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Reactions of Nucleophilic Allymetal Species Generated *in situ* through 1,4-Alkenyl-to-Allyl Metal Migrations

A thesis submitted to The University of Nottingham for the degree of Doctor of Philosophy

By

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2018

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 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.

Part of this work contains results reported in the following publications:

1. Partridge, B. M.; Callingham, M.; Lewis, W.; Lam, H. W. *Angew. Chem. Int. Ed.* **2017**, *56* (25), 7227
2. Callingham, M.; Partridge, B. M.; Lewis, W.; Lam, H. W. *Angew. Chem. Int. Ed.* **2017**, *56* (51), 16352.

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List of Abbreviations

Ac	acetyl
Am	amyl
app	apparent
aq	aqueous
Ar	aryl
BINAP	(2,2'-*bis*diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BQ	benzoquinone
br	broad
Bu	butyl
calcd	calculated
cat.	catalyst
cod	1,5-cyclooctadiene
coe	cyclooctene
cp*	1,2,3,4,5-pentamethylcyclopentadiene
d	doublet
d.r.	diastereomeric ratio
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
equiv	equivalent
Et	ethyl
g	gram
h	hour
HPLC	high-performance liquid chromatography
KHMDS	potassium bis(trimethylsilyl)amide
m	multiplet
Me	methyl
mg	milligram
min	minute
mL	millilitre
m.p.	meltingpoint
MHz	megahertz
NMP	*N*-methyl-2-pyrrolidone
PMP	*para*-methoxyphenyl
Ph	phenyl
pin	pinacol
q	quartet
rac	racemic
rt	room temperature
s	singlet
sext	sextet

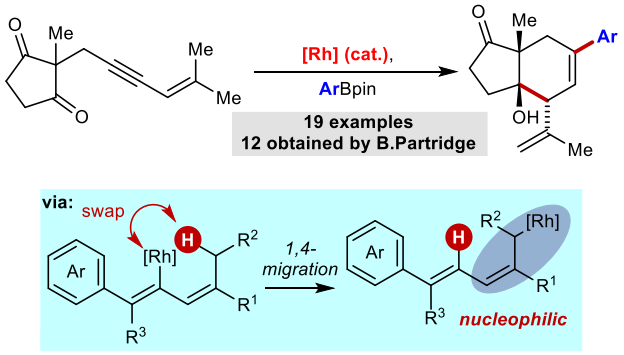
t	triplet
TBME	methyl *tert*-butyl ether
TFA	trifluoroacetic acid
THF	tetrahydrofuran
*p*TSA	*para*-toluenesulfonic acid

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

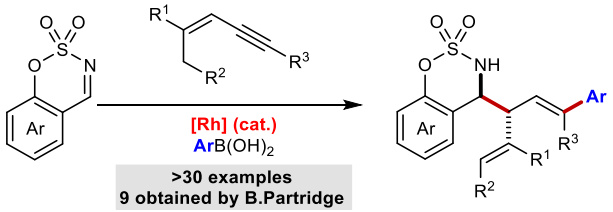
Abstract

Herein is described the catalytic *in situ* generation of nucleophilic allylmetal species through the activation of allylic C-H bonds. Reactivity is achieved through initial carbometalation of an enyne, followed by the key 1,4-alkenyl-to-allyl metal migration which generates the allylmetal intermediate.

This new mode of reactivity was firstly employed in the rhodium-catalysed diastereoselective reaction of arylboron reagents with enynones, to give products containing three contiguous stereocentres. Initial discovery and optimisation of this reaction was performed by Benjamin Partridge. Through use of a chiral sulfur olefin ligand, products could be obtained in high enantioselectivites.



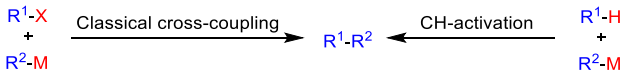
Secondly, a three-component coupling between 1,3-enynes, arylboronic acids and imines is described. The use of a chiral rhodium catalyst allowed the synthesis of a range of homoallylic amines with excellent control of stereoselectivity (>95:5 dr, up to 99% ee).



1 Introduction

1.1 1,4-Metal Migrations

Organic synthesis is centred around the formation of new bonds, particularly C-C bonds. Unfortunately, many common ways of carrying out these transformations require the pre-functionalisation of substrates to insert functional group handles. Methods of avoiding these laborious and intensive sequences are often welcomed within the field, and therefore C-H bond activation/functionalisation has now become an increasingly influential area within organic chemistry.[1] Advances in the incorporation of C-H activation into routine synthetic processes could greatly enhance the efficiency and simplicity of reaction sequences by limiting the need for manipulation of starting materials (Scheme 1).[2] With sustainability now seen as a critical concept in the scientific community, any new breakthroughs in C-H activation are looked at with great interest, as they have the potential to revolutionise the way in which chemists approach complex syntheses.[3]

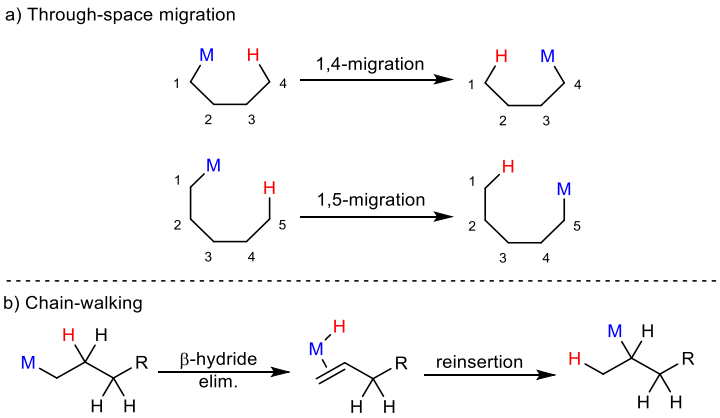


Scheme 1 – C-H activation vs classical coupling

Owing to the general lack of polarity as well as strength of most C-H bonds,[4] they are relatively unreactive compared to other functional groups. Therefore, the activation of these bonds remains a challenging pursuit. In addition, due to the ubiquitous nature of C-H bonds within most organic molecules, guaranteeing selective activation requires precise reaction tuning. In most circumstances, C-H activation is achieved either through the use of directing groups,[5] which can direct a coupling partner to a particular site, or through radical-based mechanisms.[6] The need for a directing group to be incorporated into the final compound, or the need to control a reactive radical species, sometimes make these methods undesirable.

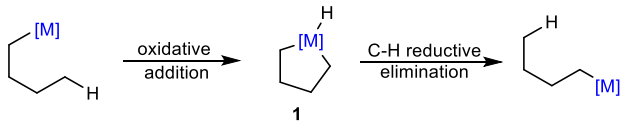
An alternative branch of C-H activation which can overcome some of these limitations is the use of transition metals in migration processes.[7] Using this approach, after the formation of a carbon-metal bond (for example by oxidative addition or migratory insertion), a through-space interaction between the metal atom and a nearby carbon-hydrogen bond can occur

(Scheme 2a). This action results in the cleavage of the C-H bond and the relocation of the metal centre to the carbon atom where the hydrogen was previously. Coinciding with this metal migration, the cleaved hydrogen atom migrates in the opposite direction. Thus, a C-H bond is activated which would have otherwise been unreactive, and a new reactive metal centre is installed. Further functionalisation of the molecule through traditional transition metal reactivity is then possible. This type of migration is distinct from another class of migrations known as 'chain-walking' which involves migration of the metal through a series of elimination and reinsertion processes (Scheme 2b).[8]



Scheme 2 – Concept of Metal Migrations

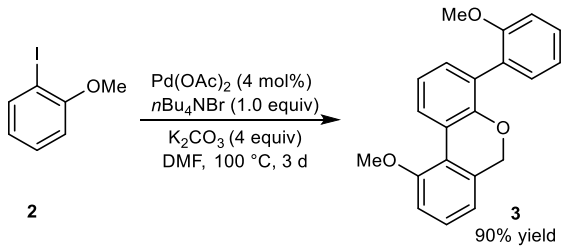
These transformations are most commonly achieved at a C-H bond 4 positions away from the metal atom, as it allows the migration to progress *via* a favourable 5-membered metallacycle (Scheme 3).[4] However, more recently, examples of 1,5-metal migrations,[9] and 1,3-migrations have been reported.[10] In most circumstances, the migration is thought to proceed *via* oxidative addition of the metal into the C-H bond, followed by C-H reductive elimination of the resulting metallacylic intermediate (**1**). Therefore, for example with rhodium(I), there is an initial oxidative addition at the C-H bond forming a Rh(III)-H complex, which then undergoes a C-H reductive elimination.



Scheme 3 - Metal-Migration Mechanism

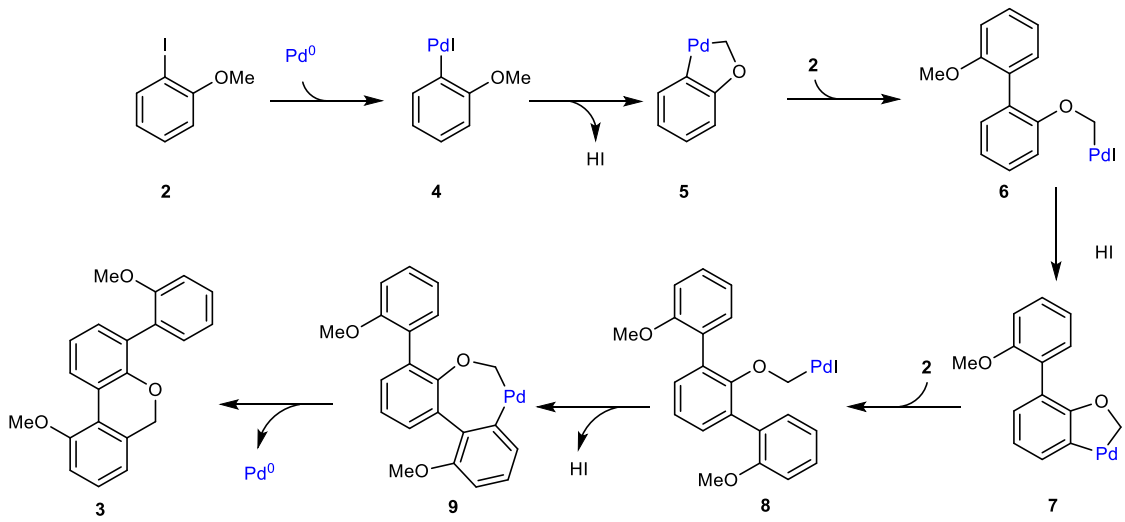
Although historically palladium and rhodium are the dominant transition metals involved in metal-hydrogen migrations,[11] recently this mode of reactivity has been extended to a number of other metals. These include platinum,[12] iridium,[13] ruthenium,[14] nickel,[15] cobalt,[16] and iron.[17] Now that a wider range of metals with differing oxidation states and d-electron configurations can undergo this process, the potential versatility and benefits in organic syntheses of using migration chemistry is substantial.

The most widely reported metal to undergo a 1,4-migration in the literature is palladium, with one of the earliest reported examples described by Dyker in 1992 (Scheme 4).[18] This reaction involved the trimerisation of *ortho*-iodoanisole (**2**) through the CH-activation of the methoxy substituent. In the presence of a palladium catalyst, condensation product **3** could be achieved in high yield (90%), albeit under relatively harsh reaction conditions.



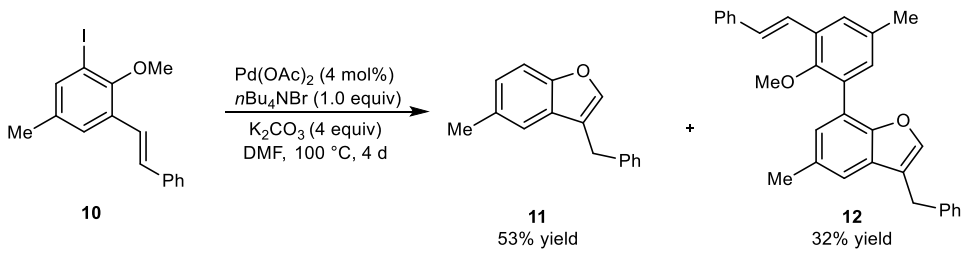
*Scheme 4 – Trimerisation of ortho-iodoanisole (**2**)*

The mechanism is believed to begin with an oxidative addition of Pd(0) with iodoanisole (**2**) to give Pd(II) species **4** (Scheme 5). This intermediate can then subsequently undergo the key cyclometalation step affording five-membered palladacycle **5**. Oxidative addition of a further molecule of **2** forms a Pd(IV) intermediate, with subsequent reductive elimination giving **6.** At this point a third molecule of **2** can undergo the cyclometalation pathway (**7** to **8**), with reductive elimination of palladacycle **9** releasing the observed product **3** and regenerating Pd(0).



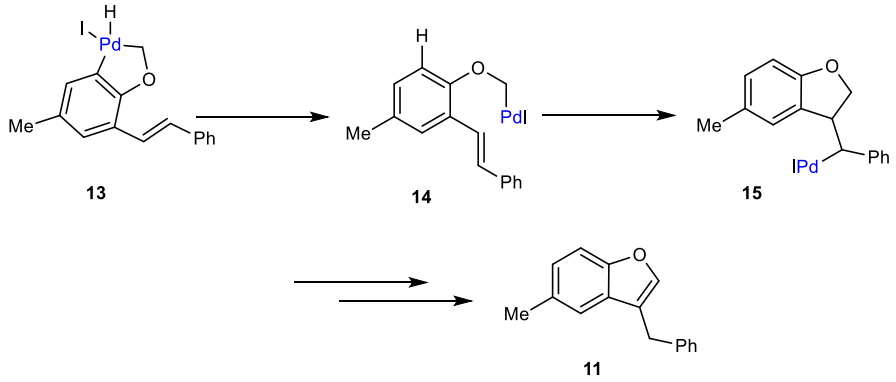
*Scheme 5 – Proposed mechanism for formation of **3***

Following this, Dyker reported that the palladium cycle generated using this methodology could be trapped by an olefin in an intramolecular Heck-type process.[19] Using functionalised stilbene **10** in the presence of $Pd(OAc)_2$, benzofuran **11** was formed as the major product, along with **12** (Scheme 6).



*Scheme 6 – Intramolecular Heck annulation of **10***

The mechanism for this reaction is similar to Scheme 5, except instead of palladacycle **13** reacting with another molecule of **10**, it undergoes a C-H reductive elimination to form alkylpalladium species **14** (Scheme 7). Insertion across the double bond would then give rise to alkylpalladium **15**, which can undergo β-hydride elimination and isomerisation to form benzofuran **11**. Unlike the first example, this reaction could be regarded as a true 1,4-migration as both the hydrogen and palladium switch locations.

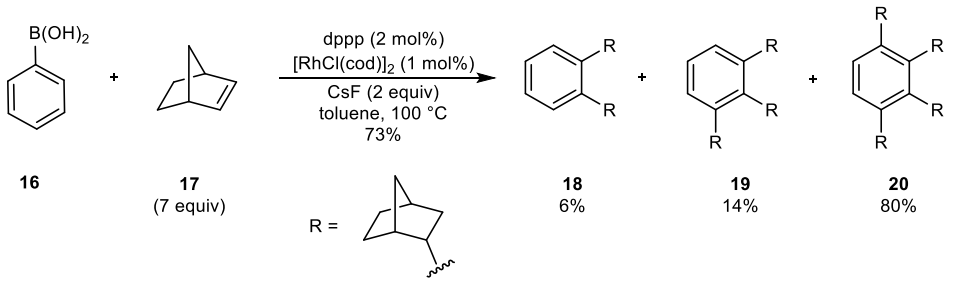


*Scheme 7 – Mechanism for the formation of **11***

Since these initial publications, many further examples of palladium 1,4-migrations have been reported.[20] These metal migrations are often classified depending upon the proton environments to which the migration is occurring. Although the work reported by Dyker was an example of migration between an C (sp^2) and C (sp^3) centre, many more examples exist of palladium migrations between two C (sp^2) centres. The reason for this is most likely due to the stability of a C (sp^2) metal centres and the ease of accessing these intermediates. At this current time, palladium migrations between vinylic,[21] aryl,[22] imidoyl,[23] acyl,[23] and alkyl[24,25] carbons have all been described. This section, however, will focus on 1,4-metal migrations between the Group 9 metals – cobalt, rhodium and iridium.

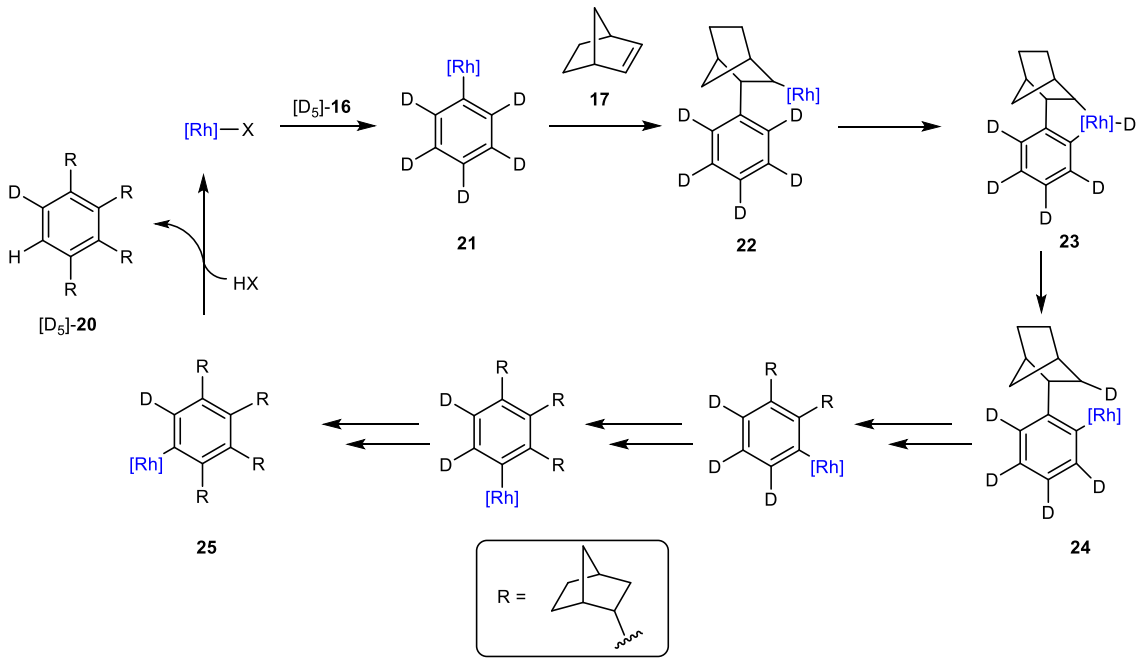
1.1.1 1,4-Rhodium Migrations

Although many of the seminal 1,4-migrations were reported using palladium, more recently rhodium has been shown to readily undergo this mode of reactivity.[11] The first observed rhodium migration was reported by Miura in 2000 and involved a migration from an alkyl sp^3 carbon to an aryl sp^2 carbon (Scheme 8).[26] A 'merry-go round' rhodium-catalysed alkylation of phenylboronic acid (**16**) with norbornene (**17**) was described, which involved multiple 1,4-rhodium migrations. When reacting **16** with **17** in the presence of a rhodium catalyst, Miura and co-workers surprisingly found the unexpected 1:4 coupled product **20** to be predominantly formed (80%), with only minor amounts of 1:2 (**18**) and 1:3 (**19**) coupled products detected.



*Scheme 8 – 'Merry -go round' alkylation of **16** - product ratios determined by GLC*

To evaluate a possible mechanism for the formation of **20**, reactions with deuterium labelled substrates were performed. When [D_5]-phenylboronic acid ([D_5]-**16**) was reacted with **17**, only one of the *ortho* deuterium atoms remained on the aromatic ring, with the others incorporated into the norbornyl-substituents. On this basis a mechanism shown in Scheme 9 was proposed. [D_5]-Phenylrhodium species **21**, formed by transmetalation of rhodium with [D_5]-**16**, could undergo a migratory insertion with norbornene (**17**) to give alkylrhodium species **22**. At this point a 1,4 migration of Rh(I) can occur, with rhodium migrating from the alkyl sp^3 carbon to the sp^2 carbon of the aryl ring. This migration is believed to proceed through an oxidative addition-reductive elimination pathway, as described in Scheme 3, *via* rhodacycle **23**. Insertion of an additional molecule of norbornene to **24** can then occur with the process repeated until the tetra-substituted aryl rhodium species **25** is formed. At this point further alkylations are unlikely due to the significant increase in steric hindrance around the aromatic ring. Protonolysis of **25** and the regeneration of the catalyst is then possible. Through reducing the of equivalents of **17** used, greater selectivity to the di- and trialkyl-substituted products (**18** and **19**) was possible as protonation could become a more dominant process.



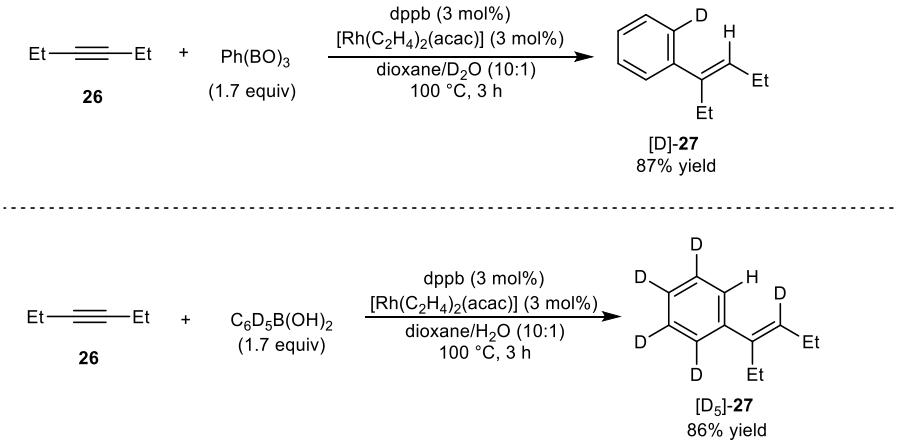
*Scheme 9 – Mechanism for the formation of **20***

For the reaction between norbornene (**17**) and phenylboronic acid (**16**) described above, DFT calculations were performed by Kantchev and co-workers.[27] These supported the Rh(I)/Rh(III) mechanism suggested for the migration step. The barrier to rhodium-norbornyl **22** protonation (20.0 kcalmol^{-1}) was much greater than for the 1,4-migration (16.3 kcalmol^{-1}) and likewise, carborhodation of intermediate **24** (13.2 kcalmol^{-1}) was also favoured over protonation (16.1 kcalmol^{-1}). Therefore, the equilibrium is pushed towards further alkylations. Interestingly, using open-chained olefins, such as *(Z)*-but-2-ene instead of strained alkene **17**, the barrier towards carborhodation relative to protonation is greatly increased and therefore only the mono-substituted product is formed. The modelling from this study was found to agree closely with experimental observations with the observed selectivity governed by the relative energetic barriers between carborhodation and protonation.

1.1.1.1 Rhodium Migrations to C (sp^2) Centres

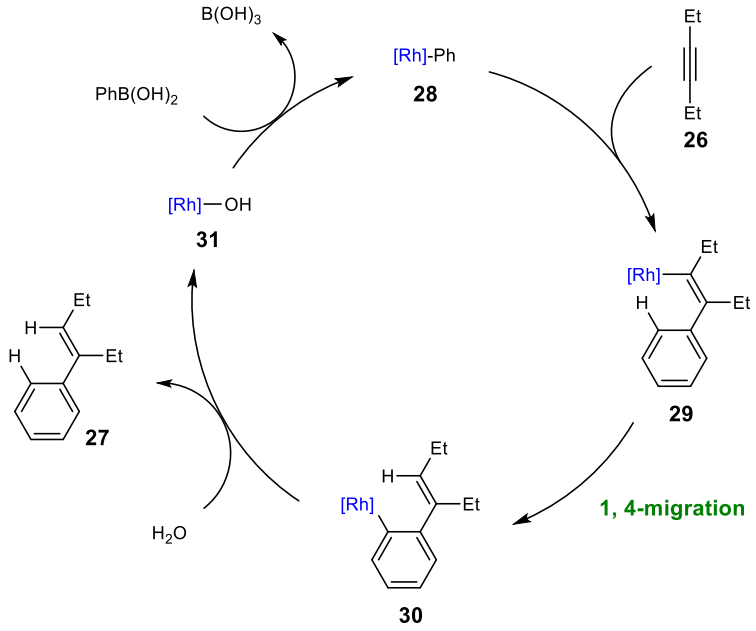
Shortly after the formative work by Miura, the group of Hayashi reported a rhodium-catalysed hydroarylation of alkynes involving a 1,4-migration step. In this chemistry the migration occurred from an alkenyl carbon to an aryl carbon (Scheme 10).[28] When the hydroarylation of alkyne **26**, was carried out using D_2O in place of H_2O, deuterium was surprisingly incorporated at the aryl ring instead of at the vinylic position ([D]-**27**).

Conversely, when reacting with deuterated phenylboronic acid ([D]$_5$-**16**), deuterium was this time incorporated at the vinylic position in addition to the aromatic ring ([D$_5$]-**27**).



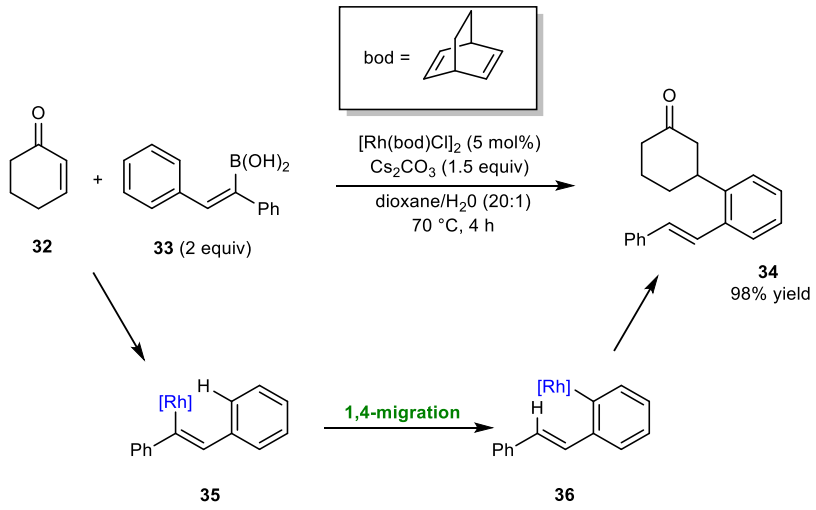
*Scheme 10 – Hydroarylation of alkyne **26***

A mechanism to account for this observation is shown in Scheme 11. Initial *syn*-addition of phenylrhodium **28** across alkyne **26** forms alkenylrhodium species **29.** A 1,4-migration of rhodium then occurs resulting in 2-(alkenyl)phenylrhodium intermediate **30**. Protonation of **30** then gives alkene **27** and regenerates **31**. The high selectivity for **27** is attributed to it being energetically unfavourable for intermediate **30** to react with an additional molecule of alkyne **29**. When water was excluded from the reaction, and the equivalents of **29** were increased, it was possible for **30** to insert across another molecule of **26.**



*Scheme 11 – Catalytic cycle for formation of **27***

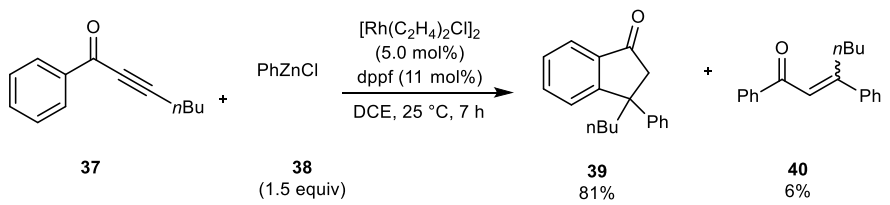
Using this methodology, Hayashi later reported the trapping of aryl-rhodium species with other electrophiles.[29] When enone **32** was reacted with vinyl boronic acid **33** in the presence of a rhodium catalyst and using the 'bod' ligand, no conversion to the classical conjugate addition product was detected (Scheme 12). Instead, nearly complete conversion to rearranged product **34** was observed.



*Scheme 12 – Rhodium-catalysed addition of vinylboronic acid **33** to enone **32***

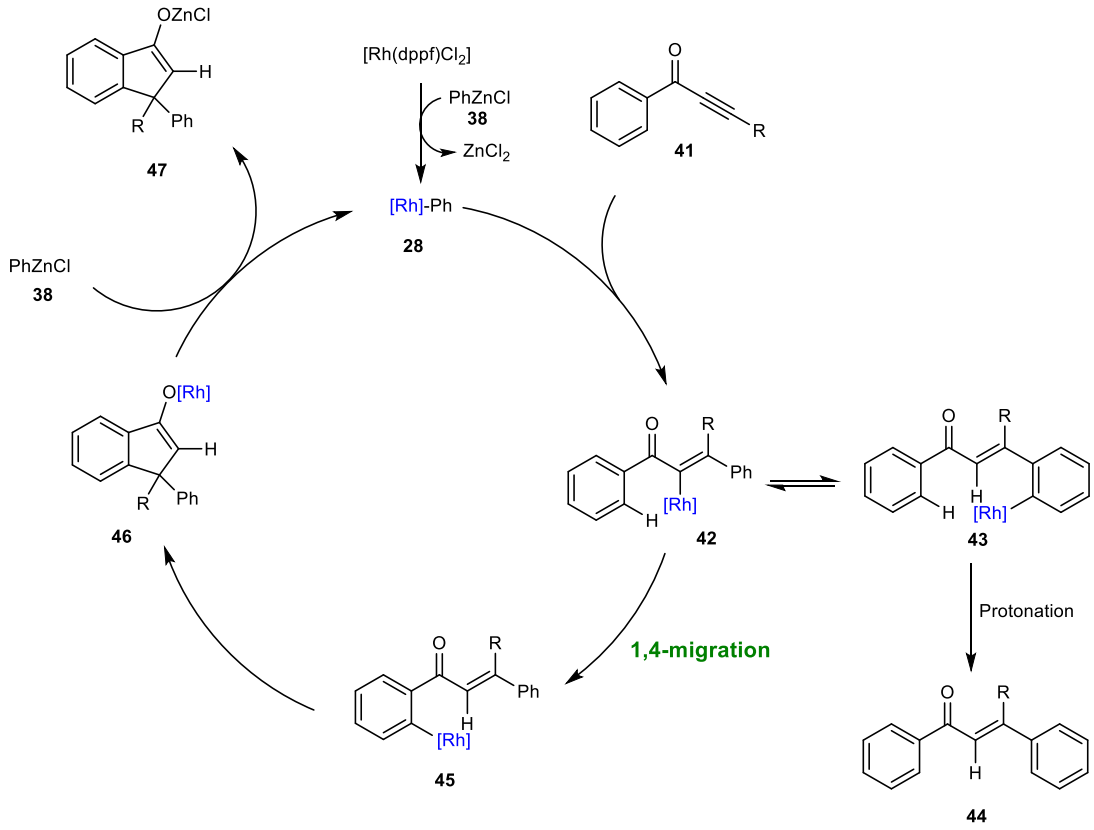
The exclusive formation of the rearranged product **34** suggested a 1,4-rhodium shift from vinylrhodium(I) intermediate **35** to arylrhodium species **36** was occurring. DFT studies again suggested that rhodium migrates *via* a successive C–H oxidative addition, reductive elimination mechanism. The driving force behind this migration was the significantly higher barrier to carborhodation of the non-rearranged substrate **35** compared to the barrier for a 1,4-rhodium migration. After migration though, the energetic requirement for carborhodation is lowered and therefore **36** can be trapped by enone **32**.[30]

In 2005, Hayashi and co-workers utilised another alkenyl-to-aryl 1,4-rhodium migration in the synthesis of β,β-disubstituted indanones (Scheme 13).[31] Using phenylzincate **38** and alkynyl ketone **37**, indanone **39** was synthesised in high yield. A phosphine ligand was essential for good conversion to **39**, as with $[Rh(cod)Cl]_2$, conversion to **40**, which arises from simple addition across the alkyne, was favoured (70% NMR yield).



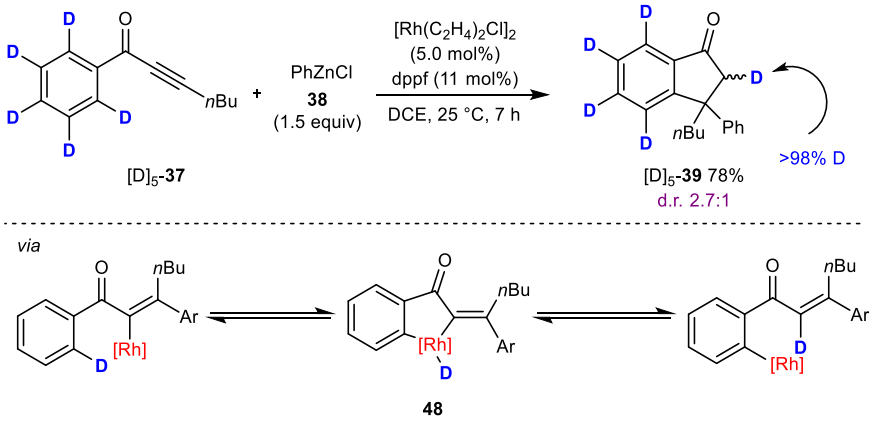
*Scheme 13 – Rhodium-catalysed addition of arylzincates to alkynone **37***

A proposed catalytic cycle for the formation of **39** (Scheme 14) would proceed similarly to those described previously. Transmetalation of the rhodium catalyst with arylzincate **38** would give arylrhodium species **28**. This intermediate can then undergo a *syn*-arylmetalation with alkynone **41.** The generated alkenylrhodium species **42** can then participate in a 1,4-migration to give the more stable arylrhodium species **45**. Theoretically, migration to either aryl rings is possible at this point. However, if migration occurs to the newly inserted aryl ring it would give arylrhodium **43** where the only outcome would be protonolysis (**44**). Intramolecular 1,4-additon of **45** would then afford rhodium enolate **46,** at which point transmetalation with **38** regenerates **28**, and liberates indanone **47**.



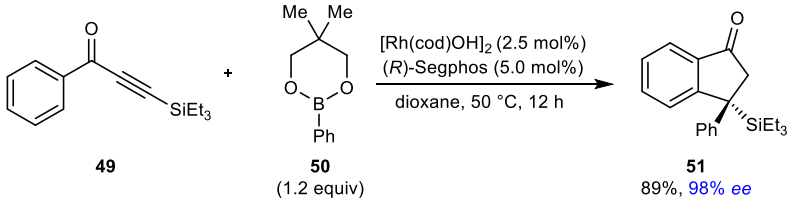
*Scheme 14 – Catalytic cycle for formation of **39***

An experiment to investigate deuterium transfer and provide evidence for a 1,4-migration is shown in Scheme 15. When reacting alkynone [D_5]-**37** with **38**, complete deuterium incorporation was observed at the α-position of indanone [D_5]-**39**. The complete transfer of deuterium suggests that migration is proceeding *via* the oxidative addition of the C-D bond, forming rhodium-deuteride intermediate **48**, followed by reductive elimination.



*Scheme 15 – Reactivity with [D_5]-**37***

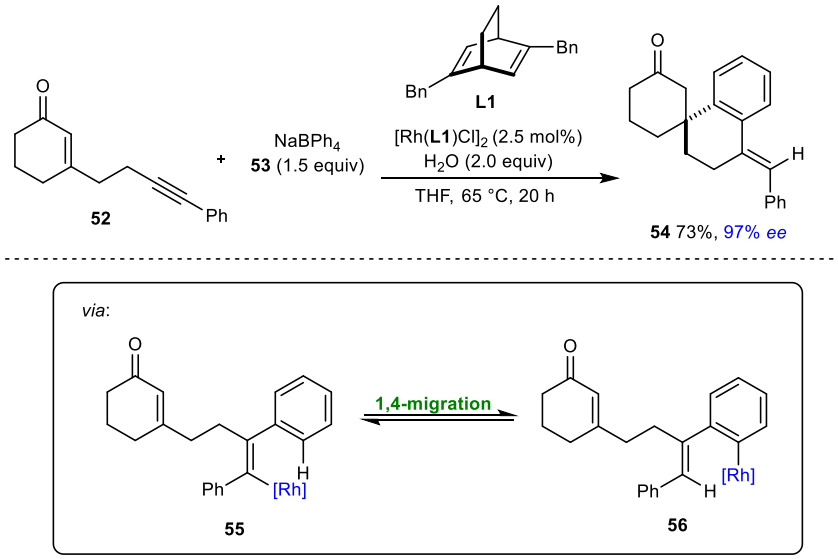
Attempts to generate an enantioselective variant using these substrates was moderately successful with an enantiomeric excess of 54% obtained when using a ferrocene-based bisphosphine. Higher enantioselectivity was obtained using (*R*)-BINAP (84% *ee*), but poor catalyst activity was observed (29% yield). However, upon switching from an arylzinc to an arylboron species, and using silyl-substituted alkynone **49**, indanone **51** was synthesised in higher yield and excellent enantioselectivity (Scheme 16).[32] Use of boronate ester **50** was required to limit the formation of undesired hyrdoarylation products (like **44**), which were prevalent when using an arylboronic acid.



*Scheme 16 – Rhodium-catalysed arylative cyclisation of **49***

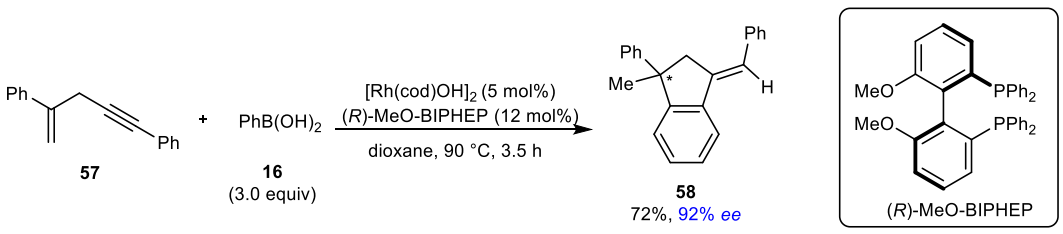
Hayashi later demonstrated that an arylrhodium species could be generated from enynone **52**, which can then subsequently participate in a conjugate addition reaction (Scheme 17).[33] With substrate **52**, insertion of the arylrhodium species (generated from transmetalation of

the catalyst with arylboronate **53**) occurs with rhodium situated this time at the distal position in relation to the carbonyl (**55**). Alkenylrhodium **55** can then undergo migration to the phenyl ring originating from **53**, giving arylrhodium species **56**. This step can then be followed by conjugate addition. Using chiral diene **L1** and sodium tetraphenylborate (**53**), spriocarbocyle **54** was synthesised in good yield and excellent enantioselectivity. The key step being the migration of rhodium to the aryl ring.



*Scheme 17 – Rhodium-catalysed spirocyclisation of **52***

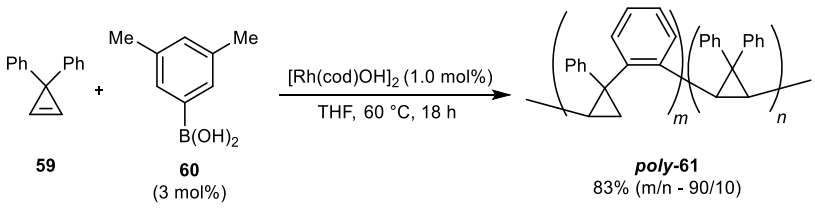
More recently, Matsuda and co-workers reported a rhodium(I)-catalysed arylative annulation of 1,4-enynes (**57**) using an arylboronic acid (Scheme 18).[34] With a bisphosphine ligand (MeO-BIPHEP), indane **58** was synthesised in high yield (72%) and with good enantioselectivity (92% *ee*). The key step was the rhodium alkenyl-to-aryl migration, with the generated arylrhodium species subsequently adding into the pendant alkene moiety.



*Scheme 18 – Enantioselective rhodium-catalysed annulation of **57***

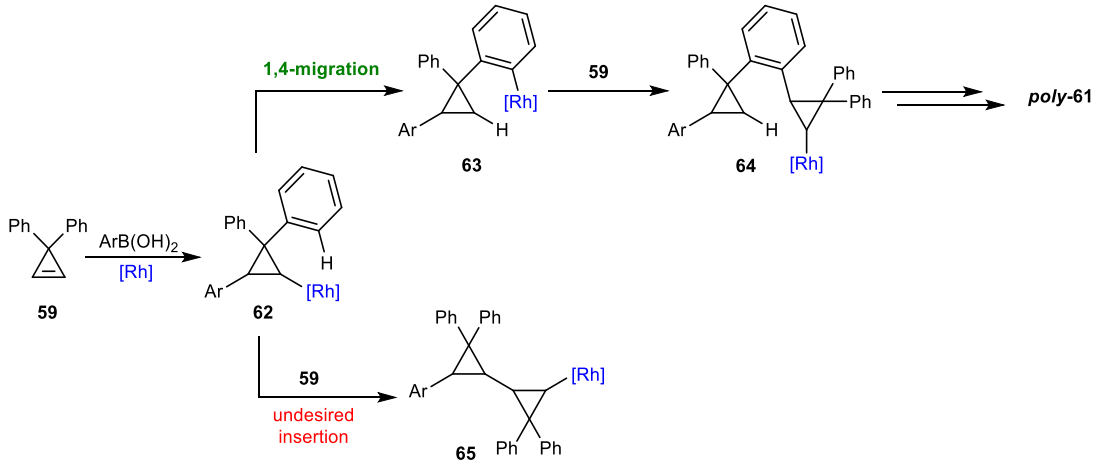
Alkenylrhodium species, as has been shown, can be readily generated by the migratory insertion of an alkyne into an arylrhodium species, with the resulting intermediate then susceptible to a 1,4-metal migration. These new arylmetal species can then be trapped by a range of electrophiles in an intermolecular or intramolecular fashion. For this reason, rhodium migrating from an alkenyl carbon to an aryl carbon is the most widely reported migration in the literature. However, a number of examples have been described where a generated alkylrhodium species subsequently undergoes a 1,4-migration. In 2014, Shitani and co-workers reported an alkyl-to-aryl migration of rhodium.[35] Alkyl to aryl rhodium migrations are often very useful as a reactive arylrhodium species can be generated from an alkylrhodium(I) species. These are generally more reactive to electrophiles and can therefore undergo further chemistry.

Using reactive cyclopropene **59** with initiator **60** and in the presence of a rhodium catalyst, a 1,4-migration caused the molecule to undergo spontaneous polymerisation (Scheme 19). This type of molecule (*poly*-**61**) would not be possible to synthesise by other conventional polymerisation techniques.[36]



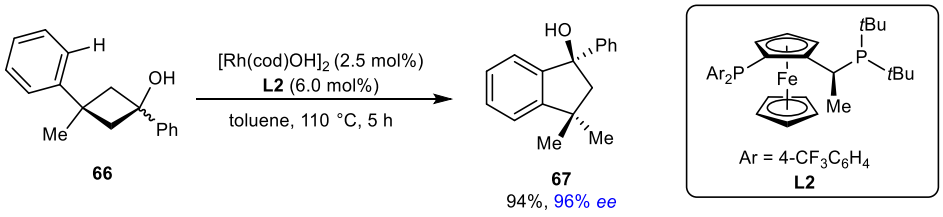
*Scheme 19 – Rhodium-catalysed polymerisation of **59***

For this polymerisation to take place, after addition of an arylrhodium species across cyclopropene **59**, the alkyl-to-aryl migration of **62** must be favoured over the undesired intermolecular insertion (**65**) (Scheme 20). Insertion of the newly formed arylrhodium species **63** with another molecule of **64** can then take place. Shintani found that the desired pathway could be favoured by limiting the concentration of **59** in the reaction mixture.



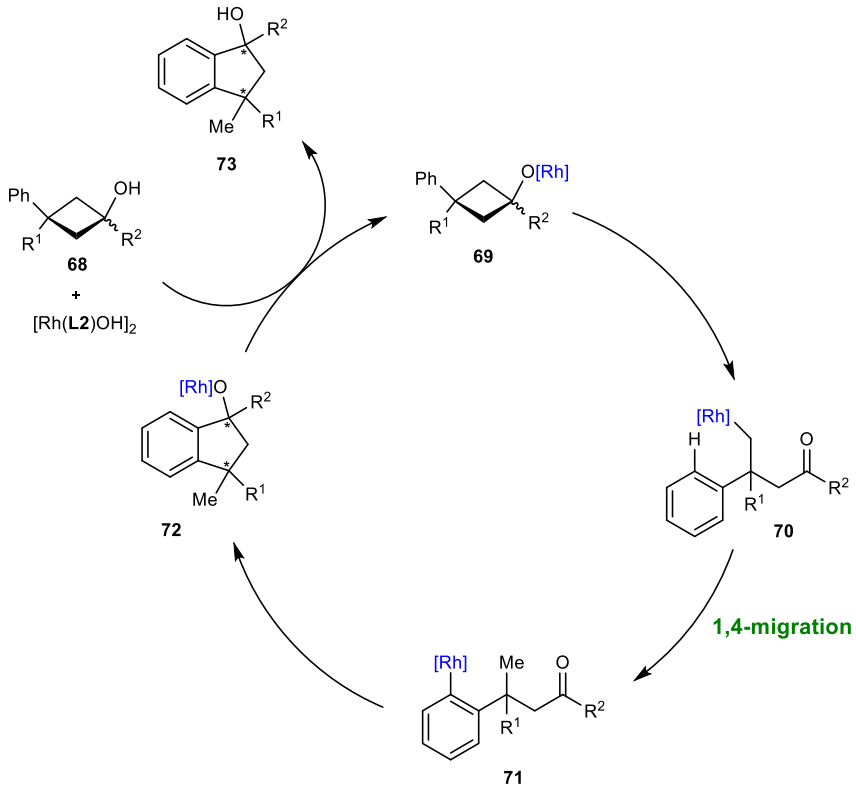
*Scheme 20 – Mechanism for the polymerisation of **59***

Metal-catalysed cleavage of carbon-carbon bonds in 4-membered cyclobutane rings is another efficient route to generating alkylmetal species.[37] In 2009, the Cramer group were investigating methods of generating these reactive alkylmetal species through the β-carbon elimination of strained 4-membered tertiary alcohols. During this process, they reported a novel alkyl-to-aryl rhodium(I) migration.[38] Using *tert*-cyclobutanol **66** and a rhodium catalyst, indanol **67** was synthesised in excellent yield and enantioselectivity (Scheme 21).



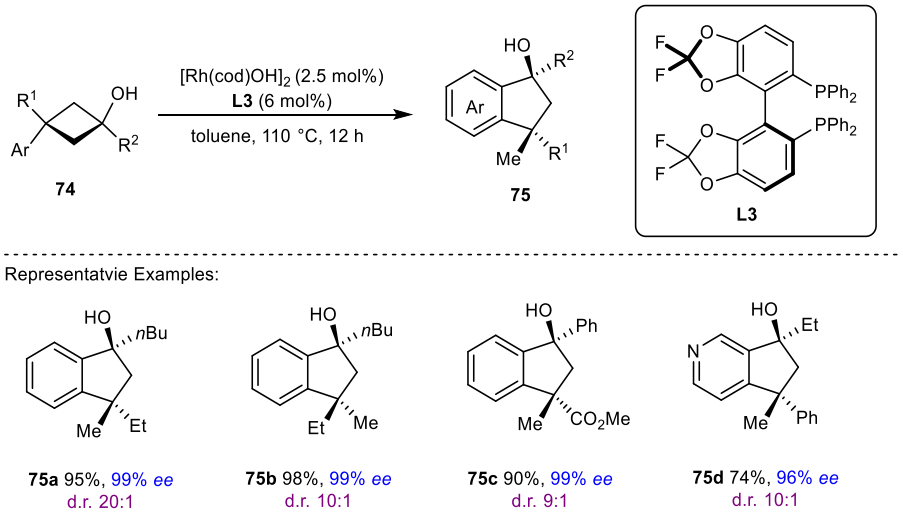
Scheme 21 – Enantioselective rhodium-cataylsed synthesis of indanones

The formation of **67** can be rationalised by the mechanism shown in Scheme 22. The rhodium catalyst and cyclobutanol **68** would initially react to give rhodium alkoxide species **69**. Selective β-carbon elimination of the C-C bond of the cyclobutane ring would form alkylrhodium species **70**. Due to this intermediate bearing no β-hydrogens, β-hydride elimination is not possible. Therefore, an alkyl-to-aryl migration can occur forming the more stable arylrhodium species **71**. Reaction with the pendant ketone is then possible, providing indanol **72**, which upon protonolysis affords **73**.



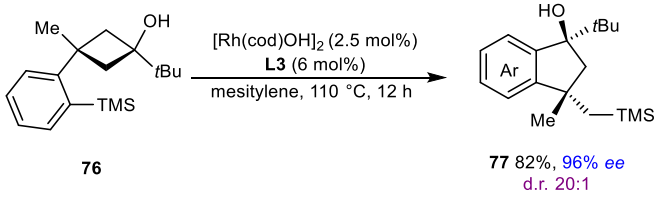
*Scheme 22 – Catalytic cycle for formation of **73***

When the cyclobutane does not have a methyl substituent ($R^1 \neq$ Me), the indanol product can exist as diastereomers (Scheme 23). Using the conditions shown in Scheme 21, **75a** could only be formed in poor diasteroeselectivity (1.2:1). However, with Difluorphos (**L3**) as a ligand, the diastereoselectivity could be greatly enhanced (20:1). The favoured diastereomer could be switched depending upon which isomer of **74** is used as the substrate (compare **75a** and **75b**). In the circumstances where R^1 is also an aryl group, the metal has a choice as to which site it would migrate to. High selectivity for product **75d** was observed with migration of rhodium to the pyridine ring favoured over migration to the phenyl ring. The indanol product which arises from migration to the phenyl ring, was only formed in 9% yield.



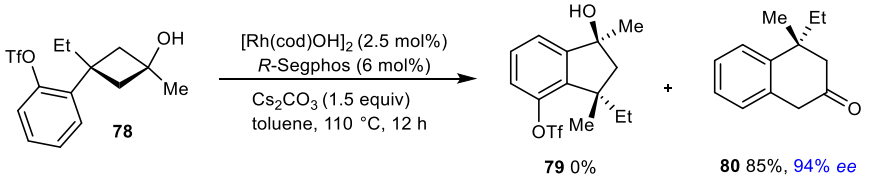
Scheme 23 – Rhodium-catalysed synthesis of indanols

Up to this point, only metal-hydrogen migrations involving insertion of a metal into a C-H bond have been presented. However, expanding on the chemistry of cyclobutanols, Cramer reported the first silicon migration in 2010 (Scheme 24).[38] Using cyclobutane **76**, migration of the silicon group was favoured over migration of a proton, giving product **77**. This new mode of reactivity could potentially be very useful as it allows both positions undergoing migration to remain functionalised.



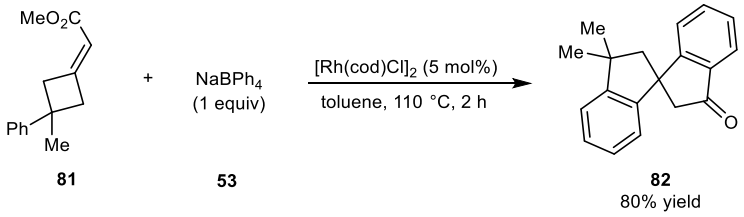
Scheme 24 – Rhodium-catalysed migration of TMS group

Cramer later demonstrated that using cyclobutane **78**, where the aryl ring incorporates a triflate substituent, products such as **80** were formed in preference to migratory product **79** (Scheme 25).[39]



*Scheme 25 – Rhodium-catalysed annulation of **78***

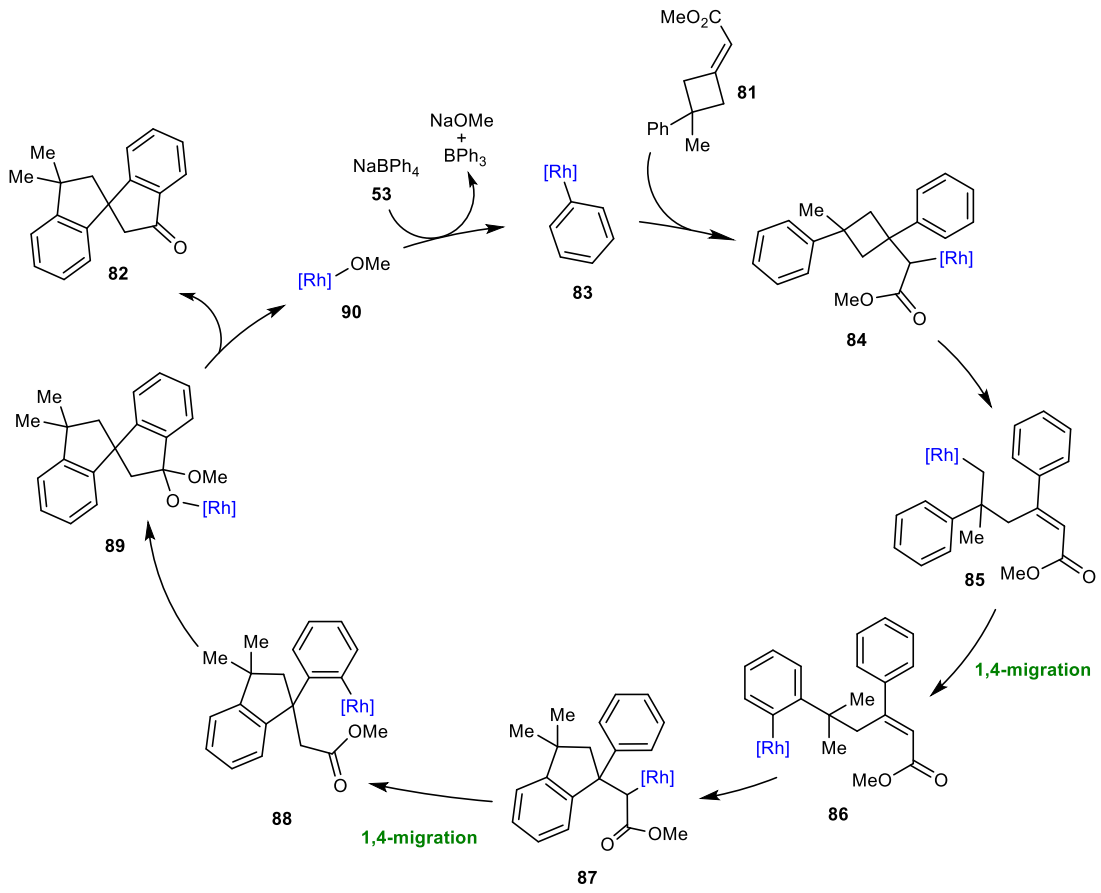
Remote activation of a C-H bond often has the potential to result in domino reaction processes with multiple or consecutive 1,4-migrations taking place.[40] In 2012, a double alkyl-to-aryl rhodium(I) migration was reported by Matsuda in the rhodium-catalysed spirocyclisation of cyclobutane **81** (Scheme 26).[41]



*Scheme 26 – Spriocyclisation of **81***

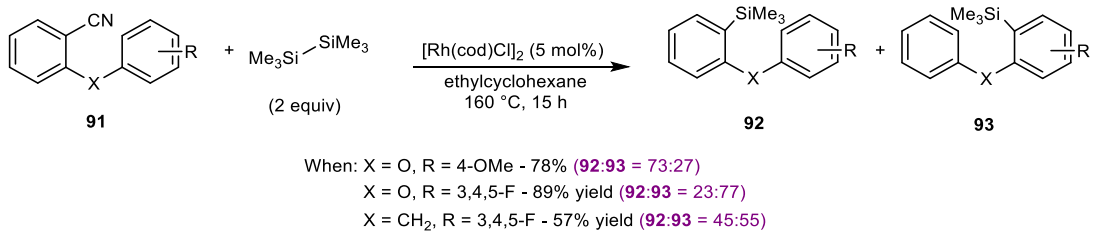
The synthesis of complex spirocycle **82** from **81** would be hard to achieve using conventional chemistry. The proposed catalytic cycle by Matsuda involves multiple 1,4-migrations, alongside several C–C and C–H bond cleavages, and three new C–C bond formations (Scheme 27). Initially, nucleophilic arylrhodium species **83**, formed by transmetalation of rhodium with sodium tertraphenylborate (**53**), would undergo a conjugate addition with **81**. β-Carbon elimination would then open the ring to form α,β-unsaturated ester **85**. The first 1,4-migration can then occur from the C (sp^3) carbon to the C (sp^2) aryl position. The newly formed arylrhodium species **86** then undergoes a second 1,4-addition with the unsaturated ester forming indane **87**. A second alkyl-to-aryl 1,4-rhodium migration can then take place giving **88**. At this point **88** can react with the electrophilic carbonyl of the ester group *via* a 1,2-addition to give **89**, with subsequent β-oxygen elimination releasing product **82** and regenerating the catalytically active rhodium methoxide (**90**).

The highly selective conversion to **82** is only possible due to the specific tuning of each reaction step. Although 1,4-migration is theoretically possible for intermediate **84**, β-carbon elimination is favoured due to a reduction in ring strain. In the final 1,4-migration step (**87** to **88**), the rhodium has the choice of migrating to two different aryl environments, the phenyl or indane ring. In this circumstance 1,4-migration occurs preferentially to the phenyl ring, which has been attributed to reduced steric hindrance at this position compared to the indane. This example highlights some of the complex and interesting products which are attainable from simple substrates using metal migration chemistry.



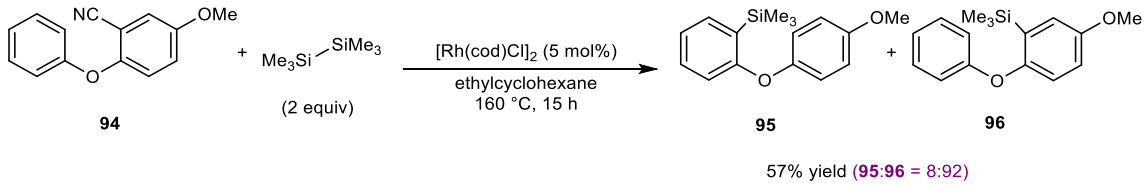
Scheme 27 – Catalytic cycle for formation of 82

Compared to 1,4-metal migrations the number of reported 1,3 or 1,5-migrations is considerably less well-described. This outcome is presumably because 1,4-migrations are more readily accessible, as they proceed *via* an energetically favourable 5-membered metallacycle rather than a 4 or 6-membered one. However, a small number of 1,5-metal migrations have been reported using palladium[42] and rhodium.[43] An aryl-to-aryl 1,5-rhodium migration was reported by Tobisu in 2012, and occurred during the decyanative silylation of aryl cyanide **91** (Scheme 28).[9] With substrates bearing electron donating groups (R = 4-OMe) the expected decyanative silylation product **92** alongside migratory product **93** (73:27) were both observed. Altering the electronics of the ring (R = 3,4,5-F), this ratio was reversed in favour of migratory product **93** (23:77). In addition, the nature of the linker had an important effect on the product distribution. When oxygen was substituted for a methylene group preference for non-migratory product **92** was increased with no selectivity between **92** and **93** obtained (45:55).



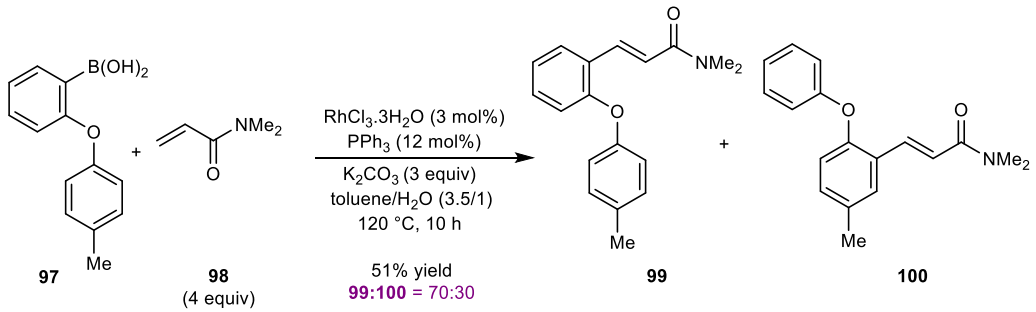
*Scheme 28 – Decyantive silylation of **91***

Interestingly, when isomeric aryl cyanide **94** was used a completely different product ratio was observed (**95**:**96** = 8:92). This result suggested that the 1,5-migration step, in this circumstance, is irreversible as opposed to being in equilibrium, and therefore directly involved in controlling product selectivity. (Scheme 29).



*Scheme 29 – Decyanative silylation of **94***

The 1,5-rhodium migration was not limited to these substrates. Tobisu also reported a 1,5-migration in the rhodium-catalysed oxidative Heck reactions of arylboronic acids with alkenes (Scheme 30). Using aryl boronic acid **97** with *N*,*N*-dimethyl acrylamide (**98**) both **99** and migratory product **100** could be isolated.

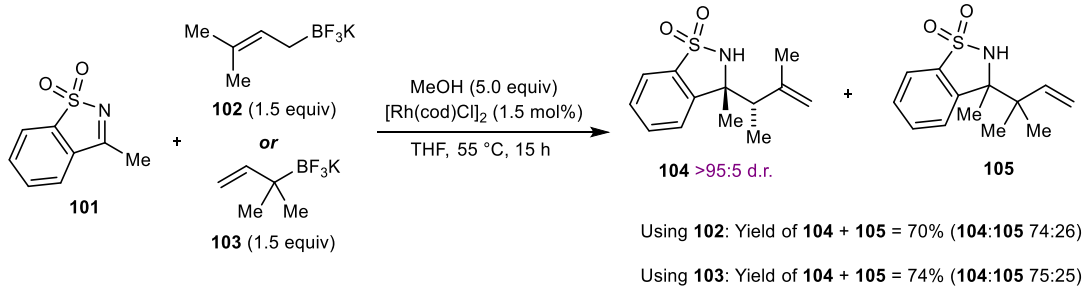


*Scheme 30 – Rhodium-catalysed Heck reaction of **98***

1.1.1.2 Rhodium Migrations to C (sp^3) Centres

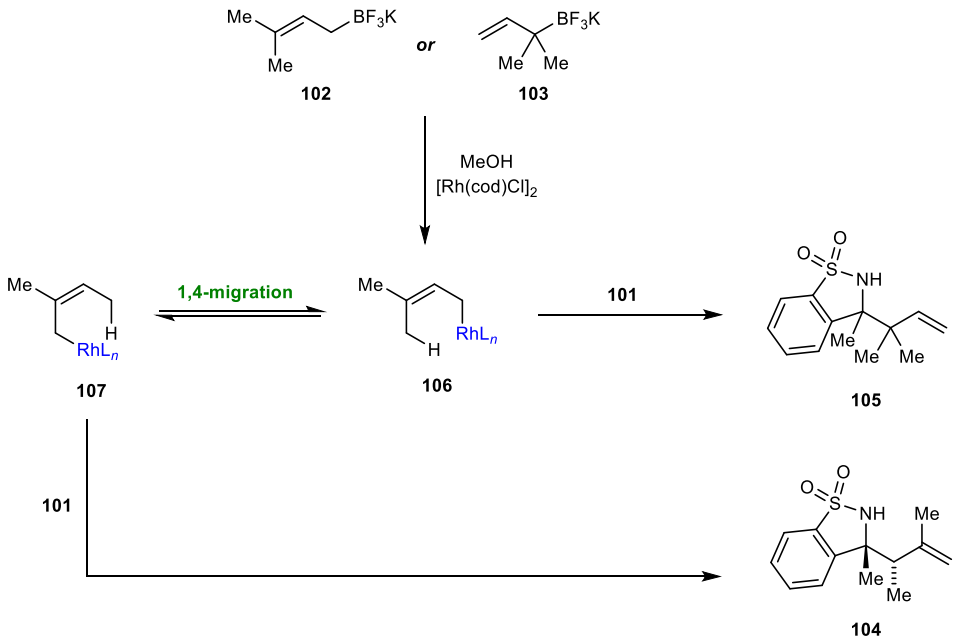
Compared with rhodium migrations to C (sp^2) centres, there is currently only limited precedent for rhodium to undergo migrations to C (sp^3) centres. This outcome is most likely a consequence of aryl or vinylrhodium species being lower in energy than the equivalent alkylrhodium species.

However, in 2014 the Lam group reported one such example of this type of migration when reacting ketimine **101** with a γ,γ- or α,α-disubstituted potassium allyltrifluoroborate (**102** or **103**) (Scheme 31).[44] Surprisingly, reverse prenylation product **105** was not observed in good yield, with homoallylic sulphonamide **104** obtained as the major product in high diastereoselectivity.



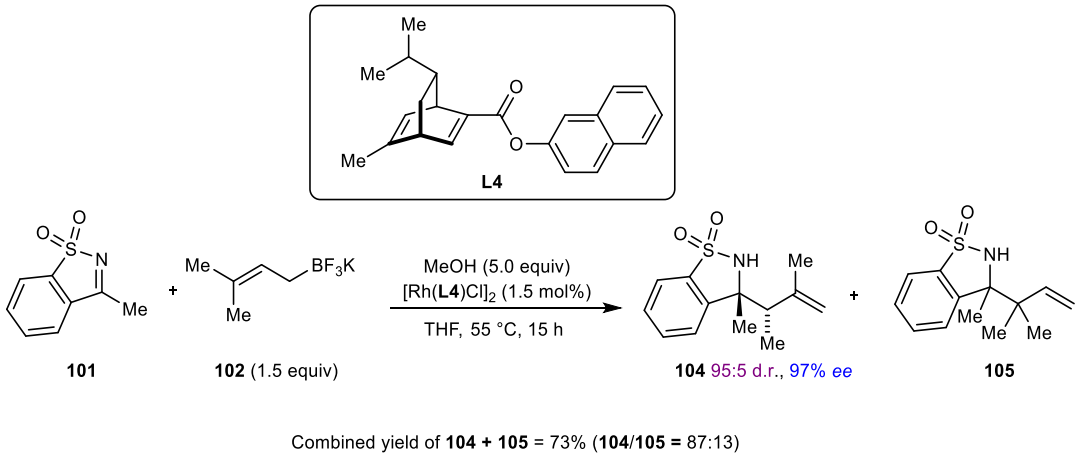
*Scheme 31 – Rhodium-catalysed allylation of **101***

Scheme 32 shows a viable route for the formation of product **104**. Transmetalation of either **102** or **103** with a rhodium catalyst, would give allylrhodium species **106**. Allylation of imine **101** with this species would afford **105**. However, owing to the poor reactivity of ketimine **101**, an allyl-to-allyl rhodium(I) 1,4-migration can take place. This migration results in the formation of allylrhodium species **107**, with nucleophilic allylation of the ketimine with this species giving the observed major product **104**.



*Scheme 32 – 1,4-migration of **106***

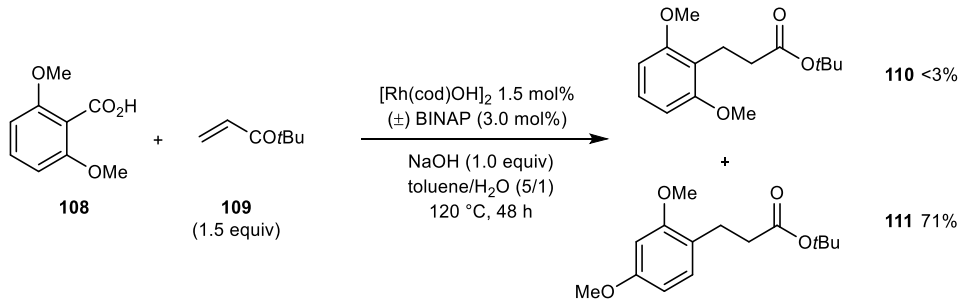
The reaction could also be performed enantioselectively (Scheme 33). With chiral diene ligand **L4** and allylboronate **102**, allylation of imine **101** proceeded in high yield and with excellent enantioselectivity.



*Scheme 33 - Enantioselective allylation of ketimine **101***

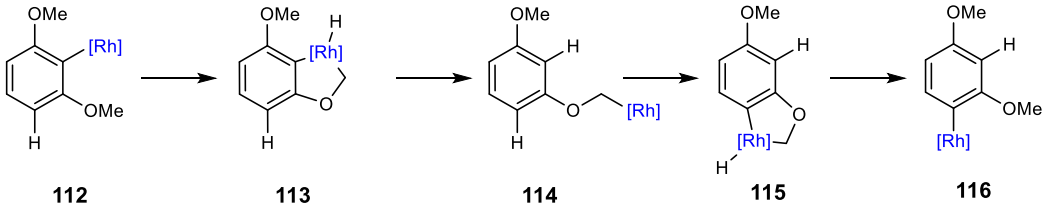
Prior to the Lam group reporting this migration, a formal 1,3-Rh(I) migration involving rhodium migrating to an alkyl carbon was reported by Zhao. During the rhodium-catalysed decarboxylative olefination of **108**, generation of product **111** was possible *via* two

consecutive 1,4-migrations, (Scheme 34).[45] Only limited conversion to *ipso*-functionalised product **110** was observed under these reaction conditions.



*Scheme 34 – Decarboxylative olefination of **108***

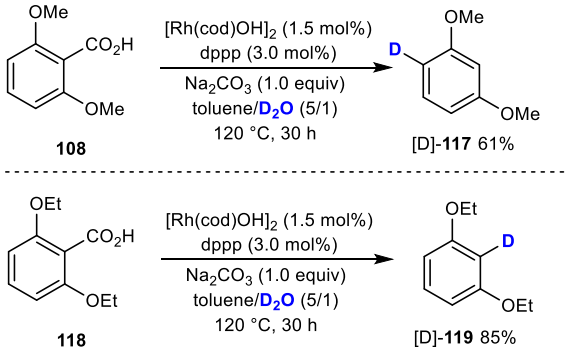
Several possible mechanisms explaining the reactivity shown in Scheme 34 were considered by Zhao. One possibility was the direct 1,3-migration. DFT calculations, however, suggested 1,3-metal migrations would be generally disfavoured due to proceeding *via* a highly strained 4-membered metallacycle.[27] An alternative was *via* decarboxylation and then protonation of **108** to form dimethoxybenzene, with an electrophilic aromatic substitution involving rhodium(I) hydroxide (directed by the two methoxy groups) giving **111**. However, no reactivity was observed when dimethoxybenzene was directly coupled with **109**. Therefore, a consecutive 1,4-migration pathway was proposed as shown in Scheme 35. After formation of arylrhodium(I) species **112**, oxidative addition of the rhodium catalyst into the activated C-H bond of one of the methoxy substituents would give cyclometalation product **113**. Subsequent reductive elimination would then give Rh(I) aryloxyalkyl intermediate **114**. This intermediate could then undergo a second 1,4 migration (alkyl-to-aryl), *via* the same pathway (**114**) to the less sterically hindered *meta*-position of the aryl ring. Intermediate **116** can then react with *tert*-butyl acrylate (**109**), affording the observed product **111**.



Scheme 35 – Consecutive 1,4-Migrations

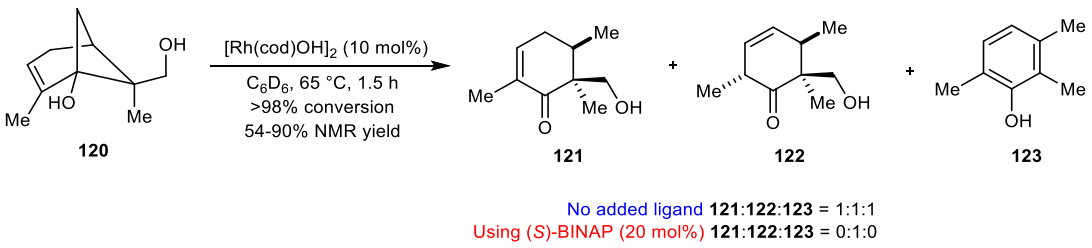
Changes in the substituents on the phenyl ring were found to have a profound effect on the reactivity, with the propensity for this 1,3-migration governed by steric factors (Scheme 36).

Methoxy-substituents prevented *ipso*-functionalisation and promoted the two consecutive 1,4-migrations. However, when these were replaced by ethoxy-substituents (**118**), deuterium incorporation was found at the *ipso*-position ([D]-**119**), suggesting the 1,4-migrations were not occurring.



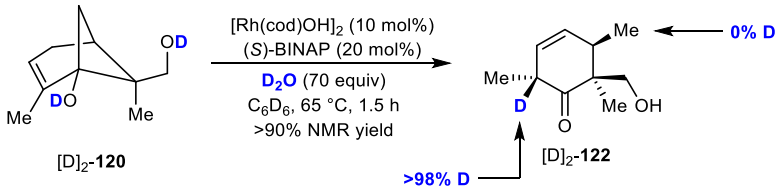
Scheme 36 – Deuterium labelling studies

In 2015, Sarpong and co-workers reported what could be described as the first true 1,3-rhodium migration when investigating the synthesis of various cyclohexanone scaffolds.[46] As shown by Cramer (see Scheme 21), it is well-established that transition metals can catalyse bond specific cleavage of cyclobutanols.[37] Using conditions previously developed by Murakami, Sarpong found that the rhodium-catalysed ring opening of strained cyclobutanol **120**, afforded compounds **121** and **122**, as well as phenol **123** in similar ratios, with diastereomer **122** formed exclusively (Scheme 37). Through decreasing the temperature and extending the reaction time (40 °C for 48 h), the selectivity towards **121** was greatly enhanced, with **122** not observed, and only trace amounts of phenol **123** seen. Interestingly, using (*S*)-BINAP with $[Rh(cod)Cl]_2$, **122** was the only product observed by analysis of the crude NMR spectrum, with no conversion to either **121** or **123**.



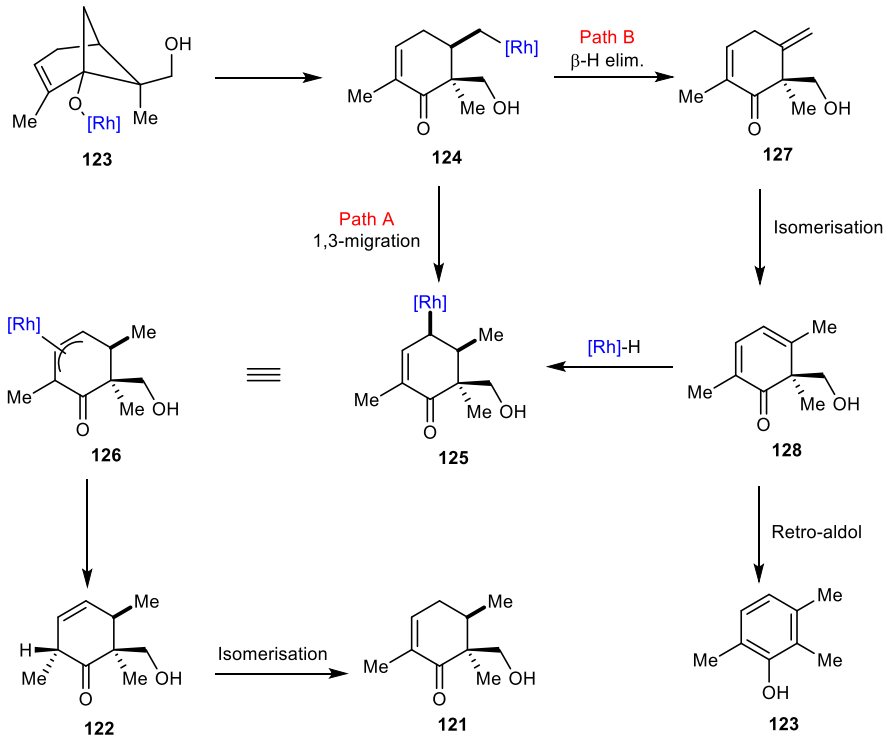
*Scheme 37 – Synthesis of cyclohexenone **121** from cyclobutanol **120***

A study using deuterium labelled substrates was performed to try and elucidate a mechanism (Scheme 38). When [D_2]-**120** was reacted using rhodium and (*S*)-BINAP in the presence of D_2O, [D_2]-**122** was observed with complete deuterium incorporation at the position α to the carbonyl. No deuterium was incorporated at the methyl position formed from cleavage of the ring, suggesting this hydrogen is therefore introduced intramolecularly.



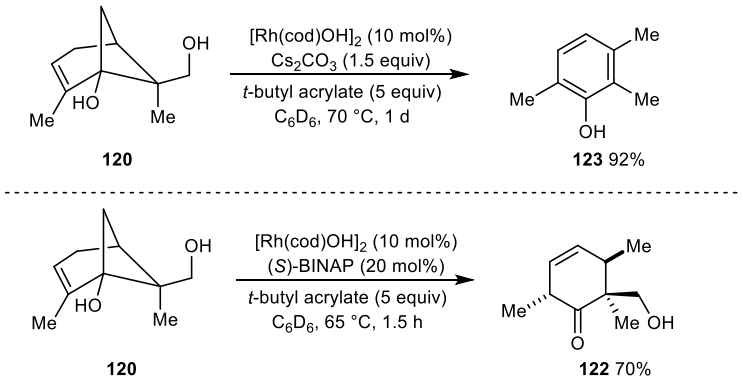
Scheme 38 – Deuterium labelling study

Taking this observation into account, a mechanism for the formation of **121** and **122** is shown in Scheme 39. After the rhodium-catalysed ring opening of **123**, alkylrhodium species **124** would be formed. Although protonolysis of this species would afford **121**, based on the existence of **122** and **123**, and the deuterium incorporation shown in Scheme 38, an alternative mechanism must be present. Two pathways were proposed. In Pathway A, the mechanism proceeds with an initial 1,3-rhodium(I) migration forming **125**. This migration is favourable as rhodium would relocate to the thermodynamically more favoured allylic C (sp^3) position. Metal enolate **126** can then be protonated forming product **122**, which can then isomerise to **121**. An alternative pathway (Pathway B) involves a series of β-hydride eliminations and isomerisations. This path would give rise to **128** from **127**, which could then either undergo rhodium-hydride addition across the double bond, giving **125**, or a retro-aldol reaction, affording phenol **123**.



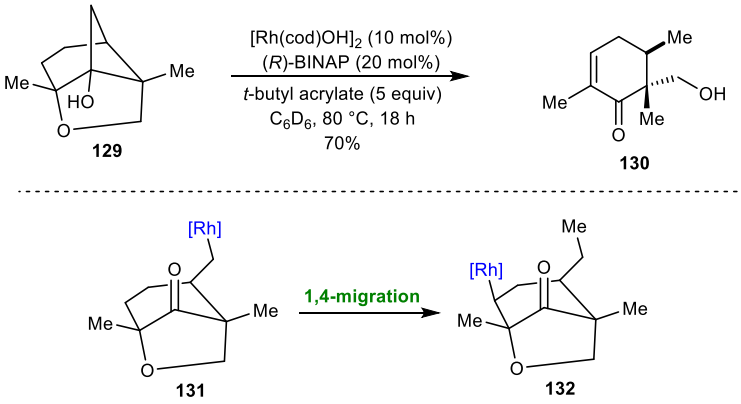
*Scheme 39 – Mechanism for formation of **121** and **123***

Sarpong hypothesised that the change in ligand was dictating which pathway the reaction was proceeding through. Further evidence was found when *t*-butyl acrylate was added to intercept any rhodium hydride species formed (Scheme 40). When the cyclooctadiene (cod) ligand was used, **121** or **122** were not observed, with only formation of phenol **123**. Conversely, using (*S*)-BINAP as a ligand, addition of *t*-butyl acrylate did not affect the reactivity, with **122** observed in high yield. This result suggested pathway A is significant when using (*S*)-BINAP, and that when using $[Rh(cod)Cl]_2$ rhodium hydride is formed.



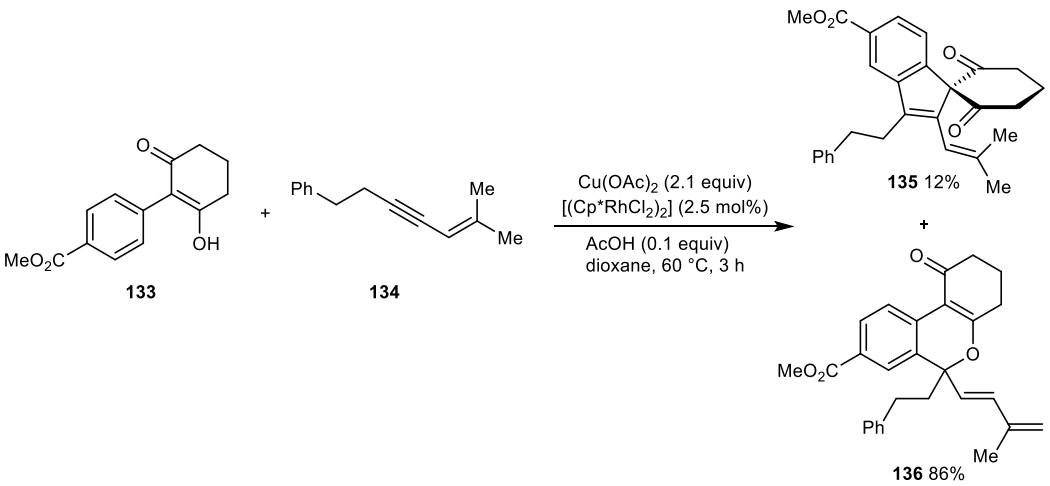
*Scheme 40 – Reactivity of **120** using t-butylacrylate as [Rh]-H scavenger*

DFT calculations were then performed to provide further insight into the experimental observations. These calculations suggested that an oxidative addition-reductive elimination pathway *via* a 4-membered rhodacycle was feasible for the rhodium 1,3-migration. The total energy barrier for migration was found to be higher with cod as the ligand as opposed to (*S*)-BINAP. Further evidence to support this type of C-H-activation was found through reacting **129** with a rhodium catalyst (Scheme 41). Enone **130** (the opposite diastereomer to **121**) could be synthesised in high yield from **129**. 1,4-Alkyl-to-allyl migration (**131** to **132**) and then subsequent β-alkoxy elimination were believed to be the key steps.



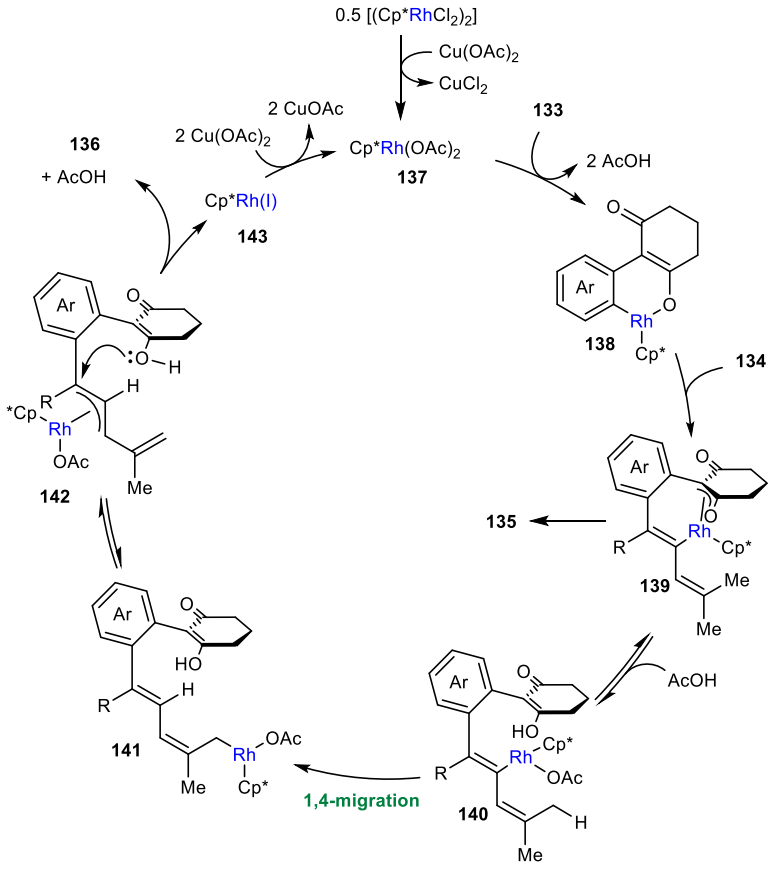
*Scheme 41 – Rhodium catalysed ring opening of **129***

Up to this point, only migrations involving rhodium(I) have been discussed. However, rhodium(III) is also known to undergo this mode of reactivity, although fewer examples exist in the literature.[47] The Lam group have published several circumstances where Rh(III) migrations have taken place.[48,49] A new mode of oxidative annulation was reported whereby 1,3-enyne **134** was able to react preferentially as a one carbon annulation partner, forming benzopyran **136** as opposed to the more traditional two carbon partner, which gives spiroindene **135** (Scheme 42).[50] This reactivity was possible due to an alkenyl-to-allyl Rh(III) migration.



*Scheme 42 – One carbon oxidative annualtion of **133***

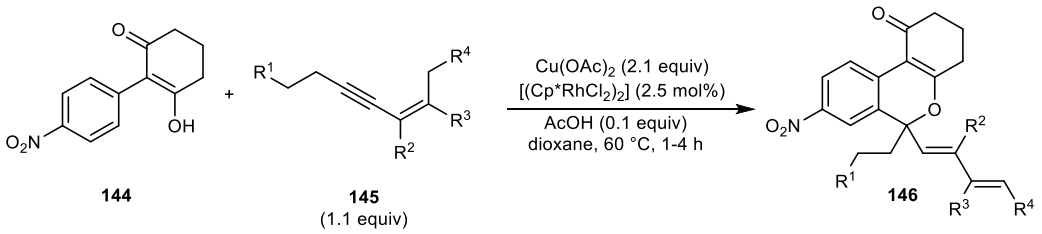
A catalytic cycle accounting for the formation of **136** is shown in Scheme 43. Generation of rhodium diacetate complex **137** from $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$ is followed by the cyclorhodation of substrate **133** to provide rhodacycle **138**. Migratory insertion of 1,3-enyne **134** then affords new rhodacycle **139**. At this point, as with simple alkynes, a reductive elimination step would give the expected spiroindene **135**. However, due to the highly selective formation of benzopyran **136**, it is thought that protonolysis of **139** with AcOH can form alkenylrhodium species **140**. This intermediate can then undergo a 1,4-alkenyl-to-allyl rhodium(III) migration. An isomerisation of the resulting σ-allylrhodium species **141** to π-allylrhodium species **142** can then follow. Nucleophilic attack by the enol at the electrophilic allylrhodium centre would then account for the formation of benzopyran **136**, with the resulting Rh(I) species **143** reoxidised to Rh(III) by copper acetate.

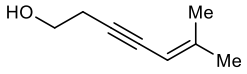
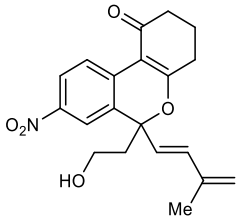
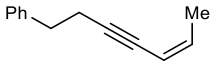
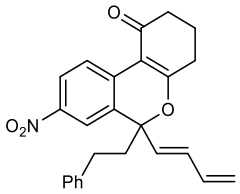
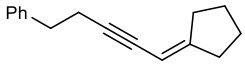
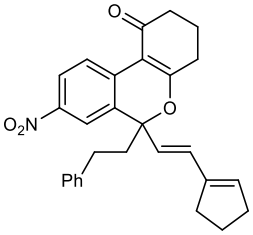
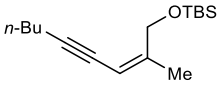
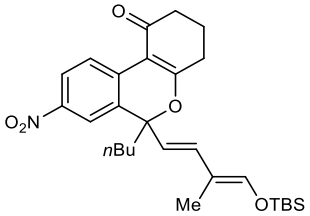
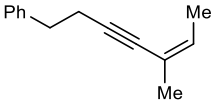
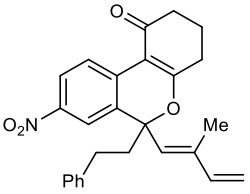


*Scheme 43 – Catalytic cycle for formation of **136***

To ensure good selectivity for products such as **136**, an electron withdrawing group was required on the aromatic ring of the cyclohexanone. When the substrate had strong electron withdrawing groups attached, such as trifluoromethyl or acetyl, the spiroindene (like **135**) was only observed in trace quantities. This outcome was rationalised by the fact that formation of **135** required a reductive elimination of Rh(III), as shown by intermediate **139**. The barriers to this reductive elimination would be increased with an electron deficient substrate as they are harder to oxidise. When the substituent was a methoxy group, there was a preference for formation of the spiroindene-type products over the equivalent benzopyran (64% vs 17% isolated yields). Some representative examples of the scope with respect to the 1,3-enyne are shown in Table 1. Various substitution patterns were well tolerated and using cyclohexanone **144** no formation of the spiroindene products were observed. Migration to *cis*-methyl groups (entries 1 and 2), as well as *cis*-methylene groups (entries 3 and 4) was possible using this chemistry.

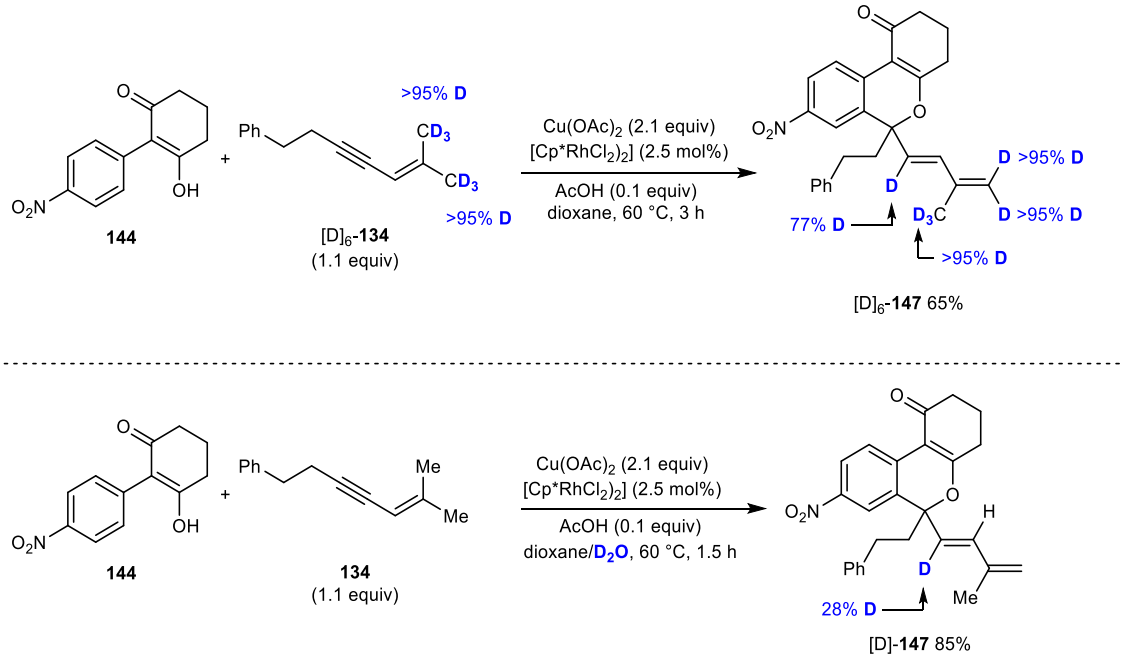
*Table 1 – Annulation of **144** with representative 1,3-enynes*



Entry	1,3-Enyne	Product	Yield
1			62%
2			64%
3			93%
4			61%
5			61%

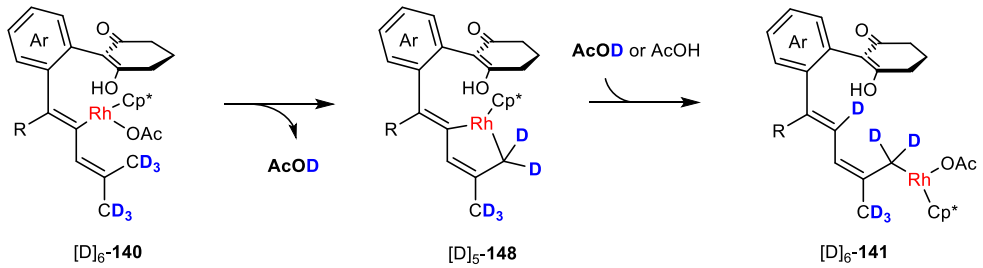
As discussed previously, rhodium(I) migrations are thought to proceed *via* an oxidative addition-reductive elimination pathway. However, based on studies of deuterium transfer, the process by which the Rh(III) migration in this reaction was occurring is thought to be different (Scheme 44). When the reaction conditions were repeated using hexadeuterated

1,3-enyne [D]$_6$-**134**, there was incomplete deuterium incorporation (77% D) at the alkenyl carbon adjacent to the quaternary centre. In addition, when 1,3-enyne **134** in a dioxane/D_2O (5:1) mixture was reacted under the standard conditions, **147** was formed with only partial deuteration observed at the alkenyl carbon and no deuteration at any other site.



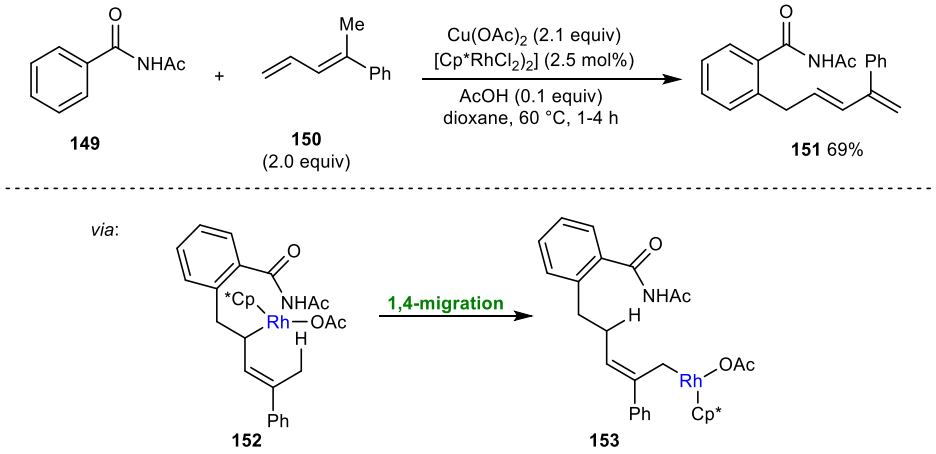
Scheme 44 – Deuterium labelling experiments

The level of deuterium incorporation found in these two experiments was consistent with the mechanism shown in Scheme 45. It was proposed that migration occurred *via* an acetate-assisted, concerted metalation-deprotonation process giving rhodacycle [D]$_5$-**148**. This step can be followed by ring opening with AcOD or AcOH, giving allylrhodium species [D]$_6$-**141**. Both hydrogen sources would be in competition, which would explain why only partial deuterium incorporation is observed.



Scheme 45 – Mechanism for the Rh(III) 1,4-migration

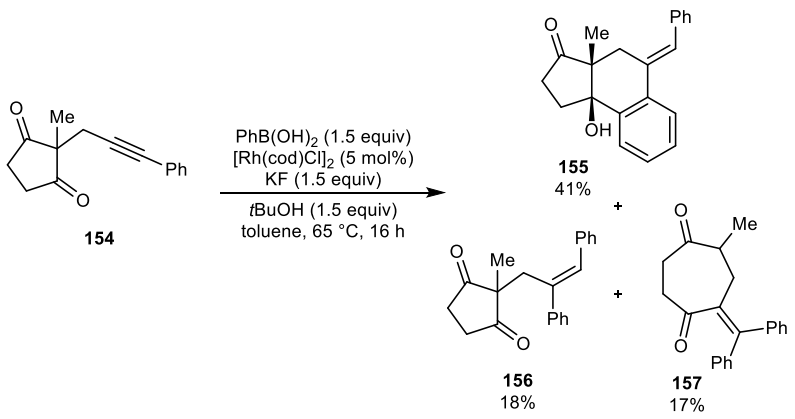
This work was then extended to using 1,3-dienes and *N*-acetylbenzamides (Scheme 46).[51] With the nitrogen acting as a directing group, activation of the *ortho* C-H bond can be followed by insertion of 1,3-diene **150** into the arylrhodium species, giving allylrhodium intermediate **152**. The key allyl-to-allyl 1,4-Rh(III) migration to the *cis*-allylic carbon was then possible generating new allyrhodium species **153**. Isomerisation and then subsequent β-hydride elimination would then give the observed products such as **151**.



*Scheme 46 – C-H Allylation of benzamide **149** with 1,3-diene **150***

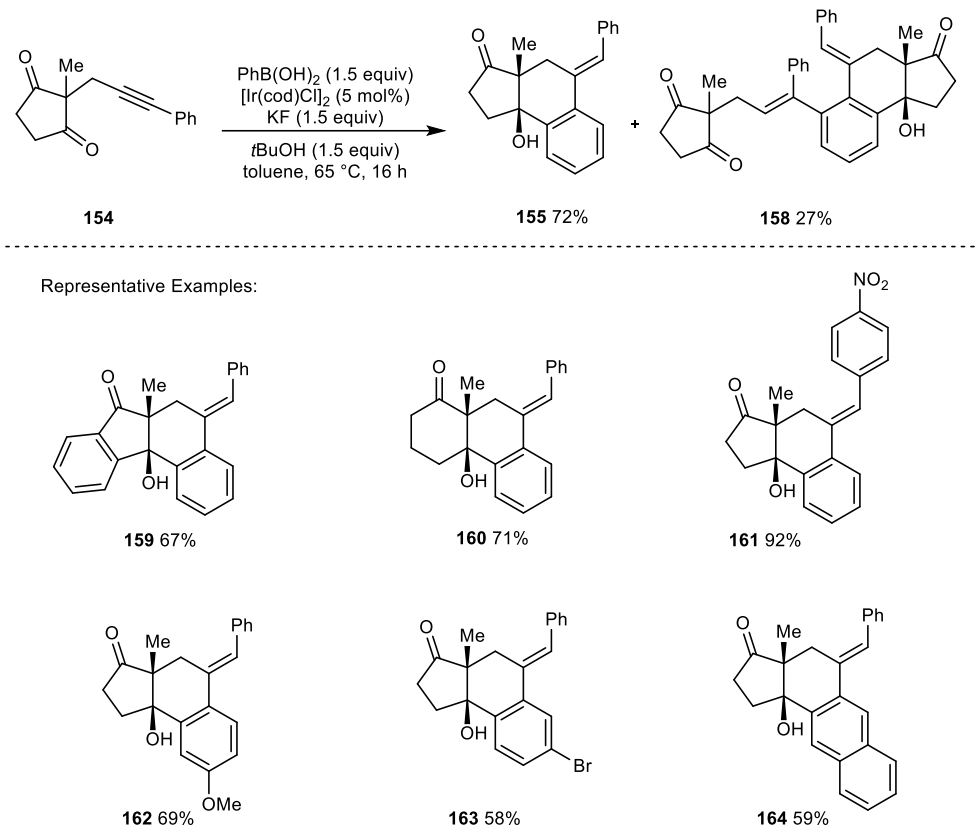
1.1.2 1,4-Iridium Migrations

Compared to rhodium, far fewer examples of iridium migrations exist in the literature. This outcome is most likely due to the more limited work surrounding iridium-catalysed processes generally, when compared to rhodium and palladium, as opposed to the metal not readily undergoing these transformations. Recently, within the Lam group, the first 1,4-iridium(I) migration was described.[13] The reaction of alkynone **154** with phenylboronic acid gave alcohol **155** (Scheme 47). This product was only possible due to an alkenyl-to-aryl 1,4-metal migration. Initial reactivity using **154** with a rhodium catalyst was disappointing (41% yield of **155**), with significant quantities of hydroarylation product **156** and ring expansion product **157** observed. The formation of **157** is attributed to initial insertion of the aryl rhodium across the alkyne occurring with opposite regiochemistry, in a process similar to one previously described by Murakami.[52]



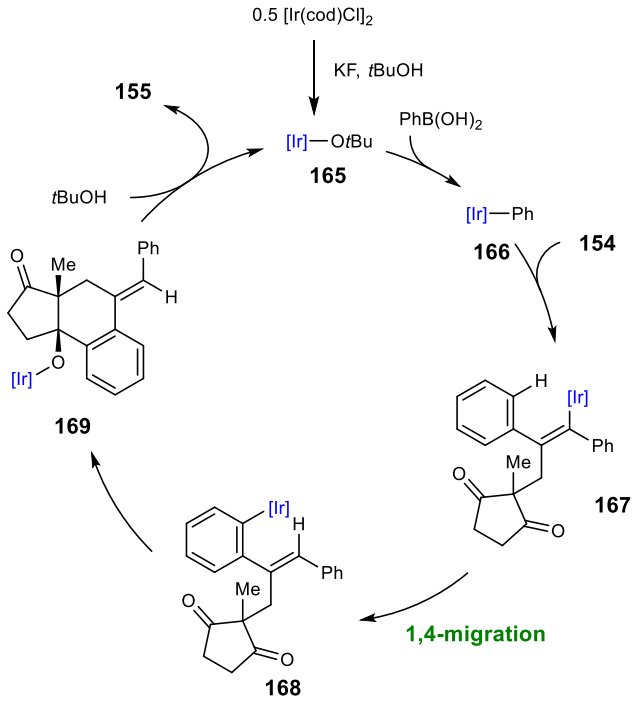
*Scheme 47 – Rhodium-catalysed arylative cyclisation of **154***

During the screening of different metal catalysts it was found that using $[Ir(cod)Cl]_2$, the yield of **155** could be greatly increased, with side products **156** and **157** not observed (Scheme 48). With this catalyst, however, the reaction also gave a 2:1 adduct of **154** and phenylboronic acid as a side-product (**158**). Some representative examples are also shown in Scheme 48. Reactivity with an indane-derived substrate and six-membered cyclic alkynone gave **159** and **160** in high yields. Substitution at the phenyl ring of the alkynone was widely tolerated, with **161** isolated in high yield. With regards to the arylboronic acid, various *para* and *meta* substituents were tolerated, as well as 2-napthyl boronic acid (**162**, **163** and **164**)



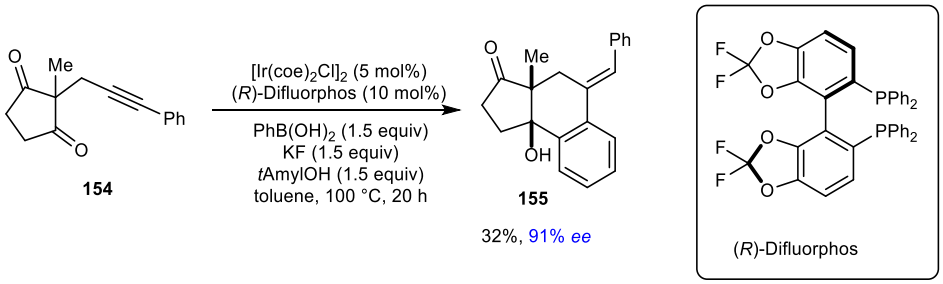
*Scheme 48 – Iridium-catalysed arylative cyclisation of **154***

A proposed reaction mechanism is shown in Scheme 49. Initial transmetalation of arylboronic acid with iridium alkoxide **165** forms arylmetal species **166**. Migratory insertion of alkynone **154** into **166** gives alkenyliridium species **167**, which can then undergo the 1,4-migration to the phenyl ring. Aryliridium species **168** can attack the ketone, generating tricyclic species **169** with two new stereocentres formed. Finally, *t*BuOH can protonate **169**, releasing **155** and regenerating the catalyst.



*Scheme 49 – Catalytic cycle for formation of **155***

Attempts at synthesising these polycycles enantioselectively was also investigated, although only limited success was achieved (Scheme 50). With Difluorphos as a ligand in conjunction with an iridium precatalyst, high enantioselectivity for a range of substrates was possible (>90%). However, the catalyst activity was low, with yields for most substrates below 50%.

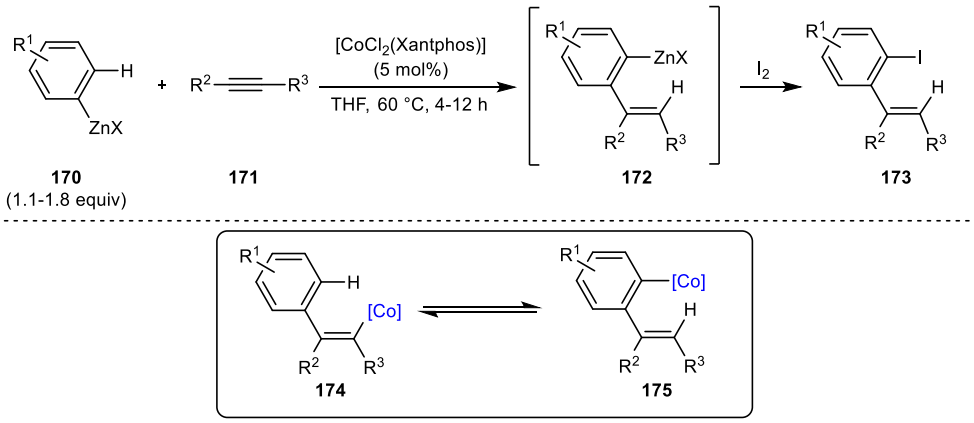


*Scheme 50 – Enantioselectvie iridium-catalysted arylative cyclisation of **154***

1.1.3 1,4-Cobalt Migrations

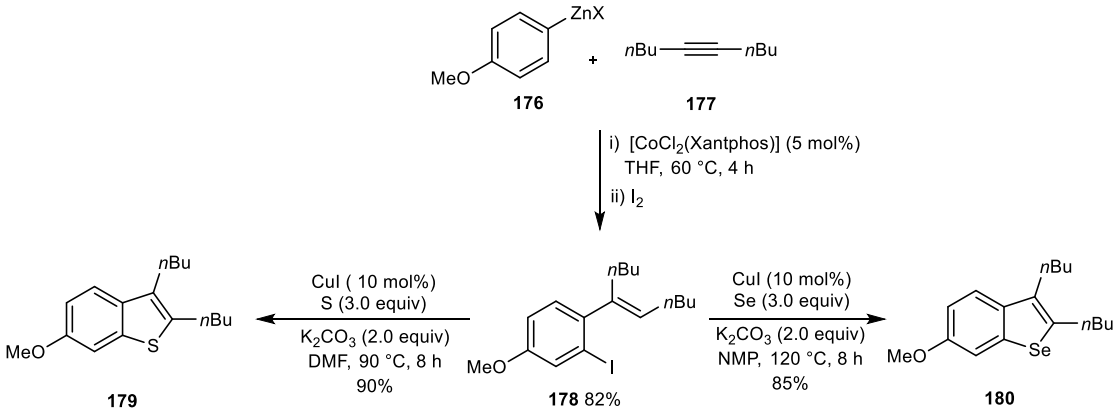
Similarly to iridium, the number of examples of cobalt metal migrations in the literature is limited. However, owing to cobalt being a first-row transition metal, advances in utilising this metal could be very beneficial.[53] Unfortunately, the general instability of cobalt catalysts

compared to rhodium or iridium often make the development of these reactions challenging. The first group to report a 1,4-cobalt migration was Yoshikai in 2012. The cobalt-catalysed addition of an arylzinc species (**170**) to an internal alkyne (**171**) proceeded *via* a cobalt alkenyl-to-aryl migration (**174** to **175**).[16] The resulting arylzincate species **172** could then be quenched with iodine to give aryl iodide **173** (Scheme 51).



*Scheme 51 – Cobalt-catalysed insertion of **170** to **171***

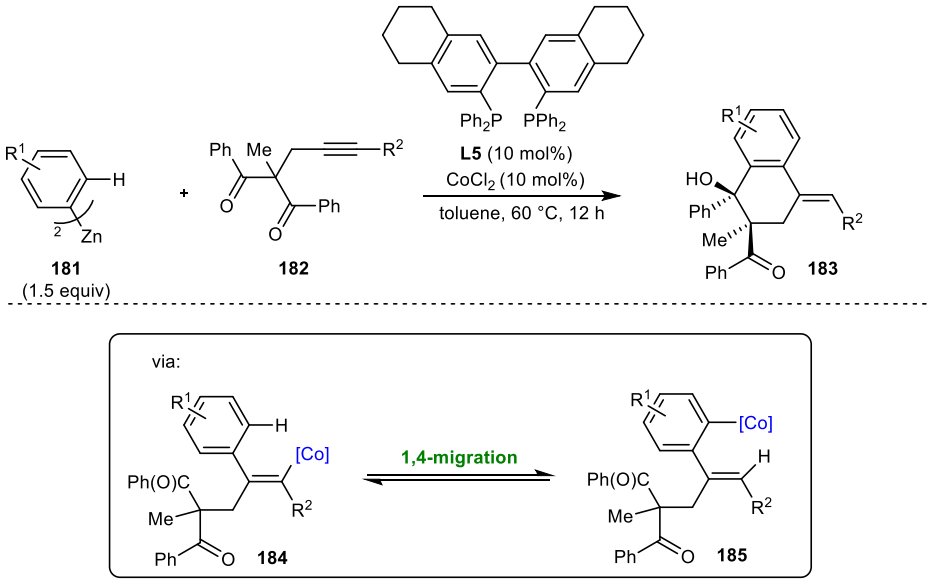
Utilising this chemistry Yoshikai and co-workers were then able to develop a new and versatile syntheses of benzothiophene **179** and benzoselephenone **180**. This work was significant as these core structures have been shown to have beneficial medicinal chemical properties (Scheme 52).[54]



Scheme 52 – Synthesis of benzothiophenes and benzoselephenones

More recently Yoshikai reported using the alkenyl-to-aryl cobalt migration in an arylative cyclisation reaction of enynones (Scheme 53).[55] This chemistry was built upon work by Miura

in 2005, where very similar substrates were used in a rhodium-catalysed process.[56] The overall reactivity is very similar to that reported using iridium in Scheme 48. Arylzincate **181** and diketone **182** in the presence of a cobalt catalyst gave **183** when using BIPHEP-type ligand **L5**. The key step was the alkenyl-to-aryl migration (**184** to **185**), at which point addition into the pendant ketone was possible.



*Scheme 53 – Cobalt-catalysed cyclisation of **182***

Representative examples of the products that could be synthesised through this chemistry is shown in Figure 1. Using various diketones, compounds **183a**, **183b** and **183c** could be synthesised in high diasteroeselectivity and reasonable yields. Symmetrical acetylenic tetraesters were also tolerated in the reaction, with **186** and **187** isolated in high yields.

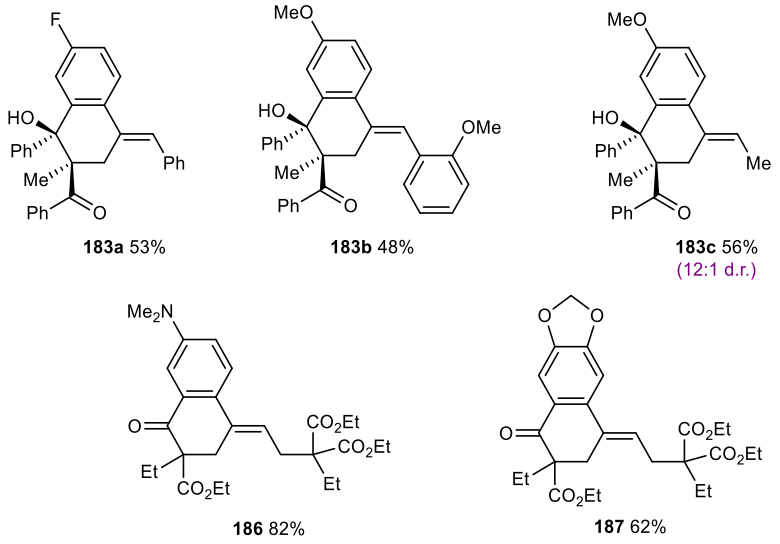
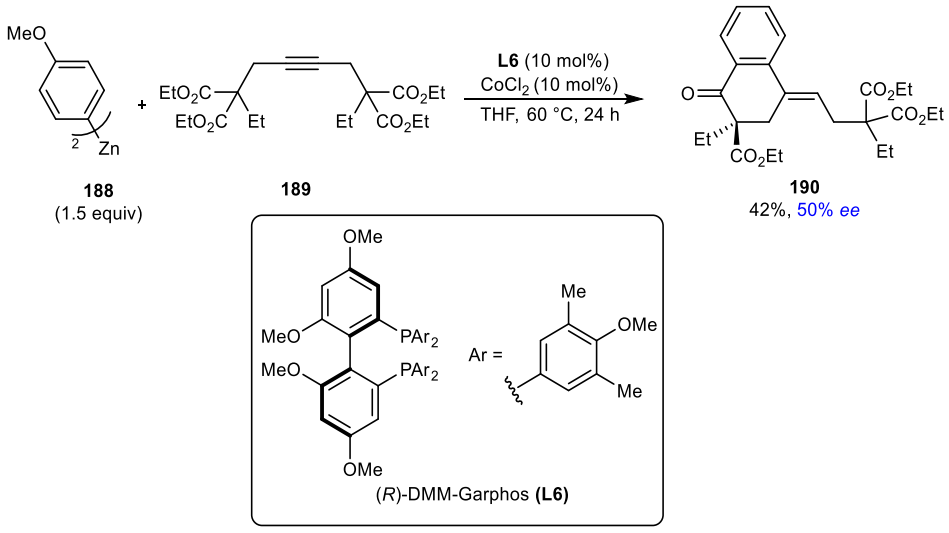


Figure 1 – Representative examples for the cobalt-catalysed cyclisation

Preliminary attempts were made to find an enantioselective variant (Scheme 54). With substrate **189**, the best results were obtained using the bisphosphine ligand, DMM-Garphos (**L6**) (Scheme 54). Using this catalyst system though, **190** was only isolated in poor yield and moderate enantioselectivity.



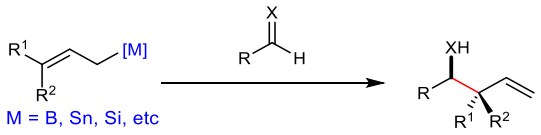
*Scheme 54 – Enantioselective cobalt-catalysed cyclisation of **180***

Significant research investigating the use of 1,4-metal migrations in organic synthesis has now been conducted, especially with palladium and rhodium. 1,4-Metal migrations are a powerful tool in the remote functionalisation of C-H bonds, and often give rise to interesting

and stereochemically well-defined products. However, much of this has been limited to migration to C (sp^2) centres, in particular alkenyl-to-aryl migrations. Therefore, any developments in migration to C (sp^3) centres would potentially provide alternatives to the challenging activation of alkyl C-H bonds and be of great interest to the wider scientific community. The new and exciting reactivity resulting from these types of migrations could provide alternate routes to complex structures that would be difficult to access by other methods.

1.1 The Nucleophilic Allylation Reaction

Nucleophilic allylations are a popular class of reactions, and an effective method of forming crucial C-C bonds.[57] The basic premise involves the reaction between an allyl metal(loid) reagent and a carbonyl or imine, which gives homoallylic alcohols or amines (Scheme 55).[58]



Scheme 55 – The nucleophilic allylation reaction

One of the reasons for nucleophilic allylations being popular within synthetic organic chemistry is the functionality that arises from formation of a homoallylic alcohol or amine. The resulting double bond, and alcohol or amine, can readily undergo further synthetic transformations, and therefore these reactions have been utilised in the synthesis of intermediates for many natural products or biologically active compounds (Figure 2).[59]

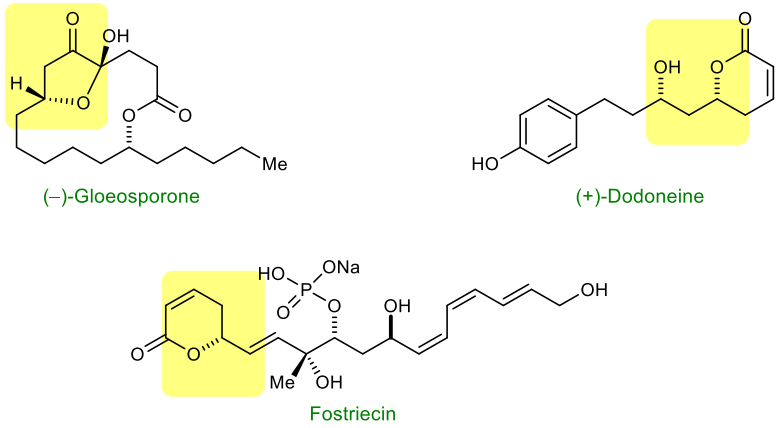
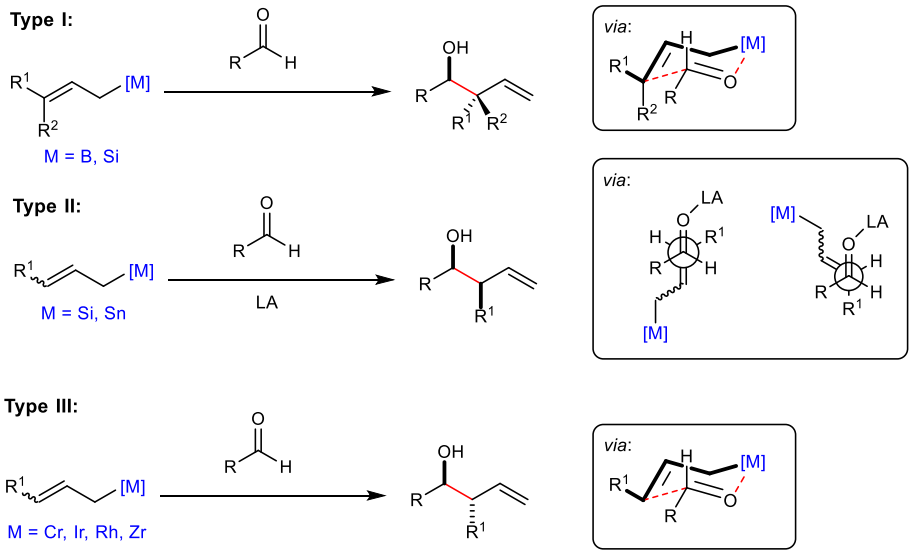


Figure 2 – Examples of natural products synthesised using allylation chemistry[60–62]

Nucleophilic allylation reactions are also popular because they often proceed with good control of stereochemistry. The reaction can frequently be classified into three distinct types, which determines the different relative stereochemistry observed (Scheme 56).[63] In Type I and Type III reactions the allylmetal reagent can coordinate to the carbonyl or imine without the need for any additional activator, and proceeds through a closed transition state.[64] Type II reactions generally require an external Lewis acid activator and proceed *via* an open transition state.[65]



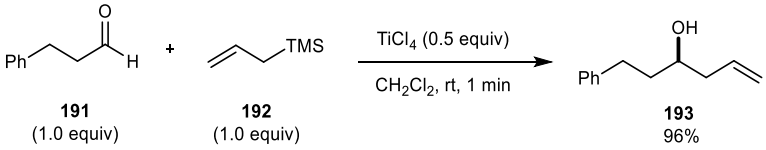
Scheme 56 – Types of nucleophilic allylation

With Type I reactions, the geometry of the starting nucleophilic allylmetal species determines the stereochemistry of the final product. A (*Z*)-allyl reagent often reacts to form the *syn*-diastereomer, whereas an (*E*)-allyl reagent reacts to give the *anti*-diastereomer.

Although Type III reactions also proceed by a closed transition state, it results in favourable formation of the *anti*-diastereomer independent of the starting geometry of the allylmetal reagent. This type of reactivity often occurs when using chromium or indium allymetal intermediates as these rapidly equilibrate to from the thermodynamically favourable (*E*)-allyl isomer.

Finally, Type II allylation reactions afford the *syn*-diasteromer irrespective of the starting geometry of the allylmetal reagent. They proceed by an open transition state with an antiperiplanar or synclinal orientation of the substituents.[65]

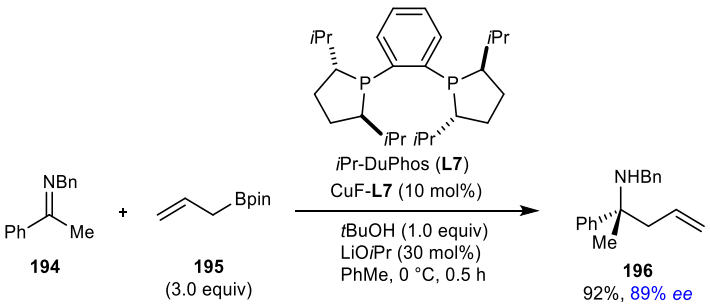
One of the earliest nucleophilic allylation reactions reported was the Hosomi-Sakurai reaction in the 1970's.[66] Using allyltrimethylsilane (**192**) with a range of aldehydes (such as **191**) in the presence of a Lewis acid (titanium tetrachloride), homoallylic alcohols (such as **193**) were prepared in excellent yields in very short reaction times.



Scheme 57 – The Hosomi-Sakurai Reaction

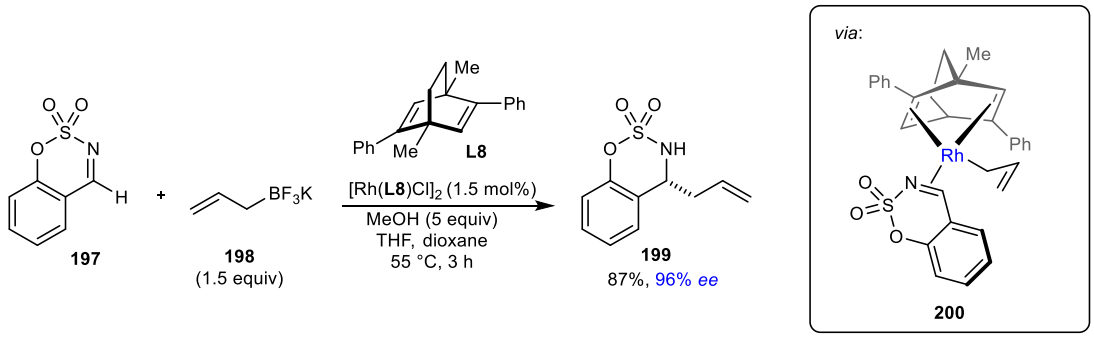
Since this time, research around allylation chemistry has exploded, and the fundamental reaction is now well understood. Generally, Type I reactions, where reactivity proceeds through a 6-membered transition state are the most widely used within syntheses. The reason being that greater control of regioselectivity, diasteroeselectivity and enantioselectivity can be achieved.

The addition of allyl species to carbonyls has been extensively developed, and high selectivity has been achieved with a variety of metal catalysts and allylmetal precursors.[67] Unsurprisingly the allylation of imines, which give synthetically useful homoallylic amines, is now also well-established. Catalytic and stereoselective allylations of imines have now been achieved with allylsilanes,[68,69] allylstannanes,[70] allyl halides,[71] and allylboronates.[72,73] Allylboron reagents are often popular due to the high functional group tolerance and ease of handling. The first catalytic enantioselective allylation using these reagents was described by Shibasaki in 2006 (Scheme 58).[74] With a copper catalyst, the addition of allylboronic acid pinacol ester (**195**) to benzyl-protected ketimine **194** was possible. Homoallylic amine **196** was synthesised in good yield as well as high enantioselectivity over a short reaction period.



Scheme 58 – Nucelophilic allylation of imines using allylboron reagents

The Lam group has also been interested in the development of this chemistry and in 2012 reported the first enantioselective rhodium-catalysed addition of an allylboron reagent to π-electrophiles (Scheme 59).[75] Cyclic imine **197** and potassium trifluoroborate **198**, in the presence of rhodium and chiral diene **L8** reacted to afford homoallylic amine **199** in high yield and high enantioselectivity. The stereodefining step is believed to proceed through a cyclic chairlike transition state (**200**), with the imine coordination occurring in a way that minimises unfavourable steric interactions with the phenyl substituent of the ligand.



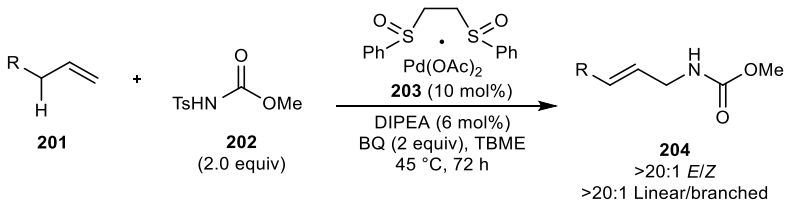
Scheme 59 – Nucleophilic allylation of cyclic imines using potassium allyltrifluoroborates

However, as these examples demonstrate, one of the major drawbacks of this process is the need for a pre-functionalised allylmetal precursor. Although advances in catalytic enantioselective nucleophilic allylation chemistry has limited the need for the synthesis of stoichiometric chiral-inducing reagents,[76,77] the allylmetal reagent is still often derived from an allylhalide, allylsilane, allyborane or allylstannane. Therefore, stoichiometric waste products are generated, and the ability to synthesise more complex allyl fragments is limited.

Methods of activating allylic C-H bonds, or forming nucleophilic allylmetal species *in situ*, without the need for prior pre-functionalisation, would therefore have the potential to greatly improve the sustainability and versatility of these reactions.

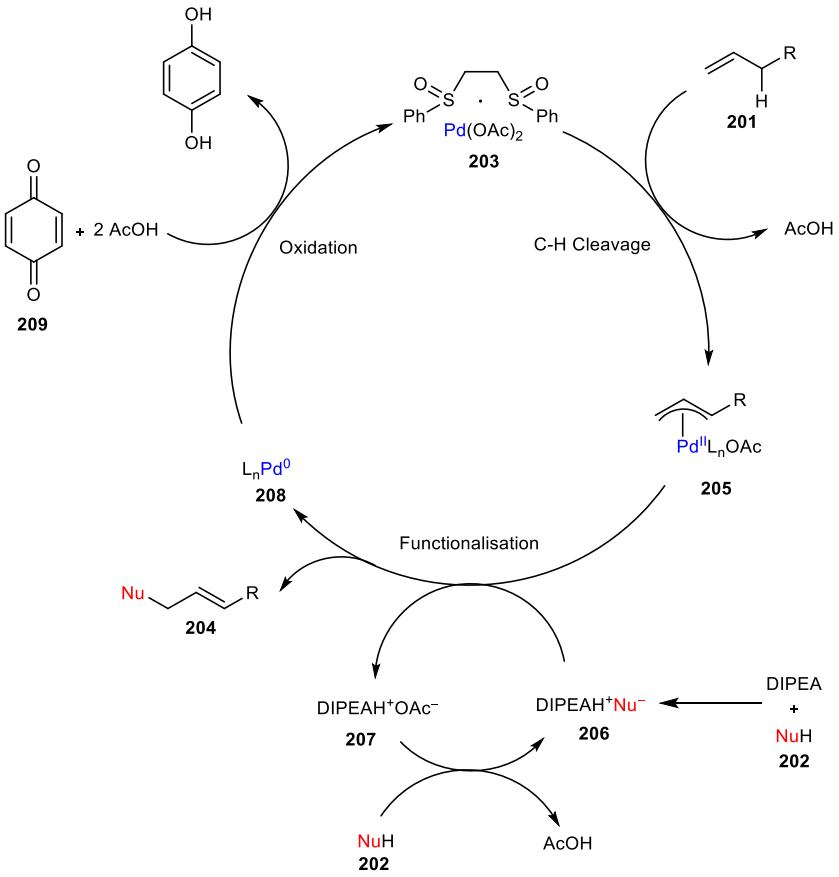
1.1.1 Allylic C-H activation

Traditionally, C-H activation catalysts have been based on high oxidation state metals [such as Pd(II) and Rh(III)], which, upon activation of an allylic C-H bond, generally lead to the formation of electrophilic allylmetal species.[78] The White group, among others, have been heavily active in this field and used these metals in the activation of allylic C-H bonds. The eponymous White catalyst (**203**) has been utilised in a number of processes, including the allylic acetoxylation,[79] esterification,[80] amination,[81] and alkylation of various substrates.[82] Scheme 60 shows an example of a C-H amination reaction using olefin **201** and **203.** Carbamate **204** could be synthesised in high selectivities and good yields, with the mild conditions allowing a variety of functional groups to be incorporated with **201**.



*Scheme 60 – Allylic C-H amination of **201***

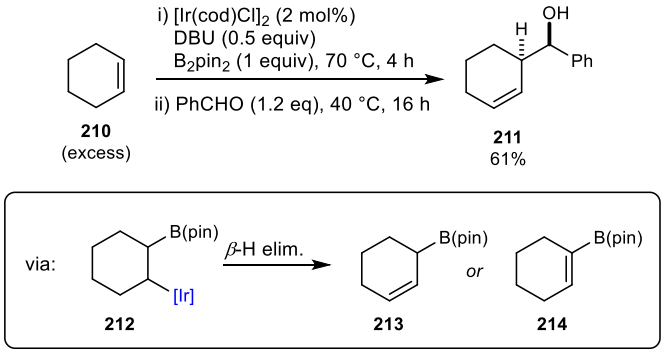
A plausible catalytic cycle for the formation of **204** is shown in Scheme 61. Initial acetate-assisted C-H activation generates π-allyl Pd(II) species **205**. DIPEA acts as a Bronsted base, activating the nucleophilic species and generating **206**. This species can subsequently participate in π-allyl Pd(II) functionalisation, affording **204** and trialkylammonium acetate species **207**. Another molecule of carbamate **202** can then react with **207** regenerating the activated nucleophile and acetic acid. The Pd(II) catalyst **203** is recycled through oxidation of Pd(0) (**208**) with benzoquinone (**209**).



*Scheme 61 – Catalytic cycle for formation of **204***

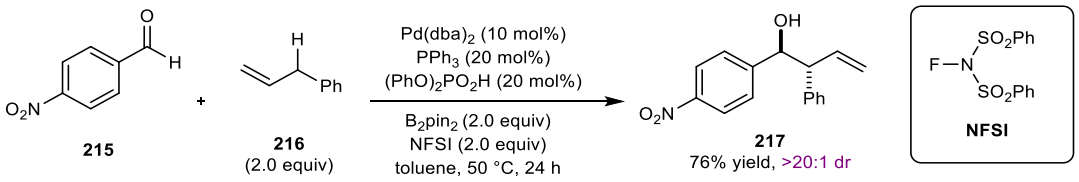
Despite advances in the *in situ* generation of electrophilic allylmetal species, there is currently limited precedent for allylic C-H activation forming the corresponding nucleophilic allylmetal species. One method developed to overcome this problem is to form a transient allylboronate which can subsequently couple with a carbonyl.[83]

In 2007, Szabo and co-workers reported the catalytic allylic C-H borylation of unactivated cycloalkenes (**210**) (Scheme 62).[84] The transient allyboronate **213** was formed by β-hydride elimination of **212**. DBU was found to be essential to ensure β-hydride elimination proceeded with high level of regiocontrol, and limit the formation of the vinylboronate species **214**. Allylboronate **213** can then react with a range of aldehydes to give products such as **211**.



*Scheme 62 – Iridium catalysed borylation of cyclohexene (**210**)*

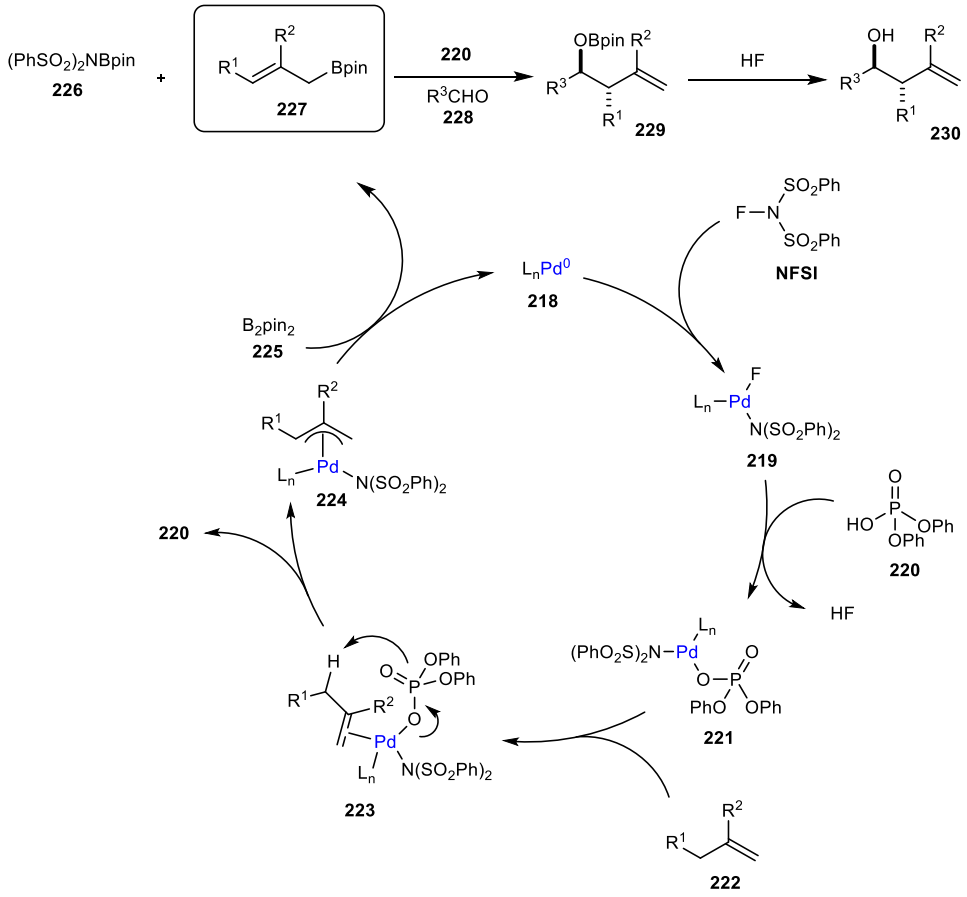
In a similar concept, Gong and co-workers reported the palladium-catalysed carbonyl allylation of simple olefins *via* a C-H oxidative borylation (Scheme 63).[85] With the White catalyst (**203**) limited conversion to **217** (20%) was observed. However, switching to $Pd(dba)_2$ and PPh_3, with a Bronsted acid as an additive, high yields of **217** were achieved in excellent diastereoselectivity.



*Scheme 63 – Palladium-catalysed carbonyl allylation with olefin **216***

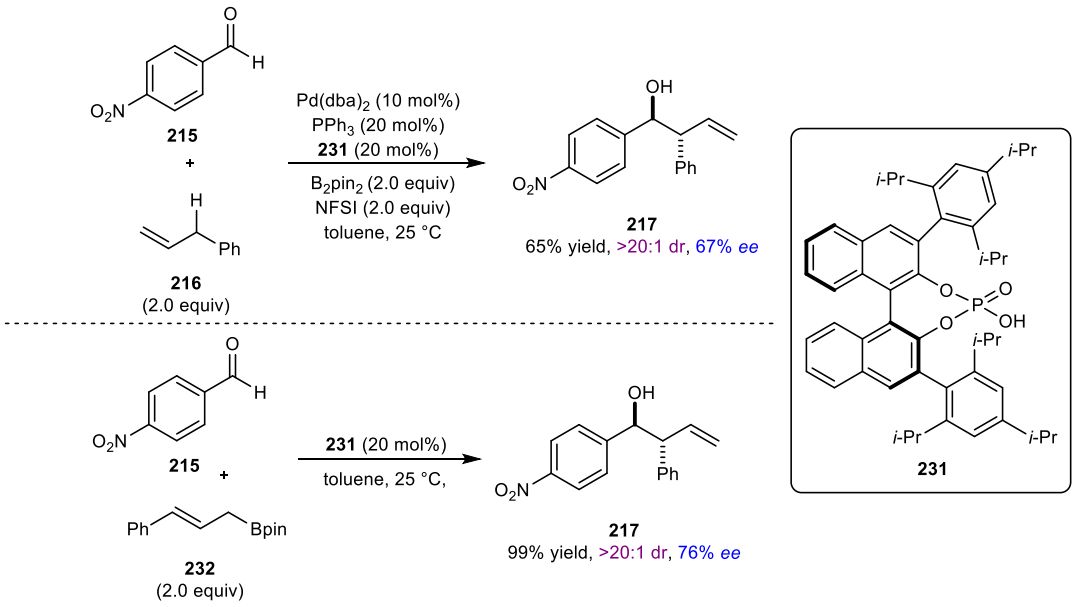
Gong proposed a mechanism as shown in Scheme 64. Palladium(0) (**218**) is first oxidised by NFSI to Pd(II) (**219**). Palladium species **219** can then react with phosphoric acid **220**,

generating palladium phosphate intermediate **221** and releasing HF. The key allylic C-H activation of olefin **222** can then take place *via* intermediate **223**, which also regenerates phosphoric acid **220**. The resulting allylpalladium species **224** then reacts with B_2pin_2 (**225**) to form pinacol allylboronate **227** and **226**. Species such as **227** are known to undergo phosphoric acid-catalysed allylations with carbonyls.[86,87] This reaction would give **229**, which upon quenching result in the observed final compound **230**.



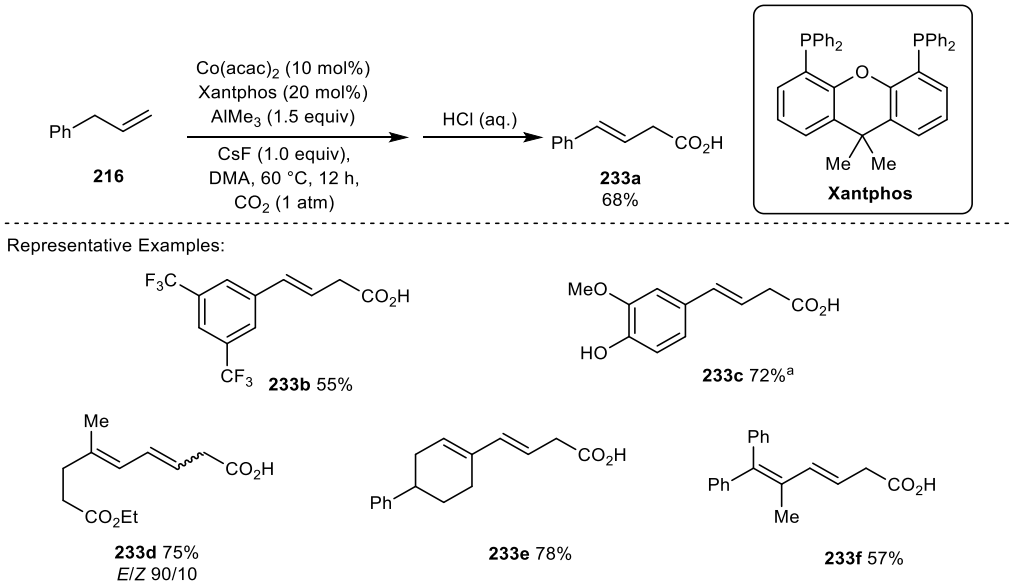
*Scheme 64 – Catalytic cycle for formation of **230***

To provide evidence that allylation of carbonyl **228** is occurring with allylboronate **227**, as opposed to a η^1-allylpalladium species, **215** was reacted with chiral phosphoric acid **231** (Scheme 65). Enantioenriched **217** was observed suggesting the chiral phosphoric acid is involved in the stereodefining step. The degree of enantioselectivity of **217** from the reaction of *in* situ generated allylboronate **227** with **215** was very similar to the reaction of pinacol allylboronate **232** and **215**, providing further evidence for the proposed mechanism above.



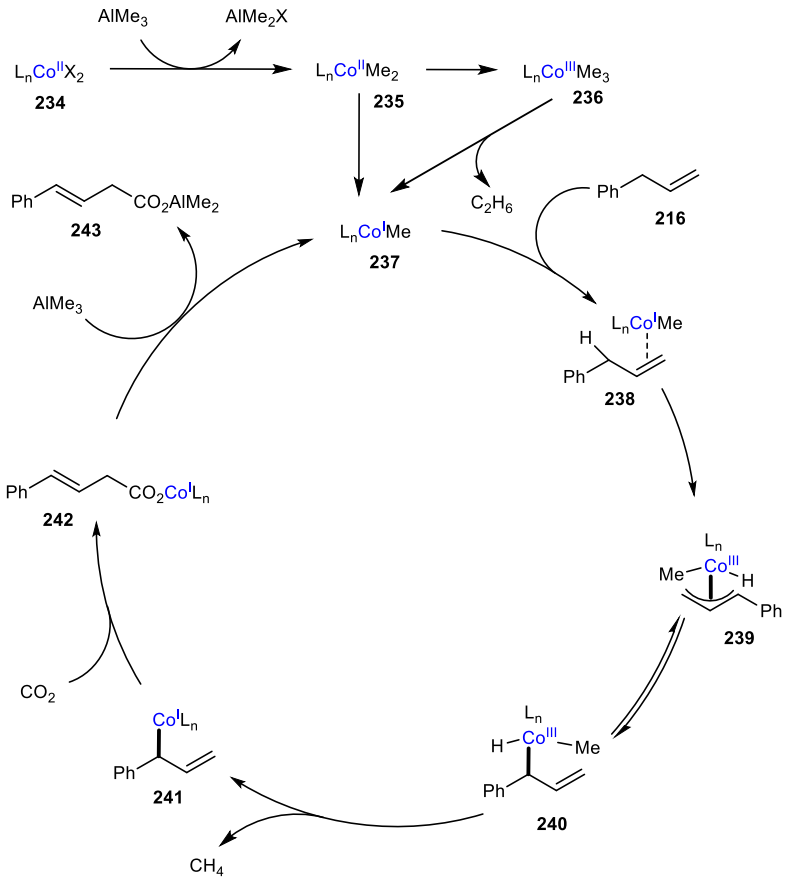
*Scheme 65 – Elucidating the mechanism for formation of **217***

More recently, methods to achieve the direct allylic activation of C(sp^3)-H bonds to form nucleophilic allymetal species have been reported. In 2017, Sato and co-workers used carbon dioxide in a cobalt-catalysed carboxylation of terminal allylarenes and 1,4-dienes (Scheme 66).[88] The reaction tolerated various substituents on the ring of the allylarene, including strong electron-withdrawing groups (**233b**), and phenolic hydroxy groups (**233c**). With 1,4-dienes, products were formed in good yield with high selectivity for the linear products observed (**233d**, **233e**, and **233f**).



*Scheme 66 – Cobalt Catalyzed Allylic CH Carboxylation of **216**. [a] 2 equiv of $AlMe_3$ used*

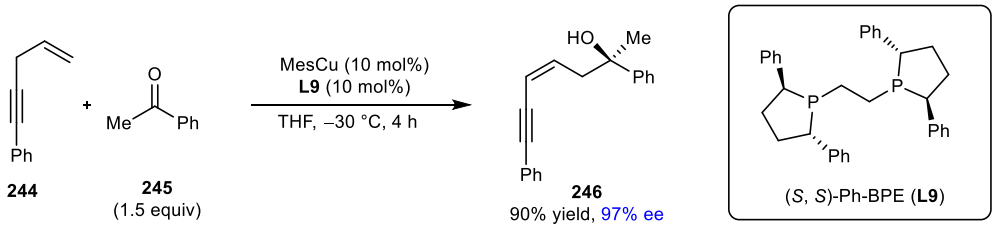
Scheme 67 shows the catalytic cycle proposed by Sato. Dialkyl Co(II) complex **235** can be generated from **234** and $AlMe_3$. Complex **235** has then previously been shown to undergo dispropotionation to Co(I) **237** and Co(III) **236**.[89] Co(III) **236** can also provide **237** *via* a reductive elimination. Coordination of the active catalyst species to olefin **216** (**238**) then enables cleavage of the C-H bond, forming π-allyl species **239**. It is thought that the oxygen atom in Xantphos can coordinate to the cobalt, with the rigid structure of the ligand favouring isomerisation to η^1-allyl species **240**. Reductive elimination of **240** expels methane and leads to low valent cobalt species **241**. This species can then react with carbon dioxide to give **242**. Subsequent transmetalation with $AlMe_3$ liberates **243** and regenerates **237**.



*Scheme 67 – Catalytic cycle for formation of **243***

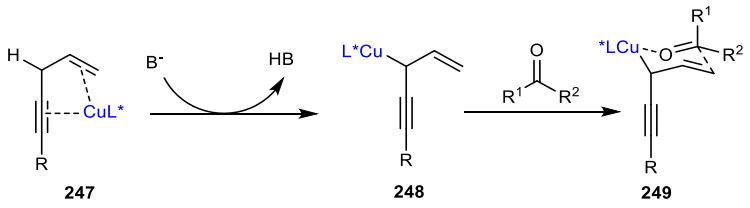
At a similar time, another example of this type of C-H activation was reported by Kanai and co-workers (Scheme 68).[90] A reactive nucleophilic allylcuprate species could be generated catalytically using mesitylcopper. Skipped enyne **244** and acetophenone (**245**) reacted to

afford conjugated enyne **246** in good yield. Using bisphosphine **L9**, the products were synthesised in excellent enantioselectivities.



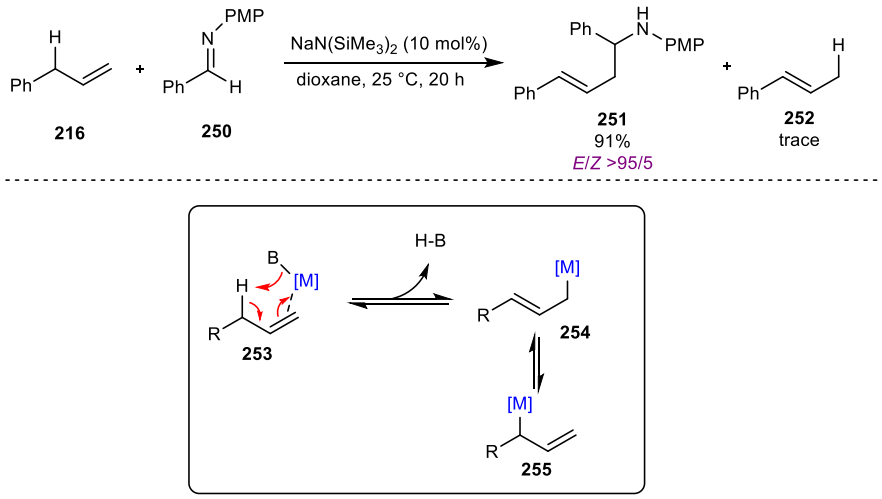
*Scheme 68 – Copper-catalysed addiion of enyne **244** to acetophenone (**245**)*

The reactive allylcuprate **248** is generated through deprotonation of the allylic C-H bond (Scheme 69). The acidity of this proton can be increased by coordination of the copper catalyst to the two π systems (**247**). Nucleophilic allylcuprate **248** can then react with a carbonyl in a classical nucleophilic allylation reaction *via* transition state **249**. Evidence for this transition state is the exclusive formation of the *Z*-isomer. The alkyne substituent occupies a pseudoaxial position to minimise the unfavourable steric interactions with the phenyl group of the ligand.



*Scheme 69 – Generating nucleophilic allylcuprate **248***

Schneider and co-workers have also described the use of an allylic C-H deprotonation in generating a nucleophilic allymetal species. The formal allylic C(sp^3)-H bond activation of simple alkenes triggered by a strong base was possible using a sodium amide (Scheme 70).[91] Homoallylic amine **251** was synthesised in high yield and excellent stereoselectivity from **216** and **252**. The pK_a of the allylic hydrogen of **216** is 34.[92] A metal π-Lewis acid, such as $NaN(SiMe_3)_2$, can coordinate to the double bond, acidifying the hydrogen and allowing deprotonation (**253**). The nucleophilic allylmetal species (**254**) generated in equilibrium with **255** can then react with a range of electrophiles.



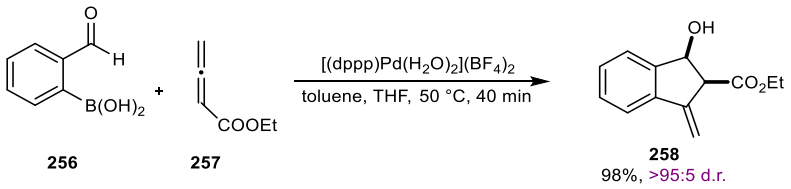
Scheme 70 – Allylic C-H bond activation using sodium amide

1.1.2 Generating Allymetal Species *in situ* through Migratory Insertions

An alternative method of generating nucleophilic allylmetal species that does not rely on the activation of allylic C-H bonds, is through metal insertion reactions of allenes or dienes. Multicomponent reactions are often a desirable and efficient way of performing chemistry as they allow complex structures to be generated rapidly from simple substrates.[93] However, the greater potential for side reactions means the successful design of these pathways relies on each reaction having high chemoselectivity at each stage of the process.

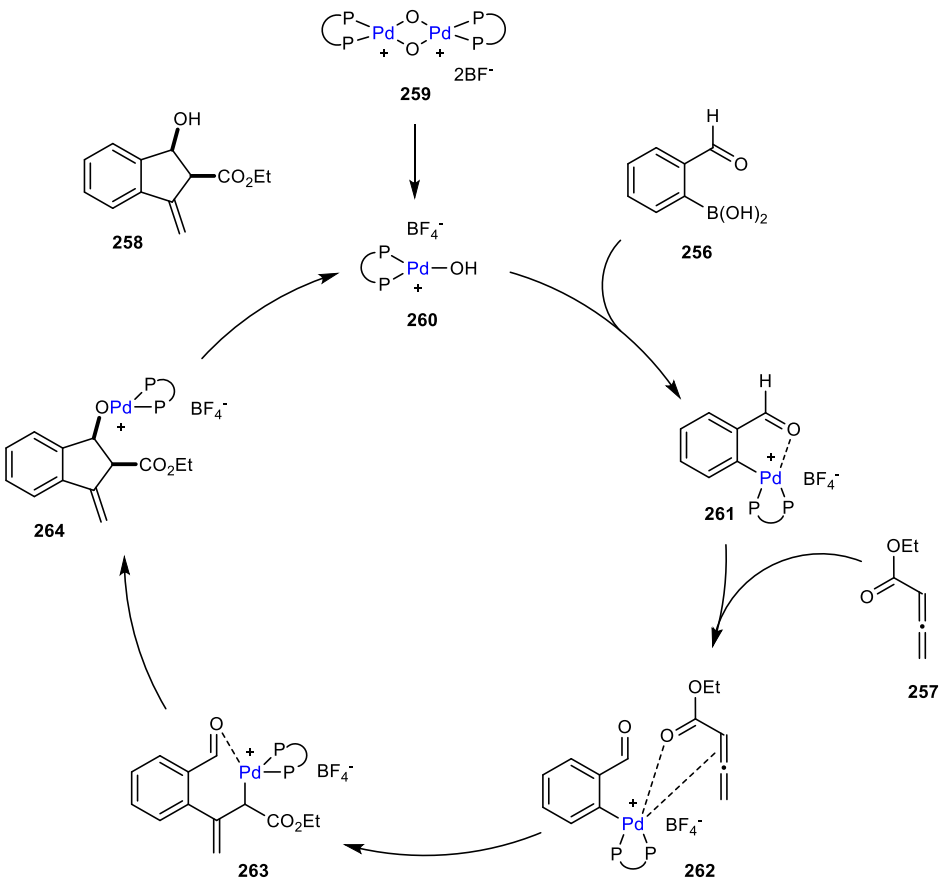
1.1.2.1 Domino Insertion-Nucleophilic Allylation Reactions

Reactions involving the migratory insertion of an allene, followed by an intramolecular allylation step have been utilised as an efficient method of generating two new carbon-carbon bonds. These processes often exhibit good control of both diastereo- and enantioselectivity. An example of this mode of reactivity was repoted by Lu and co-workers in 2009 (Scheme 71).[94] Indenol **258** was synthesised from 2-formylphenylboronic acid (**256**) and allenoate **257** in a palladium-catalysed annulation reaction.



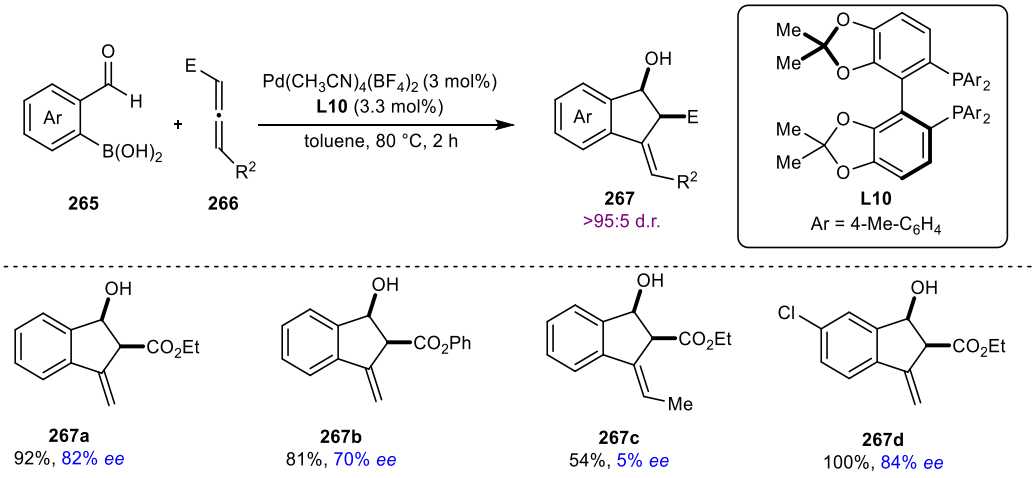
*Scheme 71 - Tandem annulation of **257** with **256***

This reaction was notable as by using a cationic palladium complex, formation of a nucleophilic η^1-allyl complex was favoured over an electrophilic η^3-allyl complex. A catalytic cycle that would give **258** is shown in Scheme 72. Catalytically active species **260** is generated from **259**. Transmetalation of **260** with arylboron reagent **256** gives arylpalladium **261**. Allenoate **257** can coordinate to the cationic palladium complex (**262**), with the insertion with **257** subsequently giving η^1-allylpalladium **263**. The high Lewis acidity of palladium complex **263** activates the carbonyl group, and the nucleophilicity of the η^1-allylpalladium species allows a 1,2-addition, giving **264**. Hydrolysis of **264** then liberates **258** and regenerates **260**. In this chemistry insertion of arylpalladium **261** into allene **257** gives η^1-allylpalladium **263**. The cationic nature of the catalyst is important for improving the reactivity with aldehyde **256**, as it allows allylation to occur before isomerisation to a unreactive η^3-allylpalladium species.



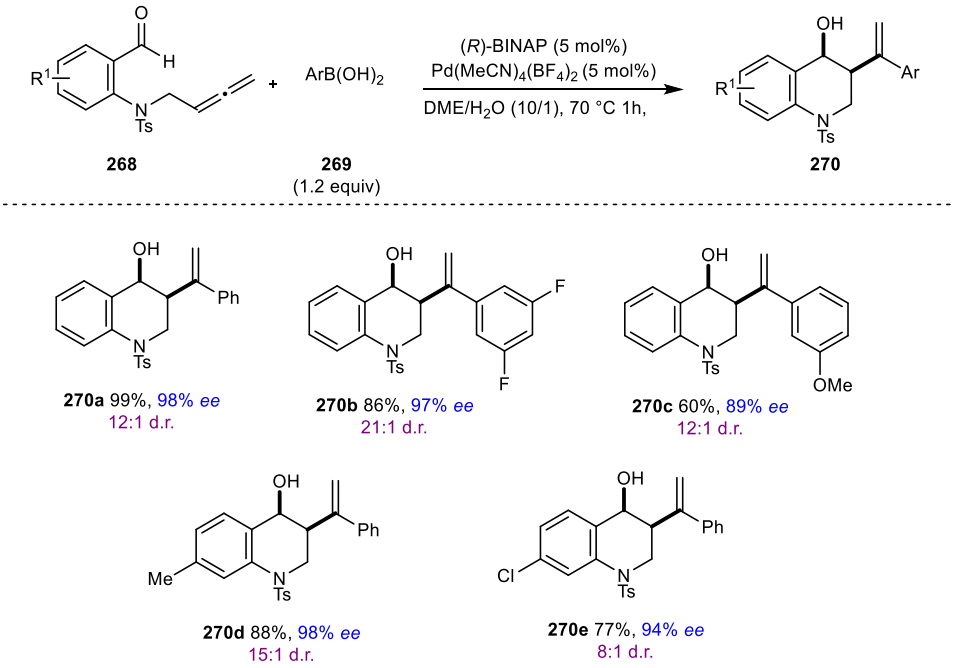
*Scheme 72 – Catalytic cycle for formation of **258***

Using bisphosphine **L10** the reaction gave a range of products in good yield and reasonable enantioselectivty (Scheme 73). Larger ester substituents reduced the yield and enantioselectivity (**267b**) and substitution at the γ-position of the allenoate also significantly reduced the enantioselectivity (**267c**).



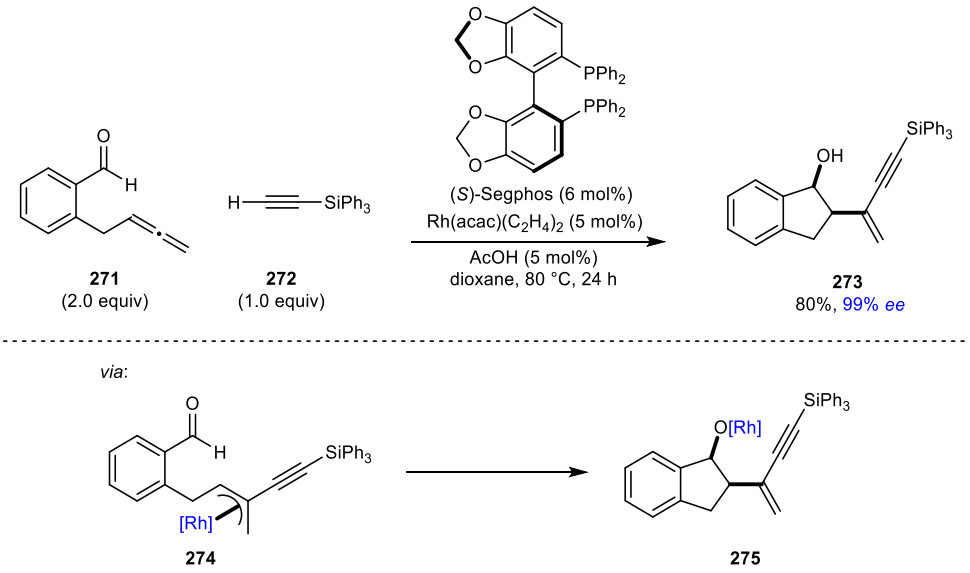
*Scheme 73 – Enantioselective Annulation of **265***

Lu later demonstrated that the electrophile could instead be tethered to the allene. Using an arylboronic acid (**269**) the palladium-catalysed cyclisation of *N*-tosyl-aniline tethered allenyl aldehydes (**268**) was possible (Scheme 74).[95] A bisphosphine ligand ((*R*)-BINAP) gave a series of tetrahydroquinoline derivatives (**270**) in high yields and excellent enantioselectivities.



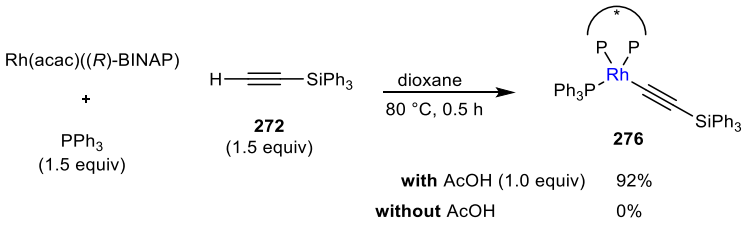
Scheme 74 – Palladium-catalysed cyclisation of allenyl aldehydes with arylboronic acids

A similar protocol was developed by Hayashi and co-workers, except alkyne **272** was used in place of an arylboronic acid as one of the coupling agents (Scheme 75).[96] With a rhodium catalyst and bisphospine ligand, a highly enantioselective alkynylative cyclisation of allenyl aldehyde **271** was achieved. Indanols such as **273** could be synthesised in high yield and high stereoselectivity. The key step was believed to be the generation of Rh(I)-allyl species **274**, which can then add into the pendant ketone to give **273** in high steroeselectivity.



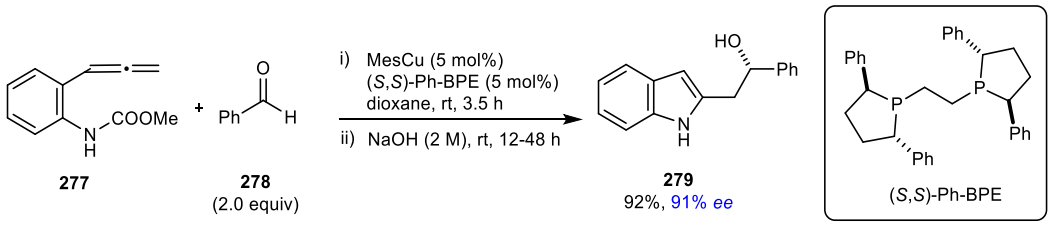
Scheme 75 – Rhodium-catalysed alkynlative cyclisation of allenyl aldehydes

The generation of intermediate **274** was found to rely on using acetic acid as an additive (Scheme 76). In the absence of acetic acid, no conversion to **276** was shown by ^{31}P NMR.



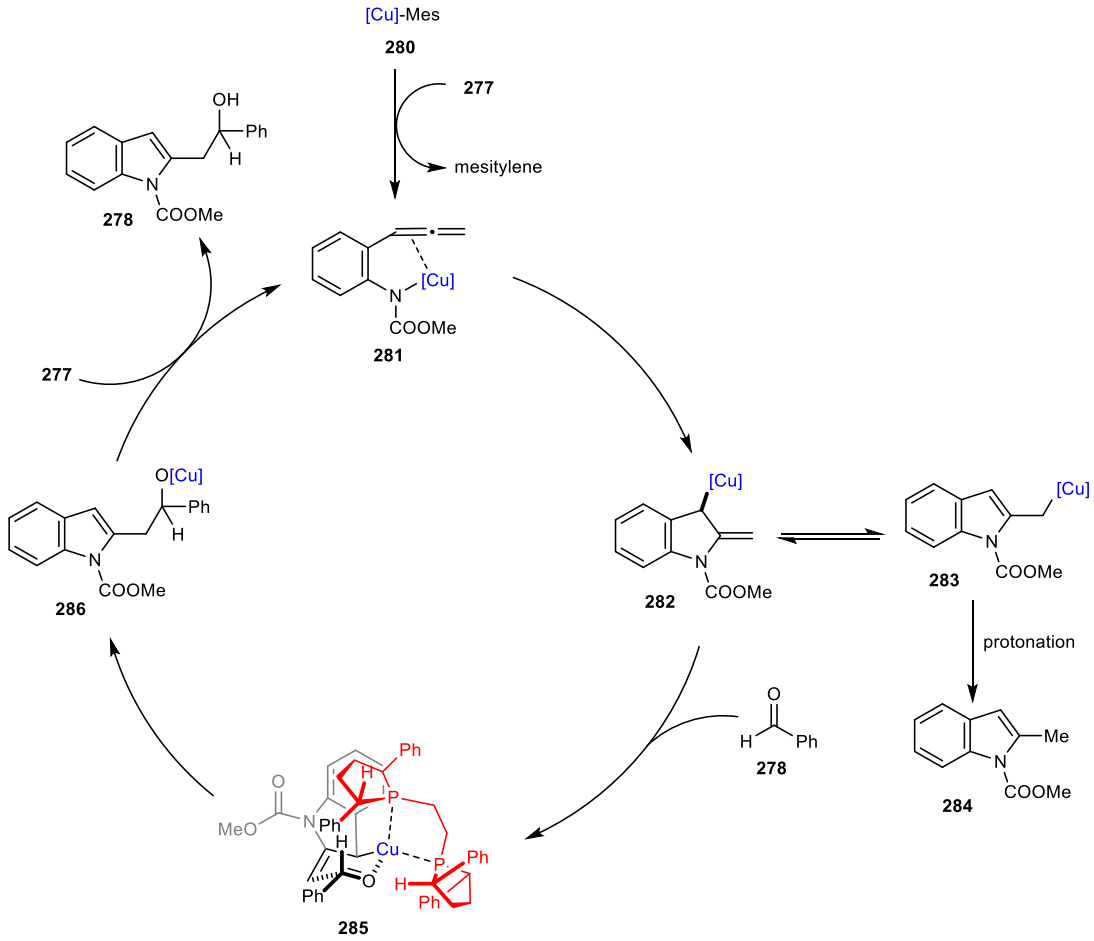
*Scheme 76 – Role of acetic acid in generation of **276***

In 2014, Kanai and co-workers utilised similar chemistry in a copper-catalysed synthesis of indoles (Scheme 77). Indole **279** was achieved through the amidocupration of allene **277**, and subsequent allylation of benzaldehyde (**278**).[97] At the time this reaction was one of the first catalytic and enantioselective methods for the synthesis of the biologically useful 2-(2-hydroxyethyl) indole scaffold.



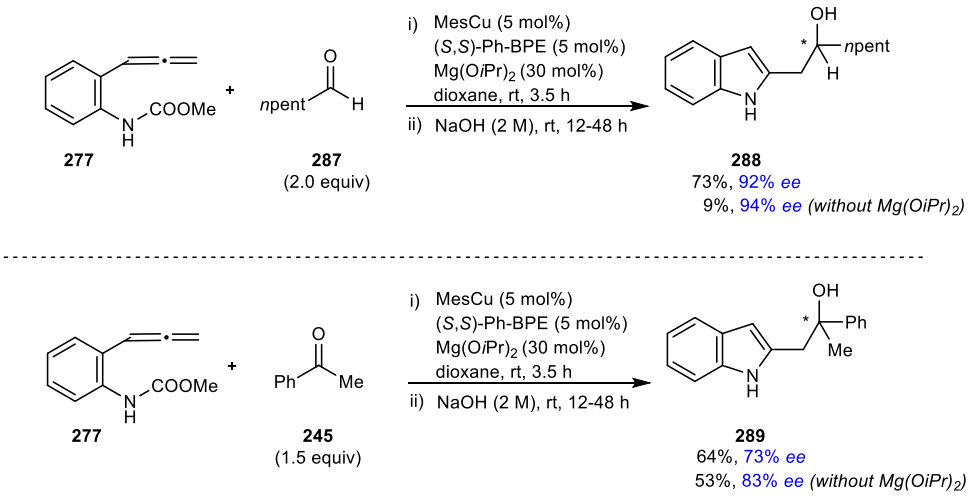
*Scheme 77 – Copper-catalysed synthesis of indole **279***

A possible catalytic cycle to give product **279** is shown in Scheme 78. Copper catalyst **280** acts as a Bronsted base giving amidocuprate **281**. Coorodination of copper to the allene activates the π-system, triggering the insertion of the allene to give allylcopper **282**. This species exists in equilibrium with **283** *via* a 1,3-allylic transposition of the metal. In cases where addition of **282** to the electrophile is slow, protonation of **283** can give simple indole **284**. When the reaction with the electrophile is favourable, allylcopper **282** can undergo addition to **278** *via* a six-membered transition state (**285**), which gives copper alkoxide **286**. Intermediate **286** then acts as a base regenerating **279** and liberating indole **278**. The absolute stereochemistry can be rationalised by allylcopper species **282** approaching the *Si*-face of the carbonyl. This approach would limit the steric clash between the phenyl groups of the ligand and the indole ring.



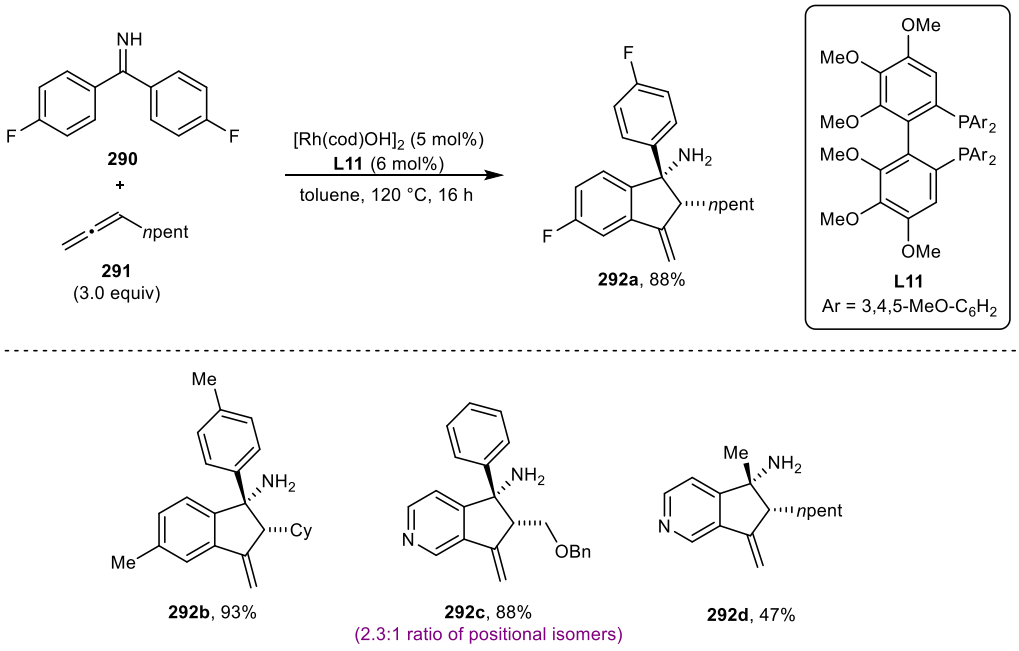
*Scheme 78 – Catalytic cycle for formation of **278***

With less reactive substrates, such as an aliphatic aldehyde or ketone, Mg(O*i*-Pr)$_2$ was required as an additive to provide acceptable yields and prevent products like **282** (Scheme 79). The beneficial effect of Mg(O*i*-Pr)$_2$ was more pronounced with aliphatic aldehyde **287** than with acetophenone (**245**). The increase in yield for these substrates when using Mg(O*i*-Pr)$_2$ as an additive was believed to be a result of the protonation of **282** or **283** being disfavoured through a decreasing of the Bronsted basicity of these allylcopper species.



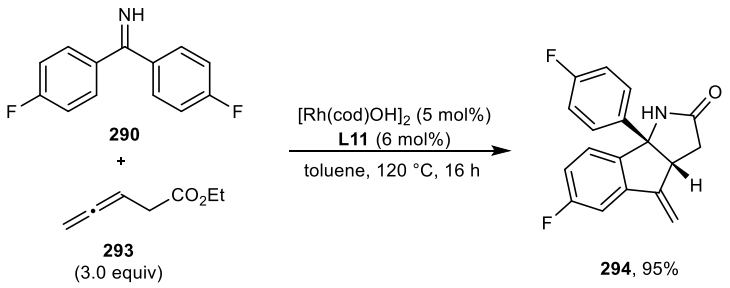
Scheme 79 – The effect of $Mg(OiPr)_2$ on reactivity with aliphatic aldehydes and ketones

Rhodium catalysts have also been used in domino-insertion reactions of allenes. Combining an aromatic CH-activation with allene insertion, Cramer was able to synthesise indane **292a** (Scheme 80).[98] Symmetrical biaryl ketimines with both electron-donating and electron-withdrawing groups reacted in high yields giving indanes as single diastereomers (**292a** and **292b**). With unsymmetrical biaryl ketimines a mixture of products were obtained (**292c**), with C-H activation favoured at the more electron deficient aromatic ring. Products such as **292d**, achieved from a mono-aryl ketimine, reacted less efficiently.



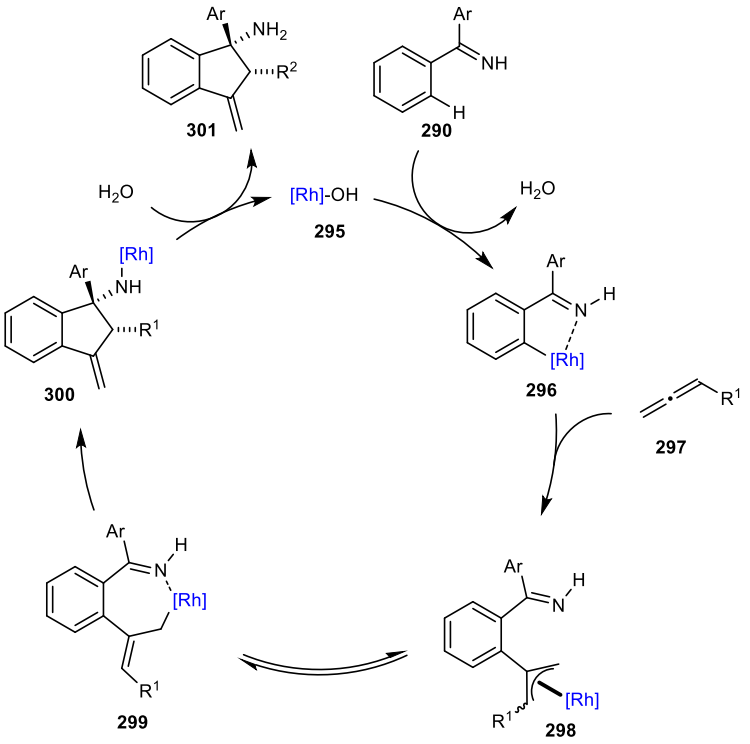
Scheme 80 – Rhodium-catlysed allylations of ketimines

Using an allene with a terminal ester group (**293**), it was also possible to synthesise 5-membered lactam **294** in excellent yield (Scheme 81).



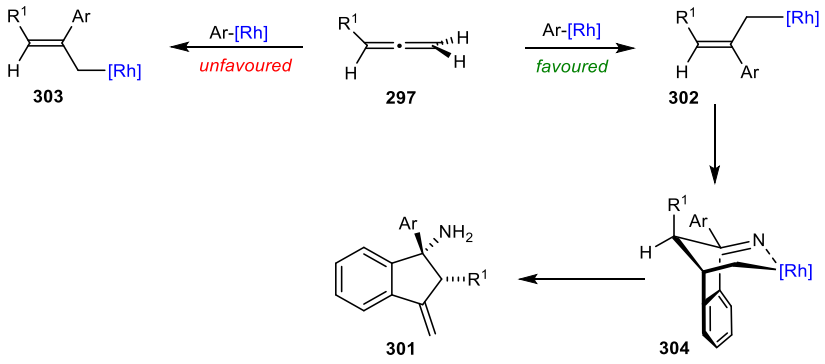
*Scheme 81 – Reaction using ester substituted allene **293***

Cramer proposed that the catalytic cycle starts with the cylometalation of imine **290** with rhodium complex **295**, giving arylrhodium species **296** (Scheme 82). *Syn*-carborhdoation of allene **297** then occurs with the resulting allylmetal species able to isomerise betweeen π-allyl species **298** and σ-allyl **299**. A stereoselective nucleophillic allylation of the tetehered imine gives amidorhodium **300**, with protonation releasing product **301** and regenerating the catalyst (**295**).



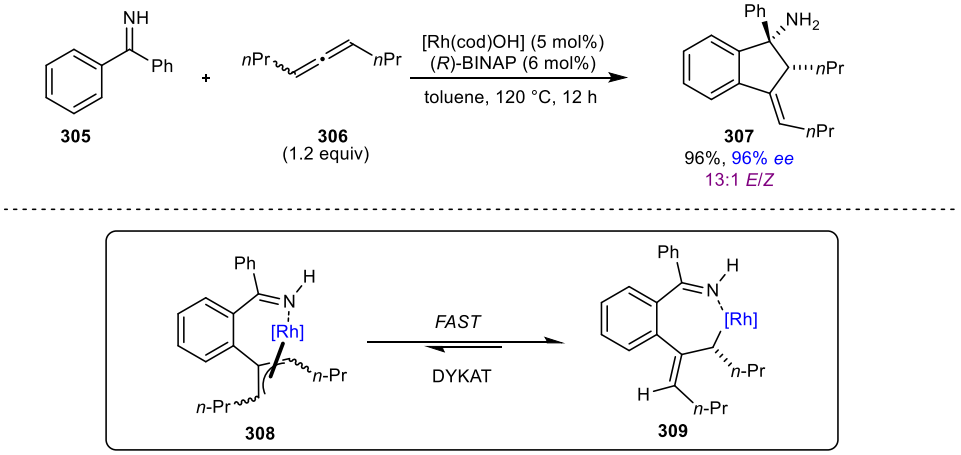
*Scheme 82 – Catalytic cycle for formation of **301***

The high level of selectivity for the cyclisation step is believed to be because initial carborhodation of the allene occurs from the less sterically-hindered face giving **302** (Scheme 83). (*Z*)-Allylrhodium **302** can react *via* a closed six-membered transition state (**304**) giving *syn*-product **301**. Carborhodation from the other face would give (*E*)-allylrhodium species **303**, which would react to give the opposite diastereomer.



Scheme 83 – Rationale for observed diastereoselectivity

Whilst terminal allenes are versatile coupling partners, 1,3-substituted variants are often challenging as they exhibit axial chirality. Therefore, with these substrates the enantiopure allene must often be used so that stereoselectivity can be transferred. In 2013 Cramer, utilising the same chemistry as before, developed a rhodium-catalysed dynamic kinetic asymmetric transformation (DYKAT) where both enantiomers of allene **306** gave the same product enantiomer **307** (Scheme 84).[99] Migratory insertion of an aryl rhodium species to allene **306** could potentially lead to multiple diastereomers. However, isomerisation of allylrhodium **308** to **309** occurs faster than the 1,2-addition of the imine, which allows control of the allylrhodium species undergoing the reaction. This isomerisation allowed indanes such as **307** to be synthesised in high yield, diasteroeselectivity and enantioselectivity.

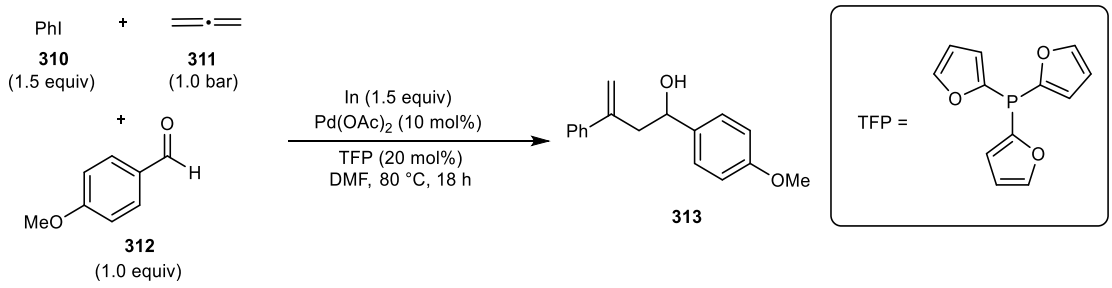


Scheme 84 – Rhodium-catalysed DYKAT of racemic allenes

1.1.2.2 Three-Component Nucleophilic Allylations

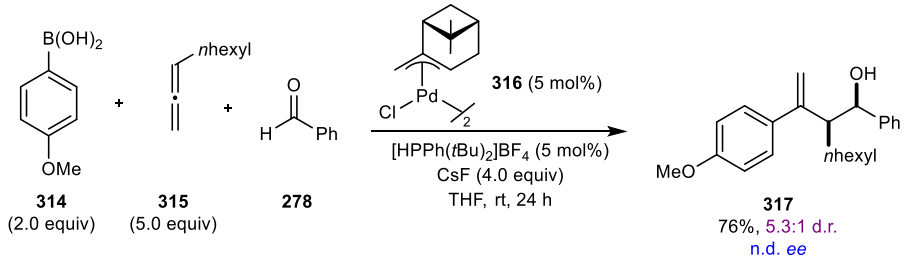
Three-component reactions incorporating a nucleophilic allylation step have also been reported. Three-component coupling reactions are often beneficial as they allow complex molecules to be synthesised rapidly from simple starting materials. However, at this current time, very limited enantioselectivities have been achieved using these methods for nucleophilic allylations where two new C-C bonds are formed.

As early as 2000, Sridharan and co-workers developed a palladium-indium mediated Barbier-type allylation of aldehydes (Scheme 85).[100] *In situ* generation of an allylindium species was possible through transmetalation of a π-allylpalladium(II) complex generated from phenyl iodide (**310**) and allene **311**. Unfortunately, this chemistry relied on using stoichiometric indium and no enantioselective variant was developed.



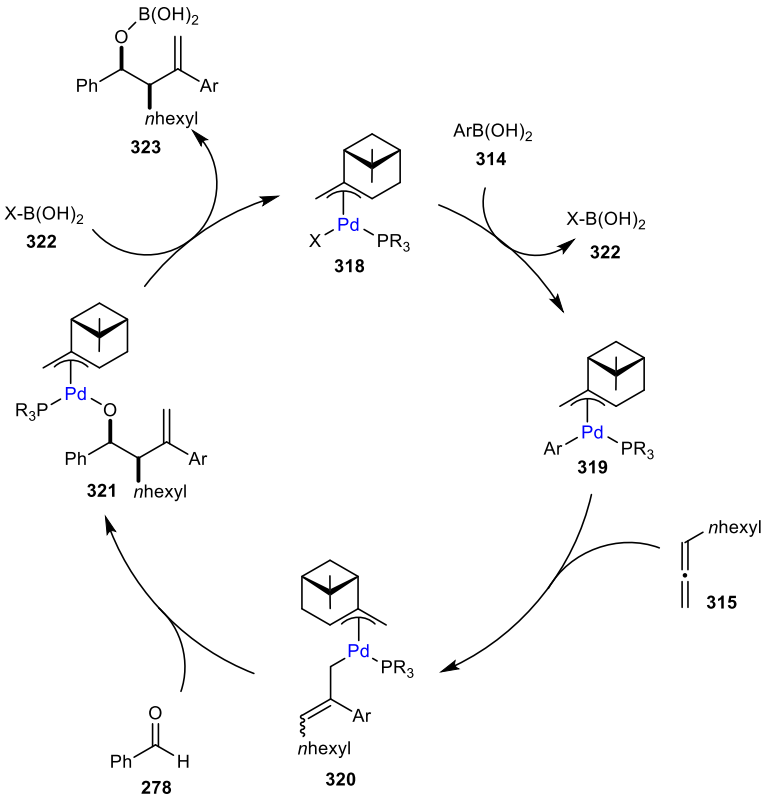
Scheme 85 – Palladium-indium mediated allylation of carbonyls

Several years later, in 2004, Malinakova and co-workers developed a synthesis of homoallylic alcohols *via* a palladium-catalysed three-component coupling of arylboronic acids (**314**), allenes (**315**) and aldehydes (**278**) (Scheme 86).[101] Homoallylic alcohol **317** could be synthesised in high yield, albeit in modest diastereoselectivity using palladium catalyst **316**.



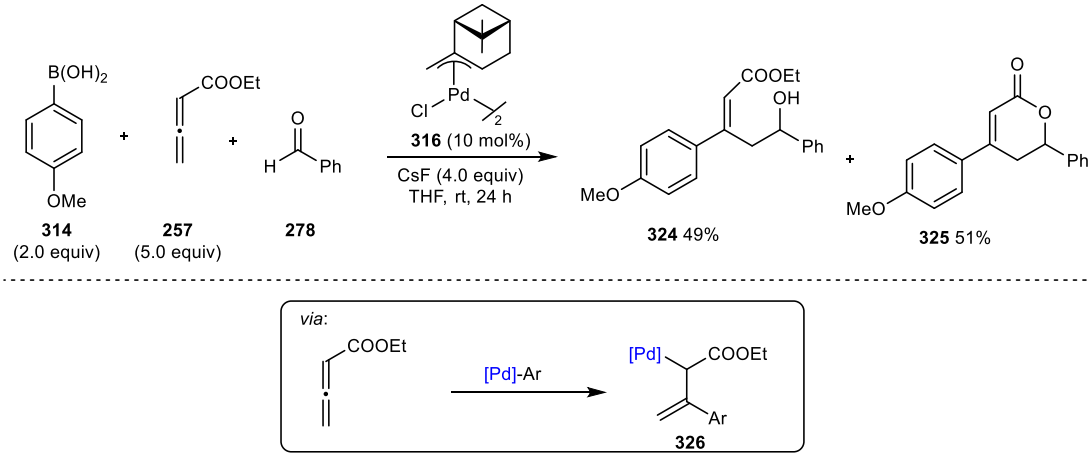
Scheme 86 – Palladium-catalysed three-component coupling of arylboronic acids, allenes and aldehydes

A proposed reaction mechanism is shown in Scheme 87. Transmetalation of arylboronic acid **314** with allylpalladium(II) complex **318** gives arylpalladium **319**. Migratory insertion of allene **315** into **319** then gives the nucleophilic σ-allylpalladium species **320**. This intermediate can add into **278** to give palladium species **321**. Regeneration of the catalyst by **322** would release **323**, which upon workup afford the observed compound. Malinakova believed allylation was most likely occuring *via* an 'open' transition state, which could possibly explain the low diastereoselectivity observed. With many other palladium(II) catalysts poor reactivity was found with precipitation of palladium(0) occurring. The β-pinene-derived allyl ligand was believed to work successfully as the "nontransferable" nature of the auxiliary allyl ligand stabilised the catalytic intermediates and ensured efficient allyl transfer of **320**. The enantioselectivity for this process was not reported.



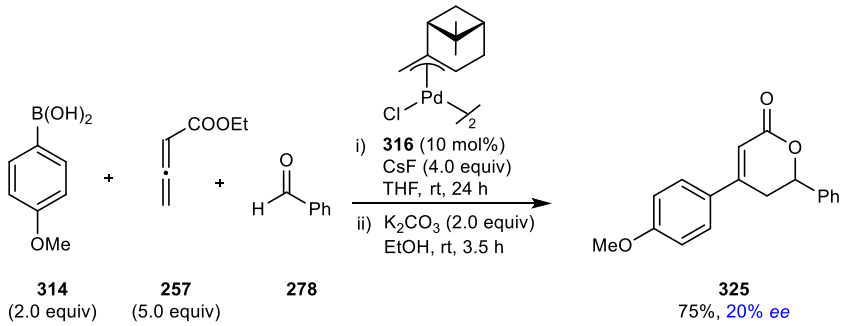
*Scheme 87 – Catalytic cycle for formation of **323***

Using allenyl ester **257**, lactone **325** was observed in addition to homoallylic alcohol **324** (Scheme 88).[102] With **257**, due to the electron-withdrawing ester substituent, the insertion of the arylmetal reagent occurred with the opposite regiochemistry to alkyl-substituted allene **315**, giving **326**. Allylpalladium **326** can then add into benzaldehyde (**278**) similarly to above. Under these reaction conditions a combined quantitative NMR yield of **324** and **325** was observed.



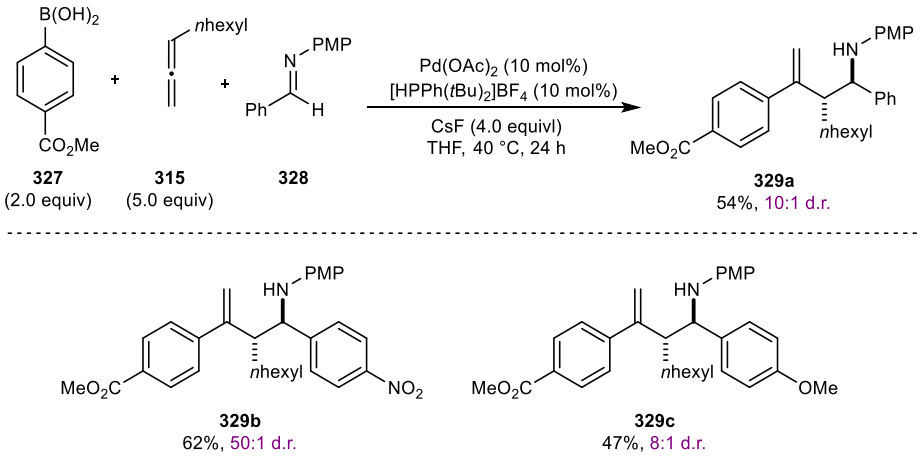
*Scheme 88 – Palladium-catalysed functionalisation of allenyl ester **257***

Using only CsF, lactonization from **324** to **325** was very slow. Therefore after 24 h, base was added to ensure complete conversion to **325**. (Scheme 89). Although **325** could be isolated in high yield, only poor enantioselectivity was ever observed (20% *ee*).



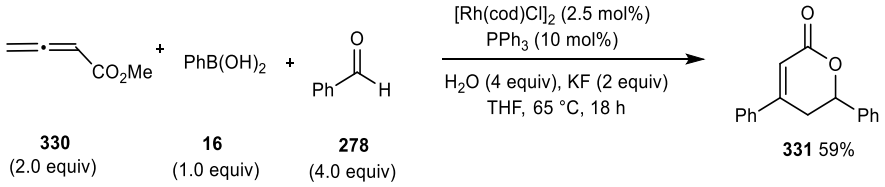
*Scheme 89 – Bis-functionalisation of allenyl ester **257** to give lactone **325***

This methodology was further extended to using imines as the electrophile (Scheme 90).[103] Interestingly, with the allylpalladium catalyst **316**, the yield (36%) was significantly worse than when $Pd(OAc)_2$ (54%) was used. Improvements in diastereoselectivity were also achieved through using the PMP-protected imine **328** as opposed to simple phenyl-protected imines. Electron-deficient aldimines reacted in greater efficiency, with 4-nitro-substituted product **329b** isolated in higher yield and diasteroeselectivity than phenyl and methoxy substituted products (**329a** and **329c**). The beneficial effect of the electronics of the PMP group on the reactivity suggested the reaction proceeded *via* a closed transition state, as coordination of allylpalladium to the Lewis basic nitrogen of the imine would be more favourable. Also, the *anti*-configuration of the products were confirmed by crystal structure suggesting a closed six-membered transition state where allylation occurs from an *E*-allylpalladium species. Interestingly the *anti*-diastereomer is the opposite diastereomer to that found when using an aldehyde as the electrophile.



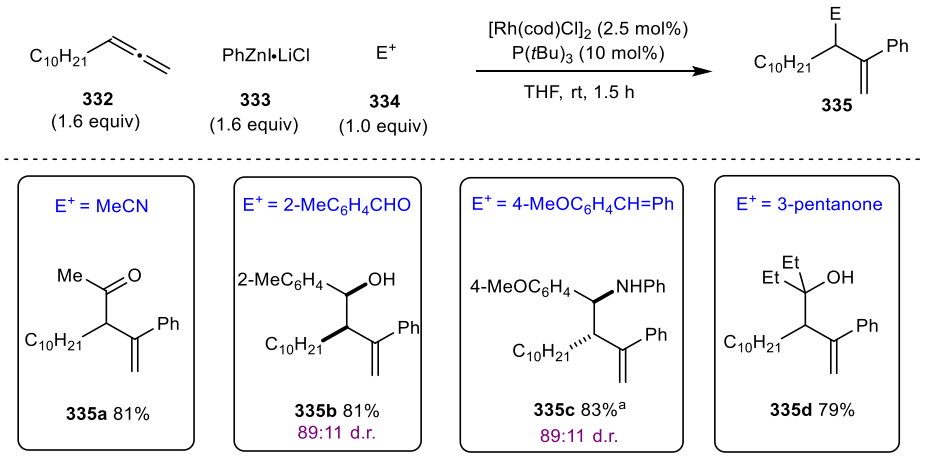
Scheme 90 – Three-component coupling of arylboronic acids, allenes, and imines

Three-component nucleophilic allylation reactions using rhodium(I) catalysts have also been described. In 2007 Jia and co-workers reported the coupling of allene **330**, phenylboronic acid (**16**) and benzaldehyde (**278**) (Scheme 91).[104] This protocol uses similar substrates to the one earlier described by Malinakova (see Scheme 89), and follows a similar mechanism.



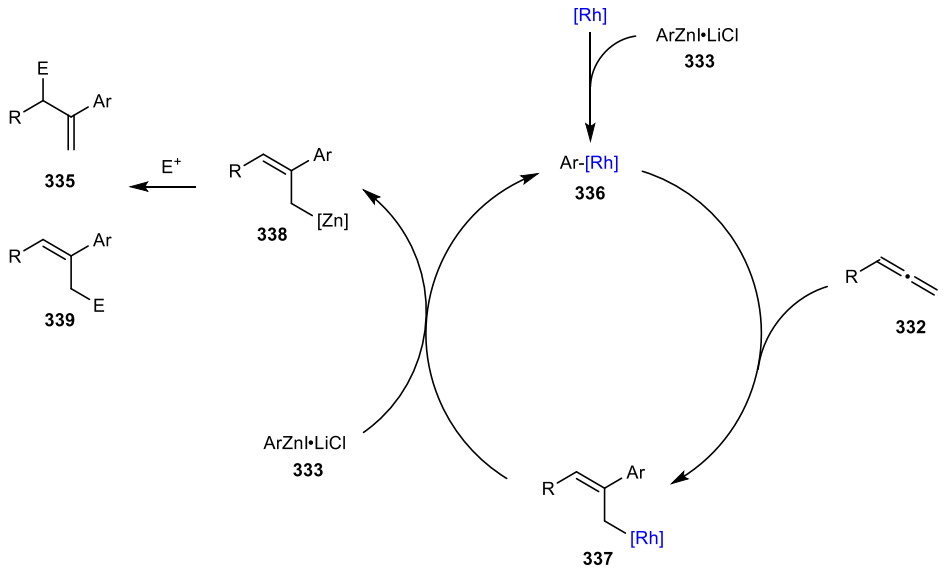
Scheme 91 – Rhodium-catalysed three-component coupling

Another rhodium-catalysed process was described in 2010 by Oshima and co-workers (Scheme 92).[105] They developed the arylzincation of terminal allenes in a three-component coupling reaction. Through changing the nature of the electrophile (**334**), a variety of different products could be observed. With acetonitrile as the electrophile synthesis of ketone **335a** was possible. With an aldehyde, imine, or ketone as the electrophile, secondary alcohols (**335b**), secondary amines (**335c**), or tertiary alcohols (**335d**) respectively, could all be formed. Interestingly, the reaction with an aldehyde gave the *syn*-diasteromer preferentially (**335b**), whereas with an imine the *anti*-diastereomer preferentially (**335c**).



*Scheme 92 – Rhodium-catalysed three-component coupling using arylzincates. [a] 10% linear isomer **339** observed*

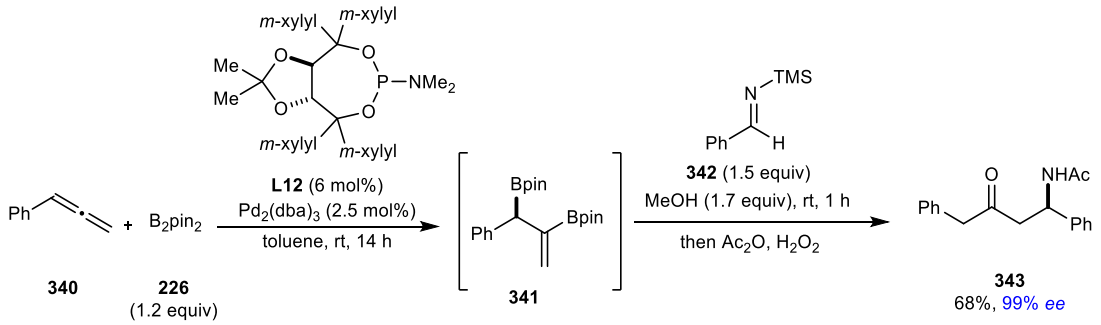
A possible catalytic cycle to explain the observed products is shown in Scheme 93. Transmetalation of rhodium with arylzincate **333** would give arylrhodium species **336**. Insertion of allene **332** into **336** gives the key nucleophilic allylrhodium species **337**. Transmetalation of **337** with a further molecule of **333** would give allylzinc species **338** and regenerate arylrhodium **336**. The allylzincate could then react with different electrophiles to give the observed products. To provide evidence that allylation occurs with allylzinc **338** as opposed to allylrhodium **337**, 2-methylbenzaldehyde was reacted directly with an allylzinc reagent. Product **335b** was observed in quantitative yield and similar d.r. (86:14) to the standard reaction conditions. Conversely, when an allyrhodium reagent derived from allylzinc underwent the reaction with an aldehyde, a complex mixture, including isomer **339**, was observed. With an imine as the electrophile, coordination of the nitrogen to allylrhodium **337** may be possible, which would explain the switch in diastereoselectivity when using these substrates.



*Scheme 93 – Catalytic cycle for formation of **335***

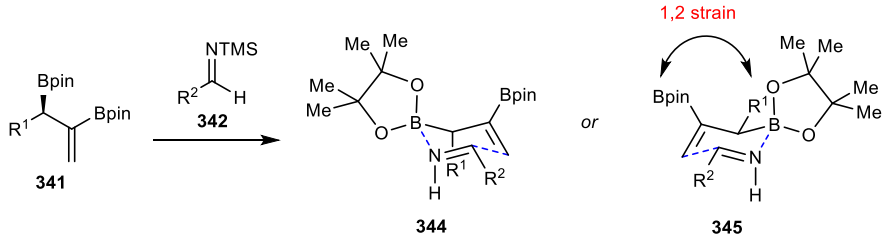
1.1.2.3 Three-Component Borylative Allylations

Whilst there are currently no examples of generating high enantioselectivity for three-component nucleophilic allylations where two new C-C bonds are formed, the corresponding borylative nucleophilic allylation has been shown to proceed with high control of stereoselectivity. In 2006, Morken and co-workers reported a palladium-catalysed asymmetric allene diboration followed by aminoallylation (Scheme 94).[106] With allene **340**, B_2pin_2 (**226**) and a palladium catalyst, diboronate **341** could be formed. This species can then undergo an allylation reaction with imine **342**, followed by protection with acetic anhydride. No reactivity was observed using benzyl or sulfonyl imines, with silylprotected imine **342** necessary for high yields and enantioselectivities.



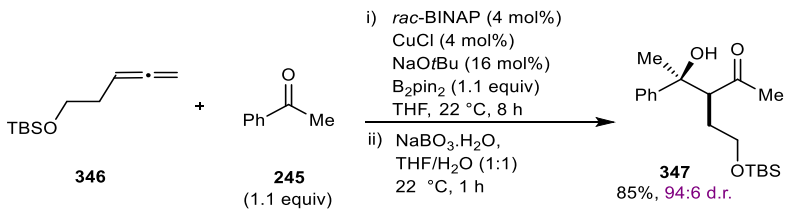
Scheme 94 – Palladium-catalysed diboration and aminoallylation

After the generation of the enantioenriched diboron species **341**, allylation of the imine is believed to proceed *via* six-membered transition state **344** (Scheme 95). Formation of the other diastereomer would be unfavourable as 1,2-strain is present in transition state **345**. Substituted (*E*)-imines would also be disfavoured as several 1,3-diaxial interactions would be present, which would explain why no reactivity was observed with *N*-substituted aldimines.



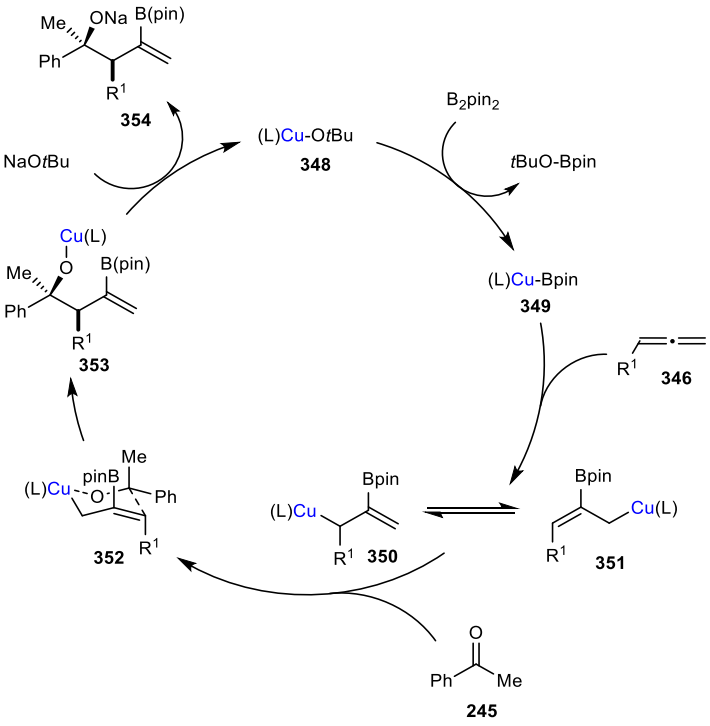
*Scheme 95 – Transition states for allylation of imine **342***

In 2013, Hoveyda and co-workers reported a copper-catalysed three-component reaction with B_2pin_2, monosubstituted allene **346** and acetophenone (**245**) (Scheme 96).[107] Greater than 98% selectivity for the branched products over linear products were obtained, with compounds such as **347** achieved in excellent yields and diastereoselectivities.



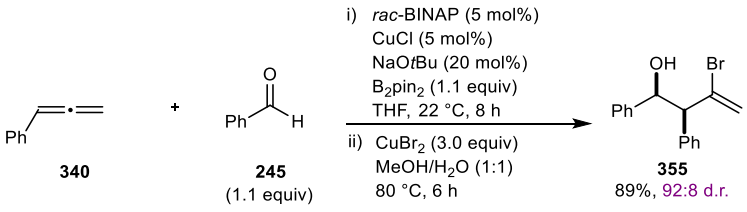
*Scheme 96 – Copper-catalysed allyation of acetophenone (**245**)*

A possible mechanism is shown in Scheme 97. Transmetalation of copper alkoxide **348** with B_2pin_2 gives copper species **349**. Addition of **349** across allene **346** would give **350** which is likely to be in equilibrium with **351**. The reaction would preferably proceed through the less congested copper centre (**351**), with allylation occurring *via* six-membered transition state **352**. NaO*t*Bu could then react with copper species **353** to regenerate **348**. The resulting vinylboronate **354** is then oxidised to the final observed compounds.



*Scheme 97 – Catalytic cycle for formation of **354***

It was also possible to access vinyl halides such as **355** in high yields by exposing the vinylboron species with $CuBr_2$ (Scheme 98).



*Scheme 98 – Synthesis of vinylbromide **355***

Hoveyda was then able to develop this process enantioselectively. When using an aldehyde as the electrophile, bisphosphine **L12** gave a range of products in excellent yields and stereoselectivities (**356**). (Figure 3). When reacting with ketones a different ligand (**L13**) was required, with the products also isolated in good yields, although with slightly poorer enantioselectivities (**357**).

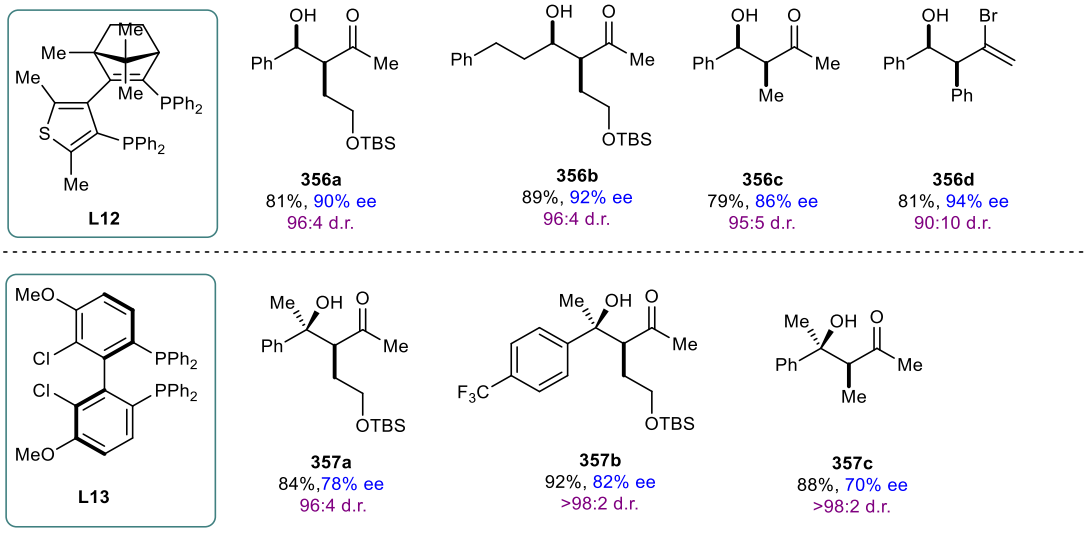
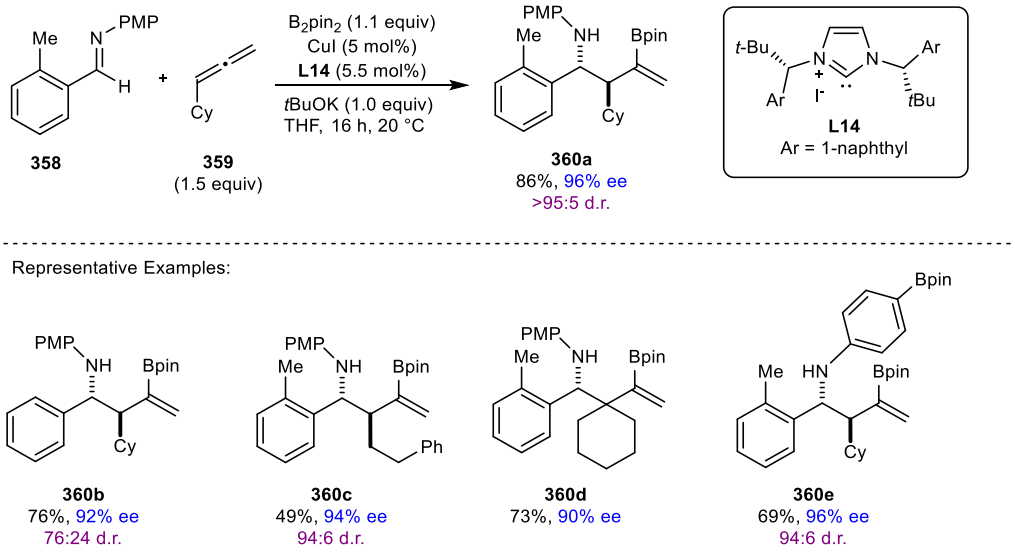


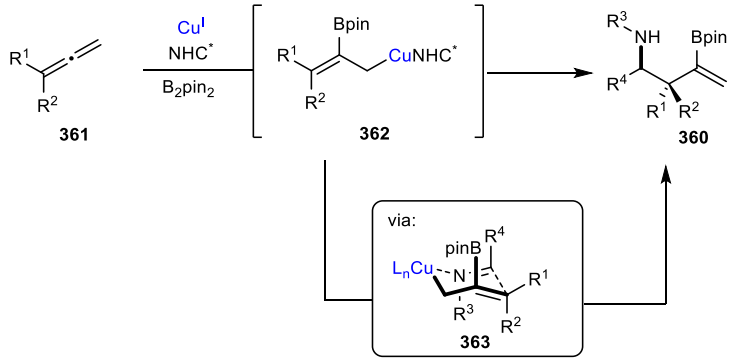
Figure 3 – Enantioselective copper-catalysed coupling with aldehydes and ketones

Using a similar principle, Procter and co-workers recently published a three-component coupling using imines as the electrophile (Scheme 99).[108] With allene **359** and B_2pin_2 the copper-catalysed allylation of imine **358** was possible, with **360a** formed in good diastereoselectivity and enantioselectivity. This reactivity was extended to a range of substrates with good overall yields maintained (**360b-360e**).



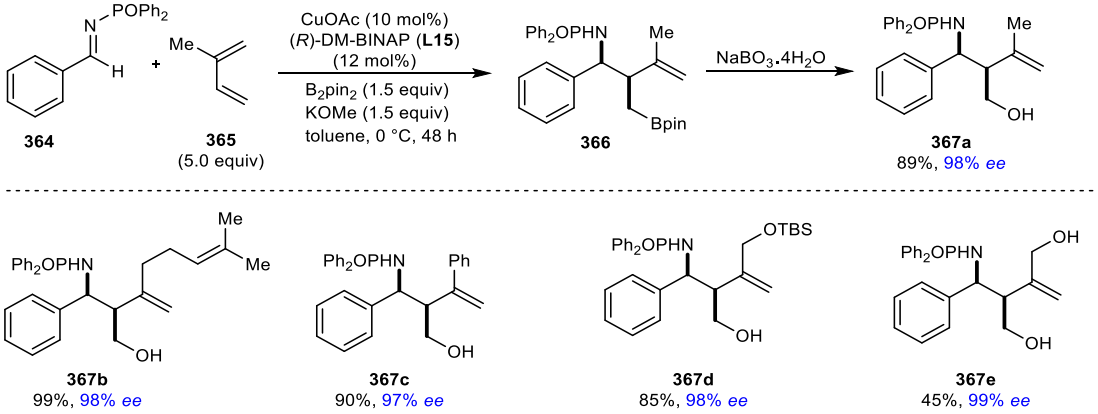
Scheme 99 – Copper-catalysed three-component allylation of aldimines

This reaction was believed to proceed through the sequence shown in Scheme 100. Addition of Cu-Bpin across the allene would give allylcuprate **362**, which could then react with an electrophile *via* **363** in a similar manner to that discussed previously.



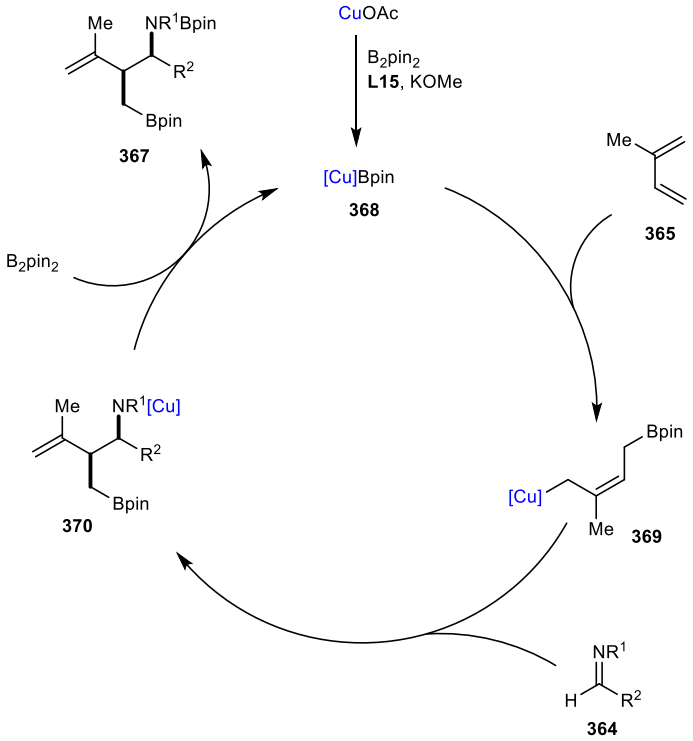
*Scheme 100 – Rationale for formation of **360***

Nucleophilic allylmetal species can also be generated through insertions with 1,3-dienes. In 2016 Liao and coworkers developed a copper-catalysed borylative coupling of 1,3-dienes and aldimines (Scheme 101).[109] Homoallylic amine **367a** could be synthesised from imine **364** and 1,3-diene **365** in high yield and enantioselectivity. With this chemistry it was possible to synthesise a range of homoallylic amines in excellent yields and enantioselectivities. *N*-diphenylphosphinoyl-protected imines were chosen, as using a bulkier protecting group, the diastereoselectivity was greatly enhanced. Increasing the steric bulk of the chiral ligand also correlated to an improvement in enantioselectivity.



Scheme 101 – Three-component allylation reaction with 1,3-dienes

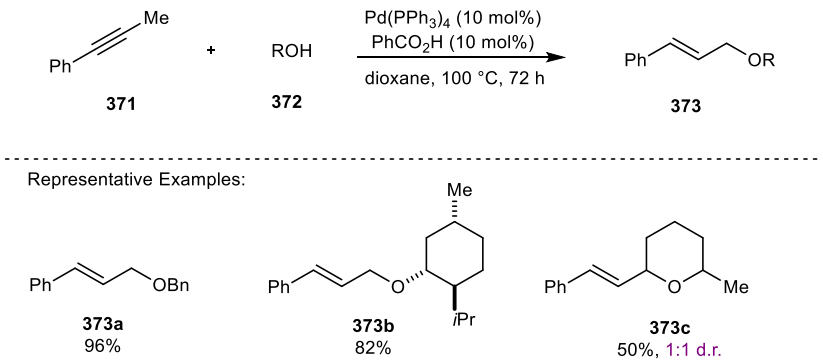
The mechanism for the formation of **367** is shown in Scheme 102. The copper-catalysed borylation of **365** gives (*Z*)-allylcopper species **369**. Intermediate **369** can then react with imine **364** to give **370** as the *syn*-diastereomer. Transmetalation of **370** with B_2pin_2 liberates the product and regenerates the catalytically active species.



*Scheme 102 – Catalytic cycle for formation of **367***

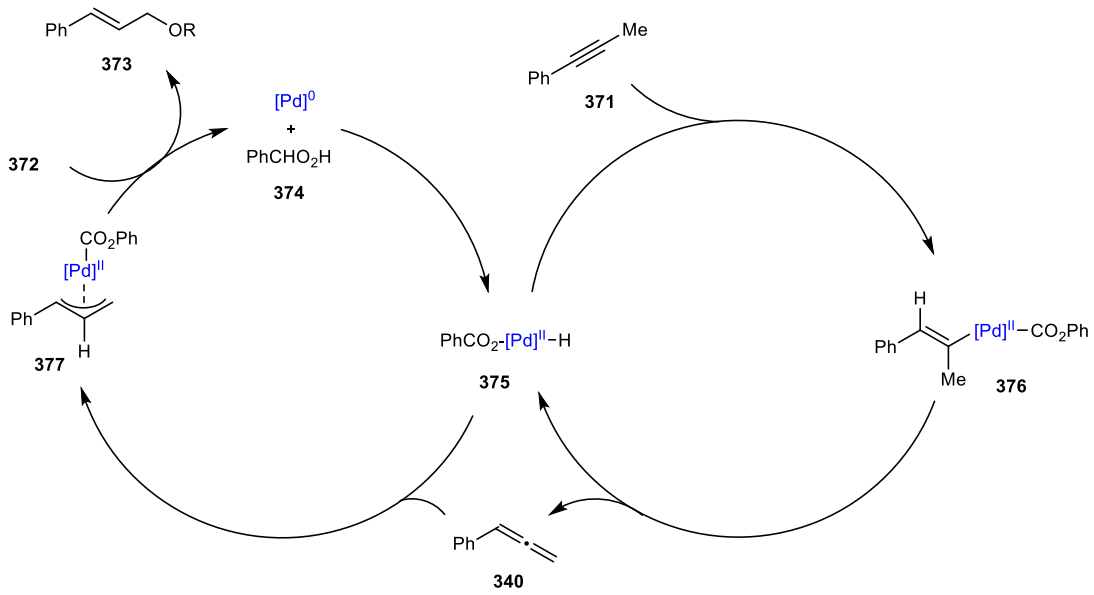
1.1.3 Generating Allymetal Precursors from Alkynes

Although extensive methodology has been developed for the atom efficient generation of allylmetal species from allenes and dienes, more recently examples of these intermediates being generated from alkynes have also been described.[110] An early of example of this mode of reactivity was discovered by Yamamoto and co-workers in 2001 and involved the generation of an electrophilic allylmetal species *in situ* (Scheme 103).[110] Using a palladium catalyst and benzoic acid as an additive, hydroalkoxylation products **373** could be synthesised from alkyne **371** and a range of alcohols (**372**). With the alcohol tethered to the alkyne it was possible to synthesise pyrans such as **373c** *via* an intramolecular hydroalkoxylation.



Scheme 103 – Palladium-catalysed hydroalkoxylation of alkynes

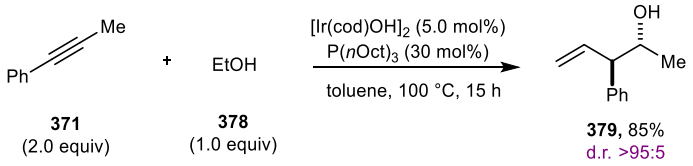
An explanation for the observed products is shown in Scheme 104. The reaction of Pd^0 and benzoic acid (**374**) would give hydridopalladium species **375**. Insertion of alkyne **371** into **375** would then give vinylpalladium species **376**. β-Hydride elimination of **376** generates phenylallene **340** and **375**. Hydropalladation of **340** with **375** gives allylpalladium species **377**, which can then react with an alcohol to give **373**.



*Scheme 104 – Catalytic cycle for formation of **373***

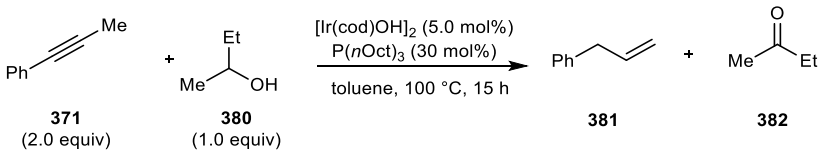
This mode of reactivity, where an electrophilic allymetal species is formed from a simple alkyne, has now been extended to be used in the formation of new carbon-nitrogen,[111] carbon-sulfur,[112] and carbon-carbon bonds.[113]

However, there are currently limited approaches for the corresponding nucleophilic allylmetal precursor to be generated from an alkyne. One early example was described by Ishii in 2011.[114] The iridium-catalysed coupling of alkyne **371** and a primary alcohol gave carbonyl allylation products **379** with the *anti*-diastereomer observed as the sole product (Scheme 105).



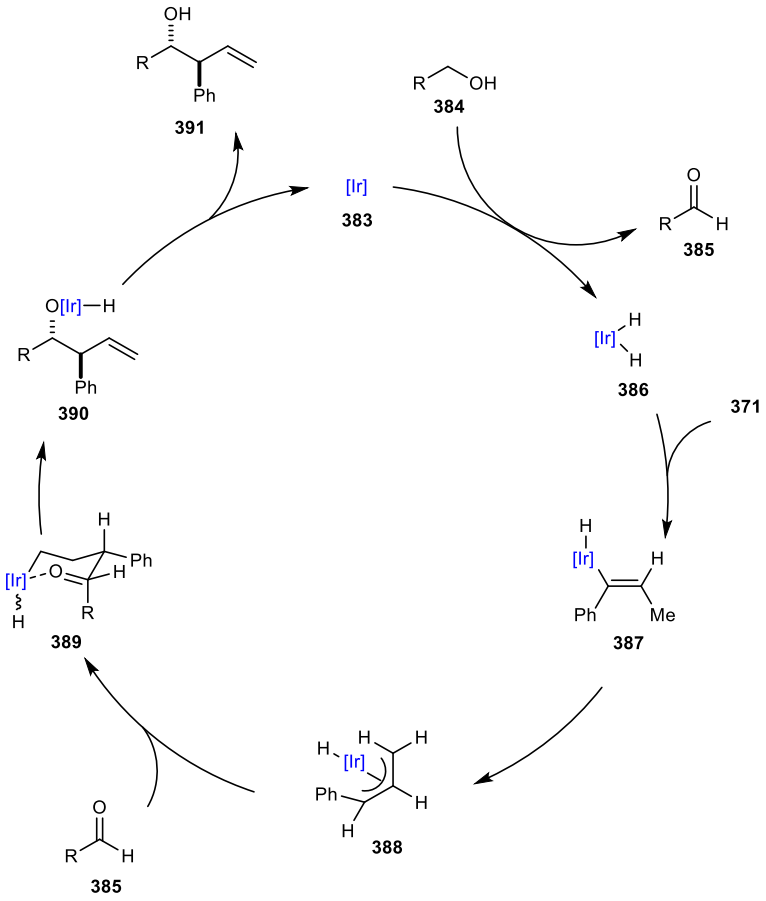
Scheme 105 – Iridium-catalysed coupling of alcohols and alkynes

To obtain mechanistic insight into this methodology, secondary alcohol **380** was reacted with **371** under the same reaction conditions (Scheme 106). Ketone **382** and allylbenzene (**381**) were formed in quantitative yield. This outcome suggested that alcohol **380** was behaving as a hydrogen donor, with the generated iridium-hydride species then able to react with **371** forming an allyliridium intermediate.



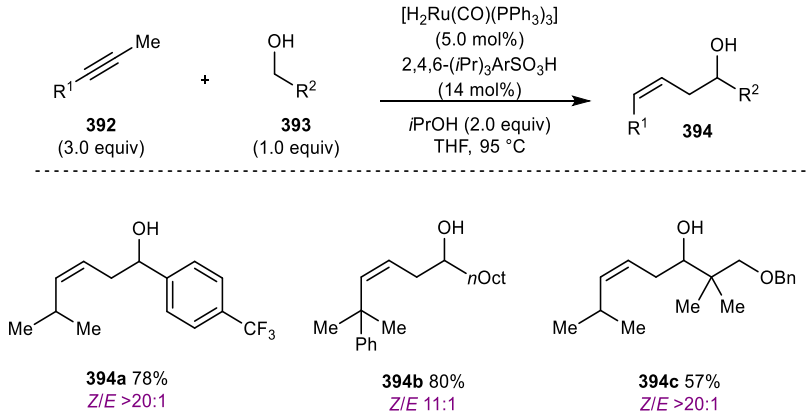
*Scheme 106 – The reaction of **371** with secondary alcohol **380***

The catalytic cycle most likely proceeds *via* a pathway shown in Scheme 107. Iridium species **383** acts as a hyrodgen acceptor, resulting in dihydroiridium **386** and generating active ketone **385**. Addition of **386** across alkyne **371** gives vinyliridium species **387**. Isomerisation of **387** to allyliridium species **388** then allows coordination to the newly generated ketone **385**. Nucleophilic allylation can then proceed through six-membered transition state **389** giving **390**, with reductive elimination liberating the product (**391**).



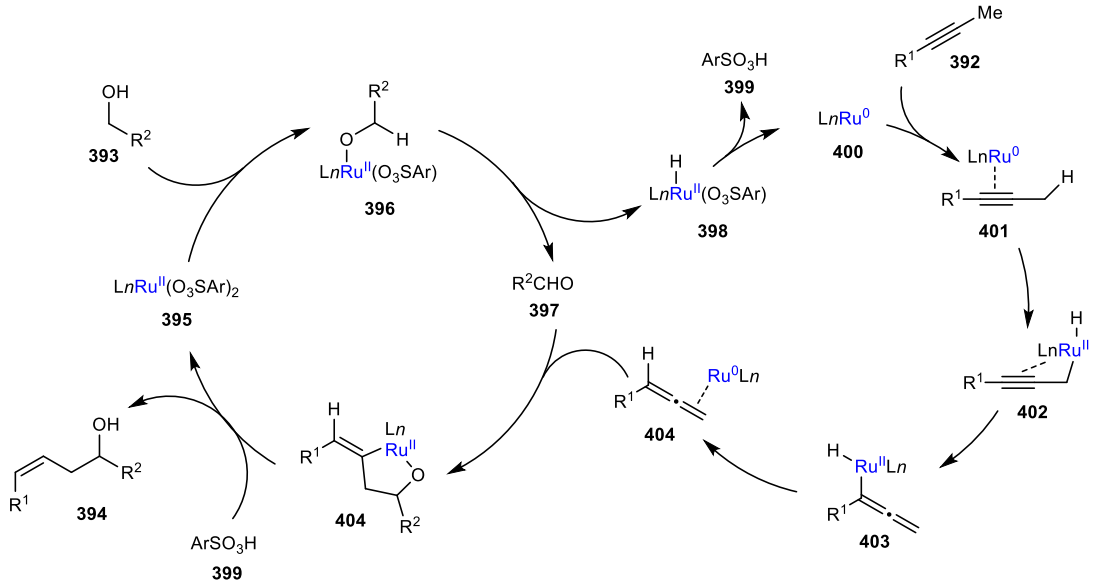
*Scheme 107 – Catalytic cycle for formation of **391***

Building on this chemistry, in 2014, Krische and co-workers developed the ruthenium-catalysed coupling of alkynes and alcohols (Scheme 108).[115] Using a cationic ruthenium catalyst generated from $H_2Ru(CO)(PPh_3)_3$ and 2,4,6-(2-*i*Pr)$_3$-$ArSO_3H$ a diverse range of alkynes and alcohols reacted to give homoallylic alcohols in good yields and stereoselectivities. *i*PrOH was required as an additive to ensure high conversion, as the reaction is in competition with simple alcohol-alkyne transfer hydrogenation. It is thought *i*PrOH can convert unreacted aldehyde back to the more reactive primary alcohol.



Scheme 108 – Ruthenium-catalysed coupling of alkynes and primary alcohols

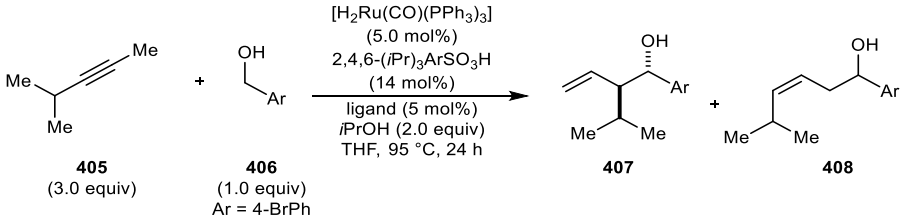
Krische proposed a catalytic mechanism as shown in Scheme 109. The ruthenium bis-sulfonate complex **395** reacts with alcohol **393** to give ruthenium alkoxide **396**. β-Hydride elimination then gives aldehyde **397** and the hydridoruthenium complex **398**. Complex **398** can then reductively eliminate to give zerovalent ruthenium complex **400**. Coordination of **400** to alkyne **392** then allows oxidative addition into the propargyl C-H bond to give **402**. Isomerisation to **403** and subsequent reductive elimination gives allene **404**. Oxidative coupling of allene **404** with aldehyde **397** gives oxaruthenacycle **404** with high selectivity for the *E*-stereoisomer. Cleavage of **404** by **399** regenerates **395** and expels product **394**.

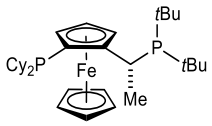


*Scheme 109 – Catalytic cycle for formation of **394***

Interestingly Krische found changes in the reaction conditions could suppress the oxidative coupling, whilst maintaining alkyne-allene isomerisation. This reactivity allowed the generation of branched homoallylic alcohol **407**.[116] The addition of iodide ions was found to inhibit the formation of **408** from alkyne **405** and alcohol **406** (Table 2 – Entry 2). In addition, using a chelating phosphine ligand gave slight conversion to **407** (entry 3). When these two conditions were combined, **407** could be synthesised in excellent yield and diastereoselectivity (entry 4). A chiral Josiphos ligand (**L16**) allowed high levels of enantioselectivity to be obtained (entry 5).

Table 2 – Ruthenium-catalysed coupling of alcohols and alkynes to give branched products

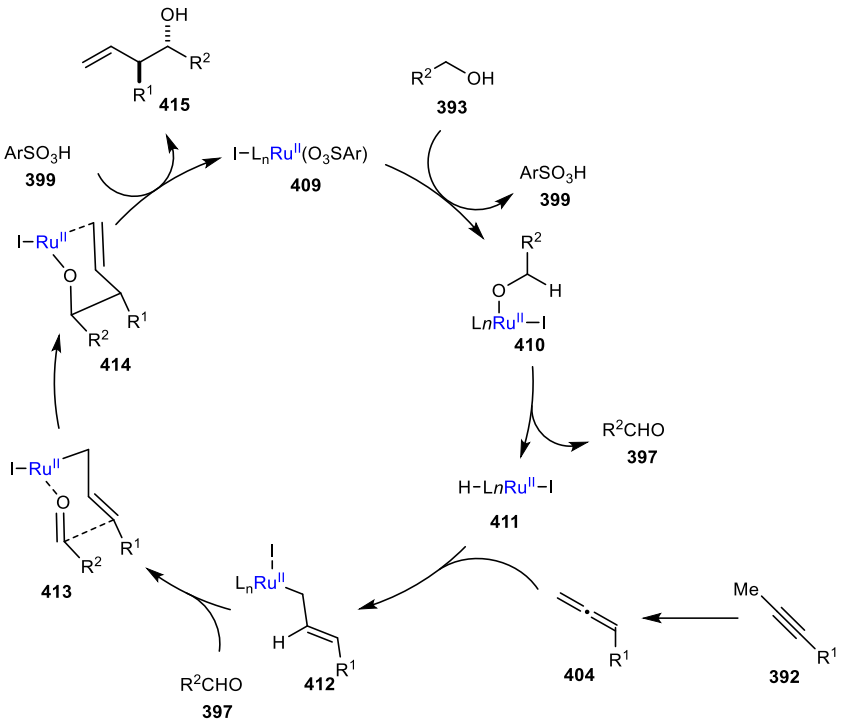


Entry	Bu_4NI	Ligand	**407** (yield, dr)	**408** (yield, *Z*:*E*)
1	-	-	-	70%, >20:1
2	10 mol%	-	-	24%, 10:1
3		dppf	21%, 7:1	26%, 5:2
4	10 mol%	dppf	83%, 15:1	-
5[a,b]	10 mol%	 **L16**	79%, >20:1, 94% ee	-

[a] 5 mol% of $ArSO_3H$. [b] THF (1 M)

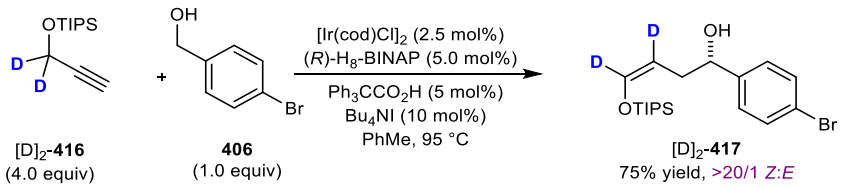
The mechanism for the formation of **407** proceeds similarly to before (Scheme 110). The presence of Bu_4NI allows the generation of iodo-ruthenium complex **409**, which reacts with alcohol **393** to give ruthenium species **410**. β-Hydride elimination again gives aldehyde **397** as well as iodoruthenium hydride species **411**. Addition of **411** across allene **404** then gives (*E*)-allylruthenium species **412**. This species can react with aldehyde **397** to provide ruthenium alkoxide **414**, with protonolysis by sulfonic acid **399** liberating product **415**. It is suspected that the iodide effect may be a result of its strong σ-donicity. This effect can destabilise the ruthenium(0) intermediate (**404**) formed after alkyne **392** to allene **404**

isomerisation. The the oxidative coupling pathway, which gives products such as **408**, would therefore be supressed.



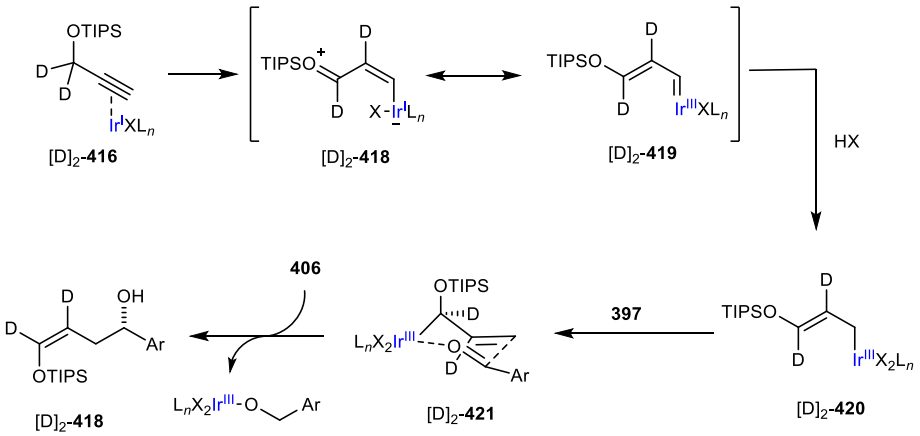
*Scheme 110 – Catalytic cycle for formation of **415***

Krische and co-workers later reported a third distinct mechanism in the coupling of alkynes and alcohols when using propargyl silyl ethers (Scheme 111). With an iridium catalyst, alcohol **406** and deuterio-alkyne **416** reacted to give homoallylic alcohol [D]$_2$-**417** in good yield, excellent *E*/*Z* selectivity and with deuterium incorporated at both vinylic positions.



*Scheme 111 – Iridium-catalysed coupling of alcohol **406** and propargyl silyl ether **416***

A plausible mechanism would start with iridium coordinating to alkyne **416** (Scheme 112). The interaction of the oxygen of the silyl ether and propargylc C-D bond promotes a 1,2-deuteride shift which gives vinylcarbene **419**. Protonation of this species would then give the nucleophilic allyliridium species **420**. This species can then react with aldehyde **397** *via* **421**, which affords **418** after protonolysis by alcohol **406**.



Scheme 112 – Mechanism to give observed deuterium incorporation

In summary, although the generation of electrophilic allylmetal species through CH-functionalisation or activation has been well described, there is currently relatively limited precedent to form the equivalent nucleophilic allylmetal variant. These species could react with carbonyls or imines to form synthetically very useful homoallylic alcohols or amines. Methods of forming nucleophilic allylmetal species *in situ* through migratory insertions of allenes provides an alternative route to forming a nucleophilic allymetal species *in situ*, however, forming two new C-C bonds using these methods has to date not generated high enantioselectivities. Therefore, if methodology could be developed which incorporates these ideas, whilst proceeding in high enantioselectivity, it would provide new opportunities in the application of this chemistry.

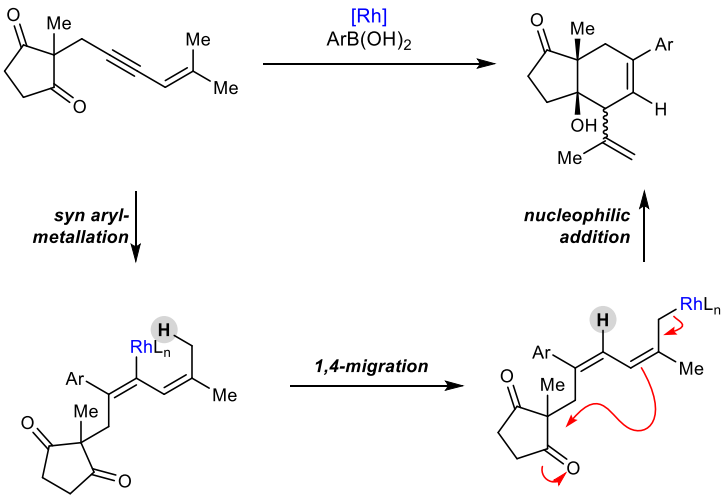
2 Results and Discussion

2.1 Arylative Intramolecular Allyation

2.1.1 Aim

The Lam group has previously reported several examples of rhodium-catalysed reactions where 1,4-migrations to allylic C (sp^3) centres occur (Scheme 32 and Scheme 42). In 2014, one of the first rhodium (III) migrations was reported, where an electrophilic allylmetal species was generated *in situ* from a 1,3-enyne.[49] At a similar time, the Lam group also described an allyl-to-allyl rhodium (I) 1,4-migration, which, owing to the more electron-rich nature of Rh(I), gave a nucleophilic allyl metal species. This species was subsequently able to react with a range of cyclic imines.[44]

Incorporating these two ideas, our aim was to demonstrate the first example of rhodium (I) migrating from an alkenyl-to-allyl carbon. This mode of reactivity would be achieved through using a 1,3-enyne tethered to an electrophile, in conjunction with a pronucleophile and rhodium catalyst (Scheme 113). An arylrhodium species would regioselectively add across the alkyne, facilitiating the key migration and generating a nucleophilic allylmetal species which would subsequently be trapped by the electrophile (tethered cyclic diketone).

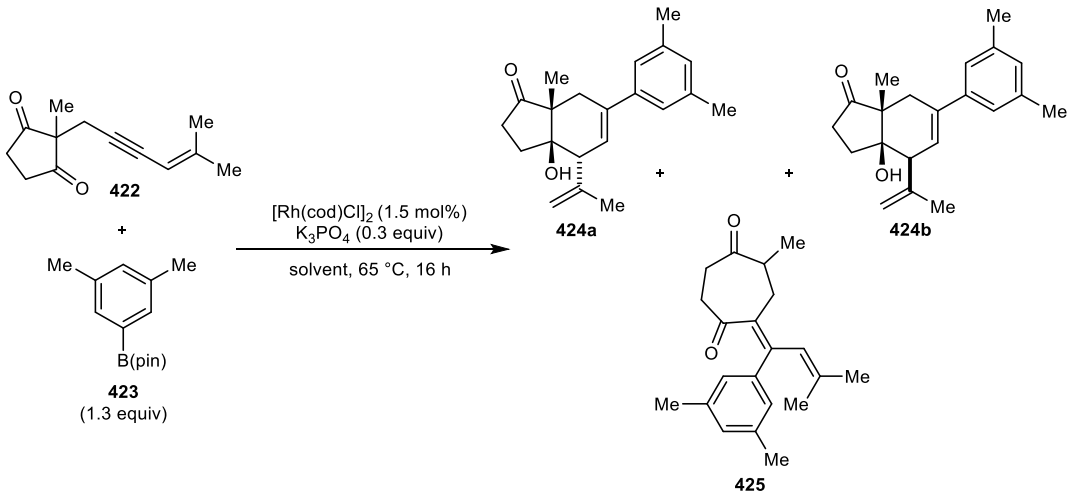


Scheme 113-Reaction Premise

2.1.2 Reaction Optimisation

Initial optimisation and substrate scope was performed by Dr B. Partridge. Pleasingly, when using 1,3-enyne **422a** and aryl pinacol boronate ester **423**, in the presence of a rhodium catalyst and base, he observed the formation of **424b** in reasonable yield and diasteroeselectivity (Table 3 – entry 1). Interestingly, changing the solvent system from THF/MeOH (10:1) to MeCN/MeOH (10:1) preferential formation of the opposite diastereomer (**424a**) was observed in both higher yield and selectivity (entry 2). Further optimisation of the nitrile solvent system gave an additional increase in diastereoselectivity, as well as greater conversion into the desired product (entry 3).

Table 3 – Solvent Screen

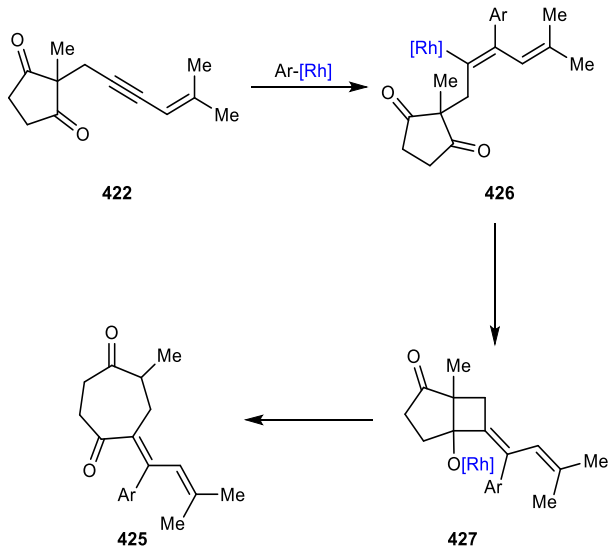


Entry	Solvent	d.r. **424a**:**424b**[a]	Yield of **424a**	Yield of **424b**	Yield of **425**
1	THF/MeOH (10:1)	17:83	11	46	n.d.
2	MeCN/MeOH (10:1)	91:9	66	5	9
3	TBME/*t*BuCN/MeOH (10:1.2:1)	94:6	73	4	14

Reactions performed by B. Partridge. Reactions employed 0.50 mmol of **422**. [a] Determined by ^{1}H NMR analysis of the crude reactions.

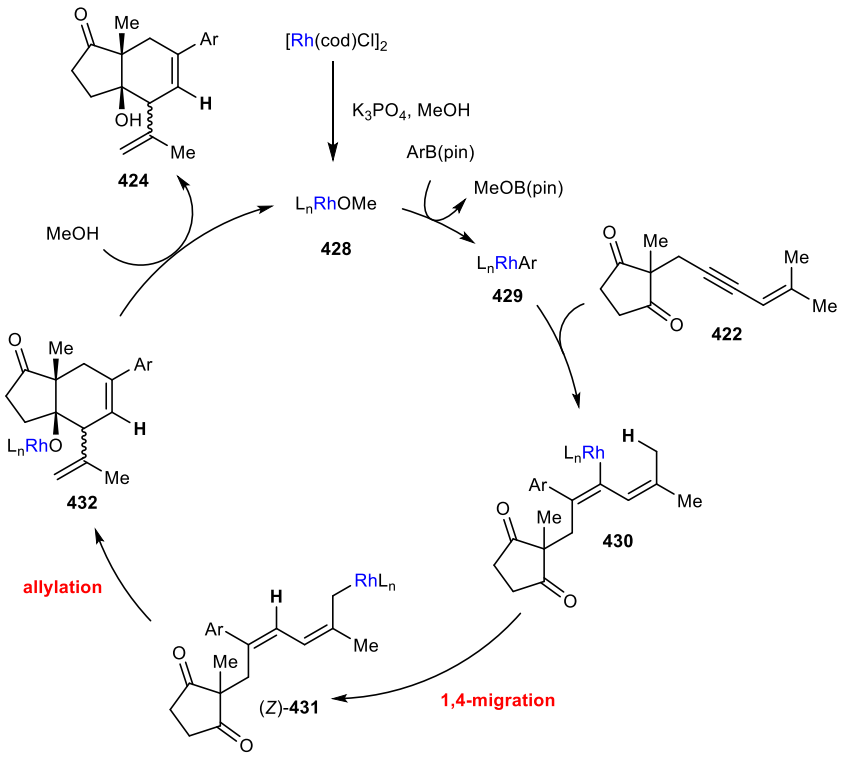
Diketone **425** was observed as a minor side product and is thought to arise from initial arylrhodation of the triple bond occurring with the opposite regioselectivity to that observed for the formation of **424a** and **424b** (Scheme 114). Alkenylrhodium species **426** can then

undergo a cyclisation-fragmentation pathway *via* intermediate **427** to give ring expansion product **425**.



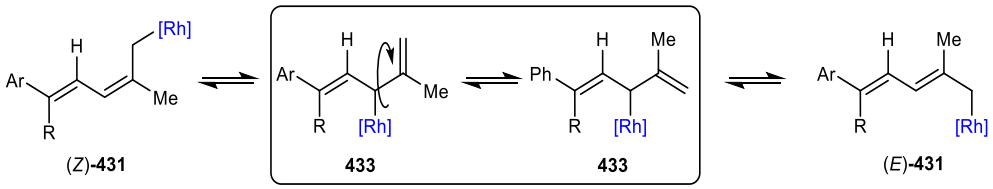
*Scheme 114 – Formation of diketone **425***

A proposed catalytic cycle for the formation of **424** is shown in Scheme 115. Arylrhodium species **429** can be formed from the transmetalation of rhodium alkoxide **428** with an arylboronate ester. Arylrhodium **429** can then undergo a migratory insertion with enynone **422** to give alkenylrhodium species **430**. At this point the alkenyl-to-allyl rhodium (I) migration can take place with the *cis*-allylic methyl substituent to give allylrhodium species (*Z*)-**431.** The nucleophilic allylmetal species can then attack the ketone to form rhodium alkoxide **432**, with methanolysis of **432** liberating **424** and regenerating the catalyst (**428**).



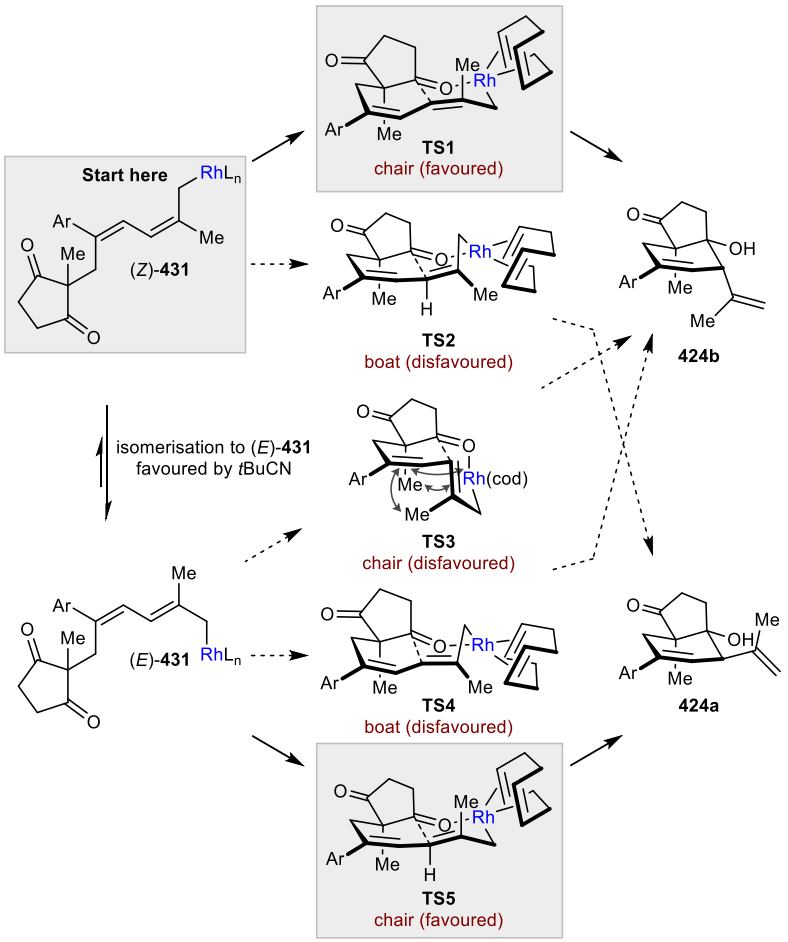
Scheme 115 – Catalytic Cycle

The stereochemically defining allylation step is thought to proceed *via* a closed cyclic six-membered transition state, as consistent with other models for transition metal-catalysed nucleophilic allylation reactions.[117] Therefore, the geometry of the allylmetal species generated is important for control of diasteroeselectivity, with (*Z*)-allylmetal species generally reacting to afford the *syn*-diasteromer, and (*E)*-allylmetal species affording the *anti*-diastereomer. In this reaction, the varying diasteroeselectivity observed when changing the solvent system is thought to arise from isomerisation of (*Z*)-allylrhodium species (*Z*)-**431** to (*E*)-allylrhodium species (*E*)-**431** through a series of rhodium 1,3-allylic transpositions (Scheme 116). Generation of alkylrhodium species **433** would allow the free rotation around the newly formed C-C single bond, and upon reisomerisation would form rhodium species (*E*)-**431**. In the presence of a coordinating nitrile solvent, we believe cyclisation can be disfavoured, which would allow isomerisation to the thermodynamically more favourable (*E*)-**431** from (*Z*)-**431** to take place.



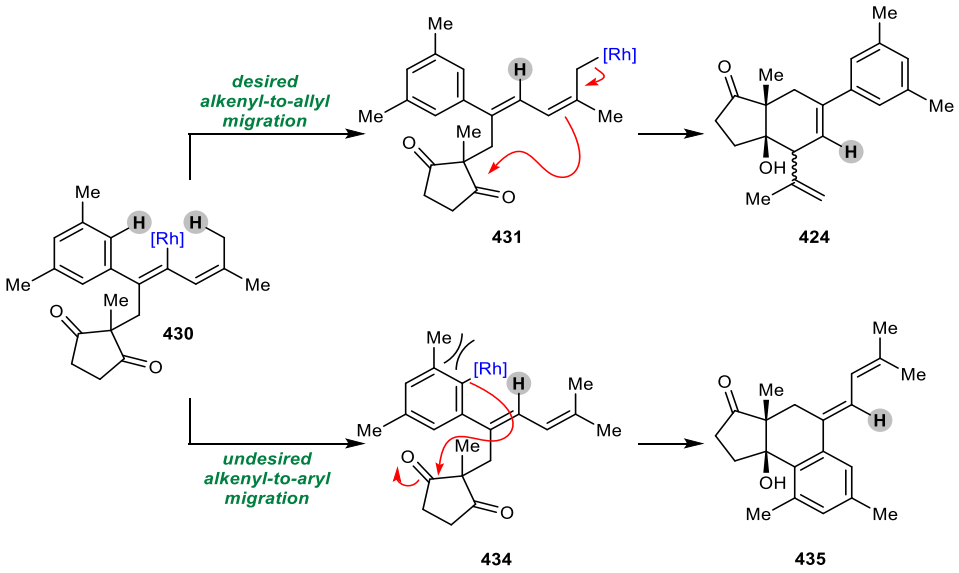
*Scheme 116 – Isomerisation of (Z)-allyrhodium species **431***

Using THF/MeOH as a solvent system we believe that cyclisation of (*Z*)-**431** occurs through a chairlike arrangement (**TS1**) (Scheme 117). The possible boatlike transition state (**TS2**), which would give diastereomer **424b** should be disfavoured due to the inherent higher energy of this conformation. Since the Rh (I) 1,4-migration occurs with the *cis*-methyl allylic substituent, (*Z*)-**431** is formed exclusively. Upon addition of a nitrile solvent, isomerisation to (*E*)-**431** can take place, which would likely react *via* transition state **TS5**. This transition state would give the opposite diastereomer (**424a**). Other feasible transitions states involving (*E*)-**431** are likely to be disfavoured. **TS4** is likely to be disfavoured due to the boatlike nature of the transition state, whilst **TS3** suffers from both disfavourable 1,3-diaxial interactions and allylic 1,3-strain. It is not possible at this point to exclude the possibility that, due to the coordinating nature of nitriles, the reaction proceeds through an open transition state. In this scenario rhodium would have preferential coordination to the nitrile over the ketone. However, as the control of diasteroeselectivity is high, a closed transition state seems more likely.



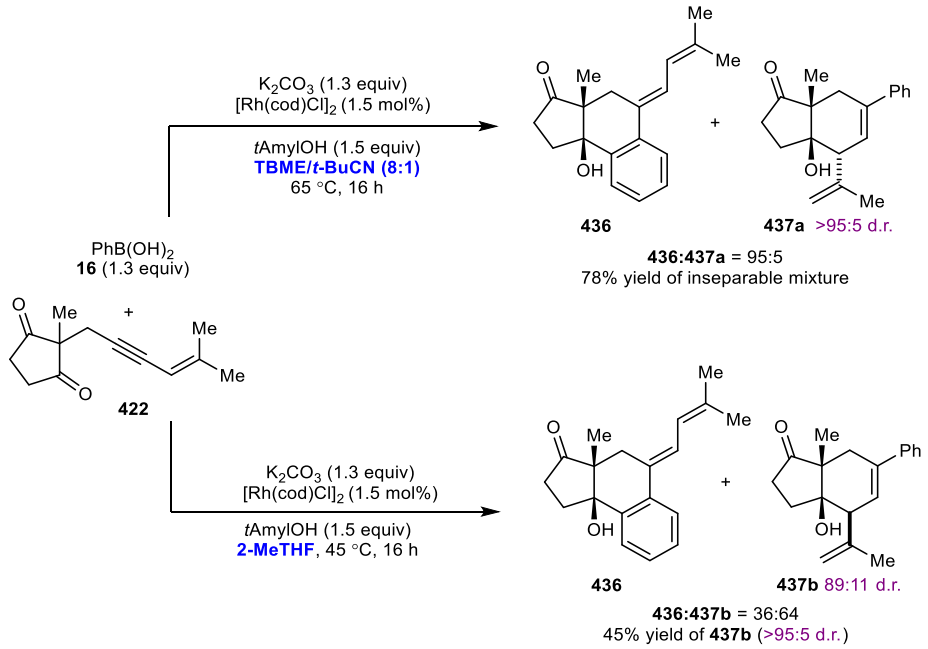
Scheme 117 – Transition states to account for observed steroechemistry

With this chemistry the observed migration is occurring between an alkenyl sp^2 (C) and allylic sp^3 (C). However, within the Lam group, we have previously reported similar structures readily undergoing alkenyl-to-aryl rhodium migrations (see Scheme 48).[13] Since alkenylrhodium species **430** is believed to be a key intermediate in the catalytic cycle, the metal could feasibly migrate to both the allylic or aryl position, with these migrations likely to be in competition with each other (Scheme 118). To minimise the unwanted migration onto the aryl ring substituted aromatic boronates were used which would sterically disfavour migration of the metal to the aryl ring (**434**), and result in the exclusive formation of desired compound **424**.



Scheme 118 – Controlling the 1,4-Migration

To test the inherent preference for rhodium(I) to migrate to either an allyl or aryl position, substrate **422** was reacted with phenylboronic acid (**16**) using the standard conditions. Interestingly, the choice of solvent system had a significant effect on the product distribution (Scheme 119). When nitrile was used as a co-solvent, product **436,** arising from migration to the aryl position, was formed in high yield (78%) and high selectivity over product **437a** (95:5). Conversely, when using 2-MeTHF, and in the absence of nitrile, conversion into product **437b** was favoured over the aryl migration product **436** (64:36). In both circumstances, the arylative allylation products were formed in very high diasteroeselectivities. The reason for this switch in chemoselectivity is currently unknown, although, based on the result using MeTHF, it would imply that allylation of the ketone is intrinsically more favourable than arylation, and that presence of nitrile does indeed inhibit allylation.

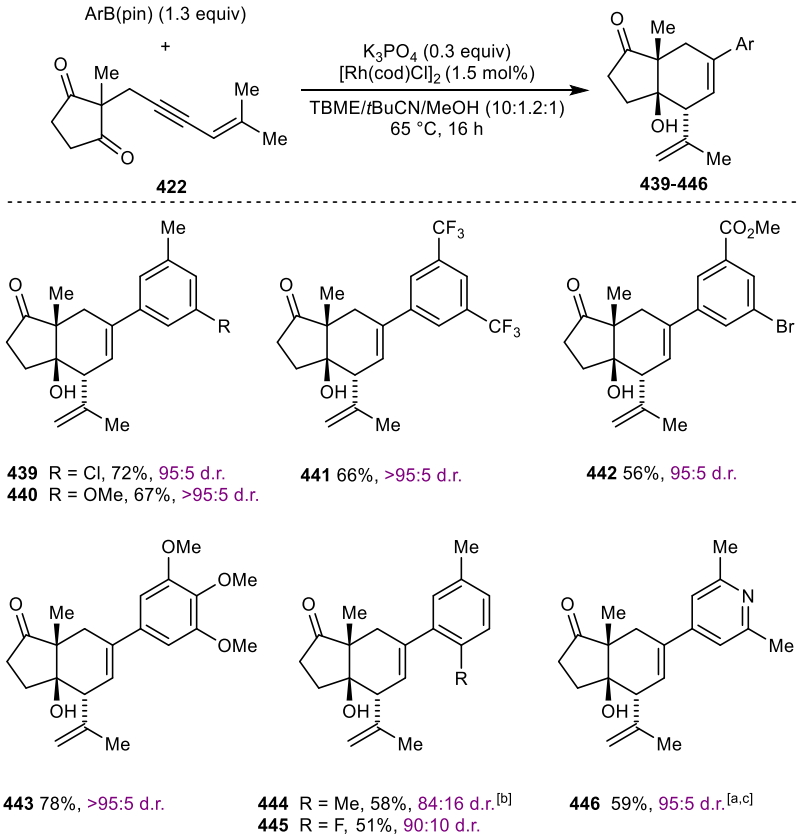


*Scheme 119 – Reaction of **422** with phenyl boronic acid. Reactions performed by B. Partridge*

2.1.3 Reaction of Different Arylboronates

Having optimised conditions for the arylative allylation of **422** with boronic ester **423**, the scope of the reaction with respect to other arylboronic acid pinacol esters was explored (Scheme 120). Pinacol esters were chosen as substrates, as these limited the products arising from simple hydroarylation across the triple bond, which were observed as side products when using boronic acids. The ease of synthesising the disubstituted variants using iridium-catalysed C–H borylation chemistry also made use of pinacol esters appealing.[118] With 3,5-substituted arylboronic esters, various electron-withdrawing and electron-donating groups were tolerated, including halide (**439**), methoxy (**440**), trifluoromethyl (**441**) and ester (**442**) groups, which all gave products in excellent diastereoselectivities. The more electron-rich 3,4,5-trimethyl-substituted boronic ester was also tolerated with **443** obtained in an excellent yield and high diastereoselectivity. Boronate esters containing 2,5-disubstition patterns underwent the reaction as well, although both **444** and **445** were isolated in reduced yields when compared the 3,5-subsituted variants. This reduction is most likely a result of the increased steric hindrance due to an *ortho*-substituent. A heteroarylboronate pinacol ester was also efficient in the reaction, with the lutidine-derived arylboronate giving **446** in high yield and diastereoselectivity. 5-Membered heteroaromatic boronates such as

2- and 3-thienylboronates were not successful, with NMR analysis of the crude reactions suggesting the products occurring from migration to the heteroaryl ring were formed exclusively (similarly to **436**, Scheme 119).

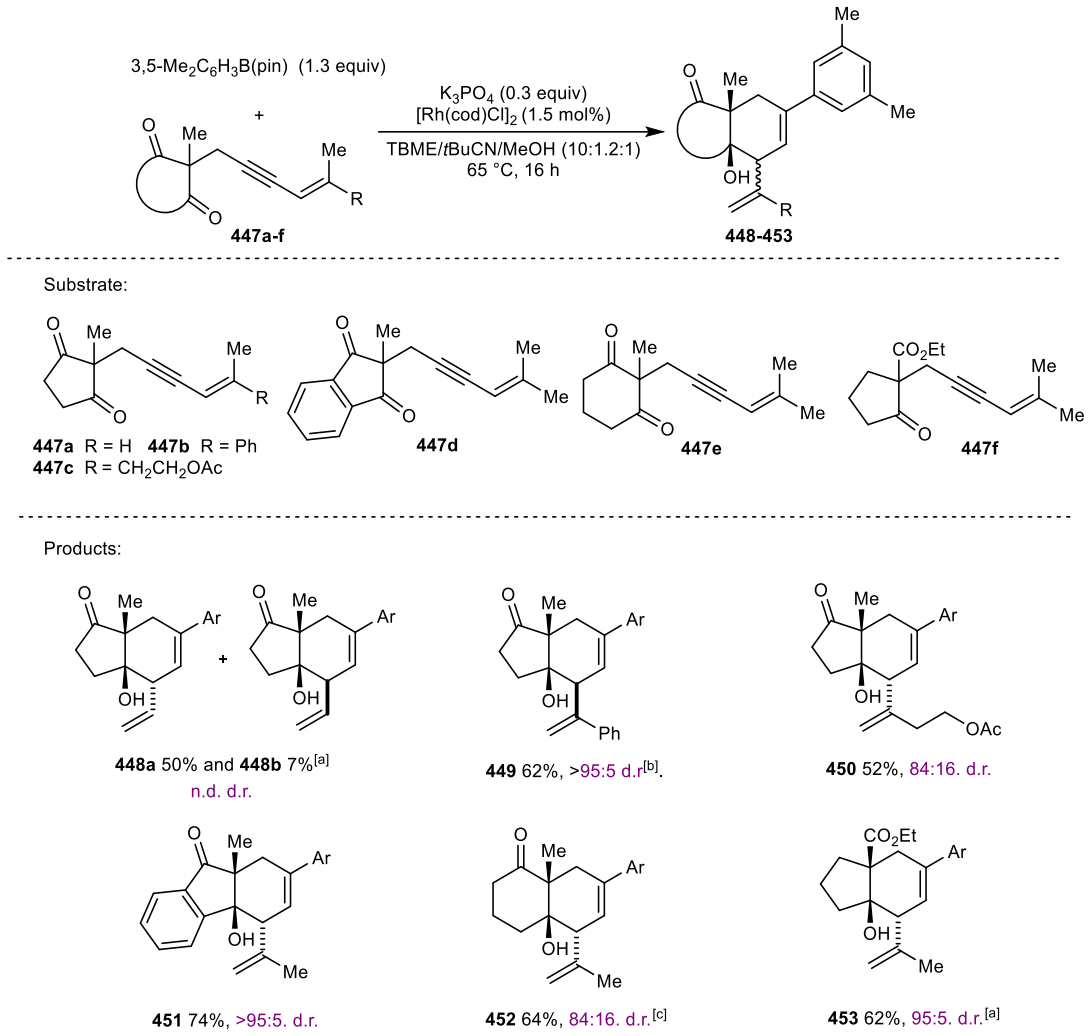


*Scheme 120 – Boronic Acid Scope. Reactions employed 0.50 mmol of **422**. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reactions. Yields are of isolated, diastereomerically pure products. Reactions performed by B. Partridge. [a] Reaction performed by M.Callingham. [b] Reaction performed with 2.5 mol% [Rh(cod)Cl]$_2$. [c] Reaction employed 0.45 mmol of **422**.*

2.1.4 Reaction of Different Enynones

The scope with respect to the enynone is shown in Scheme 121. Methyl substituents *cis* to the alkyne were a requirement for reactivity to occur, with no products observed when attempting migration to secondary alkyl carbons. Changes to the group *trans* to the alkyne were possible, with a hydrogen, phenyl and alkyl chain (**447a**, **447b**, **447c**) giving products **448a**, **449**, and **450** in reasonable yields and diasteroeselectivities. The reactivity of enynone

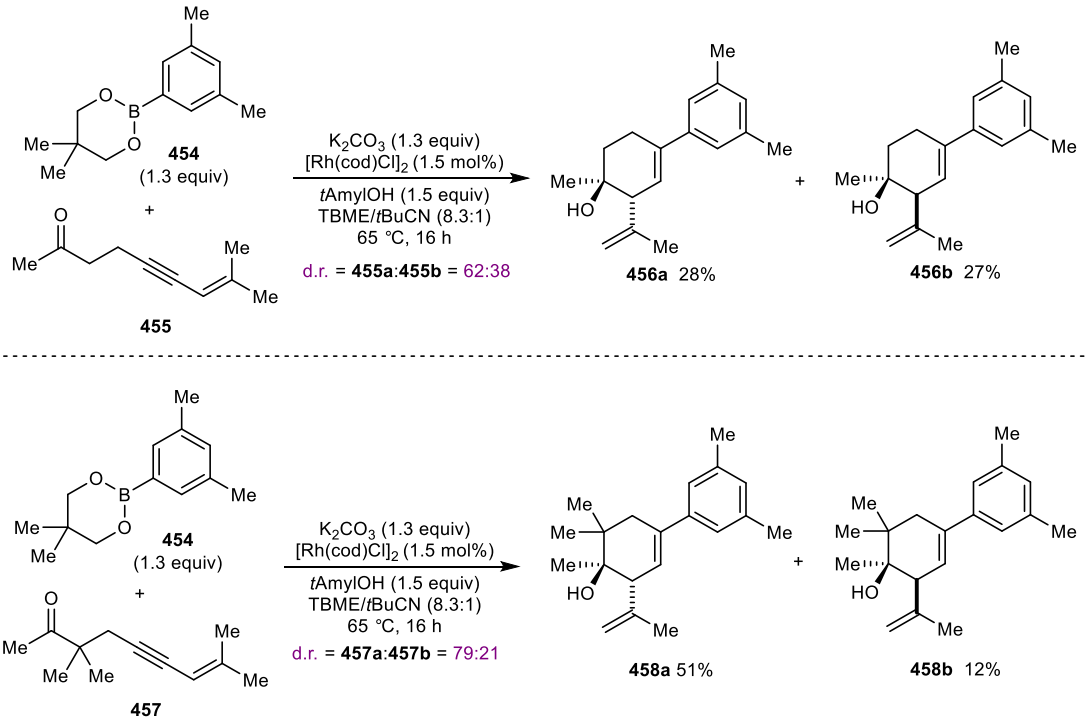
447a was poorer, and additional catalyst (2.5 mol%) was required. For this example, the diasteroeselectivity could not be calculated from the crude NMR spectrum. However, the minor *syn-syn* diastereomer **448b** was isolated in 7% yield. Using the standard reaction conditions, **447b** gave no stereoselectivity with **449** formed as a 1:1 mixture of diastereomers in only 22% yield. However, switching the solvent system to 2-MeTHF/MeOH (10:1) gave the *syn-syn* diasteromer **449** in high yield and diasteroeselectivity. This observation is most likely a result of the natural preference for **449** to be formed as the *syn-syn* diastereomer as isomerisation between the two allylrhodium species would be disfavoured by the presence of the phenyl group. Variation of the ketone portion of the substrate was also possible. Indanedione **447d** successfully underwent the arylative allylation in high yield and diastereoselectivity to give **451**. Under the standard reaction conditions, six-membered cyclic 1,3-diketone **447e** suffered from decomposition in competition with the desired pathway. Changing the boronate ester to the more reactive aryl neopentyl glycol boronate ester,[119] and using K_2CO_3 and *t*AmOH as the base and proton source, allowed **452** to be formed in good yield and reasonable diastereoselectivity. β-Ketoester **447f** also underwent the reaction successfully, although an increase in catalyst (2.5 mol%) was required to obtain satisfactory yields of **453**.



*Scheme 121 – Enyne Scope. Reactions employed 0.50 mmol of **447**. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reactions. Yields are of isolated, diastereomerically pure products. Reactions performed by B. Partridge. [a] Using 2.5 mol% of [Rh(cod)Cl]$_2$. [b] Using 2-MeTHF/MeOH (10:1) in place of TBME/tBuCN/MeOH (10:1.2:1). [c] Using 3,5-Me$_2$C$_6$H$_3$B(neo) (1.3 equiv), K$_2$CO$_3$ (1.3 equiv), and tAmylOH (1.5 equiv) as the reagents in TBME/tBuCN (8.3:1).*

Up to this point, only the reactions with a 1,3-enyne tethered to a cyclic diketone had been examined. Therefore, the utility of the reaction was explored further by investigating acyclic substrates (Scheme 122). Enynones **455** and **457** successfully underwent the arylative allylation reaction in good yields, although with reduced diastereoselectivities when compared to cyclic substrates (62:38 and 79:21 respectively). Due to the poorer reactivity

of these substrates, the more reactive aryl neopentyl glycol boronate **454** was needed to obtain reasonable yields. Using MeTHF as solvent, the sense of diasteroeselectivity could again be switched, favouring the formation of **456b** and **457b.** Using these conditions similar levels of diasteroeselectivity were observed (63:37 and 82:18), although the yields were slightly lower. The relative configurations for the diastereomers were determined through NOESY experiments. Enynone **457**, which contains a geminal dimethyl group in the tether reacted in increased yield and diastereoselectivity compared to the substrate with the methylene linker (**455**). This observation could be a result of an enhancement in reactivity through the Thorpe-Ingold effect**.**[120]

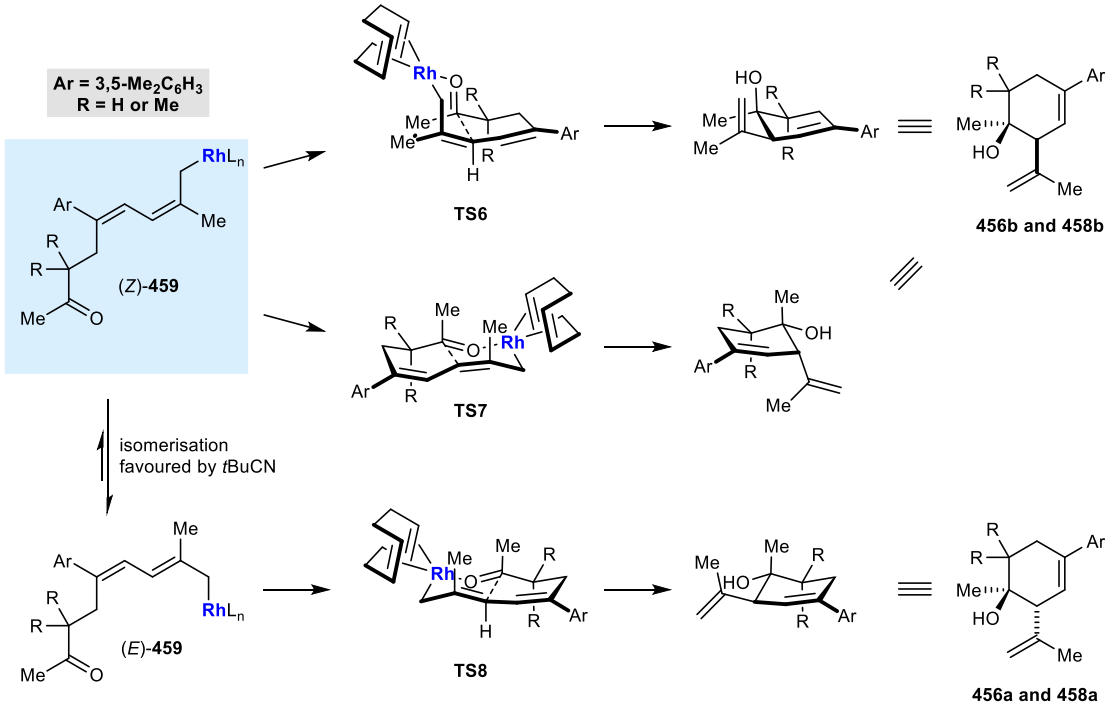


Scheme 122 – Reactivity using Acyclic Substrates

Chairlike transition states similar to those described previously have been suggested to account for the relative stereochemistry observed. (*Z*)-Allylrhodium species (*Z*)-**459**, formed directly after the 1,4-metal migration, is likely to react through **TS6** or **TS7**, forming **456b** or **458b**. In the presence of nitrile, after the 1,4-migration, isomerisation of (*Z*)-**459** to (*E*)-**459** can again occur, allowing allylation to occur through **TS8** and giving diasteromers **456a** and **458a**. The lower diastereoselectivities observed with these substrates is likely a result of the lower difference in relative energies of the transition states between the two isomers undergoing allylation. With cyclic diketone substrates a *cis*-ring junction is formed, resulting

in the well-defined geometry of the tertiary alcohol. Therefore, in these circumstances the selectivity is principally governed by the *E*/*Z* ratio of the allylrhodium species undergoing cyclisation.

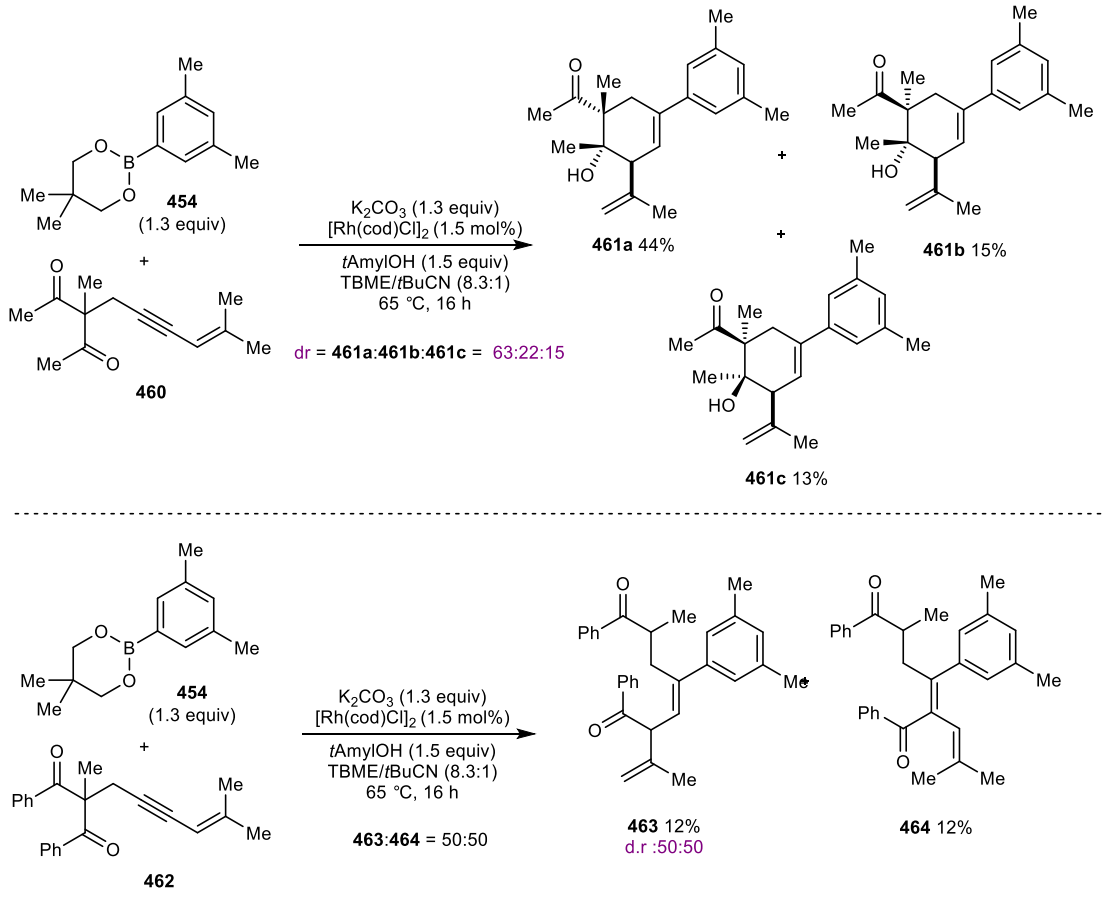
One would expect the relative ratio of the two allyl isomers to be similar between acyclic and cyclic substrates. Therefore, potentially owing to the greater flexibility of the acyclic system, the difference in energies of the transition states undergoing cyclisation are reduced, resulting in the decrease in observed diasteroselectivity. This hypothesis would suggest the observed diastereoselectivity is not a result of the ratio of (*Z*)-**459** to (*E*)-**459**, which may be in a rapid equilibrium, but of the relative energies of the transition states through which allylation is proceeding (Curtin-Hammett kinetics). An alternative rationale would be that viable low energy transiton states exist whereby (*Z*)-**459** reacts to form the *anti*-diastereomer and (*E*)-**459** affords the *syn*-diastereomer. Computational studies of this process could provide further insight towards an explanation for the observed differences.



Scheme 123 – Transition States for Acyclic Substrates

Additional acyclic substrates were also explored (Scheme 124). 1,3-Diketones **460** and **462** both exhibited the desired reactivity under the standard conditions. Unlike with substrates

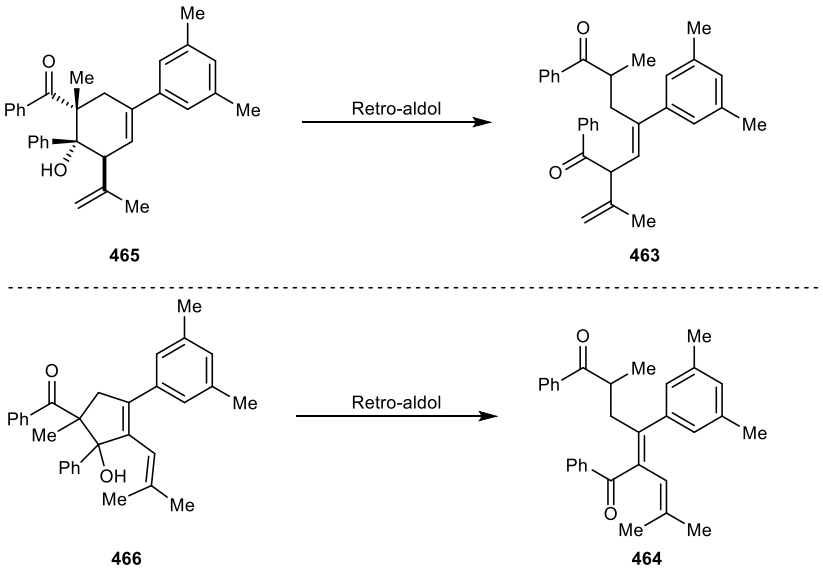
455 and **457**, an additional stereocentre would be present in the product, and therefore the complexity of these compounds is increased. Pleasingly conversion of **460** was high, with **461a**, **461b**, and **461c** obtained in good overall yield (72%) and reasonable diastereoselectivity. The ratio of the *syn*-allylation product **461a** and *anti*-allylation product **461c**, is similar to when using substrate **455.** Interestingly, with 1,3-diketone **462**, the expected product was not observed, with 1,7-diketone **463** formed in 1:1 diastereomeric ratio, alongside 1,6-diketone **464**.



Scheme 124 – Further Acyclic Substrates

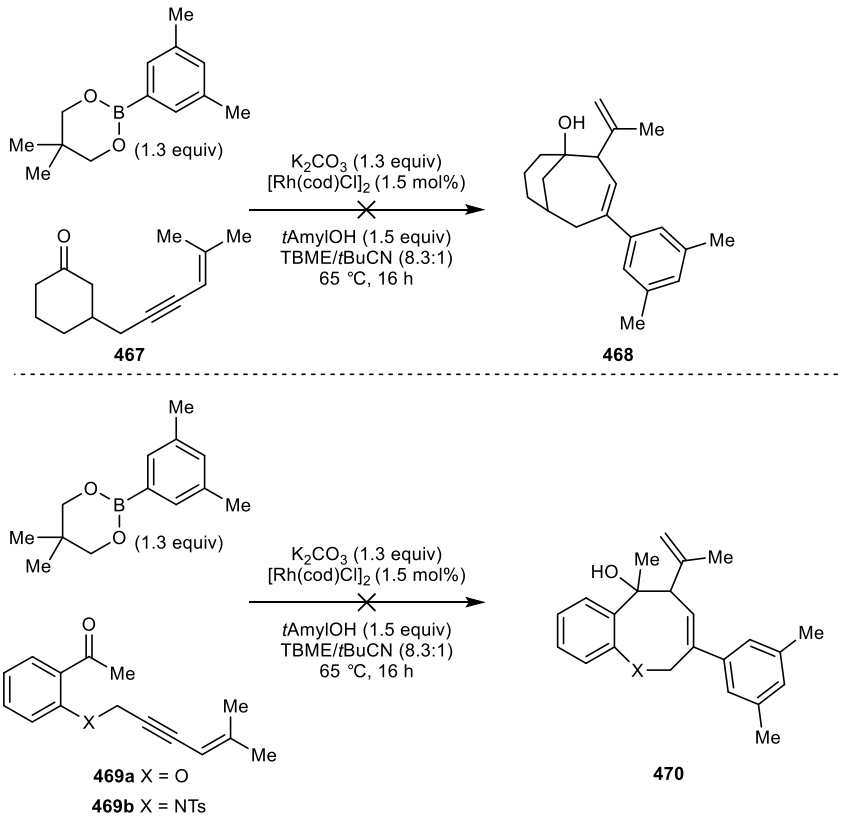
Both **463** and **464** are likely formed through a retro-aldol type reaction after initial addition to the ketone (Scheme 125). This reactivity may be a result of the weak C-C bond between the alcohol and the carbon α to the remaining ketone in **465** and **466**. 1,7-Diketone **463** is likely formed by the retro-aldol of the unstable desired target **465**, which would account for the lack of diastereoselectivity. 1,6-Diketone **464** could arise from a similar retro-aldol type reaction, but this time from **466.** Formation of **466** can be rationalised by the addition of an alkenylrhodium species, formed after arylrhodation of the alkyne and then double bond

isomerisation, to the carbonyl. This alkenyl addition was never observed with other substrates, suggesting addition of an alkenylrhodium species is feasible with a phenyl-substituted carbonyl.



*Scheme 125 – Formation of **463** and **464***

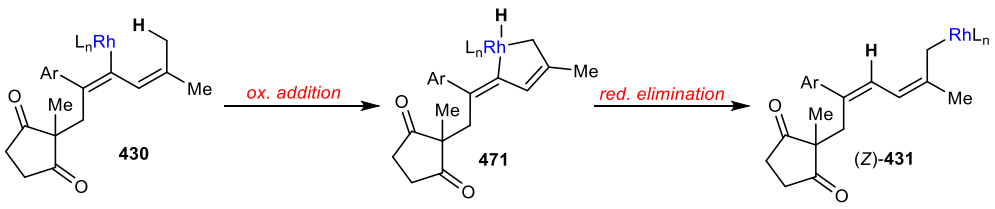
Attempts to further increase the scope were made using substrates **467** and **469**. In both cases, no reactivity was observed (Scheme 126). With **469**, the nature of the linker did not influence the reactivity, with no conversion observed using both the oxygen and tosyl-protected nitrogen substrates.



*Scheme 126 – Reactions with **467** and **469***

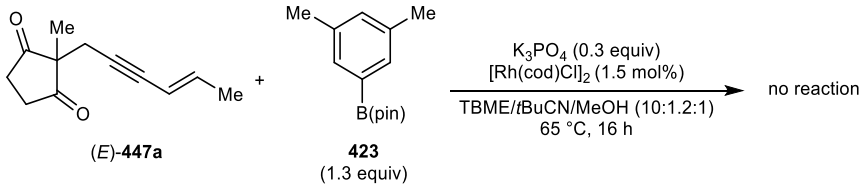
2.1.5 Investigation into the Rh (I) 1,4-Migration

1,4-Rhodium(I) migrations are believed to occur by a consecutive C-H oxidative addition/reductive elimination pathway *via* a rhodium (III) hydride intermediate (Scheme 127).[7] In this chemistry, alkenylrhodium **430** would oxidatively add into the allylic C-H bond, forming Rh(III)-H complex **471**. This intermediate could then undergo a reductive elimination forming allylrhodium (*Z*)-**431** and resulting in the overall migration of the metal species.



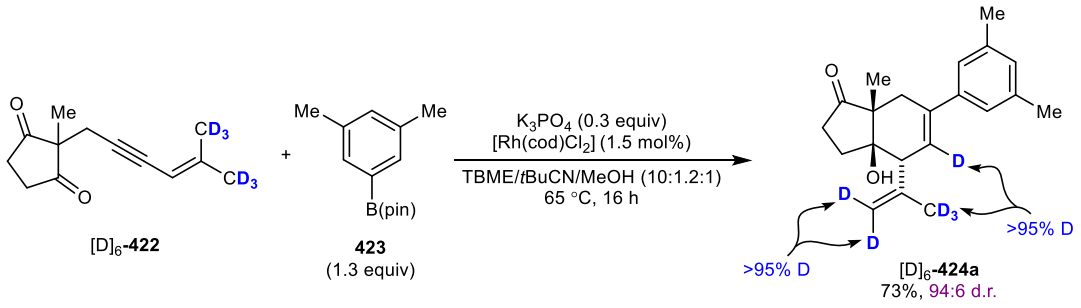
Scheme 127 – Mechanism for 1,4-Rh(I) migration

To provide evidence that the suggested 1,4-migration in this reaction proceeds *via* the route described above, (*E*)-**447a** was exposed to the reaction conditions (Scheme 128). No reactivity was observed, which suggested that there is a requirement for *cis*-allylic hydrogens to be present in the starting material so that formation of cyclic intermediate **471** is geometrically possible.



*Scheme 128 – Reaction with enynone (E)-**447a***

Reaction of hexadeuterated enynone $[D]_6$-**422** with arylboronate ester **423** gave $[D_6]$-**424a** with greater than 95% deuterium incorporation observed at the alkene C-H of the cyclohexene ring (Scheme 129). This experiment provided further evidence that the migration is indeed proceeding through a closed system and *via* a rhodium (III) hydride intermediate. If it were to proceed *via* the route that has been reported for the rhodium (III) alkenyl-to-allyl migration (see Scheme 45), one would expect there to be only partial deuterium incorporation at the internal alkene site as hydride exchange could occur from an external source.

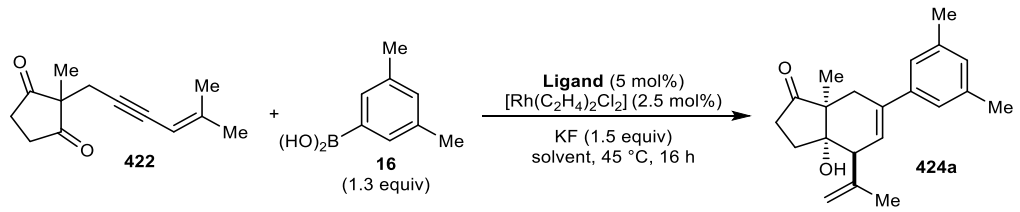


*Scheme 129 – Reaction with enynone $[D]_6$-**422***

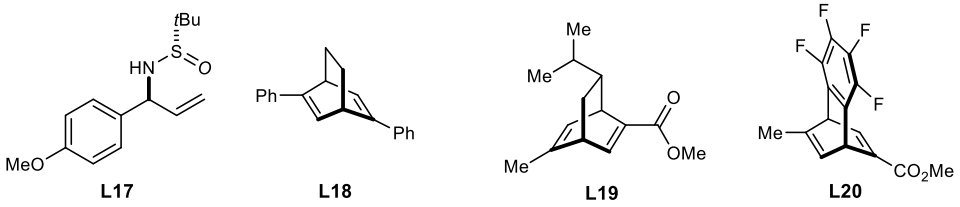
2.1.6 Enantioselective Arylative Allylation

The next logical step for this project was to explore whether an enantioselective variant would be possible. Attempts to develop an enantioselective process using $[Rh(C_2H_4)_2Cl]_2$ and chiral ligands was therefore conducted (*Table 4*). No reactivity was observed using phosphine based ligands, and therefore we investigated using chiral dienes and sulfur-olefin ligands. Over the last 20 years, the application of chiral diene ligands in transition metal catalysis, particularly in enantioselective rhodium-catalysed addition reactions has grown exponentially.[121,122] From this, chiral sulfur-containing olefins have also emerged as a newer class of hybrid ligands.[123] Pleasingly, using both chiral dienes and sulfur-olefin ligands some conversion to the desired product was observed. In all cases, using the more reactive arylboronic acid at lower temperatures over the pinacol esters was required to obtain satisfactory yields and enantioselectivity. After significant ligand screening, the sulfur-olefin ligand **L17** was found to be the most suitable. Although chiral diene ligands **L18**-**L21** (entries 2,3 and 4) also reacted to form **424a** with reasonable diasteroeselectivities and good yields, only moderate enantioselectivities were obtained. Switching the solvent system to THF, where the preference was to form *syn-syn* diastereomer **424b**, lower yields and enantioselectivities were obtained (compare entry 4 and 5). Further sulfur-olefins were also tested in the reaction, but these were significantly worse than **L17**.

Table 4 – Ligand Screening



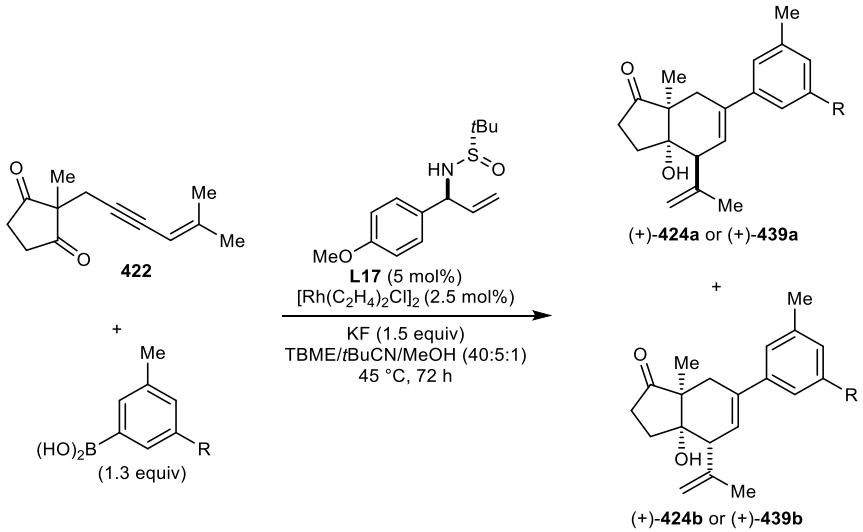
Entry	Ligand	Solvent	NMR Yield[a]	d.r. (**424a**:**424b**)	*ee* of **424a**	*ee* of **424b**
1	**L17**	TBME/*t*BuCN/MeOH (40:4.8:1)	39%	3.5:1	86%	84%
2	**L18**	TBME/*t*BuCN/MeOH (40:4.8:1)	60%	11:1	50%	n.d.
3	**L19**	TBME/*t*BuCN/MeOH (40:4.8:1)	54%	14:1	52%	n.d.
4	**L20**	TBME/*t*BuCN/MeOH (40:4.8:1)	71%	4:1	36%	78%
5	**L20**	THF/MeOH (40:1)	61%	1:3	42%	40%



Reactions performed by B. Partridge. Reactions employed 0.05 mmol of **422**. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reactions. Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [a] NMR yield of major diastereomer

Table 5 shows the isolated yields using the optimised enantioselective conditions. In these cases, the reaction times were increased to ensure good conversion of **422**. Both 3,5-dimethylphenylboronic acid and 3-chloro-5-methylphenylboronic acid gave the arylative allylation product (**424a** and **439a**) in good yield, and good stereoselectivity (entry 1 and 2). Using the commercially available Hayashi diene (**L18**),[124] similar yields could be obtained but the enantioselectivity was significantly lower (entry 3).

Table 5 – Enantioselective Reactions (0.3 mmol scale)



Entry	R	d.r.	Major Isomer (*syn-anti*)	Minor Isomer (*syn-syn*)
1	Me	80:20	61%, 91% ee	11%, 88% ee
2	Cl	78:22	47%, 90% ee	10%, 90% ee
3[a]	Me	83:17	55%, 50% ee	8%, 92% ee

d.r. was determined by analysis of the crude mixture. [a] Using **L18**

The absolute configuration for (+)-**424a** was confirmed by an x-ray crystal structure (Figure 4).

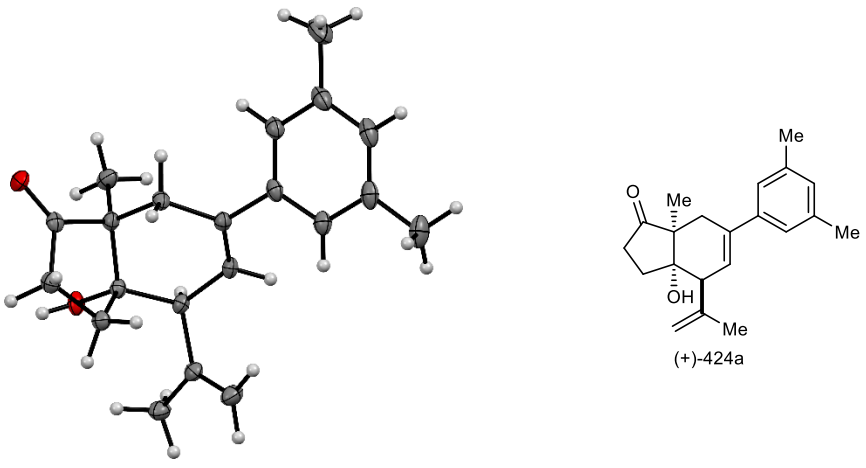
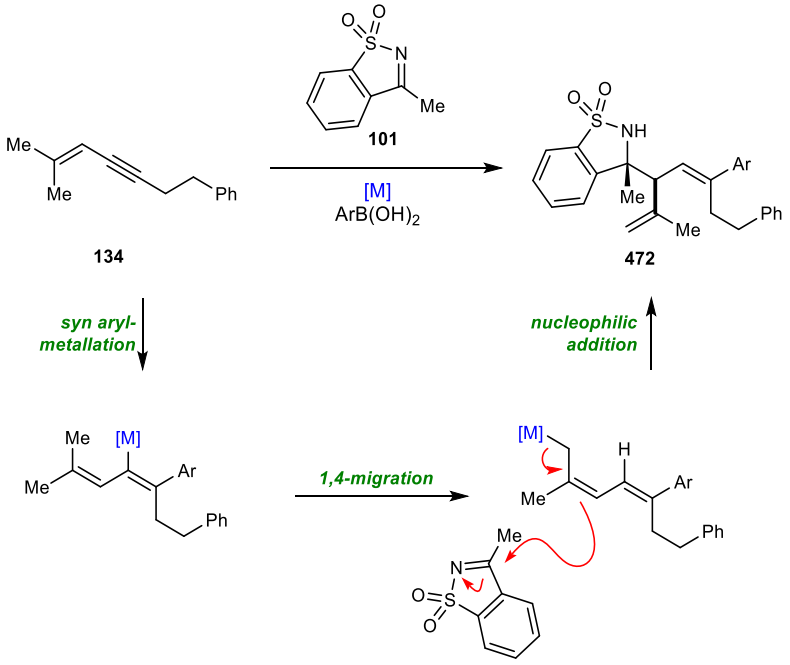


*Figure 4 – X-ray crystal structure of (+)-**424a***

2.2 Three-Component Coupling of 1,3-Enynes, Imines and Arylboronic Acids

Having successfully developed an intramolecular arylative allylation reaction, we were then interested to see whether an intermolecular variant would be possible. A three-component coupling protocol should in theory allow for simpler substrates to be used to rapidly generate structural complexity, and therefore increase the general utility of the process. Within the Lam group, we had previously reported the rhodium catalysed allylation of cyclic imines with allylboronates (see Scheme 59).[75] Therefore, initially the reaction of cyclic ketimine **101**, 1,3-enyne **134**, and 3,5-dimethylphenyl boronic acid, in the presence of a metal catalyst was investigated (Scheme 130). It was hoped that the key steps would proceed similarly to before, with alkyne arylation being followed by 1,4-migration, and subsequent nucleophilic allylation. This would allow the synthesis of cyclic sulfamates such as **472**, which is a group found in many biologically active compounds.[125]



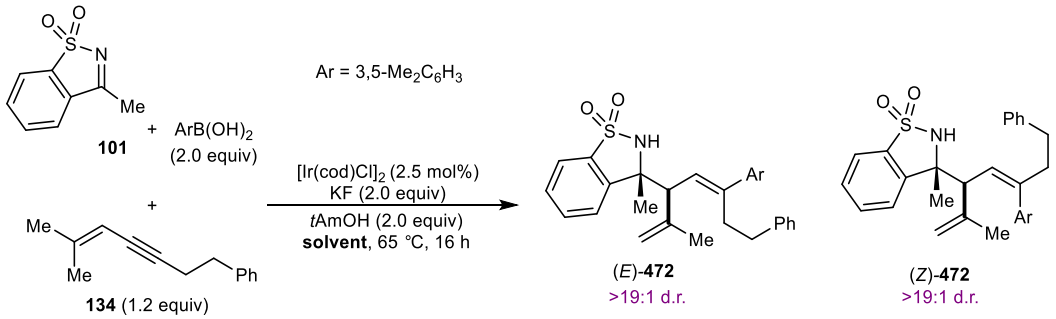
Scheme 130 – Reaction Premise

2.2.1 Reaction Optimisation

Pleasingly, using $[Ir(cod)Cl]_2$ (2.5 mol%), KF as the base, and *t*-amyl alcohol as a proton source in toluene, (*E*)-**472** was observed (17% NMR yield) (Table 6, entry 1). Switching the solvent

to THF and EtOAc resulted in an increase in yield (entries 2 and 3), with THF found to be most suitable. No conversion to (*E*)-**472** was observed using MeCN, DMF or DCE (entries 4, 5 and 6) and only trace product was formed using the alcohol as solvent (entry 7). Similar NMR yields were obtained when [Rh(cod)Cl] was used with THF (entry 8), although this gave a reduction in diasteroeselectivity, and formation of a significant number of unidentified by-products. The *E*/*Z*-isomer (*Z*)-**472** was a consistent side product in these reactions, with the ratio in favour of (*E*)-**472** far greater when using THF or EtOAc with $[Ir(cod)Cl]_2$.

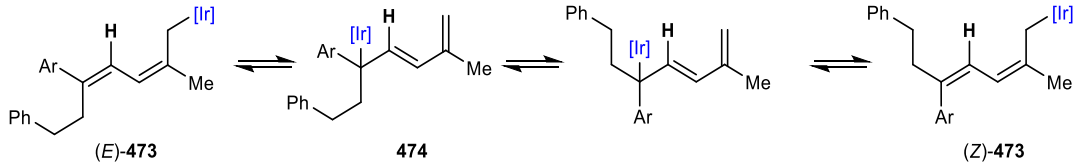
Table 6 – Solvent Screening



Entry	Solvent	NMR Yield of (*E*)-**472**[a]	(*E*)-**472**: (*Z*)-**472**
1	toluene	17	1.5:1
2	THF	44	9.8:1
3	EtOAc	34	7.4:1
4	MeCN	0	-
5	DMF	0	-
6	DCE	0	-
7	*t*AmOH	Trace	-
8[b]	THF	43 (4:1 dr)	2.2:1

Reactions employed 0.05 mmol of **101**. Isomeric ratios were determined by ^{1}H NMR analysis of the crude reactions. [a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] Using $[Rh(cod)Cl]_2$ (2.5 mol%)

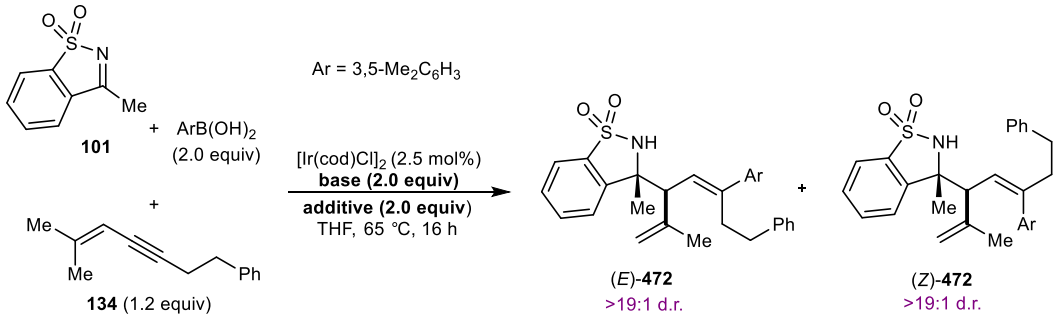
A possible explanation for the formation of (*Z*)-**472** is shown in Scheme 131. After 1,4-alkenyl-to-allyl migration, allylrhodium species (*E*)-**473** is formed. Similarly, to before (see Scheme 116), (*E*)-**473** can undergo a series of allylic 1,3-rhodium transpositions to give allylrhodium **474**. Rotation around the new C-C (sp^3) bond and then subsequent re-isomerisation to (*Z*)-**473** means the new rhodium allyl species will undergo the nucleophilic allylation with imine **101** to give (*Z*)-**472**.



*Scheme 131 – Isomerisation of (Z)-**473***

Using THF as the solvent, screening of bases and additives was then explored (Table 7). KF and $NaHCO_3$ both gave (*E*)-**472** in reasonable NMR yields (entries 1 and 4) with a similar level of isomerised product (*Z*)-**472** observed. Minimal conversion was observed with K_2CO_3 and K_3PO_4 (entries 2 and 3), and no reactivity was found with organic bases such as Et_3N or lutidine (entries 6 and 7). With regards to the proton source, a bulkier alcohol was more favourable with H_2O and MeOH shutting down the reactivity (compare entries 1, 10 and 12 with 8 and 9). Using boric acid as an additive also resulted in lower conversion to the desired compound, although in this case, (*Z*)-**472** was not observed. The presence of both base and an alcohol were crucial for reactivity, with no formation of **472** observed in their absence. Therefore, moving forward, KF was chosen as the base, and *t*AmOH was selected as the proton source, as they offered the greatest yield and selectivity.

Table 7 – Screening of Base and Additives



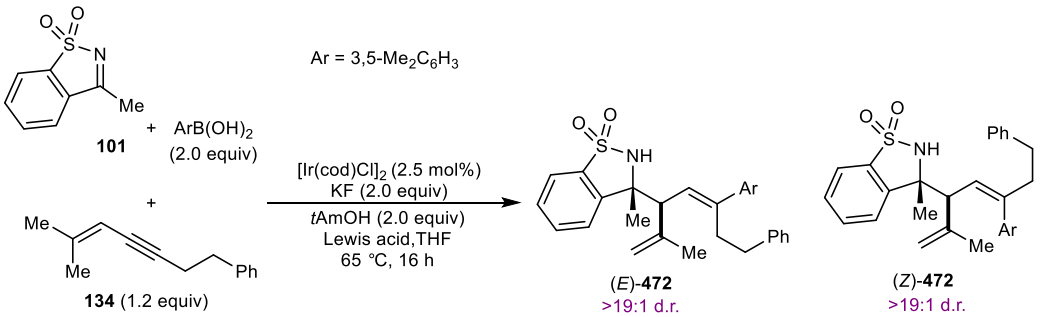
Entry	Base	Additive	NMR Yield of (*E*)-**472**[a]	*E*:*Z*
1	KF	*t*AmOH	44	9.8:1
2	K_2CO_3	*t*AmOH	9	3.3:1
3	K_3PO_4	*t*AmOH	4	2.0:1
4	$NaHCO_3$	*t*AmOH	31	7.3:1
5	CsF	*t*AmOH	0	-
6	Et_3N	*t*AmOH	0	-
7	2,6-lutidine	*t*AmOH	0	-
8	KF	H_2O	0	-
9	KF	MeOH	NR	-
10	KF	*i*PrOH	30	7.3:1
11	KF	*t*BuOH	25	8.5:1
12	KF	phenol	23	5.3:1
13	KF	$B(OH)_3$	16	N/A

Reactions employed 0.05 mmol of **101**. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reactions. [a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Up to this point NMR yields of (*E*)-**472** in excess of 50% had not been obtained. Therefore, a series of Lewis acids were added to see if conversion to (*E*)-**472** could be improved by increasing the reactivity of the electrophile (Table 8). Pleasingly, these resulted in an improvement in conversion in most circumstances, and generally increased the reliability and consistency of the reaction. Using 10 mol% of $ZnCl_2$, the combined conversion to (*E*)-**472** and (*Z*)-**472** was higher, although the selectivity towards (*E*)-**472** decreased (entry 1). Poorer reactivity was observed using $ZnOAc_2$ (entry 2) and $Sc(OTf)_3$ (entry 3); however, with CuCl (entry 3) or $Cu(OTf)_2$ (entry 4), a small increase in the NMR yield of (*E*)-**472** was observed, whilst minimising the presence of (*Z*)-**472**. Increasing the equivalents of $ZnCl_2$ improved reactivity further (entry 6), although similar improvements were not observed when increasing the equivalents of CuCl and $Cu(OTf)_3$ (entries 7 and 8). Using $ZnCl_2$ with

[Rh(cod)Cl]$_2$, high conversion of (*E*)-**472** was observed, although both the diasteroeselectivity and the degree of *E*/*Z* isomerisation was significantly worse. To ensure the increases in reactivity were not a result of the counterion, a reaction using LiCl (1 equiv) instead of a Lewis acid was conducted; however, under these condtions no reaction was observed.

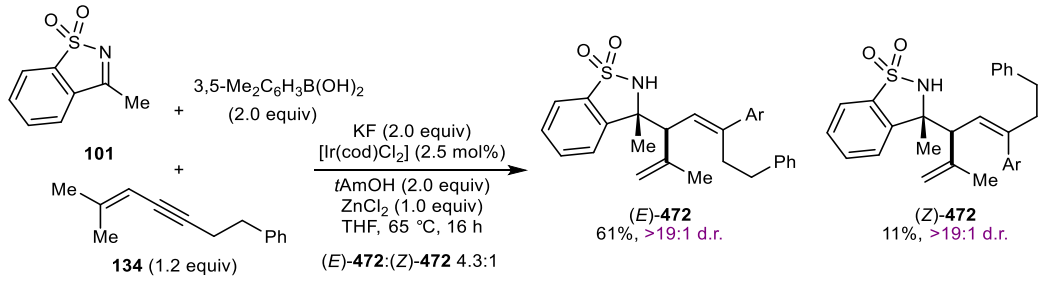
Table 8 – Screening of Lewis Acids



Entry[a]	Lewis acid	Equivalents	NMR Yield of (*E*)-**472**[a]	*E*:*Z*
1	$ZnCl_2$	0.1	42	3.4:1
2	$ZnOAc_2.H_20$	0.1	NR	-
3	$Sc(OTf)_3$	0.1	24	7.7:1
4	CuCl	0.1	50	8.4:1
5	$Cu(OTf)_2$	0.1	54	7.4:1
6	$ZnCl_2$	1.0	51	2.7:1
7	CuCl	1.0	52	5.7:1
8	$Cu(OTf)_2$	1.0	16	ND
9[b]	$ZnCl_2$	1.0	63 (3.5:1 d.r.)	2.0:1

Reactions employed 0.05 mmol of **101**. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reactions. [a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] Using [Rh(cod)Cl]$_2$

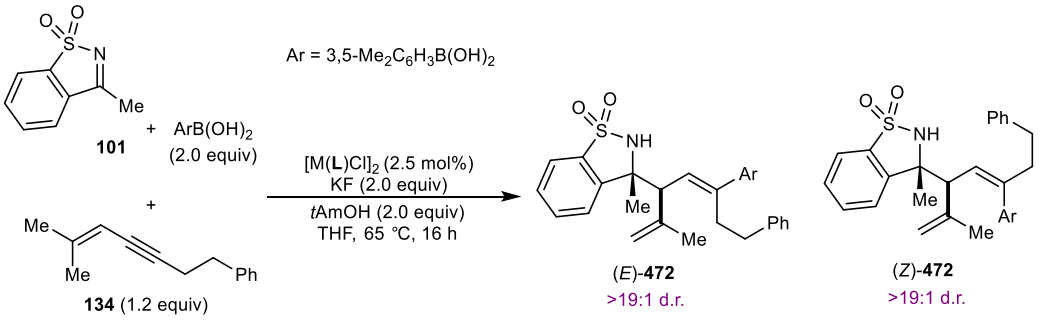
Upon repeating the conditions using 1 equivalent of $ZnCl_2$ on a larger scale (0.30 mmol), (*E*)-**472** could still be isolated in reasonable yield (61%) and diasteroeselectivity (Scheme 132). *E*/*Z* isomerisation still occurred, although a slight improvement in selectivity towards (*E*)-**472** was observed.

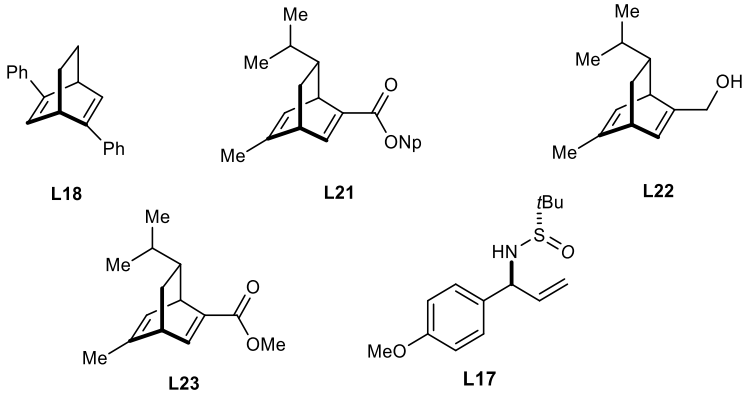


*Scheme 132 – Reaction at 0.3 mmol scale with respect to **101***

We then tried to develop an enantioselective variant of the reaction using ketimine **101** (Table 9). Using $[Ir(coe)Cl]_2$ with chiral diene ligands, no reactivity was observed (entries 1 and 3). However, switching to a rhodium chiral catalyst system, some conversion to (*E*)-**472** was found (entry 2). Using Hayashi ligand (**L18**), (*E*)-**472** was formed in trace amounts and in modest enantioselectivity. Using α-phellandrene-derived ligand **L21** an increase in the yield of (*E*)-**472** was observed along with very high enantioselectivity (entry 4). Further derivatives of this ligand showed limited catalyst activity, although high enantioselectivities were still maintained (entries 5 and 6). Unlike with the previous intramolecular allylation work (see Table 5), chiral sulfur olefin ligands showed no reactivity (entry 7). Addition of $ZnCl_2$ again increased the conversion to (*E*)-**472** with no effect on the enantioselectivity or *E*/*Z* selectivity observed (entry 8).

Table 9 – Ligand Screening



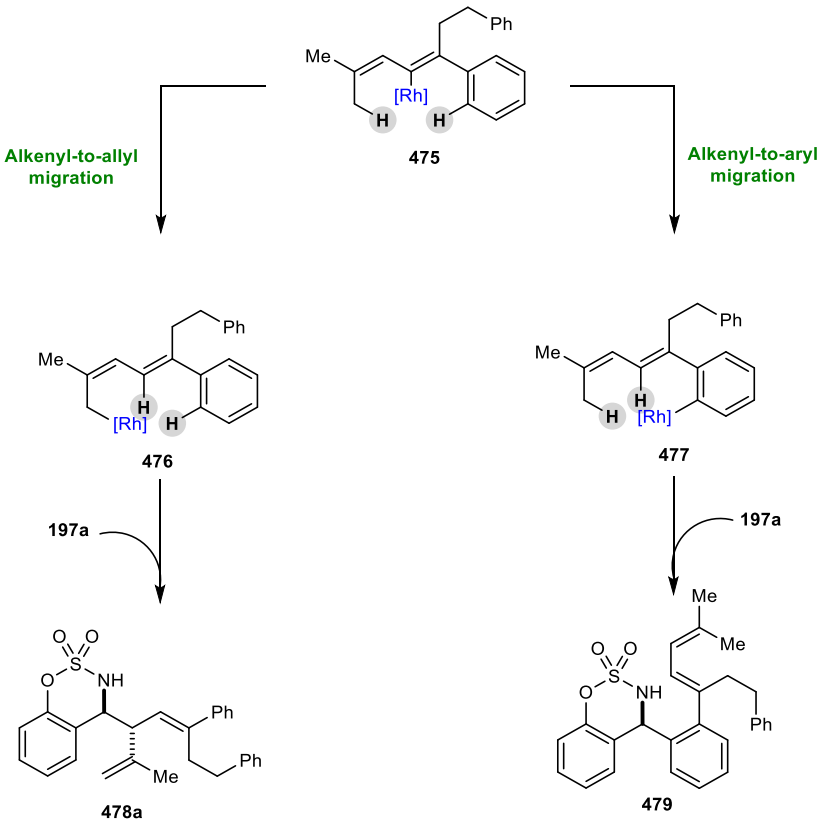


Entry[a]	Catalyst	NMR Yield of (*E*)-**472**[b]	***E*:Z**	*ee* of (*E*)-**472**
1	[Ir(**L18**)Cl_2]	0	-	-
2	[Rh(**L18**)Cl_2]	5	2.3:1	64
3	[Ir(**L21**)Cl_2]	0	-	-
4	[Rh(**L21**)Cl_2]	21 (10:1 d.r.)	2.5:1	90
5	[Rh(**L22**)Cl_2]	<5	ND	91
6	[Rh(**L23**)Cl_2]	<5	ND	98
7	[Rh(**L17**)Cl_2]	0	-	-
8[c]	[Rh(**L21**)Cl_2]	39 (5:1 d.r.)	2.2:1	92

[a] Reactions employed 0.05 mmol of **101**. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reactions. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Using $ZnCl_2$ (1.0 equiv)

With limited success in improving the reactivity using ketimine **101**, further optimisation of the enantioselective process was carried with a more reactive electrophile (aldimine **197a**). At this point, it was also found that phenylboronic acid was tolerated in the reaction, with no product arising from migration to the aryl ring formed. Scheme 133 shows the two possible products that could arise as a result of both migrations. Addition of arylrhodium across the triple bond would form alkenyl rhodium **475**, which could feasibly migrate to

either the allylic carbon, forming allylrhodium **476**, or to the phenyl ring forming arylrhodium **477**. Attack of imine **197a** with **476** or **477**, would then either give you homoallylic amine **478a** or diene **479**. In this chemistry no products resulting from migration to the aryl ring were observed. The preference for products such as **478a**, is most likely a result of steric crowding when forming diene **479** under these conditions**.**

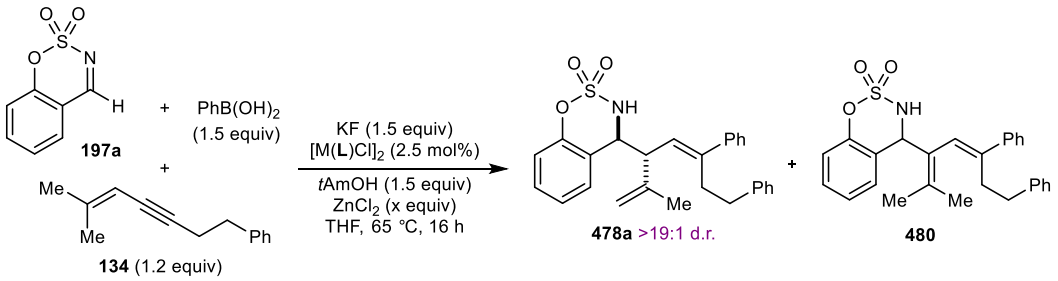


Scheme 133 – Allyl vs Aryl Migration

Similarly to ketimine **101**, aldimine **197** reacted more successfully with [Ir(cod)Cl_2] than [Rh(cod)Cl_2] (Table 10 - entries 1 and 2). Using an achiral rhodium complex, compound **478a** was formed in only 24% NMR yield, along with several side-products. Crude NMR analysis suggested a significant amount of the direct arylation product of imine **197** was present. Switching to [Ir(cod)Cl_2], the NMR yield of **478a** significantly increased, and although pleasingly the product arising from *E*/*Z* isomerisation of the double bond was not observed, conjugated diene **480** was a consistent side-product. This type of compound had not been seen when performing the reaction with ketimine **101.** Total conversion of imine **197** though, to either **478a** or **480**, was very high. Addition of $ZnCl_2$ appeared to improve the selectivity for the formation of **478a** over **480**, although the selectivity between these two compounds

was not always consistent (entry 3). The iridium-catalysed three-component coupling reaction using **197** was also performed at a much larger scale (1.50 mmol), and pleasingly **480** was isolated in a similarly high yield (entry 4).

Table 10 – Catalyst Screening

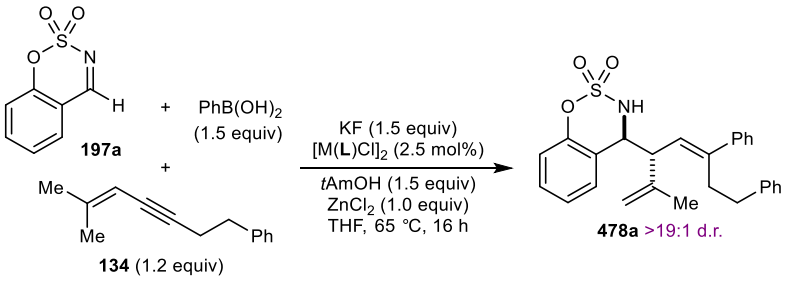


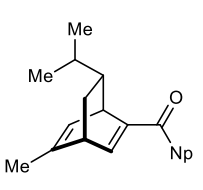
Entry[a]	Catalyst	$ZnCl_2$ (equiv)	NMR Yield of **478a**[b]	NMR Yield of **480**[b]
1	$[Rh(cod)Cl_2]$	0	24	-
2	$[Ir(cod)Cl_2]$	0	53	38
3	$[Ir(cod)Cl_2]$	1	81	19
4[c]	$[Ir(cod)Cl_2]$	1	83[d]	13[d]

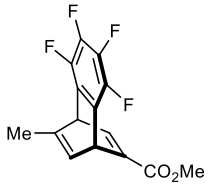
[a] Reactions employed 0.05 mmol of **197a**. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reactions. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] 1.50 mmol of **197a** used. [d] Isolated yield

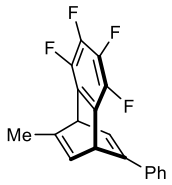
We then explored the development of an enantioselective process for the reaction with **197**. As before, no reactivity could be achieved using an iridium precatalyst ($[Ir(coe)Cl]_2$) with a chiral ligand (*Table 11* - entry 1). However, with $[Rh(C_2H_4)Cl]_2$ and a chiral diene, extremely high enantioselectivities were obtained (entries 2 and 3). Using chiral ligand **L21**, poor catalyst activity was observed (entry 2). However, changing to the electron-deficient tetrafluorobenzobarrelene (tfb) derived ligand **L20,** a very good NMR yield of the desired compound was obtained whilst maintaining high enantioselectivity (entry 7). Additional racemic tfb-derived ligands were tested to see if conversion to **478a** could be increased further. However, in all cases these were inferior to **L20.** Pleasingly, with these rhodium complexes, **480** was not observed at any point.

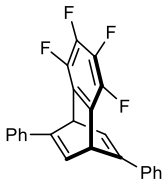
*Table 11 – Ligand Screening using Aldimine **197***

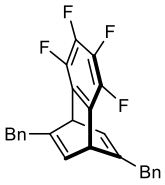


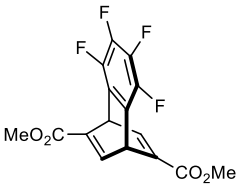

L21


L20


(±)-L24


(±)-L25


(±)-L26

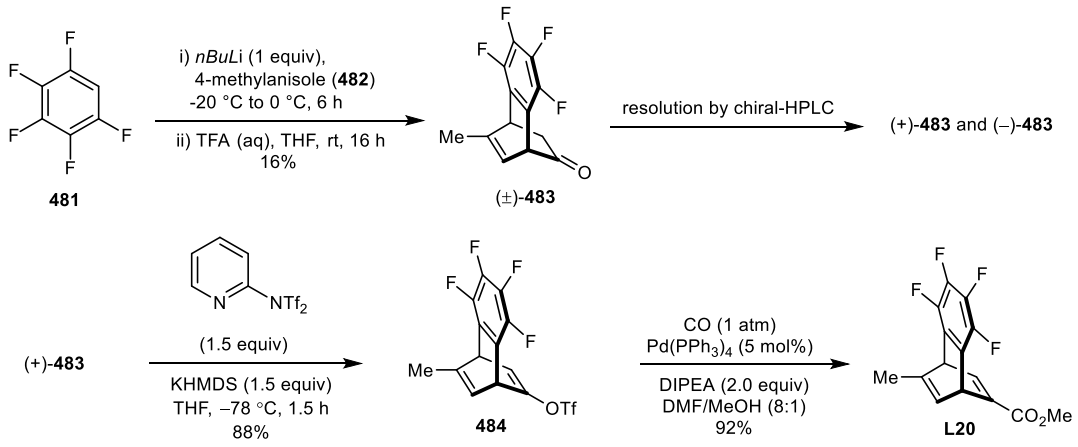

(±)-L27

Entry[a]	[M(**L**)Cl]$_2$	NMR Yield of **478a**[b]	*ee*
1	[Ir(**L21**)Cl]$_2$	0	-
2	[Rh(**L21**)Cl]$_2$	34	99
3	[Rh(**L20**)Cl]$_2$	83	99
4	[Rh(**L24**)Cl]$_2$	22	-
5	[Rh(**L25**)Cl]$_2$	35	-
6	[Rh(**L26**)Cl]$_2$	62	-
7	[Rh(**L27**)Cl]$_2$	53	-

[a] Reactions employed 0.05 mmol of **197a**. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reactions. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

The tetrafluorobenzabarrelene core present in **L20** has been known for a long time, with syntheses for these compounds reported in the 1960's.[126] Owing to their electron-deficient character, these ligands often have a high coordination ability to rhodium or iridium.[127] Therefore, with the expansion of the use of chiral dienes in enantioselective transformations, these ligands have been utilised in a number of transition metal-catalysed reactions.[128] The synthesis of the optimal ligand for this reaction is shown in Scheme 134 and is based on methodology developed by Nishimura.[129] Pentafluorobenzene (**481**), in the presence of a

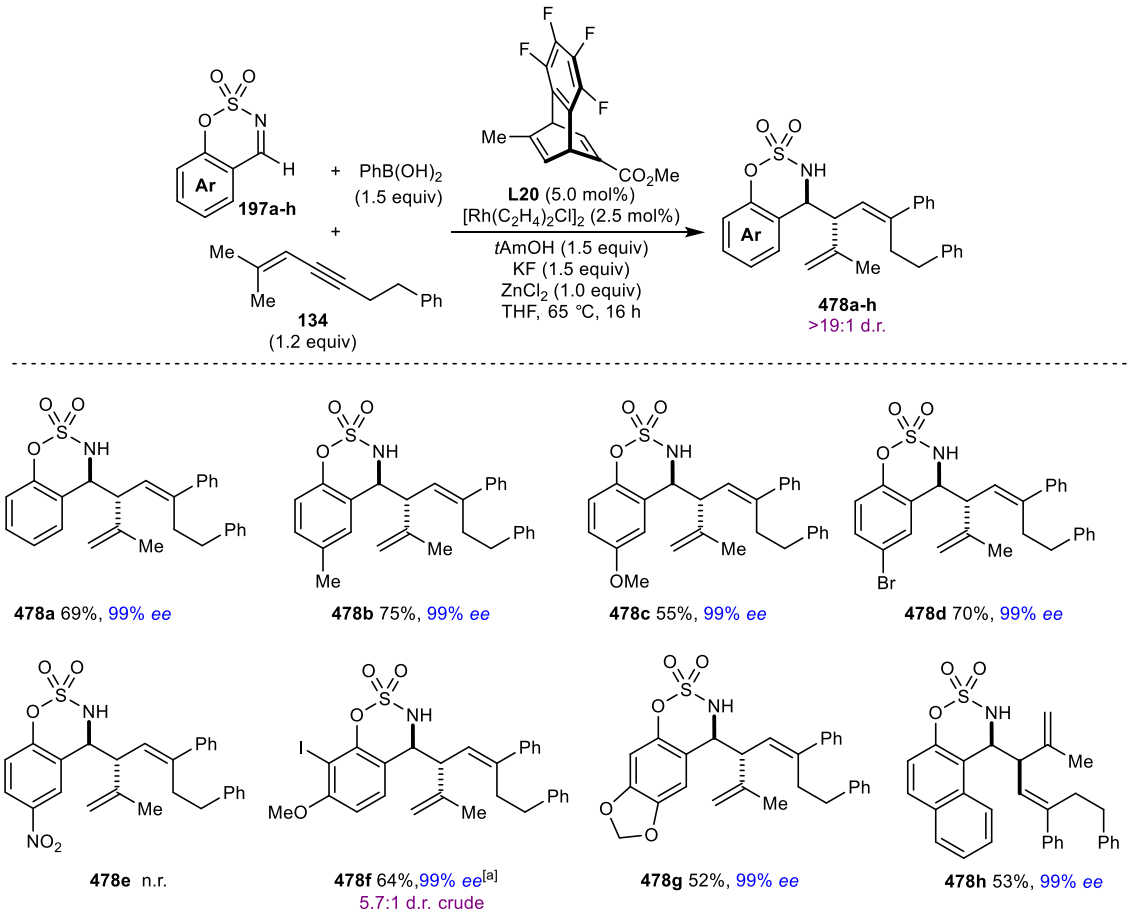
strong base, underwent an elimination reaction to form an aryne. This aryne subsequently reacted with 4-methylanisole (**482**) in a Diels-Alder reaction forming the corresponding enol ether. Upon stirring with trifluoroacetic acid, the enol ether can be converted into racemic ketone (±)-**483**. At this point, the two enantiomers were separated by chiral preparative HPLC to afford the enantiopure ketones. Ketone (+)-**483** was then converted to enol triflate **484** in high yield through use of a strong base and triflating agent. With enol triflate **484** in hand, a range of coupling reactions are possible to synthesise a variety of tfb-ligands. To obtain **L20,** a palladium-catalysed carbonylation reaction was performed on **484** using $Pd(PPh_3)_4$, DIPEA, and MeOH under an atmosphere of carbon monoxide.



*Scheme 134 – Synthesis of **L20***

2.2.2 Reaction of Various Electrophiles

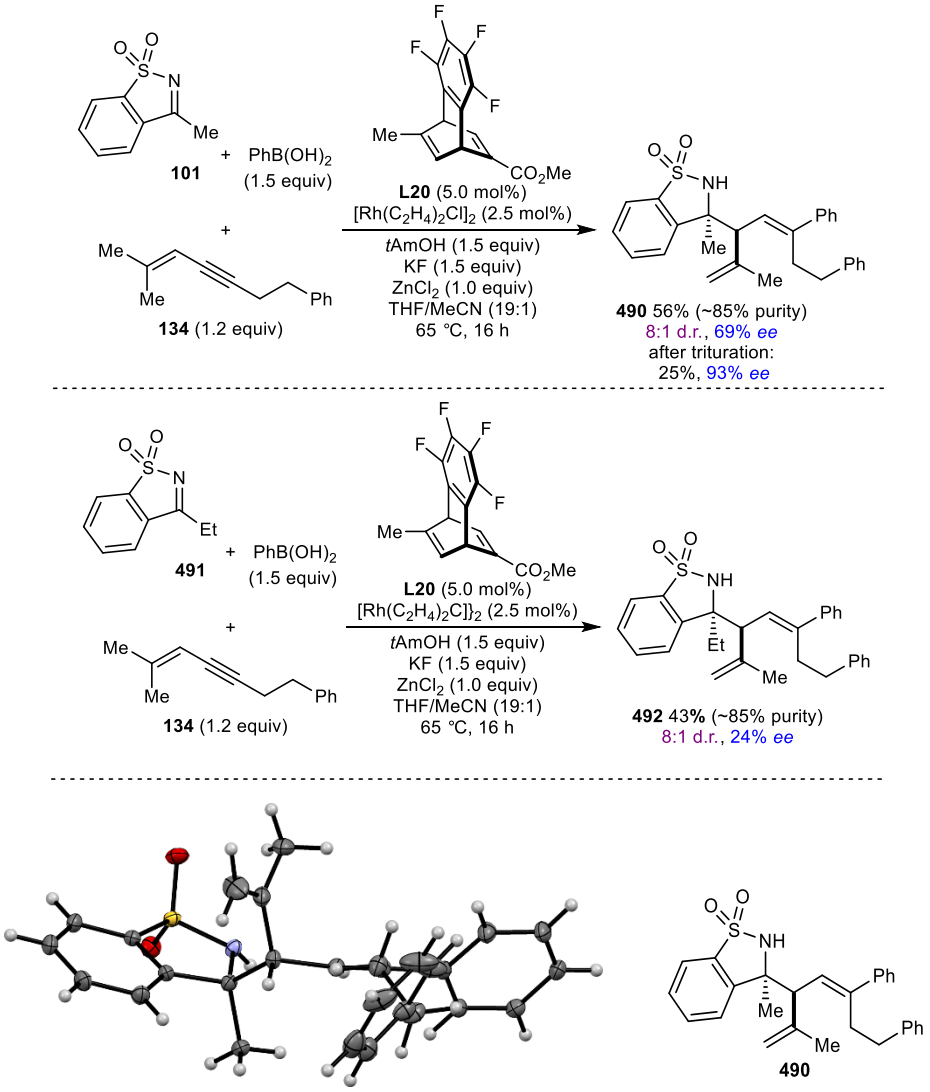
Having optimised conditions for the reaction with substrate **197a**, we then explored reactivity with further aldimines (Scheme 135). Pleasingly, all homoallylic amines were prepared in excellent diastereoselectivity and high enantioselectivity. Various substituents at the 4-position of the benzene ring were tolerated, such as electron-donating methyl and methoxy groups (**478b** and **478c**), as well as a bromide (**478d**). Unfortunately, the presence of a nitro-group completely shut down the reactivity, with only starting materials recovered. 5,6-Disubstituted imine **197f** also reacted smoothly to provide **478f** in high enantioselectivity, although with slightly reduced diasteroeselectivity. Imines **198g** and **198h,** which incorporate a dioxolane ring and naphthyl ring respectively, reacted successfully, with good yields and high enantioselectivities still maintained (**478g** and **478f**).



*Scheme 135 – Reactivity with cyclic aldimines [a] Using 0.20 mmol of imine **197f**.*

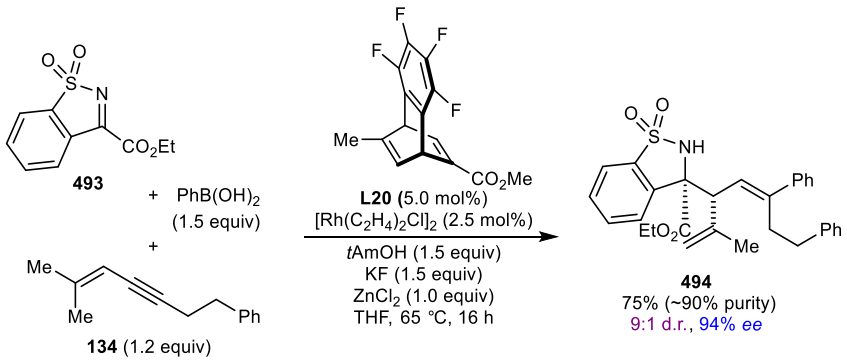
The enantioselective allylation of the less reactive cyclic ketimines was also possible. However, surprisingly, the opposite diastereomer (*anti*-allyl product) was the major diastereomer formed when using **L20**. The absolute configuration for this compound was confirmed by X-ray crystallography (Scheme 136). With THF as the solvent, the *syn*:*anti* selectivity was poor (R = Me 1:1.7, R= Et, 1:3). However, upon addition of MeCN as a co-solvent (THF/MeCN, 19:1), the selectivity towards the *anti*-diasteromer was greatly enhanced (R = Me, Et 1:8) for the synthesis of **490** and **492**. Unfortunately, formation of the *anti*-diastereomer was accompanied by a reduction in enantioselectivity, with especially poor enantioselectivity obtained using ketimine **491**. Unlike in the formation of the *syn*-products, the *anti*-products were not isolated as single compounds after column chromatography. NMR spectroscopy suggested *E/Z* isomerisation had occurred and that products were isolated as a mixture of *E*/*Z* isomers. Sulfamate **490** could be isolated as a single compound in enriched enantioselectivity through trituration of the impure sample with hot toluene and pentane. Unfortunately though, using this method, a significant loss of yield was observed.

The difference in diasteroeselectivity when using ketimines compared to aldimines is attributed to the different geometry of the allylrhodium species undergoing the allylation. With a less reactive electrophile it could be possible that after 1,4-migration and initial formation of the (*Z*)-allylrhodium species, isomerisation to the (*E*)-allylrhodium species occurs (see Scheme 116). If the allylation proceeds *via* a closed 6-membered transition state, the (*E*)-allylrhodium species would react to preferentially form the *anti*-diastereoisomer. Addition of nitrile could favour this isomerisation by slowing down the allylation step, which would explain the enhanced diasteroeselectivity upon addition of this co-solvent. The ability for the rhodium to travel along the conjugated double bond prior to allylation would also explain the presence of *E*/*Z* isomerisation as discussed earlier (see Scheme 131).



Scheme 136 – Reaction with cyclic ketimines

Surprisingly the reaction of a ketimine with an electron withdrawing ethyl ester substituent (**493**), gave allylation product **494** in excellent yield and good stereoselectivity when only using THF as a solvent (Scheme 137). Unfortunately, as before, **494** could not be isolated as a single *E*/*Z* isomer (9:1 *E*/*Z*). The relative configuration for **494** could only be assigned tentatively, as with this substrate, no reaction was found either when using $[Ir(cod)Cl]_2$ or when using THF/MeCN (19:1) as solvent. Therefore, a comparison between the two diastereomers was not possible.



*Scheme 137 – Reaction with ketimine **493***

Other cyclic electrophiles were also investigated, but in most cases no conversion to the allylation products were observed (Figure 5). With ketimines **495** or **496,** which incorporate an additional nitrogen into the heterocyclic ring, only starting materials were recovered. Furthermore, no reaction was observed with ketimines **497** and **498**, with the larger substituents potentially hindering allylation. Isatin-derived substrates **499** and **500**, as well as **501** and **502** appeared to undergo trace conversion to the desired compound by crude NMR analysis, but these compounds were not isolated.

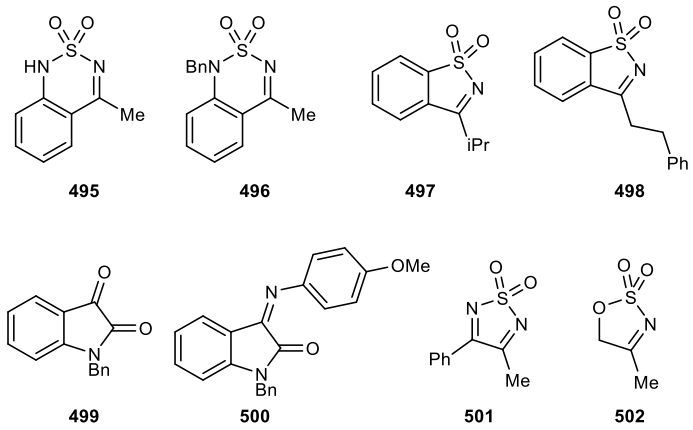
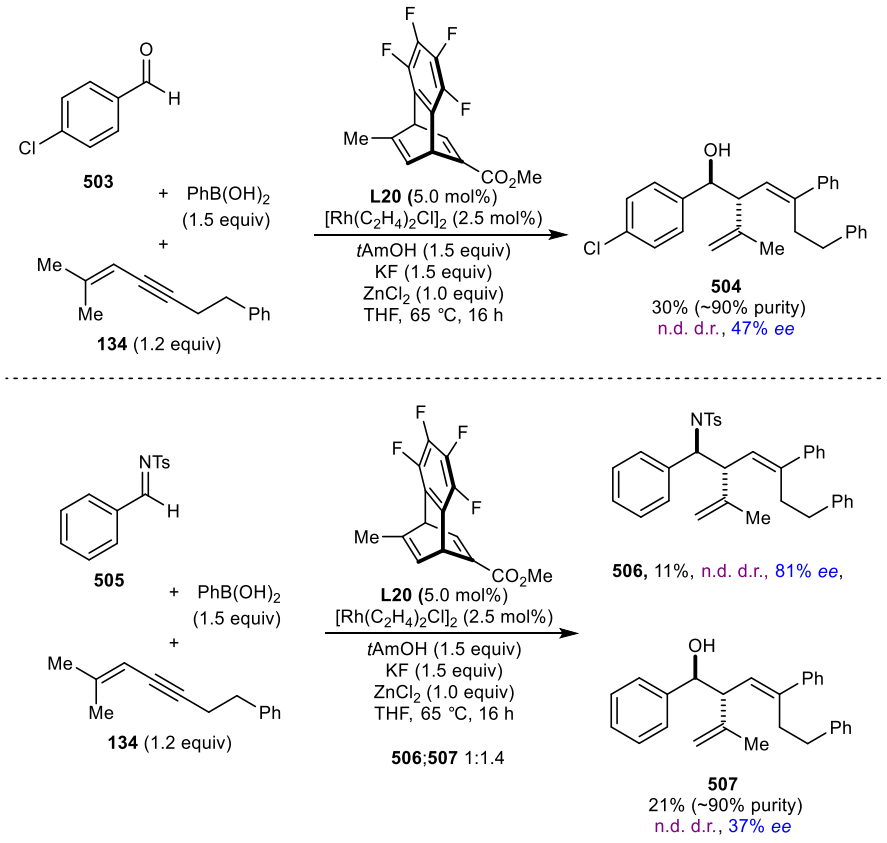


Figure 5 – Attempts to expand electrophile scope further

Up to this point, only the reaction with cyclic imines or **499** and **500** had been attempted. If acyclic electrophiles could be tolerated, this would greatly enhance the utility of the reaction by allowing the use of simpler substrates. Therefore, the reaction with *para*-chlorobenzaldehyde (**503**) and tosyl-imine **505** was investigated. Unfortunately **503** only underwent the allylation in moderate yield, and owing to the complexity of the crude NMR spectrum the diastereoselectivity could not be calculated unambiguously. The enantioselectivity was also poor with **504** being formed in only 30% *ee* (Scheme 138). In the reaction with tosyl imine **505**, two products were isolated. The major product was alcohol **507**, which is most probably formed as a result of hydrolysis of the imine prior to allylation. The expected tosyl amine product **506** was also isolated, although in very poor yield. The higher enantioselectivity of **506** compared to **504** and **505** suggests that the presence of the tosyl-group has a significant effect upon the enantiocontrol.



Scheme 138 – Acyclic electrophiles

Unfortunately, no reactivity was observed with aliphatic aldehyde **508** or acetophenone (**245**) (Figure 6).

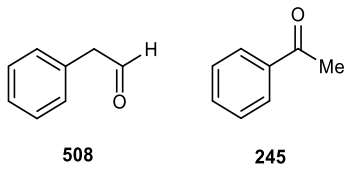
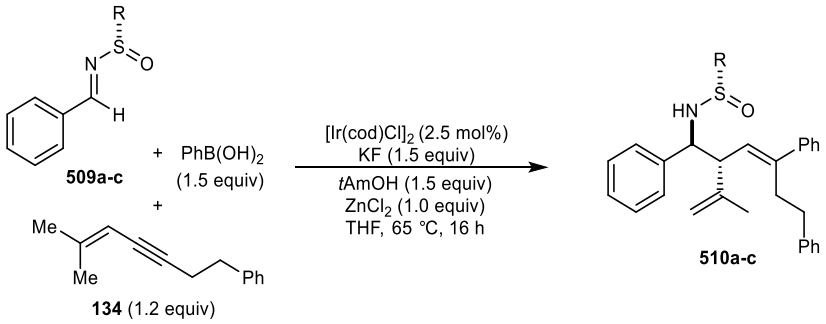


Figure 6 – Further Acyclic Substrates

To try and improve stereoselectivity with acyclic substrates, chiral sulfinamides **509a** and **509b** were synthesised and reacted with enyne **134** and phenylboronic acid. Unfortunately, using an achiral iridium catalyst no conversion to **510** was observed. Attempts to increase the reactivity of the electrophile was made by synthesising chiral sulfinamide **509c**, which incorporates the nonafluorobutane side chain. This group had previously been successfully utilised in several rhodium-catalysed addition reactions.[130] However, in this case, no conversion to the desired compound was observed, with crude NMR suggesting a minor amount of product arising from direct arylation of the imine. The reaction of these substrates using $[Rh(cod)Cl]_2$ and [Rh(*rac*-**L20**)Cl]$_2$ in place of $[Ir(cod)Cl]_2$ was also performed, but similar results were obtained.

Table 12 – Reaction with Chiral Sulfoximines

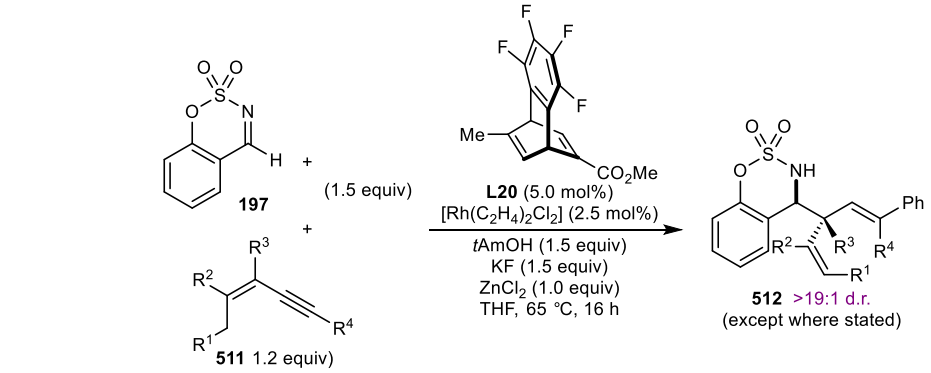


R	NMR Yield of 510[a]
*t*Bu (**509a**)	0
p-tolyl (**509b**)	0
C_4F_9 (**509c**)	0

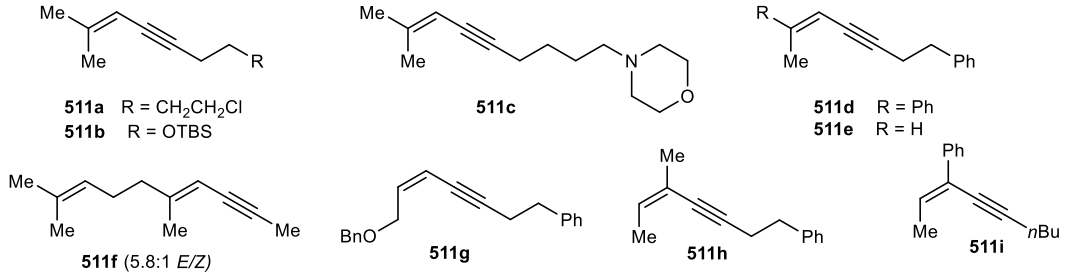
Reactions employed 0.05 mmol of **509**. [a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

2.2.3 Reaction of Various 1,3-Enynes

The scope of the reaction with respect to the enyne was then investigated (Scheme 139). The products were again, in most cases, formed in high diastereoselectivities and enantioselectivities. Significant structural diversity in the group attached directly to the alkyne of the enyne was possible, with an alkyl chloride (**511a**) and silyl ether group (**511b**) tolerated. In the case of morpholino-substrate **511c**, high yields and enantioselectivities were obtained, but with slightly reduced diasteroeselectivity. Variation at the group *trans* to the alkyne was also possible. Enyne **511d**, which has a phenyl group *trans* to the alkyne reacted in good yield and stereoselectivity, although to form appreciable yields of **512d** additional equivalents of phenyl boronic acid were added. Interestingly a 1,3-enyne with no substitution *trans* to the alkyne (**511e**) was unreactive, with only starting materials recovered. However, switching to an achiral iridium catalyst ($[Ir(cod)Cl]_2$), **512e** was formed in high yield (90%). The reason for this difference in reactivity is currently unknown, although with the previous intramolecular allylation, the substrate with a similar substitution pattern to **511e** also showed significantly diminished reactivity (see Scheme 121 – **447a**).Geraniol derived substrate **511f** also reacted in high yield and stereoselectivty. Even though **511f** was synthesized as a 5.8:1 mixture of *E*/*Z* isomers, **512f** was isolated as a single *E*/*Z* isomer. No products from reaction of the *Z*-isomer of **511f** was detected. Pleasingly 1,3-enyne **511g**, which would require migration to a secondary alkyl position, reacted smoothly under the standard conditions to give enol ether **512g** in good yield, although with more modest enantioselectivity. This result was significant, as with the previously described intramolecular arylative allylation (Scheme 121), migration to a methylene group and subsequent allylation had not been possible. 1,3-Enynes **511h** and **511i** could also react to give additional all-carbon quaternary centres. Although methyl-substituted enyne **511h** reacted to give good enantioselectivty, virtually no enantioselectivity was achieved with phenyl-substituted enyne **511i**.



1,3-Enynes



511a R = CH_2CH_2Cl
511b R = OTBS

511c

511d R = Ph
511e R = H

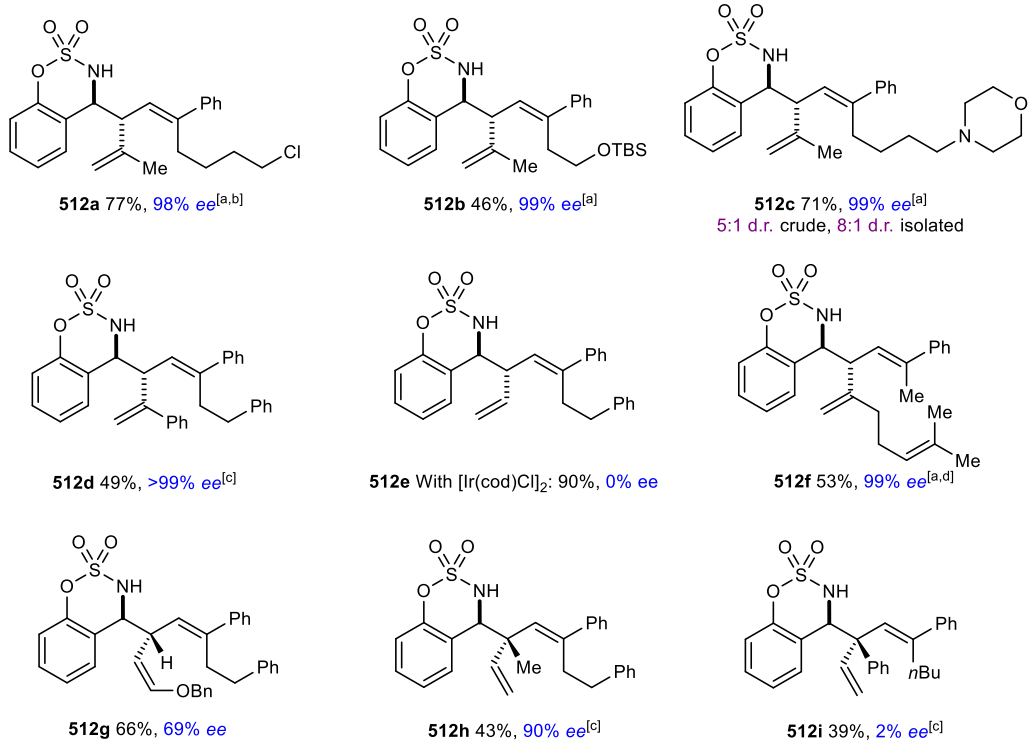
511f (5.8:1 *E/Z*)

511g

511h

511i

Products



512a 77%, 98% *ee*[a,b]

512b 46%, 99% *ee*[a]

512c 71%, 99% *ee*[a]
5:1 d.r. crude, 8:1 d.r. isolated

512d 49%, >99% *ee*[c]

512e With $[Ir(cod)Cl]_2$: 90%, 0% ee

512f 53%, 99% *ee*[a,d]

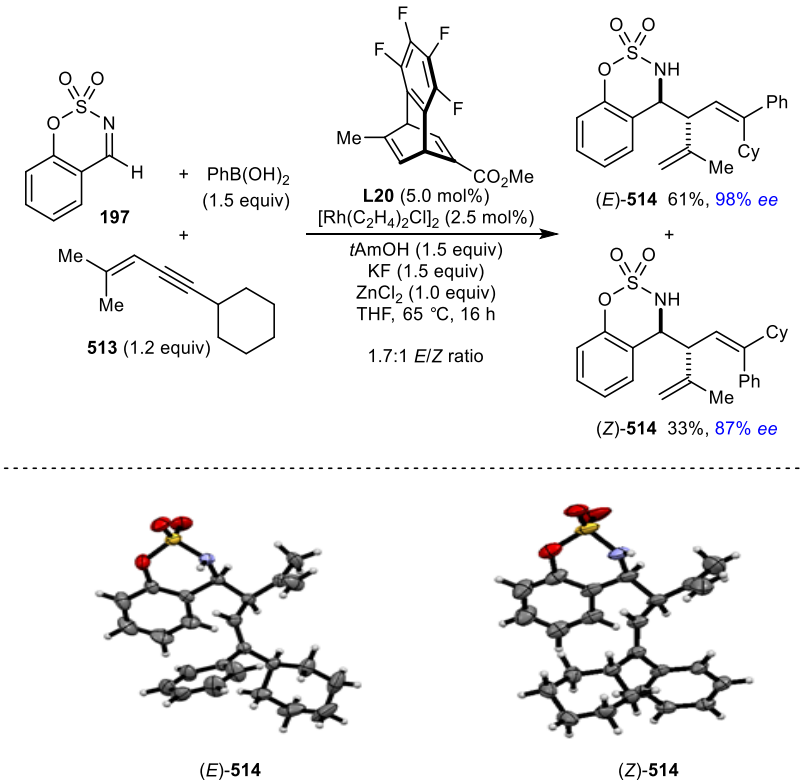
512g 66%, 69% *ee*

512h 43%, 90% *ee*[c]

512i 39%, 2% *ee*[c]

*Scheme 139 – Enyne Scope – [a] Reactions performed by B. Partridge. [b] Using 1.5 equiv of 1,3-enyne **512a**. [c] Using 3.0 equiv each of $PhB(OH)_2$ and tAmOH. [d] Using 1.5 equiv of 1,3-enyne **512f** and 2.0 equiv each of $PhB(OH)_2$, KF, and tAmOH.*

With enyne **513**, a substrate that contains a secondary alkyl group tethered directly to the alkyne, two products were isolated (Scheme 140). *E*/*Z* isomers were observed in a 1.7:1 ratio, with the expected product (*E*)-**514** formed as the major isomer. Crystal structures were obtained of both compounds confirming the absolute stereochemistry. The combined yield, as well as the enantioselectivity was very high. Formation of the minor product ((*Z*)-**514**) can be explained by rhodium undergoing a series of 1,3-allylic transpositions allowing free rotation around the carbon-carbon single bond (see Scheme 131). With this substrate, allylation may be slow relative to *E*/*Z* isomerisation, allowing a thermodynamic ratio of products to be formed. The additional size of the substituent attached to the alkyne, could make formation of (*Z*)-**514** more favourable, when compared to the other 1,3-enynes.



*Scheme 140 – Reaction with enyne **513***

Figure 7 shows further attempts to increase the substrate scope for the 1,3-enyne. However, in all cases, no conversion to the target compounds were observed. The presence of a hydroxyl group (**515**) or bulky silyl group (**516**) tethered to the alkyne, resulted in no reaction. Having been able to successfully migrate rhodium(I) to a methylene position (see **512g**), it was hoped a more diverse range of migrations would be possible. However, enynes **517** and **518** were completely unreactive and only trace conversion was observed with **519** and **520**. This outcome suggested an activated C (sp^3) centre was a prerequisite for any migration to

occur. The main limitation with regards to the enyne is the need for an alkyl group to be attached directly to the alkyne. This substitution pattern is important, as it allows the initial migratory insertion step to proceed in high regiochemical control with rhodium situated at the carbon proximal to the alkene.

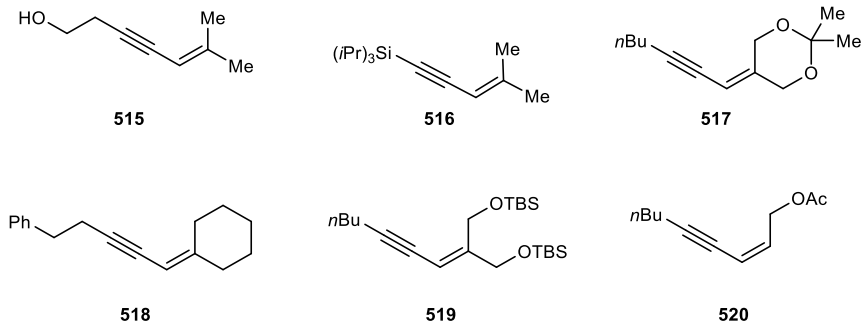
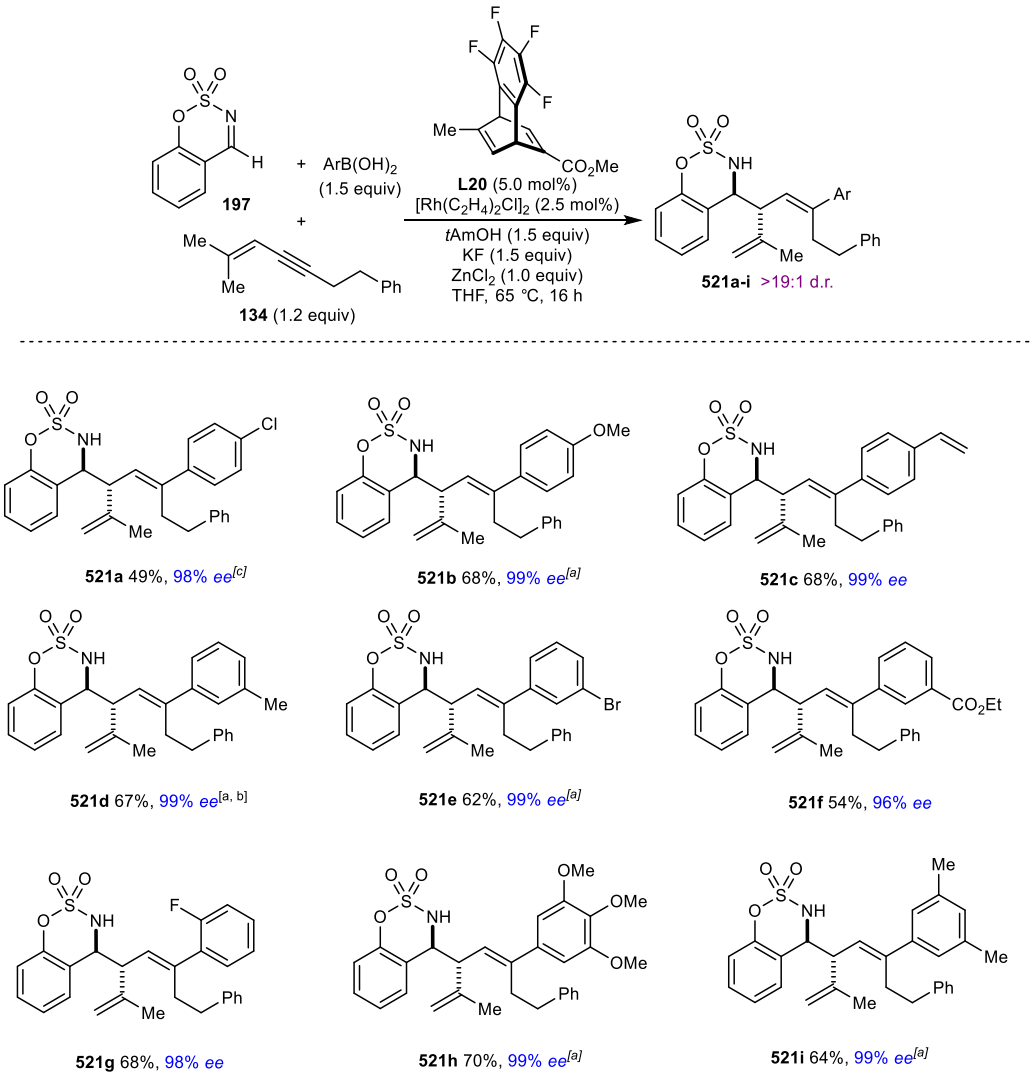


Figure 7 – Attempts to increase enyne scope

2.2.4 Reaction of Various Arylboronic Acids

Scheme 141 shows the scope of the arylboronic acid for the three-component coupling process. A range of arylboronic acids successfully underwent the reaction to give products in very high enantio- and diastereoselectivities. The reaction is highly tolerant of *para*-substituted aryl reagents, with substrates containing halides (**521a**), methoxy groups (**521b**) and olefins (**521c**) reacting to give good yields. *Meta*- and *ortho*-substituted boronic acids also reacted well, with **521d**, **521e, 521f** and **521g** achieved in excellent yields and enantioselectivities. Multisubstituted arylboronic acids also underwent the reaction, forming **521h** or **521i**, although when using 3,5-dimethylphenylboronic acid and 3,4,5-trimethoxyphenylboronic acid, the products from direct arylation of the aldimine were observed in small quantities (<15% NMR yield). Therefore, from this table, we have demonstrated that a range of substitution patterns around the aromatic ring is feasible using this chemistry. Owing to the wide range of functional groups incorporated in the final compounds, these products would readily allow for further product manipulations.



*Scheme 141 – Boronic Acid Scope – [a] Reaction performed by B. Partridge. [b] Using 1.5 equivalents of **134.** [c] Isolated in 91% purity – yield has been adjusted.*

A crystal structure was obtained of product **521i** to confirm the absolute stereochemistry drawn (Figure 8).

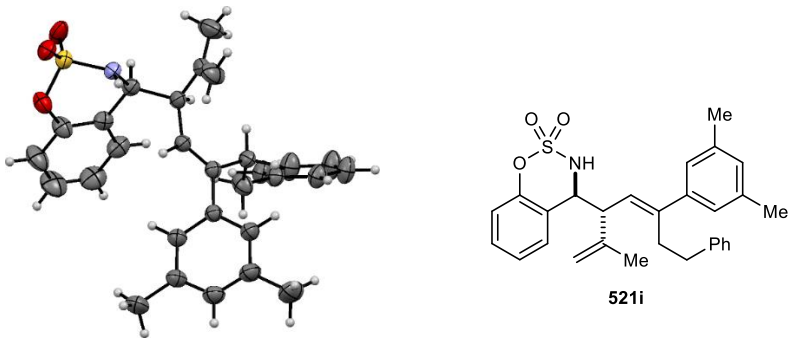
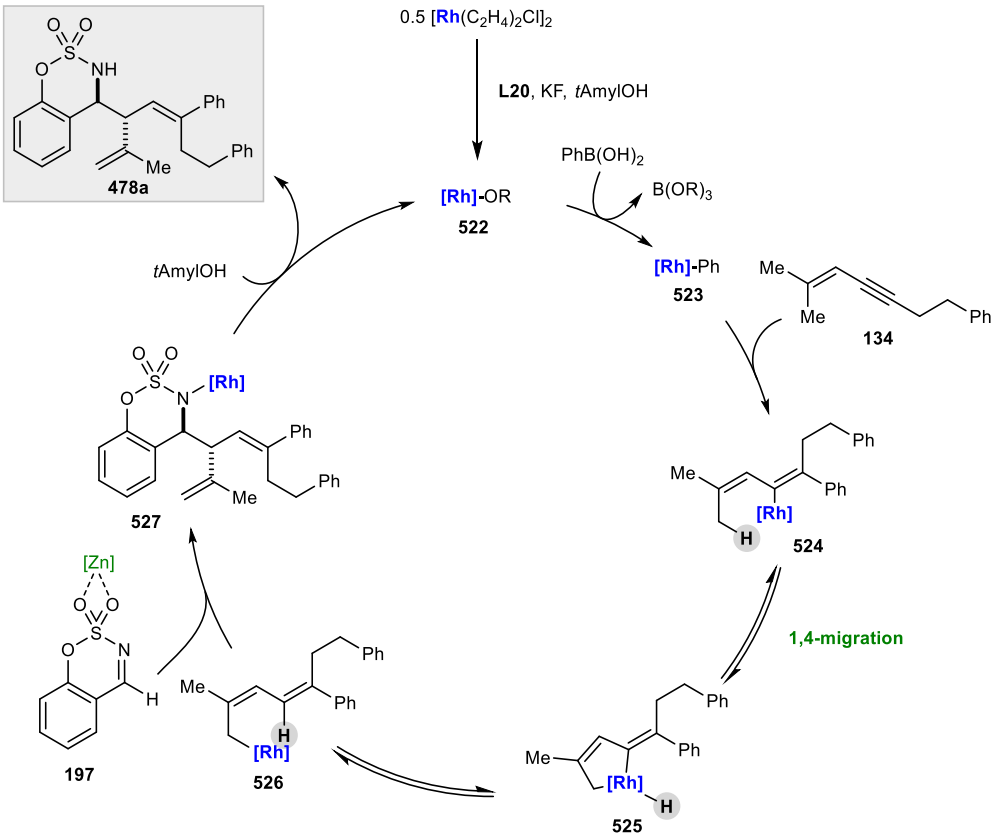


*Figure 8 – X-ray structure of **521i**. Crystal obtained by B.Partridge*

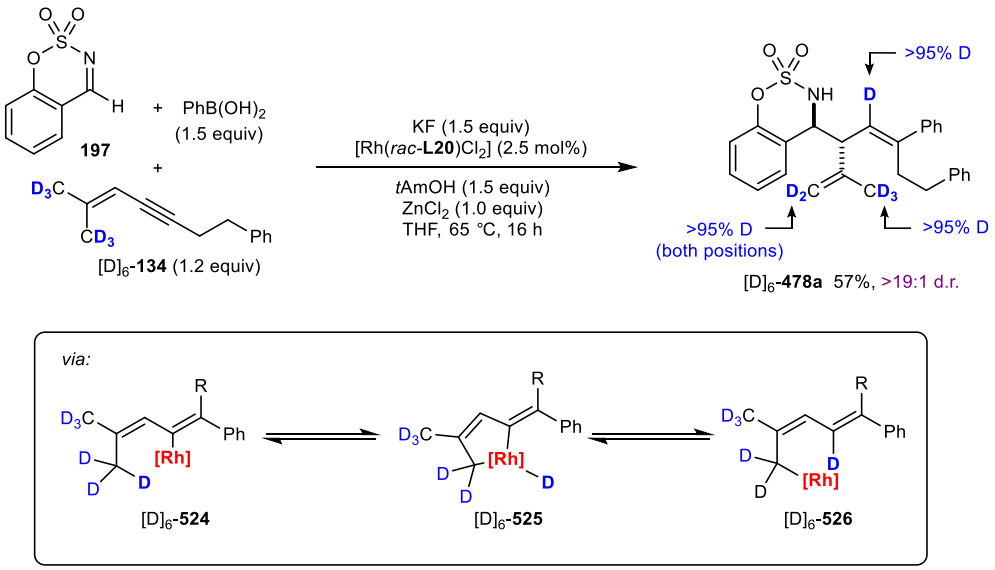
2.2.5 Mechanism

A proposed catalytic cycle to account for the formation of the products is shown in Scheme 142. This cycle is very similar to that of the intramolecular arylative allylation reaction (Scheme 115). After formation of initial rhodium complex **522** from $[Rh(C_2H_4)Cl]_2$ and **L20**, transmetalation with the arylboronic acid occurs to give arylrhodium species **523.** Intemediate **523** can then undergo a migratory insertion with **134** to give alkenylrhodium species **524**. At this point, migration of rhodium to the aryl ring or the allylic carbon is possible. If rhodium migrates from the vinyl position to the aryl ring, it is believed the resulting arylrhodium species is too sterically hindered to react with imine **197**. The reversibility of this alkenyl-to-aryl rhodium migration means that **524** can be regenerated. A 1,4-alkenyl-to-allyl rhodium migration can then take place to give allylrhodium species **526**. Intermediate **526** reacts with imine **197** in a nucleophilic allylation reaction, with protonolysis of **527** releasing the product, and regenerating the catalyst (**522**). The role of $ZnCl_2$ in this catalytic cycle is not currently known. $ZnCl_2$ could potentially improve the catalyst turnover, accelerate allylation through Lewis acid activation, or enhance the ability for the arylboron species to undergo transmetalation.



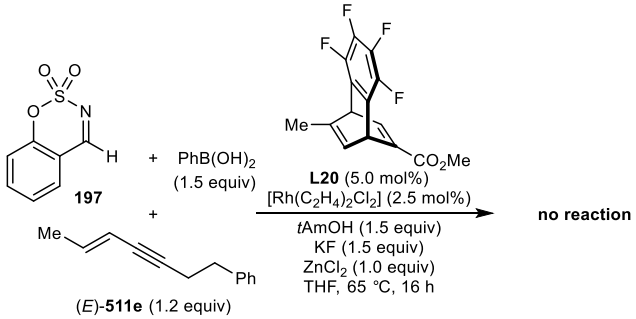
Scheme 142 – Catalytic Cycle

To see if the rhodium(I) 1,4-migration was proceeding *via* a similar mechanism as discussed earlier (see Scheme 127), imine **197**, was reacted with hexadeuterated 1,3-enyne $[D]_6$-**134** under the standard conditions (Scheme 143). Complete deuterium transfer was observed to the trisubstituted alkene. This evidence suggests migration is occurring *via* a Rh(III)-D cyclic intermediate ($[D]_6$-**525**) in an oxidative addition/reductive elimination process.



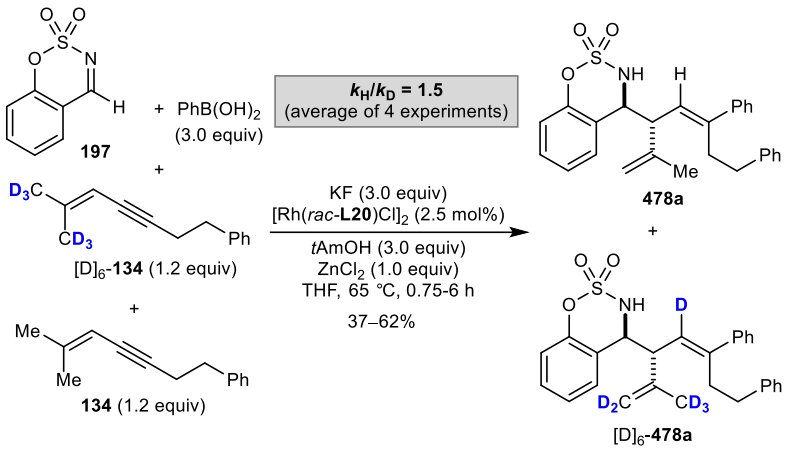
*Scheme 143 – Reaction with [D]$_6$-**134***

The standard conditions were also used with 1,3-enyne (*E*)-**511e** (Scheme 144). If migration was occurring *via* cyclic intermediate **525**, the geometry of the alkene would prohibit migration to the allylic C-H bond and therefore allylation of imine **197** would not be possible. Pleasingly, no reaction was found using this enyne, providing additional evidence that the migration is occurring as hypothesised.



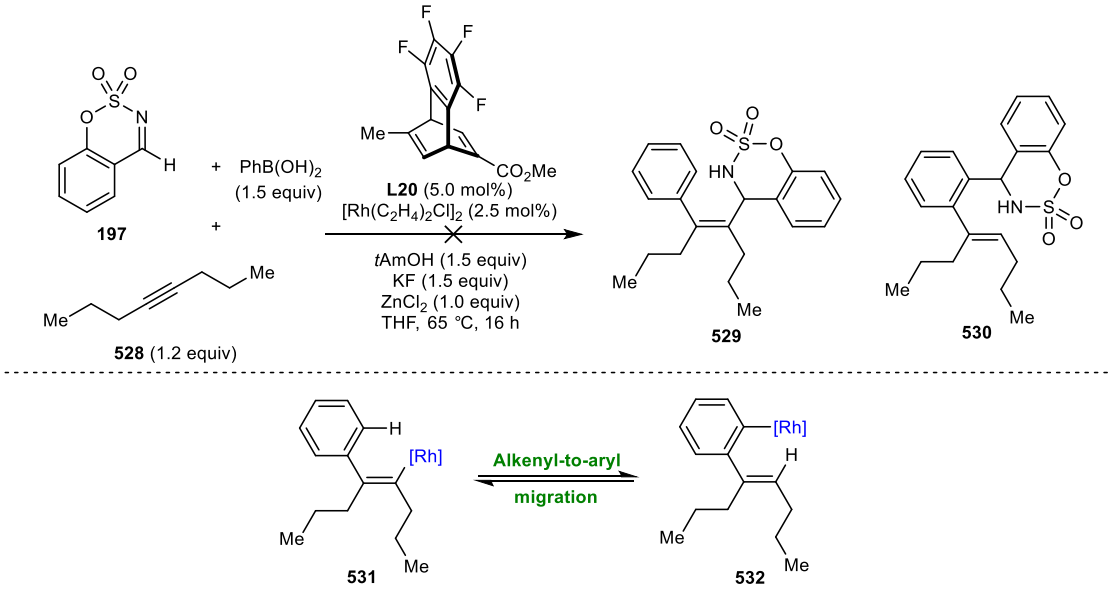
*Scheme 144 – Reaction with (E)-**511e***

To gain additional understanding of the mechanism, attempts were made to measure the kinetic isotope effect (KIE). In an intermolecular competition reaction between enynes **134** and [D]$_6$-**134**, a value of 1.5 for k_H/k_D was obtained (Scheme 145). This value suggests that there is a kinetic isotope effect present.[131,132] Attempts to measure the individual rate constant for enynes **134** and [D]$_6$-**134** in separate experiments were unfortunately not successful due to the heterogeneous nature of the reaction mixture. Therefore, at this time, it is not possible to establish conclusively whether alkenyl-to-allyl 1,4-rhodium(I) migration is the turnover-limiting step.



Scheme 145 – Intermolecular Competition Reaction

In the catalytic cycle shown in Scheme 142, insertion of the triple bond into arylrhodium **523** gave alkenylrhodium **524**. We were therefore interested to investigate whether, in the case where migration of rhodium to an allylic position was not possible, alkenylrhodium **531** or arylrhodium species **532** could be trapped by aldimine **197**. Therefore, the reaction between 4-octyne (**528**), imine **197** and phenylboronic acid was investigated using the standard conditions. (Scheme 146). Unfortunately, no products arising from vinyl addition (**529**), or aryl addition (**530**) were observed. 3,5-Dimethylphenylboronic acid, which would inhibit migration to the aryl ring, was also used in place of phenylboronic acid. However, again conversion to either types of products were not seen.



*Scheme 146 – Reactivity with 4-Octyne (**528**)*

A possible stereochemical model to account for the observed absolute stereochemistry is shown in Figure 9. The nucleophilic allylation is the stereochemical defining step of the reaction cycle. It is again proposed the reaction proceeds *via* a closed six-membered transition state, as with other rhodium-catalysed allylation reactions. The absolute stereochemistry can be rationalised by coordination of imine **197** to the rhodium complex occurring in a way as to minimize steric interactions with the Me (or ester) substituent on the ligand (**TS9**). With the other enantiomer of the ligand, unfavourable interactions would be present between the methyl group of the allylrhodium and sulfonyl group of the electrophile, and the substituents of the ligand.

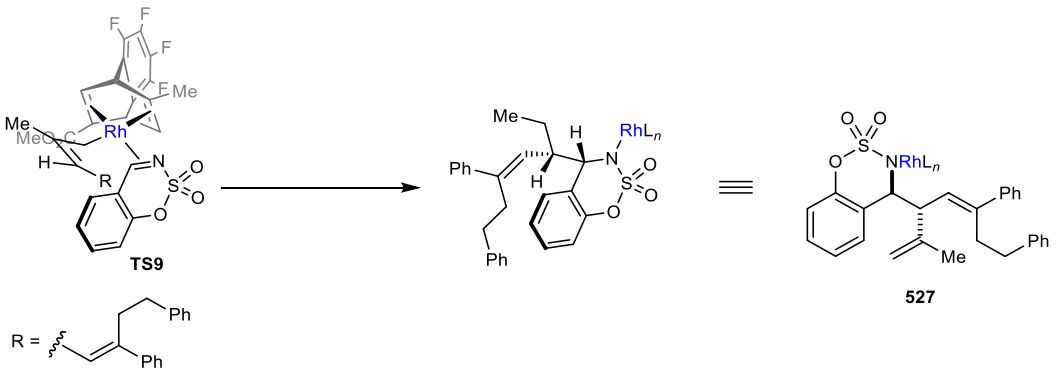
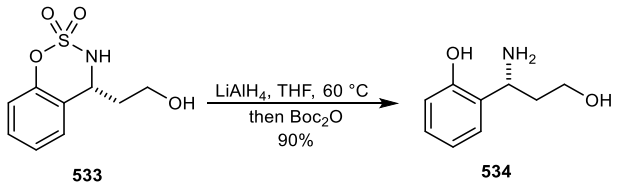


Figure 9 – Stereochemical Model

2.3 1,5-Functionalisation of 1,3-Enynes

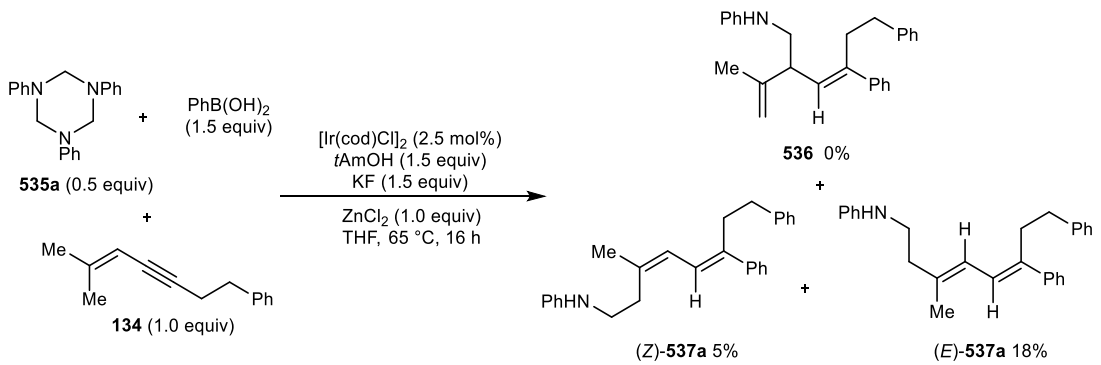
Having successfully developed a three-component coupling process, primarily utilising cyclic sulfamate substrates, we were interested in further developing the scope with respect to the electrophile. Although the Lam group has previously shown that the sulfamate group can be be readily cleaved using $LiAlH_4$ (Scheme 147),[133] the ability to use other substrates would greatly increase the utility of the reaction by limiting the need to incorporate the sulfamate group in the final compounds.



*Scheme 147 – Cleavage of sulfamate group of **533** to hydroxyamine **534** (Lam 2012)*[134]

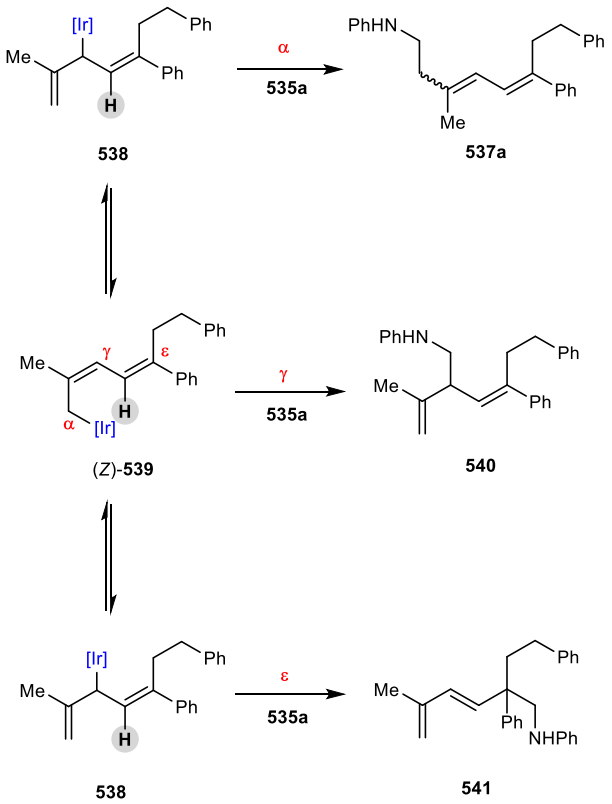
Krische and co-workers have previously reported using stable 1,3,5-tris(aryl)-triazinanes as formaldimine C1 precursors in a number of different reactions.[135, 136] These substrates can be readily prepared from paraformaldehyde (or aqueous formaldehyde) and the corresponding aniline.[137]

Therefore, based on the previous success of these electrophiles as aminomethylation reagents, we used triazinane **535a** under the standard iridium-catalysed three-component reaction conditions (see Table 10-Entry 3). Interestingly, the expected branched allylation product **536** was not obtained. Instead, product **537a** was observed as a mixture of *E*/*Z* isomers.



*Scheme 148 – Reaction with 1,3,5-triazinane **535a**. Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.*

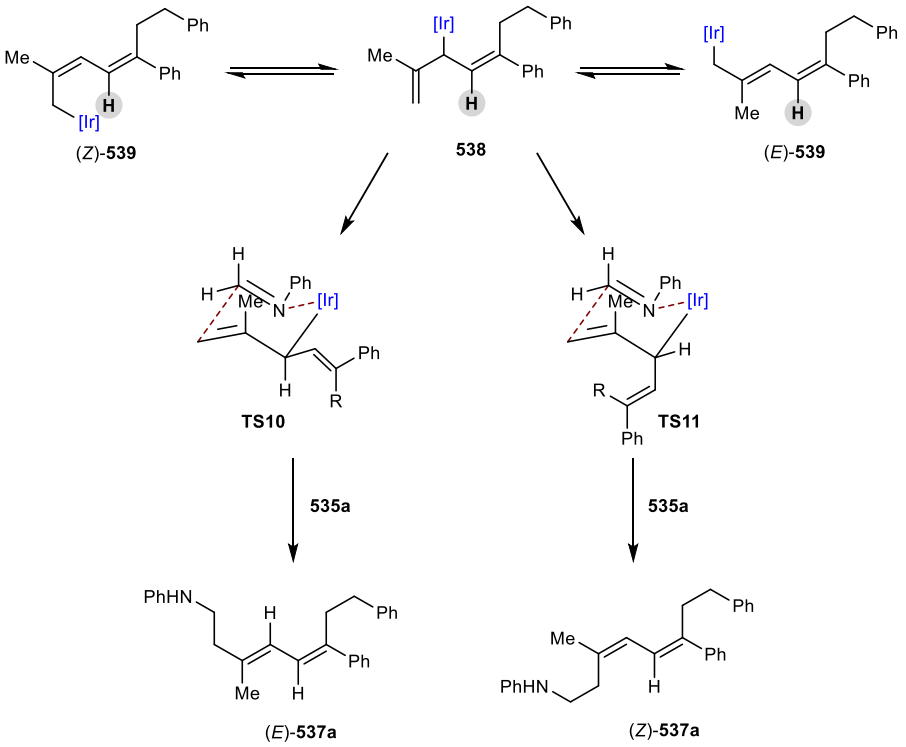
At this point, only a speculative reason for the difference in reactivity can be made with these electrophiles. Theoretically, after allylrhodium species **539** is generated from the alkenyl-to-allyl metal migration, allylation from three positions is possible (Scheme 149). ε-Allylation, which would give products such as **541**, has not been observed previously irrespective of the substrate used. These products may be disfavoured due to the sterically crowded nature of the product. When using cyclic sulfamates, such as **197**, γ-allylation is favoured, giving branched products similar to **540**. Therefore, it is hypothesised that with electrophiles such as **535a**, allylation is occurring *via* the secondary allylmetal species **538**, and a six-membered transition state.



Scheme 149 – Possible sites for allylation

Allyiridium (*Z*)-**539** formed directly after alkenyl-to-allyl migration could feasibly isomerise to either **538** or (*E*)-**539** (Scheme 150). However, the exclusive formation of the linear products with substrate **535a** would suggest allylation with **538** proceeds *via* a transition state which is significantly lower in energy than the corresponding allylation with (*Z*)-**539**. The preference for (*E*)-**537a** over (*Z*)-**537a** can be rationalised by cyclic transition states **TS10** and **TS11**. In the absence of substitution on the electrophile, the allyl fragment most likely takes precedent in controlling the energies of the transitions states. With **TS10**, the larger

substituent is in an equatorial position, as opposed to axial with **TS11**. When the alkene substitutuent is equatorial, presumably the potential interactions with the cod ligand are minimal, which would explain the higher selectivity towards (*E*)-**537a**. The low level of selectivity though would suggest the difference in energies of **TS10** and **TS11** is not substantial.



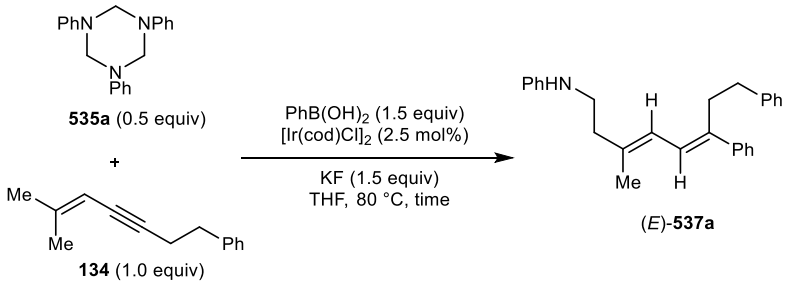
*Scheme 150 – Rationalising the E/Z selectivity for **537a***

2.3.1 Optimisation

Initial optimisation for the reaction showed that $ZnCl_2$ and *t*AmOH were unecessary for the conversion to **537a**. Pleasingly, increasing the temperature from 65 °C to 80 °C increased the NMR yield to 32% (Table 13 - entry 1). However, under these conditions the reaction proceeded very slowly, with further conversion only possible by extending the reaction time (compare entries 1, 2 and 4). The improvements in yield with increasing reaction time diminished after more than 3 days of heating at 80 °C. With regards to the catalyst, increasing the catalyst loading did not result in an increase in NMR yield (entry 3), and changing the pre-catalyst to [Rh(cod)Cl_2] or [Rh(*rac*-**L20**)Cl_2] resulted in poorer reactivity (entries 5 and 6). The *E*/*Z* isomeric ratio when using [Rh(cod)Cl_2] was much worse in

comparison to the iridium catalysts, whilst changes in the reaction duration or temperature seemed to have little effect on this ratio.

Table 13 – Initial Optimisation

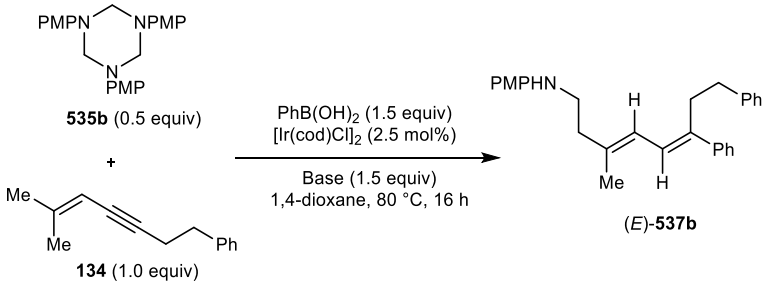


Entry	Catalyst	Time (h)	NMR Yield of (*E*)-**537a** [a]	*E*:*Z*
1	$[Ir(cod)Cl_2]$	16	32	3.5:1
2	$[Ir(cod)Cl_2]$	48	52	3.3:1
3	$[Ir(cod)Cl_2]$ (5 mol%)	48	54	3.4:1
4	$[Ir(cod)Cl_2]$	64	60	3.8:1
5	$[Rh(cod)Cl_2]$	40	26	1.5:1
6	[Rh(*rac*-L**X**)Cl_2]	75	21	ND

Reactions employed 0.05 mmol of **134**. [a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Further optimisation was carried out using the more reactive PMP-substituted triazinane **535b**. This substrate was found to react comparably to **535a**, but over a much shorter reaction time (Table 14- entry 1). 1,4-Dioxane was also chosen in place of THF due to its higher boiling point. Using **535b**, a series of bases were then screened. The reaction tolerated a variety of bases, although much poorer NMR yields were obtained using Et_3N and $NaHCO_3$ (entries 2 and 3). K_3PO_4 as the base resulted in the greatest yields (entry 4), and this could be improved further by increasing the reaction time to 24 h.

Table 14 – Optimisation of Base



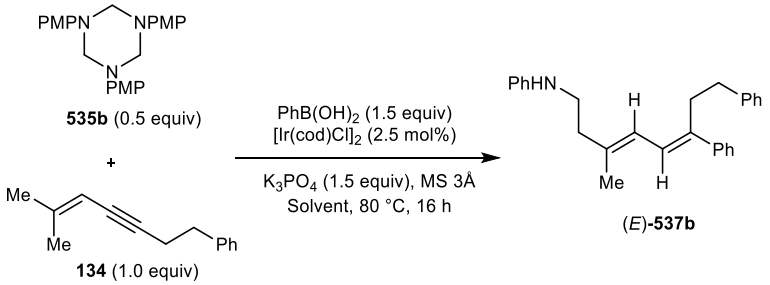
Entry	Base	NMR Yield of (*E*)-**537b** [a]	*E*/*Z*
1	KF	63	4.0:1
2	Et_3N	31	4.2:1.
3	$NaHCO_3$	26	2.9:1
4	K_2CO_3	49	3.2:1
5	K_3PO_4	72	4.0:1
6[c]	K_3PO_4	82	4.1:1

Reactions employed 0.05 mmol of **134**. [a] Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction duration 24 h.

Although high yields could now be generated using substrate **535b**, substrates, such as **535a** still reacted slowly, and gave disappointing yields after heating at 80 °C for 18 h (34% NMR yield). Addition of molecular sieves (3 Å) increased the conversion to (*E*)-**537a**, with similar yields (70% NMR yield after 18 h) now possible over a reasonable reaction time with both substrates **535a** and **535b**.

Efforts to improve the *E*/*Z* selectivity of the reaction were made by investigating the effect of nitrile as a co-solvent. Earlier, I described the intramolecular allylation of cyclic diketones (Table 3). In this chemistry the addition of nitrile as a co-solvent switched the major diastereomer observed through the believed *E*/*Z*-isomerisation of the allylrhodium species (Scheme 116). Therefore, it was hoped that by adding a nitrile as a co-solvent in this chemistry, changes in the preference for the species undergoing allylation could be favoured to allow greater selectivity for one isomer over the other. Although complete selectivity for the linear products was still observed, unfortunately, the isomeric ratio was similar to when using 1,4-dioxane. Addition of MeCN appeared to just have a negative effect on the overall yield (Table 15).

Table 15 – Effect of solvent system

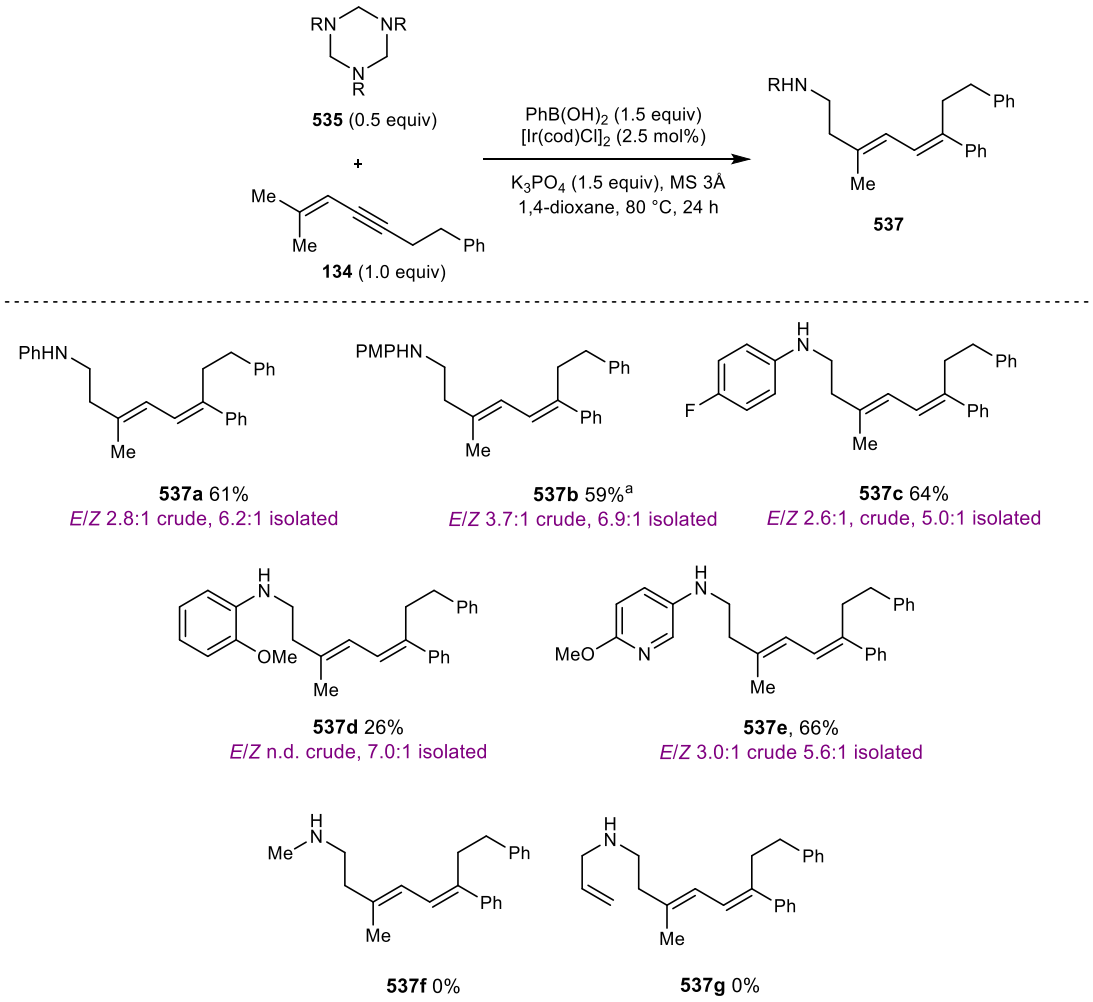


Entry	Solvent	NMR Yield of (*E*)-**537b** [a]	*E*/*Z*
1	1,4-Dioxane/MeCN (9:1)	54	3.9:1
2	1,4-Dioxane/MeCN (1:1)	43	3.4:1.
3	MeCN	26	3.9:1

Reactions employed 0.05 mmol of **134**. [a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

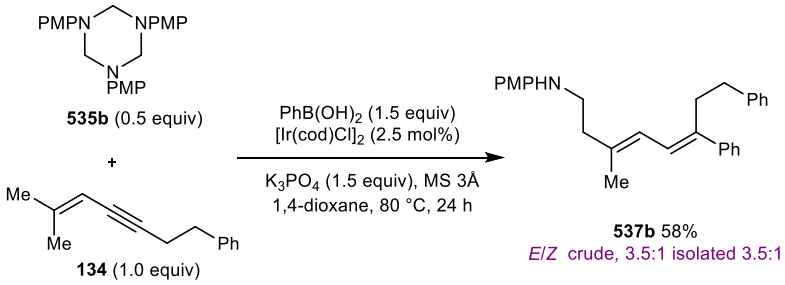
2.3.2 Initial Triazinane Scope

With more optimised conditions in hand, the reactivity with a range of triazinanes was investigated (Scheme 151). Unfortunately, the *E*/*Z* isomers, as discussed earlier, could not be separated by chromatography, and therefore all yields are reported as an isomeric mixture. Various triazinanes successfully underwent the reaction, with **537a** isolated in reasonable yield**.** Both electron-withdrawing and electron-donating substituents at the 4-position were tolerated giving methoxy-substituted **537b** and fluoro-substituted **537c** in good yield. However, *ortho*-substituted triazinanes reacted poorly, with **537d** only isolated in 26% yield. Activated heteroaromatics also underwent the reaction successfully, with **537e** obtained in high yield. Attempts to extend the scope beyond aromatic-substituted triazinanes was attempted, but no reactivity was observed when using methyl or allyl-substituted triazinanes **535f** and **535g** respectively.



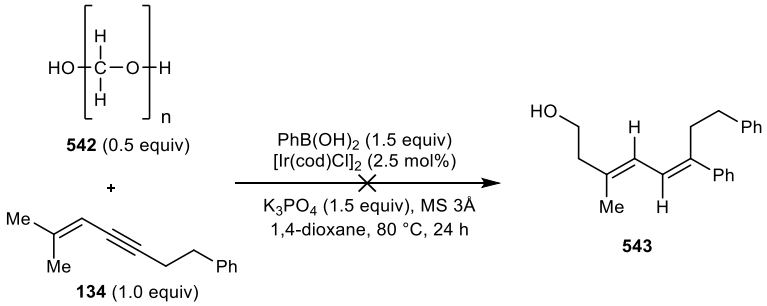
*Scheme 151 – Initial Triazinane Scope – Reactions employed 0.3 mmol of **134** [a] Reaction performed by S. Korkis*

Pleasingly, the reaction could be performed with **535b** at a much larger scale (3.75 mmol) with a reasonable yield maintained (Scheme 152). The degree of *E/Z* isomerisation shown by analysis of the crude NMR spectrum remained consistent at both the 0.30 mmol and 3.75 mmol scale.



*Scheme 152 – Reaction of **535b** at larger scale (3.75 mmol of **535b**)*

Attempts were also made to form alcohol **543**, by reacting enyne **134** with paraformaldehyde (**542**), but unfortunately this was not successful, with no consumption of **134** observed.

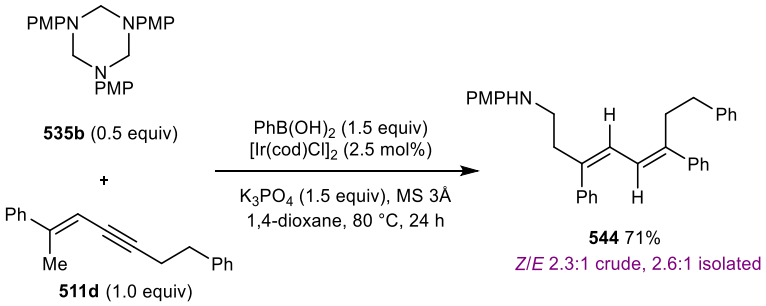


*Scheme 153 – Reaction of **134** with paraformaldehyde (**542**)*

2.3.3 Future Work

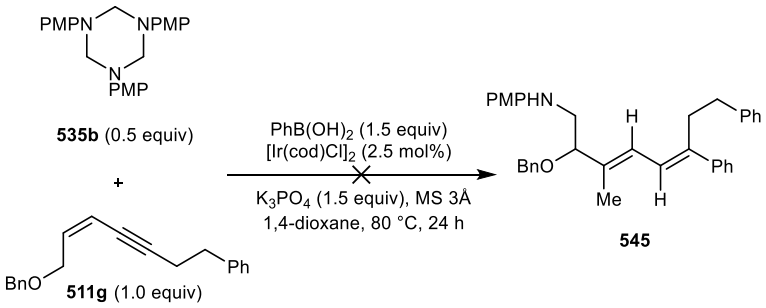
Further work is currently ongoing towards the further exploration of this chemistry. At this point in time, the scope with respect to the boronic acid has not been investigated, and only a limited number of reactions involving different 1,3-enynes has been conducted.

Enyne **511d**, with a phenyl group *trans* to the alkyne reacted to give **544** in good overall yield (71%). However, the *E*/*Z* selectivity was significantly reduced (2.3:1). The reduction in this selectivity is perhaps not surprising as with a larger phenyl substituent preference for the formation of the *E*-isomer may be increased.



*Scheme 154 – Reaction with enyne **511d***

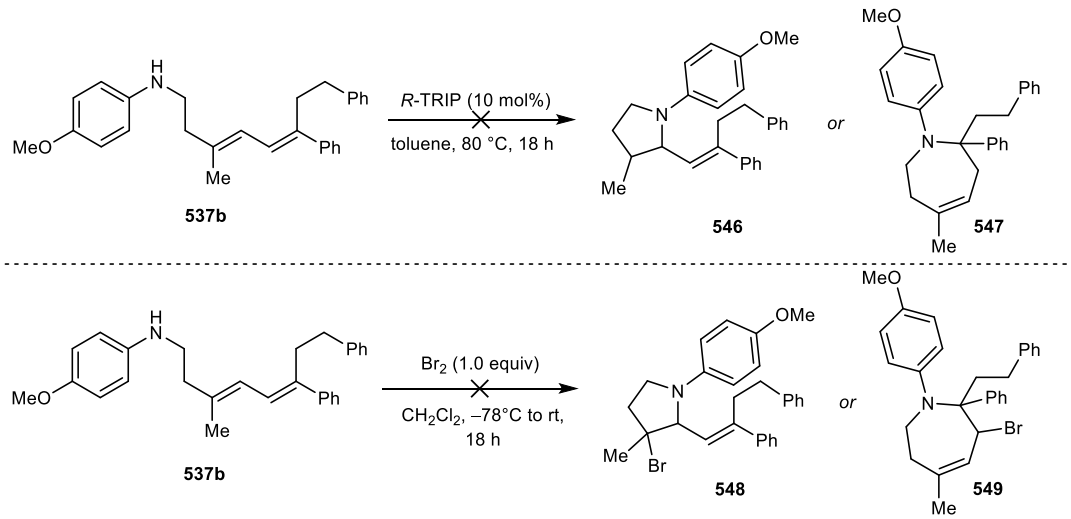
The migration of iridium to secondary allylic carbons has often been challenging. If this migration were to be possible, it would allow the synthesis of potentiall useful secondary chiral amines. Attempts were therefore made to synthesise the chiral compound **545**, using enyne **511g** (Scheme 155). Unfortunately, only starting materials were recovered when **511g** was exposed to the reaction conditions. Additional work towards using these types of substrates is currently ongoing, as the power of this methodology could be greatly enhanced by using these.



*Scheme 155 – Reaction with enyne **511g***

Whilst investigation into the scope of the reaction is still in the preliminary phase, attempts to manipulate the products has been explored. In this chemistry the core structure formed is a 1,5-functionalised diene, which contains functional groups that could readily undergo additional synthetic transformations. It was therefore hoped that further product manipulations of these compounds would increase the practicality of this chemistry. Initial attempts at performing cyclisation reactions using TRIP were conducted (Scheme 156),[138] with the hope either the 5-membered ring product **546** or the 7-membered ring **547** could be synthesised. Unfortunately, only starting materials were recovered. Diene **537b** was also

reacted with bromine in a haloetherification-type procedure,[139] but this reaction was also not sucessfuly, with a complex mixture of unidentifiable products obtained.



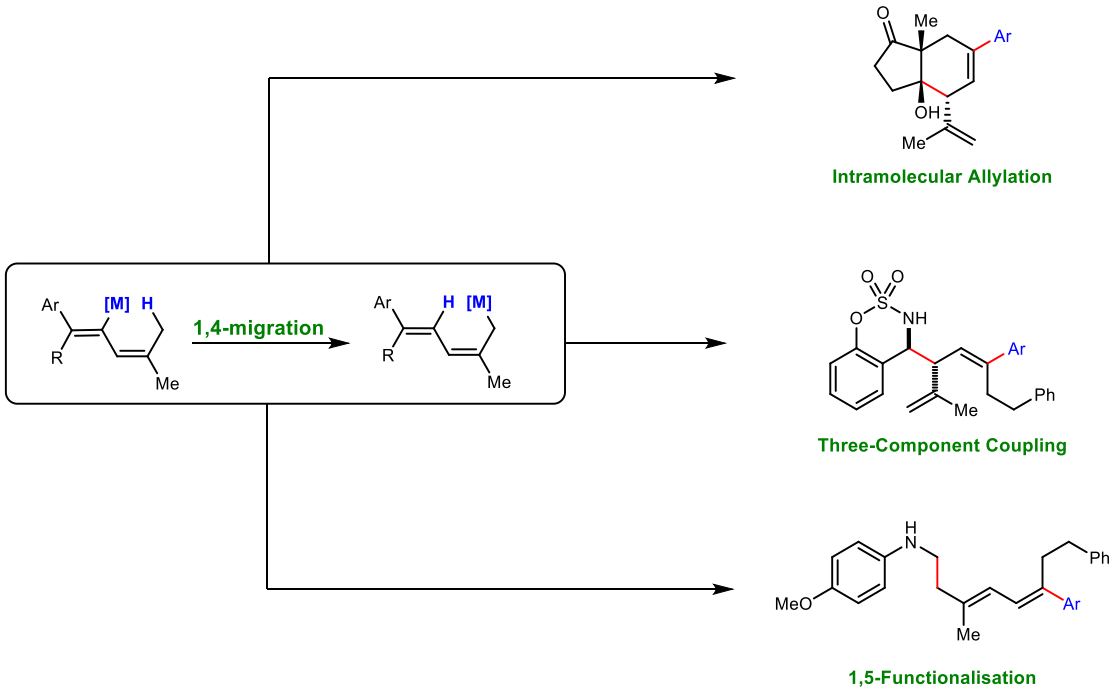
*Scheme 156 – Attempts to transform **537b***

Further manipulations of products such as **537b** are currently in progress, as well as attempts to improve the *E*/*Z* selectivity of the 1,5-functionalisation reaction.

3 Conclusions

In summary, a new mode of reactivity has been discovered, which involves a novel rhodium(I) or iridium(I) migration from an alkenyl C (sp^2) centre to an allyl C (sp^3) centre. This migration has allowed the formation of nucleophilic allyl metal species *in situ*, which can subsequently react with a range of electrophiles. This methodology bypasses the requirement to synthesise complex and stoichiometric allylmetal precursors, which can often be challenging and laborious using other methods. In this work we have described three different general reactions that incorporate this simple 1,4-migration (Scheme 157):

1. An intramolecular arylative allylation process
2. A three-component coupling of cyclic imines aryl boronic acids and 1,3-enynes
3. A 1,5-functionalisation through use of formaldimine derived triazinanes.



Scheme 157 – Reaction summary

Further work is ongoing within the Lam group to extend the applications of this promising platform for generating nucleophilic allylmetal species.

4 Experimental

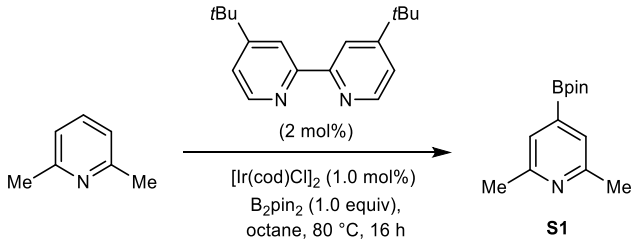
4.1 General Information

All air-sensitive reactions were carried out under a nitrogen or argon atmosphere using oven-dried apparatus. All commercially available reagents were used as received unless otherwise stated. All petroleum ether used was 40–60 °C petroleum ether. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Compounds were visualized by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35–70 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallisation is reported in parentheses. Infra-red spectra were recorded on a Nicolet Avatar 360 FT instrument on the neat compound. NMR spectra were acquired on a Bruker AV500, AV(III)500HD, AV400, AV(III)400, AV(III)400HD, DPX400 or DPX300 spectrometer. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.27 ppm for ^{1}H NMR spectroscopy and 77.0 ppm for ^{13}C NMR spectroscopy. ^{2}H NMR spectra were referenced to the residual deuterated solvent (7.27 ppm). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. HSQC and HMBC experiments were used to assist ^{1}H NMR assignments where required. ^{13}C NMR assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. ^{19}F NMR spectra were not proton-decoupled, and were referenced through the solvent lock (^{2}H) signal according to IUPAC recommended secondary referencing method the Bruker protocols. High-resolution mass spectra were recorded using electrospray ionization (ESI) or electron ionization (EI) techniques. X-ray diffraction data were collected at 120 K on an Agilent GV1000 using CuKα radiation. Chiral HPLC analysis was performed on an Agilent 1290 series or Agilent 1260 series instrument using 4.6 × 250 mm columns.

4.2 Arylative Intramolecular Allylation

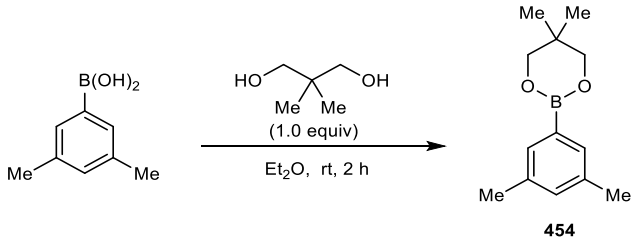
4.2.1 Synthesis of Arylboronate Esters

2,6-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (S1)



2,6-Lutidine (0.46 mL, 4.00 mmol), B_2pin_2 (1.02 g, 4.00 mmol) 4,4′-di-*tert*-butyl-2,2′-dipyridyl (21 mg, 80 μmol) and $[Ir(cod)Cl]_2$ (27 mg, 40 μmol) in octane (5 mL) was stirred at 80 °C for 16 h. The solution was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and quenched with water (10 mL). The organic layer was isolated, and the aqueous extracted with additional CH_2Cl_2 (2 × 10 mL). The organic layers were then combined, washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give *boronic ester* **S1** (580 mg, 62%) as a red solid. The compound was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, s, Ar**H**), 2.53 (6H, s ArC**H₃**), 1.36 (12H, s, C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (2 × C), 125.2 (2 × CH), 84.3 (2 × C), 24.9 (4 × CH_3), 24.3 (2 × CH_3). The quaternary carbon (C) next to boron was not observed due to quadrupolar coupling effects of ^{11}B. Data consistent with literature.[140]

5,5-Dimethyl-2-(3,5-dimethylphenyl)-1,3,2-dioxaborinane (454)

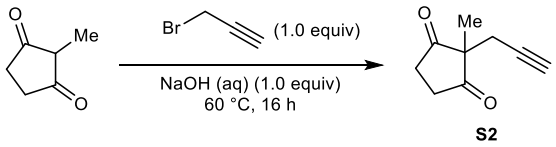


3,5-Dimethylphenyl boronic acid (2.00 g, 13.3 mmol) and dimethylpropan-1,3-diol (1.39 g, 13.3 mmol) in Et_2O (20 mL) were stirred at room temperature for 2 h. The mixture was concentrated *in vacuo* and the residue purified by column chromatography (30%

EtOAc/petroleum ether) to give *boronic ester* **454** (2.81 g, 97%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (2H, s, Ar**H**), 7.10-7.07 (1H, m, Ar**H**), 3.78 (4H, s, C**H$_2$**), 2.34-2.32 (6H, m, ArC**H$_3$**), 1.03 (6H, s, C(C**H$_3$**)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9 (2 × C), 132.4 (CH), 131.5 (2 × CH), 72.3 (2 × CH_2), 31.9 (C), 21.9 (2 × CH_3), 21.2 (2 × CH_3). The quaternary carbon (C) next to boron was not observed due to quadrupolar coupling effects of ^{11}B. Data consistent with literature.[141]

4.2.2 Synthesis of Enynones

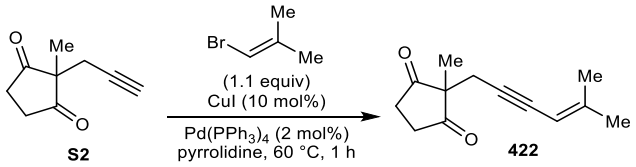
2-Methyl-2-(prop-2-yn-1-yl)cyclopentane-1,3-dione (S2)



S2

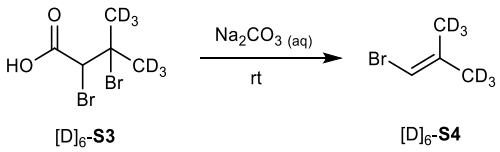
Propargyl bromide (80% wt in toluene, 1.98 mL, 17.8 mmol) was added to 2-methyl-1,3-cyclopentanedione (2.00 g, 17.8 mmol) in an aqueous NaOH solution (15 mL) and heated at 60 °C for 16 h. The reaction mixture was then cooled to room temperature and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give *alkynone* **S2** (1.43 g, 54%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86-2.81 (4H, m, C**H$_2$**C**H$_2$**), 2.48 (2H, d, *J* = 2.7 Hz, CH≡CC**H$_2$**), 1.99 (1H, t, *J* = 2.6 Hz, C≡C**H**), 1.15 (3H, s, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9 (2 × C), 78.6 (C), 70.6 (CH), 55.0 (C), 35.5 (2 × CH_2), 23.9 (CH_2), 19.0 (CH_3). Data consistent with literature.[142]

2-Methyl-2-(5-methylhex-4-en-2-yn-1-yl)cyclopentane-1,3-dione (422)



Bromo-2-methyl-1-propene (988 mg, 7.32 mmol) was added to a solution of CuI (126 mg, 0.66 mmol) and $Pd(PPh_3)_4$ (150 mg, 0.13 mmol) in pyrrolidine (15 mL). Alkynone **S2** (1.00 g, 6.66 mmol) was then added and the mixture was stirred at 60 °C for 1 h. The reaction mixture was subsequently cooled to room temperature, saturated aqueous NH_4Cl solution (20 mL) added, and the mixture extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give *enynone* **422** as an orange oil (440 mg, 33%). R_f = 0.28 (20% EtOAc/petroleum ether); IR 2912, 1710 (C=O), 1420, 1210, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.13-5.09 (1H, m, C=C**H**), 2.77 (4H, s, C**H₂**C**H₂**), 2.59 (2H, d, *J* = 2.0 Hz, C**H₂**C≡C), 1.77 (3H, s, C=C(C**H₃**)$_2$), 1.73 (3H, s, C=C(C**H₃**)$_2$), 1.11 (3H, s, O=CCC**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.7 (2 × C), 148.7 (C), 104.4 (CH), 85.5 (C), 80.7 (C), 55.6 (C), 35.8 (2 × CH_2), 26.2 (CH_2), 24.6 (CH_3), 20.8 (CH_3), 18.8 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{13}H_{16}NaO_2]^+$ $[M+Na]^+$: 227.1043, found: 227.1045.

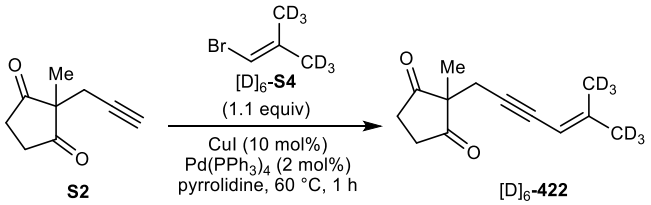
1-Bromo-2-($^2H_3$)methyl(3,3,3-$^2H_3$)prop-1-ene ([D]$_6$-S4)



Saturated aqueous Na_2CO_3 solution was added to [D]$_6$-**S3**[1] (4.69 g, 17.6 mmol) until effervescence ceased. The crude mixture was purified by distillation at atmospheric pressure (65 °C) to give *deuterio-vinyl bromide* [D]$_6$-**S4** (1.79 g, 72%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, s, C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 (C), 100.5 (CH), 23.1 (septet, *J* = 19.2 Hz, CD_3), 19.8 (septet, *J* = 19.5 Hz, CD_3). Data consistent with literature.[49]

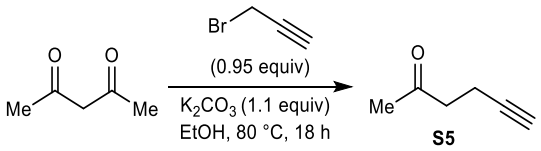
[1] Synthesised by D. Burns

2-Methyl-2-(5-($^2H_3$)methyl(6,6,6-$^2H_3$)hex-4-en-2-yn-1-yl)cyclopentane-1,3-dione ([D_6]-422).



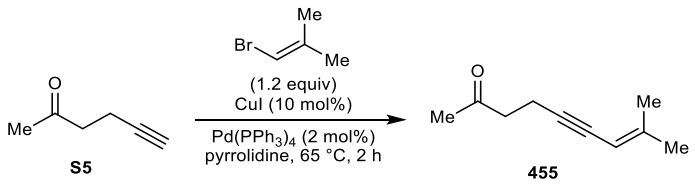
Alkene [D]$_6$-**S4** (516 mg, 3.66 mmol) was added to a solution of CuI (63 mg, 0.33 mmol) and $Pd(PPh_3)_4$ (77 mg, 67 µmol) in pyrrolidine (10 mL). Alkynone **S2** (500 mg, 3.33 mmol) was then added and the mixture was stirred at 60 °C for 1 h. After cooling to room temperature, saturated aqueous NH_4Cl solution (15 mL) was added and the mixture extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give *enynone* [D]$_6$-**422** as a red oil (357 mg, 51%). R_f = 0.32 (20% EtOAc/petroleum ether); IR 2931, 1725 (C=O), 1417, 1317, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (1H, t, *J* = 2.3, C=C**H**), 2.80 (4H, d, *J* = 0.8 Hz, C**H$_2$**C**H$_2$**), 2.62 (2H, dd, *J* = 2.3, 1.0 Hz, C**H$_2$**C≡C), 1.14 (3H, d, *J* = 0.9 Hz, O=CCC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.8 (2 × C), 148.7 (C), 104.5 (CH), 85.4 (C), 80.8 (C), 55.7 (C), 35.9 (2 × CH_2), 26.3 (CH_2), 18.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{13}H_{10}D_6NaO_2$ $[M+Na]^+$: 233.1419, found: 233.1419.

Hex-5-yn-2-one (S5)



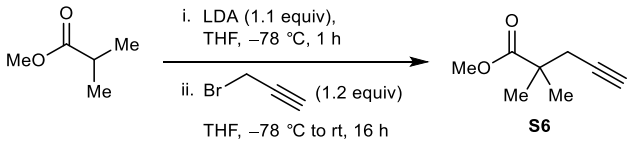
Propargyl bromide (80% wt in toluene, 10.6 mL, 95.0 mmol) was added to acetylacetone (10.3 mL, 100 mmol) and K_2CO_3 (15.2 g, 110 mmol) in EtOH (60 mL) and then heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature and diluted with H_2O (100 mL). The solution was then extracted with Et_2O (3 × 50 mL) and the combined organic phases concentrated *in vacuo*. The crude mixture was purified by distillation under reduced pressure (82 °C at 40 mbar) to give *alkynone* **S5** (2.38 g, 26%), as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71-2.66 (2H, m, C(O)C**H$_2$**), 2.47-2.41 (2H, m, CH≡CC**H$_2$**), 2.18-2.17 (3H, m, C**H$_3$**), 1.95 (1H, td, *J* = 2.7, 0.8 Hz, C≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4 (C), 83.0 (C), 68.7 (CH), 42.2 (CH_2), 29.8 (CH_3), 12.9 (CH_2). Data consistent with literature.[143]

8-Methylnon-7-en-5-yn-2-one (455)



1-Bromo-2-methyl-1-propene (667 mg, 4.94 mmol) was added to a solution of CuI (94 mg, 0.49 mmol) and $Pd(PPh_3)_4$ (116 mg, 0.100 mmol) in pyrrolidine (15 mL) at room temperature. Alkynone **S5** (432 mg, 4.49 mmol) was added (neat, using *ca.* 1 mL of pyrrolidine to rinse) and the mixture was stirred at 60 °C for 2 h. The mixture was cooled to room temperature, saturated aqueous NH_4Cl solution (30 mL) added and the mixture extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (10% Et_2O/petroleum ether) to give *enynone* **455** as a colourless oil (428 mg, 64%). R_f = 0.33 (10% Et_2O/petroleum ether); IR 2915, 1715 (C=O), 1377, 1364, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.22-5.19 (1H, m, C=C**H**), 2.72-2.66 (2H, m, C**H₂**C=O), 2.62-2.56 (2H, m, C**H₂**C≡C), 2.18 (3H, s, C**H₃**C=O), 1.86-1.84 (3H, m, C=CC**H₃**), 1.78-1.76 (3H, m, C=CC**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8 (C), 147.4 (C), 105.1 (CH), 90.1 (C), 78.9 (C), 42.9 (CH_2), 29.9 (CH_3), 24.6 (CH_3), 20.7 (CH_3), 14.2 (CH_2); HRMS (GC-MS, EI) Exact mass calcd for $[C_{10}H_{14}O]^+$ $[M]^+$: 150.1040, found: 150.1039.

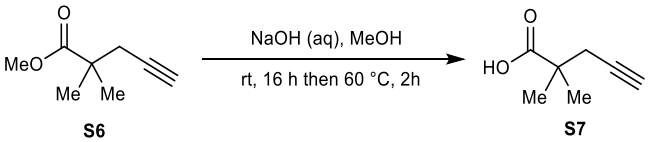
Methyl 2,2-dimethylpent-4-ynoate (S6)



*n*BuLi (18 mL, 39 mmol) was added dropwise to diisopropylamine (5.5 mL, 39 mmol) in THF (36 mL) at −78 °C and stirred for 10 min. Methyl isobutyrate (4.0 mL, 35 mmol) was subsequently added and the mixture stirred at −78 °C for 1 h. Propargyl bromide (80% wt in toluene, 2.93 mL, 26.3 mmol) was then added at −78 °C and the reaction mixture stirred for 16 h and allowed to warm to room temperature. The mixture was quenched carefully with saturated aqueous NH_4Cl solution and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by distillation under reduced pressure (50 °C at 15 mbar) to

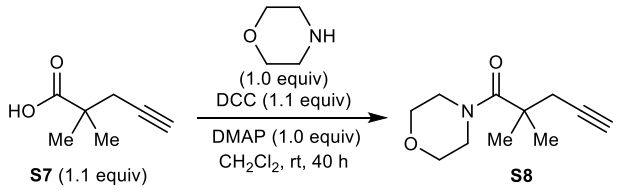
give *ester* **S6** (3.2 g, 64%), as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (3H, s, OC**H₃**), 2.45 (2H, d, *J* = 2.7 Hz, C**H₂**), 2.01 (1H, t, *J* = 2.7 Hz, C≡C**H**), 1.29 (6H, s, C(C**H₃**)$_2$);^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1 (C), 81.0 (C), 70.4 (CH), 52.0 (CH_3), 42.1 (C), 29.6 (CH_2), 24.5 (2 × CH_3). Data consistent with literature.[144]

2,2-Dimethylpent-4-ynoic acid (S7)



Aqueous NaOH solution (1.0 M, 35 mL) was added to a solution of **S6** (3.20 g, 22.8 mmol) in MeOH (30 mL) and the mixture was stirred at room temperature for 16 h and then heated at 60 °C for 2 h. The solution was cooled to room temperature and washed with EtOAc (50 mL). The aqueous phase was acidified using 10% aqueous HCl solution and then extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*, to give *carboxylic acid* **S7** (2.68 g, 93%) as an orange oil. The compound was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (2H, d, *J* = 2.7 Hz, C**H₂**), 2.11 (1H, s, O**H**), 2.05 (1H, d, *J* = 2.7 Hz, C≡C**H**), 1.33 (6H, s, C(C**H₃**)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.5 (C), 80.7 (C), 70.7 (CH), 41.9 (C), 29.3 (CH_2), 24.3 (2 × CH_3). Data consistent with literature.[144]

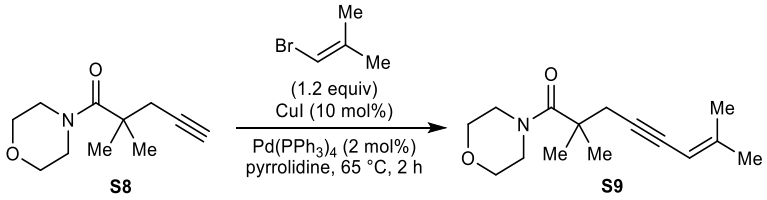
2,2-Dimethyl-1-(morpholin-4-yl)pent-4-yn-1-one (S8)



DCC (4.56 g, 22.1 mmol) was added to a solution of terminal alkyne **S7** (2.79 g, 22.1 mmol), morpholine (1.76 mL, 20.1 mmol), and DMAP (2.46 g, 20.1 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 40 h. The resulting suspension was filtered through a pad of silica using EtOAc as eluent, and concentrated *in vacuo*. The mixture was purified by column chromatography (40% EtOAc/petroleum ether) to give *alkyne* **S8** as a yellow solid (2.33 g, 59%). R_f = 0.36 (40% EtOAc/petroleum ether); m.p.

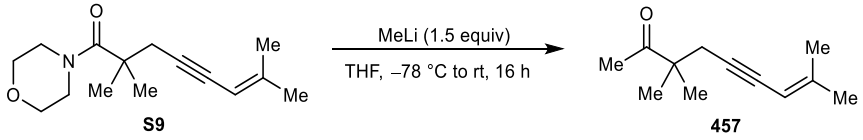
63-64 °C (Et_2O); IR 3226, 2930, 1611 (C=O), 1423, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69-3.60 (8H, m, 2 × OC**H₂**C**H₂**N), 2.50 (2H, d, *J* = 2.6 Hz, C**H₂**C≡C), 2.01 (1H, t, *J* = 2.6, C≡C**H**), 1.36 (6H, s, 2 × C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4 (C), 81.7 (C), 70.5 (CH), 66.7 (2 × CH_2), 45.7 (CH_2), 41.7 (C), 31.3 (2 × CH_2), 24.8 (2 × CH_3); HRMS (ESI) Exact mass calcd for $[C_{11}H_{18}NO_2]^+$ $[M+H]^+$: 196.1332, found: 196.1336.

2,2,7-Trimethyl-1-(morpholin-4-yl)oct-6-en-4-yn-1-one (S9)



1-Bromo-2-methyl-1-propene (1.14 g, 8.45 mmol) was added to a solution of CuI (146 mg, 0.768 mmol) and $Pd(PPh_3)_4$ (178 mg, 0.154 mmol) in pyrrolidine (25 mL). Alkyne **S8** (1.50 g, 7.68 mmol) was added (neat, using *ca.* 1 mL of pyrrolidine to rinse) and the mixture was stirred at 60 °C for 2 h. The mixture was cooled to room temperature, saturated aqueous NH_4Cl solution (30 mL) added and the mixture extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (30% EtOAc/petroleum ether) to give *enyne* **S9** as a yellow oil (1.91 g, 99%). R_f = 0.35 (30% EtOAc/petroleum ether); IR 3226, 2964, 1611 (C=O), 1423, 1109, 981 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.26–5.23 (1H, m, C=C**H**), 3.73–3.62 (8H, m, 2 × OC**H₂**C**H₂**N), 2.70–2.65 (2H, br, s, C**H₂**C≡C), 1.87 (3H, s, C=CC**H₃**), 1.78 (3H, s, C=CC**H₃**), 1.38 (6H, s, (C**H₃**)₂CC=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (C), 147.3 (C), 105.3 (CH), 88.6 (C), 80.8 (C), 66.8 (2 × CH_2), 45.8 (CH_2), 42.2 (C), 32.0 (2 × CH_2), 25.3 (2 × CH_3), 24.6 (CH_3), 20.9 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{15}H_{24}NO_2]^+$ $[M+H]^+$: 250.1802, found: 250.1790.

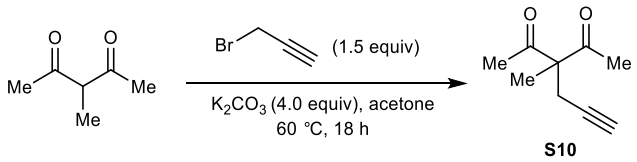
3,3,8-Trimethylnon-7-en-5-yn-2-one (457)



S9 457

MeLi (1.15 M in Et_2O, 2.95 mL, 3.39 mmol) was added dropwise to a solution of morpholine amide **S14** (500 mg, 2.26 mmol) in THF (10 mL) at −78 °C. The solution was stirred for 16 h while being allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (10% Et_2O/petroleum ether) to give *enynone* **457** as a colourless oil (295 mg, 73%). R_f = 0.29 (10% Et_2O/petroleum ether); IR 2971, 1706 (C=O), 1464, 1354, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24–5.20 (1H, m, C=C**H**), 2.55–2.52 (2H, br s, C**H₂**C≡C), 2.21–2.18 (3H, m, C**H₃**C=O), 1.85 (3H, s, C=CC**H₃**), 1.78 (3H, s, C=CC**H₃**), 1.24–1.22 (6H, m, (C**H₃**)₂CC=O); ^{13}C NMR (101 MHz, $CDCl_3$) 212.4 (C), 147.5 (C), 105.1 (CH), 88.2 (C), 80.8 (C), 47.7 (C), 30.0 (CH_2), 25.3 (CH_3), 24.6 (CH_3), 24.0 (2 × CH_3), 20.8 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{12}H_{19}O]^+$ $[M+H]^+$: 179.1430, found: 179.1423.

3-Methyl-3-(prop-2-yn-1-yl)pentane-2,4-dione (S10)

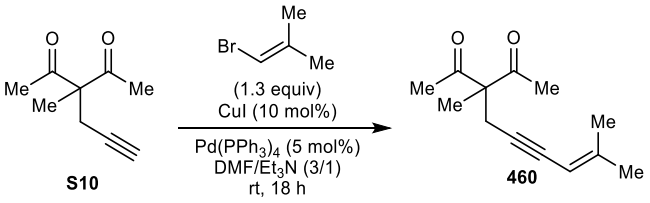


S10

Propargyl bromide (80% wt in toluene, 2.93 mL, 26.3 mmol) was added to 3-methyl-2,4-pentanedione (2.36 g, 17.5 mmol) and K_2CO_3 (9.67 g, 70.0 mmol) in acetone (100 mL) and stirred at 60 °C for 18 h. The reaction mixture was cooled to room temperature and excess K_2CO_3 removed by filtration. The solvent was concentrated *in vacuo* and the residue diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The organic phases were combined, washed with brine (20 mL) and then dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The crude mixture was purified by column chromatography (50% petroleum ether, 45% CH_2Cl_2, 5% Et_2O) to give *enynone* **S10** (1.60 g, 60%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 2.75 (2H, d, *J* = 2.7 Hz, C**H₂**), 2.17 (6H, s, C(O)C**H₃**), 2.03 (1H, t, *J* = 2.7 Hz, C≡C**H**), 1.49

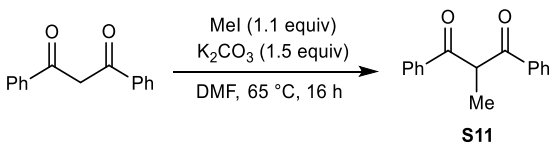
(3H, s, CC**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (C), 79.5, (C) 71.7 (CH), 66.1 (C), 26.5 (2 × CH_3), 24.4 (CH_2), 18.4 (CH_3). Data consistent with literature.[145]

3-Methyl-3-(5-methylhex-4-en-2-yn-1-yl)pentane-2,4-dione (460)



A solution of **S10** (610 mg, 3.99 mmol) in Et_3N (2.6 mL) was added to a flask containing CuI (76 mg, 0.40 mmol, 10 mol%) and $Pd(PPh_3)_4$ (231 mg, 0.200 mmol, 5 mol%). 1-Bromo-2-methylpropene (700 mg, 5.19 mmol) in DMF (8 mL) was added and the mixture stirred at room temperature for 18 h. Saturated aqueous NH_4Cl solution (30 mL) was added and the mixture extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (10% EtOAc/petroleum ether) to give *enynone* **460** as a colourless oil (340 mg, 41%). R_f = 0.27 (10% EtOAc/petroleum ether); IR 2934, 1699 (C=O), 1356, 1164, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20-5.17 (1H, m, C=C**H**), 2.90 (2H, d, *J* = 2.1 Hz, C**H₂**), 2.17 (6H, s, C**H₃**CO), 1.82 (3H, d, *J* = 1.3 Hz, C=CC**H₃**), 1.79-1.69 (3H, m, C=CC**H₃**), 1.48 (3H, s, C(O)CC**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7 (2 × C), 148.3 (C), 104.8 (CH), 86.3 (C), 81.7 (C), 66.5 (C), 26.5 (2 × CH_3), 25.6 (CH_2), 24.7 (CH_3), 20.8 (CH_3), 18.6 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{13}H_{218}NaO_2]^+$ $[M+Na]^+$: 229.1199, found: 229.1196.

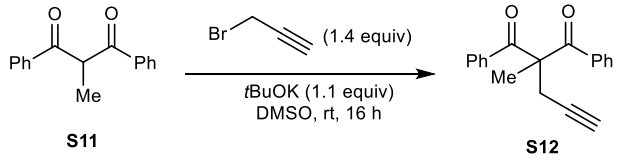
2-Methyl-1,3-diphenylpropane-1,3-dione (S11)



MeI (0.56 mL, 8.9 mmol) was added to 1,3-diphenylpropane-1,3-dione (1.82 g, 8.12 mmol) and K_2CO_3 (1.68 g, 12.2 mmol) in DMF (10 mL). The reaction mixture was heated at 65 °C for 16 h, and then cooled to room temperature. The mixture was quenched with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by

column chromatography (5% EtOAc/petroleum ether) to give *dione* **S11** (1.70 g, 88%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00-7.94 (4H, m, Ar**H**), 7.60-7.55 (2H, m, Ar**H**), 7.49-7.44 (4H, m, Ar**H**), 5.27 (1H, q, *J* = 7.0 Hz, CH_3C**H**), 1.62 (3H, d, *J* = 7.0 Hz, C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.2 (2 × C), 135.6 (2 × C), 133.5 (2 × CH), 128.9 (4 × CH), 128.5 (4 × CH), 51.1 (CH), 14.4 (CH_3). Data consistent with literature.[146]

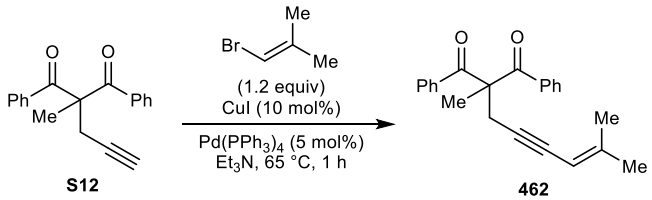
2-Methyl-1,3-diphenyl-2-(prop-2-yn-1-yl)propane-1,3-dione (S12)



S11 **S12**

Propargyl bromide (80% wt in toluene, 1.03 mL, 9.22 mmol) was added to **S11** (1.57 g, 6.59 mmol) and *t*BuOK (813 mg, 7.25 mmol) in DMSO (50 mL) and the mixture was stirred at room temperature for 16 h. The reaction mixture was then diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (60% petroleum ether, 38% CH_2Cl_2, 2% Et_2O) to give *alkynone* **S12** (1.33 g, 73%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.81 (4H, m, Ar**H**), 7.50-7.44 (2H, m, Ar**H**), 7.38-7.32 (4H, m, Ar**H**), 3.09 (2H, d, *J* = 2.7 Hz, C**H$_2$**), 2.02 (1H, t, *J* = 2.7 Hz, C≡C**H**), 1.79 (3H, s, C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2 (2 × C), 135.6 (2 × C), 133.2 (2 × CH), 129.0 (4 × CH), 128.7 (4 × CH), 79.1 (C), 72.5 (CH), 62.7 (C), 28.0 (CH_2), 22.4 (CH_3). Data consistent with literature.[147]

2-Methyl-2-(5-methylhex-4-en-2-yn-1-yl)-1,3-diphenylpropane-1,3-dione (462)

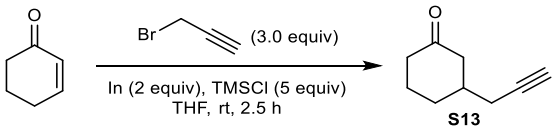


S12 **462**

1-Bromo-2-methyl-1-propene (293 mg, 2.17 mmol) was added to a solution of CuI (34 mg, 0.18 mmol) and $Pd(PPh_3)_4$ (42 mg, 36 μmol) in Et_3N (10 mL). Alkyne **S12** (500 mg, 1.81 mmol) was then added and the mixture was stirred at 65 °C for 1 h. The mixture was cooled to room

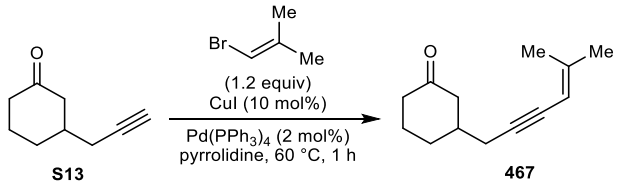
temperature, saturated aqueous NH_4Cl solution (10 mL) added, and the mixture extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (120 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (twice, the first time using 60% petroleum ether, 38% CH_2Cl_2, 2% Et_2O; the second time using 100% toluene) to give *enynone* **462** as an off-white solid (203 mg, 34%). R_f = 0.64 (100% toluene); m.p. 162-163 °C (Et_2O); IR 2921, 1658 (C=O), 1209, 955, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.81 (4H, m, Ar**H**), 7.49-7.43 (2H, m, Ar**H**), 7.37-7.31 (4H, m, Ar**H**), 5.18-5.15 (1H, m, C=C**H**), 3.24 (2H, d, *J* = 2.1 Hz, C**H₂**), 1.81-1.79 (3H, m, C=CC**H₃**), 1.79 (3H, s, CH_2CC**H₃**), 1.77-1.75 (3H, m, C=CC**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (2 × C), 148.0 (C), 135.8 (2 × C), 133.1 (2 × CH), 129.0 (4 × CH), 128.6 (4 × CH) , 105.0 (CH), 86.0 (C), 82.5 (C), 63.2 (C), 29.2 (CH_2), 24.7 (CH_3), 22.7 (CH_3), 20.8 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{23}H_{23}O_2]^+$ $[M+H]^+$: 331.1693, found: 331.1682.

3-(Prop-2-yn-1-yl)cyclohexan-1-one (S13)



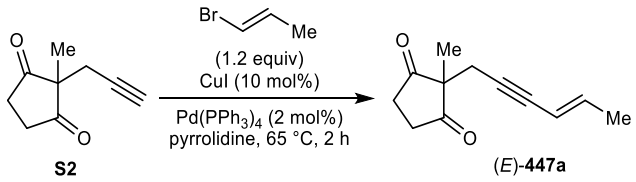
Propargyl bromide (80% wt in toluene, 2.51 mL, 22.5 mmol) was added to indium powder (1.72 g, 15.0 mmol) in THF (25 mL) and the reaction mixture was stirred at room temperature for 0.5 h. TMSCl (4.76 mL, 37.5 mmol) was then added, and the mixture stirred for a further 2 h. The reaction mixture was poured onto a pH 7.0 buffer solution (0.1 M aqueous KH_2PO_4 (50 mL) and 0.1M aqueous NaOH (29 mL)). The aqueous phase was extracted with Et_2O (3 × 30 mL) and then the combined organic phases washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography (5% EtOAc/petroleum ether) to give *alkynone* **S13** (446 mg, 45%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (1H, ddt, *J* = 13.9, 4.1, 2.1 Hz, C**H₂**), 2.39-2.30 (1H, m, C**H₂**), 2.28-2.13 (4H, m, C**H₂**), 2.10-2.02 (1H, m, C**H**), 2.01 (1H, t, *J* = 2.7 Hz, C≡C**H**), 1.99-1.90 (2H, m, C**H₂**), 1.73-1.58 (1H, m, C**H₂**), 1.57-1.43 (1H, m, C**H₂**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.8 (C), 81.3 (C), 70.4 (CH), 46.9 (CH_2), 41.0 (CH_2), 37.7 (CH), 30.2 (CH_2), 25.3 (CH_2), 24.7 (CH_2). Data consistent with literature.[147]

3-(5-Methylhex-4-en-2-yn-1-yl)cyclohexan-1-one (467)



Bromo-2-methyl-1-propene (412 mg, 2.76 mmol) was added to a solution of CuI (53 mg, 0.28 mmol) and $Pd(PPh_3)_4$ (65 mg, 56 µmol) in pyrrolidine (7 mL). Alkyne **S13** (378 mg, 2.76 mmol) in pyrrolidine (2 mL) was added and the mixture was stirred at 65 °C for 1 h. The mixture was then cooled to room temperature, saturated aqueous NH_4Cl solution (10 mL) added and the mixture extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (10% Et_2O/petroleum ether) to give *enynone* **467** as a yellow oil (434 g, 83%). R_f = 0.27 (10% Et_2O/petroleum ether); IR 2930, 1709 (C=O), 1447, 1223, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.26-5.23 (1H, m, C=C**H**), 2.49 (1H, ddt, *J* = 14.0, 4.2, 2.0 Hz, C**H₂**), 2.43-2.33 (3H, m, C**H₂**), 2.32-2.18 (2H, m, C**H₂**), 2.13-1.92 (3H, m, CH_2C**H** and C**H₂**), 1.88 (3H, s, C**H₃**), 1.79 (3H, s, C**H₃**), 1.74-1.47 (2H, m, C**H₂**).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4 (C), 147.4 (C), 105.1 (CH), 88.6 (C), 80.6 (C), 47.2 (CH_2), 41.1 (CH_2), 38.3 (CH), 30.5 (CH_2), 26.6 (CH_2), 24.9 (CH_2), 24.6 (CH_3), 20.9 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{13}H_{18}NaO]^+$ $[M+Na]^+$: 213.1250, found: 213.1249.

2-Methyl-2-[(*E*)-(5-methylhex-4-en-2-yn-1-yl)]cyclopentane-1,3-dione (14)

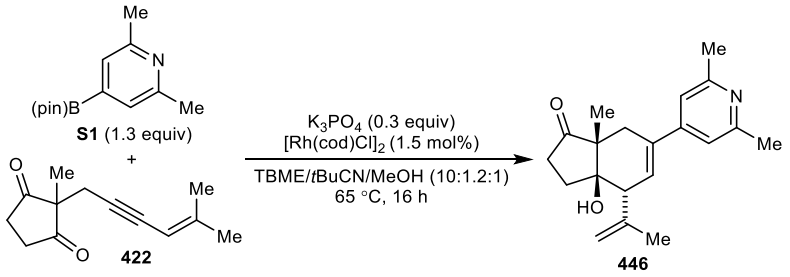


trans-1-Bromo-1-propene (443 mg, 3.66 mmol) was added to a solution of CuI (63 mg, 0.33 mmol) and $Pd(PPh_3)_4$ (77 mg, 67 µmol) in pyrrolidine (10 mL). Alkynone **S2** (500 mg, 3.33 mmol) was then added (neat, using *ca.* 1 mL of pyrrolidine to rinse) and the mixture was stirred at 60 °C for 2 h. The mixture was cooled to room temperature, saturated aqueous NH_4Cl solution (30 mL) added and the mixture extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (20%

EtOAc/petroleum ether) to give *enynone* (*E*)-**447a** as an orange oil (379 mg, 60%). R_f = 0.21 (20% EtOAc/petroleum ether); IR 2915, 1723 (C=O), 1317, 1072, 953 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.05 (1H, dq, *J* = 15.8, 6.7 Hz, =C**H**CH_3), 5.37 (1H, dq, *J* = 15.8, 2.1 Hz, C**H**=$CHCH_3$), 2.80 (4H, s, C$\mathbf{H_2}$C$\mathbf{H_2}$), 2.56 (2H, d, *J* = 2.1 Hz, C$\mathbf{H_2}$C≡C), 1.74 (3H, dt, *J* = 6.7, 0.9 Hz, =CHC$\mathbf{H_3}$), 1.12 (3H, s, CC$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.7 (2 × C), 139.9 (CH), 110.0 (CH), 81.9 (C), 81.6 (C), 55.5 (C), 35.9 (2 × CH_2), 26.1 (CH_2), 18.8 (CH_3), 18.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{12}H_{15}O_2]^+$ $[M+H]^+$: 191.1067, found: 191.1061.

4.2.3 Rhodium-Catalysed Arylative Allylations

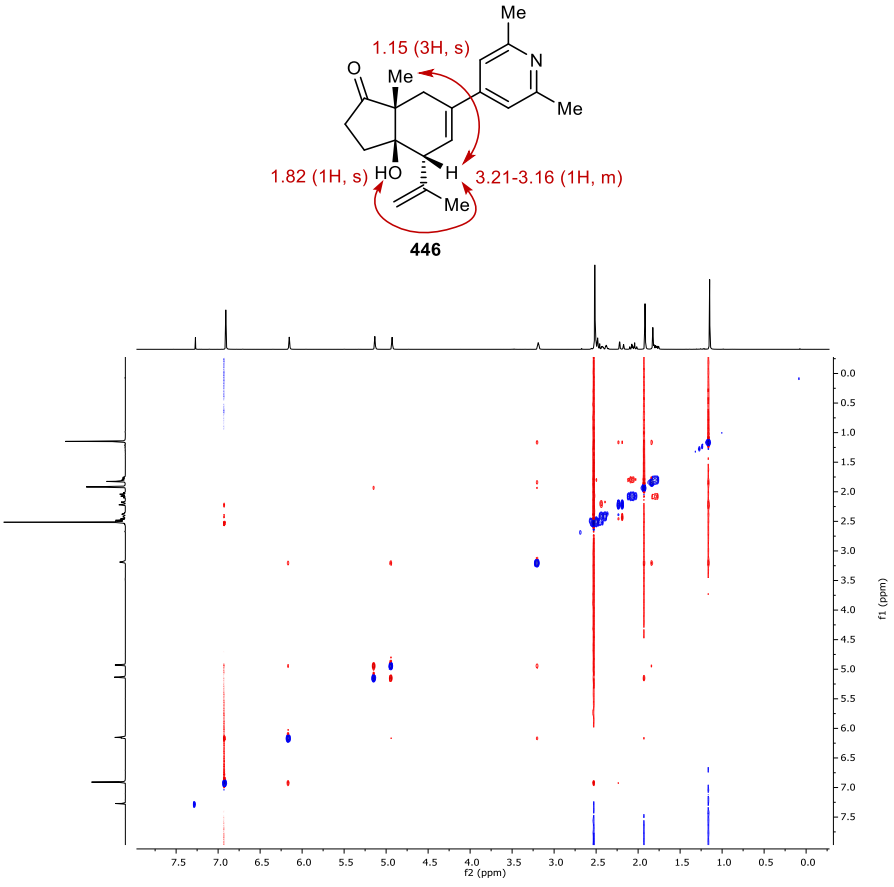
(±)-(3a*R*,4*R*,7a*R*)-6-(2,6-Dimethylpyridin-4-yl)-3a-hydroxy-7a-methyl-4-(prop-1-en-2-yl)-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one (446)



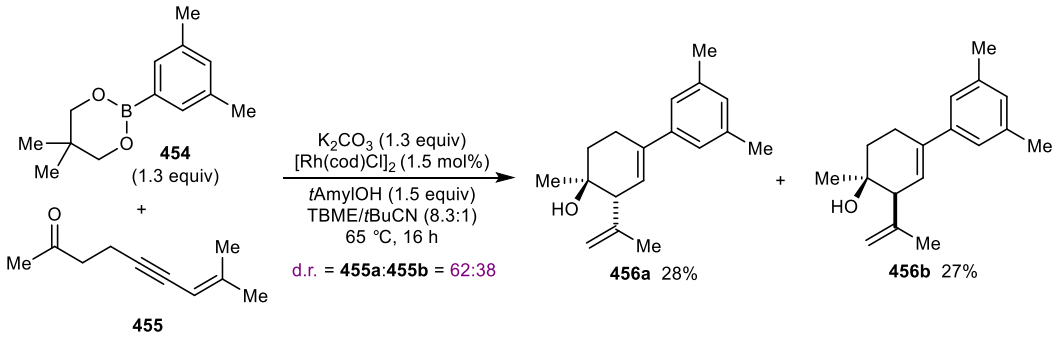
$[Rh(cod)Cl]_2$ (3.5 mg, 6.8 µmol) was added to an oven-dried microwave vial, and the vial was sealed with a septum and purged with nitrogen for 1 h. Degassed TBME (0.90 mL) and degassed *t*BuCN (0.90 mL) were added and the mixture was stirred for 30 min at room temperature. Meanwhile, in a separate oven-dried microwave vial, enynone **422** (92.0 mg, 0.450 mmol), 3,5-dimethylpyridineboronic acid pinacol ester **S1** (138 mg, 0.590 mmol), and K_3PO_4 (29.0 mg, 0.135 mmol) were added. The vial was sealed with a septum-lined microwave vial cap and purged with nitrogen for 1 h. Degassed TBME (6.6 mL), the solution of catalyst (see above), and degassed MeOH (0.75 mL) were added, and the mixture was stirred at 65 °C for 16 h. The reaction was cooled to room temperature, water (10 mL) and saturated aqueous ammonium chloride (10 mL) were added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The mixture was purified by column chromatography (twice, the first time using 70% $CHCl_3$, 29% EtOAc, 1% Et_3N; the second time using 50% EtOAc/petroleum ether) to give *alcohol* **446** (83.0 mg, 59%) as an off-white solid. R_f = 0.24 (50% EtOAc/petroleum ether); m.p. 202–204 °C (Et_2O); IR 3173 (O-H), 2963, 1732

(C=O), 1605, 1433, 1366, 1183 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (2H, s, Ar**H**), 6.14 (1H, app t, *J* = 2.5 Hz, C=C**H**), 5.15-5.12 (1H, m, C=C$\mathbf{H_A}H_B$), 4.94–4.91 (1H, m, C=C$H_A\mathbf{H_B}$), 3.21-3.16 (1H, m, C=CC**H**), 2.54-2.36 (3H, m, O=CC$\mathbf{H_2}$ and C=CC$\mathbf{H_A}H_B$), 2.52 (6H, s, 2 × ArC$\mathbf{H_3}$), 2.20 (1H, dd, *J* = 18.0, 1.8 Hz, C=CC$H_A\mathbf{H_B}$), 2.06 (1H, app dt, *J* = 13.5, 9.8 Hz, HOCC$\mathbf{H_A}H_B$), 1.93-1.90 (3H, m, C=CC$\mathbf{H_3}$), 1.82 (1H, s, O**H**), 1.78 (1H, ddd, *J* = 13.5, 8.1, 2.8 Hz, HOCC$H_A\mathbf{H_B}$), 1.15 (3H, s, O=CCC$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.1 (C), 157.9 (2 × C), 148.0 (C), 143.7 (C), 131.3 (C), 127.7 (CH), 116.3 (2 × CH), 116.0 (CH_2), 79.3 (C), 52.7 (C), 50.5 (CH), 34.8 (CH_2), 32.7 (CH_2), 29.5 (CH_2), 24.5 (2 × CH_3), 23.0 (CH_3), 13.2 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{20}H_{26}NO_2]^+$ $[M+H]^+$: 312.1958, found: 312.1961.

NOESY



(±)-(1*S*,2*R*)-4-(3,5-Dimethylphenyl)-1-methyl-2-(prop-1-en-2-yl)cyclohex-3-en-1-ol (456a) and (±)-(1*S*,2*S*)-4-(3,5-dimethylphenyl)-1-methyl-2-(prop-1-en-2-yl)cyclohex-3-en-1-ol (456b)



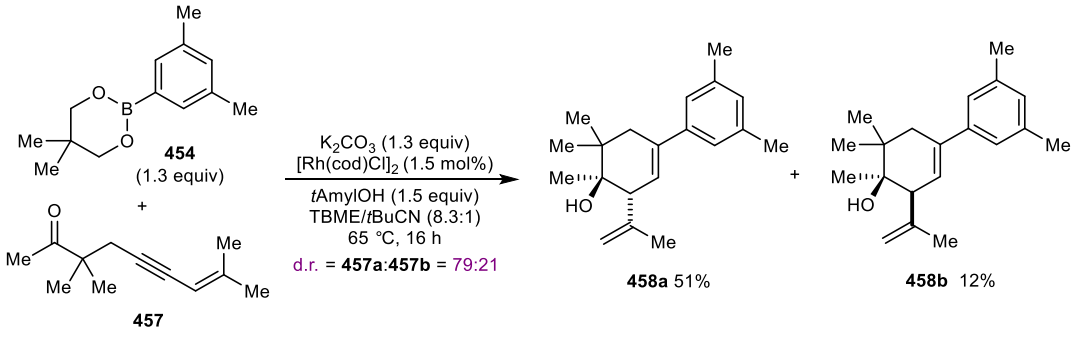
$[Rh(cod)Cl]_2$ (3.7 mg, 7.5 µmol) was added to an oven-dried microwave vial, and the vial was sealed with a septum and purged with nitrogen for 1 h. Degassed TBME (1 mL) and degassed *t*BuCN (1 mL) were added and the mixture was stirred for 30 min at room temperature. Meanwhile, in a separate oven-dried microwave vial, enynone **455** (75.1 mg, 0.500 mmol), 3,5-dimethylphenylboronic acid neopentylglycol ester **454** (142 mg, 0.650 mmol), and K_2CO_3 (89.8 mg, 0.650 mmol) were added. The vial was sealed with a septum-lined microwave vial cap and purged with nitrogen for 1 h. Degassed TBME (7.3 mL), the solution of catalyst (see above), and *t*-amyl alcohol (0.08 mL, 0.73 mmol) were added, and the mixture was stirred at 65 °C for 16 h. The reaction was cooled to room temperature, water (10 mL) and saturated aqueous NH_4Cl solution (10 mL) were added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. ^{1}H NMR analysis indicated a 62:38 mixture of diastereomers **456a** and **456b**, respectively. The mixture was purified by column chromatography (twice, the first time using 10% EtOAc/*iso*-hexane; the second time using $CHCl_3$) to give *alcohol* **456b** (35 mg, 27%) as a colourless oil followed by *alcohol* **456a** (36 mg, 28%) as a colourless oil. The relative configurations of **456a** and **456b** could not be determined unambiguously and were assigned tentatively by analogy with the reaction producing **458a** and **458b**, on the assumption that the major products in each case possess the same relative configuration.

Data for **458a**: R_f = 0.41 (10% EtOAc/petroleum ether); IR 3425 (O-H), 2920, 1599, 1447 1374, 1106, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (2H, s, Ar**H**), 6.92 (1H, s, Ar**H**), 5.92 (1H, app dt, *J* = 3.6, 1.7 Hz, C=C**H**), 5.04-5.01 (1H, m, C=C$\mathbf{H_A}$H$_B$), 4.88-4.85 (1H, m, C=CH$_A$$\mathbf{H_B}$), 3.05-3.01 (1H, m, C=CC**H**), 2.68–2.46 (2H, m, C=CC$\mathbf{H_2}$), 2.33 (6H, s, 2 × ArC$\mathbf{H_3}$), 1.97-1.77 (6H, m,

C=CCH$_2$C**H$_2$**, C=CC**H$_3$** and O**H**), 1.20 (3H, s, C**H$_3$**COH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8 (C), 141.3 (C), 137.7 (2 × C), 135.8 (C), 128.7 (CH), 125.6 (CH), 123.1 (2 × CH), 115.0 (CH_2), 70.8 (C), 55.4 (CH), 34.9 (CH_2), 25.5 (CH_2), 24.9 (CH_3), 23.3 (CH_3), 21.4 (2 × CH_3); HRMS (ESI) Exact mass calcd for $[C_{18}H_{25}O]^+$ $[M+H]^+$: 257.1900, found: 257.1886.

Data for **458b**: R_f = 0.67 (10% EtOAc/petroleum ether); IR 3466 (O-H), 2920, 1599, 1371, 1126, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (2H, s, Ar**H**), 6.92 (1H, s, Ar**H**), 5.86 (1H, app dt, *J* = 3.4, 1.7 Hz, C=C**H**), 5.14-5.11 (1H, m, C=C**H$_A$**H$_B$), 4.89 (1H, app dt, *J* = 2.3, 0.8 Hz, C=CH$_A$**H$_B$**), 3.01–2.96 (1H, m, C=CC**H**), 2.74-2.63 (1H, m, C=CC**H$_A$**H$_B$), 2.50-2.40 (1H, m, C=CCH$_A$**H$_B$**), 2.34 (6H, s, 2 × ArC**H$_3$**), 2.01-1.90 (4H, m, C=CCH$_2$C**H$_A$**H$_B$ and C=CC**H$_3$**) 1.81-1.70 (2H, m, C=CCH$_2$CH$_A$**H$_B$** and O**H**), 1.34 (3H, s, C**H$_3$**COH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5 (C), 141.5 (C), 137.7 (2 × C), 136.2 (C), 128.6 (CH), 125.9 (CH), 123.1 (2 × CH), 115.5 (CH_2), 69.3 (C), 53.9 (CH), 35.0 (CH_2), 28.5 (CH_3), 25.3 (CH_2), 24.6 (CH_3), 21.4 (2 × CH_3); HRMS (ESI) Exact mass calcd for $[C_{18}H_{24}NaO]^+$ $[M+Na]^+$: 279.1719, found: 279.1707.

(±)-(1*S*,2*R*)-4-(3,5-Dimethylphenyl)-1,6,6-trimethyl-2-(prop-1-en-2-yl)cyclohex-3-en-1-ol (458a) and (±)-(1*S*,2*S*)-4-(3,5-dimethylphenyl)-1,6,6-trimethyl-2-(prop-1-en-2-yl)cyclohex-3-en-1-ol (458b)

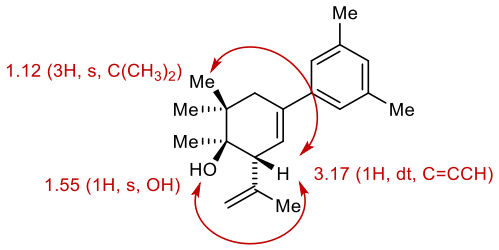


$[Rh(cod)Cl]_2$ (3.7 mg, 7.5 µmol) was added to an oven-dried microwave vial, and the vial was sealed with a septum and purged with nitrogen for 1 h. Degassed TBME (1 mL) and degassed *t*BuCN (1 mL) were added and the mixture was stirred for 30 min at room temperature. Meanwhile, in a separate oven-dried microwave vial, enynone **457** (89.1 mg, 0.500 mmol), 3,5-dimethylphenylboronic acid neopentylglycol ester **454** (142 mg, 0.650 mmol), and K_2CO_3 (89.8 mg, 0.650 mmol) were added. The vial was sealed with a septum-lined microwave vial cap and purged with nitrogen for 1 h. Degassed TBME (7.3 mL), the solution of catalyst (see above), and *t*-amyl alcohol (0.08 mL, 0.73 mmol) were added, and the mixture was stirred at 65 °C for 16 h. The reaction was cooled to room temperature, water (10 mL) and saturated aqueous NH_4Cl solution (10 mL) were added, and the mixture was extracted with EtOAc (3 x

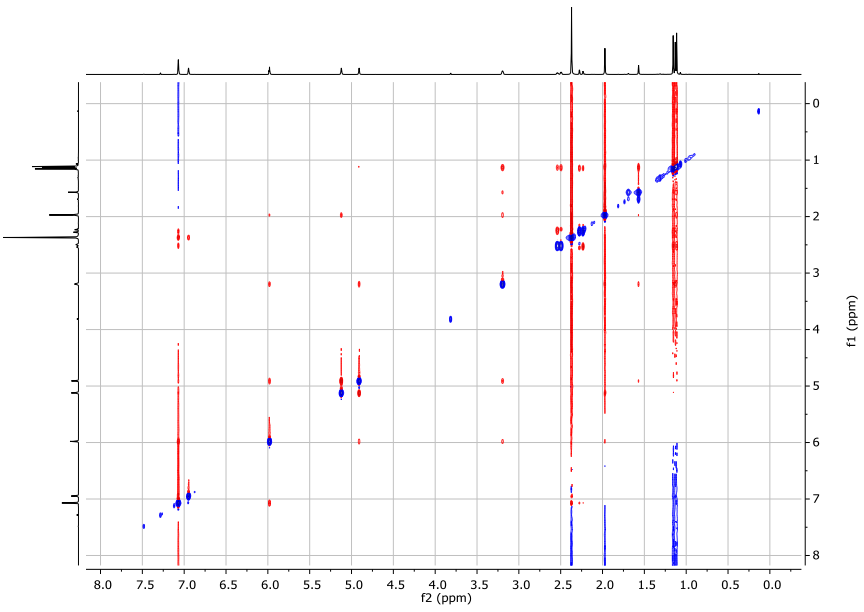
15 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. ^{1}H NMR analysis indicated a 79:21 mixture of diastereomers **458a** and **458b**, respectively. The mixture was purified by column chromatography (10% EtOAc/*iso*-hexane) to give *alcohol* **458a** (72 mg, 51%) as a pale yellow oil followed by *alcohol* **458b** in *ca.* 85% purity as determined by ^{1}H NMR analysis (17 mg, 12%, after a second column using 2% Et_2O/*iso*-hexane) as a pale yellow oil.

Data for **458a**: R_f = 0.31 (10% EtOAc/petroleum ether); IR 3580 (O-H), 2962, 1599, 1372, 1092, 844 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (2H, s, Ar**H**), 6.94 (1H, s, Ar**H**), 5.97 (1H, app t, *J* = 2.4 Hz, C=C**H**), 5.12-5.08 (1H, m, C=C$\mathbf{H_A}H_B$), 4.91-4.88 (1H, m, C=C$\mathbf{H_A}H_B$), 3.17 (1H, app dt, *J* = 4.1, 1.9 Hz, C=CC**H**), 2.54-2.45 (1H, m, C=CC$\mathbf{H_A}H_B$), 2.36 (6H, s, 2 × ArC$\mathbf{H_3}$), 2.24 (1H, dd, *J* = 17.5, 1.8 Hz, C=CC$H_A\mathbf{H_B}$), 1.98-1.93 (3H, m, C=CC$\mathbf{H_3}$), 1.55 (1H, s, O**H**), 1.14 (3H, s, C(C$\mathbf{H_3}$)$_2$), 1.12 (3H, s, C(C$\mathbf{H_3}$)$_2$), 1.10 (3H, s, C$\mathbf{H_3}$COH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6 (C), 141.6 (C), 137.7 (2 × C), 135.3 (C), 128.6 (CH), 126.2 (CH), 123.0 (2 × CH), 114.9 (CH_2), 74.8 (C), 52.1 (CH), 41.9 (CH_2), 37.9 (C), 24.3 (CH_3), 24.1 (CH_3), 22.3 (CH_3), 21.4 (2 × CH_3), 19.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{20}H_{28}NaO]^+$ [M+Na]$^+$: 307.2032, found: 307.2031.

NOESY

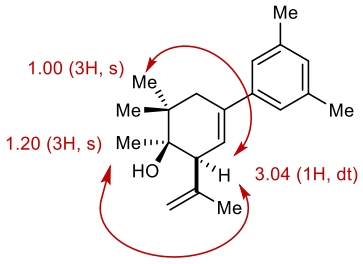


458a

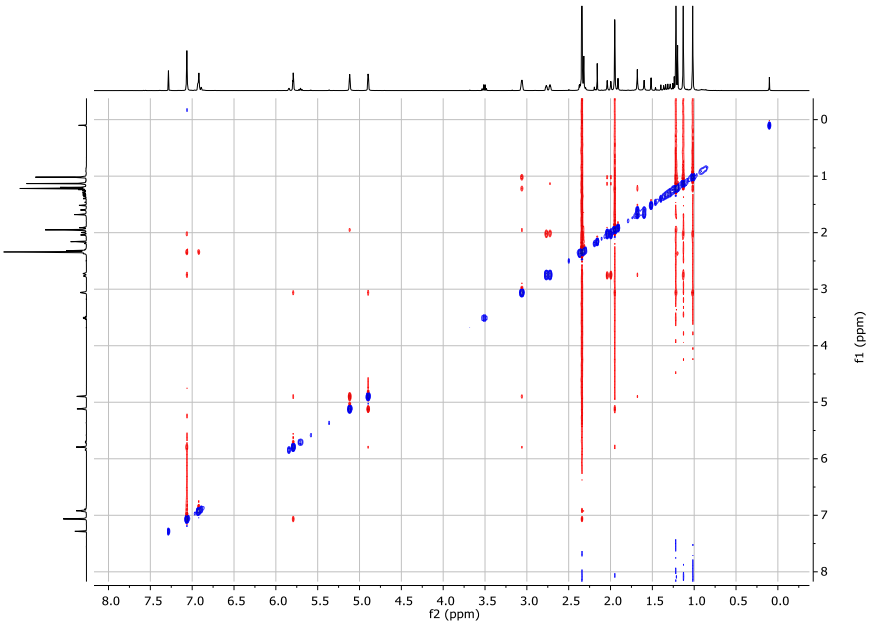


Data for **458b**: R_f = 0.35 (10% EtOAc/petroleum ether); IR 3559 (O-H), 2961, 1598, 1445, 1373, 1071, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (2H, s, Ar**H**), 6.90 (1H, s, Ar**H**), 5.78 (1H, app t, *J* = 2.4 Hz, C=C**H**), 5.12-5.09 (1H, m, C=C$\mathbf{H_A}H_B$), 4.89-4.87 (1H, m, C=C$\mathbf{H_A}H_B$), 3.04 (1H, app dt, *J* = 4.1, 1.9 Hz, C=CC**H**), 2.73 (1H, app dt, *J* = 17.3, 3.4 Hz, C=CC$\mathbf{H_A}H_B$), 2.33 (6H, s, 2 × ArC$\mathbf{H_3}$), 2.00 (1H, dd, *J* = 17.3, 1.7 Hz, C=CC$H_A\mathbf{H_B}$), 1.95-1.92 (3H, m, C=CC$\mathbf{H_3}$), 1.66 (1H, s, O**H**), 1.20 (3H, s, C$\mathbf{H_3}$COH), 1.11 (3H, s, C(C$\mathbf{H_3}$)$_2$), 1.00 (3H, s, C(C$\mathbf{H_3}$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0 (C), 141.7 (C), 137.7 (2 × C), 136.1 (C), 128.6 (CH), 125.3 (CH), 123.0 (2 × CH), 115.7 (CH_2), 73.5 (C), 51.6 (CH), 39.6 (CH_2), 37.7 (C), 24.6 (CH_3), 24.3 (2 × CH_3), 21.4 (2 × CH_3), 20.9 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{20}H_{29}O]^+$ $[M+H]^+$: 285.2213, found: 285.2204.

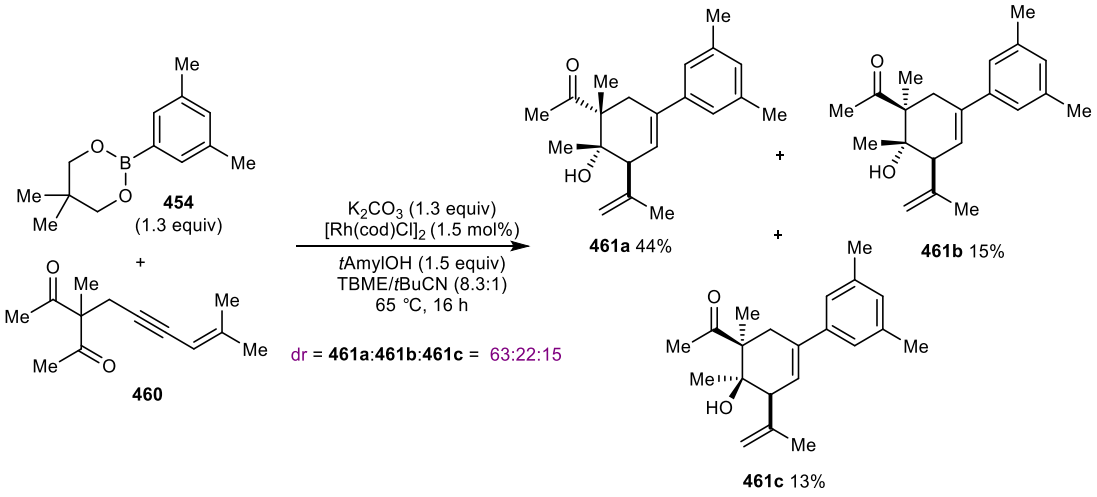
NOESY



458b



(±)-1-[(1*S*,5*R*,6*R*)-3-(3,5-Dimethylphenyl)-6-hydroxy-1,6-dimethyl-5-(prop-1-en-2-yl)cyclohex-3-en-1-yl]ethan-1-one (461a), **(±)-1-[(1*R*,5*R*,6*R*)-3-(3,5-Dimethylphenyl)-6-hydroxy-1,6-dimethyl-5-(prop-1-en-2-yl)cyclohex-3-en-1-yl]ethan-1-one (461b)** and **(±)-1-[(1*R*,5*R*,6*S*)-3-(3,5-Dimethylphenyl)-6-hydroxy-1,6-dimethyl-5-(prop-1-en-2-yl)cyclohex-3-en-1-yl]ethan-1-one (461c)**

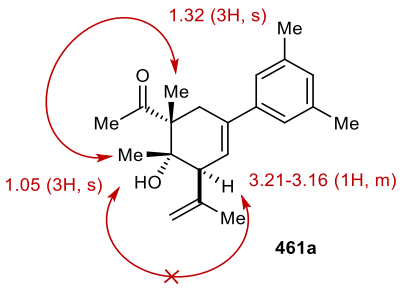


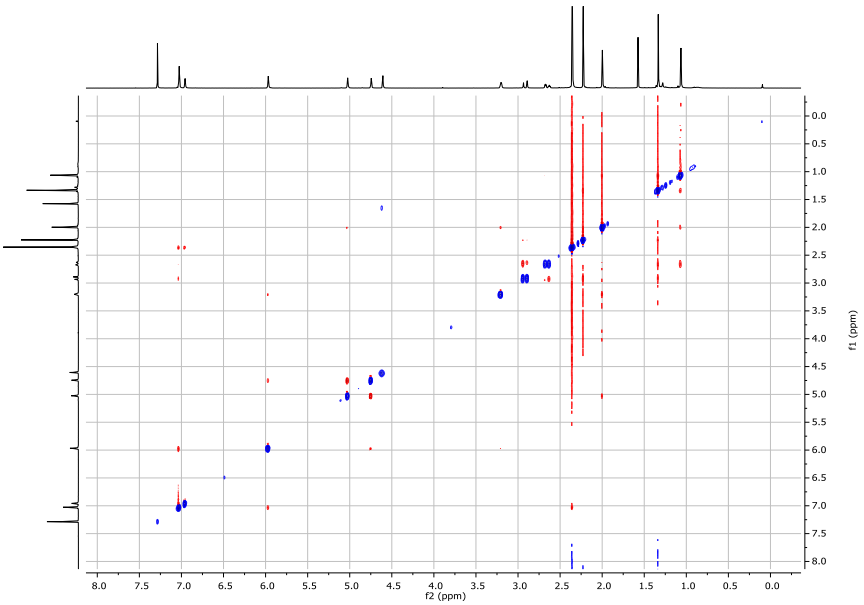
$[Rh(cod)Cl]_2$ (3.7 mg, 7.5 µmol) was added to an oven-dried microwave vial, and the vial was sealed with a septum and purged with nitrogen for 1 h. Degassed TBME (1 mL) and degassed *t*BuCN (1 mL) were added and the mixture was stirred for 30 min at room temperature. Meanwhile, in a separate oven-dried microwave vial, enynone **460** (103 mg, 0.500 mmol), 3,5-dimethylphenylboronic acid neopentylglycol ester **454** (142 mg, 0.650 mmol), and K_2CO_3 (89.8 mg, 0.650 mmol) were added. The vial was sealed with a septum-lined microwave vial cap and purged with nitrogen for 1 h. Degassed TBME (7.3 mL), the solution of catalyst (see above), and *t*-amyl alcohol (0.08 mL, 0.73 mmol) were added, and the mixture was stirred at 65 °C for 16 h. The reaction was cooled to room temperature, water (10 mL) and saturated aqueous NH_4Cl solution (10 mL) were added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. ^1H NMR analysis indicated a 63:22:15 mixture of diastereomers **461a**, **461b**, and **461c** respectively. The mixture was purified by column chromatography (70% petroleum ether, 28% CH_2Cl_2, 2% EtOAc) to separate alcohol **461c** from **461a** and **461b**. Alcohol **461c** was further purified by column chromatography (100% $CHCl_3$) to give alcohol **461c** (21 mg, 13%) as a yellow oil. The mixture of alcohols **461a** and

461b were repurifed by column chromatography (2% EtOAc/petroleum ether) to give alcohol **461a** (69 mg, 44%) as an off white-solid and alcohol **461b**[2] (24 mg, 15%) as a yellow oil.

Data for **461a**: R_f = 0.26 (70% petroleum ether, 28% CH_2Cl_2, 2% EtOAc); IR 3484 (O-H), 2922, 1682 (C=O), 1389, 891 cm^{-1}; m.p. 110-112 °C (Et_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (2H, s, Ar**H**), 6.94 (1H, s, Ar**H**), 5.95 (1H, app t, J = 2.6 Hz, C=C**H**), 5.02-4.99 (1H, m, C=C$\mathbf{H_A}H_B$), 4.74-4.71 (1H, m, C=C$H_A\mathbf{H_B}$), 4.60-4.58 (1H, m, O**H**), 3.21-3.16 (1H, m, C=CC**H**), 2.90 (1H, dd, J = 17.9, 1.4 Hz, C=CC$\mathbf{H_A}H_B$), 2.64 (1H, ddd, J = 17.9, 4.1, 2.7 Hz, C=CC$H_A\mathbf{H_B}$), 2.34 (6H, s, 2 × Ar$\mathbf{CH_3}$), 2.21 (3H, s, C(O)C$\mathbf{H_3}$), 1.98 (3H, s, C=CC$\mathbf{H_3}$), 1.32 (3H, s, C(O)CC$\mathbf{H_3}$), 1.05 (3H, d, J = 1.2 Hz, C$\mathbf{H_3}$COH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.7 (C), 146.5 (C), 140.7 (C), 138.0 (C), 134.9 (C), 129.8 (CH), 129.1 (CH), 122.8 (CH), 113.8 (CH_2), 75.3 (C), 54.5 (CH), 52.9 (C), 37.7 (CH_2), 26.9 (CH_3), 25.5 (CH_3), 21.4 (CH_3), 19.2 (2 × CH_3), 19.0 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{21}H_{28}NaO_2]^+$ [M+Na]$^+$: 335.1982, found: 335.1980.

NOESY

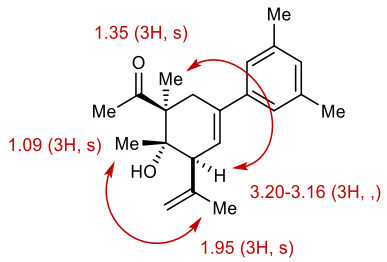




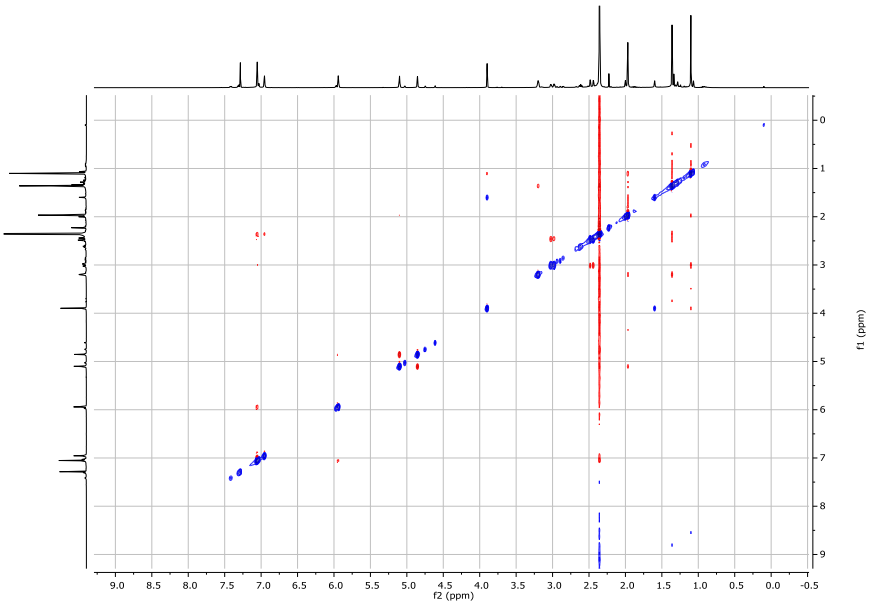
[2] **461b** isolated as a 7.5:1 mixture of diasteroisomers (**461b:461a**)

Data for **461b**: R_f = 0.26 (70% petroleum ether, 28% CH_2Cl_2, 2% EtOAc); IR 3475 (O-H), 2929, 1686 (C=O), 1257, 789 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (2H, s, Ar**H**), 6.94 (1H, s, Ar**H**), 5.93 (1H, app t, J = 2.4 Hz, C=C**H**), 5.07-5.10 (1H, m, C=C$\mathbf{H_A}H_B$), 4.85-4.83 (1H, m, C=$CH_A\mathbf{H_B}$), 3.88 (1H, s, O**H**), 3.20-3.16 (1H, m, C=CC**H**), 2.99 (1H, app dt, J = 17.3, 3.5 Hz, C=CC$\mathbf{H_A}H_B$), 2.45 (1H, dd, J = 17.3, 1.7 Hz, C=$CCH_A\mathbf{H_B}$), 2.36-2.32 (9H, m, 2 × Ar$\mathbf{CH_3}$ and 3H C(O)C$\mathbf{H_3}$), 1.95 (3H, s, C=CC$\mathbf{H_3}$), 1.35 (3H, s, C(O)CC$\mathbf{H_3}$), 1.09 (3H, s, C$\mathbf{H_3}$COH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.8 (C), 145.8 (C), 141.3 (C), 137.9 (2 × C), 133.4 (C), 128.9 (CH), 126.3 (CH), 123.1 (CH), 115.1 (CH_2), 74.0 (C), 53.7 (C), 51.2 (CH), 36.0 (CH_2), 27.9 (CH_3), 24.7 (CH_3), 21.4 (2 × CH_3), 21.3 (CH_3), 17.8 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{21}H_{28}NaO_2]^+$ [M+Na]$^+$: 335.1982, found: 335.1978.

NOESY



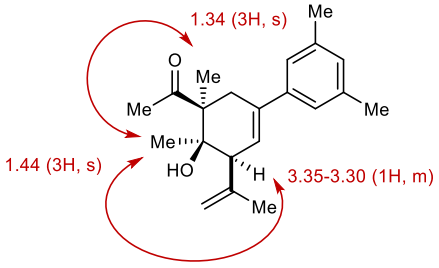
461b



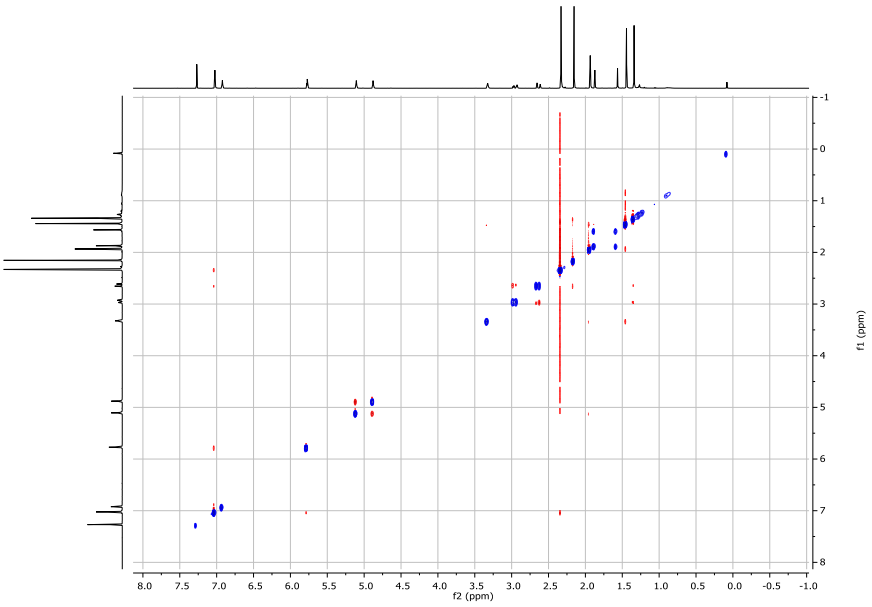
Data for **461c**: R_f = 0.37 (70% petroleum ether, 28% CH_2Cl_2, 2% EtOAc); IR 3547 (O-H), 2919, 1699 (C=O), 1352, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (2H, s, Ar**H**), 6.92 (1H, s, Ar**H**), 5.77 (1H, app t, *J* = 2.5 Hz, C=C**H**), 5.12-5.09 (1H, m, C=C$\mathbf{H_A}H_B$), 4.89-4.86 (1H, m, C=$CH_A\mathbf{H_B}$), ,

3.35-3.30 (1H, m, C=CC**H**), 2.99 (1H, ddd, *J* = 17.5, 4.0, 2.7 Hz, C=CC**H**$_A$H$_B$), 2.63 (1H, dd, *J* = 17.5, 1.5 Hz, C=CCH$_A$**H$_B$**), 2.33 (6H, s, 2 × ArC**H$_3$**), 2.15 (3H, s, C(O)C**H$_3$**), 1.93 (3H, s, C=CC**H$_3$**), 1.87 (1H, s, O**H**), 1.44 (3H, s, C**H$_3$**COH), 1.34 (3H, s, C(O)CC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.5 (C), 146.4 (C), 141.1 (C), 137.8 (2 × C), 135.5 (C), 128.9 (CH), 127.6 (CH), 122.9 (2 × CH, 116.2 (CH_2), 72.0 (C), 55.2 (C), 51.8 (CH), 35.7 (CH_2), 27.0 (CH_3), 25.0 (CH_3), 23.0 (CH_3), 21.4 (2 × CH_3), 20.0 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{21}H_{28}NaO_2]^+$ [M+Na]$^+$: 335.1982, found: 335.1976.

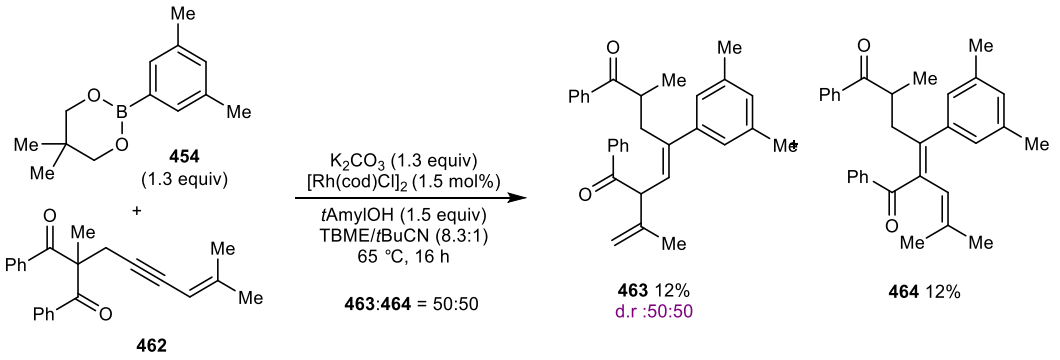
NOESY



461c



(*E*)-4-(3,5-dimethylphenyl)-6-methyl-1,7-diphenyl-2-(prop-1-en-2-yl)hept-3-ene-1,7-dione (463) and (*E*)-3-(3,5-dimethylphenyl)-5-methyl-2-(2-methylprop-1-en-1-yl)-1,6-diphenylhex-2-ene-1,6-dione (464)



$[Rh(cod)Cl]_2$ (3.7 mg, 7.5 µmol) was added to an oven-dried microwave vial, and the vial was sealed with a septum and purged with nitrogen for 1 h. Degassed TBME (1 mL) and degassed *t*BuCN (1 mL) were added and the mixture was stirred for 30 min at room temperature. Meanwhile, in a separate oven-dried microwave vial, enynone **462** (165 mg, 0.500 mmol), 3,5-dimethylphenylboronic acid neopentylglycol ester **454** (142 mg, 0.650 mmol), and K_2CO_3 (89.8 mg, 0.650 mmol) were added. The vial was sealed with a septum-lined microwave vial cap and purged with nitrogen for 1 h. Degassed TBME (7.3 mL), the solution of catalyst (see above), and *t*-amyl alcohol (0.08 mL, 0.73 mmol) were added, and the mixture was stirred at 65 °C for 16 h. The reaction was cooled to room temperature, water (10 mL) and saturated aqueous NH_4Cl solution (10 mL) were added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (twice, the first time using 70% petroleum ether, 28% CH_2Cl_2 and 2% Et_2O; the second time using 100% $CHCl_3$) to give *allylation product* **463** (50 mg, 12%) as a colourless oil in a 1:1 diastereomeric mixture and *diketone* **464** (50 mg, 12%) as a colourless oil.

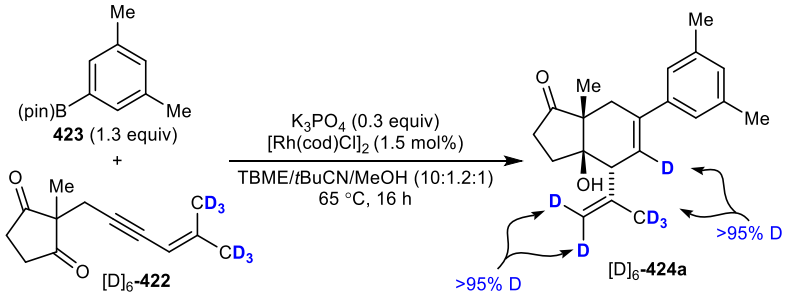
Data for **463**: R_f = 0.41 (60% petroleum ether, 38% CH_2Cl_2, 2% Et_2O); IR 2968, 1679 (C=O), 1596, 1447, 1239, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (4H, d, *J* = 7.2 Hz, Ar**H**), 7.79 (2H, d, *J*= 7.2 Hz, Ar**H**), 7.67-7.62 (2H, m, Ar**H**), 7.62-7.38 (10H, m, Ar**H**), 7.33 (2H, t, *J* = 7.7 Hz, Ar**H**), 6.99-6.95 (3H, m, Ar**H**), 6.93 (1H, s, Ar**H**), 6.87 (2H, s, Ar**H**), 6.10 (1H, d, *J* = 9.6 Hz, C=C**H**), 6.02 (1H, d, *J* = 9.5 Hz, C=C**H**), 5.22 (1H, d, *J* = 9.5 Hz, C=CHC**H**), 5.16 (1H, d, *J* = 9.7 Hz, C=CHC**H**), 5.03 (1H, s, C=C$\mathbf{H_A}H_B$), 4.98 (1H, s, C=C$H_A\mathbf{H_B}$), 4.93 (1H, m, C=C$\mathbf{H_A}H_B$), 4.91 (1H, s, C=C$H_A\mathbf{H_B}$), 3.50 (1H, app sext, *J* = 6.9 Hz, $CH_3C\mathbf{H}$), 3.47-3.37 (1H, m, $CH_3C\mathbf{H}$), 3.12 (1H, dd, *J* = 14.1, 7.2 Hz, CHC$\mathbf{H_A}H_B$), 2.98 (1H, dd, *J* = 14.4, 4.8 Hz, CHC$\mathbf{H_A}H_B$), 2.77-2.64 (2H, m, CHC$H_A\mathbf{H_B}$ and

$CHCH_A\mathbf{H_B}$), 2.34 (6H, s, 2 × C$\mathbf{H_3}$), 2.31 (6H, s, 2 × C$\mathbf{H_3}$), 1.82 (3H, s, CH_2=CC$\mathbf{H_3}$), 1.79 (3H, s, CH_2=CC$\mathbf{H_3}$), 1.16 (1H, d, *J* = 6.9 Hz, CHC$\mathbf{H_3}$), 1.01 (3H, d, *J* = 6.8 Hz, CHC$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5 (C), 204.1 (C), 199.2 (C), 199.0 (C), 143.5 (C), 143.4 (C), 142.1 (C), 141.9 (C), 140.4 (C), 140.1 (C), 137.8 (2 × C), 137.7 (2 × C), 136.73 (C), 136.65 (C), 136.4 (C), 136.1 (C), 133.1 (CH), 133.0 (CH), 132.9 (2 × CH), 129.1 (CH), 129.0 (CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.54 (2 × CH), 128.49 (4 × CH), 128.4 (4 × CH), 128.3 (2 × CH), 127.9 (CH), 127.2 (CH), 124.9 (2 × CH), 124.8 (2 × CH), 114.5 (CH_2), 114.3 (CH_2), 54.24 (CH), 54.18 (CH), 38.89 (CH), 38.86 (CH), 34.1 (CH_2), 33.6 (CH_2), 21.32 (4 × CH_3), 21.27 (CH_3), 21.0 (CH_3), 17.6 (CH_3), 16.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{31}H_{32}NaO_2]^+$ $[M+Na]^+$: 459.2295, found: 459.2305.

Data for **464**: R_f = 0.49 (60% petroleum ether, 38% CH_2Cl_2, 2% Et_2O); IR 2924, 1681 (C=O), 1644, 1596, 1236, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.92 (2H, m, Ar**H**), 7.57-7.48 (3H, m, Ar**H**), 7.44-7.38 (2H, m, Ar**H**), 7.24-7.18 (1H, m, Ar**H**), 7.12-7.05 (2H, m, Ar**H**), 6.61 (2H, s, Ar**H**), 6.53 (1H, s, Ar**H**), 6.30 (1H, s, C=C**H**), 3.87 (1H, app sext, *J* = 6.9 Hz, CH_3C**H**), 3.04 (1H, dd, *J* = 14.0, 5.9 Hz, $C\mathbf{H_A}H_B$), 2.72 (1H, dd, *J* = 14.0, 8.2 Hz, $CH_A\mathbf{H_B}$), 2.05 (6H, s, 2 × ArC$\mathbf{H_3}$), 1.88 (3H, s, C=CC$\mathbf{H_3}$), 1.38 (3H, s, C=CC$\mathbf{H_3}$), 1.27 (3H, d, *J* = 6.9 Hz, CHC$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9 (C), 201.3 (C), 144.2 (C), 140.9 (C), 139.2 (C), 137.8 (C), 137.0 (2 × C), 136.2 (C), 135.7 (C), 132.80 (CH), 131.75 (CH), 128.9 (CH), 128.7 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 127.5 (2 × CH), 127.3 (2 × CH), 124.0 (CH), 39.8 (CH), 36.2 (CH_2), 26.5 (CH_3), 20.9 (2 × CH_3), 20.2 (CH_3), 17.2 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{31}H_{33}O_2]^+$ $[M+H]^+$: 437.2475, found: 437.2477.

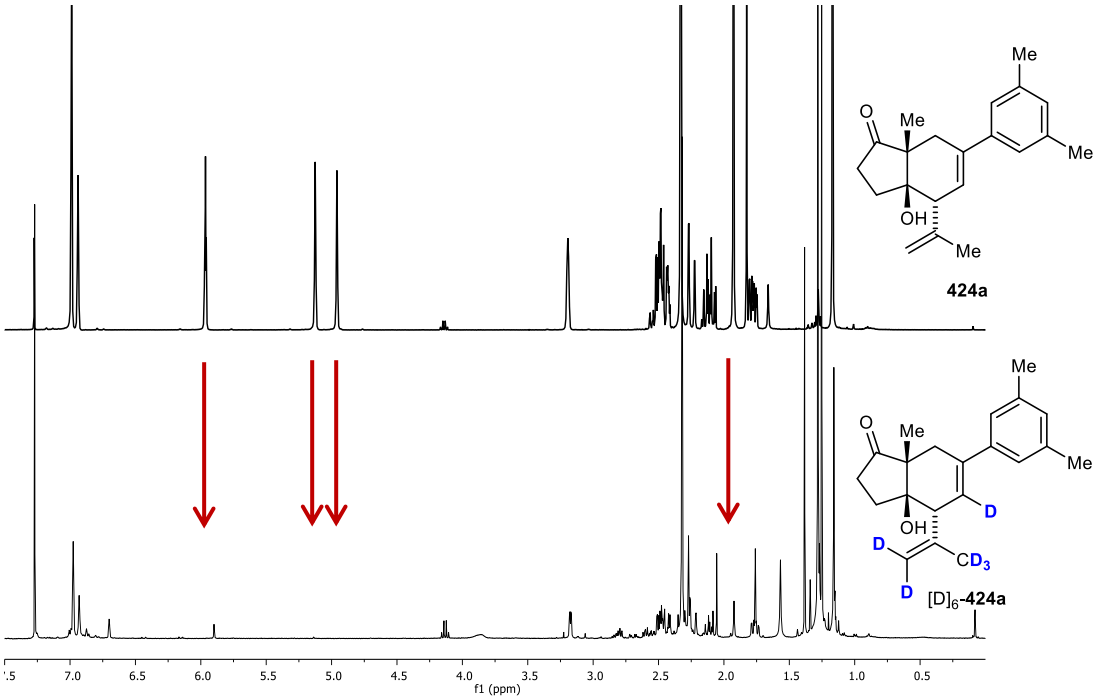
4.2.4 Investigation of Deuterium Transfer

(±)-(3a*R*,4*R*,7a*R*)-6-(3,5-Dimethylphenyl)-3a-hydroxy-7a-methyl-4-[(²H₅)prop-1-en-2-yl]-2,3,3a,4,7,7a-hexahydro(5-²H)-1*H*-inden-1-one ([D₆]-424a)



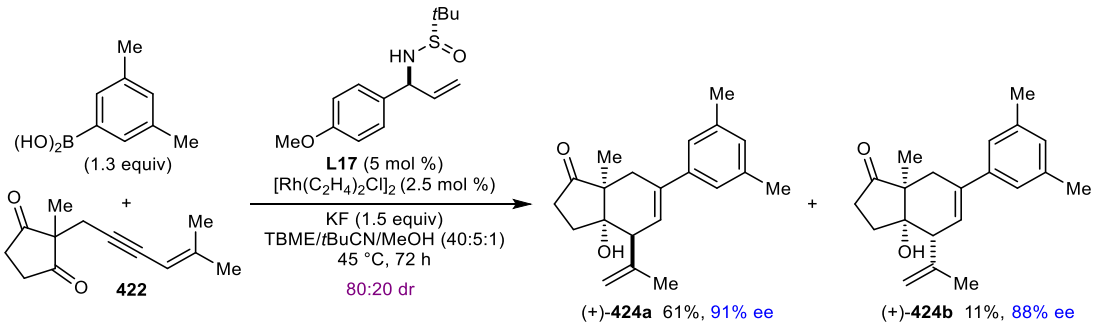
$[Rh(cod)Cl]_2$ (3.7 mg, 7.5 µmol) was added to an oven-dried microwave vial, and the vial was sealed with a septum and purged with nitrogen for 1 h. Degassed TBME (1 mL) and degassed *t*BuCN (1 mL) were added and the mixture was stirred for 30 min at room temperature. Meanwhile, in a separate oven-dried microwave vial, enynone $[D]_6$-**422** (165 mg, 0.500 mmol), 3,5-dimethylphenylboronic acid pinacol ester (151 mg, 0.650 mmol), and K_3PO_4 (31.8 mg, 0.150 mmol) were added. The vial was sealed with a septum-lined microwave vial cap and purged with nitrogen for 1 h. Degassed TBME (7.3 mL), the solution of catalyst (see above), and degassed MeOH (0.83 mL) were added, and the mixture was stirred at 65 °C for 16 h. The reaction was cooled to room temperature, water (10 mL) and saturated aqueous NH_4Cl solution (10 mL) were added, and the mixture was extracted with EtOAc (3 x 15 mL. The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (95% $CHCl_3$, 4% EtOAc, 1% Et_3N) to give *alcohol* $[D]_6$-**424a** (116 mg, 73%) as an orange solid. R_f = 0.33 (95% CH_3Cl, 4% EtOAc, 1% Et_3N); m.p. 160-162 °C (Et_2O); IR 3494 (O– H), 2924, 1724 (C=O), 1596, 1361, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (2H, s, Ar**H**), 6.93 (1H, s, Ar**H**), 3.17 (1H, dd, *J* = 4.1, 1.7 Hz, C=CC**H**), 2.57-2.40 (3H, m, O=CC**H₂** and C=CC$\mathbf{H_A}H_B$), 2.32 (3H, s, ArC$\mathbf{H_3}$), 2.32 (3H, s, ArC$\mathbf{H_3}$), 2.24 (1H, dd, *J* = 17.9, 1.7 Hz, C=C$CH_A\mathbf{H_B}$), 2.10 (1H, app dt, *J* = 13.6, 9.8 Hz, HOC$\mathbf{H_A}H_B$), 1.76 (1H, ddd, *J* = 13.6, 8.2, 2.3 Hz, HOC$\mathbf{H_A H_B}$), 1.72 (1H, br s, O**H**), 1.16 (3H, s, O=CCC$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.6 (C), 144.0 (C), 140.4 (C), 138.0 (2 × C), 133.0 (C), 129.1 (CH), 123.1 (2 × CH), 79.5 (C), 52.9 (CH), 50.4 (C), 35.6 (CH_2), 32.8 (CH_2), 29.5 (CH_2), 21.4 (2 × CH_3), 13.2 (CH_3); ^2H NMR (77 MHz, $CHCl_3$) δ 6.01 (1D, br s, C=C**D**), 5.16 (1D, br s, C=C$\mathbf{D_A}D_B$), 4.99 (1D, br s, C=C$D_A\mathbf{D_B}$), 1.89 (3D, br s, C$\mathbf{D_3}$); HRMS (ESI) Exact mass calcd for $[C_{21}H_{20}D_6NaO_2]^+$ $[M+Na]^+$: 339.2202, found: 339.2211.

Expansion of crude ^{1}H NMR spectrum:



4.2.5 Enantioselective Rhodium-Catalysed Arylative Allylation

(+)-(3a*S*,4*S*,7a*S*)-6-(3,5-Dimethylphenyl)-3a-hydroxy-7a-methyl-4-(prop-1-en-2-yl)2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one ((+)-424a) and (+)-(3a*S*,4*R*,7a*S*)-6-(3,5-dimethylphenyl)-3ahydroxy-7a-methyl-4-(prop-1-en-2-yl)-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one ((+)-424b)



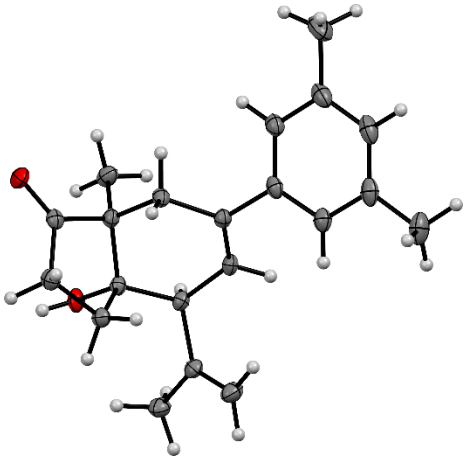
$[Rh(C_2H_4)Cl]_2$ (2.5 mg, 6.4 µmol) and **L17** (3.4 mg, 13 µmol) were added to an oven-dried microwave vial, and the vial was sealed with a septum and purged with nitrogen for 1 h. Degassed TBME (1 mL) and degassed *t*BuCN (0.5 mL) were added and the mixture was stirred for 30 min at room temperature. Meanwhile, in a separate oven-dried microwave vial, enynone **422** (51.0 mg, 0.250 mmol), 3,5-dimethylphenylboronic acid (56.3 mg, 0.375 mmol),

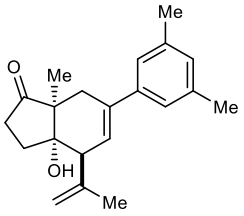
and KF (21.8 mg, 0.375 mmol) were added. The vial was sealed with a septum-lined microwave vial cap and purged with nitrogen for 1 h. Degassed TBME (3.2 mL), the solution of catalyst (see above), and MeOH (0.10 mL) were added, and the mixture was stirred at 45 °C for 72 h. The reaction was cooled to room temperature, water (10 mL) and saturated aqueous NH_4Cl solution (10 mL) were added, and the mixture was extracted with EtOAc (3 × 10 mL. The combined organic phases were washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. ^{1}H NMR analysis indicated a 80:20 mixture of diastereomers (+)-**424a** and (+)-**424b**, respectively. The mixture was purified by column chromatography (twice, the first time using 94% $CHCl_3$, 5% EtOAc, 1% Et_3N; the second time using 20% EtOAc/petroleum ether) to give alcohol (+)-**424a** (47 mg, 61%) as a white solid and alcohol (+)-**424b** (8 mg, 11%) as a colourless oil.

Data for (+)-**424a**: R_f = 0.15 (95% $CHCl_3$, 5% Et_2O); m.p. 140-141 °C (Et_2O); $[\alpha]_D^{21.0}$ +34.0 (*c* 0.47, $CHCl_3$); IR 3494 (O-H), 2963, 1725 (C=O), 1461, 1372, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (2H, s, Ar**H**), 6.93 (1H, s, Ar**H**), 5.95 (1H, app t, *J* = 2.5 Hz, C=C**H**), 5.13-5.10 (1H, m, C=C**H$_A$**H$_B$), 4.95 (1H, br s, C=CH$_A$**H$_B$**), 3.20-3.16 (1H, m, C=CC**H**), 2.57-2.39 (3H, m, O=CC**H$_2$** and C=CC**H$_A$**H$_B$), 2.32 (6H, s, 2 × ArC**H$_3$**), 2.23 (1H, dd, *J* = 18.0, 1.7 Hz, C=CCH$_A$**H$_B$**), 2.10 (1H, app dt, *J* = 13.5, 9.8 Hz, HOCC**H$_A$**H$_B$), 1.91 (3H, br s, C=CC**H$_3$**), 1.80-1.73 (2H, m, **H**OCCH$_A$**H$_B$**), 1.16 (3H, s, O=CCC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.6 (C), 144.3 (C), 140.4 (C), 137.9 (2 × C), 133.1 (C), 129.1 (CH), 124.4 (CH), 123.1 (2 × CH), 115.7 (CH_2), 79.5 (C), 52.9 (C), 50.6 (CH), 35.7 (CH_2), 32.8 (CH_2), 29.5 (CH_2), 22.9 (CH_3), 21.3 (2 × CH_3), 13.2 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{21}H_{26}NaO_2]^+$ $[M+H]^+$: 333.1825, found: 333.1827; Enantiomeric excess was determined by HPLC using a Chiralcel IC column (95:5 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 210 nm); t_r (major) = 14.6 min, t_r (minor) = 17.2 min, 91% ee.

Slow diffusion of petroleum ether into a solution of (+)–**424a** in EtOAc provided crystals that were suitable for X-ray diffraction:[3]

[3] Crystal obtained by B. Partridge

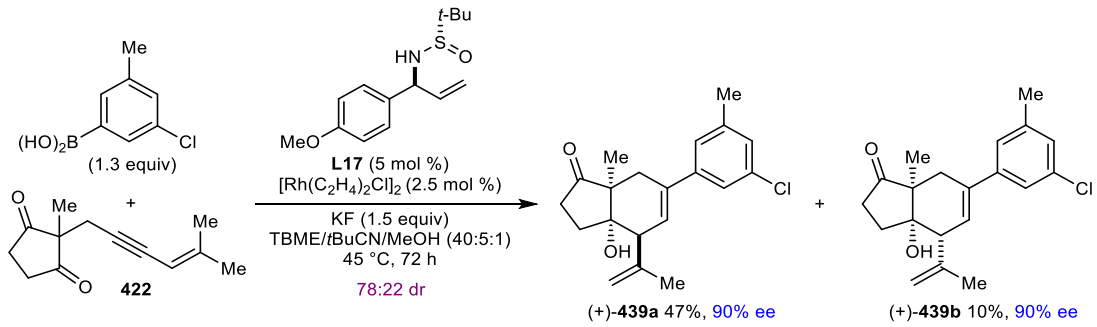




(+)-**424a**
CCDC 1535509
Flack parameter = –0.05(11)

Data for (+)-**424b**: R_f = 0.53 (94% $CHCl_3$, 5% EtOAc, 1% Et_3N); $[\alpha]_D^{21.0}$ +63.2 (*c* 0.76, $CHCl_3$); IR 3417 (O-H), 2921, 1726 (C=O), 1372, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (2H, s, Ar**H**), 6.93 (1H, s, Ar**H**), 5.93 (1H, app t, *J* = 2.8 Hz, C=C**H**), 5.19 (1H, br s, C=C$\mathbf{H_A}H_B$), 5.00 (1H, s, C=C$H_A\mathbf{H_B}$), 3.13 (1H, br s, C=CC**H**), 2.64-2.51 (2H, m, O=CC$\mathbf{H_A}H_B$ and C=CC$\mathbf{H_A}H_B$), 2.43 (1H, ddd, *J* = 19.4, 9.0, 4.4 Hz, O=CC$H_A\mathbf{H_B}$), 2.36-2.27 (1H, m, C=CC$H_A\mathbf{H_B}$), 2.33 (6H, s, 2 × Ar**CH₃**), 2.22 (1H, ddd, 13.4, 9.0, 8.1, HOCC$\mathbf{H_A}H_B$), 2.13 (1H, ddd, *J* = 13.4, 9.0, 4.4 Hz, HOCC$H_A\mathbf{H_B}$), 2.00 (1H, s, O**H**), 1.96 (3H, s, C=CC**H₃**), 1.18 (3H, s, O=CCC**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.8 (C), 145.2 (C), 140.9 (C), 137.9 (2 × C), 134.3 (C), 129.0 (CH), 125.1 (CH), 123.2 (2 × CH), 117.0 (CH_2), 77.9 (C), 52.7 (C), 51.5 (CH), 34.2 (CH_2), 33.7 (CH_2), 33.4 (CH_2), 24.4 (CH_3), 21.3 (2 × CH_3), 16.7 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{21}H_{26}NaO_2]^+$ $[M+Na]^+$: 333.1825, found: 333.1819; Enantiomeric excess was determined by HPLC using a Chiralcel IC column (95:5 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (major) = 9.2 min, t_r (minor) = 12.6 min, 88% ee.

(+)-(3a*S*,4*S*,7a*S*)-6-(3-Chloro-5-methylphenyl)-3a-hydroxy-7a-methyl-4-(prop-1-en-2-yl)-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one (439a) and (+)-(3a*S*,4*R*,7a*S*)-6-(3-chloro-5-methylphenyl)-3a-hydroxy-7a-methyl-4(prop-1-en-2-yl)-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one (439b)



$[Rh(C_2H_4)Cl]_2$ (2.5 mg, 6.4 µmol) and **L17** (3.4 mg, 13 µmol) were added to an oven-dried microwave vial, and the vial was sealed with a septum and purged with nitrogen for 1 h. Degassed TBME (1 mL) and degassed *t*BuCN (0.5 mL) were added and the mixture was stirred for 30 min at room temperature. Meanwhile, in a separate oven-dried microwave vial, enynone **422** (51.0 mg, 0.250 mmol), 3-chloro-5-methylphenylboronic acid (63.9 mg, 0.375 mmol), and KF (21.8 mg, 0.375 mmol) were added. The vial was sealed with a septum-lined microwave vial cap and purged with nitrogen for 1 h. Degassed TBME (3.2 mL), the solution of catalyst (see above), and MeOH (0.10 mL) were added, and the mixture was stirred at 45 °C for 72 h. The reaction was cooled to room temperature, water (10 mL) and saturated aqueous NH_4Cl solution (10 mL) were added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. ^{1}H NMR analysis indicated a 78:22 mixture of diastereomers (+)-**439a** and (+)-**439b**, respectively. The mixture was purified by column chromatography (94% $CHCl_3$, 5% EtOAc, 1% Et_3N) to give alcohol (+)-**439a** (39 mg, 47%) as a beige solid and alcohol (+)-**439b** (8 mg, 10%) as a colourless oil.

Data for (+)-**439a**: R_f = 0.20 (94% $CHCl_3$, 5% EtOAc, 1% Et_3N); $[\alpha]_D^{20.0}$ +9.8 (*c* 0.41, $CHCl_3$); m.p. 132-134 °C (Et_2O); IR 3415 (O-H), 2921, 1726 (C=O), 1461, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.13 (1H, m, Ar**H**), 7.09-7.06 (1H, m, Ar**H**), 7.03-7.01 (1H, m, Ar**H**), 5.97 (1H, app t, *J* = 2.5 Hz, C=C**H**), 5.12 (1H, app quin, *J* = 1.3 Hz, C=C**H**$_A$H$_B$), 4.96-4.92 (1H, m, C=CH$_A$**H**$_B$), 3.18 (1H, app dt, *J* = 4.3, 2.0 Hz, C=CC**H**), 2.57-2.36 (3H, m, O=CC**H**$_2$ and C=CC**H**$_A$H$_B$), 2.33 (3H, s, ArC**H**$_3$), 2.19 (1H, dd, *J* = 18.0, 1.7 Hz, C=CCH$_A$**H**$_B$), 2.08 (1H, app dt, *J* = 13.6, 9.8 Hz, HOCC**H**$_A$H$_B$), 1.94-1.89 (3H, m, C=CC**H**$_3$), 1.82 (1H, br s, O**H**), 1.78 (1H, ddd, *J* = 13.6, 8.0, 2.5 Hz, HOCCH$_A$**H**$_B$), 1.15 (3H, s, O=CCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.2 (C), 144.0 (C), 142.1

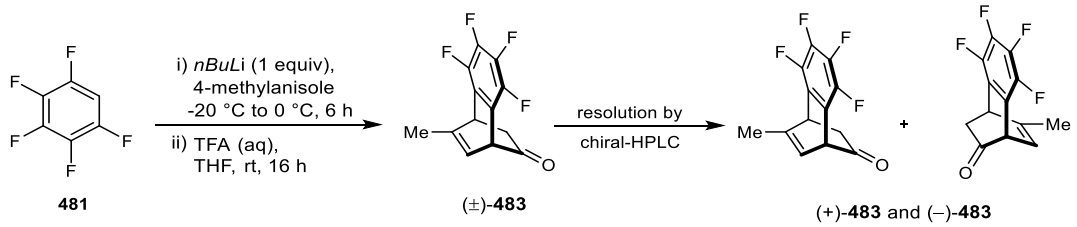
(C), 139.8 (C), 134.2 (C), 132.2 (C), 128.1 (CH), 125.9 (CH), 124.2 (CH), 122.6 (CH), 115.9 (CH_2), 79.4 (C), 52.8 (C), 50.6 (CH), 35.5 (CH_2), 32.7 (CH_2), 29.5 (CH_2), 22.9 (CH_3), 21.2 (CH_3), 13.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{20}H_{23}{}^{35}ClNaO_2]^+$ $[M+Na]^+$: 353.1279, found: 353.1282; Enantiomeric excess was determined by HPLC using a Chiralcel IC column (95:5 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 254 nm); t_r (major) = 14.7 min, t_r (minor) = 17.1 min, 90% ee.

Data for (+)-**439b**: R_f = 0.43 (94% $CHCl_3$, 5% EtOAc, 1% Et_3N); $[\alpha]_D^{21.0}$ +50.0 (*c* 0.80, $CHCl_3$). IR 3445 (O-H), 2982, 1731 (C=O), 1599, 1436, 1374, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19-7.16 (1H, m, Ar**H**), 7.10-7.08 (1H, m, Ar**H**), 7.07-7.05 (1H, s, Ar**H**), 5.93 (1H, ddd, *J* = 3.4, 2.3, 0.9 Hz, C=C**H**), 5.23-5.20 (1H, m, C=C$\mathbf{H_A}H_B$), 4.99-4.96 (1H, m, C=C$H_A\mathbf{H_B}$), 3.13-3.09 (1H, m, C=CC**H**), 2.63–2.52 (2H, m, O=CC$\mathbf{H_2}$), 2.47-2.37 (1H, m, C=CC$\mathbf{H_A}H_B$), 2.33 (3H, s, ArC$\mathbf{H_3}$), 2.29-2.09 (3H, m, C=C$CH_A\mathbf{H_B}$ and HOCC$\mathbf{H_2}$), 1.98-1.93 (4H, m, C=CC$\mathbf{H_3}$ and O**H**), 1.18 (3H, s, O=CCC$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.3 (C), 145.0 (C), 142.5 (C), 139.7 (C), 134.1 (C), 133.3 (C), 128.0 (CH), 126.4 (CH), 124.3 (CH), 122.7 (CH), 117.2 (CH_2), 77.6 (C), 52.7 (C), 51.3 (CH), 33.7 (CH_2), 33.6 (CH_2), 33.4 (CH_2), 24.5 (CH_3), 21.3 (CH_3), 17.0 (CH_3) HRMS (ESI) Exact mass calcd for $[C_{20}H_{23}{}^{35}ClNaO_2]^+$ $[M+Na]^+$: 353.1284, found: 353.1231; Enantiomeric excess was determined by HPLC using a Chiralcel IC column (95:5 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 254 nm); t_r (major) = 9.3 min, t_r (minor) = 12.6 min, 90% ee.

4.3 3-Component Coupling of 1,3-Enynes, Imines and Arylboronic Acids

4.3.1 Synthesis of L20

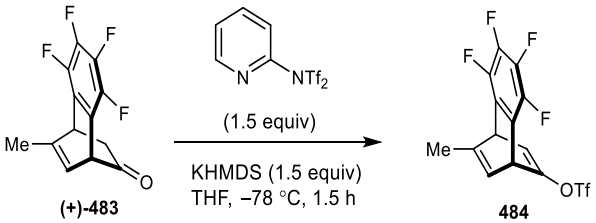
3,4,5,6-Tetrafluoro-11-methyltricyclo[6.2.2.0^{2,7}]dodeca-2,4,6,11-tetraen-9-one (483)



Pentafluorobenzene (**481**) (11.7 g, 69.6 mmol) in 4-methylanisole (45 mL) was treated with *n*BuLi (2.5 M in hexane, 28.0 mL, 69.6 mmol) dropwise at −20 °C. This mixture was stirred at 0 °C for 6 h and then allowed to warm to room temperature. The reaction mixture was then filtered through Celite®, washing with hexane, and subsequently concentrated *in vacuo*. THF (20 mL) and 50% aqueous trifluoroacetic acid solution (20 mL) were then added, and the reaction mixture stirred at room temperature for 16 h. The solution was neutralised using saturated aqueous Na_2CO_3 solution and extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography (10% EtOAc/petroleum ether) to give *ketone* (±)-**483** (2.90 g, 16%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20-6.14 (1H, m, C=C**H**), 4.62 (1H, dd, *J* = 6.3, 1.9 Hz, C(O)C**H**), 4.30 (1H, app dt, *J* = 4.5, 2.0 Hz, CH_2C**H**), 2.25 (1H, dd, *J* = 17.5, 3.0 Hz, C**H$_2$**), 2.00 (3H, d, *J* = 1.9 Hz, C**H$_3$**), 1.96 (1H, ddd, *J* = 17.5, 2.4, 0.9 Hz, C**H$_2$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0 (C), 147.7 (C), 144.2-143.1 (m, C), 141.7-141.5 (m, C) 141.0-139.7 (m, C), 138.2-137.2 (m, C), 125.1 (dt, $J_{C\text{-}F}$ = 17.7, 3.2 Hz, C), 122.3 (CH), 121.1 (dt, $J_{C\text{-}F}$ = 17.6, 3.3 Hz, C), 51.2 (CH), 39.3 (CH), 35.1 (CH_2), 19.5 (CH_3). Chiral resolution was carried out by use of a chiral stationary phase column (Chiralpak AD-H).[4] Data consistent with literature.[128]

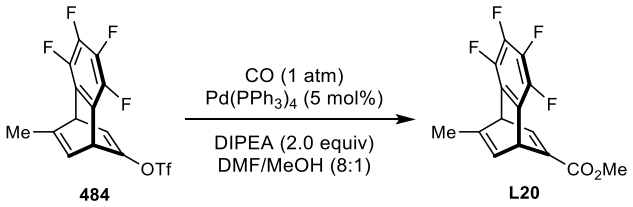
[4] Chiral resolution was carried out by Reach Separations

3,4,5,6-Tetrafluoro-11-methyltricyclo[6.2.2.0^{2,7}]dodeca-2,4,6,9,11-pentaen-9-yl trifluoromethanesulfonate (484)



KHMDS (0.5 M in toluene, 4.30 mL. 2.14 mmol) was added dropwise at −78 °C to a solution of (+)-**483** (366 mg, 1.43 mmol) and *N*-(2-pyridyl)triflimide (767 mg, 2.14 mmol) in THF (5 mL). The mixture was stirred at −78 °C for 1.5 h, and then quenched with saturated aqueous NH_4Cl solution. The aqueous was extracted with Et_2O (3 × 20 mL) and the combined organic phases dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (2% EtOAc/petroleum ether) to give *vinyl triflate* **484** (486 mg, 88%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (1H, dd, *J* = 6.8, 2.7 Hz, C**H**=COTf), 6.52-6.48 (1H, m, C**H**=CCH_3), 5.00 (1H, ddd, *J* = 5.9, 2.7, 1.9 Hz, CH_3C=CHC**H**), 4.87 (1H, dt, *J* = 6.8, 1.9 Hz, C(OTf)=CHC**H**), 1.97 (3H, d, *J* = 1.9 Hz, C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9 (C), 152.0 (C), 143.2-136.6 (4 × C, m) 130.8 (CH), 128.6 (dt, $J_{C\text{-}F}$ = 18.5, 3.1 Hz, C), 128.4 (dt, $J_{C\text{-}F}$ = 18.3, 2.9 Hz, C), 124.1 (CH), 118.4, (q, $^1J_{C\text{-}F}$ = 321 Hz, C) 45.6 (CH), 44.1 (CH), 19.0 (CH_3). Data consistent with literature.[128]

Methyl 3,4,5,6-tetrafluoro-11-methyltricyclo[6.2.2.0^{2,7}]dodeca-2,4,6,9,11-pentaene-9-carboxylate (L20)

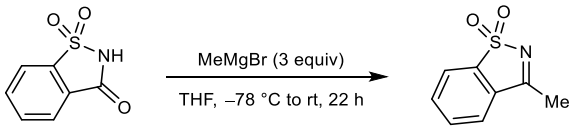


DIPEA (0.43 mL, 2.44 mmol), followed by $Pd(PPh_3)_4$ (71 mg, 60 µmol) was added to a solution of **484** (475 mg, 1.22 mmol) in DMF (2.5 mL) and MeOH (0.45 mL). The reaction mixture was stirred at room temperature for 5 h under a CO atmosphere (1 atm). The mixture was diluted with H_2O (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organics were washed with H_2O (20 ml), brine (20 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (10% EtOAc/petroleum ether) to give ligand **L20** (335 mg, 92%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, dd, *J* = 6.1, 2.0 Hz, C**H**=CCO_2Me), 6.47-6.43 (1H, m, C**H**=CCH_3), 5.66 (1H, app dt, *J* = 5.9, 2.0 Hz,

CH_3C=CHC**H**), 5.05 (1H, app dt, *J* = 6.1, 1.8 Hz, C(CO_2Me)=CHC**H**), 3.77 (3H, s, OC**H₃**), 1.94 (3H, d, *J* = 1.8 Hz, CC**H₃**; ^{19}F NMR (376 MHz, $CDCl_3$) δ −148.11 (ddd, *J* = 21.8, 15.6, 2.0 Hz), −148.84 (ddd, *J* = 21.8, 15.6, 2.0 Hz), −160.64 (dd, *J* = 21.8, 18.2 Hz), −161.51 (dd, *J* = 21.8, 18.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3 (C), 149.5 (C), 149.0 (CH), 145.6 (C), 143.2 (dd, $J_{C\text{-}F}$ = 42.3, 12.2 Hz, C), 140.7 (dd, $J_{C\text{-}F}$ = 42.9, 12.3 Hz, C), 139.2-138.3 (m, C), 136.7-135.7 (m, C), 132.0 (CH), 129.6 (dt, $J_{C\text{-}F}$ = 19.0, 3.0 Hz, C), 128.0 (dt, $J_{C\text{-}F}$ = 17.9, 3.0 Hz, C), 51.9, (CH_3) 47.2 (CH), 41.1 (CH), 18.9 (CH_3). Data consistent with literature.[129]

4.3.2 Synthesis of Imines

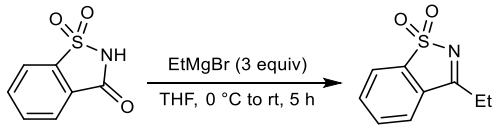
3-Methyl-1λ⁶,2-benzothiazole-1,1-dione (101)



101

Methylmagnesium bromide (3 M in Et_2O, 50.0 mL, 150 mmol) was added dropwise to a solution of saccharin (9.16 g, 150 mmol) in THF (250 mL) at −78 °C. The reaction mixture was stirred for 22 h whilst allowing to warm to room temperature. The mixture was then diluted with Et_2O (200 mL) and acidified using 10% aqueous HCl solution. The reaction mixture was stirred vigorously for 15 min, and the organic phase isolated. The organic phase was then washed with saturated aqueous $NaHCO_3$ solution (150 mL), water (150 mL), and then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give *imine* **101** (7.00 g, 77%) as an off-white solid. The compound was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.90 (1H, m, Ar**H**), 7.81-7.72 (2H, m Ar**H**), 7.72-7.68 (1H, m, Ar**H**), 2.68 (3H, s, C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (C), 139.6 (C), 133.9 (CH), 133.5 (CH), 131.5 (C), 124.1 (CH), 122.4 (CH), 17.6 (CH_3). Data consistent with literature.[148]

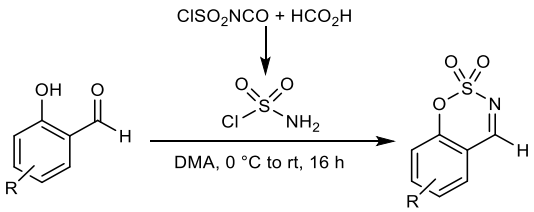
3-Ethyl-1λ⁶,2-benzothiazole-1,1-dione (491)



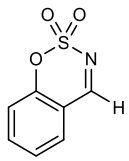
491

Ethylmagnesium bromide (3 M in Et_2O, 20 mL, 60 mmol) was added dropwise to a solution of saccharin (3.7 g, 20 mmol) in THF (50 mL) at 0 °C, and the reaction mixture was then stirred at room temperature for 5 h. The mixture was quenched with ice and acidified using 10% aqueous HCl solution. The solution was then extracted with Et_2O (3 × 50 mL), and the combined organic phases washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was recrystallised (Et_2O) to give *imine* **491** (950 mg, 24%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.87 (1H, m, Ar**H**), 7.81-7.65 (3H, m, Ar**H**), 3.03 (2H, q, *J* = 7.2 Hz, C**H₂**), 1.44 (3H, t, *J* = 7.2 Hz, C**H₃**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1 (C), 139.8 (C), 133.9 (CH), 133.5 (CH), 131.2 (C), 123.7 (CH), 122.4 (CH), 24.8 (CH_2), 9.3 (CH_3). Data consistent with literature.[148]

General Procedure A



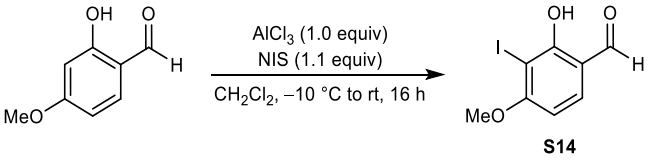
Formic acid was carefully added dropwise to chlorosulfonylisocyanate at 0 °C. The mixture was stirred for 1 h at room temperature and the resulting solid was added in small portions to a solution of the corresponding aldehyde in DMA at 0 °C. The reaction mixture was stirred at room temperature for 16 h, and then carefully quenched with water. The mixture was extracted with CH_2Cl_2 and the combined organic phases were washed with saturated aqueous $NaHCO_3$ solution, followed by brine, and then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was then purified as described.



1,2λ⁶,3-Benzoxathiazine-2,2-dione (197a). General Procedure A was followed using, formic acid (1.16 mL, 30.8 mmol), chlorosulfonylisocyanate (2.68 mL, 30.8 mmol) and salicylaldehyde (1.23 mL, 12.3 mmol). The crude mixture was filtered through silica, eluting with CH_2Cl_2, to give *imine* **197a** (1.40 g, 62%) as a

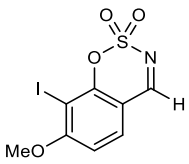
white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (1H, s, C**H**N), 7.77 (1H, ddd, *J* = 8.4, 7.6, 1.6 Hz, Ar**H**), 7.69 (1H, dd, *J* = 7.6, 1.6 Hz, Ar**H**), 7.44 (1H, app td, *J* = 7.6, 1.0 Hz, Ar**H**), 7.32 (1H, dd, *J* = 8.4, 1.0 Hz, Ar**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5 (CH), 154.3 (C), 137.6 (CH), 130.7 (CH), 126.1 (CH), 118.7 (CH), 115.4 (C). Data consistent with literature.[134]

2-Hydroxy-3-iodo-4-methoxybenzaldehyde (S14)



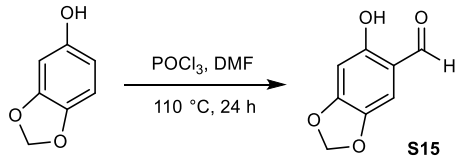
S14

$AlCl_3$ (532 mg, 4.00 mmol) was added to a solution of 2-hydroxy-4-methoxybenzaldehyde (608 mg, 4.00 mmol) in CH_2Cl_2 (24 mL) at −10 °C. NIS (990 mg, 4.40 mmol) was then added and the reaction mixture was stirred for 16 h, whilst allowing to warm to room temperature. The mixture was quenched with 10% aqueous HCl solution (20 mL) and the organic phase separated. The aqueous phase was extracted with additional CH_2Cl_2 (2 × 20 mL), and the combined organic phases were then washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give *aldehyde* **S14** (918 mg, 83%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (1H, s, C**H**O), 7.50 (1H, d, *J* = 8.6 Hz, Ar**H**), 6.53 (1H, d, *J* = 8.6 Hz, Ar**H**), 3.96 (3H, s, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9 (CH), 164.8 (C), 162.4 (C), 136.0 (CH), 115.6 (C), 103.2 (CH), 76.0 (C), 56.9 (CH_3). Data consistent with literature.[149]

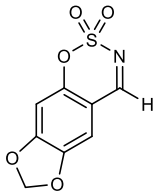


8-Iodo-7-methoxy-1,2λ^6,3-benzoxathiazine-2,2-dione (197f). General Procedure A was followed using formic acid (249 mg, 5.40 mmol), chlorosulfonylisocyanate (764 mg, 5.40 mmol) and aldehyde **S14** (500 mg, 1.8 mmol). The mixture was purified by column chromatography (50% petroleum ether/EtOAc) to give *imine* **197f** (102 mg, 17%) as a white solid. R_f = 0.12 (50% EtOAc/petroleum ether); m.p. 162-163 °C (Et_2O); IR 2991, 1580, 1387, 1133, 1065, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, s, C**H**N), 7.65 (1H, d, *J* = 8.6 Hz, Ar**H**), 6.87 (1H, d, *J* = 8.6 Hz, Ar**H**), 4.07 (3H, s, C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4 (CH), 165.8 (C), 156.1 (C), 132.9 (CH), 110.7 (C), 108.2 (CH), 78.2 (C), 57.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_8H_6INNaO_4S]^+$ $[M+Na]^+$: 361.8954, found: 361.8970.

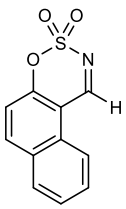
4,5-Methylenedioxy-2-hydroxybenzaldehyde (S15)



$POCl_3$ (8 mL) was added to sesamol (2.25 g, 16.3 mmol) in DMF (6 mL) at 0 °C and the reaction mixture was heated at 110 °C for 24 h. The mixture was then cooled to room temperature and poured onto saturated aqueous NaOAc solution (100 mL) and then heated at reflux for 1 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give *aldehyde* **S15** (584 mg, 22%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (1H, d, *J* = 0.6 Hz, C**H**O), 6.87 (1H, s, Ar**H**), 6.48 (1H, m, Ar**H**), 6.03 (2H, s, C**H$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0 (CH), 161.4 (C), 155.1 (C), 141.2 (C), 113.6 (C), 109.3 (CH), 102.1 (CH), 98.2 (CH_2). Data consistent with literature.[150]



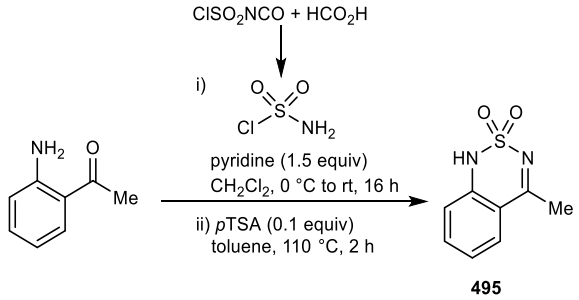
4,6,10-Trioxa-11λ^6-thia-12-azatricyclo[7.4.0.0^{3,7}]trideca-1,3(7),8,12-tetraene-11,11-dione (478g). Based on a modification of General Procedure A using aldehyde **S15** (598 mg, 3.60 mmol), freshly prepared $ClSO_2NH_2$ (10 mmol) and DMA (10 mL). The crude compound was used without further purification to give *imine* **478g** as a yellow solid (585 mg 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (1H, s, C**H**N), 6.97 (1H, s, Ar**H**), 6.76 (1H, s, Ar**H**), 6.18 (2H, s, C**H$_2$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (CH), 155.4 (C), 152.8 (C), 145.9 (C), 109.4 (C), 107.3 (CH), 103.5 (CH), 100.1 (CH_2). Data consistent with literature.[134]



4,3λ^6,2-Naphtho[1,2-e][1,2λ^6,3]oxathiazine-3,3-dione (478h). Based on a modification of General Procedure A using 2-hydroxy-1-naphthaldehyde (861 mg, 5.00 mmol), freshly prepared $ClSO_2NH_2$ (3 M in CH_2Cl_2, 5.0 mL, 15 mmol) and DMA (10 mL). The mixture was purified by recrystallisation from MeOH to give *imine* **478h** (163 mg, 19%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (1H, s, C**H**N), 8.31 (1H, d, *J* = 8.3 Hz, Ar**H**), 8.24 (1H, d, *J* = 9.0 Hz, Ar**H**), 8.01-7.95 (1H, m, Ar**H**), 7.83 (1H, ddd, *J* = 8.5, 7.0, 1.4 Hz, Ar**H**), 7.68 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz, Ar**H**), 7.39 (1H, d, *J* = 9.0 Hz, Ar**H**); ^{13}C NMR (101 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), 109.7 (C). Data consistent with literature.[134]

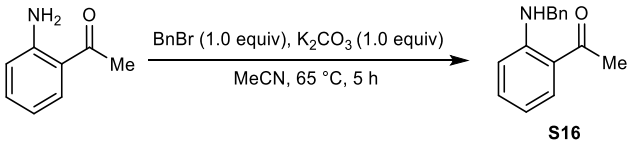
4-Methyl-1H-2λ⁶,1,3-benzothiadiazine-2,2-dione (495)



495

Formic acid (1.1 mL, 30 mmol) was carefully added dropwise to chlorosulfonylisocyanate (2.6 mL, 30 mmol) at 0 °C and then stirred at room temperature for 2 h. The resulting solid was then dissolved in CH_2Cl_2 (10 ml). This solution (2.5 mL, 7.5 mmol) was added to a solution of hydroxyacetone (0.61 mL, 5.0 mmol) and pyridine (0.61 mL, 7.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 16 h. The solution was concentrated *in vacuo* and the residue dissolved in toluene (10 mL) and *p*TSA (95 mg, 0.50 mmol) added. The mixture was heated at reflux for 2 h with azeotropic removal of water. The reaction mixture was then cooled, concentrated *in vacuo* and the crude mixture purified by column chromatography (50% EtOAc/petroleum ether) to give *imine* **495** (421 mg, 43%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.99 (1H, s, N**H**), 7.96 (1H, dd, *J* = 8.1, 1.4 Hz, Ar**H**), 7.67 (1H, ddd, *J* = 8.3, 7.2, 1.4 Hz, Ar**H**), 7.21 (1H, ddd, *J* = 8.1, 7.2, 1.2 Hz, Ar**H**), 7.10 (1H, dd, *J* = 8.3, 1.2 Hz, Ar**H**), 2.67 (3H, s, C**H₃**).; ^{13}C NMR (126 MHz, DMSO) δ 174.5 (C), 141.3 (C), 135.9 (CH), 129.3 (CH), 122.2 (CH), 117.0 (CH), 115.5 (C), 23.8 (CH_3). Data consistent with literature.[151]

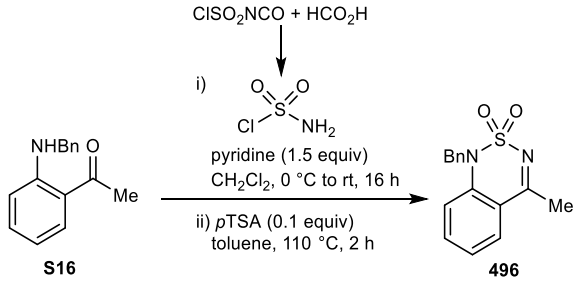
1-[2-(Benzylamino)phenyl]ethan-1-one (S16)



S16

Benzyl bromide (0.30 mL, 2.5 mmol) was added to 2-aminoacetophenone (0.30 mL, 2.5 mmol) and K_2CO_3 (343 mg, 2.50 mmol) in MeCN (2.5 mL). The mixture was stirred at 65 °C for 5 h, and then cooled to room temperature. The excess K_2CO_3 was removed by filtration and the reaction mixture concentrated *in vacuo*. The crude mixture was purified by column chromatography (10% EtOAc/petroleum ether) to give *ketone* **S16** (460 mg, 82%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (1H, s, N**H**), 7.79 (1H, dd, *J* = 8.0, 1.6 Hz, Ar**H**), 7.38-7.24 (5H, m, Ar**H**), 6.67 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.64-6.60 (1H, m, Ar**H**), 4.48 (2H, d, *J* = 5.6 Hz, C**H$_2$**), 2.62 (3H, s, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0 (C), 150.9 (C), 138.7 (C), 135.0 (CH), 132.7 (CH), 128.6 (2 × CH), 127.1 (CH), 127.0 (2 × CH), 117.8 (C), 114.4 (CH), 112.1 (CH), 46.7 (CH_2), 28.0 (CH_3). Data consistent with literature.[152]

1-Benzyl-4-methyl-1H-2λ^6,1,3-benzothiadiazine-2,2-dione (496)

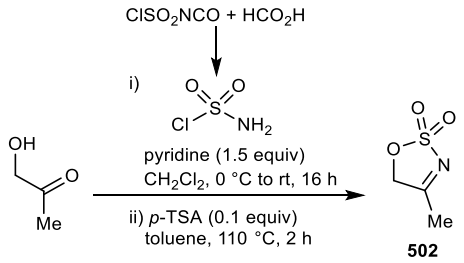


S16 **496**

Freshly prepared $ClSO_2NH_2$ (358 mg, 3.10 mmol) was added to ketone **S16** (460 mg, 2.04 mmol) and pyridine (0.27 mL, 3.10 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The solution was concentrated *in vacuo* and the residue dissolved in toluene (10 mL) and *p*TSA (38 mg, 0.20 mmol) added. This mixture was heated at reflux for 2 h with azeotropic removal of water. The reaction mixture was then cooled, concentrated *in vacuo* and the crude mixture purified by column chromatography (20% EtOAc/petroleum ether) to give *imine* **496** (358 mg, 61%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 8.1, 1.5 Hz, Ar**H**), 7.52 (1H, ddd, *J* = 8.6, 7.3, 1.5 Hz, Ar**H**), 7.44-7.39 (2H, m, Ar**H**), 7.39-7.32 (2H, m, Ar**H**), 7.32-7.28 (1H, m, Ar**H**), 7.16 (1H, ddd, *J* = 8.1, 7.3, 1.0 Hz, Ar**H**), 7.09 (1H, dd, *J* = 8.6, 1.0 Hz, Ar**H**), 5.24 (2H, s, C**H$_2$**), 2.74 (3H, s,

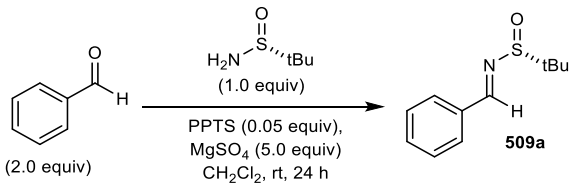
Ar**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (C), 142.5 (C), 135.6 (CH), 135.3 (C), 129.2 (CH), 128.9 (2 × CH), 127.9 (CH), 126.8 (2 × CH), 122.2 (CH), 118.5 (C), 116.7 (CH), 49.7 (CH_2), 24.3 (CH_3). Data consistent with literature.[151]

4-Methyl-5H-1,2λ⁶,3-oxathiazole-2,2-dione (502)



Formic acid (1.1 mL, 30 mmol) was carefully added dropwise to chlrosulfonylisocyanate (2.6 mL, 30 mmol) at 0 °C and then stirred at room temperature for 2 h. The resulting solid was then dissolved in CH_2Cl_2 (10 ml). This solution (2.5 mL, 7.5 mmol) was then added to a solution of hydroxyacetone (0.61 mL, 5.0 mmol) and pyridine (0.61 mL, 7.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred for 16 h. The solution was concentrated *in vacuo* and the residue dissolved in toluene (10 mL) and *p*TSA (95 mg, 0.50 mmol) added. This mixture was then heated at reflux for 2 h with azeotropic removal of water. The reaction mixture was then cooled, concentrated *in vacuo* and the crude residue purified by column chromatography (50% EtOAc/petroleum ether) to give *imine* **502** (87 mg, 13%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (2H, s, C**H₂**), 2.43 (3H, s, C**H₃**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.12 (C), 76.98 (CH_3), 17.87 (CH_2). Data consistent with literature.[153]

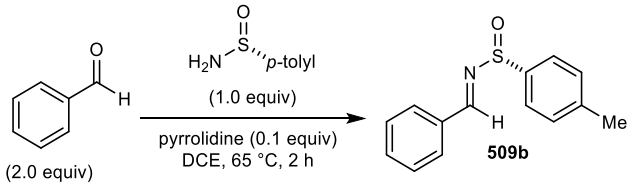
(*R*)-2-Methyl-N-[(*E*)-phenylmethylidene]propane-2-sulfinamide (509a)



Benzaldehyde (1.02 mL, 10.0 mmol) was added to (*R*)-2-methyl-2-propanesulfinamide (605 mg, 5.00 mmol), PPTS (65 mg, 0.25 mmol) and $MgSO_4$ (3.00 g, 25.0 mmol) in CH_2Cl_2 (8 mL), and the reaction mixture was stirred at room temperature for 24 h. The mixture was then

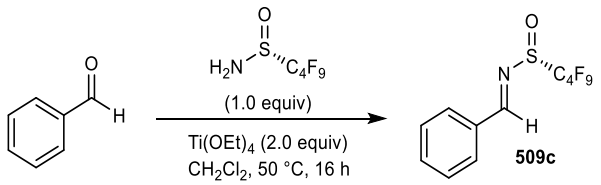
filtered through Celite®, washing with CH_2Cl_2 and the solution concentrated *in vacuo*. The crude mixture was purified by column chromatography (10% EtOAc/petroleum ether) to give *imine* **509a** (819 mg, 79%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (1H, s, C**H**N), 7.89-7.83 (2H, m, Ar**H**), 7.59-7.43 (3H, m, Ar**H**), 1.27 (9H, s, C(C**H$_3$**)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (CH), 134.1 (C), 132.4 (CH), 129.3 (2 × CH), 128.9 (2 × CH), 57.7 (C), 22.6 (3 × CH_3). Data consistent with literature.[154]

(*R*)-4-Methyl-N-[(*E*)-phenylmethylidene]benzene-1-sulfinamide (509b)



Pyrrolidine (0.21 mL, 0.25 mmol) was added to (*R*)-*p*-toluenesulfinamide (388 mg, 2.50 mmol) and benzaldehyde (0.51 mL, 5.00 mmol) in DCE (3 mL) and the mixture heated at 65 °C for 2h. The reaction mixture was then cooled to room temperature, and filtered through silica, washing with petroleum ether. The solution was concentrated *in vacuo* to give *imine* **509b** (192 mg, 32%) as an off-white solid. The compound was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (1H, s, C**H**N), 7.88-7.84 (2H, m, Ar**H**), 7.67-7.62 (2H, m, Ar**H**), 7.55-7.42 (3H, m, Ar**H**), 7.32 (2H, d, *J* = 7.7 Hz, Ar**H**), 2.41 (3H, s, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6 (CH), 141.8 (C), 141.7 (C), 133.9 (C), 132.6 (CH), 129.8 (2 × CH), 129.6 (2 × CH), 128.9 (2 × CH), 124.8 (2 × CH), 21.4 (CH_3). Data consistent with literature.[155]

(*R*)-1,1,2,2,3,3,4,4,4-Nonafluoro-N-[(*E*)-phenylmethylidene]butane-1-sulfinamide (509c)

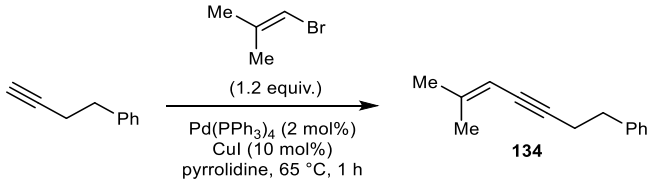


$Ti(OEt)_4$ (0.26 mL 1.06 mmol) was added to [*R*(*R*)]-1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfinamide (150 mg, 0.53 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred at room temperature for 1 min. Benzaldehyde (54 µL, 0.53 mmol) was then added, and the solution stirred at 50 °C for 16 h in a sealed vial. Brine (2 mL) was then added, and the reaction

mixture filtered through Celite®. The aqueous was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (40% CH_2Cl_2/petroleum ether) to give *imine* **509c** (156 mg, 79%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (1H, s, C**H**N), 7.96-7.91 (2H, m, Ar**H**), 7.67-7.61 (1H, m, Ar**H**), 7.58-7.51 (2H, m, Ar**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (CH), 134.3 (CH), 133.0 (C), 130.4 (2 × CH), 129.2 (2 × CH), 121.9-105.2 (m, 4 × C). Data consistent with literature.[130]

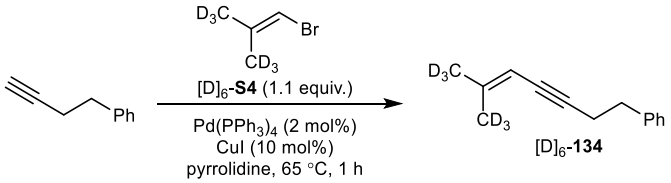
4.3.3 Synthesis of 1,3-Enynes

(6-Methylhept-5-en-3-yn-1-yl)benzene (134)



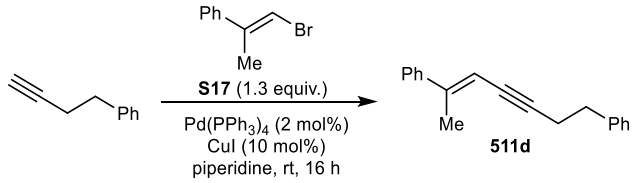
$Pd(PPh_3)_4$ (328 mg, 0.284 mmol) and CuI (270 mg, 1.42 mmol) were added to a solution of 1-bromo-2-methyl-prop-1-ene (2.11 g, 15.7 mmol) in pyrrolidine (15 mL). 4-Phenyl-1-butyne (2.00 mL, 14.2 mmol) was then added and the mixture heated at 65 °C for 1 h. The reaction mixture was then diluted with Et_2O (20 mL), washed with 1 M aqueous HCl solution (20 mL), and the aqueous layer further extracted with Et_2O (2 × 20 mL). The organic layers were combined, washed with brine (20 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude mixture was purified by column chromatography (petroleum ether) to give *alkyne* **134** (2.01 g, 77%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (5H, m, Ar**H**), 5.25-5.22 (1H, m, C**H**=C), 2.87 (2H, t, *J* = 7.6 Hz, PhC**H$_2$**), 2.64 (1H, td, *J* = 7.6, 2.0 Hz, PhCH_2C**H$_2$**), 1.83 (3H, s, C**H$_3$**), 1.80-1.76 (3H, m, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (C), 140.8 (C), 128.4 (2 × CH), 128.3 (2 × CH), 126.2 (CH), 105.3 (CH), 91.1 (C), 79.1 (C), 35.5 (CH_2), 24.6 (CH_3), 21.7 (CH_2), 20.7 (CH_3). Data consistent with literature.[49]

[6-($^2H_3$)Methyl(7,7,7-$^2H_3$)hept-5-en-3-yn-1-yl]benzene ([D]$_6$-134)



$Pd(PPh_3)_4$ (74 mg, 64 µmol), and CuI (61 mg, 0.32 mmol) were added to a solution of [D]$_6$-**S4** (500 mg, 3.55 mmol) in pyrrolidine (5 mL). 4-Phenyl-1-butyne (0.46 mL, 3.22 mmol) was then added and the mixture heated at 65 °C for 1 h. The reaction mixture was diluted with Et_2O (10 mL), washed with 1 M aqueous HCl solution (10 mL), and the aqueous layer further extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude mixture was purified by column chromatography (petroleum ether) to give *alkyne* [D]$_6$-**134** (600 mg, 98%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.15 (5H, m, Ar**H**), 5.23 (1H, t, *J* = 2.1 Hz, C=C**H**), 2.87 (2H, t, *J* = 7.5 Hz, PhC**H$_2$**), 2.64 (2H, td, *J* = 7.7, 2.1 Hz, PhCH$_2$C**H$_2$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0 (C), 140.9 (C), 128.5 (2 × CH), 128.3 (2 × CH), 126.2 (CH), 105.3 (C), 91.0 (C), 79.1 (C), 35.5 (CH_2), 21.7 (CH_2). Data consistent with literature.[49]

[(*E*)-6-Phenylhept-5-en-3-yn-1-yl]benzene (511d)

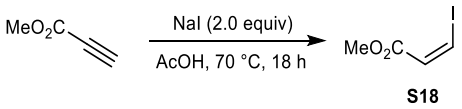


$Pd(PPh_3)_4$ (49 mg, 42 µmol), and CuI (40 mg, 0.21 mmol) were added to a solution of *vinyl bromide* **S17**[5] (535 mg, 2.70 mmol) in piperidine (10 mL). 4-Phenyl-1-butyne (0.29 mL, 2.09 mmol) was then added and the mixture stirred at room temperature for 16 h. The reaction mixture was then diluted with Et_2O (10 mL), washed with 1 M aqueous HCl solution (10 mL), and the aqueous layer further extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The mixture was purified by column chromatography (2% Et_2O/petroleum ether) to give *alkyne* **511d** (506 mg, 98%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.40 (2H, m, Ar**H**), 7.37-7.21 (8H, m, Ar**H**), 5.87 (1H, tq, *J* = 2.3, 1.2 Hz, C=C**H**), 2.93 (2H, t, *J* = 7.5 Hz, PhC**H$_2$**), 2.74 (2H,

[5] Synthesised by J Baker

td, *J* = 7.5, 2.3 Hz, $PhCH_2C\mathbf{H_2}$), 2.25 (3H, d, *J* = 1.2 Hz, $C\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (C), 141.1 (C), 140.7 (C), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 127.8 (CH), 126.3 (CH), 125.3 (2 × CH), 106.9 (CH), 95.4 (C), 79.7 (C), 35.3 (CH_2), 22.0 (CH_2), 18.4 (CH_3). Data consistent with literature.[49]

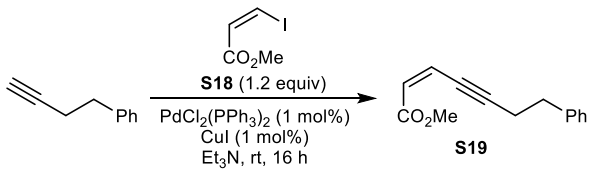
Methyl (*Z*)-3-iodoprop-2-enoate (S18)



S18

Sodium iodide (3.00 g 20.0 mmol) was added to a solution of methyl propiolate (0.89 mL 10.0 mmol) in AcOH (5 mL) and the reaction mixture stirred at 70 °C for 18 h. The mixture was then cooled to 0 °C and neutralized with 1 M aqueous NaOH solution. The aqueous was extracted with Et_2O (3 × 20 mL), and the combined organic phases washed with saturated aqueous $Na_2S_2O_4$ solution (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*, giving *vinyl iodide* **S18** (1.84 g, 87%) as a yellow oil. The compound was used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 8.9, CH=C**H**C), 6.91 (1H, d, *J* = 8.9 Hz, IC**H**), 3.78 (3H, s, $C\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (C), 129.4 (CH), 95.2 (CH), 51.6 (CH_3). Data consistent with literature.[156]

Methyl (*Z*)-7-phenylhept-2-en-4-ynoate (S19)

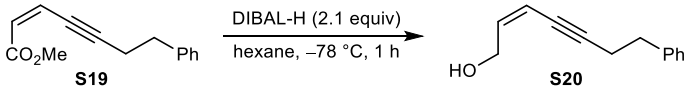


S19

(*Z*)-3-Iodopropenoic acid methyl ester (**S18**) (980 mg, 4.61 mmol) was added to a solution of $PdCl_2(PPh_3)_2$ (27 mg, 38 μmol), and CuI (7.2 mg, 38 μmol) in Et_3N (10 mL). The solution was stirred for 5 min, 4-phenyl-1-butyne (0.54 mL, 3.8 mmol) added, and the mixture then stirred at room temperature for 16 h. The reaction mixture was diluted with Et_2O (20 mL), washed with 1 M aqueous HCl solution (20 mL), and the aqueous layer was further extracted with Et_2O (2 × 20 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (5% EtOAc/petroleum ether) to give *alkyne* **S19** (637 mg, 77%) as an orange oil. R_f = 0.24 (5%

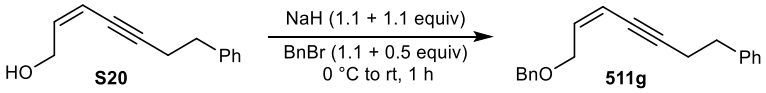
EtOAc/petroleum ether); IR 2949, 2205, 1726 (C=O), 1193, 1172, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.29 (2H, m, Ar**H**) 7.28-7.21 (3H, m, Ar**H**), 6.16 (1H, dt, *J* = 11.3, 2.3 Hz, C**H**=CHCO$_2$Me), 6.07 (1H, d, *J* = 11.3 Hz, C**H**CO$_2$Me), 3.76 (3H, s, OC**H**$_3$), 2.94 (2H, t, *J* = 7.6 Hz, PhC**H$_2$**), 2.76 (2H, td, *J* = 7.6, 2.3 Hz, PhCH$_2$C**H$_2$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2 (C), 140.4 (C), 128.4 (4 × CH), 127.2 (CH), 126.3 (CH), 124.0 (CH), 103.2 (C), 78.1 (C), 51.4 (CH_3), 34.7 (CH_2), 22.2 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{14}H_{14}NaO_2]^+$ $[M+Na]^+$: 237.0886, found: 237.0895.

(*Z*)-7-Phenylhept-2-en-4-yn-1-ol (S20)



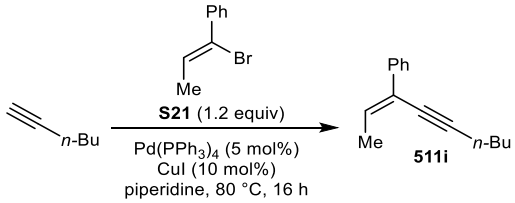
Alkyne **S19** (500 mg, 2.33 mmol) was added dropwise to a solution of DIBAL-H (1.0 M in hexane, 4.9 mL, 4.9 mmol) at −78 °C. The mixture was stirred at −78 °C for 1 h. The reaction was warmed to 0 °C and 1 M aqueous HCl solution was added dropwise until effervescence ceased. Then, Et_2O (15 mL) and 1 M aqueous HCl solution (15 mL) were added, the layers were separated, and the aqueous layer was further extracted with Et_2O (2 × 15 mL). The organic layers were combined, washed with brine (15 mL) dried, (Na_2SO_4), filtered and concentrated *in vacuo*. The mixture was purified by column chromatography (50% Et_2O/petroleum ether) to give *alcohol* **S20** (297 mg, 68%) as a yellow oil. R_f = 0.46 (66% Et_2O/petroleum ether); IR 3316 (O-H), 2925, 1453, 1015, 742, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (2H, m, Ar**H**), 7.27-7.21 (3H, m, Ar**H**), 6.01 (1H, dt, *J* = 10.8, 6.4 Hz, CH=C**H**CH$_2$), 5.61-5.54 (1H, m, C**H**=CHCH$_2$OH), 4.31 (2H, dd, *J* = 6.4, 1.4 Hz, C**H$_2$**OH), 2.87 (2H, t, *J* = 7.5 Hz, PhC**H$_2$**), 2.66 (2H, td, *J* = 7.5, 2.2 Hz, PhCH$_2$C**H$_2$**), 1.65 (1H, br s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (C), 140.2 (CH), 128.41 (2 × CH), 128.37 (2 × CH), 126.3 (CH), 111.0 (CH), 109.9 (C), 95.6 (C), 60.8 (CH_2), 34.9 (CH_2), 21.6 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{13}H_{14}NaO]^+$ $[M+Na]^+$: 209.0937, found: 209.0922.

[(*Z*)-7-(Benzyloxy)hept-5-en-3-yn-1-yl]benzene (511g)



NaH (60% wt in mineral oil, 101 mg, 2.50 mmol) was added to a stirred solution of alcohol **S20** (391 mg, 2.10 mmol) in THF (10 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Benzyl bromide (0.30 mL, 2.5 mmol) was added, the reaction was warmed to room temperature, and stirred for a further 1 h. Additional benzyl bromide (0.15 mL, 1.3 mmol) and NaH (60% wt in mineral oil, 101 mg, 2.50 mmol) were then added, and the reaction mixture stirred for 16 h at room temperature After this time 1 M aqueous HCl solution (10 mL) was added, the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 15 mL). The organic layers were combined, washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The mixture was purified by column chromatography (5% Et_2O/petroleum ether) to give *1,3-enyne* **511g** (343 mg, 59%) as a pale yellow oil. R_f = 0.40 (5% EtOAc/petroleum ether); IR 2923, 1453, 1093, 1075, 734, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (7H, m, Ar**H**), 7.26-7.19 (3H, m, Ar**H**), 6.00 (1H, dt, *J* = 10.8, 6.4 Hz, CH=C**H**CH_2), 5.66-5.59 (1H, m, CC**H**=CH), 4.49 (2H, s, PhC$\mathbf{H_2}$O), 4.22 (2H, dd, *J* = 6.4, 1.5 Hz, CH=CHC$\mathbf{H_2}$), 2.84 (2H, t, *J* = 7.4 Hz, PhC$\mathbf{H_2}$), 2.63 (2H, td, *J* = 7.4, 2.1 Hz, PhCH_2C$\mathbf{H_2}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (C), 138.3 (C), 138.2 (CH), 128.40 (2 × CH), 128.36 (2 × CH), 128.3 (2 × CH), 127.8 (2 × CH), 127.6 (CH), 126.3 (CH), 112.0 (CH), 95.5 (C), 77.1, (C), 72.2 (CH_2), 67.8 (CH_2), 35.0 (CH_2), 21.6 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{20}H_{20}NaO]^+$ $[M+Na]^+$: 299.1406, found: 299.1417.

(*Z*)-Non-2-en-4-yn-3-ylbenzene (511i)

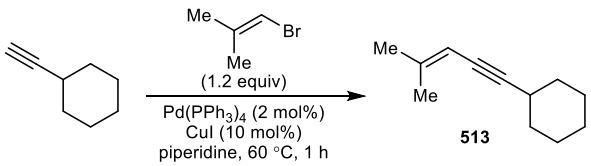


Vinyl bromide **S21**[6] (113 mg, 0.573 mmol) in piperidine (5 mL) was added to a vial containing $Pd(PPh_3)_4$ (30.1 mg, 26 µmol), and CuI (9.9 mg, 52 µmol). The solution was stirred for 5 min and 1-hexyne (60 µL, 0.52 mmol) was then added and the mixture was heated at 80 °C for

[6] Synthesised by D. Burns

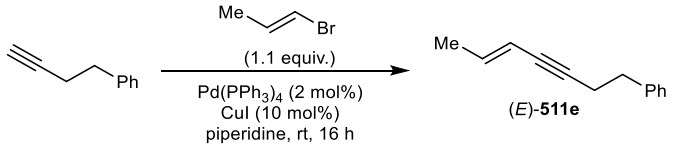
16 h. The reaction mixture was cooled to room temperature, diluted with Et_2O (10 mL), washed with 1 M aqueous HCl solution (10 mL), and the aqueous layer was further extracted with Et_2O (2 × 10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The mixture was purified by column chromatography (100% petroleum ether) to give *1,3-enyne* **511i** (65 mg, 63%) as an orange oil. R_f = 0.39 (100% petroleum ether); IR 2930, 1493, 1447, 757, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (2H, m, Ar**H**), 7.35-7.29 (2H, m, Ar**H**), 7.28-7.21 (1H, m, Ar**H**), 6.40 (1H, q, *J* = 6.9 Hz, C=C**H**), 2.49 (2H, t, *J* = 7.0 Hz, C≡CC**H₂**), 2.05 (3H, d, *J* = 6.9 Hz, C=CHC**H₃**), 1.67-1.58 (2H, m, C≡CCH_2C**H₂**), 1.57-1.46 (2H, m, C**H₂**CH_3), 0.97 (3H, t, *J* = 7.3 Hz, CH_2C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (C), 131.5 (CH), 128.2 (2 × CH), 127.1 (CH), 125.8 (2 × CH), 124.7 (C), 96.7 (C), 77.6 (C), 31.0 (CH_2), 22.0 (CH_2), 19.3 (CH_2), 16.7 (CH_3), 13.6 (CH_3); HRMS (GC-EIMS) Exact mass calcd for $[C_{15}H_{18}Na]^+$ [M+Na]$^+$: 198.1400, found: 198.1403.

(4-Methylpent-3-en-1-yn-1-yl)cyclohexane (513)



Cyclohexylacetylene (300 mg, 2.77 mmol) was added to a solution of 1-bromo-2-methyl-prop-1-ene (450 mg, 3.33 mmol), $Pd(PPh_3)_4$ (64 mg, 55 µmol) and CuI (53 mg, 28 µmol) in pyrrolidine (5 ml). The mixture was stirred at 65 °C for 1 h, and then cooled to room temperature. Saturated aqueous NH_4Cl solution (10 ml) was added and the mixture extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The mixture was purified by column chromatography (100% petroleum ether) to give *1,3-enyne* **513** (404 mg, 90%) as a colourless oil. R_f = 0.60 (100% petroleum ether); IR 2910, 1434, 1335, 1049, 821, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.28-5.25 (1H, m, C=C**H**), 2.57-2.46 (1H, m, C**H**CH_2), 1.89-1.87 (3H, m, C**H₃**), 1.87-1.79 (2H, m, (C**H₂**)$_5$) 1.79-1.77 (3H, m, C**H₃**), 1.76-1.67 (2H, m, (C**H₂**)$_5$), 1.55-1.41 (2H, m, (C**H₂**)$_5$), 1.39-1.25 (4H, m, (C**H₂**)$_5$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6 (C), 105.5 (CH), 96.4 (C), 78.3 (C), 33.0 (2 × CH_2), 29.8 (CH), 26.0 (CH_2), 24.9 (2 × CH_2), 24.6 (CH_3), 20.7 (CH_3); HRMS (GC-EIMS) Exact mass calcd for $[C_{12}H_{18}]^+$ [M]$^+$: 162.1403, found: 162.1406.

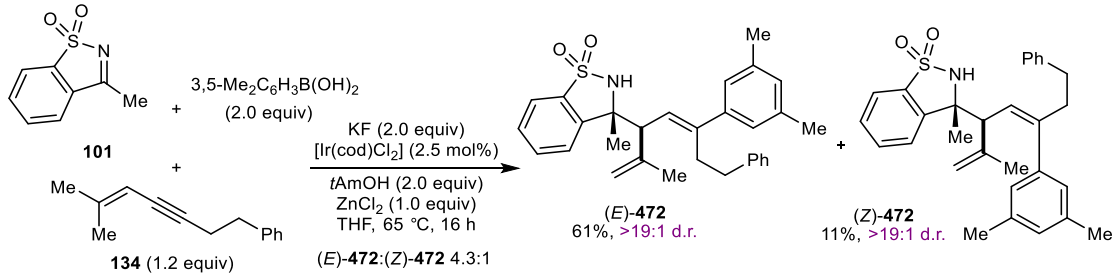
(*E*)-Hept-5-en-3-yn-1-ylbenzene [(*E*)-511e]



$Pd(PPh_3)_4$ (87 mg, 75 µmol) and CuI (72 mg, 0.38 mmol) were added to a solution of (*E*)-1-bromoprop-1-ene (500 mg, 4.13 mmol) in piperidine (10 mL). 4-Phenyl-1-butyne (0.53 mL, 3.76 mmol) was then added and the mixture stirred at room temperature for 16 h. The reaction mixture was diluted with Et_2O (10 mL), washed with 1 M aqueous HCl solution (10 mL), and the aqueous layer was further extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude mixture was purified by column chromatography (petroleum ether) to give *alkyne* (*E*)-**511e** (510 mg, 80%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.19 (5H, m, Ar**H**), 6.07 (1H, dq, *J* = 15.8, 6.8 Hz, C**H**CH_3), 5.48 (1H, dq, *J* = 15.8, 2.0 Hz, C**H**=$CHCH_3$), 2.86 (2H, t, *J* = 7.6 Hz, PhC**H₂**), 2.58 (2H, td, *J* = 7.6, 2.0 Hz, $PhCH_2C$**H₂**), 1.77 (3H, dd, *J* = 6.8, 2.0 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (C), 138.3 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 126.2 (CH), 110.9 (CH), 87.6 (C), 79.8 (C), 35.3 (CH_2), 21.57 (CH_2), 18.46 (CH_3). Data consistent with literature.[49]

4.3.4 Racemic Iridium-Catalysed Arylative Allylation

3-Methyl-3-[(3*S*,*E*)-5-(3,5-dimethylphenyl)-2-methyl-7-phenylhepta-1,4-dien-3-yl]-2,3-dihydro-1λ⁶,2benzothiazole-1,1-dione [(*E*)-472] and 3-methyl-3-[(3*S*,*Z*)-5-(3,5-dimethylphenyl)-2-methyl-7-phenylhepta-1,4-dien-3-yl]-2,3-dihydro-1λ⁶,2benzothiazole-1,1-dione ([(*Z*)-472])



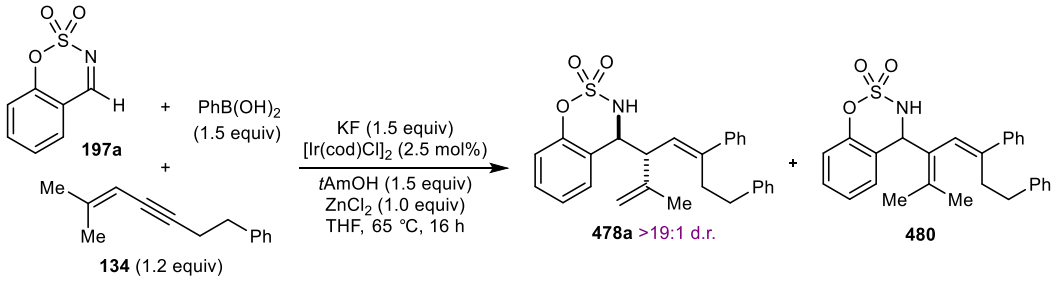
Imine **101** (54 mg, 0.30 mmol), 1,3-enyne **134** (66 mg, 0.36 mmol), 3,5-dimethylphenylboronic acid (90 mg, 0.60 mmol), KF (35 mg, 0.60 mmol), and $[Ir(cod)Cl]_2$ (5.0 mg, 7.5 µmol, 2.5 mol%) were added to an oven-dried microwave vial. The vial was purged with nitrogen for 1 h, and degassed anhydrous THF (8.9 mL) was added, followed by *t*-amyl alcohol (0.07 mL, 0.30 mmol) and $ZnCl_2$ solution (0.7 M in THF, 0.43 mL, 0.30 mmol). The mixture was stirred at 65 °C for 16 h and subsequently cooled to room temperature. The mixture was diluted with saturated aqueous NH_4Cl solution (5 mL) and water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (10% EtOAc/pentane), to give *allylation product* (*E*)-**472** (87 mg, 61%) as an off-white solid and *allylation product* (*Z*)-**472** (16 mg, 11%) as a colourless oil.

Data for (*E*)-**472:** R_f = 0.30 (10% EtOAc/pentane); m.p. 161-162 °C (Et_2O); IR 3243 (N-H), 2918, 1597, 1452, 1280, 1168, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79-7.75 (1H, m, Ar**H**), 7.57 (1H, app td, *J* = 7.5, 1.3 Hz, Ar**H**), 7.51 (1H, app td, *J* = 7.5, 1.1 Hz, Ar**H**), 7.35-7.28 (3H, m, Ar**H**), 7.25-7.19 (1H, m, Ar**H**), 7.16-7.12 (2H, m, Ar**H**), 6.88-6.86 (1H, m, Ar**H**), 6.79-6.76 (2H, m, Ar**H**), 5.84 (1H, d, *J* = 10.0 Hz, C=C**H**), 5.07 (1H, app t, *J* = 1.5 Hz, C=C$\mathbf{H_A}H_B$), 4.99 (1H, br s, C=C$H_A\mathbf{H_B}$), 4.55 (1H, s, N**H**), 3.56 (1H, d, *J* = 10.0 Hz, C=CC**H**), 2.78-2.61 (2H, m, PhC$\mathbf{H_2}$), 2.56-2.46 (1H, m, PhCH_2C$\mathbf{H_A}CH_B$), 2.37 (1H, ddd, *J* = 13.9, 10.8, 6.0 Hz, PhCH_2CH_AC$\mathbf{H_B}$), 2.29-2.26 (6H, m, ArC$\mathbf{H_3}$), 1.82-1.79 (3H, m, CH_2=CC$\mathbf{H_3}$), 1.68 (3H, s, NHCC$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (C), 143.5 (C), 142.3 (C), 142.02 (C), 141.96 (C), 137.6 (2 × C), 134.9 (C), 133.1 (CH), 129.3 (CH), 128.8 (CH), 128.4 (2 × CH), 128.2 (2 × CH), 125.9 (CH), 125.1 (CH), 124.4 (2 × CH),

123.6 (CH), 121.3 (CH), 116.3 (CH_2), 66.0 (C), 54.8 (CH), 34.4 (CH_2), 32.0 (CH_2), 27.7 (CH_3), 22.2 (CH_3), 21.4 (2 × CH_3); HRMS (ESI) Exact mass calcd for $[C_{30}H_{33}INaO_2S]^+$ $[M+Na]^+$: 494.2124, found: 494.2123.

Data for (*Z*)-**472:** R_f = 0.41 (10% EtOAc/pentane); IR 3243 (N-H), 2918, 1597, 1452, 1281, 1133 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.68 (1H, m, Ar**H**), 7.49 (1H, app td, *J* = 7.5, 1.2 Hz, Ar**H**), 7.44 (1H, app td, *J* = 7.5, 1.4 Hz, Ar**H**), 7.24-7.18 (2H, m, Ar**H**), 7.15-7.10 (1H, m, Ar**H**), 7.07-7.03 (2H, m, Ar**H**), 6.94-6.91 (1H, m, Ar**H**), 6.81-6.77 (1H, m, Ar**H**), 6.46-6.42 (2H, m, Ar**H**), 5.63 (1H, dd, *J* = 10.7, 1.3 Hz, C=C**H**), 5.03-5.01 (1H, m, C=C$\mathbf{H_A}H_B$), 4.83-4.81 (1H, m, C=$CH_A\mathbf{H_B}$), 4.37 (1H, s, N**H**), 3.12 (1H, d, *J* = 10.7 Hz, C=CHC**H**), 2.50-2.30 (10H, m, PhC$\mathbf{H_2}$C$\mathbf{H_2}$ and 2 × ArC$\mathbf{H_3}$), 1.78-1.76 (3H, m, C=CC$\mathbf{H_3}$), 1.46 (3H, s, , NHCC$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 143.6 (C), 143.3 (C), 141.8 (C), 140.4 (C), 137.1 (2 × C), 134.6 (C), 132.6 (CH), 128.9 (CH), 128.4 (3 × CH), 128.1 (2 × CH), 126.4 (2 × CH), 125.6 (CH), 123.8 (CH), 123.7 (CH), 121.0 (CH), 115.4 (CH_2), 66.2 (C), 54.5 (CH), 40.6 (CH_2), 34.3 (CH_2), 28.1 (CH_3), 22.1 (CH_3), 21.3 (2 × CH_3); HRMS (ESI) Exact mass calcd for $[C_{30}H_{33}INaO_2S]^+$ $[M+Na]^+$: 494.2124, found: 494.2115.

(*S*)-4-((*R*,*E*)-2-methyl-5,7-diphenylhepta-1,4-dien-3-yl)-3,4-dihydrobenzo[e][1,2,3]oxathiazine 2,2-dioxide (478a) and (*E*)-4-(2-Methyl-5,7-diphenylhepta-2,4-dien-3-yl)-3,4-dihydrobenzo[e][1,2,3]oxathiazine 2,2-dioxide (480)



Imine **197a** (275 mg, 1.50 mmol), 1,3-enyne **134** (332 mg, 1.80 mmol), phenylboronic acid (274 mg, 2.25 mmol), KF (131 mg, 2.25 mmol), and $[Ir(cod)Cl]_2$ (25.0 mg, 37.5 µmol, 2.50 mol%) were added to an oven-dried microwave vial. The vial was purged with nitrogen for 1 h, and degassed anhydrous THF (8.9 mL) was added, followed by *t*-amyl alcohol (0.24 mL, 2.25 mmol) and $ZnCl_2$ solution (0.7 M in THF, 2.10 mL, 1.50 mmol). The mixture was stirred at 65 °C for 16 h and subsequently cooled to room temperature. The mixture was diluted with saturated aqueous NH_4Cl solution (25 mL) and water (25 mL), and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (5%

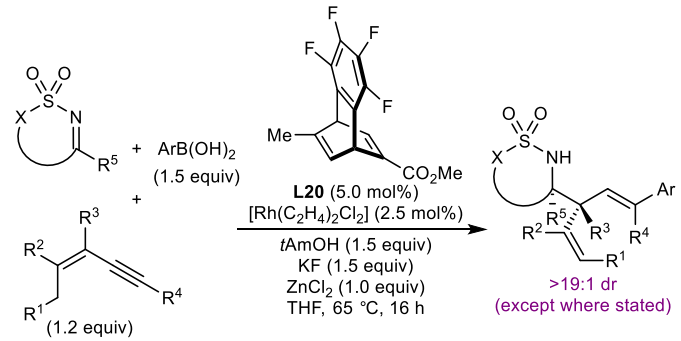
EtOAc/petroleum ether), to give *allylation product* **478a** (555 mg, 83%) as an off-white solid and *diene* **480** (84 mg, 13%) as an off-white solid.

Data for **478a**: R_f = 0.21 (10% EtOAc/petroleum ether); m.p. 109-110 °C (Et_2O); IR 3268 (N-H), 2925, 1367, 1192, 1168, 754, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (4H, m, Ar**H**), 7.26-7.18 (5H, m, Ar**H**), 7.17-7.12 (1H, m, Ar**H**), 7.11-7.01 (4H, m, Ar**H**), 5.51 (1H, d, *J* = 9.3 Hz, C=C**H**), 5.07 (1H, s, C=C$\mathbf{H_A}H_B$), 5.03-4.96 (2H, m, C=C$H_A\mathbf{H_B}$ and C**H**NH), 4.07 (1H, d, *J* = 7.3 Hz, N**H**), 3.57 (1H, dd, *J* = 9.3, 6.4 Hz, C=CC**H**), 2.83-2.71 (2H, m, PhC$\mathbf{H_2}$), 2.69-2.59 (1H, m, $PhCH_2C\mathbf{H_A}H_B$), 2.42 (1H, dt, *J* = 13.6, 8.1 Hz, $PhCH_2CH_A\mathbf{H_B}$), 1.92 (3H, s, C$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (C), 143.4 (C), 143.2 (C), 141.7 (C), 141.5 (C), 129.3 (CH), 128.47 (2 × CH), 128.45 (2 × CH), 128.4 (2 × CH), 127.5 (CH), 126.7 (CH), 126.6 (2 × CH), 126.3 (CH), 125.2 (CH), 124.8 (CH), 122.1 (C), 118.7 (CH), 115.3 (CH_2), 56.9 (CH), 49.1 (CH), 33.7 (CH_2), 31.9 (CH_2), 21.4 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{27}H_{27}NNaO_3S]^+$ $[M+Na]^+$: 468.1604, found: 468.1609.

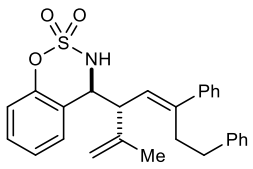
Data for **480:** R_f = 0.36 (10% EtOAc/petroleum ether); m.p. 134-136 °C (Et_2O); IR 3523 (N-H), 3028, 1403, 1365, 1211, 1166, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (8H, m, Ar**H**), 7.25-7.19 (1H, m, Ar**H**), 7.16 (1H, app td, *J* = 7.5, 1.2 Hz, Ar**H**), 7.12-7.07 (3H, m, Ar**H**), 7.02 (1H, dd, *J* = 8.2, 1.2 Hz, Ar**H**), 5.90 (1H, d, *J* = 9.9 Hz, C**H**NH), 5.68 (1H, s, C=C**H**), 4.30 (1H, d, *J* = 9.9 Hz, N**H**), 2.86-2.74 (2H, m, PhC$\mathbf{H_2}$), 2.66-2.50 (2H, m, $PhCH_2C\mathbf{H_2}$), 2.03 (3H, d, *J* = 1.8 Hz, C$\mathbf{H_3}$), 1.90 (3H, d, *J* = 1.3 Hz, C$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (C), 148.1 (C), 141.4 (C), 140.6 (C), 136.4 (C), 129.7 (CH), 128.6 (2 × CH), 128.5 (2 × CH), 128.1 (2 × CH), 127.9 (CH), 126.64 (2 × CH), 126.58 (CH), 126.3 (CH), 126.1 (C), 125.4 (CH), 122.6 (CH), 120.7 (C), 118.9 (CH), 57.7 (CH), 33.7 (CH_2), 33.0 (CH_2), 23.1 (CH_3), 20.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{27}H_{27}NNaO_3S]^+$ $[M+Na]^+$: 468.1604, found: 468.1602.

4.3.5 Enantioselective Rhodium-Catalysed Arylative Allylation

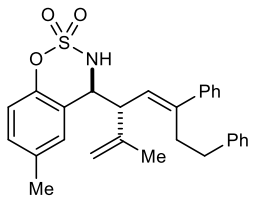
General Procedure B: Enantioselective Arylative Allylation Reaction



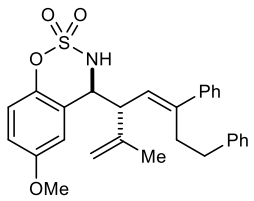
$[Rh(C_2H_4)_2Cl]_2$ (2.9 mg, 7.5 µmol, 2.5 mol%) and **L20** (4.5 mg, 15 µmol, 5.0 mol%) were added to an oven-dried microwave vial and purged with nitrogen for 1 h. Degassed anhydrous THF (1.5 mL) was added and the mixture stirred for 30 min at room temperature. Imine (0.300 mmol), 1,3-enyne (0.360 mmol), arylboronic acid (0.450 mmol), and KF (26.1 mg, 0.450 mmol) were added to a separate oven-dried microwave vial. The vial was purged with nitrogen for 1 h, and the catalyst solution was then added to the vial containing the imine. *t*-Amyl alcohol (0.05 mL, 0.45 mmol) and $ZnCl_2$ solution (0.7 M in THF, 0.43 mL, 0.30 mmol) were added and the reaction mixture was stirred at 65 °C for 16 h. The mixture was cooled to room temperature, diluted with saturated aqueous NH_4Cl solution (5 mL) and water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography to give the allylation product.



(4*S*)-4-[(3*R*,*E*)-2-Methyl-5,7-diphenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (478a). General Procedure B was followed using imine **1a** (55.0 mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol), and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (10% EtOAc/petroleum ether) to give *allylation product* **478a** (92.0 mg, 69%) as a colourless oil. $[\alpha]_D^{25.2}$ –26.2 (c 0.32, $CHCl_3$); Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm): t_r (major) = 7.3 min, t_r (minor) = 14.7 min, 99% ee.

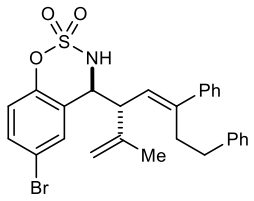


(4*S*)-6-Methyl-4-[(3*R*,*E*)-2-methyl-5,7-diphenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (478b). General Procedure B was followed using imine **197b** (59.2 mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol), and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (15% Et_2O/*iso*-hexane) to give *allylation product* **478b** (103 mg, 75%) as a pale brown solid. R_f = 0.23 (15% Et_2O/*iso*-hexane); m.p. 118-120 °C (Et_2O); $[\alpha]_D^{24.1}$ –114.4 (*c* 0.37, $CHCl_3$); IR 3310 (N-H), 2935, 1433, 852, 748, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.21 (8H, m, Ar**H)**, 7.15-7.10 (4H, m, Ar**H**), 6.99-6.91 (1H, m, Ar**H**), 5.60 (1H, d, *J* = 9.6 Hz, C=C**H**), 5.10 (1H, m, C=C**H$_A$**H$_B$), 5.06-4.97 (2H, m, C=CH$_A$**H$_B$** and C**H**NH), 4.23 (1H, d, *J* = 6.8 Hz, N**H**), 3.66 (1H, dd, *J* = 9.7, 6.0 Hz, C=CC**H**), 2.83-2.72 (2H, m, PhC**H$_2$**), 2.69-2.56 (1H, m, PhCH$_2$C**H$_A$**H$_B$), 2.52-2.40 (1H, m PhCH$_2$CH$_A$**H$_B$**), 2.35 (3H, s, ArC**H$_3$**), 1.96 (3H, C=CC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2 (C), 143.4 (C), 143.2 (C), 141.7 (C), 141.5 (C), 134.9 (C), 129.9 (CH), 128.4 (2 × CH), 128.4 (2 × CH), 128.2 (2 × CH), 127.4 (CH), 127.0 (CH), 126.6 (2 × CH), 126.2 (CH), 124.5 (CH), 121.7 (C), 118.5 (CH), 115.3 (CH_2), 57.1 (CH), 49.4 (CH), 33.9 (CH_2), 31.9 (CH_2), 21.4 (CH_3), 20.9 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{28}H_{29}NNaO_3S]^+$ $[M+Na]^+$: 482.1760, found: 482.1777; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm): t_r (major) = 6.9 min, t_r (minor) = 10.4 min, 99% ee.

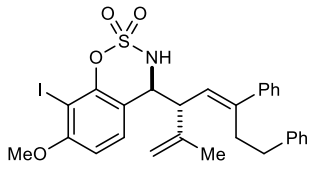


(4*S*)-6-Methoxy-4-[(3*R*,*E*)-2-methyl-5,7-diphenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (478c). General Procedure B was followed using imine **1c** (64.0 mg, 0.300 mmol), 1,3-enyne **197c** (66.3 mg, 0.360 mmol), and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (10% EtOAc/petroleum ether) to give *allylation product* **478c** (79.0 mg, 55%) as a yellow oil. R_f = 0.21 (15% EtOAc/petroleum ether); $[\alpha]_D^{24.9}$ –59.6 (*c* 0.34, $CHCl_3$); IR 3268 (N-H), 2936, 1490, 1444, 1169, 848, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.14 (8H, m, Ar**H**), 7.09-7.05 (2H, m, Ar**H**), 6.98 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.87-6.80 (2H, m, Ar**H**), 5.57 (1H, d, *J* = 9.7 Hz, C=C**H**), 5.05 (1H, m, C=C**H$_A$**H$_B$**)** 5.00 (1H, m, C=CH$_A$**H$_B$**), 4.94 (1H, dd, *J* = 7.4, 6.6 Hz, C**H**NH), 3.92 (1H, d, *J* = 7.4 Hz, N**H**), 3.75 (3H, s, OC**H$_3$**), 3.53 (1H, dd, *J* = 9.7, 6.6 Hz, C=CC**H**), 2.82-2.74 (2H, m, PhC**H$_2$**), 2.67-2.57 (1H, m, PhCH$_2$C**H$_A$**H$_B$), 2.41 (1H, dt, *J* = 13.7, 8.2 Hz, PhCH$_2$CH$_A$**H$_B$**), 1.90 (3H, s, CC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (C), 145.1 (C), 143.7 (C), 142.9 (C), 141.7 (C), 141.5 (C), 128.5 (4 × CH), 128.3 (2 × CH), 127.5 (CH), 126.7 (2 × CH), 126.3 (CH), 124.8 (CH), 123.2 (C),

119.6 (CH), 115.2 (CH_2), 114.4 (CH), 112.0 (CH), 57.1 (CH), 55.6 (CH_3), 49.6 (CH), 33.9 (CH_2), 31.8 (CH_2), 21.2 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{28}H_{29}NNaO_4S]^+$ $[M+Na]^+$: 498.1710, found: 498.1704; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (95:5 *iso*-hexane:*i*-PrOH, 0.8 mL/min, 210 nm): t_r (major) = 22.7 min, t_r (minor) = 28.5 min, 99% ee.

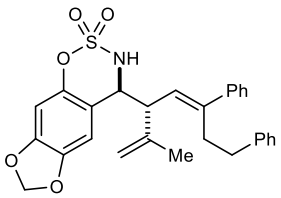


(4*S*)-6-Bromo-4-[(3*R*,*E*)-2-methyl-5,7-diphenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (478d). General Procedure B was followed using imine **197d** (78.6 mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol), and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (5% EtOAc/*iso*-hexane) to give *allylation product* **478d** (110 mg, 70%) as a pale yellow solid. R_f = 0.27 (15% Et_2O/ *iso*-hexane); m.p. 105-106 °C (Et_2O); $[\alpha]_D^{24.7}$ −119.2 (*c* 0.39, $CHCl_3$); IR 3297 (N-H), 2919, 1448, 1163, 825, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.42 (2H, m, Ar**H**) 7.38-7.28 (3H, m, Ar**H**), 7.26-7.14 (5H, m, Ar**H**) 7.11-7.06 (2H, m, Ar**H**), 6.95-6.91 (1H, m, Ar**H**), 5.48 (1H, d, *J* = 9.8 Hz, C=C**H**), 5.06 (1H, br s, C=C$\mathbf{H_A}H_B$), 4.99-4.97 (1H, m, C=C$H_A\mathbf{H_B}$), 4.94 (1H, d, *J* = 6.8 Hz, C**H**NH), 3.87 (1H, br s, N**H**), 3.49 (1H, dd, *J* = 9.8, 6.8 Hz, C=CC**H**), 2.79 (2H, dd, *J* = 8.1, 6.7 Hz, PhC$\mathbf{H_2}$), 2.65 (1H, dt, *J* = 13.7, 6.7 Hz, $PhCH_2C\mathbf{H_A}H_B$), 2.46 (1H dt, *J* = 13.7, 8.1 Hz, $PhCH_2CH_A\mathbf{H_B}$), 1.89 (3H, s, C$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (C), 143.3 (C), 143.2 (C), 141.6 (C), 141.4 (C), 132.3 (CH), 129.7 (CH), 128.54 (2 × CH), 128.51 (2 × CH), 128.4 (2 × CH), 127.7 (CH), 126.7 (2 × CH), 126.4 (CH), 124.4 (CH), 124.3 (C), 120.5 (CH), 117.8 (C), 115.5 (CH_2), 56.6 (CH), 49.2 (CH), 33.7 (CH_2), 31.8 (CH_2), 21.2 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{27}H_{26}{}^{79}BrNNaO_3S]^+$ $[M+Na]^+$: 546.0709, found: 546.0699; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (95:5 *iso*-hexane:*i*-PrOH, 0.8 mL/min, 254 nm): t_r (major) = 16.3 min, t_r (minor) = 24.5 min, 99% ee.



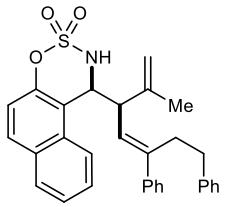
(4*S*)-8-Iodo-7-methoxy-4-[(3*R*,*E*)-2-methyl-5,7-diphenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (478f). A modification of General Procedure B was followed using imine **197f** (67.8 mg, 0.200 mmol), 1,3-enyne **134** (44.2 mg, 0.240 mmol), phenylboronic acid (36.6 mg, 0.300 mmol), KF (17.4 mg, 0.300 mmol), *t*-amyl alcohol (0.03 mL, 0.30 mmol), $[Rh(C_2H_4)_2Cl]_2$ (1.9 mg, 5.0 μmol) **L19** (4.0 mg, 10 μmol), $ZnCl_2$ solution (0.7 M in THF, 0.29 mL, 0.20 mmol), and THF (1.0 mL). The mixture was purified

by column chromatography (10% EtOAc/*iso*-hexane) to give *allylation product* **478f** (74 mg, 62%) as an off-white solid. R_f = 0.24 (20% EtOAc/petroleum ether); m.p. 151-153 °C (Et_2O); $[\alpha]_D^{25.0}$ –18.6 (*c* 0.30, $CHCl_3$); IR 3306 (N-H), 2923, 1451, 1186, 1170, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (3H, m, Ar**H**), 7.26-7.21 (2H, m, Ar**H**), 7.21-7.14 (3H, m, Ar**H**) 7.08 (1H, dd, *J* = 8.7, 0.9 Hz, Ar**H**), 7.05-7.01 (2H, m, Ar**H**) 6.61 (1H, d, *J* = 8.7 Hz, Ar**H**), 5.49 (1H, d, *J* = 9.5 Hz, C=C**H**), 5.04 (1H, br s, C=C**H**$_A$H$_B$), 4.96 (1H, br s, C=CH$_A$**H$_B$**), 4.90 (1H, dd, *J* = 7.8, 6.9 Hz, C**H**NH), 3.92 (3H, s, OC**H$_3$**), 3.81 (1H, d, *J* = 7.8 Hz, N**H**), 3.44 (1H, dd, *J* = 9.5, 6.9 Hz, C=CC**H**), 2.83-2.74 (2H, m, PhC**H$_2$**), 2.71-2.61 (1H, m, PhCH$_2$C**H$_A$**H$_B$), 2.41 (1H, dt, *J* = 13.6, 8.1 Hz, PhCH$_2$CH$_A$**H$_B$**), 1.89 (3H, s, CC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C), 151.5 (C), 143.5 (C), 142.8 (C), 141.5 (C), 141.4 (C), 128.5 (4 × CH), 128.4 (2 × CH), 127.6 (CH), 127.4 (CH), 126.7 (2 × CH), 126.4 (CH), 125.1 (CH), 116.0 (C), 115.1 (CH_2), 107.3 (CH), 78.5 (C), 56.7 (CH_3), 56.6 (CH), 49.4 (CH), 33.7 (CH_2), 31.7 (CH_2), 21.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{28}H_{28}INNaO_4S]^+$ $[M+Na]^+$: 624.0676, found: 624.0660; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm): t_r (major) = 12.6 min, t_r (minor) = 18.5 min, 99% ee.



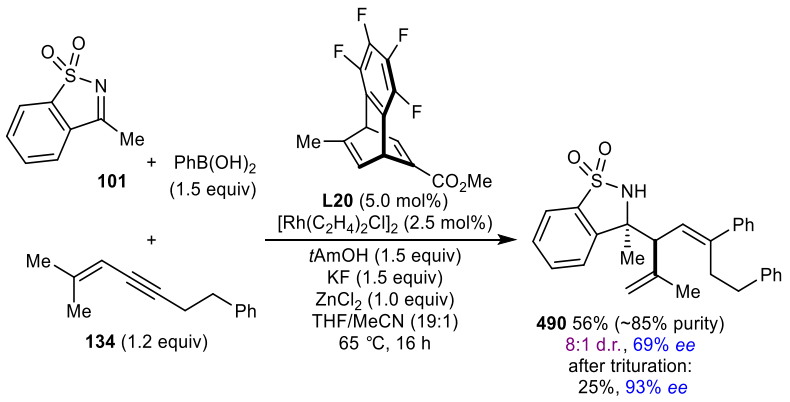
(13*S*)-13-[(3*R*,*E*)-2-Methyl-5,7-diphenylhepta-1,4-dien-3-yl]-4,6,10-trioxa-11λ^6-thia-12-azatricyclo[7.4.0.0^{3,7}]trideca-1,3(7),8-triene-11,11-dione (478g). General Procedure B was followed using imine **197g** (68.2 mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol), and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (10% EtOAc/petroleum ether) to give *allylation product* **478g** (76.0 mg, 52%) as a dark orange solid. R_f = 0.43 (20% EtOAc/petroleum ether); m.p. 108-109 °C (Et_2O); $[\alpha]_D^{25.2}$ –26.2 (*c* 0.48, $CHCl_3$); IR 3291 (N-H), 2916, 1482, 1200, 1135, 1032, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.15 (8H, m, Ar**H**), 7.10-7.04 (2H, m, Ar**H**), 6.62-6.59 (1H, m, Ar**H**), 6.55 (1H, s, Ar**H**), 6.00 (1H, d, *J* = 1.3 Hz, C**H$_A$**H$_B$O), 5.98 (1H, d, *J* = 1.3 Hz, CH$_A$**H$_B$**O), 5.54 (1H, d, *J* = 9.5 Hz, C=C**H**), 5.06-5.03 (1H, m, C=C**H$_A$**H$_B$), 4.98-4.95 (1H, m, C=CH$_A$**H$_B$**), 4.84 (1H, dd, *J* = 7.2, 6.4 Hz, C**H**NH), 3.94 (1H, d, *J* = 7.2 Hz, N**H**), 3.44 (1H, dd, *J* = 9.5, 6.4 Hz, C=CC**H**), 2.80-2.73 (2H, m, PhC**H$_2$**), 2.69-2.59 (1H, m, PhCH$_2$C**H$_A$**H$_B$), 2.41 (1H, dt, *J* = 13.7, 8.2 Hz PhCH$_2$CH$_A$**H$_B$**), 1.88 (3H, s, CC**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8 (C), 145.8 (C), 145.1 (C), 143.5 (C), 143.0 (C) , 141.6 (C), 141.5 (C), 128.5 (4 × CH), 128.3 (2 × CH), 127.6 (CH), 126.6 (2 × CH), 126.4 (CH), 124.7 (CH), 115.3 (CH_2), 114.6 (C), 105.3 (CH), 102.0 (CH_2), 100.5 (CH), 56.9 (CH), 49.4 (CH), 33.8 (CH_2), 31.9 (CH_2), 21.4 (CH_3); HRMS (ESI) Exact mass calcd for

$[C_{28}H_{27}NNaO_5S]^+$ [M+Na]$^+$: 512.1502, found: 512.1509; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm): t_r (major) = 12.6 min, t_r (minor) = 16.6 min, 99% ee.



(1*S*)-1-[(3*R*,*E*)-2-Methyl-5,7-diphenylhepta-1,4-dien-3-yl]-1H,2H-4,3λ^6,2-naphtho[1,2-e][1,2λ^6,3]oxathiazine-3,3-dione (478h). General Procedure B was followed using imine **197h** (70.0 mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol), and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (10% EtOAc/petroleum ether) to give *allylation product* **478h** (79.0 mg, 53%) as an orange oil. R_f = 0.34 (15% EtOAc/petroleum ether); $[\alpha]_D^{24.8}$ –170.3 (*c* 0.47, $CHCl_3$); IR 3306 (N-H), 2926, 1451, 1184, 1170, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, d, *J* = 8.6 Hz, Ar**H**), 7.89 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.85 (1H, d, *J* = 8.9 Hz, Ar**H**), 7.70 (1H, t, *J* = 7.8 Hz, Ar**H**), 7.55 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.36-7.22 (4H, m, Ar**H**), 7.20-7.01 (5H, m, Ar**H**), 6.65-6.60 (2H, m, Ar**H**), 5.84 (1H, dd, *J* = 3.6, 2.8 Hz, C**H**NH), 5.72 (1H, d, *J* = 10.0 Hz, C=C**H**), 5.14 (1H, d, *J* = 1.5 Hz, C=C**H$_A$**H$_B$), 5.10-5.04 (2H, m, C=CH$_A$**H$_B$** and N**H**), 4.09-4.00 (1H, m, C=CC**H**), 2.10-1.88 (6H, m, PhC**H$_2$**C**H$_A$**H$_B$ and C**H$_3$**), 1.23-1.13 (1H, m, PhCH$_2$CH$_A$**H$_B$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5 (C), 145.2 (C), 142.9 (C), 141.8 (C), 141.3 (2 × C), 131.8 (C), 130.7 (CH), 129.7 (CH), 128.4 (2 × CH), 128.1 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 127.4 (CH), 126.4 (2 × CH), 125.9 (CH), 125.7 (CH), 121.9 (CH), 121.4 (CH), 118.6 (CH), 116.4 (C), 116.2 (CH_2), 56.2 (CH), 48.8 (CH), 33.9 (CH_2), 32.0 (CH_2), 21.9 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{31}H_{29}NNaO_3S]^+$ [M+Na]$^+$: 518.1760, found: 518.1757; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm): t_r (major) = 12.2 min, t_r (minor) = 28.9 min, 99% ee.

3-Methyl-3-[(3*S*,*E*)-2-methyl-5,7-diphenylhepta-1,4-dien-3-yl]-2,3-dihydro-1λ^6,2-benzothiazole-1,1-dione (490)



$[Rh(C_2H_4)_2Cl]_2$ (2.9 mg, 7.5 µmol, 2.5 mol%) and **L20** (4.5 mg, 15 µmol, 5.0 mol%) were added to an oven-dried microwave vial and purged with nitrogen for 1 h. Degassed anhydrous THF (1.4 mL) and degassed anhydrous MeCN (0.1 mL) were added and the mixture stirred for 30 min at room temperature. Imine **101** (54.3 mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol), phenylboronic acid (54.9 mg, 0.450 mmol), and KF (26.1 mg, 0.450 mmol) were added to a separate oven-dried microwave vial. The vial was purged with nitrogen for 1 h, and the catalyst solution was then added to the vial containing the imine. *t*-Amyl alcohol (0.05 mL, 0.45 mmol) and $ZnCl_2$ solution (0.7 M in THF, 0.43 mL, 0.30 mmol) were added and the reaction mixture was stirred for at 65 °C for 16 h. The mixture was cooled to room temperature, diluted with saturated aqueous NH_4Cl solution (5 mL) and water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (10% EtOAc/petrol) to give *allylation product* **490** (80.0 mg) as an orange solid in *ca.* 85% purity as determined by ^{1}H NMR analysis, and in 69% ee. This material was further purified by the following procedure: (i) suspending it in hot pentane (*ca.* 3 mL), followed by the addition of toluene (*ca.* 0.1 mL); (ii) agitation of the mixture; (iii) removal of the solvent with a pipette, and (iv) washing the residue with additional pentane. This sequence gave *allylation product* **490** (33 mg, 25%) as an orange solid in 93% ee. Combining all of the washes from this trituration procedure and concentration *in vacuo* gave a second batch of material (45 mg) in *ca*. 60% purity as a yellow solid, which was not purified further. R_f = 0.37 (20% EtOAc/petroleum ether); m.p. 172-174 °C (Et_2O); $[\alpha]_D^{25.0}$ –13.8 (*c* 0.58, $CHCl_3$); IR 3206 (N-H), 2923, 1445, 1274, 1131, 767, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.73 (1H, m, Ar**H**), 7.61-7.55 (1H, app td, *J* = 7.6, 1.3 Hz, Ar**H**), 7.54-7.48 (1H, app td, *J* = 7.6, 1.1 Hz, Ar**H**), 7.43-7.38 (3H, m, Ar**H**), 7.37-7.31 (2H, m, Ar**H**), 7.29-7.23 (3H, m, Ar**H**), 7.21-7.15

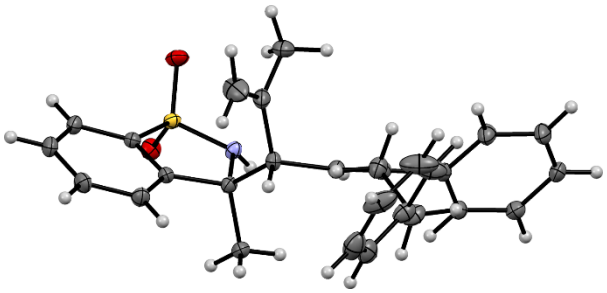
(1H, m, Ar**H**), 7.09-7.03 (2H, m, Ar**H**), 5.85 (1H, d, *J* = 10.3 Hz, C=C**H**), 4.96-4.93 (1H, m, C=C$\mathbf{H_A}$$H_B$), 4.87 (1H, br s, C=C$H_A$$\mathbf{H_B}$), 4.63 (1H, s, N**H**), 3.52 (1H, d, *J* = 10.3 Hz, C=CC**H**), 2.64-2.48 (3H, m, PhC$\mathbf{H_2}$C$\mathbf{H_A}$$H_B$), 2.35 (1H, dt, *J* = 13.2, 7.7 Hz, PhCH_2C$H_A$$\mathbf{H_B}$), 1.71 (3H, s, CH_2=CC$\mathbf{H_3}$), 1.53 (3H, s, NHCC$\mathbf{H_3}$); 13C NMR (126 MHz, CDCl3) δ 144.1 (C), 143.4 (C), 143.1 (C), 142.3 (C), 141.5 (C), 134.9 (C), 132.4 (CH), 129.3 (CH), 128.6 (2 × CH), 128.4 (4 × CH), 127.5 (CH), 126.6 (2 × CH), 126.1 (CH), 125.9 (CH), 124.5 (CH), 121.3 (CH), 117.1 (CH_2), 65.7 (C), 54.0 (CH), 34.1 (CH_2), 32.2 (CH_2), 26.4 (CH_3), 22.6 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{28}H_{29}NNaO_2S]^+$ $[M+Na]^+$: 466.1811, found: 466.1811;

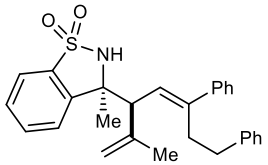
Enantiomeric excess was determined by HPLC using a Chiralcel AD-H column (90:10 *iso*-hexane:*i*-PrOH, 0.8 mL/min, 254 nm).

First batch (before trituration): t_r (minor) = 14.3 min, t_r (major) = 21.5 min, 69% ee.

Second batch (after trituration): t_r (minor) = 14.2 min, t_r (major) = 21.0, 93% ee.

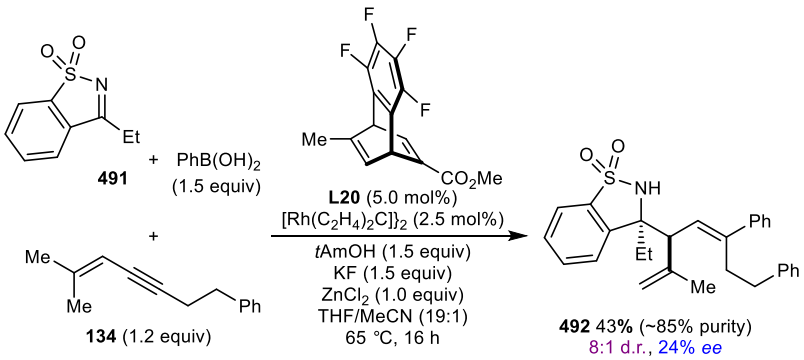
Crystals suitable for X-ray analysis were prepared by slow diffusion of petroleum ether into a solution of **490** in toluene.





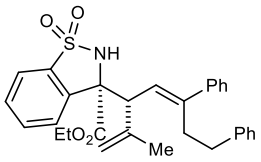
490
CCDC 1552183
Flack parameter = 0.03(3)

3-Ethyl-3-[(3*S*,*E*)-2-methyl-5,7-diphenylhepta-1,4-dien-3-yl]-2,3-dihydro-1λ^6,2-benzothiazole-1,1-dione (492)

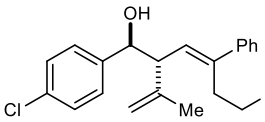


$[Rh(C_2H_4)_2Cl]_2$ (2.9 mg, 7.5 µmol, 2.5 mol%) and **L20** (4.5 mg, 15 µmol, 5.0 mol%) were added to an oven-dried microwave vial and purged with nitrogen for 1 h. Degassed anhydrous THF (1.4 mL) and degassed anhydrous MeCN (0.1 mL) were added and the mixture stirred for 30 min at room temperature. Imine **491** (58.6 mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol), phenylboronic acid (54.9 mg, 0.450 mmol), and KF (26.1 mg, 0.450 mmol) were added to a separate oven-dried microwave vial. The vial was purged with nitrogen for 1 h, and the catalyst solution was then added to the vial containing the imine. *t*-Amyl alcohol (0.05 mL, 0.45 mmol) and $ZnCl_2$ solution (0.7 M in THF, 0.43 mL, 0.30 mmol) were added and the reaction mixture was stirred for at 65 °C for 16 h. The mixture was cooled to room temperature, diluted with saturated aqueous NH_4Cl solution (5 mL) and water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (10% EtOAc/petrol), to give *allylation product* **492** (59.4 mg, 43%) as a yellow solid in *ca.* 85% purity as determined by ^{1}H NMR analysis. R_f = 0.42 (20% EtOAc/petroleum ether); m.p. 157-159 °C (Et_2O); $[\alpha]_D^{25.0}$ –13.41 (*c* 0.21, CH_3Cl); IR 3229 (N-H), 2923, 1454, 1276, 1174, 1161, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.73 (1H, m, Ar**H**), 7.63-7.56 (1H, m, Ar**H**), 7.55-7.48 (1H, m, Ar**H**), 7.45-7.24 (8H, m, Ar**H**), 7.24-7.17 (1H, m, Ar**H**), 7.11-7.05 (2H, m, Ar**H**), 5.83 (1H, d, *J* = 10.3 Hz, C=C**H**), 4.90-4.87 (1H, m, C=C**H$_A$**H$_B$), 4.78 (1H, s, C=CH$_A$**H$_B$**), 4.47-4.42 (1H, m, N**H**), 3.50 (1H, d, *J* = 10.3 Hz, C**H**C=C), 2.66 (2H, t, *J* = 7.6 Hz, PhC**H$_2$**), 2.61-2.52 (1H, m, PhCH$_2$C**H$_A$**H$_B$), 2.42 (1H, dt, *J* = 13.4, 7.9 Hz, PhCH$_2$CH$_A$**H$_B$**), 1.90 (1H, dq, *J* = 14.5, 7.3 Hz, C**H$_A$**H$_B$CH$_3$), 1.83-1.67 (4H, m, CH$_2$=CC**H$_3$** and CH$_A$**H$_B$**CH$_3$), 0.63 (3H, t, *J* = 7.3 Hz, CH$_2$C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 142.7 (C), 142.3 (C), 141.6 (C), 140.6 (C), 135.9 (C), 132.36 (CH), 129.3 (CH), 128.5 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 127.4 (CH), 126.7 (2 × CH), 126.2 (CH), 126.1 (CH), 124.5 (CH), 121.4 (CH), 117.1 (CH$_2$),

70.2 (C), 54.6 (CH), 34.1 (CH_2), 32.0 (CH_2), 31.1 (CH_2), 22.4 (CH_3), 7.8 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{29}H_{31}NNaO_2S]^+$ $[M+Na]^+$ 480.1968, found: 480.1968; Enantiomeric excess was determined by HPLC using a Chiralcel AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm): t_r (minor) =12.9 min, t_r (major) = 24.4 min, 24% ee.



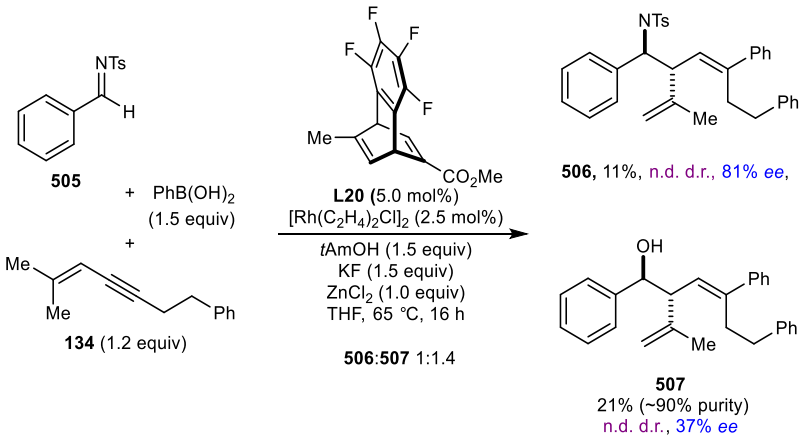
Ethyl 3-[(3*S*,*E*)-2-methyl-5,7-diphenylhepta-1,4-dien-3-yl]-1,1-dioxo-2,3dihydro-1λ⁶,2-benzothiazole-3-carboxylate (494). General Procedure B was followed using imine **493** (71.8 mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol), and phenylboronic acid (54.9 mg, 0.450 mmol) and gave, after purification by column chromatography (15% EtOAc/petroleum ether) *allylation product* **494** (113 mg, 75%) as a pale yellow oil in *ca.* 90% purity as determined by ^{1}H NMR analysis. The impurities could not be identified unambiguously. R_f = 0.26 (20% EtOAc/petroleum ether); $[\alpha]_D^{24.3}$ +25.58 (*c* 0.25, CH_3Cl); IR 3278 (N-H), 2978, 1731 (C=O), 1240, 1171, 905, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.76 (1H, m, Ar**H**), 7.71-7.67 (1H, m, Ar**H**) 7.64-7.54 (2H, m, Ar**H**), 7.40-7.11 (10H, m, Ar**H**), 5.89-5.77 (2H, m, N**H** and C=C**H**), 5.05 (1H, br s, C=C$\mathbf{H_A}H_B$), 5.00-4.96 (1H, m, C=C$H_A\mathbf{H_B}$), 4.39-4.27 (2H, m, OC$\mathbf{H_2}$), 4.17 (1H, d, *J* = 9.8 Hz, C**H**C=C), 2.77-2.61 (2H, m, PhC$\mathbf{H_2}$), 2.49 (1H, ddd, *J* = 13.9, 10.2, 6.2 Hz, PhCH_2C$\mathbf{H_A}H_B$), 2.22 (1H, ddd, *J* = 13.9, 10.8, 6.2 Hz, PhCH_2C$H_A\mathbf{H_B}$), 1.86 (3H, s, CC$\mathbf{H_3}$), 1.38 (3H, t, *J* = 7.2 Hz, CH_2C$\mathbf{H_3}$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6 (C), 144.0 (C), 143.0 (C), 141.9 (C), 141.4 (C), 136.4 (C), 135.2 (C), 133.5 (CH), 130.5 (CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.1 (2 × CH), 127.1 (CH) 126.3 (2 × CH), 126.0 (CH), 125.3 (CH), 123.3 (CH), 121.5 (CH), 115.3 (CH2), 72.9 (C), 63.7 (CH2), 53.5 (CH), 34.5 (CH2), 31.9 (CH2), 21.1 (CH3), 14.1 (CH3); HRMS (ESI) Exact mass calcd for $[C_{30}H_{31}NNaO_4S]^+$ $[M+Na]^+$: 524.1866, found: 524.1858; Enantiomeric excess was determined by HPLC using a Chiralcel AD-H column (97:3 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 254 nm): t_r (major) = 39.1 min, t_r (minor) = 79.8 min, 94% ee.



(1*S*,2*R*,*E*)-1-(4-Chlorophenyl)-4,6-diphenyl-2-(prop-1-en-2-yl)hex-3-en-1-ol (503). General Procedure B was followed using 4-chlorobenzaldehyde (42.2 mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (5% EtOAc/petroleum ether, followed by 70% petroleum ether, 29% CH_2Cl_2, 1% EtOAc), to give *allylation product* **504** (36.8 mg, 30%) as a pale yellow oil as a colourless oil in *ca.* 90% purity as determined by ^{1}H NMR analysis. R_f = 0.31 (10% EtOAc/petroleum

ether); $[\alpha]_D^{20.0}$ −38.6 (*c* 1.45, $CHCl_3$); IR 3432 (O-H), 3026, 1599, 1491, 1013, 753, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.35 (4H, m, Ar**H**), 7.33-7.17 (8H, m, Ar**H**), 7.11-7.07 (2H, m, Ar**H**), 5.86 (1H, d, *J* = 9.9 Hz, C=C**H**), 4.84 (1H, app t, *J* = 1.5 Hz, C=C$\mathbf{H_A}H_B$), 4.78-4.74 (2H, m, C=$CH_A\mathbf{H_B}$ and C**H**OH), 3.21 (1H, ddd, *J* = 9.9, 6.5, 0.8 Hz, C=CC**H**), 2.80-2.62 (2H, m, PhC$\mathbf{H_2}$), 2.60-2.50 (1H, m, $PhCH_2C\mathbf{H_A}H_B$), 2.39 (1H, ddd, *J* = 13.6, 9.7, 6.6 Hz, $PhCH_2CH_A\mathbf{H_B}$), 1.96 (1H, d, *J* = 2.6 Hz, O**H**), 1.71 (3H, dd, *J* = 1.4, 0.8 Hz, C$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (C), 143.0 (C), 142.4 (C), 141.8 (C), 140.9 (C), 133.0 (C), 128.4 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.9 (2 × CH), 127.2 (CH), 126.7 (CH), 126.6 (2 × CH), 126.0 (CH), 113.8 (CH_2), 74.6 (CH), 54.3 (CH), 34.4 (CH_2), 32.1 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{27}H_{27}{}^{35}ClNaO]^+$ $[M+Na]^+$: 425.1643, found: 425.1642; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 iso-hexane:*i*-PrOH, 1.0 mL/min, 254 nm): t_r (minor) = 7.1 min, t_r (major) = 8.9 min, 47% ee.

4-Methyl-N-[(1*S*,2*R*,*E*)-1,4,6-triphenyl-2-(prop-1-en-2-yl)hex-3-en-1-yl]benzene-1-sulfonamide (506) and (1*S*,2*R*,*E*)-1,4,6-triphenyl-2-(prop-1-en-2-yl)hex-3-en-1-ol (507)

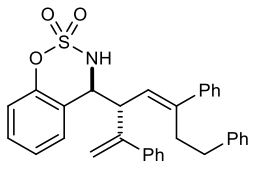


A modification of General Procedure B was followed using *N*-tosyl imine **505** (77.8. mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (5% EtOAc/petroleum ether, followed by 70% petroleum ether, 29% CH_2Cl_2, 1% EtOAc), to give *allylation product* **506** (17.0 mg, 11%) as a white solid and *allylation product* **507** (32.7 mg, 21%) as a colourless oil in *ca.* 90% purity as determined by ^1H NMR analysis.

Data for **506**: R_f = 0.21 (10% EtOAc/petroleum ether); $[\alpha]_D^{20.0}$ −21.4 (*c* 1.5, $CHCl_3$); m.p. 117-119 °C (Et_2O); IR 3288 (N-H), 2923, 1456, 1162, 895, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.30 (9H, m, Ar**H**), 7.28-7.22 (1H, m, Ar**H**), 7.15-7.11 (2H, m, Ar**H**), 7.11-7.05 (3H, m,

Ar**H**), 7.03-6.99 (2H, m, Ar**H**), 6.85-6.80 (2H, m, Ar**H**), 5.63 (1H, d, *J* = 9.4 Hz, C=C**H**), 4.57-4.53 (1H, m, C=C**H$_A$**H$_B$), 4.43 (1H, br s, C=CH$_A$**H$_B$**), 4.35 (1H, dd, *J* = 9.7, 6.6 Hz, C**H**NH), 4.01 (1H, *J* = 6.6 Hz, N**H**), 2.88 (1H, dd, *J* = 9.7, 9.4 Hz, C=CC**H**), 2.78-2.64 (3H, m, PhC**H$_2$H$_A$**H$_B$), 2.46-2.28 (1H, m, PhCH$_2$H$_A$**H$_B$**), 2.32 (3H, s, ArC**H$_3$**), 1.49-1.46 (3H, m, CH$_2$=CC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C), 142.6 (C), 142.0 (2 × C), 141.8 (C), 139.7 (C), 137.8 (C), 129.0 (4 × CH), 128.6 (2 × CH), 128.48 (2 × CH), 128.46 (CH), 127.8 (2 × CH), 127.3 (CH), 127.2 (2 × CH), 127.1 (CH), 126.9 (2 × CH), 126.8 (2 × CH), 126.1 (CH), 114.2 (CH_2), 60.3 (CH), 52.9 (CH), 33.8 (CH_2), 31.3 (CH_2), 21.4 (CH_3), 19.8 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{34}H_{35}NNaO_2S]^+$ [M+Na]$^+$: 544.2281, found: 544.2264; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 230 nm): t_r (minor) = 6.6 min, t_r (major) = 8.2 min, 81% ee.

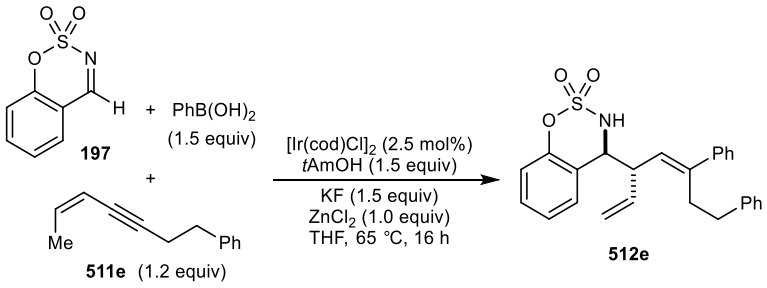
Data for **507**: R_f = 0.29 (10% EtOAc/petroleum ether); $[\alpha]_D^{20.0}$ −8.3 (*c* 0.8, $CHCl_3$); IR 3434 (O-H), 3025, 1494, 1452, 889, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (4H, m, Ar**H**), 7.34-7.32 (4H, m Ar**H**), 7.31-7.25 (4H, m, Ar**H**), 7.22-7.16 (1H, m, Ar**H**), 7.11-7.07 (2H, m, Ar**H**), 5.91 (1H, d, *J* = 9.9 Hz, C=C**H**), 4.84-4.80 (2H, m, C**H**OH and C=C**H$_A$**H$_B$), 4.78-4.76 (1H, m, C=CH$_A$**H$_B$**), 3.29 (1H, dd, *J* = 9.9, 6.4 Hz, C=CC**H**), 2.79-2.59 (2H, m, Ph**CH$_2$**), 2.51 (1H, ddd, *J* = 13.6, 9.6, 6.1 Hz, PhCH$_2$C**H$_A$**H$_B$), 2.32 (1H, ddd, *J* = 13.6, 10.1, 6.4 Hz, PhCH$_2$C**H$_A$**H$_B$), 1.96 (1H, d, *J* = 2.7 Hz, O**H**), 1.72 (3H, dd, *J* = 1.4, 0.8 Hz, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (C), 142.6 (2 × C), 142.4 (C), 142.0 (C), 128.33 (4 × CH), 128.30 (2 × CH), 128.1 (2 × CH), 127.4 (CH), 127.1 (2 × CH), 126.6 (2 × CH), 126.5 (2 × CH), 125.9 (CH), 113.4 (CH_2), 75.4 (CH), 54.3 (CH), 34.4 (CH_2), 32.1 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{27}H_{28}NaO]^+$ [M+Na]$^+$: 391.2032, found: 391.2038; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm): t_r (major) = 8.4 min, t_r (minor) = 10.4 min, 37% ee.



(4*S*)-4-[(3*R*,*E*)-2,5,7-Triphenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (512d). A modification of General Procedure B was followed using imine **197** (55.0 mg, 0.300 mmol), 1,3-enyne **511d** (88.6 mg, 0.360 mmol), phenylboronic acid (110 mg, 0.900 mmol) and *t*-amyl alcohol (0.10 mL, 0.90 mmol). The mixture was purified by column chromatography (10% EtOAc/petrol, followed by 70:28:2 petroleum ether/CH_2Cl_2/EtOAc), to give *allylation product* **512d** (75.0 mg, 49%) as a pale brown solid. R_f = 0.23 (10% EtOAc/petroleum ether); m.p. 113-114 °C (Et_2O); $[\alpha]_D^{25.4}$ +86.2 (*c* 0.39, $CHCl_3$); IR 3307 (N-H),

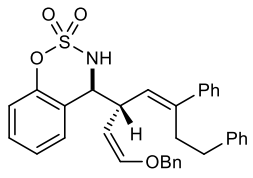
3024, 1422, 1198, 1169, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.36 (5H, m, Ar**H**), 7.36-7.21 (7H, m, Ar**H**), 7.19-7.06 (5H, m, Ar**H**), 7.03 (1H, dd, *J* = 8.3, 1.2 Hz, Ar**H**), 6.95 (1H, d, *J* = 7.8 Hz, Ar**H**), 5.60 (1H, d, *J* = 8.6 Hz, C=C**H**), 5.49 (1H, br s, C=C$\mathbf{H_A}H_B$), 5.32 (1H, s, C=$CH_A\mathbf{H_B}$), 4.81 (1H, dd, *J* = 6.3, 4.7 Hz, C**H**NH), 4.52 (1H, d, *J* = 6.3 Hz, N**H**) 4.28 (1H, dd, *J* = 8.6, 4.7 Hz, C=CC**H**), 2.82-2.69 (2H, m, PhC$\mathbf{H_2}$), 2.65-2.54 (1H, m, $PhCH_2C\mathbf{H_A}H_B$) 2.43 (1H, dt, *J* = 13.7, 8.2 Hz, $PhCH_2CH_A\mathbf{H_B}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (C), 147.5 (C), 144.5 (C), 141.59 (C), 141.56 (C), 140.1 (C), 129.2 (CH), 128.9 (2 × CH), 128.51 (2 × CH), 128.45 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 127.6 (CH), 126.62 (3 × CH), 126.56 (2 × CH), 126.2 (CH), 125.5 (CH), 123.2 (CH), 121.8 (C), 118.9 (CH), 117.7 (CH_2), 57.4 (CH), 47.1 (CH), 33.8 (CH_2), 32.5 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{32}H_{29}NNaO_3S]^+$ $[M+Na]^+$: 530.1760, found: 530.1757; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm): t_r (major) = 11.8 min, t_r (minor) = 14.6 min, >99% ee.

±(4*S*)-4-[(3*S*,*E*)-5,7-Diphenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (512e)

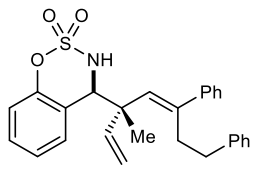


Imine **197** (55.0 mg, 0.300 mmol), 1,3-enyne **511e** (61.3 mg, 0.360 mmol), phenylboronic acid (110 mg, 0.900 mmol), KF (26.1 mg, 0.450 mmol), and $[Ir(cod)Cl]_2$ (5.0 mg, 7.5 µmol, 2.5 mol%) were added to an oven-dried microwave vial. The vial was purged with nitrogen for 1 h, and degassed anhydrous THF (1.5 mL) was added, followed by *t*-amyl alcohol (0.05 mL, 0.45 mmol) and $ZnCl_2$ solution (0.7 M in THF, 0.43 mL, 0.30 mmol). The mixture was stirred at 65 °C for 16 h and subsequently cooled to room temperature. The mixture was diluted with saturated aqueous NH_4Cl solution (5 mL) and water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% EtOAc/petroleum ether) to give *allylation product* **512e** (117 mg, 90%) as an orange oil. R_f = 0.19 (10% EtOAc/petroleum ether); IR 3272 (N-H), 2926, 1485, 1451, 1416, 1168, 755, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.11 (11H, m, Ar**H**) 7.09-7.05 (2H, m, Ar**H**), 7.02 (1H,

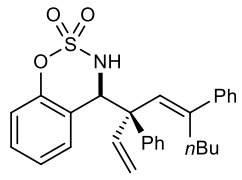
d, *J* = 8.2, 1.2, Ar**H**) 5.86 (1H, ddd, *J* = 17.0, 10.3, 6.4 Hz, CH_2=C**H**), 5.48 (1H, d, *J* = 9.2 Hz, C=C**H**), 5.26 (1H, app dt, *J* = 10.3, 1.3 Hz, C=C$\mathbf{H_A}H_B$), 5.18 (1H, app dt, *J* = 17.0, 1.3 Hz, C=$CH_A\mathbf{H_B}$), 4.83 (1H, dd, *J* = 7.7, 5.7 Hz, C**H**NH), 4.23 (1H, d, *J* = 7.7 Hz, N**H**), 3.73-3.65 (1H, m, C=CC**H**), 2.88-2.73 (2H, m, PhC$\mathbf{H_2}$), 2.68-2.58 (1H, m, $PhCH_2C\mathbf{H_A}H_B$), 2.47 (1H, dt, *J* = 13.7, 8.0 Hz, $PhCH_2CH_A\mathbf{H_B}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (C), 143.6 (C), 141.6 (C), 141.4 (C), 136.2 (CH), 129.4 (CH), 128.5 (2 × CH), 128.43 (2 × CH), 128.42 (2 × CH) 127.6 (CH), 126.9 (CH), 126.7 (2 × CH), 126.2 (CH), 125.1 (CH), 123.9 (CH), 121.6 (C), 118.9 (CH), 118.6 (CH_2), 59.4 (CH), 46.1 (CH), 33.8 (CH_2), 32.0 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{26}H_{25}NNaO_3S]^+$ $[M+Na]^+$: 454.1447, found: 454.1444.



(4*S*)-4-[(1*Z*,3*R*,4*E*)-1-(Benzyloxy)-5,7-diphenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (512g). A modification of General Procedure B was followed using imine **197** (55.0 mg, 0.300 mmol), 1,3-enyne **511g** (99.5 mg, 0.360 mmol), phenylboronic acid (110 mg, 0.900 mmol), and *t*-amyl alcohol (0.10 mL, 0.90 mmol). The mixture was purified by column chromatography (5% EtOAc/petroleum ether) to give *allylation product* **512g** (107 mg, 66%) as an orange oil. R_f = 0.14 (10% EtOAc/petroleum ether); $[\alpha]_D^{25.4}$ –24.8 (*c* 0.30, $CHCl_3$); IR 3271 (N-H), 3027, 1366, 1191, 1169, 751, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.03 (18H, m, Ar**H**), 7.00-6.96 (1H, m, Ar**H**), 6.09 (1H, d, *J* = 6.2 Hz, OC**H**=CH), 5.89 (1H, d, *J* = 9.3 Hz, C=C**H**), 4.98 (1H, d, *J* = 8.7 Hz, N**H**), 4.77 (1H, d, *J* = 12.2 Hz, OC$\mathbf{H_A}H_B$), 4.70 (1H, d, *J* = 12.2 Hz, $OCH_A\mathbf{H_B}$), 4.53 (1H, dd, *J* = 8.7, 4.6 Hz, C**H**NH), 4.23 (1H, dd, *J* = 9.3, 6.2 Hz, OCH=C**H**), 4.12 (1H, app td, *J* = 9.3, 4.6 Hz, C=CC**H**), 2.83 (2H, t, *J* = 7.6 Hz, PhC$\mathbf{H_2}$), 2.73-2.63 (1H, m, $PhCH_2C\mathbf{H_A}H_B$), 2.56-2.45 (1H, m, $PhCH_2CH_A\mathbf{H_B}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6 (C), 146.7 (CH), 141.8 (C), 141.6 (C), 141.5 (C), 136.4 (C), 129.2 (CH), 128.6 (2 × CH), 128.44 (4 × CH), 128.39 (2 × CH), 128.35 (CH), 127.6 (2 × CH), 127.3 (CH), 127.2 (CH), 126.7 (2 × CH), 126.5 (CH), 126.0 (CH), 124.7 (CH), 121.5 (C), 118.6 (CH), 102.4 (CH), 74.4 (CH_2), 60.8 (CH), 37.8 (CH), 34.2 (CH_2), 32.1 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{33}H_{31}NNaO_4S]^+$ $[M+Na]^+$: 560.1866, found: 560.1870; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/in, 254 nm): t_r (major) = 17.7 min, t_r (minor) = 28.9 min, 69% ee.



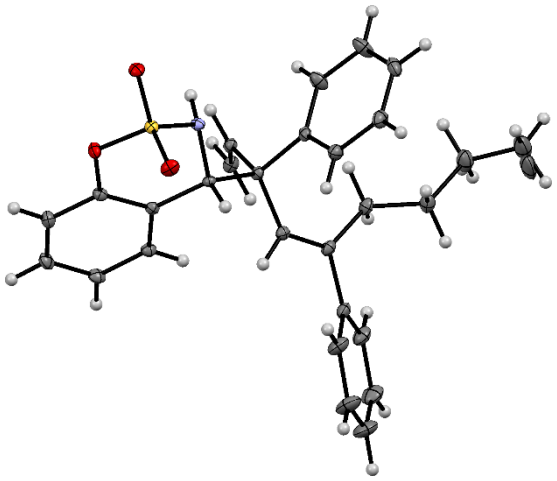
(4*S*)-4-[(3*S*,*E*)-3-Methyl-5,7-diphenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (512h). A modification of General Procedure B was followed using imine **197** (55.0 mg, 0.300 mmol), 1,3-enyne **511h** (66.3 mg, 0.360 mmol), phenylboronic acid (110 mg, 0.900 mmol), and *t*-amyl alcohol (0.10 mL, 0.90 mmol). The mixture was purified by column chromatography (80:19:1 petroleum ether/CH_2Cl_2/EtOAc, to give *allylation product* **512h** (67.0 mg, 43%) as a brown oil. R_f = 0.23 (10% EtOAc/petroleum ether); $[\alpha]_D^{25.3}$ +13.2 (*c* 0.22, $CHCl_3$); IR 3289 (N-H), 2927, 1364, 1169, 730, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.31 (8H, m, Ar**H**), 7.30-7.24 (1H, m, Ar**H**) 7.21-7.14 (2H, m, Ar**H**), 7.11-7.05 (3H, m, Ar**H**), 6.06 (1H, dd, *J* = 17.4, 10.7 Hz, **H**C=CH_2), 5.66 (1H, s, C=C**H**), 5.31 (1H, d, *J* = 10.7 Hz, HC=C**H$_A$**H$_B$), 5.20 (1H, d, *J* = 17.4 Hz, HC=CH$_A$**H$_B$**), 4.82-4.75 (2H, m, N**H** and C**H**NH), 2.91 (2H, m, PhC**H$_2$**), 2.56 (2H, t, *J* = 8.0 Hz, $PhCH_2$C**H$_2$**), 1.34 (3H, s, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (C), 144.8 (C), 143.0 (C), 141.3 (C), 140.9 (CH), 131.4 (CH), 129.7 (CH), 128.7 (CH), 128.6 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 127.5 (CH), 126.7 (2 × CH), 126.1 (CH), 125.0 (CH), 121.4 (C), 119.5 (CH), 116.4 (CH_2), 65.0 (CH), 48.2 (C), 34.0 (CH_2), 33.0 (CH_2), 21.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{27}H_{27}NNaO_3S$ $[M+Na]^+$: 468.1604, found: 468.1603; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm): t_r (major) = 8.5 min, t_r (minor) = 12.7 min, 90% ee.

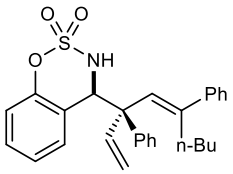


(4*S*)-4-[(3*S*,*E*)-3,5-Diphenylnona-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (512i). A modification of General Procedure B was followed using imine **197** (55.0 mg, 0.300 mmol), 1,3-enyne **511i** (71.4 mg, 0.360 mmol), phenylboronic acid (110 mg, 0.900 mmol) and *t*-amyl alcohol (0.10 mL, 0.90 mmol). The mixture was purified by column chromatography (10% EtOAc/petroleum ether, followed by 75:20:5 petroleum ether/CH_2Cl_2/Et_2O), to give *allylation product* **512i** (54.0 mg, 39%) as an off-white solid. R_f = 0.23 (10% EtOAc/petroleum ether); m.p. 127-129 °C (Et_2O); $[\alpha]_D^{25.6}$ +6.2 (*c* 0.38, $CHCl_3$); IR 3268 (N-H), 2954, 1417, 1166, 715, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (11H, m, Ar**H**), 7.04 (1H, dd, *J* = 8.3 and 1.3 Hz, Ar**H**), 6.92 (1H, app td, *J* = 7.7 and 1.3 Hz, Ar**H**), 6.60-6.49 (2H, m, CH_2=C**H** and Ar**H**), 5.99 (1H, s, C=C**H**), 5.53 (1H, dd, *J* = 10.6, 0.9 Hz, C=C**H$_A$**H$_B$), 5.38 (1H, dd, *J* = 17.3, 0.9 Hz, C=CH$_A$**H$_B$**), 5.11 (1H, d, *J* = 4.8 Hz, C**H**NH), 4.92 (1H, d, *J* = 4.8 Hz, N**H**), 2.23-2.06 (2H, m, CC**H$_2$**), 1.05-0.80 (4H, m, C**H$_2$**C**H$_2$**CH_3), 0.62 (3H, t, *J* = 6.8 Hz, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C), 148.6 (C), 142.6 (C), 140.4 (C), 138.9 (CH), 129.7 (CH), 129.4 (CH), 128.7 (4

× CH), 128.4 (2 × CH), 127.8 (CH), 127.4 (CH), 126.6 (2 × CH), 126.4 (CH), 124.7 (CH), 120.7 (C), 119.3 (CH), 118.8 (CH_2), 64.8 (CH), 57.4 (C), 32.0 (CH_2), 28.6 (CH_2), 22.8 (CH_2), 13.6 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{28}H_{29}NNaO_3S]^+$ $[M+Na]^+$: 482.1760, found: 482.1753; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm): t_r (major) = 6.3 min, t_r (minor) = 9.8 min, 2% ee.

Crystals suitable for X-ray analysis were prepared by slow diffusion of petroleum ether into a solution of **512i** in EtOAc. The resulting crystals are of the racemic compound.

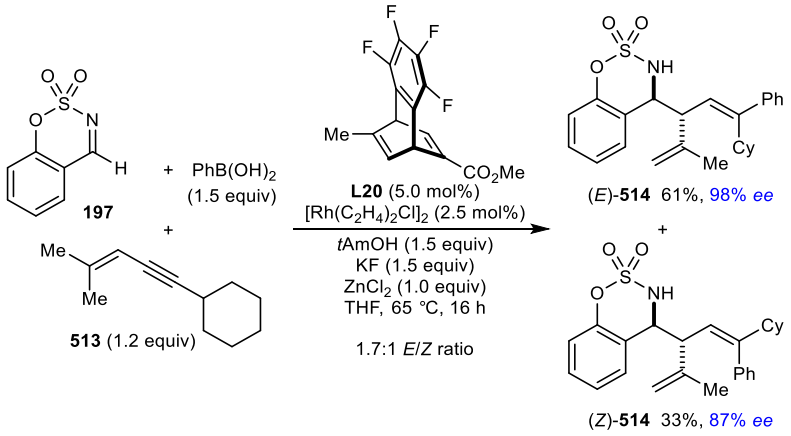




512i
CCDC 1552181

Note: In the butyl chain, the two carbon atoms at the terminal end exhibit disorder. This disorder is not shown above, for clarity.

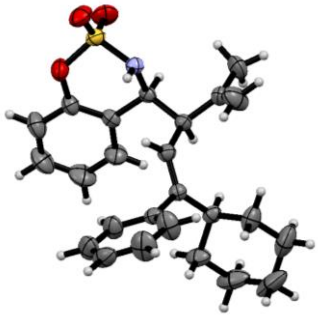
(4*S*)-4-[(3*R*,*E*)-5-Cyclohexyl-2-methyl-5-phenylpenta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione [(*E*)-514] and (4*S*)-4-[(3*R*,*Z*)-5-cyclohexyl-2-methyl-5-phenylpenta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione [(*Z*)-514]

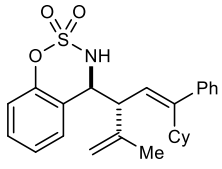


General Procedure B was followed using imine (55.0 mg, 0.300 mmol), 1,3-enyne **513** (58.0 mg, 0.360 mmol), and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (10% EtOAc/*iso*-hexane) to give *allylation product* (*Z*)-**514** (43.0 mg, 33%) as an off-white solid. Additional column chromatography (70:29:1 *iso*-hexane/CH_2Cl_2/EtOAc) gave *allylation product* (*E*)-**514** (85.0 mg, 65%) as a white solid.

Data for (*E*)-**514**: R_f = 0.35 (10% EtOAc/*iso*-hexane); m.p. 128-129 °C (Et_2O); $[\alpha]_D^{25.0}$ –50.0 (c 0.56, $CHCl_3$); IR 3280 (N-H), 2925, 1485, 1415 1192, 1168, 755, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.37-7.32 (1H, m, Ar**H**), 7.31-7.19 (5H, m, Ar**H**), 7.06 (1H, dd, *J* = 8.2, 1.3 Hz, Ar**H**), 6.83-6.79 (2H, m, Ar**H**), 5.15 (1H, dd, *J* = 6.1, 4.7 Hz, C**H**NH), 5.12-5.10 (1H, m, C=C**H$_A$**H$_B$), 5.10-5.05 (2H, m, C=CH$_A$**H$_B$** and C=C**H**), 4.64 (1H, d, *J* = 6.1 Hz, N**H**), 3.91 (1H, dd, *J* = 9.9, 4.7 Hz, C=CHC**H**), 2.38 (1H, tt, *J* = 11.3, 2.9 Hz, C**H**CH$_2$), 1.99-1.96 (3H, m, C**H$_3$**), 1.78-1.53 (4H, m, (C**H$_2$**)$_5$), 1.32-1.11 (4H, m, (C**H$_2$**)$_5$), 1.05-0.85 (2H, m, (C**H$_2$**)$_5$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (C), 151.4 (C), 143.3 (C), 142.3 (C), 129.3 (CH), 128.5 (2 × CH), 127.5 (2 × CH), 126.8 (CH), 126.6 (CH), 125.3 (CH), 122.5 (CH), 122.1 (C), 119.1 (CH), 115.6 (CH_2), 57.6 (CH), 47.9 (CH), 41.0 (CH), 31.5 (CH_2), 31.0 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 25.8 (CH_2), 21.7 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{25}H_{29}NNaO_3S]^+$ $[M+Na]^+$ 446.1760, found: 466.1745; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm): t_r (major) = 5.4 min, t_r (minor) = 8.4 min, 98% ee.

Crystals suitable for X-ray analysis were prepared by slow diffusion of petroleum ether into a solution of **514** in EtOAc.

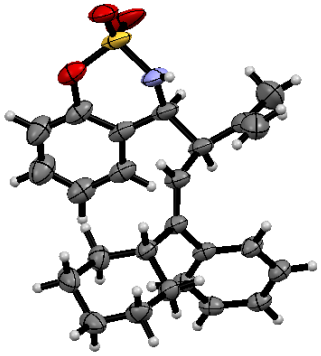


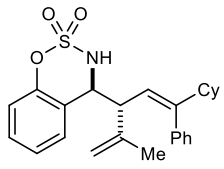


514
Flack parameter = 0.003(2)

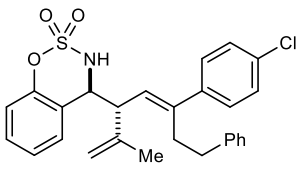
Data for (*Z*)-**514**: R_f = 0.46 (10% EtOAc/*iso*-hexane); m.p. 151-153 °C (Et_2O); $[\alpha]_D^{25.0}$ –21.3 (c 0.94, $CHCl_3$); IR 3260 (N-H), 2923, 1486 1433, 1196, 1171, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (4H, m, Ar**H**), 7.09 (1H, app td, *J* = 7.6, 1.3 Hz, Ar**H**), 7.00 (1H, dd, *J* = 8.2, 1.2 Hz, Ar**H**), 6.90-6.85 (2H, m, Ar**H**), 6.72-6.68 (1H, m, Ar**H**), 5.34 (1H, dd, *J* = 10.4, 1.1 Hz, C=C**H**), 5.14-5.11 (1H, m, C=C$\mathbf{H_A}H_B$), 5.06-5.03 (1H, m, C=C$H_A\mathbf{H_B}$), 4.94 (1H, dd, *J* = 5.1, 4.3 Hz, C**H**NH), 4.78 (1H, d, *J* = 5.1 Hz, N**H**), 3.26 (1H, dd, *J* = 10.3, 4.3 Hz, C=CHC**H**), 1.99 (1H, tt, *J* = 11.7, 4.6 Hz, C**H**CH_2), 1.83-1.80 (3H, m, C$\mathbf{H_3}$), 1.74-1.55 (3H, m, (C$\mathbf{H_2}$)$_5$), 1.54-1.43 (2H, m, (C$\mathbf{H_2}$)$_5$), 1.23-0.89 (5H, m, (C$\mathbf{H_2}$)$_5$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (C), 151.2 (C), 144.3 (C), 140.6 (C), 128.9 (CH), 127.92 (2 × CH), 127.86 (2 × CH), 127.2 (CH), 126.9 (CH), 125.2 (CH), 121.8 (C), 118.6 (CH), 118.5 (CH), 115.8 (CH_2), 57.1 (CH), 48.9 (CH), 46.2 (CH), 32.9 (CH_2), 31.8 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 21.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{25}H_{29}NNaO_3S]^+$ $[M+Na]^+$ 446.1760, found: 466.1749; Enantiomeric excess was determined by HPLC using a Chiralcel IC column (90:10 *iso*-hexane:*i*-PrOH, 0.8 mL/min, 254 nm): t_r (minor) = 8.7 min, t_r (major) = 9.6 min, 87% ee.

Crystals suitable for X-ray analysis were prepared by slow diffusion of petroleum ether into a solution of **514** in EtOAc.

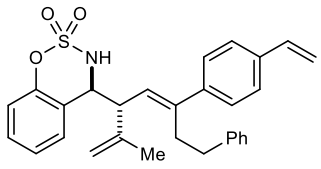




514
Flack parameter = –0.12(9)

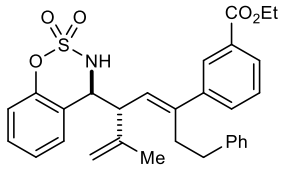


(4*S*)-4-[(3*R*,*E*)-5-(4-Chlorophenyl)-2-methyl-7-phenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (521a). General Procedure B was followed using imine **197** (55.1 mg, 0.301 mmol), 1,3-enyne **134** (65.3 mg, 0.360 mmol), and 4-chlorophenylboronic acid (70.4 mg, 0.45 mmol). The mixture was purified twice by column chromatography (15% EtOAc/petroleum ether; second column with 60:38:2 pentane/$CHCl_3$/EtOAc) to give *allylation product* **521a** (78 mg, 91% purity as determined by use of an internal standard, 49% adjusted yield) as a pale yellow oil. R_f = 0.34 (15% EtOAc/petroleum ether); $[\alpha]_D^{25.0}$ –49.8 (*c* 0.48, $CHCl_3$); IR 3268 (N-H), 2966, 1487, 1368, 1168, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (3H, m, Ar**H**), 7.23-7.15 (3H, m, Ar**H**), 7.15-7.00 (7H, m, Ar**H**), 5.48 (1H, d, *J* = 9.3 Hz, C=C**H**), 5.05 (1H, br s, C=C**H$_A$**H$_B$), 4.97 (1H, dd, *J* = 7.3, 6.5 Hz, C**H**NH), 4.94 (1H, br s, C=CH$_A$**H$_B$**), 3.97 (1H, d, *J* = 7.3 Hz, N**H**), 3.52 (1H, dd, *J* = 9.3, 6.5 Hz, C=CC**H**), 2.73 (2H, dd, *J* = 8.1, 6.5 Hz, PhC**H$_2$**), 2.62 (1H, dt, *J* = 13.6, 6.5 Hz, PhCH$_2$C**H$_A$**H$_B$), 2.38 (1H, dt, *J* = 13.6, 8.1 Hz, PhCH$_2$CH$_A$**H$_B$**), 1.90 (3H, s, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (C), 143.3 (C), 141.9 (C), 141.2 (C), 140.1 (C), 133.3 (C), 129.4 (CH), 128.6 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.0 (2 × CH), 126.7 (CH), 126.4 (CH), 125.6 (CH), 125.2 (CH), 122.0 (C), 118.8 (CH), 115.4 (CH_2), 56.8 (CH), 49.2 (CH), 33.6 (CH_2), 31.8 (CH_2), 21.4 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{27}H_{26}{}^{35}ClNNaO_3S]^+$ $[M+Na]^+$: 502.1214, found: 502.1192; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 210 nm): t_r (major) = 4.9 min, t_r (minor) = 10.9 min, 98% ee.

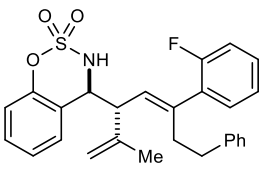


(4*S*)-4-[(3*R*,*E*)-5-(4-Ethenylphenyl)-2-methyl-7-phenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (521c). General Procedure B was followed using imine **197** (55.3 mg, 0.302 mmol), 1,3-enyne **134** (65.3 mg, 0.360 mmol), and 4-vinylphenylboronic acid (66.2 mg, 0.450 mmol). The mixture was purified by column chromatography (15% EtOAc/*iso*-hexane) to give *allylation product* **521c** (96 mg, 68%) as a yellow oil. R_f = 0.14 (15% EtOAc/petroleum ether); $[\alpha]_D^{25.2}$ –44.6 (*c* 0.25, $CHCl_3$); IR 3269 (N-H), 2935, 1368, 1168, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (2H, m, Ar**H**), 7.34-7.29 (1H, m, Ar**H**), 7.24-7.11 (6H, m, Ar**H**), 7.10-7.01 (4H, m, Ar**H**), 6.73 (1H, dd, *J* = 17.6, 10.9 Hz, C**H**=CH$_2$), 5.77 (1H, dd, *J* = 17.6, 0.9 Hz, CH=C**H$_A$**H$_B$), 5.53 (1H, d, *J* = 9.3 Hz, C=C**H**), 5.27 (1H, dd, *J* = 10.9, 0.9 Hz, CH=C**H$_A$**H$_B$), 5.05 (1H, br s, C=CH$_A$**H$_B$**), 4.99 (1H, dd, J = 7.3, 6.4 Hz, C**H**NH),

4.96 (1H, br s, C=CH$_A$**H$_B$**), 4.05 (1H, br s, N**H**), 3.55 (1H, dd, *J* = 9.3, 6.4 Hz, C=CC**H**), 2.80-2.72 (2H, m, PhC**H$_2$**), 2.64 (1H, dt, *J* = 13.5, 6.5 Hz, PhCH$_2$C**H$_A$**H$_B$), 2.42 (1H, dt, J = 13.5, 8.1 Hz, PhCH$_2$CH$_A$**H$_B$**), 1.91 (3H, s, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (C), 143.4 (C), 142.7 (C), 141.5 (C), 141.0 (C), 136.9 (CH), 136.3 (C), 129.3 (CH), 128.5 (2 × CH), 128.4 (2 × CH), 126.8 (2 × CH), 126.7 (CH), 126.3 (3 × CH), 125.2 (CH), 124.8 (CH), 122.1 (C), 118.7 (CH), 115.3 (CH_2), 113.9 (CH_2), 56.9 (CH), 49.2 (CH), 33.7 (CH_2), 31.7 (CH_2), 21.4 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{29}H_{29}NNaO_3S]^+$ [M+Na]$^+$: 494.1760, found: 494.1750; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 210 nm): t_r (major) = 4.8 min, t_r (minor) = 8.8 min, 99% ee.



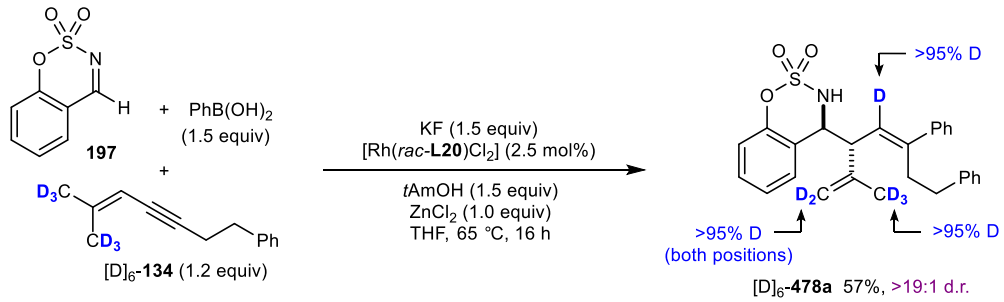
3-[(*E*,5*R*)-5-[(4*S*)-2,2-Dioxo-3,4-dihydro-1,2λ^6,3-benzoxathiazin-4-yl]-6-methyl-1-phenylhepta-3,6-dien-3-yl]benzoate (521f). General Procedure B was followed using imine **197** (54.8 mg, 0.299 mmol), 1,3-enyne **134** (65.3 mg, 0.360 mmol), and 3-(ethoxycarbonyl)phenylboronic acid (87.3 mg, 0.450 mmol). The mixture was purified twice by column chromatography (first column with 20% EtOAc/petroleum ether; second column with 60:38:2 pentane/$CHCl_3$/EtOAc) to give *allylation product* **521f** (84 mg, 54%) as a pale yellow oil. R_f = 0.19 (20% EtOAc/petroleum ether); $[\alpha]_D^{25.3}$ –32.6 (*c* 0.37, $CHCl_3$); IR 3263 (N-H), 2929, 1699, 1367, 1168, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (1H, app dt, *J* = 7.7, 1.5 Hz, Ar**H**), 7.87 (1H, app t, *J* = 1.8 Hz, Ar**H**), 7.38 (1H, app t, *J* = 7.7 Hz, Ar**H**), 7.35-7.29 (2H, m, Ar**H**), 7.24-7.16 (3H, m, Ar**H**), 7.14 (1H, app td, *J* = 7.6, 1.3 Hz, Ar**H**), 7.09-7.01 (4H, m, Ar**H**), 5.54 (1H, d, *J* = 9.3 Hz, C=C**H**), 5.06 (1H, app t, *J* = 1.6 Hz, C=C**H$_A$**H$_B$), 4.99 (1H, dd, *J* = 7.3, 6.4 Hz, C**H**NH), 4.97-4.95 (1H, m, C=CH$_A$**H$_B$**), 4.43-4.34 (2H, m, OC**H$_2$**), 4.17 (1H, d, *J* = 7.3 Hz, N**H**), 3.59 (1H, dd, *J* = 9.3, 6.4 Hz, C=CC**H**), 2.81 (1H, ddd, *J* = 14.3, 8.2, 6.1 Hz, PhC**H$_A$**CH$_B$), 2.77 (1H, dt, *J* = 14.3, 7.9, 7.4 Hz, PhCH$_A$C**H$_B$**), 2.62 (1H, ddd, *J* = 13.7, 7.4, 6.1 Hz, PhCH$_2$C**H$_A$**H$_B$), 2.39 (1H, ddd, *J* = 13.7, 8.2, 7.9 Hz, PhCH$_2$CH$_A$**H$_B$**), 1.91 (3H, s, CC**H$_3$**), 1.41 (3H, t, *J* = 7.1 Hz, CH$_2$C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5 (C), 151.4 (C), 143.2 (C), 142.4 (C), 142.0 (C), 141.3 (C), 131.2 (CH), 130.6 (C), 129.3 (CH), 128.6 (CH), 128.54 (CH), 128.50 (2 × CH), 128.3 (2 × CH), 127.5 (CH), 126.7 (CH), 126.3 (CH), 125.9 (CH), 125.2 (CH), 122.0 (C), 118.7 (CH), 115.5 (CH_2), 61.1 (CH_2), 56.9 (CH), 49.1 (CH), 33.7 (CH_2), 31.9 (CH_2), 21.4 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{30}H_{31}NNaO_5S]^+$ [M+Na]$^+$: 540.1815, found: 540.1801; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 210 nm): t_r (major) = 5.8 min, t_r (minor) = 13.2 min, 96% ee.



(4*S*)-4-[(3*R*,*E*)-5-(2-Fluorophenyl)-2-methyl-7-phenylhepta-1,4-dien-3-yl]-3,4-dihydro-1,2λ^6,3-benzoxathiazine-2,2-dione (521g). General Procedure B was followed using imine **197** (55.0 mg, 0.300 mmol), 1,3-enyne **134** (66.3 mg, 0.360 mmol), and 2-fluorophenylboronic acid (63.0 mg, 0.450 mmol). The mixture was purified by column chromatography (10% EtOAc/*iso*-hexane) to give *allylation product* **521g** (95.0 mg, 68%) as a yellow oil. R_f = 0.27 (10% EtOAc/*iso*-hexane); $[\alpha]_D^{25.0}$ –37.0 (*c* 0.54, $CHCl_3$); IR 3273 (N-H), 2923, 1485, 1450 1192, 1168, 753, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (1H, m, Ar**H**), 7.30-7.15 (5H, m, Ar**H**), 7.14-7.06 (4H, m, Ar**H**), 7.05-6.99 (2H, m, Ar**H**), 6.95 (1H, app td, *J* = 7.6, 1.8 Hz, Ar**H**), 5.43 (1H, d, *J* = 9.5 Hz, C=C**H**), 5.12-5.10 (1H, m, C=C**H$_A$**H$_B$), 5.07-5.02 (2H, m, C=CH$_A$**H$_B$** and C**H**NH), 4.31 (1H, d, *J* = 6.6 Hz, N**H**), 3.69 (1H, dd, *J* = 9.5, 5.9 Hz, C=CC**H**), 2.83-2.67 (2H, m, PhC**H$_2$**), 2.59 (1H, ddd, *J* = 13.8, 8.1, 5.8 Hz, PhCH$_2$C**H$_A$**H$_B$), 2.40 (1H, dt, *J* = 13.8, 8.1 Hz, PhCH$_2$CH$_A$**H$_B$**), 1.95 (3H, s, C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (d, $^1J_{C\text{-}F}$ = 246.6 Hz, C), 151.4 (C), 142.8 (C), 141.4 (C), 139.5 (C), 130.4 (d, $^3J_{C\text{-}F}$= 4.3 Hz, CH), 129.8 (d, $^2J_{C\text{-}F}$ = 14.6 Hz, C), 129.2 (CH), 128.9 (d, $^3J_{C\text{-}F}$= 8.1 Hz, CH), 128.4 (2 × CH), 128.3 (2 × CH), 127.2 (CH), 126.7 (CH), 126.2 (CH), 125.2 (CH), 124.1 (d, $^4J_{C\text{-}F}$ = 3.6 Hz, CH), 121.8 (C), 118.7 (CH), 115.6 (d, $^2J_{C\text{-}F}$ = 22.7 Hz, CH), 115.5 (CH_2), 56.9 (CH), 48.6 (CH), 33.7 (CH_2), 32.7 (d, $^4J_{C\text{-}F}$= 3.3 Hz, CH_2), 21.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.3 (m); HRMS (ESI) Exact mass calcd for $[C_{27}H_{26}FNNaO_3S]^+$ [M+Na]$^+$ 486.1510, found: 486.1503; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm): t_r (major) = 6.3 min, t_r (minor) = 11.8 min, 98% ee.

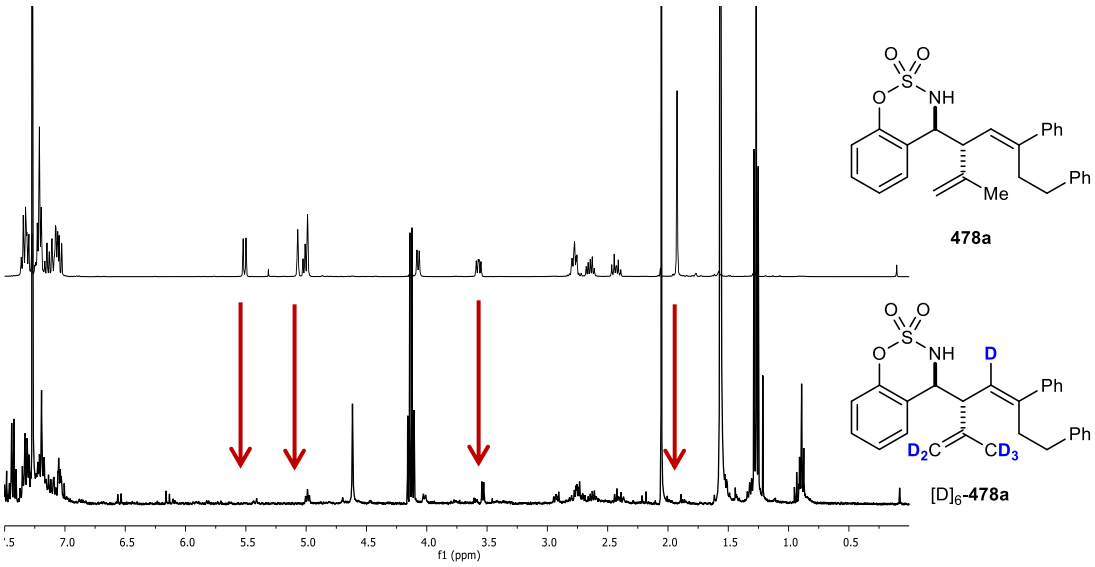
4.3.6 Investigation of Deuterium Transfer

(±)-(4*S*)-4-[(3*R*,*E*)-2-(Methyl-d_3)-5,7-diphenylhepta-1,4-dien-3-yl-1,1,4-d_3]-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide ([D]$_6$-478a)

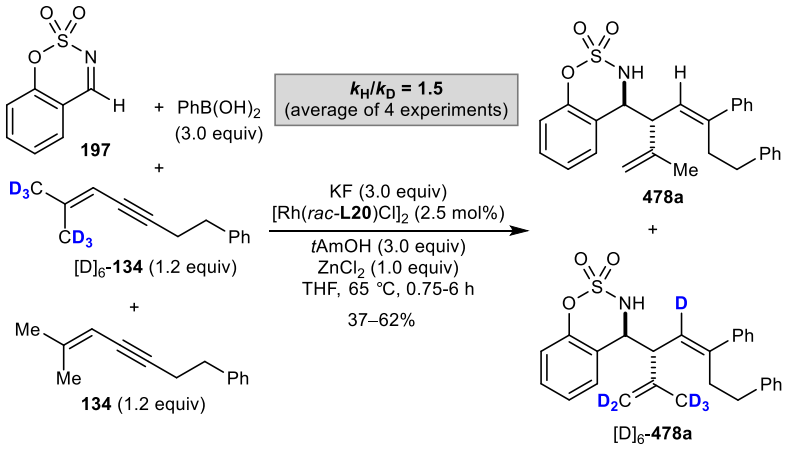


Imine **197** (36.6 mg, 0.200 mmol), 1,3-enyne [D]$_6$-**134** (45.6 mg, 0.240 mmol), phenylboronic acid (36.6 mg, 0.150 mmol), KF (17.4 mg, 0.300 mmol), and [Rh(*rac*-**L20**)Cl]$_2$ (4.4 mg, 5.6 µmol) were added to an oven-dried microwave vial. The vial was purged with nitrogen for 1 h and degassed THF (1 mL), *t*-amyl alcohol (32 µL, 0.30 mmol) and $ZnCl_2$ solution (0.7 M in THF, 0.28 mL, 0.20 mmol) were added. The reaction mixture was stirred for 16 h at 65 °C. The mixture was cooled to room temperature, diluted with saturated aqueous NH_4Cl solution (4 mL) and water (4 mL), and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The mixture was purified twice by column chromatography (first column with 5% EtOAc/*iso*-hexane; second column with 70:29:1 *iso*-hexane/CH_2Cl_2/EtOAc) to give *allylation product* [D]$_6$-**478a** (48 mg, 53%) as a pale yellow oil. R_f = 0.38 (15% EtOAc/petroleum ether); IR 3267 (N-H), 3025, 1418, 1193, 1169, 753, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (4H, m, Ar**H**), 7.24-7.16 (5H, m, Ar**H**), 7.14 (1H, app td, *J* = 7.6, 1.2 Hz, Ar**H**), 7.10-7.07 (1H, m, Ar**H**), 7.06-7.02 (3H, m, Ar**H**), 4.98 (1H, dd, *J* = 7.3, 6.3 Hz, C**H**NH), 4.03 (1H, d, *J* = 7.3 Hz, N**H**), 3.53 (1H, d, *J* = 6.3 Hz, C=CC**H**), 2.83-2.68 (2H, m, PhC**H$_2$**), 2.62 (1H, dt, *J* = 13.6, 6.6 Hz, $PhCH_2C\mathbf{H_A}H_B$), 2.40 (1H, dt, *J* = 13.6, 8.1 Hz, $PhCH_2CH_A\mathbf{H_B}$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4 (C), 143.12 (C), 143.05 (C), 141.6 (C), 141.5 (C), 129.3 (CH), 128.5 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 127.5 (CH), 126.7 (CH), 126.7 (2 × CH), 126.3 (CH), 125.2 (CH), 122.1 (C), 118.8 (CH_2), 56.9 (CH), 49.0 (CH), 33.7 (CH_2), 31.9 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{27}H_{21}D_6NNaO_3S]^+$ $[M+Na]^+$: 474.1980, found: 474.1983.

Expansion of crude ^{1}H NMR spectrum:



4.3.7 Measurement of Kinetic Isotope Effect in an Intermolecular Competition Experiment



Imine **197** (9.1 mg, 0.05 mmol), 1,3-enyne **134** (11.1 mg, 0.060 mmol), 1,3-enyne [D_6]-**134** (11.4 mg, 0.060 mmol), phenylboronic acid (18.3 mg, 0.150 mmol), KF (8.7 mg, 0.15 mmol), and [Rh(*rac*-**L20**)Cl]$_2$ (2.3 mg, 1.3 µmol) were added to an oven-dried microwave vial. The vial was purged with nitrogen for 1 h and degassed THF (1 mL), *t*-amyl alcohol (18 µL, 0.15 mmol) and $ZnCl_2$ solution (0.7 M in THF, 0.07 mL, 0.05 mmol) were added. The reaction mixture was stirred at 65 °C for 3–6 h. The mixture was cooled to room temperature, and the mixture

was diluted with saturated aqueous NH_4Cl solution (1 mL) and EtOAc (2 mL). 1,3,5-Trimethoxybenzene was added as an internal standard, and the organic phase was separated and concentrated *in vacuo*. The crude material was analysed by ^1H NMR spectroscopy.

Run 1: time: 3 h; combined yield of **478a** and [D_6]-**478a** = 62% (20% of **197** remaining). k_H/k_D = 1.35

Run 2: time: 3 h; combined yield of **478a** and [D_6]-**478a** = 60% (35% of **197** remaining). k_H/k_D = 1.47

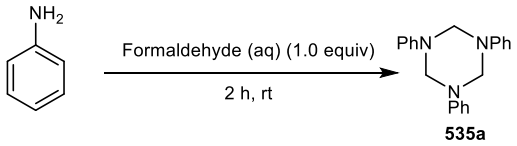
Run 3: time: 6 h; combined yield of **478a** and [D_6]-**478a** = 53% (37% of **197** remaining). k_H/k_D = 1.55

Run 4: time: 45 min; combined yield of **478a** and [D_6]-**478a** = 37% (52% of **197** remaining). k_H/k_D = 1.45

4.4 1,5- Functionalisation of 1,3-Enynes

4.4.1 Synthesis of Triazinanes

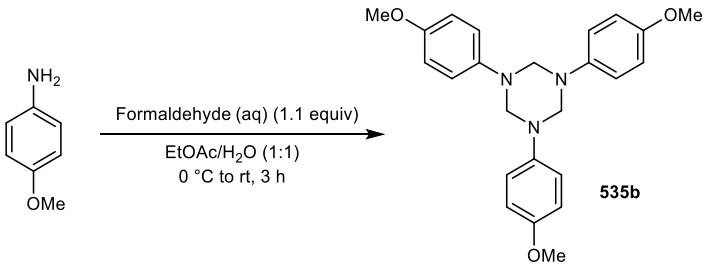
1,3,5-Triphenyl-1,3,5-triazinane (535a)



535a

Aniline (5.00 mL, 54.9 mmol) and aqueous formaldehyde (36%, 4.20 mL, 54.9 mmol) were stirred for 2 h at room temperature. Et_2O (10 mL) and H_2O (10 mL) was added and the resulting precipitate was filtered. The solid was then washed with petroleum ether (10 mL) to give *amine* **535a** (3.58 g, 62%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.18 (6H, m, Ar**H**), 7.02 (6H, dt, *J* = 7.8, 1.1 Hz, Ar**H**), 6.87 (3H, tt, *J* = 7.3, 1.1 Hz, Ar**H**), 4.90 (6H, s, C**H₂**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6 (3 × C), 129.2 (6 × CH), 120.9 (3 × CH), 117.7 (6 × CH), 68.6 (3 × CH_2). Data consistent with literature.[157]

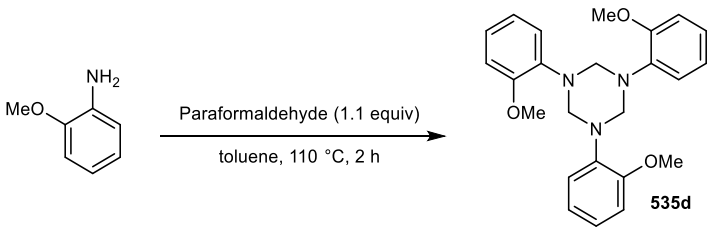
1,3,5-Tris(4-methoxyphenyl)-1,3,5-triazinane (535b)



535b

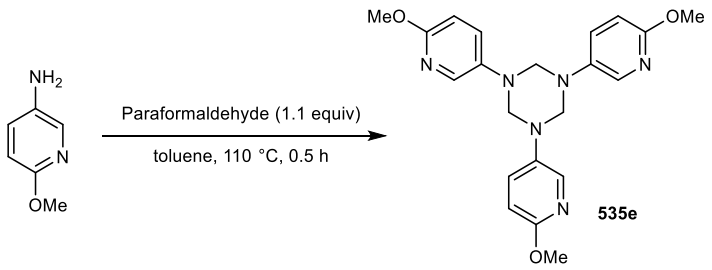
Aqueous formaldehyde (36%, 0.84 mL, 11.0 mmol) was added to *p*-anisidine (1.23 g, 10.0 mmol) in EtOAc (15 mL) and H_2O (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, warmed to room temperature and then stirred for an additional 1 h. The resulting solid was filtered and washed with H_2O, to give *triazinane* **535b** (993 mg, 74%) as a grey solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05-6.99 (6H, m, Ar**H**), 6.83-6.76 (6H, m, Ar**H**), 4.69 (6H, s, C**H₂**), 3.76 (9H, s, C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5 (3 × C), 142.6 (3 × C), 120.1 (6 × CH), 114.4 (6 × CH), 71.1 (3 × CH_2), 55.5 (3 × CH_3). Data consistent with literature.[158]

1,3,5-Tris(2-methoxyphenyl)-1,3,5-triazinane (535d)



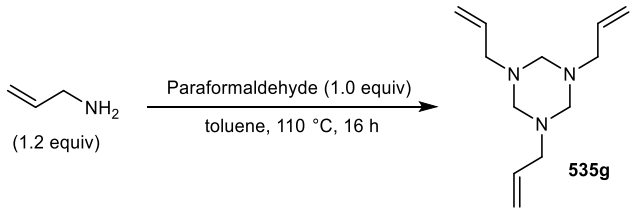
Paraformaldehyde (500 mg, 16.7 mmol) and *o*-anisidine (1.70 mL, 15.1 mmol) in toluene (15 mL) was heated at 110 °C for 2 h. The reaction mixture was concentrated *in vacuo*, and then stirred in petroleum ether (20 mL). The resulting solid was then filtered, and washed with further petroleum ether to give *triazinane* **535d** (174 mg, 9%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (3H, dd, *J* = 7.9, 1.7 Hz, Ar**H**), 6.94 (3H, app td, *J* = 7.7, 1.7 Hz, Ar**H**), 6.88-6.77 (6H, m, Ar**H**), 4.90 (6H, s, CH_2), 3.86 (9H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2 (3 × C), 138.3 (3 × C), 122.9 (3 × CH), 121.0 (3 × CH), 120.8 (3 × CH), 110.8 (3 × CH), 69.5 (3 × CH_2), 55.1 (3 × CH_3).Data consistent with literature.[159]

1,3,5-Tris(6-methoxypyridin-3-yl)-1,3,5-triazinane (535e)



Paraformaldehyde (532 mg, 17.7 mmol) was added to a solution of 5-amino-2-methoxypyridine (2.00 g, 16.1 mmol) in toluene (20 mL) and the mixture heated at 110 °C for 0.5 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and petroleum ether (20 mL) then added. The resulting solid was filtered and washed with additional petroleum ether to give *triazinane* **535e** (1.64 g, 75%) as a red solid, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (3H, dd, *J* = 3.0, 0.7 Hz, Ar**H**), 7.39 (3H, dd, *J* = 8.9, 3.0 Hz, Ar**H**), 6.61 (3H, dd, *J* = 8.9, 0.7 Hz, Ar**H**), 4.72 (6H, s, C**H**$_2$), 3.87 (9H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (3 × C), 139.2 (3 × C), 137.0 (3 × CH), 131.3 (3 × CH), 110.9 (3 × CH), 70.9 (3 × CH_2), 53.4 (3 × CH_3). Data consistent with literature.[135]

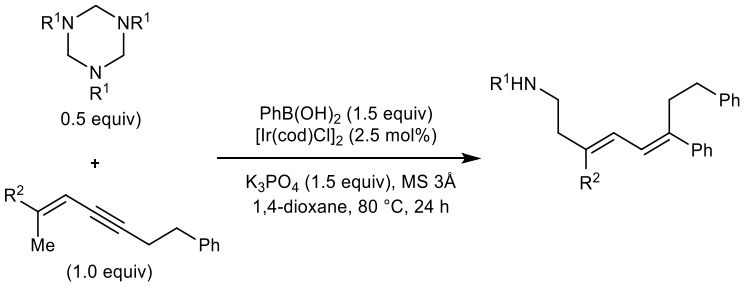
1,3,5-Tris(prop-2-en-1-yl)-1,3,5-triazinane (535g)



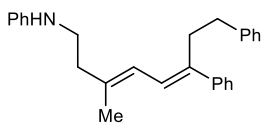
Allylamine (5.99 mL, 79.9 mmol) was added to paraformaldehyde (2.00 g, 66.6 mmol) in toluene (50 mL) and then stirred at 110 °C for 16 h. The solution was concentrated *in vacuo* to give triazinane **535g** (3.91 g, 85%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (3H, ddt, *J* = 16.6, 10.1, 6.4 Hz, CH_2=C**H**), 5.24-5.05 (6H, m, C**H$_2$**=CH), 3.34 (6H, br s, NC**H$_2$**N), 3.09 (6H, dt, *J* = 6.4, 1.4 Hz, CH_2=CHC**H$_2$**).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (3 × CH), 117.4 (3 × CH_2), 73.6 (3 × CH_2), 55.8 (3 × CH_2). Data consistent with literature.[160]

4.4.2 1,5-Functionalisation of 1,3-Enynes using Triazinanes

General Procedure C

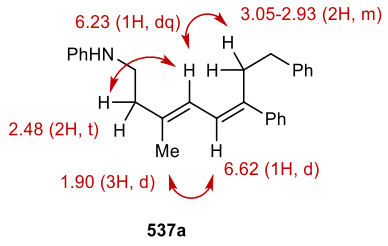


Triazinane (0.15 mmol), 1,3-enyne (0.30 mmol), phenylboronic acid (54.9 mg, 0.450 mmol), K_3PO_4 (95.5 mg, 0.450 mmol), $[Ir(cod)Cl]_2$ (5.0 mg, 7.5 µmol, 2.5 mol%) and molecular sieves (3 Å, 100 mg) were added to an oven-dried microwave vial. Degassed anhydrous dioxane (3 mL) was then added, and the mixture stirred at 80 °C for 24 h. After cooling to room temperature, the mixture was diluted with saturated aqueous NH_4Cl solution (5 mL) and water (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by column chromatography.

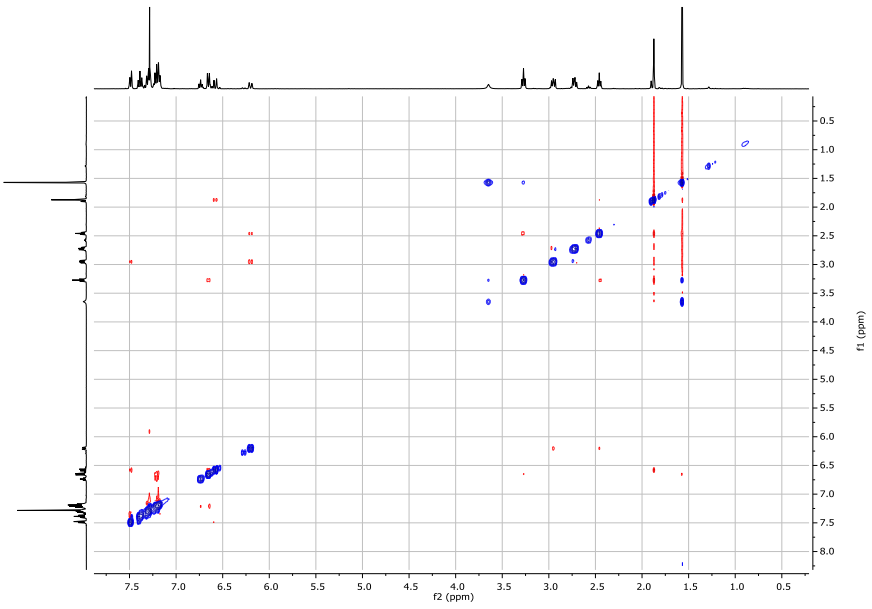


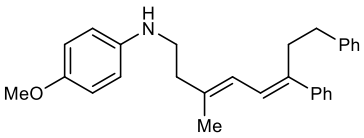
***N*-[(3*Z*,5*E*)-3-Methyl-6,8-diphenylocta-3,5-dien-1-yl]aniline (537a).** General Procedure C was followed using triazinane **535a** (47.3 mg, 0.150 mmol), 1,3-enyne **134** (55.3 mg, 0.360 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (70% petroleum ether, 29% CH_2Cl_2, 1% EtOAc, followed by 2% EtOAc/petroleum ether), to give *allylation product* **537a** (67 mg, 61%) as a pale yellow oil in a 6.2:1 mixture of *E*/*Z* isomers. R_f = 0.72 (10% EtOAc/petroleum ether); IR 3407 (N-H), 2925, 1601, 1505, 747, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.49 (2H, m, Ar**H**), 7.44-7.39 (2H, m, Ar**H**), 7.35-7.30 (3H, m, Ar**H**), 7.27-7.19 (5H, m, Ar**H**), 6.80-6.74 (1H, m, Ar**H**), 6.71-6.66 (2H, m, Ar**H**), 6.62 (1H, d, *J* = 11.3 Hz, PhC=C**H**), 6.23 (1H, dq, *J* = 11.3, 1.3 Hz, CH_3C=C**H**), 3.67 (1H, br s, N**H**), 3.30 (2H, t, *J* = 6.7 Hz, NHC**H₂**), 3.05-2.93 (2H, m, $PhCH_2C$**H₂**), 2.81-2.70 (2H, m, PhC**H₂**), 2.48 (2H, t, *J* = 6.7 Hz, $NHCH_2C$**H₂**), 1.90 (3H, d, *J* = 1.3 Hz, C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1 (C), 142.7 (C), 141.9 (C), 139.1 (C), 136.9 (C), 129.2 (2 × CH), 128.40 (2 × CH), 128.37 (2 × CH), 128.3 (2 × CH), 127.0 (CH), 126.2 (2 × CH), 125.9 (CH), 123.8 (CH), 123.2 (CH), 117.4 (CH), 112.9 (2 × CH), 41.6 (CH_2), 39.8 (CH_2), 35.3 (CH_2), 32.1 (CH_2), 16.4 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{27}H_{30}N]^+$ [M+H]$^+$: 368.2373, found: 368.2381.

NOESY

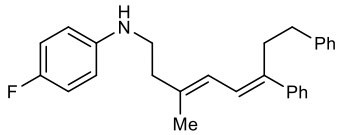


537a

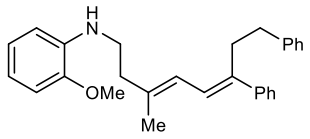




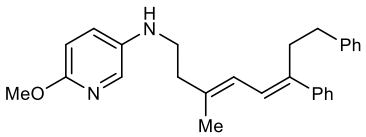
4-Methoxy-N-[(3*Z*,5*E*)-3-methyl-6,8-diphenylocta-3,5-dien-1-yl]aniline (537b). General Procedure A was followed using triazinane **535b** (507 mg, 1.25 mmol), 1,3-enyne **134** (461 mg, 2.5 mmol), phenylboronic acid (457 mg, 3.75 mmol), K_3PO_4 (796 mg, 3.75 mmol), $[Ir(cod)Cl]_2$ (42 mg, 0.063 mmol), molecular sieves (800 mg) and dioxane (25 mL). The mixture was purified by column chromatography (70% petroleum ether, 29% $CHCl_3$, 1% EtOAc), to give *allylation product* **537b** (571 mg, 58%) as a dark yellow oil in a 3.5:1 mixture of *E*/*Z* isomers. R_f = 0.42 (10% EtOAc/petroleum ether); IR 3390 (N-H), 2928, 1601, 1509, 1235, 1031, 819, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.45 (2H, m, Ar**H**), 7.40-7.33 (2H, m, Ar**H**), 7.32-7.25 (3H, m, Ar**H**), 7.24-7.15 (3H, m, Ar**H**), 6.82-6.78 (2H, m, Ar**H**), 6.63-6.59 (2H, m, Ar**H**), 6.57 (1H, d, *J* = 11.3 Hz, PhC=C**H**), 6.19 (1H, dq, *J* = 11.3, 1.3 Hz, CH_3C=C**H**), 3.76 (3H, s, OC**H₃**), 3.39 (1H, s, N**H**), 3.22 (2H, t, *J* = 6.6 Hz, NHC**H₂**), 2.96- 2.90 (2H, m, $PhCH_2C$**H₂**), 2.74-2.68 (2H, m, PhC**H₂**), 2.43 (2H, t, *J* = 6.6 Hz, $NHCH_2C$**H₂**), 1.86 (3H, d, *J* = 1.3 Hz, CC**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (C), 142.7 (C), 142.4 (C), 141.9 (C), 139.1 (C), 137.0 (C), 128.40 (2 × CH), 128.35 (2 × CH), 128.3 (2 × CH), 126.9 (CH), 126.2 (2 × CH), 125.9 (CH), 123.8 (CH), 123.1 (CH), 114.9 (2 × CH), 114.3 (2 × CH), 55.8 (CH_3), 42.6 (CH_2), 39.9 (CH_2), 35.3 (CH_2), 32.1 (CH_2), 16.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{28}H_{32}NO]^+$ $[M+H]^+$: 398.2478, found: 398.2487



4-Fluoro-N-[(3*Z*,5*E*)-3-methyl-6,8-diphenylocta-3,5-dien-1-yl]aniline (537c). General Procedure C was followed using triazinane **535c** (55.4 mg, 0.150 mmol), 1,3-enyne XX (55.3 mg, 0.360 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (5% EtOAc/petroleum ether), to give *allylation product* **537c** (74 mg, 64%) as a yellow oil in a 5.0:1 mixture of *E*/*Z* isomers. R_f = 0.64 (10% EtOAc/petroleum ether); IR 3406 (N-H), 2925, 1509, 1215, 871, 752, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.44 (2H, m, Ar**H**), 7.42-7.33 (2H, m, Ar**H**), 7.32-7.26 (2H, m, Ar**H**), 7.24-7.15 (4H, m, Ar**H**), 6.93-6.87 (2H, m, Ar**H**), 6.60-6.53 (3H, m, 2 × Ar**H** and PhC=C**H**), 6.18 (1H, dq, *J* = 11.3, 1.3 Hz, CH_3C=C**H**), 3.53 (1H, br s, N**H**), 3.22 (2H, t, *J* = 6.6 Hz, NHC**H₂**), 2.99-2.89 (2H, m, $PhCH_2C$**H₂**), 2.75-2.67 (2H, m PhC**H₂**), 2.44 (2H, t, *J* = 6.6 Hz, $NHCH_2C$**H₂**), 1.86 (3H, d, *J* = 1.3 Hz, C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (d, $^1J_{C\text{-}F}$ = 234.8 Hz, C), 144.5 (C), 142.7 (C), 141.9 (C), 139.3 (C), 136.7 (C), 128.43 (2 × CH), 128.35 (2 × CH), 128.33 (2 × CH), 127.0 (CH), 126.3 (2 × CH), 125.9 (CH), 123.7 (CH), 123.2 (CH), 115.7 (d, $^2J_{C\text{-}F}$ = 22.1 Hz, 2 × CH) 113.7 (d, $^3J_{C\text{-}F}$ = 4.7 Hz, 2 × CH), 42.3 (CH_2), 39.8 (CH_2), 35.3 (CH_2), 32.1 (CH_2), 16.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{27}H_{29}FN]^+$ $[M+H]^+$: 386.2279, found: 386.2288.



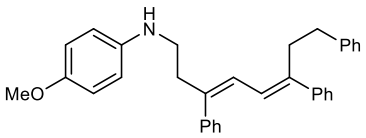
2-Methoxy-N-[(3*Z*,5*E*)-3-methyl-6,8-diphenylocta-3,5-dien-1-yl]aniline (537d). General Procedure A was followed using triazinane **535d** (60.8 mg, 0.150 mmol), 1,3-enyne **134** (55.3 mg, 0.360 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (2% EtOAc/petroleum ether, followed by 70% petroleum ether, 29% $CHCl_3$, 1% EtOAc), to give *allylation product* **537d** (31 mg, 26%) as a yellow oil in a 7.0:1 mixture of *E*/*Z* isomers. R_f = 0.34 (5% EtOAc/petroleum ether); IR 3415 (N-H), 2927, 1602, 1511, 1220, 732, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.46 (2H, m, Ar**H**), 7.41-7.35 (2H, m, Ar**H**), 7.32-7.26 (3H, m, Ar**H**), 7.23-7.16 (3H, m, Ar**H**), 6.93 (1H, app td, *J* = 7.6, 1.5 Hz, Ar**H**), 6.77 (1H, dd, *J* = 7.9, 1.5 Hz, Ar**H**), 6.73-6.66 (2H, m, Ar**H**), 6.60 (1H, d, *J* = 11.3 Hz, PhC=C**H**), 6.24 (1H, dq, *J* = 11.3, 1.3 Hz, CH_3C=C**H**), 4.29 (1H, br s, N**H**), 3.79 (3H, s, OC**H$_3$**), 3.30 (2H, t, *J* = 6.9 Hz, NHC**H$_2$**), 2.99-2.90 (2H, m, $PhCH_2C$**H$_2$**), 2.78-2.69 (2H, m, PhC**H$_2$**), 2.50 (2H, t, *J* = 6.8 Hz, $NHCH_2C$**H$_2$**), 1.90 (3H, d, *J* = 1.3 Hz, CC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9 (C), 142.8 (C), 142.0 (C), 138.9 (C), 138.1 (C), 137.2 (C), 128.39 (2 × CH), 128.36 (2 × CH), 128.33 (2 × CH), 126.9 (CH), 126.2 (2 × CH), 125.9 (CH), 123.8 (CH), 122.9 (CH), 121.3 (CH), 116.4 (CH), 109.9 (CH), 109.4 (CH), 55.3 (CH_3), 41.6 (CH_2), 39.9 (CH_2), 35.4 (CH_2), 32.3 (CH_2), 16.9 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{28}H_{32}NO]^+$ $[M+H]^+$: 398.2478, found: 398.2487.



6-Methoxy-N-[(3*Z*,5*E*)-3-methyl-6,8-diphenylocta-3,5-dien-1-yl]pyridin-3-amine (537e). General Procedure C was followed using triazinane **535e** (55.4 mg, 0.150 mmol), 1,3-enyne **134** (61.3 mg, 0.360 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (10% EtOAc/petroleum ether), to give *allylation product* **537e** (79 mg, 66%) as a yellow oil in a 5.6:1 mixture of *E*/*Z* isomers. R_f = 0.15 (10% EtOAc/petroleum ether); IR 3256 (N-H), 2930, 1493, 1373, 1256, 1032, 755, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 2.8 Hz, Ar**H**), 7.50-7.46 (2H, m, Ar**H**), 7.42-7.34 (2H, m, Ar**H**), 7.33-7.25 (3H, m, Ar**H**), 7.24-7.14 (3H, m, Ar**H**), 6.99 (1H, dd, *J* = 8.8, 3.0 Hz, Ar**H**), 6.64 (1H, dd, *J* = 8.8, 0.7 Hz, Ar**H**), 6.57 (1H, d, *J* = 11.3 Hz, PhC=C**H**), 6.21-6.13 (1H, m, CH_3C=C**H**), 3.89 (3H, s, OC**H$_3$**), 3.22 (2H, t, *J* = 6.6 Hz, NHC**H$_2$**), 2.99-2.89 (2H, m, $PhCH_2C$**H$_2$**), 2.77-2.68 (2H, m, PhC**H$_2$**), 2.44 (2H, t, *J* = 6.6 Hz, $NHCH_2C$**H$_2$**), 1.86 (3H, d, *J* = 1.3 Hz, CC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (C), 142.6 (C), 141.8 (C), 139.3 (C), 139.1 (C), 136.5 (C), 130.4 (CH), 128.4 (2 × CH), 128.34 (2 × CH), 128.30 (2 × CH), 127.0 (CH), 126.3 (2 × CH), 126.1 (CH),

126.0 (CH), 125.9 (CH), 123.7 (CH), 123.3 (CH), 110.8 (CH), 53.3 (CH_3), 42.5 (CH_2), 39.8 (CH_2), 35.2 (CH_2), 32.1 (CH_2), 16.4 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{27}H_{31}N_2O]^+$ $[M+H]^+$: 399.2431, found: 399.2446.

.



4-Methoxy-N-[(3*Z*,5*E*)-3,6,8-triphenylocta-3,5-dien-1-yl]aniline (544). General Procedure C was followed using triazinane **535b** (61 mg, 0.15 mmol), 1,3-enyne **511d** (73.9 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). The mixture was purified by column chromatography (5% EtOAc/pentane, followed by 60% pentane, 39% $CHCl_3$, 1% EtOAc), to give *allylation product* **544** (98 mg, 71%) as a pale yellow oil in a 2.6:1 mixture of *E*/*Z* isomers. R_f = 0.18 (5% EtOAc/pentane); IR 3389 (N-H), 2930, 1594, 1509, 1236, 1036, 762, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.43-7.29 (11H, m, Ar**H**), 7.26-7.18 (4H, m, Ar**H** and C**H**C**H**), 6.81-6.74 (2H, m, Ar**H**), 6.71-6.69 (2H, m, Ar**H**), 6.58-6.53 (2H, m, Ar**H**), 3.76 (3H, s, OC**H$_3$**), 3.42 (1H, br s, N**H**) 3.20 (2H, t, *J* = 6.9 Hz, NHC**H$_2$**), 3.08-2.97 (4H, m, PhC**H$_2$**C**H$_2$**), 2.81-2.74 (2H, m, NHCH$_2$C**H$_2$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (C), 142.23 (C), 142.20 (C), 142.0 (C), 141.8 (C), 141.7 (C), 139.3 (C), 128.52 (2 × CH), 128.49 (2 × CH), 128.45 (2 × CH), 128.3 (2 × CH), 127.30 (CH), 127.26 (CH), 126.31 (2 × CH), 126.29 (2 × CH), 126.0 (CH), 125.6 (CH), 124.1 (CH), 114.9 (2 × CH), 114.2 (2 × CH), 55.7 (CH_3), 43.5 (CH_2), 35.2 (CH_2), 31.9 (CH_2), 29.7 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{33}H_{34}NO]^+$ $[M+H]^+$: 460.2635, found: 460.2643.

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6 Appendix: Publications

Cyclization

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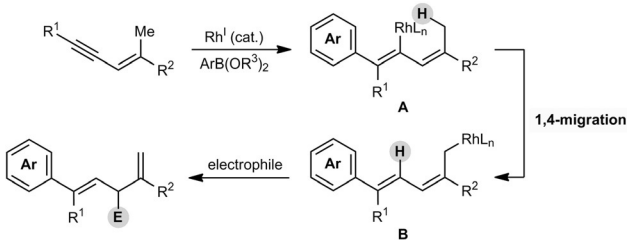
Arylative Intramolecular Allylation of Ketones with 1,3-Enynes Enabled by Catalytic Alkenyl-to-Allyl 1,4-Rhodium(I) Migration

*Benjamin M. Partridge, Michael Callingham, William Lewis, and Hon Wai Lam**

Abstract: *Alkenyl-to-allyl 1,4-rhodium(I) migration enables the generation of nucleophilic allylrhodium(I) species by remote C–H activation. This new mode of reactivity was employed in the diastereoselective reaction of arylboron reagents with substrates containing a 1,3-enyne tethered to a ketone, to give products containing three contiguous stereocenters. The products can be obtained in high enantioselectivities using a chiral sulfur-alkene ligand.*

Catalytic C–H functionalizations have revolutionized chemical synthesis by providing powerful new tools for bond construction.[1] However, a critical objective for the advancement of this field is its application to a more diverse range of transformations. Nucleophilic allylations[2] are important reactions that could benefit from C–H functionalization principles. Most typically, these processes have employed allylmetal(loid) reagents such as allyltin, allylboron, or allylsilicon compounds.[2] The generation of nucleophilic allylmetal species by the activation of allylic C–H bonds would bypass the need to prepare such reagents and potentially increase efficiency by streamlining synthetic sequences. This strategy would also be a valuable complement to nucleophilic allylations involving migratory insertions of allenes,[3,4] the use of simple π-unsaturated compounds in hydrogenative or redox-triggered additions,[5,6] hetero-ene reactions,[7] and Prins reactions.[8]

Although generating electrophilic allylmetal species by allylic C–H activation is well-known,[9,10] there is, to our knowledge, limited precedent for corresponding processes that provide nucleophilic allylmetals.[11] Very recently, the groups of Schneider,[11a] Kanai,[11b] and Mita and Sato[11c] described the formation and trapping of nucleophilic allylmetal species from simple hydrocarbons. In view of the nucleophilic character of allylrhodium(I) species,[4a,12] we envisaged that activation of a remote C–H bond by 1,4-rhodium(I) migration[12d,13,14] could also achieve this goal. Specifically, rhodium(I)-catalyzed reaction of an arylboron reagent with the alkyne of a 1,3-enyne would provide the alkenylrhodium species **A** (Scheme 1). This intermediate



Scheme 1. Proposed alkenyl-to-allyl 1,4-rhodium(I) migration.

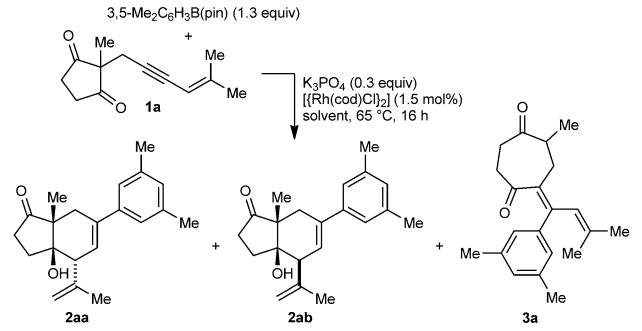
could then undergo a 1,4-rhodium(I) shift to the *cis*-allylic substituent to give the allylrhodium(I) species **B**, which could be trapped by an electrophile. This approach was expected to be challenging, given that there is only very limited precedent for rhodium(I) to migrate to C(sp^3) centers.[12d,14k,m] Nevertheless, the generation of electrophilic allylrhodium(III) species by a similar strategy in our rhodium(III)-catalyzed oxidative annulations of 1,3-enynes provided some encouragement.[10] Herein, we describe the implementation of this strategy in arylative intramolecular allylations of ketones to give stereochemically complex fused bicycles with high diastereoselectivities. Preliminary results of enantioselective reactions are also provided.

This study began with the reaction of the enynone **1a** with 3,5-dimethylphenyl pinacol boronate (1.3 equiv), [{Rh(cod)Cl}$_2$] (1.5 mol%), and K_3PO_4 (0.3 equiv) at 65 °C for 16 hours in various solvents (Table 1). A 3,5-disubstituted arylboron reagent was used to minimize 1,4-rhodium(I) migration onto the aryl group as described previously,[15] as it is well-known that migration onto an aryl ring *ortho* to a substituent is unfavorable.[14a,i,15a] Pinacol boronates were used because 3,5-disubstituted variants are easily accessed through iridium-catalyzed C–H borylation.[16] The reaction conducted in THF/MeOH (10:1) gave diastereomeric bicycles **2aa**[17] and **2ab**[18] in a 13:87 ratio (entry 1). After purification, **2aa** and **2ab** were isolated in 11 and 46% yield, respectively. Traces of the diketone **3a** were also formed, and resulted from arylrhodation of the alkyne of **1a** with the regioselectivity opposite to that seen in the formation of **2aa/2ab**, followed by a cyclization-fragmentation pathway.[15a,19] Notably, switching

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Table 1: Evaluation of solvents.[a]



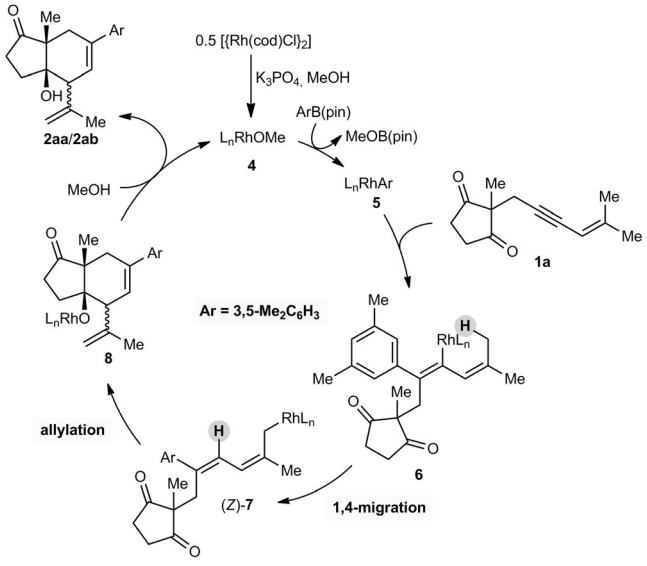
Entry	Solvent	d.r. **2aa**/**2ab**[b]	Yield [%][c] **2aa**	**2ab**	**3a**
1	THF/MeOH (10:1)	17:83	11	46	n.d.[d]
2	MeCN/MeOH (10:1)	91:9	66	5	9
3	TBME/*t*BuCN/MeOH (10:1.2:1)	94:6	73	4	14

[a] Reactions employed 0.50 mmol of **1a**. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Yield of the isolated product. [d] n.d. = not determined. cod = 1,5-cyclooctadiene, TBME = *tert*-butyl methyl ether, THF = tetrahydrofuran.

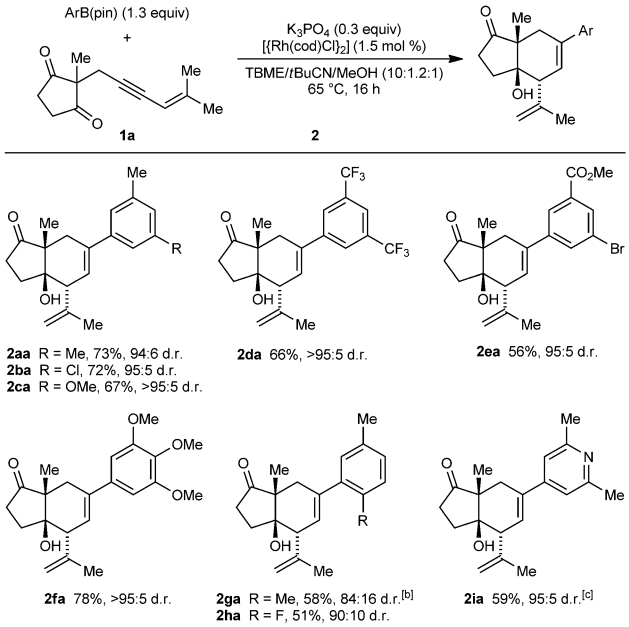
the solvent to MeCN/MeOH (10:1) reversed the sense of diastereoselectivity and gave **2aa** and **2ab** in 66 and 5% yield, respectively (entry 2). Using TBME/*t*BuCN/MeOH (10:1.2:1) gave a further increase in diastereoselectivity (entry 3).

In the proposed catalytic cycle (Scheme 2), transmetalation of the arylboronate with the rhodium methoxide **4** provides the arylrhodium species **5**, which undergoes migratory insertion with the alkyne of **1a** to give alkenylrhodium species **6**. 1,4-Rhodium migration gives the allylrhodium species (*Z*)-**7**, which cyclizes onto a ketone to provide the rhodium alkoxide **8**. Methanolysis of **8** liberates the product **2aa** or **2ab** and regenerates **4**.

Scheme 3 presents the reactions of **1a** with various arylboronic acid pinacol esters. Products analogous to **3a**



Scheme 2. Proposed catalytic cycle.



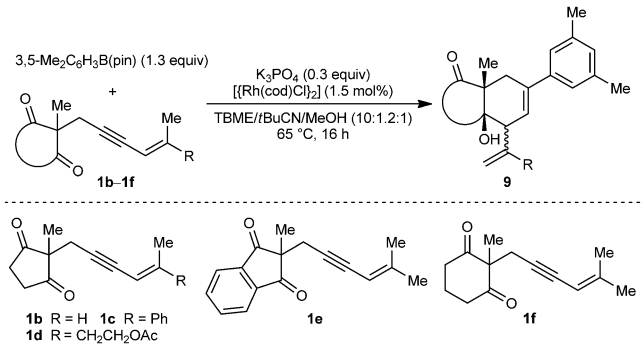
Scheme 3. [a] Reaction of **1a** with various arylboronates. Reactions employed 0.50 mmol of **1a**. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. Yields are of isolated, diastereomerically pure products. [b] Reaction performed with 2.5 mol% [{Rh(cod)Cl}$_2$]. [c] Reaction employed 0.45 mmol of **1a**.

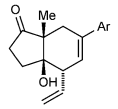
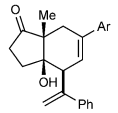
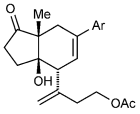
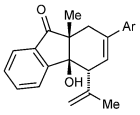
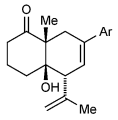
were generally formed in up to 20% yield (by ^{1}H NMR analysis of the crude reaction mixtures) but were not isolated. The reaction is tolerant of halide (**2ba**, **2ea**, and **2ha**), methoxy (**2ca** and **2fa**), trifluoromethyl (**2da**), and carbomethoxy groups (**2ea**) on the arylboronate. In addition, 3,5-disubstituted (**2aa**–**2ea**), 3,4,5-trisubstituted (**2fa**), and 2,5-disubstituted arylboronates (**2ga** and **2ha**) are tolerated. 2,5-Disubstituted arylboronates gave lower yields (**2ga** and **2ha**), which is presumably a consequence of the steric hindrance of the *ortho*-substituent. Finally, a heteroarylboronate is also tolerated (**2ia**).

Next, variation of the enynone was explored, and the substrates **1b**–**f,** containing methyl groups *cis* to the alkyne, all reacted successfully with 3,5-dimethylphenyl pinacol boronate (Table 2). Substrates containing hydrogen, phenyl, or alkyl groups *trans* to the alkyne are tolerated (entries 1–3). With the phenyl-containing substrate **1c**, however, application of the standard reaction conditions gave no diastereoselectivity (1:1 d.r.).[20] Fortunately, switching the solvent to 2-MeTHF/MeOH (10:1) gave the *syn*,*syn*-diastereomer **9cb** in greater than 95:5 d.r. and 62% yield (entry 2).[17] In contrast to our findings using rhodium(III) catalysis,[10] substrates containing methylene groups (as opposed to methyl groups) *cis* to the alkyne are unreactive. Variation of the 1,3-diketone is also possible. For example, the indane-1,3-dione **1e** gave **9ea** in 74% yield and >95:5 d.r. (entry 4).[17] Under the standard reaction conditions, the six-membered cyclic 1,3-diketone **1f** underwent decomposition in competition with arylative allylation. However, by changing the arylboronate to the more reactive neopentyl glycol ester, and using K_2CO_3 and *t*AmOH in place of K_3PO_4 and MeOH, respectively, **9fa**

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Table 2: Arylative allylation of various enynones.[a]

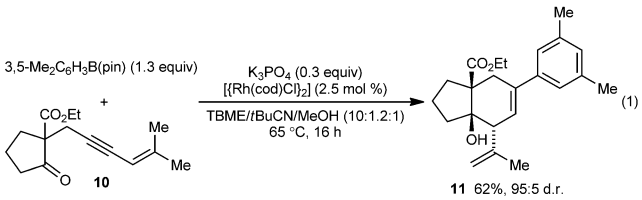


Entry	Enynone	Product (Ar = 3,5-$Me_2C_6H_3$)	d.r.[b]	Yield [%][c]
1[d]	**1b**	 **9ba**	n.d.[e]	50 (+7)[f]
2[g]	**1c**	 **9cb**	>95:5	62
3	**1d**	 **9da**	84:16	52
4	**1e**	 **9ea**	>95:5	74
5[h]	**1f**	 **9fa**	84:16	67

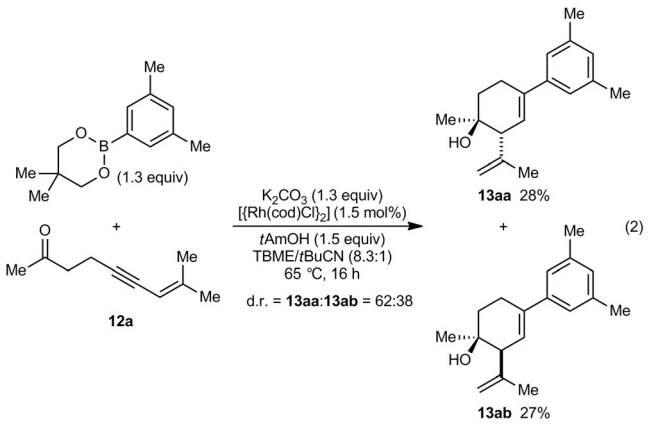
[a] Reactions employed 0.50 mmol of **1b–f**. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Yield of isolated, diastereomerically pure products. [d] Using 2.5 mol% of $[\{Rh(cod)Cl\}_2]$. [e] The d.r. value could not be determined by ^{1}H NMR analysis. [f] Yield of the isolated minor *syn-syn* diastereomer **9bb**. [g] Using 2-MeTHF/MeOH (10:1) in place of TBME/*t*BuCN/MeOH (10:1.2:1). [h] Using 3,5-$Me_2C_6H_3B$(neo) (1.3 equiv), K_2CO_3 (1.3 equiv), and *t*AmOH (1.5 equiv) as the reagents in TBME/*t*BuCN (8.3:1). neo = neopentyl glycol.

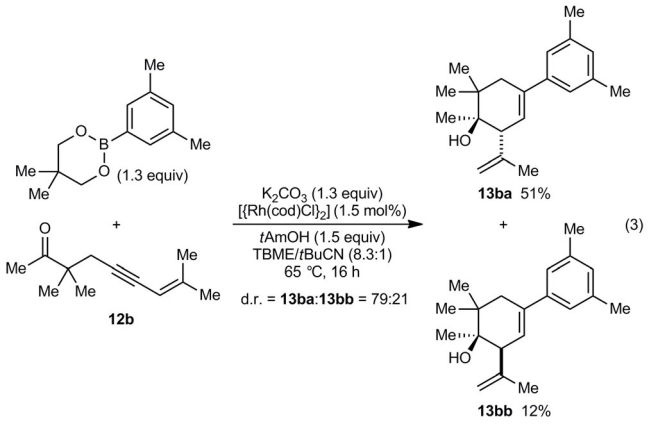
was formed in 67% yield (entry 5).[17] The process is not limited to cyclic 1,3-diketones as the β-ketoester **10** reacted smoothly using 2.5 mol% of $[\{Rh(cod)Cl\}_2]$ to give **11** in 62% yield and 95:5 d.r. [Eq. (1)].

Furthermore, the fully acyclic substrates **12a** and **12b** also underwent successful arylative intramolecular allylation



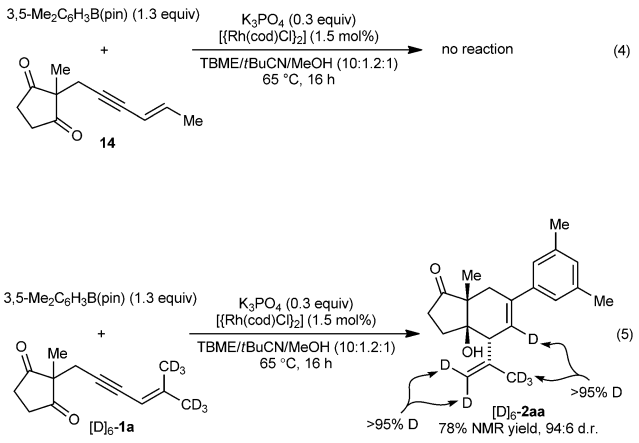
[Eq. (2) and (3)], although the diastereoselectivities were lower compared with substrates containing cyclic ketones. For acceptable yields, it was important to use neopentyl glycol boronate, K_2CO_3, and *t*AmOH. Under these reaction conditions, **12a** reacted with 3,5-dimethylphenyl neopentyl glycol boronate to give the diastereomeric products **13aa** and **13ab** in 28 and 27% yield, respectively [Eq. (2)].[21] Improved results were obtained with **12b**, which contains a geminal dimethyl group in the tether, and **13ba** and **13bb** were obtained in 51 and 12% yield, respectively [Eq. (3)].[21] The same reactions conducted in 2-MeTHF instead of TBME/*t*BuCN gave **13ab** and **13bb** as the major products, but were lower yielding.



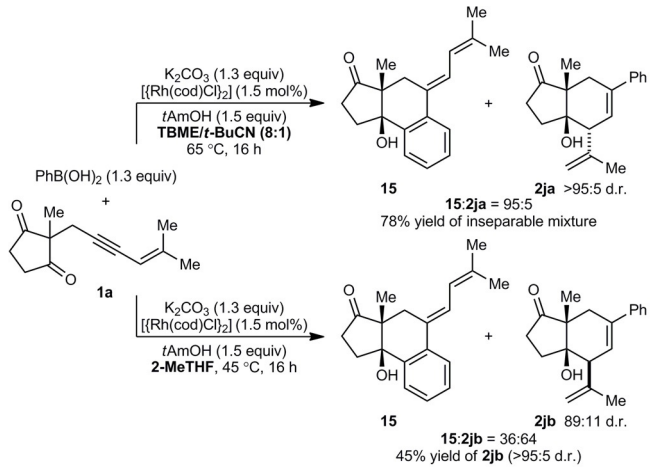


The substrate **14**, which contains an *E*-1,3-enyne, did not undergo the reaction, and only starting materials were recovered [Eq. (4)]. This result confirms the requirement for *cis*-allylic hydrogen atoms to be present in the enyne to allow 1,4-rhodium(I) migration to occur (compare with Table 2, entry 1 using the *Z*-isomer **1b**). In addition, reaction of hexadeuterated enynone $[D]_6$-**1a** with 3,5-dimethylphenylboronic acid pinacol ester gave $[D]_6$-**2aa** with greater than 95% deuterium transfer to the alkene of the cyclohexene [Eq. (5)]. This outcome is consistent with 1,4-rhodium(I) migration occurring by a C–H oxidative addition/reductive elimination through a rhodium(III) hydride intermediate as hypothesized previously for alkenyl-to-aryl 1,4-rhodium(I) migration.[14j]

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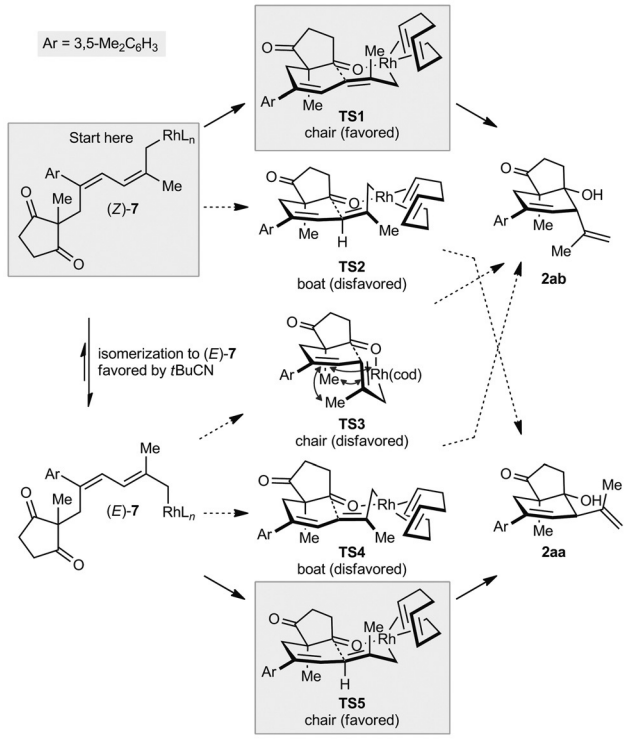


Up until this point, all of the arylboronates evaluated possess substitution patterns that disfavor 1,4-rhodium(I) migration of intermediates such as **6** onto the aryl group. To assess whether alkenyl-to-allyl 1,4-rhodium(I) migration would still be favored when a sterically more accessible site is available, **1a** was reacted with phenylboronic acid (Scheme 4). The reaction in TBME/*t*BuCN (8:1) in the presence of *t*-amyl alcohol (1.5 equiv) gave a 95:5 mixture of inseparable products, **15** and **2ja**. The product **15** results from 1,4-rhodium(I) migration onto the phenyl group followed by intramolecular ketone arylation,[15] whereas **2ja** is the arylative allylation product. When the solvent was changed to 2-MeTHF, the allylation product **2jb** was formed preferentially (36:64 ratio of **15**/**2jb**) in 89:11 d.r., and was isolated as a single diastereomer in 45% yield. The reasons for this switch in chemoselectivity are not currently known.



Scheme 4. Reaction of **1a** with $PhB(OH)_2$.

Consistent with models proposed in prior rhodium-catalyzed nucleophilic allylations,[4a,12b–e] we suggest that allylation occurs through cyclic six-membered transition states (Scheme 5). In the absence of a nitrile in the reaction medium (Table 1, entry 1), we assume that (*Z*)-**7**, formed from 1,4-rhodium(I) migration of **6**, cyclizes through a chairlike arrangement (**TS1**) to give **2aa** (Scheme 5). The boatlike structure **TS2** should be disfavored. However, when a coordinating nitrile is present (Table 1, entries 2 and 3), the rate of cyclization could be decreased, allowing isomerization of (*Z*)-**7** into (*E*)-**7**.[22] Thereafter, we assume that cyclization of (*E*)-**7** occurs through the chairlike conformation **TS5** to give **2ab** (Scheme 5). The alternative conformation **TS3** is likely to be disfavored because of 1,3-diaxial interactions and allylic 1,3-strain. The boatlike structure **TS4** is also likely to be unfavorable. However, we do not exclude the possibility that when a nitrile is present, **2aa** is formed by cyclization of (*E*)-**7** through an open transition state because of preferential coordination of rhodium to the nitrile rather than the ketone.



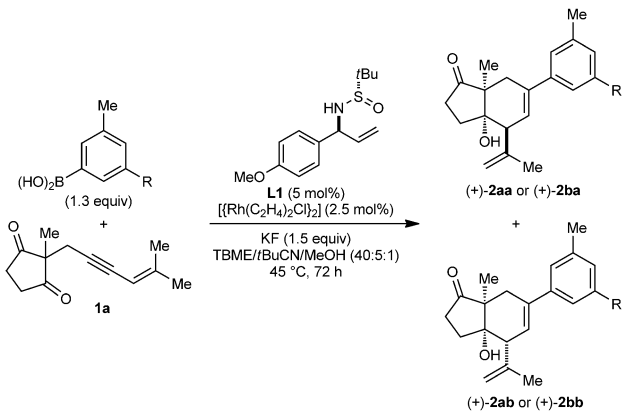
Scheme 5. Possible stereochemical models.

Similar chairlike transition states can be used to explain the outcomes of the reactions **12a** and **12b** [Eqs. (2) and (3)], and the diastereomeric ratios observed may be a consequence of their more flexible nature (see the Supporting Information).

Finally, preliminary efforts at developing enantioselective reactions were conducted (Table 3).[23] Only modest results were obtained with chiral diene ligands[24] (see Supporting Information), while no reaction occurred when chiral bisphosphines were used. However, the reaction of **1a** with 3,5-dimethylphenylboronic acid (1.3 equiv) in the presence of $[\{Rh(C_2H_4)_2Cl\}_2]$ (2.5 mol%), the sulfur-alkene **L1**[25] (5.0 mol%), and KF (1.5 equiv) in TBME/*t*BuCN/MeOH (40:5:1) gave (+)-**2aa**[17] in 61% yield and 91% *ee* (entry 1). The diastereomeric product (+)-**2ab** was obtained in 11% yield and 88% *ee*. Similar results were obtained with 3-chloro-5-methylphenylboronic acid (entry 2).

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Table 3: Enantioselective reactions.[a]



Entry	R	d.r.[b]	Major isomer[c]	Minor isomer[c]
1	Me	80:20	(+)-**2aa** 61%, 91% *ee*	(+)-**2ab** 11%, 88% *ee*
2	Cl	78:22	(+)-**2ba** 47%, 90% *ee*	(+)-**2bb** 10%, 90% *ee*

[a] Reactions employed 0.25 mmol of **1a**. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yields are of isolated, diastereomerically pure products. Enantiomeric excesses were determined HPLC analysis on a chiral stationary phase.

In summary, we have reported the rhodium-catalyzed arylative allylation of enynones with arylboron reagents. The key step of the reaction is the alkenyl-to-allyl 1,4-rhodium(I) migration, a new mode of reactivity which enables the generation of nucleophilic allylrhodium(I) species without prefunctionalization of the allylic position. Cyclization of the allylrhodium species onto a pendant ketone leads to bicyclic products containing three contiguous stereocenters with high diastereoselectivities. The products can be obtained in high enantioselectivities using a chiral sulfur-alkene ligand. Further applications of this promising platform for generating allylmetal species are in progress.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allylic compounds · cyclization · isomerization · reaction mechanisms · rhodium

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[18] The relative configurations of the majority of the products described herein were determined by NOESY experiments. The relative configurations of **2ab** and **2jb** were assigned tentatively by analogy with **9cb**, the relative configuration of which was determined by X-ray crystallography (see Ref. [17]).

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[21] The relative configurations of **13aa** and **13ab** could not be determined unambiguously and were assigned tentatively by analogy with the reaction producing **13ba** and **13bb**, on the assumption that the major products in each case possess the same relative configuration. The relative configurations of **13ba** and **13bb** were determined by NOESY experiments. The product **13bb** contained small quantities of an inseparable impurity.

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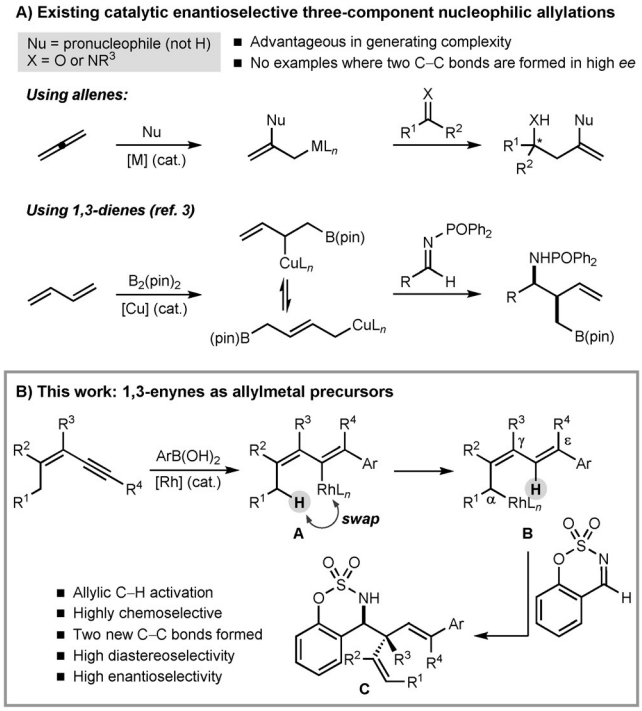
Enantioselective Rhodium-Catalyzed Coupling of Arylboronic Acids, 1,3-Enynes, and Imines by Alkenyl-to-Allyl 1,4-Rhodium(I) Migration

*Michael Callingham, Benjamin M. Partridge, William Lewis, and Hon Wai Lam**

Abstract: *A chiral rhodium complex catalyzes the highly enantioselective coupling of arylboronic acids, 1,3-enynes, and imines to give homoallylic sulfamates. The key step is the generation of allylrhodium(I) species by alkenyl-to-allyl 1,4-rhodium(I) migration.*

Catalytic enantioselective nucleophilic allylations of aldehydes, ketones, and imines are valuable reactions for the preparation of chiral homoallylic alcohols and amines, which are useful building blocks for synthesis.[1] Many of these processes utilize allyltin, allylboron, allylsilicon, or allyl halide compounds.[1d,f] Although highly successful, one drawback is that preparation of reagents containing more complex allyl fragments can be non-trivial. Of the methods that avoid such reagents,[1a-c,e] one is generation of allylmetal species by the migratory insertion of an allene[2] or a 1,3-diene[3] into a metal–element bond, followed by reaction with the electrophile (Scheme 1 A).[3–7] Advantages of such three-component reactions[3–5] are the use of simpler reactants and the ability to rapidly increase structural complexity.[8] Although highly enantioselective borylative three-component nucleophilic allylations are known,[3–5] the corresponding processes that form two carbon–carbon bonds have, to our knowledge, had limited success (up to 23 % *ee* has been obtained[6c]).[9]

Herein, we describe enantioselective three-component nucleophilic allylations that involve an allylic C–H activation, an emerging strategy to generate nucleophilic allylmetal species.[10,11] This approach uses 1,3-enynes, rather than allenes or 1,3-dienes, and provides homoallylic sulfamates with high enantioselectivities.



Scheme 1. Catalytic enantioselective three-component nucleophilic allylations.

Our reaction design is illustrated in Scheme 1 B. Rh^I-catalyzed addition of an arylboronic acid to the alkyne of a 1,3-enyne would give alkenylrhodium(I) species **A**, which could undergo alkenyl-to-allyl 1,4-rhodium(I) migration[12–15] to form allylrhodium(I) species **B**. Cyclic imines are excellent substrates for enantioselective Rh^I-catalyzed nucleophilic allylations[16] and, therefore, we hoped that they could trap species **B** to give homoallylic sulfamates **C**. Cyclic sulfamates appear in a number of biologically active compounds.[17]

Although related to the two-component arylative intramolecular allylations of ketones that we described recently,[10] this three-component coupling appeared to be significantly more challenging because numerous alternative pathways are possible. Firstly, chiral rhodium(I) complexes are known to promote the addition of arylboron reagents to cyclic imines.[18] Secondly, addition of alkenylrhodium species **A** to the imine is possible.[19] Thirdly, 1,4-migration of rhodium(I) in species **A** to the *ortho* position of the aryl group derived from the arylboronic acid is known to be competitive.[10] Finally, species **B** could potentially react with the imine in α- or ε-selective allylations. Therefore, controlling the chemoselectivity was expected to be non-trivial.

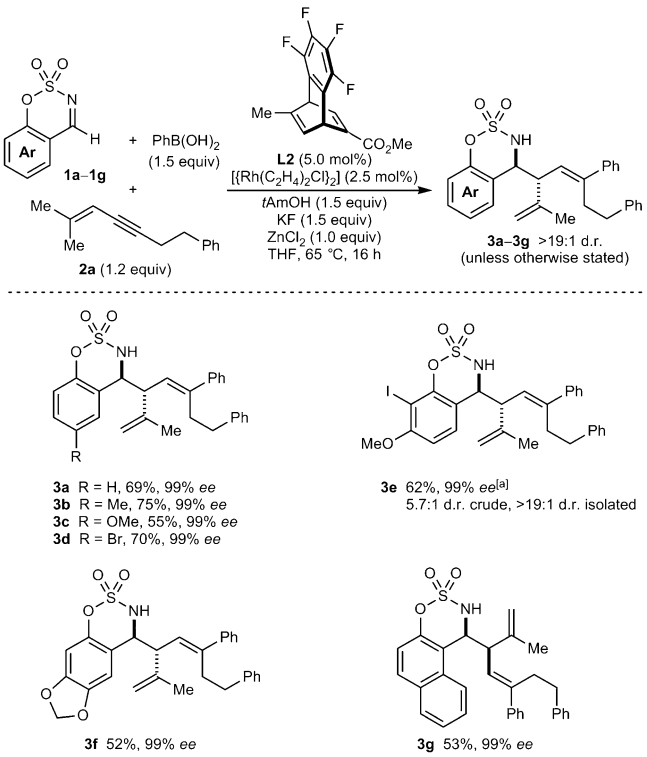
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This study began with the reaction of imine **1a** with 1,3-enyne **2a** (1.2 equiv) and $PhB(OH)_2$ (1.5 equiv) in THF at 65 °C, in the presence of $[\{Rh(cod)Cl\}_2]$ (2.5 mol%), KF (1.5 equiv), and *t*AmOH (1.5 equiv) (Table 1, entry 1). Pleasingly, allylation product (±)-**3a** was formed as a single observable diastereomer (>19:1 d.r.) in 24% NMR yield, along with several unidentified products. Using $[\{Ir(cod)Cl\}_2]$ increased the yield of (±)-**3a** to 53%, although conjugated diene (±)-**4** was also formed in 38% yield (Table 1, entry 2).[20] After screening additives, we found that $ZnCl_2$ (1.0 equiv) increased the yield of (±)-**3a** to 81%, and decreased the yield of (±)-**4** (Table 1, entry 3). Next, chiral diene ligands[21] were evaluated. An iridium complex of diene **L1**[22] returned only unchanged starting materials (Table 1, entry 4). However, the rhodium complex of **L1** gave *ent*-**3a** in 34% yield and 99% *ee*, with no trace of (±)-**4** (Table 1, entry 5). The chiral tetrafluorobenzobarrelene **L2**[23] gave **3a** in 83% yield and 99% *ee* (Table 1, entry 6). Repeating this reaction in the absence of $ZnCl_2$ gave identical results (Table 1, entry 7). Surprisingly, the product of addition of $PhB(OH)_2$ to imine **1a** was not observed in the reactions described in Table 1, entries 2–7, while it was not clear whether this product was formed in the reaction described in Table 1, entry 1.

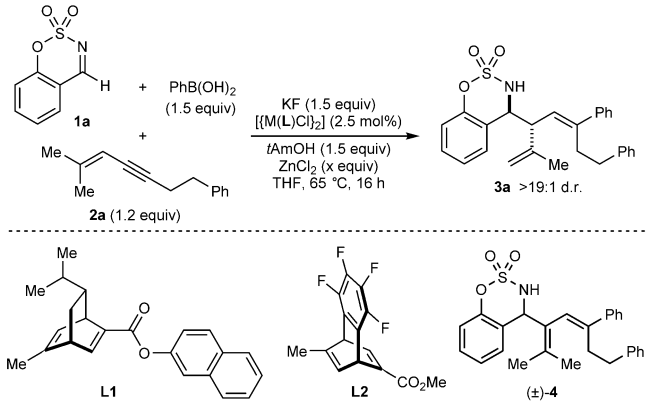
Variation of the imine was then explored by using $[\{Rh(\mathbf{L2})Cl\}_2]$ in the presence of $ZnCl_2$ (1.0 equiv) (Scheme 2). Although $ZnCl_2$ was unnecessary in the reaction of imine **1a** (Table 1, compare entries 6 and 7), its inclusion gave more consistent results across a range of examples. Aldimines **1a–1g** reacted with 1,3-enyne **2a** and $PhB(OH)_2$ to give products **3a–3g** in 52–75% yield, and with the exception of **3e**, all in >19:1 d.r. and 99% *ee*.[24] The reaction is tolerant of methyl (**3b**), methoxy (**3c** and **3e**), halide (**3d** and **3e**), dioxole (**3f**), and naphthyl groups (**3g**) within the aldimine.

Under the standard conditions, ketimine **5** reacted with 1,3-enyne **2a** and $PhB(OH)_2$ to give a 1.7:1 mixture of diastereomers, in which the major diastereomer **6** [see Eq. (1) for the structure] has the opposite absolute configuration at the stereocenter bearing the 2-propenyl group compared with the aldimine-derived products **3** (Scheme 2). However, the diastereoselectivity was increased to 8:1 d.r. by using THF/MeCN (19:1) in place of THF only [Eq. (1)]. Initial purifica-



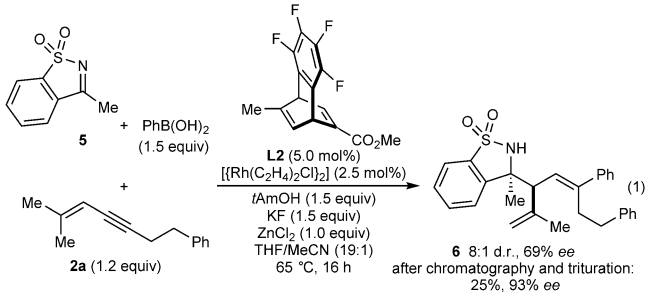
Scheme 2. Variation of the imine. Reactions employed 0.30 mmol of the imine. Diastereomeric ratios were determined by ^1H NMR analysis of the crude reactions. Yields are of isolated diastereomerically pure products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [a] Using 0.20 mmol of imine **1e**.

Table 1: Catalyst evaluation.[a]



Entry	$[M(\mathbf{L})Cl]_2$	$ZnCl_2$ (*x* equiv)	Yield [%][b]	*ee* [%][c]
1	$[\{Rh(cod)Cl\}_2]$	0	24	–
2	$[\{Ir(cod)Cl\}_2]$	0	53 (38)[d]	–
3	$[\{Ir(cod)Cl\}_2]$	1.0	81 (19)[d]	–
4	$[\{Ir(\mathbf{L1})Cl\}_2]$[e]	1.0	n.r.	–
5	$[\{Rh(\mathbf{L1})Cl\}_2]$[e]	1.0	34	−99[f]
6	$[\{Rh(\mathbf{L2})Cl\}_2]$[e]	1.0	83	99
7	$[\{Rh(\mathbf{L2})Cl\}_2]$[e]	0	83	99

[a] Reactions employed 0.05 mmol of **1a**. Diastereomeric ratios were determined by ^1H NMR analysis of the crude reactions. [b] Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC on a chiral stationary phase. [d] NMR yield of (±)-**4**. [e] Formed by prior stirring 5.0 mol% of **L1** or **L2** with 2.5 mol% of $[\{Ir(coe)Cl\}_2]$ (coe = cyclooctene) or $[\{Rh(C_2H_2)_4Cl_2\}_2]$ in THF for 30 min. [f] The enantiomer of **3a** was obtained. cod = 1,5-cyclooctadiene. *t*Am = *tert*-amyl. n.r. = no reaction.

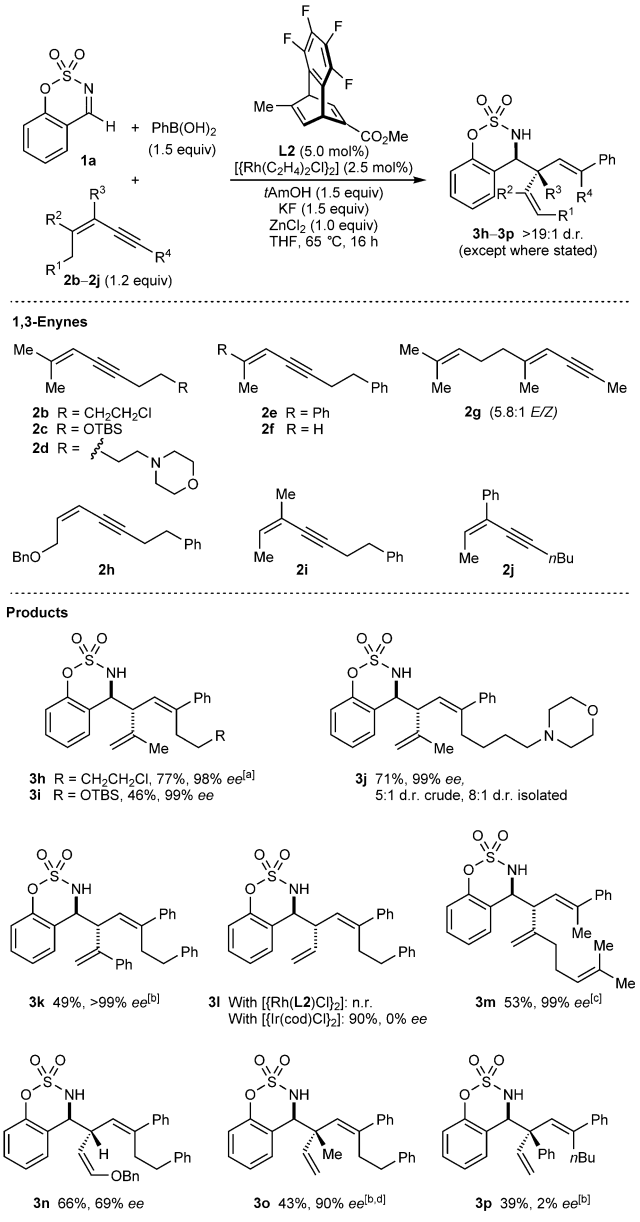


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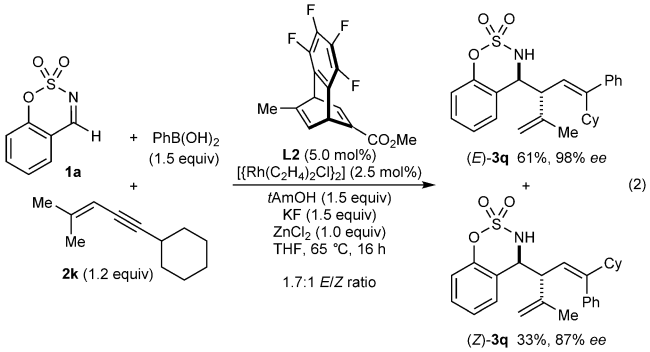
tion of the mixture by chromatography gave **6** in approximately 50% yield, 85% purity, and 69% *ee*. A second purification by trituration with pentane/toluene gave **6** with higher purity in 23% yield and 93% *ee*. This effect of nitrile co-solvents altering the diastereochemical outcome was also observed in our study of arylative intramolecular allylations of ketones.[10]

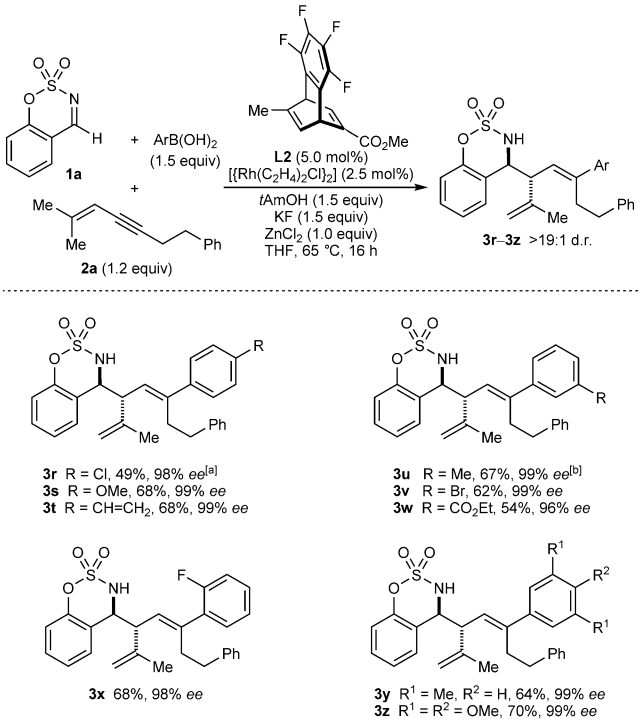
The reactions of imine **1a**, $PhB(OH)_2$, and various 1,3-enynes **2b**–**2j** were then studied (Scheme 3). In most cases, the products were formed in >19:1 d.r. and the enantioselectivities were generally high. An alkyl chloride (**3h**), silyl ether (**3i**), or morpholine (**3j**) in the 1,3-enyne are tolerated, but **3j** was formed in a modest 5:1 d.r. 1,3-Enyne **2e**, which contains a phenyl group *trans* to the alkyne, gave **3k** in 49% yield and 99% *ee*, whereas 1,3-enyne **2f**, which contains a hydrogen atom at this site, returned only unchanged starting materials. However, using $[\{Ir(cod)Cl\}_2]$ (2.5 mol%) as the precatalyst gave racemic **3l** in 90% yield. 1,3-Enyne **2g** (a 5.8:1 *E*/*Z* mixture) gave **3m** in 53% yield and 99% *ee*. In this case, no products that would be expected from reaction of the *Z* isomer of **2g** were detected. 1,3-Enyne **2h** gave enol ether **3n** in 66% yield and 69% *ee*. 1,3-Enynes **2i** and **2j** gave products **3o** and **3p** containing an all-carbon quaternary stereocenter, although **3p** was almost racemic.

Interestingly, 1,3-enyne **2k**, which contains a secondary alkyl group at the alkyne, reacted to give allylation product **3q** as a mixture of *E*/*Z* isomers in a 1.7:1 ratio [Eq. (2)]. The



Scheme 3. Variation of the 1,3-enyne. See the footnote of Scheme 2 for general considerations. [a] Using 1.5 equiv of 1,3-enyne **2b**. [b] Using 3.0 equiv each of $PhB(OH)_2$ and *t*AmOH. [c] Using 1.5 equiv of 1,3-enyne **2g** and 2.0 equiv each of $PhB(OH)_2$, KF, and *t*AmOH. [d] An 8.2:1 inseparable mixture of **3o** and the imine phenylation product was obtained (the yield of **3o** has been adjusted accordingly).





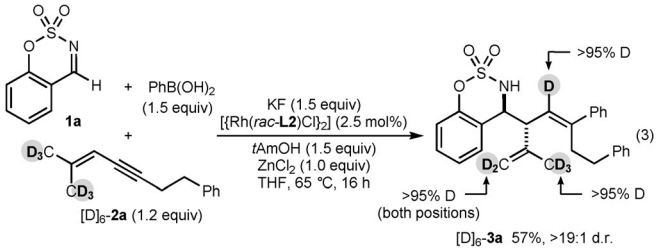
Scheme 4. Variation of the arylboronic acid. See the footnote of Scheme 2 for general considerations. [a] Isolated in approximately 91% purity (the yield has been adjusted accordingly). [b] Using 1.5 equiv of 1,3-enyne **2a**.

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E isomer was obtained in 61 % yield and 98 % *ee*, whereas the *Z* isomer was obtained in 33 % yield and 87 % *ee*.[25]

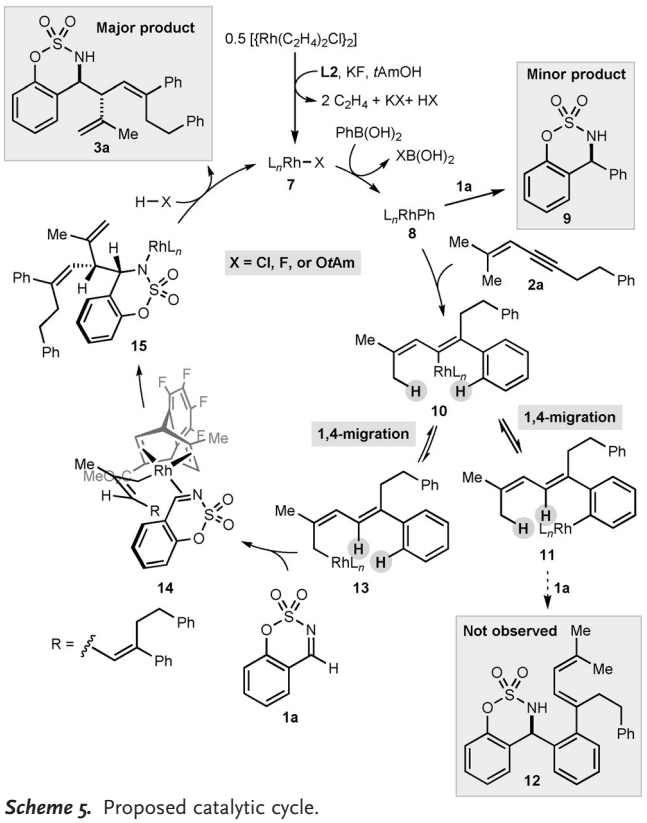
A range of arylboronic acids can be used in these reactions (Scheme 4). In all cases, the products were formed in > 19:1 d.r. and with high enantioselectivities (96–99 % *ee*). For the reactions producing **3y** and **3z**, the products of direct arylation of the imine were observed in < 15 % yield (by ^{1}H NMR analysis) but were not isolated. The reaction is tolerant of aryl halides (**3r**, **3v**, and **3x**), methoxy groups (**3s** and **3z**), alkenes (**3t**), methyl groups (**3u** and **3y**), and esters (**3w**).

The reaction of imine **1a** with $PhB(OH)_2$ and the hexadeuterated 1,3-enyne $[D]_6$-**2a**, using the rhodium complex derived from racemic **L2**, gave $[D]_6$-**3a**, in which there was > 95 % deuterium transfer to the trisubstituted alkene [Eq. (3)]. This result suggests 1,4-rhodium(I) migration occurs by C–H oxidative addition to give a rhodium(III) hydride, followed by C–H reductive elimination.[10,13a,14b,26]



A possible catalytic cycle to give product **3a** begins with formation of rhodium complex **7** from $[\{Rh(C_2H_4)_2Cl\}_2]$, chiral diene **L2**, KF, and possibly *t*AmOH (Scheme 5). Transmetalation of the arylboronic acid with **7** gives arylrhodium species **8**, which could react with imine **1a** to give **9**.[18] However, we assume that the greater π-Lewis basicity of alkynes compared to imine **1a** leads to preferential coordination of **8** to 1,3-enyne **2a**, which gives, after migratory insertion, alkenylrhodium species **10**. In a previous study, we established that alkenyl-to-aryl 1,4-rhodium(I) migration of intermediates similar to **10** to give arylrhodium species such as **11** is a significant pathway.[10] The fact that products such as **12** are not observed suggests that **11** is too sterically hindered to react with imine **1a**. Instead, **11** can undergo the reverse 1,4-rhodium(I) migration to regenerate **10**, which, after alkenyl-to-allyl 1,4-rhodium(I) migration, gives allylrhodium species **13**. Reaction of **13** with imine **1a** through conformation **14**, in which the sulfonyl group of the imine and the methyl group of the allyl ligand project towards the less hindered quadrants defined by the ligand, gives **15**. Protonolysis of **15** with HX (X = Cl, F, or O*t*Am) releases product **3a** and regenerates rhodium complex **7**. At present, the reason behind the beneficial effect of $ZnCl_2$ is not known, although possibilities include acceleration of the allylation by Lewis acid activation, or improvement of catalyst turnover.

In conclusion, we have developed highly stereoselective couplings of arylboronic acids, 1,3-enynes, and cyclic imines. These reactions rely upon alkenyl-to-allyl 1,4-metal migrations to generate nucleophilic allylmetal species, and proceed under iridium(I) catalysis to produce racemic products, or



Scheme 5. Proposed catalytic cycle.

under rhodium(I) catalysis to produce highly enantioenriched products when a chiral tetrafluorobenzobarrelene ligand is used. Given the number of other products that could arise from alternative pathways, the chemoselectivity of this process is notable.[27]

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Conflict of interest

The authors declare no conflict of interest.

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[25] Presumably, *E*/*Z* isomerization occurs by the allylrhodium intermediate **B** (Scheme 1) undergoing a series of 1,3-allylic transpositions to place rhodium at the ε-carbon, followed by bond rotation and further 1,3-allylic transpositions to reform a primary allylrhodium species.

[26] For the results of an intermolecular competition experiment between **2a** and $[D]_6$-**2a** that revealed a kinetic isotope effect is present in the C–H/C–D activation step ($k_H/k_D = 1.5$), see the Supporting Information.

[27] The research data associated with this publication can be found at DOI: https://doi.org/10.17639/nott.330.

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