Remote Transmission of Reactivity in Rhodium-Catalysed Reactions

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

By

Alistair Groves

June 2019

Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of my PhD degree in September 2015, 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. The candidate confirms that the work submitted is his own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that the appropriate credit has been given within the thesis where reference has been made to the work of others.

The following thesis contains results reported in the following publication:

Remote Nucleophilic Allylation by Allylrhodium Chain Walking.
A. Groves, J. I. Martínez, J. J. Smith, H. W. Lam, *Chem. Eur. J.*, **2018**, *24*, 13432-13436.

Contents

Prefix **5**

Acknowledgements 5

Abbreviations 6

Abstract 8

Chapter 1: Remote Nucleophilic Allylations via Allylrhodium Chain Walking **10**

1.1 Introduction **10**

1.1.1 Remote Functionalisation 10

1.1.2 Remote Functionalisation via Chain Walking 15

1.1.2.1 Early Chain Walking Examples 15

1.1.2.2 Palladium Chain Walking 18

1.1.2.3 Ruthenium Chain Walking 28

1.1.2.4 Nickel Chain Walking 31

1.1.2.5 Zirconium Chain Walking 35

1.1.2.6 Rhodium Chain Walking 40

1.1.3 Alternatives to Alkylmetal Chain Walking 46

1.1.3.1 Transmission of Non-Olefin Functional Groups via Chain Walking 46

1.1.3.2 Isomerisation of Allylmetal Species 49

1.1.4 Reductive Coupling to π-Electrophiles 55

1.1.4.1 Overview of Reductive Coupling 55

1.1.4.2 Nickel-Catalysed Reductive Coupling 55

1.1.4.3 Ruthenium-Catalysed Reductive Coupling 58

1.1.4.4 Rhodium-Catalysed Reductive Coupling 60

1.1.5 Summary 61

1.2 Results and Discussion **62**

1.2.1 Project Aims 62

1.2.2 Initial Results 63

1.2.3 Allylrhodium Chain Walking Towards Esters 64

1.2.4 Allylrhodium Chain Walking Towards Arenes 70

1.2.5 Confirmation of Diastereoselectivity 74

1.2.6 Other Electrophiles 76

1.2.7 Mechanistic Studies 83

1.2.8 Conclusions and Future Work 90

1.3 Experimental **92**

1.3.1 General Information 92

1.3.2 Preparation of Substrates 93
1.3.3 Allylation Products of Allylrhodium Chain Walking 127
1.3.4 Confirmation of Diastereoselectivity via Product Derivatisation 142
1.3.5 Chain Walking Towards Arenes With Triazinane Electrophiles 144
1.3.6 Investigation of Deuterium Transfer 146
Chapter 2: Rhodium-Catalysed Arylative Cyclisation via 1,4-Rh Migration 148
2.1 Introduction 148
2.1.1 1,4-Metal Migrations 148
2.1.2 Early 1,4-Palladium Migration 150
2.1.3 1,4-Rhodium Migrations 155
2.1.3.1 Rh^{I} Migration to sp^{2} Centres 155
2.1.3.2 Rh^{I} Migration to sp^{3} Centres 171
2.1.3.3 1,4-Rh^{III} Migration 178
2.1.4 1,4-Cobalt Migration 182
2.1.5 1,4-Iridium Migration 186
2.1.6 Summary 188
2.2 Results and Discussion 189
2.2.1 Project Aims 189
2.2.2 Initial Results 190
2.2.3 Enantioselective Arylative Cyclisation of Cyclic Alkynones 192
2.2.4 Enantioselective Arylative Cyclisation of Acyclic Alkynones 202
2.2.4.1 Reaction Optimisation 202
2.2.4.2 Substrate Scope 205
2.2.5 Conclusions and Future Work 212
2.3 Experimental 214
2.3.1 General Information 214
2.3.2 Preparation of Substrates 215
2.3.2.1 Cyclic Alkynones 215
2.3.2.2 Acyclic Alkynones 216
2.3.3 Rhodium-Catalysed Arylative Cyclisation of Alkynones via 1,4-Rh Migration 226
2.3.3.1 Cyclic Alkynones 226
2.3.3.2 Acyclic Alkynones 237
Appendix 246
References 246

Acknowledgements

After three years of postgraduate study in Nottingham (plus four more as an undergraduate), there are certainly many people that I would like to thank and acknowledge.

Firstly, I would like to thank Prof. Hon Wai Lam for his supervision and for giving me the opportunity to work within his group for the past four years. I have loved my time as a member of the Lam group and learnt so much.

I would also like to mention the people who I worked with closely throughout my studies. Firstly Dr. Jose I. Martínez, who was always available to offer advice throughout my entire PhD, even after departing the group. Your support will always be appreciated and never forgotten. Also to Dr. Joshua Smith, who helped me settle into the chain walking project in my first year. Finally, Dr. Jinwei Sun worked with me in my third year and was always hard working and helpful.

I would also like to give a special mention to Dr. Rebecca Ruscoe, Dr. James Cuthbertson and Jose (again) for proofreading various sections of this work. This is very much appreciated.

I would also like to thank all the members of the Lam group who I have worked with over the years, particularly my fellow quad members Mike, Connor and Luke. The ridiculous conversations and jokes will definitely be missed. Not forgetting Nhon, Becky, Simone, Steve, Jash, Chris, Stam, Somnath, Riccardo and everyone else who has contributed to my PhD experience. This includes my former housemates Dean, Phil, Dan and Ted who were always welcome distractions from a stressful day in the lab.

My family Sandra, Nick and Eleanor were always supportive and one phone call away, despite their bemusement at me for wanted to remain a student for another three years, and never quite understanding what I do. I hope I have made you proud.

And finally, to Rawnie. Your love and support have helped me through everything and constantly reminded me that no matter how difficult things got, some things in life are more important than chemistry.

Abbreviations

Å	Angstrom
acac	acetylacetonate
aq	aqueous
B(pin)	(pinacolato)boron
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
cod	1,5-cyclooctadiene
coe	cyclooctene
d.r.	diastereomeric ratio
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DIBAL	diisobutylaluminium hydride
DIBAL-D	diisobutylaluminium deuteride
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DTBM-Segphos	5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
equiv	equivalents
FAME	fatty acid methyl ester
g	gram
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HRMS	high resolution mass spectroscopy
MS	molecular sieves
NMR	nuclear magnetic resonance

NOESY	Nuclear Overhauser Effect Spectroscopy
PCC	pyridinium chlorochromate
Piv	Pivalyl or ^{t}BuC(O) group
PMP	*para*-methoxyphenyl
p-Tol	*para*-tolyl
r.r.	regiomeric ratio
rt	room temperature
*SP*hos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
^{t}amyl	1,1-dimethylpropyl
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBME	methyl *tert*-butyl ether
TBP	tributyl phosphate
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
Ts	tosyl

Throughout this work, ‘wedges’ have been used to indicate stereochemistry at quaternary centres and ‘blocks’ have been used to indicate stereochemistry at tertiary centres.

Numbering:

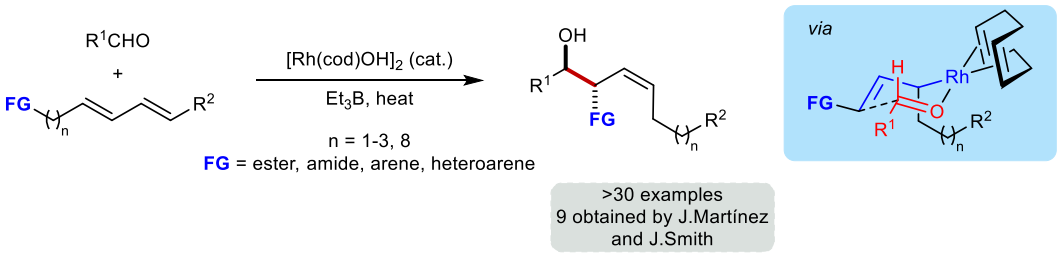
Throughout this work, the numbering of compounds has been divided up into sections. Compounds in the introductions are prefaced with the letter ‘**I**’ and are numbered **I1**, **I2**, etc. Compounds in the main text of the results and discussion are not prefaced with a letter and are numbered **1**, **2**, etc. This is consistent throughout both chapters, with the numbering continuing where the previous chapter ended. To avoid confusion, if a compound is in both the introduction and the results and discussion chapters, they have two different numbers to fit in with the relevant section’s numbering.

Additional compounds that were synthesised but do not appear in the main text are prefaced with the letter ‘**S**’ and are numbered **S1**, **S2**, etc. in the experimental section. Compounds used as ligands are prefaced with the letter **L**.

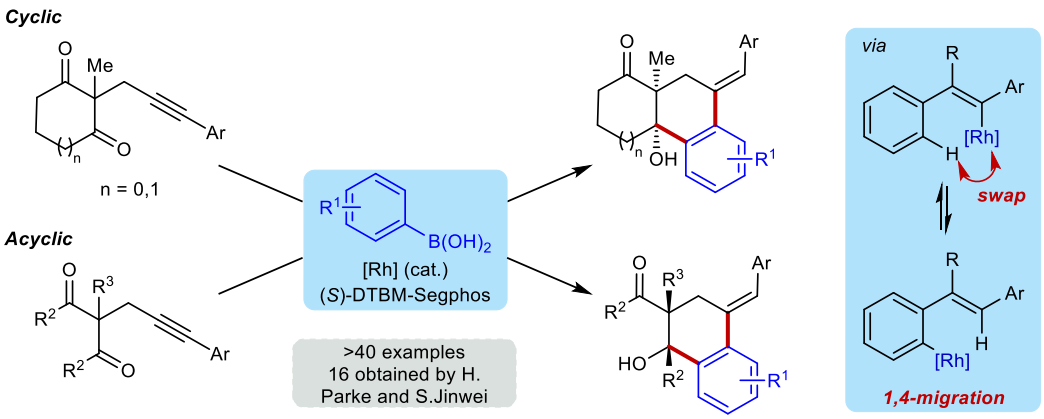
Abstract

Herein is described the remote transition of reactivity in two different rhodium-catalysed transformations.

The first example utilises the rare migration of an allylrhodium species generated *in situ* from conjugated dienes along a carbon chain towards tethered functional groups in a process known as allylrhodium chain walking. A remote nucleophilic allylation with an electrophile (aldehydes or imines) gives homoallylic alcohol or amine products in high diastereoselectivities.



The second transformation sees reactivity transmitted through an initial carbometalation of an alkyne followed by the key 1,4-alkenyl-to-aryl migration in the desymmetrisation of tethered cyclic and acyclic alkynones to give cyclisation products with an (*E*)-1-arylidene-1,2,3,4-tetrahydronaphthalene core. Using a chiral (*S*)-DTBM-Segphos® ligand gave the products in high enantioselectivities.



“Sometimes science is more art than science Morty. A lot of people don’t get that”

-Rick Sanchez

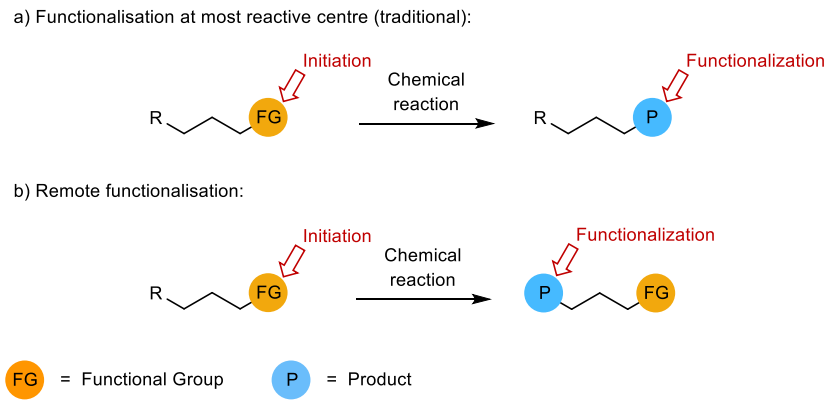
1. Chapter 1: Remote Nucleophilic Allylations via Allylrhodium Chain Walking

1.1 Introduction

1.1.1 Remote Functionalisation

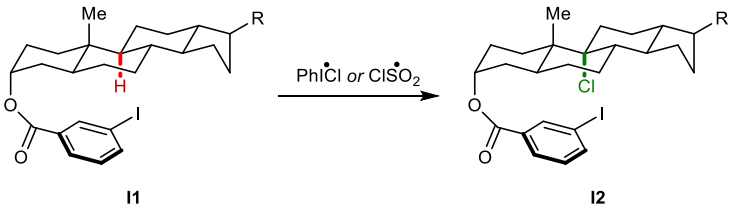
Chemical transformations have changed significantly over time and are continually evolving as methodologies become broader and more efficient. Important developments such as transition metal catalysed cross-coupling reactions [1-3] and C–H and C–C bond activations [4, 5] have rapidly expanded the toolbox of synthetic transformations available to chemists.

Remote functionalisation has the potential to further develop methodologies by introducing novel transformations that may have previously seemed too challenging to achieve by traditional methods. Most chemical reactions typically see functional group interconversion at a specific reactive site in a molecule (Scheme 1a). Remote functionalisation sees the pre-installed functional group relay reactivity to a distant location in the molecule, instead of undergoing a reaction itself (Scheme 1b).[6] Whilst this is a significant challenge to chemists, successful development would allow compounds to be derivatised in a variety of ways that have not been seen previously.



Scheme 1. Remote functionalisation vs. traditional reactivity.

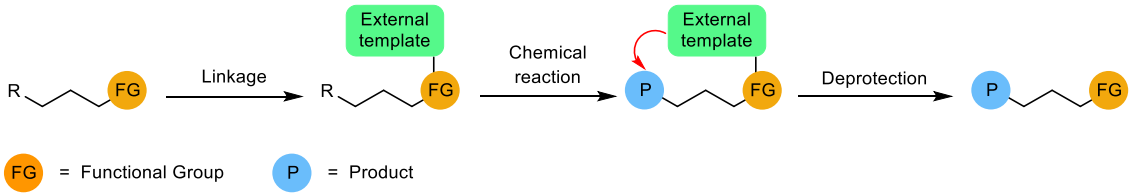
The first use of the phrase "remote functionalisation" in the literature was made by Breslow in 1974 in his work on steroid functionalisation in an intramolecular radical halogenation reaction of **I1** using a tethered iodide group to direct the radical to selectively functionalise a specific C–H bond on the steroid backbone (Scheme 2).[7] Activation of different C–H bonds can be achieved by changing the size of the tether length, altering the hydrogen atom it can access through space.



Scheme 2. First example of remote functionalisation – Breslow 1974.

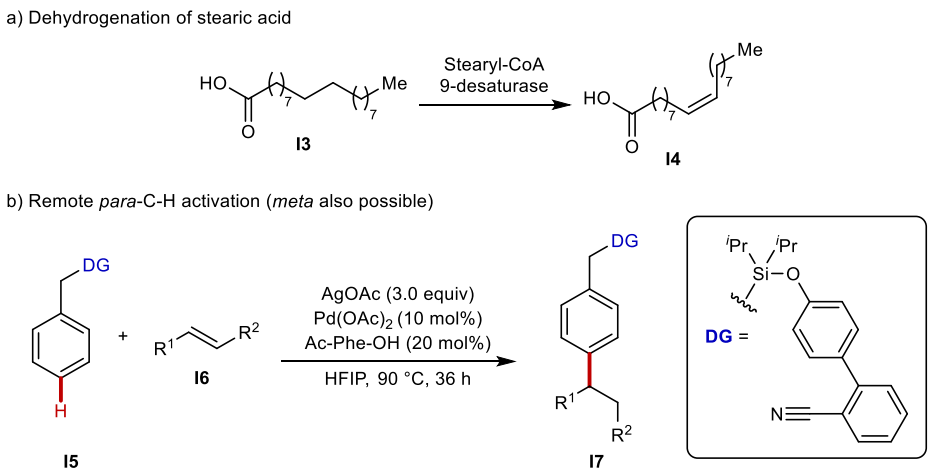
Since its initial demonstration by Breslow, many examples of remote functionalisation have been shown in the literature. These can usually be placed into one of two categories depending on the relationship between the site of initiation and the distant part of the molecule to be functionalised; external and internal remote induction.[6]

External remote induction sees the pre-installed functional group forming a binding interaction with an external template, such as an enzyme or molecular scaffold. This template then directs the distant functionalisation reaction before being removed (Scheme 3).



Scheme 3. External remote induction.

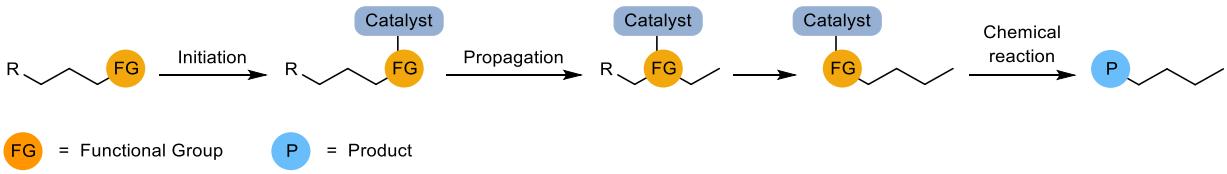
Selected examples include the enzymatic selective dehydrogenation of stearic acid **I3** to *Z*-olefin **I4** (Scheme 4a),[8] and remote C–H activation of compounds using removable templates to direct a metal to the desired *meta*- or *para*- C–H bond such as **I5** to **I7** (Scheme 4b).[9-12]



Scheme 4. Examples of external remote induction.

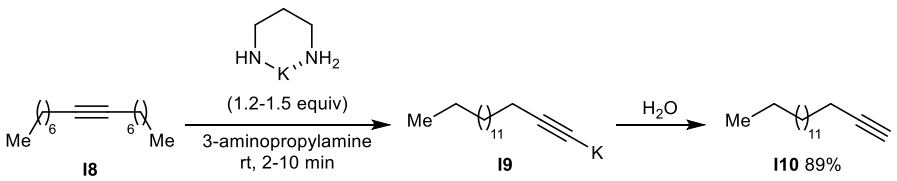
Whilst these approaches are powerful, they do require high molecular-weight linkers to relay the reactivity, which often need to be specifically designed, and must be removed once the process has ended.

The second category, which is of particular relevance to the work described in this thesis, is internal remote induction. This process involves the pre-installed functional group binding or interacting with a catalytic species, often a transition metal, which migrates the group along the carbon chain, before the reaction at the distant position (Scheme 5).[6]



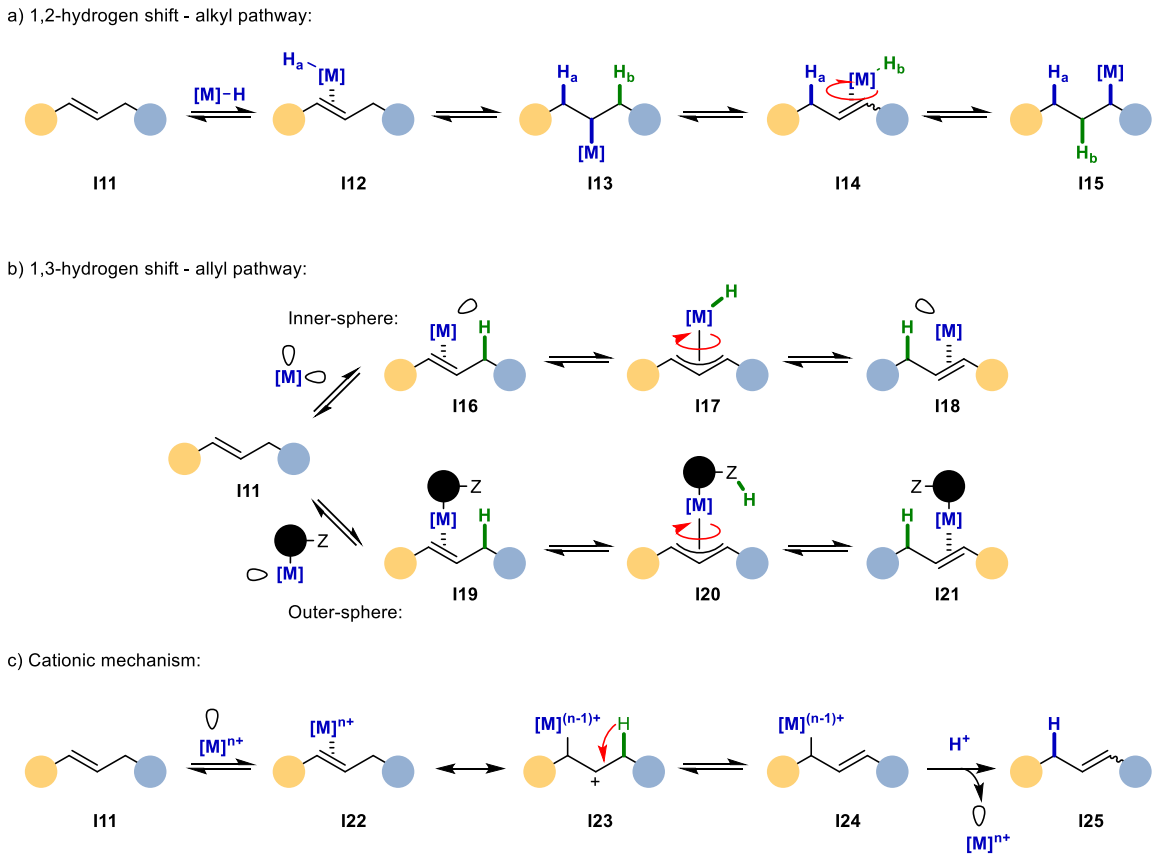
Scheme 5. Internal remote induction.

An historical example from the literature came from C. Brown in 1975, who described an "alkyne zipper" reaction where a strong potassium 3-aminopropanamide base promotes the 'contrathermodynamic' rapid isomerisation of alkynes from internal to terminal positions (Scheme 6).[13] The alkyne scope is broad and the migration is exceptionally rapid, even over longer chain lengths, with **I8** isomerising to **I10** via the stable potassium acetylide **I9**.



Scheme 6. Example of internal remote induction – alkyne zipper.

However, the most common example of this type of induction is transition metal catalysed alkene isomerisation, using the ability of transition metal complexes to readily isomerise C–C double bonds along a carbon backbone. The olefin isomerisation typically proceeds through three distinct mechanisms: 1,2-alkyl hydrogen shift, 1,3-allyl hydrogen shift or cationic (Scheme 7).[6] This process results in the metal migrating along a carbon chain and has been termed 'chain walking'.[14]



Scheme 7. Olefin isomerisation mechanisms.

1,2-Hydrogen shift (Scheme 7a) begins with coordination of a metal hydride with an alkene **I11**.[6] The subsequent species **I12** undergoes hydrometallation to **I13**. **I13** participates in a *β*-hydride elimination process of either H_a to reform **I12** or H_b to give olefin **I14**.

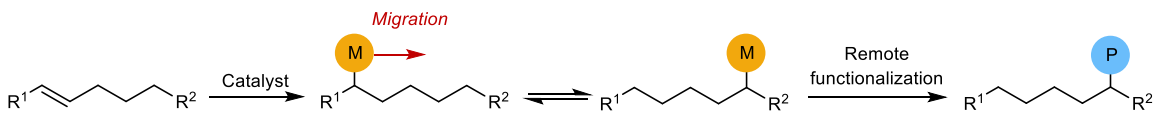
Readdition of the metal hydride after rotation of the metal-olefin bond gives **I15** with H_b being shifted one carbon to the left. **I12** to **I14** sees the net migration of the alkene across one carbon (with **I13** to **I15** seeing the net migration of the metal across the same distance). Repetitions of this sequence can result in migrations over more than one carbon atom.[15]

1,3-Hydrogen shift (Scheme 7b) proceeds through either an inner-sphere or outer-sphere mechanism. The inner-sphere mechanism requires a metal containing two vacant orbitals, one to coordinate to the olefin (giving **I16**), and the other to facilitate allylic C–H activation via oxidative addition to give η^3-allyl metal hydride **I17**. Rotation of the allyl bond and reinsertion gives the isomerised alkene **I18**. Here, **I16** to **I18** sees the net migration of the olefin across one carbon.[16]

The outer-sphere mechanism variation is significantly rarer and occurs when a ligand on the metal acts as a base (Z in Scheme 7b), with deprotonation leading to the formation of π-allyl species **I20**. As above, reinsertion gives **I21** as the isomeric form of **I19**.[17]

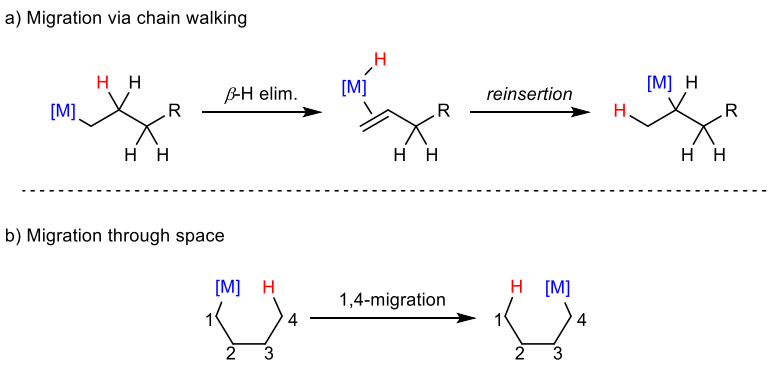
Finally, the cationic mechanism can be found with electrophilic metal complexes. Alkene interaction with the metal centre generates carbocation **I23**, which forms allylic metal species **I24** after loss of H^+ (Scheme 7c).[18] This proton then cleaves the M–C bond to give **I25**. All the discussed pathways above are reversible.

It is possible to direct this reversible isomerisation process (and hence direct the migration of the metal along a carbon chain) by providing an irreversible thermodynamically favoured termination step, such as attack of an external species, as a driving force (Scheme 8). This ultimately gives the user more control, by avoiding the formation of statistical alkene mixtures due to the reversible nature of the isomerisation process.[6]



Scheme 8. Migration of a metal along a carbon skeleton by olefin isomerisation.

Before this form of remote functionalisation via metal migration chain walking is explored in more detail, it should be noted that there is another distinct class of metal-catalysed migration. This is known as through-space migration, most commonly seen in the literature as 1,4-migration, via an interaction 'through space' between a metal atom and a nearby C–H bond (Scheme 9b – compare with 9a).[19] This class of migration will be the subject of Chapter 2.



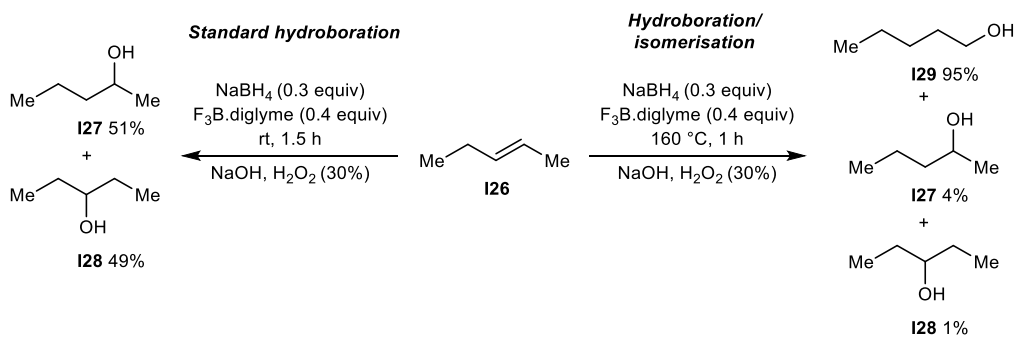
Scheme 9. Metal migration classes.

1.1.2 Remote Functionalisation via Chain Walking

1.1.2.1 Early Chain Walking Examples

Many alkylmetal compounds undergo *β*-hydride elimination to form alkene isomers. Alkylboron species are a noted example, first observed by Rosenblum in 1955 in the decomposition of tri-*n*-butylborane to but-1-ene and but-2-ene under harsh reaction conditions.[20] This process was utilised by H. Brown in a series of papers from 1959 onwards, transforming internal linear olefins to primary alcohols following a hydroboration/isomerisation sequence, walking the boron atom to the terminus of the carbon chain. Subsequent oxidation gave the corresponding alcohol.[21-28]

Whilst traditional hydroboration/oxidation of an internal olefin such as **I26** at room temperature typically yields equimolar ratios of both alcohol regioisomers **I27** and **I28**, increasing the temperature to 160 °C sees the primary alcohol **I29** as the major product in 95% yield (Scheme 10).[24]

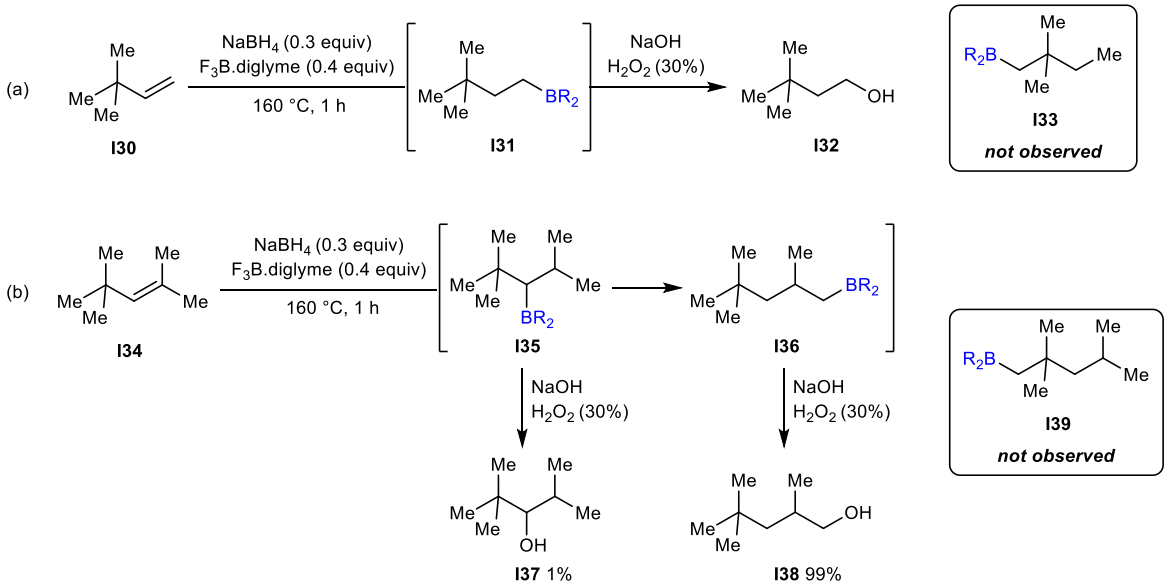


Scheme 10. Standard hydroboration vs. boron chain walking.

Using Rosenblum's observations on alkylborane decomposition, Brown hypothesised that the hydroboration process on the olefin was reversible at high temperatures and the

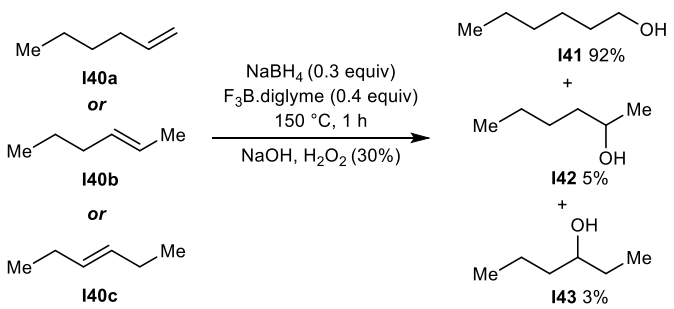
migration of boron can be rationalised by a sequence of eliminations and readditions.[21] The end result favours boron at a terminal position, most likely to minimise steric interactions.

Further insight was provided using branched chain alkenes. **I30** saw exclusive formation of alcohol **I32** from borane **I31** (Scheme 11a). As expected, there was no **I33** observed as β-hydride elimination is not possible at a quaternary centre. Using **I34** saw favourable migration of boron over a single branch (**I35** to **I36**), giving 99% yield of alcohol **I38** after oxidation (Scheme 11b). Again, migration over the double branched quaternary centre was not possible (**I39**).[26]



Scheme 11. Boron chain walking over branched alkyl chains.

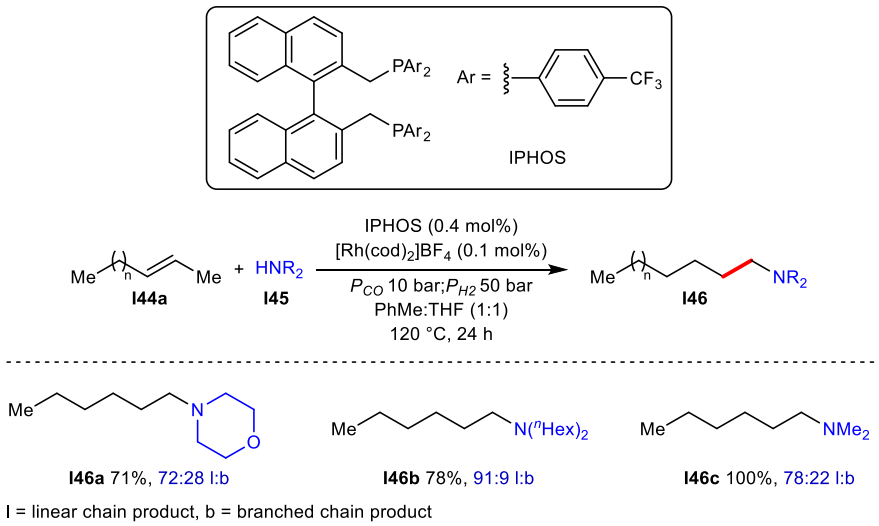
Additionally, using three different hexene isomers separately (**I40a** to **I40c**) always gives the same distribution of alcohol product isomers, with 92% of **I41** as a result of boron walking to the chain terminus (Scheme 12).



Scheme 12. Boron chain walking over different hexene isomers.

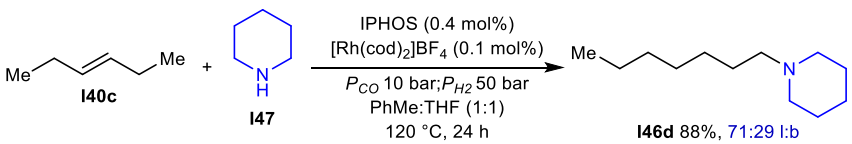
This result has useful implications, as it is possible to obtain the same product ratio from cheaper mixtures of olefin isomers instead of having to use isomerically pure materials; an important consideration in industry. Additionally, the use of hex-1-ene **I40a** results in the formation of 3-hexanol **I43**, suggesting that it is also possible for boron to migrate in the other direction away from the chain terminus. This supports the theory of the process being reversible, with boron walking along the chain until it reaches an isomeric equilibrium.

Transition metals can also catalyse this process. Originally, it was extensively utilised in olefin polymerisation chemistry, where the first reference to the phrase "chain walking" was made.[15, 29-33] However, an important early example of a transition metal catalysing this kind of isomerisation/migration mechanism in an organic reaction was demonstrated by Beller in 2002, who reported the one-pot Rh-catalysed transformation of internal olefins **I44a** to linear amines **I46** via hydroaminomethylation (Scheme 13) using an extremely low catalyst loading of 0.1 mol%.[34]



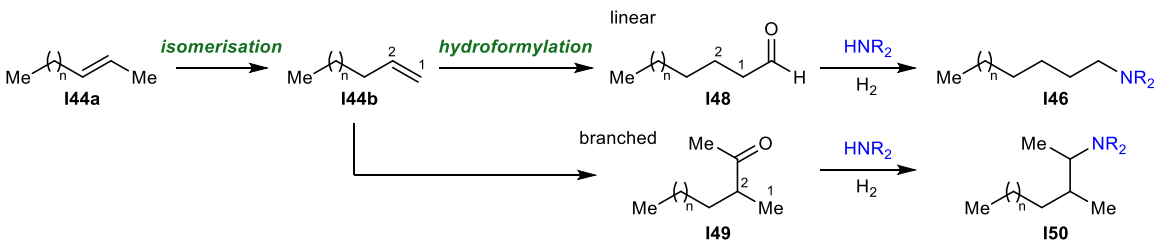
Scheme 13. Rh-catalysed hydroaminomethylation of internal olefins to linear amines.

Different 2-alkenes were successfully combined with a range of amines including morpholine **I46a** and simple dialkylamines **I46b-I46c** in up to quantitative yields. Longer range isomerisation was also observed using 3-hexene **I40c** (Scheme 14).



Scheme 14. Longer range hydroaminomethylation.

The reaction itself proceeds via a sequence of isomerisation to the terminal olefin **I44b**, hydroformylation to the aldehyde **I48** and reductive amination to give linear amines **I46** (Scheme 15). The ability to access valuable amine products from internal olefins added further utility to the hydroformylation reaction, which has rapidly emerged as a promising field of research.[35, 36] The ratio of linear:branched (l:b) products observed in Scheme 15 sees >70% of the linear amine product in most cases. Formation of the branched product **I50** is seen after the other hydroformylation regioisomer **I49** is formed at the terminal olefin **I44b**.

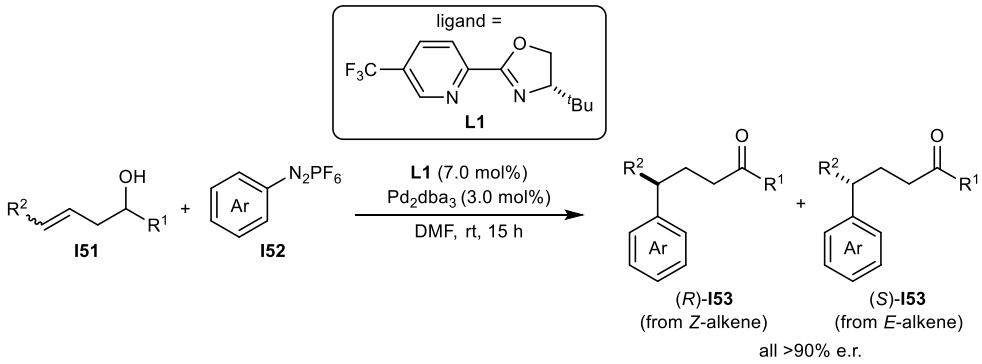


Scheme 15. Hydroaminomethylation process.

Many other transition metals are now known to chain walk in these tandem olefin isomerisation/remote functionalisation reactions. A small number of examples exist for metals like Co,[37, 38] Fe,[39] and Ir,[40, 41] but there are significantly more examples for metals like Pd, Ru, Ni, Zr and Rh, which will be explored in more detail in the rest of this section.

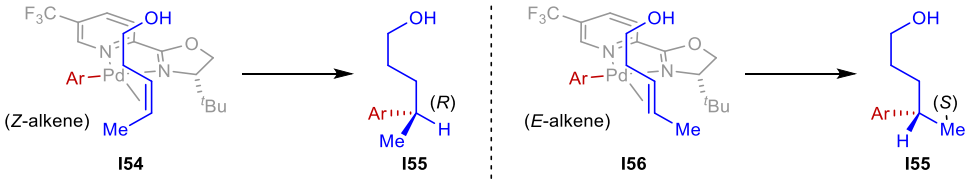
1.1.2.2 Palladium Chain Walking

Since 2012, Sigman and co-workers have published a series of papers using Pd chain walking in a Heck-initiated redox relay process on various alkenes with tethered alcohol groups. This developed initial work by Heck [42] and Chalk [43] on Heck reactions with allylic alcohols. The first example saw disubstituted alkenol **I51** undergo this tandem process, initiated by an enantioselective Heck reaction to form the alkylpalladium species which migrates towards the pendant alcohol (Scheme 16).[44] Transformation of this alcohol to the aldehyde **I53** is the thermodynamic driving force of this isomerisation and these products have remote stereocentres installed in excellent enantiomeric ratios (>90% e.r.).



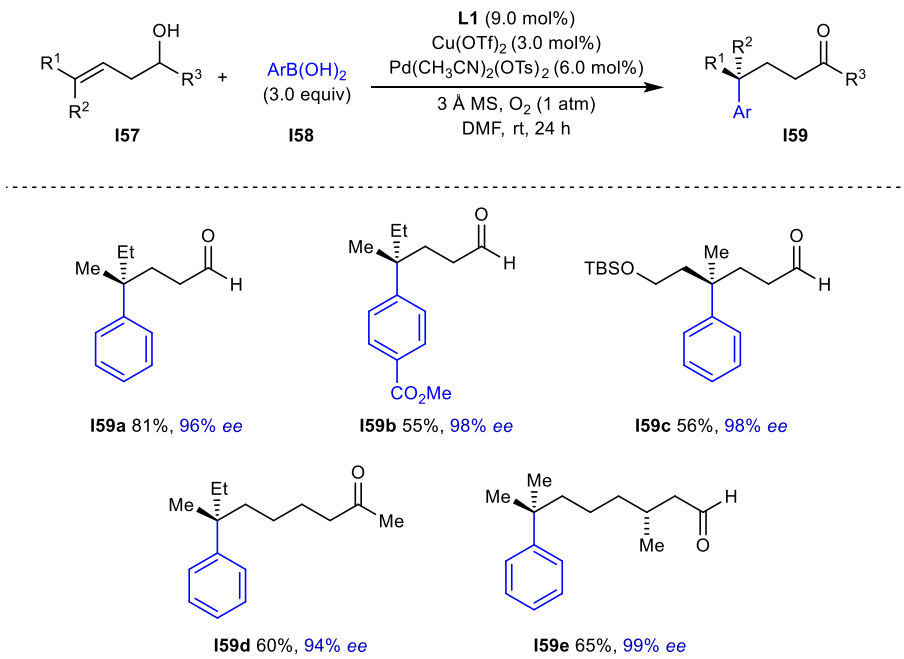
Scheme 16. First enantioselective remote Heck redox relay work.

The aryl source for the Heck reaction is the diazonium salt **I52** and the catalytic system uses Pd^0 and a Pyrox ligand **L1**. The stereochemistry of the olefin in **I51** determines the enantiomer of **I53** formed (*Z*-alkene gives *R*, *E*-alkene gives *S*). This is rationalised by the olefin adopting a favoured conformation once it coordinates to the Pd-ligand system (Scheme 17). This conformation is the same for both the *E*- and *Z*-alkenes, and therefore carbopalladation occurs exclusively from the back face of the olefin in both scenarios.



Scheme 17. Rationalisation of stereochemical outcomes of the initial Heck reaction.

Sigman later reported a variant of this chemistry using trisubstituted alkenes **I57**. This facilitated the highly desirable formation of remote quaternary stereocentres more than 3 carbons away from the carbonyl functional group (Scheme 18).[45] Whilst the Pyrox ligand **L1** remained the same, the Pd source was switched to $Pd(CH_3CN)_2(OTs)_2$ and an oxygen atmosphere was used. 3Å Molecular sieves were critical for reaction success, as they were believed to prevent catalyst deactivation via aggregration of Pd metal. $Cu(OTf)_2$ was also vital, with both additives frequently used in oxidative Pd catalysis to promote reoxidation of Pd(0), although their precise role in this transformation was not fully understood. The aryl source was also changed to an arylboronic acid, avoiding the need to prepare aryldiazonium salts. This significantly broadens the scope as there are large catalogues of cheap boronic acids readily available from commercial suppliers.

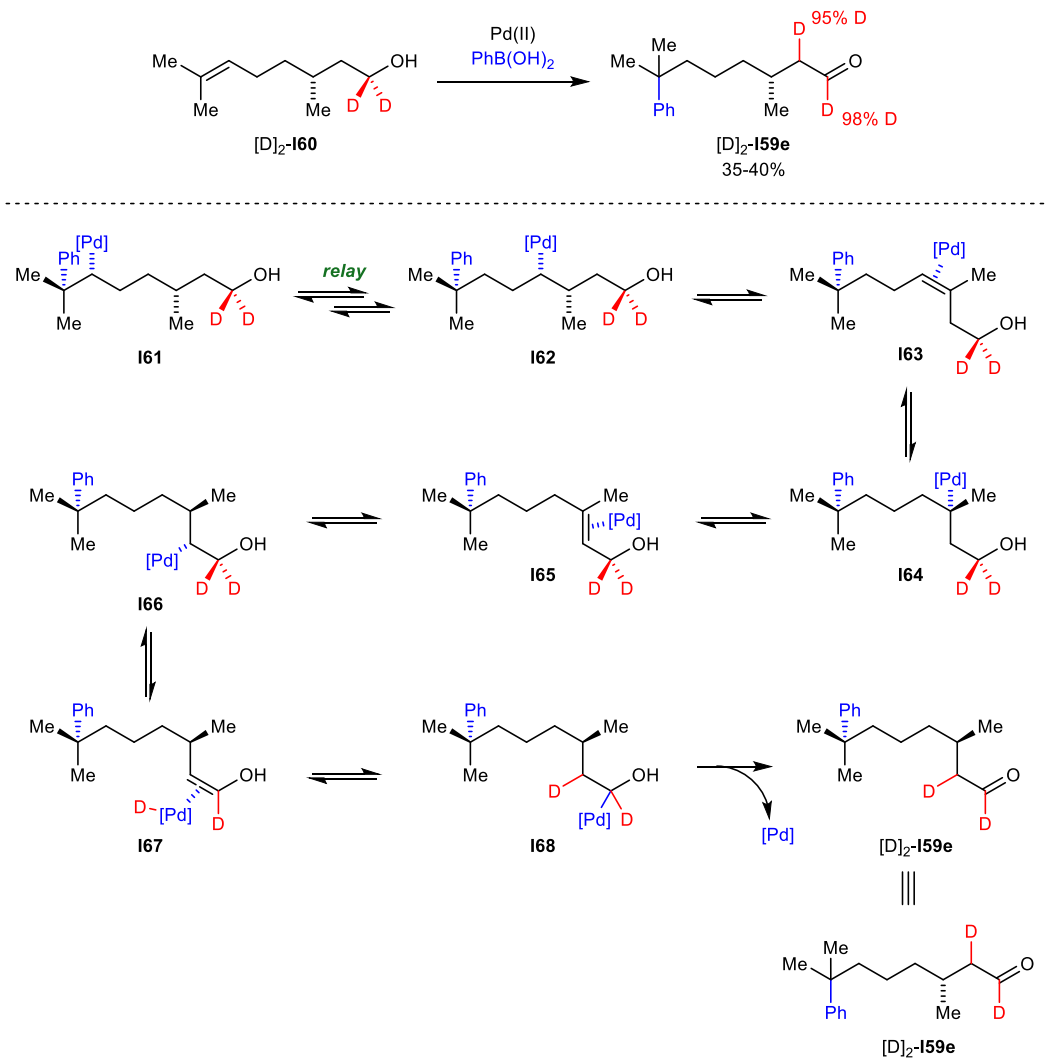


Scheme 18. Remote Heck redox relay with aryl boronic acids and trisubstituted olefins.

A range of compounds are formed with various boronic acids and R^1 groups tolerated in good yields and excellent enantioselectivities (**I59a-I59c**). Pd migration was successful over extended carbon chains, with the process being driven by transformation of secondary alcohols to ketone **I59d** with excellent levels of enantioselectivity achieved.

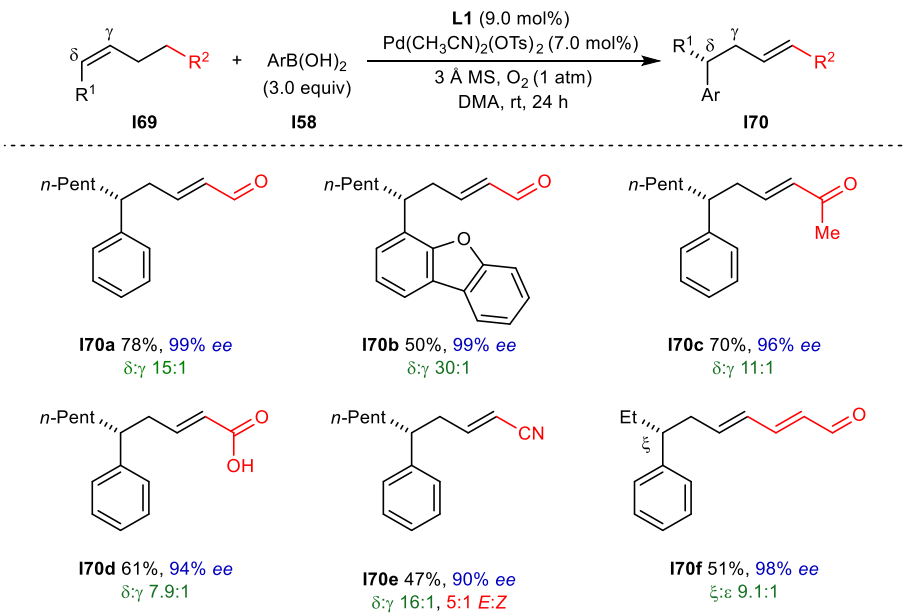
A final notable observation from Scheme 18 is the formation of **I59e** in 65% yield from a trisubstituted olefin with an additional stereocentre in the chain supplied by a methyl substituent. Interestingly, there is no racemisation of this stereocentre in the product, and **I59e** is recovered as a single enantiomer, implying that as the Pd chain walk event occurs, the catalyst never disengages from the chain and remains on the same alkene face throughout.

More information can be gleaned from this using deuterated alkenol $[D]_2$-**I60** (Scheme 19). When subjecting $[D]_2$-**I60** to the reaction conditions, the initial Heck reaction at the alkene forms the quaternary stereocentre with Pd one carbon unit along (**I61**). Pd chain walks via the relay process to **I62**, and because it remains ligated to the same olefin face, even after β-hydride elimination events, the branched stereocentre is retained (see **I62** to **I66**). At **I66**, β-deuteride elimination forces the formation of **I67**, which proceeds to give **I68** after reinsertion. From here, oxidation of the alcohol yields the aldehyde $[D]_2$-**I59e**,[46] with one of the D atoms migrated from the α-carbon to the β-carbon with 95% deuteration.



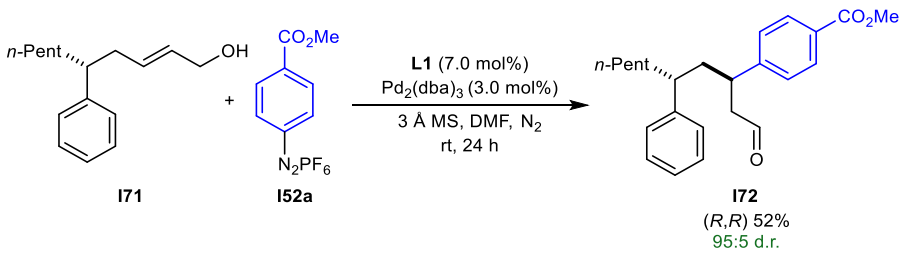
*Scheme 19. Proposed Pd chain walking mechanism of branched substrate [D]$_2$-**I60**.*

Alcohols were not the only functional groups that encourage Pd chain walking. By changing the solvent from DMF to DMA, Pd migration can be observed towards R^2 functional groups such as aldehydes, ketones, carboxylic acids or nitriles after the initial δ-regioselective Heck reaction (Scheme 20).[47] In these cases, the thermodynamic driving force of migration was the formation of conjugated compounds instead of an oxidation. Compounds **I70a-I70f** were formed in good yields (up to 78%) and excellent enantioselectvities (up to 99% *e.e.*), including the formation of an $\alpha,\beta,\gamma,\delta$-unsaturated system in **I70f** in 51% yield.



Scheme 20. Pd chain walking towards other functional groups.

I70a was reduced to allylic alcohol **I71** and then resubjected to reaction conditions very similar to the initial work with aryl diazonium salts.[44] The second Heck reaction with **I52a** installed a second aryl group enantioselectively forming 1,3-diaryl compound **I72** in excellent d.r. (Scheme 21). This is a powerful method of generating complex products with two new stereocentres from simple starting materials.

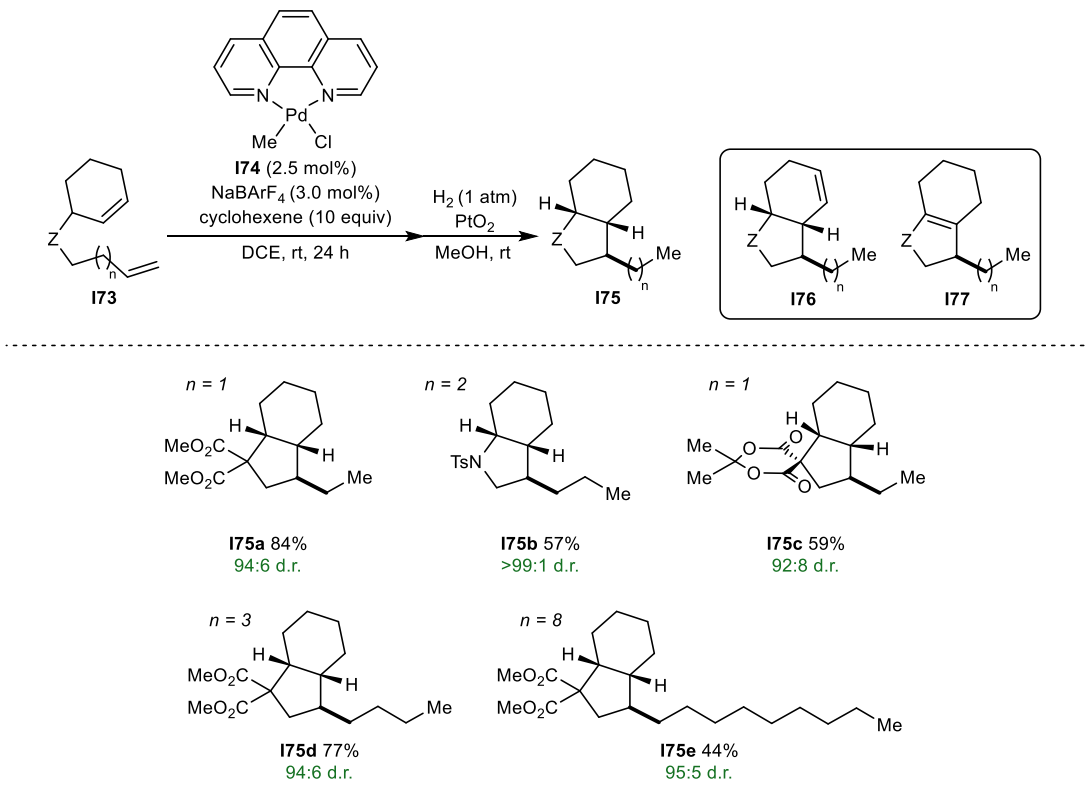


Scheme 21. A second successive Heck redox relay leading to a 1,3-diaryl compound.

A myriad of other applications of this work have been described by Sigman, installing new groups such as vinyl triflates, a dehydrogenative variation on the usual Heck reaction, and even Pd chain walking on cyclic lactams, demonstrating the wide scope this methodology possesses.[48-54]

In 2012, Kochi and co-workers reported another example of Pd chain walking via olefin isomerisation.[55] This work differs from the work by Sigman and co-workers discussed previously, in that a C–C bond forming reaction is the irreversible step that drives the Pd

migration in the cyclisation of 1,*n*-dienes **I73** to give compound **I75** (Scheme 22). The reaction system is catalysed by methyl-Pd **I74** with $NaBArF_4$ as a counterion. A PtO_2-catalysed hydrogenation reduction of the cyclisation product **I76** was necessary to determine the efficiency of the cyclisation reaction, as a range of other inseparable isomeric byproducts were also formed. It was found that 10 equivalents of cyclohexene suppressed the formation of tetrasubstituted olefin **I77**, which is not reduced in the PtO_2-catalysed hydrogenation.

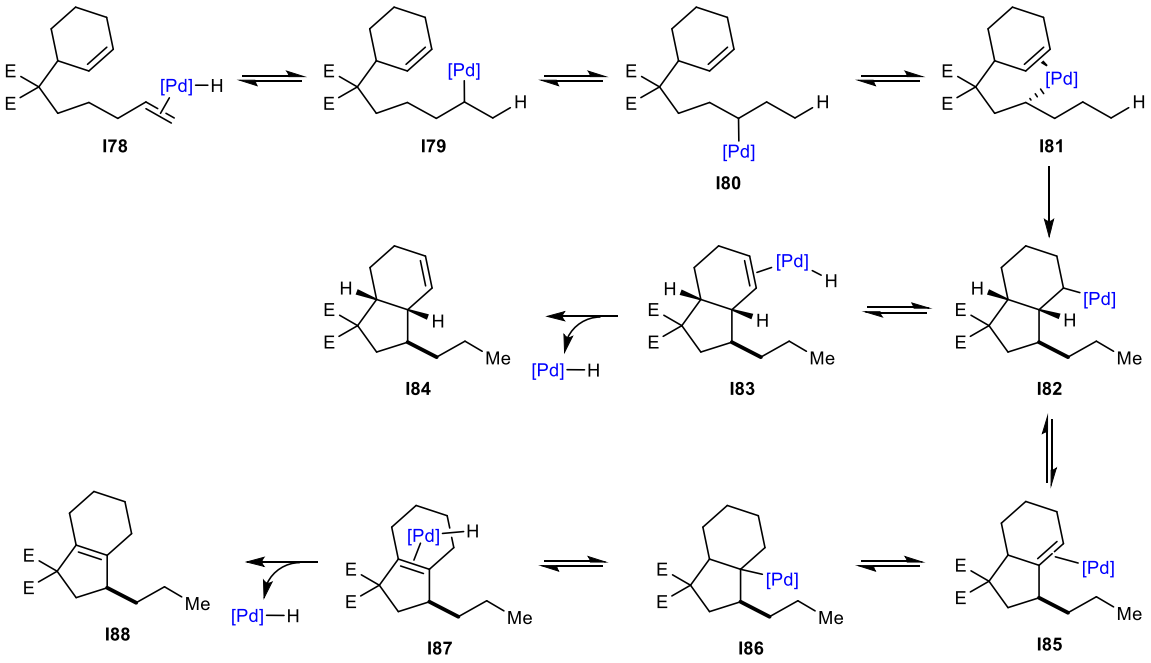


Scheme 22. Cyclisation of 1,n-dienes via Pd chain walking

Different Z linker groups such as quaternary carbons, nitrogens and even a Meldrum's acid derivative gave **I75a-I75d** in 57-84% yield and over 92:8 d.r. Longer range Pd chain walking over up to 8 carbons was displayed although the yields did decrease to 44% for **I75e** where n = 8.

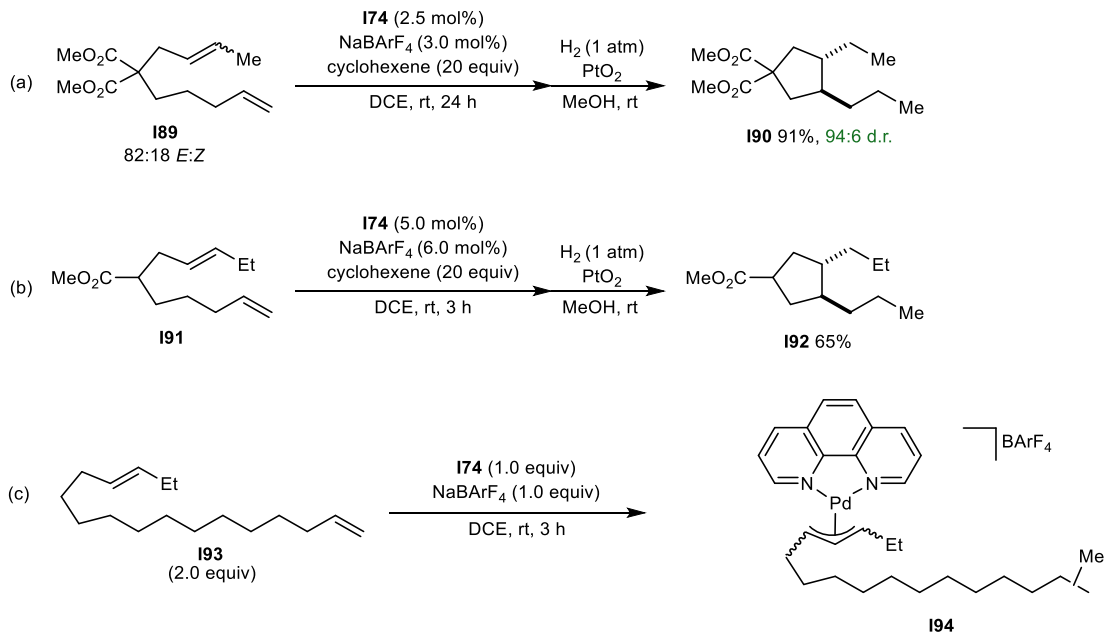
Studies into the mechanism proposed *in situ* generation of Pd–H,[56] with addition across the more accessible terminal olefin to give alkyl-Pd species **I79** which subsequently chain walks to **I81** (Scheme 23). Cyclisation to **I82** via carbopalladation of the secondary olefin provides the thermodynamic driving force for the Pd migration. This is followed by *β*-hydride elimination to **I83** and dissociation from the metal gives **I84**. The formation of side-product

I88 can be rationalised by isomerisation to trisubstituted olefin **I85**, then tetrasubstituted olefin **I87**, all mediated by Pd–H.[55]



Scheme 23. Proposed mechanism of Pd mediated isomerisation/cyclisation via chain walking.

Kochi then extended this work to dienes containing an acyclic internal alkene moiety.[57] Under almost identical reaction conditions, 1,8-diene **I89** underwent cyclisation to **I90** in 91% yield and 94:6 d.r. after hydrogenation (Scheme 24a).

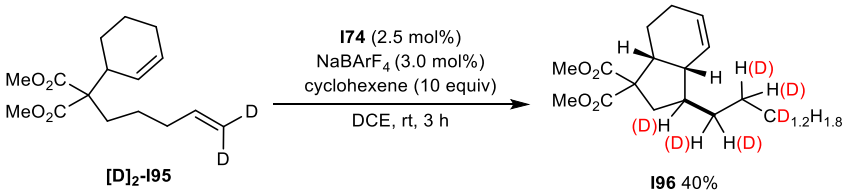


Scheme 24. Effects of removing substituents on the linker group in the 1,n-diene cyclisation.

The possibility of chain walking without a quaternary carbon as a linker separating the two olefns was then attempted. The possibility of *β*-hydride elimination at a non-quaternary centre means Pd could potentially chain walk past the linker instead of undergoing cyclisation. Fortunately, when a tertiary carbon was used as a linker in **I91**, the desired product **I92** was obtained in 65% yield (Scheme 24b).

Using a methylene group as a linker in **I93** did not give any observable cyclisation products. A stoichiometric reaction of **I93** with the Pd-catalyst system gave π-allyl palladium complex **I94**, indicating that when there is no substituent on the linker section, alkyl-Pd rapidly migrates along the chain to the other alkene, forming the π-allyl complex *in lieu* of any C–C bond forming cyclisations (Scheme 24c).

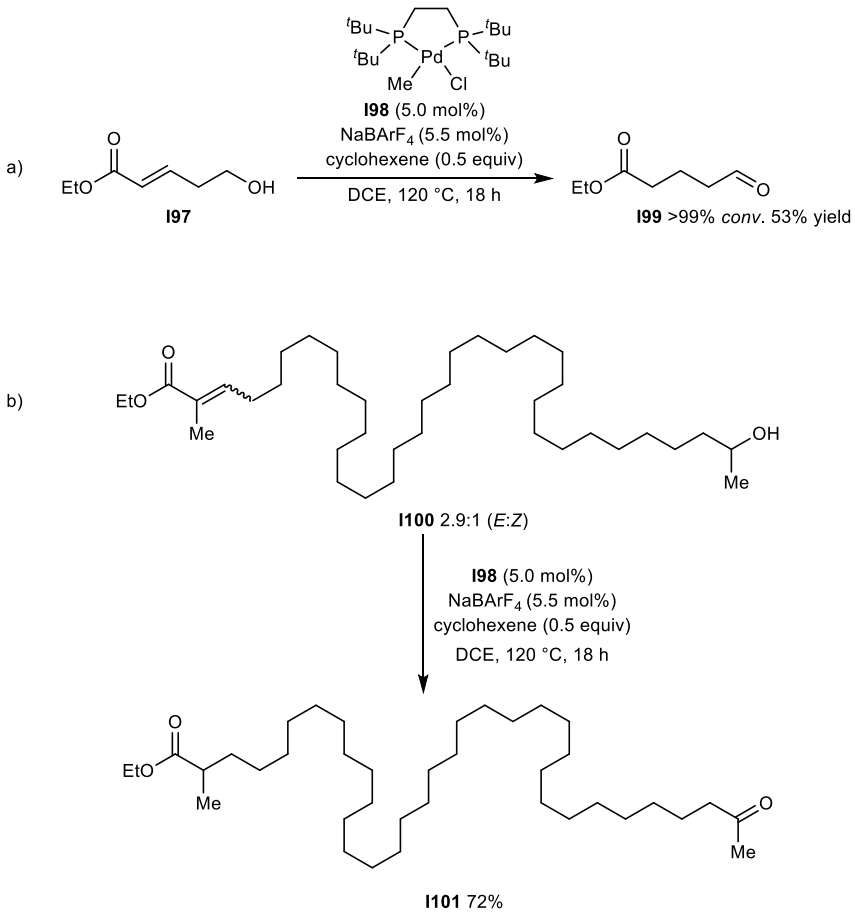
A deuteration experiment with $[D]_2$-**I95** demonstrates that the Pd chain walking process is clearly reversible, due to the incorporation of deuterium at the three carbon atoms along from the terminus of the chain, with 40% of terminal D atoms exchanged with hydrogens in **I96** (Scheme 25). Interestingly, deuterium levels diminished with distance from their original position, suggesting that Pd chain walking does not occur to an extent where H/D exchange can reach an equilibrium, and the carbopalladation step in the cyclisation to **I96** competes with the Pd chain walking process. No H/D exchange occurs in the cyclic ring as predicted.



Scheme 25. Deuteration experiment provides more mechanistic insight.

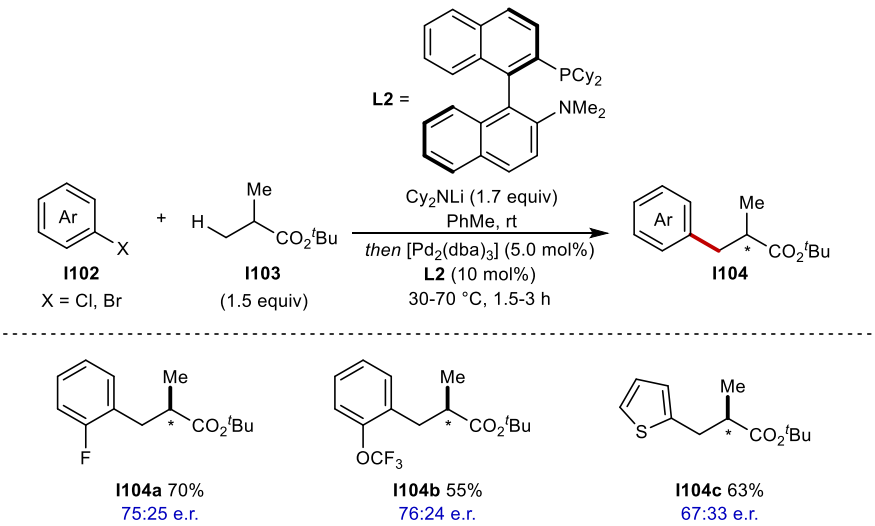
Kochi has also shown this transformation can tolerate different ligands, swapping the 1,10-phenanthroline ligand for a chiral Pyrox ligand to perform an enantioselective variation on this reaction with moderate success of 65% *e.e.*[58]

A catalytic system similar to the one used by Kochi has been utilised by Mazet in a deconjugative isomerisation reaction.[59] The oxidation of an alcohol to carbonyl as the chain walking driving force bears resemblance to Sigman's work. Using 5.0 mol% of Pd-bisphosphine complex **I98** alongside 5.5 mol% of $NaBArF_4$, the amount of cyclohexene additive could be reduced to 0.5 equivalents and at 120 °C, α,β-unsaturated ester **I97** underwent isomerisation to **I99** in 53% yield. (Scheme 26a). Extreme long range Pd chain walking over thirty carbon atoms was demonstrated as **I100** underwent isomerisation to ketone **I101** under identical reaction conditions (Scheme 26b).



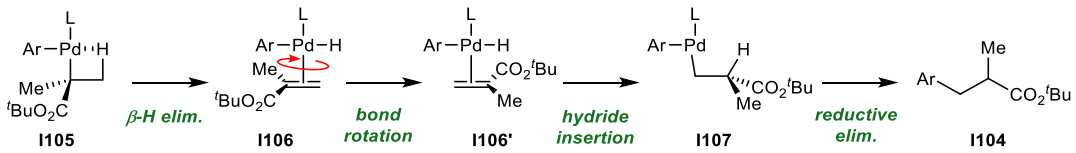
Scheme 26. Deconjugative isomerisation of α,β-unsaturated esters by long range Pd chain walking.

A slightly different Pd chain walking example was described by Baudoin in 2010, who reported a Pd-catalysed *β*-arylation of carboxylic esters.[60] This is believed to occur by formation of a lithium enolate of ester **I103** *in situ* with Cy_2NLi before a $[Pd_2(dba)_3]$-catalysed arylation using a DavePhos ligand **L2** to induce enantioselectivity at the *α*-carbon stereocentre in **I104** (Scheme 27). A range of different arylation products **I104a-I104c** were obtained in good yields (55-70%) and moderate enantiomeric ratios (>67:33 e.r.).



Scheme 27. Pd-catalysed β-arylation of carboxylic esters.

Pd-enolate **I105** is the key intermediate in this process. It forms via oxidative addition of ArX **I102** into Pd^0, followed by halogen X substitution with the ester enolate. Pd then adds into the C–X enolate bond to generate **I105**, which can undergo a *β*-hydride elimination to **I106**. Bond rotation and Pd–H reinsertion sees Pd migrate along the carbon chain by one unit (**I107**). Reductive elimination with the aryl group on the metal forms the *β*-arylation product **I104** (Scheme 28).[60]



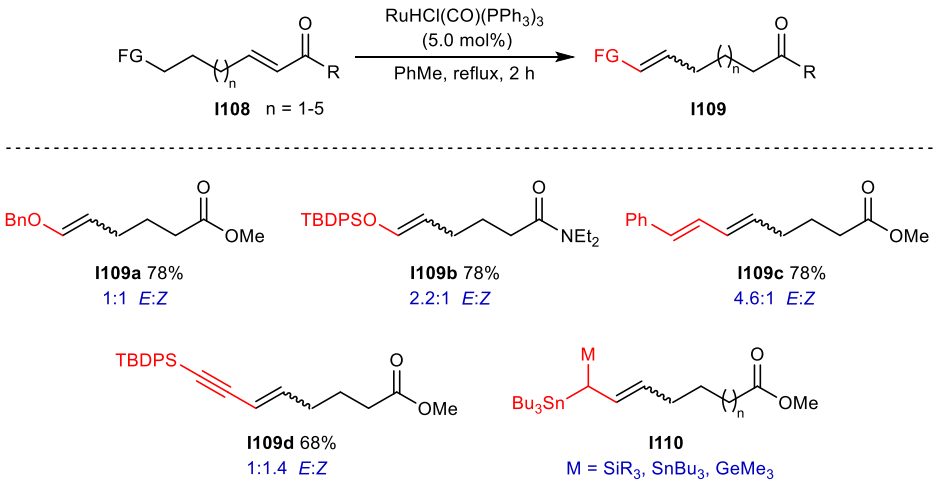
Scheme 28. Elimination/reinsertion sequence sees Pd migrate to β-carbon.

Baudoin later applied this process to *α*-amino esters and N-Boc amines, and also demonstrated the Pd chain walk mechanism over longer range carbon chains.[61-64]

1.1.2.3 Ruthenium Chain Walking

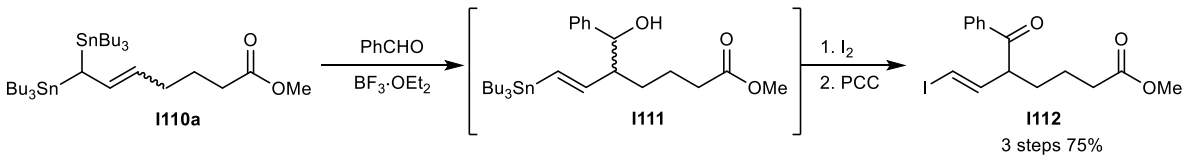
One of the earliest examples of Ru participating in a chain walking mechanism was reported by Mori in 2000, concerning the deconjugative isomerisation of *α*,*β*-unsaturated carbonyl derivatives **I108** (Scheme 29).[65] $RuHCl(CO)(PPh_3)_3$ was the commercially available catalytic source of Ru-H after refluxing in PhMe for 2 h, and the driving force of the olefin migration is a stabilising interaction with the tethered functional group, giving **I109**. Functional groups like ethers or unsaturated C–C bonds were shown to encourage the Ru chain walk by forming enol

ethers **I109a-I109b**, conjugated diene **I109c** and enyne **I109d**. Whilst the yields were good, the *E*:*Z* selectivity of the products were poor, with the best example delivering a 4.6:1 *E*:*Z* ratio of **I109c**.



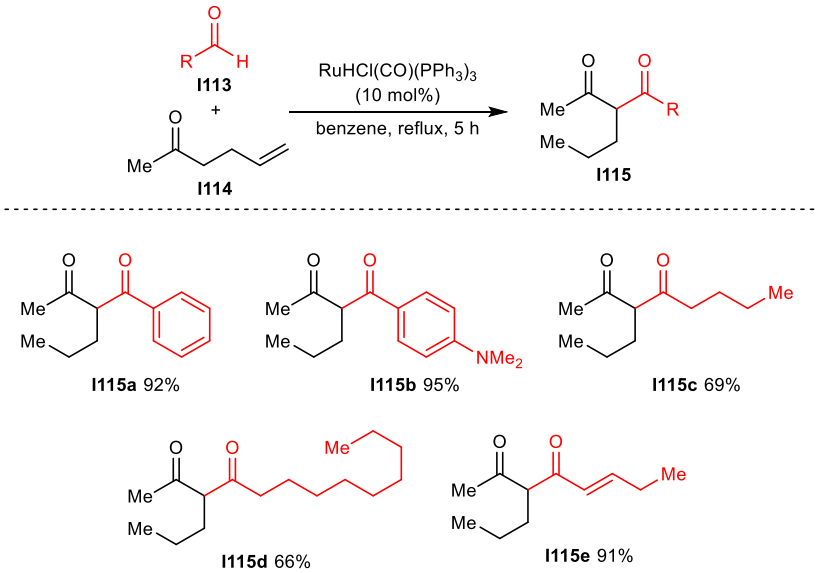
Scheme 29. Deconjugative isomerisation towards tethered FGs via Ru chain walking.

The last example in Scheme 29 shows Ru chain walking can also be driven by the formation of allyl Si, Sn or Ge reagents **I110**. This can provide a useful synthetic handle for further functionalisation at remote positions to rapidly increase molecular complexity.[66, 67] For example, nucleophilic bis-stannylated compound **I110a** underwent $BF_3{\cdot}OEt_2$ promoted allylation with benzaldehyde to form **I111**, which could be further functionalised to **I112** in 75% total yield after three steps (Scheme 30).



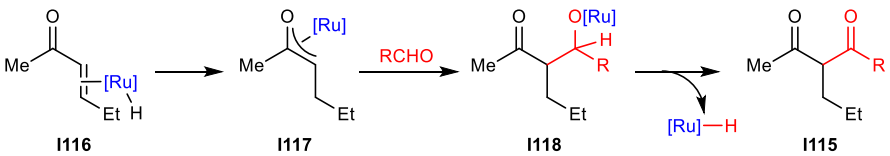
Scheme 30. Ru-catalysed olefin isomerisation can lead to remote nucleophilic allylations.

Ryu and co-workers have since reported a series of papers on Ru chain walking.[68-70] One such example involved a 1,3-diketone synthesis using a Ru-H-catalysed regioselective aldehyde addition.[69] It was noticed that unconjugated enones such as **I114** were able to participate in an aldol reaction with **I113** to form 1,3-diketones **I115** when refluxed with $RuHCl(CO)(PPh_3)_3$ in benzene (Scheme 31). Several aromatic and aliphatic aldehydes were tolerated, giving **I115a-I115e** in up to 95% yield.



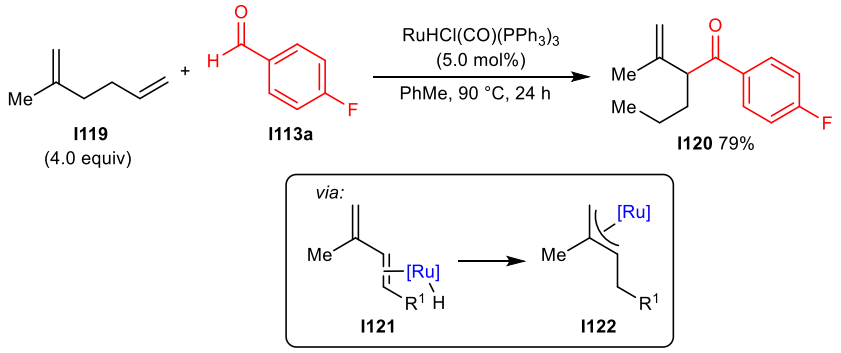
Scheme 31. Ru-H-catalysed isomerisation/aldol reaction of enones giving 1,3-diketones.

The isomerisation of the terminal olefin in **I114** is catalysed by Ru chain walking towards the carbonyl group, forming stabilised conjugated enone **I116**, which forms Ru enolate **I117** after another Ru-H reinsertion. Addition to the aldehyde then occurs to give **I118**, and *β*-hydride elimination regenerates Ru-H and gives 1,3-diketone **I115** (Scheme 32).



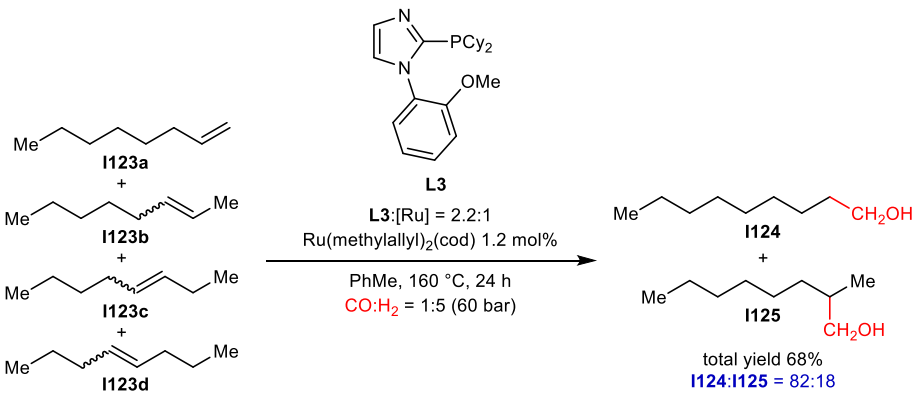
Scheme 32. Mechanism of Ru-H-catalysed synthesis of 1,3-diketones from enones and aldehydes.

Ryu later demonstrated that dienes could also follow a similar isomerisation/addition process to form unconjugated enones **I120** (Scheme 33). Using the same Ru-H catalyst in PhMe at 90 °C, the skipped 1,5-diene **I119** could isomerise via Ru chain walking to form 1,3-diene **I121**, which gives **I122** after Ru-H addition. Addition to aldehyde **I113a**, followed by *β*-hydride elimination generates **I120** in 79% yield.[70]



Scheme 33. Ru-H-catalysed isomerisation/allylation of dienes.

Inspired by his previous work on Rh tandem isomerisation/hydroformylations discussed in Section 1.1.2.1,[34] Beller subsequently used a Ru(methylallyl)$_2$(cod):**L3** 2.2:1 catalytic system to do a tandem isomerisation/hydroformylation/reduction to synthesise terminal alcohols from internal olefins. A mixture of octene isomers **I123a-I123d** gave nonanols **I124** and **I125** in 68% and a linear:branched ratio of 82:18 under these conditions (Scheme 34).[71]



Scheme 34. Tandem isomerisation/hydroformylation/reduction; internal olefins to linear alcohols.

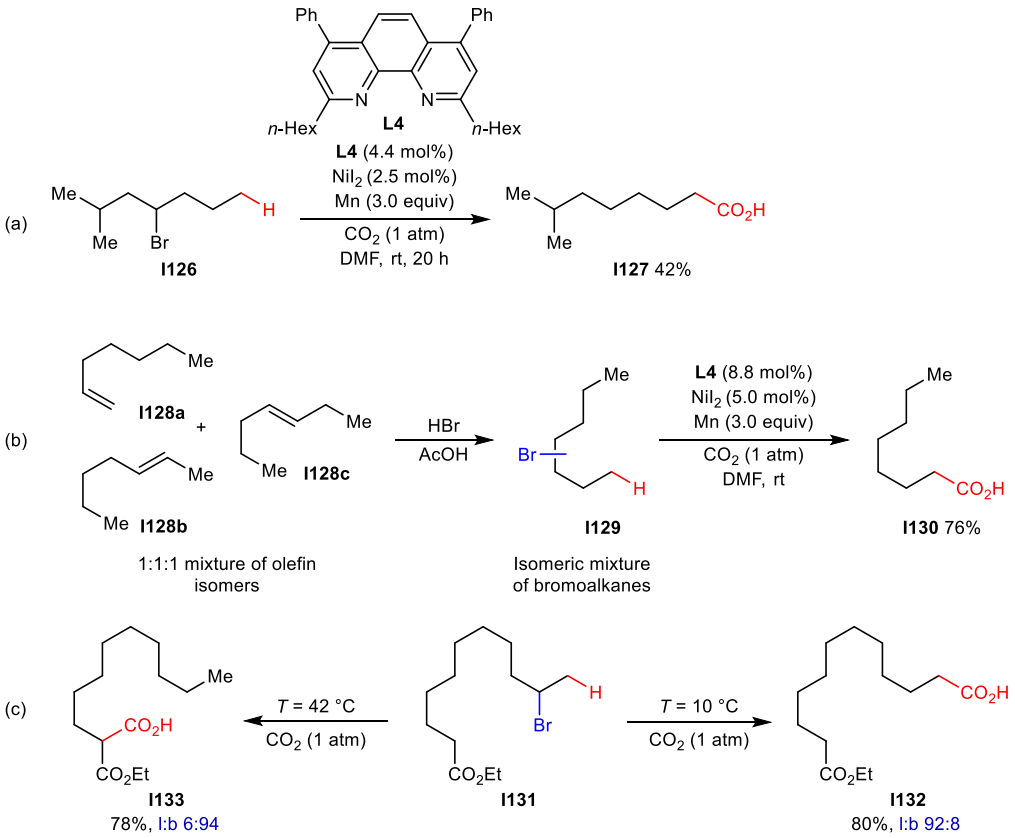
Whilst there are far fewer examples of ruthenium chain walking compared to palladium, the Ru examples often possess novel features, such as the formation of Ru-enolates to catalyse aldol-type reactions.

1.1.2.4 Nickel Chain Walking

Despite its applications in alkene polymerisation chemistry,[33] nickel has only recently emerged as a chain walking metal for synthetic transformations.[72] Nickel's place in the periodic table as

a first-row transition metal makes this especially valuable, as these are significantly more assessible, cheaper and sustainable compared to second- or third-row transition metals like Pd.[73]

In 2017 Martin demonstrated a powerful example of Ni chain walking in a remote carboxylation of halogenated aliphatic hydrocarbons using CO_2 as a feedstock.[74] Carboxylic acids are important functional groups, so producing them selectively from very simple hydrocarbons is valuable. Bromoalkane **I126** was transformed into terminal carboxylic acid **I127** in 42% yield (Scheme 35a), demonstrating selective remote functionalisation. NiI_2 with **L4** provided the active species under 1 atm of CO_2 in DMF at room temperature. A reductant was also required in this reaction, with Mn selected, and 3.0 equivalents were needed.

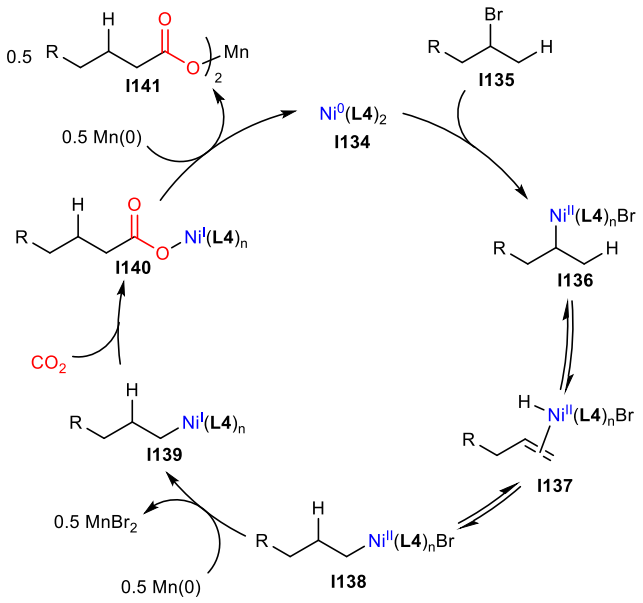


Scheme 35. Ni chain walking: remote carboxylation of aliphatic bromoalkenes with CO_2.

To further demonstrate the utility, this methodology was applied to a mixture of bromoalkanes **I129** obtained by hydrobromination of an equimolar mixture of heptene isomers **I128a-I128c**. The isomer mixture **I129** exclusively formed terminal carboxylic acid **I130** in 76% yield, showing Ni chain walks to the terminus of the chain, irrespective of where it starts off on it (Scheme 35b), possibly because only the primary alkylnickel species is reactive

enough to attack CO_2. Interestingly, the temperature could control the regioselectivity of this reaction with **I131** (Scheme 35c). Expected formation of **I132** was observed in 80% yield at 10 °C, but at 42 °C, Ni chain walked in the opposite direction towards the pendant ester group, with carboxylation occurring at the α-carbon to form **I133** in 78% yield.[74]

The reaction was proposed to proceed via initial formation of active catalyst Ni^0 *in situ* via reduction of the Ni^{II} precatalyst with Mn^0. Oxidative addition of generic alkyl bromide **I135** gave secondary alkyl Ni^{II} **I136**, which undergoes migration to the terminus of the chain via the β-hydride elimination/reinsertion chain walking sequence (**I136** to **I138**). Partial Mn reduction to Ni^I creates **I139**, which is a more nucleophilic species, and subsequently attacks CO_2 forming Ni-carboxylate **I140**. Finally reductive transmetalation with Mn forms manganese carboxylate **I141** and regenerates active Ni^0 to complete the catalytic cycle (Scheme 36).[74]

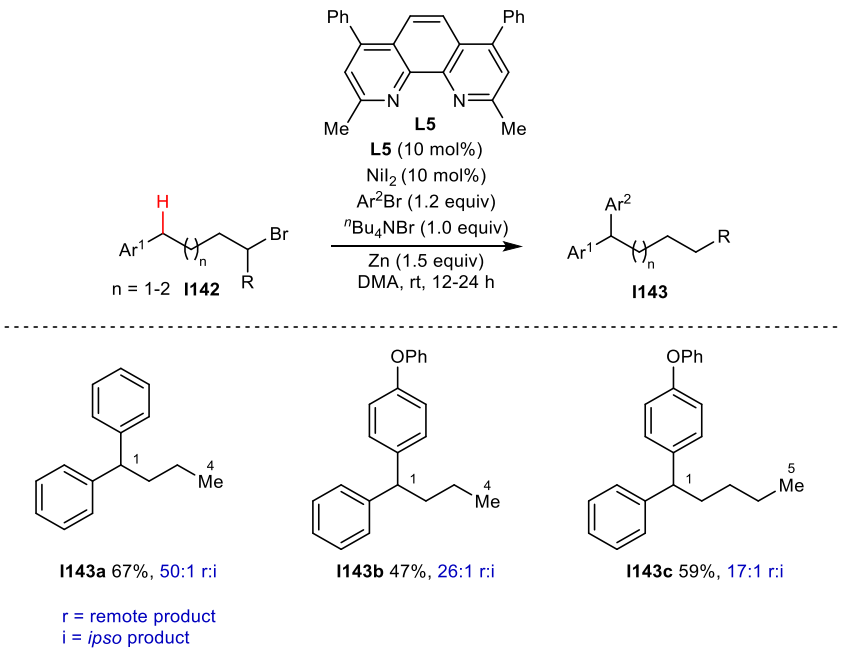


Scheme 36. Proposed mechanism.

Linking this cycle to the temperature dependant result observed in Scheme 35c suggests raising the temperature may favour the reverse migration direction. The formation of a conjugated olefin adjacent to the ethyl ester via β-hydride elimination may be promoted at higher temperatures, leading to **I133**.

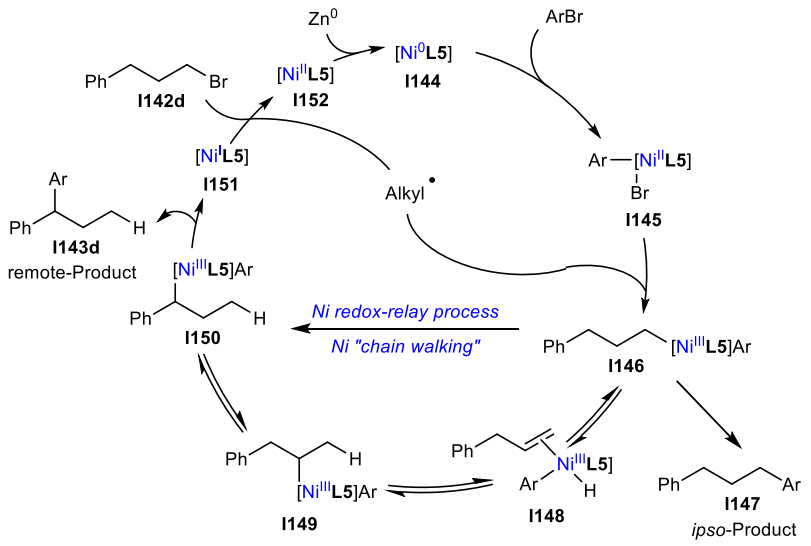
In 2018 Yin provided further compatibility of bromoalkanes with Ni chain walking, describing the reductive relay cross coupling of alkyl bromides **I142** with easily accessible aryl bromides.[75] NiI_2 and bathocuproine ligand **L5** (both 10 mol%) were used, with 1.5 equivalents of Zn as the reductant in DMA at room temperature. $^tBu_4NBr$ (1.0 equivalent) was critical for

the formation of remote 1,1-diaryl products **I143**. Simple diaryl **I143a** was formed in 67% yield with significant 50:1 favourability of the branched product compared to the ipso-substituted product. As the aryl bromide and chain length of **I142** was varied, the yields and *r*:*i* (remote:ipso) selectivities remained good, with **I143b** (47% yield and 26:1 *r*:*i*) and **I143c** (59% yield and 17:1 *r*:*i*) formed (Scheme 37).



Scheme 37. Reductive relay cross-coupling via Ni chain walking.

Active Ni^0 catalyst **I144** is generated by Zn^0 mediated *in situ* reduction of Ni^{II} (Scheme 38). **I144** then participates in a selective oxidative addition of the aryl bromide by a two-electron-transfer pathway to form **I145**. This reacts with the alkyl radical generated through single-electron transfer from **I142d**, forming Ni^{III} species **I146**, which can follow one of two pathways. Direct reductive elimination yields the *ipso*-coupling side-product **I147**. Alternatively the rapid Ni chain walking process (**I146** to **I150**) results in Ni^{III} at the benzylic position in **I150**, which undergoes reductive elimination to give the remote product **I143d** and Ni^{I} species **I151**. Another molecule of **I142d** provides the alkyl radical that generates more Ni^{III} **I146** and also results in Ni^{II} **I152** which is reduced again by Zn^0 to complete the cycle. Changing the ligand affects the favourability of the two pathways and the *r*:*i* ratio as a result.[75] The methyl groups at the 2- and 9- positions in **L5** likely hinder reductive elimination to *ipso*- product **I147**, which is the major product in the absence of the 2,9-dimethyl substituents, meaning the *β*-hydride elimination step to **I148** is more favoured.



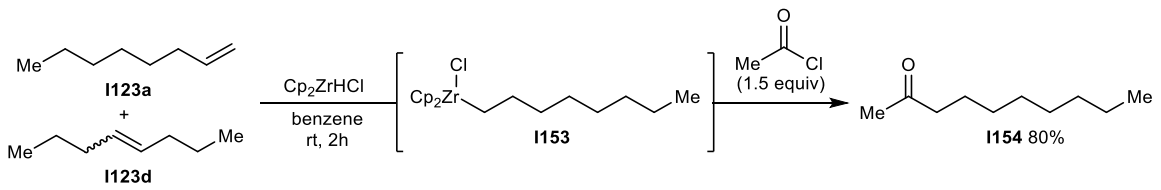
Scheme 38. Proposed mechanism of Ni-catalysed reductive relay cross coupling.

Despite its significant utility in chain walking polymerisation,[33, 76-79] nickel has only been explored as a chain walking metal for organic synthesis very recently. It has already been shown to catalyse some impressive remote reactions,[80] including the selective formation of important carboxylic acids from bromoalkane mixtures amongst others.[72, 81, 82]

1.1.2.5 Zirconium Chain Walking

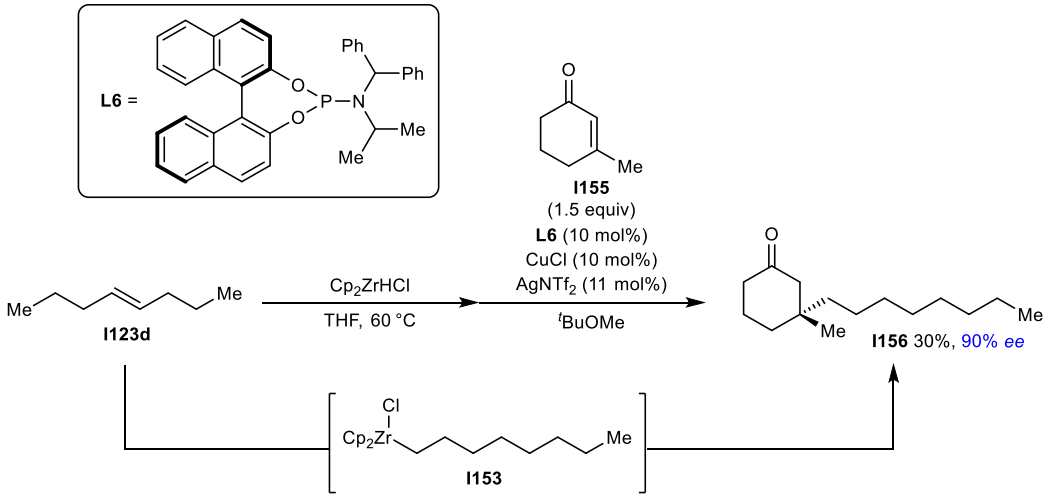
As an early transition metal, zirconium behaves slightly differently to most of the other chain walking metals, which tend to fall later in the periodic table. In some scenarios, it has been shown to follow the classic elimination/reinsertion chain walk mechanism, however in others, it proceeds via 1,3-hydrogen shift (Scheme 7b).

In 1974, Schwartz reported a hydrozirconation of octenes **I123**, seeing Zr migrate towards the terminus of the chain as the least sterically hindered position **I153**.[83] This intermediate was trapped with various electrophiles such as ethanoyl chloride to give functionalised products such as **I154** (Scheme 39). A range of studies into the mechanism determined it proceeds via *β*-hydride elimination/reinsertion of Zr-H.[84, 85]



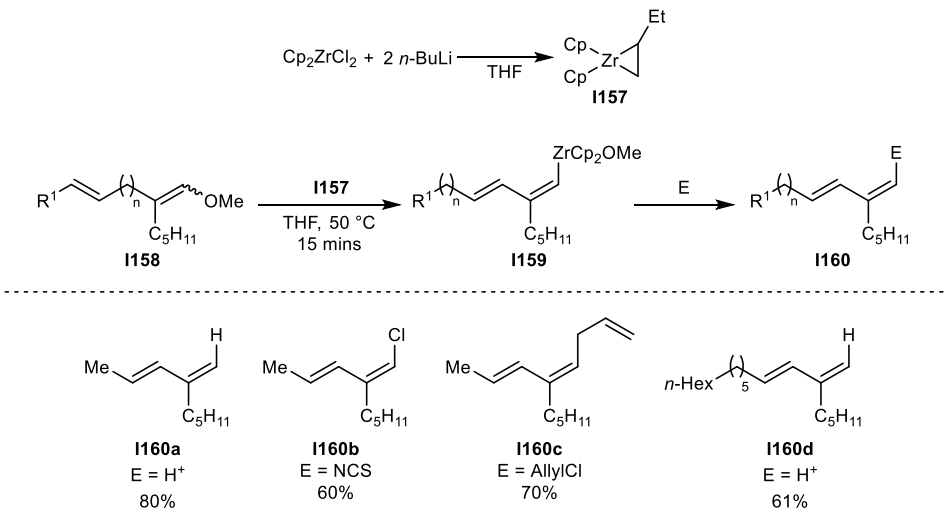
Scheme 39. Hydrozirconation of internal olefins sees Zr chain walking to chain terminus.

This was applied to an enantioselective reaction by Fletcher in 2015, where intermediate **I153** can immediately participate in an asymmetric 1,4-addition to **I155** using catalytic CuCl, a phosphoramidite ligand **L6**, and $AgNTf_2$ as an additive (Scheme 40). This led to the formation of more complex products such as **I156** in 30% yield and 90% *ee*.[86]



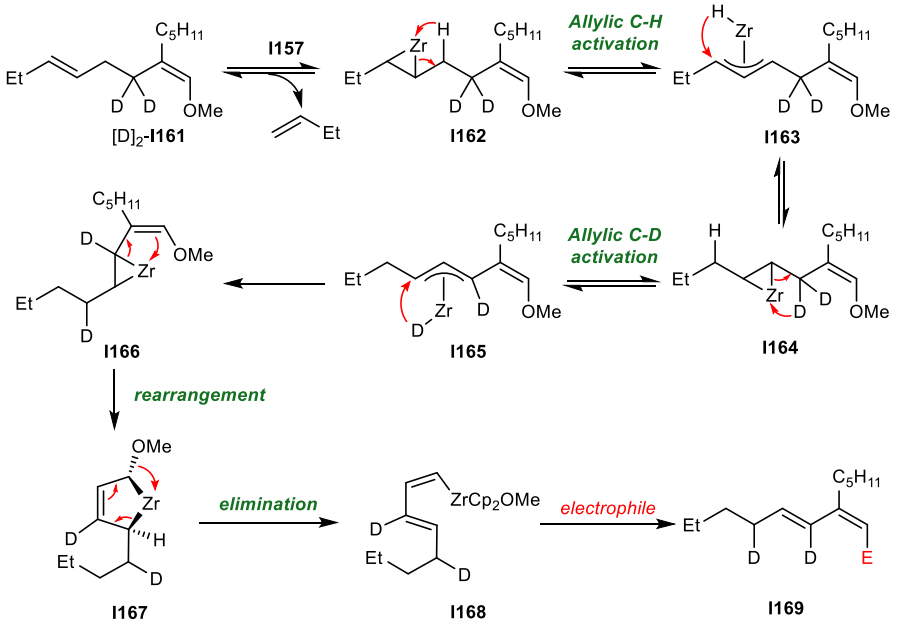
Scheme 40. Enantioselective 1,4-addition after Zr chain walk event.

The largest body of work on Zr migration is from the group of Marek and co-workers. Since 2002, they have released a series of papers, starting with a stereoselective synthesis of dienes using **I157** to facilitate isomerisation/elimination sequences (Scheme 41).[87, 88] **I157** is made *in situ* from the reaction of Cp_2ZrCl_2 and *n*-BuLi, and when skipped diene **I158** was subjected to **I157** in THF at 50 °C, it quickly isomerised to form conjugated metalated diene **I159**, which can be trapped by external electrophiles. **I160a-160c** were formed in 60-80% yield respectively using proton, chlorine or allyl electrophiles respectively. In addition, the diene migrated over five methylene units to give **I160d** with no noticeable decrease in yield (61%).



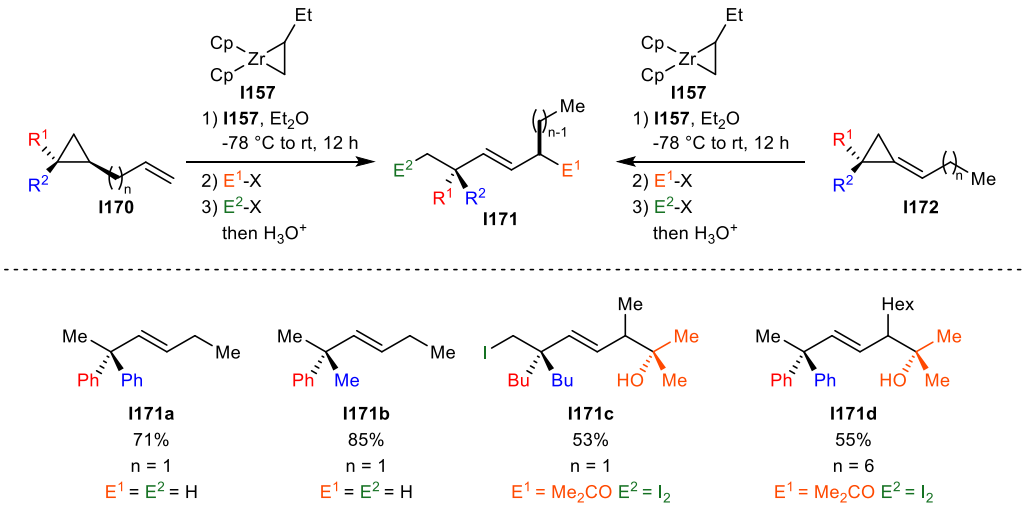
Scheme 41. Zirconium mediated diene conjugation and remote functionalisation.

Marek proved that in these examples, Zr exhibited a slightly different isomerisation mechanism to the commonly observed 1,2-hydrogen shift, as shown when deuterated diene $[D]_2$-**I161** was subjected to the reaction conditions (Scheme 42). After exchange with **I157** to give zirconacyclopropane **I162**, allylic C–H activation gave η^3-allyl intermediate **I163**. New zirconacyclopropane **I164** is formed after hydride reinsertion, which then undergoes allylic C-D activation to give **I166** after Zr–D reinsertion at **I165**. **I166** rearranges to yield zirconacycle **I167** which collapses to give Zr-diene **I168**. The reactive C–Zr bond is easily quenched by an electrophile to give **I169**. This olefin isomerisation clearly proceeds through a 1,3-hydrogen shift mechanism as confirmed by the relationship between the two deuterium atoms in **I169** after one is exclusively shifted two carbons down the chain.[88]



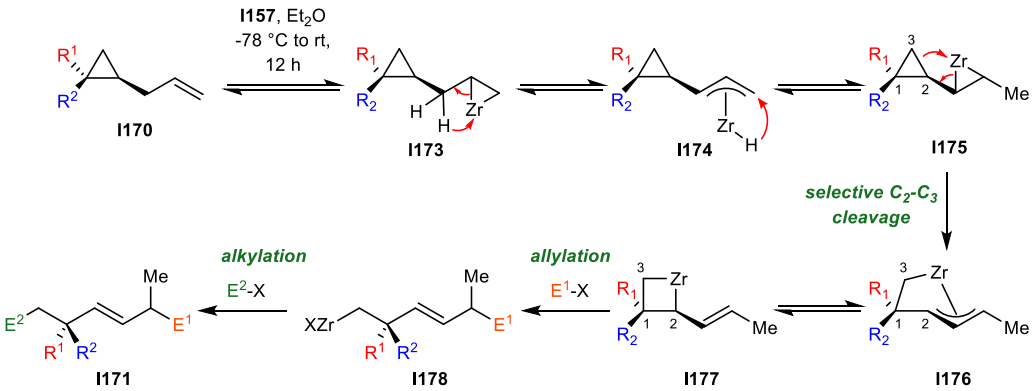
Scheme 42. 1,3-shift of a D atom shows mechanistic differences to traditional chain walking.

Further applications of this work included fatty alcohol derivatives,[89] and remote functionalisation via opening cyclopropanes.[90] Using **I157** in Et_2O, **I170** could oversee isomerisation of its tethered olefin to the cyclopropane ring and selective C–C cleavage to give acyclic products **I171** after reactions with electrophiles at opposite ends of the chain. Identical products were also obtained using alkylidenecyclopropane **I172** (Scheme 43). Migration over 1-6 carbons was possible and several different electrophiles including protons, halogens and carbonyls were tolerated giving a variety of products including **I171a-I171d** in up to 85% yield.



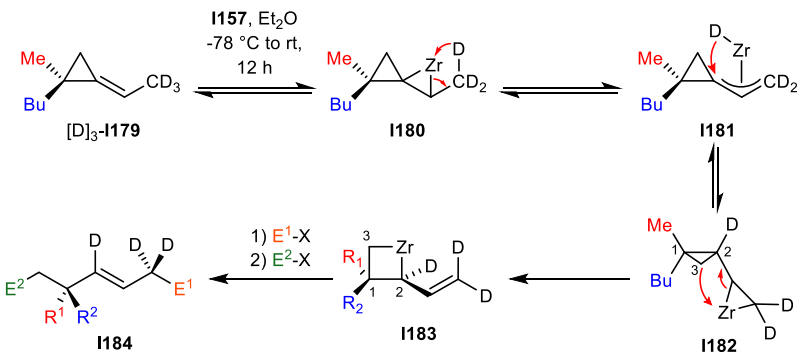
Scheme 43. Zr mediated olefin isomerisation/selective ring opening event.

The alkene isomerisation occurs in similar circumstances to Scheme 42, via 1,3-hydrogen shift (**I173** to **I175**) (Scheme 43). **I175** then undergoes selective C_2–C_3 cleavage, to give **I176** which exists in equilibrium with zirconacyclobutane **I177**. The C_2–C_3 cleavage is favoured as breaking C_1–C_2 would give a more sterically encumbered tertiary Zr species. **I177** has two reactive bonds; the more reactive allylic Zr–C_2 bond is quenched first with an electrophile E^1 to give **I178** before the alkyl Zr–C_3 bond reacts with E^2 to yield **I171**.



*Scheme 44. Proposed mechanism for tethered alkene-cyclopropane **I170**.*

When deuterated alkylidenecyclopropane $[D]_3$-**I179** was used, the reaction is believed to proceed via an alternative mechanism, where **I180** transforms into **I182** after allylic C–D activation/reinsertion (via **I181**). **I182** then undergoes C_2–C_3 cleavage to form zirconacyclobutane **I183**, which is quenched with two electrophiles to give **I184** (Scheme 45).[90]



*Scheme 45. Proposed mechanism for alkylidene cyclopropane $[D]_3$-**I179**.*

There are a number of important points to note here. Firstly, this work is a rare example of using a C–C bond breaking process as the irreversible step that provides the thermodynamic

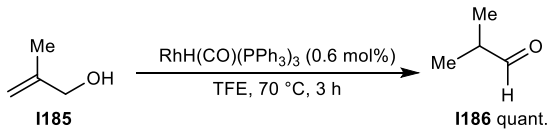
driving force for the reversible Zr assisted alkene isomerisation. The majority of the other processes discussed typically use bond formation to achieve this.

Secondly, the second addition of an electrophile provides functionalisation remote from the site of initiation, with the two separated by a quaternary centre. This is notable as it would not be possible by the standard chain walking process, as β-hydride elimination is not possible at the quaternary centre. Therefore, the cyclopropane ring opening event allows the metal to 'vault' over the quaternary centre and functionalise previously inaccessible sites. This was later exploited by combining it with Sigman's Pd chain walking work in Section 1.1.2.2, uniting the Heck redox relay process with a cyclopropane ring opening event.[91]

Zirconium is one of the only early transition metals to exhibit remote functionalisation via olefin isomerisation. Consequently, it often behaves differently to late transition metals, which more commonly facilitate these chain walking processes, with many examples of Zr-catalysed olefin isomerisation proceeding via a 1,3-hydrogen shift mechanism.[92]

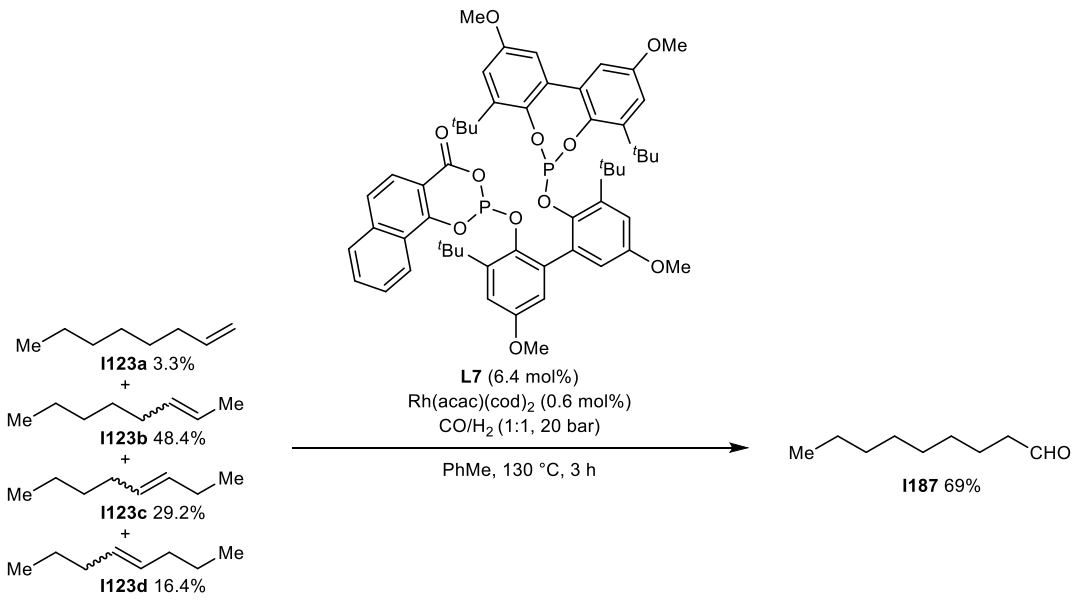
1.1.2.6 Rhodium Chain Walking

Historically, Rh has been shown to isomerise allylic alcohols **I185** into carbonyl compounds **I186** as demonstrated by Strohmeier in 1975 (Scheme 46).[93, 94]



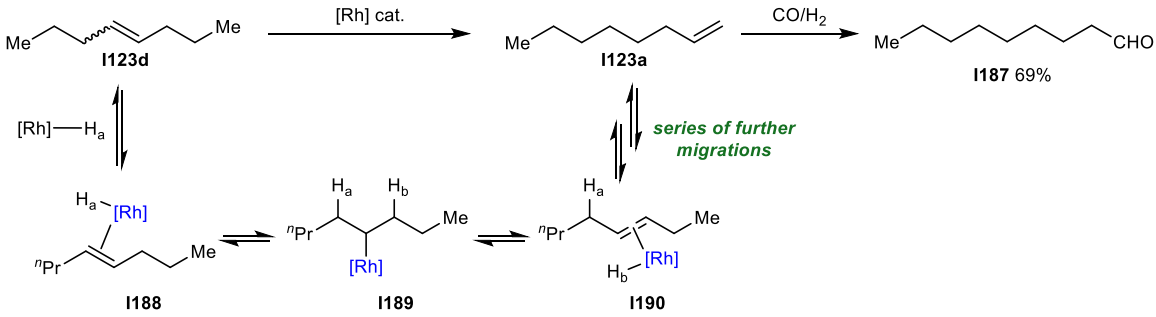
Scheme 46. Transposition of allylic alcohols to carbonyl compounds

As briefly mentioned previously, Rh is known to catalyse the tandem isomerisation-hydroformylation of internal olefins to give linear aldehydes, which can be further manipulated to give different products like linear amines or alcohols.[34, 35, 95-97] One of the best early examples was reported by Selent, who used novel phosphorus ligand **L7** and $Rh(acac)(cod)_2$ in low catalyst loading to give 69% **I187** from octene mixture **I123a-I123d** after heating for 3 h in PhMe at 130 °C (Scheme 47).[35]



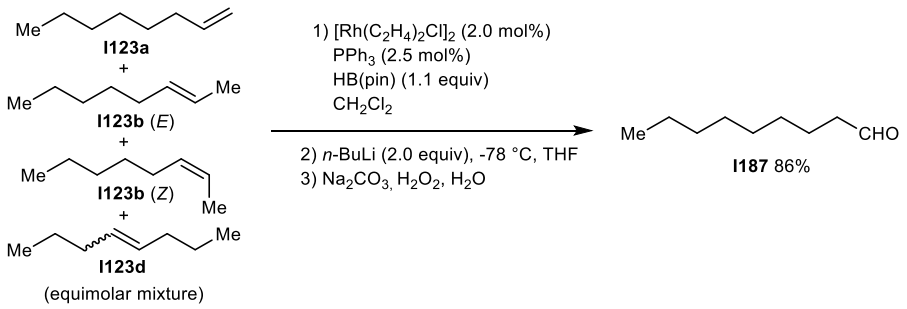
Scheme 47. Early Rh-catalysed isomerisation/hydroformylation.

This proceeds via the expected Rh chain walking mechanism to get terminal olefin **I123a** before hydroformylation gives **I187** (Scheme 48).



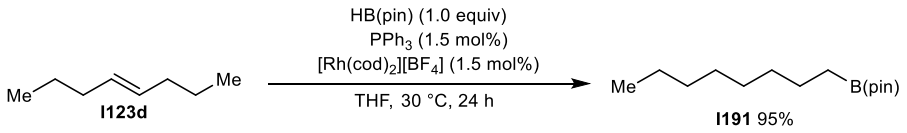
Scheme 48. Rh-catalysed isomerisation/formylation mechanism.

These hydroformylations use a mixture of CO/H_2 known as 'syngas' to install the aldehyde, with high temperatures and pressures often required.[34, 96] This requirement can be circumvented using a method developed by Crudden, who reported a CO-free hydroformylation reaction under significantly milder conditions (Scheme 49).[98] **I123a-I123d** were transformed into **I187** using catalytic $[Rh(C_2H_4)_2Cl]_2$ and PPh_3 via Rh-catalysed isomerisation and hydroboration of **I123a** with HB(pin) to give an alkylboronate which forms **I187** after sequential addition of *n*-BuLi (2.0 equivalents) and $NaHCO_3$, H_2O_2 and H_2O.



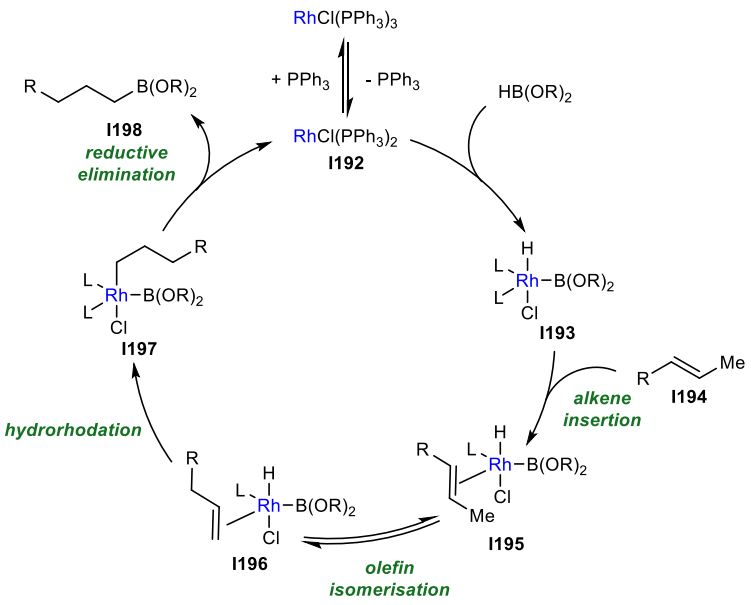
Scheme 49. CO-free hydroformylation using Rh chain walking.

In the same paper, Crudden also showed that under similar reaction conditions the Rh-catalysed tandem isomerisation/hydroboration process was able to isolate boronate **I191** in 95% yield, from **I123d**. $[Rh(cod)_2][BF_4]$ and PPh_3 catalysed the reaction at 1.5 mol% loading using THF as a solvent and heating to 30 °C for 24 h (Scheme 50).[98]



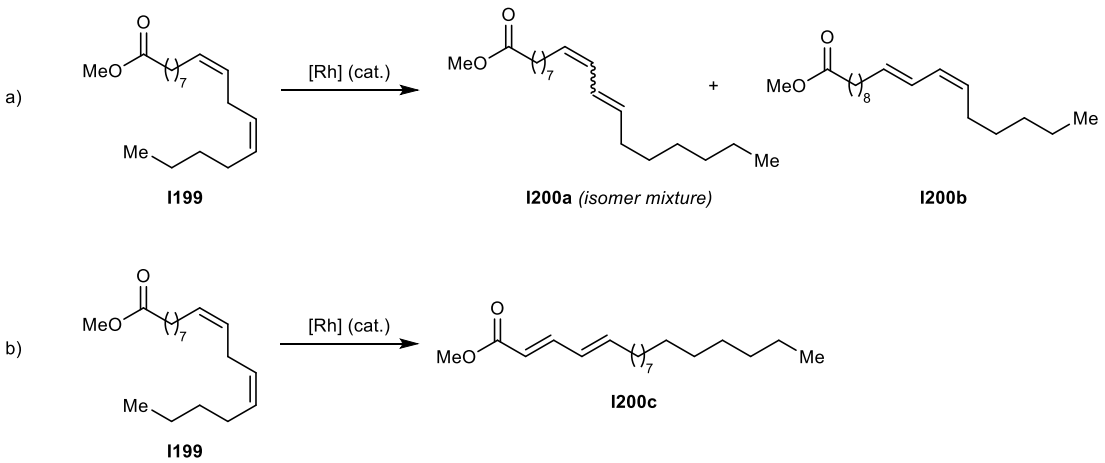
Scheme 50. Rh-catalysed isomerisation/hydroboration.

Mechanistic investigations by Noth,[99] Evans [100] and others [101, 102] determined it was Rh taking part in the chain walking process and not boron, which is known to migrate at high temperature.[21] This culminated in a proposed mechanism using a Rh^I catalyst such as Wilkinson catalyst $RhCl(PPh_3)_3$ (Scheme 51). Loss of a PPh_3 ligand frees up a site on Rh in **I192**. Oxidative addition of the B–H bond gives Rh–H **I193** which coordinates and isomerises alkene **I194** (**I195** to **I196**) with reinsertion placing Rh at the chain terminus **I197**. Reductive elimination forms the C–B bond in **I198** and completes the cycle.[99]



Scheme 51. Rh-catalysed isomerisation/hydroboration mechanism.

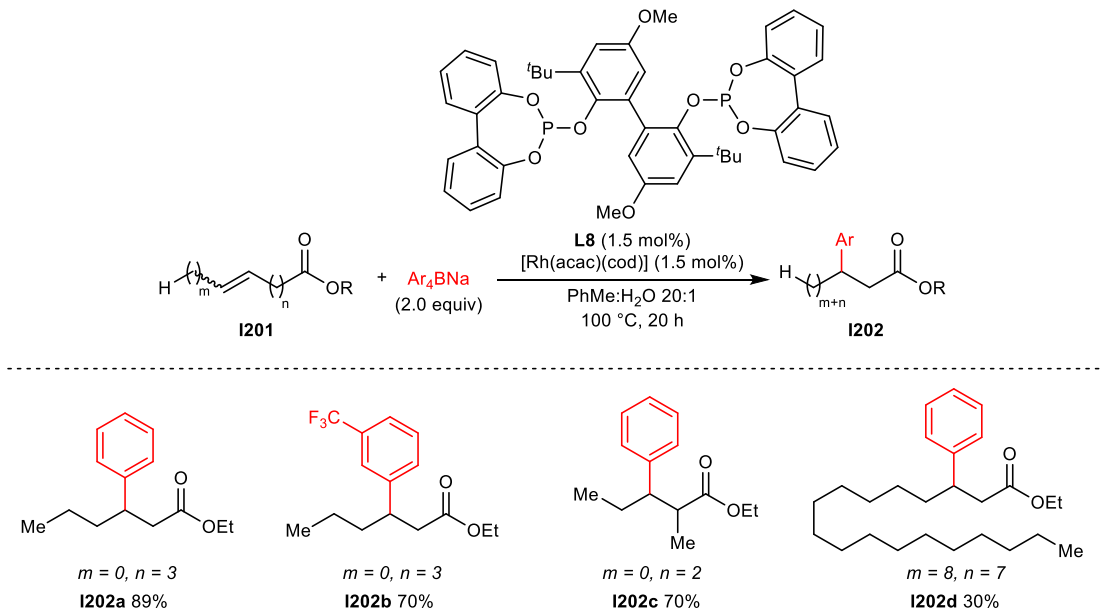
There are several other examples of Rh chain walking in the literature. One such example was an observation from Behr in 2013 on the isomerisation of FAMEs (fatty acid methyl esters), which has been notably studied before.[103] When using a Rh catalytic system to perform the isomerisation of methyl linoleate **I199** to its conjugated methyl linoleate derivatives (**I200a-I200b**) (Scheme 52a), Behr also noticed small amounts of unsaturated ester **I200c** after prolonged reaction times (Scheme 52b).[104]



Scheme 52. Rh mediated isomerisation sees long range migration of dienes.

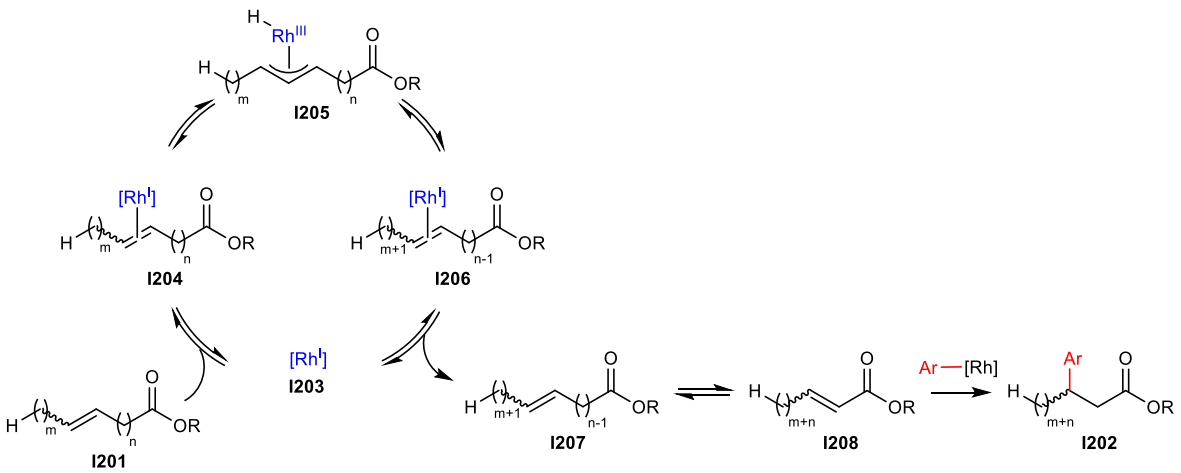
More utility with unsaturated esters has been displayed by Gooβen who reported another example of olefin isomerisation towards ester groups coupled with conjugate

addition.[105] Ar_4BNa (2.0 equivalents) supplied the C-nucleophile to create a new C–C bond to form *β*-arylation products **I202** after migration from **I201** (Scheme 53). The transformation was facilitated by 1.5 mol% of a Rh(acac)(cod)/biphephos **L8** catalytic system in a 20:1 solution of PhMe:H_2O at 100 °C. Isomerisation over two or three carbon units was promoted and different aryl borates were well tolerated (**I202a-I202c**) in >70% yield. Long range isomerisation was also observed on an unsaturated fatty ester derivative, seeing arylation after Rh chain walking over 7 carbon units to give **I202d**, although the yield did drop significantly to 30% in this case.



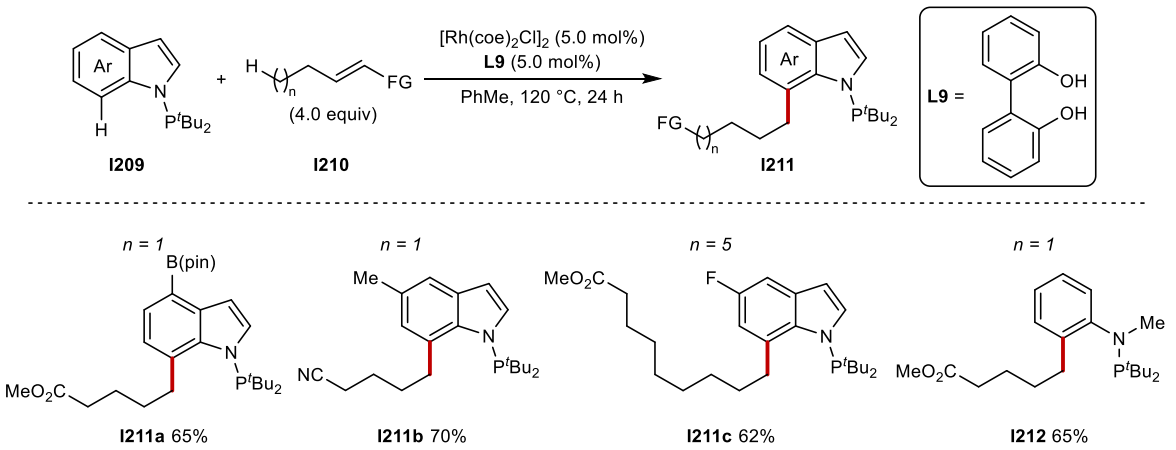
Scheme 53. Tandem Rh-catalysed isomerisation/conjugate addition.

As there was no obvious source of Rh–H formed *in situ*, the authors proposed an isomerisation catalytic cycle via 1,3-hydrogen shift. After coordination of **I201** to Rh^I, the migration can occur via η^3-allyl species **I205** to give isomerised olefin **I207** (Scheme 54). This process is completely reversible and continues to happen rapidly until conjugated enone **I208** is obtained. Arylrhodium Michael addition gives **I202** as the termination step that drives the migration equilibrium. In the same paper, this was extended to nitrogen nucleophiles to form *β*-aminoesters.[105]



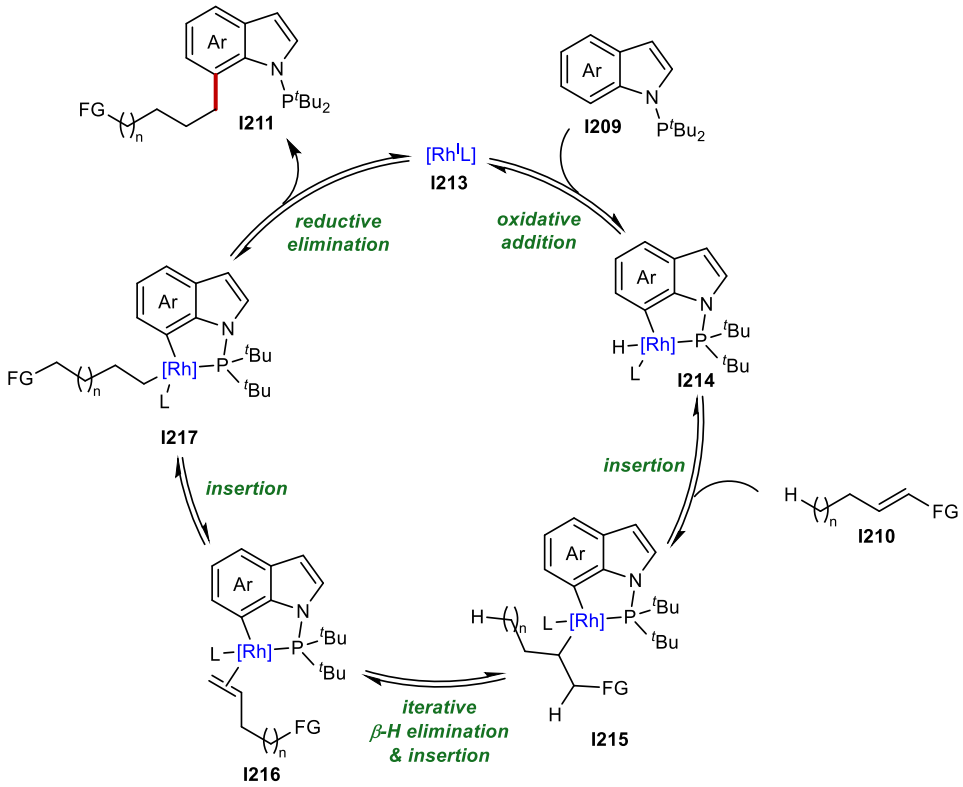
Scheme 54. Postulated mechanism of the isomerisation/conjugate addition.

Finally, a recent example was reported by Shi in 2018. This method uses a directed Rh C–H activation to initiate a deconjugative chain walking event.[106] $[Rh(coe)_2Cl]_2$ and BINOL **L9** provide the catalytic system and refluxing with indole **I209** and **I210** in toluene for 24 h sees C–C bond formation exclusively between the indole C7 position and the terminal carbon of **I210**, forming indoles **I211** (Scheme 55). A range of different indole substituent patterns were tolerated (**I211a** in 65% yield), whilst deconjugation from non-ester groups like nitriles (**I211b** in 70% yield) and long-range chain walking over up to 8 carbon units (62% yield for n = 5 in **I211c**) were also exhibited. The P^tBu_2 directing group could also facilitate C–H activation of aniline instead of an indole to give **I212** in 65% yield. The P^tBu_2 directing group is easily removed from the indole after the activation event.



Scheme 55. Remote terminal hydroarylation of olefins via deconjugative isomerisation.

This transformation is initiated by directed oxidative addition of the C–H bond using Rh^{I} **I213** to give 5-membered rhodacycle **I214** (Scheme 56). This step also generates the Rh–H bond which adds into the olefin **I210** in the next step to give alkylrhodium **I215**. Rh then chain walks via the iterative *β*-hydride elimination/reinsertion pathway to give **I217** with rhodium at the terminal carbon (via isomerised olefin **I216**). Reductive elimination completes the cycle and forms the new C–C bond in the product **I211**.[106]



Scheme 56. Proposed catalytic cycle.

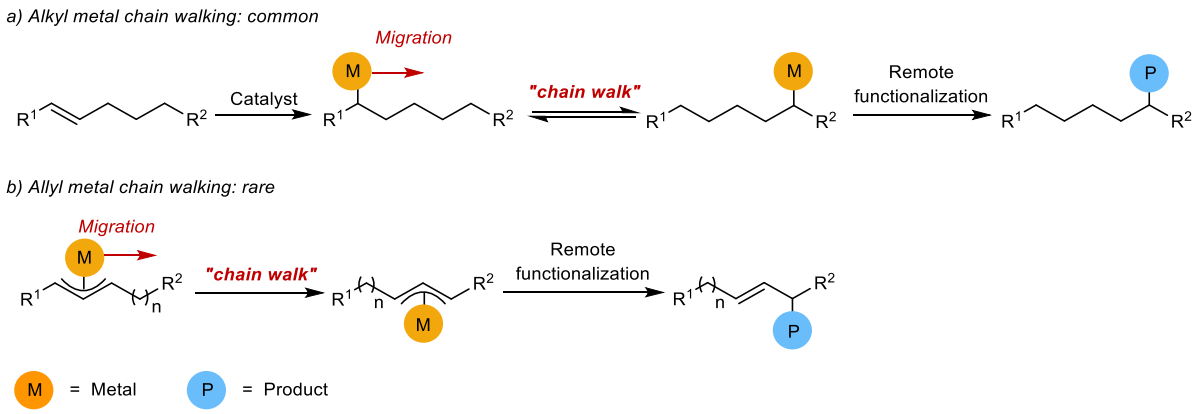
Rhodium is another transition metal which readily isomerises alkenes to deliver remote functionalisation products. It has been shown to facilitate isomerisation via different mechanisms,[105] and exploits different methods to initiate the process, including C–H activation of indoles.[106]

1.1.3 Alternatives to Alkylmetal Chain Walking

1.1.3.1 Transmission of Non-Olefin Functional Groups via Chain Walking

Remote functionalisation via alkene isomerisation is a rapidly developing field and numerous transition metals participate in chain walking along carbon chains as demonstrated throughout Section 1.1.2. In simplified terms, the net result of these chain walking processes can be

described as; 1) metal-catalysed transmission of an alkene functional group along a carbon chain to a remote position (via alkylmetal chain walking) and 2) a reaction of the migrated alkylmetal species with an external species to give products with functionalised sites remote from the position of initiation (Scheme 57a).

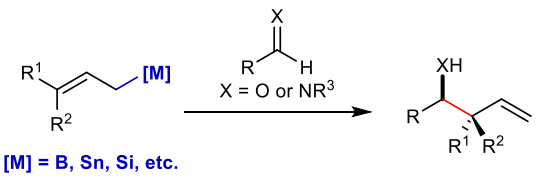


Scheme 57. Alkylmetal vs. allylmetal chain walking.

However, other types of metal chain walking along a carbon chain to initiate remote functionalisation reactions are very rare. If groups other than alkylmetal species (which usually lead to simple alkylation products) could chain walk, this would potentially lead to a far wider range of transformations available.

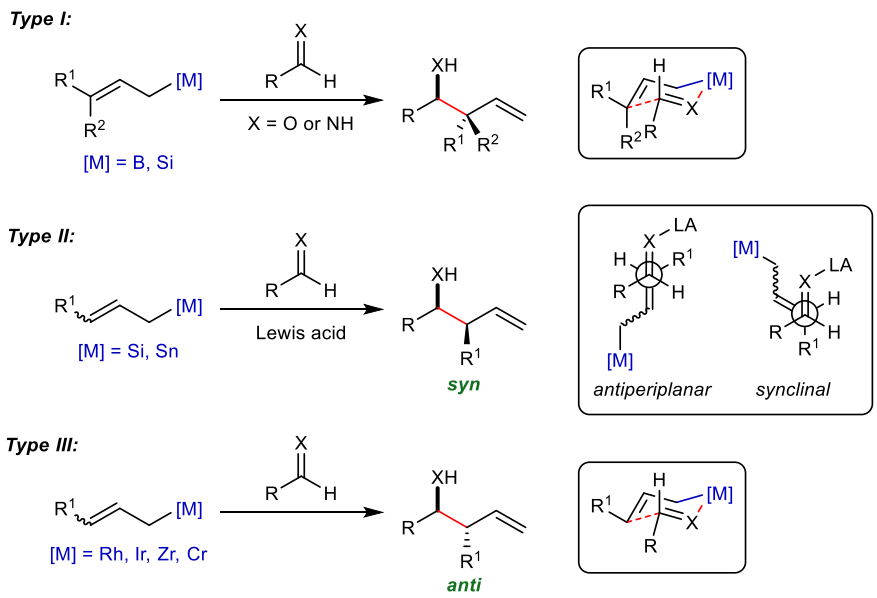
For example, chain walking of an allylmetal species would provide remote allylation products (Scheme 57b), which are more valuable than simple alkylation products in several ways:

1) Allylmetal species participate in a range of different electrophilic and nucleophilic allylation reactions.[67, 107-111]
2) Nucleophilic allylations of π-electrophiles like carbonyls and imines are well established for a myriad of different allylmetal species (Scheme 58).[67] These can be added directly or formed *in situ* to give valuable homoallylic alcohol or amine products, which can be used in the synthesis of intermediates for many natural products or biologically active compounds.[112]



Scheme 58. General nucleophilic allylation of π-electrophiles.

3) These allylations can also install a lot more stereochemical information into the final products (two contiguous stereocentres and an olefin). This is often controllable as nucleophilic allylations proceed via one of three transition state types: Type I, Type II and Type III. (Scheme 59).[67, 113-116] This means stereochemical information could be installed at a remote site in a molecule that had none to begin with.
4) Products also contain an alkene which can act as a useful synthetic handle to further manipulate the products.



Scheme 59. Three types of nucleophilic allylation transition state.

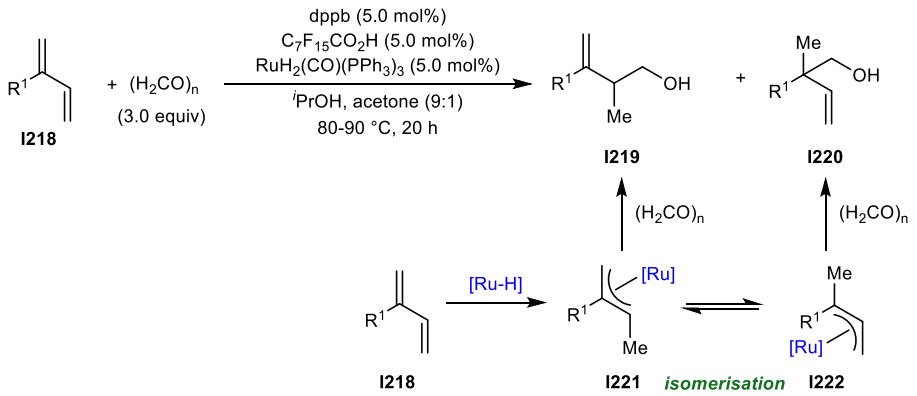
For the Type I transition state, the geometry of allylmetal species determines stereochemistry of the product, with *Z*- giving *syn* products and *E*- giving *anti*. With Type II, the *syn* product always forms and the allylation occurs via an open transition state with *antiperiplanar* or *synclinal* orientation. Finally Type III is a closed transition state similar to Type I, but always forms *anti* products as rapid equilibration of allylmetal intermediates form the thermodynamically favourable *E*-isomer.

Finally, it is important to distinguish between allylmetal chain walking and the 1,3-hydrogen shift mechanism previously discussed (Scheme 7b). The 1,3-hydrogen shift mechanism possesses allylmetal intermediates which are used as a pathway to isomerise alkenes via *alkylmetal* chain walking, usually via an allylic C–H activation process.[6] *Allylmetal* chain walking is distinct in that it is the allylmetal species takes the place of the alkylmetal

species, and it is this allylmetal group that isomerises along the carbon chain, usually via a *β*-hydride elimination/hydrometallation sequence (Scheme 57b).

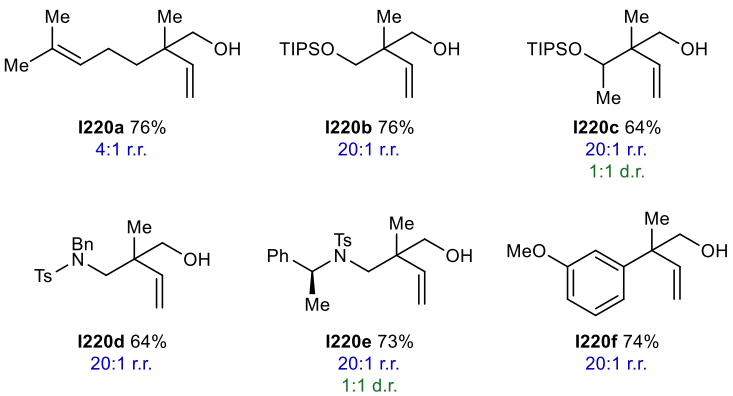
1.1.3.2 Isomerisation of Allylmetal Species

There are very few examples in the literature of tandem allylmetal isomerisation/allylation reactions. With allyl Ru complexes known to readily isomerise,[117] Krische used ruthenium to catalyse the formation of homoallylic alcohols **I220** with a quaternary centre at the 2-position from diene **I218** and paraformaldehyde (Scheme 60).[118] The active catalyst $RuH(O_2CC_7F_{15})(CO)(dppb)(PPh_3)$ was prepared *in situ* from dppb, $C_7F_{15}CO_2H$ and $RuH_2(CO)(PPh_3)_3$.Heating for 20 h in a 9:1 solution of ^{i}PrOH:acetone led to the formation of allyl Ru species **I221** after Ru-H addition across the diene. However, isomerisation to **I222** is heavily favoured over direct allylation with paraformaldehyde, meaning **I220** forms preferentially over **I219**.



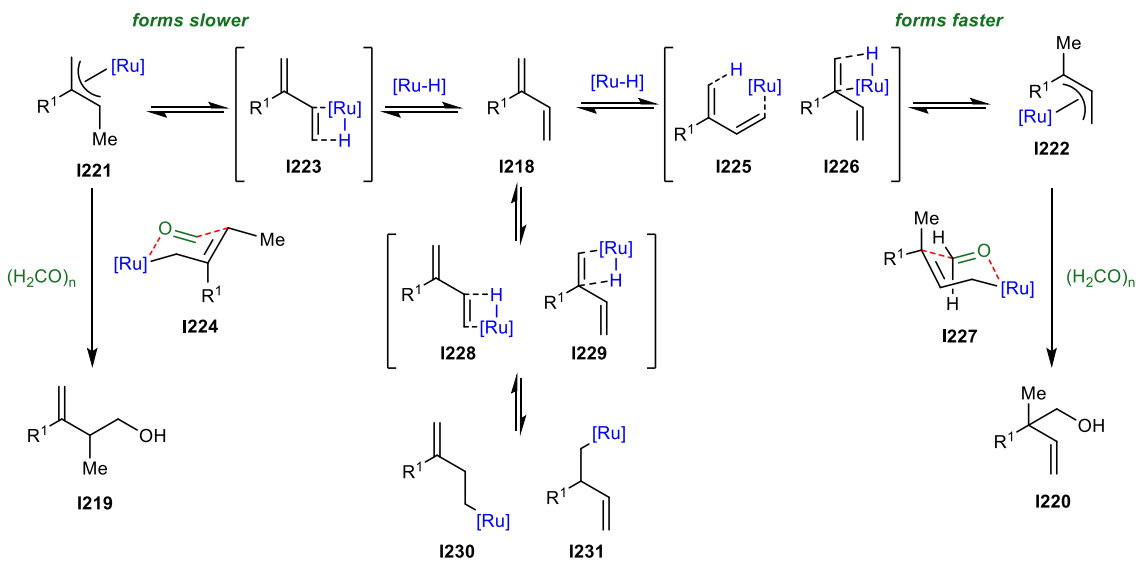
Scheme 60. Allyl Ru isomerisation to give C2 allylation products with dienes.

A range of different C2 allylation products are formed from dienes like myrcene **I220a** (76% yield), silyl protected alcohols **I220b-I220c** (64-76% yield), protected sulphonamides **I220d-I220e** (64-73% yield) and aryl groups **I220f** (74% yield) (Scheme 61). The regioisomeric ratio of C2 vs C3 allylation products **I220**:**I219** is excellent for most examples (>20:1 r.r.).



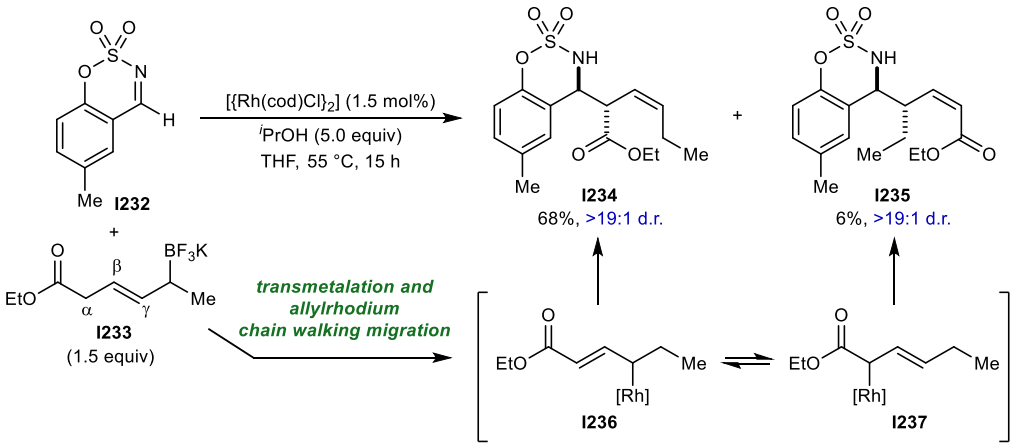
Scheme 61. C2 allylation products of allyl Ru isomerisation/allylation.

Krische proposed that the relative energies of the transition state structures for carbonyl addition dictate the product distribution. The mechanism is consistent with a diene hydrometallation and β-hydride elimination process at different positions on **I218** (Scheme 62). Addition can occur across three pathways: Ru-H addition via **I223** to form allyl Ru **I221**, Ru-H addition via **I225** or **I226** to form allyl Ru **I222**, or addition via **I228** or **I229** to form homoallylic Ru species **I230** or **I231**. Homoallylic Ru **I230** and **I231** do not react further and just reform **I218** due to the reversibility of the isomerisation process. **I222** forms much faster than **I221**. The allylation process is favoured for **I222** as its bulky C2-substituent at R^1 can occupy a lower energy equatorial position in six-membered closed transition state **I227**. In competing allylation **I224**, R^1 is forced to occupy an axial position in a higher energy transition state. These factors significantly favour formation of **I220** over **I219**.[118]



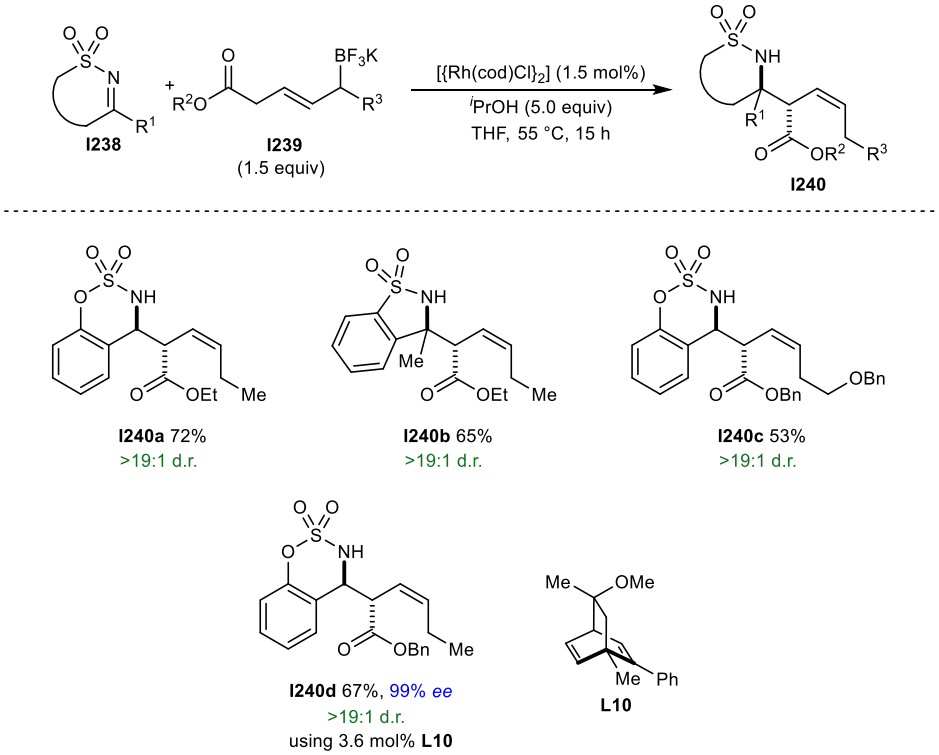
Scheme 62. Proposed mechanism.

Within the Lam group, there has been a lot of work on allyl Rh-catalysed nucleophilic additions of allyltrifluoroborates to π-electrophiles like cyclic imines.[119-121] When exploring the scope of the allyltrifluoroborates with tethered ester groups such as in **I233**, a surprising allylation product was formed with cyclic imine **I232**. Allylation was initially expected at the *β*-position of **I233**, however 68% of *α*-allylation product **I234** and 6% of *γ*-allylation product **I235** were obtained instead (Scheme 63).[122] This was a clear indication of an allyl Rh isomerisation to **I236** or **I237**, and the first observed example of allylmetal chain walking directed towards a particular functional group.



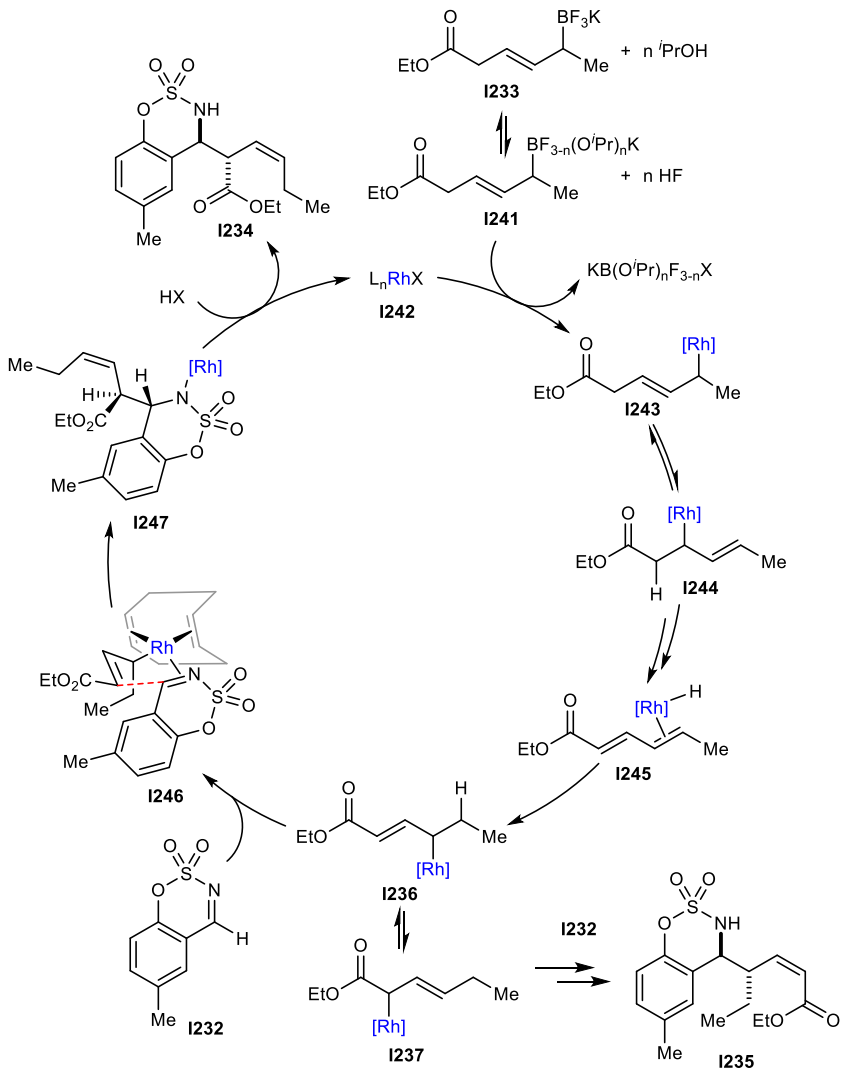
Scheme 63. The first reported example of allyl Rh chain walking.

The scope of this reaction was explored using cyclic imines **I238** and 1.5 equivalents of **I239**, catalytic $[Rh(cod)Cl]_2$ (1.5 mol%) and 5.0 equivalents of ^{i}PrOH in THF at 55 °C for 15 h to form amines **I240**. Different imines **I240a** and **I240b** were tolerated in 72% and 65% yield respectively (Scheme 64). Different R^2 and R^3 groups were also tolerated on the allyltrifluoroborate (**I240c** in 53% yield). All products were isolated in >19:1 d.r. When 3.6 mol% of chiral diene ligand **L10** was used, **I240d** was isolated in 67% yield and 99% *ee*.



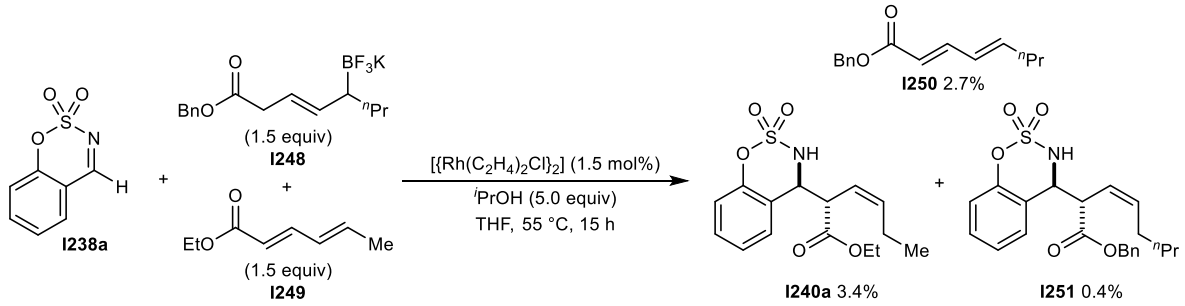
Scheme 64. Scope of allyl Rh chain walking allylation.

A mechanism was proposed using imine **I232** and allyltrifluoroborate **I233** as substrates (Scheme 65). **I233** can react reversibly with ^{i}PrOH to create mixed alkoxide/fluoride boronate complexes **I241**. **I241** then transmetalates with Rh complex **I242** to give allylrhodium species **I243**, which can readily isomerise to **I244**. β-hydride elimination gives **I245** and Rh–H is proposed to reinsert into the olefin distal to the ester group to form **I236**, which is also able to interconvert freely to its allylic isomer **I237**. It was thought that the formation of a more stable allyl Rh intermediate **I236** (via conjugation into the ester carbonyl) was a possible driving force for the chain walking migration. Nucleophilic allylation of **I236** with **I232** proceeds through a chair-like conformation **I246** where the ethyl group is forced into a pseudoaxial position to avoid unfavourable interactions with the cyclooctadiene ligand. This forms **I247** which releases **I234** via protonolysis with HF, HCl or ^{i}PrOH and regenerates **I242**. The minor regioisomer **I235** was formed from nucleophilic allylation of **I237** with **I232**.[122]



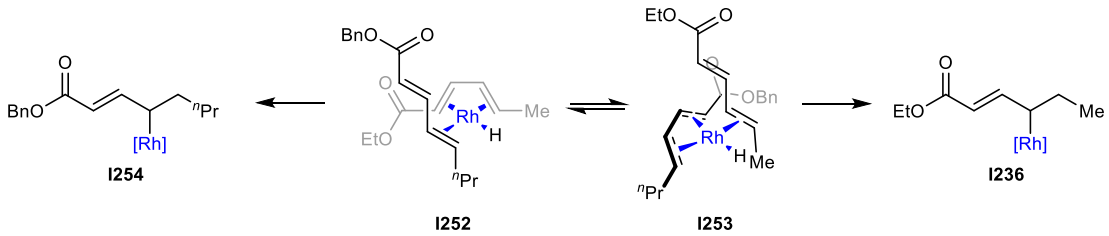
Scheme 65. Proposed mechanism of allylrhodium chain walking.

Evidence for this mechanism was provided by a reaction of aldimine **I238a**, and 1.5 equivalents of both allyltrifluoroborate **I248** and ethyl sorbate **I249** (Scheme 66). Using $[Rh(C_2H_4)_2Cl]_2$ as the pre-catalyst, mostly unreactive imine **I238a** and ethyl sorbate were recovered. However, small quantities of products were detected by HPLC-MS: 0.4% of expected product **I251** (from allyltrifluoroborate **I248**), 3.4% of the crossover product **I240a** (from ethyl sorbate) and 2.7% of benzyl sorbate **I250**.



Scheme 66. Crossover products as mechanistic evidence.

This suggested that the Rh–H catalyst could coordinate to both sorbate dienes **I249** and **I250** simultaneously and hydrorhodation of either diene was possible via structural reorganisation (**I252** and **I253**) (Scheme 67).[122]



Scheme 67. Proposal for crossover product formation.

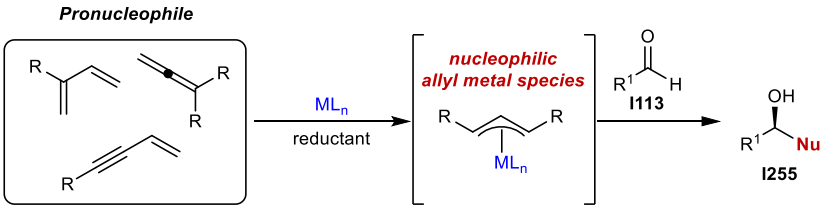
At the time of writing, there appears to be no other work that uses this form of allylic isomeration. A comparison between the two methods described shows two different ways of generating the allylmetal species *in situ*.

Krische's work is a formal reductive coupling process, defined as a strategy where electrophiles (in this case a diene and an aldehyde) are coupled in the presence of an external reductant.[82] This is more atom economical than the transmetalation method used by the Lam group which sees loss of large boronate groups from the substrates. Therefore, whilst both methods are promising approaches towards *in situ* allylmetal generation for potential chain walking isomerisation reactions, it appears that reductive coupling processes are more attractive, and are worth exploring in more detail. The following section briefly discusses some of the research in this field most relevant to the work in this thesis.

1.1.4 Reductive Coupling to π-Electrophiles

1.1.4.1 Overview of Reductive Coupling

As briefly mentioned at the end of Section 1.1.3.2, reductive coupling is a process where two shelf-stable electrophiles are coupled through use of an external reductant to form a new bond between them.[82] There is a lot of recent literature coupling π-electrophiles like carbonyls or imines and pronucleophiles like dienes, allenes and enynes (Scheme 68). The process essentially results in formation of both a new C–H and C–C bond, with formal H_2 addition across the π-unsaturated pronucleophile and the C=X π-bond.[123]



Scheme 68. Metal-catalysed reductive coupling of a pronucleophile with a π-electrophile.

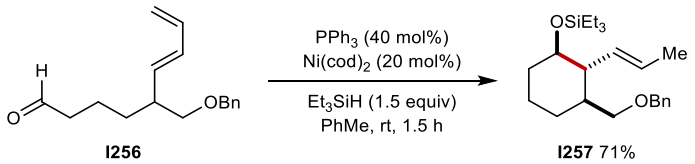
Dienes, allenes and enynes can all be coupled to π-electrophiles in processes catalysed by transition metals like Ni,[124-131] Ru,[132-139] Rh,[140, 141] Ir,[142-144] Ti,[145] Cu [146-150] and Pd.[151, 152] A few relevant examples of this procedure using commonly described transition metals as catalysts will be discussed in the following section.

It should be noted that transfer hydrogenation is another method of doing these same transformations but with an alcohol or amine instead of a carbonyl or imine.[153-156] H_2 is generated *in situ* from the alcohol or amine to form the corresponding π-electrophile and simultaneously reduce the pronucleophile and form the relevant allylmetal species. While this process is noted, it will not be investigated further here and we shall focus on discussing direct additions of π-electrophiles, not ones which are generated *in situ*.

1.1.4.2 Nickel-Catalysed Reductive Coupling

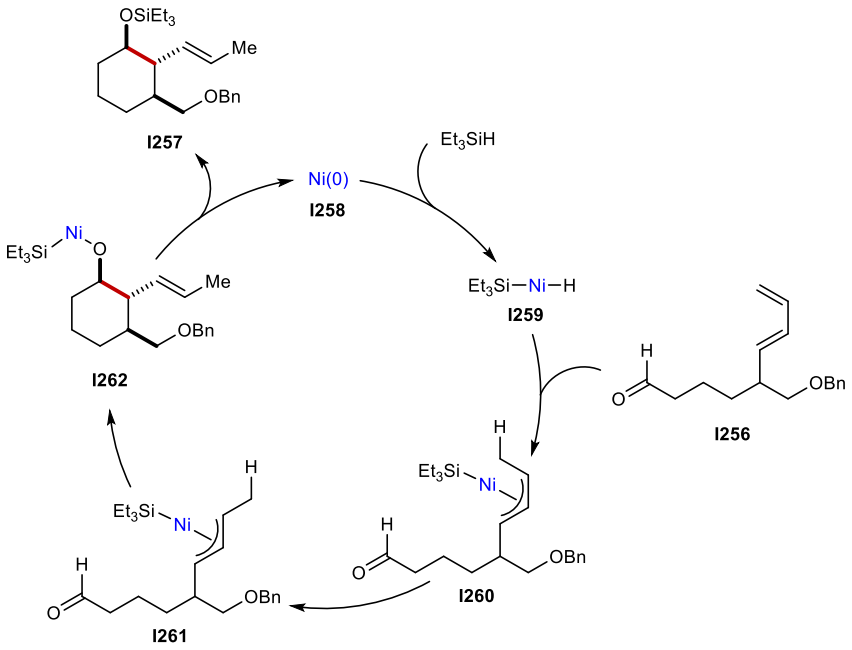
One of the earliest reported examples of a reductive coupling to a carbonyl compound was reported by Mori in 1994.[129] This seminal work described a stereoselective cyclisation via a nucleophilic π-allyl complex generated from Ni-H addition to a 1,3-diene (Scheme 69). **I256** was transformed into six-membered ring product **I257** in 71% yield using $Ni(cod)_2$ as the catalyst (20 mol%) with a PPh_3 ligand (40 mol%) and 1.5 equivalents of triethylsilane as the

reductant after stirring in PhMe for 1.5 h at room temperature. This could additionally be applied to the synthesis of five- and seven-membered rings.



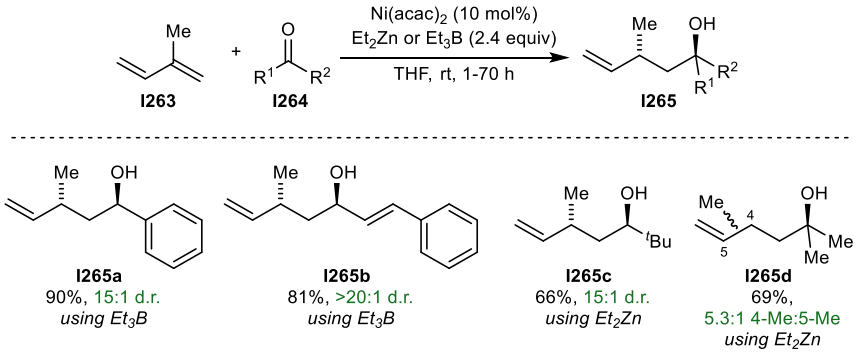
Scheme 69. Ni-catalysed reductive coupling cyclisation.

Mechanistically, this proceeds via oxidative addition of Ni^0 to triethylsilane to form Ni-H **I259**, which adds into **I256** to form nucleophilic π-allyl Ni species **I260**. The more stable allyl Ni isomer **I261**, can then participate in the cyclisation process via aldehyde allylation to generate Ni alkoxide **I262**. Reductive elimination regenerates zerovalent nickel and forms **I257** (Scheme 70).



Scheme 70. Proposed allyl Ni cyclisation mechanism.

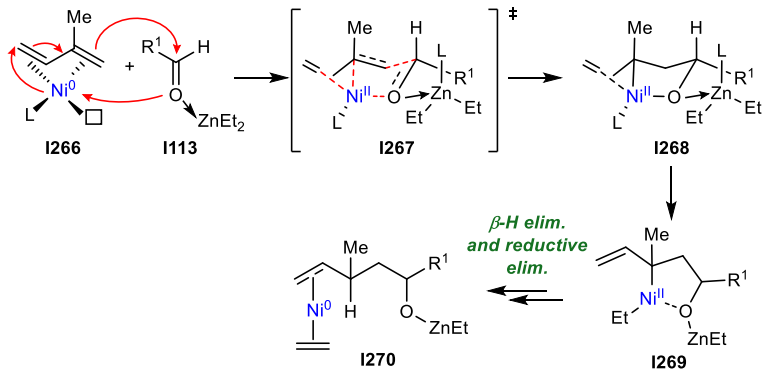
Whilst Mori then demonstrated an intermolecular variation using similar conditions,[126] Kimura demonstrated a slightly different version of this reaction, coupling 1,3-diene **I263** and carbonyl compounds **I264**, promoted by 2.4 equivalents of Et_2Zn or Et_3B when using $Ni(acac)_2$ as a catalyst (Scheme 71).[124] However, the coupling instead occurred at the C1 position in these cases to give **I265** instead of the expected allylic alcohols.



Scheme 71. Ni-catalysed allylation of carbonyls.

Addition to aromatic and aliphatic aldehydes were tolerated in respectable yields and diastereoselectivities (**I265a-I265c**) (>15:1 d.r.). Ketones were compatible as well, although the regiocontrol was partially lost in the case of **I265d**.

Whilst, the process remains a formal reductive coupling of a diene and aldehyde, with Ni^0 providing the two electrons as a reductant, the mechanism is slightly different (Scheme 72). Oxidative cyclisation of **I266** and **I113** promoted by Et_2Zn or Et_3B gives five-membered oxanickelcycle **I268** via transition state **I267**. Transfer of an ethyl group from the Zn or B atom to the Ni gives NiEt species **I269**, which forms **I270** via *β*-hydride elimination and reductive elimination.[124]

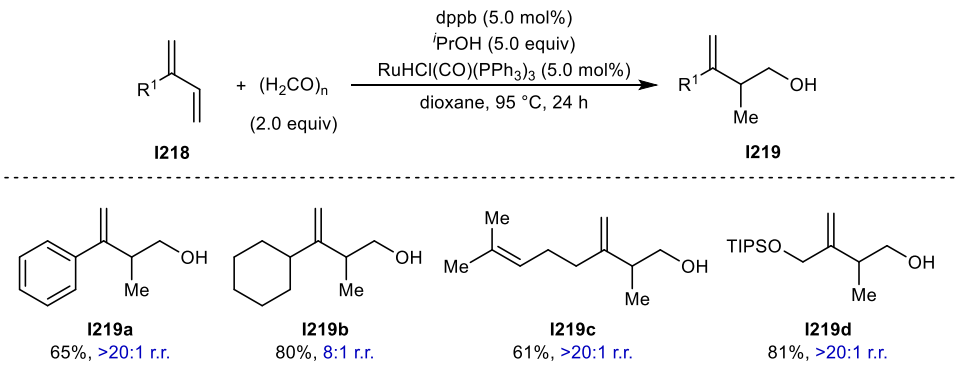


Scheme 72. Ni-catalysed homoallylation of dienes and aldehydes via oxidative cyclisation.

Both Mori and Kimura have further explored the utility of Ni to catalyse similar reductive couplings between dienes and aldehydes.[125, 157-159]

1.1.4.3 Ruthenium-Catalysed Reductive Coupling

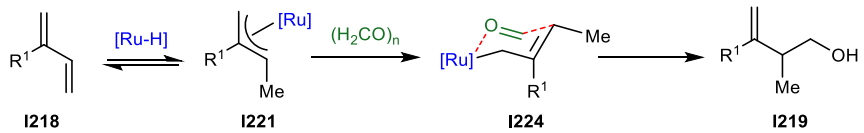
After Krische documented the first Ru-catalysed reductive coupling between dienes and formaldehyde in 2009 [118] (see Section 1.1.3.2), further work was reported whereby taking the same two coupling partners **I218** and paraformaldehyde used previously and changing the conditions slightly, it was possible to selectively allylate at the C3 position instead of C2. Using $RuHCl(CO)(PPh_3)_3$ as the catalyst alongside an ^{i}PrOH additive and changing the solvent to dioxane saw a highly selective C3 allylation at 95 °C after 24 h (Scheme 73).[160]



Scheme 73. C3 selective reductive coupling between dienes and paraformaldehyde.

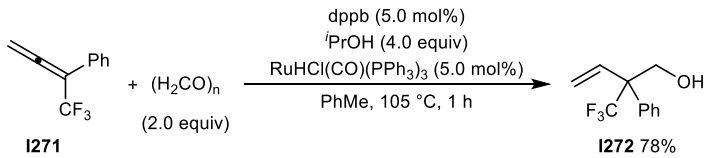
Similar substrates to the previous work were tolerated, including aryl and alkyl R^1 groups in products **I219a** and **I219b** in 65% and 80% yield respectively. Myrcene was also selectively allylated to give **I219c** in 61% yield, and finally silyl protected alcohol gave **I219d** in 81% yield. The C2:C3 regioselectivities were high throughout, with the lowest representative example being 8:1 for **I219b**.

This mechanism has been previously discussed in section 1.1.3.2 (see Scheme 62) in which several Ru-H insertion pathways are possible.[118] The resulting products are formed via C3 allylation, which is possible due to the allyl Ru species **I221** being favoured under the reaction conditions (Scheme 74). **I221** attacks paraformaldehyde via six-membered transition state **I224** to give **I219**.



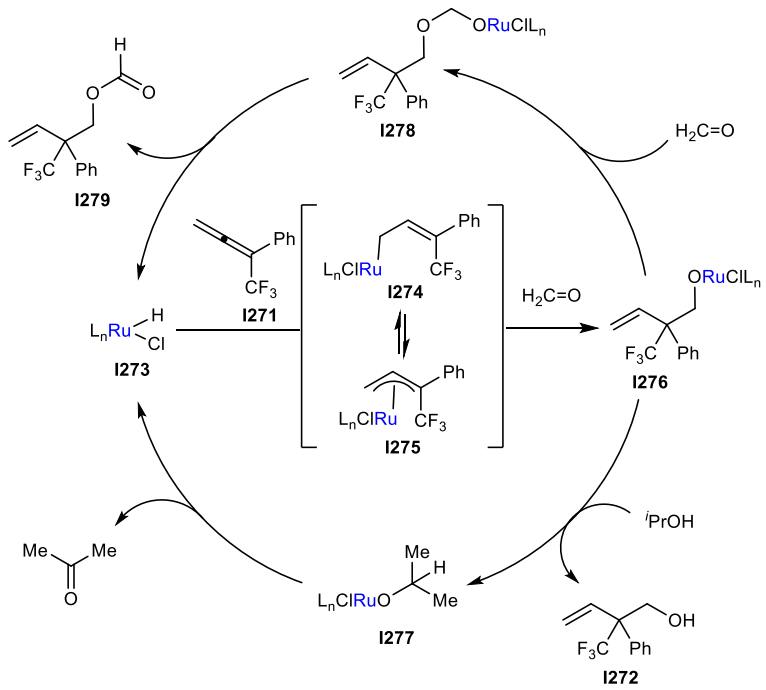
Scheme 74. Proposed reductive coupling mechanism.

Krische then extended the application of this methodology to allenes, which can also form allylmetal species from metal hydride additions.[123] Changing only the solvent and temperature (PhMe at 105 °C) and using 1.0 equivalent less of the ^{i}PrOH additive, allene **I271** could react with 2.0 equivalents of paraformaldehyde to give **I272** in 78% yield (Scheme 75).[134]



Scheme 75. Reductive coupling of an allene with paraformaldehyde.

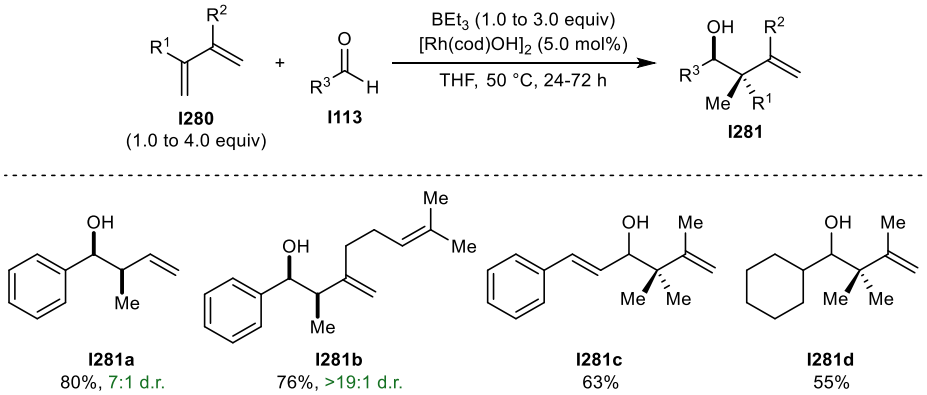
A plausible mechanism begins with hydrometallation of **I271** to give allyl Ru haptomers **I274** and **I275** (Scheme 76). Addition of paraformaldehyde to **I274** forms alkoxyruthenium species **I276**. From here, protonolysis with ^{i}PrOH can liberate **I272** and give alkoxide **I277** and subsequent elimination of acetone via β-hydride elimination reforms **I273**. Alternatively if **I276** attacks paraformaldehyde, it can form side product **I279** via **I278** and regenerate Ru-H **I273**.



Scheme 76. Proposed catalytic cycle.

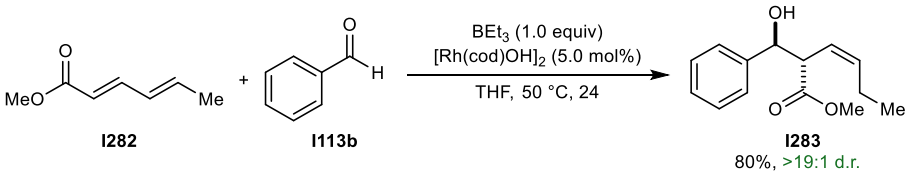
1.1.4.4 Rhodium-Catalysed Reductive Coupling

Rhodium-catalysed reductive couplings are relatively rare in the literature, particularly with diene pronucleophiles. One of the only examples was reported by Kimura in 2009 to form homoallylic alcohols **I281** from dienes **I280** and aldehydes **I113** (Scheme 77).[141] The allylation is initiated by hydrorhodation of **I280** from *in situ* generated Rh–H from catalytic $[Rh(cod)OH]_2$ and a superstiochiometric quantity of BEt_3 (1.0 to 3.0 equivalents) in THF for 24-72 h at 50 °C. A range of dienes and aldehydes were successfully coupled, with representative examples **I281a-I281d** that proceeded in good yields and diastereoselectivities.



Scheme 77. Rh-catalysed reductive coupling to dienes and aldehydes.

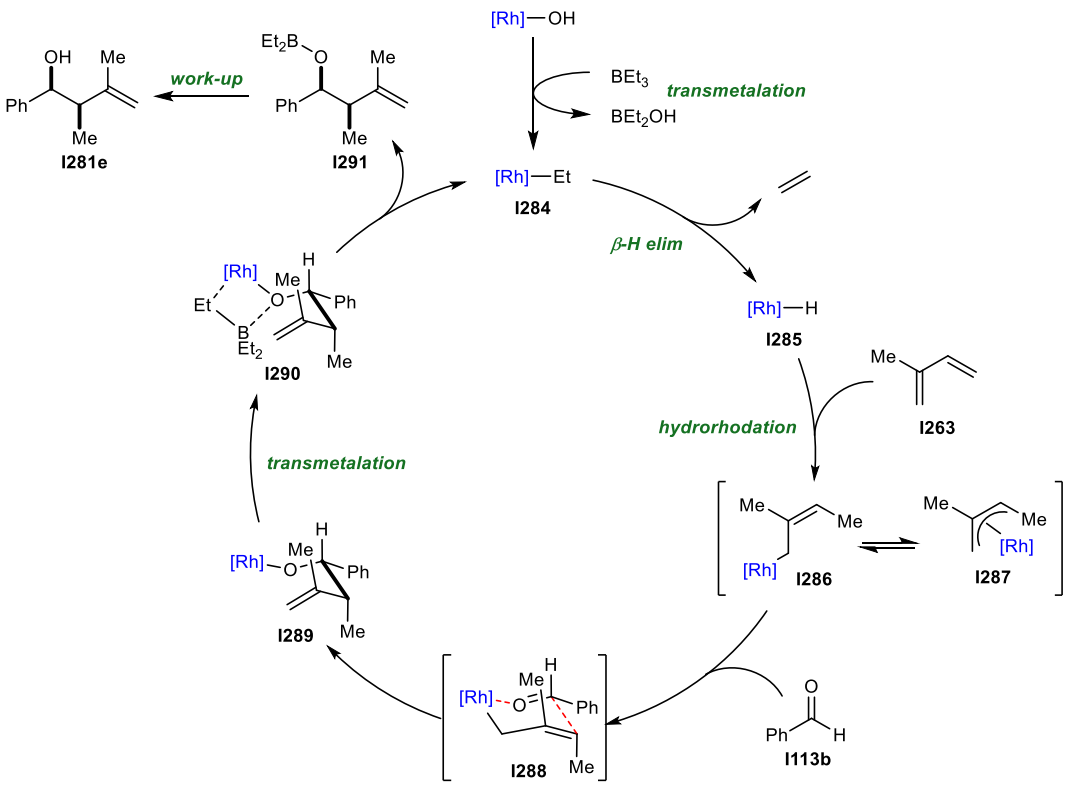
When methyl sorbate **I282** was subjected to the reaction conditions, it successfully coupled with benzaldehyde **I113b** to give **I283** in 80% yield exclusively as the *anti*-diastereoisomer (Scheme 78).



Scheme 78. Reductive coupling of benzaldehyde and methyl sorbate.

A catalytic cycle is proposed using diene **I263** and benzaldehyde **I113b** as the representative substrates (Scheme 79). The activate catalytic species ethylrhodium **I284** is formed from transmetalation of BEt_3 and $[Rh(cod)OH]_2$. This generates Rh–H **I285** via *β*-hydride elimination which adds into diene **I263** to form allyl Rh haptomers **I286** and **I287**. Addition to benzaldehyde is controlled via a six-membered transition state **I288** to give

alkoxyrhodium **I289**. Transmetalation of another ethylborane species reforms **I284** and gives boron ester **I291** which gives homoallylic alcohol **I281e** after work up.[141]



Scheme 79. Proposed mechanism.

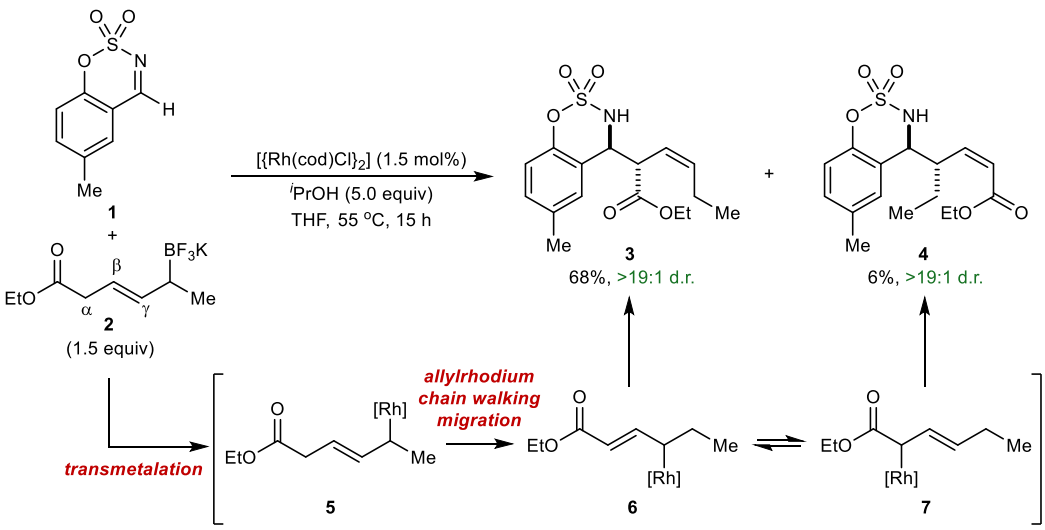
1.1.5 Summary

Remote functionalisation is a promising area of synthetic chemistry, facilitating transformations at less reactive positions to provide access to previously inaccessible products. This is often done by olefin isomerisation via a process known as chain walking. Whilst there are a multitude of reported examples, they are mostly limited to chain walking of alkylmetal species which restrict the scope. This limitation can potentially be mediated by utilising the isomerisation of allylmetal species to do remote nucleophilic allylations with π-electrophiles. A reliable method of forming allylmetal species *in situ* is the reduction of pronucleophiles like dienes or allenes in a formal metal-catalysed reductive coupling process.

1.2 Results and Discussion

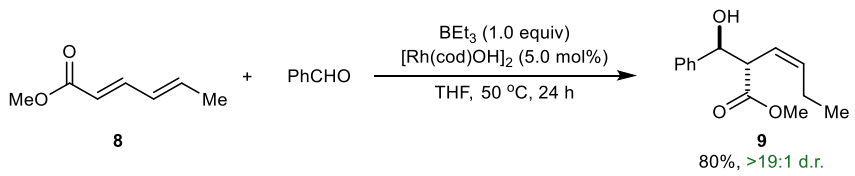
1.2.1 Project Aims

The Lam group has previously reported a range of rhodium-catalysed nucleophilic allylations of π-electrophiles, often using allyl boron compounds to form the reactive allylrhodium intermediate *in situ*.[119-122] As part of this investigation, it was observed that when using more complex *δ*-allyltrifluoroborate ester substrates, *α*-allylation product **3** was obtained, rather than the expected *β*-allylation product, suggesting allylrhodium 'chain walking' isomerisation. (Scheme 80).[122]



Scheme 80. The first reported example of allyl Rh chain walking.

As the work only reported chain walking over one carbon unit, we were interested to see if extending the length of the carbon tether could lead to longer range isomerisation and result in remote nucleophilic allylations. An alternative to the allyltrifluoroborate precursors was desired to avoid the need to make compounds with a pre-functionalised boron synthetic handle. Synthesis of allyltrifluoroborate esters with multiple methylene units between the functional groups was also very challenging and impractical. Allylrhodium formation via hydrorhodation of 1,3-dienes was reported by Kimura and used in a reductive coupling with aldehyde electrophiles, where the highly regioselective allylation of ester **8** was shown (Scheme 81).[141]

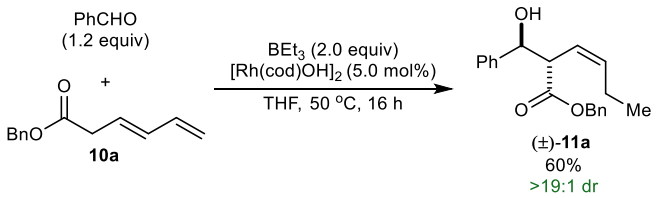


Scheme 81. Reductive coupling of benzaldehyde and methyl sorbate reported by Kimura.

We aimed to investigate whether 1,3-dienes with tethered esters could demonstrate similar reactivity, and if the allylrhodium species could chain walk through more than one carbon. Further investigation of the reaction mechanism and scope was also desired.

1.2.2 Initial Results

The initial test reactions and optimisation were carried out by Dr. Jose I. Martínez. Terminal 1,3-diene **10a** was synthesised and subjected to reductive coupling conditions with benzaldehyde, giving homoallylic alcohol **11a** in 60% yield (Scheme 82). The reaction system was comparable to Kimura's, using BEt_3 and $[Rh(cod)OH]_2$ to form rhodium hydride *in situ*. Analysis of the olefin proton coupling constants (^3J = 10.8 Hz) suggested *Z*-selectivity, and the product was isolated as a single diastereoisomer. At the time, the relative stereochemistry of the two newly created stereocentres was unknown, but was assumed to be the *anti*-configuration, parallel to Kimura's observation with methyl sorbate (Scheme 81).

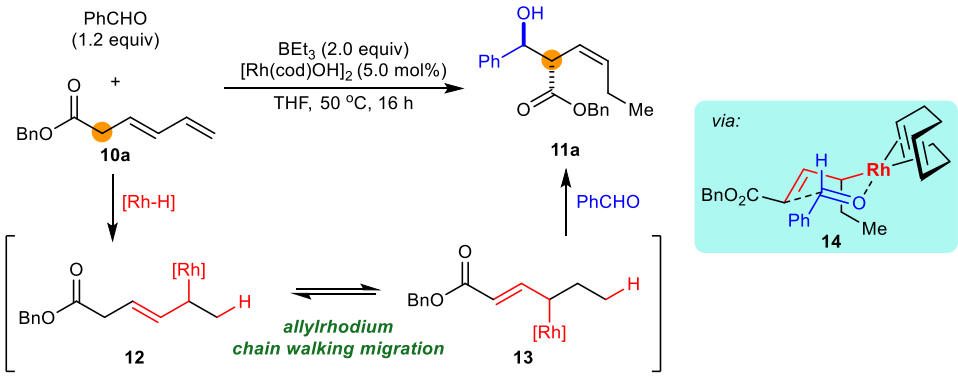


*Scheme 82. Nucleophilic allylation of benzaldehyde with diene **10a**. Reaction performed by Dr. J. I. Martínez. Substrate **10a** synthesised by Dr. J. I. Martínez.*

Dr. Jose I. Martínez and Dr. Joshua Smith then attempted to optimise the reaction by using diene **10a** or ethyl sorbate as the diene component. They found that at least 2.0 equivalents of BEt_3 was required and attempts to lower the temperature and catalyst loading saw more complex crude reaction mixtures and reduced yield. The optimal reaction time was 16 h and they also discovered it was critical to add BEt_3 to the reaction mixture last in order to ensure effective reaction conversion. Forming rhodium hydroxide *in situ* from $[Rh(cod)Cl]_2$ and aqueous KOH was compatible with ethyl sorbate but did not give reproducible or

consistent results with the chain walking substrate **10a**. Replacing BEt_3 with Et_3SiH led to no reaction. Using various rhodium-chiral diene complexes in these reactions led to low conversions and enantioselectivities.

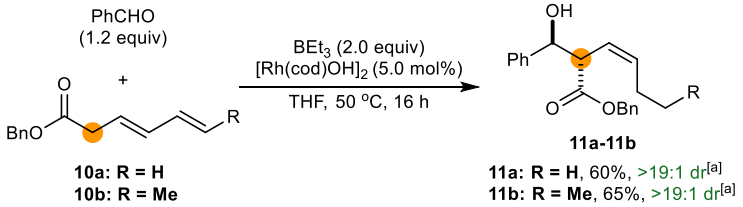
The reaction was proposed to work via diene hydrorhodation forming allylrhodium species **12**, followed by isomerisation to intermediate **13** via allylrhodium chain walking, presumably via a similar mechanism to the seminal work from the Lam group on the subject (Scheme 65 in Section 1.1.3.2). **13** is a more stabilised allylrhodium species due to its conjugation with the ester functional group. The formation of this species, which subsequently undergoes a nucleophilic allylation reaction with benzaldehyde, presumably encourages the allylmetal migration (Scheme 83). The Rh-catalysed nucleophilic allylation was thought to proceed via a Type III six-membered transition state to rationalise formation of the *anti*-product.[67]



Scheme 83. General allylrhodium chain walking mechanism.

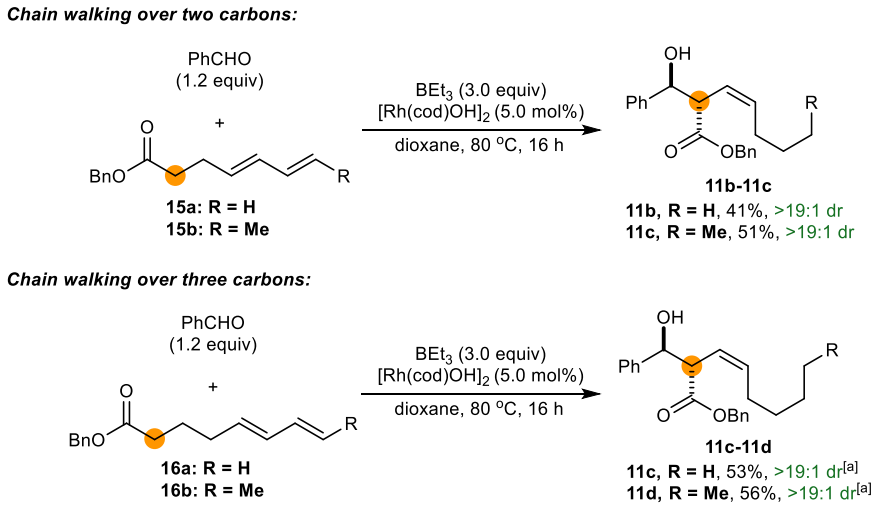
1.2.3 Allylrhodium Chain Walking Towards Esters

The reaction could also be applied to internal diene **10b** to give **11b** in 65% yield (Scheme 84). As with **11a**, the product was isolated as a single diastereoisomer after column chromatography. In these examples, and most of those that follow, the d.r. was quoted for the isolated product. This was owing to the complex nature of the crude ^{1}H NMR spectra, which contained up to 20% of impurities which were later determined to be mixtures of other allylation products (see Section 1.2.4). Whilst there was usually no sign of minor product diastereoisomers in the ^{1}H NMR spectra of the unpurified product, accurate analysis of the crude diastereometric ratios could not be achieved. It will be made clear when the d.r. of an entry was obtained from its crude ^{1}H NMR spectrum.



*Scheme 84. Allylrhodium chain walking over one carbon. [a] Reaction performed by Dr. J. I. Martínez. Substrates **10a-10b** synthesised by Dr. J. I. Martínez.*

The next step was to demonstrate that it was possible for the allylrhodium chain walking process to occur over more than one carbon. Terminal and internal diene substrates **15a-15b** were synthesised and successfully underwent α-allylation after walking over two carbons. Increasing the reaction temperature to 80 °C (in the higher boiling point solvent dioxane) and adding an extra equivalent of BEt_3 were required when walking over >1 carbon in order to achieve full conversion. The resulting homoallylic alcohols **11b-11c** were successfully isolated in 41% and 51% yield respectively and both in excellent d.r. (Scheme 85). These conditions were then applied to substrates **16a-16b** which had a three-carbon tether (Scheme 85). These corresponding chain walking products **11c-11d** were isolated in 53% and 56% yield, again as single diastereoisomers.

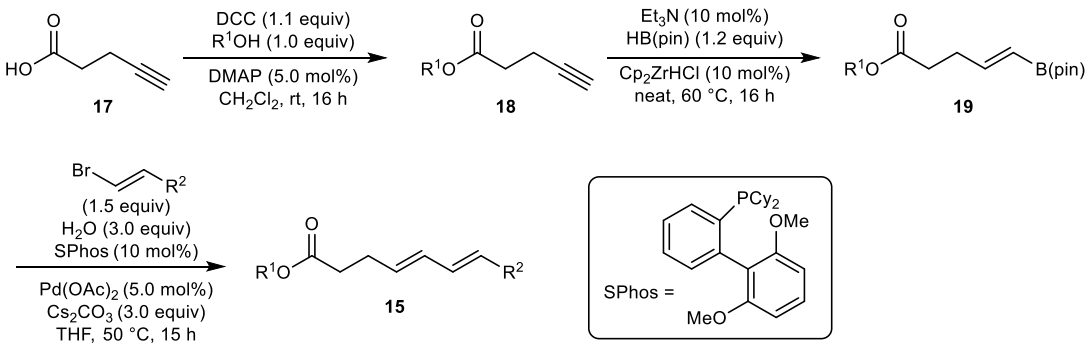


*Scheme 85. Allylrhodium chain walking over two and three carbons. [a] The synthesis of substrate **16a-16b** and the subsequent allylation reactions were both performed by Dr. J. Smith.*

The product yields might be expected to decrease as a function of tether chain length, as rhodium must participate in a greater number of steps before the stabilised allylrhodium

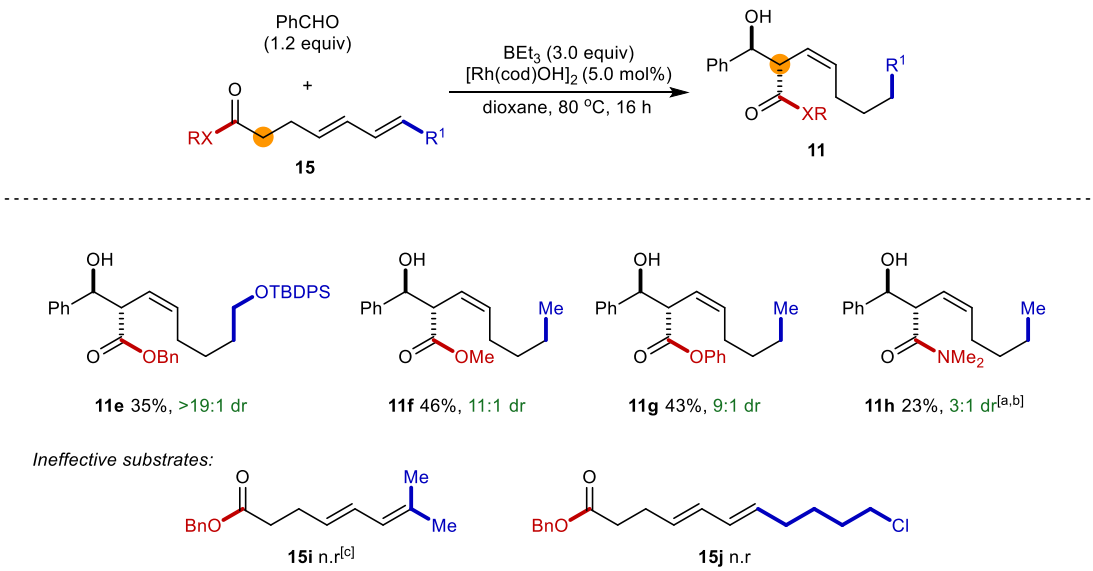
intermediate is attained, and in principle, any of the allylrhodium species can react with PhCHO to give complex product mixtures. It is therefore surprising to see substrates with carbon tether length n = 3 giving higher yields than n = 2. This phenomenon is difficult to rationalise, yet the reactions were repeated to confirm the yields were indeed accurate. In all cases, it was observed that internal dienes tend to give slightly higher yields than terminal variants.

Focusing on two carbon tethered substrates, a range of different dienes were synthesised with variation of both the diene and ester components (Scheme 86). These substrates were usually made from esterification of 4-pentynoic acid **17**, followed by alkyne hydroboration to give boronate ester **19**, and Suzuki coupling with various vinyl bromides to give **15**.



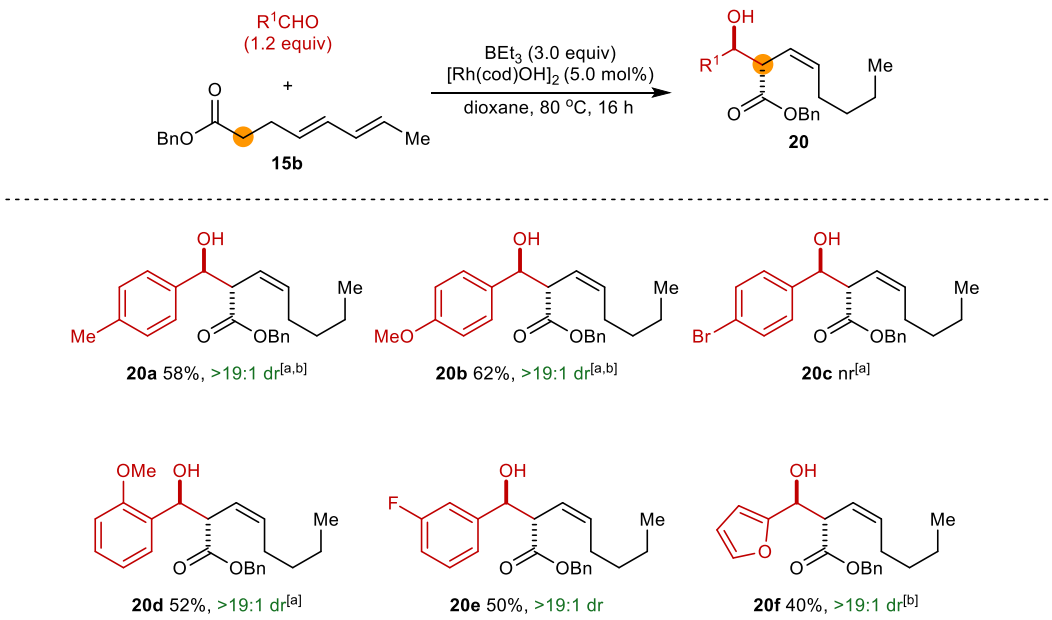
*Scheme 86. Synthetic route to diene ester substrates **15**.*

These substrates were then subjected to the reaction conditions to investigate the reaction scope (Scheme 87). Altering the R^2 group from Me to a silyl protected alcohol ($CH_2OTBDPS$ group) was tolerated, with **11e** isolated in 35% yield and >19:1 d.r. Methyl and phenyl esters could also be used forming **11f** (46% yield, 11:1 d.r.) and **11g** (43% yield, 9:1 d.r.) respectively. Chain walking towards an amide functional group was also permitted, although product **11h** was obtained in only 23% yield with a drop in the d.r. to just 3:1. This decrease could imply the *syn*- and *anti*- transition states are very close in energy so discrimination between the two is more difficult. Alternatively, an open Type II allylation transition state could be also possible.[67] A couple of other substrates **15i-15j** were also attempted but unfortunately demonstrated no reactivity with starting material recovered. Hydrorhodation of hindered trisubstituted diene **15i** was thought to be too unfavourable for reaction initiation and it was proposed for diene **15j**, which has a halogen-containing chlorobutyl R^1 group, that competing side reactions such as Rh^I addition into the carbon halogen bonds might suppress the hydrorhodation process.[161, 162]



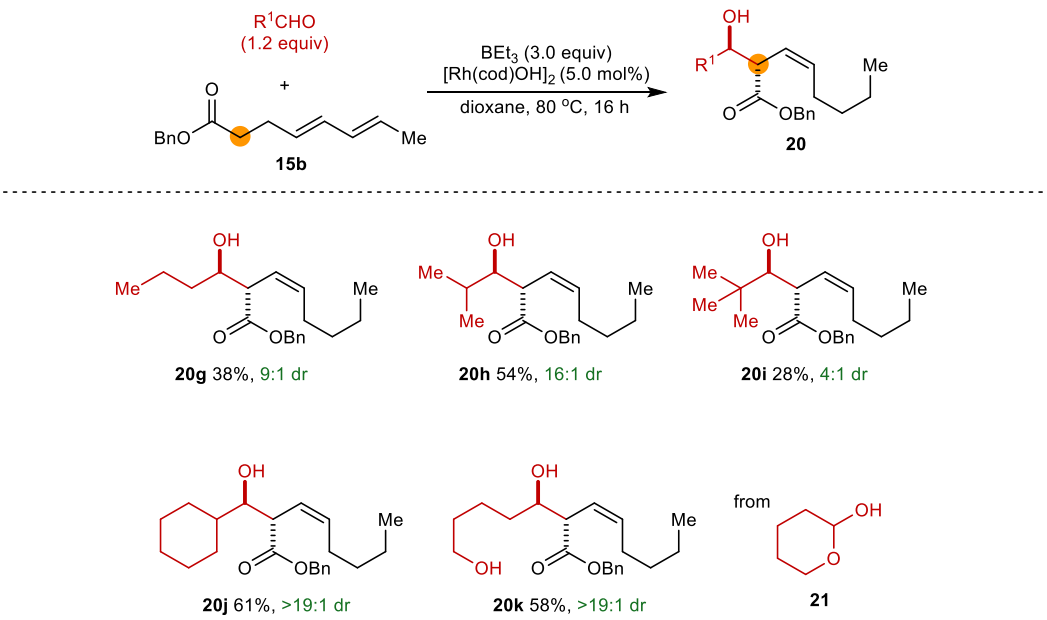
*Scheme 87. Diene substrate scope. [a] Reaction time was 40 h. [b] Diastereoselectivity determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c]The synthesis of substrate **15i** and the subsequent allylation reaction were both performed by Dr. J. Smith.*

The aldehyde scope was subsequently investigated in the reaction with diene **15b** (Scheme 88). Firstly, aromatic aldehydes were generally well tolerated: 4-tolualdehyde and 4-anisaldehyde gave **20a** and **20b** in 58% and 62% yield. Halogen-containing reagents like 4-bromobenzaldehyde again proved problematic with no **20c** observed and starting materials recovered instead. 2-Anisaldehyde and 3-fluoroaldehyde led to the successful formation of **20d** (52% yield) and **20e** (50% yield). Finally, heteroaromatic furfuraldehyde gave **20f** in 40% yield. All products were isolated as single diastereoisomers.



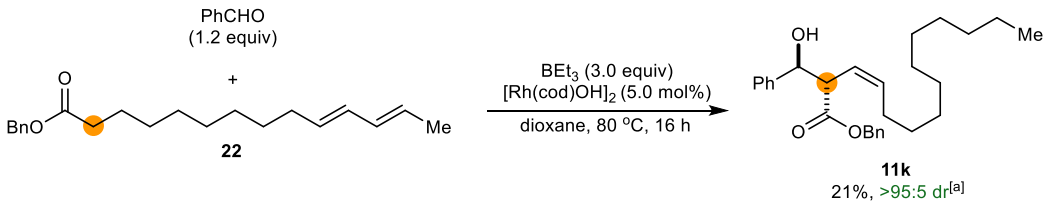
Scheme 88. Aromatic aldehyde scope. [a] Reaction performed by Dr. J. I. Martínez. [b] Diastereoselectivity determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture.

Aliphatic aldehydes were also tolerated, although the yields and diastereoselectivites were more variable (Scheme 89). The use of *n*- and *iso*-butraldehyde gave **20g** (38% yield and 9:1 d.r.) and **20h** (54% yield and 16:1 d.r.). Allylation of pivaldehyde was also possible, although the conversion was poor with only 28% yield of **20i** isolated as a 4:1 d.r. mixture. **20j** was obtained in 61% yield from cyclohexanecarboxaldehyde and diol **20k** was isolated as a single diastereoisomer in 58% yield from masked aldehyde pyranol **21**.



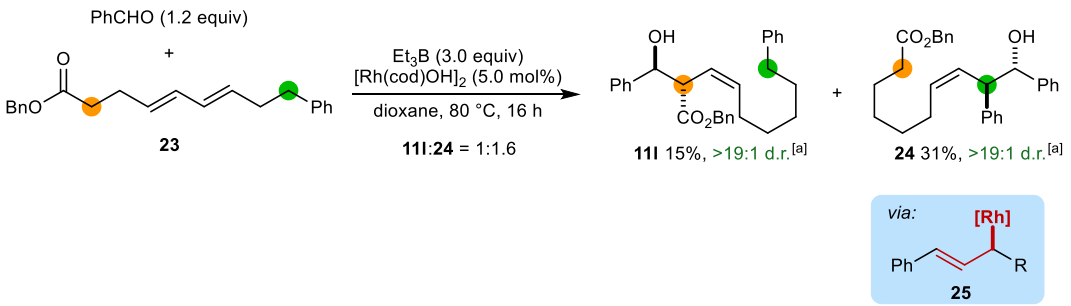
Scheme 89. Aliphatic aldehyde scope.

Impressively, the allylrhodium species could chain walk over eight methylene units to demonstrate extreme long-range remote functionalisation. Diene **22** gave chain walking allylation product **11k** in a modest 21% yield, presumably due to the large number of alternative modes of allylation available. Despite this low yield, the product was still isolated as a single diastereoisomer. This is valuable as a complex product is formed with lots of stereochemical information installed at a position very remote from the initial site of activation (Scheme 90).



*Scheme 90. Long range allylrhodium chain walking over eight carbons. [a] The synthesis of substrate **22** and the subsequent allylation reaction were both performed by Dr. J. Smith.*

Interestingly, when diene **23**, which has an ester and phenyl group at the termini, was subjected to the reaction conditions, two products were isolated and separated (Scheme 91). **11l** was the expected product via allylation α- to the ester in 15% yield, whilst the major product was **24**, where allylation occurs α- to the aromatic ring. The crude ratio of **11l**:**24** was identical to the isolated ratio and both products were single diastereoisomers.

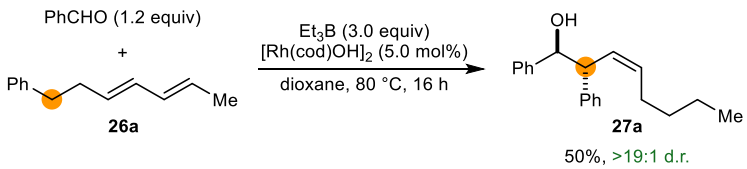


*Scheme 91. Bidirectional chain walking towards esters and aryl groups. The synthesis of substrate **11l** and the subsequent allylation reaction were both performed by Dr. J. Smith.*

The result implied that the allylrhodium species could also be stabilised via conjugation with the aromatic ring, as seen in intermediate **25**, suggesting that it was possible to chain walk towards other non-carbonyl functional groups. This would be potentially useful in further expanding the scope of this methodology.

1.2.4 Allylrhodium Chain Walking Towards Arenes

The investigation subsequently focused on allylrhodium chain walking solely towards aryl groups. Pleasingly diene **26a**, with a phenyl ring tethered by a two-methylene unit spacer was found to form **27a** as the major product in 50% yield and >19:1 d.r. (Scheme 92).

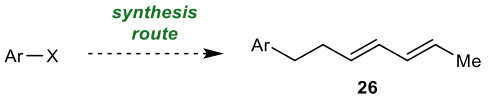


Scheme 92. Allylrhodium chain walking towards an arene.

In this example, the single impurity spot on the TLC plate was isolated via column chromatography. On further analysis, it was determined to be a complex mixture of other allylation products (18% yield), having the same HRMS product peak as **27a**, and a stretching OH IR peak. Complete characterisation was not possible by NMR techniques due to the complex nature of the spectra with multiple overlapping signals (see Experimental Section 1.3.3 for more information).

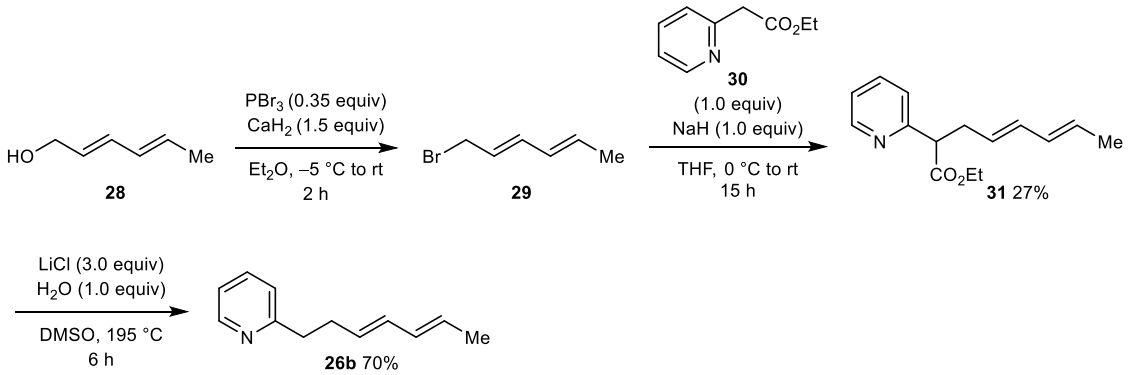
Following the successful application of **26a** to the methodology, further examples of substrates with the same aryl diene skeleton were desired. Unfortunately, synthetic routes to these substrates, with a two-carbon tether and an internal diene, were often problematic. On

searching the literature, there was not an obvious route that simply inputted different commercial aryl group starting materials and obtained aryl dienes as a result (Scheme 93).



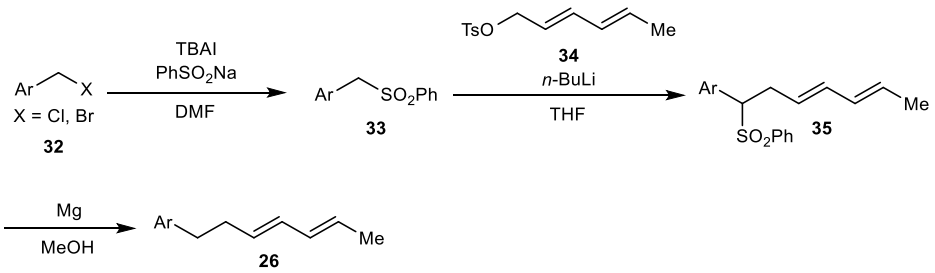
*Scheme 93. General synthesis route for **26** with aryl group variation desired.*

For example, 2-pyridyl-containing diene **26b** was synthesised via bromination of sorbyl alcohol **28** with PBr_3. The resulting allyl bromide **29** was used to allylate commercially available **30** to form **31**. Krapcho decarboxylation cleaved the CO_2Et group and gave **26b** in 70% yield (Scheme 94). However, this method was not applicable to non-pyridyl substrates, as the decarboxylation required an electron withdrawing group α- to the departing ester.



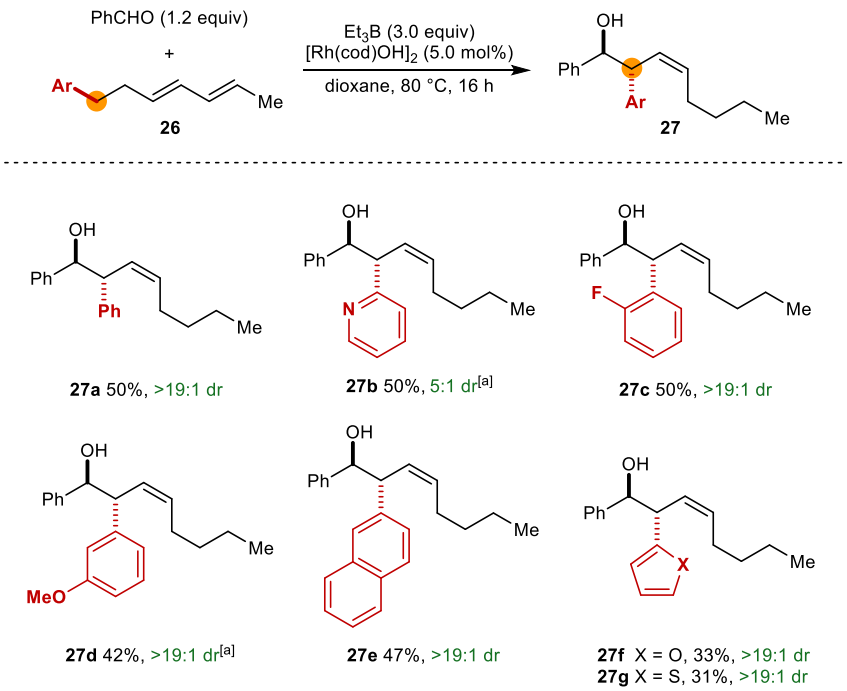
*Scheme 94. Synthesis of 2-pyridyl substrate **26b**.*

Sorbyl alcohol was a highly desirable building block due to its low cost, and its exclusive existence as the *E*,*E*-diene meant a stereoselective route did not need to be designed. Eventually a successful synthetic route was discovered, using (halomethyl)arenes **32** (Scheme 95). Alkylation of $PhSO_2Na$ with **32** using TBAI (1.0 mol%) as a catalyst gave sulfone **33**. After simultaneous *n*-BuLi-mediated deprotonation of **33** and tosylation of sorbyl alcohol (giving **34**), the two intermediates were combined to give sulfone **35**. Desulfonylation using Mg in MeOH gave diene **26**.



*Scheme 95. Synthesis of aryl diene substrates **26**.*

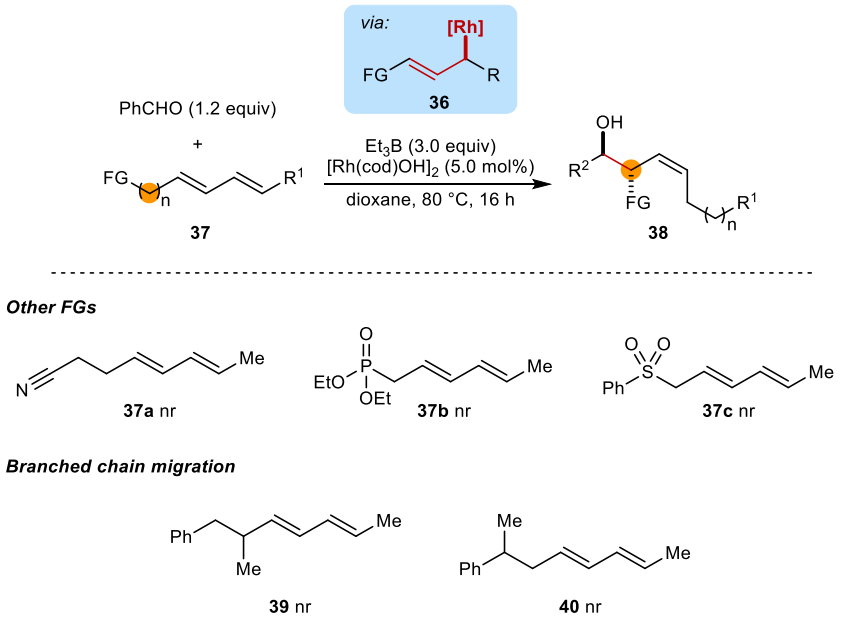
This synthesis route was generally high yielding, required only one column chromatography purification and could be applied to a range of (methylhalo)arenes. With the route designed, a range of aryl dienes **26** were synthesised and subjected to the reaction conditions (Scheme 96). 2-pyridyl diene **26b** was converted into **27b** in 50% yield and 5:1 d.r. Varying the electronic substituents on the aromatic ring demonstrated comparable results, with 2-fluoro-, 3-methoxy- and 2-naphthyl- groups in dienes **26c**, **26d** and **26e** giving **27c** (50%), **27d** (42%) and **27e** (47%) respectively as single diastereoisomers. Finally, the allylrhodium species was also observed to chain walk towards electron-rich hetereoaromatic groups such as 2-furanyl and 2-thienyl dienes in **27f** and **27g**, although the yields were slightly diminished to 33% and 31% respectively.



Scheme 96. Aryl diene scope. [a] Diastereoselectivity determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture.

These results support the idea that the tethered functional group encourages the allylrhodium chain walking process by stabilising the allylrhodium intermediate through conjugation before the remote nucleophilic allylation process. It was therefore necessary to investigate whether other functional groups could promote this process. The functional groups chosen had to be electron deficient and also able to participate in conjugation with the allylrhodium species as shown in **36** (Scheme 97).

1,3-Dienes with tethered nitrile (**37a**), phosphonate (**37b**) and sulfone (**37c**) groups were all synthesised and subjected to the reaction conditions. Unfortunately, no allylrhodium chain walking was observed, with starting material recovered in all cases. It was proposed that the nitrile, phosphonate and sulfone groups could all strongly interact with the Rh centre in some way (via coordination as donor ligands or otherwise), which suppresses its catalytic activity.

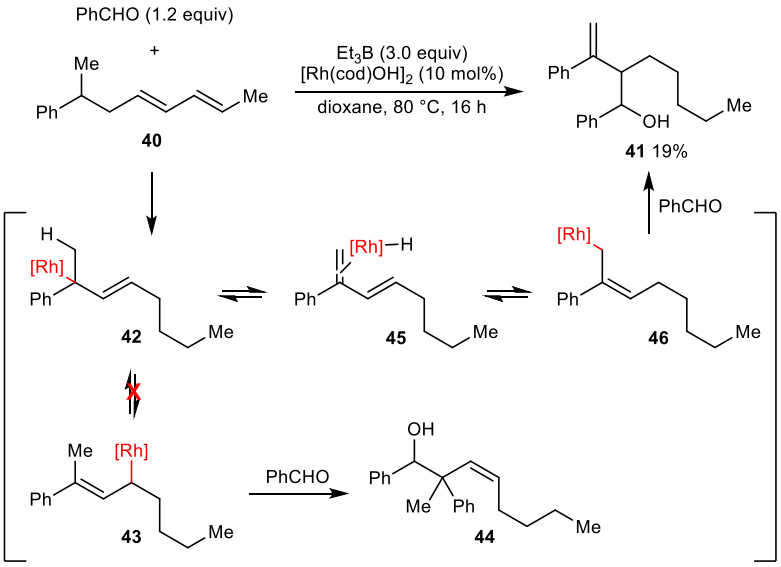


Scheme 97. Chain walking on other substrates.

Dienes with branched chains were then synthesised and subjected to the reaction conditions. Successful remote allylation of **39** would indicate if the allylrhodium species could walk through a tertiary carbon, and **40** would enable remote allylation to form a quaternary centre in the product (Scheme 97). For **39**, no chain walking was observed with starting material recovered and small quantities (*ca.* 29%) of a complex mixture of other allylation products observed in the crude NMR spectra. This suggested that the allylrhodium isomerisation pathway may be too high in energy for chain walking to be favourable,

particularly if β-hydride elimination to or hydrorhodation of a highly substituted diene is a key isomerisation step.

Substrate **40** also displayed very poor reactivity, with a very complex crude NMR spectra, and small quantities of β-allylation product **41** being the only characterisable species (Scheme 98). No α-allylation product **44** was observed or isolated. The formation of **41** was rationalised by tertiary rhodium species **42** preferring to participate in β-hydride elimination with one of the methyl hydrogens to form **45**, instead of simple allylic transposition, which would form **44** via intermediate **43**. Hydrorhodation of **45** would ultimately lead to allylrhodium **46**, which retains a conjugated stabilisation effect from the Ph group. Nucleophilic allylation with benzaldehyde would finally give **41**. The lower reactivity of the allylrhodium species **43** and the formation of a more congested C-C bond were thought to be significant obstacles in the formation of **44**.



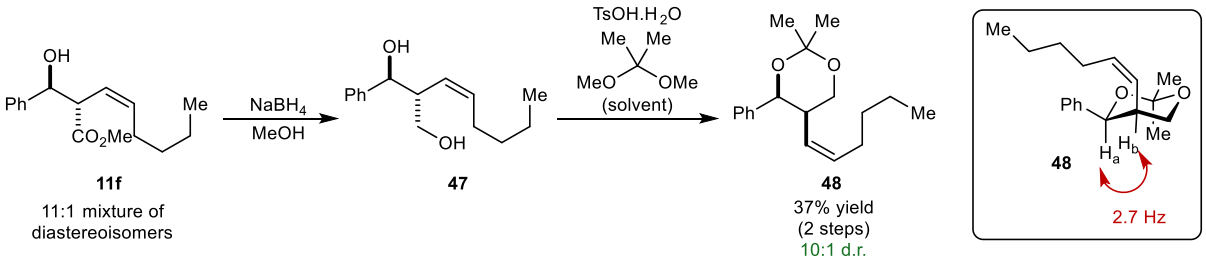
*Scheme 98. Diene **40** gave small quantities of β-allylation product **41**.*

1.2.5 Confirmation of Diastereoselectivity

The relative stereochemistry of the two contiguous stereocentres in the allylation products was predicted to be *anti*- when assuming the nucleophilic allylation proceeds via a closed six-membered Type III transition state. Attempts to grow crystals of some of these compounds and their derivatives in order to confirm this hypothesis were unsuccessful; the products existed as oils or oily solids making crystallisation very challenging.

A solution to this problem was to further functionalise the product and incorporate the two stereocentres into a locked ring environment. This would allow the relationship between

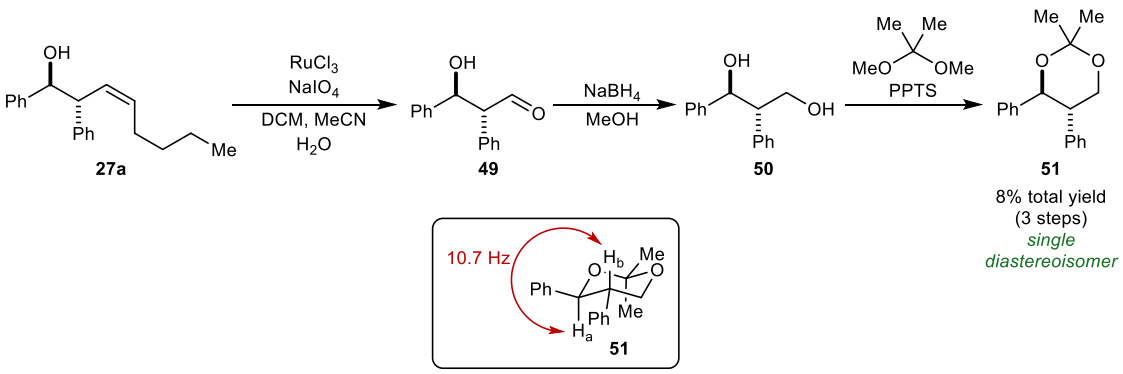
the two H's at the stereocentres to be determined via the $^3J_{HH}$ coupling constants and NOESY NMR analysis. The reaction to synthesise **11f** was scaled up to 1.0 mmol, followed by $NaBH_4$ reduction of the ester to form diol **47** (Scheme 99). Acetonide **48** was formed via acid-catalysed cyclisation with 2,2-dimethoxypropane in accordance with a previous literature procedure on a similar compound.[141]



*Scheme 99. Derivatisation of **11f** to confirm diastereoselectivity.*

NOESY NMR analysis found the benzylic H_a was axial due to its through-space interactions with the axial CH_3 group and one of the CH_2 ring hydrogens, interactions that were considered to be impossible if it was equatorial. The adjacent allylic hydrogen H_b was found to be equatorial, as it possessed through-space interactions with both CH_2 hydrogens and the benzylic H_a. This information, combined with the small $^3J_{HaHb}$ coupling constant of 2.7 Hz, provided strong evidence for the *anti*- relative stereochemistry of ester **11f**. NOESY analysis also indicated that the olefin existed in the *Z*-configuration.

A slightly different route was required in order to confirm that **27a** possessed the same structural configuration. Ru-catalysed oxidative cleavage of the olefin in **27a** gave aldehyde **49**, which could be reduced and cyclised using similar conditions to Scheme 99 to give **51** in 8% yield over three steps (Scheme 100). The product **51** is a known compound and the obtained data was consistent with the literature.[163] NOESY analysis and the $^3J_{HaHb}$ coupling constant value of 10.7 Hz confirmed H_a and H_b both occupied axial positions and therefore **27a** also possessed *anti*- relative stereochemistry.

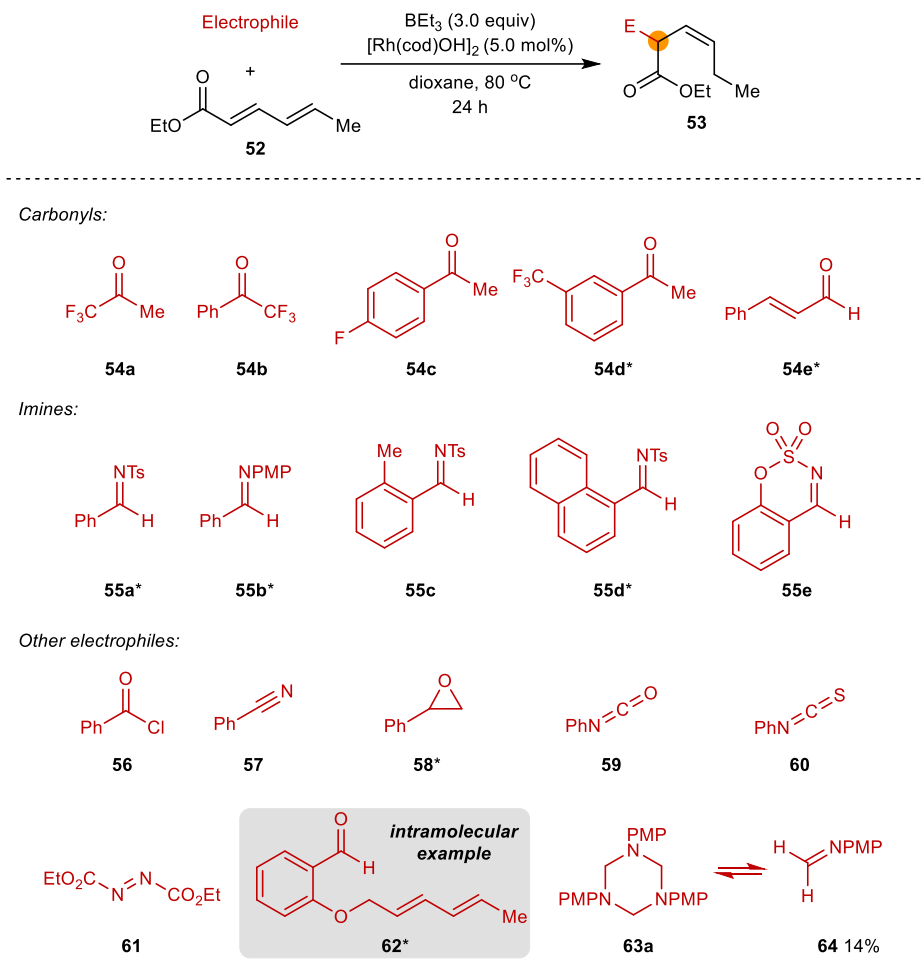


*Scheme 100. Derivatisation of **27a** to confirm diastereoselectivity.*

1.2.6 Other Electrophiles

Whilst the remote nucleophilic allylation process was shown to be tolerant of a range of aldehydes, further scope expansion with respect to the π-electrophiles used was highly desired. It was proposed that this chemistry could naturally be extended to other carbonyl derivatives, such as ketones.

Ketones **54a-54d** were screened, using the standard reaction conditions, and ethyl sorbate **52** was selected as the model diene ester to assess the success of the reductive coupling process before any chain walking attempts were made (Scheme 101). Regrettably, none of the electron-poor ketones gave any product, with only **54d** giving any sign of a possible allylation product in the HRMS spectrum, and just starting materials observed by ^{1}H NMR spectroscopic analysis. Due to the general lower reactivity of ketones compared to aldehydes, electron-poor ketones were chosen as examples with the best chance of success. Nonetheless, it appeared that the allylrhodium species was not reactive enough to favour the C-C bond forming step, and hence no nucleophilic allylation was observed. *E*-cinnamaldehyde **54e** gave no obvious 1,2- or 1,4- addition products either.



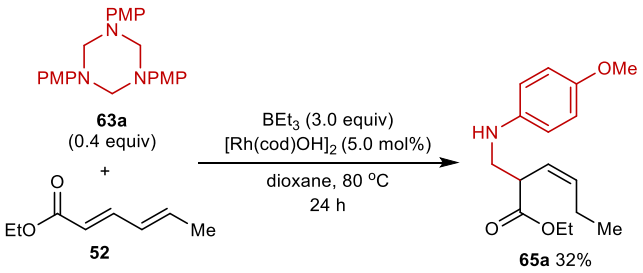
*Scheme 101. Other electrophiles tried. *Trace reactivity: no reaction by ^{1}H NMR spectroscopic analysis but product peak in HRMS.*

Similar problems were also observed with imines **55a-55e**. Trace allylation product peaks were detected via HRMS for all except **55c** but no notable products were observed by NMR spectroscopy. Cyclic imine **55e**, which was the electrophile class used in the Lam group's previous allylrhodium chain walking work, was also ineffective.

In these examples, it is again possible that the allylrhodium intermediate is not reactive enough to favour the reductive coupling process. However, there may also be other factors that explain this unreactivity. When considering the reaction mechanism proposed by Kimura,[141] the transmetalation process (see Scheme 79 in Section 1.1.4.4), which would replace the Rh–N bond with a Rh–Et bond and ultimately regenerate the Rh–H catalytic species and an aminoborane, may be more unfavourable than the Rh–O equivalent. Nitrogen atoms are strong ligand donors to Rh metal centres,[164, 165] and disturbing this interaction may be particularly energetically unfavourable. This Rh–N interaction may also disrupt the six-membered transition state and negatively influence the outcome of the reaction.

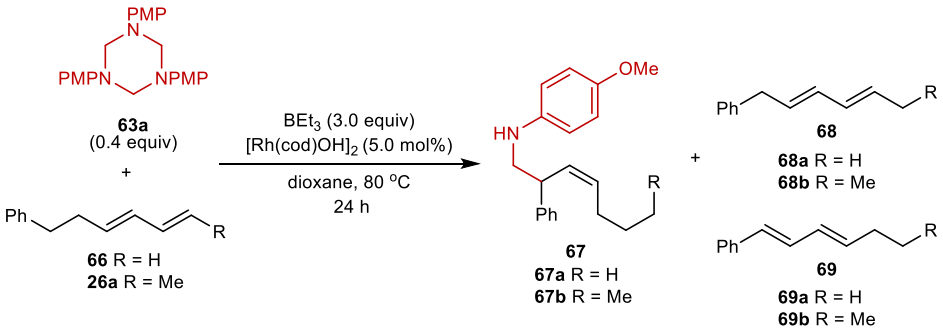
Finally, a myriad of other electrophiles were evaluated, with a particular focus on different π-electrophiles. Examples included benzoyl chloride **56**, benzonitrile **57**, styrene oxide **58**, isocyanate **59**, isothiocyanate **60**, and diethyl azodicarboxylate **61**, and none displayed any reactivity by ^{1}H NMR spectroscopic analysis. Substrate **62** was also subjected to the reaction conditions to attempt an intramolecular cyclisation reaction, which was unfortunately also unsuccessful, possibly due to the rigid aromatic tether disrupting the formation of a possible six-membered transition state.

Finally, 1,3,5-triazinane **63a** was tested. **63a** is a trimeric form of the highly reactive formyl imine species **64**, which must be generated *in situ*, usually by thermal cracking of **63a** when heated, and has previously been reported to form homoallylic amines from allylmetal reagents like Grignards.[138, 166-168] Pleasingly, the desired homoallylic amine **65a** was observed, although the crude NMR yield was only 14%. This was increased to 32% isolated yield on scale up to 0.3 mmol (Scheme 102).



*Scheme 102. Reductive coupling of **52** and **63a**.*

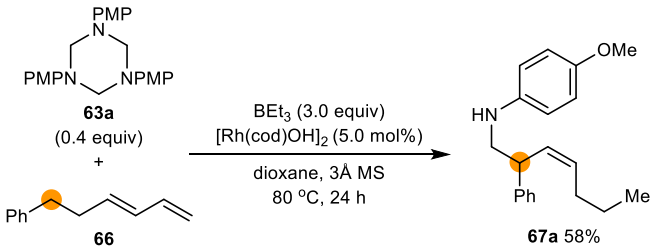
The diene component was then changed to investigate whether remote reductive coupling via allylrhodium chain walking with the triazinane electrophiles was possible. Dienes **26a** and **66** were chosen, with terminal **66** and internal **26a** dienes both trialled under the reaction conditions (Scheme 103).



*Scheme 103. Remote reductive coupling of **63a** and **26a** or **66**.*

Full consumption of **66** was observed, but only 22% of **67a** was detected by crude NMR, with 63% yield of diene isomers **68a** and **69a** in a 3.2:1 ratio also discovered. Internal diene **26a** saw very poor conversion, with only a trace amount of product and starting material recovered instead.

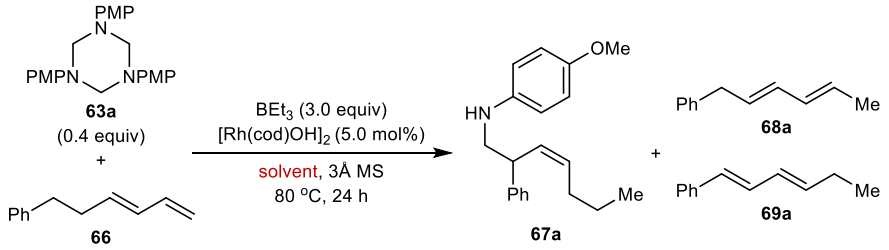
One potential explanation for the poor conversion to **67b**, was the existence of residual water in the reaction system, which could have detrimental effects on the reactivity, either by degrading the triazinane, or quenching the reactive formyl imine **64** that forms after thermal cracking takes place. Molecular sieves have often been used to assist the thermal cracking of 1,3,5-triazinanes.[167] Pleasingly, when oven dried 3Å molecular sieves were added to the reaction solution with **66**, the reaction was remarkably clean, with product **67a** formed as the sole product in 58% isolated yield (Scheme 104). Only trace amounts (<5%) of the diene isomers **68a** and **69a** were observed by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. Disappointingly, internal diene **26b** still demonstrated poor reactivity, with just starting material recovered, suggesting it was important for the dienes to be terminal in this reaction, unlike the results previously reported with aldehydes as electrophiles.



Scheme 104. Remote nucleophilic allylation of triazinane via allylrhodium chain walking.

Attempts to optimise the reaction were made in order to try to further improve the yield of **67a**. First, various protic and aprotic solvents (Table 1) and reaction temperatures (Table 2) were tested.

Table 1. Solvent screen



Solvent	67a %[a]	68a %	69a %
THF	0	10	7
THF[b]	17	6	12
Dioxane[b]	33	5	7
^{i}PrOH	9	11	12
DMF	25	9	11
DMA	0	0	0
MeCN	25	3	6
THF:MeCN (9:1)	19	3	6
PhMe	41	3	7
2Me-THF	0	0	0
DCE	35	2	13

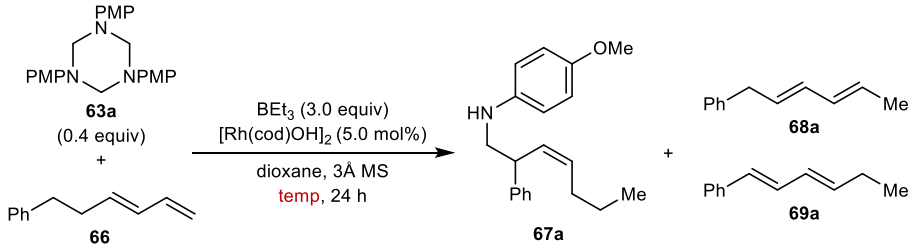
[a] Yields determined by ^{1}H NMR spectroscopic analysis using 1,4-dimethoxybenzene as an internal standard. [b] 5.0 equivalents of MeOH added.

Some form of reactivity was observed for most solvents, be that diene isomerisation to give **68a** and **69a**, successful reductive coupling to **67a** or both (Table 1). The only exceptions were DMA and 2Me-THF, which both gave just recovered starting materials. The best results were observed when using toluene and DCE, with high quantities of **67a** and low amounts of **68a** and **69a**, although the yields were still far below the 58% observed when using dioxane. The use of 5.0 equivalents of MeOH as an additive to dioxane also saw a yield decrease of 25%.

Keeping dioxane as the optimal solvent, the temperature of the reaction was then varied (Table 2). A clear trend was noticed, with 80 °C giving the highest NMR yield and clear drops at temperatures either side. The quantity of isomers was consistently low (*ca*. 10%) with the exception being at 100 °C where a significant quantity of fully conjugated diene **69a** was detected (28%). At higher temperatures, the Rh–H-catalysed isomerisation may be more

favourable, but the reductive coupling process is suppressed. The remaining mass balance at lower temperatures was usually unreacted starting material.

Table 2. Temperature screen.



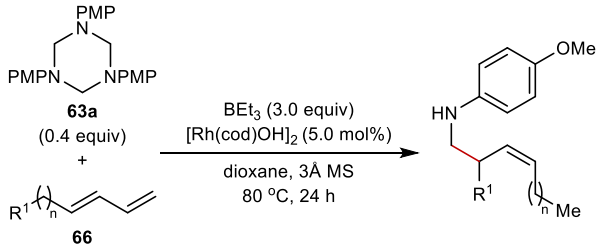
Temperature °C	67a %[a]	68a %	69a %
23	0	4	4
50	14	5	9
70	33	0	6
80	59	0	8
90	33	0	5
100	36	7	28

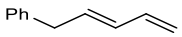
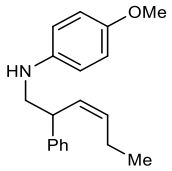
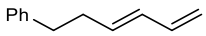
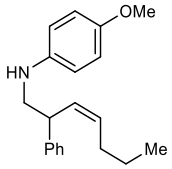
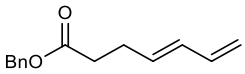
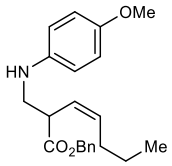
[a] Yields determined by ^{1}H NMR spectroscopic analysis using 1,4-dimethoxybenzene as an internal standard.

Altering the equivalents of BEt_3 and triazinane electrophile (from 3.0 and 0.4 equivalents respectively) and lowering the catalyst loading were all discovered to be detrimental to the yield as well.

Nonetheless, using the optimal reaction conditions, the reductive coupling of PMP triazinane **63a** with a few simple terminal dienes was attempted (Table 3). One-carbon tethered substrate **70** gave only 28% of **71** and diene ester **72** gave aminoester **73** in 25% yield. Only small quantities of the corresponding diene isomers, and no starting materials, were observed via ^{1}H NMR analysis of the unpurified reaction mixtures.

Table 3. Diene variation.

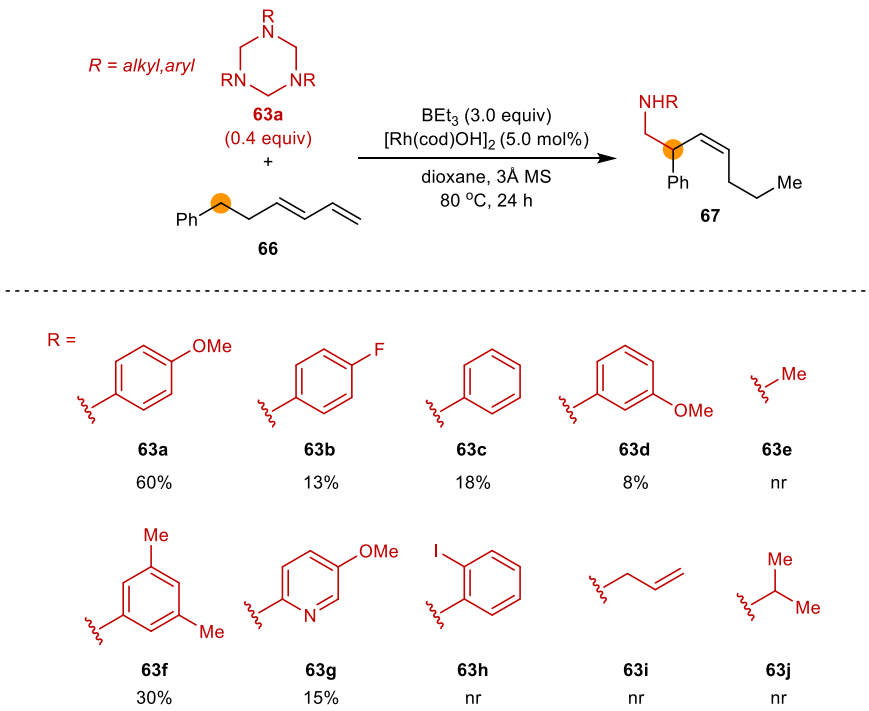


Diene[a]		Product		Yield %[b]
	**70**		**71**	28
	**66**		**67a**	58
	**72**		**73**	25

[a] Reaction conducted with 0.30 mmol of diene. [b] Yield of isolated product.

Unfortunately, the 1,3,5-triazinane scope with diene **66** was extremely limited (Scheme 105). Aryl triazinanes were largely ineffective, with only **63b** (13%), **63c** (18%), **63d** (8%), **63f** (30%) and **63g** (15%) giving any detectable reductive coupling product by ^{1}H NMR analysis of the unpurified reaction mixtures. Alkyl and allyl triazinanes **63e**, **63i** and **63j**, all failed to form the respective product. Small quantities of diene isomerisation products **68a** and **69a** were observed in most of the examples, but unreacted starting materials remained the major species observed by ^{1}H NMR.

Frustratingly, most of these results also had reproducibility issues (with the exception of **63a**) and this issue even remained on scale up with **63c** and **63f**. It was thought this could be attributed to a problem with triazinane cracking as the triazinanes were often still seen in crude NMR spectra. This issue was not addressed successfully, even when using elevated reaction temperatures or Lewis acids, including $TiCl_4$, $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, $Cu(OTf)_2$, $ZnCl_2$, $FeCl_3$, $Yb(OTf)_3$ and $SnCl_4$, to assist the formation of the reactive formyl imine species.

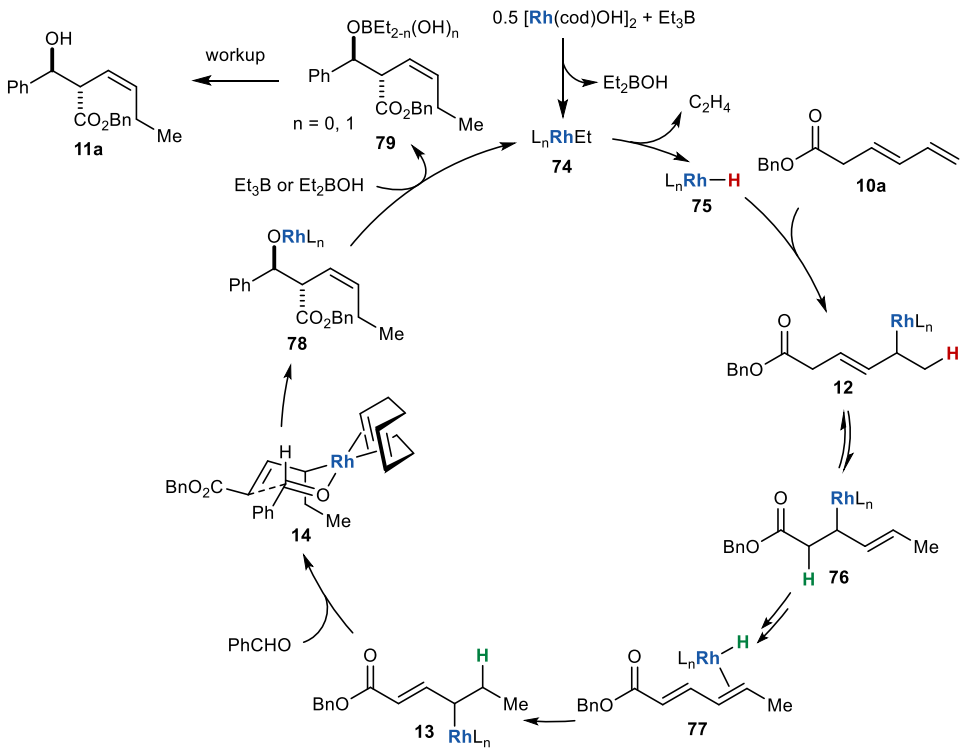


Scheme 105. Triazinane scope.

1.2.7 Mechanistic Studies

A catalytic cycle was proposed, inspired by mechanistic information from the group's previous allylrhodium chain walking work [122] and Kimura's Rh-catalysed reductive coupling of dienes and aldehydes (Scheme 106).[141]

The ethylrhodium species **74** is formed from the transmetallation reaction of $[Rh(cod)OH]_2$ with BEt_3, which then undergoes β-hydride elimination to form rhodium hydride **75** *in situ* with loss of ethylene gas. Diene **10a** was selected as the model substrate, and hydrorhodation of **10a** with **75** provides allylrhodium species **12** which undergoes σ-π-σ isomerisation to give **76**. **76** is transformed into **77** via β-hydride elimination, with rhodium hydride coordinated to benzyl sorbate. A second hydrorhodation of the alkene distal to the benzyl ester gives allylrhodium intermediate **13**, which is stabilised through conjugation with the ester carbonyl. It is believed this stabilising interaction provides a lower energy allylrhodium species and encourages the chain walking process. This migration process facilitates a net 1,4-hydrogen shift (see the green H in Scheme 106) from the carbon α- to the ester group, to methylene carbon adjacent to the terminal methyl group. Substrates with longer carbon tethers require more repetitions of the **12** to **13** process to ultimately form the stabilised allylrhodium species.



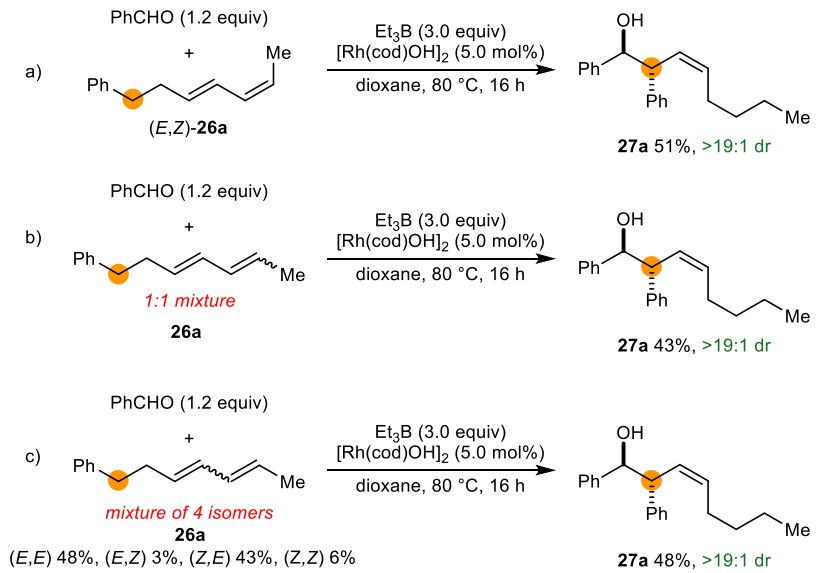
Scheme 106. Proposed catalytic cycle.

Rhodium species **13** then reacts with the benzaldehyde in a Type III nucleophilic allylation via a closed six-membered transition state **14** which can be used to rationalise the stereochemical outcome of alkoxyrhodium **78**. In **14**, the benzyl ester occupies a pseudoequatorial position after pre-equilibrium to the more stable *E*-isomer,[67, 113] and the phenyl group in benzaldehyde does the same to avoid any steric clash with axial substituents. This controls the *anti*- relationship between the two new stereocentres that are formed in this step. Finally, the ethyl group adopts a pseudoaxial configuration to minimise unfavourable non-bonding interactions with the bulky cyclooctadiene ligand, resulting in the exclusive formation of a *Z*-olefin. **78** then reacts with BEt_3 or BEt_2OH to give **79** (which forms product **11a** on workup) and regenerate the RhEt species **74**.

On further assessment of the mechanism, it was thought that the original diene stereochemistry may be inconsequential to the efficacy of the chain walking process. This would remove the need to synthesise the substrates in high stereochemical purity, as the allylrhodium species migrates to form the same stabilised intermediate regardless. This is a significant selling point of alkylmetal chain walking, where isomeric mixtures often converge to a single product.[6]

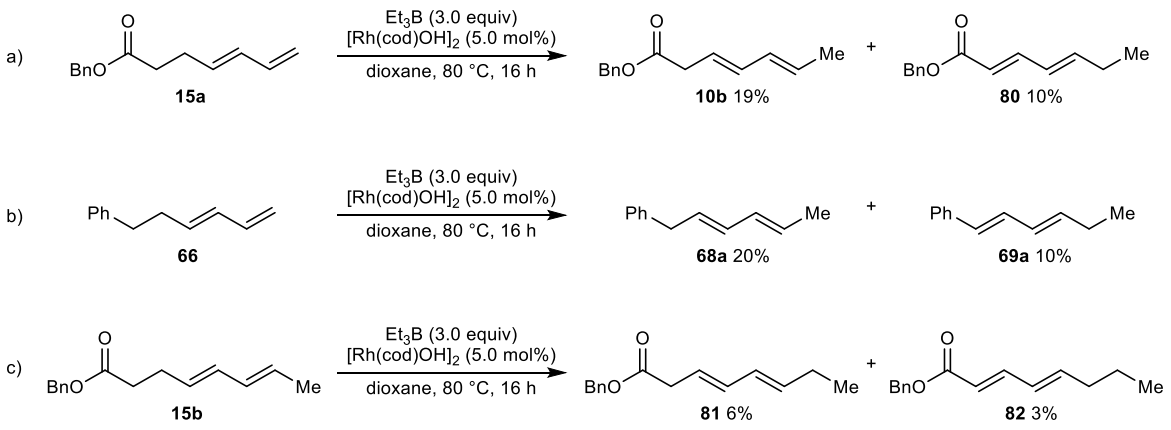
This was investigated with isomers of **26a** as the diene coupling partner. Pleasingly, (*E*,*Z*)-**26a** gave the expected product **27a** in an almost identical yield of 51% (Scheme 107a)

under the reaction conditions. This result was repeated with a comparable 43% yield of **27a** when a 1:1 mixture of (*E*,*E*)-**26a** and (*E*,*Z*)-**27a** was used (Scheme 107b). Finally, a mixture of all four possible stereoisomers of **26a** was subjected to the reaction conditions and also gave **27a** in 48% yield (Scheme 107c). The exclusive formation of the *anti*- diastereoisomer of **27a** was retained in all experiments in Scheme 107, supporting the theory that the allylrhodium chain walking process forms a common stabilised allylrhodium species before the nucleophilic allylation takes place.



Scheme 107. Allylrhodium chain walking with different diene isomers.

The role of the electrophile in the chain walking mechanism was probed further. In the absence of aldehyde, **15a** demonstrated mild isomerisation under the reaction conditions, with 19% **10b** and 10% **80** observed in the crude NMR spectrum (Scheme 108a). The remaining material was unreacted **15a**. This observation was replicated when diene **66** was used, with 20% **68a** and 10% **69a** (Scheme 108b). When this was attempted with internal diene **15b**, only very small amounts of isomerised products **81** (6%) and **82** (3%) were obtained (Scheme 108c). Additionally, for **15b**, no isomerisation in the opposite direction was detected, which would form the corresponding terminal diene. In all examples, the conjugation remained unbroken, with no skipped dienes observed in the crude NMR spectra, suggesting allylrhodium isomerisation instead of distinct migration of each olefin group.



Scheme 108. Investigation without the electrophile.

Initial hydrorhodation of the more reactive terminal dienes are likely favoured over their internal derivatives, however, the lower rate of isomerisation for **15b** compared to **15a** is still surprising given that the reductive coupling yields of internal dienes are slightly higher when aldehyde electrophiles are present. The disparity in results with and without an aldehyde suggest the electrophile plays an important role in driving the allylrhodium chain walking process.

Pleasingly, there does appear to be a small accumulation of the fully conjugated diene in all the examples, supporting the stabilised allylrhodium intermediate theory. However, the fact that a significant quantity of the unreacted starting material remained suggested that diene exchange between a conjugated isomer (for example **77** in catalytic cycle Scheme 106), and a new molecule of diene was very slow. The rapid nucleophilic allylation of the aldehyde was a much more effective way of regenerating a Rh–H species primed for another diene hydrorhodation, but in the absence of any electrophile, the former method is the only possible way to achieve this.

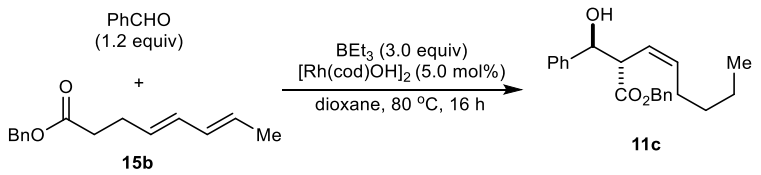
This also suggests that the allylrhodium species prefers to remain engaged to the carbon chain from initial hydrorhodation up until the remote nucleophilic allylation takes place. The lower energy allylrhodium intermediate is favoured, but the nucleophilic allylation provides the main thermodynamic driving force for the migration and completes the catalytic cycle by quickly regenerating another molecule of Rh–H **75**.

All this information may provide additional insight into why some of the substrates used in Section 1.2.4 did not work under these reaction conditions (dienes **37** in Scheme 97 and with electrophiles **54-55** in Scheme 101). The allylrhodium species needs to undergo allylation to quickly reform Rh–H *in situ*, but if it is not reactive enough to attack the

electrophile, then the chain walking and allylation is unfavourable. This results in it getting stuck on the carbon chain, with very slow β-hydride elimination and diene exchange at the Rh centre being the only way to free the Rh centre, meaning most of the starting material remains unreacted.

The transformation of **15b** into **11c** over time was monitored by ^{1}H NMR spectroscopy in the presence of an internal standard (Table 4). Whilst the ^{1}H NMR spectra of the unpurified reaction mixtures did get progressively more complex and difficult to interpret over time, presumably as the amount of the allylation side reaction impurity built up, there remained a clear decrease in the amount of **15b** over time, accompanied by a proportionate increase in the quantity of **11c**. Interestingly, there was no obvious accumulation of diene isomers **81** and **82**, supporting the theory that Rh remains engaged to the carbon chain until successful nucleophilic allylation is achieved.

Table 4. Time experiments.

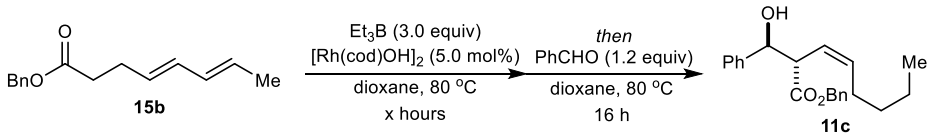


Time (h)	Unreacted 15b %	Yield of 11c %
1	60	4
2	61	9
3	39	19
4	35	22
6	30	26
16	0	63

[a] Yields determined by ^{1}H NMR spectroscopic analysis using 1,4-dimethoxybenzene as an internal standard.

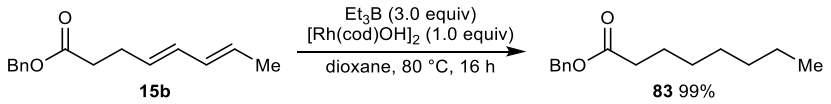
Delayed addition of benzaldehyde to diene **15b** sees yields of **11c** drop significantly and remain at *ca*. 20-30%, irrespective of the time of the delay (from 2 to 4 h). Extending the addition delay to 21 h gave just 12% of **11c**. The loss in yield originates from unreacted starting materials persisting in the crude NMRs, even though the reaction time after the addition is identical to the standard conditions (Scheme 109). This suggests partial pre-isomerisation of

the diene is not beneficial to the yield. Disturbing the inert reaction system to add the aldehyde via micro-syringe may disturb the reaction system enough to perturb the reaction efficacy.



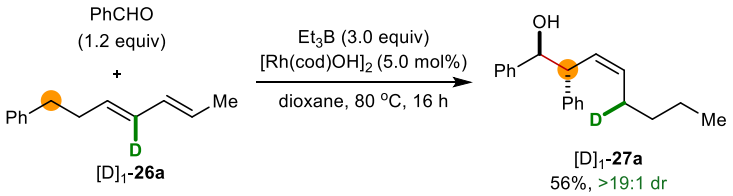
Scheme 109. Delayed addition of PhCHO.

A stoichiometric rhodium experiment with **15b** tested whether the fully conjugated diene **82** could be observed as the sole product. Whilst no **82** was detected, complete reduction of the diene was observed to give benzyl caprylate **83** in a quantitative NMR yield (Scheme 110).



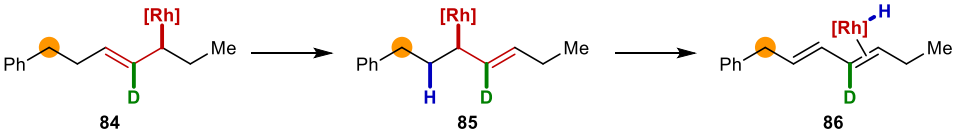
Scheme 110. Quantitative Rh–H experiment.

Deuterium labelling experiments also provided vital mechanistic insight. $[D]_1$-**26a** was synthesised and subjected to the reaction conditions, giving $[D]_1$-**27a** in 56% yield (Scheme 111).



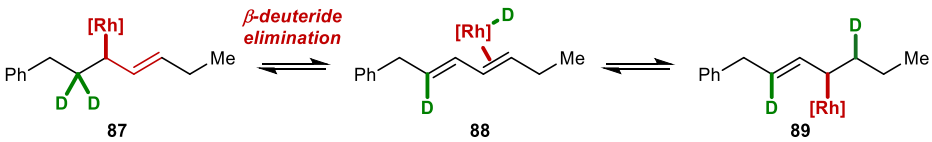
*Scheme 111. Allylrhodium chain walking with $[D]_1$-**26a**.*

No deuterium redistribution was observed, a feature which was predicted when applying the proposed reaction mechanism to the substrate. Indeed, the mechanism demonstrates that the allylrhodium species bypasses the deuterium atom, leaving it untouched in the product (Scheme 112). This also rules out the possibility of a separate isomerisation of each olefin, as seen in alkylmetal chain walking, as this typically results in at least some of the D atoms relocated along the other carbon atoms in the chain.



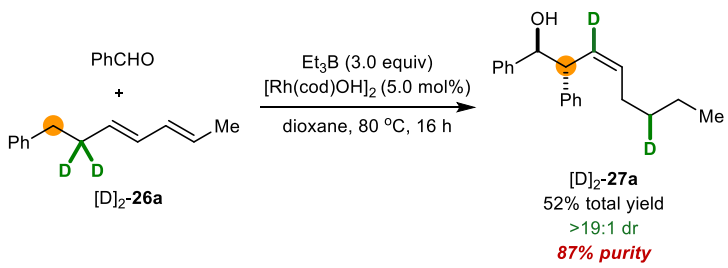
Scheme 112. Mechanism predicts no D redistribution.

Finding a method of forming rhodium deuteride *in situ* would provide useful mechanistic information on the hydrorhodation process, particularly the proposal of a 1,4-hydrogen shift during this chain walking process (**76** to **13** in the catalytic cycle in Scheme 106). Whilst the use of $[D]_{15}$-BEt_3 is possible, experimental preparation is difficult owing to its sensitivity.[169] As an alternative, $[D]_2$-**26a** diene was synthesised, as it is projected to form a Rh-D bound diene **88** *in situ* after *β*-deuteride elimination of **87** (Scheme 113). Following this, hydrorhodation at the distal olefin would install the deuterium atom on the carbon five atoms away from the phenyl group, to give allylrhodium species **89**.



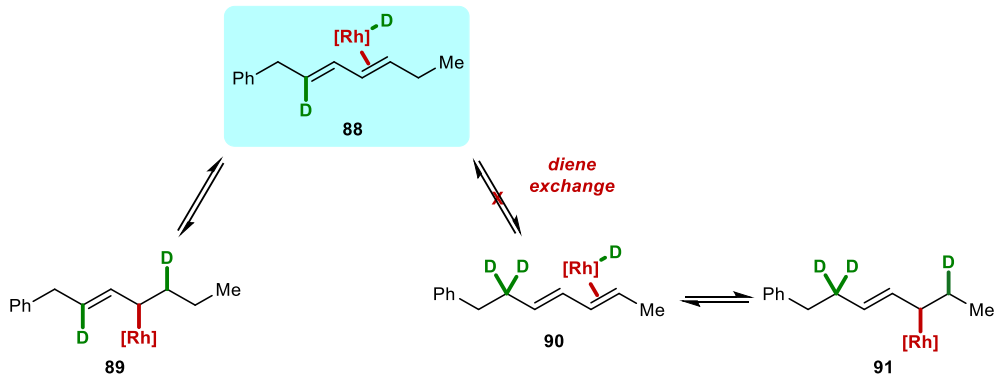
Scheme 113. 1,4-Deuterium shift predicted by proposed mechanism.

Pleasingly, when $[D]_2$-**26a** was subjected to the reaction conditions, the predicted 1,4-deuterium shift was indeed observed, with $[D]_2$-**27a** isolated in ≤87% purity (Scheme 114). Small quantities of other inseparable deuterated compounds contributed to the lower purity but were unidentifiable.[170]



*Scheme 114. Allylrhodium chain walking with $[D]_2$-**26a**.*

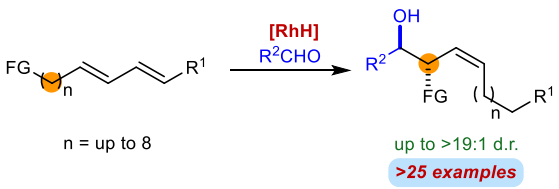
This overall deuterium shift is consistent with the proposed mechanism in Scheme 106. This result also supports the theory of Rh not disengaging from the chain until allylation has occurred. If it did manage this via diene exchange (**88** to **90** in Scheme 115), then Rh-D addition of other diene isomers such as another molecule of $[D]_2$-**26a** would install D at other positions such as in **91** and result in significant deuteration along the carbon chain in the product, which is not obviously seen in $[D]_2$-**27a**.



Scheme 115. Rh prefers to remain engaged to the carbon chain until allylation.

1.2.8 Conclusions and Future Work

In summary, the remote nucleophilic allylation of aldehydes via allylrhodium chain walking derived from hydrorhodation of 1,3-dienes has been explored, using BEt_3 and $[Rh(cod)OH]_2$ in order to generate Rh–H *in situ*. The allylrhodium species migrates towards tethered functional groups up to eight methylene units away before the nucleophilic allylation reaction with a π-electrophile, to give a range of products in good yields and excellent diastereoselectivities (Scheme 116).

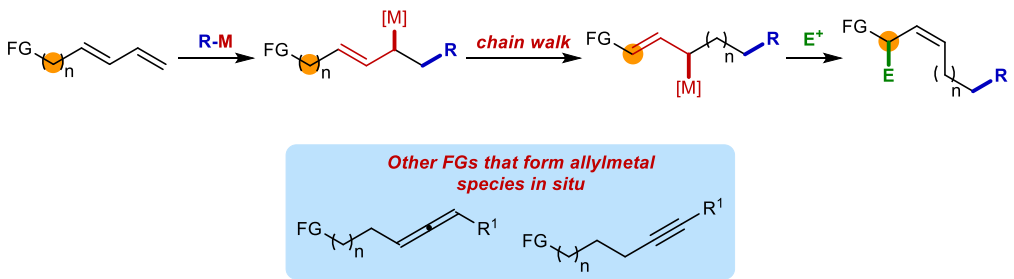


Scheme 116. Allylrhodium chain walking towards tethered functional groups during Rh-catalysed nucleophilic allylation of aldehydes.

The tethered functional groups had to provide a form of stabilising conjugative effect on the migrated allylrhodium species, with esters, amides, aryl and heteroaryl groups all

tolerated. Nucleophilic allylation of aliphatic and aromatic aldehydes, along with aryl triazinanes gave valuable homoallylic alcohols and amine products. The relative stereochemistry of the products was confirmed to be *anti*- and *Z*-olefin selective. Deuteration experiments supported the proposed chain walking mechanism proceeding via a *β*-hydride elimination/hydrorhodation sequence.

This method uses hydride as a nucleophile to form allylmetal species. In future work, changing H to a carbon nucleophile may permit carborhodation of dienes or other functional groups like allenes or alkynes, which are known to form allylmetal species *in situ* in this way. Chain walking of any allylmetal species that forms in this way and also can participate in remote nucleophilic allylations with electrophiles, would demonstrate an example of highly desirable 1,n remote functionalisation (Scheme 117).



Scheme 117. Future work: 1,n-functionalisation.

1.3 Experimental

1.3.1 General Information

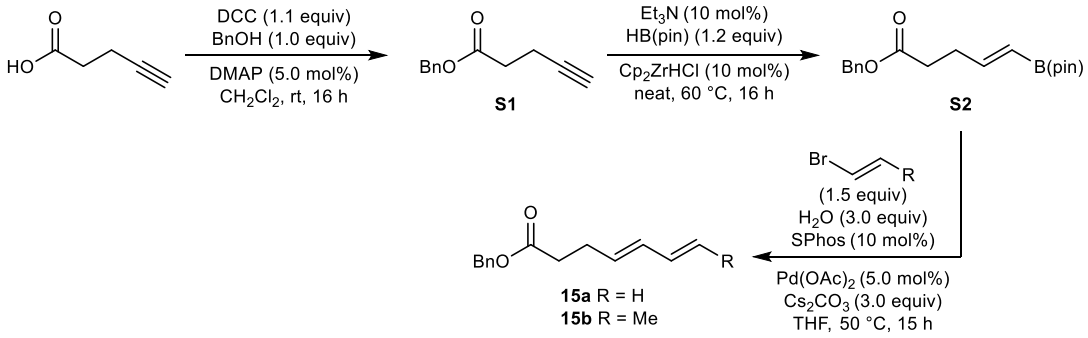
All commercially available reagents were used as received. THF was dried and purified by passage through activated alumina columns using a solvent purification system and then dried over pre-activated molecular sieves for 3 days.[171] "Petroleum ether" refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40–60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or vanillin solution as appropriate. Column chromatography was carried out using silica gel (Fisher Scientific 60Å) particle size 35-70 micron) or using an Interchim Puriflash 430 Series automated purification system with IR-50SI 50µm pre-packed columns. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Nicolet Avatar 360 FT instrument on the neat compound using an attenuated total reflection (ATR) accessory with a diamond crystal and a germanium sample plate, or on a Bruker Tensor 27 FT instrument as a $CHCl_3$ solution.

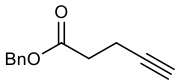
NMR spectra were acquired on Bruker AVA500, Bruker AVA400, Bruker AV(III)400, Bruker DPX400, or Bruker DPX300 spectrometers. ^{1}H and ^{13}C NMR spectra were referenced to tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported 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. Abbreviations used in the description of resonances are: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), app (apparent), br (broad), m (multiplet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ^{19}F NMR spectra were recorded on a Bruker AV(III)400 (376 MHz) spectrometer and were referenced through the solvent lock (^{2}H) signal according to the IUPAC-recommended secondary referencing method using Bruker protocols.

High-resolution mass spectra were recorded using electrospray ionization (ESI) or electron impact ionization (EI) techniques. Magnesium turnings were activated by stirring for 30 min in 1.0 M aqueous HCl solution and were then filtered and washed with H_2O (100 mL), EtOH (100 mL) and Et_2O (100 mL) before being dried under vacuum for 2 h.

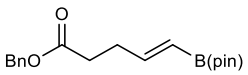
1.3.2 Preparation of Substrates

Preparation of Substrates 15a and 15b



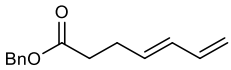


Benzyl pent-4-ynoate (S1). Pent-5-ynoic acid (4.32 g, 44.0 mmol), benzyl alcohol (4.16 mL, 40.0 mmol) and 4-dimethylaminopyridine (244 mg, 2.00 mmol) were dissolved in CH_2Cl_2 (80 mL) and the solution was cooled to 0 °C. DCC (9.08 g, 44.0 mmol) was dissolved in CH_2Cl_2 (80 mL) and the solution was cooled to 0 °C before it was transferred into the first solution *via* cannula. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 16 h. The mixture was filtered and the filtrate was washed with saturated aqueous $NaHCO_3$ solution (50 mL), 1.0 M aqueous HCl solution (50 mL) and saturated aqueous brine (50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (0%-10% EtOAc/petroleum ether) gave benzyl ester **S1** as a colorless oil (6.41 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.32 (5H, m, Ar**H**), 5.18 (2H, s, PhC**H**$_2$), 2.64 (2H, ddd, *J* = 8.0, 6.7, 1.3 Hz, O=CC**H**$_2$), 2.55 (2H, dddd, *J* = 8.0, 6.9, 2.8, 1.4 Hz, O=CCH$_2$C**H**$_2$), 2.00 (1H, t, *J* = 2.6 Hz, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C), 135.7 (C), 128.6 (2 × CH), 128.3 (CH), 128.2 (2 × CH), 82.4 (CH), 69.1 (C), 66.5 (CH$_2$), 33.4 (CH$_2$), 14.4 (CH$_2$). Spectroscopic data matched those reported previously.[172]

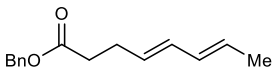


Benzyl (*E*)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enoate (S2). Pinacolborane (1.74 mL, 12.0 mmol) was added slowly to a mixture of alkyne **S1** (1.88 g, 10.0 mmol) and Cp_2ZrHCl (258 mg, 1.00 mmol) at 0 °C. Et_3N (0.14 mL, 1.00 mmol) was added and the mixture was stirred at 60 °C for 16 h. The reaction was cooled to 0 °C, quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (0%-10% EtOAc/petroleum ether with Et_3N-treated

silica) gave *alkenylboronate* **S2** as a colorless oil (1.49 g, 47%). R_f 0.45 (10% EtOAc/petroleum ether); IR 2978, 1737 (C=O), 1639, 1363, 1322, 1144, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (5H, m, Ar**H**), 6.70-6.56 (1H, dt, *J* = 17.7, 5.8 Hz, C**H**=CHB), 5.55-5.43 (1H, dt, *J* = 17.7, 1.2 Hz, CH=C**H**B), 5.13 (2H, s, PhC$\mathbf{H}_2$), 2.54-2.47 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$), 1.27 (12H, s, 4 × C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C), 151.5 (CH), 135.9 (C), 128.5 (2 × CH), 128.20 (2 × CH), 128.18 (CH), 83.1 (2 × C), 66.3 (CH_2), 32.7 (CH_2), 30.6 (CH_2), 24.8 (4 × CH_3), the carbon (CH) adjacent to boron was not observed; HRMS (ESI) Exact mass calculated for $[C_{18}H_{25}BNaO_4]^+$ $[M+Na]^+$: 339.1738, found: 339.1746.



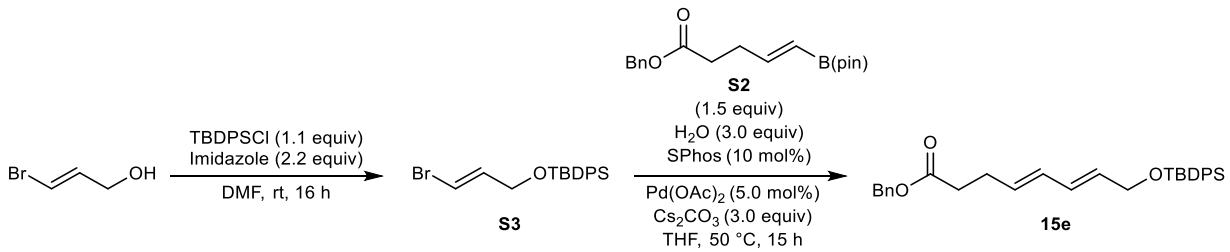
Benzyl (*E*)-hepta-4,6-dienoate (15a). To a degassed suspension of alkenylboronate **S2** (949 mg, 3.00 mmol), Cs_2CO_3 (2.93 g, 9.00 mmol), $Pd(OAc)_2$ (33.7 mg, 0.15 mmol), SPhos (123 mg, 0.30 mmol) and H_2O (0.16 mL, 9.00 mmol) in THF (40 mL) at room temperature was added vinyl bromide (1.0 M in THF, 4.50 mL, 4.50 mmol), and the mixture was stirred at 50 °C for 16 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (0%-10% EtOAc/petroleum ether) gave *diene* **15a** as a colorless oil (315 mg, 49%). R_f 0.45 (10% EtOAc/petroleum ether); IR 3031, 2932, 1731 (C=O), 1449, 1211, 1158, 1133, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (5H, m, Ar**H**), 6.29 (1H, dt, *J* = 16.9, 10.4 Hz, C**H**=CH_2), 6.09 (1H, dd, *J* = 15.0, 10.4 Hz, CH_2CH=C**H**), 5.70 (1H, dt, *J* = 15.0, 6.4 Hz, CH_2C**H**=CH), 5.16-5.08 (3H, m, CH=C$\mathbf{H}_a$$H_b$ and PhC$\mathbf{H}_2$), 5.03-4.99 (1H, m, CH=$CH_a$$\mathbf{H}_b$), 2.52-2.40 (4H, m, O=CC$\mathbf{H}_2$C$\mathbf{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C), 136.8 (CH), 135.9 (C), 132.5 (CH), 132.0 (CH), 128.5 (2 × CH), 128.2 (3 × CH), 115.8 (CH_2), 66.3 (CH_2), 33.8 (CH_2), 27.8 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{14}H_{16}NaO_2]^+$ $[M+Na]^+$: 239.1043, found: 239.1052.

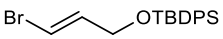


Benzyl (4*E*,6*E*)-octa-4,6-dienoate (15b). To a degassed suspension of alkenylboronate **S2** (949 mg, 3.00 mmol), Cs_2CO_3 (2.93 g, 9.00 mmol), $Pd(OAc)_2$ (33.7 mg, 0.15 mmol), SPhos (123 mg, 0.30 mmol) and H_2O (0.16 mL, 9.00 mmol) in THF (40 mL) at room temperature was added *trans*-1-bromo-1-propene (387 μL, 4.50 mmol), and the mixture was stirred at 50 °C for 16 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the

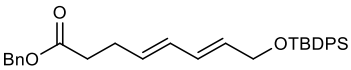
residue by column chromatography (0%-10% EtOAc/petroleum ether) gave *diene* **15b** as a colorless oil (391 mg, 57%). R_f 0.45 (10% EtOAc/petroleum ether); IR 3018, 2968, 2854, 1734 (C=O), 1512, 1454, 1379, 1161, 987, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (5H, m, Ar**H**), 6.09-5.96 (2H, m, =**H**CC**H**=), 5.66-5.48 (2H, m, **H**C=CHCH=C**H**), 5.13 (2H, s, PhC$\mathbf{H}_2$), 2.50-2.37 (4H, m, O=CC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.75-1.73 (3H, d, *J* = 6.8 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9 (C), 136.0 (C), 131.5 (CH), 131.2 (CH), 129.1 (CH), 128.5 (2 × CH), 128.20 (2 × CH), 128.16 (CH), 127.9 (CH), 66.2 (CH_2), 34.1 (CH_2), 27.8 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{18}NaO_2]^+$ $[M+Na]^+$: 253.1199, found: 253.1206.

Preparation of Substrate 15e





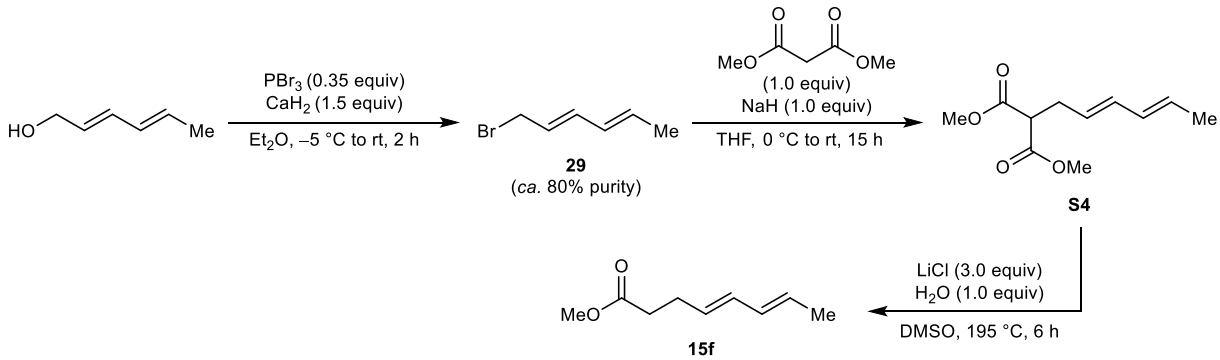
(*E*)-[(3-bromoallyl)oxy](tert-butyl)diphenylsilane (S3). *tert*-Butyldiphenylsilyl chloride (4.54 g, 16.5 mmol) was added to a solution of (*E*)-3-bromoprop-2-en-1-ol (2.06 g, 15.0 mmol) and imidazole (2.25 g, 33.0 mmol) in DMF (15 mL) and stirred for 16 h at room temperature, washed with saturated aqueous NH_4Cl solution (50 mL) and extracted with petroleum ether (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/petroleum ether) give vinyl bromide **S3** as a clear oil (3.37g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.64 (4H m, Ar**H**), 7.47-7.37 (6H, m, Ar**H**), 6.36 (1H, dt, *J* = 13.4, 1.7 Hz, =C**H**CH_2), 6.28 (1H, dt, *J* = 13.4, 4.5 Hz, =C**H**Br), 4.15 (2H, dd, *J* = 4.5, 1.7 Hz, =CHC$\mathbf{H}_2$OSi), 1.07 (9H, s, 3 × C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3 (CH), 135.5 (4 × CH), 133.1 (2 × C), 129.8 (2 × CH), 127.8 (4 × CH), 106.2 (CH), 64.0 (CH_2), 26.8 (3 × CH_3), 19.2 (C). Spectroscopic data matched those reported previously.[173]



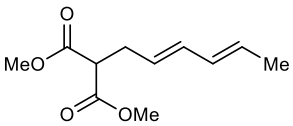
Benzyl (4*E*,6*E*)-8-[(*tert*-Butyldiphenylsilyl)oxy]octa-4,6-dienoate (15e). To a degassed suspension of alkenylboronate **S2** (949 mg, 3.00 mmol), Cs_2CO_3 (2.93 g, 9.00 mmol), $Pd(OAc)_2$ (33.7 mg, 0.15 mmol), SPhos (123 mg, 0.30 mmol) and H_2O (0.16 mL, 9.00 mmol) in THF (10 mL) was added alkenyl

bromide **S3** (1.68 g, 4.50 mmol), and the mixture was stirred at 50 °C for 16 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (5%-8% EtOAc/petroleum ether) gave *diene* **15e** as a colorless oil (650 mg, 45%). R_f 0.37 (10% EtOAc/petroleum ether); IR 3069, 2998, 2930, 2856, 1735 (C=O), 1427, 1378, 1109, 988, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (4H, m, Ar**H**), 7.43-7.35 (11H, m, Ar**H**), 6.26-6.17 (1H, m, =**H**CCH=), 6.07 (1H, dd, *J* = 15.2, 10.5 Hz =HCC**H**=), 5.66 (2H, ddd, *J* = 15.2, 10.5, 6.2 Hz, **H**C=HCCH=C**H**), 5.13 (2H, s, PhC$\mathbf{H}_2$), 4.22 (2H d, *J* = 4.3 Hz, C$\mathbf{H}_2$OSi), 2.50-2.41 (4H, m, O=CC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.06 (9H, s, 3 × C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (C), 135.5 (4 × CH), 134.8 (2 × C), 133.7 (C), 131.4 (CH), 130.92 (CH), 130.86 (CH), 129.60 (2 × CH), 129.56 (CH), 129.55 (CH), 128.5 (2 × CH), 128.2 (2 × CH), 127.6 (4 × CH), 66.2 (CH_2), 64.1 (CH_2), 34.0 (CH_2), 27.9 (CH_2), 26.8 (3 × CH_3), 19.2 (C); HRMS (ESI) Exact mass calculated for $[C_{31}H_{36}NaO_3Si]^+$ $[M+Na]^+$: 507.2331, found: 507.2321.

Preparation of Substrate 15f

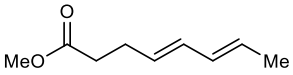


Substrate **15f** was prepared in two steps *via* intermediate **S4** according to a literature procedure.[174]



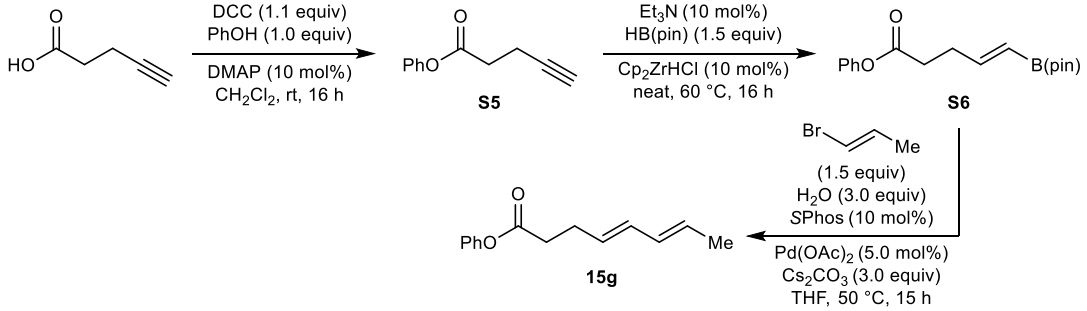
Dimethyl 2-[(2*E*,4*E*)-hexa-2,4-dien-1-yl]malonate (S4). Diene **S4** was prepared by allylation of dimethyl malonate (10.1g, 88.0 mmol) with sorbyl alcohol (12.4 mL, 110 mmol) according to a literature procedure (6.10 g, 32%).[174] ^1H NMR (400 MHz, $CDCl_3$) δ 6.12-5.95 (2H, m, =**H**CC**H**=), 5.63 (1H, dq, *J* = 13.6, 6.8 Hz, =C**H**CH_3), 5.46 (1H, dt, *J* = 14.8, 7.2 Hz, =C**H**CH_2), 3.74 (6H, s, 2 × OC$\mathbf{H}_3$), 3.44 (1H, t, *J* = 7.5 Hz, C**H**$(CO_2Me)_2$), 2.65 (2H, t, *J* = 7.5 Hz, =CHC$\mathbf{H}_2$), 1.73 (3H, d, *J* = 6.1 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (2 × C), 133.4 (CH), 131.0

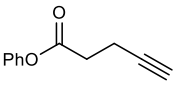
(CH), 128.9 (CH), 125.9 (CH), 52.5 (2 × CH_3), 51.8 (CH), 31.9 (CH_2), 18.0 (CH_3). Spectroscopic data matched those reported previously.[174]



Methyl (4*E*,6*E*)-octa-4,6-dienoate (15f). A degassed suspension of **S4** (6.10 g, 28.8 mmol), LiCl (3.66 g, 86.3 mmol) and H_2O (518 µL, 28.8 mmol) in DMSO (50 mL) was refluxed for 6 h, washed with saturated aqueous NH_4Cl solution and extracted into Et_2O (3 × 50 mL). The combined organic extracts were combined, washed with saturated aqueous brine solution (3 × 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petroleum ether) gave *diene* **15f** as a colorless oil (2.42 g, 20% total yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14-5.91 (2H, m, =**H**CC**H**=), 5.74-5.41 (2H, m, **H**C=CHCH=C**H**), 3.68 (3H, s, OC**H**$_3$), 2.52-2.32 (4H, m, O=CC**H**$_2$C**H**$_2$), 1.74 (3H, dd, *J* = 6.7, 1.5 Hz, =CHC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C), 131.4 (CH), 131.2 (CH), 129.2 (CH), 127.9 (CH), 51.5 (CH_3), 33.9 (CH_2), 27.8 (CH_2), 18.0 (CH_3). Spectroscopic data matched those reported previously.[174]

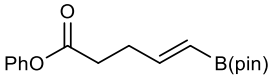
Preparation of Substrate 15g



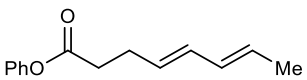


Phenyl pent-4-ynoate (S5). Pent-5-ynoic acid (1.77 g, 18.0 mmol), phenol (1.54 g, 16.4 mmol) and 4-dimethylaminopyridine (110 mg, 0.90 mmol) were dissolved in CH_2Cl_2 (35 mL) and the solution was cooled to 0 °C. DCC (3.71 g, 18.0 mmol) was dissolved in CH_2Cl_2 (35 mL) and the solution was cooled to 0 °C before it was transferred into the first solution *via* cannula. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 16 h. The mixture was filtered and the filtrate was washed with saturated aqueous $NaHCO_3$ solution (50 mL), 1.0 M aqueous HCl solution (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (5%-10% EtOAc/petroleum ether) gave *phenyl ester*

S5 as a colorless oil (2.66 g, 93%). R_f 0.30 (10% EtOAc/petroleum ether); IR 3293, 2925, 1754 (C=O), 1592, 1492, 1192, 1134, 812, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.38 (2H, m, Ar**H**), 7.30-7.23 (1H, m, Ar**H**), 7.16-7.10 (2H, m, Ar**H**), 2.85 (2H, td, *J* = 7.3, 0.8 Hz, O=CC**H**$_2$), 2.67 (2H, tdd, *J* = 7.3, 2.7, 0.8 Hz, O=CCH$_2$C**H**$_2$), 2.07 (1H, t, *J* = 2.7 Hz, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (C), 150.6 (C), 129.4 (2 × CH), 125.92 (CH), 121.5 (2 × CH), 82.0 (CH), 69.4 (C), 33.5 (CH_2), 14.5 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{11}H_{11}O_2]^+$ $[M+H]^+$: 175.0754, found: 175.0755.



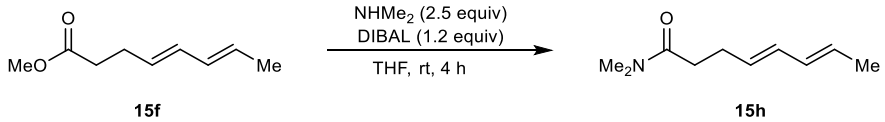
Phenyl *(E)*-5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enoate (S6). Pinacolborane (2.61 mL, 18.0 mmol) was added slowly to a mixture of alkyne **S5** (2.09 g, 12.0 mmol) and Cp_2ZrHCl (309 mg, 1.20 mmol) at 0 °C. Et_3N (167 µL, 1.20 mmol) was added and the mixture was stirred at 60 °C for 16 h. The reaction was cooled to 0 °C, quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (0%-10% EtOAc/petroleum ether with Et_3N-treated silica) gave *alkenylboronate* **S6** as a colorless oil (1.08 g, 30%). R_f 0.30 (10% EtOAc/petroleum ether); IR 2980, 2920, 1751 (C=O), 1643, 1590, 1484, 1178, 1006, 925, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (2H, m, Ar**H**), 7.22 (1H, ddt, *J* = 7.9, 6.9, 1.1 Hz, Ar**H**), 7.07 (2H, dd, *J* = 7.9, 1.1 Hz, Ar**H**), 6.68 (1H, dt, *J* = 18.0, 6.7 Hz, C**H**=CHB), 5.55 (1H, dt, *J* = 18.0, 1.5 Hz, CH=C**H**B), 2.69 (2H, dd, *J* = 6.7, 1.5 Hz, O=CC**H**$_2$), 2.65-2.55 (2H, m, O=CCH$_2$C**H**$_2$), 1.27 (12H, s, 4 × C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C), 151.1 (CH), 150.7 (C), 129.4 (2 × CH), 125.8 (CH), 121.6 (2 × CH), 83.2 (2 × C), 32.8 (CH_2), 30.6 (CH_2), 24.8 (4 × CH_3), the carbon (CH) adjacent to boron was not observed; HRMS (ESI) Exact mass calculated for $[C_{17}H_{23}BNaO_4]^+$ $[M+Na]^+$: 325.1582, found: 325.1588.

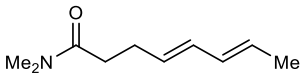


Phenyl (4*E*,6*E*)-octa-4,6-dienoate (15g). To a degassed suspension of alkenylboronate **S6** (604 mg, 2.00 mmol), Cs_2CO_3 (1.95 g, 6.00 mmol), $Pd(OAc)_2$ (22.5 mg, 0.10 mmol), SPhos (82.1 mg, 0.20 mmol) and H_2O (108 µL, 6.00 mmol) in THF (10 mL) at room temperature was added *trans*-1-bromo-1-propene (258 µL, 3.00 mmol), and the mixture was stirred at 50 °C for 16 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (0%-10% EtOAc/petroleum ether) gave *diene* **15g** as a

colorless oil (270 mg, 63%). R_f 0.38 (10% EtOAc/petroleum ether); IR 3018, 2914, 1758 (C=O), 1593, 1492, 1192, 1123, 987, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (2H, m, Ar**H**), 7.24-7.20 (1H, m, Ar**H**), 7.08-7.04 (2H, m, Ar**H**), 6.15-6.00 (2H, m, =**H**CC**H**=), 5.69-5.56 (2H, m, **H**C=CHCH=C**H**), 2.66 (2H, td, *J* = 7.2, 0.9 Hz, O=CC$\mathbf{H}_2$), 2.52 (2H, q, *J* = 7.2 Hz, O=CCH$_2$C$\mathbf{H}_2$), 1.76 (3H, d, *J* = 6.7 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (C), 150.7 (C), 131.8 (CH), 131.2 (CH), 129.4 (2 × CH), 128.7 (CH) 128.2 (CH), 125.7 (CH), 121.6 (2 × CH), 34.2 (CH_2), 27.9 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{14}H_{16}NaO_2]^+$ $[M+Na]^+$: 239.1043, found: 239.1040.

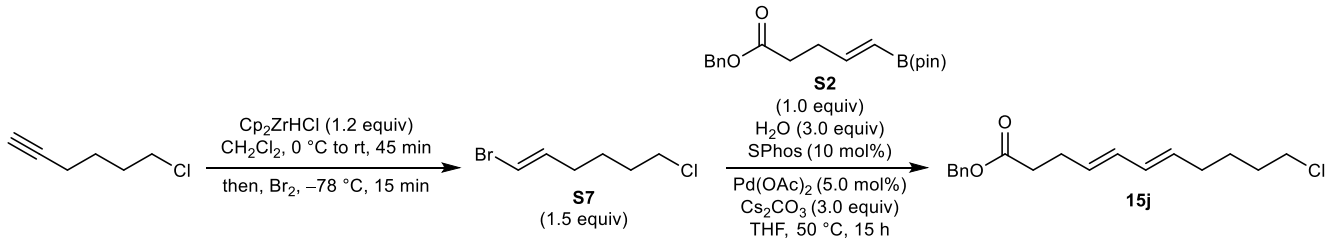
Preparation of Substrate 15h

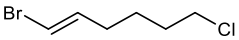




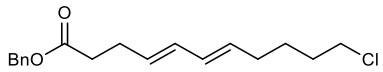
(4*E*,6*E*)-*N*,*N*-Dimethylocta-4,6-dienamide (15h). DIBAL (1.2 M, 2.75 mL, 3.30 mmol) was added dropwise to dimethylamine (2.0 M in THF, 3.75 mL, 7.50 mmol) in anhydrous THF (1 mL) at 0 °C and the mixture was stirred at room temperature for 1 h. A solution of diene **15f** (462 mg, 3.0 mmol) in THF (1 mL) was added at 0 °C and the mixture was stirred at room temperature for 3 h. The reaction was quenched carefully with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* and the residue was purified by column chromatography (50% EtOAc/petroleum ether) to give *amide* **15h** as a colorless oil (102 mg, 21%). R_f 0.20 (50% EtOAc/petroleum ether); IR 3019, 2915, 1631 (C=O), 1401, 1057, 988 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12-5.93 (2H, m, =**H**CC**H**=), 5.69-5.52 (2H, m, **H**C=HCCH=C**H**), 2.99 (3H, s, NC$\mathbf{H}_3$), 2.94 (3H, s, NC$\mathbf{H}_3$), 2.48-2.32 (4H, m, O=CC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.72 (3H, d, *J* = 6.0 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (C), 131.3 (CH), 131.0 (CH), 130.3 (CH), 127.5 (CH), 37.2 (CH_3), 35.3 (CH_3), 33.2 (CH_2), 28.1 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{10}H_{17}NNa]^+$ $[M+Na]^+$: 190.1202, found: 190.1202.

Preparation of Substrate 15j





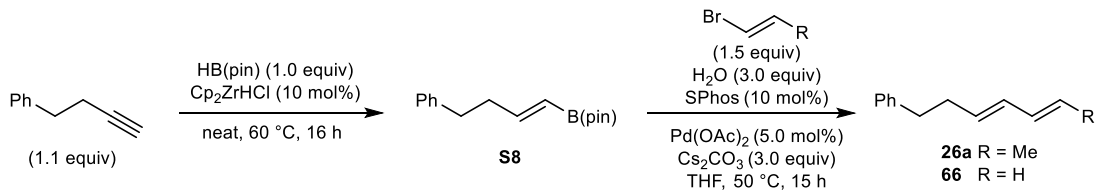
(*E*)-1-Bromo-6-chlorohex-1-ene (S7). 6-Chloro-1-hexyne (1.21 mL, 10.0 mmol) was added dropwise to a solution of Cp_2ZrHCl (3.09 g, 12.0 mmol) in CH_2Cl_2 (35 mL) protected from light at 0 °C. The resulting solution was warmed to room temperature and stirred for 45 min. The reaction was cooled to –78 °C, Br_2 (512 µL, 10.0 mmol) was added dropwise, and the mixture was stirred at this temperature for 15 min. 1.0 M Aqueous HCl solution (20 mL) was added carefully and the mixture was stirred for an additional 15 min. The reaction was warmed to room temperature and the layers were separated. The aqueous layer was extracted with pentane (3 × 20 mL), the combined organic layers were washed with a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution (total 30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (100% petroleum ether) gave alkenyl bromide **S7** as a colorless oil (1.14 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (1H, dt, *J* = 13.5, 7.2 Hz, =C**H**CH_2), 6.06 (1H, dt, *J* = 13.5, 1.4 Hz, =C**H**Br), 3.54 (2H, t, *J* = 6.6 Hz, C**H**$_2$Cl), 2.10 (2H, qd, *J* = 7.3, 1.3 Hz, =CHC**H**$_2$CH$_2$CH$_2$), 1.79 (2H, dq, *J* = 8.2, 6.6 Hz, C**H**$_2$CH$_2$Cl), 1.66-1.50 (2H, m, C**H**$_2$CH$_2$CH$_2$Cl); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3 (CH), 104.8 (CH), 44.6 (CH_2), 32.1 (CH_2), 31.7 (CH_2), 25.8 (CH_2). Spectroscopic data matched those reported previously.[175]

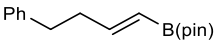


Benzyl (4*E*,6*E*)-11-chloroundeca-4,6-dienoate (15j). A degassed suspension of alkenylboronate **S2** (949 mg, 3.00 mmol), alkenyl bromide **S7** (888 mg, 4.50 mmol), Cs_2CO_3 (2.93 g, 9.00 mmol), $Pd(OAc)_2$ (33.7 mg, 0.15 mmol), SPhos (123 mg, 0.30 mmol) and H_2O (0.16 mL, 9.00 mmol) in THF (40 mL) was stirred at 50 °C for 16 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (0%-10% EtOAc/petroleum ether) gave *diene* **15j** as a colorless oil (582 mg, 63%). R_f 0.38 (2% EtOAc/petroleum ether); IR 3017, 2934, 2857, 1733 (C=O), 1497, 1454, 1159, 987, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.32 (5H, m, Ar**H**), 6.10-5.96 (2H,

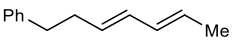
m, =**H**CC**H**=), 5.58 (2H, dt, *J* = 15.5, 6.8 Hz, **H**C=CHCH=C**H**), 5.14 (2H, s, PhC$\mathbf{H}_2$), 3.56 (2H, t, *J* = 6.6 Hz, C$\mathbf{H}_2$Cl), 2.51-2.41 (4H, m, O=CC$\mathbf{H}_2$C$\mathbf{H}_2$), 2.12 (2H, q, *J* = 6.8 Hz, =CHC$\mathbf{H}_2$CH$_2$CH$_2$), 1.85-1.76 (2H, m, C$\mathbf{H}_2$CH$_2$Cl), 1.60-1.51 (2H, m, C$\mathbf{H}_2$CH$_2$CH$_2$Cl); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.8 (C), 136.0 (C), 132.4 (CH), 131.4 (CH), 130.5 (CH), 129.9 (CH), 128.5 (2 × CH), 128.19 (2 × CH), 128.18 (CH), 66.2 (CH$_2$), 44.9 (CH$_2$), 34.0 (CH$_2$), 32.0 (CH$_2$), 31.7 (CH$_2$), 27.8 (CH$_2$), 26.5 (CH$_2$); HRMS (ESI) Exact mass calculated for [C$_{18}$ClH$_{23}$NaO$_2$]$^+$ [M+Na]$^+$: 329.1284, found: 329.1279.

Preparation of Substrates 26a and 66



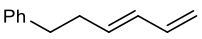


(*E*)-4,4,5,5-Tetramethyl-2-(4-phenylbut-1-en-1-yl)-1,3,2-dioxaborolane (S8). The title compound was prepared by hydroboration of 4-phenyl-1-butyne (1.41 mL, 10.0 mmol) according to a literature procedure (1.86 g, 72%).[176] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33-7.25 (2H, m, Ar**H**), 7.25-7.13 (3H, m, Ar**H**), 6.71 (1H, dt, *J* = 18.0, 6.2 Hz, C**H**=CHB), 5.51 (1H, dt, *J* = 18.0, 1.6 Hz, CH=C**H**B), 2.80-2.72 (2H, m, PhC$\mathbf{H}_2$), 2.53-2.44 (2H, m, PhCH$_2$C$\mathbf{H}_2$), 1.28 (12H, s, 4 × C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 153.4 (CH), 141.8 (C), 128.3 (4 × CH), 125.8 (CH), 83.1 (2 × C), 37.5 (CH$_2$), 34.6 (CH$_2$), 24.8 (4 × CH$_3$), the carbon (CH) adjacent to boron was not observed. Spectroscopic data matched those reported previously.[176]



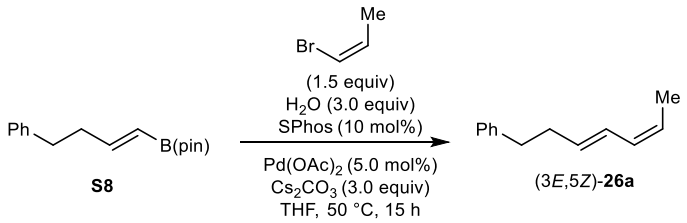
(3*E*,5*E*)-Hepta-3,5-dien-1-ylbenzene (26a). To a degassed suspension of **S8** (1.29 g, 5.00 mmol), Cs$_2$CO$_3$ (4.89 g, 15.0 mmol), Pd(OAc)$_2$ (56.1 mg, 0.25 mmol), SPhos (205 mg, 0.50 mmol) and H$_2$O (270 µL, 15.0 mmol) in THF (30 mL) and room temperature was added *trans*-1-bromo-1-propene (624 µL, 7.50 mmol), and the mixture was stirred at 50 °C for 16 h. The reaction was cooled to room temperature, diluted with H$_2$O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (100% petroleum ether) gave diene **26a** as a colorless oil (728 mg, 84%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32-7.27 (2H, m, Ar**H**), 7.23-7.17 (3H, m, Ar**H**), 6.10-5.97 (2H, m, =**H**CC**H**=), 5.67-5.52 (2H, m, **H**C=CHCH=C**H**), 2.76-2.66 (2H, m, PhC$\mathbf{H}_2$), 2.44-2.33 (2H, m,

$PhCH_2C\mathbf{H}_2$), 1.74 (3H, d, J = 6.4 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (C), 131.5 (CH), 130.9 (CH), 130.8 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 127.3 (CH), 125.8 (CH), 35.9 (CH_2), 34.4 (CH_2), 18.0 (CH_3). Spectroscopic data matched those reported previously.[177]



(*E*)-Hexa-3,5-dien-1-ylbenzene (66). To a degassed suspension of **S8** (1.03 g, 4.00 mmol), Cs_2CO_3 (3.91 g, 12.0 mmol), $Pd(OAc)_2$ (44.9 mg, 0.20 mmol), SPhos (164 mg, 0.40 mmol) and H_2O (216 µL, 12.0 mmol) in THF (10 mL) at room temperature was added vinyl bromide (1.0 M in THF, 6.0 mL, 6.0 mmol), and the mixture was stirred at 50 °C for 16 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (100% petroleum ether) gave diene **66** as a colorless oil (337 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (2H, m, Ar**H**), 7.23-7.18 (3H, m, Ar**H**), 6.32 (1H, dt, J = 17.0, 10.4 Hz, C**H**=CH_2), 6.11 (1H, dd, J = 15.0, 10.4 Hz, CH_2CH=C**H**), 5.76 (1H, dt, J = 15.0, 6.9 Hz, CH_2C**H**=CH), 5.12 (1H, dd, J = 17.0, 1.6 Hz, CH=C$\mathbf{H}_a$$H_b$), 4.99 (1H, dd, J = 10.2, 1.6 Hz, CH=$CH_a$$\mathbf{H}_b$), 2.73 (2H, dd, J = 9.0, 6.7 Hz, PhC$\mathbf{H}_2$), 2.47-2.38 (2H, m, $PhCH_2C\mathbf{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7 (C), 137.1 (CH), 134.2 (CH), 131.4 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 125.8 (CH), 115.2 (CH_2), 35.6 (CH_2), 34.4 (CH_2). Spectroscopic data matched those reported previously.[178]

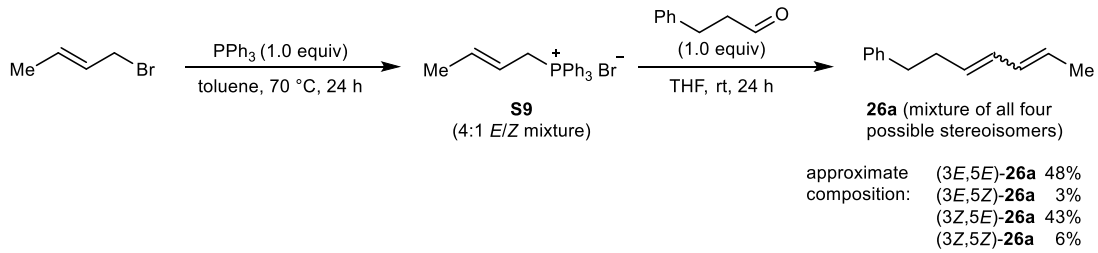
Preparation of (3*E*,5*Z*)-Hepta-3,5-dien-1-ylbenzene [(3*E*,5*Z*)-26a]

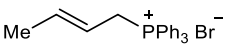


To a degassed suspension of **S8** (646 g, 2.50 mmol), Cs_2CO_3 (2.44 g, 7.50 mmol), $Pd(OAc)_2$ (28.1 mg, 0.125 mmol), *S*Phos (103 mg, 0.25 mmol) and H_2O (135 µL, 7.50 mmol) in THF (10 mL) was added *cis*-1-bromo-1-propene (319 µL, 3.75 mmol), and the mixture was stirred at 50 °C for 16 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (100% petroleum ether) gave diene (*E*,*Z*)-**26a** as a colorless oil (316 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (2H, m, Ar**H**), 7.24-7.18 (3H, m, Ar**H**), 6.39 (1H, ddt, J = 15.1, 10.9, 1.4 Hz, CH_2CH=C**H**), 5.99 (1H, tt, J = 10.9, 1.9 Hz, C**H**=$CHCH_3$), 5.72 (1H, dt, J = 14.6, 6.9 Hz,

$CH_2C\mathbf{H}$=), 5.47-5.37 (1H, m, =C**H**CH_3), 2.74 (2H, t, *J* = 7.9 Hz, PhC$\mathbf{H}_2$), 2.45 (2H, q, *J* = 7.6 Hz, $PhCH_2C\mathbf{H}_2$), 1.75 (3H, dd, *J* = 6.9, 1.8 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (C), 133.2 (CH), 129.3 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 125.9 (CH), 125.8 (CH), 124.5 (CH), 35.9 (CH_2), 34.7 (CH_2), 13.3 (CH_3). Spectroscopic data matched those reported previously.[179]

Preparation of Substrate 26a (mixture of all possible stereoisomers)



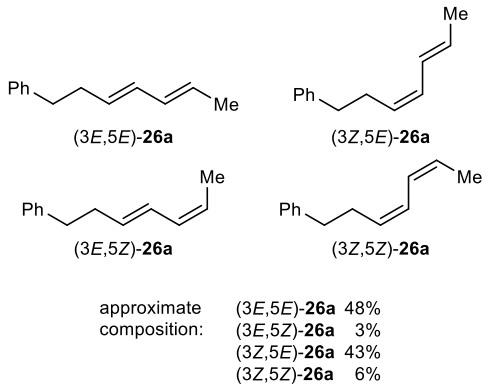


(*E*)-But-2-en-1-yltriphenylphosphonium bromide (S9). Crotyl bromide (891 µL, 6.60 mmol) was added to a suspension of triphenylphosphine (1.73 g, 6.60 mmol) in anhydrous toluene (5 mL) and the solution was heated to 70 ˚C for 24 h. The suspension was filtered and washed with cold toluene (3 × 10 mL) to give phosphonium bromide **S9** as a 4:1 mixture of *E*/*Z* isomers as a white powder (1.88 g, 72%).

Characteristic NMR data of (*E*)-***S9***: ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.60 (15H, m, Ar**H**), 6.07-5.96 (1H, m, =C**H**CH_2), 5.35-5.23 (1H, m, =C**H**CH_3), 4.79 (2H, ddd, *J* = 14.7, 7.2, 1.3 Hz, =CHC$\mathbf{H}_2$), 1.63 (3H, s, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.89 (CH, J_{CP} = 13.5 Hz), 134.87 (3 × CH, J_{CP} = 2.8 Hz), 133.99 (6 × CH, J_{CP} = 9.7 Hz), 130.23 (6 × CH, J_{CP} = 12.6 Hz), 118.33 (3 × C, J_{CP} = 85.5 Hz), 114.79 (CH, J_{CP} = 9.8 Hz), 27.88 (CH_2, J_{CP} = 49.1 Hz), 18.38 (CH_3, J_{CP} = 2.8 Hz).

Characteristic NMR data of (*Z*)-***S9***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.82 (1H, m, =C**H**CH_2), 5.49-5.37 (ddtd, *J* = 9.9, 7.6, 5.6, 1.9 Hz, =C**H**CH_3), 4.75 (2H, d, *J* = 7.9 Hz, =CHC$\mathbf{H}_2$), 1.62 (3H, s, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.92 (3 × CH, J_{CP} = 3.3 Hz), 133.94 (6 × CH, J_{CP} = 9.8 Hz), 130.28 (6 × CH, J_{CP} = 12.6 Hz), 23.68 (CH_2, J_{CP} = 50.0 Hz), 13.73 (CH_3, J_{CP} = 2.9 Hz).

Spectroscopic data matched those reported previously.[180]



Hepta-3,5-dien-1-ylbenzene (26a, mixture of all four possible stereoisomers). A mixture of (*E*)-but-2-en-1-yltriphenylphosphonium bromide (1.31 g, 3.30 mmol) and KO*t*-Bu (1.66 g, 4.20 mmol) was dissolved in anhydrous THF (10 mL) and the solution was stirred at room temperature for 30 min. 3-Phenylpropionaldehyde (395 µL, 3.00 mmol) was added and the solution was stirred at room temperature for 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*, and the residue was purified by column chromatography (100% petroleum ether) to give diene **26a** as a mixture of all four possible stereoisomers as a colorless oil (85 mg, *ca.* 17%), which also contained unidentified impurities.

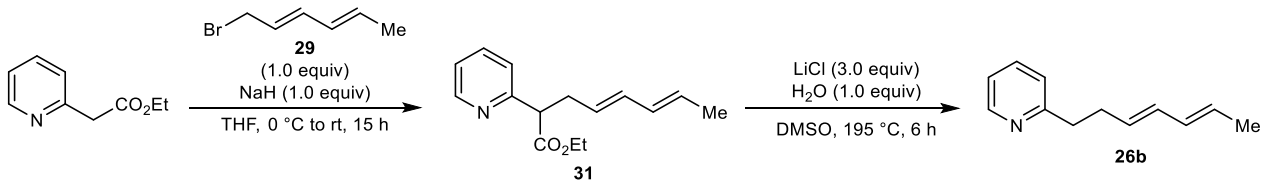
Spectroscopic data for (3*E*,5*E*)-**26a** [177] and (3*E*,5*Z*)-**26a** [179] matched those reported previously.

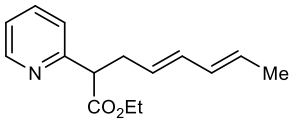
Characteristic NMR data of (3Z,5E)-**26a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38-6.29 (1H, m, **H**C=CHCH$_3$), 6.09-5.96 (1H, m, H$_2$CHC=C**H**), 5.76-5.66 (1H, m, =C**H**CH$_3$), 5.35 (1H, dt, *J* = 10.9, 7.4 Hz, =C**H**CH$_2$), 2.75-2.67 (2H, m, PhC**H**$_2$), 2.56-2.46 (2H, m, PhCH$_2$C**H**$_2$), 1.78 (3H, dd, *J* = 7.0, 1.6 Hz, CHC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (C), 130.9 (CH), 129.5 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 126.8 (CH), 125.8 (CH), 36.0 (CH$_2$), 29.6 (CH$_2$), 18.3 (CH$_3$).

Characteristic NMR data of (3Z,5Z)-**26a**: ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.5 (CH), 128.7 (CH), 126.5 (CH), 126.1 (CH), 124.3 (CH), 123.9 (CH), 35.9 (CH$_2$), 29.4 (CH$_2$), 13.2 (CH$_3$).

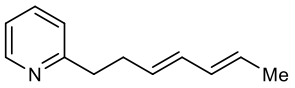
Note: not all signals for (3*Z*,5*Z*)-**26a** were identifiable due to the small proportion of material and overlap of signals with those of the other diene isomers in both the ^{1}H NMR and ^{13}C NMR spectra, especially in the aromatic and alkene regions.

Preparation of Substrate 26b





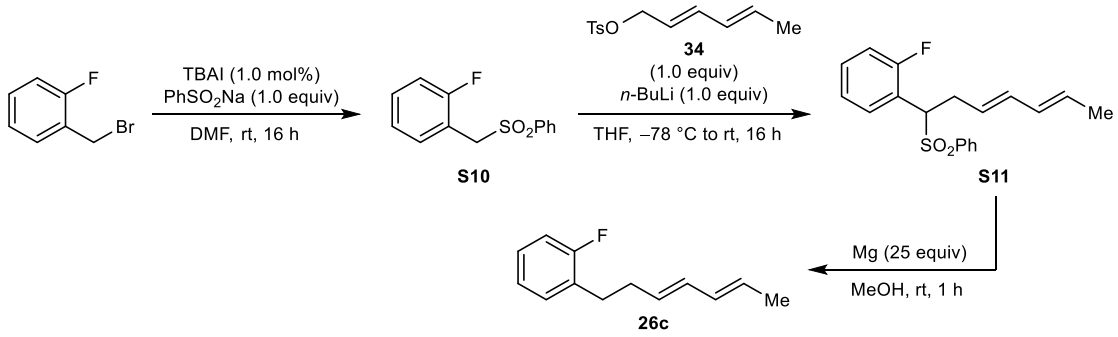
Ethyl (4*E*,6*E*)-2-(pyridin-2-yl)octa-4,6-dienoate (31). Ethyl 2-(pyridin-2-yl)acetate (1.52 mL, 10.0 mmol) was added dropwise to a solution of NaH (60% in mineral oil, 420 mg, 10.5 mmol) in THF (10 mL) at room temperature and the mixture was stirred for 2 h. The solution was cooled to 0 °C and a solution of allyl bromide **29** [174] (2.00 g, 12.5 mmol) in THF (10 mL) added dropwise over 30 min. After stirring at room temperature for 16 h, the reaction was diluted with saturated aqueous NH_4Cl solution (30 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petroleum ether) gave *diene* **31** as a yellow oil (670 mg, 27%). R_f 0.45 (10% EtOAc/petroleum ether); IR 2978, 2933, 1729 (C=O), 1588, 1570, 1470, 1434, 1149, 989, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (1H, ddd, *J* = 4.9, 1.9, 1.0 Hz, Ar**H**), 7.64 (1H, td, *J* = 7.8, 1.9 Hz, Ar**H**), 7.29 (1H, dt, *J* = 7.9, 1.1 Hz, Ar**H**), 7.17 (1H, ddd, *J* = 7.5, 4.9, 1.1 Hz, Ar**H**), 6.07-5.90 (2H, m, =**H**CC**H**=), 5.57 (1H, dq, *J* = 13.6, 6.6 Hz, =C**H**CH_3), 5.46 (1H, dt, *J* = 14.6, 7.1 Hz, CH_2C**H**=), 4.15 (2H, q, *J* = 7.1 Hz, OC$\mathbf{H}_2$), 3.85 (1H, dd, *J* = 8.2, 7.1 Hz, ArC**H**), 2.86 (1H, dt, *J* = 15.1, 7.1 Hz, C$\mathbf{H}_a$$H_b$CH=), 2.67 (1H, dt, *J* = 14.3, 7.1 Hz, $CH_a$$\mathbf{H}_b$CH=), 1.70 (3H, d, *J* = 6.8 Hz, =CHC$\mathbf{H}_3$), 1.20 (3H, t, *J* = 7.1 Hz, CH_2C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C), 158.3 (C), 149.5 (CH), 136.6 (CH), 132.7 (CH), 131.2 (CH), 128.1 (CH), 127.4 (CH), 122.6 (CH) 122.1 (CH), 60.9 (CH_2), 54.2 (CH), 35.3 (CH_2), 18.0 (CH_3), 14.2 (CH_3); HRMS (ESI) Exact mass calculated for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1494, found: 246.1506.

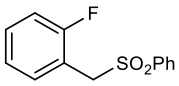


2-[(3*E*,5*E*)-Hepta-3,5-dien-1-yl]pyridine (26b). A solution of ester **31** (737 mg, 3.00 mmol), LiCl (381 mg, 9.00 mmol), H_2O (54.0 µL, 3.00 mmol) and DMSO (6 mL) was heated to reflux for 6 h, washed with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (50% EtOAc/petroleum ether) gave *diene* **26b** as a yellow oil (361 mg, 70%). R_f 0.61 (50% EtOAc/petroleum ether); IR 3013, 2913, 2851, 1589, 1568, 1473, 1433, 1148, 986, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H, ddd, *J* = 4.9, 1.9, 1.0 Hz, Ar**H**), 7.58 (1H, dt, *J* = 7.7, 1.9 Hz, Ar**H**), 7.16-7.06 (2H, m, Ar**H**), 6.08-5.92 (2H, m, =**H**CC**H**=), 5.57 (2H, ddt, *J* = 13.4, 9.2, 6.8 Hz, **H**C=HCCH=C**H**), 2.86 (2H, app dd, *J* = 8.9, 6.8 Hz, ArC$\mathbf{H}_2$), 2.49 (2H, q, *J* = 9.2 Hz, C$\mathbf{H}_2$CH=), 1.75 (3H, d, *J* = 6.8 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (C) 149.3 (CH), 136.2 (CH), 131.5 (CH), 131.0 (CH), 130.5 (CH), 127.4 (CH),

122.8 (CH), 121.0 (CH), 38.2 (CH_2), 32.7 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $C_{12}H_{16}N$ $[M+H]^+$: 174.1283, found: 174.1282.

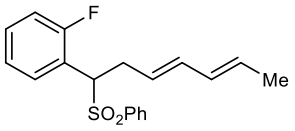
Preparation of Substrate 26c





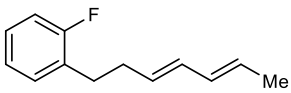
1-Fluoro-2-[(phenylsulfonyl)methyl]benzene (S10). 1-(Bromomethyl)-2-fluorobenzene (4.80 mL, 40.0 mmol) was added dropwise to a solution of $PhSO_2Na$ (6.57 g, 40.0 mmol) and TBAI (148 mg, 0.40 mmol) in DMF (50 mL) at room temperature and the mixture was stirred for 16 h. The mixture was partitioned between H_2O (100 mL) and Et_2O (200 mL) in a separating funnel, which led to the formation of a solid. The minimum quantity of CH_2Cl_2 was added to dissolve the solid, and aqueous layer was then separated and extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by trituration (Et_2O) gave sulfone **S10** as a white solid (7.10 g, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.59 (3H, m, Ar**H**), 7.51-7.44 (2H, m, Ar**H**), 7.37-7.29 (2H, m, Ar**H**), 7.13 (1H, td, J = 7.5, 1.2 Hz, Ar**H**), 6.92 (1H, ddd, J = 9.8, 8.0, 1.2 Hz, Ar**H**), 4.41 (2H, s, ArC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (d, J_{CF} = 250.0 Hz, C), 137.9 (C), 133.8 (CH), 132.7 (d, J_{CF} = 2.7 Hz, CH), 130.9 (d, J_{CF} = 8.1 Hz, CH), 128.9 (2 × CH), 128.6 (2 × CH), 124.4 (d, J_{CF} = 3.7 Hz, CH), 115.8 (d, J_{CF} = 14.4 Hz, C), 115.4 (d, J_{CF} = 21.5 Hz, CH), 55.7 (CH_2). Spectroscopic data matched those reported previously.[181]



1-Fluoro-2-[(3*E*,5*E*)-1-(phenylsulfonyl)hepta-3,5-dien-1-yl]benzene (S11). *n*-BuLi (2.12 M in hexanes, 11.8 mL, 25.0 mmol) was added dropwise to a solution of (2*E*,4*E*)-hexa-2,4-dien-1-ol (2.76 mL, 25.0 mmol) in THF (30 mL) at –78 °C under and the mixture was stirred for 15 min. A solution of *p*-toluenesulfonyl chloride (5.24 g, 27.5 mmol) in THF (10 mL) was added dropwise and the solution was stirred at –78 °C for 1 h to give a solution of allylic tosylate **S34**.

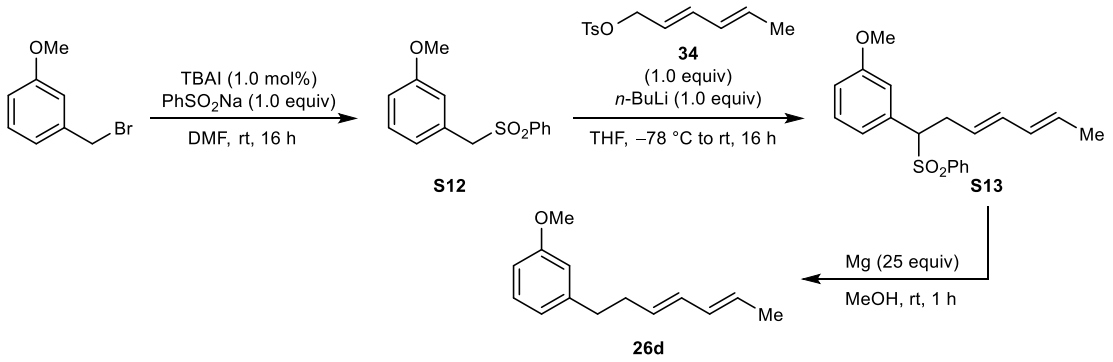
Simultaneously, in a separate flask, *n*-BuLi (2.12 M in hexanes, 11.8 mL, 25.0 mmol) was added dropwise to a solution of sulfone **S10** (6.26 g, 25.0 mmol) in THF (40 mL) at –78 °C and the mixture was stirred for 1 h. To this solution was added the solution of allylic tosylate **34** dropwise *via* cannula, and the mixture was stirred for 16 h while being warmed gradually to room temperature. The reaction was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *sulfone* **S11** as a white solid (4.76 g), which was contaminated with an unknown impurity. R_f 0.30 (20% EtOAc/petroleum ether); IR 3018, 2912, 2851, 1491, 1447, 1302, 1149, 1083, 758, 683, 566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.51 (4H, m, Ar**H**), 7.42-7.36 (2H, m, Ar**H**), 7.31-7.23 (1H, m, Ar**H**), 7.18 (1H, td, *J* = 7.6, 1.3 Hz, Ar**H**), 6.82 (1H, ddd, *J* = 9.8, 8.2, 1.3 Hz, Ar**H**), 6.03 (1H, dd, *J* = 15.1, 10.4 Hz, CH_2CH=C**H**), 5.86 (1H, ddd, *J* = 15.1, 10.4, 1.7 Hz, C**H**=$CHCH_3$), 5.67-5.50 (1H, m, =C**H**CH_3), 5.24 (1H, dt, *J* = 14.5, 7.1 Hz, CH_2C**H**=), 4.63 (1H, dd, *J* = 11.4, 4.1 Hz, $PhSO_2$C**H**), 3.22 (1H, ddd, *J* = 14.5, 7.1, 4.1 Hz, C$\mathbf{H}_a$$H_b$CH=), 2.94 (1H, ddd, *J* = 14.5, 11.4, 7.1 Hz, $CH_a$$\mathbf{H}_b$CH=), 1.68 (3H, d, *J* = 6.8 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3 (d, J_{CF} = 248.6 Hz, C), 137.4 (C), 134.1 (CH), 133.6 (CH), 130.7 (CH), 130.4 (d, J_{CF} = 8.7 Hz, CH), 129.7 (CH), 129.1 (CH), 128.9 (2 × CH), 128.6 (2 × CH), 124.37 (d, J_{CF} = 2.9 Hz, CH), 124.32 (CH), 119.6 (d, J_{CF} = 13.3 Hz, C), 115.1 (d, J_{CF} = 22.7 Hz, CH), 62.2 (CH), 30.3 (CH_2), 18.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.2; HRMS (ESI) Exact mass calculated for $[C_{19}H_{19}FNaO_2S]^+$ $[M+Na]^+$: 353.0982, found: 353.0978.

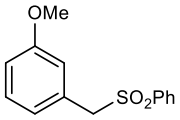


1-Fluoro-2-[(3*E*,5*E*)-hepta-3,5-dien-1-yl]benzene (26c). A suspension of activated magnesium turnings (3.04 g, 125 mmol) and the impure sulfone **S11** described above (1.65 g) in MeOH (70 mL) was stirred at room temperature for 1 h. The suspension was filtered through celite, the filter cake was washed with MeOH (50 mL), the filtrate was dilulted with saturated aqueous NH_4Cl solution and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in petroleum ether, the resulting solution was passed through a silica plug and the plug was washed with additional petroleum ether. The filtrate was concentrated *in vacuo* to give *diene* **26c** as a colorless oil (741 mg, 45% over two steps from **S10**). R_f 0.67 (10% EtOAc/petroleum ether); IR 3016, 2930, 2854, 1490, 1453, 1228, 985, 752, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.12 (2H, m, Ar**H**), 7.08-6.95 (2H, m, Ar**H**), 6.14-5.93 (2H, m, =**H**CC**H**=), 5.69-5.51 (2H, m, **H**C=HCCH=C**H**), 2.72 (2H, t, *J* =

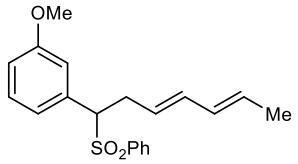
7.8 Hz, ArC**H**$_2$), 2.37 (2H, q, J = 7.3 Hz, C**H**$_2$CH=), 1.73 (3H, dd, J = 6.0, 0.9 Hz, =CHC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (d, J_{CF} = 244.4 Hz, C), 131.5 (CH), 131.0 (CH), 130.6 (d, J_{CF} = 5.2 Hz, CH), 130.5 (CH), 128.7 (d, J_{CF} = 15.5 Hz, C), 127.5 (d, J_{CF} = 8.3 Hz, CH), 127.4 (CH), 123.8 (d, J_{CF} = 3.7 Hz, CH), 115.3 (d, J_{CF} = 22.1 Hz, CH), 33.0 (CH_2), 29.1 (CH_2), 18.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –119.9; HRMS (ESI) Exact mass calculated for $[C_{13}H_{15}F]^+$ $[M]^+$: 190.1152, found 190.1146.

Preparation of Substrate 26d

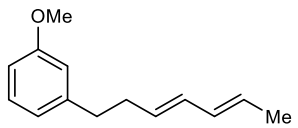




1-Methoxy-3-[(phenylsulfonyl)methyl]benzene (S12). 1-(Chloromethyl)-3-methoxybenzene (5.81 mL, 40.0 mmol) was added dropwise to a solution of $PhSO_2Na$ (6.57 g, 40.0 mmol) and TBAI (148 mg, 0.40 mmol) in DMF (50 mL) at room temperature and the mixture was stirred for 16 h. The mixture was partitioned between H_2O (100 mL) and Et_2O (200 mL) in a separating funnel, which led to the formation of a solid. The minimum quantity of CH_2Cl_2 was added to dissolve the solid, and aqueous layer was then separated and extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by trituration (Et_2O) gave sulfone **S12** as a white solid (7.90 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, dd, J = 8.4, 1.3 Hz, Ar**H**), 7.64-7.59 (1H, m, Ar**H**), 7.51-7.44 (2H, m, Ar**H**), 7.16 (1H, dd, J = 8.4, 7.5 Hz, Ar**H**), 6.86 (1H, ddd, J = 8.4, 2.6, 1.0 Hz, Ar**H**), 6.70-6.59 (2H, m, Ar**H**), 4.29 (2H, s, ArC**H**$_2$), 3.72 (3H, s, OC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (C), 137.8 (C), 133.7 (CH), 129.5 (CH), 129.4 (C), 128.8 (2 × CH), 128.6 (2 × CH), 123.1 (CH), 115.9 (CH), 114.8 (CH), 62.9 (CH_2), 55.2 (CH_3). Spectroscopic data matched those reported previously.[182]



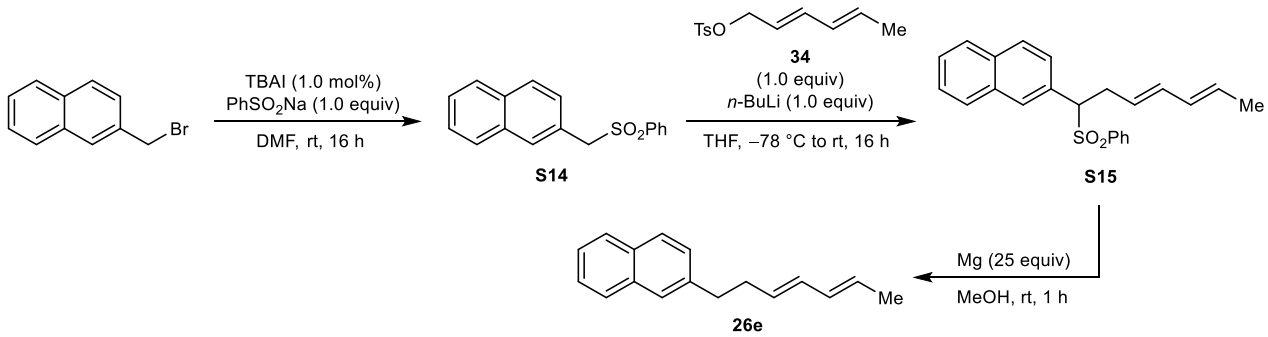
1-Methoxy-3-[(3*E*,5*E*)-1-(phenylsulfonyl)hepta-3,5-dien-1-yl]benzene (S13). *n*-BuLi (1.74 M in hexanes, 11.5 mL, 20.0 mmol) was added dropwise to a solution of (2*E*,4*E*)-hexa-2,4-dien-1-ol (2.21 mL, 20.0 mmol) in THF (20 mL) at –78 °C and the mixture was stirred for 15 min. A solution of *p*-toluenesulfonyl chloride (4.19 g, 22.0 mmol) in THF (10 mL) was added dropwise and the solution was stirred at –78 °C for 1 h to give a solution of allylic tosylate **34**. Simultaneously, in a separate flask, *n*-BuLi (1.74 M in hexanes, 11.5 mL, 20.0 mmol) was added dropwise to a solution of **S12** (5.24 g, 20.0 mmol) in THF (30 mL) at –78 °C and the mixture was stirred for 1 h. To this solution was added the solution of allylic tosylate **34** dropwise *via* cannula, and the mixture was stirred for 16 h while being warmed gradually to room temperature. The reaction was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *sulfone* **S13** as a colorless oil (2.04 g, 30%). R_f 0.21 (20% EtOAc/petroleum ether); m.p. 82-83 °C (Et_2O); IR 3013, 2937, 2840, 1610, 1581, 1491, 1447, 1294, 1250, 1231, 1178, 682, 532 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.52 (3H, m, Ar**H**), 7.38 (2H, td, *J* = 7.9, 1.4 Hz, Ar**H**), 7.12 (1H, t, *J* = 7.9 Hz, Ar**H**), 6.81 (1H, ddt, *J* = 8.3, 2.4, 1.4 Hz, Ar**H**), 6.66 (1H, d, *J* = 7.6 Hz, Ar**H**), 6.61 (1H, dt, *J* = 2.9, 1.4 Hz, Ar**H**), 6.03 (1H, dd, *J* = 15.0, 10.4 Hz, $CH_2CH{=}C$**H**), 5.90-5.81 (1H, m, C**H**=$CHCH_3$), 5.62-5.51 (1H, m, =C**H**CH_3), 5.22 (1H, dt, *J* = 14.9, 7.2 Hz, CH_2C**H**=), 4.03 (1H, dd, *J* = 11.4, 4.0 Hz, $PhSO_2C$**H**), 3.69 (3H, s, OC**H**$_3$), 3.24-3.10 (1H, m, C**H**$_a$H$_b$CH=), 3.01-2.81 (1H, m, CH$_a$**H**$_b$CH=), 1.66 (3H, d, *J* = 6.7 Hz, =CHC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (C), 137.2 (C), 133.8 (CH), 133.5 (CH), 133.3 (C), 130.8 (CH), 129.3 (CH), 129.1 (2 × CH), 129.0 (CH), 128.6 (2 × CH), 125.0, (CH), 122.4 (CH), 115.2 (CH), 114.6 (CH), 71.4 (CH), 55.2 (CH_3), 30.8 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{23}NaO_3S]^+$ $[M+Na]^+$: 365.1182, found: 365.1174.

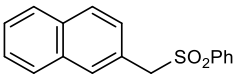


1-[(3*E*,5*E*)-Hepta-3,5-dien-1-yl]-3-methoxybenzene (26d). A suspension of activated magnesium turnings (2.43 g, 100 mmol) and sulfone **S13** (1.36 g, 4.00 mmol) in MeOH (50 mL) was stirred at room temperature for 16 h. The suspension was filtered through celite, the filter cake was washed with MeOH (50 mL) and the filtrate was diluted with saturated aqueous NH_4Cl solution and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in petroleum ether, the resulting

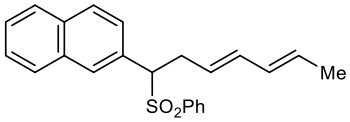
solution was passed through a silica plug and the plug was washed with additional petroleum ether. The filtrate was concentrated *in vacuo* to give *diene* **26d** as a colorless oil (449 mg, 56%). R_f 0.48 (10% EtOAc/petroleum ether); IR 3015, 2930, 2853, 2834, 1601, 1584, 1453, 1435, 1289, 1151, 986, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.17 (1H, m, Ar**H**), 6.81-6.70 (3H, m, Ar**H**), 6.11-5.96 (2H, m, =**H**CC**H**=), 5.67-5.54 (2H, m, **H**C=HCCH=C**H**), 3.80 (3H, s, OC**H**$_3$), 2.68 (2H, app dd, *J* = 9.1, 6.6 Hz, ArC**H**$_2$), 2.38 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH=), 1.74 (3H, d, *J* = 6.9 Hz, =CHC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (C), 143.6 (C), 131.5 (CH), 130.8 (2 × CH), 129.2 (CH), 127.3 (CH), 120.8 (CH), 114.2 (CH), 111.1 (CH), 55.1 (CH_3), 36.0 (CH_2), 34.3 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{14}H_{19}O]^+$ $[M+H]^+$: 203.1430, found 203.1430.

Preparation of Substrate 26e

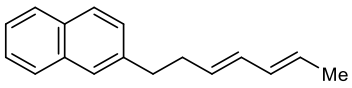




2-[(Phenylsulfonyl)methyl]naphthalene (S14). 2-(Bromomethyl)naphthylene (3.32 g, 15.0 mmol) was added dropwise to a solution of $PhSO_2Na$ (2.46 mg, 15.0 mmol) and TBAI (55.0 mg, 0.15 mmol) in DMF (30 mL) at room temperature and the mixture was stirred for 16 h. The mixture was partitioned between H_2O (100 mL) and Et_2O (100 mL) in a separating funnel, which led to the formation of a solid. The minimum quantity of CH_2Cl_2 was added to dissolve the solid, and aqueous layer was then separated and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by trituration (Et_2O) gave sulfone **S14** as a white solid (3.15 g, 74%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.86-7.79 (1H, m, Ar**H**), 7.79-7.69 (2H, m, Ar**H**), 7.68-7.57 (3H, m, Ar**H**), 7.56-7.40 (5H, m, Ar**H**), 7.21 (1H, dd, *J* = 8.4, 1.8 Hz, Ar**H**), 4.48 (2H, s, ArC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (C), 133.7 (CH), 133.1 (C), 133.0 (C), 130.5 (CH), 128.9 (2 × CH), 128.7 (2 × CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 126.7 (CH), 126.4 (CH), 125.5 (C), 63.1 (CH_2). Spectroscopic data matched those reported previously.[183]



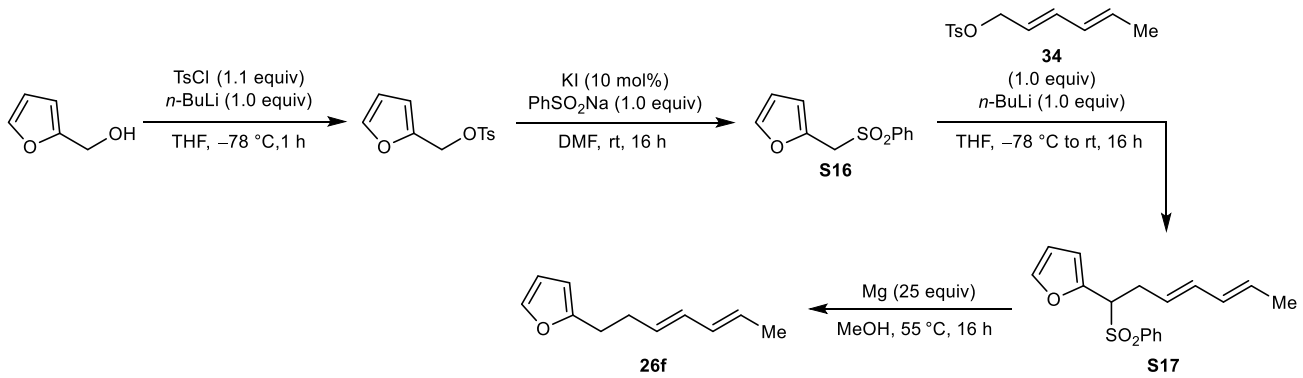
2-[(3*E*,5*E*)-1-(Phenylsulfonyl)hepta-3,5-dien-1-yl]naphthalene (S15). *n*-BuLi (2.38 M in hexanes, 2.53 mL, 6.00 mmol) was added dropwise to a solution of (2*E*,4*E*)-hexa-2,4-dien-1-ol (676 µL, 6.00 mmol) in THF (6 mL) at –78 °C and the mixture was stirred for 15 min. A solution of *p*-toluenesulfonyl chloride (1.26 g, 6.60 mmol) in THF (6 mL) was added dropwise and the mixture was stirred at –78 °C for 1 h to give a solution of allylic tosylate **34**. Simultaneously, in a separate flask, *n*-BuLi (2.38 M in hexanes, 2.53 mL, 6.00 mmol) was added dropwise to a solution of sulfone **S14** (1.69 g, 6.00 mmol) in THF (6 mL) at –78 °C and the mixture was stirred for 1 h. To this solution was added the solution of allylic tosylate **34** dropwise *via* cannula, and the mixture was stirred for 16 h while being warmed gradually to room temperature. The reaction was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *sulfone* **S15** as a white solid (1.17 g, 54%). R_f 0.32 (20% EtOAc/petroleum ether); m.p. 128-129 °C (Et_2O); IR 3058, 3019, 1446, 1291, 1024, 1015, 758, 703, 647, 478 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, dd, *J* = 7.9, 1.6 Hz, Ar**H**), 7.74 (1H, d, *J* = 8.6 Hz, Ar**H**), 7.69 (1H, dd, *J* = 7.5, 1.7 Hz, Ar**H**), 7.57-7.44 (6H, m, Ar**H**), 7.33 (2H, dd, *J* = 8.3, 7.5 Hz, Ar**H**), 7.25 (1H, dd, *J* = 8.6, 1.7 Hz, Ar**H**), 6.05 (1H, dd, *J* = 15.2, 10.3 Hz, $CH_2CH{=}C$**H**), 5.85-5.75 (1H, m, C**H**=$CHCH_3$), 5.54 (1H, dq, *J* = 13.5, 6.7 Hz, CH_3C**H**=CH), 5.23 (1H, dt, *J* = 14.8, 7.2 Hz, CH_2C**H**=CH), 4.25 (1H, dd, *J* = 11.5, 3.9 Hz, $PhSO_2C$**H**), 3.26 (1H, ddd, *J* = 14.4, 7.7, 3.9 Hz, C$\mathbf{H}_a H_b$C=), 3.06 (1H, ddd, *J* = 14.3, 11.5, 6.6 Hz, $CH_a\mathbf{H}_b$=CH), 1.64 (3H, dd, *J* = 6.8, 1.5 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1 (C), 133.9 (CH), 133.5 (CH), 133.2 (C), 132.9 (C), 130.8 (CH), 130.0 (CH), 129.3 (C), 129.1 (2 × CH), 128.6 (2 × CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 126.8 (CH), 126.6 (CH), 126.3 (CH), 124.9 (CH), 71.5 (CH), 30.9 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{22}NaO_2S]^+$ $[M+Na]^+$: 385.1233, found 385.1226. One of the CH signals of the naphthalene ring in the ^{13}C NMR spectrum was not observed in line with similar compounds previously reported in the literature.[184, 185]

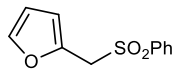


2-[(3*E*,5*E*)-Hepta-3,5-dien-1-yl]naphthalene (26e). A suspension of activated magnesium turnings (1.30 g, 54.0 mmol) and sulfone **S15** (657 mg, 1.80 mmol) in MeOH (10 mL) was stirred at room temperature for 1 h. The suspension was filtered through celite, the filter cake was washed with MeOH (50

mL), the filtrate was diluted with saturated aqueous NH_4Cl solution and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in petroleum ether, the resulting solution was passed through a silica plug and the plug was washed with additional petroleum ether. The filtrate was concentrated *in vacuo* to give *diene* **26e** as a white solid (305 mg, 76%). R_f 0.81 (10% EtOAc/petroleum ether); m.p. 45-46 °C (Et_2O); IR 3053, 2911, 2848, 1626, 1597, 1506, 1431, 989, 819, 740, 472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.74 (3H, m, Ar**H**), 7.62 (1H, s, Ar**H**), 7.49-7.39 (2H, m, Ar**H**), 7.34 (1H, dd, *J* = 8.4, 1.8 Hz, Ar**H**), 6.12-5.95 (2H, m, =**H**CC**H**=), 5.69-5.53 (2H, m, **H**C=CHCH=C**H**), 2.87 (2H, app dd, *J* = 8.9, 6.7 Hz, ArC$\mathbf{H}_2$), 2.48 (2H, q, *J* = 7.2 Hz, C$\mathbf{H}_2$CH=), 1.74 (3H, d, *J* = 6.7 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4 (C), 133.6 (C), 132.0 (C), 131.5 (CH), 130.9 (CH), 130.8 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 127.35 (CH), 127.33 (CH), 126.4 (CH), 125.8 (CH), 125.1 (CH), 36.1 (CH_2), 34.3 (CH_2), 18.0 (CH_3); HRMS (EI) Exact mass calculated for $[C_{17}H_{18}]^+$ $[M]^+$: 222.1409, found 222.1396.

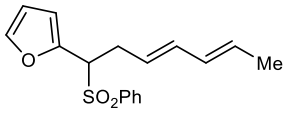
Preparation of Substrate 26f



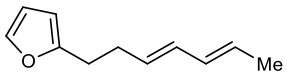


2-[(Phenylsulfonyl)methyl]furan (S16). *n*-BuLi (2.0 M in hexanes, 20 mL, 40.0 mmol) was added dropwise to a solution of furfuryl alcohol (3.46 mL, 40.0 mmol) in THF (50 mL), at –78 °C and the mixture was stirred for 15 min. A solution of *p*-toluenesulfonyl chloride (8.39 g, 44.0 mmol) in THF (15 mL) was added dropwise and the solution was stirred at –78 °C for a further 1 h. This solution was then added *via* cannula to a previously prepared solution of $PhSO_2Na$, (6.57 g, 40.0 mmol) and KI (664 mg, 4.00 mmol) in DMF (50 mL), and the mixture was stirred for 16 h while being warmed gradually to room temperature. The mixture was partitioned between H_2O (100 mL) and Et_2O (100 mL) in a separating funnel, which led to the formation of a solid. The minimum quantity of CH_2Cl_2 was

added to dissolve the solid, and aqueous layer was then separated and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave sulfone **S16** as a white solid (3.50 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.69 (2H, m, Ar**H**), 7.69-7.57 (1H, m, Ar**H**), 7.57-7.46 (2H, m, Ar**H**), 7.32 (1H, dd, *J* = 1.9, 0.8 Hz, Ar**H**), 6.34 (1H, dd, *J* = 3.3, 1.8 Hz, Ar**H**), 6.29 (1H, dq, *J* = 3.5, 0.7 Hz, Ar**H**), 4.43 (2H, s, ArC$\mathbf{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (CH), 142.3 (C), 138.2 (C), 133.9 (CH), 129.0 (2 × CH), 128.5 (2 × CH), 112.2 (CH), 111.1 (CH), 55.9 (CH_2). Spectroscopic data matched those reported previously.[186]

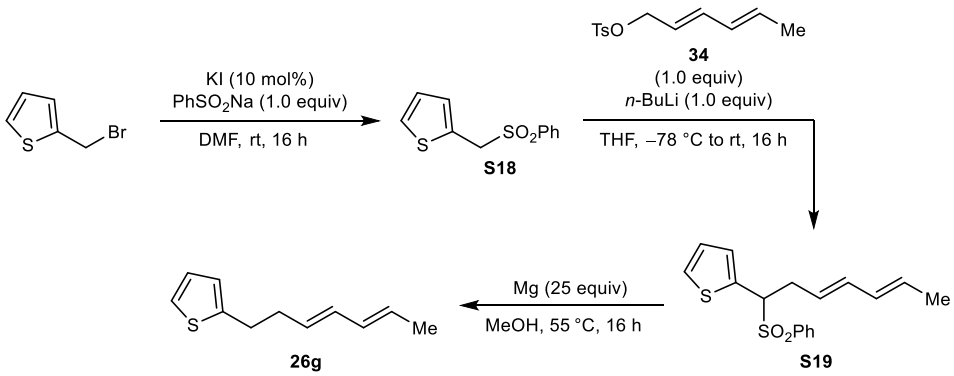


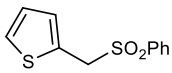
2-[(3*E*,5*E*)-1-(Phenylsulfonyl)hepta-3,5-dien-1-yl]furan (S17). *n*-BuLi (2.0 M in hexanes, 4.5 mL, 9.0 mmol) was added dropwise to a solution of (2*E*,4*E*)-hexa-2,4-dien-1-ol (993 µL, 9.00 mmol) in THF (20 mL) at –78 °C and the mixture was stirred for 15 min. A solution of *p*-toluenesulfonyl chloride (1.89 g, 9.90 mmol) in THF (10 mL) was added dropwise and the solution was stirred at –78 °C for 1 h to give a solution of allylic tosylate **34**. Simultaneously, in a separate flask, *n*-BuLi (2.0 M in hexanes, 4.5 mL, 9.0 mmol) was added dropwise to a solution of **S16** (2.00 g, 9.00 mmol) in THF (20 mL) at –78 °C and the mixture was stirred for 1 h. To this solution was added the solution of allylic tosylate **34** dropwise *via* cannula at –78 °C, and the mixture was stirred for 16 h while being warmed gradually to room temperature. The reaction was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *sulfone* **S17** as a yellow solid (721 mg, 26%). R_f 0.24 (20% EtOAc/petroleum ether); m.p. 89-90 °C (Et_2O); IR 3065, 3014, 2936, 1447, 1295, 1146, 984, 719, 621, 532 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.57 (3H, m, Ar**H**), 7.50-7.43 (2H, m, Ar**H**), 7.30-7.27 (1H, m, Ar**H**), 6.31 (1H, dd, *J* = 3.3, 1.8 Hz, Ar**H**), 6.24 (1H, dt, *J* = 3.3, 0.6 Hz, Ar**H**), 6.05 (1H, dd, *J* = 15.1, 10.4 Hz, $CH_2CH{=}C\mathbf{H}$), 5.95-5.85 (1H, m, C**H**=$CHCH_3$), 5.59 (1H, dq, *J* = 13.7, 6.7 Hz, =C**H**CH_3), 5.30 (1H, dt, *J* = 14.7, 7.2 Hz, $CH_2C\mathbf{H}$=), 4.27 (1H, dd, *J* = 11.6, 3.9 Hz, $ArSO_2C\mathbf{H}$), 3.14-3.03 (1H, m, $C\mathbf{H}_aH_bCH$=), 2.90-2.79 (1H, m, $CH_a\mathbf{H}_bCH$=), 1.69 (3H, d, *J* = 6.8 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8 (C), 143.3 (CH), 137.3 (C), 134.1 (CH), 133.7 (CH), 130.8 (CH), 129.2 (CH), 129.0 (2 × CH), 128.8 (2 × CH), 124.4 (CH), 111.8 (CH), 110.9 (CH), 65.4 (CH), 29.9 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{17}H_{18}NaO_3S]^+$ $[M+Na]^+$: 325.0869, found: 325.0872.



2-[(3*E*,5*E*)-Hepta-3,5-dien-1-yl]furan (26f). A suspension of activated magnesium turnings (1.06 g, 43.8 mmol) and sulfone **S17** (529 mg, 1.75 mmol) in MeOH (25 mL) was stirred at 55 °C for 16 h. The suspension was filtered through celite, the filter cake was washed with MeOH (50 mL) and the filtrate was diluted with saturated aqueous NH_4Cl solution and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in petroleum ether, the resulting solution was passed through a silica plug and the plug was washed with additional petroleum ether. The filtrate was concentrated *in vacuo* to give *diene* **26f** as a colorless oil (170 mg, 68%). R_f 0.76 (10% EtOAc/petroleum ether); IR 3116, 2914, 2853, 1596, 1507, 1445, 1174, 985, 924, 797, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, d, *J* = 1.9 Hz, Ar**H**), 6.58 (1H, dd, *J* = 3.2, 1.9 Hz, Ar**H**), 6.08-5.97 (3H, m, Ar**H** and =**H**CC**H**=), 5.67-5.52 (2H, m, **H**C=HCCH=C**H**), 2.72 (2H, t, *J* = 7.4 Hz, ArC$\mathbf{H}_2$), 2.41 (2H, q, *J* = 7.4 Hz, C$\mathbf{H}_2$CH=), 1.74 (3H, d, *J* = 7.5 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (C), 140.8 (CH), 131.4 (CH), 131.1 (CH), 130.2 (CH), 127.5 (CH), 110.1 (CH), 104.9 (CH), 31.0 (CH_2), 28.0 (CH_2), 18.0 (CH_3); HRMS (EI) Exact mass calculated for $[C_{11}H_{13}O]^+$ $[M]^+$: 162.1039, found 162.1045.

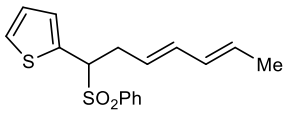
Preparation of Substrate 26g



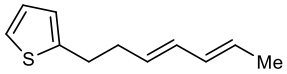


2-[(Phenylsulfonyl)methyl]thiophene (S18). 2-(Bromomethyl)thiophene [187] (4.43 mL, 25.0 mmol) was added dropwise to a solution of $PhSO_2Na$ (4.10 g, 25.0 mmol) and KI (415 mg, 2.50 mmol) in DMF (50 mL) at room temperature and the mixture was stirred for 16 h. The mixture was partitioned between H_2O (100 mL) and Et_2O (200 mL) in a separating funnel, which led to the formation of a solid. The minimum quantity of CH_2Cl_2 was added to dissolve the solid, and aqueous layer was then separated and extracted with Et_2O

(2 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by trituration (Et_2O) gave sulfone **S18** as a pale yellow solid (2.14 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (2H, dd, *J* = 8.4, 1.3 Hz, Ar**H**), 7.66-7.59 (1H, m, Ar**H**), 7.53-7.44 (2H, m, Ar**H**), 7.30-7.23 (1H, m, Ar**H**), 6.93 (1H, dd, *J* = 5.2, 3.5 Hz, Ar**H**), 6.85 (1H, dd, *J* = 3.5, 1.1 Hz, Ar**H**), 4.52 (2H, s, ArC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4 (C), 133.9 (CH), 130.2 (CH), 129.0 (2 × CH), 128.6 (2 × CH), 128.5 (C), 127.5 (CH), 127.2 (CH), 57.3 (CH_2). Spectroscopic data matched those reported previously.[186]

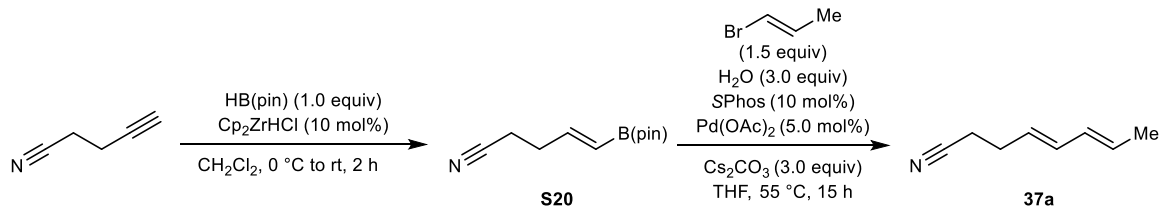


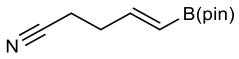
2-[(3*E*,5*E*)-1-(Phenylsulfonyl)hepta-3,5-dien-1-yl]thiophene (S19). *n*-BuLi (2.05 M in hexanes, 2.9 mL, 5.9 mmol) was added dropwise to a solution of (2*E*,4*E*)-hexa-2,4-dien-1-ol (662 µL, 6.00 mmol) in THF (10 mL) at –78 °C and the mixture was stirred for 15 min. A solution of *p*-toluenesulfonyl chloride (1.26 g, 6.60 mmol) in THF (10 mL) was added dropwise and the solution was stirred –78 °C for 1 h to give a solution of the allylic tosylate **34**. Simultaneously, in a separate flask, *n*-BuLi (2.05 M in hexanes, 2.9 mL, 5.9 mmol) was added dropwise to a solution of **S18** (1.43 g, 6.00 mmol) in THF (10 mL) at -78 °C under an argon atmosphere and stirred for 1 h. To this solution was added the solution of allylic tosylate **34** dropwise *via* cannula, and the mixture was stirred for 16 h while being warmed gradually to room temperature. The reaction was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave sulfone **S19** as a yellow solid (650 mg, 34%). R_f 0.27 (20% EtOAc/petroleum ether); m.p. 127-128 °C (Et_2O); IR 3109, 3018, 2912, 1447, 1302, 1145, 1082, 983, 719, 597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.53 (3H, m, Ar**H**), 7.46-7.37 (2H, m, Ar**H**), 7.30-7.23 (1H, m, Ar**H**), 6.89 (1H, ddd, *J* = 4.9, 3.6, 1.1 Hz, Ar**H**), 6.80 (1H, d, *J* = 3.6 Hz, Ar**H**), 6.07 (1H, dd, *J* = 15.0, 10.2 Hz, CH_2CH=C**H**), 5.95-5.83 (1H, m, C**H**=$CHCH_3$), 5.60 (1H, dq, *J* = 13.8, 6.7 Hz, =C**H**CH_3), 5.32 (1H, dt, *J* = 14.7, 7.2 Hz, CH_2C**H**=), 4.36 (1H, dd, *J* = 11.4, 3.7 Hz, $ArSO_2$C**H**), 3.22 (1H, ddd, *J* = 13.9, 7.6, 3.7 Hz, =CHC**H**$_a$H$_b$), 2.88-2.80 (1H, m, CH$_a$**H**$_b$CH=), 1.69 (3H, d, *J* = 6.7 Hz, =CHC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (C), 134.3 (CH), 134.1 (C), 133.7 (CH), 130.8 (CH), 129.27 (CH), 129.25 (CH), 129.1 (2 × CH), 128.7 (2 × CH), 127.0 (CH), 126.8 (CH), 124.5 (CH), 67.0 (CH), 32.5 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{17}H_{18}NaO_2S_2]^+$ $[M+Na]^+$: 341.0640, found: 341.0632.



2-[(3*E*,5*E*)-Hepta-3,5-dien-1-yl]thiophene (26g). A suspension of activated magnesium turnings (1.06 g, 43.8 mmol) and sulfone **S19** (557 mg, 1.75 mmol) in MeOH (25 mL) was stirred at 55 °C for 16 h. The suspension was then filtered through celite, the filter cake was washed with MeOH (50 mL) and the filtrate was diltued with saturated aqueous NH_4Cl solution and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in petroleum ether, the resulting solution was passed through a silica plug and the plug was washed with additional petroleum ether. The filtrate was concentrated *in vacuo* to give *diene* **26g** as a colorless oil (278 mg, 90%). R_f 0.58 (10% EtOAc/petroleum ether); IR 3070, 2923, 2850, 1738, 1439, 1259, 985, 849, 820, 690, 495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (1H, dd, *J* = 5.1, 1.2 Hz, Ar**H**), 6.92 (1H, dd, *J* = 5.1, 3.4 Hz, Ar**H**), 6.80 (1H, dt, *J* = 3.4, 1.2 Hz, Ar**H**), 6.12-5.98 (2H, m, =**H**CC**H**=), 5.66-5.54 (2H, m, **H**C=HCCH=C**H**), 2.92 (2H, t, *J* = 7.7 Hz, ArC$\mathbf{H}_2$), 2.45 (2H, q, *J* = 7.6 Hz, C$\mathbf{H}_2$CH=), 1.74 (3H, d, *J* = 6.2 Hz, =CHC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 131.4 (CH), 131.3 (CH), 130.1 (CH), 127.6 (CH), 126.6 (CH), 124.2 (CH), 123.0 (CH), 34.6 (CH_2), 29.9 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{11}H_{13}S]^-$: 177.0743, found 177.0738.

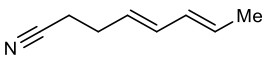
Preparation of Substrate 37a





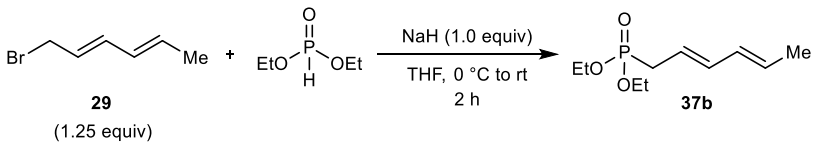
(*E*)-5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enenitrile (S20). Pinacolborane (2.18 mL, 15.0 mmol) was added slowly to a mixture of pent-4-ynenitrile (873 µL, 10.0 mmol) and Cp_2ZrHCl (258 mg, 1.00 mmol) at 0 °C. Et_3N (139 µL, 1.0 mmol) was added at 0 °C before the reaction heated to 60 °C for 2 h. The reaction was quenched with H_2O (15 mL) at 0 °C and extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. Purification of the residue by column chromatography (0%-10% EtOAc/petroleum ether with Et_3N-treated silica) gave *alkenylboronate* **S20** as a white solid (756 mg, 37%). R_f 0.13 (10%

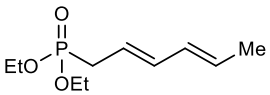
EtOAc/petroleum ether); m.p. 65-67 °C; IR 3291, 2980, 2931, 2243 (C≡N), 1642, 1361, 1325, 1140, 969, 848 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (1H, dt, *J* = 18.0, 5.8 Hz, =CB**H**), 5.56 (1H, dt, *J* = 18.0, 1.5 Hz, CH_2C**H**=), 2.55-2.40 (4H, m, C**H$_2$**C**H$_2$**), 1.26 (12H, s, 4 × C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (CH), 119.1 (C), 83.4 (2 × C), 31.0 (CH_2), 24.8 (4 × CH_3), 16.2 (CH_2). The carbon (CH) adjacent to boron was not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calculated for $C_{11}H_{18}O_2BNNa$ $[M+Na]^+$: 230.1328, found: 230.1326.



(4*E*,6*E*)-Octa-4,6-dienenitrile (37a). To a degassed suspension of **S20** (518 mg, 2.5 mmol), Cs_2CO_3 (2.44 g, 7.5 mmol), $Pd(OAc)_2$ (28.0 mg, 0.13 mmol), *S*Phos (103 mg, 0.25 mmol) and H_2O (135 µL, 7.5 mmol) in THF (10 mL) at room temperature was added *trans*-1-bromo-1-propene (324 µL, 3.75 mmol), and the mixture was stirred at 50 °C for 15 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed *in vacuo*. Purification of the residue by column chromatography (0%-10% EtOAc/petroleum ether) gave *diene* **37a** as a clear oil (126 mg, 42%). R_f 0.23 (10% EtOAc/petroleum ether); IR 3045, 3033, 3008, 2250 (C≡N), 1442, 1239, 1190, 990, 812, 724, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (1H, dd, *J* = 14.9, 10.3 Hz, CH_2CH=C**H**) 6.03 (1H, ddd, *J* = 14.9, 10.3, 1.7 Hz, CH_3CH=C**H**), 5.69 (1H, dq, *J* = 13.7, 6.8 Hz, H**3**CC**H**=), 5.56-5.48 (1H, m, H_2CC**H**=), 2.41 (4H, m, NCC**H$_2$**C**H$_2$**), 1.75 (3H, dd, *J* = 6.8, 1.7 Hz, =CHC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.3 (CH), 130.6 (CH), 129.6 (CH), 126.1 (CH), 119.2 (C), 28.4 (CH_2), 18.0 (CH_3), 17.6 (CH_2); HRMS (ESI) Exact mass calculated for $C_8H_{11}NNa$ $[M+Na]^+$: 144.0784, found 144.0775.

Preparation of Substrate 37b

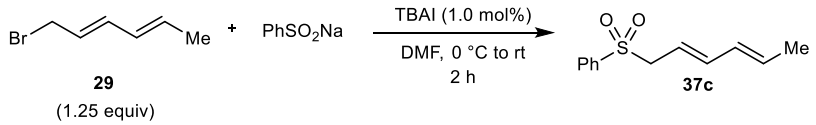


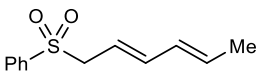


Diethyl [(2*E*,4*E*)-hexa-2,4-dien-1-yl]phosphonate (37b). Diethyl phosphite (2.58 mL, 20.0 mmol) was added dropwise to a solution of NaH (60% in mineral oil) (800 mg, 20.0 mmol) in anhydrous THF (20 mL) under an N_2

atmosphere. The solution was cooled to 0 °C and stirred for 30 minutes and then refluxed for 2 h. The solution was cooled to 0 °C and a solution of **29** (4.0 g, 25.0 mmol) in anhydrous THF (10 mL) added dropwise and stirred at room temperature for 15 h, washed with saturated aqueous NH_4Cl solution (20 mL) and extracted with diethyl ether (3 × 10 mL). The organic extracts were combined, dried (Na_2SO_4) and filtered. Purification of the residue by column chromatography (30% EtOAc/petroleum ether) gave diene **37b** as an orange oil (3.38 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20-5.97 (2H, m, =**H**CC**H=**), 5.64 (1H, dqd, *J* = 13.4, 6.7, 2.4 Hz, =C**H**CH_3), 5.47 (1H, dq, *J* = 15.0, 7.5 Hz, , CH_2C**H**=CH), 4.13-4.04 (4H, m, P(OC**H₂**CH_3)$_2$) 2.59 (2H, dd, *J* = 22.3, 7.6 Hz, PC**H₂**), 1.73 (3H, t, *J* = 6.9 Hz, =CHC**H₃**), 1.34-1.25 (6H, m, 2 × CH_2C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2 (CH), 130.8 (CH), 129.1 (CH), 119.0 (CH), 61.9 (2 × CH_2), 30.6 (d, J_{CP} = 140 Hz, CH_2), 18.0 (CH_3), 16.4 (2 × CH_3). Spectroscopic data matched those reported previously.[188]

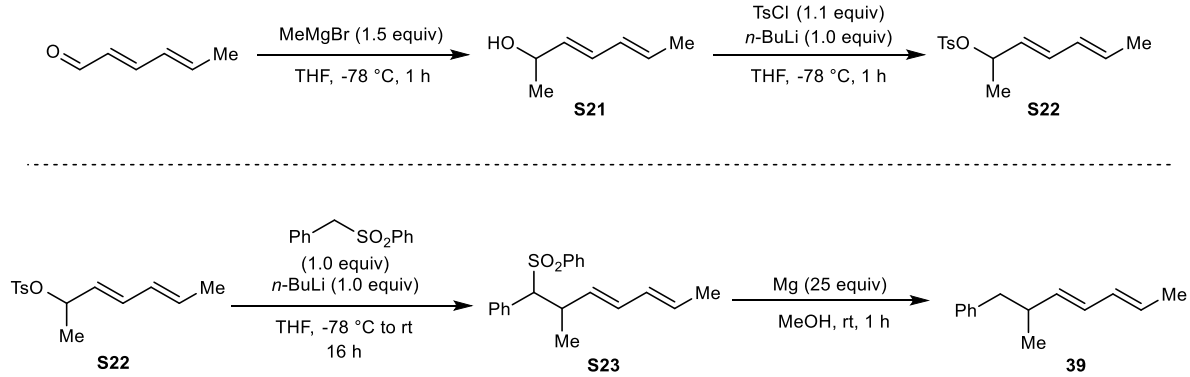
Preparation of Substrate 37c

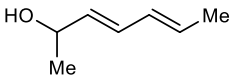




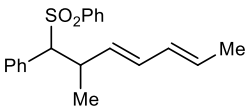
{[(2*E*,4*E*)-Hexa-2,4-dien-1-yl]sulfonyl}benzene (37c). A solution of **29** (8.0 g, 50.0 mmol) in anhydrous THF (10 mL) was added to a solution of sodium benzene sulfonic acid (6.56 g, 40.0 mmol) and TBAI (148 mg, 0.4 mmol) in anhydrous DMF (40 mL) at 0 °C. The solution was stirred at room temperature for 2 h, washed with H_2O (50 mL) and extracted with diethyl ether (3 × 50 mL). The organic extracts were combined, dried (Na_2SO_4) and filtered. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave diene **37c** as a yellow solid (6.98 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.83 (2H, m, Ar**H**,), 7.68-7.61 (1H, m, Ar**H**), 7.58-7.51 (2H, m, Ar**H**), 6.07-5.93 (2H, m, =**H**CC**H=**), 5.72-5.60 (1H, m, =C**H**CH_3), 5.47-5.36 (1H, m, CH_2C**H**=CH), 3.79 (2H, d, *J* = 7.3 Hz, SC**H₂**), 1.74 (3H, d, *J* = 6.1 Hz, =CHC**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (CH), 138.5 (C), 133.6 (CH), 132.5 (CH), 130.1 (CH), 129.0 (2 × CH), 128.5 (2 × CH) 115.1 (CH), 60.3 (CH_2), 18.2 (CH_3). Spectroscopic data matched those reported previously.[189]

Preparation of Substrate 39



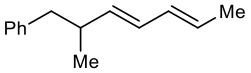


(3*E*,5*E*)-Hepta-3,5-dien-2-ol (S21). Methylmagnesium bromide (3.0 M in THF, 10.2 mL, 30.9 mmol) added dropwise to a solution of (2*E*,4*E*)-hexa-2,4-dienal (1.98 g, 20.5 mmol) in anhydrous THF (40 mL) at -78 °C and stirred for 30 minutes. Saturated aqueous NH_4HCl solution (50 mL) added and the layers separated, the aqueous layer extracted into Et_2O (2 × 50 mL) and the combined organic extracted dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave alcohol **S21** as a clear colourless oil (1.42 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (1H, dd, *J* = 15.4, 10.4 Hz, CH(CH_3)CH=C**H**), 6.09-5.99 (1H, m, C**H**=CHCH_3), 5.72 (1H, dt, *J* = 15.0, 6.8 Hz, =C**H**CH_3), 5.61 (1H, ddt, *J* = 15.2, 6.6, 0.7 Hz, CH(CH_3)C**H**=), 4.33 (1H, p, *J* = 6.3 Hz, C**H**(CH_3)), 1.76 (3H, dd, *J* = 6.9, 1.4 Hz, =CHC**H**$_3$), 1.52 (1H, br s, O**H**), 1.28 (3H, d, *J* = 6.3 Hz, C**H**(CH_3)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.3 (CH), 130.7 (CH), 130.0 (CH), 129.9 (CH), 68.6 (CH), 23.3 (CH_3), 18.1 (CH_3). Spectroscopic data matched those reported previously.[190]



[(3*E*,5*E*)-2-Methyl-1-(phenylsulfonyl)hepta-3,5-dien-1-yl]benzene (S23). *n*-Butyllithium (2.0 M, 5.5 mL, 11.0 mmol) was added dropwise to a solution of **S21** (1.23 g, 11.0 mmol) in anhydrous THF (20 mL) at -78 °C under an argon atmosphere and stirred for 15 mins. A solution of *p*-toluenesulfonyl chloride (2.31 g, 12.1 mmol) in anhydrous THF (10 mL) was added dropwise and the solution stirred for 1 h at -78 °C. Simultaneously, in a separate flask, *n*-butyllithium (2.0 M, 5.5 mL, 11.0 mmol) was added dropwise to a solution of benzylsulfonylbenzene (2.55 g, 11.0 mmol) in anhydrous THF (20 mL) at -78 °C under an argon atmosphere and stirred for 1 h. **S22** was then was added dropwise to the other solution at -78 °C, left to warm to room temperature and

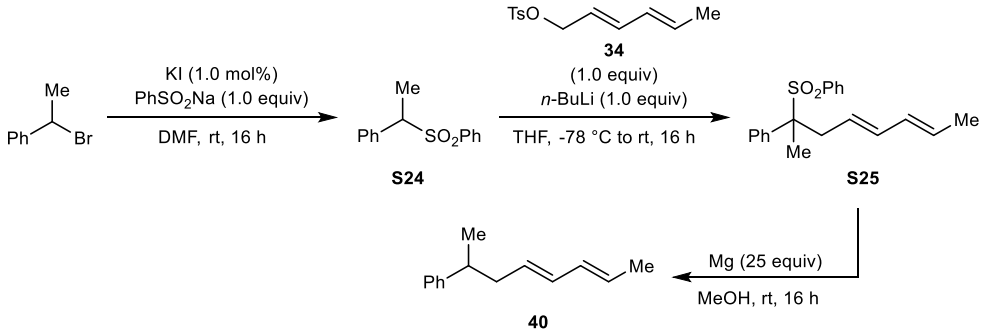
stirred for 16 h. The solution was then quenched with saturated aqueous NH_4Cl solution at 0 °C, extracted into EtOAc (3 × 50 mL), the combined organic layers were washed with saturated aqueous brine solution (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *sulfone* **S23** as a white solid as a mixture of diastereoisomers (4:1) (1.55 g, 43% total yield). R_f 0.26 (20% EtOAc/petroleum ether); m.p. 68-69 °C; IR 2934, 2915, 2874, 1447, 1305, 1145, 984, 716, 682 580 cm^{-1}; Characteristic NMR peaks of major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.06 (10H, m, Ar**H**), 6.01-5.42 (4H, m, alkenyl C**H**'s), 3.96 (1H, d, *J* = 7.0 Hz, $ArSO_2C$**H**), 3.54 (1H, h, *J* = 7.0 Hz, $ArSO_2CHC$**H**CH_3), 1.70 (3H, d, *J* = 6.8 Hz, =CHC**H$_3$**), 1.32 (3H, d, *J* = 6.8 Hz, $ArSO_2CHCHC$**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (C), 133.0 (CH), 132.1 (C), 131.6 (CH), 131.5 (CH), 131.2 (CH), 130.7 (2 × CH), 128.7 (CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 128.0 (2 × CH), 76.4 (CH), 36.5 (CH), 19.7 (CH_3), 18.04 (CH_3). Characteristic NMR peaks of minor diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.06 (10H, m, Ar**H**), 6.18-5.42 (4H, m, alkenyl C**H**'s), 4.00 (1H, d, *J* = 7.7 Hz, $ArSO_2C$**H**), 3.42 (1H, h, *J* = 7.1 Hz, $ArSO_2CHC$**H**CH_3), 1.74 (3H, dd, *J* = 6.8, 1.6 Hz, =CHC**H$_3$**), 1.07 (3H, d, *J* = 6.9 Hz, $ArSO_2CHCHC$**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (C), 132.9 (CH), 132.2 (C), 131.2 (CH), 130.8 (CH), 130.3 (CH), 129.0 (CH), 128.8 (CH), 76.3 (CH), 37.5 (CH), 19.0 (CH_3), 18.09 (CH_3); HRMS (ESI) Exact mass calculated for $C_{20}H_{22}NaO_2S$ $[M+Na]^+$: 349.1233, found: 349.1235.

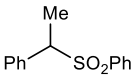


((3*E*,5*E*)-2-Methylhepta-3,5-dien-1-yl)benzene (39). A solution of activated magnesium turnings (1.80 g, 75.0 mmol) and **S23** (978 mg, 3.0 mmol) in MeOH, (40 mL) stirred at room temperature for 1 h. The suspension was then filtered through celite and washed with methanol (50 mL) and the filtrate was washed with saturated aqueous NH_4Cl solution and extracted into diethyl ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petroleum ether) gave *diene* **39** as a clear oil (267 mg, 48%). R_f 0.69 (10% EtOAc/petroleum ether); IR 3024, 2960, 2915, 1495, 1452, 1374, 985, 740, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (2H, m, Ar**H**), 7.21-7.14 (3H, m, Ar**H**), 6.07-5.92 (2H, m, =**H**CC**H**=), 5.62-5.51 (2H, m, **H**C=HCCH=C**H**), 2.75-2.66 (1H, m, ArC**H$_a$**H$_b$), 2.57-2.42 (2H, m, ArCH$_a$**H$_b$** and ArCH$_a$H$_b$C**H**), 1.74 (3H, d, *J* = 6.6 Hz, =CHC**H$_3$**), 1.00 (3H, dd, *J* = 6.6, 1.1 Hz, CH$_a$H**$_b$**CHC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7 (C), 137.0 (CH), 131.7 (CH), 129.2 (2 × CH), 128.6 (CH), 128.1 (2 × CH), 127.2 (CH), 125.8 (CH), 43.6

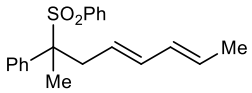
(CH_2), 38.2 (CH), 19.7 (CH_3), 18.03 (CH_3); HRMS (GC-EI) Exact mass calculated for $C_{20}H_{22}Na$ $[M+Na]^+$: 186.1403, found: 186.1416.

Preparation of Substrate 40



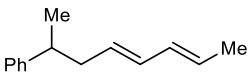


[(1-Phenylethyl)sulfonyl]benzene (S24). 1-bromoethyl benzene (4.09 mL, 30.0 mmol) was added dropwise to a solution of $PhSO_2Na$ (4.92 g, 30.0 mmol) and KI (498 mg, 3.00 mmol) in DMF (40 mL) at room temperature and stirred for 16 h. H_2O (100 mL) was added and the solid dissolved in the minimum amount of CH_2Cl_2 before separation and extraction of the aqueous layer into Et_2O (3 × 200 mL). The combined organic extracts were washed with saturated aqueous brine solution (3 × 200 mL), dried ($MgSO_4$), filtered and concentrated before purification by trituraton (Et_2O) gave sulfone **S24** as a yellow solid (5.34 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (3H, ddt, *J* = 10.0, 7.2, 1.4 Hz, Ar**H**), 7.44-7.37 (2H, m, Ar**H**), 7.26 (3H, dddd, *J* = 14.5, 8.6, 6.7, 2.1 Hz, Ar**H**), 7.17-7.12 (2H, m, Ar**H**), 4.24 (1H, q, *J* = 7.2 Hz, C**H**(CH_3)), 1.78 (3H, d, *J* = 7.2 Hz, CH(C**H**$_3$)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (C), 133.7 (C), 133.5 (CH), 129.4 (2 × CH), 129.2 (2 × CH), 128.7 (CH), 128.6 (2 × CH), 128.3 (2 × CH), 66.1 (CH), 14.0 (CH_3). Spectroscopic data matched that previously reported in the literature.[191]



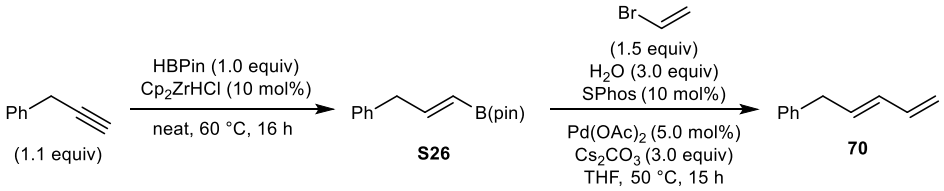
{[(4*E*,6*E*)-2-Phenylocta-4,6-dien-2-yl]sulfonyl}benzene (S25). *n*-Butyllithium (2.0 M, 7.5 mL, 15.0 mmol) was added dropwise to a solution of (2*E*,4*E*)-hexa-2,4-dien-1-ol (1.66 µL, 15.0 mmol) in anhydrous THF (30 mL) at -78 °C under an argon atmosphere and stirred for 15 mins. A solution of *p*-toluenesulfonyl chloride (3.15 g, 16.5 mmol) in anhydrous THF (10 mL) was added dropwise and the solution stirred for 1 h at -78 °C. Simultaneously, in a separate flask, *n*-butyllithium (2.0 M, 9.0 mL, 15.0 mmol) was added dropwise to a solution of **S24** (3.69 g, 15.0 mmol) in anhydrous THF

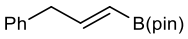
(40 mL) at -78 °C under an argon atmosphere and stirred for 1 h. **34** was then was added dropwise to the other solution at -78 °C, left to warm to room temperature and stirred for 16 h. The solution was then quenched with saturated aqueous NH_4Cl solution at 0 °C, extracted into EtOAc (3 × 50 mL), the combined organic layers were washed with saturated aqueous brine solution (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *sulfone* **S25** as a clear oil (1.91 g, 40%). R_f 0.24 (20% EtOAc/petroleum ether); IR 3020, 2957, 2932, 1446, 1292, 989, 721, 690, 595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.48 (1H, m, Ar**H**), 7.36-7.25 (9H, m, Ar**H**), 6.12 (1H, dd, *J* = 15.1, 10.3 Hz, CH_2CH=C**H**), 5.87 (1H, ddd, *J* = 15.1, 10.3, 1.8 Hz, CH_3CH=C**H**), 5.68-5.56 (1H, m, =C**H**CH_3), 5.21-5.08 (1H, m, CH_2C**H**=), 3.45 (1H, dd, *J* = 14.0, 5.7 Hz, =CHC$\mathbf{H_a}H_b$), 2.89 (1H, ddd, *J* = 14.0, 9.0, 0.9 Hz, =CH$CH_a\mathbf{H_b}$), 1.73-1.66 (6H, m, C$\mathbf{H_3}$ and =CHC$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2 (CH), 135.0 (C), 134.9 (C), 133.3 (CH), 130.9 (CH), 130.3 (2 × CH), 129.1 (2 × CH), 128.9 (CH), 128.4 (CH), 128.1 (2 × CH), 128.0 (2 × CH), 123.5 (CH), 68.9 (C), 36.7 (CH_2), 19.3 (CH_3), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $C_{20}H_{22}NaO_2S$ $[M+Na]^+$: 349.1233, found: 349.1232.



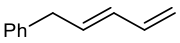
[(4*E*,6*E*)-Octa-4,6-dien-2-yl]benzene (40). A solution of activated magnesium turnings (2.13 g, 87.5 mmol) and **S25** (1.14 g, 3.5 mmol) in MeOH, (40 mL) stirred at room temperature for 16 h. The suspension was then filtered through celite and washed with methanol (50 mL) and the filtrate was washed with saturated aqueous NH_4Cl solution and extracted into diethyl ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petroleum ether) gave *diene* **40** as a clear oil (352 mg, 54%). R_f 0.65 (10% EtOAc/petroleum ether); IR 3062, 2960, 2913, 1494, 985, 759, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (2H, m, Ar**H**), 7.24-7.17 (3H, m, Ar**H**), 6.09-5.93 (2H, m, =**H**CC**H=**), 5.66-5.53 (1H, m, =C**H**CH_3), 5.52-5.42 (1H, m, CH_2C**H**=), 2.79 (1H, h, *J* = 7.1 Hz, ArC**H**), 2.41 (1H, dt, *J* = 14.1, 6.7 Hz, =CHC$\mathbf{H_a}H_b$), 2.29 (1H, dt, *J* = 14.1, 7.8 Hz, =CH$CH_a\mathbf{H_b}$), 1.74 (3H, d, *J* = 6.6 Hz, =CHC$\mathbf{H_3}$), 1.26 (dd, *J* = 7.0, 0.9 Hz, ArCHC$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (C), 131.7 (CH), 131.6 (CH), 129.9 (CH), 128.3 (2 × CH), 127.2 (CH), 126.9 (2 × CH), 125.9 (CH), 41.5 (CH_2), 40.2 (CH), 21.4 (CH_3), 18.0 (CH_3); HRMS (GC-EI) Exact mass calculated for $[C_{14}H_{18}]^+$ $[M]^+$: 186.1403, found: 186.1416.

Preparation of Substrate 70



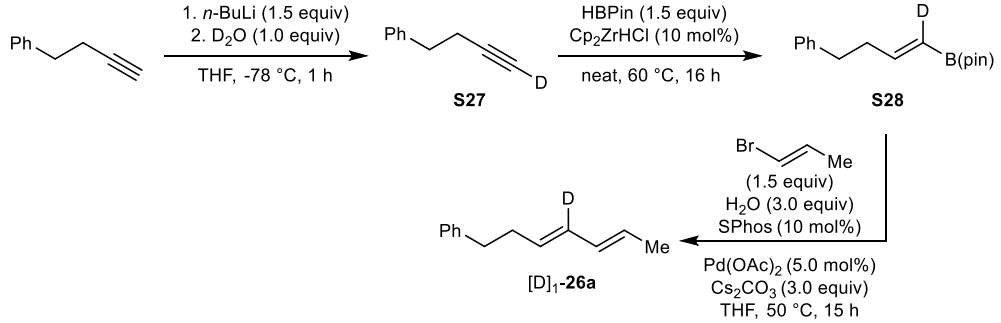


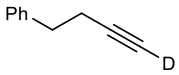
(*E*)-4,4,5,5-tetramethyl-2-(3-phenylprop-1-en-1-yl)-1,3,2-dioxaborolane (S26). The title compound was prepared by hydroboration of 3-phenyl-1-propyne (1.24 mL, 10.0 mmol) according to a literature procedure (910 mg, 37%).[176] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (2H, m, Ar**H**), 7.23-7.13 (3H, m, Ar**H**), 6.77 (1H, dt, *J* = 17.9, 6.4 Hz, C**H**=CHB), 5.46 (1H, dt, *J* = 17.8, 1.7 Hz, CH=C**H**B), 3.49 (2H, dd, *J* = 6.4, 1.6 Hz, PhC$\mathbf{H}_2$), 1.26 (12H, s, 4 × C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4 (CH), 139.1 (C), 128.9 (2 × CH), 128.4 (2 × CH), 126.1 (CH), 83.1 (2 × C), 42.3 (CH_2), 24.8 (4 × CH_3), the carbon (CH) adjacent to boron was not observed. Spectroscopic data matched those reported previously.[176]



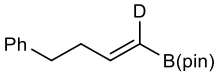
(*E*)-penta-2,4-dien-1-ylbenzene (70). To a degassed suspension of **S26** (1.03 g, 4.00 mmol), Cs_2CO_3 (3.91 g, 12.0 mmol), $Pd(OAc)_2$ (44.9 mg, 0.20 mmol), SPhos (164 mg, 0.40 mmol) and H_2O (216 µL, 12.0 mmol) in THF (10 mL) at room temperature was added vinyl bromide (1.0 M in THF, 6.0 mL, 6.0 mmol), and the mixture was stirred at 50 °C for 16 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (100% petroleum ether) gave diene **70** as a colorless oil (337 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, t, *J* = 7.5 Hz, Ar**H**), 7.24-7.18 (3H, m, Ar**H**), 6.36 (1H, dt, *J* = 16.9, 10.3 Hz, C**H**=CH_2), 6.13 (1H, dd, *J* = 15.1, 10.3 Hz, CH_2CH=C**H**), 5.87 (1H, dt, *J* = 14.7, 7.0 Hz, CH_2C**H**=CH), 5.15 (1H, dd, *J* = 17.0, 1.6 Hz, CH=C$\mathbf{H}_a$$H_b$), 5.02 (1H, dd, *J* = 10.2, 1.6 Hz, CH=$CH_a$$\mathbf{H}_b$), 3.44 (2H, d, *J* = 7.0 Hz, PhC$\mathbf{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1 (C), 136.9 (CH), 133.4 (CH), 132.1 (CH), 128.6 (2 × CH), 128.4 (2 × CH), 126.1 (CH), 115.7 (CH_2), 38.9 (CH_2). Spectroscopic data matched those reported previously.[192]

Preparation of Substrate [D]$_1$**-26a**

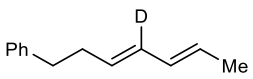




(But-3-yn-1-yl-4-*d*)benzene (S27). The title compound was made from 4-phenyl-1-butyne (1.41 mL, 10.0 mmol) according to a previously reported procedure (1.24 g, 94 %).[193] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.31 (2H, m, Ar**H**), 7.28-7.23 (3H, m, Ar**H**), 2.88 (2H, t, *J* = 7.6 Hz, PhC**H$_2$**), 2.52 (2H, t, *J* = 7.6 Hz, PhC**H$_2$**CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.4 (C), 128.5 (4 × CH), 126.3 (CH), 83.3 (C), 68.6 (C, J_{CD} = 38.1 Hz), 34.8 (CH_2), 20.5 (CH_2). Spectroscopic data matched those reported previously.[193]



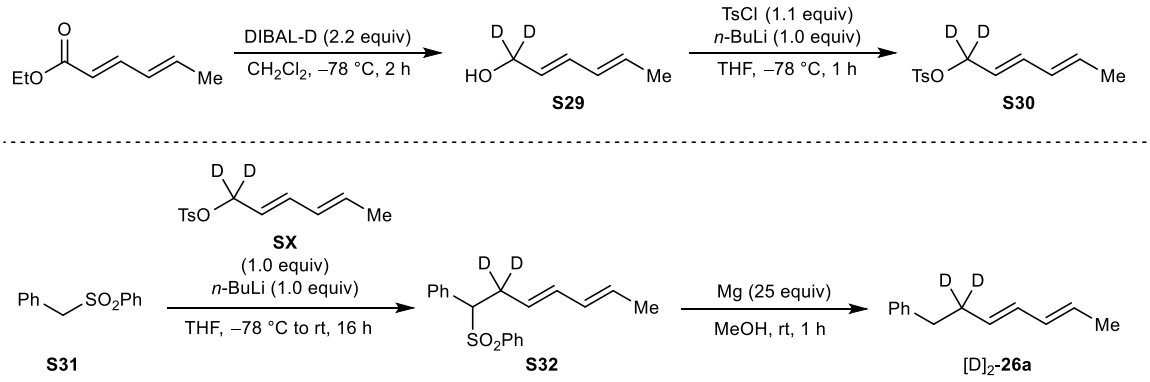
(*E*)-4,4,5,5-Tetramethyl-2-(4-phenylbut-1-en-1-yl-1-d)-1,3,2-dioxaborolane (S28). Pinacol borane (1.31 mL, 9.0 mmol) was added slowly to a mixture of **S27** (787 mg, 6.0 mmol) and Cp_2ZrHCl (155 mg, 0.60 mmol) at 0 °C. Et_3N (84 µL, 0.60 mmol) was added at 0 °C before the reaction heated to 60 °C for 16 h. The reaction was quenched with H_2O (15 mL) at 0 °C and extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. Purification of the residue by column chromatography (0%-2% EtOAc/petroleum ether with Et_3N-treated silica) gave *alkenylboronate* **S28** as a colourless oil (410 g, 26%). R_f 0.36 (2% EtOAc/petroleum ether). IR 3027, 2977, 2930, 1627, 1349, 1312, 1143, 1021, 843, 673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (2H, m, Ar**H**), 7.21-7.17 (3H, m, Ar**H**), 6.71 (1H, tt, *J* = 5.8, 2.4 Hz, C**H**=CHB), 2.78-2.72 (2H, m, PhC**H$_2$**), 2.51-2.46 (PhCH$_2$C**H$_2$**), 1.28 (12H, s, 4 × C**H$_3$**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.3 (CH), 141.8 (C), 128.3 (4 × CH), 125.8 (CH), 83.1 (CH), 37.4 (CH_2), 34.6 (CH_2), 24.8 (4 × CH_3), the carbon (C) adjacent to boron was not observed; HRMS (ESI) Exact mass calculated for $C_{16}H_{23}DBO_2$ $[M+H]^+$: 260.1927, found: 260.3052.

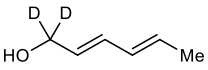


[(3*E*,5*E*)-Hepta-3,5-dien-1-yl-4-*d*]benzene ([D]$_1$**-26a).** To a degassed suspension of **S28** (259 mg, 1.00 mmol), Cs_2CO_3 (977 mg, 3.00 mmol),

$Pd(OAc)_2$ (11.2 mg, 0.05 mmol), *S*Phos (41.1 mg, 0.10 mmol) and H_2O (54 µL, 3.00 mmol) in THF (10 mL) was added *trans*-1-bromo-1-propene (129 µL, 1.50 mmol) before stirring under an N_2 atmosphere at 50 °C for 16 h. The reaction was cooled to room temperature, diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25mL). The combined organic fractions were dried (Na_2SO_4), and the solvent was removed *in vacuo*. Purification of the residue by column chromatography (100% petroleum ether to 2% EtOAc/petroleum ether) gave *diene* $[D]_1$-**26a** as a colourless oil (114 mg, 66%). R_f 0.63 (2% EtOAc/petroleum ether). IR 3063, 3025, 2926, 2853, 1496, 1453, 964, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (2H, m, Ar**H**), 7.23-7.17 (3H, m, Ar**H**), 6.03 (1H, d, *J* = 16.9 Hz, =DCC**H**=), 5.60 (2H, *J* = **H**C=CDHC=C**H**), 2.71 (2H, dd, *J* = 9.0, 6.9 Hz, PhC$\mathbf{H_2}$), 2.39 (2H, q, *J* = 7.3 Hz, $PhCH_2C\mathbf{H_2}$), 1.74 (3H, d, *J* = 6.7, 1.5 Hz, =CHC$\mathbf{H_3}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.9 (C), 131.5 (CH), 130.8 (CH), 130.5 (C, J_{CD} = 23.2 Hz), 128.4 (2 × CH), 128.3 (2 × CH), 127.3 (CH), 125.8 (CH), 35.9 (CH_2), 34.4 (CH_2), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $C_{13}H_{15}D$ $[M+H]^+$: 173.1315, found: 173.1313.

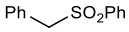
Preparation of Substrate $[D]_2$**-26a**



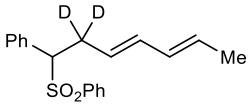


(2*E*,4*E*)-Hexa-2,4-dien-1,1-*d*$_2$-1-ol (S29). DIBAL-D (0.7 M in toluene, 47.1 mL, 33.0 mmol) was added dropwise to a solution of ethyl sorbate (2.20 mL, 15.0 mmol) in anhydrous CH_2Cl_2 (50 mL) at –78 ˚C and the mixture was stirred at this temperature for 2 h. The reaction was quenched carefully with EtOH (50 mL), solid Na_2SO_4 (10.0 g) was added, the solution was filtered through a pad of celite and the filter cake was washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography to give alcohol **S29** as an off-white oily solid (603 mg, 30%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.22 (1H, dd, *J* = 15.2, 10.4 Hz, CD_2CH=C**H**), 6.11-6.03 (1H, m, C**H**=$CHCH_3$), 5.78-5.67 (2H, m, **H**C=HCCH=C**H**), 1.77 (3H, dd, *J* = 6.7, 1.6 Hz, =CHC$\mathbf{H_3}$),

1.38 (1H, br s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.1 (CH), 130.7 (CH), 130.2 (CH), 129.0 (CH), 62.9 (m, C), 18.1 (CH_3). Spectroscopic data matched those reported previously.[194]

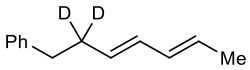


(Benzylsulfonyl)benzene (S31). Benzyl bromide (4.76 mL, 40.0 mmol) was added dropwise to a solution of $PhSO_2Na$ (6.57 g, 40.0 mmol) and KI (664 mg, 4.0 mmol) in DMF (50 mL) at room temperature and the mixture was stirred for 16 h. The mixture was partitioned between H_2O (100 mL) and Et_2O (100 mL), which led to the formation of a solid. The minimum quantity of CH_2Cl_2 was added to dissolve the solid, and aqueous layer was then separated and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by trituration (Et_2O) gave sulfone **S31** as a white solid (6.71 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.57 (3H, m, Ar**H**), 7.49-7.42 (2H, m, Ar**H**), 7.36-7.23 (3H, m, Ar**H**), 7.11-7.07 (2H, m, Ar**H**), 4.32 (2H, s, PhC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (C), 133.7 (CH), 130.8 (2 × CH), 128.9 (2 × CH), 128.7 (CH), 128.62 (2 × CH), 128.55 (2 × CH), 128.1 (C), 62.9 (CH_2). Spectroscopic data matched those reported previously.[195]



{[(3*E*,5*E*)-1-Phenylhepta-3,5-dien-1-yl-2,2-*d*$_2$]sulfonylbenzene (S32). *n*-Butyllithium (2.5 M in hexanes, 2.0 mL, 5.0 mmol) was added dropwise to a solution of **S29** (500 mg, 5.00 mmol) in THF (15 mL) at –78 °C and the mixture was stirred for 15 min. A solution of *p*-toluenesulfonyl chloride (1.05 g, 5.5 mmol) in THF (15 mL) was added dropwise and the mixture was stirred at –78 °C for 1 h to give a solution of allylic tosylate **S30**. Simultaneously, in a separate flask, *n*-Butyllithium (2.5 M in hexanes, 2.0 mL, 5.0 mmol) was added dropwise to a solution of sulfone **S31** (1.16 g, 5.0 mmol) in THF (25 mL) at –78 °C and the mixture was stirred for 1 h. To this solution was added the solution of allylic tosylate **S30** dropwise *via* cannula, and the mixture was stirred for 16 h while being warmed gradually to room temperature. The reaction was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 50 mL). The combined organic layers washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *sulfone* **S32** as a white solid (685 mg, 44%). R_f 0.30 (20% EtOAc/petroleum ether); m.p. 134-135 °C (Et_2O); IR 3016, 2933, 2849, 1447, 1300, 1083, 947, 681, 597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.51 (3H, m, Ar**H**), 7.42-7.36 (2H, m, Ar**H**), 7.33-7.28 (1H, m, Ar**H**), 7.26-7.22 (2H, m, Ar**H**), 7.12-7.08 (2H, m, Ar**H**), 6.04 (1H, dd, *J* = 15.1, 10.4 Hz, CD_2CH=C**H**), 5.89-5.83 (1H, m, C**H**=$CHCH_3$), 5.61-5.54 (1H, m, CH=C**H**CH_3), 5.23 (1H, d,

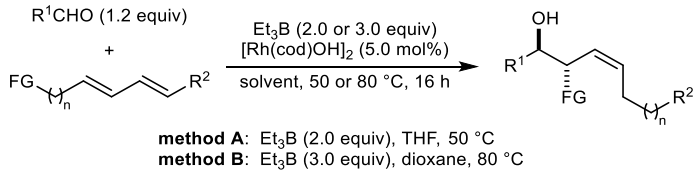
J = 15.1 Hz, CD_2C**H**=CH), 4.07 (1H, s, $PhSO_2C$**H**), 1.68 (3H, dd, *J* = 6.7, 1.6 Hz, =CHC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2 (C), 133.9 (CH), 133.5 (CH), 131.8 (C), 130.8 (CH), 130.0 (2 × CH), 129.04 (2 × CH), 128.99 (CH), 128.7 (CH), 128.6 (2 × CH), 128.4 (2 × CH), 124.8 (CH), 71.3 (CH), 18.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{19}H_{18}D_2NaO_2S]^+$ $[M+Na]^+$: 337.1202, found 337.1195.



[(3*E*,5*E*)-Hepta-3,5-dien-1-yl-2,2-*d*$_2$]benzene ([D]$_2$-**26a).** A suspension of activated magnesium turnings (911 mg, 37.5 mmol) and sulfone **S32** (471 mg, 1.50 mmol) in MeOH (20 mL) was stirred at room temperature for 1 h. The suspension was filtered through celite, the filter cake was washed with MeOH (50 mL), the filtrate was diluted with saturated aqueous NH_4Cl solution and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in petroleum ether, the resulting solution was passed through a silica plug and the plug was washed with additional petroleum ether. The filtrate was concentrated *in vacuo* to give *diene* [D]$_2$-**26a** as a colorless oil (180 mg, 52%) that required no further purification. R_f 0.67 (10% EtOAc/petroleum ether); IR 3063, 2927, 2853, 1496, 1452, 985, 740, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (2H, m, Ar**H**), 7.25-7.18 (3H, m, Ar**H**), 6.12-5.99 (2H, m, =**H**CC**H**=), 5.69-5.56 (2H, m, **H**C=CHCH=C**H**), 2.71 (2H, s, PhC**H**$_2$), 1.76 (3H, d, *J* = 6.4 Hz, =CHC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (C), 131.5 (CH), 130.84 (CH), 130.76 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 127.3 (CH), 125.8 (CH), 35.8 (CH_2), 33.8 (m, C), 18.0 (CH_3); HRMS (EI) Exact mass calculated for $[C_{13}H_{14}D_2]^+$ $[M]^+$: 174.1372, found 174.1376.

1.3.3 Allylation Products of Allylrhodium Chain Walking

General Procedure



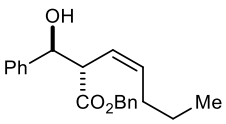
Method A

To a solution of the diene (0.30 mmol), aldehyde (0.36 mmol) and $[Rh(cod)OH]_2$ (6.8 mg, 0.015 mmol) in THF (1.5 mL) at 0 °C was added Et_3B (1.0 M in hexane, 0.60 mL, 0.60 mmol)

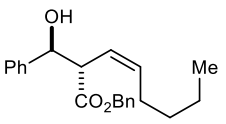
dropwise. The mixture was stirred at 0 °C for 5 min, and then at 50 °C for 16 h unless otherwise stated. The reaction was quenched carefully with 1.0 M aqueous HCl solution and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography gave the homoallylic alcohol.

Method B

To a solution of the diene (0.30 mmol), aldehyde (0.36 mmol) and $[Rh(cod)OH]_2$ (6.8 mg, 0.015 mmol) in 1,4-dioxane (1.5 mL) at 0 °C was added Et_3B (1.0 M in hexane, 0.90 mL, 0.90 mmol) dropwise. The mixture was stirred at 0 °C for 5 min, and then at 80 °C for 16 h unless otherwise stated. The reaction was quenched carefully with 1.0 M aqueous HCl solution and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography gave the homoallylic alcohol.

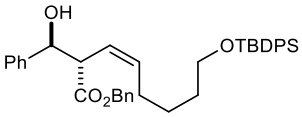


(±)-Benzyl (*S*,*Z*)-2-[(*S*)-hydroxy(phenyl)methyl]hept-3-enoate (11b). The general procedure was followed using method B with benzaldehyde (37 μL, 0.36 mmol) and diene **15a** (64.9 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **11b** as a colorless oil (39.9 mg, 41%). R_f 0.50 (20% EtOAc/petroleum ether); IR 3502 (OH), 3032, 2928, 1728 (C=O), 1496, 1158, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (8H, m, Ar**H**), 7.20-7.10 (2H, m, Ar**H**), 5.76-5.58 (2H, m, **H**C=C**H**), 5.10-4.98 (3H, m, PhC$\mathbf{H}_2$ and C**H**OH), 3.72 (1H, dd, *J* = 9.7, 6.1 Hz, O=CC**H**), 2.87 (1H, br s, O**H**), 2.03-1.79 (2H, m, =CHC$\mathbf{H}_2$), 1.31-1.14 (2H, m, C$\mathbf{H}_2CH_3$), 0.83-0.69 (3H, m, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C), 140.8 (C), 136.5 (CH), 135.5 (C), 128.5 (2 × CH), 128.19 (2 × CH) 128.17 (CH), 128.0 (2 × CH), 127.8 (CH), 126.4 (2 × CH), 122.3 (CH), 74.3 (CH), 66.5 (CH_2), 52.3 (CH), 29.6 (CH_2), 22.3 (CH_2), 13.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{24}NaO_3]^+$ $[M+Na]^+$: 347.1618, found: 347.1628.

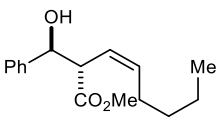


(±)-Benzyl (*S*,*Z*)-2-[(*S*)-hydroxy(phenyl)methyl]oct-3-enoate (11c). The general procedure was followed using method B with benzaldehyde (37 μL, 0.36 mmol) and diene **15b** (69.1 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **11c** as a colorless oil

(51.2 mg, 51%). R_f 0.45 (10% EtOAc/petroleum ether); IR 3455 (OH), 2956, 2924, 1710 (C=O), 1451, 1273, 1210, 1186, 1093, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (8H, m, Ar**H**), 7.21-7.16 (2H, m, Ar**H**), 5.75-5.58 (2H, m, **H**C=C**H**), 5.09-5.01 (3H, m, PhC$\mathbf{H}_2$ and C**H**OH), 3.72 (1H, dd, *J* = 9.8, 5.9 Hz, O=CC**H**), 2.89 (1H, d, *J* = 2.5 Hz, O**H**), 2.02-1.81 (2H, m, =CHC$\mathbf{H}_2$), 1.24-1.08 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_3$), 0.81 (3H, t, *J* = 7.0 Hz, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C), 140.8 (C), 136.7 (CH), 135.5 (C), 128.5 (2 × CH), 128.2 (3 × CH), 128.0 (2 × CH), 127.8 (CH), 126.4 (2 × CH), 122.0 (CH), 74.3 (CH), 66.5 (CH_2), 52.2 (CH), 31.3 (CH_2), 27.4 (CH_2), 22.2 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{26}NaO_3]^+$ $[M+Na]^+$: 361.1774, found: 361.1781.



(±)-Benzyl (*S*,*Z*)-8-[(*tert*-butyldiphenylsilyl)oxy]-2-[(*S*)-hydroxy(phenyl)methyl]oct-3-enoate (11e). The general procedure was followed using method B with benzaldehyde (37 μL, 0.36 mmol) and diene **15e** (145 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **11e** as a colorless oil (64.6 mg, 35%). R_f 0.16 (10% EtOAc/petroleum ether); IR 3508 (OH), 2930, 2857, 1729 (C=O), 1454, 1427, 1108, 737, 504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (4H, dt, *J* = 6.5, 1.6 Hz, Ar**H**), 7.48-7.18 (16H, m, Ar**H**), 5.71-5.55 (2H, m, **H**C=C**H**), 5.09-5.00 (3H, PhC$\mathbf{H}_2$ and C**H**OH), 3.67 (1H, dd, *J* = 9.3, 5.7 Hz, O=CC**H**), 3.54 (2H, t, *J* = 6.3 Hz, C$\mathbf{H}_2$OSi), 2.87 (1H, d, *J* = 2.5 Hz, O**H**), 1.94 (1H, dq, *J* = 14.5, 7.0 Hz, =CHC$\mathbf{H}_a$$H_b$), 1.82 (1H, dq, *J* = 14.5, 7.0 Hz, =CHC$H_a$$\mathbf{H}_b$), 1.42-1.36 (2H, m, C$\mathbf{H}_2$$CH_2$OSi), 1.30-1.23 (2H, m, =CHCH_2C$\mathbf{H}_2$), 1.03 (9H, s, C(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C), 140.8 (C), 136.4 (CH), 135.5 (4 × CH), 135.4 (C), 134.0 (2 × C), 129.5 (2 × CH), 128.5 (2 × CH), 128.2 (3 × CH), 128.0 (2 × CH), 127.7 (CH), 127.6 (4 × CH), 126.4 (2 × CH), 122.2 (CH), 74.3 (CH), 66.6 (CH_2), 63.6 (CH_2), 52.2 (CH), 32.0 (CH_2), 27.3 (CH_2), 26.8 (3 × CH_3), 25.4 (CH_2), 19.2 (C); HRMS (ESI) Exact mass calculated for $C_{38}H_{44}O_4SiNa$ $[M+Na]^+$: 615.2907, found: 615.2896.

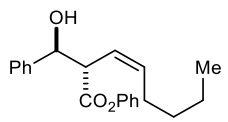


(±)-Methyl (*S*,*Z*)-2-[(*S*)-hydroxy(phenyl)methyl]oct-3-enoate (11f). The general procedure was followed using method B with benzaldehyde (37 μL, 0.36 mmol) and diene **15f** (46.2 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **11f** as an 11:1 mixture of inseparable diastereomers as a colorless oil (35.8 mg, 46%). R_f 0.22 (10% EtOAc/petroleum ether); IR 3494 (OH), 3029, 2955, 2928, 1716 (C=O), 1435, 1161, 1022,

765, 734, 699 cm^{-1}; HRMS (ESI) Exact mass calculated for $[C_{16}H_{22}NaO_3]^+$ $[M+Na]^+$: 285.1461, found: 285.1464.

NMR data of major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (5H, m, Ar**H**), 5.74-5.66 (1H, m, =C**H**CH_2), 5.64-5.56 (1H, m, CHC**H**=), 5.08 (1H, dd, *J* = 5.4, 2.5 Hz, C**H**OH), 3.67 (1H, ddd, *J* = 9.9, 5.4, 0.7 Hz, O=CC**H**), 3.64 (3H, s, OC**H**$_3$), 2.98 (1H, t, *J* = 2.5 Hz, O**H**), 2.01-1.89 (1H, m, =CHC**H**$_a$H$_b$), 1.89-1.77 (1H, m, =CHCH$_a$**H**$_b$), 1.27-1.07 (4H, m, C**H**$_2$C**H**$_2$CH$_3$), 0.84 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C), 140.9 (C), 136.5 (CH), 128.1 (2 × CH), 127.7 (CH), 126.3 (2 × CH), 121.8 (CH), 74.2 (CH), 52.0 (CH and CH_3), 31.3 (CH_2), 27.3 (CH_2), 22.2 (CH_2), 13.9 (CH_3).

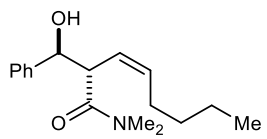
Characteristic NMR data of minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (1H, dd, *J* = 6.1, 2.4 Hz, C**H**OH), 3.61 (3H, s, OC**H**$_3$), 2.89 (1H, t, *J* = 2.6 Hz, O**H**).



(±)-Phenyl (*S*,*Z*)-2-[(*S*)-hydroxy(phenyl)methyl]oct-3-enoate (11g). The general procedure was followed using method B with benzaldehyde (37 µL, 0.36 mmol) and diene **15g** (64.8 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **11g** as a 9:1 mixture of inseparable diastereomers as a colorless oil (41.9 mg, 43%). R_f 0.21 (10% EtOAc/petroleum ether); IR 3511 (OH), 2958, 2927, 2858, 1748 (C=O), 1593, 1492, 1190, 1131, 907, 728 cm^{-1}; HRMS (ESI) Exact mass calculated for $[C_{21}H_{24}NaO_3]^+$ $[M+Na]^+$: 347.1618, found: 347.1622.

NMR data of major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.43 (2H, m, Ar**H**), 7.41-7.29 (5H, m, Ar**H**), 7.22-7.16 (1H, m, Ar**H**), 6.85-6.81 (2H, m, Ar**H**), 5.86 (1H, dtd, *J* = 11.1, 7.3, 0.8 Hz, =C**H**CH_2), 5.75 (1H, ddt, *J* = 11.1, 9.9, 1.5 Hz, CHC**H**=), 5.16 (1H, d, *J* = 6.5 Hz, C**H**OH), 3.94 (1H, ddd, *J* = 9.9, 6.5, 0.8 Hz, O=CC**H**), 2.76 (1H, d, *J* = 2.6 Hz, O**H**), 2.19-1.97 (2H, m, =CHC**H**$_2$), 1.37-1.23 (4H, m, C**H**$_2$C**H**$_2$CH$_3$), 0.87 (3H, t, *J* = 7.0 Hz, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (C), 150.3 (C), 140.7 (C), 138.3 (CH), 129.3 (2 × CH), 128.4 (2 × CH), 128.1 (CH), 126.7 (2 × CH), 126.0 (CH), 122.1 (CH), 121.3 (2 × CH), 74.6 (CH), 52.5 (CH), 31.4 (CH_2), 27.5 (CH_2), 22.3 (CH_2), 13.9 (CH_3).

Characteristic NMR data of minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (1H, dd, *J* = 7.1, 1.9 Hz, C**H**OH), 3.53 (1H, dd, *J* = 8.4, 7.1 Hz, O=CC**H**), 2.71 (1H, d, *J* = 2.5 Hz, O**H**).

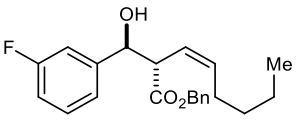


(±)-(*Z*)-2-[Hydroxy(phenyl)methyl]-*N*,*N*-dimethyloct-3-enamide (11h). To a solution of diene **15h** (40.8 mg, 0.24 mmol), benzaldehyde (30 µL, 0.29 mmol), and $[Rh(cod)OH]_2$ (5.5 mg, 0.012 mmol) in 1,4-

dioxane (1.2 mL) at 0 °C was added Et_3B (1.0 M in hexane, 0.72 mL, 0.72 mmol) dropwise. The mixture was stirred at 0 °C for 5 min, and then at 80 °C for 40 h. The reaction was quenched carefully with 1.0 M aqueous HCl solution and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **11h** as a yellow oil (3:1 dr) (15.3 mg, 23%). R_f 0.30 (50% EtOAc/petroleum ether). IR 3397 (OH), 2955, 2928, 2858, 1620 (C=O), 1494, 1398, 1143, 739, 700 cm^{-1}; HRMS (ESI) Exact mass calculated for $[C_{17}H_{25}NNaO_2]^+$ $[M+Na]^+$: 298.1771, found: 298.1774.

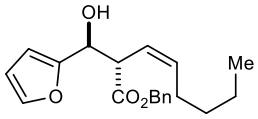
NMR data of major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.20 (5H, m, Ar**H**), 5.60-5.41 (2H, m, **H**C=C**H**), 5.17 (1H, d, *J* = 3.0 Hz, C**H**OH), 5.00 (1H, d, *J* = 1.3 Hz, O**H**), 3.64 (1H, dd, *J* = 10.1, 3.0 Hz, O=CC**H**), 2.96 (3H, s, NC$\mathbf{H}_3$), 2.89 (3H, s, NC$\mathbf{H}_3$), 1.59 (1H, m, =CHC$\mathbf{H}_a$H$_b$), 1.36-1.18 (2H, m, =CHCH$_a$**H**$_b$ and C$\mathbf{H}_a$H$_b$CH$_2$CH$_3$), 1.11-0.93 (3H, m, CH$_a$**H**$_b$CH$_2$CH$_3$ and C$\mathbf{H}_2$CH$_3$), 0.75 (3H, t, *J* = 7.1 Hz, CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (C), 141.3 (C), 135.4 (CH), 127.8 (2 × CH), 127.1 (CH), 126.4 (2 × CH), 121.1 (CH), 74.5 (CH), 48.2 (CH), 37.0 (CH_3), 35.7 (CH_3), 31.3 (CH_2), 27.3 (CH_2), 22.4 (CH_2), 13.78 (CH_3).

Characteristic NMR data of minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (1H, dtd, *J* = 15.6, 6.8, 0.8 Hz, =C**H**CH$_2$), 5.10 (1H, dd, *J* = 3.3, 1.0 Hz, C**H**OH), 4.94 (1H, d, *J* = 1.3 Hz, O**H**), 3.33 (1H, dd, *J* = 8.5, 3.3 Hz, O=CC**H**), 2.90 (3H, s, NC$\mathbf{H}_3$), 2.03-1.95 (1H, m, =CHC$\mathbf{H}_a$H$_b$), 0.85 (3H, t, *J* = 7.1 Hz, CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3 (C), 136.8 (CH), 127.8 (CH), 127.1 (CH), 126.4 (CH), 122.1 (CH), 74.0 (CH), 52.6 (CH), 37.2 (CH_3), 35.5 (CH_3), 32.3 (CH_2), 22.0 (CH_2), 13.84 (CH_3).

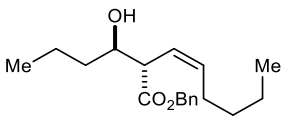


(±)-Benzyl (*S*,*Z*)-2-[(*S*)-(3-fluorophenyl)(hydroxy)methyl]oct-3-enoate (20e). The general procedure was followed using method B with 3-fluorobenzaldehyde (38 μL, 0.36 mmol) and diene **15b** (69.1 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **20e** as a yellow oil (53.1 mg, 50%). R_f 0.14 (10% EtOAc/petroleum ether); IR 3498 (OH), 2956, 2929, 2859, 1715 (C=O), 1488, 1451, 1156, 1001, 736, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.30 (3H, m, Ar**H**), 7.28-7.20 (3H, m, Ar**H**), 7.11-7.05 (2H, m, Ar**H**), 6.95 (1H, tdd, *J* = 8.5, 2.3, 1.4 Hz, Ar**H**), 5.71 (1H, dtd, *J* = 10.9, 7.3, 0.8 Hz, =C**H**CH$_2$), 5.63-5.55 (1H, m, CHC**H**=), 5.12-5.04 (3H, m, PhC$\mathbf{H}_2$ and C**H**OH), 3.68 (1H, ddd, *J* = 10.0, 5.4,

0.8 Hz, O=CC**H**), 3.04 (1H, br s, O**H**), 2.02-1.89 (1H, m, =CHC$\mathbf{H}_a$H$_b$), 1.89-1.78 (1H, m, =CHCH$_a$$\mathbf{H}_b$), 1.25-1.05 (4H, m, C$\mathbf{H}_2C\mathbf{H}_2CH_3$), 0.81 (3H, t, J = 7.0 Hz, CH$_2$CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.8 (C), 162.7 (d, J_{CF} = 245.6 Hz, C), 143.4 (d, J_{CF} = 7.0 Hz, C), 137.0 (CH), 135.4 (C), 129.6 (d, J_{CF} = 8.2 Hz, CH), 128.5 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 121.9 (d, J_{CF} = 11.4 Hz, CH), 121.4 (CH), 114.6 (d, J_{CF} = 21.2 Hz, CH), 113.5 (d, J_{CF} = 22.4 Hz, CH), 73.5 (CH), 66.7 (CH$_2$), 51.9 (CH), 31.3 (CH$_2$), 27.4 (CH$_2$), 22.2 (CH$_2$), 13.8 (CH$_3$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –113.6; HRMS (ESI) Exact mass calculated for [C$_{22}$H$_{25}$FNaO$_3$]$^+$ [M+Na]$^+$: 379.1680, found: 379.1692.



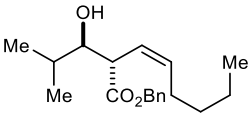
(±)-Benzyl (*S*,*Z*)-2-[(*S*)-furan-2-yl(hydroxy)methyl]oct-3-enoate (20f). The general procedure was followed using method B with furfural (30 μL, 0.36 mmol) and diene **15b** (69.1 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **20f** as a brown oil (39.0 mg, 40%). R$_f$ 0.14 (10% EtOAc/petroleum ether); IR 3468 (OH), 2956, 2928, 2859, 1729 (C=O), 1498, 1455, 1145, 1002, 732, 696 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39-7.25 (6H, m, Ar**H**), 6.30 (1H, dd, J = 3.3, 1.8 Hz, Ar**H**), 6.26 (1H, d, J = 3.3 Hz, Ar**H**), 5.74 (1H, dt, J = 10.8, 7.4 Hz, =C**H**CH$_2$), 5.60-5.53 (1H, m, CHC**H**=), 5.11 (2H, s, PhC$\mathbf{H}_2$), 5.05 (1H, d, J = 6.3 Hz, C**H**OH), 3.93 (1H, ddd, J = 10.0, 6.3, 0.9 Hz, O=CC**H**), 2.86 (1H, br s, O**H**), 2.15-1.99 (2H, m, =CHC$\mathbf{H}_2$), 1.33-1.23 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$CH$_3$), 0.87 (3H, t, J = 7.1 Hz, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.3 (C), 153.5 (C), 142.1 (CH), 136.8 (CH), 135.5 (C)¸ 128.5 (2 × CH), 128.2 (CH), 128.1 (2 × CH), 121.9 (CH), 110.2 (CH), 107.2 (CH), 68.5 (CH), 66.7 (CH$_2$), 49.3 (CH), 31.4 (CH$_2$), 27.5 (CH$_2$), 22.3 (CH$_2$), 13.9 (CH$_3$); HRMS (ESI) Exact mass calculated for [C$_{20}$H$_{24}$NaO$_4$]$^+$ [M+Na]$^+$: 351.1567, found: 351.1566.



(±)-Benzyl (*S*,*Z*)-2-[(*R*)-1-hydroxybutyl]oct-3-enoate (20g). The general procedure was followed using method B with butyraldehyde (32 μL, 0.36 mmol) and diene **15b** (69.1 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **20g** as a 9:1 mixture of inseparable diastereomers as a yellow oil (34.4 mg, 38%). R$_f$ 0.21 (10% EtOAc/petroleum ether); IR 3531 (OH), 2957, 2930, 2872, 1730 (C=O), 1498, 1456, 1158, 1001, 733, 696 cm^{-1}; HRMS (ESI) Exact mass calculated for [C$_{19}$H$_{28}$NaO$_3$]$^+$ [M+Na]$^+$: 327.1931, found: 327.1932. *NMR data of major diastereomer*: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.43-7.31 (5H, m, Ar**H**), 5.76 (1H, dt, J = 10.9, 7.4 Hz, =C**H**CH$_2$), 5.61-5.54 (1H, m, CHC**H**=), 5.17 (2H, s, PhC$\mathbf{H}_2$), 3.96

(1H, dt, J = 8.4, 4.2 Hz, C**H**OH), 3.46 (1H, dd, J = 10.0, 4.6 Hz, O=CC**H**), 2.61 (1H, br s, O**H**), 2.19-2.04 (2H, m, =CHC$\mathbf{H}_2$), 1.60-1.41 (2H, m, C$\mathbf{H}_a$H$_b$C$\mathbf{H}_a$H$_b$CHOH), 1.43-1.24 (6H, m, =CHCH$_2$C$\mathbf{H}_2$C$\mathbf{H}_2$ and CH$_a$$\mathbf{H}_bCH_a$$\mathbf{H}_b$CHOH), 0.93-0.88 (3H, m, 2 × C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.6 (C), 136.1 (CH), 135.7 (C), 128.6 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 122.1 (CH), 71.4 (CH), 66.5 (CH$_2$), 49.5 (CH), 36.2 (CH$_2$), 31.6 (CH$_2$), 27.6 (CH$_2$), 22.3 (CH$_2$), 18.9 (CH$_2$), 13.94 (CH$_3$), 13.91 (CH$_3$).

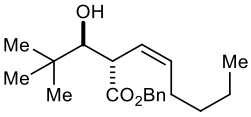
Characteristic NMR data of minor diastereomer: ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.68 (1H, dt, J = 15.5, 6.7 Hz, =C**H**CH$_2$), 3.91 (1H, dt, J = 8.6, 4.5 Hz, C**H**OH), 3.06 (dd, J = 9.1, 4.8 Hz, O=CC**H**); ^{13}C NMR (101 MHz, CDCl$_3$) δ 137.4 (CH), 122.8 (CH), 71.2 (CH), 54.9 (CH), 32.3 (CH$_2$), 31.3 (CH$_2$), 22.1 (CH$_2$), 18.8 (CH$_2$).



(±)-Benzyl (*S*,*Z*)-2-[(*R*)-1-hydroxy-2-methylpropyl]oct-3-enoate (20h). The general procedure was followed using method B with isobutyraldehyde (33 μL, 0.36 mmol) and diene **15b** (69.1 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **20h** as a 16:1 mixture of inseparable diastereomers as a yellow oil (49.4 mg, 54%). R$_f$ 0.23 (10% EtOAc/petroleum ether); IR 3533 (OH), 2958, 2929, 2872, 1715 (C=O), 1498, 1455, 1160, 995, 733, 696 cm^{-1}; HRMS (ESI) Exact mass calculated for [C$_{19}$H$_{28}$NaO$_3$]$^+$ [M+Na]$^+$: 327.1931, found: 327.1938.

NMR data of major diastereomer: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41-7.30 (5H, m, Ar**H**), 5.73 (1H, dtd, J = 10.8, 7.3, 0.8 Hz, =C**H**CH$_2$), 5.58 (1H, ddt, J = 11.4, 9.8, 1.6 Hz, CHC**H**=), 5.14 (2H, s, PhC$\mathbf{H}_2$), 3.65 (1H, dd, J = 6.8, 4.7 Hz, C**H**OH), 3.60 (1H, ddd, J = 9.8, 4.7, 0.9 Hz, O=CC**H**), 2.66 (1H, br s, O**H**), 2.17-2.05 (2H, m, =CHC$\mathbf{H}_2$), 1.65 (1H, dq, J = 13.4, 6.7 Hz, (CH$_3$)$_2$C**H**), 1.38-1.24 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$CH$_3$), 0.99 (3H, d, J = 6.7 Hz, C$\mathbf{H}_3$CH), 0.91-0.85 (6H, m, C$\mathbf{H}_3$CH and CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.8 (C), 136.0 (CH), 135.6 (C), 128.5 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 122.1 (CH), 76.4 (CH), 66.6 (CH$_2$), 47.2 (CH), 31.6 (CH$_2$), 30.8 (CH), 27.7 (CH$_2$), 22.4 (CH$_2$), 19.3 (CH$_3$), 17.7 (CH$_3$), 13.9 (CH$_3$).

Characteristic NMR data of minor diastereomer: ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.22 (1H, dd, J = 9.0, 4.9 Hz, O=CC**H**).

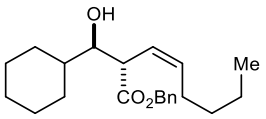


(±)-Benzyl (*S*,*Z*)-2-[(*S*)-1-hydroxy-2,2-dimethylpropyl]oct-3-enoate (20i). The general procedure was followed using method B with pivalaldehyde (39 μL, 0.36 mmol) and diene **15b** (69.1 mg, 0.30 mmol).

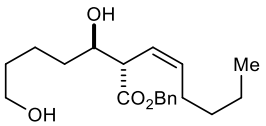
Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **20i** as a 4:1 mixture of inseparable diastereomers as a yellow oil (27.0 mg, 28%). R_f 0.30 (10% EtOAc/petroleum ether); IR 3538 (OH), 2956, 2871, 1715 (C=O), 1498, 1456, 1301, 1152, 1000, 733, 696 cm^{-1}; HRMS (ESI) Exact mass calculated for $[C_{20}H_{30}NaO_3]^+$ $[M+Na]^+$: 341.2087, found: 341.2090.

NMR data of major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.29 (5H, m, Ar**H**), 5.73-5.56 (2H, m, **H**C=C**H**), 5.18-5.07 (2H, m, PhC$\mathbf{H}_2$), 3.70 (1H, dd, *J* = 4.7, 1.3 Hz, C**H**OH), 3.66 (1H, ddd, *J* = 9.0, 4.6, 1.3 Hz, O=CC**H**), 2.17-2.17 (2H, m, =CHC$\mathbf{H}_2$), 1.37-1.25 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_3$), 0.94 (9H, s, C(C$\mathbf{H}_3$)$_3$), 0.87 (3H, t, *J* = 7.1 Hz, CH_2C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 135.6 (C), 135.2 (CH), 128.5 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 123.3 (CH), 77.9 (CH), 66.6 (CH_2), 46.2 (CH), 35.37 (C), 31.4 (CH_2), 27.7 (CH_2), 26.4 (3 × CH_3), 22.4 (CH_2), 19.3 (CH_3).

Characteristic NMR data of minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34-3.26 (1H, m, O=CC**H**), 2.08-2.04 (1H, m, =CHC$\mathbf{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (CH), 124.2 (CH), 77.6 (CH), 66.5 (CH_2), 51.7 (CH), 32.3 (CH_2), 31.1 (CH_2), 26.2 (CH_3), 22.2 (CH_2).



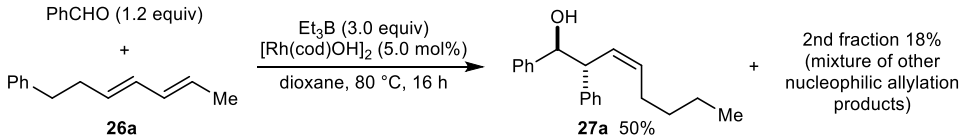
(±)-Benzyl (*S*,*Z*)-2-[(*R*)-cyclohexyl(hydroxy)methyl]oct-3-enoate (20j). The general procedure was followed using method B with cyclohexanecarboxaldehyde (44 μL, 0.36 mmol) and diene **15b** (69.1 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **20j** as a yellow oil (63.5 mg, 61%). R_f 0.20 (10% EtOAc/petroleum ether); IR 3522 (OH), 2934, 2852, 1715 (C=O), 1498, 1450, 1310, 1158, 1004, 734, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.30 (5H, m, Ar**H**), 5.72 (1H, ddd, *J* = 10.9, 7.7, 6.9 Hz, =C**H**CH_2), 5.58 (1H, ddt, *J* = 11.3, 10.0, 1.6 Hz, CHC**H**=), 5.22-5.05 (2H, m, PhC$\mathbf{H}_2$), 3.68 (1H, dd, *J* = 6.9, 4.6 Hz, (C**H**)OH), 3.61 (1H, ddd, *J* = 9.9, 4.6, 0.8 Hz, O=CC**H**), 2.57 (1H, br s, O**H**), 2.15-2.06 (2H, m, =CHC$\mathbf{H}_2$), 1.97-1.48 (5H, m, (C$\mathbf{H}_2$)$_5$), 1.39-1.25 (5H, m, C**H**(CH_2)$_5$ and C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_3$), 1.23-0.98 (5H, m, (C$\mathbf{H}_2$)$_5$), 0.87 (3H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (C), 135.9 (CH), 135.7 (C), 128.5 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 122.1 (CH), 75.6 (CH), 66.5 (CH_2), 46.7 (CH), 40.4 (CH), 31.6 (CH_2), 29.4 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 22.3 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{32}NaO_3]^+$ $[M+Na]^+$: 367.2244, found: 367.2253.



(±)-Benzyl (*S*,*Z*)-2-[(*R*)-1,5-dihydroxypentyl)oct-3-enoate (20k). general procedure was followed under method B using tetrahydro-*2H*-pyran-2-ol (37 μL, 0.36 mmol) and diene **15b** (69.1 mg, 0.30 mmol). Column chromatography (50% EtOAc/petroleum ether) gave *homoallylic alcohol* **20k** (58.5 mg, 58%) as an orange oil. R_f 0.30 (50% EtOAc/petroleum ether); IR 3378 (OH), 2927, 2859, 1729 (C=O), 1456, 1216, 1158, 1000, 735, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.30 (5H, m, Ar**H**), 5.75 (1H, dtd, *J* = 10.8, 7.4, 0.9 Hz, =C**H**CH_2), 5.55 (1H, ddt, *J* = 11.5, 10.0, 1.6 Hz, CHC**H**=), 5.15 (2H, s, PhC**H**$_2$), 3.94 (1H, dd, *J* = 8.5, 4.4 Hz, C**H**OH), 3.63 (2H, t, *J* = 6.1 Hz, C**H**$_2$OH), 3.45 (1H, ddd, *J* = 10.0, 4.7, 0.9 Hz, O=CC**H**), 2.69 (1H, br s, O**H**), 2.15-2.03 (2H, m, =CHC**H**$_2$), 1.63-1.24 (10H, m, C**H**$_2$C**H**$_2$C**H**$_2$CHOH and C**H**$_2$C**H**$_2$$CH_3$), 0.87 (3H, t, *J* = 7.1 Hz, CH_2C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (C), 136.2 (CH), 135.6 (C), 128.6 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 122.0 (CH), 71.6 (CH), 66.6 (CH_2), 62.8 (CH_2), 49.6 (CH), 33.6 (CH_2), 32.5 (CH_2), 31.6 (CH_2), 27.6 (CH_2), 22.3 (CH_2), 21.9 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{30}NaO_4]^+$ $[M+Na]^+$: 357.2036, found: 357.2045.

(±)-(1*S*,2*R*,Z)-1,2-Diphenyloct-3-en-1-ol (27a)

*From (3E,5E)-***26a***:*

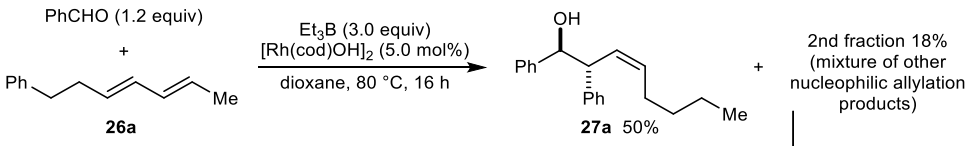


The general procedure was followed using method B with benzaldehyde (37 μL, 0.36 mmol) and diene **26a** (55.5 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave homoallylic alcohol **27a** as a yellow oil (42.3 mg, 50%) followed by another fraction as a yellow oil that appeared to be a complex mixture of other nucleophilic allylation products (15.5 mg, 18%).

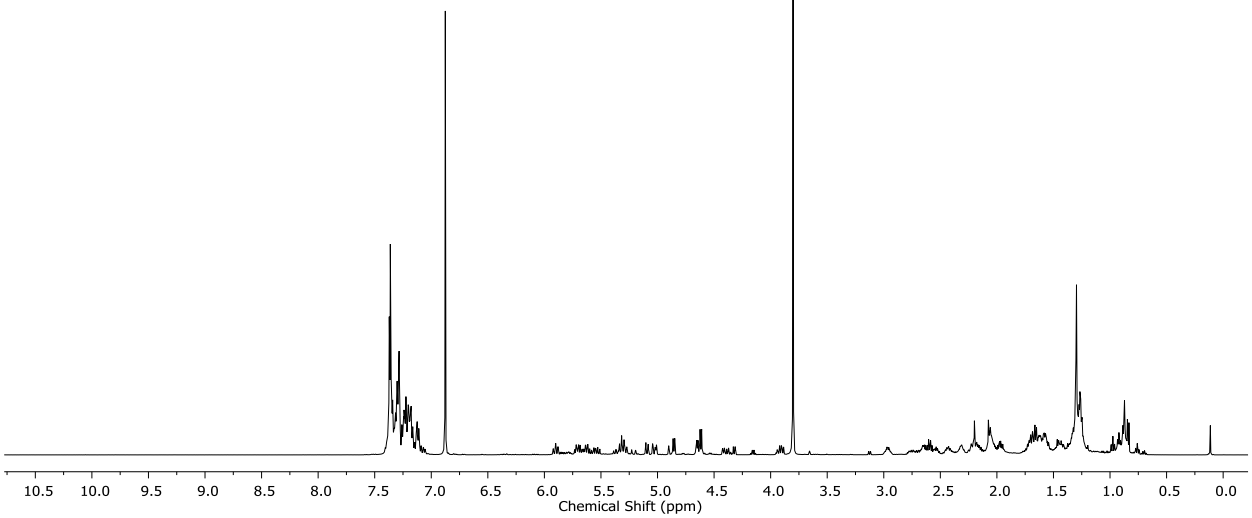
Data for **27a**: R_f 0.46 (20% EtOAc/petroleum ether); IR 3451 (OH), 2956, 2925, 2857, 1493, 1452, 1079, 1028, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.14 (8H, m, Ar**H**), 7.13-7.08 (2H, m, Ar**H**), 5.93-5.86 (1H, m, CHC**H**=), 5.70 (1H, dtd, *J* = 10.8, 7.3, 0.9 Hz, =C**H**CH_2), 4.84 (1H, d, *J* = 7.3 Hz, C**H**OH), 3.89 (1H, dd, *J* = 10.1, 7.2 Hz, PhC**H**CH=), 2.28 (1H, br s, O**H**), 2.13-1.99 (2H, m, =CHC**H**$_2$), 1.28-1.23 (4H, m, C**H**$_2$C**H**$_2$$CH_3$), 0.91-0.83 (3H, m, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (C), 141.5 (C), 134.1 (CH), 128.29 (2 × CH), 128.25 (2

× CH), 128.1 (CH), 127.8 (2 × CH), 127.3 (CH), 126.6 (2 × CH), 126.4 (CH), 78.0 (CH), 52.4 (CH), 31.5 (CH_2), 27.3 (CH_2), 22.3 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{24}NaO]^+$ $[M+Na]^+$: 303.1719, found: 303.1721. Spectroscopic data matched those reported previously.[196]

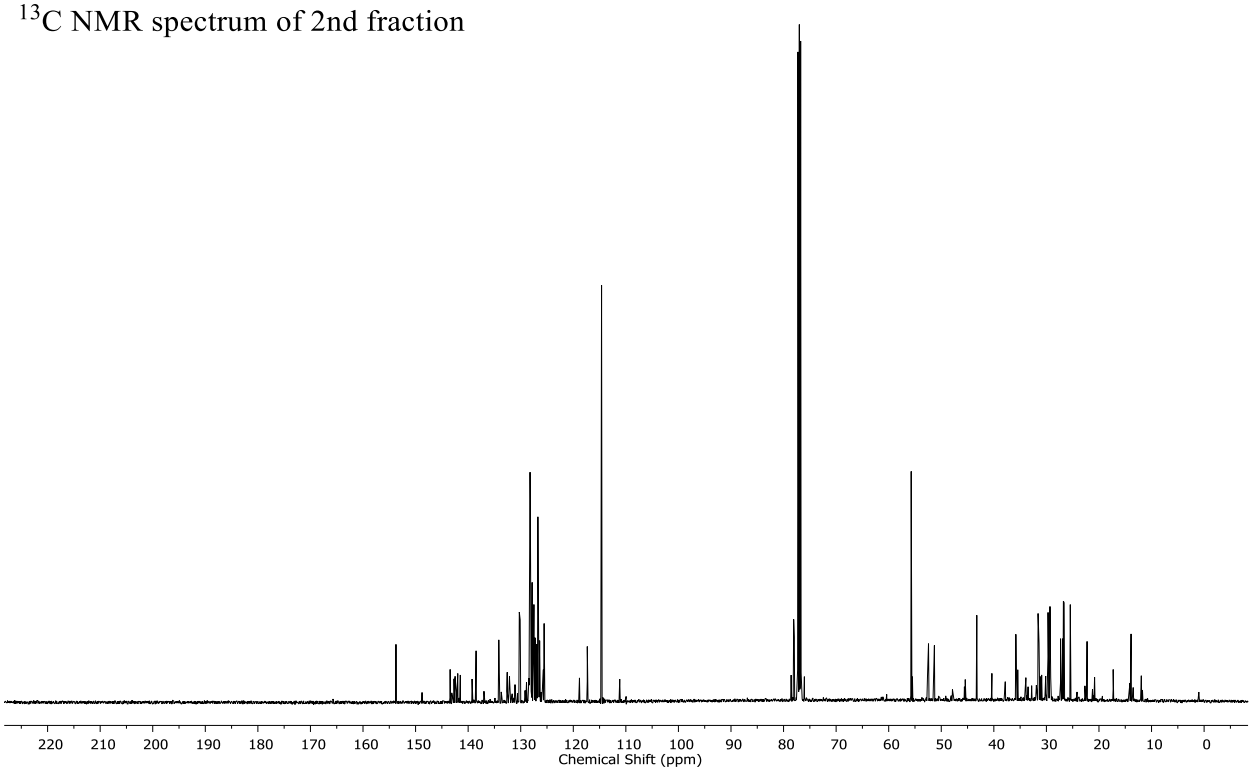
Data for 2nd fraction: Unfortunately, the complexity of the ^{1}H and ^{13}C NMR spectra prevented determination of the composition of this fraction (pictures of these spectra are shown below). However, HRMS analysis of this fraction showed the major signal has the same mass as product **27a**, suggesting this fraction consists of a complex mixture of other nucleophilic allylation products resulting from various intermediate allylrhodium species. The IR spectrum confirms the presence of a hydroxyl group (broad signal at 3444 cm^{-1}). R_f 0.40 (20% EtOAc/petroleum ether); IR 3444 (OH), 2926, 2855, 1602, 1508, 1231, 1043, 908, 730, 698 cm^{-1}; HRMS (ESI) Exact mass calculated for $[C_{20}H_{24}NaO]^+$ $[M+Na]^+$: 303.1719, found: 303.1717.



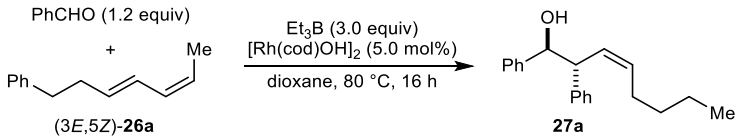
^{1}H NMR spectrum of 2nd fraction



^{13}C NMR spectrum of 2nd fraction

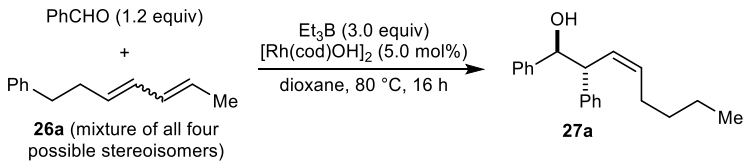


*From (3E,5Z)-***26a***:*

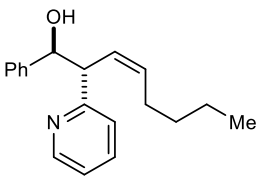


The general procedure was followed using method B with benzaldehyde (37 μL, 0.36 mmol) and diene (3*E*,5*Z*)-**26a** (51.6 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **27a** as a colorless oil (42.8 mg, 51%). (For the characterization data of **27a**, see above)

From **26a** *(Mixture of All Four Stereoisomers):*



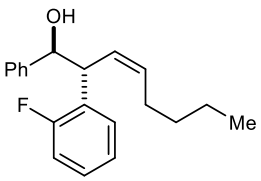
To a solution of the diene **26a** (mixture of all four possible stereoisiomers, 34.4 mg, 0.20 mmol), benzaldehyde (24 μL, 0.24 mmol), and $[Rh(cod)OH]_2$ (4.6 mg, 0.010 mmol) in 1,4-dioxane (1.0 mL) at 0 °C was added Et_3B (1.0 M in hexane, 0.60 mL, 0.60 mmol) dropwise. The mixture was stirred at 0 °C for 5 min, and then at 80 °C for 16 h. stirring at this temperature the reaction was heated to 80 °C and stirred for a period of 16 h. The reaction was quenched carefully with 1.0 M aqueous HCl solution and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **27a** as a colorless oil (26.6 mg, 48%). (For the characterization data of **27a**, see above)



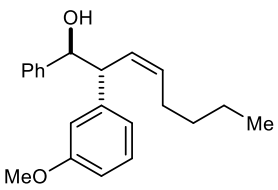
(±)-(1*S*,2*R*,*Z*)-1-Phenyl-2-(pyridin-2-yl)oct-3-en-1-ol (27b). The general procedure was followed using method B with benzaldehyde (37 μL, 0.36 mmol) and diene **26b** (51.9 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **27b** as a 5:1 mixture of inseparable diastereomers as a yellow solid (42.2 mg, 50%). R_f 0.29 (20% EtOAc/petroleum ether); m.p. 65-67 °C (Et_2O); IR 3169 (OH), 3062, 2927, 2868, 1592, 1431, 1044, 1002, 748, 701 cm^{-1}; HRMS (ESI) Exact mass calculated for $[C_{19}H_{24}NNaO]^+$ $[M+H]^+$: 282.1858, found: 282.1856.

NMR data of major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, dt, *J* = 5.2, 1.3 Hz, Ar**H**), 7.61 (1H, td, *J* = 7.7, 1.9 Hz, Ar**H**), 7.40-7.25 (4H, m, Ar**H**), 7.24-7.16 (2H, m, Ar**H**), 7.07 (1H, dd, *J* = 7.8, 1.1 Hz, Ar**H**), 5.82-5.67 (2H, m, CHC**H**= and O**H**), 5.50 (1H, dt, *J* = 10.9, 7.3 Hz, =C**H**CH_2), 5.27 (1H, d, *J* = 3.3 Hz, C**H**OH), 4.00 (1H, dd, *J* = 10.2, 3.3 Hz ArC**H**CH=), 1.86-1.79 (1H, m, =CHC$\mathbf{H}_a$$H_b$), 1.76-1.66 (1H, m, =CHC$H_a$$\mathbf{H}_b$), 1.28-0.83 (4H, m, C$\mathbf{H}_2C\mathbf{H}_2$$CH_3$), 0.79 (3H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (C), 148.5 (CH), 142.3 (C), 137.0 (CH), 133.1 (CH), 127.8 (2 × CH), 126. 90 (CH), 126.5 (2 × CH), 126.0 (CH), 123.3 (CH), 121.7 (CH), 76.1 (CH), 51.5 (CH), 31.4 (CH_2), 27.2 (CH_2), 22.2 (CH_2), 13.9 (CH_3).

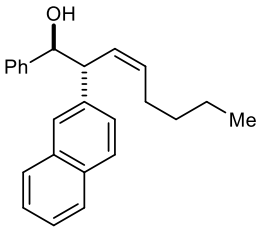
Characteristic NMR data of minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, d, *J* = 3.4 Hz, C**H**OH), 3.60 (1H, dd, *J* = 8.8, 3.6 Hz, ArC**H**CH=), 0.83 (3H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4 (CH), 142.2 (C), 136.9 (CH), 134.9 (CH), 127.7 (CH), 126.94 (CH), 126.85 (CH), 126.6 (CH), 123.5 (CH), 121.66 (CH), 75.9 (CH), 57.2 (CH), 32.3 (CH_2), 22.0 (CH_2).



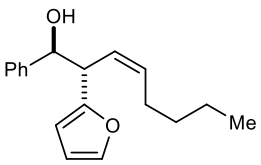
(±)-(1*S*,2*R*,*Z*)-2-(2-Fluorophenyl)-1-phenyloct-3-en-1-ol (27c). The general procedure was followed using method B with benzaldehyde (37 µL, 0.36 mmol) and diene **26c** (57.0 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **27c** as a yellow oil (45.0 mg, 50%). R_f 0.31 (10% EtOAc/petroleum ether); IR 3444 (OH), 2957, 2924, 2855, 1489, 1453, 1299, 1026, 753, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.07 (7H, m, Ar**H**), 7.00 (1H, td, *J* = 7.5, 1.4 Hz, Ar**H**), 6.92 (1H, ddd, *J* = 10.1, 8.2, 1.4 Hz, Ar**H**), 5.94-5.85 (1H, m, CHC**H**=), 5.69 (1H, dt, *J* = 10.9, 7.3 Hz, =C**H**CH_2), 4.92 (1H, d, *J* = 7.5 Hz, C**H**OH), 4.22 (1H, dd, *J* = 9.9, 7.5 Hz, ArC**H**CH=), 2.26 (1H, br s, O**H**), 2.11-1.97 (2H, m, =CHC$\mathbf{H}_2$), 1.27-1.18 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_3$), 0.90-0.80 (3H, m, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (d, J_{CF} = 244.9 Hz, C), 141.8 (C), 134.9 (CH), 129.8 (d, J_{CF} = 5.0 Hz, CH), 128.7 (d, J_{CF} = 14.3 Hz, C), 127.91 (CH), 129.76 (CH), 127.85 (CH), 127.4 (CH), 127.0 (CH), 126.4 (2 × CH), 123.9 (d, J_{CF} = 3.5 Hz, CH), 115.4 (d, J_{CF} = 22.8 Hz, CH), 76.7 (CH), 45.8 (CH), 31.5 (CH_2), 27.3 (CH_2), 22.2 (CH_2), 13.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –118.0; HRMS (ESI) Exact mass calculated for $[C_{20}FH_{23}O]^+$ $[M]^+$: 281.1727, found: 281.1702.



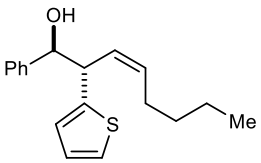
(±)-(1*S*,2*R*,Z)-2-(3-Methoxyphenyl)-1-phenyloct-3-en-1-ol (27d). The general procedure was followed using method B with benzaldehyde (37 µL, 0.36 mmol) and diene **26d** (60.6 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **27d** as a white oil (39.0 mg, 42%). R_f 0.15 (10% EtOAc/petroleum ether); IR 3454 (OH), 2955, 2919, 2850, 1600, 1584, 1489, 1454, 1261, 1045, 730, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.14 (6H, m, Ar**H**), 6.77-6.70 (2H, m, Ar**H**), 6.67-6.63 (1H, m, Ar**H**), 5.87 (1H, ddt, *J* = 10.9, 10.0, 1.6 Hz, CHC**H**=), 5.70 (1H, dtd, *J* = 10.9, 7.3, 0.9 Hz, =C**H**CH_2), 4.85 (1H, d, *J* = 7.1 Hz, C**H**OH), 3.87 (1H, ddd, *J* = 10.1, 7.1, 1.0 Hz, ArC**H**CH=), 3.76 (3H, s, OC**H**$_3$), 2.30 (1H, br s, O**H**), 2.10-2.00 (2H, m, =CHC**H**$_2$), 1.29-1.22 (4H, m, C**H**$_2$C**H**$_2$$CH_3$), 0.89-0.84 (3H, m, CH_2C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (C), 143.1 (C), 142.0 (C), 134.2 (CH), 129.3 (CH), 127.9 (3 × CH), 127.3 (CH), 126.6 (2 × CH), 120.6 (CH), 114.1 (CH), 111.7 (CH), 77.8 (CH), 55.1 (CH_3), 52.4 (CH), 31.5 (CH_2), 27.3 (CH_2), 22.3 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{26}NaO_2]^+$ $[M+Na]^+$: 333.1825, found: 333.1819.



(±)-(1*S*,2*R*,Z)-2-(Naphthalen-2-yl)-1-phenyloct-3-en-1-ol (27e). The general procedure was followed using method B with benzaldehyde (37 µL, 0.36 mmol) and diene **26e** (60.6 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **27e** as a white oil (46.9 mg, 47%). R_f 0.23 (10% EtOAc/petroleum ether); IR 3433 (OH), 3053, 2955, 2925, 2857, 1450, 1299, 1017, 744, 698, 479 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.67 (3H, m, Ar**H**), 7.56 (1H, s, Ar**H**), 7.46-7.40 (2H, m, Ar**H**), 7.30-7.15 (6H, m, Ar**H**), 5.98 (1H, td, *J* = 10.4, 9.9, 1.7 Hz, CHC**H**=), 5.72 (1H, dt, *J* = 10.7, 7.3 Hz, =C**H**CH_2), 4.96 (1H, dt, *J* = 7.1, 1.8 Hz, C**H**OH), 4.07 (1H, dd, *J* = 10.0, 7.1 Hz, ArC**H**CH=), 2.31 (1H, br s, O**H**), 2.11-2.01 (2H, m, =CHC**H**$_2$), 1.28-1.20 (4H, m, C**H**$_2$C**H**$_2$$CH_3$), 0.86-0.82 (3H, m, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (C), 139.1 (C), 134.3 (CH), 133.4 (C), 132.2 (C), 127.94 (CH), 127.89 (2 × CH), 127.7 (CH), 127.5 (CH), 127.3 (CH), 126.9 (CH), 126.7 (CH), 126.6 (2 × CH), 125.9 (CH), 125.4 (CH), 77.9 (CH), 52.4 (CH), 31.5 (CH_2) 27.4 (CH_2), 22.3 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{24}H_{26}NaO]^+$ $[M+H]^+$: 353.1876, found: 353.1866.

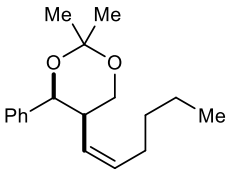


(±)-(1*S*,2*S*,*Z*)-1-Phenyl-2-(furan-2-yl)oct-3-en-1-ol (27f). The general procedure was followed using method B with benzaldehyde (37 µL, 0.36 mmol) and diene **26f** (48.6 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **27f** as a yellow oil (27.0 mg, 33%). R_f 0.26 (10% EtOAc/petroleum ether); IR 3459 (OH), 3028, 2956, 1738, 1453, 1009, 728, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (6H, m, Ar**H**), 6.27 (1H, dd, *J* = 3.2, 1.9 Hz, Ar**H**), 6.01-5.92 (1H, m, Ar**H**), 5.75-5.62 (2H, m, **H**C=C**H**), 5.03 (1H, dd, *J* = 6.0, 2.0 Hz, C**H**OH), 4.03 (1H, dd, *J* = 8.9, 6.0 Hz, ArC**H**CH=), 2.29 (1H, br s, O**H**), 2.05-1.84 (2H, m, =CHC$\mathbf{H}_2$), 1.27-1.14 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_3$), 0.85 (3H, t, *J* = 7.0 Hz, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (C), 141.7 (C), 141.3 (CH), 134.6 (CH), 127.9 (2 × CH), 127.4 (CH), 126.3 (2 × CH), 124.6 (CH), 110.2 (CH), 106.5 (CH), 75.8 (CH), 46.0 (CH), 31.4 (CH_2), 27.2 (CH_2), 22.3 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{22}NaO_2]^+$ $[M+Na]^+$: 293.1512, found: 293.1512.



(±)-(1*S*,2*S*,*Z*)-1-Phenyl-2-(2-thienyl)oct-3-en-1-ol (27g). The general procedure was followed using method B with benzaldehyde (37 µL, 0.36 mmol) and diene **26g** (53.4 mg, 0.30 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* **27g** as a yellow oil (27.0 mg, 31%). R_f 0.21 (10% EtOAc/petroleum ether); IR 3433 (OH), 3027, 2955, 2925, 2856, 1494, 1378, 1042, 783, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.22 (5H, m, Ar**H**), 7.14 (1H, dd, *J* = 5.1, 1.1 Hz, Ar**H**), 6.89 (1H, dd, *J* = 5.1, 3.5 Hz, Ar**H**), 6.72 (1H, dt, *J* = 3.5, 1.1 Hz, Ar**H**), 5.76 (1H, ddt, *J* = 11.3, 9.9, 1.5 Hz, CHC**H**=), 5.67 (1H, dtd, *J* = 10.8, 7.0, 0.8 Hz, =C**H**CH_2), 4.89 (1H, dd, *J* = 6.2, 2.4 Hz, C**H**OH), 4.20 (1H, dd, *J* = 9.9, 6.3 Hz, ArC**H**CH=), 2.29 (1H, d, *J* = 2.5 Hz, O**H**), 2.08-1.90 (2H, m, =CHC$\mathbf{H}_2$), 1.29-1.19 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_3$), 0.90-0.81 (3H, t, *J* = 7.0 Hz, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5 (C), 141.6 (C), 134.3 (CH), 128.0 (2 × CH), 127.5 (CH), 127.3 (CH), 126.61 (CH), 126.57 (2 × CH), 124.6 (CH), 123.7 (CH), 78.0 (CH), 47.3 (CH), 31.4 (CH_2), 27.2 (CH_2), 22.3 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calculated for $C_{18}H_{22}NaO_2S$ $[M+Na]^+$: 309.1284, found: 309.1284.

1.3.4 Confirmation of Diastereoselectivity via Product Derivatisation



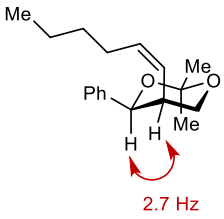
(±)-(4*S*,5*R*)-5-[(*Z*)-Hex-1-en-1-yl]-2,2-dimethyl-4-phenyl-1,3-dioxane (48).

Preparation of **47:** A solution of **11f** (11:1 mixture of diastereomers, 91.4 mg, 0.35 mmol) in MeOH (2 mL) was added to a solution of $NaBH_4$ (34.2 mg, 0.78 mmol) and MeOH (2 mL) and the solution was heated at 70˚C for 8 h. The reaction was diluted with 1 M HCl (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave **47** as an orange oil that was used without further purification.

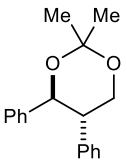
Preparation of **48:** TsOH·H_2O (2.1 mg, 0.01 mmol) was added to a solution of **47** (50.4 mg, 0.22 mmol) in 2,2-dimethoxypropane (1 mL) and the mixture was stirred at room temperature for 1 h. The reaction was diluted with Et_2O (10 mL), washed with saturated aqueous $NaHCO_3$ solution (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (5-8% EtOAc/petroleum ether) to give the *acetonide* **48** as a 10:1 mixture of inseparable diastereomers as a colorless oil (35 mg, 37% over two steps). R_f 0.30 (8% EtOAc/petroleum ether); IR 2957, 2928, 2858, 1498, 1378, 1195, 1072, 698 cm^{-1}.

NMR data of major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (4H, m, Ar**H**), 7.26-7.18 (1H, m, Ar**H**), 5.80 (1H, ddt, *J* = 11.7, 10.2, 1.7 Hz, =C**H**CH), 5.33 (1H, dt, *J* = 11.2, 7.3 Hz, CH_2C**H**=), 5.21 (1H, d, *J* = 2.8 Hz, PhC**H**), 4.38 (1H, dd, *J* = 11.3, 2.8 Hz, OC$\mathbf{H}_a$$H_b$), 3.77 (1H, dd, *J* = 11.3, 1.8 Hz, OC$H_a$$\mathbf{H}_b$), 2.64 (1H, app dtdd, *J* = 10.1, 2.8, 1.8, 1.0 Hz, PhCHC**H**), 1.78-1.65 (1H, m, C$\mathbf{H}_a$$H_b$CH=), 1.60 (3H, s, C$\mathbf{H}_3$ axial), 1.57 (3H, s, C$\mathbf{H}_3$ equatorial), 1.51 (1H, ddt, *J* = 14.3, 8.0, 1.7 Hz, $CH_a$$\mathbf{H}_b$CH=), 1.17-0.83 (4H, m, CH_3C$\mathbf{H}_2$C$\mathbf{H}_2$), 0.78 (3H, t, *J* = 7.1 Hz, CH_2C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (C), 131.8 (CH), 127.8 (2 × CH), 126.9 (CH), 125.8 (2 × CH), 125.4 (CH), 99.2 (C), 73.4 (CH), 65.9 (CH_2), 38.4 (CH), 31.4 (CH_2), 29.7 (CH_3), 27.1 (CH_2), 22.2 (CH_2), 19.1 (CH_3), 13.9 (CH_3).

Characteristic NMR data of minor diastereomer (likely an E-alkene resulting from E/Z isomerization): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (1H, ddt, *J* = 15.4, 9.2, 1.3 Hz, CHC**H**=), 5.18 (1H, d, *J* = 2.9 Hz, PhC**H**), 5.16-5.08 (1H, m, =C**H**CH_2), 3.85 (1H, dd, *J* = 11.4, 1.7 Hz, OC$H_a$$\mathbf{H}_b$).



The indicated coupling constant is consistent with similar compounds reported previously.[141]



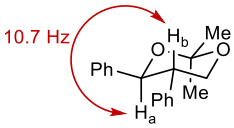
(4*R*,5*R*)-2,2-dimethyl-4,5-diphenyl-1,3-dioxane (51).

Preparation of **49:** A solution of $RuCl_3 \cdot H_2O$ (2.5 mg, 12 μmol) in MeCN (0.68 mL) was added to a solution of alkene **27a** (112 mg, 0.40 mmol) in CH_2Cl_2 (0.68 mL). A solution of $NaIO_4$ (368 mg, 1.72 mmol) in H_2O (1.08 mL) was added and the solution was stirred at room temperature for 5 h. The reaction was diluted with H_2O (10 mL), extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting black residue was used in the next step without further purification.

Preparation of **50**: A solution of aldehyde **49** (119 mg, 0.53 mmol) and $NaBH_4$ (56.9 mg, 1.50 mmol) in anhydrous MeOH (1 mL) was stirred at room temperature for 16 h. The reaction was diluted with diluted with H_2O (10 mL), extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the resulting residue was difficult due to the messiness of reaction, but a colorless oil (10.9 mg, 12%) was isolated by column chromatography (40% EtOAc/petroleum ether) containing alcohol **50** as the major product.

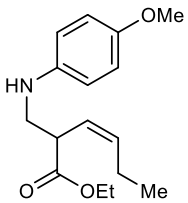
Preparation of **51:** 2,2-Dimethoxypropane (16 μL, 0.13 mmol) and pyridinium *p*-toluenesulfonate (0.3 mg, 1.3 μmol) were added to a solution of alcohol **50** (prepared as described above, 6.0 mg, 0.026 mmol) in CH_2Cl_2 (0.1 mL) and the mixture was stirred at room temperature for 1 h. The reaction was diluted with diluted with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc/petroleum ether) to give **51** was a white solid (6.8 mg, 8% overall yield from **27a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.11 (8H, m, Ar**H**), 7.05-7.01 (2H, m, Ar**H**), 5.03 (1H, d, *J* = 10.8 Hz, PhC**H**OC(CH_3)$_2$), 4.23 (1H, t, *J* = 11.7 Hz, OC**H**$_2$ axial), 3.98 (1H, dd, *J* = 11.7, 5.2 Hz, OC**H**$_2$ equatorial), 3.06 (1H, td, *J* = 10.8, 5.2 Hz, PhC**H**CH_2), 1.73 (3H, s, C**H**$_3$ axial), 1.58 (3H, s, C**H**$_3$ equatorial); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0 (C), 137.9 (C), 128.44 (2 × CH), 128.41 (2 × CH), 128.0 (2 × CH), 127.7 (CH), 127.1 (2 × CH),

127.0 (CH), 98.9 (C), 77.1 (CH), 65.3 (CH_2), 49.2 (CH), 29.8 (CH_3), 19.3 (CH_3). Spectroscopic data matched those reported previously.

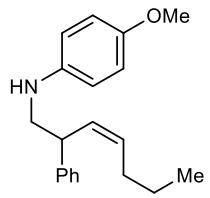


The indicated coupling constant of **51** is consistent with the previous reported literature.[197]

1.3.5 Chain Walking Towards Arenes With Triazinane Electrophiles

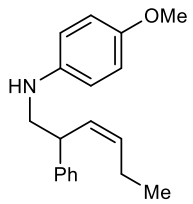


Ethyl (*Z*)-2-{[(4-methoxyphenyl)amino]methyl}hex-3-enoate (65a): The general procedure was followed under method B using 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazinane **63a** [198] (48.6 mg, 0.12 mmol) and ethyl sorbate (44 µL, 0.3 mmol). Column chromatography (10% EtOAc/petroleum ether) gave *homoallylic amine* **65a** as a brown oil (27 mg, 32%). R_f 0.31 (10% EtOAc/petroleum ether); IR 3398 (NH), 2962, 2934, 2832, 1726 (C=O), 1510, 1233, 1176, 1036, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.59 (2H, d, *J* = 9.0 Hz, Ar**H**), 5.66 (1H, dtd, *J* = 10.7, 7.1, 1.6 Hz, =C**H**CH_2), 5.37 (1H, ddt, *J* = 10.7, 9.8, 1.0 Hz, =C**H**CH), 4.16 (2H, q, *J* = 7.1 Hz, OC**H**$_2$$CH_3$), 3.76 (3H, s, OC**H**$_3$), 3.67 (1H, dddd, *J* = 9.8, 7.7, 6.8, 1.0 Hz, O=CC**H**), 3.50 (1H, dd, *J* = 12.8, 7.3 Hz, C**H**$_a$$H_b$NH), 3.17 (1H, dd, *J* = 12.8, 6.8 Hz, CH_a**H**$_b$NH), 3.05 (1H, t, *J* = 7.1 Hz, NH), 2.10-2.01 (2H, m, =C**H**CH_2), 1.26 (3H, t, *J* = 7.1 Hz, OCH_2C**H**$_3$), 0.98 (3H, t, *J* = 7.5 Hz, CH_2C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.2 (C), 152.3 (C), 141.7 (C), 136.5 (CH), 123.9 (CH), 114.9 (2 × CH), 114.5 (2 × CH), 60.8 (CH_2), 55.8 (CH_3), 46.8 (CH_2), 43.7 (CH), 21.0 (CH_2), 14.2 (CH_3), 14.1 (CH_3); HRMS (ESI) Exact mass calculated for $C_{16}H_{24}NNaO_3$ $[M+Na]^+$: 278.1751, found: 278.1763.

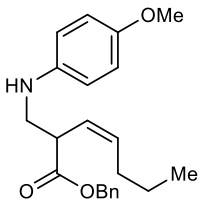


(*Z*)-4-Methoxy-*N*-(2-phenylhept-3-en-1-yl)aniline (67a). To a suspension of diene **66** (47.4 mg, 0.30 mmol), 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazinane [198] (48.6 mg, 0.12 mmol), $[Rh(cod)OH]_2$ (6.8 mg, 0.015 mmol), and powdered 3 Å molecular sieves (20 mg) in anhydrous 1,4-dioxane (1.5 mL) at 0 ˚C was slowly added Et_3B (1.0 M in hexane, 0.90 mL, 0.90 mmol). The mixture was stirred at 0 ˚C for 5 min and then at 80 ˚C for 24 h. The reaction was diluted with EtOAc (20 mL), passed through a short plug of silica gel, eluting with EtOAc (20 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc/petroleum ether) to give *homoallylic amine* **67a** as a yellow oil (46.4 mg, 58%). R_f 0.38 (10% EtOAc/petroleum

ether); IR 3382 (NH), 2955, 2929, 2831, 1510, 1233, 1037, 817, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (2H, m, Ar**H**), 7.28-7.23 (3H, m, Ar**H**), 6.80 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.59 (2H, d, *J* = 9.0 Hz, Ar**H**), 5.67-5.55 (2H, m, **H**C=C**H**), 3.95 (1H, td, *J* = 8.5, 6.6 Hz, PhC**H**), 3.77 (3H, s, OC$\mathbf{H}_3$), 3.45 (1H, br s, N**H**), 3.39 (1H, dd, *J* = 12.0, 6.9 Hz, NHC$\mathbf{H}_a$$H_b$), 3.26 (1H, dd, *J* = 12.0, 8.0 Hz, NHC$H_a$$\mathbf{H}_b$), 2.16-2.00 (2H, m, =CHC$\mathbf{H}_2$), 1.39 (2H, app heptet, *J* = 7.5 Hz, C$\mathbf{H}_2$$CH_3$), 0.90 (3H, t, *J* = 7.4 Hz, CH_2C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2 (C), 142.8 (C), 142.2 (C), 132.5 (CH), 130.6 (CH), 128.7 (2 × CH), 127.5 (2 × CH), 126.6 (CH), 114.9 (2 × CH), 114.5 (2 × CH), 55.8 (CH_3), 50.5 (CH_2), 42.9 (CH), 29.7 (CH_2), 22.8 (CH_2), 13.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{26}NO_2]^+$ $[M+H]^+$: 296.2009, found: 296.2010.

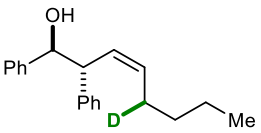


(*Z*)-4-methoxy-N-(2-phenylhex-3-en-1-yl)aniline (71). To a suspension of diene **70** (43.2 mg, 0.30 mmol), 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazinane [198] (48.6 mg, 0.12 mmol), $[Rh(cod)OH]_2$ (6.8 mg, 0.015 mmol), and powdered 3 Å molecular sieves (20 mg) in anhydrous 1,4-dioxane (1.5 mL) at 0 ˚C was slowly added Et_3B (1.0 M in hexane, 0.90 mL, 0.90 mmol). The mixture was stirred at 0 ˚C for 5 min and then at 80 ˚C for 24 h. The reaction was diluted with EtOAc (20 mL), passed through a short plug of silica gel, eluting with EtOAc (20 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc/petroleum ether) to give *homoallylic amine* **71** as a yellow oil (22.4 mg, 28%). R_f 0.35 (10% EtOAc/petroleum ether); IR 3396 (NH), 2931, 2873, 2831, 1510, 1453, 1233, 1037, 817, 730, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.33 (2H, m, Ar**H**), 7.28-7.23 (3H, m, Ar**H**), 6.80 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.59 (2H, d, *J* = 8.9 Hz, Ar**H**), 5.67-5.54 (2H, m, **H**C=C**H**), 3.94 (1H, td, *J* = 8.4, 6.7 Hz, PhC**H**), 3.77 (3H, s, OC$\mathbf{H_3}$), 3.45 (1H, s, N**H**), 3.39 (1H, dd, *J* = 12.0, 6.7 Hz, NHC$\mathbf{H_a}$$H_b$), 3.25 (1H, dd, *J* = 12.0, 8.1 Hz, NHC$H_a$$\mathbf{H_b}$), 2.18-2.05 (2H, m, =CHC$\mathbf{H_2}$), 0.97 (3H, t, *J* = 7.5 Hz, CH_2C$\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2 (C), 142.8 (C), 142.2 (C), 134.2 (CH), 129.9 (CH), 128.7 (2 × CH), 127.5 (2 × CH), 126.6 (CH), 114.9 (2 × CH), 114.5 (2 × CH), 55.8 (CH_3), 50.5 (CH_2), 42.8 (CH), 21.0 (CH_2), 14.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{19}H_{24}NO]^+$ $[M+H]^+$: 282.1852, found: 282.1856.



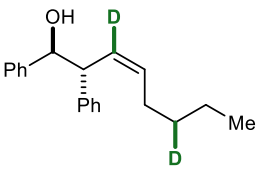
Benzyl (*Z*)-2-{[(4-methoxyphenyl)amino]methyl}hept-3-enoate (73). To a suspension of diene **72** (64.8 mg, 0.30 mmol), 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazinane [198] (48.6 mg, 0.12 mmol), $[Rh(cod)OH]_2$ (6.8 mg, 0.015 mmol), and powdered 3 Å molecular sieves (20 mg) in anhydrous 1,4-dioxane (1.5 mL) at 0 ˚C was slowly added Et_3B (1.0 M in hexane, 0.90 mL, 0.90 mmol). The mixture was stirred at 0 ˚C for 5 min and then at 80 ˚C for 24 h. The reaction was diluted with EtOAc (20 mL), passed through a short plug of silica gel, eluting with EtOAc (20 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc/petroleum ether) to give *homoallylic amine* **73** as a yellow oil (29.7 mg, 25%). R_f 0.21 (10% EtOAc/petroleum ether); IR 3397 (NH), 2957, 2930, 2832, 1728, 1511, 1455, 1234, 1157, 818, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.29 (5H, m, Ar**H**), 6.79 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.56 (2H, d, *J* = 8.9 Hz, Ar**H**), 5.67 (1H, dtd, *J* = 10.8, 7.4, 1.0 Hz, =C**H**CH_2), 5.44 (1H, ddt, *J* = 11.2, 9.8, 1.6 Hz, CHC**H**=), 5.15 (2H, d, *J* = 2.0 Hz, PhC$\mathbf{H_2}$), 3.76 (4H, m, OC$\mathbf{H_3}$ and O=CC**H**), 3.53 (1H, dd, *J* = 12.9, 7.5 Hz, NHC$\mathbf{H_a}H_b$), 3.21 (1H, dd, *J* = 12.9, 6.6 Hz, $NHCH_a\mathbf{H_b}$), 2.03 (2H, qt, *J* = 7.1, 1.4 Hz, =CHC$\mathbf{H_2}$), 1.38 (2H, hd, *J* = 7.4, 1.3 Hz, $CH_2C\mathbf{H_2}CH_3$), 0.88 (3H, t, *J* = 7.4 Hz, $CH_2CH_2C\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C), 152.4 (C), 141.5 (C), 135.9 (C), 134.9 (CH), 128.5 (2 × CH), 128.2 (CH), 128.0 (2 × CH), 124.3 (CH), 114.9 (2 × CH), 114.5 (2 × CH), 66.4 (CH_2), 55.8 (CH_3), 46.9 (CH_2), 43.8 (CH), 29.7 (CH_2), 22.6 (CH_2), 13.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{28}NO_3]^+$ $[M+H]^+$: 354.2064, found: 354.2076.

1.3.6 Investigation of Deuterium Transfer



(1*S*,2*R*,*Z*)-1,2-diphenyloct-3-en-5-*d*-1-ol ($[D]_1$**-27a).** To a solution of diene $[D]_1$**-26a** (17.3 mg, 0.10 mmol), benzaldehyde (12 μL, 0.12 mmol) and $[Rh(cod)OH]_2$ (2.3 mg, 0.005 mmol) in 1,4-dioxane (0.5 mL) at 0 °C was added Et_3B (1.0 M solution in hexane, 0.30 mL, 0.30 mmol) dropwise. The mixture was stirred at 0 °C for 5 min, and then at 80 °C for 16 h. The reaction was quenched carefully with 1.0 M aqueous HCl solution and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petroleum ether) gave *homoallylic alcohol* [D]-**27a** as a white oil (15.6 mg, 55%). R_f 0.46 (20% EtOAc/petroleum ether); IR 3445 (OH), 2956, 2925, 2858, 1493, 1452, 1186, 1025, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

7.25-7.12 (8H, m, Ar**H**), 7.11-7.08 (2H, m, Ar**H**), 5.88 (1H, td, *J* = 10.5, 1.6 Hz, CHC**H**=), 5.69 (1H, dd, *J* = 11.0, 7.2 Hz, =C**H**CHD), 4.84 (1H, d, *J* = 7.3 Hz, C**H**OH), 3.88 (1H, dd, *J* = 10.0, 7.3 Hz, PhC**H**), 2.27 (1H, br s, O**H**), 2.05-1.98 (1H, m, =CHC**H**D), 1.28-1.20 (4H, m, C**H**$_2$C**H**$_2$CH$_3$), 0.86 (3H, t, *J* = 7.0 Hz, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 142.0 (C), 141.5 (C), 134.2 (CH), 128.3 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 127.9 (2 × CH), 127.3 (CH), 126.6 (2 × CH), 126.4 (CH), 78.0 (CH), 52.5 (CH), 31.4 (CH$_2$), 27.0 (CH, J_{CD} = 19.1 Hz), 22.3 (CH$_2$), 13.9 (CH$_3$); HRMS (ESI) Exact mass calculated for [C$_{20}$H$_{23}$DNaO$_2$]$^+$ [M+Na]$^+$: 304.1782, found: 304.1780.



(±)-(1*S*,2*R*,*Z*)-1,2-Diphenyloct-3-en-3,6-*d*$_2$-1-ol **(**[D]$_2$-**27a).** To a solution of diene [D]$_2$-**26a** (34.8 mg, 0.20 mmol), benzaldehyde (24 μL, 0.24 mmol) and [Rh(cod)OH]$_2$ (4.6 mg, 0.010 mmol) in 1,4-dioxane (1.0 mL) at 0 °C was added Et$_3$B (1.0 M solution in hexane, 0.60 mL, 0.60 mmol) dropwise. The mixture was stirred at 0 °C for 5 min, and then at 80 °C for 16 h. The reaction was quenched carefully with 1.0 M aqueous HCl solution and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petroleum ether) gave a mixture of inseparable products (29.5 mg) as a yellow oil, consisting of *homoallylic alcohol* [D]$_2$-**27a** (*ca.* 45%, based upon a purity of ≤87%) and what appeared to be at least two other side products. *Data for* [D]$_2$-**27a**: R$_f$ 0.46 (20% EtOAc/petroleum ether); IR 3444 (OH), 3030, 2956, 2871, 1493, 1452, 1085, 909, 762, 698 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26-7.13 (8H, m, Ar**H**), 7.13-7.07 (2H, m, Ar**H**), 5.69 (1H, t, *J* = 7.4 Hz, =C**H**CH$_2$), 4.84 (1H, dd, *J* = 7.4, 1.7 Hz, C**H**OH), 3.88 (1H, d, *J* = 7.2 Hz, PhC**H**), 2.29 (1H, d, *J* = 2.2 Hz, O**H**), 2.04 (2H, t, *J* = 6.9 Hz, =CHC**H**$_2$), 1.31-1.18 (3H, m, C**H**DC**H**$_2$CH$_3$), 0.86 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{2}H NMR (77 MHz, CHCl$_3$) δ 5.78 (1D, br s, CHC**D**=), 1.10 (1D, br s, CH**D**CH$_2$CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 142.0 (C), 141.5 (C), 134.0 (CH), 128.30 (2 × CH), 128.25 (2 × CH), 127.8 (2 × CH), 127.3 (CH), 126.6 (2 × CH), 126.4 (CH), 78.0 (CH), 52.3 (CH), 31.1 (t, J_{CD} = 19.4 Hz, CH), 27.2 (CH$_2$), 22.2 (CH$_2$), 13.9 (CH$_3$); HRMS (ESI) Exact mass calculated for [C$_{20}$H$_{22}$D$_2$NaO]$^+$ [M+Na]$^+$: 305.1845, found: 305.1843.

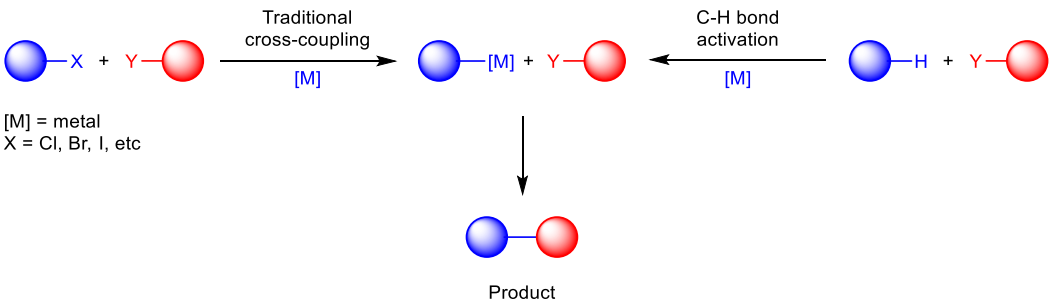
2. Chapter 2: Rhodium-Catalysed Arylative Cyclisation via 1,4-Rh Migration

2.1 Introduction

2.1.1 1,4-Metal Migrations

The development of new methods of forming carbon-carbon bonds is of fundamental importance, as these bonds make up the backbone of most organic compounds. Classically, formation of C–C bonds usually requires pre-functionalised substrates. These can often be manipulated into forming new organometallic intermediates, which can create new C–C bonds via reactions such as cross-couplings (Scheme 118). New methods that avoid these often step-intensive and uneconomical sequences are well-received by organic chemists, who are increasingly concerned by developing reactions with simplicity and sustainability in mind.[199]

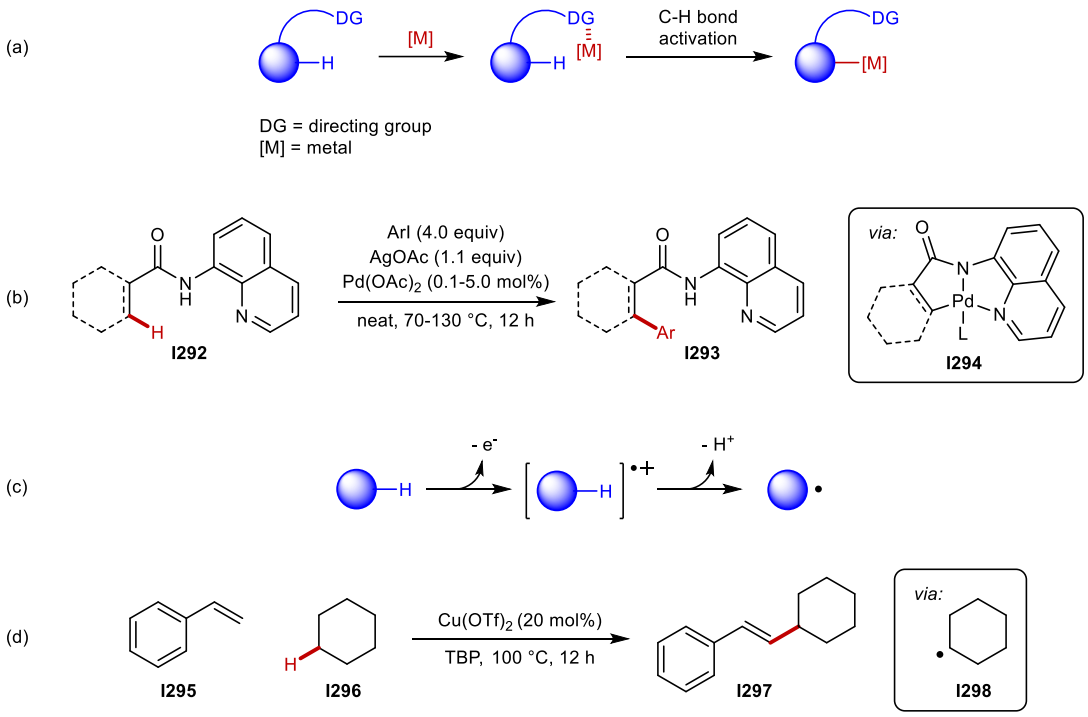
As an alternative, the activation of C–H bonds may also deliver organometallic intermediates and provide access to novel or challenging compounds using fewer steps and resources while forming less waste (Scheme 118).[200] Developing new synthetic strategies that exploit the activation of C–H bonds is therefore of substantial interest, as these can potentially reform the way chemists think about tackling more complicated syntheses.[201]



Scheme 118. Traditional cross-coupling vs C–H bond activation.

As C–H bonds are ubiquitous in organic compounds, their activation could potentially eradicate the need to prepare pre-functionalised starting materials. However, C–H bonds are typically unreactive, owing to their lack of polarity and high bond strength relative to other functional groups. This renders activation of these bonds a challenge, especially as their abundance in organic molecules raises the further problem of regioselectivity. To achieve selective C–H activation, most successful examples employ directing groups (Scheme 119a),[202] which deliver a coupling partner to a specific site. An example is the Pd-catalysed

regioselective arylation of sp^2 or sp^3 C–H bonds in **I292** to give β-arylation products **I293** using 8-aminoquinoline amides to direct Pd to the β-C–H bond (**I294**) (Scheme 119b).[203, 204] Radical-based processes have also been demonstrated (Scheme 119c), such as the copper-catalysed alkenylation of alkanes **I296** with styrenes **I295** to give alkene **I297** (Scheme 119d).[205, 206]



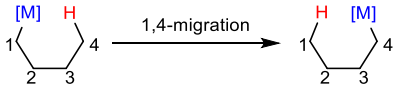
Scheme 119. Established methods of C–H activation.

These differing approaches can have disadvantages, as the addition and removal of directing groups lengthens reaction sequences, often under harsh conditions, and reactive radical species often need sensitive or specific reaction conditions to achieve successful transformations.

An alternative approach that can overcome these limitations is the use of transition metal migrations to activate C–H bonds. This topic was explored in Section 1.1 concerning metal migrations along a carbon chain, and whilst through space migration was briefly mentioned, it will be discussed in detail here.

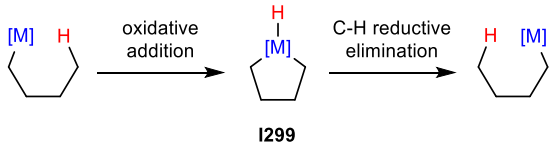
After a carbon-metal bond is formed (typically via migratory insertion or oxidative addition), an interaction between the installed metal atom and a nearby C–H bond can occur 'through space'.[19] This process sees relocation of the metal centre to the carbon atom where hydrogen was originally. Occurring simultaneously with the metal migration, the hydrogen atom from the now cleaved C–H bond migrates in the opposite direction (Scheme 120). This

results in an unreactive C–H bond becoming activated with a new reactive metal–carbon bond installed, which can undergo further functionalisation via traditional transition metal transformations.



Scheme 120. Through space migration.

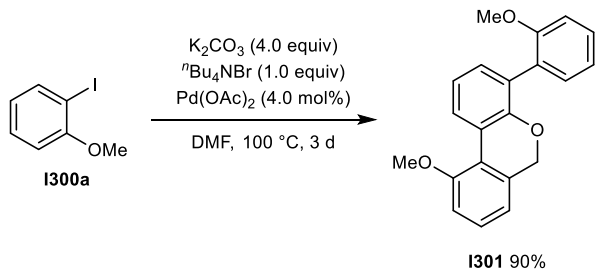
This method is often termed a 1,*n*-migration, where *n* represents the number of carbon atoms between the metal and hydrogen atoms swapping their positions. Mechanistically, it is thought that the migration begins with the metal undergoing oxidative addition of the C–H bond to form metallacycle **I299**, before C–H reductive elimination facilitates migration of the metal (Scheme 121).[19] It is most commonly observed when the metal swaps with a hydrogen atom four carbon atoms away, as this allows the migration to proceed via a highly favoured five-membered metallacycle.[207] Whilst 1,4-migrations are most common, 1,3- and 1,5-metal migrations have been recently reported.[208-210]



Scheme 121. Mechanism of 1,4-metal migration.

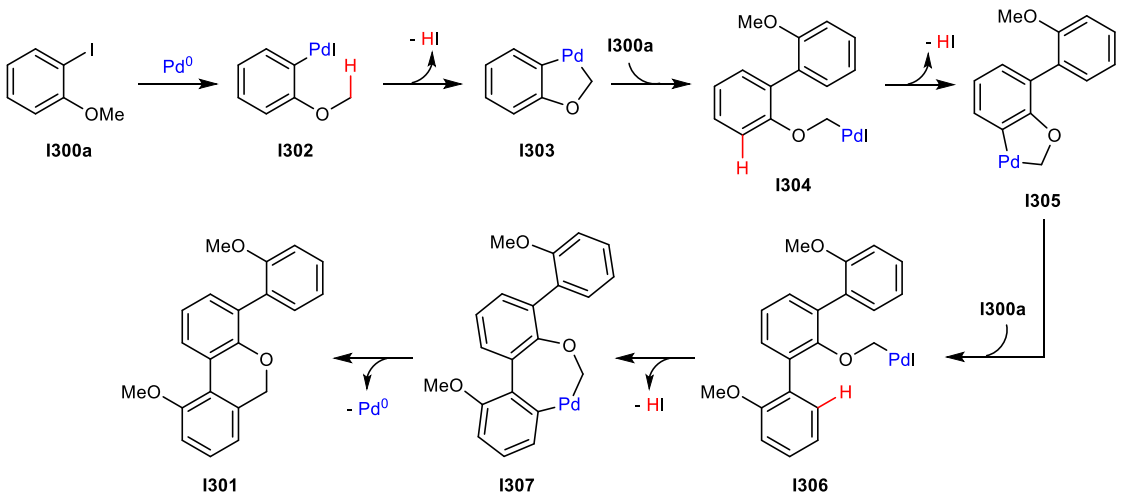
2.1.2 Early 1,4-Palladium Migration

Historically, palladium and rhodium are the metals most commonly involved in metal-hydrogen migrations,[19] with palladium being one of the most frequently reported metals to undergo 1,4-migration. One of the earliest examples of this reactivity was described by Dyker in 1992 who observed an unusual trimerisation of *ortho*-iodoanisole **I300a** (Scheme 122).[211] The $Pd(OAc)_2$ catalyst was believed to facilitate C–H activation at the methoxy group to achieve condensation product **I301**. Whilst the 90% yield was high, the reaction conditions were relatively harsh, requiring heating to 100 °C in DMF for 3 days.



*Scheme 122. Trimerisation of **I300a**.*

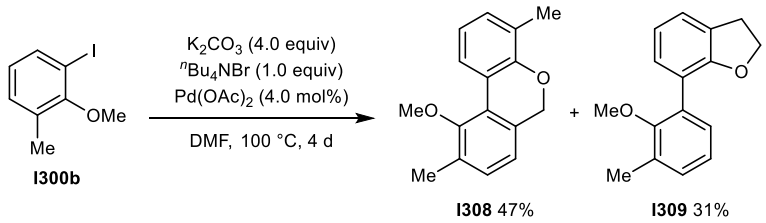
The proposed mechanism is initiated by an oxidative addition of Pd^0 with the C–I bond in **I300a** to give Pd^{II} species **I302** (Scheme 123). The important intramolecular cyclometallation step of **I302** forms five-membered palladacycle **I303** after oxidative addition of the methoxy C–H bond, followed by reductive elimination via Pd^{IV}.[212] **I303** then undergoes oxidative addition to another molecule of **I300a**, again via a Pd^{IV} intermediate, to give **I304** after another reductive elimination. A second cyclometallation sequence occurs (**I304-I305**), and a third molecule of **I300a** is incorporated to form **I306**, which gives product **I301** after reductive elimination of palladacycle **I307**. However, it is important to note that this cannot be considered a 'true' 1,4-migration, as the Pd and H atoms do not swap places in the intermediate, with the H atom lost in the elimination of HI instead.



*Scheme 123. Proposed mechanism for formation of **I301**.*

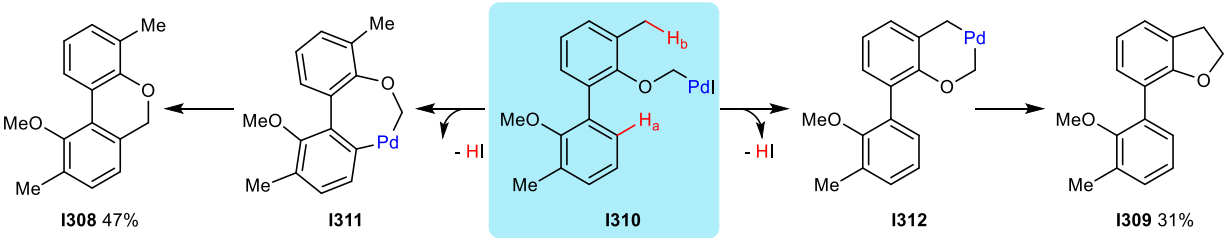
Dyker later discovered that a 1,4-Pd migration cascade could result in activation of a benzylic C–H under the reaction conditions when using iodoanisole **I300b** (Scheme 124), which has an additional methyl group *ortho*- to the methoxy group to block the second

cyclopalladation (see **I304** in Scheme 123 above). Dimerisation product **I308** and dihydrobenzofuran **I309** are formed in 47% and 31% yield respectively after 4 days.[213]



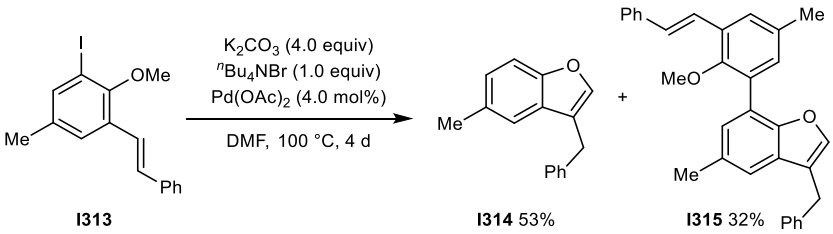
Scheme 124. Migration of Pd to facilitate benzylic C–H activation.

This mechanism deviates from Scheme 123 when intermediate **I310** is reached. As the *ortho*-methyl group prevents trimerisation, **I310** has two alternative pathways (Scheme 125). The first is activation of the aryl C–H_a bond to form dimerisation product **I308** via seven-membered palladacycle **I311**. The second is via benzylic C–H activation via six-membered palladacycle **I312** to give dihydrobenzofuran **I309**. The Pd^{IV} mechanism is proposed to be operative in both cases.



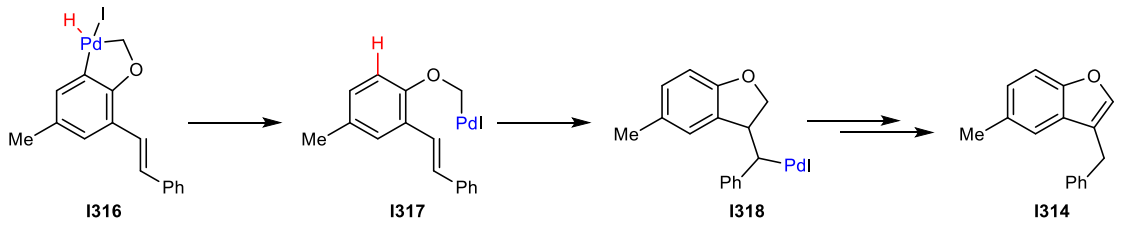
*Scheme 125. Proposed mechanisms for formation of **I308** and **I309**.*

Additionally, Dyker demonstrated an intramolecular Heck-type annulation reaction could trap out the generated palladacycle using an olefin. Under the reaction conditions, **I313** formed benzofuran **I314** in 53% yield as the major product alongside side-product **I315** (32% yield) (Scheme 126).



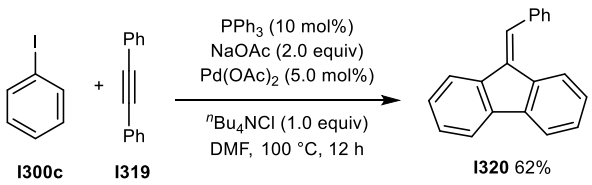
*Scheme 126. Intramolecular Heck reaction of **I313**.*

The palladacycle **I316** undergoes reductive elimination of the C–H bond to form **I317**. Insertion into the olefin gives **I318** which forms the benzofuran **I314** after *β*-hydride elimination and isomerisation (Scheme 127). Unlike the other two examples, this reaction can be considered a true 1,4-migration as both the palladium and hydrogen atoms switch positions in the molecule.



Scheme 127. Mechanism of intramolecular Heck reaction.

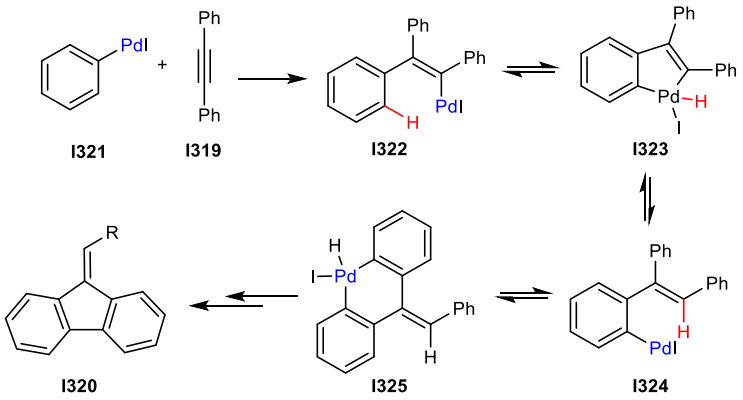
Since these seminal publications, several examples of 1,4-Pd migrations have been reported.[214] Whilst Dyker's early work in the field could be categorised as migration between an sp^2 carbon and an sp^3 carbon centre, the majority of the work that followed concerned Pd migrations between two sp^2 carbon centres. This is likely because organometallic sp^2 carbon intermediates are often readily accessible and relatively stable once formed. In 2000, Larock demonstrated this rearrangement in the $Pd(OAc)_2$-catalysed synthesis of 9-alkylidene-9*H*-fluorenes **I320** from iodoarenes and acetylenes. **I300c** and **I319** formed fluorene **I320** in 62% yield, generating structural complexity from very simple starting materials (Scheme 128).[215]



*Scheme 128. Synthesis of 9-alkylidene-9H-fluorenes **I320**.*

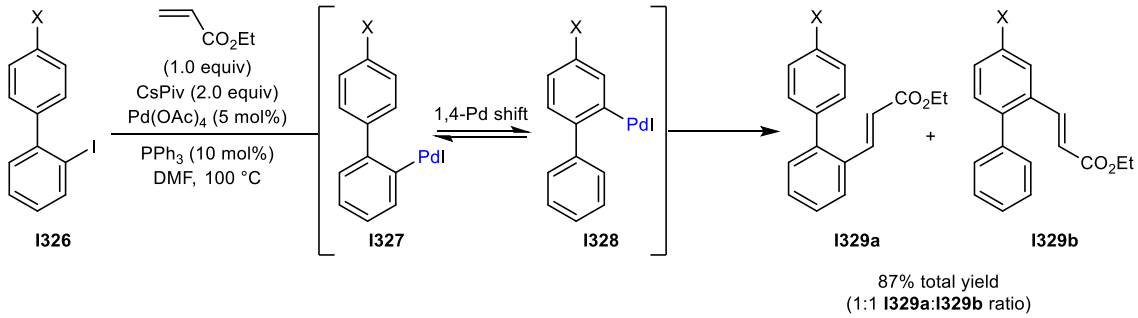
The reaction is initiated by oxidative addition of iodobenzene **I300c** with Pd^0 to give **I321**, which can insert into the alkyne to form alkenylpalladium species **I322** (Scheme 129). The key 1,4-migration step to give **I324** is enabled via oxidative addition of the aryl C–H to Pd^{IV} intermediate **I323**, followed by reductive elimination to give **I324**. Bond rotation and oxidative addition into the neighbouring phenyl ring C–H gives **I325**, which forms product

I320 after two consecutive reductive eliminations, the first ejecting HI and the second forming the new C–C bond.



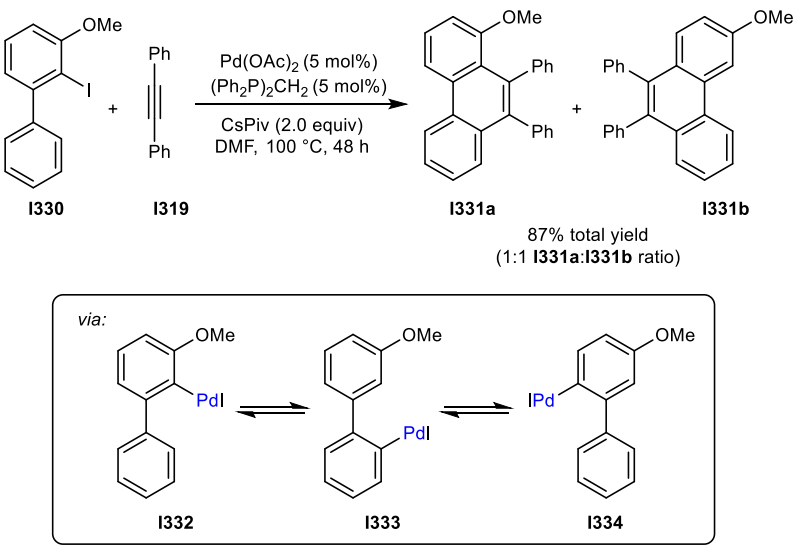
Scheme 129. Proposed mechanism.

In 2002, Larock also reported the olefination of unsymmetrical *ortho*-iodobiphenyls **I326** in a Heck reaction with ethyl acrylate (Scheme 130).[216] A 1:1 ratio of two product regioisomers **I329a** and **I329b** was observed in 87% yield, suggesting 1,4-palladium aryl-to-aryl migration (**I327** to **I328**) had occurred. Modification of the reaction conditions allowed regiomeric control of the formation of direct olefination product **I329a**. Leaving the reaction to equilibrate prior to olefin addition also lead to the 1:1 mixture of regioisomers.



Scheme 130. 1,4-Pd migration in ortho-iodobiphenyls.

In the same paper, Larock also showed symmetrical alkynes could be added to these *ortho*-biphenyls under slightly modified reaction conditions (Scheme 131). A 1:1 ratio of regioisomers **I331a** and **I331b** was formed in 87% total yield. A cascade of 1,4-Pd migrations generate intermediates **I333** and **I334**. Trapping **I333** generates both regioisomers, whilst intermediates **I332** and **I334** generate **I331a** and **I331b** respectively as single isomers.



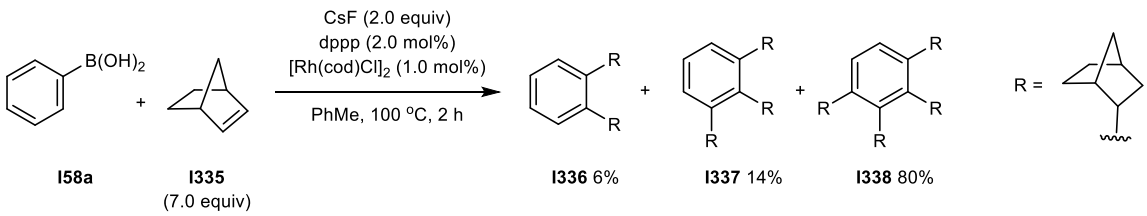
Scheme 131. Trapping the 1,4-Pd migration intermediates with symmetrical alkynes.

As this field has developed, a myriad of other Pd migrations between vinylic,[217] aryl,[215] imidoyl,[218] acyl [218] and alkyl [219, 220] carbons have all been described. In addition, a range of other transition metals have been shown to perform this type of migration. Pt,[221] Ni,[222] Fe,[223, 224] and Ru [225] all have representative examples; however this section will now focus exclusively on 1,4-metal migrations between the Group 9 metals of Rh, Ir and Co.

2.1.3 1,4-Rhodium Migrations

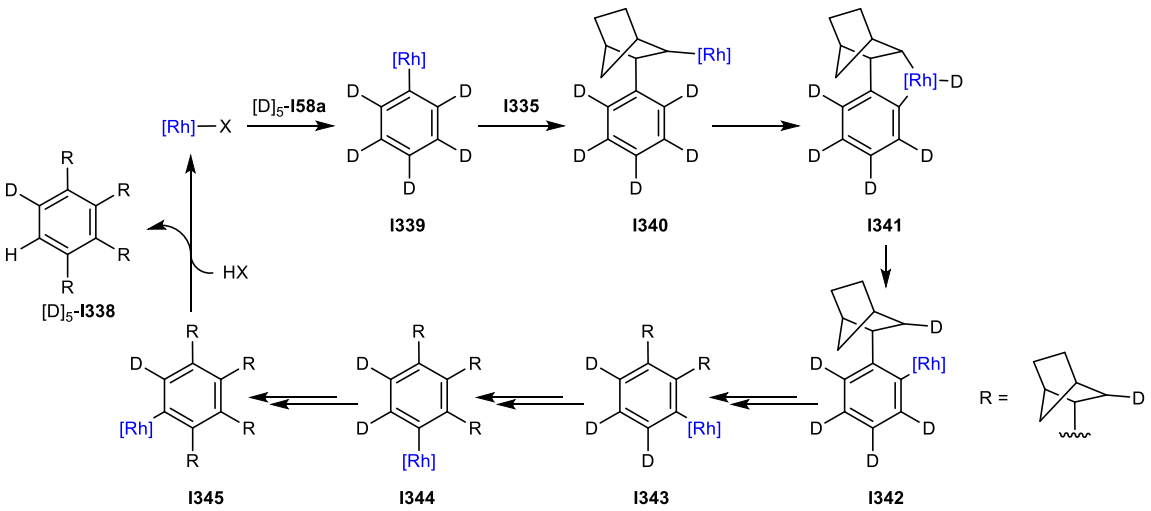
2.1.3.1 Rh^I Migration to sp^2 Centres

Whilst most of the initial 1,4-migration discoveries used palladium as a catalytic transition metal, since 2000 Rh has been shown to undergo similar reactivity. The first example was reported by Miura, who described the multi-alkylation of phenylboronic acid **I58a** via a Rh-catalysed 'merry-go-round' process, demonstrating migration from an sp^3 carbon to an sp^2 carbon (Scheme 132).[226] Using **I58a** and norbornene **I335** with $[Rh(cod)Cl]_2$, tetrasubstituted product **I338** was the major product in 80% yield. Minor amounts of tri- and disubstituted products **I337** and **I336** were formed in 14% and 6% yield respectively.



Scheme 132. Merry-go-round reaction initiated via 1,4-Rh migration.

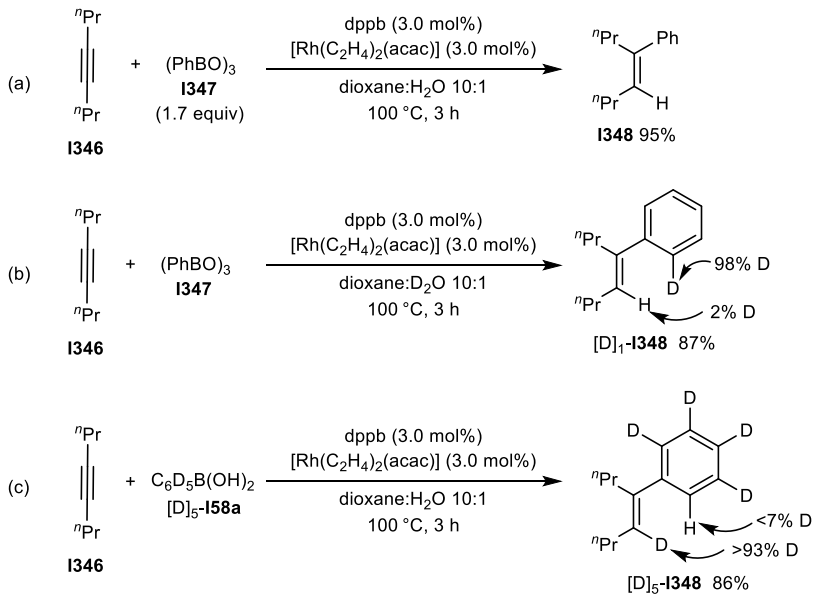
To elucidate a mechanism for the formation of **I338**, $[D]_5$-**I58a** was subjected to identical reaction conditions with **I335**. In the resulting product $[D]_5$-**I338**, four of the deuterium atoms had migrated onto the norbornene moiety, with only one deuterium remaining on the aryl group at the *ortho*- position (Scheme 133). This result was rationalised using a mechanism that begins with formation of aryl rhodium species **I339** from transmetalation of Rh with $[D]_5$-**I58a**. Migratory insertion into the olefin of **I335** gives alkyl Rh **I340**. From this intermediate, the key 1,4-migration of Rh^I can occur giving **I342** via a proposed oxidative addition of the adjacent C–D bond and reductive elimination of cyclic Rh^{III} hydride **I341**. This arylrhodium species undergoes three more repetitions of the sequence, to give **I345**, which now has significant steric congestion around the aryl ring, making further norbornene additions highly unlikely. Instead, protonolysis of **I345** gives $[D]_5$-**I338** and regenerates the active Rh^I catalyst. Protonolysis of any of the aryl or alkylrhodium intermediates in the catalytic cycle would also be possible, but insertion of norbornene **I335** is calculated to be more favourable via DFT calculations so $[D]_5$-**I338** forms as the major product. 1,4-Rh migration was also determined to be preferential to protonolysis of alkyl Rh intermediates such as **I340**.[227] Reducing the equivalents of norbornene used does see greater selectivity for **I336** and **I337** as protonation becomes a more significant process.



*Scheme 133. Mechanism of formation of $[D]_5$-**I338**.*

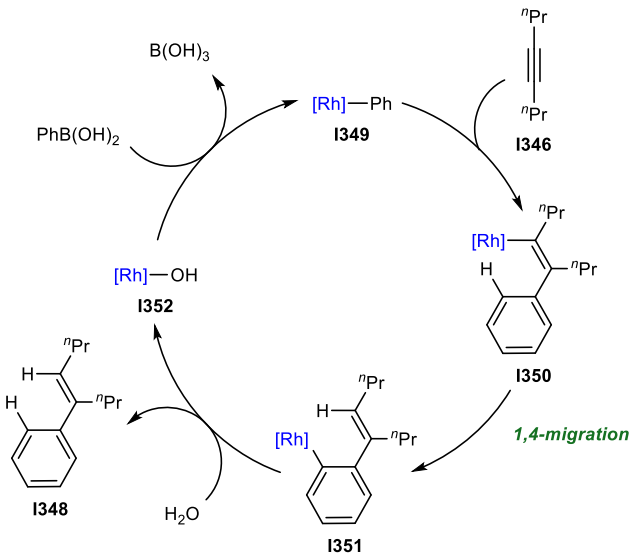
Following the seminal work by Miura, Hayashi and co-workers observed a similar Rh migration when investigating the Rh-catalysed hydroarylation of alkynes.[228] The initial result saw hydroarylation of **I346** with phenylboroxine **I347** as the aryl source. Using

$Rh(C_2H_4)_2(acac)$ and dppb as the catalyst/ligand system, **I348** was isolated in 95% yield after heating in dioxane:H_2O (10:1) for 3 h at 100 °C (Scheme 134a). This result by itself did not show any peculiar reactivity until deuteration experiments into the mechanism implied otherwise. Repeating the reaction with D_2O instead of water saw 98% deuteration at the *ortho*-position on the aromatic ring, instead of at the expected alkenyl position, which only saw 2% deuteration at $[D]_1$-**I348** (Scheme 134b). This suggested a 1,4-Rh alkenyl-to-aryl migration, which was more evident when d_5-phenyl boronic acid $[D]_5$-**I58a** was used (Scheme 134c). This time deuterium was incorporated at the alkenyl position in $[D]_5$-**I348** (>93%).



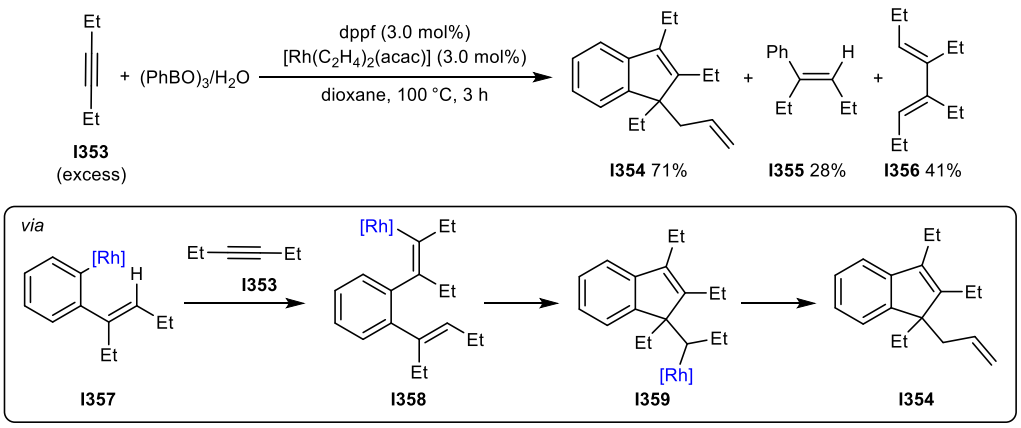
Scheme 134. 1,4-Rh alkenyl to aryl migration during hydroarylation of alkynes.

Scheme 135 shows a mechanism to rationalise these observations. Addition of phenyl rhodium **I349** in a *syn*- fashion forms alkenyl Rh species **I350**. 1,4-Migration results in **I351** with Rh on the *ortho*- position of the aromatic ring. **I351** is determined to be energetically unlikely to react with another molecule of alkyne **I346**, with protonolysis giving product **I348** and regenerating **I349** (Scheme 135).



Scheme 135. Proposed mechanism.

Removing water from the reaction suppresses protonolysis and allows the addition of intermediate **I357** to a second alkyne equivalent such as **I353** when used in excess (Scheme 136). This facilitates formation of indene **I354** in 71% yield, with hydroarylation product **I355** accounting for the remaining mass balance. The diene **I358** undergoes carborhodation to cyclise and then β-hydride elimination and isomerisation to give **I354**.[228]

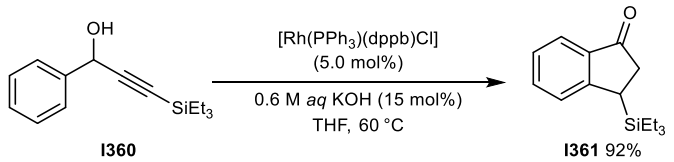


Scheme 136. Formation of indenes by trapping with a second equivalent of alkyne.

Addition across an alkyne has been shown to be a reliable method of forming alkenylmetal species. Since this work by Hayashi, the formation of these intermediates has been a very important method of initiating 1,4-metal migrations. In addition, these processes can be exploited in cascade syntheses to rapidly build up complex molecular architecture in reactions with alkynes possessing tethered functional groups.[229, 230] The best examples of these

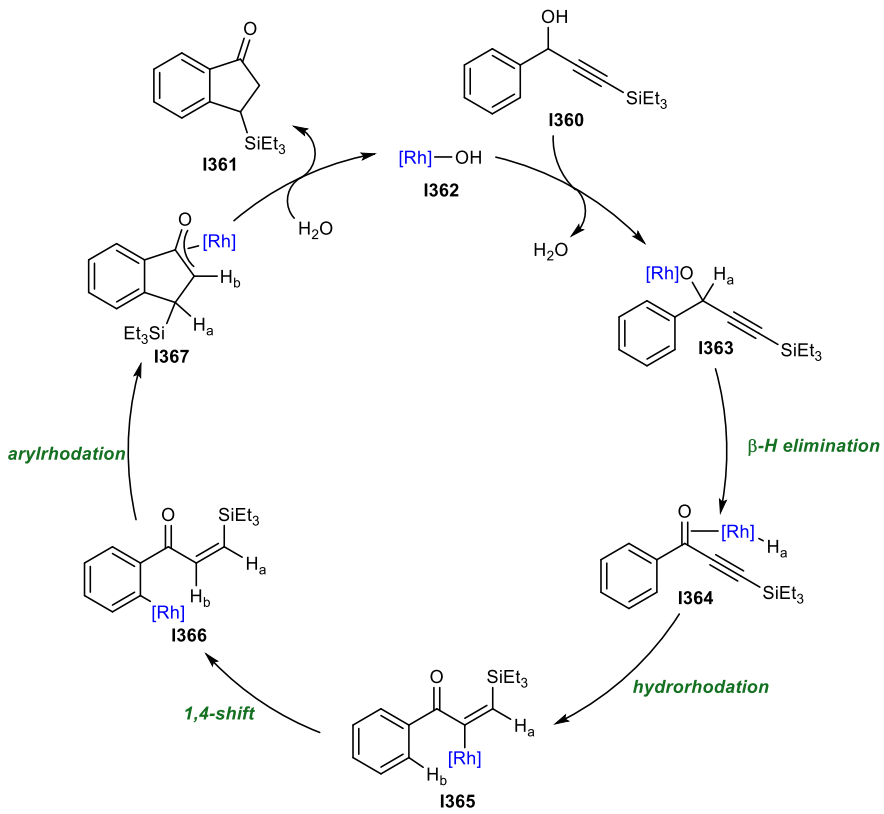
methodologies are able to control the regioselectivity issues that arise from additions to unsymmetric alkynes.[231]

In 2005, Hayashi also showed that hydrometallation of alkynes provided an alternative route to initiate a 1,4-migration process in the cyclisation of alkynol **I360** to indanone derivative **I361** (Scheme 137), catalysed by $Rh(PPh_3)(dppb)Cl$ in 92% yield.[232]



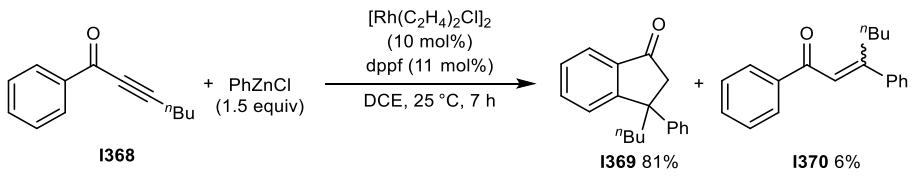
*Scheme 137. Cyclisation to indanone **I361**.*

The process is initiated by forming active Rh^I **I362** from exchange of chloride and hydroxide ligands. Deprotonation of **I360** gives Rh alkoxide **I363** which undergoes *β*-hydride elimination with H_a to form alkynone **I364** (Scheme 138). Rh–H then undergoes a regioselective addition to the alkyne, forming **I365**. 1,4-Migration of the Rh from an alkenyl to aryl position gives **I366** which can now cyclise via conjugate addition of the aryl Rh group to the enone. The resulting Rh enolate **I367** can be quenched with H_2O to release **I361** and regenerate the active catalytic species **I362**. It has also been demonstrated that *β*-carbon elimination of tertiary alcohols can also initiate similar reactivity via a very similar mechanism.[233]



Scheme 138. Proposed mechanism.

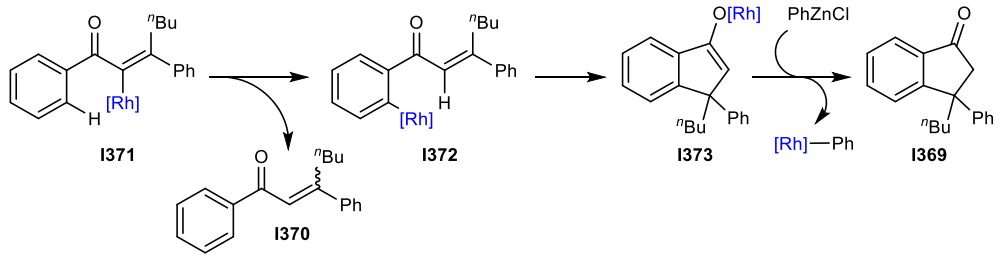
Modification of this procedure is possible by using alkynone **I368** and adding a rhodium–carbon bond across the asymmetric alkyne. The carbon nucleophile originates from aryl zincs such as PhZnCl (Scheme 139). The process is catalysed by $[Rh(C_2H_4)_2Cl]_2$ under mild conditions to give indanone **I369** in 81% yield alongside small quantities of the hydroarylation side-product **I370** (6%).[234]



*Scheme 139. Cyclisation to indanone **I369** after carborhodation of asymmetric alkyne **I368**.*

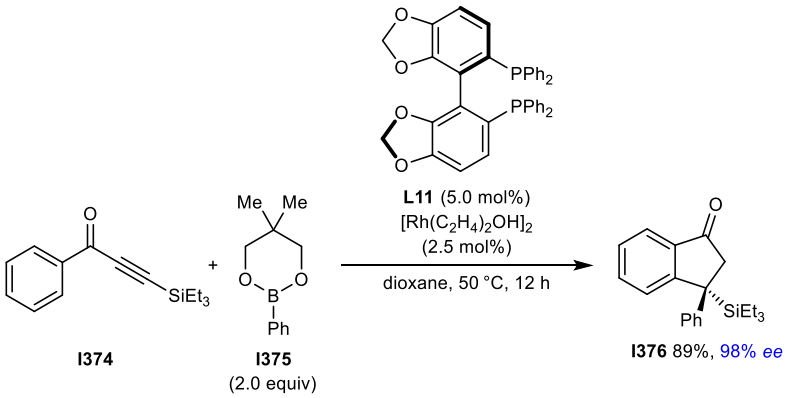
The cyclisation mechanism is extremely similar to Scheme 138. Instead of hydrorhodation, it is initiated by regioselective carborhodation of alkynone **I368** from Rh-Ph to give **I371** (Scheme 140). **I371** can then exploit the 1,4-Rh migration mechanism to form **I372**, which subsequently cyclises to form the rhodium enolate **I373**, both in identical fashion to Scheme 138. The cycle is completed via transfer of another phenyl group from PhZnCl to

cleave **I369**. The simple hydroarylation side-product **I370** is formed by quenching **I371** with a proton source.



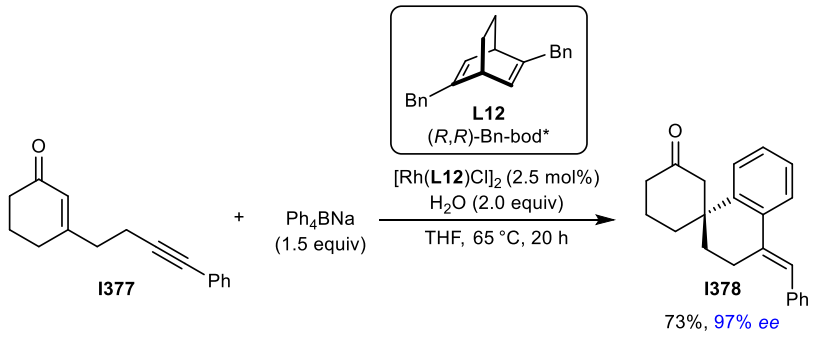
Scheme 140. Proposed mechanism.

Hayashi followed up this work with an enantioselective variation, using the chiral bisphosphine (*R*)-Segphos ligand **L11** to induce an asymmetric cyclisation on alkynone **I374** to give enantioenriched indanone **I376** in 89% yield and 98% *ee* (Scheme 141). Boronate ester **I375** was used as the aryl source in order to eliminate the hydroarylation side-products seen with arylboronic acids.[235]



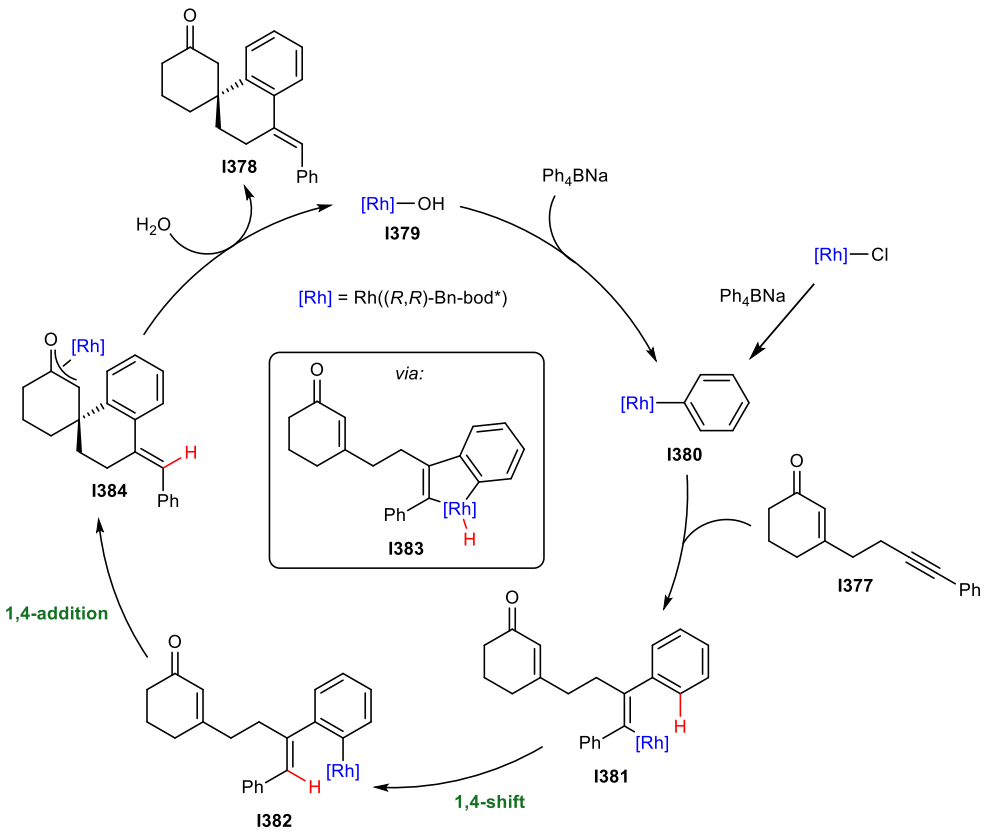
Scheme 141. Asymmetric indanone formation using a chiral bisphosphine ligand.

Hayashi later extended this work by exploiting the 1,4-migration process, followed by reaction with a tethered enone electrophile, to perform an enantioselective spirocyclisation of **I377** catalysed by the chiral $[Rh(Bn\text{-}bod)Cl]_2$ catalyst. **I378** was formed in 73% yield and 97% *ee* (Scheme 142).[236]



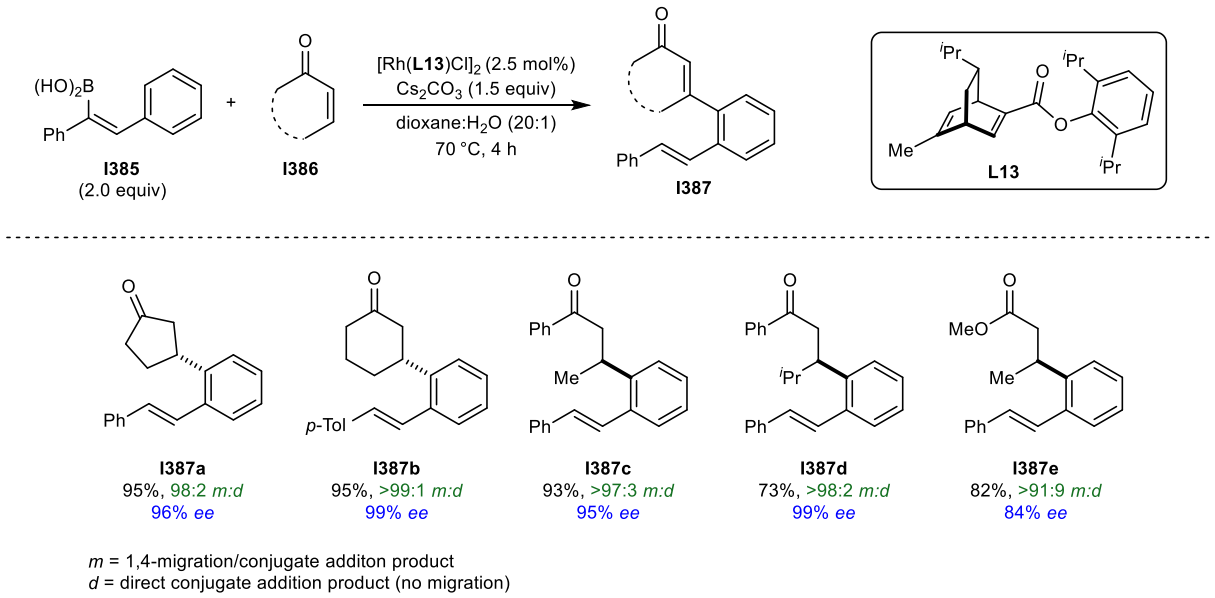
Scheme 142. Alkyne spirocyclisation with a tethered enone electrophile after 1,4-Rh migration.

Ph_4BNa is the aryl source and initiates the reaction via transmetalation with active Rh^I catalyst **I379** to form **I380**. Migratory insertion of **I377** at the alkyne generates **I381**, which then undergoes 1,4-migration to form **I382** via Rh^{III} intermediate **I383** (Scheme 143). Enantioselective conjugate addition of the aryl Rh bond to the enone, via a configuration that favours attack at the bottom face of the olefin by minimising steric interactions between the substrate and **L12**, gives Rh enolate **I384**. This can regenerate **I379** to complete the cycle and yield product **I378**.[236]



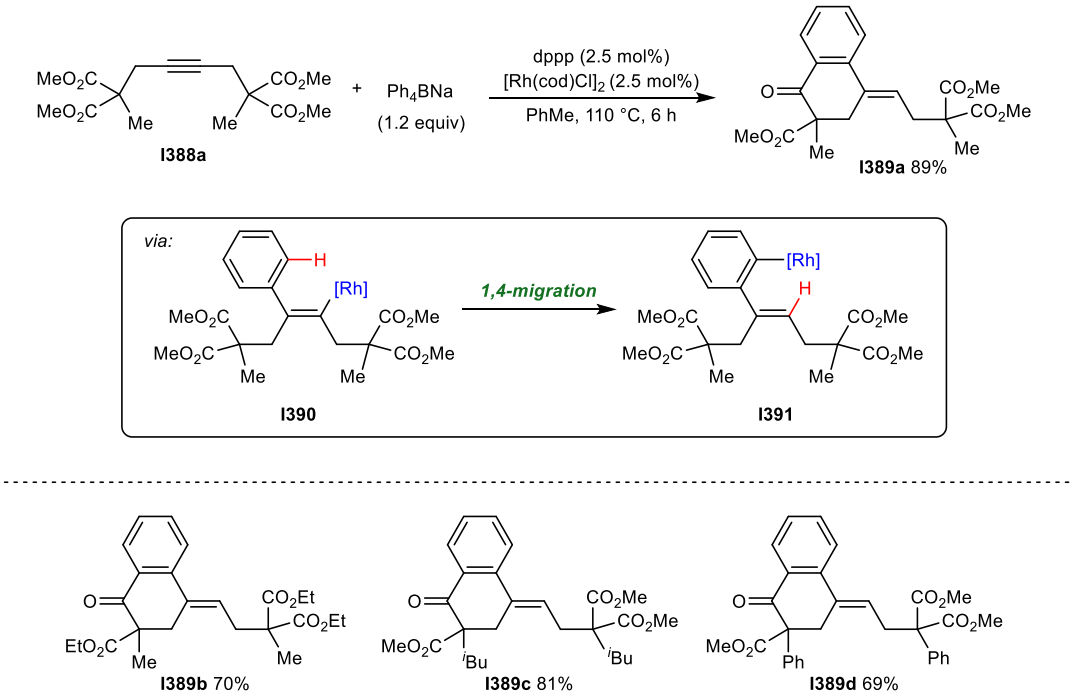
Scheme 143. Proposed mechanism.

An intermolecular variant was successful after modification of the reaction conditions. Using 1.5 equivalents of Cs_2CO_3 and chiral Rh-diene catalyst [Rh(**L13**)Cl]$_2$, *cis*-styrenyl boronic acid **I385** and enones **I386** gave arylation products **I387** when heated in dioxane:H_2O (20:1) for 4 h at 70 °C (Scheme 144). A range of cyclic and acyclic enones were tolerated in excellent yields and formed the desired products in high enantioselectivities (**I387a-I387d**). Acrylates were also compatible (**I387e** in 82% yield and 84% *ee*). After initial transmetalation of Rh onto the alkenyl position, the mechanism was proposed to be very similar to its intramolecular counterpart. The products usually possessed >97% *m*:*d* regioselectivity in favour of the 1,4-migration/addition product (*m*) over the direct conjugate addition product (*d*).[237] Detailed computational analysis of the 1,4-Rh migration pathway via DFT supported evidence of the oxidative addition/C–H reductive elimination mechanism via the five membered Rh^{III} hydride intermediate similar to the cyclic variant **I383** in Scheme 143).[238]



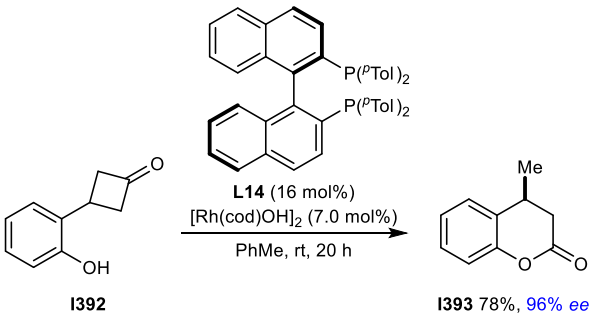
Scheme 144. Intermolecular variation of the 1,4-migration/addition transformation.

Other researchers have demonstrated similar applications of this 1,4-Rh migration mechanism to cyclisation reactions. In 2005, Murakami applied this to a symmetric alkyne with tethered malonate groups **I388a** to obtain the cyclisation product **I389a** in 89% yield after refluxing in PhMe for 6 h with Ph_4BNa and a [Rh(dppp)Cl]$_2$ catalyst system (Scheme 145).[239] The key step was the nucleophilic attack at one of the ester groups by the aryl Rh group in **I391** after 1,4-migration of **I390** into **I391**. A range of different malonate derivatives were tolerated in good yields, with **I389a-I389d** as representative examples.



*Scheme 145. Intramolecular acylation of aryl Rh species **I391** with esters to form ketones.*

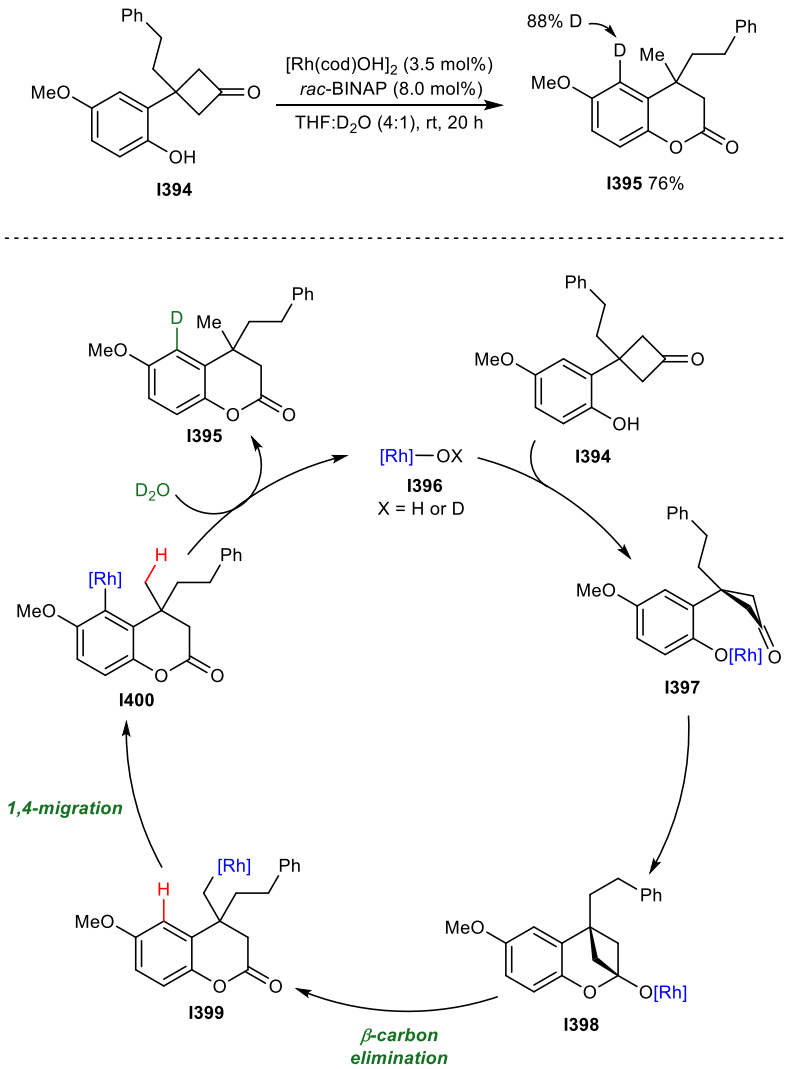
In 2007, Murakami was also able to demonstrate that 1,4-Rh migration towards an sp^2 carbon centre could originate from an sp^3 alkyl Rh carbon to form 3,4-dihydrocoumarins asymmetrically using cyclobutanones (Scheme 146). By using a chiral bisphosphine ligand **L14**, an enantioselective process was enabled. Cyclobutanone **I392** was transformed into **I393** in 78% yield and 96% *ee*.[240]



*Scheme 146. Formation of 3,4-dihydrocoumarin **I393** from cyclobutanone **I392**.*

Adding D_2O to the solvent system aided in confirming the mechanism on the reaction of substrate **I394**. High deuterium incorporation (88%) at the aryl position showed evidence of

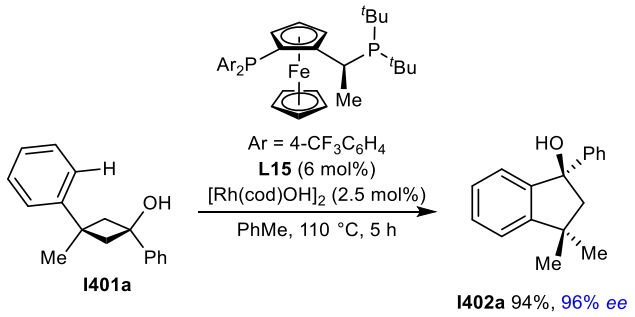
an sp^3 to sp^2 1,4-migration mechanism (Scheme 147). Originating at Rh^I hydroxide (or deuteroxide) **I396**, reaction with **I394** gives Rh^I alkoxide **I397,** which can subsequently attack the cyclobutanone carbonyl yielding **I398**. *β*-carbon elimination causes the cyclobutane ring opening event, which is the enantiodetermining step via selective cleavage of one of the two identical C–C bonds in the symmetrical cyclobutane. This generates alkyl Rh **I399**, which can now participate in the 1,4-Rh alkyl-to-aryl migration to form **I400**. Quenching with D_2O gives product **I395** and completes the catalytic cycle.[240]



*Scheme 147. Proposed catalytic cycle for the formation of **I395**.*

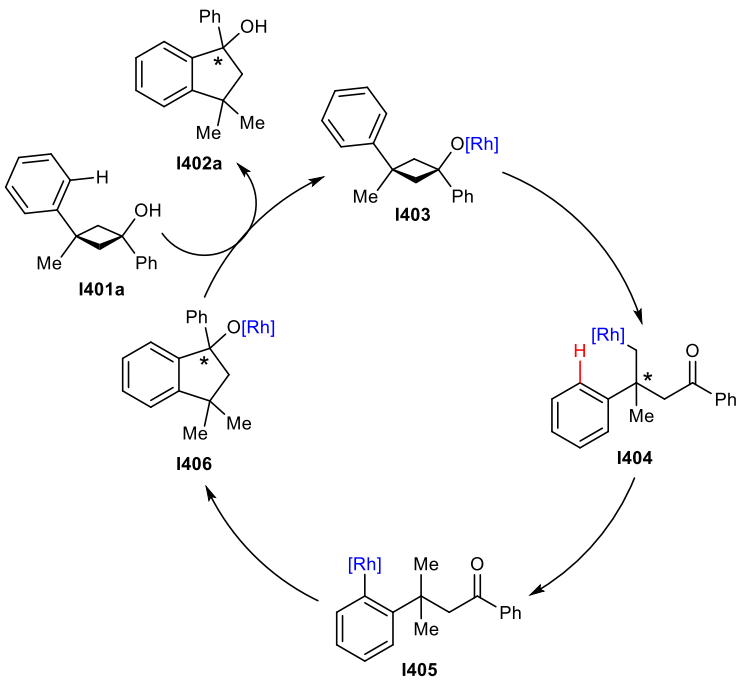
Additional research established that metal-catalysed C–C bond cleavage in cyclobutane rings is an efficient method of generating alkylmetal species.[241] Cramer demonstrated that cyclobutanols could also be ring opened to form indanols via a similar *β*-carbon elimination/1,4-Rh migration strategy (Scheme 148). In this case however, two quaternary

centres (one stereocentre) are formed in the product. Using chiral ligand **L15**, indanol **I402a** was isolated in 94% yield and 96% *ee*. [242]



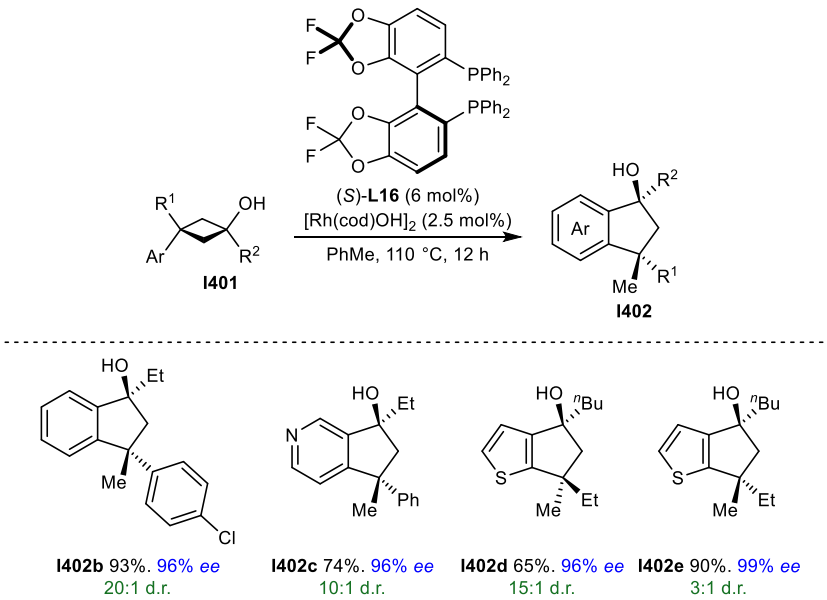
*Scheme 148. Rh-catalysed formation of indanol **I402a** from cyclobutanol **I401a**.*

Fundamentally, the mechanism is very similar to the one in Scheme 147. The Rh^{I} alkoxide **I403** undergoes *β*-carbon elimination to ketone **I404** (Scheme 149). Like in Scheme 147, this selective C–C bond cleavage of the symmetric cyclobutane ring generates the first quaternary centre at the benzylic carbon. 1,4-Rh alkyl-to-aryl migration forms **I405** from **I404** and then the aryl Rh species attacks the carbonyl to form Rh^{I} alkoxide **I406** and the stereocentre. Ligand exchange with another molecule of **I401a** cleaves the product **I402a** and reforms **I403** for another cycle.



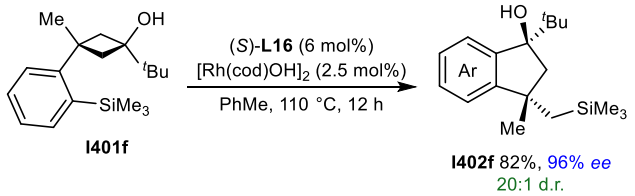
Scheme 149. Proposed mechanism.

When the methyl substituent on the cyclobutane ring was modified (R ≠ Me), **I402** can form two diastereoisomers. Control of the diastereoselectivity was unsuccessful using the current reaction conditions. Changing the ligand to (*S*)-Difluorophos **L16** enhances diastereoselectivity of a range of products (up to 20:1 in **I402b**) (Scheme 150). The sp^3 Rh^I moiety was also able to 1,4-migrate onto heteroaromatic sp^2 carbons preferentially over phenyl groups, allowing the formation of pyridyl indanol **I402c** in 74% yield and 10:1 d.r. Thiophenes were also tolerated at the Ar position (**I402d** in 65% yield and 15:1 d.r.) and swapping the Ar and R^1 groups in the starting cyclobutanol gave the opposite diastereomer **I402e** as the favoured main product (90% yield and 3:1 d.r.). The enantioselectivities remained excellent (>96 %) throughout.



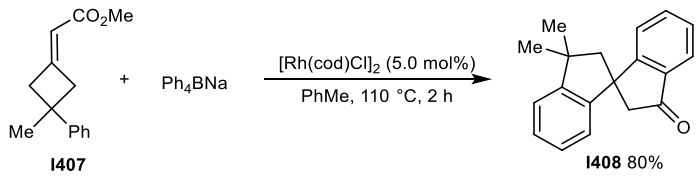
Scheme 150. Indanol scope.

At this point, metal-hydrogen migrations have been exclusively discussed with the metal and hydrogen swapping positions in the molecule via a through space interaction. However, Cramer reported the first 1,4-migration of a metal with a group other than a hydrogen atom when **I401f** was subjected to the reaction conditions (Scheme 151). The $SiMe_3$ group was an able proton substitute and indanol **I402f** was formed in 82% yield and excellent diastereo- and enantioselectivity.[243] This new reactivity is potentially very useful as both groups that have migrated remain functionalised for further possible reactivity.



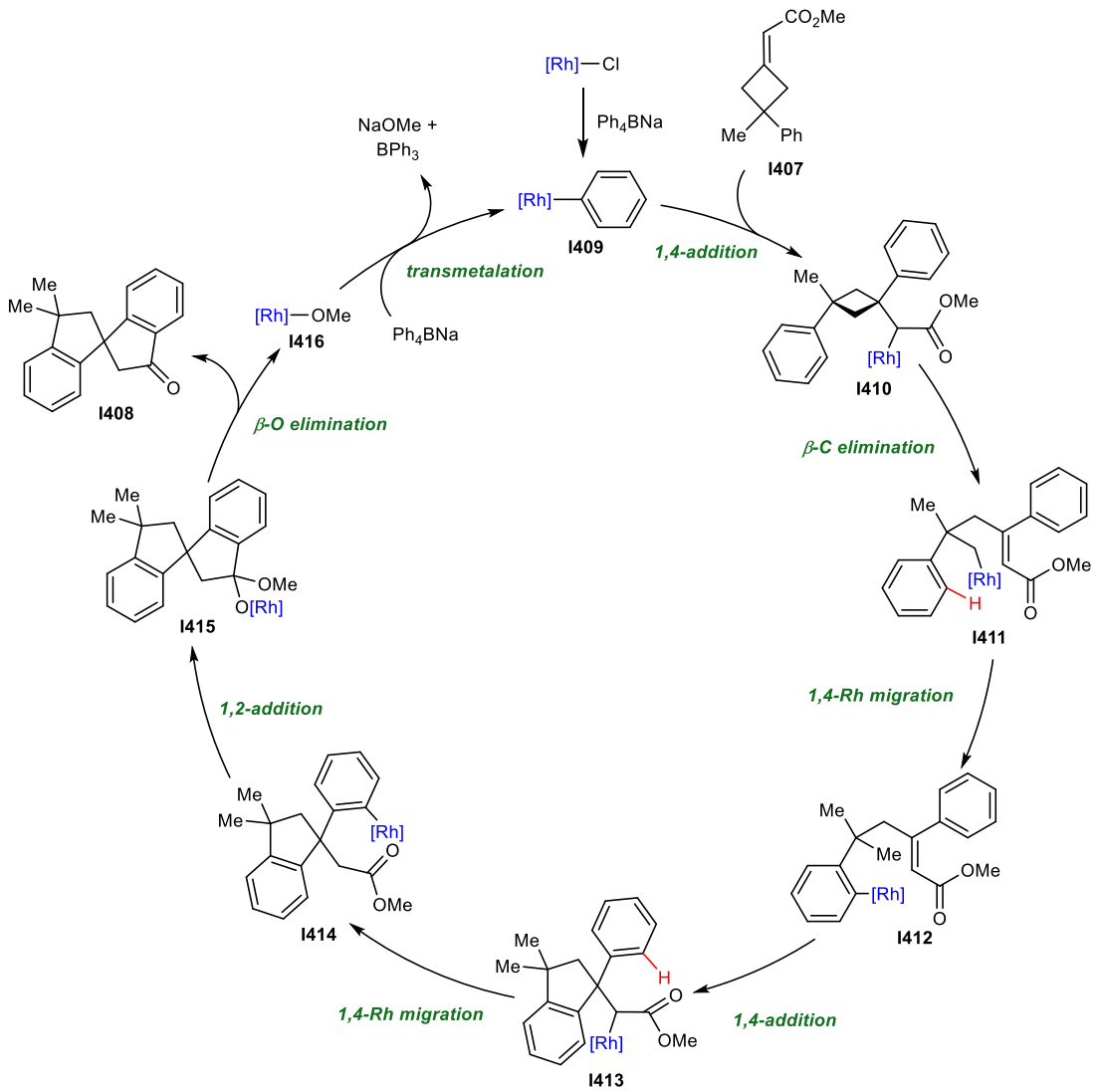
Scheme 151. Rh-catalysed migration of a $SiMe_3$ group.

Matsuda employed the *β*-carbon elimination process for cyclobutane ring opening in a 1,4-Rh migration cascade of **I407** giving spirocyclisation product **I408** in 80% yield (Scheme 152).[244]



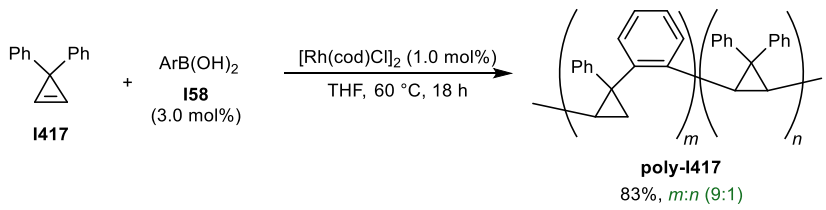
*Scheme 152. Spirocyclisation of **I407** via a 1,4-Rh migration cascade.*

The cascade is initiated by forming the active catalytic species aryl Rh **I409** from $[Rh(cod)Cl]_2$ using Ph_4BNa. **I409** then undergoes conjugate addition to **I407** to give **I410** (Scheme 153). The cyclobutane ring in **I410** is opened via *β*-carbon elimination to give enone **I411**, and alkyl to aryl Rh 1,4-migration proceeds to form **I412**. A second conjugate addition forms the first five-membered ring in **I413**, and a second 1,4-migration gives **I414**. Nucleophilic 1,2-addition to the carbonyl is the second five-membered ring closure step, and the resulting alkoxy Rh **I415** facilitates the elimination of **I408** via a *β*-oxygen elimination to give methoxy Rh **I416**, which can reform **I409** to complete the catalytic cycle via transmetalation.



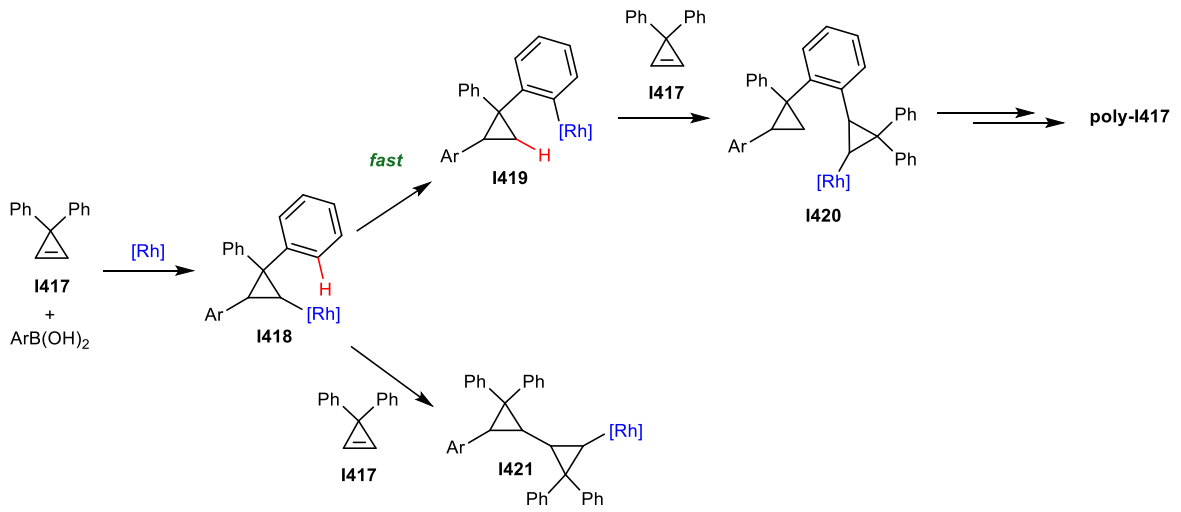
Scheme 153. Proposed spirocyclisation catalytic cycle.

1,4-Migration processes to sp^2 centres are not solely useful in small molecule syntheses; they can also have macromolecular applications in polymer chemistry. Shintani has recently reported the rapid polymerisation of cyclopropene **I417** using a Rh-catalysed 1,4 migration as the instigation step when initiator **I58** is used (Scheme 154).[245] This polymer architecture **poly-I417** is not obtainable by other traditional methods.[246]



*Scheme 154. Rh-catalysed polymerisation of **I417**.*

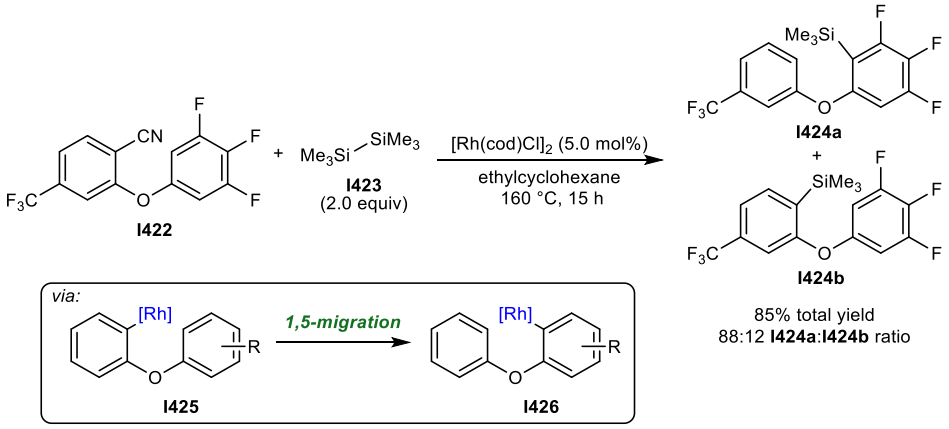
This polymerisation is initiated by addition of an aryl Rh species across **I417** (Scheme 155). The 1,4-Rh alkyl to aryl migration in **I418** to **I419** must be favoured over the undesired insertion with another molecule of **I417** (giving **I421**). Migration product **I419** can now insert into another molecule of **I417** to give **I420**. Repetition of this sequence quickly builds up the backbone of **poly-417**.



Scheme 155. Polymerisation mechanism

Whilst there is an ample number of 1,4-metal migration examples in the literature, there remains a dearth of 1,3- and 1,5-metal migration cases. This is likely because 1,4-migrations are more attainable, as they progress via energetically favourable five-membered metallocycles instead of less stable 4- or 6-membered analogues. Nonetheless, a couple of examples of 1,5-metal migrations have been noted using Pd [208, 247] and Rh.[209]

In 2012 Tobisu reported an example using Rh to catalyse a 1,5-aryl-to-aryl migration.[209] The decyanative silylation of aryl cyanide **I422** was reported (Scheme 156) using $[Rh(cod)Cl]_2$ as the catalyst. After prolonged periods of heating at high temperatures, the 1,5-Rh migration product was observed in addition to the expected decyanative silylation product. By varying the electronics on the aromatic rings, selectivity of the 1,5-migration product could be achieved, with very electron poor (3,4,5-trifluoro-) substrate **I422** favouring formation of migration product **I424a** over **I424b** (88:12 ratio) in 85% total yield.

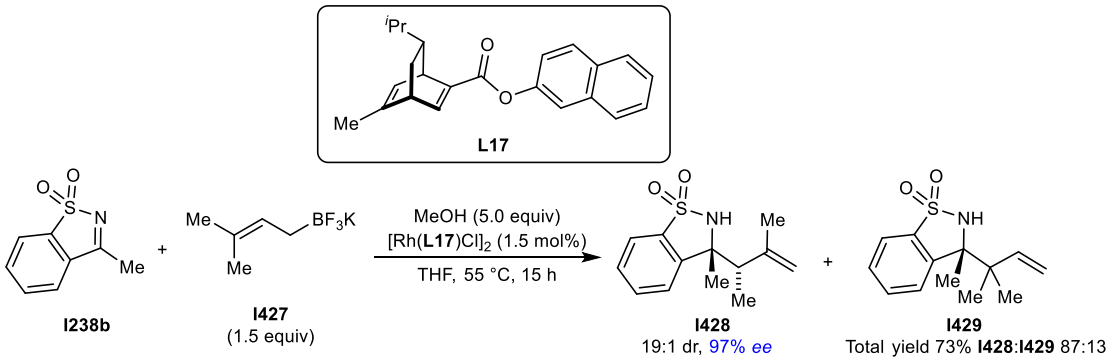


Scheme 156. Rh-catalysed decyanative silylation via 1,5-migration.

2.1.3.2 Rh^{I} Migration to sp^{3} Centres

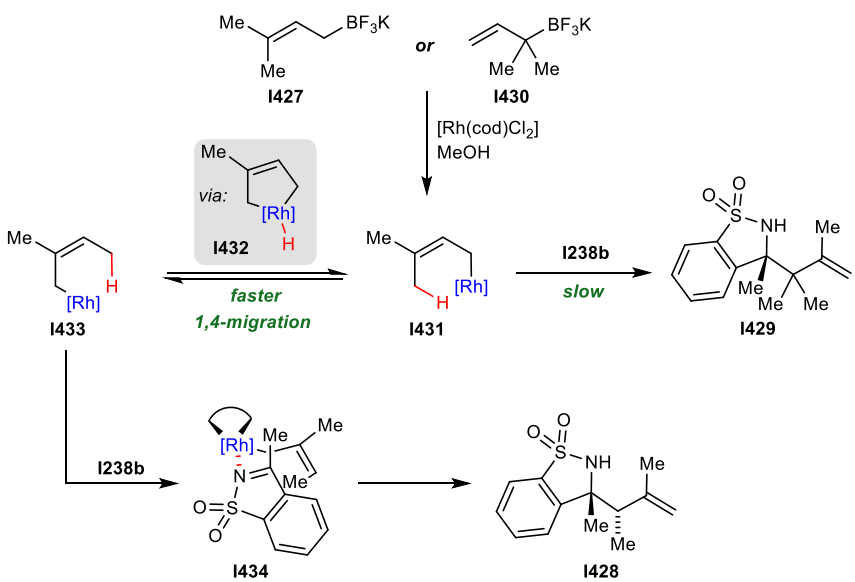
In comparison to rhodium migrations to C sp^{2} centres, examples of rhodium migrations to C sp^{3} centres are a lot less common. The reason for this is possibly due to the vinyl or aryl rhodium species being more stabilised than the corresponding alkylrhodium equivalent, a feature that is seen with most organometallic compounds. This suggests that given the choice, Rh will preferentially migrate onto an sp^{2} carbon instead of an sp^{3} carbon, and rationalises the wide range of alkyl-to-aryl 1,4-Rh migrations that were discussed in the previous section.

One particular example of migration to an C sp^{2} centre was reported in 2014 by the Lam group. When developing the Rh-catalysed allylation of cyclic imine **I238b** with allyl trifluoroborate **I427**, a 3:1 mixture of two products was isolated in 70% yield, with the expected prenylated product **I429** determined to be the minor component.[248] The major product **I428** was obtained in >19:1 d.r. and presumably resulted from an isomerisation of the allylrhodium intermediate. The reaction was employed enantioselectively using a chiral [Rh(**L17**)Cl]$_2$ catalyst with 5.0 equivalents of MeOH in THF at 55 °C for 15 h (Scheme 157). A mixture of **I428** and **I429** was again observed in 73% yield, this time with much greater favourability towards **I428** (87:13). After a second purification, **I428** was later isolated in 62% yield in 19:1 d.r. and 97% *ee*.



Scheme 157. Isomerisation of allylrhodium intermediates gives alternate allylation products.

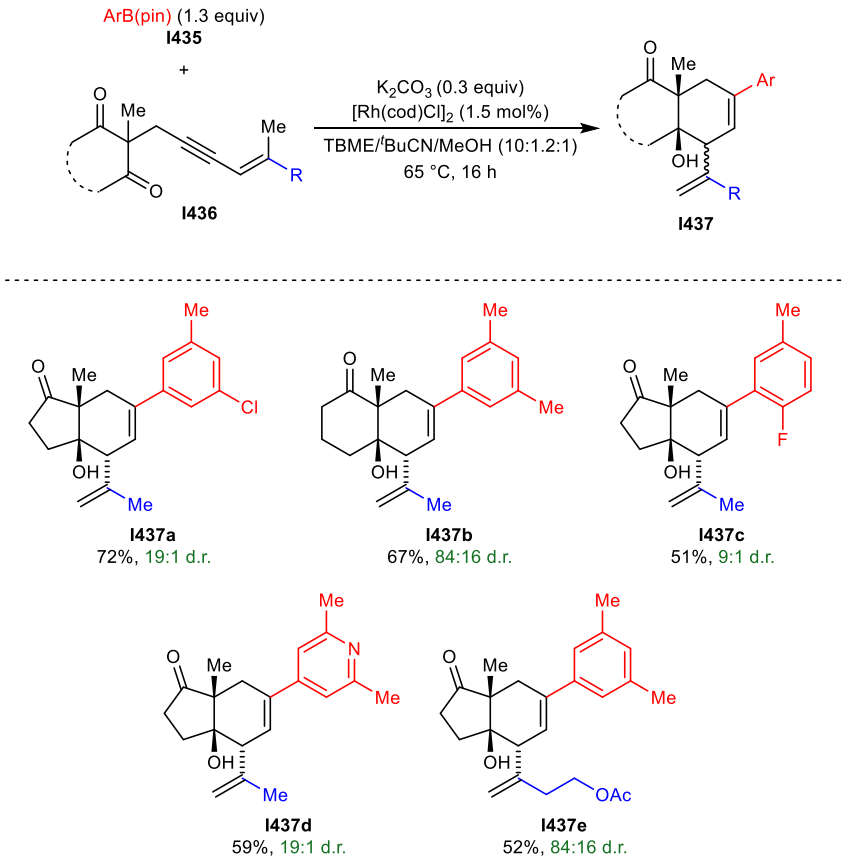
The allylrhodium intermediate **I431** forms via transmetalation with **I427** onto the Rh catalyst, promoted by MeOH. Immediate allylation of ketimine **I238b** can then occur to give prenylation product **I429** (Scheme 158). However, the ketimine is relatively unreactive, and so the allyl Rh species can instead participate in a 1,4-migration via five-membered rhodacycle **I432**, to give **I433**. Nucleophilic allylation of the isomerised intermediate **I433** gives **I428** via a chair transition state to rationalise the *anti*- stereochemical outcome. It is also important to note that both prenyl and tertiary trifluoroborate species **I427** and **I430** both give the same product, suggesting a common allylrhodium intermediate **I431** is likely.[248]



Scheme 158. Isomerisation of allyl Rh intermediates via 1,4-migration.

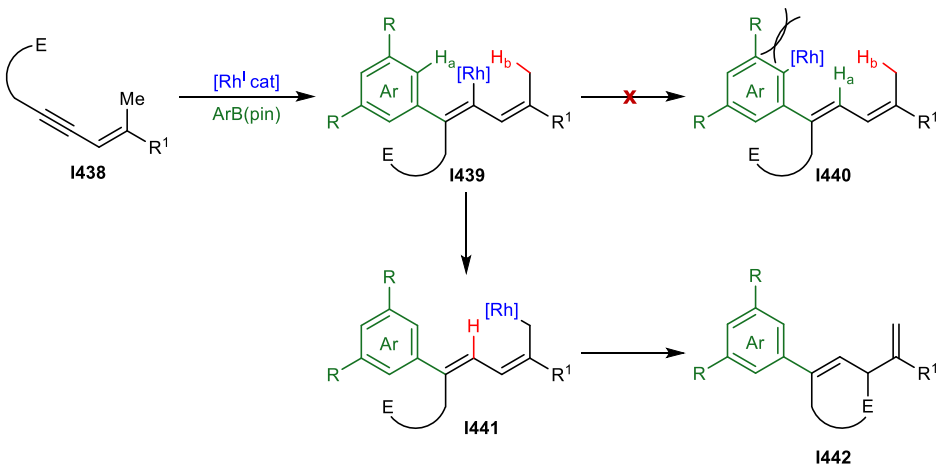
The Lam group later extended this work by using enynes with tethered 1,3 diketone electrophiles **I436** to form bicyclic products **I437** by exploiting an alkenyl-to-allyl Rh 1,4 migration (Scheme 159).[249] $[Rh(cod)Cl]_2$ catalysed the reaction of **I436** with aryl boronate

esters to form **I437** after a migration of the resulting Rh intermediates. A three-component solvent system was required to optimise the yields of **I437**, and a range of substrates with different sized 1,3-diketone rings and boronic acids (**I437a-I437d**) and enyne substituents **I437e** were tolerated in good yields (up to 72%) and excellent diastereoselectivities (>9:1). It was very important that the boronic acids used have 3,5- or 2,5-substituents on the aromatic ring in order to prevent 1,4-Rh migration onto the aryl sp^2 carbon.



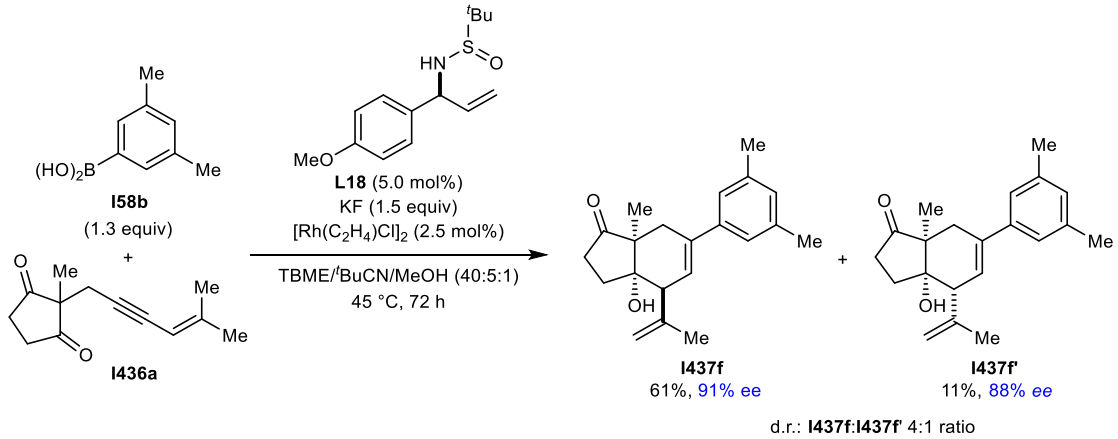
Scheme 159. Arylative intramolecular allylation via alkenyl to allyl 1,4-Rh migration.

This transformation is shown to progress first via Rh-catalysed arylation of generic enyne **I438** to form **I439**, then 1,4-Rh alkenyl-to-allyl migration swaps Rh with H_b to give **I441** (Scheme 160). 3,5-Substituents sterically hinder the theoretically more favourable alkenyl to aryl 1,4-Rh migration with H_a to **I440**. **I441** can then allylate the tethered electrophile to give cyclised product **I442**.



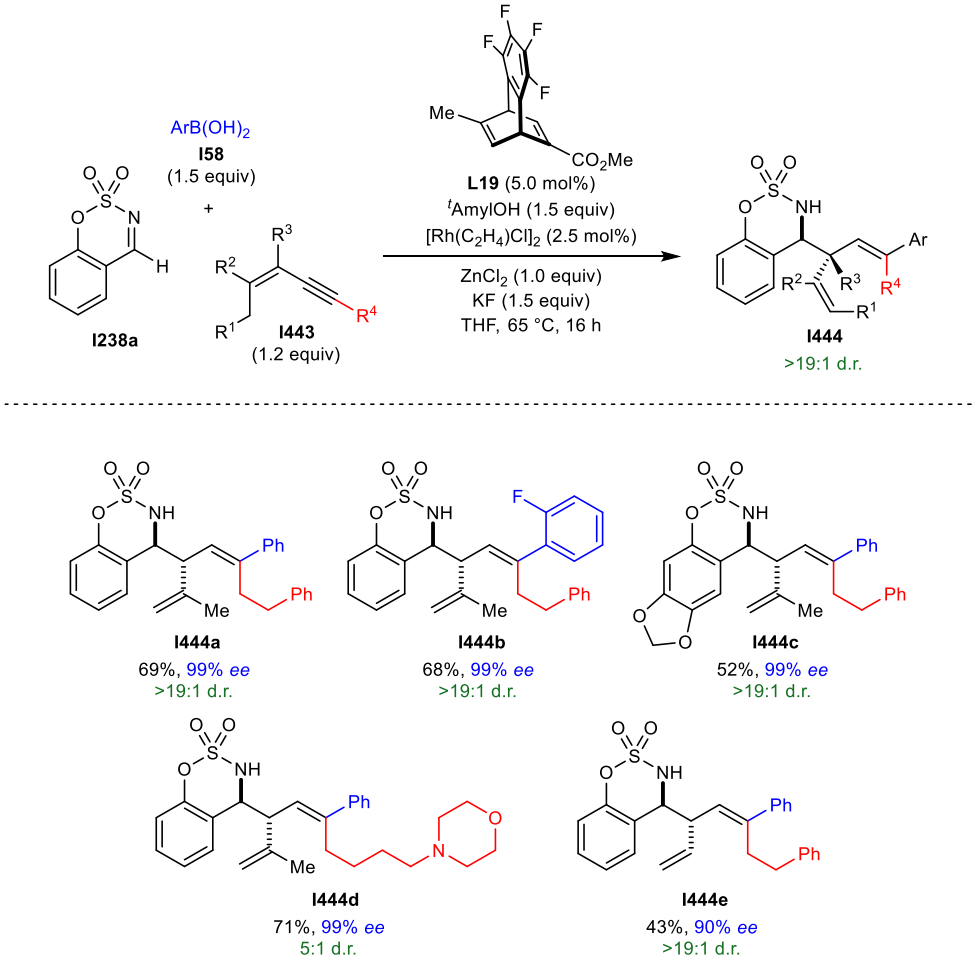
Scheme 160. The generic mechanism for the alkenyl to allyl 1,4-migration cyclisation reaction.

An enantioselective variation of this reaction was developed using modified conditions and a chiral sulfur-alkene ligand **L18** gave **I437f** and **I437f'** in a 4:1 crude d.r. ratio, with each diastereoisomer isolated in 61% yield, 99% *ee* and 11% yield, 88% *ee* respectively (Scheme 161).



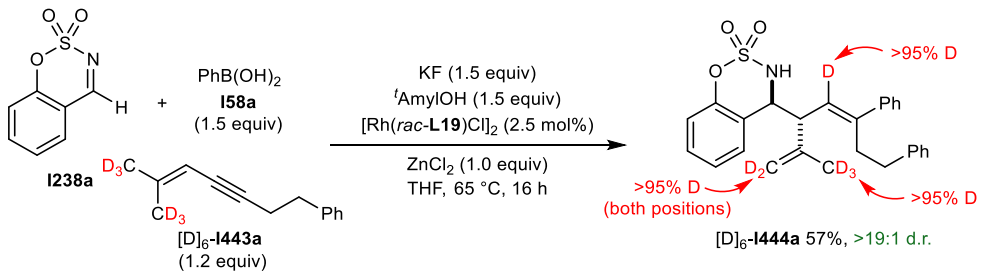
*Scheme 161. Enantioselective variant using chiral sulfur-diene ligand **L18**.*

Attempts to achieve an intermolecular three component coupling reaction by using separate enynes and electrophiles were successful. Rhodium was able to catalyse the reaction of cyclic aldimine **I238a**, aryl boronic acids and enynes **I443** together under adapted reaction conditions.[250] The process was rendered enantioselective by using chiral diene ligand **L19** (Scheme 162). $ZnCl_2$ was found to slightly increase product yields. Homoallylic amines **I444** were obtained, with variation at the sulphonamide, aryl boronic acid and the enyne all tolerated. The yields were good, with products formed as single diastereoisomers in most cases and in excellent enantioselectivity.



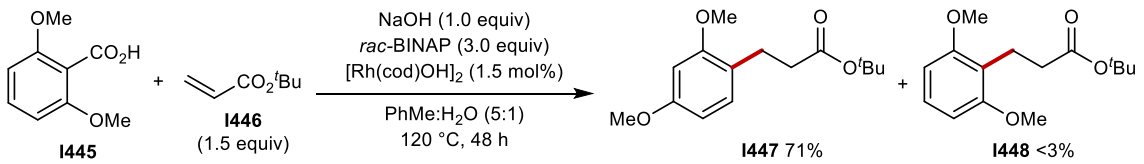
Scheme 162. Three component coupling reaction.

When hexadeuterated enyne [D]$_6$-**I443a** was subjected to the reaction conditions, with PhB(OH)$_2$ and **I238a** as coupling partners, [D]$_6$-**I444a** was formed in 57% yield as a single diastereoisomer, with almost exclusive deuterium transfer to the trisubstituted alkene (>95% D) (Scheme 163). This supports the theory that a 1,4-Rh migration mechanism is operative, occurring via the C-D oxidative addition/reductive elimination process.[250]



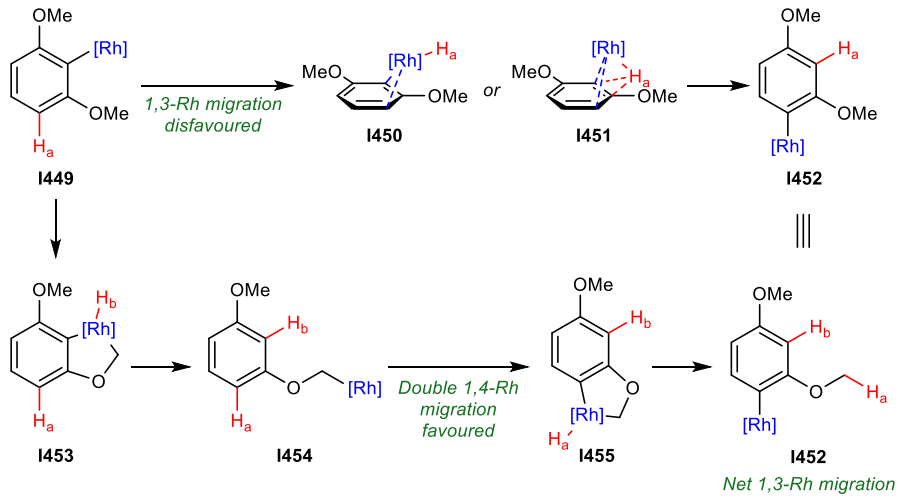
*Scheme 163. Mechanistic investigations with [D]$_6$-**I443a**.*

Prior to the observation of this 1,4-migration class, a formal 1,3-Rh^{I} migration to an sp^{3} carbon was reported by Zhao. The work documented a Rh-catalysed decarboxylative olefination of **I445** with **I446** to generate *meta*-olefination product **I447** in 71% yield, with only trace quantities of the *ipso*- product **I448** (<3%) (Scheme 164).[210]



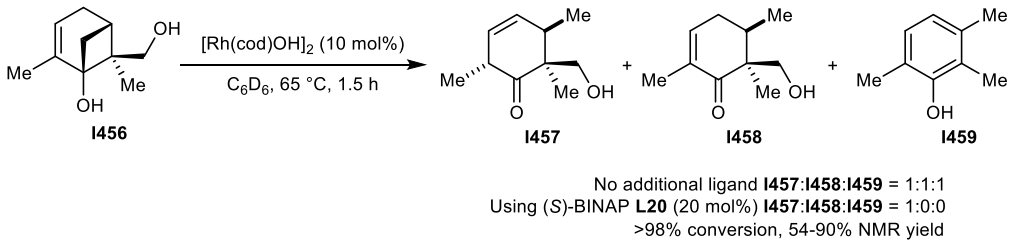
*Scheme 164. Decarboxylative olefination of **I445**.*

Possible mechanistic pathways to rationalise the observed product were explored. DFT calculations suggested 1,3-Rh migrations such as the one shown between Rh and H_a in **I450** or **I451** are generally disfavoured (Scheme 165). The true mechanism follows a double 1,4-Rh migration cascade via oxidative addition of the methoxy C–H bond to form **I454** via rhodacycle **I453**. A second 1,4-migration gives **I452**, via **I455**. The net result is a 1,3-migration of Rh^{I}.[227]



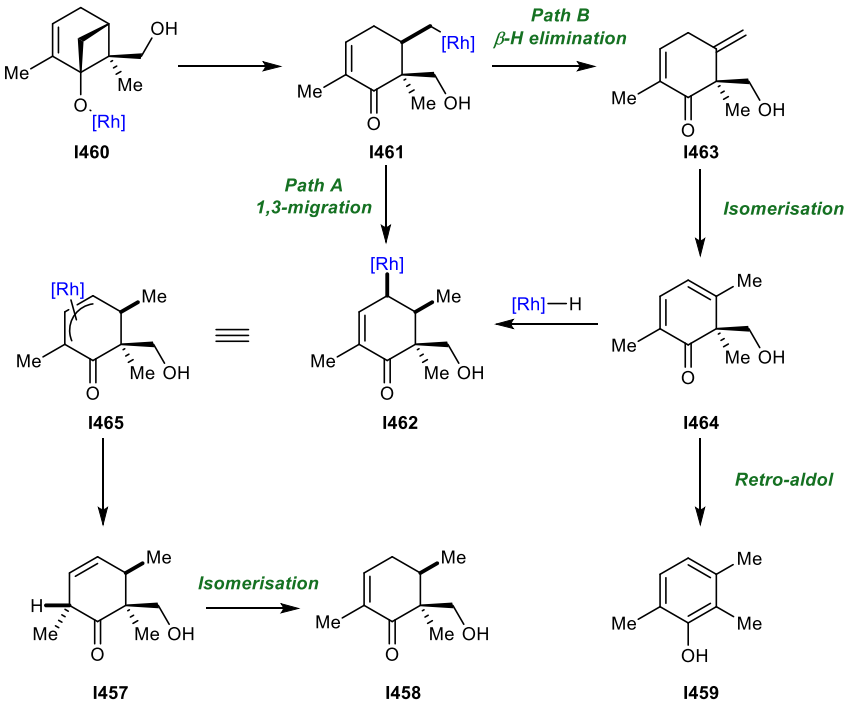
Scheme 165. Formal 1,3-migration mechanism via two consecutive 1,4-migrations.

The first true Rh 1,3-migration was reported by Sarpong in 2015 whilst investigating cyclohexanone scaffold syntheses.[251] Using the well reported capabilities of metals to facilitate specific C–C bond cleavage in cyclobutanols,[241] Sarpong replicated these conditions for the Rh-catalysed opening of cyclobutanol **I456** to form **I457**, **I458** and **I459** in equimolar ratios (Scheme 166). Through reaction optimisation, it was found that using (*S*)-BINAP as a ligand **L20** for [Rh(cod)Cl]$_2$ lead to the exclusive formation of **I457**.



*Scheme 166. Ring expansion of **I456** to **I457** via Rh-catalysed 1,3-migration.*

Scheme 167 shows the proposed mechanism can proceed via one of two pathways after the initial Rh-catalysed ring opening of **I460** to form alkylrhodium **I461**. Deuteration experiments showed that **I458** was not formed by simple protonolysis of **I461**, implying that **I458** was formed via an alternative mechanism. Following Path A, Rh 1,3-migration forms **I462** with Rh at the more thermodynamically favourable allylic position. **I462** is a Rh enolate, and protonation at the α- position gives **I457**, which can isomerise to form **I458**. Path B goes via an isomerisation sequence to **I464** via a series of β-hydride eliminations and reinsertions. Intermediate **I464** can then either undergo hydrorhodation to **I462** or a retro-aldol reaction to afford phenol **I459**.

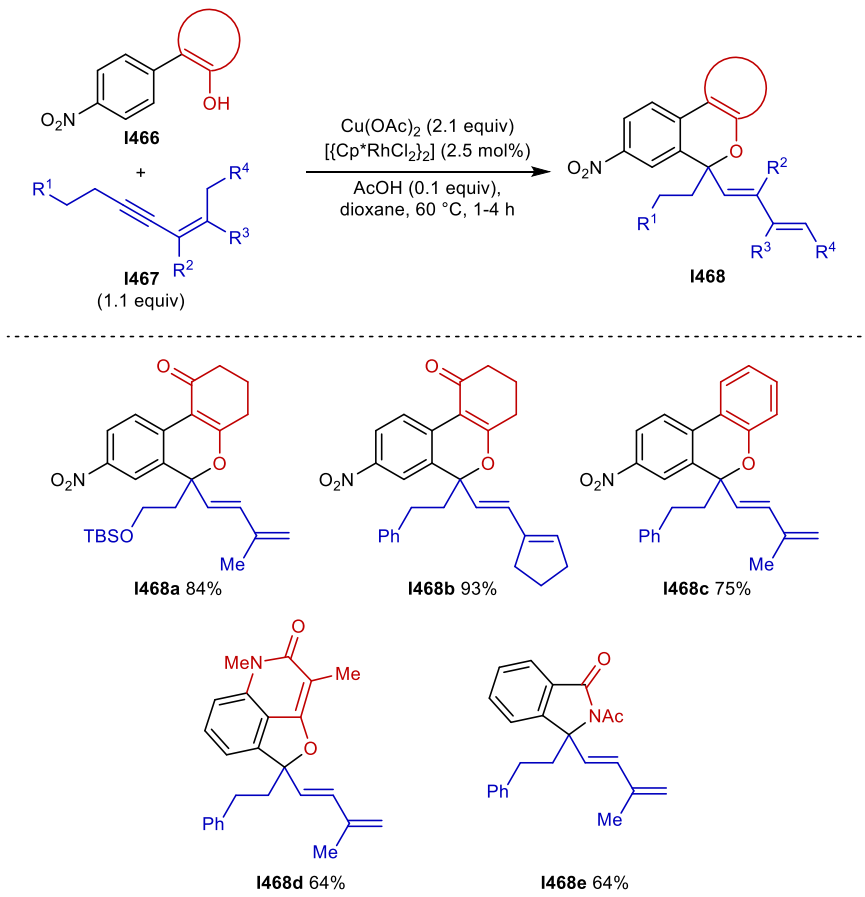


*Scheme 167. Mechanism for formation of **I457** and **I459**.*

DFT calculations show the 1,3 migration is certainly possible and Path A is heavily favoured when the BINAP ligand, is used. However, when using the cyclooctadiene ligand, Path B completes and Rh–H forms, leading to product mixtures.

2.1.3.3 1,4-Rh^{III} Migration

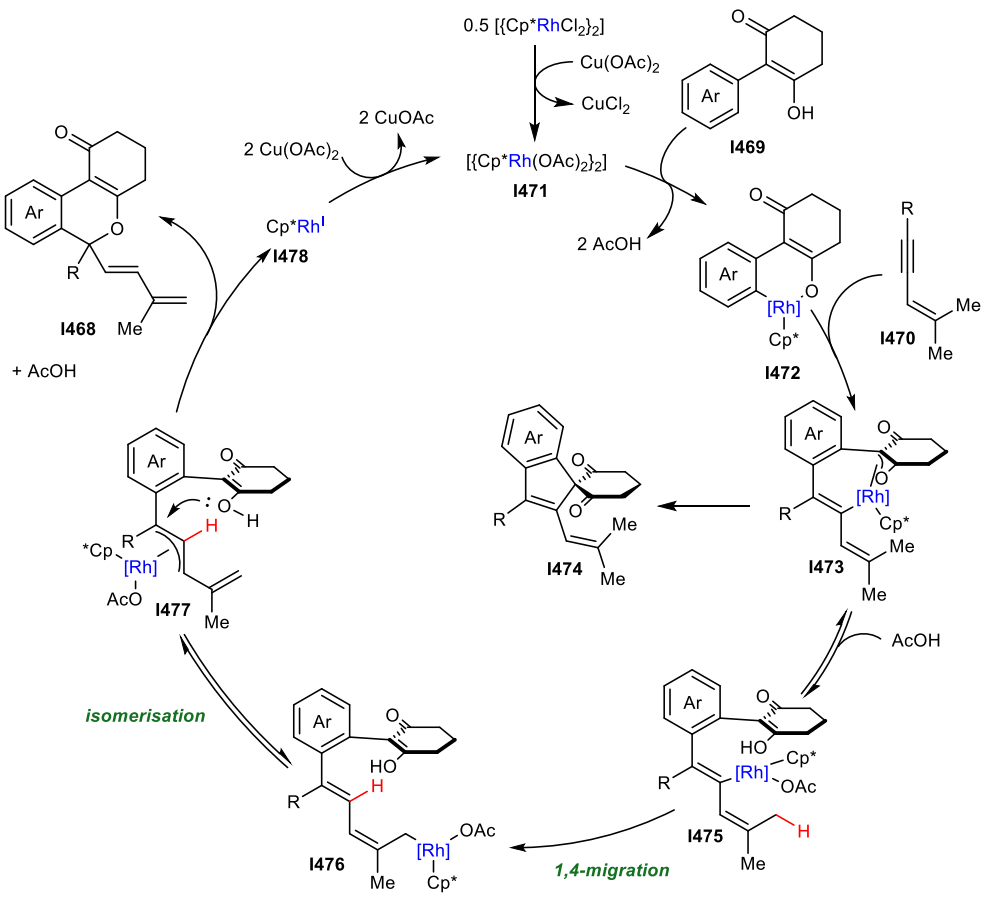
Most Rh-catalysed 1,4-migrations involve Rh^{I}. Whilst similar examples using Rh^{III} do exist, they remain relatively rare. Recently the Lam group has documented several examples using Rh^{III} that exploit this mode of reactivity.[252-255] This was first observed in a novel oxidative annulation where enynes **I467** were found to react as a one carbon annulation partner with **I466** to form benzopyran type products **I468** (Scheme 168).[253] [(Cp*RhCl$_2$)$_2$] was the optimal catalyst and a range of different products were accessed using various directing groups such as enols (**I468a-I468b**), phenol (**I468c**), barbiturates (**I468d**) and amides (**I468e**).



*Scheme 168. Oxidative one carbon annulation of **I466**.*

A catalytic cycle was proposed for generic substrates **I469** and **I470** (Scheme 169). Rhodium diacetate complex **I471** is formed from Cu(OAc)$_2$ and [(Cp*RhCl$_2$)$_2$]. C–H activation

via a concerted metalation-deprotonation pathway [256] gives rhodacycle **I472**. Insertion of enyne **I470** gives **I473**. If a simple alkyne was used instead of an enyne, then reductive elimination would give spiroindenes similar to **I474**. However, due to the observed formation of benzopyran **I468** instead, it is proposed that protonolysis with AcOH is preferred in this scenario, forming **I475**. The Rh^{III} 1,4-migration repositions alkenylrhodium **I475** to allylrhodium **I476**, which can isomerise to π-allylrhodium species **I477**. Nucleophilic attack by the enol at electrophilic Rh^{III} allyl species rationalises the formation of benzyopyran **I468**. The resulting Rh^{I} species **I478** is then reoxidised by $Cu(OAc)_2$ to complete the cycle.

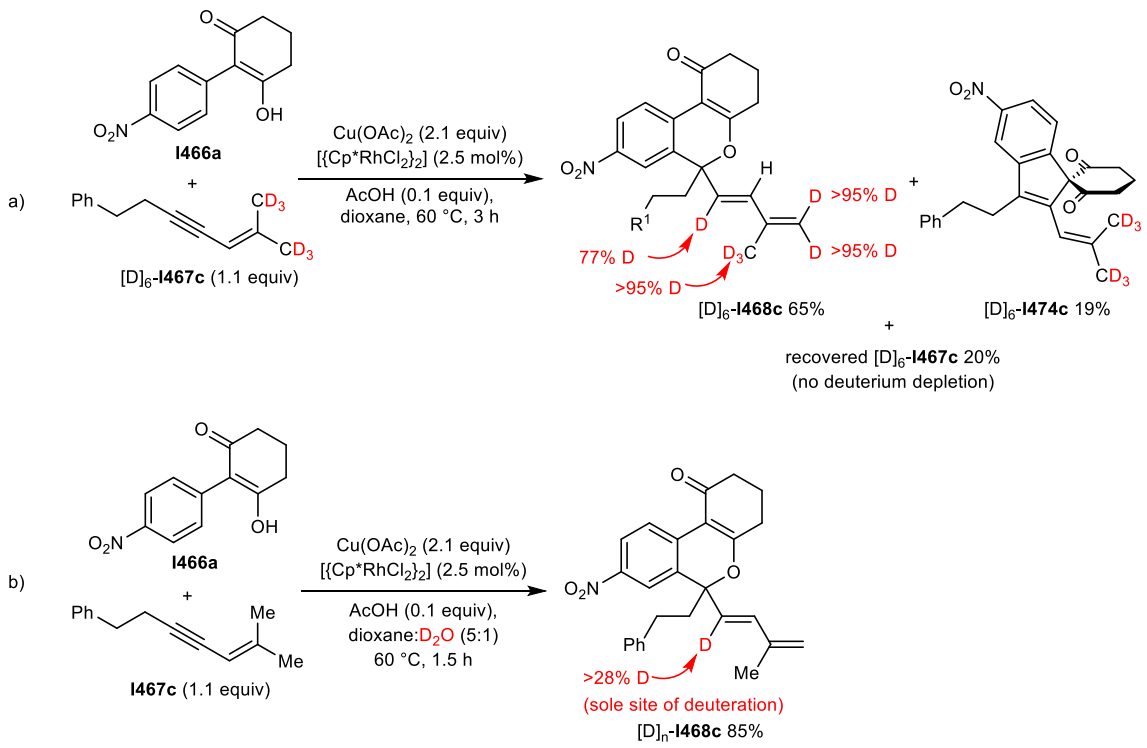


Scheme 169. Proposed catalytic cycle.

When 1,3-dicarbonyl groups were used as directing groups, substrates typically showed up to 20% formation of spiroindene **I474**. However, the use of electron-withdrawing groups on the aromatic ring suppressed this. Some electron donating groups (such as -OMe) favoured formation of spiroindene **I474** instead.

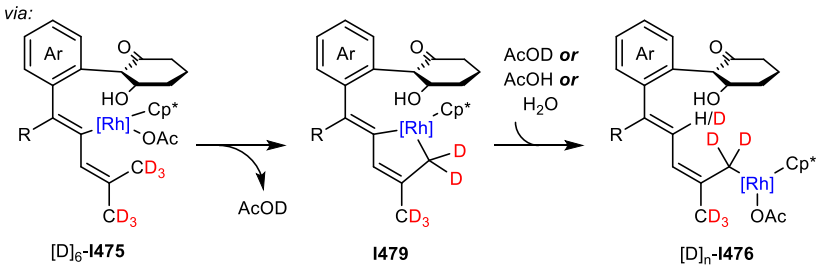
Typically, 1,4-migration of Rh^{I} is understood to proceed via a C–H oxidative addition/reductive elimination pathway. However, deuterium transfer experiments suggest that

the Rh^{III} migration in this reaction proceeds via a different mechanism. Subjecting hexadeuterated enyne $[D]_6$-**I467c** to the reaction conditions with **I466a** gave $[D]_6$-**I468c** with incomplete deuterium transfer (77% D) at the alkenyl carbon (Scheme 170a). When **I467c** was reacted using dioxane:D_2O (5:1) as the solvent system, only 28% deuteration occurred at the same carbon (Scheme 170b), with no other deuterium incorporation observed.[253]



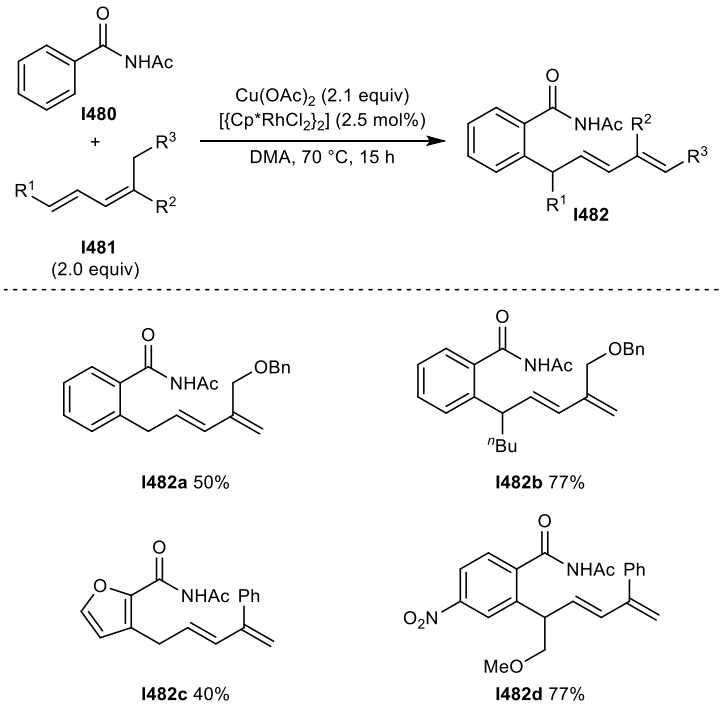
Scheme 170. Studies with deuterium labelled compounds.

It was proposed that the Rh^{III} migration occurred via a concerted metalation-deprotonation sequence. Loss of AcOD gives **I479**, and ring opening via AcOH, AcOD or H_2O gives $[D]_n$-**I476** (Scheme 171). It was proposed that this would account for the imperfect deuteration at the alkenyl site. Ishii and co-workers performed further experimental analysis of the Rh^{III} 1,4-migration mechanism and determined it to be a reversible process.[257]



Scheme 171. Acetate assisted concerted metalation-deprotonation pathway.

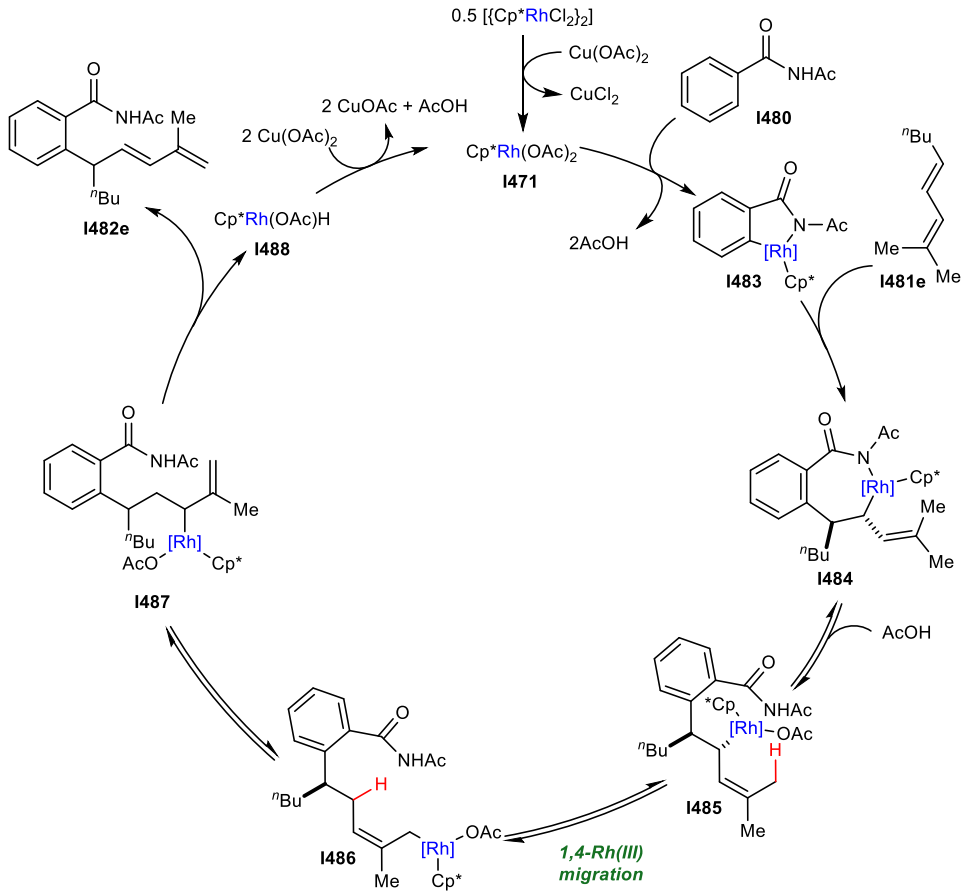
The successful annulation with an amide directing group (**I468e** in Scheme 168) inspired further investigation and was applied to an oxidative C–H allylation of 1,3-dienes via the first reported allyl-to-allyl 1,4-Rh^{III} migration (Scheme 172).[255] *N*-Acetylbenzamide **I480** coupled with dienes **I481** under similar conditions to give **I482**. Different diene partners were tolerated, including **I482a** (50%) and **I482b** (77%), as well as heteroaromatic amides **I482c** (40%) and aryl substituents **I482d** (77%).



*Scheme 172. Oxidative C–H allylation of **I480** using 1,3-dienes.*

Similar to Scheme 169, Cp*Rh(OAc)$_2$ **I471** is the active catalytic species. In this scenario, **I471** reacts with **I480** to give rhodacycle **I483** and AcOH (Scheme 173). Coordination and insertion of diene **I481e** gives **I484**, which contains an allylrhodium component. Acetolysis of **I484** gives allyl Rh^{III} species **I485**, which can now participate in the 1,4-migration to give

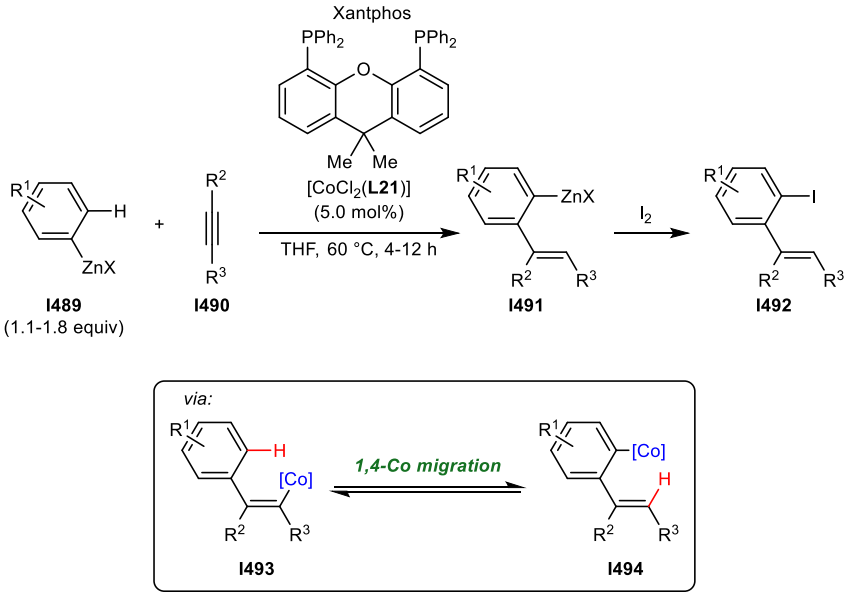
I486. This allylrhodium component can now undergo σ-π-σ isomerisation to form **I487**. *β*-Hydride elimination expels product **I482e** and gives Rh–H **I488**. Reaction of **I488** with $Cu(OAc)_2$ gives AcOH and reformed **I471** after reductive elimination.



Scheme 173. Proposed catalytic cycle.

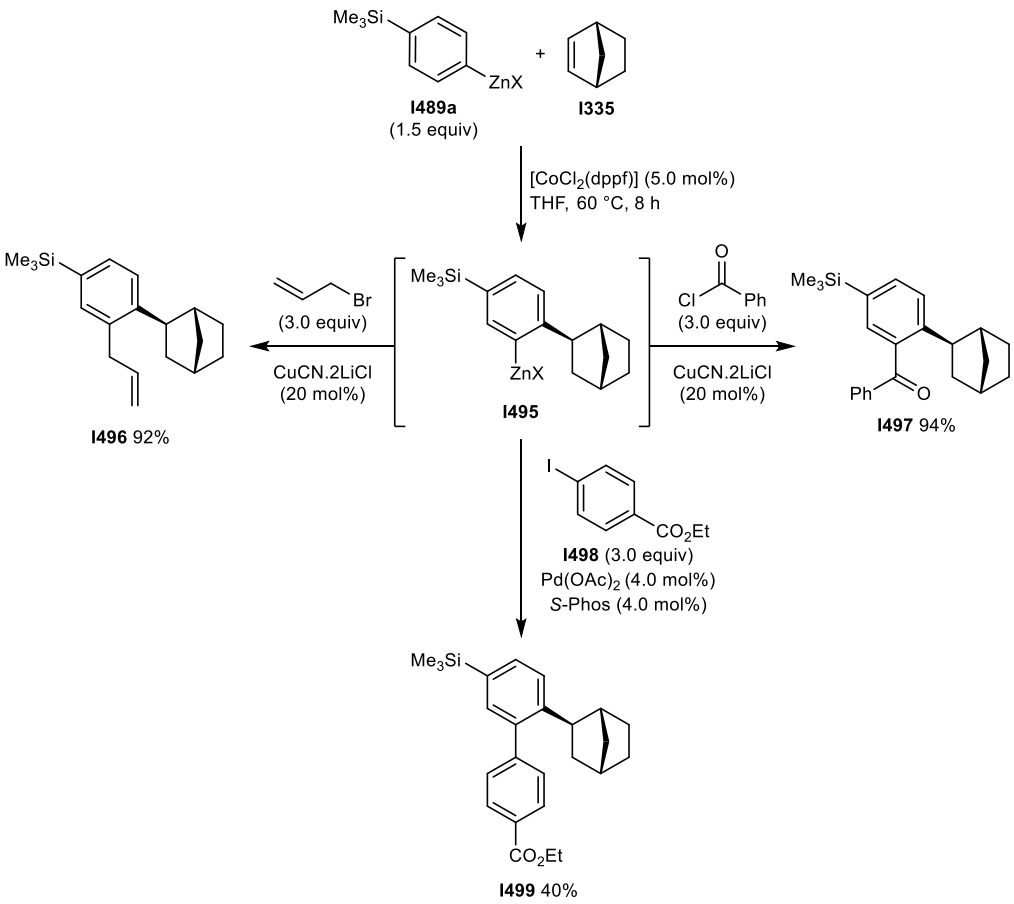
2.1.4 1,4-Cobalt Migration

As a first-row transition metal, using 1,4-cobalt migrations to perform catalytic C–H activation processes is very important, due to its lower costs and greater natural abundance compared to Rh or Pd. Unfortunately, such examples are very limited in the literature. In 2012, Yoshikai reported the first example of a Co 1,4-migration (Scheme 174).[258] Using arylzinc **I489** as the aryl source, Co-catalysed additions across alkynes **I490** gave alkenyl cobalt intermediate **I493**, which formed **I494** after 1,4 Co-migration. Transmetalation of **I494** with another molecule of arylzinc **I489** gives **I491** and an aryl Co species primed for another alkyne addition. Trapping **I491** with an external electrophile such as I_2 gives functionalised product **I492**.



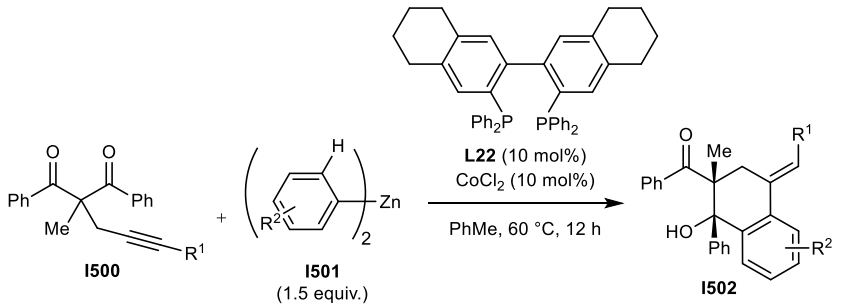
Scheme 174. First example of Co-catalysed 1,4-migration.

Yoshikai then applied this concept to the Co-catalysed addition of arylzinc **I489a** to norbornene **I335**. The resulting alkyl Co species then undergoes an alkyl-to-aryl 1,4-migration and forms **I495** after transmetalation (Scheme 175). This arylzinc species can be trapped with various electrophiles to give more complex products very quickly. Allylation product **I496** and acylation product **I497** were obtained in 92% and 94% yield respectively. **I495** could also be transmetalated onto Pd to complete a cross coupling reaction with **I498** to give **I499**.[259]



Scheme 175. Co-catalysed alkyl to aryl 1,4-migration to give further functionalised products.

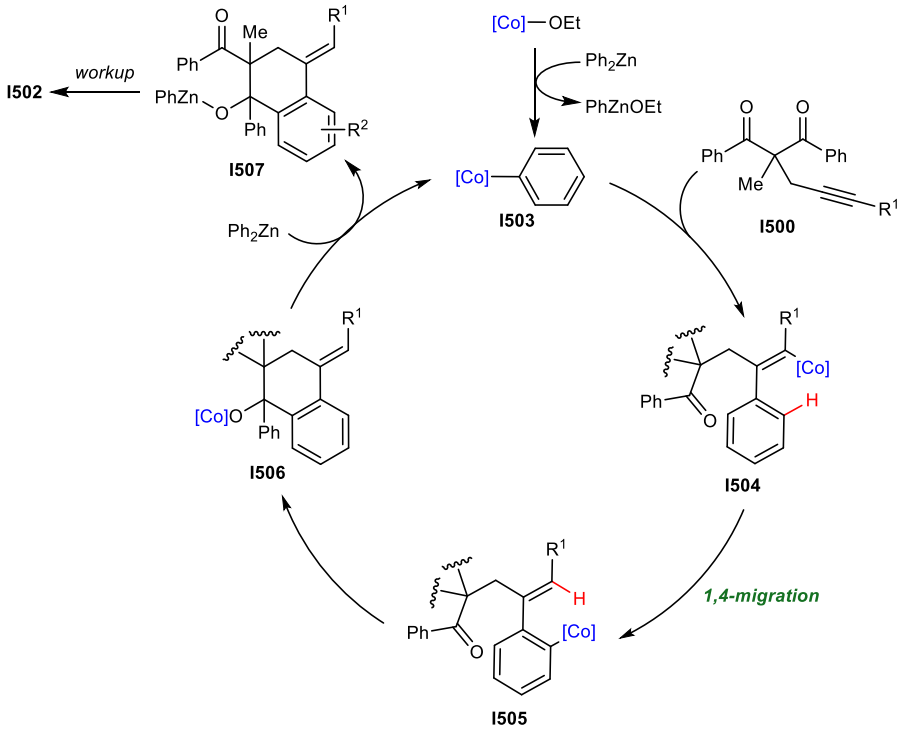
In 2016, Yoshikai extended this work to the arylative cyclisation of symmetrical and asymmetrical alkynes via a 1,4-alkenyl to aryl cobalt migration.[260] Using asymmetric alkyne **I500** which possesses a tethered 1,3-diketone and arylzinc **I501**, regioselective arylation generates **I502** (Scheme 176).



Scheme 176. Co-catalysed arylative cyclisation via 1,4-Co migration.

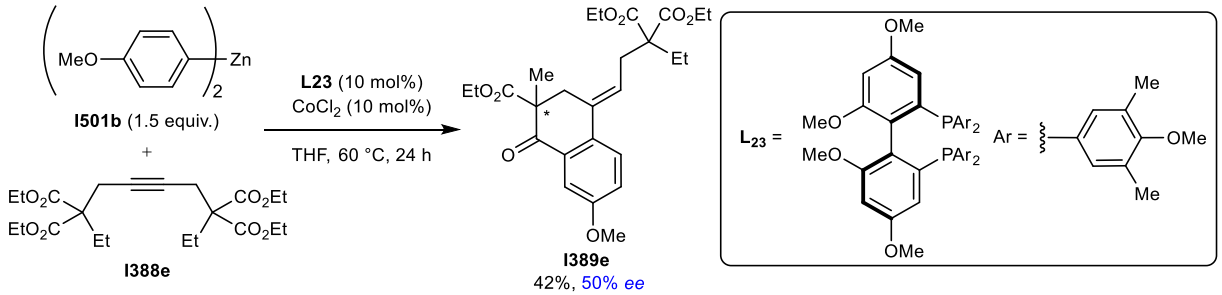
The mechanism is instigated by formation of aryl Co species **I503** after transmetalation with the diaryl zinc **I501a** (Scheme 177). Regioselective migratory insertion into the alkyne

gives alkenyl Co species **I504**, which can undergo 1,4-migration to form aryl Co **I505**. This is then trapped by one of the pendant ketones to form alkoxycobalt **I506**. Transmetalation with another diaryl zinc molecule completes the cycle and gives **I507**, which forms alcohol **I502** on workup.



Scheme 177. Proposed catalytic cycle.

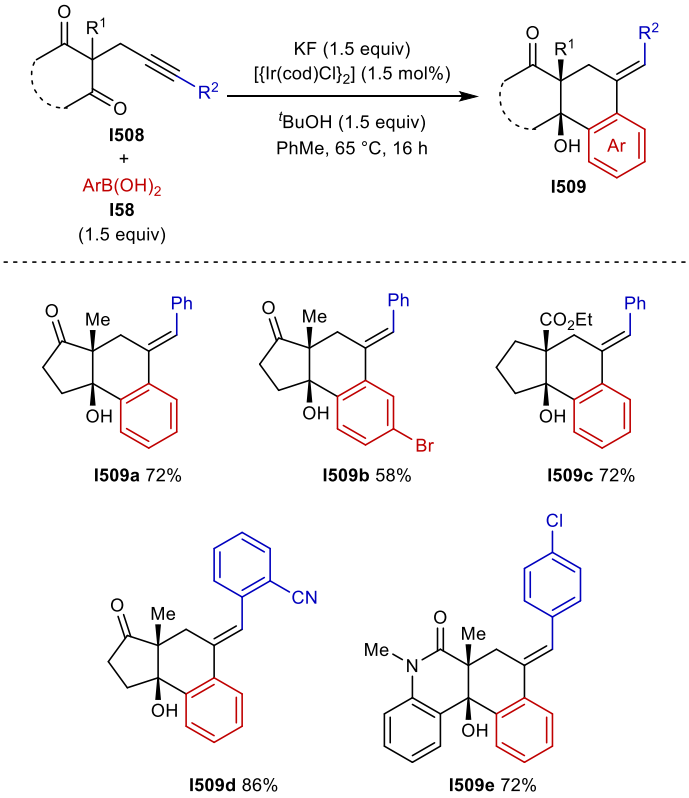
An asymmetric attempt at this reaction with (*R*)-DMM Garphos ligand **L23** did impart some enantioselectivity on symmetrical alkyne **I388e** with limited success, forming bicyclic ketone **I389e** in 42% yield but only 50% *ee* (Scheme 178). This enantioselectivity is modest and would require further optimisation.[260]



Scheme 178. Enantioselective Co-catalysed arylative cyclisation.

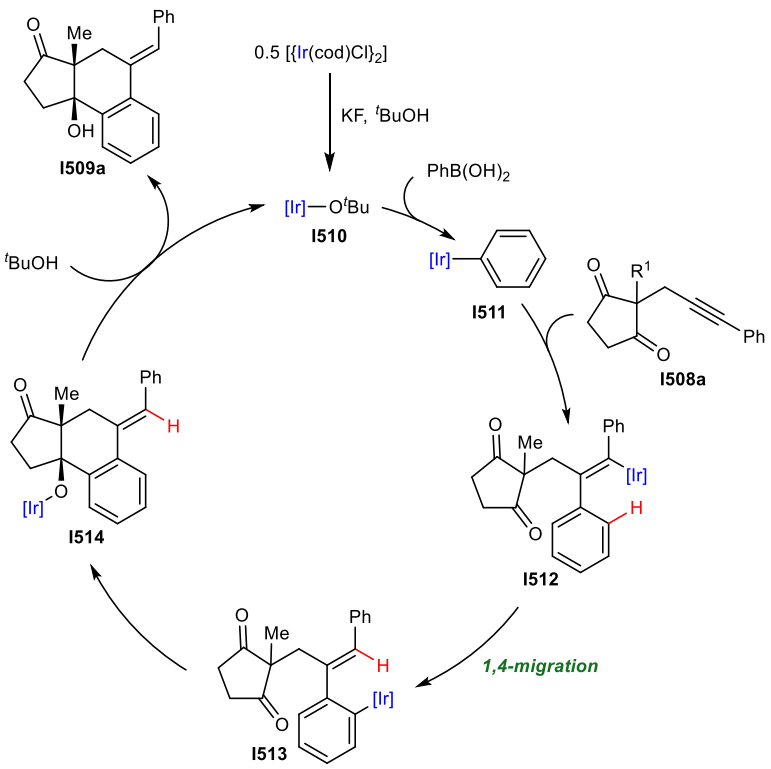
2.1.5 1,4-Iridium Migration

The first example of an Ir-catalysed 1,4-migration was reported by the Lam group in 2014, where cyclic alkynone substrates were used to form complex polycyclic structures (Scheme 179).[261] Initial results with **I508** and a rhodium catalyst gave reasonable yields of cyclic products **I509** but attempts with $[Ir(cod)Cl]_2$ were much more successful. A range of different products with varying aryl substituent patterns and polycyclic cores (**I509a-I509e**) were cyclised in moderate to excellent yields (up to 86%).



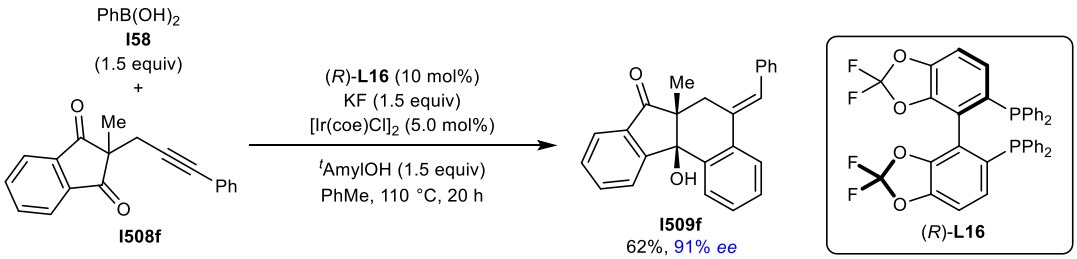
Scheme 179. Ir-catalysed 1,4-migration of cyclic alkynones.

The proposed catalytic cycle is initiated by the formation of active catalytic Ir alkoxide species **I510** after ligand exchange. This is then readily available to undergo transmetalation with the boronic acid to form **I511**, which regioselectively inserts into the alkyne **I508a**. Iridium 1,4-migration gives aryl Ir species **I513**, which is able participate in 1,2-addition to one of the tethered ketones. Protonolysis of **I514** gives polycycle **I509a** and completes the catalytic cycle (Scheme 180).



Scheme 180. Proposed catalytic cycle.

Attempts to render this process enantioselective with an Ir-bisphosphine catalyst gave modest success, with yields mostly poor and large quantities of starting materials often recovered. One of the best results was observed using the (*R*)-difluorophos ligand **L16**, which oversaw the transformation of **I508f** into **I509f** in 62% yield and 91% *ee* (Scheme 181). Significant quantities of starting material **I508f** (35%) was also recovered from the reaction mixture.[261]



Scheme 181. Asymmetric Ir-bisphosphine catalysts showed modest activity in inducing enantioselectivity.

2.1.6 Summary

C–H activation is now an important tool for synthetic organic chemists, allowing them to rethink traditional C–C bond connections and save time and materials by avoiding using pre-functionalised materials. One initiation method is to exploit through space interactions such as 1,4-migrations with transition metals to activate remote sp^2 and sp^3 C–H bonds.

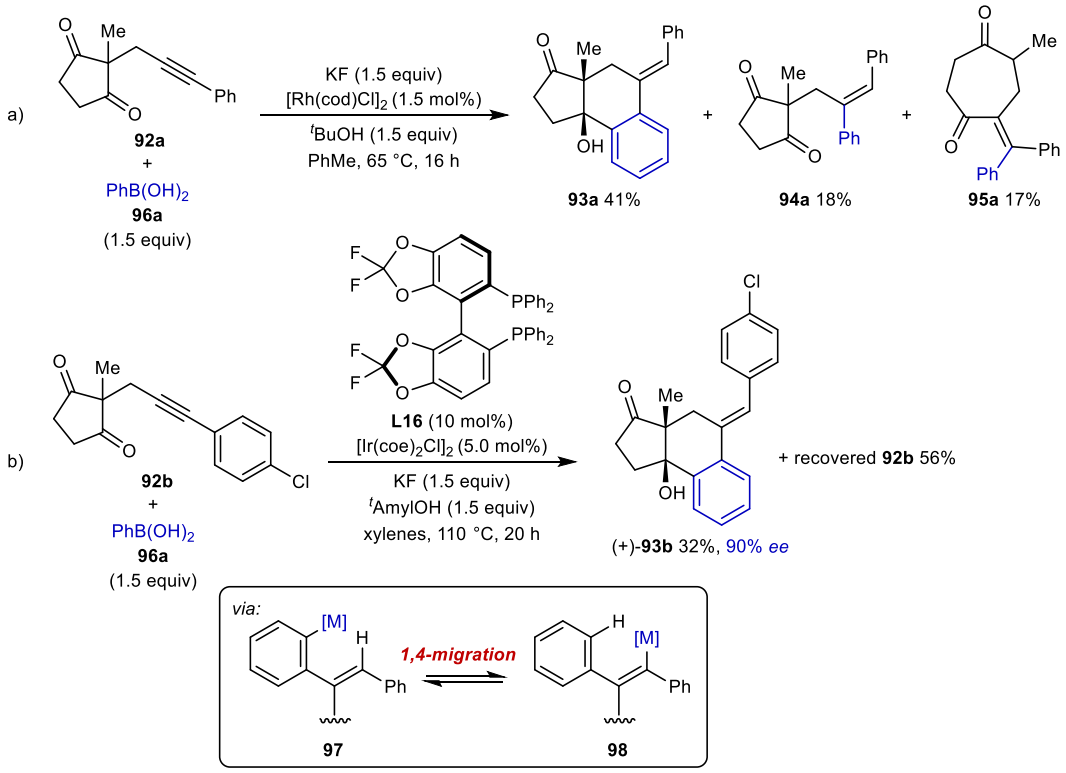
This is well precedented for Pd and Rh whilst methodologies employing other transition metals are also being developed. However, the number of enantioselective examples is extremely limited, with most cases having drawbacks such as poor conversion or yields. Developing this area is important as it has the potential to provide access to complex cores and highly functionalised novel products from simple starting materials in high enantioselectivity.

2.2 Results and Discussion

2.2.1 Project Aims

Over the past few years, the Lam group has been interested in exploiting metal-catalysed 1,4-migration processes in order to transform simple substrates into novel and complex products. The optimum outcome is to construct these structures enantioselectively through the use of a chiral metal catalyst.

The group has previously reported the arylative cyclisation of cyclic alkynone **92a**, with the key 1,4-metal migration step facilitating the formation of tricycle **93a**. Rhodium and iridium have both been reported to catalyse this process, however both routes have significant drawbacks which restrict their utility.[261] Rhodium catalysts gave moderate quantities of **93a**, but also produced significant quantities of side products from hydroarylation **94a** and ring expansion **95a** (Scheme 182a). When switching to iridium, yields of racemic products were improved, but attempts to develop an enantioselective variant were problematic, with only 32% yield of **93b** (albeit in 90% *e.e.*) and significant quantities of recovered starting material (56%) (Scheme 182b).

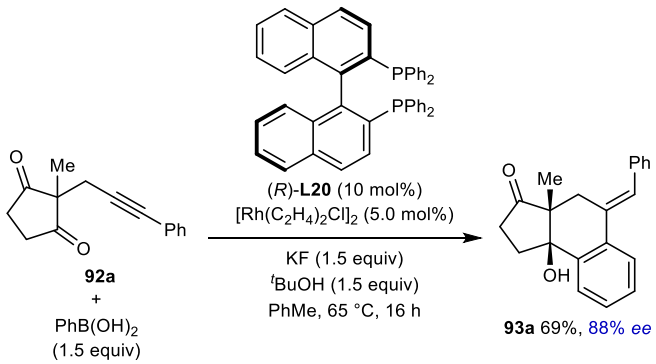


*Scheme 182. Preliminary studies on the Rh- and Ir-catalysed arylative cyclisation of **92** and PhB(OH)$_2$.*

Developing the reaction conditions and finding a suitable rhodium catalyst system may allow the effective formation of these products enantioselectively. After promising initial results with cyclic alkynones, it was hopeful similar conditions could also permit the enantioselective arylative cyclisation of acyclic alkynones.

2.2.2 Initial Results

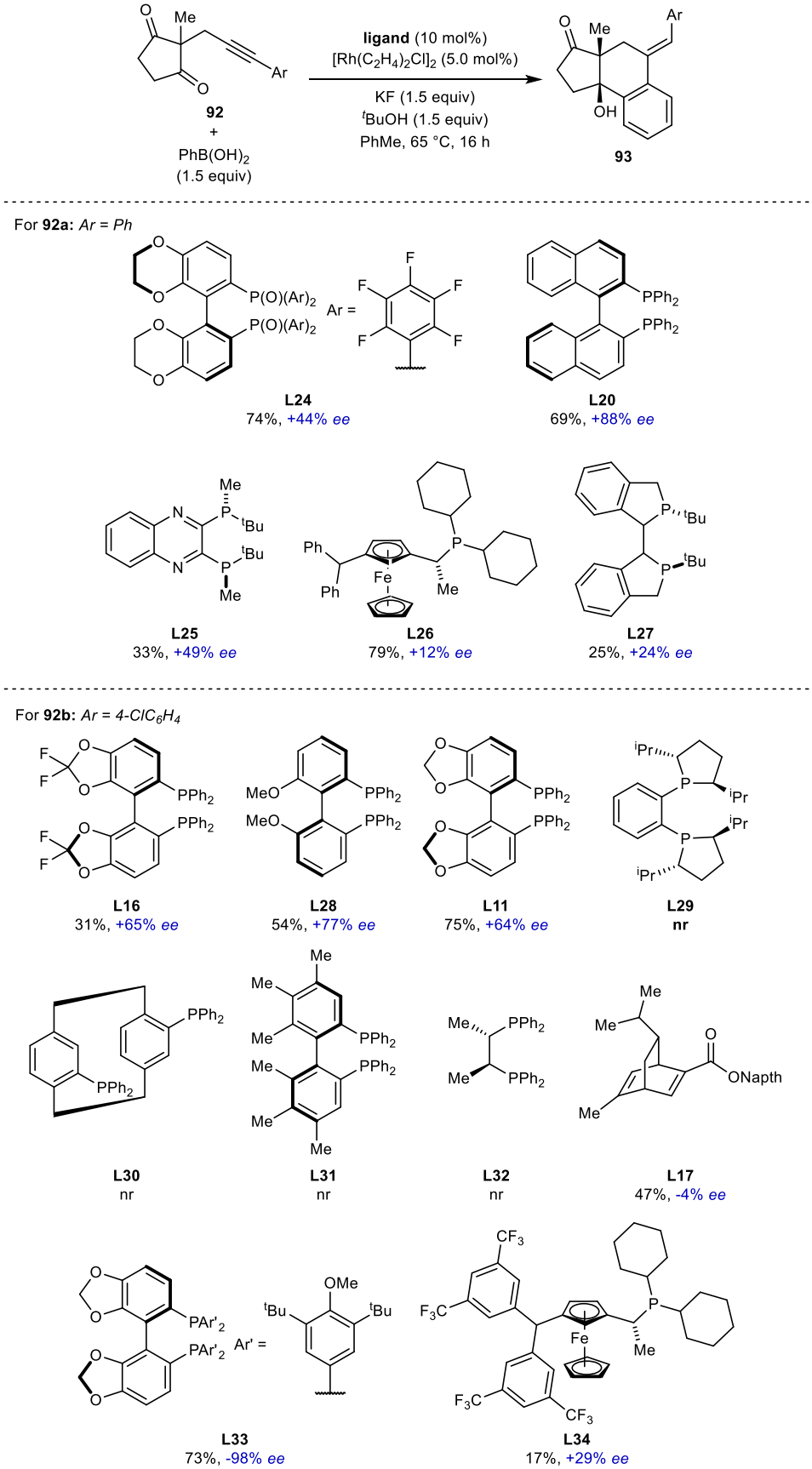
Initial work on developing this enantioselective reaction variant was performed by Dr. Michael Callingham and Hal Parke. It was discovered that addition of bisphosphine ligand (*R*)-BINAP **L20** to the rhodium catalyst system, with KF (1.5 equivalents) and ^{t}BuOH (1.5 equivalents) additives, facilitated the transformation of **92a** into **93a** in 69% yield and 88% *e.e.* (Scheme 183).



*Scheme 183. Rh-bisphosphine catalyst enables efficient conversion to **93a**. Substrate **92a** synthesised by H. Parke. Reaction performed by Dr. M. Callingham.*

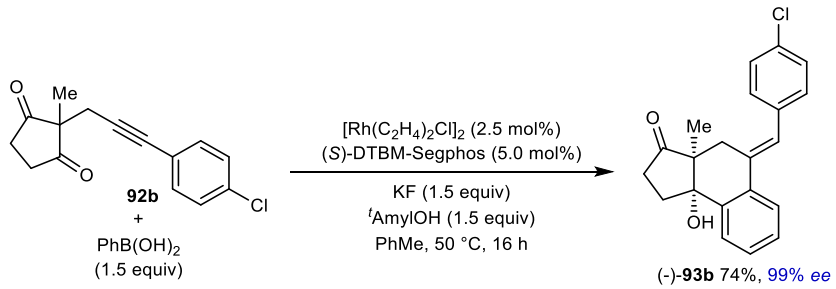
The yield was comparable to the iridium-catalysed version previously reported by the group, and the product was formed in good enantioselectivity, a combination of results that was previously difficult to obtain. In addition, side-products **94a** and **95a** were no longer observed in significant quantities.

The compatibility of a range of bisphosphine ligands was subsequently tested (Scheme 184). While some ligands demonstrated little to no reactivity (**L29-L32**), others gave good conversion but poor enantioselectivity (**L11, L24**). Eventually, this led to the discovery that (*R*)-DTBM-Segphos **L33** gave **93b** in good yield (73%) and exceptional enantioselectivity (98% *e.e.*).



*Scheme 184. (R)-DTBM-Segphos **L33** identified as the optimum ligand. All reactions were performed by Dr. M. Callingham.*

Using (*S*)-**L33**, Hal Parke successfully managed to scale up the enantioselective transformation of **92b** into **93b** (0.3 mmol). Changing the additive from ^{t}BuOH to ^{t}amylOH preserved the yield when the temperature was lowered to 50 °C. The catalyst loading could also be lowered to 2.5 mol% without any effect on the reaction productivity, and (-)-**93b** was isolated in 74% yield and 99% *e.e.* (Scheme 185).

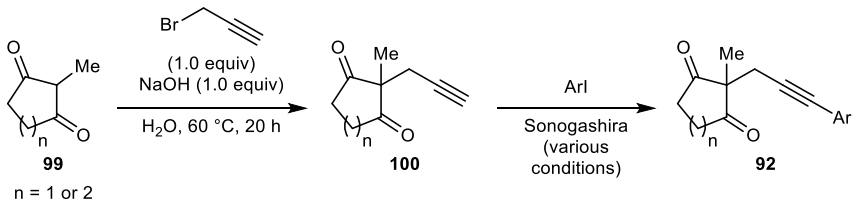


*Scheme 185. Enantioselective Rh-catalysed arylative cyclisation of **92b**. Synthesis of substrate **92b** and cyclisation reaction performed by H. Parke.*

The discovery of these conditions meant that the reaction scope could be further probed to investigate whether various cyclic or acyclic alkynones were tolerated, as well as the boronic acid partner.

2.2.3 Enantioselective Arylative Cyclisation of Cyclic Alkynones

With the optimised conditions in hand, the scope of the reaction was explored on a range of different alkynone substrates **92**. These were typically made from propargylation of cyclic 1,3-diketone **99** followed by a Sonogashira reaction with an aryl iodide to install the aryl group on the alkyne terminus (Scheme 186).

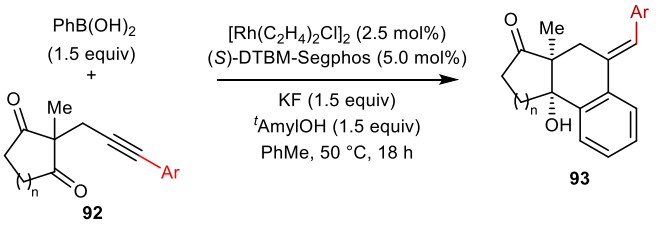


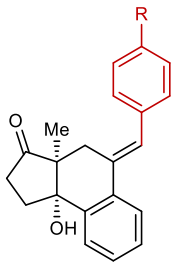
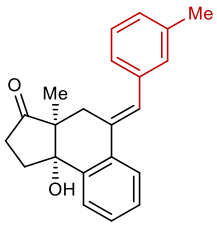
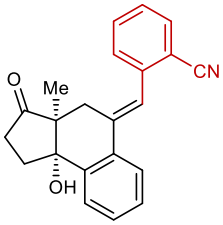
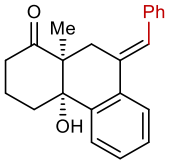
*Scheme 186. Synthesis of alkynone substrates **92**.*

Table 5 shows the effect of varying the aryl group on the alkyne. The corresponding racemic reaction was performed under identical reaction conditions but replacing (*S*)-**L33** with

(rac)-BINAP. Pleasingly, under these conditions, **92a** underwent transformation to **93a** in good yield (69%) and excellent enantioselectivity (99% *e.e.*) (Entry 1), showing comparative results with previously formed **93b** (Entry 2). Other 4-substituted arenes at the alkyne position such as 4-OMe **92c** and 4-NO_2 **92d** were also attempted (Entries 3 and 4). Whilst **93c** was isolated in a moderate yield of 39%, and excellent enantioselectivity (92%), formation of **93d** was more problematic. ^{1}H NMR analysis of the unpurified reaction mixture indicated only 16% yield, even with a higher catalyst loading and a greater excess of $PhB(OH)_2$ and so was not isolated. On further analysis, the enantioselectivty of **93d** was determined to be a moderate 57%. Aryl groups with substituents at other positions were also tested. 3-Me **92e** (Entry 5) gave **93e** in 60% yield and 99% *e.e*. Whilst 2-CN substrate **92f** did give **93f** in 64% yield with 5.0 mol% catalyst loading, the enantioselectivity did drop again, to 61% *e.e.* (Entry 6). This suggested that nitrogen-containing functional groups were not as well tolerated in the reaction, as it is possible they may interact with the Rh centre in a way that perturbs its ability to facilitate efficient reactivity or enantioselectivity. There were no obvious trends for the yields of **93** when varying the aryl group. Finally, six-membered alkynone **92g** was converted into **93g** in 64% yield and 97% *e.e*. (Entry 7).

Table 5. Alkynone scope.



Entry [a]	n	Product	Yield % [b]	*e.e.* %
1	1	 **93a** R = H	69[c]	95
2	1	**93b** R = Cl	74[c]	99
3	1	**93c** R = OMe	39	92
4	1	**93d** R = NO_2	16[d,e,f]	57
5	1	 **93e**	60[d,e]	99
6	1	 **93f**	64[d]	61
7	2	 **93g**	64[c]	97

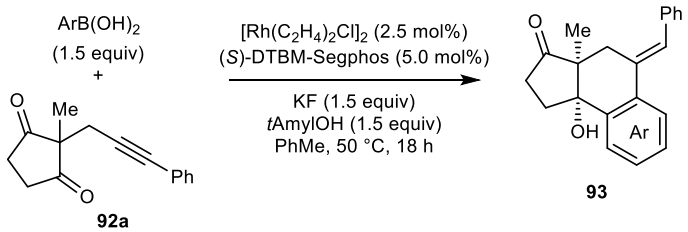
*Substrates **92a-92d** and **92g** were synthesised by H. Parke. [a] Reactions conducted with 0.30 mmol of alkynone. [b] Yield of isolated products. [c] Reaction performed by H. Parke. [d] 5.0 mol% $[Rh(C_2H_4)_2Cl]_2$ used. [e] 2.0 equivalents of $PhB(OH)_2$ used. [f] Yields determined by ^1H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard.*

In most of the examples that are described in this section, small amounts of hydroarylation product **101** (opposite regioselectivity to **94**) and ring expansion product **95** make up most of the remaining mass balance, but generally lower quantities than those in Scheme 182a are observed (*ca.* 20-25% total yield of **95** and **101**). These side-products have

been isolated in one example (see Experimental Section 2.3.3.1 for more information) and ignored for the others.

Subsequent investigation of the reaction of **92a** with a range of aryl boronic acid components delivered products in consistently high enantioselectivities (Table 6). With initial focus on 4-substituted aryl boronic acids, 4-tolyl-, 4-fluorophenyl- and 4-chlorophenylboronic acids gave **93h** (57%), **93i** (65%) and **93j** (65%) in 99%, 99% and 98% *e.e.* respectively (Entries 1-3). A test reaction using 4-bromophenyl boronic acid showed poor conversion and only gave 34% yield of **93k**, even at higher catalyst loadings so was not scaled up. However, HPLC analysis demonstrated the product was still formed as a single enantiomer (Entry 4).

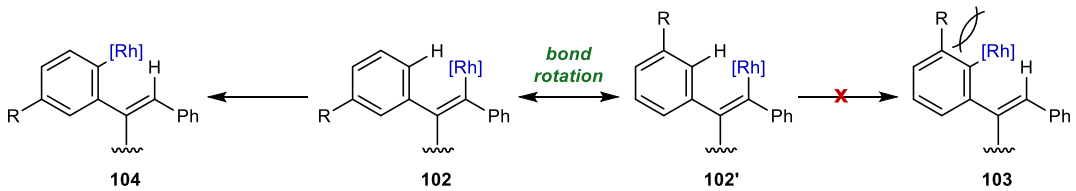
Table 6. Boronic acid scope.



Entry [a]	Ar	Product	Yield % [b]	*e.e.* %
1	4-MeC_6H_4	**93h** R = Me	57	99
2	4-FC_6H_4	**93i** R = F	65[c]	99
3	4-ClC_6H_4	**93j** R = Cl	65	98
4	4-BrC_6H_4	**93k** R = Br	34[c,d,e]	99
5	4-$MeOC_6H_4$	**93l** R = OMe	55[f]	99
6	4-$EtO_2CC_6H_4$	**93m** R = CO_2Et	65[c,g]	99
7	4-$AcOC_6H_4$	**93n** R = OAc	61[c,h]	99
8	3-MeC_6H_4	**93o** R = Me	44	98
9	3-BrC_6H_4	**93p** R = Br	61[f]	99

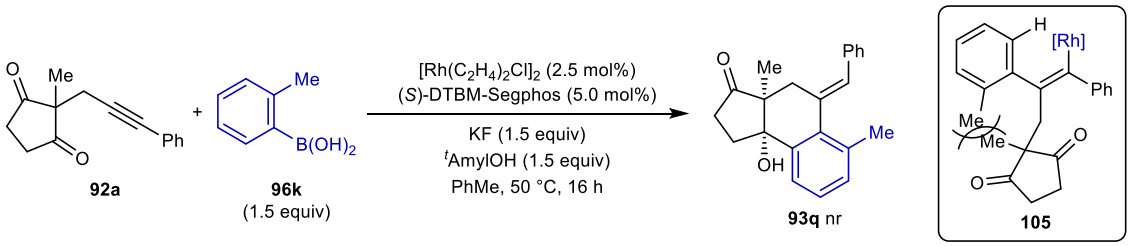
*Substrate **92a** synthesised by H. Parke. [a] Reactions conducted with 0.30 mmol of alkynone. [b] Yield of isolated products. [c] 5.0 mol% $[Rh(C_2H_4)_2Cl]_2$ used. [d] Yield determined by ^1H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard. [e] Reaction conducted with 0.05 mmol of alkynone. [f] Reaction performed by H. Parke. [g] 2.4 equivalents of $ArB(OH)_2$ used. [h] 2.0 equivalents of $ArB(OH)_2$ used.*

Compounds **93l** (55%), **93m** (65%) and **93n** (61%) were all formed from corresponding 4-methoxyphenyl-, 4-ethoxycarbonylphenyl- and 4-acetoxyphenylboronic acids in 99% *e.e.* (Entries 5-7). 3-Substituted aryl boronic acids were also successfully employed. 3-tolyl- and 3-bromophenylboronic acids gave **93o** and **93p** in 44% and 61% yield and 98% and 99% *e.e.* respectively (Entries 8 and 9). Both **93o** and **93p** were isolated as single regioisomers, with no formation of the other product isomers observed. This is presumably due to the favourability of rhodium to avoid steric clash during the 1,4-migration process from **102** to **103**, which would install Rh *ortho*- to the 3-substituent (Scheme 187). It is more likely to favour 1,4-migration from **102** to the position *para*- to the 3-substituent in **104**, which proceeds to from corresponding **93o** or **93p**.



Scheme 187. 3-Substitued aryl boronic acids lead to exclusive formation of one stereoisomer.

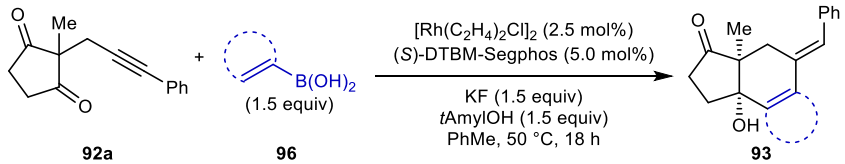
Finally, attempts with a 2-substituted aryl boronic acid were unsuccessful. The reaction of **92a** with 2-tolylboronic acid failed to give **93q**, with *ca.* 60% starting material recovered (Scheme 188). This lack of reactivity suggests that the *ortho*-substituent may restrict addition across the alkyne. In addition, this methyl group may clash with the large tethered 2-methyl-1,3-cyclopentanedione group and suppress the Rh 1,4-migration process by preventing effective oxidative addition of rhodium into the C–H bond in **105**.

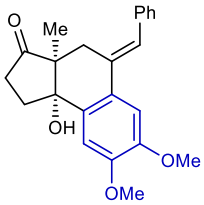
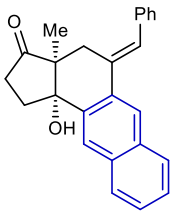
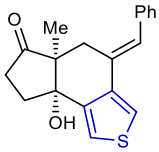
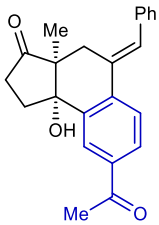
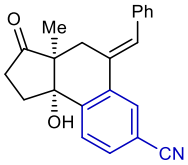
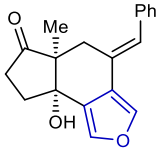


Scheme 188. Ortho substituents not tolerated on the boronic acid moiety.

Further aryl boronic acids were tested with **92a** in Table 7. 3,4-Dimethoxyphenylboronic acid gave **93r** in 46% yield and 99% *e.e.* (Entry 1) and 2-naphthylboronic acid gave **93s** in 64% yield and 95% *e.e.* (Entry 2).

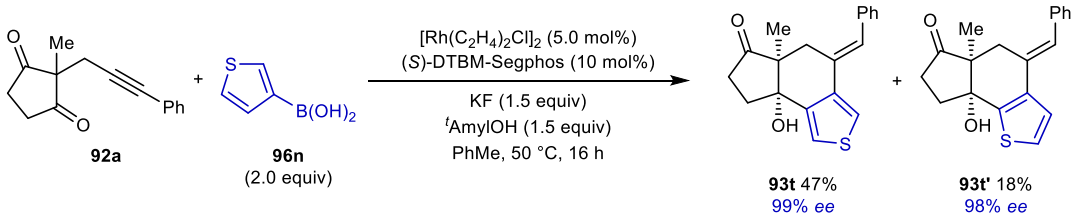
Table 7. Further boronic acid scope.



Entry [a]	R-B(OH)$_2$	Product	Yield % [b]	*e.e.* %
1	3,4-MeOC$_6$H$_3$	 **93r**	46[c,d]	99
2	2-naphthyl	 **93s**	64	95
3	3-thienyl	 **93t**	47[c,d,e]	99
4	4-MeC(O)C$_6$H$_4$	 **93u**	nr[f]	-
5	3-NCC$_6$H$_4$	 **93v**	nr[f]	-
6	3-furanyl	 **93w**	nr[f]	-

*Substrate **92a** synthesised by H. Parke. [a] Reactions conducted with 0.30 mmol of alkynone. [b] Yield of isolated products. [c] 5.0 mol% [Rh(C$_2$H$_4$)$_2$Cl]$_2$ used. [d] 2.0 equivalents of ArB(OH)$_2$ used. [e] The other regioisomer was isolated in 18% yield and 98% e.e. [f] No reaction via ^{1}H NMR analysis of the unpurified reaction mixture with **92a** recovered (using racemic conditions with rac-BINAP ligand).*

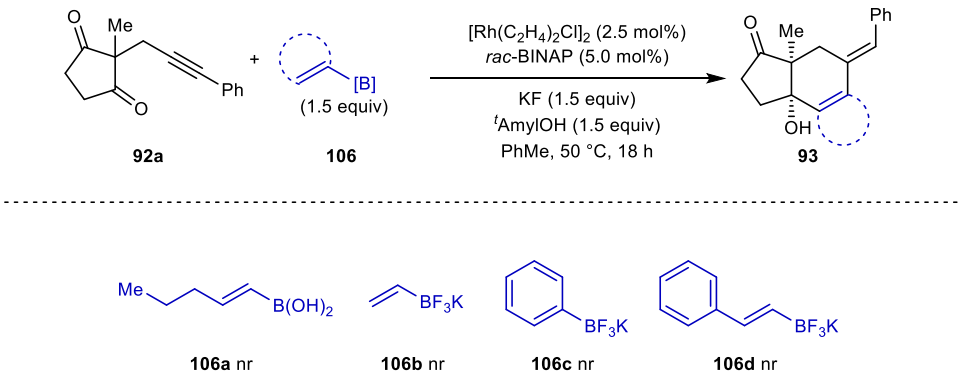
3-Thienylboronic acid was also compatible with the reaction conditions, giving **93t** in 47% yield as a single enantiomer, demonstrating Rh 1,4-migration onto a heteroaromatic ring was also possible (Entry 3). Interestingly, this was not the only cyclisation product formed, with the other regioisomer **93t'** (via Rh 1,4-migration to the 2-thienyl position instead of the 4-thienyl position) also isolated in 18% yield and 98% *e.e.* (Scheme 189).



Scheme 189. Arylative cyclisation with 3-thienylboronic acid gives two product regioisomers.

4-Acetylphenyl-, 3-cyanophenyl- and 3-furanylboronic acids all demonstrated no reactivity under the racemic reaction conditions (Entries 4-6) and so were not tested enantioselectively in order to preserve the valuable (*S*)-DTBM-Segphos ligand.

It was also desired to investigate whether the rhodium could undergo 1,4-migration onto non-aryl sp^2 carbons, which would significantly broaden the scope of the reaction (Scheme 190).

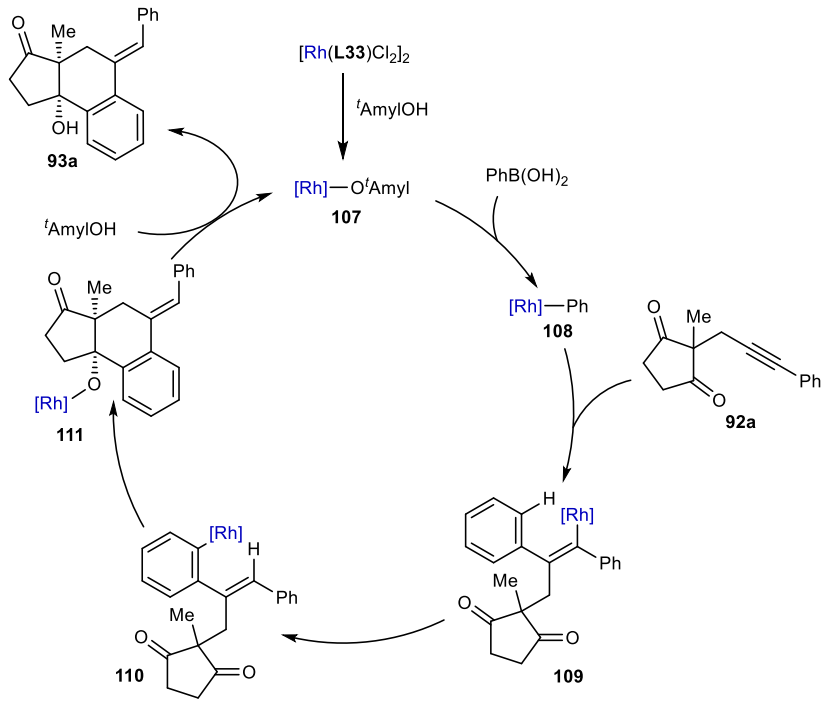


Scheme 190. Rh 1,4-migration to non-aryl sp^2 carbons.

Vinyl boronic acid **106a** demonstrated no desired reactivity, with only trace amounts of hydroarylation side-products. As simple vinyl boronic acid was unstable, the corresponding trifluoroborate salt **106b** was tested. This would elucidate whether other organoboron sources were tolerated under the reaction conditions. Unfortunately, no product was observed on reaction with **92a**. Phenyltrifluoroborate **106c** was then used to confirm whether this was down

to the Rh 1,4-migration step being unfavourable, or issues with the BF_3K group reacting with Rh to form the organorhodium species. No **93a** was formed which suggested compatibility issues with trifluoroborates. **106d** also gave no reactivity. In all cases, starting material **92a** was recovered.

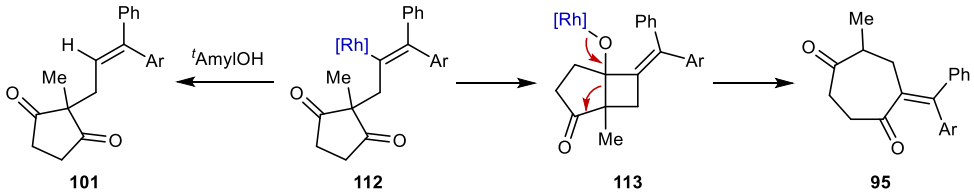
A catalytic cycle for the reaction was proposed using $PhB(OH)_2$ and **92a** as the model substrate (Scheme 191). This cycle is similar to the one proposed by the Lam group in the Ir-catalysed variant of this cyclisation. Reaction of [Rh(**L33**)Cl]$_2$ with ^{t}amylOH gives rhodium alkoxide **107**, which undergoes KF assisted transmetalation with $PhB(OH)_2$ to give **108**. This arylrhodium species then undergoes regioselective addition across the alkyne in **92a** to form alkenyl rhodium species **109**. This is followed by the key alkenyl-to-aryl 1,4-migration step to give species **110**, which is now able to attack one of the carbonyl groups in the tethered 2-methyl-1,3-cyclopentanedione moiety. The resulting rhodium alkoxide **111** can react with another molecule of ^{t}amylOH to give **93a** and reform **107** to complete the cycle.



Scheme 191. Proposed catalytic cycle.

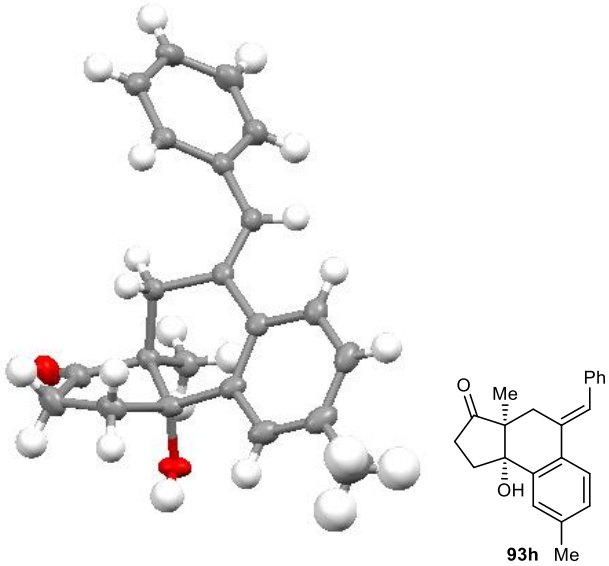
As previously mentioned, small quantities of hydroarylation and ring expansion side-products **95** and **101** are also formed in varying ratios. These products are formed when the aryl rhodium species **108** adds across the alkyne with the opposite regioselectivity to give **112** (Scheme 192). This intermediate can then undergo protonolysis with ^{t}amylOH to give **101** or

alternatively attack one of the carbonyl groups to form 4,5-bicycle **113**, which experiences a reverse aldol type C–C bond cleavage to ultimately give seven-membered product **95**.



*Scheme 192. Mechanistic rationale for the formation of **95** and **101**.*

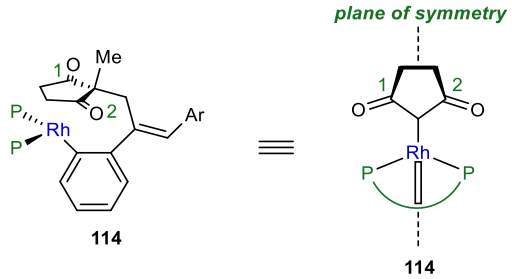
Pleasingly, a single crystal of **93h** was grown using a pentane/CH_2Cl_2 solvent system and submitted for X-ray crystal analysis to confirm the absolute stereochemical configuration of the product. Both stereocentres formed were found to possess *S*-configuration (Scheme 193).



*Scheme 193. Structure of **93h** as determined by X-ray crystallography. Sample ran by Dr. Laurence Taylor.*

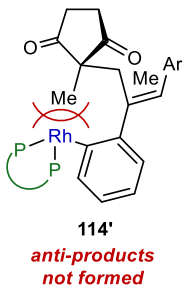
This result can be used to speculate on the observed stereochemical outcome (Scheme 194). Aryl rhodium species **110** orientates itself so that the rhodium centre can access one of the two carbonyl groups by occupying a symmetrical transition state **114**.[260] With a racemic catalyst, as represented with a generic racemic *bis*-phosphine ligand in **114**, attack at both carbonyls"1" and "2" are equally favoured. The chiral ligand is what introduces an asymmetric

environment, inflicting an energy difference between the pathways to the two enantiomers and is responsible for desymmetrisation.



*Scheme 194. Desymmetrisation of **114** is the proposed enantiodetermining step.*

The relative stereochemistry appears to be fixed by the position of the methyl group on the quaternary *α*-carbon which spaces itself away from the catalyst (Scheme 195). The opposite orientation would allow formation of the *anti*-diastereoisomers, however without this exact methyl orientation, the carbonyls are further away from the Rh centre and the methyl group may hinder a particular carbonyl group's approach towards Rh (see **114'**) meaning only the *syn*-diastereoisomer products are accessible.[260]



Scheme 195. Rationalisation of relative stereochemistry.

Computational modelling and analysis of the various transition states would need to be performed in order to determine the precise origins of the preferential formation of the (-)-enantiomer, but presumably, it is formed via *si*-face attack of carbonyl "1" in **114**. Without this more detailed analysis, it is proposed that the aryl groups on the (*S*)-DTBM-Segphos ligand provide a chiral environment similar to other chiral Rh-*bis*-phosphine catalyst systems that ultimately favours the formation of (-)-**93**.[262, 263]

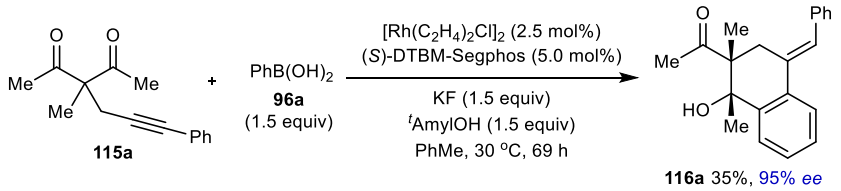
2.2.4 Enantioselective Arylative Cyclisation of Acyclic Alkynones

Whilst the rhodium-catalysed enantioselective arylative cyclisation of alkynones to give **93** has been extensively demonstrated over the previous section in good yields and excellent enantioselectivities, the reaction scope discussed was limited to cyclic alkynones. If this methodology could be applied to acyclic alkynones with similar success, then a different class of bicyclic compounds with a tetrahydronaphthylene core could also be accessed.

This was anticipated to be slightly more complicated than for cyclic substrates, as distinction between the two now freely rotating ketones from the Rh catalyst would likely be difficult as the pathways to the two product enantiomers was predicted to be much closer in energy. In addition, the ketones in the cyclic substrates are 'pinned back' by their existence in a cyclopentane ring, making them slightly more reactive than their acyclic derivatives.

2.2.4.1 Reaction Optimisation

As a starting point, **115a** was synthesised and subjected to the usual reaction conditions with $PhB(OH)_2$ from Section 2.2.3. As initially feared, a significant loss of reactivity was observed, and 35% of desired product **116a** was isolated but only by lowering the reaction temperature to 30 °C and after a prolonged reaction time of 69 h. The remaining composition of the unpurified reaction mixture was unreacted **115a**. However, the stereoselectivity was encouraging, with **116a** being obtained as a single diastereoisomer and in 95% *e.e.* (Scheme 196).



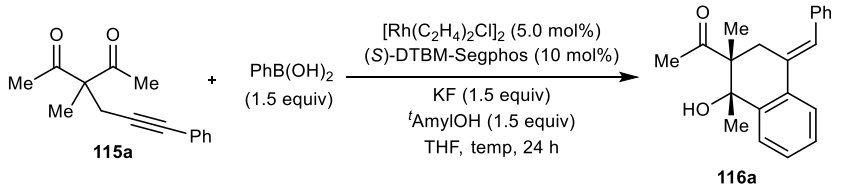
*Scheme 196. Initial reaction of acyclic alkynone **115a** with the reaction conditions used in Section 2.2.3. Reaction performed by H. Parke.*

Elevated temperatures resulted in significant loss of enantiocontrol; at 50 °C there was a drop in *e.e.* of *ca.* 40%. It was then proposed that modifying the reaction conditions may lead to more success in forming **116a**. This optimisation was performed in collaboration with Dr. Jinwei Sun.

Changing the reaction solvent to THF and increasing the catalyst loading to 5.0 mol% of Rh and 10 mol% of (*S*)-**L33**, saw formation of **116a** in a similar yield to Scheme 196 (30%), but at 50 °C and with no degradation of the product enantioselectivity (96% *e.e.*) under a more

practical reaction time (24 h). This was a promising starting point (Table 8, Entry 1). Increasing the temperature to 80 °C (Entries 2-4) saw gradual improvement in the yield of **116a**. In fact, 80 °C was determined to be the optimum temperature, with 67% yield of **116a** and 96% *e.e.* (Entry 4). Higher temperatures saw decomposition of products and lower yields (Entry 5). Finally, increasing the quantity of boronic acid used to 2.0 equivalents gave 66% isolated yield of **116a** in 94% *e.e.* on a 0.3 mmol scale (Entry 7), a result that was both comparable with the cyclic alkynone products **93** and a significant improvement on initial results.

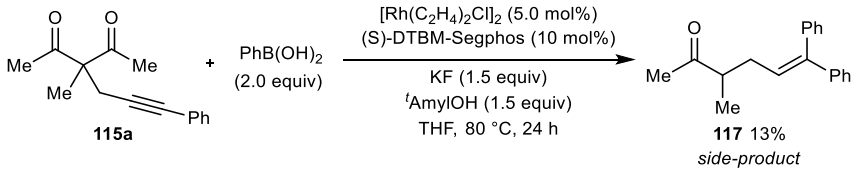
Table 8. Reaction optimisation.



Entry [a]	Temp °C	Solvent	Yield % [b]	*e.e.* %
1	50	THF	30	96
2	60	THF	38[c]	98
3	70	THF	54	95
4	80	THF	67	96
5	100	THF	48[c]	95
6	80	THF	70[d]	96
7[e]	80	THF	66[c,d,f]	94

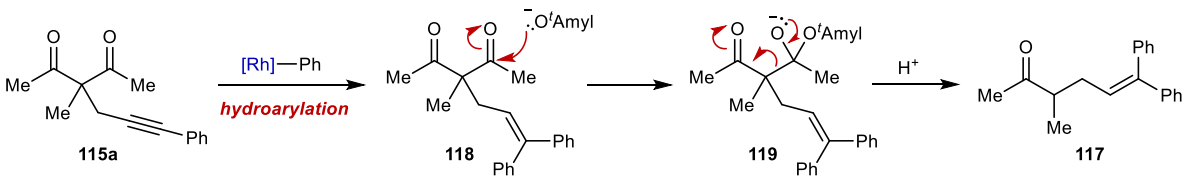
*[a] Reaction conducted with 0.05 mmol of alkynone. [b] Yields determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard, with **116a** observed as a single diastereoisomer in all cases. [c] Reaction performed by Dr. J. Sun. [d] 2.0 equivalents of PhB(OH)$_2$ used. [e] Reaction conducted on 0.30 mmol of alkynone. [f] Isolated yield.*

In this reaction and the majority of those that follow, there were no obvious side-products (such as hydroarylation of **115**, etc) observable in the crude ^{1}H NMR spectra. For **116a**, a small quantity of a side-product was isolated by column chromatography and on further analysis was determined to be **117** in 13% yield (see Experimental Section 2.3.3.2 for more information). **117** appeared to be the result of hydroarylation via the opposite regioselectivity along with loss of one of the 1,3-dicarbonyl ketones (Scheme 197). The impurity was not clearly observed in the crude ^{1}H NMR spectra of any other examples in this work, and as a result was not isolated for any other example.



*Scheme 197. Isolation of side-product **117**.*

A possible mechanism for the formation of **117** could involve hydroarylation of **115a** with the opposite regiochemistry to give **118** after protonation, followed by attack of an ^{t}amyl alkoxide to one of the ketones to form **119** (Scheme 198). Finally, a retro-Claisen mechanism may rationalise loss of one carbonyl group to form **117**. However, it may also be possible that the order of these two sequences were swapped.



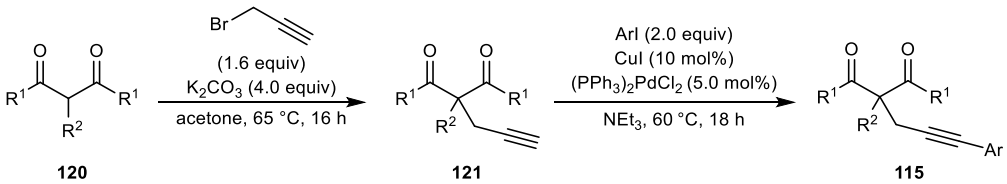
*Scheme 198. Possible mechanism for the formation of **117**.*

Further screening by Dr. Jinwei Sun showed that the conditions used in Entry 7 (Table 8) were optimal. A variety of solvents, including dioxane, 2-Me-THF, MeCN, MeOH, THF and mixtures of THF:H_2O and dioxane:H_2O all gave no conversion or access to **116a** in poor yields. Other ligands gave lower yields and enantioselectivities with selected examples including (*R*)-BINAP, (*R*)-MeO-BIPHEP (**L20** and **L28** in ligand Scheme 184) and (*R*)-DM-Segphos. Varying the additive (^{t}BuOH) and base (K_3PO_4, Cs_2CO_3, NEt_3 and ^{t}BuOK) used also saw decreasing yields of **116a**. Finally, replacing KF with K_2CO_3 sometimes gave comparative *e.e.*'s but often had a detrimental effect on the yields when different substrates were tried. It was decided that KF would be retained as the base of choice as it gave far more consistent results.

Finally, control reactions showed that the rhodium:ligand catalyst system was vital for the successful reaction, and whilst **116a** is formed in the individual absences of both KF and ^{t}amylOH, the yield is *ca.* 10-20% higher when both are present.

2.2.4.2 Substrate Scope

With the optimised reaction conditions in hand, the acyclic alkynone substrate scope was explored. A range of substrates **115** were synthesised, again via propargylation of 1,3-diketones **120** followed by a Sonogashira reaction with an aryl iodide (Scheme 199).



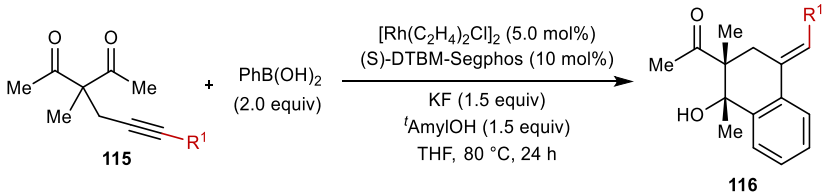
*Scheme 199. Synthesis of substrates **115**.*

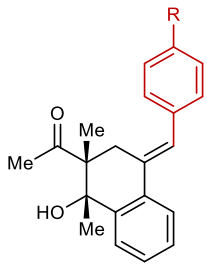
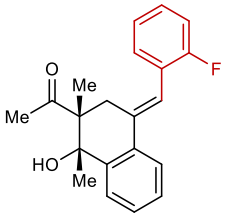
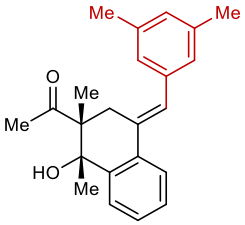
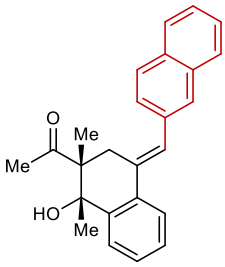
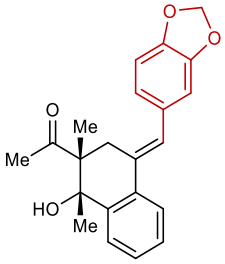
The substrate scope investigation commenced with variation of the aryl group on the alkyne (Table 9). A range of substrates with 4-aryl substituents **115b-115e** were subjected to the reaction conditions. All gave full conversion to the corresponding bicycle, with **116b** (71%), **116c** (77%), **116d** (65%) and **116e** (52%) isolated in 66-84% *e.e.* (Entries 2-5). 2-fluoro (**115f**) and 3,5-dimethyl (**115g**) substrates were also compatible, giving **116f** and **116g** in 86% and 73% yield and 74% and 75% *e.e.* respectively (Entries 6-7). 2-Naphthyl substrate **115h** gave **116h** in 70% yield and 93% *e.e.* (Entry 8) and 1,3-benzodioxole derivative **115i** gave **116i** in 50% yield and 99% *e.e.* when the temperature was lowered to 60 °C (Entry 9). Heteroarenes were also tolerated at this position, with 2-thienyl and 2-pyridyl substrates **115j** and **115k** converted to **116j** (63% yield, 81% *e.e.*) and **116k** (32% yield, 83% *e.e.*) (Entries 10 and 11).

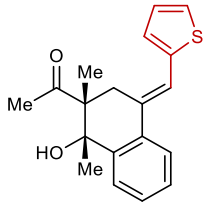
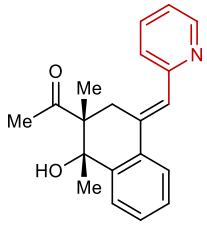
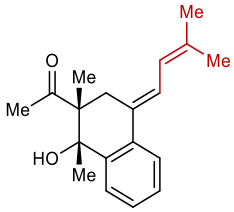
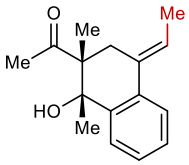
The racemic versions of these reactions were performed using slightly different reaction conditions with $[Rh(cod)Cl]_2$ used as the catalyst (see Experimental Section 2.3.3.2 for more information).

Overall, there does not appear to be an obvious trend in the yields and *e.e.*'s of **116** when the aryl group of **115** is varied. Whilst the yields usually remained >60% with a few exceptions, the *e.e.*'s did drop to below 80% in some examples, with no obvious reasons why. For all examples, all commercial reagents, including $PhB(OH)_2$, were used as received. However, it was later discovered, right before the thesis submission period, that using repurified $PhB(OH)_2$ gave **116f** in 74% yield and 97% *e.e.* (see the parentheses in Table 9, Entry 6) This suggested that the purity of the boronic acid was important for the enantioselectivity of the reaction. Further investigations into this issue are currently ongoing.

Table 9. Alkynone scope – R^1 variation.



Entry [a]	Product		Yield % [b]	*e.e.* %
1		**116a** R = H	66[c]	94
2		**116b** R = Me	71	84
3		**116c** R = Cl	77	73
4		**116d** R = OMe	65	66
5		**116e** R = Ph	52[c]	84
6		**116f**	86 [74*]	74 [97*]
7		**116g**	73	75
8		**116h**	70[c]	93
9		**116i**	50[c,d]	99

10		**116j**	63	81
11		**116k**	32[c]	83
12		**116l**	nr[e]	-
13		**116m**	nr[e]	-

*Substrates **115e**, **115h**, **115i** and **115k** were synthesised by Dr. J. Sun. *Yield and e.e. of **116f** with repurified $PhB(OH)_2$ stirred in Et_2O/H_2O at room temperature for 16 h. [a] Reactions conducted with 0.30 mmol of alkynone. [b] Yield of isolated products, which were observed as a single diastereoisomer in all cases via ^1H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Reaction performed by Dr. J. Sun. [d] Reaction performed at 60 °C. [e] No reaction via ^1H NMR spectroscopic analysis of the unpurified reaction mixture, with starting material recovered (using amended conditions – see experimental section 2.3.3.2 for more information).*

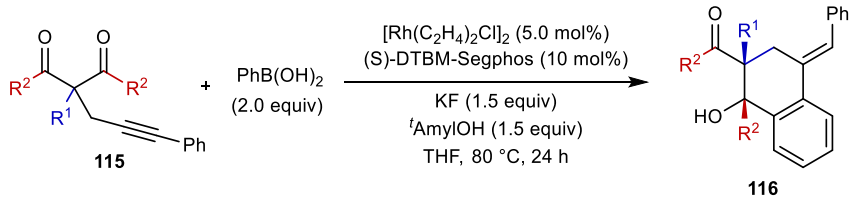
No reactivity was observed when the aryl group on the alkyne was replaced with other groups such as in enyne **115l** (Entry 12) or with a simple methyl group as in **115m** (Entry 13). The reactions with these substrates were tested using achiral $[Rh(cod)Cl]_2$ catalyst and due to the lack of success, reaction with the valuable (*S*)-DTBM-Segphos ligand was not performed.

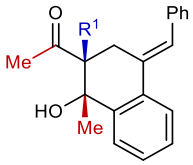
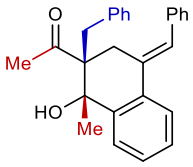
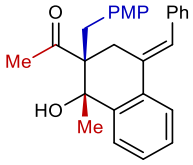
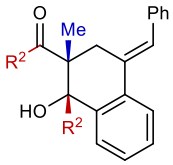
Further evaluation of the substrate scope was carried out, with variation of the R^1 α-group and the R^2 ketone groups (Table 10). Extending the alkyl chain length of the R^1 group was attempted first, with ethyl (**115n**) and ^{n}butyl (**115o**) substrates giving **116n** and **116o** in 71% and 36% yield and 97% and 87% *e.e.* respectively (Entries 2-3). These reactions were

carried out at a slightly lower reaction temperature of 60 °C as the *e.e.* for these substrates appeared to decrease at higher temperatures (at 80 °C, **116o** was formed in 63% ^{1}H NMR yield, with 1,4-dimethoxybenzene used as an internal standard, and just 38% *e.e.*). Similar modified conditions were required for benzylic substrates **115p** and **115q**. At 60 °C **116p** and **116q** were obtained in 54% and 51% yields and 91% and 96% *e.e.* (Entries 4-5). At 80 °C, **116q** was observed in both lower yields (43% ^{1}H NMR yield) and enantioselectivity (83% *e.e.*).

With the R^1 group fixed as a methyl group, the R^2 ketone groups were then varied. When R^2 was an ethyl group, the compound **116r** was isolated in 68% yield and 86% *e.e.* (Entry 6). When phenyl ketones were used instead, **116s** was obtained in 47% yield (Entry 7), but unfortunately the *e.e.* decreased significantly to only 31%. The origin of this decrease in enantioselectivity is unknown, but perhaps the size of the phenyl groups on the ketones restrict the efficacy of the substrate to perform an enantioselective reaction.

Table 10. Further alkynone scope.

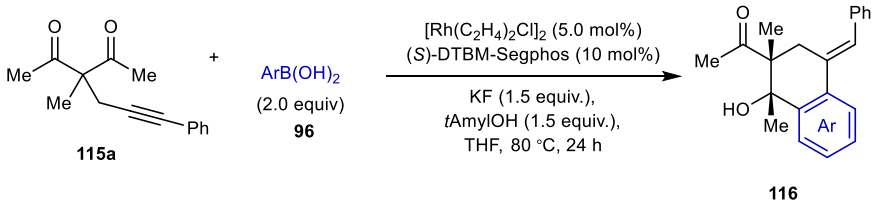


Entry [a]	Product	Yield % [b]	*e.e.* %
1	 **116a** R^1 = Me	66[c]	94
2	**116n** R^1 = Et	71[c,d]	97
3	**116o** R^1 = ^{n}Bu	36[d]	87
4	 **116p**	54[c,d]	91
5	 **116q**	51[d]	96
6	 **116r** R^2 = Et	68[c]	86
7	**116s** R^2 = Ph	47[c]	31

*Substrates **115n**, **115r** and **115s** were synthesised by Dr. J. Sun. [a] Reactions conducted with 0.30 mmol of alkynone. [b] Yield of isolated products, which were observed as a single diastereoisomer in all cases via ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Reaction performed by Dr. J. Sun. [d] Reaction performed at 60 °C.*

The boronic acid scope was also investigated using the reaction with **115a** as a model substrate (Table 11). A range of 4-substitued boronic acids were found to give the desired cyclisation products in good yields and enantioselectivities. 4-Tolyl-, 4-fluorophenyl-, 4-chlorophenyl- and 4-methoxyphenylboronic acid gave **116t** (59%), **116u** (74%), **116v** (52%) and **116w** (53%) in excellent enantioselectivities (88-96% *e.e.*) (Entries 1-4). Likewise, 3-tolylboronic acid gave **116x** as a single regioisomer in 74% yield and 90% *e.e.* (Entry 5).

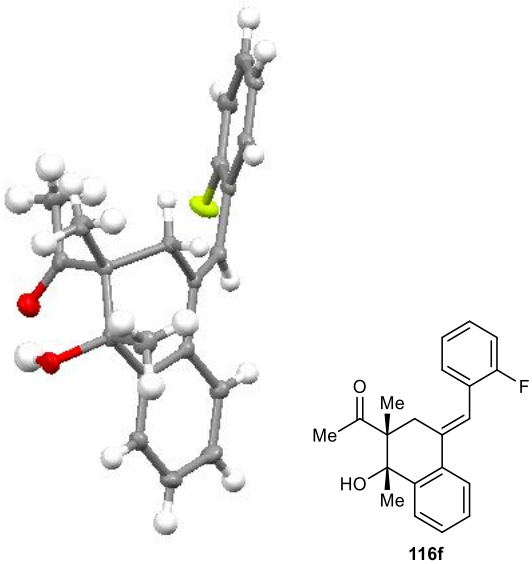
Table 11. Boronic acid scope.



Entry [a]	R-B(OH)$_2$	Product	Yield % [b]	*e.e.* %
1	4-MeC_6H_4	**116t** R = Me	59[c]	94
2	4-FC_6H_4	**116u** R = F	74	93
3	4-ClC_6H_4	**116v** R = Cl	52[c]	88
4	4-MeOC_6H_4	**116w** R = OMe	53	96
5	3-MeC_6H_4	**116x**	74	90

[a] Reactions conducted with 0.30 mmol of alkynone. [b] Yield of isolated products, which were observed as a single diastereoisomer in all cases via ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Reaction performed by Dr. J. Sun.

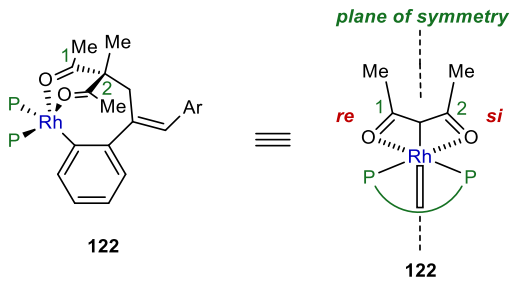
The reaction mechanism is proposed to be very similar to the catalytic cycle previously proposed for cyclic substrates in Scheme 191 and there is believed to be no difference apart from the substrate used. With the cyclic alkynone substrates **92**, the alcohol and methyl groups ended up on the same face of the fused 6,5-ring junction in tricyclic products **93**, as a result of the aryl rhodium species limited to attacking the carbonyl groups in the cyclopentanedione ring from only one face. However, with both carbonyls independent and freely moving in space in **115**, the configuration of **116** may differ in either its relative or absolute stereochemistry. In order to investigate this, a single crystal of **116f** was grown using a pentane/CH_2Cl_2 solvent system and submitted for X-ray crystal analysis (Scheme 200).



*Scheme 200. Structure of **116f** as determined by X-ray crystallography. Sample ran by Dr. Laurence Taylor.*

This analysis supports the product configuration as being (1*S*,2*R*)-**116f**, making it different to the cyclic alkynone substrates as the methyl and OH functional groups now end up on opposite sides of the newly formed six-membered ring, with both methyl groups possessing a *syn*- relationship.

This stereochemical outcome can be rationalised using a similar desymmetrisation model to the one used for cyclic alkynones in Scheme 194. In this scenario, however, the two carbonyls are independent of each other as they are not locked in a bulky five-membered ring and are far more flexible with a greater degree of freedom. Using this model, it is possible that both carbonyls could coordinate to the Rh centre as in **122** (Scheme 201). This would allow discrimination between each group's two diastereotopic faces: in either case, the aryl rhodium nucleophile must attack from the *re*-face of carbonyl "1" or the *si*-face of carbonyl "2".



*Scheme 201. Desymmetrisation of **122** is the proposed enantiodetermining step.*

The methyl group on the α-carbon likely plays a very similar role to Scheme 195, orientating itself as far away from the Rh centre as possible to minimise and hinderance in the approach of the carbonyl groups. This is also ultimately responsible for the observed *syn*-methyl diastereoselectivity (compared to **93**).

Similar to cyclic alkynones, attack at both carbonyls "1" and "2" are equally viable when a non-enantioselective catalyst is used. However, in this scenario, the absolute configuration of **116f** suggests that the latter *si*-face attack of carbonyl "2" is favoured. Likewise with the cyclic alkynone substrates, more detailed computational modelling and analysis of the various transition states with the chiral Rh-(*S*)-DTBM-Segphos catalyst system would be needed to determine the exact origins of the preferential formation of (1*S*,2*R*)-**116**.[262, 263]

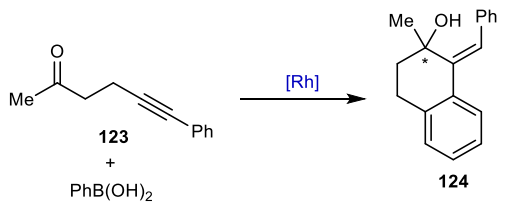
2.2.5 Conclusions and Future Work

In summary, the enantioselective arylative cyclisation of alkynones with aryl boronic acids has been described, exploiting a rhodium-catalysed 1,4-alkenyl-to-aryl migration to relay the reactivity to different parts of the molecule. Building on initial results, the substrate scope was probed using a variety of cyclic alkynones **92** and boronic acids to synthesise complex tricyclic cores **93** using this methodology, in good yields and excellent enantioselectivities (up to 99% *e.e.*).

A slight modification to the reaction conditions allowed the preparation of tetrahydronaphthylene compounds **116** from acyclic alkynones **115** in comparable yields and enantioselectivities (up to 99% *e.e.*). X-ray crystallography determined the absolute configurations of both **93** and **116**.

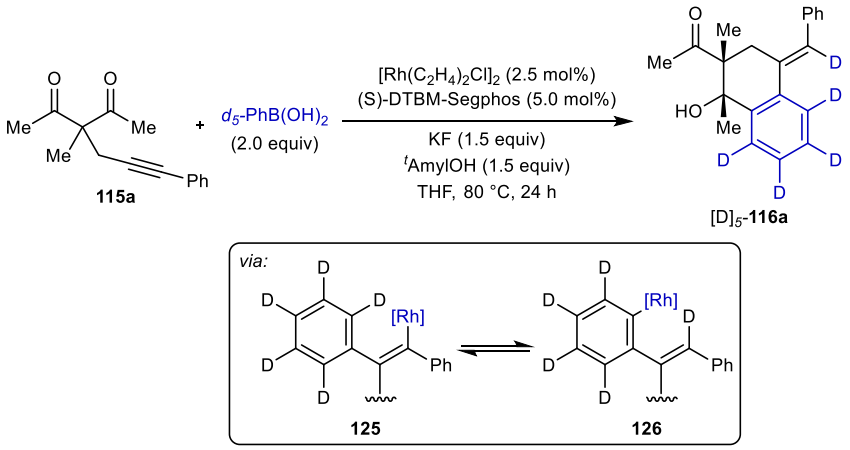
Further investigation into this work would prioritise investigating the enantioselectivity issues observed with $PhB(OH)_2$, as briefly mentioned in Section 2.2.4.2. Repetition of some entries with repurified $PhB(OH)_2$ may indicate if the *e.e.*'s are reproducible or can be further improved.

Other substrates could also be tried to further expand the scope. For example, the arylative cyclisation of mono-alkynone **123** would provide access to a slightly simpler tetrahydronaphthylene core **124** (Scheme 202).



Scheme 202. Application to other substrates would expand the scope of this methodology.

In addition, alternative boron sources such as boronate esters could be tested. Finally, some mechanistic investigations would confirm the accuracy of the proposed catalytic cycle. Using d_5-phenylboronic acid, successful Rh 1,4-migration would see one of the deuterium atoms end up on at the alkenyl position (Scheme 203).



Scheme 203. Deuterium labelling experiments to confirm Rh 1,4-migration mechanism.

2.3 Experimental

2.3.1 General Information

All commercially available reagents were used as received. Anhydrous THF was dried and purified by passage through activated alumina columns using a solvent purification system. Anhydrous dioxane (stored on molecular sieves) was purchased from Sigma-Aldrich (product 296309). “Petroleum ether” refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40–60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or vanillin solution as appropriate. Column chromatography was carried out using silica gel (Fisher Scientific 60Å) particle size 35-70 micron or using an Interchim Puriflash 430 Series automated purification system with IR-50SI 50µm pre-packed columns. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Nicolet Avatar 360 FT instrument on the neat compound using an attenuated total reflection (ATR) accessory with a diamond crystal and a germanium sample plate.

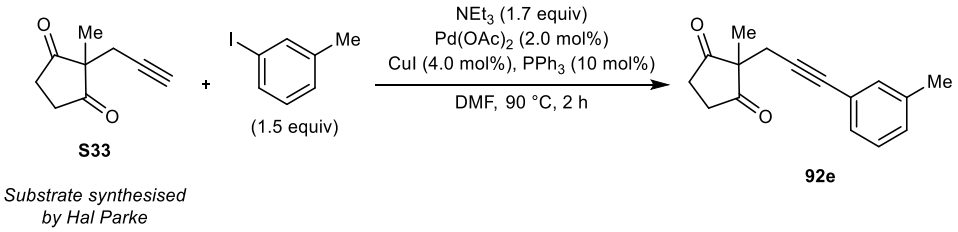
NMR spectra were acquired on Bruker AV400, Bruker AV(III)400HD, Bruker DPX400, Bruker AV500 or Bruker AV(III)500HD spectrometers. ^{1}H and ^{13}C NMR spectra were referenced to tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported 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. Abbreviations used in the description of resonances are: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), app (apparent), br (broad), m (multiplet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ^{19}F NMR spectra were recorded on a Bruker AV(III)400 (376 MHz) spectrometer and were referenced through the solvent lock (^{2}H) signal according to the IUPAC-recommended secondary referencing method using Bruker protocols.

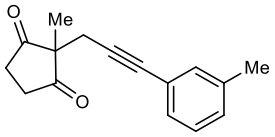
High-resolution mass spectra were recorded using electrospray ionization (ESI) or electron impact ionization (EI) techniques. X-ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuKα radiation. Chiral HPLC analysis was performed on an Agilent 1290 series instrument using 4.6 × 250 mm columns.

2.3.2 Preparation of Substrates

2.3.2.1 Cyclic Alkynones

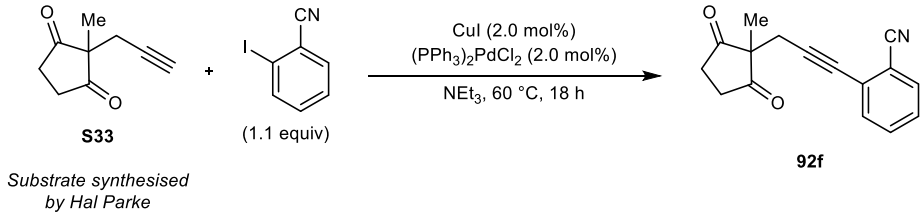
Preparation of Substrate 92e

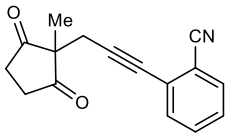




2-Methyl-2-(3-(m-tolyl)prop-2-yn-1-yl)cyclopentane-1,3-dione (92e). Alkynone **92e** was prepared by a Sonogashira coupling of **S33** (451 mg, 3.00 mmol) with 3-iodotoluene (578 µL, 4.50 mmol) according to a literature procedure (402 mg, 56%).[261] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.08 (4H, m, Ar**H**), 2.89-2.77 (4H, m, C**H**$_2$C**H**$_2$), 2.68 (2H, s, C**H**$_2$C≡C), 2.31 (3H, s, ArC**H**$_3$), 1.18 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.6 (2 × C), 138.0 (C), 132.2 (CH), 129.2 (CH), 128.7 (CH), 128.2 (CH), 122.3 (C), 83.5 (C), 83.0 (C), 55.5 (C), 36.0 (2 × CH_2), 26.0 (CH_2), 21.1 (CH_3), 18.9 (CH_3). Spectroscopic data matched those reported previously.[261]

Preparation of Substrate 92f

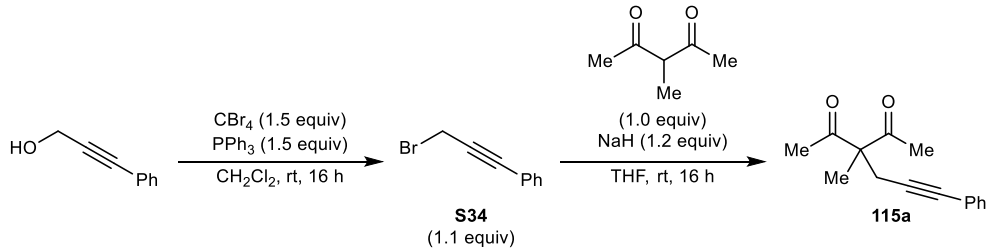


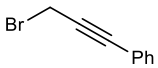


2-(3-(1-Methyl-2,5-dioxocyclopentyl)prop-1-yn-1-yl)benzonitrile (92f). Alkynone **92f** was prepared by a Sonogashira coupling of **S33** (451 mg, 3.00 mmol) with 2-iodobenzonitrile (601 mg, 3.30 mmol) according to a literature procedure (523 mg, 70%).[261] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, dd, *J* = 7.8, 1.3 Hz, Ar**H**), 7.51 (1H, td, *J* = 7.7, 1.3 Hz, Ar**H**), 7.46 (1H, dd, *J* = 7.9, 1.3 Hz, Ar**H**), 7.38 (1H, td, *J* = 7.6, 1.4 Hz, Ar**H**), 3.08-2.85 (4H, m, C**H**$_2$C**H**$_2$), 2.81 (2H, s, ≡CC**H**$_2$), 1.23 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.1 (2 × C), 132.6 (CH), 132.5 (CH), 132.3 (CH), 128.3 (CH), 126.7 (C), 117.5 (C), 115.0 (C), 91.5 (C), 78.8 (C), 55.6 (C), 35.7 (2 × CH_2), 24.5 (CH_2), 20.3 (CH_3). Spectroscopic data matched those reported previously.[261]

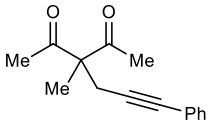
2.3.2.2 Acyclic Alkynones

Preparation of Substrate 115a



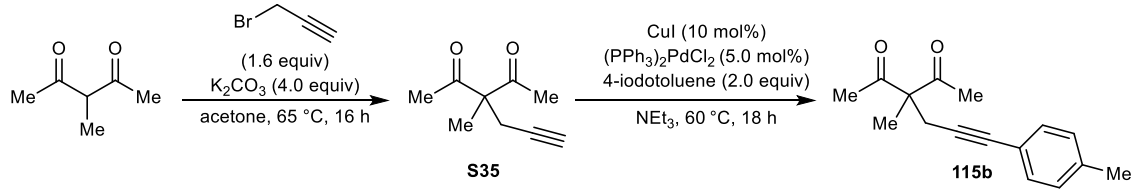


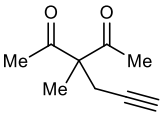
(3-Bromoprop-1-yn-1-yl)benzene (S34). Propargyl bromide **S34** was prepared by an Appel reaction of 3-phenyl-2-propyn-1-ol (5.61 mL, 45.0 mmol) according to a literature procedure (6.62 g, 75%).[264] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.31 (2H, m, Ar**H**), 7.31-7.26 (3H, m, Ar**H**), 4.20 (2H, s, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9 (2 × CH), 129.0 (CH), 128.1 (2 × CH), 122.1 (C), 86.7 (C), 84.2 (C), 15.3 (CH_2). Spectroscopic data matched those reported previously.[264]



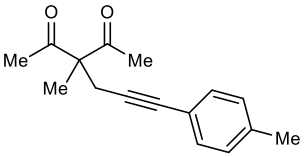
3-Methyl-3-(3-phenylprop-2-yn-1-yl)pentane-2,4-dione (115a). 3-methyl-2,4-pentanedione (1.75 mL, 15.0 mmol) was added dropwise to a solution of NaH (60% in mineral oil, 720 mg, 18.0 mmol) in THF (50 mL) at 0 ˚C under an atmosphere of argon and the resulting mixture stirred for 1 h. **S34** (80% wt solution in toluene, 4.00 g, 16.5 mmol) was added dropwise and the solution was stirred at room temperature for 16 h, quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted into Et_2O (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and the residue was purified by column chromatography (100% petroleum ether to 5% EtOAc/petroleum ether) to give alkynone **115a** as an orange oil (1.64 g, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.34 (2H, m, Ar**H**), 7.31-7.26 (3H, m, Ar**H**), 2.97 (2H, s, ≡CC**H**$_2$), 2.21 (6H, s, 2 × C**H**$_3$C=O), 1.55 (3H, s, C**H**$_3$CC=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5 (2 × C), 131.6 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 123.0 (C), 84.9 (C), 83.8 (C), 66.4 (C), 26.6 (2 × CH_3), 25.3 (CH_2), 18.7 (CH_3). Spectroscopic data matched those reported previously.[265]

Preparation of Substrate 115b



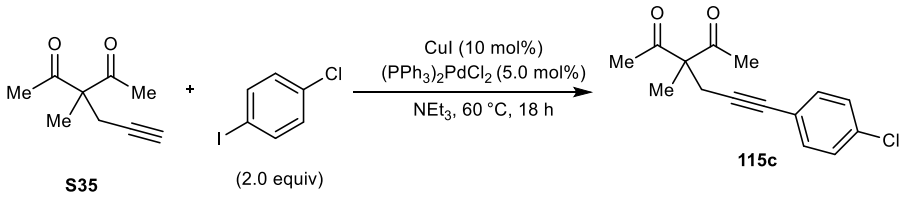


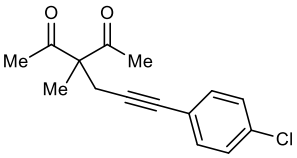
3-Methyl-3-(prop-2-yn-1-yl)pentane-2,4-dione (S35). Alkynone **S35** was prepared by a propargylation reaction of 3-methyl-2,4-pentanedione (3.56 mL, 30.7 mmol) and propargyl bromide (7.30 g, 49.1 mmol) according to a literature procedure (2.50 g, 55%).[265] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (2H, d, *J* = 2.8 Hz, ≡CC**H**$_2$), 2.16 (6H, s, 2 × C**H**$_3$C=O), 2.03 (1H, t, *J* = 2.8 Hz, C≡C**H**), 1.49 (3H, s, C**H**$_3$CC=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (2 × C), 77.9 (C), 71.7 (CH), 66.1 (C), 26.5 (2 × CH_3), 24.3 (CH_2), 18.4 (CH_3). Spectroscopic data matched those reported previously.[265]



3-Methyl-3-[3-(p-tolyl)prop-2-yn-1-yl]pentane-2,4-dione (115b). A degassed solution of **S35** (608.4 mg, 4.00 mmol), 4-iodotoluene (1.74 g, 8.00 mmol), $(PPh_3)_2PdCl_2$ (140.4 mg, 0.20 mmol) and CuI (76.2 mg, 0.40 mmol) in NEt_3 (40 mL) was heated at 60 °C for 18 h, quenched with aqueous 1.0 M HCl (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous brine solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by Puriflash column chromatography (5% EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115b** as an orange oil (415 mg, 43%). R_f = 0.21 (10% EtOAc/petroleum ether); IR (ATR) 3031, 2977, 2960, 2915, 1694 (C=O), 1509, 1355, 1160, 1097, 814, 589, 526 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.09 (2H, d, *J* = 8.2 Hz, Ar**H**), 2.96 (2H, s, ≡CC**H**$_2$), 2.34 (3H, s, ArC**H**$_3$), 2.20 (6H, s, 2 × C**H**$_3$C=O), 1.54 (3H, s, C**H**$_3$CC=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.6 (2 × C), 138.2 (C), 131.4 (2 × CH), 129.0 (2 × CH), 119.9 (C), 84.0 (C), 83.9 (C), 66.4 (C), 26.6 (2 × CH_3), 25.4 (CH_2), 21.4 (CH_3), 18.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{16}H_{18}NaO_2^+$ $[M+Na]^+$: 265.1199, found: 265.1196.

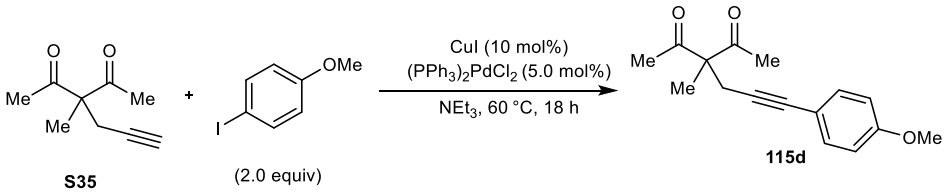
Preparation of Substrate 115c

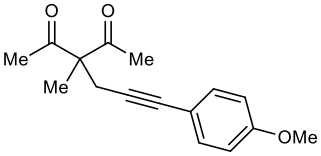




3-(3-(4-Chlorophenyl)prop-2-yn-1-yl)-3-methylpentane-2,4-dione (115c). A degassed solution of **S35** (456.3 mg, 3.00 mmol), 4-chloro-1-iodobenzene (1.43 g, 6.00 mmol), $(PPh_3)_2PdCl_2$ (105.3 mg, 0.15 mmol) and CuI (57.1 mg, 0.30 mmol) in NEt_3 (30 mL) was heated at 60 °C for 18 h, quenched with aqueous 1.0 M HCl (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous brine solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by Puriflash column chromatography (5% EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115c** as a yellow oil (373 mg, 47%). R_f = 0.20 (10% EtOAc/petroleum ether); IR (ATR) 2980, 2937, 1698 (C=O), 1489, 1356, 1089, 827, 526 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.25 (4H, m, Ar**H**), 2.97 (2H, s, ≡CC**H**$_2$), 2.21 (6H, s, 2 × C**H**$_3$C=O), 1.54 (3H, s, C**H**$_3$CC=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (2 × C), 134.1 (C), 132.8 (2 × CH), 128.5 (2 × CH), 121.4 (C), 85.9 (C), 82.7 (C), 66.3 (C), 26.5 (2 × CH_3), 25.3 (CH_2), 18.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{15}H_{15}{}^{35}ClNaO_2{}^+$ $[M+Na]^+$: 285.0653, found: 285.0645.

Preparation of Substrate 115d

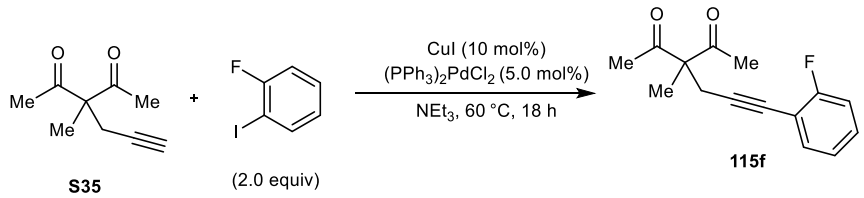


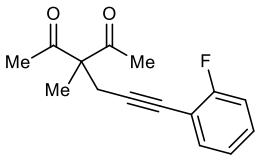


3-[3-(4-Methoxyphenyl)prop-2-yn-1-yl]-3-methylpentane-2,4-dione (115d). A degassed solution of **S35** (456.3 mg, 3.00 mmol), 4-iodoanisole (1.40 g, 6.00 mmol), $(PPh_3)_2PdCl_2$ (105.3 mg, 0.15 mmol) and CuI (57.1 mg, 0.30 mmol) in NEt_3 (30 mL) was heated at 60 °C for 18 h, quenched with aqueous 1.0 M HCl (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous brine solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by Puriflash column chromatography (5%

EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115d** as a colourless oil (500 mg, 65%). R_f = 0.10 (10% EtOAc/petroleum ether); IR (ATR) 3097, 3031, 2993, 2959, 1693 (C=O), 1509, 1245, 1091, 839, 679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (2H, d, *J* = 8.0 Hz, Ar**H**), 6.80 (2H, d, *J* = 8.0 Hz, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 2.94 (2H, s, ≡CC**H**$_2$), 2.20 (6H, s, 2 × C**H**$_3$C=O), 1.53 (3H, s, C**H**$_3$CC=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7 (2 × C), 159.4 (C), 132.9 (2 × CH), 115.1 (C), 113.8 (2 × CH), 83.6 (C), 83.2 (C), 66.4 (C), 55.3 (CH_3), 26.6 (2 × CH_3), 25.4 (CH_2), 18.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{15}H_{15}{}^{35}ClNaO_3{}^+$ $[M+Na]^+$: 281.1148, found: 281.1148.

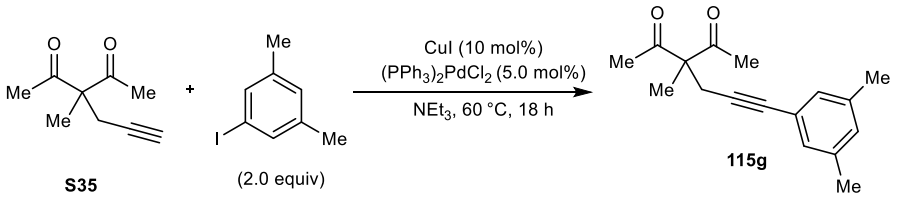
Preparation of Substrate 115f

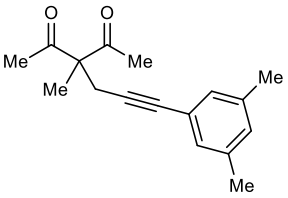




3-[3-(2-Fluorophenyl)prop-2-yn-1-yl]-3-methylpentane-2,4-dione (115f). A degassed solution of **S35** (456.3 mg, 3.00 mmol), 1-fluoro-2-iodobenzene (700 µL, 6.00 mmol), $(PPh_3)_2PdCl_2$ (105.3 mg, 0.15 mmol) and CuI (57.1 mg, 0.30 mmol) in NEt_3 (30 mL) was heated at 60 °C for 18 h, quenched with aqueous 1.0 M HCl (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous brine solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by Puriflash column chromatography (5% EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115f** as a colourless oil (526 mg, 71%). R_f = 0.12 (10% EtOAc/petroleum ether); IR (ATR) 2980, 2937, 1698 (C=O), 1492, 1357, 1215, 757, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.32 (1H, m, Ar**H**), 7.31-7.24 (1H, m, Ar**H**), 7.11-7.00 (2H, m, Ar**H**), 3.01 (2H, s, ≡CC**H**$_2$), 2.22 (6H, s, 2 × C**H**$_3$C=O), 1.57 (3H, s, C**H**$_3$CC=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5 (2 × C), 162.9 (C, J_{CF} = 251 Hz), 133.4 (CH), 129.8 (CH, J_{CF} = 7.5 Hz), 123.8 (CH, J_{CF} = 3.7 Hz), 115.4 (C, J_{CF} = 20.7 Hz), 111.5 (CH, J_{CF} = 16.0 Hz), 90.4 (C), 77.2 (C), 66.2 (C), 26.6 (2 × CH_3), 25.6 (CH_2), 18.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.5; HRMS (ESI) Exact mass calcd for $C_{15}H_{15}FNaO_2{}^+$ $[M+Na]^+$: 269.0948, found: 269.0947.

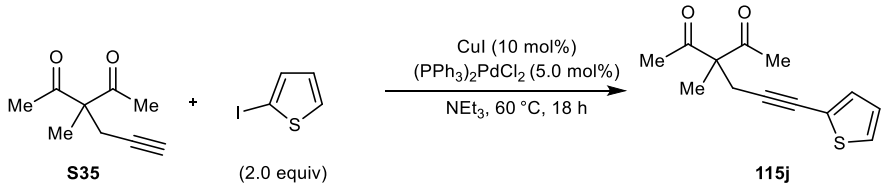
Preparation of Substrate 115g

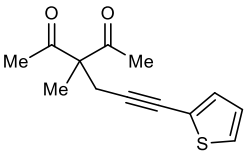




3-[3-(3,5-Dimethylphenyl)prop-2-yn-1-yl]-3-methylpentane-2,4-dione (115g). A degassed solution of **S35** (456.3 mg, 3.00 mmol), 1-iodo-3,5-dimethylbenzene (0.87 mL, 6.00 mmol), $(PPh_3)_2PdCl_2$ (105.3 mg, 0.15 mmol) and CuI (57.1 mg, 0.30 mmol) in NEt_3 (30 mL) was heated at 60 °C for 18 h, quenched with aqueous 1.0 M HCl (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous brine solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by Puriflash column chromatography (5% EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115g** as a yellow oil (537 mg, 70%). R_f = 0.21 (10% EtOAc/petroleum ether); IR (ATR) 3031, 2978, 2919, 2867, 1699 (C=O), 1598, 1355, 1162, 1092, 849, 690, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (2H, s, Ar**H**), 6.93 (1H, s, Ar**H**), 2.95 (2H, s, ≡CC**H**$_2$), 2.27 (6H, s, 2 × ArC**H**$_3$), 2.21 (6H, s, 2 × C**H**$_3$C=O), 1.54 (3H, s, C**H**$_3$CC=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.6 (2 × C), 137.8 (2 × C), 130.0 (CH), 129.2 (2 × CH), 122.6 (C), 84.1 (C), 84.0 (C), 66.4 (C), 26.6 (2 × CH_3), 25.3 (CH_2), 21.0 (2 × CH_3), 18.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{20}NaO_2^+$ $[M+Na]^+$: 279.1356, found: 279.1349.

Preparation of Substrate 115j

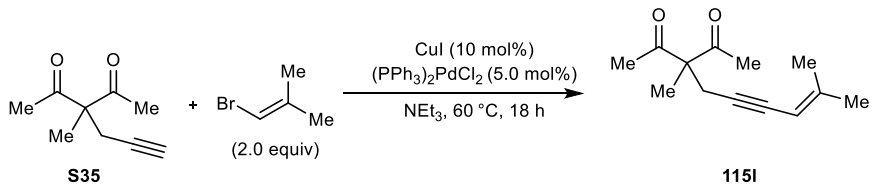


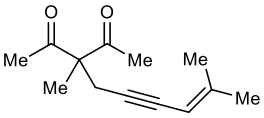


3-Methyl-3-[3-(thiophen-2-yl)prop-2-yn-1-yl]pentane-2,4-dione (115j). A degassed solution of **S35** (456.3 mg, 3.00 mmol), 2-iodothiophene (663 µL, 6.00 mmol), $(PPh_3)_2PdCl_2$ (105.3 mg, 0.15 mmol) and CuI (57.1 mg, 0.30 mmol) in NEt_3 (30 mL) was heated at 60 °C for 18 h, quenched with aqueous 1.0 M HCl (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous brine solution, dried ($MgSO_4$), filtered and

concentrated *in vacuo*. The residue was purified by Puriflash column chromatography (5% EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115j** as a yellow oil (445 mg, 63%). R_f = 0.17 (10% EtOAc/petroleum ether); IR (ATR) 2979, 2936, 1698 (C=O), 1304, 1163, 1091, 848, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (1H, dd, *J* = 5.2, 1.2 Hz, Ar**H**), 7.12 (1H, dd, *J* = 3.6, 1.2 Hz, Ar**H**), 6.94 (1H, dd, *J* = 5.2, 3.6 Hz, Ar**H**), 2.99 (2H, s, ≡CC**H**$_2$), 2.20 (6H, s, 2 × C**H**$_3$C=O), 1.54 (3H, s, C**H**$_3$CC=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.4 (2 × C), 131.7 (CH), 126.8 (CH), 126.6 (CH), 122.9 (C), 88.9 (C), 77.0 (C), 66.2 (C), 26.6 (2 × CH_3), 25.6 (CH_2), 18.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{13}H_{14}NaO_2S^+$ $[M+Na]^+$: 257.0607, found: 257.0599.

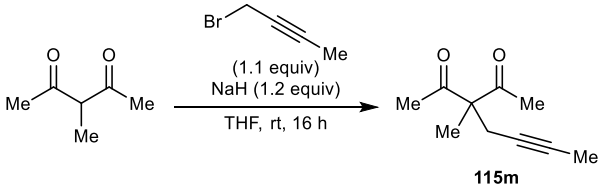
Preparation of Substrate 115l

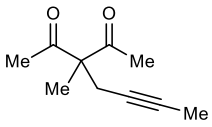




3-Methyl-3-(5-methylhex-4-en-2-yn-1-yl)pentane-2,4-dione (115l). A degassed solution of **S35** (456.3 mg, 3.00 mmol), 1-bromo-2-methylpropene (615 µL, 6.00 mmol), $(PPh_3)_2PdCl_2$ (105.3 mg, 0.15 mmol) and CuI (57.1 mg, 0.30 mmol) in NEt_3 (30 mL) was heated at 60 °C for 18 h, quenched with aqueous 1.0 M HCl (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous brine solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115l** as a colourless oil (338 mg, 55%). R_f = 0.20 (10% EtOAc/petroleum ether); IR (ATR) 2982, 2935, 2913, 1698 (C=O), 1356, 1294, 1165, 1092, 820, 791 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.18 (1H, s, C**H**), 2.90 (2H, s, ≡CC**H**$_2$), 2.16 (6H, s, 2 × C**H**$_3$), 1.82 (3H, s, CH=C(C**H**$_3$)$_a$(CH_3)$_b$), 1.77 (3H, s, CH=C(CH_3)$_a$(C**H**$_3$)$_b$), 1.48 (3H, s, C**H**$_3$); ^{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 $C_{13}H_{19}O_2^+$ $[M+H]^+$: 207.1380, found: 207.1383.

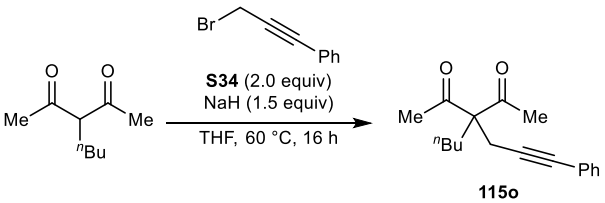
Preparation of Substrate 115m

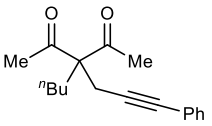




3-(But-2-yn-1-yl)-3-methylpentane-2,4-dione (115m). 3-methyl-2,4-pentanedione (582 µL, 5.0 mmol) was added to a solution of NaH (60% in mineral oil, 240 mg, 6.0 mmol) in THF (20 mL) at 0 ˚C under an atmosphere of argon and the resulting mixture stirred for 1 h at 0 °C. 1-bromo-2-butyne (482 µL, 5.5 mmol) was added dropwise and the solution was stirred at room temperature for 16 h, quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted into Et_2O (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and the residue was purified by column chromatography (5% EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115m** as a colourless oil (363 mg, 44%). R_f = 0.22 (10% EtOAc/pentane); IR (ATR) 2979, 2923, 2859, 1698 (C=O), 1356, 1166, 1092, 958, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.68 (2H, q, *J* = 2.6 Hz, ≡CC**H**$_2$), 2.15 (6H, s, 2 × C**H**$_3$), 1.75 (3H, t, *J* = 2.6 Hz, C≡CC**H**$_3$), 1.45 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.9 (2 × C), 79.1 (C), 74.0 (C), 66.4 (C), 26.5 (2 × CH_3), 24.7 (CH_2), 18.5 (CH_3), 3.4 (CH_3); HRMS (ESI) Exact mass calcd for $C_{10}H_{14}NaO_2^+$ $[M+Na]^+$: 189.0886, found: 189.0883.

Preparation of Substrate 115o

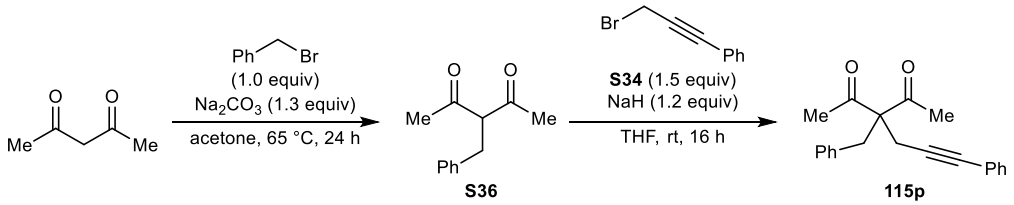


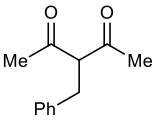


3-Butyl-3-(3-phenylprop-2-yn-1-yl)pentane-2,4-dione (115o). 3-n-butyl-2,4-pentanedione (506 µL, 3.0 mmol) was added dropwise to a solution of NaH (60% in mineral oil, 180 mg, 4.5 mmol) in THF (30 mL) at 0 ˚C under an atmosphere of argon and the resulting mixture stirred for 1 h at rt. **S34** (80% wt solution in toluene, 1.46 g, 6.0 mmol) was added dropwise and the solution was stirred at 60 °C for 16 h, quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted into Et_2O (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$), filtered,

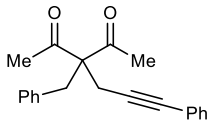
concentrated *in vacuo* and the residue was purified by column chromatography (100% petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115o** as a yellow oil (713 mg, 88%). R_f = 0.35 (10% EtOAc/pentane); IR (ATR) 2958, 2933, 2873, 1698 (C=O), 1356, 1185, 1158, 1116, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (2H, m, Ar**H**), 7.30-7.26 (3H, m, Ar**H**), 2.99 (2H, s, ≡CC**H**$_2$), 2.18 (6H, s, 2 × C**H**$_3$C=O), 2.17-2.10 (2H, m, CC**H**$_2$CH$_2$), 1.39 (2H, h, *J* = 7.4 Hz, CH$_2$C**H**$_2$CH$_3$), 1.09 (2H, dtd, *J* = 12.1, 9.2, 8.6, 6.2 Hz, C**H**$_2$CH$_2$CH$_3$), 0.93 (3H, t, *J* = 7.4 Hz, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5 (2 × C), 131.6 (2 × CH), 128.1 (2 × CH), 128.0 (CH), 123.0 (C),84.8 (C),83.7 (C),70.4 (C), 30.5 (CH$_2$), 26.9 (2 × CH$_3$), 25.9 (CH$_2$), 23.1 (CH$_2$), 21.6 (CH$_2$), 13.8 (CH$_3$); HRMS (ESI) Exact mass calcd for $C_{18}H_{22}NaO_2^+$ $[M+Na]^+$: 293.1512, found: 293.1504.

Preparation of Substrate 115p



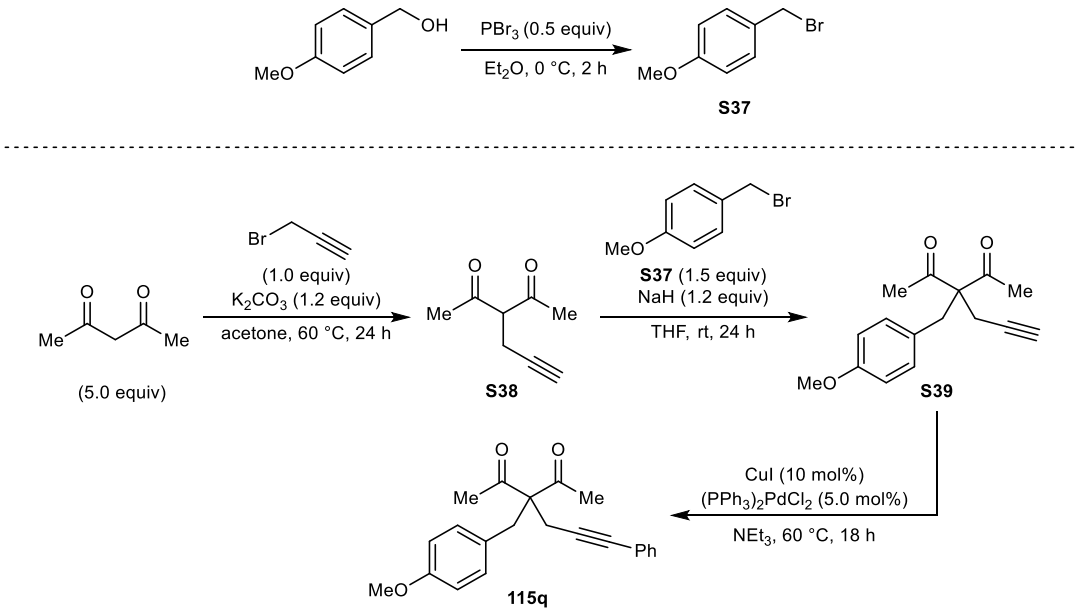


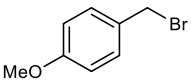
3-Benzylpentane-2,4-dione (S36). Sodium carbonate (6.86 g, 65.0 mmol) was added slowly in portions to a solution of pentane-2,4-dione (5.10 mL, 50.0 mmol) in acetone (25 mL) over 15 minutes at 0 ˚C and the solution stirred for 15 mins. Benzyl bromide (5.95 mL, 50.0 mmol) as a solution in acetone (25 mL) was added dropwise over 15 minutes and the solution was refluxed for 24 h. After cooling, the solution was filtered, the filtrate was concentrated *in vacuo*, and the residue was purified via column chromatography (10% Et_2O/petroleum ether) to give diketone **S36** as a yellow oil (24:76 ratio of keto:enol tautomers) (5.16 g, 54%). Characteristic peaks of 1,3-diketone tautomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.14 (5H, m, Ar**H**), 4.03 (1H, t, *J* = 7.5 Hz, (O=C)$_2$C**H**), 3.16 (2H, d, *J* = 7.5 Hz, PhC**H**$_2$), 2.14 (6H, s, C**H**$_3$C=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5 (2 × C), 138.0 (C), 128.7 (2 × CH), 128.6 (2 × CH), 126.7 (CH), 70.0 (CH), 34.2 (CH$_2$), 29.7 (2 × CH$_3$). Characteristic peaks of enol tautomer: ^1H NMR (400 MHz, $CDCl_3$) δ 15.47 (1H, s, O**H**), 7.35-7.14 (5H, m, Ar**H**), 3.67 (2H, s, PhC**H**$_2$), 2.09 (6H, s, 2 × C**H**$_3$C=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9 (2 × C), 139.6 (C), 128.7 (2 × CH), 127.4 (2 × CH), 126.3 (CH), 108.2 (C), 34.2 (CH$_2$), 23.2 (2 × CH$_3$). Spectroscopic data matched those reported previously.[266]



3-Benzyl-3-(3-phenylprop-2-yn-1-yl)pentane-2,4-dione (115p). **S36** (1.90 g, 10.0 mmol) was added dropwise to a solution of NaH (60% in mineral oil, 480 mg, 12.0 mmol) in THF (30 mL) at 0 ˚C under an atmosphere of argon and the resulting mixture stirred for 1 h at rt. **S34** (80% wt solution in toluene, 2.67 g, 11.0 mmol) was added dropwise and the solution was stirred at room temperature for 16 h, quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted into Et_2O (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and the residue was purified by column chromatography (100% petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115p** as an yellow oil (1.16 g, 38%). R_f = 0.19 (10% EtOAc/pentane); IR (ATR) 3069, 3029, 2956, 1695 (C=O), 1489, 1441, 1359, 1172, 1148, 755, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46-7.40 (2H, m, Ar**H**), 7.36-7.26 (6H, m, Ar**H**), 7.19-7.14 (2H, m, Ar**H**), 3.47 (2H, s, PhC**H**$_2$), 2.89 (2H, s, ≡CC**H**$_2$), 2.27 (6H, s, 2 × C**H**$_3$C=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.7 (2 × C), 135.6 (C), 131.6 (2 × CH), 129.7 (2 × CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 127.1 (CH), 122.9 (C), 84.8 (C), 84.7 (C), 71.3 (C), 36.9 (CH_2), 27.4 (2 × CH_3), 21.7 (CH_2); HRMS (ESI) Exact mass calcd for $C_{21}H_{20}NaO_2^+$ $[M+Na]^+$: 327.1356, found: 327.1355.

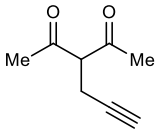
Preparation of Substrate 115q



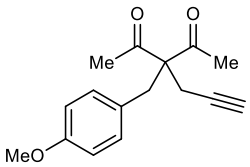


1-(Bromomethyl)-4-methoxybenzene (S37). Benzyl bromide **S37** was prepared by a bromination reaction of 4-methyoxybenzyl alcohol (11.4 mL,

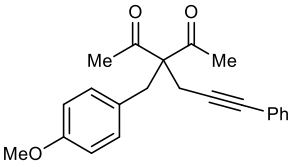
92.0 mmol) according to a literature procedure (17.95 g, 89%).[267] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.88 (2H, d, *J* = 8.7 Hz, Ar**H**), 4.52 (2H, s, C**H**$_2$Br), 3.82 (3H, s, OC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (C), 130.4 (2 × CH), 129.9 (C), 114.2 (2 × CH), 55.3 (CH_3), 34.0 (CH_2). Spectroscopic data matched those reported previously.[267]



3-(Prop-2-yn-1-yl)pentane-2,4-dione (S38). Alkynone **S38** was prepared by propargylation of pentane-2,4-dione (25.8 mL, 250 mmol, 5.0 equiv) according to a literature procedure (5.23 g, 76%).[268] Characteristic peaks of 1,3-diketone tautomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (1H, t, *J* = 7.5 Hz, C**H**CH$_2$), 2.67 (2H, dd, *J* = 7.5, 2.7 Hz, CHC**H**$_2$), 2.20 (6H, s, 2 × C**H**$_3$C=O), 2.02 (1H, t, *J* = 2.3 Hz, C≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.1 (2 × C), 29.3 (2 × CH_3), 17.3 (CH_2). Characteristic peaks of enol tautomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (2H, d, *J* = 2.7 Hz, ≡CC**H**$_2$), 2.23 (6H, s, 2 × C**H**$_3$C=O), 2.02 (1H, t, *J* = 2.3 Hz, C≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190. (2 × C), 106.4 (C), 17.3 (CH_2). The remaining ^{13}C NMR peaks are included below; 81.6 (C), 80.2 (C), 70.7 (C), 68.6 (CH), 66.6 (CH). Spectroscopic data matched those reported previously.[268]



3-(4-Methoxybenzyl)-3-(prop-2-yn-1-yl)pentane-2,4-dione (S39). **S38** (690 mg, 5.0 mmol) was added dropwise to a solution of NaH (60% in mineral oil, 240 mg, 6.0 mmol) in THF (30 mL) at 0 ˚C under an atmosphere of argon and the resulting mixture stirred for 1 h at rt. **S37** (1.08 mL, 5.5 mmol) was added dropwise and the solution was stirred at room temperature for 24 h, quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted into Et_2O (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and the residue was purified by column chromatography (20% EtOAc/petroleum ether) to give *alkynone* **S39** as a yellow oil (771 mg, 60%). R_f = 0.33 (20% EtOAc/pentane); IR (ATR) 2959, 1696 (C=O), 1513, 1360, 1266, 1171, 1151, 1027, 755, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.80 (2H, d, *J* = 8.5 Hz, Ar**H**), 3.78 (3H, s, OC**H**$_3$), 3.34 (2H, s, ArC**H**$_2$), 2.64 (2H, d, *J* = 2.7 Hz, ≡CC**H**$_2$), 2.20 (6H, s, 2 × C**H**$_3$C=O), 2.14 (1H, t, *J* = 2.7 Hz, C≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (2 × C), 158.7 (C), 130.7 (2 × CH), 127.3 (C), 113.9 (2 × CH), 79.7 (C), 72.6 (C), 71.1 (CH), 55.2 (CH_3), 35.8 (CH_2), 27.4 (2 × CH_2), 20.7 (CH_2); HRMS (ESI) Exact mass calcd for $C_{16}H_{18}NaO_3^+$ $[M+Na]^+$: 281.1148, found: 281.1149.

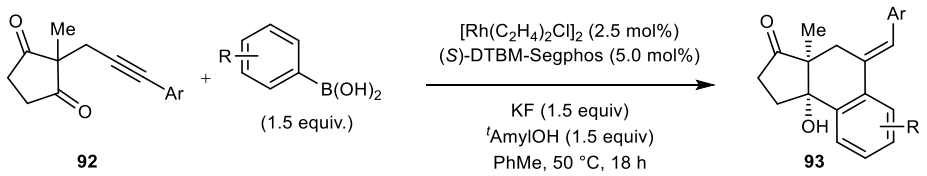


3-(4-Methoxybenzyl)-3-(3-phenylprop-2-yn-1-yl)pentane-2,4-dione (115q). A degassed solution of **S39** (516 mg, 2.00 mmol), iodobenzene (448 µL, 4.00 mmol), $(PPh_3)_2PdCl_2$ (70.2 mg, 0.10 mmol) and CuI (38.1 mg, 0.2 mmol) in NEt_3 (20 mL) was heated at 60 °C for 18 h, quenched with aqueous 1.0 M HCl (25 mL) and extracted into EtOAc (3 × 25 mL). The combined organic layers were washed with saturated aqueous brine solution, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by Puriflash column chromatography (5% EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give *alkynone* **115q** as a brown oil (525 mg, 79%). R_f = 0.20 (20% EtOAc/petroleum ether); IR (ATR) 2997, 2958, 2933, 1720 (C=O), 1512, 1356, 1246, 1176, 1032, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46-7.37 (2H, m, Ar**H**), 7.36-7.30 (3H, m, Ar**H**), 7.07 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.81 (2H, d, *J* = 8.7 Hz, Ar**H**), 3.78 (3H, s, OC$\mathbf{H}_3$), 3.40 (2H, s, ArC$\mathbf{H}_2$), 2.87 (2H, s, ≡CC$\mathbf{H}_2$), 2.24 (6H, s, 2 × C$\mathbf{H}_3$C=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9 (2 × C), 158.7 (C), 131.6 (2 × CH), 130.7 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 127.4 (C), 123.0 (C), 114.0 (2 × CH), 84.9 (C), 84.6 (C), 71.4 (C), 55.2 (CH_3), 36.1 (CH_2), 27.5 (2 × CH_3), 21.7 (CH_2); HRMS (ESI) Exact mass calcd for $C_{22}H_{22}NaO_3^+$ $[M+Na]^+$: 357.1461, found: 357.1460.

2.3.3 Rhodium-Catalysed Arylative Cyclisation of Alkynones via 1,4-Rh Migration

2.3.3.1 Cyclic Alkynones

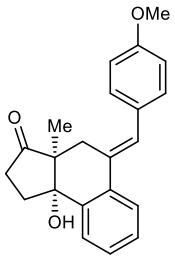
General Procedure 1:



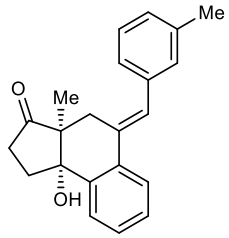
$[Rh(C_2H_4)_2Cl]_2$ (2.9 mg, 0.0075 mmol) and (*S*)-DTBM-Segphos (17.7 mg, 0.015 mmol) were added to an oven-dried microwave vial, which was sealed with a septum, and purged with argon for 30 mins. Degassed toluene (3 mL) was added and the mixture was stirred at room temperature for 30 mins, under argon. In a separate oven-dried microwave vial the alkynone (0.30 mmol), boronic acid (0.45 mmol), and KF (26.1 mg, 0.45 mmol) were added. A septum was fitted and the vial was purged with argon for 30 mins. The catalyst solution was added to the vial containing the alkynone. ^{t}amyl alcohol (49 µL, 0.45 mmol) was added and the mixture

was stirred at 50 ˚C for 18 h. The reaction was cooled to room temperature, diluted with water and saturated aqueous NH_4Cl solution was added. The mixture was extracted with EtOAc, the organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography gave alcohol **93**. In most cases, small quantities of minor products **95** and **101** were also observed in the ^{1}H NMR spectra of the crude material, but with the exception of the reaction forming arylative cyclization product **93h** (*vide infra*), these were not isolated.

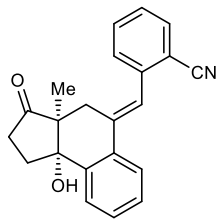
In order to determine the *e.e.* via HPLC, the corresponding non-enantioselective reaction was performed under identical reaction conditions using *rac*-BINAP as the ligand instead of (*S*)-DTBM-Segphos.



(-)-(3a*S*,9b*S*)-9b-Hydroxy-5-[(*E*)-4-methoxybenzylidene]-3a-methyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (93c). General procedure 1 was followed using alkynone **92c** (76.8 mg, 0.30 mmol) and phenylboronic acid (54.8 mg, 0.45 mmol). Column chromatography (20% EtOAc/pentane) gave *alcohol* **93c** (37.7 mg, 39%) as a white solid. R_f = 0.27 (10% Et_2O/CH_2Cl_2); m.p. (Et_2O) 173-175 ˚C; IR (ATR) 3450 (OH), 2926, 1731 (C=O), 1452, 1246, 1071, 826, 729 cm^{-1}; $[\alpha]_D^{20.1}$ -172 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (1H, dd, *J* = 7.6, 1.5 Hz, Ar**H**), 7.66 (1H, dd, *J* = 7.9, 1.4 Hz, Ar**H**), 7.38 (1H, td, *J* = 7.5, 1.4 Hz, Ar**H**), 7.33 (1H, td, *J* = 7.6, 1.6 Hz, Ar**H**), 7.22 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.17 (1H, d, *J* = 2.0 Hz, C=C**H**), 6.90 (2H, d, *J* = 8.7 Hz, Ar**H**), 3.84 (3H, s, OC**H**$_3$), 2.79 (1H, d, *J* = 14.1 Hz, C**H**$_a$H$_b$C=C), 2.66-2.56 (2H, m, CH$_a$**H**$_b$C=C and C**H**$_a$H$_b$C=O), 2.53-2.27 (3H, m, CH$_a$**H**$_b$C=O and C**H**$_2$COH), 1.89 (1H, d, *J* = 1.8 Hz, br s, O**H**), 1.00 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.0 (C), 158.6 (C), 139.9 (C), 134.5 (C), 130.7 (C), 130.4 (2 × CH), 129.6 (C), 128.5 (CH), 128.1 (CH), 127.5 (CH), 126.5 (CH), 124.0 (CH), 113.9 (2 × CH), 80.1 (C), 55.3 (CH_3), 54.1 (C), 35.9 (CH_2), 35.1 (CH_2), 34.3 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{22}NaO_3^+$ $[M+Na]^+$: 357.1461, found 357.1463: Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 23 °C): tr (minor) = 9.6 min, tr (major) = 17.3 min; 92% *ee*. Data matches those previously reported in the literature.[261]

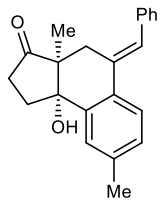


(3a*S*,9b*S*)-9b-Hydroxy-3a-methyl-5-[(*E*)-3-methylbenzylidene]-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (93e). A modification of the general procedure 1 was followed using alkynone **92e** (81.3 mg, 0.30 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol, 5.0 mol%), (*S*)-DTBM-Segphos (35.4 mg, 0.03 mmol, 10 mol%) and phenylboronic acid (73.2 mg, 0.60 mmol). Column chromatography (10% Et_2O/CH_2Cl_2) gave *alcohol* **93e** (57.0 mg, 60%) as a white solid. R_f = 0.27 (10% Et_2O/CH_2Cl_2); m.p. (Et_2O) 144-146 ˚C; IR (ATR) 3390 (OH), 2968, 2939, 1722 (C=O), 1451, 1231, 1087, 837, 698 cm^{-1}; $[\alpha]_D^{20.1}$ -204 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74-7.71 (1H, m, Ar**H**), 7.67 (1H, dd, *J* = 7.8, 1.4 Hz, Ar**H**), 7.42-7.32 (2H, m, Ar**H**), 7.25 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.21 (1H, d, *J* = 2.0 Hz, C=C**H**), 7.11-7.05 (3H, m, Ar**H**), 2.80 (1H, d, *J* = 14.1 Hz, C$\mathbf{H}_a$$H_b$C=C), 2.69-2.57 (2H, m, $CH_a$$\mathbf{H}_b$C=C and C$\mathbf{H}_a$$H_b$C=O), 2.54-2.28 (6H, m, $CH_a$$\mathbf{H}_b$C=O, C$\mathbf{H}_2$COH and ArC$\mathbf{H}_3$), 1.81 (1H, d, *J* = 2.2 Hz, br s, O**H**), 1.01 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.9 (C), 140.1 (C), 138.0 (C), 137.0 (C), 134.3 (C), 131.9 (C), 129.8 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 126.5 (CH), 126.2 (CH), 124.2 (CH), 80.2 (C), 54.2 (C), 35.9 (CH_2), 35.2 (CH_2), 34.4 (CH_2), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{22}NaO_2^+$ $[M+Na]^+$: 341.1512, found: 341.1508. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 23 °C): tr (minor) = 18.8 min, tr (major) = 22.9 min; 99% *ee*. Data matches those previously reported in the literature.[261]



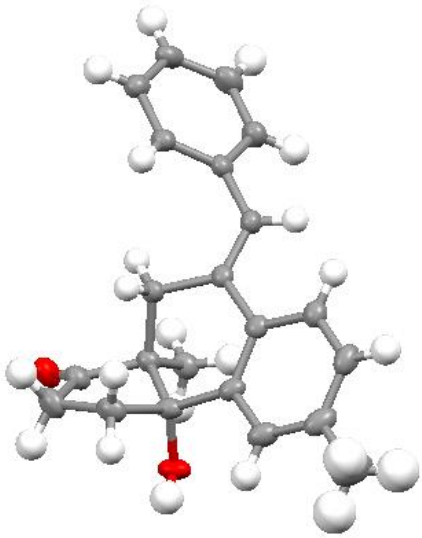
2-{(*E*)-[(3a*S*,9b*S*)-9b-Hydroxy-3a-methyl-3-oxo-1,2,3,3a,4,9b-hexahydro-5*H*-cyclopenta[*a*]naphthalen-5-ylidene]methyl}benzonitrile (93f). A modification of the general procedure 1 was followed using alkynone **92f** (75.3 mg, 0.30 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol, 5.0 mol%), (*S*)-DTBM-Segphos (35.4 mg, 0.03 mmol, 10 mol%) and phenylboronic acid (54.9 mg, 0.45 mmol). Column chromatography (10% Et_2O/CH_2Cl_2) gave *alcohol* **93f** (63.0 mg, 64%) as a white solid. R_f = 0.23 (10% Et_2O/CH_2Cl_2); m.p. (Et_2O) 153-155 ˚C; IR (ATR) 3419 (OH), 2958, 2916, 2229 (C≡N), 1718 (C=O), 1278, 1086, 841, 703 cm^{-1}; $[\alpha]_D^{20.1}$ -116 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.68 (3H, m, Ar**H**), 7.60 (1H, td, *J* = 7.7, 1.4 Hz, Ar**H**), 7.49-7.35 (4H, m, Ar**H**), 7.28 (1H, d, *J* = 2.0 Hz, C=C**H**), 2.71-2.57 (2H, m, C$\mathbf{H}_a$$H_b$C=C and C$\mathbf{H}_a$$H_b$C=O), 2.54-2.30 (4H, m, $CH_a$$\mathbf{H}_b$C=C, $CH_a$$\mathbf{H_b}$C=O and C$\mathbf{H}_2$COH), 1.87 (1H, d, *J* = 2.1 Hz, O**H**), 1.03

(3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.7 (C), 140.9 (C), 140.6 (C), 136.8 (C), 133.3 (C), 133.0 (CH), 132.7 (CH), 129.9 (CH), 129.8 (CH), 128.4 (CH), 127.6 (CH), 126.7 (CH), 124.7 (CH), 123.7 (CH), 118.0 (C), 112.7 (C), 80.0 (C), 54.3 (C), 35.9 (CH_2), 35.4 (CH_2), 34.7 (CH_2), 14.2 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{19}NaO_2^+$ $[M+Na]^+$: 352.1308, found: 352.1308. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 23 °C): tr (minor) = 12.7 min, tr (major) = 29.6 min; 61% *ee*. Data matches those previously reported in the literature.[261]

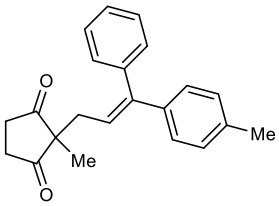


(-)-(3a*S*,9b*S*)-5-[(*E*)-Benzylidene]-9b-hydroxy-3a,8-dimethyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (93h). General procedure 1 was followed using alkynone **92a** (67.8 mg, 0.30 mmol) and 4-methylphenylboronic acid (61.2 mg, 0.45 mmol). Column chromatography (20% EtOAc/pentane) gave *alcohol* **93h** (54.5 mg, 57%) as a yellow solid. R_f = 0.25 (30% EtOAc/pentane); m.p. (Et_2O) 152-154 ˚C IR (ATR) 3414 (OH), 2922, 1720 (C=O), 1446, 1200, 1069, 841, 705 cm^{-1}; $[\alpha]_D^{20.1}$ -172 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.52 (1H, s, Ar**H**), 7.36 (2H, dd, *J* = 8.2, 7.0 Hz, Ar**H**), 7.29-7.24 (3H, m, Ar**H**), (2H, m, Ar**H** and C=C**H**), 2.77 (1H, d, *J* = 14.1 Hz, C**H**$_a$H$_b$C=C), 2.68-2.57 (2H, m, CH$_a$**H**$_b$C=C and C**H**$_a$H$_b$C=O), 2.54-2.27 (6H, m, CH$_a$**H**$_b$C=O and C**H**$_2$COH and C**H**$_3$), 1.80 (1H, br s, O**H**), 1.00 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.0 (C), 139.9 (C), 138.8 (C), 137.2 (C), 132.0 (C), 131.5 (C), 129.14 (CH), 129.09 (2 × CH), 128.4 (2 × CH), 127.0 (2 × CH), 126.9 (CH), 124.1 (CH), 80.1 (C), 54.2 (C), 34.9 (CH_2), 35.2 (CH_2), 34.3 (CH_2), 21.3 (CH_3), 13.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{22}NaO_2^+$ $[M+Na]^+$: 341.1517, found: 341.1506. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 7.0 min, tr (major) = 10.6 min; 99% *ee*.

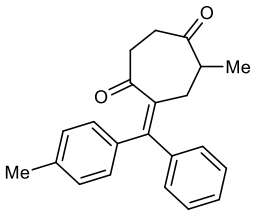
An X-ray crystal structure of **93h** was obtained by recrystallization in pentane/CH_2Cl_2.



An impurity was also isolated (22.7 mg, 23%) which was determined to be a mixture of hydroarylation product **101h** and ring expansion product **95h** in a 3:1 **101h**:**95h** ratio.



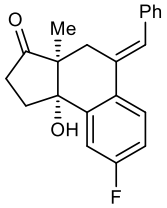
Characteristic peaks of hydroarylation product **101h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-6.97 (9H, m, Ar**H**), 5.87 (1H, t, *J* = 7.6 Hz, =C**H**), 2.43 (2H, d, *J* = 7.6 Hz, =CHC**H**$_2$), 2.80-2.65 (4H, 2 × C**H**$_2$), 2.32 (3H, s, ArC**H**$_3$), 1.12 (3H, s, C**H**$_3$); δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.5 (2 × C), 145.6 (C), 141.9 (C), 139.2 (C), 139.1 (C), 137.3 (C), 131.6 (C), 129.8 (2 × CH), 128.9 (2 × CH), 128.3 (2 × CH), 127.3 (CH), 127.2 (2 × CH), 120.3 (CH), 57.0 (C), 35.8 (CH_2), 35.1 (2 × CH_2), 21.08 (CH_3), 17.2 (CH_3).



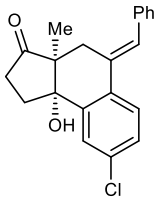
Characteristic peaks of ring expansion product **95h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-6.97 (9H, m, Ar**H**), 2.80-2.65 (6H, 3 × C**H**$_2$), 2.31 (3H, s, ArC**H**$_3$), 2.28-2.19 (1H, m, C**H**CH_3), 0.99 (3H, d, *J* = 6.4 Hz, CHC**H**$_3$); δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.7 (C), 207.8 (C), 144.7 (C), 140.1 (C), 139.1 (C), 138.1 (C), 45.3 (CH), 39.0 (CH_2), 37.6 (CH_2), 34.4 (CH_2), 21.20 (CH_3), 15.6 (CH_3).

Exact identification of some of the Ar**H** peaks in the ^{13}C NMR spectrum of the impurity mixture was difficult regarding which compound they belonged too. Any unidentified peaks are listed here: 129.11, 129.06, 128.9, 128.5, 128.4, 127.8.

Small quantities of these impurities were observed in the crude NMR spectra of all cyclisation reactions but was only isolated in and characterized for **116h**.

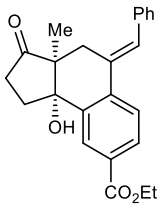


(-)-(3a*S*,9b*S*)-5-[(*E*)-Benzylidene]-8-fluoro-9b-hydroxy-3a-methyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (93i). A modification of the general procedure 1 was followed using alkynone **92a** (67.8 mg, 0.30 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol, 5.0 mol%), (*S*)-DTBM-Segphos (35.4 mg, 0.03 mmol, 10 mol%) and 4-fluorophenylboronic acid (63.0 mg, 0.45 mmol). Column chromatography (20% EtOAc/pentane) gave *alcohol* **93i** (63.4 mg, 65%) as an off-white solid. R_f = 0.42 (40% EtOAc/petroleum ether); m.p. (Et_2O) 70-72 ˚C; IR (ATR) 3447 (OH), 2966, 1729 (C=O), 1605, 1582, 1446, 1239, 838, 697 cm^{-1}; $[\alpha]_D^{20.1}$ -200 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, dd, *J* = 8.8, 5.5 Hz, Ar**H**), 7.43 (1H, dd, *J* = 9.6, 2.8 Hz, Ar**H**), 7.38 (2H, dd, *J* = 8.2, 6.9 Hz, Ar**H**), 7.31-7.25 (3H, m, Ar**H**), 7.17 (1H, s, C=C**H**), 7.06 (1H, ddd, *J* = 8.8, 8.0, 2.8 Hz, Ar**H**), 2.80 (1H, d, *J* = 14.1 Hz, C$\mathbf{H}_a$$H_b$C=C), 2.68-2.58 (2H, m, $CH_a$$\mathbf{H}_b$C=C and C$\mathbf{H}_a$$H_b$C=O), 2.52 (1H, ddd, *J* = 19.1, 9.0, 2.5 Hz, $CH_a$$\mathbf{H}_b$C=O), 2.45-2.29 (2H, m, C$\mathbf{H}_2$COH), 1.84 (1H, d, *J* = 2.3 Hz, O**H**), 1.02 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.3 (C), 163.2 (C, J_{CF} = 248.0 Hz), 142.4 (C, J_{CF} = 6.5 Hz), 136.9 (C), 131.2 (C), 130.4 (C, J_{CF} = 3.6 Hz), 129.1 (2 × CH), 128.5 (2 × CH), 127.7 (CH), 127.2 (CH), 126.3 (CH, J_{CF} = 8.1 Hz), 115.6 (CH, J_{CF} = 21.8 Hz), 113.1 (CH, J_{CF} = 22.0 Hz) 80.0 (C), 54.0 (C), 35.8 (CH_2), 35.0 (CH_2), 34.4 (CH_2), 13.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.2; HRMS (ESI) Exact mass calcd for $C_{21}H_{19}FNaO_2^+$ $[M+Na]^+$: 345.1261, found: 345.1259. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 23 °C): tr (minor) = 6.5 min, tr (major) = 10.5 min; 99% *ee*.

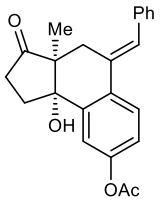


(-)-(3a*S*,9b*S*)-5-[(*E*)-Benzylidene]-8-chloro-9b-hydroxy-3a-methyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (93j). General procedure 1 was followed using alkynone **92a** (67.8 mg, 0.30 mmol) and 4-chlorophenylboronic acid (70.4 mg, 0.45 mmol). Column chromatography (20% EtOAc/pentane) gave *alcohol* **93j** (66.1 mg, 65%) as an off-white solid. R_f = 0.43 (40% EtOAc/petroleum ether); m.p. (Et_2O) 78-80 ˚C; IR (ATR) 3433 (OH), 2968, 1729 (C=O), 1445, 1230, 1072, 839, 697 cm^{-1}; $[\alpha]_D^{20.1}$ -224 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, d, *J* = 2.2 Hz, Ar**H**), 7.63 (1H, d, *J* = 8.6 Hz, Ar**H**), 7.39 (2H, t, *J* = 7.6 Hz, Ar**H**), 7.34-7.26 (4H, m, Ar**H**), 7.22 (1H, d, *J* = 2.1 Hz, C=C**H**), 2.80 (1H, d, *J* = 14.2 Hz, C$\mathbf{H}_a$$H_b$C=C), 2.71-2.59 (2H, m, $CH_a$$\mathbf{H}_b$C=C and C$\mathbf{H}_a$$H_b$C=O), 2.55-2.29 (3H, m, $CH_a$$\mathbf{H}_b$C=O and C$\mathbf{H}_2$COH), 1.83 (1H, d, *J* = 2.2 Hz, O**H**), 1.01 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ

219.2 (C),141.8 (C), 136.8 (C), 134.6 (C), 132.7 (C), 131.1 (C), 129.1 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 127.5 (CH), 126.7 (CH), 125.7 (CH), 79.9 (C), 53.9 (C), 35.8 (CH_2), 35.0 (CH_2), 34.2 (CH_2), 13.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{21}H_{19}{}^{35}ClNaO_2{}^+$ $[M+Na]^+$: 361.0966, found: 361.0968. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 6.9 min, tr (major) = 12.3 min; 98% *ee*. Data matches those previously reported in the literature.[261]

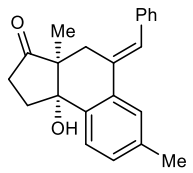


(-)-Ethyl(3a*S*,9b*S*)-5-[(*E*)-benzylidene]-9b-hydroxy-3a-methyl-3-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-8-carboxylate (93m). A modification of the general procedure 1 was followed using alkynone **92a** (67.8 mg, 0.30 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol, 5.0 mol%), (*S*)-DTBM-Segphos (35.4 mg, 0.03 mmol, 10 mol%) and 4-ethoxycarbonylphenylboronic acid (139.7 mg, 0.72 mmol, 2.4 equiv). Column chromatography (10% Et_2O/CH_2Cl_2) gave *alcohol* **93m** (73.4 mg, 65%) as an oily solid. R_f = 0.30 (10% Et_2O/CH_2Cl_2); IR (ATR) 3466 (OH), 2976, 1711, 1708 (C=O), 1446, 1072, 844, 697 cm^{-1}; $[\alpha]_D^{20.1}$ -180 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (1H, d, *J* = 1.9 Hz, Ar**H**), 7.99 (1H, dd, *J* = 8.3, 1.9 Hz, Ar**H**), 7.74 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.42-7.36 (2H, m, Ar**H**), 7.34-7.26 (4H, m, Ar**H** and C=C**H**), 4.42 (2H, qd, *J* = 7.1, 1.0 Hz, OC**H**$_2$CH$_3$), 2.81 (1H, d, *J* = 14.3 Hz, C**H**$_a$H$_b$C=C), 2.70-2.58 (2H, m, CH$_a$**H**$_b$C=C and C**H**$_a$H$_b$C=O), 2.54-2.43 (2H, m, CH$_a$**H**$_b$C=O and C**H**$_a$H$_b$COH), 2.37-2.29 (1H, m, CH$_a$**H**$_b$COH), 1.90 (1H, s, O**H**), 1.44 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.01 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.3 (C), 166.2 (C), 140.2 (C), 138.5 (C), 136.6 (C), 131.5 (C), 130.6 (C), 130.2 (CH), 129.1 (2 × CH), 129.0 (CH), 128.5 (2 × CH), 128.1 (CH), 127.5 (CH), 124.3 (CH), 79.9 (C), 61.2 (CH_2), 54.0 (C), 35.9 (CH_2), 35.1 (CH_2), 34.2 (CH_2), 14.4 (CH_3), 13.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{24}H_{24}NaO_4{}^+$ $[M+Na]^+$: 399.1567, found: 399.1570. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 20.9 min, tr (major) = 29.6 min; 99% *ee*. Data matches those previously reported in the literature.[261]

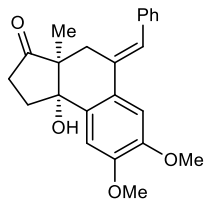


(-)-(3a*S*,9b*S*)-5-[(*E*)-Benzylidene]-9b-hydroxy-3a-methyl-3-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalen-8-yl acetate (93n). A modification of the general procedure 1 was followed using alkynone **92a** (67.8 mg, 0.30 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol, 5.0 mol%), (*S*)-DTBM-Segphos (35.4 mg, 0.03 mmol, 10 mol%) and 4-acetoxyphenylboronic acid (108.0 mg, 0.6 mmol, 2.0 equiv). Column chromatography (10% Et_2O/CH_2Cl_2) gave *alcohol* **93n** (66.0 mg,

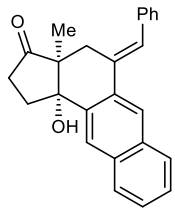
61%) as a yellow solid. R_f = 0.30 (10% Et_2O/CH_2Cl_2); m.p. (Et_2O) 95-97 ˚C; IR (ATR) 3466 (OH), 2955, 1735 (C=O), 1493, 1368, 1200, 815, 698 cm^{-1}; $[\alpha]_D^{20.1}$ -208 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, d, *J* = 8.7 Hz, Ar**H**), 7.44 (1H, d, *J* = 2.5 Hz, Ar**H**), 7.37 (2H, dd, *J* = 8.2, 6.9 Hz, Ar**H**), 7.27 (3H, d, *J* = 3.8 Hz, Ar**H**), 7.19 (1H, d, *J* = 2.1 Hz, C=C**H**), 7.08 (1H, dd, *J* = 8.6, 2.5 Hz, Ar**H**), 2.79 (1H, d, *J* = 14.2 Hz, C$\mathbf{H}_a$$H_b$C=C), 2.67-2.57 (2H, m, $CH_a$$\mathbf{H}_b$C=C and C$\mathbf{H}_a$$H_b$C=O), 2.50 (1H, ddd, *J* = 19.1, 8.8, 2.6 Hz, $CH_a$$\mathbf{H}_b$C=O), 2.42-2.29 (5H, m, C$\mathbf{H}_2$COH and O=CC$\mathbf{H}_3$), 1.86 (1H, d, *J* = 2.3 Hz, O**H**), 1.00 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.5 (C), 169.5 (C), 151.1 (C), 141.6 (C), 136.9 (C), 132.0 (C), 131.3 (C), 129.1 (2 × CH), 128.5 (2 × CH), 128.2 (CH), 127.2 (CH), 125.6 (CH), 121.7 (CH), 119.5 (CH), 80.0 (C), 54.0 (C), 35.8 (CH_2), 35.1 (CH_2), 34.4 (CH_2), 21.2 (CH_3), 13.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{23}H_{22}NaO_4^+$ $[M+Na]^+$: 385.1410, found: 385.1411. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 7.5 min, tr (major) = 10.6 min; 99% *ee*.



(-)-(3a*S*,9b*S*)-5-[(*E*)-Benzylidene]-9b-hydroxy-3a,7-dimethyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (93o). General procedure 1 was followed using alkynone **92a** (67.8 mg, 0.30 mmol) and 3-methylphenylboronic acid (61.2 mg, 0.45 mmol). Column chromatography (20% EtOAc/pentane) gave alcohol **93o** (42.4 mg, 44%) as a white solid. R_f = 0.25 (30% EtOAc/petroleum ether); m.p. (Et_2O) 142-143˚C; IR (ATR) 3434 (OH), 3022, 2970, 1715 (C=O), 1445, 1208, 1081, 838, 696 cm^{-1}; $[\alpha]_D^{20.1}$ -180 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.49 (1H, s, Ar**H**), 7.39-7.33 (2H, m, Ar**H**), 7.31-7.20 (5H, m, Ar**H** and C=C**H**), 2.77 (1H, d, *J* = 13.9 Hz, C$\mathbf{H}_a$$H_b$C=C), 2.67-2.55 (2H, m, $CH_a$$\mathbf{H}_b$C=C and C$\mathbf{H}_a$$H_b$C=O), 2.51-2.26 (6H, m, $CH_a$$\mathbf{H}_b$C=O and C$\mathbf{H}_2$COH and C$\mathbf{H}_3$), 1.78 (1H, br s, O**H**), 1.00 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.0 (C), 137.8 (C), 137.4 (C), 137.2 (C), 134.1 (C), 132.2 (C), 129.8 (CH), 129.1 (2 × CH), 128.4 (2 × CH), 127.7 (CH), 127.0 (CH), 126.5 (CH), 124.6 (CH), 80.0 (C), 54.2 (C), 35.9 (CH_2), 35.4 (CH_2), 34.4 (CH_2), 21.3 (CH_3), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{22}NaO_2^+$ $[M+Na]^+$: 341.1517, found: 341.1514. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 7.3 min, tr (major) = 10.4 min; 98% *ee*. Data matches those previously reported in the literature.[261]



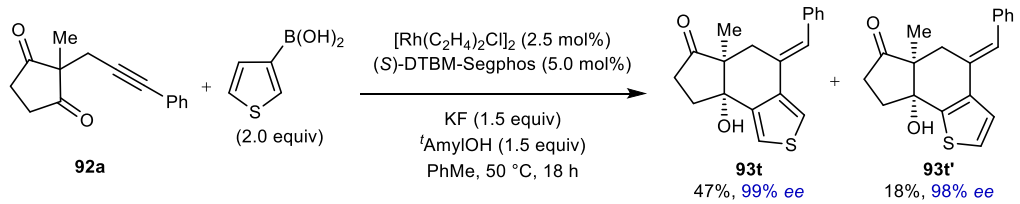
(-)-(3a*S*,9b*S*)-5-[(*E*)-Benzylidene]-9b-hydroxy-7,8-dimethoxy-3a-methyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (93r). A modification of the general procedure 1 was followed using alkynone **92a** (67.8 mg, 0.30 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol, 5.0 mol%), (*S*)-DTBM-Segphos (35.4 mg, 0.03 mmol, 10 mol%) and 3,4-dimethoxyphenylboronic acid (96.1 mg, 0.6 mmol, 2.0 equiv). Column chromatography (10% Et_2O/CH_2Cl_2) gave *alcohol* **93r** (50.7 mg, 46%) as a yellow solid. R_f = 0.33 (10% Et_2O/DCM); m.p. (Et_2O) 91-93 ˚C; IR (ATR) 3467 (OH), 2959, 2835, 1731 (C=O), 1446, 1200, 1052, 845, 698 cm^{-1}; $[\alpha]_D^{20.1}$ -164 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (2H, m, Ar**H**), 7.30-7.26 (3H, m, Ar**H**), 7.21 (1H, s, Ar**H**), 7.14 (1H, s, Ar**H**), 7.12 (1H, d, *J* = 2.0 Hz, C=C**H**), 3.98 (6H, s, 2 × OC$\mathbf{H}_3$), 2.77 (1H, d, *J* = 14.0 Hz, C$\mathbf{H}_a$H$_b$C=C), 2.68-2.57 (2H, m, CH$_a$$\mathbf{H}_b$C=C and C$\mathbf{H}_aH_b$C=O), 2.54-2.29 (3H, m, CH$_a$$\mathbf{H}_b$C=O and C$\mathbf{H}_2$COH), 1.79 (1H, d, *J* = 2.2 Hz, O**H**), 1.02 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.8 (C), 150.1 (C), 149.0 (C), 137.2 (C), 132.9 (C), 132.0 (C), 129.1 (2 × CH), 128.4 (2 × CH), 126.9 (CH), 126.1 (CH), 108.6 (CH), 106.5 (CH), 80.1 (C), 56.05 (CH_3), 55.98 (CH_3), 54.2 (C), 35.7 (CH_2), 35.4 (CH_2), 34.5 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{23}H_{24}NaO_4^+$ $[M+Na]^+$: 387.1567, found: 387.1573. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (85:15 hexane:*i*-PrOH, 0.3 mL/min, 210 nm, 23 °C): tr (minor) = 40.9 min, tr (major) = 42.4 min; 99% *ee*.

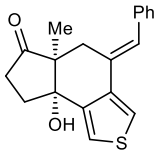


(-)-(3a*S*,11b*S*)-5-[(*E*)-Benzylidene]-11b-hydroxy-3a-methyl-1,2,3a,4,5,11b-hexahydro-3*H*-cyclopenta[*a*]anthracen-3-one (93s). General procedure 1 was followed using alkynone **92a** (67.8 mg, 0.30 mmol) and 2-naphthylboronic acid (77.4 mg, 0.45 mmol). Column chromatography (20% EtOAc/pentane) gave *alcohol* **93s** (66.0 mg, 64%) as an off-white solid. R_f = 0.39 (40% EtOAc/pentane); m.p. (Et_2O) 179-180 ˚C; IR (ATR) 3424 (OH), 2971, 2932, 1726 (C=O), 1461, 1225, 1025, 852, 696 cm^{-1}; $[\alpha]_D^{20.1}$ -212 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (1H, s, Ar**H**), 8.15 (1H, s, Ar**H**), 7.93-7.83 (2H, m, Ar**H**), 7.59-7.46 (2H, m, Ar**H**), 7.44-7.36 (3H, m, Ar**H** and C=C**H**), 7.36-7.26 (3H, m, Ar**H**), 2.89 (1H, d, *J* = 14.1 Hz, C$\mathbf{H}_a$H$_b$C=C), 2.74-2.62 (2H, m, CH$_a$$\mathbf{H}_b$C=C and C$\mathbf{H}_aH_b$C=O), 2.58-2.34 (3H, m, CH$_a$$\mathbf{H}_b$C=O and C$\mathbf{H}_2$COH), 1.97 (1H, d, *J* = 2.3 Hz, O**H**), 1.04 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.7 (C),138.9 (C), 137.1 (C), 133.5 (C), 133.1 (C), 133.0 (C), 132.3 (C), 129.2 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 128.0 (CH), 127.6 (CH), 127.2 (CH), 126.5 (CH), 126.4 (CH),

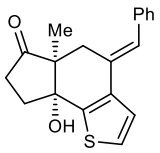
125.5 (CH), 123.2 (CH), 80.5 (C), 54.4 (C), 36.5 (CH_2), 35.1 (CH_2), 34.6 (CH_2), 13.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{25}H_{22}NaO_2^+$ $[M+Na]^+$: 377.1512, found: 377.1518. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (95:5 hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 23 °C): tr (minor) = 30.8 min, tr (major) = 33.7 min; 95% *ee*. Data matches those previously reported in the literature.[261]

Entry with 3-thienylboronic acid





(5a*S*,8a*R*)-4-[(*E*)-Benzylidene]-8a-hydroxy-5a-methyl-4,5,5a,7,8,8a-hexahydro-6H-indeno[4,5-*c*]thiophen-6-one (93t). A modification of the general procedure 1 was followed using alkynone **92a** (67.8 mg, 0.30 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol, 5 mol%), (*S*)-DTBM-Segphos (35.4 mg, 0.03 mmol, 10 mol%) and 3-thienylboronic acid (76.8 mg, 0.60 mmol, 2.0 equiv). Column chromatography (10% Et_2O/CH_2Cl_2) gave *alcohol* **93t** (43.5 mg, 47%) as a yellow solid. R_f = 0.19 (10% Et_2O/CH_2Cl_2); m.p. (Et_2O) 126-128 ˚C; IR (ATR) 3434 (OH), 2958, 2924, 2852, 1730 (C=O), 1442, 1050, 962, 792, 696 cm^{-1}; $[\alpha]_D^{20.1}$ -196 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, d, *J* = 3.1 Hz, Ar**H**), 7.48 (1H, d, *J* = 3.1 Hz, Ar**H**), 7.36 (2H, dd, *J* = 8.2, 7.0 Hz, Ar**H**), 7.27 (3H, s, Ar**H**), 7.16 (1H, d, *J* = 2.3 Hz, C=C**H**), 2.75 (1H, dd, *J* = 14.8, 1.0 Hz, C$\mathbf{H}_a$$H_b$C=C), 2.68-2.56 (2H, m, $CH_a$$\mathbf{H}_b$C=C and C$\mathbf{H}_a$$H_b$C=O), 2.52-2.36 (3H, m, $CH_a$$\mathbf{H}_b$C=O and C$\mathbf{H}_2$COH), 1.90 (1H, d, *J* = 2.0 Hz, O**H**), 0.99 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.2 (C), 142.9 (C), 137.5 (C), 136.6 (C), 129.1 (2 × CH), 128.44 (C), 128.39 (2 × CH), 127.0 (CH), 126.5 (CH), 122.3 (CH), 118.5 (CH), 79.4 (C), 55.1 (C), 35.4 (CH_2), 35.0 (CH_2), 34.8 (CH_2), 13.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{19}H_{18}NaO_2S^+$ $[M+Na]^+$: 333.0920, found: 333.0920. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 23 °C): tr (major) = 12.5 min, tr (minor) = 14.1 min; 99% *ee*.

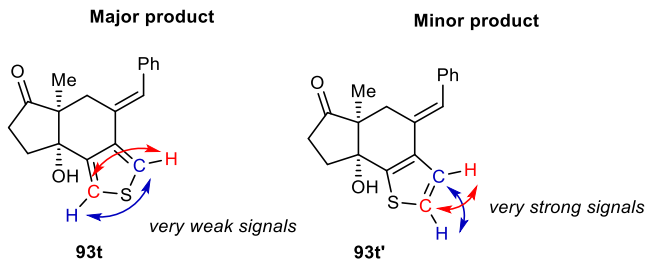


(-)-(5a*S*,8a*R*)-4-[(*E*)-Benzylidene]-8a-hydroxy-5a-methyl-4,5,5a,7,8,8a-hexahydro-6*H*-indeno[4,5-*b*]thiophen-6-one (93t'). (16.7 mg, 18 %) R_f = 0.14 (10% Et_2O/CH_2Cl_2); m.p. (Et_2O) 157-159 ˚C; IR (ATR) 3362 (OH), 2948, 2928,

1721 (C=O), 1395, 1126, 1073, 755, 698 cm^{-1}; $[\alpha]_D^{20.1}$ -8.00 (c 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.28 (6H, m, Ar**H**), 7.24 (1H, d, *J* = 5.3 Hz, Ar**H**), 7.01 (1H, s, C=C**H**), 2.92 (1H, dd, *J* = 15.2, 1.9 Hz, C$\mathbf{H}_a$$H_b$C=C), 2.63 (1H, dd, *J* = 15.2, 1.6 Hz, $CH_a$$\mathbf{H}_b$C=C), 2.59-2.41 (3H, m, C$\mathbf{H}_2$C=O and C$\mathbf{H}_a$$H_b$COH), 2.35-2.25 (1H, m, $CH_a$$\mathbf{H}_b$COH), 2.13-2.02 (1H, br s, O**H**), 1.10 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.9 (C), 141.9 (C), 138.1 (C), 136.7 (C), 129.1 (2 × CH), 129.0 (C), 128.4 (2 × CH), 127.0 (CH), 126.3 (CH), 125.9 (CH), 123.4 (CH), 78.2 (C), 54.9 (C), 35.8 (CH_2), 35.2 (CH_2), 33.2 (CH_2), 15.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{19}H_{18}NaO_2S^+$ $[M+Na]^+$: 333.0920, found: 333.0927. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (95:5 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (major) = 23.0 min, tr (minor) = 29.2 min; 98% *ee*.

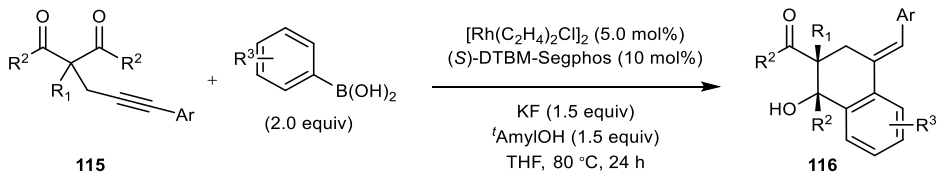
Due to structural similarity of the two products, exact determination of the two compounds is challenging. However, the slightly higher ^1H NMR *J* values of the two thiophene Ar**H**'s of **93t'** are indicative of a 1,2 thiophene relationship (^2J = 5.3 Hz vs value of similar compounds of *ca*. 5 Hz), whereas the two thiophene Ar**H**'s in major product **93t** have a lower coupling constant indicative of a 1,4 thiophene relationship (^4J = 3.1 Hz vs value of similar compounds of *ca*. 0-3 Hz). [269, 270]

Additionally, the HMBC 2D NMR of the minor product shows very strong coupling between the two thiophene Ar**H**'s and the adjacent carbon. This differs from the corresponding spectra of the major product which has very weak coupling between the corresponding protons and carbons, suggesting a greater separation between the interacting signals.



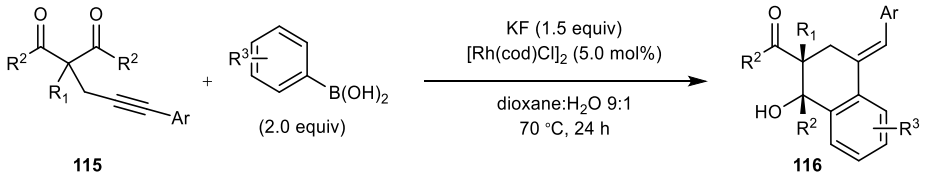
2.3.3.2 Acyclic Alkynones

General Procedure 2:

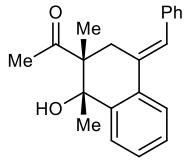


$[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol) and (*S*)-DTBM-Segphos (35.4 mg, 0.03 mmol) were added to an oven-dried microwave vial, which was sealed with a septum, and purged with argon for 30 mins. Degassed THF (6 mL) was added and the mixture was stirred at room temperature for 30 mins, under argon. In a separate oven-dried microwave vial the alkynone (0.30 mmol), boronic acid (0.60 mmol), and KF (26.1 mg, 0.45 mmol) were added. A septum was fitted and the vial was purged with argon for 30 mins. The catalyst solution was added to the vial containing the alkynone. ^{t}amyl alcohol (49 µL, 0.45 mmol) was added and the mixture was stirred at 80 ˚C for 24 h. The reaction was cooled to room temperature, diluted with water and saturated aqueous NH_4Cl solution was added. The mixture was extracted with EtOAc, the organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography gave alcohol **116**.

Non-enantioselective reaction conditions:



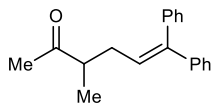
Alkynone (0.05 mmol), $[Rh(cod)Cl]_2$ (0.0025 mmol), boronic acid (0.10 mmol), and KF (0.075 mmol) were added to an oven-dried microwave vial which was sealed with a septum and purged with argon for 30 mins. A 9:1 mixture of dioxane and water (1 mL, both solvents degassed separately under argon for 30 mins) was added and the reaction solution was heated to 70 ˚C for 24 h. The reaction was cooled to room temperature, diluted with water and saturated aqueous NH_4Cl solution was added. The mixture was extracted with EtOAc, the organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The mixture was purified by preparative TLC (10% EtOAc/petroleum ether – ran three times) to obtain racemic traces.



1-{(1*S*,2*R*)-4-[(*E*)-Benzylidene]-1-hydroxy-1,2-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116a). General procedure 2 was followed using alkynone **115a** (68.4 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). Column chromatography (10% EtOAc/pentane) gave *alcohol* **116a** (67.1 mg, 73%) as a yellow solid. R_f = 0.15 (10% EtOAc/petroleum ether); m.p. (Et_2O) 128-129 ˚C; IR (ATR) 3476 (OH), 2995, 2970, 2927, 1683 (C=O), 1453, 1353, 1076, 918, 693 cm^{-1}; $[\alpha]_D^{20.1}$ -196 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.81 (1H, dd, *J* = 7.8, 1.5 Hz, Ar**H**), 7.65 (1H, dd, *J* = 8.1, 1.3 Hz, Ar**H**), 7.46-7.28 (6H, m, Ar**H**), 7.23 (1H, ddd, *J* = 8.6, 7.2, 1.5 Hz, Ar**H**), 7.17 (1H, d, *J* = 2.4 Hz, C=C**H**), 4.87 (1H, d, *J* = 1.3 Hz, O**H**), 3.41 (1H, dd, *J* = 16.6, 1.2 Hz, CC$\mathbf{H}_a$H$_b$), 2.94 (1H, dd, *J* = 16.5, 2.6 Hz, CCH$_a$$\mathbf{H}_b$), 1.90 (3H, s, O=CC$\mathbf{H}_3$), 1.41 (3H, d, *J* = 1.3 Hz, HOCC$\mathbf{H}_3$), 1.37 (3H, s, O=CCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) 217.5 (C), 145.9 (C), 137.3 (C), 132.89 (C), 132.88 (C), 129.3 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 127.1 (CH), 127.0 (CH), 125.7 (CH), 125.3 (CH), 123.3 (CH), 75.0 (C), 54.7 (C), 36.9 (CH_2), 26.8 (CH_3), 26.1 (CH_3), 18.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{21}H_{22}NaO_2^+$ $[M+Na]^+$: 329.1512, found: 329.1502. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 5.2 min, tr (major) = 5.9 min; 86% *ee*.

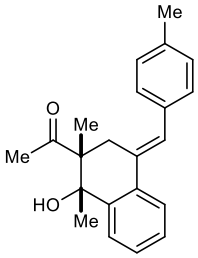
This result was a repeat reaction performed by the author of this thesis. This reaction was carried out by Dr. Jinwei Sun in the Results and Discussion section.

A side-product was also isolated which was determined to be **117**.

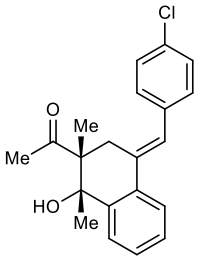


3-Methyl-6,6-diphenylhex-5-en-2-one (117): (10.0 mg, 13%). R_f = 0.30 (10% EtOAc/pentane); IR (ATR) 2964, 2924, 2852, 1709 (C=O), 1494, 1359, 1074, 758, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.29 (4H, m, Ar**H**), 7.26-7.15 (6H, m, Ar**H**), 6.01 (1H, t, *J* = 7.4 Hz, =C**H**CH$_2$), 2.63 (1H, p, *J* = 6.8 Hz, O=CC**H**), 2.47 (1H, dt, *J* = 14.7, 6.8 Hz, O=CCHC$\mathbf{H}_a$H$_b$), 2.23 (1H, dt, *J* = 14.9, 7.5 Hz, O=CCHCH$_a$$\mathbf{H}_b$), 2.09 (3H, s, O=CC$\mathbf{H}_3$), 1.11 (3H, d, *J* = 7.0 Hz, CHC$\mathbf{H}_3$); δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.8 (C), 143.6 (C), 142.4 (C), 139.8 (C), 129.8 (2 × CH), 128.3 (2 × CH), 128.1 (2 × CH), 127.2 (2 × CH), 127.1 (2 × CH), 126.2 (CH), 47.6 (CH), 32.7 (CH_2), 28.1 (CH_3), 15.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{19}H_{20}NaO^+$ $[M+Na]^+$: 287.1406, found: 287.1395.

This impurity was not obviously present in any of the crude ^{1}H NMR spectra of these cyclisation reactions, and so was only isolated and characterized for **116a**.

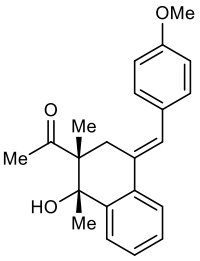


1-{1*S*,2*R*)-1-Hydroxy-1,2-dimethyl-4-[(*E*)-4-methylbenzylidene]-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116b). General procedure 2 was followed using alkynone **115b** (72.6 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). Column chromatography (10% EtOAc/pentane) gave *alcohol* **116b** (68.2 mg, 71%) as a yellow solid. R_f = 0.12 (10% EtOAc/petroleum ether); m.p. (Et_2O) 89-91 ˚C; IR (ATR) 3442 (OH), 3002, 2918, 2871, 1683 (C=O), 1510, 1354, 1072, 817, 699 cm^{-1}; $[\alpha]_D^{20.1}$ -224 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, dd, *J* = 7.8, 1.5 Hz, Ar**H**), 7.65 (1H, dd, *J* = 8.1, 1.3 Hz, Ar**H**), 7.36-7.21 (6H, m, Ar**H**), 7.15 (1H, d, *J* = 2.4 Hz, C=C**H**), 4.89 (1H, d, *J* = 1.3 Hz, O**H**), 3.43 (1H, dd, *J* = 16.6, 1.2 Hz, CC$\mathbf{H}_a$$H_b$), 2.94 (1H, dd, *J* = 16.6, 2.6 Hz, CC$H_a$$\mathbf{H}_b$), 2.42 (3H, s, ArC$\mathbf{H}_3$), 1.91 (3H, s, O=CC$\mathbf{H}_3$), 1.42 (3H, d, *J* = 1.3 Hz, HOCC$\mathbf{H}_3$), 1.38 (3H, s, O=CCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.6 (C), 145.8 (C), 137.0 (C), 134.4 (C), 133.1 (C), 132.2 (C), 129.24 (2 × CH), 129.22 (2 × CH), 128.4 (CH), 127.0 (CH), 125.8 (CH), 125.3 (CH), 123.2 (CH), 75.1 (C), 54.7 (C), 37.0 (CH_2), 26.7 (CH_3), 26.1 (CH_3), 21.3 (CH_3), 18.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{24}NaO_2^+$ $[M+Na]^+$: 343.1669, found: 343.1668. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 4.7 min, tr (major) = 5.7 min; 84% *ee*.

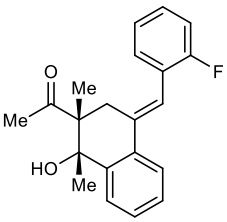


1-{(1*S*,2*R*)-4-[(*E*)-4-Chlorobenzylidene]-1-hydroxy-1,2-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116c). General procedure 2 was followed using alkynone **115c** (78.6 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). Column chromatography (10% EtOAc/pentane) gave *alcohol* **116c** (78.7 mg, 77%) as a yellow solid. R_f = 0.13 (10% EtOAc/petroleum ether); m.p. (Et_2O) 144-146 ˚C; IR (ATR) 3448 (OH), 2971, 2936, 1681 (C=O), 1562, 1354, 1073, 825, 691 cm^{-1}; $[\alpha]_D^{20.1}$ -80.0 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, dd, *J* = 8.0, 1.4 Hz, Ar**H**), 7.63 (1H, dd, *J* = 8.0, 1.2 Hz, Ar**H**), 7.41-7.37 (2H, m, Ar**H**), 7.36-7.28 (3H, m, Ar**H**), 7.23 (1H, ddd, *J* = 8.6, 7.3, 1.4 Hz, Ar**H**), 7.10 (1H, d, *J* = 1.8 Hz, C=C**H**), 4.84 (1H, d, *J* = 1.3 Hz, O**H**), 3.34 (1H, dd, *J* = 16.5, 1.1 Hz, CC$\mathbf{H}_a$$H_b$), 2.91 (1H, dd, *J* = 16.5, 2.7 Hz, CC$H_a$$\mathbf{H}_b$), 1.89 (3H, s, O=CC$\mathbf{H}_3$), 1.41 (3H, d, *J* = 1.4 Hz, HOCC$\mathbf{H}_3$), 1.37 (3H, s, O=CCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.2 (C), 146.0 (C), 135.7 (C), 133.6 (C), 132.9 (C), 132.6 (C), 130.5 (2 × CH), 128.9 (CH), 128.7 (2 × CH), 127.1 (CH), 125.4 (CH), 124.4 (CH), 123.3 (CH), 75.0 (C), 54.8 (C), 36.9 (CH_2), 26.8 (CH_3), 26.0

(CH_3), 18.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{21}ClH_{21}NaO_2^+$ $[M+Na]^+$: 363.1122, found: 363.1114. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 5.2 min, tr (major) = 7.0 min; 73% *ee*.



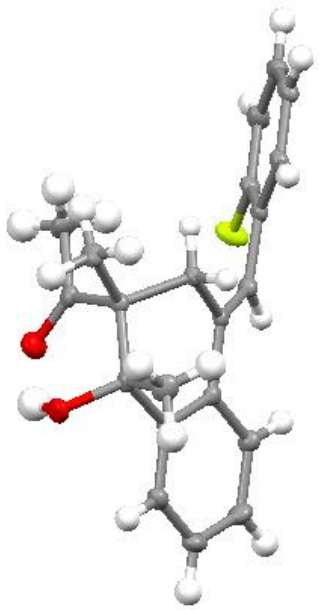
1-{(1*S*,2*R*)-1-Hydroxy-4-[(*E*)-4-methoxybenzylidene]-1,2-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116d). General procedure 2 was followed using alkynone **115d** (77.4 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). Column chromatography (10% EtOAc/pentane) gave *alcohol* **116d** (66.0 mg, 65%) as a yellow oil. R_f = 0.15 (10% EtOAc/petroleum ether); IR (ATR) 3454 (OH), 2971, 2934, 1686 (C=O), 1604, 1509, 1175, 1073, 826, 701 cm^{-1}; $[\alpha]_D^{20.1}$ -172 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, dd, *J* = 7.8, 1.4 Hz, Ar**H**), 7.62 (1H, dd, *J* = 8.0, 1.3 Hz, Ar**H**), 7.36-7.28 (3H, m, Ar**H**), 7.24-7.19 (1H, m, Ar**H**), 7.10 (1H, d, *J* = 2.5 Hz, C=C**H**), 6.99-6.93 (2H, m, Ar**H**), 4.88 (1H, d, *J* = 1.4 Hz, O**H**), 3.87 (3H, s, OC$\mathbf{H}_3$), 3.41 (1H, dd, *J* = 16.5, 1.1 Hz, CC$\mathbf{H}_a$$H_b$), 2.92 (1H, dd, *J* = 16.5, 2.6 Hz, CC$H_a$$\mathbf{H}_b$), 1.90 (3H, s, O=CC$\mathbf{H}_3$), 1.41 (3H, d, *J* = 1.3 Hz, HOCC$\mathbf{H}_3$), 1.37 (3H, s, O=CCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.6 (C), 158.6 (C), 145.6 (C), 133.2 (C), 131.3 (C), 130.6 (2 × CH), 129.9 (C), 128.3 (CH), 127.0 (CH), 125.4 (CH), 125.2 (CH), 123.1 (CH), 113.9 (2 × CH), 75.1 (C), 55.3 (CH_3), 54.6 (C), 37.0 (CH_2), 26.7 (CH_3), 26.1 (CH_3), 18.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{24}NaO_3^+$ $[M+Na]^+$: 359.1618, found: 359.1617. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 6.2 min, tr (major) = 8.2 min; 66% *ee*.

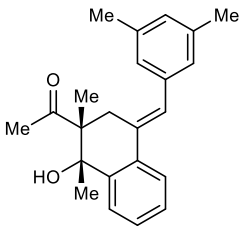


1-{(1*S*,2*R*)-4-[(*E*)-2-Fluorobenzylidene]-1-hydroxy-1,2-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116f). General procedure 2 was followed using alkynone **115f** (73.8 mg, 0.30 mmol) and repurified phenylboronic acid (73.2 mg, 0.60 mmol). Column chromatography (10% EtOAc/pentane) gave *alcohol* **116f** (71.9 mg, 74%) as a yellow solid. R_f = 0.15 (10% EtOAc/pentane); m.p. (Et_2O) 126-128 ˚C; IR (ATR) 3472 (OH), 2993, 2971, 2875, 1685 (C=O), 1485, 1352, 1229, 763, 694 cm^{-1}; $[\alpha]_D^{20.1}$ -164 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, dd, *J* = 7.9, 1.4 Hz, Ar**H**), 7.67 (1H, dd, *J* = 8.0, 1.2 Hz, Ar**H**), 7.39-7.28 (3H, m, Ar**H**), 7.26-7.13 (3H, m, Ar**H**), 7.12 (1H, d, *J* = 1.8 Hz, C=C**H**), 4.90 (1H, d, *J* = 1.5 Hz, O**H**), 3.18 (1H, dd, *J* = 16.6, 1.1 Hz, CC$\mathbf{H}_a$$H_b$), 2.88 (1H, dd,

J = 16.6, 2.7 Hz, $CCH_a\mathbf{H}_b$), 1.92 (3H, s, O=CC$\mathbf{H}_3$), 1.42 (3H, d, J = 1.0 Hz, HOCC$\mathbf{H}_3$), 1.35 (3H, s, O=CCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.4 (C), 160.2 (C, J_{CF} = 247.9 Hz), 146.1 (C), 135.1 (C), 132.3 (C), 130.7 (CH), 129.1 (CH, J_{CF} = 8.3 Hz), 128.9 (CH), 127.0 (CH), 125.5 (CH), 125.0 (C, J_{CF} = 14.6 Hz), 124.0 (CH, J_{CF} = 3.6 Hz), 123.5 (CH), 118.2 (CH), 115.8 (CH, J_{CF} = 22.0 Hz), 75.1 (C), 54.8 (C), 36.8 (CH_2), 26.9 (CH_3), 25.8 (CH_3), 18.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.1; HRMS (ESI) Exact mass calcd for $C_{21}H_{21}FNaO_2^+$ $[M+Na]^+$: 347.1418, found: 347.1413. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 5.2 min, tr (major) = 6.1 min; 97% *ee*.

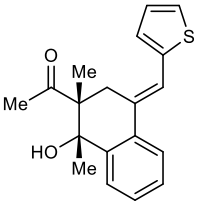
An X-ray crystal structure of **116f** was obtained by recrystallization in pentane/CH_2Cl_2.



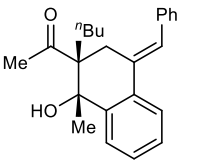


1-{(1*S*,2*R*)-4-[(*E*)-3,5-Dimethylbenzylidene]-1-hydroxy-1,2-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116g). General procedure 2 was followed using alkynone **115g** (76.8 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). Column chromatography (10% EtOAc/pentane) gave *alcohol* **116g** (72.9 mg, 73%) as a yellow oil. R_f = 0.14 (10% EtOAc/petroleum ether); IR (ATR) 3461 (OH), 2977, 2918, 2865, 1687 (C=O), 1596, 1353, 1073, 841, 683 cm^{-1}; $[\alpha]_D^{20.1}$ -204 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, dd, J = 7.8, 1.4 Hz, Ar**H**), 7.63 (1H, dd, J = 8.0, 1.2 Hz, Ar**H**), 7.32 (1H, td, J = 7.5, 1.3 Hz, Ar**H**), 7.22 (1H, ddd, J = 8.5, 7.3, 1.5 Hz, Ar**H**), 7.11 (1H, d, J = 2.5 Hz, C=C**H**), 6.98 (2H, s, Ar**H**), 6.95 (1H, s, Ar**H**), 4.89 (1H, d, J = 1.3 Hz, O**H**), 3.41

(1H, dd, J = 16.5, 1.1 Hz, CC**H**$_a$H$_b$), 2.93 (1H, dd, J = 16.5, 2.6 Hz, CCH$_a$**H**$_b$), 2.38 (6H, s, 2 × ArC**H**$_3$), 1.92 (3H, s, O=CC**H**$_3$), 1.42 (3H, d, J = 1.3 Hz, HOCC**H**$_3$), 1.37 (3H, s, O=CCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.7 (C), 145.8 (C), 137.9 (2 × C), 137.2 (C), 133.1 (C)¸132.4 (C), 128.9 (CH), 128.4 (CH), 127.1 (2 × CH), 127.0 (CH), 126.0 (CH), 125.3 (CH), 123.2 (CH), 75.1 (C), 54.7 (C), 36.9 (CH_2), 26.7 (CH_3), 26.2 (CH_3), 21.4 (CH_3), 18.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{23}H_{26}NaO_2^+$ $[M+Na]^+$: 357.1825, found: 357.1821. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 4.1 min, tr (major) = 4.6 min; 75% *ee*.

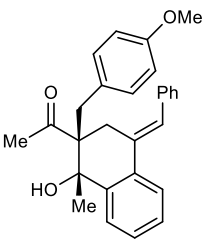


1-{(1S,2*R*,*E*)-1-Hydroxy-1,2-dimethyl-4-(thiophen-2-ylmethylene)-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116j). General procedure 2 was followed using alkynone **115j** (70.2 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). Column chromatography (10% EtOAc/pentane) gave *alcohol* **116j** (58.7 mg, 63%) as a yellow oil. R_f = 0.11 (10% EtOAc/petroleum ether); IR (ATR) 3461 (OH), 3064, 2974, 2928, 1684 (C=O), 1352, 1073, 758, 693 cm^{-1}; $[\alpha]_D^{20.1}$ -168 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, dd, J = 7.8, 1.4 Hz, Ar**H**), 7.62 (1H, dd, J = 8.0, 1.3 Hz, Ar**H**), 7.41 (1H, dd, J = 5.2, 1.0 Hz, Ar**H**), 7.34-7.28 (2H, m, Ar**H** and C=C**H**), 7.25-7.19 (2H, m, Ar**H**), 7.14 (1H, dd, J = 5.1, 3.6 Hz, Ar**H**), 4.92 (1H, s, O**H**), 3.55 (1H, dd, J = 17.9, 1.7 Hz, CC**H**$_a$H$_b$), 2.91 (1H, dd, J = 17.9, 2.6 Hz, CCH$_a$**H**$_b$), 2.01 (3H, s, O=CC**H**$_3$), 1.47 (3H, s, HOCC**H**$_3$), 1.35 (3H, s, O=CCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.4 (C), 145.8 (C), 140.7 (C), 133.2 (C), 130.3 (C), 128.6 (CH), 128.3 (CH), 127.4 (CH), 127.2 (CH), 126.2 (CH), 124.6 (CH), 123.2 (CH), 119.1 (CH), 75.0 (C), 53.7 (C), 37.5 (CH_2), 27.2 (CH_3), 25.3 (CH_3), 19.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{19}H_{20}NaO_2S^+$ $[M+Na]^+$: 335.1076, found: 335.1072. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 6.0 min, tr (major) = 7.2 min; 81% *ee*.

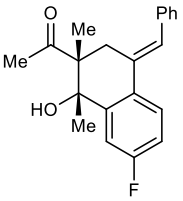


1-{(1*S*,2*R*)-4-[(*E*)-Benzylidene]-2-butyl-1-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116o). A modification of general procedure 2 was followed using alkynone **115o** (81.0 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol) at 60 °C. Column chromatography (10% EtOAc/pentane) gave *alcohol* **116o** (38.8 mg, 36%) as a yellow oil. R_f = 0.17 (10% EtOAc/petroleum ether); IR (ATR) 3443 (OH), 2956, 2929, 2870, 1684 (C=O), 1354, 1038, 758, 697 cm^{-1}; $[\alpha]_D^{20.1}$ -48.0 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, dd, J =

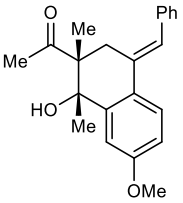
7.8, 1.5 Hz, Ar**H**), 7.62 (1H, dd, *J* = 8.0, 1.3 Hz, Ar**H**), 7.47-7.38 (4H, m, Ar**H**), 7.36-7.28 (2H, m, Ar**H**), 7.29-7.19 (1H, m, Ar**H**), 7.12 (1H, t, *J* = 1.9 Hz, C=C**H**), 4.81 (1H, d, *J* = 1.3 Hz, O**H**), 3.49 (1H, dd, *J* = 17.0, 1.5 Hz, CC$\mathbf{H}_a$$H_b$), 2.87 (1H, dd, *J* = 17.0, 2.6 Hz, CC$H_a$$\mathbf{H}_b$), 2.16 (1H, td, *J* = 13.5, 4.3 Hz, O=CCC$\mathbf{H}_a$$H_b$), 1.87 (3H, s, O=CC$\mathbf{H}_3$), 1.61-1.57 (1H, m, O=CCC$H_a$$\mathbf{H}_b$), 1.50-1.21 (7H, m, HOCC$\mathbf{H}_3$ and C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_3$), 0.91 (3H, t, *J* = 7.1 Hz, CH_2CH_2C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.5 (C), 145.9 (C), 137.4 (C), 133.6 (C), 133.2 (C), 129.3 (2 × CH), 128.54 (2 × CH), 128.53 (CH), 127.2 (CH), 127.1 (CH), 126.0 (CH), 125.0 (CH), 123.4 (CH), 75.7 (C), 57.4 (C), 35.8 (CH_2), 35.3 (CH_2), 28.7 (CH_3), 27.6 (CH_2), 26.2 (CH_3), 23.7 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{24}H_{28}NaO_2^+$ $[M+Na]^+$: 371.1982, found: 371.1973. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 4.3 min, tr (major) = 5.7 min; 87% *ee*.



1-{(1*S*,2*R*)-4-[(*E*)-Benzylidene]-1-hydroxy-2-(4-methoxybenzyl)-1-methyl-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116q). A modification of general procedure 2 was followed using alkynone **115q** (100 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol) at 60 °C. Column chromatography (10% EtOAc/pentane) gave *alcohol* **116q** (62.7 mg, 51%) as a yellow oil. R_f = 0.15 (10% EtOAc/petroleum ether); IR 3433 (OH), 2956, 2934, 1678 (C=O), 1511, 1353, 1246, 1032, 759, 693 (ATR) cm^{-1}; $[\alpha]_D^{20.1}$ +140 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, dd, *J* = 7.9, 1.4 Hz, Ar**H**), 7.64 (1H, dd, *J* = 7.9, 1.2 Hz, Ar**H**), 7.48-7.40 (4H, m, Ar**H**), 7.40-7.22 (3H, m, Ar**H**), 7.12-7.04 (3H, m, Ar**H** and C=C**H**), 6.84 (2H, d, *J* = 8.6 Hz, Ar**H**), 5.30 (1H, m, O**H**), 3.80 (3H, s, OC$\mathbf{H}_3$), 3.61 (1H, d, *J* = 13.3 Hz, ArC$\mathbf{H}_a$$H_b$), 3.54 (1H, dd, *J* = 18.2, 2.1 Hz, C=CC$\mathbf{H}_a$$H_b$), 3.04 (1H, dd, *J* = 18.2, 2.6 Hz, C=CC$H_a$$\mathbf{H}_b$), 2.84 (1H, d, *J* = 13.3 Hz, ArC$H_a$$\mathbf{H}_b$), 1.43 (3H, d, *J* = 1.4 Hz, HOCC$\mathbf{H}_3$), 1.41 (3H, s, O=CCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.0 (C), 158.5 (C), 145.4 (C), 137.3 (C), 134.3 (C), 132.8 (C), 131.0 (2 × CH), 129.3 (2 × CH), 128.5 (2 × CH), 128.4 (CH), 128.3 (C), 127.4 (CH), 127.1 (CH), 126.5 (CH), 124.3 (CH), 123.6 (CH), 113.8 (2 × CH), 75.6 (C), 57.2 (C), 55.2 (CH_3), 39.5 (CH_2), 35.0 (CH_2), 31.5 (CH_3), 25.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{28}H_{28}NaO_3^+$ $[M+Na]^+$: 435.1931, found: 435.1927. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 23 °C): tr (major) = 6.7 min, tr (minor) = 8.2 min; 96% *ee*.

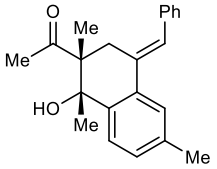


1-{(1*S*,2*R*)-4-[(*E*)-Benzylidene]-7-fluoro-1-hydroxy-1,2-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116u). General procedure 2 was followed using alkynone **115a** (68.4 mg, 0.30 mmol) and 4-fluorophenylboronic acid (84.0 mg, 0.60 mmol). Column chromatography (10% EtOAc/pentane) gave *alcohol* **116u** (72.3 mg, 74%) as a yellow solid. R_f = 0.11 (10% EtOAc/petroleum ether); m.p. (Et_2O) 129-131 ˚C; IR (ATR) 3475 (OH), 2973, 2919, 1686 (C=O), 1479, 1374, 1064, 769, 696 cm^{-1}; $[\alpha]_D^{20.1}$ -228 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, dd, *J* = 8.8, 5.5 Hz, Ar**H**), 7.50 (1H, dd, *J* = 10.0, 2.8 Hz, Ar**H**), 7.46-7.40 (2H, m, Ar**H**), 7.38-7.29 (3H, m, Ar**H**), 7.08 (1H, d, *J* = 1.7 Hz, C=C**H**), 6.92 (1H, ddd, *J* = 8.8, 7.9, 2.8 Hz, Ar**H**), 4.91 (1H, d, *J* = 1.4 Hz, O**H**), 3.39 (1H, dd, *J* = 16.6, 1.1 Hz, CC$\mathbf{H}_a$$H_b$), 2.91 (1H, dd, *J* = 16.6, 2.7 Hz, CC$H_a$$\mathbf{H}_b$), 1.89 (3H, s, O=CC$\mathbf{H}_3$), 1.40 (3H, d, *J* = 1.4 Hz, HOCC$\mathbf{H}_3$), 1.36 (3H, s, O=CCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.3 (C), 163.3 (C, J_{CF} = 248.0 Hz), 148.6 (C), 137.1 (C), 131.9 (C), 129.2 (2 × CH), 129.0 (C), 128.6 (2 × CH), 127.2 (CH), 125.4 (CH), 125.3 (CH, J_{CF} = 7.9 Hz), 114.4 (CH, J_{CF} = 22.0 Hz), 112.1 (CH, J_{CF} = 22.7 Hz), 74.9 (C), 54.7 (C), 36.8 (CH_2), 26.7 (CH_3), 25.9 (CH_3), 18.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.1; HRMS (ESI) Exact mass calcd for $C_{21}H_{21}FNaO_2^+$ $[M+Na]^+$: 347.1418, found: 347.1416. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 6.3 min, tr (major) = 6.7 min; 93% *ee*.



1-{(1*S*,2*R*)-4-[(*E*)-Benzylidene]-1-hydroxy-7-methoxy-1,2-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116w). General procedure 2 was followed using alkynone **115a** (68.4 mg, 0.30 mmol) and 4-methoxyphenylboronic acid (91.8 mg, 0.60 mmol). Column chromatography (10% EtOAc/pentane) gave *alcohol* **116w** (53.2 mg, 53%) as a yellow oil. R_f = 0.15 (10% EtOAc/petroleum ether); IR (ATR) 3450 (OH), 2965, 2935, 1686 (C=O), 1600, 1354, 1068, 1030, 768, 697 cm^{-1}; $[\alpha]_D^{20.1}$ -200 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 8.7 Hz, Ar**H**), 7.41 (2H, t, *J* = 7.7 Hz, Ar**H**), 7.38-7.32 (3H, m, Ar**H**), 7.31-7.28 (1H, m, Ar**H**), 7.04 (1H, d, *J* = 2.5 Hz, C=C**H**), 6.79 (1H, dd, *J* = 8.8, 2.8 Hz, Ar**H**), 4.96 (1H, d, *J* = 1.4 Hz, O**H**), 3.86 (3H, s, OC$\mathbf{H}_3$), 3.38 (1H, dd, *J* = 16.7, 1.2 Hz, CC$\mathbf{H}_a$$H_b$), 2.92 (1H, dd, *J* = 16.7, 2.7 Hz, CC$H_a$$\mathbf{H}_b$), 1.90 (3H, s, O=CC$\mathbf{H}_3$), 1.41 (3H, d, *J* = 1.4 Hz, HOCC$\mathbf{H}_3$), 1.36 (3H, s, O=CCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.8 (C), 160.1 (C), 147.8 (C), 137.5 (C), 132.4 (C), 129.2 (2 × CH), 128.5 (2 × CH), 126.8 (CH), 125.6 (C), 124.9 (CH), 123.5 (CH), 114.1

(CH), 109.2 (CH), 75.2 (C), 55.3 (CH_3), 54.6 (C), 37.0 (CH_2), 26.6 (CH_3), 26.1 (CH_3), 18.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{24}NaO_3^+$ $[M+Na]^+$: 359.1618, found: 359.1614. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 6.1 min, tr (major) = 8.5 min; 96% *ee*.



1-{(1*S*,2*R*)-4-[(*E*)-Benzylidene]-1-hydroxy-1,2,6-trimethyl-1,2,3,4-tetrahydronaphthalen-2-yl}ethan-1-one (116x). General procedure 2 was followed using alkynone **115a** (68.4 mg, 0.30 mmol) and 3-methylphenylboronic acid (81.6 mg, 0.60 mmol). Column chromatography (10% EtOAc/pentane) gave *alcohol* **116x** (70.8 mg, 74%) as a yellow oil. R_f = 0.14 (10% EtOAc/petroleum ether); IR (ATR) 3471 (OH), 3021, 2979, 1681 (C=O), 1352, 1073, 768, 699 cm^{-1}; $[\alpha]_D^{20.1}$ -208 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.48-7.40 (3H, m, Ar**H**), 7.39-7.35 (2H, m, Ar**H**), 7.34-7.28 (1H, m, Ar**H**), 7.19-7.12 (2H, m, C=C**H** and Ar**H**), 4.85 (1H, d, *J* = 1.3 Hz, O**H**), 3.40 (1H, dd, *J* = 16.6, 1.2 Hz, CC$\mathbf{H}_a$$H_b$ 1H), 2.92 (1H, dd, *J* = 16.6, 2.7 Hz, $CCH_a\mathbf{H}_b$), 2.36 (3H, s, ArC$\mathbf{H}_3$), 1.89 (3H, s, O=CC$\mathbf{H}_3$), 1.40 (1H, d, *J* = 1.4 Hz, HOCC$\mathbf{H}_3$), 1.35 (3H, s, O=CCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.5 (C), 143.1 (C), 137.3 (C), 136.4 (C), 132.9 (C), 132.7 (C), 129.6 (CH), 129.3 (2 × CH), 128.5 (2 × CH), 127.0 (CH), 125.5 (CH), 125.3 (CH), 123.7 (CH), 75.0 (C), 54.8 (C), 36.9 (CH_2), 26.8 (CH_3), 26.1 (CH_3), 21.2 (CH_3), 18.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{24}NaO_2^+$ $[M+Na]^+$: 343.1669, found: 343.1663. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (95:5 hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 23 °C): tr (minor) = 7.1 min, tr (major) = 7.8 min; 90% *ee*.

References

1. N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457-2483.
2. D. Roy and Y. Uozumi, *Adv. Synth. Catal.*, 2018, **360**, 602-625.
3. R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417-1492.
4. R. H. Crabtree and A. Lei, *Chem. Rev.*, 2017, **117**, 8481-8482.
5. H. M. L. Davies and D. Morton, *ACS Central Science*, 2017, **3**, 936-943.
6. A. Vasseur, J. Bruffaerts and I. Marek, *Nat Chem*, 2016, **8**, 209-219.
7. R. Breslow, R. J. Corcoran and B. B. Snider, *J. Am. Chem. Soc.*, 1974, **96**, 6791-6792.
8. J. M. Ntambi, *J. Lipid Res.*, 1999, **40**, 1549-1558.
9. S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera and D. Maiti, *J. Am. Chem. Soc.*, 2015, **137**, 11888-11891.
10. X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle and J.-Q. Yu, *Nature*, 2015, **519**, 334-338.
11. J. J. Topczewski, P. J. Cabrera, N. I. Saper and M. S. Sanford, *Nature*, 2016, **531**, 220-224.
12. Y. Liu and H. Ge, *Nat. Chem.*, 2017, **9**, 26-32.
13. C. A. Brown and A. Yamashita, *J. Am. Chem. Soc.*, 1975, **97**, 891-892.
14. H. Sommer, F. Juliá-Hernández, R. Martin and I. Marek, *ACS Central Science*, 2018, **4**, 153-165.
15. S. D. Ittel, L. K. Johnson and M. Brookhart, *Chem. Rev.*, 2000, **100**, 1169-1203.
16. R. S. Coffey, *Tetrahedron Lett.*, 1965, **6**, 3809-3811.
17. B. Grotjahn Douglas, *Pure Appl. Chem.*, 2010, **82**, 635-647.
18. D. A. Geselowitz and H. Taube, *Inorg. Chem.*, 1981, **20**, 4036-4036.
19. S. Ma and Z. Gu, *Angew. Chem., Int. Ed.*, 2005, **44**, 7512-7517.
20. L. Rosenblum, *J. Am. Chem. Soc.*, 1955, **77**, 5016-5017.
21. H. C. Brown and B. C. S. Rao, *J. Am. Chem. Soc.*, 1959, **81**, 6434-6437.
22. H. C. Brown and B. C. S. Rao, *J. Am. Chem. Soc.*, 1959, **81**, 6428-6434.
23. H. C. Brown and M. V. Bhatt, *J. Am. Chem. Soc.*, 1960, **82**, 2074-2075.
24. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1960, **82**, 4708-4712.
25. H. C. Brown and M. V. Bhatt, *J. Am. Chem. Soc.*, 1966, **88**, 1440-1443.
26. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1966, **88**, 1433-1439.
27. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1967, **89**, 561-566.
28. S. P. Acharya, H. C. Brown, A. Suzuki, S. Nozawa and M. Itoh, *J. Org. Chem.*, 1969, **34**, 3015-3022.
29. G. F. Schmidt and M. Brookhart, *J. Am. Chem. Soc.*, 1985, **107**, 1443-1444.
30. M. Brookhart, A. F. Volpe, D. M. Lincoln, I. T. Horvath and J. M. Millar, *J. Am. Chem. Soc.*, 1990, **112**, 5634-5636.
31. L. K. Johnson, C. M. Killian and M. Brookhart, *J. Am. Chem. Soc.*, 1995, **117**, 6414-6415.
32. L. H. Shultz and M. Brookhart, *Organometallics*, 2001, **20**, 3975-3982.
33. T. Vaidya, K. Klimovica, A. M. LaPointe, I. Keresztes, E. B. Lobkovsky, O. Daugulis and G. W. Coates, *J. Am. Chem. Soc.*, 2014, **136**, 7213-7216.
34. M. A. A. Seayad, H. Klein, R. Jackstell, T. Gross, M. Beller, *Science*, 2002, **297**, 1676-1678.
35. D. Selent, D. Hess, K.-D. Wiese, D. Röttger, C. Kunze and A. Börner, *Angew. Chem., Int. Ed.*, 2001, **40**, 1696-1698.
36. M. Vilches-Herrera, L. Domke and A. Börner, *ACS Catal.*, 2014, **4**, 1706-1724.
37. J. V. Obligacion and P. J. Chirik, *J. Am. Chem. Soc.*, 2013, **135**, 19107-19110.
38. C. C. Atienza, T. Diao, K. J. Weller, S. A. Nye, K. M. Lewis, J. G. Delis, J. L. Boyer, A. K. Roy and P. J. Chirik, *J. Am. Chem. Soc.*, 2014, **136**, 12108-12118.
39. J. V. Obligacion and P. J. Chirik, *Org. Lett.*, 2013, **15**, 2680-2683.
40. H. Li and C. Mazet, *Acc. Chem. Res.*, 2016, **49**, 1232-1241.
41. Y. Ebe, M. Onoda, T. Nishimura and H. Yorimitsu, *Angew. Chem., Int. Ed.*, 2017, **56**, 5607-5611.
42. J. B. Melpolder and R. F. Heck, *J. Org. Chem.*, 1976, **41**, 265-272.

43. A. J. Chalk and S. A. Magennis, *J. Org. Chem.*, 1976, **41**, 1206-1209.
44. E. W. Werner, T.-S. Mei, A. J. Burckle and M. S. Sigman, *Science*, 2012, **338**, 1455-1458.
45. T.-S. Mei, H. H. Patel and M. S. Sigman, *Nature*, 2014, **508**, 340-344.
46. L. Xu, *J. Am. Chem. Soc.*, 2014, **136**, 1960-1967.
47. C. Zhang, C. B. Santiago, L. Kou and M. S. Sigman, *J. Am. Chem. Soc.*, 2015, **137**, 7290-7293.
48. T.-S. Mei, E. W. Werner, A. J. Burckle and M. S. Sigman, *J. Am. Chem. Soc.*, 2013, **135**, 6830-6833.
49. M. J. Hilton, L.-P. Xu, P.-O. Norrby, Y.-D. Wu, O. Wiest and M. S. Sigman, *J. Org. Chem.*, 2014, **79**, 11841-11850.
50. H. H. Patel and M. S. Sigman, *J. Am. Chem. Soc.*, 2015, **137**, 3462-3465.
51. V. Saini, M. O'Dair and M. S. Sigman, *J. Am. Chem. Soc.*, 2015, **137**, 608-611.
52. C. Zhang, C. B. Santiago, J. M. Crawford and M. S. Sigman, *J. Am. Chem. Soc.*, 2015, **137**, 15668-15671.
53. Z.-M. Chen, M. J. Hilton and M. S. Sigman, *J. Am. Chem. Soc.*, 2016, **138**, 11461-11464.
54. H. H. Patel and M. S. Sigman, *J. Am. Chem. Soc.*, 2016, **138**, 14226-14229.
55. T. Kochi, T. Hamasaki, Y. Aoyama, J. Kawasaki and F. Kakiuchi, *J. Am. Chem. Soc.*, 2012, **134**, 16544-16547.
56. L. A. Goj and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2001, **123**, 11133-11147.
57. T. Hamasaki, Y. Aoyama, J. Kawasaki, F. Kakiuchi and T. Kochi, *J. Am. Chem. Soc.*, 2015, **137**, 16163-16171.
58. H. Taro, K. Fumitoshi and K. Takuya, *Chem. Lett.*, 2016, **45**, 297-299.
59. L. Lin, C. Romano and C. Mazet, *J. Am. Chem. Soc.*, 2016, **138**, 10344-10350.
60. A. Renaudat, L. Jean-Gérard, R. Jazzar, C. E. Kefalidis, E. Clot and O. Baudoin, *Angew. Chem. Int. Ed.*, 2010, **49**, 7261-7265.
61. S. Aspin, A.-S. Goutierre, P. Larini, R. Jazzar and O. Baudoin, *Angew. Chem. Int. Ed.*, 2012, **51**, 10808-10811.
62. P. Larini, C. E. Kefalidis, R. Jazzar, A. Renaudat, E. Clot and O. Baudoin, *Chem. Eur. J.*, 2012, **18**, 1932-1944.
63. A. Millet, P. Larini, E. Clot and O. Baudoin, *Chemical Science*, 2013, **4**, 2241-2247.
64. A. Millet, D. Dailler, P. Larini and O. Baudoin, *Angew. Chem., Int. Ed.*, 2014, **53**, 2678-2682.
65. H. Wakamatsu, *J. Org. Chem.*, 2000, **65**, 3966-3970.
66. M. Hada, H. Nakatsuji, J. Ushio, M. Izawa and H. Yokono, *Organometallics*, 1993, **12**, 3398-3404.
67. S. E. Denmark and J. Fu, *Chem. Rev.*, 2003, **103**, 2763-2794.
68. T. Doi, T. Fukuyama, S. Minamino, G. Husson and I. Ryu, *Chem. Commun.*, 2006, **17**, 1875-1877.
69. T. Fukuyama, T. Doi, S. Minamino, S. Omura and I. Ryu, *Angew. Chem., Int. Ed.*, 2007, **46**, 5559-5561.
70. S. Omura, T. Fukuyama, J. Horiguchi, Y. Murakami and I. Ryu, *J. Am. Chem. Soc.*, 2008, **130**, 14094-14095.
71. L. Wu, I. Fleischer, R. Jackstell, I. Profir, R. Franke and M. Beller, *J. Am. Chem. Soc.*, 2013, **135**, 14306-14312.
72. J. S. Bair, Y. Schramm, A. G. Sergeev, E. Clot, O. Eisenstein and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 13098-13101.
73. S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299-309.
74. F. Juliá-Hernández, T. Moragas, J. Cornella and R. Martin, *Nature*, 2017, **545**, 84-88.
75. L. Peng, Y. Li, Y. Li, W. Wang, H. Pang and G. Yin, *ACS Catal.*, 2018, **8**, 310-313.
76. S. D. Ittel, L. K. Johnson and M. Brookhart, *Chem. Rev.*, 2000, **100**, 1169-1204.
77. F. Wang, R. Tanaka, Q. Li, Y. Nakayama and T. Shiono, *Organometallics*, 2018, **37**, 1358-1367.
78. M. M. Wegner, A. K. Ott and B. Rieger, *Macromolecules*, 2010, **43**, 3624-3633.
79. D. N. Vaccarello, K. S. O'Connor, P. Iacono, J. M. Rose, A. E. Cherian and G. W. Coates, *J. Am. Chem. Soc.*, 2018, **140**, 6208-6211.
80. F. Zhou, J. Zhu, Y. Zhang and S. Zhu, *Angew. Chem., Int. Ed.*, 2018, **57**, 4058-4062.

81. Y. He, Y. Cai and S. Zhu, *J. Am. Chem. Soc.*, 2017, **139**, 1061-1064.
82. F. Chen, K. Chen, Y. Zhang, Y. He, Y.-M. Wang and S. Zhu, *J. Am. Chem. Soc.*, 2017, **139**, 13929-13935.
83. D. W. Hart and J. Schwartz, *J. Am. Chem. Soc.*, 1974, **96**, 8115-8116.
84. S. S. Pereira, M.,, *J. Am. Chem. Soc.*, 1996, **118**, 909-910.
85. P. J. Chirik, M. W. Day, J. A. Labinger and J. E. Bercaw, *J. Am. Chem. Soc.*, 1999, **121**, 10308-10317.
86. L. Mola, M. Sidera and S. P. Fletcher, *Aust. J. Chem.*, 2015, **68**, 401-403.
87. N. Chinkov, S. Majumdar and I. Marek, *J. Am. Chem. Soc.*, 2002, **124**, 10282-10283.
88. N. Chinkov, S. Majumdar and I. Marek, *J. Am. Chem. Soc.*, 2003, **125**, 13258-13264.
89. N. Chinkov, A. Levin and I. Marek, *Angew. Chem., Int. Ed.*, 2006, **45**, 465-468.
90. A. Masarwa, D. Didier, T. Zabrodski, M. Schinkel, L. Ackermann and I. Marek, *Nature*, 2014, **505**, 199-203.
91. S. Singh, J. Bruffaerts, A. Vasseur and I. Marek, *Nat. Commun.*, 2017, **8**, 14200.
92. A. Vasseur, L. Perrin, O. Eisenstein and I. Marek, *Chem. Sci.*, 2015, **6**, 2770-2776.
93. W. Strohmeier and L. Weigelt, *J. Organomet. Chem.*, 1975, **86**, C17-C19.
94. R. Uma, C. Crevisy and R. Gree, *Chem. Rev.*, 2003, **103**, 27-51.
95. M. Ahmed, R. P. Bronger, R. Jackstell, P. C. Kamer, P. W. van Leeuwen and M. Beller, *Chem. Eur. J.*, 2006, **12**, 8979-8988.
96. Y. Yuki, K. Takahashi, Y. Tanaka and K. Nozaki, *J. Am. Chem. Soc.*, 2013, **135**, 17393-17400.
97. K. Takahashi, M. Yamashita and K. Nozaki, *J. Am. Chem. Soc.*, 2012, **134**, 18746-18757.
98. C. J. Lata and C. M. Crudden, *J. Am. Chem. Soc.*, 2010, **132**, 131-137.
99. D. Männig and H. Nöth, *Angew. Chem. Int. Ed. Engl.*, 1985, **24**, 878-879.
100. D. A. Evans, G. C. Fu and B. A. Anderson, *J. Am. Chem. Soc.*, 1992, **114**, 6679-6685.
101. S. W. Hadebe and R. S. Robinson, *Tetrahedron Lett.*, 2006, **47**, 1299-1302.
102. S. Pereira and M. Srebnik, *Tetrahedron Lett.*, 1996, **37**, 3283-3286.
103. D. D. Andjelkovic, B. Min, D. Ahn and R. C. Larock, *J. Agric. Food Chem.*, 2006, **54**, 9535-9543.
104. A. Philippaerts, J. V. Aelst and B. Sels, *Eur. J. Lipid Sci. Technol.*, 2013, **115**, 721-728.
105. D. M. Ohlmann, L. J. Gooen and M. Dierker, *Chem. Eur. J.*, 2011, **17**, 9508-9519.
106. A. J. Borah and Z. Shi, *J. Am. Chem. Soc.*, 2018, **140**, 6062-6066.
107. Y. Yamamoto and N. Asao, *Chem. Rev.*, 1993, **93**, 2207-2293.
108. Z. Lu and S. Ma, *Angew. Chem. Int. Ed.*, 2008, **47**, 258-297.
109. P. Koschker and B. Breit, *Acc. Chem. Res.*, 2016, **49**, 1524-1536.
110. B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921-2944.
111. P.-S. Wang, M.-L. Shen and L.-Z. Gong, *Synthesis*, 2018, **50**, 956-967.
112. M. Yus, J. C. González-Gómez and F. Foubelo, *Chem. Rev.*, 2013, **113**, 5595-5698.
113. S. E. Denmark and E. J. Weber, *Helv. Chim. Acta*, 1983, **66**, 1655-1660.
114. T. Mejuch, N. Gilboa, E. Gayon, H. Wang, K. N. Houk and I. Marek, *Acc. Chem. Res.*, 2013, **46**, 1659-1669.
115. M. Yus, J. C. González-Gómez and F. Foubelo, *Chem. Rev.*, 2011, **111**, 7774-7854.
116. G. E. Keck, K. A. Savin, E. N. K. Cressman and D. E. Abbott, *J. Org. Chem.*, 1994, **59**, 7889-7896.
117. P. Xue, S. Bi, H. H. Y. Sung, I. D. Williams, Z. Lin and G. Jia, *Organometallics*, 2004, **23**, 4735-4743.
118. T. Smejkal, H. Han, B. Breit and M. J. Krische, *J. Am. Chem. Soc.*, 2009, **131**, 10366-10367.
119. H. Lam, H. Hepburn, N. Chotsaeng and Y. Luo, *Synthesis*, 2013, **45**, 2649-2661.
120. Y. Luo, H. B. Hepburn, N. Chotsaeng and H. W. Lam, *Angew. Chem. Int. Ed.*, 2012, **51**, 8309-8313.
121. H. B. Hepburn and H. W. Lam, *Angew. Chem. Int. Ed.*, 2014, **53**, 11605-11610.
122. J. I. Martinez, J. J. Smith, H. B. Hepburn and H. W. Lam, *Angew. Chem. Int. Ed.*, 2016, **55**, 1108-1112.
123. M. Holmes, L. A. Schwartz and M. J. Krische, *Chem. Rev.*, 2018, **118**, 6026-6052.

124. M. Kimura, H. Fujimatsu, A. Ezoe, K. Shibata, M. Shimizu, S. Matsumoto and Y. Tamaru, *Angew. Chem., Int. Ed.*, 1999, **38**, 397-400.
125. M. Kimura, A. Ezoe, K. Shibata and Y. Tamaru, *J. Am. Chem. Soc.*, 1998, **120**, 4033-4034.
126. M. Takimoto, Y. Hiraga, Y. Sato and M. Mori, *Tetrahedron Lett.*, 1998, **39**, 4543-4546.
127. Y. Sato, Y. Hinata, R. Seki, Y. Oonishi and N. Saito, *Org. Lett.*, 2007, **9**, 5597-5599.
128. S.-S. Ng and T. F. Jamison, *J. Am. Chem. Soc.*, 2005, **127**, 7320-7321.
129. Y. Sato, M. Takimoto, K. Hayashi, T. Katsuhara, K. Takagi and M. Mori, *J. Am. Chem. Soc.*, 1994, **116**, 9771-9772.
130. S.-S. Ng and T. F. Jamison, *Tetrahedron*, 2005, **61**, 11405-11417.
131. M. Kimura, A. Miyachi, K. Kojima, S. Tanaka and Y. Tamaru, *J. Am. Chem. Soc.*, 2004, **126**, 14360-14361.
132. K. Hiraki, N. Ochi, Y. Sasada, H. Hayashida, Y. Fuchita and S. Yamanaka, *J. Chem. Soc., Dalton Trans.*, 1985, **5**, 873-877.
133. T.-Y. Chen, R. Tsutsumi, T. P. Montgomery, I. Volchkov and M. J. Krische, *J. Am. Chem. Soc.*, 2015, **137**, 1798-1801.
134. B. Sam, T. P. Montgomery and M. J. Krische, *Org. Lett.*, 2013, **15**, 3790-3793.
135. L. M. Geary, B. W. Glasspoole, M. M. Kim and M. J. Krische, *J. Am. Chem. Soc.*, 2013, **135**, 3796-3799.
136. R. L. Patman, V. M. Williams, J. F. Bower and M. J. Krische, *Angew. Chem., Int. Ed.*, 2008, **47**, 5220-5223.
137. F. Shibahara, J. F. Bower and M. J. Krische, *J. Am. Chem. Soc.*, 2008, **130**, 6338-6339.
138. S. Oda, B. Sam and M. J. Krische, *Angew. Chem., Int. Ed.*, 2015, **54**, 8525-8528.
139. B. Y. Park, T. P. Montgomery, V. J. Garza and M. J. Krische, *J. Am. Chem. Soc.*, 2013, **135**, 16320-16323.
140. Y.-T. Hong, C.-W. Cho, E. Skucas and M. J. Krische, *Org. Lett.*, 2007, **9**, 3745-3748.
141. M. Kimura, D. Nojiri, M. Fukushima, S. Oi, Y. Sonoda and Y. Inoue, *Org. Lett.*, 2009, **11**, 3794-3797.
142. J. R. Zbieg, T. Fukuzumi and M. J. Krische, *Adv. Synth. Catal.*, 2010, **352**, 2416-2420.
143. L. M. Geary, S. K. Woo, J. C. Leung and M. J. Krische, *Angew. Chem., Int. Ed.*, 2012, **51**, 2972-2976.
144. E. Skucas, J. F. Bower and M. J. Krische, *J. Am. Chem. Soc.*, 2007, **129**, 12678-12679.
145. L. Bareille, P. Le Gendre and C. Moïse, *Chem. Commun.*, 2005, **6**, 775-777.
146. Y. Yang, I. B. Perry, G. Lu, P. Liu and S. L. Buchwald, *Science*, 2016, **353**, 144-150.
147. K. Li, X. Shao, L. Tseng and S. J. Malcolmson, *J. Am. Chem. Soc.*, 2018, **140**, 598-601.
148. E. Y. Tsai, R. Y. Liu, Y. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2018, **140**, 2007-2011.
149. X. Shao, K. Li and S. J. Malcolmson, *J. Am. Chem. Soc.*, 2018, **140**, 7083-7087.
150. R. Y. Liu, Y. Yang and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2016, **55**, 14077-14080.
151. H.-M. Chang and C.-H. Cheng, *Org. Lett.*, 2000, **2**, 3439-3442.
152. T. Fujihara, T. Hosomi, C. Cong, T. Hosoki, J. Terao and Y. Tsuji, *Tetrahedron*, 2015, **71**, 4570-4574.
153. H. C. Maytum, B. Tavassoli and J. M. J. Williams, *Org. Lett.*, 2007, **9**, 4387-4389.
154. D. C. Schmitt, J. Lee, A.-M. R. Dechert-Schmitt, E. Yamaguchi and M. J. Krische, *Chem. Commun.*, 2013, **49**, 6096-6098.
155. J. F. Bower, E. Skucas, R. L. Patman and M. J. Krische, *J. Am. Chem. Soc.*, 2007, **129**, 15134-15135.
156. J. C. Leung, L. M. Geary, T.-Y. Chen, J. R. Zbieg and M. J. Krische, *J. Am. Chem. Soc.*, 2012, **134**, 15700-15703.
157. K. Shibata, M. Kimura, M. Shimizu and Y. Tamaru, *Org. Lett.*, 2001, **3**, 2181-2183.
158. M. Kimura, A. Ezoe, S. Tanaka and Y. Tamaru, *Angew. Chem., Int. Ed.*, 2001, **40**, 3600-3602.
159. M. Kimura, A. Ezoe, M. Mori, K. Iwata and Y. Tamaru, *J. Am. Chem. Soc.*, 2006, **128**, 8559-8568.
160. A. Köpfer, B. Sam, B. Breit and M. J. Krische, *Chem. Sci.*, 2013, **4**, 1876-1880.
161. Y. Jiao, W. W. Brennessel and W. D. Jones, *Organometallics*, 2015, **34**, 1552-1566.

162. S. Gatard, R. Çelenligil-Çetin, C. Guo, B. M. Foxman and O. V. Ozerov, *J. Am. Chem. Soc.*, 2006, **128**, 2808-2809.
163. Y. Horino, A. Aimono and H. Abe, *Org. Lett.*, 2015, **17**, 2824-2827.
164. M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, T. E. Müller and A. Zapf, *J. Organomet. Chem.*, 1998, **566**, 277-285.
165. M. G. L. Petrucci, A.-M. Lebuis and A. K. Kakkar, *Organometallics*, 1998, **17**, 4966-4975.
166. S. Oda, J. Franke and M. J. Krische, *Chem. Sci.*, 2016, **7**, 136-141.
167. R. E. Ruscoe, M. Callingham, J. A. Baker, S. E. Korkis and H. W. Lam, *Chem. Commun.*, 2019, **55**, 838-841.
168. H.-J. Ha, Y.-G. Ahn and J.-K. Chon, *J. Chem. Soc., Perkin Trans. 1*, 1995, **20**, 2631-2634.
169. F. Allais, J. Boivin and V. T. Nguyen, *Beilstein J. Org. Chem.*, 2007, **3**, No. 46.
170. A. Groves, J. I. Martínez, J. J. Smith and H. W. Lam, *Chem. Eur. J.*, 2018, **24**, 13432-13436.
171. D. B. G. Williams and M. Lawton, *J. Org. Chem.*, 2010, **75**, 8351-8354.
172. W. R. Roush, K. Koyama, M. L. Curtin and K. J. Moriarty, *J. Am. Chem. Soc.*, 1996, **118**, 7502-7512.
173. A. B. Weinstein, D. P. Schuman, Z. X. Tan and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2013, **52**, 11867-11870.
174. B. Flachsbarth, M. Fritzsche, P. J. Weldon and S. Schulz, *Chem. Biodiversity*, 2009, **6**, 1-37.
175. A. Abou, F. Foubelo and M. Yus, *Tetrahedron*, 2007, **63**, 6625-6634.
176. J. R. Coombs, L. Zhang and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 16140-16143.
177. F. Lacombe, K. Radkowski, G. Seidel and A. Fürstner, *Tetrahedron*, 2004, **60**, 7315-7324.
178. N. J. Adamson, E. Hull and S. J. Malcolmson, *J. Am. Chem. Soc.*, 2017, **139**, 7180-7183.
179. J. i. Uenishi, R. Kawahama, Y. Izaki and O. Yonemitsu, *Tetrahedron*, 2000, **56**, 3493-3500.
180. U. Groenhagen, M. Maczka, J. S. Dickschat and S. Schulz, *Beilstein J. Org. Chem.*, 2014, **10**, 1421-1432.
181. J. P. Scott, D. C. Hammond, E. M. Beck, K. M. J. Brands, A. J. Davies, U.-H. Dolling and D. J. Kennedy, *Tetrahedron Lett.*, 2004, **45**, 3345-3348.
182. D. Collins, G. Fallon and C. Skene, *Aust. J. Chem.*, 1992, **45**, 71-97.
183. G. Blessley, P. Holden, M. Walker, J. M. Brown and V. Gouverneur, *Org. Lett.*, 2012, **14**, 2754-2757.
184. Y. Li, Z. Huang, X. Wu, P.-F. Xu, J. Jin, Y. Zhang and J. Wang, *Tetrahedron*, 2012, **68**, 5234-5240.
185. H.-H. Li, D.-J. Dong, Y.-H. Jin and S.-K. Tian, *J. Org. Chem.*, 2009, **74**, 9501-9504.
186. B. D. Gupta, M. Roy, S. Roy, M. Kumar and I. Das, *J. Chem. Soc., Perkin Trans. 2*, 1990, **4**, 537-543.
187. H. V. Huynh and Y. X. Chew, *Inorg. Chim. Acta*, 2010, **363**, 1979-1983.
188. V. André, H. Lahrache, S. Robin and G. Rousseau, *Tetrahedron*, 2007, **63**, 10059-10066.
189. X.-S. Wu, Y. Chen, M.-B. Li, M.-G. Zhou and S.-K. Tian, *J. Am. Chem. Soc.*, 2012, **134**, 14694-14697.
190. H. Yamamoto, E. Ho, I. Sasaki, M. Mitsutake, Y. Takagi, H. Imagawa and M. Nishizawa, *Eur. J. Org. Chem.*, 2011, **2011**, 2417-2420.
191. Y. Fang, M. Yuan, J. Zhang, L. Zhang, X. Jin, R. Li and J. Li, *Tetrahedron Lett.*, 2016, **57**, 1460-1463.
192. E. Roversi, F. Monnat, P. Vogel, K. Schenk and P. Roversi, *Helv. Chim. Acta*, 2002, **85**, 733-760.
193. C. Weatherly, J. M. Alderson, J. F. Berry, J. E. Hein and J. M. Schomaker, *Organometallics*, 2017, **36**, 1649-1661.
194. J. A. S. Howell, P. J. O'Leary, M. G. Palin, G. Jaouen and S. Top, *Tetrahedron: Asymmetry*, 1996, **7**, 307-315.
195. Y. Chen, Y. Lam and Y.-H. Lai, *Org. Lett.*, 2003, **5**, 1067-1069.
196. G. Y. Fang and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2007, **46**, 359-362.
197. Y. Horino, M. Sugata, I. Mutsuura, K. Tomohara and H. Abe, *Org. Lett.*, 2017, **19**, 5968-5971.
198. C. Zhu, G. Xu and J. Sun, *Angew. Chem., Int. Ed.*, 2016, **55**, 11867-11871.
199. R. A. Sheldon, *Chem. Soc. Rev.*, 2012, **41**, 1437-1451.

200. K. Godula and D. Sames, *Science*, 2006, **312**, 67-72.
201. C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335-344.
202. G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726-11743.
203. D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2010, **132**, 3965-3972.
204. V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154-13155.
205. Y. Zhu and Y. Wei, *Chemical Science*, 2014, **5**, 2379-2382.
206. H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.*, 2017, **117**, 9016-9085.
207. J. A. Kerr, *Chem. Rev.*, 1966, **66**, 465-500.
208. R. Shintani, H. Otomo, K. Ota and T. Hayashi, *J. Am. Chem. Soc.*, 2012, **134**, 7305-7308.
209. M. Tobisu, J. Hasegawa, Y. Kita, H. Kinuta and N. Chatani, *Chem. Commun.*, 2012, **48**, 11437-11439.
210. J. Zhang, J.-F. Liu, A. Ugrinov, A. F. X. Pillai, Z.-M. Sun and P. Zhao, *J. Am. Chem. Soc.*, 2013, **135**, 17270-17273.
211. G. Dyker, *Angew. Chem. Int. Ed. Engl.*, 1992, **31**, 1023-1025.
212. A. J. Canty, *Acc. Chem. Res.*, 1992, **25**, 83-90.
213. G. Dyker, *Chem. Ber.*, 1994, **127**, 739-742.
214. M. A. Campo, H. Zhang, T. Yao, A. Ibdah, R. D. McCulla, Q. Huang, J. Zhao, W. S. Jenks and R. C. Larock, *J. Am. Chem. Soc.*, 2007, **129**, 6298-6307.
215. Q. Tian and R. C. Larock, *Org. Lett.*, 2000, **2**, 3329-3332.
216. M. A. Campo and R. C. Larock, *J. Am. Chem. Soc.*, 2002, **124**, 14326-14327.
217. T.-J. Hu, G. Zhang, Y.-H. Chen, C.-G. Feng and G.-Q. Lin, *J. Am. Chem. Soc.*, 2016, **138**, 2897-2900.
218. J. Zhao, D. Yue, M. A. Campo and R. C. Larock, *J. Am. Chem. Soc.*, 2007, **129**, 5288-5295.
219. T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685-4696.
220. G. Dyker, *J. Org. Chem.*, 1993, **58**, 6426-6428.
221. A. Singh and P. R. Sharp, *J. Am. Chem. Soc.*, 2006, **128**, 5998-5999.
222. A. L. Keen, M. Doster and S. A. Johnson, *J. Am. Chem. Soc.*, 2007, **129**, 810-819.
223. S. E. Kalman, T. B. Gunnoe and M. Sabat, *Organometallics*, 2014, **33**, 5457-5463.
224. J. Mo, T. Müller, J. C. A. Oliveira and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 7719-7723.
225. K. Takano, Y. Ikeda, S. Kodama and Y. Ishii, *Chem. Commun.*, 2015, **51**, 4981-4984.
226. K. Oguma, M. Miura, T. Satoh and M. Nomura, *J. Am. Chem. Soc.*, 2000, **122**, 10464-10465.
227. E. A. B. Kantchev , S. R. Pangestu, F. Zhou, M. B. Sullivan and H.-B. Su, *Chem. Eur. J.*, 2014, **20**, 15625-15634.
228. T. Hayashi, K. Inoue, N. Taniguchi and M. Ogasawara, *J. Am. Chem. Soc.*, 2001, **123**, 9918-9919.
229. R. Shintani, K. Okamoto, Y. Otomaru, K. Ueyama and T. Hayashi, *J. Am. Chem. Soc.*, 2005, **127**, 54-55.
230. T. Miura, M. Shimada and M. Murakami, *Tetrahedron*, 2007, **63**, 6131-6140.
231. A. Antonio, A. Massimiliano, C. Marco, F. Giovanni and M. Fabio, *Adv. Synth. Catal.*, 2010, **352**, 493-498.
232. R. Shintani, K. Okamoto and T. Hayashi, *J. Am. Chem. Soc.*, 2005, **127**, 2872-2873.
233. R. Shintani, K. Takatsu, T. Katoh, T. Nishimura and T. Hayashi, *Angew. Chem., Int. Ed.*, 2008, **47**, 1447-1449.
234. R. Shintani and T. Hayashi, *Org. Lett.*, 2005, **7**, 2071-2073.
235. R. Shintani, K. Takatsu and T. Hayashi, *Angew. Chem., Int. Ed.*, 2007, **46**, 3735-3737.
236. R. Shintani, S. Isobe, M. Takeda and T. Hayashi, *Angew. Chem., Int. Ed.*, 2010, **49**, 3795-3798.
237. K. Sasaki and T. Hayashi, *Tetrahedron: Asymmetry*, 2012, **23**, 373-380.
238. K. Sasaki, T. Nishimura, R. Shintani, E. A. B. Kantchev and T. Hayashi, *Chemical Science*, 2012, **3**, 1278-1283.
239. T. Miura, T. Sasaki, H. Nakazawa and M. Murakami, *J. Am. Chem. Soc.*, 2005, **127**, 1390-1391.

240. T. Matsuda, M. Shigeno and M. Murakami, *J. Am. Chem. Soc.*, 2007, **129**, 12086-12087.
241. A. Yada, S. Fujita and M. Murakami, *J. Am. Chem. Soc.*, 2014, **136**, 7217-7220.
242. T. Seiser, O. A. Roth and N. Cramer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6320-6323.
243. T. Seiser and N. Cramer, *Angew. Chem., Int. Ed.*, 2010, **49**, 10163-10167.
244. T. Matsuda, Y. Suda and A. Takahashi, *Chem. Commun.*, 2012, **48**, 2988-2990.
245. R. Shintani, R. Iino and K. Nozaki, *J. Am. Chem. Soc.*, 2014, **136**, 7849-7852.
246. S. Rush, A. Reinmuth and W. Risse, *Macromolecules*, 1997, **30**, 7375-7385.
247. A. J. Mota, A. Dedieu, C. Bour and J. Suffert, *J. Am. Chem. Soc.*, 2005, **127**, 7171-7182.
248. H. B. Hepburn and H. W. Lam, *Angew. Chem., Int. Ed.*, 2014, **53**, 11605-11610.
249. B. M. Partridge, M. Callingham, W. Lewis and H. W. Lam, *Angew. Chem., Int. Ed.*, 2017, **56**, 7227-7232.
250. M. Callingham, B. M. Partridge, W. Lewis and H. W. Lam, *Angew. Chem., Int. Ed.*, 2017, **56**, 16352-16356.
251. A. Masarwa, M. Weber and R. Sarpong, *J. Am. Chem. Soc.*, 2015, **137**, 6327-6334.
252. J. D. Dooley and H. W. Lam, *Chem. Eur. J.*, 2018, **24**, 4050-4054.
253. D. J. Burns and H. W. Lam, *Angew. Chem., Int. Ed.*, 2014, **53**, 9931-9935.
254. D. J. Burns, D. Best, M. D. Wieczysty and H. W. Lam, *Angew. Chem., Int. Ed.*, 2015, **54**, 9958-9962.
255. S. E. Korkis, D. J. Burns and H. W. Lam, *J. Am. Chem. Soc.*, 2016, **138**, 12252-12257.
256. L. David and F. Keith, *Chem. Lett.*, 2010, **39**, 1118-1126.
257. Y. Ikeda, K. Takano, M. Waragai, S. Kodama, N. Tsuchida, K. Takano and Y. Ishii, *Organometallics*, 2014, **33**, 2142-2145.
258. B. H. Tan, J. Dong and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2012, **51**, 9610-9614.
259. B.-H. Tan and N. Yoshikai, *Org. Lett.*, 2014, **16**, 3392-3395.
260. J. Yan and N. Yoshikai, *ACS Catal.*, 2016, **6**, 3738-3742.
261. B. M. Partridge, J. S. González and H. W. Lam, *Angew. Chem., Int. Ed.*, 2014, **53**, 6523-6527.
262. S. Akutagawa, *Applied Catalysis A: General*, 1995, **128**, 171-207.
263. I. D. Gridnev and T. Imamoto, *Acc. Chem. Res.*, 2004, **37**, 633-644.
264. A. I. Oliva, U. Christmann, D. Font, F. Cuevas, P. Ballester, H. Buschmann, A. Torrens, S. Yenes and M. A. Pericàs, *Org. Lett.*, 2008, **10**, 1617-1619.
265. S. Kallepu, K. K. Gollapelli, J. B. Nanubolu and R. Chegondi, *Chem. Commun.*, 2015, **51**, 16840-16843.
266. M. Kenny, J. Christensen, S. J. Coles and V. Franckevičius, *Org. Lett.*, 2015, **17**, 3926-3929.
267. A. K. Ghosh and D. D. Anderson, *Org. Lett.*, 2012, **14**, 4730-4733.
268. I. Misztalewska, A. Z. Wilczewska, O. Wojtasik, K. H. Markiewicz, P. Kuchlewski and A. M. Majcher, *RSC Advances*, 2015, **5**, 100281-100289.
269. H. Jullien, B. Quiclet-Sire, T. Tétart and S. Z. Zard, *Org. Lett.*, 2014, **16**, 302-305.
270. R. Cano, J. M. Pérez, D. J. Ramón and G. P. McGlacken, *Tetrahedron*, 2016, **72**, 1043-1050.