METAL-MEDIATED INTRAMOLECULAR HYDROAMINATION AND HYDRO(ACY)ALKOXYLATION REACTIONS

A DISSERTATION FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

FROM IMPERIAL COLLEGE LONDON

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DECLARATION

I confirm that this report is my own work and where reference is made to other research this is referenced in text.

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Abstract

This PhD thesis describes work undertaken to effect asymmetric catalysis in hydroamination and hydro(acy)alkoxylation reactions of allenes. The introductory Chapter provides an overview of recent advances in asymmetric heterofunctionalisation reactions of allenes. This includes intra- and inter-molecular reactions involving C-N and C-O bond formations.

Chapter 2 begins by comparing the preparation of a γ-allenic alcohol by two different synthetic routes and its subsequent use in intramolecular hydroalkoxylation reactions using copper(II) and silver(I) salts. From this study, the ability of silver diphosphine complexes to facilitate enantioselective hydroalkoxylation reactions in a 5-*exo*-*trig* fashion was discovered. Extensive reaction optimisation was undertaken, however only moderate ee's and conversions were observed.

In Chapter 3, the use of other metal Lewis acids to catalyse hydroalkoxylation reactions of γ-allenic alcohols is presented. DFT calculations undertaken by a colleague (Prof H. S. Rzepa) were used to rationalise the observed regioselectivities with silver(I), zinc(II), and tin(II) triflates. From DFT calculations, the metal counteranion was found to be intimately involved in the C-O bond formation.

In the following two Chapters, the possibility of asymmetric synthesis by using chiral anionic ligands is discussed. In Chapter 4, additional γ-allenic alcohols and β-allenic acids were synthesised for intramolecular hydroalkoxylation or hydroacyalkoxylation reactions respectively. In Chapter 5, the respective γ-allenic amines were prepared for intramolecular hydroamination. In both cases, the outcome, scope and limitations of the reaction are discussed.

In Chapter 6, an overall conclusion and future work is discussed.

The last Chapter contains experimental procedures and characterisation data of all the compounds synthesised during the course of this project.

Table of Contents

Abbreviations

[α]	specific rotation
Ac	acetyl group
Ad	1-adamantyl
Ar	a general aryl moiety
atm	atmosphere(s)
BINAM	1,1′-binaphthyl-2,2′-diamine
BINAP	2, 2'-*bis*(diphenylphosphino)-1, 1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl group
bp	boiling point
br	broad (spectral)
Boc	*tert*-butyloxycarbonyl group
3, 5-DTBM-MeOBIPHEP	6,6′-dimethoxybiphenyl-2,2′-diyl)*bis*[*bis*(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine
Bz	benzoyl
c	concentration
Cat.	catalyst
Calcd.	calculated
Cbz	carbamates
CI	chemical ionization
Cl-MeO-BIPHEP	5, 5'-dichloro-6, 6'-dimethoxy-2, 2'-*bis*(diphenylphosphino)-1, 1'-biphenyl
cod	1,5-cyclooctadiene
COSY	correlation spectroscopy
CSA	camphor sulfonic acid
d	doublet (spectral)
DACH Naphthyl Trost ligand	1,2-diaminocyclohexane-*N,N′-bis*(2-diphenylphosphino-1-naphthyl)
dba	dibenzylideneacetone
DBU	1, 8-diazabicyclo-[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DEPT	distortionless enhancement by polarization transfer
DIPAMP	ethylene *bis*[(2-methoxyphenyl)phenylphosphine]
DIOP	4, 5-*bis*(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DMAP	4-(dimethylamino)pyridine
DMF	*N,N′*-dimethylformamide
DMPU	*N,N′*-dimethylpropylene urea
DMSO	dimethyl sulfoxide
dppe	1,1-*bis*(diphenylphospino)ethane
dppm	1,1-*bis*(diphenylphospino)methane

d.r	diastereoselective ratio
DTBM-SEGPHOS	5,5′-b*is*[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
ee	enantiomeric excess
EI	electron impact
equiv	number of equivalents
ESI	electrospray ionisation
Et-FerroTANE	1,1'-*bis*(2, 4-diethylphosphonato)ferrocene
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
FT-IR	fourier transform infrared spectroscopy
GC	gas chromatography
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HSQC	heteronuclear Single Quantum Coherence
IR	infrared
J	coupling constant (Hz)
JohnPhos	2-(di-*tert*-butyl-phosphino)biphenyl
Josiphos	(*R*)-1-[(S_p)-2-(di-*tert*-butylphosphino)ferrocenyl]ethyl*bis*(2-methylphenyl)phosphine
LAH	lithium aluminium hydride
LHMDS	lithium *bis*(trimethylsilyl)amide
Lit.	literature
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
M^+	parent molecular ion
m	multiplet (spectral)
M:L	metal-to-ligand ratio
m/z	mass-to-charge ratio
max	maximum
Me-BPE	1,2-*bis*(2, 5-dimethylphospholano)ethane
MeO-BIPHEP	6,6'-dimethoxy-2, 2'-*bis*(diphenylphosphino)-1,1'-biphenyl
Ms	mesylate
Monophos	(3,5-dioxa-4-phospha-cyclohepta[2,1-a; 3,4-a']dinaphthalen-4-yl)dimethylamine
mp	melting point
MS	mass spectrometry
Mts	2-mesitylenesulfonyl

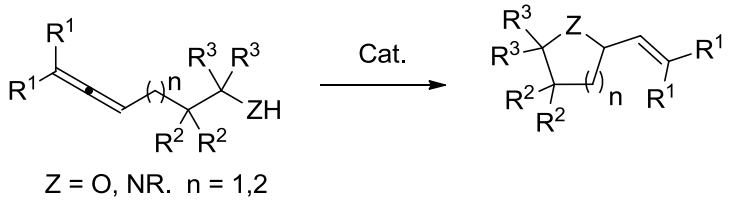
Nf	nonafluorobutanesufonyl
NOSEY	nuclear overhauser effect spectroscopy
NMR	nuclear magnetic resonance
Np	naphthyl
OPNB	*p*-nitrobenzoate
p	pentet (spectral)
Ph	phenyl group
Phanephos	4,12-*bis*(diphenylphosphino)-[2.2]-paracyclophane
Pr	propyl
P-Phos	2,2′,6,6′-tetramethoxy-4,4′-*bis*(diphenylphosphino)-3,3′-bipyridine
Py	pyridine
q	quartet (spectral)
R	unspecified (alkyl or aryl) group; gas constant
rel	relative
RENORPHOS	*trans*-2,3-bis(diphenylphosphino)bicyclo[2.2.1]heptane
R_f	retention factor (in chromatography)
r.t	room temperature
s	singlet (spectral)
δ	chemical shift, in part per million down-field of internal standard
SEGPHOS	5,5′-*bis*[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
Spirophos	1, 6-*bis*(diphenylphosphinoxy)spiro[4.4]nonane
T	temperature
t	time; triplet (spectral)
TADDOL	*trans*-(dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol)
TFA	trifluoroacetic acid
TfOH	triflic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
tolyl-BINAP	2, 2'-*bis*(di-*p*-tolylphosphino)-1,1'-binaphthyl
tolyl-RENORPHOS	*trans*-2,3-*bis*(ditolylphosphino)bicyclo[2.2.1]heptane
Tf	trifluoromethanesulfonyl
R_f	retention time (in chromatography)
Ts	4-toluenesulfonyl
xylyl-BINAP	2,2′-*bis*[di(3,5-xylyl)phoshino]-1,1′-binaphthyl
3, 5-Xyl-MeOBIPHEP	*bis*[*bis*(3,5-dimethyl)phosphino]-6,6′-dimethoxy-1,1′-biphenyl
Xylyl -Phanephos	5,11-*bis*(3,5-xylylphosphino)tricyclo[8.2.2]
Xylyl-P-Phos	2,2′,6,6′-tetramethoxy-4,4′-*bis*(di(3,5-xylyl)phosphino)-3,3′-bipyridine

Chapter 1: Introduction

Oxygen and nitrogen-containing heterocycles are important sub-units in the majority of natural and biologically active compounds, *e.g* polyether antibiotics,[1,2] mycotoxins,[3,4] antifungal compounds,[5,6] and enzyme inhibitors.[7,8] The ability to synthesise these heterocyclic sub-units by direct and atom-economical processes is therefore highly desirable,[9] and the development of chiral variants of these reactions remains a highly topical subject in organic chemistry.

By far, 1,3-dipolar cycloadditions[10] and hetero-Diels-Alder reactions[11,12] are the most common reactions used in the enantioselective synthesis of these heterocycles. However, the intramolecular addition of an N-H, O-H or CO_2H functionality across an unsaturated carbon-carbon bond is also a very attractive methodology. Known as hydroamination, hydroalkoxylation or hydroacyalkoxylation reactions, respectively, they are particularly attractive as they proceed with 100% atom efficiency, often from readily available and inexpensive precursors.

To date, a variety of chiral metal catalysts have been successfully applied for asymmetric intramolecular heterofunctionalisation reactions of olefins and alkynes.[13-34] In contrast, there are only a few chiral catalysts that have been reported for asymmetric heterofunctionalisation additions of O-H and N-H to allenes (Scheme 1.1).[17,33,35-53]



Scheme 1.1: General scheme for intramolecular hydroamination and hydroalkoxylation reactions of allenes.

Heterofunctionalisation reactions of allenes have a number of advantages over additions to alkenes and alkynes. Allenes consist of a strained cumulated double bond rendering them roughly 10 kcal mol^{-1} less stable than an alkene,[54] and therefore more reactive towards π-activation.[54-58] Also, the inherent axial chirality of allenes offers

the potential for enantioselective and diastereoselective reactions to take place, with the added bonus of one of the double bonds remaining in the product for further transformations.

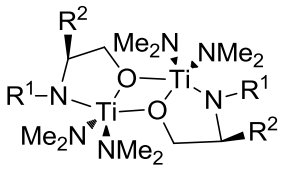
The interest in heterofunctionalisation reactions of allenes has intensified over recent years. However, there is still relatively little literature precedence for asymmetric examples; reports on C-N bond formation far outweighing those of C-O bond formation. The last comprehensive review on the cyclisation of allenes by nucleophilic metal catalysts was published by Bates in 2002.[50] In the following sections, asymmetric hydroamination, hydroalkoxylation and hydroacyalkoxylation reactions of allenes will be presented, based on literature reports dated from this review. Reactions will be classified by the type of metal catalysts, arranged by their positions in the Periodic Table.

1.1 Early Transition Metals

The most prominent early transition metal catalysts for asymmetric intramolecular hydroamination reactions have been titanium from group IV and tantalum from group V. To date, there are no publications on the corresponding asymmetric hydroalkoxylation reaction using these metals.

1.1.1 Titanium

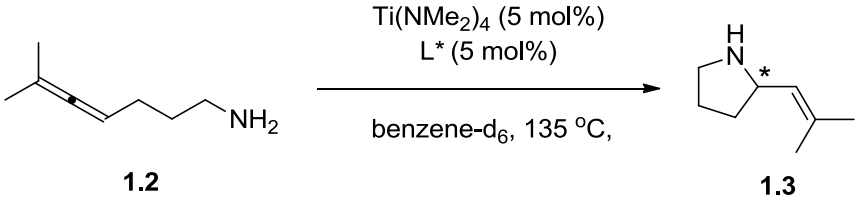
In 2004, the first catalytic asymmetric intramolecular hydroamination of γ-allenic amines was reported using a range of dimeric titanium amino-alcohol complexes **1.1a** to **1.1f**.[59] Complexes **1.1a** to **1.1f** were prepared from equimolar quantities of $Ti(NMe_2)_4$ and ligand (L*), where L* = *S*-valinol (**1.1a**-**1.1b**), *S*-phenylalaninol (**1.1c**-**1.1d**), or *R*-phenylglycinol (**1.1e**-**1.1f**) (Figure 1.1).



1.1a: $R^1 = R^2 =$ *i*-Pr
1.1b: R^1 = 2-Ad, $R^2 =$ *i*-Pr
1.1c: $R^1 =$ *i*-Pr, R^2 = Bn
1.1d: R^1 = 2-Ad, R^2 = Bn
1.1e: $R^1 =$ *i*-Pr, R^2 = Ph
1.1f: R^1 = 2-Ad, R^2 = Ph

Figure 1.1: Proposed structure of dimeric complexes with ligands **1.1a** to **1.1f**.

Using γ-allenic amine **1.2** as a model substrate, the cyclisation reaction was conducted in the presence of 5 mol% of $[Ti(NMe_2)_2(L^*)]_2$ to furnish tetrahydropyridine **1.3** at an elevated temperature of 135 ^oC (Scheme 1.2, Table 1.1).



Scheme 1.2: Cyclisation of **1.2** to tetrahydropyridine **1.3**.

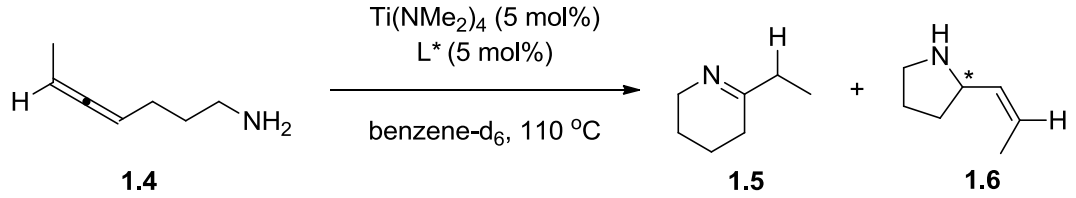
Valine-derived ligands and those of phenylalanine and phenylglycine with small R^1 substituents produced very low ees, but with fast conversion rates (entries 1-3 and 5). The best ee of 15% was achieved with the bulky ligand **1.1d** (entry 4). However, to reach full conversion with this catalyst a longer reaction time of 20 hours was required. Overall, the bulkier the ligand, the longer the reaction time and the higher the ee achieved (entries 2, 4 and 6). In the absence of ligands, $Ti(NMe_2)_4$ catalysed the formation of the 5-*exo*-*trig* product **1.3**, but required a longer reaction time and only reached 95% conversion (entry 10). The absolute configuration of **1.3** was not reported.

Table 1.1: Hydroamination of **1.2** with dimeric titanium catalysts.[a]

Entry	L*	t (h)	% Conversion[b]	% ee[c]
1	*S*-**1.1a**	18	100	4
2	*S*-**1.1b**	17	100	5
3	*S*-**1.1c**	16	100	3
4	*S*-**1.1d**	20	100	15
5	*R*-**1.1e**	17	100	3
6	*R*-**1.1f**	15	100	10
7	none	67	95	0

[a]Reaction conditions: **1.2** (0.17 mmol., 1.6 M), $Ti(NMe_2)_4$ (5 mol%), Ligand (5 mol%), benzene-d_6, 135 ^oC. [b] Determined by ^1H NMR integration. [c] Determined by chiral GC.

Using γ-allenic amine **1.4**, a mixture of 5- and 6- membered rings (**1.5**, *Z*-**1.6** and *E*-**1.6**) were produced (Scheme 1.3, Table 1.2).



1.4 **1.5** **1.6**

Scheme 1.3: Cyclisation of **1.4** to **1.5** and isomers *Z*-**1.6** and *E*-**1.6**.

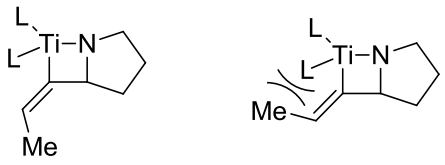
The formation of both **1.5** and **1.6** is possibly due to using a less hindered γ-allenic amine, where both C=C bonds are available for *N*-nucleophilic attack. In all cases, the 5-*exo* product was preferred over the 6-*endo* product, where the ratio of *exo* to *endo* products ranged from 1.7:1 (*i.e* entry 3) to 4.5:1 (*i.e* entry 6). This observation suggests the reaction is sensitive to the presence of the methyl group. The trend previously observed for the cyclisation of **1.2** appears to also operate in the cyclisation of **1.4**, where the bulkier adamantyl substituted ligands produced the highest ee's (entries 4 and 6). However, the highest enantioselectivity achieved was only 16% ee (entry 4). Again, valine derived ligands produced very low ee's of 4% to 5% (entries 1 and 2). In these cases, they were also very slow, requiring 48 to 94 hours, to reach full conversions.

Table 1.2: Hydroamination of **1.4** with dimeric titanium catalysts.[a]

Entry	**L***	**t (h)**	**% Yield**[b,c]		
			1.5	***Z*-1.6**	***E*-1.6**
1	*S*-**1.1a**	48	20	41 (1)	39 (4)
2	*S*-**1.1b**	91	19	41 (0)	41 (5)
3	*S*-**1.1c**	22	33	24 (6)	33 (4)
4	*S*-**1.1d**	43	22	42 (7)	36 (16)
5	*R*-**1.1e**	24	20	50 (2)	30 (4)
6	*R*-**1.1f**	22	18	51 (11)	31 (15)

[a]Reaction conditions: **1.4** (0.12 mmol., 1.2 M), $Ti(NMe_2)_4$, Ligand (5.0 mol%), benzene-d_6, 110 °C. [b] Determined by ^{1}H NMR integration. [c] ee values given in parenthesis.

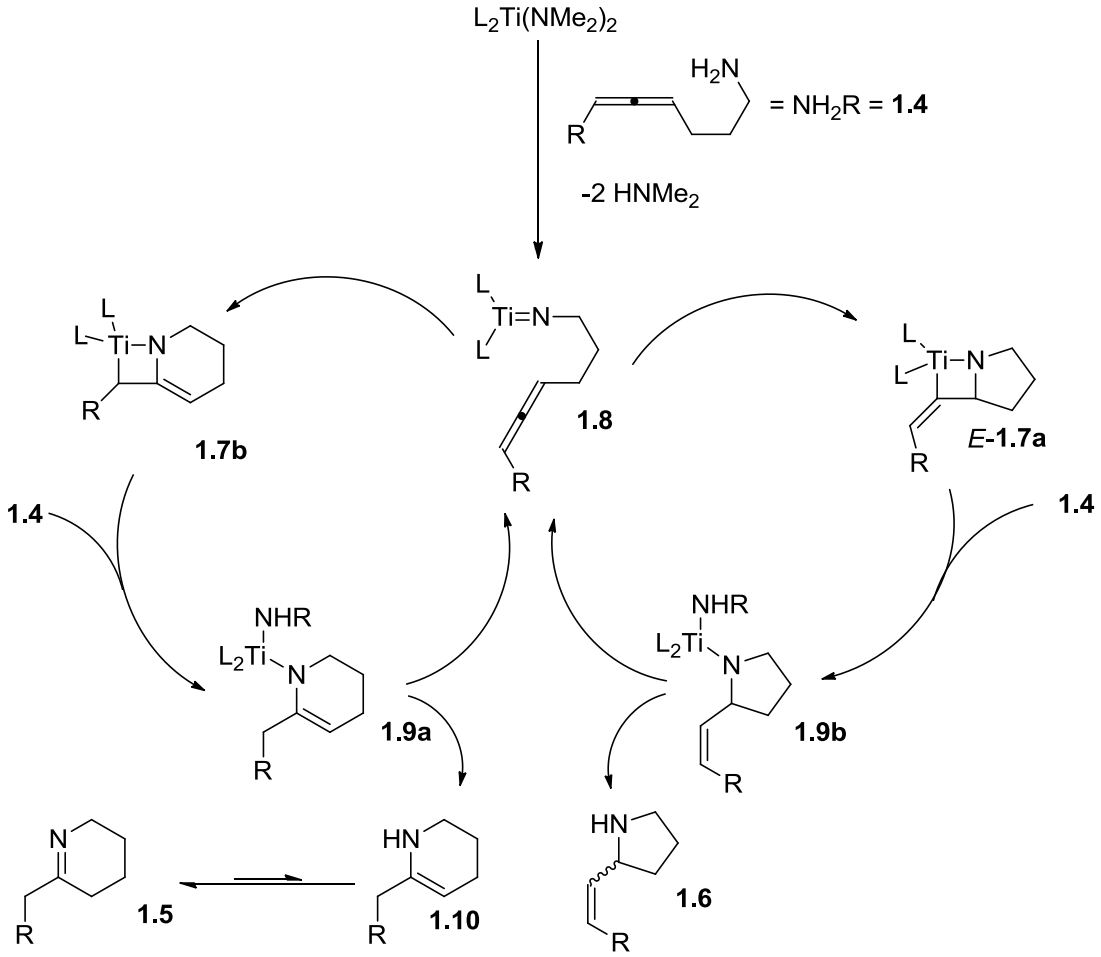
It transpired that both the *Z* and *E* 5-*exo* pyrrolidine products *Z*-**1.6** and *E*-**1.6** were formed and could be isolated separately. The *Z/E* ratio of isomers ranged between 1:0.7 to 1.6:1, where the lower ratio was observed with valine and phenylalanine derived ligands (entries 1 to 4) and the larger ratio with the bulkier ligands (entries 5 to 6). The enantioselectivity of the *E* isomer was found to be larger than that of the *Z* isomer, except when using ligand *S*-**1.1c**. Both observations are associated with the steric bulk associated with the terminal methyl group and the ligands of the titanium complex. For the formation of *E*-**1.6** *via* the intermediate *Z*-**1.7a**, the methyl group will be closer to the metal centre where it will experience the steric bulk of the ligands (Figure 1.2). Due to the methyl group's proximity to the chiral ligands, it should also cyclise with a higher ee. So overall *Z*-**1.6** will form preferentially, but have lower ee.



E-**1.7a** *Z*-**1.7a**

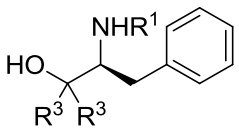
Figure 1.2: Intermediates in the titanium hydroamination mechanism.

These results were rationalised by a proposed mechanism where the catalytic cycle initiates with a reaction of the catalyst precursor $[Ti(NMe_2)_2(L^*)]_2$ with the γ-allenic amine **1.4** to form an imido complex **1.8**, with loss of two molecules of $HNMe_2$ (Scheme 1.4).[59] Subsequent [2+2] cycloaddition can then occur resulting in the 6-*endo* or 5-*exo* ring structures **1.7b** or **1.7a**, respectively, depending on which double bond of the allene is involved. Upon addition of another molecule of starting material, protonolysis of **1.9a** to **1.10** or **1.9b** to **1.6** occurs with regeneration of the imido complex **1.8**. Enamine **1.10** will then rearrange to the more stable imine structure **1.5**.



Scheme 1.4: Hydroamination mechanism for group IV complexes.[59]

In 2009, the same research group reported their work on further modification of ligands **1.1c** and **1.1d**, by changing the nitrogen protecting group R^1 and introducing further R^3 substituent α to the hydroxyl moiety (Figure 1.3). These ligands (**1.11a-1.11e**) were used in the cyclisation of γ-allenic amine **1.2**. [35,43]



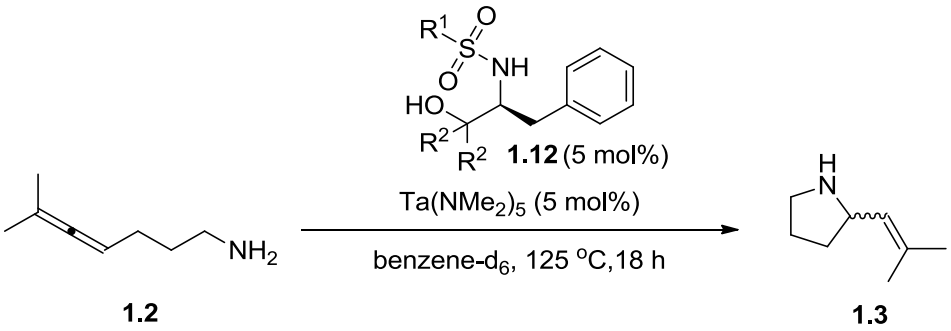
1.11a: R^1 = *i*-Pr, R^3 = Ph
1.11b: R^1 = *c*-C_6H_{11}, R^3 = *n*-Bu
1.11c: R^1 = 2-Ad, R^3 = H
1.11d: R^1 = 2-Ad, R^3 = CH_3
1.11e: R^1 = 2-Ad, R^3 = *n*-Bu

Figure 1.3: Modified ligands.

Unfortunately, these ligand modifications did not lead to any improvements in enantioselectivity.

1.1.2 Tantalum

In 2009, Hickmann *et al.* investigated the ability of tantalum complexes containing bidentate sulfonamide alcohol ligands (**1.12a**-**1.12d**) to mediate intramolecular hydroamination reactions (Scheme 1.5, Table 1.3).[35]



1.12a: R^1 = 4-CF_3-C_6H_4, R^2 = H **1.12c:** R^1 = 4-Me-C_6H_4, R^2 = Me

1.12b: R^1 = 3,5-$(CF_3)_2$-C_6H_4, R^2 = H **1.12d:** R^1 = 4-Me-C_6H_4, R^2 = Me

Scheme 1.5: Tantalum-catalysed intramolecular hydroamination reactions.

Generally, the reactions catalysed by the Ta(V) complexes afforded higher enantioselectivities than Ti(IV) catalysts. The reaction also take places at the slightly lower temperature of 125 °C (entries 1 to 4) and in some cases, full conversions can be achieved (entries 2 and 4).

Table 1.3: Hydroamination of **1.2** with tantalum catalysts.[a]

Entry	L*	t (h)	% Conversion [b]	% ee[c]
1	*S*-**1.12a**	115	85	28
2	*S*-**1.12b**	71	100	34
3	*S*-**1.12c**	17	88	24
4	*S*-**1.12d**	15	100	23

[a]Reaction conditions: **1.2** (0.15 mmol., 1.5 M), $Ta(NMe_2)_5$ (5 mol%), ligand (5 mol%), benzene-d_6. [b] Determined by ^{1}H NMR integration. [c] Determined by chiral GC.

1.1.3 Summary of Early Transition Metals in Heterofunctionalisation Reactions

Overall, the use of early transition metals in enantioselective heterofunctionalisation of allenes is limited. The two examples reported so far employ Ti(IV) or Ta(V) catalyses and low levels of enantioselectivities were attained. The Ti(IV) catalytic system is sensitive to substituents on the terminal allenic carbon atom and only 16% ee can be achieved using aminoalcohol derivatives. Higher enantioselectivities of 34% can be obtained using Ta(V) catalysts, but the same limiting factors are observed. Both catalysts are relatively air- and moisture-sensitive and reactions need to be performed in a glove box. As such, none of these reactions have been demonstrated on a preparative scale.

1.2 Group 9 and 10 Transition Metals

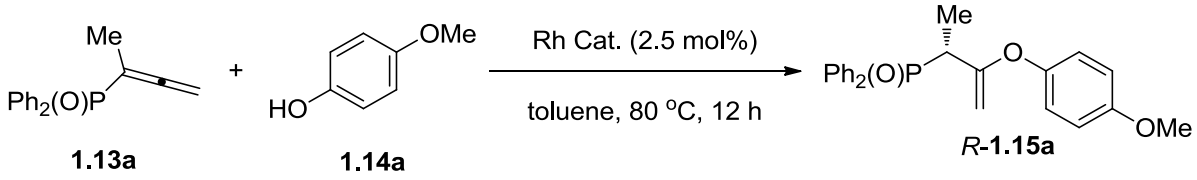
A few palladium and rhodium complexes have been used in the asymmetric heterofunctionalisation reactions of allenes. Alkyne examples will also be included in this discussion, as the addition to this particular π-system is believed to proceed *via* allenic intermediates.[14,60]

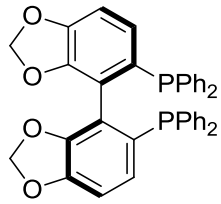
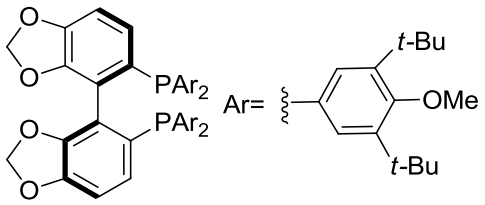
1.2.1 Rhodium

In 2009, the first asymmetric intermolecular hydroalkoxylation reaction mediated by Rh(I) catalysts was published.[42] In the paper, the addition of phenols (**1.14**) to diphenylphosphinylallenes (**1.13**) furnished chiral vinyl ethers (**1.15**) in high yields and enantioselectivities. Using methyl-substituted diphenylphosphinylallene **1.13a** and *p*-methoxyphenol **1.14a** as model substrates several chiral *bis*-phosphine ligands were examined (Table 1.4). Utilising 2.5 mol% of the pre-formed complex $[Rh(OH)(R\text{-BINAP})]_2$, the relative stoichiometry of the starting materials was found to influence the enantioselectivity; changing the **1.13a**:**1.14a** ratio from 1:2 to 2:1 increased the ee of the product *R*-**1.15a** from 23% to 55% after 12 hours at 80 ^{o}C, but with concomitant reduction in conversion (entry 1 vs 2). An ee enhancement of 11% and decrease in conversion (40%) were observed by switching the catalyst to one that

was formed *in situ*, from a 1:1.2 ratio of $[Rh(OH)(cod)]_2$ and *R*-SEGPHOS (entry 2 *vs* 3). Modifying the ligand to *R*-DTBM-SEGPHOS increased both conversion and ee (entry 4). Finally, *t*-BuOH was identified as the optimum solvent as it afforded 99% conversion to *R*-**1.15a** with 82% ee after 12 hours at 80 °C (entry 5).

Table 1.4: Addition of *p*-methoxyphenol **1.14a** to diphenylphosphinylallene **1.13a**.[a]



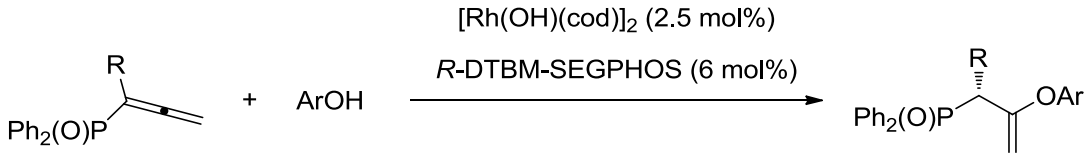
Entry	Ratio of 1.13a:1.14a (mmol.)	Catalyst (mol%)	% Conversion [b]	% ee (*R*/*S*)[c]
1	0.2:0.4	$[Rh(OH)(R\text{-BINAP})]_2$ (2.5 mol%)	85	23 (*R*)
2	0.4:0.2	$[Rh(OH)(R\text{-BINAP})]_2$ (2.5 mol%)	72	55 (*R*)
3	0.4:0.2	$[Rh(OH)(cod)]_2$ (2.5 mol%)  *R*-SEGPHOS (6 mol%)	32	64 (*R*)
4	0.4:0.2	$[Rh(OH)(cod)]_2$ (2.5 mol%)  *R*-DTBM-SEGPHOS (6 mol%)	69	80 (*R*)
5[d]	0.4:0.2	$[Rh(OH)(cod)]_2$ (2.5 mol%) *R*-DTBM-SEGPHOS (6 mol%)	99	82 (*R*)

[a]Reaction conditions: **1.13a** and **1.14a**, Rh Cat., toluene (0.4 mL), 80 °C, 12 h. [b] Determined with CH_3NO_2 as an internal standard. [c] Determined by chiral HPLC analysis. [d] *t*-BuOH (0.4 mL).

Under the optimised reaction conditions, this protocol can be applied to substrates containing aryl phenols with electron withdrawing substituents (Table 1.5).

The addition of **1.14b** to **1.13a** produced *R*-**1.15b** in 96% yield and 80% ee (entry 1). Using the more electron-deficient **1.14c** produced *R*-**1.15c** with a higher ee, but lower yield (entry 2). 1-Naphthol was also tolerated well and produced *R*-**1.15d** with the highest enantioselectivity of 97% (entry 3). Increasing the steric bulk of the R substituent on the allene hindered the reaction, but did not increase the ee of the product (entries 4 and 5). Introducing a butyl group on the allene decreased the yield to 51% (entry 4), whilst the introduction of a phenyl group required a higher temperature and an extended reaction time of 48 hours (entry 5). Overall, increasing the steric bulk of the R substituent on the allenic moiety decreased the yield and the enantioselectivity.

Table 1.5: Asymmetric addition of phenols to diphenylphosphinylallene.[a]

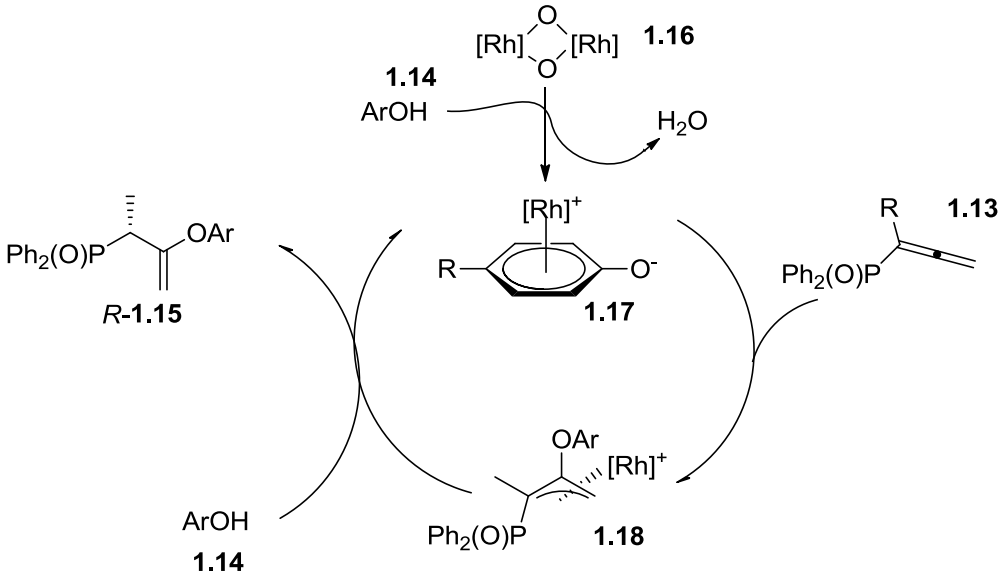


Entry	R	(Ar)	Product	% Yield[b]	% ee (*R/S*) [c]
1	Me (**1.13a**)	4-Me-C_6H_4 (**1.14b**)	**1.15b**	96	80 (*R*)
2	Me (**1.13a**)	4-Cl-C_6H_4 (**1.14c**)	**1.15c**	92	93 (*R*)
3	Me (**1.13a**)	1-Np (**1.14d**)	**1.15d**	99	97 (*R*)
4	Bu (**1.13b**)	4-Me-C_6H_4 (**1.14b**)	**1.15e**	51	88 (*R*)
5	Ph (**1.13c**)	4-Me-C_6H_4 (**1.14b**)	**1.15f**	78[d]	74 (*R*)

[a] Reaction conditions conditions: **1.13** (0.40 mmol.), **1.14** (0.20 mmol.), $[Rh(OH)(cod)]_2$ (2.5 mol%), *R*-DTBM-SEGPHOS (6 mol%), *t*-BuOH (0.4 mL), 80 °C, 24 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] *sec*-BuOH (0.4 mL), 100 °C, 48 h.

The proposed mechanism involved the formation of an aryl rhodium species, **1.17** by the reaction of the rhodium dimer **1.16** with the phenol (**1.14**) (Scheme 1.6). On the addition of the diphenylphosphineallene (**1.13**), a π-allylrhodium intermediate **1.18,** is formed. Subsequent protonolysis of **1.18** is promoted by an additional molecule of **1.14**, furnishing the hydroalkoxylation product *R*-**1.15** and regenerates the intermediate **1.17**. ^{31}P and ^{1}H NMR studies carried out during the reaction suggested the formation of intermediates **1.16**, **1.17** and **1.18**. The absolute configuration of

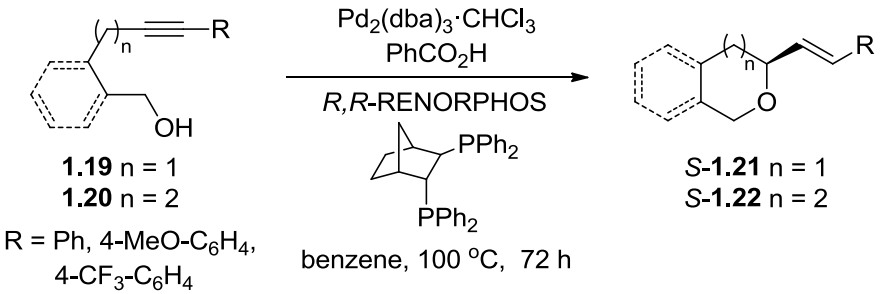
1.15 was determined to be *R* by X-ray analysis, which implies that the π–allyl protonation of **1.18** occurs on the *Si* face of the molecule.



Scheme 1.6: Proposed catalytic cycle.

1.2.2 Palladium

In 2006, the first asymmetric palladium-catalysed intramolecular hydroalkoxylation of alkynols **1.19** (n = 1) and **1.20** (n = 2) was reported, using a catalyst generated *in situ* from a mixture of $Pd_2(dba)_3{\cdot}CHCl_3$, benzoic acid and *R,R*-RENORPHOS (Scheme 1.7).[61]

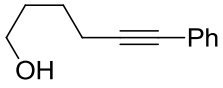
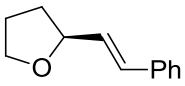
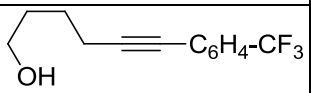
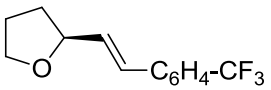
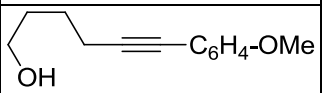
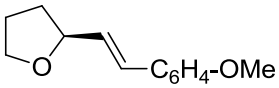
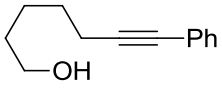
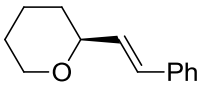
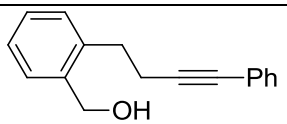
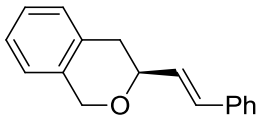


Scheme 1.7: Pd-catalysed cyclisation of alkynols.

Using 10 mol% of Pd(0), in a 1:2:6 ratio of Pd(0): $PhCO_2H$: *R,R*-RENORPHOS, furans and pyrans could be synthesised in moderate yields and enantioselectivities within 72 hours (Table 1.6). This system was capable of cyclising alkynols with terminal alkyne aryl groups; phenyl and 4-(trifluoromethyl)phenyl substituted

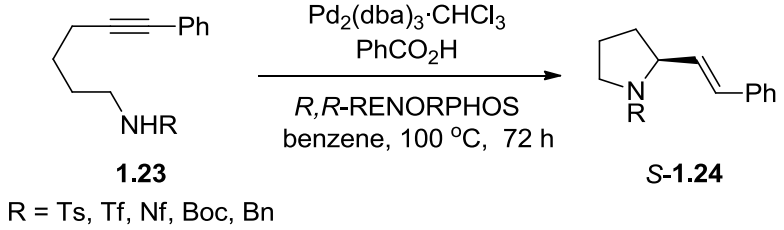
aminoalkynes (**1.19a** and **1.19b**) produced the respective tetrahydrofurans (**1.21a** and **1.21b**) in 52-60% yield and 80-82% ee (entries 1 and 2), whereas the introduction of 4-methoxyphenyl (**1.19c**) at the alkyne terminus decreased both yield and enantioselectivity (entry 3). Pyrans (*S*-**1.22a** and *S*-**1.22b**) were also obtained from the corresponding alkynols in 57-61% yield and 78-86% ee (entries 4 and 5).

Table 1.6: Hydroalkoxylation of alkynols.[a]

Entry	Substrate	Product	% Yield[b]	% ee (*R/S*)[c]
1	 **1.19a**	 **1.21a**	52	80 (*S*)
2	 **1.19b**	 **1.21b**	60	82 (*S*)
3	 **1.19c**	 **1.21c**	48	40 (*S*)
4	 **1.20a**	 **1.22a**	61	78 (*S*)
5	 **1.20b**	 **1.22b**	57	86 (*S*)

[a]Reaction conditions: Substrate (0.13 mmol., 500 mM), $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mol%), $PhCO_2H$ (20 mol%), *R,R*-RENORPHOS (60 mol%), benzene, 100 ^oC, 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

This protocol was also applied in the cyclisation of aminoalkynes **1.23** to their corresponding pyrrolidines *S*-**1.24** by altering the ratio of Pd(0):PhC_2OH: *R,R*-RENORPHOS to 1:2:5 (Scheme 1.8, Table 1.7).[14,22]



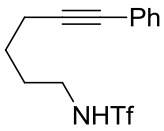
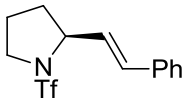
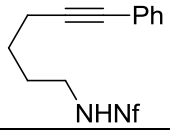
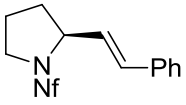
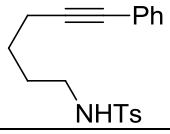
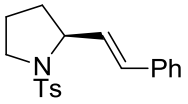
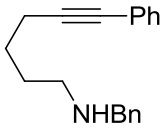
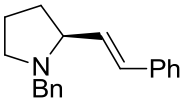
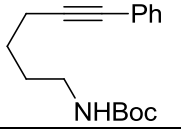
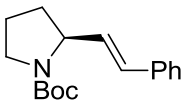
1.23 **S-1.24**

R = Ts, Tf, Nf, Boc, Bn

Scheme 1.8: Pd-catalysed cyclisation of alkyne amines.

Under these reactions conditions, the substrate scope is somewhat limited to aminoalkynes containing bulky electron-withdrawing sulfonyl protecting groups; 65% yield and 82% ee were achieved using trifluoromethanesulfonyl (Tf) as the *N*-protecting group (entry 1), which increased to 68% yield and 88% ee by using nonafluorobutanesufonyl (Nf) (entry 2). On the other hand, the use of tosyl and carbamate protecting groups produced pyrrolidines ***S*-1.24c** and ***S*-1.24e** in 25% and 0% yield respectively (entries 3 and 5), whereas benzyl protected pyrrolidine ***S*-1.24d** was obtained in the highest yield (95%), but only 8% ee (entry 4).

Table 1.7: Hydroamination reaction of aminoalkynes.[a]

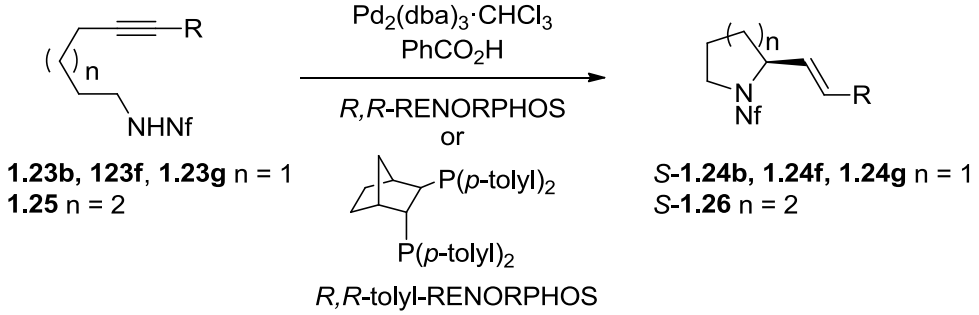
Entry	Substrate	Product	% Yield[b]	% ee (*R*/*S*)[c]
1	 **1.23a**	 **1.24a**	65	82 (*S*)
2	 **1.23b**	 **1.24b**	68	88 (*S*)
3	 **1.23c**	 **1.24c**	25	47 (*S*)
4	 **1.23d**	 **1.24d**	95	8 (*S*)
5	 **1.23e**	 **1.24e**	0	-

[a]Reaction conditions: Substrate (0.13 mmol., 500 mM), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol%), $PhCO_2H$ (10 mol%), *R*,*R*-RENORPHOS (25 mol%), benzene, 100 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Using Nf protected **1.23b**, the catalytic reaction was optimised (Table 1.8). Ultimately, an improvement to 95% yield and 90% ee was achieved by switching to the bulkier tolyl-RENORPHOS, increasing the catalytic loading to 20 mol%, decreasing the temperature to 80 °C and using a solvent mixture comprising of a 1:1 ratio of benzene to hexane (entry 1 *vs* 2).[22]

Under these reactions conditions, aminoalkynes (n = 1) with terminal aryl groups such as 4-methoxyphenyl (**1.23f**) and 4-(trifluoromethyl)phenyl (**1.23g**) proceeded to give yields and enantioselectivities of 90-93% and 88-90% respectively within 72 hours (entries 3 and 4). This protocol also allowed the cyclisation of an aminoalkyne **1.25** (n = 2), with a terminal aryl substituent, to produce the respective piperidine *S*-**1.26** in 88% yield and 86% ee (entry 5).

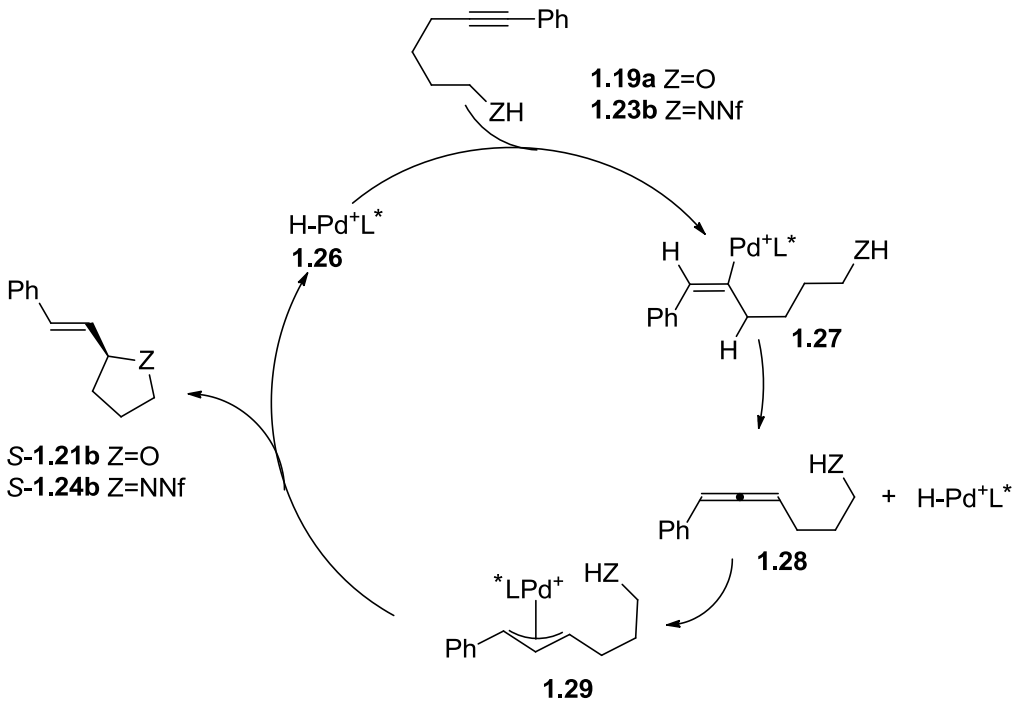
Table 1.8: Hydroamination of Nf protected aminoalkynes.[a]



Entry	Substrate		t (h)	% Yield[b]	% ee (*R*/*S*) [c]
	R	n			
1	Ph (**1.23b**)	1	72	68	83 (*S*)
2[d]	Ph (**1.23b**)	1	72	95	90 (*S*)
3[d]	4-MeO-C_6H_4 (**1.23f**)	1	72	93	88 (*S*)
4[d]	4-CF_3-C_6H_4 (**1.23g**)	1	72	90	90 (*S*)
5[d]	Ph (**1.25**)	2	72	88	86 (*S*)

[a]Reaction conditions: Substrate (0.13 mmol., 500 mM), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%), $PhCO_2H$ (10 mol%), *R*,*R*-RENORPHOS (25 mol%), benzene, 100 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] $Pd_2(dba)_3{\cdot}CHCl_3$ (20 mol%), $PhCO_2H$ (40 mol%), *R*,*R*-tolyl-RENORPHOS (20 mol%), benzene:hexane (2:1), 80 °C.

Yamamoto *et al.*[61] proposed a mechanism whereby the reaction initiated with the hydropalladation of alkyne **1.19a** (Z = O) or **1.23b** (Z = NNf) by a H-Pd^+L species, formed by Pd(0) and benzoic acid (Scheme 1.9). β-Hydride elimination from vinylpalladium species **1.27** formed allene intermediate **1.28** and the H-Pd^+L species, which recombine to give π-allyl-Pd species **1.29**. Subsequent intramolecular nucleophilic attack results in the formation of the 5-membered product *S*-**1.21a** (Z = O) or *S*-**1.24b** (Z = NNf) and regeneration of H-Pd^+L.



Scheme 1.9: Palladium mediated hydroamination and hydroalkoxylation of alkyne **1.19b** (Z = O) or **1.23b** (Z = NNf).

A DFT study was performed to investigate possible intermediates formed during the reaction. From these studies, intermediates **1.29a** and **1.29b,** where nucleophilic attack can occur to the *Si* or the *Re* face of the ayllpalladium intermediate **1.29** were identified (Figure 1.4).

1.29a (*S*) **1.29b** (*R*)

Figure 1.4: Intermediates **1.29a** and **1.29b**.

From these, transition states for the C-Z bond formation were calculated (Table 1.9). Comparing the relative energies of **1.29a** and **1.29b**, intermediate **1.29a** was found to have a slightly lower energy (0.8 for Z=NNf and 0.0 for Z=O) than **1.29b**.

Table 1.9: Relative energies (B3LYP/SDD) calculated for transitions states of **1.29a** and **1.29b**

Entry	Z	Intermediate	Resulting Enantiomer	Relative Energy (kcal mol^{-1})
1	NNf	**1.29a**	*S*	0.8
2	NNf	**1.29b**	*R*	1.4
3	O	**1.29a**	*S*	0.0
4	O	**1.29b**	*R*	0.7

1.2.3 Summary of Late Transition Metals in Heterofunctionalisation Reactions

Overall, the use of late transition metals (exclude the coinage metals) for hydroalkoxylation and hydroamination reactions of allenes is limited. Generally, high temperatures and long reactions times are required. The use of Rh(I) is constrained to intermolecular hydroalkoxylation reactions of phenols to diphenylphosphinylallenes. Nonetheless, high yields and enantioselectivities could be obtained. The cyclisation of alkynols and aminoalkynes by Pd(0) *via* allenic intermediates has been achieved asymmetrically; furans and pyrans could be furnished in low to moderate yields (48-61%) and enantioselectivities (40-86%), while aminoalkynes proceeded to the corresponding pyrrolidines and piperidines in moderate to high yields (68-95%) and enantioselectivities (83-91%). However, these high yields and ee's are limited to aminoalkynes with bulky electron withdrawing sulfonyl protecting groups.

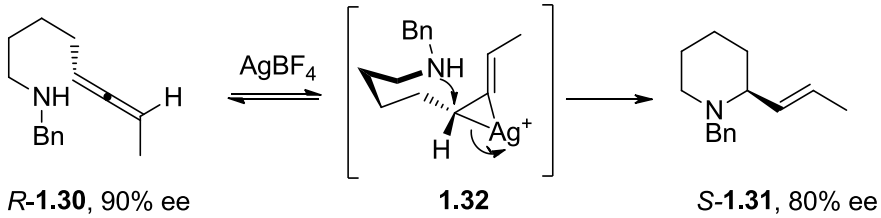
1.3 Group 11 Metals

In this section, the ability of silver and gold to catalyse hydroamination and hydro(acy)alkoxylation reactions will be discussed.

1.3.1 Silver

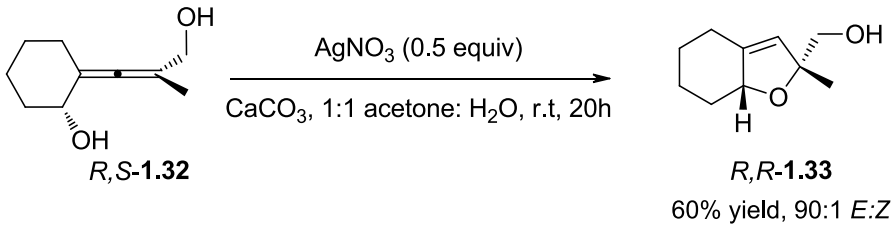
The use of silver in asymmetric heterofunctionalisation reactions of allenes is limited to the transfer of chirality from the precursor to afford an optically active product. [62-65]

For example, in a reported synthesis of *R*-(-)-Coniine, the chiral δ-allenic substrate ***R*-1.30**, was cyclised in the presence of $AgBF_4$ (50 mol%) to the 6-*exo* product ***S*-1.31** in 86% yield (Scheme 1.10, reaction times were not reported),[62] A small amount of racemisation was observed (10%) and the reaction was thought to proceed *via* a silver allene intermediate **1.32**.



Scheme 1.10: Hydroamination of chiral δ-allenic amine *R*-**1.30** with retention of chirality.

Retention of chirality was also observed in the cyclisation of substrate *R,S*-**1.32** (Scheme 1.11).[64] It was established that the secondary alcohol was cyclised in preference to the primary alcohol to form *R,R*-**1.33** in 60% yield with complete stereocontrol.[64]

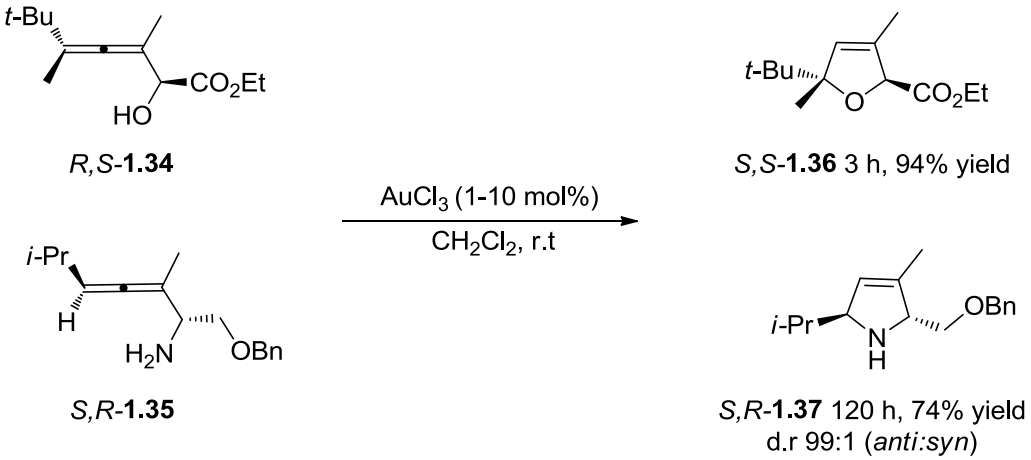


Scheme 1.11: Preferential cyclisation of secondary alcohols.

1.3.2 Gold

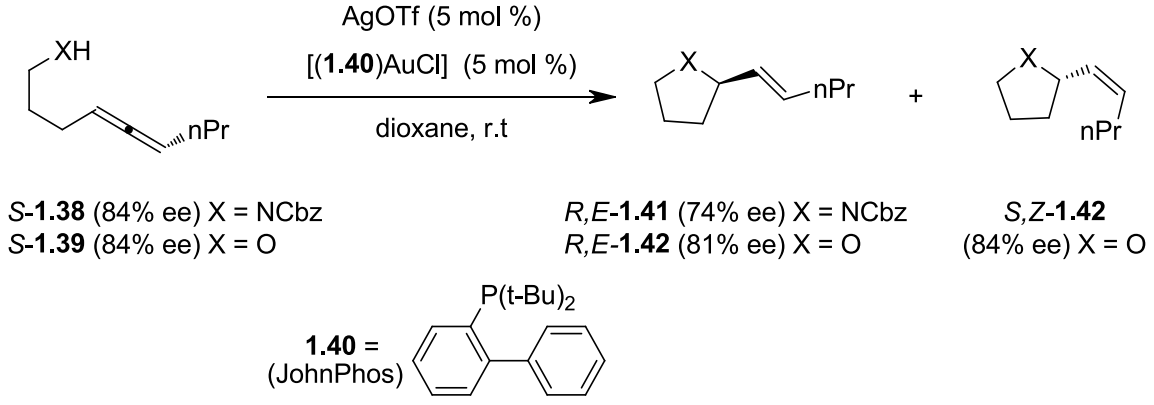
Up until 2006, chirality transfer from an optically active starting material to product (as was described for silver) was the only approach available to furnish chiral heterofunctionalisation products using gold catalysis.[49,54,66-73] For example, Krause *et al.* was able to show for the first time that α-allenic alcohols (**1.34**) and α-allenic amines (**1.35**) could be converted into 2,5-dihydrofurans (**1.36**) and 3-pyrrolines (**1.37**) respectively, in the presence of gold(III) chloride ($AuCl_3$), with complete chirality transfer (Scheme 1.12). [49,66-73] The cyclisation of *S,S*-**1.34** could be achieved

in 94% within 3 hours,[66] while the cyclisation of α-allenic amine *S,R*-**1.35** required a longer reaction time of 120 hours, but afforded 3-pyrroline *S,R*-**1.37** in 74% yield (99:1 *anti:syn* ratio).[49,67]



Scheme 1.12: Cyclisation of α-allenic alcohols (*S,S*-**1.34**) and amine (*S,R*-**1.35**) using $AuCl_3$.

Chirality could also be transferred in the cyclisation of γ-allenic carbamate *S*-**1.38** and alcohol *S*-**1.39** using a catalytic system generated from a mixture of [(**1.40**)AuCl] and AgOTf in a 1:1 ratio (Scheme 1.13).[58] Cyclisation of γ-allenic carbamate *S*-**1.38** (84% ee) furnished (*R,E*)-**1.41** in 96% yield and 74% ee with ≥50:1 selective formation of the *E*-alkene, whereas cyclisation of γ-allenic alcohol *S*-**1.40** (84% ee) resulted in the formation of *R,E*-**1.42a** (81% ee) and *S,Z*-**1.42b** (84% ee) in a 5.5:1 ratio.



Scheme 1.13: Hydroamination and hydroalkoxylation reactions using [**1.40**AuCl] as a catalyst.

Enantioselective catalysis was achieved a year later by Widenhoefer *et al.* using a dimeric Au(I) complex, $[Au_2(P–P)Cl_2]$ (where P–P = *S*-3,5-DTBM-MeOBIPHEP, **1.43**), activated by Ag salts (Figure 1.5).[37,45] Using this catalyst, enantioselectivities of up to 96% can be achieved in heterofunctionalisation reactions involving allenes.

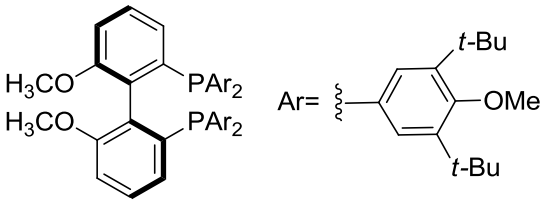
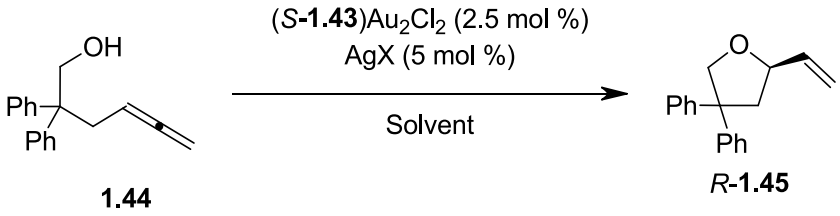


Figure 1.5: Structure of *S*-3,5-DTBM-MeOBIPHEP, **1.43**.

While optimising the cyclisation reaction of γ-allenic alcohol **1.44** to tetrahydrofuran *R*-**1.45**, the reaction was found to have a strong dependence on the counteranion and solvent used (Table 1.10).[45]

Table 1.10: Optimisation study using allenic alcohol **1.44**.[a]



1.44 *R*-**1.45**

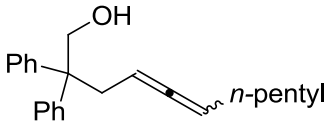
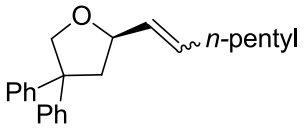
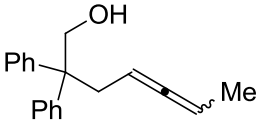
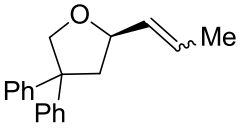
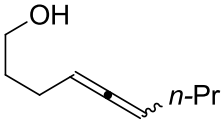
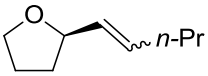
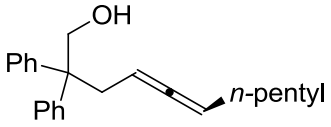
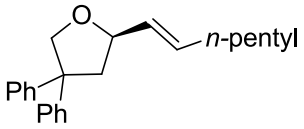
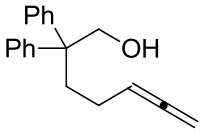
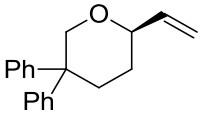
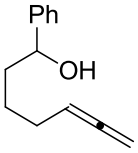
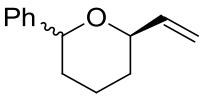
Entry	Solvent	X	T (^oC)	Concentration (mM)	t (h)	%Yield[b]	% ee (*R/S*)[c]
1	Dioxane	ClO_4	r.t	125	2	75	28 (*R*)
2	Dioxane	OTs	r.t	125	1	38	86 (*R*)
3	Dioxane	OAc	r.t	125	17	0	-
4	Toluene	OTs	r.t	125	<0.1	73	86 (*R*)
5	MeOH	OTs	r.t	125	47	91	22 (*R*)
6	Toluene	OTs	-20	125	4.5	59	94 (*R*)
7	Toluene	OTs	-20	63	18	76	93 (*R*)

[a] Reaction conditions: **1.44** (31.3 mg , 0.13 mmol.), (*S*-**1.43**)Au_2Cl_2 (2.5 mol%), AgX (5 mol%), Solvent (1.0-2.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC/GC analysis.

Cyclisation of γ-allenic alcohol **1.44** with $AgClO_4$, in dioxane, produced *R*-**1.45** in 2 hours with 75% yield and 28% ee (entry 1). Changing the counteranion from ClO_4 to OTs increased the enantioselectivity from 28% to 86% (entry 2), whereas no reaction was observed using OAc (entry 3). Switching the solvent from dioxane to toluene was found to decrease the conversion time to less than 10 minutes without affecting the ee or yield (entry 2 *vs* 4). On the other hand, the use of MeOH diminished both enantioselectivity and rate, requiring 47 hours to obtain *R*-**1.45** in 22% ee (entry 5). Lowering the temperature to -20 ^{o}C, increased the enantioselectivity to 94%, but with only 59% yield within 4.5 hours (entry 6). Overall, by carrying out the reaction at -20 ^{o}C with a two-fold dilution, *R*-**1.45** was obtained in 76% yield and 93% ee in 18 hours (entry 7).

Using the optimised conditions, γ-allenic alcohols possessing aryl substituents along the allene backbone (Table 1.11, entries 1, 2 and 4) and alkyl substituents on the terminal allenic carbon atom (entries 1 to 4) could be cyclised to the corresponding tetrahydrofurans in high yields and enantioselectivities; the reaction of γ-allenic alcohol **1.46a** furnished **1.47a** in a 1:1 ratio of *E:Z* isomers with 94% yield and >95% ee (entry 1). Switching the *n*-pentyl for a methyl group (**1.46b**) also afforded **1.47b** in high yield and ee (entry 2). However, diminished enantioselectivity was observed when the β-allenic substituents were removed (entry 3), thus suggesting this reaction outcome is substrate dependant. Cyclisation of chiral *R*-**1.46d** proceeded to tetrahydrofuran *R*-**1.46d** exclusively in >95% ee with a >20:1 selectivity for the *E* isomer (entry 4). δ-Allenic alcohols possessing mono or diaryl substitution along the allene chain could also be cyclised using this protocol; subjecting **1.48a** to the catalytic conditions furnished *R*-**1.49a** in 96% yield with an enantioselectivity of 88% (entry 5), whereas a 1:3.3 ratio of *anti* to *syn* isomers were formed using substrate **1.48b** (entry 6).

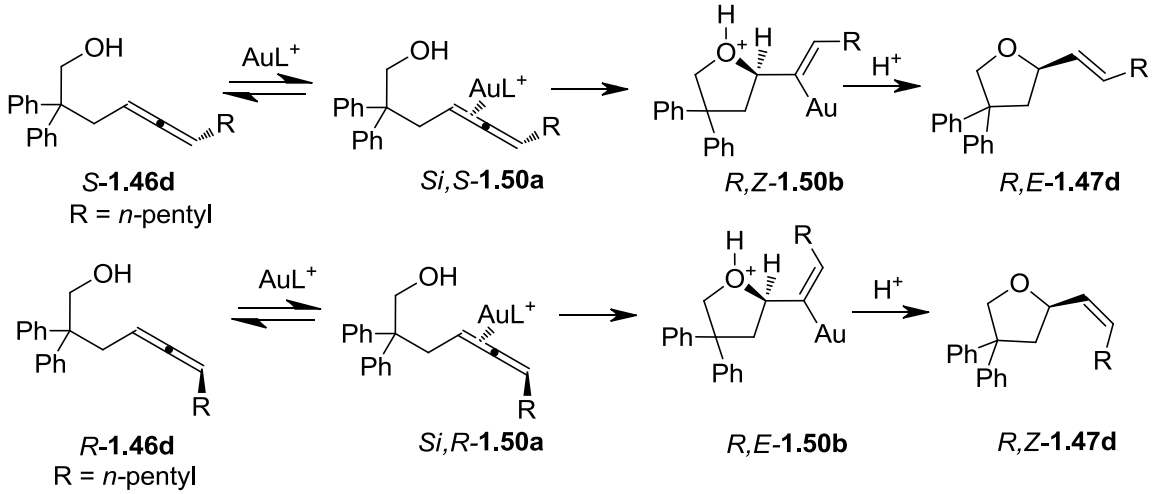
Table 1.11: Intramolecular hydroalkoxylation of δ- and γ-allenic alcohols.[a]

Entry	Substrate	Product	Isomer ratio (E/Z)[b]	% Yield[c]	% ee (*R*/*S*)[d]
1	 **1.46a**	 **1.47a**	1:1	94	>95/>95 (*R*)
2	 **1.46b**	 **1.47b**	1:1	95	93/95 (*R*)
3	 **1.46c**	 **1.47c**	1.5:1	94	28/39 (*R*)
4	 ***R*-1.46d**	 **1.47d**	>20:1	86	>95 (*R*)
5	 **1.48a**	 **1.49a**	-	96	88 (*R*)
6	 **1.48b**	 **1.49b**	1:3.3[e]	95	88/45 (*R*)

[a]Reaction conditions: Substrate (0.13 mmol., 125 mM), (*S*-**1.43**)Au_2Cl_2 (2.5 mol%), AgOTs (5 mol%), toluene (1.0 mL), r.t, 12-24 h. [b] Determined by ^{1}H NMR integration. [c] Isolated yield. [d] Determined by chiral HPLC/GC analysis. [e] *anti/syn* ratio.

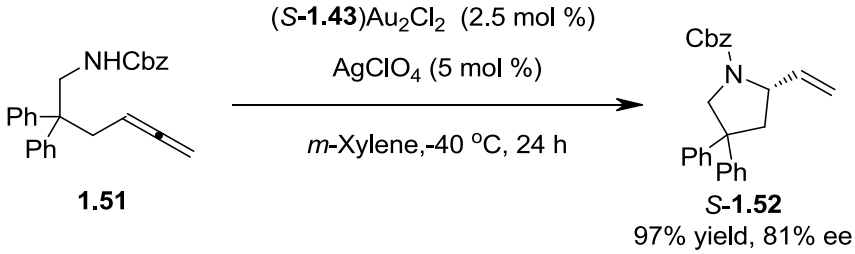
Interesting match-mismatch effects were observed between the catalyst and substrates containing alkyl substituents on the terminal allenic carbon atom. For example, using (*S*-**1.43**)Au_2Cl_2 and substrate *R*-**1.46d**, preference for the *Z* isomer was observed,

whereas preference for the *E* isomer was observed using (*S*-**1.43**)Au_2Cl_2 with substrate *S*-**1.46d** (Scheme 1.14). This led the authors to propose a mechanism involving an outer-sphere cyclisation of **1.46d**, and subsequent protonolysis of **1.50b**. Complexion of the Au(I) catalyst *E* to the terminal allenic moiety would form the preferred product *R,Z*-**1.47d** *via Si,R*-**1.50a** and *R,E*-**1.50b**, whereas for the formation of *R,E*-**1.47d** complexion of the gold complex would have to occur *Z* to the terminal allenic moiety (*Si,S*-**1.49**). This indicated that a stereochemical relationship between the catalyst and substrate combined to determine the relative configuration about the C=C bond.



Scheme 1.14: Cyclisation of *S*-**1.46d** and *R*-**1.46d** where R = *n*-pentyl.

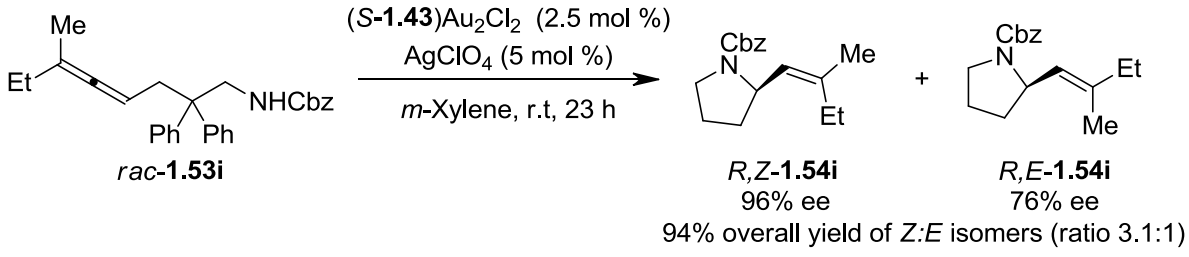
For subsequent hydroamination reactions, the conditions used in the respective hydroalkoxylation reactions were re-optimised using the same catalyst.[37] This led to the use of $AgClO_4$, reduction of temperature to -40 ^oC and by using a *m*-xylene solution. Interestingly, in contrast to hydroalkoxylation reactions the opposite stereochemistry was observed using the same catalyst; pyrrolidine **1.52** could be isolated in 97% yield with 81% ee from γ-allenic carbamate **1.51** (Scheme 1.15).



Scheme 1.15: Hydroamination of *N*-allenyl carbamates by (*S*-**1.43**)Au_2Cl_2.

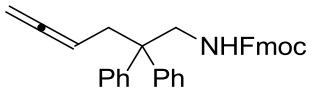
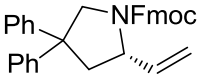
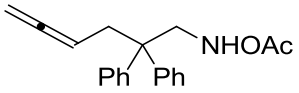
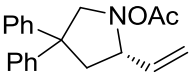
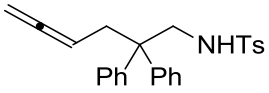
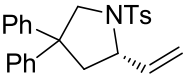
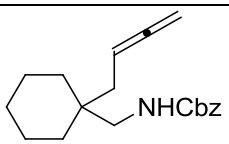
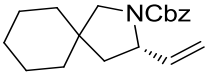
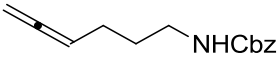
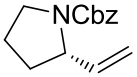
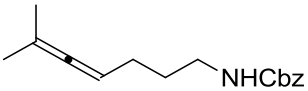
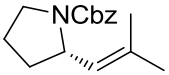
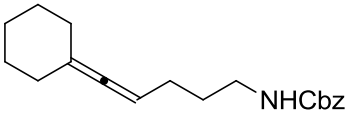
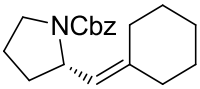
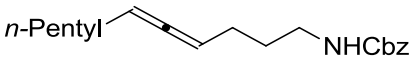
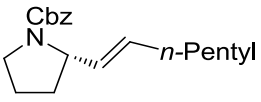
This gold catalyst has a relatively wide scope, incorporating a number of protecting groups including acetyl and fluorenylmethyloxycarbonyl (Fmoc) to produce the corresponding pyrrolidines **1.54a** and **1.54b** in high yields (83-84%) and enantioselectivities of 97% and 61%, respectively (Table 1.12, entries 1 and 2). In contrast, the cyclisation of *γ*-allenic sulfonamide **1.53c** proceeded in only 8% ee (entry 3). Overall, the enantioselectivity was found to be sensitive to the nature of the functional groups present at the β-position of the alkyl chain. For example, the cyclohexyl-substituted *γ*-allenic carbamate **1.53d** furnished pyrrolidine **1.54d** in 98% yield, but with only 50% ee (entry 4). This was further demonstrated by the cyclisation of **1.53e**, where removal of all substituents saw a decrease in the ee to 34% (entry 5). This protocol was also tolerant of alkyl substituents on the terminal allenic carbon (entries 6 and 7), where the presence of methyl and cyclohexyl groups required a higher temperature, but still gave modest ee values of 80% and 76% respectively. On the other hand, cyclisation of racemic **1.53h** afforded *E*-**1.54h** exclusively with 6% ee (entry 8). This suggested that interconversion between the enantiomers of the starting material had occurred.

To investigate this further, cyclisation of racemic trisubsituted allenic carbamate **1.53i** was found to afford a 3.1:1 ratio of *R,Z*-**1.54i** and *R,E*-**1.54i** isomers, where the major diastereoisomer (*Z*-**1.54i**) exhibited a higher degree of enantiomeric enrichment (Scheme 1.16).[38] This observation of stereoselective control was explained by a similar mechanism to the one proposed for hydroalkoxylation reactions, except that (*S*-**1.43**)Au_2Cl_2/$AgClO_4$ is able to reversibly convert *S*-**1.53i** to *R*-**1.53i**.[38]



Scheme 1.16: Cyclisation of racemic **1.53i** to diastereoisomers *R,Z*-**1.54i** and *R,E*-**1.54i**.

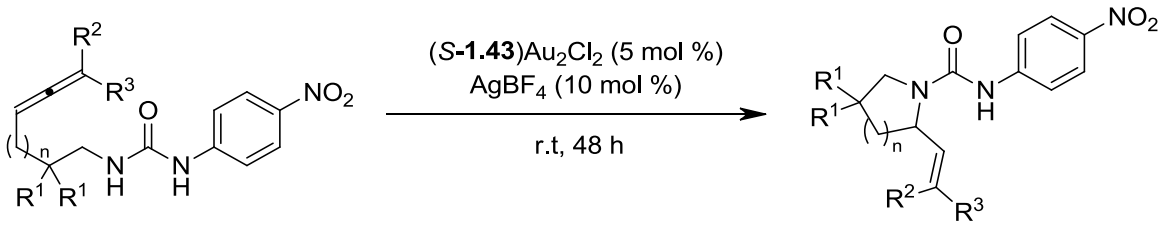
Table 1.12: Intramolecular hydroamination of γ-allenic carbamates.[a]

Entry	Substrate	Product	T (°C)	t (h)	% Yield[b]	% ee (*R/S*) [c]
1	 **1.53a**	 **1.54a**	-20	48	61	83(*S*)
2	 **1.53b**	 **1.54b**	-20 then r.t	72	97	84 (*S*)
3	 **1.53c**	 **1.54c**	-20	48	66	8 (*S*)
4	 **1.53d**	 **1.54d**	-20	48	98	50 (*S*)
5	 **1.53e**	 **1.54e**	-20	24	99	34 (*S*)
6	 **1.53f**	 **1.54f**	-20	48	80	80 (*S*)
7	 **1.53g**	 **1.54g**	0	24	91	76 (*S*)
8	 *rac*-**1.53h**	 *E*-**1.54h**	-20	24	86[b]	6 (*S*)

[a]Reaction conditions: Substrate (0.3 mmol., 300 mM), (*S*-**1.43**)Au_2Cl_2 (2.5 mol%), $AgClO_4$ (5 mol%), *m*-Xylene (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC/GC analysis.

This protocol was recently extended to include the cyclisation of the less nucleophilic *N*-allenyl ureas (**1.57a** to **1.57e**) by switching the solvent to Et_2O and silver salt to $AgBF_4$ (Table 1.13).[41]

Table 1.13: Au-catalysed cyclisation of *N*-allenyl ureas.[a]

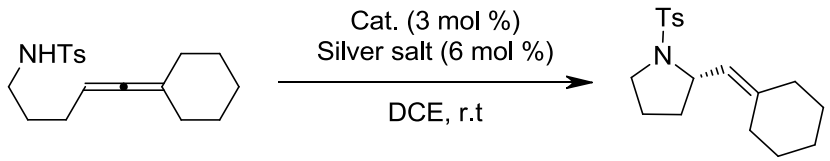


Entry	Starting material		T (^{o}C)	% Yield[b]	% ee [c]
	R	n			
1	**1.57a** R^1 = Ph, R^2 = R^3 = H	1	r.t	90	93
2	**1.57b**, R^1 = Ph R^2 = R^3 = Me	1	r.t	82	53
3	**1.57c** R^1 = R^2 = R^3 = H	1	r.t	89	7
4	**1.57d** R^1 = Ph, R^2 = R^3 = H	2	r.t	91	56
5[d]	**1.57e** R^1 = Ph, R^2 = Et, R^3 = n-hexyl	1	0	89	91/90[e]

[a] Reaction conditions: Substrate (0.05 mmol., 101 mM), (*S*-**1.43**)Au_2Cl_2 (5 mol%), $AgBF_4$ (10 mol%), Et_2O (0.5 mL), r.t, 48 h [b] Isolated yield. [c] Determined by chiral HPLC analysis.
[d] Et_2O: $CHCl_3$ 3:1 ratio (0.5 mL) [e] 1:1 ratio of *Z:E* isomer.

Moderate to high enantioselectivities could be attained for *N*-allenyl ureas within 48 hours (entries 1, 2, 4 and 5), but the reaction was sensitive to substitution along the alkyl chain (entry 3); *N*-allenyl urea **1.57a** with β-phenyl substituents, furnished the respective tetrahydrofuran in 93% ee (entry 1), whereas the introduction of methyl substituents on the terminal carbon atom (**1.57b**) decreased the selectivity to 53% (entry 2). As an extreme, removal of all substituents resulted in an almost racemic product (entry 3), which suggested the reaction for *N*-allenyl ureas is also substrate-dependant. Cyclisation of **1.57d**, the δ-allenic equivalent to **1.57a**, decreased the ee from 93 to 56% (entry 1 *vs* 4), while cyclisation of chiral **1.57e** afforded a 1:1 ratio of *Z:E* diastereoisomers at 0 ^{o}C, using a 3:1 mixture of Et_2O to $CHCl_3$. This suggested racemisation of chiral **1.57e** is slower in comparison to the respective hydroamination reactions of γ-allenic amines described in Table 1.12.

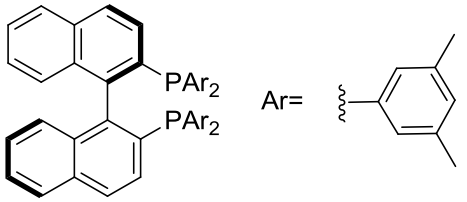
Concurrently, Toste *et al.* reported on similar reactions using chiral dinuclear Au(I)-phosphine complexes to cyclise *γ*- and *δ*-allenic sulfonamides to the respective pyrrolidines and piperidines.[40] Optimisation reactions involving *γ*-allenic amine **1.58** also identified a pronounced effect of the counteranion (Scheme 1.17, Table 1.14).



1.58 **S-1.59**

Scheme 1.17: Hydroamination using $[Au_2(P\text{-}P)Cl_2]$ as a catalyst.

Table 1.14: Cyclisation of γ-allenic amine **1.58** by isolated and pre-catalysts.[a]

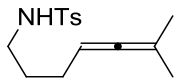
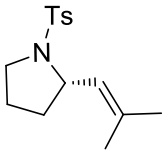
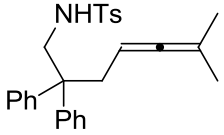
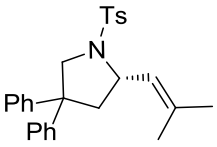
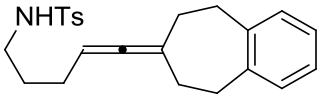
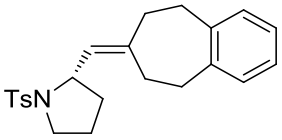
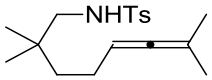
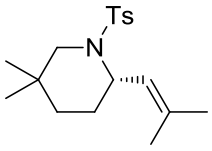
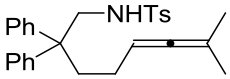
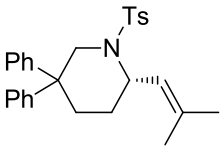
Entry	Catalyst	t (h)	% Yield[b]	% ee (*R*/*S*)[c]
1	3 mol% *R*-xylyl-BINAP$(AuCl)_2$/6 mol% $AgBF_4$ 	0.5	82	1
2	3 mol% *R*-xylyl-BINAP$(AuCl)_2$/6 mol% AgOPNB	24	27	98 (*S*)
3	3 mol% *R*-xylyl-BINAP$(AuOPNB)_2$	17	88	98 (*S*)

[a]Reaction conditions: DCE, r.t. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] CH_2Cl_2.

An amplification in enantiomeric excess was observed when benzoate counterions were employed. The cyclisation of γ-allenic amine **1.58**, with a catalyst generated from a mixture of *R*-xylyl-BINAP$(AuCl)_2$ and $AgBF_4$ furnished the respective pyrrolidine product, *S*-**1.59** in an excellent yield, but with only 1% ee (entry 1). When the silver counterion was exchanged for AgOPNB, where PNB = p-nitrobenzoate, the yield diminished from 82% to only 27%, but the enantiomeric excess of the product rose dramatically to 98% (entry 2). When the isolated catalyst, *R*-xylyl-BINAP$(AuOPNB)_2$ generated from a mixture of *R*-xylyl-BINAP$(AuCl)_2$ and AgOPNB was utilised, the yield rose to a respective 88% (entry 3).

This protocol was able to cyclise cyclic and linear γ-allenic substrates **1.60a** to **1.60c** to the corresponding pyrrolidines (*S*-**1.61a** to *S*-**1.61c**) in high yields and enantioselectivities (Table 1.15, entries 1 to 3).

Table 1.15: Intramolecular hydroamination of δ- and γ-allenic substrates.[a]

Entry	Substrate	Product	% Yield[b]	% ee (*R*/*S*)[c]
1	 **1.60a**	 **1.61a**	98	99 (*S*)
2	 **1.60b**	 **1.61b**	99	87 (*S*)
3	 **1.60c**	 **1.61c**	80	98 (*S*)
4[e]	 **1.60d**	 **1.61d**	70	98 (*S*)
5[e]	 **1.60e**	 **1.61e**	70	88 (*S*)

[a]Reaction conditions: *R*-xylyl-BINAP(AuOPNB)$_2$ (3 mol%), DCE, rt., 15 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d]Reaction took 25 h.[e] *R*-Cl-MeO-BIPHEP(AuOPNB)$_2$ (5 mol%), $MeNO_2$, 50 ^oC, 24 h.

All these examples contained substituents on the terminal allenic carbon atom and tosyl as the *N*-protecting group. Overall, increasing the steric bulk of the terminal allenic substituent(s) was observed to decrease the yield (entries 1 and 2 *vs* 3). For the formation of chiral piperidines *S*-**1.61d** and *S*-**1.61e**, high yields (70%) and enantioselectivities of 88% to 98% were achieved by using *R*-Cl-MeO-BIPHEP (Figure 1.6) at 50 ^oC in nitromethane (entries 4 and 5).

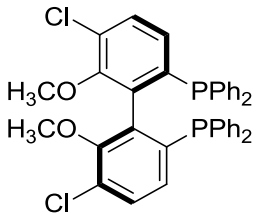
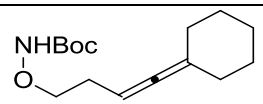
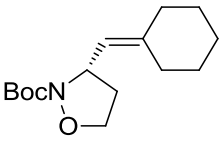
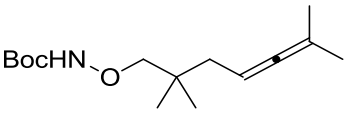
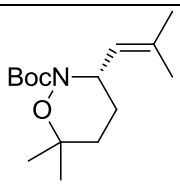
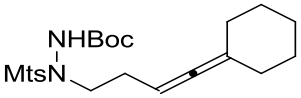
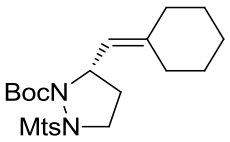


Figure 1.6: Structure of *R*-Cl-MeO-BIPHEP

This protocol was extended to include the formation of cyclic structures with two heteroatoms (Table 1.16).[44]

Table 1.16: Intramolecular hydroamination of β-allenic hydrazine, β- and γ-allenic hydroxylamines.[a]

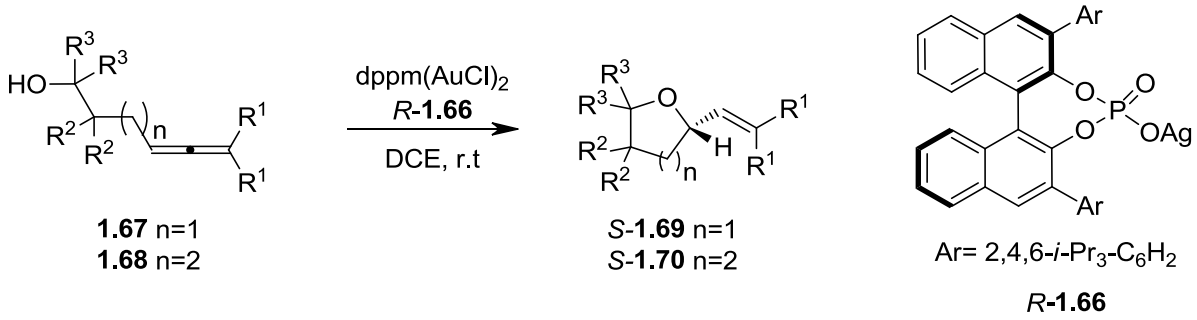
Entry	Substrate	Product	% Yield[b]	% ee (*R/S*) [c]
1	 **1.62a**	 **1.63a**	93	93 (*S*)
2[d]	 **1.62b**	 **1.63b**	93	93 (*S*)
3[e]	 **1.64** Mts = 2-mesitylenesulfonyl	 **1.65**	78	97 (*S*)

[a] **1.62a** (100 mM), *R*-xylyl-BINAP(AuOPNB)$_2$ (3 mol%), DCM, r.t, 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] **1.62b** (300 mM), *R*-xylyl-BINAP(AuOPNB)$_2$ (5 mol%), $MeNO_2$, 50 ^oC, 24 h. [e] **1.64** (300 mM), *R*-DTBM-SEGPHOS(AuOPNB)$_2$ (5 mol%), 15 h.

Under the original reaction conditions, **1.62a** was cyclised with 3 mol% of *R*-xylyl-BINAP(AuOPNB)$_2$, in DCE at room temperature, to afford isoxazolidine *S*-**1.63a** in 93% ee after 24 hours (entry 1). Conversely, tetrahydrooxazine *S*-**1.63b** could be furnished in 93% yield by switching the solvent to nitromethane, and by increasing both the catalytic loading and temperature (entry 2), while cyclisation of β-allenic hydrazine **1.64** afforded pyrazolidine *S*-**1.65** in 97% ee after 15 hours by modifying the diphosphine ligand to *R*-DTBM-SEGPHOS (entry 3).

Toste and co-workers also reported the use of a catalyst produced from achiral dppm(AuCl)$_2$ (where dppm = 1,1-*bis*(diphenylphospino)methane) and a chiral silver phosphate *R*-**1.66**, to facilitate hydroalkoxylation reactions of γ- (**1.67**) and δ-allenic (**1.68**) alcohols (Scheme 1.18).[36] This alternative approach was established from the

noticeable counteranion effects in their previous work,[40] and takes advantage of the interaction of an ion pair, containing a cationic Au(I) catalyst and a chiral counteranion, to induce asymmetry.



Scheme 1.18: Hydroalkoxylation reactions using *R*-**1.66** as the source of chirality.

The catalytic system was used to cyclise γ-allenic alcohol substrates with dialkyl substituents at the allene terminus (Table 1.17, entries 1-5) and at the β-position (entry 3) in excellent enantioselectivities and yields after 1-2 hours. In comparison, methyl (**1.67d**) and especially phenyl (**1.67e**) substituents in the α-position required extended reaction times to cyclise to the corresponding tetrahydrofurans **1.69d** and **1.69e** (entries 4 and 5). The highest enantioselectivities were obtained for allenes possessing a terminus cyclohexyl group (entries 2 to 5). Only two δ-allenic alcohols **1.68a** and **1.68b** were cyclised under this protocol (entries 6 and 7); methyl substituents at the allene terminus provided the corresponding tetrahydropyran **1.70a** in a high yield and enantioselectivity of 81% and 90% respectively (entry 6). However, the unsubstituted δ-allenic alcohol **1.68b** afforded **1.70b** in a lower enantioselectivity of 80% (entry 7). Yet again, this protocol seems to be substrate dependant. The enantioselectivity achieved in the cyclisation of unsubstituted δ-allenic alcohols **1.68b** to **1.70b** could be increased to 92% ee by using a catalytic mixture of chiral *S*,*S*-DIPAMP(AuCl)$_2$ (Figure 1.7) and *R*-**1.66** (entry 7, value in parenthesis).

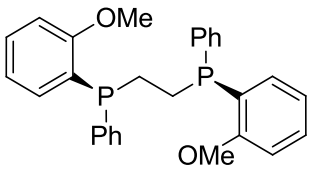
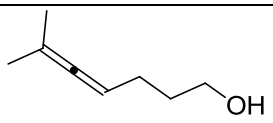
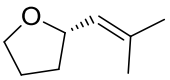
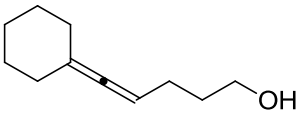
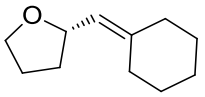
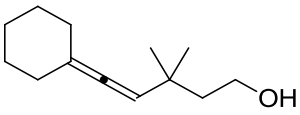
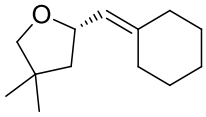
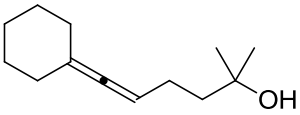
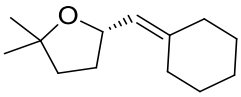
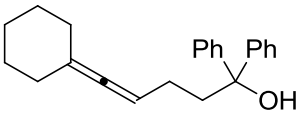
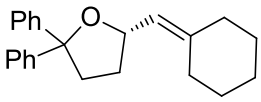
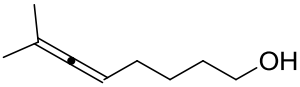
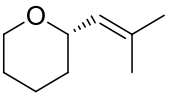
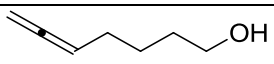
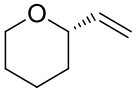


Figure 1.7: Structure of *S*,*S*-DIPAMP.

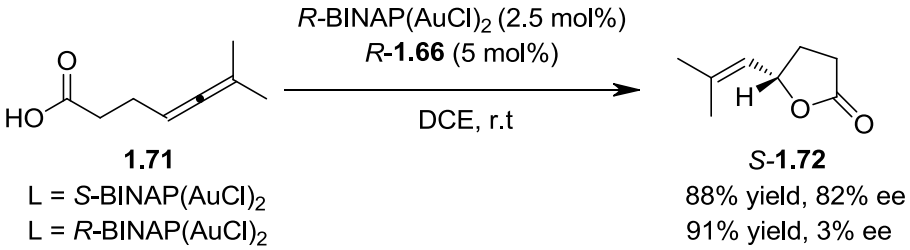
Table 1.17: Enantioselective hydroalkoxylation of γ- and δ-allenic alcohols using chiral counteranions.[a]

Entry	Substrate	Product	t (h)	% Yield[b]	% ee (*R*/*S*)[c]
1	 **1.67a**	 **1.69a**	1	91	95 (*S*)
2	 **1.67b**	 **1.69b**	1	90	97 (*S*)
3	 **1.67c**	 **1.69c**	13	91	95 (*S*)
4	 **1.67d**	 **1.69d**	2	79	99 (*S*)
5	 **1.67e**	 **1.69e**	30	86	92 (*S*)
6	 **1.68a**	 **1.70a**	15	81	90 (*S*)
7	 **1.68b**	 **1.70b**	24	96	80 (92)[d] (*S*)

[a] Reaction conditions: Substrate (0.2 mmol., 100 mM), dppm$(AuCl)_2$ (5 mol%), *R*-**1.66** (5 mol%), benzene (2.0 mL), r.t. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] *S*,*S*-DIPAMP$(AuCl)_2$ (2.5 mol%).

The same approach was applied in the enantioselective cyclisation of β-allenoic acids. For example, using a mixture of the pre-catalyst *S*-BINAP$(AuCl)_2$ and *R*-**1.66**, cyclisation of β-allenoic acid **1.71** afforded lactone *S*-**1.72** in 88% yield with 82% ee

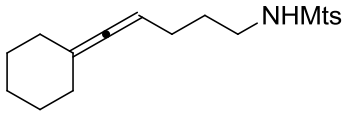
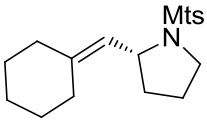
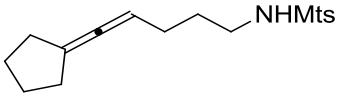
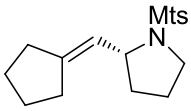
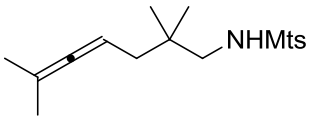
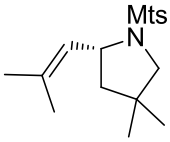
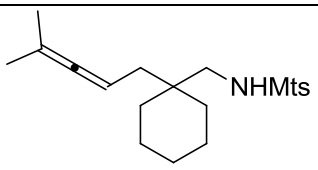
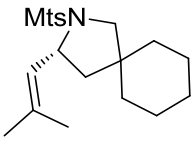
(Scheme 1.19). In contrast, the use of *R*-BINAP(AuCl)$_2$ identified a mismatch between the chiral diphosphine ligand and chiral counteranion, producing lactone *S*-**1.72** in only 3% ee.



Scheme 1.19: Cyclisation of β-allenoic acid **1.71**.

Toste and co-workers were also able to cyclise *γ*-allenic sulfonamides **1.73** to the corresponding pyrrolidines *R*-**1.74** in high enantioselectivities by using equal quantities of *R*-**1.66** and PhMe$_2$PAuCl (Table 1.18).[36]

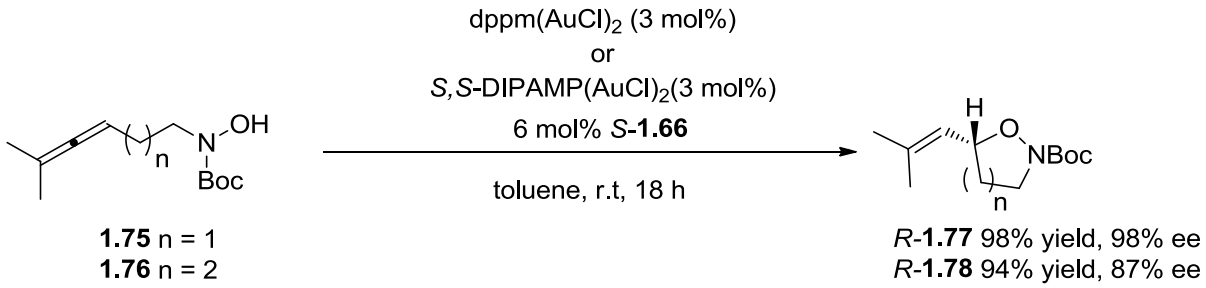
Table 1.18: Hydroamination of *γ*-allenic sulfonamides.[a]

Entry	Substrate	Product	% Yield[b]	% ee (*R*/*S*) [c]
1	 **1.73a**	 **1.74a**	97	96 (*R*)
2	 **1.73b**	 **1.74b**	88	98 (*R*)
3	 **1.73c**	 **1.74c**	84	99 (*R*)
4	 **1.73d**	 **1.74d**	73	98 (*R*)

[a]Reaction conditions: **1.74** (0.2 mmol., 100 mM), PhMe$_2$PAuCl (5 mol%), *R*-**1.66** (5 mol%), benzene (2.0 mL), r.t, 48h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

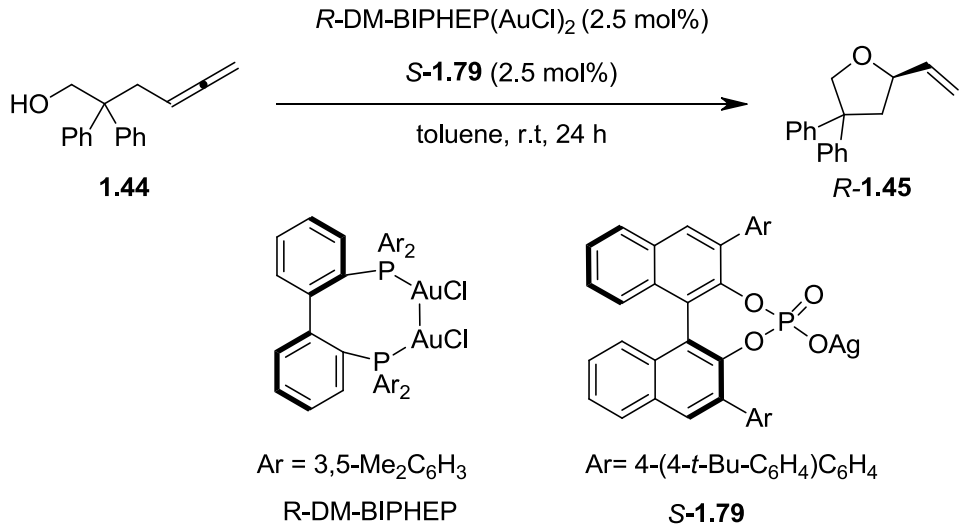
This protocol was tolerant of dialkyl substituents on the allene terminus (entries 1 to 4) and at the α- and β-positions (entries 3 and 4), affording excellent enantioselectivities and yields. However, effective hydroamination reactions were restricted to bulky *γ*-allenic sulfonamides and of substrates with terminal disubstitution.

This protocol was extended to include *N*-linked hydroxylamines **1.75** and **1.76** (Scheme 1.20).[44] Cyclisation of 1.**75** furnished the respective vinyl-isoxazolidine **1.77** in high yield (98%) and enantioselectivity (98%) in the presence of 3 mol% of dppm$(AuCl)_2$ and 6 mol% of *S*-**1.66**, whereas the use of 3 mol% of *S,S*-DIPAMP$(AuCl)_2$ (Figure 1.7) proved superior for the cyclisation of **1.76** to the corresponding tetrahydrooxazine *R*-**1.78** in 94% yield and 87% ee.



Scheme 1.20: Cyclisation of N-linked hydroxylamines **1.75** and **1.76**.

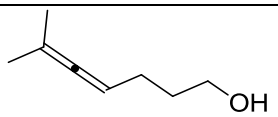
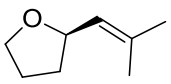
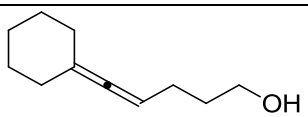
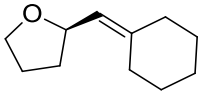
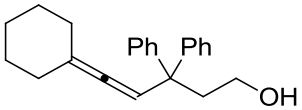
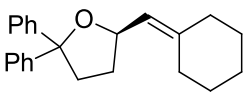
The research group of Mikami were able to utilise the combination of a chiral diphosphine ligand and a chiral counteranion synergistically for hydroalkoxylation reactions.[68] Interesting match-mismatch effects were observed between the chiral diphosphine ligand, *R*-DM-BIPHEP and chiral counteranion **1.79**; *R*-diphosphine with *S*-**1.79** produced the tetrahydrofuran *R*-**1.45** in 42% ee with a 33% yield, whereas *R*-diphosphine with *R*-**1.79** produced the tetrahydrofuran *R*-**1.45** in a 94% yield with 87% ee (Scheme 1.21).



Scheme 1.21: Hydroalkoxylation of **1.44** using an ion pair containing DM-BIPHEP(AuCl)$_2$ and *R*-**1.79**.

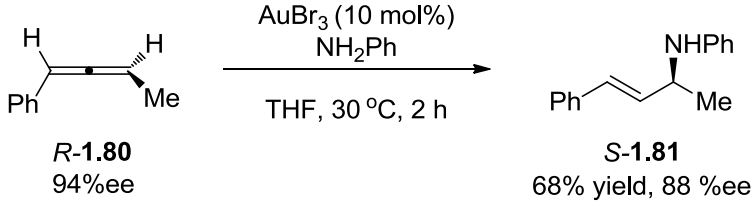
This protocol tolerated substrates with β-aryl substituents and dialkyl substitution of the terminal allenic carbon atom (Table 1.19). Higher enantioselectivities were observed for substrates containing terminal allenic substituents (entries 1 and 2), except when phenyl groups were also present in the β-position (entry 3). The reaction could also be carried out at sub-zero temperatures, to produce high yields and enantioselectivities of up to 95% (entries 1 and 2).

Table 1.19: Hydroalkoxylation of γ-allenic alcohols.[a]

Entry	Substrate	Product	T (^{o}C)	% Yield[b]	% ee (*R*/*S*)[c]
1			-20	97	93 (*R*)
2			-20	98	95 (*R*)
3			10	92	75 (*R*)

[a]Reaction conditions: substrate (0.16 mmol., 161 mM), *R*-DM-BIPHEP(AuCl)$_2$ (2.5 mol%), *S*-**1.79** (5 mol%), toluene (1.3 mL), 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

In recent years, much attention has also been devoted to the intermolecular hydrofunctionalisation reactions of allenes. However, the ability of gold to furnish chiral heterofunctionalisation products from allenes is limited to axis-to-centre chirality transfer from an optically active starting material to product.[69,70] For example, hydroamination of chiral 1,3-disubstitued allene *R*-**1.80** (94%) with aniline in the presence of $AuBr_3$, produced the respective allylamine *S*-**1.81** (88%) (Scheme **1.22**).[70] Although, rapid racemisation of *R*-**1.80** was observed in the absence of a nucleophile.

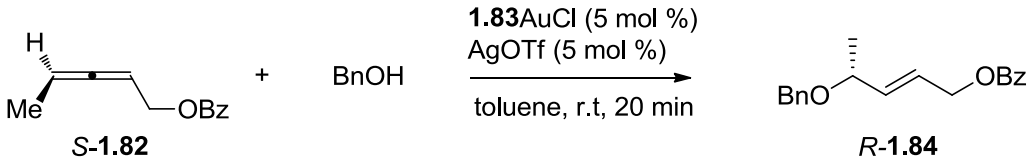


R-**1.80**
94%ee

S-**1.81**
68% yield, 88 %ee

Scheme 1.22: Axis-to-centre chirality transfer of *R*-**1.80** to *S*-**1.81**.

Following this work, Widenhoefer reported the intermolecular hydroalkoxylation of allene *S*-**1.82** with benzyl alcohol, using an Au(I)NHC complex generated from (**1.83**)AuCl with AgOTf,[39] where **1.83** = 1,3-*bis*(2,6-diisopropylphenyl)imidazol-2-ylidine). *R*-**1.84** could be formed regioselectivity in a high yield of 83% with 64% ee (Scheme 1.23). Chirality could be enhanced by using a higher benzyl alcohol concentration of 1.76 M. Conversely, treatment of *S*-**1.82** without the addition of benzyl alcohol led to complete racemisation after 30 minutes.

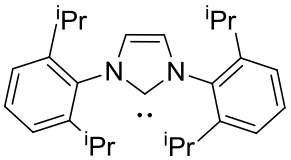


S-**1.82**

R-**1.84**

0.44 M	30 min	83% yield	64% ee
1.76 M	20 min	83% yield	79% ee

1.83 =



Scheme 1.23: Intermolecular hydroalkoxylation of chiral allene *S*-**1.82**.

1.3.3 Summary of Group 11 Metals in Heterofunctionalisation Reactions

Overall, cationic Au complexes are able to produce high levels of enantioselectivity in intramolecular heterofunctionalisation reactions of allenes. Reactions can proceed at sub-zero temperatures without a large reduction in rate, in the presence of 1-10% catalytic loading and with a wide scope of substrates. Au(III) was mostly used in earlier work concerning axis-to-centre chirality transfer, whereas more recently, the use of Au(I) has enabled asymmetric synthesis with racemic substrates. Two different strategies have been implemented; the first uses a chiral ligand with an achiral silver salt to form the "active" cationic species in solution, while the second takes advantage of an ion-pair consisting of a chiral silver salt and a chiral/non-chiral ligand. One disadvantage is that Au(I) complexes have linear geometries so often require large substituents on the ligand/counteranion to obtain high levels of enantioselectivity. Au(I) and Au(III) complexes have also been used for intermolecular additions with variable results. In some cases, axis-to-centre chirality transfer can be achieved, but in the absence of a nucleophile, complete racemisation of the optically active allene is observed.

On the other hand, silver is also capable of mediating intramolecular hydroamination and hydroalkoxylation reactions of allenes. However, cyclisation reactions mostly require long reaction times, high temperatures and/or stoichiometric quantities of the catalyst. So far, the application of silver in heterofunctionalisation of C=C bonds is limited to transfer of chirality from the starting material into the cyclised product. Before the start of this work, asymmetric synthesis using racemic substrates with silver and chiral ligands/counteranions was not known.

1.4 Project Aims

The object of this research project is to design and develop novel catalytic methodologies to effect intramolecular hydro(acy)alkoxylation and hydroamination reactions of allenes, preferably in a stereoselective manner.

In the beginning of this project in 2007, only cationic Au(I) complexes were reported to produce high enantioselectivities in the addition of O-H, CO_2H and N-H bonds to allenes. However, Au(I) complexes can be quite expensive and their linear geometries often require large substituents on the ligand/counteranion to obtain high levels of enantioselectivity. Silver and copper, the other group 11 metals, are known to catalyse heterofunctionalisation reactions, but enantioselective processes are unknown. They are less expensive and may provide a complementary and/or cost-effective alternative to these gold-catalysed reactions.

The potential of silver and copper in enantioselective intramolecular hydro(acy)alkoxylation and hydroamination reactions of allenes will therefore be explored in the present work. Catalysts which are active will be optimised by varying reaction conditions, *e.g.* catalytic loading, solvent, temperature, metal-to-ligand ratio. A range of appropriate substrates will be synthesised, screened and the absolute configurations of hydroalkoxylation and hydroamination reaction products will also be determined. Finally, if possible, mechanistic investigations will be conducted using DFT calculations, through a collaboration with Prof. Henry Rzepa.

Chapter 2: Copper- and Silver-Catalysed Intramolecular Hydroalkoxylation reactions of Allenes

To date there have only been a few chiral catalysts which have been successful for asymmetric heterofunctionalisation reactions of allenes.[50,71] The majority of reported catalysts are cationic gold(I) compexes. Often, the active catalyst is generated *in situ* from a mixture of a gold(I) halide complex (LAuX) and a silver salt (AgY). The use of other group 11 catalysts is limited; Ag(I) has been known since 1979 to catalyse intramolecular heterofunctionalisation reactions of allenes,[55,62,63,72-81] alkenes[82] and alkynes.[83,84] On the other hand, previous work in our research group found that copper(II) triflate, [$Cu(OTf)_2$] exhibits interesting catalytic activity in inter- and intra-molecular additions of O-H and N-H to alkenes.[85-87] Both Cu(II) and Ag(I) salts are relatively inexpensive in comparison to Au(I) catalysts and unlike Au(I), they can form bi-, tri- and tetra-coordinated complexes.[88] This Chapter will set out to investigate the use of these cheaper coinage metals in hydroalkoxylation reactions of allenes; catalytically and asymmetrically.

The model substrate chosen for our initial study is a terminal γ-allenic alcohol, 2,2-diphenylhexa-4,5-dien-1-ol, **1.44** (Figure 2.1). Previously used in similar studies, it would provide direct comparison of results.[45,58]

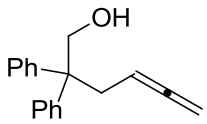
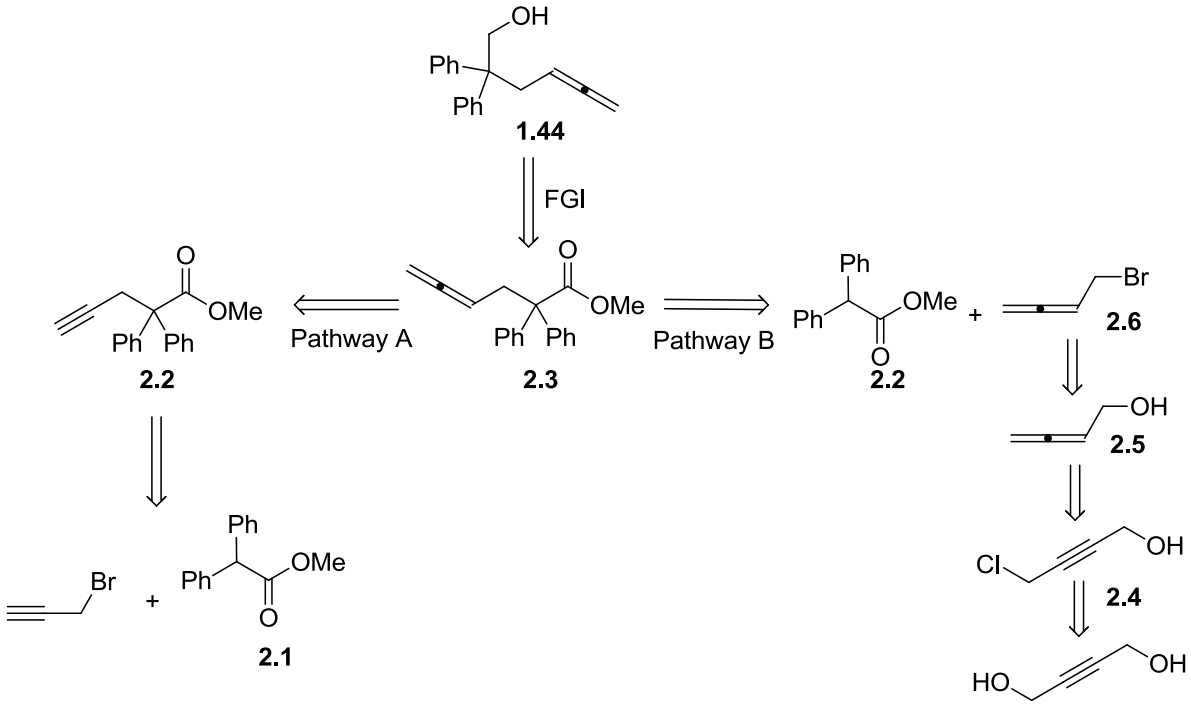


Figure 2.1: Model substrate **1.44**.

2.1 Synthetic Strategy for 2,2-Diphenylhexa-4,5-dien-1-ol

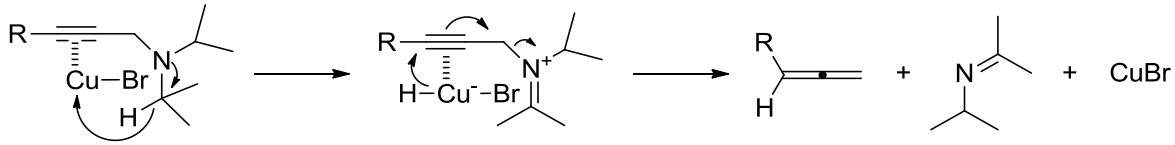
Two synthetic routes were envisaged for the preparation of model substrate **1.44**, both involving the allenic ester intermediate **2.3** (Scheme 2.1). In pathway A it can be obtained from the alkyne ester **2.2** by a Crabbé reaction.[89-92] This alkyne should be accessible from the propargylation of methyl 2,2-diphenylacetate **2.1**. In pathway B the allenic ester can be obtained from the reaction of methyl 2,2-diphenylacetate **2.1**

with bromoallene **2.6**, which should in turn be accessible from but-2-yne-1,4-diol in 3 steps *via* mono-chlorination and a propargylic rearrangement reaction using lithium aluminium hydride, LAH. [93-95]



Scheme 2.1: Retrosynthesis routes to model substrate **1.44**.

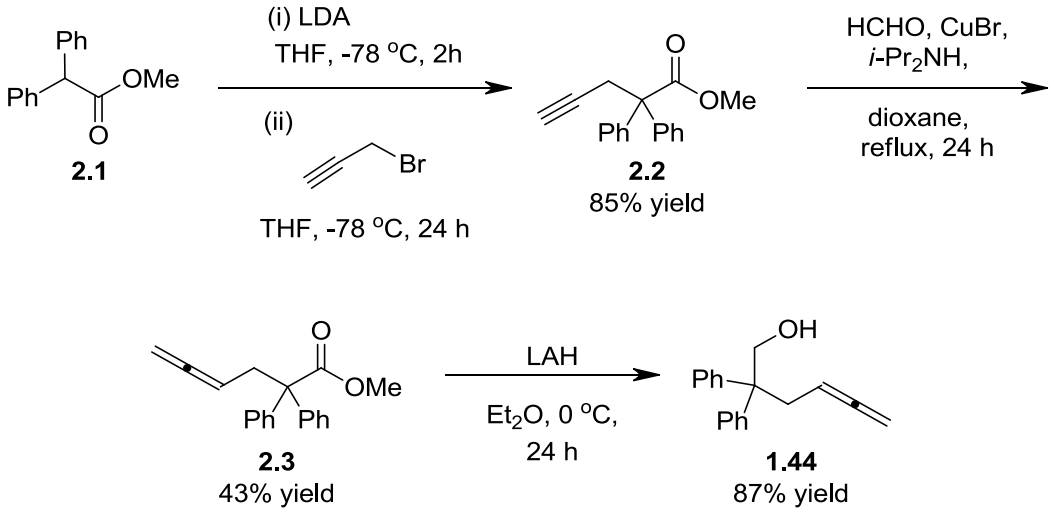
Both pathways use an acetylene-allene rearrangement to create an allenic functionality. Pathway B uses a propargylic rearrangement reaction, which is generally categorised as an S_N2 reaction. The nucleophile is either a hydride or an organometallic species.[96,97] Pathway A uses the Crabbé reaction, where a stoichiometric amount of cuprous bromide is used to transform the acetylenic group into a terminal allene by the transfer of a hydride from the amine moiety to the C≡C bond *via* the formation of a hydridocopper(I) complex (Scheme 2.2).[89-92] The Crabbé reaction proceeds under mild conditions in one pot and is the most common method used for the synthesis of terminal allenes.



Scheme 2.2: 1,5-sigmatropic rearrangement.

2.1.1 Synthesis of Model Substrate 1.44 *via* Pathway A

The literature procedure previously described[45] was duplicated in this work (Scheme 2.3).



Scheme 2.3: Synthesis of **1.44** by pathway A.

Firstly, methyl 2,2-diphenylacetate **2.1** was prepared by a simple esterification of the commercially available diphenylacetic acid.[98] The propargylation was carried out with propargyl bromide using LDA, prepared *in situ* from freshly distilled diisopropylamine and *n*-butyllithium at -78 °C,[99] to afford **2.2** in a comparable yield to the literature value, after purification by column chromatography.[58]

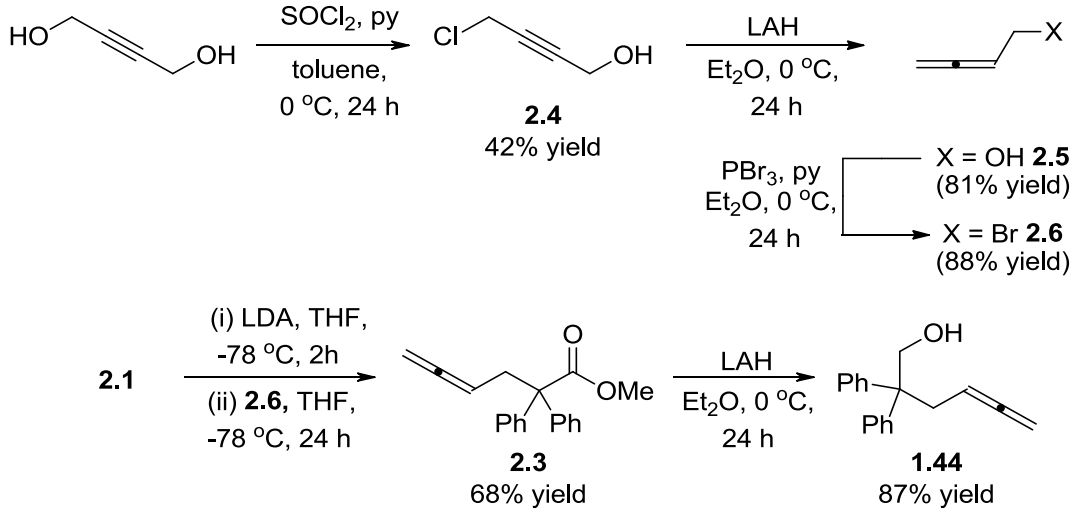
Next, the Crabbé reaction was performed using stoichiometric amounts of cuprous bromide and (excess) paraformaldehyde. This step was reported to proceed with 32% yield.[58] However, only 15% yield was obtained on the first attempt, even after refluxing for 24 hours. The crude reaction mixture containing a large amount of solid precipitate, which was dry-packed with silica prior to column chromatography. By increasing the amount of cuprous bromide from 0.2 to 0.5 equivalents, the yield of **2.3** can be increased to 43%. Finally, LAH reduction of **2.3** provided reliable yields of **1.44** (87%), replicating the literature yield.[58]

The structure of the model substrate **1.44** (Figure 2.1) was confirmed by comparison of its characterisation data with literature values.[58] The OH moiety could be observed

by its IR absorption peak at 3424 cm^{-1} and the allene by peaks at 1954 and 1020 cm^{-1}. In the ^{13}C NMR spectrum, the sp-hybridised carbon was identified by its signal at 209 ppm, while the sp^2-hybridised carbon atoms are identified as signals at 85.6 and 74.0 ppm (supported by HSQC). The positioning of a CH_2 group, identified by DEPT, at 68.1 ppm gives evidence for attachment to an OH moiety. In the ^1H NMR spectrum, the allene moiety is identified as the muliplet at 4.78 ppm and triplets at 4.55 and 4.53 ppm (supported by COSY). A singlet at 4.23 ppm correlating to two protons corresponds to a CH_2OH group and the broad singlet at 1.47 correlates to the OH moiety. Finally, MS in CI mode confirmed the expected mass of the compound ($[MNH_4]^+ = 251$).

2.1.2 Synthesis of Model Substrate 1.44 *via* Pathway B

Pathway B (Scheme 2.4) was attempted in order to increase the overall yield. Although it involves more steps, it bypasses the low yielding Crabbé reaction.



Scheme 2.4: Synthesis of **1.44** by pathway B.

Formation of bromoallene **2.6** was achieved in three steps. First mono-chlorination of but-2-yne-1,4-diol by thionyl chloride at 0 °C was carried out. In the first attempt, the literature procedure[56] was replicated. Using benzene as the solvent, thionyl chloride was added slowly to a solution of but-2-yne-1,4-diol and pyridine, maintaining a low temperature. Under these conditions, the reaction produced a mixture of mono- and di-substituted products. In the reported procedure, distillation at 50-55 °C with a

liquid nitrogen trap at a reduced pressure of 1.0 torr was used to obtain the product in a relatively low yield of 40%. In our hands, a 30-cm long Vigreux column was required for adequate separation of the mono-substituted product **2.4**, which was obtained with 42% yield. The reaction was subsequently repeated with toluene, a safer and less toxic solvent. However, the reaction mixture became too viscous for effective stirring. Repeating the procedure with a mechanical stirrer and at a more dilute concentration, the reaction mixture remained homogeneous during the reaction, to afford 42% of the mono-substituted product **2.4** after distillation.

The second step involved a LAH propargylic rearrangement reaction to the allenic alcohol **2.5** at 0 ^{o}C.[56] A consistent moderate product yield of between 79-81% was obtained after purification by distillation. Once purified, **2.5** decomposed overnight, so as a consequence must be used immediately in the next step or placed in a freezer for no more than 2 days. The bromination of buta-2,3-dien-ol proceeded with PBr_3 to form bromoallene **2.6** in a high yield of 88%.[56] The product was purified by distillation at 760 torr (105-110 ^{o}C).

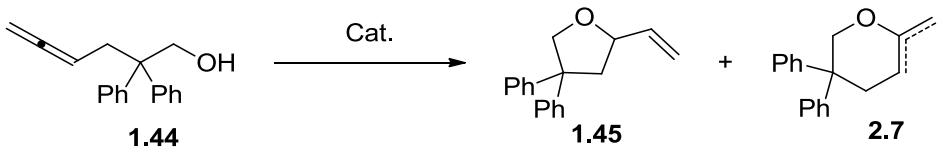
The reaction between bromoallene **2.6** and 2,2-diphenylacetate **2.1** using LDA as a base proceeded with 68% yield. The desired product **1.44** was purified using column chromatography. Finally, reduction of the ester to the alcohol moiety was achieved in 87% yield.[58]

2.1.3 Comparison of Pathways A and B

Both pathways were comparable in terms of overall yields. On one hand, pathway A, starting from ester **2.1**, was quite efficient as a three step synthesis, but extensive purification methods and the low yielding Crabbé reaction can be challenging. If a 43% yield is obtained for the Crabbé reaction, an overall yield of 59% over the three steps can be realised. On the other hand, pathway B involved a longer synthesis, producing an overall yield of 56% over five steps. Then again, **2.4** was formed in a low yield of 42%. This is generally not a significant problem as it was the first step in the synthesis, but the considerable amounts of thionyl chloride could be problematic upon scale up, particularly the need to maintain homogeneity of the reaction mixture.

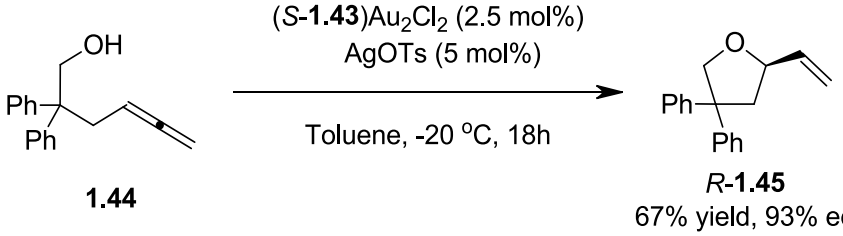
2.2 Initial Screening of Copper in Hydroalkoxylation Reactions

The intramolecular cyclisation of γ-allenic alcohol **1.44** can potentially afford 5- and 6-membered O-heterocycles **1.45** and **2.7** respectively (Scheme 2.5).[50]



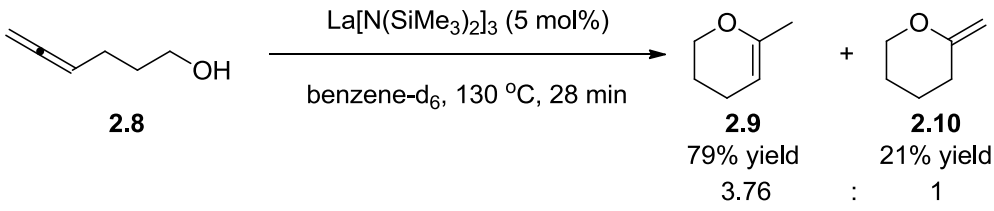
Scheme 2.5: General cyclisation of **1.44** to **1.45** and **2.7**.

Most hydroalkoxylation catalysts, such as gold, produce the 5-membered heterocycle **1.45** in high yields and enantioselectivities.[36,68,45] For example, the cyclisation of **1.44** by a dimeric gold complex, $[Au_2(P–P)Cl_2]$ (where P–P = *S*-DTBM-MeOBIPHEP, **1.43**), activated by AgOTs, resulted in formation of tetrahydrofuran **1.45** in 67% yield with 93% ee (Scheme 2.6).[45]



Scheme 2.6: Cyclisation of allenic alcohol with (*S*-**1.43**)Au_2Cl_2 and AgOTs.

The only known catalytic example of a 6-*endo/exo-dig* cyclisation was achieved using a lanthanide amide complex (Scheme 2.7).[100] This rarer cyclisation requires high temperatures of 130 °C to form double bond isomers **2.9** and **2.10**.



Scheme 2.7: Cyclisation of **2.8** to double bond isomers **2.9** and **2.10**.

Guided by previous work performed in our group, copper catalysis was first explored by utilising 5 mol% of $Cu(OTf)_2$, with and without triphenylphosphine as a ligand (Table 2.1).

Table 2.1: Hydroalkoxylation of **1.44** catalysed by Cu(II) and Brønsted acid.[a]

1.44 **1.45** **2.11**

Entry	Catalyst	T (^oC)	Time (h)	Isolated yield of **1.45** (%)[b]	Isolated yield of **2.11** (%)[b]
1	$Cu(OTf)_2$	50	33	21	39
2	$Cu(OTf)_2$	r.t	33	9	38
3[c]	$Cu(OTf)_2$, PPh_3	50	33	11	47
4[d]	TfOH	r.t	25	-	65

[a] Reaction conditions: **1.44** (50 mg, 0.2 mmol., 667 mM), $Cu(OTf)_2$ (5 mol%), DCE (0.3 mL), 33 h. [b] Isolated yield after column chromatography. [c] PPh_3 (10 mol%). [d]10 mol% TfOH.

After 33 hours at 60 ^oC, TLC analysis showed that the starting material had been totally consumed. An initial ^1H NMR anaylsis showed a complex mixture of products, from which two main components can be isolated after column chromatography. The expected 5-*exo*-*trig* product **1.45** was isolated in 21% yield (entry 1) and characterised by comparison with literature data:[58] both IR and NMR spectra revealed the absence of the allene moiety. In the ^1H NMR spectrum, the observation of a double double doublet resonance at 5.93 ppm and two doublets at 5.28 and 5.14 ppm supported the presence of an alkene moiety. ^{13}C NMR signals at 138.82 and 115.92 ppm are also in agreement with reported alkene resonances.[58] The other product, isolated in 39% yield was identified by crystallography as benzopyran **2.11**. Its formation, involving 6-*exo*-dig cyclisation, will be explained in Chapter 3.

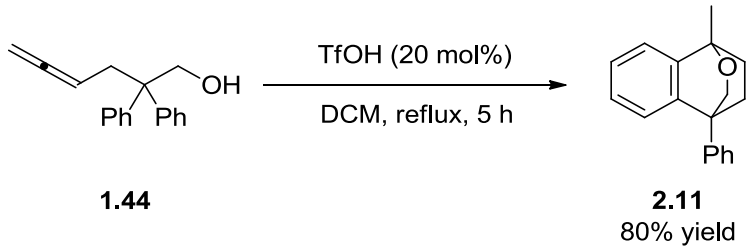
In an attempt to prevent catalyst decomposition, the reaction was repeated at room temperature. This gave roughly the same isolated yield of **2.11**, but with a decreased

yield of the 5-*exo-trig* product **1.45** (entry 2). The addition of triphenylphosphine (to stabilise the catalyst) proved ineffective (entry 3).

2.2.1 Brønsted Acid-Catalysed Reaction

Brønsted acids have sometimes been implied as being the active catalyst in Lewis acid mediated processes.[101,102] Previously, this was encountered in the cyclisation of γ and δ-allenic alcohols and acids by $Cu(OTf)_2$, where the expected tetrahydrofurans and pyrans could also be obtained by employing 10% TfOH as the catalyst.[87]

During the course of our investigations, a paper by Akiyama *et al.* reported the formation of benzopyran **2.11** catalysed by 20 mol% TfOH (Scheme 2.8), along with the publication of its crystal structure.[103] The benzopyran was formed exclusively in 80% yield after 5 hours refluxing in DCM.



1.44 **2.11** 80% yield

Scheme 2.8: Cyclisation of **1.44** to **2.11** using TfOH.

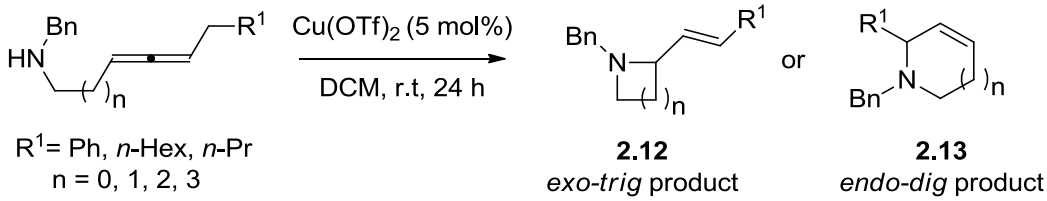
To clarify the involvement of Brønsted acids, the reaction was also perfomed in the presence of 10 mol% of TfOH, the maximum amount of acid that could theoretically be formed in our reactions. Indeed, this reaction proceeded at room temperature to furnish **2.11** in a lower yield of 65% after 25 hours (Scheme 2.8, Table 2.1, entry 4). The ^{1}H NMR spectrum of the crude reaction mixture, however, showed several unidentifiable by-products, but the 5-*exo-trig* product **1.45** was not observed.

The observation that $Cu(OTf)_2$ and TfOH can both form a common product **2.11** suggests that Brønsted acid can be generated during Cu(II)-mediated hydroalkoxylation of γ-allenic alcohols. However, the metal-catalysed process cannot be ruled out entirely as a small amount of the 5-*exo-trig* product was also observed.

The addition of a phosphine ligand improved the formation of benzopyran (Table 2.1, entry 3), perhaps by binding to Cu and allowing TfOH to form more readily.

2.2.2 Conclusion of Copper-Catalysed Heterofunctionalisation Reactions

Initial results indicated that $Cu(OTf)_2$ was not an efficient catalyst. Low conversions to the 5-*exo*-*trig* product were observed and there was significant catalyst decomposition. Furthermore, Brønsted acid catalysis seemed to play an important role in these reactions. Given that the addition of triphenylphosphine hindered the formation of the 5-*exo*-*trig* product, the possibility of adding chiral diphosphine ligands was not investigated. However, since we performed this work, the application of $Cu(OTf)_2$ to facilitate intramolecular hydroamination reactions of allenic amines to the corresponding 3-pyrrolines **2.12** or 2-alkenylpyrrolidines **2.13** in 88-98% yields has been reported (Scheme 2.9).[104] The system was limited to the cyclisation of α- (n=0) and γ- (n=2) allenic amines, while the corresponding reactions of β- (n=1) and δ- (n=3) allenic amines were unsuccessful; 81% of the δ-allenic amine (n=3) was recovered after two days and a capricious mixture was observed with the β-allenic amine (n=1). The *N*-protecting group was also limited to benzyl only, and the additon of phosphine ligands was found to inhibit the reaction.

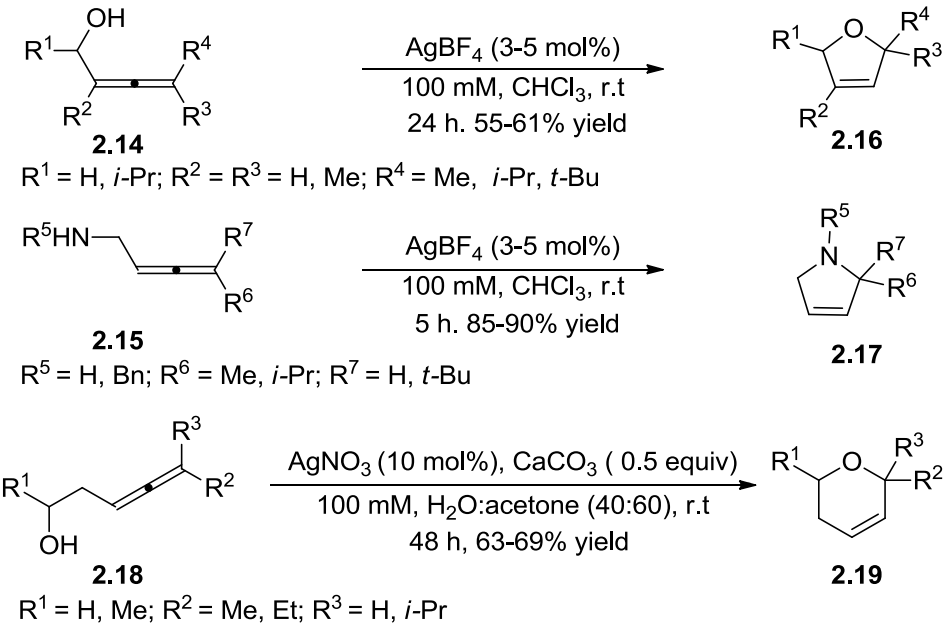


Scheme 2.9: Cu(II)-catalysed intramolecular hydroamination of allenic amines

2.3 Initial Screening of Silver in Hydroalkoxylation Reactions

Silver tetrafluoroborate ($AgBF_4$) and silver nitrate ($AgNO_3$) are two of the most common Ag(I) salts employed for hydroalkoxylation and hydroamination reactions of allenes (Scheme 2.10). $AgBF_4$ is predominately used in non-polar, non-coordinating solvents due to its greater solubility. For example, 3-5 mol% of $AgBF_4$ in chloroform furnished 2,5-dihydrofurans **2.16** in 55-61% yields from the corresponding α-allenic

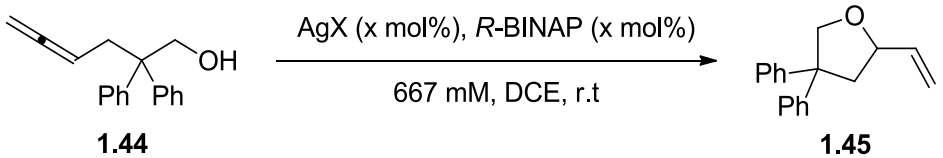
alcohols **2.14** and the respective 3-pyrrolines **2.17** from α-allenic amines **2.15** in 85-90% yield.[72,73] On the other hand, $AgNO_3$ is mainly used in water/polar solvent mixtures with calcium carbonate as an additive.[72,78,80] For example, cyclisation of β-allenic alcohols **2.18** to their corresponding 5,6-dihydro-2*H*-pyrans **2.19** proceeded in 63-69% yield in 48 hours.



Scheme 2.10: Ag(I) mediated cyclisation of α-allenic alcohols and amines**.**

2.3.1 Effect of Counteranion

Initially, cyclisation of the model substrate **1.44** in the presence of Ag(I) salts containing weakly (triflate, tetrafluoroborate, hexafluoroantimonate, hexafluorophosphate and perchlorate) and strongly (acetate, carbonate, nitrate and sulfate) coordinating counteranions were investigated (Scheme 2.11, Table 2.2). The corresponding pK_a values of conjugate acids are included for comparison.



Scheme 2.11: Model reaction for optimisation of Ag(I) catalyst.

Concurrently, a chiral phosphine ligand was also added to explore the potential for enantioselectivity. *R*-BINAP was chosen as it is a 'privileged' ligand structure widely

used to achieve enantioselectivity in many mechanistically different catalytic reactions,[41] particularly transition metals including Ru(II), Rh(I), Pd(II) and Ir(I) in hydrogenation,[105,106] isomerisation,[107] hydroboration,[108,109] allylic alkylation[110-112] and Heck reactions.[113,114] It has also been used with Ag(I) salts for Mukaiyama aldol reactions.[115-118]

Table 2.2: Investigating counteranion effects.[a]

Entry	X	pK_a of conjugate acid[b]	Ligand	Catalytic loading (mol%)	t (h)	% Conversion[c]	% ee (*R*/*S*)[d]
1	SO_4	-3.0[119]	-	15	72	100	-
2	SO_4		*R*-BINAP	15	72	0	-
3	CO_3	3.9[120]	-	15	48	100	-
4	CO_3		*R*-BINAP	15	48	0	-
5	OAc	4.8[121]	-	15	72	0	-
6	NO_3	-1.3[119]	-	15	72	27	-
7	NO_3		*R*-BINAP	15	72	0	-
8	OTf	-14[122]	-	15	16	100	-
9	OTf		*R*-BINAP	15	>168	2	-
10	PF_6	-20[123]	-	15	48	100	-
11	PF_6		-	5	36	100	-
12	PF_6		*R*-BINAP	15	63	94	31 (*S*)
13	SbF_6	-13[123]	-	15	>168	40	-
14	SbF_6		*R*-BINAP	15	>168	5	34 (*S*)
15	ClO_4	-10[124]	-	15	48	87	-
16	ClO_4		*R*-BINAP	15	72	49	55 (*S*)
17	BF_4	-4.9[125]	-	15	48	85	-
18	BF_4		*R*-BINAP	5	36	42	47 (*S*)
19	BF_4		*R*-BINAP	15	63	52	60 (*S*)

[a] Reaction conditions: **1.44** (50 mg, 0.2 mmol., 667 mM), AgX (x mol%), DCE (0.3 mL), r.t. [b] Determined in H_2O. [c] Determined by ^1H NMR integration. [d] Determined by chiral HPLC and optical rotation values.

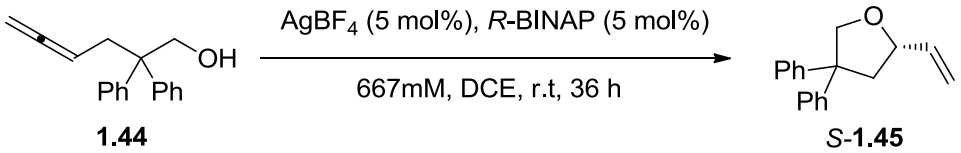
In the absence of added ligand, the outcome of the intramolecular hydroalkoxylation reaction is dependent on the counteranion employed. Full conversion was observed using silver sulfate and carbonate within 72 hours (entries 1 to 4). However, no conversion was observed with acetate salt (entry 5). For weakly coordinating counteranions (PF_6, BF_4 and ClO_4), conversions of 100%, 85% and 87% were achieved, respectively (entries 8, 10 and 15) in 48 hours, whereas full conversion using OTf only required 16 hours (entry 18). In contrast, NO_3 gave 27% conversion after 72 hours (entry 6) and SbF_6 furnished 40% conversion after 168 hours (entry 13). The reactivity of the Ag(I) salts seems to increase in the order: $SbF_6 < NO_3 < BF_4 < ClO_4 < SO_4^2 < PF_6 \approx CO_3 <$ OTf. In some cases, the catalytic loading can be reduced. For example, using 5 mol% of $AgPF_6$, the reaction proceeded to give full conversion after 36 hours (entry 11). There was no observable correlation between the pK_a values and the rate of conversion.

In all cases, the addition of *R*-BINAP decreased the product yield dramatically (entries 2, 4, 7, 9, 12, 14, 16, 18 and 19), which was particularly significant for SO_4, CO_3 and NO_3 (pK_a -3.0, 3.9 and -1.3) where the addition of *R*-BINAP completely inhibited the reaction (entries 2, 4 and 7). For OTf and SbF_6 the reaction gave only 2 and 5% conversions (entries 9 and 14), respectively. This observation proved that Ag(I) salts can catalyse the reaction on their own, which can give rise to competitive racemic reactions. Enantiomers of the 5-*exo*-*trig* product, **1.45** can be separated by chiral HPLC and it was encouraging to observe detectable levels of selectivity in these reactions; up to 60% ee can be attained when *R*-BINAP was used in combination with $AgBF_4$ (entry 19). By comparison of optical rotation values and HPLC traces with that reported, the major enantiomer was assigned *S* (see section 2.4). The enantiomeric excess increases in the order: $PF_6 < SbF_6 < ClO_4 < BF_4$ (entries 12, 14, 16 and 19) and appears to correspond to decreasing pK_a values, where the less acidic conjugate acid (BF_4) gave the highest enantioselectivity (entry 18). However, when *R*-BINAP was introduced to Ag(I) salts of even less acidic conjugate acids (pK_a between -3 and +4) the reaction was inhibited (entries 2, 4 and 7). Enantioselectivity was found to be dependent upon catalytic loading: 5 mol% $AgBF_4$ and *R*-BINAP proceeded to give an enantiomeric excess of 47% in 42 hours, which increased to 60% by increasing the catalytic loading from 5 to 15 mol% (entries 18 and 19).

In summary, in the presence of *R*-BINAP, Ag(I) salts containing weakly coordinating counteranions were capable of chiral induction in the cyclisation of **1.44**. $AgPF_6$ provided the highest yield, but a low enantiomeric excess (entry 12), whereas $AgBF_4$ produced the highest enantioselectivity (60%) with a moderate conversion of 52% in 63 hours (entry 18). Therefore, $AgBF_4$ was used in further studies.

2.3.2 Solvent Screen

The catalytic performance of $AgBF_4$ was investigated in various solvents at 5 mol% loading, to identify the best medium for optimal rate of conversion and enantiomeric excess (Scheme 2.12, Table 2.3).



1.44 *S*-**1.45**

Scheme 2.12: Initial reaction conditions adopted for Ag(I) screening.

Table 2.3: Solvent study using $AgBF_4$ as a catalyst.[a]

Entry	Solvent	% Conversion [b]	% ee (*R*/*S*) [c]
1	DCE	41	47 (*S*)
2	Toluene	31	36 (*S*)
3	THF	62	12 (*S*)
4	Dioxane	5	27 (*S*)
5	Acetonitrile	0	0

[a] Reaction conditions: **1.44** (50 mg, 0.2 mmol., 667 mM), $AgBF_4$ (5 mol%), *R*-BINAP (5 mol%), solvent (0.3 mL), r.t, 36 h. [b] Determined by ^{1}H NMR integration. [c] Determined by chiral HPLC and optical rotation values.

Within this preliminary study DCE proved to be the best solvent, providing the highest ee of 47% (entry 1). The less polar toluene decreased the yield and ee by 9% (entry 2), while apotic polar solvent THF afforded the highest conversion of 62%, but with a poor enantioselectivity (entry 3). Conversely, dioxane gave 5% conversion,

but with only 27% ee (entry 4). Finally, acetonitrile was found to completely inhibit the reaction (entry 5). The major enantiomer *S* was formed in all cases.

During the study, the solubility of the catalyst was observed to increase in the order: acetonitrile < dioxane < THF < toluene < DCE, with DCE being the only solvent that produced a homogeneous solution. Given that selectivity is dependent on catalyst concentration, the dilution of the reaction mixture was therefore increased. These reactions were also replicated with a wider selection of additional solvents, employing an effective substrate concentration of 100 mM at 15 mol% catalytic loading (Table 2.4).

Table 2.4: Solvent study at 100 mM.[a]

Entry	Solvent	% Conversion [b]	% ee (*R*/*S*)[c]
Polar Protic Solvents			
1	MeOH	0	-
2	EtOH	0	-
Non-Polar Solvents			
3	Hexane	0	-
4	Et_2O	0	-
5	Chloroform	26	35 (*S*)
6	Toluene	49	38 (*S*)
7	Benzene	59	19 (*S*)
Aprotic Solvents			
8	Acetone	0	-
9	DMF	0	-
10	Dioxane	5	21(*S*)
11	CH_2Cl_2	45	41 (*S*)
12	DMSO	50	19 (*S*)
13	DCE	52	60 (*S*)
14	THF	64	36 (*S*)
15	EtOAc	75	36 (*S*)

[a] Reaction conditions: **1.44** (25 mg, 0.1 mmol., 100 mM), $AgBF_4$ (15 mol%), *R*-BINAP (15 mol%), solvent (1.0 mL) r.t, 63 h. [b] Determined by ^{1}H NMR integration. [c] Determined by chiral HPLC and optical rotation values.

Reactions carried out in protic solvents did not afford any turnover after 63 hours (entries 1-2). This was attributed to strong binding of the solvent to the metal centre, which inhibits the activation of the substrate. Reaction carried out in non-polar solvents gave a variety of results, depending on the solubility of the catalyst (entries 3 to 7); low solubility in hexane and Et_2O resulted in 0% conversion (entries 3 and 4). An increase in conversion to 26% was observed when the catalyst had a moderate solubility in chloroform (entry 5) and up to 59% conversion with benzene (entry 7). Unfortunately, the high conversion with benzene did not correlate to a high ee. Repeating with toluene at the more dilute concentration (100 mM) afforded a higher conversion to the initial study, but with no great increase in ee (entry 6).

Polar aprotic solvents also gave a variety of results, depending on the solubility of the catalyst (entries 8 to 15); low solubility of the catalyst in DMF and acetone contributed to the 0% conversion observed (entries 8 and 9). Repeating with dioxane afforded similar values (5% conversion, 21% ee) to the initial study (entry 10). This suggests that solubility is still a problem and that dioxane, may itself, also coordinate to the metal centre.[126] Good homogeneity of the Ag(I) catalyst in the remaining aprotic solvents, gave modest conversions ranging from 45 to 75% and enantioselectivities between 36 to 60% (entries 11 to 15). One observation was CH_2Cl_2 and DCE produced very similar conversion and enantioselectivity values (entries 11 and 13), however high conversions with DMSO, THF or EtOAc as the solvent, did not correlate to a high ee (entries 12, 14 and 15). Comparing both reactions in THF, the ee in a more dilute solution dropped from 36 to 12% ee, suggesting dilution has a dramatic effect on the ee (Table 2.3, entry 3 *vs* Table 2.4, entry 14). This phenomenon was not observed with any other solvents.

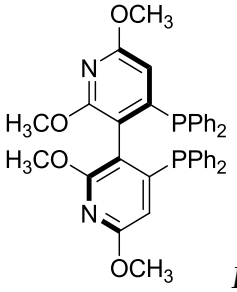
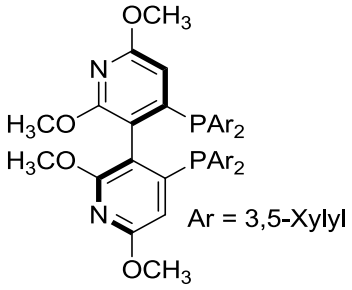
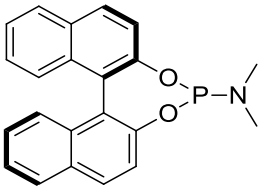
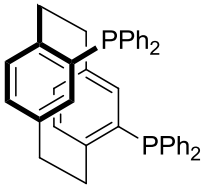
Overall, although DCE does not have the highest conversion, the ee of 60% is far in excess of that attained with any other solvent (entry 13). Further studies were therefore employed to improve the conversion and ee.

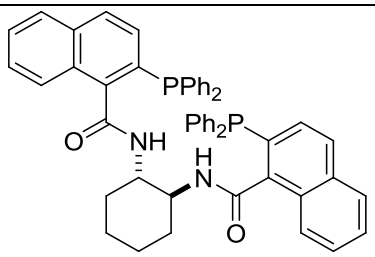
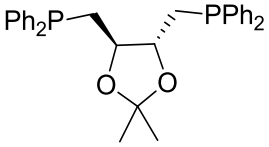
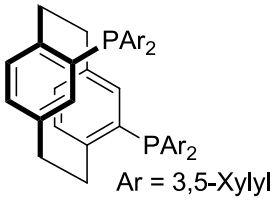
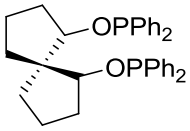
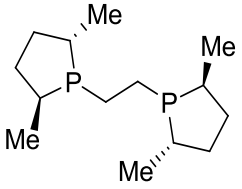
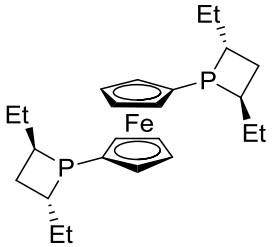
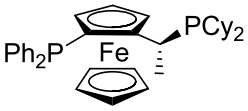
2.3.3 Ligand Screen

Next, a variety of diphosphine ligands containing different elements of chirality

(axial, planar, or central) were assessed. Reactions screened were performed at 15 mol% catalytic loading and 100 mM (Table 2.5). All bidentate ligands were employed with a M:L ratio of 1:1 and 1:2 ratio with monodentate ligands.

Table 2.5: Ligand study.[a]

Entry	Ligand	% Conversion[b]	% ee[c] (*R*/*S*)
Axial Chirality			
1	*R*-Cl-MeO-BIPHEP	40	62 (*S*)
2	*R*-MeO-BIPHEP	50	68 (*S*)
3	*R*-BINAP	52	60 (*S*)
4	*R*-SEGPHOS	50	62 (*S*)
5	 *R*-P-Phos	59	18 (*S*)
6	 *R*-Xylyl-P-Phos	38	44 (*S*)
7	 *R*-Monophos	100	14 (*R*)
Planar and/or Central Chirality			
8	 *R*-Phanephos	100	10 (*R*)

9	 *S*,*S*-DACH Naphthyl Trost Ligand	100	0
10	 *R*,*R*-DIOP	100	14 (*R*)
11	 *R*-Xylyl-phanephos	0	-
12	 *R*-spirophos	81	0
13	 *S*,*S*-Me-BPE	2	-
14	 *S*,*S*-Et-FerroTANE	0	-
15	 R, S_p-Josiphos	11	5 (*R*)

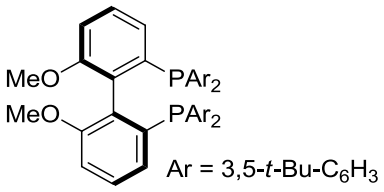
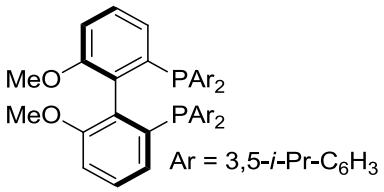
[a] Reaction conditions: **1.44** (25 mg, 0.1 mmol., 100mM), $AgBF_4$ (15 mol%), ligand (15-30 mol%), DCE (1.0 mL), r.t, 63 h. [b] Determined by ^1H NMR integration. [c] Determined by chiral HPLC and optical rotation values.

From this ligand screen, a profound effect of employing diphosphine ligands with axial chirality was revealed (entries 1 to 6). The BIPHEP family afforded the highest enantioselectivities of >60% (entries 1 and 2). BINAP and SEGPHOS also afforded moderate yields (~50%) and enantioselectivities of ~60% (entries 3 and 4), while results obtained with the P-Phos family showed that the introduction of bulky groups on the P-substituent can furnished higher enantioselectivities, albeit with a reduction in yield (entries 5 and 6). All axial diphosphine ligands produced *S*-**1.45**, whereas attempting to cyclise **1.44** with *R*-Monophos furnished *R*-**1.45** in 6% yield with an 8% ee (entry 7).

Very clean, full conversion can be obtained using *R*-Phanephos, *S,S*-DACH Naphthyl Trost, *R-R*-DIOP and ligands, but afforded *R*-**1.45** with low enantioselectivities (entries 8, 9 and 10). Increasing the steric hindrance of the phosphine substitution on *R*-Phanephos was found to inhibit the reaction (entry 11); perhaps the bulky xylyl group prevented the allenic alcohol from binding to Ag. *R*-spirophos was also able to afford *R*-**1.45** with a high conversion (81%), but with no enantioselectivity (entry 12). *S,S*-Me-BPE and *S,S*-Et-FerroTANE proved inefficient ligands by inhibiting the reaction (entries 13 and 14), and Josiphos produced *R*-**1.45** in low conversion with poor enantioselectivity (entry 15).

Encouraged by the results obtained by *R*-MeO-BIPHEP and *R*-Cl-MeO-BIPHEP, a range of related ligands from the BIPHEP family were subsequently investigated (Table 2.6). Previously, the ligand *S*-DTBM-MeOBIPHEP (*S*-**1.43**) was found to be an effective in gold intramolecular hydroamination and hydroalkoxylation reactions involving allenes (Scheme 2.6).[37,45] Disappointingly, none of the BIPHEP ligand derivatives improved the performance of the Ag catalyst. Increasing the steric bulk of the phosphine ligands inhibited the reaction (entries 1 and 2), with *S*-3,5-*i*-Pr-MeOBIPHEP only affording 1% conversion after 336 hours (entry 3). Only *S*-DM-MeOBIPHEP produced adequate material for enantiomeric excess determination (entry 4), which was assigned *R*, the same observed in the gold-mediated reaction.

Table 2.6: Ligand study of the BIPHEP family.[a]

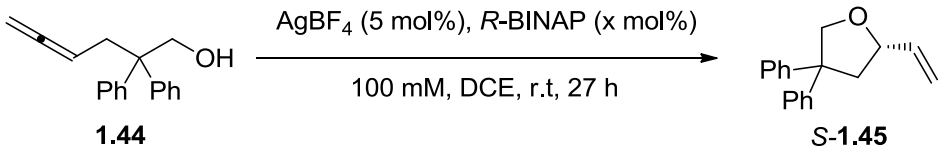
Entry	Ligand	% Conversion [b]	% ee (*R*/*S*)[c]
1	*S*-DTBM-MeOBIPHEP	0	-
2	 *S*-3,5-*t*-Bu-MeOBIPHEP	0	-
3	 *S*-3,5-*i*-Pr-MeOBIPHEP	1	-
4	*S*-DM-MeOBIPHEP	18	64 (*R*)

[a] Reaction conditions: **1.44** (25 mg, 0.1 mmol., 100 mM), $AgBF_4$ (15 mol%), Ligand (15 mol%), DCE (1.0 mL), r.t, 336 h. [b] Determined by ^1H NMR integration. [c] Determined by chiral HPLC and optical rotation values.

Given the little difference between *R*-MeO-BIPHEP and *R*-BINAP in conversion and enantiomeric excess (Table 2.5, entries 2and 3), *R*-BINAP was chosen for further studies, as it is significantly cheaper.

2.3.4 Metal:Ligand Ratio

Once the optimum solvent, dilution factor and chiral ligand had been established, the metal-to-ligand ratio (M:L) was investigated (Scheme 2.13, Table 2.7).



1.44 *S*-**1.45**

Scheme 2.13: Model reaction for optimisation of Ag(I) catalyst.

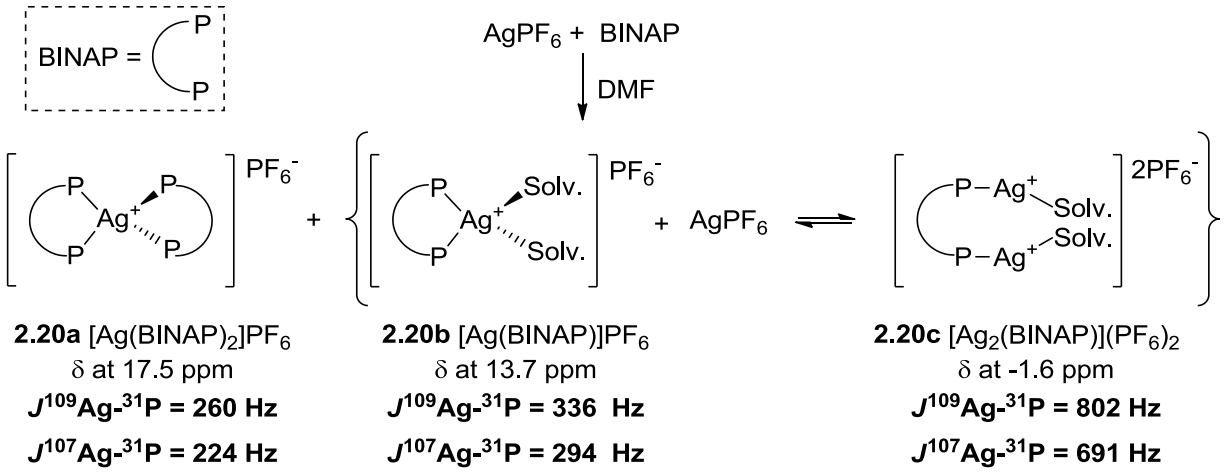
Table 2.7: M:L study.[a]

Entry	*R*-BINAP (mol%)	M:L	% Conversion [b]	% ee (*R*/*S*)[c]
1	2.5	2:1	100	11 (*S*)
2	5	1:1	25	59(*S*)
3	10	1:2	0	-

[a] Reaction conditions: **1.44** (25 mg, 0.1 mmol., 100 mM), $AgBF_4$ (5 mol%), *R*-BINAP (x mol%), DCE (1.0 mL), r.t, 27 h. [b] Determined by ^1H NMR integration. [c] Determined by chiral HPLC and optical rotation values.

It was found that a 1:1 ratio was required for optimum enantioselectivity (entry 2). Reducing the amount of ligand resulted in a fast reaction and full conversion, but only 10% ee was obtained, probably due to a competitive racemic reaction of unligated $AgBF_4$ (entry 1). Conversely, increasing the ratio to 1:2 deactivated the catalyst (entry 3).

Silver has two stable isotopes ^{107}Ag and ^{109}Ag, both have a nuclear spin of 1/2 and will thus display Ag-P coupling. This gives a useful tool to determine the number of coordinated phosphorus atoms. In an earlier study of an $AgPF_6$-BINAP system by Yamamoto, 1:1 mixtures of *S*-BINAP and $AgPF_6$ were analysed by ^{31}P NMR,[117] where three complexes: $[Ag(S\text{-BINAP})_2]PF_6$ **2.20a** (the major species, but catalytically inactive), $[Ag(S\text{-BINAP})]PF_6$ (**2.20b**) and $[Ag_2(S\text{-BINAP})](PF_6)_2$ (**2.20c**) were identified (Scheme 2.14). In the 1:2 mixture, the complex **2.20a** was the only species observed, whereas in the 1:1 mixture all three species were observed.



Scheme 2.14: Formation of $AgPF_6$-BINAP complexes in solution.[117]

In 2004, the same authors suggested that the various complexes have different reactivities and selectivities in the enantioselective O- and N-nitroso aldol reactions of tin enolates.[127] The distribution of silver complexes is dependent on the silver anion employed. Overall, the highest stereoselectivity is achieved by using a M:L ratio of 1:1.

Accordingly, 1:1 and 1:2 mixtures of $AgBF_4$ and *R*-BINAP were generated in DCE and examined by ^{31}P NMR spectroscopy, as well as mass spectroscopy (Figure 2.2 and Figure 2.3) at room temperature. Complex **2.20a** was the only species observed in the 1:2 mixture, which displayed a characteristic ^{31}P resonance at 15.3 ppm with *J* values of 242 and 241 Hz for coupling to ^{109}Ag and ^{107}Ag, respectively. This was supported by a single $[M]^+$ ion of 1353 in the MS spectrum, indicating the formation of a ML_2 complex (Figure 2.2, structure **2.21a**). This complex will be catalytically inactive, as there is no free coordination site. There was also a small signal observed at $[M]^+$ 1369, due to oxidation of one of the phosphorus atoms (structure **2.21b**).

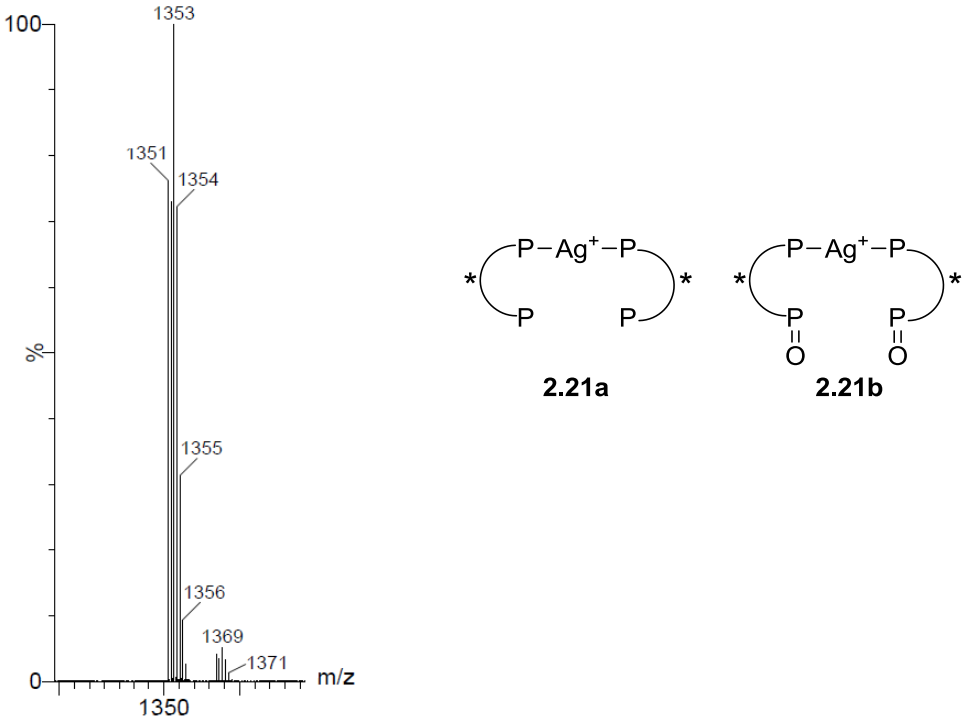


Figure 2.2: a) MS spectrum for a 1:2 ratio (M:L). **b)** Ag-BINAP complexes **2.21a** and **2.21b**.

For the 1:1 mixture of $AgBF_4$ and BINAP, the formation of two silver complexes were observed in the ^{31}P NMR spectrum, one of which corresponds to **2.21a**. The

other species displayed δ_P at 10.9 ppm with *J* values for ^{109}Ag-^{31}P and ^{107}Ag-^{31}P at 862 and 851 Hz respectively. These values do not seem to correlate to any of the three structures previously observed by Yamamoto *et al* (Scheme 2.14). The MS spectrum showed a capricious mixture, for which five major species with $[M]^+$ 731, 772, 1353, 1369 and 1493 were identified (Figure 2.3). The mass ions 1353 and 1369 had been assigned as **2.21a** and **2.21b** respectively (Figure 2.2). The mass ion of 731 was assigned to **2.21d** (Figure 2.3) where one *R*-BINAP ligand binds to one Ag atom, most likely to be the catalytically active species. The signal with a mass ion of 772 corresponds to **2.21d**, where one solvent molecule (acetonitrile used in EI analysis) is present. The signal with a mass of 1493 agrees with the dimeric structure **2.21c**, plus a MeOH solvent (also used in EI analysis). However, the study revealed that the inactive species **2.21a** can be generated from a M:L ratio of 1:1, which could account for the lengthy reaction times.

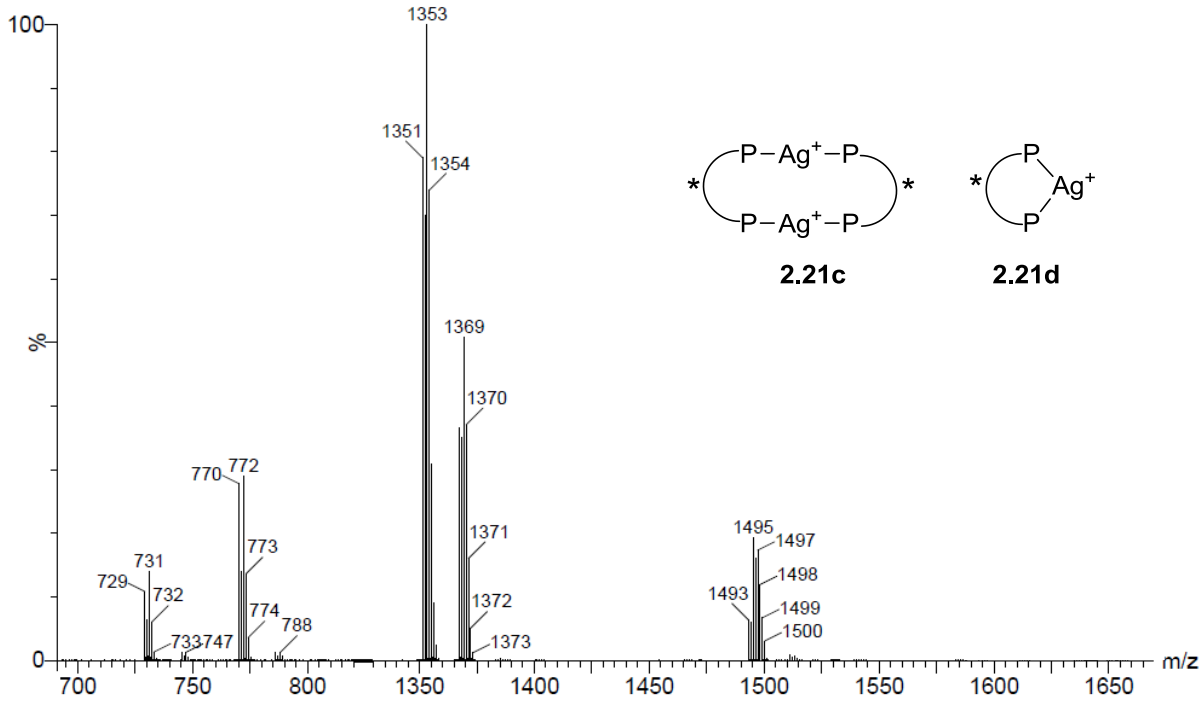


Figure 2.3: MS spectrum for a 1:2 ratio (M:L).

2.3.5 Effect of Temperature

A temperature study was conducted in an attempt to improve the rate of the reaction (Table 2.8, entry 2).

Table 2.8: Temperature study.[a]

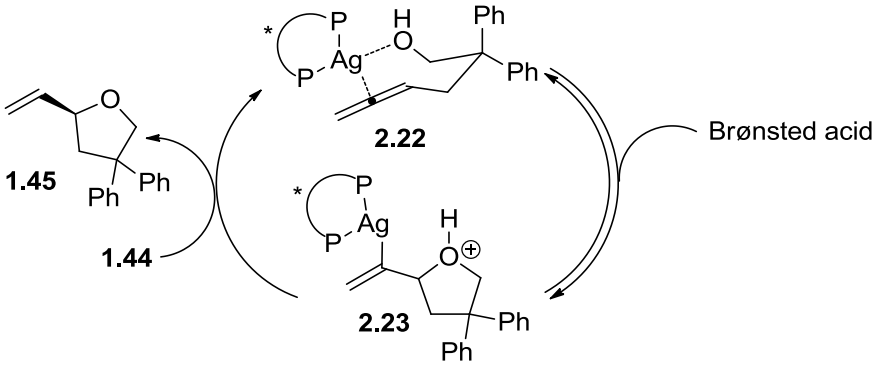
Entry	Temperature ^{o}C	t (h)	% Conversion [b]	% ee (*R*/*S*)[c]
1	0	336	42	62 (*S*)
2	rt	63	51	60 (*S*)
3	40	28	78	36 (*S*)

[a] Reaction conditions: **1.44** (25 mg, 0.1 mmol., 100 mM), $AgBF_4$ (15 mol%), *R*-BINAP (15 mol%), DCE (1.0 mL), r.t [b] Determined by ^{1}H NMR integration. [c] Determined by chiral HPLC and optical rotation values.

Increasing the reaction temperature to 40 ^{o}C increased the rate, but the enantioselectivity decreased from 60 to less than 40% (entry 2 *vs* 3). Conversely, reducing the temperature to 0 ^{o}C increased the enantioselectivity by only 2%, but dramatically lowered the reaction rate from 63 to 336 hours (entry 1 *vs 2*).

2.3.6 Acid Addition Effects - Achiral

At this juncture it was speculated that the C-O and C-H bond formation steps of the hydroalkoxylation reaction may occur sequentially (Scheme 2.15).[78] Assuming protonolysis (**2.23** to **1.45**) to be the rate determining and irreversible step, the reaction may be facilitated by the presence of Brønsted acids.



Scheme 2.15: Proposed key steps of the intramolecular hydroalkoxylation reaction**.**

To test this theory, a range of achiral Brønsted acids were examined as additives (Table 2.9). One equivalent of Brønsted acid was employed in all reactions: reactions listed in entries 1 to 9 were performed at 125 mM with 10 mol% catalytic loading, whilst reactions in entries 10 to 14 were performed at 100 mM with 5 or 15 mol%

catalytic loading. For comparison, the pK_a valves of the various protic additives are presented.

Table 2.9: Investigating the effect of Brønsted acids.[a]

Entry	Proton Source	pk_a[b]	x (mol%)	*t* (h)	% Conversion [c]	% ee (*R*/*S*)[d]
1	-	-	10	36	73	36 (*S*)
2	*rac*-CSA	-1	10	36	40	0
3	benzoic acid	4.2	10	36	79	27 (*S*)
4	pentafluorophenol	5.2	10	36	9	2 (*S*)
5	4-chlorophenol	9.43	10	36	100	35 (*S*)
6	2-naphthol	9.5	10	36	100	30 (*S*)
7	2-methoxyphenol	9.93	10	36	9	-
8	phenol	9.95	10	36	50	43 (*S*)
9	4-methoxyphenol	10.26	10	36	-	-
10	-	-	15	48	40	44 (*S*)
11[e]	2, 4-di-*t*-Bu-phenol	16.77[f]	15	48	39	38 (*S*)
12[e]	2, 6-di-*t*-Bu-phenol	17.20[f]	15	48	11	38 (*S*)

[a] Reaction conditions: **1.44** (25 mg , 0.1 mmol., 100 mM), $AgBF_4$ (x mol%), *R*-BINAP (x mol%), additive (0.1 mmol.), DCE (1.0 mL), r.t. [b] In H_2O.[128] [c] Determined by ^1H NMR integration. [d] Determined by chiral HPLC and optical rotation values.[e] 40°C. [f] In MeOH. [129]

The reaction outcome does appear to be dependent on a proton source with a pK_a value between 9.4 - 10.0; full conversions with similar enantioselectivities were observed using 4-chlorophenol (pK_a of 9.43) and 2-naphthol (pK_a of 9.5) (entry 1 *vs* 5 and 6). Phenol (with a higher pK_a of 9.95) provided a slightly lower yield, but increased the ee to 46% (entry 8). Lying outside the 9.4 - 10.0 pK_a range, 0% conversion was observed with electron donating 4-methyoxyphenol (entry 9). Also less acidic 2,4- and 2,6-di-*t*-Bu phenols decreased the rate of the reaction (entry 10 *vs* 11 and 12), more so for the more sterically hindered 2,6-di-*tert*-butyl-phenol, where the conversion dropped from 40% to 11% (entry 12).

At the other end of the scale, zero to low conversions were observed using acidic camphor sulfonic acid (CSA), and pentafluorophenol as additives (entries 2 and 4). 2-Methoxyphenol with a pK_a of 9.93 only produced 9% conversion, so does not fit in the trend observed with the other differentially substituted phenols (entry 7). This is possibly due to the close proximity of the methoxy to the hydroxyl group imposing additional steric hindrance. Following the trend, benzoic acid with a pK_a of 4.2 should produce a low conversion and ee. In spite of this, a high conversion of 79% was observed (entry 3), which suggests the trend only applies for phenols. Overall, 4-chlorophenol and 2-naphthol do seem to increase the rate of the reaction.

2.3.7 Acid Addition Effects – Chiral

Encouraged by the positive effects of 4-chlorophenol and 2-naphthol (achiral proton additives), match-mismatch effects between chiral diphosphine ligands with a chiral protic additive, BINOL (pK_a 9.3),[130] was investigated (Table 2.10).

Table 2.10: Investigating the effect of BINOL.[a]

Entry	BINOL	x (mol%)	T (^oC)	% Conversion [b]	% ee (*R/S*)[c]
1	-	5	r.t	94	39 (*R*)
2	*R*-BINOL	5	r.t	27	58 (*R*)
3	*S*-BINOL	5	r.t	100	25 (*R*)
4	-	5	40	68	36 (*R*)
5	*R*-BINOL	5	40	10	37 (*R*)
6	*S*-BINOL	5	40	100	31 (*R*)
7	-	15	r.t	50	59 (*R*)
8	*R*-BINOL	15	r.t	15	37 (*R*)
9	*S*-BINOL	15	r.t	100	40 (*R*)

[a] Reaction conditions: **1.44** (25 mg , 0.1 mmol., 100 mM), $AgBF_4$ (x mol%), *R*-BINAP (x mol%), additive (0.1 mmol.), DCE (1.0 mL), 63 h. [b] Determined by ^1H NMR integration. [c] Determined by chiral HPLC and optical rotation values.

Interesting match-mismatch effects were observed with *R*- and *S*-BINOL at 5 mol% and 15 mol%. *R*-BINOL seemed to hinder the reaction, but produce a higher

enantioselectivity (entries 3, 6 and 8), whereas the reverse was observed with *S*-BINOL (entries 2, 5 and 8), in comparison to the reaction without an additive (entries 1, 4 and 7). At an elevated temperature of 40 ^{o}C, the difference in enantioselectivity between *R*- and *S*-BINOL was reduced, but not the rate (entries 4 to 6).

Next, the amount of *S*-BINOL was lowered to see if the conversion or enantiomeric excess are affected (Table 2.11).

Table 2.11: Investigating the effect of *S*-BINOL.[a]

Entry	***S*-BINOL (mol%)**	**% Conversion** [b]	**% ee (*R/S*)** [c]
1	100	55	45 (*S*)
2	50	45	48 (*S*)
3	25	14	40 (*S*)
4	10	57	45 (*S*)
5	5	5	-
6	2.5	45	58 (*S*)

[a] Reaction conditions: **1.44** (25 mg , 0.1 mmol., 100 mM), $AgBF_4$ (15 mol%), *S*-BINOL (x %), DCE (1.0 mL), r.t, 36 h. [b] Determined by ^{1}H NMR integration. [c] Determined by chiral HPLC and optical rotation values.

After 36 hours at room temperature, conversion and enantioselectivity were maintained in the presence of 10-100 mol% of BINOL (entries 1 to 4). The use of 5% of the additive appeared to hinder the reaction (entry 5) whereas 2.5% provided moderate conversion with a respective enantioselectivity (entry 6), indicating a possible switch in the nature of the catalytic active species. Overall, there is no beneficial improvement in the rate of conversion.

As a control, the reaction was performed in the absence of the *R*-BINAP ligand to check whether BINOL can behave as a ligand itself (Table 2.12). As only racemic products were obtained, BINOL is clearly not an effective ligand for the asymmetric process (entries 1 to 3).

Table 2.12: Using *R*-BINOL as a ligand.[a]

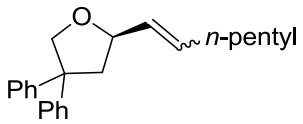
Entry	R-BINOL (% with respect to $AgBF_4$)	Conversion %[b]	ee%[c]
1	-	93	0
2	7.5	100	0
3	15	63	0

[a] Reaction conditions: **1.44** (25 mg, 0.1 mmol., 100 mM), $AgBF_4$ (15 mol%), additive (x mmol.), DCE (1.0 mL), r.t, 21 h. [b] Determined by ^{1}H NMR integration. [c] Determined by chiral HPLC.

2.4 Determination of Absolute Stereochemistry

During this work, we have uncovered a contradiction between the reported optical rotation[68] and chiral HPLC data[45,68] for optically active tetrahydrofuran **1.45**, which prevented an unambiguous determination of its absolute stereochemistry.

The chiral HPLC chromatogram of **1.45** has been previously recorded independently by two research groups using very similar conditions: Chirapak AD-H column, 1% IPA in *n*-hexane with 0.5 mL/min or 1.0 mL/min flow rates, respectively. Widenhoefer and co-workers reported that the major isomer was the first eluting peak at 17.4 min (Figure 2.5a).[45] The absolute stereochemistry was assigned tentatively as *R* by analogy with *R,E*-**1.48d** and *R,Z*-**1.48d**,[45] which were determined by comparison to an authentic sample of *R*-**1.48d** (*Z*/*E*=25:1, 84% ee) prepared by an independent route from a chiral precursor (Figure 2.4). On the other hand, Mikami and co-workers reported that the major isomer was the second eluting peak at 7.61 min, but also assigned it as *R* (Figure 2.5b). [68]



R-**1.48d** (*Z*/*E*=25:1,84%ee)

Figure 2.4: Structure of tetrahydrofuran *R*-**1.48d**.

For the sample **1.45** produced using $AgBF_4$/R-BINAP, the major enantiomer can be observed as the second eluting peak at 16.7 min (Figure 2.5c).

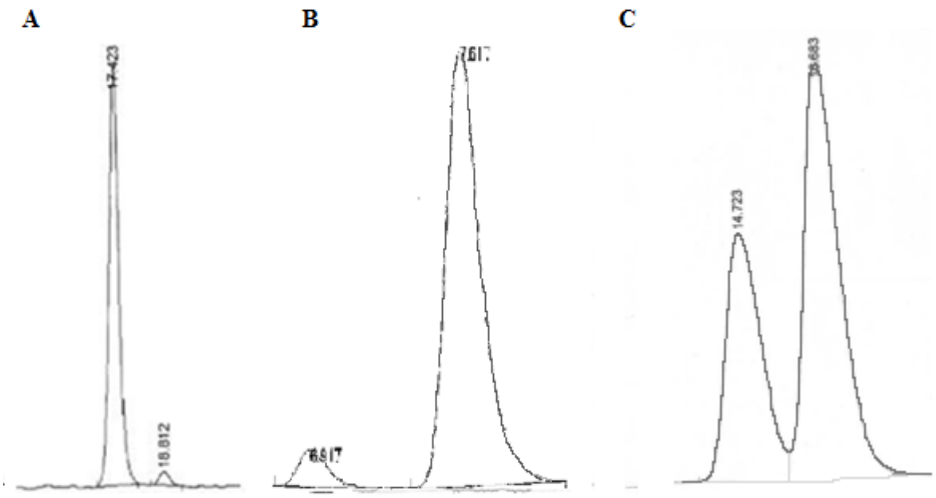


Figure 2.5: Chiral HPLC chromatograms of **1.45** recorded by: **a)** Aikawa *et al*.[68] **b)** Widenhoefer *et al*.[45] **c)** this work using Chirapak AD-H column at 1.0 and 0.5 mL/min respectively.

In 2009, the optical rotation and crystal structure for **2.24**, was published by Fu *et al.* where its absolute stereochemistry *R* was correlated with an optical rotation of +54º (*c* = 0.36 in $CHCl_3$) (Figure 2.6).[131]

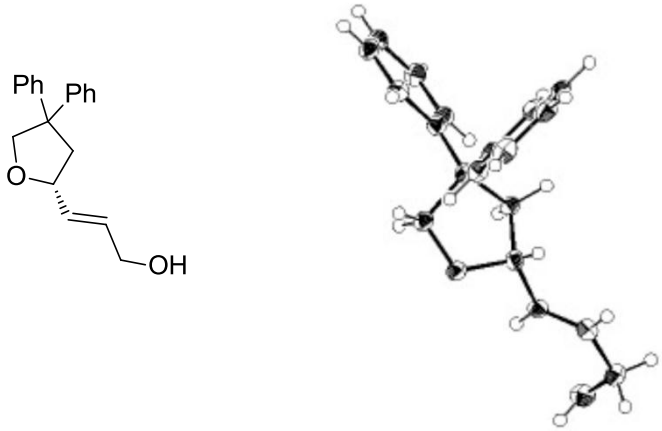
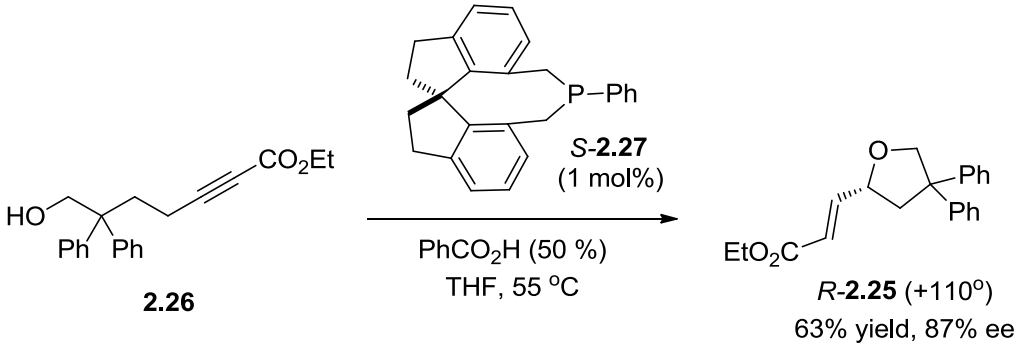


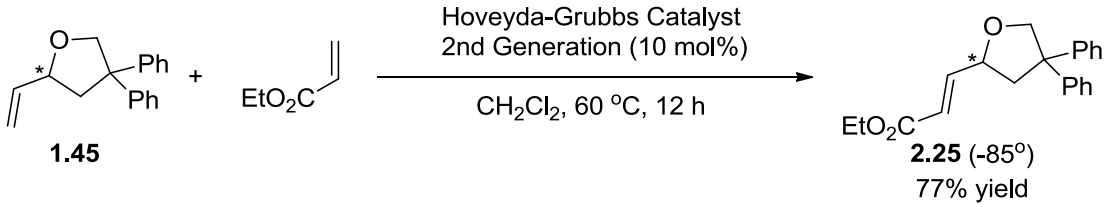
Figure 2.6: Structure and crystal structure of R-(+)-**2.24**.

The compound **2.24** was prepared from the reduction of the 2-vinyl tetrahydrofuran **2.25**, formed by phosphine-catalysed cyclisation of hydroxy-2-alkynoate **2.26** in 87% ee using *S*-**2.27** (Scheme 2.16).[131] The absolute configuration of **2.25** was therefore determined to be *R* with an optical rotation of +110º (*c* 1.0, $CHCl_3$).



Scheme 2.16: Phosphine mediated cyclisation of **2.26.**

In 2010, Mikami *et al.* determined the absolute stereochemistry of **1.45** by transforming it into ester **2.25** by a cross metathesis reaction with ethyl acrylate (Scheme 2.17) and comparing the optical rotation of **2.25** ($[\alpha]_D^{25}$ = -85.0°, *c* = 0.36 in $CHCl_3$).[68]



Scheme 2.17: Cross metathesis of **1.45** to **2.25**.

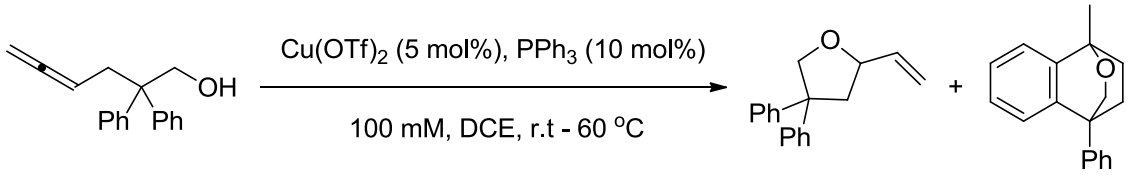
Although the optical values for **2.25** are contradictory to the literature value published by Fu *et al.*,[131] Mikami and co-workers incorrectly assigned the absolute stereochemistry of **2.25** and subsequently **1.45** ($[\alpha]_D^{25}$ = -110.4° (*c* = 0.39, $CHCl_3$, 87% ee) as *R*.[68] Having spoken with Prof Mikami over this issue, the stereochemical assignments of **1.45** and **2.25** have been reviewed and corrections have been submitted to the relevant journal.

For the sample **1.45** produced using $AgBF_4$/*R*-BINAP, the optical rotation was measured as $[\alpha]_D^{25}$ = -56° for 60% ee (*c* = 0.4, $CHCl_3$). Thus, by comparing the HPLC traces and optical rotations, we can confidently deduce that $AgBF_4$/*R*-BINAP favoured the formation of the *S* enantiomer.

2.5 Conclusion

Two different synthetic procedures to prepare the model substrate (**1.44**) were compared. Overall, pathway A was utilised for the preparation of **1.44** on a large scale since it was higher yielding and had a shorter synthesis.[36,45,58]

The use of $Cu(OTf)_2$ in hydroalkoxylation reactions proved inefficient. At room temperature and 60 ^oC a range of products were observed, with **1.45** and **2.11** being the most predominant (Scheme 2.18). Decomposition of the catalyst was observed and the possible involvement of TfOH formed during the reaction, promoted the formation of **2.11**.



1.44 **1.45** **2.11**

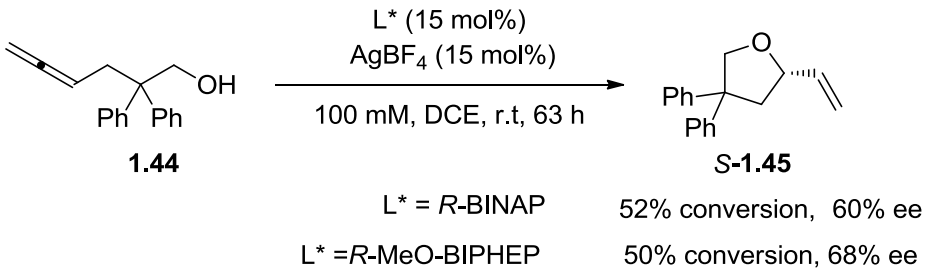
Scheme 2.18: Cu(II) mediated intramolecular hydroalkoxylation.

Ag(I) proved superior to Cu(II) by furnishing the 5-*exo*-*trig* product exclusively with modest rates. The reaction was found to be dependent on the counteranion employed; in increasing order of reactivity: $SbF_6^- < NO_3^- < BF_4^- < OTf^- < ClO_4^- < SO_4^{2-} < PF_6^- = CO_3^-$. On the other hand, the addition of chiral phosphine ligands hindered conversion of **1.44** to tetrahydrofuran **1.45** in the order: $BF_4^- < ClO_4^- < PF_6^- < SbF_6^-$. For all other counteranions, the formation of **1.45** was inhibited by the presence of phosphine. Moderate enantioselectivities of 68% were observed using the *R*-MeO-BIPHEP/$AgBF_4$ system, compared to 60% attained with *R*-BINAP/$AgBF_4$.

Conversion is also an important issue for these reactions; for the *R*-BINAP/$AgBF_4$ system 52% conversion was observed after 63 hours. MS and ^{31}P NMR studies implied that the major species generated from a M:L ratio of 1:1 contains the catalytically inactive species (**2.21a**). Instability/decomposition of the catalyst over time could also be a contributing factor.

Brønsted acid additives were examined and were found to be largely futile. However, interesting match-mismatch effects were observed when chiral additives *S*- and *R*-BINOL were used in the *R*-BINAP/$AgBF_4$ system.

Overall the best reaction conditions identified for Ag(I)-catalysed intramolecular hydroalkoxylation are summarised in Scheme 2.19.



Scheme 2.19: Ag(I)-mediated intramolecular hydroalkoxylation.

Chapter 3: Regioselectivity in the Metal-Catalysed Intramolecular Cyclisation of γ-Allenic Alcohols

Having demonstrated that Ag(I) salts are active catalysts in intramolecular hydroalkoxylation reactions of γ-allenic alcohols, and that $Cu(OTf)_2$ shows some 5-*exo-trig* selectivity, the catalytic activity of other Lewis acids were examined. In this Chapter, the origins of regioselectivity will also be examined, with the aid of DFT calculations.

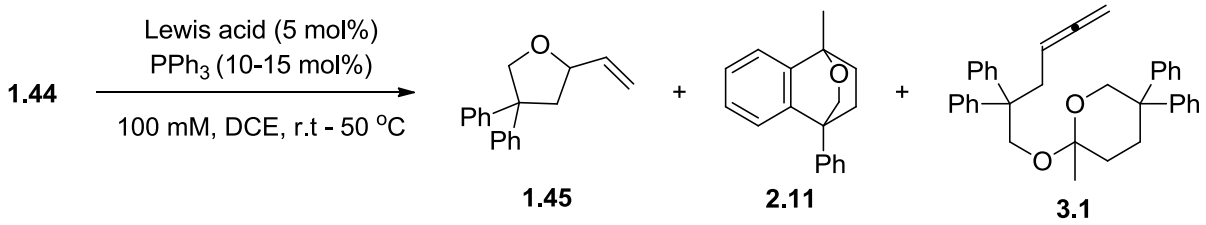
3.1 Initial Screening of Metal Lewis Acids in Hydroalkoxylation Reactions

Initially, the model substrate, **1.44** was employed in the catalyst screening, which included hard (Sc^{3+} and Yb^{3+}), medium (Zn^{2+}, Sn^{2+} and Ni^{2+}) and soft (Pd^{2+}) Lewis acids, with and without triphenylphosphine added as a ligand (Scheme 3.1, Table 3.1).

Table 3.1: Investigation of other metal Lewis acids for hydroalkoxylation.[a]

Entry	Lewis acid	Ligand (mol%)	T (°C)	t (h)	Yield of 1.45 (%)[b]	Yield of 2.11 (%)[b]	Yield of 3.1 (%)[b]
1	$Ni(OTf)_2$	-	50	>168	0	0	0
2	$Ni(OTf)_2$	PPh_3 (10)	50	>168	0	0	0
3	$Pd(OTf)_2$	-	50	>168	0	0	0
4	$Pd(OTf)_2$	PPh_3 (10)	50	>168	0	0	0
5	$Yb(OTf)_3$	-	50	>168	0	0	0
6	$Yb(OTf)_3$	PPh_3 (15)	50	>168	0	0	0
7	$Sc(OTf)_3$	-	50	>168	0	0	0
8	$Sc(OTf)_3$	PPh_3 (15)	50	>168	0	0	0
9	$Sn(OTf)_2$	-	r.t	72	4	63	0
10	$Sn(OTf)_2$	PPh_3 (10)	r.t	72	7	0	0
11	$Zn(OTf)_2$	-	50	>168	10	0	74
12	$Zn(OTf)_2$	PPh_3 (10)	50	>168	22	0	59

[a] Reaction conditions: **1.44** (100 mg, 0.4 mmol., 133 mM), Lewis acid (5 mol%), PPh_3 (10-15 mol%), DCE (0.3 mL). [b] Isolated yield after column chromatography.



Scheme 3.1: Model reaction for screening other Lewis acids for hydroalkoxylation reactions.

From this study, the lanthanide and group 10 salts $Yb(OTf)_3$, $Sc(OTf)_3$, $Ni(OTf)_2$ and $Pd(OTf)_2$ were found to be ineffective catalysts (entries 1 to 8). In the $Sn(OTf)_2$ catalysed reaction, the major compound isolated in 63% was found to be benzopyran **2.11** (entry 9), the same product that was obtained using $Cu(OTf)_2$ and TfOH in Chapter 2. When triphenylphosphine was present, conversion to **2.11** was not observed (entry 10). $Zn(OTf)_2$ on the other hand, furnished dimer **3.1** as the major product, in yields of 59% (entry 11) and 74%, with and without the addition of triphenylphosphine, respectively (entry 12). The 5-membered ring **1.45** was also isolated in both $Sn(OTf)_2$ and $Zn(OTf)_2$ catalysed reactions as a minor product (4-22%). The rates of all four reactions were very slow, taking more than 168 hours to complete. When **1.45** was isolated and left exposed to $Zn(OTf)_2$ or $Sn(OTf)_2$ it did not interconvert into **2.11** or **3.1**. Similarly **2.11** and **3.1** remained intact when left exposed to AgOTf. This suggested that all three products were formed by competitive and irreversible processes.

Both benzopyran **2.11** and acetal structure **3.1** were isolated and characterised by single crystal X-ray analysis (Figure 3.1, Appendix 1 and Appendix 2), obtained from slow evaporation of solutions of these compounds in hexane.

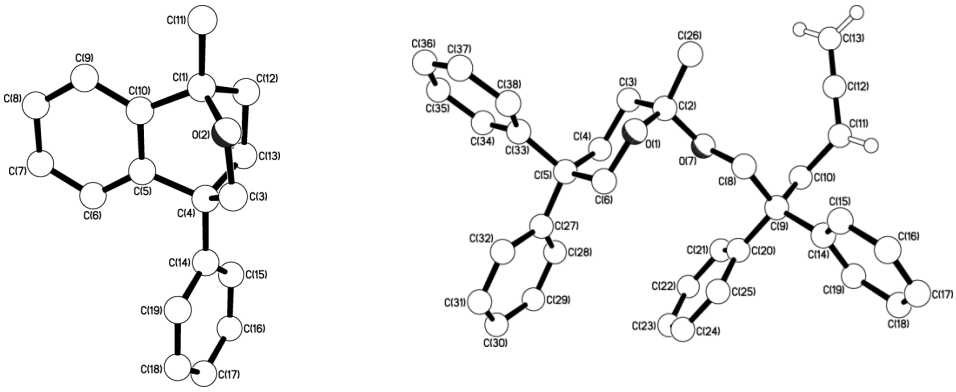


Figure 3.1: Crystal structures of benzopyran **2.11** and acetal structure **3.1**.

During the course of our work, the crystal structure of benzopyran **2.11** was also reported by Akiyama *et al.*[103] In the ^{1}H NMR spectrum, nine protons were present in the aromatic region, suggesting aryl substitution. This was supported by the presence of three quaternary ^{13}C NMR signals in the aromatic region. The presence of the methyl group was indicated as the singlet at 1.77 ppm and 21.8 ppm in ^{1}H and ^{13}C NMR spectra respectively. The ^{1}H NMR spectrum also shows a diastereotopic CH_2 group, presented as a doublet and a double doublet at 4.09 and 3.90 ppm (supported by COSY). The ^{13}C NMR spectrum, assisted by DEPT, also identified one quaternary centre present in the aliphatic region. MS, in CI mode, confirmed the expected mass of the compound ($[MNH_4^+] = 268$).

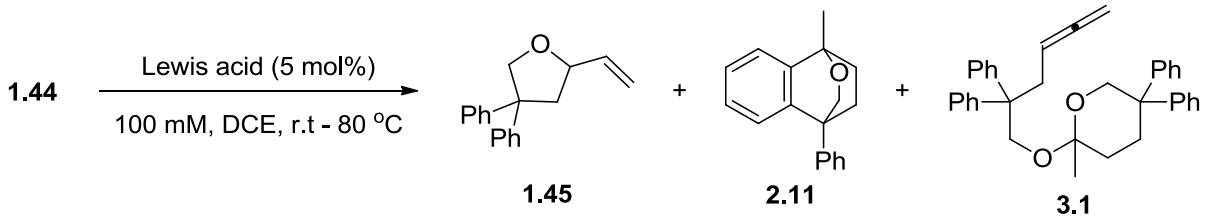
The crystal structure of **3.1** was also supported by NMR and IR techniques, but not by mass spectroscopy as the product fragmented extensively, under EI, CI and ESI ionisation methods, to the monomer ($[MH]^+ = 251$). The ^{1}H NMR spectrum indicated twice as many distinct protons present in comparison to the starting material (20H in the aromatic and 16H in the aliphatic region) indicating the formation of a dimer. Two multiplets at 4.64 and 4.46 ppm, which correspond to one and two protons respectively, indicated the presence of an allene moiety. This was supported by the peak at 1954 cm^{-1} in the IR spectrum and signals at 209.4, 85.7 and 73.6 ppm in the ^{13}C NMR spectrum.

From the preliminary investigation of Lewis acids in the intramolecular hydroalkoxylation of the γ-allenic alcohol **1.44**, $Sn(OTf)_2$ and $Zn(OTf)_2$ were found to afford the unexpected products **2.11** and **3.1**. Both structures result from the rarer 6-*exo-dig* cyclisation, which hitherto had only been achieved catalytically using the lanthanide amide complex $La[N(SiMe_3)_2]_3$ at 130 ^{o}C.[100]

3.2 Optimisation of Sn(II) and Zn(II) Triflate Catalysed Reactions

In the initial screen of $Sn(OTf)_2$ and $Zn(OTf)_2$, cyclisation proceeded to give **2.11** or **3.1** respectively in 336 hours. However, the 5-membered ring **1.45** was also formed as a minor product. An optimisation study was conducted in an attempt to improve the rate of the reaction and produce the 6-membered ring exclusively (Table 3.2).

Table 3.2: Optimisation of $Sn(OTf)_2$ and $Zn(OTf)_2$ conditions.[a]



Entry	Lewis acid	T (°C)	t (h)	Yield of 1.45 (%)[b]	Yield of 2.11 (%)[b]	Yield of 3.1 (%)[b]
1	$Sn(OTf)_2$	r.t	28	6	79	0
2	$Zn(OTf)_2$	80	36	13	0	61

[a] Reaction conditions: **1.44** (100 mg , 0.4 mmol., 133 mM), Lewis acid (15 mol%), DCE (0.3 mL).

[b] Isolated yields after column chromatography.

By increasing the catalytic loading from 5 to 15 mol% the reaction mediated by $Sn(OTf)_2$ was completed in 28 hours (Table 3.2, entry 1 *vs* Table 3.1, entry 9). For the reaction mediated by $Zn(OTf)_2$, a higher temperature of 80 °C was also required to produce **3.1** in 36 hours (Table 3.2, entry 2 *vs* Table 3.1, entry 11). However, a small quantity (6-13%) of the 5-*exo-trig* product **1.45** was also isolated from both reaction mixtures.

3.3 Brønsted Acid Catalysis

For benzopyran **2.11** to form, C-O and C-C bond forming at the central allenic carbon have to occur consecutively *via* hydroalkoxylation and electrophilic substitution reactions (Figure 3.2).

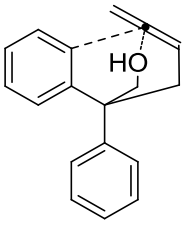
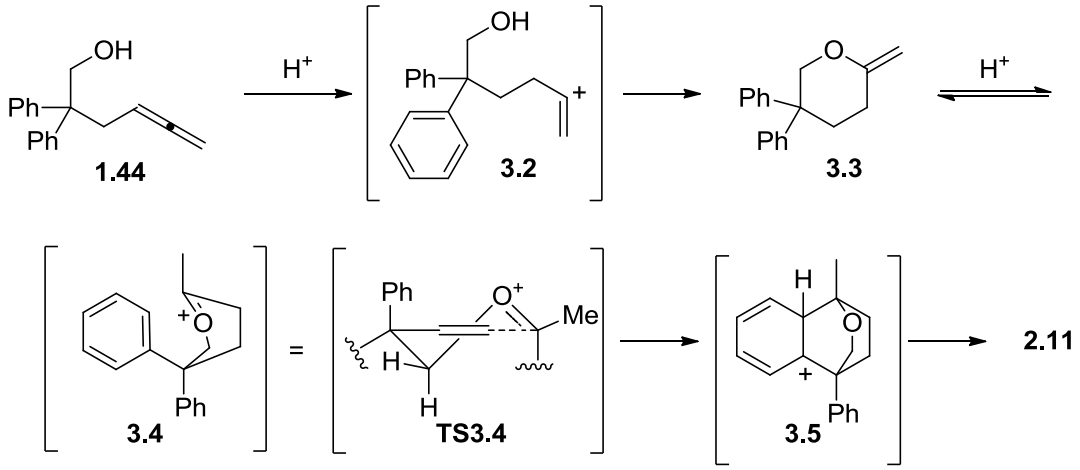


Figure 3.2: Two consecutive bond formations involved for compound **2.11**.

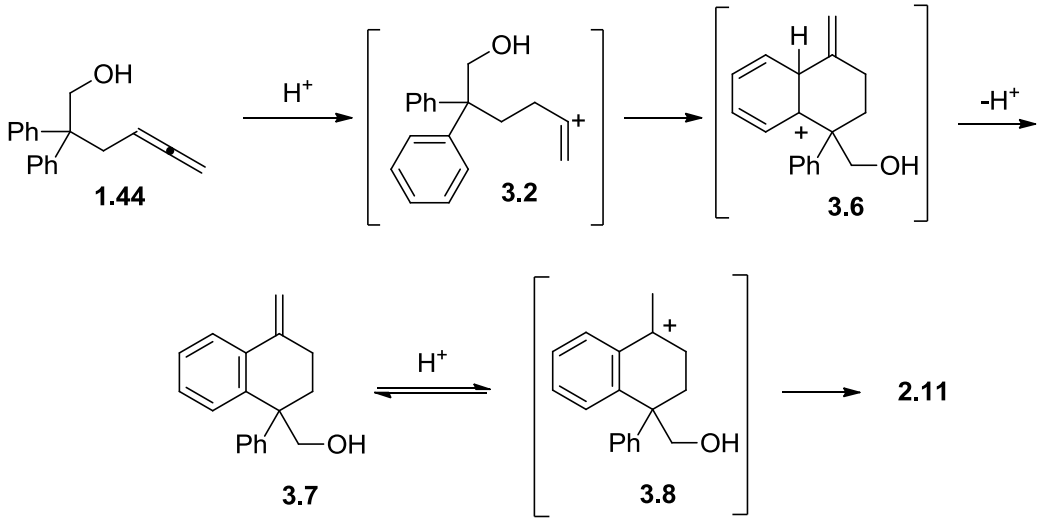
Akiyama *et al.*[103] described two plausible mechanisms for the formation of benzopyran **2.11** under Brønsted acid catalysis (Scheme 3.2 and Scheme 3.3). The

first mechanism (pathway A), involved protonation of the terminal allene (**3.2**) followed by *O*-nucleophilic addition to the vinyl cation to form **3.3** in a 6-*endo*-*dig* cyclisation (Scheme 3.2). Subsequent formation of an oxonium cation (**3.4**) followed by aromatic substitution of one of the phenyl rings *via* **TS3.4** (where the phenyl ring involved in C=C bond formation is shown as the double bond) to form the carbocation intermediate **3.5**. Finally, re-aromatisation furnishes **2.11**.



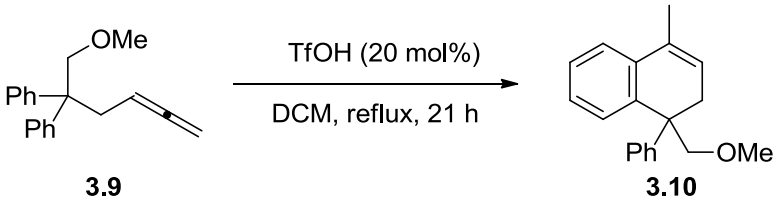
Scheme 3.2: Plausible pathway A for the Brønsted acid formation of benzopyran **2.11**.[103]

The second suggested mechanism (pathway B), also contained a 6-*endo*-*dig* cyclisation and Friedel Craft/aromatic substitution, but the order is reversed (**3.2** to **3.8**) (Scheme 3.3).



Scheme 3.3: Plausible pathway B for the Brønsted acid formation of benzopyran **2.11**.[103]

To differentiate between the two possible pathways, cyclisation of (1-methoxyhexa-4,5-diene-2,2-diyl)dibenzene, **3.9**, was examined by the same authors (Scheme 3.4).[103] The reaction proceeded to give the Friedel Craft product **3.10**, but was extremely slow with 61% of the starting material recovered after 21 hours at reflux. This observation was used to support the operation of pathway A in this reaction.



3.9 **3.10**

Scheme 3.4: Cyclisation of (1-methoxyhexa-4,5-diene-2,2-diyl)dibenzene, **3.9**.[103]

3.4 DFT Calculations

We turned to DFT models in order to rationalise the observed regioselectivities with Ag(I), Zn(II), and Sn(II) triflates. The transition states will be predicted and their free energies, $\Delta G^{\ddagger}$ calculated.

The term $\Delta G^{\ddagger}$, is defined as activation energy, for example, the difference in energy between the starting material (SM) and the transition state (TS), whereas ΔG^{o} is the thermodynamic parameter, denoting the energy difference between SM and product (P) (Figure 3.3).[132]

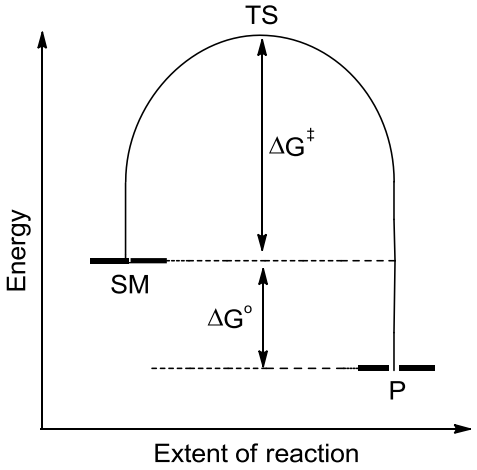
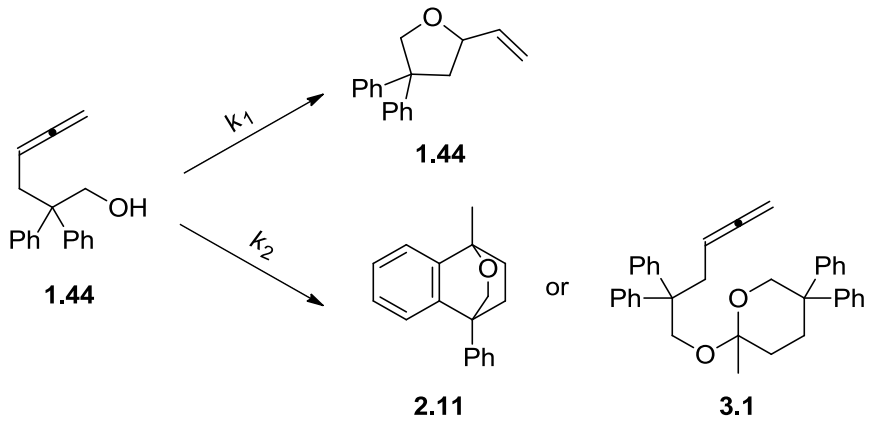


Figure 3.3: Energy diagram.[132]

From earlier investigations, the formation of 5- and 6-membered heterocyclic rings are formed by parallel, but irreversible processes (Scheme 3.5).



Scheme 3.5: Formation of **1.45**, **2.11** and **3.1** by competitive and irreversible processes.

In irreversible reactions, the product formed depends only on the reaction rate *k* and is therefore said to be kinetically controlled. The major product, at constant temperature, would therefore be the one with the smallest activation energy barrier ($\Delta G^{\ddagger}$) and largest rate coefficient (*k*). This is show mathematically in the Arrhenius equation, where R is the gas constant, T the temperature and A an exponential factor (Equation 3.1). [133]

$$k = A \exp(-\Delta G^{\ddagger}/RT) \qquad \textbf{Equation 3.1}$$

Several factors, entropy ($\Delta S^{\ddagger}$), enthalpy ($\Delta H^{\ddagger}$) and temperature, will also affect the ease of ring closure.[134,135] They are related to the free energy ($\Delta G^{\ddagger}$) *via* Equation 3.2 and will contribute to the size of the activation barrier, which in turn will affect the rate of the reaction (*k*).[132]

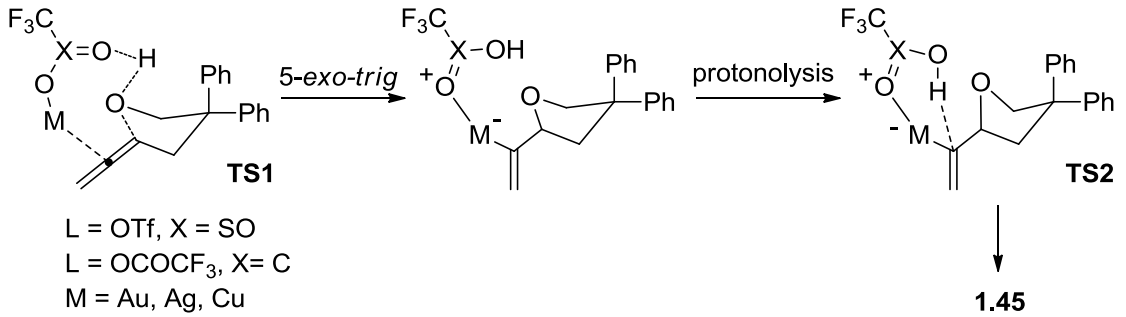
$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \qquad \textbf{Equation 3.2}$$

The aim of this work is to calculate the free energies ($\Delta G^{\ddagger}$) associated with the transition states of 5- and 6-membered ring formation for Ag(I), Sn(II) and Zn(II) triflates.

3.4.1 DFT Calculations for Group 11 Metals

Firstly, DFT models were constructed of the 5-*exo-trig* transition state **TS1** (Scheme 3.6) with triflate (OTf, X = SO) or trifluoroacetate ($OCOCF_3$, X = C) as counteranions for group 11 metals (Cu, Ag and Au). All calculations were undertaken at the B3LYP/cc-pVDZ level of theory and cc-pVDZ-pp for the metal by Prof. Henry S. Rzepa

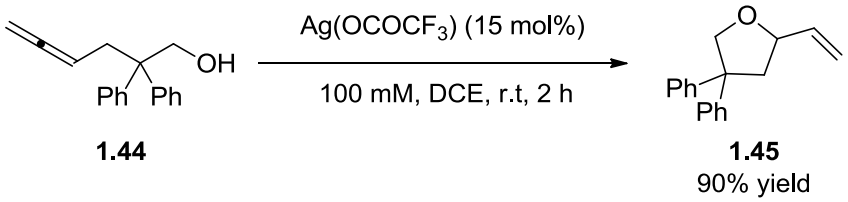
In the proposed mechanism, the metal binds to the central carbon of the allene moiety, and the anion is bound to the metal centre, and interacts with the proton of the OH group (cyclic **TS1**). In **TS1**, the bond angle around the metal (O-M-C) was found to be 170, 164, and 171^o when M = Au, Ag and Cu respectively, thus indicating a nearly linear geometry.[88] C-O bond formation occurs by O-nucleophilic attack, where the linear geometry of the metal defines the formation of the smaller 5-membered ring. Subsequent deprotonation of the oxonium by the counteranion followed by protonolysis of **TS2**, will result in the formation of tetrahydrofuran **1.45**.



Scheme 3.6: Mechanism of 5-*exo-trig* cyclisation.

The activation free energies ($\Delta G^{\ddagger}$) for the formation of **TS1**, with $OCOCF_3$ as the counteranion, were calculated for the group 11 metals (Cu, Ag and Au) as 26.7, 18.1 and 12.2 kcal mol^{-1} respectively. This decrease in free energy down group 11 is consistent with experimental data; where gold can facilitate heterofunctionalisation reactions at sub-zero temperatures,[45,58] silver at room temperature[62,78] and copper mostly at elevated temperatures.[87] Activation free energies for the formation of the 6-membered ring were not calculated as this product was not observed.[45]

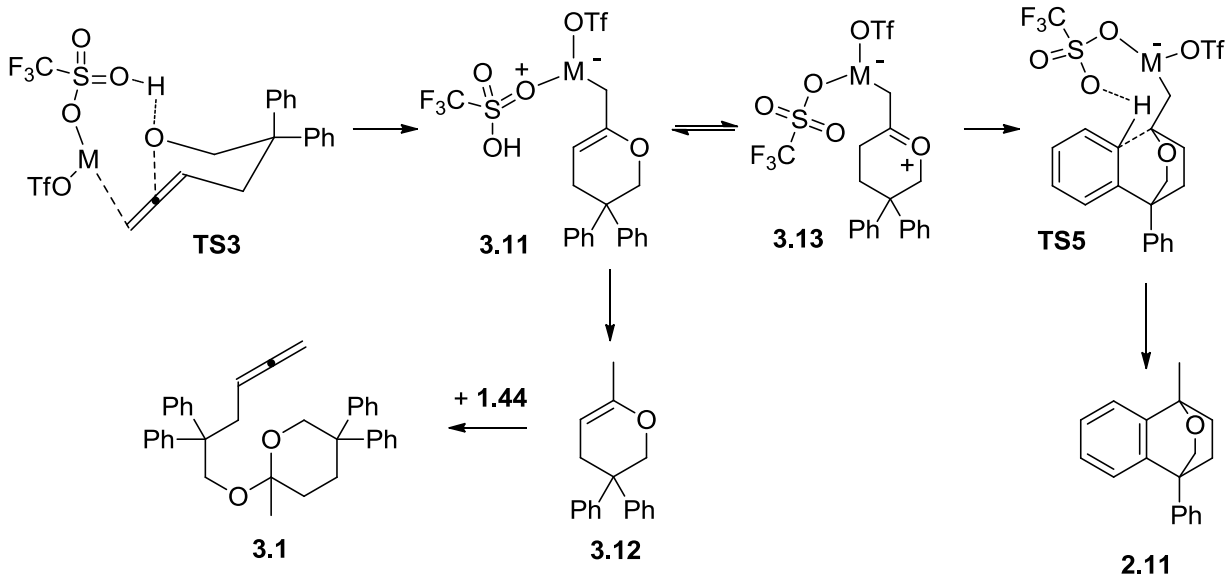
Modelling **TS1** with OTf (pK_a -14)[122] instead of $OCOCF_3$ (pK_a 0.23)[136] was calculated to increase the activation barrier by 1.5 kcal mol^{-1}. Carrying out the intramolecular hydroalkoxylation reaction with the counteranion $OCOCF_3$ was therefore predicted to increase the rate of the reaction 13-fold. Indeed, the reaction with 15 mol% $Ag(OCOCF_3)$ at room temperature afforded tetrahydrofuran **1.45** in 90% yield after only 2 hours (Scheme 3.7). In contrast, the reaction required 16 hours with AgOTf for completion.



Scheme 3.7: Cyclisation of **1.44** with $Ag(OCOCF_3)$.

3.4.2 DFT Calculations for Zn(II) and Sn(II) Triflates

Modelling studies for the divalent metals are more complex due to the ability of the counteranion to coordinate to the metal as a mono- or bi-dentate ligand. DFT calculation suggested that both structures **2.11** and **3.1** can be formed by a common transition state **TS3** (Scheme 3.8).



Scheme 3.8: Proposed pathway for the $Zn(OTf)_2$ and $Sn(OTf)_2$ mediated reactions.

For the formation of acetal **3.1** using $Zn(OTf)_2$, protonolysis of **3.11** to the cyclic enol ether **3.12** occurs and this is subsequently trapped by another molecule of **1.44**. On the other hand, for the formation of **2.11**, internal proton transfer of **3.11** occurs to form the oxonium ion **3.13**. Aromatic substitution presumably proceeds *via* a nascent-Wheland intermediate where deprotonation is assisted by the sulfonyl group to form **2.11** and this is shown in **TS5**.

Modelling studies of **TS3** where M = Zn or Sn revealed tetrahedral and hemi-directed geometries, respectively, around the metal centre. In both transition states, one of the oxygen atoms from the monodentate ligand acts as the base for proton removal (Figure 3.4). These transition states with a crowded metal centre are vastly different from the linear arrangement observed for group 11 metals, which may explain the observed change in regioselectivity with Zn(II)- and Sn(II) catalysed reactions.

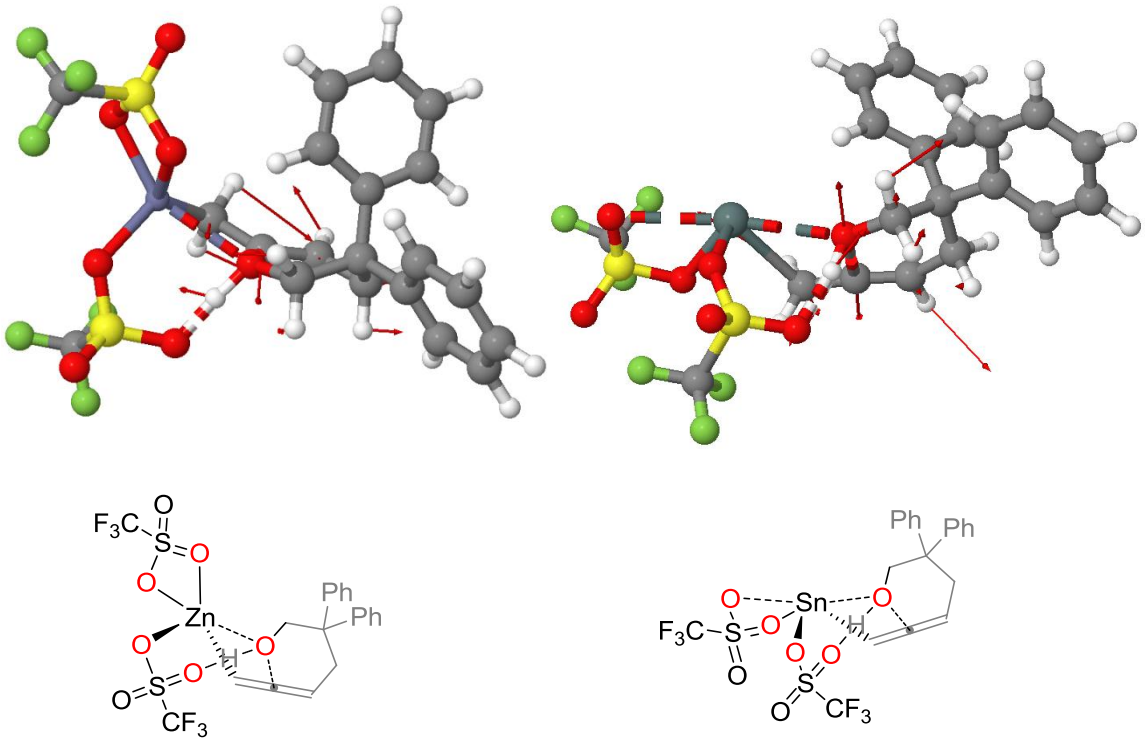
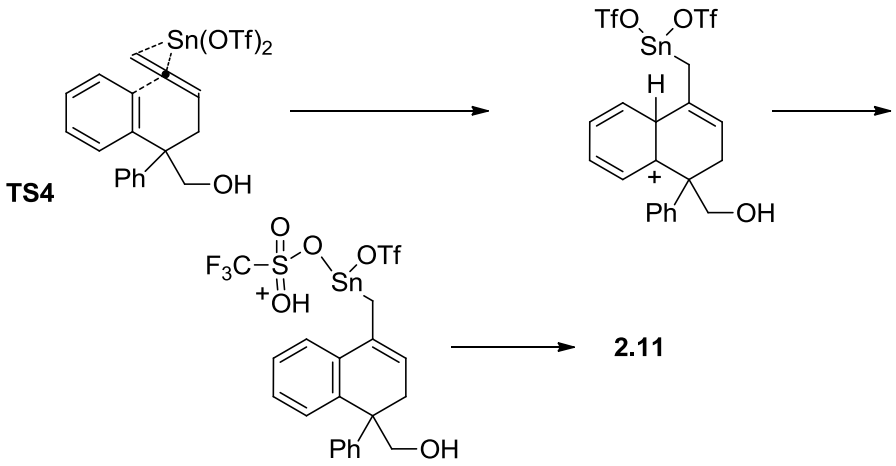


Figure 3.4: Transition states **TS3** (M = Zn or Sn).

Calculating the relative free energies of **TS1** and **TS3**, where M = Zn, **TS3** was found to be 1.3 kcal mol^{-1} lower in free energy than **TS1**, accounting for the formation of the 6-membered ring. However, the 5-membered ring was also obtained as a minor product, which suggests that the small energy difference between **TS1** and **TS3** can be

overcome under the reaction conditions. On the other hand, calculating the relative free energies of **TS1** and **TS3**, where M = Sn, **TS1** was found to be 4.7 kcal mol^{-1} *lower* in free energy than **TS3**, which contradicted the experimental observation, as this will suggest that the 5-membered ring should be the favoured product. On the other hand, an alternative mechanism whereby C-C bond formation occurs first (Scheme 3.9) is ruled out by an even higher $\Delta G^{\ddagger}$ calculated for transition state **TS4** (17 kcal mol^{-1} higher than TS1), and further experimental evidence (*vide infra*).



Scheme 3.9: Alternative pathway for $Sn(OTf)_2$ cyclisation of **1.44**.

Overall, the theoretical calculations are able to the support the $Zn(OTf)_2$ mechanism shown in Scheme 3.8, but the result is less convincing for $Sn(OTf)_2$. Also as TfOH has the ability to catalyse the reaction of **1.44** to **2.11**, the involvement of Brønsted acids cannot be ruled out (Scheme 3.2 and Scheme 3.3).

3.5 Investigating Regioselectivity with Other Substrates

The regiodiversity of AgOTf, $Sn(OTf)_2$ and $Zn(OTf)_2$ catalysed reactions was explored with two other γ-allenic alcohols **3.17** and **3.18** (Figure 3.5). Their preparation will be discussed in Chapter 4.

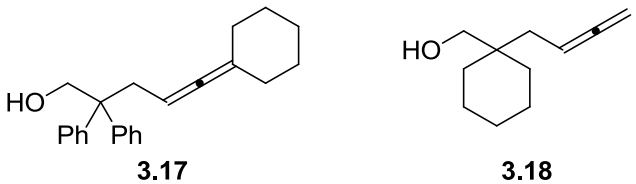
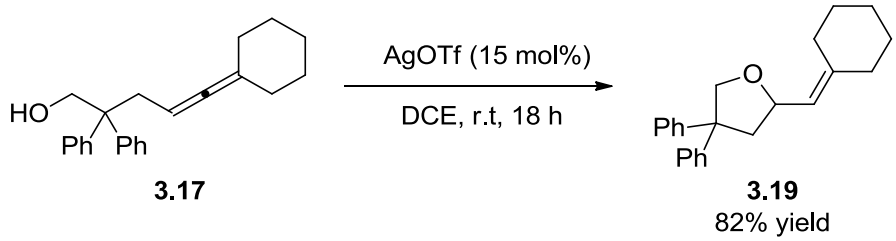


Figure 3.5: γ-allenic alcohols **3.17** and **3.18**.

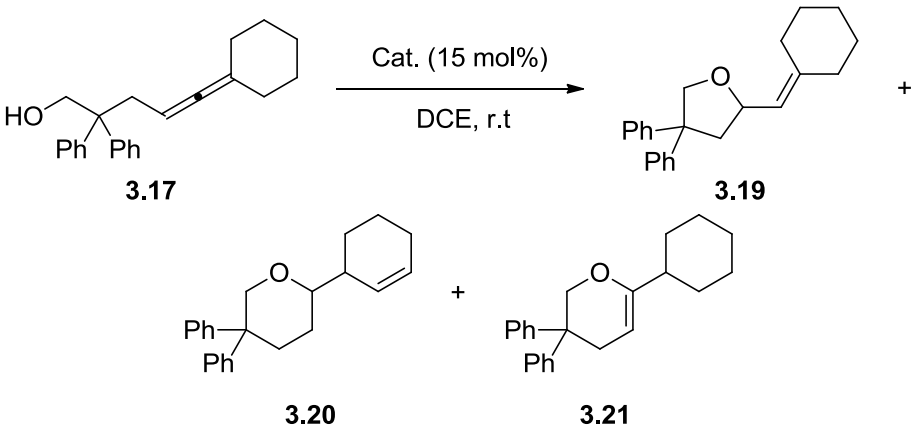
5-*Exo-trig* cyclisation of **3.17** with 15 mol% AgOTf afforded cyclic ether **3.19** in 82% yield (Scheme 3.10).



3.17 **3.19**
82% yield

Scheme 3.10: Cyclisation of γ-allenic alcohol **3.17** using AgOTf.

The corresponding reactions using $Sn(OTf)_2$ and $Zn(OTf)_2$ as catalysts afforded double bond isomers **3.20** and **3.21**, *via* 6-*exo*-dig cyclisation, as the major products (Scheme 3.11), along with the 5-membered ring as a minor product. Presumably, acetal and benzopyran formation were prohibited for steric reasons, associated with the presence of the cyclohexane ring. The observation of **3.20** and **3.21** in the Sn(II)-catalysed reaction supports the earlier proposal that the reaction proceeds *via* C-O bond formation first (thus ruling out the mechanism in Scheme 3.9).

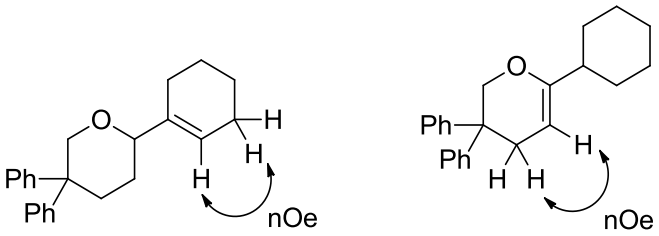


3.17 **3.19** **3.20** **3.21**

Scheme 3.11: Cyclisation of γ-allenic alcohol **3.17** using $Sn(OTf)_2$ and $Zn(OTf)_2$.

These double bond isomers **3.20** and **3.21** were isolated separately and characterised by ^{1}H NMR spectroscopy, which was supported by 2D NOESY. The only difference between **3.20** and **3.21** was the positioning of the alkene moiety (Figure 3.6). In the ^{1}H NMR spectrum of **3.21**, the presence of a cyclohexyl ring was revealed by the observation of 5 pairs of adjacent methylene groups, whereas **3.20** contains only 4 pairs of adjacent methylene groups. Additionally, the NOSEY spectrum of **3.20** revealed close proximity of the proton of the alkene moiety to the protons of the

cyclohexane ring, whereas the proton of the alkene moiety in **3.21** interacted more strongly with the CH_2 group in the THP ring.



3.20 **3.21**

Figure 3.6: Double bond isomers **3.20** and **3.21**.

With $Zn(OTf)_2$ as the catalyst, increasing the temperature lead to a switch in selectivity in favour of the 5-membered ring (Table 3.3, entry 1 *vs* 2). This suggests that the activation energy barriers for 5- and 6-membered ring formation are close in energy and at higher temperatures the selectivity is reduced. The ratio of **3.20** and **3.21** also changed from 1:11.5 to 1:1 at the higher temperature (entry 1 *vs* 2). Conversely, only a minor change in selectivity and ratio of **3.20** and **3.21** was observed in the reaction catalysed by $Sn(OTf)_2$ at room temperature and 50 ^oC (entry 3 vs 4).

Table 3.3: Cyclisation of γ-allenic alcohol **3.17** using $Sn(OTf)_2$, $Zn(OTf)_2$ and TfOH.[a]

Entry	**Cat.**	**T (^oC)**	**t (h)**	**Yield of 3.19 (%)[b]**	**Yield of 3.20 and 3.21 (%)[b]**
1	$Zn(OTf)_2$	r.t	28	9	75 (1 : 11.5)
2	$Zn(OTf)_2$	50	34	70	15 (1 : 1)
3	$Sn(OTf)_2$	r.t	28	6	82 (1 : 9.3)
4	$Sn(OTf)_2$	50	34	2	84 (1 : 8.3)
5	TfOH	r.t	23	0	67 (1 : 6)

[a] Typical reaction conditions: **3.17** (127 mg, 0.4 mmol., 133 mM), Cat. (15 mol%), DCE (0.3 mL).

[b] Isolated yields after column chromatography. Values in parenthesis denote ratio of **3.20**:**3.21**(determined by ^1H NMR).

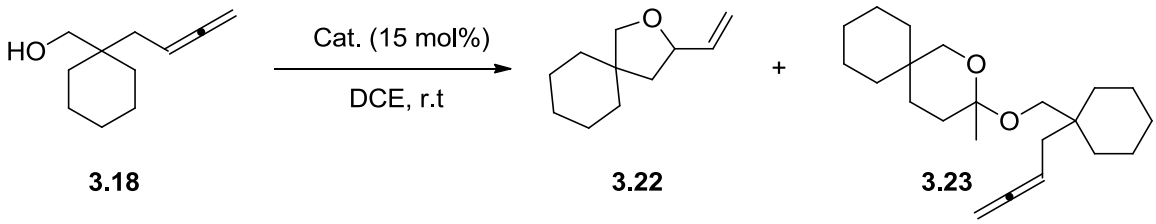
As Brønsted acid catalysis may play a role in the $Sn(OTf)_2$ mediated system, the reaction was also performed in the presence of 30 mol% TfOH. This reaction

proceeded to give **3.20** and **3.21** exclusively, in a lower yield of 67% and with a lower preference for **3.21** compared to **3.21** (1:93 *vs* 1:6) (entries 3 and 4 *vs* 5). This indicates that the 6-*exo-dig* cyclisation of **3.17** to form isomers **3.20** and **3.21** can also be mediated by Brønsted acids.

For γ-allenic alcohol **3.18**, 5-*exo-trig* cyclisation with AgOTf afforded tetrahydrofuran **3.22** exclusively in 12 hours with 76% yield (Scheme 3.12).

Scheme 3.12: Cyclisation of γ-allenic alcohol **3.18** using AgOTf.

The corresponding reactions using $Sn(OTf)_2$ and $Zn(OTf)_2$ afforded **3.22** and the acetal structure **3.23**, formed *via* 6-*exo-dig* cyclisation and entrapment with another molecule of **3.18** (Scheme 3.13).



Scheme 3.13: Cyclisation of γ-allenic alcohol **3.18** using different Lewis acids.

The $Sn(OTf)_2$ mediated reaction of **3.18** was somewhat lower in comparison to the cyclisation of **1.44** and **3.17**, even at an elevated temperature of 35 ^{o}C (Table 3.4, entry 1). At this temperature the 5-membered ring formation became competitive. The reaction catalysed by $Zn(OTf)_2$ was also sluggish at room temperature (entry 2). Even after 144 hours, 25% of the starting material was recovered. To promote 100% conversion the temperature was increased to 50 ^{o}C. However, this changed the selectivity of the reaction in favour of the 5-membered ring (entry 3). Again, Brønsted acid catalysis was investigated with 30 mol% TfOH, but surprisingly, **3.18**

remained inert over 6 days at room temperature (entry 4), thus suggesting that the cyclisation of this substrate is catalysed by $Sn(OTf)_2$.

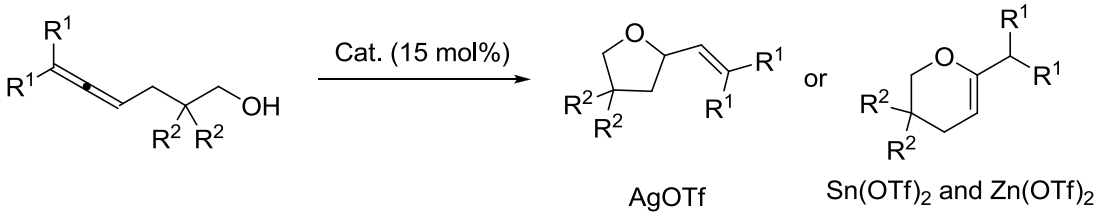
Table 3.4: Cyclisation of γ-allenol **3.18** using different Lewis acids.[a]

Entry	Cat.	T (^oC)	t (h)	Yield of 3.22 (%)[b]	Yield of 3.23 (%)[b]
1	$Sn(OTf)_2$	35	144	40	29
2	$Zn(OTf)_2$	r.t	144	9[c]	45
3	$Zn(OTf)_2$	50	36	52	9
4	TfOH	r.t	144	0	0

[a] Typical reaction conditions: **3.18** (66 mg, 0.4 mmol., 133 mM), Cat. (15 mol%), DCE (0.3 mL). [b] Isolated yields after column chromatography. [c] **3.18** recovered in 25% yield.

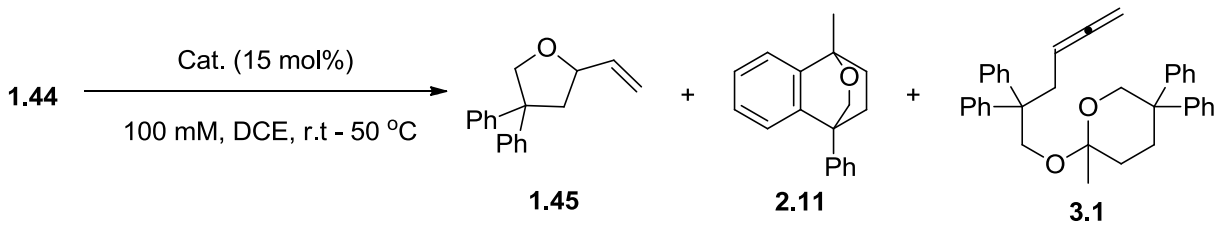
3.6 Conclusions

Overall, three different metal Lewis acids have been found to direct regioselective cyclisation of γ-allenic alcohols, by variation in coordination number and geometry. AgOTf forms linear complexes and favours the 5-*exo-trig* cyclisation (Scheme 3.14). $Zn(OTf)_2$ and $Sn(OTf)_2$, on the other hand, have tetrahedral or hemi-directed geometries respectively and direct selectivity towards 6-membered ring formation.



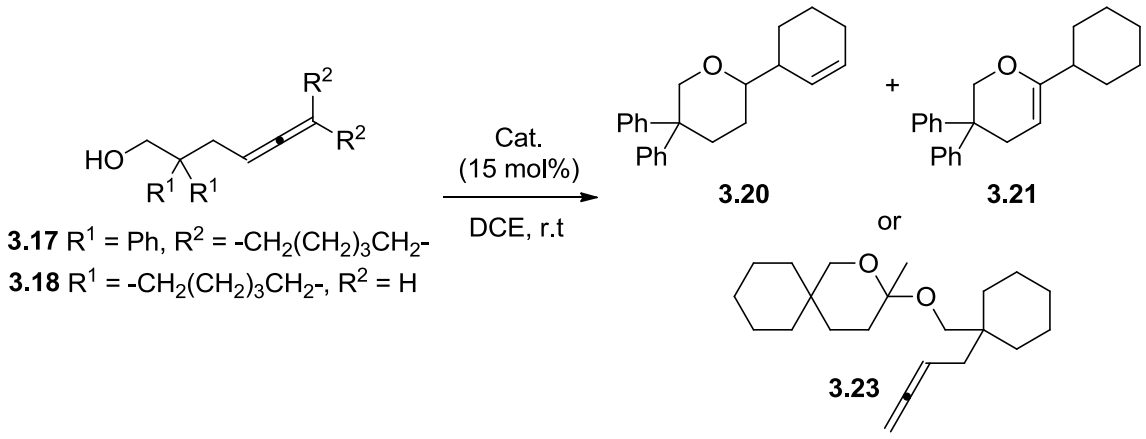
Scheme 3.14: Regioselectivity in the cyclisation of γ-allenic alcohols.

For model substrate **1.44**, $Sn(OTf)_2$ formed the benzopyran structure **2.11** via sequential C-O and C-C bond formation, whereas $Zn(OTf)_2$ formed the acetal structure **3.1** *via* two C-O bonds (Scheme 3.15). Both structures were characterised and supported by crystal structures. By experimentation, all three products (**1.45**, **2.11** and **3.1**) were expected to be formed by competitive and irreversible processes.



Scheme 3.15: Formation of **2.11** and **3.1**.

For acyclic substrates **3.17**and **3.18**, the divalent metals formed double bond isomers (**3.20** and **3.21**) and an acetal structure **3.23**, respectively, as the major products (Scheme 3.16).



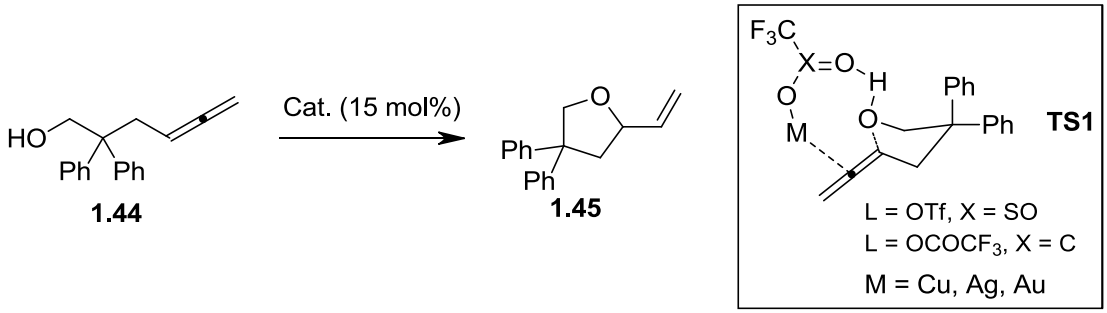
Scheme 3.16: Formation of **3.20**, **3.21** and **3.23.**

From DFT calculations, the counteranion was found to be intimately involved in C-O bond formation. From this, **TS1** for 5-*exo-trig* and **TS3** for 6-*exo-dig* cyclisation were proposed. **TS4** (M=Sn), to form benzopyran **2.11** *via* aromatic substitution then 6-*exo-dig* cyclisation was discarded as the free energy was higher than for **TS3**. DFT calculations also correctly predicted that the rate of the reaction was dependent on the counteranion employed.

In summary, while the involvement of Brønsted acids in the Ag(I)- and Zn(II)-catalysed reactions can be ruled out, the same cannot be said for the corresponding reactions performed using $Sn(OTf)_2$.

Chapter 4: Asymmetric Silver-Catalysed Intramolecular Hydroalkoxylation and Hydroacyalkoxylation Reactions

Previously in Chapter 3, DFT models were employed for the intramolecular hydroalkoxylation reaction of γ-allenic alcohol **1.44** catalysed by group 11 metals (M = Au, Ag, Cu) (Scheme 4.1). This study revealed that the counteranion (L = $OCOCF_3$ or OTf) is intimately involved in C-O bond formation, by remaining bound to the metal centre during the reaction.



Scheme 4.1: Cyclisation of **1.44** and cyclic transition state **TS1**.

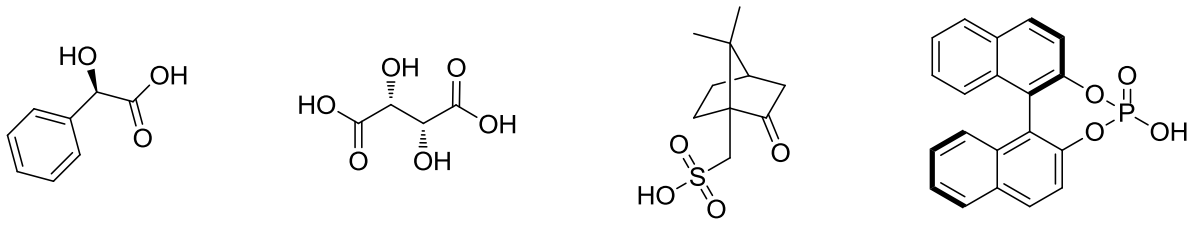
From this observation, we were inspired to investigate the possibility of asymmetric catalysis by the use of chiral anionic ligands. This concept has already been partially demonstrated for heterofunctionalisation reactions using Au(I) catalysis, in which a chiral Brønsted acid, mainly a phosphoric acid, is combined with an achiral/chiral Au(I) complex to afford high yields and enantioselectivities, although the precise role of the chiral anion was not defined.[36,44,68] On the other hand, asymmetric reactions catalysed by silver are limited. In most cases, the type of chiral ligands used in these reactions are P(III) donors (diphosphines or mixed-donor phosphines); but even so, enantioselectivities of >90% are rare.[137]

4.1 Use of Anionic Ligands in Asymmetric Hydroalkoxylation Reactions

4.1.1 Synthesis of Ag(I) Complexes 4.4-Ag to 4.7-Ag

Firstly, four chiral Ag(I) complexes were prepared from commercially available mandelic acid (*R*-**4.4**-H), tartaric acid (*R*-**4.5**-H), camphor sulfonic acid (*R*-**4.6**-H) and

binaphthalene-2,2′-diyl hydrogen phosphate (*R*-**4.7**-H) (Figure 4.1). Complexes *R*-**4.4**-Ag and *R,R*-**4.5**-Ag were prepared by the method by Cuin *et al.* (method 1),[138] whereby the chiral acids are deprotonated by treating with a slight excess of NaOH to generate a water-soluble salt, to which an equal quantity of $AgNO_3$ was added. The resultant Ag(I) complexes precipitated out of solution as white solids and were characterised by comparison with literature data.[138] In the infrared spectra, the C=O moiety of the Ag(I) complexes (*R*-**4.4**-Ag and *R,R*-**4.5**-Ag) were observed at lower frequencies than the C=O moiety of the carboxylic acids *R*-**4.4**-H and *R,R*-**4.5**-H. Finally, MS in FAB mode confirmed the expected mass of *R*-**4.4**-Ag ($[M]^+$ = 260), while the composition of *R,R*-**4.5**-Ag was determined by elemental analysis.



R-**4.4**-H *R,R*-**4.5**-H *R*-**4.6**-H *R*-**4.7**-H

Figure 4.1: Chiral acids **4.4**-H to **4.7**-H.

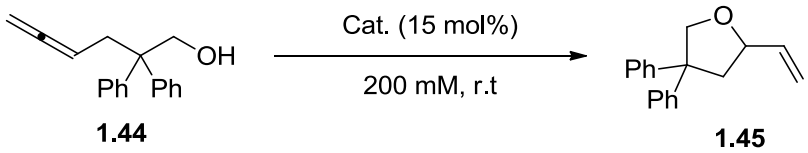
Attempting this method (method 1) for the formation of complex *R*-**4.6**-Ag afforded a dark solid, which suggested some decomposition. To overcome this, a modified procedure (method 2) reported by Sordo *et al.*[139,140] was used, whereby a mixture of Ag_2CO_3 and chiral acid (1:2 ratio) was stirred in ethanol overnight. This afforded a quantitative yield of *R*-**4.6**-Ag, which was characterised by FAB mass spectrometry ($[M]^+$ = 339) and elemental analysis.

BINOL-based phosphoric acids have been successfully implemented in gold heterofunctionalisation reactions,[36,44,68] and therefore a similar complex to *R*-**4.7**-Ag was generated by the addition of 0.5 equivalents of $AgCO_3$ to *R*-**4.7**-H in a 1:1 mixture of water to CH_2Cl_2 (method 3).[36] This furnished the silver phosphate salt in a low yield of 42%. In comparison, by using the modified method of Sordo *et al.*,[139,140] *R*-**4.7**-Ag can be obtained as a white solid in 88% yield. The formation of *R*-**4.7**-Ag was indicated by a shift of the ^{31}P NMR resonance from 4.5 to 9.4 ppm and the observation of a parent ion peak of 455 in MS (FAB mode).

4.1.2 Initial Screening of Ag(I) Complexes 4.4-Ag to 4.7-Ag in Hydroalkoxylation Reactions

These four complexes were subsequently screened in the cyclisation of γ-allenic alcohol **1.44** (Table 4.1). All reactions were conducted in the dark.

Table 4.1: Cyclisation of **1.44** with catalysts **4.4**-Ag to **4.7**-Ag. [a]



1.44 **1.45**

Entry	Catalyst	Solvent	t (h)	% Conversion[b]	% ee (*R*/*S*)[c]
1	*R*-**4.4**-Ag	DCE	36	100	0
2	*R*-**4.4**-Ag	THF	36	67	0
3	*R*-**4.4**-Ag	Toluene	36	27	0
4	*R*-**4.4**-Ag	MeOH	36	100	0
5	*R,R*-**4.5**-Ag	DCE	20	46	0
6	*R,R*-**4.5**-Ag	MeOH	20	100	0
7	*R*-**4.6**-Ag	DCE	20	100	0
8	*R*-**4.7**-Ag	DCE	0.25	100	15 (*R*)

[a]Reaction conditions: **1.44** (25 mg, 0.1 mmol., 200 mM), Cat. (15 mol%, 0.015 mmol.), Solvent (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

All four complexes were found to catalyse the cyclisation of **1.44**, in a 5-*exo*-*trig* fashion, to tetrahydrofuran **1.45**. However, the only complex able to induce chirality was *R*-**4.7**-Ag (entry 8). Although a low ee of 15% was obtained, the reaction was complete in just 15 minutes, thus supporting the hypothesis that a chiral counteranion is involved in the rate determining step. By comparing the optical rotation of the product to literature values,[45,68,131] the major enantiomer can be assigned as *R*.

This initial study also revealed that the solvent can greatly influence the reaction time. Using *R*-**4.4**-Ag as the catalyst, full conversion was obtained in DCE within 36 hours, but this decreased to 67% in THF and further to 27% in toluene (entries 1 to 3). We hypothesised that this was due to the solubility of the complex in these solvents. Cyclisation of **1.44** with *R*-**4.6**-Ag was faster, requiring 20 hours to reach full conversion in DCE (entry 7), whereas cyclisation of **1.44** using *R,R*-**4.5**-Ag in DCE reached only 46% conversion in 20 hours (entry 5). Switching to MeOH resulted in a homogeneous mixture and full conversion within 20 hours (entry 6).

The conversion time observed with *R*-**4.4**-Ag could be compared to the cyclisation of **1.44** with 15 mol% Ag_2CO_3 (Chapter 2) due to the similarities in pK_a (pK_a of mandelic acid = 3.41,[128] pK_a of Ag_2CO_3H = 3.9),[120] which proceeded to give full conversion within 48 hours. Cyclisation of **1.44** with the more acidic *R*-**4.6**-Ag (pK_a of CSA = 1.2)[128] in DCE proceeded in a faster reaction time (entry 7), whereas cyclisation with the less acidic *R,R*-**4.5**-Ag **(**pK_a of tartaric acid = 3.16)[141] in DCE was slower (entry 5). However, cyclisation of **1.44** with *R,R*-**4.5**-Ag in MeOH afforded full conversion to **1.45** in 20 hours (entry 6). This suggested that solubility may play a larger role than pK_a in these reactions.

In comparison to catalysts **4.4**-Ag to **4.6**-Ag, the short reaction time observed using *R*-**4.7**-Ag could be attributed to the acidic nature of the ligand (pK_a of diphenyl hydrogen phosphate is 0.26 in H_2O).[142] From Chapter 3, it was found that the cyclisation of **1.44** to **1.45** occurred faster when the weaker/less acidic counteranion, $OCOCF_3$ (pK_a of TFA = 0.23)[136] was used in place of OTf (pK_a of TfOH = -14).[122] The similarities in the pK_a of *R*-**4.7**-H (pK_a = 0.26) and TFA (pK_a = 0.23) may influence the ability of both to enable cyclisation quickly and efficiently. However, the solubility of *R*-**4.7**-Ag in the reaction medium could also be a contributing factor.

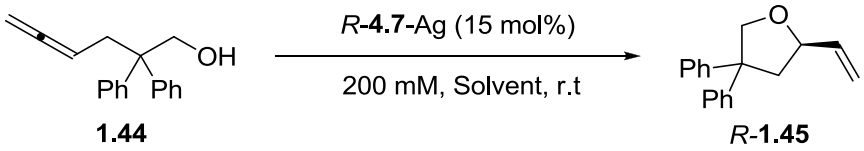
Further optimisation studies were thus conducted using phosphate *R*-**4.7**-Ag as a catalyst.

4.2 Use of *R*-4.7-Ag in Silver-Catalysed Hydroalkoxylation Reactions

4.2.1 Solvent Screen

Previously, the highest enantioselectivities were achieved using $AgBF_4$/*R*-BINAP in toluene, THF or DCE (Chapter 2). Accordingly, a solvent screen was performed with these three solvents (Table 4.2). Switching the solvent from DCE to toluene had little effect on conversion rate (entry 1 *vs* 2), whereas full conversion with THF required an extended reaction time of three hours (entry 3). In all cases, the enantioselectivity was unaffected. Thus, DCE was used as the solvent of choice.

Table 4.2: Cyclisation of **1.44** with 15 mol% *R*-**4.7**-Ag.[a]



Entry	Solvent	T (^oC)	t (h)	% ee (*R*/*S*) [b]
1	DCE	r.t	0.25	15 (*R*)
2	Toluene	r.t	0.25	16 (*R*)
3	THF	r.t	3	14 (*R*)

[a]Reaction conditions: **1.44** (25 mg, 0.1 mmol., 200 mM), *R*-**4.7**-Ag (15 mol%, 0.015 mmol.), Solvent (0.5 mL), r.t. [b] Determined by chiral HPLC analysis and optical rotation values.

4.2.2 Catalytic Loading and Dilution Screen

Next, effects of catalytic loading and dilution were investigated (Table 4.3). Decreasing the catalytic loading from 15 to 5 mol% was found to decrease the enantioselectivity (entry 1 *vs* 2), whereas increasing the catalytic loading to 30 and 50 mol% had no effect on either rate or enantioselectivity (entries 3 and 4). Conversely, increasing the dilution of the reaction reduced the reaction time (entries 5 and 6). In summary, alterations in catalytic loading and dilution had no overall positive effect on conversion or enantioselectivity.

Table 4.3: Cyclisation of **1.44** with *R*-**4.7**-Ag. [a]

Entry	x (mol%)	y (mL)	t (h)	% ee (*R*/*S*) [b]
1	5	0.5	0.25	6 (*R*)
2	15	0.5	0.25	15 (*R*)
3	30	1.0	0.3	12 (*R*)
4	50	1.0	0.3	12 (*R*)
5	5	1.0	1	9 (*R*)
6	5	3.0	3	10 (*R*)

[a]Reaction conditions: **1.44** (25 mg, 0.1 mmol.), *R*-**4.7**-Ag (x mol%, x mmol.), DCE (y mL), r.t.

[b] Determined by chiral HPLC analysis and optical rotation values.

4.2.3 Effect of Temperature

Next, the performance of *R*-**4.7**-Ag at low reaction temperatures was investigated (Table 4.4). Reducing the temperature to 0 ºC was found to dramatically decrease the rate of the reaction from 15 minutes to 5 hours, but only increase the enantioselectivity by 3% (entry 1 *vs* 2). Further reductions in temperature did not lead to any enhancement in ee (entries 3 and 4).

Table 4.4: Cyclisation of **1.44** with 15 mol% *R*-**4.7**-Ag. [a]

Entry	T (^{o}C)	t (h)	% ee (*R*/*S*) [b]
1	r.t	0.25	15 (*R*)
2	0	5	18 (*R*)
3	-5	6	18 (*R*)
4	-20	9	17 (*R*)

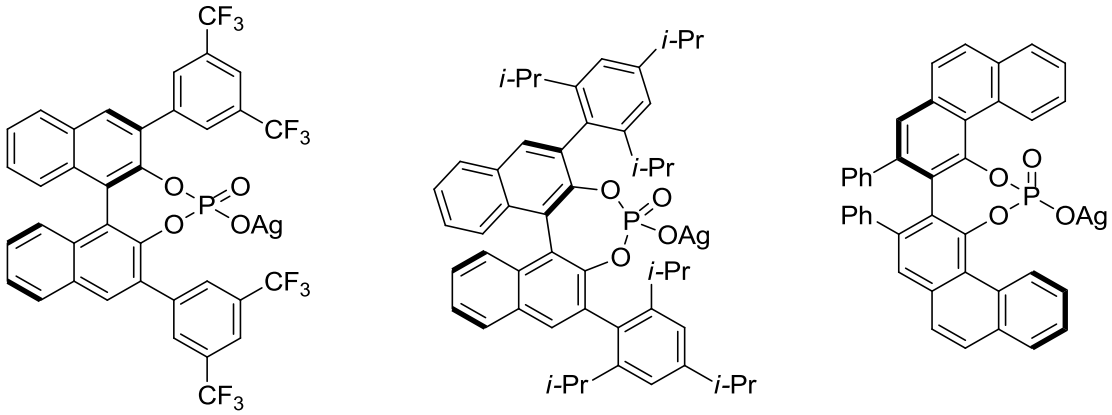
[a]Reaction conditions: **1.44** (25 mg, 0.1 mmol., 200 mM), *R*-**4.7**-Ag (15 mol%, 0.015 mmol.), DCE (0.5 mL). [b] Determined by chiral HPLC analysis and optical rotation values.

4.2.4 Synthesis of Ag(I) Complexes 1.66, 4.8-Ag and 4.9-Ag

It has been well-documented in literature that the introduction of bulky aryl groups at the 3,3'-position can often improve the enantioselectivity of reactions catalysed by chiral phosphoric acids.[36,68,137] By considering the DFT model (Figure 4.2), bulky aryl

groups at C-3 should also facilitate the transfer of chirality from the ligand backbone to the site of C-O bond formation.

With this in mind, further catalysts **4.8**-**Ag**, ***R***-**1.66** and **4.9**-**Ag** were prepared from the corresponding phosphoric acids (**4.8**-H, **1.66**-H and **4.9**-H) as white solids in 94%, 90%, and 85% yields, respectively (Figure 4.2).[36] The phosphoric acid **4.9**-H was kindly donated by Prof. J. Antilla from the University of South Florida, while the others were procured commercially. The preparative procedure and characterisation data for Ag(I) complexes *S*-**4.8**-Ag and *R*-**1.66**-Ag have been published by research groups of Mikami[68,143] and Toste[36] respectively, while *S*-**4.9**-Ag is a novel Ag(I) complex. The structures of *R*-**4.8**-Ag and *R*-**1.66** were confirmed by comparison of their characterisation data to published literature values.[36,68,143] For *R*-**4.8**-Ag, a ^{31}P resonance signal at 14.1 ppm and a -63.1 ppm signal in ^{19}F NMR were observed, but due to the extensive product fragmentation in MS, *R*-**4.8**-Ag was further characterised by elemental analysis. On the other hand, a ^{31}P NMR resonance at 14.8 ppm and MS in FAB mode confirmed the expected mass ($[MH]^+$ = 861). The structure of *S*-**4.9**-Ag was confirmed by a signal shift in ^{31}P NMR from 0.9 to 1.1 ppm and a $[M]^+$ mass peak at 707 in MS (FAB mode).



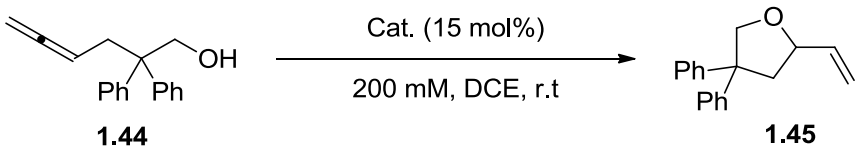
R-**4.8**-Ag *R*-**1.66** *S*-**4.9**-Ag

Figure 4.2: Ag(I) complexes *R*-**4.8**-Ag, *R*-**1.66** and *S*-**4.9**-Ag.

4.2.5 Screening of Ag(I) Complexes *R*-4.8-Ag, *R*-1.66 and *S*-4.9-Ag in Hydroalkoxylation Reactions

These three complexes were subsequently used in the cyclisation of **1.44** (Table 4.5). The introduction of aryl groups at the 3,3'-position improved the enantioselectivity, but by only a modest amount (up to 23% ee). The fastest reaction time was observed using *R*-**4.8**-Ag; cyclisation of **1.44** was complete in 15 minutes at room temperature to afford *R*-**1.45** with 22% ee (entry 1). Carrying out the reaction at -10 ^{o}C failed to enhance the selectivity (entry 2). Using the sterically bulky *R*-**1.66** afforded **1.45** in 23% ee, but with a decrease in rate from 15 minutes to 5.5 hours (entry 3), while *S*-**4.9**-Ag afforded *S*-**1.45** in 12 hours with just 7% ee (entry 4).

Table 4.5: Cyclisation of **1.44** with catalysts *R*-**4.8**-Ag, *R*-**1.66** and *S*-**4.9**-Ag. [a]



1.44 **1.45**

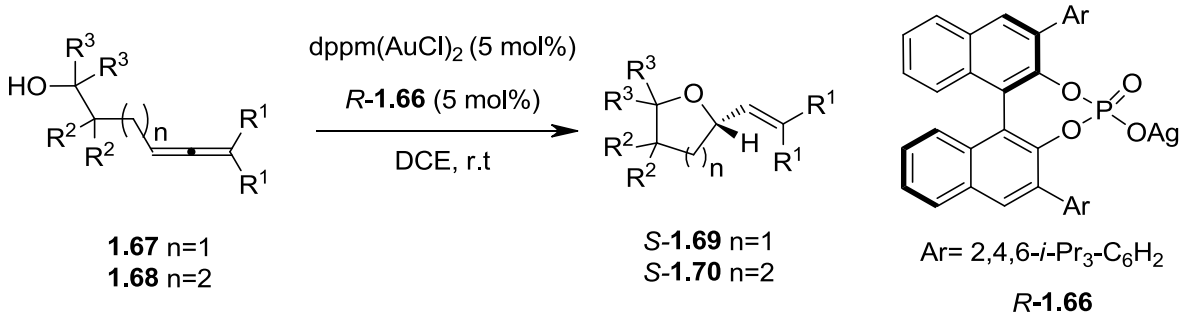
Entry	Catalyst	T (^{o}C)	t (h)	% ee (*R*/*S*) [b]
1	*R*-**4.8**-Ag	r.t	0.25	22 (*R*)
2	*R*-**4.8**-Ag	-10	24	22 (*R*)
3	*R*-**1.66**-Ag	r.t	5.5	23 (*R*)
4	*S*-**4.9**-Ag	r.t	12	7 (*S*)

[a]Reaction conditions: **1.44** (25 mg, 0.1 mmol., 200 mM), Cat. (15 mol%, 0.015 mmol.), DCE (0.5 mL). [b] Determined by chiral HPLC analysis and optical rotation values.

4.2.6 Control Experiments Conducted with Ag(I) Salts

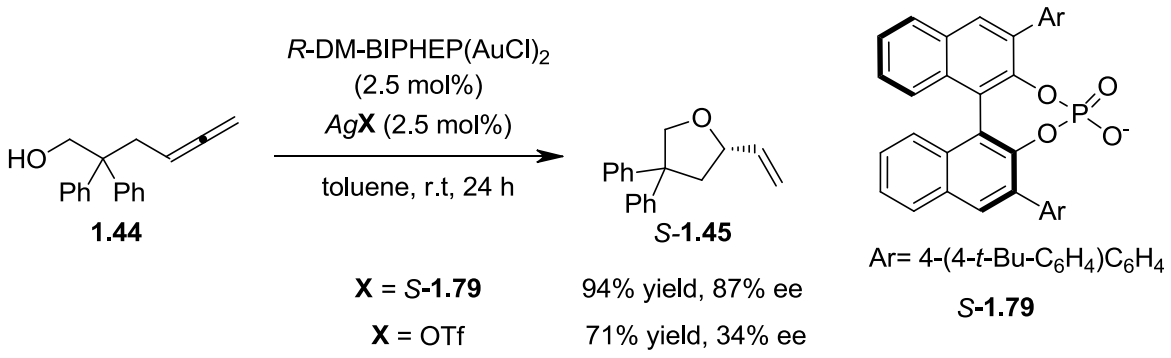
In light of the observed enantioselectivities achieved using BINOL-derived phosphate Ag(I) complexes we decided to examine control experiments conducted with Ag(I) salts reported in previous reports where chiral Ag(I) salts were used in the generation of the cationic gold complexes for catalysis.[36,68] In the paper published by Toste and co-workers,[36] it was reported that 5 mol% of *R*-**1.66** was unable to produce an appreciable background reaction at room temperature in the cyclisation of γ-allenic alcohols. The timescale of these control reactions was not discussed, although

hydroalkoxylation of γ-allenic alcohols (**1.67** and **1.68**) using dppm(AuCl)$_2$ and *R*-**1.66** produced the corresponding **1.69** and **1.70** in 1-30 hours depending on their substitution pattern (Scheme 4.2).[36]



Scheme 4.2: Hydroalkoxylation reactions using dppm(AuCl)$_2$ and *R*-**1.66**.

Conversely, Mikami *et al.*[68] did not describe any control reactions with Ag-BINOL complexes. However, the reaction performed using the chiral diphosphine ligand, DM-BIPHEP and achiral AgOTf was found to have a lower enantioselectivity than the corresponding reaction using *S*-**1.79** as the counteranion (Scheme 4.3). It is interesting to note that the opposite stereoinduction is observed in this system compared to Toste's (Scheme 4.2).



Scheme 4.3: Cyclisation of **1.44** using DM-BIPHEP(AuCl)$_2$ and *S*-**1.79**.

In comparison, we have shown that the cyclisation of **1.44** to *R*-**1.45** occurred in the presence of 15 mol% of *R*-**1.66** to full conversion within 5.5 hours at room temperature. Even at 2.5-5 mol% of catalyst there should theoretically be a moderate background reaction in the above systems after 24 hours.

4.3 Use of TADDOL Derived Ligands in Asymmetric Silver-Catalysed Hydroalkoxylation Reactions

Next, we turned our attention towards chiral anionic ligands with better chiral discriminating reagents, particularly those with similar pK_a values to TFA and *R*-**4.7**-H. On this basis, the chiral phosphoric acid derived from TADDOL looked particularly promising (Figure 4.3). Previously, this class of chiral Brønsted acids are known to be effective in enantioselective Mannich-type[144] and Simmons–Smith cyclopropanation reactions.[145]

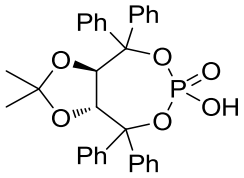


Figure 4.3: Chiral phosphoric acid *R*,*R*-**4.10**-H.

Comparing the reported crystal structures of *R*-**4.7**-H and *R*,*R*-**4.10**-H it can be observed that bond lengths around the phosphorus atom are very similar (Figure 4.5).[145,146] However, the positioning of the Ph groups in *R*,*R*-**4.10**-H, are closer to the reaction centre and may exhibit a stronger directing effect on the outcome of the reaction.

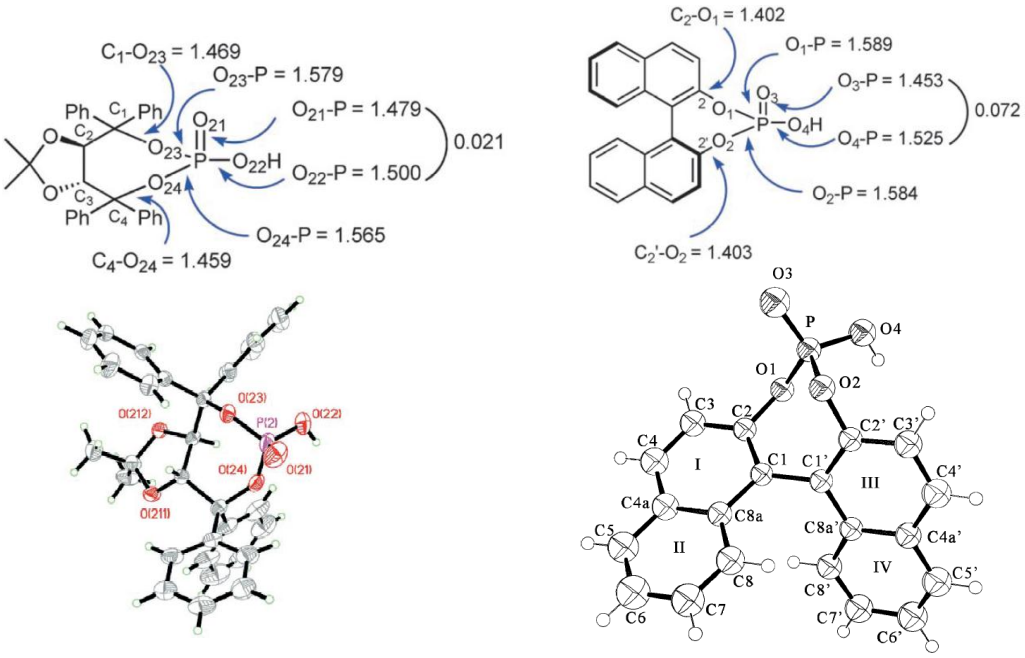
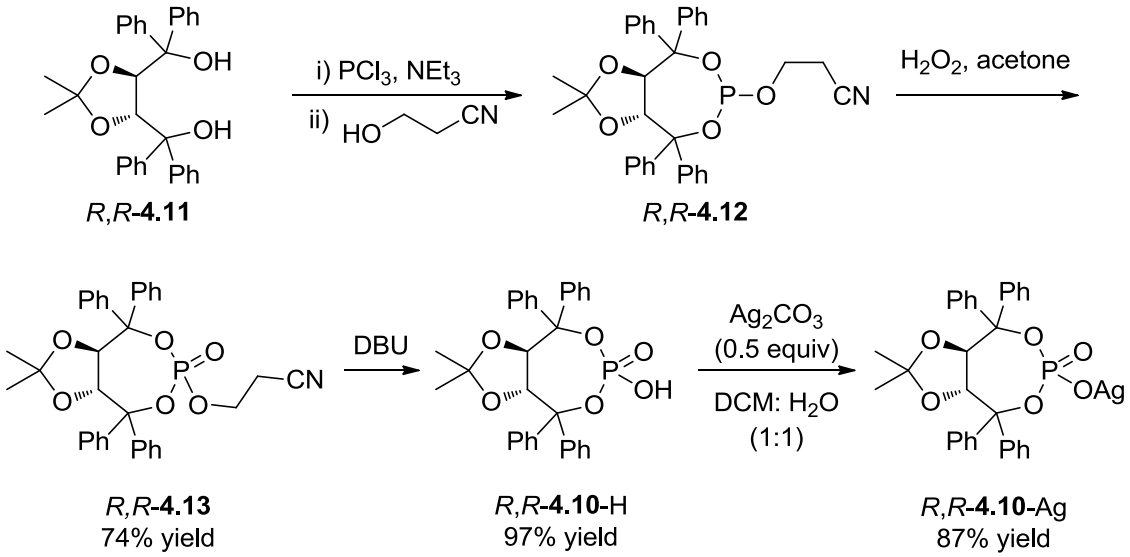


Figure 4.4: Crystal structures of *R*-**4.7**-H and *R*,*R*-**4.10**-H.[145,146]

4.3.1 Synthesis of *R,R*-4.10-Ag

Following a literature procedure, the synthesis of phosphate *R,R*-**4.10**-Ag was achieved in four steps from the TADDOL-derived diol precursor *R,R*-**4.11** (Scheme 4.4). Firstly, *R,R*-**4.11** was treated with PCl_3 in the presence of NEt_3, followed by the addition of 3-hydroxypropionitrile to form phosphonite intermediate *R,R*-**4.12**. This was immediately oxidised to phosphonate *R,R*-**4.13** using 30% aq. H_2O_2 and was isolated in 74% yield after purification by column chromatography. Deprotection of the phosphorus atom was carried out by the addition of DBU, and this was followed by an acidic work-up to afford *R,R*-**4.10**-H in 97% yield. The structure of *R,R*-**4.10**-H was confirmed by comparison of its characterisation data to published literature values.[145] Finally, the desired product *R,R*-**4.10**-Ag was formed by stirring the phosphoric acid *R,R*-**4.10**-H with 0.5 equivalents of Ag_2CO_3 in a 1:1 mixture of CH_2Cl_2 and H_2O for 2 hours (Method 3).[36] This afforded *R,R*-**4.10**-Ag as a white solid in 87% yield. The formation of *R,R*-**4.10**-Ag was indicated by a shift of the ^{31}P NMR resonance from -8.0 to -0.15 ppm, FAB mass spectrometry ($[M]^+$ = 635) and elemental analysis.

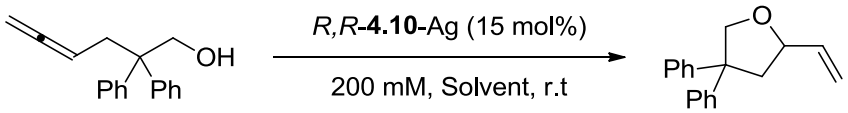


Scheme 4.4: Synthesis of *R,R*-**4.10**-Ag.

4.3.2 Screening of Ag(I) Complex *R,R*-4.10-Ag in Hydroalkoxylation Reactions

The TADDOL-based complex *R,R*-**4.10**-Ag was subsequently used in the cyclisation of **1.44** (Table 4.6). The reaction with *R,R*-**4.10**-Ag required a longer reaction time of 8 hours, compared to the 15 minutes with *R*-**4.7**-Ag. DCE promoted full conversion and afforded an ee of 17% (entry 1). Changing the solvent to THF or less polar toluene had little effect on the enantioselectivity, but decreased the conversion to 52 and 65% respectively, probably due to the limited solubility of the catalyst in these solvents (entries 2 and 3). Similarly, the use of dioxane led to poorer conversion and ee due to solubility issues (entry 4). Notably, the use of phosphoric acid *R,R*-**4.10**-H was unable to catalyse the reaction.

Table 4.6: Cyclisation of **1.44** with catalyst *R,R*-**4.10**-Ag.[a]



1.44 **1.45**

Entry	Solvent	% Conversion after 8 hours[b]	% ee (*R*/*S*)[c]
1	DCE	100	17 (*S*)
2	Toluene	65	15 (*S*)
3	THF	52	15 (*S*)
4	Dioxane	15	7 (*S*)

[a]Reaction conditions: Substrate **1.44** (25 mg, 0.1 mmol., 200 mM), *R,R*-**4.10**-Ag (15 mol%, 0.015 mmol.), Solvent (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

4.3.3 Synthesis and Screening of Ag(I) Complex S,*S*-4.14-Ag in Hydroalkoxylation Reactions

In an attempt to improve the enantioselectivity of the reaction, *S,S*-**4.14**-Ag, with naphyl α-position groups, was also synthesised using the same procedure described for *R,R*-**4.10**-Ag (Figure 4.5). The structure of *S,S*-**4.14**-H was confirmed by comparison of its characterisation data to published literature values,[145] while the

formation of the desired product *S,S*-**4.14**-Ag was indicated by a shift of the ^{31}P NMR resonance from -7.43 to -0.5 ppm, FAB mass spectrometry ($[MH]^+$ = 835) and the composition was confirmed by elemental analysis.

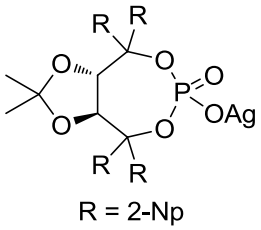
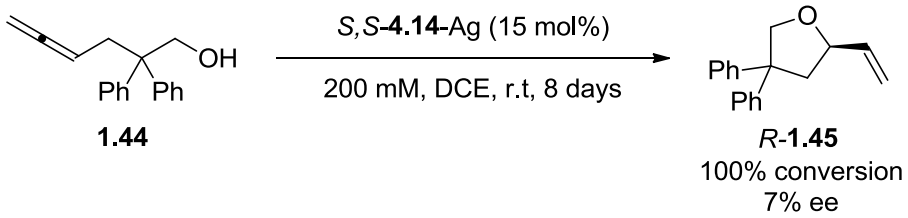


Figure 4.5: Chiral phosphate *S,S*-**4.14**-Ag.

The complex *S,S*-**4.14**-Ag was subsequently used in the cyclisation of **1.44** in DCE at room temperature (Scheme 4.5). Disappointingly, increasing the steric bulk of the aryl substituent only led to a loss in reaction rate and enantioselectivity.

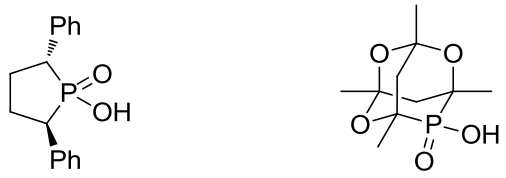


Scheme 4.5: Cyclisation of **1.44** with catalyst *S,S*-**4.14**-Ag.

4.4 Use of Phosphinic acids as Ligands in Asymmetric Silver-Catalysed Hydroalkoxylation Reactions

After these disappointing results, we decided to look at other phosphorus species. Phosphinic acids are inherently less acidic (pK_a around 3.08 in H_2O for dimethylphosphinic acid) than phosphoric acids,[147] but have the potential for introducing chiral groups α to the phosphorus atom, which could facilitate enantioselectivity. A literature search identified two interesting candidates: *R,R*-**4.15**-H and β-**4.16**-H (Figure 4.6). *R,R*-**4.15**-H was kindly donated by Prof. J-C. Fiaud of the University of Paris-Sud 11, while β-**4.16**-H was obtained from Prof. P. Pringle of the University of Bristol.

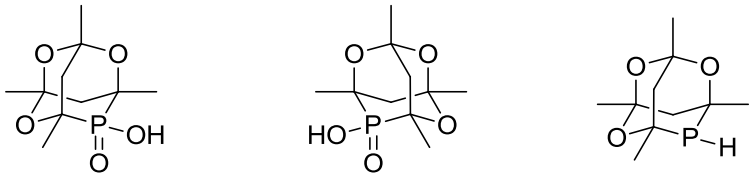
Both compounds were synthesised as intermediates in the formation of phosphine oxide and phosphate compounds, respectively, which were applied as ligands in asymmetric hydrogenation reactions.[148,149]



R,R-**4.15**-H β-**4.16**-H

Figure 4.6: Structures of chiral phosphinic acids *R,R*-**4.15**-H and β-**4.16**-H.

R,R-**4.15**-H has a 2,5-diaryl frame and appears to be a promising ligand due to phenyl groups adjacent to the phosphorus atom. However, a major problem is its low solubility in most organic solvents. It is insoluble in toluene or THF, and only partially soluble in MeOH and CH_2Cl_2. [150] The phosphinic acid β-**4.16**-H, on the other hand, contains a C_1-symmetric cage structure with relatively little steric/chiral elements. The main asymmetry lies in the groups β to the phosphorus (O or CH_2) which are normally regarded as isosteric (Figure 4.7). Despite its apparently 'weak' chirality the derived phosphine ligand β-**4.17**-H afforded up to 90% ee in the ruthenium-catalysed asymmetric hydrogenation of methyl acetamidocinnamate and methyl acetamidoacrylate.[149]



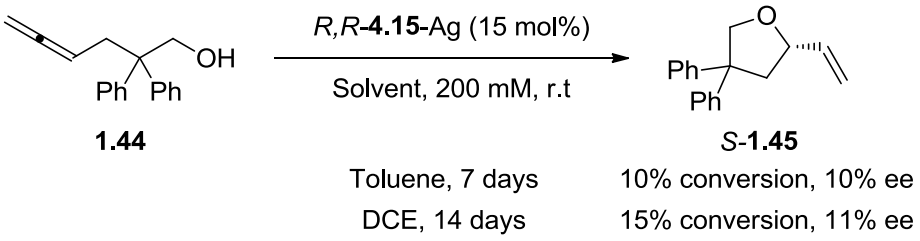
β-**4.16-H** α-**4.16-H** β-**4.17**-H

Figure 4.7: Structures of α- and β-**4.16**-H and phosphine β-**4.17**-H.

4.4.1 Synthesis and Screening of Ag(I) Complex *R,R*-4.15-Ag in Hydroalkoxylation Reactions

R,R-**1.15**-Ag was formed as a white solid in 98% yield from *R,R*-**1.15**-H using method 3.[36] However, the Ag(I) salt is even less soluble in organic solvents than the starting material. Characterisation of this compound is therefore incomplete. The structure was confirmed by the $[M]^+$ mass peak at 635 in MS (FAB mode) and the composition

was confirmed by elemental analysis. Cyclisation of **1.44** to **1.45** was carried out in DCE at room temperature (Scheme 4.6). Unfortunately, due to its limited solubility, product formation only proceeded in 10% conversion with 10% ee after 14 days. The complex is slightly more soluble in toluene, but the reaction still only reached 15% conversion after 7 days.



Scheme 4.6: Cyclisation of **1.44** with catalyst *R,R*-**1.15**-Ag.

4.4.2 Synthesis and Initial Screening of β-4.16-Ag in Hydroalkoxylation Reactions

β-**4.16**-Ag was subsequently prepared as a white solid in 87% yield using method 2.[139,140] The formation of β-**4.16**-Ag was indicated by a shift of the ^{31}P NMR resonance from 33.2 to 31.0 ppm and ICP-OES and elemental analysis of the solid sample revealed a metal-to-ligand ratio of 1:1. In addition to the $[M]^+$ ion at 355, additional peaks at 1527 and 1173 were also observed in the mass spectrum (Figure 4.8). These were assigned to $[M_3Ag_4]^+$ and $[M_4Ag_5]^+$ respectively, as indicated by the isotope distribution pattern, which supported the presence of four and five Ag atoms. This suggests that β-**4.16**-Ag can exist in an aggregated/polymeric form.

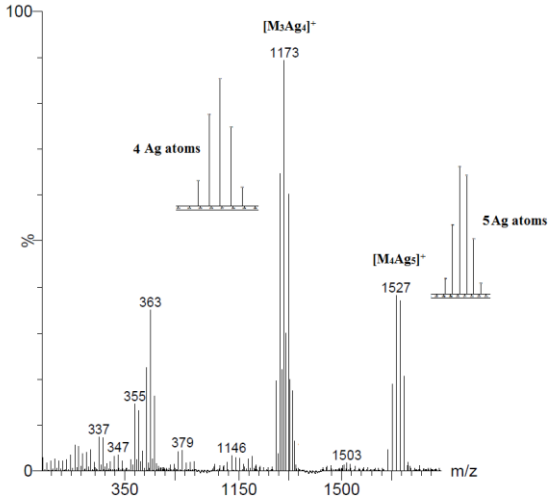
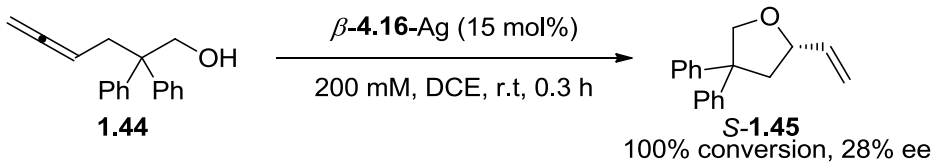


Figure 4.8: Condensed MS spectrum of *β*-**4.16**-Ag with isotopic distribution patterns.

The complex β-**4.16**-Ag was subsequently used in the cyclisation of **1.44** using DCE as the solvent (Scheme 4.8). Gratifyingly, the cyclisation of **1.44** proceeded, with full conversion in 20 minutes to afford *S*-**1.45** with 28% ee. Notably, the use of phosphinic acid β-**4.16**-H was unable to catalyse the reaction.



Scheme 4.7: Cyclisation of **1.44** using catalyst β-**4.16**-Ag.

4.4.2.1 Solvent Screen

Once again, DCE was found to furnish *S*-**1.45** in the shortest reaction time (20 minutes) and the highest ee (Table 4.7, entry 1). Reactions carried out in other aprotic solvents gave a variety of results, which is attributed to the limited solubility of the catalyst (entries 2 to 6); extended reaction times using acetone and DMF were required to reach full conversions (entries 3 and 4), whereas <4 hours were required for CH_2Cl_2, THF and dioxane (entries 2, 5 and 6). Generally, using solvents DCE, CH_2Cl_2, acetone and DMF, the enantioselectivity of *S*-**1.45** remained above 24% ee (entries 1 to 4), but dropped to <20% ee using THF and dioxane (entries 5 and 6). Reactions carried out in non-polar solvents were fast (1 hour), but the ee was reduced (entries 7 and 8). The reaction in MeOH required 13 hours to complete and diminished the ee (entry 9).

Table 4.7: Solvent screen using β-**4.16**-Ag.[a]

Entry	Solvent	t (h)[b]	% ee (*R*/*S*)[c]	Entry	Solvent	t (h)[b]	% ee (*R*/*S*)[c]
1	DCE	0.3	28 (*S*)	6	Dioxane	4	17 (*S*)
2	CH_2Cl_2	1	26 (*S*)	7	Chloroform	1	17 (*S*)
3	Acetone	17	25 (*S*)	8	Toluene	1	13 (*S*)
4	DMF	24	24 (*S*)	9	MeOH	13	6 (*S*)
5	THF	3	18 (*S*)				

[a]Reaction conditions: **1.44** (25 mg, 0.1 mmol., 200 mM), β-**4.16**-Ag (15 mol%, 0.015 mmol.), Solvent (0.5 mL), r.t. [b] All conversions were 100% (determined by ^{1}H NMR). [c] Determined by chiral HPLC analysis and optical rotation values.

4.4.2.2 Catalytic Loading and Dilution Screen

Decreasing the catalytic loading from 15 to 2.5 mol% was found to have a negative effect on the conversion; 10 mol% of β-**4.16**-Ag required 1 hour to reach completion, while 5 mol% required 2 hours (Table 4.8, entries 1 to 3). As an extreme, the reaction time was decreased to 7 hours when 2.5 mol% of β-**4.16**-Ag was used (entry 4). Increasing the volume of solvent from 0.5 to 1 mL was observed to reduce the reaction time from 2 to 3 hours (entry 3 *vs* 6), whereas the opposite was observed by decreasing the volume to 0.25 mL (entry 3 *vs* 5). On a positive note, the enantioselectivity remained uniformly between 27-30%. This suggests that the catalytic loading could easily be decreased to 5 mol% without any adverse effects on the enantioselectivity.

Table 4.8: Cyclisation of **1.44** with β-**4.16**-Ag. [a]

Entry	x (mol%)	Volume (mL)	t (h)	% ee[b]
1	15	0.5	0.3	28 (*S*)
2	10	0.5	1	27 (*S*)
3	5	0.5	2	30 (*S*)
4	2.5	0.5	7	29 (*S*)
5	5	0.25	1	28 (*S*)
6	5	1	3	29 (*S*)

[a]Reaction conditions: **1.44** (25 mg, 0.1 mmol., x mM), β-**4.16**-Ag (x mol%, x mmol.), DCE (x mL), r.t. [b] Determined by chiral HPLC analysis and optical rotation values.

4.4.2.3 Effect of Temperature

The performance of β-**4.16**-Ag at low temperatures was investigated (Table 4.9). From this study, reducing the temperature to 0 ºC was found to increase the enantioselectivity by only 5% and decrease the reaction time from 20 minutes to 4 hours (entry 1 *vs* 2). Further reducing the temperature to -10 ^{o}C decreased the reaction time to 17 hours, but without an increase in ee (entry 3). Further reactions were therefore conducted at room temperature.

Table 4.9: Cyclisation of **1.44** with 15 mol% β-**4.16**-Ag. [a]

Entry	Catalytic loading (mol%)	T (^{o}C)	t (h)	% ee (*R*/*S*) [b]
1	15	r.t	0.3	28 (*S*)
2	15	0	4	33 (*S*)
3	15	-10	17	33 (*S*)

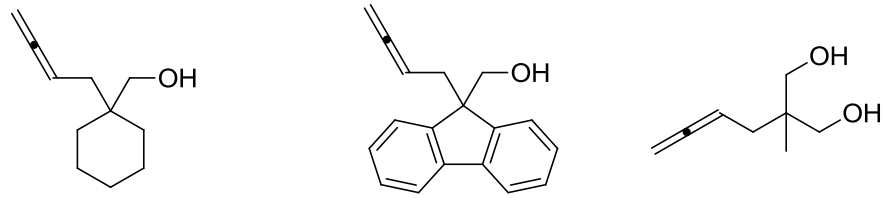
[a]Reaction conditions: Substrate **1.44** (25 mg, 0.1 mmol., 200 mM), β-**4.16**-Ag (15 mol%, 0.015 mmol.), DCE (0.5 mL). [b] Determined by chiral HPLC analysis and optical rotation values.

Overall, by using β-**4.16**-Ag for the cyclisation of **1.44** to tetrahydrofuran *S*-**1.45** a moderate enantioselectivity of 28% can be achieved. To examine the scope of this catalyst a range of allenic alcohols and acids were prepared and subjected to catalysis by 5 mol% β-**4.16**-Ag in DCE at room temperature.

4.5 Synthesis of Substrates

4.5.1 Synthesis of Terminal γ-Allenic Alcohols

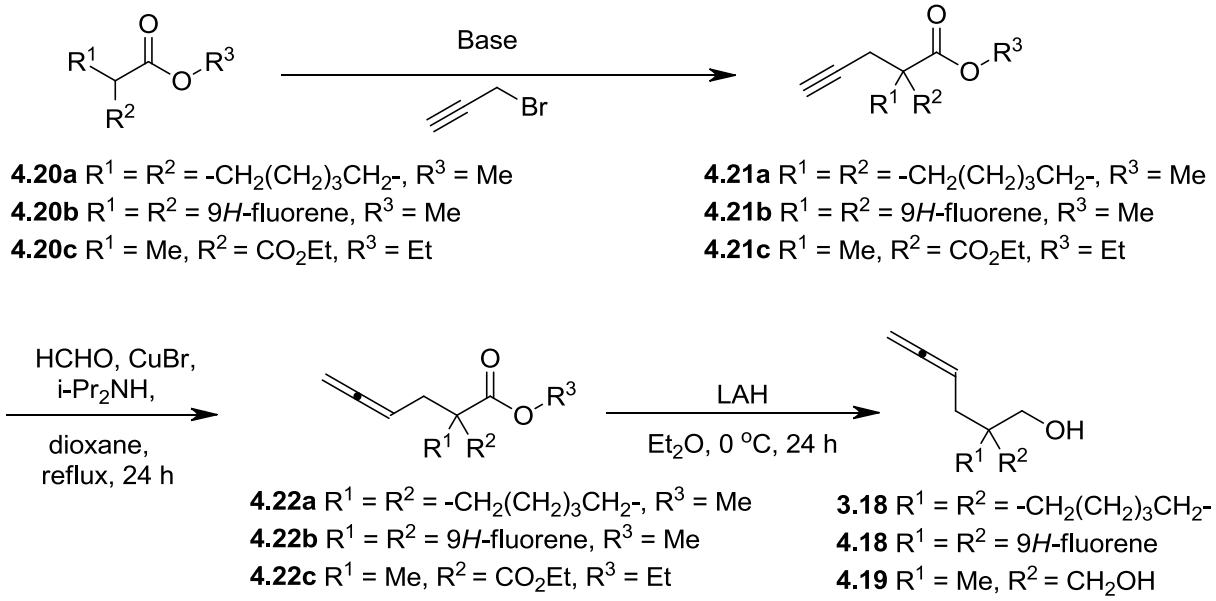
Utilising pathway A, previously described in Chapter 2, three novel γ-allenic alcohols were prepared (Figure 4.9).



3.18 **4.18** **4.19**

Figure 4.9: Novel terminal γ-allenic alcohols.

All three novel terminal γ-allenic alcohols (**3.18**, **4.18** and **4.19**) were formed in a similar manner to γ-allenic alcohol **1.44** (Scheme 4.8).[45]



4.20a $R^1 = R^2 = -CH_2(CH_2)_3CH_2-$, R^3 = Me
4.20b $R^1 = R^2$ = 9*H*-fluorene, R^3 = Me
4.20c R^1 = Me, $R^2 = CO_2Et$, R^3 = Et

4.21a $R^1 = R^2 = -CH_2(CH_2)_3CH_2-$, R^3 = Me
4.21b $R^1 = R^2$ = 9*H*-fluorene, R^3 = Me
4.21c R^1 = Me, $R^2 = CO_2Et$, R^3 = Et

4.22a $R^1 = R^2 = -CH_2(CH_2)_3CH_2-$, R^3 = Me
4.22b $R^1 = R^2$ = 9*H*-fluorene, R^3 = Me
4.22c R^1 = Me, $R^2 = CO_2Et$, R^3 = Et

3.18 $R^1 = R^2 = -CH_2(CH_2)_3CH_2-$
4.18 $R^1 = R^2$ = 9*H*-fluorene
4.19 R^1 = Me, $R^2 = CH_2OH$

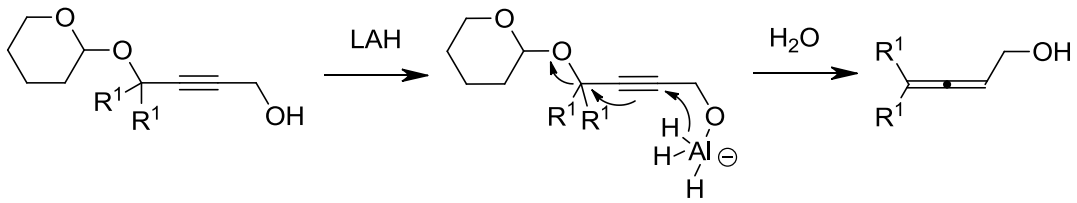
Scheme 4.8: Synthesis of terminal γ-allenic alcohols **3.18**, **4.18** and **4.19.**

Propargylation of all three esters **4.20a** to **4.20c** were performed to furnish **4.21a**, **4.21b** and **4.21c** in yields of 73%, 86% and 85% respectively. In the case of **4.20a**, this was achieved using freshly prepared LDA,[58] whereas less basic sodium methoxide was able to deprotonate **4.20b** and **4.20c**.[151] Next, the Crabbé reaction was performed to furnish **4.22a**, **4.22b** and **4.22c** in 40%, 45% and 58% yields respectively, after purification by column chromatography.[58] Finally the LAH reduction to **3.18**, **4.18** and **4.19** proceeded in between 85-89% yields.[58]

γ-Allenic alcohol **3.18** was fully characterised: The OH moiety could be observed by its IR absorption peak at 3339 cm^{-1} and the allene moiety as peaks at 1953 and 1028 cm^{-1}, further supported by ^{13}C NMR signals at 209.4, 85.72 and 73.7 ppm, and ^{1}H NMR signals as a triple triplet at 5.11 and two triplets at 4.69 and 4.67 ppm. Finally, MS in CI mode confirmed the expected mass of the compound ($[MNH_4]^+ = 184$). The structures of **4.18** and **4.19** were similarly characterised using IR, MS and NMR techniques.

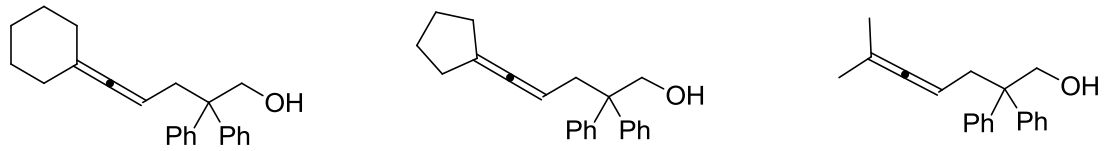
4.5.2 Synthesis of Internal γ-Allenic Alcohols

Internal allenic alcohols can be formed by a propargylic rearrangement reaction involving mono-O-tetrahydropyran protected propargyl diols (Scheme 4.9).[152]



Scheme 4.9: Formation of internal γ-allenic alcohols.[152]

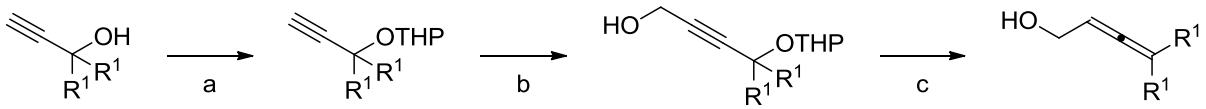
In this work, three novel internal allenic alcohols were prepared using this method (Figure 4.10).[94,152-154]



3.17 **4.23** **4.24**

Figure 4.10: Internal γ-allenic alcohols.

The allenol intermediates, R^1 = -$CH_2(CH_2)_nCH_2$- (where n = 3, **4.25a**; n = 2, **4.25b**), or Me (**4.25c**), were formed in three steps from the appropriate 3-hydroxyl alkyne (Scheme 4.10).



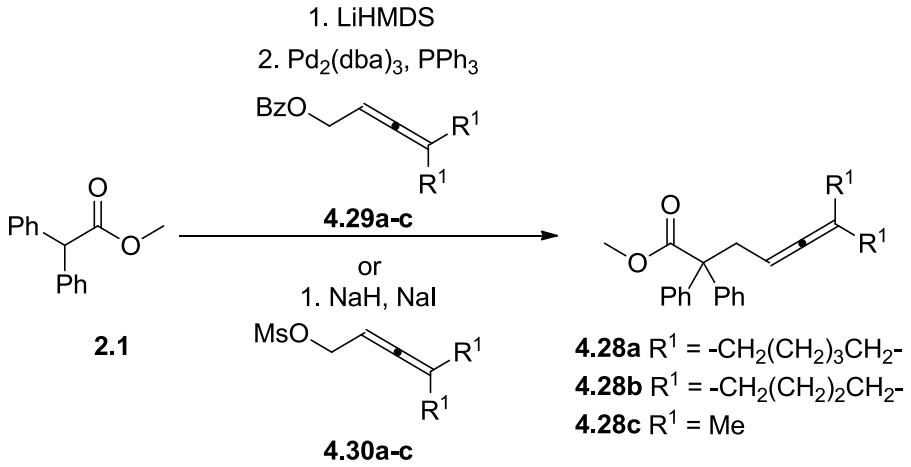
4.26a-c **4.27a-c** **4.25a-c**

Scheme 4.10: Reaction conditions: **a)** 3,4-dihydro-*2H*-pyran, *p*-TsOH, CH_2Cl_2, 0 ^oC, 2h. **b)** *n*-BuLi, HMPA/or DMPU, THF, -70 to 0 ^oC; HCHO, 24 h. **c)** LAH, THF, 0 ^oC, 24h.

Firstly, the THP protected alcohols (**4.26a**, **4.26b** and **4.26c**) were obtained from the relevant 3-hydroxyl alkyne by a standard procedure. [155] In the case of **4.26a** and **4.26c**, purification was achieved by distillation with a 30 cm long vigreux column, affording pure products in 90% and 62% yields respectively, while **4.26b** was isolated in 94% after purification by column chromatography. The next step required the addition of paraformaldehyde, which utilises HMPA to obtain intermediates **4.27a** in a 63% yield after purification by column chromatography. To avoid the use of the extremely toxic HMPA, it was substituted with DMPU, which resulted in 20% yield of **4.27a** in the first attempt, following an NH_4Cl work-up. Subsequently, the workup

procedure was modified to incorporate a phosphate buffer, followed by neutralisation of the aqueous layer. This resulted in an improvement in product yield to 67%, showing that DMPU can be a viable alternative for future reactions. This optimised and safer procedure was subsequently utilised in the formation of **4.27b** and **4.27c** to afford pure products in 94% and 83% yields respectively. Finally, the LAH propargylic rearrangement reaction proceeded to give **4.25a**, **4.25b** and **4.25c** in 73%, 80% and 93% yields respectively. α-Allenic alcohol **4.25a** was characterised by ^{13}C signals 197.2, 105.9 and 89.7 corresponding to the allene moiety. IR spectrum of the compound contained characteristic C=C allenic stretches at 1964 and 1053 cm^{-1} and O-H stretch at 3304 cm^{-1}. Finally, MS in EI mode confirmed the expected mass of the compound ($[M]^+ = 138$). α-Allenic alcohols **4.25b** and **4.25c** were also characterised by NMR and MS in CI mode, which confirmed the expected mass of the **4.25b** ($[MNH_4]^+ = 142$) and **4.25c** ($[MNH_4]^+ = 116$).

These α-allenic alcohols (**4.25a, 4.25b** and **4.25c**) were used to form allenic ester **4.28a**, **4.28b** and **4.28c**. This could be achieved in two different ways (Scheme 4.11).

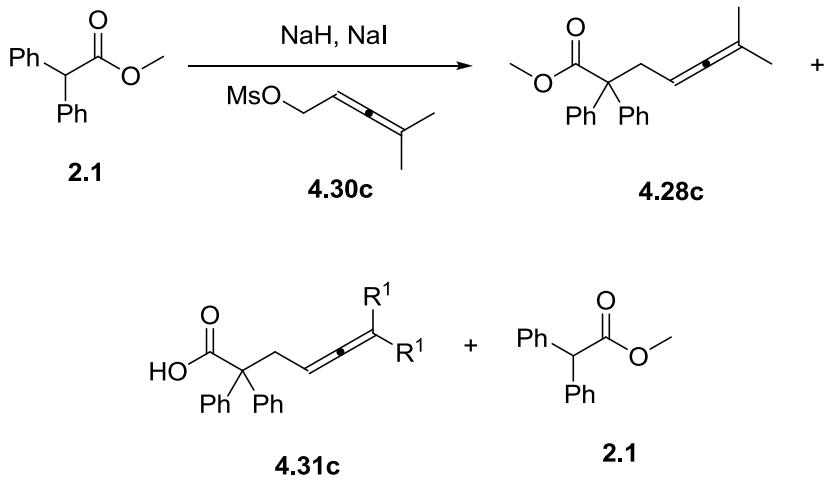


Scheme 4.11: Synthesis of allenic esters **4.28a**, **4.28b** and **4.28c**.

In the first route, the α-allenic alcohols **4.25** are converted into benzoyl ester **4.29** and are used in a modified Pd-catalysed coupling reaction with 2,2-diphenylacetate **2.1**.[45,58] In the second route, the α-allenic alcohols **4.25** are converted into mesylate esters (**4.30**) and used to form the corresponding allenic ester (**4.28**) in a direct nucleophilic substitution reaction with **2.1**.[26,34]

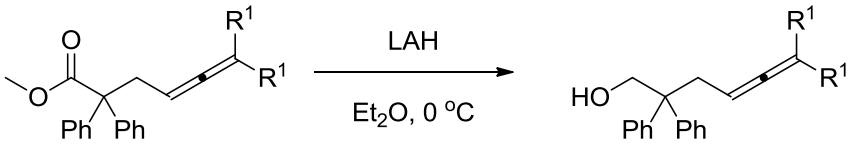
Both synthetic routes were employed in the preparation of **4.28a**. First, **4.25a** was converted to the benzoyl ester **4.31a** in 98% yield, which has limited stability (partial decomposition was observed during purification by column chromatography) so was used immediately, or kept in the freezer until required. This was coupled to 2,2-diphenylacetate **2.1** to afford the desired product **4.28a** in 58% yield after purification by column chromatography. Alternatively, **4.25a** was converted to the mesylate **4.30a** to furnish **4.28a** in 94% yield after purification by column chromatography. This second pathway is clearly more efficient, and can also be employed to synthesise the corresponding γ-allenic amines (Chapter 5).

Subsequently, the second route was used for the synthesis of **4.28b** and **4.28c**. Allenic ester **4.28b** was formed in 89% yield after purification by column chromatography. However, the reaction to provide **4.28c** proved to be capricious. Analysis by LC-MS revealed the presence of the desired product (**4.28c**), starting material (**2.1**) and the corresponding carboxylic acid (**4.33**) (Scheme 4.12). Attempts to separate the mixture by column chromatography proved futile as all three products co-eluted. Thus, the first pathway was implemented: the benzoyl ester **4.29c** was prepared from **4.25c** in 59% yield and coupled to 2,2-diphenylacetate **2.1** under Pd catalysis to provide the **4.28c** in 47% yield after column chromatography.



Scheme 4.12: Side product **4.31** formed in the coupling of **4.30c** to **2.1**.

Finally, reduction to the alcohol was achieved using lithium aluminium hydride (Scheme 4.13). **3.17**, **4.23** and **4.24** were furnished in 86%, 78% and 50% yield respectively after purification by column chromatography. γ-Allenic alcohol **3.17** was fully characterised; the allenic moiety was observed as ^{13}C signals 200.2, 101.7 and 84.2 ppm, ^{1}H signal 4.65 ppm and IR absorption bands at 1964 and 1044 cm^{-1}. The OH moiety gave rise to an IR absorption band at 3558 cm^{-1} and resonated at 4.21 ppm in the ^{1}H NMR spectrum. MS provided the correct mass of the compounds ($[MH]^+$ = 318) and the composition was confirmed by elemental analysis. γ-Allenic alcohols **4.23** and **4.24** were also characterised by NMR and IR spectra, while MS in CI mode confirmed the expected mass of **4.23** ($[MNH_4]^+$ =332) and **4.24** ($[MNH_4]^+$ = 296) and the composition determined by elemental analysis.



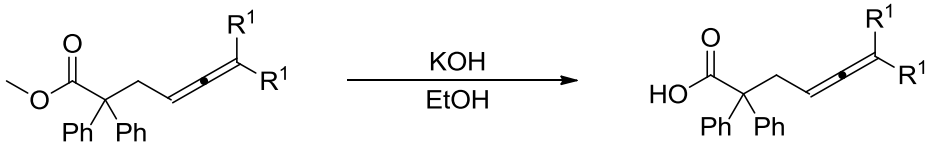
4.28a R^1 = $-CH_2(CH_2)_3CH_2-$
4.28b R^1 = $-CH_2(CH_2)_2CH_2-$
4.28c R^1 = Me

3.17 R^1 = $-CH_2(CH_2)_3CH_2-$
4.23 R^1 = $-CH_2(CH_2)_2CH_2-$
4.24 R^1 = Me

Scheme 4.13: LAH reduction of **4.28a**, **4.28b** and **4.28c**.

4.5.3 Synthesis of β-Allenoic Acids

Four novel β-allenoic acids (**4.31** to **4.34**) were also prepared from the corresponding allenic ester using KOH as the base in refluxing ethanol (Scheme 4.14).



2.3 R^1 = H
4.28a R^1 = $-CH_2(CH_2)_3CH_2-$
4.28b R^1 = $-CH_2(CH_2)_2CH_2-$
4.28c R^1 = Me

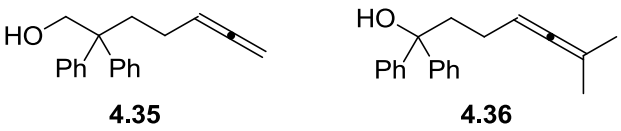
4.32 R^1 = H (71% yield)
4.33 R^1 = $-CH_2(CH_2)_3CH_2-$ (97% yield)
4.34 R^1 = $-CH_2(CH_2)_2CH_2-$ (95% yield)
4.31 R^1 = Me (96% yield)

Scheme 4.14: Synthesis of β-allenoic acids from the corresponding γ-allenic ester.

All four β-allenoic acids (**4.31** to **4.34**) were formed in high yields (71-97%) after purification by column chromatography. These compounds were fully characterised by IR, NMR, MS and their composition confirmed by elemental analysis.

4.5.4 Allenic Alcohols Synthesised by Other Members of the Group

Concurrently, δ-allenic alcohol **4.35**[45,58] and γ-allenic alcohol **4.36**[156] were also prepared and provided by two colleagues (Figure 4.11) by procedures described in literature.



4.35 **4.36**

Figure 4.11: δ-allenic alcohol **4.35** and γ-allenic alcohol **4.36**.

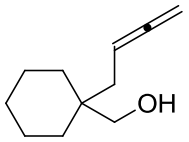
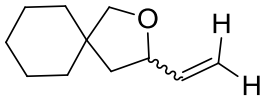
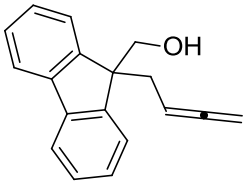
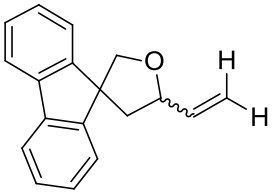
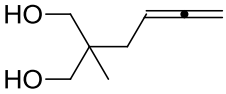
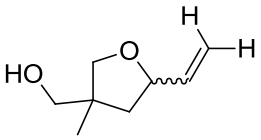
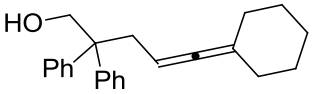
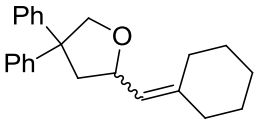
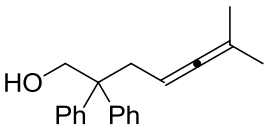
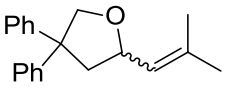
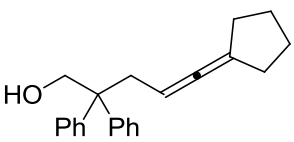
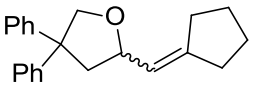
4.6 Cyclisation of Substrates

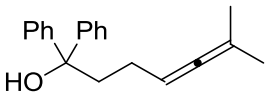
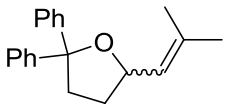
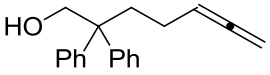
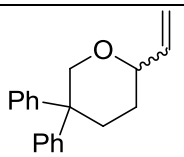
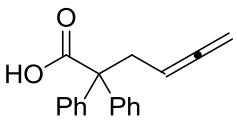
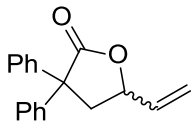
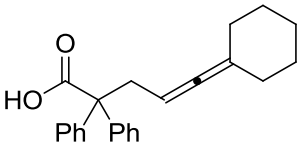
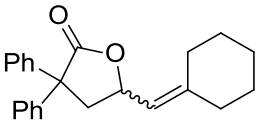
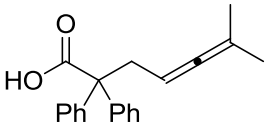
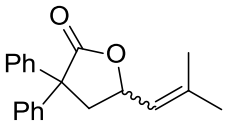
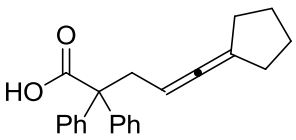
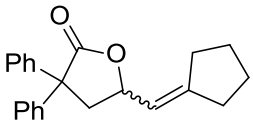
4.6.1 Cyclisation of Substrates Using Ag(OCOCF$_3$)

To provide racemic samples for the development of chiral HPLC methods, the twelve substrates were first subjected to racemic reactions, using 15 mol% Ag(OCOCF$_3$) in 0.5 mL DCE at room temperature (Table 4.10). In all cases, the γ-allenic alcohols cyclised to the respective tetrahydrofurans products exclusively (entries 1 to 7). The terminal γ-allenic alcohol **3.18** cyclised to the spirocyclic structure **3.22** in one hour (entry 1), whereas 24 hours was required to cyclise fluorenol-derived **4.18** to **4.37** (entry 2). Cyclisation of diol **4.19** afforded a mixture of diastereoisomers in a 2:1 ratio after 1 hour (entry 3). The reaction of internal γ-allenic alcohols (**3.17**, **4.23** and **4.24**) with phenyl substituents at the β position on the allenic chain, furnished **3.19**, **4.39** and **4.40** in 93% to 96% yields after 2 hours (entries 4 to 6). No difference in conversion was observed by changing the methyl groups for cyclohexane or cyclopentane. Moving the phenyl substituents closer to the oxygen atom (**4.36**) lengthened the reaction time to 16 hours (entry 7). δ-Allenic alcohol **4.35** could also be tolerated; tetrahydropyran **4.42** was isolated in 86% yield after 6 hours (entry 8).

Novel β-allenoic acids **4.31** to **4.34** cyclised to the respective lactones (**4.43** to **4.46**) in high yields of 92% to 96% within 2 hours (entry 9 to 12).

Table 4.10: Hydroalkoxylation and hydroacyalkoxylation reactions using $Ag(OCOCF_3)$ [a]

Entry	Substrate	Product	t (h)	% Yield[b]
1	 **3.18**	 **3.22**	1	76
2	 **4.18**	 **4.37**	24	92
3	 **4.19**	 **4.38**	1	87[c]
4	 **3.17**	 **3.19**	2	96
5	 **4.24**	 **4.39**	2	93
6	 **4.23**	 **4.40**	2	95

7	 **4.36**	 **4.41**	16	89
8	 **4.35**	 **4.42**	6	86
9	 **4.32**	 **4.43**	1	94
10	 **4.33**	 **4.44**	2	98
11	 **4.31**	 **4.45**	2	92
12	 **4.34**	 **4.46**	2	96

[a]Reaction conditions: Substrate (0.1 mmol., 200 mM), $Ag(OCOCF_3)$ (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] 2:1 ratio of diastereoisomers.

The structures of **4.38**, **3.19**, **4.39**, **4.41** and **4.42** were confirmed by comparison of their characterisation data to published literature values.[58,68,157] The structures of novel tetrahydrofurans **3.22**, **4.37** and **4.40** were fully characterised. In the ^{1}H NMR spectrum of **3.22** and **4.37**, the observation of a double double doublet resonance at 5.88 - 6.17 ppm and two double triplets at 5.24 - 5.47 and 5.09 ppm supported the presence of an alkene moiety, supported by further signals at 138.4 - 139.5 and 115.1 - 116.0 ppm in ^{13}C NMR spectrum. For **4.40**, the observation of a multiplet at 5.45 - 5.36 ppm in the ^{1}H NMR spectrum and the signal 147.9 ppm in the ^{13}C NMR

supported the presence of an alkene. Finally, MS in CI mode furnished the expected mass ions of **3.22**, **4.37** and **4.40** and the composition was further determined by elemental analysis.

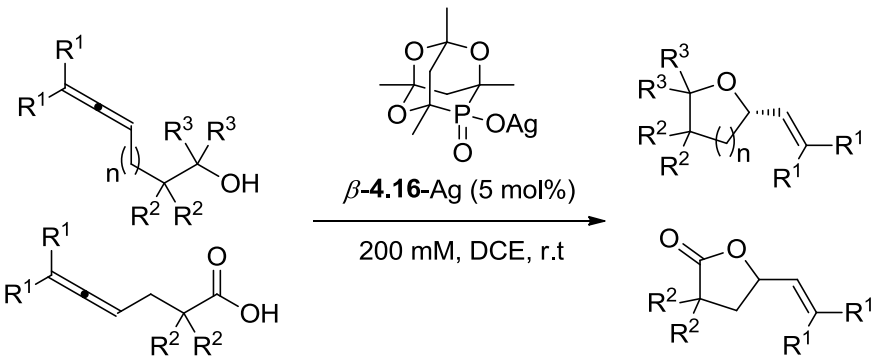
Novel lactones **4.43** to **4.46** were also fully characterised; for lactone **4.43**, the presence of an alkene moiety was observed as a double double doublet resonance at 5.96 ppm and two doublets at 5.45 and 5.34 ppm in the ^{1}H NMR spectrum. ^{13}C NMR signals at 135.0 and 118.9 ppm also supported the presents of an alkene moiety. For lactones **4.44**, **4.45** and **4.46**, the presence of the alkene moiety was supported by a multiplet at 5.50 - 5.23 ppm in the ^{1}H NMR. From ^{13}C NMR the sp-hybridised carbon of the alkene was identified (supported by HSQC and HMBC) as the signal 140.8-152.5 ppm while the sp^{2}-hybridised carbon atom was identified as the signal 117.3-122.1 ppm. The structures of all four lactones were also established by MS in CI mode and the composition confirmed by elemental analysis.

With the racemic material in hand, chiral HPLC methods were developed to separate enantiomers of all products, except **3.22** and **4.37**. In the former case, the lack of a chromophore prevented analysis by chiral HPLC (UV detection), whereas **4.37** failed to resolve on available columns (Daicel Chiralcel OJ-H, OD-H, AS-H, AD-H or OC columns). Hence, **3.22** and **4.37** were omitted in further investigations.

4.6.2 Cyclisation of Substrates Using *β*-4.16-Ag

The remaining 10 substrates were subsequently cyclised in the presence of *β*-**4.16**-Ag (Table 4.11).

Table 4.11: Hydro(acy)alkoxylation reactions using 5 mol% *β*-**4.16**-Ag.[a]



Entry	Substrate	Product	t (h)	% Yield[b]	% ee (*R*/*S*) [c]
1	**3.17** R^1 = -$CH_2(CH_2)_3CH_2$-, R^2 = Ph, R^3 = H, n = 1	**3.19**	2	96	57 (*S*)
2	**4.24** R^1 = CH_3, R^2 = Ph, R^3 = H, n = 1	**4.39**	2	97	36 (*S*)
3	**4.23** R^1 = -$CH_2(CH_2)_2CH_2$-,R^2 = Ph, R^3 = H, n = 1	**4.40**	2	99	16 (*S*)
4	**4.35** R^1 = R^3 = H, R^2 = Ph, n = 2	**4.42**	5	98	19 (*S*)
5	**4.36** R^1 = CH_3, R^2 = H, R^3 = Ph, n = 1	**4.41**	15	95	43 (*S*)
6	**4.19** R^1 = R^3 = H, R^2 = CH_2OH, n = 1	**4.38**	2	96	4/4[d]
7	**4.32** R^1 = R^3 = H, R^2 = Ph	**4.43**	2	99	8[e]
8	**4.33** R^1 = -$CH_2(CH_2)_3CH_2$-, R^2 = Ph, R^3 = H	**4.44**	2	98	24[e]
9	**4.31** R^1 = CH_3, R^2 = H, R^3 = Ph	**4.45**	2	96	18[e]
10	**4.34** R^1 = -$CH_2(CH_2)_2CH_2$-, R^2 = Ph, R^3 = H	**4.46**	2	98	15[e]
11	**1.44** R^1 = R^3 = H,R^2 = Ph, n = 1	**1.45**	2	95	30 (*S*)

[a]Reaction conditions: Substrate (0.1 mmol., 200 mM), β-**4.16**-Ag (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values. [d] 2:1 ratio of diastereoisomers. [e]The absolute stereochemistry is not determined.

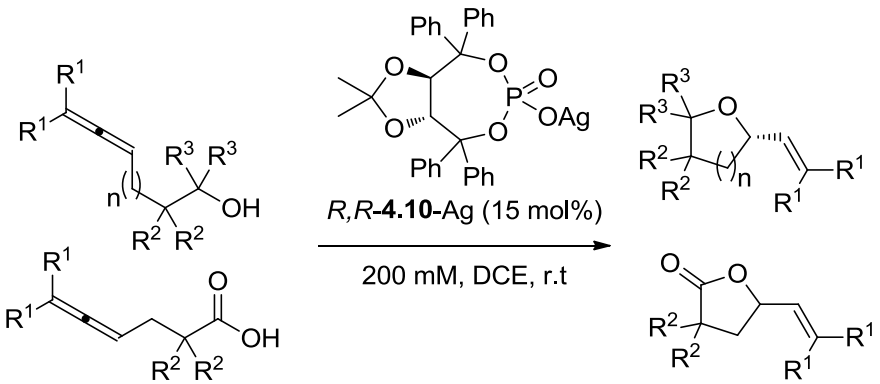
This study showed that selectivity is dependent on the structure of the substrate. Hydroalkoxylation of internal γ- allenic alcohol **3.17**, containing a cyclohexane group at the terminal position of the allene, afforded tetrahydrofuran **3.19** in two hours with 57% ee (entry 1). The introduction of methyl groups at the terminus reduced the ee to 36% (entry 2) and cyclopentane even further to 16% ee (entry 3). The cyclisation of **4.35** was slower and much less selective, taking 5 hours to furnish **4.42** in 19% ee (entry 4), while the cyclisation of the sterically demanding 2,2-diphenyl-substituted allenol **4.36** required 15 hours (entry 5). Unfortunately, only a moderate amplification of enantioselectivity (7%) was observed by moving the phenyl substituents closer to the oxygen atom (entry 2 *vs* 5). Desymmetrisation of diol **4.19** proceeded to give

diastereoisomers in a 2:1 ratio, but with extremely low enantioselectivies (entry 6). Hydroacyalkoxylation of all four β-allenoic acids to their requisite lactones proceeded in 2 hours, but with low enantioselectivities (entries 7 to 10). The highest enantioselectivity was observed for the cyclisation of internal β-allenoic acid **4.33** to **4.44** (24% ee) and the lowest with terminal β-allenoic acid **4.32** to **4.43** (8% ee) (entries 7 and 8).

4.6.3 Cyclisation of Substrates Using *R,R*-4.10-Ag

Next, as the reaction of *β*-**4.16**-Ag appears to be substrate dependant, the cyclisation of all substrates were repeated using the TADDOL derived catalyst *R,R*-**4.10**-Ag (Table 4.12). Due to its lower activity (Section 4.4), a higher catalytic loading of 15 mol% was used. The same trend was observed using *R,R*-**4.10**-Ag. The introduction of a cyclohexane group at the allenic terminus afford the highest ee of 73% in 8 hours (entry 1). Lower ees of 36% and 15% were observed with the remaining internal γ-allenic alcohols **4.23** and **4.24** respectively (entry 2 and 3). The cyclisation of the sterically demanding 2,2-diphenyl-substituted allenol **4.36** was much slower, taking 168 hours to reach 33% conversion (entry 4). The formation of tetrahydropyran **4.42** was also slower, requiring 12 hours to be formed in 13% ee (entry 5). Cyclisation of the diol **4.19** proceeded to give diastereoisomers in a 2:1 ratio, but with only 3% ee for each isomer (entry 6). In comparison, the intramolecular hydroacylalkoxylation of β-allenoic acids were much faster than with the corresponding alcohols; conversions to γ-lactones were complete within two hours (entries 7 to 10). Very surprisingly, cyclisation of terminal β-allenoic acid **4.32** furnished the respective γ-lactone in a higher ee (23%) than the internal β-allenoic acid **4.33** (entries 7 and 8).

Table 4.12: Hydro(acy)alkoxylation reactions using 15 mol% *R,R*-**4.10**-Ag.[a]



Entry	Substrate	Product	t (h)	% Yield[b]	% ee (*R*/*S*) [c]
1	**3.17** R^1 = -$CH_2(CH_2)_3CH_2$-, R^2 = Ph, R^3 = H, n = 1	**3.19**	8	99	73 (*S*)
2	**4.24** R^1 = CH_3, R^2 = Ph, R^3 = H, n = 1	**4.39**	8	98	15 (*S*)
3	**4.23** R^1 = -$CH_2(CH_2)_2CH_2$-,R^2 = Ph, R^3 = H, n = 1	**4.40**	8	98	36 (*S*)
4	**4.35** R^1 = R^3 = H, R^2 = Ph, n = 2	**4.41**	168	33[d]	34 (*S*)
5	**4.36** R^1 = CH_3, R^2 = H, R^3 = Ph, n = 1	**4.42**	12	91	13 (*S*)
6	**4.19** R^1 = R^3 = H, R^2 = CH_2OH, n = 1	**4.38**	8	94	3/3[e]
7	**4.32** R^1 = R^3 = H, R^2 = Ph	**4.43**	2	99	23[f]
8	**4.33** R^1 = -$CH_2(CH_2)_3CH_2$-, R^2 = Ph, R^3 = H	**4.44**	2	96	15[f]
9	**4.31** R^1 = CH_3, R^2 = H, R^3 = Ph	**4.45**	2	98	7[f]
10	**4.34** R^1 = -$CH_2(CH_2)_2CH_2$-, R^2 = Ph, R^3 = H	**4.46**	2	98	5[f]
11	**1.44** R^1 = R^3 = H,R^2 = Ph, n = 1	**1.45**	8	96	17 (*S*)

[a]Reaction conditions: Substrate (0.1 mmol., 200 mM), *R*,*R*-**4.10**-Ag (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values. [d] % conversion.[e] 2:1 ratio of diastereoisomers.[f] The absolute stereochemistry is not determined.

Overall, there is a clear dependence of selectivity on the substrate structure and the catalyst. The highest selectivity of 73% ee can be achieved with substrate **3.17**, containing a cyclohexane on the allenic terminus (entry 1). This suggested that substituents on the terminal allenic carbon is important. This is in accordance with the asymmetric hydroalkoxylation reaction paper published by Toste *et al.*,[36] where the majority of substrates contain a cyclohexane group and no substrates containing cyclopentane substituents or terminal γ-allenic alcohols were reported. A higher level of enantioselectivity in the cyclisation of β-allenoic acids was also observed using *β*-**4.16**-Ag (entries 7 to 10). However, the level of selectivity was modest. For the

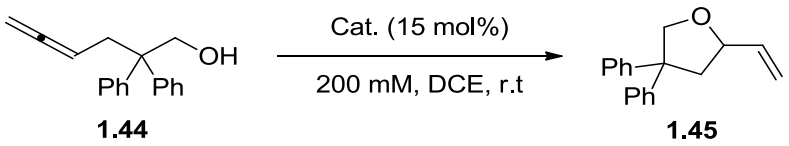
cyclisation of δ- and γ-allenic alcohols, neither catalyst *β*-**4.16**-Ag or *R,R*-**4.10**-Ag was superior. Tetrahydrofurans **1.45** (Table 4.6, entry 1 *vs* Table 4.8, entry 3), **4.38**, **4.39**, **4.41** and tetrahydropyran **4.42** were formed in higher enantioselectivities using *β*-**4.16**-Ag, whereas *R,R*-**4.10**-Ag produced **3.19** and **4.40** with higher ee's.

4.7 Determination of absolute stereochemistry

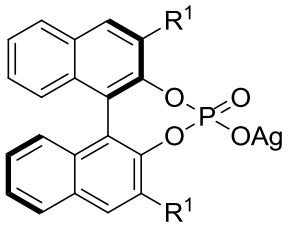
The optical rotation values of tetrahydrofurans **3.19** and **4.39** have been published by Mikami *et al.*[68] Optical rotation values of -82.7° (*c* = 0.25 in $CHCl_3$, 75% *ee*) and -74.9° (*c* = 0.36 in $CHCl_3$, 70% ee) were reported respectively, but were wrongly assigned (Chapter 2). Following clarification, we can assign the major enantiomer obtained with *β*-**4.16**-Ag and *R,R*-**4.10**-Ag as *S*. Tetrahydrofurans **4.40** and **4.41** were tentatively assigned *S* by analogy. Tetrahydropyran **4.42** was assigned *S* by comparison of HPLC data to that reported by Widenhoefer *et al*.[45] However, we were unable to determine the absolute configurations of γ-lactones **4.43** to **4.46**, as no optical rotation data or HPLC traces have been published.

4.8 Conclusion

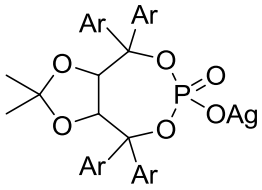
The use of DFT models in Chapter 3 proposed that the Ag(I) counteranion (L = $OCOCF_3$ or OTf) is intimately involved in C-O bond formation. From this observation, the potential of chiral anionic ligands in Ag asymmetric hydroalkoxylation and hydroacyalkoxylation reactions was explored. Several Ag(I) complexes containing chiral anionic ligands were subsequently prepared. Screening of their catalytic activity with model substrate **1.44** identified BINOL-derived catalysts *R*-**4.7**-Ag, *R*-**1.66** and *S*-**4.9**-Ag, TADDOL-derived catalysts *R,R*-**4.10**-Ag and *S,S*-**4.14**-Ag and phosphinate β-**4.16**-Ag as promising candidates, which afforded **1.45** with up to 73% ee (Scheme 4.15).



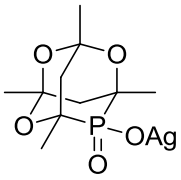
1.44 **1.45**



R-**4.7**-Ag, R^1 = H
R-**4.9**-Ag, R^1 = 3,5-CF_3-C_6H_3
R-**1.67**-Ag, R^1 = 2,4,6-iPr-C_6H_2



R,R-**4.10**-Ag Ar = Ph
S,S-**4.14**-Ag Ar = 1-Np



β-**4.16**-Ag

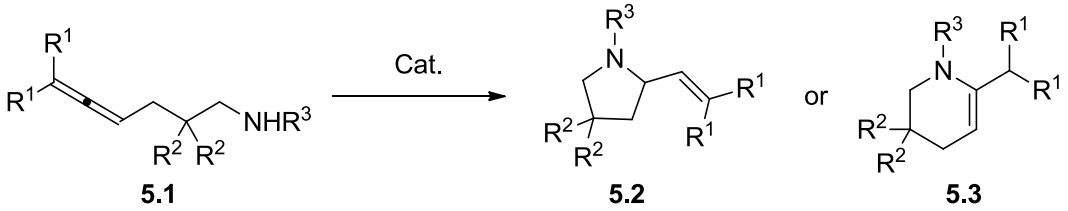
Scheme 4.15: Cyclisation of **1.44** to **1.45** using phosphate and phophinate Ag(I) complexes.

Both catalysts, β-**4.16**-Ag and *R,R*-**4.10**-Ag showed that there was a clear dependence of selectivity on the substrate structure and the highest ee of 73% can be obtained. The absolute stereochemistry of the tetrahydrofurans and tetrahydropyran compound were assigned *S*. A higher level of enantioselectivity was observed using β-**4.16**-Ag in the cyclisation of β-allenoic acids, but overall the ee remained <24% ee. For the cyclisation of δ- and γ-allenic alcohols neither catalyst β-**4.16**-Ag or *R,R*-**4.10**-Ag was superior. Although, reactions took place quicker with β-**4.16**-Ag and a lower catalytic loading could be used. On the other hand, the structure of *R,R*-**4.10**-Ag could be easily modified to allow for a greater flexibility in catalyst design.

Overall, the discovery of silver asymmetric heterofunctionalisation reactions of allenes with up to 73% enantioselectivities is highly significant. Prior to this, only cationic Au(I) complexes have been reported to afford high enantioselectivities in O-H and CO_2H addition to allenes. Ag(I) salts are often used to generate cationic Au(I) complexes *in situ* and therefore the ability of Ag complexes to generate chiral products will have an important impact on the interpretation of some of the results catalysed by gold.

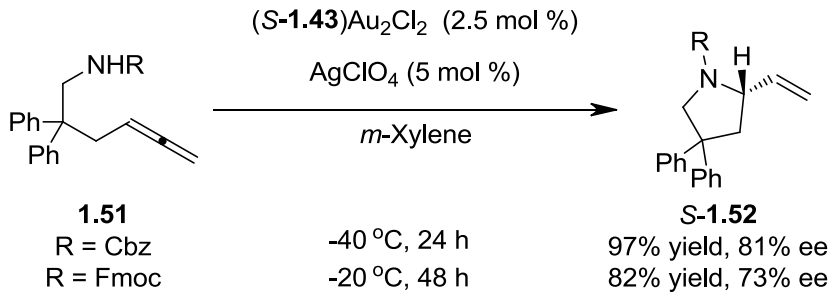
Chapter 5: Asymmetric Silver-Catalysed Intramolecular Hydroamination Reactions

This Chapter will describe the work performed on the intramolecular hydroamination reactions of *γ*-allenic amine **5.1** catalysed by silver (Scheme 5.1).



Scheme 5.1: Intramolecular cyclisation of γ-allenic amine **5.1**.

To date, only Au(I) complexes are reported to furnish 2-vinyl substituted pyrrolidine **5.2** in high yields and enantioselectivities.[36,37,40] To the best of our knowledge the cyclisation of *γ*-allenic amine **5.1** to piperidine **5.3** has not been reported. The majority of NH substrates utilised in Au(I)-catalysed hydroamination reactions are protected as carbamates[37] and sulfonamides.[36,40] For example, cyclisation of **1.51**, where R = Cbz, using the dimeric Au(I) complex (*S*-**1.43**)Au_2Cl_2 furnished pyrrolidine *S*-**1.52** in 97% yield with 81% ee after 24 hours at -40 ^oC, whereas the cyclisation of **1.51**, where R = Fmoc, afford pyrrolidine *S*-**1.52** in a lower yield and enantioselectivity after an extended reaction time (Scheme 5.2).[37]



Scheme 5.2: Cyclisation of allenic amine with (*S*-**1.43**)Au_2Cl_2 and $AgClO_4$.

On the other hand, benzyl-protected allenic amines are reported to undergo intramolecular hydroamination reactions in the presence of Cu(II), Ag(I) and Au(III) salts, but only racemically.[104]

This Chapter will set out to investigate if β-**4.16**-Ag and *R,R*-**4.10**-Ag as viable catalysts for asymmetric intramolecular hydroamination reactions. In particular, the role of the *N*-protecting group will be examined.

5.1 Synthesis of Terminal γ-Allenic Amine 5.4

The model NH substrate chosen for our initial study was differently *N*-protected γ-allenic substrate **5.4** (Figure 5.1), which would provide a comparison to the hydroalkoxylation work conducted with the γ-allenic alcohol **1.44** (Chapter 4). Different protecting groups, including tosyl **5.4a** (Ts), carbamate **5.4b** (Cbz) and benzyl **5.4c** (Bn), were chosen as these have been previously used in Au(I)- and Cu(II)-catalysed hydroamination reactions.[37,40,104] Amides **5.4d** and **5.4e** were also prepared, to see if they too could be effective protecting groups.

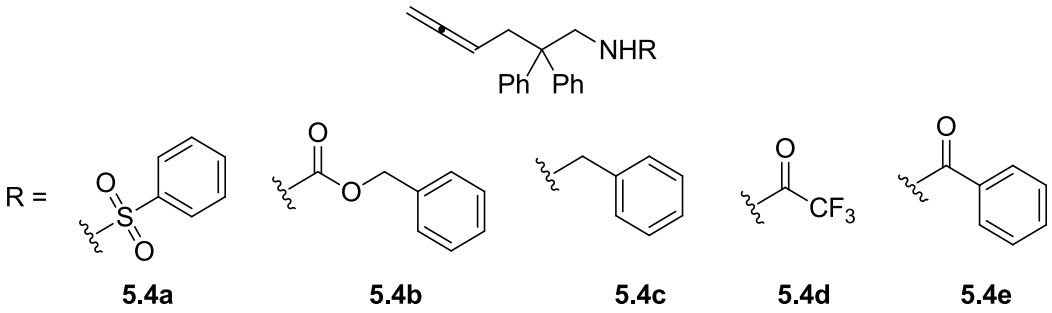
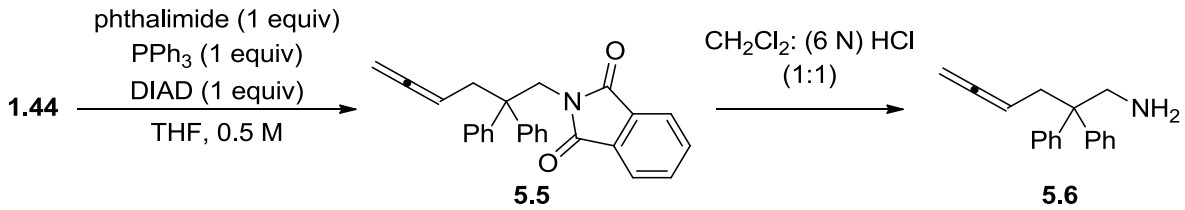


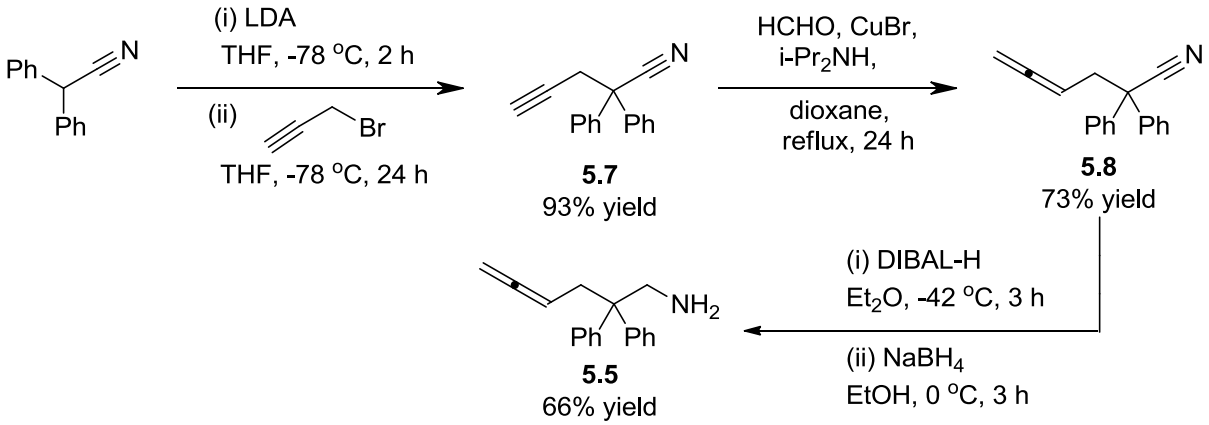
Figure 5.1: γ-allenic substrates **5.4a** to **5.4e**.

Initially, it was anticipated that some of these substrates may be prepared by subjecting the γ-allenic alcohol **1.44** to Mitsunobu conditions; converting directly into the unprotected amine **5.6** *via* the formation of **5.5** (Scheme 5.3).[158] This would allow for a quick preparation of NH substrates from the available allenic alcohols.



Scheme 5.3: Attempted conversion of alcohol **1.44** to amine **5.6**.

To prepare phthalimide **5.6**, a solution of triphenylphosphine in THF was added dropwise to a stirred solution of γ-allenic alcohol **1.44** at 0 °C. After 30 minutes, phthalimide was added to the reaction mixture and the reaction stirred at room temperature overnight. However, only the starting material was recovered from the reaction mixture after column chromatography. Hence, it was decided to adopt a published procedure for the preparation of **5.5**, [37,58] performed in three steps from the commercially available 2,2-diphenylacetonitrile (Scheme 5.4).



Scheme 5.4: Preparation of amine **5.5** from 2,2-diphenylacetonitrile.

Propargylation of 2,2-diphenylacetonitrile afforded **5.7** in comparable yield to the literature value.[58] A good yield (73%) was obtained for the Crabbé reaction to afford **5.8.**[58] The structure of which was confirmed by comparison of its characterisation data with literature values;[58] the presence of the C≡N moiety could be observed by its IR absorption peak at 2236 cm^{-1} and by its unique ^{13}C signal at 139.5 ppm. The allene moiety was identified by IR absorption peaks at 1953 and 1018 cm^{-1} and in the NMR spectra, the presence of a ^{1}H multiplet at 5.06 ppm, and triplets at 4.70 and 4.69 ppm, and ^{13}C signals at 210.5, 84.5 and 75.4 ppm. MS in CI mode also confirmed the expected mass of the compound ($[MNH_4]^+ = 263$). The reduction of the nitrile group was performed in two steps; firstly using DIBAL-H to reduce the nitrile to the imine, which was then reduced by $NaBH_4$ to the amine affording **5.5** in 66% yield.[37] This two-step reduction procedure was necessary to prevent over reduction of the allene moiety. The formation of **5.5** was confirmed by the observation of two new resonance signals at 3.41 and 2.8 ppm in the ^{1}H NMR spectrum, which correlate to the *N*-CH_2 group and NH_2 moiety.

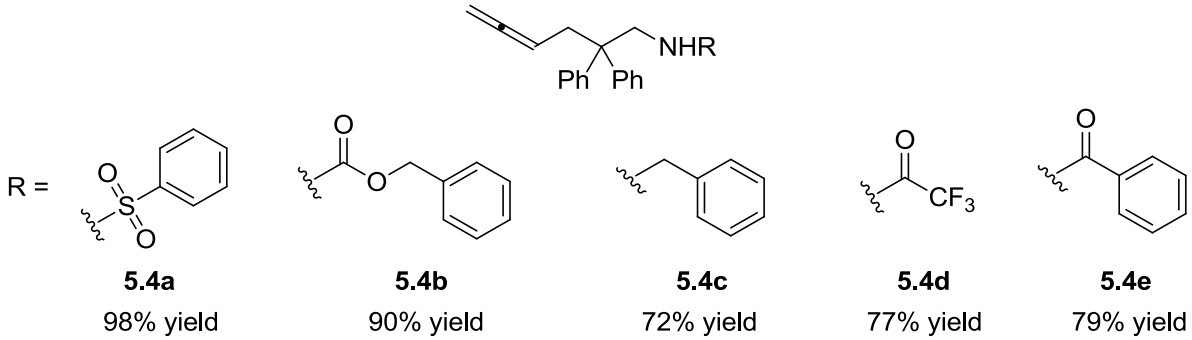


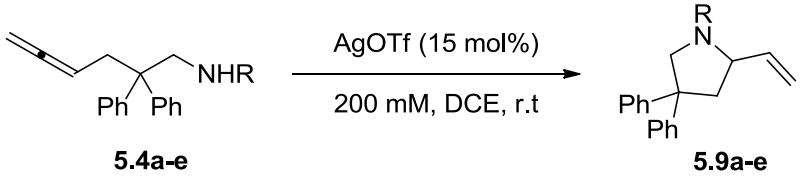
Figure 5.2: γ-Allenic substrates **5.4a** to **5.4e** and the yields for the *N*-protection step.

Protection of **5.5** with the relevant protecting group was then performed using the standard procedures (Figure 5.2). Sulfonamide **5.4a** was obtained in 98% yield by the slow addition of toluenesulfonyl chloride to a solution of **5.5** and triethylamine in CH_2Cl_2.[159] Benzyl carbamate **5.4b** was obtained in 90% yield by added benzyl chloroformate slowly to a mixture of $NaHCO_3$ in aqueous EtOH.[160] Benzylamine **5.4c** was obtained in 72% yield by stirring benzaldehyde and **5.4c** at room temperature overnight followed by $NaBH_4$ reduction in ethanol.[161] Trifluoroacetamide **5.4d** was obtained in 77% yield by the dropwise addition of trifluoroacetic anhydride to a vigorously stirred solution of **5.4c** in CH_2Cl_2.[162] Finally, benzamide **5.4e** was obtained in 79% yield by adding benzoyl chloride slowly to a solution of **5.5c** in CH_2Cl_2.[163] The structures of **5.4b** and **5.4c** were confirmed by comparison of their characterisation data to literature values,[37,104] whereas the novel structures of **5.4a, 5.4d** and **5.4e** were fully characterised by NMR, MS and elemental analysis.

5.2 Initial Screening of Silver in Hydroamination Reactions

Firstly, racemic pyrrolidines were obtained from all five substrates using 15 mol% AgOTf in DCE at room temperature (Table 5.1).

Table 5.1: Cyclisation of NH substrates using AgOTf.[a]



Entry	R	AgX	t (h)	% Conversion[b]
1	Ts (**5.4a**)	OTf	3	100
2	Cbz (**5.4b**)	OTf	6	100
3	Bn (**5.4c**)	OTf	0.75	100
4	trifluoroacetamide (**5.4d**)	OTf	24	0
5	benzamide (**5.4e**)	OTf	24	0
6	Ts (**5.4a**)	$OCOCF_3$	48	100

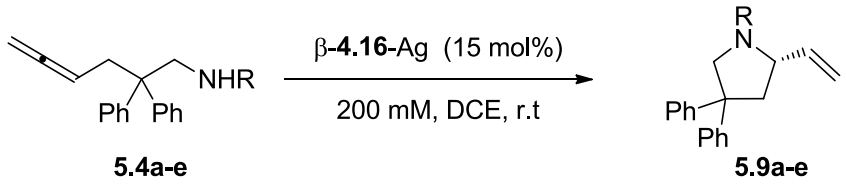
[a]Reaction conditions: Substrate (0.1 mmol., 200 mM), AgOTf (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR.

As expected, changing the protecting group on the amine had an important effect on the conversion (entries 1 to 5). Full conversions were observed with *N*-tosyl protected **5.4a**, *N*-carbamate substrate **5.4b** and *N*-benzyl substrate **5.4c**, (entries 1 to 3); *N*-benzyl substrate **5.4c** was cyclised to the respective pyrrolidine **5.9c** in 45 minutes (0.75 h), whereas **5.4a** and **5.4b** took 3 and 6 hours respectively to reach full conversion. In contrast, there was no conversion even after 24 hours for amides **5.4d** and **5.4e** (entries 4 and 5). Changing the counteranion of the silver salt also had an effect on the rate; by switching to Ag($OCOCF_3$) the cyclisation of **5.4a** to **5.9a** required an extended reaction time of 48 hours to reach completion (entry 6) compared to 3 hours required with AgOTf (entry 2). The structures of **5.9b** and **5.9c** were confirmed by comparison of their characterisation data to literature values,[37,104] whereas the novel structure of **5.9a** was fully characterised by NMR, MS and elemental analysis. Enantiomers of the 5-*exo-trig* products, **5.9a, 5.9b** and **5.9c** can be separated by chiral HPLC.

5.3 Use of β-4.16-Ag in Asymmetric Silver-Catalysed Hydroamination Reactions

The cyclisation of five NH substrates (**5.4a** to **5.4e**) were examined in the presence of 15 mol% of β-**4.16**-Ag (Table 5.2).

Table 5.2: Cyclisation of NH substrates using β-**4.16**-Ag. [a]



5.4a-e **5.9a-e**

Entry	R	t (days)	% Conversion[b]	% ee (*R*/*S*)[c]
1	Ts (**5.4a**)	2.5	100	65 (*S*)
2	Cbz (**5.4b**)	2.5	76	49 (*S*)
3	Bn (**5.4c**)	2.5	100	5
4	trifluoroacetamide (**5.4d**)	2.5	0	-
5	benzamide (**5.4e**)	2.5	0	-

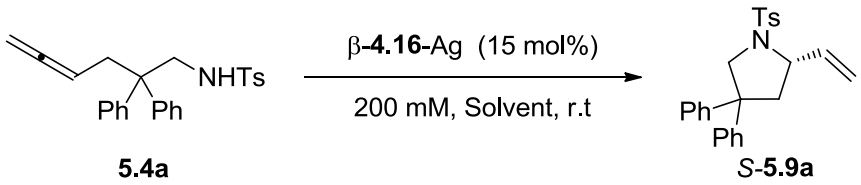
[a]Reaction conditions: Substrate (0.1 mmol., 200 mM), β-**4.16**-Ag (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

To our delight, the *N*-tosyl substrate **5.4a** proceeded with full conversion to furnish the pyrrolidine **5.9a** in 65% ee. Although, the reaction required 2.5 days to reach completion (entry 1). The *N*-carbamate substrate **5.4b** was slower and less selective, producing **5.9b** in 49% ee with 76% conversion after 2.5 days (entry 2), whereas the *N*-benzyl substrate **5.4c** was practically unselective (entry 3). Conversely, no conversion was observed for **5.4d** and **5.4e** even after 2.5 days (entries 4 and 5). A control experiment was also conducted to examine if the substrates **5.4a**, **5.4b** and **5.4c** were capable of uncatalysed reactions. It was found that *N*-benzyl **5.4c** cyclised to the pyrrolidine **5.9c** just by stirring in DCE for 2.5 days. This would explain the low selectivity observed. Based on this observation, **5.4c** was discarded from further investigations. By comparison of HPLC traces published by Widenhoefer *et al.*, the major enantiomer of **5.9b** was assigned as *S*, which correlates with an optical rotation of -2.5^o (*c* = 0.5).[45] **5.9a** has an optical rotation of -2.7^o (*c* = 3.0), and was also assumed to produce *S*-enantiomer as the major isomer, in analogy to that obtained with **5.9b**. In summary, cyclisation of *N*-tosyl protected **5.4a** providing the highest ee of 65% after 2.5 days. Thus, further studies were conducted employing *N*-tosyl substrate **5.4a**.

5.3.1 Solvent Screen

The performance of β-**4.16**-Ag, in the cyclisation of *N*-tosyl **5.4a**, was investigated in various solvents at 15 mol% loading to identify the best medium for optimal rate and enantiomeric excess (Table 5.3).

Table 5.3: Solvent studies using β-**4.16**-Ag as the catalyst.[a]



5.4a *S*-**5.9a**

Entry	Solvent	t (days)	% Conversion[b]	%ee (*R*/*S*) [c]
1	DCE	2.5	100	65 (*S*)
2	CH_2Cl_2	2.5	90	62 (*S*)
3	Acetone	2.5	54	74 (*S*)
4	DMF	2.5	19	40 (*S*)
5	THF	2.5	76	62 (*S*)
6	Dioxane	2.5	26	71 (*S*)
7	Chloroform	2.5	100	66 (*S*)
8	Toluene	2.5	50	65 (*S*)
9	Methanol	2.5	0	-

[a]Reaction conditions: Substrate **5.4a** (40.3 mg, 0.1 mmol., 200 mM), β-**4.16**-Ag (15 mol%, 0.015 mmol.), Solvent (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

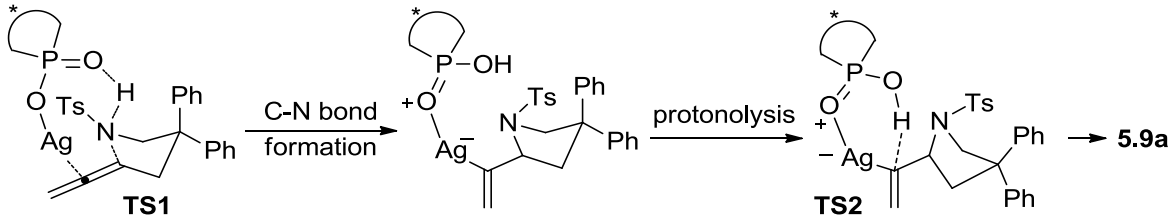
Within this study, improvements to the reaction rate were not observed by changing the solvent. Reactions carried out in other aprotic solvents gave a variety of results, which was attributed to the solubility of the catalyst (entries 1 to 6); conversions of 100%, 90% and 76% were observed using DCE, CH_2Cl_2, and THF respectively (entries 1, 2 and 5), while conversions of only 54% and 26% were observed using acetone and dioxane (entries 3 and 6). Conversely, even though the reaction mixture was homogeneous in DMF, only 19% conversion was observed (entry 4). Reactions carried out in non-polar solvents gave very different conversions with full conversion observed using chloroform (entry 7), but only 50% conversion using toluene (entry 8).

Finally, carried out the reaction in protic solvent MeOH did not afford any product after 2.5 days (entry 9). On the other hand, the enantioselectivity was found to remain constant between 62-74% ee for all the solvent tested, the only exception being DMF, which afforded 40% ee (entry 4).

Overall, the highest enantioselectivities were observed using polar aprotic solvents acetone (74% ee) and dioxane (71% ee), but low conversions were observed due to solubility issues (entries 3 and 6). Full conversions were only observed with DCE and chloroform and as the enantioselectivities of each are more or less the same, it was decided to continue using the less volatile DCE as the solvent.

5.3.2 Base Addition Effects

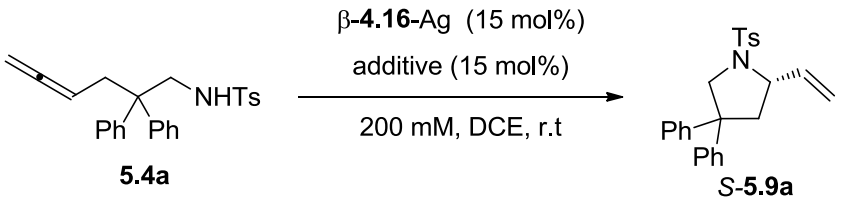
At this juncture it was speculated that slow proton transfer from the substrate to the anionic ligand (stereodefining step, **TS1**) and/or the subsequent protonolysis (**TS2**) may be responsible for the reduced reactivity observed in hydroamination reactions (Scheme 5.6).



Scheme 5.5: Proposed mechanism and transition states for the intramolecular hydroamination reaction.

To test this theory, a range of inorganic and organic bases were used as additives (Table 5.4). 15 mol% of additive was employed in each reaction. For comparison, the pK_a values (of the conjugate acids) are presented.

Table 5.4: Investigating the effect of inorganic and organic bases.[a]



Entry	Additive	pKa	t (h)	% Conversion[b]	% ee (*R*/*S*)[c]
1	-	-	24	31	65 (*S*)
2	Cs_2CO_3	~10.33 (H_2O)[164]	24	100	0
3	K_2CO_3	10.33(H_2O)[164]	24	65	9 (*S*)
4	2-phenylpyridine	4.55 (H_2O)[165]	24	57	60 (*S*)
5	2,6-di-*t*-Bu-pyridine	4.95 (H_2O)[166]	24	67	62 (*S*)
6	2-picoline	5.95 (H_2O)[167]	24	88	61 (*S*)
7	pyridine	5.37 (H_2O)[168]	24	100	68 (*S*)
8	2,3-lutidine	6.57 (H_2O)[169]	24	100	57 (*S*)
9	2,6-lutidine	6.77 (H_2O)[170]	24	54	41 (*S*)
10	DMAP	9.87 (H_2O)[171]	24	82	45 (*S*)
11	NEt_3	10.65(H_2O)[172]	24	95	29 (*S*)
12	N*i*-Pr_2Et	11.44 (H_2O)[173]	24	44	33 (*S*)
13	Proton sponge	12.1 (H_2O)[174]	24	0	-

[a]Reaction conditions: Substrate **5.4a** (40.3 mg, 0.1 mmol., 200 mM), β-**4.16**-Ag (15 mol%, 0.015 mmol.), Additive (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

This study revealed that the addition of a base with a pK_a value between 4.5 and 11.5, does appear to have an accelerating effect on the rate; by using Cs_2CO_3, pyridine or 2,3-lutidine, full conversion to **5.9a** can be achieved in 24 hours, rather than 2.5 days (entries 2, 7 and 8). However, the inorganic bases, Cs_2CO_3 and K_2CO_3, destroy the selectivity (entries 2 and 3). We postulate that this may be due to the chiral anion being replaced by carbonate, which would form a more active yet unselective catalyst. On the other hand, a definite trend was observed using pyridine and pyridine derivatives (entries 4 to 9). An increase in pK_a from 4.55 (2-phenylpyridine) to 6.57 (2,3-lutidine) showed an amplification in conversion from 57% to 100%, but a decrease in enantioselectivity (entries 4 to 8), while further increasing the pK_a to 6.77 (2,6-lutidine) proved detrimental for both conversion and enantioselectivity (entry 9). Only pyridine was able to accelerate the reaction without decreasing the enantioselectivity (entry 1 *vs* 7). The addition of more basic DMAP (pK_a = 9.87) and

triethylamine (pK_a = 10.65) increased conversion, but reduced product enantioselectivity (entry 10 and 11). Increasing the steric bulk and basicity by using diisopropylethylamine (pK_a = 11.44) was observed to have an adverse effect on conversion and the product ee (entry 12), but produced a higher conversion than the reaction with no additive added (entry 1 *vs* 12). No conversion of **5.4a** to **5.9a** was observed in the presence of 1,8-*bis*(dimethylamino)naphthalene (proton sponge), a bulky non *N*-nucleophilic base (entry 13). This suggested that complete removal of the *N*-H proton (pK_a = ~11.6) by the base (pK_a = 12.1) inhibits the reaction.

Overall, the addition of a base with a pK_a value between 4.5 and 11.5 was found to increase the rate of intramolecular hydroamination reactions of γ-allenic sulfonamides. From this observation, pyridine was chosen as the optimal additive for further investigations as it is able to accelerate the reaction without impacting on the enantioselectivity (entry 7). Correspondingly, the sense of stereoinduction was not affected by the presence of pyridine. This suggests that the stereodefining and rate-limiting steps operate independently of each other in the catalytic cycle (Scheme 5.5). Encouraged by the positive effects of pyridine, the dilution and amount of pyridine were investigated in an attempt to improve conversion and enantiomeric excess (Table 5.5).

Table 5.5: Investigating the effect of dilution and amount of pyridine.[a]

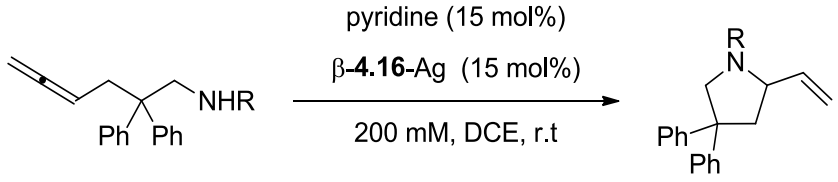
Entry	% β-4.16-Ag	% Pyridine	Volume (mL)	t (h)	% conversion[b]	% ee (*R/S*)[c]
1	15	15	0.5	24	100	65 (*S*)
2	15	15	1	24	50	63 (*S*)
3	15	15	0.25	24	67	49 (*S*)
4	15	30	1	24	30	48 (*S*)
5	15	75	1	24	11	42 (*S*)
6	15	150	1	24	3	-
7	0	15	1	24	0	-

[a]Reaction conditions: Substrate **5.4a** (40.3 mg , 0.1 mmol.), β-**4.16**-Ag (15 mol%, 0.015 mmol.), pyridine (15-150 mol%), DCE (0.25-1.0 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

Overall, there is no improvement in rate or enantioselectivity by altering either the amount of pyridine or the concentration of the reaction mixture; a higher dilution did not have a major impact on the enantioselectivity, but decreased the conversion from 100% to 50% (entry 1 *vs* 2), whereas both enantioselectivity and rate were affected by decreasing the solvent volume to 0.25 mL (entry 3), probably resulting from issues with catalyst solubility. On the other hand, increasing the amount of pyridine was found to have a negative effect on rate and enantioselectivity (entries 4 to 6). Using a 2:1 ratio of pyridine to catalyst, the conversion decreased from 50% to 30% with a 20% decrease in ee (entry 2 *vs* 4), while a 3:1 ratio decrease the conversion to 11% (entry 2 *vs* 5). As an extreme, the reaction was inhibited by using a 10:1 ratio of additive to catalyst (entry 6). This suggested that pyridine at high concentrations may be binding to the catalyst. Lastly, 15 mol% pyridine was unable to catalyse the reaction without the presence of β-**4.16**-Ag (entry 7).

The optimised conditions identified for hydroamination of the *N*-tosyl substrate **5.4a** was applied for the cyclisation of **5.4b**, **5.4d** and **5.4e** (Table 5.6).

Table 5.6: Screening substrates **5.4b**, **5.4d** and **5.4e** with pyridine as an additive.[a]



5.4b, d and e **5.9b, d and e**

Entry	Substrate (R)	Additive	t (h)	% Conversion[b]	% ee (*R*/*S*)[c]
1	**5.4b** (Cbz)	-	60	76	49 (*S*)
2	**5.4b** (Cbz)	pyridine	24	84	52 (*S*)
4	**5.4d** (trifluoroacetamide)	-	60	0	-
5	**5.4d** (trifluoroacetamide)	pyridine	24	0	-
6	**5.4e**(benzamide)	-	60	0	-
7	**5.4e** (benzamide)	pyridine	24	0	-

[a]Reaction conditions: Substrate (0.1 mmol., 200 mM), β-**4.16**-Ag (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

Only a marginal accelerating effect was observed in the cyclisation of the *N*-Cbz substrate **5.4b** using pyridine as an additive (entry 1 *vs* 2). Again, substrates **5.4d** and **5.4e** were inert under these conditions (entries 4 to 7). In summary, the highest enantioselectivity of 68% was observed in the cyclisation of *N*-tosyl substrate **5.4a** to the corresponding pyrrolidine **5.9a** within 24 hours using pyridine as an additive.

5.4 Synthesis and Screening of Sulfonamide Derivatives with β-4.16-Ag and AgOTf

Compared to Ag(I)-catalysed intramolecular hydroalkoxylation reactions (Chapter 4), the corresponding hydroamination reaction of **5.4a** produced higher enantioselectivities of >60%. This was achieved by screening for the most suitable *N*-protecting group. With this in hand, other allenic sulfonamide substrates were examined. Accordingly, different sulfonamides **5.10a** to **5.10d** were prepared from the unprotected amine **5.5**, in high yields of 65 to 96% (Figure 5.3) and were fully characterised by NMR, IR, MS and elemental analysis.[159]

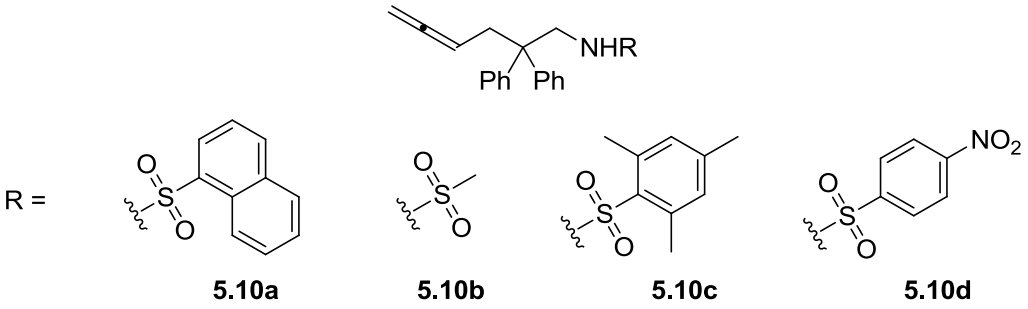
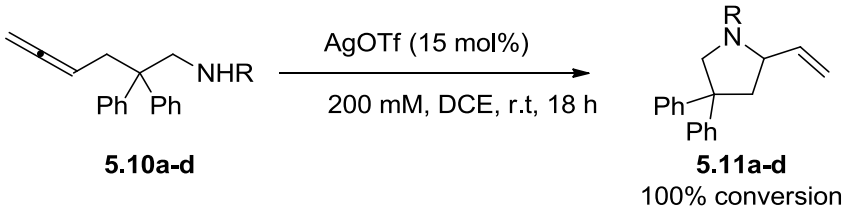


Figure 5.3: γ-Allenic substrates **5.10a** to **5.10d**.

All four substrates (**5.10a** to **5.10d**) were first subjected to racemic conditions by exposing them to AgOTf (15 mol%) in DCE at room temperature (Scheme 5.6). In all cases, full conversions to the respective pyrrolidines (**5.11a** to **5.11d**) were observed in 18 hours. The enantiomers of all four products could be resolved by HPLC analysis. The systems were assumed to produce the *S*-enantiomer as the major isomer, in analogy to that obtained with **5.9a** and **5.9b**.

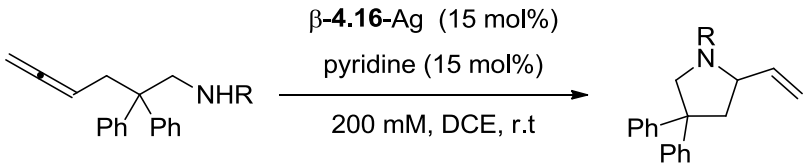


5.10a-d **5.11a-d** 100% conversion

Scheme 5.6: Cyclisation of **5.10a-d** using 15 mol% AgOTf.

Subsequently, the reactions were repeated using 15 mol% of β-**4.16**-Ag as the catalyst (Table 5.7). Overall, only the *N*-tosyl substrate **5.4a** reached full conversion in 24 hours, to furnish the respective pyrrolidine with the highest ee of 65% (entry 1). The introduction of a 1-naphthyl sulfonyl group (**5.10a**) slightly decreased the rate and selectivity (entry 1 *vs* 2), whereas conversion and ee drastically decreased to 38 and 39% respectively by the introduction of a mesitylene sulfonyl group (**5.10c**) (entry 1 *vs* 4). Conversely, cyclisation of methanesulfonyl (**5.10b**) proceeded in a higher ee (53%) than either **5.10a** or **5.10c** (entry 3 *vs* entries 2 and 4), but was still slower than the cyclisation of *N*-tosyl **5.4a** (entry 1 *vs* 3). The introduction of an electron-withdrawing nosyl group also had a negative impact on the enantioselectivity by producing **5.11d** with only 14% ee (entry 5).

Table 5.7: Screening substrates **5.10a** to **5.10d** with β-**4.16**-Ag and pyridine.[a]



5.10a-d **5.11a-d**

Entry	R	% Conversion[b]	% ee (*R/S*)[c]
1	Ts (**5.4a**)	100	65 (*S*)
2	1-Np (**5.10a**)	84	46 (*S*)
3	Ms (**5.10b**)	57	53 (*S*)
4	Mts (**5.10c**)	38	39 (*S*)
5	Ns (**5.10d**)	62	14 (*S*)

[a]Reaction conditions: Substrate (0.1 mmol., 200 mM), β-**4.16**-Ag (15 mol%, 0.015 mmol.), pyridine (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

5.5 Synthesis of a Range of γ-Allenic Sulfonamides

To examine the scope of catalyst β-**4.16**-Ag, four novel NHTs substrates (**5.12** to **5.15**) were prepared (Figure 5.4).

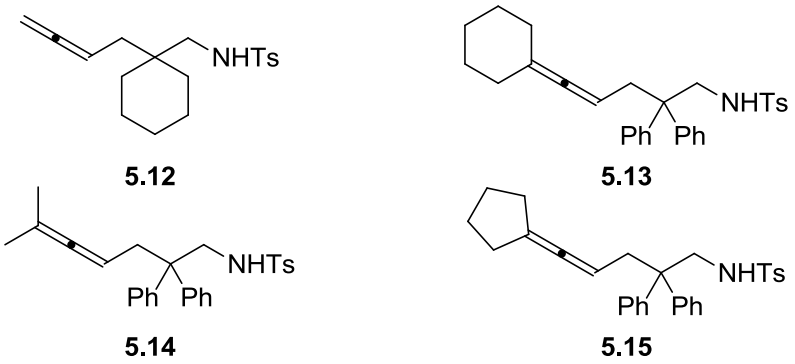
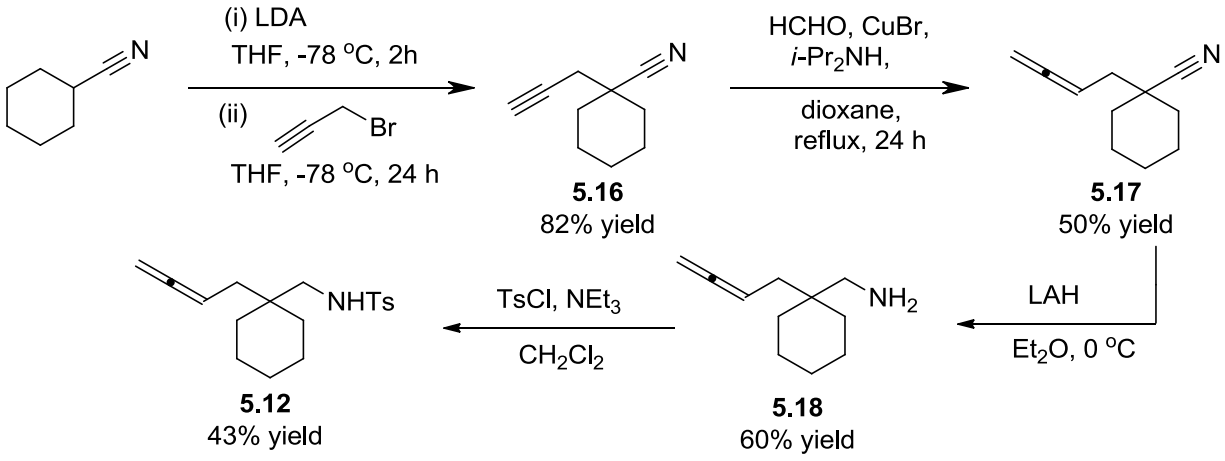


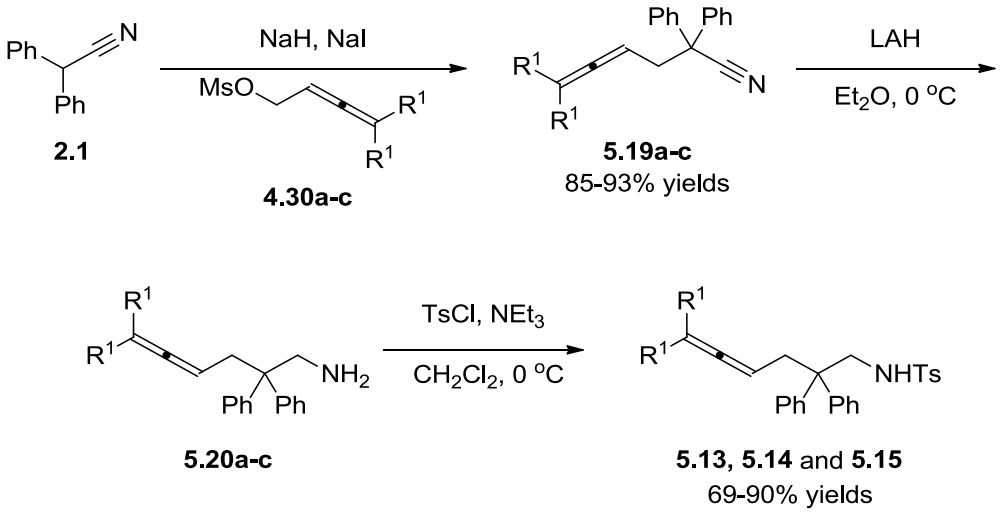
Figure 5.4: γ-allenic substrates **5.12** to **5.15**.

γ-Allenic sulfonamide **5.12** was prepared in four steps from the commercially available cyclohexanecarbonitrile (Scheme 5.7) by a similar procedure employed for the preparation of **5.4a**,[58] except LAH reduction was used in the last step for the global reduction of the nitrile. Propargylation of cyclohexanecarbonitrile was achieved with propargyl bromide, using LDA, to afford **5.16** in 82% yield. Next, the Crabbé reaction furnished **5.17** with 50% yield. LAH reduction to **5.18** proceeded in 60% yield and finally, tosyl protection of **5.19** to γ-allenic sulfonamide **5.12** was achieved in 43% yield.[159]



Scheme 5.7: Preparation of terminal γ-allenic sulfonamide **5.12**.

Internal γ-allenic sulfonamides were prepared utilising the same procedure (method B) described for internal γ-allenic alcohols in Chapter 4.[37] The mesylate esters **4.30a**, **4.30b** and **4.30c**, where R^1 = -$CH_2(CH_2)_nCH_2$- (where n = 3, **4.25a**; n = 2, **4.25b**), or Me (**4.25c**), where used to prepare **5.19a, 5.19b** and **5.19c** in 85% to 93% yields (Scheme 5.8). Reduction of amines **5.20a, 5.20b** and **5.20c** was achieved using LAH and finally, tosyl protection was performed to furnish the γ-allenic sulfonamides **5.13**, **5.14** and **5.15** in 69-90% yields over the two steps.



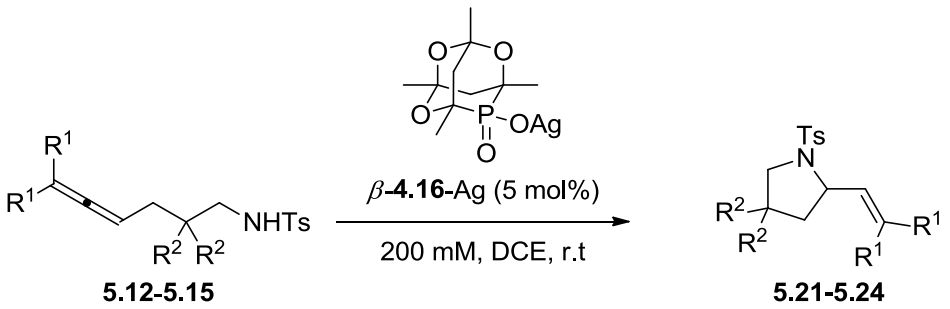
Scheme 5.8: Preparation of **5.13**, **5.14** and **5.15**.

Compound **5.13** was characterised fully; the characteristic allenic moiety was identified by the observation of ^{13}C signals at 200.5, 101.9 and 83.3 ppm, ^1H signal at 4.55 ppm and IR absorption bands at 1970 and 1085 cm^{-1}. The presence of the tosyl group was confirmed by the presence of 14 protons in the aromatic region of the ^1H NMR spectrum and the methyl group at 2.45 ppm. Finally, MS in ESI mode confirmed the expected mass of the compound ($[MH]^+$ = 472) and the composition was validated by elemental analysis. Similarly, the structures of **5.14** and **5.15** were verified by NMR, IR, MS and elemental analysis.

5.6 Cyclisation of γ-Allenic Sulfonamides Using AgOTf and β-4.16-Ag

γ-Allenic sulfonamides **5.12** to **5.15** were subjected to 15 mol% of AgOTf and 15 mol% of *β*-**4.16**-Ag/pyridine in 0.5 mL DCE at room temperature (Table 5.8).

Table 5.8: Screening of substrates **5.12** to **5.15** with AgOTf and β-**4.16**-Ag/pyridine.[a]



Entry	Substrate	Cat.	Product	t (h)	% Conversion[b]	% ee (*R/S*)[c]
1	**5.12** R^1 = H R^2 = -$CH_2(CH_2)_2CH_2$-	AgOTf	**5.21**	3	100	-
2		β-**4.16**-Ag		96	100	51 (*S*)
3	**5.13** R^1 = -$CH_2(CH_2)_3CH_2$- R^2 = Ph)	AgOTf	**5.22**	15	100	-
4		β-**4.16**-Ag		168	0	-
5	**5.14** R^1 = -$CH_2(CH_2)_2CH_2$-, R^2 = Ph	AgOTf	**5.23**	15	100	-
6		β-**4.16**-Ag		168	0	-
7	**5.15** R^1 = CH_3, R^2 = Ph R^1	AgOTf	**5.24**	15	100	-
8		β-**4.16**-Ag		168	0	-

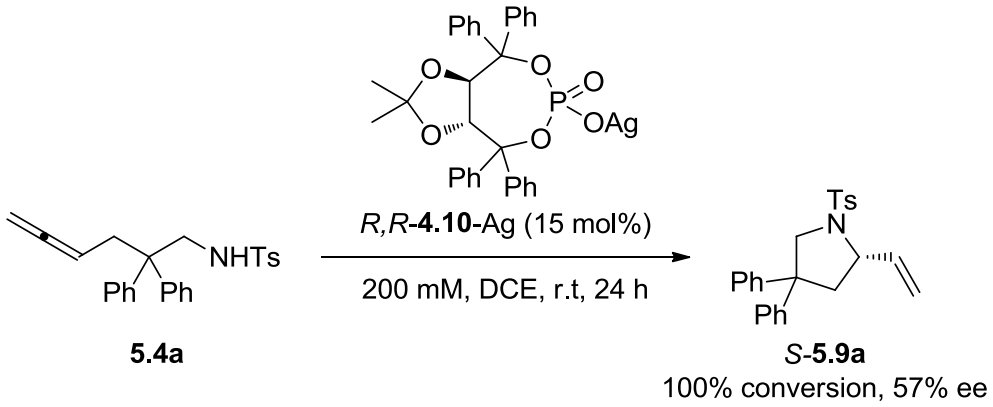
[a]Reaction conditions: Substrate (0.1 mmol., 200 mM), Catalyst (15 mol%, 0.015 mmol.), Pyridine (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

Using AgOTf as the catalyst, the azospiro structure **5.21** was obtained quantitatively in three hours from **5.12** (entry 1). Conversely, full conversion of γ-allenic sulfonamines **5.13**, **5.14** and **5.15** to the respective pyrrolidines (**5.22** to **5.24**) required an extended reaction time of 15 hours (entries 3, 5 and 7). Rather disappointingly, enantioselectivity was observed in only one of the four reactions when AgOTf was replaced by *β*-**4.16**-Ag: cyclisation of **5.12** to **5.21** proceeded in a respectable 51% ee, but required 96 hours (entry 2). The stereoselectivity of pyrrolidine **5.21** was tentatively assigned *S* in analogy to previous assignments. No conversion of internal γ-allenic tosylamines (**5.13** to **3.15**) to the respective pyrrolidine was observed even with prolonged reaction times (entries 4, 6 and 8). This was suspected to be from the steric effects between the terminal allenic substituents and the *N*-tosyl protecting

group. The novel compounds **5.21** to **5.24** were fully characterised by NMR, MS and elemental analysis.

5.4 Use of *R,R*-4.10-Ag in Asymmetric Silver-Catalysed Hydroamination Reactions

The catalyst activity of phosphate *R,R*-**4.10**-Ag was also examined in the hydroamination reactions. Firstly, sulfonamide **5.4a** was exposed to 15 mol% of *R,R*-**4.10**-Ag in DCE (Scheme 5.9).



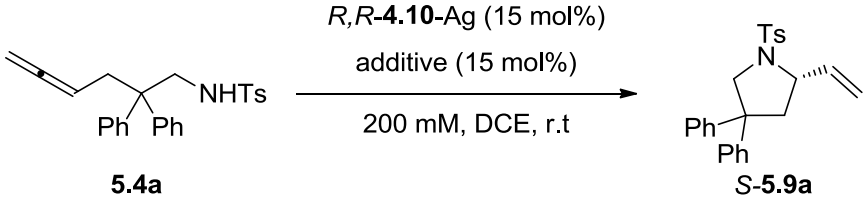
Scheme 5.9: Cyclisation of **5.4a** using 15 mol% of *R,R*-**4.10**-Ag

Pleasingly, conversion of **5.4a** was completed in 24 hours to furnish pyrrolidine *S*-**5.9a** in 57% ee. In comparison to the reaction carried out with phosphinate *β*-**4.16**-Ag, the reaction was faster, but less selective.

5.4.1 Base Addition Effects

To investigate if the reaction rate could be enhanced, a selection of inorganic and organic bases was used as additives (Table 5.9).

Table 5.9: Investigating the effect of inorganic and organic bases.[a]



Entry	Additive	pKa	t (h)	% Conversion[b]	% ee (*R*/*S*)[c]
1	-	-	24	100	57 (*S*)
2	2,6-di-*t*-Bu-pyridine	4.95 (H_2O)[166]	24	0	-
3	2-picoline	5.95 (H_2O)[167]	24	0	-
4	pyridine	5.37 (H_2O)[168]	24	4	26 (*S*)
5	Cs_2CO_3	~10.33 (H_2O)[164]	24	59	0
6	DMAP	9.87 (H_2O)[171]	24	21	0

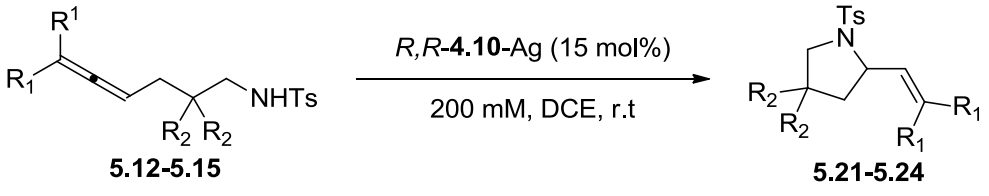
[a]Reaction conditions: **5.4a** (40.3 mg, 0.1 mmol., 200mM), *R,R*-**4.10**-Ag (15 mol%, 0.015 mmol.), Additive (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

In contrast to the positive effects of pyridine observed in the reaction catalysed by *β*-**4.16**-Ag, the addition of base appeared to have a detrimental effect on the catalytic activity of *R,R*-**4.10**-Ag; Cs_2CO_3 and DMAP, with pK_a values around 10, decreased conversion and destroyed the selectivity (entries 5 and 6). With pyridine as an additive, *S*-**5.9a** was obtained in only 4% yield with 26% ee (entry 4); while complete inhibition was observed by introducing alkyl-substituents onto the pyridine ring (entries 2 and 3). Therefore the use of additives in the *R,R*-**4.10**-Ag catalysed reaction was not continued.

5.4.2 Cyclisation of γ-Allenic Sulfonamides Using *R,R*-4.10-Ag

Lastly, the remaining sulfonamines (**5.12** to **5.15**) were exposed to 15 mol% of *R,R*-**4.10**-Ag in DCE (Table 5.10). Once again, only the cyclisation of **5.12** to pyrrolidine **5.21** was observed, (entry 1) with 48% ee while no conversion to **5.22, 5.23 or 5.24** was detected (entries 2 to 4).

Table 5.10: Screening substrates **5.12** to **5.15** with *R,R*-**4.10**-Ag.[a]



Entry	Substrate	Product	t (h)	% Conversion[b]	% ee (*R/S*)[c]
1	**5.12** R^1 = H, R^2 = -$CH_2(CH_2)_2CH_2$	**5.21**	36	100	48 (*S*)
2	**5.13** R^1 = -$CH_2(CH_2)_3CH_2$-, R^2 = Ph	**5.22**	168	0	-
3	**5.14** R^1 = -$CH_2(CH_2)_2CH_2$- R^2 = Ph	**5.23**	168	0	-
4	**5.15** R^1 = CH_3, R^2 = Ph	**5.24**	168	0	-

[a]Reaction conditions: Substrate (0.1 mmol., 200mM), *R,R*-**4.10**-Ag (15 mol%, 0.015 mmol.), DCE (0.5 mL), r.t. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis and optical rotation values.

5.5 Conclusion

Within this chapter, a variety of NH substrates were synthesised and cyclised in the presence of β-**4.16**-Ag and *R,R*-**4.10**-Ag. On the whole, reactions are slower than the corresponding O-H additions. Optimisation studies performed using β-**4.16**-Ag as the catalyst identified tosyl as the best protecting group for high enantioselectivities. The addition of an organic base with a pK_a value between 4.5 and 11.5 accelerated the cyclisation of **5.4a**, using pyridine, the level and sense of stereoinduction were not affected. This suggested that the stereodefining (C-N bond formation) and rate-limiting (protonolysis) steps operate independently of each other in the catalytic cycle. Investigating the use of *R,R*-**4.10**-Ag as the catalyst in the cyclisation of **5.4a** afforded *S*-**5.9a** with a faster rate, but lower enantioselectivity of 57%. In this case, the addition of pyridine had a detrimental effect on the catalytic activity. To examine the scope of both catalysts, a number of novel allenic *N*-sulfonamides were synthesised and screened. However, no conversion of internal γ-allenic amines **5.13**, **5.14** or **5.15** was detected.

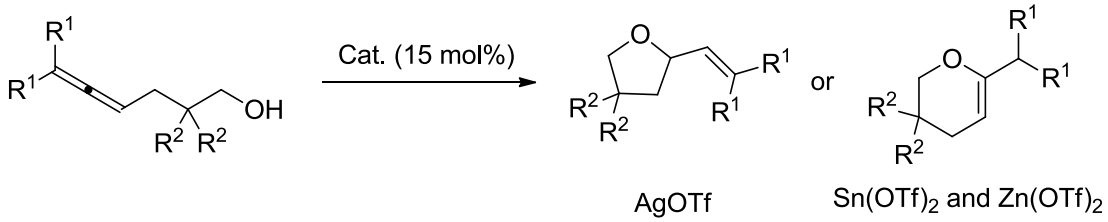
Overall, the discovery of silver asymmetric hydroamination reactions of allenes with up to 68% enantioselectivities is highly significant. Prior to this, only cationic Au(I) complexes have been reported to afford high enantioselectivities in these reactions. By using either β-**4.16**-Ag or *R,R*-**4.10**-Ag as the catalyst, the *S*-isomer predominated as the preferred enantiomer.

Chapter 6: Conclusion and Future Work

6.1 Conclusion

This thesis describes the development of Ag(I)-catalysed intramolecular heterofunctionisation reactions, including the preparation of a variety of γ-allenic alcohols, amines and β-allenoic acids.

During this work, three metal Lewis acids were found to direct cyclisation of γ-allenic alcohols with different regioselectivities. The origin of this was examined by DFT calculations, and was found to be dependent on variations in coordination number and geometry at the metal centre. The linear geometry observed for AgOTf, directed selectivity towards formation of the 5-membered ring, whereas the tetrahedral or hemi-directed geometries observed for $Zn(OTf)_2$ and $Sn(OTf)_2$ respectively, favoured 6-*exo*-*dig* cyclisations (Scheme 6.1).



Scheme 6.1: Regioselectivity in the cyclisation of γ-allenic alcohols.

DFT calculations also discovered that the metal counteranion (L = $OCOCF_3$ or OTf) is intimately involved in C-O bond formation (**TS1** and **TS3**) (Figure 6.1).

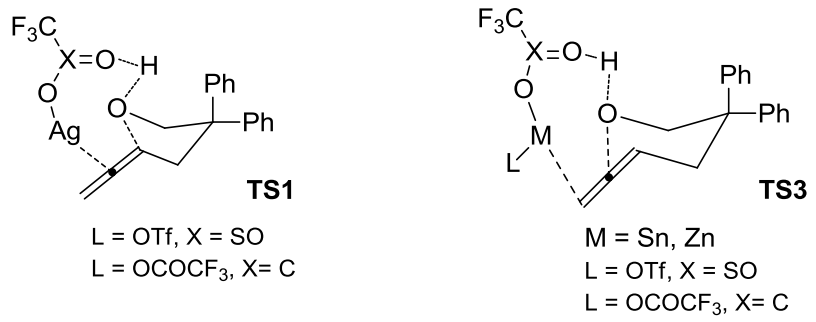
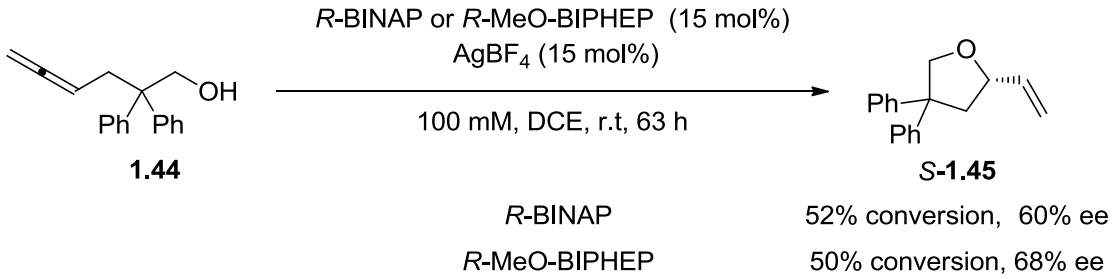


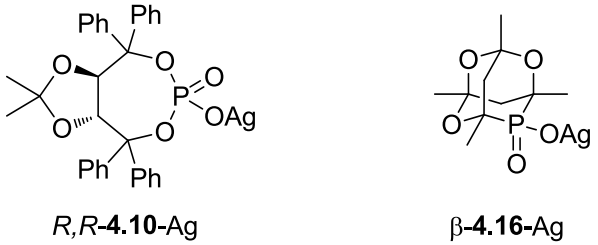
Figure 6.1: Transition states **TS1** and **TS3.**

The first strategy for asymmetric catalysis uses an achiral silver salt ($AgBF_4$) and a chiral ligand (*R*-BINAP or *R*-MeO-BIPHEP), in a 1:1 ratio, to form the active species in solution. With this system, up to 68% ee can be achieved for the hydroalkoxylation reaction of γ-allenic alcohol **1.44** to tetrahydrofuran *S*-**1.45** (Scheme 6.2). However, the reaction is very slow, requiring 63 hours to reach only 50 - 52% conversion.



Scheme 6.2: Ag(I) mediated intramolecular hydroalkoxylation of **1.44**.

The second strategy for asymmetric catalysis uses pre-formed Ag(I) complexes (*R,R*,-**4.10**-Ag or β-**4.16**-Ag), which contain a chiral anionic ligand (Figure 6.2).

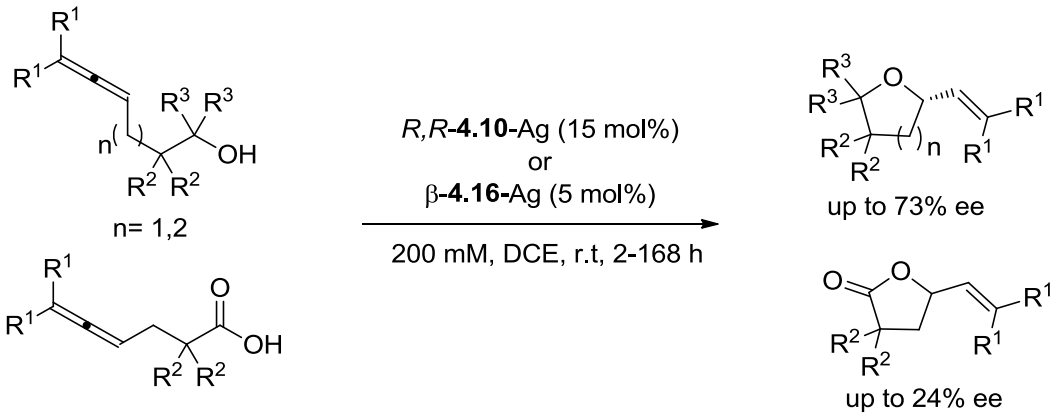


R,R-**4.10**-Ag β-**4.16**-Ag

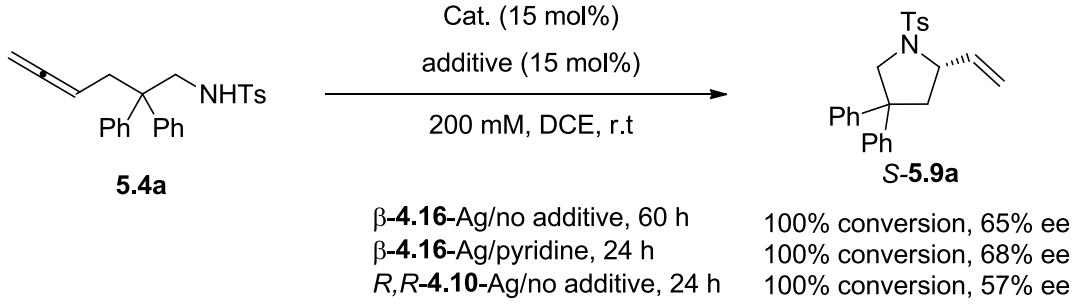
Figure 6.2: Structures of Ag(I) phosphate and Ag(I) phosphinate complexes.

By using this system, up to 73% ee in hydroalkoxylation reactions and up to 68% ee in hydroamination reactions of the relevant γ-allenic substrates could be achieved (Scheme 6.3 and Scheme 6.4). For hydroalkoxylation reactions, the conversion times vary depending on the substitution pattern, with the majority of cyclisations being completed within 2 hours using β-**4.16**-Ag and 8 hours using *R,R*,-**4.10**-Ag. The subsequent hydroamination reactions were found to be more sensitive to terminal allenic substituents and were also slower than the corresponding O-H additions, especially when using β-**4.16**-Ag.

Nevertheless, the addition of sub-stoichiometric amount of pyridine enhanced the catalytic activity of β-**4.16**-Ag. The intramolecular hydroacyalkoxylation of β-allenoic acids to the corresponding lactones can also be accomplished in 2 hours, but with low enantioselectivities (5% to 24%) (Scheme 6.3).

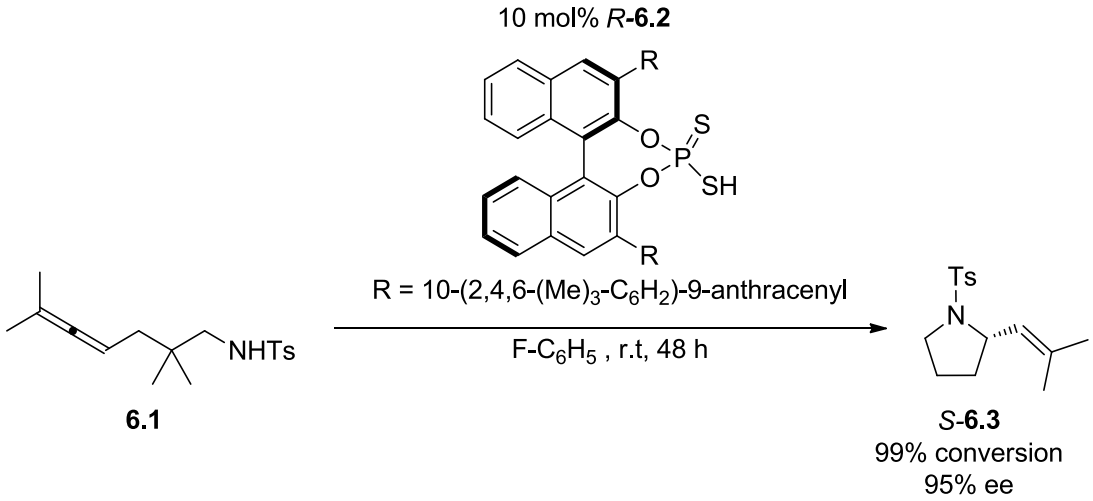


Scheme 6.3: Ag(I) intramolecular hydro(acy)alkoxylation reactions of allenes.



Scheme 6.4: The Ag(I) intramolecular hydroamination reaction of allene **5.4a**.

Prior to this discovery of asymmetric Ag(I)-catalysed heterofunctionalisation reactions of allenes, the only catalysts able to afford high enantioselectivities in intramolecular O-H, N-H and CO_2H additions to allenes have been cationic Au(I) complexes.[37,45,36,40,44,68] However, during the preparation of this thesis, chiral Brønsted acid catalysis, using dithiophosphoric acids, have also been reported to afford high enantioselectivities in the hydroamination reactions of allenes. For example the cyclisation of *N*-tosyl protected **6.1** using 10 mol% *R*-**6.2** furnished pyrrolidine *S*-**6.3** in 95% ee after 48 hours at room temperature (Scheme 6.5).[175]

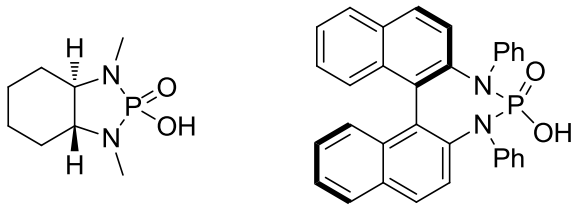


Scheme 6.5: Hydroamination of **6.1** using dithiophosphoric acid **6.2**.

6.2 Future work

Future work will include the development of further generation(s) of silver catalysts, to achieve highly enantioselective Ag(I)-catalysed intramolecular hydro(acy)alkoxylation and hydroamination reactions, preferably with over 90% ee.

Having shown that pre-formed Ag(I) complexes of chiral anionic oxophosphorus(V) ligand are able to induce significant levels of enantioselectivity, it is envisaged that greater stereodifferentiation can be achieved by the synthesis of phosphorodiamidate Ag(I) complexes. These molecules include nitrogen atoms adjacent to the phosphorus and could have the potential to induce higher enantioselectivities. A literature search identified phosphorodiamidic acids *R,R*-**6.4**-H[176] and *R*-**6.5**-H[177] as interesting candidates (Figure 6.3).



S,S-**6.4**-H *R*-**6.5**H

Figure 6.3: Structures of *R,R*-**6.4**-H and *R*-**6.5**-H.

It is envisaged that both *R,R*-**6.4**-H and *R*-**6.5**-H may be similarly prepared from the corresponding *N*-tosyldiamines.[176-178] As a precaution, control experiments should also be performed with the phosphorodiamidic acids, to rule out Brønsted acid catalysis.

Intermolecular hydroamination and hydro(acy)alkoxylation reactions of allenes can also be investigated; catalytically and enantioselectivity. Successful methodologies can then be adapted for the synthesis of interesting molecules, particularly those with potential biological applications.

Chapter 7: Experimental

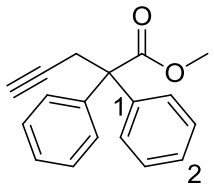
Unless otherwise stated, all precursors and reagents were procured commercially and used as received. Solvents were dried by passing through columns of molecular sieves in a solvent purification system. Lithium diisopropyl amide (LDA) was generated *in situ* from the reaction of *n*-BuLi and diisopropylamine in THF at -78 °C.[179] We are grateful to Prof. J. Antilla (University of South Florida) for the gift of VAPOL, Roche (Switzerland) for the donation of MeOBIPHEP phosphine ligands, Prof. P. Pringle (University of Bristol) for the donation of β-**4.16**-H and Prof. J-C. Fiaud (University of Paris-Sud 11) for the donation of *R,R*-**4.15**-H. The synthesis and resolution of β-**4.16**-H has been previously described.[149] All reactions involving air-sensitive reagents were performed using standard Schlenk techniques and oven dried glassware. Column chromatography and TLC were performed on silica gel (Kieselgel 60). Catalytic reactions were generally performed in the dark using Radley tubes in a Radley's 12-place reaction carousel, or in screw-cap vials.

Unless otherwise started, ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra were recorded on Bruker AVANCE machines operating at 400 MHz, 100 MHz, 162 MHz and 376 MHz respectively. Chemical shifts are reported in δ (ppm), referenced to TMS, and *J* values are given in Hz. Multiplicity is abbreviated to s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet) and m (multiplet). Where required, 2D NMR (COSY, DEPT, HSQC, HMBC) experiments were used to distinguish and assign ^{1}H and ^{13}C peaks. Infrared spectra were recorded using a Perkin Elmer 100 series FT-IR spectrometer, equipped with an ATR accessory. Optical rotations were recorded using a Perkin Elmer 241 polarimeter; specific rotations ($[\alpha]_D^t$) were calculated by $100\alpha/(cl)$, in which, *c* (concentration) is quoted in mg/mL; *l* = 1.0 dm; *D* refers to the D-line of Na (589 nm); temperature (*t*) is given in degrees Celsius (^{o}C). Melting points were recorded using an Electrothermal Gallenhamp apparatus, and were uncorrected. Single crystal X-ray diffraction was performed using an Oxford Diffraction Xcalibur PX Ultra, 1.54248 Å diffractometer.

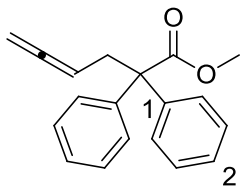
Chiral HPLC was performed on Gilson and Hewlett Packard HPLC systems, each equipped with variable wavelength UV detectors set at 254 nm and auto-injectors

with 20μL loops, using Daicel Chiralcel OJ-H, OD-H, AS-H or AD-H columns (250 x 4.6 mm). Mass spectra (MS) were recorded on either a Micromass Autospec Premier or a VG Platform II spectrometer using EI, CI, ESI or FAB^+ techniques. Elemental analyses were carried out by the Science Technical Support Unit at London Metropolitan University. ICP-OES analyses were performed using an optima 200 DV optical emission spectrometer. Nitric acid (65%, m/v) was used for the digestion of samples. Silver standards (1, 10 and 20 mg/L) were prepared from a 0.01 M solution of $AgNO_3$ in acetic acid (Fluka). All solutions were prepared using deionised water. Single crystal X-ray diffraction was performed using an Oxford Diffraction Xcalibur PX Ultra, 1.54248 Å diffractometer.

7.1 Compounds Used in Chapter 2

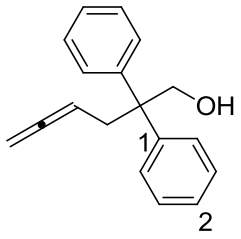


Methyl 2,2-diphenylpent-4-ynoate 2.2. Prepared using a modified propargylation procedure:[58] A solution of methyl 2,2-diphenylacetate **2.1**[180] (5.83 g, 22.1 mmol.) in dry THF (20 mL) was added dropwise to a solution of pre-formed LDA (1 M in THF, 33.2 mmol.) at -78 °C. After stirring for 4 h propargyl bromide (80% in toluene, 2.9 mL, 26.5 mmol.) was added dropwise. The reaction mixture was then left to warm slowly to room temperature overnight. The resulting mixture was treated with sat. NH_4Cl (70 mL) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum to give **2.1** as a pale yellow oil (3.00 g, 85%) after purification by column chromatography. R_f = 0.38 (hexanes:acetone, 30:1); ν_{max}/cm^{-1}: 3317, 3288 (C≡C), 3028, (C-H), 2992 (C-H), 1736 (C=O), 1056 (C=C); δ_H ($CDCl_3$): 7.42 - 7.25 (10H, m, Ar), 3.77 (3H, s, CH_3), 3.32 (2H, d, *J* 2.6, CH_2), 1.95 (1H, t, *J* 2.6, CH); δ_C ($CDCl_3$): 173.8 (C=O), 141.3 (C-1), 128.8 (Ar), 127.9 (Ar), 127.3 (C-2) 80.9 (≡C), 71.8 (≡CH), 59.7 (C), 52.7 (CH_3), 29.3 (CH_2); *m/z* (EI): 264 ($[M]^+$, 5%), 225 (83), 205 (100).

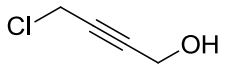


Methyl 2,2-diphenylhexa-4,5-dienoate 2.3. Prepared using a modified *Crabbé* procedure:[58] Propargylation product **2.2** (5.28 g, 20.0 mmol.) was added to a suspension of paraformaldehyde (1.20 g, 40.0 mmol.), copper bromide (1.4 g, 10.0 mmol.) and diisopropylamine (2.80 mL, 40.0 mmol.) in dioxane (120 mL). The reaction mixture

was refluxed for 24 h, before being cooled to room temperature and concentrated under vacuum to give **2.3** as a pale yellow oil (2.40 g, 43%) after purification by column chromatography. R_f = 0.40 (hexanes:acetone, 40:1); ν_{max}/cm^{-1}: 3089, 3058 (C-H), 2950 (C-H), 2850 (C-H), 1956 (C=C=C), 1731 (C=O), 1078 (C=C=C); δ_H ($CDCl_3$): δ 7.37 - 7.22 (10H, m, Ar), 4.95 - 4.83 (1H, m, CH), 4.48 (1H, t, *J* = 2.5, $=CH_2$), 4.46 (1H, t, *J* = 2.5, $=CH_2$), 3.73 (3H, s, CH_3), 3.14 (2H, dt, *J* = 2.5, 7.7, CH_2); δ_C ($CDCl_3$): 210.1 (=C=), 174.4 (C=O), 142.2 (C-1), 129.0 (Ar), 127.9 (Ar), 126.9 (C-2), 85.8 ($=CH_2$), 73.8 (CH), 60.6 (C), 52.4 (CH_3), 38.1 (CH_2); *m/z* (CI): 296 ($[MNH_4]^+$, 100%), 279 ($[MH]^+$, 26).

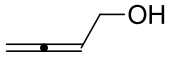


2,2-diphenylhepta-5,6-dien-1-ol 1.44. According to the literature procedure,[58] a solution of allenic ester **2.3** (5.00 g, 18.0 mmol.) in dry Et_2O (70 mL) was added dropwise to cooled (0 °C) suspension of $LiAlH_4$ (1.37 g, 36.0 mmol.) in dry Et_2O (140 mL). The reaction was stirred overnight, quenched with H2O (1.2 mL), 2N NaOH (1.2 mL) and again with H_2O (3.6 mL) at 0 °C. The resulting suspension was filtered and washed with Et_2O (2 x 25 mL). The combined organic extracts were washed with H_2O (50 mL) then brine (25 mL), dried ($MgSO_4$) and concentrated under vacuum to give **1.44** as a colourless oil (3.90 g, 87%) after purification by column chromatography. R_f = 0.55 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3424 (O-H), 3057 (C-H), 2932 (C-H), 2882 (C-H), 1954 (C=C=C), 1020 (C=C=C); δ_H ($CDCl_3$): 7.41-7.17 (10H, m, Ar), 4.79-4.68 (1H, m, CH), 4.55 (1H, t, *J* 2.4, $=CH_2$), 4.53 (1H, t, *J* 2.4, $=CH_2$), 4.23 (2H d, *J* 5.0, O-CH_2), 2.96 (2H, dt, *J* 2.4, 7.7, CH_2), 1.47 (1H, br s, OH); δ_C ($CDCl_3$): 209.6 (=C=), 144.9 (C-1), 128.3 (Ar), 126.5 (C-2), 85.6 (=CH), 74.0 ($=CH_2$), 68.1 (O-CH_2), 51.9 (C), 36.3 (CH_2); *m/z* (CI): 268 ($[MNH_4]^+$, 100%), 251 ($[MH]^+$, 3).

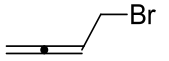


4-Chlorobut-2-yn-1-ol 2.4. According to literature procedures,[94,152,154] thionyl chloride (41.00 mL, 56.4 mmol.) was added dropwise at 0^{o}C over 2.5 h to a solution of but-2-yne-1,4-diol (32.30 g, 37.6 mmol.) in benzene (38 mL) and pyridine (45.5 mL, 56.4 mmol.). After being allowed to warm to room temperature overnight the reaction mixture was poured in to ice H_2O (100 mL) and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with aq. $NaHCO_3$, 1N HCl, dried over $MgSO_4$ and concentrated. The crude

product was purified by distillation. The product, **2.4** was obtained as a colourless oil (16.40 g, 42%). bp: 50-55 ^{o}C, 1.0 torr (lit[181] 50 ^{o}C, 0.5 torr); ν_{max}/cm^{-1}: 3601 (O-H), 3351 (C≡C), 2926 (C-H), 2868 (C-H); δ_H ($CDCl_3$): 4.35 (1H, t, *J* 1.9, O-CH_2), 4.20 (1H, t, *J* 1.9, CH_2Cl), 1.86 (1H, bs, OH); δ_C ($CDCl_3$): 84.64 (-C≡), 80.54 (≡C-), 51.05 (CH_2OH), 30.36 (CH_2Cl); *m/z* (CI): 122 ([$^{35}MNH_4$]$^+$, 22%), 124 ([$^{37}MNH_4$]$^+$, 7).



Buta-2,3-dien-1-ol 2.5. According to the literature procedures,[94,152,154] $LiAlH_4$ (5.49g, 144.6 mmol., 1.1 equiv) was added slowly to a solution of **2.4** (14.00 g, 134.6 mmol.) and Et_2O (250 mL), maintaining a gentle reflux. When the addition of the solid was complete, the addition funnel was rinsed with Et_2O and the suspension was stirred for an additional hour. The reaction mixture was quenched by the addition of H2O (5.4 mL), 4N NaOH solution (5.4mL) and ice H2O (16.8 mL). The grey slurry was stirred overnight and filtered, dried over $MgSO_4$, evaporated and purified by distillation. The pure material decomposed so should be used immediately or kept in the freezer. The product, **2.5** was obtained as a colourless oil (7.58 g, 81%). bp: 100-125 ^{o}C, 760 torr (lit.[182] 126-128 ^{o}C, 756 torr); δ_H ($CDCl_3$): 5.38 - 5.30 (1H, m, CH), 4.87 - 4.82 (2H, m, =CH_2), 4.14 (2H, dt, *J* 3.0, 5.9, CH_2), 2.18 (1H, bs, OH).



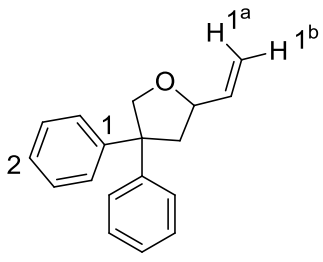
4-Bromobuta-1,2-diene 2.6. According to literature procedures,[94,152,154] a mixture of **2.5** (7.50 g, 107.1 mmol.) and pyridine (4.33 mL, 53.5 mmol.) was added slowly to a solution of PBr_3 (4.03 mL, 42.84 mmol.) in Et_2O (10 mL) at 0 ^{o}C. The reaction mixture was left to stir overnight, while warming to room temperature. Excess reagent was quenched by the addition of H_2O (10 mL). The aqueous layer was extracted with n-pentane (3 x 10 mL), and the combined organic extracts washed with brine and dried over $MgSO_4$. The solvent was removed by distillation at atmospheric pressure. The product, **2.6** was obtained as a colourless oil (5.0 g, 88%). bp: 105-110 ^{o}C, 760 torr (lit.[182] 109-111 ^{o}C, 760 torr); ν_{max}/cm^{-1}: 1945 (C=C=C), 1205 (C=C=C); δ_H ($CDCl_3$): 5.38 (1H, dt, *J* 4.0, 8.0 CH), 4.89 (2H, dt, *J* 3.0, 6.2, CH_2=), 4.20-4.18 (2H, m, CH_2); δ_C ($CDCl_3$): 209.11 (=C=), 86.45 (CH), 75.32 (=CH_2), 31.38 (CH_2); *m/z* (EI) = 131 ([^{79}M]$^+$, 100%), 133 ([^{81}M]$^+$, 97).

Methyl 2,2-diphenylhexa-4,5-dienoate 2.3 was prepared using a modified propargylation procedure:[94,152,154] A solution of LDA was prepared from

diisopropylamine (4.82 mL, 34.4 mmol.) and butyllithium (1.6M in hexanes, 21.48 mL, 34.4 mmol.) in dry THF (20 mL) under a nitrogen atmosphere at -78^{o}C. This was allowed to warm to 0^{o}C for 1 h before being cooled again to -78^{o}C. A solution of methyl 2,2-diphenylacetate **2.1** (7.78 g, 34.4 mmol., 1.2 equiv) in dry THF (30 mL) was then added dropwise to the stirring solution, keeping the temperature below -60 ^{o}C. The mixture was stirred for an hour before **2.6** (2.92 g, 28.6 mmol.) was added, and the reaction mixture was left to stir overnight, warming to room temperature. The mixture was treated with sat. NH_4Cl (2 x 15 mL). The aqueous layer was extracted with Et_2O (2 x 15 mL), the combined organic extracts dried over $MgSO_4$ and concentrated under vacuum to give **2.3** as a pale yellow oil (5.40 g, 68%) after purification by column chromatography R_f = 0.40 (hexanes:acetone, 40:1).

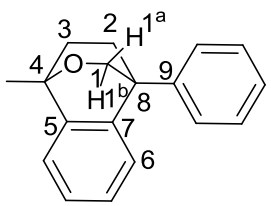
Typical procedure for catalytic reactions described in Chapter 2:

A Radley's reaction tube was charged with a magnetic stir bar, metal salt (5-15%), ligand (5-15%, if used) and additive (if used). Solvent was added and, if required, the reaction temperature was adjusted and controlled *via* a thermostat. This was stirred in the dark for 1 h to generate the catalytically active species before **1.44** was added and conversion monitored by TLC and/or NMR integration. Upon completion, the solvent was evaporated, or, if Brønsted acids were used, 1N NaOH (1 mL) was added, the aqueous layer extracted with Et_2O and the combined organic extracts dried ($MgSO_4$). The product was purified by column chromatography.



4,4-Diphenyl-2- vinyltetrahydrofuran 1.45:[45,68,131] Isolated from **1.44** (0.4 mmol.) as colourless oil using $AgBF_4$/*R*-BINAP the catalyst (52.0 mg, 52%). R_f = 0.39 (hexanes:EtOAc, 20:1); ν_{max}/cm^{-1}: 2866 (C-H), 1493, 1445; δ_H ($CDCl_3$): 7.40 - 7.17 (10 H, m, Ar), 5.93 (1H, ddd, *J* 17.2, 10.0, 7.2, =CH), 5.28 (1H, d, *J* 17.2, H-1^{a}), 5.14 (1H, d, *J* 10.0, H-1^{b}), 4.71 (1H, d, *J* 8.8, O-CH_2), 4.52 - 4.42 (1H, m, CH), 4.19 (1H, d, *J* 8.8, O-CH_2), 2.69 (1H, dd, *J* 12.0, 6.0, CH_2), 2.48 (1H, dd, *J* 12.0, 9.6, CH_2); δ_C ($CDCl_3$): 146.0 (C-1), 145.6 (C-1), 138.8 (=CH), 128.5 (Ar), 128.4 (Ar), 127.3 (Ar), 127.2 (Ar), 126.5 (C-2), 126.3 (C-2), 115.9 (=C), 79.72 (CH), 76.7 (O-CH_2), 56.2 (C), 45.2 (CH_2); (CI): 268 ($[MNH_4]^+$, 100%), 251 ($[MH]^+$, 4%), 269 (33). Lit.[68] $[\alpha]_D^{28}$ = -110.4 (c = 0.39 in $CHCl_3$, 87% ee, *S*-isomer). HPLC conditions: Chirapak OJ-H column, 5 % IPA in *n*-

hexane, 1.0 mL/min, t_R(major) = 16.6 min, t_R(minor) = 21.2 min; $[\alpha]_D^{25}$ = -56.0 ^{o} (c = 0.4, $CHCl_3$, 60% ee obtained with $AgBF_4$/*R*-BINAP). Lit.[68] $[\alpha]_D^{28}$ = -110.4 (c = 0.39 in $CHCl_3$, 87% ee, *S*-isomer).



2.11:[103] Isolated from **1.44** as a crystalline solid (recrystallised from hexane) using $Cu(OTf)_2$ as the catalyst (19.5 mg, 39%). mp: 83-86 ^oC; R_f = 0.23 (hexanes:EtOAc, 20:1); ν_{max}/cm^{-1}: 2950 (C-H), 2932 (C-H), 2858 (C-H); δ_H ($CDCl_3$) 7.49-7.15 (8H, m, Ar), 6.76 (1H, d, *J* 7.6, H-6), 4.07 (1H, d, *J* 7.6, H-1^b), 3.88 (1H, dd, *J* 3.6, 7.6, H-1^a), 2.34-2.18 (2H, m, H-2 and H-3), 2.09-1.94 (1H, m, H-2), 1.75 (3H, s, CH_3), 1.69-1.59 (1H, m, H-3); δ_C ($CDCl_3$): 143.24 (C-5, 7 or 9), 142.57 (C-5, 7 or 9), 140.25 (C-5, 7 or 9), 128.54 (Ar), 127.44 (Ar), 127.18 (Ar), 127.14 (Ar), 126.24 (Ar), 123.32 (C-6), 120.30 (Ar), 72.23 (C-1), 71.35 (C-4), 42.83 (C-8), 33.69 (C-3), 29.27 (C-2), 21.87 (CH_3); *m/z* (CI): 268 ($[MNH_4]^+$, 100%), 251 ($[MH]^+$, 33), 220 (11), 52 (57); HRMS (ESI) 251.1431 ($[MH]^+$, $C_{18}H_{19}O$ requires 251.1436); Anal. Calcd for $C_{18}H_{18}O$: C, 86.36%; H, 7.25%. Found: C, 86.46%, H, 7.17%.

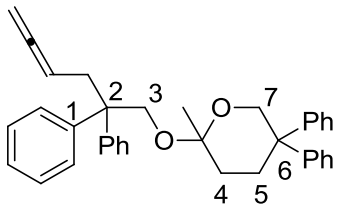
7.2 Compounds Used in Chapter 3

Typical procedure for catalytic reactions in Chapter 3:

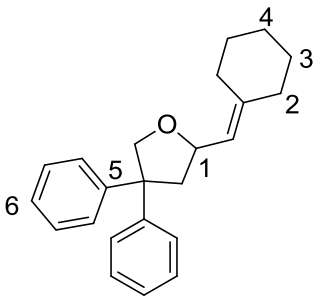
A Radley's reaction tube was charged with a magnetic stir bar, the catalyst AgOTf, $Sn(OTf)_2$ or $Zn(OTf)_2$ (15 mol%) and the corresponding γ-allenic alcohol (0.4 mmol.). A PTFE screwcap was fitted, and DCE (0.3 mL) was added to the contents of the tube *via* the rubber septum. The tube was positioned in a reaction carousel, and left to stir at room temperature. Conversions were monitored by TLC and/or NMR integration. Upon completion, the solvent was evaporated and the residue purified by column chromatography.

4,4-Diphenyl-2-vinyltetrahydrofuran 1.45 was obtained from **1.44** as colourless oil using AgOTf as the catalyst (92%);

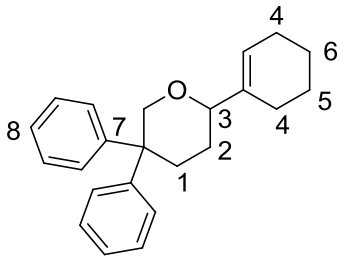
2.11:[103] Isolated from **1.44** as a crystalline solid using $Sn(OTf)_2$ as the catalyst (79 mg, 79%);

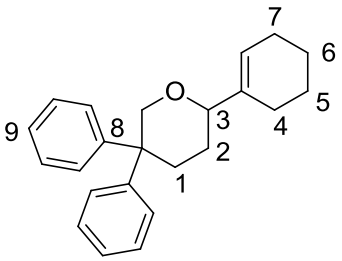


3.1: Isolated from **1.44** as a crystalline solid (recrystallised from hexane) using $Zn(OTf)_2$ as the catalyst (78 mg, 61%). R_f = 0.27 (hexanes:EtOAc, 20:1); mp: 102-108 ^oC; ν_{max}/cm^{-1}: 2924 (C-H), 2853 (C-H), 1954 (C=C=C), 1055 (C=C=C); δ_H ($CDCl_3$): 7.37 - 7.09 (17 H, m, Ar), 7.00-6.95 (1H, m, Ar), 6.89 - 6.82 (2H, m, Ar), 4.70 - 4.56 (1H, m, =CH), 4.54 - 4.36 (2H, m, $=CH_2$), 4.15 (1H, d, *J* = 8.4, H-3), 3.94 (1H, dd, *J* = 11.6, 2.8, H-7), 3.89 (1H, d, *J* 8.4, H-3), 3.20 - 3.08 (1H, m, $=CHCH_2$), 2.95 - 2.87 (1H, m, $=CHCH_2$), 2.85 (1H, d, *J* 11.6, H-7), 2.38 (1H, td, *J* 13.2, 3.6, H-5), 1.97 (1H, m, *J* 9.2, 3.6, H-5),1.63 (1H, dt, *J* 13.2, 3.6, H-4), 1.32 -1.26 (1H, m, H-4), 1.22 (3H, s, CH_3); δ_C ($CDCl_3$): 209.7 (=C=), 146.5 (C-1), 146.2 (C-1), 146.1 (C-1), 145.6 (C-1), 128.5 (Ar), 128.2 (Ar), 128.0 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 127.2 (Ar), 126.0 (Ar), 125.9 (Ar), 125.6 (Ar), 97.0 (C), 85.9 (CH), 73.6 ($=CH_2$), 67.5 (C-7), 64.9 (C-3), 50.3 (C-2), 45.0 (C-6), 36.3 ($=CHCH_2$), 32.3 (C-4), 29.3 (C-5), 23.9 (CH_3); Product fragmentised using MS; *m/z* (CI): 268 ($[MNH_4]^+$, 20%), 251 ($[MH]^+$, 100); Anal. Calcd for $C_{36}H_{36}O_2$: C, 86.36%; H, 7.25%. Found: C, 86.27%, H, 7.08%.

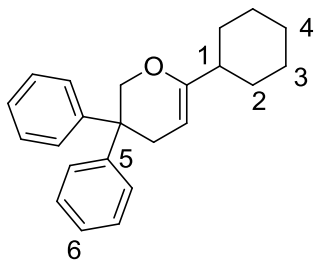


2-(Cyclohexylidenemethyl)-4,4-diphenyltetrahydrofuran 3.19:[68] isolated from **3.18** as a colourless oil using AgOTf as the catalyst (104 mg, 82%). R_f = 0.31 (hexanes:EtOAc, 10:1); ν_{max}/cm^{-1}: 2924 (C-H), 2863 (C-H); δ_H ($CDCl_3$): 7.40 - 7.18 (10H, m, Ar), 5.26 (1H, d, *J* 8.8, =CH), 4.80 (1H, td, *J* 9.0, 5.6, H-1), 4.66 (1H, d, *J* 9.0, O-CH_2), 4.18 (1H, d, *J* 9.0, O-CH_2), 2.64 (1H, dd, *J* 12.0, 5.6, CH_2), 2.42 (1H, dd, *J* 12.0, 9.6, CH_2), 2.26 - 2.03 (4 H, m, H-2), 1.66 - 1.39 (6H, H-3 and H-4); δ_C ($CDCl_3$): 146.3 (C-5), 146.1 (C-6), 144.1 (=C), 128.4 (Ar), 128.3 (Ar), 127.2 (Ar), 126.4 (C-6), 126.2 (C-6), 122.5 ($=CH_2$), 76.9 (O-CH_2), 74.3 (C-1), 56.4 (C), 45.8 (CH_2), 37.1 (CH), 29.2 (CH), 28.31 (CH), 27.8 (CH), 26.7 (CH); *m/z* (EI): 318 ($[M]^+$, 100%), 288 (54), 241 (48), 205 (60), 81 (68); HRMS (EI) 318.1985 (M^+, $C_{23}H_{26}O$ requires 318.1984); Anal. Calcd for $C_{23}H_{26}O$: C, 86.75%; H, 8.23%. Found: C, 86.89%, H, 8.17%.

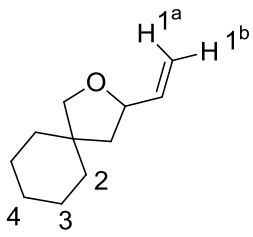




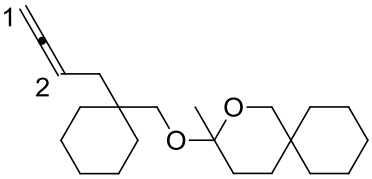
2-Cyclohexenyl-5,5-diphenyltetrahydro-2H-pyran, 3.20: isolated from **3.17** as a colourless oil using $Sn(OTf)_2$ (94 mg, 74%) or $Zn(OTf)_2$ (87.8 mg, 69%) as the catalyst. R_f = 0.26 (hexanes:EtOAc, 10:1); ν_{max}/cm^{-1}: 3023 (C-H), 2924 (C-H), 2862 (C-H); δ_H ($CDCl_3$): 7.53 - 6.99 (10H, m, Ar), 5.50 - 5.61 (1H, m, =CH), 4.61 (1H, d, *J* 8.8, O-CH_2), 4.26 - 4.19 (1H, m, H-3), 4.18 (1H, d, *J* 8.8, O-CH_2), 2.62 (1H, dd, *J* 12.4, 6.0, H-1), 2.40 - 2.28 (2H, m, H-1 and H-2), 2.14 (1H, dd, *J* 14.0, 6.0, H-2), 2.03 - 1.93 (4H, m, H-4 and H-7), 1.67 - 1.52 (4H, m, H-5 and H-6); δ_C ($CDCl_3$): 146.4 (C-8), 146.2 (C-8), 134.8 (Ar), 128.4 (Ar), 128.3 (Ar), 127.2 (Ar), 127.1 (Ar), 126.3 (C-9), 126.1 (C-9), 123.2 (=CH), 76.8 (C), 76.8 (C-3), 55.9 (O-CH_2), 44.9 (C-1 or C-2), 44.7 (C-1 or C-2), 28.8 (C-4 or C-7), 25.3 (C-4 or C-7), 22.9 (C-5 or C-6), 22.3 (C-5 or C-6). *m/z* (CI): 336 ($[MNH_4]^+$, 100%), 319 ($[MH]^+$, 38), 240 (78), 223 (33); HRMS (ESI) 319.2053 ($[MH]^+$, $C_{23}H_{27}O$ requires 319.2062); Anal. Calcd for $C_{23}H_{26}O$: C, 86.75%; H, 8.23%. Found: C, 86.70%, H, 8.19%.



6-Cyclohexyl-3,3-diphenyl-3,4-dihydro-*2H*-pyran, 3.21: isolated from **3.17** as a white solid using $Sn(OTf)_2$ (10 mg, 8%) or $Zn(OTf)_2$ (8 mg, 6%) as the catalyst. mp: 82-84 ^oC; R_f = 0.28 (hexanes:EtOAc, 10:1); ν_{max}/cm^{-1}: 2922 (C-H), 2856 (C-H); δ_H ($CDCl_3$) 7.52 - 7.11 (10H, m, Ar), 5.75-5.71 (1H, m, =CH), 4.69 (1H, d, *J* 12.0, O-CH_2), 3.80 (1H, d, *J* 10.8, H-1), 3.59 (1H, d, *J* 12.0, O-CH_2), 2.53 - 2.46 (2H, m, CH_2), 2.09 - 2.00 (3H, m, H-2), 2.09 - 2.00 (1H, m, CH, H-2), 1.90 (6H, m, CH, H-3 and H-4); δ_C ($CDCl_3$): 146.7 (C-5), 146.0 (C-5), 138.5 (Ar), 129.1 (Ar), 128.2 (Ar), 127.9 (Ar), 127.0 (Ar), 126.3 (C-6), 125.6 (C-6), 123.4 (=CH), 82.4 (C-1), 75.1 (O-CH_2), 45.9 (C), 34.9 (CH_2), 26.5 (CH), 25.0 (CH), 24.3 (CH), 22.6 (CH), 22.5 (CH); *m/z* (CI): 336 ($[MNH_4]^+$, 100%), 319 ($[MH]^+$, 51), 301 (49); HRMS (ESI) 319.2054 ($[MH]^+$, $C_{23}H_{27}O$ requires 319.2062); Anal. Calcd for $C_{23}H_{26}O$: C, 86.75%; H, 8.23%. Found: C, 86.67%, H, 8.16%.



3-Vinyl-2-oxaspiro[4.5]decane, 3.22: isolated from **3.18** as a colourless oil using AgOTf as the catalyst (51 mg, 76%). R_f = 0.28 (hexanes:EtOAc, 10:1); ν_{max}/cm^{-1}: 2922 (C-H), 2880 (C-H); δ_H ($CDCl_3$): 5.88 (1H, ddd, *J* 17.1, 10.3, 6.7, =CH), 5.24 (1H, dt, *J* 17.1, 1.6, H-1^a), 5.09 (1H, dt, *J* 10.3, 1.6, H-1^b), 4.37 (1H, dd, *J* 15.5, 6.7, O-CH_2), 3.62 (2H, close AB, O-CH_2), 1.95 (1H, dd, *J* 12.5, 6.8, CH_2), 1.58 - 1.35 (11H, m, CH_2 and H-2 to H-4); δ_C ($CDCl_3$): 139.5 (=CH), 115.1 (=C), 79.7 (C-3), 78.6 (O-CH), 44.8 (C), 44.1 (CH_2), 36.8 (CH), 35.5 (CH), 26.0 (CH), 24.1 (CH), 23.6 (CH); *m/z* (CI): 350 ([MNH_4]$^+$, 4%), 333 ([MH]$^+$, 2), 184 (23), 167 (100), 153 (18); HRMS (CI) 167.1430 ([MH]$^+$, $C_{11}H_{19}O$ requires 167.1436); Anal. Calcd for $C_{11}H_{18}O$: C, 79.46%; H, 10.91%. Found: C, 79.58%, H, 10.87%



3.23: Isolated as a colourless oil from **3.18** using $Sn(OTf)_2$ (47 mg, 35%) or $Zn(OTf)_2$ (60 mg, 45%) as the catalyst. R_f = 0.56 (hexanes:EtOAc, 20:1); ν_{max}/cm^{-1}: 2921 (C-H), 2850 (C-H), 1954 (C=C=C), 1044 (C=C=C); Two conformational isomers can be identified in solution (ratio = 1 : 1.26); δ_H (C_7D_8, 373K), 5.05 (minor, 1H, tt, *J* 6.7, 8.0, H-3), 4.92 (major, 1 H, tt, *J* 6.7, 8.1, H-3), 4.47 (minor, 2 H, dt, *J* 2.6, 6.7, H-1), 4.43 (major, 2 H, dt, *J* 2.5, 6.7, H-1), 3.46 - 3.44 (minor, 2 H, m), 3.38 - 3.26 (major, 2 H, m), 3.22 - 3.14 (major, 2 H, m), 3.16 - 3.15 (minor, 2 H, m), 2.14 - 2.07 (minor, 2 H, m), 1.93 (major, 2 H, dt, *J* 2.5, 8.1), 1.63 - 1.59 (3 H, m), 1.52 - 1.49 (2 H, m), 1.40 - 1.10 (48 H, m), 1.04 - 0.97 (1 H, m); Due to the existence of two conformational isomers the carbon spectra was too complicated to be assigned. *m/z* (CI): 350 ([MNH_4]$^+$, 2%), 333 ([MH]$^+$, 4), 184 (24), 167 (100), 153 (17); HRMS (CI) 333.2798 ([MH]$^+$, $C_{22}H_{37}O_2$ requires 333.2794); Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46%; H, 10.91%. Found: C, 79.36%, H, 10.59%.

7.3 Compounds Used in Chapter 4

General method for propargylation:[58]

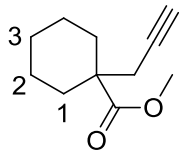
A solution of ester (1 equiv) in dry THF (30 mL) was added dropwise to a solution of freshly prepared LDA (1.5 equiv) at -78 °C. After stirring for 4 h, propargyl bromide (80% in toluene, 1.2 equiv) was added dropwise. The reaction mixture was then left to warm slowly to room temperature overnight. The resulting mixture was treated with sat. aq. NH_4Cl (90 mL) and extracted with Et_2O (2 x 60 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under vacuum.

General method for the Crabbè reaction:[58]

Propargylation product (1 equiv) was added to a suspension of paraformaldehyde (2 equiv), copper bromide (0.5 equiv) and diisopropylamine (2 equiv) in dioxane (180 mL). The reaction mixture was refluxed for 24 h, before being cooled to room temperature and concentrated under vacuum.

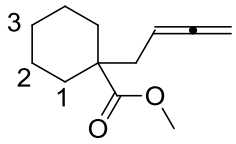
General method for LAH reduction:[58]

A solution of allenic ester (1 equiv) in dry Et_2O (40 mL) was added dropwise to cooled (0 °C) suspension of $LiAlH_4$ (2 equiv) in dry Et_2O (80 mL). The reaction was stirred overnight, quenched successively by the addition of H_2O (0.9 mL), 2N NaOH (0.9 mL) and H_2O (2.7 mL) at 0 °C. The resulting suspension was filtered and extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with H_2O (25 mL) then brine (15 mL), dried ($MgSO_4$) and concentrated under vacuum.

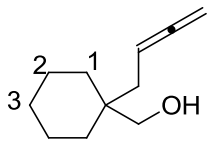


Methyl-1-(prop-2-ynyl)cyclohexanecarboxylate 4.21a. Prepared on a 39.0 mmol. scale using the general method for propargylation and was isolated as a pale yellow oil (5.12 g, 73%) after purification by column chromatography. R_f = 0.07 (hexanes:acetone, 20:1); ν_{max}/cm^{-1}: 3419 (C-H), 2923 (C-H), 2851 (C-H), 1718 (C=O); δ_H ($CDCl_3$): 3.73 (3H, s, CH_3), 2.43 (2H, close AB, CH_2), 2.03 (1H, t, *J* 2.7, ≡CH), 1.64-1.51 (3H, m, H-1 and H-2), 1.50-1.36 (4H, m, H-2 and H-3), 1.28-1.25 (1H, m, H-3); δ_C ($CDCl_3$): 176.0 (C=O), 80.3 (≡C), 70.8 (≡CH), 51.8 (CH_3), 46.7 (CH_2), 33.1 (C-1), 29.0 (C), 25.5 (C-3), 22.9 (C-2); *m/z* (CI): 198 ($[MNH_4]^+$, 100%), 181 ($[MH]^+$, 18), 52 (11); HRMS (ESI) 181.1228 (MH^+,

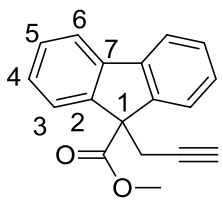
$C_{11}H_{17}O_2$ requires 181.1229); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30%; H, 8.95%; Found: C, 72.97%, H, 8.80%.



Methyl-1-(buta-2,3-dienyl)cyclohexanecarboxylate 4.22a. Prepared on a 29.4 mmol. scale using the general method for the Crabbè reaction and was isolated as a yellow oil (2.30 g, 40%) after purification by column chromatography. R_f = 0.33 (hexanes:EtOAc, 20:1); ν_{max}/cm^{-1}: 2956 (C-H), 2945 (C-H), 2854 (C-H),1962 (C=C=C), 1714 (C=O), 1052 (C=C=C); δ_H ($CDCl_3$): 4.98 (1H, tt, *J* 6.7, 8.1, =CH), 4.65 (1H, t, *J* 2.5, =CH_2), 4.63 (1H, t, *J* 2.5, =CH_2) 3.70 (3H, s, CH_3), 2.23 (2H, dt, *J* 2.4, 8.0, CH_2), 2.14 - 2.01 (2H, m, H-1), 1.65 - 1.50 (3H, m, H-1 and H-2), 1.43- 1.23 (5H, m, H-2 and H-3); δ_C ($CDCl_3$): 209.53(=C=), 176.7 (C=O), 85.1 (=CH), 73.9 (=CH_2), 51.5 (CH_3), 47.5 (C), 39.2 (CH_2), 33.6 (C-1), 25.8 (C-2), 23.1 (C-3); *m/z* (CI): 212 ($[MNH_3]^+$, 100%), 195 ($[MH]^+$, 49); HRMS (EI) 195.1388 ($[MH]^+$, $C_{12}H_{19}O_2$ requires 195.1385); Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19%; H, 9.34%; Found: C, 74.1%, H, 9.27%.

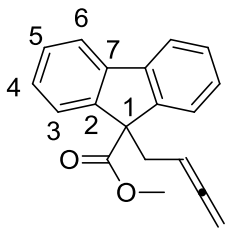


(1-(Buta-2,3-dienyl)cyclohexyl)methanol 3.18. Prepared on a 11.4 mmol. scale using the general method for LAH reduction and was isolated as a colourless oil (1.60 g, 85%) after purification by column chromatography. R_f = 0.54 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3339 (O-H), 2922 (C-H), 2851 (C-H), 1953 (C=C=C), 1452, 1042 (C=C=C); δ_H ($CDCl_3$): 5.11 (1H, tt, *J* 6.7, 8.3, =CH), 4.69 (1H, t, *J* 2.4, =CH_2), 4.67 (1H, t, *J* 2.4, =CH_2), 3.48 (2H, close AB, O-CH_2), 2.11 (2H, dt, *J* 2.4, 8.3, CH_2) 1.47 (6H, m, H-1 and H-3), 1.36 (4H, m, H-2); δ_C ($CDCl_3$): 209.4 (=C=), 85.72 (=CH), 73.7 (=CH_2), 68.6 (O-CH_2), 38.0 (C), 34.5 (CH_2), 32.2 (C-1), 26.3 (C-2), 21.5 (C-3); *m/z* (CI): 184 ($[MNH_4]^+$, 100%), 167 ($[MH]^+$, 9), 95 (19), 52 (20); HRMS (CI) 184.1704 ($[MH]^+$ $C_{11}H_{19}O$ requires 184.1701); Anal. Calcd for $C_{11}H_{18}O$: C, 79.46%; H, 10.91%; Found: C, 79.39%, H, 10.98%.



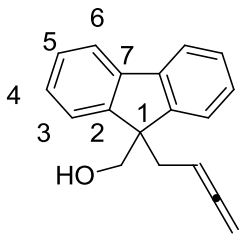
Methyl-9-(prop-2-yn-1-yl)-9H-fluorene-9-carboxylate 4.21b. According to literature procedure,[45] In small quantities Na metal (1.00 g, 89.2 mmol.) was added to MeOH (150 mL). Once dissolved, the ester **4.20b**[180] (10.00 g, 44.6 mmol.) was added and the mixture left to stir for 30 minutes. Propargyl bromide (80% in toluene, 3.70 mL,

66.9 mmol.) was then added and the mixture left stirring for one h. The resulting mixture was diluted with H_2O (50 mL) followed by extraction into CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and concentrated under vacuum to give **4.21b** as a pale yellow solid (5.40 g, 86%). mp 115-118 ^oC (lit.[151] 117-119 ^oC); ν_{max}/cm^{-1}: 3486 (C-H), 3311 (C-H), 3058 (C-H), 3019 (C-H), 2955 (C-H), 1726 (C=O); δ_H ($CDCl_3$): 7.78 (1H, d, *J* 7.5, H-6), 7.74 (1H, d, *J* 7.5, H-3), 7.47 (1H, dt, *J* 1.0, 7.5, H-5), 7.38 (1H, dt, *J* 1.1, 7.5, H-4), 3.68 (4H, s, CH_3), 3.09 (2H, d, *J* 2.6, CH_2), 1.97 (1H, t, *J* 2.6, ≡CH); δ_C ($CDCl_3$): 172.66 (C=O), 144.5 (C-2), 140.8 (C-7), 128.6 (C-3), 127.6 (C-4), 123.6 (C-5),120.1 (C-6), 80.3 (≡C), 70.5 (≡CH), 59.5 (C-1), 52.8 (CH_3), 28.1 (CH_2); *m/z* (EI): 262 ($[M]^+$, 88%), 223 (100), 181 (90).



Methyl-9-(buta-2,3-dien-1-yl)-9H-fluorene-9-carboxylate

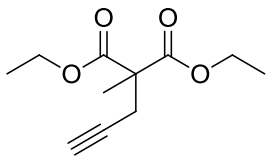
4.22b. Prepared on a 24.0 mmol. scale using the general method for the Crabbè reaction and was isolated as a colourless oil (3.00 g, 45%) after purification by column chromatography. R_f = 0.42 (hexanes:EtOAc, 10:1); ν_{max}/cm^{-1}: 3068 (C-H), 2951 (C-H), 1955 (C=C=C), 1724 (C=O), 1065 (C=C=C); δ_H ($CDCl_3$): 7.76 (2H, d, *J* 7.5, H-6), 7.61 (2H, d, *J* 7.5, H-7), 7.44 (1H, td, *J* 1.0, 7.5, H-5), 7.36 (1H, td, *J* 1.1, 7.7, H-4), 4.72 - 4.59 (1H, m, =CH), 4.45 (1H, t, *J* 2.4, $=CH_2$), 4.43 (1H, t, *J* 2.4, $=CH_2$), 3.64 (3H, s, CH_3), 3.00 (2H, dt, *J* 7.7, 2.4, CH_2); δ_C ($CDCl_3$): 210.1 (=C=), 173.4 (C=O), 144.8 (C-2), 141.0 (C-7), 128.2 (C-3), 127.4 (C-4), 124.9 (C-5), 120.0 (C-6), 84.5 (=CH), 74.2 ($=CH_2$), 61.2 (C), 52.6 (CH_3), 37.1 (CH_2); *m/z* (CI): 294 ($[MNH_4]^+$, 100%), 277 ($[MH]^+$, 13); HRMS (CI) 277.1223 ($[MH]^+$, $C_{19}H_{17}O_2$ requires 277.1229); Anal. Calcd for $C_{19+}H_{16}O_2$: C, 82.58%; H, 5.84%; Found: C, 82.64%, H, 5.94%.



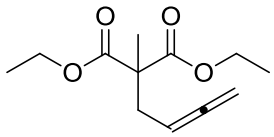
(9-(Buta-2,3-dien-1-yl)-9H-fluoren-9-yl)methanol 4.18.

Prepared on a 9.6 mmol. scale using the general method for LAH reduction and was isolated as a colourless oil (2.10 g, 89%) after purification by column chromatography. R_f = 0.55 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3379 (O-H), 3065 (C-H), 2917 (C-H), 2866 (C-H), 1953 (C=C=C), 1447, 1043 (C=C=C); δ_H ($CDCl_3$): 7.78 (2H, d, *J* 7.5, H-6), 7.54 (2H, d, *J* 7.4, H-3), 7.42 (2H, td, *J* 7.4, 1.1, H-5), 7.36 (2H, td, *J* 7.4, 1.1, H-4), 4.69 - 4.55 (1H, m, =CH), 4.46 (1H, t, *J* 2.5, $=CH_2$), 4.44 (1H, t, *J* 2.5,

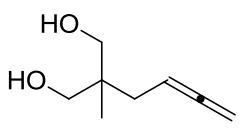
=CH_2), 3.90 (2H, close AB, O-CH_2), 2.81 (2H, dt, *J* 7.8, 2.5, CH_2) 1.48 (1H, t, *J* 6.5, OH); δ_C ($CDCl_3$): 209.6 (=C=), 147.3 (C-2), 141.2 (C-7), 127.8 (C-3), 127.2 (C-4), 123.9 (C-5), 120.2 (C-6), 85.0 (=CH), 74.0 (=CH_2), 68.8 (O=CH_2), 56.7 (C-1), 34.1 (CH_2); *m/z* (CI): 266 ($[MNH_4]^+$, 100%), 249 ($[MH]^+$, 3), 217 (10); HRMS (CI) 266.1558 ($[MNH_4]^+$, $C_{18}H_{20}O$ requires 266.1545); Anal. Calcd for $C_{18}H_{20}O$: C, 87.06%; H, 6.49%; Found: C, 86.95%, H, 6.34%.



Diethyl-2-methyl-2-(prop-2-yn-1-yl)malonate 4.21c. Prepared on a 28.7 mmol. scale by the same method used to form **4.21b** and was isolated as a colourless oil (4.30 g, 85%) after purification by column chromatography. R_f = 0.29 (hexanes:EtOAc, 20:1); ν_{max}/cm^{-1}: 3285 (C≡C), 2986 (C-H), 2940 (C-H), 2906 (C-H), 2123 (C≡C), 1736 (C=O), 1152 (OEt); δ_H ($CDCl_3$): 4.20 - 4.13 (4H, m, O-CH_2), 2.75 - 2.73 (2H, m, CH_2), 2.01 - 1.98 (1H, m, ≡CH), 1.50 (3H, d, *J* 2.4, CH_3), 1.22 (3H, t, *J* 7.1, $CH_2C\mathit{H}_3$), 1.21 (3H, t, *J* 7.1, $CH_2C\mathit{H}_3$); δ_C ($CDCl_3$): 170.7 (C=O), 79.1 (≡C), 71.2 (≡CH), 61.6 (-CH_2), 53.0 (C), 25.7 (CH_2), 19.6 (CH_3), 13.93 ($CH_2C\mathit{H}_3$); *m/z* (CI): 230 ($[MNH_4]^+$, 100%), 213 ($[MH]^+$, 26).

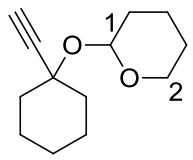


Diethyl-2-(buta-2,3-dienyl)-2-methylmalonate 4.22c. Prepared on a 19.8 mmol. scale using the general method for the Crabbè reaction and was isolated as a yellow oil (2.60 g, 58%) after purification by column chromatography. R_f = 0.32 (hexanes:EtOAc, 10:1); ν_{max}/cm^{-1}: 2984 (C-H), 2876 (C-H), 1957 (C=C=C), 1733 (C=O), 1024 (C=C=C); δ_H ($CDCl_3$): 5.03 - 4.92 (1H, m, =CH), 4.64 - 4.61 (2H, m, =CH_2), 4.15 (4H, q, *J* 7.1, O-CH_2), 2.59 - 2.47 (2H, m, CH_2), 1.39 (3H, d, *J* 1.4, CH_3), 1.22 (3H, t, *J* 7.2, $CH_2C\mathit{H}_3$), 1.22 (3H, t, *J* 7.2, $CH_2C\mathit{H}_3$); δ_C ($CDCl_3$): 210.1 (=C=) 171.7 (C=O), 84.6 (=CH), 74.4 (=CH_2), 61.2 (O-CH_2), 53.8 (C), 35.1 (CH_2), 19.6 (CH_3), 14.0 ($CH_2C\mathit{H}_3$); *m/z* (CI): 244 ($[MNH_4]^+$, 88%), 227 ($[MH]^+$, 100). HRMS (CI) 227.1293 ($[MH]^+$, $C_{12}H_{19}O_4$ requires 227.1293); Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.7%; H, 8.0%; Found: C, 60.2%, H, 8.2%.



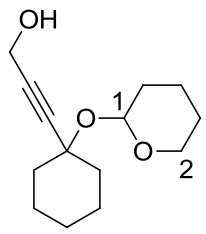
2-(Buta-2,3-dienyl)-2-methylpropane-1,3-diol 4.19. Prepared on a 8.8 mmol. scale using the general method for LAH reduction

and was isolated as a pale yellow oil (1.10 g, 88%) after purification by column chromatography. R_f = 0.58 (EtOAc); ν_{max}/cm^{-1}: 3349 (O-H), 2929 (C-H), 2876 (C-H), 1954 (C=C=C), 1041 (C=C=C); δ_H ($CDCl_3$): 5.14 – 5.07 (1H, m, =CH), 4.69 (1H, t, *J* 2.4, =CH_2), 4.68 (1H, t, *J* 2.4, CH_2), 3.67 - 3.52 (4H, close AB, O-CH_2), 2.24 (2H, bs, OH), 2.13 (2H, dt, *J* 8.0, 2.4, CH_2), 0.86 (3H, s, CH_3); δ_C ($CDCl_3$) 209.8 (=C=), 85.2 (=CH), 74.0 (=CH_2), 69.8 (O-CH_2), 39.8 (CH_2), 33.4 (C), 18.3 (CH_3); *m/z* (CI): 160 ([MNH_4]$^+$, 100%), 143 ([MH]$^+$, 60); HRMS (CI) 143.1075 ([MH]$^+$, $C_8H_{14}O_2$ requires 143.1072); Anal. Calcd for $C_8H_{14}O_2$: C, 67.57%; H, 9.92%; Found: C, 67.41%, H, 9.81%.



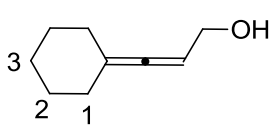
2-((1-Ethynylcyclohexyl)oxy)tetrahydro-2H-pyran 4.26a.

According to the literature procedures,[155,183] 3,4-dihydro-*2H*-pyran (11.0 mL, 120 mmol.) was added to to a cooled solution of 1-ethynylcyclohexanol (10.16 mL, 80.0 mmol.) in $CHCl_3$ (60 mL) at 0 °C, *p*-TsOH.H_2O (30.4 mg, 0.0016 mmol.) was added and the mixture was stirred for 2 h. The resulting solution was washed with sat. aq. $NaHCO_3$ (2 x 50 mL), brine (25 mL), dried ($MgSO_4$), filtered and concentrated under vacuum to give **4.26a** as a colourless oil (15.00 g, 90%) after purification by distillation. bp: 115-120 °C, 6 torr (lit[183] 101-103 ^{o}C, 3.6 torr); ν_{max}/cm^{-1}: 3307 (C=C), 2937 (C-H), 2860 (C-H), 2258 (C=C); δ_H ($CDCl_3$): 5.15 - 5.13 (1H, m, H-1), 4.01 - 3.94 (1H, m, H-2), 3.56 - 3.49 (1H, m, H-2), 2.50 (1H, s, ≡CH), 2.13 - 2.00 (1H, m, CH), 1.97 - 1.81 (2H, m, CH), 1.78 - 1.62 (6H, m, CH) 1.61 - 1.45 (6H, m, CH), 1.33 - 1.18 (1H, m, CH); δ_C ($CDCl_3$): 95.7 (C-1), 85.3 (≡C), 74.8 (≡CH), 73.8 (C), 63.4 (C-2), 38.6, (CH) 38.4 (CH), 32.1 (CH), 25.4 (CH), 25.3 (CH), 23.1 (CH), 22.9 (CH), 20.4 (CH); MS (CI): 226 ([MNH_4]$^+$, 15%), 209 ([MH]$^+$, 5), 102 (100), 85 (36).

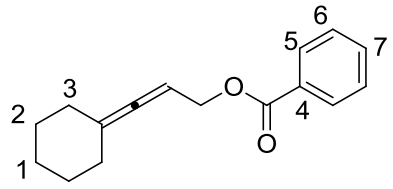


3-(1-((Tetrahydro-2H-pyran-2-yl)oxy)cyclohexyl)prop-2-yn-1-ol 4.27a. According to the literature procedure,[153] *n*-BuLi (2.5 M in hexanes, 36.2 mL, 90.6 mmol.) was added slowly to a stirring solution of THP-protected alcohol **4.26a** (14.50 g, 69.7 mmol.) in dry THF (100 mL) at -78 °C, keeping the internal temperature below -65 ^{o}C. After stirring for 2 h at -78 ^{o}C, the solution was warmed to 0 °C, whereupon DMPU (20 mL) was added. This was stirred for a further 30 minutes before paraformaldehyde (4.18 g, 139.4 mmol.) was added in one portion. The

reaction mixture was allowed to warm to room temperature and stirred overnight, before quenching with sat. NH_4Cl (30 mL). The solution was extracted with Et_2O (2 x 25 mL) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated under vacuum to give **4.27a** as a colourless oil (12.80 g, 77%) after purification by column chromatography. R_f = 0.37 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3399 (O-H), 2934 (C-H), 2857 (C-H); δ_H ($CDCl_3$): 5.15 - 5.13 (1H, m, H-1), 4.34 (2H, close AB, O-CH_2), 4.02 - 3.93 (1H, m, H-2), 3.56 - 3.49 (1H, m, H-2), 2.00 - 1.97 (2H, m, CH), 1.87 - 1.85 (2H, m, CH), 1.75 - 1.65 (5H, m, CH), 1.60 - 1.47 (7H, m, CH), 1.32-1.21 (1H, m, CH); δ_C ($CDCl_3$): 95.4 (C-1), 87.2 (≡C), 84.3 (≡*C*-CH_2), 74.7 (C), 63.3 (C-2), 51.2 (O-CH_2), 38.8 (CH), 32.1 (CH), 25.4 (CH), 23.3 (CH), 20.2 (CH); *m/z* (CI): 256 ($[MNH_4]^+$, 100%), 239 ($[MH]^+$, 5), 221 (78), 203 (60), 102 (93).

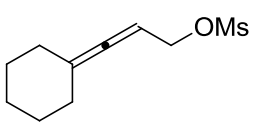


3-Cyclohexylideneprop-2-en-1-ol 4.25a. Prepared on a 22.2 mmol. scale using the general method for LAH reduction and was isolated as a colourless oil (2.55 g, 83%) after purification by column chromatography. R_f = 0.4 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3304 (O-H), 2923 (C-H), 2852 (C-H), 1964 (C=C=C), 1053 (C=C=C); δ_H ($CDCl_3$): 5.23 (1H, m,=CH), 4.09 (2H, close AB, O-CH_2), 2.22 - 2.09 (4H, m, H-1), 1.65 - 1.52 (6H, m, H-2 and H-3), 1.48 (1H, t, *J* 5.6, OH); δ_C ($CDCl_3$): 197.2 (=C=), 105.9 (=C), 89.7 (O-CH_2), 61.1 (=CH), 32.8 (C-1), 27.4 (C-2), 26.0 (C-3); *m/z* (EI): 138 (M^+, 8%), 84 (72), 55 (78), 49 (100).



3-Cyclohexylideneallyl benzoate 4.29a. According to the literature procedure,[58] benzoyl chloride (3.20 mL, 27.8 mmol.) was added dropwise to a stirred solution of **4.25a** (2.50 g, 18.5 mmol.), DMAP (226.0 mg, 1.85 mmol.) and pyridine (1.79 mL, 22.2 mmol.) in CH_2Cl_2 (20 mL) at 0 °C,. After stirring overnight at room temperature, the resulting suspension was diluted with CH_2Cl_2 (100 mL), washed with 1N HCl solution (2 x 50 mL), H2O (50 mL) and aq. 2N $NaHCO_3$ (50 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and concentrated under vacuum to give **4.29a** as a pale yellow oil (4.40 g, 98%) after purification by column chromatography. R_f = 0.38 (hexanes:EtOAc, 20:1); ν_{max}/cm^{-1}: 2928 (CH), 2855 (C-H), 1968 (C=C=C), 1717 (C=O), 1069 (C=C=C); δ_H ($CDCl_3$): 8.11 - 8.08, (2H, m, H-5), 7.69-7.56 (1H, m, H-7), 7.56-7.44 (2H, m, H-6) 5.26 (1H, m, =CH), 4.81 (2H,

close AB, O-CH_2), 2.19 - 2.10 (4H, m, H-3), 1.61 - 1.50 (6H, m, H-1 and H-2); δ_C ($CDCl_3$): 199.9 (=C=), 166.4(C=O), 132.8 (C-4), 130.4 (C-11), 129.6 (C-5) 128.3 (C-6), 104.7 (=C), 84.7 (=CH), 63.8 (O-CH_2), 31.1 (C-3), 27. 2 (C-2), 26.0 (C-1); m/z (CI): 260 ($[MNH_4]^+$,61%), 243 ($[MH]^+$, 100), 225 (42), 105 (80).



3-Cyclohexylideneallyl methanesulfonate 4.30a. According to the literature procedure,[58] methanesulfonylchloride (1.44 mL, 18.2 mmol.) was added dropwise to a solution of **4.25a** (15.2 mmol.), DMAP (186 mg, 1.52 mmol.), and Et_3N (3.17 mL, 22.8 mmol.) in CH_2Cl_2 (80 mL) at 0 °C. The resulting suspension was stirred for 1 h, treated with H_2O (40 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with 1 M HCl (40 mL), sat. aq. $NaHCO_3$ (40 mL), and brine (30 mL), dried ($MgSO_4$), and concentrated. **4.30a** was used immediately in the subsequent coupling step without further purification.

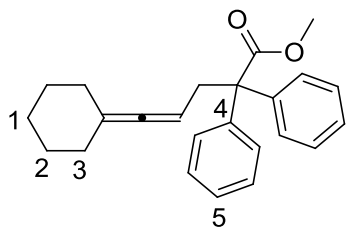
Method A: Coupling using the benzoyl ester (a modified procedure).[4]

At -78 °C, LiHMDS (1 M in THF, 50.70 mL, 50.7 mmol.) was added dropwise over 1 h, to a solution of methyl 2,2-diphenylacetate, **2.1** (2.73 g, 12.1 mmol.) in dry THF (100 mL). Stirring was continued for 2 h at -78 °C. Meanwhile, a mixture of $Pd_2(dba)_3$[184,185] (583 mg, 10 mol%) and PPh_3 (798 mg, 30 mol%) was stirred in dry THF (30 mL) for 1 h at room temperature. Compound **4.29** (2.50 g, 10.1 mmol.) was added to this catalytic mixture and stirred for a further 2 h, before the mixture was transferred by syringe into the first solution at -78 °C. The combined mixture was warmed to room temperature stirred overnight. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and concentrated under vacuum.

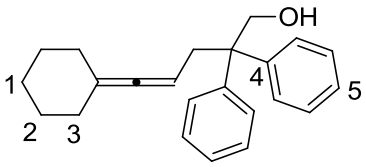
Method B: Coupling using the mesylate ester[37,58]

A solution of methyl 2,2-diphenylacetate, **2.1** (1.84 g, 6.9 mmol.) in DMF (15 mL) was added dropwise to a suspension of NaH (60% suspension in hexanes, 331 mg, 8.2 mmol.) in THF (40 mL) at 0 °C. The resulting mixture was stirred vigorously for 1 h, treated sequentially with half the solution of crude **4.30** in DMF (10 mL) and a single

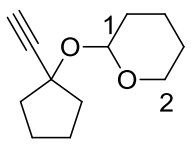
portion of NaI (1.23 g, 8.2 mmol.), and warmed to room temperature overnight with stirring. The resulting mixture was treated with H_2O (40 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and concentrated under vacuum.



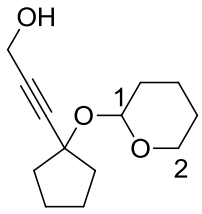
Methyl-5-cyclohexylidene-2,2-diphenylpent-4-enoate 4.28a was formed by coupling methods A and B. By Method A, **4.28a** was obtained as a colourless oil (2.00 g, 58%) after purification by column chromatography. By Method B, **4.28a** was obtained as a colourless oil (2.50 g, 94%) after column chromatography; R_f = 0.26 (hexanes:CH_2Cl_2, 5:2). ν_{max}/cm^{-1}: 2926 (C-H), 2852 (C-H), 1965 (C=C=C), 1728 (C=O), 1058 (C=C=C); δ_H ($CDCl_3$): 7.37 - 7.18 (10H, m, Ar), 4.73 (1H, s, =CH), 3.72 (3H, s, CH_3), 3.12 (2H, close AB, CH_2), 1.96 - 1.84 (4H, m, H-3), 1.56 - 1.41 (6 H, m, H-2 an H-1); δ_C ($CDCl_3$): 200.5 (=C=), 174.6 (C=O), 142.5 (C-4), 129.1 (Ar), 127.8 (Ar), 126.7 (C-5), 101.8 (=C), 84.4 (=CH), 60.5 (C), 52.4 (CH_3), 39.5 (CH_2), 31.1 (C-3), 27.3 (C-2), 26.1 (C-1); *m/z* (CI): 364 ([MNH_4]$^+$, 100%), 347 ([MH]$^+$, 17), 287 (21), 268 (34); HRMS (EI) 347.2015 ([MH]$^+$, $C_{24}H_{27}O_2$ requires 347.2011); Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.20%; H, 7.56%. Found: C, 83.26%, H, 7.43%.



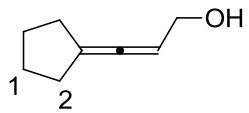
5-Cyclohexylidene-2,2-diphenylpent-4-en-1-ol 3.17.[68] Prepared on a 7.0 mmol. scale using the general method for LAH reduction and was isolated as a white solid (1.90 g, 86%) after purification by column chromatography. R_f = 0.13 (hexanes:EtOAc, 20:1); mp 49 - 55 °C; ν_{max}/cm^{-1}: 3558 (O-H), 3058 (C-H), 2921 (C-H), 2851 (C-H), 1964 (C=C=C), 1069 (C=C=C); δ_H ($CDCl_3$): 7.36 - 7.16 (10 H, m, Ar), 4.70 - 4.60 (1H, m, =CH), 4.21 (2H, close AB, O-CH_2), 2.90 (2H, close AB, CH_2), 1.98 (4H, d, *J* 4.9, H-3), 1.54-1.46 (6H, m, H-2 and H-1); δ_C ($CDCl_3$): 200.2 (=C=), 145.2 (C-4), 128.4 (Ar), 128.2 (Ar), 122.9 (C-5), 101.7 (=C), 84.2 (=CH), 68.4 (O-CH_2), 52.2 (C), 37.8 (CH_2), 31.3 (C-3), 27.4 (C-2), 26.1 (C-1); *m/z* (EI): 318 (M$^+$,5%), 287 (64), 227 (40), 197 (100), 105 (91), 91 (82); HRMS (EI) 318.1983 ([M]$^+$, $C_{23}H_{26}O$ requires 318.1984); Anal. Calcd for $C_{23}H_{26}O$: C, 86.75%; H, 8.23%. Found: C, 86.69%, H, 8.18%.



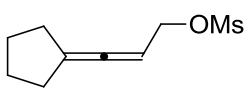
2-((1-Ethynylcyclopentyl)oxy)tetrahydro-2H-pyran 4.26b. Prepared from 1-ethynylcyclopentanol on a 45.4 mmol. scale, by the same method used to form **4.26a** and was isolated as a colourless oil (8.30 g, 94%) after purification by column chromatography. R_f = 0.34 (hexanes:EtOAc, 20:1); ν_{max}/cm^{-1}: 3293 (C=C), 2943 (C-H), 2874 (C-H); δ_H ($CDCl_3$) 5.10-5.08 (1H, m, H-1), 4.00 - 3.89 (1H, m, H-2), 3.58 - 3.52 (1H, m, H-2), 2.49 (1H, s, ≡CH), 2.27 - 2.23 (1H, m, CH), 2.10 - 1.96 (2H, m, CH), 1.95 - 1.67 (7H, m, CH), 1.64 - 1.47 (4H, m, CH); δ_C ($CDCl_3$): 96.5 (C-1), 85.7 (≡C), 80.5 (C), 72.5 (≡CH), 63.4 (C-2), 41.2 (CH), 40.0 (CH), 31.9 (CH), 25.4 (CH), 23.3 (CH), 22.8 (CH), 20.2 (CH): MS (CI): 212 ($[MNH_4]^+$, 21%), 195 ($[MH]^+$, 65), 169 (100), 102 (51), 85 (72).



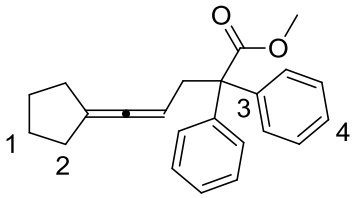
3-(1-((Tetrahydro-2H-pyran-2-yl)oxy)cyclopentyl)prop-2-yn-1-ol 4.27b. Prepared on a 42.0 mmol. scale, by the same method used to form **4.27a** and was isolated as a colourless oil (7.70 g, 82%) after purification by column chromatography. R_f = 0.30 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3412 (O-H), 2942 (C-H), 2870 (C-H); δ_H ($CDCl_3$): 5.05 (1H, t, *J* 3.9, H-1), 4.24 (2H, close AB, O-CH_2), 3.92 - 3.87 (1H, m, H-2), 3.61 - 3.43 (1H, m, H-2), 2.23 - 2.08 (1H, m, CH), 2.01 - 1.60 (9H, m, CH), 1.58 - 1.42 (4H, m, CH); δ_C ($CDCl_3$): 96.0 (C-1), 86.6 (≡C), 83.3 (≡*C*-CH_2), 80.6 (C), 63.0 (C-2), 50.6 (O-CH_2), 41.0 (CH), 40.2 (CH), 31.8 (CH), 25.4 (CH), 23.3 (CH), 22.8 (CH), 19.8 (CH); *m/z* (CI): 242 ($[MNH_4]^+$, 49%), 225 ($[MH]^+$, 4), 207 (50), 102 (100).



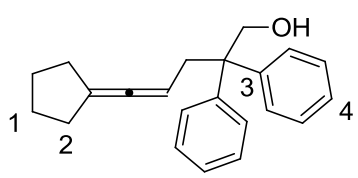
3-Cyclopentylideneprop-2-en-1-ol 4.25b. Prepared on a 22.3 mmol. scale using the general method for LAH reduction and was isolated as a colourless oil (2.10 g, 80%) after purification by column chromatography. R_f = 0.38 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3342 (O-H), 2953 (C-H), 2868 (C-H), 1962 (C=C=C), 1056 (C=C=C); δ_H ($CDCl_3$): 5.41 - 5.26 (1H, m, =CH), 4.12 (2H, close AB, O-CH_2), 2.49 - 2.34 (4H, m, H-2), 1.76 - 1.66 (4H, m, H-1), 1.53 (1H, t, *J* 5.6, OH); δ_C ($CDCl_3$): 195.8 (=C=), 107.2 (=C), 92.4 (=CH), 61.1 (O-CH_2), 31.4 (C-2), 27.0 (C-1); *m/z* (CI): 142 ($[MNH_4]^+$,48%), 124 ($[MH]^+$, 63), 102 (100), 52 (47).



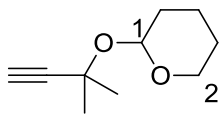
3-Cyclopentylideneallyl methanesulfonate 4.30b. Prepared on a 2.9 mmol. scale, by the same method used to form **4.30a**. **4.30b** was used immediately in the subsequent coupling step without further purification.



Methyl-5-cyclopentylidene-2,2-diphenylpent-4-enoate, **4.28b** was formed by Method B on a 7.4 mmol. as a colourless oil (2.19 g, 89%) after purification by column chromatography. R_f = 0.27 (hexanes:EtOAc, 3:1); ν_{max} /cm^{-1}: 2951 (C-H), 2867 (C-H), 1967 (C=C=C), 1730 (C=O), 1059 (C=C=C); δ_H ($CDCl_3$): 7.40 - 7.19 (10H, m, Ar), 4.90 - 4.82 (1H, m, =CH), 3.73 (3H, s, CH_3), 3.13 (2H, close AB, CH_2), 2.18 - 2.14 (4H, m, H-2), 1.68 - 1.53 (4H, m, H-1): δ_C ($CDCl_3$): 199.30 (=C=), 174.57 (C=O), 142.48 (C-3), 129.07 (Ar), 127.75 (Ar), 126.71 (C-4), 103.11 (=C), 87.02 (=CH), 60.49 (C), 52.33 (CH_3), 39.16 (CH_2), 30.77 (C-2), 26.90 (C-1). *m/z* (CI): 350 ([MNH_4]$^+$, 100), 333 ([MH]$^+$, 43), 187 (71), 122 (86); Anal. Calcd for $C_{23}H_{24}O_2$: C, 83.10%; H, 7.28%. Found: C, 83.05%, H, 7.31%.

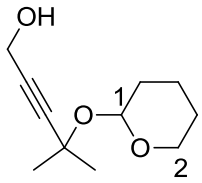


6- Cyclopentylidene-2,2-diphenylocta-4,5-dien-1-ol 4.23. Prepared on a 3.0 mmol. scale using the general method for LAH reduction and was isolated as a white solid (711.3 mg, 78%) after purification by column chromatography. R_f = 0.29 (hexanes:EtOAc, 10:1); mp: 56 - 61 °C; ν_{max} /cm^{-1}: 3325 (O-H), 3058 (C-H), 2953 (C-H), 2867 (C-H), 1967 (C=C=C), 1045 (C=C=C); δ_H ($CDCl_3$): 7.41 - 7.18 (12H, m, Ar), 4.81 - 4.72 (1H, m, CH), 4.24 (2H, close AB, O-CH_2), 2.92 (2H, d, *J* 7.6, CH_2), 2.39 - 2.18 (4H, m, H-2), 1.76 - 1.61 (4H, m, H-1), 1.33 - 1.27 (1H, m, OH); δ_C ($CDCl_3$): 198.9 (=C=), 145.2 (C=3), 128.3 (Ar), 128.2 (Ar), 126.4 (C-4), 103.1 (=C), 86.9 (=CH), 68.4 (O-CH_2), 52.2 (C), 37.4 (CH_2), 30.99 (C-2), 27.0 (C-1); *m/z* (CI): 322 ([MNH_4]$^+$, 75%), 305 ([MH]$^+$, 36), 287 (100), 240 (45); HRMS (CI) 305.1909 ([MH]$^+$, $C_{22}H_{25}O$ requires 305.1905); Anal. Calcd for $C_{22}H_{24}O$: C, 86.8%; H, 7.95%. Found: C, 86.63%, H, 8.14%.

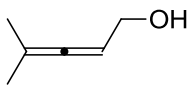


2-((2-Methylbut-3-yn-2-yl)oxy)tetrahydro-2H-pyran 4.26c. Prepared from 2-methylbut-3-yn-2-ol, on a 119.0 mmol. scale, by

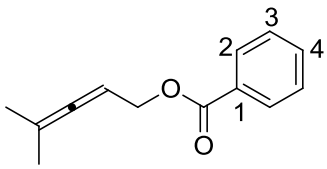
the same method used to form **4.26a** and was isolated as a colourless oil (12.40 g, 62%) after purification by distillation. bp: 70-78 °C, 6 torr (lit[155] 65-66°C, 8 torr); ν_{max}/cm^{-1}: 3426 (C=C), 2941 (C-H), 2870 (C-H); δ_H ($CDCl_3$): 5.10 - 5.08 (1H, m, H-1), 4.02 - 3.95 (1H, m, H-2), 3.56 - 3.51 (1H, m, H-2), 2.46 (1H, s, ≡CH), 1.92 - 1.86 (1H, m, CH), 1.78 - 1.70 (1H, m, CH), 1.58 (3H, s, CH_3), 1.61 - 1.55 (4H, m, CH), 1.54 (3H, s, CH_3); δ_C ($CDCl_3$): 96.0 (C-1), 86.2 (≡C), 71.9 (≡CH), 70.8 (C), 63.2 (C-2), 31.8 (CH), 30.5 (CH_3), 29.7 (CH_3), 25.3 (CH), 20.3 (CH); MS (CI): 186 ($[MNH_4]^+$, 8%), 169 ($[MH]^+$, 5), 102 (100), 85 (20).



4-Methyl-4-((tetrahydro-2H-pyran-2-yl)oxy)pent-2-yn-1-ol 4.27c. Prepared on a 60.0 mmol. scale, by the same method used to form **4.27a** and was isolated as a colourless oil (9.86 g, 83%) after purification by column chromatography. R_f = 0.23 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3427 (C=O), 2983 (C-H), 2940 (C-H), 2866 (C-H): δ_H ($CDCl_3$): 5.13 - 5.04 (1H, m, H-1), 4.32 (2H, close AB, O-CH_2), 4.05 - 3.92 (1H, m, H-2), 3.56 - 3.51 (1H, m, H-2), 2.06 (1H, s, OH), 1.91 - 187 (1H, m, CH), 1.76 - 172 (1H, m, CH), 1.61 - 1.53 (4H, m, CH), 1.56 (3H, s, CH_3), 1.51 (3H, s, CH_3); δ_C ($CDCl_3$): 95.8 (C-1), 86.2 (≡C), 82.3 (≡*C*-CH_2), 70.9 (C), 63.1 (C-2), 51.1 (O-CH_2), 31.9 (CH), 30.5 (CH_3), 29.9 (CH_3), 25.4 (CH), 20.3 (CH); *m/z* (CI): 216 ($[MNH_4]^+$, 23%), 199 ($[MH]^+$, 2), 181 (20), 102 (100).

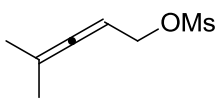


4-Methylpenta-2,3-dien-1-ol 4.25c. Prepared on a 30.3 mmol. scale using the general method for LAH reduction and was isolated as a colourless oil (2.76 g, 93%) after purification by column chromatography. R_f = 0.41 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3336 (O-H), 2982 (C-H), 2910 (C-H), 2870 (C-H), 1968 (C=C=C), 1075 (C=C=C); δ_H ($CDCl_3$: 5.23 (1H, m, =CH), 4.10 (2H, close AB, O-CH_2), 1.75 (3H, s, CH_3), 1.75 (3H, s, CH_3), 1.51 (1H, t, *J* 5.7, OH); δ_C ($CDCl_3$): 200.5 (=C=), 98.6 (=C), 90.0 (=CH), 61.0 (O=CH_2), 20.6 (CH_3); *m/z* (CI): 116 ($[MNH_4]^+$, 41%), 102 (100), 99 ($[MH]^+$, 20), 85 (68).

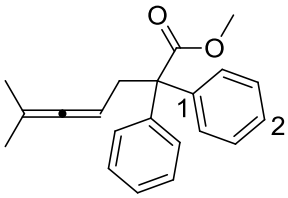


4-Methylpenta-2,3-dien-1-yl benzoate 4.29c. Prepared on a 27.6 mmol. scale, by the same method used to form **4.29c** and was isolated as a pale yellow oil (3.29 g, 59%)

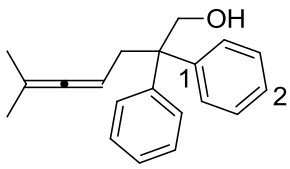
after column chromatography. R_f = 0.32 (hexanes:EtOAc, 10:1); ν_{max}/cm^{-1}: 2930 (CH), 2857 (C-H), 1965 (C=C=C), 1718 (C=O), 1054 (C=C=C); δ_H ($CDCl_3$): 8.10 - 8.07, (2H, m, H-2), 7.69 - 7.56 (1H, m, H-4), 7.55-7.43 (2H, m, H-3) 5.27 (1H, m, =CH), 4.8 (2H, close AB, O-CH_2), 1.70 (3H, d, *J* 2.7, CH_3) 1.69 (3H, d, *J* 2.7, CH_3); δ_C ($CDCl_3$): 203.5 (=C=), 166.6 (C=O), 130.7 (C-4), 130.1 (C-1), 129.8 (C-2), 128.5 (C-3), 97.7 (C-=C), 85.1 (=CH), 63.9 (O-CH_2), 20.5 (CH_3); *m/z* (CI): 220 ([MNH_4]$^+$, 100%), 203 ([MH]$^+$, 57).



4-Methylpenta-2,3-dien-1-yl methanesulfonate 4.30c. Prepared on a 2.9 mmol. scale, by the same method used to form **4.30c**. **4.30c** was used immediately in the subsequent coupling step without further purification.



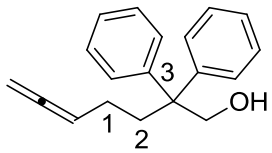
Methyl-6-methyl-2,2-diphenylhepta-4,5-dienoate 4.28c was formed by method A on a 15.8 mmol. scale and was isolated as a colourless oil (1.50 g, 47%) after purification by column chromatography. R_f = 0.25 (hexanes:EtOAc, 3:1); ν_{max} /cm^{-1}: 3030 (C-H), 2944 (C-H), 2982 (C-H), 1962 (C=C=C), 1728 (C=O), 1023 (C=C=C); δ_H ($CDCl_3$) 7.47 - 7.19 (10H, m, Ar), 4.79 - 4.72 (1H, m, =CH), 3.74 (3H, s, O-CH_3), 3.13 (2H, close AB, CH_2), 1.53 (3H, s, CH_3), 1.52 (3H, s, CH_3); δ_C ($CDCl_3$): 203.6 (=C=), 172.5 (C=O), 136.2 (C-1), 128.3 (Ar), 128.0 (Ar), 126.7 (C-2), 94.7 (=C), 83.5 (=CH), 63.9 (C), 57.1 (O-CH_3), 38.1 (CH_2), 20.3 (CH_3); *m/z* (ESI): 308 ([MH]$^+$, 100%), 251 (19), 191 (12); Anal. Calcd for $C_{21}H_{22}O$: C, 82.32%; H, 7.24%. Found: C, 2.12%, H, 7.32%.



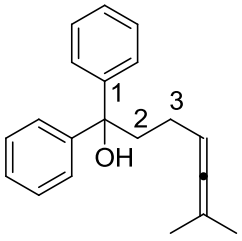
6-Methyl-2,2-diphenylocta-4,5-dien-1-ol 4.24. Prepared on a 3.26 mmol. scale using the general method for LAH reduction and was isolated as a white solid (453.1 mg, 50%) after purification by column chromatography. R_f = 0.22 (hexanes:EtOAc, 10:1); mp: 40-44 °C; ν_{max} /cm^{-1}: 3581 (O-H), 3463 (O-H), 2974 (C-H), 2928 (C-H), 2845 (C-H), 1971 (C=C=C), 1017 (C=C=C); δ_H ($CDCl_3$): 7.46 – 7.15 (10H, m, Ar), 4.74 - 4.54 (1H, m, =CH), 4.24 (2H, close AB, CH_2OH), 2.90 (2H, close AB, CH_2), 1.59 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.26 (1H, t, *J* 7.0, OH); δ_C ($CDCl_3$): 203.6 (=C=), 145.2 (C-1), 128.3 (Ar), 128.2 (Ar), 126.4 (C-2), 94.5 (=C),

84.4 (=CH), 68.4 (O-CH_2), 52.2 (C), 37.3 (CH_2), 20.4 (CH_3); *m/z* (CI): 296 ($[MNH_4]^+$, 100%), 279 ($[MH]^+$, 5), 261 (58), 240 (30); HRMS (CI) 296.2014 ($[MNH_4]^+$, $C_{20}H_{26}NO$ requires 296.2014); Anal. Calcd for $C_{20}H_{22}O$: C, 86.29%; H, 7.97%. Found: C, 86.21%, H, 7.84%.

Compounds prepared by other members of the group



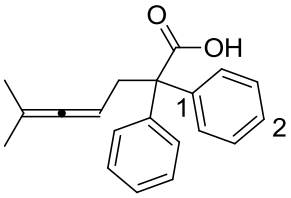
2,2-Diphenylhepta-5,6-dien-1-ol 4.35 was synthesed by the literature procedures of Widenhoefer.[45,58] ν_{max} /cm^{-1}: 3087 (O-H), 3055 (C-H), 2923 (C-H), 2879 (C-H), 1966 (C=C=C), 1087 (C=C=C); δ_H ($CDCl_3$): 7.48 - 7.02 (10H, m, Ar), 5.13 (1H, apparent p, *J* 6.8, =CH), 4.75 (1H, t, *J* 6.8, $=CH_2$), 4.74 (1H, t, *J* 6.8, $=CH_2$), 4.18 (2H, close AB, O-CH_2), 2.40 - 2.28 (2H, m, H-1), 1.89 - 1.71 (2H, m, H-2), 1.44 (1H, s, OH); δ_C ($CDCl_3$): 208.3 (=C=), 145.4 (C-3), 128.5 (Ar), 126.4 (C-4), 90.2 (=CH), 75.5 ($=CH_2$), 68.2 (O-CH_2), 51.9 (C), 35.5 (C-1), 23.1 (C-2); *m/z* (CI): 282 ($[MNH_4]^+$, 100%), 265 ($[MH]^+$, 25).



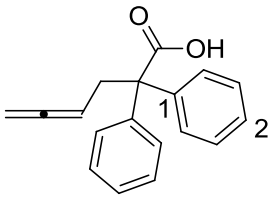
7-Methyl-1,1-diphenylocta-5,6-dien-1-ol 4.36 was synthesised by the literature procedure of Kolakowski.[156] Colourless oil; ν_{max} /cm^{-1}: 3473 (O-H), 2932 (C-H), 1965 (C=C=C), 1057 (C=C=C); δ_H ($CDCl_3$): 7.50 - 7.40 (4H, m, Ar), 7.37-7.31 (4H, m, Ar), 7.28 - 7.22 (2H, m, Ar), 5.02 (1H, ddd, *J* 9.2, 6.1, 3.0, CH), 2.46 - 2.35 (2H, m, H-2), 2.28 (1H, s, OH), 2.04 - 1.95 (2H, m, H-3), 1.71 (3H, s, CH_3), 1.70 (3H, s, CH_3); δ_C ($CDCl_3$): 201.5 (=C=), 147.0 (C-1), 128.1 (Ar), 126.8 (Ar), 126.1 (Ar), 88.6 (=C), 78.4 (=CH), 60.4 (C), 41.0 (C-2), 24.0 (C-3), 20.8 (CH_3); *m/z* (EI): 278 ($[MH]^+$, 20%), 222 (32), 180 (100).

General method for Hydrolysis[185]

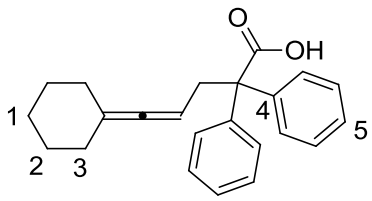
A mixture of the ester (10 mmol., 1 equiv) and KOH (100 mmol., 10 equiv) and EtOH (20 mL) was refluxed for 24 h. The reaction mixture was cooled, poured onto ice and acidified to pH 2 by the addition of 1 N HCl. The aqueous layer was washed with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (until pH 6-7), dried ($MgSO_4$) and concentrated under vacuum.



6-Methyl-2,2-diphenylocta-4,5-dienoic acid 4.31 was obtained as a white solid (2.80 g, 96%) after purification by column chromatography. R_f = 0.35 (hexanes:EtOAc, 3:1); mp: 98-101 ^oC; ν_{max} (thin film)/cm^{-1}: 3061 (C-H), 2972 (C-H), 2901 (C-H), 2849 (C-H), 1969 (C=C=C), 1694 (C=O), 1019 (C=C=C); δ_H ($CDCl_3$) 7.43 - 7.18 (10H, m, Ar), 4.82 - 4.61 (1H, m, =CH), 3.11 (2H, close AB, CH_2), 1.49 (3H, s, CH_3), 1.48 (3H, s, CH_3); δ_C ($CDCl_3$): 203.9 (=C=), 178.8 (C=O), 141.9 (C-1), 129.2 (Ar), 127.9 (Ar), 127.0 (C-2), 94.7 (=C), 84.4 (=CH), 60.3 (C), 38.9 (CH_2), 20.1 (CH_3); *m/z* (CI): 310 ($[MNH_4]^+$, 100%), 293 ($[MH]^+$, 4), 254 (40), 230 (17); HRMS (CI) 310.1812 (MNH_4^+, $C_{20}H_{24}NO_2$ requires 310.1807); Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16%; H, 6.69%. Found: C, 82.02%, H, 6.75%.

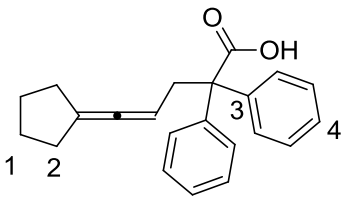


2,2-Diphenylhexa-4,5-dienoic acid 4.32 was obtained as a pale yellow solid (1.87 g, 71%) after purification by column chromatography. R_f = 0.15 (hexanes:EtOAc, 3:1); mp: 65 - 68 ^oC; ν_{max} (thin film)/cm^{-1}: 2889 (C-H), 1960 (C=C=C), 1694 (C=O), 1053 (C=C=C); δ_H ($CDCl_3$): 7.39 - 7.22 (10H, m, Ar), 4.89 (1H, apparent p, *J* 7.3, =CH), 4.52 - 4.36 (2H, m, $=CH_2$), 3.15 - 3.12 (2H, m, CH_2); δ_C ($CDCl_3$): 210.2 (=C=), 170.2 (C=O), 141.6 (C-1), 129.2 (Ar), 127.9 (Ar), 127.2 (C-2), 85.6 (=CH), 74.0 ($=CH_2$), 60.7 (C), 37.8 (CH_2); *m/z* (CI): 282 ($[MNH_4]^+$, 62%), 265 ($[MH]^+$, 2), 230 (100), 167 (13); HRMS (CI) 282.1493 ($[MNH_4]^+$, $C_{18}H_{22}NO_2$ requires 282.1494); Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79%; H, 6.10%. Found: C, 82.09%, H, 5.62%.



5-Cyclohexylidene-2,2-diphenylpent-4-enoic acid 4.33 was obtained as a pale yellow solid (3.22 g, 97%) after purification by column chromatography. R_f = 0.42 (hexanes:EtOAc, 3:1); mp: 156-160 ^oC; ν_{max} (thin film)/cm^{-1}: 2932 (C-H), 2855 (C-H), 1966 (C=C=C), 1697 (C=O), 1062 (C=C=C); δ_H ($CDCl_3$): 7.50 - 7.21 (10H, m, Ar), 4.84 - 4.66 (1H, m, =CH), 3.12 (2H, close AB, CH_2), 1.92 - 1.87 (4H, m, H-3), 1.50 - 1.42 (6H, m, H-2 and H-1); δ_C ($CDCl_3$): 200.6 (=C=), 179.6 (C=O), 142.0 (C-4), 129.2 (Ar), 127.8 (Ar), 127.0 (C-5), 102.0 (=C), 84.1 (=CH), 60.4 (C), 39.3 (CH_2), 31.0 (C-3), 27.3 (C-2), 26.1 (C-1); *m/z* (CI): 350 ($[MNH_4]^+$, 18%), 333 ($[MH]^+$, 3), 230 (100), 167 (14);

HRMS (CI) 333.1853 ($[MH]^+$, $C_{23}H_{25}O_2$ requires 333.1855); Anal. Calcd for $C_{23}H_{24}O_2$: C, 83.10%; H, 7.28%. Found: C, 82.92%, H, 7.37%.



5-Cyclopentylidene-2,2-diphenylpent-4-enoic acid 4.34 was obtained as a white solid (3.02 g, 95%) after purification by column chromatography. R_f = 0.22 (hexanes:EtOAc, 3:1); mp: 129-132 ^oC; ν_{max} (thin film)/cm^{-1}: 3057 (C-H), 2954 (C-H), 2920 (C-H), 2866 (C-H), 1962 (C=C=C), 1696 (C=O), 1034 (C=C=C); δ_H ($CDCl_3$): 7.44 - 7.21 (10H, m, Ar), 4.88 (1H, tt, *J* 7.4, 3.9, =CH), 3.14 (2H, close AB, CH_2), 2.18 - 2.12 (4H, m, H-2), 1.62 - 1.56 (4H, m, H-1); δ_C ($CDCl_3$): 199.6 (=C=), 178.1 (C=O), 141.9 (C-3), 129.2 (Ar), 127.9 (Ar), 127.0 (C-5), 103.4 (=C), 86.8 (=CH), 60.3 (C), 39.0 (CH_2), 30.7 (C-2), 26.9 (C-1); *m/z* (CI): 336 ($[MNH_4]^+$, 90%), 319 ($[MH]^+$, 31), 317 (100), 300 (91), 291 (78), 230 (57); HRMS (CI) 336.1964 (MNH_4^+, $C_{22}H_{26}NO_2$ requires 336.1964); Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99%; H, 6.96%. Found: C, 82.81%, H, 6.83%.

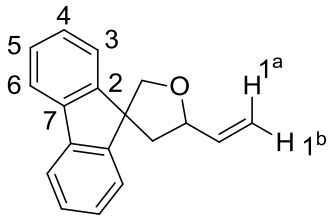
Typical procedure for catalytic reactions involving Ag Complexes:

A screw-cap vial was charged with a magnetic stir bar, Ag complex or salt (5-15 mol%) and the requisite substrate (0.1 mmol.). DCE (0.5 mL) was added and the reaction was stirred in the dark at room temperature. Conversions were monitored by TLC and/or NMR integration. Upon completion, the solvent was evaporated and the product purified by column chromatography.

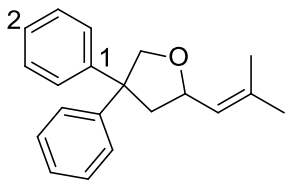
4,4-Diphenyl-2- vinyltetrahydrofuran 1.45:[45,68,131] from **1.44** as colourless oil using 5 mol% *β*-**4.16**-Ag as the catalyst (24 mg, 95%). R_f = 0.39 (hexanes:EtOAc, 20:1); HPLC conditions: Chirapak OJ-H column, 5 % IPA in *n*-hexane, 1.0 mL/min, t_R(major) = 16.6 min, t_R(minor) = 21.2 min; $[\alpha]_D^{25}$ = -30.6 ^{o} (c = 0.15, $CHCl_3$, 28% ee obtained with *β*-**4.16**-Ag). Lit.[68] $[\alpha]_D^{28}$ = -110.4 (c = 0.39 in $CHCl_3$, 87% ee, *S*-isomer).

2-(Cyclohexylidenemethyl)-4,4-diphenyltetrahydrofuran 3.19:[68] Isolated from **3.17** as colourless oil using 15 mol% *R,R*-**4.11**-Ag as the catalyst (32 mg, 99%). R_f = 0.31; HPLC conditions: Chirapak AD-H column, 0.5% IPA in *n*-hexane, 1.0 mL/min,

t_R(minor) = 14.6 min, t_R(major) = 21.2 min,; $[\alpha]_D^{25}$ = -67.5° (c = 0.24, $CHCl_3$, 73% ee with *R,R*-**4.11**-Ag). Lit.[68] $[\alpha]_D^{28}$ = -82.7 (c = 0.25 in $CHCl_3$, 75% ee, *S* isomer).

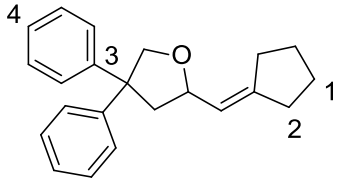


5'-Vinyl-4',5'-dihydro-2'H-spiro[fluorene-9,3'-furan] 4.37: Isolated from **4.18** as a white solid using 15 mol% AgTFA as the catalyst (23, 92%). mp: 40-42 °C; R_f = 0.7 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 2972 (C-H), 2855 (C-H); δ_H ($CDCl_3$): 7.77 - 7.73 (2H, m, H-3), 7.63 - 7.59 (1H, m, H-4), 7.57 - 7.55 (1H, m, H-4), 7.44 -7.33 (4H, m, H-5 and H-6), 6.17 (1H, ddd, *J* 17.0, 10.3, 6.2, =CH), 5.47 (1H, dt, *J* 17.0, 1.2, H-1^a), 5.29 (1H, dt, *J* 10.3, 1.2, H-1^b), 5.01 - 4.90 (1H, m, CH), 4.23 (1H, d, *J* 8.6, O-CH_2), 4.05 (1H, d, *J* 8.6, O-CH_2), 2.54 (1H, dd, *J* 13.2, 7.2, CH_2), 2.35 (1H, dd, *J* 13.2, 8.8, CH_2); δ_C ($CDCl_3$): 150.2 (C-2), 149.4 (C-2), 134.0 (C-7), 139.8 (C-7), 138.4 (=CH), 127.8 (C-5 and C-6), 127.8 (C-5 and C-6), 127.5 (C-5 and C-6), 123.3 (C-4), 123.1 (C-4), 119.9 (C-3), 119.8 (C-3), 116.0 (=CH_2), 81.3 (CH), 77.7 (O-CH_2), 58.3 (C), 45.4 (CH_2); *m/z* (CI): 266 ($[MNH_4]^+$, 100%), 248 ($[MH]^+$, 34), 231 (29), 218 (35); HRMS (CI) 266.1545 ($[MH]^+$, $C_{18}H_{20}NO$ requires 266.1545); Anal. Calcd for $C_{18}H_{16}O$: C, 87.06%; H, 6.49%. Found: C, 87.12%, H, 6.53%. Enantiomers could not be resolved by HPLC or GC analysis.



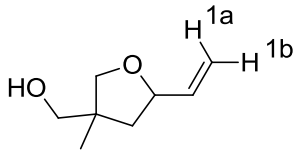
2-(2-Methylprop-1-en-1-yl)-4,4-diphenyltetrahydrofuran 4.39: Isolated from **4.24** as colourless oil using 5 mol% *β*-**4.16**-Ag as the catalyst (28 mg, 96%). R_f = 0.68 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3060 (C-H), 3025 (C-H), 2919 (C-H), 2860 (C-H); δ_H ($CDCl_3$) 7.54 - 7.11 (10H, m, Ar), 5.36 - 5.27 (1H, m, =CH), 4.76 (1H, td, *J* 9.2, 6.0, CH), 4.65 (1H, dd, *J* 8.6, O-CH_2), 4.20 (1H, d, *J* 8.6, O-CH_2), 2.67 (1H, ddd, *J* 12.4, 6.0, 1.0, CH_2), 2.41 (1H, dd, *J* 12.4, 9.2, CH_2), 1.76 (3H, d, *J* 1.0, CH_3), 1.67 (3H, d, *J* 1.0, CH_3); δ_C ($CDCl_3$): 146.3 (C-1), 146.2 (C-1), 136.4 (=C), 128.4 (Ar), 128.4 (Ar), 127.2 (Ar), 126.4 (C-2), 126.3 (C-2), 125.8 (=CH), 76.9 (O-CH_2) 75.2 (CH), 56.3 (C), 45.5 (CH_2), 25.9 (CH_3), 18.2 (CH_3); *m/z* (CI): 296 ($[MNH_4]^+$, 100%), 279 ($[MH]^+$, 22), 261 (61), 240 (72); HRMS (CI) 296.2010 ($[MH]^+$, $C_{20}H_{23}O$ requires 296.2014); Anal. Calcd for $C_{20}H_{22}O$: C, 86.29%; H, 7.97%. Found: C, 86.20, H, 7.86%; HPLC conditions: Chirapak AD-H column, 2% IPA in *n*-hexane, 1.0 mL/min, t_R(minor) = 7.4 min, t_R(major) = 8.9 min;

$[\alpha]_D^{25}$ = -25.0^o (c = 0.22 in $CHCl_3$, 36% ee obtained with *β*-**4.16**-Ag). Lit.[68] $[\alpha]_D^{28}$ = -74.9 (c = 0.36 in $CHCl_3$, 70% ee, *S*-isomer).



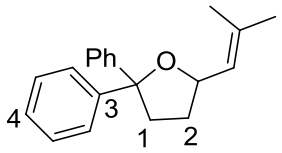
2-(Cyclopentylidenemethyl)-4,4-diphenyltetrahydrofuran 4.40: Isolated from **4.23** as white solid using 15 mol% *R,R*-**4.11**-Ag as the catalyst (30 mg, 98%). mp: 52-55 ^oC; R_f = 0.79 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3024 (C-H), 2949 (C-H), 2850 (C-H); δ_H ($CDCl_3$): 7.38 - 7.18 (10H, m, Ar), 5.45 - 5.36 (1H, m, =CH), 4.71 - 4.60 (2H, m, CH and O-CH_2), 4.20 (1H, d, *J* 8.8, O-CH_2), 2.69 (1H, dd, *J* 12.0, 6.0, CH_2), 2.42 (1H, dd, *J* 12.0, 9.6, CH_2), 2.36 - 2.12 (4H, m, H-2), 1.72 - 1.57 (4H, m, H-1); δ_C ($CDCl_3$): 147.9 (=C), 146.3 (C-3), 146.2 (C-3), 128.39 (Ar), 128.34 (Ar), 127.2 (Ar), 126.4 (C-4), 126.2 (C-4), 120.9 (=CH), 76.8 (O-CH_2), 56.3 (CH), 45.2 (C), 33.8 (CH_2), 28.8 (C-2), 26.3 (C-2), 25.9 (C-1); *m/z* (CI): 322 ($[MNH_4]^+$, 100%), 305 ($[MH]^+$, 82), 287 (74), 240 (49); HRMS (CI) 305.1903 ($[MH]^+$, $C_{22}H_{25}O$ requires 305.1905); Anal. Calcd for $C_{22}H_{24}O$: C, 86.80%; H, 7.95%. Found: C, 86.40%, H, 8.13%; HPLC conditions: Chirapak AD-H column, 2% IPA in *n*-hexane, 1.0 mL/min, t_R(minor) = 8.1 min, t_R(major) = 9.6 min; $[\alpha]_D^{25}$ = –45.5^o (c = 0.56, $CHCl_3$, 41% ee with *R,R*-**4.11**-Ag), tentatively assigned *S* by analogy.

3-Vinyl-2-oxaspiro[4.5]decane, 3.22: Isolated from **3.18** as colourless oil using 15 mol% AgTFA as the catalyst (13 mg, 76%). R_f = 0.28 (hexanes:EtOAc, 3:1); Enantiomers could not be resolved by HPLC or GC analysis.

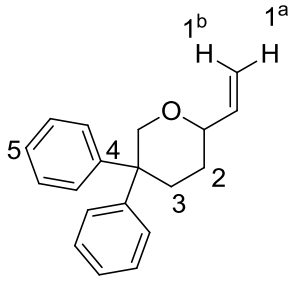


(3 -Methyl-5-vinyltetrahydrofuran-3-yl)methanol 4.38:[186] Isolated from **4.19** as colourless oil ia a 2:1 ratio of cis to trans isomers using 5 mol% *β*-**4.16**-Ag as the catalyst (14 mg, 96%).R_f = 0.6 (petrolum ether:Et_2O, 1:1); ν_{max}/cm^{-1}: 3325 (O-H), 1678, 1427, 1382; δ_H ($CDCl_3$): *Cis* isomer 5.89 (1H, ddd, *J* 17.1, 10.3, 6.6, =CH), 5.23 (1H, dt, *J* 17.1, 1.4, H-1^a), 5.09 (1H, dt, *J* 10.3, 1.4, H-1^b), 4.47 - 4.36 (1H, m, CH), 3.87 (1H, d, *J* 8.7, O-CH_2), 3.55 - 3.48 (2H, m, CH_2OH), 3.44 (1H, d, *J* 8.7, O-CH_2), 1.80 (1H, dd, *J* 12.8, 7.2, CH_2), 1.62 (1H, dd, *J* 12.8, 8.7, CH_2), 1.15 (3H, s, CH_3); δ_C ($CDCl_3$): 138.5 (=CH), 113.6 (=CH_2), 79.9 (O-CH_2), 76.1 (CH), 69.7 (CH_2OH), 45.6 (CH_2), 42.1 (C), 21.8 (CH_3). *Trans* isomer 5.89 (1H, ddd, *J* 17.1,

10.3, 6.6, =CH), 5.21 (1H, dt, *J* 17.1, 1.4, H-1^a), 5.07 (1H, dt, *J* 10.3, 1.4, H-1^b), 4.47 – 4.36 (1H, m, CH), 3.74 (1H, d, *J* 8.7, O-CH_2), 3.57 (1H, d, *J* 8.7, O-CH_2), 3.55 - 3.48 (2H, m, CH_2OH), 2.11 (1H, dd, *J* 12.8, 7.2, CH_2), 1.45 (1H, dd, *J* 12.8, 8.7, CH_2), 1.14 (3H, s, CH_3); δ_C ($CDCl_3$): 139.0 (=CH), 144.4 (=CH_2), 80.3 (O-CH_2), 74.2 (CH), 68.8 (CH_2OH), 45.2 (CH_2), 42.4 (C), 21.8 (CH_3); *m/z* (EI): 142 ([M]$^+$, 22%), 129 (49), 91 (37), 47 (28); HPLC conditions: Chirapak OJ-H column, 10% IPA in *n*-hexane, 1.0 mL/min, t_R(major) = 16.3 and 17.6 min, t_R(minor) = 27.5 and 34.4 min; Optical purity was too low (4,4%) for accurate determination of $[\alpha]_D$.

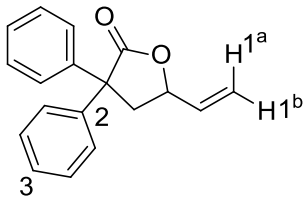


2-(2-Methylprop-1-en-1-yl)-4,4-diphenyltetrahydrofuran 4.41: Isolated from **4.36** as a white solid using 5 mol% *β*-**4.16**-Ag as the catalyst (26 mg, 95%). mp: 51-52 ^oC; R_f = 0.83 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3062 (C-H), 3028 (C-H), 2921 (C-H), 2865 (C-H); δ_H ($CDCl_3$): 7.57 - 7.44 (4H, m, Ar), 7.32 (4H, m, Ar), 7.27 - 7.15 (2 H, m, Ar), 5.41 (1H, dq, *J* 8.4, 1.2, =CH), 4.85 (1H, dd, *J* 14.9, 8.4, CH), 2.81 - 2.55 (2H, m, H-1), 2.17 - 2.01 (1H, m, H-2), 1.80 (3H, s, CH_3), 1.78 (3H, s, CH_3), 1.73 (4H, m, CH_3 and H-2); δ_C ($CDCl_3$): 147.3 (C-3), 146.9 (C-3), 135.5 (=C), 128.2 (Ar), 128.0 (Ar), 126.6 (Ar), 126.5 (Ar), 126.4 (Ar), 126.01 (=CH), 125.95 (Ar), 87.9 (C), 75.9 (CH), 39.4 (C-1), 32.7 (C-2), 25.9 (CH_3), 18.3 (CH_3); *m/z* (EI): 278 ([MH]$^+$, 15%), 222 (41), 180 (100); HRMS (EI) 278.3852 ([M]$^+$, $C_{20}H_{22}O$ requires 278.3856); Anal. Calcd for $C_{20}H_{22}O$: C, 86.29%; H, 5.75%. Found: C, 86.34%, H, 5.82%. HPLC conditions: Chirapak OJ-H column, 1% IPA in *n*-hexane, 0.5 mL/min, t_R(major) = 40.3 min, t_R(minor) = 46.5 min; $[\alpha]_D^{25}$ = +15.0^o (c = 0.1, $CHCl_3$, 43% ee with *β*-**4.16**-Ag), tentatively assigned *S* by analogy.

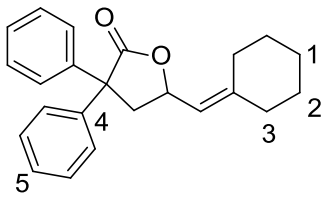


5,5-Diphenyl-2-vinyltetrahydro-2H-pyran 4.42: Isolated from **4.35** as a colourless oil using 5 mol% *β*-**4.16**-Ag as the catalyst (26 mg, 98%). R_f = 0.82 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 2952 (C-H), 1732, 1486, 1251; δ_H ($CDCl_3$): 7.51-7.18 (10H, m, Ar), 5.88 (1H, ddd, *J* 17.0, 10.4, 5.6, =CH), 5.19 (1H, dd, *J* 17.0, 1.5, H-1^a), 5.10 (1H, dd, *J* 10.4, 1.5, H-1^b), 4.69 (1H, dd, *J* 12.1, 2.4, CH), 4.04 - 3.93 (1H, m, O-CH_2), 3.64 (1H, d, *J* 12.1, O-CH_2), 2.64 - 2.39 (2H, m, H-3), 1.63 (1H, m, H-2), 1.46-1.31 (1H, m, H-2); δ_C ($CDCl_3$): 146.0 (C-4), 145.7 (C-4), 138.9 (=CH), 128.9 (Ar), 128.3 (Ar), 128.0 (Ar),

127.0 (Ar), 126.3 (C-5), 125.7 (C-5), 115.3 (=C), 78.4 (CH), 74.7 (O-CH_2), 45.8 (C), 34.5 (C-3), 28.0 (C-2); *m/z* (CI): 283 ($[MNH_4]^+$, 100%), 265 ($[MH]^+$, 35); HPLC conditions: Chirapak AD-H column, 2% IPA in *n*-hexane, 1.0 mL/min, t_R(minor) = 5.2 min, t_R(major) = 6.1 min; $[\alpha]_D^{25}$ = +24.0^o (c =1.0, $CHCl_3$, 19% with *β*-**4.16**-Ag). Assigned *S* by comparison of HPLC data reported.[45]

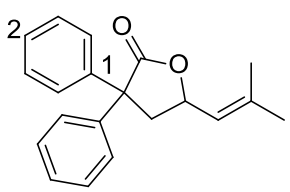


3,3-Diphenyl-5-vinyldihydrofuran-2(3H)-one 4.43: Isolated from **4.32** as a colourless oil using 5 mol% *β*-**4.16**-Ag as the catalyst (25 mg, 96%). R_f = 0.46 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3060 (C-H), 3024 (C-H), 2939 (C-H), 1767 (C=O); δ_H ($CDCl_3$): 7.49 - 7.21 (10H, m, Ar), 5.96 (1H, ddd, *J* 17.2, 10.4, 6.4, =CH), 5.45 (1H, d, *J* 17.2, H-1^a), 5.34 (1H, d, *J* 10.4, H-1^b), 4.88 - 4.74 (1 H, m, CH, 3.14 (1 H, dd, *J* 13.0, 5.0, CH_2), 2.79 (1 H, dd, *J* 13.0, 10.4, CH_2); δ_C ($CDCl_3$): 176.9 (C=O), 141.7 (C-2), 139.7 (C-2), 135.0 (=C), 129.0 (Ar) 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 127.4 (C-3), 127.3 (C-3), 118.9 (=CH), 77.5 (CH), 58.1 (C), 43.8 (CH_2); *m/z* (CI): 282 ($[MNH_4]^+$, 100%), 265 ($[MH]^+$, 10), 220 (14); HRMS (CI) 265.1222 ($[MH]^+$, $C_{18}H_{17}O_2$ requires 265.1229); Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79%; H, 6.10%. Found: C, 82.00%, H, 5.64%. HPLC conditions: Chirapak OD-H column, 5% IPA in *n*-hexane, 1.0 mL/min, t_R(major) = 8.1 min, t_R(minor) = 9.7 min; $[\alpha]_D^{25}$ = -10.0^o (c = 0.45, $CHCl_3$, 23% ee with *β*-**4.16**-Ag).

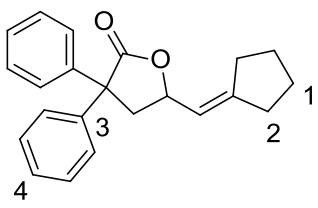


5-(Cyclohexylidenemethyl)-3,3-diphenyldihydrofuran-2(3H)-one 4.44: Isolated from **4.33** as a white solid using 5 mol% *β*-**4.16**-Ag as the catalyst (32 mg, 96%). mp: 94-97 ^{o}C; R_f = 0.65 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3067 (C-H), 2924 (C-H), 2853 (C-H), 1754 (C=O); δ_H ($CDCl_3$): 7.51 - 7.21 (10H, m, Ar), 5.26 - 5.23 (1H, m, =CH), 5.13 (1H, ddd, *J* 10.5, 8.6, 4.8, CH), 3.07 (1H, dd, *J* 13.2, 4.8, CH_2), 2.73 (1H, dd, *J* 13.2, 10.5, CH_2), 2.30 - 2.04 (4H, m, H-3), 1.69 - 1.47 (6H, m, H-1 and H-2); δ_C ($CDCl_3$): 177.3 (C=O), 148.6 (=C), 142.2 (C-4), 139.8 (C-4), 129.0 (Ar), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 127.4 (C-5), 127.2 (C-5), 118.9 (=CH), 73.3 (CH), 58.3 (CH_2), 44.6 (C-3), 37.0 (C-3), 29.6 (C-2), 28.2 (C-2), 27.8 (C-1), 26.5 (C-1); *m/z* (CI): 350 ($[MNH_4]^+$, 59%), 333 ($[MH]^+$, 9), 269 (30), 102 (100); HRMS (CI) 333.1852 ($[MH]^+$, $C_{23}H_{25}O_2$ requires 333.1855); Anal. Calcd for $C_{23}H_{24}O_2$: C, 83.10%; H, 7.28%. Found: C, 82.88%, H, 7.34%. HPLC conditions: Chirapak OD-H

column, 5% IPA in *n*-hexane, 1.0 mL/min, t_R(major) = 6.5 min, t_R(minor) = 13.6 min; $[\alpha]_D^{25}$ = -44.4^o (c = 0.4, $CHCl_3$, 24% ee with *β*-**4.16**-Ag).

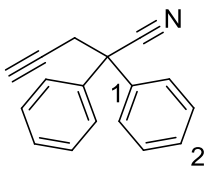


5-(2-Methylprop-1-en-1-yl)-3,3-diphenyldihydrofuran-2(3H)-one 4.45: Isolated from **4.31** as a colourless oil using 5 mol% *β*-**4.16**-Ag as the catalyst (27 mg, 98%). R_f = 0.5 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3060 (C-H), 3024 (C-H), 2917 (C-H), 1762 (C=O); δ_H ($CDCl_3$): 7.77 - 6.92 (10H, m, Ar), 5.49 - 5.22 (1H, m, =CH), 5.08 (1H, ddd, *J* 10.6, 8.4, 4.8, CH), 3.09 (1H, dd, *J* 13.2, 4.8, CH_3), 2.72 (1H, dd, *J* 13.2, 10.6, CH_2), 1.81 (3H, d, *J* 1.2, CH_3), 1.72 (3H, d, *J* 1.2, CH_3); δ_C ($CDCl_3$): 177.2 (C=O), 142.2 (C-1), 140.8 (=C), 139.7 (C-1), 128.9 (Ar), 128.3 (Ar), 127.7 (Ar), 127.4 (C-2), 127.1 (C-2), 122.1 (=CH), 74.0 (CH), 58.2 (C), 44.2 (CH_2), 25.8 (CH_3), 18.6 (CH_3); *m/z* (CI): 310 ($[MNH_4]^+$, 100%), 293 ($[MH]^+$, 22), 248 (19); HRMS (CI) 293.1550 ($[MH]^+$, $C_{20}H_{21}O_2$ requires 293.1542); Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16%; H, 6.89%. Found: C, 82.01, H, 6.73%; HPLC conditions: HPLC conditions: Chirapak 5% IPA in *n*-hexane, OD-H, 1.0 mL/min, t_R(major) = 7.1 min, t_R(minor) = 13.1 min; $[\alpha]_D^{25}$ = -17.4^o (c = 0.27, $CHCl_3$, 18% ee with *β*-**4.16**-Ag).

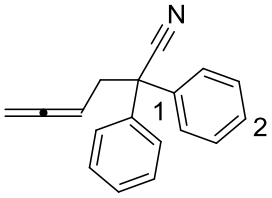


5-(Cyclopentylidenemethyl)-3,3-diphenyldihydrofuran-2(3H)-one 4.46: Isolated from **4.34** as a white solid using 5 mol% *β*-**4.16**-Ag as the catalyst (31 mg, 98%). mp: 93-95 ^{o}C; R_f = 0.57 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3060 (C-H), 2964 (C-H), 2858 (C-H), 1752 (C=O); δ_H ($CDCl_3$): 7.49 - 7.22 (10 H, m, Ar), 5.48 - 5.34 (1H, m, =CH), 4.98 (1H, ddd, *J* 10.4, 8.8, 4.8, CH), 3.10 (1H, dd, *J* 13.2, 4.8, CH_2), 2.73 (1H, dd, *J* 13.2, 10.4, CH_2), 2.49 - 2.13 (4H, m, H-2), 1.83 - 1.55 (4H, m, H-1); δ_C ($CDCl_3$): 177.2 (C=O), 152.5 (=C), 142.26 (C-3), 139.8 (C-3), 129.0 (Ar), 128.4 (Ar), 127.74 (Ar), 127.69 (Ar), 127.4 (C-4), 127.2 (C-4), 117.3 (=CH), 75.6 (CH), 58.2 (C), 44.1 (CH_2), 34.0 (C-2), 29.2 (C-2), 26.2 (C-1), 25.9 (C-1); *m/z* (CI): 336 ($[MNH_4]^+$, 100%), 319 ($[MH]^+$, 13), 274 (8), 102 (29); HRMS (CI) 319.1693 ($[MH]^+$, $C_{22}H_{23}O_2$ requires 319.1698); Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99%; H, 6.96%. Found: C, 82.82%, H, 6.82%. HPLC conditions: Chirapak OD-H column, 5% IPA in *n*-hexane, OD-H, 1.0 mL/min, t_R(major) = 7.7 min, t_R(minor) = 13.7 min; $[\alpha]_D^{25}$ = -12.7^o (c = 0.3, $CHCl_3$, 15% ee with *β*-**4.16**-Ag).

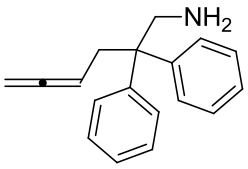
7.4 Compounds Used in Chapter 5



2,2-Diphenylpent-4-ynenitrile 5.7. Prepared on a 51.8 mmol. scale using the general method for propargylation and was isolated as a yellow oil (11.08 g, 93%) after purification by column chromatography. R_f = 0.30 (hexanes:EtOAc, 10:1); ν_{max}/cm^{-1}: 3055 (C-H), 3023 (C-H), 2929 (C-H), 2235 (C≡N); δ_H ($CDCl_3$): 7.60 - 7.24 (10H, m, Ar), 3.29 (2 H, d, *J* 2.6, CH_2), 2.17 (1 H, t, *J* 2.6, ≡CH); δ_C ($CDCl_3$): 138.9 (C-1), 128.9 (Ar), 128.4 (Ar), 127,1 (C-2), 121.6 (C≡N), 78.3 (≡C), 73.3 (≡CH), 51.2 (C), 30.9 (CH_2); *m/z* (EI): 231 ([M]$^+$, 12), 192 (100), 165 (72).

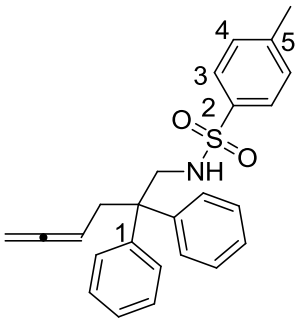


2,2-Diphenylhexa-4,5-dienenitrile 5.8. Prepared on a 38.7 mmol. scale using the general method for the Crabbè reaction and was isolated as a yellow oil (8.58 g, 73%). R_f = 0.26 (hexanes:EtOAc, 1:20); ν_{max}/cm^{-1}: 3059 (C-H), 2987 (C-H), 2236 (C≡N), 1953 (C=C=C), 1018 (C=C=C); δ_H ($CDCl_3$): 7.45 - 7.31 (10H, m, Ar), 5.12 - 5.01 (1H, m, =CH), 4.70 (1H, t, *J* 2.5, =CH_2), 4.69 (1H, t, *J* 2.5, =CH_2), 3.14 (2H, dt, *J* 7.5, 2.5, CH_2); δ_C ($CDCl_3$): 210.5 (=C=), 139.5 (≡C), 128.9 (C-1), 128.0 (Ar), 127.1 (Ar), 121.9 (C-2), 84.5 (=CH), 75.4 (=CH_2), 52.0 (C), 39.4 (CH_2); *m/z* (CI) : 263 ([MNH_4]$^+$, 100%), 245 ([MH]$^+$, 8).

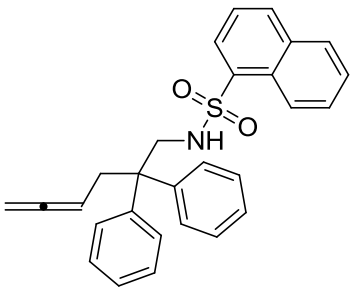


2,2-Diphenylhexa-4,5-dien-1-amine 5.5.[37] of DIBAL-H (1 M in toluene, 20.00 mL, 20.0 mmol.) was added to a solution of **5.8** (3.26 g, 13.3 mmol.) in Et_2O (100 mL) at -42 °C over 30 min and stirred for 3 h. $NaBH_4$ (1.52 g, 40.2 mmol.) was then added in one portion, followed by slow addition of EtOH (100 mL) over 30 min. Vigorous stirring of the mixture was maintained for 3 h at 0 °C, before it was diluted with Et_2O (75 mL), and washed with sat. aq. K_2CO_3 (2 x 75 mL). The layers were separated and the organic layer was extracted with further portions of 1 M HCl (3 x 75 mL). The combined acidic extracts were rendered basic (pH ≥ 13) by the addition of 15% aq. NaOH (75 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give **5.5** as a pale yellow oil (5.4 g, 66%). This was used in subsequent reactions without further purification.

Typical procedure for the preparation of the sulfonamide derivatives 5.4a and 5.10a-d:[159] The requisite sulfonyl chloride (2.0 mmol., 1.0 equiv) was added slowly to a solution of **5.5** (2.0 mmol., 1.0 equiv) and triethylamine (0.79 mL, 2.0 mmol., 1.0 equiv) in CH_2Cl_2 (25 mL) at 0 ^oC. The mixture was allowed to stir for 4 h, before the reaction was quenched by the addition of H_2O (15 mL). The resulting suspension was diluted with CH_2Cl_2 (30 mL), washed with 1N HCl (3 x 15 mL) and H_2O (15 mL). The combined organic extracts were then washed with brine (15 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was then purified by column chromatography.

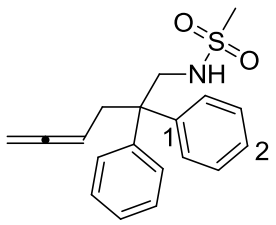


N-(2,2-diphenylhexa-4,5-dien-1-yl)-4-methylbenzene Sulfonamide 5.4a[103] was obtained as a white solid (790 mg, 98%). R_f = 0.23 (hexanes:EtOAc, 5:1); mp: 89-92 ^oC; ν_{max}/cm^{-1}: 3251 (N-H), 2969 (C-H), 2882 (C-H), 1958 (C=C=C), 1325 (S=O), 1159 (S=O), 1023 (C=C=C); δ_H ($CDCl_3$): 7.64 - 7.61 (2H, m, H-3), 7.36 - 7.19 (10H, m, Ar), 7.09 (2H, m, H-4), 4.72 - 4.59 (1H, m, =CH), 4.51 (1H, t, *J* 2.4, $=CH_2$), 4.50 (1H, t, *J* 2.4, $= CH_2$), 3.88 (1H, t, *J* 6.5, NH), 3.61 (2H, d, *J* 6.5, N-CH_2), 2.90 (2H, dt, *J* 7.8, 2.4, CH_2), 2.46 (3H, s, CH_3); δ_C ($CDCl_3$): 209.9 (=C=), 144.2 (C-1), 143.5 (C-2), 136.3 (C-5), 129.7 (C-4), 128.4 (Ar), 127.9 (Ar), 127.1 (Ar), 126.8 (Ar), 84.6 (=CH), 74.1 ($=CH_2$), 50.1 (N-CH_2), 49.6 (C), 36.9 (CH_2), 21.6 (CH_3); *m/z* (ESI) : 404 ($[MH]^+$, 100%); HRMS (ESI) 404.5410 ($[MH]^+$, $C_{25}H_{25}N_2O_2S$ requires 404.5417); Anal. Calcd for $C_{25}H_{25}N_2O_2S$: C, 74.41%; H, 6.24%; N, 3.47%. Found: C, 74.56%, H, 6.28%, N, 3.46%.

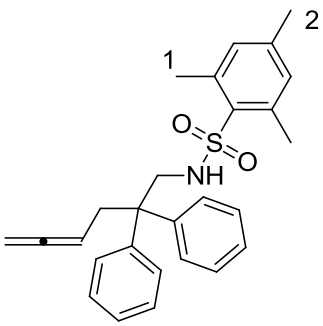


N-(2,2-diphenylhexa-4,5-dien-1-yl)naphthalene-1-sulfonamide 5.10a was obtained as a white solid (843 mg, 96%). R_f = 0.43 (hexanes:EtOAc, 3:1); mp: 78 - 80 ^oC; ν_{max}/cm^{-1}: 3271 (N-H), 3028 (C-H), 2932 (C-H), 1955 (C=C=C), 1317 (S=O), 1155 (S=O), 1072 (C=C=C); δ_H ($CDCl_3$) 8.31 - 8.23 (2H, m, Ar), 8.10 (1H, d, *J* 8.3, Ar), 7.96 (1H, d, *J* 7.7, Ar), 7.68 - 7.48 (3H, m, Ar), 7.19 - 7.13 (6H, m, Ar), 6.99 - 6.96 (4H, m, Ar), 4.54 - 4.41 (1H, m, =CH), 4.42 - 4.35 (2H, m, $=CH_2$), 4.16 (1H, t, *J* 6.4, NH), 3.55 (2H, d, *J* 6.4, N-CH_2), 2. 76 (2H, dt, *J* 7.6, 2.5, CH_2); δ_C

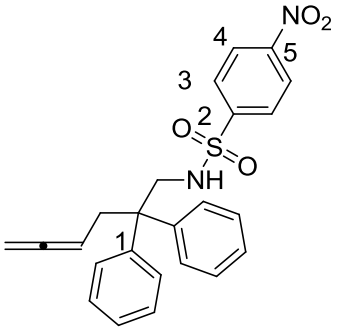
($CDCl_3$): 209.7 (=C=), 144.0 (Ar), 134.4 (Ar), 134.2 (Ar), 133.7 (Ar), 129.9 (Ar), 129.1 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.1 (Ar), 127.7 (Ar), 126.8 (Ar), 124.1 (Ar), 124.0 (Ar), 84.5 (=CH), 74.0 (=CH_2), 50.0 (N-CH_2), 49.7 (C), 36.8 (CH_2); *m/z* (CI): 457 ($[MNH_4]^+$ 100%), 440 ($[MH]^+$, 32), 250 (44); HRMS (ESI) 440.1693 ($[MH]^+$, $C_{28}H_{26}NO_2S$ requires 440.1684); Anal. Calcd for $C_{28}H_{25}NO_2S$: C, 76.51%; H, 5.73%; N, 3.19%. Found: C, 76.64%, H, 5.69%, N, 3.11%.



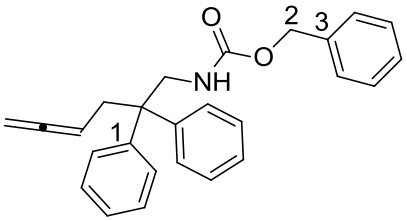
N-(2,2-diphenylhexa-4,5-dien-1-yl)methanesulfonamide 5.10b was obtained as a white solid (621 mg, 95%). R_f = 25 (hexanes:EtOAc, 3:1); mp: 58-64 ^oC; ν_{max}/cm^{-1}: 3301 (N-H), 3058 (C-H), 2940 (C-H), 1954 (C=C=C), 1323 (S=O), 1134 (S=O), 1027 (C=C=C); δ_H ($CDCl_3$): 7.38 - 7.17 (10H, m, Ar), 4.71 - 4.64 (1H, m, =CH), 4.64 - 4.59 (2 H, m, =CH_2), 3.91 - 3.86 (2 H, m, N-CH_2), 2.95 (2 H, dt, *J* 7.7, 2.6, CH_2), 2.70 (3H, s, CH_3); δ_C ($CDCl_3$): 209.8 (=C=), 144.5 (C-1), 128.5 (Ar), 127.9 (Ar), 126.9 (C-2), 84.9 (=CH_2), 74.5 (=CH), 50.1 (C), 49.8 (N-CH_2), 40.1 (CH_3), 36.6 (CH_2); *m/z* (CI): 345 ($[MNH_4]^+$, 100%); HRMS (ESI): 328.1363 ($[MH]^+$, $C_{19}H_{22}NO_2S$ requires 328.1371); Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.69%; H, 6.46%; N, 4.28%. Found: C, 69.73%, H, 6.51%, N, 4.17%.



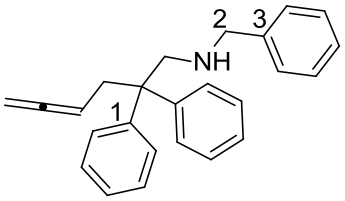
N-(2,2-diphenylhexa-4,5-dien-1-yl)-2,4,6-trimethylbenzenesulfonamide 5.10c was obtained as a white solid (828 mg, 96%). R_f = 0.57 (hexanes:EtOAc, 3:1); mp: 95-98 ^oC; ν_{max}/cm^{-1}: 3315 (N-H), 3025 (C-H), 2928 (C-H), 1958 (C=C=C), 1322 (S=O), 1157 (S=O), 1057 (C=C=C); δ_H ($CDCl_3$): 7.36 - 7.18 (8 H, m, Ar), 7.12 - 7.05 (4 H, m, Ar), 4.62 - 4.51 (1H, m, =CH), 4.51 - 4.45 (2H, m, =CH_2), 4.00 (1H, t, *J* 6.5, NH), 3.51 (2H, d, *J* 6.5, N-CH_2), 2.87 (2H, dt, *J* 7.7, 2.4, CH_2), 2.44 (6H, s, H-1), 2.33 (3H, s, H-2); δ_C ($CDCl_3$): 209.8 (=C=), 144.2 (Ar), 142.2 (Ar), 139.1 (Ar), 132.6 (Ar), 131.9 (Ar), 128.4 (Ar), 127.9 (Ar), 126.9 (Ar), 84.6 (=CH_2), 74.1 (=CH), 50.0 (C), 49.1 (N-CH_2), 37.1 (CH_2), 22.6 (C-1), 21.0 (C-2); *m/z* (CI): 449 ($[MNH_4]^+$, 81), 432 ($[MH]^+$, 100), 401 (68), 384 (51); HRMS (ESI) 432.2001 ($[MH]^+$, $C_{27}H_{29}NO_2S$ requires 432.1997); Anal. Calcd for $C_{27}H_{29}NO_2S$: C, 75.14%; H, 6.77%; N, 3.25%. Found: C, 75.19%, H, 6.85%, N, 3.19%.



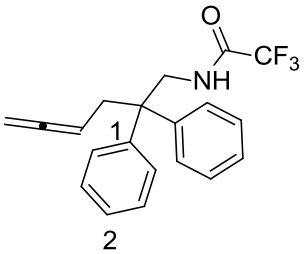
N-(2,2-diphenylhexa-4,5-dien-1-yl)-4-nitrobenzenesulfonamide 5.10d was obtained as a yellow solid (564 mg, 65%). R_f = 0.45 (CH_2Cl_2); mp: 48-56 ^oC; ν_{max}/cm^{-1}: 3331 (N-H), 3055 (C-H), 3026 (C-H), 2921 (C-H), 2857 (C-H), 1953 (C=C=C), 1508 (N=O), 1331 (S=O), 1108 (S=O), 1079 (C=C=C); δ_H ($CDCl_3$): 8.14 - 8.06 (2H, m, H-4), 7.42 - 7.18 (10H, m, Ar), 7.12 - 7.06 (2H, m, H-3), 4.70 - 4.60 (1H, m, =CH), 4.61 - 4.54 (2H, m, $=CH_2$), 3.72 (2H, d, *J* 6.4, N-CH_2), 3.03 (2H, dt, *J* 7.7, 2.5, CH_2), 2.47 (1H, t, *J* 6.4, NH); δ_C ($CDCl_3$): 209.8 (=C=), 152.9 (C-2 and C-5), 145.1 (C-1), 128.4 (Ar), 128.0 (Ar), 126.7 (Ar), 123.9 (Ar), 121.9 (Ar), 85.3 (=CH), 74.2 ($=CH_2$), 59.1 (N-CH_2), 51.3 (C), 36.7 (CH_2); *m/z* (ESI): 452 ($[MNH_4]^+$, 100%), 435 ($[MH]^+$, 90); HRMS (ESI) 435.1370 ($[MH]^+$, $C_{24}H_{23}N_2O_4S$ requires 435.1379); Anal. Calcd for $C_{24}H_{22}N_2O_4S$: C, 66.34%; H, 5.10%; N, 6.45%. Found: C, 66.18%, H, 4.87%, N, 6.36%.



Benzyl-(2,2-diphenylhexa-4,5-dien-1-yl)carbamate 5.4b:[160] Benzyl chloroformate (690 μL, 4.8 mmol.) was added slowly to a mixture of **5.5** (1.00 g, 4.0 mmol.) and $NaHCO_3$ (0.60 g, 7.2 mmol.) in EtOH:H_2O (3:2, 25 mL) at room temperature. The resulting suspension was stirred for 1 h. H_2O (40 mL) was added, and the resulting mixture was extracted with Et_2O (2 x 50 mL). The combined ether extracts were washed with brine (25 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was then purified by column chromatography. **5.4b** was obtained as a colourless oil (1.38 g, 90%). R_f = 0.23 (hexanes:EtOAc, 10:1); ν_{max} (thin film)/cm^{-1}: 3432 (N-H), 3095 (C-H), 3030 (C-H), 2936 (C-H), 1954 (C=C=C), 1715 (C=O), 1005 (C=C=C; δ_H ($CDCl_3$): 7.54 - 7.04 (15H, m, Ar), 5.07 (2H, s, H-2), 4.81 - 4.67 (1H, m, =CH), 4.54 (1H, t, *J* 2.6, $=CH_2$), 4.52 (1H, t, *J* 2.6, $=CH_2$), 4.38 (1H, t, *J* 5.8, NH), 4.01 (2H, close AB, N-CH_2), 2.86 (2H, dt, *J* 7.9, 2.6, CH_2); δ_C ($CDCl_3$): 210.0 (=C=), 156.3 (C=O), 144.9 (C-1), 136.5 (C-3), 128.6 (Ar), 128.4 (Ar), 128.2 (Ar), 128.2 (Ar), 128.1 (Ar), 126.6 (Ar), 85.1 (=CH), 74.0 ($=CH_2$), 66.7 (C-2), 50.6 (C), 47.8 (N-CH_2), 37.3 (CH_2); *m/z* (CI): 401 ($[MNH_4]^+$, 100%), 384 ($[MH]^+$, 99), 219 (22).

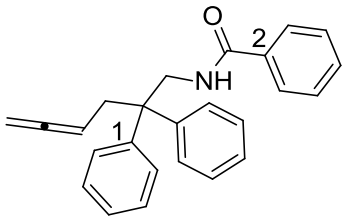


N-benzyl-2,2-diphenylhexa-4,5-dien-1-amine 5.4c:[161] Benzaldehyde (265 μL, 2.61 mmol.) and **5.5** (690 mg, 2.8 mmol.) in MeOH (25 mL) were stirred at room temperature overnight. $NaBH_4$ (167.0 mg, 4.4 mmol.) was added and the reaction mixture was stirred for 30 minutes. The reaction mixture was then quenched with 1N NaOH (20 mL) and the product extracted with Et_2O (2 x 25 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was then purified by column chromatography. **15g** was obtained as a yellow oil (683 mg, 72%). R_f = 0.15 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3059 (C-H), 3024 (C-H), 2908 (C-H), 2813 (C-H), 1954 (C=C=C), 1027 (C=C=C); δ_H ($CDCl_3$): 7.35 - 7.16 (15H, m, Ar), 4.70 - 4.63 (1H, m, =CH), 4.50 (1H, t, *J* 2.4, =CH_2), 4.47 (1H, t, *J* 2.4, =CH_2), 3.77 (2H, close AB, H-2), 3.30 (2H, close AB, N-CH_2), 3.04 (2H, dt, *J* 7.6, 2.4, CH_2); δ_C ($CDCl_3$): 209.8 (=C=), 146.5 (C-1), 140.7 (C-3), 128.3 (Ar), 128.2 (Ar), 128.02 (Ar), 127.99 (Ar), 126.8 (Ar), 126.1 (Ar), 85.9 (=CH), 73.5 (=CH_2), 55.5 (N-CH_2), 54.2 (C-2), 50.7 (C), 37.0 (CH_2); *m/z* (EI) : 340 ([MH]$^+$, 100%); HRMS (EI) 340.2059 ([MH]$^+$, $C_{25}H_{26}N$ requires 340.2065); Anal. Calcd for $C_{25}H_{25}N$: C, 88.45%; H, 7.42%; N, 4.13%. Found: C, 88.59%, H, 7.35%, N, 4.05%.

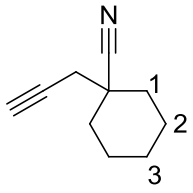


N-(2,2-diphenylhexa-4,5-dien-1-yl)-2,2,2-trifluoroacetamide 5.4d:[162] Trifluoroacetic anhydride (0.84 ml, 6.0 mmol.) was added dropwise to a vigorously stirred solution of **5.5** (1.00 g, 4.0 mmol.) in CH_2Cl_2 (8 mL) at 0 ^oC. After 3 h the reaction was quenched with H_2O (40 ml), diluted with CH_2Cl_2 (40 ml) and the organic layer washed with H_2O (2 x 10 ml). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was then purified by column chromatography. **5.4d** was obtained as a white solid (1.06 g, 77%). R_f = 0.59 (hexanes:EtOAc, 3:1); mp: 63 - 66 ^oC; ν_{max}/cm^{-1}: 3284 (N-H), 3090 (C-H), 3032 (C-H), 2942 (C-H), 1958 (C=C=C), 1701 (C=O), 1175 (C-F), 1153 (C-F), 1028 (C=C=C); δ_H ($CDCl_3$): 7.43 - 7.15 (10 H, m, Ar), 5.85 (1H, brs, NH), 4.73 - 4.64 (1H, m, =CH), 4.63 - 4.58 (2H, m, =CH_2), 4.11 (2 H, close AB, N-CH_2), 2.86 (2H, dt, *J* 7.7, 2.4, CH_2); δ_C ($CDCl_3$): 210.0 (=C=), 156.9 (q, *J* 36.8, C=O), 144.0 (C-1), 128.7

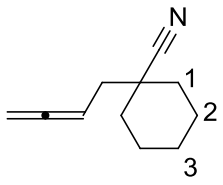
(Ar), 127.8 (Ar), 127.1 (C-2), 115.7 (q, *J* 288.2, CF_3), 84.5 (=CH), 74.3 (=CH_2), 50..2 (C), 46.1 (N-CH_2), 37.5 (CH_2); δ_F ($CDCl_3$): -76.12 (s); *m/z* (ESI): 346 ($[MH]^+$, 100%), 295 (25), 233 (21); HRMS (ESI) 346.1425 ($[MH]^+$, $C_{20}H_{19}NOF_3$ requires 346.1419); Anal. Calcd for $C_{22}H_{29}NF_3$: C, 69.56%; H, 5.25%; N, 4.06%. Found: C, 69.48%, H, 5.10%, N, 3.92%.



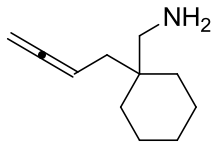
N-(2,2-diphenylhexa-4,5-dien-1-yl)benzamide 5.4e:[163] A solution of benzoyl chloride (0.55 ml, 4.8 mmol.) in CH_2Cl_2 (8.0 mL) was added slowly to a solution of **5.5** (1.00 g, 4.0 mmol.) in pyridine (10.60 ml, 132.0 mmol.) at 0 ^oC and stirred for 3.5 h. The reaction mixture was then concentrated, dissolved in $CHCl_3$, with $NaHCO_3$ (2 x 10 mL) and brine (10 ml), dried ($MgSO_4$) and concentrated under vacuum. The residue was then purified by column chromatography. **5.4e** was obtained as a yellow oil (1.12 g, 79%). R_f = 0.83 (hexanes:EtOAc, 1:1); ν_{max}/cm^{-1}: 3443 (N-H), 3057 (C-H), 2981 (C-H), 1958 (C=C=C), 1665 (C=O), 1024 (C=C=C); δ_H ($CDCl_3$): 7.58 - 7.52 (2H, m, Ar), 7.51 - 7.44 (1H, m, Ar), 7.44 - 7.35 (6H, m, Ar), 7.33 - 7.25 (6H, m, Ar), 5.72 (1H, t, *J* = 5.7, NH), 4.89 - 4.72 (1 H, m, =CH), 4.55 (1 H, t, *J* 2.4, =CH_2), 4.53 (1 H, t, *J* 2.4, =CH_2), 4.23 (2 H, close AB, N-CH_2), 2.93 (2H, dt, *J* 7.7, 2.4, CH_2); δ_C ($CDCl_3$): 210.0 (=C=), 167.2 (C=O), 144.9 (C-1), 134.7 (C-2), 131.4 (Ar), 128.6 (Ar), 128.5 (Ar), 128.1 (Ar), 126.8 (Ar), 126.7 (Ar), 85.1 (=CH), 74.0 (=CH_2), 50.9 (N-CH_2), 46.5 (C), 37.9 (CH_2); *m/z* (CI): 354 ($[MH]^+$, 30%), 292 (100%), 263 (62%).



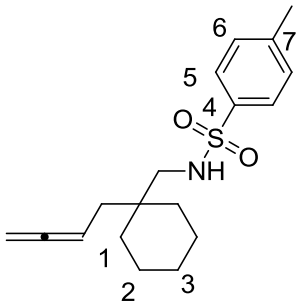
1-(Prop-2-yn-1-yl) cyclohexanecarbonitrile 5.16.[37] Prepared on a 64.0 mmol. scale using the general method for propargylation and was isolated as a pale yellow oil (7.71 g, 82%) after purification by column chromatography. R_f = 0.74 (hexanes:CH_2Cl_2, 1:1); ν_{max}/cm^{-1}: 2936 (C-H), 2861 (C-H), 2224 (C≡N); δ_H ($CDCl_3$): 2.50 (2H, d, *J* 2.6, CH_2), 2.19 (1H, t, *J* 2.6, ≡CH), 2.10 - 2.04 (2H, m, H-1), 1.82 - 1.77 (3H, m, H-2 and H-3), 1.71 - 1.60 (2 H, m, H-2), 1.41 (2 H, td, *J* 13.1, 3.3, H-1, 1.27 - 1.11 (1 H, m, H-3); δ_C ($CDCl_3$): 122.6 (C≡N), 78.2 (≡C), 72.4 (≡CH), 38.7 (C), 34.8 (C-1), 30.3 (CH_2), 25.0 (C-3), 23.0 (C-2); *m/z* (CI): 165 ($[MNH_4]^+$, 100%), 147 ($[M]^+$, 3).



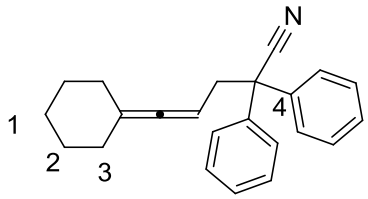
1-(Buta-2,3-dien-1-yl)cyclohexanecarbonitrile 5.17.[37] Prepared on a 52.3 mmol. scale using the general method for the Crabbè reaction and was isolated as a colourless oil (4.21 g, 50%). R_f = 0.35 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 2934 (C-H), 2859 (C-H), 2234 (C≡N), 1956 (C=C=C), 1086 (C=C=C); δ_H ($CDCl_3$): 5.25 - 5.14 (1H, m, =CH), 4.78 (1H, t, *J* 2.4, =CH_2), 4.76 (1H, t, *J* 2.4, =CH_2), 2.28 (2H, dt, *J* 7.9, 2.4, CH_2), 2.06 - 2.00 (2H, m, H-1), 1.8 - 1.74 (3H, m, H-2 and H-3), 1.72 - 1.59 (2H, m, H-2), 1.29 (2H, m, H-1), 1.23 - 1.13 (1H, m, H-3); δ_C ($CDCl_3$): 210.2 (=C=), 123.2 (C≡N), 84.1 (=CH), 74.9 (=CH_2), 39.8 (CH_2), 39.4 (C), 35.2 (C-1), 25.3 (C-3), 23.0 (C-2); *m/z* (CI) : 179 ([MNH_4]$^+$, 100%), 161 ([M]$^+$, 2).



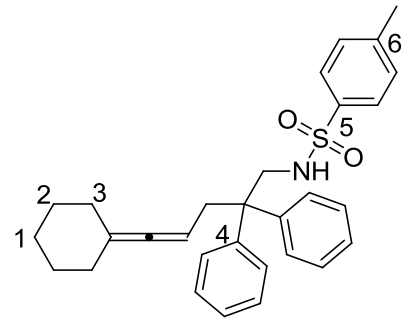
(1-(Buta-2,3-dien-1-yl)cyclohexyl)methanamine 5.18.[37] Prepared on a 12.4 mmol. scale using the general method for LAH reduction and was isolated as a pale yellow oil (1.2 g, 60%) which was used immediately in the subsequent step without further purification.



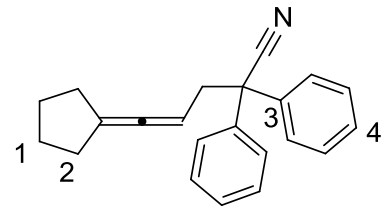
N-((1-(buta-2,3-dien-1-yl)cyclohexyl)methyl)-4-methylbenzenesulfonamide 5.12. Tosyl protection was carried out on a 3.0 mmol. scale, by the same method used to form **5.4a**.[159] **5.12** was isolated as a white solid (4.11 g, 43%). R_f = 0.55 (hexanes:EtOAc, 3:1); mp: 72-74 ^oC; ν_{max}/cm^{-1}: 3288 (N-H), 2919 (C-H), 2847 (C-H), 1953 (C=C=C), 1317 (S=O), 1158 (S=O), 1096 (C=C=C); δ_H ($CDCl_3$); 7.76 (2H, d, *J* 8.4, H-5), 7.35 (2H, d, *J* 8.4, H-6), 5.23 - 5.16 (1H, m, =CH), 4.61 (1H, t, *J* 2.4, =CH_2), 4.60 (1H, t, *J* 2.4, =CH_2), 4.33 (1H, t, *J* 6.8, NH), 2.82 (2H, t, *J* 6.8, N-CH_2), 2.47 (3H, s, CH_3), 2.01 (2H, dt, *J* 8.4, 2.4, CH_2), 1.50 - 1.35 (6H, m, H-2 and H-3), 1.35 - 1.23 (4H, m, H-1); δ_C ($CDCl_3$): 209.3 (=C=), 143.3 (C-4), 137.0 (C-7), 129.7 (C-5), 127.1 (C-6), 85.0 (=CH), 74.1 (=CH_2), 49.1 (N-CH_2), 36.9 (CH_2), 35.3 (C-1), 22.6 (C-3), 21.5 (CH_3), 21.3 (C-2); *m/z* (CI): 337 ([MNH_4]$^+$, 100%), 320 ([MH]$^+$, 39), 285 (70), 262 (27); HRMS (ESI) 320.1680 ([MH]$^+$, $C_{18}H_{26}NO_2S$ requires 320.1684); Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.67%; H, 7.89%; N, 4.38%. Found: C, 67.76%, H, 7.75%, N, 4.38%.



5-Cyclohexylidene-2,2-diphenylpent-4-enenitrile 5.19a[37] was formed by Method B on a 6.3 mmol. scale and was isolated as a white solid (1.67 g, 85%). R_f = 0.3 (hexanes:CH_2Cl_2, 3:1); mp: 72-74 ^oC; ν_{max}/cm^{-1}: 3062, (C-H), 3029 (C-H), 2890 (C-H), 2848 (C-H), 1967 (C=C=C), 1033 (C=C=C); δ_H ($CDCl_3$): 7.50 - 7.24 (10 H, m, Ar), 5.00 - 4.94 (1H, m, =CH), 3.08 (2 H, d, *J* 7.0, CH_2), 2.00 - 1.94 (4 H, m, H-3), 1.57 - 1.43 (6 H, m, H-2 and H-1); δ_C ($CDCl_3$): 201.1 (=C=), 140.0 (C-4), 128.8 (Ar), 127.8 (Ar), 127.2 (Ar), 122.1 (C≡N), 103.4 (=C), 82.9 (=CH), 52.1 (C), 40.7 (CH_2), 31.0 (C-3), 27.1 (C-2), 26.0 (C-1); *m/z* (ESI): 314 ($[MH]^+$, 100%), 259 (23).

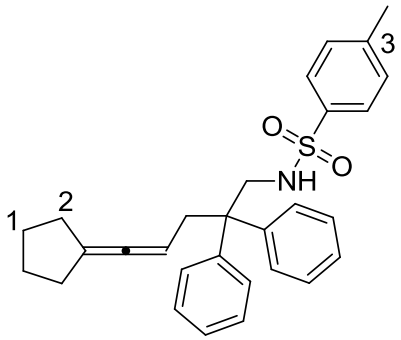


N-(5-cyclohexylidene-2,2-diphenylpent-4-en-1-yl)-4-methylbenzenesulfonamide 5.13. *Step1:* The unprotected amine was prepared on a 2.9 mmol. scale using the general method for LAH reduction.[37] *Step2*: Tosyl protection was carried on a 0.8 mmol. scale, by the same method used to form **5.4a**.[159] **5.13** was isolated as a white solid (310 mg, 69%, over the two steps). R_f = 0.23 (hexanes:EtOAc, 3:1); mp: 54-60 ^oC; ν_{max}/cm^{-1}: 3240 (N-H), 2925 (C-H), 2849 (C-H), 2833 (C-H), 1970 (C=C=C), 1322 (S=O), 1162 (S=O), 1085 (C=C=C): δ_H ($CDCl_3$): 7.77 - 7.53 (2 H, m, Ar), 7.53 - 7.17 (8 H, m, Ar), 7.17 - 6.93 (4 H, m, Ar), 4.58 - 4.52 (1H, m, =CH), 3.92 (1H, t, *J* 6.4, NH), 3.61 (2H, d, *J* 6.4, N-CH_2), 2.86 (2H, d, *J* 7.6, CH_2), 2.45 (3H, s, CH_3), 1.97 - 1.92 (4H, m, H-3), 1.55 - 1.44 (6H, m, H-2 and H-1); δ_C ($CDCl_3$): 200.5 (=C=), 144.5 (C-4), 143.4 (C-5), 136.3 (C-6), 129.7 (Ar), 128.3 (Ar), 128.0 (Ar), 127.1 (Ar), 126.6 (Ar), 101.9 (=C), 83.3 (=CH), 50.1 (C), 49.9 (N-CH_2), 38.6 (CH_2), 31.2 (C-3), 27.3 (C-2), 26.1 (C-1), 21.5 (CH_3); *m/z* (ESI): 472 ($[MH]^+$, 100%); HRMS (ESI) 472.1309 ($[MH]^+$, $C_{30}H_{34}NO_2S$ requires 472.2310); Anal. Calcd for $C_{30}H_{33}NO_2S$: C, 76.40%; H, 7.05%; N, 2.97%. Found: C, 76.41%, H, 6.89%, N, 2.85%.

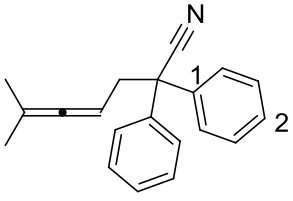


6-Cyclopentylidene-2,2-diphenylocta-4,5-dienenitrile 5.19b. Prepared by Method B on a 7.4 mmol. scale.[37] **5.19b** was isolated as a colourless oil

(1.88 g, 85%). R_f = 0.23 (hexanes:CH_2Cl_2, 7:3); ν_{max} (thin film)/cm^{-1}: 3063, 2951 (C-H), 2893 (C-H), 1957 (C=C=C), 1596, 1494, 1449, 1215, 1034 (C=C=C); δ_H ($CDCl_3$): 7.49 - 7.26 (10H, m, Ar), 5.13 - 5.02 (1H, m, =CH), 3.08 (2H, d, *J* 6.8, CH_2), 2.30 - 2.08 (4H, m, H-2), 1.63 - 1.56 (4H, m, H-1); δ_C ($CDCl_3$): 199.8 (=C=), 134.0 (C-3), 128.8 (Ar), 127.8 (Ar), 127.1 (C-4), 122.3 (C≡N), 105.3 (=C), 85.5 (=CH), 52.0 (C), 40.4 (CH_2), 30.9 (C-2), 26.9 (C-1); *m/z* (CI): 317 ($[MNH_4]^+$, 100%), 300 ($[MH]^+$, 95), 192 (39).

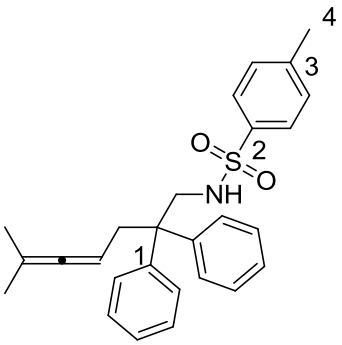


N-(6- cyclopentylidene -2,2-diphenylocta-4,5-dien-1-yl)-4-methylbenzenesulfonamide 5.14. *Step1:* The unprotected amine was prepared on a 2.3 mmol. scale using the general method for LAH reduction.[37] *Step2*: Tosyl protection was carried on a 2.0 mmol. scale, by the same method used to form **5.4a**.[159] **5.14** was isolated as a white solid (850 mg, 90%, over two steps). R_f = 0.15 (hexanes:EtOAc, 10:1); mp: 177 - 140 ^oC; ν_{max}/cm^{-1}: 3282 (N-H), 2942 (C-H), 2865 (C-H), 1970 (C=C=C), 1327 (S=O), 1160 (S=O), 1089 (C=C=C); δ_H ($CDCl_3$): 7.61 - 7.57 (2 H, m, Ar), 7.38 - 7.17 (8 H, m, Ar), 7.12 - 7.08 (4 H, m, Ar), 4.63 (1 H, tt, *J* 7.6, 4.0, =CH), 3.93 (1H, t, *J* 6.4, NH), 3.61 (2H, d, *J* 6.4, N-CH_2), 2.86 (2 H, d, *J* 7.6, CH_2), 2.45 (3 H, s, CH_3), 2.21 (4 H, td, *J* 7.2, 4.0, H-2), 1.66 - 1.59 (4 H, m, H-1); δ_C ($CDCl_3$): 199.2 (=C=), 144.4 (Ar), 143.4 (Ar), 136.1 (C-3), 129.7 (Ar), 128.3 (Ar), 128.0 (Ar), 127.1 (Ar), 126.6 (Ar), 103.3 (=C), 85.9 (=CH), 50.0 (C), 49.8 (N-CH_2), 38.1 (CH_2), 30.9 (C-2), 27.0 (C-1), 21.5 (CH_3); *m/z* (ESI): 458 ($[MH]^+$, 95%); HRMS (ESI) (458.2150 $[MH]^+$, $C_{29}H_{32}NO_2S$ requires 458.2154); Anal. Calcd for $C_{29}H_{31}NO_2S$: C, 76.10%; H, 6.83%; N, 3.06%. Found: C, 76.10%, H, 6.75%, N, 2.98%.



6-Methyl-2,2-diphenylocta-4,5-dienenitrile 5.19c. Prepared by Method B on a 13.8 mmol. scale.[37] **5.19c** was isolated as a colourless oil (3.50 g, 93%). R_f = 0.36 (hexanes:CH_2Cl_2, 3:7); ν_{max}/cm^{-1}: 3062, 2982 (C-H), 2854 (C-H), 1967 (C=C=C), 1033 (C=C=C); δ_H ($CDCl_3$): 7.48 - 7.29 (10H, m, Ar), 5.02 - 4.80 (1H, m, =CH), 3.07 (2H, d, *J* 7.0, CH_2), 1.55 (3H, s, CH_3), 1.54 (3H, s, CH_3); δ_C ($CDCl_3$): 204.4 (=C=), 139.9 (C-1), 128.8 (Ar), 127.8 (Ar), 127.1 (C-2), 122.2 (C≡N), 96.5 (=C), 83.1

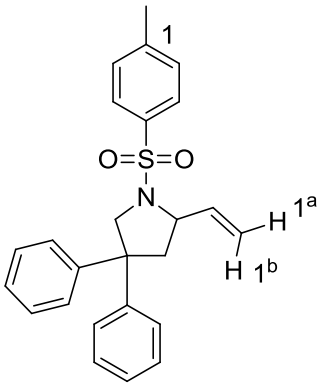
(=CH), 52.0 (C), 40.4 (CH_2), 20.1 (CH_3); *m/z* (CI): 291 ($[MNH_4]^+$, 100%), 274 ($[MH]^+$, 30), 192 (21).



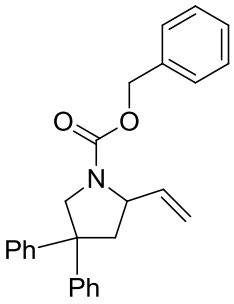
N-(6-methyl-2,2-diphenylocta-4,5-dien-1-yl)-4-methylbenzenesulfonamide 5.15. *Step1:* The unprotected amine was prepared on a 6.2 mmol. scale using the general method for LAH reduction.[37] *Step2*: Tosyl protection was carried on a 2.2 mmol. scale, by the same method used to form **5.4**.[159] **5.15** was isolated as a white solid (610 mg, 71%, over two steps). R_f = 0.55 (hexanes:EtOAc, 1:1); mp: 177 - 140 ^oC; ν_{max} (thin film)/cm^{-1}: 3290 (N-H), 2978 (C-H), 2934 (C-H), 1975 (C=C=C), 1323 (S=O), 1161 (S=O), 1068 (C=C=C); δ_H ($CDCl_3$): 7.64 - 7.57 (2H, m, Ar), 7.33 - 7.19 (7H, m, Ar), 7.13 - 7.05 (5H, m, Ar), 4.57 - 4.48 (1H, m, =CH), 3.90 (1H, t, *J* 6.4, NH), 3.60 (2H, d, *J* 6.4, N-CH_2), 2.84 (2H, d, *J* 7.5, CH_2), 2.45 (3H, s, H-4), 1.54 (3H, s, CH_3), 1.53 (3H, s, CH_3); δ_C ($CDCl_3$): 203.8 (=C=), 144.4 (C-1), 143.4 (C-2), 136.2 (C-3), 129.7 (Ar), 128.3 (Ar), 128.0 (Ar), 127.1 (Ar), 126.7 (Ar), 94.7 (=C), 83.5 (=CH), 50.0 (C), 49.8 (N- CH_2), 38.1 (CH_2), 21.5 (C-4), 20.3 (CH_3); *m/z* (ESI): 432 ($[MH]^+$, 100%). HRMS (ESI) 432.5945 ($[MH]^+$, $C_{27}H_{29}NO_2S$ requires 432.5944); Anal. Calcd for $C_{27}H_{29}NO_2S$: C, 75.14%; H, 6.77%; N, 3.25%. Found: C, 75.10%, H, 6.70%, N, 3.19%.

Typical procedure for catalytic reaction in Chapter 5:

A screw-cap vial was charged with a magnetic stir bar, Ag complex or salt (15 mol%), substrate (0.1 mmol.) and additive (0.1 mmol.). DCE (0.5 mL) was added and the reaction was stirred at room temperature in the dark. Conversions were monitored by NMR integration. Upon completion, the solvent was evaporated, or, if a base was used, K_2CO_3 (1 mL) was added, the aqueous layer extracted with Et_2O and the combined organic extracts dried ($MgSO_4$). The product was purified by column chromatography.

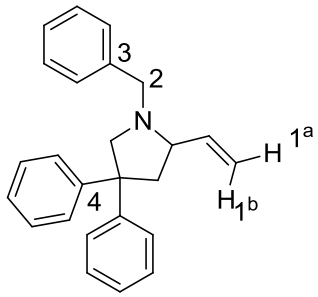


4,4-Diphenyl-1-tosyl-2-vinylpyrrolidine 5.9a: Isolated from **5.4a** using 15 mol% β-**4.16**-Ag with 15 mol% pyridine (39 mg, 96%). mp: 80-86 ^{o}C; R_f = 0.38 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3053 (C-H), 3110 (C-H), 2880 (C-H), 1342 (S=O), 1156 (S=O); δ_H ($CDCl_3$): 7.78 - 7.63 (2H, m, Ar), 7.43 - 6.99 (12H, m, Ar), 5.80 (1H, ddd, *J* 17.2, 10.0, 7.2, =CH), 5.24 (1H, d, *J* 17.2, H-1^b), 5.10 (1H, d, *J* 10.0, H-1^a), 4.33 - 4.19 (m, 2H, C and N-CH_2), 4.02 (1H, d, *J* 10.2, N-CH_2), 2.83 (1H, dd, *J* 12.8, 8.0, CH_2), 2.49 (1H, dd, *J* 12.8, 6.8, CH_2); δ_C ($CDCl_3$): 144.9 (Ar), 144.4 (Ar), 143.5 (Ar), 138.9 (=CH), 134.9 (C-1), 129.7 (Ar), 128.62 (Ar), 128.59 (Ar), 127.5 (Ar), 126.72 (Ar), 126.69 (Ar)126.5 (Ar), 126.4 (Ar), 113.1 (C-1), 61.6 (C-6), 58.3 (C-3), 52.6 (C-5), 45.4 (C-4), 21.5 (CH_3); *m/z* (EI) : 404 ([MH]$^+$, 100), 340 (41), 467 (42); HRMS (ESI) 404.5412 ([MH]$^+$, $C_{25}H_{25}N_2O_2S$ requires 404.5417); Anal. Calcd for $C_{25}H_{25}N_2O_2S$: C, 74.41%; H, 6.24%; N, 3.47%. Found: C, 74.43%, H, 6.25%, N, 3.42%. HPLC conditons: Chirapak OD-H column: 10% IPA in *n*-hexane, 1.0 mL/min, t_R(minor) = 14.2 min, t_R(major) = 18.1 min; $[\alpha]_D^{25}$ = -2.7^o (c = 3.0, $CHCl_3$, 65% ee, with β-**4.16**-Ag), tentatively assigned *S* by analogy.

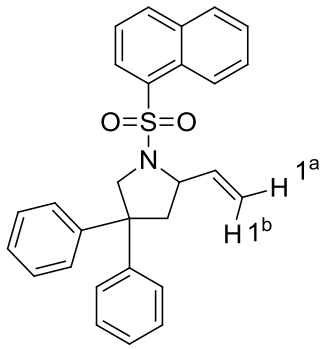


Benzyl 4,4-diphenyl-2-vinylpyrrolidine-1-carboxylate 5.9b: Isolated from **5.4b** as a colourless oil using 15 mol% β-**4.16**-Ag with 15 mol% pyridine (30 mg, 79% yield, 84% conversion). R_f = 0.42 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3061 (C-H), 3032 (C-H), 2975 (C-H), 2879 (C-H), 1699 (C=O); δ_H ($CDCl_3$, 1:1 mixture of rotamers): 7.48-7.07 (15H, m, Ar), 5.92-5.70 (1H, m, =CH), 5.39-5.02 (4H, m, =CH_2 and O-CH_2), 4.81 (0.5 H, dd, *J* 11.5, 1.6, CH), 4.65 (0.5 H, dd, *J* 11.5, 1.6, CH), 4.24 - 4.02 (1H, m, N-CH_2), 3.80 - 3.69 (1H, m, N-CH_2), 2.92 - 2.76 (1H, m, CH_2), 2.57 - 2.41 (1H, m, CH_2); δ_C ($CDCl_3$,1:1 mixture of rotamers): 155.5 (C=O), 154.7 (C=O), 145.4 (Ar), 144.9 (Ar), 139.2 (=C), 138.5 (=C), 137.0 (Ar), 136.8 (Ar), 128.7 (Ar), 128.6 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 127.7 (Ar), 127.5 (Ar), 126.8 (Ar), 126.6 (Ar), 126.5 (Ar), 115.7 (=CH_2), 115.2 (=CH_2), 66.9 (O-CH_2), 59.5 (N-CH_2), 59.2 (N-CH_2), 56.2 (CH), 53.0 (C), 52.7 (C), 45.6 (CH_2), 44.6 (CH_2). *m/z* (CI): 401 ([MNH_4]$^+$, 100%), 383 ([MH]$^+$, 55); HPLC conditions: Chirapak AD-H column, 30% IPA in *n*-hexane, 0.5 mL/min, t_R(major) = 14.9 min, t_R(minor) =

18.5 min; $[\alpha]_D^{25} = -2.5^o$ (c = 0.5, $CHCl_3$, 52% ee, with β-**4.16**-Ag). Assigned *S* by comparison of chiral HPLC data with that reported.[45]

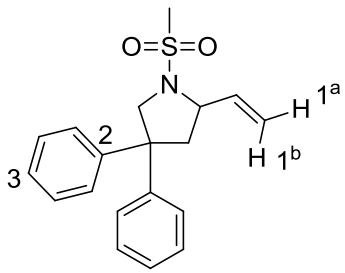


1-Benzyl-4,4-diphenyl-2-vinylpyrrolidine 5.9c:[187] Isolated from **5.4c** as a colourless oil using 15 mol% β-**4.16**-Ag with 15 mol% pyridine (28 mg, 82%). R_f = 0.85 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3060 (C-H), 3027 (C-H), 2789 (C-H); δ_H ($CDCl_3$) 7.60 - 7.05 (15H, m, Ar), 5.93 - 5.78 (1H, m, =CH), 5.25 (1H, dd, *J* 16.8, 1.6, H-1^b), 5.14 (1H, dd, *J* 10.0, 1.6, H-1^a), 4.14 (1H, d, *J* 13.6, H-2), 3.70 (1H, d, *J* 9.6, N-CH_2), 3.30 - 3.23 (2H, m, CH and H-2), 2.97 (1H, dd, *J* 13.2, 8.0, CH_2), 2.88 (1H, d, *J* 9.6, N-CH_2), 2.44 (1H, dd, *J* 13.2, 8.0, CH_2). δ_C ($CDCl_3$): 150.3 (C-4), 148.4 (C-4), 140.7 (=CH), 140.0 (C-3), 128.6 (Ar), 128.2 (Ar), 127.9 (Ar), 127.5 (Ar), 127.2 (Ar), 127.0 (Ar), 126.8 (Ar), 125.9 (Ar), 125.6 (Ar), 116.5 (=CH_2), 68.1 (CH), 65.6 (N-CH_2), 57.7 (C-2), 53.1 (C), 46.6 (CH_2); *m/z* (ESI) : 340 ($[MH]^+$, 100%), 340 (40); HRMS (ESI) 340.2074 ($[MH]^+$, $C_{25}H_{26}N$ requires 340.2065); Anal. Calcd for $C_{25}H_{26}N$: C, 75.14%; H, 6.77%; N, 3.25%. Found: C, 74.77%, H, 6.60%; N, 4.15%; HPLC conditons: Chirapak AD-H column: 2% IPA in *n*-hexane, 1.0 mL/min, t_R(major) = 4.2, t_R(minor) = 5.0; Optical purity was too low (5%) for accurate determination of $[\alpha]_D$.

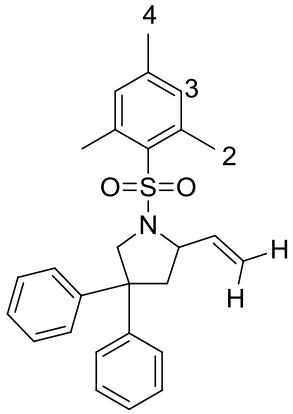


1-(Naphthalen-1-ylsulfonyl)-4,4-diphenyl-2-vinylpyrrolidine 5.11a: Isolated from **5.10a** as a white solid using 15 mol% β-**4.16**-Ag with 15 mol% pyridine (35 mg, 79% yield, 84% conversion). mp: 62-67 ^oC; R_f = 0.43 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3060 (C-H), 2883 (C-H), 1333 (S=O), 1202, 1129 (S=O); δ_H ($CDCl_3$): 8.81 - 8.72 (1H, m, Ar), 8.20 (1H, dd, *J* 7.4, 1.0, Ar), 8.05 (1H, d, *J* 8.4, Ar), 8.00 - 7.91 (1H, m, Ar), 7.68 - 7.57 (2H, m, Ar), 7.54 - 7.45 (1H, m, Ar), 7.37 - 7.08 (10H, m, Ar), 5.31 (1H, ddd, *J* 16.8, 10.0, 8.4, =CH), 5.06 (1H, d, *J* 16.8, H-1^b), 4.83 (1H, d, *J* 10.0, H-1^a), 4.65 (1H, dd, *J* 10.4, 1.1, N-CH_2), 4.35 - 4.29 (1H, m, CH), 4.04 (1H, d, *J* 10.4, N-CH_2), 2.84 (1H, ddd, *J* 8.4, 6.8, 1.1, CH_2), 2.49 (1H, dd, *J* 12.4, 8.4, CH_2); δ_C ($CDCl_3$): 145.1 (Ar), 144.1 (Ar), 137.8 (=CH), 135.5 (Ar), 134.3 (Ar), 130.1 (Ar), 128.9 (Ar), 128.8 (Ar), 128.6 (Ar), 128.5 (Ar), 127.9 (Ar), 126.72 (Ar), 126.68 (Ar), 126.6 (Ar), 126.5 (Ar), 125.1 (Ar), 124.0 (Ar), 116.4 (C-1),

61.9 (CH), 56.0 (N-CH_2), 52.6 (C), 45.9 (CH_2); *m/z* (ESI) : 462 ($[MNa]^+$, 23%), 440 ($[MH]^+$, 100); HRMS (ESI) 440.1678 ($[MH]^+$, $C_{28}H_{26}NO_2S$ requires 440.1684); Anal. Calcd for $C_{28}H_{25}NO_2S$; C, 76.51%; H, 5.73%; N, 3.19%. Found: C, 76.67%, H, 5.69%; N, 3.07%; HPLC conditions: Chirapak AS-H column, 3% IPA in *n*-hexane, 1.0 mL/min, t_R(major) = 35.2 min, t_R(minor) = 44.6 min; $[\alpha]_D^{25}$ = -2.3° (c = 0.56, $CHCl_3$, 46% ee, with β-**4.16**-Ag), tentatively assigned *S* by analogy.

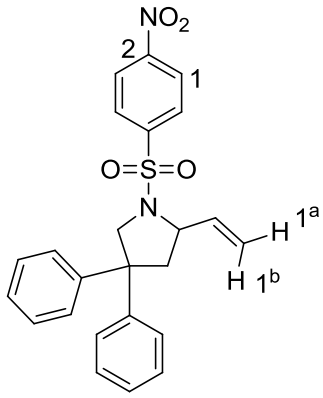


1-(Methylsulfonyl)-4,4-diphenyl-2-vinylpyrrolidine 5.11b: Isolated from **5.10b** as a white solid using 15 mol% β-**4.16**-Ag with 15 mol% pyridine (16 mg, 48% yield, 57% conversion). mp: 76-82 °C; R_f = 0.39 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3056 (C-H), 3036 (C-H), 2929 (C-H), 2883 (C-H), 1327 (S=O), 1142 (S=O); δ_H ($CDCl_3$) 7.45 - 7.41 (2 H, m, Ar), 7.39 - 7.28 (4 H, m, Ar), 7.28 - 7.18 (4H, m, Ar), 5.78 (1H, ddd, *J* 17.2, 10.0, 8.0, =CH), 5.30 (1H, d, *J* 17.2, H-1^b), 5.19 (1H, d, *J* 10.0, H-1^a), 4.55 (1 H, dd, *J* 10.8, 1.8, N-CH_2), 4.28 - 4.22 (H, m, CH), 3.97 (1H, d, *J* 10.8, N-CH_2), 3.07 (1H, ddd, *J* 12.8, 6.8, 1.8, CH_2), 2.65 (3H, s, CH_3), 2.51 (1H, dd, *J* 12.8, 9.0, CH_2); δ_C ($CDCl_3$): 145.0 (C-2), 144.2 (C-2), 138.1 (=CH), 128.9 (Ar), 128.7 (Ar), 126.9 (Ar), 126.75 (Ar), 126.73 (Ar), 126.6 (Ar), 117.8 (=CH_2), 61.6 (CH), 58.3 (N-CH_2), 53.0 (C), 45.3 (CH_2), 39.6 (CH_3); *m/z* (ESI) : 345 ($[MNH_4]^+$, 28%), 328 ($[MH]^+$, 100), 273 (89); HRMS (ESI) 328.1360 ($[MH]^+$, $C_{19}H_{22}NO_2S$ requires 328.1371); Anal. Calcd for $C_{19}H_{21}NO_2S$; C, 69.69%; H, 6.46%; N, 4.28%. Found: C, 69.77%, H, 6.60%; N, 4.15%; HPLC conditons: Chirapak -H column, Chirapak OD-H column, 5% IPA in *n*-hexane, 1.0 mL/min, t_R(minor) = 21.6 min, t_R(major) = 23.4 min; $[\alpha]_D^{25}$ = -3.4° (c = 1.0, $CHCl_3$, 53% ee, with β-**4.16**-Ag), tentatively assigned *S* by analogy.

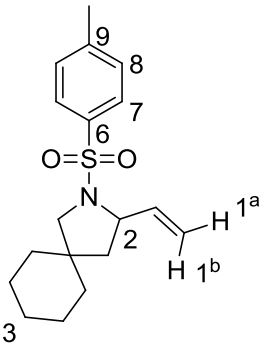


1-(Mesitylsulfonyl)-4,4-diphenyl-2-vinylpyrrolidine 5.11c: Isolated from **5.10c** as a white solid using 15 mol% β-**4.16**-Ag with 15 mol% pyridine (12 mg, 27% yield, 38% conversion). mp: 87-90 °C; R_f = 0.57 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3027 (C-H), 2920 (C-H), 1312 (S=O), 1145 (S=O); δ_H ($CDCl_3$): 7.44 - 7.16 (10H, m, Ar), 6.91 (2H, H-

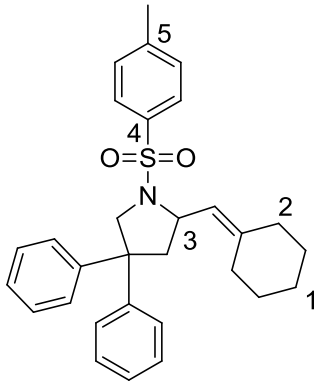
3), 5.29 - 5.19 (1H, m, =CH), 5.00 (1H, d, *J* 16.8, $=CH_2$), 4.41- 4.68 (2H, m, $=CH_2$ and N-CH_2), 5.29 - 5.19 (1H, m, CH), 3.89 (1H, d, *J* 10.8, N-CH_2), 2.87 (1H, ddd, *J* 8.4, 6.8, 1.1, CH_2), 2.66 - 2.51 (1H, m, CH_2 and H-2), 2.32 (3H, s, H-4); δ_C ($CDCl_3$): 145.4 (Ar), 144.4 (Ar), 142.2 (Ar), 139.9 (Ar), 137.5 (C-2), 135.0 (Ar), 131.6 (Ar), 128.61 (Ar), 128.59 (Ar), 126.8 (Ar), 126.7 (Ar), 126.7 (Ar), 126.6 (Ar), 116.4 ($=CH_2$), 61.6 (CH), 57.6 (N-CH_2), 52.6 (C), 46.2 (CH_2), 23.0 (C-2), 21.0 (C-4); *m/z* (ESI) : 454 ($[MNa]^+$, 94%), 432 ($[MH]^+$, 100), 250 (56); HRMS (ESI) 432.1991 ($[MH]^+$, $C_{27}H_{30}NO_2S$ requires 432.1997); Anal. Calcd for $C_{27}H_{30}NO_2S$; C, 88.45%; H, 7.42%; N, 4.13%. Found: C, 88.60%, H, 7.37%; N, 4.08%; HPLC conditons: Chirapak OD-H column, 10% IPA in *n*-hexane, 1.0 mL/min, t_R(minor) = 6.6 min, t_R(major) = 10.1 min; $[\alpha]_D^{25}$ = -2.1° (c = 0.45, $CHCl_3$, 39% ee, with β-**4.16**-Ag), tentatively assigned *S* by analogy.



1-((4-Nitrophenyl)sulfonyl)-4,4-diphenyl-2-vinylpyrrolidine 5.11d: Isolated from **5.10d** as a yellow oil using 15 mol% β- β-**4.16**-Ag with 15 mol% pyridine (24 mg, 55% yield, 62% conversion). R_f = 0.25 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 2922 (C-H), 2860 (C-H), 1576, 1506 (N=O), 1331 (S=O), 1107 (S=O); δ_H ($CDCl_3$): 8.06 (2H, d, *J* 8.3, H-1), 7.53 - 7.05 (12H, m, Ar), 5.74 (1H, ddd, *J* 17.1, 9.8, 8.6, =CH), 5.15 (1H, d, *J* 17.1, H-1^b), 5.08 (1H, d, *J* 9.8, H-1^a), 4.21 - 3.95 (3H, m, CH and N-CH_2), 2.98 - 2.82 (1H, m, CH_2), 2.58 (1H, close AB, CH_2); δ_C ($CDCl_3$): 154.1 (C-8), 146.1 (Ar), 145.6 (Ar), 145.0 (Ar), 138.3 (=CH), 128.7 (Ar), 128.6 (Ar), 126.79 (Ar), 126.76 (Ar), 126.7 (Ar), 126.6 (Ar), 123.9 (Ar), 121.5 (Ar), 118.3 ($=CH_2$), 67.4 (N-CH_2), 64.4 (CH), 54.1 (C), 45.2 (CH_2); *m/z* (CI): 452 ($[MNH_4]^+$, 100%), 435 ($[MH]^+$, 85); HRMS (ESI) 435.1372 ($[MH]^+$, $C_{24}H_{23}N_2O_4S$ requires 435.1379); Anal. Calcd for $C_{24}H_{22}N_2O_4S$: C, 66.34%; H, 5.10%; N, 6.45%. Found: C, 66.17%, H, 4.84%, N, 6.39%. HPLC conditons: Chirapak OD-H column, 2% IPA in *n*-hexane, 1.0 mL/min, t_R(minor) = 19.6 min, t_R(major) = 25.8min; $[\alpha]_D^{25}$ = -0.8 ° (c = 0.5, $CHCl_3$, 14% ee, with β-**4.16**-Ag), tentatively assigned *S* by analogy.

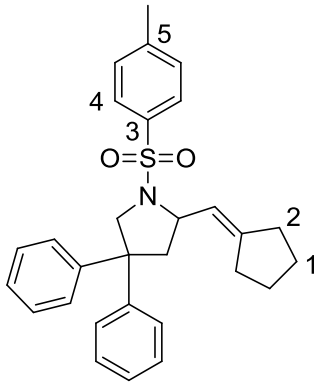


2-Tosyl-3-vinyl-2-azaspiro[4.5]decane 5.21: Isolated from **5.12** as a white solid using 15 mol% β-**4.16**-Ag with 15 mol% pyridine (30 mg, 95%). mp: 53 - 55 ^{o}C; Rf = 0.58 (hexanes:EtOAc, 3:1); v_{max}/cm^{-1}: 3077 (C-H), 2916 (C-H), 2857 (C-H), 1341 (S=O), 1163(S=O); δ_H ($CDCl_3$): 7.74 (2H, d, *J* 8.2, H-7), 7.33 (2H, d, *J* 8.2, H-8), 5.90 (1H, ddd, *J* 17.2, 10.2, 7.4, =CH), 5.19 (1H, d, *J* 17.2, H-1^{b}), 5.10 (1H, d, *J* 10.2, H-1^{a}), 3.98 - 9.92 (1H, m, H-2), 3.25 (2H, close AB, N-CH_2), 2.46 (3H, s, CH_3), 1.82 (1H, dd, *J* 12.8, 7.6, CH_2), 1.56 (1H, dd, *J* 12.8, 8.4, CH_2), 1.50 - 1.16 (8H, m, CH), 1.05 - 0.83 (2H, m, H-5); δ_C ($CDCl_3$): 143.2 (C-6), 140.0 (=CH), 135.1 (C-9), 129.5 (C-8), 127.6 (C-7), 115.0 (=CH_2), 61.6 (C-2), 58.9 (N-CH_2), 45.5 (CH_2), 41.3 (C), 36.4 (CH), 34.6 (C-5), 25.8 (CH), 23.6 (CH), 22.9 (CH), 21.5 (CH_3); *m/z* (ESI) : 320 ([MH]$^{+}$, 100%), 296 (19); HRMS (ESI) 320.1677 ([MH]$^{+}$, $C_{18}H_{26}NO_2S$ requires 320.1684); Anal. Calcd for $C_{18}H_{25}NO_2S$; C, 67.67%; H, 7.89%; N, 4.38%. Found: C, 69.77%, H, 6.60%; N, 4.15%. HPLC conditons: Chirapak AD-H column, 5% IPA in *n*-hexane, 1.0 mL/min, t_R(major) = 12.2 , t_R(minor) = 14.2; $[\alpha]_D^{25}$ = -3.1^{o} (c = 1.0, $CHCl_3$, 51% ee, with β-**4.16**-Ag), tentatively assigned *S* by analogy.

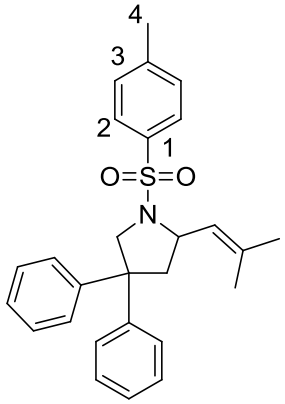


2-(Cyclohexylidenemethyl)-4,4-diphenyl-1-tosylpyrrolidine 2-tosyl-3-vinyl-2-azaspiro[4.5]decane 5.22: Isolated from **5.13** as a white solid using 15 mol% AgOTf (43 mg, 92%). mp: 141-143 ^{o}C; Rf = 0.61 (hexanes:EtOAc, 3:1); v_{max}/cm^{-1}: 2928 (C-H), 2863 (C-H), 1447, 1341 (S=O), 1161 (S=O); δ_H (500 MHz, $CDCl_3$): 7.73 - 7.43 (3H, m, Ar), 7.36 - 7.08 (11H, m, Ar), 4.75 (1H, d, *J* 9.5, =CH), 4.54 - 4.38 (2H, m, CH and N-CH_2), 3.87 (1H, d, *J* 10.0, N-CH_2), 2.72 (1H, ddd, *J* 12.5, 6.8, 1.3, CH_2), 2.39 (2H, s, CH_3), 2.34 (1H, dd, *J* 12.5, 8.6, CH_2), 2.26 - 2.14 (1H, m, H-3), 2.13 - 1.99 (1H, m, H-3), 1.96 - 1.89 (2H, m, H-3), 1.70 - 1.38 (6H, m, CH); δ_C (500 MHz, $CDCl_3$): 145.6 (Ar), 144.8 (Ar), 142.6 (Ar), 142.1 (=C), 137.7 (C-5), 129.2 (Ar), 128.6 (Ar), 128.5 (Ar), 127.2 (Ar), 126.7 (Ar), 126.6 (Ar), 126.5 (Ar), 126.4 (Ar), 122.2 (=CH), 57.8 (N-CH_2), 56.1 (CH), 52.6 (C), 46.3 (CH_2), 36.9 (C-3), 29.1 (C-3), 28.1 (CH), 27.5 (CH), 26.7 (CH), 21.5 (CH_3); *m/z* (ESI): 472 ([MH]$^{+}$, 100%); HRMS (ESI) 472.1312

([MH]$^+$, $C_{30}H_{34}NO_2S$ requires 472.2310); Anal. Calcd for $C_{30}H_{33}NO_2S$: C, 76.40%; H, 7.05%; N, 2.97%. Found: C, 76.43%, H, 6.96%, N, 2.92%.



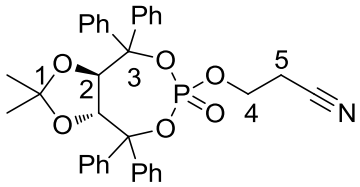
2-(Cyclopentylidenemethyl)-4,4-diphenyl-1-tosylpyrrolidine 5.23: Isolated from **5.14** as a white solid using 15 mol% AgOTf (41 mg, 90%); mp: 104-106 ^oC; Rf = 0.54 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3041(C-H), 2934 (C-H), 2846 (C-H), 1340 (S=O), 1160 (S=O); δ_H (500 MHz, $CDCl_3$): 7.62 (2H, d, *J* 8.1, H-4), 7.33 - 7.04 (12H, m, Ar), 5.21 - 5.18 (1H, m, =CH), 4.33 (1H, d, *J* 10.3, N-CH_2), 3.87 - 3.77 (1H, m, CH), 3.74 (1H, d, *J* 10.3, N-CH_2), 2.78 (1H, d, *J* 13.4, H-2), 2.63 (1H, dd, *J* 12.8, 8.1, CH_2), 2.41 - 2.34 (4H, m, CH_2 and CH_3), 2.30 - 2.24 (2H, m, H-2), 2.24 - 2.12 (2H, m, H-1), 1.92 - 1.78 (3H, m, H-1 and H-2); δ_C (500 MHz, $CDCl_3$): 145.4 (Ar), 145.1 (Ar), 143.1 (C-3), 141.1 (=C), 134.7 (C-5), 129.6 (Ar), 128.5 (Ar), 128.4 (Ar), 127.36 (Ar), 127.34 (Ar), 126.8 (Ar), 126.4 (Ar), 126.3 (Ar), 126.0 (=CH), 58.31 (CH), 58.29 (N-CH_2), 52.3 (C), 42.6 (CH_2), 37.6 (C-2), 35.2 (C-2), 32.4 (C-1), 23.4 (C-1), 21.5 (CH_3); *m/z* (ESI): 458 ([MH]$^+$, 100%); HRMS (ESI) (458.2152 [MH]$^+$, $C_{29}H_{32}NO_2S$ requires 458.2154); Anal. Calcd for $C_{29}H_{31}NO_2S$: C, 76.10%; H, 6.83%; N, 3.06%. Found: C, 76.12%, H, 6.79%, N, 3.08%.



2-(2-Methylprop-1-en-1-yl)-4,4-diphenyl-1-tosylpyrrolidine 2-tosyl-3-vinyl-2-azaspiro[4.5]decane 5.24: Isolated from **5.15** as a white solid using 15 mol% AgOTf (37 mg, 86%); mp: 65-66 ^oC; Rf = 0.57 (hexanes:EtOAc, 3:1); ν_{max}/cm^{-1}: 3057 (C-H), 2977 (C-H), 2929 (C-H), 1336 (S=O), 1156 (S=O); δ_H (500 MHz, $CDCl_3$): 7.60 (2H, d, *J* 8.3, H-2), 7.29 - 7.12 (12H, m, Ar), 4.81 - 4.77 (1H, m, =CH), 4.49 - 4.33 (2H, m, CH and N-CH_2), 3.87 (1H, d, *J* 10.2, N-CH_2), 2.75 (1H, ddd, *J* 12.4, 6.9, 1.5, CH_2), 2.39 (3H, s, H-4), 2.33 (1H, dd, *J* 12.4, 8.5, CH_2), 1.65 (3H, d, *J* 1.2, CH_3), 1.58 (3H, d, *J* 1.2, CH_3); δ_C (500 MHz, $CDCl_3$): 145.6 (Ar), 144.8 (Ar), 142.7 (C-1), 137.5 (C-3), 134.5 (=C), 129.2 (Ar), 128.6 (Ar), 128.5 (Ar), 127.1 (Ar), 126.7 (Ar), 126.6 (Ar), 126.5 (Ar), 126.4 (Ar), 125.3 (=CH), 57.7 (N-CH_2), 57.0 (CH), 52.6 (C), 45.8 (CH_2), 25.7

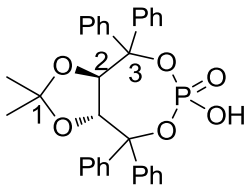
(CH_3), 21.5 (C-4), 18.0 (CH_3); *m/z* (ESI): 432 ($[MH]^+$, 100%); HRMS (ESI) 432.5940 ($[MH]^+$, $C_{27}H_{29}NO_2S$ requires 432.5944); Anal. Calcd for $C_{27}H_{29}NO_2S$: C, 75.14%; H, 6.77%; N, 3.25%. Found: C, 75.16%, H, 6.74%, N, 3.21%.

7.5 Catalysts

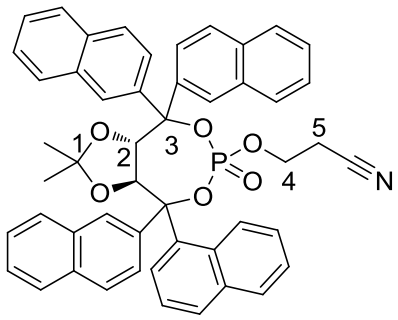


3-((3a*R*,8a*R*)-2,2-Dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)propane nitrile, *R,R*-4.13.[146] PCl_3 (75 µL, 0.85 mmol.) was added dropwise to solution of *R,R*-**4.11** (379 mg, 0.81 mmol.) and triethylamine (385 µL, 2.76 mmol.) in dry THF (5 mL) a 0 °C. The resulting mixture was stirred at 0 °C for a further 30 min before 3-hydroxypropionitrile (61 µL, 0.89 mmol.) in dry THF (5 mL) was added dropwise *via* cannula. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then diluted with Et_2O and the triethylammonium chloride salts were filtered through a celite pad. The solvent was then removed under vacuum to obtain the phosphite *R,R*-**4.12** as a light yellow solid which was used without purification in the oxidation step. 30% aqueous H_2O_2 (640 µL, 4.8 mmol.) was add to the crude phosphite in CH_2Cl_2 (10 mL). The biphasic mixture was stirred vigorously for 30 min and then quenched by the addition of 20 mL of saturated aqueous $NaHCO_3$ solution. The aqueous extracts were extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic extracts were washed with brine (2 x 5 mL), dried ($MgSO_4$) and concentrated under vacuum. *R,R*-**4.13** was isolated as a white solid (350 mg, 74% over two steps) after purification by column chromatography (hexanes:Et_2O, 1:4 to pure Et_2O). Rf= 0.43 (pure Et_2O); mp: 112-16 ^oC (lit 114-116 ^oC)[151]; ν_{max}/cm^{-1}: 3062 (C-H), 3006 (C-H), 2935 (C-H), 2865 (C-H), 2254 (C≡N), 1290 (P=O), 1008 (P-O-C); δ_H ($CDCl_3$): 7.69 - 7.19 (20H, m, Ar), 5.46 (1H, d, *J* 8.0, H-2), 5.17 (1H, d, *J* 8.0, H-2), 3.92 - 3.98 (1H, m, H-4), 3.42 (1H, m, H-4), 2.35 -2.13 (1H, m, H-5), 2.00 (1H, dt, *J* 16.9, 6.5, H-5), 0.88 (3H, s, CH_3), 0.52 (3H, s, CH_3); δ_C ($CDCl_3$): 143.8 (Ar), 143.7 (Ar), 143.2 (Ar), 139.5 (d, *J* 6.4, Ar), 139.0 (d, *J* 10.5, Ar), 129.0 (Ar), 128.6 (Ar), 128.4 (Ar), 128.3 (Ar), 128.0 (Ar), 127.7 (Ar), 127.3 (Ar), 126.9 (Ar), 116.1 (C-1), 113.9 (C≡N), 88.9 (d, *J* 7.8, C-3), 88.4 (d, *J* 8.1, C-3), 78.0 (C-2), 78.2 (C-2), 70.0 (d, *J* 4.6, C-4), 26.9 (CH_3), 26.2 (CH_3), 19.0 (d,

J = 8.9, 2H, C-5); δ_P ($CDCl_3$): -12.77; *m/z* (ESI): 604 ($[MNa]^+$, 100%), 431 (27); $[\alpha]_D^{25}$ = -342° (c = 1.0, $CHCl_3$).

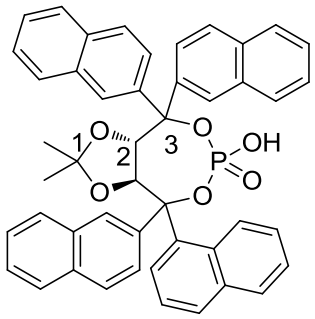


(3a*R*,8a*R*)-6-hydroxy-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide *R,R*-4.10-H.[145] DBU (95 µL, 0.60 mmol.) was added dropwise to a solution of *R,R*-**4.13** (350 mg, 0.60 mmol.) in dry CH_2Cl_2 (10 mL). The solution was stirred at room temperature and monitored by TLC. Once the reaction was complete AcOH (35 µL) was added, followed by H_2O (14 mL). The organic layer was then washed with 0.3 N HCl (2 x 10), saturated aqueous NaCl (10 mL), dried ($MgSO_4$) and concentrated under vacuum. The resulting white solid was dried under vacuum to afford *R,R*-**4.10**-H (307 mg 97%); mp: 150-155 °C (lit 154-156 °C)[151]; ν_{max}/cm^{-1}: 3062 (C-H), 2987 (C-H), 2935 (C-H), 2572 (P=O), 1602 (O=P-O), 1009 (P-O); δ_H ($CDCl_3$): 7.56 (4H, d, *J* 6.6, Ar), 7.48 - 7.14 (16H, m, Ar), 5.46 (1H, bs, OH), 5.22 (2H, s, H-2), 0.67 (6H, s, CH_3); δ_C ($CDCl_3$): 143.3 (Ar), 139.5 (d, *J* 9.2, Ar), 128.7 (Ar), 128.2 (Ar), 128.1 (Ar), 127.5 (Ar), 127.2 (Ar), 127.09 (Ar), 113.6 (C-1), 87.8 (d, *J* 7.0, C-3), 79.8 (C-2), 26.2 (CH_3); δ_P ($CDCl_3$): -8.03; *m/z* (ESI): 551 ($[MNa]^+$, 100%), 431 (30); [α]D = -216.0° (c = 1.0, $CHCl_3$).



3-(((3a*S*,8a*S*)-2,2-dimethyl-4-(naphthalen-1-yl)-4,8,8-tri(naphthalen-2-yl)-6-oxidotetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)propanenitrile was obtained by a similar procedure to *R,R*-**4.13**[145] on a 0.93 mmol. scale as a white solid (530 mg, 75% over two steps); R_f = 0.5 (pure Et_2O); mp: 125 - 128 °C (lit 124 - 126 °C)[151]; ν_{max} (thin film)/cm^{-1}: 3056 (C-H), 2988 (C-H), 2255 (CN), 1289 (P=O), 1000 (P-O-C); δ_H ($CDCl_3$): 8.27 - 8.24 (3H, d, *J* 2.6, Ar), 8.20 (1H, d, *J* 1.4, Ar), 8.07 - 7.92 (4H, m, Ar), 7.89 -7.79 (6H, m, Ar), 7.75 (1H, d, *J* 8.8, Ar), 7.68 (1H, d, *J* 8.8, Ar), 7.65 - 7.49 (10H, m, Ar), 7.47 (1H, dd, *J* 8.7, 1.8, Ar), 7.33 (1H, dd, *J* 8.7, 1.8, Ar), 5.83 (1H, d, *J* 8.0, H-2), 5.54 (1H, d, *J* 8.0, H-2), 4.01 - 3.94 (1H, m, H-4), 3.51 - 3.31 (1H, m, H-4), 2.18 - 2.08 (1H, m, H-5), 1.89 - 1.78 (1H, m, H-5), 0.93 (3H, s, CH_3), 0.56 (3H, s, CH_3); δ_C ($CDCl_3$): 140.4

(Ar), 140.30 (Ar), 140.27 (Ar), 136.8 (d, J_{PC}7.1, Ar), 136.4 (d, J_{PC} 10.0, Ar), 133.2 (Ar), 132.9 (Ar), 132.8 (Ar), 132.7 (Ar), 132.6 (Ar), 132.5 (Ar), 132.4 (Ar), 128.9 (Ar), 128.86 (Ar), 128.83 (Ar), 128.77 (Ar), 128.5 (Ar), 128.3 (Ar), 127.8 (Ar), 127.6 (Ar), 127.4 (Ar), 127.4 (Ar), 127.3 (Ar), 127.07 (Ar), 127.05 (Ar), 126.8 (Ar), 126.7 (Ar), 126.7 (Ar), 126.7 (Ar), 126.63 (Ar), 126.58 (Ar), 126.30 (Ar), 126.28 (Ar), 126.2 (Ar), 125.8 (Ar), 125.7 (Ar), 125.33 (Ar), 125.29 (Ar), 115.81 (C-1), 114.2 (C≡N), 89.1 (d, J = 7.3, C-3), 88.8 (d, J_{PC} 8.1, C-3), 80.4 (C-2), 78.7 (C-2), 62.1 (d, J_{PC} 4.6, 1H, C-4), 27.0 (CH_3), 26.5 (CH_3), 18.9 (d, J_{PC} 8.2, C-5); δ_P ($CDCl_3$): -12.40; *m/z* (ESI): 804 ($[MNa]^+$, 100%), 631 (20); $[\alpha]_D^{25}$ = +128.0^o (c = 0.7, $CHCl_3$).

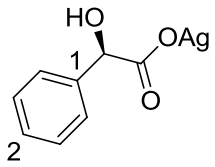


(3aR,8aR)-6-hydroxy-2,2-dimethyl-4-(naphthalen-1-yl)-4,8,8-tri(naphthalen-2-yl)tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide *S,S*-4.14-H was obtained by a similar procedure to *R,R*-**4.10**-H on a 0.69 mmol. scale as a white solid after being dried for several days on a vacuum pump.[145] (482 mg, 96%); R_f = 0.5 (pure Et_2O); mp: 189 - 202 ^{o}C (lit 186 - 188 °C)[151]; ν_{max} (thin film)/cm^{-1}: 3059 (C-H), 2964 (C-H) 2344 (P=O), 1597 (O=P-O), 1051 (P-O); δ_H ($CDCl_3$): 8.19 (4H, s, Ar), 7.95 - 7.88 (2H, m, Ar), 7.86 - 7.82 (2H, m, Ar), 7.77 - 7.67 (6H, m, Ar), 7.61 (2H, dd, J 8.8, 1.6, Ar), 7.56 (2H, d, J 8.8, Ar), 7.53 - 7.42 (8H, m, Ar), 7.33 (2H, dd, J 8.8, 1.6, Ar), 6.45 (1H, bs, OH), 5.56 (2H, s, H-2), 0.69 (6 H, s, CH_3); δ_C ($CDCl_3$): 140.47 (Ar), 136.9 (d, J_{PC} 8.6, Ar), 133.4 (Ar), 132.8 (Ar), 132.6 (Ar), 132.4 (Ar), 129.0 (Ar), 128.7 (Ar), 128.2 (Ar), 127.8 (Ar), 127.5 (Ar), 127.4 (Ar), 127.0 (Ar), 126.6 (Ar), 126.5 (Ar), 126.4 (Ar), 126.2 (Ar), 125.9 (Ar), 125.4 (Ar), 125.3 (Ar), 114.1 (C-1), 88.2 (d, J_{PC} 3.3, C-3), 80.0 (C-2), 26.8 (CH_3); δ_P ($CDCl_3$): -7.43; *m/z* (ESI): 751 ($[MNa]^+$, 12%), 631 (84), 573 (100); $[\alpha]_D^{25}$ = +277.9^o (c = 1.0, $CHCl_3$).

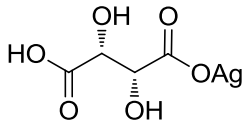
All Ag catalysts were prepared from the corresponding carboxylic acid by methods 1, 2 or 3.

Method 1[138]

The acid (1 equiv) was stirred in H_2O (1 mL) in the dark. To this NaOH (1 equiv) in H_2O (1 mL) was added. Then $AgNO_3$ (1 equiv) in H_2O (1 mL) was added and the product precipitated out of solution. The mixture was then filtered, washed with cold EtOH (5 mL) and dried overnight on a vacuum pump.



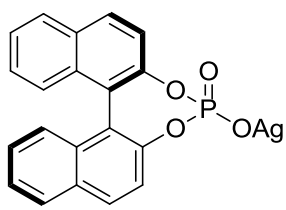
R-**4.4**-Ag was obtained from *R*-2-hydroxy-2-phenylacetic acid as a fluffy white solid (1.63 g, 96%);[138] mp: >240 ^oC (dec.); ν_{max} (thin film)/cm^{-1}: 3324 (O-H), 1951 (C-H), 1854 (C-H), 1544 (C=O); δ_H (d^6-DMSO): 7.42 (2H, d, *J* 7.2, Ar), 7.28 (2H, t, *J* 7.2, Ar), 7.23 - 7.17 (1H, m, H-2), 4.84 (1H, s, CH), 3.38 (1H, bs, OH); δ_C (d^6-DMSO): 176.1 (C=O), 143.3 (C-1), 128.0 (Ar), 127.0 (Ar), 126.9 (C-2), 74.6 (CH); *m/z* (FAB): 260 ($[M]^+$, 20%), 154 (100); $[\alpha]_D^{25} = -32^o$ (c = 0.5, DMSO).



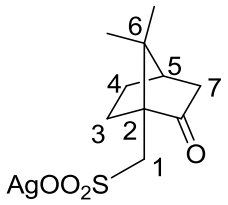
R,*R*-**4.5**-Ag was obtained from (2*R*,3*R*)-2,3-dihydroxysuccinic acid as a fluffy white solid (1.66 g, 97%);[138] mp: >220 ^oC (dec.); ν_{max} (thin film)/cm^{-1}: 3538 (O-H), 3169 (O-H), 1678 (C=O), 1588 (C=O); δ_H (D_2O): 4.38 (2 H, s, CH); δ_C (D_2O): 176.6 (C=O), 72.9 (CH); Anal. Calcd for $C_4H_5AgO_6$: C, 18.7%; H, 1.96%. Found: C, 19.0%, H, 2.06%; $[\alpha]_D^{25}$ = $+7.3^o$ (c = 1.0, H_2O).

Method 2[139,140]

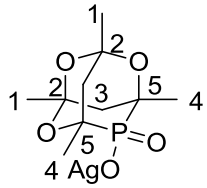
Ag_2CO_3 (0.5 equiv) was added in one portion to a solution of acid (1 equiv) in EtOH (5 mL) in the dark. The resulting mixture was protected from light and stirred vigorously overnight. The mixture was centrifuged and the solvent was decanted. A further portion of EtOH (5 mL) was added to the remaining solid. This was placed in the centrifuge and then decanted again. The EtOH extracts were combined and concentrated under vacuum. The resulting silver salt was dried overnight in vacuo.



R-**4.7**-Ag was obtained from *R*-(+)-1,1'-Binaphthalene-2,2'-diyl hydrogen phosphate as a white solid (574 mg, 88%); mp: >261 ^{o}C (dec.); ν_{max} (thin film)/cm^{-1}: 3056 (C-H), 2926 (C-H), 1233 (P=O), 1065 (P-O-Ar); δ_H (d^6-DMSO): 8.20 (2H, d, *J* 8.8, Ar), 8.11 (2H, d, *J* 8.0, Ar), 7.58 (2H, d, *J* 8.8, Ar), 7.54 (2H, dd, *J* 8.8, Ar), 7.39 (2H, dd, 8.8, Ar), 7.25 (2 H, d, *J* 8.4, Ar); δ_C (d^6-DMSO): 148.1 (d, J_{PC} 9.1, Ar), 132.1 (Ar), 131.5 (Ar), 129.1 (Ar), 127.3 (Ar), 126.6 (d, J_{PC} 3.0, Ar), 126.0 (Ar), 121.6 (Ar), 121.5 (Ar); δ_P (d^6-DMSO): 9.42; *m/z* (FAB): 455 ([M]$^+$, 100%); $[\alpha]_D^{25}$ = +274^{o} (c = 1.0, $CHCl_3$).



R-**4.6**-Ag was obtained from 1*R*-(-)-10-camphorsulfonic acid as a fluffy white solid (1.40 g, 96%); mp: >300 ^{o}C (dec.); ν_{max} (thin film)/cm^{-1}: 2960 (C-H), 1714 (C=O), 1250 (S=O); δ_H (D_2O): 3.17 (1H, d, *J* 15.0, H-1), 2.75 (1H, d, *J* 15.0, H-1), 2.37 - 2.20 (2H, m, H-7 and H-3), 2.05 (1H, t, *J* 4.5, H-5), 1.99 - 1.90 (1H, m, H-4), 1.88 (1H, d, *J* 18.9, H-7), 1.53 (1H, ddd, *J* 14.0, 9.4, 4.3, H-3), 1.34 (1H, ddd, *J* 12.9, 9.4, 4.3, H-4), 0.92 (3H, s, CH_3), 0.72 (3H, s, CH_3); δ_C (D_2O): 221.9 (C=O), 60.9 (C-2), 50.6 (C-6), 49.6 (C-1), 45.0 (C-7), 44.7 (C-5), 28.6 (C-4), 27.0 (C-3), 21.3 (CH_3), 21.1 (CH_3); *m/z* (FAB): 339 ([M]$^+$, 5%), 154 (100), 136 (79); Anal. Calcd for $C_{10}H_{15}AgO_4S$: C, 35.40%; H, 4.46%. Found: C, 35.32%, H, 4.34%; $[\alpha]_D^{25}$ = -24.6^{o} (c = 1.0, CH_3OH).

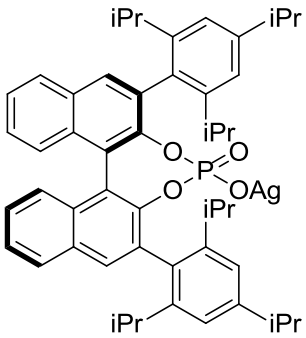


β-**4.16**-Ag was obtained from β-**4.16**-H as a fluffy white solid (622 mg, 87%); mp: >300 ^{o}C (dec.); ν_{max} (thin film)/cm^{-1}: 3001 (C-H), 2921 (C-H), 1451 (P-C), 1202 (P=O); δ_H ($CDCl_3$): 2.43 (2H, dd, *J* 13.2, 1.9, H-3), 1.96 (2H, dd, J_{PH} 23.6, 13.2, H-3), 1.43 (6H, s, H-1), 1.34 (6H, d, J_{PH} 11.5, H-4); δ_C ($CDCl_3$): 96.5 (C-2), 71.7 (d, J_{PC} 93.5, C-5), 43.4 (C-3), 27.2 (C-4), 18.9 (C-1); δ_P ($CDCl_3$): 31.0; *m/z* (FAB): 1527 ([M_4Ag_5]$^+$, 40%), 1173 ([M_3Ag_4]$^+$, 89%), 355 ([M]$^+$, 15); Anal. Calcd for $C_{10}H_{16}AgO_5P$: C, 33.83%; H, 4.54%. Found: C, 34.01%, H, 4.54%; $[\alpha]_D^{25}$ = +39.0^{o} (c = 0.5, $CHCl_3$).

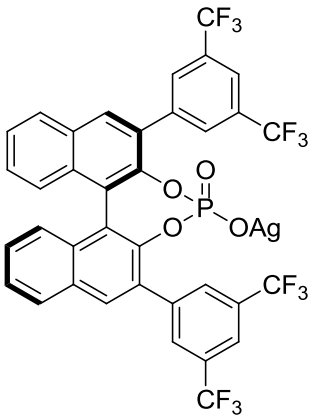
Method 3[36]

Ag_2CO_3 (0.5 equiv) was added in one portion to a solution of acid (1 equiv) in CH_2Cl_2 (5 mL) followed by H_2O (5 mL). The resulting mixture was protected from light, and

stirred vigorously for 2 h. After this time, the mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The biphasic suspension were separated and the aqueous layer extracted with further portions of CH_2Cl_2 (2 x 15 mL). The combined organic extracts were filtered through celite and concentrated under vacuum. The resulting silver salt was dried overnight in vacuo.

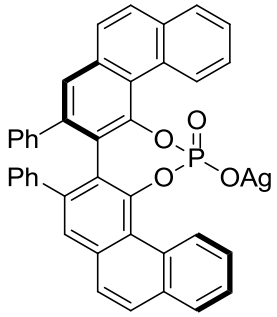


***R*-1.66** was obtained from *R*-3,3´-*bis*(2,4,6triisopropylphenyl)-1,1´-binaphthyl-2,2´-diylhydrogenphosphate as a fluffy white solid (525 mg, 94%);[36] mp: >251 ^oC (dec.) (lit. 250-254 dec.)[36]; ν_{max} (thin film)/cm^{-1}: 2965 (C-H), 1275 (P=O), 1123 (P-O-Ar), 1077 (P-O-Ar); δ_H ($CDCl_3$): 7.91 (2H, d, *J* 8.2, Ar), 7.84 (2H, s, Ar), 7.58 - 7.45 (2H, m, Ar), 7.41 - 7.31 (4H, m, Ar), 6.99 (2H, s, Ar), 6.96 (2H, s, Ar), 3.99 (1H, septet, *J* 6.1, CH), 2.87 (2H, septet, *J* 6.8, CH), 2.71 -2.50 (3H, m, CH), 1.25 (12H, d, *J* 6.8, CH), 1.17 (4H, dd, *J* 6.1, 2.8, CH), 1.06 (12H, dd, *J* 15.2, 6.4, CH),0.92 (6H, d, *J* 6.8, CH); δ_C ($CDCl_3$): 148.3 (Ar), 148.0 (Ar), 147.5 (Ar), 146.3 (Ar), 146.1 (Ar), 132.5 (d, J_{PC} 8.9, Ar), 132.3 (Ar), 130.9 (Ar), 129.5 (Ar), 128.1 (Ar), 127.4 (Ar), 126.1 (d, J_{PC} 3.0, Ar), 125.5 (Ar), 122.0 (Ar), 121.1 (Ar), 120.2 (Ar), 34.2 (CH), 30.9 (CH), 30.7 (CH), 26.3 (CH), 25.1 (CH), 25.0 (CH), *2*4.0 (CH), 23.3 (CH); δ_P ($CDCl_3$): 14.8; *m/z* (FAB): 879 (45%), 861 ($[MH]^+$, 10); $[\alpha]_D^{25}$ = -116.9^o (c = 0.5, $CHCl_3$).

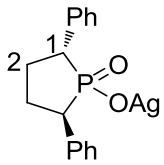


***R*-4.8**-Ag was obtained from *R*-3,3'-*Bis*[3,5bis(trifluoromethyl)phenyl]-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate as a fluffy white solid (451 mg, 90%);[143] mp: >300 ^oC (dec.); ν_{max} (thin film)/cm^{-1}: 2960 (C-H), 2869 (C-H), 1410 (C-F), 1242 (P=O), 1083 (P-O-Ar); δ_H ($CDCl_3$): 8.07 (1H, s, Ar), 8.04 (7H, s, Ar), 7.68 - 7.57 (4H, m, Ar), 7.50 - 7.39 (4H, m, Ar); δ_C ($CDCl_3$): 143.6 (d, J_{PC} 9.3, Ar), 138.6 (Ar), 132.3 (Ar), 132.0 (Ar), 131.4 (Ar), 131.4 (q, J_{FC} 33.4, Ar), 131.1 (d, J_{PC} 3.1, Ar), 130.9 (Ar), 128.7 (Ar), 127.6 (Ar), 127.1 (Ar), 126.8 (Ar), 123.5 (q, J_{FC} 344.0, Ar), 121.8 (d, J_{PC} 1.9, Ar), 121.6 (Ar); δ_P ($CDCl_3$): 14.1; δ_F ($CDCl_3$): -63.1; Product fragmentised using MS; *m/z*

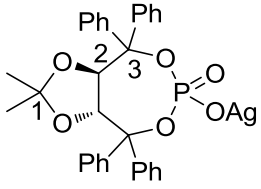
(FAB): 791 (100%); Anal. Calcd for $C_{36}H_{16}AgF_{12}O_4P$: C, 49.28%; H, 1.83%. Found: C, 49.28%, H, 1.80%; $[\alpha]_D^{25}$ = -187.5^o (c = 1.0, $CHCl_3$).



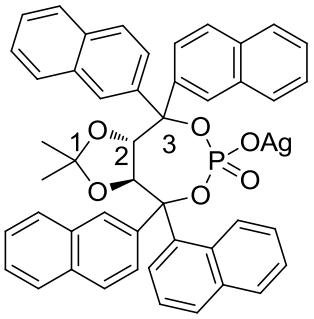
S-**4.9**-Ag was obtained from *S*-2,2′-Diphenyl-(4-biphenanthrol) as a fluffy white solid (297 mg, 85%); mp: >245 ^{o}C (dec.); ν_{max} (thin film)/cm^{-1}: 3054 (C-H), 2916 (C-H), 1223 (P=O), 1050 (P-O-Ar); δ_H (d^6-DMSO) 10.02 - 9.87 (2H, m, Ar), 8.08 - 7.97 (2H, m, Ar), 7.88 (4H, close AB, Ar), 7.78 - 7.63 (4H, m, Ar), 7.53 (2H, s, Ar), 7.10 (2H, t, *J* 7.2, Ar), 6.95 (4H, t, *J* 7.6, Ar), 6.45 (4H, d, *J* 7.6, Ar); δ_C (d^6-DMSO): 165.3 (Ar), 165.1 (d, J_{PC} 2.9, Ar), 151.6 (Ar), 141.0 (Ar), 140.4 (Ar), 134.1 (Ar), 133.1 (Ar), 130.4 (Ar), 129.4 (Ar), 129.2 (Ar), 128.7 (Ar), 128.4 (Ar), 127.9 (Ar), 127.5 (Ar), 127.0 (Ar), 126.8 (d, J_{PC} 4.6, Ar), 125.2 (Ar), 122.1 (Ar); δ_P (d^6-DMSO): 1.1; *m/z* (FAB): 815 ([MAg]$^+$, 54%), 707 ([M]$^+$, 68), 55 (100); $[\alpha]_D^{25}$ = +474^o (c = 0.6, CH_3OH).



R,R-**4.15**-Ag was obtained from *R,R*-1-hydroxy-1-oxo-2,5-*trans*-diphenylphospholane (*R,R*-**4.15**-H) as a fluffy white solid (681 mg, 98%); mp: >300 ^{o}C (dec.); ν_{max} (thin film)/cm^{-1}: 3059 (C-H), 3026 (C-H), 2947 (C-H), 2865 (C-H), 1449 (P-C), 1220 (P=O), 1022 (P-O-Ar); δ_H (D_2O): 7.38 - 7.12 (10H, m, Ar), 3.16 - 2.93 (2H, m, H-1), 2.30 - 2.20 (2H, m, H-2), 2.01 - 1.98 (2H, m, H-2). *m/z* (FAB): 379 ([M]$^+$, 10%), 262 (29), 55 (100); Anal. Calcd for $C_{16}H_{16}AgO_2P$: C, 50.69%; H, 4.25%. Found: C, 50.58%, H, 4.19%.

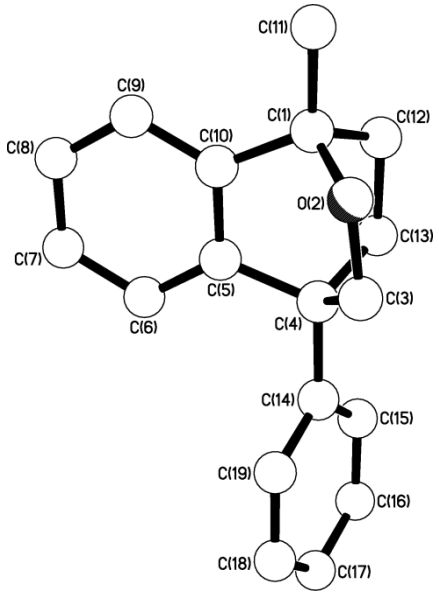


R,R-**4.10**-Ag was obtained from *R,R*-**4.10**-H as a fluffy white solid (240 mg 87%); mp: >234 ^{o}C (dec.); ν_{max} (thin film)/cm^{-1}: 3057 (C-H), 2991 (C-H), 1210 (P=O), 1036 (P-O-Ar); δ_H ($CDCl_3$): 7.61 (4H, d, *J* 7.6, Ar), 7.52 (4H, d, *J* 7.6, Ar), 7.37 - 7.06 (12H, m, Ar), 5.18 (2H, s, H-2), 0.82 (6 H, s, CH_3); δ_C ($CDCl_3$): 143.5 (Ar), 139.6 (d, J_{PC} 9.2, Ar), 128.8 (Ar), 128.2 (Ar), 128.1 (Ar), 127.6 (Ar), 127.2 (Ar), 126.9 (Ar), 113.7 (C-1), 87.9 (d, J_{PC} 7.0, C-3), 79.4 (C-2), 26.5 (CH_3); δ_P ($CDCl_3$): - 0.15 (br. s); *m/z* (FAB): 635 ([M]$^+$, 31%), 431 (45), 179 (100); Anal. Calcd for $C_{31}H_{28}AgO_6P$: C, 58.60%; H, 4.44%. Found: C, 58.45%, H, 4.36%; $[\alpha]_D^{25}$ = -219.0^o (c = 1.0, $CHCl_3$).



S,S-**4.14**-Ag was obtained from *S,S*-**4.14**-H as a white solid (183 mg, 80%); mp >220 ^{o}C (dec.); ν_{max} (thin film)/cm^{-1}: 3066 (C-H), 2989 (C-H), 1213 (P=O), 1041 (P-O-Ar); δ_H ($CDCl_3$): 8.52 (2H, s, Ar), 8.20 (2H, s, Ar), 7.95 (2H, d, *J* 8.0, Ar), 7.87 (2H, d, *J* 8.0, Ar), 7.72 (4H, t, *J* 8.0, Ar), 7.61 (2H, d, *J* 8.0, Ar), 7.56 - 7.37 (12H, m, Ar), 7.33 (2H, t, *J* 7.4, Ar), 5.43 (2 H, s, H-2), 0.88 (6H, s, CH_3); δ_C ($CDCl_3$): 140.4 (Ar), 136.9 (d, J_{PC} 8.6, Ar), 133.1 (Ar), 132.7 (Ar), 132.6 (Ar), 132.5 (Ar), 128.9 (Ar), 128.8 (Ar), 128.2 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 126.9 (Ar), 126.6 (Ar), 126.5 (Ar), 126.4 (Ar), 126.2 (Ar), 16.0 (Ar), 125.4 (Ar), 125.3 (Ar), 114.0 (C-1), 88.2 (d, J_{PC} 3.3, C-3), 80.0 (C-2), 26.8 (CH_3); δ_P ($CDCl_3$): -0.51; *m/z* (FAB): 835 ([MH]$^+$, 11%), 737 (50), 267 (100); Anal. Calcd for $C_{47}H_{36}AgO_6P$: C, 67.55%; H, 4.34%. Found: C, 68.0%, H, 4.04%. $[\alpha]_D^{25}$ = +279.3^o (c = 1.0, $CHCl_3$).

Appendix 1: Crystal data and structure refinement for **2.11**.



Identification code	MH0802	
Empirical formula	C18 H18 O	
Formula weight	250.32	
Temperature	173(2) K	
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å	
Crystal system, space group	Orthorhombic, Pna2(1)	
Unit cell dimensions	a = 14.1920(13) Å	α = 90°
	b = 12.8979(13) Å	β = 90°
	c = 7.4178(6) Å	γ = 90°
Volume, Z	1357.8(2) $Å^3$, 4	
Density (calculated)	1.225 Mg/m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	536	
Crystal colour / morphology	Colourless platy needles	
Crystal size	0.15 x 0.05 x 0.01 mm^3	
θ range for data collection	3.97 to 27.50°	
Index ranges	-17<=h<=16, -15<=k<=13, -7<=l<=9	
Reflns collected / unique	5103 / 2203 [R(int) = 0.0798]	
Reflns observed [F>4σ(F)]	1140	

Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2203 / 1 / 172
Goodness-of-fit on F^2	0.853
Final R indices [F>4σ(F)]	R1 = 0.0497, wR2 = 0.0803
	R1+ = 0.0497, wR2+ = 0.0803
	R1- = 0.0497, wR2- = 0.0803
R indices (all data)	R1 = 0.1215, wR2 = 0.0981
Absolute structure parameter	x+ = 0(3), x- = 1(3)
Largest diff. peak, hole	0.186, -0.153 eÅ^{-3}
Mean and maximum shift/error	0.000 and 0.000

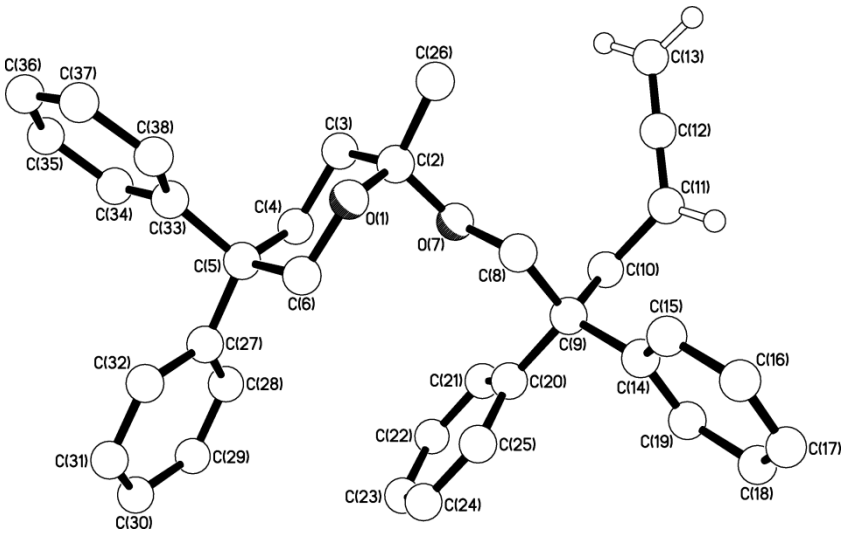
Bond lengths [Å] and angles [°] for **2.11**.

C(1)-O(2)	1.464(4)
C(1)-C(10)	1.487(5)
C(1)-C(11)	1.505(5)
C(1)-C(12)	1.543(5)
O(2)-C(3)	1.433(4)
C(3)-C(4)	1.546(4)
C(4)-C(14)	1.519(4)
C(4)-C(5)	1.521(4)
C(4)-C(13)	1.534(4)
C(5)-C(6)	1.369(4)
C(5)-C(10)	1.410(4)
C(6)-C(7)	1.393(4)
C(7)-C(8)	1.386(5)
C(8)-C(9)	1.370(5)
C(9)-C(10)	1.391(5)
C(12)-C(13)	1.543(4)
C(14)-C(19)	1.385(5)
C(14)-C(15)	1.390(5)
C(15)-C(16)	1.378(5)
C(16)-C(17)	1.369(6)
C(17)-C(18)	1.374(5)
C(18)-C(19)	1.384(5)

O(2)-C(1)-C(10)	108.2(3)
O(2)-C(1)-C(11)	105.5(3)
C(10)-C(1)-C(11)	115.8(3)
O(2)-C(1)-C(12)	106.4(3)
C(10)-C(1)-C(12)	108.2(3)
C(11)-C(1)-C(12)	112.2(3)
C(3)-O(2)-C(1)	112.9(2)
O(2)-C(3)-C(4)	112.0(3)
C(14)-C(4)-C(5)	112.8(3)

C(14)-C(4)-C(13)	114.8(3)
C(5)-C(4)-C(13)	105.8(3)
C(14)-C(4)-C(3)	109.8(3)
C(5)-C(4)-C(3)	108.0(3)
C(13)-C(4)-C(3)	105.1(3)
C(6)-C(5)-C(10)	120.4(3)
C(6)-C(5)-C(4)	126.8(3)
C(10)-C(5)-C(4)	112.6(3)
C(5)-C(6)-C(7)	119.8(3)
C(8)-C(7)-C(6)	120.0(3)
C(9)-C(8)-C(7)	120.5(3)
C(8)-C(9)-C(10)	120.3(4)
C(9)-C(10)-C(5)	119.0(3)
C(9)-C(10)-C(1)	127.6(4)
C(5)-C(10)-C(1)	113.4(3)
C(1)-C(12)-C(13)	109.7(3)
C(4)-C(13)-C(12)	109.8(3)
C(19)-C(14)-C(15)	117.8(3)
C(19)-C(14)-C(4)	120.0(3)
C(15)-C(14)-C(4)	122.2(3)
C(16)-C(15)-C(14)	120.4(4)
C(17)-C(16)-C(15)	120.8(4)
C(16)-C(17)-C(18)	120.0(4)
C(17)-C(18)-C(19)	119.3(5)
C(18)-C(19)-C(14)	121.7(4)

Appendix 2: Crystal data and structure refinement for **3.1**.



Identification code	MH0901	
Empirical formula	C36 H36 O2	
Formula weight	500.65	
Temperature	293(2) K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Monoclinic, P2(1)/c	
Unit cell dimensions	a = 6.3771(3) Å	α = 90°
	b = 19.8345(8) Å	β = 97.321(4)°
	c = 23.2868(12) Å	γ = 90°
Volume, Z	2921.5(2) $Å^3$, 4	
Density (calculated)	1.138 Mg/m^3	
Absorption coefficient	0.530 mm^{-1}	
F(000)	1072	
Crystal colour / morphology	Colourless needles	
Crystal size	0.18 x 0.06 x 0.03 mm^3	
θ range for data collection	2.94 to 63.18°	
Index ranges	-7<=h<=4, -21<=k<=22, -26<=l<=23	
Reflns collected / unique	8043 / 4532 [R(int) = 0.0278]	
Reflns observed [F>4σ(F)]	2460	
Absorption correction	Analytical	

Max. and min. transmission	0.987 and 0.949
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4532 / 24 / 357
Goodness-of-fit on F^2	0.840
Final R indices [F>4σ(F)]	R1 = 0.0483, wR2 = 0.1162
R indices (all data)	R1 = 0.0859, wR2 = 0.1279
Extinction coefficient	0.0018(2)
Largest diff. peak, hole	0.160, -0.170 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Bond lengths [Å] and angles [°] for **3.1**.

O(1)-C(2)	1.425(2)
O(1)-C(6)	1.428(2)
C(2)-O(7)	1.421(2)
C(2)-C(3)	1.510(3)
C(2)-C(26)	1.511(3)
C(3)-C(4)	1.509(3)
C(4)-C(5)	1.540(3)
C(5)-C(27)	1.523(3)
C(5)-C(33)	1.532(3)
C(5)-C(6)	1.540(3)
O(7)-C(8)	1.416(2)
C(8)-C(9)	1.536(3)
C(9)-C(20)	1.527(3)
C(9)-C(14)	1.531(3)
C(9)-C(10)	1.541(3)
C(10)-C(11')	1.492(16)
C(10)-C(11)	1.494(5)
C(11)-C(12)	1.282(6)
C(12)-C(13)	1.292(5)
C(11')-C(12')	1.277(14)
C(12')-C(13')	1.327(14)
C(14)-C(15)	1.379(3)
C(14)-C(19)	1.382(3)
C(15)-C(16)	1.374(3)
C(16)-C(17)	1.359(4)
C(17)-C(18)	1.368(4)
C(18)-C(19)	1.388(3)
C(20)-C(21)	1.388(3)
C(20)-C(25)	1.394(3)
C(21)-C(22)	1.388(3)
C(22)-C(23)	1.366(4)
C(23)-C(24)	1.367(4)

C(24)-C(25)	1.382(4)
C(27)-C(28)	1.376(3)
C(27)-C(32)	1.381(3)
C(28)-C(29)	1.384(3)
C(29)-C(30)	1.364(4)
C(30)-C(31)	1.355(4)
C(31)-C(32)	1.382(4)
C(33)-C(38)	1.375(3)
C(33)-C(34)	1.384(3)
C(34)-C(35)	1.376(3)
C(35)-C(36)	1.367(4)
C(36)-C(37)	1.361(3)
C(37)-C(38)	1.382(3)

C(2)-O(1)-C(6)	114.34(15)
O(7)-C(2)-O(1)	110.76(16)
O(7)-C(2)-C(3)	104.54(17)
O(1)-C(2)-C(3)	110.56(16)
O(7)-C(2)-C(26)	112.68(17)
O(1)-C(2)-C(26)	105.58(17)
C(3)-C(2)-C(26)	112.84(19)
C(4)-C(3)-C(2)	111.97(18)
C(3)-C(4)-C(5)	110.59(17)
C(27)-C(5)-C(33)	108.17(16)
C(27)-C(5)-C(4)	113.46(17)
C(33)-C(5)-C(4)	109.75(17)
C(27)-C(5)-C(6)	106.71(16)
C(33)-C(5)-C(6)	113.31(17)
C(4)-C(5)-C(6)	105.51(16)
O(1)-C(6)-C(5)	114.34(17)
C(8)-O(7)-C(2)	117.00(15)
O(7)-C(8)-C(9)	107.41(16)
C(20)-C(9)-C(14)	109.85(17)
C(20)-C(9)-C(8)	107.61(16)

C(14)-C(9)-C(8)	110.59(17)
C(20)-C(9)-C(10)	110.99(17)
C(14)-C(9)-C(10)	108.83(16)
C(8)-C(9)-C(10)	108.97(17)
C(11')-C(10)-C(9)	116.1(14)
C(11)-C(10)-C(9)	113.8(3)
C(12)-C(11)-C(10)	124.5(5)
C(11)-C(12)-C(13)	179.2(7)
C(12')-C(11')-C(10)	124(2)
C(11')-C(12')-C(13')	172(3)
C(15)-C(14)-C(19)	117.0(2)
C(15)-C(14)-C(9)	124.0(2)
C(19)-C(14)-C(9)	119.0(2)
C(16)-C(15)-C(14)	121.6(2)
C(17)-C(16)-C(15)	120.7(3)
C(16)-C(17)-C(18)	119.4(3)
C(17)-C(18)-C(19)	119.9(3)
C(14)-C(19)-C(18)	121.4(3)
C(21)-C(20)-C(25)	116.2(2)
C(21)-C(20)-C(9)	123.9(2)
C(25)-C(20)-C(9)	119.8(2)
C(22)-C(21)-C(20)	121.7(2)
C(23)-C(22)-C(21)	120.4(3)
C(22)-C(23)-C(24)	119.5(3)
C(23)-C(24)-C(25)	120.2(3)
C(24)-C(25)-C(20)	122.0(3)
C(28)-C(27)-C(32)	116.4(2)
C(28)-C(27)-C(5)	124.1(2)
C(32)-C(27)-C(5)	119.6(2)
C(27)-C(28)-C(29)	121.4(2)
C(30)-C(29)-C(28)	121.0(3)
C(31)-C(30)-C(29)	118.7(3)
C(30)-C(31)-C(32)	120.4(3)
C(27)-C(32)-C(31)	122.1(3)

C(38)-C(33)-C(34)	116.7(2)
C(38)-C(33)-C(5)	123.99(19)
C(34)-C(33)-C(5)	119.2(2)
C(35)-C(34)-C(33)	121.7(3)
C(36)-C(35)-C(34)	120.4(3)
C(37)-C(36)-C(35)	119.1(3)
C(36)-C(37)-C(38)	120.4(3)
C(33)-C(38)-C(37)	121.7(2)

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