

**Rhodium-Catalysed Allylic Substitution with
Unstabilised Carbon Nucleophiles: Asymmetric
Construction of Carbon-Carbon Bonds**

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Abstract

The controlled formation of carbon-carbon bonds is the bedrock of organic chemistry, with the asymmetric construction of stereogenic carbon-carbon bonds remaining a key motivation for the development of novel synthetic methodologies. Transition metal catalysis provides an important strategy in the arsenal of the modern synthetic chemist. While there is a plethora of transition metal-catalysed cross-couplings for the formation of sp^2 - sp^2 and achiral sp^2 - sp^3 carbon bonds, there are relatively few methodologies for the selective formation of stereogenic sp - sp^3 , sp^2 - sp^3 and sp^3 - sp^3 carbon-carbon bonds, the number of which that involve highly reactive organometallic reagents are fewer still. Two methodologies that can enable this asymmetric coupling are copper-catalysed S_N2' allylic alkylation and transition metal-catalysed allylic substitution. The overall utility of both these methods is described in the introductory review, which seeks to compare and contrast the relative advantages and disadvantage of both approaches. The asymmetric formation of carbon-carbon bonds utilising unstabilised carbon nucleophiles is generally dominated by the copper-catalysed S_N2' allylic alkylation. However, the copper-catalysed reaction suffers from poor substrate scope, in which electronically biased or symmetrical substrates are required in order to ensure favourable regioselectivities. Another restriction is that, for the formation of a stereocenter, the reaction is mechanistically limited to disubstituted allylic substrates. These linear substrates often require a multistep synthesis which involves a selective olefination, as an isomeric mixture of alkenes would result in the erosion of asymmetric induction. In contrast, there has been very little development of the analogous transition metal-catalysed allylic substitution utilising unstabilised carbon nucleophiles, especially in comparison to the analogous methodologies utilising

stabilised carbon and heteroatom nucleophiles. Despite the numerous potential advantages that are afforded by this approach, a general method for the regio- and stereoselective transition-metal catalysed allylic substitution utilising unstabilised carbon nucleophiles has yet to be reported.

Chapter 2 describes the development of a novel regio- and stereoselective rhodium-catalysed allylic substitution reaction, which utilises benzyl magnesium bromide as an unstabilised carbon nucleophile. Following a brief introduction to the rhodium-catalysed allylic substitution reaction, this chapter is organised into four distinct sections. The first of these outlines the identification of a suitable nucleophile, and the subsequent development of reaction conditions for the regioselective alkylation of secondary allylic carbonates with a range of benzyl magnesium bromides transmetallated with zinc iodide. Then the next section will deal with studies toward the development of the stereospecific variant, these studies will highlight the main challenges of deploying a sp^3 -hybridised carbon nucleophile. This section will also determine the absolute stereochemical outcome of the reaction, thus confirming the inner sphere mechanism of the reaction. The third section will demonstrate that how the limitation of the stereospecific reaction, namely the fluxionality of the rhodium-*enyl*, can be utilised to develop a regio- and diastereoselective alkylation for the formation of 1,2-stereoarrays containing tertiary and quaternary carbon stereocenters. Finally, preliminary studies towards the expansion of this methodology to include an sp^2 -hybridised vinylic nucleophiles for the preparation of 1,4-skipped dienes will be detailed. Overall, we have developed a novel, highly regioselective rhodium-catalysed allylic substitution of secondary allylic carbonates utilising highly unstabilised carbon nucleophiles. We also have developed a highly diastereoselective allylic substitution for the construction of both tertiary and quaternary carbon

stereocenters, which to best of our knowledge, has yet to be described in the context of rhodium-catalysed allylic substitution utilising an unstabilised carbon nucleophile. We have successfully carried out preliminary studies towards the development of a rhodium-catalysed allylic substitution utilising a vinyl organometallic reagent as nucleophile, as well.

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List of Abbreviations

Å	angstrom
Ac	acetyl
acac	acetylacetonato
APT	attached proton test
Ar	aryl
atm.	atmosphere
BINAP	2,2'-bis(diphenylphosphino)-1-1'-binaphthyl
bipy	bipyridine
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
ⁱ Bu	<i>iso</i> -butyl
ⁿ Bu	<i>n</i> -butyl
^s Bu	<i>sec</i> -butyl
^t Bu	<i>tert</i> -butyl
Bz	benzoyl
<i>c</i>	concentration
°C	degrees Celsius
CAN	cerium ammonium nitrate
Cb	N,N-diisopropylcarbonyl
<i>cee</i>	conservation of enantiomeric excess
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
δ	chemical shift
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DIBAL-H	di- <i>iso</i> -butylaluminium hydride
DME	dimethoxyethane
DMF	dimethylformamide

DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
DYKAT	dynamic kinetic asymmetric transformation
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
<i>dr</i>	diastereomeric ratio
<i>ds</i>	diastereoselectivity
<i>E</i>	entgegen
<i>ee</i>	enantiomeric excess
ESI	electrospray ionisation
<i>ent</i>	enantiomer
eq.	equation
Et	ethyl
equiv.	equivalent
FCC	flash column chromatography
FTIR	Fourier transform infrared spectroscopy
g	gram
h	hours
^c Hex	<i>cyclo</i> -hexyl
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
<i>J</i>	coupling constant
L _n	ligand set
LDA	lithium diisopropylamide
Lg	leaving group
LUMO	lowest unoccupied molecular orbital
M	molar
M ⁿ	metal with an oxidation state n

Me	methyl
MEM	β -methoxyethoxymethyl
Mes	mesitylene
mg	milligram
MHz	megahertz
mL	millilitre
mm	millimetre
mmol	millimol
MS	molecular sieves
MTBE	methyl <i>tert</i> -butyl ether
NHC	N-heterocyclic carbene
N	normal
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
pin	pinacolato
Piv	pivalyl
pKa	logarithmic acid dissociation constant
ppm	parts per million
^{<i>i</i>} Pr	<i>iso</i> -propyl
^{<i>n</i>} Pr	<i>n</i> -propyl
RT	room temperature
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAT	tetra- <i>n</i> -butylammonium triphenyldifluorosilicate
TBD	1,5,6-triazabicyclo[4.4.0]dec-1-ene
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	toluenesulfonyl
UV	ultraviolet

v/v	volume/volume
Z	zusammen
$[\alpha]_D^t$	specific rotation at temperature t and wavelength of sodium D line
μL	microlitre
μm	micrometre

List of Schemes

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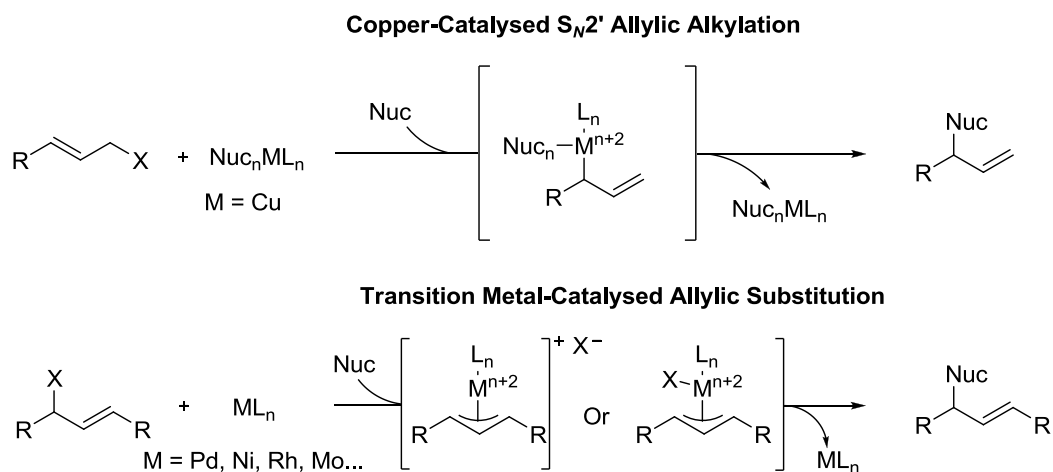
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Chapter 1

Copper-Catalysed S_N2' Allylic Alkylation vs Transition Metal-Catalysed Allylic Substitution

1.1. Introduction

Carbon-carbon bond formation is one of the most important chemical transformations and remains a key motivation for the development of novel synthetic methodologies. Transition metal catalysis provides an important strategy in the arsenal of the modern synthetic chemist. While there is a plethora of transition metal-catalysed cross-couplings for the formation of sp^2 - sp^2 and achiral sp^2 - sp^3 carbon bonds, there are relatively few methodologies for the selective formation of stereogenic sp - sp^3 , sp^2 - sp^3 and sp^3 - sp^3 carbon-carbon bonds. Two methodologies that enable these transformations are the copper-catalysed S_N2' allylic alkylation and transition metal-catalysed allylic substitution (**Scheme 1**).^{1,2}



Scheme 1: Copper-Catalysed S_N2' Allylic Alkylation vs Transition Metal-Catalysed Allylic Substitution

The similarities between the two reactions are that they both involve the oxidative addition of a transition-metal to an olefin that possesses a leaving group at the allylic position, it is at this point that the two reactions divert mechanistically. For the copper-catalysed S_N2' allylic alkylation the reaction proceeds *via* a highly transient σ -allyl complex containing both the nucleophile and the electrophile. This highly unstable complex undergoes rapid reductive elimination (ideally), affording the coupled S_N2' product and returning the metal complex back to its original oxidation state.

In contrast the transition metal-catalysed allylic substitution proceeds *via* a perdurable π -allyl complex. This electrophilic π -allyl complex can then undergo nucleophilic attack either externally on the opposite face of the π -allyl to the metal (outer sphere) or directly on to the metal (inner sphere), in both cases the reaction eliminates the catalyst back to its original oxidation state and affords the coupled product as either the S_N2 or S_N2' adduct, depending on the nature of the metal and the ligands used.

While the copper-catalysed S_N2' allylic alkylation allows the enantioselective deployment of unstabilised carbon nucleophiles it suffers from poor substrate scope and only simple alkyl nucleophiles are utilised. The transition metal-catalysed allylic substitution, on the other hand, tolerates a vast array of nucleophilic coupling partners that grant access to a myriad of sp^3 - sp^3 and sp^3 -hetero atom cross coupled products.¹ *However, the transition metal-catalysed allylic substitution of unstabilised carbon nucleophiles still represents a challenging cross-coupling for the construction of tertiary and quaternary carbon stereogenic centres.* These transformations remain difficult due to the inherent issues associated with the basic

nature of the organometallic nucleophiles, which can readily promote elimination of the metal-allyl or hydrolysis of the electrophilic coupling partner.

The aim of the following review is to highlight the use of unstabilised carbon nucleophiles in copper-catalysed S_N2' allylic alkylations and transition metal-catalysed allylic substitution. The review will outline both the initial development and the latest additions to the literature for methodologies catalysed by group 8 to 11 transition metals (iron, cobalt, rhodium, iridium, palladium, nickel and copper). It will only chart reactions involving unstabilised carbon nucleophiles with a purely organometallic nature representing a carbanion equivalent. These nucleophiles will only include common/easily prepared organometallics reagents made up from alkali (lithium), alkaline earth (magnesium), transition (zinc) and post-transition (aluminium) metals.

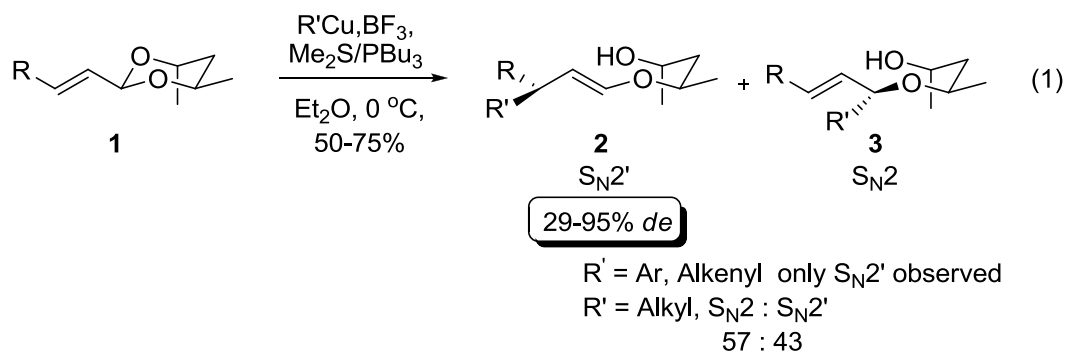
1.2. Copper-Catalysed S_N2' Allylic Alkylation of Unstabilised Carbon

1.2.1. Introduction

Copper is one of the most adept metals for the deployment of unstabilised nucleophiles and has been used as an organometallic reagent both stoichiometrically and catalytically. Copper's ability to catalyse the addition of unstabilised nucleophiles has been known since 1941 when Kharash noted that the chemoselectivity of a Grignard addition to cyclohexenone was swapped from 1,2-addition to 1,4-addition in the presence of 1 mol% $CuCl$.³

The first copper-catalysed S_N2' propargylic and allylic alkylation was reported much later by Claesson *et al* in 1975.⁴ wherein they demonstrated that propargylic and allylic ethers could be alkylated with $MeMgI$ in the presence of copper(I)iodide to afford the S_N2' product in moderate yield and selectivity.⁴ The first successful

diastereoselective S_N2' addition was performed by Alexakis and co-workers using stoichiometric organocopper reagent and a chiral leaving group (Eq. 1).⁵



It was only in 1995 that the catalytic enantioselective process was described by Bäckvall and van Koten, although it only gave moderate *ee* of 42% it lay as a proof of principle.⁶ Since this first asymmetric methodology was disclosed, a plethora of ligand classes and organometallic nucleophiles have since been developed for enantioselective manifold. Nucleophiles consisting of Grignard, organozinc, organoaluminium and organolithium reagents have been utilised. Other non-metals and metalloid based pronucleophiles have been successfully deployed in the context of both copper catalysed conjugate addition and allylic alkylation.^{2c} However, these are beyond the scope of this chapter which solely deals with unstabilised carbon nucleophiles of a purely organometallic nature representing a carbanion equivalent.

The following section will present an overview of the main organometallic reagents that have been used in the copper-catalysed S_N2' allylic alkylation. Each subsection will detail the various ligand/catalyst/nucleophile systems that have been developed in each case. Then the mechanistic characteristic of the reaction will be discussed to

give a general overview of what is required to perform a successful copper-catalysed S_N2' allylic alkylation.

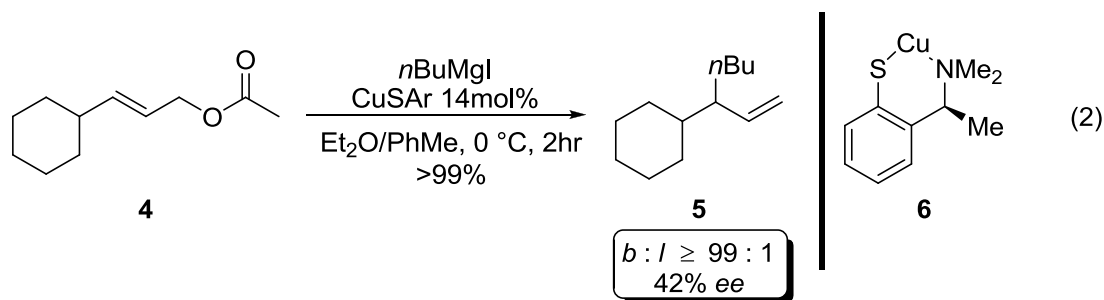
1.2.2. Grignard as Nucleophiles

1.2.2.1. Introduction

A careful review of the literature reveals that the most successful copper catalysed S_N2' allylic alkylations using Grignard reagents as nucleophiles can be characterised into three main catalyst/ligand systems, these are thiolatocopper(I) compounds, phosphorus based ligands, and N- heterocyclic carbene (NHC) ligands. This section will be divided up into the main ligand/catalyst systems used for Grignard based nucleophiles.

1.2.2.2. Thiolatocopper(I) compounds

The first asymmetric copper catalysed S_N2' allylic alkylation was not disclosed until 1995 when Bäckvall and van Koten found that the chiral arenethiolatocopper(I) complex **6** catalysed the substitution of acyclic allylic acetates/phosphonates with Grignard reagents (Eq. 2).⁶ The reaction gave excellent yield and *b/l* selectivity, however, the asymmetric induction was modest (up to 42% *ee.*) (Eq. 2).⁶



After several generations the enantioselectivity for these reactions was improved by the same group to 64% enantiomeric excess by using the copperthiolate complex **7** based on a ferrocene backbone (**Figure 1**).⁷ The enantiomeric excess is extremely sensitive to temperature, the coordinating ability of the leaving group, and the method of addition of both the Grignard and the substrate.⁷

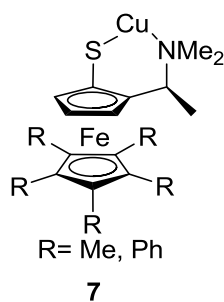
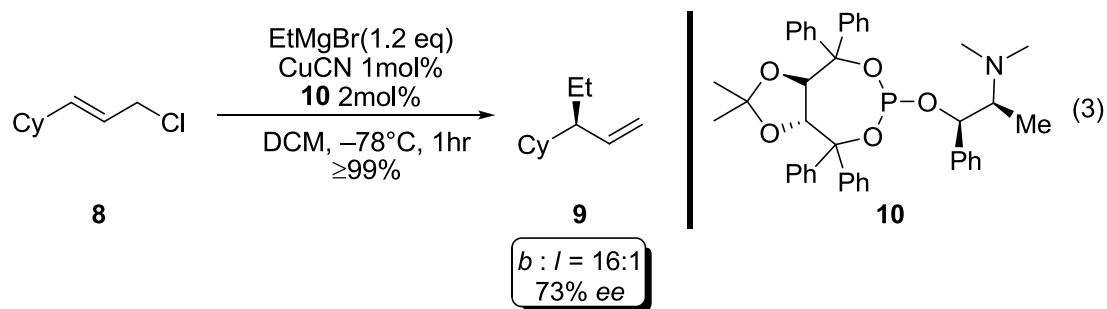


Figure 1: Chiral Copperthiolate Complex with Ferrocene Backbone.⁸

Despite initially showing great promise as a ligand/catalyst class, further development of chiral copperthiolate complexes stalled, as other more modular and tuneable catalyst/ligand systems became available.

1.2.2.3. Phosphorus based ligand systems

Phosphorus based ligand systems were first reported by Alexakis and co-workers,⁸ wherein they described the screening of a multitude of phosphite and phosphoramidite based ligands. The optimal ligand found during their investigation was a TADDOL-based phosphate amine **10**. When this ligand was used in conjunction with a catalytic amount of copper(I)cyanide and ethyl magnesium bromide as a nucleophile in dichloromethane at -78 °C, they were able to alkylate the allylic chloride **8** in excellent yield and regioselectivity (>99% and *b:l* = 16:1), giving enantioselectivities up to 73% *ee* (eq. 3).⁸



In subsequent publications, the same group went on to demonstrate that it was possible to achieve higher enantioselectivities, up to 79% *ee*, when using phosphoramidite **11a** (Figure 2) as a ligand.^{9a} They also improved the reaction in terms of scope for both the electrophilic and the nucleophilic coupling partners.^{9a-c} In the following years Alexakis *et al.* demonstrated that phosphoramidite **11b**, containing methoxy groups at the 2-position of the aryl groups, afforded higher regio- and enantioselectivities. Ligand **11b** afforded *ee*'s of >91% and regioselectivities of >97%. The phosphoramidite based system is compatible with a variety of Grignard reagents and with a series of di- and trisubstituted and endocyclic allylic chlorides and also for 1,4-halo-2-butene substrates.^{9e}

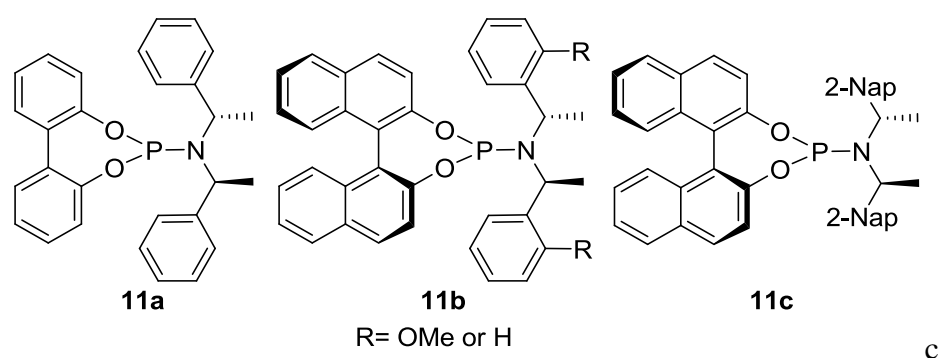
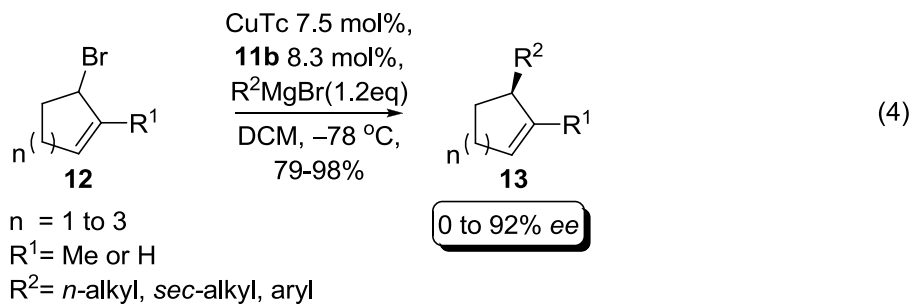
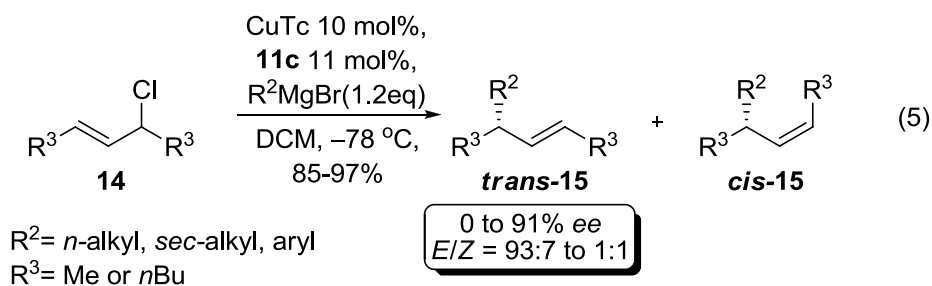


Figure 2: 1,1'-Binaphthalene Based Phosphoramidite Ligands.

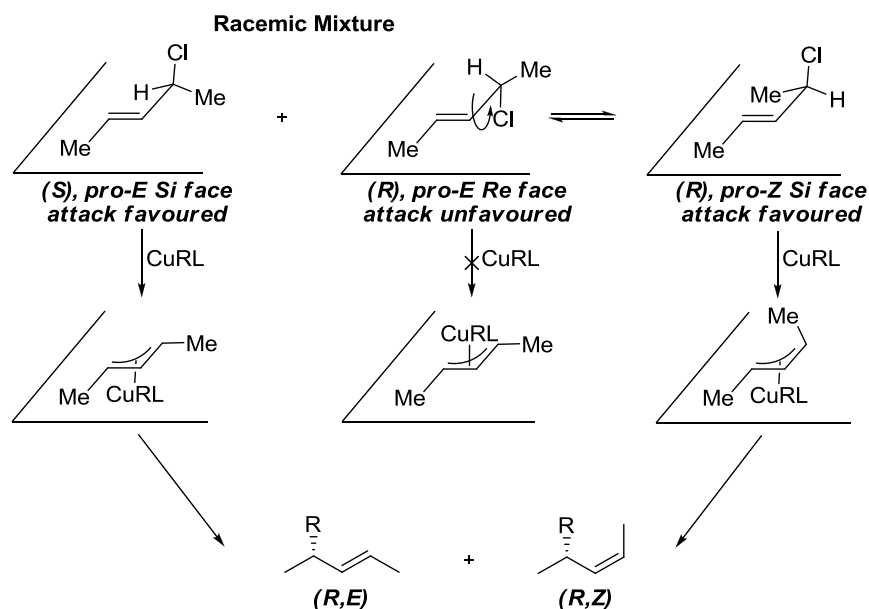
Interestingly Alexakis and co-workers went on to utilise **11b** and **11c** in an attempt to develop a copper-catalysed dynamic kinetic asymmetric transformation for both cyclic and acyclic allylic halides (eq. 4 and 5).^{10,11,12}



In 2007 Bäckvall and Norinder demonstrated that a copper-catalysed DYKAT was viable by developing a copper-catalyzed racemisation of enantiopure allylic acetates.¹³ Using this as a springboard, in 2009 Alexakis and Langlois went onto develop the first copper-catalysed DYKAT, utilising **11b** as ligand and a series of cyclic allylic halides **12** as the substrates (eq 4).^{10,11} Depending on the Grignard reagent used the enantioselectivities ranged from 92% *ee* to racemic, the highest *ee*'s were obtained using linear alkyl nucleophiles.^{10,11} For secondary nucleophiles good *ee*'s were afforded (e.g. cyclohexyl magnesium bromide gave 70% *ee*), however, when an aryl Grignard was utilised only racemic product was afforded.^{10,11} The regioselectivity of this reaction is moot point as the substrates form a symmetrical π -allyl and attack at either terminus of the allyl results in the same regioisomer. The same authors went on to develop the acyclic variant,¹² again they were able achieve relatively high enantioselectivities for a range of linear alkyl Grignard reagents (74 to 91% *ee*) (eq. 5).¹²



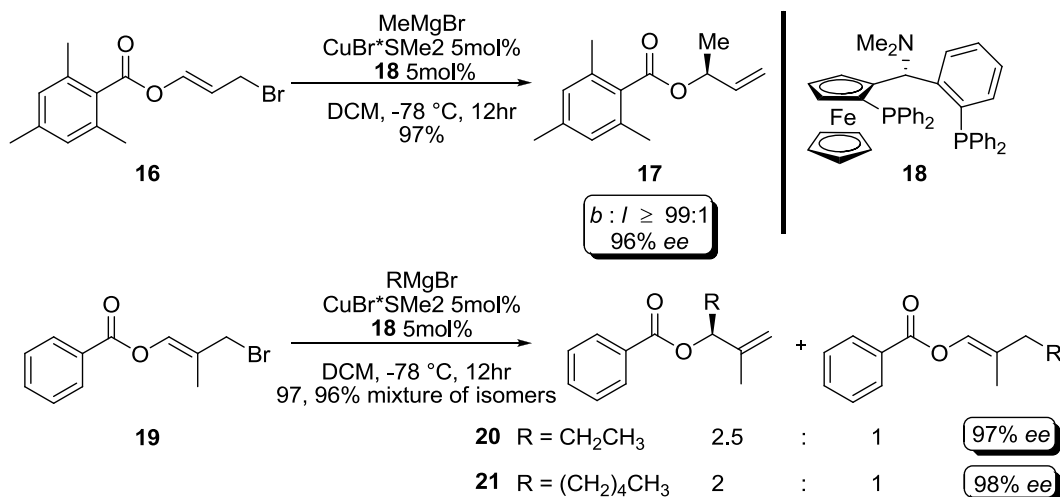
The acyclic reaction actually gave a higher enantioselectivity for the secondary cyclohexyl-substituted Grignard, which afforded the requisite alkylated product in 80% *ee* (vs 70% *ee* for the cyclic reaction).^{10,12} Unlike the previous methodology, in which the alkene was tethered in a ring, the acyclic variant resulted in a mixture of geometric isomers (~1:1 in most cases). The authors postulated that mixture of geometric isomers is due to free rotation of the C-C bond adjacent to the chloride prior the selective attack of the chiral catalyst on one enantiotopic face of the disubstituted olefin (**Scheme 2**).



Scheme 2 : The origin of the mixture of geometric isomers.

The facial selectivity might be ascribed to steric interactions between the chiral ligand and the vinylic methyl group, *ergo* the need for a rotation of the vinylic bond proximal to the chloride prior to oxidative addition. This would explain why in most cases where the *ee* is high the *E:Z* ratio is ~1:1, as this rotation is the means with which the racemic substrate is equilibrated to give the favoured *pro-Si* face for the enantioselective attack of the copper-catalyst (**Scheme 2**). For example the biphenyl-substituted substrate, the product was afforded with an *E:Z* ratio of 93:7 and it was found to be racemic. The energy barrier for rotation is too high for this due to the extended conjugation present, which explain the high *E:Z* ratio of 93:7 and total lack of enantioselectivity.

As well as monodentate phosphoramidites, bidentate phosphine ligands also proved to be highly successful in the copper-catalysed S_N2' allylic alkylation. Feringa and co-workers first reported the use of the ferrocene based diphosphine ligand **18** TaniaPhos (**Scheme 3**) as a ligand in the asymmetric copper-catalysed allylic alkylation of cinnamyl/alkyl derived allylic halides in 2006.¹⁴ In the same year, the Feringa group went on to develop the highly enantioselective copper-catalysed hetero-allylic alkylation utilising TaniaPhos **18** (**Scheme 3**).¹⁵



Scheme 3: The Copper-Catalysed Hetero-Allylic Asymmetric Alkylation.

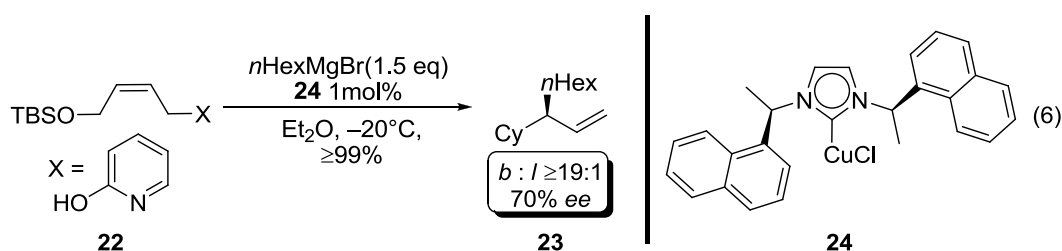
This methodology grants easy access to a series of benzoyl and cinnamoyl protected secondary allylic alcohols in good to excellent yields and enantioselectivities.¹⁵ The reaction proved to be highly general, allowing for a range of alkyl Grignard reagents to be deployed as nucleophiles and utilising a series of allylic bromides containing various benzoate and cinnamates as electrophiles. For the majority of the examples both the regio- and enantiocontrol were excellent, however, when the tri-substituted enol ester **19** was employed as a substrate, a drastic drop in regioselectivity was observed ($b:l = 2:1$ and $2.5:1$). The authors proposed this was due to the inductive effect of the attached methyl group (**Scheme 3**).

The Feringa group went on to use the same catalyst/ligand system in a similar vein as Alexakis *et al.* had done with 1,4-halo-2-butene substrates.^{9e} Instead of dihalide substrates, they utilised silyl/benzyl protected (*E*)-4-bromobut-2-en-1-ol and tosyl/boc protected (*E*)-4-bromobut-2-en-1-amine.¹⁶ This gave access to a series of enantioenriched bifunctionalised building blocks. The same catalyst system was initially used in the copper-catalysed allylic alkylation of phosphonates/phosphine oxides with Grignard reagents.¹⁷ However, unlike the previous methodologies they

found that the enantioselectivity of the reaction dropped when longer chain Grignard reagents were deployed (Et/MeMgBr gave 96/99% *ee* while *n*HexMgBr gave 64% *ee*).¹⁷ In the same paper the authors went on to screen a series of phosphoramidites, which gave significantly improved selectivities.¹⁷

1.2.2.4. N-Heterocyclic Carbene based catalysts

In the late 1990's and early 2000's the popularity of N-heterocyclic carbene (NHC) ligands rose, with them being used in plethora of transition metal-catalysed reactions.¹⁸ The use of NHC based catalyst systems for the copper-catalysed S_N2' allylic alkylation with Grignard reagents was first introduced by Okamoto and co-workers (eq. 6).¹⁹



The binaphthalene containing NHC **24** (eq. 6) afforded good enantioselectivity (up to 70% *ee*) for bifunctionalised substrates with (*Z*)-double bond stereochemistry. Interestingly the (*E*)-isomer afforded the opposite enantiomer, but in slightly lower *ee*'s (up to 60%).¹⁹

In 2011 the Tomioka group developed a copper-catalysed S_N2' allylic arylation, which utilised aryl Grignard reagents as nucleophiles and the highly arylated NHC complex **25** as a catalyst (**Figure 3**).²⁰ They were able to achieve enantioselectivities up to 94 and 96% *ee* for both alkyl- and aryl-substituted allylic bromide substrates

respectively, where previously only a maximum of 30% *ee* had been achieved in copper-catalysed asymmetric allylic arylation utilising aryl Grignard reagents.²¹ Despite affording high regio- and enantioselectivities for a minority of the examples, the reaction was not very general with regards to substrate scope.²⁰

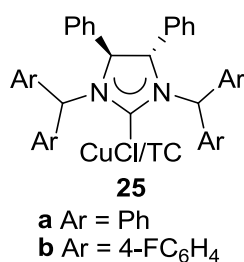
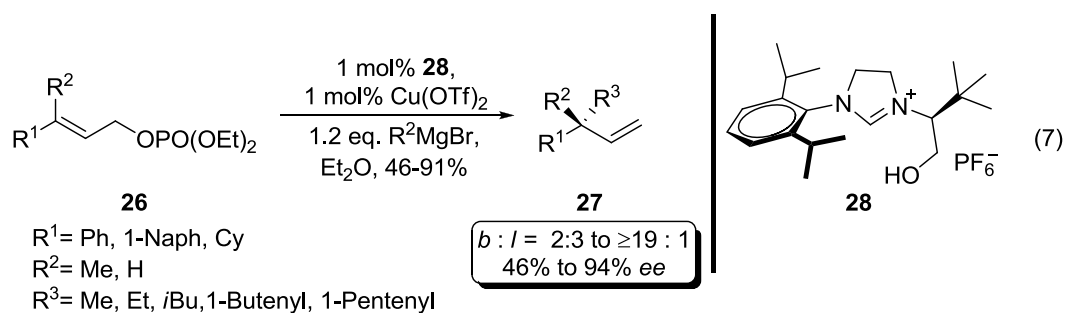


Figure 3: Highly Arylated Chiral NHC Complex.

In 2013 Mauduit *et al.* introduced the hydroxyalkyl imidazolium salt **28** as a precursor ligand, which in the presence of excess nucleophile should form the carbene *in situ*.²² Using this readily available chiral ligand, the alkylation of cinnamyl type phosphates **26** was achieved in enantioselectivities up to 94% *ee* (eq 7). Interestingly this is contrary to previous studies by Feringa and Alexakis,^{14,23} wherein they had demonstrated that allylic phosphates utilised in combination with Grignard based nucleophiles gave poor regio- and enantioselectivities when compared with allylic halides.^{14,23}



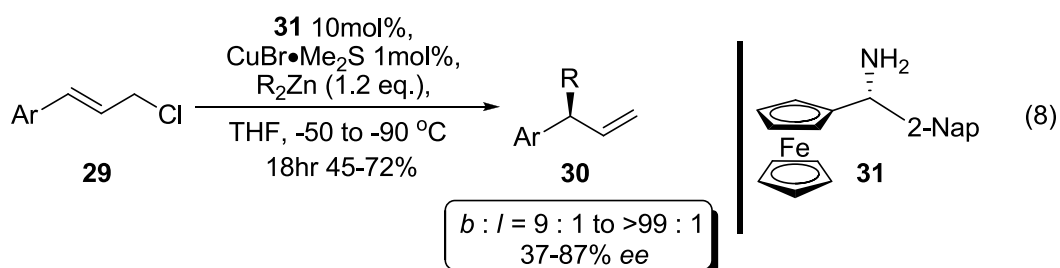
1.2.3. Diorganozinc as Nucleophiles

1.2.3.1. Introduction

Due to the lower basicity of organozinc reagents their relative stability, functional group tolerance and ease of preparation in comparison to organolithium and Grignard reagents, they have been utilised in a myriad of transition metal-catalysed cross couplings. For the same reasons organozinc reagents can be considered as one the most successful nucleophiles for the copper-catalysed S_N2' allylic alkylation. As with Grignard based nucleophiles the literature for organozinc reagents can be categorised into the ligand systems that have found the most success. There are five main ligand systems that have been utilised: amine-based, phosphorus-based, sulphonamide-based, peptides with an imine core, and carbene-based ligands. This section will be divided up into the main ligand/catalyst systems used for organozinc based nucleophiles.

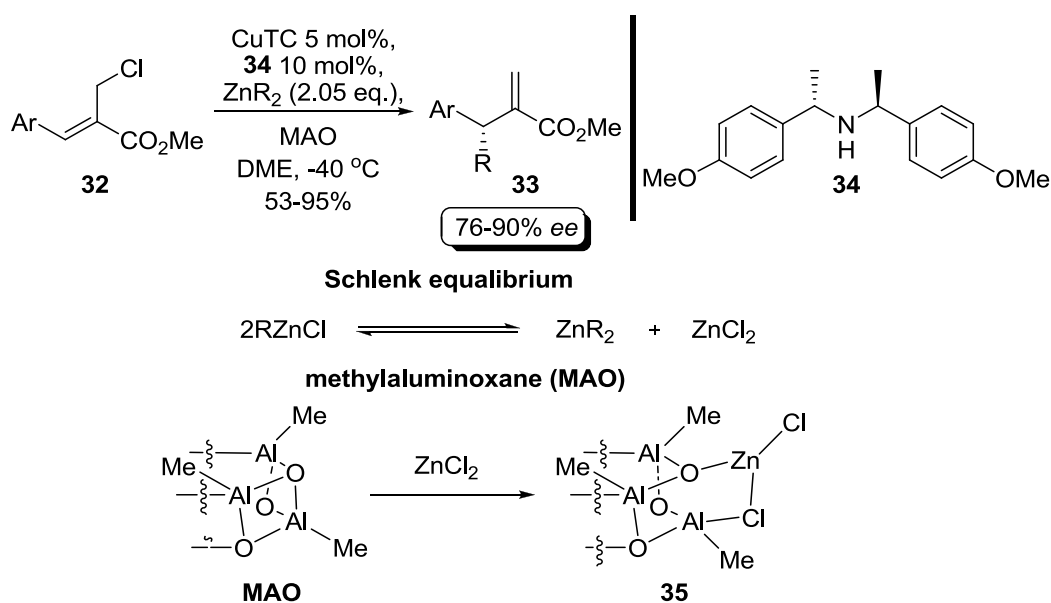
1.2.3.2. Amine based ligands

The first allylic substitution using diorganozinc reagents was reported by Dübner and Knochel in 1999.²⁴ Using chiral amine **31** in combination with copper (I) bromide-dimethyl sulphide complex, they were able to alkylated cinnamyl derivatives **29** in moderate to good enantioinduction in fair to good yields (Eq. 8). However, the reaction required very low operating temperatures and large bulky dialkylzincs to ensure good asymmetric induction.



The same group later improved the reaction by replacing the 2-naphthyl substituent of amine **31** with the bulky 3,5-ditertbutylbenzene derivative, which afforded enantioselectivities of up to 96% *ee* at a more practical reaction temperature (−30 °C).²⁵

Later Woodward and co-workers showed that copper(I)-thiophene-2-carboxylate (CuTC) in the presence of amine **34** could catalyse the asymmetric S_N2' addition of linear dialkylzincs into ester-functionalised allylic halide derivatives **32** (Scheme 4).²⁶



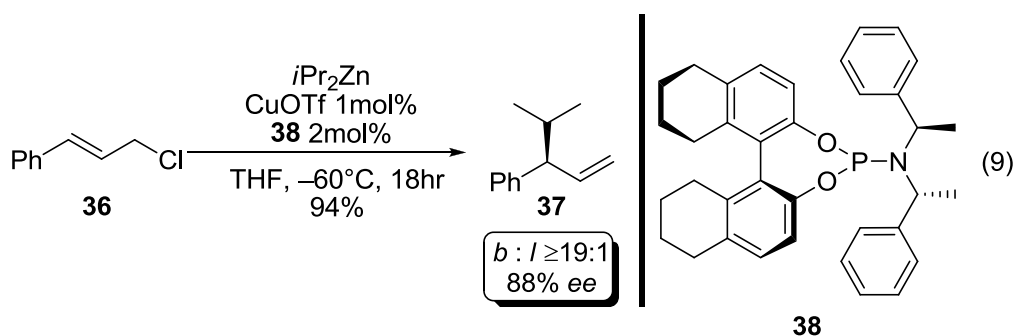
Scheme 4: Enantioselective S_N2' addition by MAO Promotion of the Schlenk Equilibrium.

This transformation allowed access to β,β-disubstituted α-methylenepropionates **33** in fair to excellent yields and in good enantiomeric excess.²⁶ Interestingly, they demonstrated that the asymmetric induction degraded as the reaction progressed, which was attributed to the gradual increase of free chloride within the reaction, which pushing the Schlenk equilibrium towards the unselective EtZnCl (Scheme 4).²⁶ This was combated with the addition of methylaluminoxane (MAO) which is

known to strongly scavenge halides via the “latent Lewis acid” complex **35**.²⁶ This paper highlights just how critical the nature of the organometallic nucleophile can be with respect to the enantioselectivity of the reaction.

1.2.3.3. Phosphoramidite ligands

Like Grignard reagents, organozinc reagents have been successfully deployed in combination with phosphorus based ligand systems. Feringa first utilised phosphoramidite ligands for the copper-catalysed enantioselective conjugate addition of dialkylzinc reagents to cyclic and acyclic enones.²⁷ Then in 2001 the same group described the copper-catalysed S_N2' allylic alkylation of cinnamyl type allylic bromides, affording the alkylated products in enantioselectivities up to 77% *ee*.²⁸ The phosphoramidite systems showed promise due to their highly modular and tuneable nature, and in 2004 the Feringa group further improved the enantioinduction in the reaction by screening a large library of easily prepared phosphoramidite ligands.²⁹ They found that the H8-BINOL-derived phosphoramidite **38** gave enantioselectivities of up to 88% *ee* when utilised in combination with cinnamyl type substrates **36** (eq. 9).²⁹

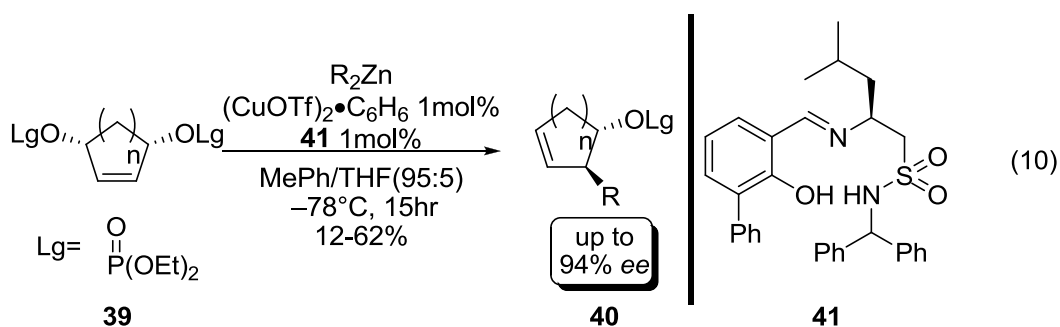


In the same year Alexakis and co-workers reported higher enantioselectivities (up to 91% *ee*), utilising the methoxy containing phosphoramidite ligand **11b**,^{9b} which had previously been demonstrated as an excellent ligand for Grignard based nucleophiles (*vide supra*). The same ligand **11b** was also successfully utilised in the desymmetrisation of *meso* cyclic allylic bis(diethylphosphates) and the allylic alkylation of vinyloxiranes to afford the requisite products in excellent enantioselectivities (up to 94% and 96% *ee* respectively).^{30,31}

1.2.3.4. Chiral Sulfonamides ligands

Another group of highly modular ligands which have been assayed in the copper-catalysed S_N2' allylic alkylation were chiral sulfonamides.³² For example, Gennari *et al.* carried out an extensive investigation of a combinatorial library of 125 chiral sulfonamides, however, they were only able to achieve low enantioselectivities (*ee*'s up to 30%) for the alkylations of cinnamyl- type allylic phosphates.³²

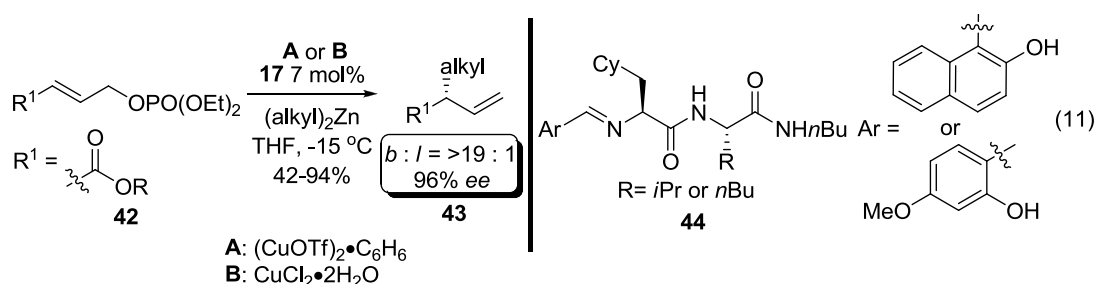
The same group went on to demonstrate that chiral sulfonamide **41** (eq. 10) provided excellent enantioselectivity for the copper-catalysed desymmetrisation of *meso* cyclic allylic bis(diethylphosphates) **39** with dialkylzinc reagents, and were able to generate the requisite products **40** in *ee*'s up to 94% (eq 10).³³



Despite the highly modular nature of this ligand class and the ease with which a large library of analogues can be prepared,³² they have not widely developed as a ligand system for the copper-catalysed S_N2' allylic alkylation, their appeal as a ligand system seemingly tarnished by their relative lack of success when compared to already well established ligand classes.

1.2.3.5. Imine Containing Peptides as Ligands

Similar to the previously mentioned chiral sulfonamides (*vide supra*), Hoveyda and co-workers developed a series of highly modular peptide ligands bearing an imine core.^{34a-d} The highly modular nature of the ligands allowed the authors to prepare a large library of ligands.^{34a} Following a combinatorial approach, they were able to achieve good enantioselectivities for the alkylation of cinnamyl type allylic phosphates with diethylzinc (up to 87% *ee*),^{34a} and for the enantioselective formation of all carbon quaternary centres from the requisite trisubstituted allylic phosphates (up to 90% *ee*).^{34a}



In the following years the same group further refined the peptide ligands by the inclusion of hydroxynaphthalene and hydroxyanisole groups at the imine core **44** (eq. 11).^{34b} These modifications, coupled with the utilisation of unsaturated esters that

possess an allylic phosphate **42**, allowed for the highly enantioselective preparation of α -alkyl- β,γ -unsaturated esters **43** (eq. 11).^{34b} The synthetic utility of the methodology was demonstrated *via* the enantioselective total synthesis of (*R*)-(-)-elenic acid (**Figure 4**), which was achieved in >6% overall yield over 6 steps and in 90% *ee*.^{34b}

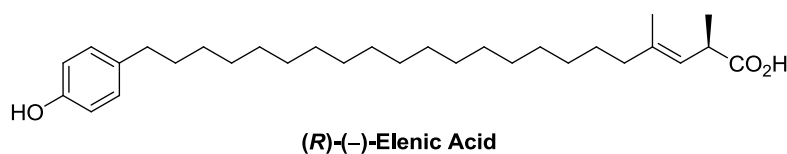


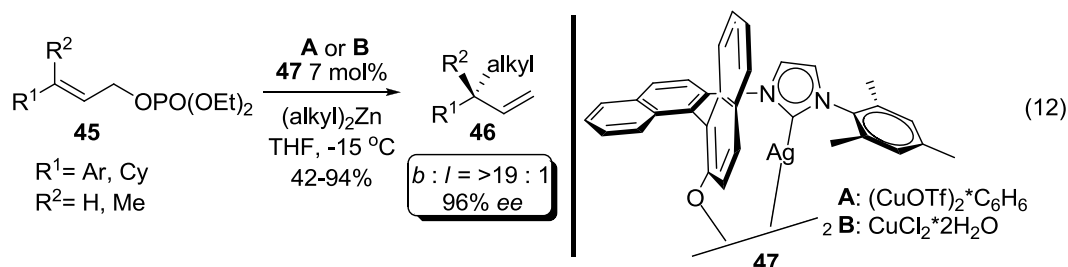
Figure 4: Marine Natural product (*R*)-(-)-Elenic Acid

Hoveyda and Murphy further expanded the scope of the methodology to include unsaturated esters that contain a trisubstituted olefin, this in turn afforded the requisite α,α' -disubstituted- β,γ -unsaturated esters in excellent regio- and enantioselectivities.^{34d} The enantiocontrolled formation of all carbon quaternary centre alpha to an ester moiety is a particular challenging transformations. The classical approach for the enantioselective construction of α -substituted esters is enolate alkylation, however, these methods remain challenging in the acyclic manifold, particularly for quaternary carbon stereogenic centres.³⁵

1.2.3.6. N-Heterocyclic Carbene (NHC) based catalysts

In 2004, the Hoveyda group developed their first generation of bidentate chiral NHC ligands. The air stable dimeric silver salt **47** was based on the imidazolium salt precursor that had previously been used to prepare a chiral ruthenium NHC catalyst for enantioselective ring opening- and cross-metathesis reactions.³⁶ NHC silver salt **47** was deployed in combination with copper(II)chloride hydrate or copper(I)trifluoromethanesulfonate to catalyse the S_N2' substitution of allylic

phosphonates **45** with dialkylzincs, yielding products containing tertiary and quaternary stereocenters (eq. 12).³⁷ This transformation was achieved in moderate to excellent yields with good to excellent asymmetric induction (up to 96% *ee*).



In the following year the same group published a full article detailing an improved catalyst system, in which they replace the binaphthalyl unit with a biphenyl moiety (**Figure 5**).³⁸ The source of chirality was installed on the NHC backbone by the use of a chiral diamine as opposed to the atropisomerism of the binaphthalene unit of the previous catalyst generation.

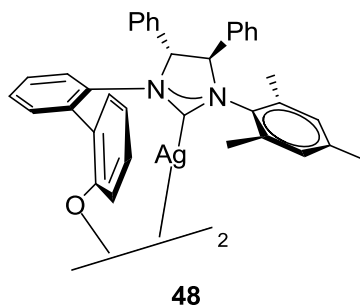


Figure 5: biphenyl chiral diamine based NHC silver salt dimer.

The improved catalyst **48** was significantly more effective in terms of scope and enantioselectivity.³⁸ This allowed for the addition of methyl, ethyl, *n*-butyl and the more sterically demanding *iso*-propyl organozinc reagents to allylic phosphates for the formation of both tertiary and quaternary centres in excellent enantioselectivities up to 98% *ee*.³⁸

Hoveyda *et al.* further expanded the scope of the reaction by utilising silyl substituted allylic phosphate **49**, which afforded optically enriched allylsilanes **50** or **51**, depending on the nucleophile deployed, bearing tertiary and quaternary Si-substituted carbon stereocenters in enantioselectivities up to 98% *ee* (eq 13).³⁹ Using a combination of the first and second generation NHC precatalysts, as well as the previously mentioned imine containing peptide ligands developed by the same group (*vide supra*), they were able to deploy both alkyl and aryl organozinc reagents, allowing access to a large range of enantiomerically enriched tertiary and quaternary allylsilanes in moderate to excellent *ee*'s (eq. 13).³⁹



1.2.4. Triorganoaluminum as Nucleophiles

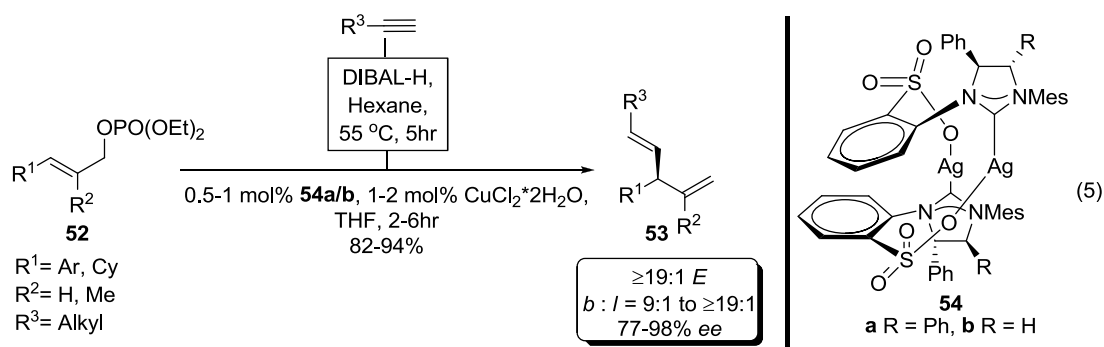
1.2.4.1. Introduction

Up to 2008, there were only a few papers on the use of triorganoaluminum reagents as nucleophiles in the contexts of copper-catalysed allylic alkylation.⁴⁰ These have mainly been used on the context of copper-catalyzed nucleophilic ring opening of bicyclic hydrazines using trialkylaluminum as a nucleophile.⁴⁰ However, since 2008 there has been a massive expansion in the scope of organoaluminum reagents that have been deployed in copper-catalysed allylic alkylation, initially from the trialkyl aluminium reagents previously mentioned (*vide supra*). We can now access methodologies that utilise (*Z*)-, (*E*)-, and α -substituted vinylaluminium reagents, with highly stereocontrolled formation of the nucleophile,^{41,43,46,47} alkynyl aluminium

reagents which allow facile access to enantioselective synthesis of carbon-carbon *sp*-*sp*³ stereogenic bonds,⁴⁸ and aryl/heteroaryl aluminium reagents which allow the construction of all carbon quaternary stereocenters, which were previously unobtainable *via* direct enantioselective arylation.⁴⁹

1.2.4.2. Vinylaluminium Reagents

The first steps in expanding the range of organoaluminium reagents that may be utilised in copper-catalysed allylic alkylations were taken by Hoveyda *et al.* In 2008 they published the first account of a vinylaluminium reagent being deployed in the context of the asymmetric NHC-copper-catalysed allylic alkylation of several allylic phosphates (*ee*'s up to 98%).⁴¹

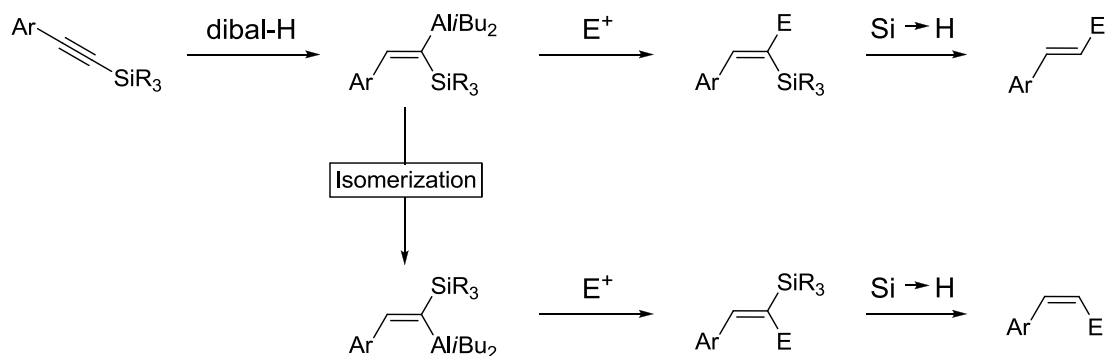


This system was based on the chiral NHC silver salt **54** utilised in combination with the air and moisture stable CuCl₂·H₂O salt as a precatalyst. The vinylaluminium reagent is formed *in situ* *via* the hydroalumination of a terminal alkyne by DIBAL-H. The diisobutylvinylaluminium species formed was then deployed in the copper-catalysed allylic alkylation of the allylic phosphonates **52** to yield a variety of skipped dienes **53** in good to excellent yields and with enantioselectivities up to 98%. Previously, two-step protocols that involved alkyne hydrozirconation with the more

costly and sensitive Cp₂ZrHCl (or hydroboration) followed by transmetallation with Me₂Zn, were required to access vinyl organometallics, which had previously only been utilised in enantioselective 1,4-conjugate additions.⁴² The methodology proved to be highly general, tolerating a variety of substituted aryl groups as well as limited alkyl substitution on the allylic phosphonate, only suffering a drop in regioselectivity with the highly electron rich *ortho*-methoxy substituted aryl Substituent (*b:l* = 10:1) and when the ethylbenzene substituted allylic phosphonate was deployed (77% *ee*). The reaction gave access to a variety of *trans*-alkenes, however, there was no real route towards forming the opposite geometry except for one notable example, in which the vinylaluminium substituted with an allylic *t*-butyl ether afforded the *cis*-alkene with near complete stereoselectivity. The authors attributed this reversal in selectivity, to the proximal Lewis basic (though sterically demanding) oxygen of the *t*-butyl ether, which directs the initial hydroalumination to generate the *cis*-vinylaluminium.⁴¹

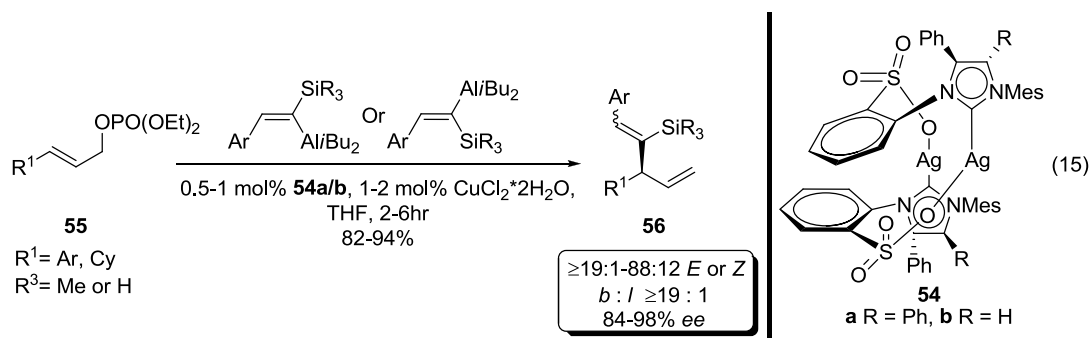
In order to overcome the main limitations of the previous methodology, namely that it failed to provide a general route to the *cis*-vinylaluminium reagents, and that aryl-substituted vinylaluminium reagents could not be utilised since the corresponding hydroaluminations are inefficient,⁴³ the same group developed a second iteration of the methodology. This reaction employs the same combination of pre-catalyst and silver salt NHC **54a/b** as before, but rather than a terminal alkyne utilises a silyl-substituted pronucleophile.⁴³ The authors hypothesised that the silyl substituent would allow for hydroaluminations of aryl-substituted substrates to proceed readily and with minimal by-product formation (**Scheme 5**).⁴³ The efficiency of such a hydroalumination would arise from stabilisation of the incipient electron density at

the carbon of the C–Al bond by the d orbitals of silicon, or through hyperconjugation with the low-lying σ^* orbital of the adjacent C–Si.⁴⁴



Scheme 5: Synthesis of a *cis*- or *trans*-disubstituted alkene.

To access the requisite *cis*-vinylmetals, Hoveyda took advantage of the pioneering investigations of Eisch,⁴⁵ who described the treatment of trimethylsilyl-substituted phenyl acetylene with DIBAL-H in hexane (55 °C, 2 h) afforded the *cis*-vinylaluminum in $\geq 98\%$ *E*-selectivity ($\geq 98\%$ conv.).⁴⁵ When the same alkyne was treated with DIBAL-H in the presence of a 5:1 Hexane:THF the *trans*-vinylaluminum was afforded $\geq 98\%$ *Z*-selectivity.⁴⁵ Eisch's rationale for such a dichotomy in regioselectivity, was that in the absence of Lewis basic THF, alkene isomerization occurs readily, as the energetically accessible and unoccupied *p* orbital of the aluminium are available. These unoccupied orbitals act as an electron sink to allow a change in hybridisation of the adjacent carbons, which in turn allows free rotation about the adjacent bond to give the isomerised product. When THF is present, it coordinates to the Lewis acidic aluminium, thereby occupying the empty *p* orbital and inhibiting the isomerisation.⁴⁵



This second iteration of the methodology proved to be equally as general for the formation of *cis*-alkenes as the first methodology was for the formation of *trans*-alkenes.⁴¹ The selectivities were high regardless of the steric/electronic constraints in the aryl substituents on the allylic phosphate **55** and even alkyl-substituted substrates could be effectively utilised with only a modest drop in enantioselectivity (88% *ee*), with all substrates providing excellent regioselectivity ($b:l \geq 19:1$).⁴³ As for the scope of the nucleophilic coupling partner, this proved to be fairly general allowing a range of silyl-substituted alkynes with a variety of electron rich and poor aryls (*ee*'s from 98-84%). The regioselectivity was uniformly high ($b:l \geq 19:1$), as was the (*E*)-selectivity ($E:Z \geq 19:1$) in all examples except for the *para*-CF₃ substituted aryl, in which the *E:Z* was only 88:12. This incomplete vinylaluminum isomerisation, the authors surmise, was due to destabilization of the zwitterionic isomerisation transition state by the electron withdrawing *para*-CF₃, however, the isolable (*E*)-isomer was still afforded with high regio- and enantiocontrol ($b:l \geq 19:1$, 94% *ee*).⁴³

The group went onto test a range of aryl substituted (*Z*)-vinylaluminum reagents (obtained *via* hydroalumination in the presence of 5:1 Hexane:THF solvent mix), which would otherwise not be accessible *via* the direct hydroalumination of the requisite alkynes not containing the silyl substituent. Similar to the reaction with (*E*)-vinylaluminum reagents both high regio- and enantioselectivity were uniformly

observed ($rs \geq 19:1$ and 91–97% *ee*). For most of the examples the (*Z*)-selectivity was nearly complete,⁴³ the only exception was the *para*-methoxy substituent which afforded the product as a 10:1 *Z:E* mixture due to the methoxy substituent facilitating the olefin isomerisation of the vinyl aluminium. In contrast to the reactions of (*E*)-vinylaluminium, 7–28% of the products observed came from the addition of an isobutyl group (no *iso*-butyl addition was observed with the (*E*)-vinylaluminium reagents). In the same report the group demonstrated the synthetic utility of the 2nd generation methodology by performing the first enantioselective synthesis of niasol (**Figure 6**), which was achieved in 97% *ee*, $\geq 19:1$ *E* and *b:l* selectivity, and 42% overall yield in a three-step procedure from the commercially available trimethylsilylacetylene.⁴³

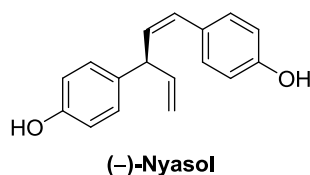
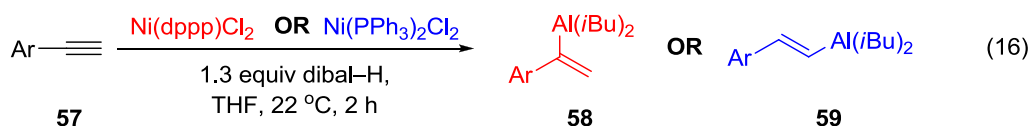


Figure 6: Naturally Occurring Norlignan (-)-Nyasol.

The ability to access both the (*E*)- and (*Z*)-isomers of the vinylaluminium reagent has extreme synthetic utility, however, the ability to form the vinylaluminium reagent at the internal position did not exist until 2010. Hoveyda *et al.* developed a nickel catalysed hydroalumination of aryl- and alkyl-substituted terminal alkynes (eq. 16).⁴⁶



Depending on the nickel complex deployed as a catalyst both the internal and the *trans*-vinylaluminium reagents can be accessed in high selectivity (up to $\geq 19:1$ for $\alpha:\beta$ and $\beta:\alpha$) and yield.⁴⁶ 1,3-Bis(diphenylphosphino)propanenickel(II) chloride

(Ni(dppp)Cl₂) catalyst gave the internal vinylaluminium **58**, whereas the bis(triphenylphosphine)nickel(II) chloride (Ni(PPh₃)₂Cl₂) gave the *trans*-isomer of the terminal vinylaluminium **59**.⁴⁶ Both sets of vinylaluminium reagents were confirmed as viable nucleophiles for the asymmetric NHC-copper-catalysed allylic alkylation.⁴⁶

Later that year the same group published a full article combining all their methods for the synthesis of the *cis*- or *trans*-isomers of vinylaluminium reagents, and their application in the enantioselective construction of quaternary carbon stereocenters *via* asymmetric NHC-copper-catalysed allylic alkylation. This article cumulated in the highly concise and enantioselective synthesis of bakuchiol (**Figure 7**).⁴⁷ The three-pot process, involving geraniol and commercially available 4-ethynylanisole as starting materials, and proceeded in 82% *ee* and 72% overall yield, whereas the shortest previous synthesis delivered the target in 10 steps and 49% overall yield.⁴⁷

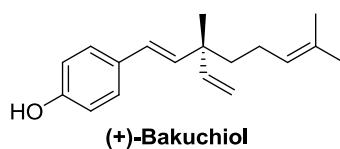
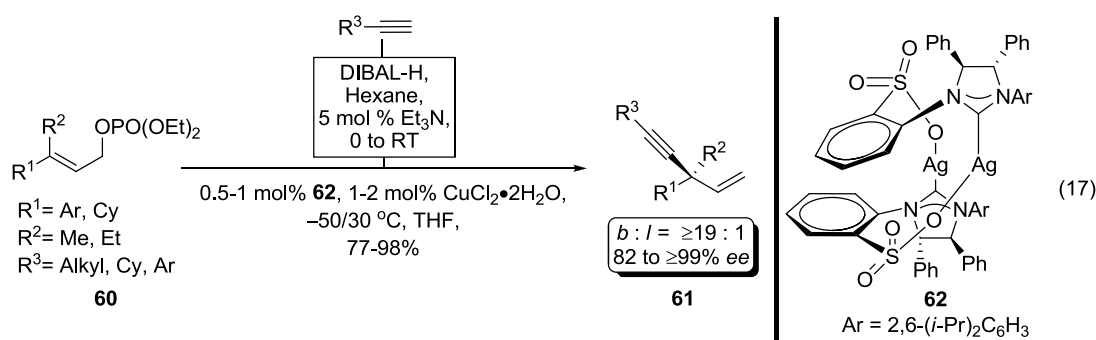


Figure 7: Naturally Occurring Terpenophenol (+)-Bakuchiol.

1.2.4.3. Alkynyl Aluminium Reagents.

The ability to deploy alkynyl aluminium reagents as nucleophiles in the asymmetric NHC-copper-catalysed allylic alkylation is a by-product of the inefficient hydroalumination of aryl substituted alkynes that was first described by Hoveyda in 2008.⁴¹ These efficiencies were circumvented in several papers in the convening years (*vide supra*), however, it wasn't until 2011 that the same group published a methodology utilising the alkynyl aluminium reagents as a nucleophile (eq. 17).⁴⁸

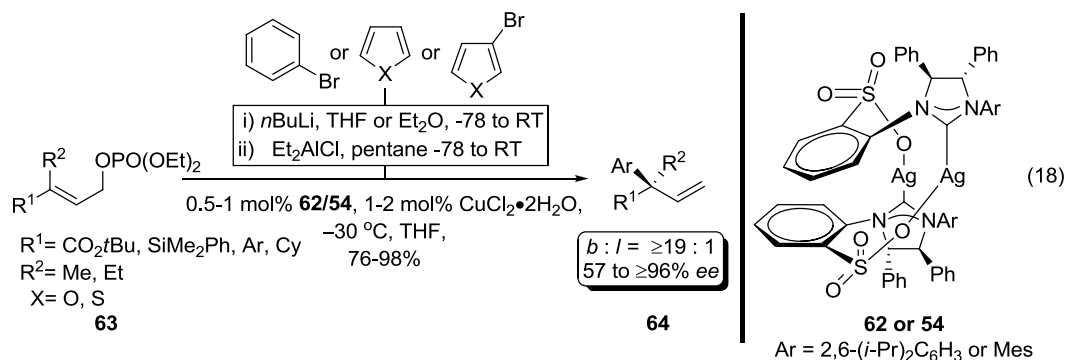


The methodology utilised the same chiral NHC silver salt **62**/ $\text{Cu(II)Cl}_2 \cdot \text{H}_2\text{O}$ salt precatalyst combination (eq. 17), which had previously been utilised in the asymmetric NHC-copper-catalysed allylic vinylation reaction. The key difference between the allylic vinylation and this allylic alkylation is the preparation of the nucleophile. In the original papers it was found that the hydroalumination of alkenyl/aryl substituted alkynes resulted in ~30-50% of the alkynyl aluminium instead of the desired vinyl aluminium. To improve this selectivity for the alkynyl aluminium species, the authors used studies by Binger and the more recent work published by Micouin *et al.*,⁴⁹ which demonstrated that an addition of 5 mol % Et_3N in the presence of DIBAL-H at ambient temperature allows exclusive access to the requisite alkynylaluminum. Much like the allylic vinylation, this reaction proved to be as general with the majority of substrates and nucleophiles affording the associated products in excellent regioselectivity, enantioselectivity and yield (up to $b:l$ up to $\geq 19:1$, 82-99% *ee*, and up to $\geq 99\%$ yield).⁴⁸ The reaction tolerates a whole series of electron rich and poor aryls substituents on the electrophilic coupling partner with only a small variation in enantioselectivity (82 to $\geq 99\%$ *ee*). The scope of the nucleophilic coupling partner is almost as broad, with both cyclic and linear alkyl substituents, as well as aryl- and alkenyl-substituted alkynes being tolerated as

pronucleophiles. The reaction does not however tolerate extremely electron poor aryl substituents on the alkyne such as *para*-CF₃-C₆H₄, which failed to react.⁴⁸

1.2.4.4. Aryl/Hetero Aryl Aluminium Reagents as Nucleophiles.

There is a near complete dearth of asymmetric allylic alkylations involving organometallic aryl nucleophiles that afford all carbon quaternary centres, and protocols which involve heteroarylmets did not exist (including those that furnish tertiary C–C bonds) until very recently. The first such efficient, catalytic and enantioselective methods was described by Hoveyda *et al.* in 2010 (eq. 18).⁵⁰



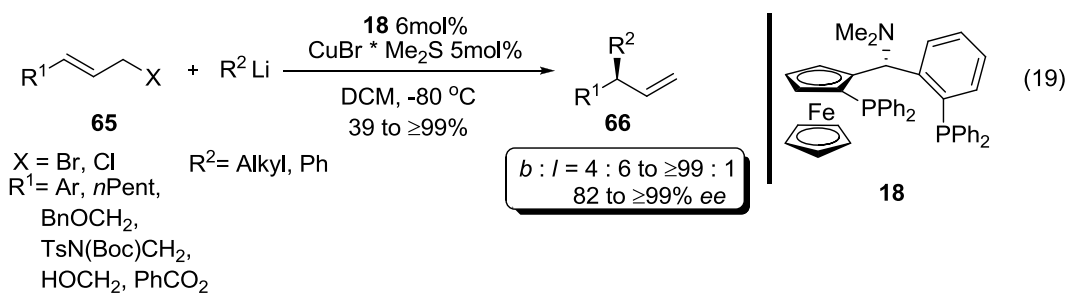
Utilising the same precatalyst/NHC silver salt combination that had previously been deployed to great effect with vinyl and alkynyl organoaluminiums, they were able to achieve the allylic arylation/heteroarylation of a variety of allylic phosphates **63** in excellent yields and selectivities.⁵⁰ The aryl aluminium reagents were prepared from the addition of requisite aryl/heteroaryl lithiums (either commercially available or prepared from lithium halogen exchange/selective deprotonation) to diethylaluminium chloride. Like the previous methodologies utilising the organoaluminiums, the scope of the both the nucleophilic and electrophilic coupling partners is extremely broad. The authors were able to prepare a range of tertiary and quaternary all carbon stereocenters in good to excellent enantioselectivities (up to

96% *ee*).⁵⁰ Remarkably the authors were also able to utilise substrates that included ester substitution, giving access to an aryl- containing α -quaternary substituted esters **64**. As previously mentioned, the classical route to such stereocenters is enolate alkylation. However, these methods fail when it comes to the formation of quaternary centres in the acyclic manifold, especially those containing an aryl-group.³⁵

1.2.5. Organolithium as Nucleophiles

Remarkably, for extremely reactive organolithium compounds, which are among the most broadly used reagents in chemical synthesis, a general catalytic methodology for enantioselective C–C formation has proven elusive. This is due to the highly reactive and basic nature of such nucleophiles. Most of the problems with these species are related to their incompatibility with the substrates deployed and their inability to inhibit the background reactions of such reactive organometallic reagents, whilst simultaneously promoting the desired transformation. Until fairly recently in the context of alkylation and 1,4-conjugate additions, organolithium reagents had only been utilised in conjunction with copper salts to form stoichiometric cuprates.

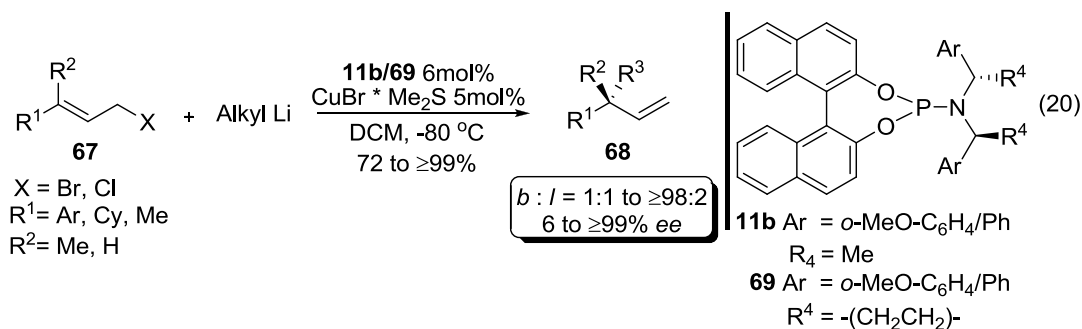
The catalytic asymmetric manifold has only recently been described by Feringa *et al*, wherein they reported the synthesis of tertiary stereogenic centres *via* a copper-catalysed allylic alkylation utilising organolithium nucleophiles.⁵¹ By using TaniaPhos **18** in combination with copper (I) bromide-dimethyl sulphide complex, they were able to alkylate allylic halide derivative **65**, in excellent to near total enantioinduction in up to quantitative yield and excellent regioselectivity with a range of organolithiums as nucleophiles (Eq. 19).⁵¹



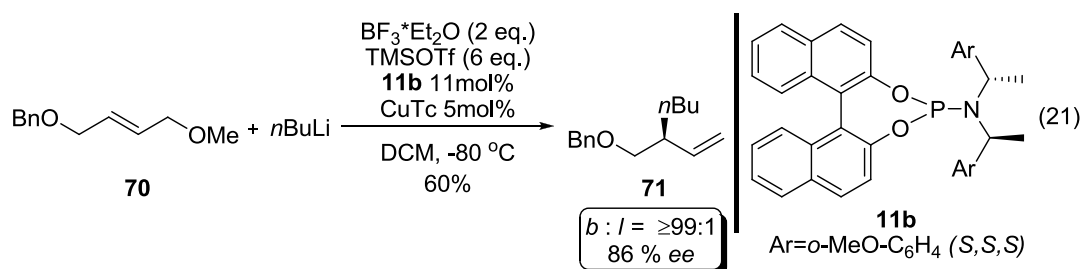
They demonstrated that the rate/order of addition, reaction temperature, nature of the solvent and the pre-catalyst were essential, allowing almost complete control with respect to side reactions and non-catalysed ‘background’ S_N2 transformation. Dichloromethane was found to be the optimal solvent, as more polar ethereal solvents like diethyl ether and methyl tert-butyl ether resulted in a massive decrease in both regio- and enantiocontrol. Following detailed *in situ* ¹H, ³¹P, and ⁶Li/⁷Li NMR studies, they showed that the chiral complex most likely to be responsible for the reaction is a TaniaPhos-CuMe species, which is formed exclusively at –80 °C in DCM in the absence of ethereal solvents.⁵¹ The detrimental effect of ethereal solvents on enantioselectivity was proposed to be due to the formation of multiple copper species, including the anionic TaniaPhos-CuMe₂Li complex and the high order cuprate Gilman’s reagent (lithium dimethylcopper).⁵¹ The reactivity of alkylolithium reagents is highly dependent on their structure and aggregation state, so by choosing a non-polar like DCM they were able to promote the catalytic reaction without the formation of highly reactive organolithiums species.⁵¹

The same group further improved the methodology by switching from the TaniaPhos ligand system to a phosphoramidite based ligand system **11b/69**, which allowed them to deploy simple allyl chlorides/bromide **67** as a substrate and secondary organolithium nucleophiles, both with excellent regio- and enantioselectivity (eq. 20).⁵² Using the same phosphoramidites **11b/69** they were able to construct all-

carbon quaternary stereogenic centres in an enantioselective manner, the first to do so utilising highly unstabilised organolithium nucleophiles (eq. 20).⁵²



The 3rd iteration of this methodology focused on the ability to use more robust substrates such as allylic ethers as opposed to allylic halides.⁵³ In this report, they were able to use allylic benzyl/methyl ethers as substrates in combination with a catalytic amount of copper(I)-thiophene-2-carboxylate and phosphoramidite ligand **11b**, a super stoichiometric amount of BF₃·OEt₂:TMSOTf(1:3) as a Lewis acid and a series of alkylolithiums as nucleophiles.⁵³ Remarkably they were also able to utilise a diether substrate that was composed of orthogonally protected oxygens and the reaction was able to differentiate between the methoxy and the benzyloxy ether terminus of the substrate **70**, giving complete selectivity for the methoxy ether as the leaving group **71** (eq. 21).

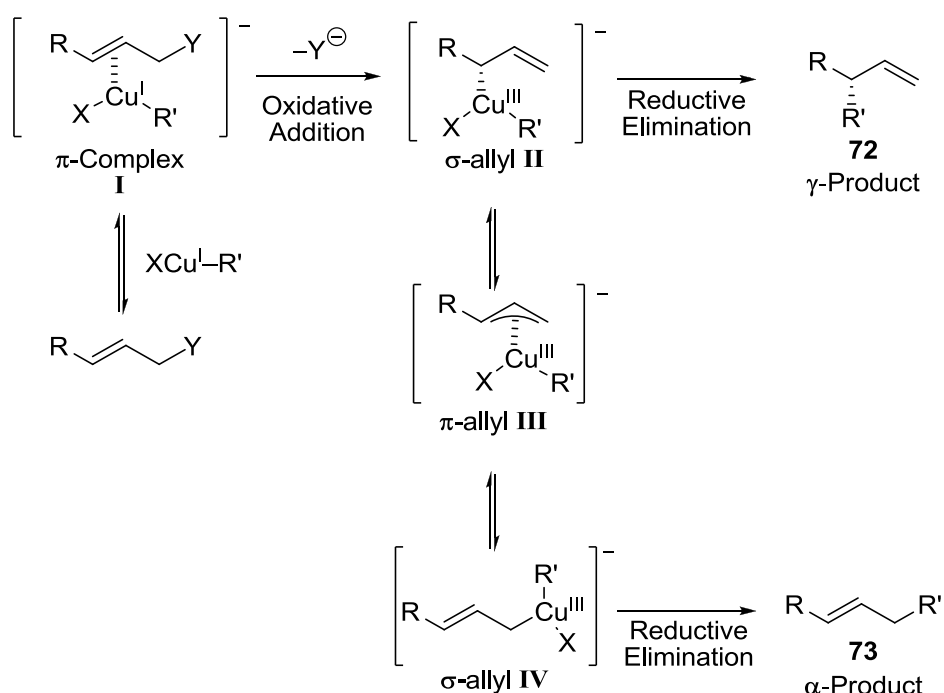


This was contrary to what was demonstrated in the scope study, as the benzyloxy ethers appeared to be the more reactive substrates compared to the methoxy ethers. The authors surmised that there was a possible interaction between the aromatic ring

of the benzyl group and the copper complex which could control the regioselectivity.⁵³

1.2.6. Mechanistic Features

The generally accepted mechanism for the Cu-catalysed S_N2' reaction was first described by Bäckvall and van Koten, and proceeds *via* a transient Cu^{III} intermediate (Scheme 6).⁶



Scheme 6: Copper-Catalysed S_N2' Allylic Alkylation.

Initially the substrate reversibly chelates to form the π -complex **I**, the Cu catalyst then irreversibly adds to the preferred *pro-Si* or *Re* face during the enantio-determining oxidative addition step. The resultant Cu^{III} σ -allyl can then undergo a facile reductive elimination to afford the γ -product **72**. However, if ligand **X** is sufficiently electron rich to stabilise the highly transient Cu^{III} species, the σ -allyl **II** can isomerise *via* π -allyl species **III** to give the thermodynamically more stable σ -allyl **IV**, which in turn undergoes reductive elimination to afford the α -product **73**.

Taking these basic mechanistic features, it is possible to explain the overall trends in the literature in terms of scope and the conditions deployed for majority of successful copper catalysed S_N2' allylic alkylations. A facile reductive elimination is required to ensure high levels of regioselectivity towards the chiral γ -product **72**, which accounts for the prolonged addition times of nucleophiles throughout the literature. These cautious additions avoid the formation of dialkyl cuprates, which contain an extra alkyl ligand, which are sufficiently electron rich enough to promote alkylation at the α -position. The popularity of cinnamyl type substrates can also be rationalised, as the electron withdrawing nature of the aryl group promotes reductive elimination at the γ position.

Another trend in substrate scope which arose to circumvent issues of regiocontrol, is the utilisation of substrates that contain a heteroatom at the ϵ position, which theoretically stabilised the Cu^{III} intermediate *via* the donation of electron density into the empty d orbitals of the copper, thereby tethering the metal at the γ position (**Figure 8**).^{9e,54}

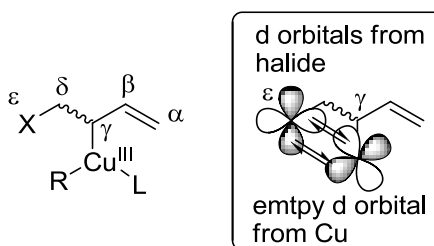


Figure 8: regiocontrol *via* directing properties of X⁵³

This rationale was first introduced by Alexakis, who utilised it to explain the almost total regioselectivity afforded by utilising 1,4-dihalo-2-butenes as a substrate class.^{9e,54} This same rationale can also be used to explain the high levels of regiocontrol garnered by several other groups, have used a range of heteroatoms at

the ϵ position, including carbonyl motifs,^{15,34b,50} protected oxygens,^{19,51} and protected nitrogen groups.^{16,53}

In terms of stereoselectivity, the key mechanistic feature is that enantioselection occurs at the outset of the catalytic cycle *via* the enantioselective oxidative addition to the preferred *pro-Si* or *Re* face of the substrate. This is in contrast to other transition metal-catalysed allylic substitutions (classically palladium-catalysed), which proceed *via* a fluxional π -allyl intermediate that undergoes rapid facial exchange of the metal.

1.3. Transition Metal-Catalysed Allylic Substitution of Unstabilised Carbon Nucleophiles

1.3.1. Introduction

Since the inception of the transition metal-catalysed allylic substitution in 1965, it has become an extremely potent synthetic tool.¹ This can be attributed to the almost limitless scope and versatility of this process, which allows for the catalytic asymmetric construction of a wide range of C-C, C-N, C-O and C-S bonds.¹ The most successful and widely used metal is palladium however, a number of different metals have since been shown to be effective, including molybdenum,^{55,56} tungsten,⁵⁶ iridium,⁵⁷ rhodium,⁵⁸ ruthenium,⁵⁹ nickel,⁶⁰ copper,² cobalt,⁶¹ platinum,⁶² and iron.⁶³ However, the deployment of unstabilised carbon nucleophiles in the context of this reaction has been limited to only a few examples.

The following section will present an overview of the group 8-10 transition metals (not including ruthenium, osmium, and platinum) that have been successfully used as catalysts in allylic substitutions involving unstabilised carbon nucleophiles. Each

subsection will detail the initial development to the latest entries in the literature for each individual metal.

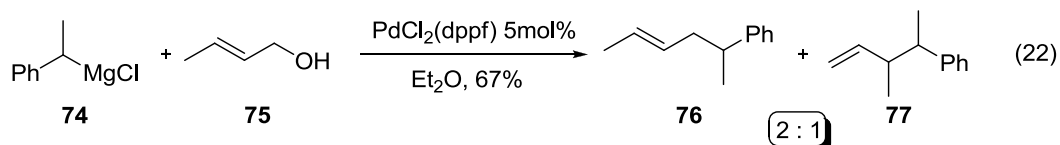
1.3.2. Palladium-Catalysed Allylic Alkylation of Unstabilised Carbon Nucleophiles

1.3.2.1. Introduction

Palladium has classically been the most successful of the transition metals in terms of allylic substitution, with a substrate scope that has grown to include a large range of stabilised carbon and heteroatom nucleophiles, which can be successfully coupled with a vast array of allylic electrophiles to afford products with up to two new stereogenic centres. However, in terms of utilising organometallic reagents, which represent a carbanion equivalent, as there has been very little progress.

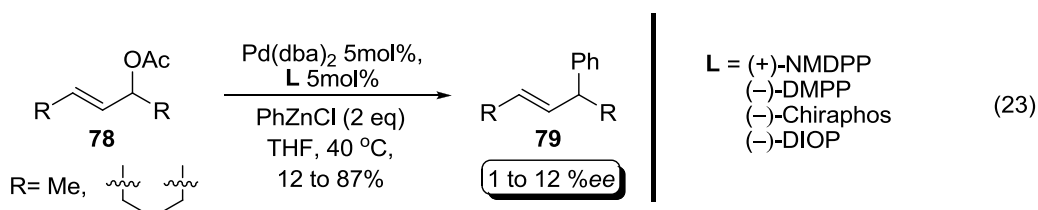
1.3.2.2. Palladium-catalysed allylic substitutions utilising organometallic nucleophiles

The first palladium-catalysed allylic substitutions to utilise an organometallic reagent as a nucleophile was performed by Kumada *et al.* in the early 1980's, who demonstrated that it was possible to alkylate allyl alcohol with a secondary alkyl Grignard reagent in the presence of dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) (PdCl₂(dppf)) affording the racemic coupled products in excellent yields (95 and 91%).⁶⁴ In the same paper, they postulated that the reaction proceeds *via* π -allylpalladium intermediate, as two regioisomers of the coupled product **76** and **77** were produced in a 2:1 ratio, when crotyl alcohol **75** was deployed as a substrate (eq. 22).⁶⁴



In the same year Schwartz and Temple published the stoichiometric alkylation of a π -allylpalladium complex with an alkenyl zirconium reagent, for the synthesis of steroids.⁶⁵ The following year the same authors disclosed the catalytic manifold of the reaction in which they used a preformed palladium(II)allyl as a precatalyst.⁶⁶

The first attempted enantioselective palladium-catalysed allylic substitution utilizing an unstabilised organometallic as a nucleophile came in 1985.⁶⁷ Fiaud and Aribi-Zouieche demonstrated that bis(dibenzylideneacetone)palladium(0) ($\text{Pd}(\text{dba})_2$) in combination with either a chiral monophosphine or diphosphine could catalyse the asymmetric substitution of acyclic and cyclic allylic acetates **78** with phenylzinc chloride (eq 23).⁶⁷ However, the enantioinduction was poor, which the authors attributed to the formation of a four coordinate neutral π -allylpalladium intermediate that only contains a single chiral phosphine ligand.⁶⁷



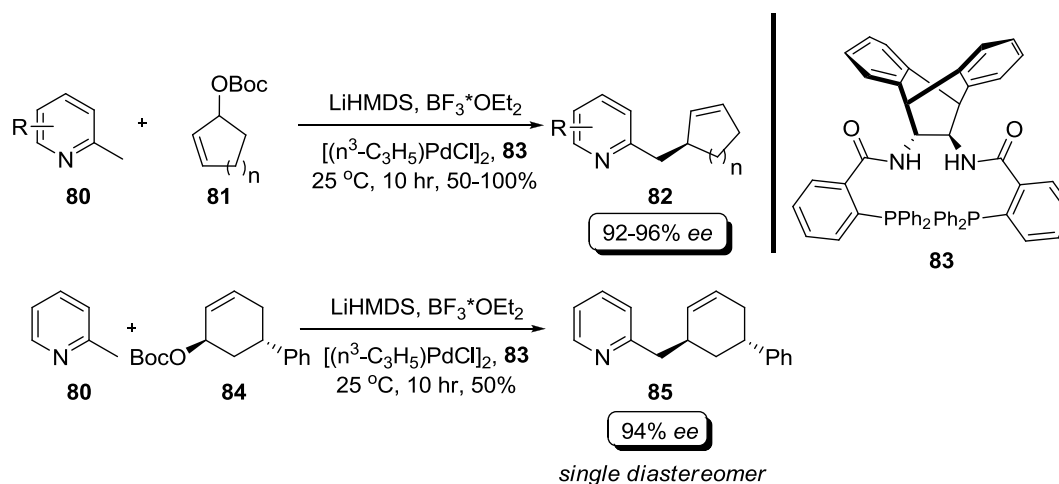
Even though the enantioselectivity of this reaction was extremely poor, this remained the sole enantioselective example of a palladium-catalysed allylic substitution utilizing an unstabilised organometallic nucleophile for nearly a quarter of a century. In the subsequent years the only further entries into the literature concerning the use of unstabilised/hard nucleophiles, revolved around the stereospecific reaction and

determining whether the reaction was indeed inner sphere,⁶⁸ or on tuning the regioselectivity to give the linear achiral product.⁶⁹

The difficulty in employing unstabilised nucleophiles for the asymmetric palladium-catalysed allylic substitution reaction is seemingly twofold. Firstly the palladium-catalysed reaction naturally favours the formation of the linear achiral product, even though these issues have largely been addressed in terms of stabilised nucleophiles,^{1,70} However, for the analogous unstabilised nucleophiles, there is a severe lack of similar strategies, other than employing substrates that form symmetrical π -allyl's. Secondly, the ability to induce a high level of enantioselectivity is particularly difficult for the inner sphere reaction, as the transient palladium(II)allyl species only has a hapticity of 3, so other than the allyl ligand and the metal bound nucleophile there is only one vacant site left for a chiral ligand.

1.3.2.3. Strategies for “Softening” Unstabilised Carbon Nucleophiles.

In 2008, Trost developed a strategy for employing unstabilised carbon nucleophiles in which the 2-methylpyridyl derived pronucleophiles **80** were deprotonated in the presence of the strong Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$.⁷¹ The then metalated nucleophile was utilised in the asymmetric allylic alkylation of the cyclic carbonates **81** to afford the associated alkylated products **82** in excellent yield and enantioselectivity (**Scheme. 7**).⁷¹

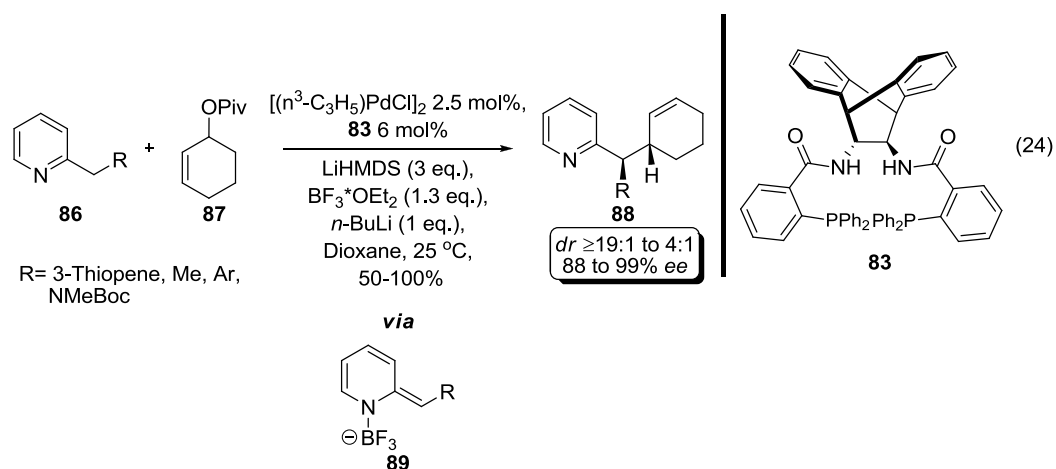


Scheme 7: Trost's Strategy for Employing Unstabilized Carbon Nucleophiles in Palladium-Catalysed Asymmetric Allylic Alkylations.

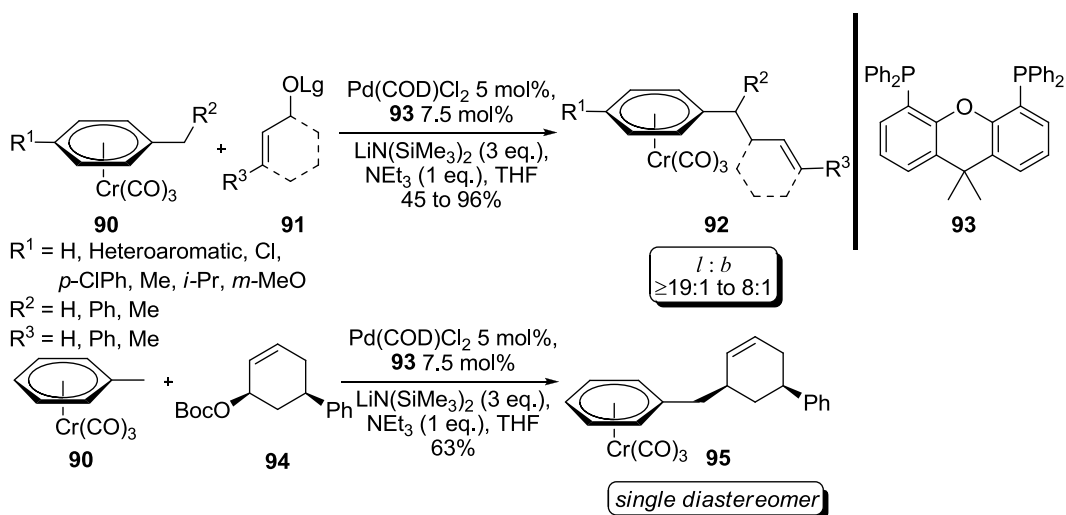
Prechelating the nitrogen atom of 2-methylpyridyl with $\text{BF}_3 \cdot \text{OEt}_2$ significantly reduces the pK_a of the adjacent methyl group and therefore stabilises the resultant anion after deprotonation. This reduction in pK_a means the supposedly unstabilised nucleophile is actually a stabilised nucleophile. This fact was highlighted further when the stereospecific allylic alkylation of enantiomerically enriched substrate **84** proceeded to afford the alkylated product **85** with retention of stereochemistry as opposed to inversion (**Scheme 7**).⁷¹ Thus, the alkylation proceeds through a double inversion mechanism, behaving as a stabilised nucleophile, rather than the addition of an unstabilised nucleophile onto the metal centre followed by the subsequent reductive elimination, which provides net inversion of stereochemistry.

The following year, Trost and Thaisrivongs developed a highly enantioselective and diastereoselective palladium-catalysed allylic substitution for the construction of contiguous ternary-ternary all carbon stereocenters.⁷² In much the same manner as the previous study they deprotonated the pyridine pronucleophile **86** was deprotonated in the presence of the strong Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$. The prechelation of the basic nitrogen coupled with the substitution at the benzylic position, resulted in

the selective formation of a single geometrical isomer of the requisite enamine **89**, affording the alkylated product **88** in a highly diastereoselective manner (eq. 24).⁷²



In 2011 a similar strategy was adopted by the Walsh group (Scheme 8),⁷³ who utilised toluene-derived pronucleophiles activated by tricarbonylchromium, the η^6 -arene coordination of which is known to activate benzylic C–H bonds toward deprotonation.⁷⁴ The requisite chromium η^6 -arenes **90** were then deprotonated at the benzylic position with LiHMDS, and deployed as nucleophiles in the racemic allylic substitution of acyclic and cyclic carbonates/benzoates **91** (Scheme 8).⁷³



Scheme 8: Walsh's Strategy for Employing Unstabilized Carbon Nucleophiles in Palladium-Catalysed Allylic Alkylations.

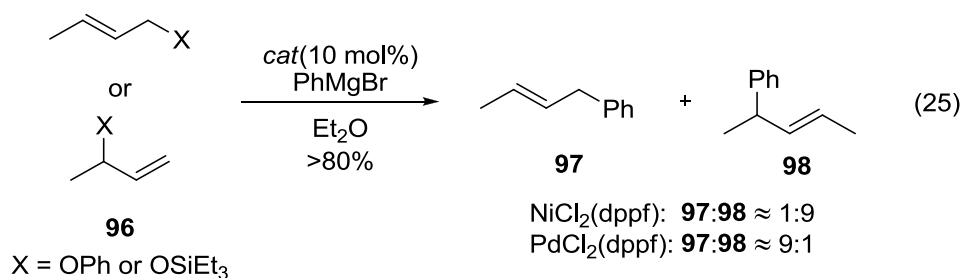
The reaction afforded the requisite racemic coupled products **92** in fair to excellent yields and regioselectivities. However, when a simple allyl carbonate was utilised as a substrate, there was a total lack of chemoselectivity between the unalkylated nucleophile and the coupled product, resulting in overalkylation.⁷³ The reaction was demonstrated to be stereospecific and to proceed *via* a classical double inversion mechanism, which is characteristic of the outer sphere alkylation of a stabilised carbon nucleophile. The reaction remains racemic as the authors have so far failed to achieve any asymmetric induction, despite screening a number of Trost type ligands, which failed to afford the desired product. Future studies are set to correct this, however, as yet there has not been a second entry into the literature detailing the enantioselective manifold.

Both of the above methodologies demonstrate an elegant means with which to obviate the challenges associated with deploying unstabilised carbon nucleophiles in the palladium-catalysed allylic alkylation. However, they do not represent a general solution in terms of efficiency and atom economy, as both methodologies require a stoichiometric amount of a Lewis acid to activate the pronucleophiles. Additionally, once the reaction has reached completion, both methodologies require either relatively harsh or prolonged reactions to remove the activating Lewis acid from the associated products.⁷¹⁻⁷³

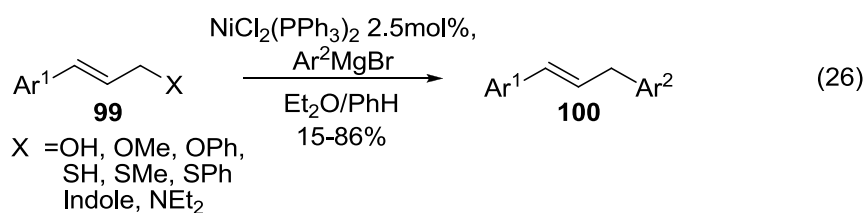
1.3.3. Nickel-Catalysed Allylic Alkylation of Unstabilised Carbon Nucleophiles.

Unlike palladium, the majority of the nucleophiles that have been deployed in the nickel-catalysed reaction have been hard nucleophiles such as Grignard reagents. The regioselectivity of the nickel-catalysed allylic substitution is inverted when compared to that of the palladium-catalysed reaction.⁷⁵ Independent of which regioisomer of

the substrate **96** is utilised, the palladium-catalysed reaction yields the linear alkylated product **97** as the major product, whereas the nickel-catalysed reaction gives the opposite selectivity and favours the formation of the branched product **98** (eq. 25).⁷⁵

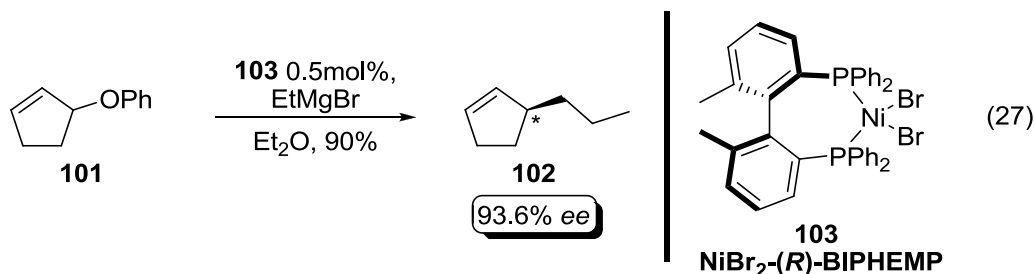


However, a severe dependence on substrate and/or catalyst system is usually observed. For example, the preservation of conjugation may reverse the above selectivity when a phenyl substituent is used (eq. 26).⁷⁶ Wenkert *et al.* demonstrated that in the presence of a catalytic amount of bis(triphenylphosphine)nickel(II)chloride ($\text{NiCl}_2(\text{PPh}_3)_2$), cinnamyl derived substrates **99** underwent allylic arylation to afford the associated 1,3-diphenylpropenes **100** in fair to good yields, and in total regioselectivity giving the linear product as the (*E*)-isomer (eq. 26).⁷⁶

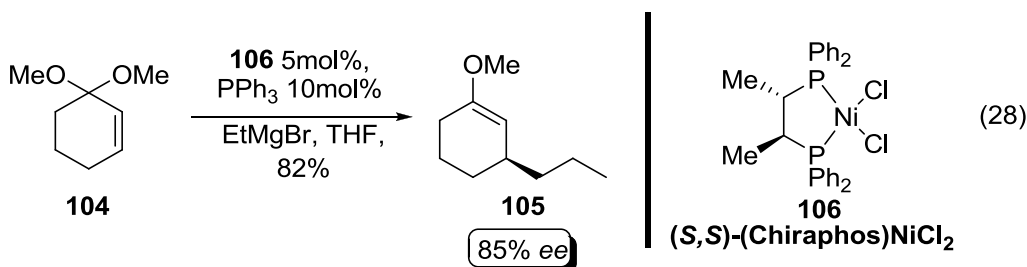


The first successful nickel-catalysed asymmetric allylic alkylation utilising Grignard reagents as nucleophiles was disclosed by Consiglio and Indolese in 1991,⁷⁷ they were able to alkylate allyl phenyl ethers **101** with Grignard reagents in the presence of a catalytic amount of a complex of NiBr_2 and (*R*)-(6,6'-dimethylbiphenyl-2,2'-diyl)bis(diphenylphosphine) (NiBr_2 -(*R*)-BIPHEMP) **103** (eq. 27).⁷⁷ Good yields and

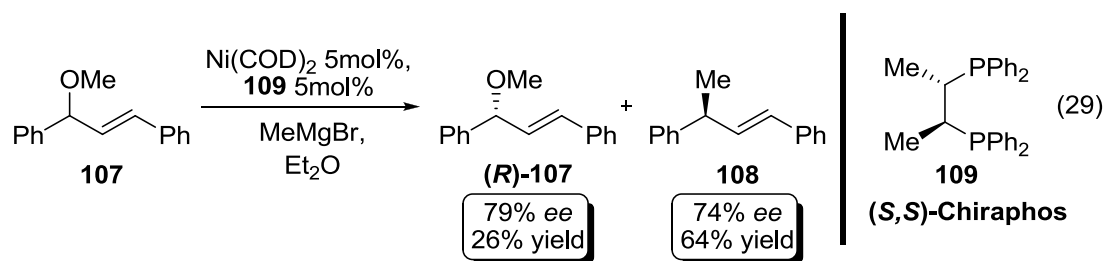
ee's were obtained for the reactions with EtMgBr as a nucleophile, however, a significant decrease in the yield and/or *ee* was observed when sterically smaller or larger Grignard reagents (e.g., MeMgBr, *n*PrMgBr) were deployed.⁷⁸



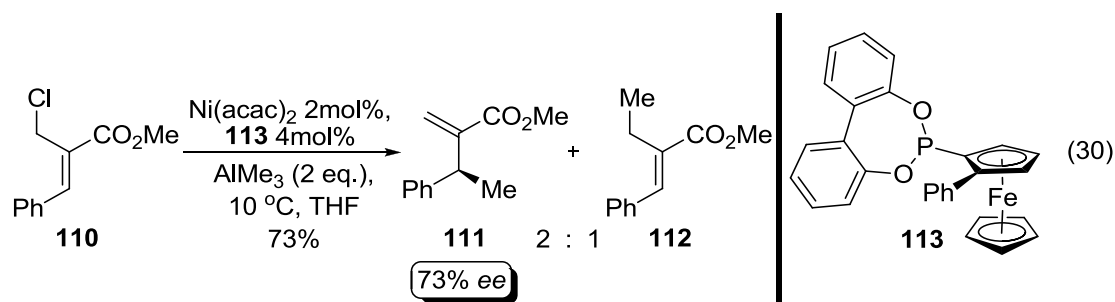
In 1998 Hoveyda *et al.* described the nickel-catalysed asymmetric allylic alkylation of dimethyl acetals of 2-cyclohexen-1-ones **104** with a range Grignard reagents (eq. 28).⁷⁹ In the presence of NiCl₂-(*S,S*)-chiraphos complex **106**, both 3-substituted cyclohexanones and the requisite enol ethers **105** were obtained in good *ee*'s, depending on whether an acidic (gives the cyclic ketones) or basic (gives enol ethers) work up was performed.⁷⁹ For the formation of cyclic ketones, the overall transformation is an alternative to the asymmetric conjugate addition to α,β -enones. Interestingly, the presence of the achiral ligand PPh₃ in the catalyst system was essential for the high enantioselectivity. When 5 mol% of NiCl₂((*S,S*)-chiraphos) **106** is used without any additional PPh₃, the product is obtained in very low *ee* (~80% yield, ~10% *ee*), whereas when the same reaction was performed in the presence of 10 mol% of PPh₃, the enantioselectivity was significantly improved (up to 85% *ee*).⁷⁹



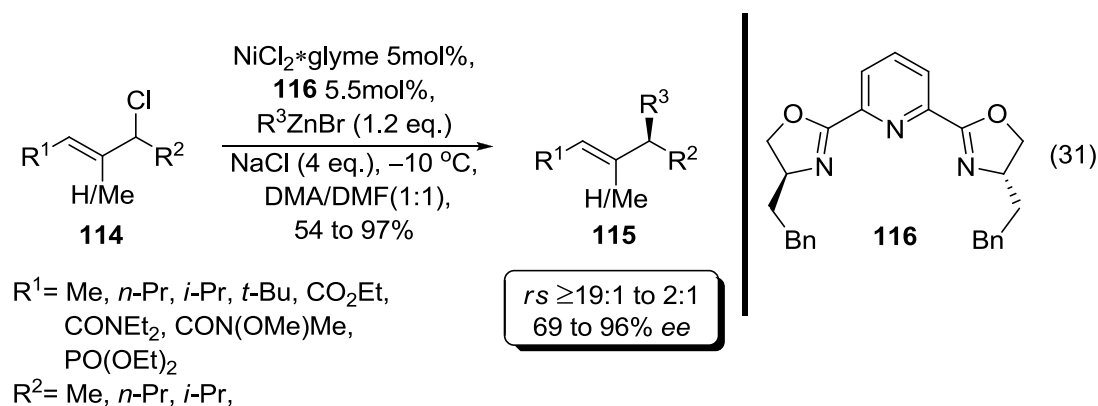
Compared with the cyclic allylic substrates described above, the corresponding acyclic substrates have met even less success in the nickel-catalysed asymmetric allylic alkylation utilising unstabilised carbon nucleophiles. It wasn't until 1997 that RajanBabu and Nomura demonstrated that a Ni/(S,S)-chiraphos complex could catalyse the enantioselective allylic alkylation of acyclic allylic ether **107** with alkyl Grignard reagents with relatively high enantioselection (up to 79% *ee*).⁸⁰ Interestingly, when the reaction was stopped prior to reaching completion, a kinetic resolution had taken place (eq. 29).⁸⁰



Ten years later Woodward *et al.* disclosed an enantioselective nickel-catalysed allylation reaction utilising substrates that gave unsymmetrical π -allyls. They demonstrate that the Baylis-Hillman derived allylic chloride **110** could be alkylated AlMe_3 in the presence of $\text{Ni}(\text{acac})_2$ and a Ferrophite-Ligand **113** to afford the requisite product **111** good yield and moderate enantioselectivity (eq. 30).⁸¹ Although this paper represents a significant departure for the nickel-catalysed asymmetric allylic alkylation, specifically in terms of using unsymmetrical acyclic substrates. The authors failed to gain more than moderate control over regioselectivity, achieving a branch to linear selectivity of only 2:1 under the optimal conditions (eq. 30).⁸¹



In the following year the Fu group published a duo of papers describing the nickel-catalysed asymmetric cross-coupling of racemic propargylic and allylic halides with organozinc reagents.^{82,83} The two papers centred around utilising a nickel(II)chloride glyme complex and pybox type ligand **116**, for the asymmetric coupling between the allylic chlorides **114** and alkylzinc reagents, (*S*)-BnCH₂-Pybox **116** was shown to be the optimal ligand(eq. 31).⁸³



They were able to alkylate a series of symmetrical and unsymmetrical allylic chlorides **114**, utilising a range of simple and functionalised alkylzinc reagents.⁸³ The requisite products **115** were afforded in good to excellent yields and enantioselectivities (up to 96% *ee*). The regioselectivity was uniformly high (*rs* ≥19:1), favouring alkylation at the least hindered end of the π -allyl intermediate. The only exception to this is when the substrate had very little steric/electronic difference between either termini of the requisite π -allyl (e.g. Me vs *n*Bu, *rs* = 2:1).

Interestingly, when substrates were sterically well differentiated at either termini of the allyl, it was possible to employ the allylic chloride as mixture of regioisomers and still achieve excellent regioselectivity ($rs = \geq 19:1$). To highlight the synthetic utility of this methodology, the authors applied the reaction to two key steps of a formal total synthesis of fluvirucinine A₁ (**Figure 9**).⁸³

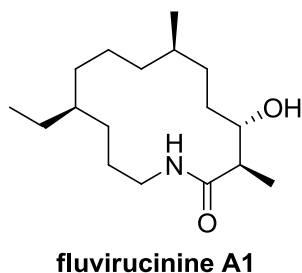
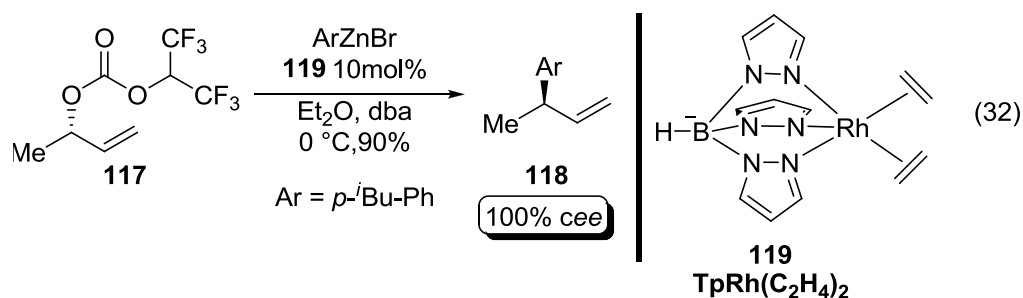


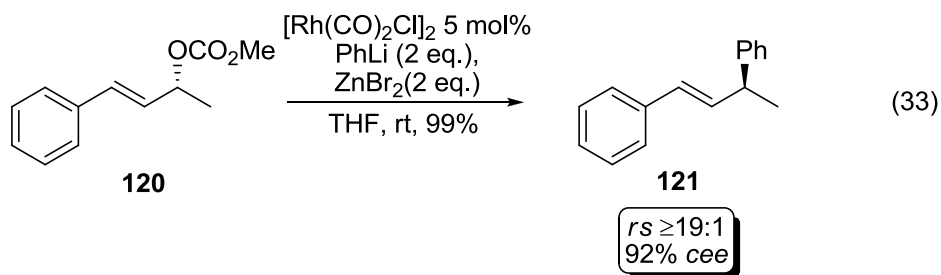
Figure 9: Naturally Occurring Macrolactam antibiotic Fluvirucinine A.

1.3.4. Rhodium-Catalysed Allylic Alkylation of Unstabilised Carbon Nucleophiles

The rhodium-catalysed allylic substitution has been demonstrated to be extremely general with both stabilised carbon and heteroatom nucleophiles.^{58b} However, the deployment of unstabilised carbon nucleophiles lagged far behind due to the difficulties associated with the basic nature of these species, which can promote the elimination of the metal–allyl intermediates or hydrolysis of the leaving group in the allyl alcohol. It wasn't until 2003 that the first rhodium-catalysed allylic substitution utilising an unstabilised nucleophile was published by Evans and Uraguchi, wherein they disclosed the highly regio- and stereospecific rhodium-catalysed allylic arylation of unsymmetrical branched allylic carbonates **117** (Eq. 32).⁸⁴

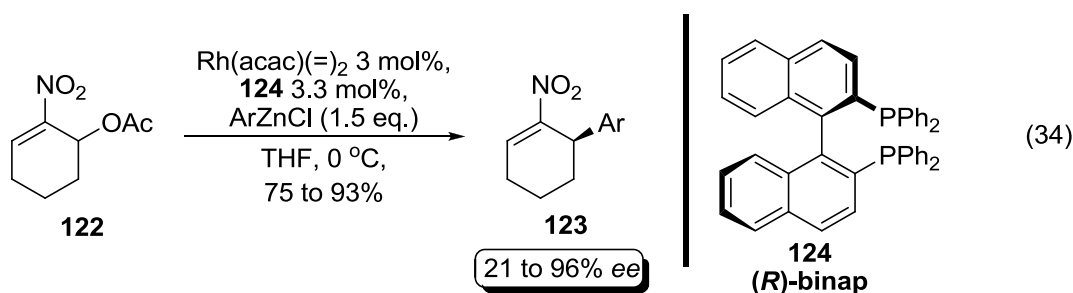


Preliminary studies demonstrated that the trimethyl phosphite-modified Wilkinson's catalyst that had proven so general for the allylic alkylation using stabilised carbon and heteroatom nucleophiles was not an effective catalyst with organozinc reagents.⁸⁴ Interestingly, although the application of a hydrotris(pyrazolyl)-borate rhodium complex ($\text{TpRh}(\text{C}_2\text{H}_4)_2$) **119** had not been examined in the context of an allylic substitution reaction, this catalyst proved optimum for organozinc reagents.⁸⁴ The stereospecific reaction afforded the arylated product **118** with net inversion of absolute stereochemistry in 100% conservation of enantiomeric excess (*cee*), which unequivocally demonstrated that the nucleophile was in fact unstabilised.⁸⁴



In 2007, Martin and co-workers demonstrated that similar results could be achieved utilising $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ as catalyst and an enantioenriched allylic methyl carbonate (eq. 33).⁸⁵ When enantioenriched methyl carbonate **120** (100% *ee*) was treated with a premixed solution of PhLi and ZnBr₂ in the presence of $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (5 mol %), the arylated product **121** was obtained in 99% yield with complete inversion of stereochemistry (eq. 33).⁸⁵

In 2006, Gong *et al.* disclosed the rhodium-catalysed asymmetric allylic arylation of cyclic nitroallyl acetates **122** utilising arylzinc chlorides as a nucleophile (eq. 34).⁸⁶ In the presence of a catalytic amount of Rh(acac)(C₂H₄)₂ and (*R*)-BINAP **124**, the asymmetric allylic substitution of cyclic nitroallyl acetates **122** with a series of arylzinc chlorides proceeded readily, to afford the requisite 2-nitrocyclohex-2-enyl aryls **123** in good to excellent yields and enantioselectivities (up to 96% *ee*).⁸⁶



To highlight the synthetic utility of the reaction the authors carried out the first total synthesis of optically pure (+)- β -lycorane (**Figure 10**). The overall stereochemical array for the natural product was set in the first step *via* the rhodium-catalysed asymmetric allylic arylation.⁸⁶

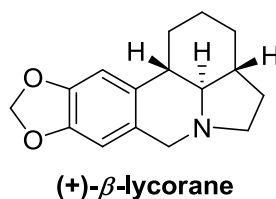
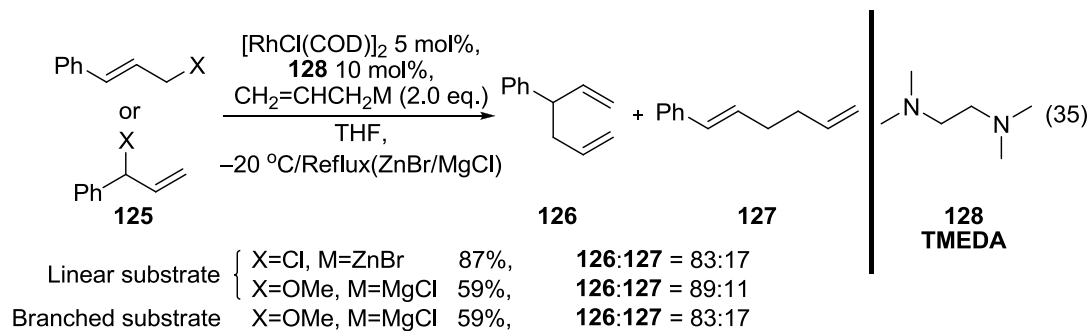


Figure 10: Naturally Occurring Amaryllidaceae alkaloid (+)- β -lycorane.

Although there has been a relatively limited amount of development in terms of unstabilised carbon nucleophiles with *sp*² hybridised carbons, there is an even greater dearth of rhodium-catalysed allylic substitutions involving unstabilised *sp*³ based carbon nucleophiles. The only citation in the literature for one such coupling, thus far, was published in 2006 by Oshima and co-workers.⁸⁷ They disclosed a rhodium-

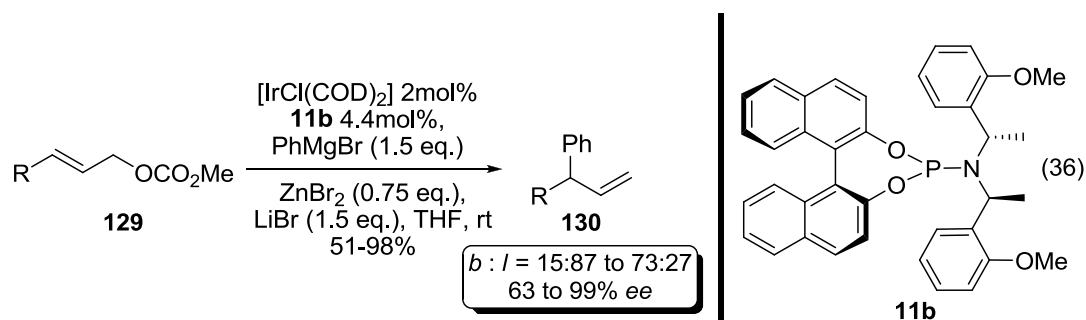
catalysed allylic allylation reaction with allylchloride derivatives **125** and allylzinc/allyl Grignard reagents. The expected diene **126** was obtained with good yield and regioselectivity. The best yield and selectivity were observed with $[\text{Rh}(\text{COD})\text{Cl}]_2$ and the bidentate nitrogen ligand **128** (eq. 35).⁸⁷



Interestingly, the reaction proceeded to give the branched allylated product **126** regioselectively, regardless of which isomer of the substrate was subjected to the reaction conditions (eq. 35).⁸⁷ This is contrary to previous studies by Evans group, in which they had demonstrated that the reaction was regiospecific for both stabilised and unstabilised carbon nucleophiles.^{58b,84}

1.3.5. Iridium-Catalysed Allylic Alkylation of Unstabilised Carbon Nucleophiles.

Iridium has been demonstrated as a particularly successful transition metal for the deployment of stabilised carbon and heteroatom nucleophiles, showing both high levels of regio- and enantioselectivity.⁵⁷ However, for the deployment of organometallic reagents there are only two entries into the literature, both by the same author.⁸⁸

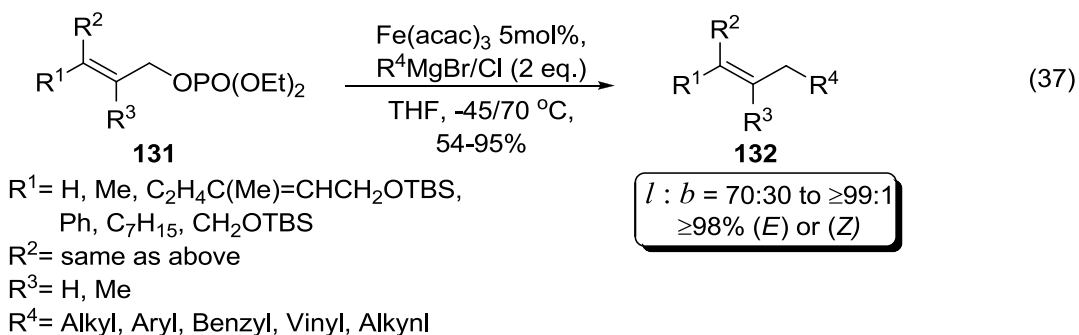


In 2007, the Alexakis group published the first enantioselective iridium-catalysed allylic substitution utilising an unstabilised carbon nucleophile (eq. 36).^{88a} Directly influenced by the success of the regio- and stereospecific rhodium-catalysed allylic arylation, published by the Evans group, they attempted to develop an enantioselective iridium-catalysed analogue (eq. 36). They demonstrated that good enantioselectivities could be achieved when arylzinc halides were utilised as the nucleophiles. However, the regioselectivity of the reaction was extremely poor, and for the highest enantioselectivities there was no perceivable regiocontrol at all ($b:l \approx 1:1$).⁸⁸

1.3.6. Iron-Catalysed Allylic Alkylation of Unstabilised Carbon Nucleophiles.

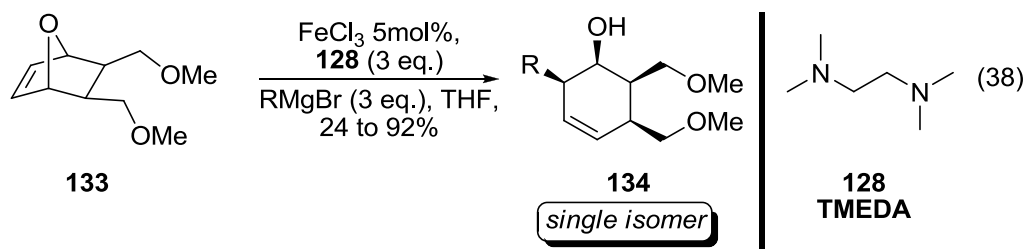
Iron catalysed-allylic substitution represents an attractive alternative to the platinum group-catalysed alternative, due to the large natural abundance and cheap extraction cost of iron. Despite being in its infancy iron catalysis has been demonstrated to be successful for a number of stabilised carbon and heteroatom based nucleophiles.⁶³

The first iron-catalysed allylic alkylation utilising an unstabilised carbon nucleophile was described by Yamamoto and co-workers in 1991,^{89a} who demonstrated that allylic phosphates **131** could undergo alkylation by series of Grignard reagents in the presence of a catalytic amount of Tris(acetylacetonato)iron(III) ($\text{Fe}(\text{acac})_3$) complex (eq. 37).⁸⁹



The reaction afforded the requisite coupled products **132** in fair to excellent yields and regioselectivities. Interestingly, the reaction was tolerant to silyl protected oxygen groups and alkene functionality in the allylic phosphate. A range of different Grignard reagents were deployed as nucleophiles, including alkyl, benzyl, aryl, alkynyl, and vinyl-substituted derivatives. For the latter the stereochemistry of the alkenes in both the substrate and the nucleophile was maintained during the reaction.⁸⁹

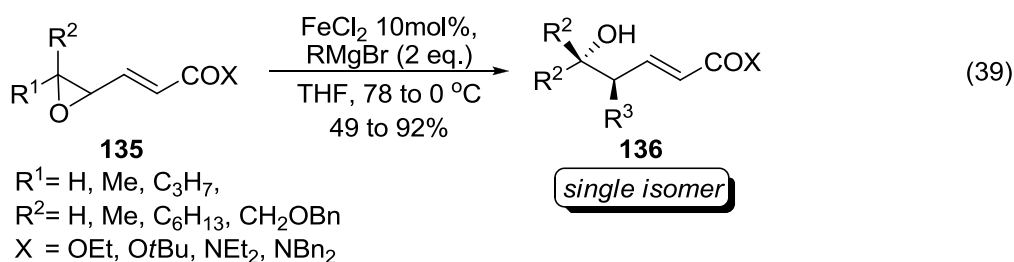
In 2000 Nakamura *et al.* described an iron-catalysed arylation ring opening of oxanorbornenes **133** as part of a communication on iron-catalysed olefin carbometalation.⁹⁰ Three years later the same group fully developed the methodology to include alkenyl- and aryl- based Grignard reagents as nucleophiles (eq. 38).⁹¹



They demonstrated that in the presence of a catalytic amount of Fe(III)Cl_3 and super stoichiometric amount of TMEDA **128**, could catalyse the nucleophilic ring opening of oxanorbornene **133** to afford the requisite arylated and alkenylated products **134**

as a single regio- and diastereoisomer in poor to excellent yields (eq. 38).⁹¹ Interestingly, the catalyst attacks the double bond from the *exo* face of the oxanorbornene, which suggests a precoordination between the iron complex and the oxygen bridge prior to oxidative addition. The coordination of the resultant oxygen anion during the reaction could also account for the high levels of regio- and diastereocontrol, as the catalyst is tethered and therefore the resultant arylation/alkenylation is directed to the adjacent carbon and on the same face as the oxygen anion.

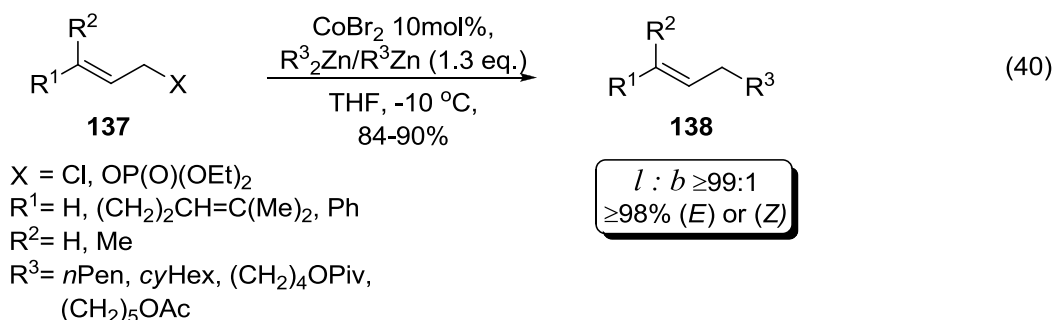
Following a similar oxygen directing stratagem, in 2010 Urabe and co-workers, developed an iron-catalysed substitution of γ,δ -epoxy- α,β -unsaturated esters/amides **135** with Grignard Reagents (eq. 39).⁹² Using a Fe(II)Cl₂ catalyst, they were able to employ aryl, alkenyl, alkynyl and methyl Grignard reagents in the nucleophilic ring opening of allylic epoxides **135**.⁹² The requisite homoallylic alcohols **136** were afforded in fair to excellent yield, and as single regio- and diastereoisomers, with the exception of the alkynyl Grignard, which gave a 3:1 mixture of diastereoisomers (eq. 39).



1.3.7. Cobalt-Catalysed Allylic Alkylation of Unstabilised Carbon Nucleophiles.

Like iron, cobalt catalysts offer a tantalising alternative to noble/platinum group metals, due to the low cost of cobalt complexes. Cobalt-catalysed allylic substitutions have not been extensively studied when compared to analogous reactions using other transition-metals of the same group (rhodium and iridium). However, the growing number of studies proves that the popularity of the metal is increasing.⁶¹

In 1996 Knochel and Reddy disclosed the first cobalt-catalysed allylic alkylation utilising an unstabilised organometallic reagent as a nucleophile.⁹³ In the presence of a catalytic amount of CoBr_2 , they were able to catalyse the alkylation of allylic chlorides/phosphates **137**, giving the linear coupled products **138** in good to excellent yields, with complete regiocontrol and retention of the stereochemistry of the starting secondary olefin (eq 40).⁹³



Just over a decade later Knochel further expanded the scope of the reaction to include functionalised diaryl and diheteroarylzinc reagents as nucleophiles.⁹⁴ The functionalised arylzinc reagents were prepared *in situ* according to a procedure developed by the same group,⁹⁵ and *N*-methyl-2-pyrrolidone (NMP) was used as a solvent. This solvent system was incompatible with the original catalyst system, so the cobalt source was switched to cobalt(II) acetylacetonate ($\text{Co}(\text{acac})_2$).⁹⁴ A range of

substituted aryls and thiopenes which contain a variety functional groups including esters, ketones, bromides, and nitriles.⁹⁴ The reaction again proceeded in good to excellent yields, complete regioselectivity and with retention of the stereochemistry of the starting secondary alkene (≥ 98 *E* or *Z*).⁹⁴ To highlight the synthetic utility of this methodology, Knochel and Dunet performed the expedient synthesis of Nocarasin C in three steps and in 46.8% overall yield (**Figure 11**).⁹⁴

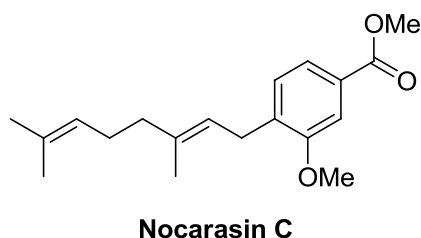
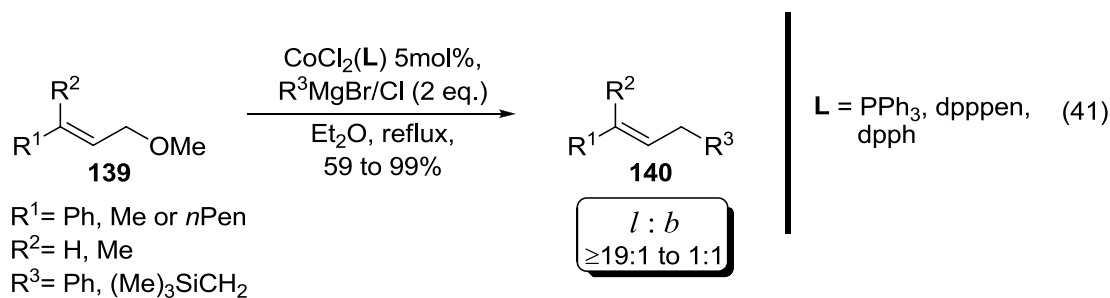


Figure 11: Nocarasin C, a Metabolite from the Actinomycete *Nocardia Brasiliensis*.

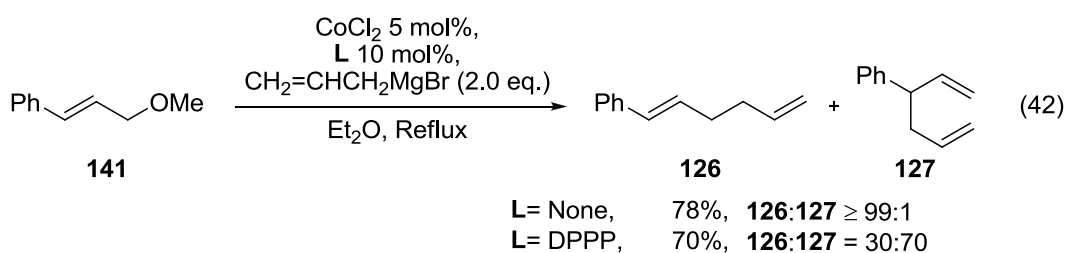
In 2004 Oshima *et al.* expanded the scope of the reaction by utilising Grignard reagents as nucleophiles, including phenyl and trimethylsilylmethyl-substituted Grignard reagents (eq. 41).⁹⁶ They were able to alkylate a series of allylic ethers, in the presence of cobalt-phosphine complexes, to afford the requisite products in fair to excellent yield and with poor to excellent levels of regiocontrol.⁹⁶



Unlike the previously mentioned methodology, which utilised alkyl- and aryl-substituted organozinc reagents (*vide supra*),⁹⁴ the reaction showed a strong

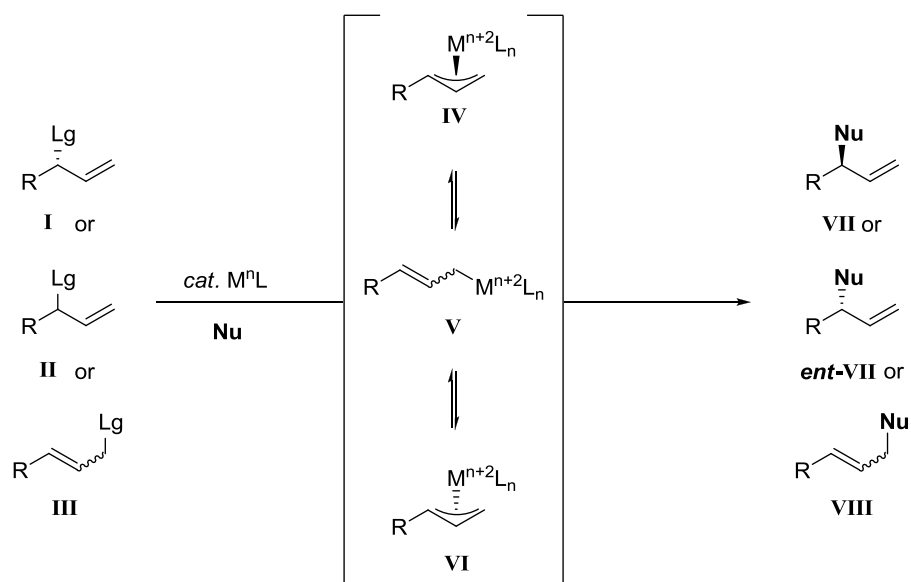
dependence on the allylic substrate, the ligand and the nucleophile.⁹⁶ When aliphatic allylic ethers were deployed there was a severe drop in regioselectivity for both nucleophiles. Phenyl magnesium bromide gave a higher degradation in regiocontrol, affording the lowest selectivity, even when several ligands were assayed it failed to improve the regiocontrol above 3:1 (*l:b*).⁹⁶

Two years later the same group further extended the scope of the cobalt-catalysed allylic alkylation, utilising allyl Grignard as a nucleophile for the allylation of cinnamyl methyl ether (eq. 42).⁸⁷ Cobalt(II) chloride (CoCl₂) in the absence of an exogenous ligand could catalyse the allylic allylation of cinnamyl methyl ether to afford the linear product exclusively.⁸⁷ Interestingly, when the catalyst was modified with a bidentate phosphine ligand the overall regioselectivity was reversed. 1,3-Bis(diphenylphosphino)propane (DPPP) was demonstrated to be the optimal ligand, however, a branched to linear ratio of just above 2:1 was still only achieved (eq. 42).⁸⁷



1.3.8. Mechanistic Features.

Though there have been a range of metals investigated, all varying in terms of electronic/chemical properties a general mechanistic scheme can still be given (Scheme 9).



Scheme 9: A general mechanism for the asymmetric transition metal-catalysed allylic substitution reaction

As previously mentioned, transition metals can oxidatively add into olefins that possess a leaving group at the allylic position (**I**, **II** and **III**), forming electrophilic metal-allyls (**IV** and **VI**). These metal-allyls can interconvert *via* the σ -allyl complex **V**, and this π - σ - π isomerisation is essential for the enantioselective manifold of the reaction. Following a reductive elimination between the catalyst-bonded nucleophile and the allyl to the requisite products (**VII**, **ent-VII** and **VIII**) and the catalyst is returned to its original oxidation state.

The regio- and stereochemical outcome of the reaction are both dependent on the nature of the metal and the conditions utilised. These factors cause the large

variations often observed between different metals (even in the same group) in terms of regio- and enantioselectivity, for example the stark difference between the levels of enantioselectivity between the palladium and nickel catalysed allylic substitution reaction utilising unstabilised carbon nucleophiles (up to 12% *ee* and maximum of 96% *ee* respectively).^{77,67} This difference can be attributed to the much smaller atomic radii of the nickel centre, which affords a more intimate chiral environment. The snug ligand sphere of the nickel allows for a greater degree of stereochemical communication between chiral ligand and the coupling partners. This same trend had previously been observed in an asymmetric nickel-catalysed α -arylation of α -substituted γ -butyrolactones developed by Buchwald and Spielvogel.⁹⁷

The regiochemical outcome of the allylic substitution reaction represents a compromise between various steric and electronic factors for each metal. For the majority of the metals detailed, steric factors tend to predominate, and the achiral linear regioisomer **VIII** is favoured regardless of which isomer of the starting material is employed. This explains the trend in the literature for successful asymmetric allylic substitution to utilise cyclic/acyclic substrates that form symmetrical π -allyls and disubstituted allylic systems (both regioisomers form a stereocenter).^{67,78-80,83,88} Rhodium however, bucks this trend as the reaction is regiospecific in most cases,^{58b,84,85} so depending on which regioisomer of the allylic substrate is utilised, the regiochemical outcome of the reaction can be predicted. This also allows challenging substrates that contain a vinyl group to be utilised, which if the regioselectivity was sterically driven, as it is for the other metals detailed in this section, would result in the formation of the achiral linear product **VIII**. The regiospecificity coupled with the highly stereospecific nature of the rhodium-catalysed reaction,^{58b} allows facile access to the formation of new stereogenic

carbon-carbon bonds, as demonstrated by the Evans group and much later the Martin group.^{84,85}

1.4. Concluding Remarks.

This review has highlighted a number of elegant methods for the asymmetric and racemic construction of carbon-carbon bonds *via* copper-catalysed S_N2' allylic alkylation and the alternative transition metal-catalysed allylic substitution. The methodologies described utilise a series of purely organometallic reagents that represent carbanion equivalents, which are challenging synthons due to their highly reactive and basic natures. This work is generally dominated by the copper-catalysed S_N2' allylic alkylation, which has demonstrated a high level of potency for the enantioselective deployment of a large range organometallic nucleophiles. However, the copper-catalysed reaction suffers from poor substrate scope, in which electronically biased or symmetrical substrates are required in order to ensure favourable regioselectivities. Another restriction is that, for the formation of a stereocenter, the reaction is mechanistically limited to disubstituted allylic substrates. These linear substrates often require a multistep synthesis which involves a selective olefination, as an isomeric mixture of alkenes would result in the erosion of asymmetric induction.¹⁹

In contrast, there has been very little development of the analogous transition metal-catalysed allylic substitution utilising unstabilised carbon nucleophiles, especially in comparison to the analogous methodologies utilising stabilised carbon and heteroatom nucleophiles.^{1b} Of the transition metals that have been assayed in this reaction, nickel has provided the highest levels of enantioinduction with organometallic nucleophiles ranging from Grignard, organozinc and

organoaluminum reagents. Although, the Fu group successfully developed an enantioselective nickel-catalysed allylic substitution utilising unsymmetrical acyclic substrates, the regioselectivity is still an issue. The reaction is sterically driven to provide alkylation at the least encumbered end of the π -allyl, so if there is only a small steric differentiation there is very little regiocontrol (i.e. Me vs *n*Bu, *rs* = 2:1), or if the substrate possesses a primary alkene, the reaction would afford the achiral linear product.⁸³ The issue of regioselectivity plagues all of the metals that have been detailed, except for rhodium which demonstrates a unique regiospecificity when compare to the other metals.^{58b,84,85} Rhodium's regiospecificity is opposite and complimentary to the regioselectivity of the copper-catalysed S_N2' allylic alkylation, and provides a unique opportunity to develop a general solution to the formation of stereogenic carbon-carbon bonds using both stabilised and unstabilised carbon nucleophiles.

The following chapter will describe our efforts to expand the scope of the rhodium-catalysed allylic substitution to include unstabilised *sp*³-hybridised carbon nucleophiles.

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Chapter 2

Rhodium-Catalysed Allylic Substitution with an Unstabilised Carbon Nucleophile: Asymmetric Construction of Acyclic Tertiary and Cyclic Quaternary Carbon Stereogenic Centres.

2.1. Rhodium-Catalysed Allylic Substitution Reactions

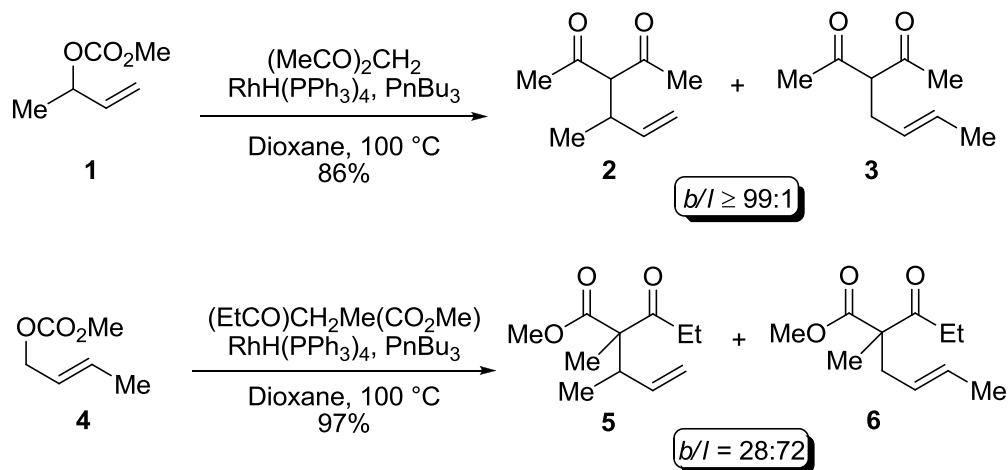
2.1.1. Introduction

Allylic substitution provides a highly powerful means for the asymmetric installation of a large range of carbon-carbon and carbon-heteroatom bonds. The reaction has been extensively investigated utilising a plethora of transition metal complexes. Despite palladium and the other transition metals prevalent utilisation in allylic substitution, the rhodium-catalysed variant has recently emerged as a potent method for target directed synthesis.¹ This is due to the impressive regio- and stereospecificity that can be achieved using rhodium complexes, especially in the alkylation of secondary vinyl substituted allylic alcohol derivatives. The stereospecific manifold is particularly germane, as it yields a complementary method to the enantioselective transition metal-catalysed allylic substitution reaction. While these processes are often sensitive to subtle structural modifications in the nucleophile or electrophile, the rhodium-catalysed allylic substitution affords predictably high levels of regio- and stereocontrol in a vast array of substrates, making it a highly potent method for the asymmetric construction of a wide range of C-C, C-N and C-O bonds.

2.1.2. Seminal Work

The palladium-catalysed allylic substitution reaction had been substantially investigated by the mid-1980's, and the focus of these studies had advanced firmly towards the development of the enantioselective manifold. In contrast, there had only

been one report of a rhodium-catalysed allylic substitution, in which Wilkinson's catalyst was shown to facilitate the allylation of a cyclohexanone-derived enamine.² In 1984 the seminal work of Tsuji was the first demonstration of the regiospecific nature of the rhodium-catalysed allylic alkylation of unsymmetrical acyclic allylic carbonates with stabilised carbon nucleophiles (**Scheme 1**)³

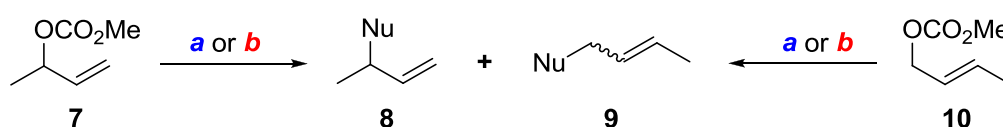


Scheme 1: Regiospecific Rhodium-Catalysed Allylic Alkylation.

Following the development of a rhodium-catalysed decarboxylative allylation reaction,⁴ Tsuji reported the first regiospecific rhodium-catalysed allylic alkylation of stabilised carbon nucleophiles (**Scheme 1**).³ Treatment of the branched allylic carbonate **1** with acetylacetone in the presence of catalytic $\text{RhH}(\text{PPh}_3)_4$ and tri-*n*-butylphosphine furnished the branched alkylation adduct **2** in excellent yield, and with complete regioselectivity. The use of a carbonate leaving group, which liberates methoxide upon oxidative addition of the metal, allows the alkylation to proceed readily under neutral conditions.⁵ However, the most striking feature of this transformation is the unique regioselectivity, as the allylic alkylation of monosubstituted derivatives such as **1** would generally be expected to provide the product of alkylation at the less sterically hindered allylic terminus, namely the linear regioisomer **3**. In the same paper the authors also demonstrated that the linear

carbonate **4** underwent a regioselective alkylation with a β -keto ester, to afford the linear alkylated product **6** as the major product, albeit in reduce regioselectivity (*l:b*=72:28).³

Tsuji attributed the high levels of regioselectivity to the nature of the organometallic intermediate.³ This is in contrast to the analogous palladium-catalysed reaction, which proceeds through a classical π -allyl intermediate. Tsuji proposed that the rhodium-catalysed reaction proceeds via an σ -allyl organorhodium complex.³ The difference between the two catalytic systems was further highlighted when the same group performed a direct comparison between the two metals (**Scheme 2**).⁶



a. RhH(PPh₃)₄, PⁿBu₃, NuH, Dioxane, 100 °C; **b.** Pd₂(dba)₃·CHCl₃, PPh₃, NuH, THF, RT
(NuH = EtCOCH₂CO₂Me)

From **7**: **a.** **8:9 = 6:1, 81%**; **b.** **8:9 = 1:3, 89%**
From **10**: **a.** **8:9 = 1:3, 97%**; **b.** **8:9 = 1:3, 93%**

Scheme 2: Rhodium vs Palladium comparison.

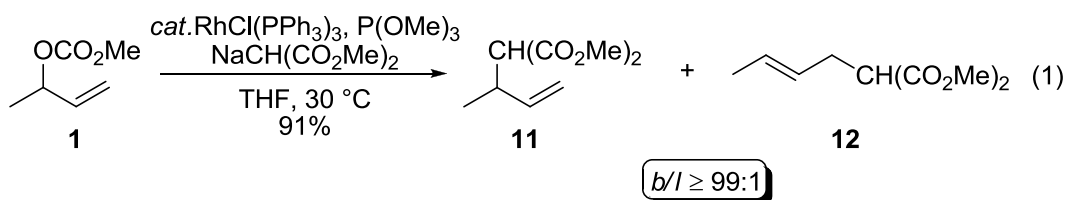
In this subsequent study, the rhodium-catalysed allylic alkylation employing the branched carbonate **7** affords the branched isomer **8** as the major product in a regioisomeric mixture. When the linear carbonate **10** was utilised the opposite selectivity was observed with the linear isomer **9** being the major product. Thus, the reaction displays an apparent “memory effect”, in which the substitution is largely affected at the allylic terminus that originally bore the leaving group. However, in the palladium-catalysed system the same regioisomeric mixture of **8:9** is observed regardless of which isomer is subjected to the reaction conditions. This remarkable result further corroborated Tsuji original hypothesis that the rhodium-catalysed

allylic alkylation proceed, *via* a σ -allyl organorhodium complex, and not through a classical π -allyl intermediate which is invoked for the palladium-catalysed reaction. Despite highlighting the differences in reactivity and invoking a fundamentally different organometallic intermediate, no further investigation was carried out to fully elucidate the exact nature of the organorhodium intermediate.

2.1.3. Regio- and Stereospecific Rhodium-Catalysed Allylic Substitution Reactions

2.1.3.1. Seminal Work

The rhodium-catalysed allylic substitution reaction lay dormant until 1998 when it was reinvestigated by Evans and Nelson. They demonstrated that *in situ* triorganophosphite modified Wilkinson's catalyst ($\text{RhCl}(\text{PPh}_3)_3$) could facilitate the allylic alkylation of secondary and tertiary allylic carbonates with sodium dimethyl malonate salt in a highly regioselective manner (eq. 1).⁷



Shortly after, the regioselective alkylation of the corresponding allylic acetates was shown to proceed under almost identical conditions.⁸ The use of strong π -acceptor phosphite ligands, which presumably increases the electrophilicity of the allyl intermediate, was shown to be essential in both cases. For allylic carbonates in particular, these ligands allowed the reaction to proceed at significantly lower temperatures than those employed by Tsuji.³ The strong π -accepting character of the phosphite ligands also impacted the regioselectivity of the alkylation. For example, while the use of unmodified Wilkinson's catalyst afforded a 2:1 mixture of the

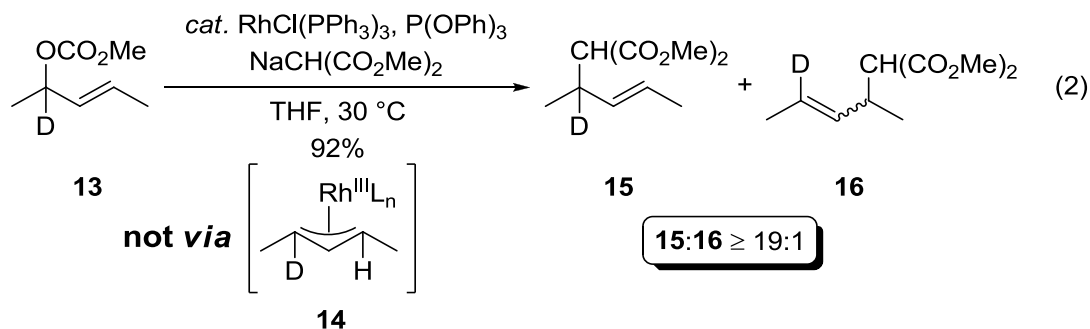
branched and linear adducts **11** and **12**, the addition of trimethyl phosphite provided solely the branched regioisomer **11**, and in excellent yield (eq. 1). Importantly, the allylic alkylation of tertiary carbonates was equally regioselective, and afforded products containing all carbon quaternary stereogenic centres.⁷

2.1.3.2. Mechanistic Studies

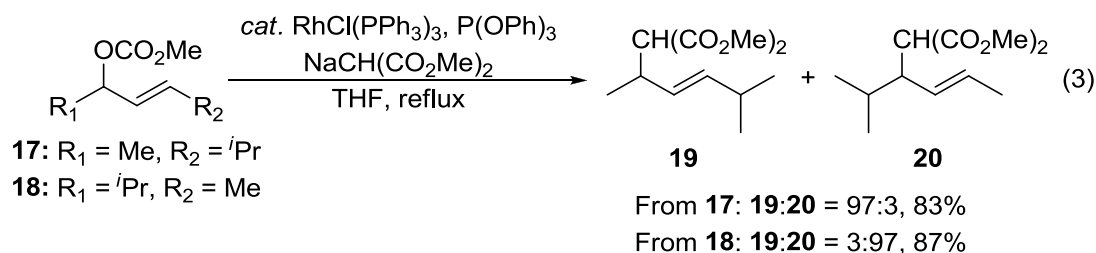
The excellent levels of regioselectivity obtained with phosphite ligands are due to their π -accepting character.⁹ Metal-allyl intermediates derived from rhodium-phosphite complexes should be more cationic in nature than those derived from rhodium-phosphine complexes. Hence, as the stability of a carbocationic species increases with increasing substitution ($3^\circ > 2^\circ > 1^\circ$), the bulk of the positive charge character should reside at the more substituted secondary allylic terminus, thus making this site significantly more electrophilic. However, the observed regioselectivity cannot be rationalised solely in electronic terms, as the analogous linear carbonate **10** was shown to afford the branched product **11**, albeit with substantially lower selectivity (**11:12** = 2:1).¹⁰ This correlates well with Tsuji's original observations,⁶ and is indicative of two different π -allyl intermediates being formed from the oxidative addition of the rhodium(I) catalyst to the isomeric branched and linear allylic carbonates.

In order to scrutinise the origins of this unique selectivity, the deuterated carbonate **13** was subjected to the rhodium-catalysed allylic alkylation (eq. 2).¹⁰ This experiment was designed to test whether a symmetrical π -allyl intermediate was formed, as the π -allyl complex **14**, which could result from **13**, contains two sterically and electronically equivalent allylic termini. Therefore, if the reaction were to proceed *via* symmetrical π -allyl **14**, it would be expected to afford a statistical 1:1

mixture of the alkylation products **15** and **16**, as the malonate anion would be unable to distinguish between the two electrophilic sites.

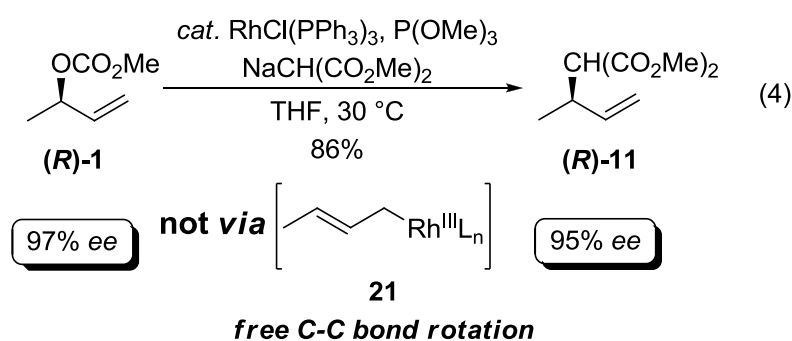


Remarkably, the rhodium-catalysed allylic substitution of the deuterated carbonate **13** afforded the requisite adduct **15** with complete retention of regiochemistry (eq. 2). This result evidently demonstrates that the regiospecific rhodium-catalysed allylic alkylation does not proceed *via* the symmetrical π -allyl intermediate **14**, as the regiocontrol is not strongly influenced by steric factors. This is in contrast to the palladium and iridium-catalysed variants that in the above reaction (eq. 2), both afford a 2:1 mixture of **15** and **16**.¹⁰ Thus, while both of these metals appear to hold little “memory” of the regiochemistry, the rhodium-catalysed system has the ability to direct the alkylation exclusively to the allylic terminus that originally bore the leaving group, despite the highly symmetrical nature of the substrate.



This “memory effect” was also demonstrated for the alkylation of unsymmetrical allylic carbonates **17** and **18** (eq. 3), indicating that the alkylation is tolerant of a sterically congested environment. Overall, these observations suggest that the reaction proceeds *via* an σ -allylrhodium intermediate, the nucleophilic displacement of which is significantly faster than σ - π - σ isomerisation.

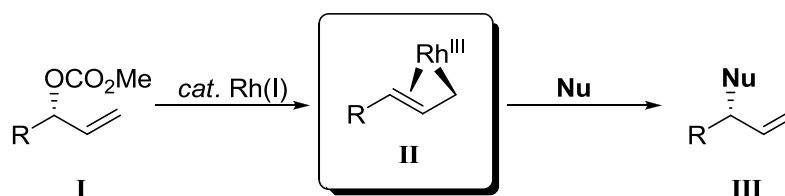
For the branched allylic alcohol derivative **1**, the above evidence correlates well with a S_N2' alkylation of the primary σ -allyl intermediate **21** (eq. 4). Direct insertion of the metal into the C-O bond of the leaving group, followed by S_N2 alkylation of the resultant secondary σ -organorhodium species, would also give the same net result.⁸ However, based on the observation that increased alkene substitution significantly reduces the rate of the allylic alkylation, the primary σ -allyl **21** is a more probable intermediate. In order to fully elucidate this mechanistic pathway, the rhodium-catalysed allylic substitution of the optically active allylic alcohol derivative (**R**)-**1** was examined (eq. 4).



Based on previous experimental studies, oxidative addition of the rhodium(I) complex to (**R**)-**1** was expected to provide the *achiral* primary σ -allyl intermediate **21**, in which both π -faces of the alkene are equally accessible to the nucleophile. Therefore, if the reaction proceed *via* this *achiral* σ -allyl intermediate **12**, S_N2'

addition of the malonate nucleophile should occur in the absence of any stereocontrol, yielding the alkylated product **11** racemically.

However, when the enantiomerically enriched allylic carbonate (**R**)-**1** (97% *ee*) was alkylated with the sodium salt of dimethyl malonate in the presence of catalytic amount of RhCl(PPh₃)₃, modified with trimethyl phosphite, it furnished the branched product (**R**)-**11** in excellent yield, and with near total retention of enantiomeric excess and absolute configuration (95% *ee*) (eq. 4).¹⁰ In providing a valuable and novel means for stereocontrolled formation of acyclic stereocenters, this reaction also demises the possible the reaction proceeding *via* the *achiral* σ -allyl intermediate **21**. As the regio- and stereochemical outcomes of the reaction are not consistent with the formation of either a π - or σ -allylrhodium intermediate. Following the rigorous mechanistic investigation, the stereo- and regiochemical results of the rhodium-catalysed allylic substitution was rationalised to proceed *via* a configurationally stable distorted rhodium(III)-allyl, or *enyl*, intermediate (**Scheme 3**).



Scheme 3: Proposed *enyl* intermediate in the rhodium-catalysed allylic substitution reaction.

Both the regio- and stereochemical outcome of the rhodium-catalysed allylic substitution was attributed to the formation of the configurationally stable rhodium-($\sigma + \pi$)-*enyl* intermediate **II** (**Scheme 3**). A Metal-*enyl* is defined as metal complex that contains discrete π - and σ -metal-carbon interactions with a single allyl ligand. There is a body of evidence in the literature that supports the existence of rhodium-

enyl complexes (**Figure 1**). Among the first isolated rhodium(III)-allyl complexes, described by Wilkinson in 1966,¹¹ two of which are proposed to be ($\sigma + \pi$)-bound. In addition to these complexes, which were characterised by ¹H NMR and IR spectroscopy, single crystal X-ray analysis of isolated $[\text{Rh}(\eta^3\text{-C}_3\text{H}_5)_2\text{OH}]_2$ demonstrates an unusual asymmetric binding in the allyl component.¹² As depicted, the Rh-C3 bond is significantly longer than the Rh-C1 and Rh-C2 bonds, this is indicative of an *enyl*. The bond length values are in accord with those reported for Rh-C σ - and Rh-C π -interactions, respectively. Similar structural characteristics have also been observed in both $[\text{RhBr}(\eta^3\text{-C}_3\text{H}_5)_2]_2$ ¹³ and $[\text{RhCl}(\eta^3\text{-C}_3\text{H}_5)_2]_2$.¹⁴ There are number of *enyl* complexes with other metals, including cobalt and platinum that have also been characterised in the literature. Fundamentally, these *enyl* complexes display notable deviations from the analogous palladium π -allyl complexes, which is congruous with the essentially different modes of reactivity observed between the palladium- and rhodium-catalysed allylic substitutions. It could be envisioned, that the asymmetric environment created by the octahedral coordination of d⁶ Rh(III) complexes are essential to the unsymmetrical ligation of the allyl species, especially in comparison to the requisite d⁸ Pd(II) complexes, which are generally restricted to a square planar geometry.

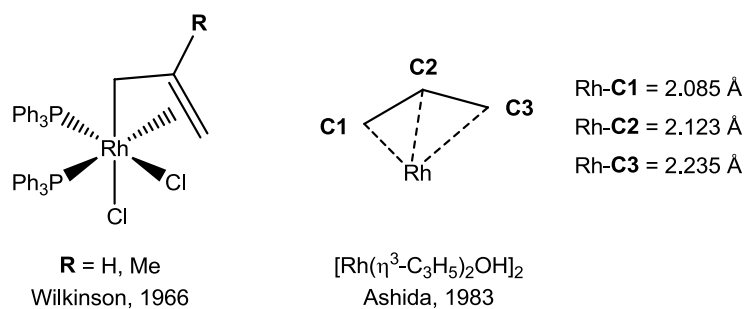
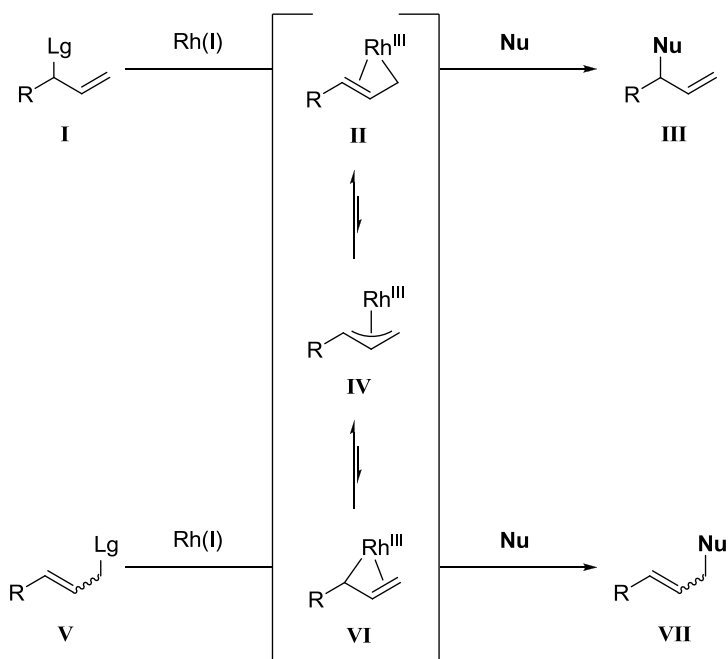


Figure 1: Experimental evidence for the *enyl* binding mode in rhodium-allyl complexes.

Using the mechanistic model detailed in **Scheme 4** it is possible to rationalise the regioselective nature of the rhodium-catalysed allylic substitution. The rhodium-*enyl* complex **II** is proposed to form *via* oxidative addition of a rhodium(I) complex to the branched allylic system **I**. Subsequent S_N2' addition of a nucleophile then affords the branched alkylation product **III**. The isomeric *enyl* complex **VI** may be derived from the linear derivative **V**, or *via* σ - π - σ isomerisation of **II**, which can be envisaged to proceed *via* the symmetrical π -allyl complex **III**. The intermediate **VI** provides the linear product **VI** upon alkylation. Thus, in order to obtain high levels of regioselectivity for the branched product **III**, alkylation of the rhodium-*enyl* **II** must be faster than σ - π - σ isomerisation *via* **IV**. Experimental evidence suggests that the rhodium-*enyl* intermediate is more strongly influenced by the degree of substitution in the σ -component than the steric nature of the substituent R (*cf.* eq. 3). As a result, the isomerisation of **II** (primary σ -component) to **VI** (secondary σ -component) is generally slower than nucleophilic displacement, which explains the high levels of regioselectivity obtained with branched allylic carbonates. Conversely, **VI** will more readily isomerise to **II**, so the allylic alkylation of the linear derivative **IV** is expected to provide a mixture of regioisomers. This hypothesis is strongly supported by the experimental findings of both Evans and Tsuji.^{6,10} However, Martin has demonstrated

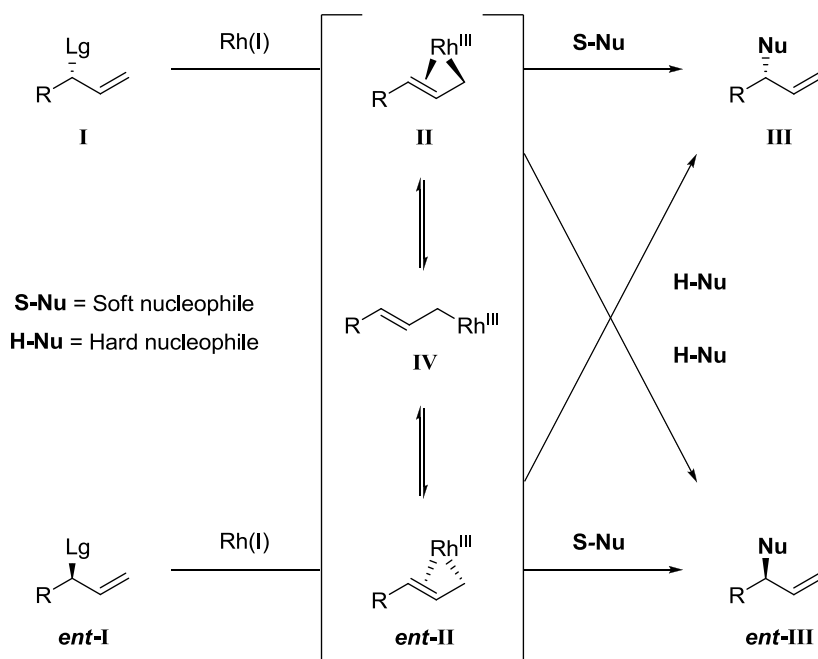
that complete regioselectivity can be obtained for either product in the presence of $[\text{Rh}(\text{CO})_2\text{Cl}]_2$, which is presumably a function of the unusually high π -acidity of the CO ligands.¹⁵



Scheme 4: Mechanistic model for the regioselective rhodium-catalysed allylic substitution reaction.

The extremely high levels of stereospecificity for rhodium-catalysed allylic substitution can be rationalised by the relatively configurationally stable rhodium-*enyl* complex **II** (Scheme 5). Oxidative addition of the metal to the optically active substrate **I** proceeds on opposite face of the leaving group, to afford the enantiomerically enriched *enyl* complex **II** with inversion of absolute configuration. The stereochemical outcome of the reaction is then dependent on whether the attacking nucleophile is stabilised (soft) or unstabilised (hard). A stabilised (soft) nucleophile would attack in an outer sphere manner, on the opposite face of the *enyl* to that of the metal centre to afford **III**, which would result in inversion of the stereocenter. Overall, the reaction proceeds *via* a classical double inversion

mechanism, which provides a net retention of absolute configuration. Although the *enyl* complex **II** is seemingly not prone to rapid π - σ - π isomerisation, nucleophilic displacement of the rhodium-*enyl* **II** must occur at a higher rate than isomerisation to the *achiral* σ -allyl **IV** in order to achieve a high level of stereospecificity. For unstabilised nucleophiles, the reaction proceeds *via* an inner sphere mechanism. The hard nucleophile adds directly to the metal centre, then proceeds through a *syn*-addition/reductive elimination to afford the product *ent*-**III**, which gives net inversion of stereochemistry. This pathway is well demonstrated by the rhodium-catalysed allylic arylation,¹⁶ developed by Evans and Uraguchi, which proceeds with overall inversion of configuration. Due to the configurationally stable nature of the rhodium-*enyl* intermediate, enantioselective rhodium-catalysed allylic substitutions are rare, and usually require electronically biased or symmetrical substrates.^{17,18}

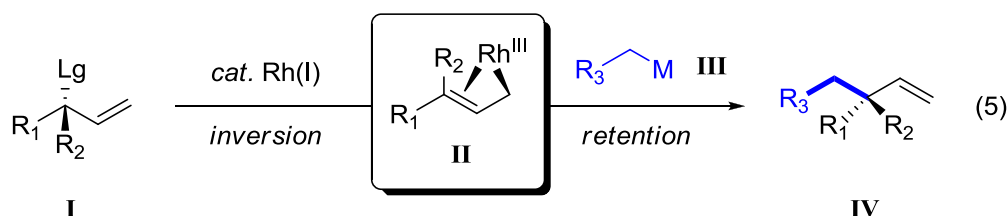


Scheme 5: Mechanistic model for the stereospecific rhodium-catalysed allylic substitution reaction.

2.2. Rhodium-Catalysed Allylic Substitution with unstabilised carbon nucleophiles

2.2.1. Introduction

The highly regio- and stereospecific nature of the rhodium-catalysed allylic substitution has been demonstrated with a large variety of carbon and heteroatom based nucleophiles over the last decade. Within the range of carbon based nucleophiles that have been deployed, there have only been a few examples of a highly unstabilised organometallic reagents being used. Out of these examples it could be argued that the best system was developed by Evans and Uraguchi, in which they used arylzinc bromides as highly unstabilised carbon nucleophiles for the regio- and stereospecific allylic arylation of unsymmetrical allylic alcohol derivatives.¹⁶ Recognising this, we aimed to expand the scope of this process to include sp^3 hybridised carbon nucleophiles. More specifically, we envisaged that the enantiomerically enriched allylic alcohol derivatives **I** could undergo a regio- and stereospecific alkylation with the highly unstabilised carbon nucleophile **III**, to potentially afford enantiomerically enriched ternary and quaternary all carbon stereocenters of the opposite stereochemistry of the starting material (eq 5).



Although the stereospecific allylic substitution reaction is well preceded for the rhodium catalysed allylic arylation,¹⁶ the analogous reaction utilising a sp^3 based nucleophile as **III** is potentially more challenging, and has not yet been demonstrated using a rhodium catalyst. We expected the nature of the organometallic **III** to be an important component, as deploying such highly reactive and basic synthons can potentially result in the elimination of the metal-allyl intermediate or hydrolysis of the leaving group in the allylic alcohol fragment. Despite the rhodium catalysed allylic alkylation being demonstrated to have a number of potential advantages in terms of regio- and stereoselectivity, the utilisation of unstabilised carbon nucleophiles has not been widely studied. Among the few reported examples, only one study utilised a sp^3 based nucleophile. That particular methodology developed by Oshima *et al.*¹⁹ was only performed racemically and gave the requisite products with fairly poor levels of regiocontrol, which illustrates some of the challenges associated with developing this type of transformation.

The following discussion will outline our successful development of a rhodium-catalysed allylic alkylation that utilising a sp^3 hybridised carbon nucleophile, and will be organised into three distinct sections, describing:

- the initial development of a highly regioselective rhodium-catalysed allylic substitution with utilising an unstabilised carbon nucleophile
- studies toward the development of a stereospecific variant
- studies toward the development of a diastereoselective variant
- studies toward the expansion of the methodology to include vinylic nucleophiles

2.2.2. Initial Nucleophile Screening

The hydrotris(pyrazolyl)-borate rhodium ($\text{TpRh}(\text{C}_2\text{H}_4)_2$) complex used in combination with dibenzylideneacetone (DBA) that had previously been demonstrated to be a successful catalyst system with unstabilised carbon nucleophiles (**Figure 2**).¹⁶ Taking these conditions which had already been developed for the rhodium-catalysed allylic arylation, a series of unstabilised alkyl nucleophiles were screened (**Table 1**).

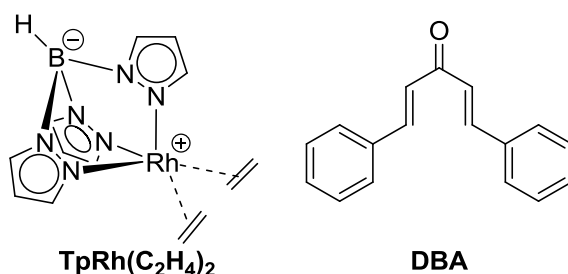
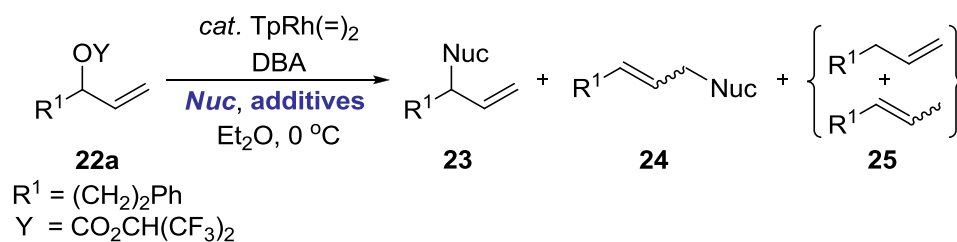


Figure 2: Hydrotris(pyrazolyl)borate rhodium ($\text{TpRh}(\text{C}_2\text{H}_4)_2$) complex and dibenzylideneacetone (DBA).

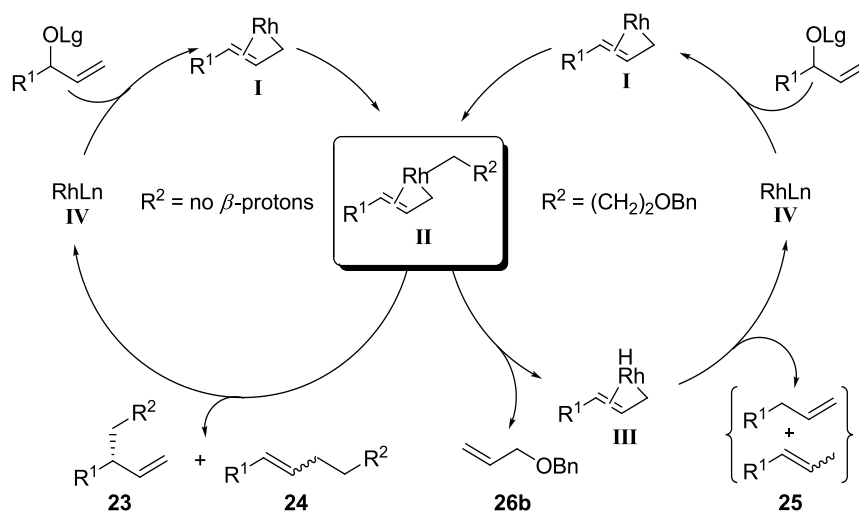
Table 1: Initial Nucleophile screening



Entry ^a	nucleophile	Additive	23 yield(%) ^b	33:34 ^c
1	<i>n</i> BuLi	ZnBr ₂ , LiBr	0(25)	n/a
2	<i>n</i> BuMgBr	“	0(25)	n/a
3	<i>n</i> BuZnBr	LiBr	0(25)	n/a
4	BnO(CH ₂) ₃ I	<i>t</i> -BuLi, ZnBr ₂ , LiBr	0(25+26a+26b)	n/a
5	BnO(CH ₂) ₃ MgBr	ZnBr ₂ , LiBr	0(25+26a+26b)	n/a

^aAll reactions were carried out on a 0.1 mmol scale (0.025 M). ^bGLC yields relative to the internal standard *n*-pentadecane. ^cRegioselectivity was determined using capillary GLC on the crude reaction

Our initial efforts were focused on utilising pre-formed organometallic reagents and transmetalating with ZnBr_2 to form the alkylzinc nucleophile *in situ*, or pre-forming the alkylzinc reagent directly and utilising it in the presence of LiBr as an additive (**Table 1**). When allylic carbonate **22a** was treated with these linear alkyl nucleophiles in presence of $\text{TpRh}(\text{C}_2\text{H}_4)_2$ (**Table 1**, entries 1 and 2) the reaction proceeded to go to completion, however, none of the desired alkylation product was observed. The starting material was fully consumed to afford an isomeric mixture of the reduced carbonate **25**, when pronucleophiles of higher molecular weight were utilised (**Table**, entries 4 and 5), both the protonated **26a** and eliminated **26b** forms of the nucleophile were isolated. This observation led to the conclusion that the nucleophiles were acting as a source of hydride *via* addition to the rhodium centre, followed by β -hydride elimination (**Scheme 6**).

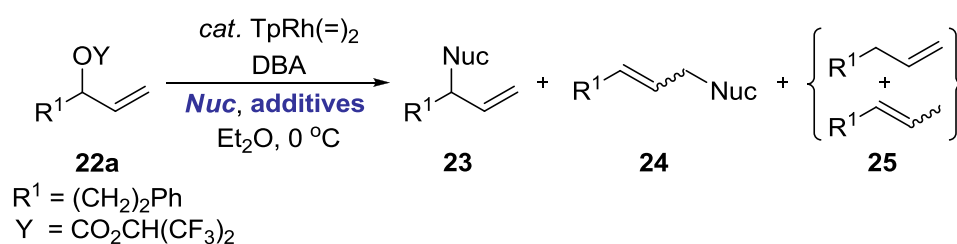


Scheme 6: Competing β -Hydride Elimination and Reductive Elimination Pathways.

It was clear that the substrate did indeed undergo oxidative addition to form the rhodium-allyl complex **I**, the unstabilised alkyl nucleophile then added to the metal centre to form the rhodium-*enyl* complex **II**. At this stage the nucleophile β -hydride

eliminated from the metal centre affording **26b** and the rhodium hydride complex **III**, which in turn afforded the isomeric mixture of the reduced substrate **25** and the active catalyst **IV** via reductive elimination. We hypothesised that removing these β -protons would shut down this pathway and force the reaction to form the product **23/24** via reductive elimination (**Scheme 6**)

Table 2: Further Nucleophile Screening



Entry ^a	Nuc	Additive	33 yield(%) ^b	33:34 ^c
1	(CH ₃) ₃ CCH ₂ Br	t-BuLi, ZnBr ₂ , LiBr	0	n/a
2	(CH ₃) ₃ CCH ₂ MgBr	ZnBr ₂ , LiBr	0	n/a
3	BnBr	t-BuLi, ZnBr ₂	0	n/a
4	BnI	“	16	6:1
5	BnMgBr	None	70	4:1
6	“	ZnBr ₂ , LiBr	0	n/a
7	“	ZnBr₂	53	16:1

^aAll reactions were carried out on a 0.1 mmol scale (0.025 M). ^bGLC yields relative to the internal standard *n*-pentadecane. ^cRatios of regioisomers were determined using capillary GLC on the crude reaction mixture.

This hypothesis was then scrutinized with the deployment of *neo*-pentyl and benzyl nucleophiles, both of which do not have any β -hydrogens to eliminate (**Table 2**). The hypothesis proved to be valid, since no reduced carbonate **25** was observed for either nucleophile. However, there was no product formation observed for the *neo*-pentyl derived nucleophiles (**Table 2**, entries 1 and 2) and the benzyl derivative only afforded the product **23** in poor yield and with little regiocontrol (**Table 2**, entry 4).

Utilising the discrete Grignard reagent gave a significantly improved yield over *in situ* metallation and transmetallation, however, there was a degradation in regiocontrol of the reaction (**Table 2**, entries 4 vs 5). Nonetheless, it was later demonstrated that the *in situ* transmetallation of the discrete Grignard with ZnBr₂ gave a far superior branched to linear selectivity, albeit in a slightly reduced yield (**Table 2**, entry 7). Interestingly, when this transmetalation was attempted in the presence of the lithium bromide the reaction was shut down (**Table 2**, entries 6 vs 7). This is contrary to the previous study utilising arylzinc bromide as nucleophiles, wherein it was found that the inclusion of lithium bromide was beneficial in term of selectivity and reproducibility.¹⁶

2.2.3. Regiospecific Rhodium-Catalysed Benzylation of Unsymmetrical Fluorinated Acyclic Allylic Carbonates.

2.2.3.1. Introduction

The resultant “3-benzyl propenyl” moiety maps onto a large number of biologically important natural and non-natural products (**Figure 3**). With applications ranging from medicinal agents for hyperkalemia,²⁰ Alzheimer’s,²¹ and urinary tract diseases,²² to cosmetics,²³ antibiotics,²⁴ and phytoncides,²⁵ there is a large impetus to develop this methodology.

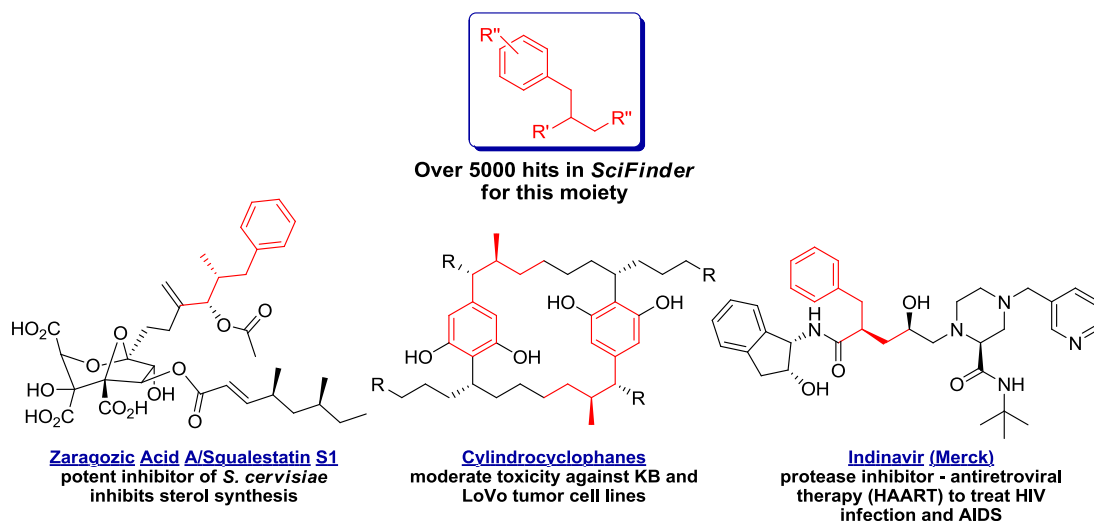


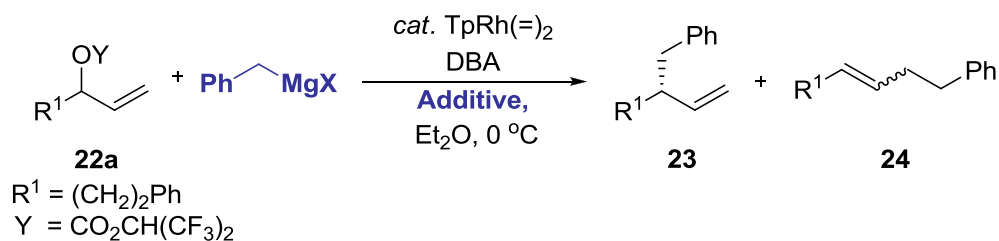
Figure 3: “3-benzyl propenyl” containing bioactive compounds and natural products containing this motif.

2.2.3.2. Reaction Optimisation

Having demonstrated that benzyl derived organometallic reagents were a capable nucleophiles in the rhodium-catalysed allylic alkylation, the nature of the nucleophile was then assayed to improve both the yield and selectivity of the reaction. The initial

optimisation focused on the counter ion effects on both the Grignard and the zinc halide component of the reaction (**Table 3**).

Table 3: Counter Ion Effect for Grignard and Zinc Halide Salt



Entry ^a	X	additive	33 yield(%) ^b	23:24 ^{c, d}
1	Cl	ZnCl ₂	34	5:1
2	“	ZnBr ₂	45	9:1
3	“	ZnI ₂	61	17:1
4	Br	ZnCl ₂	35	10:1
5	“	ZnBr ₂	53	16:1
6	“	ZnI₂	83	≥19:1
7	I	ZnCl ₂	-	-
8	“	ZnBr ₂	42	17:1
9	“	ZnI ₂	31	6:1

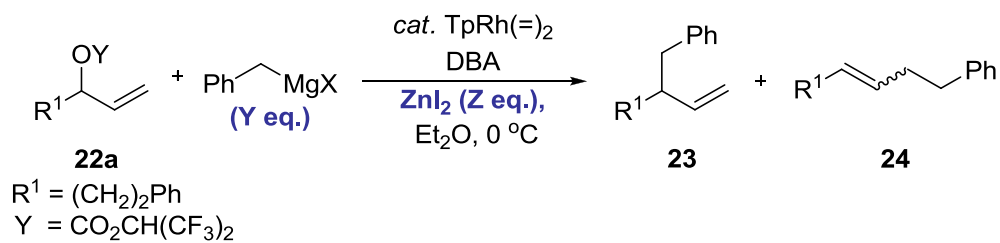
^aAll reactions were carried out on a 0.1 mmol scale (0.025 M). ^bGLC yields relative to the internal standard *n*-pentadecane. ^cRatios of regioisomers were determined using capillary GLC on the crude reaction mixture.

A range of zinc halide salts and easily prepared benzyl Grignard reagents from there requisite benzyl halides were assayed (**Table 3**). When the more reactive benzyl magnesium chloride was deployed with zinc bromide there was a significant drop in both yield and selectivity (**Table 3**, entry 2 vs. 5). However, there was a moderate increase in yield and selectivity when benzyl magnesium chloride was utilised in combination with zinc iodide (**Table 3**, entry 3 vs. 5). Gratifyingly, a more pronounced improvement was observed with benzyl magnesium bromide and zinc

iodide (**Table 3**, entry 6). This same improvement was not observed with the benzyl magnesium iodide in combination with zinc iodide (**Table 3**, entry 9).

The effect of the counter ion on both the Grignard and the zinc salt is due to the nature of the resulting organozinc. It is known that organozincs formed from the metathesis of an organometallic and zinc salts, show accelerated reactivity when compared with organozinc prepared from the direct insertion of metallic zinc into an organohalide.^{26a,b} This increased reactivity is due to the co-complexation between the organometallic reagent and the resultant metallic halide.^{26c} The metallic salt of the co-complex acts as an intimate Lewis acid that activates any approaching electrophile.^{26b} Tuning the Lewis acidity and the steric encumbrance of the co-complexed nucleophile is clearly crucial.

Table 4: Stoichiometry between the Grignard and Zinc Halide salt



Entry ^a	Y	Z	Zn species	33 yield(%)^b	33:34^{c, d}
1	2	2	BnZnI	83	≥19:1
2	4	2	Bn ₂ Zn	87	≥19:1
3	6	2	Bn ₃ ZnMgX ₂ ^d	95	≥19:1
4	3	1	“	95	≥19:1

^aAll reactions were carried out on a 0.1 mmol scale (0.025 M). ^bGLC yields relative to the internal standard *n*-pentadecane. ^cRatios of regioisomers were determined using capillary GLC on the crude reaction mixture. ^dThe identity of X is unknown, but it is thought to be a mixed halide species BrMgI.

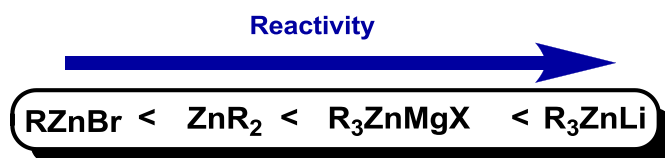
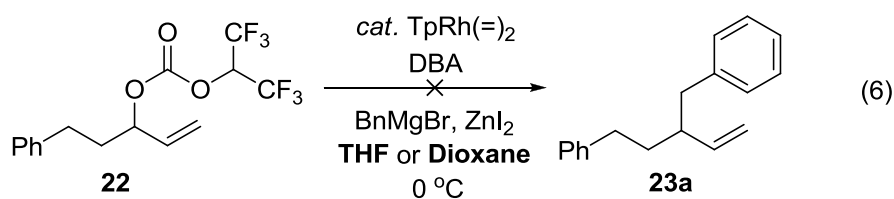


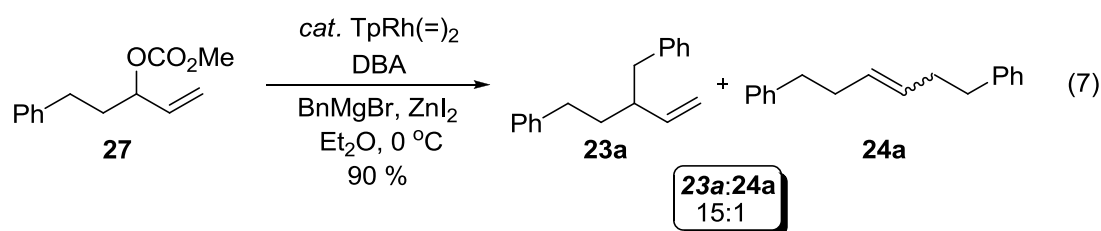
Figure 4: Reactivity order of zinc organometallics with increasing electron negativity.^{26d}

With the optimal combination of Grignard and zinc salt in hand, the stoichiometry, and therefore the nature of the organozinc species formed, was investigated. The reactivity of the inferred organozinc species increases with the excess of negative charge of the zinc centre (**Figure 4**).^{26d} This was mirrored in the yield of the reaction, which increased with the Grignard to zinc salt ratio (**Table 4**, entries 1-3). Finally, the more reactive zincate species also allowed the number of equivalents of the zinc salt to be lowered from two to one (**Table 4**, entry 4 vs. entries 1-3).

Another critical factor affecting the nature of the organometallic species is the aggregation state of nucleophile in solution. For example, the aggregation state organolithium reagents can have a profound effect on reactivity of a nucleophile.^{27,28} In this vain the solvent effects on the reaction were assayed. Utilising diethyl ether (Et₂O) as a solvent was particular critical as other similar polar aprotic ethereal solvents failed to produce any observable product. The reaction was completely shut down when tetrahydrofuran(THF) or dioxane was utilised as a solvent (eq 6). Non-polar solvent were unsuitable as they failed to solubilise the zinc salt which is essential.



Secondary unsymmetrical fluorinated acyclic allylic carbonate **22a** was chosen as the optimal substrate, based on previous studies that demonstrated superior branched to linear selectivity was obtained utilising the fluorinated carbonates.¹⁶ Hence, to test whether comparable results could not be achieved with a more economically leaving group, methyl carbonate **27** was subjected to the optimal reaction condition describe above (eq. 7). The reaction proceeded in excellent yield, however, the regioselectivity was slightly diminished when compared to that of the fluorinated carbonate **22a**. Following this result it was elected to continue utilising the hexafluoro-2-propanol based carbonate as our optimal leaving group for the remainder of the study.

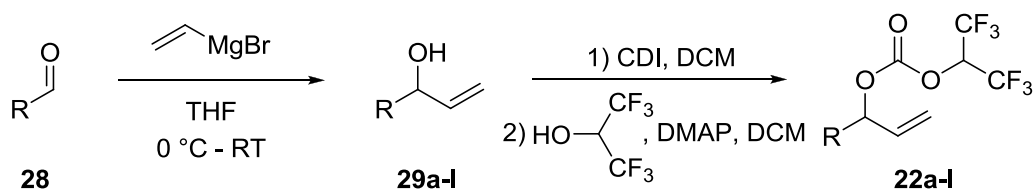


2.2.3.3. Scope

2.2.3.3.1. Substrate Synthesis

In order to examine the substrate scope of this process, with respect to both reaction components, a number of benzyl Grignard reagents and secondary allylic carbonates were prepared. All of the secondary allylic carbonates used in this study were obtained from the corresponding allylic alcohols, as outlined in **Scheme 9**. Addition of vinylmagnesium bromide to the commercially available aldehydes **28** furnished the desired secondary allylic alcohols **29**. Then, following a 2 step procedure developed by Morrow and Whelan,²⁹ the fluorinated carbonates **22** were prepared

from the corresponding allylic alcohols by the 1,1'-carbonyldiimidazole (CDI) coupling with hexafluoro-2-propanol in fair to good yields (**Table 5**).



Scheme 7: Synthesis of the secondary fluorinated allylic carbonates 22a-l.

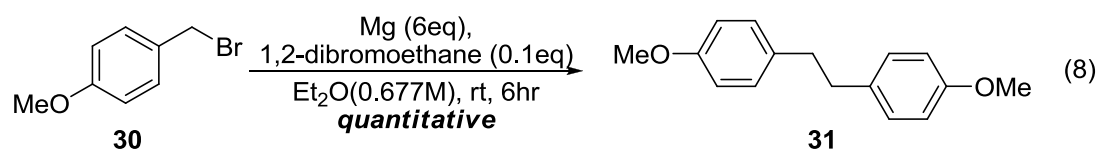
Table 5: Preparation of Secondary Fluorinated Acyclic Allylic Carbonates



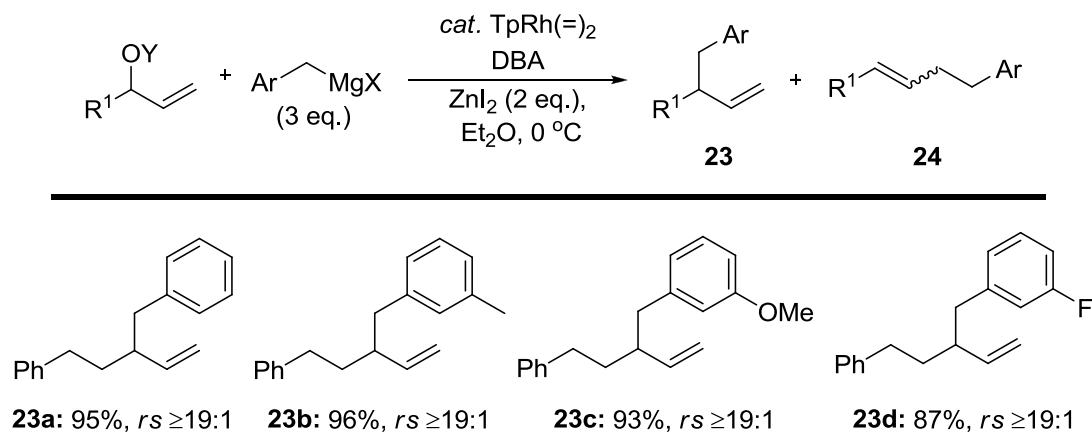
entry	allylic alcohol R =	22	yield (%)
1	Ph(CH ₂) ₂	a	75
2	PhCH ₂	b	72
3	PhCH ₂ OCH ₂	c	80
4	TIPSO(CH ₂) ₂	d	60
5	TBSO(CH ₂) ₅	e	65
6	Me	f	45
7	<i>i</i> Pr	g	51
8	<i>c</i> Hex	h	56
9	<i>i</i> Bu	i	65
10	<i>i</i> Pen	j	68
11	CH ₂ =CH(CH ₂) ₂	k	75
12	<i>n</i> Pen	l	78

2.2.3.3.2. Nucleophile Scope

First the scope of the nucleophilic coupling partner was assayed by deploying a series of *meta*-substituted electron rich and electron poor benzylic Grignard reagents. Substitution was limited to the *meta* position of the aryl component of the benzylic Grignard, due to issues associated with the preparation of electron rich *para*- and *ortho*-substituted benzylic Grignard reagent in diethyl ether (eq 8). Attempting to form either the *para*- or the *ortho*-methoxy substituted in ether, resulted in the quantitative formation of the Wurtz coupled product **31**. This homocoupled product could be avoided by preparing the Grignard reagent in THF rather than ether, however, THF is an unsuitable solvent for the rhodium catalysed allylic benzylation (*vide supra*).



The rhodium-catalysed reaction is tolerant to both mildly electron rich (**Table 5**, **23b**) and electron poor (**Table 5**, **23c-d**) substitution on the benzylic nucleophile. There was only a minor variation in yield between Grignard reagents deployed (87 to 96%), and the regioselectivity was excellent in all case (*rs* ≥ 19:1) (**Table 5**).

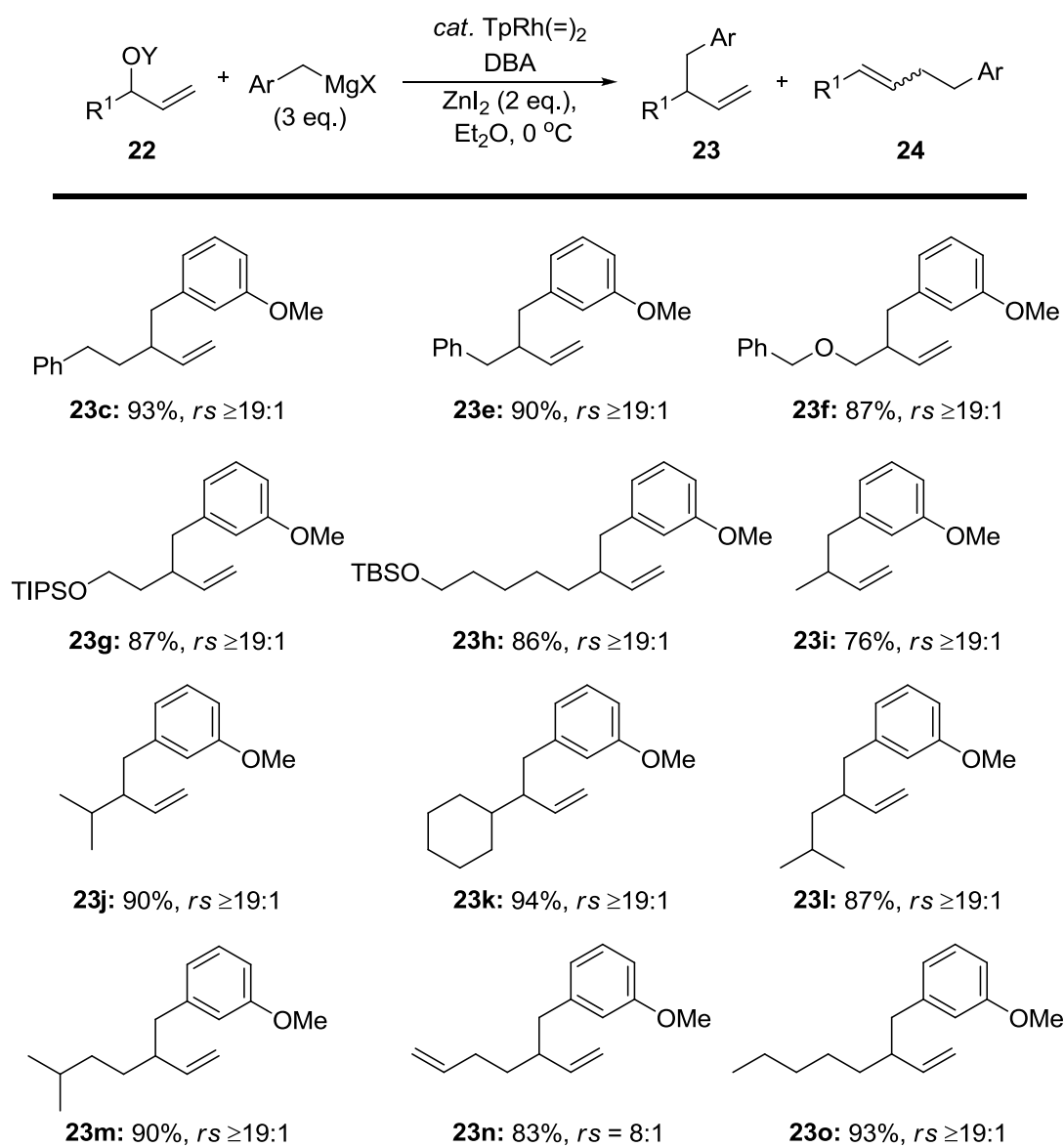
Table 6: Nucleophile scope

2.2.3.3.3. Electrophile Scope

A wide variety of secondary allylic carbonates were successfully employed in the rhodium-catalysed allylic benzylation. As outlined in **Table 6**, a number of linear alkyl-substituted secondary allylic carbonates could be utilised with excellent regioselectivity. The reaction proceeds in excellent yield and regioselectivity for substrates containing substitution at the α , β , and γ positions ($rs \geq 19:1$) (**Table 6**, **23j-m**). A number of functional groups could also be successfully deployed in the reaction, both benzyl and silyl protected oxygens are well tolerated, affording the desired products in excellent yield and regioselectivity (**Table 6**, **23f-h**), these substrates as are particular advantageous as they provide a synthetic handle for post-reaction modification. All substrates deployed proceeded in excellent yield and regioselectivity with the exception of **23n**, which suffer a reduction in regiocontrol affording the benzylated product in only rs of 8:1. This aberration in regioselectivity is probably due to the presence of a free alkene within the substrate. This pendant π -system likely ligates the metal centre and distorts the rhodium-*enyl* intermediate thereby causing this erosion in regioselectivity. This is further exemplified when a

straight chain alkyl carbonate is subjected to the reaction conditions, as the desired product is afforded in excellent yield and regioselectivity (**Table 2, 23n vs 23o**). Interestingly, no such reduction in regiocontrol is observed for phenyl or heteroatom containing systems, which could potentially ligate the metal centre as well. (**Table 6, 23c-h**)

Table 7: Electrophile scope



2.2.3.4. Concluding Remarks

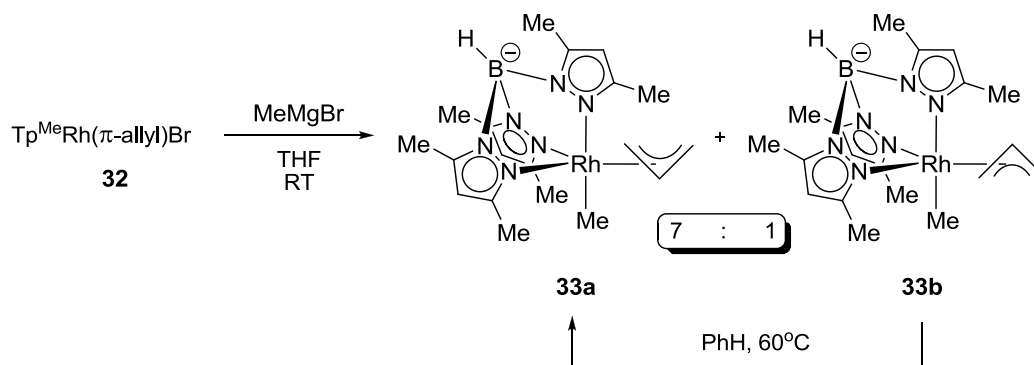
We have developed a highly regioselective rhodium-catalysed allylic substitution of secondary allylic carbonates utilising a highly unstabilised carbon nucleophile. In doing so we have further expanded the scope of the rhodium-catalysed allylic alkylation utilising unstabilised nucleophiles to include a sp^3 -hybridised carbon nucleophile. This direct and operationally simple procedure involves the coupling of two readily available reaction partners and, following our initial optimisation, provides facile access to a range of racemic ternary all carbon stereocenters. However, in order for this method to find widespread applicability in organic synthesis, we considered the development of an asymmetric variant to be essential.

2.2.4. Stereospecific Rhodium-Catalysed Benzylolation of Unsymmetrical Fluorinated Acyclic Allylic Carbonates: Asymmetric Construction of Acyclic Carbon Stereocenters.

2.2.4.1. Introduction

The stereoselective synthesis of carbon-carbon stereogenic bonds represents one of the most important and widely studied areas of investigation in organic chemistry. In the context of allylic substitution utilising stabilised carbon nucleophiles this area has been exhaustively studied for both enantioselective (catalysed by Pd,³⁰ Ir,³¹ Mo,³² W,³³ and Pt³⁴) and stereospecific (catalysed by Rh¹⁰) methodologies. However, the same cannot be said for analogous allylic substitutions involving highly unstabilised carbon nucleophiles. A limited number of methodologies have been developed for the enantioselective manifold (see chapter 1, section 1.3), however, there remains an almost complete dearth for the stereospecific manifold. Of the two stereospecific rhodium-catalysed methodologies that have been developed, both utilised arylzinc organometallic reagents as a nucleophile. The stereospecific deployment of an unstabilised sp^3 hybridised carbon nucleophile has yet to be disclosed. This is not a trivial transformation due to the inner sphere mechanism of the reaction, in addition to the slower rate of reductive elimination from the metal centres between two sp^3 hybridised carbons as opposed to that between sp^2 and sp^3 centres which is well documented.³⁵ This is likely to have an impact on the level stereospecificity of the reaction, especially when compared with the two other stereospecific rhodium-catalysed methodologies that utilised phenylzinc nucleophiles.^{15,16} The sp^2 hybridised carbon of the aryl nucleophiles have significant s character, and are therefore not very directional in nature and can support multi-centred bonding during the transition state. In contrast the benzyl nucleophile uses an sp^3 hybridised carbon, which is more

directional due to the added p character, leading to a higher relative activation energy and a lower rate of reductive elimination. Further evidence for the potential challenges facing a stereospecific allylic substitution utilising an unstabilised sp^3 hybridised carbon nucleophiles come from a publication in 1998 by the Ozawa group.³⁶ In this study, the preparation and subsequent reactions of the allyl rhodium complex **32**, a 3,5-dimethylpyrazolyl analogue of the same $\text{TpRh}(\text{C}_2\text{H}_4)_2$ catalyst utilised in the stereospecific rhodium-catalysed allylic arylation, is described. Upon treatment of **32** with methyl magnesium, two stereoisomers of the methyl allyl rhodium complex **33a/b** were formed (Scheme 10).³⁴ What is remarkable is the stability of this relatively electron rich complex, as the authors were able to reflux the complex in benzene to fully equilibrate both stereoisomers to **33a** with no observed reductive elimination occurring between the methyl and allyl ligands.



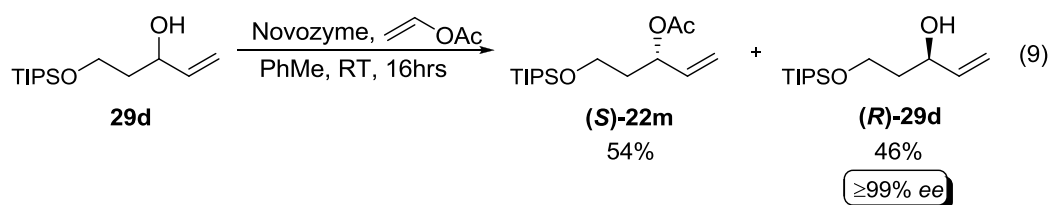
Scheme 8: The inferred stability of complex **33 to reductive elimination.**

The electron rich nature of the hydrotris(3,5-dimethylpyrazolyl)borate (Tp^{me}) ligand combined with the purely sp^3 character of the methyl ligand may account for the stability against reductive elimination in complex **33**. However, this still

demonstrates the potential challenges facing a stereospecific rhodium-catalysed allylic alkylation utilising an unstabilised sp^3 hybridised carbon nucleophile.

2.2.4.2. Substrate Synthesis

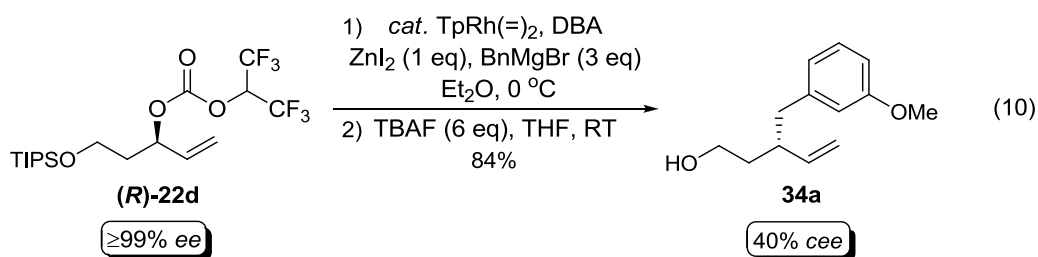
Due to the relatively non-polar nature of the products of the rhodium-catalysed allylic benzylation, a substrate containing a free heteroatom with an easily removed silyl protecting group was selected. This was to aid with the separation of enantiomers *via* chiral HPLC in order to accurately measure the enantiomeric excess of the reaction. There are a multitude of methods for the generation of secondary allylic alcohols, ranging from kinetic resolution to the Sharpless epoxidation to enantioselective alkenylation of aldehydes.^{37,38} A particularly advantageous method is enzymatic resolution, due to its ease of operation, reliability, scalability and near perfect stereocontrol.³⁹ Utilising a procedure disclosed by Han and Singh, racemic allylic alcohol **29d** was resolved to afford the enantiomerically enriched allylic alcohol (**R**)-**29d** in absolute optical purity (eq. 9).⁴⁰



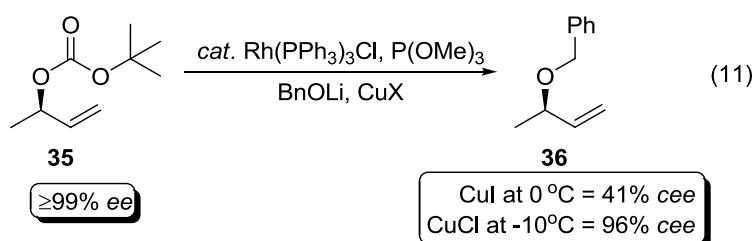
The enantiomerically enriched allylic alcohol (**R**)-**29d** was then subjected to 1,1'-carbonyldiimidazole (CDI) coupling with hexafluoro-2-propanol, to afford the optically pure secondary fluorinated allylic carbonate (**R**)-**22d** in good yield (see section 2.2.3.3.1., **Table 5**).

2.2.4.3. Reaction Optimisation

The ability to obtain excellent regioselectivity prompted the examination of the enantiomerically enriched allylic carbonate **(R)-22d** in the stereospecific manifold of the reaction. Treatment of **(R)-22d** ($\geq 99\%$ *ee*) under the optimised reaction conditions, followed by tetra-*n*-butyl ammonium fluoride (TBAF) deprotection afforded 3-(3-methoxybenzyl)pent-4-en-1-ol **34a** in 93% yield (*b:l* $\geq 19:1$),¹² albeit with poor enantiospecificity (40% *cee*) (eq. 10).



This was a significant departure from previous studies involving stabilised carbon nucleophiles.¹ The poor stereospecificity of the reaction can be partly explained by the challenging nature of deploying an unstabilised *sp*³ hybridised carbon nucleophile, however, another factor that could also account for stereochemical leakage is halide ion effects.⁴¹ A historical example of this is the influence of the copper(I) halide salt on the enantiospecificity of the rhodium-catalyzed allylic etherification developed by Evans and Leahy (eq. 11).⁴²



The optimal copper(I) salt to form the copper alkoxide in the racemic reaction was copper(I) iodide, however, this salt only afforded 41% *cee* for the stereospecific reaction. After a brief re-optimisation of the copper salt and the temperature, the stereospecificity was increased to 96% *cee*.⁴⁰ The result of this previous study within our group prompted the re-examination of the zinc halide salt and the temperature. Treatment of the allylic carbonate (**R**)-**22d** with the trialkyl zincate derived from benzyl Grignard with both zinc bromide and chloride furnished the allylic alkylation adducts **34a** with improved chirality transfer, in which the chloride salt gave the largest overall improvement in *cee* (**Table 7**, entries 2 and 3). Interestingly, the trend for enantiospecificity is the reverse of that for regioselectivity, illustrating that they are independent (*cf.* **Table 3**). Although the origin of the erosion of enantiospecificity with zinc iodide is unclear, it is most likely the result of the equilibration of the rhodium-allyl intermediate.⁴¹ Temperature effects were then investigated, in an attempt to slow the rate of racemisation. Gratifyingly lowering the temperature yielded further improvement in the stereospecificity (**Table 7**, entries 4 and 5). However, unlike the previous study performed with copper(I) alkoxide nucleophiles the stereospecificity is far from complete.⁴²

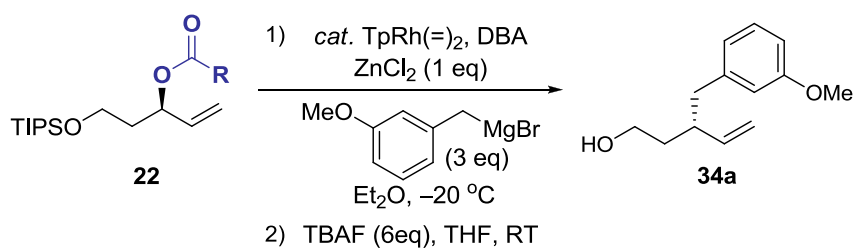
Table 8: Zinc Halide Salt and Temperature Effects on Stereospecificity.

1) *cat.* TpRh(=)₂, DBA
ZnX₂ (1 eq), BnMgBr (3 eq)
Et₂O, T °C
2) TBAF (6eq), THF, RT

Entry ^a	X	T(°C)	<i>b:l</i> ^c	34a yield(%) ^b	<i>cee</i> (%) ^d
1	I	0	≥19:1	84	40
2	Br	“	10:1	87	44
3	Cl	“	9:1	83	50
4	“	-10	“	84	58
5	“	-20	“	84	65

^aAll reactions were carried out on a 0.1 mmol scale (0.025 M). ^bGLC yields relative to the internal standard *n*-pentadecane. ^cRatios of regioisomers were determined using capillary GLC on the crude reaction mixture. ^dThe identity of X is unknown, but it is thought to be a mixed halide species BrMgI.

In order to further improve the stereospecificity of the reaction a range of alternative leaving groups were then assayed (**Table 8**), the hypothesis being that a less labile leaving group would result in a later stage transition state, which would in turn afford a higher degree of stereospecificity, as the time for epimerisation would be minimised. Unfortunately, of the leaving groups investigated only the methyl carbonate was demonstrated to be a viable leaving group, with both the acetate and the benzoate being found to be unreactive (**Table 8**). When compared to the fluorinated leaving group, the methyl carbonate leaving group resulted in a lower yield, and degradation in both the regioselectivity and the stereospecificity of the reaction (**Table 8**, entries 1 vs 2).

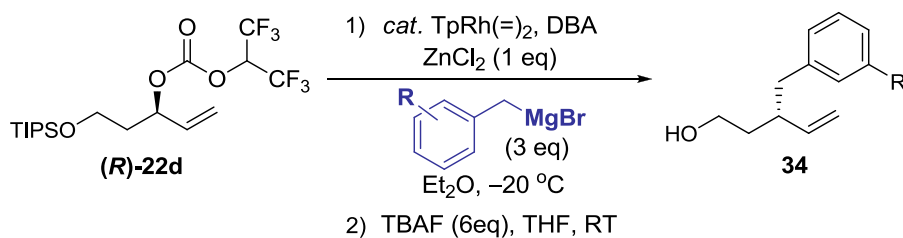
Table 9: Leaving Group Effect on the Stereospecificity

Entry ^a	R	22	<i>b:l</i> ^b	yield(%) ^c	<i>cee</i> (%) ^d
1	OCH(CF ₃) ₂	d	9:1	84	65
2	OMe	n	6:1	67	52
3	Me	m	n/a	NR	n/a
4	Ph	o	n/a	NR	n/a

^aAll reactions were carried out on a 0.1 mmol scale (0.025 M). ^bRegioselectivity was determined by 500 MHz ¹H NMR on the crude reaction mixtures

^cisolated yields. ^d*cee* values were determined by chiral HPLC on the isolated products.

Our focus then shifted towards utilising an alternative nucleophile, as changing the electronics of aryl component should directly affect the rate of reductive elimination between the benzyl and the allyl ligands on the metal centre, and therefore the level of stereospecificity (**Table 9**).

Table 10: The effect of Substituted Benzylic Grignard Reagents on the Stereospecificity.

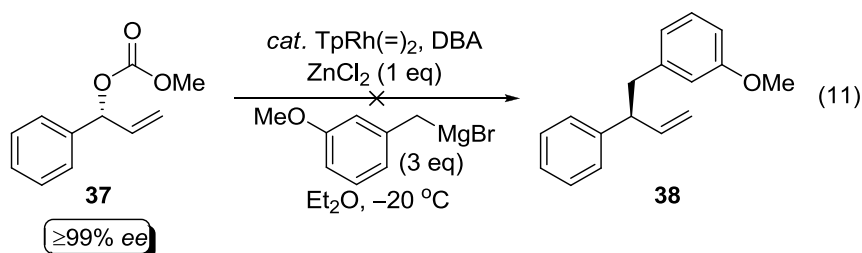
Entry ^{a,b}	R	34	σ_m	yield(%) ^c	<i>cee</i> (%) ^d
1	F-2,3,4,5,6	-	-	NR	NR
2	3-F	b	0.34	93	69
3	3-MeO	a	0.12	84	65
4	Me	c	-0.07	87	44

^aAll reactions were carried out on a 0.1 mmol scale (0.025 M). ^bRegioselectivity was 9:1 in all cases.

^cisolated yields. ^d*cee* values were determined by chiral HPLC on the isolated products.

Initially the electron poor hexafluoro benzyl Grignard was assayed as nucleophile (**Table 9**, entry 1), however, no reactivity was observed for the extremely electron deficient nucleophile. Gratifyingly, the *meta*-fluoro benzyl Grignard yielded an improved yield and stereospecificity, however, the improvement was only minimal (**Table 9**, entry 2). At the opposite end of the scale, the mildly electron rich *meta*-methyl nucleophile, gave a significant degradation in the stereospecificity, thus validating the original hypothesis. Interestingly, in all examples the regioselectivity remained the same, again highlighting the independence between the stereospecificity and the regioselectivity of the reaction (*cf.* **Table 5**). Though not yielding a great improvement in the level of stereospecificity, the above study demonstrates that changing the electronics of rhodium-bound nucleophile could affect the rate of reductive elimination, and therefore the *cee* of the reaction.

In the same vein an, the substrate **32**, which contains an aryl group was assayed. The electron withdrawing ability of an aryl group could potentially promote the reductive elimination. However, due to an inability to prepare the fluorinated carbonate,⁴³ the enantiomerically enriched methyl carbonate **37** was instead subjected to the reaction conditions (eq. 11). Unfortunately the aryl substitution on the substrate was not tolerated in the reaction, as there was no observable formation of the enantioenriched product **38**.



Our focus then shifted to adjusting the electronics of the catalyst itself, by preparing known alternative scorpionate complexes **39** and **40** (**Figure 3**).^{44,45} The fairly electron rich complex **39** should yield lower stereospecificity as the increased electron density on the metal centre should promote stereochemical leakage *via* π - σ - π isomerisation of the rhodium allyl. Interestingly, complex **40** contains a full dative bond from the rhodium back to the borane, in a Z-type ligand interaction.⁴⁶ This donation from rhodium to the borane back bone of the scorpionate ligand should render the metal-centre relatively electron poor and increase the rate of reductive elimination.

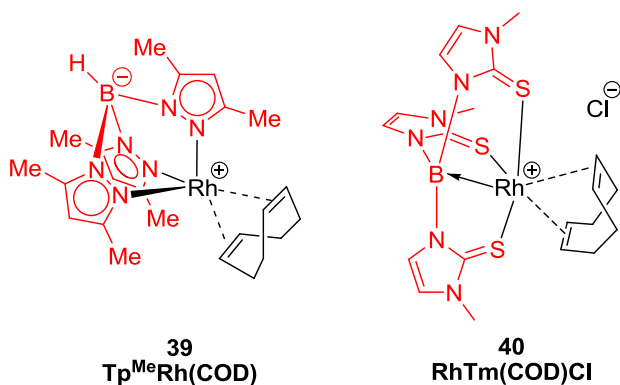


Figure 5: Alternative scorpionate ligand complexes.

Both alternative scorpionate catalysts afforded little variation in the stereospecificity of the reaction (**Table 10**, entries 2 and 3). As expected the electron rich complex **39** gave a slightly reduced stereospecificity, however, the reduction in *cee* was far from significant (**Table 10**, entry 3). The more electron deficient metal of the scorpionate complex **40** afforded slightly improved stereospecificity, but again the level of improvement was almost negligible (**Table 10**, entry 3). As well as the alternative scorpionate complexes **39** and **40**, a range of standard precatalysts and phosphite ligand systems that had classically been demonstrated as successful precatalysts for

previous rhodium-catalysed allylic substitution reactions were also examined (**Table 10**). In accordance with the rhodium-catalysed allylic arylation,¹⁶ both phosphite modified and unmodified Wilkinson's catalyst failed to demonstrate any reactivity (**Table 10**, entries 4 and 5). The phosphite modified chloro(1,5-cyclooctadiene)rhodium(I) dimer also failed to demonstrate any reactivity, and, interestingly, the unmodified dimer gave comparable yield and stereospecificity to the optimal $\text{TpRh}(=)_2$ catalyst (**Table 10**, entries 1 vs 7). A more remarkable result that was the air-stable rhodium(III) trichloride hydrate precatalyst afforded an increased stereospecificity, comparable yield and regioselectivity to the $\text{TpRh}(=)_2$ catalyst system (**Table 10**, entries 1 vs 8).

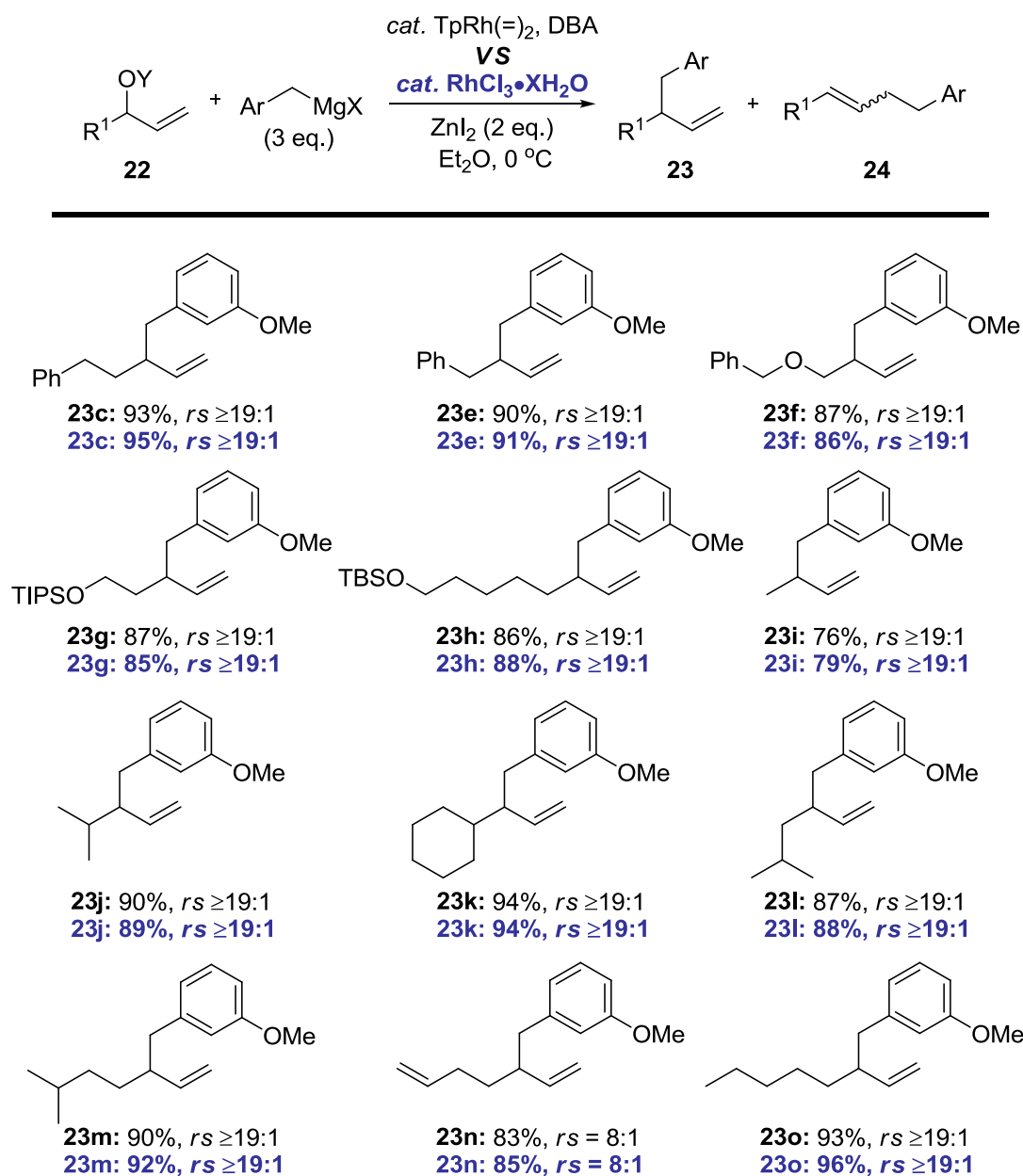
Table 11: Alternative Precatalysts Assayed.

Entry ^{a,c}	"Rh"	yield(%) ^c	cee(%) ^d
1	$\text{TpRh}(=)_2$	84	65
2	$\text{Tp}^{\text{me}}\text{Rh}(\text{COD})$	58	62
3	$\text{TmRh}(\text{COD})$	87	68
4	$\text{RhCl}(\text{PPh}_3)_3/\text{P}(\text{OPh})_3$	NR	NR
5	$\text{RhCl}(\text{PPh}_3)_3$	NR	NR
6	$[\text{Rh}(\text{COD})\text{Cl}]_2/\text{P}(\text{OPh})_3$	NR	NR
7	$[\text{Rh}(\text{COD})\text{Cl}]_2$	84	65
8	$\text{RhCl}_3 \cdot \text{XH}_2\text{O}$	87	71

^aAll reactions were carried out on a 0.1 mmol scale (0.025 M). ^b Regioselectivity was 9:1 in all cases. ^c isolated yields. ^d cee values were determined by chiral HPLC on the isolated products.

This result prompted us to re-investigate electrophile scope of the racemic reaction, as the air stable $\text{RhCl}_3 \cdot \text{XH}_2\text{O}$ precatalysts allow us to develop an operationally uncomplicated alternative to the racemic rhodium-catalysed allylic benzylation (see section 2.2.3.3.3.) (**Table 11**). One of the main advantages is of $\text{RhCl}_3 \cdot \text{XH}_2\text{O}$ is that it is the simplest and most widely available rhodium pre-catalyst, which requires no synthesis and can be stored easily without fear of decomposition.

Table 12: Re-Examination of the Electrophile scope with Alternative Precatalyst.



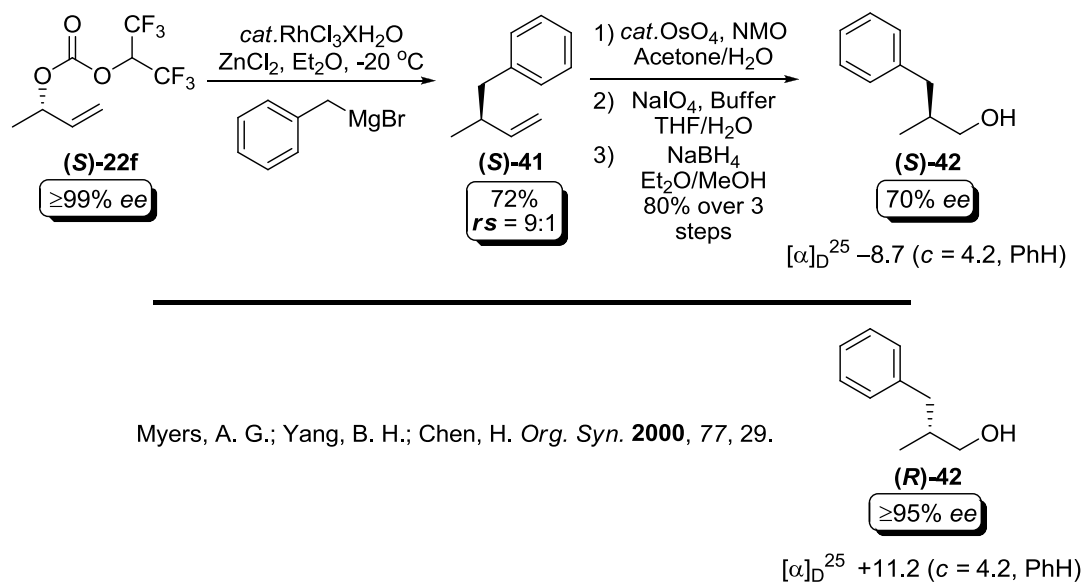
Throughout the examples re-examined the variation in yield and regioselectivity between the two catalyst systems was negligible. This led us to believe that the nature of the active catalyst formed *in situ* must be equivalent in both cases. The exact nature of the catalyst remains unknown, as our attempts to isolate and

characterise the active complex have thus far failed. However, it is possible to envisage that the excess of the benzyl nucleophile is acting as ligand and forming the catalytically active complex. There have been a number of η^1 - and η^3 -benzyl complexes with a range of transition metals described in the literature,⁴⁷ and evidence that suggests zinc halide salts can promote the formation of η^3 -benzyl transition metal-complexes,⁴⁸ so it is within reason that the active rhodium catalyst is a complex of this type. This would correlate well with the fact that there was little variation in the stereospecificity and regioselectivity between the various precatalysts assayed (**Table 10**), as the nature of the active catalyst was derived from benzylic nucleophile, that remained constant, rather than any other exogenous ligands utilised. This hypothesis was further reinforced when we observed the more pronounced effect the electronic of the benzylic Grignard had on the enantiospecificity (**Table 9**). Future studies will focus on fully elucidating the nature of the active catalyst in the reaction.

2.2.4.4. Proof of Absolute Configuration

To ascertain whether the reaction was an indeed inner sphere, the stereochemical course of the transformation was confirmed by the benzylation of the known optically pure allylic carbonate (*S*)-**22f**. The requisite product (*S*)-**41** was then elaborated to the known alcohol (*S*)-**42**, via osmium-catalysed dihydroxylation, oxidative cleavage and then sodium borohydride reduction in 70 % *cee* and 80% overall yield (**Scheme 11**). This alcohol fragment has been utilised as a key starting material for the synthesis of the C1 side chain of zaragozic acid C (**Figure 2**),⁴⁹ the absolute stereochemistry of this compound is also well established in a myriad of further studies. The overall transformation led to an inversion of stereochemistry, this

result is consistent with direct addition of the nucleophile to the metal followed by reductive elimination, thereby confirming an inner sphere mechanism.



Scheme 9: Proof of Absolute Configuration.⁵⁰

2.2.4.5. Concluding Remarks

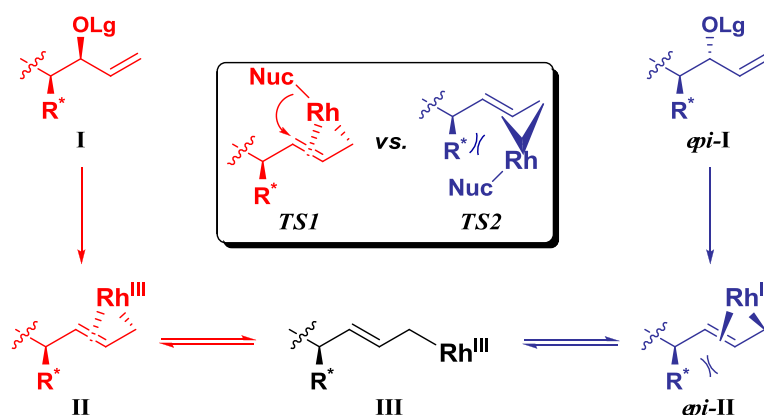
In conclusion, we have developed a stereospecific rhodium-catalysed allylic substitution utilising an unstabilised sp^3 carbon nucleophile which, to our knowledge, has yet to be achieved in rhodium-catalysed allylic substitution. In doing so we have highlighted the major issues associated with this transformation i.e. the perturbed rate of reductive elimination between sp^3 hybridised carbons. This low rate of reductive elimination, in relation to the rate of π - σ - π isomerisation, explains the lower enantiospecificity of the unstabilised sp^3 based benzyl nucleophiles when compared to the analogous rhodium-catalysed allylic arylation that utilised unstabilised sp^2 based arylzinc nucleophiles. While trying to improve the stereospecificity of the reaction by investigating a range of electron poor and rich rhodium precatalysts, we have identified an operationally uncomplicated procedure that utilises the air stable and the simplest commercially available rhodium pre-catalyst $\text{RhCl}_3\text{XH}_2\text{O}$. We have

also determined the overall stereochemical outcome of the reaction and confirmed that the allylic benzylation proceeds *via* an inner sphere mechanism.

2.2.5. Diastereoselective Rhodium-Catalysed Benzylation of Unsymmetrical Fluorinated Acyclic Allylic Carbonates: Asymmetric Construction of Contiguous Carbon Stereocenters.

2.2.5.1. Introduction.

Our previous study focused on the development of regio- and stereospecific rhodium-catalysed allylic substitutions utilising highly unstabilised benzyl nucleophile. However, due to the challenging nature of deploying an unstabilised sp^3 hybridised carbon nucleophile, the level of stereospecificity gained was far from complete. This is likely due to the perturbed rate of reductive elimination from the metal between two sp^3 hybridised carbons compared to sp^2 centres, which results in a more fluxional rhodium-allyl species. This fluxional intermediate presents an opportunity to develop a dynamic kinetic asymmetric transformation *via* two diastereomers of the possible *enyl* (π - σ) intermediates **II** and *epi-II* (Scheme 10).



Scheme 10: Diastereoselective rhodium-catalysed allylic alkylation.

We can envisage rhodium oxidatively adding to the opposite face of both allylic alcohol derivatives **I** and *epi-I*, to afford both diastereomeric *enyl*-complexes **II** and *epi-II*. It is possible to imagine a Curtin–Hammett type process arising, as the two diastereomeric complexes **II** and *epi-II* can interconvert *via* the σ -allyl complex **III**, providing the rate of equilibration is higher than the rate of alkylation. The level of diastereoselectivity afforded in the process would be dependent on the relative energy difference between the two diastereomeric transition states *TS1* and *TS2*.

Based on the above hypothesis we envision that a diastereoselective sp^3 - sp^3 cross coupling for the formation of ternary/quaternary stereocenters could be developed. This methodology could afford facile access to biologically important 1,2-stereo arrays, which are found in a myriad of lignan based natural products.⁵¹

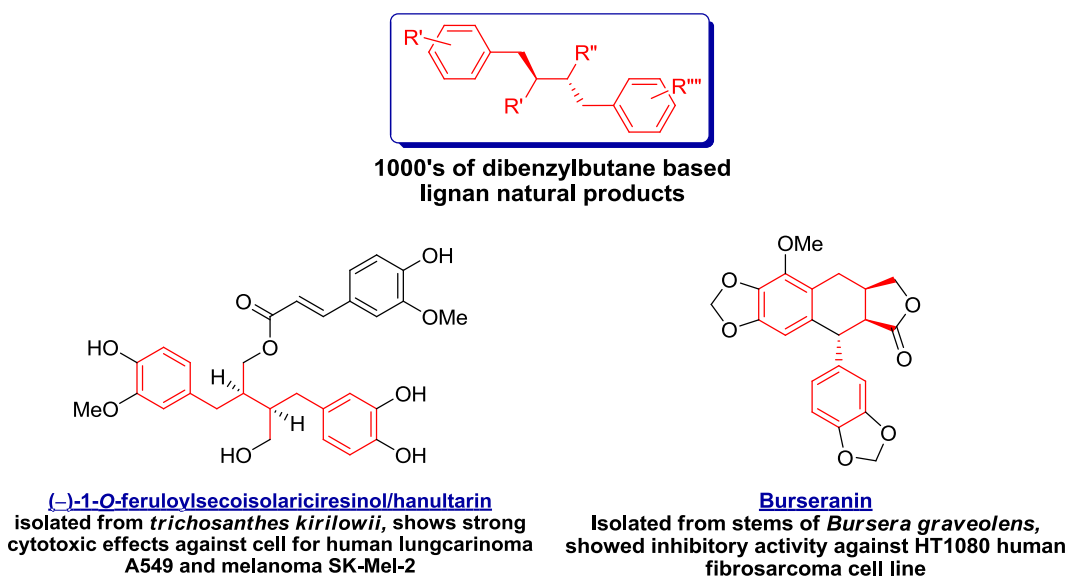
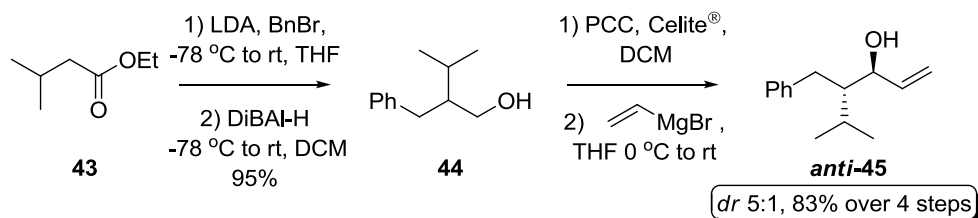


Figure 6: biologically active lignan natural products containing benzyl

substituted 1,2-stereo arrays.⁵¹

2.2.5.2. Substrate Synthesis

The above hypothesis predicts the possibility that there could be a matched and a mismatched scenario, therefore it is important to prepare both *syn*- and *anti*-diastereomers of the associated carbonate. The *anti*-diastereoisomer of the secondary allylic carbonate **anti-45**, was prepared *via* the enolate alkylation of the commercially available ester **43** with benzyl bromide in the presence of lithium diisopropylamine (LDA). The requisite alkylated product was immediately subjected to diisobutylaluminium hydride (DIBAL-H) reduction to afford the alcohol **44** in excellent yield. Alcohol **44** was then oxidised using pyridinium chlorochromate (PCC) and the resultant aldehyde was used in the addition of vinylmagnesium bromide, without purification, to afford the *anti*-diastereoisomer of allylic alcohol **45** in 83% yield over 4 steps and in 5:1 *anti:syn* diastereoselectivity (**Scheme 13**).



Scheme 11: Synthesis of the *anti*-diastereoisomer of allylic alcohol **45.**

The diastereochemical outcome of this synthesis is predicted by the Felkin-Ahn model,^{52,53} which predicts the attack of the vinyl magnesium bromide from the opposite face of the aldehyde to the bulky *iso*-propyl and adjacent to the proton at the Bürgi–Dunitz angle (**Figure 7**).

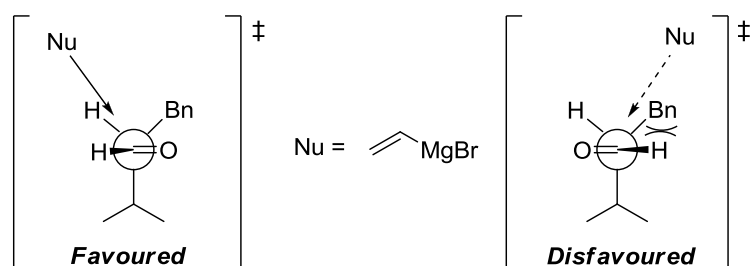
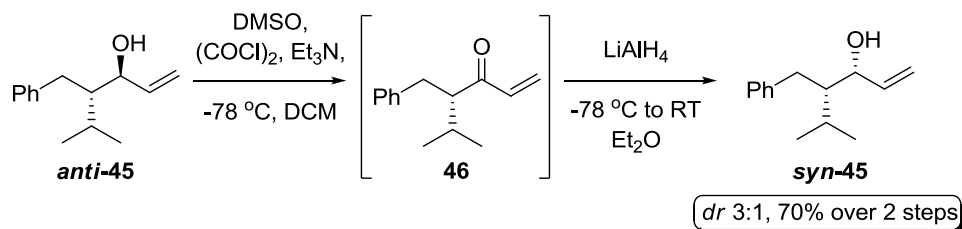


Figure 7: The diastereoselective rational for the preparation of the *anti*-diastereoisomer of allylic alcohol **45.**

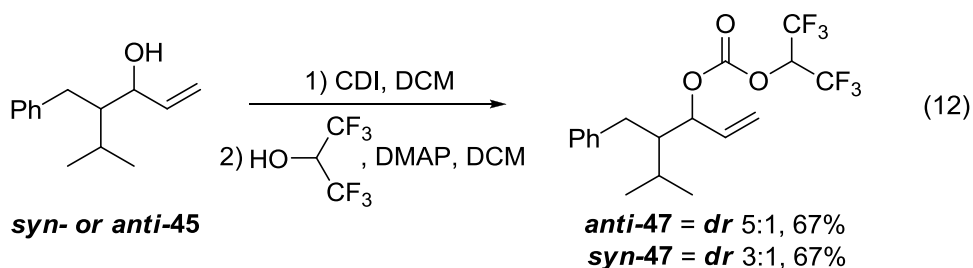
Though the relative stereochemistry of allylic alcohol *anti*-**45** has yet to be confirmed experimentally, the preparation of the opposite diastereoisomer *syn*-**45** via the two step procedure detailed in **Scheme 14** somewhat confirms this assignment.

The allylic alcohol *anti*-**45** was first oxidised *via* Swern oxidation, then the requisite enone **46** was telescoped through a lithium aluminium hydride reduction, affording the *syn*-diastereoisomer of allylic alcohol **45** in 70% yield over 2 steps and in 3:1 *syn:anti* diastereoselectivity (**Scheme 14**). The addition of the hydride to the carbonyl of enone **46** is thought to proceed onto the opposite face to the sterically bulky *iso*-propyl group affording the desired diastereomer, which is opposite to that prepared in **Scheme 13**.



Scheme 12: Synthesis of the *syn*-diastereoisomer of allylic alcohol **45.**

Both fluorinated carbonates *syn-47* and *anti-47* were prepared separately *via* the 1,1'-carbonyldiimidazole (CDI) coupling with hexafluoro-2-propanol and the requisite allylic alcohols. Both diastereomers of the allylic carbonate **47** were afforded in good yields, whilst maintaining their original levels of diastereomeric purity (eq. 12).

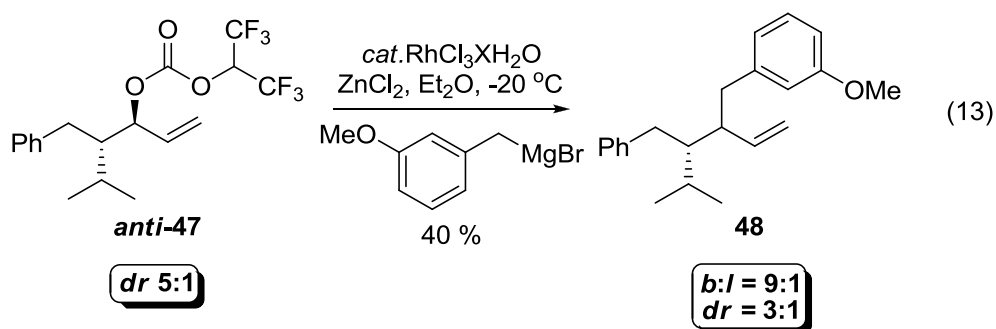


2.2.5.3. Diastereoselective Construction of Tertiary Carbon Stereocenters *via* Rhodium-Catalysed Allylic Benzylation.

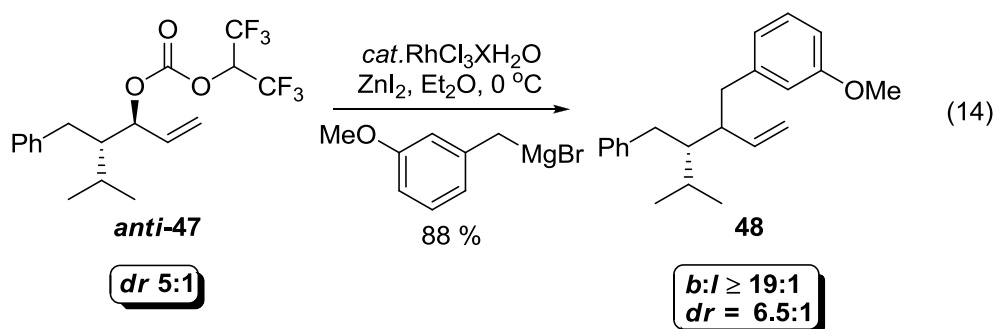
2.2.5.3.1. Mismatched Scenario.

As predicted in the model detailed in **Scheme 12**, the *anti*-diastereomer of the allylic carbonate **47** should result in a mismatched scenario, as the rhodium catalyst would have to oxidatively add on the same face as the bulky *iso*-propyl group. The approach on this sterically encumbered face could hinder the initial oxidative addition and the alkylation event. Additionally, the level of diastereocontrol in the reaction will also be affected by the zinc salt and temperature utilised. Performing the reaction in the presence of zinc chloride and at $-20\text{ }^{\circ}\text{C}$ should provide poor diastereocontrol, as these condition afforded the highest levels of stereospecificity, *ergo* the lowest rate of equilibration between the two diastereomeric *enyl* complexes **II** and *epi-II* (see **Scheme 12**). On the other hand, performing the reaction in the presence of zinc iodide at $0\text{ }^{\circ}\text{C}$, should result in higher levels of diastereocontrol, as

these conditions gave the poorest enantiospecificity, *ergo* a more fluxional *enyl* species with a higher rate of equilibration between intermediates **II** and *epi-II*.



To test this hypothesis, the allylic carbonate *anti-47* was initially subjected to the optimised conditions for the stereospecific reaction (eq. 13). Gratifyingly, this validated our hypothesis, as the reaction failed to reach completion, affording the alkylated product **48** in only 40% yield (eq. 13). The level of diastereocontrol for the reaction was poor, affording the product in a *dr* of only 3:1, however, the level regiocontrol remained the same as the stereospecific reaction (see Section 2.2.4.3.).

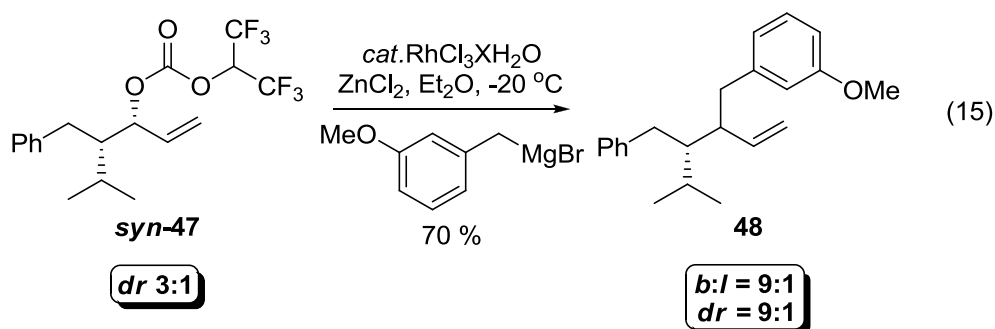


We then went on to subject the allylic carbonate *anti-47* to the optimised conditions for the racemic reaction, which had yielded a lower level of stereospecificity (see section 2.2.4.3.). Gratifyingly, both the yield and the diastereocontrol of the reaction were improved (eq. 14). Nonetheless, the diastereoselectivity of the reaction was far from synthetically useful, although, the branched to linear ratio was significantly improved affording **48** in $\geq 19:1$ regioselectivity. Interestingly, level of regiocontrol

remained unaffected by the addition of an adjacent stereocenter, whilst utilising both sets of conditions, this correlates well with the racemic reaction, which was tolerant to α and β branching (see section 2.2.3.3.3.).

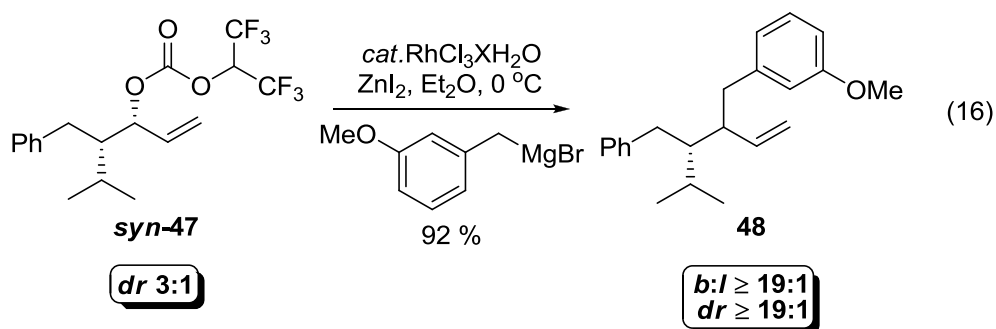
2.2.5.3.2. Matched Scenario.

Based on the above study the *syn*-diastereomer of allylic carbonate **47** should result in a matched scenario, as the rhodium catalyst would oxidatively add to the opposite face of the carbonate, to both the bulky *iso*-propyl group and the fluorinated leaving group. For this substrate, both sets of conditions should garner a higher diastereoselectivity and yield than in the mismatched case, as the majority of the carbonate should afford the less sterically congested *enyl* complex **II** after the initial oxidative addition (**Scheme 12**). However, the level of diastereocontrol between the two sets of conditions would differ, as it is still dependent on the rates of epimerisation of the minor mismatched isomer. The optimised conditions for the stereospecific reaction (ZnCl_2 at $-20\text{ }^\circ\text{C}$), should again afford the lowest level of stereocontrol, whereas the racemic conditions should yield highest diastereocontrol.



To test this hypothesis the allylic carbonate **syn-47** was subjected to the optimised conditions for the stereospecific reaction (eq. 15). Utilising the *syn*-diastereomer afforded an improved yield and diastereoselectivity, however, the reaction still failed to go to completion. Interestingly, the remaining starting material maintained its

original *syn:anti* ratio, thus ruling out a kinetic resolution. The regioselectivity for the reaction was the same as the mismatched example.

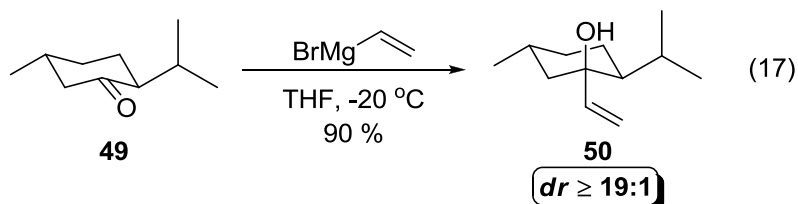


The matched substrate **syn-47** was then subjected to the optimised conditions for the racemic reaction (ZnI_2 at $0\text{ }^\circ\text{C}$) and, remarkably **48** was afforded as a single diastereomer and in excellent yield and regioselectivity (eq. 16). Interestingly, for both the mismatched and matched carbonates the same diastereomer of **48** was afforded as the major product. This truly validates the hypothesis in **Scheme 12**, as regardless of the whether the *syn*- or *anti*-diastereomer of the carbonate was utilised, the majority of the product was converted to the same diastereomer of **48** via the equilibration between intermediates **II** and *epi-II*.

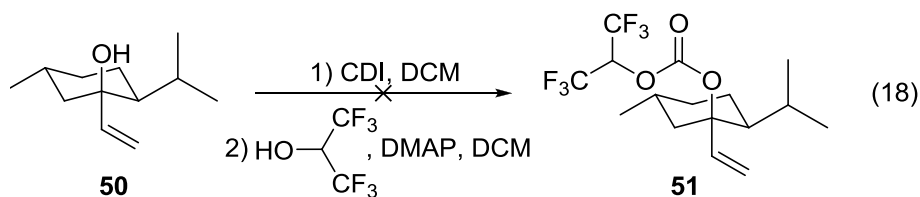
2.2.5.4. Diastereoselective Preparation of an all Carbon Quaternary Stereocenter via the Rhodium-Catalysed Allylic Benzylolation.

Bolstered with the success of the ternary example, we then went on to expand the scope of the diastereoselective reaction to the formation of an all carbon quaternary stereocenter. Mindful of the possibility of a matched and mismatched scenario, it was important to prepare the *syn*-diastereomer of any possible substrate. In the literature, the number of tertiary allylic alcohols containing an adjacent stereocenter with *syn*-stereochemistry is extremely low. However, in one fortuitous example described by

Hart and co-workers,⁵⁴ it was demonstrated that the addition of vinyl magnesium bromide to L-menthone is highly diastereoselective. Utilising this highly diastereoselective Grignard addition we prepared the known tertiary allylic alcohol derivative **50** as a single diastereoisomer (eq. 17).

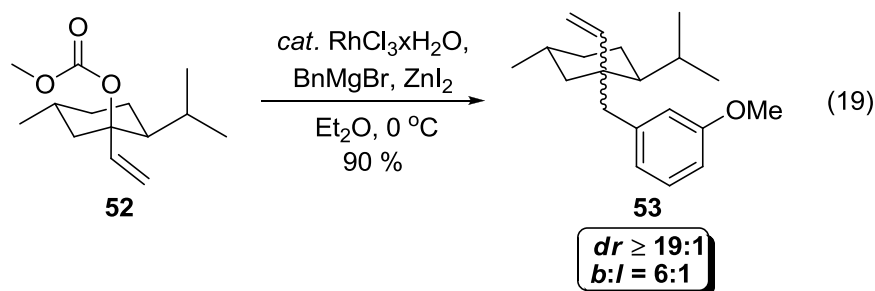


Due to the highly sterically encumbered nature of tertiary alcohol derivative **50**, we were unable to prepare the fluorinated allylic carbonate **51**, despite several attempts (eq. 18).



Instead we elected to prepare the methyl carbonate derivative **52**, in spite of our early studies demonstrating that the methyl carbonate afforded a poorer branched to linear ratio in the rhodium-catalysed allylic benzylation (see section 2.2.3.2.). Menthone-derived allylic carbonate **52** was subjected to the optimal conditions and afforded the alkylated product **53** in excellent yield (eq. 19). However, the regioselectivity was considerably inferior to the previous examples. The reduction in regiocontrol is probably due to the methyl carbonate leaving group being utilised instead of the optimal fluorinated carbonate. This is also compounded by the sterically congested nature of the allylic alcohol **52**. Remarkable, the benzylated product **53** was afforded as a single diastereomer, which particularly germane as the

asymmetric construction of all carbon quaternary centres represents a longstanding challenge in synthetic organic chemistry.



2.2.5.5. Concluding Remarks

In conclusion, taking advantage of the more fluxional rhodium-*enyl* intermediate afforded by the utilisation of a sp^3 hybridised carbon nucleophile, we have developed a diastereoselective sp^3 - sp^3 cross coupling. With the judicious choice of conditions and substrate we were able to prepare tertiary and quaternary carbon stereocenters of 1,2-stereoarrays in a highly diastereoselective fashion. Remarkably, the equilibria between the two possible diastereomeric *enyl*-complexes **II** and *epi*-**II** (Scheme 12), was such that even the mismatched substrate was turned over to give the same major diastereomer as the matched substrate. To best of our knowledge, the diastereoselective synthesis of 1,2-stereoarrays *via* allylic substitution utilising a unstabilised carbon nucleophile has yet to be described in the context of rhodium-catalysed allylic substitution. Future studies will focus on conclusively assigning the relative stereochemistry of the products for both the tertiary and quaternary examples, in addition to expanding the scope of the asymmetric transformation.

2.2.6. Rhodium-Catalysed Allylic Substitution with Alkenyl organometallic Pronucleophiles: Expanding the Scope of the Unstabilised Carbon Nucleophiles

2.2.6.1. Introduction

Our first study focused on the development of stereospecific rhodium-catalysed allylic substitutions utilising highly unstabilised sp^3 -hybridised carbon nucleophile. However, due to the challenging nature of deploying an unstabilised sp^3 -hybridised carbon nucleophile, the level of stereospecificity gained was far from complete. Our second study attempted to obviate the limited ability of this process to install a stereogenic carbon-carbon bonds, by taking advantage of the fluxionality of the rhodium-*enyl* and developing a diastereoselective sp^3 - sp^3 cross coupling. However, another means to ensure the asymmetric installation of a carbon-carbon bond is to guarantee a facile reductive elimination, in the stereospecific manifold, between the two coupling partners from the metal centre. Having already highlighted the limitation associated with utilising an unstabilised sp^3 based carbon nucleophile, an obvious route would be to change the hybridisation of the unstabilised carbon nucleophile. Given the high levels of stereospecificity obtained for the allylic arylation developed by our group, sp^2 hybridised nucleophiles provide alluring candidates.¹⁶ Out of the potentially sp^2 hybridised nucleophiles, vinyl organometallic reagents represent interesting synthons, as the particular moiety maps on to a myriad of biologically important natural products (**Figure 8**).

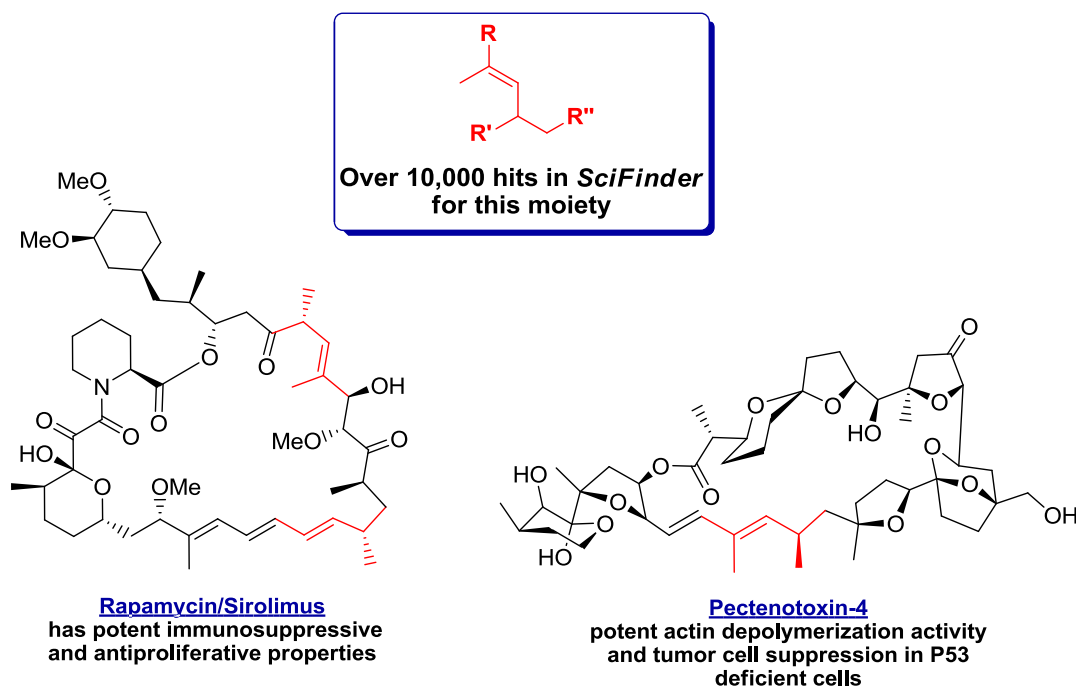
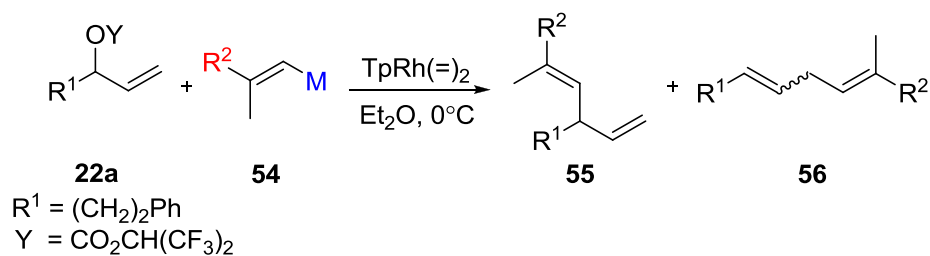


Figure 8: Bioactive natural products containing “Stereogenic Vinyl” motif.

The cornucopia of biologically important compounds that this methodology could potentially provide facile access to provides a large impetus to develop this methodology.

2.2.6.2. Initial Nucleophile Screening

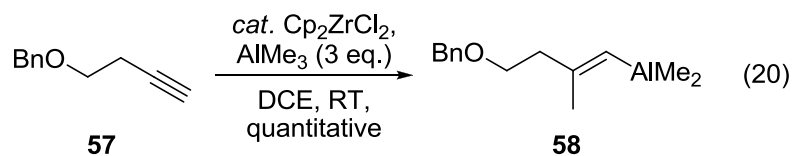
Despite demonstrating that $\text{RhCl}_3\text{XH}_2\text{O}$ could be successfully utilised as a precatalyst for rhodium catalysed allylic benzylation, the scorpionate complex $\text{TpRh}(\text{C}_2\text{H}_4)_2$ was initially selected as a precatalyst. This was due to the fundamentally different nature of the organometallic pronucleophiles to be assayed and on account that this scorpionate complex had previously been utilised with an unstabilised sp^2 hybridised carbon nucleophile. A series of vinyl organometallic reagents were screened (**Table 13**).

Table 13: Initial Vinyl Nucleophile screening.

Entry ^a	M	R ²	55 yield(%) ^b	55:56 ^c
1	MgBr/ZnBr	Me	NR	n/a
2	MgBr/ZnI	“	NR	n/a
3	Br/Li/ZnBr	“	NR	n/a
4	AlMe ₂ /ZnBr	BnO(CH ₂) ₂	9	1:4.4
5	AlMe ₂ /ZnI	“	23	1:2

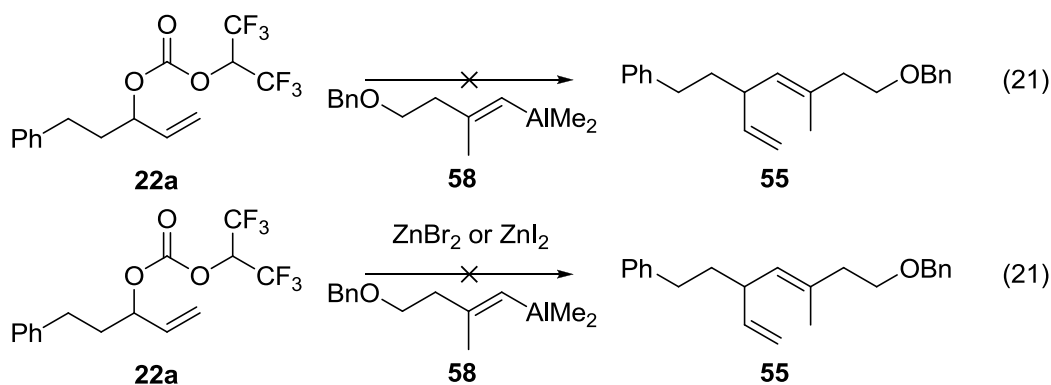
^aAll reactions were carried out on a 0.1 mmol scale (0.025 M). ^bGLC yields relative to the internal standard *n*-pentadecane. ^cRatios of regioisomers were determined using capillary GLC on the crude reaction mixture.

Initially our primary focus was on utilising 2-methyl-1-propenyl magnesium bromide as a nucleophile and transmetalating *in situ* with zinc bromide and iodide, however, no reaction was observed (Table 12, entries 1 and 2). We then tried forming the associated vinylzinc *via* the lithium halogen exchange of 1-bromo-2-methyl-1-propene, followed by transmetalation with zinc bromide, unfortunately this failed to afford any observable conversion either (Table 12, entry 3). We then decide to prepare the vinylaluminium reagent **58**, *via* the zirconocene-mediated methyl aluminations of alkyne **57** (eq. 20).



The requisite aluminium reagent was then transmetalated *in situ* with zinc bromide before being deployed as a nucleophile (Table 12, entries 4 and 5). Gratifyingly,

both reactions afforded the associated coupled product, albeit in poor yield and regiocontrol, giving the linear product **56** as the major product. This reversal in regioselectivity prompted us to conduct two control reactions, the aim of which was to rule out whether the substrate **22a** was simply undergoing S_N2' and S_N2 addition of the nucleophile, without involving the rhodium catalyst. In the absence of rhodium both the vinylaluminium and the *in situ* prepared vinylzinc reagent failed to afford any of the requisite products (eq. 21 and 22).



Gratifyingly, both sets of control experiments demonstrated that rhodium was essential for the coupling and the reaction was not an uncatalysed background reaction between the substrate and the nucleophile.

2.2.6.3. Concluding Remarks

In conclusion, we have demonstrated the initial proof of principle that other unstabilised sp^2 based carbon nucleophiles can be deployed in the rhodium-catalysed allylic substitution. We have successfully expanded the nucleophile scope to include an unstabilised alkenyl nucleophile. Despite the poor regiocontrol and yield of the reaction, with further development, we anticipate that this transformation could become an extremely potent vehicle for the asymmetric installation of alkenyl

moieties. Future studies will focus on the optimisation of the reaction and development of the stereospecific manifold with the eventual application in target directed synthesis, particularly in the preparation of complex bioactive pharmaceuticals and natural products that contain the “2-methyl-1-propenyl” motif.

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- ⁵³ Mengel, A.; Reiser, O. *Chem. Rev.*, **1999**, *99*, 1191.
- ⁵⁴ Chillous, S.; Hart, D. J.; Hutchinson, D. K. *J. Org. Chem.*, **1982**, *47*, 5418.

Chapter 3

Representative Experimental Procedures and Supplemental Data

3.1 General Information

All reactions were carried out under an argon atmosphere with anhydrous solvents. All commercially available reagents were purchased and used as received. All compounds were purified by flash chromatography using silica gel 60 (40-63 μm , *FluoroChem*) and gave spectroscopic data consistent with being $\geq 95\%$ the assigned structure. Analytical thin layer chromatography (TLC) was performed on pre-coated 0.25 mm thick silica gel 60-F₂₅₄ plates (*Whatman PE SIL G/UV*); visualised using UV light and by treatment with a KMnO_4 dip, followed by heating. Optical rotations ($[\alpha]_{\text{D}}^{20}$) were measured on a *Perkin-Elmer Model 343 plus* polarimeter with a sodium lamp (D line, 589 nm) at ambient temperature (indicated in $^{\circ}\text{C}$ as superscript) using a 1 mL quartz cell of 100 mm length; solution concentration (c) are given in g/100 mL. IR spectra were recorded on a *Perkin-Elmer FT-IR Spectrum 100* (ATR) spectrometer; wavenumbers (ν) are given in cm^{-1} . Mass spectra were obtained through the Chemistry Department Mass Spectrometry Service, University of Liverpool or the EPSRC National Mass Spectrometry Service, Swansea. High resolution chemical ionization (CI) and electrospray ionisation (ESI) mass spectra were recorded on a *Fisons Trio-1000* or *LTQ Orbitrap*, and *Micromass LTC* mass spectrometers, respectively. ^1H NMR and ^{13}C NMR spectra were recorded on a *Bruker Avance DRX-500* spectrometer in CDCl_3 at ambient temperature; chemical shifts (δ) are given in ppm and calibrated using the signal of residual undeuterated solvent as internal reference ($\delta_{\text{H}} = 7.26$ ppm and $\delta_{\text{C}} = 77.17$ ppm). ^1H NMR data are reported as follows: chemical shift (multiplicity, 2nd order spin system if available, coupling constant, integration). Coupling constants (J) are reported in Hz and

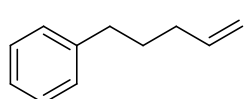
apparent splitting patterns are designated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), app. (apparent) and the appropriate combinations. ^{13}C NMR spectra with complete proton decoupling were described with the aid of an APT sequence, separating methylene and quaternary carbons (e, even), from methyl and methine carbons (o, odd).

Unless otherwise indicated, all reactions were carried out in flame dried round bottom flasks and under an inert atmosphere of argon. Syringes and needles were oven-dried (125°C) and cooled in a desiccator. All reactions were carried out under an argon (Ar) atmosphere in oven-dried glassware. All substrates were purified by column chromatography or distillation. ZnCl_2 , ZnBr_2 and ZnI_2 were dried at $100\text{--}200^\circ\text{C}$ under high-vacuum for 2 hours and stored in the glove box. Diethyl ether and dichloromethane were used from Grubbs' still solvent system. All starting materials were purchased from Acros, Aldrich, Alfa Aesar or Strem chemical companies and used without further purification unless otherwise noted.

3.2. Representative Experimental Procedures and Spectral Data

3.2.1. Regiospecific Rhodium-Catalysed Benzylolation of Unsymmetrical Fluorinated Acyclic Allylic Carbonates.

3.2.1.1. Spectral Data for the reduce carbonate **25** and β -Hydride Eliminated Nucleophile **26b**.



Pent-4-enylbenzene (25b)

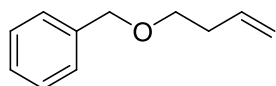
Colour and State: Colourless oil.

All spectral data matched the published values.¹

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.31–7.28 (m, 2H), 7.20–7.19 (m, 3H), 5.85 (ddt, $J = 17.0, 10.5, 6.5$ Hz, 1H), 5.06 (ddt, $J = 17.5, 2.0, 0.5$ Hz, 1H), 4.99 (ddt, $J = 10.5, 1.5, 0.5$ Hz, 1H), 2.64 (t, $J = 7.5$ Hz, 2H), 2.13–2.09 (m, 2H), 1.77–1.70 (m, 2H).

¹³C-NMR (125, MHz CDCl₃) δ 142.7 (e), 138.8 (o), 128.7 (o), 128.5 (o), 125.9 (o), 114.9 (e), 35.5 (e), 33.5 (e), 30.8 (e).

IR (Neat) 2923, 2853, 1640, 1496, 1454, 910 cm⁻¹.



((but-3-enyloxy)methyl)benzene (26b)

Colour and State: Yellow oil.

All spectral data matched the published values.¹

¹H-NMR (500 MHz, CDCl₃) δ 7.38–7.27 (m, 5H), 5.86 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.12 (ddt, *J* = 17.5, 2.0, 1.5 Hz, 1H), 5.06 (ddt, *J* = 10.5, 2.0, 1.5 Hz, 1H), 4.54 (s, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.40 (app. qt, *J* = 6.5, 1.5 Hz, 2H)

¹³C-NMR (125, MHz CDCl₃) δ 138.7 (e), 135.5 (o), 128.6 (o), 127.9 (o), 127.8 (o), 116.6 (e), 73.1 (e), 69.8 (e), 34.5 (e).

IR (Neat) 3031, 2926, 2855, 1642, 1454, 1362, 1101 cm⁻¹.

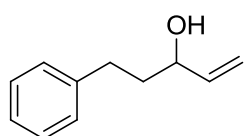
3.2.1.2. Representative Experimental Procedure for the Synthesis of secondary allylic alcohols.

With the exception of but-3-en-2-ol **29f**, which is commercially available, all the allylic alcohols were prepared via the addition of vinylmagnesium bromide to the requisite known and/or commercially available aldehydes *via* the following representative procedure.

Under an argon atmosphere, a stirred solution of vinylmagnesium bromide (1.0 M in THF, 13 ml, 13 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to 0 °C, and 3-phenylpropanal aldehyde **28a** (1.412g, 10 mmol) was added dropwise *via* syringe. The solution was allowed to warm to ambient temperature for 2 hours (TLC control), and then quenched at 0 °C by slow addition of 1M HCl (aq). The solution was extracted by using diethyl ether (3 X 10 ml) followed by washing the organic

extracts with brine. The organic phase was dried (MgSO_4), filtered and concentrated in *vacuo* to afford a crude oil. Purification by flash column chromatography (eluting with 3-9% diethyl ether/hexane) yielded the secondary allylic alcohol **29a** (1.541g, 95%) as a yellow oil.

3.2.1.3. Spectral Data for the Allylic Alcohols 29a-e and 29g-l.



5-phenylpent-1-en-3-ol (29a).

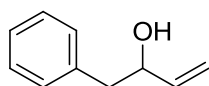
Colour and State: Yellow oil.

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.29-7.18 (m, 5H), 5.90 (ddd, $J = 17.2, 10.4, 6.1$ Hz, 1H), 5.24 (dt, $J = 17.2, 1.4$ Hz, 1H), 5.13 (dt, $J = 10.4, 1.3$ Hz, 1H), 4.12 (m, 1H), 2.75-2.69 (m, 2H), 1.88-1.85 (m, 2H), 1.53 (d, $J = 4.1$ Hz, 1H).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 142.02 (e), 141.24 (o), 128.63 (o), 128.49 (o), 126.04 (o), 115.60 (e), 72.68 (o), 38.70 (e), 31.84 (e).

IR (Neat) 3354, 2926, 1496, 1453, 1041, 990, 923 cm^{-1} .

HRMS (ESI $[\text{M}+\text{Na}]^+$) calcd for $\text{C}_{11}\text{H}_{13}\text{NaO}$ 184.0864, found 184.0866.



1-phenylbut-3-en-2-ol (29b).

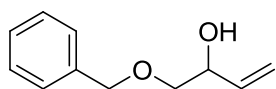
Colour and State: Yellow oil.

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.42–7.05 (m, 5H), 5.94 (ddd, $J = 17.0, 10.3, 5.8$ Hz, 1H), 5.34–4.95 (2H, m); 4.62–4.57 (m, 1H), 2.87–2.60 (m, 2H), 2.40 (bs, 1H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 140.09 (e), 137.70 (o), 129.54 (o), 128.41 (o), 126.50 (o), 114.90 (e), 73.63 (o), 43.80 (e).

IR (Neat) 3375, 3028, 2921, 2852, 1496, 1454, 991, 922 cm^{-1} .

HRMS (ESI $[\text{M}+\text{H}-\text{H}_2\text{O}]$) calcd For $\text{C}_{10}\text{H}_{11}$ 131.0861, found 131.0858.



1-(benzyloxy)but-3-en-2-ol (29c).

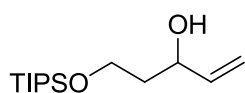
Colour and State: Yellow oil.

All spectral data matched the published values.²

¹H-NMR (500 MHz, CDCl₃) δ 7.38–7.29 (m, 5H), 5.83 (ddd, $J = 17.4, 10.6, 5.9$ Hz, 1H), 5.38 (dt, $J = 17.4, 1.4$ Hz, 1H), 5.21 (dt, $J = 10.6, 1.4$, 1H), 4.58 (s, H₂), 4.35 (m, 1H), 3.55 (d, A of ABM, $J_{ABM} = 9.6, 3.4$ Hz, 1H), 3.39 (d, B of ABM, $J_{ABM} = 9.6, 7.9$ Hz, 1H), 2.79 (bs, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 137.80 (e), 136.64 (o), 128.57 (o), 127.90 (o), 116.51 (e), 74.00 (o), 73.41 (e), 71.56 (e).

IR (Neat) 3375, 3028, 2921, 2852, 1496, 1454 cm⁻¹.



5-(triisopropylsilyloxy)pent-1-en-3-ol (29d).

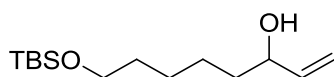
Colour and State: Yellow oil.

All spectral data matched the published values.³

¹H-NMR (500 MHz, CDCl₃) δ 5.81 (ddd, $J = 18.2, 10.5, 5.9$ Hz, 1H), 5.21 (d, $J = 18.2$ Hz, 1H), 5.02 (d, $J = 10.5$ Hz, 1H), 4.31 (m, 1H), 3.92 (m, 1H), 3.83 (m, 1H), 3.52 (s, 1H), 1.70 (m, 2H), 1.02 (m, 21H).

¹³C NMR (125 MHz, CDCl₃) δ 140.80 (o), 114.17 (e), 72.63 (o), 62.53 (e), 38.55 (e), 18.00 (o), 12.17 (o).

IR (Neat) 3410, 2930, 2885, 1100 cm⁻¹.



8-(tert-butyldimethylsilyloxy)oct-1-en-3-ol (29e).

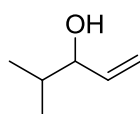
Colour and State: Colourless oil.

All spectral data matched the published values.⁴

¹H-NMR (500 MHz, CDCl₃) δ 5.84 (ddd, *J* = 17.1, 10.4, 6.4 Hz, 1H), 5.19 (dt, *J* = 17.4, 1.4 Hz, 1H), 5.07 (dt, *J* = 10.2, 1.2 Hz, 1H), 4.07 (q, *J* = 6.0 Hz, 1H), 3.57 (t, *J* = 6.4 Hz, 2H), 1.58-1.21 (m, 9H), 0.86 (s, 9H), 0.02 (s, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 141.51 (o), 114.78 (e), 73.42 (o), 63.37 (e), 37.25 (e), 32.99 (e), 26.20 (o), 25.98 (e), 25.35 (e), 18.58 (e), -5.06 (o).

IR (neat) 3360, 2931, 2858, 1644, 1472, 1463 cm⁻¹.



4-methylpent-1-en-3-ol (29g).

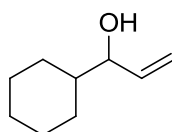
Colour and State: Yellow oil.

All spectral data matched the published values.⁵

¹H-NMR (500 MHz, CDCl₃) δ 5.87 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H), 5.23 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H), 5.16 (ddd, *J* = 10.5, 1.7, 1.2 Hz, 1H), 3.86 (dd, *J* = 5.9, 5.9 Hz, 1H), 1.74 (sept, *J* = 6.8, 5.9 Hz, 1H), 1.61 (bs, 1H), 0.94 (d, *J* = 6.8 Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃) δ 139.60 (o), 115.74 (e), 78.39 (o), 33.74 (o), 18.19 (o), 17.80 (o).

IR (Neat) 3361, 3052, 1717 cm⁻¹.



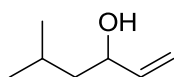
1-cyclohexylprop-2-en-1-ol (29h).

Colour and State: Yellow oil.

All spectral data matched the published values.⁶

¹H-NMR (500 MHz, CDCl₃) δ 5.86 (ddd, *J* = 17.3, 13.4, 3.9 Hz, 1H), 5.20 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.14 (dt, *J* = 10.4, 1.4 Hz, 1H), 3.85 (m, 1H), 1.81-1.88 (m, 1H), 1.63-1.78 (m, 4H), 0.94-1.44 (m, 6H).

¹³C-NMR (100 MHz, CDCl₃) δ 140.02 (o), 115.60 (e), 77.91 (o), 43.74 (o), 28.90 (e), 28.50 (e), 26.74 (e), 26.37 (e), 26.19(e).



5-methylhex-1-en-3-ol (29i).

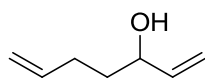
Colour and State: Yellow oil.

All spectral data matched the published values.⁷

¹H-NMR (500 MHz, CDCl₃) δ 5.86 (ddd, *J* = 17.2, 10.2, 6.2 Hz, 1H), 5.22 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.09 (ddd, *J* = 10.2, 1.4 Hz, 1H), 4.17 (m, 1 H), 1.75 (bs, 1H), 1.47 (m, 1H), 1.32 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H) 0.91 (d, *J* = 6.6 Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃) δ 141.70 (o), 114.44 (e), 71.62 (o) 46.29 (e), 24.50 (o), 23.11 (o), 22.44 (o).

IR (neat) 3465, 1654 cm⁻¹.



hepta-1,6-dien-3-ol (29k).

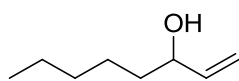
Colour and State: Yellow oil.

All spectral data matched the published values.⁸

¹H-NMR (500 MHz, CDCl₃) δ 5.88–5.73 (m, 2 H), 5.19 (ddd, *J* = 17.2, 1.6, 1.4 Hz, 1 H), 5.07 (ddd, *J* = 10.4, 1.6, 1.4 Hz, 1H), 5.01 (ddd, *J* = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (ddd, *J* = 10.2, 3.5, 1.6 Hz, 1H), 4.08 (ddd, *J* = 6.4, 6.3, 1.2 Hz, 1H), 2.31 (s, 1 H), 2.16–2.06 (m, 2H), 1.68–1.50 (m, 2H).

¹³C-NMR (125 MHz, CDCl₃) δ 141.00 (o), 138.34 (o), 114.79 (e), 114.72 (e), 72.50 (o), 36.02 (e), 29.57 (e).

IR (Neat) 3350, 2934, 1641, 1425, 991 cm⁻¹.



oct-1-en-3-ol (29l)

Colour and State: Yellow oil.

All spectral data matched the published values.⁹

¹H-NMR (500 MHz, CDCl₃) δ 5.85 (ddd, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.16 (ddd, *J* = 17.1, 1.6, 1.3 Hz, 1H), 5.05 (ddd, *J* = 10.2, 1.3, 1.0 Hz, 1H), 4.08 (m, 1H), 1.51 (m, 2H), 1.34 (m, 6H), 0.89 (m, 3H).

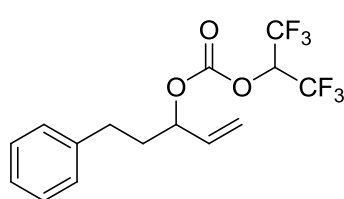
¹³C-NMR (125 MHz, CDCl₃) δ 141.28 (o), 114.42 (e), 73.25 (o), 37.01 (e), 31.70 (e), 25.03 (e), 22.62 (e), 14.04 (o).

IR (Neat) 3370, 1640 cm⁻¹.

3.2.1.4. Representative Experimental Procedure for the Preparation of Fluorinated Carbonates.

To a solution of carbonyldiimidazole (1.946 g, 12 mmol) in dichloromethane (10 ml, 1M) was added 5-phenylpent-1-en-3-ol **29a** (1.622 g, 10 mmol) at room temperature and the resulting solution was allowed to stir for ≥3 hours (TLC control). The yellow solution was partitioned between dichloromethane and water, and the organic phase washed with water (2x) to remove any residual imidazole. The organic phase was dried (Na₂SO₄), filtered and concentrated in *vacuo* to afford a crude oil. The residue was redissolved into dichloromethane (10 ml, 1M) and treated with hexafluoro-2-propanol (3.12 ml, 30 mmol) and a catalytic amount of 4-(*N,N*-dimethylamino)pyridine (0.122 g, 1 mmol) at room temperature for *ca.* 18 hours (TLC control). Purification by flash chromatography (eluting with a 100/0-10/1 petroleum ether (30-40°C) /dichloromethane gradient) furnished the allylic carbonate **32a** (2.67g, 75% yield) as a colourless oil.

3.2.1.5. Spectral Data for the Allylic Carbonates **22a-l**.



1-(2-Phenylethyl)prop-2-en-1-yl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl carbonate (22a).

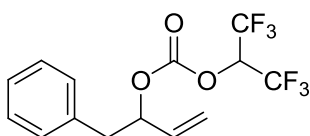
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 7.28 (t, *J* = 7.2 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 5.82 (ddd, *J* = 17.4, 10.4, 6.8 Hz, 1H), 5.54 (sept, *J*_{H-F} = 6.0 Hz, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 5.10 (brq, *J* = 6.8 Hz, 1H), 2.74-2.62 (m, 2H), 2.10 (dddd, *J* = 14.0, 8.8, 7.6, 6.4 Hz, 1H), 1.97 (dddd, *J* = 10.0, 8.8, 6.8, 5.6 Hz, 1H);

¹³C NMR (125 MHz, CDCl₃) δ 152.22 (e), 140.41 (e), 134.29 (o), 128.60 (o), 128.03 (o), 126.34 (o), 120.32 (e; q, *J*_{C-F} = 280.1 Hz), 119.20 (e), 81.05 (o), 70.11 (o; sept, *J*_{C-F} = 34.9 Hz), 35.50 (e), 31.03 (e);

IR (neat) 3030, 2972, 1776, 1650, 1605, 1498, 1456, 1386, cm⁻¹.



1-Benzylprop-2-en-1-yl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl carbonate (22b).

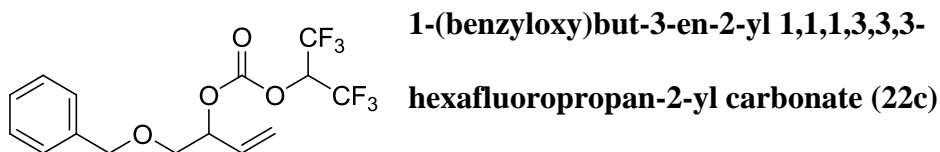
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 7.29 (t, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 2H), 5.84 (ddd, *J* = 17.2, 10.6, 6.6 Hz, 1H), 5.45 (sept, *J*_{H-F} = 6.0 Hz, 1H), 5.33 (brq, *J* = 6.8 Hz, 1H), 5.30 (d, *J* = 13.2 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 3.05 (dd, A of ABX, *J*_{AB} = 14.0 Hz, *J*_{AX} = 7.6 Hz, 1H), 2.96 (dd, B of ABX, *J*_{AB} = 14.0 Hz, *J*_{BX} = 6.0 Hz, 1H).

¹³C-NMR (125 MHz, CDCl₃) δ 152.13 (e), 135.62 (e), 133.95 (o), 129.54 (o), 128.50 (o), 127.03 (o), 120.21 (e; q, *J*_{C-F} = 280.8 Hz), 119.00 (e), 82.03 (o), 70.14 (o; sept, *J*_{C-F} = 34.9 Hz), 40.75 (e).

IR (neat) 3034, 2974, 1775, 1650, 1606, 1498, 1456 cm⁻¹.



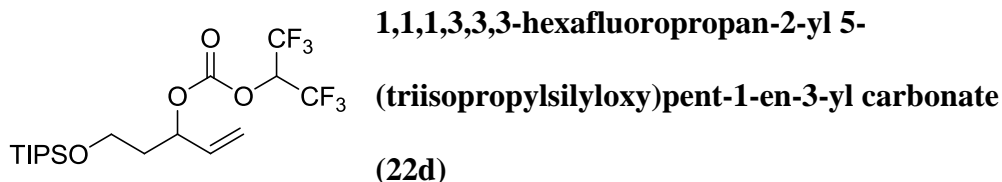
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 7.37-7.28 (m, 5H), 5.85 (ddd, $J = 17.2, 10.6, 6.6$ Hz, 1H), 5.57 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.45-5.35 (M, 3H), 4.59 (d, A of AB $J_{\text{AB}} = 12.1$ Hz, 1H), 4.56 (d, B of AB $J_{\text{AB}} = 12.1$ Hz, 1H) 3.63 (d, $J = 5.6$ Hz, 2H), 2.96 (dd, B of ABX, $J_{\text{AB}} = 14.0$ Hz, $J_{\text{BX}} = 6.0$ Hz, 1H).

¹³C-NMR (125 MHz, CDCl₃) δ 152.10 (e), 137.57 (e), 134.87 (o), 129.51 (o), 128.47 (o), 127.03 (o), 120.22 (e; q, $J_{\text{C-F}} = 280.8$ Hz), 118.57 (e), 82.30 (o), 73.86 (e), 73.01 (e), 70.10 (o; sept, $J_{\text{C-F}} = 34.9$ Hz).

IR (neat) 3034, 2974, 1775, 1650, 1606, 1498, 1456 cm⁻¹.



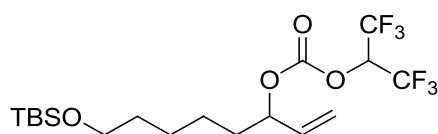
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H NMR (500 MHz, CDCl₃) δ 5.85 (ddd, $J = 17.3, 10.4, 6.8$ Hz, 1H), 5.53 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.43-5.35 (m, 2H), 5.29 (d, $J = 10.4$ Hz, 2H), 3.82-3.72 (m, 2H), 2.02-1.95 (m, 1H), 1.92-1.85 (m, 1H), 1.05 (s, 18H).

¹³C NMR (125 MHz, CDCl₃) δ 152.31 (e), 134.78 (o), 120.33 (e; q, $J_{\text{C-F}} = 280.9$ Hz), 118.86 (e), 79.41 (o), 70.13 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 58.76 (e), 37.33 (e), 18.0 (o), 12.2 (o).

IR (Neat) 2934, 2861, 1777, 1650, 1473, 1464 cm⁻¹.



1-[6-(*tert*-Butyldimethylsiloxy)hexyl]prop-2-en-1-yl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl carbonate (22e)

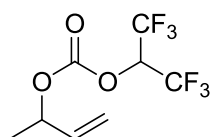
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 5.78 (ddd, $J = 17.2, 10.4, 7.0$ Hz, 1H), 5.53 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.31 (d, $J = 17.2$ Hz, 1H), 5.26 (d, $J = 10.4$ Hz, 1H), 5.10 (q, $J = 6.8$ Hz, 1H), 3.58 (t, $J = 6.4$ Hz, 2H), 1.80-1.70 (m, 1H), 1.70-1.61 (m, 1H), 1.52-1.44 (m, 2H), 1.40-1.28 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H).

¹³C-NMR (125 MHz, CDCl₃) δ 152.07 (e), 134.65 (o), 120.28 (e; q, $J_{\text{C-F}} = 282.6$ Hz), 118.82 (e), 82.43 (o), 70.14 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 62.85 (e), 33.90 (e), 32.55 (e), 25.93 (o), 25.52 (e), 24.59 (e), 18.30 (e), -5.42 (o).

IR (Neat) 2934, 2861, 1777, 1650, 1473, 1464 cm⁻¹.



1-Methylprop-2-en-1-yl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl carbonate (22f)

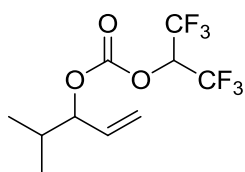
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 5.85 (ddd, $J = 17.2, 10.4, 6.4$ Hz, 1H), 5.53 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.33 (d, $J = 17.2$ Hz, 1H), 5.25 (brquin, $J = 6.4$ Hz, 1H), 5.24 (d, $J = 10.4$ Hz, 1H), 1.43 (d, $J = 6.4$ Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃) δ 3C δ 152.12 (e), 135.64 (o), 120.29 (e; q, $J_{\text{C-F}} = 280.8$ Hz), 117.92 (e), 78.54 (o), 70.14 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 19.73 (o).

IR (Neat) 2991, 1775, 1651, 1455, cm⁻¹.



1-Isopropylprop-2-en-1-yl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl carbonate (22g).

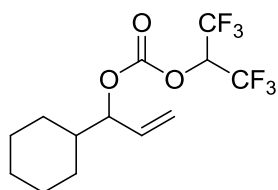
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 5.77 (ddd, $J = 17.2, 10.4, 7.2$ Hz, 1H), 5.54 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.31 (d, $J = 17.2$ Hz, 1H), 5.30 (d, $J = 10.4$ Hz, 1H), 4.90 (t, $J = 6.8$ Hz, 1H), 1.96 (octet, $J = 6.8$ Hz, 1H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃) δ 152.4 (e), 132.9 (o), 120.3 (e; q, $J_{\text{C-F}} = 280.8$ Hz), 119.6 (e), 87.0 (o), 70.1 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 31.8 (o), 17.8 (o), 17.7 (o).

IR (Neat) 2975, 1776, 1650, 1473, cm⁻¹.



1-Cyclohexylprop-2-en-1-yl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl carbonate (22h).

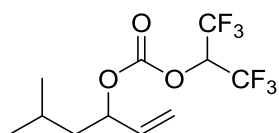
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 5.77 (ddd, $J = 17.6, 10.4, 7.6$ Hz, 1H), 5.53 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.29 (d, $J = 17.2$ Hz, 1H), 5.29 (d, $J = 10.4$ Hz, 1H), 4.89 (t, $J = 7.2$ Hz, 1H), 1.82-1.58 (m, 6H), 1.28-1.07 (m, 3H), 1.06-0.91 (m, 2H).

¹³C-NMR (125 MHz, CDCl₃) δ 152.4 (e), 133.2 (o), 120.3 (e; q, $J_{\text{C-F}} = 280.8$ Hz), 119.6 (e), 86.6 (o), 70.1 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 41.3 (o), 28.3 (e), 28.2 (e), 26.1 (e), 25.73 (e), 25.67 (e).

IR (Neat) 2935 (s), 2859 (s), 1775 (vs), 1648 (w), 1454 (m) cm⁻¹.



1-Isobutylprop-2-en-1-yl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl carbonate (22i).

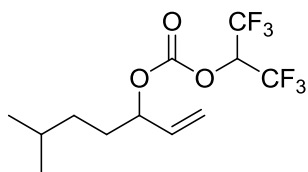
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H NMR (500 MHz, CDCl₃) δ 5.78 (ddd, $J = 17.2, 10.4, 7.0$ Hz, 1H), 5.53 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.33 (d, $J = 17.2$ Hz, 1H), 5.26 (d, $J = 10.4$ Hz, 1H), 5.18 (brq, $J = 6.8$ Hz, 1H), 1.73-1.62 (m, 2H), 1.46 (sept, $J = 6.0$ Hz, 1H), 0.92 (d, $J = 6.0$ Hz, 6H).

¹³C NMR (125 MHz, CDCl₃) δ 152.35 (e), 134.96 (o), 120.27 (e; q, $J_{\text{C-F}} = 280.9$ Hz), 118.71 (e), 81.12 (o), 70.07 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 42.82 (e), 24.34 (o), 22.49 (o), 22.18 (o).

IR (Neat) 2966, 2877, 1772, 1651, 1472 cm⁻¹.



1,1,1,3,3,3-hexafluoropropan-2-yl 6-methylhept-1-en-3-yl carbonate (22j)

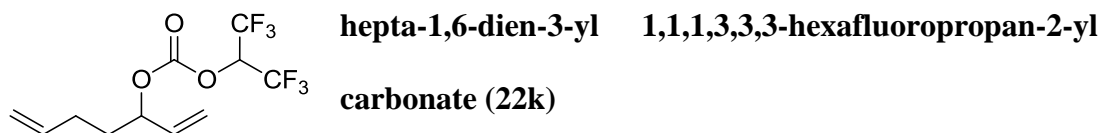
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 5.80 (ddd, $J = 17.3, 10.5, 7.0$ Hz, 1H), 5.55 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.35 (d, $J = 17.3$ Hz, 1H), 5.29 (d, $J = 10.5$ Hz, 1H), 5.10 (brq, $J = 6.8$ Hz, 1H), 1.80-1.64 (m, 2H), 1.56 (sept, $J = 6.0$ Hz, 1H), 1.32-1.17 (m, 2H), 0.89 (d, $J = 7.0$ Hz, 1H).

¹³C-NMR (125 MHz, CDCl₃) δ 152.32 (e), 135.04 (o), 120.25 (e; q, $J_{\text{C-F}} = 280.9$ Hz), 119.16 (e), 80.87 (o), 70.14 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 42.80 (e), 38.22 (e) 24.33 (o), 22.47 (o), 22.21 (o).

IR (Neat) 2966, 2877, 1770, 1654, 1470 cm⁻¹.



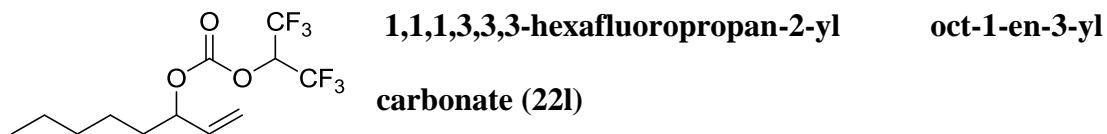
Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 5.85-5.75 (m, 2H), 5.55 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.35 (d, $J = 17.3$ Hz, 1H), 5.30 (d, $J = 10.7$ Hz, 1H), 5.15 (brq, $J = 6.9$ Hz, 1H), 2.14 (brq, $J = 7.3$ Hz, 2H), 1.93-1.86 (m, 1H), 1.80-1.73 (m, 1H).

¹³C-NMR (125 MHz, CDCl₃) δ 152.24 (e), 136.72 (o), 134.46 (o), 120.30 (e; q, $J_{\text{C-F}} = 280.9$ Hz), 119.21 (e), 119.04 (e), 81.60 (o), 70.11 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 33.00 (e), 29.01 (e).

IR (Neat) 2966, 2877, 1770, 1654, 1470, 1425 cm⁻¹.



Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 5.80 (ddd, $J = 17.2, 10.7, 7.0$ Hz, 1H), 5.55 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.34 (d, $J = 17.2$ Hz, 1H), 5.28 (d, $J = 10.7$ Hz, 1H), 5.13 (brq, $J = 6.8$ Hz, 1H), 1.80-1.73 (m, 1H), 1.70-1.63 (m, 1H), 1.39-1.27 (m, 6H), 0.88 (t, $J = 6.9$ Hz, 3H).

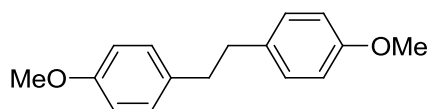
¹³C-NMR (125 MHz, CDCl₃) δ 152.5 (e), 134.84 (o), 120.31 (e; q, $J_{\text{C-F}} = 280.9$ Hz), 118.91 (e), 82.74 (o), 70.16 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 34.13 (e), 31.50 (e), 24.57 (e), 22.62 (e), 14.09 (o).

IR (Neat) 2975, 1770, 1648, 1473, cm⁻¹.

3.2.1.6. Representative Experimental Procedure for the preparation of benzyl Grignard Grignard General method for the preparation of benzyl Grignard Reagents.

A 100ml round bottom flask equipped with an addition funnel and stirrer bar, was charged with magnesium turnings (2.88g, 120mmol) and flame dried under vacuum. The flask was allowed to cool before being backfilled with argon. The magnesium turnings were then covered with 5ml of anhydrous diethyl ether and 1,2-dibromoethane (100 μ l, 0.2mmol) was added *via* a syringe. The resulting solution was stirred for *ca.* 30 minutes until ethylene evanescence ceased. The addition funnel was then charge with benzyl bromide (3.42g 20mmol) in anhydrous diethyl ether (25 ml). The bromide solution was then added dropwise to the vigorously stirring magnesium turnings over 120 minutes. Once the addition was complete the resultant grey solution was sealed under argon and stored in a fridge until required.

3.2.1.7. Spectral Data for the Wurtz Coupled of *Para*-Methoxy-Benzyl Bromide



1,2-Bis(4-methoxyphenyl)ethane (31).

Colour and State: White solid mp = 125-126 °C

All spectral data matched the published values.¹¹

¹H-NMR (500 MHz, CDCl₃) δ 2.83 (s, 4H), 3.79 (s, 6H), 6.82 (d, J = 8.7 Hz, 4H), 7.09 (d, J = 8.4 Hz, 4H).

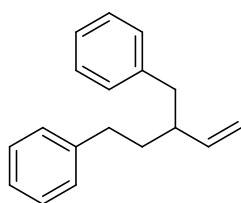
¹³C-NMR (500 MHz, CDCl₃) 157.82 (e), 134.03 (e), 129.40 (o), 113.73 (o), 55.24 (o), 37.19 (e).

IR (Neat) 3010, 2932, 1610, 1508, 1463, 1242, 1174, 1029, 830 cm⁻¹.

3.2.1.8. Representative experimental procedure for the regioselective rhodium-catalysed allylic benzylation.

TpRh(C₂H₄)₂ (3.7 mg, 0.01 mmol) and dibenzylidenacetone (4.7 mg, 0.02 mmol) were dissolved in anhydrous diethyl ether (3 mL) at room temperature and then stirred for ca. 1 h before being cooled to 0 °C. Zinc iodide (32 mg, 0.1 mmol) was dissolved in anhydrous diethyl ether (0.560 mL) and benzylmagnesiumbromide (0.440 mL, 0.3 mmol, 0.667 M) was then added dropwise at room temperature to the zinc iodide solution. The resulting mixture was stirred for ca. 45 min before being cooled to 0°C. The catalyst solution was then added to the organozinc solution *via* Telfon[®] cannula, followed by immediate addition of the allylic carbonate **22a** (35.6 mg, 0.1 mmol) *via* a tared 100 µl gastight syringe. The resulting reaction mixture was then stirred at 0 °C for 15 min (TLC control). The reaction mixture was then quenched (aq NH₄Cl) and partitioned between saturated aqueous NH₄Cl solution and petroleum ether (30-40 °C). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated in *vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0/100-2/98 dichloromethane/petroleum ether (30-40°C)) furnished the 3-benzyl propenyl derivatives **23a** (22.4 mg, 95%) as a colourless oil.

3.2.1.9. Spectral Data for Benzylated products 23a-l.



(3-benzylpent-4-en-1-yl)benzene (23a)

Colour and State: Colourless oil.

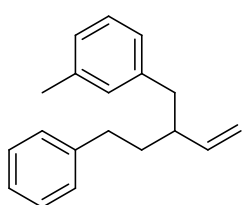
¹H-NMR (500 MHz, CDCl₃) δ 7.31-7.12 (M, 10H), 5.68 (ddd, *J* = 17.2, 10.2, 8.6 Hz, 1H), 5.02 (dd, *J* = 10.2, 1.3 Hz, 1H), 4.93 (d, *J* = 17.2, 1.3, 0.6 Hz, 1H), 2.73-

2.63 (m, 3H), 2.53 (ddd, $J = 13.8, 10.3, 6.5$ Hz, 1H), 2.39-2.33 (m, 1H), 1.77 (dddd, $J = 13.4, 10.6, 6.5, 4.1$ Hz, 1H), 1.62-1.55 (m, 1H).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 142.61 (e), 138.94 (o), 138.65 (e), 129.41 (o), 128.81 (o), 128.31 (o), 127.80 (o), 126.23 (o), 125.84 (o), 115.17 (e), 42.10 (e), 40.36 (o), 35.65 (e), 34.90 (e).

IR (Neat) 3026, 2921, 2854, 1639, 1607, 1496, 1454 cm^{-1} .

HRMS (ESI[M+Na] $^+$) calcd for $\text{C}_{18}\text{H}_{20}\text{Na}$ 259.1463, found 259.1467.



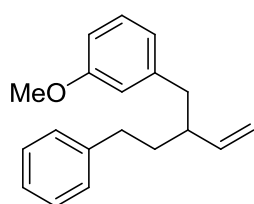
1-methyl-3-[2-(2-phenylethyl)but-3-en-1-yl]benzene (23b).

Colour and State: Colourless oil.

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.31-7.121(M, 9H), 5.68 (ddd, $J = 17.2, 10.2, 8.6$ Hz, 1H), 5.03 (dd, $J = 10.2, 1.3$ Hz, 1H), 4.93 (d, $J = 17.2, 1.3, 0.6$ Hz, 1H), 2.73-2.63 (m, 3H), 2.53 (ddd, $J = 13.8, 10.3, 6.5$ Hz, 1H), 2.39-2.33 (m, 1H), 2.32 (s, 3H), 1.77 (dddd, $J = 13.4, 10.6, 6.5, 4.1$ Hz, 1H), 1.62-1.55 (m, 1H);

IR (Neat) 3026(w), 2921(w), 2854(w), 1639(w), 1607(m), 1496(m), 1454(m), 1419(w), 1377(w), 1171(w), 1031(m), 995(w), 912(m), 778(m), 738(m), 697(s)

HRMS (ESI[M+Na] $^+$) calcd for $\text{C}_{19}\text{H}_{22}\text{Na}$ 273.1619, found 273.1622.



1-methoxy-3-[2-(2-phenylethyl)but-3-en-1-yl]benzene (23c)

Colour and State: Colourless oil.

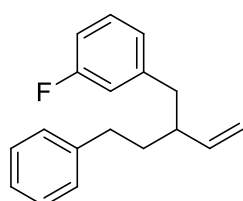
$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.27-7.24 (m, 1H), 7.19-7.13 (m, 4H), 6.73-6.67 (m, 3H), 5.67 (ddd, $J = 17.2, 10.2, 8.6$ Hz, 1H), 5.03 (dd, $J = 10.2, 1.3$ Hz, 1H), 4.97-4.93 (m, 1H), 3.78 (s, 3H), 2.72-2.60 (m, 3H), 2.52 (ddd, $J = 13.8, 10.3, 6.5$ Hz, 1H), 2.39-2.31 (m, 1H), 1.77 (dddd, $J = 13.4, 10.6, 6.5, 4.1$ Hz, 1H), 1.61-1.53 (m, 1H).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 159.34 (e), 142.60 (e), 142.52 (e), 138.88 (o), 129.50

(o), 128.57 (o), 128.10 (o), 125.76 (o), 121.76 (o), 115.14 (o), 114.37 (e), 110.07 (o), 55.13 (o), 45.04 (o), 41.84 (e), 35.76 (e), 33.45 (e).

IR (Neat) 3026, 2919, 2853, 1638, 1601, 1584, 1489, 1454 cm^{-1} .

HRMS (ESI[M+Na]⁺) calcd for C₁₉H₂₂NaO 289.1568, found 289.1564.



1-fluoro-3-[2-(2-phenylethyl)but-3-en-1-yl]benzene (23d)

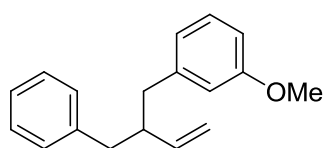
Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.32-7.14 (m, 6H), 6.91-6.82 (m, 3H), 5.64 (ddd, $J = 17.4, 10.4, 8.8$ Hz, 1H), 5.04 (dd, $J = 10.4, 1.6$ Hz, 1H), 4.94 (d, $J = 17.4$ Hz, 1H), 2.73-2.61 (m, 3H), 2.56-2.50 (m, 1H), 2.38-2.30 (m, 1H), 1.79-1.72 (m, 1H), 1.63-1.56 (m, 1H).

¹³C-NMR (125 MHz, CDCl₃) δ 162.70 (e; d, $J_{\text{C-F}} = 279.7$ Hz), 142.60 (e), 141.71 (o), 140.20 (e; d, $J = 8.4$), 129.56 (o; d, $J_{\text{C-F}} = 8.6$ Hz), 128.53 (o), 128.46 (o), 125.87 (o), 125.08 (o; d, $J_{\text{C-F}} = 2.3$ Hz), 116.15 (o; d, $J_{\text{C-F}} = 20.9$ Hz), 115.72 (e), 112.85 (o; d, $J_{\text{C-F}} = 21.1$ Hz), 45.19 (o), 41.67(e), 35.99 (e), 33.56 (e).

IR (Neat) 3026, 2919, 2853, 1638, 1601, 1584, 1489, 1454, 1110 cm^{-1} .

HRMS (ESI[M+Na]⁺) calcd for C₁₈H₁₉FNa 277.1368, found 277.1372.



1-(2-benzylbut-3-enyl)-3-methoxybenzene (23e).

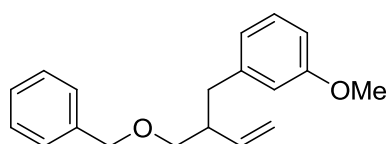
Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.28-7.25 (m, 1H), 7.20-7.13 (m, 4H), 6.75-6.69 (m, 3H), 5.77 (ddd, $J = 17.3, 10.2, 7.0$ Hz, 1H), 4.90 (dd, $J = 10.2, 1.2$ Hz, 1H), 4.80 (d, $J = 17.3$ Hz, 1H), 3.79 (s, 3H), 2.75-2.58 (m, 5H).

¹³C-NMR (125 MHz, CDCl₃) δ 159.34 (e), 142.60 (e), 142.52 (e), 138.88 (o), 129.50 (o), 128.57 (o), 128.10 (o), 125.76 (o), 121.76 (o), 115.14 (o), 114.37 (e), 110.07 (o), 55.13 (o), 45.04 (o), 42.56 (e), 41.84 (e).

IR (Neat) 3026, 2919, 2834, 1640, 1601, 1584, 1488, 1454 cm⁻¹

HRMS (ESI[M+Na]⁺) calcd for C₁₈H₂₀NaO 275.1412, found 275.1410.



1-(2-(benzyloxymethyl)but-3-enyl)-3-

methoxybenzene (23f)

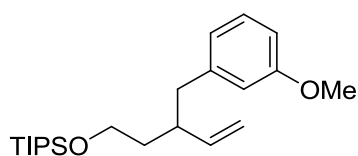
Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.28-7.25 (m, 1H), 7.20-7.13 (m, 5H), 6.75-6.69 (m, 3H), 5.78 (ddd, *J* = 17.3, 10.3, 7.3 Hz, 1H), 5.04-5.00 (m, 2H), 4.51 (s, 2H), 3.79 (s, 3H), 3.42 (d, *J* = 5.7 Hz, 2H), 2.85 (dd, A of ABM, *J*_{AB} = 12.4 Hz, *J*_{AM} = 5.5 Hz, 1H), 2.70-2.60 (m, 2H).

¹³C-NMR (125 MHz, CDCl₃) δ 159.34 (e), 142.60 (e), 142.52 (e), 139.88 (o), 129.50 (o), 128.57 (o), 128.10 (o), 125.76 (o), 121.76 (o), 115.14 (o), 115.02 (e) 110.07 (o), 80.02 (e), 74.50 (e), 55.13 (o), 45.04 (o), 41.84 (e).

IR (Neat) 3032, 2925, 2827, 1640, 1601, 1574, 1484, 1447 cm⁻¹.

HRMS (ESI[M+Na]⁺) calcd for C₁₉H₂₂NaO₂ 305.1517, found 305.1520.



triisopropyl(3-(3-methoxybenzyl)pent-4-

enyloxy)silane (23g)

Colour and State: Colourless oil.

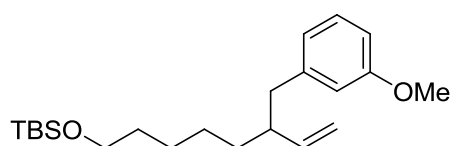
¹H-NMR (500 MHz, CDCl₃) δ 7.18 (t, *J* = 7.2, 1H), 6.74-6.69 (m, 3H), 5.64 (ddd, *J* = 17.3, 10.3, 8.9 Hz, 1H), 4.94 (dd, *J* = 10.3, 1.8 Hz, 1H), 4.92-4.89 (m, 1H), 3.79 (s, 3H), 3.73-3.68 (m, 1H), 3.66-3.61 (m, 1H), 2.67 (dd, A of ABM, *J*_{AB} = 13.4 Hz, *J*_{AM}

= 6.7 Hz, 1H), 2.59 (dd, B of ABM, $J_{AB} = 13.4$ Hz, $J_{BM} = 7.8$ Hz, 1H), 2.55-2.48 (m, 1H), 1.73-1.60 (m, 2H), 1.52-1.45 (m, 1H).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 159.49 (e), 142.64 (e), 142.49 (o), 129.13 (o), 121.93 (o), 115.23 (o), 114.78 (e), 111.09 (o), 63.36 (e), 55.29 (o), 45.05 (o), 43.04 (e), 34.02 (e), 18.0 (o), 12.2 (o).

IR (Neat) 3040, 2932, 2827, 1645, 1601, 1574, 1484, 1447 cm^{-1} .

HRMS (ESI[M+Na] $^+$) calcd for $\text{C}_{22}\text{H}_{38}\text{NaO}_2\text{Si}$ 385.2539, found 385.2542.



***tert*-butyl(6-(3-methoxybenzyl)oct-7-enyloxy)dimethylsilane (23h)**

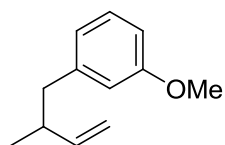
Colour and State: Colourless oil.

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.18 (t, $J = 7.2$, 1H), 6.74-6.69 (m, 3H), 5.59 (ddd, $J = 17.2, 10.3, 8.6$ Hz, 1H), 4.94 (dd, $J = 10.3, 1.8$ Hz, 1H), 4.88 (dd, $J = 17.2, 1.4$ Hz, 1H), 3.79 (s, 3H), 3.57 (t, $J = 6.6$ Hz, 2H), 2.62 (dd, A of ABM, $J_{AB} = 13.5$ Hz, $J_{AM} = 6.8$ Hz, 1H), 2.57 (dd, B of ABM, $J_{AB} = 13.5$ Hz, $J_{BM} = 7.5$ Hz, 1H), 2.32-2.25 (m, 1H), 1.53-1.20 (m, 8H), 0.88 (s, 9H), 0.03 (s, 6H).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 159.53 (e), 142.52 (e), 142.49 (o), 129.13 (o), 121.93 (o), 115.23 (o), 114.78 (e), 111.09 (o), 63.36 (e), 55.29 (o), 45.71 (o), 42.04 (e), 34.02 (e), 33.02 (e), 32.6 (e), 26.17 (o), 23.53 (e), 18.56 (e), -5.08 (o).

IR (Neat) 3032, 2925, 2827, 1640, 1601, 1574, 1484, 1447 cm^{-1} .

HRMS (ESI[M+Na] $^+$) calcd for $\text{C}_{22}\text{H}_{38}\text{NaO}_2\text{Si}$ 385.2539, found 385.2535.



1-methoxy-3-(2-methylbut-3-enyl)benzene (23i)

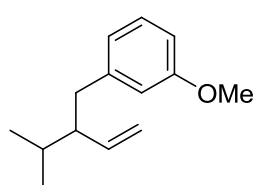
Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.20 (t, *J* = 7.2, 1H), 6.74-6.69 (m, 3H), 5.80 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1H), 4.98-4.91 (m, 2H), 3.79 (s, 3H), 2.67 (dd, A of ABM, *J*_{AB} = 12.8 Hz, *J*_{AM} = 6.3 Hz, 1H), 2.52-2.43 (m, 2H), 0.99 (d, *J* = 6.5 Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃) δ 159.53 (e), 142.52 (e), 141.09 (o), 129.13 (o), 121.93 (o), 115.23 (o), 114.78 (e), 111.09 (o), 55.29(o), 44.98(o), 42.30 (e), 23.01(o).

IR (Neat) 3032, 2925, 2827, 1640, 1601, 1574, 1484, 1447 cm⁻¹.

HRMS (ESI[M+Na]⁺) calcd for C₁₂H₁₆NaO 199.1099, found 199.1102.



1-(2-isopropylbut-3-enyl)-3-methoxybenzene (23j).

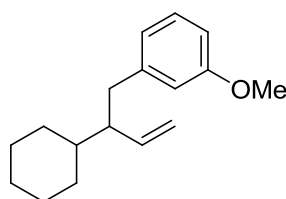
Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.17 (t, *J* = 7.9 Hz, 1H), 6.75-6.69 (m, 3H), 5.64 (dt, *J* = 17.3, 10.5 Hz, 1H), 4.97 (dd, *J* = 10.5, 1.7 Hz, 1H), 4.83 (d, *J* = 17.3 Hz, 1H), 3.79 (s, 3H), 2.74 (dd, A of ABM, *J*_{AB} = 13.6 Hz, *J*_{AM} = 6.5 Hz, 1H), 2.55 (dd, B of ABM, *J*_{AB} = 13.6 Hz, *J*_{AM} = 8.9 Hz, 1H), 2.19-2.13 (M, 1H), 1.66 (octet, *J* = 6.9 Hz 1H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H)

¹³C-NMR (125 MHz, CDCl₃) δ 159.36 (e) 142.88 (e), 139.54 (o), 128.94 (o), 121.68 (o), 115.87 (e), 115.05 (o), 110.77 (o), 55.12 (o), 51.88 (o), 38.74 (e), 30.62 (o), 20.95 (o), 18.15 (o).

IR (Neat) 2957, 2872, 2834, 1637, 1602, 1584, 1488, 1455, 1437 cm⁻¹.

HRMS (ESI[M+Na]⁺) calcd for C₁₄H₂₀NaO 227.1412, found 227.1410.



1-(2-cyclohexylbut-3-enyl)-3-methoxybenzene (23k).

Colour and State: Colourless oil.

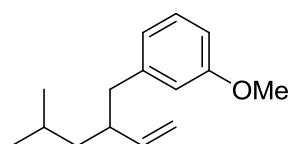
¹H-NMR (500 MHz, CDCl₃) δ 7.17 (t, *J* = 7.8 Hz, 1H), 6.75-6.69 (m, 3H), 5.63 (dt, *J* = 17.2, 9.7 Hz, 1H), 4.93 (dd, *J* = 9.7, 2.0 Hz, 1H), 4.79 (ddd, *J* = 17.3, 2.0, 0.9 Hz,

1H), 3.79 (s, 3H), 2.79 (dd, A of ABX, $J_{AB} = 13.5$ Hz, $J_{AX} = 5.7$ Hz, 1H), 2.55 (dd, B of ABX, $J_{AB} = 13.5$ Hz, $J_{AX} = 8.9$ Hz, 1H), 2.18-2.12 (M, 1H), 1.79-1.61 (m, 5H), 1.45-0.88 (m, 6H).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 159.36 (e) 142.97 (e), 140.32 (o), 128.91 (o), 121.73 (o), 115.50 (e), 115.05 (o), 110.78 (o), 55.12 (o), 51.63 (o), 41.08 (o), 38.49 (e), 31.24 (e), 29.10 (e), 26.72 (e), 26.66 (e) 26.62 (e).

IR (Neat) 3068, 2922, 2851, 1636, 1601, 1584, 1488, 1450 cm^{-1} .

HRMS (ESI[M+Na] $^+$) calcd for $\text{C}_{17}\text{H}_{24}\text{NaO}$ 267.1725, found 267.1715.



1-methoxy-3-(4-methyl-2-vinylpentyl)benzene (23l).

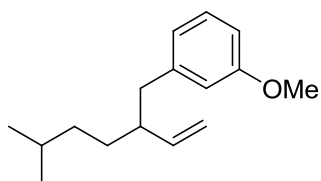
Colour and State: Colourless oil.

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.18 (t, $J = 7.9$ Hz, 1H), 6.79-6.70 (m, 3H), 5.64 (ddd, $J = 17.3, 10.4, 8.6$ Hz, 1H), 4.93 (dd, $J = 10.4, 1.8$ Hz, 1H), 4.88 (dd, $J = 17.3, 1.8$ Hz, 1H), 3.8 (s, 3H), 2.62 (dd, A of ABM, $J_{AB} = 13.6$ Hz, $J_{AM} = 6.6$ Hz, 1H), 2.54 (dd, B of ABM, $J_{AB} = 13.6$ Hz, $J_{BM} = 7.8$ Hz, 1H), 2.43-2.36 (M, 1H), 1.67-1.59 (m, 1H), 1.27-1.15 (m, 2H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.83 (d, $J = 6.8$ Hz, 3H).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 159.35 (e), 142.54 (o), 142.31 (e), 128.91 (o), 121.80 (o), 115.14 (o), 114.37 (e), 110.88 (o), 55.13 (o), 43.71 (e), 43.38 (o), 42.33 (e), 25.30 (o), 23.61 (o), 21.63 (o)

IR (Neat) 2954, 2923, 2869, 1641, 1602, 1585, 1489, 1466, 1454, 1437 cm^{-1} .

HRMS (ESI[M+Na] $^+$) calcd for $\text{C}_{15}\text{H}_{22}\text{NaO}$ 241.1568, found 241.1575.



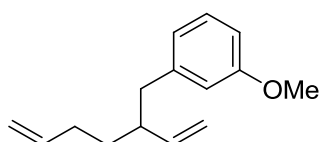
1-methoxy-3-(5-methyl-2-vinylhexyl)benzene (23n)

Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.18 (t, *J* = 7.9 Hz, 1H), 6.79-6.70 (m, 3H), 5.59 (ddd, *J* = 17.2, 10.4, 8.6 Hz, 1H), 4.93 (dd, *J* = 10.4, 1.9 Hz, 1H), 4.86 (dd, *J* = 17.2, 1.2 Hz, 1H), 3.79 (s, 3H), 2.63 (dd, A of ABM, *J*_{AB} = 13.5 Hz, *J*_{AM} = 6.6 Hz, 1H), 2.54 (dd, B of ABM, *J*_{AB} = 13.5 Hz, *J*_{BM} = 7.7 Hz, 1H), 2.28-2.20 (m, 1H), 1.53-1.67-1.59 (m, 2H), 1.27-1.08 (m, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H).

IR (Neat) 2954, 2867, 2830, 1625, 1602, 1584, 1488, 1455, 1437 cm⁻¹.

HRMS (ESI[M+Na]⁺) calcd for C₁₆H₂₄NaO 255.1725, found 255.1733.

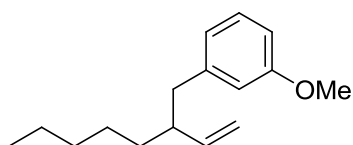


1-methoxy-3-(2-vinylhex-5-enyl)benzene (23m)

Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.18 (t, *J* = 7.9 Hz, 1H), 6.79-6.70 (m, 3H), 5.78 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.61 (ddd, *J* = 17.2, 10.4, 8.6 Hz, 1H), 5.01-4.90 (m, 4H), 3.79 (s, 3H), 2.65 (dd, A of ABM, *J*_{AB} = 13.6 Hz, *J*_{AM} = 6.9 Hz, 1H), 2.61 (dd, B of ABM, *J*_{AB} = 13.6 Hz, *J*_{BM} = 7.6 Hz, 1H), 2.17-1.96 (m, 3H), 1.56-1.49 (m, 1H), 1.40-1.30 (m, 1H).

HRMS (ESI[M+Na]⁺) calcd for C₁₅H₂₀NaO 239.1412, found 239.1422.



1-methoxy-3-(2-vinylheptyl)benzene (23o)

Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.18 (t, *J* = 7.9 Hz, 1H), 6.75-6.69 (m, 3H), 5.60 (ddd, *J* = 17.2, 10.3, 8.6 Hz, 1H), 4.93 (d, *J* = 10.3, 1.9 Hz, 1H), 4.90-4.86 (m, 1H), 3.79 (s, 3H), 2.63 (dd, A of ABM, *J*_{AB} = 13.5 Hz, *J*_{AM} = 6.7 Hz, 1H), 2.61 (dd, B of ABM, *J*_{AB} = 13.5 Hz, *J*_{BM} = 7.6 Hz, 1H), 2.32-2.25 (m, 1H), 1.42-1.20 (m, 8H), 0.87 (t, *J* = 7.2 Hz, 3H).

IR (Neat) 2960, 2870, 2834, 1640, 1602, 1584, 1488, 1455, 1437 cm⁻¹.

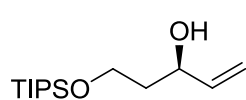
HRMS (ESI[M+Na]⁺) calcd for C₁₆H₂₄NaO 255.1725, found 255.1730.

3.2.2. Stereospecific Rhodium-Catalysed Benzylation of Unsymmetrical Fluorinated Acyclic Allylic Carbonates.

3.2.2.1. Representative experimental procedure for the Kinetic resolution of 5-(triisopropylsilyloxy)pent-1-en-3-ol.

To a solution of (*RS*)-5-(triisopropylsilyloxy)pent-1-en-3-ol (**29d**) (1.29 g, 5 mmol) in toluene (10 mL) were added vinyl acetate (0.43 g, 5 mmol) and Novozyme 435 (100 mg). The reaction mixture was stirred at ambient temperature for 24 h and monitored by TLC at regular intervals. The reaction was stopped at 54 % conversion, as determined by ¹H NMR of the reaction mixture, by filtering the enzyme on a sintered glass funnel. The filtrate was concentrated in *vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0/100-2/98 diethyl ether/petroleum ether (30-40°C)) furnished the allylic alcohol (**R-29d**).

3.2.2.2. Spectre Data for (*R*)-5-(triisopropylsilyloxy)pent-1-en-3-ol (**R-29d**).



(*R*)-5-(triisopropylsilyloxy)pent-1-en-3-ol (R-29d**).**

Colour and State: Yellow oil.

All spectral data matched the published values.¹²

¹H-NMR (500 MHz, CDCl₃) δ 5.81 (ddd, *J* = 18.2, 10.5, 5.9 Hz, 1H), 5.21 (d, *J* = 18.2 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 1H), 4.31 (m, 1H), 3.92 (m, 1H), 3.83(m, 1H), 3.52 (s, 1H), 1.70 (m, 2H), 1.02 (m, 21H).

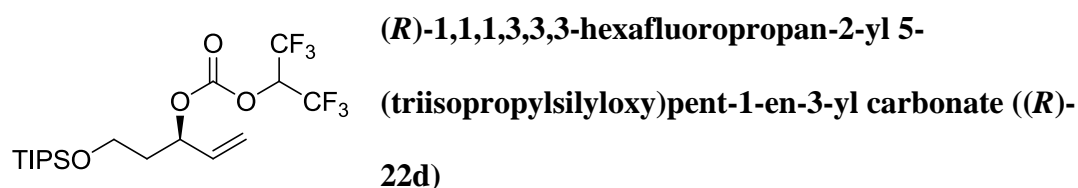
¹³C NMR (125 MHz, CDCl₃) δ 140.80 (o), 114.17 (e), 72.63 (o), 62.53 (e), 38.55 (e), 18.00 (o), 12.17 (o).

IR (Neat) 3410, 2930, 2885, 1100 cm⁻¹.

The enantiomeric excess was determined to be >99% by HPLC (Chiralcel OD-H, 0.4% iPrOH in hexane, 220 nm, flow rate 1 mL/ min): (*major*)-isomer t_R 23.46 min, (*minor*)-isomer t_R 37.84 min:

$$[\alpha]_D^{25} = -10.65 \text{ (c, 1.95, CHCl}_3\text{)}$$

3.2.2.3. Spectre Data for Enantiomerically enriched carbonates (*R*)-22d and (*S*)-22f



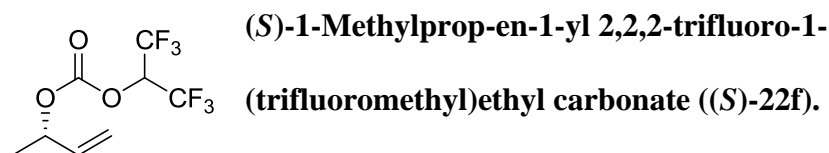
Colour and State: Colourless oil.

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 5.85 (ddd, $J = 17.3, 10.4, 6.8$ Hz, 1H), 5.53 (sept, $J_{\text{H-F}} = 6.0$ Hz, 1H), 5.43-5.35 (m, 2H), 5.29 (d, $J = 10.4$ Hz, 2H), 3.82-3.72 (m, 2H), 2.02-1.95 (m, 1H), 1.92-1.85 (m, 1H), 1.05 (s, 18H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 152.31 (e), 134.78 (o), 120.3 (e; q, $J_{\text{C-F}} = 280.9$ Hz), 118.86 (e), 79.41 (o), 70.1 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 58.76 (e), 37.33 (e), 18.0 (o), 12.2 (o).

IR (Neat) 2934, 2861, 1777, 1650, 1473, 1464 cm^{-1} .

$$[\alpha]_D^{25} = +17.20 \text{ (c, 1.95, CHCl}_3\text{)}.$$



Colour and State: Colourless oil.

All spectral data matched the published values.¹⁰

¹H-NMR (500 MHz, CDCl₃) δ 5.85 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.53 (sept, *J*_{H-F} = 6.0 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.25 (brquin, *J* = 6.4 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 1.43 (d, *J* = 6.4 Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃) δ 152.1 (e), 135.6 (o), 120.3 (e; q, *J*_{C-F} = 280.8 Hz), 117.9 (e), 78.5 (o), 70.1 (o; sept, *J*_{C-F} = 34.9 Hz), 19.7 (o).

IR (Neat) 2991, 1775, 1651, 1455, cm⁻¹.

The enantiomeric excess was determined to be ≥99% chiral GLC on the corresponding methyl carbonate using an Astec CHIRALDEXTM G-TA column.

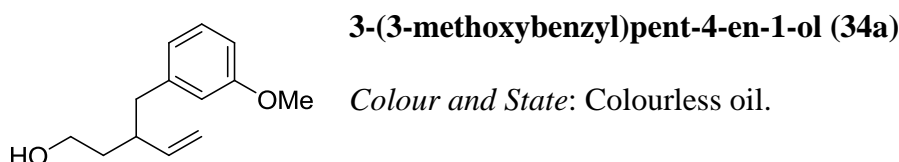
[α]_D²⁰ = -15.7 (c, 0.56, CHCl₃).

3.2.2.4. Representative experimental procedure for the stereospecific rhodium-catalysed allylic alkylation.

TpRh(C₂H₄)₂ (3.7 mg, 0.01 mmol) and dibenzylidenacetone (4.7 mg, 0.02 mmol) were dissolved in anhydrous diethyl ether (3 mL) at room temperature and then stirred for ca. 1 h before being cooled to -20 °C. Zinc chloride (1M, in diethyl ether, 0.1ml, 0.1 mmol) was dissolved in anhydrous diethyl ether (0.560 mL) and benzyl magnesium bromide (0.440 mL, 0.3 mmol, 0.667 M) was then added dropwise at room temperature to the zinc chloride solution. The resulting mixture was stirred for ca. 45 min before being cooled to -20 °C. The catalyst solution was then added to the organozinc solution *via* Telfon[®] cannula, followed by immediate addition of the allylic carbonate (**R**)-**22d** (45.0 mg, 0.1 mmol) *via* a tared 100 μl gastight syringe. The resulting reaction mixture was then stirred at -20 °C for 45 min (TLC control). The reaction mixture was then quenched (aq NH₄Cl) and partitioned between saturated aqueous NH₄Cl solution and petroleum ether (30-40 °C). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated in *vacuo* to afford a

crude oil. The crude oil was then redissolved in tetrahydrofuran (1 ml), and tetra-*n*-butylammonium fluoride (1.0 M in THF, 0.6 ml, 0.6 mmol) was added *via* a syringe. The resultant solution was then allowed to stir at ambient temperature for 18 hours (TLC control). The reaction was then quenched (water), and partitioned between water and diethyl ether. The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated in *vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0/100-10/90 diethyl ether and petroleum ether (30-40°C)) furnished the primary alcohol **34a** (22.4 mg, 95%) as a colourless oil.

3.2.2.5. Spectral Data for Benzylated products 34a-c and (S)-41.



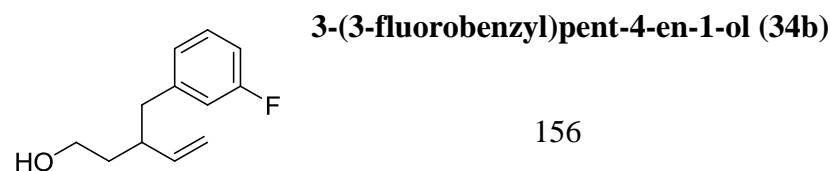
¹H-NMR (500 MHz, CDCl₃) δ 7.19 (t, *J* = 7.2, 1H), 6.75-6.70 (m, 3H), 5.65 (ddd, *J* = 17.0, 10.2, 8.7 Hz, 1H), 5.00-4.95 (m, 2H), 3.79 (s, 3H), 3.70-3.65 (m, 1H), 3.63-3.59 (m, 1H), 2.67-2.60 (m, 2H), 2.51-2.44 (m, 1H), 1.75-1.68 (m, 1H), 1.54-1.47 (m, 1H).

¹³C-NMR (125 MHz) δ 159.29 (e), 142.05 (e), 138.49 (o), 129.20 (o), 121.93 (o), 115.88 (o), 114.89 (e), 111.09 (o), 68.36 (e), 55.15 (o), 45.05 (o), 43.04 (e), 36.02 (e).

IR (Neat) 3361, 3075, 2960, 1600, 1488, 1316, 1157, 1041, 916 cm⁻¹.

HRMS (ESI[M+Na]⁺) calcd for C₁₃H₁₈NaO₂ 229.1204, found 229.1222.

The enantiomeric excess was determined to be 65% by HPLC (Chiralcel OD, 5% iPrOH in hexane, 220 nm, flow rate 1 mL/ min): (*minor*)-isomer *t_R* min, (*major*)-isomer *t_R* min.



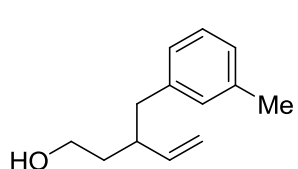
Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.32-7.14 (m, 1H), 6.91-6.82 (m, 3H), 5.64 (dt, *J* = 17.2, 10.0 Hz, 1H), 5.01 (d, *J* = 10.0 Hz, 1H), 4.96 (d, *J* = 17.0 Hz, 1H), 3.74-3.69 (m, 1H), 3.67-3.62 (m, 1H), 2.69 (dd, A of ABM, *J*_{AB} = 13.4 Hz, *J*_{AM} = 6.7 Hz, 1H), 2.63 (dd, B of ABM, *J*_{AB} = 13.4 Hz, *J*_{BM} = 7.6 Hz, 1H), 2.50-2.43 (m, 1H), 1.77-1.70 (m, 1H), 1.57-1.50 (m, 1H).

¹³C-NMR δ 162.70 (e; d, *J*_{C-F} = 279.7 Hz), 141.71 (o), 140.20 (e; d, *J* = 8.4), 129.56 (o; d, *J*_{C-F} = 8.6 Hz), 125.08 (o; d, *J*_{C-F} = 2.3 Hz), 116.15 (o; d, *J*_{C-F} = 20.9 Hz), 115.72 (e) 112.85 (o; d, *J*_{C-F} = 21.1 Hz).

HRMS (ESI[M+Na]⁺) calcd for C₁₂H₁₅FNaO 217.1005, found 217.1025.

The enantiomeric excess was determined to be 69% by HPLC (Chiralcel OD, 5% iPrOH in hexane, 220 nm, flow rate 1 mL/ min): (*major*)-isomer *t*_R min, (*minor*)-isomer *t*_R min.



3-(3-methylbenzyl)pent-4-en-1-ol (34c)

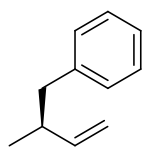
Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.16 (t, *J* = 7.6 Hz, 1H), 7.00-6.93 (m, 3H), 5.66 (dt, *J* = 17.3, 10.1 Hz, 1H), 5.00-4.95 (m, 2H), 3.70-3.58 (m, 2H), 2.66-2.59 (m, 2H), 2.50-2.43 (m, 1H), 2.32 (s, 3H), 1.74-1.68 (m, 1H), 1.54-1.47 (m, 1H).

IR (Neat) 3342, 3027, 2962, 1637, 1452, 1029, 913, 701 cm⁻¹.

HRMS (ESI[M+Na]⁺) calcd for C₁₃H₁₈NaO 213.1255, found 213.1270.

The enantiomeric excess was determined to be 44% by HPLC (Chiralcel OD, 5% iPrOH in hexane, 220 nm, flow rate 1 mL/ min): (*Major*)-isomer *t*_R min, (*minor*)-isomer *t*_R min.



(S)-(2-methylbut-3-enyl)benzene ((S)-41)

Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.20-7.00 (m, 5H), 5.85 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1H), 4.98-4.91 (m, 2H), 2.60 (dd, A of ABM, *J*_{AB} = 12.8 Hz, *J*_{AM} = 6.3 Hz, 1H), 2.48-2.40 (m, 2H), 0.99 (d, *J* = 6.5 Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃) δ 138.87 (o), 138.62 (e), 129.38 (o), 128.82 (o), 126.23 (o), 115.27 (e), 44.45(o), 42.30 (e), 22.31(o).

IR (Neat) 3032, 2925, 2827, 1640, 1601, 1574, 1484, 1447 cm⁻¹.

HRMS (ESI[M+Na]⁺) calcd for C₁₁H₁₄Na 169.0993, found 169.0985.

[α]_D²⁰ = -1.7 (c, 0.25, CHCl₃).

3.2.2.6. Representative for the operationally simple rhodium-catalysed allylic Benzylation.

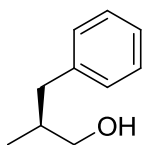
RhCl₃XH₂O (2 mg, 0.01 mmol) and zinc iodide (32 mg, 0.1 mmol) were dissolved in anhydrous diethyl ether (4 mL) at room temperature and then stirred until the zinc salt was fully dissolved (*ca.* 45 minutes). Then a solution of 3-methoxy benzyl magnesium bromide (0.440 mL, 0.3 mmol, 0.667 M) was added *via* a syringe, the resultant brown solution was stirred for 30 minutes before being cooled to 0 °C (ice bath). Allylic carbonate **22a** (35.6 mg, 0.1 mmol) was then added to the cooled reaction mixture *via* a tared 100 μl gastight syringe. The resulting reaction mixture was then stirred at 0 °C for 15 min (TLC control). The reaction mixture was then quenched (aq NH₄Cl) and partitioned between saturated aqueous NH₄Cl solution and petroleum ether (30-40 °C). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated in *vacuo* to afford a crude oil. Purification by flash

chromatography (eluting with 0/100-2/98 dichloromethane/petroleum ether (30-40°C)) furnished the benzylated product **23a** (22.4 mg, 95%) as a colourless oil.

3.2.2.7. Representative Experimental Procedure for the preparation of (S)-2-methyl-3-phenylpropan-1-ol ((S)-42)

To a solution of (S)-(2-methylbut-3-enyl)benzene ((S)-**41**) (10.5 mg, 0.072 mmol) in acetone (0.8 ml) and water (0.2 ml) were added 4-methylmorpholine N-oxide (NMO, 17 mg, 0.145 mmol), and a catalytic amount of OsO₄ (10 µL, 2% wt solution in H₂O). The mixture was then stirred for 2.5 h at room temperature (TLC control). After the addition of Na₂S₂O₄ (20 mg, 0.115 mmol), the mixture was filtered through a Celite pad. The filtrate was diluted with diethyl ether (1 mL), and washed with brine (0.5 mL×2), and dried (Na₂SO₄), filtered, and concentrated in *vacuo* to afford a crude oil. The residue was redissolved in tetrahydrofuran (0.75 ml) and water (0.25ml), then 2 mL of 0.1 M phosphate buffer (pH 7) was added and the resultant solution was cooled to 0 °C (ice bath). Sodium periodate (17.1 mg, 0.08 mmol) was added then added to the cooled solution and the mixture was stirred for 2 h at 0 °C (TLC control). The reaction was diluted with water (5 mL) and extracted with ether (2 × 2.5 mL). The ether extracts were dried (Na₂SO₄) and filtered, the volume was then reduce by half *via* slow rotary evaporation and 1 mL of methanol was added. The resultant solution was cooled to 0 °C (ice bath) and NaBH₄ (6 mg, 0.160mmol) was added, the reaction was stirred at 0 °C for 1 h (TLC control), before being diluted with 2 mL of water and extracted with ether (2 × 5 mL). The ether extracts were dried (Na₂SO₄), filtered, and concentrated in *vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0/100-20/80 diethyl ether/petroleum ether (30-40°C)) furnished the primary alcohol derivative (S)-**42** (8.7 mg, 80% over three steps) as a colourless oil.

3.2.2.8. Spectral Data for (S)-(2-methylbut-3-enyl)benzene ((S)-41)



(S)-(2-methylbut-3-enyl)benzene ((S)-41)

Colour and State: Colourless oil.

All spectral data matched the published values.^{13,14}

¹H-NMR (500 MHz, CDCl₃) δ 7.23 (t, *J* = 7.1 Hz, 2H), 7.14 (d, *J* = 6.9 Hz, 2H), 7.12 (t, *J* = 7.1 Hz, 1H), 3.46 (dd, A of ABM, *J*_{AB} = 10.6 Hz, *J*_{AM} = 5.9 Hz, 1H), 3.40 (dd, B of ABM, *J*_{AB} = 10.6 Hz, *J*_{AM} = 5.9 Hz, 1H), 2.68 (dd, A of ABM, *J*_{AB} = 13.4 Hz, *J*_{AM} = 6.3 Hz, 1H), 2.35 (dd, B of ABM, *J*_{AB} = 13.4 Hz, *J*_{AM} = 8.0 Hz, 1H), 1.92-1.82 (m, 1H), 1.31 (brs, 1H), 0.85 (d, *J* = 6.8 Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃) δ 140.57 (e), 129.03 (o), 128.19 (o), 125.70 (o), 67.44 (e), 39.63 (e), 37.67 (o), 16.37 (o)

IR (Neat) 3332, 3001, 2956, 2922, 2872, 1603, 1495, 1454 cm⁻¹.

The enantiomeric excess was determined to be 70% by HPLC (Chiralcel OD, 5% iPrOH in hexane, 220 nm, flow rate 1 mL/ min): (*S*)-isomer *t*_R 8.5 min (major), (*R*)-isomer *t*_R 10.0 min (minor).

[α]_D²⁵ = -8.7 (c, 4.2, PhH).

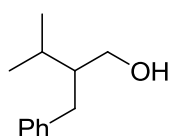
3.2.3. Diastereoselective Rhodium-Catalysed Benzylolation of Unsymmetrical Fluorinated Acyclic Allylic Carbonates.

3.2.3.1. Representative experimental procedure for the Preparation of 2-benzyl-3-methylbutan-1-ol (44).

Methyl isovalerate (2.32 g, 20 mmol) was added dropwise *via* a syringe, to a cooled (-78 °C, dry ice/acetone bath) solution of lithium diisopropylamine (2 M in THF,

12.5 mL, 25 mmol) in tetrahydrofuran (40 mL), under an argon atmosphere. The resultant reaction mixture was allowed to stir for 2 h at $-78\text{ }^{\circ}\text{C}$ (dry ice/acetone bath), before benzyl bromide (2.97 mL, 4.28 g, 25 mmol) was added in one portion. The reaction mixture was then quenched (aq NH_4Cl) and partitioned between saturated aqueous NH_4Cl solution and diethyl ether. The organic layers were combined, dried (MgSO_4), filtered, and concentrated in *vacuo* to afford a crude oil. This crude was then redissolved in dichloromethane (5 mL) and cooled to $-78\text{ }^{\circ}\text{C}$ (dry ice/acetone bath), before DIBAL-H (58.0 mL, 0.95 M in hexane, 55.1 mmol) was added dropwise, under an argon atmosphere. The reaction was allowed to stir for 2 h at $-78\text{ }^{\circ}\text{C}$, before being quenched (aq rochelle's salt, 100 ml). The resultant biphasic mixture was allowed to acclimate to ambient temperature and stir until both phases became clear (*ca* 8 h). The biphasic solution was then partitioned between saturated aqueous rochelle's salt solution and ethyl acetate. The aqueous layer was extracted ethyl acetate ($2 \times 50\text{ mL}$), the combine organic layers were then washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated in *vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0/100-20/80 diethyl ether/petroleum ether ($30\text{-}40^{\circ}\text{C}$)) furnished the primary alcohol derivative **44** (3.39 mg, 95% over 2 steps) as a colourless oil.

3.2.3.2. Spectral Data for 2-benzyl-3-methylbutan-1-ol (**44**)



2-benzyl-3-methylbutan-1-ol (44**)**

Colour and State: Colourless oil.

All spectral data matched the published values.¹⁵

$^1\text{H-NMR}$ (500 MHz, CDCl_3) 7.30-7.27 (m, 2H), 7.20-7.14 (m, 3H), 3.52 (d, $J = 5.7$ Hz, 2H), 2.69 (dd, A of ABM, $J_{AB} = 13.7$ Hz, $J_{Am} = 5.5$ Hz, 1H), 2.50 (dd, B of

ABM, $J_{AB} = 13.7$ Hz, $J_{Am} = 9.2$ Hz, 1H), 1.85 (dq, $J = 9.1, 6.8, 6.8$ Hz, 1 H), 1.65 (m, 1H), 1.47 (brs, 1H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.94 (d, $J = 6.8$ Hz, 3H).

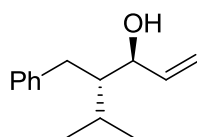
$^{13}\text{C-NMR}$ (125 MHz, CDCl_3) 141.37 (e), 129.02 (o), 128.27 (o), 125.68 (o), 62.82 (e), 48.70 (o), 34.34 (e), 27.60 (o), 19.59 (o), 19.44 (o).

IR (Neat) 3328, 3005, 2950, 2928, 2870, 1603, 1495, 1454 cm^{-1} .

3.2.3.3. Representative experimental procedure for the Preparation of the Anti-Diastereomer of allylic alcohol 45.

2-Benzyl-3-methylbutan-1-ol (**44**) (4.27 g, 24 mmol) was added *via* a tared syringe to a solution of Pyridinium chlorochromate (10.34 g, 48 mmol) and Celite[®] (10 g), in dichloromethane (80 mL). The resultant brown slurry was allowed to stir for *ca* 2 h (TLC control). The heterogeneous slurry was then concentrated in *vacuo* to afford an amorphous black solid, which was then slurried with diethyl ether (200 mL) and filtered through a SiO_2 and Celite[®] plug. The filtrate was then concentrated in *vacuo*, affording the crude aldehyde. The crude aldehyde was then added as solution in diethyl ether (10 mL, plus 5 mL washings), to a cooled (0 °C, ice bath) solution of vinylmagnesium bromide (1.0 M in THF, 30 mL, 30 mmol) in anhydrous tetrahydrofuran (30 mL), under an argon atmosphere. The resultant solution was allowed to warm to ambient temperature for 2 hours (TLC control), and then quenched at 0 °C by slow addition of 1M HCl (aq). The solution was extracted by using diethyl ether (3 X 10 mL) followed by washing the organic extracts with brine. The organic phase was dried (MgSO_4), filtered and concentrated in *vacuo* to afford a crude oil. Purification by flash column chromatography (eluting with 3-9% diethyl ether/hexane) yielded the secondary allylic alcohol *anti*-**45** (3.920 g, 19.19mmol, 80% over 2 steps, as 5:1 mixture of diastereomers) as a yellow oil.

3.2.3.4. Spectral Data for (*anti*)-(+/-)-4-benzyl-5-methylhex-1-en-3-ol (*anti*-45)



(*anti*)-(+/-)-4-benzyl-5-methylhex-1-en-3-ol (*anti*-45)

Colour and State: Yellow oil.

¹H-NMR (500 MHz, CDCl₃) 7.28-7.25 (m, 2.4H), 7.22-7.15 (m, 3.6H), 5.92 (ddd, *J* = 17.3, 10.4, 5.9 Hz, 1H, major), 5.87 (ddd, *J* = 17.3, 10.6, 6.0 Hz, 0.2H, minor), 5.26 (dt, *J* = 17.3, Hz, 1H, major), 5.24 (dt, *J* = 17.6, 1.5 Hz, 0.2H, minor), 5.16 (dt, *J* = 10.6, 1.5 Hz, 1H, major), 5.15-5.13 (m, 0.2H, Minor), 4.30-4.26 (m, 1H, major), 4.17-4.14 (m, 0.2H, minor), 2.72 (dd, A of ABM, *J*_{AB} = 14.4 Hz, *J*_{Am} = 6.2 Hz, 1H, major), 2.68-2.60 (m, 1.4H), 1.80-1.71 (m, 1.2H), 1.01 (d, *J* = 6.8, 3H, major), 0.98 (d, *J* = 1.7Hz, 0.6H, minor), 0.97 (d, *J* = 1.7Hz, 0.6H, minor), 0.92 (d, *J* = 6.8, 3H, major).

¹³C-NMR (125 MHz, CDCl₃) 142.50 (e), 142.28 (e), 140.79 (o), 140.61 (o), 129.54 (o), 129.24 (o), 128.53 (o), 128.43 (o), 125.81 (o), 115.34 (e), 115.02 (e), 74.14 (o), 74.10 (o), 51.60 (o), 51.61 (o), 32.69 (e), 32.61 (e), 28.52 (o), 27.61 (o), 21.53 (o), 20.75 (o), 20.53 (o), 20.15 (o), 19.73 (o).

IR (Neat) 3354, 2926, 1496, 1453, 1041, 990, 923 cm⁻¹.

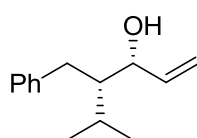
HRMS (ESI[M+Na]⁺) calcd for C₁₄H₂₀NaO 227.1412, found 227.1418.

3.2.3.5. Representative experimental procedure for the Preparation of the Anti-Diastereomer of allylic alcohol 45.

Oxalyl chloride (0.970 mL, 11.08 mmol) was added dropwise to a cooled (-78 °C, dry ice/acetone bath) solution of dimethyl sulfoxide (1.448 ml, 20.40 mmol), in dichloromethane (40 mL), under an argon atmosphere. The resultant solution was stirred for 15 minutes before (*anti*)-(+/-)-4-benzyl-5-methylhex-1-en-3-ol (*anti*-45) (2.08 g, 10.20 mmol) was added as dropwise *via* a syringe. The reaction was then

stirred for *ca* 2 h (TLC control), before being quenched with triethylamine (5.69 mL, 40.8 mmol) and allowed to acclimate to ambient temperature. The reaction concentrated in *vacuo* to afford a crude oil, which was redissolved in diethyl ether (40 mL), and then partitioned between diethyl ether and 1M HCl(aq). The aqueous was extracted with diethyl ether (2 X 20 mL), followed by washing the organic extracts with brine. The organic phase was dried (MgSO₄), filtered and concentrated in *vacuo* to afford a crude oil. The crude enone was then redissolved in diethyl ether (10 mL, plus 5 mL washings) and added dropwise to a cooled solution $-78\text{ }^{\circ}\text{C}$ (dry ice/acetone bath) of lithium aluminium hydride (0.456 g, 12 mmol), in diethyl ether (20 mL), under an argon atmosphere. The reaction was allowed to stir for 2 h (TLC control), before being quenched (aq NH₄Cl) and partitioned between saturated aqueous NH₄Cl solution and diethyl ether. The organic phase was dried (MgSO₄), filtered and concentrated in *vacuo* to afford a crude oil. Purification by flash column chromatography (eluting with 3-9% diethyl ether/hexane) yielded the secondary allylic alcohol ***syn*-45** (1.459 g, 7.14 mmol, 70% over 2 steps, as 3:1 mixture of diastereomers) as a yellow oil.

3.2.3.6. Spectral Data for (*syn*)-(+/-)-4-benzyl-5-methylhex-1-en-3-ol (*syn*-45)



(*syn*)-(+/-)-4-benzyl-5-methylhex-1-en-3-ol (*syn*-45)

Colour and State: Yellow oil.

¹H-NMR (500 MHz, CDCl₃) 7.28-7.25 (m, 2.66H), 7.22-7.15 (m, 1H), 5.92 (ddd, *J* = 17.3, 10.4, 5.9 Hz, 0.33H, minor), 5.87 (ddd, *J* = 17.3, 10.6, 6.0 Hz, 1H, major), 5.26 (dt, *J* = 17.3, Hz, 0.33H, minor), 5.24 (dt, *J* = 17.6, 1.5 Hz, 1H, major), 5.17 (dt, *J* = 10.6, 1.6 Hz, 1H, Major), 5.16 (dt, *J* = 10.6, 1.5 Hz, 0.33H, minor), 4.30-4.26 (m, 0.33H, minor), 4.17-4.14 (m, 1H, major), 2.78-2.68 (m, 1.66H), 2.64 (dd, B of ABM, *J*_{AB} = 14.1 Hz, *J*_{BM} = 5.6 Hz, 1H, major), 1.80-1.71 (m, 1.33H), 1.01 (d, *J* =

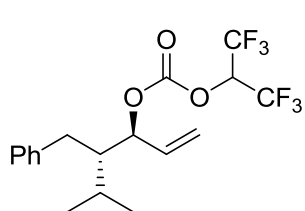
6.8, 1H, minor), 0.98 (d, $J = 1.7$ Hz, 3H, major), 0.97 (d, $J = 1.7$ Hz, 3H, major), 0.92 (d, $J = 6.8$, 1H, minor).

13 C-NMR (125 MHz, CDCl_3) 142.50 (e), 142.28 (e), 140.79 (o), 140.61 (o), 129.54 (o), 129.24 (o), 128.53 (o), 128.43 (o), 125.81 (o), 115.34 (e), 115.02 (e), 74.14 (o), 74.10 (o), 51.60 (o), 51.61 (o), 32.69 (e), 32.61 (e), 28.52 (o), 27.61 (o), 21.53 (o), 20.75 (o), 20.53 (o), 20.15 (o), 19.73 (o).

IR (Neat) 3354, 2926, 1496, 1453, 1041, 990, 923 cm^{-1}

HRMS (ESI[M+Na] $^+$) calcd for $\text{C}_{14}\text{H}_{20}\text{NaO}$ 227.1412, found 227.1418.

3.2.3.7. Spectral Data for *anti* and *syn* diastereomers of allylic carbonate 47.



(*anti*)-(+/-)-4-benzyl-5-methylhex-1-en-3-yl 1,1,1,3,3,3-hexafluoropropan-2-yl carbonate (*anti*-47)

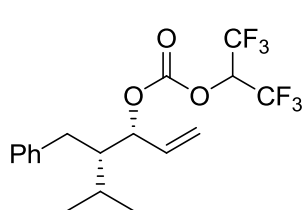
Colour and State: Yellow oil.

$^1\text{H-NMR}$ (500 MHz, CDCl_3) 7.30-7.27 (m, 2.4H), 7.20-7.11 (m, 3.6H), 5.84 (ddd, $J = 17.0, 10.4, 6.9$ Hz, 1H, major), 5.77 (ddd, $J = 17.1, 10.4, 6.7$ Hz, 0.2H, minor), 5.33 (sept, $J = 6$ Hz, 1.2H), 5.33-5.26 (m, 3.4H), 5.14-5.12 (m, 0.2H, minor), 2.77-2.66 (m, 2.2H), 2.45 (dd, B of ABM, $J_{AB} = 14.2$ Hz, $J_{Am} = 7.5$ Hz, 0.2H, minor), 2.00-1.91 (m, 1.2H), 1.88-1.81 (m, 1.2H), 1.00 (d, $J = 6.6$ Hz, 0.6H, minor), 0.97 (d, $J = 6.6$ Hz, 0.6H, minor), 0.94 (d, $J = 2.6$ Hz, 3H, major), 0.92 (d, $J = 2.6$ Hz, 3H, major).

13 C-NMR (125 MHz, CDCl_3) 152.21 (e), 152.17 (e), 140.99 (e), 140.61 (e), 134.09 (o), 133.70 (o), 129.17 (o), 128.94 (o), 128.55 (o), 128.47 (o), 126.09 (o), 125.99 (o), 120.34 (e; q, $J_{\text{C-F}} = 280.0$ Hz), 120.26 (e; q, $J_{\text{C-F}} = 280.0$ Hz), 118.77 (e), 118.48 (e), 84.76 (o), 82.96 (o), 70.10 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 70.06 (o; sept, $J_{\text{C-F}} = 34.9$ Hz), 49.51 (o), 49.47 (o), 32.64 (e), 32.29 (e), 28.47 (o), 27.55 (o), 21.58 (o), 20.77 (o), 20.54 (o), 20.12 (o), 19.47 (o), 19.17(o).

IR (neat) 3030, 2972, 1776, 1650, 1605, 1498, 1456, 1386, cm^{-1} .

HRMS (ESI[M+NH₄]⁺) calcd for C₁₈H₂₄F₆NO₃ 416.1660, found 416.1650.



(syn)-(+/-)-4-benzyl-5-methylhex-1-en-3-yl 1,1,1,3,3,3-hexafluoropropan-2-yl carbonate (syn-47)

Colour and State: Yellow oil.

¹H-NMR (500 MHz, CDCl₃) 7.30-7.27 (m, 2.66H), 7.20-7.11 (m, 4H), 5.84 (ddd, $J = 17.0, 10.4, 6.9$ Hz, 0.33H, minor), 5.77 (ddd, $J = 17.1, 10.4, 6.7$ Hz, 1H, major), 5.33 (sept, $J = 6$ Hz, 1.33H), 5.33-5.26 (m, 3H), 5.14-5.12 (m, 1H, major), 2.77-2.71 (m, 0.66H), 2.68 (dd, A of ABM, $J_{AB} = 14.2$ Hz, $J_{AM} = 6.0$ Hz, 1H, major), 2.45 (dd, B of ABM, $J_{AB} = 14.2$ Hz, $J_{AB} = 7.5$ Hz, 1H, major), 2.00-1.91 (m, 1.33H), 1.88-1.81 (m, 1.33H), 1.00 (d, $J = 6.6$ Hz, 3H, major), 0.97 (d, $J = 6.6$ Hz, 3H, major), 0.94 (d, $J = 2.6$ Hz, 1H, minor), 0.92 (d, $J = 2.6$ Hz, 1H, minor).

¹³C-NMR (125 MHz, CDCl₃) 152.21 (e), 152.17 (e), 140.99 (e), 140.61 (e), 134.09 (o), 133.70 (o), 129.17 (o), 128.94 (o), 128.55 (o), 128.47 (o), 126.09 (o), 125.99 (o), 120.34 (e; q, $J_{C-F} = 280.0$ Hz), 120.26 (e; q, $J_{C-F} = 280.0$ Hz), 118.77 (e), 118.48 (e), 84.76 (o), 82.96 (o), 70.10 (o; sept, $J_{C-F} = 34.9$ Hz), 70.06 (o; sept, $J_{C-F} = 34.9$ Hz), 49.51 (o), 49.47 (o), 32.64 (e), 32.29 (e), 28.47 (o), 27.55 (o), 21.58 (o), 20.77 (o), 20.54 (o), 20.12 (o), 19.47 (o), 19.17(o).

IR (neat) 3030, 2972, 1776, 1650, 1605, 1498, 1456, 1386, cm^{-1} .

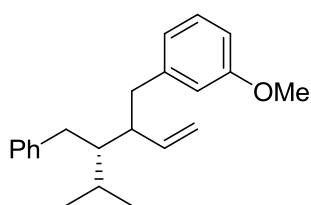
HRMS (ESI[M+NH₄]⁺) calcd for C₁₈H₂₄F₆NO₃ 416.1660, found 416.1650.

3.2.3.8. Representative experimental procedure for the diastereoselective rhodium-catalysed allylic benzylation.

RhCl₃XH₂O (2 mg, 0.01 mmol) and zinc iodide (32 mg, 0.1 mmol) were dissolved in anhydrous diethyl ether (4 mL) at room temperature and then stirred until the zinc

salt was fully dissolved (*ca.* 45 minutes). Then a solution of 3-methoxy benzyl magnesium bromide (0.440 mL, 0.3 mmol, 0.667 M) was added *via* a syringe, the resultant brown solution was stirred for 30 minutes before being cooled to 0 °C (ice bath). Allylic carbonate (*syn*)-**47** (40 mg, 0.1 mmol) was then added to the cooled reaction mixture *via* a tared 100 µl gastight syringe. The resulting reaction mixture was then stirred at 0 °C for 15 min (TLC control). The reaction mixture was then quenched (aq NH₄Cl) and partitioned between saturated aqueous NH₄Cl solution and petroleum ether (30-40 °C). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated in *vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0/100-2/98 dichloromethane/petroleum ether (30-40°C)) furnished the benzylated product **48** (28.0 mg, 95%, *ds* ≥19:1) as a colourless oil.

3.2.3.9. Spectral Data for Benzylated product 48.



(+/-)-1-((S/R,S/R)-3-benzyl-4-methyl-2-vinylpentyl)-3-methoxybenzene (**48**)

Colour and State: Colourless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.27-7.24 (m, 1H), 7.19-7.13 (m, 4H), 6.73-6.67 (m, 3H), 5.82 (ddd, *J* = 17.3, 10.4, 8.1 Hz, 1H), 4.99 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.89 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.79 (s, 3H), 2.80-2.71 (m, 2H), 2.67-2.57 (m, 3H), 1.77-1.69 (m, 2H), 0.92 (d, *J* = 6.9, 3H), 0.83 (d, *J* = 6.9, 3H).

¹³C-NMR δ 159.34 (e), 142.60 (e), 142.52 (e), 138.88 (o), 129.50 (o), 128.57 (o), 128.52 (o), 125.80 (o), 121.72 (o), 115.10 (o), 114.44 (e), 110.10 (o), 55.13 (o), 45.04 (o), 46.53 (o), 41.84 (e), 35.76 (e), 28.64 (o), 20.12 (o), 19.47 (o).

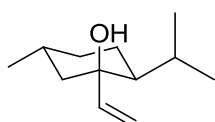
IR (Neat) 3016, 2920, 2850, 1645, 1601, 1584, 1489, 1454 cm⁻¹.

HRMS (ESI[M+Na]⁺) calcd for C₂₂H₂₈NaO 331.2038, found 331.2030.

3.2.3.10. Representative Experimental Procedure for the Preparation of the L-Menthone Derived Allylic Alcohol **50**.

Under an argon atmosphere, a stirred solution of vinylmagnesium bromide (1.0 M in THF, 5.2 ml, 5.2 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to -20 °C, and a solution of L-menthone **49** (0.701 g, 5 mmol) was added dropwise *via* syringe. The solution was allowed to warm to ambient temperature for 2 hours (TLC control), and then quenched at 0 °C by slow addition of 1M HCl (aq). The solution was extracted by using diethyl ether (3 X 10 ml) followed by washing the organic extracts with brine. The organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash column chromatography (eluting with 3-9% diethyl ether/hexane) yielded the secondary allylic alcohol **50** (0.799 g, 4.75 mmol, 95%, as a single diastereoisomer) as a yellow oil

3.2.3.11. Spectral Data for the L-Menthone derived allylic alcohol **50**.



(1R,2S,5R)-1-Vinyl-2-iso-propyl-5-methylcyclohexan-1-ol (50)

Colour and State: Colourless oil.

All spectral data matched the published values.¹⁶

¹**H-NMR** (500 MHz, CDCl₃) δ 5.86 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.25 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.07 (dd, *J* = 10.8, 1.5 Hz, 1H), 1.95 (quintd, *J* = 6.9, 2.0 Hz, 1H), 1.90–1.60 (m, 2H), 1.58-1.38 (m, 3H), 1.20-1.05 (m, 2H), 0.87 (d, *J* = 7.1 Hz, 6H), 0.85 (d, *J*=6.9 Hz, 3H), 0.97 (m, 1H).

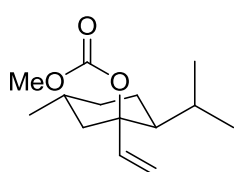
IR (Neat) 3373, 3331, 1325, 1195, 1084, 921 cm⁻¹.

[α]_D²⁰ = -20.0 (c 1.02, CHCl₃)

3.2.3.12. Representative Experimental Procedure for the Preparation of the L-Menthone Derived Tertiary Allylic Carbonate 52.

Lithium bis(trimethylsilyl)amide (1M solution in tetrahydrofuran, 6.0 mL, 6.0 mmol) was added dropwise to a stirring solution of (1R,2S,5R)-1-vinyl-2-iso-propyl-5-methylcyclohexan-1-ol (**50**) (1.095 g, 6.01 mmol) in anhydrous tetrahydrofuran (12 mL) at 0 °C under an atmosphere of argon. The mixture was stirred for *ca.* 30 minutes and methyl chloroformate (0.465 mL, 6.01 mmol) was added dropwise. The reaction was allowed to slowly warm to room temperature, stirred for *ca.* 4 hours and quenched by the dropwise addition of water (2.5 mL). The reaction mixture was then partitioned between diethyl ether and saturated aqueous ammonium chloride solution. The combined organic phases were dried (MgSO₄), filtered and concentrated in *vacuo* to afford the crude product. Purification by flash column chromatography (eluting with 3-9% diethyl ether/hexane) afforded the tertiary allylic carbonate 1a (1.079 g, 4.49 mmol, 74%) as a colorless oil.

3.2.3.13. Spectral Data for the L-Menthone derived allylic carbonate 52.



(1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexyl methyl carbonate (52)

Colour and State: Colourless oil.

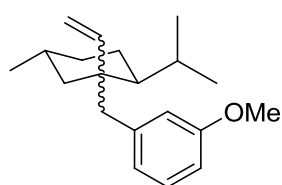
¹H-NMR (500 MHz, CDCl₃) δ 6.10 (dd, *J* = 17.7, 11.3 Hz, 1H), 5.17 (d, *J* = 11.3 Hz, 1H), 5.03 (d, *J* = 17.7 Hz, 1H), 3.72 (s, 3H), 2.69 (dt, *J* = 14.2, 2.8 Hz, 1H), 2.15 (dsept, *J* = 6.8, 1.9 Hz, 1H), 1.82-1.77 (m, 1H), 1.61-1.53 (m, 3H), 1.19-1.13 (m, 2H), 0.91 (d, *J* = 5.3 Hz, 3H), 0.89 (d, *J* = 5.0 Hz, 3H), 0.86 (d, *J* = 7.2 Hz, 3H).

$^{13}\text{C-NMR}$ δ 154.04 (e), 141.81 (o), 112.78 (e), 87.66 (e), 54.03 (o), 52.53 (o), 41.57 (e), 34.85 (e), 27.60 (o), 26.36 (o), 23.67 (o), 22.15 (o), 20.73 (e), 17.93 (o).

IR (Neat) 2992, 2931, 1745, 1644, 1414, 1257, 791 cm^{-1} .

HRMS (ESI[M+NH₄]⁺) calcd for C₁₄H₂₈NO₃ 258.2069, found 258.2072.

3.2.3.14. Spectral Data for the Benzylated L-Menthone Derivative 52.



1-(((5R)-2-isopropyl-5-methyl-1-vinylcyclohexyl)methyl)-3-methoxybenzene (53)

Colour and State: Colourless oil.

$^1\text{H-NMR}$ (500 MHz, CDCl₃) δ 7.16 (t, J = 7.9 Hz, 1H), 6.76-6.68 (m, 3H), 6.16 (dd, J = 17.8, 11.2 Hz, 1H), 5.11 (dd, J = 11.2, 1.4 Hz, 1H), 4.89 (dd, J = 17.8, 1.4 Hz, 1H), 3.79 (s, 3H), 2.77 (d, A of AB, J_{AB} = 13.2 Hz, 1H), 2.72 (d, B of AB, J_{AB} = 13.2 Hz, 1H), 2.29-2.21 (m, 1H), 1.74-1.56 (m, 3H), 1.47-1.42 (m, 2H), 1.33-1.20 (m, 2H), 1.11-1.08 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H), 0.78 (d, J = 6.4 Hz, 3H).

$^{13}\text{C-NMR}$ (125 MHz, CDCl₃) δ 159.36 (e) 142.97 (e), 140.32 (o), 128.91 (o), 121.73 (o), 115.50 (e), 115.05 (o), 110.78 (o), 55.12 (o), 51.63 (o), 42.83 (e), 41.57 (e), 34.85 (e), 33.45 (e), 27.60 (o), 26.36 (o), 23.57 (o), 22.05 (o), 20.45 (e), 18.03 (o).

IR (Neat) 3064, 2928, 2845, 1636, 1601, 1584, 1488, 1450 cm^{-1} .

HRMS (ESI[M+Na]⁺) calcd for C₂₀H₃₀NaO 309.2194, found 309.2194.

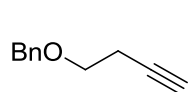
$[\alpha]_{\text{D}}^{20}$ = -8.0 (c 1.00, CHCl₃)

3.2.4. Rhodium-Catalysed Allylic Substitution with Alkenyl organometallic Pronucleophiles: Expanding the Scope of the Unstabilised Carbon Nucleophiles.

3.2.4.1. Representative experimental procedure for the Preparation of 4-(benzyl-oxy)butyne (57).

To a suspension of NaH (60% in oil, 0.971 g, 24.28 mmol,) in anhydrous tetrahydrofuran (50 mL) at 0 °C, was slowly added a solution of but-3-yn-1-ol (1.597 g, 22.79 mmol) in diethyl ether (20 mL, plus 5 mL washings) and the mixture was stirred for 20 min at 20 °C. To this mixture were added a solution of benzyl bromide (2.98 ml, 25.06 mmol) in anhydrous tetrahydrofuran (25 mL) and NaI (34 mg, 0.228 mmol). After stirring for 8 h at 20 °C, the mixture was treated at 0 °C with 1 M aq HCl (5 mL) and extracted with Et₂O (2 X 30 mL). The combined organic phases were washed with brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (eluting with 3-9% diethyl ether/hexane) afforded the 4-(benzyl-oxy)butyne (**57**) (3.43 g, 94%) as a colourless oil.

3.2.4.2. Spectral Data for 4-(benzyl-oxy)butyne 57.



4-(benzyl-oxy)butyne (57)

Colour and State: Colourless oil.

All spectral data matched the published values.¹⁷

¹H-NMR (500 MHz, CDCl₃) δ 7.45-7.29 (m, 5H), 4.60 (s, 2H), 3.64 (t, *J* = 7.0 Hz, 2H), 2.55 (dt, *J* = 7.0, 2.5 Hz, 2H), 2.05(t, *J* = 2.5 Hz, 1H).

¹³C-NMR (125 MHz, CDCl₃) δ 137.89 (e), 128.34 (o), 127.54 (o; C x 3), 81.10 (e), 72.83 (e; alkynyl), 69.29 (e), 68.00 (e), 19.74 (e).

IR (Neat) 3410, 3060, 3010, 3005, 2900, 2865, 1960, 1720, 1700, 1600, 1480, 1360, 1200 cm^{-1} .

3.2.4.3. Representative experimental procedure for the Preparation of Vinylaluminium reagent (58).

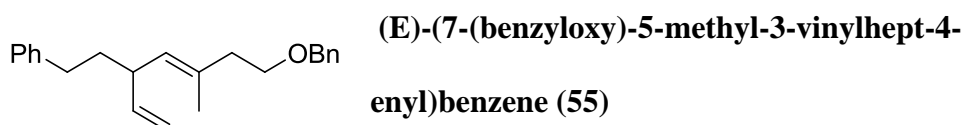
To a slurry of Cp_2ZrCl_2 (0.868 mg, 2.97 mmol) in 1,2-dichloroethane (20 mL) was added 2.0 M toluene solution of Me_3Al (2.0 M, 7.5 mL, 15 mmol), under an argon atmosphere and at ambient temperature. The resultant mixture was allowed to stir for *ca.* 10 min, the reaction was then cooled to 0 °C (ice bath), before 4-(benzyl-oxy)butyne (**57**) (0.8027 g, 5.01 mmol) was added dropwise *via* a syringe. The solution was then allowed to acclimate to ambient temperature for *ca.* 2 h, the resultant yellow solution was then refrigerated until use.

3.2.4.4. Representative experimental procedure for the rhodium-catalysed allylic Vinylation.

$\text{TpRh}(\text{C}_2\text{H}_4)_2$ (3.7 mg, 0.01 mmol) was dissolved in anhydrous diethyl ether (3 mL) at room temperature and then stirred for *ca.* 1 h before being cooled to 0 °C. Zinc iodide (64 mg, 0.2 mmol) was then dissolved in anhydrous diethyl ether (0.560 mL) and vinylaluminium **58** (0.250 M, in 1,2-DCE, 4 mL, 0.4 mmol) was then added dropwise at room temperature to the zinc iodide solution. The resulting mixture was stirred for *ca.* 45 min before being cooled to 0°C. The catalyst solution was then added to the organozinc solution *via* Telfon[®] cannula, followed by immediate addition of the allylic carbonate **22a** (35.6 mg, 0.1 mmol) *via* a tared 100 μl gastight syringe. The resulting reaction mixture was then allowed to acclimate to ambient temperature and was stirred for *ca.* 18h (TLC control). The reaction mixture was then quenched (aq NH_4Cl) and partitioned between saturated aqueous NH_4Cl solution and

diethyl ether. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated in *vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0/100-5/95 diethyl ether/petroleum ether (30-40°C)) furnished the vinylated product **55** (3.8 mg, 23%) as a colourless oil.

3.2.4.5. Spectral Data for vinylated product **55**.



Colour and State: Colourless oil.

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.38-7.28 (m, 5H), 7.24-7.17 (m, 5H), 5.74 (ddd, $J = 17.2, 10.3, 7.2$ Hz, 1H), 5.04-4.97 (m, 2H), 4.82 (s, 2H), 3.59-3.56 (m, 2H), 2.65-2.56 (m, 3H), 2.06-1.99 (m, 2H), 1.78 (s, 3H), 1.70-1.68 (m, 2H).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 142.88 (e), 138.32 (e), 137.89 (e), 129.47 (o), 128.92 (o), 128.01 (o), 127.80 (o), 127.21 (o), 125.91 (o), 124.00 (o), 115.60 (e), 74.80 (e), 69.41 (e), 42.83 (e), 36.80 (e), 35.72 (o), 34.98 (e), 34.03 (e), 17.02 (o).

HRMS (ESI[M+Na]⁺) calcd for $\text{C}_{23}\text{H}_{28}\text{NaO}$ 343.2038, found 343.2025.

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