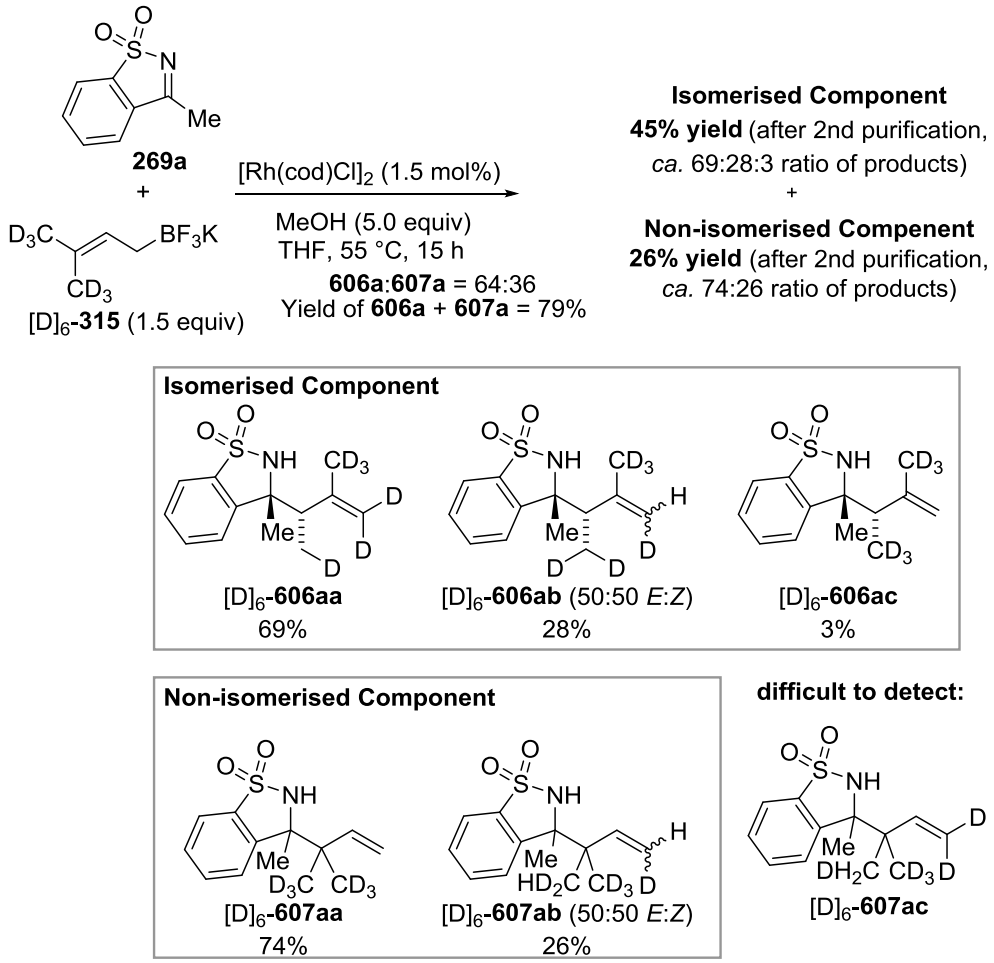
vinylmagnesium chloride gave [D]$_6$-allylic alcohol **658**. Palladium-catalysed borylation of alcohol **658** gave the isomeric pinacol ester species **659** which was converted readily into the [D]$_6$-trifluoroborate **315** in 78% yield.



Scheme 8.20: Synthesis of [D]$_6$-**315**

Using [D]$_6$-species **315**, the 1,4-migration reaction was attempted in order to see if any deuterium was incorporated in product **606a**. The reaction was successful, giving a mixture of products **606a** and **607a** in 79% yield with a 64:36 ratio in favour of the isomerised product **606a**. The isomerised **606a** and non-isomerised products **607a** could be separated by chromatography, but each component actually consisted of multiple isomeric species, each with deuterium incorporated at different positions (Scheme 8.21).

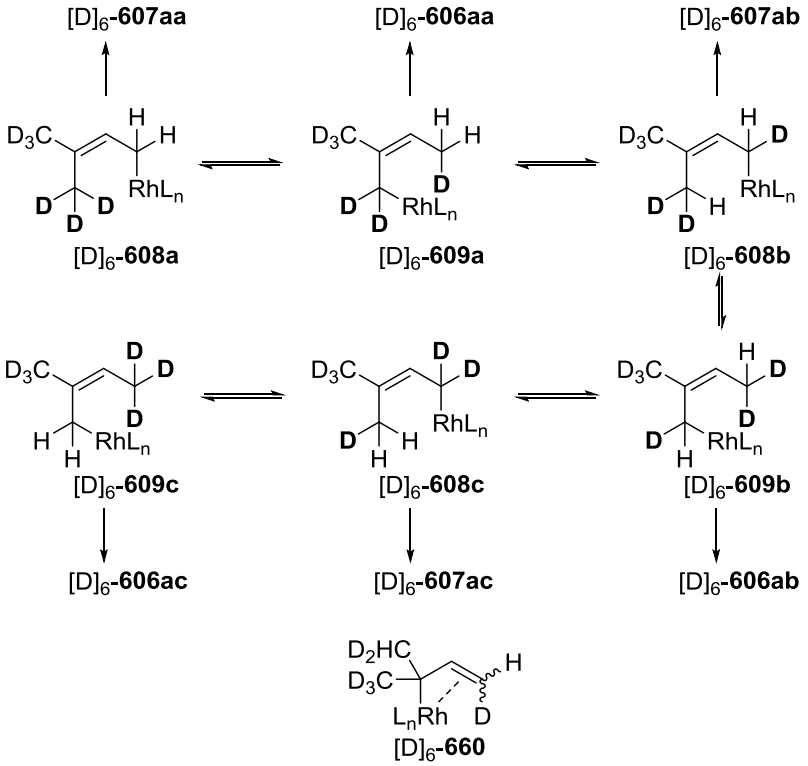
Several conclusions can be drawn from this reaction. First, the lower ratio between isomerised product **606a** and non-isomerised product **607a** compared to the analogous non-deuterated reaction (64:36 compared to 74:26) suggests that the 1,4-rhodium migration of the deuterium is the product determining step, although not necessarily the rate-determining step.[221]



Scheme 8.21: Deuterium studies

Secondly, explaining the observed product distribution is quite complex. The major component of both the isomerised product and non-isomerised product arises from the standard allylation by allyl species **608a** (**607aa**) or a singular 1,4-migration followed by allylation by allyl species **609a** (**606aa**). There were also appreciable amounts of other products (**606ab**, **606ac**, and **607ab**) that demonstrated further deuterium migration. These species suggest the process of 1,4-migration occurs and is readily reversible. In the non-isomerised product, 26% contained an alkenyl-deuterium atom. This product **607ab** (in a 1:1 *E*:*Z* ratio) presumably arises from a 1,4-migration, transferring a deuterium to give **609a**, followed by a second 1,4-migration involving a proton leading to allyl species **608b**. Similarly, 28% of the isomerised product was product **606ab** (in a 1:1 *E*:*Z* ratio) that presumably arises from a 1,4-migration, followed by a second 1,4-migration involving a proton (rather than a deuterium), followed by a third 1,4-migration leading to **609b** with two

deuterium atoms in the terminal position. Although product **607ac** is difficult to detect and was not observed by ^{1}H NMR, product **606ac** was observed in about 3% yield and presumably arises from a total of five 1,4-migrations (Scheme 8.22).



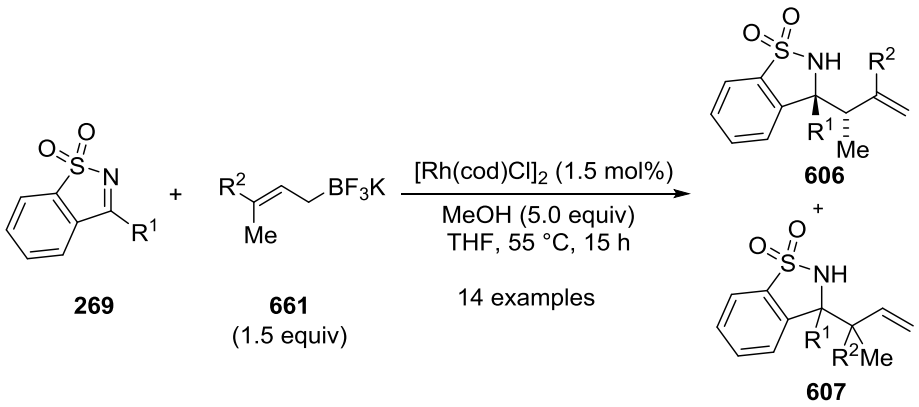
Scheme 8.22: Origin of multiple deuterium migrations

The evidence favouring 1,4-migration over *β*-hydride elimination was strengthened by these deuterium studies, as according to the *β*-hydride elimination, intermediate **660** would be formed after one deuterium has been "transferred." In order for a second deuterium to transfer, *β*-hydride elimination should occur from either methyl groups equally, leading to loss of deuterium incorporation at the *β*-methyl in product **607ab**. However, deuterium scrambling at this position was not observed in any of the products suggesting intermediate **660** is not present in the reaction pathway (Scheme 8.22).

Although these deuterium experiments are not conclusive, the observation of products that indicate the 1,4-migration is reversible combined with the lack of *β*-methyl deuterium scrambling strengthens the case for a 1,4-migration mechanism while weakening the *β*-hydride elimination pathways.

4.0 Conclusions

In summary, allylrhodium intermediates generated from α,α- or γ,γ-disubstituted trifluoroborate salts can undergo isomerisation to form alternative allylrhodium species. These species can undergo an allylation to a range of ketimines and aldimines giving more complex products in good yields and diastereomeric ratios (Scheme 9.1).



Scheme 9.1: Isomerisation of allylrhodium species leading to homoallylic amines

By employing chiral diene ligands it was possible to synthesise the same isomerised products in excellent enantioselectivities. Deuterium studies suggest that a reversible process 1,4-migration occurs during the reaction mechanism.

Further work is ongoing within in the Lam group to extend the concept of a Rh(I) allyl species undergoing 1,4-migration to form an alternative allyl species before undergoing nucleophilic attack. This work involves substrates that would be highly unlikely to undergo allylic transposition and β-hydride elimination, and further suggest that these proceed *via* a 1,4-migration mechanism.

Chapter 3: Experimental

General Information

All commercially available reagents were used as received. Anhydrous dioxane and DMA were purchased from Sigma-Aldrich and used without further purification. "Petrol" refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40-60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or vanilin solution as appropriate. Flash column chromatography was carried out using column (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[222] Melting points were recorded on a Gallenkamp melting point apparatus (University of Edinburgh) or a Griffin melting point apparatus (University of Nottingham) and are uncorrected. Infra-red spectra were recorded on a Shimadzu IRAffinity-1 instrument as a thin film or as a solid (University of Edinburgh) or a Nicolet Avatar 360 FT instrument on the neat compound using an attenuated total reflection (ATR) accessory with a diamond crystal and a germanium sample plate (University of Nottingham). ^{1}H NMR spectra were recorded on a Bruker AVA500 (500 MHz) spectrometer or a Bruker AVA400 (400 MHz) spectrometer (University of Edinburgh) or a Bruker AVA500 (500 MHz), Bruker AVA400 (400 MHz), or Bruker DPX300 (300 MHz) spectrometers (University of Nottingham). Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm, CD_3CN at 1.94 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad), m (multiplet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AVA500 (125.8 MHz) spectrometer or a Bruker AVA400 (100.6 MHz) spectrometer (University of Edinburgh) or a Bruker AVA500 (125.8 MHz) spectrometer or a Bruker AVA400 (100.6 MHz) spectrometer (University of Nottingham). Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm, CD_3CN at 118.26 ppm). Assignments were made using the

DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ^{19}F NMR spectra were recorded on a Bruker AVA400 (376 MHz) spectrometer (University of Edinburgh) or a Bruker DPX300 (282 MHz) or a Bruker AV(III)400 (376 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of $CFCl_3$ (δ = 0 ppm), using fluorobenzene as internal standard (C_6H_5F at –113.5 ppm). High resolution mass spectra were recorded using electrospray ionization (ESI) or electron impact ionization (EI) techniques. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter (University of Edinburgh) or a Bellingham and Stanley ADP 400 polarimeter (University of Nottingham). Chiral HPLC analysis was performed on an Agilent 1100 series instrument using 4.6 x 250 mm columns or an Agilient 1200 series instrument using 4.6 x 250 mm columns.

1.1 Experimental for Chapter 1

1.1.1 The Synthesis of Chiral Ligands

Ligand **7** was purchased from Sigma Aldrich

Ligand **645** and **48** were synthesised by Nawasit Chotsaeng

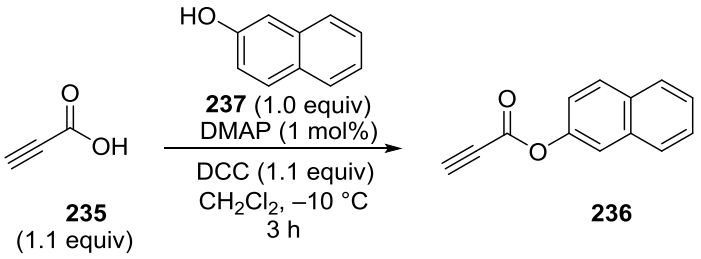
Ligands **540** and **243** were synthesised by Dr Alan Burns

Ligand **255** was purchased from Manchester Organics

Ligand **256** was synthesised by Dr Yunfei Luo

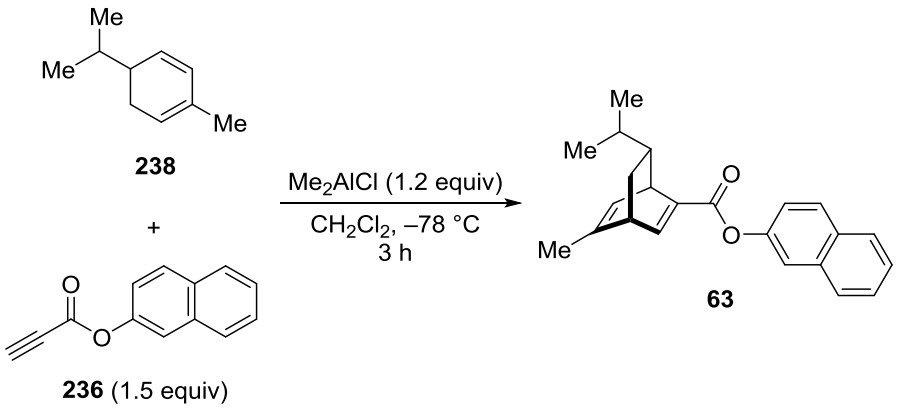
Ligand **648** was synthesised by Dr Benjamin Partridge

2-Naphthyl propiolate (236):



To a solution of 2-naphthol (15.0 g, 105 mmol) and *N*,*N*-dimethylaminopyridine (126 mg, 1.05 mmol) was added CH_2Cl_2 (400 mL), followed by *N*,*N*'-dicyclohexylcarbodiimide (23.61 g, 115.5 mmol). The solution was cooled to –10 °C and propiolic acid (7.05 mL, 105 mmol) was added over 5 minutes. The solution was warmed to room temperature and stirred for 3 hours. The precipitate was filtered off and the filtrate concentrated *in vacuo*. Purification of the residue by flash column chromatography (60:40 petrol:EtOAc) gave the *naphthyl ester* **236** (11.38 g, 56%) as a peach solid that displayed spectroscopic data consistent with those reported previously.[49] m.p. 70-72 °C (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.80 (3H, m, Ar**H**), 7.64 (1H, d, *J* = 2.3 Hz, Ar**H**), 7.53 (1H, td, *J* = 6.8, 1.6 Hz, Ar**H**), 7.50 (1H, td, *J* = 6.9, 1.6 Hz, Ar**H**), 7.28 (1H, dd, *J* = 11.2, 2.3 Hz, Ar**H**), 3.11 (1H, s, CC**H**).

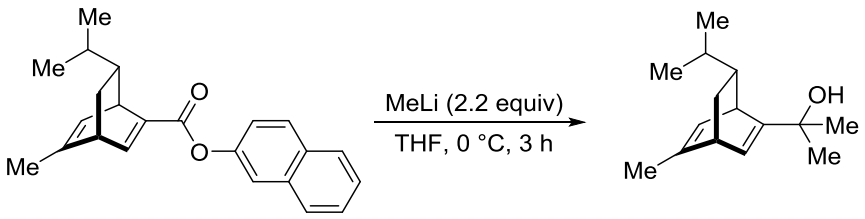
(1*R*,4*R*,7*R*)-2-Naphthyl-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate (63):



To a solution of naphthyl ester **236** (2.89 g, 15 mmol) was added CH_2Cl_2 (125 mL) was added *α*-phellandrene (3.54 mL, 22.5 mmol). The solution was cooled to –78 °C and dimethylaluminium chloride (1.0 M in hexane, 18 mL, 18 mmol) was added slowly and the solution was stirred for 2 hours. The solution was warmed to room temperature and stirred for 1 hour before being quenched slowly with ice-cold 1M HCl (150 mL). The mixture was filtered then extracted with CH_2Cl_2 (3 x 100 mL) and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (90:10 petrol:EtOAc) gave the *chiral diene* **63** (2.15 g, 43%) as a white solid. The solid was dissolved in hexane:CH_2Cl_2 (40:1, 20 mL) and stored at 0 °C for 12 hours. The crystals precipitated were filtered and washed with ice-cooled hexane before being collected to give *chiral diene* **63** (1.20 g, 24%) as white needles with enantiomeric purity = >99% ee that displayed spectroscopic data consistent with those reported previously.[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.82 (2H, m, Ar**H**), 7.79 (1H, d, *J* = 7.8 Hz, C**H**=CCO), 7.58-7.61 (2H, m, Ar**H**), 7.48 (1H, t, *J* = 6.8 Hz, Ar**H**), 7.45 (1H, t, *J* = 6.9 Hz, Ar**H**), 7.26 (1H, dd, *J* = 8.9, 2.3 Hz, Ar**H**), 5.90 (1H, d, *J* = 6.0 Hz, CH_3C=C**H**), 4.22 (1H, dt, *J* = 6,1, 1.9 Hz, CHC**H**C), 3.49 (1H, dq, *J* = 6.2, 2.5 Hz, CC**H**CH), 1.88 (3H, d, *J* = 1.7 Hz, C**H**$_3$C=), 1.67 (1H, ddd, *J* = 11.7, 8.9, 2.9 Hz, C**H**$_2$CH), 1.25-1.35 (1H, m, C**H**CH_2), 1.10-1.20 (1H, m, $(CH_3)_2$C**H**), 1.05 (1H, ddd, *J* = 11.7, 4.9, 2.4 Hz, C**H**$_2$CH), 1.02 (3H, d, *J* = 6.6 Hz, (C**H**$_3)_2$CH), 0.86 (3H, d, *J* = 6.4 Hz, (C**H**$_3)_2$CH); HRMS (ESI) Exact mass calculated for $C_{23}H_{24}O_2Na$ $[M + Na]^+$: 355.1669, found: 355.1676; Enantiomeric excess was

determined by HPLC with a Chiralpak AD-H column (95:5 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 230.4 nm, 25 °C); t_r (major) = 10.4 min, t_r (minor) = 14.4 min; >99% ee.

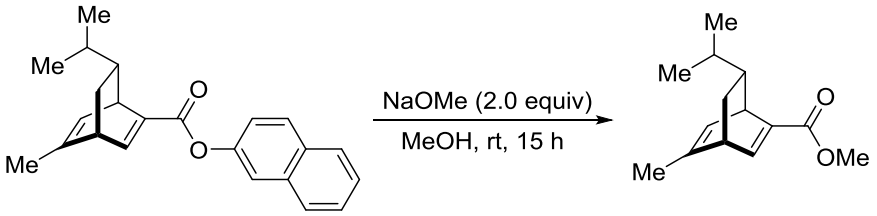
(1*R*,4*R*,7*R*)-7-Isopropyl-2-(1-Hydroxy-1-methylethyl)-5-methylbicyclo[2.2.2]octa-2,5-diene (74):



63 **74**

To a solution of *naphthyl ester* **63** (150 mg, 0.45 mmol) in THF at 0 °C was added MeLi (1.6 M in THF, 0.7 mL, 1.125 mmol) and the solution was stirred for 3 hours. The reaction was quenched by the addition of NH_4Cl (25 mL). The mixture was extracted with EtOAc (3 x 50 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash column chromatography (72:25 petrol:EtOAc) gave the *chiral diene* **74** (64 mg, 65%) as a colourless oil that displayed spectroscopic data consistent with those reported previously.[52] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (1H, dd, *J* = 6.2,2.1 Hz, C**H**=CCOH), 5.75 (1H, dq, *J* = 6.1, 1.8 Hz, CH_3C=C**H**), 3.61 (1H, dt, *J* = 6.1, 1.9 Hz, =CHC**H**C), 3.18 (1H, dq, *J* = 5.1, 2.2 Hz, CC**H**CH=), 1.80 (3H, d, *J* = 1.6 Hz, C**H**$_3$C=), 1.56 (1H, ddd,, *J* = 11.2, 8.6, 3.1 Hz, CHC**H**$_2$CH), 1.36 (1H, br s, O**H**), 1.34 (3H, s, C**H**$_3$COH), 1.32 (3H, s, C**H**$_3$COH), 1.05-1.15 (2H, m, C**H**C**H**CH_2), 0.96 (3H, d, *J* = 6.1 Hz, (C**H**$_3$)$_2$CH), 0.88 (1H, ddd, *J* = 11.2, 4.5, 2.3 Hz, CHC**H**$_2$CH), 0.81 (3H, d, *J* = 6.2 Hz, (C**H**$_3$)$_2$CH; HRMS (ESI) Exact mass calculated for $C_{15}H_{24}ONa$ $[M + Na]^+$: 243.1719, found: 243.1722.

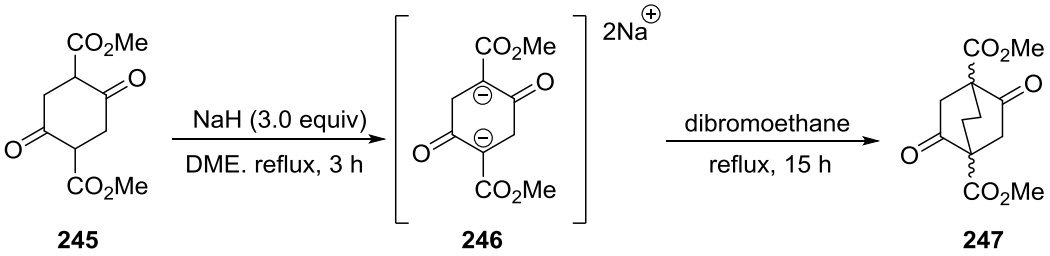
(1*R*,4*R*,7*R*)-2-Methyl-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate (647):



63 **647**

To a solution of *naphthyl ester* **63** (830 mg, 2.50 mmol) in MeOH (50 mL) was added sodium methoxide (270 mg, 5.0 mmol). The solution was stirred at room temperature for 15 hours. The mixture was concentrated *in vacuo*. Purification of the residue by flash column chromatography (98:02 petrol:EtOAc) gave *methyl ester* **647** (454 mg, 83%) as a colourless oil that displayed spectroscopic data consistent with those reported previously.[52] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, dd, *J* = 6.3, 1.8 Hz, C**H**=), 5.80 (1H, d, *J* = 6.0 Hz, C**H**=), 4.07 (1H, dt, *J* = 6.0, 1.9 Hz, =CC**H**), 3.72 (3H, s, OC**H**$_3$), 3.37 (1H, dq, *J* = 6.2, 2.3 Hz, CHC**H**C=), 1.82 (3H, d, *J* = 1.7 Hz, =CC**H**$_3$), 1.55 (1H, ddd, *J* = 11.3, 8.5, 2.9 Hz, CH_2C**H**), 1.20-1.05 (2H, m, C**H**$_2$CH), 0.99 (3H, d, *J* = 6.5 Hz, C**H**$_3$), 0.96 (1H, ddd, *J* = 11.6, 4.7, 2.3 Hz, C**H**$(CH_3)_2$), 0.82 (3H, d, *J* = 6.5 Hz, C**H**$_3$); HRMS (ESI) Exact mass calculated for $C_{14}H_{29}O_2Na$ $[M + Na]^+$: 243.1356, found: 243.1357.

(±)-1,4-di(methoxycarbonyl) bicyclo[2.2.2]octane-2,5-dione (247):

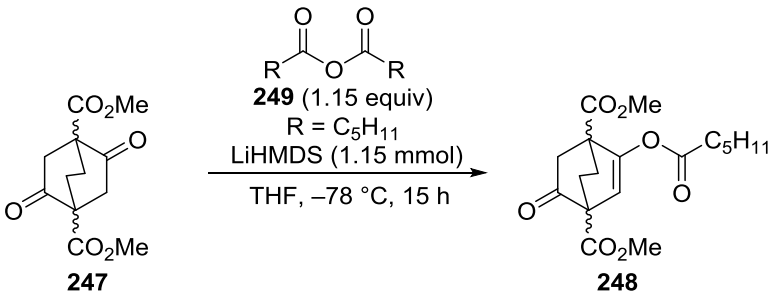


245 **246** **247**

To a solution of *diester* **245** (32.0 g, 0.14 mol) in DME (150 mL) under N_2 was added NaH (60% in mineral oil, 16.8 g, 0.42 mol) portionwise. The reaction was heated under reflux for 3 hours before being cooled to room temperature. The DME was removed by distillation to give *dianion* **246** which was dried under high vacuum for 15 hours. To *dianion* **246** was added dibromoethane (200 mL) and the solution

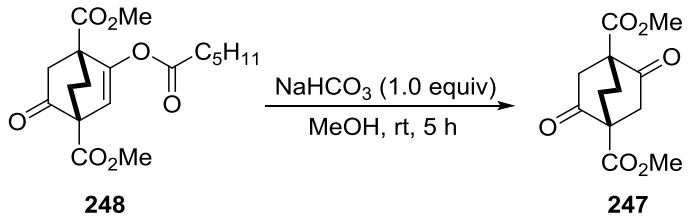
was heated at reflux for 15 hours. The mixture was cooled to room temperature, filtered, washed with water, MeOH and hexanes to give *bridged diester* **247** (17.42 g, 49%) as a pale brown solid that displayed spectroscopic data consistent with those reported previously.[136] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (6H, s, 2 x CO_2CH_3), 3.07 (2H, dd, J = 20.0, 3.0 Hz, C=OC**H**$_2$), 2.73 (2H, d, J = 20 Hz, C=OC**H**$_3$), 2.56-2.47 (2H, m, CC**H**$_2$CH$_2$), 2.16-2.09 (2H, m, CCH$_2$C**H**$_2$); HRMS (ESI) Exact mass calculated for $C_{12}H_{14}O_6Na$ $[M + Na]^+$: 277.0688, found: 277.0678.

(±)-1,4-di(methoxycarbonyl)-2-hexanoyloxybicyclo[2.2.2]octane-2-en-5-one (248):



To a solution of *bridged diester* **247** (19.05 g, 75 mmol) in THF (200 mL) at –78 °C was slowly added LiHMDS (1.0 M in THF, 81 mL, 86.25 mmol) over 30 minutes. The reaction mixture was stirred at –78 °C for an addition 30 minutes before hexanoic anhydride (19.85 mL, 86.25 mmol) was added. The mixture was stirred for 1 hour before being warmed to room temperature and quenched with NH_4Cl (100 mL). The mixture was extracted with EtOAc (3 x 150 mL) and the organic layers were combined, washed with brine (150 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in hexane/EtOAc (20:1). The crystal precipitates were filtered and washed with cooled hexanes to give *enol ester* **248** (18 g, 68%) as white crystals that displayed spectroscopic data consistent with those reported previously.[136] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (1H, s, C**H**=C), 3.84 (3H, s, CO_2CH_3), 3.75 (3H, s, CO_2CH_3), 2.45-2.33 (4H, m, OC**H**$_2$C**H**$_2$), 2.29-2.19 (2H, m, COC**H**$_2$), 2.09-1.91 (2H, m, CC**H**$_2$CH$_2$), 1.69-1.58 (2H, m, CCH$_2$C**H**$_2$), 1.39-1.28 (4H, m, C**H**$_2$C**H**$_2$CH$_3$), 0.91 (3H, t, J = 7.1 Hz, CH$_2$C**H**$_3$); HRMS (ESI) Exact mass calculated for $C_{18}H_{24}O_7Na$ $[M + Na]^+$: 375.1420, found: 375.1417.

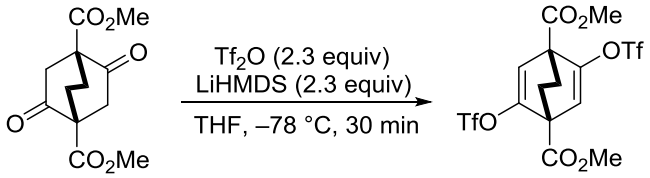
(*S*,*S*)-1,4-di(methoxycarbonyl) bicyclo[2.2.2]octane-2,5-dione (247):



248 **247**

To a solution of *enol ester* **248** (1.875 g, 5.25 mmol) in MeOH (50 mL) was added $NaHCO_3$ (0.42 mg, 5 mmol) and the mixture was stirred at room temperature for 6 hours. The solution was filtered through a Celite pad and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL), washed with water (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *dione* **247** (1.34 g, 98%) as a white solid that displayed spectroscopic data consistent with those reported previously.[136] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (6H, s, 2 x $CO_2C\mathbf{H}_3$), 3.07 (2H, dd, J = 20.0, 3.0 Hz, C=OC$\mathbf{H}_2$), 2.73 (2H, d, J = 20 Hz, C=OC$\mathbf{H}_3$), 2.56-2.47 (2H, m, CC$\mathbf{H}_2$CH$_2$), 2.16-2.09 (2H, m, CCH$_2$C$\mathbf{H}_2$); HRMS (ESI) Exact mass calculated for $C_{12}H_{14}O_6Na$ [M + Na]$^+$: 277.0688, found: 277.0678.

(*S*,*S*)-1,4-di(methoxycarbonyl)-2,5-ditriflatebicyclo[2.2.2]octan-2,5-diene (251):

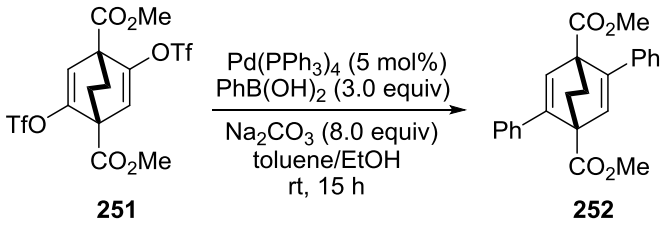


247 **251**

To 4 separate solutions of *dione* **247** (127 mg, 0.5 mmol) in THF (2.5 mL) at –78 °C was added LiHMDS (1.0 M in THF, 1.15 mL, 1.15 mmol). The solution was stirred for 30 minutes then Tf_2O (0.193 mL, 1.15 mmol) was added. After 5 minutes the reaction was quenched with $NaHCO_3$ (5 mL). The four solutions were combined and extracted with EtOAc (3 x 15 mL) and the organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *bis enol triflate* **251** (563 mg, 62%) as a colourless oil that was sufficiently pure to take onto

the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (2H, s, 2 x C**H**=C), 3.92 (6H, s, 2 x CO_2CH_3), 2.38-2.32 (2H, m, CCH_2CH_2), 1.97-1.90 (2H, m, CCH_2CH_2).

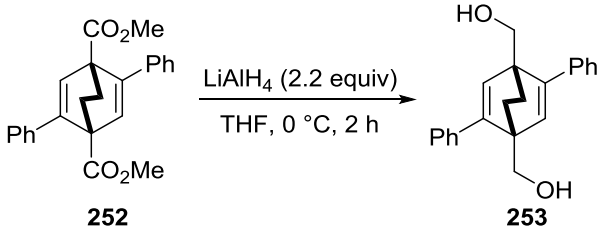
(*S*,*S*)-1,4-di(methoxycarbonyl)-2,5-diphenylbicyclo[2.2.2]octan-2,5-diene (252):



251 **252**

To a solution of *bis enol triflate* **251** (0.908 g, 2 mmol) in toluene (40 mL) and EtOH (14 mL) was added phenylboronic acid (732 mg, 6 mmol), Na_2CO_3 solution (2.0 M, 9 mL, 18 mmol), and $Pd(PPh_3)_4$ (126 mg, 0.1 mmol). The solution was stirred at room temperature for 15 hours. The mixture was extracted with Et_2O (3 x 50 mL) and the organic layers were combined, washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (90:10 hexanes:EtOAc) gave *diene* **252** (702 mg, 81%) as a white solid that displayed spectroscopic data consistent with those previously reported.[136] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (6H, m, Ar**H**), 7.17-7.15 (4H, m, Ar**H**), 6.64 (2H, s, 2 x C**H**=C), 3.51 (6H, s, 2 x CO_2CH_3), 2.18-2.12 (2H, m, CCH_2CH_2), 1.92-1.87 (2H, m CCH_2CH_2); HRMS (ESI) Exact mass calculated for $C_{24}H_{22}O_4Na$ $[M + Na]^+$: 429.1314, found: 429.1319.

(*S*,*S*)-1,4-Di(hydroxylmethyl)-2,5-diphenylbicyclo[2.2.2]octan-2,5-diene (253):

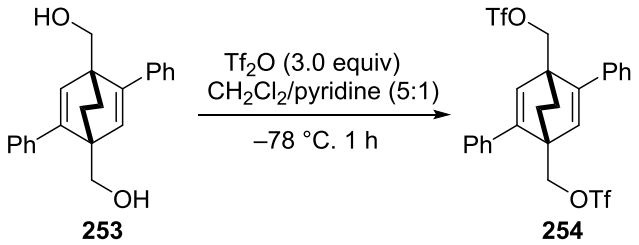


252 **253**

To a solution of *ester* **252** (100 mg, 0.26 mmol) in THF (2.5 mL) at 0 °C was added $LiAlH_4$ solution (2.2 M in THF, 0.26 mL, 0.572 mmol). The solution was stirred for 2 hours. The reaction was quenched by the addition of EtOAc (5 mL) then extracted

with EtOAc (3 x 20 mL). The organic layers were combined and washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *diol* **253** (50 mg, 61%) as a colourless oil that displayed spectroscopic data consistent with those previously reported.[136] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (10H, m, Ar**H**), 6.27 (2H, s, 2 x C**H**=C), 4.15 (2H, dd, *J* = 11.5 Hz, 2 x C**H**$_2$OH), 4.00 (2H, d, *J* = 11.5 Hz, 2 x C**H**$_2$OH), 1.77-1.70 (2H, m, CC**H**$_2$CH$_2$), 1.65-1.58 (2H, m, CCH$_2$C**H**$_2$), 1.26-1.17 (2H, m, 2 x O**H**); HRMS (ESI) Exact mass calculated for $C_{22}H_{20}O_2Na$ $[M + Na]^+$: 341.1517, found: 341.1513.

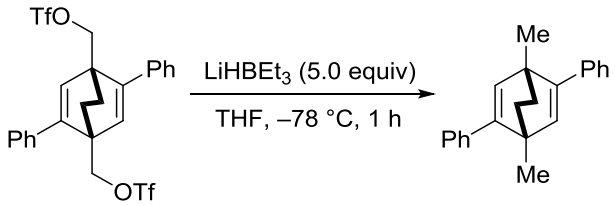
(*S*,*S*)-1,4-Di(triflatemethyl)-2,5-diphenylbicyclo[2.2.2]octan-2,5-diene (254):



253 **254**

To a solution of *diol* **253** (57 mg, 0.18 mmol) in CH_2Cl_2/pyridine solution (5:1 10 mL) at –78 °C was added Tf_2O (0.95 mL, 0.54 mmol). The solution was stirred for 1 hour then warmed to room temperature and quenched with 1M HCl (5 mL). The mixture was extracted with EtOAc (3 x 15 mL) and the organic layers were combined, washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give crude *bistriflate* **254** (98 mg, 97%) as a colourless oil was taken on without further purification.

(*S*,*S*)-1,4-Di(methyl)-2,5-diphenylbicyclo[2.2.2]octan-2,5-diene (92):



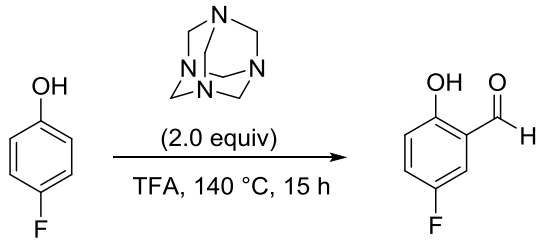
254 **92**

To a solution of *bis triflate* **254** (291 mg, 0.5 mmol) in THF (10 mL) at –78 °C was added $LiHBEt_3$ (1 M in THF, 2.5 mL, 2.5 mmol) and the solution was warmed to

room temperature. The solution was stirred for 1 hour before silica gel (5 g) was added and the solution was concentrated *in vacuo*. The resultant silica was loaded onto a short silica pad and washed with hexanes to give *chiral diene* **92** (167 mg, 90%) as a colourless oil that displayed spectroscopic data consistent with those reported previously.[136] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.15 (10H, m, Ar**H**), 5.97 (2H, s, 2 x C**H**=C), 1.66-1.58 (2H, m, CC**H**$_2$CH$_2$), 1.54-1.46 (2H, m, CCH$_2$C**H**$_2$), 1.42 (6H, s, 2 x C**H**$_3$); HRMS (ESI) Exact mass calculated for $C_{22}H_{23}Na$ $[M + Na]^+$: 310.1697, found: 310.1695.

1.1.2 The Synthesis of Cyclic Imines

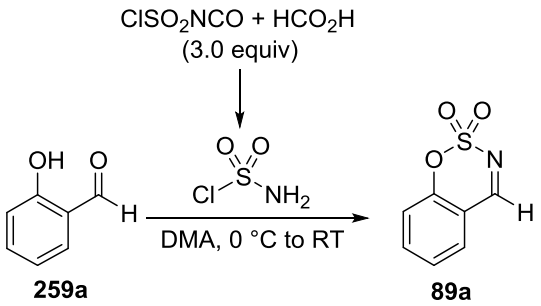
5-Fluorosalicylaldehyde (259g):



260 **259g**

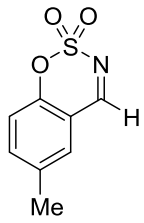
To a solution of 4-fluorophenol (5.6 g, 50 mmol) in TFA (40 mL) was added hexamethylenetriamine (14.0 g, 100 mmol). The solution was heated at 140 °C for 15 hours then cooled to room temperature. The mixture was extracted with CH_2Cl_2 (3 x 50 mL) and washed with water (3 x 50 mL), saturated $NaHCO_3$ solution (3 x 50 mL), brine (50 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (80:20 hexanes:EtOAc) gave *aldehyde* **259g** (3.34 g, 48%) as a yellow solid that displayed spectroscopic data consistent with those previously reported.[223] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.79 (1H, s, C**H**=O), 9.86 (1H, s, O**H**), 7.30-7.24 (2H, m, Ar**H**), 6.99-6.96 (1H, m, Ar**H**); ^{13}C NMR ($CDCl_3$ 125.8 MHz) δ 195.4 (CH), 157.9 (C), 156.8 (CH), 154.5 (CH), 124.8 (C, d, J = 23.5 Hz), 119.2 (CH, d, J = 6.8 Hz), 118.1 (CH, d, J = 6.9 Hz).

Representative Procedure: [1,2,3]-benzoxathiazine-2,2-dioxide (89a):



259a **89a**

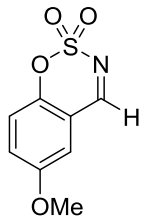
Formic acid (1.70 mL, 45 mmol) was carefully added dropwise to chlorosulfonylisocyanate (3.92 mL, 45 mmol) at 0 °C (caution: large volume of gas evolved). The mixture was stirred for 1 h at room temperature and then diluted with MeCN (5 mL). The resulting solution was then added dropwise to a solution of salicylaldehyde (1.83 g, 15 mmol) in DMA at 0 °C and the resulting mixture was stirred at room temperature for 12 h. The reaction was diluted with EtOAc (100 mL), washed with H_2O (2 x 50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was heated to 180 °C under vacuum to remove volatile impurities to give *cyclic imine* **89a** (1.80 g, 85%) as a white solid. R_F = 0.26 (80:20 hexanes:EtOAc); m.p. 64-66 °C (Et_2O); IR (film) 1606, 1562, 1390, 1359, 1234, 1182, 1116, 908, 817, 761, 732, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (1H, s, N=C**H**), 7.79-7.75 (1H, m, Ar**H**), 7.71 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.44 (1H, td, *J* = 7.6, 1.0 Hz, Ar**H**), 7.29 (1H, d, *J* = 8.0 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.7 (CH), 154.1 (C), 137.6 (CH), 130.8 (CH), 126.2 (CH), 118.5 (CH), 115.3 (C); HRMS (EI) Exact mass calcd for $C_7H_5NO_3S$ $[M]^+$: 182.9985, found: 182.9985.



89b

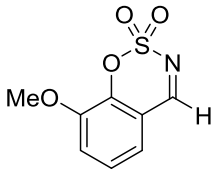
6-Methyl-[1,2,3]-benzoxathiazine-2,2-dioxide (89b). The title compound was prepared according to the Representative Procedure from 5-methylsalicylaldehyde (2.00 g, 14.7 mmol) to give *imine* **89b** (2.90 g, 99%) as a yellow solid**.** R_F = 0.31 (80:20 hexanes:EtOAc); m.p. 72-76 °C (Et_2O); IR (film) 1608, 1571, 1382, 1205, 1186, 846, 761, 641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (1H, s, N=C**H**), 7.55 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.47 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.17 (1H, d, *J* = 8.0

Hz, Ar**H**), 2.46 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.8 (CH), 152.2 (C), 138.4 (CH), 136.4 (C), 130.6 (CH), 118.2 (CH), 115.1 (C), 20.6 (CH_3); HRMS (EI) Exact mass calcd for $C_8H_7NO_3S$ $[M]^+$: 197.0141, found: 197.0141.



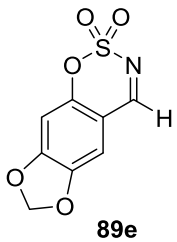
89c

6-Methoxy-[1,2,3]-benzoxathiazine-2,2-dioxide (89c). The title compound was prepared according to the Representative Procedure from 5-methoxysalicylaldehyde (900 mg, 5.90 mmol) to give *imine* **89c** (1.10 g, 87%) as a light yellow solid. R_F = 0.27 (80:20 hexanes:EtOAc); m.p. 112-116 °C (Et_2O); IR (film) 1610, 1568, 1485, 1386, 1346, 1267, 1203, 1170, 1028, 848, 756, 736, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (1H, s, N=C**H**), 7.34-7.27 (1H, m, Ar**H**), 7.26 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.14 (1H, d, *J* = 3.0 Hz, Ar**H**), 3.90 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.6 (CH), 157.1 (C), 148.0 (C), 124.5 (CH), 119.7 (CH), 115.7 (C), 113.1 (CH), 56.1 (CH_3); HRMS (EI) Exact mass calcd for $C_8H_7NO_4S$ $[M]^+$: 213.0090, found: 213.0086.



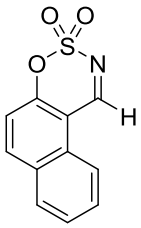
89d

8-Methoxy-[1,2,3]-benzoxathiazine-2,2-dioxide (89d). The title compound was prepared according to the Representative Procedure from 3-methoxysalicylaldehyde (4.00 g, 26.0 mmol) and was further purified by column chromatography (80:20 hexane/EtOAc) to give *imine* **89d** (3.50 g, 62%) as a green solid. R_F = 0.34 (80:20 hexanes:EtOAc); m.p. 128-132 °C (Et_2O); IR (film) 1600, 1571, 1475, 1382, 1359, 1286, 1201, 1188, 1172, 970, 869, 773, 729, 603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (1H, s, N=C**H**), 7.38-7.30 (2H, m, Ar**H**), 7.28-7.24 (1H, m, Ar**H**), 3.96 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.0 (CH), 148.3 (C), 143.5 (C), 126.1 (CH), 121.5 (CH), 119.8 (CH), 116.0 (CH), 56.6 (CH_3); HRMS (EI) Exact mass calcd for $C_8H_7NO_4S$ $[M]^+$: 213.0090, found: 213.0090.



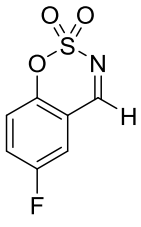
89e

1,3,5-Trioxa-6-thia-7-azacyclopenta[*b*]naphthalene 6,6-dioxide (89e). The title compound was prepared according to the Representative Procedure from 6-hydroxybenzo[1,3]dioxole-5-carboxaldehyde (500 mg, 3.00 mmol) and was further purified by recrystallization from MeOH to give *imine* **89e** (420 mg, 87%) as a bright yellow solid. R_F = 0.23 (80:20 hexanes:EtOAc); m.p. 154-156 °C (MeOH); IR (film) 1633, 1616, 1560, 1504, 1481, 1384, 1274, 1192, 1149, 1089, 927, 867, 835, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (1H, s, N=C**H**), 6.98 (1H, s, Ar**H**), 6.75 (1H, s, Ar**H**), 6.19 (2H, s, C**H**$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.5 (CH), 155.4 (C), 152.7 (C), 145.9 (C), 109.4 (C), 107.3 (CH), 103.5 (CH), 100.0 (CH_2); HRMS (EI) Exact mass calcd for $C_8H_5NO_5S$ $[M]^+$: 226.9883, found: 226.9886.



89f

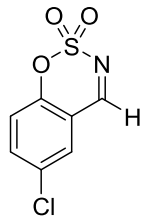
1-Oxa-2-thia-3-azaphenanthrene 2,2-dioxide (89f). The title compound was prepared according to the Representative Procedure from 2-hydroxy-1-napthylaldehyde (2.40 g, 13.9 mmol) and was further purified by recrystallization from MeOH to give *imine* **89f** (2.10 g, 65%) as a yellow solid. R_F = 0.41 (80:20 hexanes:EtOAc); m.p. 192-196 °C (MeOH); IR (film) 1625, 1554, 1392, 1375, 1213, 1184, 829, 804, 748, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (1H, s, N=C**H**), 8.30 (1H, d, *J* = 8.5 Hz, Ar**H**), 8.24 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.98 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.85-7.80 (1H, m, Ar**H**), 7.70-7.66 (1H, m, Ar**H**), 7.38 (1H, d, *J* = 9.0 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.5 (CH), 155.7 (C), 139.6 (CH), 130.7 (C), 130.6 (CH), 129.7 (C and CH), 127.3 (CH), 120.6 (CH), 117.2 (CH), 109.6 (C); HRMS (EI) Exact mass calcd for $C_{11}H_7NO_3S$ $[M]^+$: 233.0141, found: 233.0142.



89g

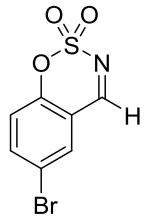
6-Fluoro-[1,2,3]-benzoxathiazine-2,2-dioxide (89g). The title compound was prepared according to the Representative Procedure from 5-fluorosalicylaldehyde (560 mg, 4 mmol) to give *imine* **89g** (510 mg, 515) as a white solid. R_F = 0.34 (80:20 hexanes:EtOAc); m.p. 133-135 °C (Et_2O); IR (film): 1573, 1562, 1475, 1384, 1352, 1265, 1207, 1190, 1153, 850, 765 cm^{-1} ; ^1H NMR ($CDCl_3$ 500 MHz) δ: 8.65 (1H, s, N=C**H**), 7.49 (1H, ddd, *J* = 9.1, 7.7, 3.0 Hz, Ar**H**), 7.40 (1H, dd, *J* = 6.9, 3.0 Hz,

Ar**H**), 7.33 (1H, dd, *J* = 9.1, 4.1 Hz, Ar**H**); ^{13}C NMR ($CDCl_3$ 125.8 MHz) δ: 166.5 (d, *J* = 2.3Hz, CH), 159.1 (d, *J* = 256.3 Hz, C), 150.2 (d, *J* = 2.6 Hz, C), 124.8 (d, *J* = 24.2 Hz, CH), 120.6 (d, *J* = 7.9 Hz, CH), 116.3 (d, *J* = 24.4 Hz, CH), 115.8 (d, *J* = 8.0 Hz, C); ^{19}F NMR (376 MHz, (CD_3Cl)) δ: -133.05; HRMS (EI) Exact mass calcd for $C_7H_4O_3N_1F_1S_1$ $[M]^+$: 200.9890, found: 207.9896.



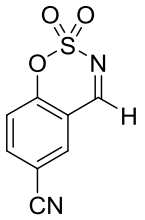
89h

6-Chloro-[1,2,3]-benzoxathiazine-2,2-dioxide (89h). The title compound was prepared according to the Representative Procedure from 5-chlorosalicylaldehyde (1.39 g, 8.90 mmol) give *imine* **89h** (1.60 g, 84%) as a colourless solid. R_F = 0.34 (80:20 hexanes:EtOAc); m.p. 143-146 °C (Et_2O); IR (film) 1602, 1560, 1467, 1382, 1346, 1220, 1176, 829, 788, 765, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (1H, s, N=C**H**), 7.70 (1H, dd, *J* = 8.5, 2.5 Hz, Ar**H**), 7.68 (1H, d, *J* = 2.5 Hz, Ar**H**), 7.27 (1H, d, *J* = 8.5 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.5 (CH), 152.6 (C), 137.3 (CH), 131.6 (C), 130.0 (CH), 120.2 (CH), 116.1 (C); HRMS (EI) Exact mass calcd for $C_7H_4ClNO_3S$ $[M]^+$: 216.9595, found: 216.9596.



89i

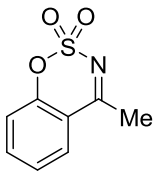
6-Bromo-[1,2,3]-benzoxathiazine-2,2-dioxide (89i). The title compound was prepared according to the Representative Procedure from 5-bromosalicylaldehyde (1.49 g, 7.5 mmol) to give *imine* **89i** (1.19 g, 61%) as a beige solid. R_F = 0.40 (80:20 hexanes:EtOAC); mp = 131-133 °C (Et_2O); IR (film) 1602, 1554, 1465, 1377, 1344, 1174, 1128, 1076, 823, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.63 (1H, s, N=C**H**), 7.87-7.82 (2H, m, Ar**H**), 7.22 (1H, d, *J* = 8.6 Hz, Ar**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.2 (CH), 153.2 (C), 140.2 (CH), 132.9 (CH), 120.5 (CH), 118.7 (C), 116.5 (C); HRMS (ESI) Exact mass calc for $C_7H_4BrNO_3S$ $[M]^+$: 260.91, found 260.908865



89j

6-Cyano-[1,2,3]-benzoxathiazine-2,2-dioxide (89j). The title compound was prepared according to the Representative Procedure from 5-cyanosalicylaldehyde (290 mg, 2 mmol) to give *imine* **89j** (200 mg, 50%) as a white solid. R_F = 0.39 (80:20 hexanes:EtOAc); m.p. 144-

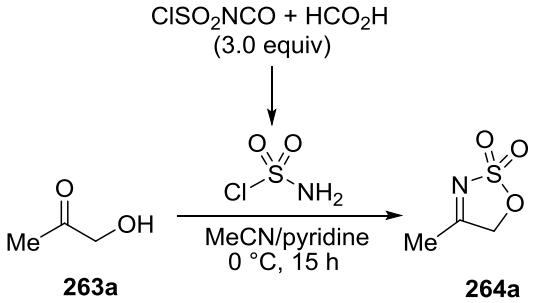
146 °C (Et_2O); IR (film): 1642, 1400, 1195, 833, 742, 704, 551 cm^{-1} ; ^1H NMR ($CDCl_3$ 500 MHz) δ: 8.72 (1H, s, N=C**H**), 8.04 (1H, d, *J* = 1.4 Hz, Ar**H**), 8.02 (1H, dd, *J* = 8.5, 2.0 Hz, Ar**H**), 7.45 (1H, d, *J* = 8.5 Hz, Ar**H**); ^{13}C NMR ($CDCl_3$ 125.8 MHz) δ: 165.6 (CH), 156.6 (C), 140.1 (CH), 134.7 (CH), 120.3 (CH), 115.9 (C), 115.5 (C), 110.7 (C); HRMS (ES) Exact mass calcd for $C_8H_4O_3N_2S_1$ $[M]^+$: 207.9943, found: 207.9940.



262

4-Methy1,2,3]-benzoxathiazine-2,2-dioxide (262). The title compound was prepared according to the Representative Procedure from 2'-hydroxyacetophenone (1.80 mL, 15 mmol) to give *imine* **262** (686 mg, 22%) as a white solid which displayed spectroscopic data consistent with those previously reported.[224] ^1H NMR ($CDCl_3$ 400 MHz) δ 7.81 (dd, *J* = 7.9, 1.3 Hz, Ar**H**), 7.75-7.70 (1H, m, Ar**H**), 7.40 (1H, t, *J* = 7.7 Hz, Ar**H**), 7.30 (1H, d, *J* = 8.3 Hz, Ar**H**), 2.74 (3H, s, C$\mathbf{H}_3$); HRMS (ESI) Exact mass calcd for $C_8H_7NO_3S_1Na$ $[M+Na]^+$: 234.0075, found: 234.0078.

4-Methyl-[1,2,3]oxathiazole 2,2-Dioxide (264a):

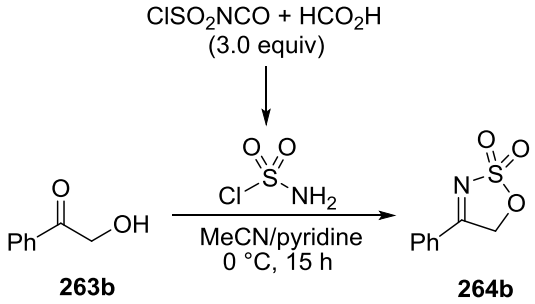


263a **264a**

Formic acid (1.47 mL, 39 mmol) was carefully added dropwise to chlorosulfonylisocyanate (3.39 mL, 39 mmol) at 0 °C (caution: large volume of gas evolved). The mixture was stirred for 1 h at room temperature and then diluted with MeCN (5 mL). The resulting solution was then added dropwise to a solution of *α*-hydroxypropan-2-one (0.96 g, 13 mmol) in MeCN:Pyridine (50 mL, 5:1) at 0 °C and the resulting mixture was stirred at room temperature for 12 h. The reaction was diluted with EtOAc (100 mL), washed with H_2O (2 x 50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystalised from hexanes:EtOAc (5:1)

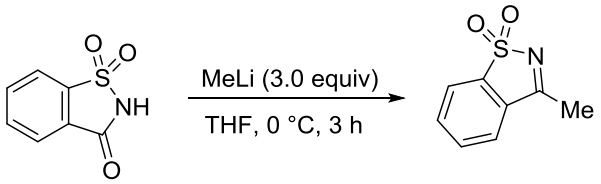
to give *imine* **264a** (355 mg, 22%) as a white solid that displayed spectroscopic data consistent with those reported previously.[224] ^{1}H NMR ($CDCl_3$ 400 MHz) δ 5.07 (2H, s, CC**H**$_2$O), 2.42 (3H, s, C**H**$_3$); HRMS (ESI) Exact mass calcd for $C_3H_5NO_3SNa$ $[M+Na]^+$: 157.9990, found: 157.9986.

4-Phenyl-[1,2,3]oxathiazole 2,2-Dioxide (264b):



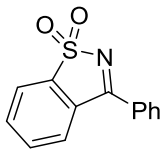
Formic acid (0.42 mL, 11.1 mmol) was carefully added dropwise to chlorosulfonylisocyanate (1.02 mL, 11.1 mmol) at 0 °C (caution: large volume of gas evolved). The mixture was stirred for 1 h at room temperature and then diluted with MeCN (5 mL). The resulting solution was then added dropwise to a solution of *α*-hydroxyacetophenone (500 mg, 3.7 mmol) in MeCN:Pyridine (20 mL, 5:1) at 0 °C and the resulting mixture was stirred at room temperature for 12 h. The reaction was diluted with EtOAc (100 mL), washed with H_2O (2 x 50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystalised from hexanes:EtOAc (5:1) to give *imine* **264b** (105 mg, 14%) as a yellow solid that displayed spectroscopic data consistent with those reported previously.[224] ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.95-7.93 (2H, m, Ar**H**), 7.75 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.61-7.56 (2H, m, Ar**H**), 5.60 (2H, s, C**H**$_2$); HRMS (ESI) Exact mass calcd for $C_8H_7NO_3SNa$ $[M+Na]^+$: 220.0044, found: 220.0043

Representative Procedure: 3-Methylbenzo[*d*]isothiazole 1,1-dioxide (269a):



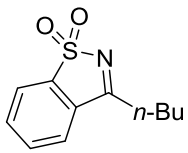
268 **269a**

To a solution of saccharin (5.49 g, 30 mmol) in THF (250 mL) at –78 °C was added MeLi (1.0 M in THF, 90 mL, 90 mmol) dropwise. The solution was stirred for 15 hours then quenched by the addition of ice cool water (100 mL). NaOH (2 M) was added until the solution had a pH of 9. The mixture was extracted with Et_2O (4 x 200 mL) and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give *imine* **269a** (4.29 g, 79%) as a white solid that displayed spectroscopic data consistent with those previously reported.[142] m.p. 211-213 °C (Et_2O); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.93-7.91 (1H, m, Ar**H**), 7.76-7.73 (2H, m, Ar**H**), 7.70-7.68 (1H, m, Ar**H**), 2.67 (3H, s, C**H**$_3$).



269b

3-Phenylbenzo[*d*]isothiazole 1,1-dioxide (269b). The title compound was prepared according to the Representative Procedure from saccharin (3.66 g, 20 mmol) and phenylmagnesium bromide (1M in THF, 60 mL, 60 mmol) to give *imine* **269b** (1.65 g, 35%) as a white solid that was displayed spectroscopic data consistent with those previously reported.[142] m.p. 159-161 °C (Et_2O); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 8.02 (1H, d, J = 7.5 Hz, Ar**H**), 7.98 (2H, d, J = 7.5 Hz, Ar**H**), 7.91 (1H, d, J = 8.0 Hz, Ar**H**), 7.81-7.69 (3H, m, Ar**H**), 7.61 (2H, d, J = 7.5 Hz, Ar**H**).

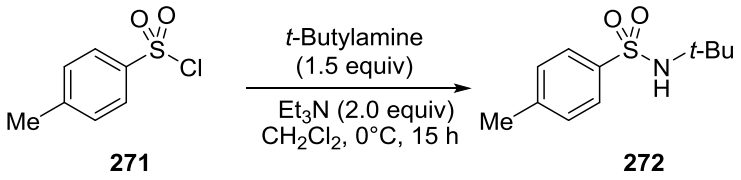


269c

3-*n*-Butylbenzo[*d*]isothiazole 1,1-dioxide (269c). The title compound was prepared according to the Representative Procedure from saccharin (5.49 g, 30 mmol) and *n*-BuLi (1.6M in hexanes, 56.25 mL, 90 mmol) to give *imine* **269c** (2.00 g, 30%) as a white solid that displayed spectroscopic data consistent with those previously reported.[142] m.p. 95-97 °C (Et_2O); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.89 (1H, t, J = 3.0 Hz, Ar**H**),

7.75-7.68 (3H, m, Ar**H**), 2.96 (2H, t, *J* = 7.5 Hz, CC**H**$_2$), 1.89-1.82 (2H, m, C**H**$_2$), 1.54-1.47 (2H, m, C**H**$_2$), 0.98 (3H, t, *J* = 7.0 Hz, C**H**$_3$).

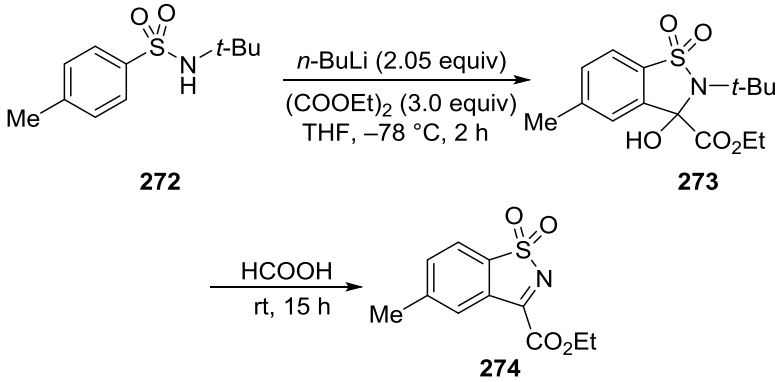
4-methyl-*N*-*tert*-butylbenzenesulfonamide (272):



271 **272**

To a solution of *tert*-butylamine (3.14 mL, 30 mmol) and triethylamine (4.0 mL, 40 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added *p*-tolylsulfonyl chloride (3.8 g, 20 mmol). The mixture was stirred for 15 hours at room temperature then extracted with CH_2Cl_2 (3 x 50 mL) and the organic layers were combined and washed with $NaHCO_3$ solution (2 M, 50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *sulfonamide* **272** (3.74 g, 83%) as a cream solid that was not purified further.

3-Ethylcarboxyl-5-methylbenzo[*d*]isothiazole 1,1-dioxide (274):

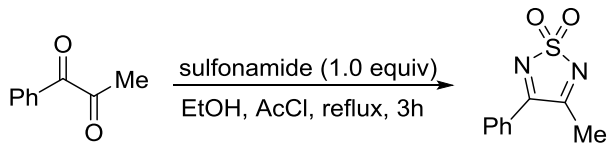


272 **273** **274**

To a solution of *sulfonamide* **272** (2.80 g, 12.3 mmol) in THF (100 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 15.8 mL, 25.215 mmol) and the mixture was stirred for 20 minutes. The mixture was cooled to –78 °C and diethyl oxalate (5.00 mL, 36.9 mmol) was added. The solution was warmed to room temperature and stirred for 2 hours before being quenched by ice-cooled HCl (2 M, 50 mL). The

mixture was extracted with Et_2O (3 x 100 mL) and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in formic acid (50 mL) and stirred at room temperature for 15 hours. The mixture was concentrated *in vacuo* and purification of the residue by flash column chromatography (90:10 hexanes:EtOAc) gave *imine* **274** (863 mg, 29 %) as a white solid that displayed spectroscopic data consistent with those reported previously.[225] ^{1}H NMR ($CDCl_3$ 400 MHz) δ 8.60 (1H, s, Ar**H**), 7.80 (1H, d, *J* = 5.7 Hz, Ar**H**), 7.57 (1H, d, *J* = 5.7 Hz, Ar**H**), 4.53 (2H, q, *J* = 5.4 Hz, OC**H**$_2$), 2.52 (3H, s, PhC**H**$_3$), 1.47 (3H, t, *J* = 5.7 Hz, OCH_2C**H**$_3$); HRMS (ESI) Exact mass calcd for $C_{11}H_{11}NO_4SNa$ $[M+Na]^+$: 276.0306, found: 276.0313.

4-Methyl-3-phenyl-1,2,5-thiadiazole-1,1-dioxide (276a):

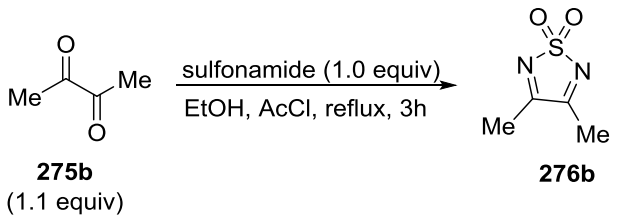


275a
(1.1 equiv)

276a

To a solution of 1-phenylpropan-1,2-dione (1.63 g, 11 mmol) and sulfonamide (0.96 g, 10 mmol) in EtOH (100 mL) was added acetyl chloride (2.5 mL). The solution was heated at reflux for 3 hours before being cooled to room temperature. The mixture was filtered to give *imine* **276a** (2.03 g, 98%) as a peach solid that displayed spectroscopic data consistent with those previously reported.[143] ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.91-7.87 (2H, m, Ar**H**), 7.73-7.71 (1H, m, Ar**H**), 7.59-7.57 (2H, m, Ar**H**), 2.77 (3H, s, C**H**$_3$); HRMS (ESI) Exact mass calcd for $C_9H_8N_2O_2SNa$ $[M+Na]^+$: 207.0204, found: 207.0199.

3,4-Dimethyl-1,2,5-thiadiazole-1,1-dioxide (276b):

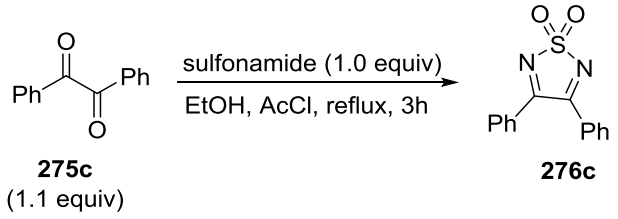


275b
(1.1 equiv)

276b

To a solution of butan-2,3-dione (946 mg, 11 mmol) and sulfonamide (0.96 g, 10 mmol) in EtOH (100 mL) was added acetyl chloride (2.5 mL). The solution was heated at reflux for 3 hours before being cooled to room temperature. The mixture was filtered to give *imine* **276b** (854 mg, 58%) as a beige solid that displayed spectroscopic data consistent with those previously reported.[143] ^{1}H NMR ($CDCl_3$ 400 MHz) δ 2.91 (6H, s, 2 x C**H**$_3$); HRMS (ESI) Exact mass calcd for $C_4H_6N_2O_2SNa$ $[M+Na]^+$: 169.0048, found: 169.0047.

3,4-Diphenyl-1,2,5-thiadiazole-1,1-dioxide (276c):



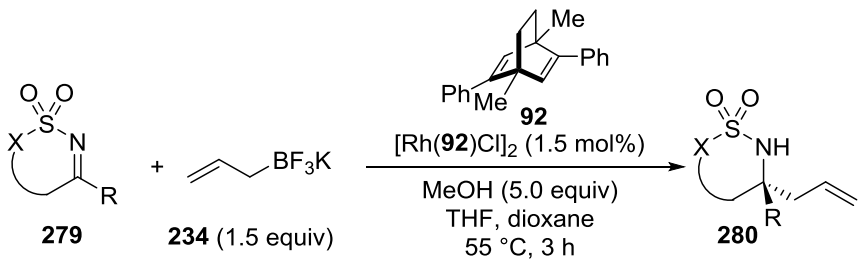
275c
(1.1 equiv)

276c

To a solution of benzil (2.1 g, 11 mmol) and sulfonamide (0.96 g, 10 mmol) in EtOH (100 mL) was added acetyl chloride (2.5 mL). The solution was heated at reflux for 3 hours before being cooled to room temperature. The mixture was filtered to give *imine* **276c** (888 mg, 33%) as a beige solid that displayed spectroscopic data consistent with those previously reported.[143] ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.67-7.63 (2H, m, Ar**H**), 7.58-7.56 (4H, m, Ar**H**), 7.46-7.40 (4H, m, Ar**H**); HRMS (ESI) Exact mass calcd for $C_{14}H_{10}N_2O_2SNa$ $[M+Na]^+$: 293.0355, found: 207.0354.

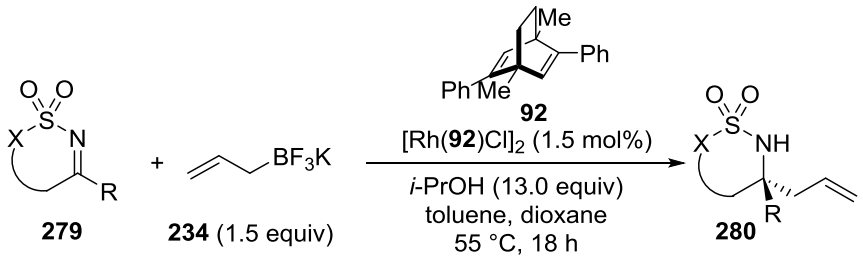
1.1.3 Synthesis and Characterisation of Simple Allylation Products

Enantioselective Allylation of Cyclic Imines in THF/Dioxane/MeOH: General Procedure A



A Schlenk tube containing the appropriate cyclic imine (0.30 mmol) and potassium allyltrifluoroborate **234** (67 mg, 0.45 mmol) was flushed with nitrogen before anhydrous THF (3 mL) was added. To this solution was added a stock solution of the rhodium–chiral diene complex (11.5 mM in anhydrous dioxane,* 0.39 mL, 0.0045 mmol = 3 mol% Rh), and MeOH (60 μL, 1.50 mmol), and the resulting mixture was heated to 55 °C for 3 h. The reaction was cooled to room temperature, diluted with Et_2O (50 mL), filtered through a short plug of silica using Et_2O as eluent, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the allylated product.

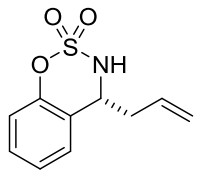
Enantioselective Allylation of Cyclic Imines in Toluene/Dioxane/*i*-PrOH: General Procedure B



A Schlenk tube containing the appropriate benzoxathiazine-2,2-dioxide (0.30 mmol) and potassium allyltrifluoroborate **234** (67 mg, 0.45 mmol) was flushed with

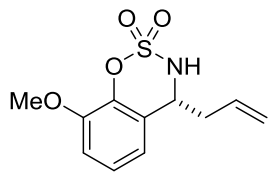
* . Prepared by dissolving 270 mg of [Rh(**92**)Cl]$_2$ in 27 mL of anhydrous dioxane.

nitrogen before anhydrous toluene (2.7 mL) and *i*-PrOH (0.30 mL, 3.92 mmol) was added. To this solution was added a stock solution of the rhodium–chiral diene complex (11.5 mM in anhydrous dioxane,[Error! Bookmark not defined.] 0.39 mL, 0.0045 mol = 3 mol% Rh) and the resulting mixture was heated to 55 °C for 18 h. The reaction was cooled to room temperature, diluted with Et_2O (50 mL), filtered through a silica plug using Et_2O as eluent, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the allylated product.



233a

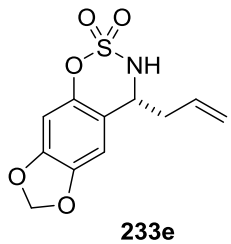
(*R*)-4-(Prop-2-en-1-yl)-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (233a). The title compound was prepared according to General Procedure A from benzoxathiazine-2,2-dioxide **89a** (55 mg, 0.30 mmol) and was purified by column chromatography (80:20 hexanes:EtOAc) to give *sulfonamide* **233a** (59 mg, 87%) as an orange oil. R_F = 0.43 (80:20 hexanes:EtOAc); $[\alpha]_D^{20}$ +177.9 (*c* 0.24, $CHCl_3$); IR (film) 3259 (NH), 1357, 1186, 1157, 1103, 900, 850, 831, 755, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (1H, m, Ar**H**), 7.30-7.28 (1H, m, Ar**H**), 7.24-7.21 (1H, m, Ar**H**), 7.04 (1H, dd, *J* = 8.3, 1.1 Hz, Ar**H**), 5.69 (1H, dddd, *J* = 17.0, 10.1, 8.5, 5.8 Hz, C**H**=CH_2), 5.34-5.26 (2H, m, =C**H**$_2$), 4.93 (1H, ddd, *J* = 9.0, 7.0, 4.2 Hz, C**H**), 4.56 (1H, d, *J* = 9.0 Hz, N**H**), 3.01-2.94 (1H, m, C**H**$_2$), 2.82-2.75 (1H, m, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 151.5 (C), 131.2 (CH), 129.6 (CH), 126.1 (CH), 125.5 (CH), 121.4 (C), 121.4 (CH_2), 119.1 (CH), 55.8 (CH), 37.5 (CH_2); HRMS (ESI) Exact mass calcd for $C_{10}H_{10}NO_3S$ $[M–H]^–$: 224.0387, found: 224.0388. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 14.8 min, t_r (major) = 18.0 min; 96% ee.



233d

(*R*)-8-Methoxy-4-(prop-2-en-1-yl)-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (233d). The title compound was prepared according to General Procedure A from benzoxathiazine-2,2-dioxide **89d** (64 mg, 0.30 mmol) and was purified by column chromatography (80:20 hexanes:Et_2O) to give *sulfonamide* **233d** (75 mg, >95%) as a yellow solid. R_F = 0.40

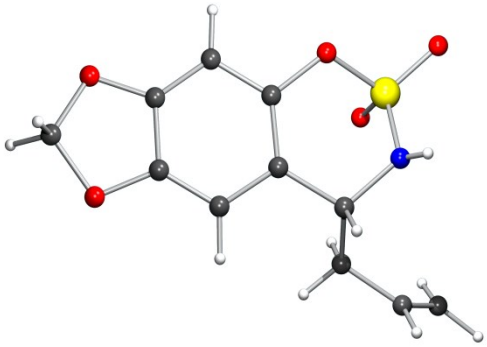
(80:20 hexanes:EtOAc); m.p. 118-120 °C; $[\alpha]_D^{20}$ +150.9 (*c* 1.06, $CHCl_3$); IR (film) 3257 (NH), 1481, 1398, 1199, 1156, 1082, 871, 856, 786, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.91 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.85 (1H, dt, *J* = 8.0, 1.0 Hz, Ar**H**), 5.67 (1H, dddd, *J* = 17.0, 10.1, 8.7, 5.7 Hz, C**H**=CH_2), 5.33-5.25 (2H, m, =C**H**$_2$), 4.95-4.90 (1H, m, NC**H**), 4.56 (1H, d, *J* = 9.0 Hz, N**H**), 3.88 (3H, s, OC**H**$_3$), 2.99-2.93 (1H, m, C**H**$_2$), 2.78-2.71 (1H, m, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 148.9 (C), 141.2 (C), 131.3 (CH), 125.1 (CH), 122.4 (C), 121.4 (CH_2), 117.1 (CH), 111.8 (CH), 56.2 (CH_3), 55.9 (CH), 37.6 (CH_2); HRMS (ESI) Exact mass calcd for $C_{11}H_{12}NO_4S$ $[M–H]^–$: 254.0493, found: 254.0493. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 21.2 min, t_r (major) = 24.4 min; 95% ee.

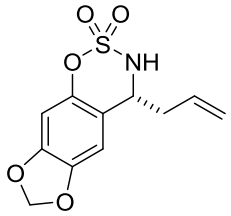


233e

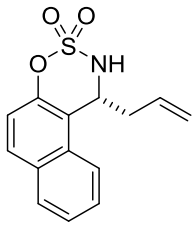
(*R*)-8-(Prop-2-en-1-yl)-7,8-dihydro-1,3,5-trioxa-6-thia-7-azacyclopenta[*b*]naphthalene-6,6-dioxide (233e). The title compound was prepared according to General Procedure A from benzoxathiazine-2,2-dioxide **89e** (68 mg, 0.30 mmol) and was purified by column chromatography (85:15 hexanes:EtOAc) to give *sulfonamide* **233e** (74 mg, 94%) as a yellow solid. R_F = 0.46 (80:20 hexanes:EtOAc); m.p. 114-116 °C (Et_2O); $[\alpha]_D^{20}$ +198.7 (*c* 0.32, $CHCl_3$); IR (film) 3275 (NH), 1483, 1427, 1246, 1196, 1136, 1034, 930, 867, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.68 (1H, d, *J* = 0.5 Hz, Ar**H**), 6.53 (1H, s, Ar**H**), 6.02 (1H, d, *J* = 1.3 Hz, OC**H**$_2$O), 6.00 (1H, d, *J* = 1.3 Hz, OC**H**$_2$O), 5.70 (1H, dddd, *J* = 17.0, 10.0, 8.6, 5.7 Hz, C**H**=CH_2), 5.33-5.26 (2H, m, =C**H**$_2$), 4.82-4.77 (1H, m, NC**H**), 4.47 (1H, d, *J* = 9.0 Hz, N**H**), 2.92-2.84 (1H, m, C**H**$_2$), 2.74-2.66 (1H, m, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 148.1 (C), 145.9 (C), 145.4 (C), 131.2 (CH), 121.4 (CH_2), 113.7 (C), 104.6 (CH), 102.1 (CH_2), 100.6 (CH), 55.7 (CH), 37.7 (CH_2); HRMS (ESI) Exact mass calcd for $C_{11}H_{10}NO_5S$ $[M–H]^–$: 268.0285, found: 268.0286. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 33.2 min, t_r (major) = 43.9 min; 98% ee.

Slow evaporation of a solution of **233e** in Et_2O/petrol gave crystals that were suitable for X-ray diffraction:



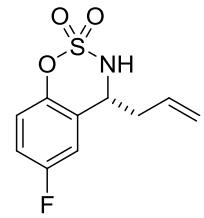


233e
CCDC = 880901



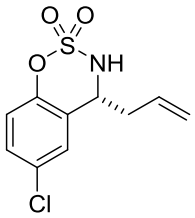
233f

(*R*)-(Prop-2-en-1-yl)-3,4-dihydro-1-oxa-2-thia-3-azaphenanthrene-2,2-dioxide (233f). The title compound was prepared according to General Procedure A from benzoxathiazine-2,2-dioxide **89f** (70 mg, 0.30 mmol) and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **233f** (79 mg, 95%) as an orange oil. R_F = 0.52 (80:20 hexanes:EtOAc); $[\alpha]_D^{20}$ +70.1 (*c* 0.32, $CHCl_3$); IR (film) 3255 (NH), 1348, 1171, 1159, 1083, 949, 835, 816, 752, 661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.84 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.77 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.64-7.61 (1H, m, Ar**H**), 7.55-7.52 (1H, m, Ar**H**), 7.17 (1H, d, *J* = 9.0 Hz, Ar**H**), 5.97 (1H, ddt, *J* = 17.1, 10.2, 7.0 Hz, C**H**=CH_2), 5.35 (1H, app ddd, *J* = 17.1, 2.8, 1.3 Hz, =C**H**$_2$), 5.30 (1H, dd, *J* = 10.2, 1.3 Hz, =C**H**$_2$), 5.26-5.22 (1H, m, NC**H**), 4.93 (1H, d, *J* = 5.7 Hz, N**H**), 3.21-3.14 (1H, m, C**H**$_2$), 2.85-2.79 (1H, m, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 148.9 (C), 133.0 (CH), 131.3 (C), 130.7 (CH), 129.6 (C), 129.3 (CH), 127.8 (CH), 125.7 (CH), 122.3 (CH), 119.7 (CH_2), 118.5 (CH), 115.6 (C), 56.3 (CH), 37.9 (CH_2); HRMS (ESI) Exact mass calcd for $C_{14}H_{12}NO_3S$ $[M–H]^-$: 274.0543, found: 274.0545. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 17.1 min, t_r (major) = 19.7 min; 93% ee.



233g

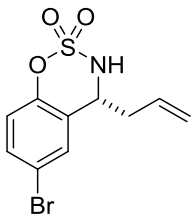
(*R*)-6-Fluoro-4-(prop-2-en-1-yl)-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (233g). The title compound was prepared according to General Procedure B from benzoxathiazine-2,2-dioxide **89g** (60 mg, 0.30 mmol) and was purified by column chromatography (75:25 hexanes:EtOAc) to give *sulfonamide* **233g** (62 mg, 86%) as a light yellow solid. R_F = 0.45 (80:20 hexanes:EtOAc); m.p. 49-51 °C (Et_2O); $[\alpha]_D^{20}$ +144.0 (*c* 1.06, $CHCl_3$); IR (film) 3300, 1487, 1425, 1371, 1201, 1163, 854, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06-6.97 (3H, m, Ar**H**), 5.71 (1H, dddd, *J* = 17.0, 10.1, 8.3, 6.0 Hz, C**H**=CH_2), 5.35-5.28 (2H, m, =C**H**$_2$), 4.91-4.84 (1H, m, C**H**), 4.67 (1H, d, *J* = 8.8 Hz, N**H**), 2.95-2.86 (1H, m, C**H**$_2$), 2.81-2.72 (1H, m, C**H**$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.4 (d, *J* = 245.7 Hz, C), 147.3 (d, *J* = 2.3 Hz, C), 130.9 (CH), 123.2 (d, *J* = 7.0 Hz, C), 121.6 (CH_2), 120.6 (d, *J* = 8.5 Hz, CH), 116.6 (d, *J* = 23.7 Hz, CH), 112.9 (d, *J* = 24.9 Hz, CH), 55.7 (d, *J* = 1.7 Hz, CH), 37.5 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.6 (1F, s); HRMS (EI) Exact mass calcd for $C_{10}H_{10}FNO_3S$ $[M]^+$: 243.0360, found: 243.0354. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 18.2 min, t_r (major) = 20.2 min; 98% ee.



233h

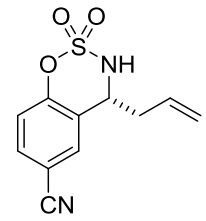
(*R*)-6-Chloro-4-(prop-2-en-1-yl)-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (233h). The title compound was prepared according to General Procedure B from benzoxathiazine-2,2,-dioxide **89h** (65 mg, 0.30 mmol) and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **233h** (74 mg, 96%) as a pale yellow oil. R_F = 0.38 (80:20 hexanes:EtOAc); $[\alpha]_D^{20}$ +184.0 (*c* 0.88, $CHCl_3$); IR (film) 3271 (NH), 1475, 1421, 1408, 1367, 1190, 1162, 1111, 807, 767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.29 (1H, m, Ar**H**), 7.29-7.27 (1H, m, Ar**H**), 6.99 (1H, d, *J* = 8.7 Hz, Ar**H**), 5.69 (1H, dddd, *J* = 16.8, 9.9, 8.6, 5.8 Hz, C**H**=CH_2), 5.36-5.29 (2H, m, =C**H**$_2$), 4.92-4.88 (1H, m, NC**H**), 4.58 (1H, d, *J* = 9.1 Hz, N**H**), 2.98-2.91 (1H, m, C**H**$_2$), 2.80-2.74 (1H, m, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 150.0 (C), 130.7 (CH), 129.7 (CH), 126.1 (CH), 123.0 (C), 121.8 (CH_2 and C), 120.5 (CH), 55.5 (CH), 37.4 (CH_2);

HRMS (ESI) Exact mass calcd for $C_{10}H_9ClNO_3S$ $[M–H]^-$: 257.9997, found: 257.9997. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 15.8 min, t_r (major) = 17.2 min; 96% ee.



233i

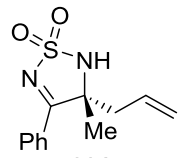
(*R*)-6-Bromo-4-(prop-2-en-1-yl)-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (233i). The title compound was prepared according to General Procedure B from benzoxathiazine-2,2,-dioxide **89i** (78 mg, 0.30 mmol) and was purified by column chromatography (89:11 hexanes:EtOAc) to give *sulfonamide* **233i** as a light yellow gum. R_F = 0.43 (80:20 hexanes:EtOAc); $[\alpha]_D^{20}$ +153.0 (*c* 1.15, $CHCl_3$); IR (film) 3271 (NH), 1471, 1423, 1367, 1188, 1165, 1111, 925, 812, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.43 (2H, m, Ar**H**), 6.93 (1H, d, *J* = 8.7 Hz, Ar**H**), 5.69 (1H, dddd, *J* = 17.0, 10.0, 8.6, 5.8 Hz, C**H**=CH_2), 5.36-5.29 (2H, m, =C**H**$_2$), 4.93-4.87 (1H, m, C**H**), 4.55 (1H, d, *J* = 9.0 Hz, N**H**), 2.97-2.91 (1H, m, C**H**$_2$), 2.81-2.74 (1H, m, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 150.6 (C), 132.7 (CH), 130.8 (CH), 129.1 (CH), 123.4 (C), 121.8 (CH_2), 120.8 (CH), 118.2 (C), 55.5 (CH), 37.4 (CH_2); HRMS (EI) Exact mass calcd for $C_{10}H_{10}BrNO_3S$ $[M]^+$: 302.9559, found: 302.9562. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 15.0 min, t_r (major) = 18.9 min; 94% ee.



233j

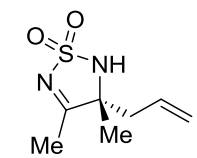
(*R*)-6-Cyano-4-(prop-2-en-1-yl)-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (233j). The title compound was prepared according to General Procedure B from benzoxathiazine-2,2,-dioxide **89j** (63 mg, 0.30 mmol) and was purified by column chromatography (66:34 hexanes:EtOAc) to give *sulfonamide* **233j** (73 mg, 97%) as a pale yellow solid. R_F = 0.34 (80:20 hexanes:EtOAc); m.p. 92-94 °C (Et_2O); $[\alpha]_D^{20}$ +214.2 (*c* 1.10, $CHCl_3$); IR (film) 2230 (C≡N), 1431, 1411, 1377, 1207, 1185, 927, 835, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (1H, dd, *J* = 7.3, 1.9 Hz, Ar**H**), 7.62 (1H, s, Ar**H**), 7.13 (1H, dd, *J* = 7.2, 1.9 Hz, Ar**H**); 5.70 (1H, dddd, *J* = 17.0, 10.1, 8.1, 6.0 Hz, C**H**=CH_2), 5.34 (1H,

ddd, J = 17.1, 2.8, 1.3 Hz, =C**H**$_2$), 5.32 (1H, dd, J = 10.1, 1.0 Hz, =C**H**$_2$), 4.93 (2H, br s, NC**H** and N**H**), 3.00-2.90 (1H, m, C**H**$_2$), 2.87-2.77 (1H, m, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.4 (C), 133.4 (CH), 130.8 (CH), 130.4 (CH), 123.2 (C), 121.9 (CH), 120.3 (CH), 117.5 (C), 109.3 (C), 55.5 (CH), 37.3 (CH_2); HRMS (EI) Exact mass calcd for $C_{11}H_{10}N_2O_3S$ $[M]^+$: 250.0406, found: 250.0400. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 28.6 min, t_r (major) = 32.4 min; 98% ee.



281a

(*R*)-(Prop-2-en-1-yl)-3-methyl-4-phenyl-2,3-dihydro-[1,2,5]thiadiazole 1,1-dioxide (281a). The title compound was prepared according to a slight modification of General Procedure A (in that the reaction time was 12 h) from [1,2,5]thiadiazole 1,1-dioxide **276a** (62 mg, 0.30 mmol) and was purified by column chromatography (80:20 hexanes:EtOAc) to give *sulfonamide* **281a** (66 mg, 88%) an orange oil. R_F = 0.45 (80:20 hexanes:EtOAc); $[\alpha]_D^{20}$ −29.9 (*c* 0.74, $CHCl_3$); IR (film) 3244 (NH), 1557, 1315, 1158, 995, 818, 779, 700, 652, 561 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05-8.02 (2H, m, Ar**H**), 7.65 (1H, t, J = 7.5 Hz, Ar**H**), 7.56-7.52 (2H, m, Ar**H**), 5.72-5.63 (1H, m, C**H**=CH_2), 5.28 (1H, d, J = 10.1 Hz, =C**H**$_2$), 5.21 (1H, dd, J = 1.0, 17.0 Hz, =C**H**$_2$), 4.53 (1H, br s, N**H**), 2.91 (1H, dd, J = 14.6, 6.5 Hz, C**H**$_2$), 2.70 (1H, dd, J = 14.6, 8.0 Hz, C**H**$_2$), 1.82 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 181.6 (C), 133.8 (CH), 130.1 (CH), 130.0 (2 x CH), 129.2 (2 x CH), 128.8 (C), 122.4 (CH_2), 72.3 (C), 43.6 (CH_2), 26.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{12}H_{15}N_2O_2S$ $[M+H]^+$: 251.0849. found 251.0848; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min 280 nm, 25 °C); t_r (minor) = 43.7 min, t_r (major) = 48.2 min; 97% ee.

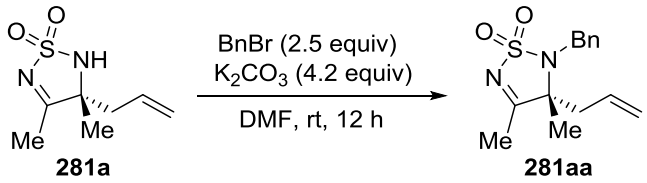


281b

(*R*)-(Prop-2-en-1-yl)-3-methyl-4-methyl-2,3-dihydro-[1,2,5]thiadiazole 1,1-dioxide (281b). The title compound was prepared according to a slight modification of General Procedure A (in that the reaction time was 15 h) from [1,2,5]thiadiazole 1,1-dioxide **276b** (47 mg, 0.30 mmol) and was purified by column chromatography

(80:20 hexanes:EtOAc) to give *sulfonamide* **281b** (44 mg, 84%) as an orange oil. R_F = 0.45 (80:20 hexanes:EtOAc) $[\alpha]_D^{20}$ −74.0 (1.00, $CHCl_3$); IR (film) 3256 (NH), 1612, 1371, 1315, 1159, 930, 883, 816, 623, 598 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (1H, ddt, *J* = 17.2, 10.2, 7.2 Hz, C**H**=CH_2), 5.33 (1H, dd, *J* = 10.2, 1.2 Hz, =C**H**$_2$), 5.27 (1H, dd, *J* = 17.2, 1.4 Hz, =C**H**$_2$), 4.32 (1H, br s, N**H**), 2.56-2.48 (2H, m, C**H**$_2$CH=), 2.30 (3H, s, C**H**$_3$C=N), 1.53 (3H, s, C**H**$_3$CNH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 186.1 (C), 129.9 (CH), 122.1 (CH_2), 72.2 (C), 42.3 (CH_2), 24.4 (CH_3), 16.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_7H_{13}N_2O_2S$ $[M+H]^+$: 189.0692, found 189.0692. To facilitate determination of enantiomeric excess, **281a** was converted into the corresponding *N*-benzyl derivative **281aa** using the following procedure:

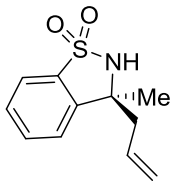
_N_-Benzyl-(_R_)-(prop-2-en-1-yl)-3-methyl-4-methyl-2,3-dihydro-[1,2,5]thiadiazole-1,1-dioxide (281aa):



281a **281aa**

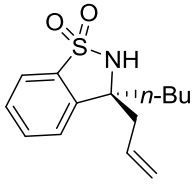
To a solution of 2,3-dihydro-[1,2,5]thiadiazole 1,1-dioxide **281a** (10 mg, 0.053 mmol) and K_2CO_3 (30 mg, 0.22 mmol) in DMF (1 mL) at room temperature was added benzyl bromide (15 μL, 0.13 mmol) and the mixture was stirred at room temperature for 12 h. The reaction was diluted with EtOAc (5 mL), washed with H_2O (3 x 5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane) gave the *benzylated derivative* **281aa** (7.8 mg, 53%) as a white solid. R_F = 0.33 (95:5 hexanes:EtOAc); m.p. 78-80 °C (Et_2O); $[\alpha]_D^{20}$ −25.0 (*c* 0.56, $CHCl_3$); IR (film) 1296, 1223, 1163, 1130, 1003, 864, 833, 714, 604, 588 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 7.1 Hz, Ar**H**), 7.38-7.35 (2H, m, Ar**H**), 7.34-7.32 (1H, m, Ar**H**), 5.54 (1H, dddd, *J* = 17.0, 10.3, 8.6, 5.2 Hz, C**H**=CH_2), 5.13 (1H, d, *J* = 10.3 Hz, =C**H**$_2$), 5.05 (1H, dd, *J* = 17.0, 1.1 Hz, =C**H**$_2$), 4.47 (1H, d, *J* = 15.5 Hz, C**H**$_2$Ph), 4.31 (1H, d, *J* = 15.5 Hz, C**H**$_2$Ph), 2.36 (1H, ddt, *J* = 15.2, 5.0, 1.6 Hz, C**H**$_2$C=), 2.29-2.24 (1H, m, C**H**$_2$C=), 2.24 (3H, s, C**H**$_3$C=N), 1.36 (3H, s, C**H**$_3$CCH$_2$); ^{13}C

NMR (125.8 MHz, $CDCl_3$) δ 185.7 (C), 135.6 (C), 130.4 (CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.2 (CH), 119.9 (CH_2), 74.1 (C), 44.9 (CH_2), 40.2 (CH_2), 22.3 (CH_3), 16.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{14}H_{19}N_2O_2S$ $[M+H]^+$: 279.1162, found 279.1156. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 210 nm, 25 °C); t_r (major) = 24.4 min, t_r (minor) = 30.6 min; 99% ee.



283a

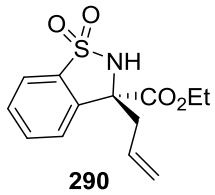
(*S*)-3-Methyl-3-(prop-2-en-1-yl)-2,3-dihydro-[1,2]-benzothiazole-1,1-dioxide (283a). The title compound was prepared according to a slight modification of General Procedure A (in that the reaction time was 15 h) from imine **269a** (54 mg, 0.30 mmol) using ligand *ent*-**92** and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **283a** (38 mg, 57%) as a yellow oil. R_f = 0.32 (30% EtOAc/hexane); $[\alpha]_D^{20}$ –54.2 (*c* 0.70, $CHCl_3$); IR 3250 (NH), 1373, 1271, 1254, 1148, 1121, 1049, 916, 770, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.64 (1H, td, *J* = 7.7, 1.1 Hz, Ar**H**), 7.53 (1H, td, *J* = 7.7, 1.0 Hz, Ar**H**), 7.39 (1H, d, *J* = 7.8 Hz, Ar**H**), 5.68 (1H, dddd, *J* = 17.0, 10.3, 7.9, 6.7 Hz, C**H**=CH_2), 5.24-5.17 (2H, m, =C$\mathbf{H}_2$), 4.65 (1H, br s, N**H**), 2.71 (1H, dd, *J* = 14.1, 7.1 Hz, C$\mathbf{H}_2$), 2.60 (1H, dd, *J* = 14.1, 7.9 Hz, C$\mathbf{H}_2$), 1.64 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 144.6 (C), 135.7 (C), 133.3 (CH), 131.7 (CH), 129.2 (CH), 123.0 (CH), 121.3 (CH), 121.2 (CH_2), 62.9 (C), 45.7 (CH_2), 27.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{11}H_{14}NO_2S$ $[M+H]^+$: 224.0740, found: 224.0735; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 17.8 min, t_r (minor) = 24.0 min; 96% ee.



283c

(*S*)-3-Butyl-3-(prop-2-en-1-yl)-2,3-dihydro-[1,2]-benzothiazole-1,1-dioxide (283c). The title compound was prepared according to a slight modification of General Procedure A (in that the reaction time was 15 h) from imine **269c** (67 mg, 0.30 mmol) using ligand *ent*-**92** and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **283c** (51 mg, 64%) as a yellow oil. R_f = 0.45

(30% EtOAc/hexane); $[\alpha]_D^{20}$ –30.3 (*c* 1.45, $CHCl_3$); IR 3281 (NH), 1466, 1375, 1271, 1153, 1132, 1034, 930, 766, 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.64 (1H, td, *J* = 7.7, 1.1 Hz, Ar**H**), 7.53 (1H, td, *J* = 7.7, 1.0 Hz, Ar**H**), 7.35 (1H, d, *J* = 7.8 Hz, Ar**H**), 5.63 (1H, dddd, *J* = 17.1, 10.2, 7.6, 7.0 Hz, C**H**=CH_2), 5.20-5.14 (2H, m, =C**H**$_2$), 4.54 (1H, s, N**H**), 2.70-2.60 (2H, m, C**H**$_2$CH=), 1.93-1.87 (2H, m, C**H**$_2$$CH_2CH_2CH_3$), 1.45-1.36 (1H, m, C**H**$_2$C**H**$_2$$CH_3$), 1.32-1.23 (2H, m, C**H**$_2$C**H**$_2$$CH_3$), 1.01-0.97 (1H, m, C**H**$_2$C**H**$_2$$CH_3$), 0.85 (3H, t, *J* = 7.3 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 142.9 (C), 136.0 (C), 133.2 (CH), 131.6 (CH), 129.3 (CH), 123.3 (CH), 121.5 (CH), 121.1 (CH_2), 66.3 (C), 45.1 (CH_2), 40.0 (CH_2), 25.7 (CH_2), 22.6 (CH_2), 13.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{14}H_{20}NO_2S$ $[M+H]^+$: 266.1209, found: 266.1205; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 211 nm, 25 °C); t_r (major) = 24.7 min, t_r (minor) = 29.2 min; 96% ee.

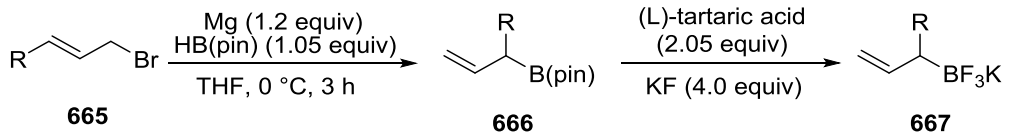


290

(*S*)-Ethyl -5-methyl-1,1-dioxo-3-(prop-2-en-1-yl)-2,3-dihydro-[1,2]-benzothiazole-3-carboxylate (290). The title compound was prepared according to General Procedure B from imine **274** (76 mg, 0.30 mmol) using ligand *ent*-**92** and was purified by column chromatography (90:10 hexane:EtOAc) to give *sulfonamide* **290** (49 mg, 55%) as a colourless oil. R_f = 0.35 (30% EtOAc/hexane); $[\alpha]_D^{20}$ –22.4 (*c* 0.90, $CHCl_3$); IR 3258 (NH), 1722 (C=O), 1261, 1231, 1182, 1144, 1134, 1040, 702, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.51 (1H, s, Ar**H**), 7.38 (1H, d, *J* = 8.0 Hz, Ar**H**), 5.77 (1H, dddd, *J* = 16.9, 10.2, 7.8, 6.4 Hz, C**H**=CH_2), 5.69 (1H, s, N**H**), 5.23-5.17 (2H, m, =C**H**$_2$), 4.36-4.26 (2H, m, OC**H**$_2$$CH_3$), 2.96 (1H, dd, *J* = 13.9, 7.8 Hz, C**H**$_2$C=), 2.71 (1H, dd, *J* = 13.9, 6.4 Hz, C**H**$_2$C=), 2.49 (3H, s, ArC**H**$_3$), 1.34 (3H, t, *J* = 7.1 Hz, OCH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.5 (C), 144.6 (C), 138.0 (C) 132.7 (C), 131.4 (CH), 131.0 (CH), 125.1 (CH), 121.1 (CH), 120.7 (CH_2), 68.5 (C), 63.4 (CH_2), 44.6 (CH_2), 21.8 (CH_3), 14.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{14}H_{18}NO_4S$ $[M+H]^+$: 296.0951, found: 296.0951; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 211 nm, 25 °C); t_r (minor) = 13.9 min, t_r (major) = 18.4 min; 21% ee.

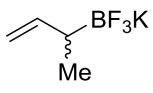
1.1.4 The Synthesis of Allyltrifluoroborates with Higher Degrees of Substitution

Preparation of Potassium Allyltrifluoroborates: General Procedure C



665 **666** **667**

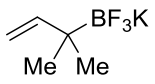
Following a slight modification of the procedure of Lennox and Lloyd-Jones,[150] to a solution of the appropriate allylboronic acid pinacol ester (1.0 equiv) in MeOH (2 mL/mmol) and MeCN (2 mL/mmol) at room temperature was added a solution of KF (4.0 equiv) in H_2O (0.1 mL/mmol), and the mixture was stirred for 5 min until complete dissolution occurred. To this solution was added a solution of L-(+)-tartaric acid (2.05 equiv) in THF (1.5 mL/mmol of allylboronic acid pinacol ester) dropwise, and the resulting mixture was stirred at room temperature for 1 h. MeCN (5 mL/mmol of allylboronic acid pinacol ester) was added and the reaction was stirred for an additional 5 min before being filtered and concentrated *in vacuo* to leave a mixture of the potassium allyltrifluoroborate and pinacol. This residue was heated under reduced pressure to remove pinacol to leave the potassium allyltrifluoroborate as a white solid.



308

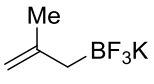
(±)-Potassium α-methylallyltrifluoroborate (308). To a solution of magnesium (400 mg, 16.44 mmol) and pinacol borane (1.99 mL, 13.7 mmol) in THF (25 mL) at 0 °C was slowly added crotyl bromide (1.20 mL, 13.7 mmol). The reaction was stirring for 30 minutes and additional crotyl bromide (1.20 mL, 13.7 mmol) was added. After 90 minutes, the reaction was diluted with hexanes (50 mL) and quenched with HCl (2 M, 10 mL). The mixture was extract with hexanes (3 x 50 mL), the organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *allylboronic ester* (1.86 g, 75 %) as a colourless oil. The title compound was then prepared according to General Procedure C from the corresponding *allylboronic pinacol ester* (910 mg, 5.00 mmol), KF (1.16 g, 20.0 mmol), and L-(+)-tartaric acid (1.54 g, 10.3 mmol) to give *allyltrifluoroborate* **308** (570 mg, 70%) as a white solid. m.p. >300 °C

(acetone); ^{1}H NMR (400 MHz, CD_3CN) δ 6.04 (1H, ddd, *J* = 17.3, 10.3, 6.9 Hz, C**H**=CH_2), 4.66 (1H, d, *J* = 17.3 Hz, =C**H**$_2$), 4.60 (1H, d, *J* = 10.3 Hz, =C**H**$_2$), 1.14 (1H, br s, C**H**B), 0.85 (3H, d, *J* = 6.7 Hz, C**H**$_3$); ^{13}C NMR (100.6 MHz, CD_3CN) δ 110.9 (CH), 107.0 (CH_2), 25.1 (CH), 14.4 (CH_3); ^{19}F NMR (376 MHz, CD_3CN) δ –146.5.



309

Potassium α,α-dimethylallyltrifluoroborate (309). To a solution of magnesium (207 mg, 8.64 mmol) and pinacol borane (1.08 mL, 7.5 mmol) in THF (25 mL) at 0 °C was slowly added prenyl bromide (0.86 mL, 7.5 mmol). The reaction was stirring for 30 minutes and additional prenyl bromide (0.86 mL, 7.5 mmol) was added. After 90 minutes, the reaction was diluted with hexanes (50 mL) and quenched with HCl (2 M, 10 mL). The mixture was extract with hexanes (3 x 50 mL), the organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *allylboronic ester* (1.37 g, 90 %) as a colourless oil. The title compound was then prepared according to General Procedure C from the corresponding *allylboronic pinacol ester* (550 mg, 2.80 mmol), KF (0.65 g, 11.2 mmol), and L-(+)-tartaric acid (0.86 g, 5.74 mmol) to give *allyltrifluoroborate* **309** (330 mg, 67%) as a white solid. m.p. >300 °C (acetone); ^{1}H NMR (400 MHz, CD_3CN) δ 6.07-6.00 (1H, m, C**H**=CH_2), 4.61-4.55 (2H, m, =C**H**$_2$), 0.79 (6H, s, 2 x C**H**$_3$); ^{13}C (100.6 MHz, CD_3CN) δ 111.1 (CH), 105.1 (CH_2), 23.7 (2 x CH_3), the quaternary carbon adjacent to the boron was not observed; ^{19}F NMR (376 MHz, CD_3CN) δ –151.3.

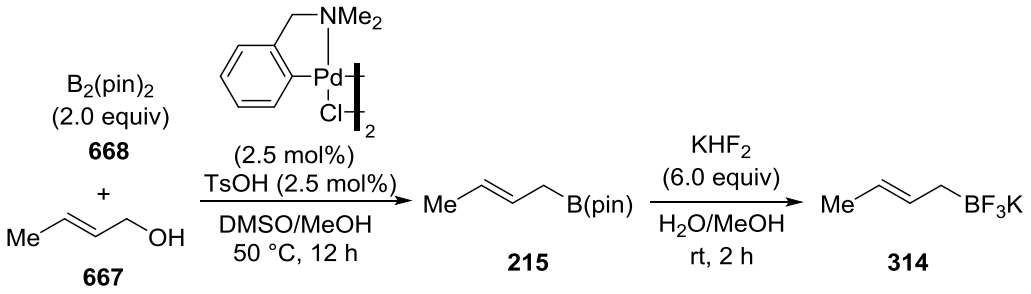


310

Potassium 2-methallyltrifluoroborate (310). To a solution of magnesium (207 mg, 8.64 mmol) and pinacol borane (1.08 mL, 7.5 mmol) in THF (25 mL) at 0 °C was slowly added 2-methylallyl bromide (0.75 mL, 7.5 mmol). The reaction was stirring for 30 minutes and additional 2-methylallyl bromide (0.75 mL, 7.5 mmol) was added. After 90 minutes, the reaction was diluted with hexanes (50 mL) and quenched with HCl (2 M, 10 mL). The mixture was extract with hexanes (3 x 50 mL), the organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *allylboronic ester* (847 mg, 62 %) as a colourless oil. The title compound was then prepared according to General Procedure C from the corresponding *allylboronic*

pinacol ester (478 mg, 2.63 mmol), KF (0.61 g, 10.5 mmol), and L-(+)-tartaric acid (0.81 g, 5.38 mmol) to give *allyltrifluoroborate* **310** (248 mg, 58%) as a white solid. m.p. >300 °C (acetone); ^{1}H NMR (400 MHz CD_3CN) δ 4.34 (1H, s, =C**H**$_2$), 4.32 (1H, s, =C**H**$_2$), 1.69 (3H, s, C**H**$_3$), 1.14 (2H, br s, C**H**$_2$); ^{13}C NMR (100.6 MHz, CD_3CN) δ 116.5 (C), 110.3 (CH_2), 25.0 (CH_3), the carbon adjacent to the boron was not observed; ^{19}F NMR (376 MHz, CD_3CN) δ –152.4.

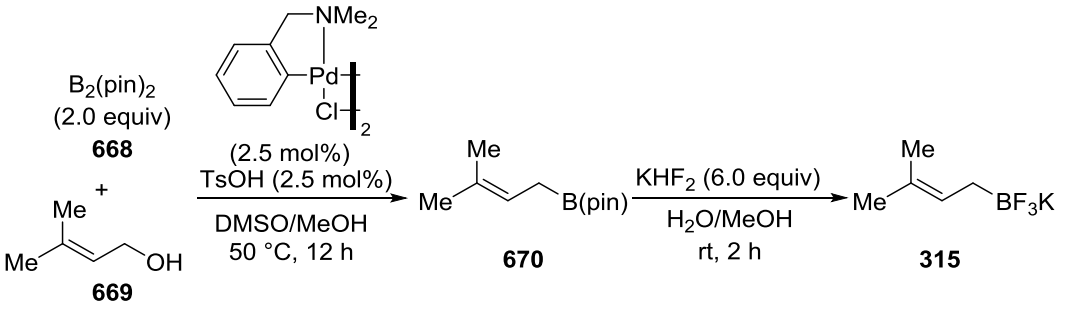
Potassium (*E*)-2-butenyltrifluoroborate (314):



To a solution of *trans*-crotyl alcohol (360 mg, 5.00 mmol) in MeOH (10 mL) and DMSO (10 mL) was added TsOH (24 mg, 0.125 mmol), di-μ-chlorobis(2-[(dimethylamino)methyl]phenyl-C,N)dipalladium(II) (68 mg, 0.125 mmol) and B_2Pin_2 (2.54 g, 10.0 mmol), and the solution was heated at 50 °C for 12 h. The reaction was cooled to room temperature, diluted with H_2O (50 mL), and extracted with Et_2O (3 x 50 mL), and the combined organic layers were dried, and concentrated *in vacuo* to leave the *allyl pinacolboronic ester* which was used immediately in the next step without further purification. To a solution of the above-mentioned *allyl pinacolboronic ester* in H_2O (20 mL) and MeOH (20 mL) was added KHF_2 (2.10 g, 30.0 mmol) and the mixture was stirred at room temperature for 2 h. The reaction was concentrated *in vacuo* and the resulting solid was extracted with acetone (3 x 50 mL). The combined acetone extracts were filtered and concentrated *in vacuo*. The residue was stirred with Et_2O (10 mL) and the resulting suspension was filtered to leave the *potassium allyltrifluoroborate* **314** (232 mg, 26%) as a white solid that displayed spectroscopic data consistent with those reported previously.[226] ^{1}H NMR (400 MHz $(CD_3)_2CO$) δ 5.58-5.49 (1H, m, C**H**=CH), 5.11-

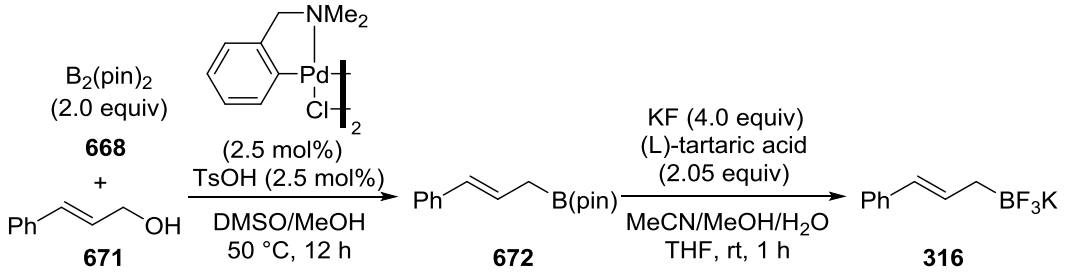
5.01 (1H, m, CH=C**H**), 1.53 (3H, qd, *J* = 6.4, 1.3 Hz, C**H**$_3$CH=CH), 1.00 (2H, br s, C**H**$_2$B); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –140.6.

Potassium 3-methyl-2-butenyltrifluoroborate (315):



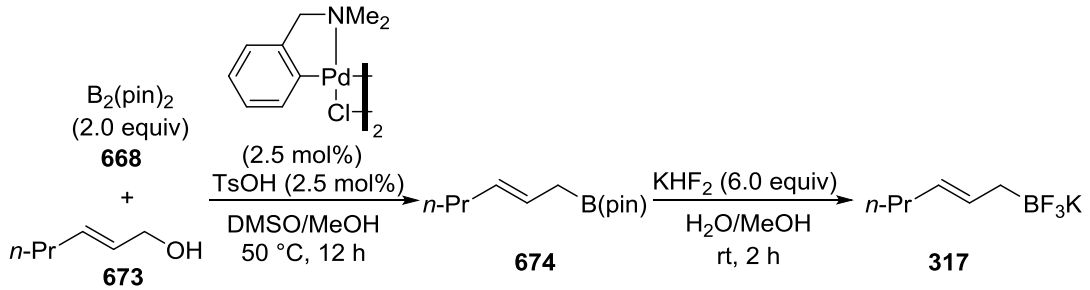
To a solution of 3-methylbut-2-en-1-ol (344 mg, 4.00 mmol) in MeOH (10 mL) and DMSO (10 mL) was added TsOH (19 mg, 0.10 mmol), di-μ-chlorobis(2-[(dimethylamino)methyl]phenyl-C,N)dipalladium(II) (55 mg, 0.10 mmol) and B_2Pin_2 (2.03 g, 8.0 mmol), and the solution was heated at 50 °C for 12 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL), and extracted with Et_2O (3 x 25 mL), and the combined organic layers were dried, and concentrated *in vacuo* to leave the *allyl pinacolboronic ester* which was used immediately in the next step without further purification. To a solution of the above-mentioned *allyl pinacolboronic ester* in H_2O (15 mL) and MeOH (15 mL) was added KHF_2 (1.83 g, 24.0 mmol) and the mixture was stirred at room temperature for 2 h. The reaction was concentrated *in vacuo* and the resulting solid was extracted with acetone (3 x 25 mL). The combined acetone extracts were filtered and concentrated *in vacuo*. The residue was stirred with Et_2O (10 mL) and the resulting suspension was filtered to leave the *potassium allyltrifluoroborate* **315** (354 mg, 50%) as a white solid that displayed spectroscopic data consistent with those reported previously.[227] ^{1}H NMR (400 MHz $(CD_3)_2CO$) δ 5.29 (1H, t, *J* = 7.9 Hz, C=C**H**), 1.59 (3H, s, C**H**$_3$), 1.51 (3H, s, C**H**$_3$), 0.96 (2H, br s, C**H**$_2$B); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –140.5.

Potassium (*E*)-3-phenylprop-2-en-1-yltrifluoroborate (316):



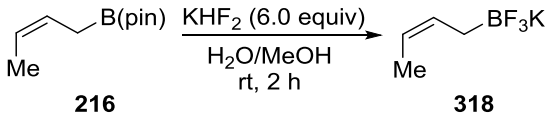
To a solution of cinnamyl alcohol (536 mg, 4.00 mmol) in MeOH (10 mL) and DMSO (10 mL) was added TsOH (19 mg, 0.10 mmol), di-μ-chlorobis(2-[(dimethylamino)methyl]phenyl-C,N)dipalladium(II) (55 mg, 0.10 mmol) and B_2Pin_2 (2.03 g, 8.0 mmol), and the solution was heated at 50 °C for 12 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL), and extracted with Et_2O (3 x 25 mL), and the combined organic layers were dried, and concentrated *in vacuo* to leave the *allyl pinacolboronic ester* which was used immediately in the next step without further purification. The title compound then was prepared according to General Procedure C from the corresponding *allylboronic acid pinacol ester* (488 mg, 2.00 mmol), KF (0.46 g, 8.00 mmol), and L-(+)-tartaric acid (0.62 g, 4.13 mmol) to give *allyltrifluoroborate* **316** (327 mg, 37%) as a white solid that displayed spectroscopic data consistent with those reported previously.[226] ^{1}H NMR (400 MHz $(CD_3)_2CO$) δ 7.26 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.19 (2H, t, *J* = 7.9 Hz, Ar**H**), 7.02 (1H, t, *J* = 7.9 Hz, Ar**H**), 6.51 (1H, td, *J* = 15.8, 7.8 Hz, C**H**=CH), 6.08 (1H, d, *J* = 15.8 Hz, CH=C**H**), 1.25 (2H, br s, C$\mathbf{H}_2$B); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –139.9.

Potassium (*E*)-2-hexen-1-yltrifluoroborate (317)



To a solution of *trans*-2-hexen-1-ol (400 mg, 4.00 mmol) in MeOH (10 mL) and DMSO (10 mL) was added TsOH (19 mg, 0.10 mmol), di-μ-chlorobis(2-[(dimethylamino)methyl]phenyl-C,N)dipalladium(II) (55 mg, 0.10 mmol) and B_2Pin_2 (2.03 g, 8.0 mmol), and the solution was heated at 50 °C for 12 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL), and extracted with Et_2O (3 x 25 mL), and the combined organic layers were dried, and concentrated *in vacuo* to leave the *allyl pinacolboronic ester* which was used immediately in the next step without further purification. To a solution of the above-mentioned *allyl pinacolboronic ester* in H_2O (15 mL) and MeOH (15 mL) was added KHF_2 (1.83 g, 24.0 mmol) and the mixture was stirred at room temperature for 2 h. The reaction was concentrated *in vacuo* and the resulting solid was extracted with acetone (3 x 25 mL). The combined acetone extracts were filtered and concentrated *in vacuo*. The residue was stirred with Et_2O (10 mL) and the resulting suspension was filtered to leave the *potassium allyltrifluoroborate* **317** (640 mg, 84%) as a white solid that displayed spectroscopic data consistent with those observed previously.[226] ^{1}H NMR (400 MHz $(CD_3)_2CO$) δ 5.54 (1H, dt, *J* = 15.0, 7.4 Hz, C**H**=CH), 5.08 (1H, dt, *J* = 15.0, 6.8 Hz, CH=C**H**), 1.88 (2H, q, *J* = 7.4 Hz, C**H**$_2$CH), 1.30 (2H, m, C**H**$_2$CH$_2$), 1.02 (2H, br s, C**H**$_2$B), 0.85 (3H, t, *J* = 7.4 Hz, C**H**$_3$CH$_2$); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –141.0.

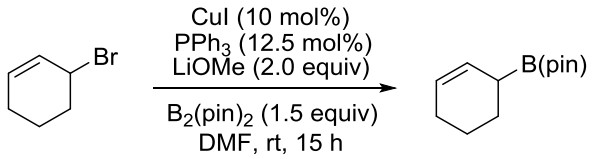
Potassium (*Z*)-2-butenyltrifluoroborate (318):



To a solution of (*Z*)-2-buten-1-yl-boronic acid pinacol ester (273 mg, 1.50 mmol) in MeOH (10 mL) and H_2O (10 mL) was added KHF_2 (702 mg, 9.00 mmol) and the mixture was stirred at room temperature for 2 h. The reaction was concentrated *in vacuo* and the resulting solid was extracted with acetone (3 x 25 mL). The combined acetone extracts were filtered and concentrated *in vacuo*. The residue was stirred with Et_2O (10 mL) and the resulting suspension was filtered to leave the *potassium*

allyltrifluoroborate 318 (201 mg, 83%) as a white solid that displayed spectroscopic data consistent with those reported previously.[228]

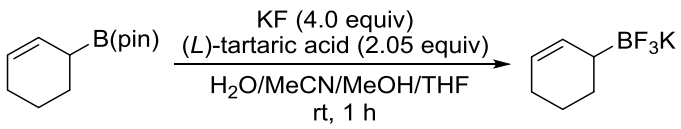
2-(cyclohex-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (320):



319 **320**

To a solution of copper(I) iodide (96 mg, 0.5 mmol), PPh_3 (172 mg, 0.65 mmol), LiOMe (400 mg, 10 mmol), B_2Pin_2 (2.0 g, 7.5 mmol) in DMF (10 mL) at room temperature was added cyclohex-2-enyl bromide (0.57 mL, 5.0 mmol). The mixture was stirred for 15 hours then extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *allylboronic ester* **320** (996 mg, 95%) as a colourless oil that displayed spectroscopic data consistent with those reported previously.[153] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.65 (2H, m, C**H**=C**H**), 2.00-1.94 (2H, m, C$\mathbf{H}_2$), 1.79-1.62 (5H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$C**H**), 1.24 (12H, s, 2 x (C$\mathbf{H}_3$)$_2$C); HRMS (ESI) Exact mass calcd for $C_{12}H_{21}BO_2$ $[M]^+$: 208.1635, found: 208.1633.

Potassium (2-Cyclohexenyl)trifluoroborate (321):



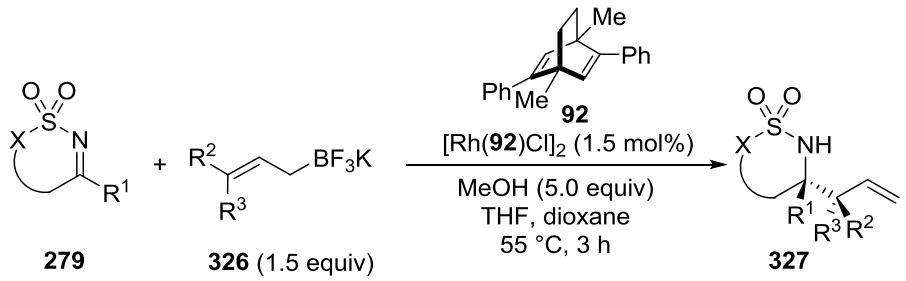
320 **321**

The title compound was prepared according to General Procedure C from the corresponding *allylboronic pinacol ester* (416 mg, 2.0 mmol), KF (0.46 g, 8.0 mmol), and L-(+)-tartaric acid (0.615 g, 4.1 mmol) to give *allyltrifluoroborate* **321** (290 mg, 78%) as a white solid. m.p. >300 °C (acetone); ^{1}H NMR (400 MHz CD_3CN) δ 5.80 (1H, d, *J* = 10.1 Hz, C**H**=CH), 5.34 (1H, dq, *J* = 10.1, 3.4 Hz,

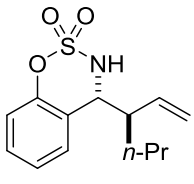
CH=C**H**), 1.87-1.85 (2H, m, C$\mathbf{H}_2$), 1.72-1.70 (1H, m, C$\mathbf{H}_2$), 1.63-1.61 (1H, m, C$\mathbf{H}_2$), 1.41-1.34 (2H, m, C$\mathbf{H}_2$), 1.09 (1H, br s, C**H**B); ^{19}F NMR (376 MHz, CD_3CN) δ –146.5

1.1.5 Synthesis and Characterisation of Allylation Products with Higher Degrees of Substitution

General Procedure D: **Enantioselective Allylation of Cyclic Imines with Various Allyltrifluoroborates**



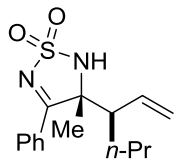
A Schlenk tube containing the appropriate cyclic imine (0.30 mmol) and the appropriate potassium allyltrifluoroborate (0.45 mmol) was flushed with nitrogen before anhydrous THF (3 mL) was added. To this solution was added a stock solution of the rhodium–chiral diene complex (11.5 mM in anhydrous dioxane, 0.39 mL, 0.0045 mmol = 3 mol% Rh), and MeOH (60 μL, 1.50 mmol), and the resulting mixture was heated to 55 °C for 15 h. The reaction was cooled to room temperature, diluted with Et_2O (50 mL), filtered through a short plug of silica using Et_2O as eluent, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the allylated product.



323

(*R*)-4-[(*R*)-Hex-1-en-3-yl]-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (323). The title compound was prepared according to General Procedure D from benzoxathiazine-2,2-dioxide **89a** (53 mg, 0.30 mmol) and the potassium allyltrifluoroborate **317** (86 mg, 0.45 mmol) and was purified by column chromatography (90:10 hexane:EtOAc) to give *sulfonamide* **323** (61 mg, 76%) as an 11:1 inseparable mixture of diastereomers and an orange solid. R_F = 0.45 (80:20 hexane:EtOAc); [α]

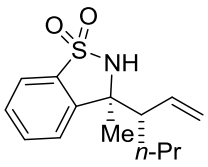
$[\alpha]_D^{20}$ +167.3 (*c* 0.49, $CHCl_3$); m.p. 48-50 °C (Et_2O); IR (film) 1485, 1452, 1373, 1198, 1022, 760, 664, 631, 565 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (2H, m, Ar**H**), 7.24-7.21 (1H, m, Ar**H**), 7.05-7.03 (1H, m, Ar**H**), 5.59 (1H, ddd, *J* = 17.1, 10.8, 6.0 Hz, C**H**=CH_2), 5.28 (1H, d, *J* = 10.8, =C**H**$_2$), 5.21 (1H, dt, *J* = 17.1, 1.3 Hz, =C**H**$_2$), 4.92 (1H, dd, *J* = 9.8, 3.3 Hz, NC**H**), 4.35 (1H, d, *J* = 9.8 Hz, N**H**), 3.12-3.07 (1H, m, C**H**CH=), 1.75-1.63 (2H, m, C**H**$_2$), 1.55-1.43 (2H, m, C**H**$_2$), 1.02 (3H, t, *J* = 7.3 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 152.0 (C), 134.5 (CH), 129.5 (CH), 125.9 (CH), 125.4 (CH), 121.5 (C), 120.0 (CH_2), 119.2 (CH), 58.8 (CH), 43.4 (CH), 31.0 (CH_2), 20.4 (CH_2), 14.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{13}H_{18}NO_3S$ $[M+H]^+$: 268.1002, found 268.1007. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 9.0 min, t_r (major) = 12.1 min; 99% ee.



324

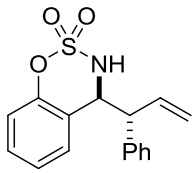
3*R*-3-[(3*R*)-Hex-1-en-3-yl]-3-methyl-4-phenyl-2,3-dihydro-[1,2,5]thiadiazole 1,1-dioxide (324). The title compound was prepared according to General Procedure D from [1,2,5]thiadiazole 1,1-dioxide **276a** (62 mg, 0.30 mmol) and the potassium allyltrifluoroborate **317** (86 mg, 0.45 mmol) and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **324** (53 mg, 61%) as a 17:1 inseparable mixture of diastereomers and an orange oil. R_F = 0.40 (80:20 hexane:EtOAc); $[\alpha]_D^{20}$ −65.6 (*c* 0.34, $CHCl_3$); IR (film) 3255 (NH) 1558, 1314, 1152, 1001, 997, 922, 822, 689, 652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (2H, dd, *J* = 8.5, 1.1 Hz, Ar**H**), 7.64-7.60 (1H, m, Ar**H**), 7.52-7.49 (2H, m, Ar**H**), 5.57 (1H, app dt, *J* = 17.0, 9.9 Hz, C**H**=CH_2), 4.97 (1H, dd, *J* = 10.3, 1.5 Hz, =C**H**$_2$), 4.57 (1H, dd, *J* = 17.0, 1.5 Hz, =C**H**$_2$), 4.57 (1H, s, N**H**), 2.64-2.59 (1H, m, C**H**CH=), 1.88 (3H, s, C**H**$_3$CNH), 1.68 (1H, ddt, *J* = 9.9, 6.6, 3.1 Hz, C**H**$_2$), 1.49-1.33 (2H, m, C**H**$_2$), 1.22-1.15 (1H, m, C**H**$_2$), 0.93 (3H, t, *J* = 7.3 Hz, CH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 181.6 (C), 134.9 (CH), 133.6 (CH), 130.3 (2 x CH), 129.4 (C), 128.9 (2 x CH), 119.6 (CH_2), 76.1 (C), 51.6 (CH), 30.7 (CH_2), 25.1 (CH_3), 20.3 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{15}H_{21}N_2O_2S$ $[M+H]^+$: 293.1318, found 293.1315. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H

column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (minor) = 21.0 min, t_r (major) = 43.2 min; 99% ee.



325

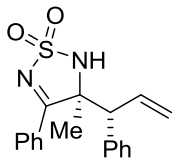
(*S*)-3-Methyl-3-[(*S*)-1-hex-1-en-3-yl]-2,3-dihydro-[1,2]-benzothiazole-1,1-dioxide (325) The title compound was prepared according to General Procedure D from imine **269a** (54 mg, 0.30 mmol) and allyltrifluoroborate **317** (86 mg, 0.45 mmol), using ligand *ent*-**92** and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **325** (38 mg, 48%) as a yellow oil. R_f = 0.38 (70:30 hexanes:EtOAC); $[\alpha]_D^{20}$ –23.3 (*c* 0.60, $CHCl_3$); IR 3219 (NH), 1389, 1377, 1271, 1238, 1153, 1134, 918, 770, 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.62 (1H, td, *J* = 7.8, 1.1 Hz, Ar**H**), 7.52 (1H, td, *J* = 7.7, 0.9 Hz, Ar**H**), 7.37 (1H, d, *J* = 7.9 Hz, Ar**H**), 5.59 (1H, app dt, *J* = 17.0, 10.1 Hz, C**H**=CH_2), 5.09 (1H, dd, *J* = 10.3, 1.8 Hz, =C**H**$_2$), 4.99 (1H, dd, *J* = 17.1, 1.7 Hz, =C**H**$_2$), 4.61 (1H, s, N**H**), 2.43-2.37 (1H, m, C**H**C=CH_2), 1.70-1.64 (1H, m, C**H**$_2$$CH_2CH_3$), 1.63 (3H, s, CC**H**$_3$), 1.46-1.35 (1H, m, C**H**$_2$$CH_2CH_3$), 1.30-1.21 (1H, m, C**H**$_2$$CH_3$), 1.20-1.10 (1H, m, C**H**$_2$$CH_3$), 0.88 (3H, t, *J* = 7.3 Hz, CH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 143.6 (C), 136.8 (CH), 134.8 (C), 132.9 (CH), 129.2 (CH), 124.0 (CH), 121.4 (CH), 119.8 (CH_2), 65.9 (C), 53.7 (CH), 30.8 (CH_2), 26.0 (CH), 20.6 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{14}H_{20}NO_2S$ $[M+H]^+$: 266.1209, found: 266.1208; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 211 nm, 25 °C); t_r (major) = 11.6 min, t_r (minor) = 18.6 min; 98% ee.



328

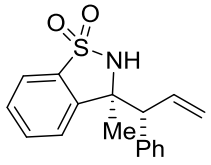
(*S*)-4-[(*R*)-1-phenylprop-2-en-1-yl]-3,4-dihydro-[1,2,3]-benzoxathiazine-2,2-dioxide (328). The title compound was prepared according to General Procedure D from imine **89a** (55 mg, 0.30 mmol) and allyltrifluoroborate **316** (101 mg, 0.45 mmol) using ligand *ent*-**92** and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **328** (81 mg, 90%) as a yellow oil. R_f = 0.50 (70:30 hexanes:EtOAc); $[\alpha]_D^{20}$ –85.0 (*c* 0.80, $CHCl_3$); IR 3273 (NH), 1414, 1364, 1321, 1165, 1103, 874, 822, 756, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ

7.42-7.37 (2H, m, Ar**H**), 7.35-7.31 (4H, m, Ar**H**), 7.12 (1H, td, *J* = 7.5, 1.2 Hz, Ar**H**), 7.08-7.05 (2H, m, Ar**H**), 6.04 (1H, ddd, *J* = 17.4, 10.4, 7.2 Hz, C**H**=CH_2), 5.34 (1H, dt, *J* = 10.4, 1.3 Hz, =C**H**$_2$), 5.16-5.12 (1H, m, C**H**NH), 5.11 (1H, dt, *J* = 17.3, 1.3 Hz, =C**H**$_2$), 4.75 (1H, d, *J* = 7.4 Hz, N**H**) 4.24 (1H, dd, *J* = 13.3, 6.6 Hz, C**H**Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 151.5 (C), 138.6 (C), 134.8 (CH), 129.7 (CH), 129.0 (2 x CH), 128.6 (2 x CH), 127.7 (CH), 126.9 (CH), 125.3 (CH), 121.5 (C), 121.1 (CH_2), 119.2 (CH), 60.2 (CH), 52.5 (CH); HRMS (ESI) Exact mass calcd for $C_{16}H_{16}NO_3S$ $[M+H]^+$: 302.0845, found: 302.0846; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 211 nm, 25 °C); t_r (major) = 13.8 min, t_r (minor) = 15.8 min; 95% ee.



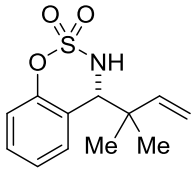
329

(*S*)-3-Methyl-4-phenyl-3[(*R*)-1-Phenylprop-2-en-1-yl]-2,3-dihydro-[1,2,5]-thiadiazole-1,1-dioxide (329). The title compound was prepared according to General Procedure D from imine **276a** (62 mg, 0.30 mmol) and allyltrifluoroborate **316** (101 mg, 0.45 mmol) using ligand *ent*-**92** and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **329** (84 mg, 86%) as a colourless gum. R_f = 0.26 (70:30 hexanes:EtOAc); $[\alpha]_D^{20}$+52.7 (*c* 2.20, $CHCl_3$); IR 3242 (NH), 1558, 1315, 1175, 1146, 995, 820, 710, 689, 652 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12-8.08 (2H, m, Ar**H**), 7.70-7.65 (1H, m, Ar**H**), 7.59-7.54 (2H, m, Ar**H**), 7.42-7.38 (4H, m, Ar**H**), 7.35-7.31 (1H, m, Ar**H**), 6.24 (1H, ddd, *J* = 17.0, 10.1, 9.4 Hz, C**H**=CH_2), 5.03 (1H, dd, *J* = 10.2, 1.2 Hz, =C**H**$_2$), 4.97 (1H, d, *J* = 17.0 Hz, =C**H**$_2$), 4.48 (1H, s, N**H**), 3.88 (1H, d, *J* = 9.3 Hz, C**H**Ph), 1.67 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 181.0 (C), 138.1 (C), 134.4 (CH), 133.7 (CH), 130.2 (2 x CH), 129.4 (2 x CH), 129.3 (C), 129.1 (2 x CH), 128.9 (2 x CH), 128.0 (CH_2), 119.5 (CH), 75.9 (C), 57.2 (CH), 26.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{19}N_2O_2S$ $[M+H]^+$: 327.1162, found: 327.1160; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 23.9 min, t_r (minor) 25.2 min; 95% ee.



330

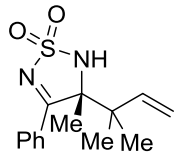
(*S*)-3-Methyl-3-[(*R*)-1-phenylprop-2-en-1-yl]-2,3-dihydro-[1,2]-benzothiazole-1,1-dione (330). The title compound was prepared according to General Procedure D from imine **269a** (54 mg, 0.30 mmol) and allyltrifluoroborate **316** (100 mg, 0.45 mmol) using ligand *ent*-**92** and was purified by column chromatography (80:20 hexanes:EtOAc) to give *sulfonamide* **330** (77 mg, 865) a gum that solidified on standing to give a white solid. R_f = 0.26 (70:30 hexanes:EtOAc); m.p. 78-79 °C (EtOAc/hexane); $[\alpha]_D^{20}$ –88.6 (*c* 3.70, $CHCl_3$); IR 3233 (NH), 1389, 1373, 1275, 1153, 1132, 930, 891, 756, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.60 (1H, td, *J* = 7.6, 1.3 Hz, Ar**H**), 7.53 (1H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 7.39-7.27 (5H, m, Ar**H**), 7.17 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.17 (1H, ddd, *J* = 17.0, 10.2, 9.1 Hz, C**H**=CH_2), 5.03 (1H, dd, *J* = 10.2, 1.2 Hz, =C**H**$_2$), 4.95 (1H, ddd, *J* = 17.0, 1.4, 1.0 Hz, =C**H**$_2$), 4.52 (1H, s, N**H**), 3.69 (1H, d, *J* = 9.0 Hz, C**H**Ph), 1.51 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 143.0 (C), 139.1 (C), 135.9 (CH), 135.0 (C), 133.0 (CH), 129.3 (CH), 129.3 (2 x CH), 128.6 (2 x CH), 127.6 (CH), 123.8 (CH), 121.4 (CH), 119.2 (CH_2), 66.0 (C), 59.6 (CH), 27.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{18}NO_2S$ $[M+H]^+$: 300.1053, found: 300.1051; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 22.4 min, t_r (minor) = 32.8 min; 91% ee.



331

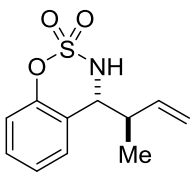
(*R*)-(1,1-Dimethylprop-2-en-1-yl)-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (331). The title compound was prepared according to General Procedure D from benzoxathiazine-2,2-dioxide **89a** (53 mg, 0.30 mmol) and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol) and was purified by column chromatography (80:20 hexanes:EtOAc) to give *sulfonamide* **331** (69 mg, 91%) as an orange oil. R_F = 0.45 (80:20 hexanes:EtOAc); $[\alpha]_D^{20}$ +66.2 (*c* 0.76, $CHCl_3$); IR (film) 2952, 1364, 1183, 1103, 922, 874, 858, 818, 762, 563 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.33 (2H, m, Ar**H**), 7.23-7.19 (1H, m, Ar**H**), 7.10 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.86 (1H, dd, *J* = 17.5, 10.7 Hz, C**H**=CH_2), 5.28 (1H, d, *J* = 10.7 Hz, =C**H**$_2$), 5.22 (1H, d, *J* = 17.5 Hz, =C**H**$_2$), 4.81 (1H, br d, *J* = 3.4 Hz, NC**H**), 4.50

(1H, d, *J* = 4.6 Hz, N**H**), 1.15 (3H, s, C**H**$_3$), 1.10 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 151.7 (C), 143.5 (CH), 129.7 (CH), 129.1 (CH), 125.1 (CH), 121.4 (C), 119.7 (CH), 115.8 (CH_2), 64.7 (CH), 43.1 (C), 23.9 (CH_3), 21.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{12}H_{16}NO_3S$ $[M+H]^+$: 254.0845, found 254.0850. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 210 nm 25 °C); t_r (minor) = 12.1 min, t_r (major) = 20.5 min; 97% ee.



332

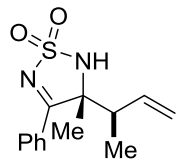
(*R*)-3-Methyl-3-(2-methylbut-3-en-2-yl)-3-methyl-4-phenyl-2,3-dihydro-[1,2,5]thiadiazole 1,1-dioxide (332). The title compound was prepared according to General Procedure D from [1,2,5]thiadiazole 1,1-dioxide **276a** (62 mg, 0.30 mmol) and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol) and was purified by column chromatography (80:20 hexanes:EtOAc) to give *sulfonamide* **332** (63 mg, 755) as an orange solid. R_F = 0.28 (80:20 hexanes:EtOAc); $[\alpha]_D^{20}$ −41.8 (*c* 0.43, $CHCl_3$); m.p. 89-92 °C; IR (film) 3093 (NH), 1585, 1304, 1169, 1140, 1111, 993, 935, 766, 577 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.69 (2H, m, Ar**H**), 7.59-7.56 (1H, m, Ar**H**), 7.49-7.45 (2H, m, Ar**H**), 5.74 (1H, dd, *J* = 17.4, 10.8 Hz, C**H**=CH_2), 5.05 (1H, dd, *J* = 10.8, 0.7 Hz, =C**H**$_2$), 4.97 (1H, dd, *J* = 17.4, 0.7 Hz, =C**H**$_2$), 4.64 (1H, s, N**H**), 1.93 (3H, s, C**H**$_3$CNH), 1.06 (3H, s, C(C**H**$_3$)$_2$), 0.98 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 183.4 (C), 142.2 (CH), 133.0 (C), 132.2 (CH), 129.2 (CH), 128.6 (CH), 115.6 (CH_2), 79.5 (C), 44.3 (C), 23.3 (CH_3), 22.6 (CH_3), 21.9 (CH_3); HRMS Exact mass calcd for $C_{14}H_{19}N_2O_2S$ $[M+H]^+$: 279.1162, found 279.1158; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (minor) = 27.3 min, t_r (major) = 37.6 min; 95% ee.



334

(*R*)-4-[(*R*)-But-3-en-2-yl]-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (334). The title compound was prepared according to General Procedure D from benzoxathiazine-2,2-dioxide **89a** (53 mg, 0.30 mmol) and the potassium allyltrifluoroborate **314** (73 mg, 0.45 mmol) and was purified by column chromatography (80:20

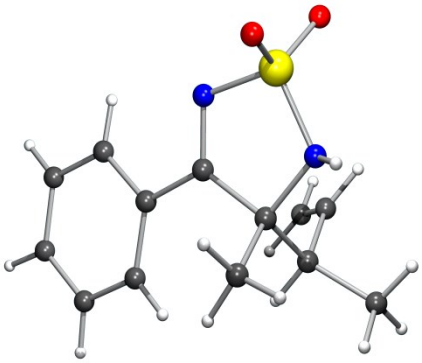
hexanes:EtOAc) to give *sulfonamide* **334** (65 mg, 91%) as an orange oil. R_F = 0.53 (80:20 hexanes:EtOAc); $[\alpha]_D^{20}$ +85.4 (*c* 0.59, $CHCl_3$); IR (film) 3271 (NH), 1452, 1416, 1368, 1196, 1171, 881, 833, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (2H, m, Ar**H**), 7.26-7.22 (1H, m, Ar**H**), 7.06-7.03 (1H, m, Ar**H**), 5.67 (1H, ddd, *J* = 17.4, 10.8, 4.7 Hz, C**H**=CH_2), 5.32-5.26 (2H, m, =C**H**$_2$), 4.84 (1H, dd, *J* = 9.8, 3.3 Hz, NC**H**), 4.31 (1H, d, *J* = 9.7 Hz, N**H**), 3.36-3.33 (1H, m, C**H**CH_3), 1.36 (3H, d, *J* = 6.9 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 151.9 (C), 135.1 (CH), 129.6 (CH), 125.9 (CH), 125.5 (CH), 121.2 (C), 119.6 (CH_2), 119.2 (CH), 60.6 (CH), 38.0 (CH), 14.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{11}H_{14}NO_3S$ $[M+H]^+$: 240.0689, found: 240.0694; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 15.6 min, t_r (major) = 26.4 min; 99% ee.

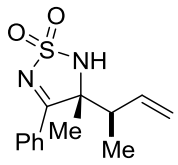


335

3*R*-3-[(*R*)-But-3-en-2-yl]-3-methyl-4-phenyl-2,3-dihydro-[1,2,5]thiadiazole 1,1-dioxide (335). The title compound was prepared according to General Procedure D from [1,2,5]thiadiazole 1,1-dioxide **276a** (62 mg, 0.30 mmol) and the potassium allyltrifluoroborate **314** (73 mg, 0.45 mmol) and was purified by column chromatography (80:20 hexanes:EtOAc) to give *sulfonamide* **335** (54 mg, 68%) as a white solid. R_F = 0.29 (80:20 hexanes:EtOAc); m.p. 128-130 °C (Et_2O); $[\alpha]_D^{20}$ −19.0 (*c* 0.42, $CHCl_3$); IR (film) 2924 (NH), 1555, 1300, 1149, 997, 926, 831, 781, 704, 656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05-8.01 (2H, m, Ar**H**), 7.65-7.61 (1H, m, Ar**H**), 7.53-7.49 (2H, m, Ar**H**), 5.65 (1H, ddd, *J* = 17.2, 10.4, 7.9 Hz, C**H**=CH_2), 5.00 (1H, d, *J* = 10.4 Hz, =C**H**$_2$), 4.78 (1H, dt, *J* = 17.1, 1.1 Hz, =C**H**$_2$), 4.61 (1H, s, N**H**), 2.94 (1H, quint, *J* = 6.9 Hz, C**H**CH_3), 1.87 (3H, s, C**H**$_3$CNH), 1.23 (3H, d, *J* = 6.8 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 182.0 (C), 136.3 (CH), 133.7 (CH), 130.1 (2 x CH), 129.2 (C), 129.0 (2 x CH), 118.4 (CH_2), 76.0 (C), 45.0 (CH), 25.1 (CH_3), 14.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{13}H_{17}N_2O_2S$ $[M+H]^+$: 265.1005, found 265.1002; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (minor) = 14.9 min, t_r (major) = 26.5 min; 97% ee.

Slow evaporation of a solution of **335** in Et_2O/petrol gave crystals that were suitable for X-ray diffraction:





335

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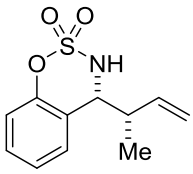
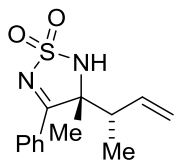


336

(*R*)-4-[(*S*)-But-3-en-2-yl]-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (336). The title compound was prepared according to General Procedure D from benzoxathiazine-2,2-dioxide **89a** (53 mg, 0.30 mmol) and the potassium allyltrifluoroborate **318** (73 mg, 0.45 mmol) and was purified by column chromatography (80:20 hexanes:EtOAc) to give *sulfonamide* **336** (64% 89%) as a 6:1 inseparable mixture of diastereomers and an orange solid. R_F = 0.38 (80:20 hexanes:EtOAc); m.p. 79-81 °C (Et_2O); $[\alpha]_D^{20}$ +85.4 (*c* 0.52, $CHCl_3$); IR (film) 3287 (NH), 1420, 1369, 1194, 1172, 881, 829, 760, 554 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (1H, m, Ar**H**), 7.28-7.20 (2H, m, Ar**H**), 7.06 (1H, dd, *J* = 8.3, 0.9 Hz, Ar**H**), 5.95 (1H, ddd, *J* = 16.9, 10.5, 6.0 Hz, C**H**=CH_2), 5.30-5.23 (2H, m, =C**H**$_2$), 4.87 (1H, dd, *J* = 7.5, 4.3 Hz, C**H**N), 4.48 (1H, d, *J* = 7.2 Hz, N**H**), 3.16-3.10 (2H, m, C**H**$_2$CH=), 1.03 (3H, d, *J* = 7.0 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 151.8 (C), 138.4 (CH), 129.5 (CH), 126.3 (CH), 125.4 (CH), 121.5 (C), 119.2 (CH), 117.3 (CH_2), 60.4 (CH), 39.8 (CH), 12.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{11}H_{14}NO_3S$ $[M+H]^+$: 240.0689, found: 240.0681; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:0 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 30.5 min, t_r (major) = 54.7 min; 99% ee.

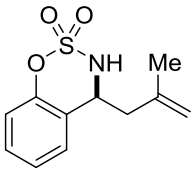


337

3*R*-3-[(*R*)-But-3-en-2-yl]-3-methyl-4-phenyl-2,3-dihydro-[1,2,5]thiadiazole 1,1-dioxide (337). The title compound was prepared according to a modification of General Procedure D (in

that the reaction time was 12 h) from the [1,2,5]thiadiazole 1,1-dioxide **276a** (62 mg, 0.30 mmol) and the potassium allyltrifluoroborate **318** (73 mg, 0.45 mmol) was purified by column chromatography (80:20 hexanes:EtOAc) to give *sulfonamide* **337** (70 mg, 89%) as an orange oil. R_F = 0.25 (80:20 hexanes:EtOAc); $[\alpha]_D^{20}$ –92.5 (*c* 0.61, $CHCl_3$); IR (film) 3258 (NH), 1557, 1314, 1188, 1167, 995, 822, 700, 652, 579 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10-8.06 (2H, m, Ar**H**), 7.68-7.65 (1H, m, Ar**H**), 7.57-7.53 (2H, m, Ar**H**), 5.83 (1H, ddd, *J* = 17.2, 10.3, 8.0 Hz, C**H**=CH_2), 5.31-5.24 (2H, m, =C**H**$_2$), 4.33 (1H, s, N**H**), 2.90 (1H, quint, *J* = 6.8 Hz, C**H**CH_3), 1.81 (3H, s, C**H**$_3$CNH), 0.97 (3H, d, *J* = 6.8 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 181.1 (C), 137.1 (CH), 134.0 (CH), 130.0 (2 x CH), 129.2 (2 x CH), 129.0 (C), 119.0 (CH_2), 75.8 (C), 45.7 (CH), 26.5 (CH_3), 14.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{13}H_{17}N_2O_2S$ $[M+H]^+$: 265.1005, found 265.1006. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C;); t_r (minor) = 14.0 min, t_r (major) = 18.7 min; 99% ee.

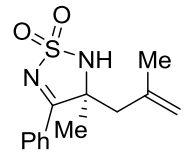
(*S*)-4-(2-Methylprop-2-en-1-yl)-3,4-dihydro-[1,2,3]-benzoxathiazine-2,2-dioxide



343

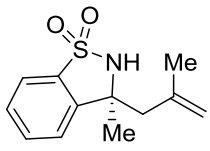
(343). The title compound was prepared according to General Procedure D, but using toluene (2.7 mL) and *i*-PrOH (0.3 mL) rather than THF/MeOH from imine **89a** (55 mg, 0.30 mmol) and allyltrifluoroborate **310** (73 mg, 0.45 mmol) using ligand *ent*-**92** and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **343** (47 mg, 65%) as a colourless oil. R_f = 0.56 (70:30 hexanes:EtOAc); $[\alpha]_D^{20}$ –45.2 (*c* 0.85, $CHCl_3$); IR 3273 (NH), 1406, 1360, 1188, 1165, 1103, 891, 816, 758, 675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.30 (1H, m, Ar**H**), 7.28-7.26 (1H, m, Ar**H**), 7.24-7.20 (1H, m, Ar**H**), 7.04 (1H, dd, *J* = 8.2, 1.1 Hz, Ar**H**), 5.01 (1H, d, *J* = 0.5 Hz, =C**H**$_2$), 4.96 (1H, app td, *J* = 8.6, 4.7 Hz, C**H**NH), 4.91 (1H, s, =C**H**$_2$), 4.63 (1H, d, *J* = 7.8 Hz, N**H**), 2.88 (1H, dd, *J* = 14.5, 4.7 Hz, C**H**$_2$), 2.69 (1H, ddd, *J* = 14.5, 9.2, 0.7 Hz, C**H**$_2$), 1.76 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 151.0 (C), 139.9 (C), 129.5 (CH), 126.3 (CH), 125.4 (CH), 122.4 (C), 119.1 (CH), 116.2 (CH_2), 54.4 (CH), 42.6 (CH_2), 22.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{11}H_{13}NO_3S$ [M+Na]+: 262.0508, found:

262.0509; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 20.2 min, t_r (minor) = 23.3 min; 79% ee.



344

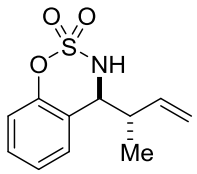
(*S*)-3-Methyl-3-(2-methylprop-2-en-1-yl)-4-phenyl-2,3-dihydro-[1,2,5]-thiadiazole-1,1-dioxide (344) The title compound was prepared according to General Procedure D from imine **276a** (62 mg, 0.30 mmol) and allyltrifluoroborate **309** (73 mg, 0.45 mmol) using ligand *ent*-**92** and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **344** (71 mg, 90%) as a yellow oil. R_f = 0.26 (70:30 hexanes:EtOAc); $[\alpha]_D^{20}$ –25.0 (*c* 0.80, $CHCl_3$); IR 3300 (NH), 1553, 1294, 1175, 1144, 907, 824, 783, 692, 654 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (2H, dd, *J* = 8.5, 1.2 Hz, Ar**H**), 7.67-7.62 (1H, m, Ar**H**), 7.57-7.52 (2H, m, Ar**H**), 5.08-5.04 (1H, m, =C**H**$_2$), 4.87 (1H, s, =C**H**$_2$), 4.74 (1H, s, N**H**), 2.98 (1H, d, *J* = 14.5 Hz, C**H**$_2$), 2.73 (1H, dd, *J* = 14.5, 0.6 Hz, C**H**$_2$), 1.84 (3H, s, C**H**$_3$C=), 1.67 (3H, s, C**H**$_3$CNH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 182.3 (C), 139.5 (C), 133.8 (CH), 130.2 (2 x CH), 129.2 (2 x CH), 128.9 (C), 118.6 (CH_2), 71.6 (C), 46.7 (CH_2), 27.5 (CH_3), 23.4 (CH_3); HRMS (ESI) Exact mass calcd for $C_{13}H_{17}N_2O_2S$ $[M+H]^+$: 265.1005, found: 265.1000; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 16.1 min, t_r (minor) = 19.2 min; 97% ee.



345

(*S*)-3-Methyl-3-(2-methylprop-2-en-1-yl)-2,3-dihydro-[1,2]-benzothiazole-1,1-dione (345). The title compound was prepared according to General Procedure D from imine **269a** (54 mg, 0.30 mmol) and allyltrifluoroborate **309** (73 mg, 0.45 mmol) using ligand *ent*-**92** and was purified by column chromatography (90:10 hexanes:EtOAc) to give a *sulfonamide* **345** (40 mg, 56%) as a yellow gum. R_f = 0.31 (30% EtOAc/hexane); $[\alpha]_D^{20}$ –61.8 (*c* 0.55, $CHCl_3$); IR 3273 (NH), 1369, 1277, 1263, 1163, 1150, 1128, 1057, 893, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (1H, t, *J* = 14.1 Hz, Ar**H**), 7.64 (1H, td, *J* = 7.7, 0.9 Hz, Ar**H**), 7.53 (1H, td, *J* = 7.6, 0.6 Hz, Ar**H**), 7.43 (1H, d, *J* = 7.8 Hz, Ar**H**), 5.02-5.01 (1H, m, =C**H**$_2$), 4.84 (1H, s, =C**H**$_2$),

4.75 (1H, s, N**H**), 2.74 (1H, d, *J* = 13.9 Hz, C**H**$_2$), 2.59 (1H, d, *J* = 13.9 Hz, C**H**$_2$), 1.65 (3H, s, C**H**$_3$), 1.57 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 145.4 (C), 140.6 (C), 135.4 (C), 133.1 (CH), 129.2 (CH), 123.2 (CH), 121.4 (CH), 117.8 (CH_2), 62.5 (C), 48.9 (CH_2), 29.0 (CH_3), 23.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{12}H_{16}NO_2S$ $[M+H]^+$: 238.0896, found: 238.0893; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 211 nm, 25 °C); t_r (major) = 20.6 min, t_r (minor) = 25.6 min; 98% ee.



ent-**334**

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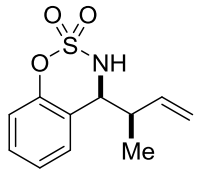
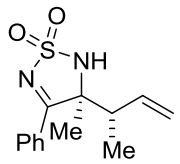


ent-**336**

(*S*)-4-[(*S*)-But-3-en-2-yl]-3,4-dihydro-[1,2,3]-benzoxathiazine-2,2-dioxide (*ent*-334) and (*S*)-4-[(*R*)-but-3-en-2-yl]-3,4-dihydro-[1,2,3]-benzoxathiazine-2,2-dioxide (*ent*-336). The title compounds were prepared according to General Procedure D using imine **89a** (55 mg, 0.30 mmol) and allyltrifluoroborate **308** (73 mg, 0.45 mmol) using ligand *ent*-**92**. Purification by column chromatography (80:20 hexanes:EtOAc) gave a 2:1 inseparable mixture of the *sulfonamides ent*-**334** and *ent*-**336** (43 mg, 60%) as a yellow oil that displayed spectroscopic data consistent with those reported previously (**334** and **336**) R_f = 0.52 (70:30 hexanes:EtOAc). Data for *ent*-**334**: Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 225 nm, 25 °C); t_r (major) = 18.5 min, t_r (minor) = 38.6 min; 93% ee. Data for *ent*-**336**: Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 225 nm, 25 °C); t_r (major) = 21.7 min, t_r (minor) = 43.0 min; 97% ee.



ent-**335**

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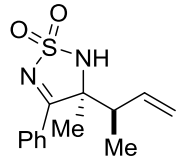
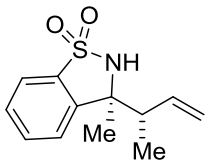


ent-**337**

3(*S*)-3-[(*S*)-But-3-en-2-yl]-3-methyl-4-phenyl-2,3-dihydro-[1,2,5]-thiadiazole 1,1-dioxide (*ent*-335) and 3(*S*)-3-[(*R*)-but-3-en-2-yl]-3-methyl-4-phenyl-2,3-dihydro-[1,2,5]-thiadiazole-1,1-dioxide (*ent*-337). The title compounds were prepared according to General Procedure D using imine **276a** (62 mg, 0.30 mmol) and allyltrifluoroborate **308** (73 mg, 0.45 mmol) using ligand *ent*-**92**. Purification by column chromatography (90:10 hexanes:EtOAc) gave *sulfonamide* ent-**337** (13 mg, 16%) as a yellow oil followed by the *sulfonamide* ent-**335** (38 mg, 48%) as a yellow oil that displayed spectroscopic data consistent with those reported previously (**335** and **337**). Both *ent*-**335** and *ent*-**337** were contaminated with small quantities (<10%) of each other. Data for *ent*-**335**: R_f = 0.22 (70:30 hexanes:EtOAc); $[\alpha]_D^{20}$+23.0 (*c* 1.00, $CHCl_3$); Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 13.0 min, t_r (minor) = 22.2 min; 97% ee. Data for *ent*-**337**: R_f = 0.30 (30% EtOAc/hexane); $[\alpha]_D^{20}$+16.6 (*c* 0.30, $CHCl_3$); Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 11.0 min, t_r (minor) = 17.3 min; 91% ee.



346

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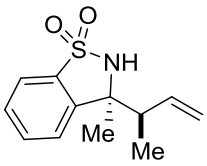
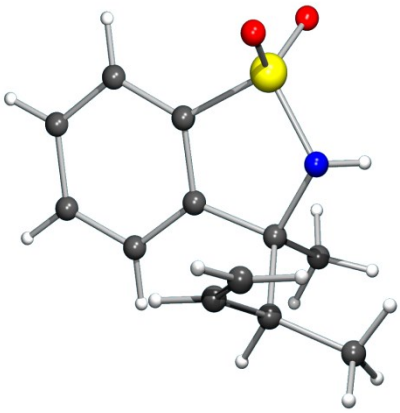


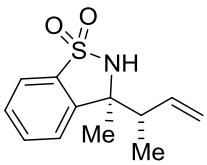
347

(*S*)-3-Methyl-3-[(*S*)-but-3-en-1-yl)-2,3-dihydro-[1,2]-benzothiazole-1,1-dione (346) and (*S*)-3-methyl-3-[(*R*)-but-3-en-1-yl)-2,3-dihydro-[1,2]-benzothiazole-1,1-dione (347). The title compounds were prepared according to General Procedure D using imine **269a (**54 mg, 0.30 mmol) and allyltrifluoroborate **308** (73 mg, 0.45 mmol) using ligand *ent*-**92**. Purification by column chromatography (90:10 hexanes:EtOAc) gave the *sulfonamide* **346** (47 mg, 66%) as a white solid followed by *sulfonamide* **347** (17 mg, 24%) as a white solid. Recrystallization of **346** from Et_2O gave colourless crystals, which enabled the stereochemistry to be determined by X-ray crystallography. Data for **346**: R_f = 0.33 (70:30 hexanes:EtOAc); m.p. 72-74 °C (Et_2O); $[\alpha]_D^{20}$–67.8 (*c* 1.15, $CHCl_3$); IR 3250 (NH), 1267, 1234, 1157, 1134, 1125, 891, 766, 718, 586 cm^{-1}; ^1H NMR (500 MHz,

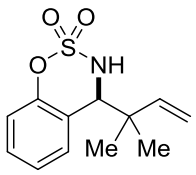
$CDCl_3$) δ 7.75 (1H, d, *J* = 7.8, Ar**H**), 7.62 (1H, td, *J* = 7.8, 1.1 Hz, Ar**H**), 7.52 (1H, td, *J* = 7.8, 0.9 Hz, Ar**H**), 7.37 (1H, d, *J* = 5.7 Hz, Ar**H**), 5.71 (1H, ddd, *J* = 16.6, 11.0, 7.9 Hz, C**H**=CH_2), 5.08-5.02 (2H, m, =C**H**$_2$), 4.64 (1H, s, N**H**), 2.74-2.67 (1H, m, C**H**CH_3), 1.63 (3H, s, CC**H**$_3$) 1.17 (3H, d, *J* = 6.9 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 143.8 (C), 138.1 (CH), 135.2 (C), 133.0 (CH), 129.2 (CH), 123.7 (CH), 121.4 (CH), 117.9 (CH_2), 65.9 (C), 47.0 (CH), 26.0 (CH_3), 14.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{12}H_{16}NO_2S$ $[M+H]^+$: 238.0896, found: 238.0898; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 211 nm, 25 °C); t_r (major) = 15.0 min, t_r (minor) = 22.5 min; 98% ee. Data for **347**: R_f = 0.29 (70:30 hexanes:EtOAc); m.p. 134-136 °C (Et_2O); $[\alpha]_D^{20}$ –65.2 (*c* 0.50, $CHCl_3$); IR 3283 (NH), 1366, 1273, 1234, 1177, 1152, 1134, 934, 764, 590 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.66 (1H, td, *J* = 7.8, 1.1 Hz, Ar**H**), 7.55 (1H, td, *J* = 7.8, 0.9 Hz, Ar**H**), 7.37 (1H, d, *J* = 7.9 Hz, Ar**H**), 5.85 (1H, ddd, *J* = 17.1, 10.3, 8.4 Hz, C**H**=CH_2), 5.24 (1H, dd, *J* = 10.3, 1.0 Hz, =C**H**$_2$), 5.22-5.17 (1H, m, =C**H**$_2$), 4.33 (1H, s, N**H**), 2.67-2.61 (1H, m, C**H**CH_3), 1.62 (3H, s, CC**H**$_3$), 0.87 (3H, d, *J* = 6.8 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 143.7 (C), 138.2 (CH), 135.2 (C), 133.3 (CH), 129.3 (CH), 123.2 (CH), 121.5 (CH), 118.1 (CH_2), 66.0 (C), 47.3 (CH), 27.7 (CH_3), 15.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{12}H_{16}NO_2S$ $[M+H]^+$: 238.0896, found: 238.0897; Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 211 nm, 25 °C); t_r (major) = 13.6 min, t_r (minor) = 22.2 min; 98% ee.

Slow evaporation of a solution of **346** in Et_2O/petrol gave crystals that were suitable for X-ray diffraction:



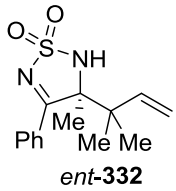


346
CCDC = 948887



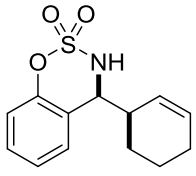
ent-**331**

(*S*)-(2-Methylbut-3-en-2-yl)-3,4-dihydro-[1,2,3]-benzoxathiazine-2,2-dioxide (*ent*-331). The title compound was prepared according to General Procedure D from imine **89a** (55 mg, 0.30 mmol) and allyltrifluoroborate **309** (79 mg, 0.45 mmol) using ligand *ent*-**92** and was purified by column chromatography (80:20 hexanes:EtOAc) to give *sulfonamide ent*-**331** (54 mg, 71%) as a yellow oil that displayed spectroscopic data consistent with those reported previously (**331**). R_f = 0.54 (70:30 hexanes:EtOAc); $[\alpha]_D^{20}$ –60.0 (*c* 0.50, $CHCl_3$); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 211 nm, 25 °C); t_r (major) = 13.9 min, t_r (minor) = 25.1 min; 90% ee.



ent-**332**

(*S*)-3-Methyl-3-(2-methylbut-3-en-2-yl)-4-phenyl-2,3-dihydro-[1,2,5]-thiadiazole-1,1-dioxide (*ent*-332). The title compound was prepared according to General Procedure D from imine **276a** (62 mg, 0.30 mmol) and allyltrifluoroborate **309** (79 mg, 0.45 mmol) using ligand *ent*-**92** and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide ent*-**332** (72 mg, 875) as a yellow solid that displayed spectroscopic data consistent with those reported previously (**332**). R_f = 0.25 (70:30 hexanes:EtOAc); $[\alpha]_D^{20}$ +40.7 (*c* 1.40, $CHCl_3$); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 211 nm, 25 °C); t_r (major) = 22.1 min, t_r (minor) = 29.2 min; 91% ee.

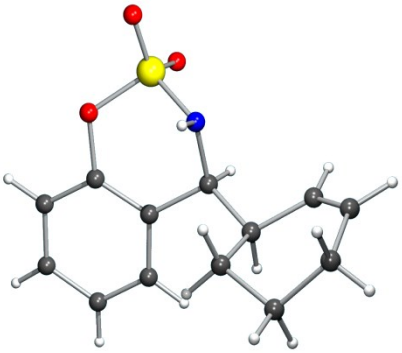


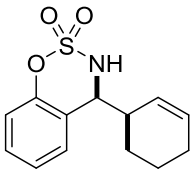
349

(*S*)-4-[(*R*)-Cyclohex-2-en-1-yl]-3,4-dihydro-[1,2,3]-benzoxathiazine-2,2-dioxide (349). The title compound was prepared according to General Procedure D from imine **89a** (55 mg, 0.30 mmol) and allyltrifluoroborate **321** (85 mg, 0.45 mmol) using ligand *ent*-**92** and was purified by column chromatography (90:10 hexanes:EtOAc) to give *sulfonamide* **349** (29 mg, 36%) as a 10:1 inseparable mixture of diastereomers and a white solid. R_f = 0.54 (70:30 hexanes:EtOAc); m.p. 128-130 °C (Et_2O); $[\alpha]_D^{20}$ –38.4 (*c* 1.25, $CHCl_3$); IR 3273 (NH), 1408, 1369, 1184, 1171, 1161, 878, 826, 766, 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.31 (1H,

m, Ar**H**), 7.25-7.22 (2H, m, Ar**H**), 7.06-7.04 (1H, m, Ar**H**), 6.04-5.99 (1H, m, C**H**=CH), 5.62-5.58 (1H, m, C**H**=CH), 4.90 (1H, dd, *J* = 6.4, 5.0 Hz, C**H**NH), 4.54 (1H, d, *J* = 6.2 Hz, N**H**), 3.13-3.06 (1H, m, C**H**CH=CH), 2.08-2.00 (2H, m, C$\mathbf{H}_2$CH=CH), 1.82-1.75 (1H, m, CHC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.59-1.49 (2H, m, CHC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.27-1.18 (1H, m, CHC$\mathbf{H}_2$C$\mathbf{H}_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 151.6 (C), 132.3 (CH), 129.3 (CH), 126.6 (CH), 126.3 (CH), 125.5 (CH), 121.4 (C), 119.2 (CH), 60.1 (CH), 39.0 (CH), 24.9 (CH_2), 22.2 (CH_2), 21.4 (CH_2); HRMS (ESI) Exact mass calcd for $C_{13}H_{16}NO_3S$ $[M+H]^+$: 266.0845, found: 266.0846; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 14.2 min, t_r (minor) = 24.2 min; 93% ee.

Slow evaporation of a solution of **349** in Et_2O/petrol gave crystals that were suitable for X-ray diffraction:

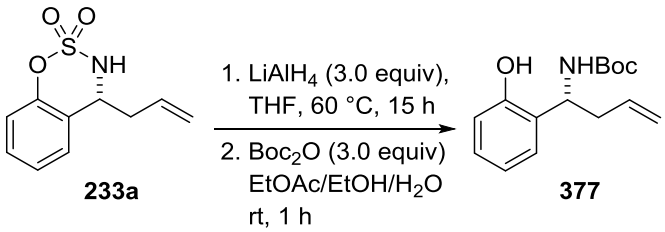




349
CCDC = 948888

1.1.6 The Derivitisation of the Products

***tert*-Butyl *N*-[(*R*)-1-(2-hydroxyphenyl)but-3-en-1-yl]carbamate (377):**

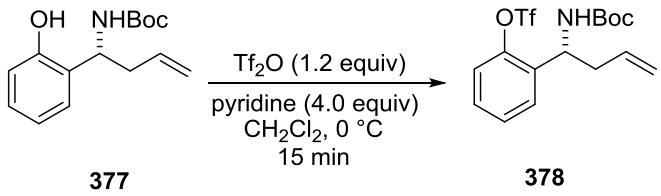


233a **377**

To a solution of *sulfonamide* **233a** (27 mg, 0.12 mmol) in THF (1 mL) at room temperature was added $LiAlH_4$ (1.0 M in THF, 0.37 mL, 0.37 mmol) over 1 min at room temperature. The mixture was heated at 60 °C for 15 h, allowed to cool to

temperature, and then cooled with an ice bath. The reaction was quenched carefully with EtOAc (1 mL), followed by the addition of EtOH (1 mL) and H_2O (2 mL). To the resulting turbid mixture was added Boc_2O (81 mg, 0.37 mmol) in 1 portion and the resulting mixture was stirred at room temperature for 1 h. The reaction was diluted with EtOAc (20 mL) and acidified with 2 M HCl until the aqueous layer became clear. The aqueous layer was separated and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (86:14 hexane:Et_2O→66:34 hexane:Et_2O) gave the *carbamate* **377** (28 mg, 85) as a colourless oil. R_f = 0.54 (70:30 hexane:EtOAc); $[\alpha]_D^{20}$ +45.2 (*c* 1.15, $CHCl_3$); IR 3310 (OH), 2925, 1680, 1502, 1456, 1367, 1170, 1043, 918, 860, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.50 (1H, br s, ArO**H**), 7.16-7.07 (2H, m, Ar**H**), 6.88-6.80 (2H, m, Ar**H**), 5.75 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, C**H**=CH_2), 5.27 (1H, br s, N**H**), 5.13 (1H, dd, *J* = 17.2, 1.0 Hz, =C**H**$_2$), 5.09 (1H, d, *J* = 10.4 Hz, =C**H**$_2$), 4.89 (1H, br s, C**H**N), 2.62 (2H, t, *J* = 7.0 Hz, C**H**$_2$), 1.47 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.0 (C), 154.7 (C), 134.6 (CH), 128.5 (CH), 127.9 (C), 126.6 (CH), 119.8 (CH), 117.8 (CH_2), 117.0 (CH), 80.7 (C), 48.9 (CH), 38.6 (CH_2), 28.4 (3 x CH_3); HRMS (EI) Exact mass calcd for $C_{15}H_{22}O_3N$ $[M]^+$: 264.1594, found: 264.1599; Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 23.1 min, t_r (minor) = 30.6 min; 93% ee.

***tert*-Butyl *N*-[(*R*)-1-(2-triflatephenyl)but-3-en-1-yl]carbamate (378):**

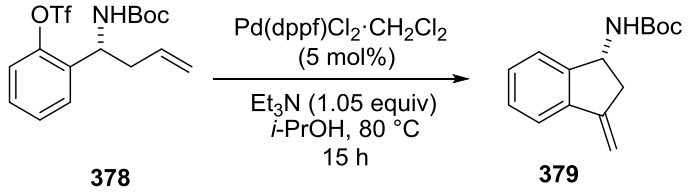


377 **378**

To a solution of *carbamate* **377** (131 mg, 0.5 mmol) and pyridine (0.16 mL, 2.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added triflic anhydride (0.1 mL, 0.6 mmol). The solution was stirred for 15 minutes then quenched with HCl (1 M, 20 mL). The solution was extracted with CH_2Cl_2 (3 x 50 mL) and the organic layers were

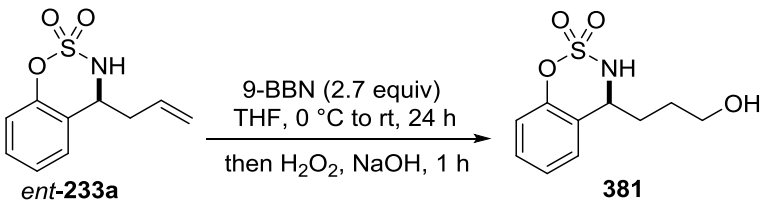
combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *triflate* **378** (114 mg, 58%) as a colourless oil that was used without further purification,

***tert*-Butyl *N*-(3-methylidene-2,3-dihydro-1H-inden-1-yl)carbamate (379):**



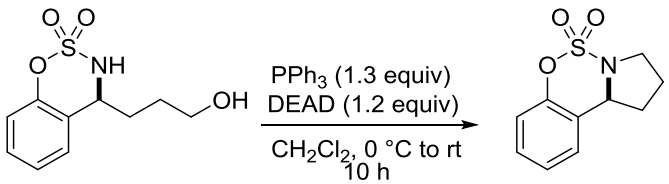
To a solution of *triflate* **378** (39 mg, 0.1 mmol) and palladium(dppf)dichloride CH_2Cl_2 adduct (4 mg, 0.005 mmol) in *i*-PrOH (2 mL) was added triethylamine (0.015 mL, 0.105 mmol) and the solution was heated at 80 °C for 15 hours. The solution was cooled and concentration *in vacuo*. Purification of the residue by flash column chromatography (90:10 petrol:EtOAc) gave *carbamate* **379** (21 mg, 88%) as a white solid. R_f = 0.32 (90:10 petrol:EtOAc); $[\alpha]_D^{20}$ +64.3 (*c* 1.07, $CHCl_3$); IR 3354, 2925, 2358, 2343, 1678 (C=O), 1519, 1247, 1165, 1051, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.49 (1H, m, Ar**H**), 7.44-7.38 (1H, m, Ar**H**), 7.35-7.28 (2H, m, Ar**H**), 5.50 (1H, t, *J* = 2.4 Hz, =C$\mathbf{H}_2$), 5.10 (1H, t, *J* = 2.0 Hz, =C$\mathbf{H}_2$), 4.89 (1H, ddd, *J* = 10.3, 7.9, 5.1 Hz, C**H**NH), 3.38 (1H, ddt, *J* = 17.0, 7.9, 1.9 Hz, CHC$\mathbf{H}_2$), 2.79 (1H, ddt, *J* = 17.0, 5.0, 2.5 Hz, CHC$\mathbf{H}_2$), 1.26 (9H, s, C(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 158.1 (C), 146.4 (C), 145.9 (C), 140.5 (C), 128.9 (CH), 128.8 (CH), 125.5 (CH), 120.8 (CH), 104.6 (CH_2), 59.8 (CH), 56.3 (C), 42.7 (CH_2), 19,4 (3 x CH_3); HRMS (ESI) Exact mass calcd for $C_{15}H_{19}O_2NNa$ $[M+Na]^+$: 268.1308, found: 268.1297.

(*S*)-4-(3-Hydroxypropyl)-3,4-dihydro-[1,2,3]-benzoxathiazine-2,2-dioxide (381):



To a solution of the *sulfonamide ent*-**233a** (prepared as described previously by the reaction of imine **89a** with potassium allyltrifluoroborate **234**, but using chiral diene *ent*-**92**) (1 g, 4.40 mmol) in THF (20 mL) at 0 °C was added 9-BBN (0.5 M in THF, 24.0 mL, 12.0 mmol) over 2 min. The mixture was warmed to room temperature over 1 h and then stirred for a further 23 h. The reaction was cooled to 0 °C and 3 M NaOH (12 mL) and H_2O_2 (30 wt.% in H_2O, 24 mL) were added successively. The resulting mixture was stirred for 1 h at room temperature, diluted with H_2O (50 mL), acidified with 2 M HCl, and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (80:20 hexanes:EtOAc) gave *alcohol* **381** (939 mg, 88%) as a white solid. R_f = 0.36 (70:30 hexanes:EtOAc); m.p. 112-113°C (CH_2Cl_2); $[\alpha]_D^{20}$ –36.7 (*c* 0.49, $CHCl_3$); IR 3255 (OH), 2880, 1485, 1452, 1425, 1371, 1175, 1107, 883, 760 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.40 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.36 (1H, *J* = 8.3, 4.5, 1.1 Hz, Ar**H**), 7.24 (1H, td, *J* = 1.6, 1.2 Hz, Ar**H**), 7.02 (1H, dd, *J* = 8.2, 1.2 Hz, Ar**H**), 4.70 (1H, dd, *J* = 10.9, 3.8 Hz, C**H**N), 3.70-3.61 (2H, m, C**H**$_2$OH), 2.26-2.18 (1H, m, C**H**$_2$CH$_2$CH$_2$OH), 2.03-1.95 (1H, m, C**H**$_2$CH$_2$CH$_2$OH), 1.90-1.82 (1H, m, C**H**$_2$CH$_2$OH), 1.76-1.67 (1H, m, C**H**$_2$CH$_2$OH); ^{13}C NMR (125.8 MHz, CD_3OD) δ 152.8 (C), 130.2 (CH), 127.9 (CH), 126.1 (CH), 125.0 (C), 119.3 (CH), 62.3 (CH), 57.9 (CH_2), 31.3 (CH_2), 29.6 (CH_2); HRMS (ESI) Exact mass calcd for $C_{10}H_{14}NO_4S$ $[M+H]^+$: 244.0638, found: 244.0640.

(*S*)-8-Oxa-7λ^6-thia-6-azatricyclo[7.4.0.0^{2,6}]trideca-1(9),10,12-triene-7,7-dioxide (382):

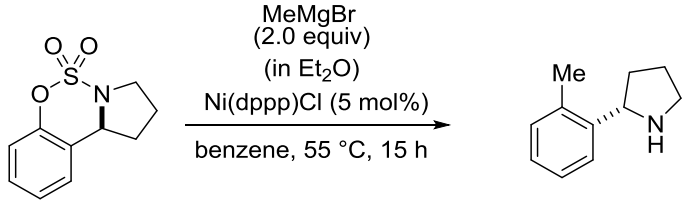


381 **382**

To a solution of the *alcohol* **381** (730 mg, 3.0 mmol) and PPh_3 (262 mg, 3.9 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added a solution of DEAD (626 mg, 3.6 mmol) in CH_2Cl_2 (10 mL). The mixture was allowed to warm to room temperature over 1 h.

The reaction was quenched with EtOH (10 mL) and concentrated *in vacuo*. Purification of the residue by column chromatography (90:10 hexane:EtOAc) gave *tricycle* **382** (611 mg, 91%) as a white solid. R_f = 0.57 (70:30 hexanes:EtOAc); m.p. 85-86 °C (CH_2Cl_2/hexane); $[\alpha]_D^{20}$ –125.0 (*c* 0.40, $CHCl_3$); IR 2982, 1485, 1450, 1392, 1206, 1175, 1103, 1005, 856, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (1H, dddd, *J* = 8.1, 7.3, 1.7, 0.8 Hz, Ar**H**), 7.21 (1H, td, *J* = 7.5, 1.2 Hz, Ar**H**), 7.15 (1H, dt, *J* = 7.5, 1.0 Hz, Ar**H**), 7.01 (1H, dd, *J* = 8.2, 1.2 Hz, Ar**H**), 5.20 (1H, dd, *J* = 7.4, 2.5 Hz, C**H**N), 3.61-3.56 (1H, m, C$\mathbf{H}_2$N), 3.51 (1H, ddd, *J* = 10.1, 8.6, 5.8 Hz, C$\mathbf{H}_2$N), 2.59 (1H, ddd, *J* = 16.5, 12.8, 7.7 Hz, CHC$\mathbf{H}_2$C$\mathbf{H}_2$), 2.30-2.24 (1H, m, CHC$\mathbf{H}_2$C$\mathbf{H}_2$), 2.07-1.99 (1H, m, CHC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.92-1.83 (1H, m, CHC$\mathbf{H}_2$C$\mathbf{H}_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 151.0 (C), 129.1 (CH), 126.6 (CH), 125.6 (CH), 122.5 (C), 118.8 (CH), 62.7 (CH), 49.7 (CH_2), 34.0 (CH_2), 23.4 (CH_2); HRMS (EI) Exact mass calcd for $C_{10}H_{12}NO_3S$ $[M+H]^+$: 226.0532, found: 226.0529; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min 280 nm 25 °C); t_r (minor) = 18.6 min, t_r (major) = 20.2 min; 92% ee.

2-(2-methylphenyl)-pyrrolidine (383a):

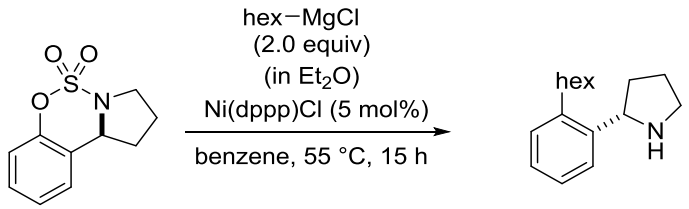


382 **383a**

To a solution of *tricycle* **382** (22.5 mg, 0.1 mmol) and $NiCl_2$(dppp) (4 mg, 0.01 mmol) in benzene (1 mL) was added methylmagnesium bromide (1 M in Et_2O. 0.2 mL, 0.2 mmol). The solution was heated at 55 °C for 15 hours then concentrated *in vacuo*. The residue was taken up in 2 M HCl in EtOH (1 mL) and stirred at 55 °C for 15 hours. The solution was basified with $NaHCO_3$ solution (2 M) and extracted with Et_2O (2 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentration *in vacuo*. Purification of the residue by flash column chromatography (90:8:2 hexane:EtOAc:Et_3N) gave *amine* **383a** (11 mg,

68%) as a colourless oil that displayed spectroscopic data consistent with those previously reported.[229] R_f = 0.34 (20% EtOAc/hexane with 2% Et_3N); ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 7.3 Hz, Ar**H**), 7.19-7.10 (3H, m, Ar**H**), 4.32-4.28 (1H, m, C**H**), 3.24-3.17 (1H, m, C$\mathbf{H}_2$), 3.04-2.95 (1H, m, C$\mathbf{H}_2$), 2.33 (3H, s, C$\mathbf{H}_3$), 2.24-2.04 (2H, m, C$\mathbf{H}_2$), 1.97-1.75 (2H, m, C$\mathbf{H}_2$), 1.60-1.48 (1H, m, C$\mathbf{H}_2$).

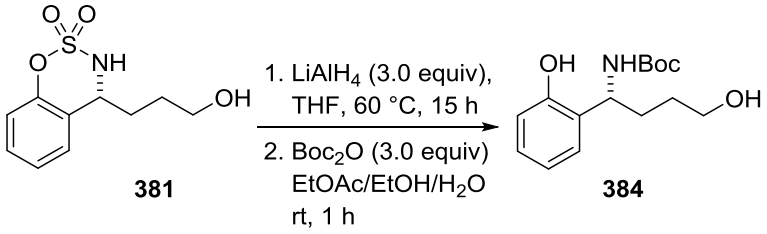
2-(2-hexylphenyl)-pyrrolidine (383b):



382 **383b**

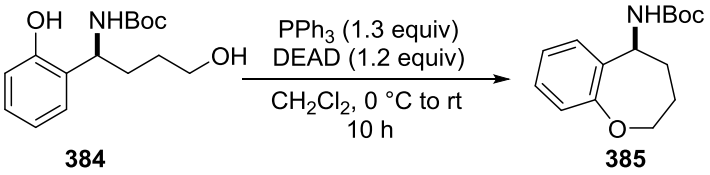
To a solution of *tricycle* **382** (22.5 mg, 0.1 mmol) and $NiCl_2$(dppp) (4 mg, 0.01 mmol) in benzene (1 mL) was added hexylmagnesium chloride (1 M in Et_2O. 0.2 mL, 0.2 mmol). The solution was heated at 55 °C for 15 hours then concentrated *in vacuo*. The residue was taken up in 2 M HCl in EtOH (1 mL) and stirred at 55 °C for 15 hours. The solution was basified with $NaHCO_3$ solution (2 M) and extracted with Et_2O (2 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentration *in vacuo*. Purification of the residue by flash column chromatography (90:8:2 hexane:EtOAc:Et_3N) gave *amine* **383b** (18 mg, 78%) as a colourless oil. R_f = 0.25 (10% EtOAc/hexane with 2% Et_3N); IR 3347, 2396, 1385, 1203, 1165, 1113, 1073, 934, 904, 883 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (1H, d *J* = 7.3 Hz, Ar**H**), 7.22-7.17 (1H, m, Ar**H**), 7.16-7.13 (2H, m, Ar**H**), 4.39-4.34 (1H, m, C**H**NH), 3.30-3.22 (1H, m, C$\mathbf{H}_2$), 3.07-2.99 (1H, m, C$\mathbf{H}_2$), 2.72-2.63 (2H, m, C$\mathbf{H}_2$), 2.20-2.17 (1H, m, C$\mathbf{H}_2$), 2.03-1.87 (3H, m, C$\mathbf{H}_2$ x 3), 1.66-1.55 (3H, m, C$\mathbf{H}_2$ x 3), 1.43-1.39 (5H, m, C$\mathbf{H}_2$ x 5), 0.92-0.88 (3H, m, C$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 142.5 (C), 140.3 (C), 129.2 (CH), 126.5 (CH), 126.1 (CH), 125.5 (CH), 58.0 (CH), 47.1 (CH_2), 34.2 (CH_2), 32.8 (CH_2), 31,8 (CH_2), 31,7 (CH_2), 29.4 (CH_2), 25.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{16}H_{25}NNa$ $[M+Na]^+$: 254.1885, found: 254.1879.

***tert*-Butyl-*N*-[(*S*)-4-hydroxy-1-(2-hydroxyphenyl)butyl] carbamate (384)**



To a solution of *alcohol* **381** (100 mg, 0.41 mmol) in THF (2 mL) at room temperature was added $LiAlH_4$ (2.0 M in THF, 0.62 mL, 1.24 mmol) dropwise over 4 min. The mixture was heated at 60 °C for 2 h, allowed to cool to room temperature, and then cooled with an ice bath. The reaction was quenched carefully with EtOAc (2 mL), followed by the addition of EtOH (2 mL) and H_2O (2 mL). To the resulting turbid mixture was added Boc_2O (268 mg, 1.24 mmol) in one portion and the resulting mixture was stirred at room temperature for 1 h. The reaction was diluted with EtOAc (40 mL) and acidified with 2 M HCl until the aqueous layer became clear. The aqueous layer was separated and extracted with EtOAc (2 x 40 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (80:20 hexanes:EtOAc) gave the *carbamate* **384** (87 mg, 75%) as a colorless gum. $R_f = 0.42$ (30% EtOAc/hexane); $[\alpha]_D^{20}$ –33.6 (*c* 0.24, $CHCl_3$); IR 3305 (OH and NH), 2980, 1680 (C=O), 1502, 1456, 1367, 1292, 1253, 1165, 752, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (1H, br s, O**H**), 7.18 (2H, dd, *J* = 12.1, 4.5 Hz, Ar**H**), 6.93 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.90 (1H, dt, *J* = 7.5, 1.1 Hz, Ar**H**), 5.13 (1H, s, N**H**), 4.86 (1H, d, *J* = 6.9 Hz, C**H**N), 3.72 (2H, dt, *J* = 6.2, 0.9 Hz, C**H**$_2$OH), 2.06-1.95 (2H, m, CHC**H**$_2$C**H**$_2$), 1.73-1.58 (2H, m, CHC**H**$_2$C**H**$_2$), 1.45 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.3 (C), 154.9 (C), 128.8 (C), 128.4 (CH), 126.3 (CH), 120.3 (CH), 117.8 (CH), 80.8 (C), 62.3 (CH_2), 49.0 (CH), 30.6 (CH_2), 29.5 (CH_2), 28.3 (3 x CH_3); HRMS (ESI) Exact mass calcd for $C_{15}H_{24}NO_4$ $[M+H]^+$: 282.1700, found: 282.1696.

***tert*-Butyl *N*-[(*S*)-2,3,4,5-tetrahydro-1-benzoxepin-5-yl] carbamate (384)**

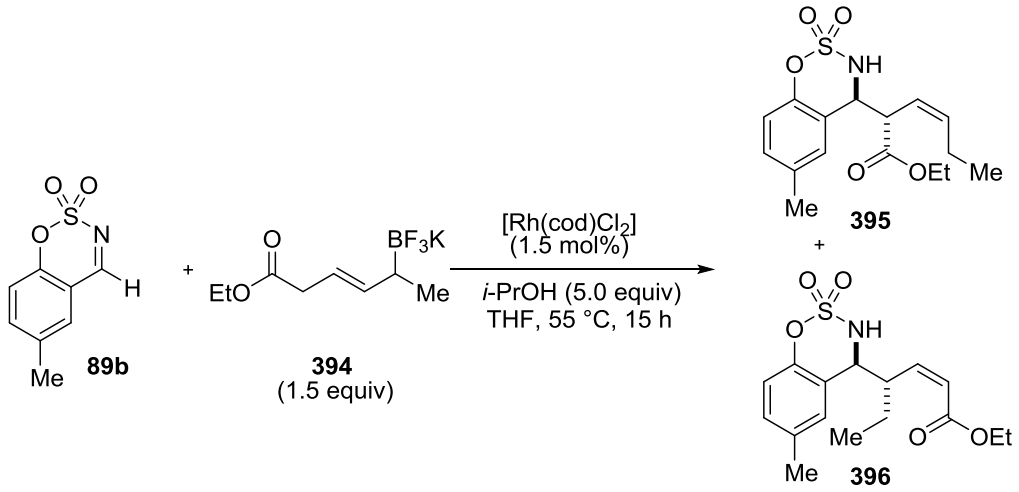


384 **385**

To a solution of the *diol* **384** (68 mg, 0.24 mmol) and PPh_3 (82 mg, 0.31 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added a solution of DEAD (51 mg, 0.29 mmol) in CH_2Cl_2 (1 mL). The mixture was allowed to warm to room temperature over 1 h and then stirred for an additional 9 h. The reaction was quenched with EtOH (1 mL) and concentrated *in vacuo*. Purification of the residue by column chromatography (80:20 hexanes:EtOAc) gave the *tetrahydrobenzoxepine* **385** (43 mg, 68%) as a white solid. R_f = 0.40 (70:30 hexane:EtOAc); m.p. 105-106°C (CH_2Cl_2/hexane); $[\alpha]_D^{20}$ –40.0 (*c* 0.15, $CHCl_3$); IR 3300 (NH), 2976, 2930, 1713(C=O), 1450, 1366, 1236, 1224, 1170, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.26 (1H, m, Ar**H**), 7.20 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.05 (1H, td, *J* = 7.5, 1.3 Hz, Ar**H**), 7.01 (1H, dd, *J* = 7.5, 1.3 Hz, Ar**H**), 5.29 (1H, d, *J* = 7.8 Hz, N**H**), 4.91 (1H, t, *J* = 7.1 Hz, C**H**N), 4.30 (1H, app d, *J* = 11.9 Hz, C$\mathbf{H}_2$O), 3.75 (1H, app t, *J* = 11.2 Hz, C$\mathbf{H}_2$O), 2.30-2.10 (2H, m, C$\mathbf{H}_2$), 1.88-1.81 (1H, m, C$\mathbf{H}_2$), 1.79-1.72 (1H, m, C$\mathbf{H}_2$), 1.44 (9H, s, C(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.3 (C), 155.0 (C), 135.5 (C), 129.3 (CH), 128.9 (CH), 124.2 (CH), 122.0 (CH), 79.3 (C), 73.8 (CH_2), 53.9 (CH), 30.8 (CH_2), 28.4 (3 x CH_3), 26.7 (CH_2); HRMS (ESI) Exact mass calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1594, found: 264.1595; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min 280 nm 25 °C); t_r (major) = 12.5 min, t_r (minor) = 15.6 min; 90% ee.

1.1.7 Future Work

Ethyl (3Z)-2-(2,2-dioxo-3,4-dihydro-1,2,3-benzoxathiazin-4-yl)hex-3-enoate (395) and ethyl (2Z)-4-(2,2-dioxo-3,4-dihydro-1,2,3-benzoxathiazin-4-yl)hex-2-enoate (396):



A microwave vial containing the imine **89b** (59 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (2.2 mg, 0.0045 mmol), and potassium allyltrifluoroborate **394** (112 mg, 0.45 mmol) was flushed with N_2 before anhydrous THF (3 mL) and *i*-PrOH (115 μL, 1.5 mmol) were added. The mixture was heated at 55 °C for 15 h. The reaction was cooled to room temperature, diluted with EtOAc (10 mL), and filtered through a silica plug eluting with EtOAc. The filtrate was concentrated *in vacuo*. Purification by flash column chromatography (95:05 petrol:EtOAc) gave the *sulfonamide* **396** (6 mg, 6%) as a white solid, followed by *sulfonamide* **395** (69 mg, 68%) as a white solid. *Sulfonamide* **396**: m.p. 84-86 °C (Et_2O); IR 3245, 2933, 1635 (C=O), 1205, 1194, 1137, 1048, 1021, 904, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (1H, s, Ar**H**), 7.09 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.90 (1H, d, *J* = 8,3 Hz, Ar**H**), 5.99-5.87 (2H, m, -C**H**=C**H**-), 4.91 (1H, dd, *J* = 8.7, 4.6 Hz, NHC**H**), 4.74 (1H, d, *J* = 8.5 Hz, N**H**), 4.44-4.36 (1H, m, C**H**C=), 4.20 (2H, q, *J* = 7.1 Hz, OC$\mathbf{H}_2$CH$_3$), 2.29 (3H, s, ArC$\mathbf{H}_3$), 1.82-1.69 (1H, m, =CHC$\mathbf{H}_2$), 1.66-1.57 (1H, m, =CHC$\mathbf{H}_2$), 1.30 (3H, t, *J* = 7.1 Hz, OCH$_2$C$\mathbf{H}_3$), 1.03 (3H, t, *J* = 7.4 Hz, CHCH$_2$C$\mathbf{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.2 (C), 145.3 (CH), 142.8 (C), 135.0 (C), 130.1 (CH), 127.1 (CH), 123.7 (CH), 121.3 (C), 118.5 (CH), 60.4 (CH_2), 59.4 (CH), 41.2 (CH), 24.6 (CH_2), 20.8 (CH_3),

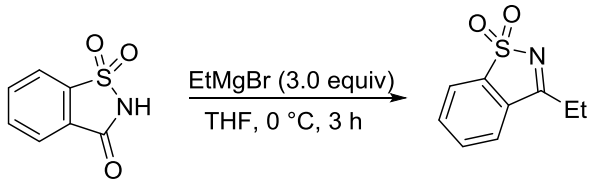
14.2 (CH_3) 11.5 (CH_3); HRMS (ESI) Exact mass calculated for $C_{16}H_{21}NO_5SNa$ [M+Na]: 362.1033, found: 362.1036.

Sulfonamide **395**: m.p. 95-97 °C (Et_2O); IR 3275, 3105, 2741, 1594 (C=O), 1305, 1182, 1093, 993, 974, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (1H, ddd, *J* = 8.4, 1.4, 0.6 Hz, Ar**H**), 7.00-6.97 (1H, m, Ar**H**), 6.93 (1H, d, *J* = 8.4 Hz, Ar**H**), 5.69 (1H, dtd, *J* = 10.8, 7.5, 0.7 Hz, =C**H**CH_2), 5.56-5.47 (2H, m, C**H**= + N**H**), 5.12 (1H, t, *J* = 5.9 Hz, NHC**H**), 4.27-4.13 (2H, m, OC$\mathbf{H}_2$), 4.06 (1H, ddd, *J* = 9.7, 5.5, 0.8 Hz, CHC**H**CH=), 2.31 (3H, s, ArC$\mathbf{H}_3$), 2.16-1.95 (2H, m, =CHC$\mathbf{H}_2$), 1.24 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$), 0.91 (3H, t, *J* = 7.5 Hz, $=CHCH_2C\mathbf{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.9 (C), 149.1 (C), 138.7 (CH), 135.2 (C), 130.3 (CH), 126.7 (CH), 120.4 (C), 120.3 (CH), 118.9 (CH), 61.7 (CH_2), 58.2 (CH), 47.6 (CH), 21.3 (CH_2), 20.8 (CH_3), 14.0 (CH_3), 13.5 (CH_3); HRMS (ESI) Exact mass calculated for $C_{16}H_{21}NO_5SNa$ [M+Na]: 362.1033, found: 362.1030.

1.2 Experimental for Chapter 2

1.2.1 Synthesis of Ketimines

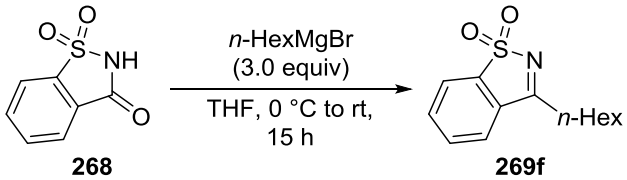
3-Ethylbenzo[*d*]isothiazole 1,1-dioxide (269e):



268 **269e**

To a solution of saccharin (3.66 g, 20 mmol) in THF (150 mL) at –78 °C was added EtMgBr (1.0 M in THF, 60 mL, 60 mmol) dropwise. The solution was stirred for 15 hours then quenched by the addition of ice cool water (100 mL) and acidified with 2 M HCL (100 mL). The mixture was extracted with Et_2O (4 x 100 mL) and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a white solid. Recrystalisation of this solid from Et_2O gave ket*imine* **269e** (1.87 g, 46%) as a white solid that displayed spectroscopic data consistent with those previously reported.[230] m.p. 140-142 °C (Et_2O); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 8.32-7.45 (5H, m, Ar**H**), 2.38 (2H, q, J = 7.4 Hz, C**H**$_2$CH$_3$), 1.10 (3H, t, J = 7.4 Hz, CH$_2$C**H**$_3$).

3-Hexylbenzo[*d*]isothiazole 1,1-dioxide (269f):

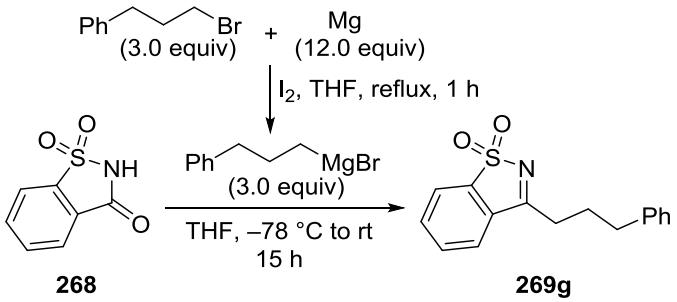


268 **269f**

Saccharin (1.83 g, 10.0 mmol) was dissolved in THF (50 mL) under N_2 at 0 °C. *n*-Hexylmagnesium bromide (2 M in THF, 15 mL, 30.0 mmol) was added slowly and the solution was stirred for 15 h while slowly warming to room temperature. The reaction was poured carefully onto ice and the solution was acidified (2 M HCl). The aqueous layer was extracted with EtOAc (4 x 100 mL) and the organic layers

combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (80:20 hexane:EtOAc) gave the *ketimine* **269f** (1.11 g, 44%) as a cream solid. R_f = 0.35 (80:20 hexane:EtOAc); m.p. 88-90 °C (Et_2O); IR 2820, 2734, 1652, 1428, 1394, 1279, 1204, 1174, 1023, 946 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.90 (1H, m, Ar**H**), 7.79-7.67 (3H, m, Ar**H**), 2.97 (2H, t, *J* = 7.7 Hz, N=CC**H**$_2$), 1.90 (2H, dt, *J* = 15.2, 7.6 Hz, N=CCH$_2$C**H**$_2$), 1.56-1.46 (2H, m, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.39-1.31 (4H, m, C**H**$_2$C**H**$_2$CH$_3$), 0.91 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.3 (C), 139.8 (C), 133.8 (CH), 133.5 (CH), 131.3 (C), 128.3 (CH), 122.5 (CH), 31.4 (CH_2), 31.2 (CH_2), 28.9 (CH_2), 25.4 (CH_2), 22.4 (CH_2), 14.0 (CH_3); HRMS (ESI) Exact mass calculated for $C_{13}H_{18}NO_2S$ $[M+H]^+$: 252.1053, found: 252.1060.

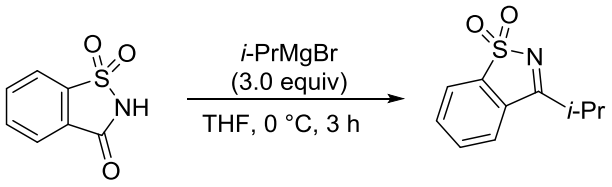
3-(3-Phenylpropyl)benzo[*d*]isothiazole 1,1-dioxide (269g):



1-Bromo-3-phenylpropane (4.53 mL, 30.0 mmol) was added dropwise to a suspension of magnesium turnings (1.10 g, 120 mmol) and a crystal of iodine under N_2 in THF (100 mL). The solution was heated at reflux for 1 h, cooled to room temperature, and then transferred *via* cannula into a solution of saccharin (1.83 g, 10.0 mmol) in THF (50 mL) at 0 °C. The solution was stirred for 15 h while slowly warming to room temperature. The reaction was poured carefully onto ice and the solution was acidified (2 M HCl). The aqueous layer was extracted with Et_2O (4 x 100 mL) and the organic layers combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to leave a white solid. Recrystallization of the solid from Et_2O gave the *ketimine* **269g** (1.63 g, 57%) as a white solid that displayed spectroscopic data consistent with those reported previously.[231] m.p. 148-150 °C (Et_2O); ^1H NMR ($CDCl_3$ 400 MHz) δ 7.91-7.88 (1H, m, Ar**H**), 7.75-7.72 (1H, m,

Ar**H**), 7.70-7.68 (1H, m, Ar**H**), 7.59-7.55 (1H, m, Ar**H**), 7.33-7.28 (2H, m, Ar**H**), 7.24-7.19 (3H, m, Ar**H**), 2.95 (2H, t, J = 7.4 Hz, CC**H**$_2$), 2.82 (2H, t, J = 7.2 Hz, $CH_2C\mathbf{H}_2Ph$), 2.24 (2H, q, J = 7.4 Hz, $CH_2C\mathbf{H}_2CH_2$).

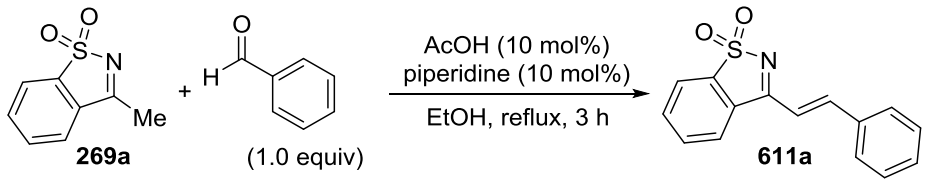
3-*iso*-Propylbenzo[*d*]isothiazole 1,1-dioxide (269h):



268 **269h**

To a solution of saccharin (3.66 g, 20 mmol) in THF (150 mL) at –78 °C was added *i*-PrMgBr (1.0 M in THF, 60 mL, 60 mmol) dropwise. The solution was stirred for 15 hours then quenched by the addition of ice cool water (100 mL) and acidified with 2 M HCL (100 mL). The mixture was extracted with Et_2O (4 x 100 mL) and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a white solid. Recrystalisation of this solid from Et_2O gave ket*imine* **269h** (1.88 g, 45%) as a white solid that displayed spectroscopic data consistent with those previously reported.[230] m.p. 87-89 °C (Et_2O); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.80-7.63 (4H, m, Ar**H**), 3.32 (1H, sept, J = 6.8 Hz, C**H**$(CH_3)_2$), 1.40 (6H, d, J = 6.4 Hz, $CH(C\mathbf{H}_3)_2$).

3-[(*E*)-2-(Phenyl)ethenyl]benzo[*d*]isothiazole 1,1-dioxide (611a):

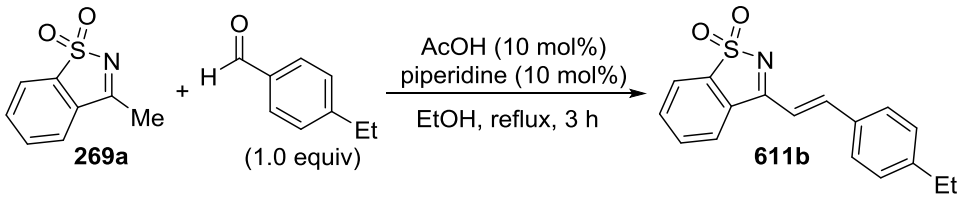


269a **611a**

A solution of 3-(methyl)-1,2-benzisothiazole 1,1-dioxide **269a** (905 mg, 5.00 mmol), benzaldehyde (0.51 mL, 5.00 mmol), piperidine (49 µL, 0.05 mmol), and AcOH (29 µL, 0.05 mmol) in EtOH (50 mL) was heated at reflux for 3 h. The reaction was cooled to 0 °C then filtered. The resulting solid was washed with cold EtOH to give

the *ketimine* **611a** (1.13 g, 84%) as a yellow solid that displayed spectroscopic data consistent with those previously reported.[232] m.p. decomposed at 250 °C (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (1H, d, *J* = 15.6 Hz, C**H**=CH), 7.98-7.96 (1H, m, Ar**H**), 7.90-7.88 (1H, m, Ar**H**), 7.78-7.76 (2H, m, Ar**H**), 7.72-7.70 (2H, m, Ar**H**), 7.49-7.45 (3H, m, Ar**H**), 7.30 (1H, d, *J* = 15.6 Hz, CH=C**H**).

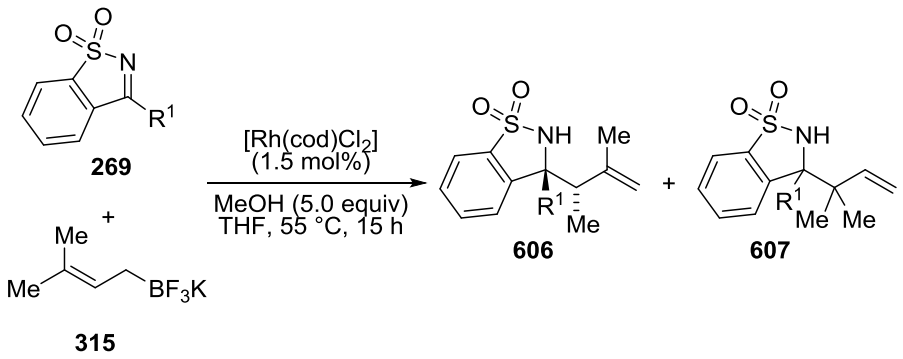
3-[(*E*)-2-(4-Ethylphenyl)ethenyl]benzo[*d*]isothiazole 1,1-dioxide (611b)



A solution of 3-(methyl)-1,2-benzisothiazole 1,1-dioxide **269a** (905 mg, 5.00 mmol), 4-ethylbenzaldehyde (0.53 mL, 5.00 mmol), piperidine (49 μL, 0.05 mmol), and AcOH (29 μL, 0.05 mmol) in EtOH (50 mL) was heated at reflux for 3 h. The reaction was cooled to 0 °C then filtered. The resulting solid was washed with cold EtOH to give the *ketimine* **611b** (705 mg, 60%) as a yellow solid. R_f = 0.15 (80:20 petrol:EtOAc); m.p. decomposed at 250 °C (Et_2O); IR 2978, 2901, 1394, 1340, 1288, 1174, 1049, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (1H, d, *J* = 15.6 Hz, CH=C**H**Ar), 7.99-7.95 (1H, m, Ar**H**), 7.93-7.88 (1H, m, Ar**H**), 7.79-7.74 (2H, m, Ar**H**), 7.64 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.32 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.26 (1H, d, *J* = 15.6 Hz, C**H**=CHAr), 2.73 (2H, q, *J* = 7.6 Hz, C**H**$_2$CH$_3$), 1.29 (3H, t, *J* = 7.6 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 149.0 (C), 148.1 (CH), 140.7 (C), 133.51 (CH), 133.47 (CH), 129.3 (2 x CH), 128.9 (2 x CH), 128.2 (C), 128.0 (C), 123.7 (CH), 122.8 (CH), 112.4 (CH), 29.0 (CH_2), 15.2 (CH_3); HRMS (ESI) Exact mass calculated for $C_{17}H_{16}NO_2S$ $[M]^+$: 298.0896, found: 298.0883.

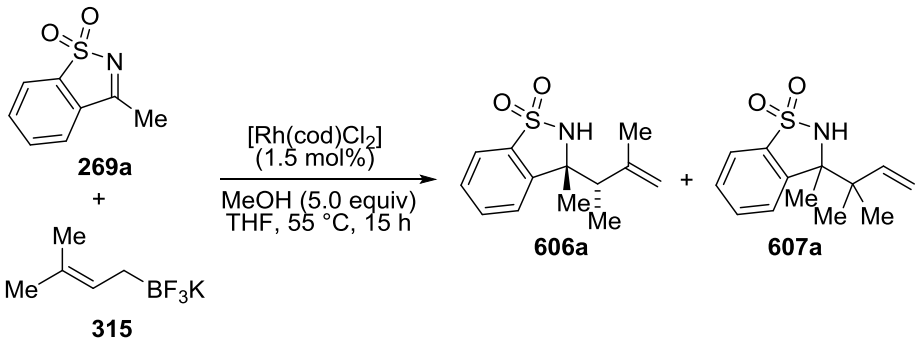
1.2.2 The Isomerisation of Allylrhodium Intermediates in Nucleophilic Allylation

Allylation of 1,2-Benzo[*d*]isothiazole 1,1-dioxides: General Procedure E



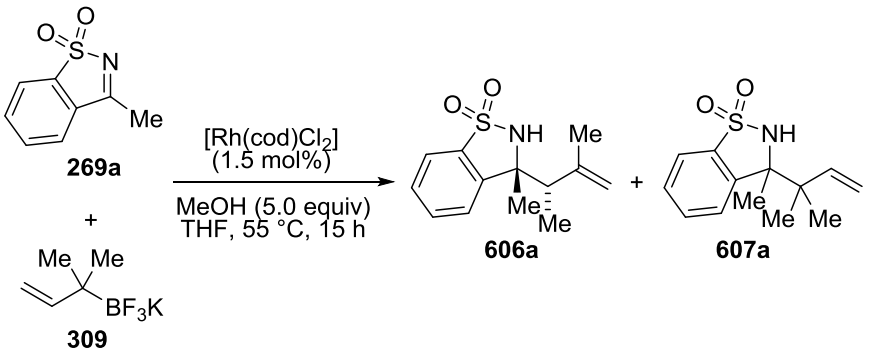
A microwave vial containing the appropriate 1,2-benzo[*d*]isothiazole 1,1-dioxide (0.30 mmol), $[Rh(cod)Cl]_2$ (2.2 mg, 0.0045 mmol), and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol) was flushed with N_2 before anhydrous THF (3 mL) and MeOH (60 µL, 1.5 mmol) were added. The mixture was heated at 55 °C for 15 h. The reaction was cooled to room temperature, diluted with EtOAc (10 mL), and filtered through a silica plug eluting with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography to give a mixture of allylation products **606** and **607**. This mixture was further purified by flash column chromatography to give product **606**.

(±)-(*R*)-3-Methyl-3-[(*S*)-3-methylbut-3-en-2-yl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (606a):



General Procedure E was followed using the ketimine **269a** (54 mg, 0.30 mmol) and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol). Purification by flash column chromatography (80:20 hexanes:EtOAc) gave a 74:26 mixture of **606a** and **607a** (53 mg, 70%) that was further purified by flash column chromatography (95:5 *iso*-hexane:EtOAc) to give the *sulfonamide* **606a** (36 mg, 48%) as a white solid (the reverse prenylation product **607a** could not be isolated cleanly from this experiment). R_f = 0.32 (80:20 petrol:EtOAc); m.p. 144-146 °C (Et_2O); IR 3232 (NH), 2976, 1449, 1277, 1225, 1158, 1039, 898, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80-7.76 (1H, m, Ar**H**), 7.68-7.64 (1H, m, Ar**H**), 7.57-7.53 (1H, m, Ar**H**), 7.42-7.38 (1H, m, Ar**H**), 5.02-5.00 (1H, m, =C**H**$_2$), 4.97-4.95 (1H, m, =C**H**$_2$), 4.33 (1H, br s, N**H**), 2.69 (1H, q, *J* = 7.0 Hz, C**H**CH$_3$), 1.82 (3H, s, =CC**H**$_3$), 1.61 (3H, s, xNHCC**H**$_3$), 0.89 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 145.9 (C), 144.2 (C), 134.9 (C), 133.4 (CH), 129.3 (CH), 122.9 (CH), 121.5 (CH), 114.9 (CH_2), 66.2 (C), 50.1 (CH), 28.5 (CH_3), 21.8 (CH_3), 14.9 (CH_3); HRMS (ESI) Exact mass calculated for $C_{13}H_{17}NO_2SNa$ [M+Na]:274.0872, found: 274.0868.

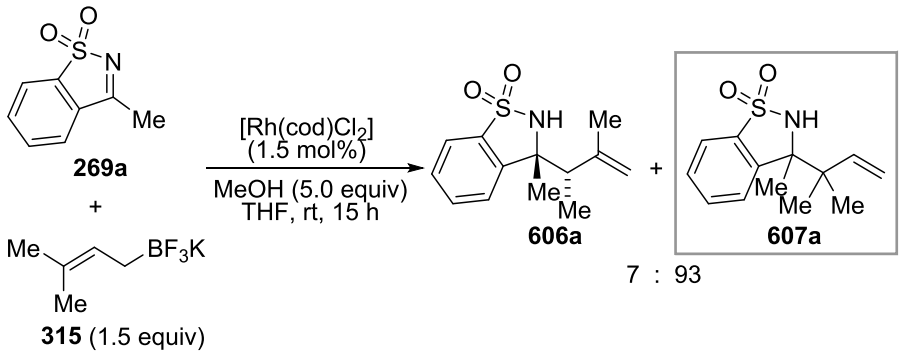
Using trifluoroborate **309***:*



General Procedure E was followed using the ketimine **269a** (54 mg, 0.30 mmol) and the potassium allyltrifluoroborate **309** (79 mg, 0.45 mmol). Purification by flash column chromatography (80:20 hexanes:EtOAc) gave a 75:25 mixture of **606a** and **607a** (56 mg, 74%) that was further purified by flash column chromatography (95:5 *iso*-hexane:EtOAc) to give the *sulfonamide* **606a** (39 mg, 52%) as a white solid (the reverse prenylation product **607a** could not be isolated cleanly from this experiment).

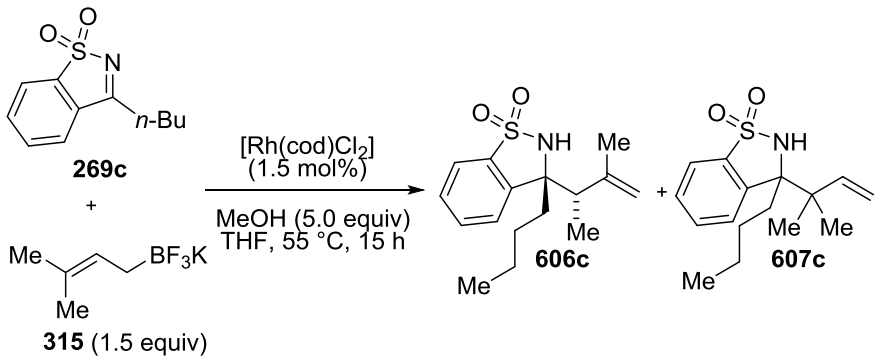
Unexpectedly, a pure sample of the reverse prenylation product **607a** could be obtained by repeating the rhodium-catalysed reaction of imine **269a** with allyltrifluoroborate **315** at room temperature as described below. The reason why **607a** is the major product from this experiment is currently unclear.

3-Methyl-3-(2-methylbut-3-en-2-yl)-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (607a):



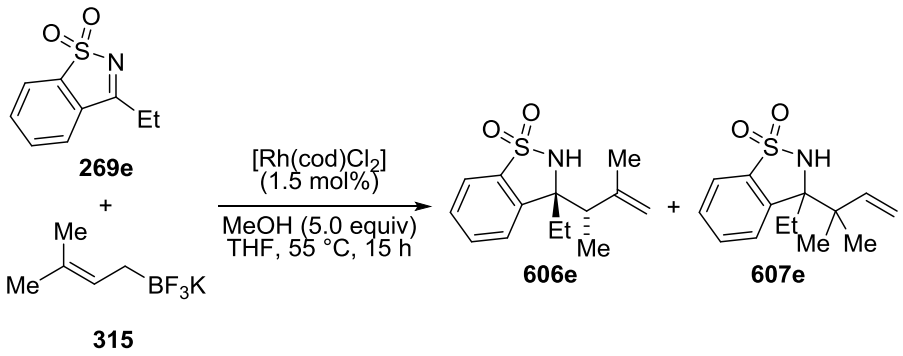
A microwave vial containing imine **269a** (59 mg, 0.30 mmol), $[Rh(cod)Cl]_2$ (2.2 mg, 0.0045 mmol), and potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol) was flushed with N_2 before anhydrous THF (3 mL) and MeOH (60 μL, 1.5 mmol) were added. The mixture was stirred at room temperature for 15 h, diluted with EtOAc (10 mL), filtered through a silica plug eluting with EtOAc, and concentrated *in vacuo*. ^{1}H NMR analysis of the residue indicated a 7:93 mixture of allylation products **606a** and **607a**. Purification of this residue by flash column chromatography (80:20 hexanes:EtOAc) gave a small sample of *sulfonamide* **607a** as a colourless oil. R_f = 0.32 (80:20 petrol:EtOAc); IR 3210 (NH), 2932, 2254, 1878, 1860, 1466, 1381, 1150, 888 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.74 (1H, m, Ar**H**), 7.64-7.48 (3H, m, Ar**H**) 6.08 (1H, dd, *J* = 17.5, 10.8 Hz, C**H**=CH_2), 5.24 (1H, dd, *J* = 10.8, 1.0 Hz, CH=C**H**$_2$), 5.14 (1H, dd, *J* = 17.5, 1.0 Hz, CH=C**H**$_2$), 4.47 (1H, s, N**H**), 1.66 (3H, s, NCC**H**$_3$) 1.104 (3H, s, C(C**H**$_3$)$_2$), 1.096 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.2 (CH), 142.5 (C), 135.2 (C), 132.6 (CH), 129.3 (CH), 124.7 (CH), 121.5 (CH), 115.6 (CH_2), 68.8 (C), 44.9 (C), 25.2 (CH_3), 23.0 (CH_3), 22.5 (CH_3); HRMS (ESI) Exact mass calculated for $C_{13}H_{17}NO_2SNa$ $[M+Na]^+$: 274.0872, found: 274.0872.

(±)-(*R*)-3-Butyl-3-[(*S*)-3-methylbut-3-en-2-yl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (606c):



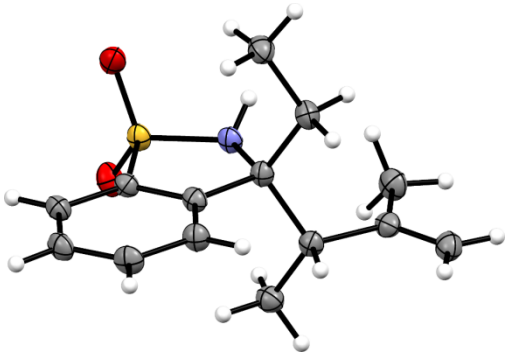
General Procedure E was followed using the ketimine **269c** (67 mg, 0.30 mmol) and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol). Purification by flash column chromatography (95:5 petrol:EtOAc) gave a 75:25 mixture of **606c** and **607c** (58 mg, 66%) that was further purified by flash column chromatography (30:70 *iso*-hexane:CH_2Cl_2) to give the *sulfonamide* **606c** (44 mg, 50%) as a white solid. R_f = 0.35 (80:20 petrol:EtOAc); m.p. 154-156 °C (Et_2O); IR 3251 (NH), 2963, 2929, 2871, 1386, 1275, 1170, 1151, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (1H, d, *J* = 7.8 HZ, Ar**H**), 7.66 (1H, td, *J* = 7.8, 1.1 Hz, Ar**H**), 7.55 (1H, td, *J* = 7.8, 0.9 Hz, Ar**H**), 7.35 (1H, d, *J* = 7.9 Hz, Ar**H**), 5.02-4.97 (1H, m, =C**H**$_2$), 4.95 (1H, s, =C**H**$_2$), 4.30 (1H, s, N**H**), 2.68 (1H, q, *J* = 7 Hz, C**H**CH_3), 1.91-1.84 (2H, m, CC**H**$_2$), 1.83-1.79 (3H, m, C**H**$_3$C=), 1.34-1.13 (3H, m, C**H**$_2$C**H**$_2CH_3$), 0.86 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 0.79 (3H, t, *J* = 7.3 Hz, CH_2C**H**$_3$), 0.75-0.65 (1H, m, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 146.1 (C), 142.2 (C), 135.8 (C), 133.4 (CH), 129.3 (CH), 123.0 (CH), 121.5 (CH), 114.8 (CH_2), 69.9 (C), 50.6 (CH), 39.6 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 21.7 (CH_3), 14.9 (CH_3), 13.8 (CH_3); HRMS (ESI) Exact mass calculated for $C_{16}H_{23}NO_2SNa$ $[M+Na]^+$: 316.1342, found: 316.1323.

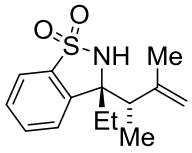
(±)-(*R*)-3-Ethyl-3-[(*S*)-3-methylbut-3-en-2-yl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (606e):



General Procedure E was followed using the ketimine **269e** (59 mg, 0.30 mmol) and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol). Purification by flash column chromatography (85:15 petrol:EtOAc) gave a 76:24 mixture of **606e** and **607e** (67 mg, 84%) that was further purified by flash column chromatography (30:70 *iso*-hexane:CH_2Cl_2) to give the *sulfonamide* **606e** (49 mg, 62%) as a white solid. R_f = 0.36 (80:20 petrol:EtOAc); m.p. 145-147 °C (Et_2O); IR 3256 (NH), 2963, 2932, 1387, 1275, 1169, 1149, 1129, 909, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.66 (1H, td, *J* = 7.8, 1.1 Hz, Ar**H**), 7.54 (1H, td, *J* = 7.8, 0.9 Hz, Ar**H**), 7.35 (1H, d, *J* = 7.9 Hz, Ar**H**), 4.98-4.96 (1H, m, =C**H**$_2$), 4.94 (1H, s, =C**H**$_2$), 4.40 (1H, s, N**H**), 2.69 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 2.01-1.85 (2H, m, C**H**$_2CH_3$), 1.80 (3H, dd, *J* = 1.3, 0.7 Hz, C**H**$_3$C=), 0.87 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$), 0.57 (3H, t, *J* = 7.4 Hz, CH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 146.1 (C), 141.8 (C), 136.0 (C), 133.4 (CH), 129.3 (CH), 123.0 (CH), 121.4 (CH), 114.7 (CH_2), 70.4 (C), 50.4 (CH), 32.6 (CH_2), 21.7 (CH_3), 15.0 (CH_3), 8.0 (CH_3); HRMS (ESI) Exact mass calculated for $C_{14}H_{19}NO_2SNa$ $[M+Na]^+$: 288.1029, found: 288.1014.

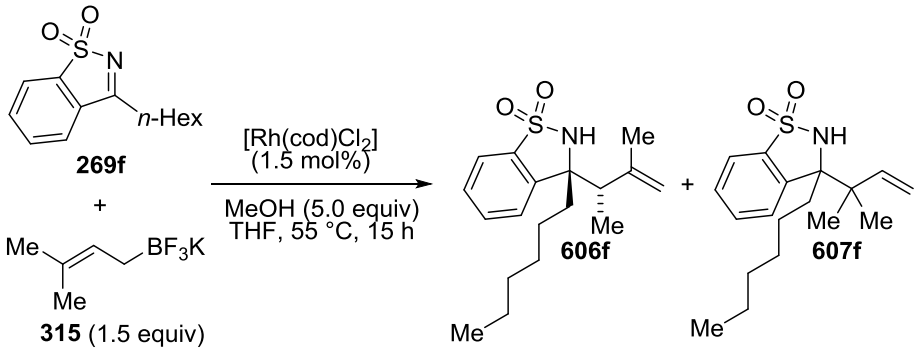
Slow evaporation of a solution of **606e** in Et_2O/petrol gave crystals that were suitable for X-ray diffraction:





606e
CCDC 1013875

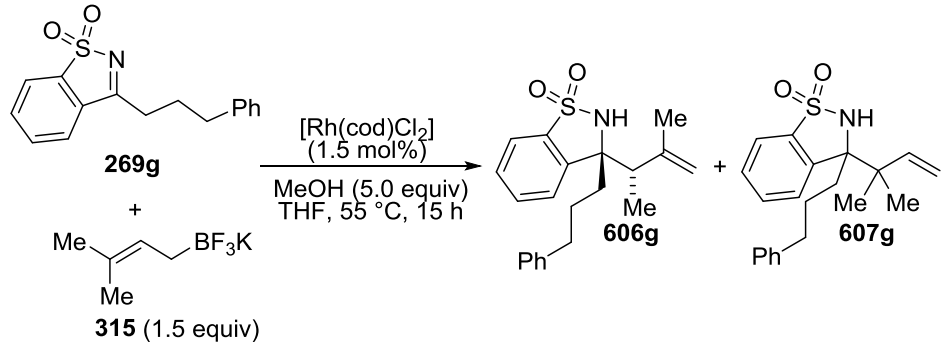
(±)-(*R*)-3-Hexyl-3-[(*S*)-3-methylbut-3-en-2-yl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (606f):



General Procedure E was followed using the ketimine **269f** (75 mg, 0.30 mmol) and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol). Purification by flash column chromatography (80:20 petrol:EtOAc) gave a 79:21 mixture of **606f** and **607f** (88 mg, 91%) that was further purified by flash column chromatography (95:5 *iso*-hexane:EtOAc) to give the *sulfonamide* **606f** (58 mg, 61%) as a white solid. R_f = 0.40 (80:20 petrol:EtOAc); m.p. 134-136 °C (Et_2O); IR 3189 (NH), 2843, 1394, 1284, 1201, 1174, 1129, 1094, 945, 901 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.74 (1H, m, Ar**H**), 7.69-7.63 (1H, m, Ar**H**), 7.58-7.51 (1H, m, Ar**H**), 7.35 (1H, d, *J* = 7.9 Hz, Ar**H**), 5.00-4.97 (1H, m, =C$\mathbf{H}_2$), 4.95 (1H, s, =C$\mathbf{H}_2$), 4.31 (1H, s, N**H**), 2.68 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 1.86 (2H, dd, *J* = 9.2, 7.4 Hz, CC$\mathbf{H}_2$), 1.81 (3H, dd, *J* = 1.2, 0.7 Hz, =CC$\mathbf{H}_3$), 1.32-1.24 (1H, m, C$\mathbf{H}_2$), 1.24-1.08 (6H, m, 3 x C$\mathbf{H}_2$), 0.86 (3H, d, *J* = 7.0 Hz, CHC$\mathbf{H}_3$), 0.81 (3H, t, *J* = 7.0 Hz, CH_2C$\mathbf{H}_3$), 0.76-0.66 (1H, m, C$\mathbf{H}_2$);^{13}C NMR (125.8 MHz, $CDCl_3$) δ 146.1 (C), 142.2 (C), 135.8 (C), 133.4 (CH), 129.3 (CH), 123.0 (CH), 121.5 (CH), 114.8 (CH_2), 69.9 (C), 50.5 (CH), 39.9

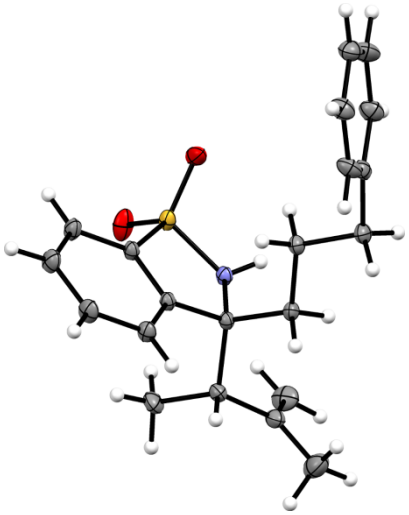
(CH_2), 31.5 (CH_2), 29.2 (CH_2), 23.4 (CH_2), 22.5 (CH_2), 21.7 (CH_3), 14.9 (CH_3), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $C_{18}H_{27}NO_2SNa$ $[M+Na]^+$: 344.1655, found: 344.1644.

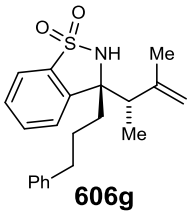
(±)-(*R*)-3-[(*S*)-3-Methylbut-3-en-2-yl]-3-(3-phenylpropyl)-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (606g):



General Procedure E was followed using the ketimine **269g** (86 mg, 0.30 mmol) and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol). Purification by flash column chromatography (80:20 petrol:EtOAc) gave a 76:24 mixture of **606g** and **607g** (74 mg, 69%) that was further purified by flash column chromatography (95:5 *iso*-hexane:EtOAc) to give the *sulfonamide* **606g** (50 mg, 47%) as a colourless solid. R_f = 0.40 (80:20 petrol:EtOAc); m.p. 126-128 °C (Et_2O), IR 3257 (NH), 2927, 2852, 1452, 1279, 1217, 1174, 1155, 1132, 897 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.78 (1H, m, Ar**H**), 7.63 (1H, td, *J* = 7.6, 1.2 Hz, Ar**H**), 7.53 (1H, td, *J* = 7.6, 1.0 Hz, Ar**H**), 7.28-7.21 (3H, m, Ar**H**), 7.19-7.14 (1H, m, Ar**H**), 7.06-7.02 (2H, m, Ar**H**), 4.98-4.96 (1H, m, =C**H**$_2$), 4.92 (1H, s, =C**H**$_2$), 4.36 (1H, s, N**H**), 2.65 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 2.61-2.42 (2H, m, C**H**$_2$Ph), 1.94-1.84 (2H, m, C**H**$_2CH_2CH_2$Ph), 1.77-1.75 (3H, m, C**H**$_3$C=), 1.72-1.56 (1H, m, C**H**$_2CH_2$Ph), 1.17-1.01 (1H, m, C**H**$_2CH_2$Ph), 0.84 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 146.0 (C), 141.9 (C), 141.3 (C), 135.8 (C), 133.4 (CH), 129.3 (CH), 128.4 (2 x CH), 128.3 (2 x CH), 125.9 (CH), 122.9 (CH), 121.5 (CH), 114.9 (CH_2), 69.7 (C), 50.5 (CH), 39.1 (CH_2), 35.4 (CH_2), 25.0 (CH_2), 21.7 (CH_3), 14.8 (CH_3); HRMS (ESI) Exact mass calculated for $C_{21}H_{25}NO_2SNa$ $[M+Na]^+$: 378.1498, found: 378.1494.

Slow evaporation of a solution of **606g** in Et_2O/petrol gave crystals that were suitable for X-ray diffraction:

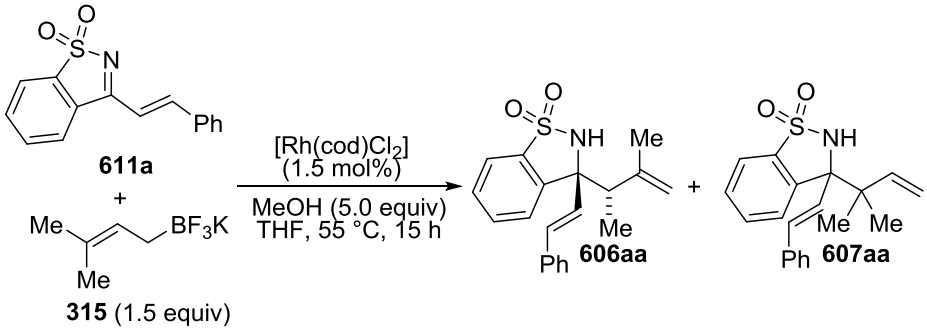




606g

CCDC 1013876

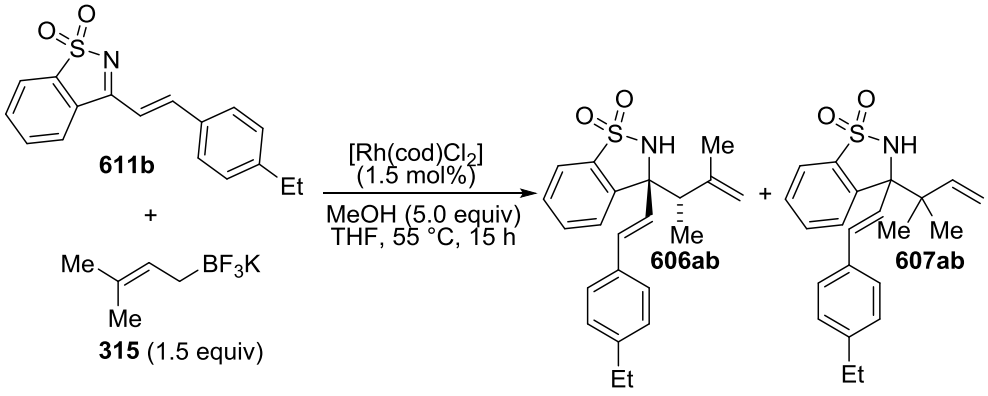
(±)-(*R*)-3-[(*S*)-3-Methylbut-3-en-2-yl]-3-[(*E*)-2-phenylethenyl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (606aa):



General Procedure E was followed using the ketimine **611a** (81 mg, 0.30 mmol) and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol). Purification by flash column chromatography (90:10 petrol:EtOAc) gave a 72:28 mixture of **606aa** and **607aa** (65 mg, 68%) that was further purified by flash column chromatography (30:70 *iso*-hexane:CH_2Cl_2) to give the *sulfonamide* **606aa** (57 mg, 56%) as a white solid. R_f = 0.45 (80:20 petrol:EtOAc); m.p. 127-129 °C (Et_2O); IR 3307 (NH), 1732, 1340, 1278, 1204, 1169, 1132, 893, 840, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.67 (1H, td, *J* = 7.7, 1.0 Hz, Ar**H**), 7.55 (1H, td, *J* = 7.6, 0.6 Hz, Ar**H**), 7.48 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.35-7.21 (5H, m, Ar**H**), 6.72 (1H, d, *J* = 15.7 Hz, C**H**=CH), 6.47 (1H, d, *J* = 15.7 Hz, CH=C**H**), 5.05-5.03 (1H, m,

=C**H**$_2$), 5.00 (1H, s, =C**H**$_2$), 4.81 (1H, s, N**H**), 2.99 (1H, q, *J* = 7.0 Hz, C**H**CH$_3$), 1.81 (3H, s, C**H**$_3$C=), 0.96 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 145.9 (C), 141.7 (C), 136.0 (C), 134.1 (C), 133.5 (CH), 130.8 (CH), 129.8 (CH), 129.5 (CH), 128.6 (2 x CH), 128.1 (CH), 126.7 (2 x CH), 123.7 (CH), 121.8 (CH), 115.0 (CH_2), 69.2 (C), 49.8 (CH), 23.1 (CH_3), 14.6 (CH_3); HRMS (ESI) Exact mass calculated for $C_{20}H_{21}NO_2SNa$ $[M+Na]^+$: 362.1185, found: 362.1177.

(±)-(*R*)-3-[(*E*)-2-(4-Ethylphenyl)ethenyl]-3-[(*S*)-3-methylbut-3-en-2-yl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (606ab):

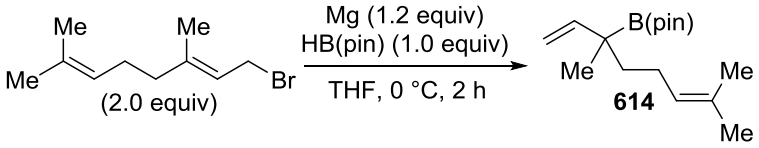


General Procedure E was followed using the ketimine **611b** (89 mg, 0.30 mmol) and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol). Purification by flash column chromatography (90:10 petrol:EtOAc) gave a 82:18 mixture of **606ab** and **607ab** (82 mg, 75%) that was further purified by flash column chromatography (30:70 *iso*-hexane:CH_2Cl_2) to give the *sulfonamide* **606ab** (47 mg, 46%) as a white solid. R_f = 0.43 (80:20 petrol:EtOAc); m.p. 136-138 °C (Et_2O); IR 3306 (NH), 2989, 1652, 1352, 1279, 1172, 1149, 887, 820, 787 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.68-7.64 (1H, m, Ar**H**), 7.57-7.53 (1H, m, Ar**H**), 7.47 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.27-7.25 (2H, m, Ar**H**), 7.13 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.67 (1H, d, *J* = 15.7, C**H**=CH), 6.43 (1H, d, *J* = 15.7 Hz, CH=C**H**), 5.03-5.02 (1H, m, =C**H**$_2$), 4.99 (1H, s, =C**H**$_2$), 4.76 (1H, s, N**H**), 2.97 (1H, q, *J* = 7.0 Hz, C**H**CH$_3$), 2.62 (2H, q, *J* = 7.6 Hz, C**H**$_2$CH$_3$), 1.81 (3H, s, C**H**$_3$C=), 1.21 (3H, t, *J* = 7.6 Hz, CH$_2$C**H**$_3$), 0.95 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 146.0 (C), 144.5 (C), 141.9 (C), 134.1 (C), 133.4 (CH), 133.4 (C), 129.8 (CH),

129.7 (CH), 129.4 (CH), 128.1 (2 x CH), 126.7 (2 x CH), 123.7 (CH), 121.7 (CH), 114.9 (CH_2), 69.2 (C), 49.9 (CH), 28.6 (CH_2), 23.1 (CH_3), 15.5 (CH_3), 14.6 (CH_3); HRMS (ESI) Exact mass calculated for $C_{22}H_{25}NO_2SNa$ $[M+Na]^+$: 390.1498, found: 390.1497.

1.2.3 Synthesis of Other Boron Species

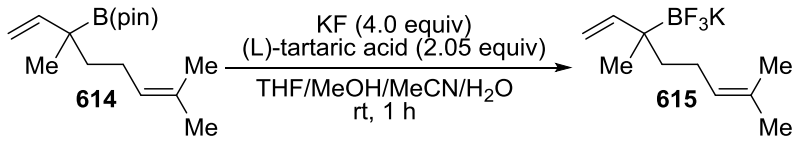
2-(3,7-Dimethylocta-1,6-dien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (614):



Magnesium turnings (138 mg, 6.00 mmol) were suspended in THF (20 mL) at 0 °C under N_2. Pinacolborane (0.72 mL, 5.00 mmol) was added then, geranyl bromide (0.98 mL, 5.00 mmol) was slowly added dropwise over 5 min. The solution was warmed to room temperature and stirred for 30 min, then additional geranyl bromide (0.98 mL, 5.00 mmol) was added dropwise and the solution was stirred for a further 1.5 h. The reaction was diluted with hexanes (50 mL) and then quenched carefully with the slow addition of 2 M HCl (10 mL). The mixture was extracted with hexanes (3 x 50 mL) and the organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (98:2 hexanes:EtOAc) gave the *allylboronic acid pinacol ester* **614** as a colourless oil (900 mg, 68%). R_f = 0.67 (95:5 hexane:EtOAc); IR 3234, 3014, 2856, 1405, 1378, 1204, 1182, 1126, 1020, 940 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (1H, q, *J* = 17.4, 10.8 Hz, C**H**=CH_2), 5.16-5.10 (1H, m, CH_2C**H**=), 5.00-4.94 (2H, m, =C**H**$_2$), 2.01-1.91 (2H, m, C**H**$_2$C=), 1.70 (3H, s, =C(C**H**$_3$)$_2$), 1.62 (3H, s, =C(C**H**$_3$)$_2$), 1.54 (1H, ddd, *J* = 13.2, 11.1, 6.0 Hz, BCC**H**$_2$), 1.39 (1H, ddd, *J* = 13.2, 11.0, 6.1 Hz, BCC**H**$_2$), 1.25 (12H, s, 2 x C(C**H**$_3$)$_2$), 1.09 (3H, s, BCC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 145.4 (CH), 131.0 (C), 125.1 (CH), 111.0 (CH_2), 83.1 (2 x C), 38.3 (CH_2), 25.7 (CH_3), 24.7 (2 x CH_3), 24.6 (2 x CH_3), 24.4 (CH_2), 19.5 (CH_3), 17.5 (CH_3), the secondary carbon (CH_2) next to boron

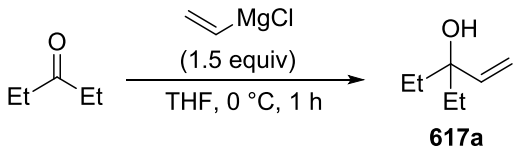
was not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calculated for $C_{16}H_{30}BO_2Na$ $[M+Na]^+$: 287.2153, found: 287.2147.

(3,7-Dimethylocta-1,6-dien-3-yl)trifluoro-λ⁴-borane potassium (615):



To a solution of the allylboronic acid pinacol ester **614** (450 mg, 1.70 mmol) in MeCN (6 mL) and MeOH (6 mL) at room temperature was added a solution of KF (394 mg, 6.80 mmol) in 0.5 mL of H_2O. A solution of (L)-tartaric acid (502 mg, 3.49 mmol) in THF (5 mL) was then slowly added dropwise with vigorous stirring. The mixture was stirred for 30 min, then MeCN (5 mL) was added and the solution was stirred for an additional 30 min. The reaction was filtered, the filter cake was washed with MeCN (3 x 5 mL), and the filtrate was concentrated *in vacuo*. The residue was dried under high vacuum for 1 h with gentle heating to leave the *allyltrifluoroborate* **615** as a white solid (180 mg, 43%). m.p. >300 °C (Et_2O); IR 3123, 2657, 1343, 1301, 1232, 1208, 1145, 1095, 1075, 987 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 5.97 (1H, q, *J* = 17.6, 10.8 Hz, C**H**=CH_2), 5.12 (1H, dddd, *J* = 7.3, 5.8, 2.8, 1.4 Hz, CH_2C**H**=), 4.64 (1H, dd, *J* = 10.8. 2.8 Hz, =C**H**$_2$), 4.55 (1H, dd, *J* = 17.6, 2.8 Hz, =C**H**$_2$), 1.85-1.70 (2H, m, BCCH_2C**H**$_2$), 1.64 (3H, d, *J* = 1.0 Hz, =C(C**H**$_3$)$_2$), 1.56 (3H, s, =C(C**H**$_3$)$_2$), 1.35-1.25 (2H, m, BCC**H**$_2$) 0.79 (3H, s, BCC**H**$_3$); ^{13}C NMR (125.8 MHz, CD_3CN) δ 152.4 (CH), 130.2 (C), 127.9 (CH), 107.0 (CH_2), 37.8 (CH_2), 25.8 (CH_2), 23.9 (CH_3), 18.2 (CH_3), 17.5 (CH_3), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B; ^{19}F NMR (376 MHz, CD_3CN) δ −150.0.

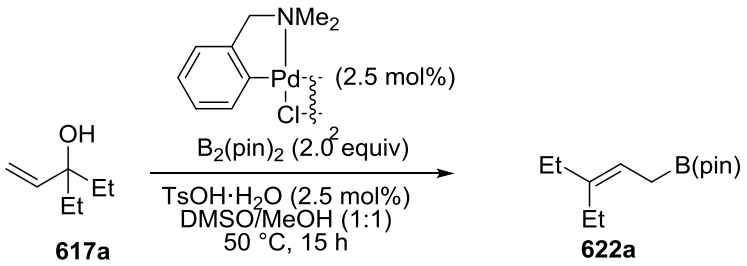
3-Ethyl-1-penten-3-ol (617a)



617a

To a solution of pentan-3-one (2.11 mL, 20 mmol) in THF (100 mL) at 0 °C was added vinylmagnesium chloride (1.6 M in THF, 18.75 mL, 30 mmol) over *ca.* 5 min. The solution was stirred for 1 h and then quenched carefully by the addition of saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with Et_2O (3 x 100 mL) and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* at 700 mbar at 25 °C to give the *allylic alcohol* **617a** (1.93 g, 85%) as a yellow oil that displayed spectroscopic data consistent with those reported previously.[233] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (1H, dd, *J* = 17.4, 10.8 Hz, C**H**=CH_2), 5.21 (1H, dd, *J* = 17.4, 1.4 Hz, CH=C**H**$_2$), 5.13 (1H, dd, *J* = 10.8, 1.4 Hz, CH=C**H**$_2$), 1.61-1.49 (4H, m, (C**H**$_2$$CH_3$)$_2$), 0.87 (6H, t, *J* = 7.5 Hz, (CH_2C**H**$_3$)$_2$); HRMS (ESI) Exact mass calculated for $C_7H_{15}O$ $[M+H]^+$: 115.1929, found: 115.1925.

4,4,5,5-Tetramethyl-2-[(*E*)-3-ethyl-pent-2-en-1-yl]-1,3,2-dioxaborolane (622a):

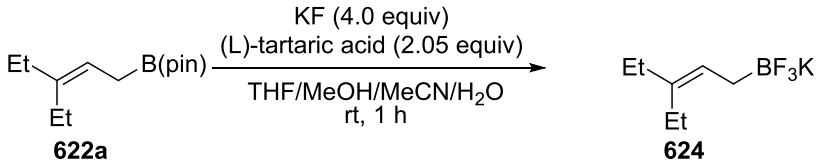


617a **622a**

3-Ethyl-1-penten-3-ol (**617a**) (456 mg, 4.00 mmol), bis(pinacolato)diboron (2.04 mg, 8.00 mmol), palladium *N,N*-dimethylbenzylamide chloride dimer (69.0 mg, 0.1 mmol), and TsOH·H_2O (24.0 mg, 0.1 mmol) were dissolved in DMSO (10 mL) and MeOH (10 mL) under N_2. The solution was stirred at 50 °C for 15 h and cooled to room temperature. The reaction was diluted with Et_2O (100 mL), washed with brine (3 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue

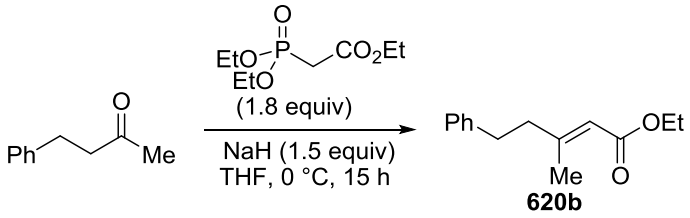
by flash column chromatography (95:5 petrol:EtOAc) gave the *allylboronic acid pinacol ester* **622a** (510 mg, 57%) as a colourless oil. R_f = 0.62 (95:5 petrol:EtOAc); IR 2837, 2510, 1458, 1382, 1321, 1279, 1174, 1103, 983, 906 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.20 (1H, t, *J* = 7.8 Hz, C**H**=), 2.09-1.97 (4H, m, (C**H**$_2$CH$_3$)$_2$), 1.63 (2H, d, *J* = 7.8 Hz, C**H**$_2$B), 1.25 (12H, s, 2 x (C**H**$_3$)$_2$), 0.97 (6H, dd, *J* = 15.7 , 7.5 Hz, (CH$_2$C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.5 (C), 116.6 (CH), 83.0 (2 x C), 29.3 (CH_2), 24.7 (4 x CH_3), 22.9 (CH_2), 13.0 (CH_3), 12.8 (CH_3) the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calculated for $C_{13}H_{25}BO_2Na$ $[M+Na]^+$: 247.1845, found: 247.1839.

Trifluoro[(*E*)-3-ethyl-5-pent-2-en-1-yl]-λ^4-borane potassium (624)



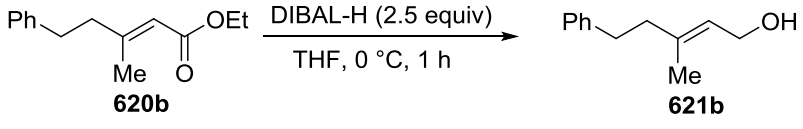
To a solution of the *allylboronic acid pinacol ester* **622a** (510 mg, 2.3 mmol) in MeCN (5 mL) and MeOH (5 mL) at room temperature was added a solution of KF (530 mg, 9.20 mmol) in H_2O (0.5 mL). A solution of (L)-tartaric acid (685 mg, 4.715 mmol) in THF (3.5 mL) was then added dropwise with vigorous stirring. The mixture was stirred for 30 min, then MeCN (5 mL) was added and the solution was stirred for an additional 30 min. The reaction was filtered, the filter cake was washed with MeCN (3 x 5 mL), and the filtrate was concentrated *in vacuo*. The residue was dried under high vacuum for 1 h with gentle heating, suspended in Et_2O, and filtered to leave the *allyltrifluoroborate* **624** (395 mg, 84%) as a white solid. m.p. >300 °C (Et_2O); ^1H NMR (CD_3CN, 300 MHz) δ 5.25 (1H, t, *J* = 8.0 Hz, C**H**=), 2.01-1.94 (4H, m, (C**H**$_2$CH$_3$)$_2$), 0.96 (6H, dd, *J* = 14.6, 7.4 Hz, (CH$_2$C**H**$_3$)$_2$), 0.92 (2H, br s, C**H**$_2$B); ^{13}C NMR (75 MHz, CD_3CN) δ 128.8 (C), 125.3 (CH), 29.3 (CH_2), 22.3 (CH_2), 12.7 (CH_3), 12,5 (CH_3) the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B and one further quaternary carbon is not clearly visible in the spectrum; ^{19}F NMR (376 MHz, CD_3CN) δ −139.5.

(*E*)-3-Methyl-5-phenyl-2-pentenoic acid ethyl ester (620b):



To a solution of NaH (60% in mineral oil, 1.80 g, 45 mmol) in THF at 0 °C was slowly added triethyl phosphonoacetate (10.7 mL, 54 mmol). The solution was stirred for 45 minutes then 4-phenylbutan-2-one (4.50 mL, 30 mmol) was added and the solution was stirred for 15 hours. The reaction was quenched by the addition of H_2O (100 mL) and the mixture was extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with brine (150 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a 4:1 *E*:*Z* mixture. Purification of the residue by flash column chromatography (99.5:0.5 petrol:EtOAc) gave the *ester* **620b** (2.93 g, 45%) as a 2.8:1 *E*:*Z* mixture of isomers followed by pure (*E*)-*ester* **620b** (1.93 g, 30%) as a colourless oil that displayed spectroscopic data consistent with those reported previously.[234] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.15 (5H, m, Ar**H**), 5.70 (1H, d, *J* = 1.3 Hz, C**H**=), 4.15 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 2.96-2.88 (2H, m, PhC**H**$_2$), 2.83-2.74 (2H, m, PhCH$_2$C**H**$_2$), 1.89 (3H, d, *J* = 1.4 Hz, =CC**H**$_3$), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); HRMS (ESI) Exact mass calculated for $C_{14}H_{19}O_2$ $[M]^+$: 219.1380, found: 219.1383. The stereochemistry of the alkene was assigned on the basis of NOESY spectra.

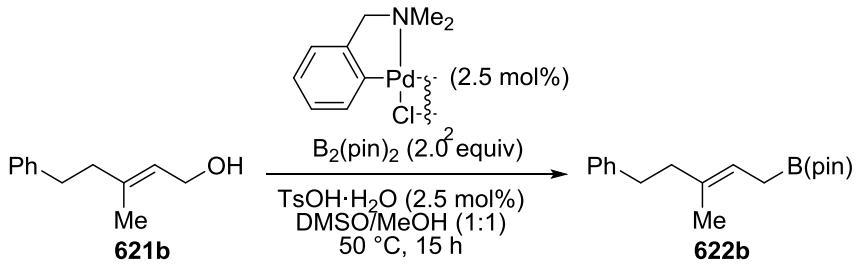
(*E*)-3-Methyl-5-phenylpent-2-enol (621b)



To a solution of *ester* **620b** (1.09 g, 5.0 mmol) in THF (100 mL) at 0 °C was slowly added DIBAL-H solution (1 M in hexanes, 12.5 mL, 12.5 mmol). The solution was stirred for 1 hour before being quenched by the addition of saturated potassium

sodium tartrate solution (100 mL). The mixture was stirred for 1 hour at room temperature before being extracted with Et_2O (3 x 100 mL). The organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *alcohol* **621b** (770 mg, 88%) as a colourless oil that displayed spectroscopic data consistent with those reported previously.[234] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.25 (2H, m, Ar**H**), 7.23-7.16 (3H, m, Ar**H**), 5.48-5.39 (1H, m, C**H**=), 4.16 (2H, d, *J* = 6.7 Hz, C**H**$_2$OH), 2.80-2.70 (2H, m, PhC**H**$_2$), 2.39-2.28 (2H, m, PhCH$_2$C**H**$_2$), 1.74 (3H, s, =CC**H**$_3$); HRMS (ESI) Exact mass calculated for $C_{12}H_{14}$ [M-H_2O]$^+$: 158.1096, found: 158.1097. The stereochemistry of the alkene was assigned on the basis of NOESY spectra.

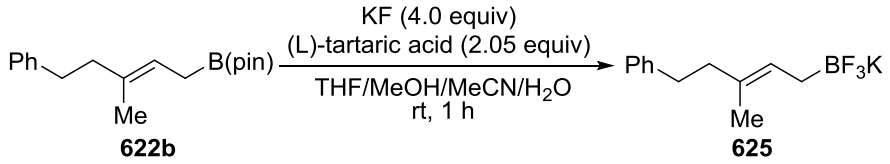
4,4,5,5-Tetramethyl-2-[(*E*)-3-methyl-5-phenylpent-2-en-1-yl]-1,3,2-dioxaborolane (622b):



(*E*)-3-Methyl-5-phenylpent-2-enol (**621b**) (176 mg, 1.00 mmol), bis(pinacolato)diboron (508 mg, 2.00 mmol), palladium *N,N*-dimethylbenzylamide chloride dimer (18.0 mg, 0.025 mmol), and TsOH·H_2O (6.0 mg, 0.025 mmol) were dissolved in DMSO (5 mL) and MeOH (5 mL) under N_2. The solution was stirred at 50 °C for 15 h and cooled to room temperature. The reaction was diluted with Et_2O (100 mL), washed with brine (3 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (98:2 petrol:EtOAc) gave the *allylboronic acid pinacol ester* **622b** as a colourless oil (141 mg, 49%). R_f = 0.62 (95:5 petrol:EtOAc); IR 3023, 2747, 1389, 1302, 1248, 1187, 1031, 936, 914, 849 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (2H, m, Ar**H**), 7.21-7.15 (3H, m, Ar**H**), 5.33-5.26 (1H, m, C**H**=), 2.74-2.68 (2H, m, PhC**H**$_2$), 2.33-2.27 (2H, m, PhCH$_2$C**H**$_2$), 1.65 (3H, d, *J* = 0.9 Hz, =CC**H**$_3$), 1.62 (2H, br d, *J* = 7.8 Hz, C**H**$_2$B), 1.23 (12H, s, 2 x C(C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6 (C),

134.7 (C), 128.4 (2 x CH), 128.2 (2 x CH), 125.6 (CH), 119.0 (CH), 83.1 (2 x C), 41.6 (CH_2), 34.9 (CH_2), 24.7 (4 x CH_3), 16.1 (CH_3), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calculated for $C_{18}H_{27}BO_2Na$ $[M+Na]^+$: 309.2002, found: 309.2010. The stereochemistry of the alkene was assigned on the basis of NOESY spectra.

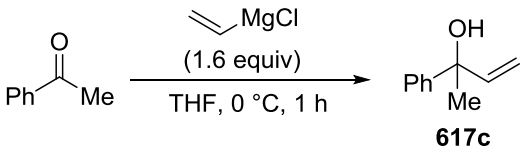
Trifluoro[(*E*)-3-methyl-5-phenylpent-2-en-1-yl]-λ^4-borane potassium (625):



622b **625**

To a solution of the *allylboronic acid pinacol ester* **622b** (141 mg, 0.50 mmol) in MeCN (2 mL) and MeOH (2 mL) at room temperature was added a solution of KF (116 mg, 2.00 mmol) in H_2O (0.5 mL). A solution of (L)-tartaric acid (153 mg, 1.025 mmol) in THF (1 mL) was then added dropwise with vigorous stirring. The mixture was stirred for 30 min, then MeCN (5 mL) was added and the solution was stirred for an additional 30 min. The reaction was filtered, the filter cake was washed with MeCN (3 x 5 mL), and the filtrate was concentrated *in vacuo*. The residue was dried under high vacuum for 1 h with gentle heating, suspended in Et_2O, and filtered to leave the *allyltrifluoroborate* **625** as a white solid (94 mg, 71%) m.p. >300 °C (Et_2O); IR 3027, 2948, 1494, 1243, 1109, 1078, 1015, 965, 940, 865 cm^{-1}; ^1H NMR (CD_3CN, 300 MHz) δ 7.28-7.20 (4H, m, Ar**H**), 7.17-7.14 (1H, m, Ar**H**), 5.33 (1H, t, *J* = 7.5 Hz, C**H**=C), 2.69-2.64 (2H, m, PhC$\mathbf{H}_2$), 2.24-2.19 (2H, m, $PhCH_2C\mathbf{H}_2$), 1.60 (3H, s, C$\mathbf{H}_3$), 0.89 (2H, br s, C$\mathbf{H}_2$B); ^{13}C NMR (75 MHz, CD_3CN) δ 144.3 (C), 129.3 (2 x CH), 129.1 (2 x CH), 128.7 (CH), 126.4 (CH), 43.2 (CH_2), 35.9 (CH_2), 15.9 (CH_3), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B and one further quaternary carbon is not clearly visible in the spectrum; ^{19}F NMR (376 MHz, CD_3CN) δ −139.2. The stereochemistry of the alkene was assigned on the basis of NOESY spectra.

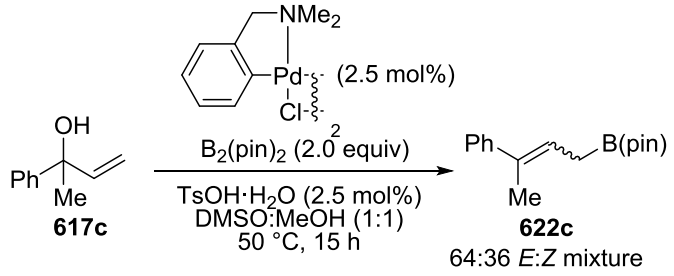
2-Hydroxy-2-phenyl-3-butene (617c)



617c

To a solution of acetophenone (1.16 mL, 10 mmol) in THF (50 mL) at 0 °C was added vinylmagnesium chloride (1.6 M in THF, 10 mL, 16 mmol) over *ca.* 5 min. The solution was stirred for 1 h and then quenched carefully by the addition of saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with Et_2O (3 x 100 mL) and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* at 700 mbar at 25 °C to give the *allylic alcohol* **617c** (1.40 g, 95%) as a yellow oil that displayed spectroscopic data consistent with those reported previously.[235] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.46 (2H, m, Ar**H**), 7.40-7.33 (2H, m, Ar**H**), 7.30-7.23 (1H, m, Ar**H**), 6.19 (1H, dd, *J* = 17.3, 10.6 Hz, C**H**=CH_2), 5.31 (1H, dd, *J* = 17.3, 1.3 Hz, CH=C**H**$_2$), 5.16 (1H, dd, *J* = 10.6, 1.3 Hz, CH=C**H**$_2$), 1.67 (3H, s, C**H**$_3$); HRMS (ESI) Exact mass calculated for $C_{10}H_{12}ONa$ $[M+Na]^+$: 170.0786, found: 170.0785.

4,4,5,5-Tetramethyl-2-[(*E*)-3-phenylbut-2-en-1-yl]-1,3,2-dioxaborolane (622c):



617c **622c**

64:36 *E*:*Z* mixture

2-Hydroxy-2-phenyl-3-butene (740 mg, 5.00 mmol), bis(pinacolato)diboron (2.54 g, 10.0 mmol), palladium *N,N*-dimethylbenzylamide chloride dimer (69.0 mg, 0.125 mmol), and TsOH·H_2O (24.0 mg, 0.125 mmol) were dissolved in DMSO (20 mL) and MeOH (20 mL) under N_2. The solution was stirred at 50 °C for 15 h and cooled to room temperature. The reaction was diluted with Et_2O (100 mL), washed with

brine (3 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (98:2 petrol:EtOAc) gave the *allylboronic acid pinacol ester* **622c** as a colourless oil (589 mg, 46%) as a 64:36 inseparable mixture of *E*:*Z* isomers.

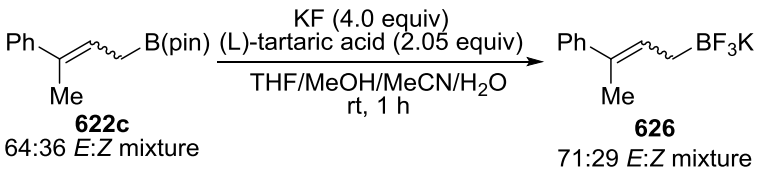
Data for major *E*-isomer: R_f = 0.71 (95:5 petrol:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.17 (5H, m, Ar**H**), 5.93 (1H, tq, *J* = 7.9, 1.3 Hz, C**H**=), 2.04-2.03 (3H, m, C**H**$_3$C=), 1.84 (2H, d, *J* = 7.9 Hz, C**H**$_2$B), 1.25 (12H, s, 2 x C(C**H**$_3$)$_2$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1 (C), 134.5 (C), 128.0 (2 x CH), 126.2 (2 x CH), 125.6 (CH), 123.1 (CH), 83.3 (2 x C), 24.8 (4 x CH_3), 15.7 (CH_3), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B.

Data for minor *Z*-isomer: R_f = 0.71 (95:5 petrol:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.17 (5H, m, Ar**H**), 5.61 (1H, tq, *J* = 8.0, 1.3 Hz, C**H**=), 2.06-2.04 (3H, m, C**H**$_3$C=), 1.64 (2H, d, *J* = 7.7 Hz, C**H**$_2$B), 1.24 (12H, s, 2 x C(C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1 (C), 134.5 (C), 128.1 (2 x CH), 128.0 (2 x CH), 126.3 (CH), 121.8 (CH), 83.1 (2 x C), 25.5 (CH_3), 24.8 (4 x CH_3), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calculated for $C_{16}H_{23}BO_2Na$ $[M+Na]^+$: 281.1683, found: 281.1678.

If this reaction is conducted with geometrically pure (*E*)-3-phenylprop-2-en-1-ol, the allylboronic acid pinacol ester **622c** is obtained in the same isomeric ratio as described above.

The stereochemistries of the alkenes in the major and minor isomers were assigned on the basis of NOESY spectra.

Trifluoro[(*E*)-3-phenylbut-2-en-1-yl]-λ^4-borane potassium (626):



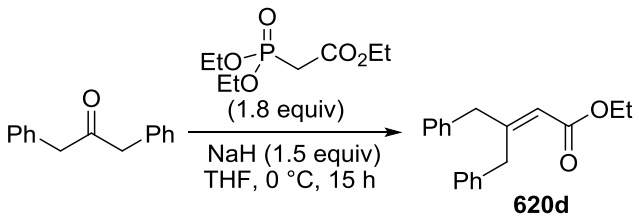
To a solution of the allylboronic acid pinacol ester **622c** (64:36 *E*:*Z* mixture, 310 mg, 1.20 mmol) in MeCN (6 mL) and MeOH (6 mL) at room temperature was added a solution of KF (278 mg, 4.80 mmol) in H_2O (1 mL). A solution of (L)-tartaric acid (369 mg, 2.46 mmol) in THF (4 mL) was then added dropwise with vigorous stirring. The mixture was stirred for 30 min, then MeCN (5 mL) was added and the solution was stirred for an additional 30 min. The reaction was filtered, the filter cake was washed with MeCN (3 x 5 mL), and the filtrate was concentrated *in vacuo*. The residue was dried under high vacuum for 1 h with gentle heating, suspended in Et_2O, and filtered to leave the *allyltrifluoroborate* **626** as a white solid (154 mg, 54 %) as a 71:29 inseparable mixture of *E*:*Z* isomers. m.p. >300 °C (Et_2O); IR 3187, 3064, 1472, 1302, 1295, 1263, 1241, 1109, 1046, 962 cm^{-1}.

Data for major *E*-Isomer: ^{1}H NMR (300 MHz, CD_3CN) δ 7.40-7.10 (5H, m, Ar**H**), 6.10-6.02 (1H, m, C**H**=), 1.98-1.96 (3H, m, C**H**$_3$), 1.19 (2H, br s, C**H**$_2$B); ^{13}C NMR (75 MHz, CD_3CN) δ 146.1 (C), 133.3 (CH), 128.9 (2 x CH), 128.5 (CH), 125.8 (2 x CH), 15.3 (CH_3), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B and further quaternary carbon (C) is not visible in the spectrum; ^{19}F NMR (376 MHz, CD_3CN) δ −139.0.

Data for minor *Z*-Isomer: ^{1}H NMR (300 MHz, CD_3CN) δ 7.40-7.10 (5H, m, Ar**H**), 5.72-5.63 (1H, m, C**H**=), 2.00-1.98 (3H, m, C**H**$_3$), 0.97 (2H, br s, C**H**$_2$B); ^{13}C NMR (75 MHz, CD_3CN) δ 146.1 (C), 133.3 (CH), 129.4 (2 x CH), 126.4 (CH), 126.0 (2 x CH), 25.6 (CH_3), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B and further quaternary carbon (C) is not visible in the spectra; ^{19}F NMR (376 MHz, CD_3CN) δ −139.0.

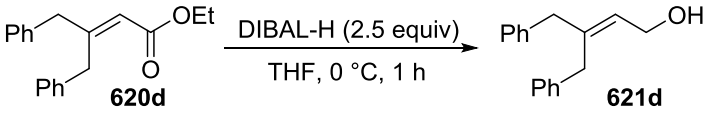
The stereochemistries of the alkenes in the major and minor isomers were assigned on the basis of NOESY spectra.

Ethyl 2-benzyl-1-phenylbut-2-enoate (620d)



To a solution of NaH (60% in mineral oil, 2.40 g, 60 mmol) in THF (200 mL) at 0 °C was slowly added triethyl phosphonoacetate (14.24 mL, 75 mmol). The solution was stirred for 45 minutes then 1,3-diphenylacetone (8.40 g, 40 mmol) was added and the solution was stirred for 15 hours. The reaction was quenched by the addition of H_2O (100 mL) and the mixture was extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with brine (150 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (95:05 petrol:EtOAc) gave the *ester* **620d** (7.90 g, 71%) as a colourless oil that displayed spectroscopic data consistent with those reported previously.[236] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.20 (8H, m, Ar**H**), 7.15-7.06 (2H, m, Ar**H**), 5.75 (1H, s, C=C**H**), 4.20 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 4.00 (2H, s, PhC**H**$_2$), 3.35 (2H, s, PhC**H**$_2$), 1.30 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); HRMS (ESI) Exact mass calculated for $C_{19}H_{20}O_2Na$ $[M+Na]^+$: 303.1361 found: 303.1367.

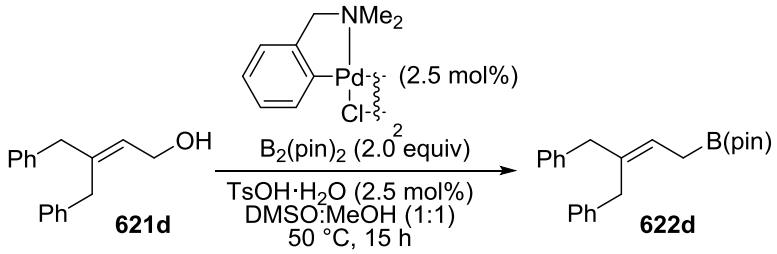
3-Benzyl-4-phenylbut-2-en-1-ol (621d):



Ethyl 2-benzyl-1-phenylbut-2-enoate (**620d**, 2.80 g, 10.0 mmol) was dissolved in THF (100 mL) under N_2 at 0 °C. DIBAL-H (1 M in hexanes, 25 mL, 25.0 mmol) was slowly added dropwise then the solution was stirred at room temperature for 1 h. The reaction was quenched carefully by the slow addition of 1 M HCl (10 mL) before the addition of saturated aqueous potassium sodium tartrate solution (100

mL). The biphasic mixture was stirred for 1 h until the organic layer was clear, then extracted with EtOAc (3 x 100 mL), washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to leave the *allylic alcohol* **621d** as a white solid (2.08 g, 87%) that required no further purification. R_f = 0.29 (70:30 petrol:EtOAc); m.p. 68-70 C (Et_2O); IR 3373, 2987 (OH), 2902, 1492, 1436, 1394, 1336, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.29 (4H, m, Ar**H**), 7.28-7.22 (2H, m, Ar**H**), 7.20-7.15 (4H, m, Ar**H**), 5.65 (1H, t, *J* = 6.9 Hz, C**H**=), 4.34 (2H, d, *J* = 6.9 Hz, C**H**$_2$OH), 3.39 (2H, s, PhC**H**$_2$), 3.29 (2H, s, PhC**H**$_2$), 1.52 (1H, br s, O**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4 (C), 139.2 (C), 129.2 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.3 (2 x CH), 127.0 (C), 126.21 (CH), 126.20 (CH), 126.17 (CH), 59.4 (CH_2), 42.8 (CH_2), 35.7 (CH_2); HRMS (ESI) Exact mass calculated for $C_{17}H_{18}ONa$ $[M+Na]^+$: 261.1250, found: 261.1243.

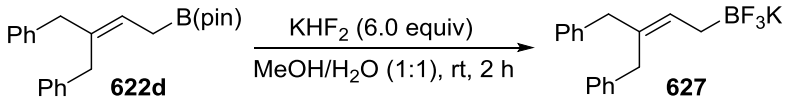
2-(3-Benzyl-4-phenylbut-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (622d):



The *allylic alcohol* **621d** (952 mg, 4.00 mmol), bis(pinacolato)diboron (2.08 g, 8.00 mmol), palladium *N,N*-dimethylbenzylamide chloride dimer (55 mg, 0.10 mmol), and TsOH·H_2O (19 mg, 0.10 mmol) were dissolved in DMSO (20 mL) and MeOH (20 mL) under N_2. The solution was stirred at 50 °C for 15 h and cooled to room temperature. The reaction was diluted with Et_2O (100 mL), washed with brine (3 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (98:2 petrol:EtOAc) gave the *allylboronic acid pinacol ester* **622d** as a colourless oil (607 mg, 47%). R_f = 0.71 (95:5 petrol:EtOAc); IR 3305, 3149, 2741, 1406, 1362, 1318, 1219, 1163, 1103, 1003 cm^{-1}; ^1H NMR (300 MHz, CD Cl_3) δ 7.31-7.22 (4H, m, Ar**H**), 7.22-7.11 (6H, m, Ar**H**), 5.61 (1H, t, *J* = 8.0 Hz, C**H**=), 3.27 (2H, s, PhC**H**$_2$), 3.22 (2H, s, PhC**H**$_2$), 1.83 (2H, d, *J* = 8.0 Hz,

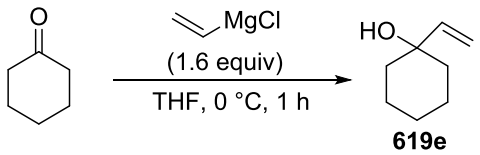
C**H**$_2$B), 1.27 (12H, s, 2 x C(C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ:140.6 (C), 140.0 (C), 136.9 (C), 129.0 (2 x CH), 128.8 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 125.8 (CH), 125.8 (CH), 123.1 (CH), 83.5 (C), 83.3 (C), 43.0 (CH_2), 34.8 (CH_2), 25.0 (2 x CH_3), 24.8 (2 x CH_3), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calculated for $C_{23}H_{29}BO_2Na$ $[M+Na]^+$: 371.2158, found: 371.2152.

(3-Benzyl-4-phenylbut-2-en-1-yl)trifluoro-λ^4-borane potassium (627)



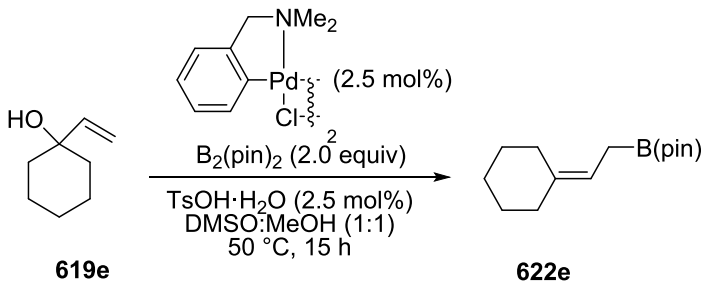
To a solution of the *allylboronic acid pinacol ester* **622d** (607 mg, 1.70 mmol) in H_2O (10 mL) and MeOH (10 mL) at room temperature was added KHF_2 (936 mg, 10.2 mmol) and the mixture was stirred for 2 h. The reaction was concentrated *in vacuo* and the resulting solid was dissolved in warm acetone. The solution was filtered through cotton wool and concentrated *in vacuo* to leave the *allyltrifluoroborate* **627** as a white solid (457 mg, 82%). m.p. >300 °C; IR 3026, 2924, 1493, 1453, 1440, 1233, 1067, 1029, 983, 941 cm^{-1}; ^{1}H NMR (300 MHz, CD_3CN) δ 7.33-7.23 (6H, m, Ar**H**), 7.23-7.13 (4H, m, Ar**H**), 5.57 (1H, t, *J* = 8.2 Hz, C**H**=), 3.24 (2H, s, PhC**H**$_2$), 3.09 (2H, s, PhC**H**$_2$), 1.12 (2H, br s, C**H**$_2$B); ^{13}C NMR (75 MHz, CD_3CN) δ 142.4 (2 x C), 132.6 (C), 131.9 (CH), 129.8 (4 x CH), 129.0 (4 x CH), 126.5 (CH), 126.3 (CH), 43.7 (CH_2), 35.4 (CH_2), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B; ^{19}F NMR (376 MHz, CD_3CN) δ −139.1.

1-Hydroxy-1-vinylcyclohexane (619e):



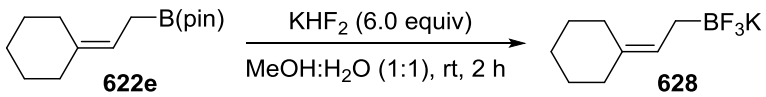
To a solution of cyclohexanone (2.58 mL, 25 mmol) in THF (100 mL) at 0 °C was added vinylmagnesium chloride (1.6 M in THF, 25 mL, 40 mmol) over *ca.* 5 min. The solution was stirred for 1 h and then quenched carefully by the addition of saturated aqueous NH_4Cl solution (50 mL). The mixture was extracted with Et_2O (3 x 100 mL) and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* at 700 mbar at 25 °C to give the *allylic alcohol* **619e** (1.17 g, 37%) as a yellow oil that displayed spectroscopic data consistent with those reported previously. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (1H, dd, J = 17.4, 10.8 Hz, C**H**=CH_2), 5.24 (1H, dd, J^{237}= 17.4, 1.3 Hz, CH=C**H**$_2$), 5.03 (1H, dd, J = 10.8, 1.3 Hz, CH=C**H**$_2$), 1.71-1.40 (8H, m, 4 x -C**H**$_2$-), 1.35-1.24 (2H, m, -C**H**$_2$-); HRMS (ESI) Exact mass calculated for $C_8H_{14}ONa$ $[M+Na]^+$: 149.0942, found: 149.0936.

4,4,5,5-Tetramethyl-(cyclohexylallyl)-1,3,2-dioxaborolane (622e):



1-Hydroxy-1-vinylcyclohexane (**619e**, 200 mg, 1.60 mmol), bis(pinacolato)diboron (0.80 g, 3.20 mmol), palladium *N,N*-dimethylbenzylamide chloride dimer (22.0 mg, 0.04 mmol), and $TsOH{\cdot}H_2O$ (4.0 mg, 0.04 mmol) were dissolved in DMSO (4 mL) and MeOH (4 mL) under N_2. The solution was stirred at 50 °C for 15 h and cooled to room temperature. The reaction was diluted with Et_2O (50 mL), washed with brine (3 x 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting *allylboronic ester* **622e** was taken on without further purification.[238]

(Cyclohexylallyl)trifluoro-λ⁴-borane potassium (628):

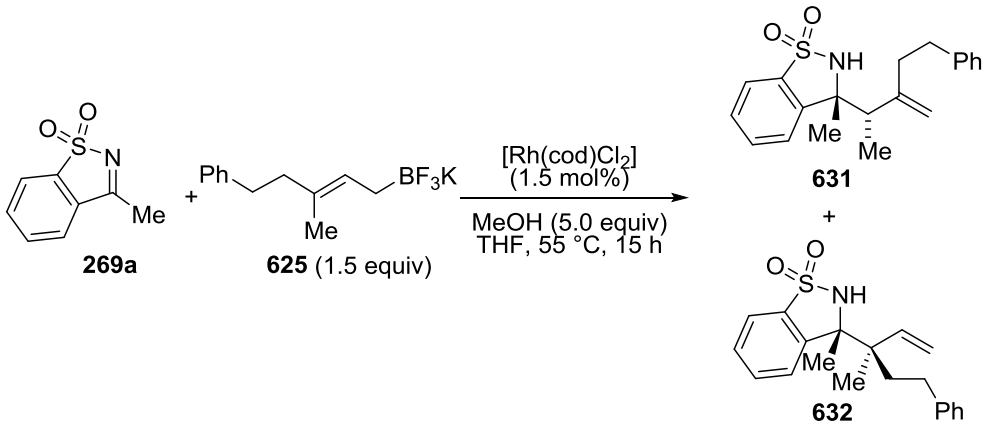


622e 628

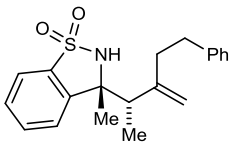
To a solution of the *allylboronic acid pinacol ester* **622e** (378 mg, 1.60 mmol) in H_2O (10 mL) and MeOH (10 mL) at room temperature was added KHF_2 (936 mg, 10.2 mmol) and the mixture was stirred for 2 h. The reaction was concentrated *in vacuo* and the resulting solid was dissolved in warm acetone. The solution was filtered through cotton wool and concentrated *in vacuo* to leave the *allyltrifluoroborate* **628** as a white solid (222 mg, 32%). m.p. >300 °C; IR 3149, 2847, 1403, 1273, 1204, 1140, 1107, 1005, 975, 903 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 5.21 (1H, t, *J* = 8.1 Hz, C**H**=), 2.16-2.09 (2H, m, -C**H**$_2$-), 2.09-2.01 (2H, m, -C**H**$_2$-), 1.63-1.38 (6H, m, 3 x –C**H**$_2$-), 0.89 (2H, br s, C**H**$_2$B); ^{13}C NMR (75 MHz, CD_3CN) δ 134.6 (C), 118.4 (CH), 22.5 (CH_2), 22.2 (CH_2), 20.4 (CH_2), 19.7 (CH_2), 19.0 (CH_2), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B; ^{19}F NMR (376 MHz, CD_3CN) δ −139.5.

1.2.4 Allylation Reactions Using Other Boron Reagents

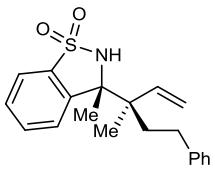
(±)-(*R*)-3-Methyl-3-[(*S*)-3-methylidene-5-phenylpentan-2-yl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (631) and (±)-(*R*)-3-methyl-3-[(*R*)-3-methyl-5-phenylpent-1-en-3-yl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (632):



General Procedure E was followed using the ketimine **269a** (54 mg, 0.30 mmol) and the potassium allyltrifluoroborate **625** (120 mg, 0.45 mmol). Purification by flash column chromatography (90:10 petrol:EtOAc) gave the *sulfonamide* **631** (75 mg, 73%) as a white solid followed by the *sulfonamide* **632** (10 mg, 10%) as a white solid.

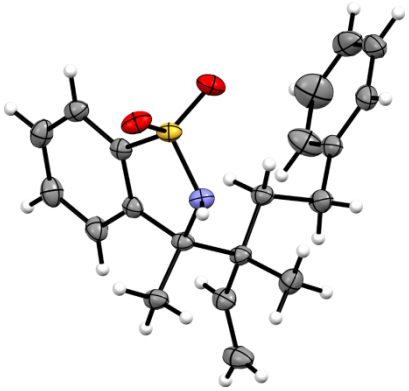


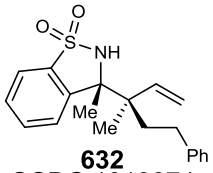
Data for 631: R_f = 0.36 (80:20 petrol:EtOAc); m.p. 116-118 °C (Et_2O); IR 3337, 3302, 3233 (NH), 1560, 1455, 1373, 1285, 1153, 1132, 898 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, dd, *J* = 7.2, 0.6 Hz, Ar**H**), 7.65 (1H, td, *J* = 7.7, 1.2 Hz, Ar**H**), 7.54 (1H, td, *J* = 7.6, 1.0 Hz, Ar**H**), 7.36 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.34-7.26 (2H, m, Ar**H**), 7.25-7.18 (3H, m, Ar**H**), 5.13 (2H, br s, =C**H**$_2$), 4.45 (1H, br s, N**H**), 2.91-2.71 (2H, m, C**H**$_2$Ph), 2.65 (1H, q, *J* = 7.0 Hz, C**H**CH$_3$), 2.52-2.29 (2H, m, C**H**$_2$CH$_2$Ph), 1.58 (3H, s, C**H**$_3$C=), 0.90 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 149.9 (C), 144.0 (C), 141.6 (C), 134.9 (C), 133.4 (CH), 129.3 (CH), 128.41 (2 x CH), 128.38 (2 x CH), 126.0 (CH), 122.9 (CH), 121.5 (CH), 113.1 (CH_2), 66.3 (C), 48.9 (CH), 38.6 (CH_2), 34.5 (CH_2), 28.1 (CH_3), 15.8 (CH_3); HRMS (ESI) Exact mass calculated for $C_{20}H_{23}NO_2SNa$ $[M+Na]^+$: 364.1342, found: 364.1343.



Data for 632: R_f = 0.30 (80:20 petrol:EtOAc); m.p. 120-122 °C (Et_2O); IR 3233 (NH), 2977, 2934, 1449, 1378, 1278, 1158, 1135, 1039, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.75 (1H, m, Ar**H**), 7.63-7.58 (1H, m, Ar**H**), 7.57-7.53 (1H, m, Ar**H**), 7.52-7.46 (1H, m, Ar**H**), 7.31-7.24 (2H, m, Ar**H**), 7.22-7.12 (3H, m, Ar**H**), 6.08 (1H, dd, *J* = 17.5, 10.9 Hz, C**H**=CH_2), 5.44 (1H, dd, *J* = 10.9, 0.9 Hz, =C**H**$_2$), 5.25 (1H, dd, *J* = 17.6, 0.9 Hz, =C**H**$_2$), 4.60 (1H, br s, N**H**), 2.55-2.35 (2H, m, C**H**$_2$Ph), 2.06 (1H, td, *J* = 12.6, 6.1 Hz, C**H**$_2$$CH_2$Ph), 1.69 (1H, td, *J* = 12.6, 4.5 Hz, C**H**$_2$$CH_2$Ph), 1.65 (3H, s, C**H**$_3$), 1.12 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 142.24 (C), 142.21 (C), 141.4 (CH), 135.3 (C), 132.8 (CH), 129.4 (CH), 128.5 (2 x CH), 128.3 (2 x CH), 125.9 (CH), 124.8 (CH), 121.8 (CH), 118.1 (CH_2), 69.2 (C), 48.5 (C), 37.3 (CH_2), 31.1 (CH_2), 25.2 (CH_3), 17.4 (CH_3); HRMS (ESI) Exact mass calculated for $C_{20}H_{23}NO_2SNa$ $[M+Na]^+$: 364.1342, found: 364.1337.

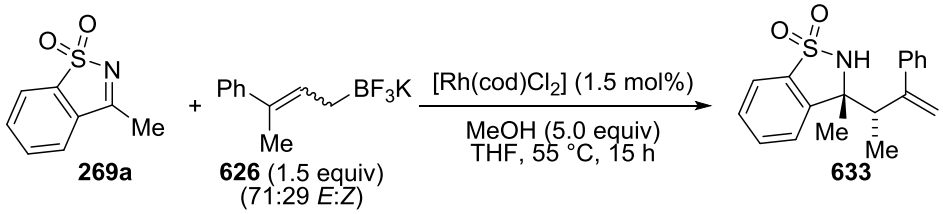
Slow evaporation of a solution of **632** in Et_2O/petrol gave crystals that were suitable for X-ray diffraction:





632
CCDC 1019074

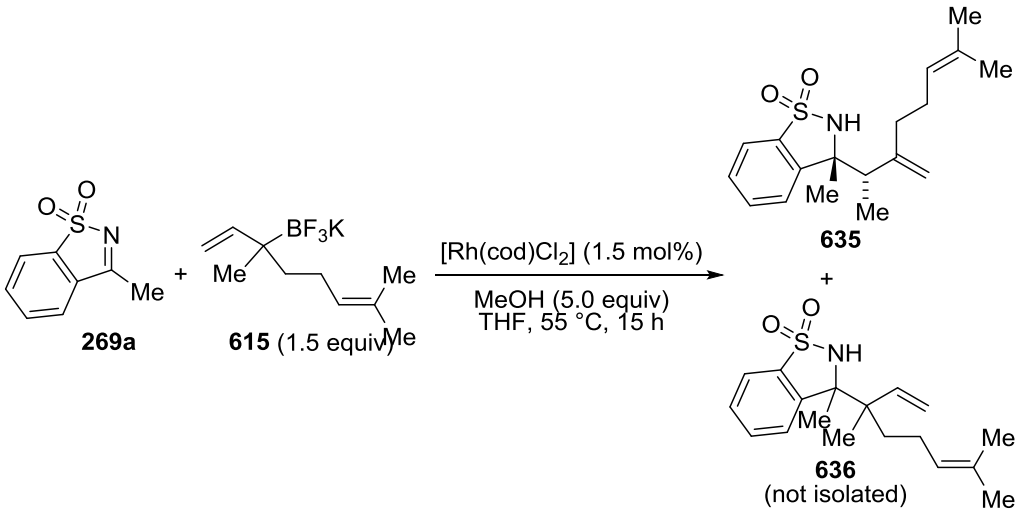
(±)-(*R*)-3-Methyl-3-[(*S*)-3-phenylbut-3-en-2-yl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (633) :



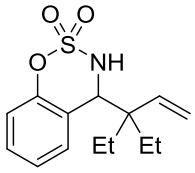
General Procedure E was followed using the ketimine **269a** (54 mg, 0.30 mmol) and the potassium allyltrifluoroborate **626** (71:29 *E*:*Z* mixture, 108 mg, 0.45 mmol). Purification by flash column chromatography (80:20 petrol:EtOAc) gave the *sulfonamide* **633** (75 mg, 78%) as a yellow oil, as a 76:24 mixture of diastereomers that were difficult to separate cleanly. A small sample of the pure major diastereomer of **633** was isolated from a second purification by flash column chromatography (90:10 petrol:EtOAc). R_f = 0.45 (80:20 petrol:EtOAc); IR 3489, 3354, 3277, 3233 (NH), 3178, 3983, 1284, 1153, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, ddd, *J* = 7.7, 1.1, 0.6 Hz, Ar**H**), 7.65 (1H, td, *J* = 7.6, 1.2 Hz, Ar**H**), 7.54 (1H, td, *J* = 7.6 Hz, 1.0 Hz, Ar**H**), 7.43-7.31 (6H, m, Ar**H**), 5.50 (1H, s, =C**H**$_2$), 5.43 (1H, s, =C**H**$_2$), 4.50 (1H, br s, N**H**), 3.33 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 1.43 (3H, s, NCC**H**$_3$), 1.06 (3H, d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 150.6 (C), 143.9 (C), 143.7 (C), 134.7 (C), 133.5 (CH), 129.4 (CH), 128.7 (2 x CH), 127.7 (CH), 126.3 (2 x CH), 122.7 (CH), 121.5 (CH), 116.5 (CH_2), 66.8 (C), 46.8 (CH), 29.0 (CH_3), 16.8 (CH_3); HRMS (ESI) Exact mass calculated for $C_{18}H_{19}NO_2SNa$ $[M+Na]^+$: 336.1029, found: 336.1017.

Diagnostic peaks in the ^1H NMR spectrum for the minor diastereomer were observed at: ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (1H, s, =C**H**$_2$), 5.29 (1H, s, =C**H**$_2$), 4.57 (1H, br s, N**H**), 3.44 (1H, q, *J* = 7.2 Hz, C**H**CH_3), 1.63 (3H, s, NCC**H**$_3$), 1.47 (3H, d, *J* = 7.1 Hz, CHC**H**$_3$).

(±)-(*R*)-3-Methyl-3-[(*S*)-7-methyl-3-methylideneoct-6-en-2-yl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (635):

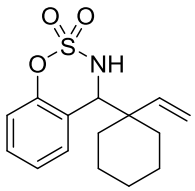


General Procedure D was followed using the ketimine **269a** (54 mg, 0.30 mmol) and the potassium allyltrifluoroborate **315** (110 mg, 0.45 mmol). Purification by flash column chromatography (80:20 petrol:EtOAc) gave a 69:31 mixture of **635** and **636** (78 mg, 82%) that was further purified by flash column chromatography (95:5 *iso*-hexane:EtOAc) to give the *sulfonamide* **635** (46 mg, 48%) as a colourless oil. R_f = 0.53 (80:20 petrol:EtOAc); IR 2948 (NH), 1558, 1495, 1243, 1108, 1078, 1015, 965, 941, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.76 (1H, m, Ar**H**), 7.68-7.63 (1H, m, Ar**H**), 7.54 (1H, td, *J* = 7.0, 1.0 Hz Ar**H**), 7.40-7.38 (1H, m, Ar**H**), 5.15-5.10 (1H, m, $CH_2C\mathbf{H}$=C), 5.08 (1H, s, =C$\mathbf{H}_2$), 5.05 (1H, s, =C$\mathbf{H}_2$), 4.49 (1H, s, N**H**), 2.64 (1H, q, *J* = 7.0 Hz, C**H**CH_3), 2.28-1.96 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$), 1.70 (3H, d, *J* = 0.6 Hz, =C(C$\mathbf{H}_3$)$_2$), 1.63 (3H, s, =C(C$\mathbf{H}_3$)$_2$), 1.60 (3H, s, NCC$\mathbf{H}_3$), 0.88 (3H, d, *J* = 7.0 Hz, CHC$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 150.4 (C), 144.1 (C), 134.8 (C), 133.4 (CH), 132.1 (C), 129.3 (CH), 123.7 (CH), 122.9 (CH), 121.4 (CH), 112.6 (CH_2), 66.4 (C), 48.7 (CH), 37.0 (CH_2), 28.2 (CH_3), 26.5 (CH_2), 25.7 (CH_3), 17.7 (CH_3), 15.8 (CH_3); HRMS (ESI) Exact mass calculated for $C_{18}H_{25}NO_2SNa$ $[M+Na]^+$: 342.1470, found: 342.1476.



638

(1,1-Diethylprop-2-en-1-yl)-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (638). The title compound was prepared according to General Procedure E from benzoxathiazine-2,2-dioxide **89a** (53 mg, 0.30 mmol) and the potassium allyltrifluoroborate **624** (91 mg, 0.45 mmol) and was purified by column chromatography (80:20 hexanes:EtOAc) to give *sulfonamide* **638** (78 mg, 92%) as an orange oil. R_F = 0.40 (80:20 hexanes:EtOAc); IR 2899, 2305, 1375, 1304, 1284, 1239, 1104, 1056, 903, 875 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.29 (2H, m, Ar**H**), 7.19 (1H, td, *J* = 7.6, 1.3 Hz, Ar**H**), 7.08 (1H, dd, *J* = 8.0, 1.3 Hz, Ar**H**), 5.63 (1H, dd, *J* = 17.7, 11.1 Hz, C**H**=CH_2), 5.37 (1H, dd, *J* = 11.0, 0.8 Hz, CH=C**H**$_2$), 5.15 (1H, dd, *J* = 17.7, 0.8 Hz, CH=C**H**$_2$), 4.71 (1H, d, *J* = 6.3 Hz, C**H**NH), 4.63 (1H, d, *J* = 6.0 Hz, N**H**), 1.76-1.49 (4H, m, 2 x C**H**$_2$$CH_3$), 0.95 (3H, t, *J* = 7.5 Hz, CH_2C**H**$_3$), 0.82 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 152.0 (C), 140.1 (CH), 129.5 (CH), 129.0 (CH), 124.9 (CH), 121.9 (C), 119.7 (CH), 118.0 (CH_2), 61.3 (CH), 47.3 (C), 25.7 (CH_2), 23.2 (CH_2), 7.9 (CH_3), 7.5 (CH_3); HRMS (ESI) Exact mass calcd for $C_{14}H_{19}NO_3SNa$ $[M+Na]^+$: 304.0983, found 304.0977.

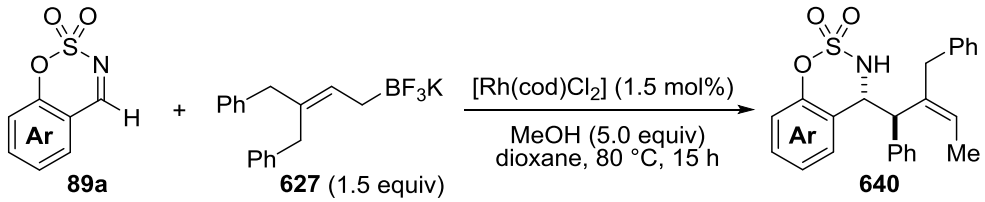


639

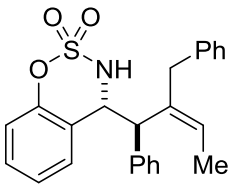
(1,1-Cyclopropyl-prop-2-en-1-yl)-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (639). The title compound was prepared according to General Procedure C from benzoxathiazine-2,2-dioxide **89a** (53 mg, 0.30 mmol) and the potassium allyltrifluoroborate **628** (97 mg, 0.45 mmol) and was purified by column chromatography (90:10 petrol:EtOAc) to give *sulfonamide* **639** (58 mg, 66%) as an yellow oil. R_F = 0.43 (80:20 hexanes:EtOAc); IR 3269, 3106, 1203, 1185, 1139, 1075, 1021, 992, 904, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (1H, m, Ar**H**), 7.33-7.28 (1H, m, Ar**H**), 7.25-7.19 (1H, m, Ar**H**), 7.11 (1H, dd, *J* = 8.1, 1.2 Hz, Ar**H**), 5.56 (1H, dd, *J* = 17.4, 11.0 Hz, C**H**=CH_2), 5.47 (1H, dd, *J* = 11.0, 1.3 Hz, CH=C**H**$_2$), 5.21 (1H, dd, *J* = 17.4, 1.3 Hz, CH=C**H**$_2$), 4.84 (1H, d, *J* = 3.9 Hz, N**H**), 4.44 (1H, d, *J* = 4.7 Hz, C**H**NH), 1.95-1.73 (2H, m, -C**H**$_2$-), 1.70-1.35 (8H, m, 4 x –C**H**$_2$-); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.7 (C), 140.2 (CH), 129.6 (CH), 129.5 (CH), 125.1 (CH), 121.5 (C), 119.7 (CH), 119.3 (CH_2), 64.9 (CH), 46.4

(C), 32.4 (CH_2), 31.0 (CH_2), 25.8 (CH_2), 21.9 (CH_2), 21.7 (CH_2); HRMS (ESI) Exact mass calcd for $C_{15}H_{19}NO_3SNa$ $[M+Na]^+$: 316.0.983, found 316.0988.

Allylation of Benzoxathiazine-2,2-dioxides: General Procedure F



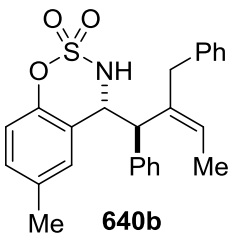
A microwave vial containing the appropriate benzoxathiazine-2,2-dioxide **89** (0.30 mmol), $[Rh(cod)Cl]_2$ (2.2 mg, 0.0045 mmol), and the potassium allyltrifluoroborate **627** (148 mg, 0.45 mmol) was flushed with N_2 before anhydrous dioxane (3 mL) and MeOH (60 µL, 1.5 mmol) were added. The mixture was heated at 80 °C for 15 h. The reaction was cooled to room temperature, diluted with EtOAc (10 mL), and filtered through a silica plug eluting with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography to give the allylation product **640**.



640a

(±)-(*R*)-4-[(*S*,*Z*)-2-Benzyl-1-phenylbut-2-en-1-yl]-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (640a). The title compound was prepared using General Procedure F from benzoxathiazine-2,2-dioxide **89a** (55 mg, 0.30 mmol) and was purified by flash column chromatography (96:4 petrol:EtOAc) to give *sulfonamide* **640a** (72 mg, 59%) as a white solid. R_f = 0.47 (80:20 petrol:EtOAc); m.p. 171-173 °C (Et_2O); IR 3231 (NH), 2975, 2923, 1450, 1278, 1181, 1158, 1135, 1039, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.16 (10H, m, Ar**H**), 7.08 (1H, dd, *J* = 8.2, 1.1 Hz, Ar**H**), 7.04-7.02 (1H, m, Ar**H**), 7.00-6.95 (1H, m, Ar**H**), 6.85 (1H, d, *J* = 7.8 Hz, Ar**H**), 5.54 (1H, app t, *J* = 9.0 Hz, C**H**NH), 5.20 (1H, q, *J* = 7.0 Hz, =C**H**CH_3), 4.66 (1H, d, *J* = 8.6 Hz, N**H**), 4.58 (1H, d, *J* = 9.5 Hz, C**H**Ph), 3.38 (1H, d, *J* = 15.9 Hz, C$\mathbf{H}_2$Ph), 3.23 (1H, d, *J* = 15.9 Hz, C$\mathbf{H}_2$Ph), 1.72 (3H, dt, *J* = 7.0, 1.5 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 161.0 (C), 151.6 (C), 139.4 (C), 138.7 (C), 129.8 (2 x CH), 129.5 (CH), 129.1 (2 x CH), 128.3

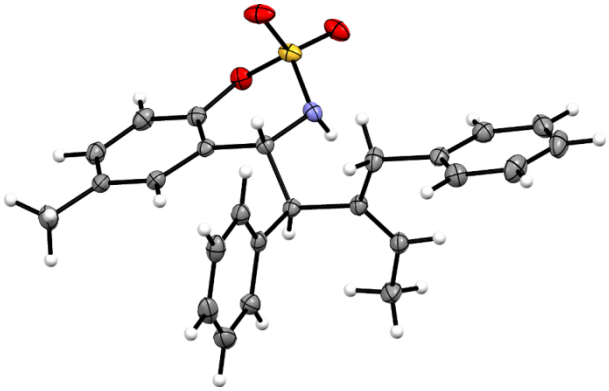
(2 x CH), 128.2 (2 x CH), 127.5 (CH), 127.1 (CH), 126.2 (CH), 125.9 (CH), 125.1 (CH), 123.7 (C), 118.9 (CH), 55.8 (CH), 49.9 (CH), 38.9 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $C_{24}H_{23}NO_3SNa$ $[M+Na]^+$: 428.1291, found: 428.1313.

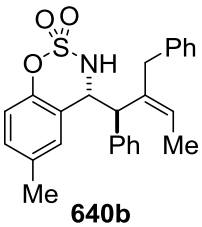


640b

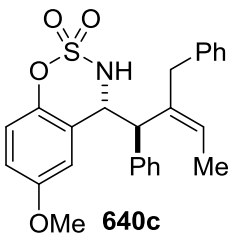
(±)-(*R*)-4-[(*S*,*Z*)-2-Benzyl-1-phenylbut-2-en-1-yl]-6-methyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (640b). The title compound was prepared using General Procedure F from benzoxathiazine-2,2-dioxide **89b** (59 mg, 0.30 mmol) and was purified by flash column chromatography (90:10 petrol:EtOAc) to give *sulfonamide* **640b** (93 mg, 74%) as a white solid. R_f = 0.48 (80:20 petrol:EtOAc); m.p. 175-177 °C (Et_2O); IR 3232 (NH), 2923, 1493, 1451, 1375, 1278, 1180, 1158, 1135, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.32 (5H, m, Ar**H**), 7.28-7.18 (3H, m, Ar**H**), 7.08 (1H, dd, *J* = 8.3, 2.0 Hz, Ar**H**), 7.03-7.00 (2H, m, Ar**H**), 6.96 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.58 (1H, d, *J* = 0.8 Hz, Ar**H**), 5.47 (1H, app t, *J* = 8.6 Hz, C**H**NH), 5.23 (1H, q, *J* = 7.0 Hz, =C**H**CH_3), 4.63 (1H, d, *J* = 8.3 Hz, N**H**), 4,51 (1H, d, *J* = 8.9 Hz, C**H**Ph), 3.33 (1H, d, *J* = 15.8 Hz, C$\mathbf{H}_2$Ph), 3.24 (1H, d, *J* = 15.8 Hz, C$\mathbf{H}_2$Ph), 2.11 (3H, s, ArC$\mathbf{H}_3$), 1.67 (3H, dt, *J* = 7.0, 1.5 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 149.3 (C), 139.6 (C), 138.8 (C), 138.6 (C), 134.7 (C), 130.0 (CH), 129.8 (2 x CH), 128.9 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 127.6 (CH), 127.4 (CH), 126.5 (CH), 126.3 (CH), 123.0 (C), 118.6 (CH), 56.2 (CH), 50.1 (CH), 39.5 (CH_2), 20.8 (CH_3), 14.0 (CH_3); HRMS (ESI) Exact mass calculated for $C_{25}H_{25}NO_3SNa$ $[M+Na]^+$: 442.1447, found: 442.1441.

Slow evaporation of a solution of **640b** in Et_2O/petrol gave crystals that were suitable for X-ray diffraction:



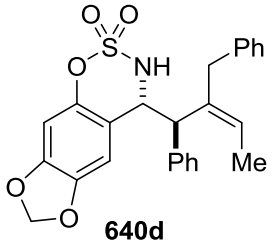


640b
CCDC 1013877



640c

(±)-(*R*)-4[(*S*,*Z*)-2-Benzyl-1-phenylbut-2-en-1-yl]-6-methoxy-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (640c). The title compound was prepared using General Procedure F from benzoxathiazine-2,2-dioxide **89c** (64 mg, 0.30 mmol) and was purified by flash column chromatography (95:5 petrol:EtOAc) to give *sulfonamide* **640c** (72 mg, 55%) as a white solid. R_f = 0.50 (80:20 petrol:EtOAc); m.p. 170-172 °C (Et_2O); IR 3010 (NH), 2739, 1492, 1450, 1395, 1305, 1274, 1208, 1174, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.35 (4H, m, Ar**H**), 7.30-7.24 (2H, m, Ar**H**), 7.23-7.16 (2H, m, Ar**H**), 7.08-7.02 (2H, m, Ar**H**), 6.98 (1H, d *J* = 9.0 Hz, Ar**H**), 6.80 (1H, ddd, *J* = 9.0, 2.9, 0.4 Hz, Ar**H**), 6.28 (1H, d, *J* = 2.5 Hz, Ar**H**), 5.48 (1H, app t, *J* = 8.9 Hz, C**H**NH), 5.18 (1H, qt, *J* = 6.7, 1.2 Hz, =C**H**CH_3), 4.61 (1H, d, *J* = 8.2 Hz, N**H**), 4.52 (1H, d, *J* = 9.7 Hz, C**H**Ph), 3.43-3.40 (1H, m, C$\mathbf{H}_2$Ph), 3.40 (3H, s, OC$\mathbf{H}_3$), 3.31-3.24 (1H, m, C$\mathbf{H}_2$Ph), 1.72 (3H, dt, *J* = 7.0, 1.6 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 156.2 (C), 144.9 (C), 139.6 (C), 138.7 (C), 138.5 (C), 129.8 (2 x CH), 129.1 (2 x CH), 128.42 (2 x CH), 128.36 (2 x CH), 127.5 (CH), 126.3 (CH), 126.1 (CH), 124.1 (C), 119.8 (CH), 115.7 (CH), 111.4 (CH), 56.1 (CH), 55.2 (CH_3), 50.5 (CH), 38.7 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $C_{25}H_{25}NO_4SNa$ $[M+Na]^+$: 458.1397, found: 458.1387.

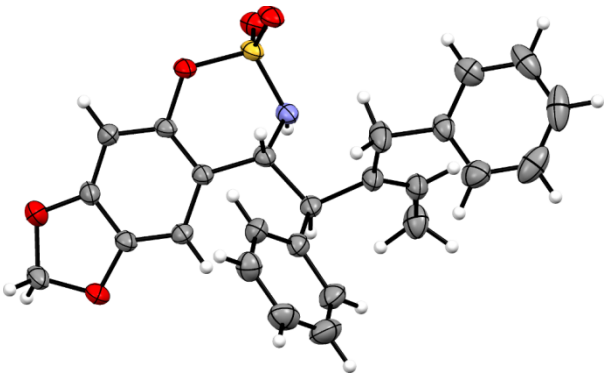


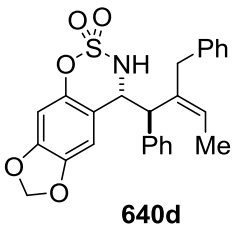
640d

(±)-(*S*)-4-[(*R*,*Z*)-2-Benzyl-1-phenylbut-2-en-1-yl]-3,4-dihydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-*e*][1,2,3]oxathiazine 2,2-dioxide (640d). The title compound was prepared using General Procedure F from benzoxathiazine-2,2-dioxide **89e** (69 mg, 0.30 mmol) and was purified by flash column chromatography (95:5 petrol:EtOAc) to give *sulfonamide* **640d** (84 mg, 63%) as a white solid. R_f = 0.55 (80:20 petrol:EtOAc); m.p. 188-190 ºC (Et_2O); IR 2920 (NH), 2852, 1479, 1305, 1233, 1187, 1138, 1124, 1036, 983 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.30 (6H, m, Ar**H**), 7.28-7.17 (3H, m, Ar**H**), 7.03-7.00 (2H, m, Ar**H**), 6.58 (1H, s, Ar**H**), 6.23 (1H, d, *J* = 0.4 Hz, Ar**H**), 5.94 (1H, d, *J* = 1.3 Hz, OC$\mathbf{H}_2$O), 5.91 (1H, d, *J* = 1.3 Hz, OC$\mathbf{H}_2$O), 5.39 (1H, app t, *J* = 8.8 Hz, C**H**NH), 5.18 (1H, q, *J* = 7.0 Hz,

=C**H**CH_3), 4.56 (1H, d, *J* = 8.4 Hz, N**H**), 4.47 (1H, d, *J* = 9.5 Hz, C**H**Ph), 3.36 (1H, d, *J* = 15.9 Hz, C**H**$_2$Ph), 3.20 (1H, d, *J* = 15.9 Hz, C**H**$_2$Ph), 1.71 (3H, dt, *J* = 7.0, 1.6 Hz, =CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 147.9 (C), 146.1 (C), 144.9 (C), 139.2 (C), 138.7 (C), 138.7 (C), 129.8 (2 x CH), 129.1 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.6 (CH), 126.2 (CH), 126.0 (CH), 116.4 (C), 106.0 (CH), 102.0 (CH_2), 100.7 (CH), 55.8 (CH), 50.2 (CH), 38.8 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $C_{25}H_{23}NO_5SNa$ $[M+Na]^+$: 472.1189, found: 472.1186.

Slow evaporation of a solution of **640d** in Et_2O/petrol gave crystals that were suitable for X-ray diffraction:

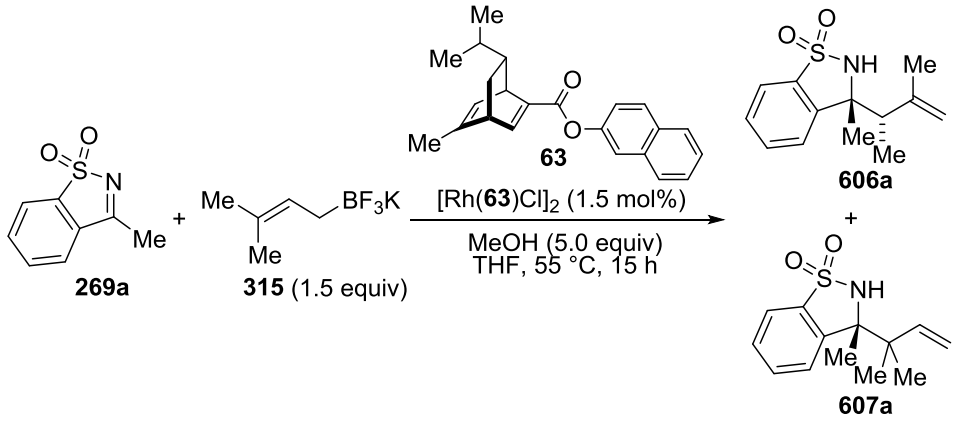




640d
CCDC 1013878

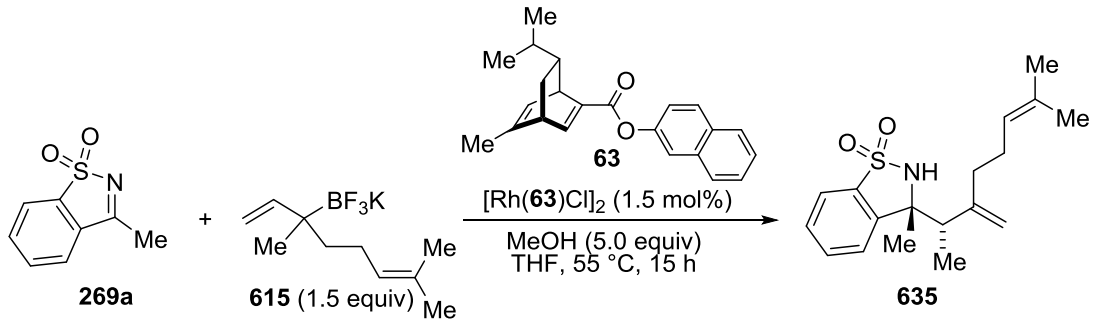
1.2.5 Enantioselective Variant of Allylation Reaction

(*R*)-3-Methyl-3-[(*S*)-3-methylbut-3-en-2-yl]-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (606a) :



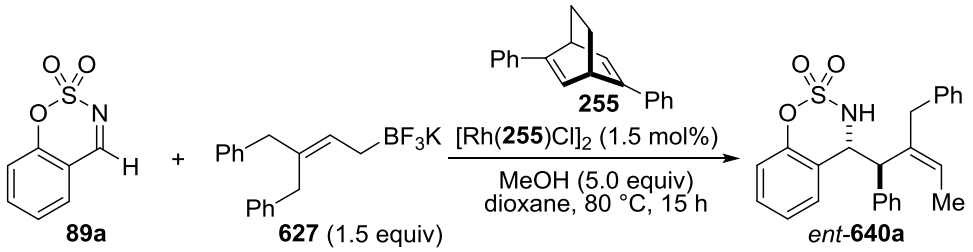
A microwave vial containing the ketimine **269a** (54 mg, 0.30 mmol), [Rh(**63**)Cl]$_2$ (4.2 mg, 0.0045 mmol) and the potassium allyltrifluoroborate **315** (79 mg, 0.45 mmol) was flushed with N_2 before anhydrous THF (3 mL) and MeOH (60 µL, 1.5 mmol) were added. The reaction was heated at 55 °C for 15 h. The reaction was cooled to room temperature, diluted with EtOAc (10 mL), and filtered through a silica plug eluting with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (80:20 petrol:EtOAc) to give an 87:13 mixture of allylation products **606a** and **607a** (55 mg, 73%) that was further purified by flash column chromatography (95:5 *iso*-hexane:EtOAc) to *sulfonamide* **606a** (47 mg, 62%) as a white solid. Spectroscopic data for **606a** were consistent with those described above. $[\alpha]_D^{20}$ +12.4 (*c* 2.00, $CHCl_3$); m.p. 142-144 °C (Et_2O); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 210 nm, 25 °C); t_r (minor) = 13.3 min, t_r (major) = 19.7 min; 97% ee.

(*R*)-3-Methyl-3-[(*S*)-7-methyl-3-methylideneoct-6-en-2-yl]-2,3-dihydro-1,2-benzo[*d*]isothiazole-1,1-dioxide (635):



A microwave vial containing the ketimine **269a** (54 mg, 0.30 mmol), [Rh(**63**)Cl]$_2$ (4.2 mg, 0.0045 mmol) and the potassium allyltrifluoroborate **615** (110 mg, 0.45 mmol) was flushed with N_2 before anhydrous THF (3 mL) and MeOH (60 µL, 1.5 mmol) were added. The reaction was heated at 55 °C for 15 h. The reaction was cooled to room temperature, diluted with EtOAc (10 mL), and filtered through a silica plug eluting with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (80:20 petrol:EtOAc) to give the *sulfonamide* **635** (53 mg, 55%) as a colourless oil which displayed spectroscopic data consistent with those reported above. $[\alpha]_D^{20}$ +29.9 (*c* 1.00, $CHCl_3$); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 210 nm, 25 °C); t_r (minor) = 18.7 min, t_r (major) = 25.2 min; 99% ee.

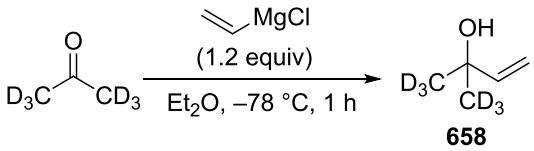
(*S*)-4-[(*R*,*Z*)-2-Benzyl-1-phenylbut-2-en-1-yl]-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (*ent*-640a):



A microwave vial containing the aldimine **89a** (54 mg, 0.30 mmol), [Rh(**255**)Cl]$_2$ (3.6 mg, 0.0045 mmol) and the potassium allyltrifluoroborate **627** (148 mg, 0.45 mmol) was flushed with N_2 before anhydrous dioxane (3 mL) and MeOH (60 μL, 1.5 mmol) were added. The reaction was heated at 80 °C for 15 h. The reaction was cooled to room temperature, diluted with EtOAc (10 mL) and filtered through a silica plug eluting with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (96:4 petrol:EtOAc) to give the *sulfonamide* *ent*-**640a** (76 mg, 62%) as a white solid which displayed spectroscopic data consistent with those reported above. $[\alpha]_D^{20}$ –24.4 (*c* 1.00, $CHCl_3$); m.p. 173-175 °C (Et_2O); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 230.4 nm, 25 °C); t_r (major) = 12.5 min, t_r (minor) = 16.4 min; 96% ee.

1.2.6 Synthesis and Analysis of Deuterated Compounds

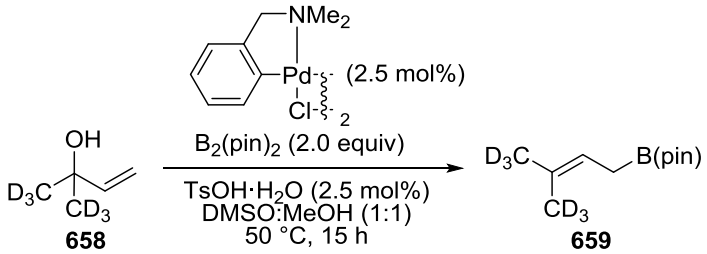
2-($^2H_3$)Methyl(1,1,1-$^2H_3$)but-3-en-2-ol (658):



658

To a solution of $[D]_6$-acetone (3.0 mL, 40.8 mmol) in Et_2O (150 mL) at –78 °C was added vinylmagnesium chloride (1.6 M in THF, 30 mL, 50 mmol) over *ca.* 5 min. The solution was stirred for 2 h and then quenched carefully by the addition of saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with Et_2O (3 x 100 mL) and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* at 700 mbar at 25 °C to give the *allylic alcohol* **658** (1.34 g, 34%). The compound was volatile (b.p. around 80-90 °C) and was therefore not evaporated to dryness, resulting in an 8% contamination by THF. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (1H, dd, *J* = 17.4, 10.7 Hz, C**H**=CH_2), 5.21 (1H, dd, *J* = 17.4, 0.4 Hz, CH=C**H**$_2$), 5.00 (1H, dd, *J* = 10.7, 0.5 Hz, CH=C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1 (CH), 110.8 (CH_2), the CD_3 carbons and the quaternary carbon were not observed due to the coupling and relaxation effects caused by deuterium.

4,4,5,5-Tetramethyl-2-[3-($^2H_3$)methyl(4,4,4-$^2H_3$)but-2-en-1-yl]-1,3,2-dioxaborolane (659):

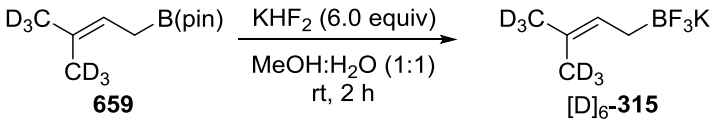


658 **659**

The allylic alcohol **658** (552 mg, 6.00 mmol), bis(pinacolato)diboron (3.05 g, 12.0 mmol), palladium *N,N*-dimethylbenzylamide chloride dimer (83 mg, 0.15 mmol),

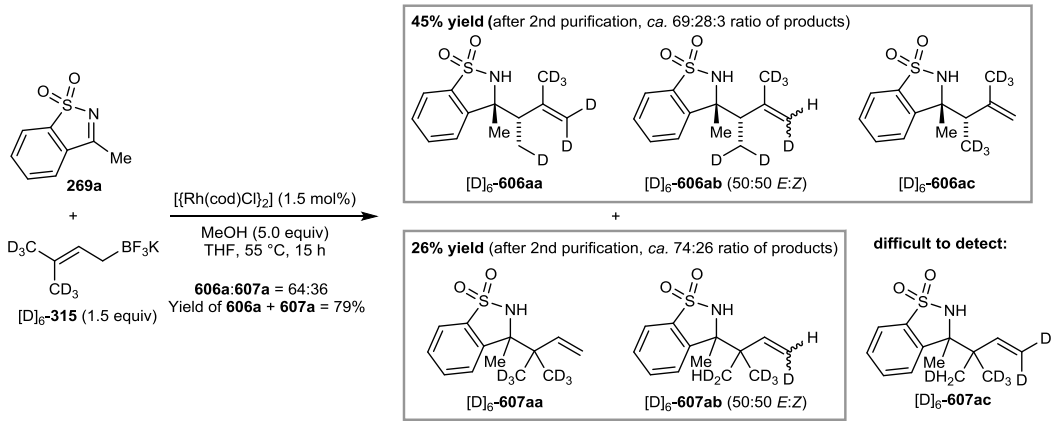
and $TsOH{\cdot}H_2O$ (29 mg, 0.15 mmol) were dissolved in DMSO (20 mL) and MeOH (20 mL) under N_2. The solution was stirred at 50 °C for 15 h and cooled to room temperature. The reaction was diluted with Et_2O (100 mL), washed with brine (3 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (98:2 petrol:EtOAc) gave the *allylboronic acid pinacol ester* **659** as a colourless oil (612 mg, 50%). R_f = 0.55 (95:5 petrol:EtOAc); (IR 3028, 2840, 1420, 1383, 1329, 1284, 1150, 1049, 1003, 940 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.23 (1H, t, *J* = 7.6 Hz, C**H**=C$(CD_3)_2$), 1.60 (2H, d, *J* = 7.6 Hz, C**H**$_2$B), 1.25 (12H, s, 2 x C(C**H**$_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.5 (CH), 83.1 (2 x C), 24.8 (4 x CH_3), the secondary carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B, the CD_3 carbons and the olefin quaternary carbon were not observed due to the coupling and relaxation effects caused by deuterium; HRMS (ESI) Exact mass calculated for $C_{11}H_{15}BO_2D_6Na$ $[M+Na]^+$: 225.2002, found: 225.1998.

Trifluoro[3-(²H$_3$)methyl(4,4,4-²H$_3$)but-2-en-1-yl]-λ^4-borane potassium ([D]$_6$-315):



To a solution of the allylboronic acid pinacol ester **659** (612 mg, 3.00 mmol) in H_2O (10 mL) and MeOH (10 mL) at room temperature was added KHF_2 (1.40 g, 18.0 mmol) and the mixture was stirred for 2 h. The reaction was concentrated *in vacuo* and the resulting solid was dissolved in warm acetone. The solution was filtered through cotton wool and concentrated *in vacuo* to leave the *allyltrifluoroborate* [D]$_6$-**315** as a white solid (428 mg, 78%). m.p. >300 °C (Et_2O); IR 3355, 2981, 1678, 1267, 1082, 1064, 1052, 1009, 955, 856 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 5.23 (1H, t, *J* = 8.0 Hz, =C**H**), 0.88 (2H, br s, C**H**$_2$B); ^{13}C NMR (75 MHz, CD_3CN) δ 127.1 (CH), 126.2 (C), 16.6 (2 x CD_3, app quin, *J* = 19.8 Hz), the carbon (CH_2) next to boron was not observed due to quadrupolar coupling effects of ^{11}B; ^{19}F NMR (376 MHz, CD_3CN) δ −139.2.

Reaction with Hexadeuterated Allyltrifluoroborate [D]$_6$-315



General Procedure E was followed using the ketimine **269** (54 mg, 0.30 mmol) and the potassium allyltrifluoroborate [D]$_6$-**315** (82 mg, 0.45 mmol). Purification by flash column chromatography (80:20 *iso*-hexane:EtOAc) gave a 64:36 combined mixture of isomerized ([D]$_6$-**606aa** + [D]$_6$-**606ab** + [D]$_6$-**606ac**) to non-isomerized ([D]$_6$-**607aa** + [D]$_6$-**607ab** + [D]$_6$-**607ac**) products, respectively (61 mg, 79%). This mixture was further purified by flash column chromatography (95:5 *iso*-hexane:EtOAc) to give the *isomerized products* ([D]$_6$-**606aa** + [D]$_6$-**606ab** + [D]$_6$-**606ac**, 35 mg, 45%) as a white solid followed by the *non-isomerized products* ([D]$_6$-**607aa** + [D]$_6$-**607ab** + [D]$_6$-**607ac**, 20 mg, 26%) as a white solid.

Data for Isomerized Products:

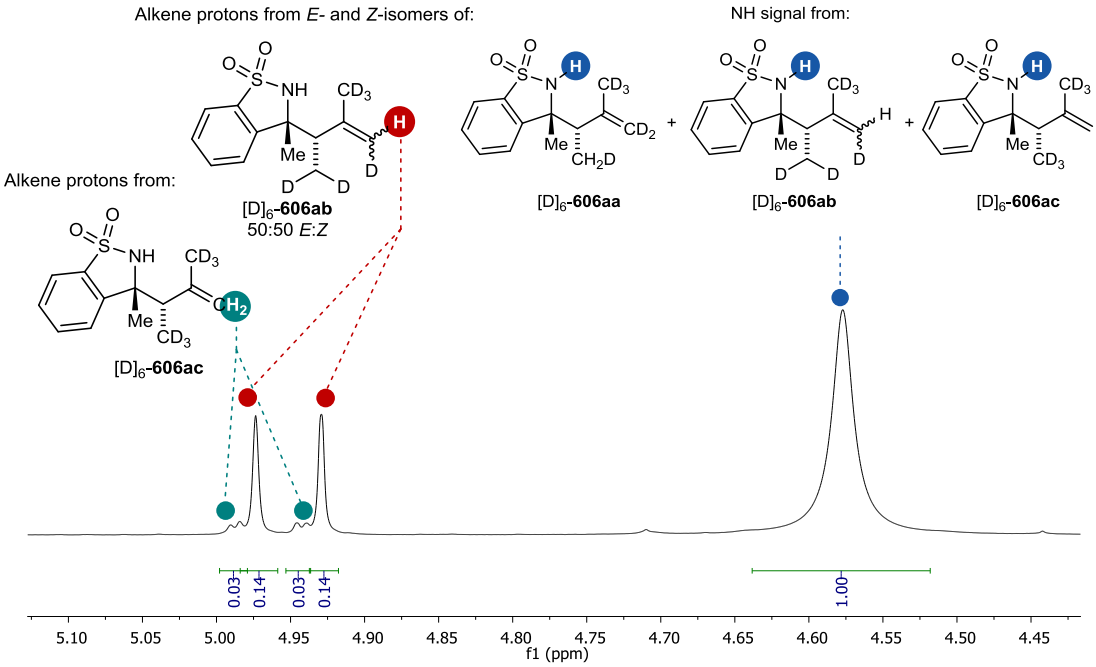
R_f = 0.22 (95:05 *iso*-hexane:EtOAc); m.p. 130-132 °C (Et_2O); IR 2947 (NH), 1494, 1455, 1243, 1109, 1077, 1016, 965, 940, 762 cm^{-1}; HRMS (ESI) Exact mass calculated for $C_{13}H_{11}D_6NO_2SNa$ $[M+Na]^+$: 280.1230, found: 280.1233.

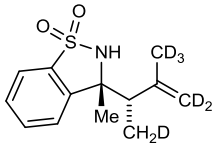
The approximate composition of the isomerized products was as follows:

[D]$_6$-**606aa**: *ca.* 69%

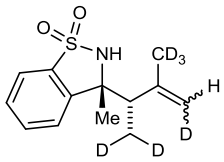
[D]$_6$-**606ab** (a 50:50 *E*:*Z* mixture): *ca.* 28%

[D]$_6$-**606ab**: *ca.* 3%

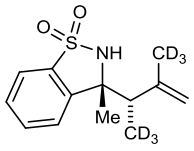




NMR Data for [D]$_6$-606aa: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.76 (1H, m, Ar**H**), 7.66 (1H, ddd, J = 7.9, 7.4, 1.2 Hz, Ar**H**), 7.57-7.53 (1H, m, Ar**H**), 7.42-7.38 (1H, m, Ar**H**), 4.35 (1H, s, N**H**), 2.68 (1H, t, J = 7.0 Hz, C**H**CH_2D), 1.60 (3H, s, C**H**$_3$), 0.87 (2H, dt, J = 6.9, 1.6 Hz, C**H**$_2$D); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 145.6 (C), 144.3 (C), 134.8 (C), 133.4 (CH), 129.3 (CH), 122.9 (CH), 121.4 (CH), 114.9-113.9 (m, CD_2), 66.2 (C), 50.0 (CH), 28.3 (CH_3), 21.0-20.4 (m, CD_3), 14.5 (CH_2D, t, J = 19.5 Hz).

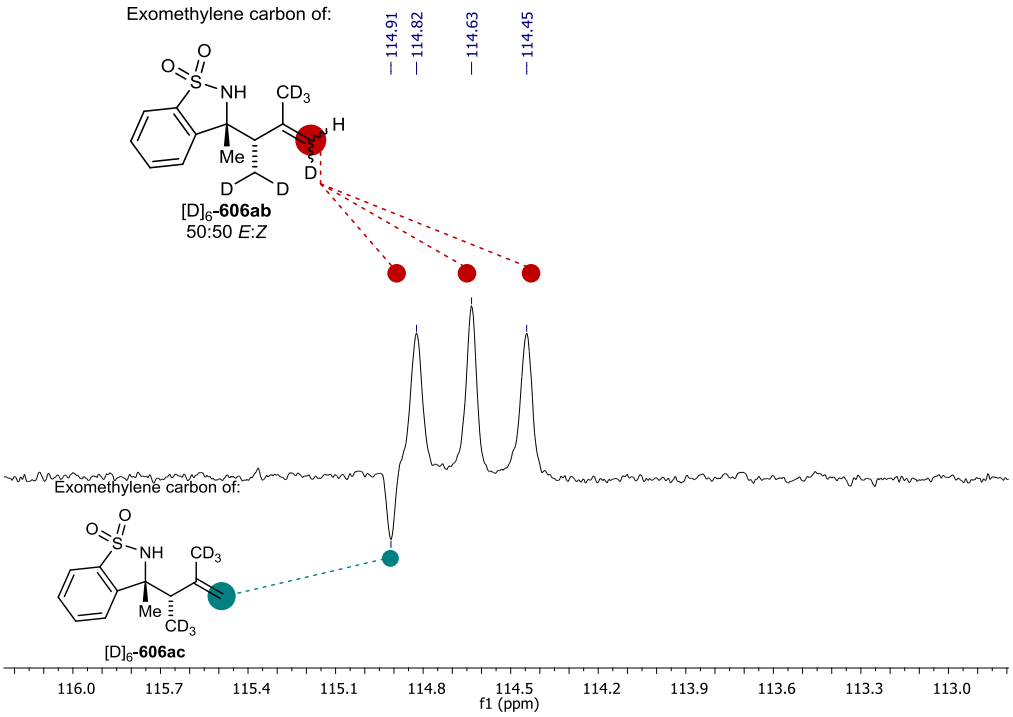


NMR Data for [D]$_6$-606ab (a 50:50 *E*:*Z* mixture): Many of the NMR signals overlap with those of [D]$_6$-**606aa**, but the following signals are diagnostic: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (0.5H, s, =C**H**D of one *E*:*Z* isomer), 4.93 (0.5H, s, =C**H**D of the second *E*:*Z* isomer); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 145.7 (C), 114.6 (t, J = 23.5 Hz, CHD), 14.7-14.0 (m, CHD_2).



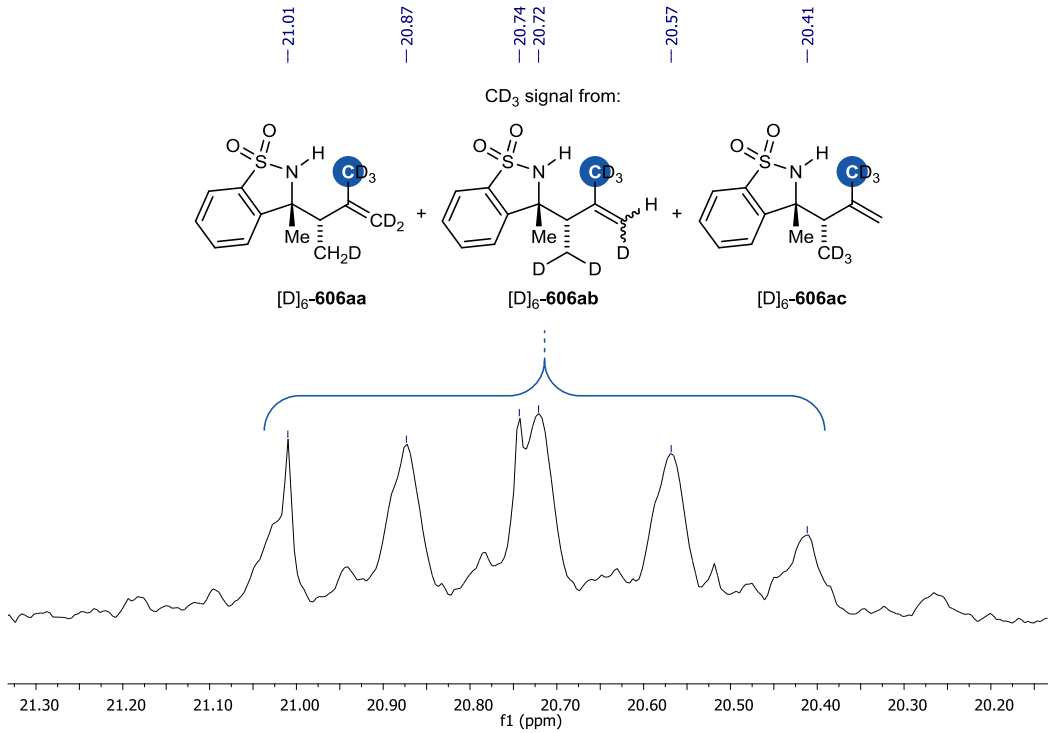
NMR Data for [D]$_6$-606ac: Many of the NMR signals overlap with those of [D]$_6$-**606aa**, but the following signals are diagnostic: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (1H, dd, J = 1.9 Hz, =C**H**$_2$), 4.94 (1H, dd, J = 1.9 Hz, =C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 114.9 (CH_2).

DEPT 135 spectrum:

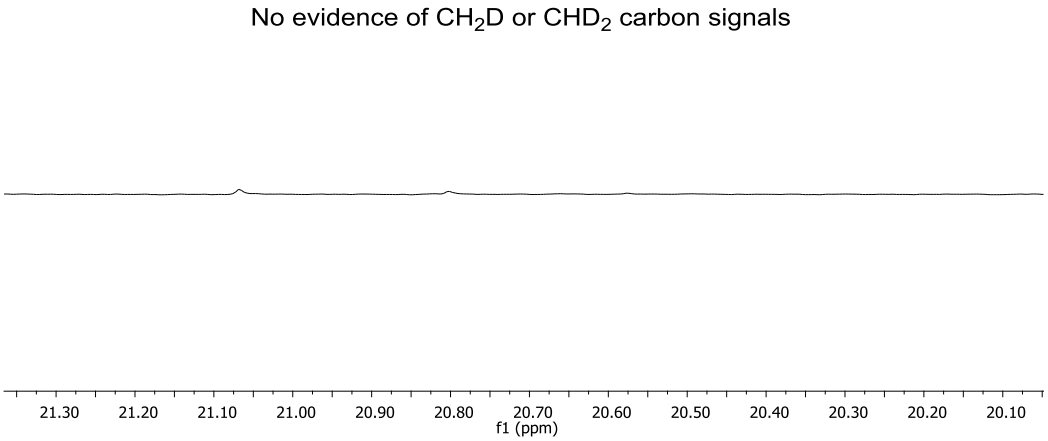


There was no evidence of any deuterium depletion at the CD_3 group attached to the alkene in D]$_6$-**606aa**, [D]$_6$-**606ab**, and [D]$_6$-**606ac**:

^{13}C NMR spectrum:



DEPT 135 spectrum:



Data for Non-Isomerized Products:

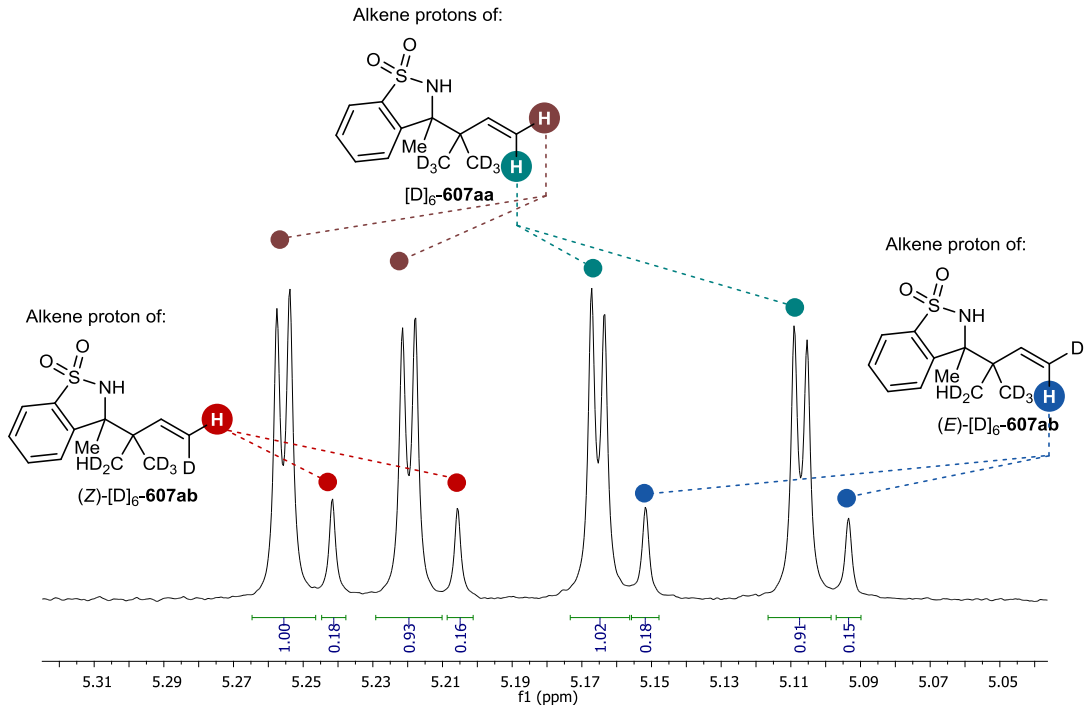
R_f = 0.19 (95:5 *iso*-hexane:EtOAc); m.p. 126-128 °C (Et_2O); IR 3256 (NH), 1736, 1388, 1374, 1276, 1222, 1172, 1132, 886, 756 cm^{-1}; HRMS (ESI) Exact mass calculated for $C_{13}H_{11}D_6NO_2SNa$ $[M+Na]^+$: 280.1249, found: 280.1239.

The approximate composition of the isomerized products was as follows:

$[D]_6$-**607aa**: *ca.* 74%

$[D]_6$-**607ab** (a 50:50 *E*:*Z* mixture): *ca.* 26%

$[D]_6$-**607ac**: *very hard to detect*



NMR Data for [D]$_6$-607aa: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.74 (1H, m, Ar**H**), 7.70-7.47 (3H, m, Ar**H**) 6.08 (1H, dd, *J* = 17.5, 9.8 Hz, C**H**=CH_2), 5.24 (1H, dd, *J* = 10.8, 1.1 Hz, CH=C**H**$_2$), 5.14 (1H, dd, *J* = 17.5, 1.1 Hz, CH=C**H**$_2$), 4.50 (1H, s, N**H**), 1.64 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 143.2 (C), 142.6 (C), 135.2 (CH), 132.6 (CH), 129.3 (CH), 124.7 (CH), 121.5 (CH), 115.6 (CH_2), 68.8 (C), 44.5 (C), 25.2 (CH_3), the CD_3 carbons were not observed due to the coupling and relaxation effects caused by deuterium.

NMR Data for [D]$_6$-607ab (a 50:50 *E*:*Z* mixture): Many of the NMR signals overlap with those of [D]$_6$-**607aa**, but the following signals are diagnostic: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (0.5H, d, *J* = 10.8 Hz, =C**H**D of one *E*:*Z* isomer), 5.12 (0.5H, d, *J* = 17.5 Hz, =C**H**D of the second *E*:*Z* isomer), 1.61 (3H, s, NCC**H**$_3$).

1.3 X-Ray Crystallography Data

The X-ray crystallography data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 10.1: X-Ray Crystallography Data

Compound Number	CCDC Number
233e	880901
335	880902
346	948887
349	948888
606e	1013875
606g	1013876
632	1019074
640b	1013877
640d	1013878

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