Reactions of Allenylpalladium Intermediates in Organic Synthesis

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Summary

This thesis describes our examination of the reactivity of allenylpalladium intermediates generated from the reaction of palladium(0) with propargylic electrophiles.

Chapter 1 provides a general overview of the literature reported to date concerning the nature and reactivity of allenylpalladium intermediates.

The coupling of a variety of propargylic electrophiles with aryl boronic acids to form allenes is examined in *Chapter 2*. However, when employing diastereomerically pure electrophiles, some erosion of stereochemistry was observed in the allene products. This effect was examined further, and epimerisation of the allene product was found to be the origin of the loss of stereochemistry. Evidence for the species likely responsible for this epimerisation is presented.

The serendipitous formation of tetrahydrofurans (THFs) from propargylic 7-membered cyclic carbonates prompted an in-depth examination of this reactivity, as described in *Chapter 3*. The reaction of these cyclic carbonates was rendered stereoselective and the stereochemical outcome of the reaction elucidated. The methodology was extended to propargylic *acyclic* carbonates which allowed the formation of tetrahydropyrans (THPs). The effect of ring-size and substituents on the cyclisations was examined, culminating in the formation of two rings in a single step from diol-containing *bis*-carbonates.

Chapter 4 describes the extension of this methodology to the formation of azacyclic products. This built upon foundation work conducted by a Part II student within the group,[i] and further improved the selectivity of the reaction. Two diverse azacyclic skeletons could be formed from the same substrate by the employment of different bidentate phosphine ligands, and a variety of substrates were examined under these conditions.

Chapter 5 draws general conclusions and sets out possible future directions for the methodology, and full experimental details are outlined in *Chapter 6*.

Part of this work is published in peer-reviewed literature.[ii]

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[i] A. S. Jones, *Cascade Reactions Involving Allenylpalladium Intermediates*, Part II Thesis, **2011**

[ii] D. S. B. Daniels, A. L. Thompson and E. A. Anderson, *Angew. Chem. Int. Ed.* **2011**, *50*, 11506-11510

Declaration

The work presented in this thesis was carried out at the Chemistry Research Laboratory at the University of Oxford between Michaelmas 2008 and Trinity 2012 under the supervision of Dr. Edward Anderson. All the work presented is my own, except where otherwise stated, and has not been submitted in full or in part for any other degree at this or any other university.

David S. B Daniels

October 2012

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Abbreviations

acac	acetylacetone
AIBN	2,2'-azobis(2-methyl propionitrile)
ATR	attenuated total reflectance
BAIB	[bis(acetoxy)-iodo]benzene
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	(1,1'-binaphthalene-2,2'-diyl) bis(diphenylphosphine)
brsm	based on recovered starting material
Bs	benzenesulfonyl
BT	benzothiazole
CAN	ceric(IV) ammonium nitrate
CI	chemical ionisation
COSY	correlation spectroscopy
CSA	camphor-10-sulfonic acid
Cy	cyclohexyl
DAST	(diethylamino)sulfur trifluoride
DavePhos	2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino) biphenyl
dba	(*E*,*E*)-dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMM	dimethoxymethane
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetra hydro-2(1*H*)-pyrimidinone
DPEN	diphenylethylenediamine
DPEphos	(oxydi-2,1-phenylene)bis (diphenylphosphine)
dppb	1,4-bis(diphenylphosphino) butane
dppe	1,2-bis(diphenylphosphino) ethane
dppep	2-(2-(diphenylphosphino) ethyl) pyridine
dppf	1,1'-bis(diphenylphosphino) ferrocene
dpph	1,6-bis(diphenylphosphino) hexane
dppm	bis(diphenylphosphino) methane
dppp	1,3-bis(diphenylphosphino) propane
dpppe	1,5-bis(diphenylphosphino) pentane
dr	diastereomeric ratio
ee	enantiomeric excess
eq.	equivalents
ESI	electrospray ionisation
FI	field ionisation
FT-IR	fourier transform infra-red

FWHM	full width at half maximum
GC/MS	gas chromatography / mass spectrometry
HMBC	heteronuclear multiple-bond correlation spectroscopy
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
hr	hour
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
ImH	imidazole
L	general ligand
LG	leaving group
LUMO	lowest unoccupied molecular orbital
M	general metal
m-CPBA	*meta*-chloroperbenzoic acid
MIDA	*N*-methyliminodiacetic acid
MOM	methoxymethyl
Mosher's acid chloride	α-methoxy-α-(trifluoro methyl) phenylacetyl chloride
Ms	methanesulfonyl
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
4-Ns	4-nitrobenzenesulfonyl
Nu	nucleophile
Oxone®	potassium peroxymonosulfate
PCC	pyridinium chlorochloromate
PDC	pyridinium dichromate
Phox	2-[2-(diphenylphosphino) phenyl]-4,5-dihydro-4-isopropyl -oxazole
PMP	*p*-methoxyphenyl
ppm	parts-per million
PPTS	pyridinium *p*-toluenesulfonate
py.	pyridine
R	general substituent
R_f	retention factor
RT	room temperature
SAD	Sharpless asymmetric dihydroxylation
sat.	saturated
TBAF	tetrabutylammonium fluoride
t-Bu-dppf	1,1'-bis(di-*tert*-butylphosphino)ferrocene
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TFA	2,2,2-trifluroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TOF	time-of-flight
o-tol	*ortho*-tolyl
TLC	thin-layer chromatography
t_R	retention time
Ts	*p*-toluenesulfonyl
X	general anion
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Chapter 1. Introduction

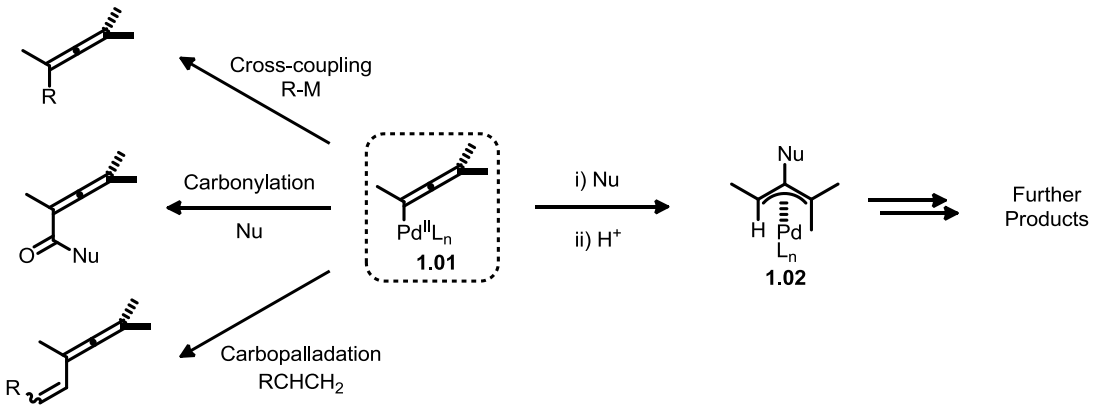
1.1 Overview

Organopalladium chemistry has emerged as one of the most powerful carbon-carbon and carbon-heteroatom bond forming processes known to the organic chemist; its development culminating in the award of the Nobel prize in chemistry 2010[1-2] to three of the major contributors: Richard Heck,[3] Ei-ichi Negishi[4-5] and Akira Suzuki.[6] Since the development of the first homogeneous palladium-catalysed reaction in 1959, the Wacker process,[7-8] palladium catalysis has been applied to a wide range of reactions. This includes, but is not limited to, carbopalladation of alkenes[9] and alkynes,[10] carbonylation,[11] π-allyl (Tsuji-Trost)[12] reactions, cross-coupling with organometallic reagents[13] and C−H activation.[14]

The versatility of organopalladium to undergo all of these reactions and more demonstrates that research into palladium catalysis continues to be a fruitful endeavour.[15]

1.2 Allenylpalladium Intermediates

Whilst the processes described above have received considerable attention, the field of allenylpalladium chemistry has been much less studied. Allenylpalladium intermediates (**1.01**) are a class of organopalladium complex that can undergo a multitude of reactions, either through direct reaction at palladium (cross-coupling, carbonylation, carbopalladation etc.),[16-17] or with nucleophilic attack on the allenyl ligand itself to form π-allyl complexes (**1.02**) that are able to undergo further functionalisations (*Scheme 1.1*).[18]

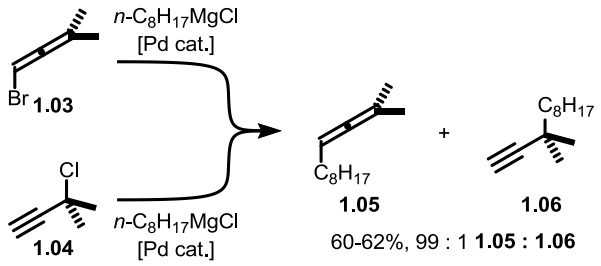


Scheme 1.1

1.2.1 Formation

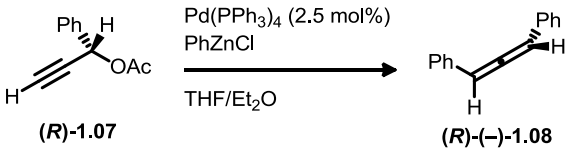
Allenylpalladium intermediates (e.g. **1.01**) are most often formed in one of two ways; either through

oxidative addition into a haloallene **1.03**, or a suitable propargylic system bearing a leaving group **1.04**. These processes were demonstrated in 1980 by Jeffrey-Luong and Linstrumelle in the first report of the palladium-mediated formation of allenes (**1.05**); in this case from the cross-coupling of **1.03** and **1.04** with Grignard reagents (*Scheme 1.2*).[19] The active Pd(0) catalyst was generated from the *in situ* reduction of $PdCl_2(PPh_3)_2$ by DIBAL-H.



Scheme 1.2

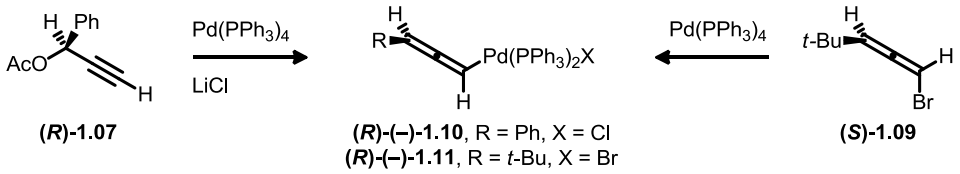
Allenes are inherently chiral molecules as predicted by Van't Hoff in 1875;[20] this chirality originating from the axis of the allene. Therefore, the stereochemical outcome of oxidative addition of palladium to a suitable electrophile is of prime importance. In 1983, Vermeer described the reaction of enantiopure propargylic ester **(*R*)-1.07** with phenylzinc chloride under palladium catalysis, showing it to be a 1,3-*anti*-substitution (*Scheme 1.3*).[21]



Scheme 1.3

The absolute configuration of the levorotatory allene product **(*R*)-(−)-1.08** was assigned through the application of the Lowe-Brewster rule,[22-23] which correlates the sign of optical rotation of an allene to its absolute configuration through consideration of the polarizability of the allene substituents. Vermeer proposed that an *anti*-S_N2' displacement of the leaving group by palladium is the origin of the observed inversion of configuration. The transmetallation and reductive elimination steps were proposed to proceed with retention of stereochemistry.

Further studies were made by Vermeer to ratify this mechanistic proposal by isolating and measuring the optical properties of the allenylpalladium intermediates **(*R*)-1.10** and **(*R*)-1.11** (*Scheme 1.4*).[24]

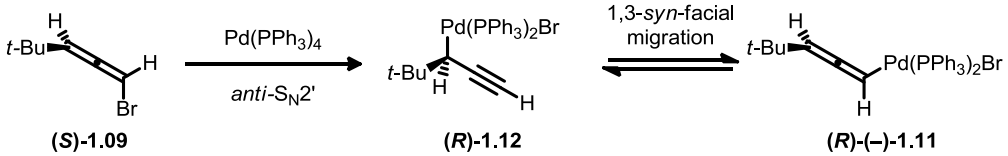


(*R*)-1.07 **(*R*)-(–)-1.10**, R = Ph, X = Cl; **(*R*)-(–)-1.11**, R = *t*-Bu, X = Br **(*S*)-1.09**

Scheme 1.4

The allenylpalladium intermediates **(*R*)-1.10** and **(*R*)-1.11** were isolated as moderately air stable solids, but were found to be very sensitive to oxidation when in solution. Their formation was confirmed by ^{13}C NMR spectroscopy (δ_C of central carbon *ca.* 195 ppm) and IR spectroscopy (weak absorption at ν_{max} = 1900 cm^{-1}). The Lowe-Brewster rule was again applied to the sign of the optical rotation, allowing the absolute configuration of both intermediates to be assigned as (*R*). As expected this indicated that the displacement of the acetate group in **(*R*)-1.07** by palladium had proceeded *anti* to give **(*R*)-1.10** with inversion of configuration.

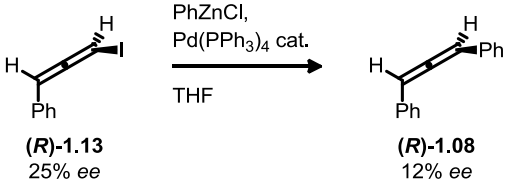
Interestingly however, oxidative addition to allenylbromide **(*S*)-1.09** had also proceeded with inversion to give **(*R*)-1.11**. The reason for this is not immediately obvious, as direct oxidative addition into the C−Br bond would be expected to proceed with retention. Vermeer proposed that the oxidative addition proceeds in an *anti*-S_N2' fashion to afford the propargylpalladium species **(*R*)-1.12**. This can undergo a reversible 1,3-*syn*-facial migration to afford the less sterically hindered allenylpalladium species **(*R*)-1.11** (*Scheme 1.5*). A similar S_N2' displacement and 1,3-*syn*-facial migration had been proposed by Corey to explain the stereochemical outcome of the reaction of organocuprates with haloallenes.[25]



(*S*)-1.09 **(*R*)-1.12** **(*R*)-(–)-1.11**

Scheme 1.5

Further studies by Vermeer and Elsevier showed that although this stereochemical outcome holds true for chloro- and bromoallenes; interestingly, oxidative addition into iodoallenes (**(*R*)-1.13**) instead occurs with predominant *retention* (*Scheme 1.6*).[26]



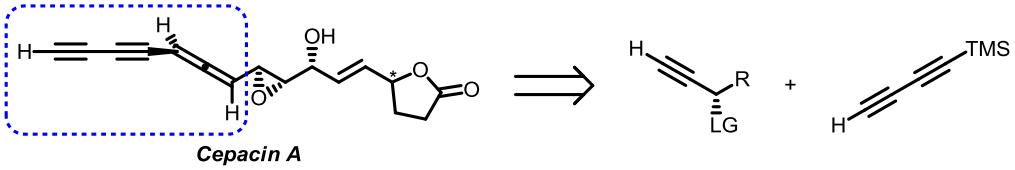
(*R*)-1.13 25% *ee* **(*R*)-1.08** 12% *ee*

Scheme 1.6

This result was reasoned based on the reactivity of vinyl halides towards Pd (in the order I > Br > Cl), and suggests a dominating direct oxidative addition of Pd(0) into the C−I bond, although competing S_N2' oxidative addition may explain the observed loss of enantiopurity. Unfortunately, isolation of a Pd(II) complex of type **1.10** (X = I) could not be achieved, so direct evidence for the formation of the allenylpalladium with retention of configuration could not be gained.

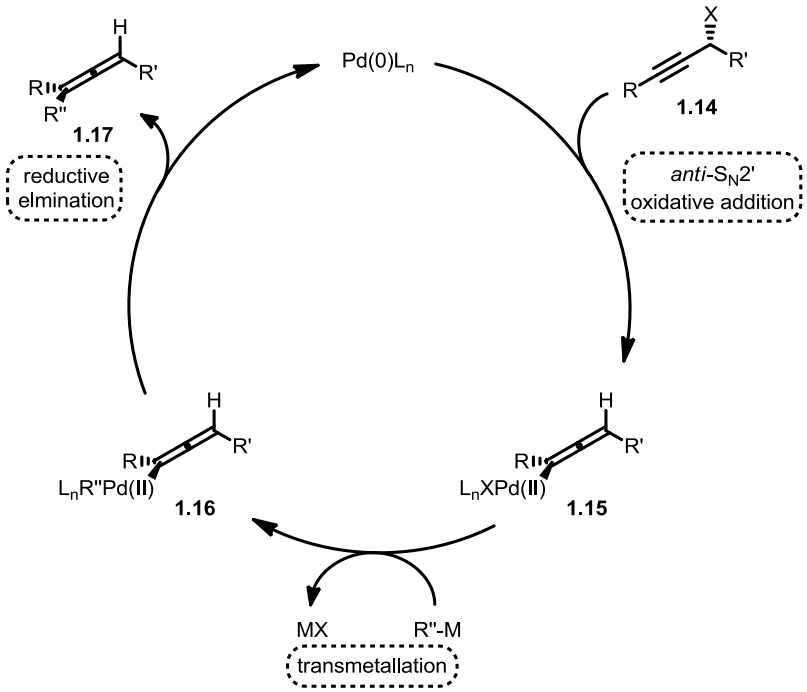
1.3 Cross-coupling of Allenylpalladium Intermediates

Our interest in allenylpalladium derived from a retrosynthetic analysis of the allene-diyne unit contained in the natural product cepacin A.[27] We envisaged that the allene core could be generated from Sonogashira coupling of a suitable electrophile, perhaps in a cascade-type process (*Scheme 1.7*).



Scheme 1.7

The early investigations by Linstrumelle[19] and Vermeer[21] suggested that palladium catalysis would be a viable route for the formation of enantioenriched allenes from suitable propargylic or allenic electrophiles.



Scheme 1.8: General catalytic cycle for palladium-catalysed allene synthesis through cross-coupling

The overall catalytic cycle for cross-coupling of a propargylic electrophile under palladium catalysis is shown in *Scheme 1.8*. When considering enantiopure electrophiles, *anti*-S_N2' oxidative addition

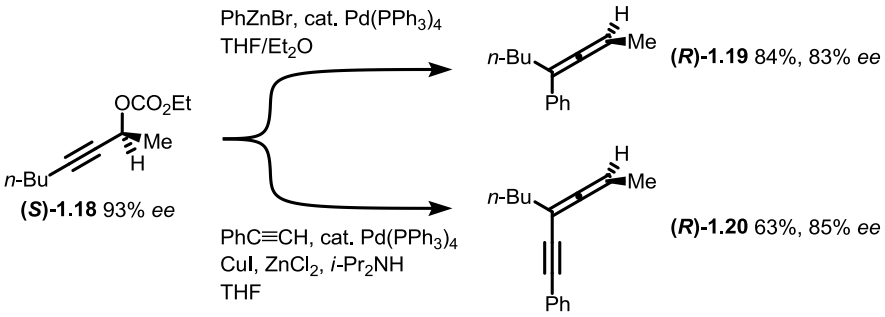
affords the stereodefined allenylpalladium(II) species **1.15**. This undergoes transmetallation and reductive elimination, both with retention, to afford the cross-coupled product **1.17** and regenerate Pd(0). Thus, the reaction is an overall invertive process, as described by Vermeer.[21]

1.3.1 Asymmetric Examples

There have been relatively few examples of cross-coupling of enantioenriched propargylic electrophiles to form chiral, non-racemic allenes and these demonstrate varying fidelities of stereochemical transfer.

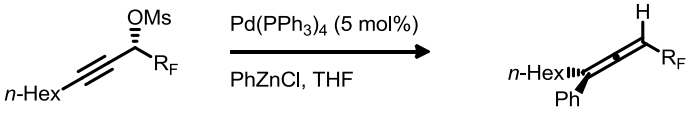
The first example of an asymmetric cross-coupling was disclosed by Vermeer (*Scheme 1.3, vide supra*),[21] starting from acetate **(*R*)-1.07** with an enantiomeric excess of 28%. The degree of stereochemical transfer was found to be 82 : 18 (*anti* : *syn*), quantified through extrapolation of the optical rotation of the allene product to the known literature value for the enantiopure allene.

Later in 1997, Dixneuf and co-workers described the reaction of propargylic carbonates under Negishi cross-coupling conditions (*Scheme 1.9*).[28] These reactions proceeded with fairly high stereoselectivity to form enantioenriched allenes in good yields.



Scheme 1.9: Dixneuf's cross-coupling under Negishi conditions

In 2000, Konno and co-workers described the coupling of perfluoroalkylated propargylic mesylates under Negishi conditions, giving enantioenriched allenes with complete transfer of stereochemistry (*Scheme 1.10*).[29]



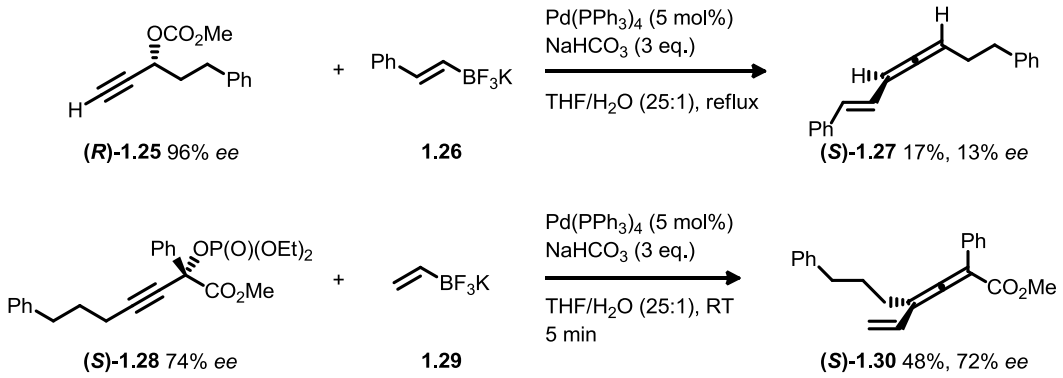
(***S*)-1.21** $R_F = CF_3$ (96% *ee*)
(***S*)-1.22** $R_F = C_2F_5$ (94% *ee*)
(***S*)-1.23** $R_F = CF_3$ (77%, 96% *ee*)
(***S*)-1.24** $R_F = C_2F_5$ (70%, 96% *ee*)

Scheme 1.10: Konno's cross-coupling with perfluoroalkylated electrophiles

The presence of a strongly electron-withdrawing perfluoroalkyl group may reduce the reactivity of the allene towards Pd(II) species, thereby negating any isomerisation pathway promoted by Pd(II) (*vide*

infra).

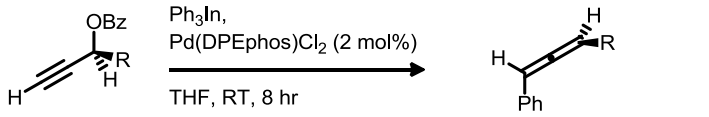
Molander and co-workers described the coupling of alkenyl potassium trifluoroborate salts with propargylic carbonates and phosphates.[30] The degree of stereochemical transfer varied greatly, dependent on both the substrate and coupling partner, with most examples giving poor selectivity (*Scheme 1.11*). The reaction of phosphate **(*S*)-1.28** is an unusual example, giving a high level of stereochemical transfer albeit in low isolated yield. Noticeably, **(*S*)-1.28** again features an electron-withdrawing group, but was also formed at room temperature.



Scheme 1.11: Molander's cross-coupling with trifluoroborate salts

Studies of the reaction showed that isomerisation occurred both during the reaction and after starting material had been consumed, suggesting that Pd(0) is able to promote the isomerisation of these ene-allenes.

In 2006, Sarandeses and co-workers described the palladium-catalysed coupling of triorganoindium species with propargylic esters, achieving good selectivity (*Scheme 1.12*).[31] The enantiomeric excess of the products **(*R*)-1.33** and **(*R*)-1.34** were determined through NMR with chiral shift reagents; **(*R*)-1.34** showed a single peak at the limits of detection, hence its assignment as >95% *ee*.



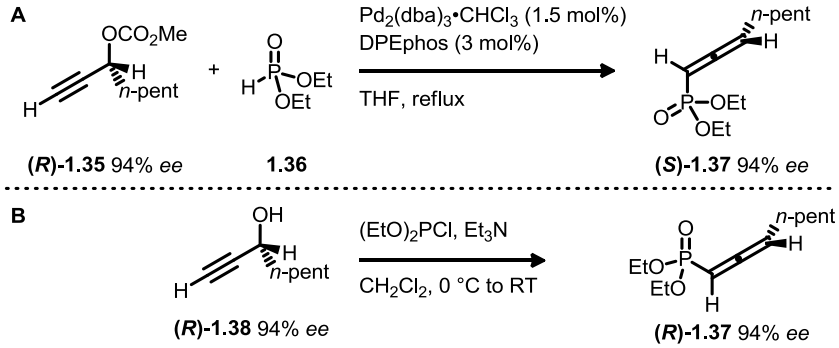
(***R*)-1.31** R = Ph
(***S*)-1.32** R = Me
both >99% *ee*

(***R*)-1.33** R = Ph, 70%, 84% *ee*
(***R*)-1.34** R = Me, 80%, >95% *ee*

Scheme 1.12: Sarandeses' coupling of triorganoindium reagents

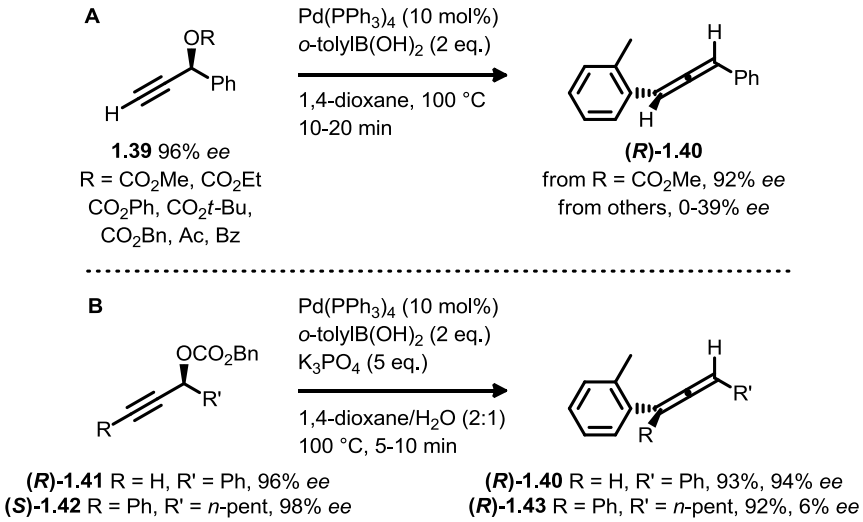
Recently, Stawinski and Kalek disclosed the stereoselective synthesis of allenylphosphonates through the cross-coupling of propargylic carbonates (**(*R*)-1.35**) with phosphonate diesters (**1.36**) (*Scheme 1.13, A*).[32] This method was found to be complementary to the usual method for the synthesis of allenylphosphonates, namely the spontaneous [2,3]-sigmatropic rearrangement of propargylic

phosphite esters, which yields products with opposite allene stereochemistry (*Scheme 1.13, B*).[33]



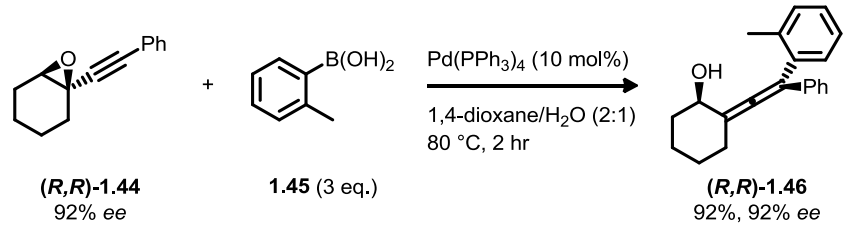
Scheme 1.13: Stawinski's synthesis of allenylphosphonates

In 2007, Yoshida and co-workers detailed a wide-ranging examination of the cross-coupling of non-racemic propargylic carbonates and esters under Suzuki conditions.[34] Surprisingly, they found that although all of the trialled carbonates and esters reacted under the simple conditions, only the methyl carbonate returned allene **(*R*)-1.40** with a high enantiomeric excess (*Scheme 1.14, A*). Further optimisation of the reaction enabled high selectivity to be achieved with the benzyl carbonate **(*R*)-1.41**, although even these optimised conditions proved to be very substrate dependent (*Scheme 1.14, B*).



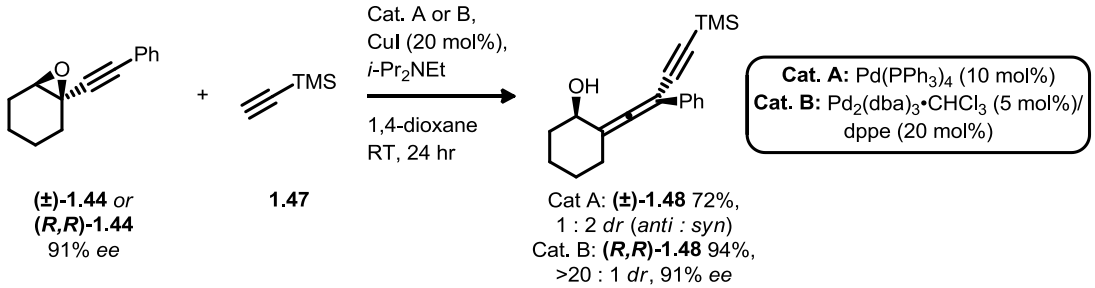
Scheme 1.14

The group have also examined the reaction of propargylic epoxides under Suzuki cross-coupling conditions.[35] These substrates yielded exclusively the *anti*-diastereomers of the α-allenyl alcohol products and, for example, the reaction of enantioenriched epoxide **(*R,R*)-1.44** formed allene **(*R,R*)-1.46** in excellent yield (*Scheme 1.15*).



Scheme 1.15

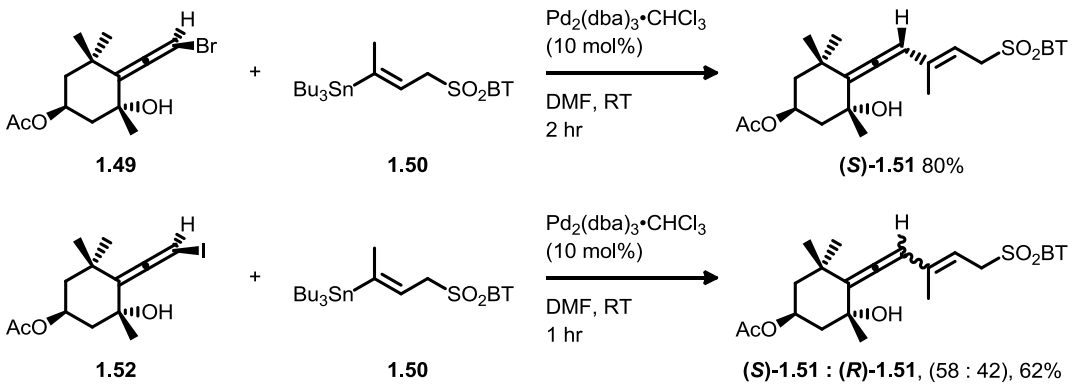
These cyclohexene-derived substrates were also used by Yoshida to demonstrate the highly diastereoselective synthesis of yne-allenes.[36] They found that the use of a bidentate ligand was crucial to the formation of allene **1.48** with high *anti*-diastereoselectivity and that dppe performed best out of the ligands employed (*Scheme 1.16*).



Scheme 1.16

As with the related Suzuki coupling, these conditions were applied to the coupling of **(*R,R*)-1.44** and afforded the allene product **(*R,R*)-1.48** without loss of enantioenrichment.

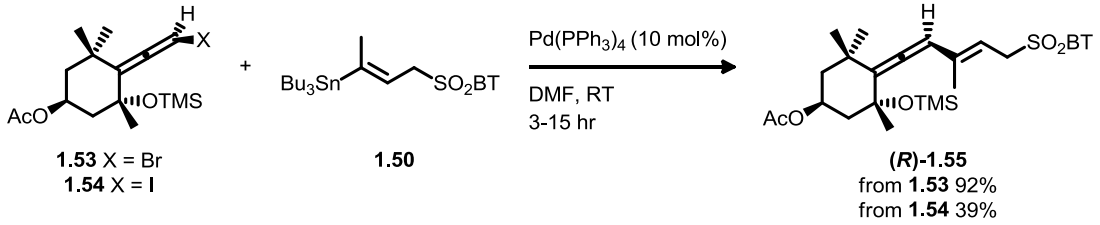
Lera and co-workers have performed a comprehensive study of the Stille coupling of haloallenes with vinylstannanes.[37] As expected in light of the studies by Vermeer,[24] bromoallene **1.49** coupled with inversion to give allene **(*S*)-1.51** in high yield as a single diastereomer (*Scheme 1.17*). However, the coupling of iodoallene **1.52**, which was expected to proceed with predominant retention,[26] afforded a diastereomeric mixture of allene products with a slight excess of the inversion product **(*S*)-1.51**. This is likely due to competing S_N2' oxidative addition, possibly aided by the free hydroxyl group.



Scheme 1.17

Interestingly, it was found that by protecting the free hydroxyl as the TMS-ether the selectivity in the

cross-coupling of either bromoallene **1.53** or iodoallene **1.54** could be tuned to yield only the retention product **(*R*)-1.55** (*Scheme 1.18*). The presence of a bulky TMS-ether blocks S_N2' oxidative addition by palladium, resulting instead in direct oxidative addition into the carbon-halogen bond.



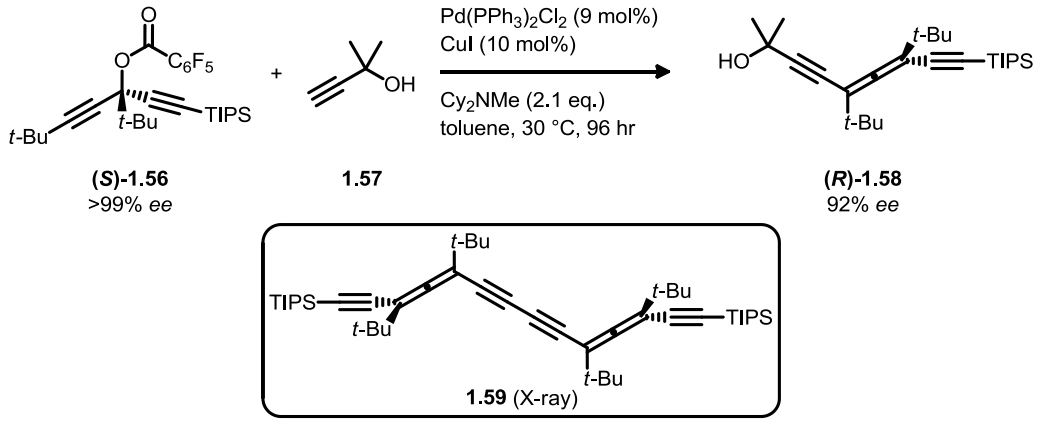
1.53 X = Br
1.54 X = I

1.50

(*R*)-1.55
from **1.53** 92%
from **1.54** 39%

Scheme 1.18

In 2008, Diederich and co-workers described the *syn*-S_N2' substitution of bulky propargylic ester **(*S*)-1.56** under Sonogashira conditions (*Scheme 1.19*).[38] This is the only (albeit rather specialised) example to date of an enantioselective *syn*-S_N2'-substitution involving palladium catalysis. The absolute configuration of the product **(*R*)-1.58** was determined through X-ray crystallographic analysis of the dimer **1.59**.



(*S*)-1.56
>99% *ee*

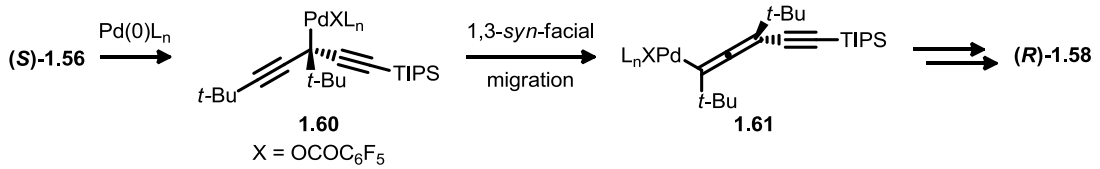
1.57

(*R*)-1.58
92% *ee*

1.59 (X-ray)

Scheme 1.19: Diederich's *syn*-selective cross-coupling

This selectivity can be explained by considering that owing to the steric bulk of the *tert*-butyl alkyne substituent, Pd(0) instead undergoes direct oxidative addition into the propargylic ester with retention of configuration, forming η^1-propargylpalladium species **1.60**. This then undergoes the usual 1,3-*syn*-facial migration to the least sterically hindered η^1-allenylpalladium species, **1.61**. Transmetallation and reductive elimination (both with retention) gives the formal *syn*-S_N2' substitution product **(*R*)-1.58** (*Scheme 1.20*).



1.60
X = $OCOC_6F_5$

1.61

Scheme 1.20: Plausible mechanism for *syn*-substitution

1.3.2 Examples in Natural Product Synthesis

The group of Yikang Wu has been especially active in the application of allenylpalladium chemistry to the synthesis of allene-containing natural products. They have targeted marasin,[39] nemotin,[40] scorodonin,[41] phomallenic acid C[42] and cepacin A (*Figure 1.1*).[43-44] In most cases, Wu employed the cross-coupling of bromoallenes under Negishi conditions to afford the allene-yne or allene-diyne cores of these natural products.

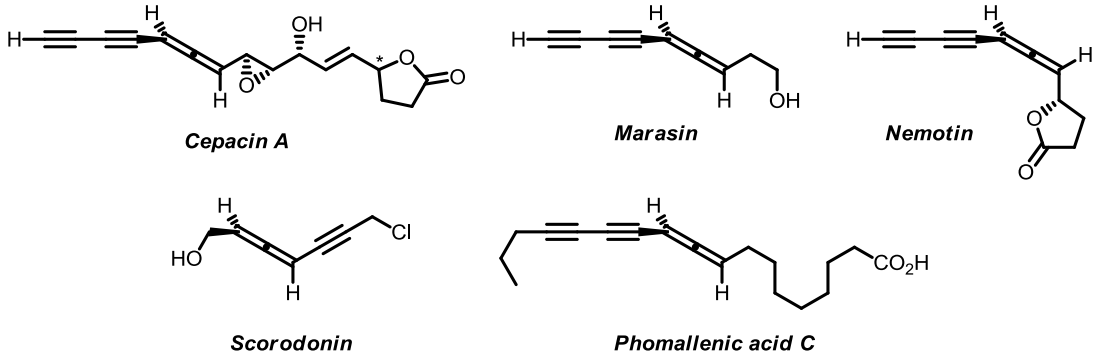
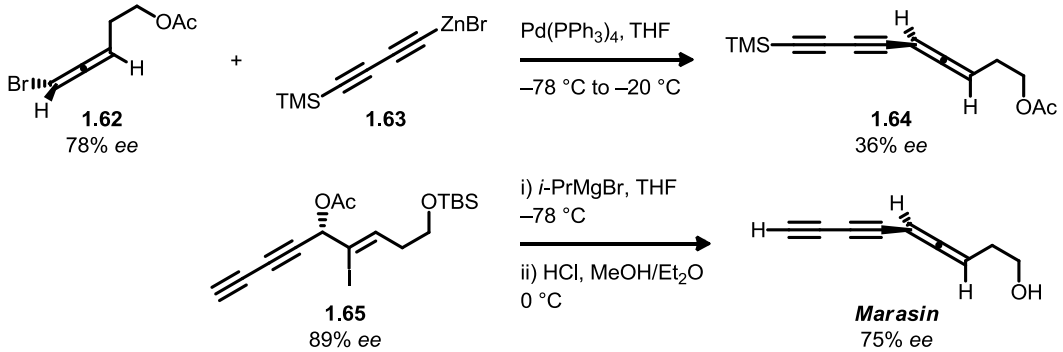


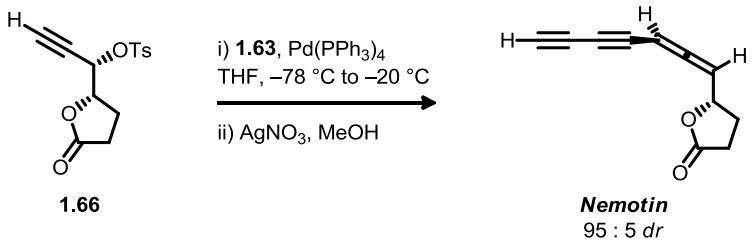
Figure 1.1

Marasin was initially targeted through the coupling of bromide **1.62** with diynylzinc species **1.63** (*Scheme 1.21*).[39] However, bromide **1.62** could not be synthesised in enantiopure fashion and the coupling reaction led to significant epimerisation of the allene centre, and the development of a new strategy was required. In the event, Wu completed the synthesis through stereospecific elimination from acetate **1.65** to install the allene moiety, although some epimerisation was also observed with this route.



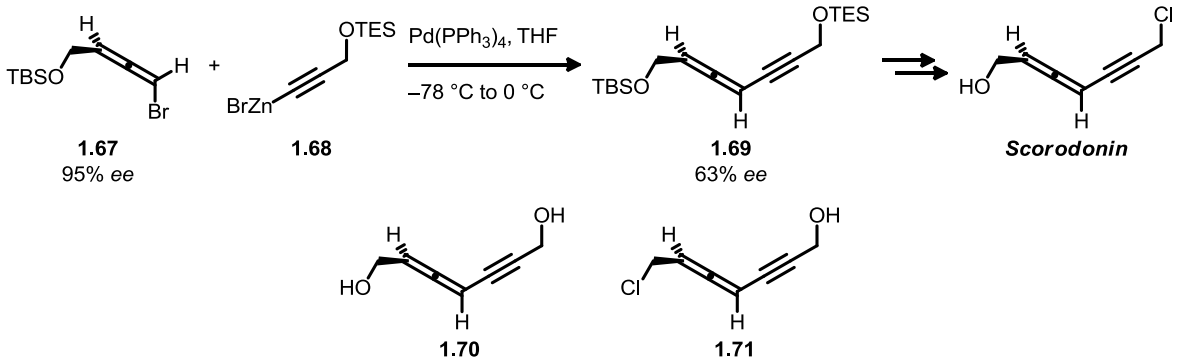
Scheme 1.21: Wu's synthesis of marasin

The group had more success when synthesising nemotin, this time using enantio- and diastereomerically pure propargylic tosylate **1.66** as the electrophile in combination with diyne **1.63** (*Scheme 1.22*).[40] This led to formation of the desired allene-diyne with good stereoselectivity (95 : 5 *dr*), and afforded nemotin after desilylation with $AgNO_3$.



Scheme 1.22: Wu's synthesis of nemotin

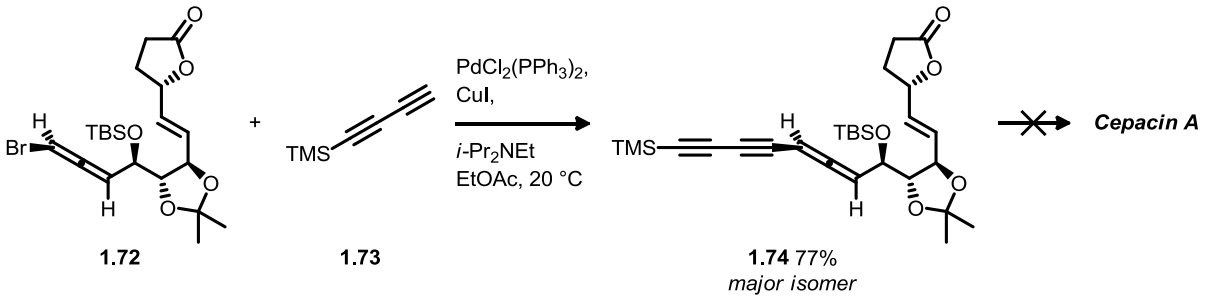
The synthesis of the proposed structure of the allene-yne containing natural product scorodonin was achieved through the coupling of enantioenriched bromide **1.67** with alkynylzinc species **1.68**, although this again proceeded with significant epimerisation of the allene axis (*Scheme 1.23*).[41]



Scheme 1.23: Wu's synthesis of scorodonin

Some discrepancies in the ^{13}C NMR spectra of synthetic and natural scorodonin for two of the seven carbons led the group to synthesise the diol and OH-Cl switched analogues **1.70** and **1.71**. However, the spectra proved to be even further removed from the natural sample, suggesting that the original structure was the most likely for natural scorodonin.

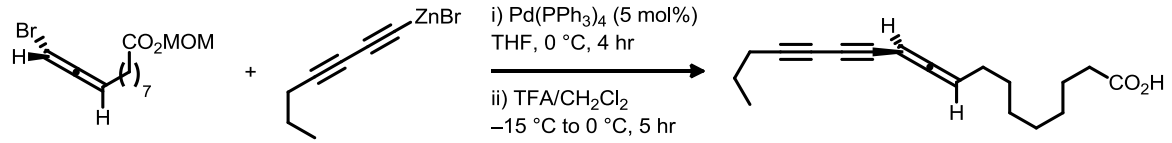
Wu and co-workers have also published two studies towards cepacin A (*Figure 1.1*),[43-44] although to date they have not completed a total synthesis of this challenging molecule. The synthesis was advanced as far as bromoallene **1.72**, which could be successfully coupled to afford allene-diyne **1.74** as an unquantified mixture of isomers, although it was inferred that the desired isomer predominated through measurement of the sign of optical rotation (*Scheme 1.24*).[44] However, no formal assignment of the allene stereochemistry was made, and the opposite isomer to that drawn would be expected to dominate through inversion of the allene axis.[24] Further transformations of **1.74** failed, with both protecting group manipulations and epoxide formation having been attempted.



1.72 **1.73** **1.74** 77% *major isomer*

Scheme 1.24

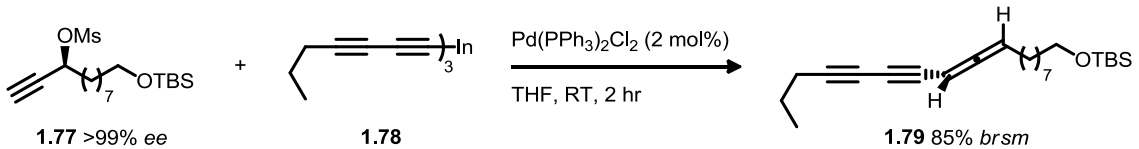
Wu and co-workers also achieved the first total synthesis of phomallenic acid C in 2007, through a Negishi coupling of bromoallene **1.75** and diynylzinc **1.76**.[42] This afforded the desired natural product in 88% *ee*, after deprotection with TFA (*Scheme 1.25*). Interestingly, the stereoselectivity of the coupling step was greatly reduced when a Sonogashira coupling of the terminal diyne with **1.75** was performed.



1.75 88% *ee* **1.76** ***Phomallenic acid C*** 85% *2 steps,* 88% *ee*

Scheme 1.25: Wu's synthesis of phomallenic acid C[42]

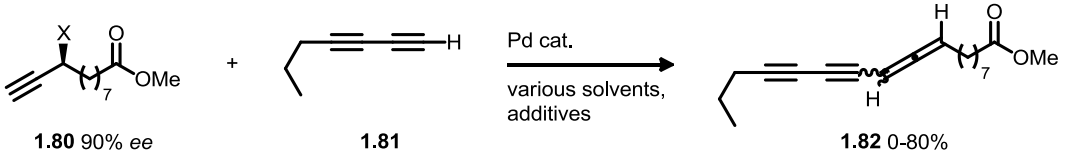
In 2009, Ishigami and co-workers published a further total synthesis of phomallenic acid C, utilising a palladium-catalysed cross-coupling of propargylic mesylate **1.77** with organoindium species **1.78** generated *in situ* from the terminal alkyne, *n*-butyllithium and $InCl_3$ (*Scheme 1.26*).[45] This protocol allowed the natural product to be synthesised with improved enantioselectivity (96% *ee*).



1.77 >99% *ee* **1.78** **1.79** 85% *brsm* 98% *ee*

Scheme 1.26: Key step of Ishigami's synthesis of phomallenic acid C[45]

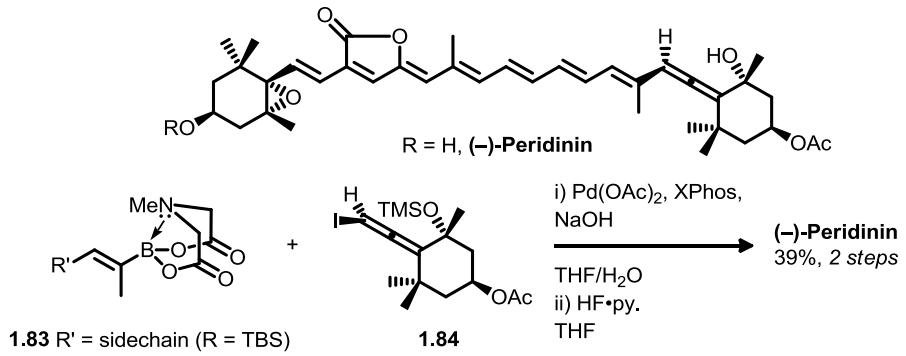
Yoshida and co-workers have also addressed the asymmetric synthesis of phomallenic acid C.[46] However, their attempted Sonogashira coupling of propargylic electrophiles (**1.80**) all gave racemic **1.82** (*Scheme 1.27*), which is perhaps unsurprising given the findings of Wu and co-workers.[42]



1.80 90% *ee* X = OTs, OAc and OCO_2Me **1.81** **1.82** 0-80% *racemic*

Scheme 1.27: Yoshida's racemic coupling en route to phomallenic acid C[46]

In 2010, Burke and co-workers described the stereoselective synthesis of (−)-peridinin employing a late stage Suzuki coupling of MIDA-boronate **1.83** and iodoallene **1.84** (*Scheme 1.28*).[47] The reaction proceeded with complete retention of configuration of the allene axis, and afforded (−)-peridinin in good yield after desilylation. This retention of configuration is in line with the studies performed by Lera and co-workers on the Stille coupling of related haloallenes (*vide supra*).[37]



Scheme 1.28: Burke's synthesis of (−)-peridinin

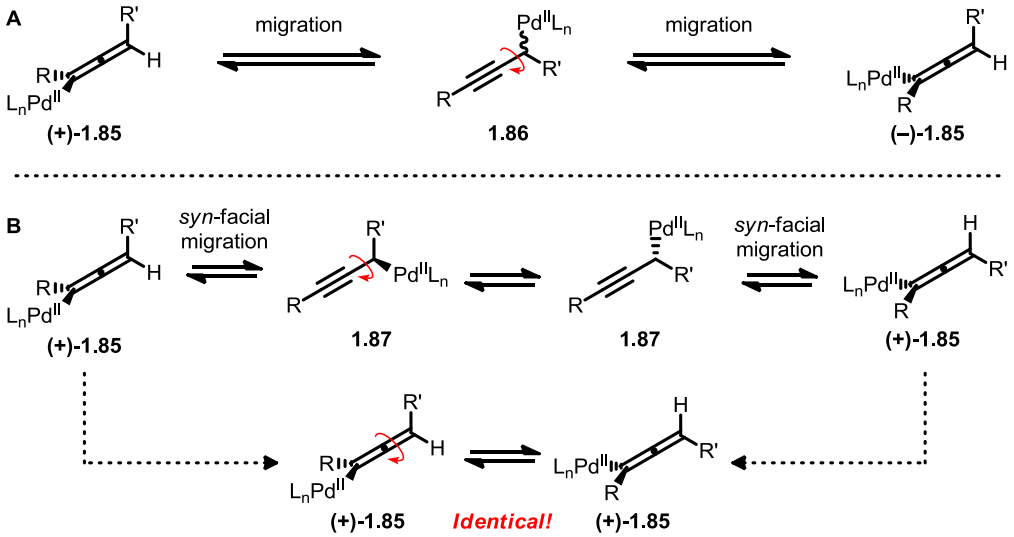
These examples highlight the scope and some of the shortcomings of synthesising chiral, non-racemic allenes through palladium catalysis. The reactions that have been studied are often somewhat limited, in that slight variations in the substrate lead to distinct differences in stereochemical outcome. A general methodology for the synthesis of chiral, non-racemic allenes from propargylic or allenic electrophiles with a high degree of stereocontrol has yet to be developed.

1.3.3 Proposed Literature Mechanisms for Allene Isomerisation Involving Palladium

The significant epimerisation observed in most asymmetric literature syntheses of non-racemic allenes under palladium catalysis requires consideration of possible mechanisms for palladium-mediated isomerisation. There are three main mechanistic proposals for allene isomerisation involving palladium species present in the literature, and these can be split into two groups: firstly, the mechanisms of allenylpalladium(II) isomerisation described by Mikami[48] and Ogoshi,[49] and secondly the mechanism of allene isomerisation outlined by Bäckvall.[50]

The mechanism for allenylpalladium(II) isomerisation first suggested by Mikami and Yoshida involves the racemisation of η^1-allenylpalladium species **(+)-1.85** and **(−)-1.85** (+ and − are arbitrary) through their reversible migration to η^1-propargylpalladium species **1.86**,[48] although the exact mechanism for this is not discussed in the paper. Molander and co-workers have described this isomerisation as arising from the ability of propargylpalladium **1.86** to undergo free rotation around

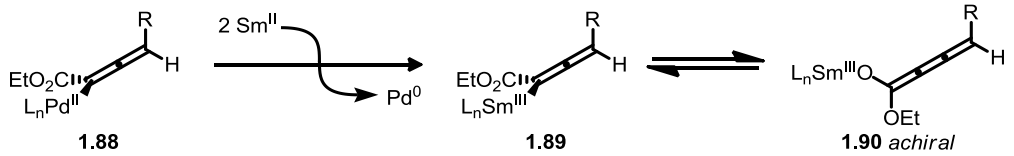
the C−C single bond.[30] Reversible migration from **1.86** to either **(+)-1.85** or **(−)-1.85** is stated to give an overall racemic allenylpalladium(II) intermediate (*Scheme 1.29*, *A*).



Scheme 1.29: [A]: Mikami's proposal for allenylpalladium isomerisation.[48] [B]: Mechanism in light of the stereochemical outcome of *syn*-facial migration shown by Vermeer.[24]

However, if the migration of palladium is stereospecific then the two allenylpalladium(II) species shown in *Scheme 1.29* (*B*) are in fact *identical*. As described previously, Vermeer and co-workers had shown this process of allenyl- to propargylpalladium isomerisation to be *syn*-facial.[24] This leads to a stereodefined η^1-propargylpalladium **1.87** which, even after free rotation and isomerisation, returns the same η^1-allenylpalladium complex **(+)-1.85** with identical stereochemistry. Therefore, this mechanism *cannot* account for allenylpalladium isomerisation.

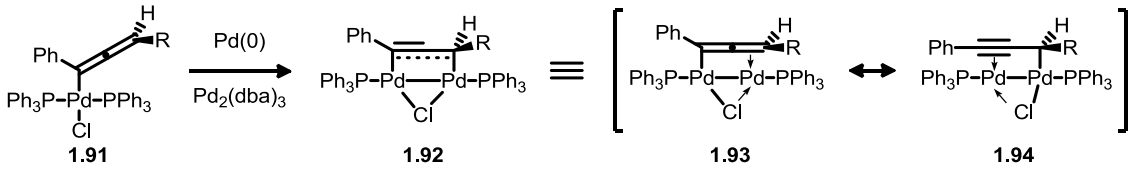
There is a corollary to the above in regards to the report by Mikami; the reaction examined involves the transmetallation of allenylpalladium(II) intermediate **1.88** to an allenylsamarium(III) intermediate **1.89** (*Scheme 1.30*).[48] Isomerisation of **1.89** to the achiral cumulene **1.90** can be envisaged which may explain the observed isomerisation.



Scheme 1.30

The second proposed mechanism for isomerisation of allenylpalladium intermediates was described by Ogoshi and co-workers and involves the formation of dinuclear palladium complexes.[49] These complexes are thought to arise from the action of Pd(0) on the mononuclear η^1-allenylpalladium(II) complex (e.g. **1.91**) to form a dinuclear μ-η^3-allenyl/propargyl complex **1.92**, which can exist in two

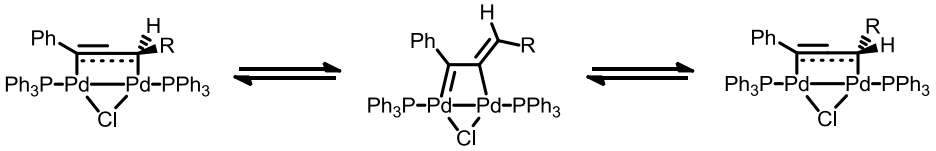
tautomeric forms **1.93** and **1.94** (*Scheme 1.31*).



1.91 **1.92** **1.93** **1.94**

Scheme 1.31

The exact mechanism for epimerisation of **1.92** is not known, but Ogoshi proposes an achiral μ-η^1:η^1-vinyldipalladium intermediate **1.95** as a likely candidate for the loss of stereochemical information (*Scheme 1.32*).

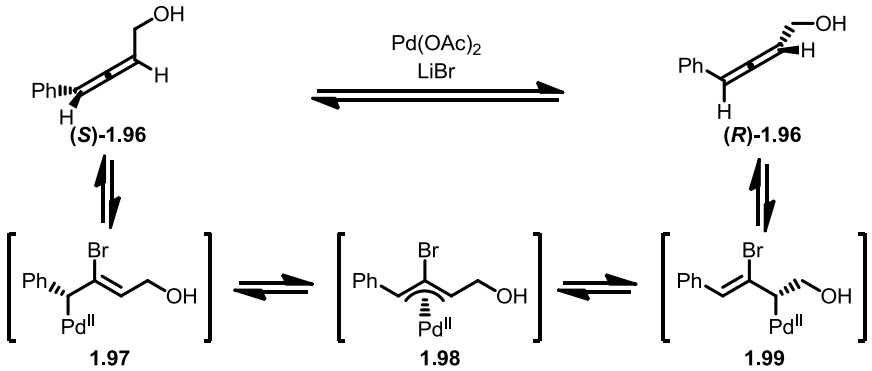


1.92 **1.95** *achiral* ***ent*-1.92**

Scheme 1.32

It is important to note that the epimerisation of allenylpalladium **1.91** was entirely suppressed on the addition of 10 mol% PPh_3, or when $Pd(PPh_3)_4$ was used instead of $Pd_2(dba)_3$. Ogoshi rationalises this through re-formation of the mononuclear complex **1.91** and $Pd(PPh_3)_x$ (x = 3 or 4) from **1.92** through the action of PPh_3. Therefore this mechanism is unlikely to be operating in reactions where the molar ratio of phosphine to palladium is greater than 1:1.

Palladium-mediated isomerisation of allenes themselves has been examined by Horváth and Bäckvall, finding that $Pd(OAc)_2$ alone was able to isomerise enantiopure allenes in various solvents.[50] However, most of their studies were conducted with the more reactive combination of $Pd(OAc)_2$ and LiBr (5 mol% / 10 mol%) in acetonitrile, and this led them to propose a mechanism for isomerisation involving *anti*-bromopalladation as the initial step (*Scheme 1.33*).



(*S*)-1.96 **(*R*)-1.96**

1.97 **1.98** **1.99**

Scheme 1.33

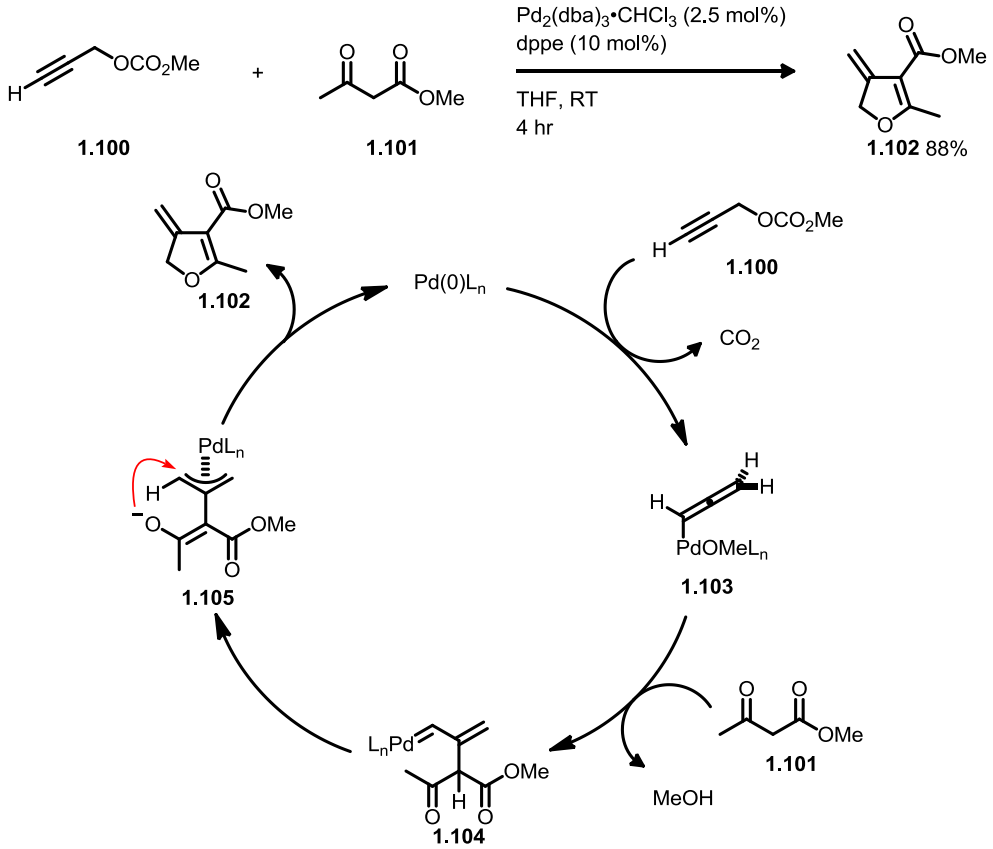
Thus, σ-complex **1.97** formed from **(*S*)-1.96** can isomerise to σ-complex **1.99** *via* the intermediate

π-allyl complex **1.98**. *anti*-Elimination of bromide and Pd(II) gives the enantiomeric allene **(*R*)-1.96**. It is inconsequential which double bond of the allene is activated by Pd(II), as palladation of either will result in σ-complexes that can isomerise.

This palladium(II)-mediated racemisation may account for the varying amounts of isomerisation observed in the cross-couplings of enantioenriched propargylic electrophiles (*vide supra*). As palladium(II) species are intermediates of such reactions, isomerisation of allene products by an intermediate involved in their formation could explain the erosion of stereochemistry.

1.4 Nucleophilic Attack on the Allenyl Ligand

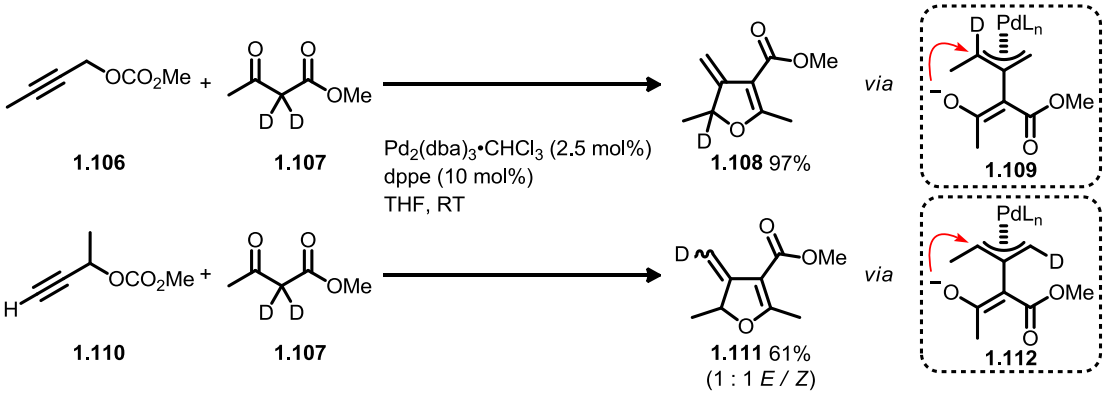
The attack of soft nucleophiles on the allenyl ligand of palladium was first demonstrated by Tsuji and co-workers in 1985 (*Scheme 1.34*).[18] Tsuji proposed that methoxide released from oxidative addition into propargylic carbonate **1.100** deprotonates the acetoacetate **1.101**, and this soft enolate nucleophile attacks the central carbon of the η^1-allenylpalladium species **1.103**. This leads to the palladium carbene **1.104** which undergoes an intramolecular protonation to give π-allyl species **1.105**, which undergoes intramolecular attack by the enolate to afford dihydrofuran product **1.102**.



Scheme 1.34

Deuteration studies by Tsuji lent weight to the proposed intramolecular protonation, and showed that

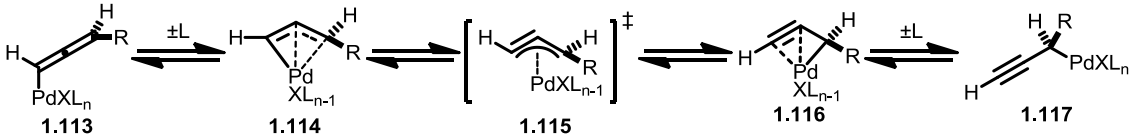
intramolecular attack by the enolate oxygen occurs on the more substituted end of the π-allyl system in **1.109** and **1.112** (*Scheme 1.35*).[18]



Scheme 1.35

1.4.1 Mechanistic Considerations

Further consideration of the reactive species proposed by Tsuji must be made. Attack at the central carbon of an η[1]-allenyl complex (e.g. **1.113**) is not known,[51] and we must consider the related η[3]-allenyl species (e.g. **1.114**) to be the more likely candidate for the reactive species (*Scheme 1.36*). This species can be considered as an intermediate of the 1,3-*syn*-facial migration process (between **1.113** and **1.117**), where the distal double-bond of the η[1]-allenylpalladium **1.113** has co-ordinated to palladium with loss of a ligand.



Scheme 1.36: Isomerisation pathway between **1.113** and **1.117**

The usual representation of this η[3] species described in the literature is **1.115**, but this is likely better thought of as the transition state between **1.114** and **1.116**. The representation **1.114** is preferred (by us) as it clearly indicates the presence of a formal Pd−C σ-bond, along with bending of the allenyl ligand. This bending of the allenyl ligand is likely the origin of its reactivity towards nucleophiles, through increased electrophilicity of the strained central carbon.

These η[3]-allenylpalladium species are well characterised. Seminal work by Ogoshi and co-workers has led to the isolation and X-ray crystallographic analysis of both neutral[52] and cationic[53-54] η[3]-complexes of palladium. In the latter work,[54] Ogoshi showed that the combination of a bidentate ligand (dppe) and polar solvents (e.g. DMF) led to preferential formation of the η[3]-allenylpalladium complex **1.118** over the η[1]-complex **1.119** in solution (*Scheme 1.37*, *Table 1.1*). The chloride is the dissociating ligand

in this case, forming the cationic η^3-allenyl species. Interestingly, when $Pd(PPh_3)_4$ was used to form these complexes only the η^1-allenylpalladium complex was observed, irrespective of the solvent employed.



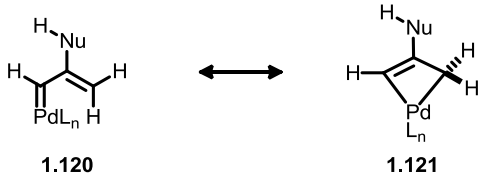
1.118 **1.119**

Scheme 1.37

Entry	Solvent	Ratio (1.118 : 1.119)[a]
1	$CDCl_3$	75 : 25
2	DMF-d_7	89 : 11
3	C_6D_6	0 : 100

Table 1.1: [a] Determined by ^{1}H NMR spectroscopy

Also of consideration is the nature of the species formed after attack of the first nucleophile. Tsuji proposed a palladium vinylcarbene (**1.120**), but the isomeric palladacyclobutene **1.121** can also be envisaged (*Scheme 1.38*).



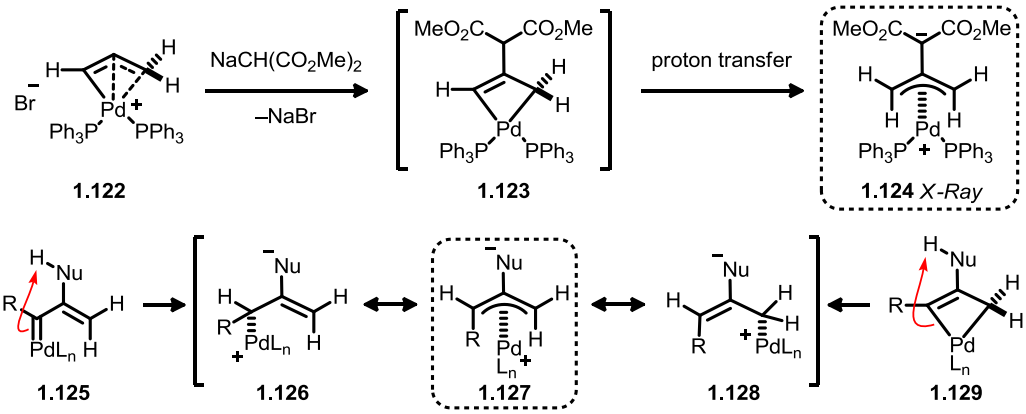
1.120 **1.121**

Scheme 1.38

These two extreme forms of the intermediate can, in theory, be interconverted through 4π pericyclic processes (electrocyclisation/electrocylic ring opening). As these intermediates are believed to undergo facile intermolecular protonation or intramolecular proton transfer, their existence is likely transient. To the best of our knowledge there is no direct evidence for the characterisation of either species with palladium,[51] although vinylcarbenes have been characterised with tungsten,[55] iron[56] and rhenium,[51] and metallocyclobutenes are known for rhenium,[51] platinum,[57] iridium[57-58] and titanium.[59] Palladium carbenes have been implicated as possible pathways for the *E/Z* isomerisation of vinylpalladium species generated either from carbopalladation of alkynes[60-61] or oxidative addition into vinyl halides.[62-64] With regards to palladacyclobutene intermediates, Sinou and co-workers have performed DFT calculations which show their formation to be plausible.[65] However, no comparative calculations for vinylcarbenes were performed in that study.

Chen and co-workers found evidence for intermediacy of π-allyl complexes in this reaction;[66] the

reaction of complex **1.122** with sodium malonate formed zwitterionic π-allyl complex **1.124** (the product of intramolecular proton transfer in **1.123**), which was characterised by X-ray diffraction (*Scheme 1.39*).

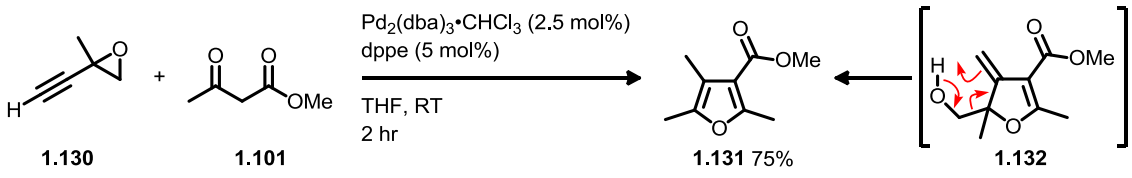


Scheme 1.39

Intramolecular protonation of vinylcarbene **1.125** proceeds from the Pd−C π-bond giving σ-allyl complex **1.126** (*Scheme 1.39*). For palladacyclobutene **1.129**, intramolecular protonation proceeds from the Pd−C σ-bond, which occurs with *inversion* to give the σ-allyl complex **1.128**. These two complexes are interchangeable through the σ-π-σ isomerisation of π-allyl species **1.127**. These proton transfers may be concomitant with attack of the nucleophile, meaning that vinylcarbene **1.125** and palladacyclobutene **1.129** may in fact be transition states between **1.122** and **1.124** rather than distinct reaction intermediates.

1.4.2 Further Examples

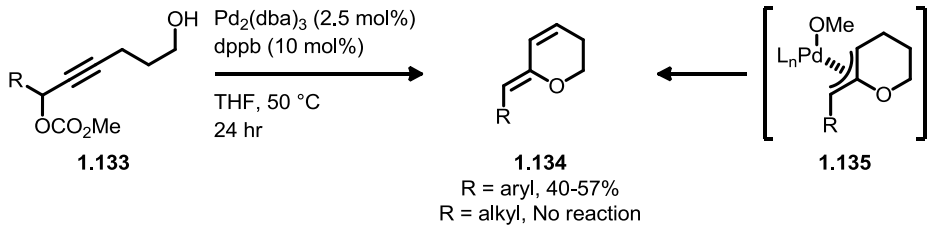
Tsuji continued to develop this methodology, summing up a decade of work in a review published in 1996.[67] One particularly nice example from Tsuji's work is the extension to the use of propargylic epoxides as electrophiles.[68] This results in the regioselective formation of furans (e.g. **1.131**), with the product being formed through loss of formaldehyde from intermediate **1.132** (*Scheme 1.40*).



Scheme 1.40

In 1996, Sinou and co-workers published a communication examining the reaction of propargylic carbonates **1.133** containing an internal nucleophile (*Scheme 1.41*).[69] A range of aromatic groups were tolerated, all forming the dihydropyran products **1.134** as a single geometrical isomer. These products

were proposed to result from a β-hydride elimination from the π-allyl intermediate **1.135** in the absence of a second nucleophile. However, when the aromatic substituent R was replaced with an alkyl group (e.g. *n*-hexyl, *c*-hex or *t*-butyl), no reaction occurred.

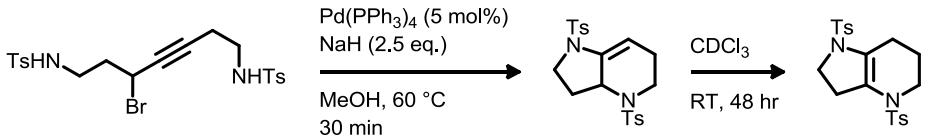


1.133 **1.134** **1.135**

R = aryl, 40-57%
R = alkyl, No reaction

Scheme 1.41

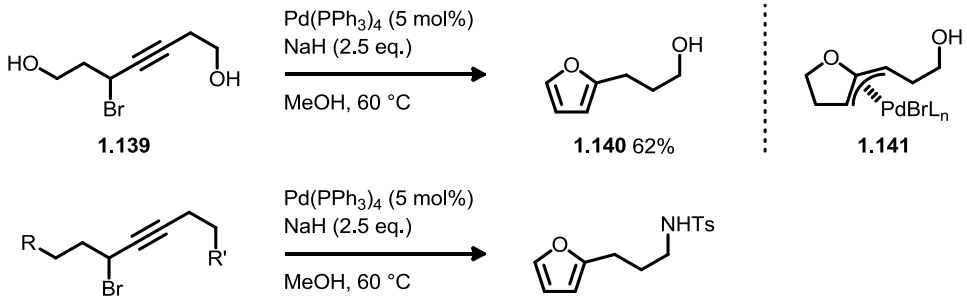
In 2008, Ohno and co-workers reported the domino cyclisation of propargylic bromides containing two internal nitrogen nucleophiles (*Scheme 1.42*).[70] This yielded the bis-heterocyclic product **1.137** which readily isomerised to **1.138** in the presence of acid.



1.136 **1.137** 89% **1.138** quant.

Scheme 1.42

Also within this communication, Ohno disclosed the attempted domino cyclisation of related compounds containing either two hydroxyl nucleophiles **1.139** or a mixture of hydroxyl and nitrogen nucleophiles **1.142** and **1.143** (*Scheme 1.43*). Somewhat surprisingly, only the furan products **1.140** and **1.144** resulted from these reactions, suggesting initial attack of the hydroxyl nucleophile is more favourable than attack of nitrogen.



1.139 **1.140** 62% **1.141**

1.142 R = OH, R' = NHTs
1.143 R = NHTs, R' = OH

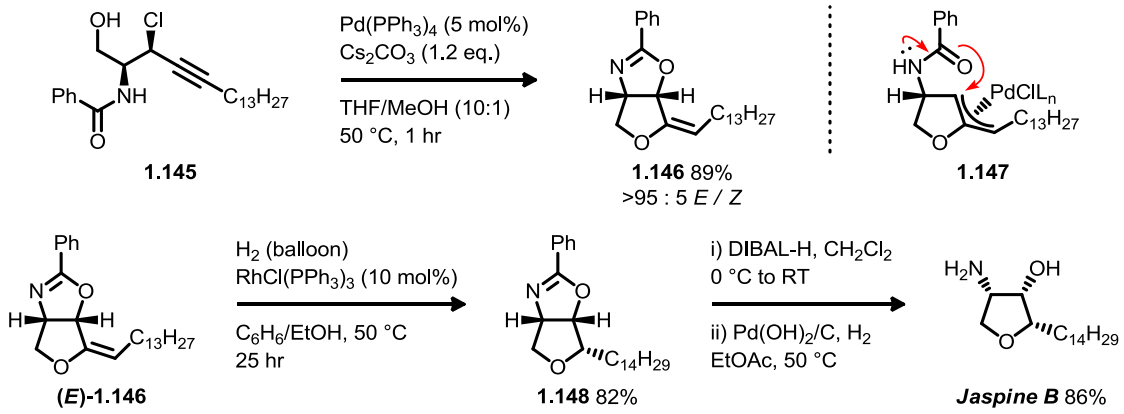
1.144
52% from **1.142**
64% from **1.143**

Scheme 1.43

Formation of the furan product was reasoned through β-hydride elimination from π-allyl intermediate **1.141** followed by aromatisation. The formation of **1.140** and **1.144** suggests a subtle difference in reactivity between the intermediates of this reaction and of the related *bis*-nitrogen cyclisation to form

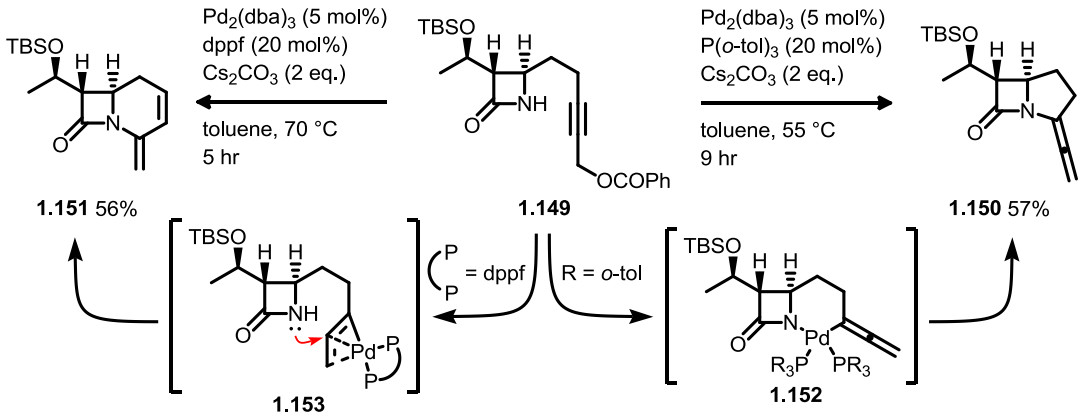
1.137 (*Scheme 1.42*). It appears that β-hydride elimination is the more favourable reaction pathway for the π-allyl intermediate formed from attack of oxygen (e.g. **1.141**), no matter the nature of the second nucleophile.

Ohno and co-workers applied this double cyclisation methodology to the synthesis of the tetrahydrofuran-containing natural product jaspine B (*Scheme 1.44*).[71] Initial cyclisation of the hydroxyl group gives the π-allyl intermediate **1.147** which in this case is able to undergo a second cyclisation with the amide carbonyl group, forming bicycle **1.146** in excellent yield. Pure **(*E*)-1.146** was converted into jaspine B in three steps.



Scheme 1.44

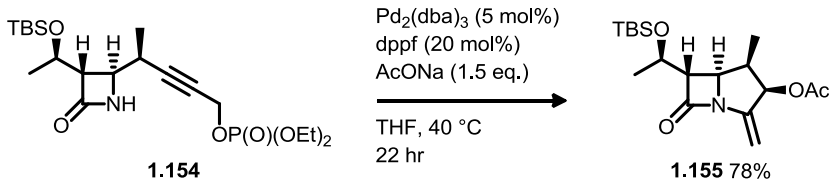
Mori and co-workers discovered an interesting ligand effect when attempting to synthesise carbapenams (*Scheme 1.45*).[72-73] When monodentate ligands were employed in the reaction of propargylic ester **1.149**, allenyl-carbapenam **1.150** was formed in moderate yield. However, the use of bidentate ligands switched the selectivity to the formation of carbacepham **1.151**.



Scheme 1.45

The formation of **1.150** could be explained through the co-ordination of nitrogen to palladium in the η^1-allenylpalladium intermediate **1.152**, followed by reductive elimination. Mori suggests that the use

of bidentate ligands disfavours the formation of **1.152** on steric grounds, thus the cyclisation occurs instead at the central carbon of the η^3-allenylpalladium intermediate **1.153**, which leads to the formation of **1.151**. This unexpected reactivity with bidentate ligands was exploited to selectively form the desired carbapenam structures. For example, the combination of propargylic phosphate **1.154** and sodium acetate formed carbapenam **1.155** as a single diastereomer in good yield (*Scheme 1.46*).

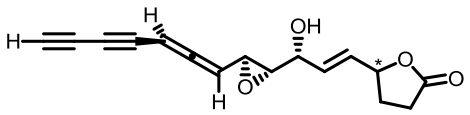


1.154 **1.155** 78%

Scheme 1.46

1.5 Summary

While allenylpalladium intermediates have been exploited for the synthesis of a diverse range of structures, it is clear that there is vast potential for the development of novel methodologies based on their use. As noted previously, there is a lack of a general methodology for the synthesis of chiral, non-racemic allenes from propargylic or allenic electrophiles. We decided to investigate this problem with a view to the synthesis of the allene containing natural product cepacin A (*Figure 1.2*).[27]



Cepacin A

Figure 1.2

Chapter 2. Cross-coupling of Allenylpalladium Intermediates

2.1 Aims

As noted in *Chapter 1*, a general and reliable method for the preparation of enantioenriched allenes through palladium-catalysed processes has not yet been developed. To begin our investigations into this problem we planned to prepare a range of substrates and examine their reactivity under a variety of cross-coupling manifolds. We also wished to examine the processes responsible for allene racemisation under palladium catalysis, with a view to suppressing their action.

We hoped these investigations would lead to a better understanding of the factors controlling selective chirality transfer to the allene axis, thus enabling the stereocontrolled synthesis of biologically active allene-containing natural products.[27, 74]

2.2 Planned Substrates

A set of seven substrates were selected to examine reactivity which can be split into three main groups (*Figure 2.1*). The first set (**2.01**), derived from benzaldehyde, were selected to serve as a benchmark for further investigations. Yoshida and co-workers have demonstrated their use in the synthesis of substituted allenes under Suzuki cross-coupling conditions,[75] and they are easily prepared in two steps from benzaldehyde. The second set, derived from cyclohexanone, would allow the synthesis of more complex substrates. These include the acyclic carbonates (**2.02**) which would afford tri- and tetrasubstituted allenes. More interestingly, the epoxides (**2.03**) and cyclic carbonates (**2.04**) would both generate the same α-allenyl alcohol products, thus allowing the direct comparison of the effect of the two electrophiles on the reaction stereoselectivity.

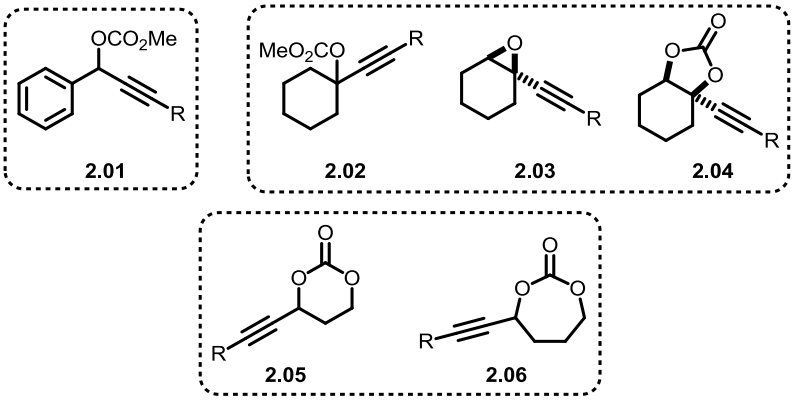


Figure 2.1

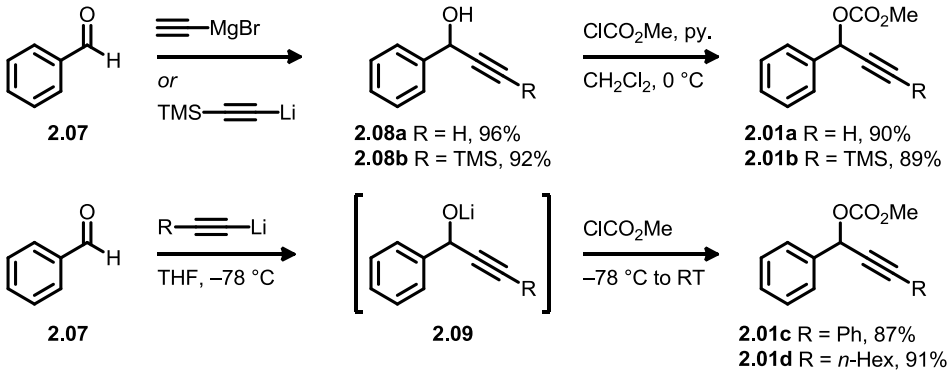
Finally, 6- (**2.05**) and 7-membered (**2.06**) cyclic carbonates represent an underexplored class of

substrates in allene forming reactions, which would result in allene products containing residual alcohol functionality.

A variety of alkyne substituents were chosen to give a spectrum of steric bulk and electronic properties. In fulfilling these ideals the terminal (R = H (**a**)), TMS (**b**), phenyl (**c**) and *n*-hexyl (**d**) alkyne substituents were included in these investigations.

2.3 Benzaldehyde Derived Substrates

The addition of ethynylmagnesium bromide to benzaldehyde at −78 °C gave propargylic alcohol **2.08a** in 96% yield (*Scheme 2.1*). Carbonate formation was achieved with methyl chloroformate and pyridine in dichloromethane, affording carbonate **2.01a** in excellent yield. The synthesis of the silyl-containing substrate **2.01b** was achieved similarly, with addition of lithium TMS-acetylide followed by carbonate formation.

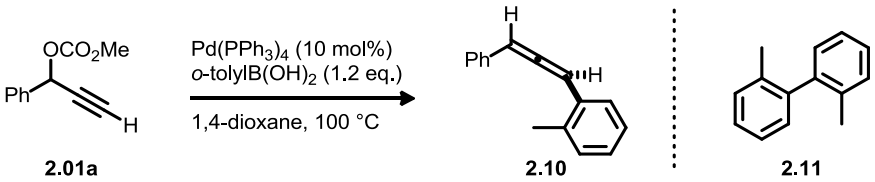


Scheme 2.1

At this point we considered the possibility of telescoping this two-step protocol. As a metal alkoxide (e.g. **2.09**) is formed on addition of the alkyne, this species should be reactive towards methyl chloroformate, thereby allowing direct formation of the desired carbonates from the aldehyde. This was indeed the case, and the desired phenyl **2.01c** and *n*-hexyl **2.01d** substrates could be obtained in excellent yields on quenching the reaction with a slight excess of methyl chloroformate.

With these substrates in hand we set about investigating allene formation. The Suzuki-coupling conditions described by Yoshida were employed, utilising $Pd(PPh_3)_4$ as the catalyst with *o*-tolyl boronic acid in "wet" (i.e. reagent grade) 1,4-dioxane (*Scheme 2.2*).[75] This reaction proceeds without the need for added base as methoxide is generated on oxidative addition into the propargylic carbonate which can perform this role. Yoshida employs two equivalents of boronic acid for this reaction, which we found could be reduced to 1.2 equivalents without significant detriment to reactivity. We

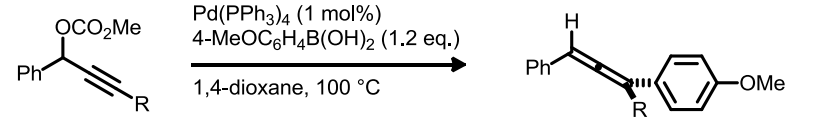
confirmed the formation of the desired allene product **2.10** through IR (ν_{max} = 1950-2000 cm^{-1}) and ^{13}C NMR (δ_C >200 ppm for the central allene carbon) spectroscopy.



2.01a **2.10** **2.11**

Scheme 2.2

However, this reaction was plagued by a chromatographically inseparable byproduct, which was determined to be 2,2'-dimethyl-1,1'-biphenyl **2.11** from ^{1}H and ^{13}C NMR spectroscopic analysis of the product mixtures. This byproduct arises from an oxidative dimerisation of the boronic acid, likely mediated by Pd(II) species and dissolved oxygen gas.[76] Although the reaction mixture was degassed (argon sparge) prior to catalyst addition, we could not rule out the introduction of oxygen on adding the catalyst. With a desire to keep the procedure operationally simple and without resorting to rigorous Schlenk techniques, we decided to change the boronic acid to one containing a polar group. This would assist purification through the increased polarity of the reaction products. Thus, switching to 4-methoxyphenyl boronic acid allowed the isolation of pure allene products **2.12a**, **c** and **d** in moderate to good yields (*Scheme 2.3*).



2.01a R = H
2.01b R = TMS
2.01c R = Ph
2.01d R = *n*-Hex

2.12a R = H, 44% (57% from **2.01b**)
2.12c R = Ph, 77%
2.12d R = *n*-Hex, 81%

Scheme 2.3

The TMS substituted carbonate **2.01b** gave predominantly the deprotected allene product **2.12a**. We believe this deprotection occurs on the alkynyl silane starting material (as fluoride is typically needed to deprotect an allenyl silane)[77-78] and is mediated by methoxide released from the carbonate on oxidative addition by palladium. A trace amount of the TMS-containing allene was observed in the crude reaction mixture, likely formed from the first turnover of the reaction. Once the deprotection takes over, however, the significantly less hindered terminal alkyne undergoes faster oxidative addition by palladium resulting in the predominant formation of **2.12a**.

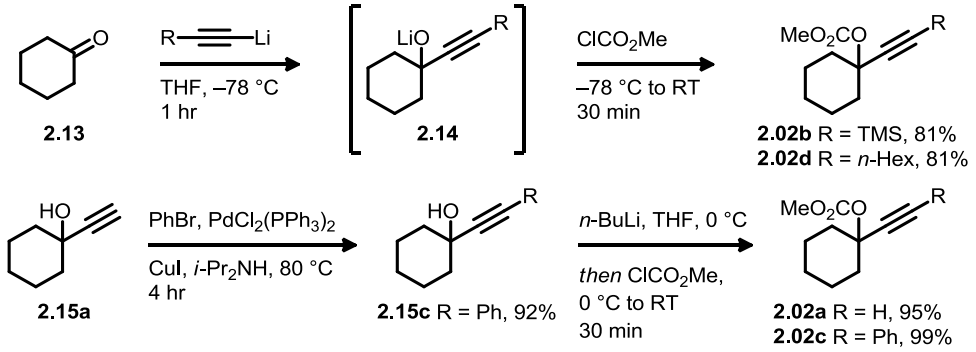
The yields of these reactions correlate with the degree of substitution of the allene core; the

disubstituted allene **2.12a** formed from both **2.01a** and **b** was recovered in only moderate yield, whereas the trisubstituted allenes **2.12c** and **d** were isolated in significantly higher yields, likely owing to their greater stability towards palladium species in the reaction.

2.4 Cyclohexanone Derived Substrates

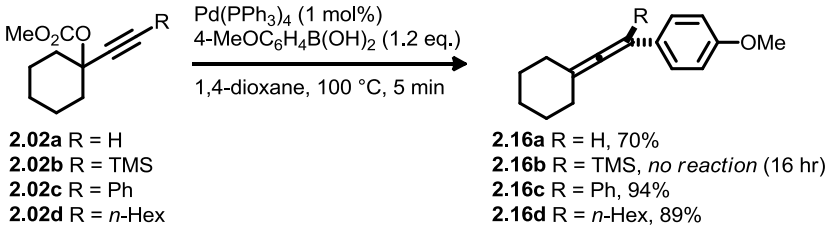
2.4.1 Acyclic Carbonates

The telescoped procedure was successfully utilised for the synthesis of the *n*-hexyl and TMS acyclic carbonates **2.02b** and **d** from cyclohexanone (*Scheme 2.4*). The phenyl-substituted acyclic carbonate **2.02c** was synthesised from commercially available 1-ethynylcyclohexanol **2.15a** through inexpensive and scalable Sonogashira coupling with bromobenzene,[79] which gave the alcohol **2.15c** in excellent yield. In this case however, carbonate formation was problematic, and after some investigation it was found that deprotonation of **2.15c** with *n*-butyllithium at 0 °C and quenching with a slight excess of methyl chloroformate gave the desired carbonate **2.02c** in quantitative yield. This protocol was also used for the synthesis of the terminal alkyne substrate **2.02a** from **2.15a**.



Scheme 2.4

With these carbonates in hand we repeated our previous conditions for allene formation. Pleasingly, this gave the desired allene products in good to excellent yields (*Scheme 2.5*). Surprisingly, however, the TMS substituted carbonate **2.02b** failed to react under these conditions, returning only starting material even after extended reaction times.



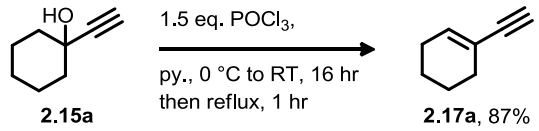
Scheme 2.5

The isolated yields of the allenes again correlated with the degree of substitution, the trisubstituted

allene **2.16a** being isolated in good yield, but inferior to excellent yields of the tetrasubstituted allenes **2.16c** and **d**. These results, in combination with those from the benzaldehyde series (*Scheme 2.3*), show that yield clearly increases with the degree of substitution of the allene.

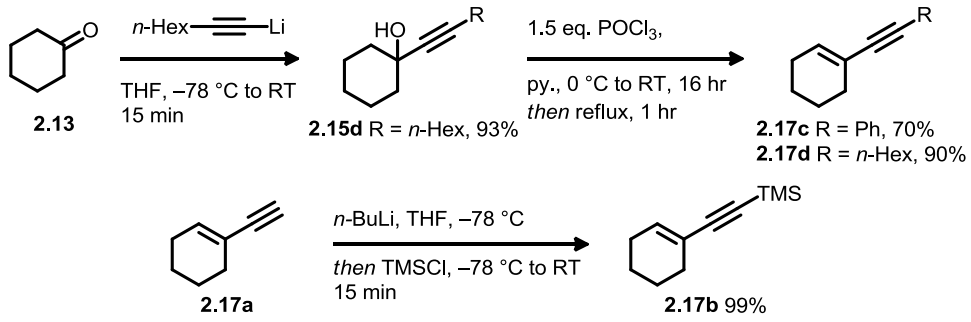
2.4.2 Epoxides

The enyne precursors required for epoxide (**2.03**) formation were prepared *via* dehydration of the corresponding tertiary alcohols. Exposure of a solution of **2.14a** in pyridine to $POCl_3$ gave the desired enyne **2.17a** in 78% yield after distillation (*Scheme 2.6*).[80] However, we found that simply washing the organic layer from work-up with 6 N aqueous HCl to remove the remaining pyridine gave analytically pure **2.17a** in 87% yield, without the need for further purification. **2.17a** was prone to decomposition on storage, and as such was stored at −25 °C under argon to slow this process.



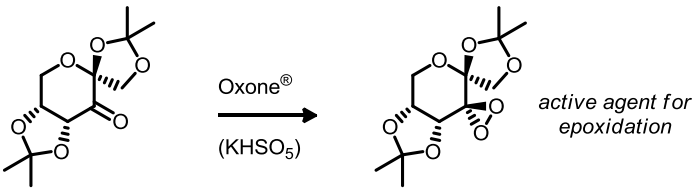
Scheme 2.6

The same protocol was successfully employed to give the phenyl and *n*-hexyl substituted enynes **2.17c** and **d** in high yields, the starting alcohol **2.15d** for **2.17d** being synthesised from 1-octyne and cyclohexanone (*Scheme 2.7*). Finally, deprotonation of terminal enyne **2.17a** with *n*-butyllithium and quenching of the resulting alkynyllithium with trimethylsilyl chloride afforded the TMS-substituted enyne **2.17b** in quantitative yield.



Scheme 2.7

A suitable method for asymmetric epoxidation to synthesise enantioenriched epoxides was sought. A report by Shi and co-workers on the asymmetric epoxidation of enynes was considered to be the most promising given that it included the successful epoxidation of substrates **2.17a** and **b**.[81] The powerful methodology developed by Shi utilises the D-fructose-derived ketone **2.18** to effect epoxidation through a transient dioxirane **2.19** generated from the action of Oxone® (*Scheme 2.8*).[82]



Scheme 2.8

Epoxidations by dioxiranes can proceed through either spiro **TS-2.20** or planar **TS-2.21** transition states (*Figure 2.2*). Studies by Baumstark *et al.* on the relative rates of epoxidation of *cis* and *trans* alkenes by DMDO showed that the spiro transition state dominates the reaction.[83-84] Calculations by Bach *et al.* on the epoxidation of ethylene by DMDO predicted the spiro transition state and a stabilising secondary orbital interaction of an oxygen lone pair on DMDO with the π* of the alkene.[85] Through stereochemical analysis of the reaction Shi has proposed two favoured transition states for dioxirane **2.19**, spiro **TS-2.22** and planar **TS-2.23** (*Figure 2.2*). As each transition state gives the opposite enantiomer of epoxide product, the stereochemical outcome of the reaction suggests that is it the spiro **TS-2.22** that may dominate.[86]

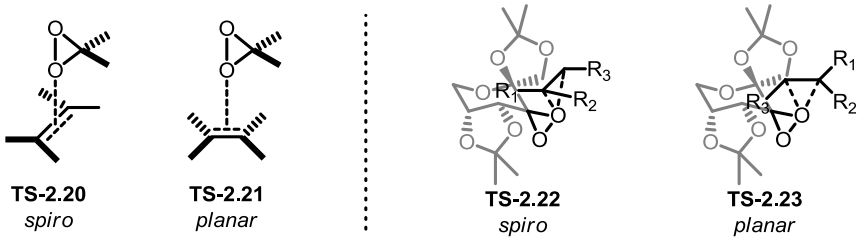


Figure 2.2: Transition states for epoxidations

For the epoxidation of our enyne substrates there is a further consideration. The alkyne conjugation serves to lower the LUMO of the alkene, resulting in better overlap of the dioxirane oxygen lone pair with the π* LUMO of the alkene.[81] This leads the spiro transition state to be even more favourable than the corresponding planar transition state, and is shown with our substrate (**TS-2.24**, *Figure 2.3*).

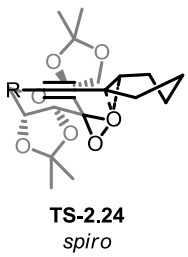
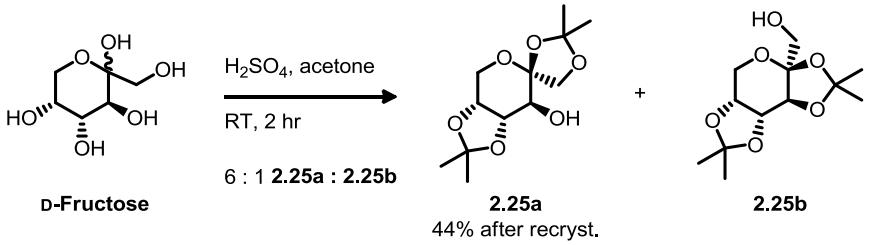


Figure 2.3: Spiro transition state for our substrates **2.17a-d**

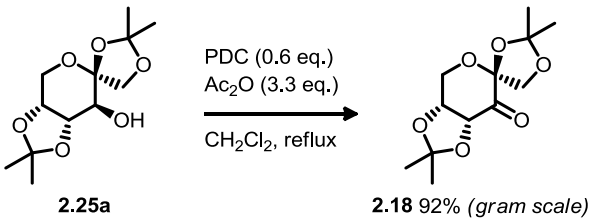
Shi's sugar derived ketone **2.18** is synthesised in two steps from D-fructose, through double acetonide protection of the free sugar to give **2.25a**, followed by oxidation of the remaining free alcohol.

Protection conditions of H_2SO_4 in acetone resulted in a 6 : 1 ratio of **2.25a** : **b** (*Scheme 2.9*), and this mixture was successfully recrystallised to isomeric purity using Et_2O / hexane giving **2.25a** in 44% yield.[87] The reaction could be performed on multi-gram scale, yielding synthetically useful amounts of **2.25a** from a single recrystallisation.



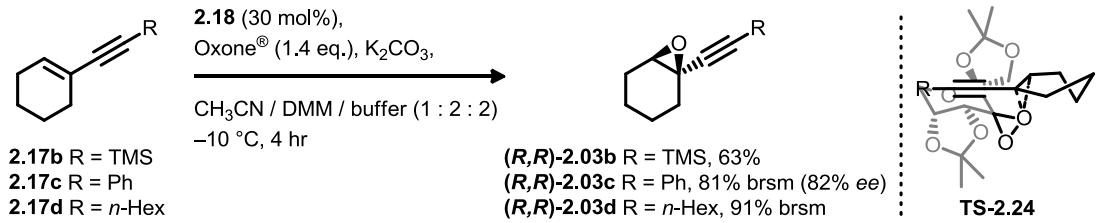
Scheme 2.9

The oxidation of **2.25a** was achieved using 0.6 equivalents of pyridinium dichromate (PDC) as the active oxidant in the presence of acetic anhydride, an additive well known to accelerate chromium oxidations.[88-89] Simple filtration of the reaction mixture through a Celite® / silica gel pad and azeotropic removal of any remaining acetic acid with toluene gave analytically pure **2.18** in excellent yield (*Scheme 2.10*).



Scheme 2.10

With the catalyst **2.18** in hand, Shi's methodology was applied to the synthesis of enantioenriched epoxides **(*R,R*)-2.03b-d** (*Scheme 2.11*). The procedure requires careful control of pH throughout the reaction, using an initial biphasic pH 9.3 buffer / CH_3CN / dimethoxymethane (DMM) solution of alkene and catalyst (30 mol%).[81] To this was added, separately and simultaneously at −10 °C *via* syringe pump, aqueous solutions of Oxone® and K_2CO_3 (to maintain a basic pH). This gave the enantioenriched epoxides **(*R,R*)-2.03b-d** in good yields after flash chromatography on silica gel buffered with Et_3N (2.5% by volume).

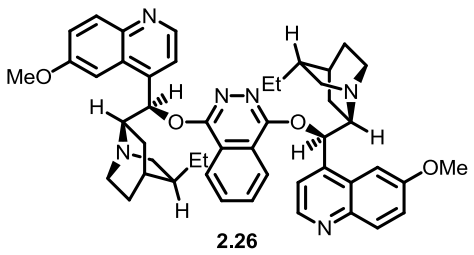


Scheme 2.11

The enantiomeric excess of the phenyl substituted epoxide **(*R*,*R*)-2.03c** could be measured directly by chiral HPLC and found to be quite high (82% *ee*). Without a suitable chromophore for UV detection, the *ee* of the TMS and *n*-hexyl epoxides **(*R*,*R*)-2.03b** and **(*R*,*R*)-2.03d** could not be measured directly. Comparison of the sign of optical rotation of the epoxides to that reported[36, 81] allowed tentative assignment of the absolute configuration as (*R*,*R*). This is the absolute configuration predicted if the reaction indeed proceeds through the spiro transition state **TS-2.24**. The terminal alkyne substrate **2.17a** was epoxidised using *m*-CPBA which afforded racemic **(±)-2.03a** in moderate 43% yield.

2.4.3 Cyclic Carbonates

Sharpless asymmetric dihydroxylation (SAD) is a powerful tool for the asymmetric synthesis of *syn*-1,2-diols from alkenes.[90-91] The reaction makes use of the highly selective reactivity of $K_2OsO_4 \cdot (H_2O)_2$ towards alkenes,[92] along with a chiral ligand to induce asymmetry. The use of a co-oxidant, normally $K_3Fe(CN)_6$, renders the reaction catalytic in the expensive and highly toxic $K_2OsO_4 \cdot (H_2O)_2$. A report by Sharpless and co-workers in 1992 demonstrated the application of this methodology to enynes, and found cinchona alkaloid ligands based on the phthalazine linker (e.g. $(DHQ)_2PHAL$ **2.26**, *Figure 2.4*) to be superior for the dihydroxylation of this class of substrate.[93]

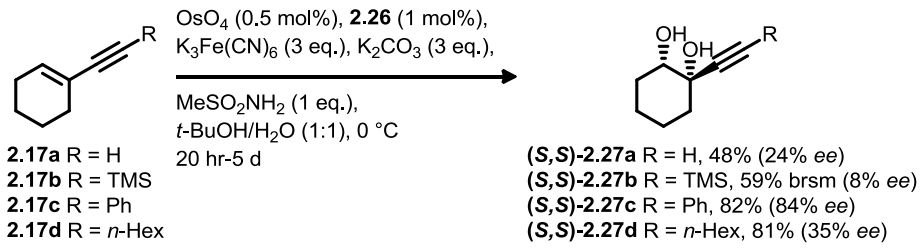


2.26

Figure 2.4: $(DHQ)_2PHAL$

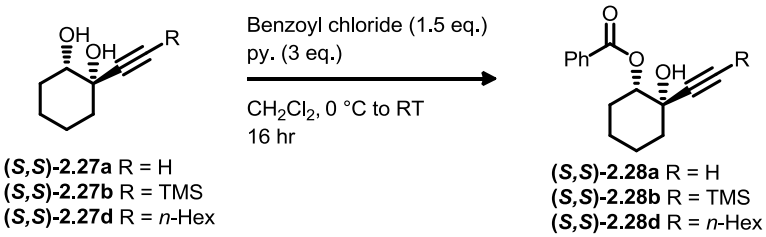
It has also been found that the addition of methanesulfonamide significantly accelerates the rate of dihydroxylation of non-terminal alkenes.[94] A recent report by Junttila and Hormi found that this additive has a two-fold effect: it acts as a phase-transfer catalyst to shuttle hydroxide ions into the organic phase, as well as acting as a general acid catalyst during osmate ester hydrolysis.[95]

In our hands, the enyne substrates **2.17a-d** were subjected to SAD (using OsO_4 itself) to afford the corresponding 1,2-diols **2.27a-d** (*Scheme 2.12*). To the best of our knowledge, asymmetric dihydroxylations have not been performed on substrates of this type.



Scheme 2.12

These enynes, in general, proved to be poor substrates for SAD. Reactivity was poor except for phenyl substrate **2.17c** which was consumed in 20 hours giving satisfactory yield and enantiomeric excess of diol **(*S,S*)-2.27c**. The other substrates required extended reaction times (2-5 days), and this poor reactivity correlated with poor levels of stereoinduction being observed. Enantiomeric excess was measured by chiral HPLC directly for **(*S,S*)-2.27c**; whereas for diols **(*S,S*)-2.27a**, **b** and **d** derivitisation with benzoyl chloride gave the mono-benzoate esters **(*S,S*)-2.28a**, **b** and **d** that could be visualised by chiral HPLC (*Scheme 2.13*).



Scheme 2.13: Preparation of benzoate derivatives for chiral HPLC

The absolute stereochemistry of diols **(*S,S*)-2.27a-d** was predicted using the Sharpless mnemonic,[91] by considering the alkyne substituent to be R_L so that the alkene proton points into the hindered "South-East" quadrant (*Figure 2.5*). With the $(DHQ)_2PHAL$ ("α"-ligand) we expected bottom-face dihydroxylation (corresponding to (*S,S*)) and this assignment was reinforced by comparison of the eventual allene products with those from the Shi epoxidation (*vide infra*). The "North-West" quadrant is also hindered, and the cyclic nature of the alkene imposes the necessity of having a bulky substituent (cyclohexyl ring tether) at this position, which could explain the poor stereoselectivity observed with these substrates (*Figure 2.5*). Another possibility is that a slow, non-stereoselective background reaction may be a competing process with the unreactive substrates **2.17a**, **b** and **d**, resulting in poor overall stereoinduction. In the case of **2.17c**, a favourable π-stacking interaction between the phenyl ring and the ligand is suggested as a possible reason for the improved reactivity and stereoselectivity observed with this substrate.

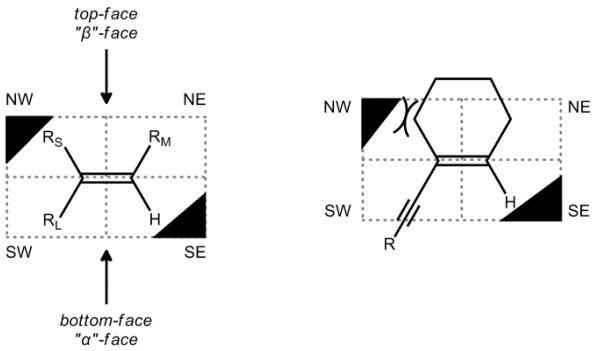
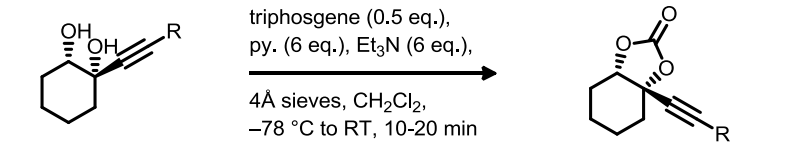


Figure 2.5: Sharpless mnemonic

With the diols in hand we examined formation of the cyclic carbonates. Triphosgene was chosen as a highly reactive and easy-to-handle source of phosgene.[96] Investigations by the Holmes group found that the use of an excess of both pyridine and triethylamine was crucial to achieving high yields in this transformation.[97] Thus, treatment of diols **(*S,S*)-2.27a-d** with half of an equivalent of triphosgene (corresponding to one and a half equivalents of phosgene) at −78 °C in the presence of six equivalents of both pyridine and triethylamine afforded the desired cyclic carbonates **(*S,S*)-2.04a-d** in excellent yield (*Scheme 2.14*). To ensure the reaction medium was anhydrous, freshly powdered 4Å molecular sieves were also added.



(*S,S*)-2.27a R = H
(***S,S***)**-2.27b** R = TMS
(*S,S*)-2.27c R = Ph
(*S,S*)-2.27d R = *n*-Hex

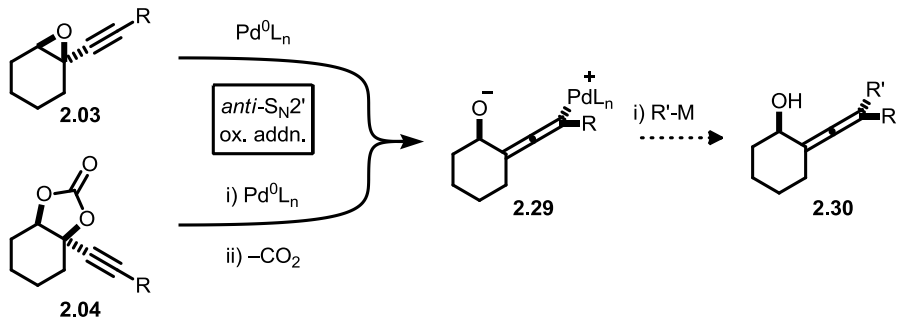
(*S,S*)-2.04a R = H, 96%
(*S,S*)-2.04b R = TMS, 87%
(*S,S*)-2.04c R = Ph, 98% brsm
(*S,S*)-2.04d R = *n*-Hex, 85%

Scheme 2.14: Synthesis of cyclic carbonates

Formation of the cyclic carbonates was confirmed through IR (disappearance of broad OH stretches at *ca.* 3400 cm^{-1} and appearance of a carbonyl stretch at *ca.* 1810 cm^{-1}) and ^{13}C NMR (carbonyl δ_C 153-154 ppm) spectroscopy.

2.4.4 Comparison of Epoxide and Cyclic Carbonate Reactivity

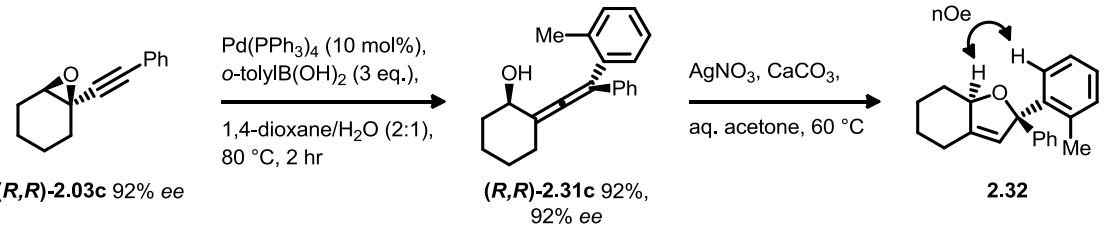
We were now in the position to compare the reactivity of epoxides and cyclic carbonates under allene forming conditions. Both substrate types should proceed through the same alkoxide intermediate **2.29**, which is formed directly from the epoxide **2.03** after oxidative addition, and indirectly after loss of CO_2 from the cyclic carbonate **2.04** (*Scheme 2.15*).



Scheme 2.15: Similarities in the reaction pathway from **2.03** and **2.04**

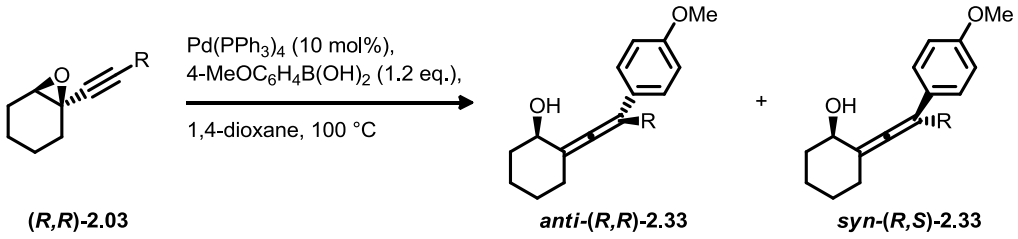
The oxidative addition step for both should be *anti*-S_N2', as described in *Chapter 1*, leading to the stereospecific formation of intermediate **2.29**. Transmetallation and reductive elimination should occur with retention of this configuration, leading to a single diastereomer of product **2.30**.

Indeed, Yoshida has examined the Suzuki cross-coupling of enantioenriched epoxide **(*R,R*)-2.03c** with *o*-tolyl boronic acid, yielding an allene product **(*R,R*)-2.31c** with identical enantiomeric excess to the starting material (*Scheme 2.16*).[35] More significantly, a single allene diastereomer resulted from Yoshida's reaction. It was shown that the forming C−C bond was *anti* with respect to the breaking C−O bond through nOe experiments after conversion to dihydrofuran **2.32**.[98-99] The formation of **(*R,R*)-2.31c** with complete stereospecificity suggests that the α-hydroxyl substitutent is configurationally stable under these reaction conditions.



Scheme 2.16: Yoshida's reaction of **(*R,R*)-2.03c** and determination of relative stereochemistry[35]

In light of this precedent we set about a systematic comparison of the epoxides and cyclic carbonates, commencing with the epoxides **2.03a-d** (*Scheme 2.17*). However, under our conditions we also observed the formation of the *syn* diastereomer, which was not reported by Yoshida.



Scheme 2.17: Suzuki coupling with epoxides **2.03a-d**

Entry	Epoxide (*ee*)	R	Time	Product	Yield	*dr* (*anti* : *syn*)	*ee* (*anti* / *syn*)
1	**2.03a** (*rac*)	H	2 min	**2.33a**	45%	6.1 : 1	-
2	**(*R,R*)-2.03b** (n.d.)	TMS	10 min	**2.33a**	*trace*[b]	-	-
3	**(*R,R*)-2.03c** (82%)	Ph	10 min	**2.33c**	78%	4.8 : 1	81% / 84%
4	**(*R,R*)-2.03d** (87%)[a]	*n*-Hex	10 min	**2.33d**	67%	6.7 : 1	87% / 87%

Table 2.1: Epoxide results. [a] See text; [b] Trace **2.33a** observed by crude ^{1}H NMR spectroscopy

The results set out in *Table 2.1* show variability in the diastereomeric ratio (*dr*) of the isolated allenes, with all reactions containing significant amounts of the *syn* diastereomer. The reactions were run until complete consumption of starting material was observed by TLC. The reaction of the terminal epoxide **2.03a** (*Entry 1*) was considerably faster than the substituted epoxides, although predictably a lower isolated yield of allene isomers was obtained. The major diastereomer from the reaction of **2.03a** could be isolated through silica gel chromatography and was found to be crystalline. Single crystal X-ray diffraction showed the relative stereochemistry of the major diastereomer to be *anti* (*Figure 2.6*).

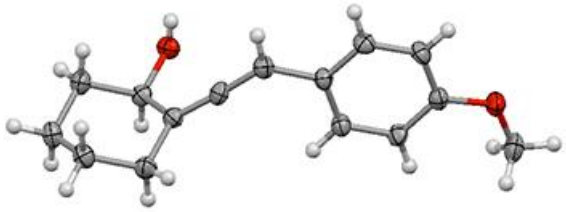
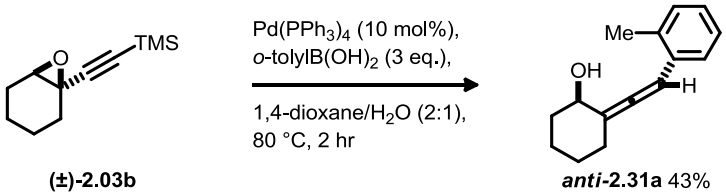


Figure 2.6: X-Ray structure of ***anti*-2.33a**

Surprisingly, the TMS substituted epoxide **(*R,R*)-2.03b** failed to give any isolable amounts of allene products even though it was completely consumed under the reaction conditions (*Entry 2*). A trace of the deprotected allene **2.33a** was observed by crude ^{1}H NMR spectroscopy, but this turned out to be a negligible amount when the crude mixture was subjected to silica gel purification. This result is in contrast to that reported by Yoshida, where the reaction of **(±)-2.03b** with *o*-tolyl boronic acid yields the deprotected allene ***anti*-2.31a** as a single diastereomer, albeit in a moderate 43% yield (*Scheme 2.18*).[35] When we reproduced Yoshida's reaction conditions for **(±)-2.03b**, complete consumption of starting material was observed in less than 5 minutes, and upon purification a diastereomeric mixture of allene **2.31a** (5.0 : 1, *anti : syn*) was obtained in 35% isolated yield.

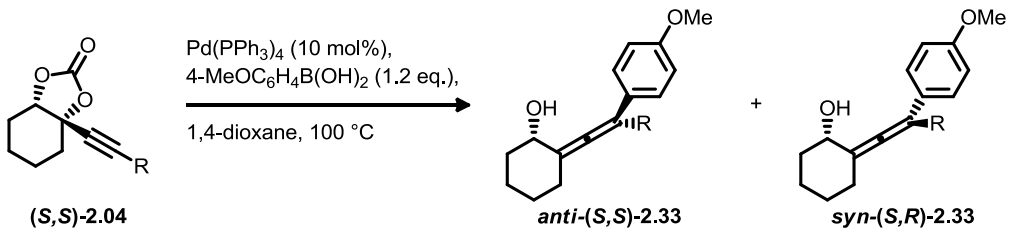


Scheme 2.18: Yoshida's result with epoxide **(±)-2.03b**[35]

The phenyl and *n*-hexyl epoxides **(*R,R*)-2.03c** and **d** (*Entries 3 and 4*) afforded the desired allenes in

good yields, although the *dr* of the isolated allene was significantly lower from the phenyl epoxide than from either the terminal or *n*-hexyl epoxide. The enantiomeric excess of each allene diastereomer was measured for **2.33c**, and the measured *ee*'s (81 and 84%) correlated well with that for the starting material **(*R*,*R*)-2.03c** (82% *ee*). Using this result and the measured *ee*'s for the allene diastereomers of **2.33d**, we tentatively proposed that the *n*-hexyl epoxide **(*R*,*R*)-2.03d** (which could not be measured directly by HPLC) had an *ee* of approximately 87%.

With the epoxide results in hand we subjected the cyclic carbonates to the same reaction conditions (*Scheme 2.19*).



Scheme 2.19: Suzuki coupling with cyclic carbonates **(*S*,*S*)-2.04a-d**

Entry	Cyclic Carbonate (*ee*)	R	Time	Product	Yield	*dr* (*anti* : *syn*)	*ee* (*anti* / *syn*)
1	**(*S*,*S*)-2.04a** (24% *ee*)	H	5 min	**2.33a**	52%	5.0 : 1	17% / 23%
2	**(*S*,*S*)-2.04b** (8% *ee*)	TMS	30 min	NR[a]	-	-	-
3	**(*S*,*S*)-2.04c** (84% *ee*)	Ph	20 min	**2.33c**	64%	2.1 : 1	85% / 85%
4	**(*S*,*S*)-2.04d** (35% *ee*)	*n*-Hex	20 min	**2.33d**	64%	2.2 : 1	34% / 39%

Table 2.2: Cyclic carbonate results. [a] No reaction (see text).

These reactions were significantly slower than their epoxide counterparts, taking on average twice as long to go to completion by TLC analysis (*Table 2.2*). The major effect of these extended reaction times appears to be drastically lower *dr* of the isolated allene products. In contrast to the epoxide **(*R*,*R*)-2.03b**, the TMS substrate **(*S*,*S*)-2.04b** failed to react under these conditions, returning only starting material. However, this result did correlate with that observed for acyclic carbonate **2.02b** which also failed to react. The measured *ee*'s of the allene products correlated well with those of the starting material, giving yet more evidence that the α-hydroxy substituent is configurationally stable. This suggests that the origin of the diastereomers is the presence of a mixture of allene stereocentres relative to the stable α-hydroxy stereocentre. For each diastereomer, the major enantiomer was opposite to that formed in the analogous reactions of the epoxides, strongly supporting the predictions of absolute stereochemistry made using the Shi transition state and Sharpless mnemonic (*vide supra*).

To examine whether the reaction time had any meaningful effect on the *dr* of the allene products we repeated the reaction of *n*-hexyl epoxide **(*R*,*R*)-2.03d**, this time running the reaction for 20 minutes

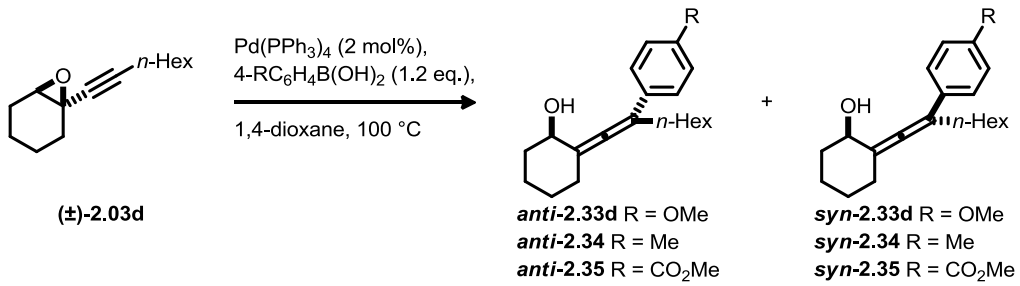
(*Table 2.3, entry 2*). This gave a direct comparison with carbonate **(*S*,*S*)-2.04d** (*Entry 3*).

Entry	Starting Material	Reaction Time	Product	Yield	*dr* (*anti*:*syn*)
1	**(*R*,*R*)-2.03d**	10 min	**2.33d**	67%	6.7 : 1
2	**(*R*,*R*)-2.03d**	20 min	**2.33d**	82%	5.5 : 1
3	**(*S*,*S*)-2.04d**	20 min	**2.33d**	64%	2.1 : 1

Table 2.3: Further comparison of epoxide **2.03d** with carbonate **2.03d**

This showed that reaction time could not be the sole reason for the differing stereochemical outcome between the epoxides and cyclic carbonates. However, the stereoselectivity after 20 minutes for **(*R*,*R*)-2.33d** was lower, suggesting that there are processes that are able to isomerise the allene product after the starting material has been consumed and the reaction is complete.

To further examine the origin of loss of stereoselectivity we varied the electronic character of the boronic acid (*Scheme 2.20*). The transmetallation of aryl boronic acid species has been proposed to be a σ-metathesis of a palladium hydroxide species,[100] thus the more electron-rich (and therefore nucleophilic) the boronic acid, the faster transmetallation should occur onto the electrophilic Pd(II) centre. If transmetallation is the rate determining step of the reaction, a difference in reaction rate would therefore be observed on varying the coupling partner and this might manifest itself as a change in stereoselectivity. To this end we conducted the reaction of epoxide **(±)-2.03d** with 4-$MeOC_6H_4B(OH)_2$ (electron-rich), 4-$MeC_6H_4B(OH)_2$ (neutral) and 4-$MeO_2CC_6H_4B(OH)_2$ (electron poor) and compared reaction times and stereoselectivities (*Scheme 2.20*).



Scheme 2.20

Entry	R	Reaction Time	Product	Yield	*dr* (*anti* : *syn*)
1	OMe	12 min	**2.33d**	64%	6.1 : 1
2	Me	17 min	**2.34**	65%	5.3 : 1
3	CO_2Me	20 min	**2.35**	61%	2.7 : 1

Table 2.4: Effect of boronic acid coupling partner

Table 2.4 outlines the results from these experiments, showing a clear difference in both reaction time and selectivity as the electronic character of the coupling partner is changed, supporting the hypothesis that transmetallation is the rate determining step of the reaction. There is also a clear trend between

reaction time and the isolated *dr* of the allene product; the longer-lived the allenylpalladium intermediate, the greater the degree of stereochemical erosion. This highlighted two possibilities: either that the allenylpalladium intermediate itself was isomerising prior to transmetallation, or another process involving the intermediate was isomerising the product.

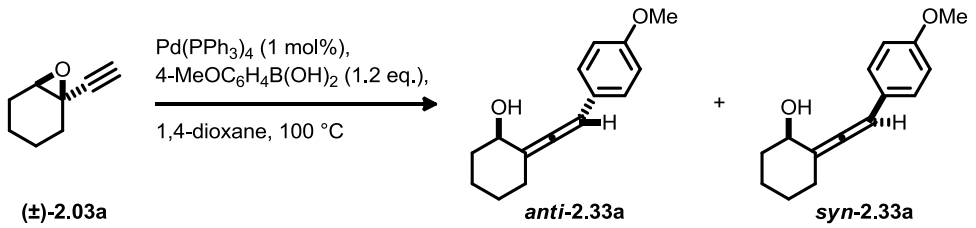
These results encouraged us to try and elucidate possible mechanisms for the loss of stereoselectivity, and to this end some simple time-course experiments were carried out in an attempt to shed light on this phenomenon.

2.4.5 Time-course Studies

A requirement for reaction monitoring was the need for reaction conditions and sampling methods that would give us both reproducible and usable results. We first examined the coupling of terminal propargylic epoxide **(±)-2.03a** with 4-$MeOC_6H_4B(OH)_2$ (*Scheme 2.21*). The reaction was sampled (through a rubber septum) with a flat metal TLC needle to draw a few microlitres of the reaction mixture, which was immediately rinsed into an HPLC vial containing hexane to quench the reaction. Sampling was conducted at regular intervals over *ca.* 10 minutes to examine how the *dr* of the allene product varied with time. Measurement of the *dr* was made through integration of the HPLC traces and are relative (no internal standard was used). The samples from the reaction were also analysed by TLC to observe qualitatively the point at which starting material was consumed.

Our initial attempts consisted of heating a mixture of starting materials and catalyst from room temperature to 100 °C (in a preheated oil bath) and led to inconsistent results. We proposed this to be owing to an inability to accurately define the starting point of the reaction as we were adding the catalyst as a solid to a solution of starting materials, and this could introduce errors through rate of dissolution of the catalyst, introduction of varying amounts of oxygen or variable rates of heating.

After some experimentation we found that adding a solution of the starting materials in degassed 1,4-dioxane *via* syringe to a preheated (100 °C) solution of catalyst gave reproducible results with which we were confident enough to begin drawing conclusions. Thus, the reaction of epoxide **(±)-2.03a** was studied (*Scheme 2.21*).



Scheme 2.21: Initial time-course experiment

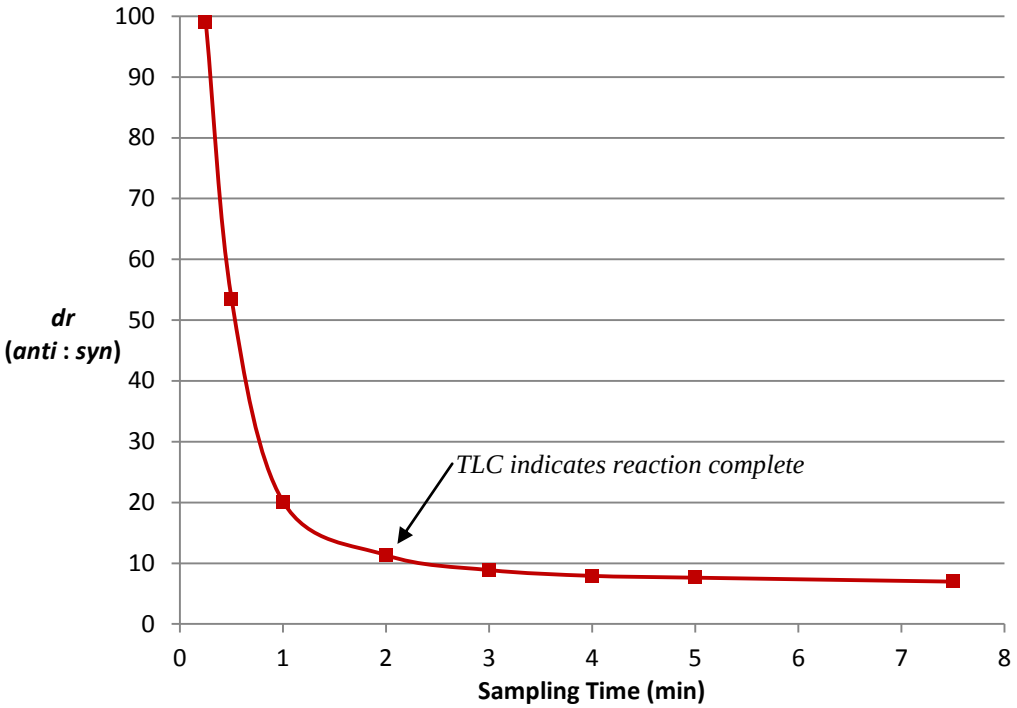
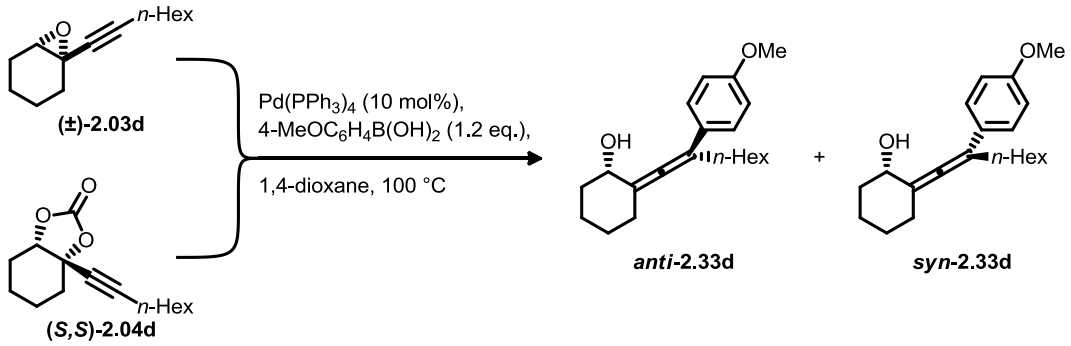


Figure 2.7: *dr* of allene **2.33a** over the course of the reaction

The graph in *Figure 2.7* shows the average of two runs of the reaction which were virtually identical. This clearly shows that at the start of the reaction the *dr* of the formed product is very high (~99 : 1 *dr* at t = 0.25 min), but that as the reaction proceeds there is a significant drop in stereoselectivity. The *dr* then plateaus (with a subsequent gradual erosion of *dr* at a much slower rate) and finishes as ~7 : 1 *dr* at t = 7.5 min. The start of this plateau region appears to correspond with the consumption of starting material, which occurs around t = 2 min as evidenced by TLC analysis. This was a very surprising result as it shows that the initial turnover of the reaction occurs with complete stereoselectivity to generate only *anti* allene **2.33a**. Thus, isomerisation of the allenylpalladium intermediate is not occurring for the epoxide, and the transmetallation and reductive elimination steps proceed with retention of configuration of the allenylpalladium species. It also appears that little isomerisation of the product occurs once the starting material has been consumed, and this suggests that it is a Pd(II) reaction intermediate that promotes isomerisation. Pd(II) is a π-acid,[8] so it is feasible to propose that it can interact with the π-system of the allene products and bring about isomerisation. This hypothesis is

backed up by the results from varying the boronic acid (*Table 2.4*), suggesting that a longer-lived intermediate has more time to isomerise allene product and leads to products with lower overall stereoselectivity. This will be discussed later in further detail.

We next compared the reaction course of *n*-hexyl epoxide **(±)-2.03d** with the *n*-hexyl cyclic carbonate **(*S*,*S*)-2.04d** to examine the differing stereochemical outcome of these electrophiles (*Scheme 2.22*, *Figure 2.8*).



Scheme 2.22

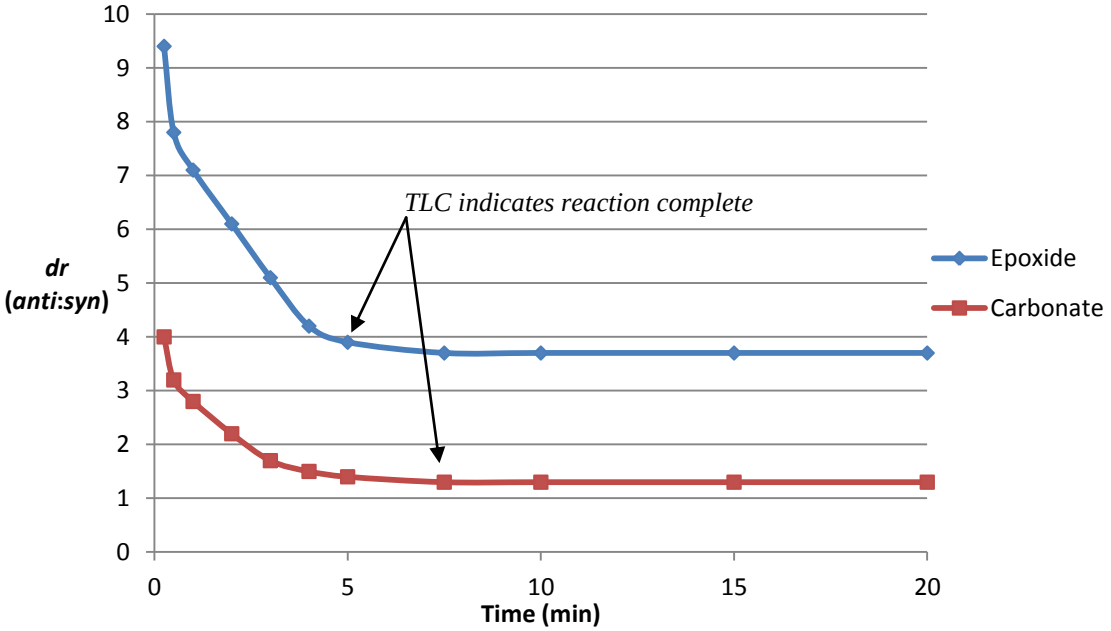
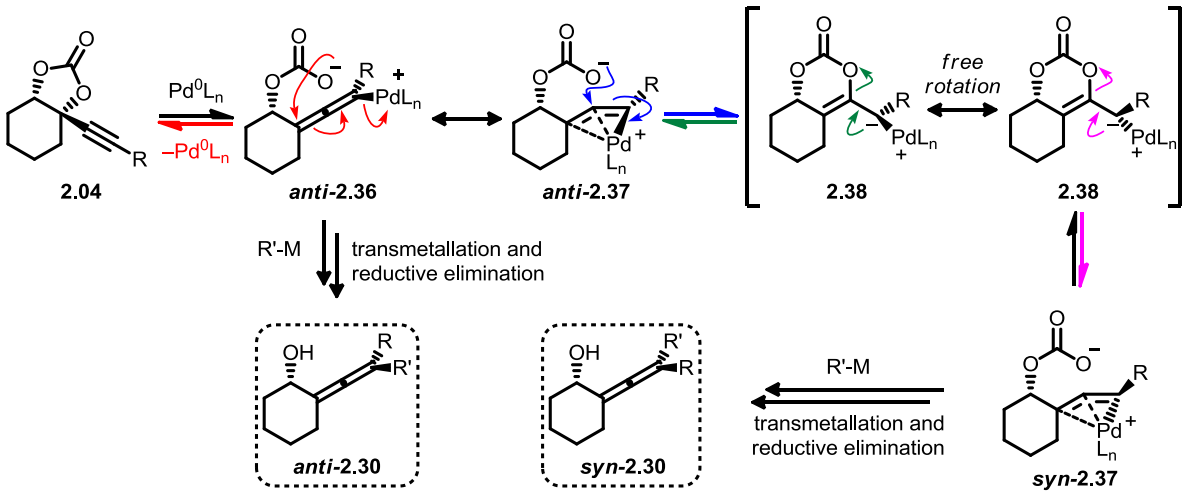


Figure 2.8: Time-course of **(±)-2.03d** *vs.* **(*S*,*S*)-2.04d**

As observed with the related epoxide **(±)-2.03a**, both epoxide **(±)-2.03d** and cyclic carbonate **(*S*,*S*)-2.04d** showed rapid isomerisation during the reaction that plateaus once the starting material is consumed and the reaction is complete. The high initial *dr* observed with epoxide **(±)-2.03d** again suggests isomerisation of allenylpalladium is not occurring with this substrate class. However, the initial *dr* for the cyclic carbonate is significantly lower (*ca.* 4.1 : 1 at t = 0.25 min), and this suggests one of two possibilities: either that the allenylpalladium intermediate is longer lived and able to

promote further product isomerisation; or that the allenylpalladium intermediate itself is undergoing isomerisation.

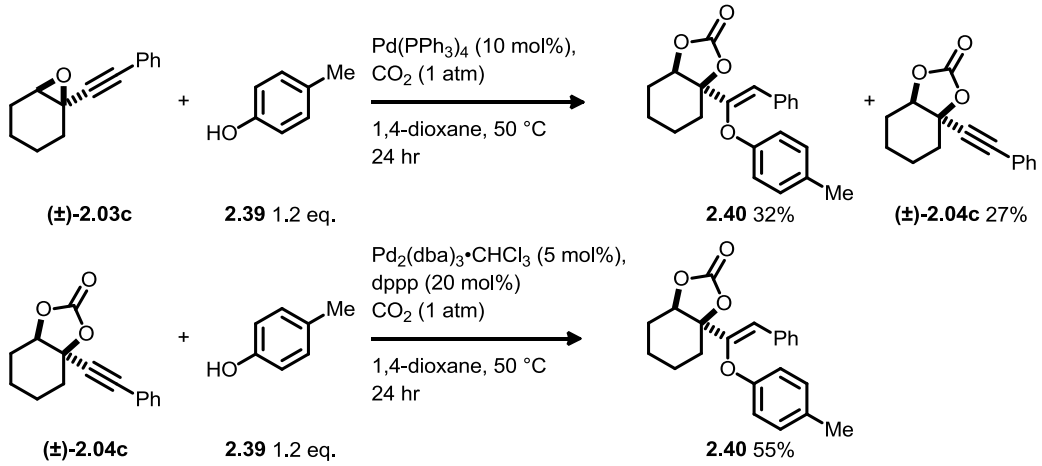
In comparing these results, it is clear from the reaction times that the epoxides are more reactive than the cyclic carbonates. This increased reactivity is possibly owing to the release of considerable strain on opening the three-membered epoxide ring, making it a more favourable process than for the 5-membered cyclic carbonate. Also, the first intermediate formed on oxidative addition into the cyclic carbonate is likely the carbonate anion ***anti*-2.36** (*Scheme 2.23*). The formation of this species may well be reversible, with attack of the carbonate and elimination of palladium(II) from ***anti*-2.36** regenerating **2.04** with complete stereospecificity, but slowing the overall reaction. As detailed in *Chapter 1* the η^1-allenylpalladium ***anti*-2.36** is in equilibrium with the η^3-allenylpalladium ***anti*-2.37**, which can undergo attack of the carbonate anion on the central carbon of the allenylpalladium. This has the potential to generate palladium carbene **2.38** (shown here as charge separated), again in a reversible fashion. Free rotation around the newly formed C−C single bond in **2.38** followed by elimination would form intermediate ***syn*-2.37**, which gives allene ***syn*-2.30** after transmetallation and reductive elimination. This isomerisation may account for the lower *dr* observed in the reaction of the carbonates, although as we have no clear evidence for its operation this is entirely speculative. The alkoxide intermediate generated from oxidative addition into the epoxides (or after loss of CO_2 from ***anti*-2.36**) is unlikely to undergo this isomerisation pathway as formation of the requisite four-membered oxetene intermediate would be highly unfavourable.



Scheme 2.23: Possible reaction pathways for the cyclic carbonates

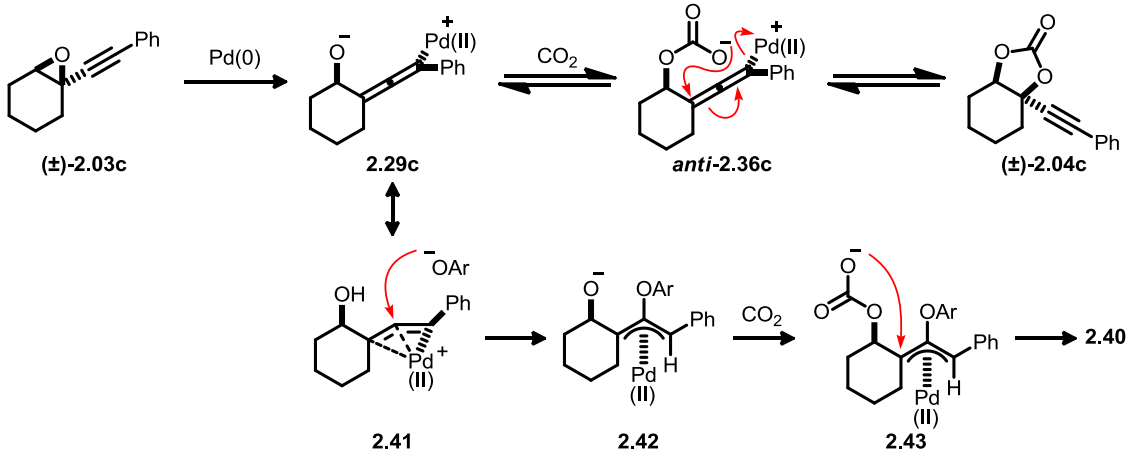
The possibility for reversible oxidative addition has been demonstrated in the work of Yoshida and co-

workers on the palladium-catalysed reaction of propargylic epoxides with phenols under an atmosphere of CO_2.[101] When the reaction is conducted with $Pd(PPh_3)_4$ as the catalyst a 1.2 : 1 mixture of enol ether **2.40** and propargylic cyclic carbonate **(±)-2.04c** is formed (*Scheme 2.24*). Propargylic cyclic carbonate **(±)-2.04c** was found to be a competent substrate for the formation of **2.40** under similar conditions, with the combination of $Pd_2(dba)_3{\cdot}CHCl_3$ and bidentate ligand dppp replacing $Pd(PPh_3)_4$. This is in line with the observation made by Ogoshi and co-workers that bidentate ligands promote the formation of η^3-allenylpalladium species in polar solvents.[54]



Scheme 2.24: Yoshida's reaction of propargylic electrophiles with *p*-cresol **2.39** under an atmosphere of CO_2[101]

The formation of **(±)-2.04c** was explained by the fixation of CO_2 by the alkoxide **2.29c**, followed by the S_N2' displacement of palladium by the resulting carbonate anion of ***anti*-2.36c** (*Scheme 2.25*). The proposed mechanism for the formation of **2.40** proceeds *via* the η^3-allenylpalladium complex **2.41** with the phenolate and carbonate anions acting as the two nucleophilic species.

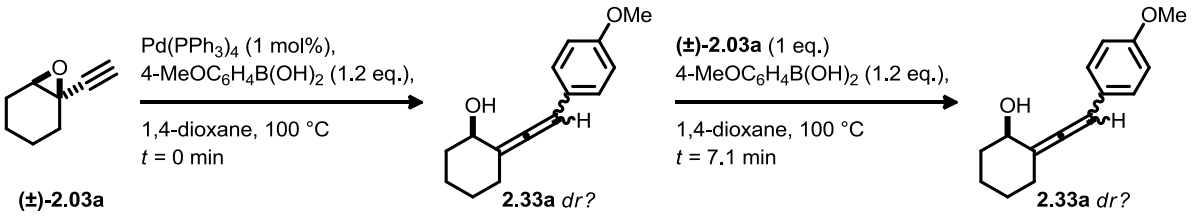


Scheme 2.25: Yoshida's mechanistic rationale for the formation of **(±)-2.04c** and **2.40**[101]

This study by Yoshida supports our proposals for the differing reactivity with the cyclic carbonates by demonstrating that the oxidative addition is reversible, and that the η^3-allenylpalladium species

required for central-carbon attack is formed in the presence of $Pd(PPh_3)_4$.

We devised further reactions to test our hypotheses for the isomerisation of allene product. If the intermediate of the reaction is isomerising the product, we should observe further isomerisation if a second addition of starting materials is made *after* the completion of the initial reaction, as long as the Pd(0) catalyst is still active in solution. To this end we proposed adding a second batch of starting materials to the reaction of **(±)-2.03a** at a time well after completion of the initial reaction, and observing the change in *dr*, if any, that this caused (*Scheme 2.26*, *Figure 2.9*). As the initial reaction should take *ca.* 2 minutes to go to completion we considered a second addition of starting materials at t = 7.1 min (after taking a sample at t = 7 min) to be suitable to ensure this.



Scheme 2.26: "Double addition" experiment

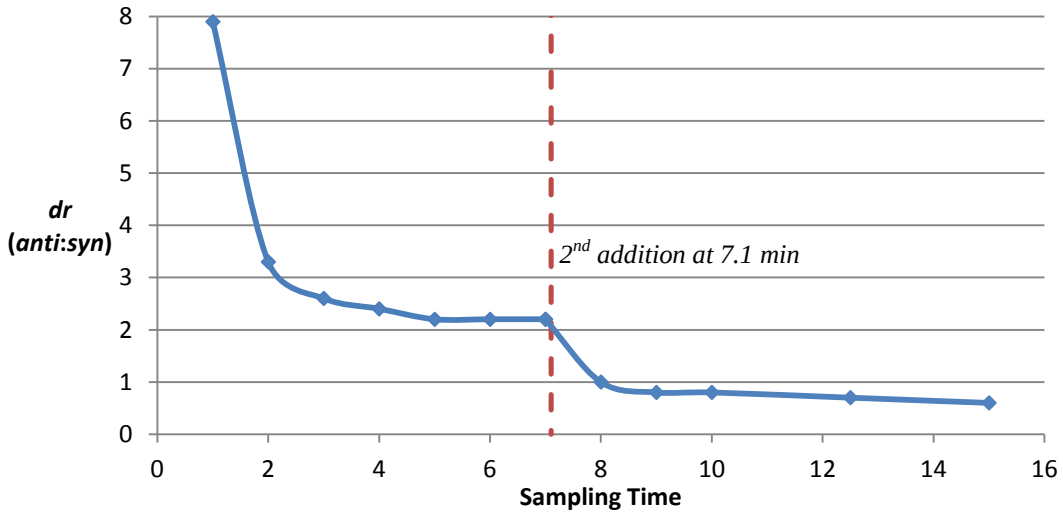
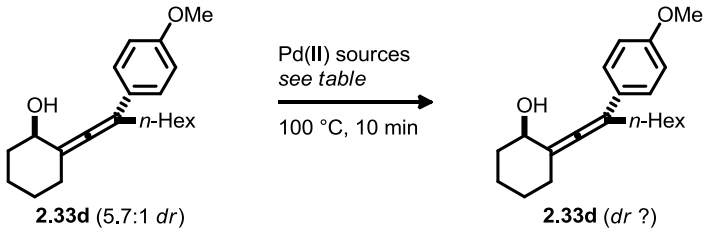


Figure 2.9: Double addition experiment

As expected, the initial reaction is complete between 2 and 3 minutes, as indicated both by TLC and the plateau of the graph (*dr* = 2.2 : 1 at t = 7 min). On addition of a second batch of starting materials at t = 7.1 min there is a clear and sudden drop in *dr* of the product already present in the reaction. This is likely due to the formation of more Pd(II) intermediates from oxidative addition into fresh epoxide **(±)-2.03a**. These intermediates further isomerise the product formed from the initial reaction, as the product is now in relatively high concentration. The isomerisation again plateaus 1 to 2 minutes after this second addition, at *ca.* 0.7 : 1 *dr*, indicating that the *syn*-diastereomer is now the major component

of the product. If the Pd(II) intermediate was unable to isomerise already formed allene product we would have observed (on addition of a second batch of starting materials) either no change in the trend of *dr* or an increase in *dr* owing to formation of more *anti*-allene. As a sharp drop occurred, this proved that an intermediate of the reaction was key to the problem of isomerisation.

To gain further insight into the nature of the species that bring about isomerisation we conducted some further reactions with isolated allene products of known *dr*. Firstly, we exposed allene **2.33d** (5.7 : 1 *dr*) to sources of Pd(II) to examine the effects (*Scheme 2.27*).



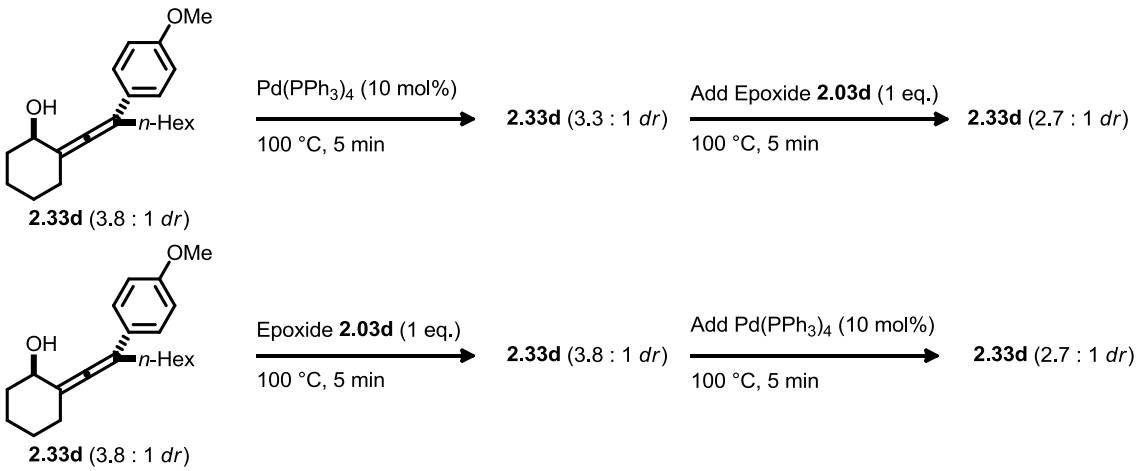
Scheme 2.27

Entry	Pd(II) source[a]	Other additives	Product	*dr* (*anti* : *syn*)
1	$PdCl_2$	None	-[b]	-[a]
2	$PdCl_2(PPh_3)_2$	None	**2.33d**	5.7 : 1
3	$PdCl_2(PPh_3)_2$	Epoxide **2.03d** (1 eq.)	**2.33d**	5.7 : 1

Table 2.5: [a] 10 mol%; [b] Unknown product formed, no allene **2.33d** remaining

The results outlined in *Table 2.5* show that the Pd(II) sources trialled are not able to promote isomerisation. $PdCl_2$ is strongly Lewis acidic, so unsurprisingly reacted with **2.33d** to form an unknown product (*Entry 1*). $PdCl_2(PPh_3)_2$ did not react in this way, presumably because of the presence of stabilising PPh_3 ligands, but was unable to promote isomerisation of allene **2.33d** (*Entry 2*). Adding epoxide starting material along with $PdCl_2(PPh_3)_2$ also failed to promote isomerisation (*Entry 3*). This was not unexpected as Pd(II) is unable to undergo oxidative addition into **2.03d** and form intermediates capable of promoting isomerisation.

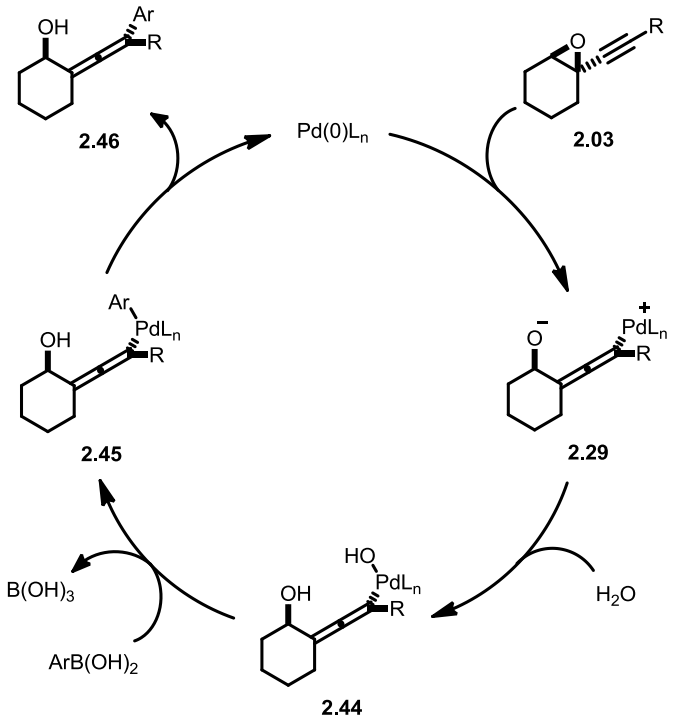
As a final investigation we exposed isolated allene **2.33d** (3.8 : 1 *dr*) to Pd(0) and epoxide **2.03d** sequentially (*Scheme 2.28*). These results show that there are two competing processes for allene isomerisation. Firstly, Pd(0) seems to be able to promote moderate loss of stereoselectivity under these conditions. This is likely the reason for the slow tail-off in *dr* observed in *Figures 2.7-9*. Secondly, the more pronounced isomerisation is promoted by the allenylpalladium(II) species formed on oxidative addition, as evidenced by the stark drops in stereoselectivity observed when both Pd(0) and epoxide are present together in the reaction.



Scheme 2.28: Further evidence for intermediate promoted isomerisation

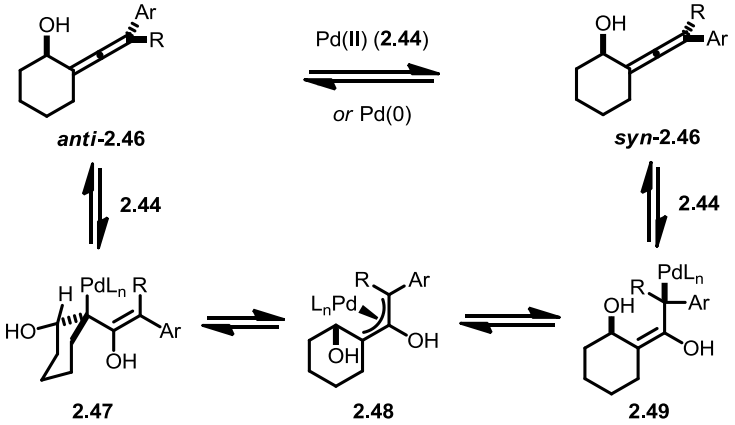
We therefore propose that isomerisation of allene products occurs through two processes: a Pd(0) promoted process, coupled with a Pd(II) mediated process that operates only during the reaction. Of the proposed mechanisms in the literature for allene isomerisation outlined in *Section 1.33* the bimetallic mechanism (*Scheme 1.31*) is unlikely to be operating in this case. This is owing to our use of $Pd(PPh_3)_4$, which was found by Ogoshi to be unable to promote allene isomerisation by this bimetallic pathway.[49] One further piece of evidence discounting this mechanism is the initial formation of allene product with complete stereospecificity (*Figure 2.7*); if the bimetallic pathway were operating we would observe allenylpalladium isomerisation prior to transmetallation. It is therefore possible that isomerisation of allene product by a Pd(II) intermediate of the reaction is occurring *via* a mechanism similar to that outlined by Bäckvall.[50]

We propose an overall catalytic cycle for the reaction of epoxides **2.03a-d** (*Scheme 2.29*). Oxidative addition into epoxide **2.03** gives the stereodefined zwitterionic species **2.29** which is neutralised by water to form Pd(II) hydroxide species **2.44**.[102-103] Transmetallation of the Pd(II) hydroxide **2.44** with boronic acid yields species **2.45** with loss of boric acid, and this subsequently undergoes reductive elimination to give stereodefined allene **2.46** and regenerate Pd(0).[100] The reaction of the cyclic carbonates **2.04** may be more complex and not stereospecific, owing to the possibility of reversibility and competing pathways other than direct transmetallation (*vide supra*).



Scheme 2.29: Proposed catalytic cycle

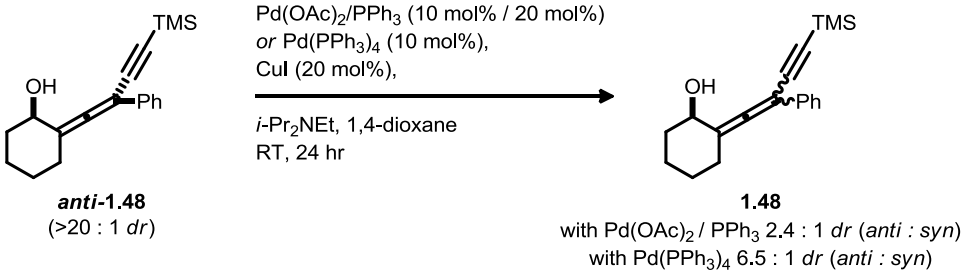
We consider that allenylpalladium(II) species **2.44** (or similar) is a candidate for the isomerisation of allene product. A plausible mechanism for isomerisation by **2.44** is outlined in *Scheme 2.30*. In an analogous way to that proposed by Bäckvall,[50] σ-π-σ isomerisation of a complex (**2.47** or **2.49**) formed through *anti*-hydroxypalladation of **2.46** leads to overall inversion of the allene axis. It is inconsequential which double bond of the allene reacts in the initial palladation step, but it is feasible to propose hydroxyl directed addition of palladium to the top face of the proximal double bond (as shown in **2.47**). This isomerisation is, of course, a reversible process.



Scheme 2.30: Plausible pathway for isomerisation

Indeed, Yoshida and co-workers have demonstrated this isomerisation in their cross-coupling of propargylic epoxides with alkynes.[36] Isolated ***anti*-1.48** was exposed to the reaction conditions (with $Pd(OAc)_2$ replacing the Pd catalyst) which led to significant isomerisation of the allene axis (*Scheme*

2.31). When $Pd(PPh_3)_4$ was employed in place of $Pd(OAc)_2$ isomerisation was still observed, although to a lesser degree.



Scheme 2.31: Yoshida's demonstration of allene isomerisation by $Pd(OAc)_2$[36]

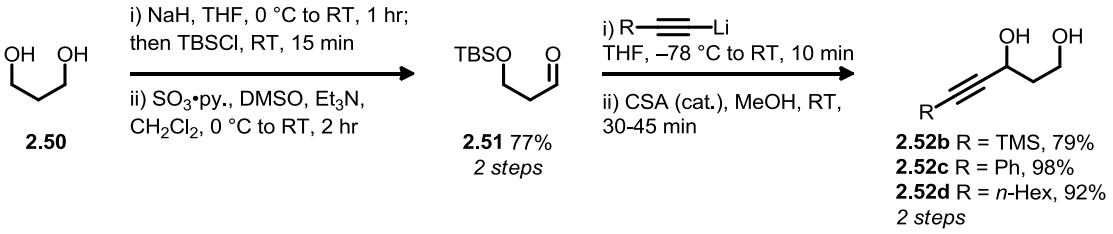
Our studies have shown that there are complex processes occurring in what would appear to be a relatively simple transformation. We have only conducted a limited study, and further work is needed to elucidate the true species responsible for isomerisation and to find conditions that suppress either their formation or action. However, unexpected results from the cross-coupling of the larger ring cyclic carbonates (*vide infra*) led this project in another direction.

2.5 6- and 7-Membered Cyclic Carbonates

It was proposed that the synthesis of these substrates could be achieved from the corresponding 1,3- and 1,4-diols through reaction with triphosgene. Buoyed by the success of forming the 5-membered cyclic carbonates **2.04a-d** we set about synthesising these diols.

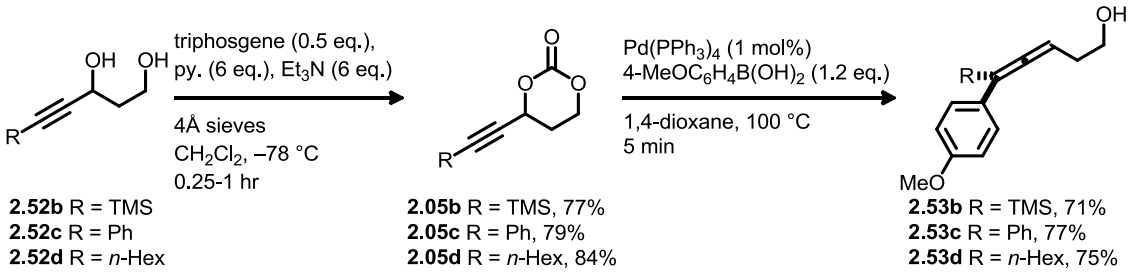
2.5.1 6-Membered Cyclic Carbonates

The 1,3-diols were synthesised in a 4-step sequence, as outlined in *Scheme 2.32*. Mono-protection[104] of propane-1,3-diol **2.50** as the TBS ether followed by Parikh-Doering oxidation[105] afforded aldehyde **2.51**. Additions of the TMS, phenyl and *n*-hexyl alkynyllithiums to **2.51** gave the mono-protected 1,3-diols, which were submitted to silyl deprotection without purification. This was achieved using catalytic (±)-camphor-10-sulfonic acid (CSA) in the presence of a nucleophilic solvent (methanol) to afford the desired 1,3-diols **2.52b-d** in excellent yields.[106]



Scheme 2.32

With these diols in hand, carbonate formation was performed using triphosgene. However, with these substrates it was found that warming the reaction to room temperature had a detrimental effect on the yield, so the reaction was quenched at −78 °C before being allowed to warm. This slightly modified procedure afforded the desired 6-membered carbonates **2.05b-d** in high yields (*Scheme 2.33*).

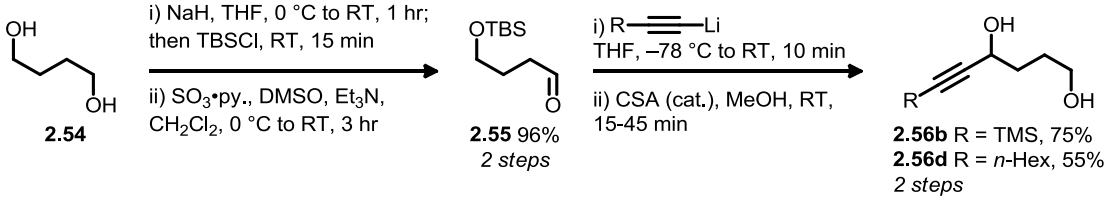


Scheme 2.33: Synthesis of 6-membered carbonates **2.05b-d** and their cross-coupling

On subjecting these carbonates **2.05b-d** to the cross-coupling conditions, the corresponding β-allenyl alcohols **2.53b-d** were formed in good yields (*Scheme 2.33*). This was an extremely pleasing result as, to the best of our knowledge, substrates of this type have not been used previously in allene forming reactions. Surprisingly, in contrast to the result from the TMS-substituted acyclic carbonate **2.01b** (*vide supra*), we observed no deprotection of the allene **2.53b**. This is likely owing to the differing nature of the alkoxide base generated in the reaction, with methoxide generated from acyclic carbonate **2.01b** being the better nucleophile than the zwitterionic intermediate generated from cyclic carbonate **2.05b**.

2.5.2 7-Membered Cyclic Carbonates

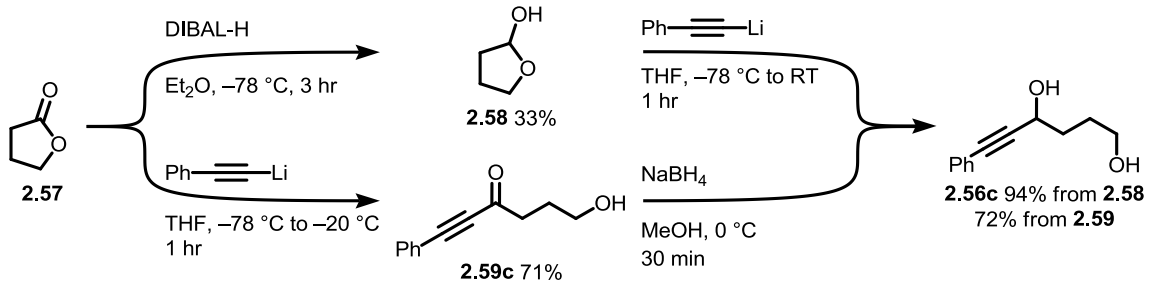
Initially, the homologous 7-membered cyclic carbonates were synthesised from butane-1,4-diol **2.54** using a conceptually identical sequence. Mono-protection of butane-1,4-diol as the TBS ether and oxidation afforded the aldehyde **2.55** in 96% overall yield (*Scheme 2.34*). Additions of the TMS and *n*-hexyl alkynyllithiums to **2.55** and immediate deprotection of the crude product afforded the 1,4-diols **2.56b** and **d** in moderate to good yields.



Scheme 2.34

At this point we considered other, more direct routes to the required carbonate precursors.

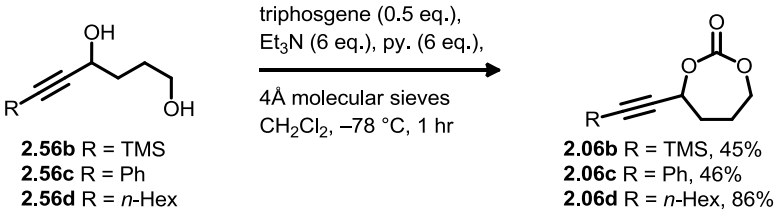
Tetrahydrofuran-2-ol **2.58** was considered to be a suitable precursor as addition of alkynyllithiums to γ-lactols is well-known to afford propargylic 1,4-diols.[107-108] DIBAL-H reduction of γ-butyrolactone **2.57** gave, after distillation, a moderate 33% yield of **2.58**. Subjecting **2.58** to 3 equivalents of (phenylethynyl)lithium at −78 °C afforded the desired 1,4-diol **2.56c** in excellent yield (*Scheme 2.35*).



Scheme 2.35: Concise routes to diol **2.56c**

Whilst this route improved on step economy in forming the 1,4-diol (2 *vs.* 4 steps), it was far from efficient. The poor-yielding reduction step in combination with the requirement for 3 equivalents of alkynyllithium for the subsequent addition step rendered the sequence undesirable. We considered simply reversing the order of the reduction and addition steps, and a search of the literature revealed a report by Wedler and Schick on the addition of alkynyllithiums to γ- and δ-lactones.[109] Within this report was the synthesis of our desired ynone **2.59c**, and following their conditions, **2.59c** was prepared in pleasing 71% yield from **2.57** (*Scheme 2.35*). The subsequent reduction was trivial; simply subjecting **2.59c** to $NaBH_4$ in MeOH afforded **2.56c** in good yield.

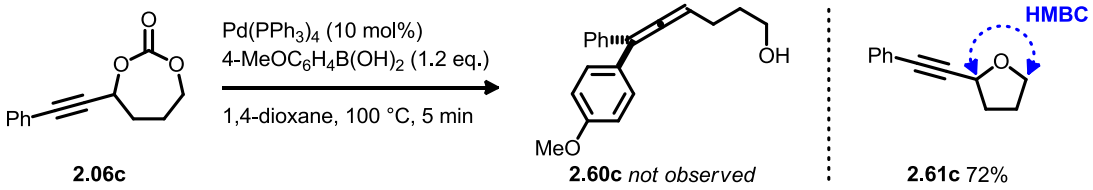
Formation of the challenging 7-membered cyclic carbonate was achieved under the previously employed conditions; we found again that allowing the reaction to warm from −78 °C was detrimental to the yield of the reaction. This afforded the desired 7-membered cyclic carbonates **2.06b-d** in moderate to good yields (*Scheme 2.36*).



Scheme 2.36

With the 7-membered carbonates in hand we subjected **2.06c** to our standard conditions for testing allene formation, fully expecting to synthesise the homologous γ-allenyl alcohol **2.60c** (*Scheme 2.37*). However, examination of the ^1H NMR spectrum of the crude reaction mixture from carbonate **2.06c**

showed none of the characteristic peaks associated with allene formation (*cf.* **2.53c**), but instead a major product that appeared *cyclic* in nature owing to the presence of diastereotopic protons. This is clearly evident by comparison of the ^{1}H NMR spectra of **2.53c** and **2.61c** (*Figure 2.10*). This product was isolated, and through the use of 2D NMR (COSY, HSQC and HMBC) in combination with high resolution mass spectrometry we determined the structure to be the 2-alkynyl tetrahydrofuran (THF) **2.61c**. A key HMBC correlation across the heteroatom was used to confirm the connectivity. Final confirmation of the structure came from comparison of the ^{1}H and ^{13}C NMR spectra with those reported in the literature for THF **2.61c**.[110]



Scheme 2.37: Unexpected formation of **2.61c**

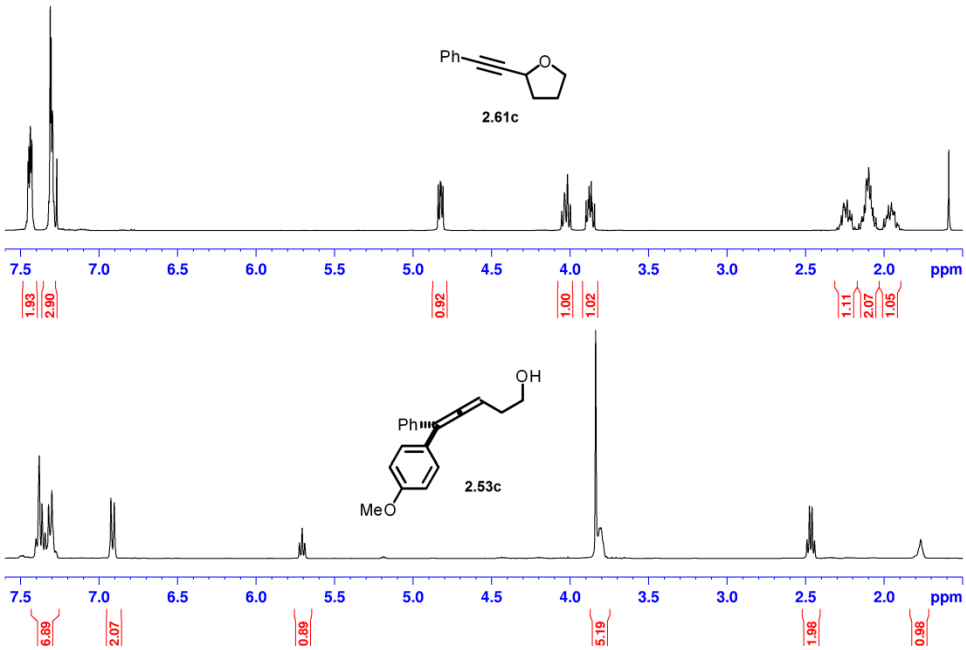
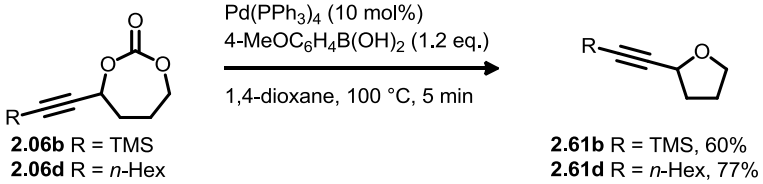


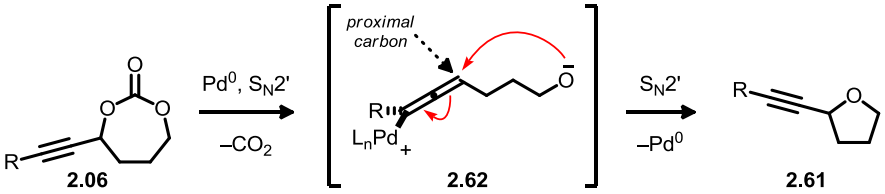
Figure 2.10: ^{1}H NMR spectra of **2.61c** and **2.53c** (purified)

Similarly, the TMS and *n*-hexyl substituted alkynyl THFs **2.06b** and **d** were synthesised in good yields (*Scheme 2.38*). We again observed no silyl deprotection in the formation of THF **2.06b**, however any deprotected THF would likely be volatile.



Scheme 2.38: Synthesis of THFs **2.61b** and **d**

These results were, perhaps, not surprising when we considered a mechanism for the formation of **2.61b-d**. An initial simplistic understanding could arise from the realisation that the alkoxide released from oxidative addition can attack the carbon of the η^1-allenylpalladium species **2.62** proximal to it, resulting in the reductive elimination of palladium and the formation of **2.61** (*Scheme 2.39*).



Scheme 2.39: Plausible mechanism for formation of THF **2.61**

2.6 Conclusions

In conclusion, we have examined the Suzuki cross-coupling of a variety of propargylic electrophiles to form substituted allenes. We have observed significant differences in stereochemical outcome between the epoxide and 5-membered cyclic carbonates, and have conducted preliminary experiments to try and elucidate the reasons both for this difference, and the overall erosion of stereochemistry observed with these substrates. These investigations have led to the proposal that the major species responsible for product isomerisation is, in fact, the intermediate of the reaction itself. Finally, we observed a serendipitous reaction of the 7-membered cyclic carbonates to afford THFs.

We recognised the potential in this unexpected transformation for the synthesis of 2-alkynyl substituted heterocycles, and were intrigued by the questions that these experiments raised: what is the overall stereochemical outcome of the reaction, and could it hint towards a possible mechanism? Could we render the reaction stereoselective, and if performed on enantio- and diastereomerically pure starting materials could this offer a general and practical route to 2-alkynyl heterocycles? Attempting to answer these questions became the main focus of the project, and will be described in the following chapters.

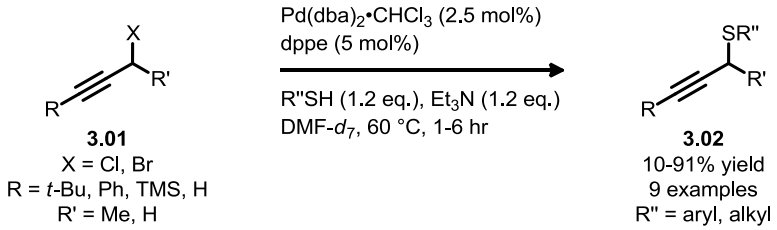
Chapter 3. 2-Alkynyl Oxacycles

3.1 Introduction

3.1.1 Propargylic Products from Allenylpalladium Intermediates

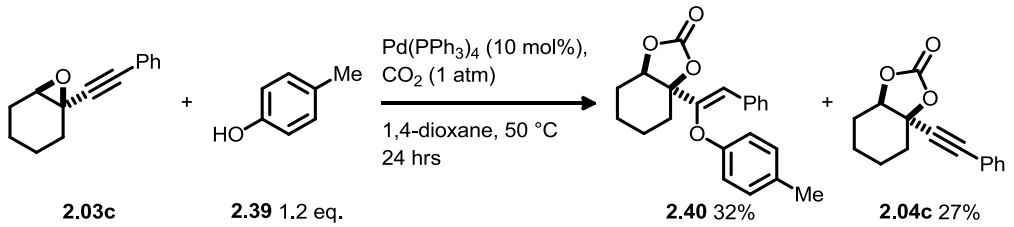
With our discovery of the serendipitous reactivity of propargylic 7-membered cyclic carbonates under Suzuki cross-coupling conditions, we performed a search of the literature to ascertain whether this was a novel process. This revealed only a few examples of the formation of propargylic substitution products from allenylpalladium intermediates,[71, 101, 111] of which only the report by Ohno and co-workers held much similarity to our observations.[71]

In 2004, Tsutsumi and co-workers described the intermolecular substitution of propargylic halides **3.01** with thiols under palladium catalysis (*Scheme 3.1*).[111] The reason for the observed selectivity with thiol nucleophiles under these conditions is not clear, as attack at the central carbon of the η^3-allenylpalladium species would be the expected outcome with excellent nucleophiles, owing to the electrophilicity of the central carbon (*vide supra*).[68, 112]



Scheme 3.1

As described previously, Yoshida and co-workers observed the formation of propargylic 5-membered cyclic carbonate (**2.04c**) from propargylic epoxide **2.03c** under an atmosphere of CO_2 (*Scheme 3.2*).[101]

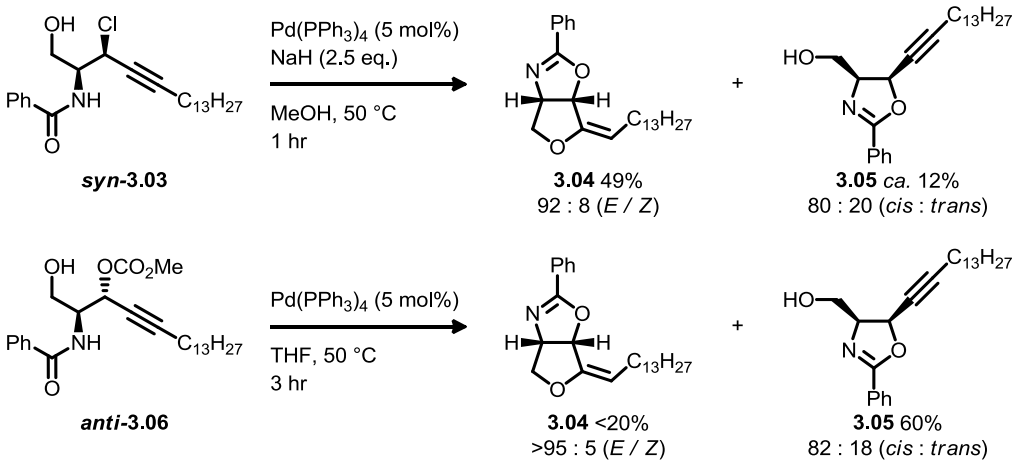


Scheme 3.2

However, this propargylic substitution reaction was only observed with monodentate ligands; the use of bidentate ligands led to the exclusive formation of enol ether **2.40**.

Recently, Ohno and co-workers observed propargylic substitution as the minor product of the cascade cyclisation of propargylic chloride ***syn*-3.03** (*Scheme 3.3*).[71] Interestingly, when the propargylic

carbonate ***anti*-3.06** was employed, **3.05** became the major product of the reaction; a reversal in stereochemical outcome for the formation of **3.05** was also observed, compared to chloride ***syn*-3.03**.



Scheme 3.3

The retention of stereochemistry of the propargylic centre in the formation of ***cis*-3.05** from ***anti*-3.06** suggests that an *anti*-S_N2' reductive elimination of palladium from the allenylpalladium intermediate had occurred. The opposite result with chloride ***syn*-3.03** may be a consequence of direct oxidative addition into the C−Cl bond, followed by *syn*-facial migration and S_N2' reductive elimination.

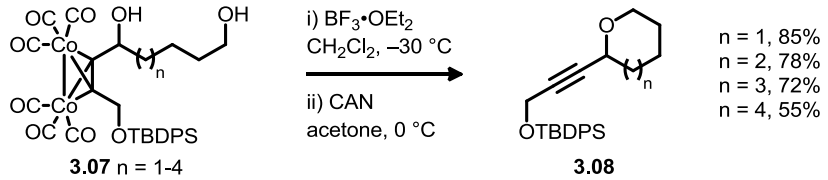
These few examples of propargylic substitution suffer from extremely narrow substrate scope, and as such, allenylpalladium intermediates appear to have been underexplored as a method for the formation of propargylic compounds. However, the report by Ohno and co-workers suggested that such reactions had the potential to be stereoselective when employing enantio- and diastereomerically enriched substrates.[71]

3.1.2 Methods for the Formation of 2-Alkynyl Oxacycles

There are many methods for the stereoselective formation of THFs and THPs. These include, but are not limited to: intramolecular Williamson ether synthesis,[113-114] ring closing metathesis,[115] intramolecular allylation,[116] epoxide-opening cascades,[117-118] ring-contraction of 1,3-dioxepins,[119] intramolecular oxa-Michael reactions[120] and intramolecular etherification of π-allylpalladium intermediates.[121] However, there are far fewer examples of the formation of 2-alkynyl oxacycles.

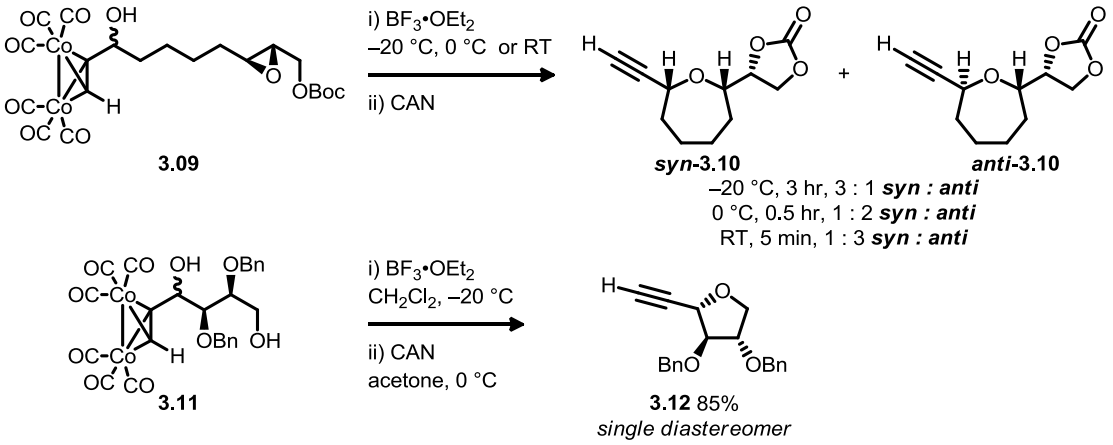
In 2007, Martín and co-workers published a review of the Nicholas reaction in the formation of propargylic ether linkages, mainly concerning the synthesis of 2-alkynyl oxacycles.[122] The use of a stoichiometric dicolbalt hexacarbonyl complex of the alkyne activates the propargylic alcohol (e.g. **3.07**) towards acids, and allows the formation of a propargylic cation which can undergo attack by

nucleophiles.[123] Of particular interest is the ability of this reaction to form medium-ring oxacycles **3.08** (*Scheme 3.4*).[124]



Scheme 3.4

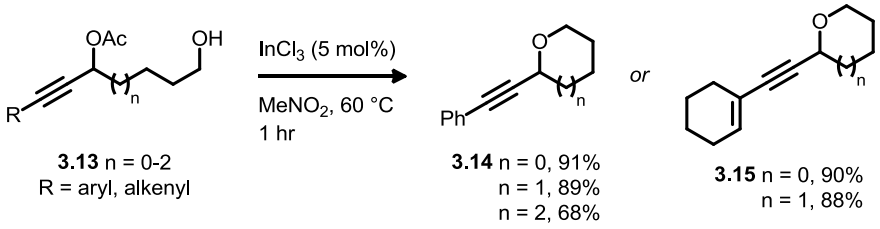
The reaction is able to proceed under both kinetic and thermodynamic control as indicated by the stark temperature dependence observed with certain substrates (e.g. **3.09**, *Scheme 3.5*).[125] In some cases the reaction produces a single diastereomer of the product oxacycle, most often when multiple substituents aid the cyclisation as in **3.11**.[126]



Scheme 3.5

However, the need for the use of toxic cobalt in stoichiometric amounts limits the usefulness of this approach to oxacycles.

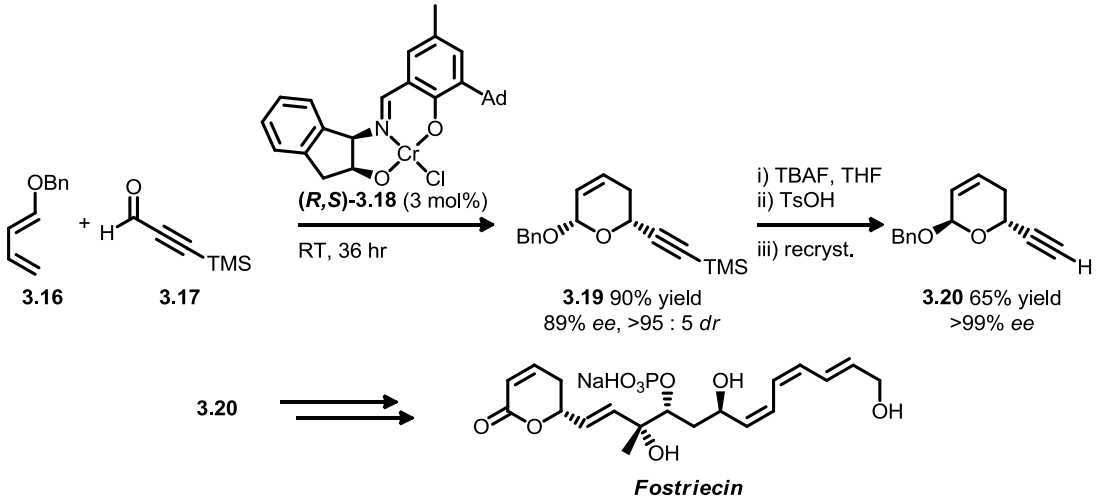
Recently, Zhan and co-workers reported the indium(III) chloride catalysed inter- and intramolecular substitution of propargylic acetates (**3.13**) by carbon, oxygen, sulphur and nitrogen nucelophiles.[127] Within this they demonstrated the formation of THF, THP and oxepane rings, although all in racemic fashion (*Scheme 3.6*).



Scheme 3.6

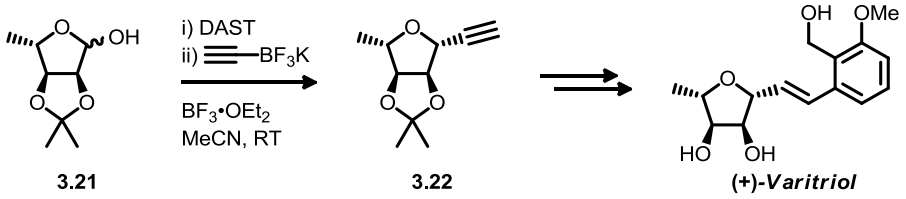
In 2001, Chavez and Jacobsen described the total synthesis of fostriecin, using a hetero-Diels-Alder

approach to form precursor to the lactone ring.[128] The chiral chromium catalyst **3.18**[129] was employed for the reaction of diene and ynal **3.16** and **3.17**, affording oxacycle **3.19** in excellent yield and enantioselectivity (*Scheme 3.7*). Conversion to **3.20** and recrystallisation afforded a single enantiomer of the desired oxacycle, which was further transformed into fostriecin.



Scheme 3.7

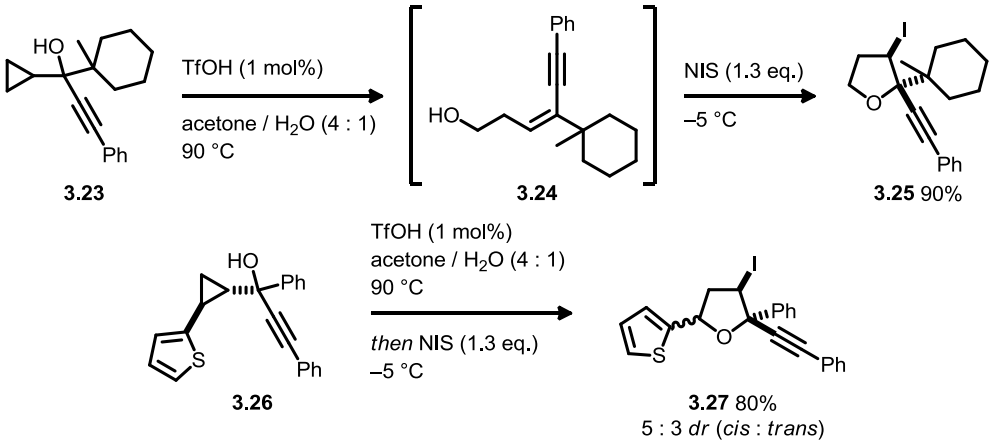
In 2011, Liu and co-workers disclosed the development of an acid-mediated *C*-glycosylation of glycosyl fluorides with potassium organotrifluoroborates.[130] Their reactions proceeded with moderate to high stereoselectivity with a wide range of trifluoroborates and sugar-derived fluorides. A nice example is the synthesis of THF **3.22** as a single diastereomer, which enabled the synthesis of the anti-cancer natural product (+)-varitriol (*Scheme 3.8*).



Scheme 3.8

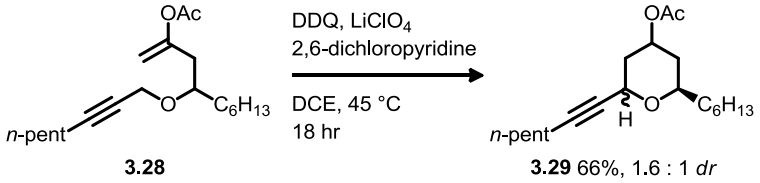
Although this is powerful methodology, it relies upon the multiple chiral centres decorating the ring to afford products with high stereoselectivity, thus limiting its generality.

Also in 2011, Chan and co-workers reported the one-pot synthesis of THFs from cyclopropyl methanols (**3.23**), an acid catalyst and an electrophilic halogen source (e.g. NIS).[131] Exposure of **3.23** to triflic acid leads to the intermediate homoallyl alcohol (**3.24**), which undergoes intramolecular iodo-etherification on addition of NIS (*Scheme 3.9*). The diastereomerically pure substrate **3.26**, however, led to a mixture of diastereomers of the THF ring.



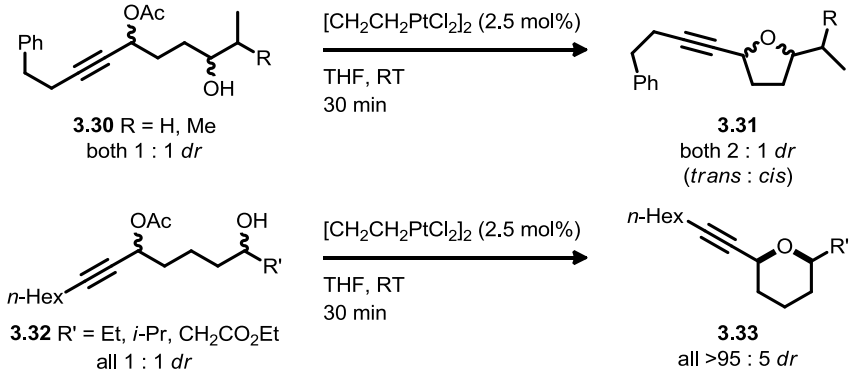
Scheme 3.9

In 2010, Floreancig and Liu reported the oxidative cyclisation of enol-acetates (**3.28**) to afford 2-alkynyl THPs **3.29** (*Scheme 3.10*).[132] However, the diastereoselectivity observed for the formation of **3.29** was poor.



Scheme 3.10

Finally, De Brabander and co-workers have described the platinum(II) catalysed cycloetherification of propargylic acetates to form 2-alkynyl THFs and THPs **3.31** and **3.33** (*Scheme 3.11*).[133]



Scheme 3.11

Diastereomeric mixtures of the starting acetates **3.32** converged to form enriched products, with almost exclusive formation of the *cis*-THPs **3.33**, and therefore, the reaction is proceeding under thermodynamic control to form the most stable products.

3.1.3 Uses of 2-Alkynyl Oxacycles

When considering the development of any methodology, the usefulness of the products it generates must be considered. Unsaturated oxacycles (e.g. THFs and THPs) are one of the most common motifs

present in bioactive molecules.[134-136] Specifically related to 2-alkynyl oxacycles, the mutafuran family of natural products, contain the same enyne-THF core and vary only in the nature of the side chain (*Figure 3.1*).[137] Although a full screen of biological activity has yet to be performed, the mutafurans demonstrate antifungal properties and as such would be interesting targets for total synthesis. Another example of a natural product family containing the 2-alkynyl oxacycle motif is the panaxfuraynes.[138]

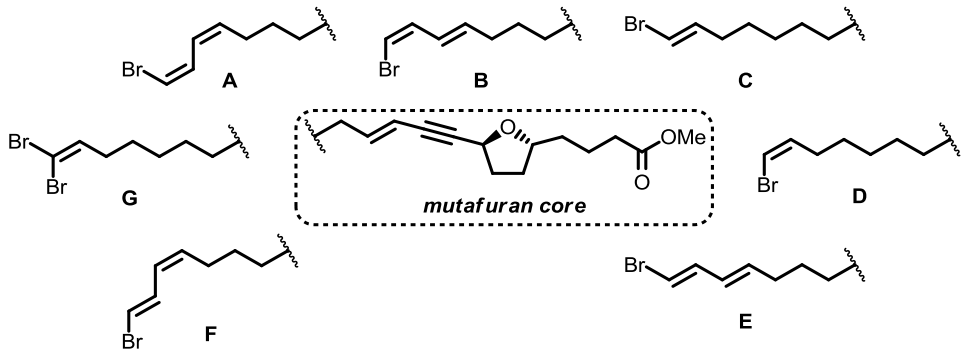
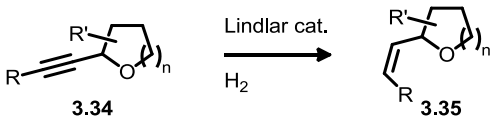


Figure 3.1: Mutafuran A-G

More generally, the alkyne motif itself is valuable for its ability to undergo a wide variety of transformations. Perhaps the most important of these is the ability of alkynes to undergo stereoselective (*E*)[139] and (*Z*)[140] reductions. The formation of 2-*E*-alkenyl oxacycles is well known,[141-143] however the synthesis of the corresponding *Z*-isomers (**3.35**) remains a challenge.[144] Therefore, it can be envisaged that the (*Z*)-selective hydrogenation of 2-alkynyl oxacycles **3.34** would allow the stereocontrolled synthesis of these motifs (*Scheme 3.12*).



Scheme 3.12

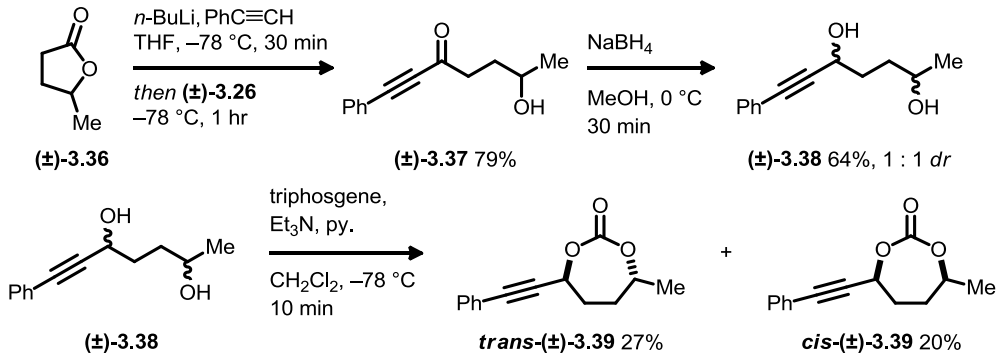
This highlights just one of the many possible transformations that the alkyne functionality can undergo, beyond any interesting biological properties that the alkynyl oxacycle itself may confer to the overall molecule.

3.2 Aims

We aimed to answer the questions that came from our initial results from the 7-membered cyclic carbonates, especially concerning the potential for the *stereoselective* formation of 2-alkynyl oxacycles. We hoped this would lead to the development of a fully-fledged methodology that would, at the very least, complement known methods for the synthesis of these motifs.

3.3 Disubstituted Cyclic Carbonates

The first question to be addressed was whether this reaction could be rendered stereoselective, and what insight the stereochemical outcome of the reaction would give us into the mechanism. To this end we set about the synthesis of a pair of diastereomeric disubstituted 7-membered cyclic carbonates ***trans*-(±)-3.39** and ***cis*-(±)-3.39**. Diol **(±)-3.38** was synthesised as an inseparable 1:1 mixture of diastereomers using our lactone addition / ketone reduction strategy, starting from commercially available γ-valerolactone **(±)-3.36** (*Scheme 3.13*). Pleasingly, formation of the cyclic carbonates allowed separation of the diastereomers by silica gel chromatography, giving pure ***trans*-(±)-3.39** and ***cis*-(±)-3.39**.



Scheme 3.13

One of the diastereomers was crystalline, allowing assignment of its relative configuration through single-crystal X-ray diffraction, which showed it to be ***trans*-(±)-3.39** (*Figure 3.2*).

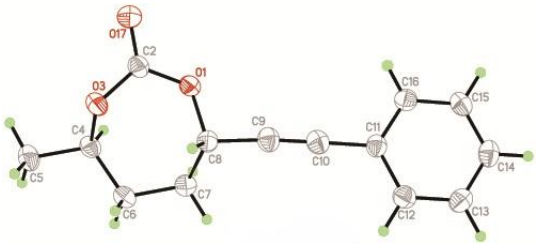
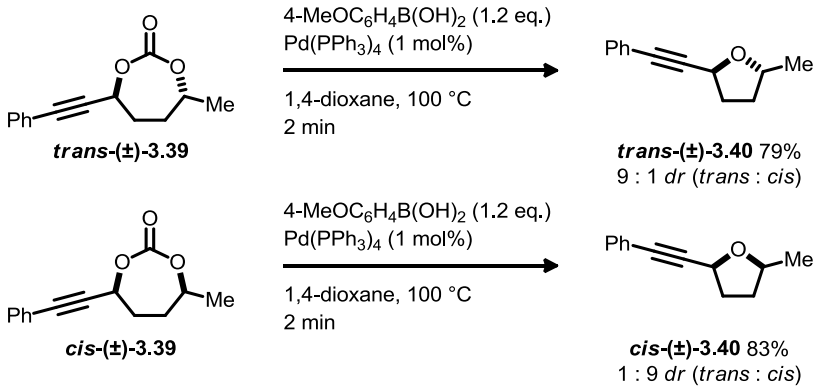


Figure 3.2: X-ray structure of ***trans*-(±)-3.39**

With the pure diastereomers in hand we submitted them to the conditions that had resulted in THF formation from 7-membered cyclic carbonates (*Scheme 3.14*). This resulted in a complementary 9:1 mixture of diastereomers of the disubstituted THFs ***trans*-(±)-3.40** and ***cis*-(±)-3.40**, as measured by ^{1}H NMR spectroscopy of the crude reaction mixtures.



Scheme 3.14

As neither THF product was crystalline, their relative configurations were assigned through nOe experiments. A clear enhancement between H2 and H5 was observed for one of the diastereomers, leading us to assign it as ***cis*-(±)-3.40** (*Figure 3.3*); an absence of a similar enhancement for the other diastereomer supported this assignment.

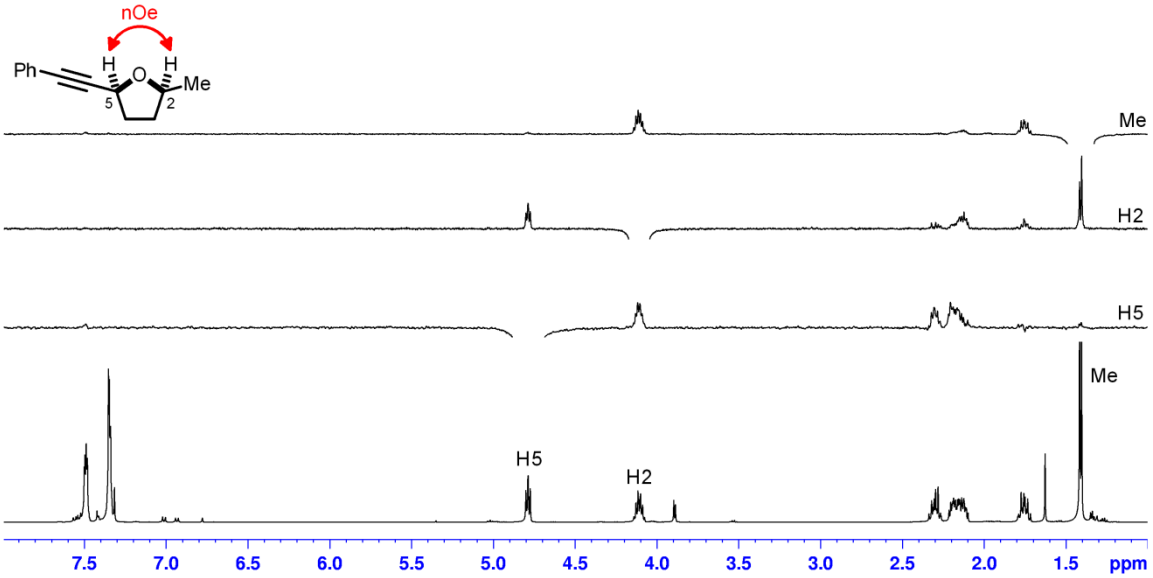
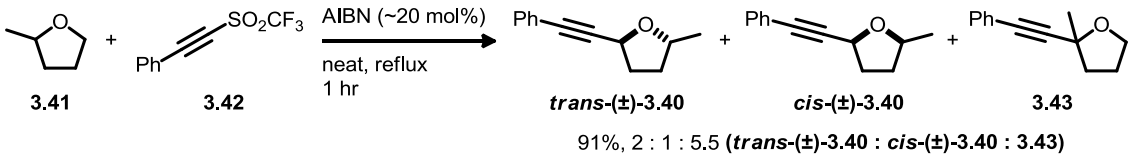


Figure 3.3: 1D ^{1}H nOe spectra for ***cis*-(±)-3.40**

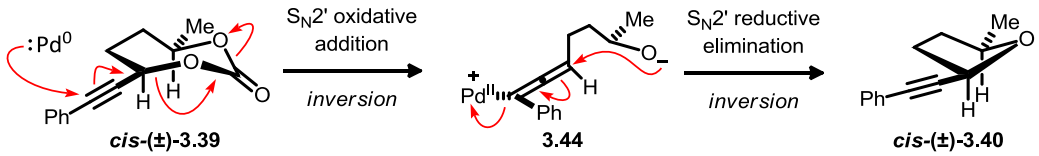
These THFs ***trans*-(±)-3.40** and ***cis*-(±)-3.40** had been synthesised previously by Gong and Fuchs as minor products of the reaction of **3.41** with triflone **3.42** (*Scheme 3.15*).[145] Although an assignment of the relative stereochemistry was made in the paper, no evidence for this assignment was presented, and was opposite to our unambiguous assignment.



Scheme 3.15: Fuchs' synthesis of ***trans*-(±)-3.30** and ***cis*-(±)-3.30** (assignments as stated in the paper)[145]

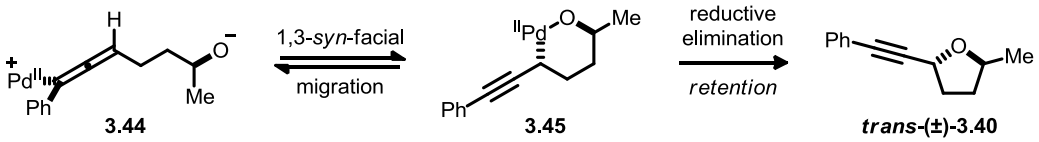
Our nOe experiments indicated that both reactions had proceeded predominantly with retention of

stereochemistry at the propargylic centre. This suggested that a double inversion mechanism was operating, as we would expect the initial oxidative addition to be S_N2'.[21] Therefore, *anti*-S_N2' oxidative addition into ***cis*-(±)-3.39** gives the η^1-allenylpalladium species **3.44** with inversion (*Scheme 3.16*). This intermediate can undergo attack by the alkoxide, again in an S_N2' fashion, to generate THF ***cis*-(±)-3.40**, resulting in overall retention at the propargylic centre.



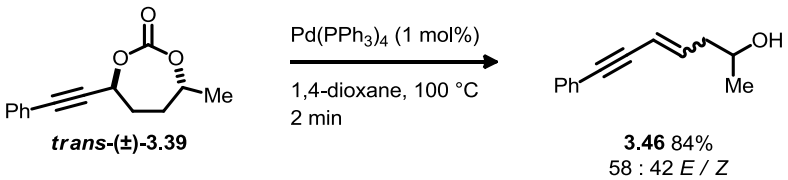
Scheme 3.16

One plausible explanation for the formation of the minor diastereomer is an isomerisation of the η^1-allenylpalladium species **3.44** to the η^1-propargypalladium species **3.45** through a 1,3-*syn*-facial migration.[24] This would allow co-ordination of the alkoxide to the cationic palladium(II) and, following reductive elimination (with retention), form the opposite diastereomer ***trans*-(±)-3.40** (*Scheme 3.17*).



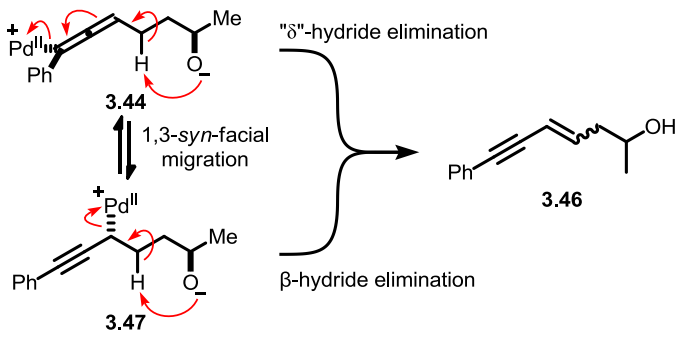
Scheme 3.17: Plausible mechanism for the formation of the minor diasteroemer

With these promising initial results, we set about optimising the reaction to attempt to improve the stereoselectivity. As no cross-coupling is taking place we reasoned that the reaction should proceed in the absence of boronic acid. However, when ***trans*-(±)-3.39** was subjected to 1 mol% $Pd(PPh_3)_4$ alone, none of the desired THF was formed. Instead, enyne **3.46** was formed in high yield and as a *ca.* 1 : 1 *E* / *Z* mixture (*Scheme 3.18*).



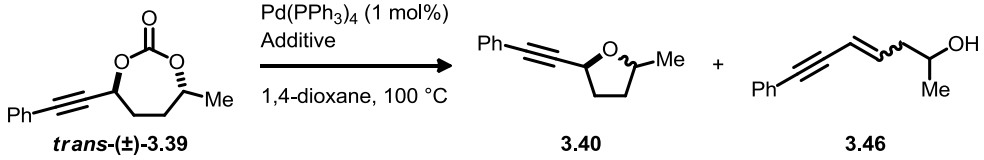
Scheme 3.18

It appeared that in the absence of an acidic additive, the alkoxide acts as a base rather than a nucleophile, promoting elimination of palladium. This can be envisaged as an alkoxide mediated formal "δ-hydride elimination" from allenylpalladium **3.44** or as a β-hydride elimination from propargylpalladium **3.47** (*Scheme 3.19*).



Scheme 3.19

To test this hypothesis we tested a range of acidic additives with carbonate ***trans*-(±)-3.39** (*Scheme 3.20*, *Table 3.1*). Boric acid restored the desired reactivity, although disappointingly returned the product with lower stereoselectivity (*Entry 1*). The stoichiometry of the additive was also examined: 3 equivalents of boric acid retarded the reaction, although slightly improved the selectivity (*Entry 2*). However, catalytic boric acid led to inferior results with the major product being enyne **3.46** (*Entry 3*).



Scheme 3.20

Entry	Carbonate	Additive	Time	Product Ratio (3.39 : 3.40 : 3.46)[a]	Yield	3.40 *dr* (*trans* : *cis*)[a]
1	***trans*-(±)-3.39**	$B(OH)_3$ (1.2 eq.)	2 min	0 : 100 : 0	85%	80 : 20
2	***trans*-(±)-3.39**	$B(OH)_3$ (3 eq.)	2 min	60 : 40 : 0	-	92 : 8
3	***trans*-(±)-3.39**	$B(OH)_3$ (0.1 eq.)	2 min	7 : 16 : 77	-	-
4	***trans*-(±)-3.39**	$B(OMe)_3$ (1.2 eq.)	2 min	0 : 52 : 48	-	94 : 6
5	***trans*-(±)-3.39**	AcOH (1.2 eq.)	2 min	80 : 0 : 20	-	-
6	***trans*-(±)-3.39**	NH_4Cl (1.2 eq.)	2 min	80 : 0 : 20	-	-
7	***trans*-(±)-3.39**	PPTS (1.2 eq.)	2 min	0 : 100 : 0	85%	95 : 5
8[b]	***trans*-(±)-3.39**	PPTS (0.1 eq.)	5 min	0 : 100 : 0	99%	99 : 1
9[b]	***cis*-(±)-3.39**	PPTS (0.1 eq.)	5 min	0 : 100 : 0	99%	5 : 95

Table 3.1: [a] Measured by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] Conducted at 50 °C

We considered that the beneficial effect of the boronic or boric acid may actually result from its ability to act as a Lewis acid rather than a Brønsted acid. This was tested by using trimethylborate as additive, which can only act as a Lewis acid (*Entry 4*). However, this gave a mixture of THF **3.40** and enyne **3.46**, suggesting a purely Lewis acidic role for the boronic or boric acid to be unlikely. With this in mind we trialled a variety of common acids (*Entries 5-7*) and found that although AcOH and NH_4Cl were unable to prevent enyne formation, PPTS was able to do so, and returned ***trans*-(±)-3.40** with high stereoselectivity. A catalytic loading of PPTS coupled with a reduction in reaction temperature to 50 °C rendered the reaction almost totally stereoselective, giving ***trans*-(±)-3.40** in excellent yield and

diastereoselectivity (*Entry 8*). These conditions were applied to carbonate ***cis*-(±)-3.39**, which afforded the THF ***cis*-(±)-3.40** in similarly excellent yield and diastereoselectivity (*Entry 9*).

It appears that protonation of the alkoxide serves to temper its reactivity and allow it to react as a nucleophile rather than as a base. The improvement in stereoselectivity with PPTS could be a consequence of the presence of pyridine, which may act as general base catalyst and aid deprotonation of the alcohol during cyclisation.

3.4 Further Cyclic Carbonate Substrates

With optimised conditions for the stereoselective cyclisation of these disubstituted 7-membered cyclic carbonates achieved, we decided to explore the substrate scope of this reaction.

We set out to synthesise a range of mono- and disubstituted cyclic carbonates in an enantio- and diastereoselective manner. To test a range of substituents with the monosubstituted cyclic carbonates we targeted silyl- (**b**), aryl- (**c**), alkyl- (**e**), heteroaryl- (**f**) and alkenyl-substituted (**g**) carbonates **(*R*)-2.06** (*Figure 3.4*). The benzyloxy substituent in **(*R*)-2.06e** was chosen to allow the product to be visualised by chiral HPLC under UV detection.

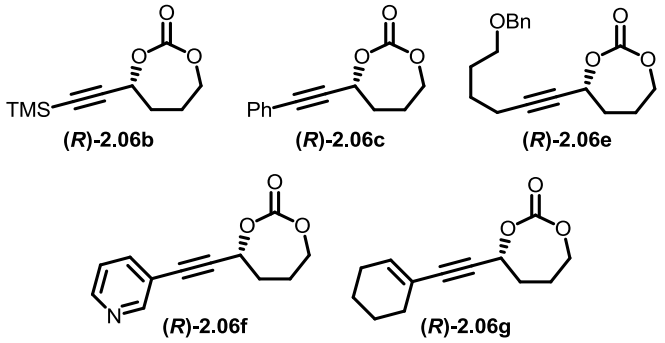
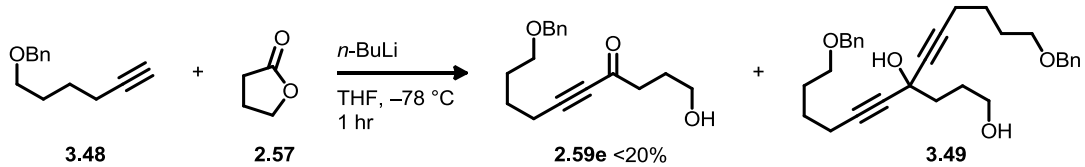


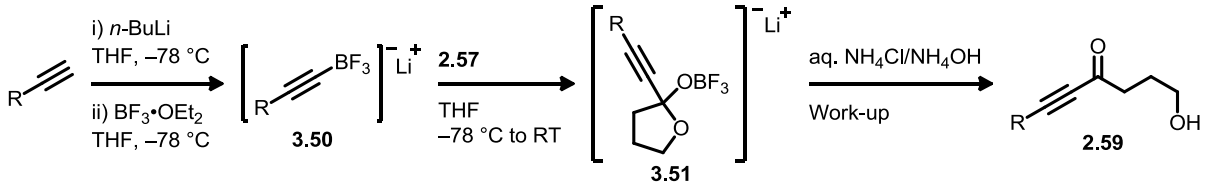
Figure 3.4

Our synthetic plan for these substrates was simply to perform an enantioselective reduction of ynones derived from γ-butyrolactone (**2.57**). However, although addition of lithium phenylacetylide gave consistently good yields of ynone **2.59c**, initial attempts to form alkyl ynone **2.59e** gave disappointingly low yields along with significant amounts of the double addition product **3.49** as an inseparable mixture (*Scheme 3.21*).



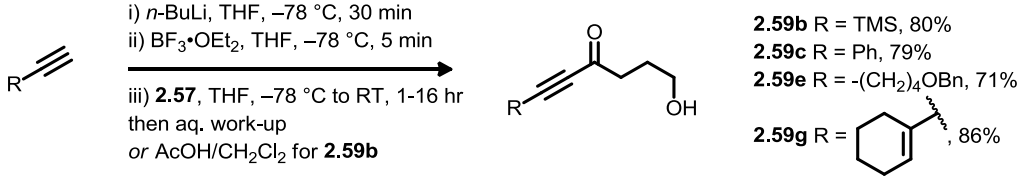
Scheme 3.21

In 2003,[146] Koutek and co-workers described a modification to the methodology developed by Wedler and Schick,[109] employing an equivalent of $BF_3 \cdot OEt_2$ to modulate the reactivity of the acetylide through the *in situ* formation of a lithium alkynyl trifluoroborate **3.50**. This can be reasoned through the formation of a stable tetrahedral intermediate (**3.51**) which collapses only on work-up, thus preventing double addition of the acetylide (*Scheme 3.22*).



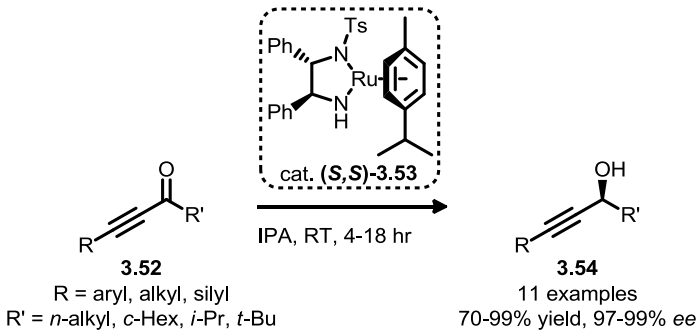
Scheme 3.22: Koutek's modified alkynylation conditions[146]

This modified procedure gave our desired ynones **2.59c**, **e** and **g** in high yield; however, aqueous work-up led to immediate decomposition of silylated ynone **2.59b** (*Scheme 3.23*). An acidic, non-aqueous quench with an excess of AcOH in dichloromethane gave **2.59b** in good yield.



Scheme 3.23

With these ynones in hand we considered methods for the enantioselective reduction. In 1997, Noyori and co-workers described the catalytic transfer hydrogenation of ynones using chiral ruthenium complex **3.53** (*Scheme 3.24*).[147]

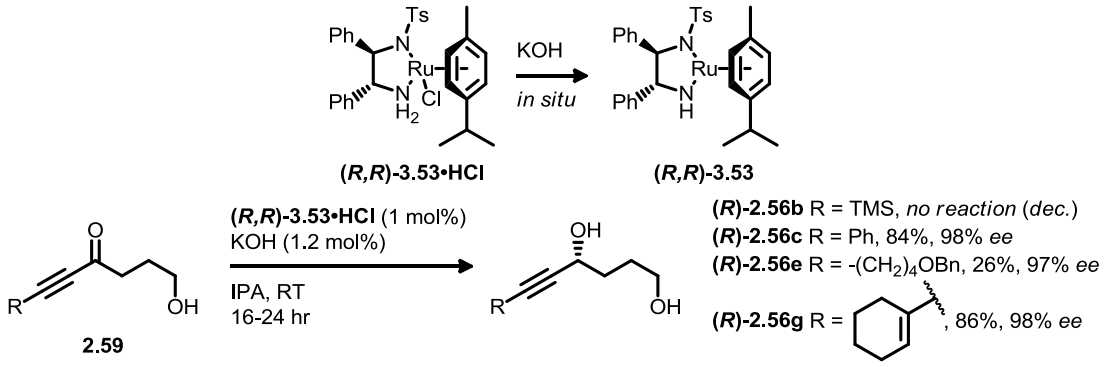


Scheme 3.24: Noyori reduction[147]

We considered this to be the best solution to the challenge because of its wide substrate scope (**3.52**), giving propargylic alcohols (**3.54**) with consistently high yields and enantioselectivities.

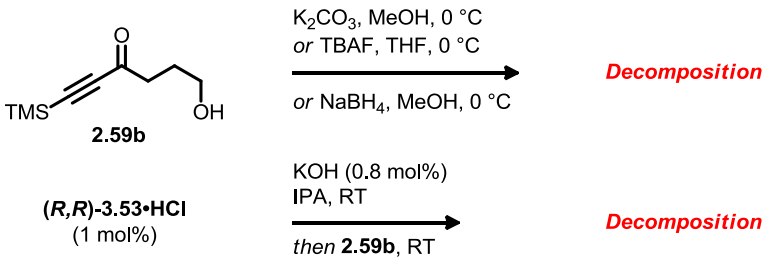
These reductions can be performed using the commercially available HCl salt of the catalyst, which is activated *in situ* through deprotonation with a slight excess of KOH (*Scheme 3.25*). This gave the

desired enantioenriched diols **(*R*)-2.56c**, **e** and **g** in moderate to excellent yield and consistently high enantioselectivity as determined by chiral HPLC. Again, however, the silyl-substituted ynone **2.59b** proved troublesome and these conditions led only to decomposition of starting material. Conversion of alkyl ynone **2.59e** was poor, although remaining starting material could be recovered. The absolute configuration was assigned by analogy to that reported by Noyori and co-workers.[147]



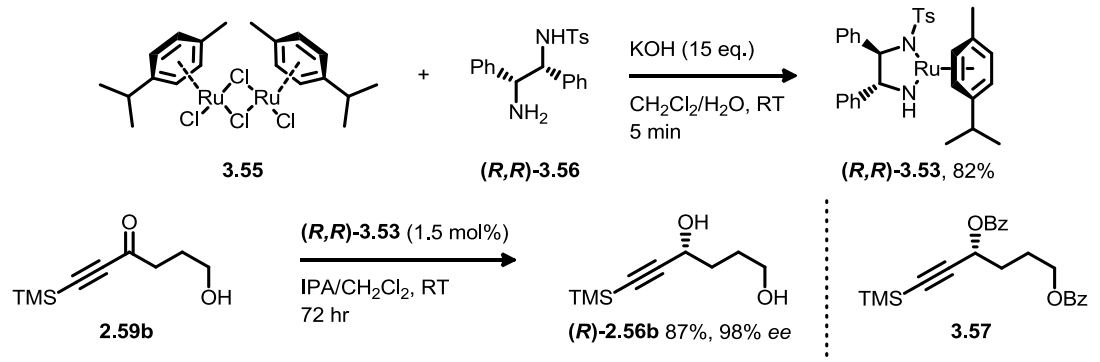
Scheme 3.25

We reasoned that the decomposition of **2.59b** may be owing to competing deprotection of the silyl alkyne by the slight excess of KOH present in the reaction, as other experiments had shown that silyl deprotection of **2.59b** was not possible with either K_2CO_3 or TBAF (*Scheme 3.26*). It is also of note that the attempted racemic reduction of ynone **2.59b** with $NaBH_4$ in MeOH also led solely to decomposition. Pre-forming the active catalyst using a slight excess of **(*R*,*R*)-3.53·HCl** (to ensure no KOH remained in solution) followed by addition of the starting material, again led to decomposition.



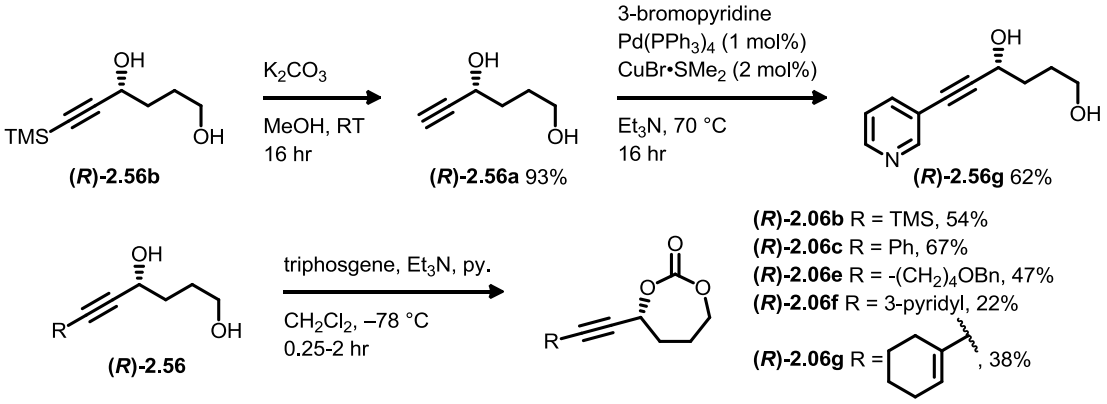
Scheme 3.26: Failed reactions with silyl ynone **2.59b**

Noyori had shown that reduction of silyl ynones is possible using the isolated 16 electron complex **(*R*,*R*)-3.53**.[147] This catalyst was synthesised from commercially available Ru(II) dimer **3.55** and ligand **(*R*,*R*)-3.56** in excellent yield as an air-stable solid (*Scheme 3.27*).[148] Pleasingly, use of this catalyst led to the formation of diol **(*R*)-2.56b** in both excellent yield and enantioselectivity. The enantiomeric excess of **(*R*)-2.56b** was determined through chiral HPLC analysis of the *bis*-benzoate ester **(*R*)-3.57**.



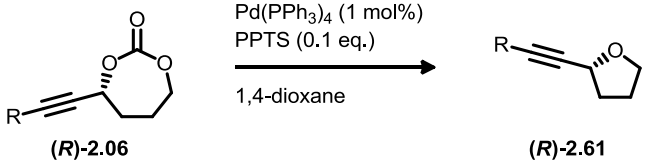
Scheme 3.27

In contrast to the parent ynone **2.59b**, deprotection of diol **(*R*)-2.56b** could be achieved using K_2CO_3 in MeOH. Subsequent Sonogashira coupling with 3-bromopyridine proceeded smoothly to give diol **(*R*)-2.56f** in good yield (*Scheme 3.28*).[149] The diols were converted to the cyclic carbonates, giving enantiomerically enriched substrates **(*R*)-2.06b**, **c**, **e**, **f** and **g** in low to moderate yields.



Scheme 3.28

These cyclic carbonates were subjected to the optimised cyclisation conditions (*Scheme 3.29, Table 3.2*). Carbonates **(*R*)-2.06c** and **e** reacted smoothly to give the desired THFs **(*R*)-2.61c** and **e** in excellent yield and enantioselectivity (*Entries 1 and 2*). Cyclic carbonate **(*R*)-2.06f** did not react at 50 °C, but the temperature could be raised to 100 °C without compromising the stereoselectivity of the reaction with this substrate (*Entries 3 and 4*). Surprisingly, silyl-containing cyclic carbonate **(*R*)-2.06b** failed to react under these optimised conditions (*Entry 5*).

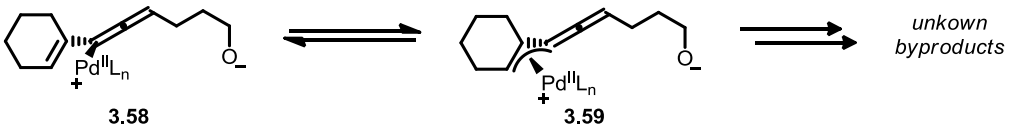


Scheme 3.29

Entry	Carbonate	R	Temp.	Time	Product	Yield	% *ee*[a]
1	**(*R*)-2.06c**	Ph	50 °C	12 min	**(*R*)-2.61c**	99%	95
2	**(*R*)-2.06e**	-$(CH_2)_4$OBn	50 °C	25 min	**(*R*)-2.61e**	96%	95
3	**(*R*)-2.06f**	3-pyridyl	50 °C	60 min	NR[b]	-	-
4	**(*R*)-2.06f**	3-pyridyl	100 °C	10 min	**(*R*)-2.61f**	80%	98
5	**(*R*)-2.06b**	TMS	50 °C	30 min	NR[b]	-	-
6	**(*R*)-2.06b**	TMS[c]	100 °C	30 min	NR[b]	-	-
7	**(*R*)-2.06b**	TMS[d]	100 °C	30 min	NR[b]	-	-
8	**(*R*)-2.06g**		100 °C	2 min	-[e]	-	-

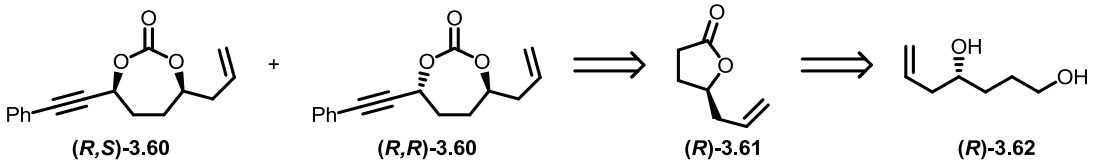
Table 3.2: [a] Determined through chiral HPLC analysis; [b] No reaction, starting material recovered; [c] Conducted with $B(OH)_3$ (1.1 eq.) as additive; [d] Conducted without additive; [e] Unknown product formed

The reaction of **(*R*)-2.06b** was also conducted in the presence of boric acid and without an additive at elevated temperatures, but both of these reactions also failed to promote the reaction and only starting material was recovered (*Entries 6 and 7*). This lack of reactivity is in stark contrast to the initial result with the racemic carbonate **(±)-2.06b** under Suzuki cross-coupling conditions (*vide supra*), and it is not clear why this is the case. Alkene-substituted cyclic carbonate **(*R*)-2.06g** reacted under these conditions, although none of the desired THF product could be detected by ^{1}H NMR spectroscopy of the crude reaction mixture. A large amount of polymeric material was formed from the reaction, and could not be easily identified. The formation of unwanted products could result from the potential of η^1-allenylpalladium intermediate **3.58** to form an allenyl-π-allyl species **3.59** with the alkene substituent (*Scheme 3.30*). This highly reactive species could undergo a wide variety of unwanted transformations.



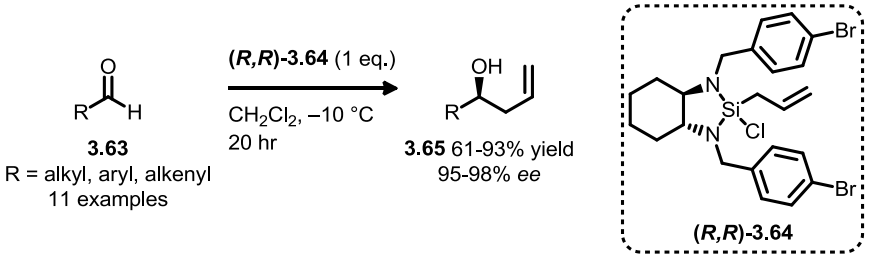
Scheme 3.30

With the successful formation of aryl, heteroaryl and alkyl substituted alkynyl THFs from monosubstituted cyclic carbonates we examined the enantio- and diastereoselective formation of a pair of disubstituted 7-membered cyclic carbonates **(*R,S*)-3.60** and **(*R,R*)-3.60**. Our synthetic plan considered addition of phenyl acetylene to an enantioenriched lactone substituted at the γ-position (*Scheme 3.31*). This lactone could be derived from the oxidation of diol **(*R*)-3.62**, and as such we chose to install an allyl side-chain as the enantioselective allylation of aldehydes is a well known transformation.



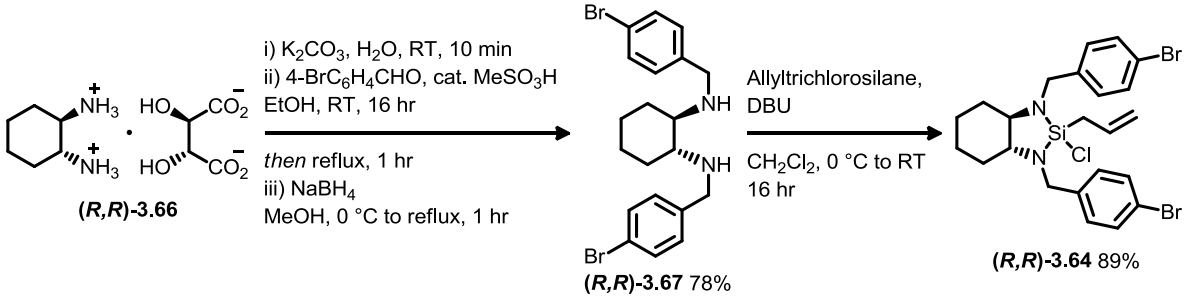
Scheme 3.31

In 2003, Kubota and Leighton described the enantioselective allylation of aldehydes using the reagent **(*R,R*)-3.64**, derived from allyl trichlorosilane and a chiral diamine (*Scheme 3.32*).[150] This reagent installed the allyl group into a wide range of aldehydes in excellent yield and enantioselectivity.



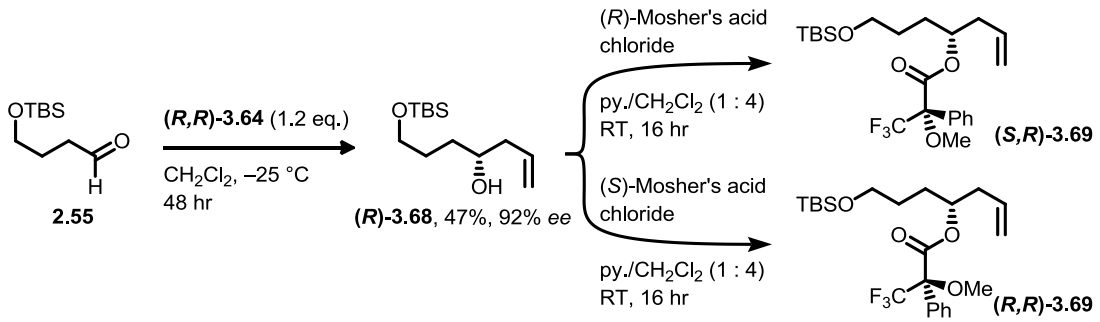
Scheme 3.32: Leighton allylation using reagent **3.64**[150]

Leighton's reagent **(*R,R*)-3.64** was synthesised in two steps from the diamine tartrate salt **(*R,R*)-3.66** (*Scheme 3.33*). The modified work-up procedure described by Johnson and co-workers was used for the isolation of **(*R,R*)-3.64**, affording the reagent in high yield.[151] Rather than isolation as a solid (which proved difficult), **(*R,R*)-3.64** was stored as a solution in dichloromethane at −25 °C under an inert atmosphere.



Scheme 3.33: Synthesis of Leighton's reagent **(*R,R*)-3.64**

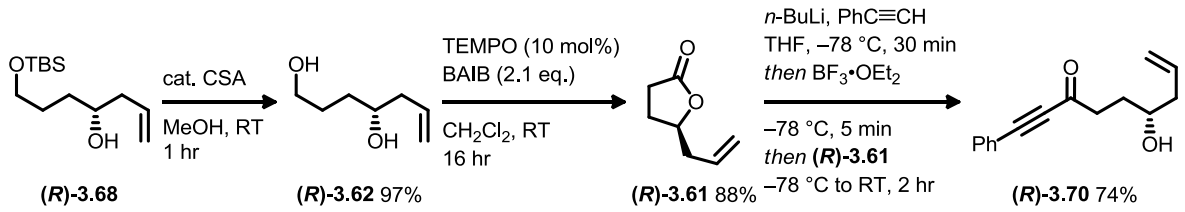
With the reagent in hand, the allylation of the previously synthesised aldehyde **2.55** was performed (*Scheme 3.34*). This formed the desired alcohol **(*R*)-3.68** in moderate yield and high enantioselectivity. The enantiomeric excess of **(*R*)-3.68** was determined through the formation of the diastereomeric Mosher's ester derivatives **(*S,R*)-3.69** and **(*R,R*)-3.69**.[152-153] Integration of either ^{19}F NMR spectrum of **(*S,R*)-3.69** or **(*R,R*)-3.69** showed a 96 : 4 ratio of diastereomers, indicating an enantiomeric excess of 92%.



Scheme 3.34

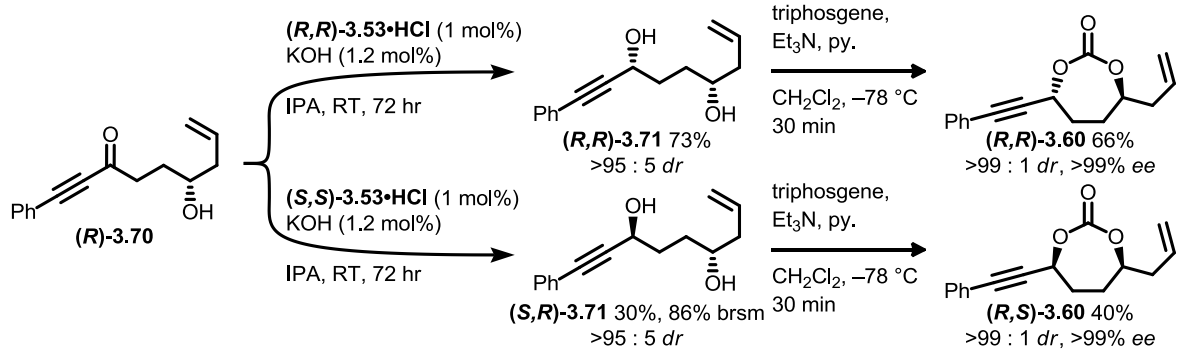
Analysis of the chemical shift differences† in the ^{1}H NMR spectra of **(*S,R*)-3.69** and **(*R,R*)-3.69** allowed assignment of the absolute configuration as (*R*),[154] which was confirmed through comparison of the sign of optical rotation to that reported in the literature.[155]

Lactone **(*R*)-3.61** was synthesised in two further steps through silyl deprotection of **(*R*)-3.68** with CSA and subsequent TEMPO-BAIB oxidation.[156-157] Addition of phenyl acetylene to **(*R*)-3.61** using the $BF_3{\cdot}OEt_2$ protocol afforded the ynone **(*R*)-3.70** in good yield (*Scheme 3.35*).



Scheme 3.35

At this point the syntheses diverged and **(*R*)-3.70** was subjected to either hand of Noyori's catalyst to afford the diastereomeric diols **(*R,R*)-3.71** and **(*S,R*)-3.71** in high yields and stereoselectivities (*Scheme 3.36*). These diols were converted to the cyclic carbonates using the standard conditions, giving **(*R,R*)-3.60** and **(*R,S*)-3.60** as single diastereomers, albeit in moderate yields.

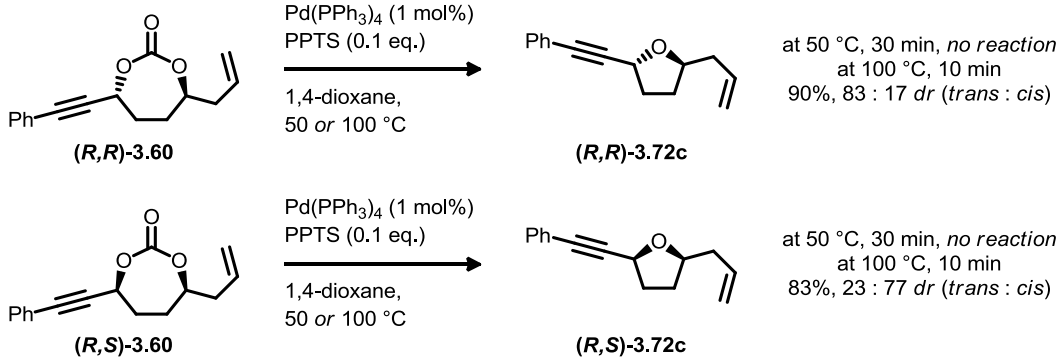


Scheme 3.36

Unexpectedly, cyclic carbonates **(*R,R*)-3.60** and **(*R,S*)-3.60** failed to react under the optimised conditions, returning only starting material. Increasing the reaction temperature restored reactivity, to

† See Experimental for details (*Table 6.1*)

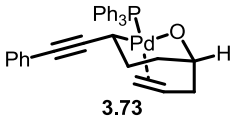
the detriment of stereoselectivity, giving THFs **(*R*,*R*)-3.72c** and **(*R*,*S*)-3.72c** in high yields but only moderate stereoselectivities (*Scheme 3.37*). Further optimisation was not performed on these substrates.



Scheme 3.37

The major diastereomer for each reaction could be isolated cleanly, and 1D ^{1}H NMR nOe spectra of **(*R*,*S*)-3.72c** showed a clear enhancement between H2 and H5.[†] This further supported our mechanistic proposal that the reaction proceeds with retention of stereoechemistry at the propargylic centre.

These results were particularly surprising given the similarity of these substrates to the methyl substituted cyclic carbonates ***trans*-(±)-3.39** and ***cis*-(±)-3.39** from which the optimised cyclisation conditions were derived. Although we have no firm theories for the discrepancy in reactivity, there is the possibility of formation of an intramolecular alkoxide-alkene chelate in the η^1-propargylpalladium species (e.g. **3.73**), thus reducing the reactivity of the alkoxide as a nucleophile (*Figure 3.5*). Elevated temperatures may serve to break up such chelates and restore reactivity, but the formation of the chelate would also aid formation of the undesired diastereomer.



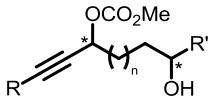
3.73

Figure 3.5

At this point we considered changing a change of approach, because although our results were promising, the cyclic carbonates suffered from a number of drawbacks. The often poorly yielding carbonate formation step was a matter for concern from both an economic and practical viewpoint. Also, the use of cyclic carbonates was limiting the reaction; products were likely restricted to 5-membered rings, as the formation of tetrahydropyrans (THPs) would require the synthesis of challenging 8-membered cyclic carbonates. These limitations, coupled with the poor stereoselectivities

[†] See Appendix for nOe spectra

observed with the allyl substituted cyclic carbonates, led us to contemplate propargylic *acyclic* carbonates **3.74** as an alternative (*Figure 3.6*).



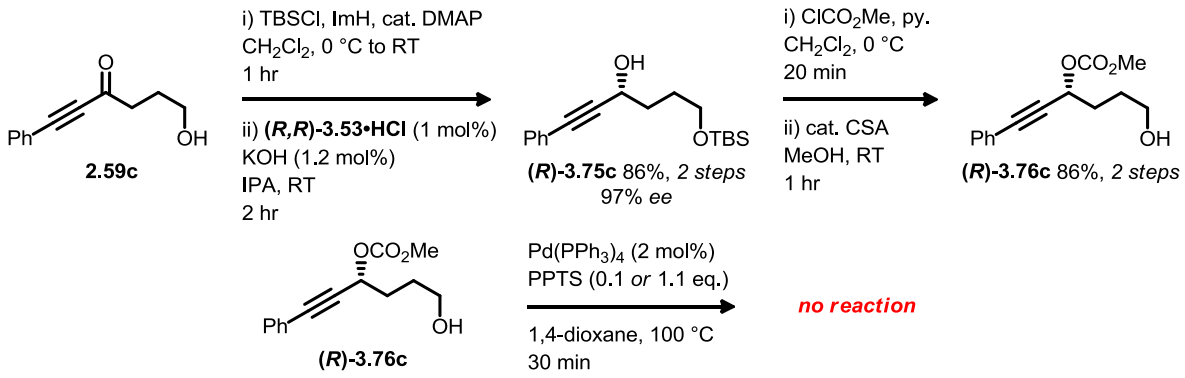
3.74

Figure 3.6

3.5 Acyclic Carbonates

3.5.1 Initial Investigations and Mechanistic Insight

To test whether acyclic carbonates containing a hydroxyl substituent were competent substrates for the formation of oxacycles we synthesised enantioenriched carbonate **(*R*)-3.76c**, employing a similar synthetic route to that used for the enantiopure cyclic carbonates. Protection of hydroxy-ynone **2.59c** as the TBS-ether and Noyori reduction afforded enantioenriched alcohol **(*R*)-3.75c** in excellent yield and enantioselectivity (*Scheme 3.38*). The Mosher ester method[154] was again used to confirm the absolute configuration of **(*R*)-3.75c**.[†] Formation of the carbonate followed by acidic deprotection afforded **(*R*)-3.76c** in excellent yield. However, when carbonate **(*R*)-3.76c** was subjected to the conditions which had been successful for the cyclic carbonates, no reaction occurred.



Scheme 3.38

We considered reasons for this disparate reactivity with cyclic and acyclic carbonates, and contemplated that the slight difference in the nature of the initially-formed allenylpalladium intermediates may be key (*Figure 3.7*). The intermediate generated from oxidative addition into cyclic carbonates is likely the zwitterionic species **3.77**. In contrast, the intermediate formed from oxidative addition into acyclic carbonates is likely the neutral complex **3.78**.

[†] See Experimental for details (*Table 6.2*)

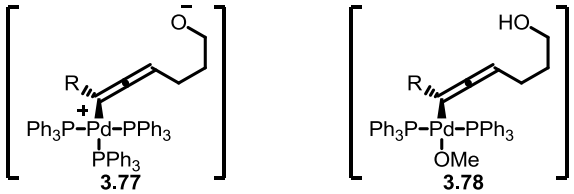
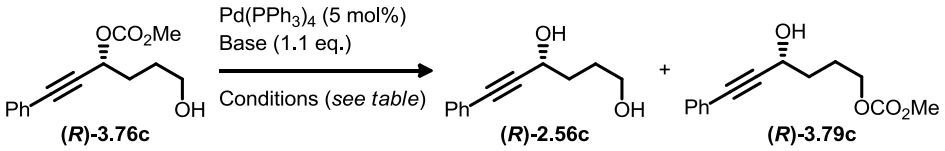


Figure 3.7

We concluded from this that an additional base may be required to facilitate deprotonation of the hydroxyl group and increase its nucleophilicity. To this end we screened a range of bases and conditions to test this hypothesis (*Scheme 3.39, Table 3.3*).



Scheme 3.39

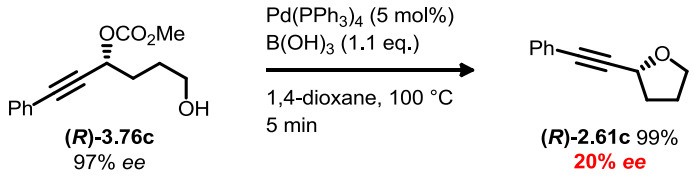
Entry	Base	Solvent	Temp.	Time	Product(s)
1	NaH	"Wet" 1,4-dioxane[a]	RT	30 min	**(*R*)-2.56c**
2	NaH	Distilled 1,4-dioxane[b]	RT	30 min	**(*R*)-2.56c**
3	Na_2CO_3	1,4-dioxane/H_2O (1 : 1)	100 °C	5 min	**(*R*)-3.76c** + **(*R*)-2.56c** + **(*R*)-3.79c**
4	$NaHCO_3$	1,4-dioxane/H_2O (1 : 1)	100 °C	5 min	**(*R*)-3.76c** + **(*R*)-2.56c** + **(*R*)-3.79c**
5	$NaHCO_3$	1,4-dioxane/H_2O (9 : 1)	100 °C	5 min	**(*R*)-3.76c** + **(*R*)-2.56c** + **(*R*)-3.79c**

Table 3.3: [a] Taken directly from a Winchester; [b] Freshly distilled from CaH_2

Unfortunately, as outlined in *Table 3.3*, these conditions also failed to promote the desired reaction. When NaH was used it is probable that trace amounts of hydroxide generated from adventitious water present in the solvent served to cleave the methyl carbonate and generate diol **(*R*)-2.56c** as the sole product (*Entries 1 and 2*). This could not be prevented even when using freshly distilled 1,4-dioxane (*Entry 2*). To avoid this problem we tested the weaker carbonate bases (*Entries 3-5*), although these also failed to generate any of the desired THF product. Examination of the crude reaction mixtures by ^{1}H NMR spectroscopy showed them to be a mixture of starting material **(*R*)-3.76c**, diol **(*R*)-2.56c** and a compound that was tentatively assigned as the carbonate transfer product **(*R*)-3.79c**. However, isolation and full assignment of this compound was not undertaken.

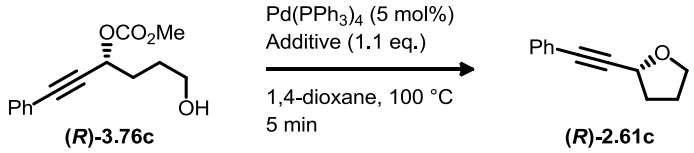
With the failure of bases to promote the desired reactivity, we considered that an activating species may be required to sequester methoxide from palladium and heighten the electrophilicity of the allenylpalladium. We had found previously with the 7-membered cyclic carbonates that boron based acids afforded the desired THF products (*vide supra*), and we decided to trial their use with acyclic carbonate **(*R*)-3.76c**. Pleasingly, the addition of a slight excess of boric acid led to the formation of

THF **(*R*)-2.61c** in quantitative yield (*Scheme 3.40*). However, although we had achieved the desired reactivity, **(*R*)-2.61c** was isolated in a disappointing 20% *ee*.



Scheme 3.40

We considered that the reason for the success of boric acid in promoting the desired reaction might stem from its ability to act as a Lewis acid, as the purely Brønsted acidity of PPTS had failed to induce cyclisation. Thus, we began screening other Lewis acids, beginning with alkyl borates (*Scheme 3.41*, *Table 3.4*).

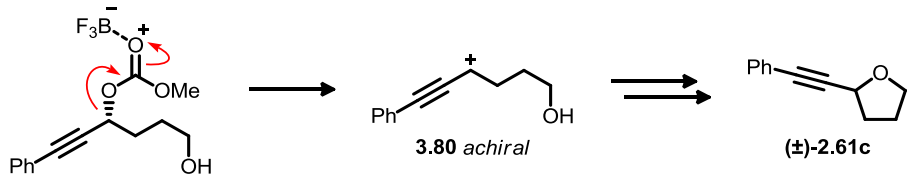


Scheme 3.41

Entry	Additive	Product(s)	Yield ((*R*)-2.61c)	*ee* ((*R*)-2.61c)[a]
1	$B(OMe)_3$	**(*R*)-2.61c**	>90%	46%
2	$B(OEt)_3$	**(*R*)-2.61c**	>90%	48%
3	$B(O\textit{i}\text{-}Pr)_3$	**(*R*)-2.61c**	>90%	53%
4	$B(O\textit{t}\text{-}Bu)_3$	**(*R*)-2.61c**	>90%	26%
5	$B(OPh)_3$	**(*R*)-2.61c**	>90%	11%
6	$BF_3{\cdot}OEt_2$	**(*R*)-3.76c** + **(*R*)-2.61c**	n.d.[b]	7%
7	$FeCl_3{\cdot}(H_2O)_6$	**(*R*)-3.76c**	-[c]	-[c]

Table 3.4: [a] Determined through chiral HPLC analysis; [b] Not determined; [c] No reaction

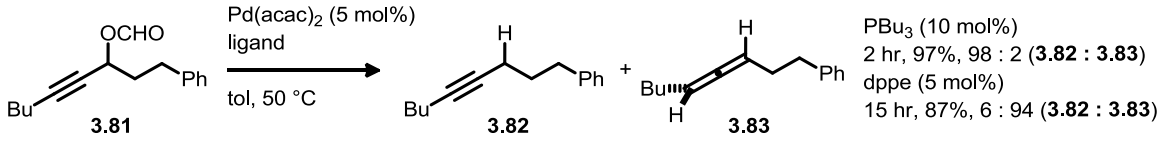
Pleasingly, all the alkyl borate Lewis acids trialled were able to promote the desired reaction and gave THF **(*R*)-2.61c** in excellent yield (*Entries 1-5*). The enantioselectivities, however, remained poor and varied greatly depending on the borate employed. A trend was observed whereby increasing the inductive electron-donating power of the alkoxy groups on boron led to an increase in enantioselectivity (*i*-Pr > Et > Me, *entries 1-3*). However, the use of $B(O\textit{t}\text{-}Bu)_3$ led to a stark drop in enantioselectivity (*Entry 4*), perhaps because of the increased steric crowding around the boron centre. $B(OPh)_3$ (*Entry 5*) follows the general trend, as the phenyl groups are electron withdrawing rather than donating. The use of BF_3 led to incomplete conversion of the starting material (*Entry 6*); the low *ee* observed with BF_3 could be due to a racemic background reaction where BF_3 promotes the formation of a propargylic cation **3.80** (*Scheme 3.41*). Finally, $FeCl_3$ failed completely in promoting the desired reaction (*Entry 7*).



Scheme 3.41: Possible non-stereoselective side reaction with BF_3

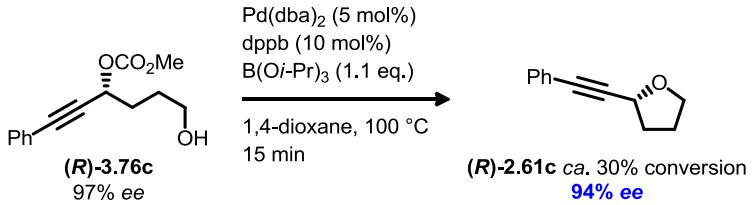
Although we had successfully promoted the desired reaction with the borate additives, instead of conducting a more exhaustive additive screen we decided to explore other aspects of the reaction. We considered the loss of stereoselectivity to be occurring through *syn*-reductive elmination from the propargylpalladium intermediate (e.g. **3.45**, *Scheme 3.17*), and we hypothesised that preventing the formation of species of this type would result in a stereoselective reaction.

Reports in the literature indicated that the use of a bidentate ligand serves to prevent the formation of the propargylpalladium species.[158-159] Sawamura and co-workers showed that synthesis of alkynes or allenes (e.g. **3.82** or **3.83**) from the reductive hydrogenolysis of propargylic formates (e.g. **3.81**) could be tuned according to the nature of the ligand employed (*Scheme 3.42*).[159]



Scheme 3.42: Ligand effects in the reductive hydrogenolysis of propargylic formates[159]

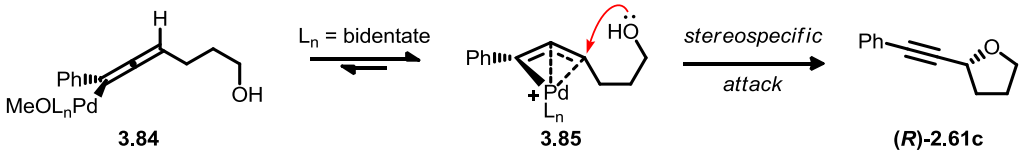
Thus, we repeated the reaction using $[Pd_2dba_3 \cdot dba]$[160] (referred to as $Pd(dba)_2$ throughout) and dppb in the presence of B(O*i*-Pr)$_3$ as additive (*Scheme 3.43*). We were delighted to discover that although the reaction did not go to completion, THF **(*R*)-2.61c** had been formed with excellent enantioselectivity.



Scheme 3.43

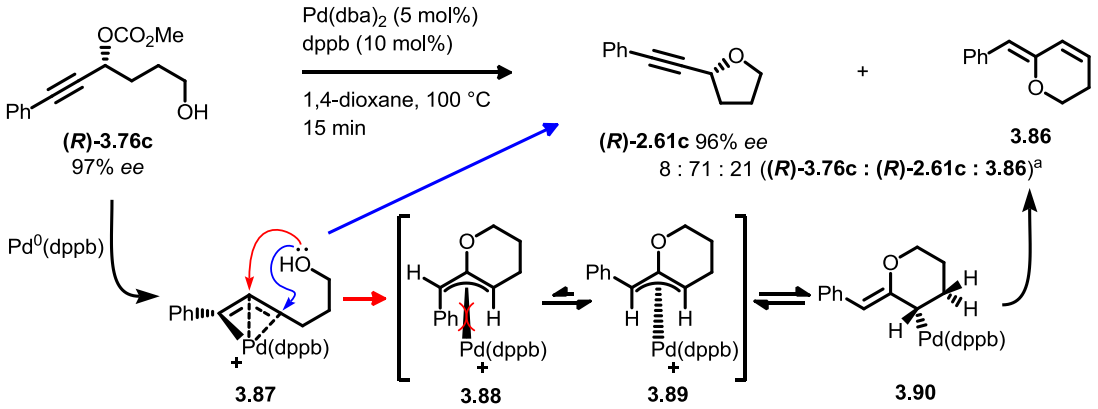
It is possible that the presence of a bulky bidentate ligand has a two-fold effect: first making formation of the propargylpalladium less favourable by increasing steric crowding around the palladium centre, and secondly, making intramolecular co-ordination of oxygen to palladium less favourable, also on steric grounds. These combined effects would render the reaction stereoselective by reducing the postulated *syn*-reductive pathway to negligible levels. Another possibility is that the bidentate ligand promotes the formation of the η^3-allenylpalladium species **3.85**,[54] which allows the stereospecific

formation of **(*R*)-2.61c** through attack on the proximal carbon (*Scheme 3.44*).



Scheme 3.44

We began optimising this result and found that, in contrast to the use of $Pd(PPh_3)_4$, the formation of THF **(*R*)-2.61c** could be promoted with the bidentate ligand system without the need for an additive (*Scheme 3.45*). Without the borate additive the reaction now proceeded almost to completion, however competing formation of the cyclic enol ether **3.86** was observed, presumably through competing attack of oxygen on the central carbon of the η^3-allenylpalladium species **3.87**.

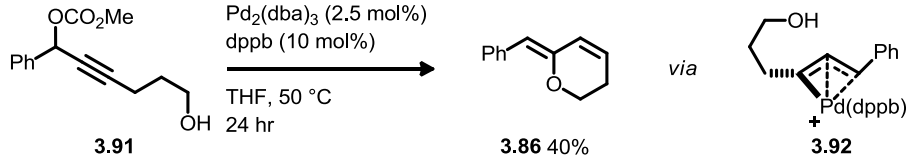


Scheme 3.45: [a] Measured by ^{1}H NMR spectroscopy of the crude reaction mixture

Enol ether **3.86** was formed as a single geometrical isomer, confirmed as *Z* by 1D nOe experiments,[†] and this can be explained by considering the π-σ-π isomerisation of the π-allyl complexes **3.88** and **3.89** to form the lowest energy intermediate **3.89** which avoids the 1,3-allylic strain between the proton and phenyl group in **3.88**. Subsequent β-hydride elimination from σ-allyl complex **3.90** gives enol ether **3.86**. We did not observe formation of **3.86** with $Pd(PPh_3)_4$, which is in line with the observations made by Ogoshi, who did not observe the formation of η^3-allenylpalladium species in solution when $Pd(PPh_3)_4$ was used.[54]

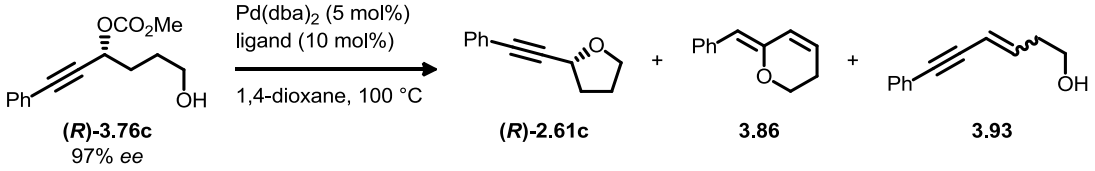
This enol ether byproduct had been formed previously by Sinou and co-workers starting from a related propargylic carbonate **3.91**,[69] although the positioning of the leaving group in their case leads to a subtly different η^3-allenylpalladium species (**3.92**), which permits solely formation of enol ether **3.86** (*Scheme 3.46*).

[†] See appendix for nOe spectra



Scheme 3.46: Sinou's formation of enol ether **3.86**[69]

Although the products **(*R*)-2.61c** and **3.86** could be separated by careful column chromatography, we wished to suppress the formation of **3.86**, and to this end began screening other bidentate ligands (*Scheme 3.47, Table 3.5*).



Scheme 3.47

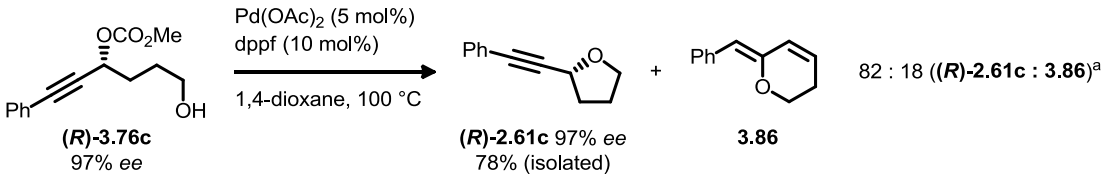
Entry	Ligand	Time	Product Ratio ((*R*)-2.61c : 3.86)[a]	Yield ((*R*)-2.61c)	*ee* ((*R*)-2.61c)[b]
1	None	10 min	NR[c]	-	-
2	dppm	10 min	See footnote[d]	n.d.[e]	87%
3	dppe	16 hr	19 : 81	n.d.[e]	71%
4	dppp	16 hr	44 : 56	n.d.[e]	96%
5	dppf	10 min	83 : 17	79%[f]	96%
6	*t*-Bu-dppf	10 min	NR[c]	-	-
7	Xantphos	30 min	NR[c]	-	-

Table 3.5: [a] Measured by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] Measured through chiral HPLC analysis; [c] No reaction; [d] 28 : 11 : 61 mixture of **(*R*)-3.76c** : **(*R*)-2.61c** : **3.93**; [e] Not determined; [f] Contaminated with inseparable dba

The reaction did not proceed in the absence of phosphine ligand (*Entry 1*) suggesting that the resultant allenylpalladium intermediate is not sufficiently reactive to induce cyclisation. Dppm appeared to act in a similar way to PPh_3, with none of the byproduct **3.86** being formed (*Entry 2*). However, a significant amount of elimination was observed, forming enyne **3.93** as the major product. Enyne **3.93** was not isolated, but was tentatively assigned by comparison to the similar enyne **3.46**. We next assessed the common ligands dppe, dppp and dppf (*Entries 3-5*). Dppe produced enol ether **3.86** as the major product, and returned **(*R*)-2.61c** with decreased enantioselectivity, perhaps due to the relatively compact size of this ligand allowing significant amounts of *syn*-reductive elimination to occur (*vide supra*). Dppp and dppf, however, returned **(*R*)-2.61c** with excellent enantioselectivity; dppf in particular formed **(*R*)-2.61c** as the major product (*Entry 5*). The product isolated from this reaction was contaminated with inseparable dba (*Entry 5*), and the yield was estimated by ^{1}H NMR spectroscopy. Interestingly, *t*-Bu-dppf (where the phenyl groups on the phosphines are replaced by

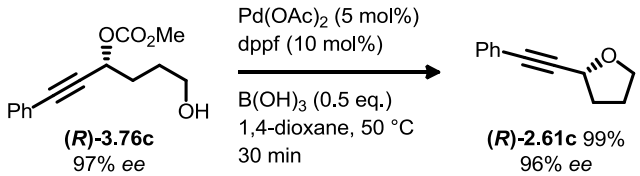
tert-butyl groups) failed to promote any reaction (*Entry 6*). This may be owing to either the increased steric bulk or the increased electron donating power of these phosphines over phenyl groups. Xantphos also failed to promote the reaction (*Entry 7*); the reason for this may lie in its rigidity or its ability to bind *trans* to palladium.[161]

We considered methods for eliminating dba from the reaction mixture (e.g. reduction with $NaBH_4$), but we thought this undesirable from the point of view of the potential scope of the reaction. Instead, we decided to employ palladium(II) acetate as the pre-catalyst; the oxidation of excess phosphine to phosphine oxide in the presence of adventitious water generating the active palladium(0) catalyst *in situ*.[162] Thus, we repeated the reaction with the combination of $Pd(OAc)_2$ and dppf (*Scheme 3.48*), giving a similar ratio of **(*R*)-2.61c** and **3.86** to that observed before (*Table 3.5, entry 5*), suggesting no significant influence on the reaction by phosphine oxide ligands. Pure THF **(*R*)-2.61c** could be easily isolated in high yield and excellent enantioselectivity.



Scheme 3.48: [a] By ^1H NMR spectroscopy of the crude reaction mixture

When we initiated this study of bidentate ligands, the formation of enol ether **3.86** was not observed, and it was reasoned that this was owing to the presence of the borate additive, $B(O\textit{i}\text{-}Pr)_3$ (*Scheme 3.43*). We hoped that our optimisation of the ligand in combination with a boron-based additive might serve to suppress the formation of **3.86** whilst maintaining reactivity. We first employed boric acid because of its low cost and ease of handling, and were delighted to discover that a sub-stoichiometric amount rendered the reaction completely selective for THF **(*R*)-2.61c** (*Scheme 3.49*). The reaction temperature could also be reduced to 50 °C without a great increase in reaction time, although the reaction was sluggish below this temperature.



Scheme 3.49

3.5.2 Mechanistic Considerations

It appears that the 2-alkynyl THF product **(*R*)-2.61c** arises from the unique nature of our substrate. The

internal nucleophile and the positioning of it relative to the allenylpalladium allows the formation of the propargylic product, as to the best of our knowledge, there are no examples of propargylic products being formed through the intermolecular addition of an alcohol to an allenylpalladium intermediate. Instead, intermolecular attack by oxygen nucleophiles is known to form enol ethers through central-carbon attack, as demonstrated by Wojcicki and co-workers.[112] As mentioned before, Sinou and co-workers found that a different positioning of the internal nucleophile relative to palladium led solely to the formation of enol ether **3.86** (*Scheme 3.46*).[69]

We believe that the enol ether byproduct **3.86** arises from attack of oxygen on the strained central carbon of the η^3-allenylpalladium intermediate **3.87** (*Scheme 3.45*). Changing the bidentate ligand may subtly alter the nature of this intermediate and lead to the observed differences in the selectivity of the reaction. The selectivity appears to vary with the bite angle of the bidentate ligand (θ), from dppe (85°, 81% **3.86**) to dppf (99°, 17% **3.86**).[163] This may manifest itself as a change in the degree of bending of the allenyl ligand in the η^3-allenylpalladium intermediate **3.94**, as increasing the bite angle of the bidentate phosphine increases the steric interactions between itself and the substituents on the allenyl ligand. This serves to reduce the degree of bending of the allenyl ligand, and in turn the degree of strain on the central carbon (**3.95**, *Figure 3.8*). This reduces the electrophilicity of the central carbon and its reactivity towards the nucleophile. This may enable competing formation of THF **(*R*)-2.61c** from the η^3-allenylpalladium complex.

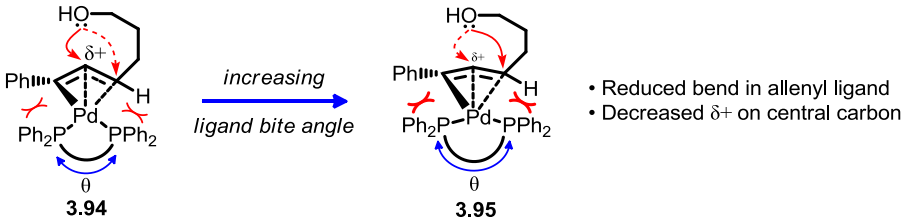
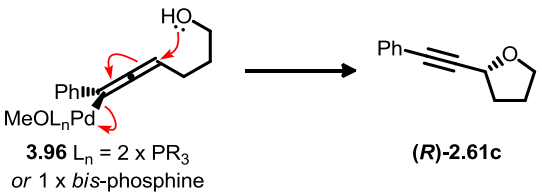


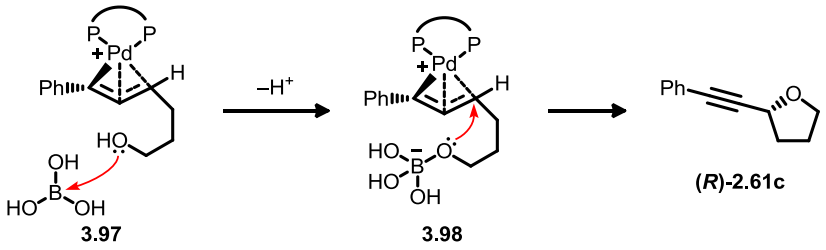
Figure 3.8

We also propose that formation of **(*R*)-2.61c** can also occur from the η^1-allenylpalladium species **3.96**, through the S_N2' displacement of Pd(II) (*Scheme 3.50*), and is the most likely reaction pathway in the presence of monodentate ligands. This is in light of the studies performed by Ogoshi and co-workers, who did not observe the formation of η^3-allenylpalladium complexes in solution with $Pd(PPh_3)_4$.[54] This η^1-allenylpalladium pathway can, of course, also result in the formation of **(*R*)-2.61c** in the presence of bidentate ligands.



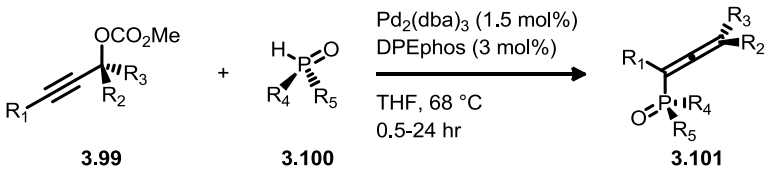
Scheme 3.50

The boric acid additive may increase the electrophilicity of the η^1- or η^3-allenylpalladium intermediates by sequestering the methoxide released from the *in situ* decomposition of the carbonate leaving group. This would make formation of the THF **(*R*)-2.61c** the preferred outcome as the formation of 5-membered rings is kinetically favoured over the corresponding 6-membered **3.86**. Another possibility is that the additive forms a borate species with the alcohol nucleophile (**3.97**), thereby facilitating its deprotonation and increasing its nucleophilicity (**3.98**), again contributing to favourable formation of **(*R*)-2.61c** (*Scheme 3.51*).



Scheme 3.51

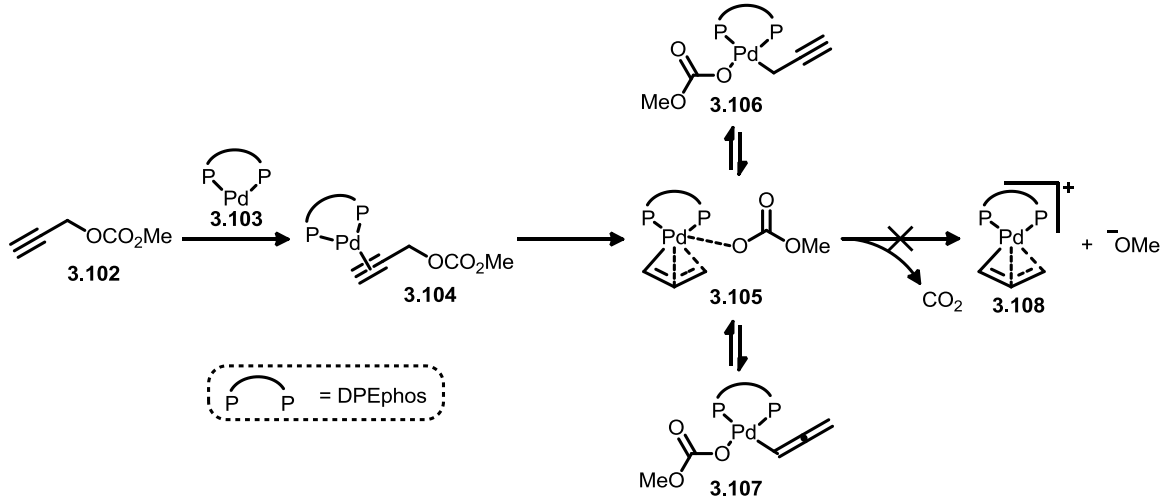
We must also consider a recent report by Stawinski and co-workers, which describes a comprehensive computational study of the formation of allenylphosphonates **3.101** from acyclic carbonates **3.99** (*Scheme 3.52*).[164]



Scheme 3.52: Stawinski's synthesis of allenylphosphonates[32, 165]

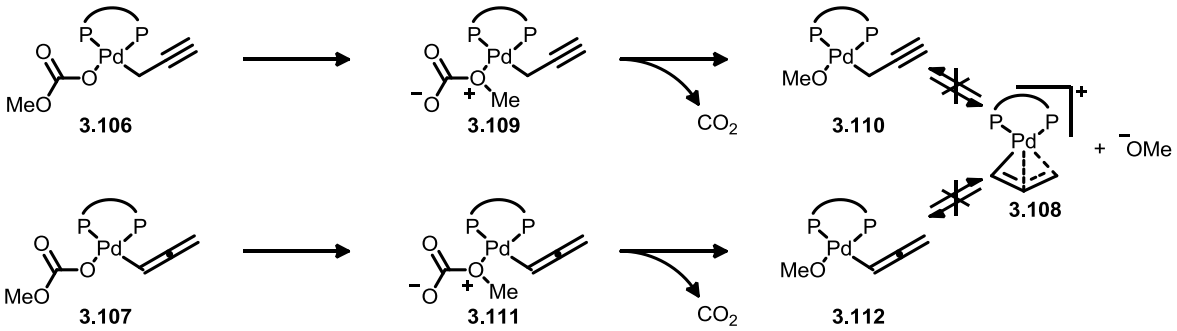
They first examined the oxidative addition step with the simple carbonate **3.102** and [Pd(DPEphos)] **3.103**, and found the mostly likely first intermediate of the reaction to be η^3-allenylpalladium intermediate **3.105**, with the carbonate anion in the second co-ordination sphere of palladium (*Scheme 3.53*). Based on the calculated transition state energies, intermediate **3.105** was found to be in equilibrium with both η^1-propargylpalladium and η^1-allenylpalladium intermediates **3.106** and **3.107**, although the allenylpalladium intermediate **3.107** was found to be 4.5 kcal mol^{-1} lower in energy than propargylpalladium **3.106**. Importantly, formation of the cationic η^3-allenylpalladium intermediate

3.108 was ruled out as it was found to be 22.1 kcal mol^{-1} higher in energy than **3.105**.



Scheme 3.53: Computationally-derived mechanism for oxidative addition[164]

The most likely mechanism for decarboxylation was found to proceed in two steps: the carbonate changes co-ordination to bind through the methoxy oxygen (**3.109** and **3.111**), followed by release of CO_2 to form the methoxide ligated complexes **3.110** and **3.112** (*Scheme 3.54*).

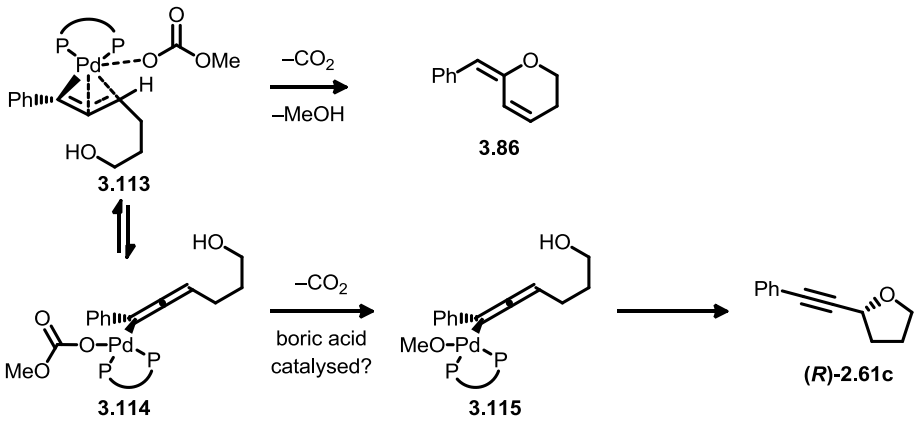


Scheme 3.54: Computationally-derived mechanism for decarboxylation[164]

These calculations indicate that the cationic η^3-allenylpalladium intermediate **3.108** formed from release of methoxide is too high in energy to form. This suggests that **3.110** and **3.112** *cannot* interconvert through a *syn*-facial 1,3-migration at this stage if the formation of a cationic intermediate similar to **3.108** is required. If these calculations are correct it suggests that our proposal of a cationic η^3-allenylpalladium complex (e.g. **3.87**, *Scheme 3.45*) as the intermediate responsible for formation of enol ether **3.86** is wrong. However, these studies were conducted without substituents on the allenyl ligand, so are perhaps not directly applicable to our system.

The studies by Stawinski suggest that if we must rule out a cationic η^3-allenylpalladium intermediate (e.g. **3.87**) as the source of enol ether **3.86**, then the formation of **3.86** would likely occur instead from the carbonate bound η^3-allenylpalladium complex **3.113** (*Scheme 3.55*). Our proposal for the degree of

bending of the allenyl ligand underlying the observed differences in reaction outcome with different bidentate ligands would still hold for this species. It also offers up another possible role for the boric acid, which may catalyse decarboxylation from the carbonate bound η^1-allenylpalladium intermediate **3.114**. This would irreversibly generate complex **3.115**, as CO_2 is lost, and lead only to the formation of THF **(*R*)-2.61c**.



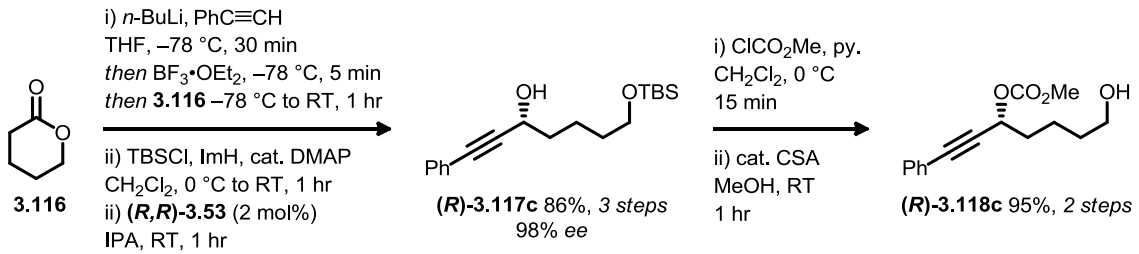
Scheme 3.55

This mechanistic rationale is only tentative, however, and we have no clear evidence for it. No further studies to try and elucidate the true mechanistic pathways were conducted.

3.6 Further Substrates

3.6.1 Monosubstituted THFs and THPs

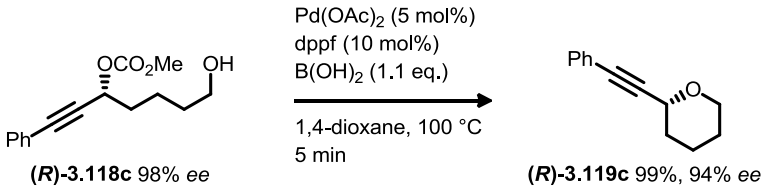
With the success in forming THF **(*R*)-2.61c** from an acyclic carbonate we wished to explore the possibility of forming larger ring sizes using this methodology. Thus, the homologous acyclic carbonate **(*R*)-3.118c** was synthesised in five steps from δ-valerolactone **3.116**, in excellent yield and enantioselectivity (*Scheme 3.56*).



Scheme 3.56

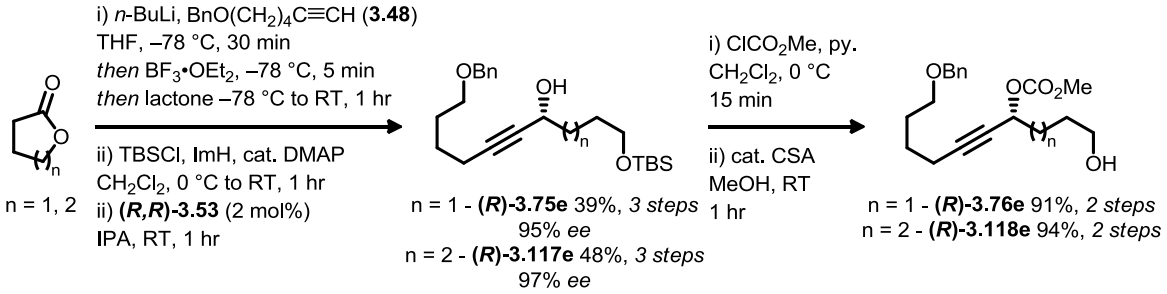
However, when subjected to the above optimised conditions (i.e. 0.5 eq. $B(OH)_3$, 50 °C) the reaction did not proceed. We found that increasing both the reaction temperature and loading of boric acid restored reactivity, yielding THP **(*R*)-3.119c** in excellent yield and enantioselectivity (*Scheme 3.57*).

This result was particularly pleasing as **(*R*)-3.119c** would be difficult to form from a cyclic carbonate starting material because of the difficulty in forming the requisite 8-membered ring.



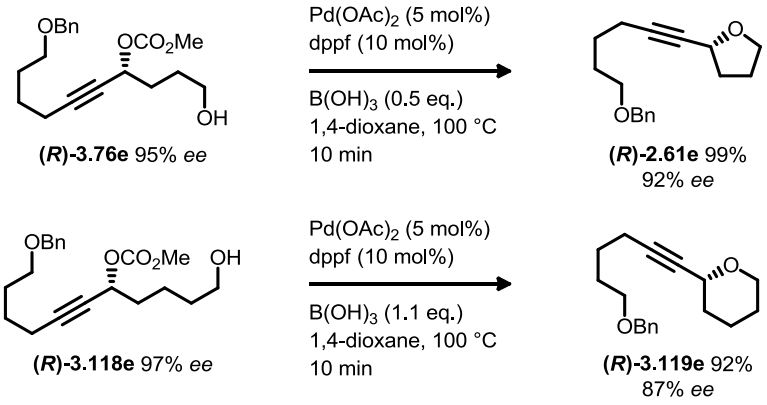
Scheme 3.57

To test whether an alkyl substituent would also be tolerated in this reaction the carbonates **(*R*)-3.76e** and **(*R*)-3.118e** were synthesised, in analogous fashion to **(*R*)-3.119c** (*Scheme 3.58*).



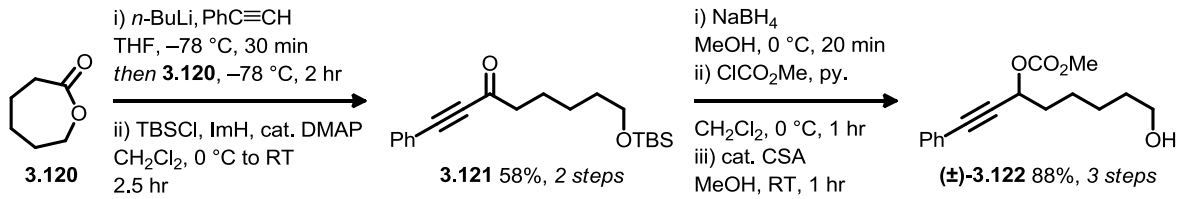
Scheme 3.58

These carbonates proved to be competent substrates for the reaction and formed the desired THF and THP **(*R*)-2.61e** and **(*R*)-3.119e** in excellent yield and stereoselectivity (*Scheme 3.59*). However, elevated reaction temperature was required to enable complete conversion of **(*R*)-3.76e**, and some erosion of enantiomeric purity was observed for both **(*R*)-2.61e** and **(*R*)-3.119e**. We reasoned this to be due to the reduced reactivity of these substrates compared to the phenyl substituted analogues **(*R*)-3.76c** and **(*R*)-3.118c**.



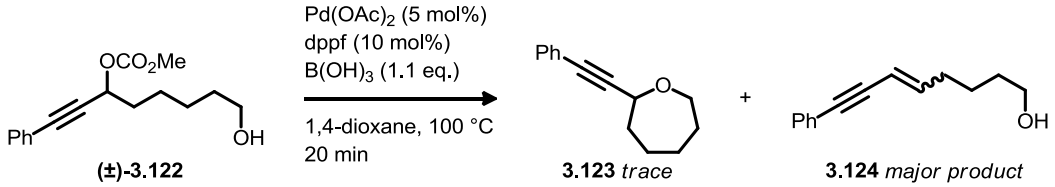
Scheme 3.59

As an aside, we also attempted the formation of an oxepane ring using this methodology, synthesising the acyclic carbonate **3.122** in racemic fashion from ε-caprolactone **3.120** (*Scheme 3.60*).



Scheme 3.60

However, when carbonate **(±)-3.122** was submitted to the reaction conditions, conversion was poor and only a trace of desired oxepane **3.123** was observed by ^{1}H NMR spectroscopy of the crude reaction mixture (*Scheme 3.61*). This proved to be a negligible amount when the crude mixture was purified by silica gel chromatography. The significant product appeared to be enyne **3.124**, with tentative assignment made based on comparison to the similar enynes **3.46** and **3.93**, although carbonate **(±)-3.122** was the major component of the crude reaction mixture.

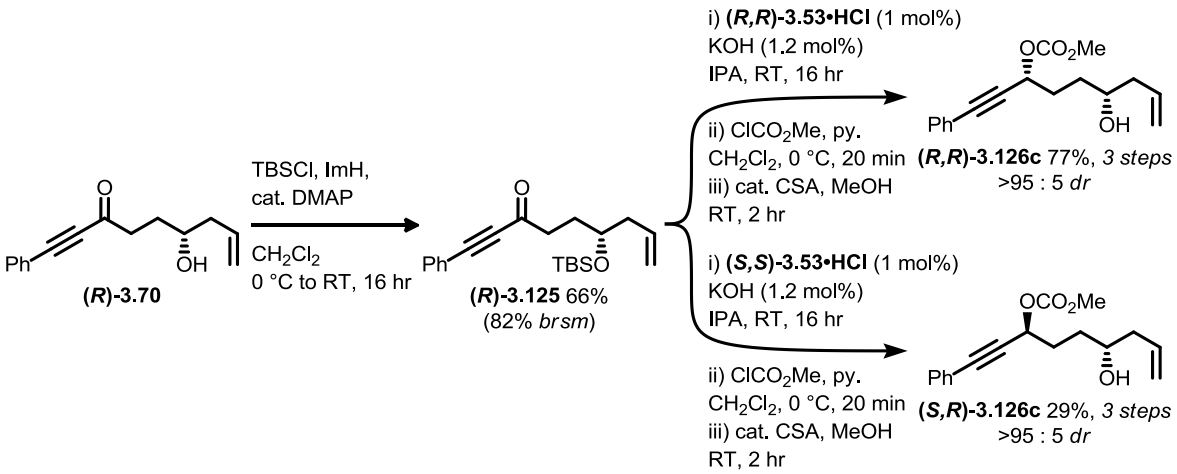


Scheme 3.61

It appears there is an unfavourable kinetic barrier to the cyclisation of carbonate **(±)-3.122**, perhaps due to the entropic cost of ordering the highly flexible tether. Installation of substituents on the tether may aid cyclisation through increased tether rigidity or Thorpe-Ingold effects,[166] but this was not explored.

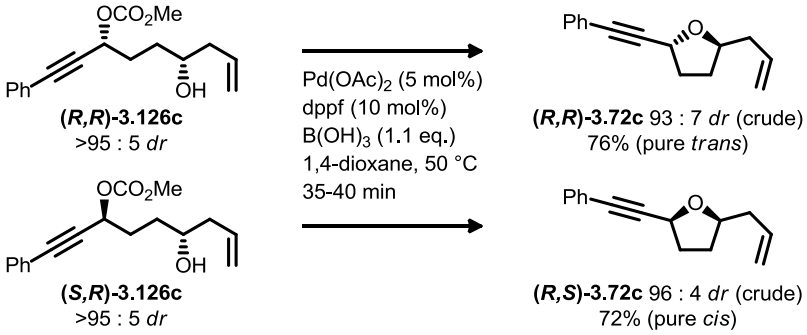
3.6.2 Allyl-substituted THFs and THPs

One of the shortcomings of the 7-membered cyclic carbonates had been the poor stereoselectivity observed when attempting to form the allyl-substituted THFs **(*R*,*R*)-3.72c** and **(*R*,*S*)-3.72c** (*vide supra*). With this in mind, we synthesised the diastereomeric disubstituted acyclic carbonates **(*R*,*R*)-3.126c** and **(*S*,*R*)-3.126c** from ketone **(*R*)-3.70** to test the corresponding reactivity in the acyclic carbonate series (*Scheme 3.62*). In contrast to the cyclic carbonates, the minor diastereomers of **(*R*,*R*)-3.126c** and **(*S*,*R*)-3.126c** could not be removed *via* silica gel chromatography, so were submitted to the cyclisation reaction as mixtures. Both were >95 : 5 *dr* as measured by ^{1}H NMR spectroscopy.



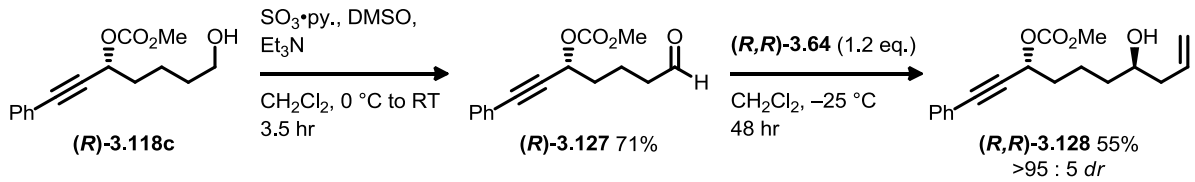
Scheme 3.62

Pleasingly, these substrates did react at 50 °C and afforded the desired allyl substituted THFs **(*R*,*R*)-3.72c** and **(*R*,*S*)-3.72c** in excellent stereoselectivity as measured by ^{1}H NMR spectroscopy of the crude reaction mixtures (*Scheme 3.63*). The minor diastereomers of the THFs could be removed *via* silica gel chromatography, giving diastereomerically pure **(*R*,*R*)-3.72c** and **(*R*,*S*)-3.72c** in high yields.



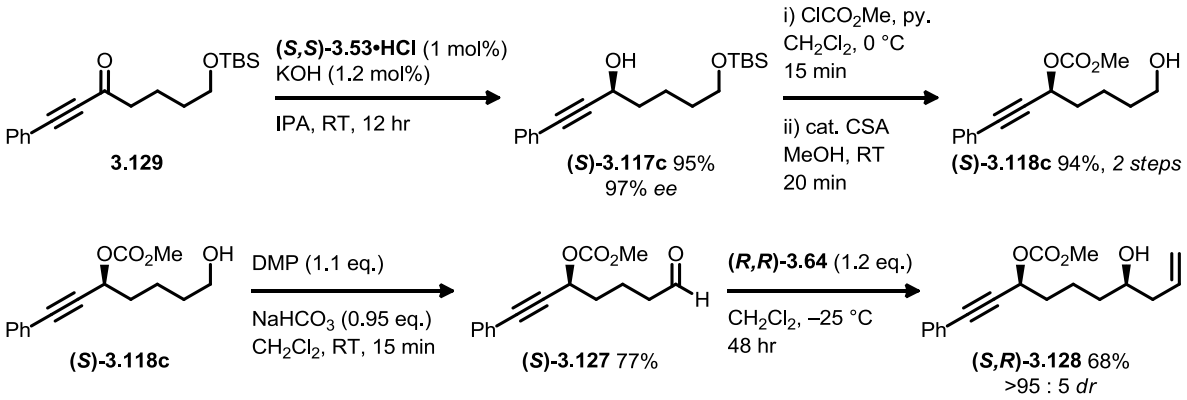
Scheme 3.63

We next looked at forming the corresponding allyl-substituted THPs. A desire to simplify the synthesis of these substrates led us to attempt the allylation of aldehyde **(*R*)-3.127** which was derived from carbonate **(*R*)-3.118c**. Parikh-Doering oxidation of **(*R*)-3.118c** afforded aldehyde **(*R*)-3.127**, which was subjected immediately to reaction with an excess of Leighton's reagent (*Scheme 3.64*). This gave the desired cyclisation substrate **(*R*,*R*)-3.128** in good yield and excellent stereoselectivity, with the minor diastereomer again inseparable by silica gel chromatography.



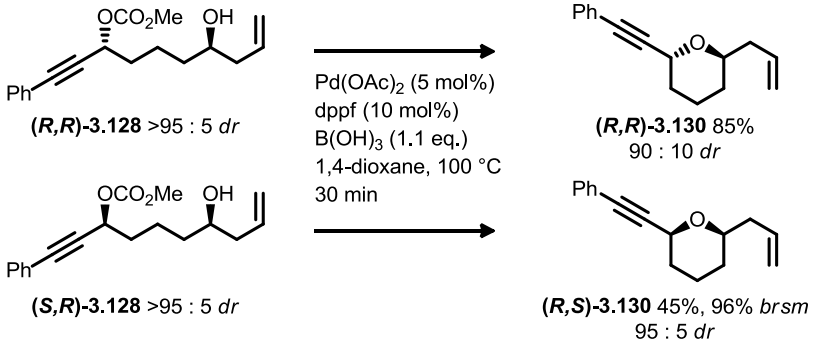
Scheme 3.64

With the success of this route, we set about the stereoselective synthesis of the opposite diastereomer, first requiring synthesis of carbonate **(*S*)-3.118c** (*Scheme 3.65*). Oxidation to aldehyde **(*S*)-3.127** proceeded smoothly, this time employing Dess-Martin periodinane,[167] and reaction with the same hand of Leighton's reagent afforded the opposite carbonate diastereomer **(*S,R*)-3.128** in high yield.



Scheme 3.65

Submission of these enantiopure diastereomeric carbonates to the cyclisation reaction returned the THPs **(*R,R*)-3.130** and **(*R,S*)-3.130** in excellent stereoselectivity and yield (*Scheme 3.66*). The reaction of **(*S,R*)-3.128** was surprising, consistently resulting in only *ca.* 50% conversion on multiple occasions, even with extended reaction times (16 hr). However, remaining carbonate **(*S,R*)-3.128** could be recovered in high yield in all cases.



Scheme 3.66

In contrast to the diastereomeric THFs, the diastereomers of the THPs could not easily be separated by silica gel chromatography, and as such **(*R,R*)-3.130** and **(*R,S*)-3.130** were isolated as diastereomeric mixtures. Once again, the relative configuration of each diastereomer was confirmed through 1D nOe experiments.[†]

It is interesting to note that this reaction overcomes any thermodynamic bias inherent in the formation of 2,6-disubstituted THPs, as the formation of the thermodynamically more stable *cis*-THP

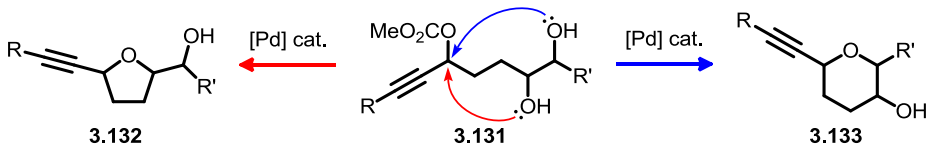
[†] See Appendix for nOe spectra

(*R*,*S*)-3.130 would otherwise be expected as it is able to place both ring substituents equatorial. As such, both *cis* and *trans* disubstituted THFs and THPs are accessible using a single, kinetically-controlled, reaction strategy.

3.7 Complex Substrates

3.7.1 Diol-containing Substrates

With the success in forming THFs and THPs from these relatively simple substrates, we looked at a set of more complex substrates to conduct further investigations into the selectivity of this reaction. Thus, we set about the synthesis of a series of diol-containing substrates that would test the selectivity of the reaction for the formation of competing ring sizes. For example, a suitably placed diol relative to the propargylic carbonate (e.g. **3.131**), would test the propensity of the reaction to form THFs (**3.132**) or THPs (**3.133**) when both options are possible in the same molecule (*Scheme 3.67*).

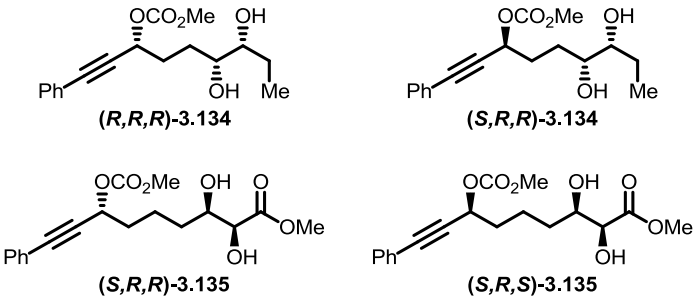


3.132 **3.131** **3.133**

Scheme 3.67

We considered a late stage Sharpless asymmetric dihydroxylation (SAD)[91] of an (*E*)-alkene-containing propargylic carbonate to be the most promising synthetic route to these compounds, as it would avoid the need for differentiation of the diol and propargylic alcohol moieties. As we wished to synthesise these substrates with complete control of enantio- and diastereoselectivity, we targeted (*E*)-alkenes as SAD would achieve higher stereoselectivites than the corresponding (*Z*)-alkene.[91] Noyori transfer hydrogenation would again be used to install the propargylic stereocentre.[147]

Our first targets were two pairs of diol-containing carbonates **3.134** and **3.135** which would examine the formation of 5- *vs.* 6- and 6- *vs.* 7-membered rings; each pair containing either propargylic stereocentre relative to the *syn*-diol introduced by SAD (*Figure 3.9*).

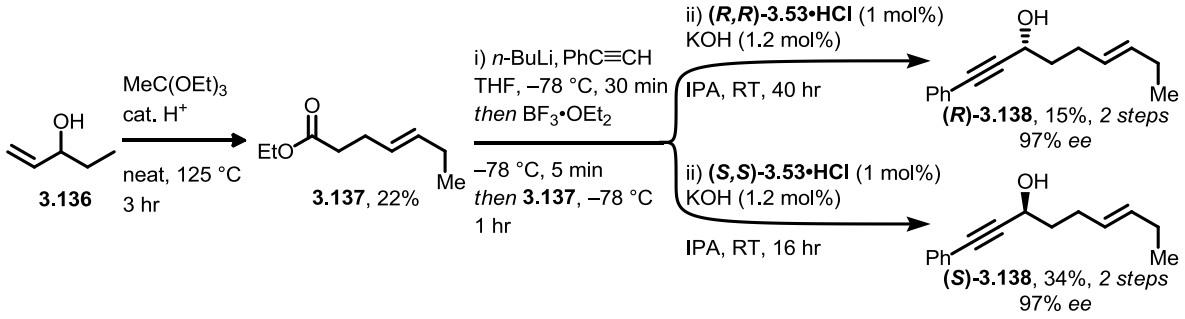


(*R*,*R*,*R*)-3.134 **(*S*,*R*,*R*)-3.134**

(*S*,*R*,*R*)-3.135 **(*S*,*R*,*S*)-3.135**

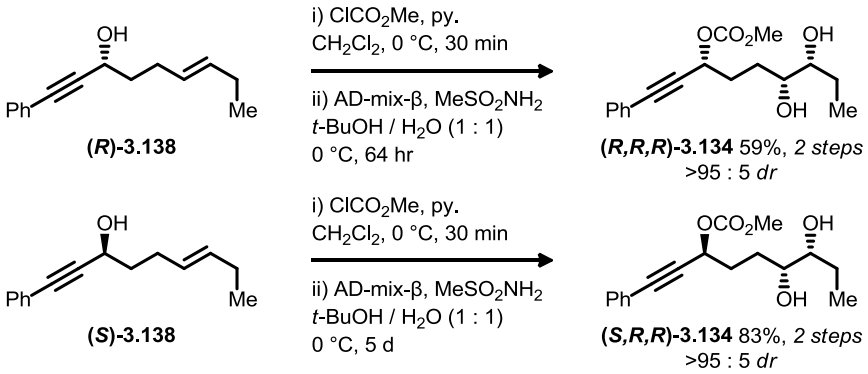
Figure 3.9

Synthesis of **(*R,R,R*)-3.134** and **(*S,R,R*)-3.134** commenced with the Johnson-Claisen rearrangement[168] of commercially available allylic alcohol **3.136** and triethyl orthoacetate in the presence of catalytic propionic acid to form alkenyl ester **3.137** as a single geometrical isomer (*Scheme 3.68*). Mono-addition of alkynes to esters using an identical *n*-butyllithium / $BF_3{\cdot}OEt_2$ protocol that we had employed for lactones is well known,[169] and was applied to addition of phenyl acetylene to ester **3.137**. Unfortunately, full conversion of **3.137** could not be achieved and remaining ester **3.137** proved to be inseparable from the ynone product. Therefore, the crude ynone was submitted directly to Noyori transfer hydrogenation, affording the propargylic alcohols **(*R*)-3.138** and **(*S*)-3.138** which could be easily separated from the remaining ester **3.137**.



Scheme 3.68

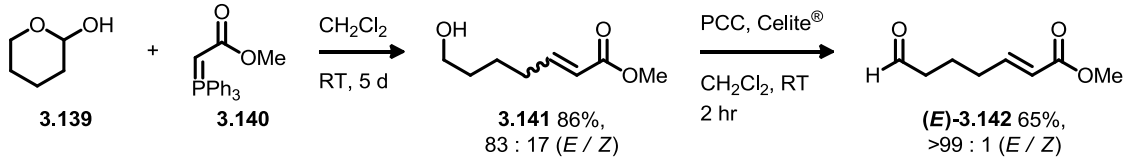
Although this sequence was poor-yielding, it was not optimised, and afforded enough of each hand of alcohol **3.138** (with high enantiomeric purity) to use in subsequent transformations. Thus, carbonate formation and subsequent SAD using the commercially available AD-mix-β[94] afforded the desired cyclisation substrates **(*R,R,R*)-3.134** and **(*S,R,R*)-3.134** in excellent yield and selectivity (*Scheme 3.69*). The absolute configuration of the *syn*-diols was predicted using the Sharpless mnemonic.[91]



Scheme 3.69

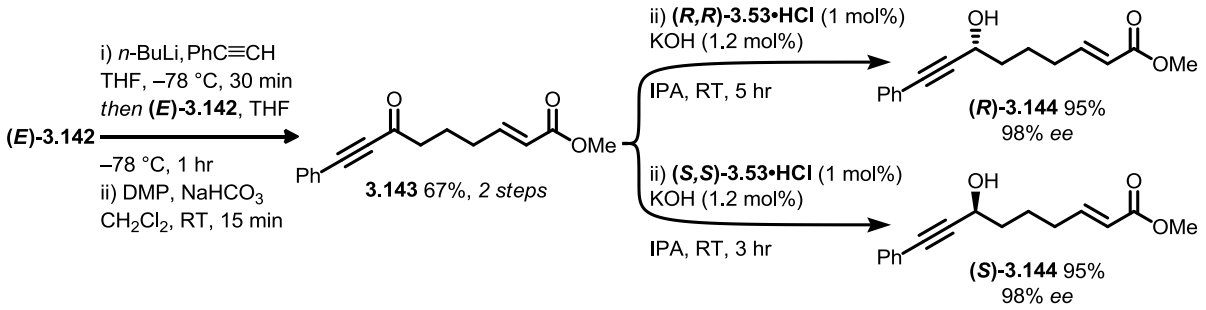
The synthesis of the homologous carbonates **(*S,R,R*)-3.135** and **(*S,R,S*)-3.135** began with reaction of commercially available tetrahydro-2*H*-pyran-2-ol **3.139** and stabilised Wittig reagent **3.140** to give

α,β-unsaturated ester **3.141** in high yield and reasonable *E* / *Z* selectivity (*Scheme 3.70*).[170-171] Subsequent oxidation of the alcohol functionality using PCC[172] afforded aldehyde **3.142**, and pleasingly allowed chromatographic separation of the isomers, giving pure **(*E*)-3.142** in good yield.



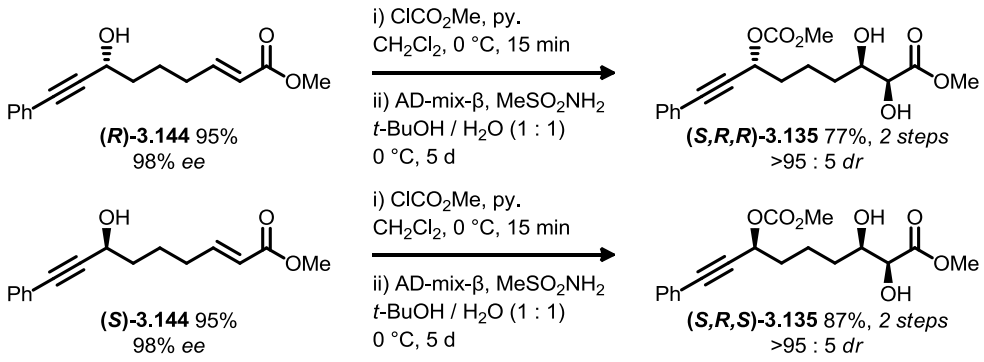
Scheme 3.70

Careful addition of lithium phenylacetylide to **(*E*)-3.142** at −78 °C to prevent competing addition to the ester moiety, followed by a second oxidation using Dess-Martin periodinane, afforded ynone **3.143** in good yield (*Scheme 3.71*). Ynone **3.143** marked the point of divergence for this sequence, and was submitted to each hand of Noyori's catalyst to afford the enantiomerically enriched alcohols **(*R*)-3.144** and **(*S*)-3.144** with excellent enantioselectivity.



Scheme 3.71

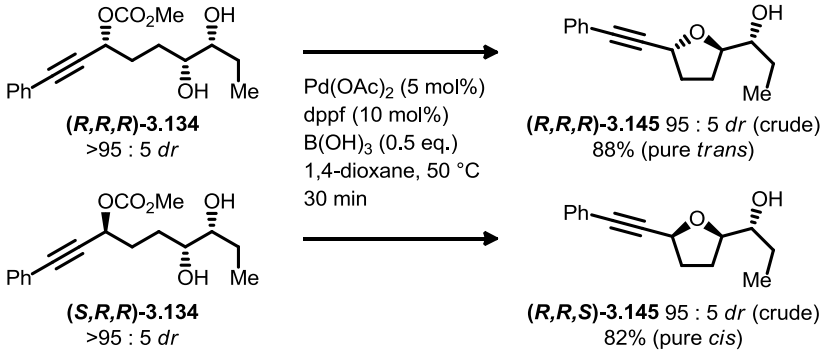
As before, carbonate formation and SAD with AD-mix-β afforded the desired cyclisation substrates **(*S,R,R*)-3.135** and **(*S,R,S*)-3.135** in excellent yield (*Scheme 3.72*).



Scheme 3.72

On submission to the cyclisation reaction carbonates **(*R,R,R*)-3.134** and **(*S,R,R*)-3.134** reacted smoothly, and perhaps unsurprisingly on kinetic grounds, only the THFs **(*R,R,R*)-3.145** and **(*R,R,S*)-3.145** were observed by ^{1}H NMR spectroscopy of the crude reaction mixtures (*Scheme 3.73*). The minor diastereomer of each THF could easily be removed by silica gel chromatography, affording

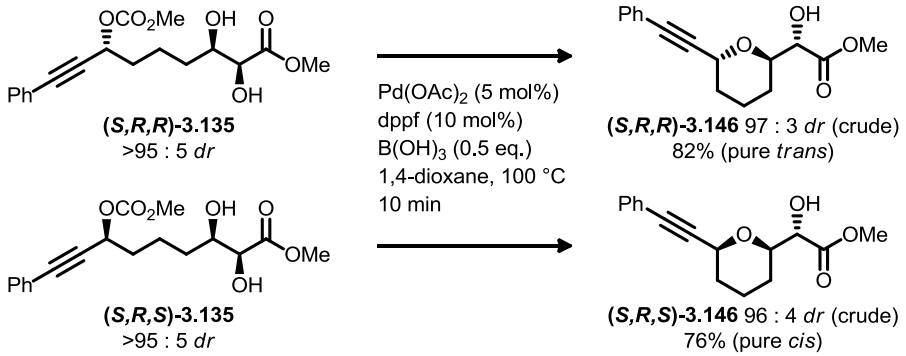
pure single diastereomers in excellent yield.



Scheme 3.73

This result showed that the formation of 5-membered rings in this reaction is very much more favourable than 6-membered rings. This observation, coupled with the excellent stereoselectivities for either THF diastereomer, again suggests that the reaction is operating under kinetic control.

As might have been expected from the above result, carbonates **(*S,R,R*)-3.135** and **(*S,R,S*)-3.135** reacted to give exclusively the THP derivatives **(*S,R,R*)-3.146** and **(*S,R,S*)-3.146** as observed by ^{1}H NMR spectroscopy of the crude reaction mixtures (*Scheme 3.74*). Once again, the minor diastereomer could be removed through silica gel chromatography, and the predicted stereochemistry for these diastereomers was confirmed through the presence of a transannular enhancement between H2 and H6 in the 1D nOe spectra of **(*S,R,S*)-3.146**.[†] The exclusive formation of THPs was unsurprising either on kinetic grounds or in light of our failure when trying to form oxepanes under these conditions (*vide supra*). The reactions were stereoselective and overrode any thermodynamic bias for the formation of the more stable *cis*-THP.



Scheme 3.74

In light of these excellent results we decided to push the formation of 5- *vs*. 6-membered rings to the limit using substrates **(*R,R,R*)-3.147** and **(*S,R,R*)-3.147** (*Figure 3.9*), where the steric crowding around

[†] See Appendix for nOe spectra

the tertiary alcohol may allow competing cyclisation by the secondary alcohol to form THPs.

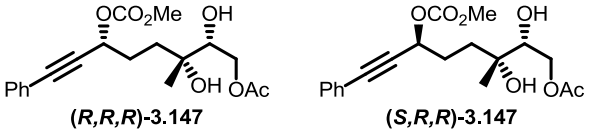
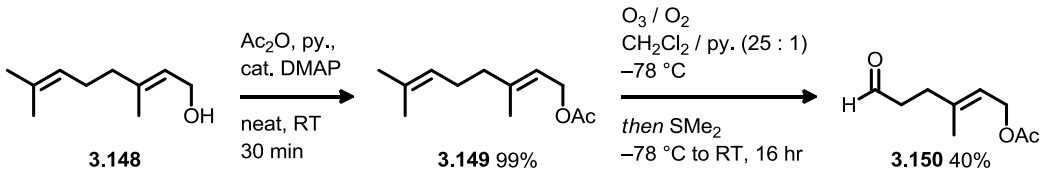


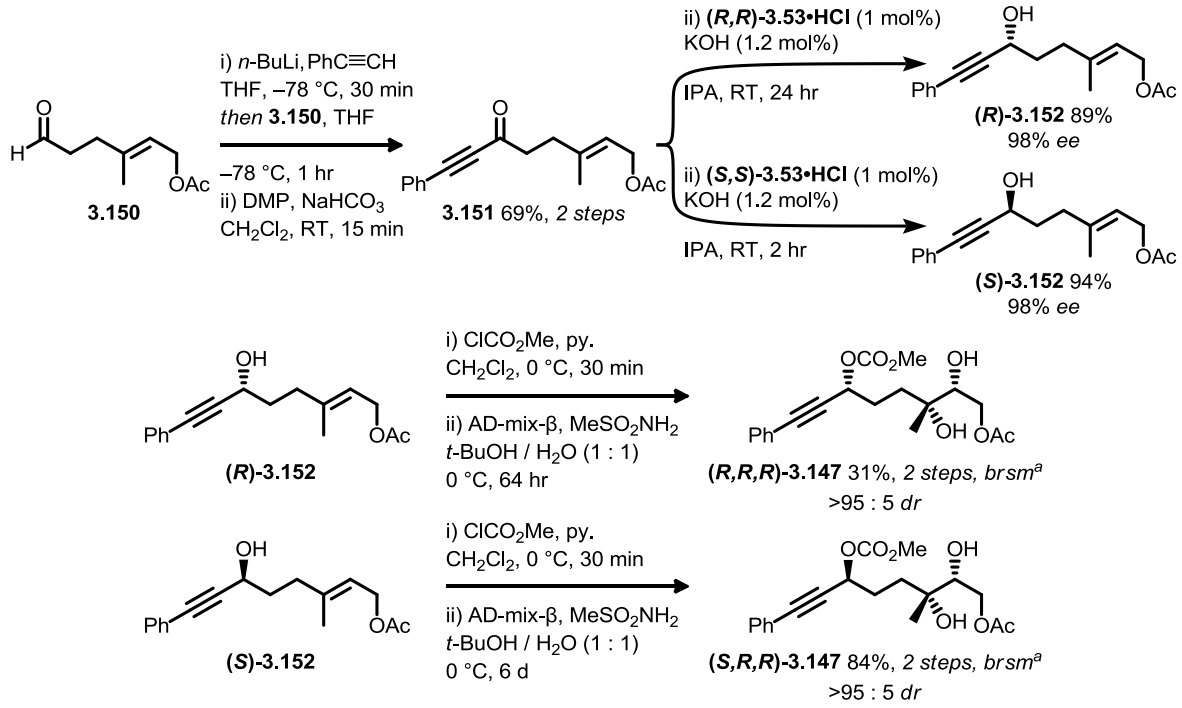
Figure 3.9

Synthesis of these carbonates commenced with selective ozonolysis of the more electron-rich alkene of geraniol acetate **3.149**,[173] affording aldehyde **3.150** in moderate yield (*Scheme 3.75*). However, this reaction could be performed on large scale (*ca.* 8 g) generating synthetically useful amounts of **3.149**.



Scheme 3.75

An identical sequence to that employed for the synthesis of **(*S*,*R*,*R*)-3.135** and **(*S*,*R*,*S*)-3.135** was then followed, namely careful addition of lithium phenylacetylide to **3.150** and oxidation to form ynone **3.151**, followed by Noyori reduction, carbonate formation and SAD (*Schemes 3.76*).

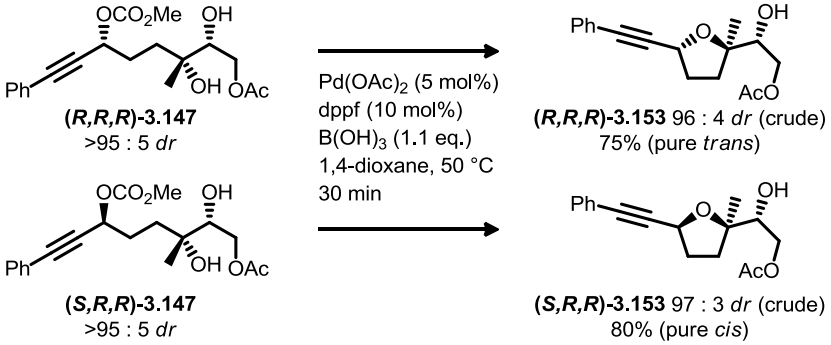


Scheme 3.76: [a] Based on recovered carbonate **(*R*)-3.152.1** and **(*S*)-3.152.1** after SAD

As expected the dihydroxylations were sluggish, due to the combination of a trisubstituted and electron-poor alkene. However, synthetically useful amounts of both carbonates **(*R*,*R*,*R*)-3.147** and **(*R*,*R*,*S*)-3.147** were formed in moderate to good yield.

With these carbonates in hand we tested cyclisation, and were delighted to discover that only the THF

derivatives **(*R,R,R*)-3.153** and **(*R,R,S*)-3.153** formed under these conditions, as indicated by ^{1}H NMR spectroscopy of the crude reaction mixtures (*Scheme 3.77*). We were very pleased with this result, as it clearly shows that substitution around the nucleophile is well tolerated in this reaction.



Scheme 3.77

Silica gel chromatography allowed isolation of the single diastereomers in excellent yield, and once again, the predicted stereochemistry was confirmed by 1D ^{1}H nOe spectroscopy.[†] Also of note is the stability of the acetate-protected primary alcohol, as we observed no loss or transfer of this protecting group under the reaction conditions.

These three sets of diastereomeric diol-containing carbonates had given us a clear understanding of the regio- and stereochemical outcome of the cyclisations of these acyclic carbonates. We envisaged a final demonstration of the power of this methodology, through the formation of two rings in a single step from a diol-containing *bis*-carbonate.

3.7.2 Two-directional Substrates

The octahydrobifuran motif **3.154** (*Figure 3.10*) is present in many natural products, including the annonaceous acetogenins (**3.155**)[174] and polyether ionophores[134] (e.g. ionomycin[175]).

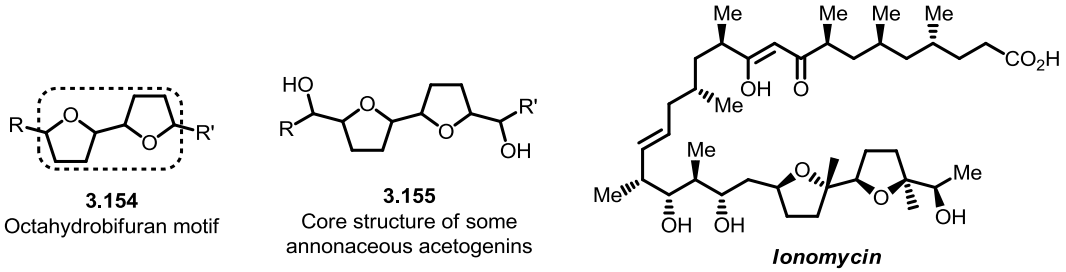
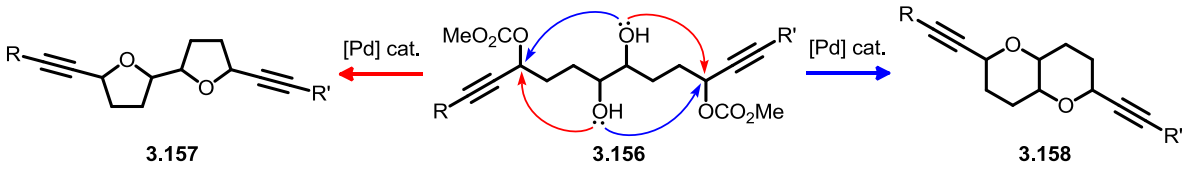


Figure 3.10

We considered that the octahydrobifuran motif (e.g. **3.157**) could be formed from the double cyclisation of a diol-containing *bis*-carbonate, e.g. **3.156** (*Scheme 3.78*). A substrate of this type could

[†] See Appendix for nOe spectra

also undergo cyclisation to the octahydropyranopyran type structure **3.158**, although our previous results would suggest this to be unlikely.

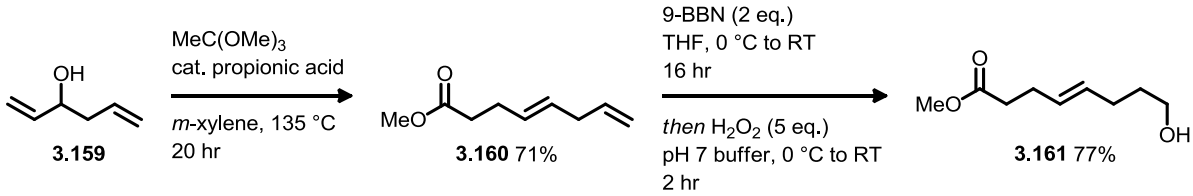


3.157 **3.156** **3.158**

Scheme 3.78

We set about the synthesis of this *bis*-carbonate-diol substrate, targeting four separate diastereomers through installation of two different alkyne substituents and branching of the synthetic sequence at two of the asymmetric steps.

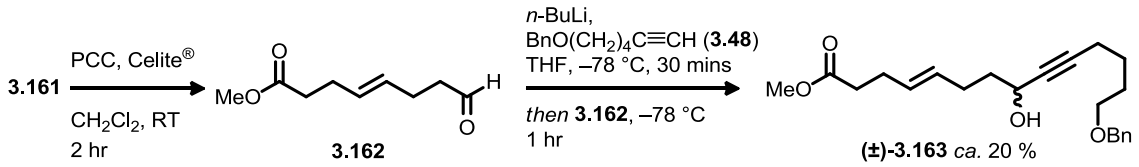
This commenced with the Johnson-Claisen rearrangement of commercially available **3.159** and trimethyl orthoacetate, affording skipped diene **3.160** as a single geometric isomer in good yield (*Scheme 3.79*). Selective hydroboration with 9-BBN,[176] followed by *in situ* oxidation with hydrogen peroxide afforded alcohol **3.161** as a single regioisomer in high yield.



3.159 **3.160** 71% **3.161** 77%

Scheme 3.79

At this point we had considered following a similar synthetic sequence to that employed before, namely an oxidation / alkyne addition / reoxidation / Noyori reduction sequence to install the first alkyne substituent and chiral centre. Although the oxidation to aldehyde **3.162** proceeded smoothly, the addition of lithiated benzyloxy alkyne proved to be poor yielding, returning only *ca.* 20% yield of **(±)-3.163** despite complete consumption of **3.162** (*Scheme 3.80*). We reasoned this may be due to competing self-condensation of the aldehyde **3.162**.

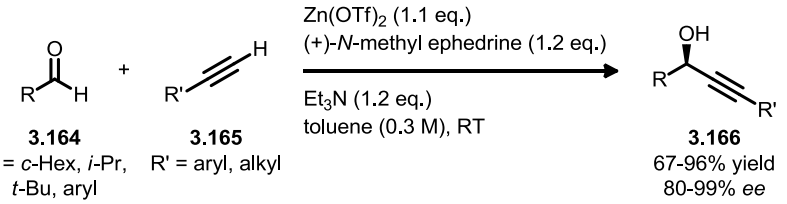


3.162 **(±)-3.163** *ca.* 20 %

Scheme 3.80

This prompted us to look at performing a direct asymmetric addition of the alkyne to aldehyde **3.162** to reduce the number of steps. Carriera and co-workers have developed a method for the asymmetric addition of alkynes to aldehydes employing stoichiometric $Zn(OTf)_2$ and (+)-*N*-methyl ephedrine to

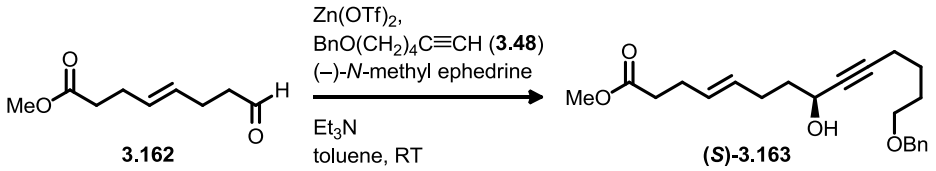
form a chiral organometallic reagent (*Scheme 3.80*).[177]



Scheme 3.80: Carriera's zinc / ephedrine-mediated enantioselective addition of alkynes to aldehydes[177]

Although this methodology is known to give reduced yields with linear aldehydes (like **3.162**) due to aldehyde self-condensation,[178] we hoped that the application of this methodology would allow us to obtain synthetically useful amounts of enantioenriched **3.163**.

When we applied Carreira's standard conditions to a test scale reaction of **3.162** and **3.48** (*Scheme 3.81*), we generated a small amount of desired alcohol **(*S*)-3.163** with good enantioselectivity (*Table 3.6, entry 1*). The absolute configuration of **(*S*)-3.163** was inferred from those reported by Carreira for (+)-*N*-methyl ephedrine.[177] Disappointingly, this yield failed to improve significantly on scale-up of the reaction (*Entry 2*), and we decided to further optimise the process.



Scheme 3.81

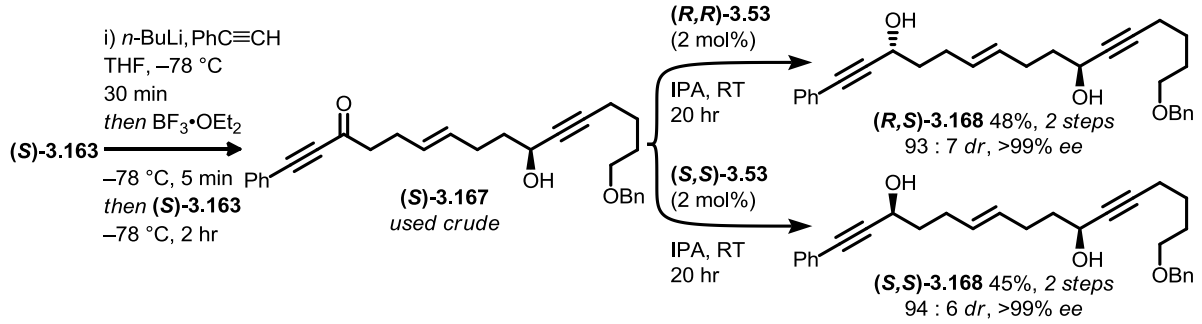
Entry	Equivalents				Molarity	Addition Time[a]	Yield (*S*)-3.163	*ee* (*S*)-3.163[b]
	$Zn(OTf)_2$	(−)-*N*-methyl ephedrine	Et_3N	3.48				
1[c]	1.1	1.2	1.2	1.2	0.3 M	<1 min	<10%	85%
2[d]	1.1	1.2	1.2	1.2	0.3 M	<1 min	12%	92%
3[e]	1.1	1.2	1.2	1.2	0.3 M	~4 hr	20%	93%
4[e]	2.0	2.1	2.1	2.1	1 M	~12 hr	37%	90%
5[f]	2.0	2.1	2.1	2.1	1 M	16 hr	55%	89%

Table 3.6: [a] Time period for addition of **3.162**, total reaction time 16-18 hr; [b] Determined by chiral HPLC; [c] 50 mg **3.162**; [d] 415 mg **3.162**; [e] 130 mg **3.162**; [f] 800 mg **3.162**

As we suspected that aldehyde **3.162** was self-condensing, we first considered adding it over an extended period (*via* syringe pump) to reduce the amount present in the reaction mixture at any one time (*Entry 3*). This led to a slight improvement in isolated yield, but this was still disappointingly low. Multiple equivalents of reagents have been used by Carreira for challenging substrates,[179] and coupled with an increase in both addition time and reaction concentration, we were able to almost double the isolated yield of **(*S*)-3.163** (*Entry 4*). This improved further still on scale-up, which allowed an even longer addition time to be employed, and afforded synthetically useful amounts of **(*S*)-3.163**

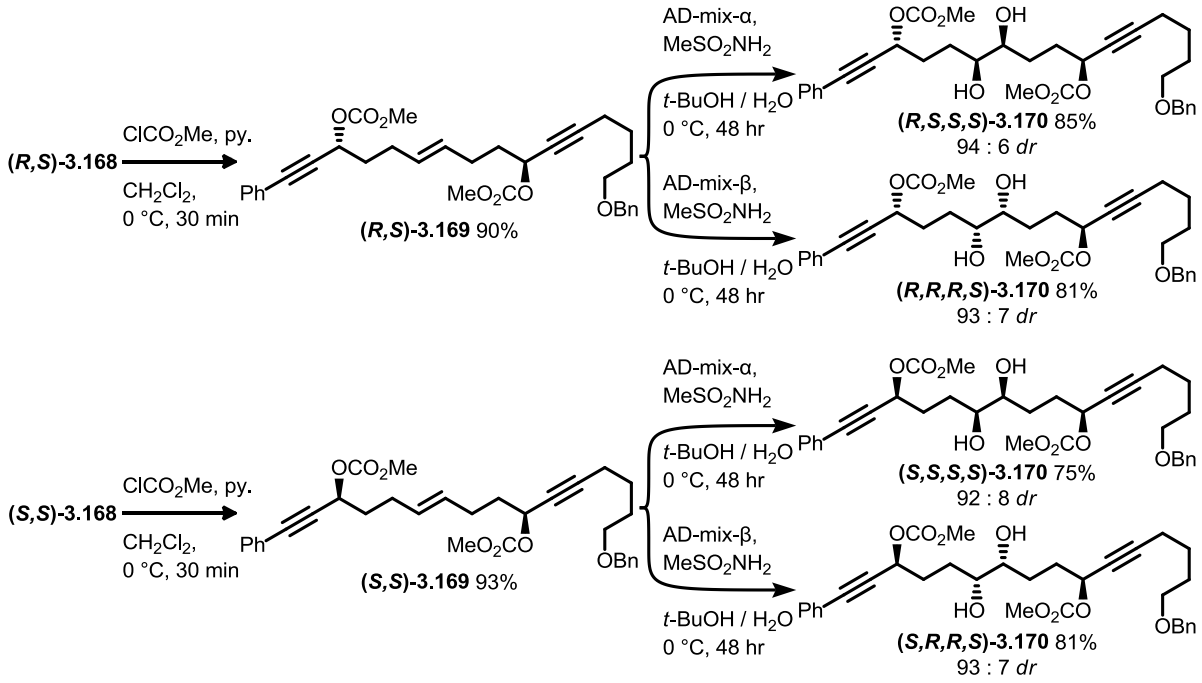
in moderate yield and high enantioselectivity (*Entry 5*).

The next step required mono-addition of phenyl acetylene to the ester moiety to afford ynone **(*S*)-3.167** (*Scheme 3.82*). As before, this reaction failed to go to completion even with four equivalents of the alkynyl trifluoroborate, and **(*S*)-3.167** proved to be inseparable from the remaining ester **(*S*)-3.163**. Thus, crude **(*S*)-3.167** was submitted to either hand of Noyori reduction which afforded pure diastereomeric diols **(*R,S*)-3.168** and **(*S,S*)-3.168** in moderate yield and excellent diastereoselectivity and enantioselectivity (as measured by chiral HPLC).



Scheme 3.82

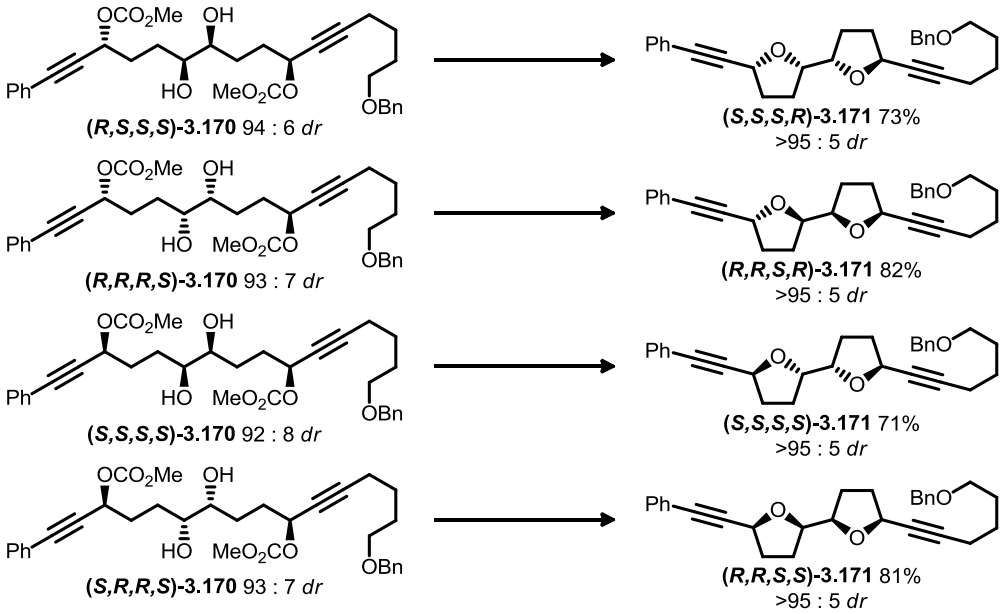
Formation of the *bis*-carbonates **(*R,S*)-3.169** and **(*S,S*)-3.169** proceeded smoothly, and we completed the synthesis of the desired substrates through the application of both AD-mix-α and β, thereby generating four separate diastereomers of **3.170** (*Scheme 3.83*).



Scheme 3.83

The cyclisations of these substrates proved sluggish at 50 °C, failing to go to completion even after extended reaction times (16 hr). Increasing the temperature to 100 °C led to complete conversion in

less than 1 hour, however, significant decomposition was observed leading to the isolation of only trace amounts of cyclised material. We found that the happy medium of 75 °C led to smooth conversion of **3.170** to **3.171** in 16 hours (*Scheme 3.84*).



Scheme 3.84: Conditions: $Pd(OAc)_2$ (5 mol%), dppf (10 mol%), $B(OH)_3$ (0.5 eq.), 1,4-dioxane, 75 °C, 16 hr

The four separate diastereomers of bifuran **3.171** were all isolated in excellent yield and stereoselectivity (all >95 : 5 *dr*), and the predicted stereochemistry for each diastereomer was confirmed by the presence of transannular nOes in the *syn*-2,5-disubstituted THFs.[†]

In order to confirm the formation of the linked 5,5-ring system *vs.* the fused 6,6-ring system, we examined the ^{13}C NMR spectra. A computational and synthetic study of these structures by Burton and co-workers has shown that the chemical shifts of the carbons at the ring junction are characteristic of either structure and allow them to be distinguished.[180-181] If these carbons are >76 ppm it indicates the linked 5,5-system **3.172**, and <76 ppm indicates the fused 6,6-system **3.173** (*Figure 3.11*), with >98% of synthesised structures fitting this pattern.[181]

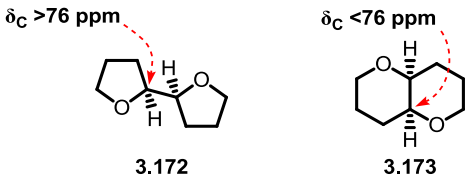


Figure 3.11

In our case, all of the ring junction carbons had resonances of 80-83 ppm, confirming the expected formation of the octahydrobifuran motif (*Figure 3.12*). Individual assignment of the linking carbons in

[†] See Appendix for nOe spectra

(*S,S,S,S*)-3.171 and **(*R,R,S,S*)-3.171** was complicated by overlapping signals for the corresponding protons in the ^{1}H NMR spectra.

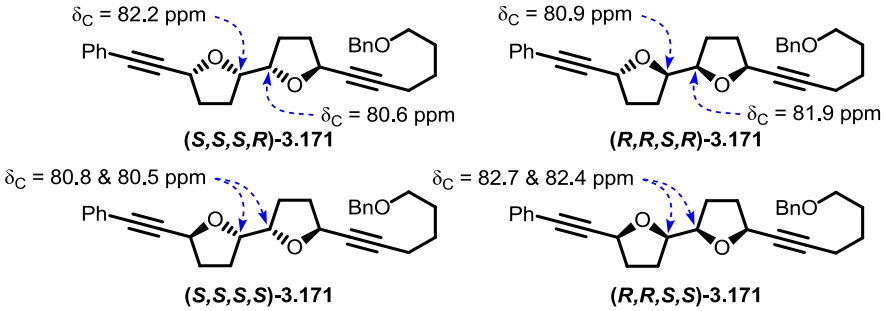


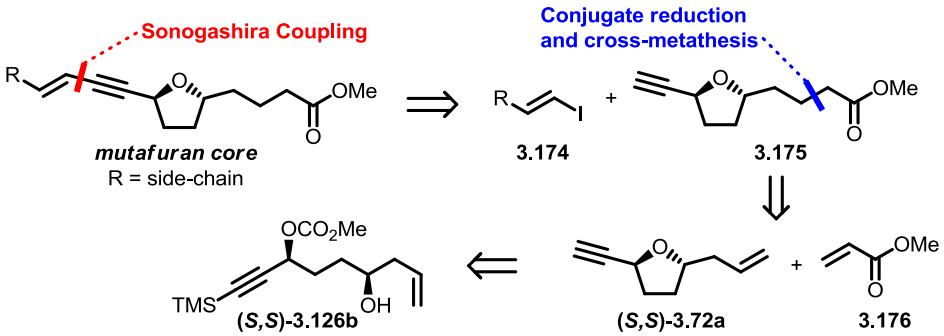
Figure 3.12

This result was extremely pleasing as it gave a final demonstration of the power of this methodology to deliver 2-alkynyl oxacycles with complete control of regio- and stereoselectivity, overriding any thermodynamic bias.

3.8 Studies Towards the Mutafuran Family of Natural Products

With the successful development of a methodology for the synthesis of 2-alkynyl oxacycles, we decided to apply it to the synthesis of a natural product to further demonstrate synthetic utility. Thus, we targeted the enyne-THF containing natural product family, the mutafurans.[137]

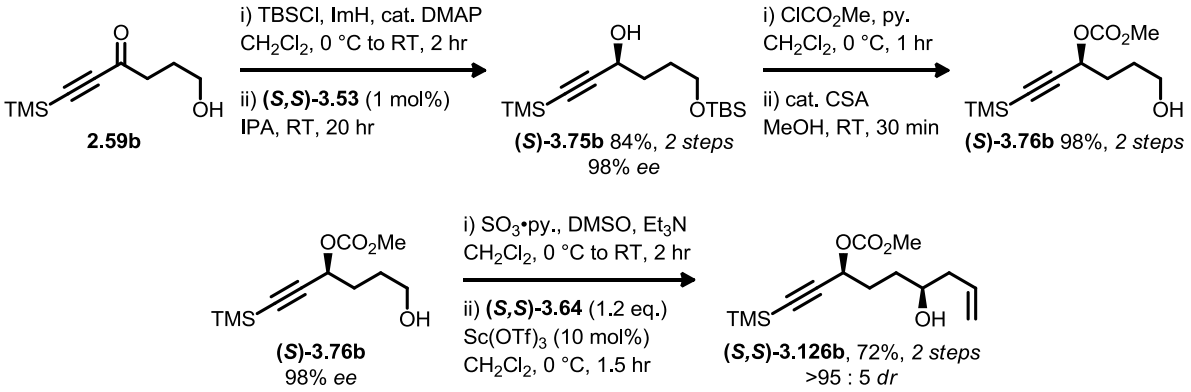
Our retrosynthetic analysis of the mutafurans involved a late stage Sonogashira cross-coupling between the vinyl iodide **3.174** and terminal alkyne **3.175** (*Scheme 3.85*). This would hopefully allow installation of all the side-chains at a late stage, and render the synthesis convergent from a single common core structure (**3.175**).



Scheme 3.85: See *Figure 3.1* for details of the side-chains

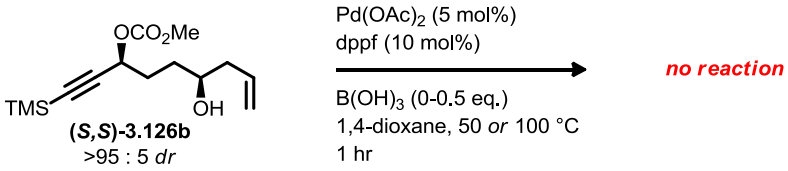
Further disconnection of **3.175** (through an α,β-unsaturated ester) leads to allyl-substituted THF **(*S,S*)-3.72a**, which comes from the cyclisation of carbonate **(*S,S*)-3.126b**. The synthesis of **(*S,S*)-3.126b** would follow an identical route to that employed before for the allyl-substituted acyclic carbonates.

Carbonate **(*S,S*)-3.126b** was synthesised in six steps from ketone **2.59b** (*Scheme 3.86*). The enantiomeric excess of **(*S*)-3.75b** was determined through synthesis of the Mosher ester[152] derivatives and integration of the diastereomeric peaks in the ^{19}F NMR spectra.† Allylation with Leighton's reagent (**(*S,S*)-3.64**) was performed under the recently reported and improved conditions employing catalytic $Sc(OTf)_3$, which accelerates conversion and improves isolated yield.[182]



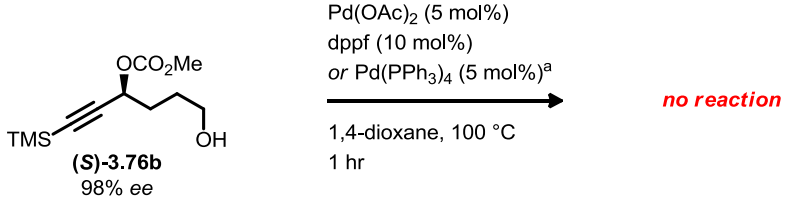
Scheme 3.86

Surprisingly, when carbonate **(*S,S*)-3.126b** was subjected to the optimised conditions for THF formation no reaction occurred (*Scheme 3.87*). This remained the case at elevated temperatures and in the absence of boric acid additive; the reaction returned only starting material **(*S,S*)-3.126b**.



Scheme 3.87

Owing to the value of **(*S,S*)-3.126b**, we employed the precursor **(*S*)-3.76b** to test more reaction conditions. Again, however, this substrate failed to react under either of the catalytic systems trialled, returning only starting material (*Scheme 3.88*).

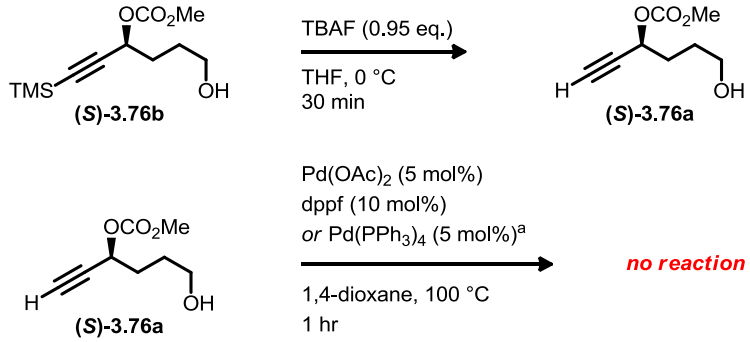


Scheme 3.88: [a] Reaction with $Pd(PPh_3)_4$ conducted in the presence of $B(OH)_3$ (0.5 eq.)

At this point we considered whether the bulky TMS group was preventing oxidative addition into the propargylic carbonate, as had been observed with some substrates examined under cross-coupling

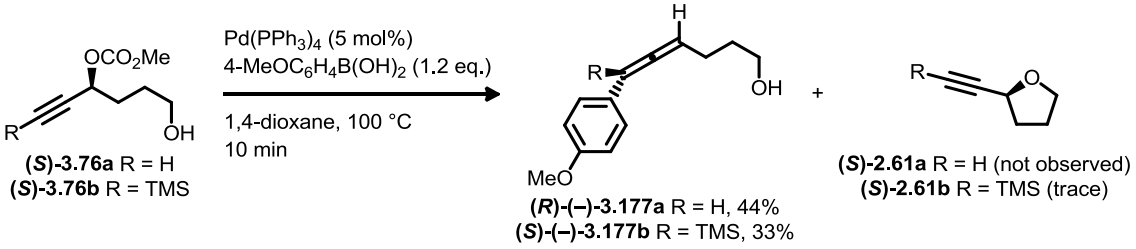
† See Experimental for details

conditions (*vide supra, Chapter 2*). Thus we decided to deprotect **(*S*)-3.76b** and attempt cyclisation with the terminal alkyne **(*S*)-3.76a**, and this was achieved with TBAF (*Scheme 3.89*).[106] Surprisingly, once again cyclisation was not observed with **(*S*)-3.76a** and the reaction returned only starting material.



Scheme 3.89: [a] Reaction with $Pd(PPh_3)_4$ conducted in the presence of $B(OH)_3$ (0.5 eq.)

With this disappointing lack of reactivity we attempted one further reaction to try and deduce a reason for the failure of **(*S*)-3.76a** and **b** to cyclise. Thus, we attempted to cross-couple these substrates under Suzuki conditions to see if lack of oxidative addition was the problem. **(*S*)-3.76a** and **b** were submitted to cross-coupling under the same conditions employed for the synthesis of allenes (*Scheme 3.90*).

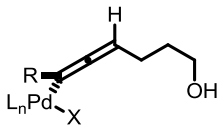


Scheme 3.90

These carbonates both underwent cross-coupling to form the levorotatory allenes **(*R*)-3.177a** and **(*S*)-3.177b** in moderate yield. The absolute configuration of **(*R*)-3.177a** was assigned by applying the Lowe-Brewster rule,[22-23] and showed the expected inversion of configuration of the allene axis brought about by *anti*-S_N2' oxidative addition by palladium(0). The assignment of **(*S*)-3.177b** is more tentative, although the assignment as (*S*) would follow from the expected inversion of configuration. Surprisingly, in the reaction of **(*S*)-3.76b** we observed a trace of the desired THF **(*S*)-2.61b** in the ^1H NMR spectrum of the crude reaction mixture, however this proved to be a negligible amount on purification. The THF **(*S*)-2.61a** was not observed, although this is perhaps due to its expected volatility. The poor mass recovery from either reaction may be explained by the formation of **(*S*)-2.61a** and its subsequent loss, as we had previously observed deprotection of TMS-alkynes under

these cross-coupling conditions. These results proved that oxidative addition (by $Pd(PPh_3)_4$ at least) into either **(*S*)-3.76a** or **b** is occurring, suggesting there is a more subtle reason for the lack of reactivity observed when attempting cyclisation.

It appears that the allenylpalladium intermediate (**3.178**) formed from oxidative addition into either **(*S*)-3.76a** or **b** (R = H, TMS) is less electrophilic than that formed from **(*R*)-3.76c** or **e** (R = phenyl, alkyl) (*Figure 3.13*), as the nature of the nucleophile and catalyst system remains unchanged between these substrates. The reason for this subtle difference is not clear.



3.178

X = OCO_2Me *or* OMe

Figure 3.13

A solution to this problem has not been forthcoming, although the observation of trace THF **(*S*)-2.61b** in the presence of 4-methoxyphenyl boronic acid suggests that investigation of boronic acids as additives in the cyclisation reaction may prove productive. However, no further work was conducted in this regard due to time pressures and more fruitful investigations into replacing the oxygen nucleophile with nitrogen. This work will be described in the following chapter.

3.9 Conclusions and Future Work

In conclusion, we have developed two distinct catalytic systems for the stereoselective synthesis of 2-alkynyl oxacycles from both cyclic and acyclic carbonates. The use of acyclic carbonates led to the synthesis of both THFs and THPs, alongside a clear understanding of the preference for the formation of different ring sizes with predictable stereochemistry. The culmination of this work was the synthesis of a bifuran motif from the double cyclisation of a diol-containing *bis*-carbonate, with complete control of all four stereocentres.

Although aromatic and alkyl substituents on the alkyne are tolerated in these cyclisations, further work is required to allow alkenyl, TMS or terminal alkynes to act as competent substrates. This may allow a continuation of the efforts towards the synthesis of the mutafuran family of natural products. Other possibilities for the synthesis of the mutafurans may be the use of other alkyne protecting groups (e.g. **3.179** or **3.180**) which are based on alkyl substituents (*Figure 3.14*).

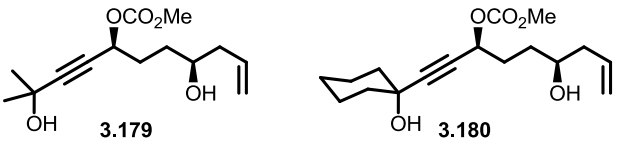


Figure 3.14

Chapter 4. 2-Alkynyl Azacycles

4.1 Pyrrolidines and Piperidines

Pyrrolidines and piperidines are saturated nitrogen heterocycles that are commonplace in both nature and pharmaceuticals.[183-187] Perhaps the most widely known example is proline, one of the twenty-one human amino acids (*Figure 4.1*). Other examples include the natural products nicotine[188] and ergotamine,[189] and the pharmaceuticals procyclidine[186] and paroxetine (seroxat).[187]

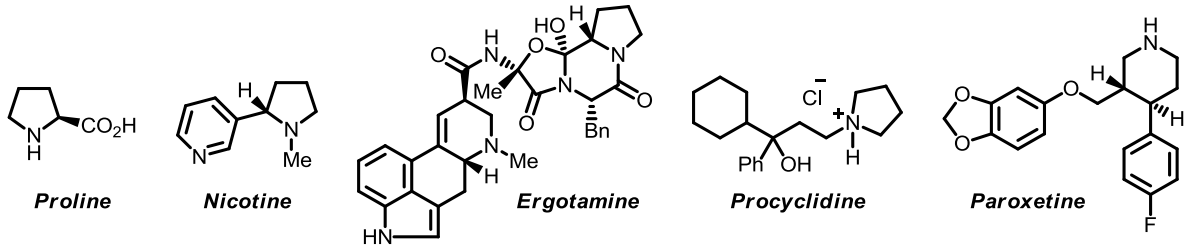


Figure 4.1

Given the ubiquitous nature of these motifs, the development of novel methods for their stereoselective synthesis remains an area of prime importance to organic chemists.[190-191] We hoped that our methodology for the synthesis of saturated alkynyl oxacycles could be extended to the synthesis of saturated alkynyl azacycles.

To the best of our knowledge there are only two examples of natural products containing 2-alkynyl azacycles, the structurally similar dynemicin A[192] and uncialamycin,[193] although these are not saturated azacycles (*Figure 4.2*).

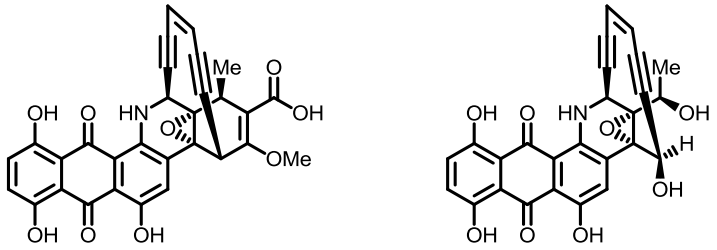


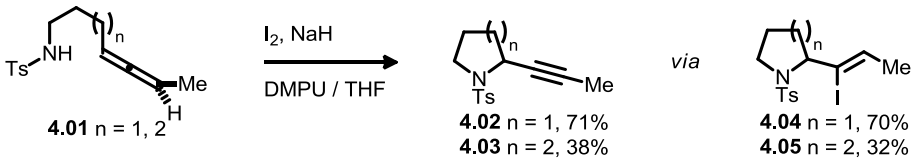
Figure 4.2

4.2 Literature Syntheses of 2-Alkynyl Azacycles

Of specific interest to us is the literature synthesis of 2-alkynyl azacycles; some of the more interesting examples are described below.

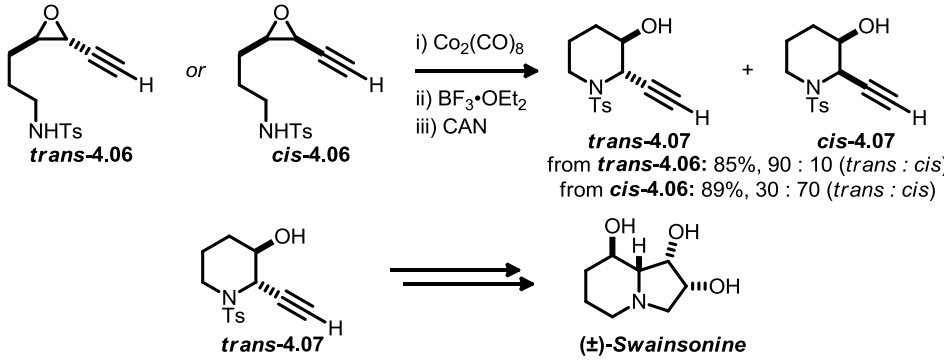
In 1994, Gallagher and co-workers reported the iodine-mediated intramolecular cyclisation of sulfonamides with allenes (**4.01**) to form pyrrolidine **4.02** and piperidine **4.03** (*Scheme 4.1*).[194-195] In

the absence of NaH and the polar co-solvent (DMPU), the reaction stopped at the vinyliodide intermediates **4.04** or **4.05**. However, the reaction was not explored beyond these two substrates.



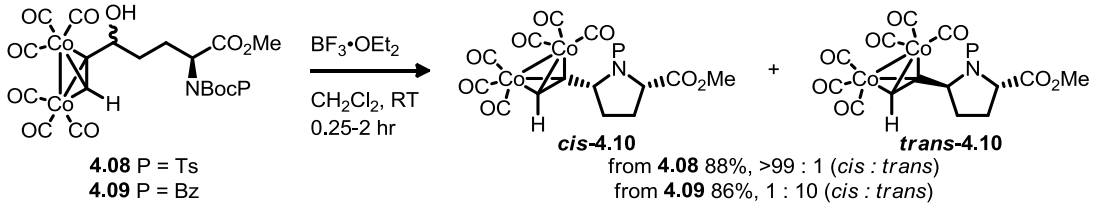
Scheme 4.1

In 1998, Mukai and co-workers described the *endo*-mode cyclisation of propargylic epoxides using the Nicholas reaction (*Scheme 4.2*).[196] The cyclisation of either ***trans*-4.06** or ***cis*-4.06** proceeded with complete selectivity for the piperidine, forming the diastereomers of **4.07** with moderate to high stereoselectivity. Pure ***trans*-4.07** was further elaborated into the natural product (±)-swainsonine.[197]



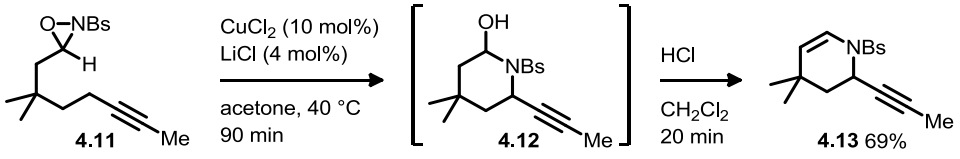
Scheme 4.2

Martín and co-workers have also employed the Nicholas reaction in the formation of 2,5-disubstituted pyrrolidines **4.10** (*Scheme 4.3*).[198] They found that the diastereoselectivity of the reaction was dependent on the nitrogen protecting group employed.



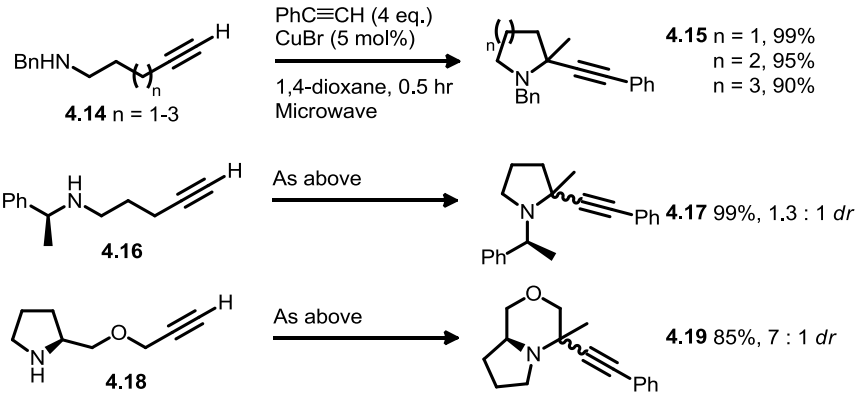
Scheme 4.3

In 2009, Yoon and co-workers described the intramolecular amination of activated sp^3 C–H bonds.[199] Within this work was a single example of a propargylic amination, forming cyclic enamide **4.13** in good yield (*Scheme 4.4*).



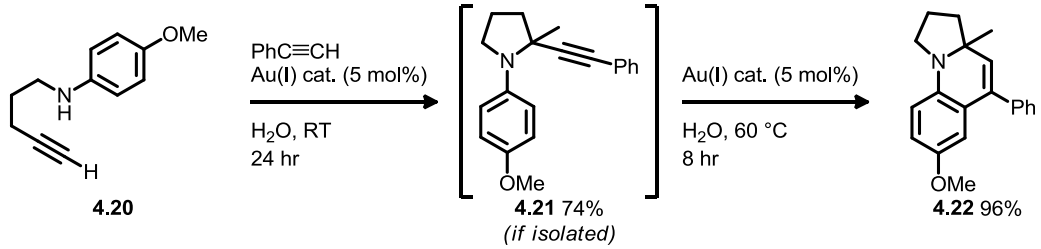
Scheme 4.4

Also in 2009, Hammond and co-workers described the tandem hydroamination / alkynylation of acyclic alkynyl amines.[200] This enabled the synthesis of 5- to 7-membered azacycles in excellent yield (*Scheme 4.5*). Two enantiopure starting materials (**4.16** and **4.18**) were employed, although the diastereoselectivity observed in the products varied greatly.



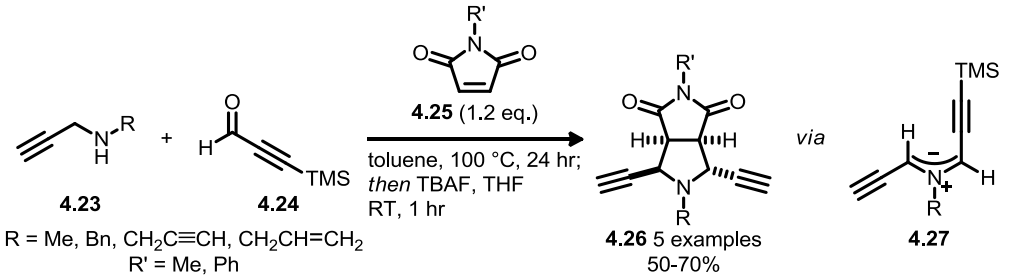
Scheme 4.5

Che and Liu reported a similar transformation using a gold(I) catalyst, although the intermediate 2-alkynyl azacycles were reacted further to afford pyrrolo[1,2-*a*]quinolines (e.g. **4.22**) in one pot (*Scheme 4.6*).[201]



Scheme 4.6: Au(I) cat. = [Au(P(*t*-Bu)$_2$(*o*-biphenyl))]Cl / $AgSbF_6$ (1 : 1)

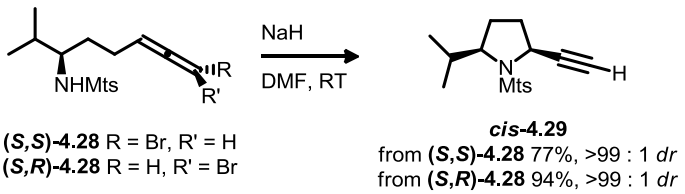
Grigg and co-workers described the formation of 2,5-dialkynyl diazabicycles (**4.26**) through the [3+2] cycloaddition of azomethine ylides **4.27** and maleimides **4.25**.[202] This afforded a range of substituted bicycles in moderate to good yields as single diastereomers (*Scheme 4.7*).



Scheme 4.7

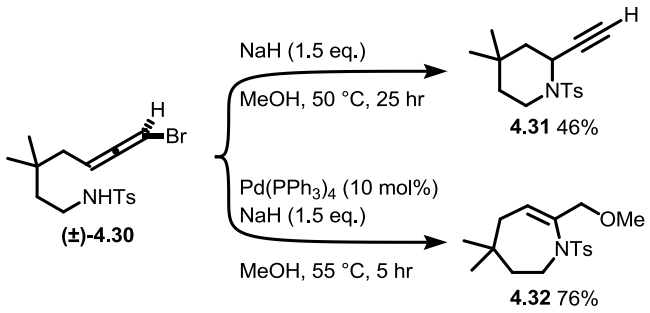
Finally, Tanaka and co-workers have examined the formation of 3- to 5-membered azacycles through the S_N2' substitution of bromoallenes.[203] Of particular interest to us are the formation of pyrrolidines,

and the cyclisations of either diastereomer of **4.28** formed ***cis*-4.29** with excellent diastereoselectivity (*Scheme 4.8*).



Scheme 4.8

Tanaka later examined the synthesis of a piperidine (**4.31**) using this methodology.[204] However, and more significant to us (*vide infra*), in the presence of palladium catalyst the reaction proceeded to form 7-membered azacycle **4.32** exclusively (*Scheme 4.9*).

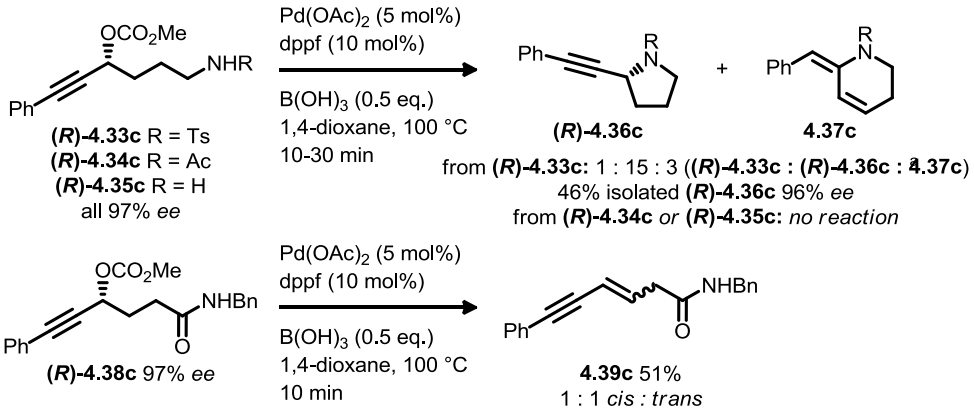


Scheme 4.9

4.3 Early Investigations

To the best of our knowledge there are no examples in the literature of the formation of 2-alkynyl azacycles from the propargylic substitution of allenylpalladium intermediates. All previous examples of the reaction of nitrogen nucleophiles with allenylpalladium intermediates appear to proceed with attack at the central carbon of the allenyl ligand (*vide supra*).[70, 72-73, 204] The initial investigations into this were carried out by a Part II student,[205] and are detailed in this section.

Firstly, the nature of the nitrogen nucleophile was examined through the use of a variety of protecting groups. Of those trialled, only the sulfonamide **(*R*)-4.33c** led to successful cyclisation, forming the desired pyrrolidine **(*R*)-4.36c** as a 5 : 1 mixture with the cyclic enamide **4.37c** (*Scheme 4.10*). In contrast to the related oxygen cyclisations, boric acid did not completely suppress the formation of byproduct under these conditions. The acetamide and primary amine **(*R*)-4.34c** and **(*R*)-4.35c** returned only starting material, and although benzylamide **(*R*)-4.38c** reacted, it resulted in the exclusive formation of enyne **4.39c**.



Scheme 4.10: [a] Measured by crude ^{1}H NMR spectroscopy

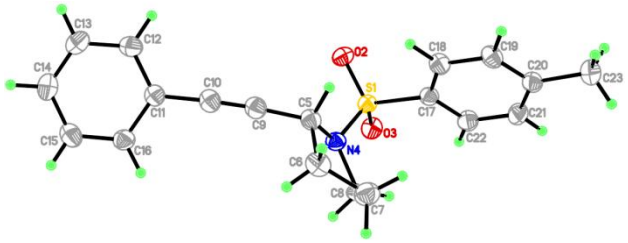
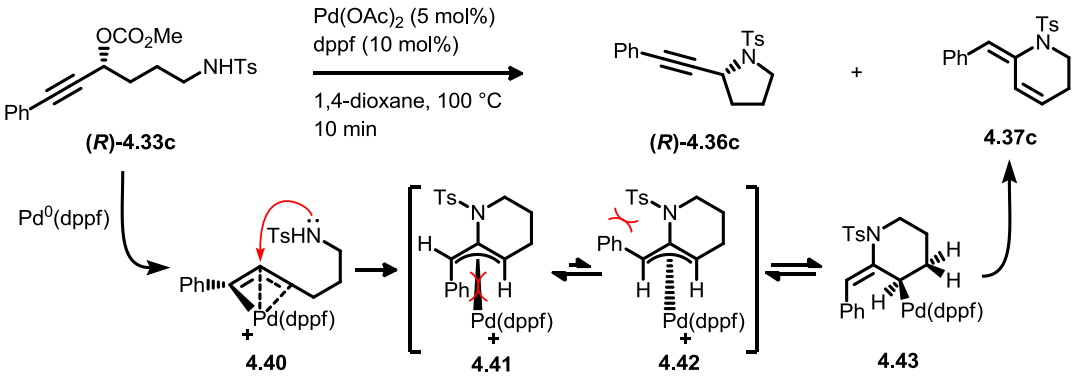


Figure 4.3: X-ray structure of pyrrolidine **(*R*)-4.36c**

The products were separable; single crystal X-ray diffraction confirmed the absolute configuration of **(*R*)-4.36c** (*Figure 4.3*), and the geometry of **4.37c** was confirmed through 1D nOe experiments.[†] Interestingly, the geometry of **4.37c** was opposite to that of the corresponding enol ether **3.86** (*vide supra*), and this can be reasoned based on the increased 1,3-allylic strain between the phenyl group and the *N*-tosyl group. Although both of the π-allyl intermediates (**4.41** and **4.42**) should experience some degree of steric strain, it appears that the 1,3-allylic strain between the phenyl and *N*-tosyl groups in **4.42** is more significant. Therefore, the reaction proceeds with β-hydride elimination from the σ-allyl complex **4.43** (*Scheme 4.11*).



Scheme 4.11

No in-depth optimisation of the reaction was performed, although the reaction was repeated without boric acid additive, and with $Pd(PPh_3)_4$ as catalyst. The absence of boric acid predictably led to the

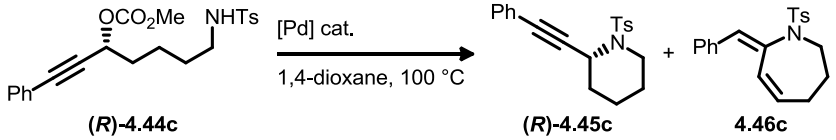
[†] See Appendix for 1D nOe spectra of **4.37c**

formation of more byproduct (*Table 4.1*); however, unlike the related oxygen cyclisation the reaction with $Pd(PPh_3)_4$ proceeded in the absence of an additive, and afforded an identical ratio of **(*R*)-4.36c** to **4.37c**, albeit with reduced enantioselectivity.

Entry	[Pd] cat.	Temp.	Time	Product Ratio ((*R*)-4.36c : 4.37c)[a]	Yield	% *ee*[b] (*R*)-4.36c
1	$Pd(OAc)_2$ / dppf (5 / 10 mol%)	100 °C	5 min	3 : 1	59% (combined)	96
2	$Pd(PPh_3)_4$ (5 mol%)	100 °C	10 min	3 : 1	85% (combined)	89

Table 4.1: [a] Measured by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] Measured by chiral HPLC.

To examine the formation of piperidines the homologous substrate **(*R*)-4.44c** was synthesised and subjected to the reaction conditions. This time, however, the presence of boric acid served to inhibit the reaction (*Scheme 4.12*, *Table 4.2*). In the absence of additive reactivity was restored, although surprisingly on kinetic grounds, the undesired enamide **4.46c** was observed in higher proportions than **4.37c**. Unfortunately, **(*R*)-4.45c** and **4.46c** proved to be inseparable by silica gel chromatography. The formation of piperidine **(*R*)-4.45c** was especially pleasing given the outcome observed by Tanaka and co-workers when employing a similar substrate, where only enamide was observed (*vide supra*).[204]



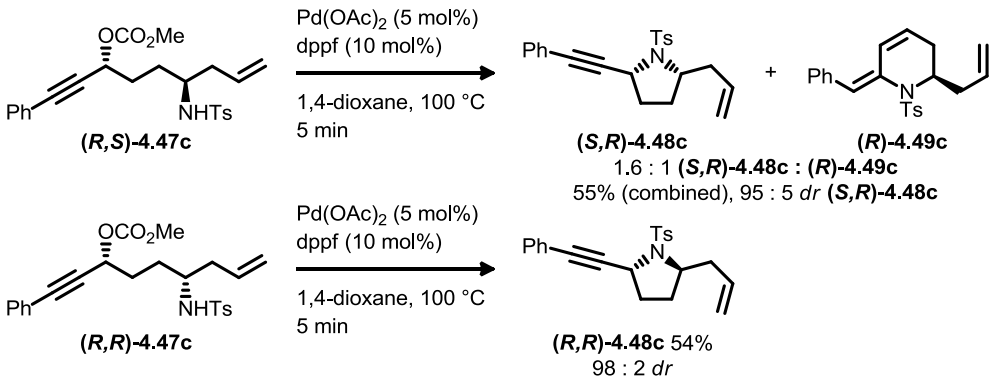
(*R*)-4.44c (*R*)-4.45c 4.46c

Scheme 4.12

Entry	[Pd] cat.	Additive	Time	Product Ratio ((*R*)-4.45c : 4.46c)[a]	Yield	% *ee*[b] (*R*)-4.45c
1	$Pd(OAc)_2$ / dppf (5 / 10 mol%)	$B(OH)_3$ (0.5 eq.)	60 min	No Reaction	-	-
2	$Pd(OAc)_2$ / dppf (5 / 10 mol%)	-	5 min	2 : 1	50% (combined)	98
3	$Pd(PPh_3)_4$ (5 mol%)	-	10 min	1 : 1	34% (combined)	84

Table 4.2: [a] Measured by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] Measured by chiral HPLC.

With the success in forming piperidine **(*R*)-4.45c**, the formation of 2,5-disubstituted piperidines was investigated as a conclusion to the project. To this end, the diastereomeric acyclic carbonates **(*R,S*)-4.47c** and **(*R,R*)-4.47c** were synthesised and submitted to the reaction conditions (*Scheme 4.13*). The cyclisation of **(*R,S*)-4.47c** gave a mixture of the desired pyrrolidine **(*S,R*)-4.48c** and enamide **(*R*)-4.49c**, although **(*S,R*)-4.48c** formed with excellent diastereoselectivity. Surprisingly, however, the cyclisation of the diastereomeric carbonate **(*R,R*)-4.47c** led to *exclusive* formation of the desired pyrrolidine **(*R,R*)-4.48c** with excellent diastereoselectivity.



Scheme 4.13

The relative configurations of pyrrolidines **(*S*,*R*)-4.48c** and **(*R*,*R*)-4.48c** could not be confirmed through 1D nOe spectroscopy, as neither diastereomer showed an enhancement between H2 and H5. However, both were crystalline and suitable crystals for X-ray diffraction were grown, allowing their unambiguous assignment as *cis* and *trans* respectively (*Figure 4.4*). The crystal of **(*R*,*R*)-4.48c** contained two conformations in equal proportions, and both are shown overlaid.

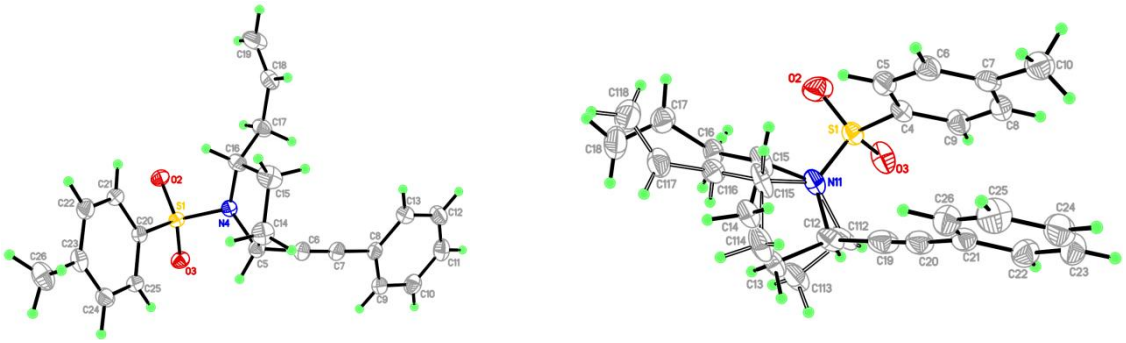
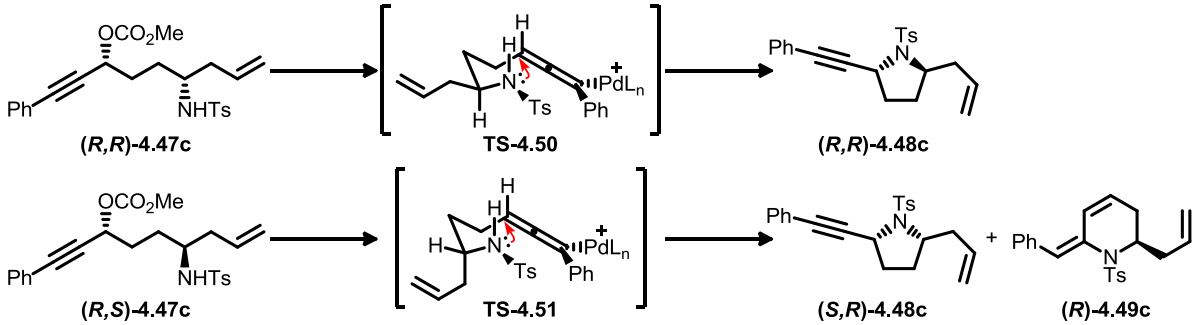


Figure 4.4: X-ray crystal structures of **(*S*,*R*)-4.48c** and **(*R*,*R*)-4.48c**

It was proposed that the difference in reaction outcome between **(*R*,*S*)-4.47c** and **(*R*,*R*)-4.47c** was due to the preferred conformations for cyclisation. As depicted in *Scheme 4.14*, the conformation for the cyclisation of **(*R*,*R*)-4.47c** (**TS-4.50**) places the allyl group *pseudo*-equatorial, whereas the conformation for cyclisation of **(*R*,*S*)-4.47c** (**TS-4.51**) places this group *pseudo*-axial.



Scheme 4.14

Therefore, **TS-4.50** is lower in energy compared to **TS-4.51** as it avoids significant 1,3-diaxial

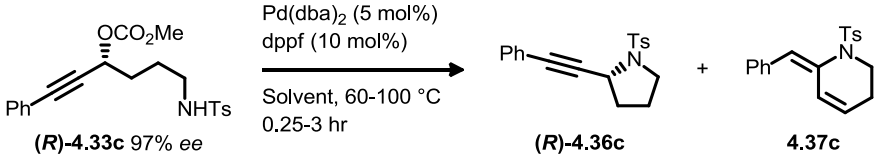
interactions, and the reaction proceeds exclusively *via* this pathway. However, **TS-4.51** is higher in energy because of these significant 1,3-diaxial interactions, and allows competing enamide formation. These initial investigations had shown that propargylic substitution with a nitrogen nucleophile was possible, and given us a good grounding from which to further develop the methodology.

4.4 Further Optimisation Studies

With the basic reactivity of these substrates having been examined,[205] we set about a systematic attempt to improve this reaction and eliminate the enamide byproduct.

4.4.1 Reaction Optimisation: Solvent, Ligand and Additive

Firstly, we conducted an examination of the reaction solvent, ligand and additives to try and improve the selectivity of the reaction, beginning with the solvent. We considered the usual range of solvent types, namely apolar, polar aprotic and polar protic, with the requirement that they be high boiling (>80 °C). This was to ensure that any failure to react in a particular solvent was not owing to an inability to achieve sufficient reaction temperature. The results are set out in *Table 4.3*, and we used $Pd(dba)_2$ as the source of Pd(0) as dba is separable from both **(*R*)-4.36c** and **4.37c** by silica gel chromatography. Carbonate **(*R*)-4.33c** was readily available, having been synthesised previously.[†]



Scheme 4.15

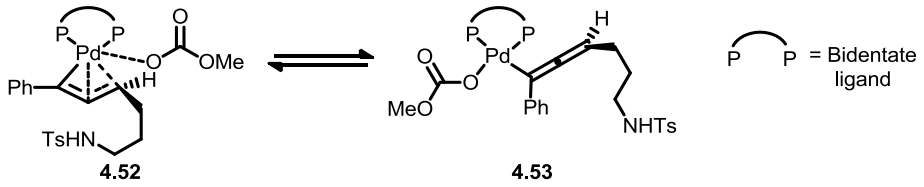
Entry	Solvent	Temp (°C)	Time (hr)	Product Ratio ((*R*)-4.33c : (*R*)-4.36c : 4.37c)[a]	Yield (*R*)-4.36c	*ee*[b] (*R*)-4.36c
1	1,4-dioxane	100	0.25	0 : 71 : 29	63	96
2	toluene	100	0.25	0 : 71 : 29	65	95
3	DMF	100	1	100 : 0 : 0	NR[c]	NR[c]
4	chlorobenzene	100	0.25	0 : 70 : 30	n.d.[d]	95
5	butan-1-ol	100	0.25	0 : 71 : 29	n.d.[d]	94
6	$MeNO_2$	100	1	40 : 50 : 10	n.d.[d]	n.d.[d]
7	DME	85	0.25	0 : 70 : 30	n.d.[d]	95
8	DCE	85	0.25	0 : 60 : 40	n.d.[d]	95
9	toluene	80	0.25	0 : 71 : 29	n.d.[d]	95
10	toluene	60	0.25	0 : 71 : 29	48	95
11	toluene	RT	3	33 : 44 : 23	n.d.[d]	95

Table 4.3: [a] Measured by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] Measured by chiral HPLC; [c] No Reaction; [d] Not determined.

[†] Synthesised by Alison Jones, see Appendix for details

These results showed that the reaction solvent made practically no difference to the outcome of the reaction. From apolar (e.g. toluene, *Entry 2*), polar aprotic (e.g. 1,4-dioxane, DME, DCE, *Entries 1, 7 and 8*) to polar protic (e.g. butan-1-ol, *Entry 5*) there was no significant change in either the ratio of products formed or the enantioselectivity of **(*R*)-4.36c**. The only anomalous results were with DMF (*Entry 3*), in which no reaction took place, and $MeNO_2$ (*Entry 6*), in which the reaction was sluggish. We believe that the active catalyst did not form properly in these solvents. Toluene appeared to give the cleanest reaction, by inspection of the ^{1}H NMR spectra of the crude reaction mixtures, and we examined the effect of temperature on this solvent. The temperature could be reduced to 60 °C without affecting the reaction (*Entry 10*); the challenging separation of **(*R*)-4.36c** and **4.37c** is the underlying reason for the moderate yield in this case. At RT (*Entry 11*), however, the reaction was very sluggish and appeared to be forming more of the undesired enamide **4.37c** (trending to 66 : 34 **(*R*)-4.36c : 4.37c** at 100% conversion).

These results suggest that neither of the intermediates that lead to the formation of **(*R*)-4.36c** or **4.37c** are charged, as there is no difference in the outcome of the reaction on changing the ability to solvate charged intermediates. Therefore, the key equilibrium between these two species is unaffected by a change in solvent. This supports our earlier proposition that the key equilibrium may be between the carbonate bound η^3-allenylpalladium species **4.52** and the η^1-allenylpalladium species **4.53** (*Scheme 4.16*).

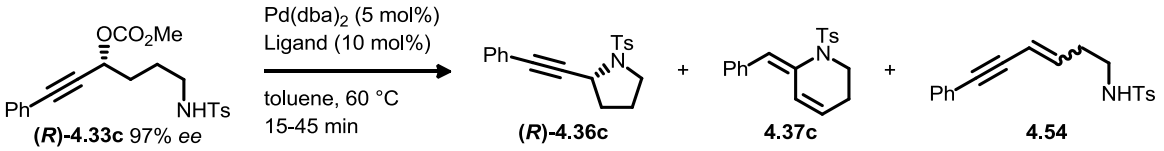


4.52 **4.53**

Scheme 4.16

We had seen with the related oxygen cyclisations that changing the ligand had had the greatest effect on the outcome of the reaction. To this end we conducted a screen of bidentate ligands to try and improve the selectivity (*Scheme 4.17*), and these results are set out in *Table 4.4*. Once again we observed a significant effect on the selectivity of the reaction by changing the ligand. Dppm required elevated temperature to promote any reactivity (*Entries 2 and 3*). As the length of the alkyl tether between the phosphines was increased, from dppe (*Entry 4*) to dpppe (*Entry 7*), the proportion of **(*R*)-4.36c** increased greatly. This was in line with our observations with the related oxygen

cyclisations; however, in this case we observed excellent enantioselectivity with all of these ligands.



Scheme 4.17

Entry	Ligand	Time (min)	Product Ratio ((*R*)-4.33c : (*R*)-4.36c : 4.54)[a]	% Yield (*R*)-4.36c	% *ee*[b] (*R*)-4.36c	Ligand Bite Angle (°)[c]
1	dppf	15	0 : 71 : 29	48	95	99
2	dppm	15	100 : 0 : 0	NR[d]	NR[d]	72
3	dppm[e]	60	0 : 40 : 60	n.d.[f]	93	72
4	**dppe**	**30**	**11 : 17 : 72**	**60[g]**	**95**	**85**
5	dppp	15	0 : 32 : 68	n.d.[f]	95	91
6	dppb	15	0 : 48 : 52	n.d.[f]	96	98
7	dpppe	30	0 : 69 : 31	n.d.[f]	95	-
8	dpph	30	47 : 27 : 26	n.d.[f]	96	-
9	**DPEphos**	**45**	**0 : 89 : 11**	**78**	**94**	**102**
10	Xantphos	30	0 : 80 : 8[h]	n.d.[f]	91	111
11	(*R*)-BINAP	45	85 : 7 : 8	n.d.[f]	90	92
12	(*S*)-BINAP	45	77 : 15 : 8	n.d.[f]	97	92
13	(*R*)-Phox[i]	15	65 : 19 : 16	n.d.[f]	97	89
14	(*S*)-Phox[i]	15	72 : 16 : 12	n.d.[f]	97	89
15	DavePhos[i]	15	0 : 45 : 5[h]	n.d.[f]	94	-
16	dppep[i]	30	15 : 37 : 48	n.d.[f]	94	-

Table 4.4: [a] Measured by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] Measured by chiral HPLC; [c] Taken from literature;[163, 206] [d] No Reaction; [e] Conducted at 100 °C; [f] Not determined; [g] Yield of enamide **4.37c**; [h] Remainder enyne **4.54**; [i] See *Figure 4.5*.

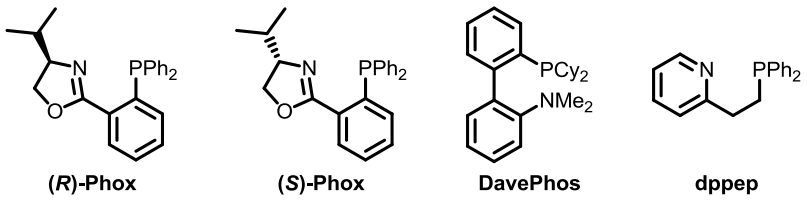
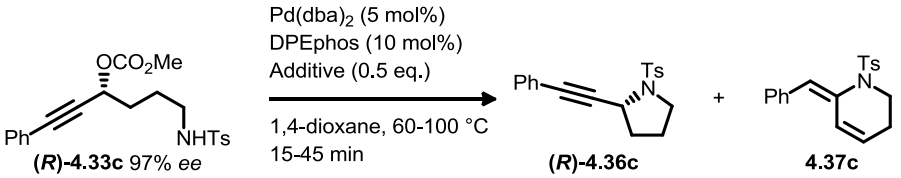


Figure 4.5

Increasing the tether still further, to dpph (*Entry 8*), resulted in reduced reactivity and selectivity, and this is perhaps due to the propensity of dpph to act as a bridging monodentate ligand rather than a bidentate ligand.[207] We considered again that the bite angle of the ligand was key to the observed selectivity, and hoped to improve the ratio further by employing ligands with even larger bite angles. Therefore, we tested DPEphos and Xantphos, ligands with bite angles of 102° and 111° respectively (*Entries 9 and 10*).[163] This led to a great improvement, both achieving *ca*. 9 : 1 selectivity in favour of **(*R*)-4.36c**, although to the detriment of enantioselectivity. The use of Xantphos also led to the formation of small amounts of enyne **4.54**, which was tentatively identified by comparison to enynes formed previously. Next, we tested both hands of BINAP, to negate any possible effects from kinetic

resolution as we were employing an enantiopure starting material (*Entries 11 and 12*). We did observe a difference in both reaction selectivity and enantioselectivity with these ligands, although overall reactivity was very poor for both. Finally, we tested a variety of *P*,*N*-ligands (*Entries 13-16*), although we were ultimately unsuccessful in improving the reaction further. Only DavePhos (*Entry 15*) gave promising results that were comparable to DPEphos, although enyne **4.54** was formed in significant amounts. In summary, from the investigation of the ligand we found that DPEphos (*Entry 9*) gave the best overall results, with **(*R*)-4.36c** being isolated in high yield and enantioselectivity.

Finally, we decided to examine additives to the reaction in the hope of rendering the reaction both regio- and stereoselective (*Scheme 4.18*, *Table 4.5*). Surprisingly however, adding a catalytic amount of boric acid to the reaction in toluene made no difference to the outcome (*Entry 1*). On repeating the same conditions in 1,4-dioxane we were delighted to observe that the enamide byproduct was eliminated, although disappointingly, the enantioselectivity was reduced (*Entry 2*). This is perhaps due to the ability of a polar solvent (1,4-dioxane) to better solvate the boric acid than apolar toluene.



Scheme 4.18

Entry[a]	Additive	Temp (°C)	Time (min)	Product Ratio ((*R*)-4.33c : (*R*)-4.36c : 4.37c)[b]	Yield (*R*)-4.36c	*ee*[c] (*R*)-4.37c
1[d]	$B(OH)_3$	100	15	0 : 89 : 11	n.d.[e]	95
2	$B(OH)_3$	100	15	0 : 100 : 0	82	88
3[d]	none	60	45	0 : 89 : 11	78	94
4	none	60	45	0 : 88 : 12	77	97
5	$B(OH)_3$	80	15	0 : 100 : 0	86	90
6	$B(OMe)_3$	80	15	0 : 100 : 0	83	92
7	$B(O\textit{i}\text{-Pr})_3$	80	15	0 : 89 : 11	n.d.[e]	97
8	$B(OMe)_3$	60	30	30 : 70 : 0	88[f]	96
9[g]	$B(OMe)_3$	60	180	0 : 100 : 0	83	55

Table 4.5: [a] All reactions (bar *Entry 9*) conducted on 10 mg **(*R*)-4.33c** [b] Measured by ^{1}H NMR spectroscopy of the crude reaction mixture; [c] Measured by chiral HPLC; [d] In toluene; [e] Not determined; [f] Based on recovered **(*R*)-4.33c**; [g] Conducted on 40 mg **(*R*)-4.33c**.

Therefore, we decided to return to our original solvent, and found there was a small, but significant, effect on the enantioselectivity between toluene and 1,4-dioxane in the absence of additive (*Entries 3 and 4*). We began examining different boron-based additives alongside the reaction temperature, and found that whilst boric acid and trimethylborate could both suppress the formation of **4.37c** (*Entries 5*

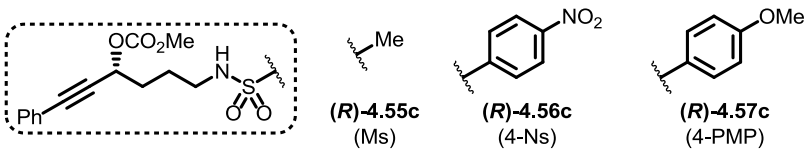
and 6), triisopropylborate failed entirely (*Entry 7*). Interestingly, it produced a result identical to that found when performing the reaction in the absence of additive, suggesting it did not interfere with the reaction at all. Trimethylborate returned **(*R*)-4.36c** with higher enantioselectivity than boric acid, so we examined this additive at still lower reaction temperatures. Reaction at 60 °C was sluggish, although on a test scale returned **(*R*)-4.36c** with excellent enantioselectivity (*Entry 8*). However, on running the reaction to completion on a larger scale, we observed a significant reduction in enantioselectivity (*Entry 9*), although **(*R*)-4.36c** was formed exclusively. We appeared to be observing an interplay between overall reactivity, which decreased significantly as the reaction temperature was lowered, and enantioselectivity, which improved. However, we could not strike a reproducible balance between these effects.

The capricious effect of additives on the enantioselectivity of the reaction led us to run all further reactions in their absence, as we preferred high stereoselectivity over regioselectivity. A thorough screen of a wide range of other non-boron based additives was not performed due to both time and material constraints.

4.4.2 Nature of the Sulfonamide Nucleophile

With the failure to render this reaction selective through modification of the reaction conditions, we looked at varying the sulfonamide group attached to nitrogen. We wondered whether the electronic nature of the sulfonamide group was crucial to the selectivity of the reaction, or more fundamentally, the success of the reaction itself.

To this end we synthesised three further carbonates **(*R*)-4.55c**-**4.57c**, containing a variety of sulfonamide groups (*Figure 4.6*). As an aside, we also attempted the synthesis of the trifluoromethane-substituted sulfonamide ($-CF_3$), although this substrate could not easily be obtained.

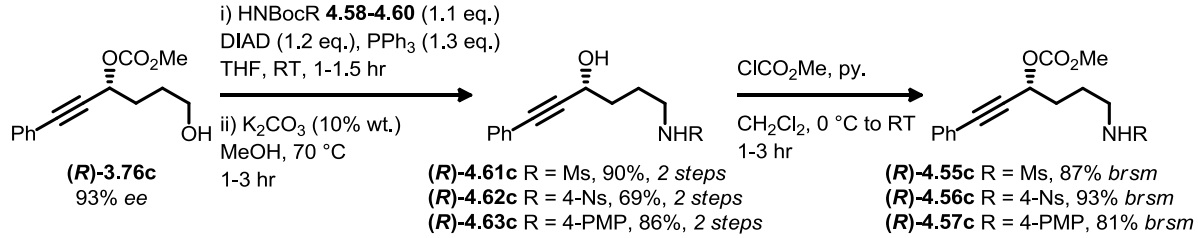


(*R*)-4.55c (Ms) **(*R*)-4.56c** (4-Ns) **(*R*)-4.57c** (4-PMP)

Figure 4.6

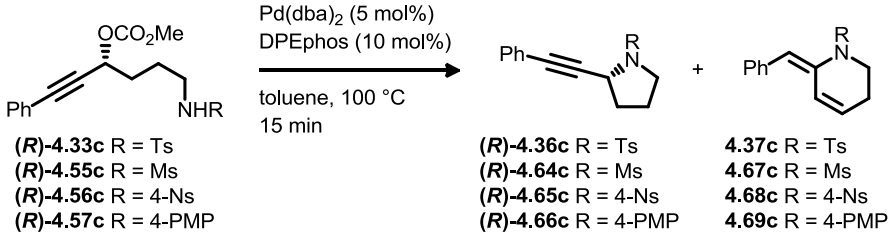
These substrates were synthesised from carbonate **(*R*)-3.76c** using a three-step sequence: Mitsonobu reaction[208] with the Boc-sulfonamides **4.58**-**4.60**, global deprotection with K_2CO_3[106] and finally reformation of the propargylic carbonate (*Scheme 4.19*). The requisite Boc-sulfonamides (**4.58**-**4.60**)

were formed according to a literature procedure.[209] This route was considered the most efficient as we had a large stock of enantioenriched **(*R*)-3.76c**, and it delivered sulfonamides **(*R*)-4.55c-4.57c** in high yield.



Scheme 4.19

With these carbonates in hand we submitted them to the cyclisation conditions in toluene (*Scheme 4.20*, *Table 4.6*). All of these sulfonamides reacted successfully to afford a mixture of pyrrolidine and enamide, suggesting that modification of the sulfonamide does not affect overall reactivity. The enantiomeric excess of the pyrrolidine products **(*R*)-4.64c-4.66c** was not measured as the corresponding racemates were not synthesised.



Scheme 4.20

Entry	Carbonate	R	Product Ratio (pyrrolidine : enamide)[a]	Yield (pyrrolidine)
1	**(*R*)-4.33c** (97% *ee*)	Ts	89 : 11	78[b]
2	**(*R*)-4.55c** (93% *ee*)	Ms	87 : 13	72
3	**(*R*)-4.56c** (93% *ee*)	4-Ns	74 : 26	55
4	**(*R*)-4.57c** (93% *ee*)	4-PMP	86 : 14	73

Table 4.6: [a] Measured by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] 94% *ee* as measured by chiral HPLC

There was little variation in the amount of enamide byproduct formed when employing relatively electron-neutral (*Entries 1 and 2*) and electron-donating sulfonamide substituents (*Entry 4*). However, the electron-withdrawing *N*-4-nosyl carbonate **(*R*)-4.56c** afforded significantly more enamide **4.68c** (*Entry 3*). Although unable to improve the selectivity of the reaction by employing different sulfonamide groups, we had been somewhat fortunate to select the *N*-tosyl group in the first instance.

4.5 Mechanistic Considerations

Comparing our phenyl substituted carbonates **(*R*)-3.76c** and **(*R*)-4.33c**, the cyclisation of the oxygen-containing substrate **(*R*)-3.76c** with dppf gave 83 : 17 in favour of THF **(*R*)-2.61c** over enol ether **3.86**, whereas the analogous nitrogen-containing substrate **(*R*)-4.33c** gave 71 : 29 in favour of pyrrolidine **(*R*)-4.36c** over enamide **4.37c**. The central allene carbon may have a larger LUMO coefficient than the proximal carbon in the η^3-allenylpalladium intermediate, as suggested by the usual reaction outcome of this species with nucleophiles, which attack at the central carbon.[67, 112] Nitrogen is softer and more diffuse than oxygen by virtue of its lower atomic number, so the overlap between the HOMO of nitrogen with the LUMO of the central carbon is likely better matched than the equivalent interaction with oxygen.

Another possibility for this difference is the presence of the tosyl protecting group on nitrogen which increases the steric bulk of the nucleophile. This may interfere with the cyclisation to form the alkynyl azacycles (**TS-4.70**) more than the cyclisation to form enamides (**TS-4.71**), as the necessity of placing the tosyl group *pseudo*-equatorial places it in close proximity to the substituent on the η^1-allenylpalladium in **TS-4.70** (*Figure 4.7*).

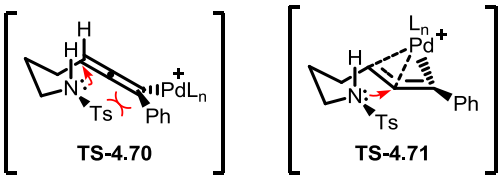


Figure 4.7

Although boric acid or trimethylborate appear to suppress the formation of enamide entirely, their presence also suppresses any reaction below 60 °C and greatly affects the stereochemical outcome of the reaction. It is not clear at this time why either the reactivity or stereoselectivity suffers in the presence of additives, although the reduced stereoselectivity suggests that formation of the η^1-propargylpalladium intermediate is promoted with additives. Of note is the failure of triisopropylborate to have any effect on the reaction, perhaps because of the increased steric bulk of the isopropyl groups preventing co-ordination of nitrogen to boron.

4.6 Further Substrates

4.6.1 Monosubstituted Azacycles

With somewhat improved conditions for this reaction we examined the cyclisation of a range of

further substrates. Firstly, we examined the alkyne substituent in pyrrolidine formation, targeting the unsubstituted, alkyl- and TMS-substituted propargylic carbonates **(*S*)-4.33a, b** and **d** (*Figure 4.8*).

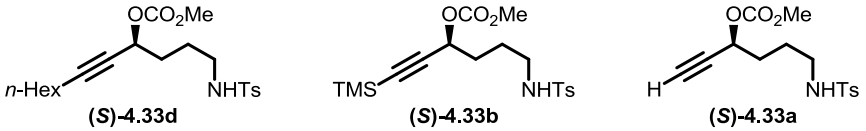
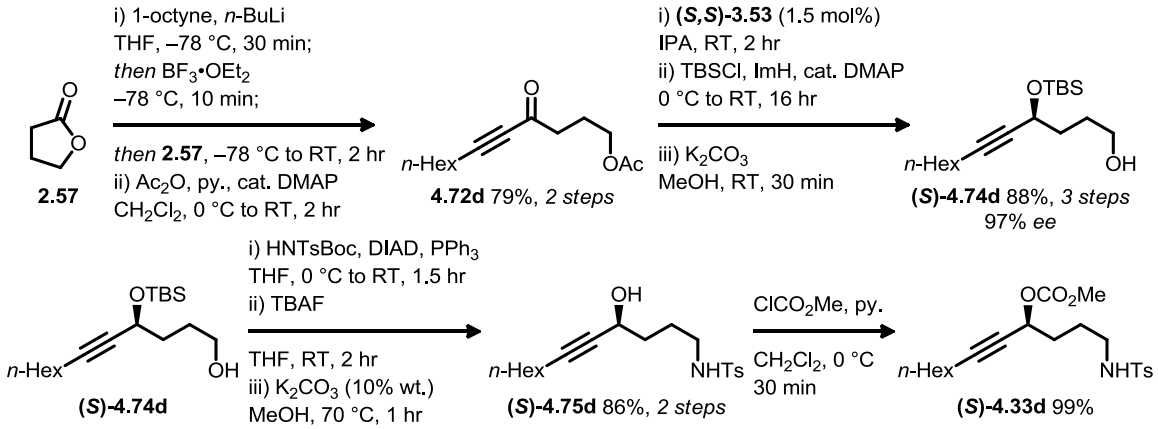


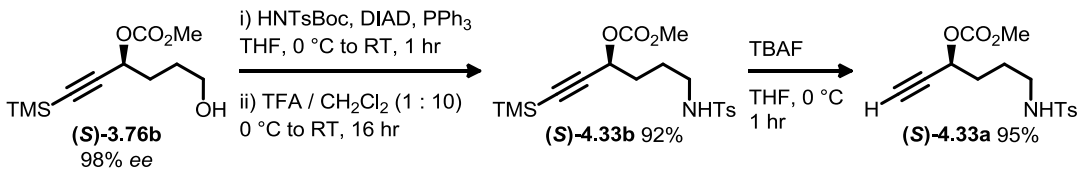
Figure 4.8

Alkyl substituted **(*S*)-4.33d** was synthesised in nine steps from γ-butyrolactone **2.57** (*Scheme 4.21*). Formation of ynone-acetate **4.72d** proceeded smoothly, and was followed by Noyori reduction with **(*S,S*)-3.53** which afforded alcohol **(*S*)-4.73d** in excellent enantioselectivity. Protecting group manipulations afforded primary alcohol **(*S*)-4.74d**, which was submitted to Mitsonobu conditions to install the sulfonamide. Further deprotection of the TBS-ether and Boc-carbamate afforded amido-alcohol **(*S*)-4.75d**, which was converted into carbonate **(*S*)-4.33d** in excellent yield.



Scheme 4.21

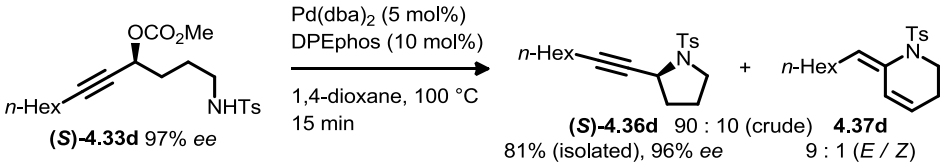
The TMS-substituted and terminal carbonates **(*S*)-4.33b** and **a** were synthesised from carbonate **(*S*)-3.76b** in two and three steps respectively (*Scheme 4.22*). Mitsonobu reaction and deprotection, this time using TFA,[106] afforded TMS substituted carbonate **(*S*)-4.33b** in excellent yield. Deprotection of the silyl-alkyne using TBAF afforded terminal propargylic carbonate **(*S*)-4.33a**.



Scheme 4.22

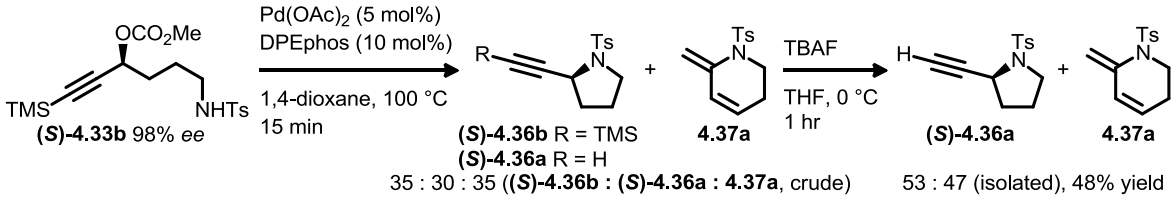
With these carbonates in hand we submitted them to our preferred cyclisation conditions. Alkyl-substituted carbonate **(*S*)-4.33d** reacted to yield a similar ratio of pyrrolidine **(*S*)-4.36d** and enamide **4.37d** products to phenyl-substituted carbonate **(*R*)-4.33c** (*Scheme 4.23*). A small amount of the

(*Z*)-isomer of enamide **4.37d** was present in the crude reaction mixture.



Scheme 4.23

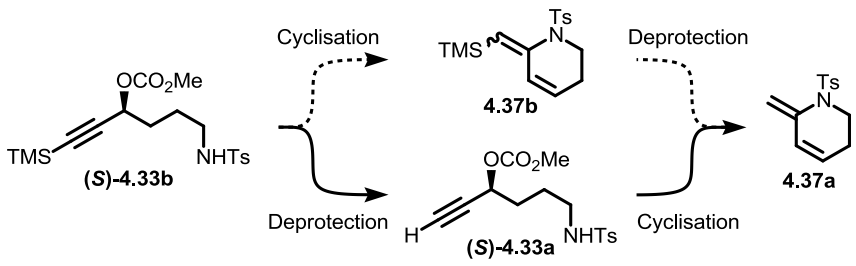
Unlike the oxygen analogue **(*S*)-3.76b**, TMS-substituted carbonate **(*S*)-4.33b** reacted successfully to form an inseparable mixture of terminal and TMS-alkynyl pyrrolidines **(*S*)-4.36a** and **b**, and enamide **4.37a** (*Scheme 4.24*); enamide furnished with a TMS group was not observed in the crude ^{1}H NMR spectrum. $Pd(OAc)_2$ was used as the pre-catalyst as these products proved inseparable from dba. To aid characterisation of these compounds the crude mixture was exposed TBAF, affording a mixture of **(*S*)-4.36a** and **4.37a** in moderate yield.



Scheme 4.24

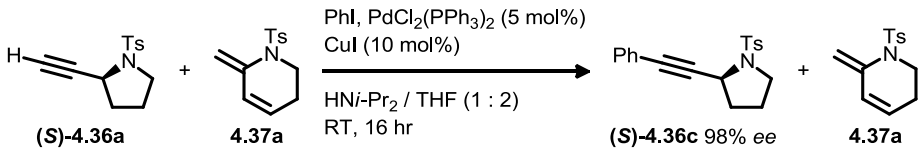
It appeared that some of the pyrrolidine **(*S*)-4.36a** had been lost on reaction with TBAF, as evidenced by both the change in observed ratio of products and by the low isolated yield. We considered this to be either due to instability of this compound towards silica gel, or unexpected volatility.

To the best of our knowledge there are no reported deprotections of enamide vinylsilanes (e.g. **4.37b**), so it is difficult to predict whether enamide **4.37a** arises from the complete deprotection of **4.37b** under the reaction conditions (which seems unlikely), or from central carbon attack on the η^3-allenylpalladium intermediate formed from deprotected starting material **(*S*)-4.33a** (*Scheme 4.25*).



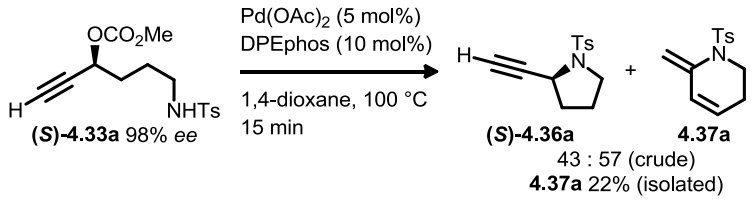
Scheme 4.25

Formation of the phenyl-substituted pyrrolidine **(*S*)-4.36c** under Sonogashira conditions allowed measurement of the enantiomeric excess of through chiral HPLC analysis (*Scheme 4.26*). This showed that complete retention of stereochemistry had been observed with this substrate.



Scheme 4.26

Similarly, terminal propargylic carbonate **(*S*)-4.33a** reacted to form a mixture of pyrrolidine **(*S*)-4.36a** and enamide **4.37a**, with **4.37a** the major component (*Scheme 4.27*). However, when this mixture was subjected to purification by silica gel chromatography only enamide **4.37a** was isolated in low yield. This suggested that pyrrolidine **(*S*)-4.36a** was indeed unstable to silica gel purification.

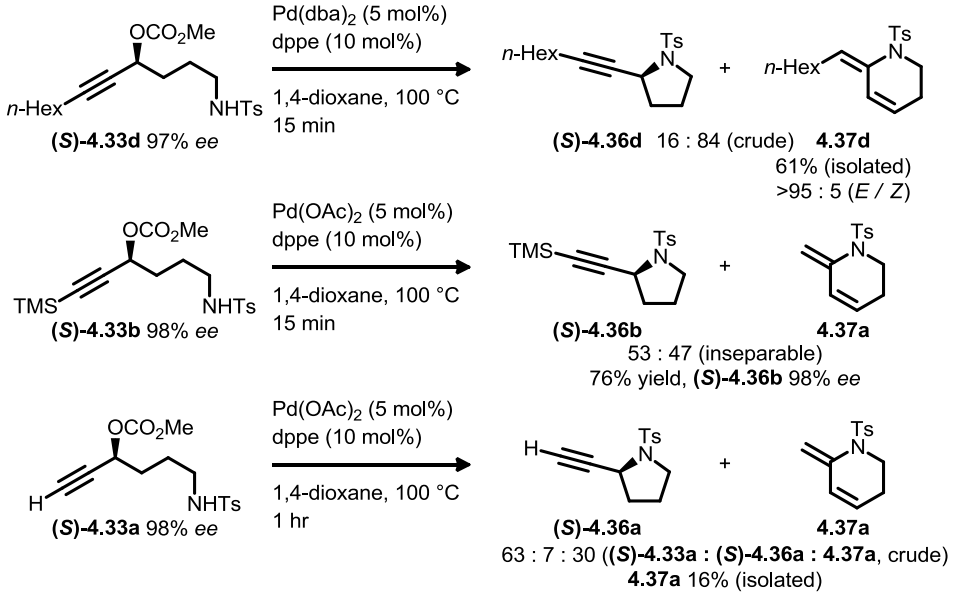


Scheme 4.27

It appears that the sulfonamide is a better nucleophile in this system than the hydroxyl group, as evidenced by the successful reaction of both the terminal and TMS-substituted carbonates **(*S*)-4.36a** and **b**, as their oxygen analogues failed to generate any desired product under these conditions (*vide supra*). However, although the cyclisation of the alkyl-substituted carbonate **(*S*)-4.33d** was highly selective, we were disappointed by the poor selectivity observed with **(*S*)-4.33a** and **b**.

We had observed high selectivity for the formation of enamide **4.37c** when employing dppe as the ligand (*Table 4.4, Entry 4*), and we considered an extension to the methodology by testing the ability of these substrates to form enamides selectivity. This would hopefully allow the synthesis of two diverse skeletons from a single substrate by a simple ligand switch.

Therefore, we subjected our pyrrolidine substrates to reaction with dppe as ligand in the hope of forming enamides selectively (*Scheme 4.28*). Alkyl-substituted carbonate **(*S*)-4.33d** reacted cleanly to form enamide **4.37d** as the major product, with **4.37d** isolated in good yield. The stereoselectivity of **4.37d** was better than that formed with DPEphos (*vide supra*), with only a trace of the (*Z*)-isomer observed by ^{1}H NMR spectroscopy.



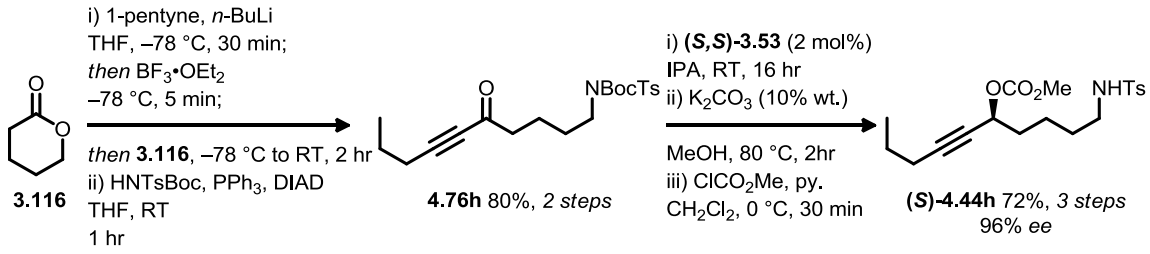
Scheme 4.28

When TMS-containing carbonate **(*S*)-4.33b** was reacted under these conditions a mixture of pyrrolidine and enamide was again observed, although surprisingly on this occasion, none of the terminal pyrrolidine **(*S*)-4.36a** was present in the crude reaction mixture by ^{1}H NMR spectroscopy. The reaction was poorly selective, affording a *ca.* 1 : 1 mixture of pyrrolidine and enamide, although the pyrrolidine was formed with high enantioselectivity. The enantiomeric excess of **(*S*)-4.36b** was measured in an identical fashion to that above, first through removal of the silyl group with TBAF and subsequent Sonogashira coupling to form **(*S*)-4.36c**, which was analysed by chiral HPLC. One possible explanation for the absence of terminal pyrrolidine **(*S*)-4.36a** in this reaction is that any deprotection occurs prior to reaction, and the deprotected starting material reacts solely to produce enamide **4.37a**. However, the result from the reaction of terminal carbonate **(*S*)-4.33a** suggests that this is not the case, as the reaction was very sluggish and afforded a mixture of pyrrolidine **(*S*)-4.36a** and **4.37a**. The reason for this poor reactivity with dppe as the ligand is not clear at this time.

We next looked at the formation of piperidines, employing the phenyl- and alkyl-substituted (**h**) propargylic carbonates **(*R*)-4.44c** and **(*S*)-4.44h**.[205] Carbonate **(*R*)-4.44c** was readily available having been synthesised previously,[†] and **(*S*)-4.44h** was obtained in five steps from δ-valerolactone **3.116** (*Scheme 4.29*). We improved the efficiency of the synthesis by reducing the need for protecting groups; performing the Mitsonobu reaction on the ynone formed from **3.116** negated the requirement for differentiation of the two hydroxy groups at a later stage (as in the synthesis of **(*S*)-4.33d**, *vide*

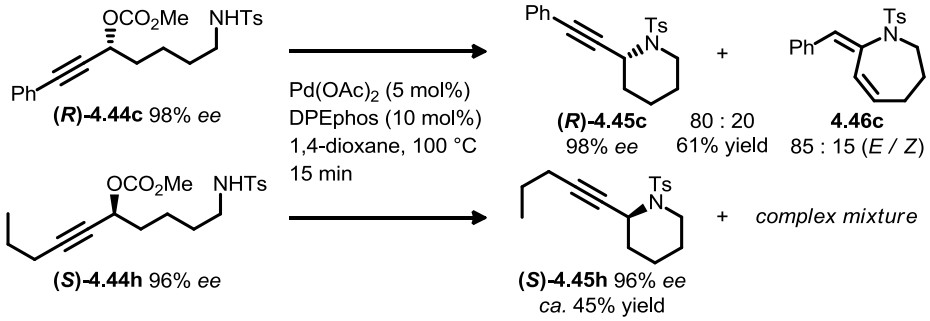
[†] Synthesised by Alison Jones, see Appendix for details

supra).



Scheme 4.29

These carbonates were submitted to the cyclisation conditions, employing both DPEphos (*Scheme 4.30*) and dppe (*Scheme 4.31*) as ligands. DPEphos greatly improved the ratio of products from **(*R*)-4.44c** compared to dppf (*vide supra*),[205] forming piperidine **(*R*)-4.45c** and enamide **4.46c** as an inseparable 4 : 1 mixture in good yield. Whilst piperidine **(*R*)-4.45c** was formed with excellent enantioselectivity, enamide **4.46c** was isolated as a mixture of isomers.



Scheme 4.30

Alkyl-substituted carbonate **(*S*)-4.44h** led to a complex mixture of products from which was isolated a mixture of piperidine **(*S*)-4.45h** and at least four other compounds. We assume these other compounds to be double-bond isomers of the expected enamides (**4.46h**, **4.77h** and **4.78h**, *Figure 4.9*), although firm assignment of these compounds was not possible because of the complexity of the NMR spectra. Based on this assumption and integration of the ^{1}H NMR spectrum, piperidine **(*S*)-4.45h** made up *ca.* 60% of the material isolated, corresponding to *ca.* 45% yield of **(*S*)-4.45h**. It is not clear why compounds other than the expected piperidine and enamide **(*S*)-4.45h** and **4.46h** are formed, as we were expecting a similar outcome to the reaction as with the hexyl-substituted carbonate **(*S*)-4.33d** (*vide supra*).

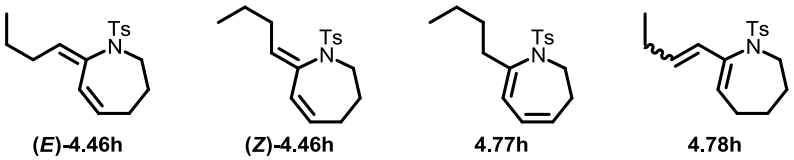
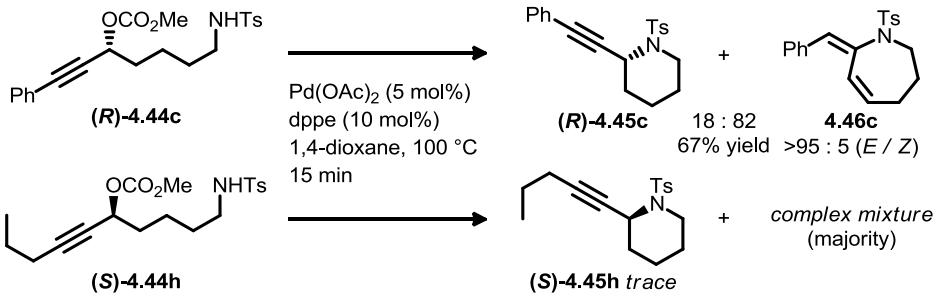


Figure 4.9

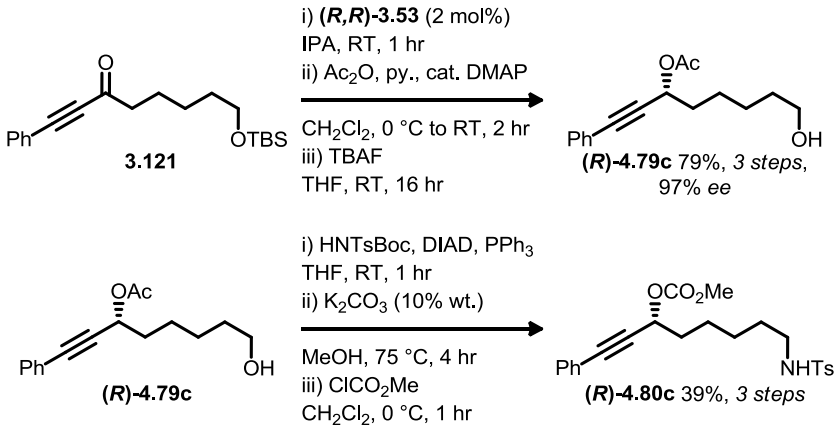
When **(*R*)-4.44c** and **(*S*)-4.44h** were submitted to reaction with dppe as ligand, the expected reversal in selectivity was observed (*Scheme 4.31*). Enamide **4.46c** was the major component of the reaction of **(*R*)-4.44c**, and was formed in excellent stereoselectivity.



Scheme 4.31

The reaction of alkyl-substituted carbonate **(*S*)-4.44h** again resulted in a complex mixture of products from which was isolated the same major compounds from the reaction with DPEphos above. However, piperidine **(*S*)-4.45h** was now present in only trace amounts, along with at least three other compounds which made up the majority of the sample.

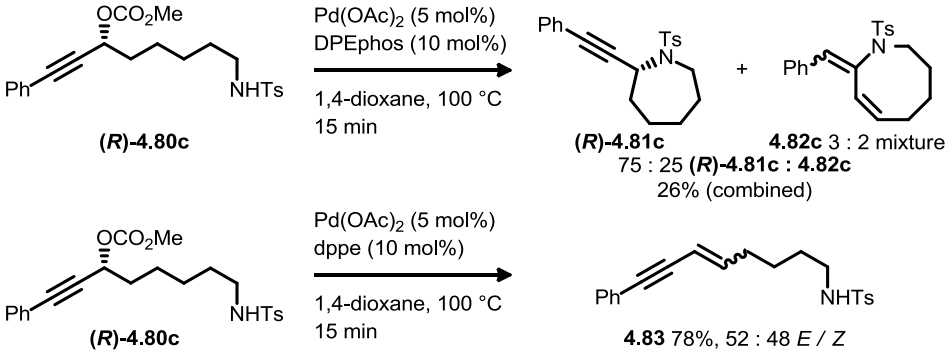
We decided to attempt the formation of a 7-membered azepane ring, synthesising the requisite substrate **(*R*)-4.80c** in six steps from **3.121** (*Scheme 4.32*)



Scheme 4.32

With carbonate **(*R*)-4.80c** in hand, we submitted it to the reaction with both DPEphos and dppe (*Scheme 4.33*). Although the reaction with DPEphos went to completion, it was very messy and produced a complex mixture of products. Only a small amount of a mixture of compounds was isolated from this, and these were tentatively assigned as azepane **(*R*)-4.81c** and enamide **4.82c**. We were very surprised by the formation of enamide **4.82c**, given the enthalpic and entropic barriers to formation of 8-membered rings. Enamide **4.82c** was isolated as a mixture of geometrical isomers, although the major isomer was not elucidated, and the enantiomeric purity of **(*R*)-4.81c** was not

measured as the corresponding racemate was not synthesised.

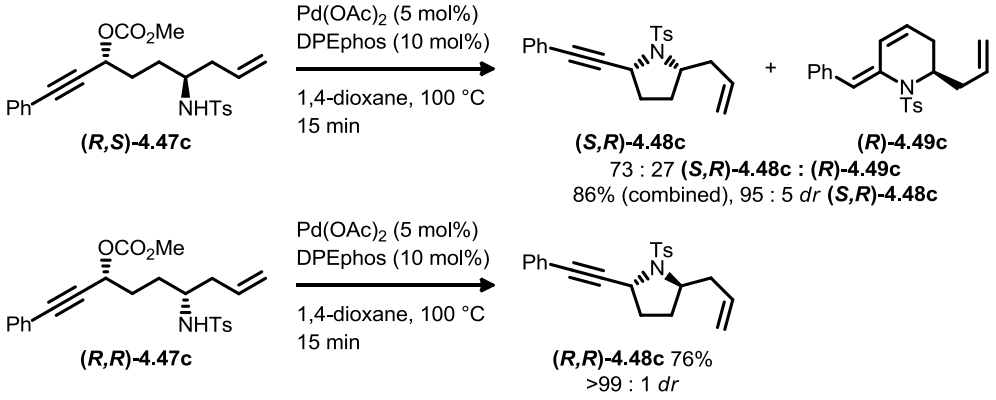


Scheme 4.33

Surprisingly, with dppe the reaction formed only enyne **4.83** in high yield. This was unexpected given the formation of enamide **4.82c** with DPEphos, and the reason for this is not clear at this time.

4.6.2 Disubstituted Azacycles

We re-examined the synthesis of the disubstituted pyrrolidines **(*S,R*)-4.48c** and **(*R,R*)-4.48c** using DPEphos, hoping to improve the selectivity for **(*S,R*)-4.48c** (*Scheme 4.34*); substrates **(*R,S*)-4.47c** and **(*R,R*)-4.47c** were readily available.[†]



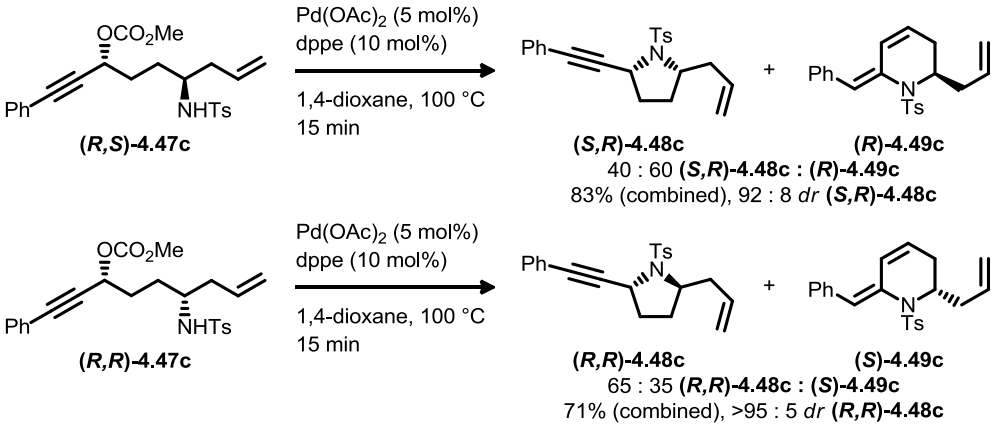
Scheme 4.34

Although we observed some improvement in both selectivity and yield with carbonate **(*R,S*)-4.47c** (*vs. ca.* 62 : 38 with dppf, 55% yield),[205] significant amounts of enamide **(*R*)-4.49c** was still present in the reaction. As expected with carbonate **(*R,R*)-4.47c**, pyrrolidine **(*R,R*)-4.48c** was the only product isolated from the reaction mixture and was isolated in excellent stereoselectivity and yield.

We considered that reaction of carbonate **(*R,S*)-4.47c** with dppe may result in selective formation of enamide **(*R*)-4.49c**, as the combination of the unfavourable transition state for formation of **(*S,R*)-4.48c** and the previously observed effect of the ligand would be expected to reinforce one

[†] Synthesised by Alison Jones, see Appendix for details

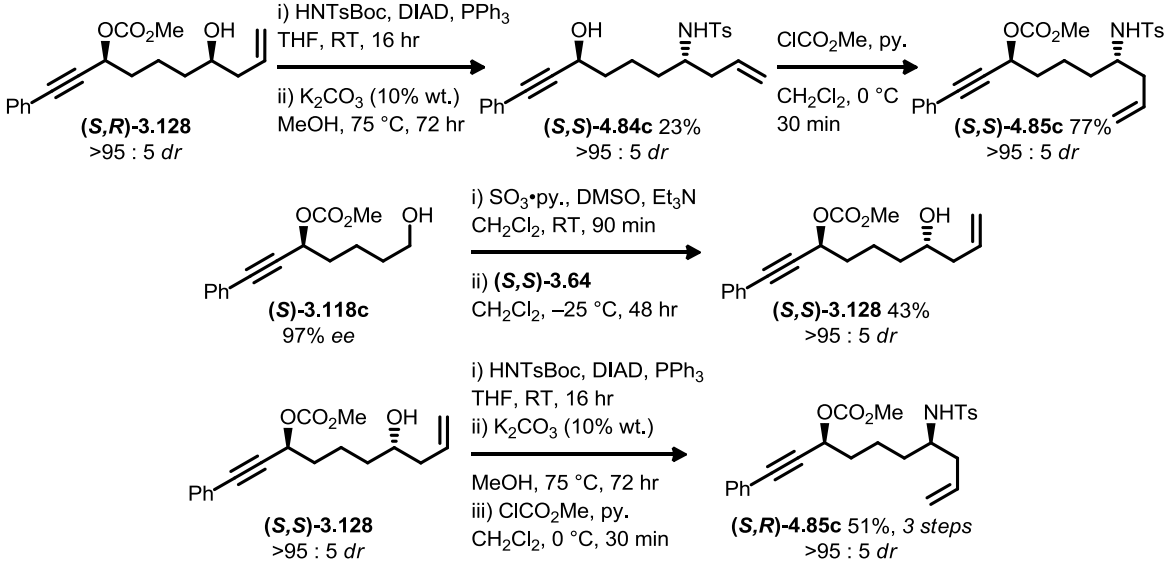
another (*Scheme 4.35*).



Scheme 4.35

However, the reaction was only marginally selective for the formation of enamide **(*R*)-4.49c**. This was unexpected given the ratio of products observed with monosubstituted carbonates **(*R*)-4.33c** and **(*S*)-4.33d** under these conditions (*ca.* 80 : 20 in favour of enamide). The reaction of carbonate **(*R,R*)-4.47c** under these conditions followed a similar trend, with pyrrolidine **(*R,R*)-4.48c** remaining the major product of the reaction. This suggests that with a substituent on the tether, and with appropriate stereochemistry, formation of the pyrrolidine is much more favourable, perhaps due to a Thorpe-Ingold effect accelerating the cyclisation.[166]

Finally, we investigated the cyclisation of the homologous disubstituted carbonates **(*S,S*)-4.85c** and **(*S,R*)-4.85c**. We had a stock of carbonate **(*S,R*)-3.128** in hand, and this was converted to **(*S,S*)-4.85c** in three steps (*Scheme 4.36*).

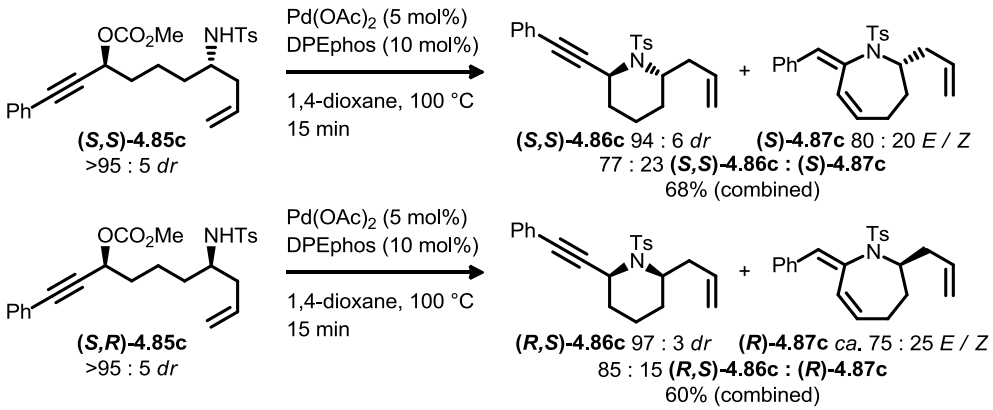


Scheme 4.36

This proved more challenging than expected, as the Mitsonobu reaction was poorly yielding and the

deprotection of the Boc-carbamate was unexpectedly sluggish. However, enough carbonate **(*S*,*S*)-4.85c** could be synthesised to test the cyclisation reaction with both ligands. The diastereomer **(*S*,*R*)-4.85c** was synthesised through a similar route, this time starting from carbonate **(*S*)-3.118c**. The Mitsonobu reaction was again poorly yielding, although significantly more of this carbonate **(*S*,*R*)-4.85c** was synthesised.

With these carbonates in hand we submitted them to reaction with DPEphos, expecting to observe a difference in the outcome of the reaction for each diastereomer (*Scheme 4.37*). On this occasion, enamide **4.87c** was observed in both reactions, although the selectivity for piperidine was greater for carbonate **(*S*,*R*)-4.85c**. Both **(*S*,*S*)-4.86c** and **(*R*,*S*)-4.86c** were formed in excellent diastereoselectivity, although as with the monosubstituted piperidines (*vide supra*), we were unable to separate them from the enamide byproducts.



Scheme 4.37

The improved selectivity for piperidine in the reaction of carbonate **(*S*,*R*)-4.85c** can be explained by considering the preferred conformations for cyclisation to form **4.86c** (*Figure 4.10*). The allyl group is *pseudo*-axial in **TS-4.88** (from carbonate **(*S*,*S*)-4.85c**), and so suffers from significant 1,3-diaxial interactions in the conformation required for the formation of piperidine **(*S*,*S*)-4.86c**. However, with **TS-4.89** the allyl group is placed *pseudo*-equatorial, thus making this conformation more favourable. It is clear from the observed ratios that this effect is not as significant as for the pyrrolidines **(*R*,*R*)-4.48c** and **(*S*,*R*)-4.48c** (*vide supra*), as it results in only an 8% difference in the outcome.

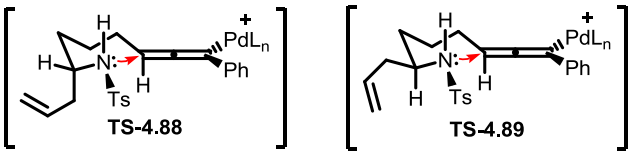
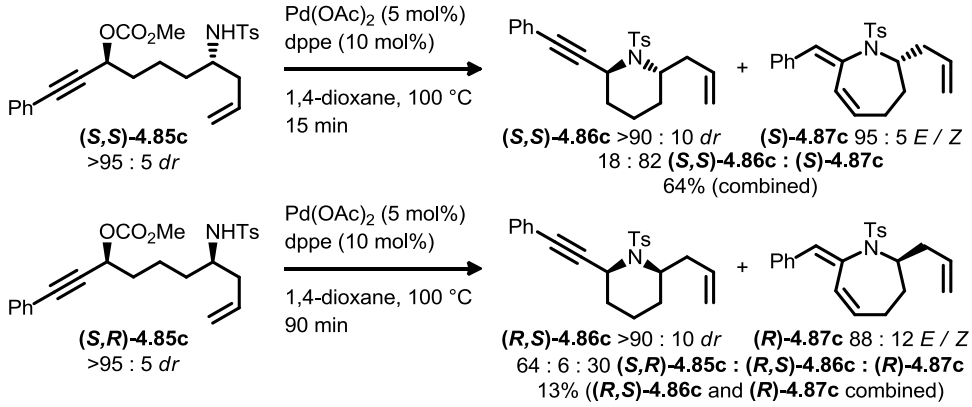


Figure 4.10

When the reactions were repeated with dppe as ligand, enamide **4.87c** became the major component of both reactions (*Scheme 4.38*). The reaction of carbonate **(*S,S*)-4.85c** went to completion, affording a good isolated yield of products, enamide **(*S*)-4.87c** being formed with excellent stereoselectivity. However, the reaction of **(*S,R*)-4.85c** was sluggish, with only *ca.* 35% conversion after 90 minutes. Only a small amount of the desired products was isolated, in a similar ratio to that formed from **(*S,S*)-4.85c**. The reason for the poor reactivity of **(*S,R*)-4.85c** under these conditions is not clear at this time.

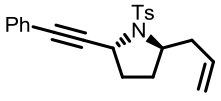


Scheme 4.38

4.7 Conclusions and Future Work

In conclusion, we have been partially successful in rendering the reaction selective for the formation of 2-alkynyl azacycles over their corresponding enamides. We examined many reaction variables, including the solvent, ligand, additive and the nature of the nucleophile; finding that some improvement could be made over the original conditions[205] by employing DPEphos as ligand. Also, whilst we found that additives could render the reaction selective for the alkynyl product, reaction in their presence was capricious and led to products formed with varying levels of enantioselectivity.

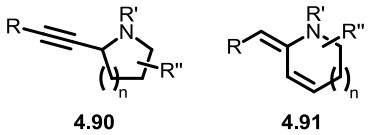
For this reason we submitted all further substrates to reaction without additive to ensure, at the very least, high enantioselectivity. This allowed the synthesis of a range of mono- and disubstituted pyrrolidines and piperidines with good to excellent selectivity over the corresponding enamides. Pleasingly, disubstituted pyrrolidine **(*R,R*)-4.48c** was formed with complete selectivity under these conditions (*Figure 4.11*).



(*R,R*)-4.48c

Figure 4.11

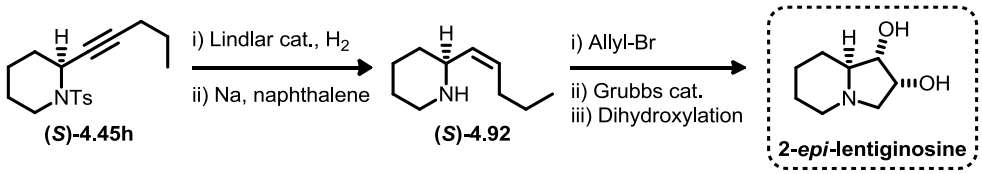
These substrates were also exposed to reaction with dppe as ligand, as we had observed high selectivity for the enamide product with this ligand. This allowed the formation of enamide as the major product in all but one reaction, that of disubstituted carbonate **(*R*,*R*)-4.48c**. With this simple ligand switch we were able to generate two diverse product skeletons (either **4.90** or **4.91**, *Figure 4.12*) from a single substrate, demonstrating the potential utility of this methodology.



Scheme 4.12

Future investigations should centre on the additive, conducting a more in depth screen of different types other than just the boron-based examples explored in this study. Another possibility for the isolation of pure 2-alkynyl azacycles is through selective removal of the enamide byproduct. For example, the enamide could potentially be hydrolysed under acidic conditions.

We had hoped to utilise piperidine **(*S*)-4.45h** to complete a synthesis of the natural product 2-*epi*-lentiginosine,[210-211] perhaps using the route outlined in *Scheme 4.39*. Reduction and removal of the *N*-tosyl protecting group[196] would afford **(*S*)-4.92**. Allylation of the amine affords a diene system suitable for ring closing metathesis,[212] with final dihydroxylation[91] giving the natural product. However, owing to time pressure no further studies were performed in this regard.



Scheme 4.39

Other potential targets that could be considered include the structurally similar swainsonine,[197] (−)-coniceine[213] and (+)-tylophorine (*Figure 4.13*).[214]

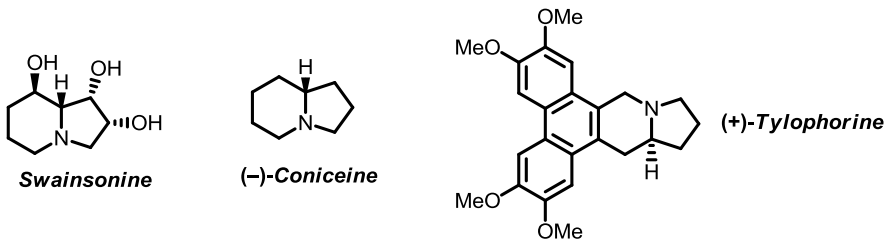


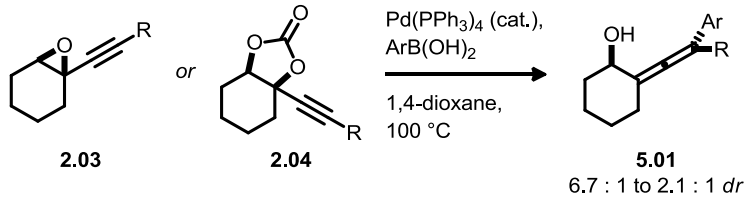
Figure 4.13

Chapter 5. General Conclusions and Future Work

5.1 General Conclusions

In conclusion, we have examined some aspects of allenylpalladium chemistry, which has led to the development of novel methodology for the stereoselective synthesis of saturated 2-alkynyl heterocycles.

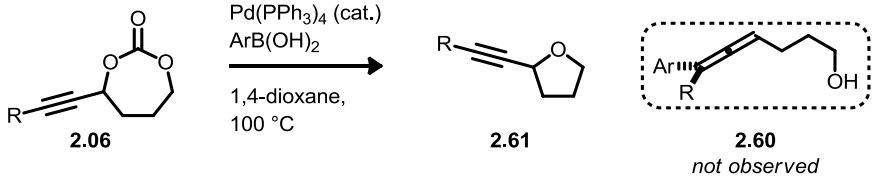
This work commenced with an examination of the cross-coupling of a range of propargylic electrophiles with boronic acids to form allenes. With the diastereomerically pure epoxides and carbonates **2.03** and **2.04** we observed loss of stereochemistry in the formation of allene products **5.01** (*Scheme 5.1*).



Scheme 5.1

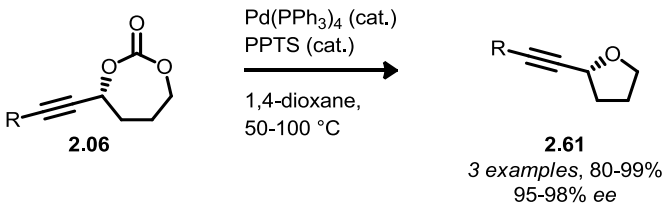
Investigations were conducted into this poor stereochemical transfer, and it was found that the allene product itself was being epimerised, not an intermediate of the reaction. Our investigations suggested two possible pathways for this epimerisation: one rapid process mediated by the Pd(II) intermediate of the reaction itself, and the other a background process mediated by Pd(0).

Within the electrophiles tested under allene-forming conditions were the 7-membered cyclic carbonates **2.06**, which led to the serendipitous discovery of a cyclisation to form THFs **2.61** instead of the expected β-allenyl alcohols **2.60** (*Scheme 5.2*).



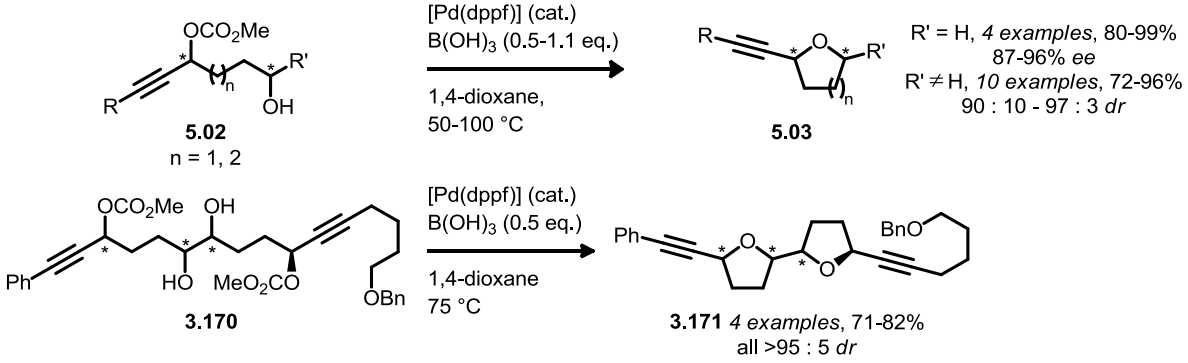
Scheme 5.2

Further investigations of this reaction allowed, with some optimisation, stereoselective formation of the 2-alkynyl THFs. This facilitated elucidation of the overall stereochemical outcome of the reaction, and we achieved the formation of a range of monosubstituted THFs with excellent enantioselectivity (*Scheme 5.3*).



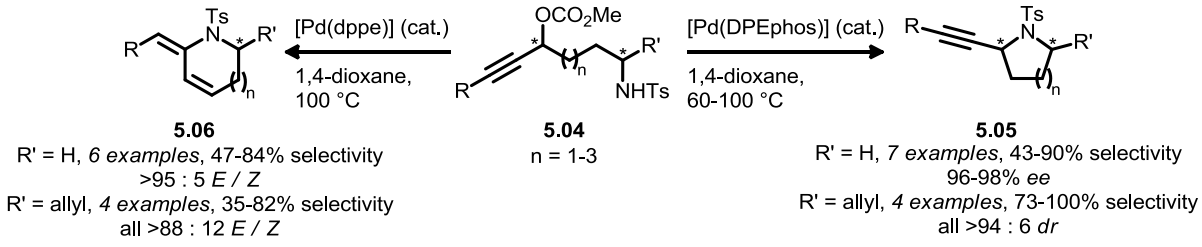
Scheme 5.3

However, poor results with disubstituted THFs and the likely restriction to the formation of 5-membered rings with these cyclic carbonates led us to examine acyclic carbonates as electrophiles. This proved to be the most fruitful extension of the methodology, and after subtle changes to the catalytic system used in the cyclisation reaction, a wide range of mono- and disubstituted THFs and THPs were synthesised with excellent stereoselectivity (*Scheme 5.4*). The acyclic carbonates also allowed us to easily examine the effect that both ring size and additional substituents had on the outcome of the reaction, allowing the reliable prediction of the products that would be formed. As a final demonstration of the power of this methodology, four diastereomers of a bifuran motif were synthesised through a double cyclisation, with complete control of all four stereocentres.



Scheme 5.4

Finally, the formation of azacycles was examined, building upon the foundation work conducted by a Part II student within the group.[205] Although we were only partially successful in achieving complete selectivity for the desired 2-alkynyl azacycles (**5.05**), significant improvements to this reaction were made (*Scheme 5.5*). The selective formation of the cyclic enamide skeleton (**5.06**) was also examined by switching the ligand, and moderate to high selectivity for these products was achieved.



Scheme 5.5

5.2 Future Work

With the basic methodology having been developed over the course of this project, the stage is now set for the further examination of this reaction. There is an almost unending list of possible electrophiles and nucleophiles that could be studied in this reaction, to form a wide range of different hetero- and carbocyclic products. A few examples of possible substrates are given in *Figure 5.1*. This is, of course, in addition to the natural products that could be synthesised using this methodology (*vide supra*).

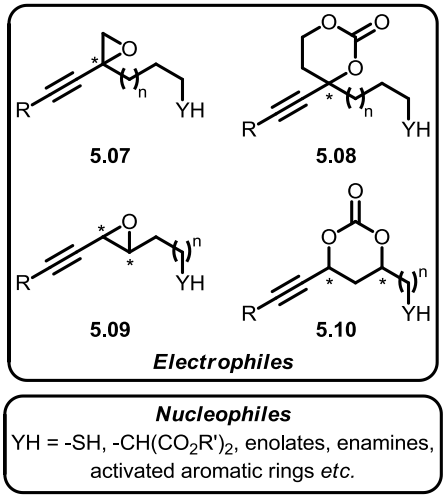
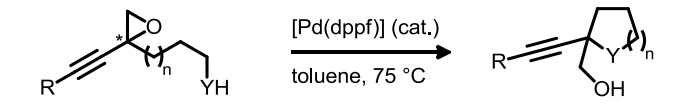


Figure 5.1

Some of these have already begun to be studied; a Part II student found that 1,1-epoxides **5.07** formed the expected THFs, THPs and pyrrolidines with excellent stereochemical transfer (*Scheme 5.6*).[215] Current projects within the group are continuing in this regard.



5.07
R = Ph, *n*-hexyl, Y = O, NTs
n = 1-2, 47-49% *ee*

5.13
5 examples, 56-96%
44-49% *ee*

Scheme 5.6

Chapter 6. Experimental

6.1 General Remarks

Materials: All reagents, obtained from Acros, Apollo, Sigma-Aldrich, Fluka, Lancaster, Strem and Fluorochem fine chemical suppliers were used directly as supplied or purified by the methods described by Armarego and Chai.[216] Et_3N and pyridine were stored over KOH. Non-aqueous reactions using anhydrous solvents (distilled from CaH_2 or obtained from a solvent purification system) were performed in oven or flame dried apparatus under argon or nitrogen atmosphere. The solvents used for the cross-coupling and cyclisation reactions were used directly from the Winchester without pre-drying or purification. Where applicable, solvents were degassed by sparging with dry argon gas for 15-30 minutes. Petroleum Ether (pet. ether) refers to the fraction with boiling point 40-60 °C.

Techniques: Reactions were monitored by GC/MS or by thin layer chromatography (TLC) on pre-coated aluminium-backed plates (Merck Kieselgel 60 with fluorescent indicator UV_{254}). Spots were visualised either by quenching of UV fluorescence or by staining with potassium permanganate, anisaldehyde, vannilin or ninhydrin dips. Flash column chromatography was performed according to the method described by Still, Khan and Mitra[217] with silica gel 60 (0.040-0.063 mm) (VWR) applying head pressure by means of nitrogen.

NMR spectra: ^1H NMR spectra were recorded using an internal deuterium lock for the residual protons in $CDCl_3$ (δ_H 7.27 ppm), C_6D_6 (δ_H 7.15 ppm), MeOH-d_4 (δ_H 3.31 ppm), tol-d_8 (δ_H 2.08 ppm) and acetone-d_6 (δ_H 2.05 ppm) at ambient probe temperatures on the following instruments: Bruker AV400 (400 MHz), Bruker AMX500 (500 MHz), Bruker DPX200 (200 MHz) or Bruker DPX250 (250 MHz). Data is presented as follows: chemical shift, peak multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, *apt* = apparent), coupling constants and interpretations (Ar refers to aromatic peaks). Chemical shifts are expressed in ppm on a δ scale relative to δ_{TMS} (0 ppm) and coupling constants, *J*, are rounded to the nearest 0.5 Hz. Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, 2D NMR experiments (COSY, HSQC, HMBC), or by analogy to fully interpreted spectra for structurally related compounds.

^{13}C NMR spectra were recorded using an internal deuterium lock using solvents $CDCl_3$ (δ_C 77.0 ppm),

C_6D_6 (δ_C 128.1 ppm), MeOH-d_4 (δ_C 49.0 ppm) and acetone-d_6 (δ_C 206.3 ppm) at ambient probe temperatures on the following instruments: DPX250 (63 MHz), Bruker AV400 (100 MHz) or Bruker AMX500 (125 MHz).

^{19}F NMR spetra were recorded on a Bruker AVANCE AV400 (377 MHz) using CCl_3F as the external reference.

^{11}B NMR spectra were recorded on a Bruker AVANCE DPX250 (80 MHz) using $BF_3{\cdot}OEt_2$ as the external reference.

Infra-red spectra: Recorded on a Bruker Tensor 27 FT-IR spectrometer with the sample being prepared as a thin film between NaCl plates, or using a PIKE-Miracle Diamond/ZnSe ATR module.

Mass spectra: Accurate mass (HRMS) data was determined under conditions of ESI on a Bruker MicrOTOF (resolution = 5000 FWHM) using tetraoctylammonium bromide as a lock-mass in positive ion mode, or under conditions of FI or CI on a Micromass GCT (resolution = 7000 FWHM) using isoamyl acetate as a lock-mass.

Melting points were obtained using a Reichert-Koffler block and are uncorrected.

Optical rotations were obtained on a Perkin-Elmer 341 polarimeter using a 1 dm path length cell. The concentration (*c*) is expressed in g/100 cm^3 (equivalent to g/0.1 dm^3). Specific rotations are denoted as $[\alpha]_D^T$ and are given in units of $°dm^2g^{-1}$ (T = temp °C).

GC/MS was performed on a Micromass GCT system consisting of a reflectron TOF mass spectrometer operated in CI+ mode and an Agilent GC 6890 system fitted with a ZB.5 15 m long column.

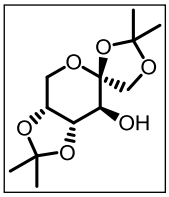
HPLC was carried out on an Agilent 1200 series running in normal phase under UV (210-254 nm) detection using a ZORBAX RX-SIL (5 μm, 150 mm x 4.6 mm ID) as the analytical column. Chiral analysis was carried out using a DAICEL CHIRALPAK-IA, IB or IC (5 μm, 250 mm x 4.6 mm ID).

Elemental Analysis was carried out externally by the Science Centre, London Metropolitan University.

Section 6.2 contains the synthesis of all bulk reagents and catalysts that were used on multiple occasions throughout the work. *Section 6.3* contains all other compounds in the order in which they appear in the text.

6.2 Synthesis of Bulk Reagents and Catalysts

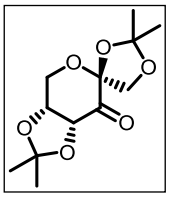
1,2:4,5-di-*O*-isopropylidene-*β*-D-fructopyranose – 2.25a[87]



To a stirred suspension of D-fructose (10.0 g, 55.6 mmol, 1 eq.) in acetone (200 mL) was added conc. H_2SO_4 (1.0 mL, 33 mol%). The reaction mixture was stirred until the solid had completely dissolved (2 hours). The mixture was cooled to 0 °C and a solution of NaOH (3.12 g) in water (28 mL) was added. The acetone was removed *in vacuo* and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed sequentially with water (1 x 50 mL), brine (1 x 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was recrystallised from Et_2O/hexane to leave pure protected sugar **2.25a** (6.40 g, 24.6 mmol, 44%) as white needles.

m.p. 118 °C (lit.[87] 117.5-118 °C); $[\alpha]_D^{25}$ −139.5 (*c* = 1.0, $CHCl_3$), [lit.[86] −144.2 (*c* = 1.0, $CHCl_3$)]; $\mathbf{R_f}$ 0.12 (1:1 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.22 (1H, ddd, *J* = 6.0, 2.5 and 0.5 Hz), 4.19 (1H, d, *J* = 9.0 Hz), 4.15-4.11 (2H, m), 4.04-4.00 (1H, m), 3.99 (1H, d, *J* = 9.0 Hz), 3.67 (1H, dd, *J* = 8.5 and 7.0 Hz), 1.95 (1H, d, *J* = 8.5 Hz, O*H*), 1.54 (3H, s, *Me*), 1.52 (3H, s, *Me*), 1.45 (3H, s, *Me*), 1.38 (3H, s, *Me*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 111.8, 109.4, 104.5, 77.3, 73.3, 72.3, 70.4, 60.7, 27.9, 26.4, 26.2, 25.9. Data consistent with literature.[87]

1,2:4,5-di-*O*-isopropylidene-D-erythro-2,3-hexodiuro-2,6-pyranose – 2.18[86]

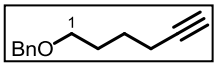


To a stirred solution of protected sugar **2.25a** (2.14 g, 8.22 mmol, 1 eq.) and Ac_2O (2.56 mL, 27.13 mmol, 3.3 eq.) in anhydrous CH_2Cl_2 (20 mL) was added PDC (1.86 g, 4.93 mmol, 0.6 eq.). The reaction was heated to reflux for 2.5 hours, allowed to cool and the solvent removed *in vacuo.* The reaction mixture was passed through a layered pad of silica gel with Celite® on top (EtOAc eluent). The solvent was removed *in vacuo* and the residue azeotroped with toluene (3 x 10 mL) to leave pure keto-sugar **2.18** (1.95 g, 7.55 mmol, 92%) as a white solid.

m.p. 101-102 °C (lit.[218] 101-102.5 °C); $\mathbf{R_f}$ 0.33 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ −121.2 (*c* = 1.0, $CHCl_3$),

[lit.[86] −125.4 (*c* = 1.0, $CHCl_3$)]; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.74 (1H, d, *J* = 5.5 Hz), 4.62 (1H, d, *J* = 9.5 Hz), 4.55 (1H, ddd, *J* = 9.5, 2.0 and 1.0 Hz), 4.40 (1H, dd, *J* = 13.5 and 2.0 Hz), 4.13 (1H, d, *J* = 13.5 Hz), 4.00 (1H, d, *J* = 9.5 Hz), 1.56 (3H, s, *Me*), 1.47 (3H, s, *Me*), 1.41 (6H, s, *Me*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 196.9, 113.8, 110.6, 104.1, 77.9, 75.9, 70.0, 60.1, 27.1, 26.5, 26.0, 25.9. Data consistent with literature.[86]

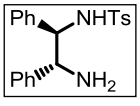
((hex-5-ynyloxy)methyl)benzene – 3.48[219]



A 2-necked flask was charged with NaH (60% in mineral oil, 306 mg, 7.65 mmol, 1.5 eq.) and placed under an argon atmosphere. The NaH was washed with anhydrous pentane (3 x 5 mL) and subsequently suspended in anhydrous THF (5 mL). The stirred solution was cooled to 0 °C and 5-hexyn-1-ol (500 mg, 5.1 mmol, 1 eq.) was added dropwise. The reaction was allowed to warm to RT and stirred for 30 minutes. BnBr (0.58 mL, 4.85 mmol, 0.95 eq.) was added and the reaction stirred for a further 16 hours. The reaction was quenched *via* slow addition of water (5 mL), the layers separated and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:99→1:19 Et_2O/pet. ether) to leave pure alkyne **3.48** (727 mg, 3.86 mmol, 80%) as a colourless oil.

R_f 0.66 (Et_2O/pet. ether 1:9); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.40-7.28 (5H, m, Ph), 4.53 (2H, s, PhC*H*$_2$O), 3.52 (2H, t, *J* = 6.0 Hz, H1), 2.24 (2H, td, *J* = 7.0 and 2.5 Hz, H4), 1.97 (1H, t, *J* = 2.5 Hz, H6), 1.81-1.72 (2H, m, H2), 1.71-1.62 (2H, m, H3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 138.7, 128.5, 127.7, 127.6, 84.4, 73.0, 69.8, 68.5, 28.9, 25.3, 18.3. Data consistent with literature.[219]

N-((1*R*,2*R*)-2-amino-1,2-diphenylethyl)-4-methylbenzenesulfonamide – (*R*,*R*)-3.56[220]

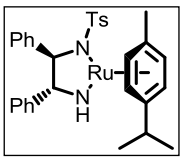


To a stirred solution of (*R*,*R*)-DPEN (100 mg, 0.47 mmol, 1 eq.) and Et_3N (0.19 mL, 1.41 mmol, 3 eq.) in anhydrous THF (5 mL) at 0 °C under argon was added a solution of *p*-tosyl chloride (97 mg, 0.51 mmol, 1.08 eq.) in anhydrous THF (1 mL) *via* syringe pump over 30 minutes. The reaction was left to stir overnight, the solvent was removed *in vacuo* and the residue partitioned between sat. aq. $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine

(10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 EtOAc/pet. ether→EtOAc) to leave pure (*R,R*)-TsDPEN **(*R,R*)-3.56** (143 mg, 0.39 mmol, 83%) as a white solid.

m.p. 128-129 °C (lit.[220] 127-128 °C); $\mathbf{R_f}$ 0.28 (EtOAc); $[\alpha]_D^{25}$ −36.4 (*c* = 0.66, $CHCl_3$) [lit.[221] −36.7 (*c* = 1.0, $CHCl_3$)]; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.32 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.20-7.10 (10H, m, Ph), 6.98 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.05 (1H, bs, N*H*Ts), 4.38 (1H, d, *J* = 5.0 Hz, C*H*NHTs), 4.14 (1H, d, *J* = 5.0 Hz, C*H*NH_2), 2.33 (3H, s, Ts*Me*), 1.44 (2H, bs, NH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 142.6, 141.6, 139.4, 137.3, 129.3, 128.6, 128.4, 127.6, 127.5, 127.1, 127.0, 26.6, 63.3, 60.7, 21.5. Data consistent with literature.[220]

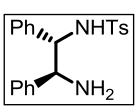
(1*R*,2*R*)-(-)-*N*-tosyl-1,2-diphenylethane-1,2-diamine[η^6-1-isopropyl-4-methylbenzene)-ruthenium(II)] - (*R,R*)-3.53[222]



To a stirred solution of (*R,R*)-TsDPEN **(*R,R*)-3.56** (50 mg, 0.136 mmol, 2 eq.) and $[RuCl_2(p\text{-cymene})]_2$ **3.55** (42 mg, 68 μmol, 1 eq.) in CH_2Cl_2 (1 mL) was added freshly powdered KOH (114 mg, 2.04 mmol, 15 eq.). The resulting solution was stirred for 5 minutes, and to it added distilled water (1.5 mL). The biphasic mixture was stirred until the organic phase turned a deep purple colour. The layers were separated and the organic layer washed with water (1.5 mL). The organic phase was dried over powdered CaH_2 and the solvent removed *in vacuo* to leave [Ru((*R,R*)-TsDPEN)(*p*-cymene)] **(*R,R*)-3.53** (67 mg, 0.112 mmol, 82%) as a fine purple powder.

^{1}H NMR (250 MHz, tol-d_8): δ_H 7.47 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.50-7.00 (10H, m, Ph), 6.66 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.38 (1H, bs, N*H*), 5.17 (1H, d, *J* = 6.0 Hz, *p*-cymene-*H*), 5.05 (1H, d, *J* = 6.0 Hz, *p*-cymene-*H*), 5.01 (1H, d, *J* = 6.0 Hz, *p*-cymene-*H*), 4.89 (1H, d, *J* = 6.0 Hz, *p*-cymene-*H*), 4.69 (1H, s, PhC*H*NTs), 3.87 (1H, d, *J* = 4.5 Hz, PhC*H*NH), 2.38-2.26 (1H, m, C*H*$(CH_3)_2$), 2.01 (3H, s, Ts*Me*), 1.83 (3H, s, *p*-cymene-*Me*), 1.04 (3H, d, *J* = 7.0 Hz, CH(CH_3)), 0.99 (3H, d, *J* = 7.0 Hz, CH(CH_3)). Data consistent with literature.[222]

N-((1*S*,2*S*)-2-amino-1,2-diphenylethyl)-4-methylbenzenesulfonamide - (*S,S*)-3.56[223]

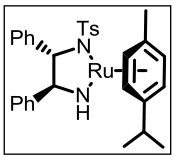


To a stirred solution of (*S,S*)-DPEN (250 mg, 1.18 mmol, 1 eq.) and Et_3N (0.49 mL,

3.54 mmol, 3 eq.) in anhydrous THF (12 mL) at 0 °C under argon was added a solution of *p*-tosyl chloride (242 mg, 1.27 mmol, 1.08 eq.) in anhydrous THF (2 mL) *via* syringe pump over 30 minutes. The reaction was left to stir overnight, the solvent was removed *in vacuo* and the residue partitioned between sat. aq. $NaHCO_3$ (15 mL) and CH_2Cl_2 (15 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 EtOAc/pet. ether→EtOAc) to leave pure (*S*,*S*)-TsDPEN **(*S*,*S*)-3.56** (370 mg, 1.01 mmol, 86%) as a white solid.

m.p. 126-127 °C (lit.[223] 125-126 °C); $\mathbf{R_f}$ 0.28 (EtOAc); $[\alpha]_D^{25}$ +35.4 (*c* = 0.52, $CHCl_3$) [**(*R*,*R*)-3.56** $[\alpha]_D^{25}$ −36.4 (*c* = 0.66, $CHCl_3$)]. All other spectroscopic data identical to **(*R*,*R*)-3.56** prepared previously.

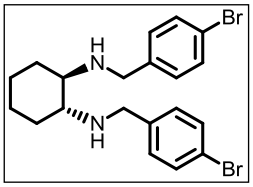
(1*S*,2*S*)-(−)-*N*-tosyl-1,2-diphenylethane-1,2-diamine[η^6-1-isopropyl-4-methylbenzene)-ruthenium(II)] - (*S*,*S*)-3.53[222]



To a stirred solution of (*S*,*S*)-TsDPEN **(*S*,*S*)-3.56** (100 mg, 0.273 mmol, 2 eq.) and [$RuCl_2$(*p*-cymene)]$_2$ **3.55** (84 mg, 0.138 mmol, 1 eq.) in CH_2Cl_2 (2 mL) was added freshly powdered KOH (114 mg, 2.04 mmol, 15 eq.). The resulting solution was stirred for 5 minutes, and to it added distilled water (3 mL). The biphasic mixture was stirred until the organic phase turned a deep purple colour. The layers were separated and the organic layer washed with water (3 mL). The organic phase was dried over powdered CaH_2 and the solvent removed *in vacuo* to leave [Ru((*S*,*S*)-TsDPEN)(*p*-cymene)] **(*S*,*S*)-3.53** (155 mg, 0.258 mmol, 95%) as a fine purple powder.

^{1}H NMR spectrum identical to **(*R*,*R*)-3.53** prepared previously.

(1*R*,2*R*)-*N*,*N'*-bis(4-bromobenzyl)cyclohexane-1,2-diamine - (*R*,*R*)-3.67[150]

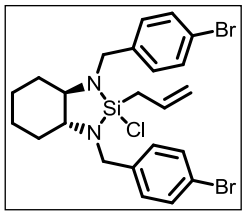


To a stirred suspension of (1*R*,2*R*)-cyclohexane-1,2-diamine·L-tartrate **(*R*,*R*)-3.66** (2.85 g, 10.8 mmol, 1 eq.) in water (50 mL) was added K_2CO_3 (2.99 g, 21.6 mmol, 2 eq.). To this mixture was added EtOH (25 mL) and a solution of 4-bromobenzaldehyde (4.0 g, 21.6 mmol, 2 eq.) and methanesulfonic acid (125 mg, 1.30 mmol, 0.12 eq.) in CH_2Cl_2 (50 mL). The biphasic mixture was stirred overnight at RT then heated to reflux

for 1 hour. The reaction was concentrated *in vacuo* and the residue diluted with water. The mixture was filtered and the solid residue dissolved in MeOH (15 mL). The solution was cooled to 0 °C and $NaBH_4$ (920 mg, 24.3 mmol, 2.25 eq.) added. After gaseous evolution had ceased the reaction was heated to reflux for 1 hour. The reaction was allowed to cool, concentrated *in vacuo* and 1N NaOH (10 mL), EtOAc (10 mL) and pet. ether (10 mL) added. The layers were separated and the aqueous layer extracted with EtOAc/pet. ether (1:1, 2 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4 EtOAc/pet. ether→1:1:0.1 EtOAc/pet. ether/Et_3N) to leave pure diamine **(*R*,*R*)-3.67** (3.8 g, 8.40 mmol, 78%) as a viscous colourless oil.

$[\alpha]_D^{25}$ −39.5 (*c* = 1.49, $CHCl_3$) [lit.[224] −39.6 (*c* = 1.12, $CHCl_3$)]; **^{1}H NMR** (500 MHz, C_6D_6): δ_H 7.40 (4H, dt, *J* = 8.5 and 2.0 Hz), 7.04 (4H, dt, *J* = 8.5 and 2.0 Hz), 3.63 (2H, d, *J* = 14.0 Hz), 3.43 (2H, d, *J* = 14.0 Hz), 2.19-2.12 (2H, m), 2.01-1.95 (2H, m), 1.70-1.62 (2H, m), 1.47 (2H, bs, N*H*), 1.21-1.11 (2H, m), 0.98-0.88 (2H, m); **^{13}C NMR** (125 MHz, C_6D_6): δ_C 140.9, 131.6, 130.0, 120.8, 61.2, 50.4, 31.6, 25.2. Data consistent with literature.[150]

(3a*R*,7a*R*)-2-allyl-1,3-bis(4-bromobenzyl)-2-chlorooctahydro-1*H*-benzo[*d*][1,3,2] diazasilole - (*R*,*R*)-3.64[150]

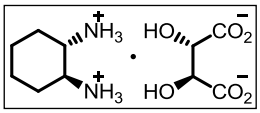


To a stirred solution of freshly distilled allyltrichlorosilane (1.92 mL, 13.26 mmol, 1.2 eq.) and freshly distilled DBU (3.96 mL, 26.52 mmol, 2.4 eq.) in anhydrous CH_2Cl_2 (50 mL) at 0 °C under argon was added a solution of diamine **(*R*,*R*)-3.67** (5.0 g, 11.05 mmol, 1 eq.) in anhydrous CH_2Cl_2 (20 mL) *via* syringe pump over 45 minutes. The reaction was allowed to warm to RT and stirred overnight. The CH_2Cl_2 was removed by distillation under argon, and the resulting residue dried under high vacuum. Anhydrous pentane (60 mL) was added and the solution stirred vigorously under argon for 3 hours. The mixture was filtered under argon and the residue washed with a further portion of anhydrous pentane (10 mL). The solvent was removed *in vacuo* to leave **(*R*,*R*)-3.64** (5.46 g, 9.84 mmol, 89%) as a colourless oil which was stored in the freezer under argon as a solution of known molarity in anhydrous CH_2Cl_2.

^{1}H NMR (250 MHz, C_6D_6): δ_H 7.42 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.41 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.16 (2H,

d, *J* = 8.5 Hz, Ar*H*), 7.14 (2H, d, *J* = 8.5 Hz, Ar*H*), 5.79-5.62 (1H, m, C*H*=CH_2), 5.00-4.88 (2H, m, CH=CH_2), 3.95 (2H, d, *J* = 16.0 Hz, one of NCH_2Ar), 3.93 (1H, d, *J* = 15.0 Hz, one of NCH_2Ar), 3.61 (1H, d, *J* = 15.0 Hz, one of NCH_2Ar), 3.60 (1H, d, *J* = 16.0 Hz, one of NCH_2Ar), 2.70-2.62 (2H, m, C*H*N), 1.79-1.42 (6H, m, four of Cy*H* and SiCH_2CH=CH_2), 1.04-0.80 (4H, m, Cy*H*); **^{13}C NMR** (C_6D_6, 100 MHz): δ_C 141.4, 140.5, 131.5, 131.5, 131.2, 130.1, 129.3, 121.0, 120.7, 116.4, 66.6, 65.6, 48.0, 47.3, 30.9, 30.5, 24.9, 24.7. Data consistent with literature.[150]

(*S*,*S*)-1,2-diaminocyclohexane mono-(−)-tartrate – (*S*,*S*)-3.66[225]



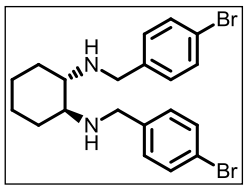
To a 2-necked 250 mL flask containing a stirrer bar and fitted with a thermometer and rubber septum was added distilled water (85 mL) followed by D-(−)-tartaric acid (25 g, 0.167 mol, 1 eq.) in one portion with vigorous stirring. To this solution was added (±)-*trans*-1,2-diaminocyclohexane (40 mL, 0.333 mol, 2 eq.) slowly, taking care not to let the internal temperature exceed 90 °C. A slurry formed initially, with complete dissolution observed once addition was complete. Glacial acetic acid (16.7 mL) was added slowly, again taking care not to let the internal temperature exceed 90 °C. The flask was wrapped in cotton wool and foil and the reaction mixture allowed to cool slowly to RT over 3 hours. The flask was placed in an ice bath, and cooled to <5 °C internal temperature. This temperature was maintained for a further 1 hour. The product was isolated by filtration, the filter cake being washed with cold (<5 °C) water (1 x 20 mL) and ambient temperature MeOH (4 x 20 mL) to leave the product as a white powder. The aqueous filtrates were retained (for recovery of the (*R*,*R*) isomer) and the methanol washes discarded. The product was dried *in vacuo* at 45 °C to leave **(*S*,*S*)-3.66** as a free-flowing white powder (29.5 g, 0.112 mol, 67%, 99% *ee*).

$[\alpha]_D^{25}$ −13.4 (*c* = 1.34, H_2O) [lit.[225] −11.1 (*c* = 1, H_2O)].

Enantiomeric excess was determined as follows: a test tube was charged with the salt (25 mg), CH_2Cl_2 (1.5 mL) and 4N aq. NaOH (0.5 mL). The resulting biphasic mixture was vigorously stirred for 30 seconds, and *m*-toluoyl chloride (50 μL) was added in one portion. The reaction was stirred for a further 30 seconds and the layers allowed to separate. A 250 μL portion of the lower organic layer was taken and diluted to 10 mL in IPA. 5 μL of this solution was used for HPLC analysis, a comparison made against the racemate formed from the racemic diamine (11 mg) as per the above method.

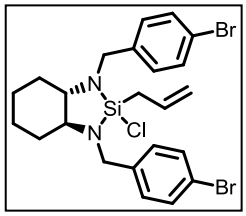
99% *ee* (CHIRALPAK IA, 15% IPA/Hexane, 1 mL/min): t_R (*S*,*S*) = 5.79 min, t_R (*R*,*R*) = 9.68 min.

(1*S*,2*S*)-*N*,*N'*-bis(4-bromobenzyl)cyclohexane-1,2-diamine - (*S*,*S*)-3.67[150]



To a stirred suspension of (1*S*,2*S*)-cyclohexane-1,2-diamine·D-tartrate **(*S*,*S*)-3.66** (14.25 g, 53.9 mmol, 1 eq.) in water (250 mL) was added K_2CO_3 (14.90 g, 107.8 mmol, 2 eq.). To this mixture was added EtOH (125 mL) and a solution of 4-bromobenzaldehyde (20.0 g, 107.8 mmol, 2 eq.) and methanesulfonic acid (0.42 mL, 6.49 mmol, 0.12 eq.) in CH_2Cl_2 (250 mL). The biphasic mixture was stirred overnight at RT then heated to reflux for 1 hour. The reaction was concentrated *in vacuo* and the residue diluted with water. The mixture was filtered and the solid residue dissolved in MeOH (15 mL). The solution was cooled to 0 °C and $NaBH_4$ (4.59 g, 121.8 mmol, 2.25 eq.) added. After gaseous evolution had ceased the reaction was heated to reflux for 1 hour. The reaction was allowed to cool, concentrated *in vacuo* and 1N NaOH (50 mL), EtOAc (50 mL) and pet. ether (50 mL) added. The layers were separated and the aqueous layer extracted with EtOAc/pet. ether (1:1, 2 x 50 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4 EtOAc/ pet. ether→1:1:0.1 EtOAc/pet. ether/Et_3N) to leave pure diamine **(*S*,*S*)-3.67** (17.80 g, 39.4 mmol, 73%) as a viscous colourless oil. $[\alpha]_D^{25}$ +41.5 (*c* = 1.18, $CHCl_3$) [**(*R*,*R*)-3.67** −39.5 (*c* = 1.49, $CHCl_3$)]; All other spectroscopic data identical to **(*R*,*R*)-3.67** prepared previously.

(3a*S*,7a*S*)-2-allyl-1,3-bis(4-bromobenzyl)-2-chlorooctahydro-1*H*-benzo[*d*][1,3,2] diazasilole - (*S*,*S*)-3.64[150]



To a stirred solution of freshly distilled allyltrichlorosilane (1.92 mL, 13.26 mmol, 1.2 eq.) and freshly distilled DBU (3.96 mL, 26.52 mmol, 2.4 eq.) in anhydrous CH_2Cl_2 (50 mL) at 0 °C under argon was added a solution of diamine **(*S*,*S*)-3.67** (5.0 g, 11.05 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) *via* syringe pump over 45 minutes. The reaction was allowed to warm to RT and stirred overnight. The CH_2Cl_2 was removed by distillation under argon, and the resulting residue dried under high vacuum. Anhydrous pentane (60 mL) was added and the solution stirred vigorously for 3 hours under argon. The mixture was filtered under argon and the residue washed with anhydrous pentane (2 x 10 mL).

The solvent was removed *in vacuo* to leave **(*S*,*S*)-3.64** (5.73 g, 10.33 mmol, 93%) as a colourless oil which was dissolved in anhydrous CH_2Cl_2 to give a solution of known molarity and stored under argon in the fridge.

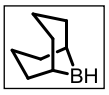
Spectroscopic data identical to **(*R*,*R*)-3.64** prepared previously.

tri-*tert*-butyl borate[226]

A flame-dried, 2-necked 250 mL flask fitted with a reflux condenser vented to the top of the fume hood was charged with *t*-BuOH (60 mL) and $NaBH_4$ (2.0 g, 52.8 mmol, 1 eq.). Glacial AcOH (3.33 mL, 58.2 mmol, 1.1 eq.) was added dropwise and the reaction heated to 100 °C for 4 hours. The reaction was allowed to cool, and the reflux condenser replaced with a still head. The *t*-BuOH was removed *via* distillation (50 °C @ 300 mbar) and a fraction column packed with glass beads fitted between the flask and the still head. The product was fractionally distilled (60 °C @ 15 mbar) to leave pure tri-*tert*-butyl borate (5.71 g, 24.8 mmol, 47%) as a colourless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.30 (27H, s); **^{13}C NMR** (63 MHz, $CDCl_3$): δ_C 72.1, 30.3; **^{11}B NMR** (80 MHz, $CDCl_3$): δ_B 18.8 (bs). Data consistent with literature.[226]

9-borabicyclo[3.3.1]nonane[227]

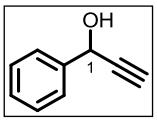


A 3-necked, 250 mL round bottom flask containing a stirrer bar and fitted with a thermometer and dropping funnel was flame dried and allowed to cool to RT under a sparge of argon. The gas adapter was replaced with a distillation setup and the flask charged with anhydrous DME (freshly distilled from CaH_2, 35 mL) and $BH_3{\cdot}SMe_2$ complex (9.7 mL, 0.101 mol, 1.01 eq.). The dropping funnel was charged with 1,5-cyclooctadiene (freshly distilled from $LiAlH_4$, 12.3 mL, 0.100 mol, 1 eq.) and added to the reaction dropwise at a sufficient rate to maintain an internal temperature of 50-60 °C. The dropping funnel was rinsed with anhydrous DME (5 mL) and this was added to the reaction in one portion. The dropping funnel and thermometer were replaced with stoppers and the reaction mixture heated until approx. 25 mL of DME had distilled over. The boiling point of the distillate reached 85 °C, indicating that all the SMe_2 had been removed. The mixture was allowed to cool, and the distillation apparatus replaced with a septum. Anhydrous DME (40 mL) was added and the resulting suspension warmed until all the solid had dissolved. The solution was allowed to cool

slowly to 0 °C, and the supernatant removed *via* syringe. Anhydrous DME (70 mL) was added and the resulting suspension again warmed until all the solid had dissolved. The supernatant was again removed and the solid dried under high vacuum overnight to leave pure 9-BBN (6.74 g, 55.2 mmol, 55%) as white crystals which were transferred to a bottle and stored in the dry box under nitrogen. **m.p.** 149-150 °C [lit.[227] 152-154 °C].

6.3 Experimental Data

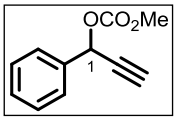
1-phenylprop-2-yn-1-ol – 2.08a[228]



To a solution of benzaldehyde **2.07** (500 mg, 4.71 mmol, 1 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added ethynyl magnesium bromide (0.5 M in THF, 14.1 mL, 7.07 mmol, 1.5 eq.) dropwise. The reaction was allowed to warm to RT and stirred for 30 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and the THF removed *in vacuo*. The aqueous layer was extracted with Et_2O (3 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4 Et_2O/pet. ether) to leave pure alcohol **2.08a** (600 mg, 4.54 mmol, 96%) as a colourless oil.

R_f 0.15 (1:4 Et_2O/pet. ether); **^{1}H NMR** (200 MHz, $CDCl_3$): δ_H 7.63-7.53 (2H, m, Ph), 7.47-7.31 (3H, m, Ph), 5.49 (1H, dd, *J* = 6.0 and 2.0 Hz, H1), 2.69 (1H, d, *J* = 2.0 Hz, H3), 2.24 (1H, dd, *J* = 6.0 and 2.0 Hz, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_c 140.0, 128.5, 128.3, 126.6, 83.4, 74.8, 64.2. Data consistent with literature.[228]

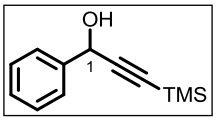
methyl 1-phenylprop-2-ynyl carbonate – 2.01a[229]



To a stirred solution of alcohol **2.08a** (600 mg, 4.54 mmol, 1 eq.) and pyridine (2.93 mL, 36.3 mmol, 8 eq.) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under argon was added methyl chloroformate (1.05 mL, 13.6 mmol, 3 eq.) dropwise. The reaction was stirred for 15 minutes and quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4 Et_2O/pet. ether) to leave pure carbonate **2.01a** (780 mg, 4.10 mmol, 90%) as a pale yellow oil.

R_f 0.30 (1:4 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3036, 2958, 2127, 1752, 1442, 1259, 1196, 997, 931; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.59-7.54 (2H, m, Ph), 7.44-7.38 (3H, m, Ph), 6.30 (1H, d, *J* = 2.0 Hz, H1), 3.83 (3H, s, O*Me*), 2.73 (1H, d, *J* = 2.0 Hz, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.8, 135.8, 129.3, 128.7, 127.7, 79.5, 76.4, 69.3, 55.1. **HRMS** (CI+): calc for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708, found 191.0707.

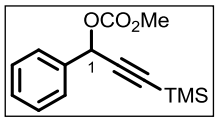
1-phenyl-3-(trimethylsilyl)prop-2-yn-1-ol – 2.08b[230]



To a stirred solution of trimethylsilyl acetylene (0.8 mL, 0.57 mmol, 1.2 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 2.26 mL, 0.57 mmol, 1.2 eq.). The resulting mixture was stirred for 30 minutes and to it added a solution of benzaldehyde (500 mg, 0.471 mmol, 1 eq.) in anhydrous THF (5 mL). The reaction was allowed to warm to RT and stirred for 15 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and the THF removed *in vacuo*. The aqueous layer was extracted with Et_2O (3 x 20 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo* to leave alcohol **2.08a** (0.88 g, 4.31 mmol, 92%) as a colourless oil.

R_f 0.50 (1:1 Et_2O/pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.57-7.54 (2H, m, Ph), 7.42-7.33 (3H, m, Ph), 5.47 (1H, d, *J* = 6.5 Hz, H1), 2.16 (1H, d, *J* = 6.5 Hz, O*H*), 0.22 (9H, s, SiMe_3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 140.3, 128.6, 128.4, 126.7, 104.8, 91.6, 65.0, −0.2. Data consistent with literature.[230]

methyl 1-phenyl-3-(trimethylsilyl)prop-2-ynyl carbonate – 2.01b

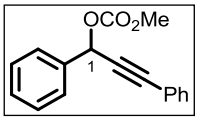


To a solution of alcohol **2.08b** (870 mg, 4.26 mmol, 1 eq.) in anhydrous CH_2Cl_2 (40 mL) at 0 °C under argon was added pyridine (2.76 mL, 34.1 mmol, 8 eq.). To this solution was added methyl chloroformate (0.99 mL, 12.8 mmol, 3 eq.) dropwise. The reaction was stirred for 15 minutes and quenched with sat. aq. $NaHCO_3$ (25 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure carbonate **2.01b** (1.00 g, 3.81 mmol, 89%) as a pale yellow oil.

R_f 0.41 (1:4 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2959, 2213, 1752, 1442, 1320, 1260, 1044, 934;

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.57-7.54 (2H, m, Ph), 7.42-7.36 (3H, m, Ph), 6.32 (1H, s, H1), 3.81 (3H, s, O*Me*), 0.20 (9H, s, Si*Me*$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.8, 136.3, 129.2, 128.6, 127.9, 100.4, 93.6, 70.0, 55.0, −0.3; **HRMS** (ESI+): calc for $C_{14}H_{18}O_3SiNa$ $[M+Na]^+$ 285.0917, found 285.0919.

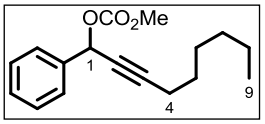
1,3-diphenylprop-2-ynyl methyl carbonate – 2.01c[231]



To a solution of phenylacetylene (1.03 mL, 9.42 mmol, 1 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added dropwise *n*-butyllithium (2.5 M in hexanes, 3.77 mL, 9.42 mmol, 1 eq.). The reaction was stirred for 30 minutes and to it added benzaldehyde (1.0 g, 9.42 mmol, 1 eq.) dropwise. The reaction was stirred for 30 minutes at −78 °C and quenched with methyl chloroformate (0.87 mL, 11.3 mmol, 1.2 eq.). The reaction was allowed to warm to RT and sat. aq. $NaHCO_3$ (20 mL) was added. The THF was removed *in vacuo*, the aqueous layer extracted with Et_2O (3 x 20 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19 Et_2O/pet ether) to leave carbonate **2.01c** (2.19 g, 8.22 mmol, 87%) as a pale yellow oil.

R_f 0.35 (1:4 Et_2O/pet ether); **^{1}H NMR** (400 MHz, acetone-d_6): δ_H 7.70-7.65 (2H, m, Ph), 7.55-7.38 (8H, m, Ph), 6.58 (1H, s, H1), 3.81 (3H, s, O*Me*); **^{13}C NMR** (100 MHz, acetone-d_6): δ_C 154.1, 137.3, 132.1, 129.6, 129.6, 129.1, 129.0, 128.1, 122.2, 87.8, 85.6, 70.0, 55.0. Data consistent with literature.[231]

methyl 1-phenylnon-2-ynyl carbonate – 2.01d[232]

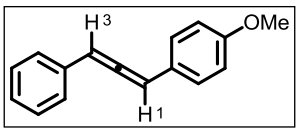


To solution of 1-octyne (1.39 mL, 9.42 mmol, 1 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 3.77 mL, 9.42 mmol, 1 eq.) dropwise. The reaction was stirred for 30 minutes and to it added benzaldehyde (1.0 g, 9.42 mmol, 1 eq.) dropwise. The reaction was stirred for 30 minutes at −78 °C and quenched with methyl chloroformate (0.87 mL, 11.3 mmol, 1.2 eq.). The reaction was allowed to warm to RT and sat. aq. $NaHCO_3$ (20 mL) added. The THF was removed *in vacuo*, the aqueous layer extracted with Et_2O (3 x 20 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:50

Et_2O/pet. ether) to leave carbonate **2.01d** (2.35 g, 8.57 mmol, 91%) as a pale yellow oil.

R_f 0.51 (1:4 Et_2O/pet ether); **IR** (thin film, cm^{-1}): 2932, 2243, 1749, 1442, 1324, 1260, 1145, 933; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.57-7.53 (2H, m, Ph), 7.41-7.37 (3H, m, Ph), 6.29 (1H, t, *J* = 2.0 Hz, H1), 3.80 (3H, s, O*Me*), 2.27 (2H, td, *J* = 7.0 and 2.0 Hz, H4), 1.57-1.50 (2H, m, H5), 1.42-1.35 (2H, m, H6), 1.34-1.24 (4H, m, H7 and 8), 0.89 (3H, t, *J* = 7.0 Hz, H9); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.9, 137.0, 129.0, 128.6, 127.7, 89.6, 76.1, 70.2, 54.9, 31.2, 28.5, 28.3, 22.5, 18.8, 14.0; **HRMS** (ESI+): calc for $C_{17}H_{22}O_3Na$ $[M+Na]^+$ 297.1461, found 297.1460.

1-methoxy-4-(3-phenylpropa-1,2-dienyl)benzene – 2.12a[34]

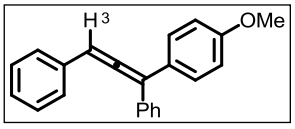


To a degassed solution of carbonate **2.01a** (50 mg, 0.263 mmol, 1 eq.) and 4-methoxyphenylboronic acid (48 mg, 0.316 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (3 mg, 1 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (Et_2O/pet. ether 1:99) to leave pure allene **2.12a** (26 mg, 0.117 mmol, 44%) as a yellow oil.

R_f 0.34 (1:19 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.39-7.32 (4H, m, Ph), 7.30 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.26-7.21 (1H, m, Ph), 6.88 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.59 (2H, s, H1 and 3), 3.82 (3H, s, O*Me*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 207.2, 159.1, 133.9, 128.7, 128.1, 127.2, 126.9, 125.8, 114.3, 98.4, 97.9, 55.3. Data consistent with literature.[34]

Also synthesised from carbonate **2.01b** (50 mg, 0.191 mmol), 4-methoxyphenylboronic acid (35 mg, 0.229 mmol) and $Pd(PPh_3)_4$ (2 mg, 1 mol%) in 1,4-dioxane (1 mL). Reaction for 10 mins, work-up and purification as above gave allene **2.12a** (24 mg, 0.108 mmol, 57%).

(1-(4-methoxyphenyl)propa-1,2-diene-1,3-diyl)dibenzene – 2.12c[233]

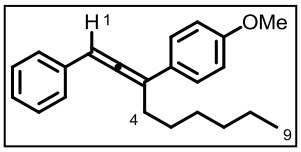


To a degassed solution of carbonate **2.01c** (50 mg, 0.188 mmol, 1 eq.) and 4-methoxyphenylboronic acid (35 mg, 0.230 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (2 mg, 1 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica

gel (1:99 Et_2O/pet. ether) to leave pure allene **2.12c** (43 mg, 0.144 mmol, 77%) as a yellow oil.

R_f 0.24 (1:99 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3029, 2836, 1927, 1604, 1509, 1249, 1175, 1033, 884; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.47-7.41 (4H, m, Ph), 7.37 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.37-7.29 (5H, m, Ph), 7.25 (1H, tt, *J* = 3.5 and 1.5 Hz, Ph), 6.91 (2H, d, *J* = 9.0 Hz, Ar*H*), 6.71 (1H, s, H3), 3.84 (3H, s, O*Me*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 208.0, 159.2, 136.5, 134.1, 129.6, 128.8, 128.5, 128.4, 128.3, 127.5, 127.3, 126.9, 113.9, 113.3, 97.5, 55.3.

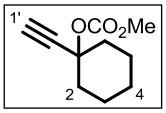
1-methoxy-4-(1-phenylnona-1,2-dien-3-yl)benzene – 2.12d[234]



To a degassed solution of carbonate **2.01d** (50 mg, 0.182 mmol, 1 eq.) and 4-methoxyphenylboronic acid (33 mg, 0.217 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (2 mg, 1 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:99 Et_2O/pet. ether) to leave pure allene **2.12d** (45 mg, 0.147 mmol, 81%) as a pale yellow oil.

R_f 0.36 (1:19 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.40 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.38-7.30 (4H, m, Ph), 7.24-7.20 (1H, m, Ph), 6.88 (2H, d, *J* = 9.0 Hz, Ar*H*), 6.52 (1H, t, *J* = 3.0 Hz, H1), 3.82 (3H, s, O*Me*), 2.62-2.48 (2H, m, H4), 1.68-1.56 (2H, m, H5), 1.47-1.38 (2H, m, H6), 1.33-1.27 (4H, m, H7 and 8), 0.88 (3H, t, *J* = 7.0 Hz, 9); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 206.1, 158.8, 135.0, 128.7, 128.4, 127.2, 126.8, 126.7, 113.9, 109.5, 97.7, 55.3, 31.7, 30.3, 29.3, 27.9, 22.7, 14.1. Data consistent with literature.[234]

1-ethynylcyclohexyl methyl carbonate – 2.02a[235]

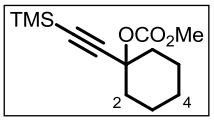


To a stirred solution of 1-ethynylcyclohexanol **2.15a** (1.0 g, 8.05 mmol, 1 eq.) in anhydrous THF (25 mL) at 0 °C under an argon atmosphere was added dropwise *n*-butyllithium (2.5 M in hexanes, 3.86 mL, 9.66 mmol, 1.2 eq.). The resulting mixture was stirred for 30 minutes and to it added methyl chloroformate (0.75 mL, 9.66 mmol, 1.2 eq.). The reaction was allowed to warm to RT, stirred for 10 minutes and quenched with sat. aq. $NaHCO_3$ (25 mL). The THF was removed *in vacuo* and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic

layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4 Et_2O/pet. ether) to leave pure carbonate **2.02a** (1.40 g, 7.68 mmol, 95%) as a colourless oil.

R_f 0.52 (1:1 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.79 (3H, s, O*Me*), 2.64 (1H, s, H1'), 2.21-2.14 (2H, m, H2), 1.92-1.84 (2H, m, H2), 1.73-1.50 (5H, m, H3 and 4), 1.39-1.29 (1H, m, H4); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 153.4, 83.0, 77.4, 74.7, 54.3, 36.8, 24.9, 22.5. Data consistent with literature.[235]

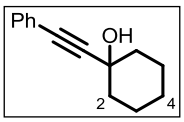
methyl 1-((trimethylsilyl)ethynyl)cyclohexyl carbonate – 2.02b[235]



To a stirred solution of trimethylsilyl acetylene (1.44 mL, 10.2 mmol, 1 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 4.08 mL, 10.2 mmol, 1 eq.) dropwise. The resulting solution was stirred for 30 minutes at −78 °C and to it added cyclohexanone (1.06 mL, 10.2 mmol, 1 eq.) in one portion. The mixture was stirred at −78 °C and when complete (TLC analysis, 1 hour), quenched with methyl chloroformate (0.95 mL, 12.24 mmol, 1.2 eq.) and allowed to warm to RT. Sat. aq. $NaHCO_3$ (10 mL) was added and the THF removed *in vacuo*. The aqueous layer was extracted with Et_2O (3 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19 Et_2O/pet. ether) to leave pure carbonate **2.02b** (2.10 g, 8.25 mmol, 81%) as a colourless oil.

R_f 0.32 (1:19 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.76 (3H, s, O*Me*), 2.20-2.12 (2H, m, H2), 1.88-1.79 (2H, m, H2), 1.71-1.50 (5H, m, H3 and 4), 1.36-1.25 (1H, m, H4), 0.18 (9H, s, Si*Me*$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 153.1, 104.5, 91.5, 78.0, 54.2, 36.9, 25.0, 22.7, −0.1. Data consistent with literature.[235]

1-(phenylethynyl)cyclohexanol – 2.15c[236]

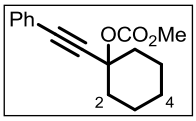


To a stirred solution of 1-ethynylcyclohexanol **2.15a** (750 mg, 6.04 mmol, 1 eq.) and bromobenzene (0.70 mL, 6.64 mmol, 1.1 eq.) in *i*-Pr_2NH (10 mL) under argon was added sequentially $PdCl_2(PPh_3)_2$ (60 mg, 1.5 mol%) and CuI (35 mg, 3 mol%). The resulting mixture was heated to 80 °C and stirred until the reaction was complete as monitored by GC/MS (4 hours).

The reaction was allowed to cool and diluted with Et_2O (25 mL) and sat. aq. NH_4Cl (25 mL). The layers were separated, the aqueous layer extracted with Et_2O (3 x 20 mL) and the combined organic layers washed sequentially with sat. aq. NH_4Cl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:3 Et_2O/pet. ether) to leave pure alcohol **2.15c** (1.11 g, 5.54 mmol, 92%) as an off-white solid.

m.p. 59 °C (lit.[237] 59-60 °C); $\mathbf{R_f}$ 0.29 (1:2 Et_2O/pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.34-7.29 (3H, m, Ph), 2.08 (1H, bs, O*H*), 2.05-1.98 (2H, m, H2), 1.80-1.55 (7H, m, H2, 3 and 4), 1.35-1.25 (1H, m, H4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.6, 128.2, 128.1, 122.9, 92.7, 84.3, 69.1, 40.0, 25.2, 23.4. Data consistent with literature.[236]

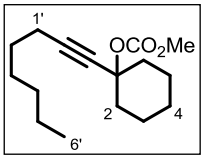
methyl 1-(phenylethynyl)cyclohexyl carbonate – 2.02c[235]



To a stirred solution of alcohol **2.15c** (900 mg, 4.49 mmol, 1 eq.) in anhydrous THF (40 mL) at 0 °C under argon was added *n*-butyllitium (2.5 M in hexanes, 2.16 mL, 5.40 mmol, 1.2 eq.) dropwise. The resulting mixture was stirred for 30 minutes and quenched with methyl chloroformate (0.42 mL, 5.40 mmol, 1.2 eq.). The reaction was allowed to warm to RT and sat. aq. $NaHCO_3$ (25 mL) was added. The THF was removed *in vacuo* and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:16→1:9 Et_2O/pet. ether) to leave carbonate **2.02c** (1.15 g, 4.45 mmol, 99%) as a colourless oil.

$\mathbf{R_f}$ 0.32 (1:9 Et_2O/pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.48-7.45 (2H, m, Ph), 7.33-7.29 (3H, m, Ph), 3.78 (3H, s, O*Me*), 2.31-2.25 (2H, m, H2), 1.99-1.91 (2H, m, H2), 1.76-1.63 (4H, m, H3), 1.61-1.54 (1H, m, H4), 1.40-1.32 (1H, m, H4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 153.3, 131.9, 128.4, 128.2, 122.6, 88.4, 86.7, 78.3, 54.3, 37.1, 25.1, 22.8. Data consistent with literature.[235]

methyl 1-(oct-1-ynyl)cyclohexyl carbonate – 2.02d

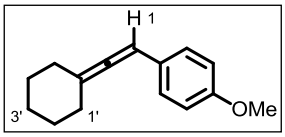


To a stirred solution of 1-octyne (1.5 mL, 10.2 mmol, 1 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added dropwise *n*-butyllithium (2.5 M in hexanes, 4.08 mL, 10.2 mmol, 1 eq.). The resulting mixture was stirred for 30

minutes at −78 °C and to it added cyclohexanone (1.06 mL, 10.2 mmol, 1 eq.) in one portion. The mixture was stirred at −78 °C and when complete (TLC analysis, 1 hour), quenched with methyl chloroformate (0.95 mL, 12.2 mmol, 1.2 eq.) and allowed to warm to RT. Sat. aq. $NaHCO_3$ (10 mL) was added and the THF removed *in vacuo*. The aqueous layer was extracted with Et_2O (3 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19 Et_2O/pet. ether) to leave pure carbonate **2.02d** (2.20 g, 8.26 mmol, 81%) as a colourless oil.

R_f 0.22 (1:19 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2935, 2860, 2242, 1756, 1441, 1273, 1247, 1016; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.75 (3H, s, O*Me*), 2.24 (2H, t, *J* = 7.0 Hz, H1'), 2.17-2.11 (2H, m, H2), 1.87-1.78 (2H, m, H2), 1.69-1.57 (4H, m, H3), 1.57-1.49 (3H, m, H4 and 2'), 1.42-1.36 (2H, m, H3'), 1.34-1.25 (5H, m, H4, 4' and 5'), 0.89 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 153.3, 87.5, 79.4, 78.4, 54.1, 37.3, 31.3, 28.5, 28.4, 25.1, 22.8, 22.5, 18.7, 14.0; **HRMS** (ESI+): calc for $C_{16}H_{26}O_3Na$ $[M+Na]^+$ 289.1774, found 289.1773.

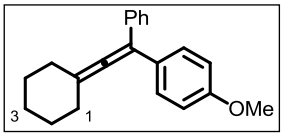
1-(2-cyclohexylidenevinyl)-4-methoxybenzene – 2.16a[238]



To a degassed solution of carbonate **2.02a** (50 mg, 0.274 mmol, 1 eq.) and 4-methoxyphenylboronic acid (50 mg, 0.329 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (31 mg, 10 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:99 Et_2O/pet. ether) to leave pure allene **2.16a** (41 mg, 0.191 mmol, 70%) as a colourless oil.

R_f 0.38 (1:19 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.23 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.86 (2H, d, *J* = 8.5 Hz, Ar*H*), 5.98 (1H, quintet, *J* = 2.0 Hz, H1), 3.81 (3H, s, O*Me*), 2.32-2.17 (4H, m, H1'), 1.77-1.51 (6H, m, H2' and 3'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 198.9, 158.3, 128.5, 127.5, 114.0, 106.4, 91.7, 55.3, 31.5, 27.8, 26.2; **HRMS** (CI+): calc for $C_{15}H_{19}O$ $[M+H]^+$ 215.1436, found 215.1442. Data consistent with literature.[238]

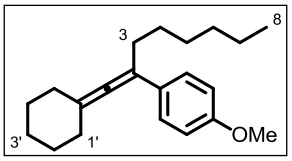
1-(2-cyclohexylidene-1-phenylvinyl)-4-methoxybenzene – 2.16c[239]



To a degassed solution of carbonate **2.02c** (50 mg, 0.194 mmol, 1 eq.) and 4-methoxyphenylboronic acid (35 mg, 0.230 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (2 mg, 1 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:99 Et_2O/pet. ether) to leave pure allene **2.16c** (53 mg, 0.183 mmol, 94%) as a colourless oil.

R_f 0.40 (1:19 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.39-7.31 (4H, m, Ph), 7.29 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.28-7.24 (1H, m, Ph), 6.90 (2H, d, *J* = 9.0 Hz, Ar*H*), 3.84 (3H, s, O*Me*), 2.32 (4H, dd, *J* = 7.0 and 5.0 Hz, H1), 1.74-1.68 (4H, m, H2), 1.64-1.58 (2H, m, H3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 200.0, 158.5, 138.5, 130.5, 129.6, 128.4, 128.2, 126.6, 113.7, 106.9, 105.4, 55.3, 31.6, 27.7, 26.2; **HRMS** (ESI+): calc for $C_{21}H_{22}ONa$ $[M+Na]^+$ 313.1563, found 313.1560. Data consistent with literature.[239]

1-(1-cyclohexylideneoct-1-en-2-yl)-4-methoxybenzene – 2.16d

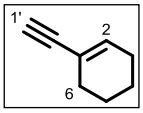


To a degassed solution of carbonate **2.02d** (50 mg, 0.188 mmol, 1 eq.) and 4-methoxyphenylboronic acid (35 mg, 0.230 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (2 mg, 1 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:99 Et_2O/pet. ether) to leave pure allene **2.16d** (50 mg, 0.168 mmol, 89%) as a colourless oil.

R_f 0.48 (1:9 Et_2O/pet. ether 1:9); **IR** (thin film, cm^{-1}) 2927, 2854, 1883, 1607, 1509, 1245, 1177, 1040, 830; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.33 (2H, d, *J* = 9.0 Hz, Ar*H*), 6.86 (2H, d, *J* = 9.0 Hz, Ar*H*), 3.81 (3H, s, O*Me*), 2.37 (2H, t, *J* = 7.0 Hz, H3), 2.26-2.17 (4H, m, H1'), 1.73-1.63 (4H, m, H2'), 1.60 (2H, *apt* q, *J* = 5.0 Hz, H3'), 1.52 (2H, *apt* q, *J* = 7.0 Hz, H4), 1.43-1.28 (6H, m, H5, 6 and 7), 0.91 (3H, t, *J* = 7.0 Hz, H8); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 197.5, 158.0, 131.0, 126.9, 113.7, 105.5, 102.5, 55.3, 31.9, 31.7, 30.2, 29.1, 27.9, 27.9, 26.3, 22.8, 14.1; **HRMS** (ESI+): calc for $C_{21}H_{31}O$

$[M+H]^+$ 299.2369, found 299.2369.

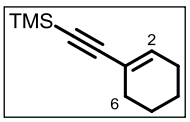
1-ethynylcyclohex-1-ene – 2.17a[240]



To a stirred solution of 1-ethynylcyclohexanol **2.15a** (10.0 g, 80.6 mmol, 1 eq.) in pyridine (60 mL) at 0 °C under argon was added $POCl_3$ (11.26 mL, 120.9 mmol, 1.5 eq.) over 30 minutes *via* syringe pump. The reaction was allowed to warm to RT and stirred overnight. The reaction was heated to 70 °C for 45 minutes, cooled to 0 °C and quenched *carefully via* addition of water (50 mL) dropwise. The mixture was extracted with Et_2O (3 x 50 mL) and the combined organic layers washed sequentially with aq. 6N HCl (3 x 50 mL) and sat. aq. $NaHCO_3$ (1 x 50 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to leave enyne **2.17a** (7.47 g, 70.4 mmol, 87%) as a colourless oil. The product was kept at −25 °C to prevent decomposition.

b.p. 70 °C @ 80 mbar [lit.[240] 71-72 °C @ 80 mbar]; $\mathbf{R_f}$ 0.69 (pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.23-6.19 (1H, m, H2), 2.81 (1H, s, H1'), 2.17-2.06 (4H, m, H3 and 6), 1.68-1.55 (4H, m, H4 and 5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 136.5, 119.7, 85.7, 74.3, 29.0, 25.5, 22.1, 21.4. Data consistent with literature.[240]

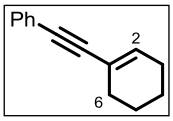
(cyclohexenylethynyl)trimethylsilane – 2.17b[240]



To a stirred solution of enyne **2.17a** (1.0 g, 9.42 mmol, 1 eq.) in anhydrous THF (15 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 4.52 mL, 11.30 mmol, 1.2 eq.) dropwise. The resulting yellow solution was stirred for 1 hour at −78 °C. Freshly distilled trimethylsilyl chloride (1.43 mL, 11.30 mmol, 1.2 eq.) was then added dropwise and the reaction allowed to warm to RT. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and the THF removed *in vacuo*. The aqueous layer was extracted with pet. ether (3 x 10 mL) and the combined organic layers dried over $MgSO_4$. The organic layer was passed through a short plug of silica gel (pet. ether) and the solvent removed *in vacuo* to leave pure enyne **2.17b** (1.67 g, 9.37 mmol, 99%) as a colourless oil.

$\mathbf{R_f}$ 0.71 (pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.21-6.17 (1H, m, H2), 2.16-2.06 (4H, m, H3 and 6), 1.66-1.54 (4H, m, H4 and 5), 0.18 (9H, s, SiMe_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 136.3, 120.7, 107.3, 90.8, 29.0, 25.6, 22.2, 21.4, 0.1. Data consistent with literature.[240]

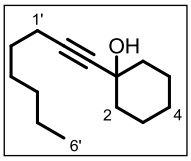
1-(phenylethynyl)cyclohex-1-ene – 2.17c[240]



To a stirred solution of alcohol **2.15c** (1.0 g, 4.99 mmol, 1 eq.) in pyridine (6 mL) at 0 °C under argon was added $POCl_3$ (0.7 mL, 7.49 mmol, 1.5 eq.) over 30 minutes *via* syringe pump. The reaction was allowed to warm to RT and stirred overnight. The reaction was heated to 70 °C for 45 minutes, cooled to 0 °C and quenched <u>*carefully*</u> *via* addition of water (10 mL) dropwise. The mixture was extracted with Et_2O (3 x 10 mL) and the combined organic layers washed sequentially with aq. 6N HCl (3 x 10 mL) and sat. aq. $NaHCO_3$ (1 x 10 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to leave enyne **2.17c** (635 mg, 3.48 mmol, 70%) as a yellow oil.

R_f 0.66 (1:1 EtOAc/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph), 7.33-7.27 (3H, m, Ph), 6.24-6.21 (1H, m, H2), 2.27-2.21 (2H, m, H3 and 6), 2.19-2.13 (2H, m, H3 and 6), 1.73-1.59 (4H, m, H4 and 5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 135.2, 131.4, 128.2, 127.7, 123.7, 120.7, 91.2, 86.7, 29.2, 25.8, 22.3, 21.5. Data consistent with literature.[240]

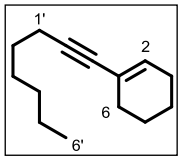
1-(oct-1-ynyl)cyclohexanol – 2.15d[241]



To a stirred solution of 1-octyne (5.41 mL, 36.7 mmol, 1.2 eq.) in anhydrous THF (60 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 14.7 mL, 36.7 mmol, 1.2 eq.) dropwise. The mixture was stirred for 30 minutes at −78 °C and to it added a solution of cyclohexanone (3.0 g, 30.6 mmol, 1 eq.) in anhydrous THF (10 mL). The reaction was allowed to warm to RT and stirred for a further 15 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (50 mL) and the THF removed *in vacuo*. The aqueous layer was extracted with Et_2O (3 x 50 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure alcohol **2.15d** (6.0 g, 28.8 mmol, 93%) as a colourless oil.

R_f 0.61 (1:1 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 2.21 (2H, t, J = 7.0 Hz, H1'), 1.92 (1H, bs, O*H*), 1.89-1.83 (2H, m, H2), 1.71-1.64 (2H, m, H2), 1.58-1.42 (7H, m, H3, 4 and 2'), 1.43-1.35 (2H, m, H3'), 1.35-1.24 (5H, m, H4, 4' and 5'), 0.89 (3H, t, J = 7.0 Hz, H6'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 84.8, 83.8, 68.8, 40.3, 31.3, 28.7, 28.5, 25.2, 23.5, 22.5, 18.6, 14.0. Data consistent with literature.[241]

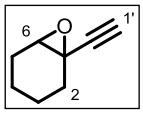
1-(oct-1-ynyl)cyclohex-1-ene – 2.17d[242]



To a stirred solution of alcohol **2.15d** (1.0 g, 4.80 mmol, 1 eq.) in pyridine (6 mL) at 0 °C under argon was added $POCl_3$ (0.67 mL, 7.20 mmol, 1.5 eq.) over 30 minutes *via* syringe pump. The resulting mixture was allowed to warm to RT and stirred overnight. The reaction was heated to 70 °C for 45 minutes, cooled to 0 °C and quenched <u>*carefully*</u> *via* addition of water (5 mL). The reaction mixture was diluted with Et_2O (5 mL), the layers separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organic layers were washed sequentially with aq. 6N HCl (3 x 20 mL) and sat. aq. $NaHCO_3$ (1 x 20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure enyne **2.17d** (825 mg, 4.33 mmol, 90%) as a pale yellow oil.

R_f 0.79 (1:1 EtOAc/pet. ether); **IR** (thin film, cm^{-1}): 2931, 2858, 2313, 1436, 1347, 918, 815; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.03-6.00 (1H, m, H2), 2.29 (2H, t, *J* = 7.0 Hz, H1'), 2.12-2.04 (4H, m, H3 and 6), 1.65-1.49 (6H, m, H4, 5 and 2'), 1.43-1.35 (2H, m, H3'), 1.35-1.26 (4H, m, H4' and 5'), 0.89 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 133.1, 121.0, 87.4, 82.3, 31.4, 29.6, 28.9, 28.6, 25.5, 22.5, 22.4, 21.6, 19.3, 14.0; **HRMS** (CI+): calc for $C_{14}H_{23}$ $[M+H]^+$ 191.1800, found 191.1793.

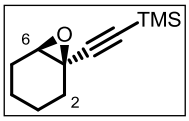
1-ethynyl-7-oxabicyclo[4.1.0]heptane – (±)-2.03a[240]



To a stirred solution of enyne **2.17a** (1.0 g, 9.41 mmol, 1 eq.) in CH_2Cl_2 at 0 °C was added a solution of *m*-CPBA (70% in water, 2.79 g, 11.29 mmol, 1.2 eq.) in CH_2Cl_2 (20 mL). The reaction was allowed to warm to RT and stirred for 2 hours. Water (10 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic layers washed with 10% aq. Na_2SO_3 (2 x 30 mL). The organic layer was dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:20 Et_2O/pet. ether) to leave epoxide **(±)-2.03a** (500 mg, 4.09 mmol, 43%) as a white solid.

m.p. 39-40 °C (lit.[243] 41.5-42 °C); **R_f** 0.45 (1:9 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.36 (1H, t, *J* = 2.5 Hz, H6), 2.32 (1H, s, H1'), 2.16 (1H, m, H2), 2.02 (1H, m, H2), 1.92 (2H, m, H3), 1.48-1.20 (4H, m, H4 and 5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 84.2, 70.2, 59.8, 49.8, 29.4, 24.0, 19.3, 18.8. Data consistent with literature.[240]

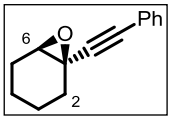
((1*R*,6*R*)-7-oxabicyclo[4.1.0]heptan-1-ylethynyl)trimethylsilane – (*R*,*R*)-2.03b[240]



To a stirred solution of enyne **2.17b** (223 mg, 1.25 mmol, 1 eq.) and Shi's ketone **2.18** (97 mg, 30 mol%) in dimethoxymethane/CH_3CN (2:1 v:v, 10 mL) was added a catalytic amount of TBAHS and buffer (6.25 mL, made by adding 0.5 mL of glacial AcOH to 100 mL of 0.1 M K_2CO_3 solution, pH 9.3). The mixture was cooled to −10 °C and solutions of Oxone® (1.076 g, 1.75 mmol, 1.4 eq.) in Na_2(EDTA) solution (4 x 10^{-4} M, 5 mL) and K_2CO_3 in water (1.0 g in 5 mL) were added separately and simultaneously over 3 hours *via* syringe pump. The reaction was stirred for a further 1 hour at −10 °C then quenched with pet. ether (10 mL) and water (10 mL). The layers were separated and the aqueous layer extracted with pet. ether (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:99 Et_2O/pet. ether buffered with 2.5% Et_3N by volume) to leave pure epoxide **(*R*,*R*)-2.03b** (152 mg, 0.782 mmol, 63%) as a colourless oil.

R_f 0.19 (pet. ether); **$[\alpha]_D^{26}$** +9.2 (*c* = 1.0, $CHCl_3$), [lit.[81] **$[\alpha]_D^{23}$** +11.7 (*c* = 1.02, $CHCl_3$) for 93% *ee*]; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.33-3.31 (1H, m, H6), 2.15-2.07 (1H, m, H2), 2.04-1.95 (1H, m, H2), 1.91-1.86 (2H, m, H5), 1.43-1.17 (4H, m, H3 and 4), 0.15 (9H, s, Si*Me*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 105.8, 86.9, 60.2, 50.3, 29.5, 24.1, 19.4, 18.8, −0.2. Data consistent with literature.[240]

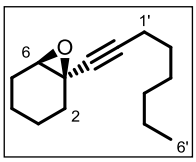
(1*R*,6*R*)-1-(phenylethynyl)-7-oxabicyclo[4.1.0]heptane – (*R*,*R*)-2.03c[240]



To a stirred solution of enyne **2.17c** (228 mg, 1.25 mmol, 1 eq.) and Shi's ketone **2.18** (97 mg, 30 mol%) in DMM/CH_3CN (2:1 v:v, 10 mL) was added a catalytic amount of TBAHS and buffer (6.25 mL, made by adding 0.5 mL of AcOH to 100 mL of 0.1 M K_2CO_3 solution, pH 9.3). The mixture was cooled to −10 °C and solutions of Oxone® (538 mg, 0.88 mmol, 0.7 eq.) in Na_2(EDTA) solution (4 x 10^{-4} M, 5 mL) and K_2CO_3 in water (1.0 g in 5 mL) were added separately and simultaneously over 3 hours *via* syringe pump. The reaction was stirred for a further 1 hour at −10 °C then quenched with pet. ether (10 mL) and water (10 mL). The layers were separated and the aqueous layer extracted with pet. ether (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:99 Et_2O/pet. ether buffered with 2.5% Et_3N by volume) to leave pure epoxide **(*R*,*R*)-2.03c** (74 mg, 0.37 mmol, 30%, 81% brsm) as a colourless oil.

R_f 0.24 (pet. ether); **82% *ee*** (CHIRALPAK-IA, 1.25 mL/min, 1% IPA/Hexane) t_R (*S*,*S*): 4.45 min, t_R (*R*,*R*): 4.71 min); $[\alpha]_D^{25}$ +20.1 (*c* = 0.9, $CHCl_3$), [lit.[36] $[\alpha]_D^{23}$ +22 (*c* = 1.00, $CHCl_3$) for 91% *ee*]; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.33-7.28 (3H, m, Ph), 3.46-3.44 (1H, m, H6), 2.25 (1H, dt, *J* = 15.0 and 6.0 Hz, H2), 2.11 (1H, ddd, *J* = 15.0, 7.5 and 5.5 Hz, H2), 1.98-1.94 (2H, m, H5), 1.51-1.23 (4H, m, H3 and 4); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 131.8, 128.5, 128.3, 122.3, 89.7, 82.0, 60.4, 50.7, 29.8, 24.2, 19.5, 18.9. Data consistent with literature values.[240]

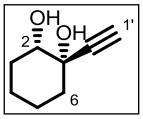
(1*R*,6*R*)-1-(oct-1-ynyl)-7-oxabicyclo[4.1.0]heptane – (*R*,*R*)-2.03d



To a stirred solution of enyne **2.17d** (238 mg, 1.25 mmol, 1 eq.) and Shi's ketone **2.18** (97 mg, 30 mol%) in DMM/CH_3CN (2:1, 10 mL) was added a catalytic amount of TBAHS and buffer (6.25 mL, made by adding 0.5 mL of AcOH to 100 mL of 0.1 M K_2CO_3 solution). The mixture was cooled to −10 °C and solutions of Oxone® (1.076 g, 1.75 mmol, 1.4 eq.) in Na_2(EDTA) solution (4 x 10^{-4} M, 5 mL) and K_2CO_3 in water (1.0 g in 5 mL) were added separately and simultaneously over 3 hours *via* syringe pump. The reaction was stirred for a further 1 hour at −10 °C then quenched with pet. ether. (10 mL) and water (10 mL). The layers were separated and the aqueous layer extracted with pet. ether (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:99 Et_2O/pet. ether buffered with 2.5% Et_3N by volume) to leave pure epoxide **(*R*,*R*)-2.03d** (127 mg, 0.62 mmol, 50%, 91% brsm) as a colourless oil.

R_f 0.29 (pet. ether); $[\alpha]_D^{26}$ +9.9 (*c* = 1.0, $CHCl_3$); **IR** (thin film, cm^{-1}): 2935, 2859, 2245, 1434, 1221, 916, 843; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 3.27 (1H, t, *J* = 2.0 Hz, H6), 2.17 (2H, t, *J* = 7.0 Hz, H1'), 2.11 (1H, dt, *J* = 15.6 and 6.0 Hz, H2), 1.95 (1H, ddd, *J* = 15.0, 7.5 and 6.0 Hz, H2), 1.88 (2H, td, *J* = 6.0 and 2.0 Hz, H5), 1.48 (2H, quintet, *J* = 7.5 Hz, H2'), 1.42-1.18 (10H, m, H3, 4, 3', 4' and 5'), 0.87 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 83.0, 80.6, 60.0, 50.5, 31.3, 30.1, 28.5, 28.4, 24.2, 22.5, 19.4, 18.9, 18.7, 14.0; **HRMS** (CI+): calc for $C_{14}H_{23}O$ $[M+H]^+$ 207.1749, found 207.1746.

(1*S*,2*S*)-1-ethynylcyclohexane-1,2-diol – (*S*,*S*)-2.27a[243]

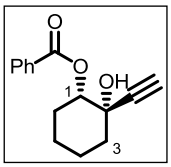


To a stirred solution of enyne **2.17a** (1.0 g, 9.41 mmol, 1 eq.), $(DHQ)_2PHAL$ (73 mg, 1 mol%), $K_3Fe(CN)_6$ (9.29 g, 28.23 mmol, 3 eq.), K_2CO_3 (3.90 g, 28.23 mmol, 3 eq.) and

methanesulfonamide (895 mg, 9.41 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 90 mL) at 0°C was added OsO_4 (2.5% wt. in *t*-BuOH, 0.19 mL, 0.2 mol%). The resulting suspension was stirred vigorously at 0 °C for 5 days. Solid Na_2SO_3 (10 g) was added *carefully* portionwise at 0 °C and the reaction mixture diluted with EtOAc (60 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 40 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (2:3 EtOAc/pet. ether) to leave pure diol **(*S*,*S*)-2.27a** (630 mg, 4.49 mmol, 48%) as a white solid.

R_f 0.30 (1:1 EtOAc/pet. ether); **m.p.** 67-68 °C (lit.[243] 68.5-69 °C); **24% *ee*** (see below); $[\alpha]_D^{25}$ −0.5 (*c* = 1.0, $CHCl_3$, for 24% *ee*); **IR** (thin film, cm^{-1}): 3396, 3302, 2940, 2864, 2108, 1447, 1073, 1006, 977; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.71 (1H, m, H2), 2.62 (1H, bs, O*H*), 2.49 (1H, s, H1'), 2.38 (1H, bs, O*H*), 2.09-2.01 (1H, m, H6), 1.74-1.83 (1H, m, H3), 1.71-1.55 (4H, m, H3, 4, 5 and 6), 1.45-1.53 (1H, m, H4), 1.27-1.38 (1H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 86.4, 74.0, 72.6, 70.0, 35.5, 28.4, 22.0, 20.9. **HRMS** (CI+): calc for $C_8H_{16}NO_2$ $[M+NH_4]^+$ 158.1181, found 158.1175.

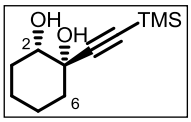
Enantiomeric excess was determined by derivitisation with benzoyl chloride to give the benzoate ester **2.28a**. The HPLC trace was compared to a racemic sample (CHIRALPAK-IB, 1.3 mL/min, 2% IPA/Hexane) t_R (*S*,*S*): 10.38 min, t_R (*R*,*R*): 10.98 min.



(1*S*,2*S*)-2-ethynyl-2-hydroxycyclohexyl benzoate – 2.28a:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.08 (2H, d, *J* = 7.5 Hz, Ph), 7.59 (1H, t, *J* = 7.5 Hz, Ph), 7.47 (2H, t, *J* = 7.5 Hz, Ph), 5.25 (1H, dd, *J* = 8.0 and 4.0 Hz, H1), 2.48 (1H, bs, O*H*), 2.47 (1H, s, C≡C*H*), 2.11 (1H, ddd, *J* = 13.5, 7.5 and 3.5 Hz, H3), 1.96-2.02 (1H, m, H6), 1.82-1.93 (2H, m, H3 and 6), 1.68-1.77 (2H, m, H4 and 5), 1.58-1.65 (1H, m, H4), 1.47-1.55 (1H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 166.0, 133.1, 130.2, 129.7, 128.4, 85.3, 76.2, 73.1, 69.2, 36.1, 27.1, 21.9, 21.1.

(1*S*,2*S*)-1-((trimethylsilyl)ethynyl)cyclohexane-1,2-diol – (*S*,*S*)-2.27b

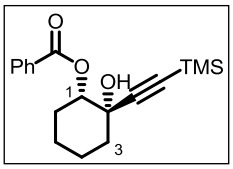


To a stirred solution of enyne **2.17b** (0.75 g, 4.21 mmol, 1 eq.), $(DHQ)_2PHAL$ (33 mg, 1 mol%), $K_3Fe(CN)_6$ (4.15 g, 12.62 mmol, 3 eq.), K_2CO_3 (1.74 g, 12.62 mmol, 3 eq.) and methanesulfonamide (400 mg, 4.21 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 70 mL) at 0 °C was added OsO_4 (2.5% wt. in *t*-BuOH, 0.26 mL, 0.5 mol%). The resulting suspension was

stirred vigorously at 0°C for 4 days. Solid Na_2SO_3 (7 g) was added *carefully* portionwise at 0°C and the reaction mixture diluted with EtOAc (50 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 40 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4 EtOAc/pet. ether) to leave pure diol **(*R*,*R*)-2.27b** (150 mg, 0.71 mmol, 17%, 59% brsm) as a white solid.

m.p. 127-128 °C; $\mathbf{R_f}$ 0.33 (1:2 EtOAc/pet. ether); **8% *ee*** (see below); $[\alpha]_D^{25}$ +4.3 (*c* = 1.0, $CHCl_3$, for 8% *ee*); **IR** (thin film, cm^{-1}): 3287, 2941, 2863, 2178, 1443, 1391, 1249, 1077, 840; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 3.74-3.71 (1H, m, H2), 2.56 (1H, bs, O*H*), 2.40 (1H, bs, O*H*), 2.03-1.97 (1H, m, H6), 1.80-1.74 (1H, m, H3), 1.71-1.54 (4H, m, H3, 4, 5 and 6), 1.51-1.44 (1H, m, H5), 1.36-1.28 (1H, m, H4), 0.17 (9H, s, Si*Me*$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 108.0, 89.2, 73.9, 70.4, 35.3, 28.4, 21.7, 21.2, −0.1; **HRMS** (FI+): calc for $C_{11}H_{20}O_2Si$ $[M]^+$ 212.1233, found 212.1230.

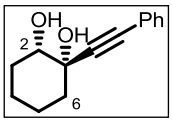
Enantiomeric excess was determined by derivitisation with benzoyl chloride to give the benzoate ester **2.28b**. The HPLC trace was compared to a racemic sample (CHIRALPAK-IB, 1.3 mL/min, 1.5% IPA/Hexane) t_R (*S*,*S*): 5.56 min, t_R (*R*,*R*): 5.93 min.



(1*S*,2*S*)-2-hydroxy-2-((trimethylsilyl)ethynyl)cyclohexyl benzoate – 2.28b:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.07 (2H, d, *J* = 7.5 Hz, Ph), 7.58 (1H, t, *J* = 7.5 Hz, Ph), 7.46 (2H, t, *J* = 7.5 Hz, Ph), 5.25 (1H, dd, *J* = 8.0 and 3.5 Hz, H1), 2.39 (1H, bs, O*H*), 2.02-2.08 (1H, m, H3), 1.94-2.00 (1H, m, H6), 1.86-1.93 (1H, m, H6), 1.79-1.85 (1H, m, H3), 1.66-1.75 (2H, m, H4 and 5), 1.56-1.64 (1H, m, H4), 1.47-1.54 (1H, m, H5), 0.09 (9H, s, Si*Me*$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 166.0, 133.0, 130.3, 129.7, 128.3, 106.9, 89.8, 76.4, 69.6, 35.9, 27.3, 21.9, 21.3, –0.3.

(1*S*,2*S*)-1-(phenylethynyl)cyclohexane-1,2-diol – (*S*,*S*)-2.27c[244]

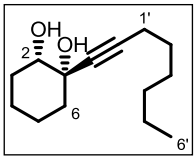


To a stirred solution of enyne **2.17c** (0.75 g, 4.12 mmol, 1 eq.), $(DHQ)_2PHAL$ (32 mg, 1 mol%), $K_3Fe(CN)_6$ (4.05 g, 12.3 mmol, 3 eq.), K_2CO_3 (1.71 g, 12.3 mmol, 3 eq.) and methanesulfonamide (392 mg, 4.12 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 70 mL) at 0 °C was added OsO_4 (2.5% wt. in *t*-BuOH, 0.26 mL, 0.5 mol%). The resulting suspension was stirred vigorously at 0 °C for 18 hours. Solid Na_2SO_3 (7 g) was added *carefully* portionwise at 0 °C and the reaction mixture

diluted with EtOAc (50 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 40 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:9→1:4 EtOAc/pet. ether) to leave pure diol **(*S*,*S*)-2.27c** (726 mg, 3.36 mmol, 82%) as a pale yellow solid.

m.p. 49-50 °C; $\mathbf{R_f}$ 0.32 (1:1 EtOAc/pet. ether); **84% *ee*** (CHIRALPAK-IB, 1.2 mL/min, 10% IPA/Hexane) t_R (*R*,*R*): 5.81 min, t_R (*S*,*S*): 6.54 min; $[\alpha]_D^{25}$ +10.8 (*c* = 1.0, $CHCl_3$, for 84% *ee*); **IR** (thin film, cm^{-1}): 3406, 2939, 2861, 2225, 1599, 1490, 1444, 1070, 759; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph), 7.33-7.28 (3H, m, Ph), 3.85 (1H, dd, *J* =7.0 and 4.0 Hz, H2), 2.78 (2H, bs, 2 x O*H*), 2.11 (1H, ddd, *J* = 13.0, 7.5 and 3.5 Hz, H6), 1.86-1.88 (1H, m, H3), 1.78-1.72 (2H, m, H3 and 6), 1.71-1.60 (2H, m, H4 and 5), 1.57-1.50 (1H, m, H4), 1.39-1.31 (1H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.7, 128.4, 128.3, 122.4, 91.3, 84.8, 74.0, 70.6, 35.5, 28.7, 1.7, 21.4; **HRMS** (CI+): calc for $C_{14}H_{20}NO_2$ $[M+NH_4]^+$ 234.1494, found 234.1502.

(1*S*,2*S*)-1-(oct-1-ynyl)cyclohexane-1,2-diol – (*S*,*S*)-2.27d

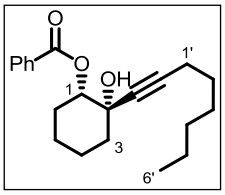


To a stirred solution of enyne **2.17d** (1.0 g, 5.25 mmol, 1 eq.), $(DHQ)_2PHAL$ (41 mg, 1 mol%), $K_3Fe(CN)_6$ (5.19 g, 15.8 mmol, 3 eq.), K_2CO_3 (2.18 g, 15.8 mmol, 3 eq.) and methanesulfonamide (500 mg, 5.25 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 90 mL) at 0 °C was added OsO_4 (2.5% wt. in *t*-BuOH, 0.33 mL, 0.5 mol%). The resulting suspension was stirred vigorously at 0 °C for 48 hours. Solid Na_2SO_3 (8 g) was added <u>*carefully*</u> portionwise at 0°C and the reaction mixture diluted with EtOAc (50 mL). The layers were separated, the aqueous layer extracted with EtOAc (3 x 40 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4 EtOAc/pet. ether) to leave pure diol **(*S*,*S*)-2.27d** (955 mg, 4.26 mmol, 81%) as a colourless oil.

$\mathbf{R_f}$ 0.19 (1:4 EtOAc/pet. ether); **35% *ee*** (see below); $[\alpha]_D^{25}$ +1.6 (*c* = 1.4, $CHCl_3$, for 35% *ee*); **IR** (thin film, cm^{-1}): 3406, 2934, 2238, 1446, 1065, 999; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.70-3.66 (1H, m, H2), 2.51 (1H, bs, O*H*), 2.44 (1H, bs, O*H*), 2.20 (2H, t, *J* = 7.0 Hz, H1'), 2.00-1.95 (1H, m, H6), 1.79-1.73 (1H, m, H3), 1.70-1.56 (4H, m, H3, 4, 5 and 6), 1.52-1.44 (3H, m, H4 and 2'), 1.41-1.23 (7H, m,

H5, 3', 4' and 5'), 0.88 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 85.6, 82.4, 74.3, 70.2, 35.6, 31.3, 28.6, 28.5, 28.5, 22.5, 21.7, 21.4, 18.6, 14.0; **HRMS** (CI+): calc for $C_{14}H_{24}O_2$ $[M]^+$ 224.1776, found 224.1779.

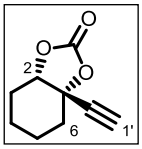
Enantiomeric excess was determined by derivitisation with benzoyl chloride to give the benzoate ester **2.28d**. The HPLC trace was compared to a racemic sample (CHIRALPAK-IA, 1.2 mL/min, 5% IPA/Hexane) t_R (*R*,*R*): 6.95 min, t_R (*S*,*S*): 7.69 min.



(1*S*,2*S*)-2-hydroxy-2-(oct-1-ynyl)cyclohexyl benzoate – 2.28d:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.07 (2H, dt, *J* = 7.5 and 1.5 Hz, Ph), 7.57 (1H, tt, *J* = 7.5 and 1.5 Hz, Ph), 7.45 (2H, tt, *J* = 7.5 and 1.5 Hz, Ph), 5.21 (1H, dd, *J* = 7.5 and 3.5 Hz, H1), 2.37 (1H, bs, O*H*), 2.15 (2H, t, *J* = 7.0 Hz, H1'), 1.46-2.08 (8H, m, H3, 4, 5 and 6), 1.41 (2H, quintet, *J* = 7.0 Hz, H2'), 1.33-1.51 (6H, m, H3', 4' and 5'), 0.84 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 166.0, 133.0, 130.4, 129.7, 128.4, 86.0, 81.6, 76.7, 69.4, 36.3, 31.2, 28.4, 28.4, 27.4, 22.4, 21.8, 21.6, 18.6, 14.0.

(3a*S*,7a*S*)-3a-ethynylhexahydrobenzo[*d*][1,3]dioxol-2-one – (*S*,*S*)-2.04a

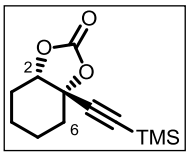


To a stirred solution of diol **(*S*,*S*)-2.27a** (500 mg, 3.57 mmol, 1 eq.) in anhydrous CH_2Cl_2 (40 mL) under argon was added Et_3N (2.99 mL, 21.4 mmol, 6 eq.), pyridine (1.73 mL, 21.4 mmol, 6 eq.) and powered 4Å molecular sieves (1 g). The mixture was cooled to −78 °C and to it added a solution of triphosgene (529 mg, 1.79 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (10 mL) dropwise. The reaction was stirred at −78 °C for 20 minutes, quenched with sat. aq. $NaHCO_3$ (30 mL) and the mixture allowed to warm to RT. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2 Et_2O/pet. ether) to leave pure carbonate **(*S*,*S*)-2.27a** (570 mg, 3.43 mmol, 96%) as a yellow solid.

R_f 0.33 (1:1 Et_2O/pet. ether); **m.p.** 40 °C; $[\alpha]_D^{25}$ −5.2 (*c* = 1.0, $CHCl_3$, for 24% *ee*); **IR** (thin film, cm^{-1}): 2951, 2868, 2126, 1808, 1553, 1451, 1291, 1218, 1132, 1030; **^{1}H NMR** (500 MHz, C_6D_6): δ_H 3.92 (1H, t, *J* = 4.0 Hz, H2), 1.92 (1H, s, H1'), 1.66 (1H, ddd, *J* = 14.0, 6.0 and 3.5 Hz, H6), 1.43-1.35 (2H, m, H3 and 6), 1.08-1.00 (1H, m, H3), 1.00-0.72 (4H, m, H4 and 5); **^{13}C NMR** (125 MHz, C_6D_6):

δ_C 153.2, 79.9, 79.4, 76.5, 76.2, 33.8, 25.3, 19.9, 18.4; **HRMS** (FI+): calc for $C_9H_{10}O_3$ $[M]^+$ 166.0630, found 166.0631.

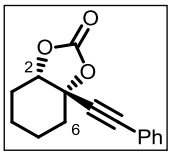
(3a*S*,7a*S*)-3a-((trimethylsilyl)ethynyl)hexahydrobenzo[*d*][1,3]dioxol-2-one – (*S*,*S*)-2.04b



To a stirred solution of diol **(*S*,*S*)-2.27b** (75 mg, 0.353 mmol, 1 eq.) in anhydrous CH_2Cl_2 (3 mL) under argon was added Et_3N (0.30 mL, 2.12 mmol, 6 eq.), pyridine (0.17 mL, 2.12 mmol, 6 eq.) and powered 4Å molecular sieves (100 mg). The mixture was cooled to −78 °C and to it added a solution of triphosgene (52 mg, 0.117 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (1 mL) dropwise. The reaction was stirred at −78 °C for 20 minutes, allowed to warm to RT and quenched with sat. aq. $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1N aq. HCl (2 x 20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9 Et_2O/pet. ether) to leave pure carbonate **(*S*,*S*)-2.04b** (73 mg, 0.306 mmol, 87%) as a colourless oil.

R_f 0.49 (1:3 Et_2O/pet. ether); $[\alpha]_D^{20}$ −1.6 (*c* = 0.80, $CHCl_3$, for 8% *ee*); **IR** (thin film, cm^{-1}): 2955, 2868, 2179, 1811, 1289, 1251, 1217, 1188, 1133, 1033, 1015, 842; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.62 (1H, t, *J* = 3.5 Hz, H2), 2.18 (1H, ddd, *J* = 14.0, 6.5 and 4.0 Hz, H6), 2.06 (1H, dq, *J* = 15.5 and 4.0 Hz, H3), 1.89-1.79 (2H, m, H3 and 6), 1.72-1.64 (1H, m, H5), 1.61-1.37 (3H, m, H4 and 5), 0.18 (9H, s, Si*Me*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 153.7, 99.9, 94.2, 80.0, 77.6, 34.0, 25.3, 19.9, 18.4, −0.5; **HRMS** (ESI+): calc for $C_{12}H_{18}O_3SiNa$ $[M+Na]^+$ 261.0917, found 261.0915.

(3a*S*,7a*S*)-3a-(phenylethynyl)hexahydrobenzo[*d*][1,3]dioxol-2-one – (*S*,*S*)-2.04c[101]

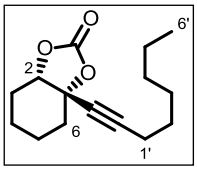


To a stirred solution of diol **(*S*,*S*)-2.27c** (500 mg, 2.31 mmol, 1 eq.) in anhydrous CH_2Cl_2 (40 mL) under argon was added Et_3N (1.93 mL, 13.9 mmol, 6 eq.), pyridine (1.12 mL, 13.9 mmol, 6 eq.) and powered 4Å molecular sieves (1 g). The mixture was cooled to −78 °C and to it added a solution of triphosgene (343 mg, 1.16 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (5 mL) dropwise. The reaction was stirred at −78 °C for 20 minutes, quenched with sat. aq. $NaHCO_3$ (50 mL) and the mixture allowed to warm to RT. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine

(50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9 EtOAc/pet. ether) to leave pure carbonate **(*S*,*S*)-2.04c** (433 mg, 1.79 mmol, 77%, 98% brsm) as a yellow oil.

R_f 0.60 (1:1 EtOAc/pet. ether); $[\alpha]_D^{23}$ −14.4 (*c* = 1.0, $CHCl_3$, for 84% *ee*); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.48-7.45 (2H, m, Ph), 7.41-7.33 (3H, m, Ph), 4.76 (1H, t, *J* = 4.0 Hz, H2), 2.33 (1H, ddd, *J* = 14.0, 6.5 and 3.5 Hz, H6), 2.18-2.12 (1H, m, H6), 2.01-1.89 (2H, m, H3), 1.79-1.73 (1H, m, H4), 1.65-1.49 (3H, m, H4 and 5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 153.8, 132.0, 129.5, 128.4, 120.9, 88.3, 84.1, 80.2, 78.1, 34.2, 25.4, 20.1, 18.6. Data consistent with (±) in the literature.[101]

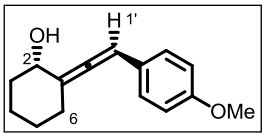
(3a*S*,7a*S*)-3a-(oct-1-ynyl)hexahydrobenzo[*d*][1,3]dioxol-2-one – (*S*,*S*)-2.04d



To a stirred solution of diol **(*S*,*S*)-2.27d** (700 mg, 3.12 mmol, 1 eq.) in anhydrous CH_2Cl_2 (70 mL) under argon was added Et_3N (2.61 mL, 18.7 mmol, 6 eq.) pyridine (1.51 mL, 18.7 mmol, 6 eq.) and powered 4Å molecular sieves (1.5 g). The mixture was cooled to −78 °C and to it added a solution of triphosgene (462 mg, 1.56 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (5 mL) dropwise. The reaction was stirred at −78 °C for 10 minutes, quenched with sat. aq. $NaHCO_3$ solution (50 mL) and the mixture allowed to warm to RT. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9 EtOAc/pet. ether) to leave pure carbonate **(*S*,*S*)-2.04d** (667 mg, 2.66 mmol, 85%) as a colourless oil.

R_f 0.64 (1:1 EtOAc/pet. ether); $[\alpha]_D^{23}$ −5.4 (*c* = 1.0, $CHCl_3$, for 35% *ee*); **IR** (thin film, cm^{-1}): 2934, 2862, 2248, 1810, 1452, 1295, 1229, 1194, 1017, 776. **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 4.59 (1H, t, *J* = 4.0 Hz, H2), 2.25 (2H, t, *J* = 7.0 Hz, H1'), 2.19 (1H, ddd, *J* = 13.5, 5.5 and 3.5 Hz, H6), 2.10 (1H, ddtd, *J* = 15.5, 4.0, 4.0 and 1.0 Hz, H3), 1.88-1.79 (2H, m, H3 and 6), 1.74-1.67 (1H, m, H5), 1.60-1.49 (4H, m, H4 and 2'), 1.49-1.35 (3H, m, H5 and H3'), 1.35-1.25 (4H, m, H4' and 5'), 0.90 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.0, 90.1, 80.4, 78.1, 75.8, 34.5, 31.2, 28.4, 28.1, 25.3, 22.5, 20.2, 18.7, 18.6, 14.0; **HRMS** (CI+): calc for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found 251.1649.

(*S*)-2-((*S*)-2-(4-methoxyphenyl)vinylidene)cyclohexanol – (*S,S*)-2.33a[245]



To a degassed solution of carbonate **(*S,S*)-2.04a** (50 mg, 0.301 mmol, 1 eq.) and 4-methoxyphenylboronic acid (55 mg, 0.362 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (35 mg, 10 mol%). The resulting mixture was heated to 100 °C for 5 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4 Et_2O/pet. ether) to leave pure allene **(*S,S*)-2.33a** (36 mg, 0.156 mmol, 52%) as an off-white solid.

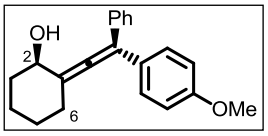
5.0:1 *dr* (*anti*:*syn*); **m.p.** 71-72 °C; $\mathbf{R_f}$ 0.21 (1:2 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3460, 2975, 1950, 1606, 1514, 1463, 1241, 1037, 844; **^{1}H NMR** (*anti* isomer, 500 MHz, $CDCl_3$): δ_H 7.22 (2H, dt, *J* = 9.0 and 2.0 Hz, Ar*H*), 6.86 (2H, dt, *J* = 9.0 and 2.0 Hz, Ar*H*), 6.34-6.32 (1H, m, H1'), 4.21-4.17 (1H, m, H2), 3.81 (3H, s, O*Me*), 2.54-2.48 (1H, m, H6), 2.17-2.09 (2H, m, H3 and 6), 1.90 (1H, d, *J* = 4.0 Hz, O*H*), 1.89-1.81 (1H, m, H5), 1.79-1.73 (1H, m, H4), 1.54-1.44 (3H, m, H3, 4 and 5); **^{13}C NMR** (*anti* isomer, 125 MHz, $CDCl_3$): δ_C 195.6, 158.8, 127.8, 127.3, 114.1, 111.7, 97.7, 69.2, 55.3, 36.0, 29.8, 26.7, 23.6; **HRMS** (ESI+): $C_{15}H_{18}O_2Na$ $[M+Na]^+$ 253.1199, found 253.1197.

Enantiomeric excess of each diastereomer was determined by chiral HPLC: (CHIRALPAK IB, 1.3 mL/min, 5% IPA/Hexane): *anti* isomer (**17% *ee***): t_R (*R,R*): 6.98 min, t_R (*S,S*): 9.12 min; *syn* isomer (**23% *ee***): t_R (*R,S*): 8.21 min, t_R (*S,R*): 12.42 min.

(±)-2.33a also prepared from epoxide **(±)-2.03a** as follows:

To a degassed solution of epoxide **(±)-2.03a** (20.0 mg, 0.164 mmol, 1 eq.) and 4-methoxyphenylboronic acid (30 mg, 0.197 mmol, 1.2 eq.) in 1,4-dioxane (0.5 mL) was added $Pd(PPh_3)_4$ (18 mg, 10 mol%). The resulting mixture was heated to 100 °C for 2 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4 Et_2O/pet. ether) to leave pure allene **(±)-2.33a** (17 mg, 73.8 μmol, 45%) as an off-white solid. **6.1:1 *dr*** (*anti*:*syn*); all spectral data identical to allene **(*S,S*)-2.33a**.

(*R*)-2-((*R*)-2-(4-methoxyphenyl)-2-phenylvinylidene)cyclohexanol – (*R,R*)-2.33c[35]

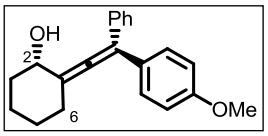


To a degassed solution of epoxide **(*R,R*)-2.03c** (20.0 mg, 0.101 mmol, 1 eq.) and 4-methoxyphenylboronic acid (18 mg, 0.119 mmol, 1.2 eq.) in 1,4-dioxane (0.5 mL) was added $Pd(PPh_3)_4$ (12 mg, 10 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→1:2 Et_2O/pet. ether) to leave pure allene **(*R,R*)-2.33c** (24 mg, 78.3 μmol, 78%) as a pale yellow oil.

6.7:1 *dr*: (*anti*:*syn*); $\mathbf{R_f}$ 0.26 (1:2 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3417, 2934, 1948, 1606, 1510, 1448, 1247, 1034, 909; **^{1}H NMR** (*anti* isomer, 500 MHz, $CDCl_3$): δ_H 7.41-7.27 (7H, m, Ph and Ar*H*), 6.89 (2H, dt, *J* = 9.0 and 2.0 Hz, Ar*H*), 4.19 (1H, *apt* quintet, *J* = 5.0 Hz, H2), 3.83 (3H, s, O*Me*), 2.60 (1H, dt, *J* = 13.0 and 3.0 Hz, H6), 2.21-2.14 (2H, m, H3 and 6), 1.90 (1H, d, *J* = 5.0 Hz, O*H*), 1.91-1.86 (1H, m, H5), 1.83-1.77 (1H, m, H4), 1.54-1.46 (3H, m, H3, 4 and 5); **^{13}C NMR** (*anti* isomer, 125 MHz, $CDCl_3$): δ_C 196.6, 159.0, 137.6, 129.7, 129.5, 128.3, 128.2, 127.1, 113.9, 113.2, 111.1, 69.7, 55.3, 36.3, 30.1, 26.9, 23.8; **HRMS** (ESI+): $C_{21}H_{22}O_2Na$ $[M+Na]^+$ 329.1512, found 329.1508.

Enantiomeric excess of each diastereomer was determined by chiral HPLC: (CHIRALPAK IA, 1.25 mL/min, 2% IPA/Hexane): *anti* isomer (**81% *ee***): t_R (*S,S*): 17.82 min, t_R (*R,R*): 20.96 min; *syn* isomer (**84% *ee***): t_R (*R,S*): 23.82 min, t_R (*S,R*): 25.51 min.

(*S*)-2-((*S*)-2-(4-methoxyphenyl)-2-phenylvinylidene)cyclohexanol – (*S,S*)-2.33c[35]



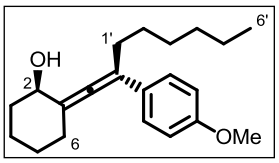
To a degassed solution of carbonate **(*S,S*)-2.04c** (50 mg, 0.206 mmol, 1 eq.) and 4-methoxyphenylboronic acid (38 mg, 0.250 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (24 mg, 10 mol%). The resulting mixture was heated to 100 °C for 20 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→1:2 Et_2O/pet. ether) to leave pure allene **(*S,S*)-2.33c** (40 mg, 0.131 mmol, 64%) as a pale yellow oil.

2.1:1 *dr* (*anti*:*syn*); all spectral data identical to allene **(*R,R*)-2.33c**.

Enantiomeric excess of each diastereomer was determined by chiral HPLC: (CHIRALPAK IA,

1.25 mL/min, 2% IPA/Hexane): *anti* isomer (**85% *ee***): t_R (*S*,*S*): 17.31 min, t_R (*R*,*R*): 20.50 min; *syn* isomer (**85% *ee***): t_R (*R*,*S*): 23.29 min, t_R (*S*,*R*): 24.85 min.

(*R*)-2-((*R*)-2-(4-methoxyphenyl)oct-1-en-1-ylidene)cyclohexanol – (*R*,*R*)-2.33d

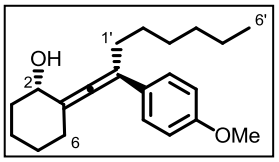


To a degassed solution of epoxide **(*R*,*R*)-2.03d** (50 mg, 0.242 mmol, 1 eq.) and 4-methoxyphenylboronic acid (44 mg, 0.290 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (28 mg, 10 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4 Et_2O/pet. ether) to leave pure allene **(*R*,*R*)-2.33d** (51 mg, 0.162 mmol, 67%) as a pale yellow oil.

4.8:1 *dr* (*anti*:*syn*); **R_f** 0.28 (1:2 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3443, 2929, 1951, 1607, 1510, 1248, 1178, 1037, 831; **^{1}H NMR** (*anti* isomer, 500 MHz, $CDCl_3$): δ_H 7.33 (2H, dt, *J* = 9.0 and 2.0 Hz, Ar*H*), 6.87 (2H, dt, *J* = 9.0 and 2.0 Hz, Ar*H*), 4.15-4.07 (1H, m, H2), 3.81 (3H, s, O*Me*), 2.51-2.46 (1H, m, H6), 2.44 (2H, t, *J* = 7.5 Hz, H1'), 2.18-2.10 (2H, m, H3 and 6), 1.90-1.86 (2H, m, H5 and O*H*), 1.82-1.76 (1H, m, H4), 1.58-1.38 (7H, m, H3, 4, 5, 2' and 3'), 1.35-1.30 (4H, m, H4' and 5'), 0.91 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (*anti* isomer, 125 MHz, $CDCl_3$): δ_C 193.4, 158.6, 129.8, 127.1, 113.7, 111.5, 110.2, 69.4, 55.3, 36.6, 31.8, 30.4, 30.3, 29.1, 28.1, 27.1, 24.0, 22.7, 14.1; **HRMS** (ESI+): calc for $C_{21}H_{30}O_2Na$ $[M+Na]^+$ 337.2138, found 337.2136.

Enantiomeric excess of each diastereomer was determined by chiral HPLC: (CHIRALPAK IA, 1.25 mL/min, 2% IPA/Hexane): *anti* isomer (**87% *ee***): t_R (*R*,*R*): 12.85 min, t_R (*S*,*S*): 13.96 min; *syn* isomer (**87% *ee***): t_R (*R*,*S*): 21.43 min, t_R (*S*,*R*): 22.92 min.

(*S*)-2-((*S*)-2-(4-methoxyphenyl)oct-1-en-1-ylidene)cyclohexanol – (*S*,*S*)-2.33d



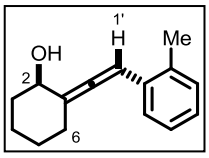
To a degassed solution of carbonate **(*S*,*S*)-2.04d** (50 mg, 0.200 mmol, 1 eq.) and 4-methoxyphenylboronic acid (36 mg, 0.237 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (23 mg, 10 mol%). The resulting mixture was heated to 100 °C for 20 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product

purified by flash chromatography on silica gel (1:4 Et_2O/pet. ether) to leave pure allene **(*S*,*S*)-2.33d** (40 mg, 0.127 mmol, 64%) as a pale yellow oil.

2.2:1 *dr* (*anti:syn*); all spectral data consistent with allene **(*R*,*R*)-2.33d**.

Enantiomeric excess of each diastereomer was determined by chiral HPLC: (CHIRALPAK IA, 1.25 mL/min, 2% IPA/Hexane): *anti* isomer (**34% *ee***): t_R (*R*,*R*): 12.61 min, t_R (*S*,*S*): 13.81 min; *syn* isomer (**39% *ee***): t_R (*R*,*S*): 21.14 min, t_R (*S*,*R*): 22.60 min.

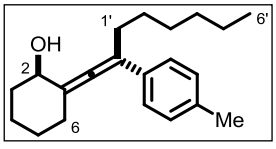
2-(2-(o-tolyl)vinylidene)cyclohexanol – (±)-2.31a[35]



To a solution of epoxide **(±)-2.03b** (50 mg, 0.257 mmol, 1 eq.) and *o*-tolylboronic acid (105 mg, 0.772 mmol, 3 eq.) in 1,4-dioxane/H_2O (2:1 v:v, 2.6 mL) under argon was added $Pd(PPh_3)_4$ (30 mg, 10 mol%). The reaction was stirred and heated to 80 °C for 5 minutes. The reaction was allowed to cool to RT and passed through a short plug of silica gel (EtOAc eluent). The layers were separated, the organic layer washed with 1N aq. NaOH (1 x 5 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave pure allene **(±)-2.31a** (19 mg, 89 μmol, 35%) as a pale yellow oil.

R_f 0.36 (1:2 Et_2O/pet. ether); **5.0:1 *dr***; **IR** (thin film, cm^{-1}): 3456, 3016, 2932, 2855, 1953, 1739, 1444, 1368, 1229, 1216, 1075, 983; **^{1}H NMR** (500 MHz, $CDCl_3$, *anti*-isomer): δ_H 7.35-7.33 (1H, m, Ar*H*), 7.18-7.10 (3H, m, Ar*H*), 6.56-6.53 (1H, m, H1'), 4.23-4.18 (1H, m, H2), 2.56-2.50 (1H, m, H6), 2.38 (3H, s, Ar*Me*), 2.21-2.15 (1H, m, H6), 2.15-2.09 (1H, m, H3), 1.91 (1H, d, *J* = 4.5 Hz, O*H*), 1.91-1.85 (1H, m, H4), 1.81-1.74 (1H, m, H5), 1.56-1.44 (3H, m, H3, 4 and 5); **^{13}C NMR** (125 MHz, $CDCl_3$ *anti*-isomer): δ_C 197.5, 135.1, 133.1, 130.6, 127.3, 126.9, 126.1, 110.4, 95.5, 69.1, 35.8, 29.6, 26.5, 23.4, 19.9; **HRMS** (ESI+): calc for $C_{15}H_{18}ONa$ $[M+Na]^+$ 237.1250, found 237.1247.

2-(2-*p*-tolyloct-1-enylidene)cyclohexanol – 2.34

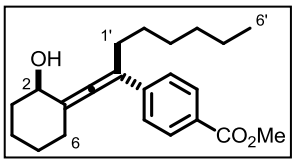


To a degassed solution of epoxide **(±)-2.03d** (100 mg, 0.484 mmol, 1 eq.) and *p*-tolyl boronic acid (79 mg, 0.581 mmol, 1.2 eq.) in 1,4-dioxane (1.93 mL) was added $Pd(PPh_3)_4$ (11 mg, 2 mol%). The resulting solution was heated to 100 °C for 17 minutes. The reaction was cooled and passed through a short plug of silica gel (Et_2O

eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:9→2:7 Et_2O/pet. ether, buffered with 1% Et_3N by volume) to leave pure allene **2.34** (94 mg, 0.315 mmol, 65%) as a colourless oil.

5.3:1 *dr* (*anti:syn*); **R_f** 0.4 (2:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3424, 2929, 2856, 1952, 1511, 1446, 1075, 818; **^{1}H NMR** (*anti* isomer, 500 MHz, $CDCl_3$): δ_H 7.30 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.13 (2H, d, *J* = 8.0 Hz, Ar*H*), 4.16-4.08 (1H, m, H2), 2.52-2.46 (1H, m, H6), 2.45 (2H, t, *J* = 7.5 Hz, H1'), 2.35 (3H, s, Ar*Me*), 2.19-2.10 (2H, m, H3 and 6), 1.91-1.77 (3H, m, H4, 5 and O*H*), 1.58-1.38 (7H, m, H3, 4, 5, 2' and 3'), 1.35-1.22 (4H, m, H4' and 5'), 0.91 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (*anti* isomer, 125 MHz, $CDCl_3$): δ_C 194.0, 136.7, 134.7, 129.2, 126.0, 111.6, 110.7, 69.5, 36.6, 32.0, 30.5, 30.4, 29.2, 28.2, 27.2, 24.1, 22.9, 21.2, 14.3; **HRMS** (ESI+): calc for $C_{21}H_{30}ONa$ $[M+Na]^+$ 321.2189, found 321.2187.

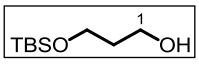
methyl 4-(1-(2-hydroxycyclohexylidene)oct-1-en-2-yl)benzoate – 2.35



To a degassed solution of epoxide **(±)-2.03d** (100 mg, 0.484 mmol, 1 eq.) and 4-(methoxycarbonyl)phenylboronic acid (105 mg, 0.581 mmol, 1.2 eq.) in 1,4-dioxane (1.93 mL) was added $Pd(PPh_3)_4$ (11 mg, 2 mol%). The resulting solution was heated to 100 °C for 20 minutes. The reaction was cooled and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→1:2 Et_2O/pet. ether, buffered with 1% Et_3N by volume) to leave pure allene **2.35** (102 mg, 0.298 mmol, 62%) as a colourless oil.

2.7:1 *dr* (*anti:syn*); **R_f** 0.19 (1:2 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3475, 2930, 2856, 1950, 1722, 1606, 1436, 1278, 1111, 809; **^{1}H NMR** (*anti* isomer, 500 MHz, $CDCl_3$): δ_H 7.97 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.44 (2H, d, *J* = 8.5 Hz, Ar*H*), 4.20-4.13 (1H, m, H2), 3.91 (3H, s, O*Me*), 2.53-2.44 (3H, m, H6 and 1'), 2.19-2.12 (2H, m, H6 and 3), 1.89 (1H, m, H5), 1.82-1.76 (2H, m, H4 and O*H*), 1.58-1.37 (7H, m, H3, 4, 5, 2' and 3'), 1.35-1.29 (4H, m, H4' and 5'), 0.90 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (*anti* isomer, 125 MHz, $CDCl_3$): δ_C 196.0, 167.1, 142.7, 129.8, 128.3, 125.9, 112.2, 109.9, 69.5, 52.2, 36.6, 31.9, 30.2, 30.1, 29.2, 28.2, 27.1, 23.9, 22.8, 14.2; **HRMS** (ESI+): calc for $C_{22}H_{30}O_3Na$ $[M+Na]^+$ 365.2087, found 365.2087.

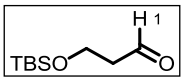
3-(*tert*-butyldimethylsilyloxy)propan-1-ol – 2.50.1[246]



To a stirred suspension of NaH (60% in mineral oil, 1.05 g, 26.3 mmol, 1 eq.) in anhydrous THF (40 mL) at 0 °C under argon was added 1,3-propanediol **2.50** (1.9 mL, 26.3 mmol, 1 eq.) dropwise. The mixture was allowed to warm to RT and stirred for 1 hour during which time a white precipitate formed. The reaction was cooled to 0 °C and TBSCl (3.96 g, 26.3 mmol, 1 eq.) was added portionwise. The reaction was stirred for 15 minutes and quenched with sat. aq. $NaHCO_3$ (40 mL). The THF was removed *in vacuo* and the aqueous layer extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→3:7 EtOAc/pet. ether) to leave pure mono-protected diol **2.50.1** (4.43 g, 23.3 mmol, 89%) as a colourless oil.

R_f 0.24 (1:9 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.84-3.75 (4H, m, H1 and 3), 2.75 (1H, t, *J* = 4.0 Hz, O*H*), 1.80-1.72 (2H, m, H2), 0.89 (9H, s, Si*t-Bu*), 0.07 (6H, s, Si*Me*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 62.8, 62.3, 34.1, 25.8, 18.1, −5.5. Data consistent with literature.[246]

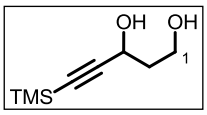
3-(*tert*-butyldimethylsilyloxy)propanal – 2.51[247]



To a stirred solution of alcohol **2.50.1** (4.10 g, 21.5 mmol, 1 eq.), Et_3N (21.0 mL, 0.151 mol, 7 eq.) and DMSO (14.6 mL, 0.205 mmol, 9.5 eq.) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added SO_3·pyridine complex (10.3 g, 64.6 mmol, 3 eq.) portionwise over 10 minutes. The reaction was stirred at 0 °C for 1 hour, allowed to warm to RT and stirred for a further 1 hour. The reaction was quenched with aq. 1N HCl (100 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were sequentially washed with aq. 1N HCl (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19→1:9 Et_2O/pet ether) to leave aldehyde **2.51** (3.46 g, 18.4 mmol, 86%) as a colourless oil.

R_f 0.36 (1:9 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 9.81 (1H, t, *J* = 2.0 Hz, H1), 4.00 (2H, t, *J* = 6.0 Hz, H3), 2.61 (2H, td, *J* = 6.0 and 2.0 Hz, H2), 0.89 (9H, s, Si*t-Bu*), 0.07 (6H, s, Si*Me*$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 202.1, 57.4, 46.5, 25.8, 18.2, −5.5. Data consistent with literature.[247]

5-(trimethylsilyl)pent-4-yne-1,3-diol – 2.52b[248]

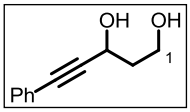


To a stirred solution of trimethylsilyl acetylene (844 mg, 8.6 mmol, 1.2 eq.) in anhydrous THF (20 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 3.44 mL, 8.6 mmol, 1.2 eq.). The solution was stirred at −78 °C for 30 minutes and to it added a solution of aldehyde **2.51** (1.35 g, 7.17 mmol) in anhydrous THF (10 mL). The reaction was allowed to warm to RT, stirred for 10 minutes and quenched with sat. aq. $NaHCO_3$ (30 mL). The THF was removed *in vacuo* and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave the crude protected alcohol (2.0 g) which was used directly in the next step without further purification.

The above crude protected alcohol (2.0 g) was taken up in methanol (30 mL) and to it added a catalytic amount of CSA. The resulting mixture was stirred for 30 minutes, the methanol removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave diol **2.52b** (0.97 g, 5.63 mmol, 79%, *2 steps*) as a colourless oil.

R_f 0.32 (4:1 Et_2O/pet. ether); **^{1}H NMR** (250 MHz, $CDCl_3$): δ_H 4.65 (1H, m, H3), 4.00 (1H, m, H1), 3.88 (1H, m, H1), 2.58 (1H, d, *J* = 5.0 Hz, O*H*), 2.07 (1H, t, *J* = 5.0 Hz, O*H*), 1.99 (2H, m, H2), 0.19 (9H, s, Si*Me*$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 105.8, 90.1, 62.1, 60.5, 38.9, −0.2. Data consistent with literature.[248]

5-phenylpent-4-yne-1,3-diol – 2.52c[249]



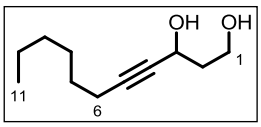
To a stirred solution of phenylacetylene (0.70 mL, 6.37 mmol, 1.2 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 2.55 mL, 6.37 mmol). The solution was stirred at −78 °C for 30 minutes and to it added a solution of aldehyde **2.51** (1.0 g, 5.31 mmol, 1 eq.) in anhydrous THF (10 mL). The mixture was allowed to warm to RT, stirred for 10 minutes and quenched with sat. aq. $NaHCO_3$ (30 mL). The THF was removed *in vacuo* and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave the crude protected alcohol (1.54 g) which was used directly in the next step without further purification.

The above crude protected alcohol (1.54 g) was taken up in methanol (20 mL) and to it added a catalytic amount of CSA. The resulting mixture was stirred for 45 minutes, the methanol removed *in*

vacuo and the crude product purified by flash chromatography on silica gel (1:2→1:1 EtOAc/pet. ether) to leave diol **2.52c** (912 mg, 5.18 mmol, 98%, *2 steps*) as a colourless oil.

R_f 0.12 (1:1 EtOAc/pet. ether); **IR** (thin film, cm^{-1}): 3356, 2954, 2232, 1599, 1572, 1490, 1052. **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.43 (2H, m, Ph), 7.34-7.30 (3H, m, Ph), 4.89 (1H, dd, *J* = 7.0 and 4.5 Hz, H3), 4.12-4.05 (1H, m, H1), 3.97-3.91 (1H, m, H1), 2.57 (1H, bs, O*H*), 2.43 (1H, bs, O*H*), 2.16-2.02 (2H, m, H2); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.7, 128.5, 128.3, 122.4, 89.2, 85.3, 62.3, 60.6, 39.0; **HRMS** (ESI+): calc for $C_{11}H_{12}O_2Na$ $[M+Na]^+$ 199.0730, found 199.0736.

undec-4-yne-1,3-diol – 2.52d

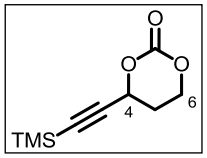


To a stirred solution of 1-octyne (0.94 mL, 6.37 mmol, 1.2 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 2.55 mL, 6.37 mmol, 1.2 eq.). The solution was stirred at −78 °C for 30 minutes and to it added a solution of aldehyde **2.51** (1.0 g, 5.31 mmol) in anhydrous THF (10 mL). The mixture was allowed to warm to RT, stirred for 10 minutes and quenched with sat. aq. $NaHCO_3$ (30 mL). The THF was removed *in vacuo* and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave the crude protected alcohol (1.58 g) which was used directly in the next step without further purification.

The above crude protected alcohol (1.58 g) was taken up in methanol (20 mL) and to it added a catalytic amount of CSA. The resulting mixture was stirred for 45 minutes, the methanol removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:2→1:1 EtOAc/pet. ether) to leave diol **2.52d** (895 mg, 4.86 mmol, 92%, *2 steps*) as a colourless oil.

R_f 0.18 (1:1 EtOAc/pet. ether); **IR** (thin film, cm^{-1}): 3356, 2931, 2859, 2234, 1466, 1433, 1054, 888; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.61-4.49 (1H, m, H3), 4.00-3.92 (1H, m, H1), 3.85-3.79 (1H, m, H1), 3.01 (1H, bs, O*H*), 2.64 (1H, bs, O*H*), 2.20 (2H, td, *J* = 7.0 and 2.0 Hz, H6), 2.01-1.85 (2H, m, H2), 1.53-1.45 (2H, m, H7), 1.40-1.23 (6H, m, H8, 9 and 10), 0.88 (3H, t, *J* = 7.0 Hz, H11); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 86.1, 80.5, 61.9, 60.5, 39.3, 31.3, 28.6, 28.5, 22.5, 18.7, 14.0; **HRMS** (ESI+): calc for $C_{11}H_{20}O_2Na$ $[M+Na]^+$ 207.1356, found 207.1364.

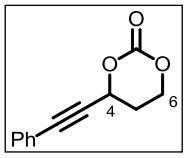
4-((trimethylsilyl)ethynyl)-1,3-dioxan-2-one – 2.05b



To a stirred solution of diol **2.52b** (500 mg, 2.90 mmol, 1 eq.) in anhydrous CH_2Cl_2 (40 mL) under argon was added Et_3N (2.43 mL, 17.4 mmol, 6 eq.), pyridine (1.41 mL, 17.4 mmol, 6 eq.) and powered 4Å molecular sieves (500 mg). The resulting mixture was cooled to −78 °C and to it added a solution of triphosgene (431 mg, 1.45 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (10 mL) dropwise. After 15 minutes at −78 °C the reaction was quenched with sat. aq. $NaHCO_3$ (50 mL), and allowed to warm to RT. The layers were separated, the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers washed with brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (2:1 Et_2O/pet ether→Et_2O) to leave pure carbonate **2.05b** (442 mg, 2.23 mmol, 77%) as an off-white solid.

R_f 0.23 (4:1 Et_2O/pet. ether); **m.p.** 89-92 °C; **IR** (thin film, cm^{-1}): 2967, 2176, 1745, 1473, 1248, 1114, 846; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 5.20 (1H, t, *J* = 5.0 Hz, H4), 4.68 (1H, ddd, *J* = 11.0, 9.0 and 4.0 Hz, H6), 4.43 (1H, m, H6), 2.36 (1H, m, H5), 2.16 (1H, m, H5), 0.20 (9H, s, Si*Me*$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 147.3, 98.9, 94.5, 68.3, 65.8, 27.5, −0.5; **HRMS** (CI+): calc for $C_9H_{18}NO_3Si$ $[M+NH_4]^+$ 216.1056, found 216.1052.

4-(phenylethynyl)-1,3-dioxan-2-one – 2.05c

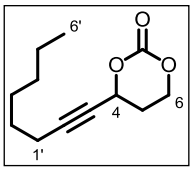


To a stirred solution of diol **2.52c** (500 mg, 2.84 mmol, 1 eq.) in anhydrous CH_2Cl_2 (50 mL) under argon was added Et_3N (2.38 mL, 17.0 mmol, 6 eq.), pyridine (1.37 mL, 17.0 mmol, 6 eq.) and powered 4Å molecular sieves (500 mg). The resulting mixture was cooled to −78 °C and a solution of triphosgene (421 mg, 1.42 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (5 mL) was added dropwise. After 30 minutes at −78 °C the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL) and allowed to warm to RT. The layers were separated, the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers washed with brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→1:2 EtOAc/pet. ether) to leave pure carbonate **2.05c** (455 mg, 2.25 mmol, 79%) as a yellow solid.

R_f 0.07 (1:4 EtOAc/pet. ether); **m.p.** 64-65 °C; **IR** (thin film, cm^{-1}): 2952, 2238, 1748, 1490, 1407,

1110, 759; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46 (2H, dt, *J* = 6.5 and 1.5 Hz, Ph), 7.39-7.32 (3H, m, Ph), 5.46 (1H, t, *J* = 5.0 Hz, H4), 4.73 (1H, ddd, *J* = 11.0, 9.0 and 4.0 Hz, H6), 4.49 (1H, dt, *J* = 11.0 and 4.5 Hz, H6), 2.50-2.43 (1H, m, H5), 2.31-2.24 (1H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 147.4, 131.9, 129.4, 128.5, 121.0, 88.5, 83.1, 68.6, 66.0, 27.6; **HRMS** (ESI+): calc for $C_{12}H_{10}O_3Na$ $[M+Na]^+$ 225.0522, found 225.0523.

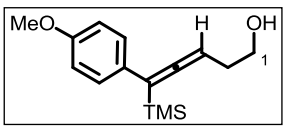
4-(oct-1-ynyl)-1,3-dioxan-2-one – 2.05d



To a stirred solution of diol **2.52d** (500 mg, 2.71 mmol, 1 eq.) in anhydrous CH_2Cl_2 (50 mL) under argon was added Et_3N (2.27 mL, 16.3 mmol, 6 eq.), pyridine (1.32mL, 16.3 mmol, 6 eq.) and powered 4Å molecular sieves (500 mg). The resulting mixture was cooled to −78 °C and to it added a solution of triphosgene (403 mg, 1.36 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (5 mL) dropwise. After 1 hour at −78 °C the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL) and allowed to warm to RT. The layers were separated, the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers washed with brine (25 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:5→1:4 EtOAc/pet. ether) to leave pure carbonate **2.05d** (480 mg, 2.28 mmol, 84%) as a yellow oil.

R_f 0.16 (1:4 EtOAc/pet. ether); **IR** (thin film, cm^{-1}): 2932, 2860, 2239, 1760, 1468, 1408, 1256, 1186, 1121; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 5.22-5.19 (1H, m, H4), 4.68 (1H, ddd, *J* = 11.0, 9.0 and 4.0 Hz, H6), 4.42 (1H, ddd, *J* = 11.0, 5.0 and 5.0 Hz, H6), 2.37-2.31 (1H, m, H5), 2.25 (2H, td, *J* = 7.0 and 2.0 Hz, H1'), 2.14-2.08 (1H, m, H5), 1.53 (2H, quintet, *J* = 7.0 Hz, H2'), 1.41-1.21 (6H, m, H3', 4' and 5'), 0.90 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 147.6, 90.1, 74.8, 68.4, 65.9, 31.2, 28.5, 28.1, 27.8, 22.5, 18.6, 14.0; **HRMS** (CI+): calc for $C_{12}H_{22}NO_3$ $[M+NH_4]^+$ 228.1600, found 228.1609.

5-(4-methoxyphenyl)-5-(trimethylsilyl)penta-3,4-dien-1-ol – 2.53b

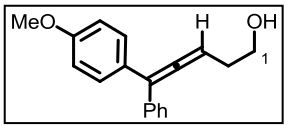


To a degassed solution of carbonate **2.05b** (50 mg, 0.252 mmol, 1 eq.) and 4-methoxyphenylboronic acid (46 mg, 0.303 mmol, 1.2 eq.) in 1,4 dioxane (1 mL) was added $Pd(PPh_3)_4$ (2.9 mg, 1 mol%). The resulting mixture was heated to 100 °C for 5

minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→1:2 Et_2O/pet. ether) to leave pure allene **2.53b** (47 mg, 0.179 mmol, 71%) as a pale yellow oil.

R_f 0.07 (1:4 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3356, 2955, 1925, 1605, 1507, 1248, 1177, 1038, 839; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.24 (2H, dt, *J* = 9.0 and 2.5 Hz, Ar*H*), 6.86 (2H, dt, *J* = 9.0 and 2.5 Hz, Ar*H*), 5.14 (1H, t, *J* = 7.0 Hz, H3), 3.80 (3H, s, O*Me*), 3.82-3.69 (2H, m, H1), 2.34 (2H, q, *J* = 6.5 Hz, H2), 1.57 (1H, bs, O*H*), 0.24 (9H, s, Si*Me*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 208.1, 158.2, 129.5, 114.0, 100.0, 83.1, 62.4, 55.3, 31.8, −0.3; **HRMS** (CI+): calc for $C_{15}H_{23}O_2Si$ $[M+H]^+$ 263.1467, found 263.1463.

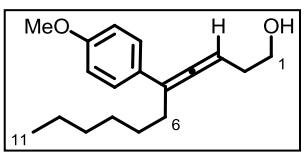
5-(4-methoxyphenyl)-5-phenylpenta-3,4-dien-1-ol – 2.53c



To a degassed solution of carbonate **2.05c** (50 mg, 0.247 mmol, 1 eq.) and 4-methoxyphenylboronic acid (45 mg, 0.296 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (2.9 mg, 1 mol%). The resulting mixture was heated to 100 °C for 5 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:2→1:1 Et_2O/pet. ether) to leave pure allene **2.53c** (51 mg, 0.191 mmol, 77%) as a yellow oil.

R_f 0.15 (2:3 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3374, 2954, 1942, 1605, 1509, 1248, 1176, 1034, 834; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.40-7.30 (5H, m, Ph), 7.29 (2H, dt, *J* = 9.0 and 2.5 Hz, Ar*H*), 6.90 (2H, dt, *J* = 9.0 and 2.5 Hz, Ar*H*), 5.70 (1H, t, *J* = 6.5 Hz, H3), 3.83 (3H, s, O*Me*), 3.84-3.77 (2H, m, H1), 2.46 (2H, q, *J* = 6.5 Hz, H2), 1.57 (1H, bs, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 205.8, 158.9, 137.0, 129.5, 128.9, 128.4, 128.3, 127.2, 113.9, 109.8, 90.4, 62.0, 55.3, 32.5; **HRMS** (CI+): calc for $C_{18}H_{19}O_2$ $[M+H]^+$ 267.1385, found 267.1384.

5-(4-methoxyphenyl)undeca-3,4-dien-1-ol – 2.53d

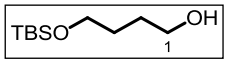


To a degassed solution of carbonate **2.05d** (50 mg, 0.238 mmol, 1 eq.) and 4-methoxyphenylboronic acid (43 mg, 0.283 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (2.8 mg, 1 mol%). The resulting mixture was

heated to 100 °C for 5 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:3 Et_2O/pet. ether) to leave pure allene **2.53d** (49 mg, 0.179 mmol, 75%) as a pale yellow oil.

R_f 0.07 (1:4 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3375, 2929, 1947, 1606, 1510, 1304, 1248, 1177, 1039; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.33 (2H, dt, *J* = 9.0 and 2.0 Hz, Ar*H*), 6.87 (2H, dt, *J* = 9.0 and 2.0 Hz, Ar*H*), 5.50 (1H, tt, *J* = 6.0 and 3.0 Hz, H3), 3.81 (3H, s, O*Me*), 3.77 (2H, *apt* q, *J* = 6.0 Hz, H1), 2.40 (2H, td, *J* = 7.0 and 3.0 Hz, H6), 2.38 (2H, *apt* q, *J* = 6.0 Hz, H2), 1.60-1.48 (2H, m, H7 and O*H*), 1.43-1.35 (2H, m, H8), 1.35-1.27 (4H, m, H9 and 10), 0.90 (3H, t, *J* = 7.0 Hz, H11); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 204.0, 158.4, 135.5, 127.0, 113.9, 105.9, 90.4, 62.2, 55.3, 32.6, 31.7, 30.1, 29.2, 28.0, 22.7, 14.1; **HRMS** (ESI+): calc for $C_{18}H_{26}O_2Na$ $[M+Na]^+$ 297.1825, found 297.1817.

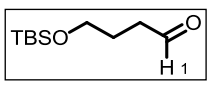
4-(*tert*-butyldimethylsilyloxy)butan-1-ol – 2.54.1[104]



To a stirred solution of NaH (60% in mineral oil, 1.33 g, 33.3 mmol, 1 eq.) in anhydrous THF (70 mL) under argon was added 1,4-butanediol (2.95 mL, 33.3 mmol, 1 eq.) dropwise. The mixture was stirred for 1 hour during which time a white precipitate formed. The reaction was cooled to 0 °C and to it added TBSCl (5.02 g, 33.3 mmol, 1 eq.) portionwise. The reaction was stirred for 15 minutes and poured into Et_2O (100 mL). The organic layer was washed with 10% aq. K_2CO_3 (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (3:7 EtOAc/pet. ether) to leave pure mono-protected diol **2.54.1** (6.62 g, 32.4 mmol, 97%) as a colourless oil.

R_f 0.29 (3:7 EtOAc/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.69-3.59 (4H, m, H1 and 4), 2.79 (1H, bs, O*H*), 1.69-1.57 (4H, m, H2 and 3), 0.89 (9H, s, Si*t-Bu*), 0.06 (6H, s, Si*Me_2*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 63.3, 62.8, 30.3, 29.9, 25.9, 18.3, −5.4. Data consistent with literature.[250]

4-(*tert*-butyldimethylsilyloxy)butanal – 2.55[250]

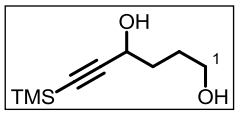


To a stirred solution of alcohol **2.54.1** (1.82 g, 8.91 mmol, 1 eq.) in anhydrous CH_2Cl_2 (50 mL) under argon was added Et_3N (8.68 mL, 62.3 mmol, 7 eq.) and DMSO (6 mL, 84.6, 9.5 eq.). The resulting mixture was cooled to 0 °C and SO_3·pyridine (4.25 g,

26.7 mmol, 3 eq.) was added portionwise over 10 minutes. The reaction was stirred for 1 hour at 0 °C, allowed to warm to RT and stirred for a further 2 hours. The reaction was quenched with saturated aqueous NH_4Cl solution (50 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9 Et_2O/pet. ether) to leave pure aldehyde **2.55** (1.80 g, 8.89 mmol, 99%) as a pale yellow oil.

R_f 0.29 (3:7 EtOAc/pet. ether); **^{1}H NMR** (250 MHz, $CDCl_3$): δ_H 9.80 (1H, t, *J* = 1.5 Hz, H1), 3.66 (2H, t, *J* = 6.0 Hz, H4), 2.51 (2H, td, *J* = 7.0 and 1.5 Hz, H2), 1.87 (2H, tt, *J* = 6.0 and 7.0 Hz, H3), 0.90 (9H, s, Si*t-Bu*), 0.05 (6H, s, Si*Me*$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 202.6, 62.0, 40.8, 25.9, 25.5, 18.2, −5.4. Data consistent with literature.[250]

6-(trimethylsilyl)hex-5-yne-1,4-diol – 2.56b[251]

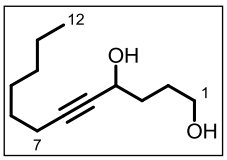


To a stirred solution of trimethylsilyl acetylene (1.22 mL, 8.60 mmol, 1.2 eq.) in anhydrous THF (20 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 8.60 mmol, 1.2 eq.) dropwise. The resulting mixture was stirred for 30 minutes and to it added a solution of aldehyde **2.55** (1.45 g, 7.17 mmol, 1 eq.) in anhydrous THF (20 mL). The reaction was warmed to RT and quenched with sat. aq. $NaHCO_3$ (25 mL). The THF was removed *in vacuo* and the aqueous layer extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* to leave the crude protected alcohol (1.60 g) as a pale yellow oil which was used directly in the next step without further purification.

The above crude protected alcohol (1.60 g) was taken up in methanol (30 mL) and to it added a catalytic amount of CSA. The reaction was stirred for 15 minutes, the methanol removed *in vacuo* and the crude product purified by flash chromatography on silica gel (3:1 Et_2O/pet. ether) to leave pure diol **2.56b** (1.0 g, 5.37 mmol, 75%, *2 steps*) as an off-white solid.

m.p. 31-32 °C; **R_f** 0.26 (4:1 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.45 (1H, m, H4), 3.78-3.67 (2H, m, H1), 3.25 (1H, bs, O*H*), 2.53 (1H, bs, O*H*), 1.87-1.72 (4H, m, H2 and 3), 0.18 (9H, s, Si*Me*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 106.5, 89.4, 62.5, 62.4, 34.7, 28.3, −0.1. Data consistent with literature.[251]

dodec-5-yne-1,4-diol – 2.56d

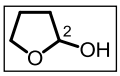


To a stirred solution of 1-octyne (0.96 mL, 6.52 mmol, 1.2 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 2.61 mL, 6.52 mmol, 1.2 eq.). The solution was stirred at −78 °C for 30 minutes and to it added a solution of aldehyde **2.55** (1.1 g, 5.44 mmol) in anhydrous THF (5 mL). The mixture was allowed to warm to RT, stirred for 10 minutes and quenched with sat. aq. $NaHCO_3$ (20 mL). The THF was removed *in vacuo* and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave the crude protected alcohol (1.45 g) which was used directly in the next step without further purification.

The above crude protected alcohol (1.45 g) was taken up in methanol (25 mL) and to it added a catalytic amount of CSA. The resulting mixture was stirred for 45 minutes, the methanol removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave diol **2.56d** (0.59 g, 2.98 mmol, 55%, *2 steps*) as a colourless oil.

R_f 0.08 (4:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3318, 2929, 2858, 2235, 1456, 1330, 1140, 1029; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 4.47-4.42 (1H, m, H4), 3.76-3.66 (2H, m, H1), 2.41 (1H, d, *J* = 5.0 Hz, O*H*), 2.21 (2H, td, *J* = 7.0 and 2.0 Hz, H7), 1.86-1.71 (5H, m, H2, 3 and O*H*), 1.53-1.48 (2H, m, H8), 1.25-1.41 (6H, m, H9, 10 and 11), 0.90 (3H, t, *J* = 7.0 Hz, H12); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 85.9, 80.9, 62.7, 62.4, 35.0, 31.3, 28.6, 28.5, 28.4, 22.5, 18.6, 14.0; **HRMS** (ESI+): calc for $C_{12}H_{22}O_2Na$ $[M+Na]^+$ 221.1512, found 221.1514.

tetrahydrofuran-2-ol – 2.58[252]

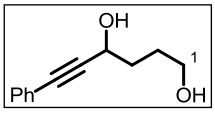


To a stirred solution of γ-butyrolactone **2.57** (1.0 g, 11.6 mmol, 1 eq.) in anhydrous Et_2O (15 mL) at −78 °C under argon was added DIBAL-H (1.2 M in toluene, 10.65 mL, 12.8 mmol, 1.1 eq.) dropwise. The reaction was stirred for 3 hours and quenched with MeOH (3 mL). The mixture was allowed to warm to 0 °C and brine (25 mL) was added. The reaction mixture was passed through Celite® (Et_2O eluent) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product purified by distillation to leave pure lactol **2.58** (340 mg, 3.86 mmol, 33%) as a colourless oil.

b.p. 72 °C @ 30 mbar (lit.[253] 63-65 °C @ 20 mbar); **R_f** 0.35 (9:1 EtOAc/CH_2Cl_2); **^{1}H NMR** (400

MHz, $CDCl_3$): δ_H 5.56-5.53 (1H, m, H2), 4.08-4.03 (1H, m, H5), 3.89-3.83 (1H, m, H5), 2.99 (1H, bs, O*H*), 2.12-2.02 (1H, m, H3), 1.99-1.82 (3H, m, H3 and 4); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 98.4, 67.4, 33.2, 23.4. Data consistent with literature.[252]

6-phenylhex-5-yne-1,4-diol – (±)-2.56c

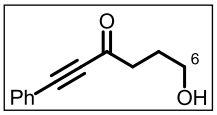


To a stirred solution of phenyl acetylene (0.37 mL, 3.40 mmol, 3 eq.) in anhydrous THF (8 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 1.36 mL, 3.40 mmol, 3 eq.) dropwise. The resulting solution was stirred for 1 hour and to it added a solution of lactol **2.58** (100 mg, 1.13 mmol, 1 eq.) in anhydrous THF (2 mL). The reaction was allowed to warm to RT, stirred for 10 minutes and quenched with sat. aq. $NaHCO_3$ (10 mL). The THF was removed *in vacuo* and the aqueous layer extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave pure diol **(±)-2.56c** (202 mg, 1.06 mmol, 94%) as a white solid.

R_f 0.39 (EtOAc); **m.p.** 37-38 °C; **IR** (CH_2Cl_2, cm^{-1}): 3332, 2948, 2228, 1599, 1490, 1028, 757; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.45-7.40 (2H, m, Ph), 7.32-7.28 (2H, m, Ph), 4.67 (1H, dt, *J* = 5.0 and 5.0 Hz, H4), 3.79-3.65 (2H, m, H1), 3.64 (1H, bs, O*H*), 2.78 (1H, bs, O*H*), 1.96-1.73 (4H, m, H2 and 3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 131.7, 128.4, 128.3, 122.6, 89.9, 84.9, 62.5, 62.4, 34.9, 28.4; **HRMS** (ESI+): calc for $C_{12}H_{14}O_2Na$ $[M+Na]^+$ 213.0886, found 213.0884.

Also prepared from ketone **2.59c** in 72% yield using $NaBH_4$/MeOH. See the synthesis of diol **(±)-3.38** for a representative procedure.

6-hydroxy-1-phenylhex-1-yn-3-one – 2.59c[146]



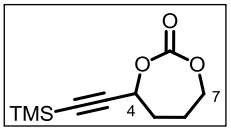
To a stirred solution of phenyl acetylene (1.53 mL, 13.9 mmol, 1.2 eq.) in anhydrous THF (20 mL) at −20 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 5.58 mL, 13.9 mmol, 1.2 eq.) dropwise. The resulting mixture was warmed to RT and stirred for 30 minutes. The reaction was cooled to −78 °C and a solution of γ-butyrolactone **2.57** (1.0 g, 11.6 mmol, 1 eq.) in anhydrous THF (6 mL) was added dropwise. The reaction was stirred at −78 °C for 1 hour, warmed to −20 °C and quenched with sat. aq. NH_4Cl (25 mL). The THF was

removed *in vacuo* and the aqueous layer extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→1:2 EtOAc/pet. ether) to leave pure ketone **2.59c** (1.55 g, 8.24 mmol, 71%) as a yellow oil.

R_f 0.36 (1:1 EtOAc/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.54 (2H, dt, *J* = 7.5 and 1.5 Hz, Ph), 7.42 (1H, tt, *J* = 7.5 and 1.5 Hz, Ph), 7.35 (2H, dt, *J* = 7.5 and 1.5 Hz, Ph), 3.68 (2H, td, *J* = 7.0 and 5.0 Hz, H6), 2.79 (2H, t, *J* = 7.0 Hz, H4), 2.53 (1H, t, *J* = 5.0 Hz, O*H*), 1.96 (2H, quintet, *J* = 7.0 Hz, H5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.0, 133.1, 130.8, 128.6, 119.8, 91.2, 87.7, 61.6, 42.1, 26.8. Data consistent with literature.[146]

Also prepared in 79% yield using the $BF_3{\cdot}OEt_2$ modification,[146] see the synthesis of ketone **2.59e** for a representative procedure.

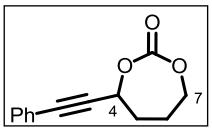
4-((trimethylsilyl)ethynyl)-1,3-dioxepan-2-one - (±)-2.06b



To a stirred solution of diol **2.56b** (500 mg, 2.68 mmol, 1 eq.) in anhydrous CH_2Cl_2 (40 mL) under argon was added Et_3N (2.25 mL, 16.1 mmol, 6 eq.), pyridine (1.36 mL, 16.1 mmol, 6 eq.) and powered 4Å molecular sieves (500 mg). The resulting mixture was cooled to −78 °C and to it added a solution of triphosgene (398 mg, 1.34 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (5 mL) dropwise. After 1 hour at −78 °C the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL) and allowed to warm to RT. The layers were separated, the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers washed with brine (25 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether) to leave pure carbonate **(±)-2.06b** (256 mg, 1.21 mmol, 45%) as an off-white solid.

R_f 0.21 (1:1 Et_2O/pet. ether); **m.p.** 73-75 °C; **IR** (thin film, cm^{-1}): 2961, 2178, 1763, 1393, 1251, 1164, 1059, 847; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 5.02 (1H, dd, *J* = 6.0 and 3.0 Hz, H4), 4.25-4.14 (2H, m, H7), 2.2-2.04 (3H, m, H5 and 6), 1.94-1.87 (1H, m, H6), 0.19 (9H, s, Si*Me*$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 153.4, 99.0, 95.0, 70.8, 70.3, 33.5, 25.1,−0.4; **HRMS** (CI+): calc for $C_{10}H_{20}NO_3Si$ $[M+NH_4]^+$ 230.1212, found 230.1214.

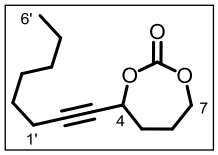
4-(phenylethynyl)-1,3-dioxepan-2-one - (±)-2.06c



To a stirred solution of diol **(±)-2.56c** (200 mg, 1.05 mmol, 1 eq.) in anhydrous CH_2Cl_2 (15 mL) under argon was added Et_3N (0.88 mL, 6.30 mmol, 6 eq.), pyridine (0.51 mL, 6.30 mmol, 6 eq.) and powered 4Å molecular sieves (200 mg). The resulting mixture was cooled to −78 °C and to it added a solution of triphosgene (156 mg, 0.53 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (2 mL) dropwise. After 1 hour at −78 °C the reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and allowed to warm to RT. The layers were separated, the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers washed with brine (15 mL). The organic layer was dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:2→1:1 Et_2O/pet. ether) to leave pure carbonate **(±)-2.06c** (105 mg, 0.486 mmol, 46%) as a yellow solid.

m.p. 78-79 °C; $\mathbf{R_f}$ 0.15 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2958, 2254, 1758, 1491, 1204, 1167, 1056, 818; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.45 (2H, dd, *J* = 8.0 and 1.5 Hz, Ph), 7.37-7.30 (3H, m, Ph), 5.28 (1H, dd, *J* = 5.0 and 3.0 Hz, H4), 4.31-4.18 (2H, m, H7), 2.32-2.14 (3H, m, H5 and 6), 2.02-1.90 (1H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 153.6, 131.9, 129.2, 128.4, 121.4, 89.2, 83.1, 71.1, 70.5, 33.6, 25.2; **HRMS** (ESI+): calc for $C_{13}H_{12}O_3Na$ $[M+Na]^+$ 239.0679, found 239.0680.

4-(oct-1-ynyl)-1,3-dioxepan-2-one – 2.06d

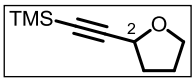


To a stirred solution of diol **2.56d** (770 mg, 3.88 mmol, 1 eq.) in anhydrous CH_2Cl_2 (75 mL) under argon was added Et_3N (3.36 mL, 23.2 mmol, 6 eq.), pyridine (1.92 mL, 23.2 mmol, 6 eq.) and powered 4Å molecular sieves (1.0 g). The resulting mixture was cooled to −78 °C and to it added a solution of triphosgene (576 mg, 1.94 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (5 mL) dropwise. After 1 hour at −78 °C the reaction was quenched with sat. aq. $NaHCO_3$ (50 mL) and allowed to warm to RT. The layers were separated, the aqueous layer extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic layers washed with brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2→1:1 Et_2O/pet. ether) to leave pure carbonate **2.06d** (750 mg, 3.34 mmol, 86%) as a yellow oil.

$\mathbf{R_f}$ 0.34 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2931, 2247, 1768, 1466, 1393, 1287, 1241, 1167,

1047; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 5.07-5.04 (1H, m, H4), 4.22 (1H, ddd, *J* = 12.0, 6.5 and 2.0 Hz, H7), 4.15 (1H, ddd, *J* = 12.0, 9.0 and 2.0 Hz, H7), 2.23 (2H, td, *J* = 7.0 and 2.0 Hz, H1'), 2.22-2.17 (1H, m, H6), 2.16-2.09 (1H, m, H5), 2.06-2.00 (1H, m, H5), 1.91-1.84 (1H, m, H6), 1.54-1.48 (2H, m, H2'), 1.40-1.34 (2H, m, H3'), 1.33-1.23 (4H, m, H4' and 5'), 0.89 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 153.7, 90.9, 74.5, 71.0, 70.3, 33.8, 31.2, 28.4, 28.2, 24.9, 22.5, 18.6, 14.0; **HRMS** (ESI+): calc for $C_{13}H_{20}O_3Na$ $[M+Na]^+$ 247.1305, found 247.1301.

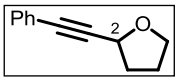
trimethyl((tetrahydrofuran-2-yl)ethynyl)silane - (±)-2.61b[254]



To a degassed solution of carbonate **(±)-2.06b** (50 mg, 0.235 mmol, 1 eq.) and 4-methoxyphenylboronic acid (43 mg, 0.283 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (28 mg, 10 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:9 Et_2O/pet. ether) to leave pure THF **(±)-2.61b** (24 mg, 0.141 mmol, 60%) as a colourless oil.

R_f 0.22 (1:9 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2960, 2173, 1332, 1054, 843, 760; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.56 (1H, dd, *J* = 7.0 and 5.5 Hz, H2), 3.96 (1H, td, *J* = 8.0 and 6.5 Hz, H5), 3.80 (1H, td, *J* = 8.0 and 5.5 Hz, H5), 2.19-2.12 (1H, m, H3), 2.08-1.85 (3H, m, H3 and 4), 0.17 (9H, s, Si*Me*$_3$);**^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 105.5, 89.0, 68.5, 67.9, 33.3, 25.4, −0.1.

2-(phenylethynyl)tetrahydrofuran - (±)-2.61c[110]

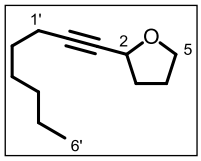


To a degassed solution of carbonate **(±)-2.06c** (50 mg, 0.231 μmol, 1 eq.) and 4-methoxyphenylboronic acid (42 mg, 0.277 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (10 mg, 10 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:9 Et_2O/pet. ether) to leave pure THF **(±)-2.61c** (28 mg, 0.166 mmol, 72%) as a colourless oil.

R_f 0.20 (1:9 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.47-7.42 (2H, m, Ph), 7.32-7.29 (3H, m, Ph), 4.82 (1H, dd, *J* = 7.0 and 5.0 Hz, H2), 4.05-4.00 (1H, m, H5), 3.87 (1H, td, *J* = 8.0 and 6.0 Hz,

H5), 2.26-2.21 (1H, m, H3), 2.14-2.05 (2H, m, H3 and 4), 2.00-1.91 (1H, m, H4); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 131.7, 128.2, 128.2, 122.8, 89.0, 84.4, 68.6, 67.9, 33.4, 25.5. Data consistent with literature.[110]

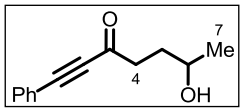
2-(oct-1-ynyl)tetrahydrofuran – 2.61d[145]



To a degassed solution of carbonate **2.06d** (50 mg, 0.223 mmol, 1 eq.) and 4-methoxyphenylboronic acid (34 mg, 0.267 mmol, 1.2 eq.) in 1,4-dioxane (1 mL) was added $Pd(PPh_3)_4$ (25 mg, 10 mol%). The resulting mixture was heated to 100 °C for 10 minutes. The reaction was allowed to cool and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:9 Et_2O/pet. ether) to leave pure THF **2.61d** (31 mg, 0.177 mmol, 77%) as a colourless oil.

R_f 0.21 (1:9 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.58-4.54 (1H, m, H2), 3.94 (1H, td, *J* = 8.0 and 6.0 Hz, H5), 3.78 (1H, td, 8.0 and 6.0 Hz, H5), 2.19 (2H, td, *J* = 7.0 and 2.0 Hz, H1'), 2.16-2.08 (1H, m, H3), 2.06-1.98 (1H, m, H4), 1.95-1.83 (2H, m, H3 and 4), 1.50 (2H, quintet, *J* = 7.0 Hz, H2'), 1.40-1.31 (2H, m, H3'), 1.33-1.24 (4H, m, H4' and 5'), 0.89 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 85.3, 79.9, 68.4, 67.6, 33.5, 31.3, 28.6, 28.5, 25.4, 22.5, 18.7, 14.0. Data consistent with literature.[145]

6-hydroxy-1-phenylhept-1-yn-3-one - (±)-3.37[255]

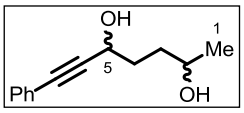


To a stirred solution of phenyl acetylene (2.19 mL, 20 mmol, 2 eq.) in anhydrous THF (20 mL) at −20 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 8.0 mL, 20 mmol, 2 eq.) dropwise. The resulting solution was warmed to RT stirred for 30 minutes. The reaction was cooled to −78 °C and to it added a solution of (±)-γ-valerolactone **(±)-3.36** (1.0 g, 9.99 mmol, 1 eq.) in anhydrous THF (6 mL) dropwise. The reaction was stirred at −78 °C for 1 hour, warmed to −20 °C and quenched with sat. aq. NH_4Cl (25 mL). The THF was removed *in vacuo* and the aqueous layer extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→1:2 EtOAc/pet. ether) to leave pure ketone

(±)-3.37 (1.60 g, 7.91 mmol, 79%) as a yellow oil.

R_f 0.38 (1:1 EtOAc/pet. ether); **IR** (thin film, cm^{-1}): 3429, 2969, 2930, 2203, 1668, 1490, 1279, 1071, 999; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.53 (2H, dt, *J* = 7.5 and 1.5 Hz, Ph), 7.41 (1H, tt, *J* = 7.5 and 1.5 Hz, Ph), 7.34 (2H, dt, *J* = 7.5 and 1.5 Hz, Ph), 3.88-3.80 (1H, m, H6), 2.87-2.72 (2H, m, H4), 2.45 (1H, bs, O*H*), 1.92-1.75 (2H, m, H5), 1.21 (3H, d, *J* = 6.0 Hz, H7); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.2, 133.0, 130.7, 128.6, 119.8, 91.1, 87.8, 67.0, 41.9, 32.9, 23.6; **HRMS** (FI+): calc for $C_{13}H_{14}O_2$ $[M]^+$ 202.0994, found 202.0992.

7-phenylhept-6-yne-2,5-diol - (±)-3.38



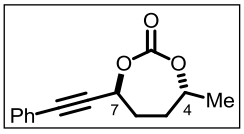
To a stirred solution of ketone **(±)-3.37** (250 mg, 1.24 mmol, 1 eq.) in anhydrous MeOH (5 mL) at 0 °C under argon was added $NaBH_4$ (23 mg, 0.62 mmol, 0.5 eq.). The reaction was stirred at 0 °C for 30 minutes and quenched with water (5 mL). The MeOH was removed *in vacuo* and the aqueous layer extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 EtOAc/pet. ether 1:1) to leave pure diol **(±)-3.38** (163 mg, 0.798 mmol, 64%) as a colourless oil.

1 : 1 *dr*. **R_f** 0.23 (1:1 EtOAc/pet. ether); **IR** (thin film, cm^{-1}): 3336, 2966, 2929, 2869, 2226, 1490, 1443, 1376, 1132, 1028; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph), 7.31-7.28 (3H, m, Ph), 4.68 (1H, t, *J* = 5.5 Hz, H5), 4.64 (1H, t, *J* = 6.5 Hz, H5), 3.97-3.82 (2H, m, H2 and O*H*), 2.94 (1H, bs, O*H*), 2.86 (1H, bs, O*H*), 1.96-1.90 (2H, m, H4), 1.80-1.59 (2H, m, H3), 1.23 (3H, d, *J* = 6.5 Hz, H1), 1.22 (3H, d, *J* = 6.0 Hz, H1); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 131.7, 128.4, 128.3, 122.7, 90.0 and 89.9, 84.9 and 84.8, 68.0 and 67.8, 62.8 and 62.5, 34.9 and 34.5, 34.2 and 34.2, 23.7 and 23.5; **HRMS** (ESI+): calc for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227.1043, found 227.1048.

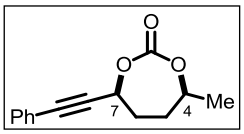
trans- and cis-4-methyl-7-(phenylethynyl)-1,3-dioxepan-2-one – *trans*-(±)-3.39 and *cis*-(±)-3.39

To a stirred solution of diol **(±)-3.38** (240 mg, 1.17 mmol, 1 eq.) in anhydrous CH_2Cl_2 (20 mL) under argon was added Et_3N (0.98 mL, 7.05 mmol, 6 eq.), pyridine (0.57 mL, 7.05 mmol, 6 eq.) and powered 4Å molecular sieves (250 mg). The resulting mixture was cooled to −78 °C and to it added a solution of triphosgene (174 mg, 0.59 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (5 mL) dropwise. After 10

minutes at −78 °C the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL) and allowed to warm to RT. The layers were separated, the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers washed with brine (20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→1:1 Et_2O/pet. ether) to leave pure diastereomers of carbonate **(±)-3.39** (***trans*:** white solid, 73 mg, 0.317 mmol, 27% and ***cis*:** colourless oil, 55 mg, 0.239 mmol, 20%).

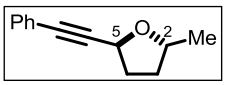


***trans*-(±)-3.39: R_f** 0.29 (1:1 Et_2O/pet. ether); **m.p.** 95-96 °C; **IR** (thin film, cm^{-1}): 2929, 2234, 1756, 1491, 1224, 1060, 759; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45 (2H, dd, *J* = 7.5 and 1.5 Hz, Ph), 7.37-7.31 (3H, m, Ph), 5.18 (1H, dd, *J* = 9.5 and 2.0 Hz, H7), 4.53 (1H, ddtd, *J* = 10.5, 6.5, 6.5 and 2.0 Hz, H4), 2.30 (1H, dtd, *J* = 15.0, 4.5 and 2.0 Hz, H6), 2.25-2.18 (1H, m, H6), 2.05 (1H, dtd, *J* = 15.0, 4.5 and 1.5 Hz, H5), 1.90-1.83 (1H, m, H5), 1.43 (3H, d, *J* = 6.5 Hz, *Me*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 153.1, 131.8, 129.0, 128.3, 121.6, 87.3, 84.5, 78.4, 71.6, 33.4, 33.4, 21.6; **HRMS** (ESI+): calc for $C_{14}H_{14}O_3Na$ $[M+Na]^+$ 253.0835, found 252.0830.



***cis*-(±)-3.39: R_f** 0.22 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2935, 2231, 1750, 1490, 1370, 1215, 1059, 759; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46 (2H, dd, *J* = 8.0 and 1.5 Hz, Ph), 7.38-7.31 (3H, m, Ph), 5.35 (1H, apt t, *J* = 3.5 Hz, H7), 4.50-4.43 (1H, m, H4), 2.30-2.20 (2H, m, H5 and 6), 2.17-2.10 (1H, m, H6), 1.93-1.86 (1H, m, H5), 1.44 (3H, d, *J* = 6.5 Hz, *Me*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_c 152.9, 131.9, 129.1, 128.3, 121.4, 89.9, 82.6, 78.8, 70.1, 32.5, 31.1, 21.9; **HRMS** (ESI+): calc for $C_{14}H_{14}O_3Na$ $[M+Na]^+$ 253.0835, found 252.0832.

trans-2-methyl-5-(phenylethynyl)tetrahydrofuran - *trans*-(±)-3.40[145]

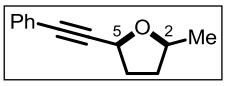


To a degassed solution of cyclic carbonate ***trans*-(±)-3.39** (20.0 mg, 86.9 μmol, 1 eq.) and PPTS (2.2 mg, 8.7 μmol, 0.1 eq.) in 1,4-dioxane (0.5 mL) under argon was added $Pd(PPh_3)_4$ (1.0 mg, 1 mol%). The reaction was heated to 50 °C and stirred for 5 minutes. The reaction was cooled and quenched *via* addition of pet. ether (1 mL). The resulting mixture was filtered through a short plug of silica gel (Et_2O eluent) and the solvent removed *in vacuo* to leave pure THF ***trans*-(±)-3.39** (14.0 mg, 75.2 μmol, 87%) as a colourless oil.

R_f 0.50 (1:1 Et_2O/pet. ether); **99:1 *dr***; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.47-7.39 (2H, m, Ph), 7.35-7.26 (3H, m, Ph), 4.93 (1H, dd, *J* = 7.0 and 5.5 Hz, H5), 4.38-4.21 (1H, m, H2), 2.40-2.01 (3H, m, H3

and 4), 1.60-1.43 (1H, m, H3), 1.29 (3H, d, *J* = 6.0 Hz, *Me*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.7, 128.2, 122.9, 89.6, 84.3, 75.1, 68.3, 33.9, 33.1, 20.8; **HRMS** (ESI+): calc for $C_{13}H_{14}ONa$ $[M+Na]^+$ 209.0937, found 209.0940.

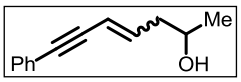
cis-2-methyl-5-(phenylethynyl)tetrahydrofuran - *cis*-(±)-3.40[145]



To a degassed solution of cyclic carbonate ***cis*-(±)-3.39** (20.0 mg, 86.9 μmol, 1 eq.) and PPTS (2.2 mg, 8.7 μmol, 0.1 eq.) in 1,4-dioxane (0.5 mL) under argon was added $Pd(PPh_3)_4$ (1.0 mg, 1 mol%). The reaction was heated to 50 °C and stirred for 5 minutes. The reaction was cooled and quenched *via* addition of pet. ether (1 mL). The resulting mixture was filtered through a short plug of silica gel (Et_2O eluent) and the solvent removed *in vacuo* to leave pure THF ***cis*-(±)-3.40** (15.0 mg, 80.5 μmol, 93%) as a colourless oil.

5:95 ***dr*** (*trans:cis*); **R_f** 0.54 (1:1 Et_2O/pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.31-7.28 (3H, m, Ph), 4.74 (1H, dd, *J* = 7.0 and 6.0 Hz, H5), 4.09-4.03 (1H, m, H2), 2.29-2.21 (1H, m, H4), 2.17-2.05 (2H, m, H3 and 4), 1.74-1.67 (1H, m, H3), 1.36 (3H, d, *J* = 6.0 Hz, *Me*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.7, 128.2, 128.2, 122.9, 89.4, 84.3, 76.3, 68.5, 33.7, 32.9, 21.5; **HRMS** (ESI+): calc for $C_{13}H_{14}ONa$ $[M+Na]^+$ 209.0937, found 209.0941.

7-phenylhept-4-en-6-yn-2-ol – 3.46

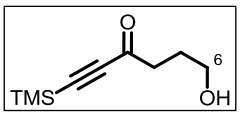


To a degassed solution of carbonate ***trans*-(±)-3.39** (20.0 mg, 86.9 μmol, 1 eq.) in 1,4-dioxane (0.5 mL) under argon was added $Pd(PPh_3)_4$ (1.0 mg, 1 mol%). The reaction was heated to 100 °C for 2 minutes, allowed to cool and quenched *via* addition of pet. ether (1 mL). The resulting solution was passed through a short plug of silica gel (Et_2O eluent) to leave pure enyne **3.46** (13.6 mg, 73.0 μmol, 84%) as a colourless oil.

58:42 *E/Z*. **R_f** 0.31 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3363, 2967, 2928, 2202, 1596, 1489, 1442, 1123, 1071, 957; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.47-7.41 (2H, m, Ph), 7.35-7.29 (3H, m, Ph), 6.25 (1H, dt, *J* = 16.0 and 7.5 Hz, *E*-H4), 6.06 (1H, dt, *J* = 10.5 and 7.5 Hz, *Z*-H4), 5.85 (1H, d, *J* = 10.5 Hz, *Z*-H5), 5.81 (1H, d, *J* = 16.0 Hz, *E*-H5), 4.03-3.96 (1H, m, *Z*-H2), 3.96-3.89 (1H, m, *E*-H2), 2.64-2.55 (2H, m, *Z*-H3), 2.40-2.28 (2H, m, *E*-H3), 1.56 (1H, d, *J* = 4.5 Hz, *E*-O*H*), 1.54 (1H, d, *J* = 4.5 Hz, *Z*-O*H*), 1.28 (3H, d, *J* = 6.5 Hz, *Z*-H1), 1.25 (3H, d, *J* = 6.5 Hz, *E*-H1); **^{13}C NMR** (125 MHz,

$CDCl_3$): δ_C 140.3, 139.3, 131.4, 131.4, 128.3, 128.3, 128.2, 128.1, 123.4, 123.3, 112.8, 111.7, 94.0, 88.6, 87.8, 86.0, 67.6, 67.1, 43.0, 40.0, 23.2, 23.0; **HRMS** (ESI+): calc for $C_{13}H_{14}ONa$ $[M+Na]^+$ 209.0937, found 209.0939.

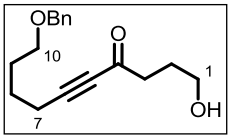
6-hydroxy-1-(trimethylsilyl)hex-1-yn-3-one – 2.59b[256]



To a stirred solution of trimethylsilyl acetylene (500 mg, 5.09 mmol, 1.2 eq.) in anhydrous THF (15 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 2.04 mL, 5.09 mmol, 1.2 eq.) dropwise. The resultant solution was warmed to −30 °C and stirred for 30 minutes. The reaction was cooled to −78 °C, $BF_3{\cdot}OEt_2$ (0.63 mL, 5.09 mmol, 1.2 eq.) was added dropwise, and the solution stirred for 10 minutes. γ-butyrolactone **2.57** (0.33 mL, 4.24 mmol, 1 eq.) was added in one portion and the reaction allowed to warm to RT over 1 hour. The reaction was quenched *via* addition of AcOH (0.37 mL, 6.36 mmol, 1.5 eq.) in CH_2Cl_2 (15 mL). The mixture was diluted with sat. aq. $NaHCO_3$ (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:2→2:1 Et_2O/pet. ether) to leave pure ketone **2.59b** (625 mg, 3.39 mmol, 80%) as a colourless oil.

R_f 0.24 (1:1 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.68 (2H, *apt* q, *J* = 5.5 Hz, H6), 2.72 (2H, t, *J* = 7.0 Hz, H4), 1.92 (2H, *apt* quintet, *J* = 6.5 Hz, H5), 1.56 (1H, bs, O*H*), 0.25 (9H, s, Si*Me*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 187.5, 101.9, 98.2, 61.8, 41.9, 26.6, −0.8. Data consistent with literature.[256]

10-(benzyloxy)-1-hydroxydec-5-yn-4-one – 2.59e

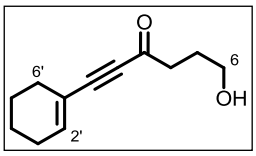


To a stirred solution of alkyne **3.48** (420 mg, 2.23 mmol, 1.1 eq.) in anhydrous THF (10 mL) at −78 °C was added *n*-butyllithium (2.5 M in hexanes, 0.97 mL, 2.43 mmol, 1.2 eq.) dropwise. The resulting solution was allowed to warm to −30 °C and stirred for 30 minutes. The solution was cooled to −78 °C and $BF_3{\cdot}OEt_2$ (0.28 mL, 2.23 mmol, 1.1 eq.) added dropwise. After a further 10 minutes at −78 °C, γ-butyrolactone **2.57** (0.16 mL, 2.03 mmol, 1 eq.) was added in one portion. The reaction was allowed to warm to RT and stirred for 2 hours. The reaction was quenched with sat. aq. NH_4OH/NH_4Cl (1:2 v:v, 10 mL) and the mixture

diluted with water (20 mL). The mixture was extracted with Et_2O (4 x 20 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave pure ketone **2.59e** (398 mg, 1.45 mmol, 71%) as a colourless oil.

R_f 0.37 (Et_2O); **IR** (thin film, cm^{-1}): 3442, 2939, 2868, 2211, 1670, 1455, 1369, 1241, 1106; **^{1}H NMR** (250 MHz, $CDCl_3$): δ_H 7.37-7.27 (5H, m, Ph), 4.51 (2H, s, PhC*H*$_2$O), 3.68-3.64 (2H, m, H1), 3.50 (2H, t, *J* = 6.0 Hz, H10), 2.67 (2H, t, *J* = 7.0 Hz, H3), 2.40 (2H, t, *J* = 6.5 Hz, H7), 1.91 (2H, quintet, *J* = 7.0 Hz, H2), 1.77-1.66 (5H, m, H8, 9 and O*H*); **^{13}C NMR** (63 MHz, $CDCl_3$): δ_C 188.2, 138.5, 128.5, 127.8, 127.7, 94.5, 81.1, 73.1, 69.6, 61.9, 42.3, 29.0, 26.9, 24.7, 18.9; **HRMS** (ESI+): calc for $C_{17}H_{22}O_3Na$ $[M+Na]^+$ 297.1461, found 297.1457.

1-(cyclohex-1-en-1-yl)-6-hydroxyhex-1-yn-3-one – 2.59g

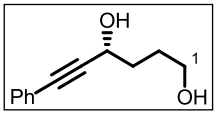


To a stirred solution of alkyne **2.17a** (679 mg, 6.39 mmol, 1.1 eq.) in anhydrous THF (25 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 2.79 mL, 6.97 mmol, 1.2 eq.) dropwise. The resulting solution was allowed to warm to −30 °C and stirred for 30 minutes. The solution was cooled to −78 °C and to it added $BF_3{\cdot}OEt_2$ (0.95 mL, 7.55 mmol, 1.3 eq.) in one portion. The resultant solution was stirred for 10 minutes before γ-butyrolactone **2.57** (0.45 mL, 5.81 mmol, 1 eq.) was added in one portion. The reaction was stirred and allowed to warm slowly to RT overnight before being quenched with sat. aq. NH_4Cl/NH_4OH (2:1 v:v, 25 mL). The reaction was diluted with Et_2O (25 mL), the layers separated and the aqueous layer extracted with Et_2O (4 x 25 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→1:1 Et_2O/pet. ether) to leave pure ketone **2.59g** (966 mg, 5.02 mmol, 86%) as a pale yellow oil.

R_f 0.45 (Et_2O); **IR** (thin film, cm^{-1}): 3411, 2932, 2182, 1662, 1620, 1435, 1361, 1248, 1051, 964, 919; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.45-6.41 (1H, m, H2'), 3.64 (2H, t, *J* = 6.5 Hz, H6), 2.69 (2H, t, *J* = 7.0 Hz, H4), 2.17-2.11 (4H, m, H3' and 6'), 2.10 (1H, bs, O*H*), 1.90 (2H, *apt* quintet, *J* = 7.0 Hz, H5), 1.66-1.55 (4H, m, H4' and 5'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.1, 142.6, 118.8, 93.8, 86.0, 61.7, 42.0, 28.2, 26.9, 26.0, 21.8, 21.0; **HRMS** (ESI+): calc for $C_{12}H_{16}O_2Na$ $[M+Na]^+$ 215.1043, found

215.1037.

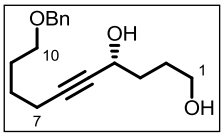
(*R*)-6-phenylhex-5-yne-1,4-diol – (*R*)-2.56c



To a stirred solution of ketone **2.59c** (94 mg, 0.50 mmol, 1 eq.) and [RuCl((*R,R*)-TsDPEN)(*p*-cymene)] **(*R,R*)-3.53·HCl** (3.4 mg, 1 mol%) in IPA (4.75 mL) under argon was added a solution of KOH in IPA (0.34 mg in 0.25 mL, 1.2 mol%). The reaction was stirred overnight and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2 EtOAc/pet. ether→EtOAc) to leave pure diol **(*R*)-2.56c** (80 mg, 0.42 mmol, 84%) as a yellow oil.

R_f 0.05 (1:2 EtOAc/pet. ether); **98% *ee*** (CHIRALPAK IA, 1.25 mL/min, 4% IPA/Hexane): t_R (*S*) = 36.79 min, t_R (*R*) = 39.21 min; $[\alpha]_D^{25}$ +11.0 (*c* = 0.48, CH_2Cl_2). All other spectroscopic data identical to **(±)-2.56c** prepared previously.

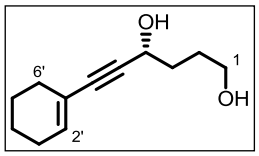
(*R*)-10-(benzyloxy)dec-5-yne-1,4-diol – (*R*)-2.56e



To a stirred solution of ketone **2.59e** (200 mg, 0.73 mmol, 1 eq.) and [RuCl((*R,R*)-TsDPEN)(*p*-cymene)] **(*R,R*)-3.53·HCl** (4.6 mg, 1 mol%) in IPA (7.2 mL) was added a solution of KOH (0.5 mg in 0.1 mL IPA, 1.2 mol%). The resulting solution was stirred for 72 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:1→3:1 EtOAc/pet. ether) to leave pure diol **(*R*)-2.56e** (55 mg, 0.19 mmol, 26%) as a pale yellow oil.

R_f 0.27 (EtOAc); **IR** (thin film, cm^{-1}): 3383, 2940, 2866, 2241, 1496, 1076, 912, 735; $[\alpha]_D^{25}$ +6.4 (*c* = 0.33, $CHCl_3$); **97% ee** (CHIRALPAK IB, 1.3 mL/min, 6% IPA/Hexane): t_R (*S*) = 23.35 min, t_R (*R*) = 25.00 min; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.37-7.27 (5H, m, Ph), 4.51 (2H, s, Ph*C*H_2O), 4.44-4.41 (1H, m, H4), 3.71-3.62 (2H, m, H1), 3.50 (2H, t, *J* = 6.5 Hz, H10), 2.67 (1H, bs, O*H*), 2.24 (2H, td, *J* = 7.0 and 2.0 Hz, H7), 1.83-1.76 (3H, m, H3 and O*H*), 1.76-1.67 (4H, m, H2 and 9), 1.64-1.57 (2H, m, H8); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 138.4, 128.4, 127.6, 127.6, 85.3, 81.3, 72.9, 69.8, 62.6, 62.3, 35.0, 28.8, 28.4, 25.4, 18.5; **HRMS** (ESI+): calc for $C_{17}H_{24}O_3Na$ $[M+Na]^+$ 299.1618, found 299.1617.

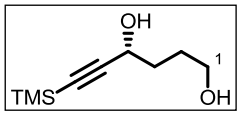
(*R*)-6-(cyclohex-1-en-1-yl)hex-5-yne-1,4-diol – (*R*)-2.56g



A solution of ketone **2.59g** (250 mg, 1.30 mmol, 1 eq.) in IPA (3 mL) was degassed for 30 minutes. Alongside this a solution of [RuCl((*R,R*)-TsDPEN)(*p*-cymene)] **(*R,R*)-3.53·HCl** (8.3 mg, 1 mol%) in IPA (3.4 mL) was degassed for 30 minutes. A solution of KOH (0.88 mg, 1.2 mol%) in IPA (0.1 mL) was added to the catalyst solution and the resulting mixture stirred until a yellow colour developed. The catalyst solution was transferred *via* syringe to the ketone and the reaction stirred overnight. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:2→2:1 EtOAc/pet. ether) to leave pure diol **(*R*)-2.56g** (217 mg, 1.12 mmol, 86%) as a colourless oil.

R_f 0.18 (1:1 EtOAc/pet. ether); **98% *ee*** (CHIRALPAK IB, 1.25 mL/min, 10% IPA/Hexane): t_R (*R*) = 7.39 min, t_R (*S*) = 8.06 min; $[\alpha]_D^{25}$ +11.8 (*c* = 1.01, $CHCl_3$); **IR** (thin film, cm^{-1}): 3316, 2929, 2859, 2218, 1632, 1436, 1336, 1206, 1048, 955, 919, 842; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.09-6.06 (1H, m, H2'), 4.55-4.51 (1H, m, H4), 3.72-3.61 (2H, m, H1), 3.48 (1H, bs, O*H*), 2.95 (1H, bs, O*H*), 2.11-2.02 (4H, m, H3' and 6'), 1.85-1.67 (4H, m, H2 and 3), 1.64-1.52 (4H, m, H4' and 5'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 135.1, 120.1, 87.2, 86.6, 62.3, 34.9, 29.1, 28.3, 25.5, 22.2, 21.4; **HRMS** (ESI+): calc for $C_{12}H_{18}O_2Na$ $[M+Na]^+$ 217.1199, found 217.1193.

(*R*)-6-(trimethylsilyl)hex-5-yne-1,4-diol – (*R*)-2.56b[251]

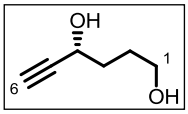


IPA (11 mL) was degassed for 30 minutes and to it added ketone **2.59b** (500 mg, 2.71 mmol, 1 eq.) and a solution of [Ru((*R,R*)-TsDPEN)(*p*-cymene)] **(*R,R*)-3.53** (24.5 mg, 1.5 mol%) in anhydrous CH_2Cl_2 (0.2 mL). The resulting solution was stirred and degassed for a further 10 minutes. Stirring was continued for 72 hours, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:2→2:1 EtOAc/pet. ether) to leave pure diol **(*R*)-2.56b** (438 mg, 2.35 mmol, 87%) as an off-white solid.

m.p. 51.5-52 °C; **R_f** 0.26 (4:1 Et_2O/pet. ether); **98% *ee*** (see below); $[\alpha]_D^{25}$ +15.5 (*c* = 0.91, $CHCl_3$). All other spectroscopic data identical to **(±)-2.56b** prepared previously.

Enantiomeric excess was determined by derivitisation with benzoyl chloride in pyridine to give **(*R*)-6-(trimethylsilyl)hex-5-yne-1,4-diyl dibenzoate (3.57)**. (CHIRALPAK IB, 1.3 mL/min, 0.7% IPA/Hexane): t_R (*S*) = 5.78 min, t_R (*R*) = 6.31 min.

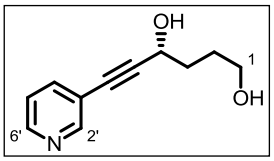
(*R*)-hex-5-yne-1,4-diol – (*R*)-2.56a



To a stirred solution of diol **(*R*)-2.56b** (422 mg, 2.26 mmol, 1 eq.) in MeOH (10 mL) was added K_2CO_3 (376 mg, 2.72 mmol, 1.2 eq.). The reaction was stirred for 16 hours and quenched with glacial AcOH (0.31 mL, 5.44 mmol, 2.4 eq.). Silica gel (1 g) was added and the solvent removed *in vacuo*. The crude product purified by flash chromatography on silica gel (1:1 EtOAc/pet. ether→EtOAc) to leave pure diol **(*R*)-2.56a** (240 mg, 0.210 mmol, 93%) as a colourless oil.

R_f 0.18 (2:1 EtOAc/pet. ether); **$[\alpha]_D^{25}$** +20.0 (*c* = 1.00, $CHCl_3$); **IR** (thin film, cm^{-1}): 3312, 3286, 2926, 2872, 2113, 1744, 1641, 1434, 1046; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 4.48 (1H, m, H4), 3.76-3.66 (2H, m, H1), 2.86 (2H, bs, O*H*), 2.48 (1H, d, *J* = 2.0 Hz, H6), 1.89-1.81 (3H, m, H2 and 3), 1.80-1.71 (1H, m, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 84.7, 73.0, 62.4, 61.8, 34.6, 28.1; **HRMS** (CI+): calc for $C_6H_{11}O_2$ $[M+H]^+$ 115.0759, found 115.0761.

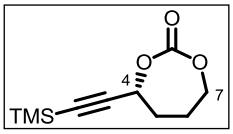
(*R*)-6-(pyridin-3-yl)hex-5-yne-1,4-diol – (*R*)-2.56f



To a stirred solution of diol **(*R*)-2.56a** (91 mg, 0.797 mmol, 1 eq.) and 3-bromopyridine (84 μL, 0.877 mmol, 1.1 eq.) in Et_3N (1.6 mL) under argon was added $Pd(PPh_3)_4$ (9.2 mg, 1 mol%) and $CuBr{\cdot}SMe_2$ complex (3.3 mg, 2 mol%). The reaction was heated to 70 °C and stirred overnight. The reaction mixture was filtered and the filter cake washed with EtOAc (5 mL). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:1 EtOAc/pet. ether→9:1 EtOAc/MeOH) to leave pure diol **(*R*)-2.56f** (95 mg, 0.497 mmol, 62%) as a pale yellow oil.

R_f 0.20 (EtOAc); **$[\alpha]_D^{25}$** +11.2 (*c* = 1.21, MeOH); **IR** (thin film, cm^{-1}): 3262, 2933, 2867, 2227, 1567, 1477, 1409, 1333, 1188, 1024, 807; **^{1}H NMR** (400 MHz, MeOH-d_4): δ_H 8.57 (1H, bs, H2'), 8.48 (1H, dd, *J* = 5.0 and 1.5 Hz, H6'), 7.85 (1H, ddd, *J* = 8.0, 2.0 and 1.5 Hz, H4'), 7.40 (1H, ddd, *J* = 8.0, 5.0 and 1.0 Hz, H5'), 4.88 (2H, bs, 2 x O*H*), 4.60 (1H, t, *J* = 6.5 Hz, H4), 3.63 (2H, t, *J* = 6.5 Hz, H1), 1.88-1.80 (2H, m, H3), 1.80-1.71 (2H, m, H2); **^{13}C NMR** (100 MHz, MeOH-d_4): δ_C 152.4, 149.1, 140.5, 125.0, 121.2, 95.7, 81.2, 62.9, 62.6, 35.4, 29.5; **HRMS** (ESI+): calc for $C_{11}H_{13}NO_2Na$ $[M+Na]^+$ 214.0838, found 214.0832.

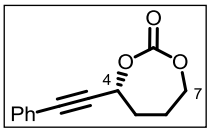
(*R*)-4-((trimethylsilyl)ethynyl)-1,3-dioxepan-2-one – (*R*)-2.06b



To a stirred suspension of diol **(*R*)-2.56b** (100 mg, 0.537 mmol, 1 eq.), pyridine (0.26 mL, 3.22 mmol, 6 eq.), Et_3N (0.45 mL, 3.22 mmol, 6 eq.) and powdered 4Å molecular sieves (100 mg) in anhydrous CH_2Cl_2 (4 mL) at −78 °C under argon was added a solution of triphosgene (80 mg, 0.268 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (1.4 mL) dropwise. The reaction was stirred for 2 hours at −78 °C and quenched with sat. aq. NH_4Cl (5 mL). The mixture was allowed to warm to RT, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1N aq. HCl (1 x 15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:2 EtOAc/pet. ether) to leave pure carbonate **(*R*)-2.06b** (62 mg, 0.292 mmol, 54%) as a white solid.

m.p. 42-43 °C; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +58.2 (*c* = 0.98, $CHCl_3$). All other spectroscopic data identical to **(±)-2.06b** prepared previously.

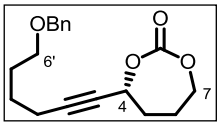
(*R*)-4-(phenylethynyl)-1,3-dioxepan-2-one – (*R*)-2.06c



To a stirred solution of diol **(*R*)-2.56c** (80 mg, 0.42 mmol, 1 eq.), Et_3N (0.35 mL, 2.52 mmol, 6 eq.), pyridine (0.20 mL, 2.52 mmol, 6 eq.) and powdered 4Å molecular sieves (200 mg) in anhydrous CH_2Cl_2 (6 mL) at −78 °C under argon was added a solution of triphosgene (62 mg, 0.21 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (2 mL) dropwise. The reaction was stirred for 15 minutes and quenched at −78 °C with sat. aq. $NaHCO_3$ (10 mL). The mixture was allowed to warm to RT, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N aq. HCl (2 x 30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:4 EtOAc/pet. ether) to leave pure carbonate **(*R*)-2.06c** (60 mg, 0.28 mmol, 67%) as a pale yellow solid.

m.p. 78-79 °C; $\mathbf{R_f}$ 0.15 (1:1 Et_2O/pet. ether); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +72.6 (*c* = 0.46, CH_2Cl_2). All other spectroscopic data identical to **(±)-2.06c** prepared previously.

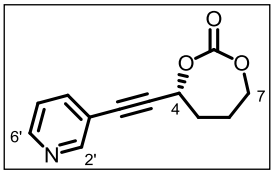
(*R*)-4-(6-(benzyloxy)hex-1-ynyl)-1,3-dioxepan-2-one – (*R*)-2.06e



To a stirred solution of diol **(*R*)-2.56e** (51 mg, 0.184 mmol, 1 eq.), Et_3N (0.15 mL, 1.10 mmol, 6 eq.) and pyridine (0.09 mL, 1.10 mmol, 6 eq.) in anhydrous CH_2Cl_2 (2 mL) was added powdered 4Å molecular sieves (100 mg). The resulting solution was cooled to −78 °C and a solution of triphosgene (27 mg, 92 μmol, 0.5 eq.) in anhydrous CH_2Cl_2 (0.5 mL) was added dropwise. The reaction was stirred for 1 hour at −78 °C, quenched with sat. aq. $NaHCO_3$ solution (3 mL) and allowed to warm to RT. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1N aq. HCl (2 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo.* The crude product was purified by flash chromatography on silica gel (1:2→2:1 Et_2O/pet. ether) to leave pure carbonate **(*R*)-2.06e** (26 mg, 86 μmol, 47%) as a pale yellow oil.

R_f 0.49 (Et_2O); **IR** (thin film, cm^{-1}): 2939, 2863, 2247, 1759, 1455, 1168, 1095, 738; $[\alpha]_D^{24}$ +49.3 (*c* = 0.27, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.37-7.27 (5H, m, Ph), 5.07-5.03 (1H, m, H4), 4.51 (2H, s, PhC*H*$_2$O), 4.22 (1H, ddd, *J* = 12.0, 6.5 and 2.0 Hz, H7), 4.14 (1H, ddd, *J* = 12.0, 9.0 and 2.0 Hz, H7), 3.50 (2H, t, *J* = 6.0 Hz, H6'), 2.28 (2H, td, *J* = 7.0 and 2.0 Hz, H3'), 2.24-2.16 (1H, m, H6), 2.17-2.08 (1H, m, H5), 2.06-1.99 (1H, m, H5), 1.90-1.83 (1H, m, H6), 1.75-1.68 (2H, m, H5'), 1.67-1.60 (2H, m, H4'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 153.7, 138.5, 128.3, 127.6, 127.5, 90.5, 74.8, 72.8, 71.0, 70.3, 69.6, 33.7, 28.7, 25.1, 18.4; **HRMS** (ESI+): calc for $C_{18}H_{22}O_4Na$ $[M+Na]^+$ 325.1410, found 325.1408.

(*R*)-4-(pyridin-3-ylethynyl)-1,3-dioxepan-2-one – (*R*)-2.06f

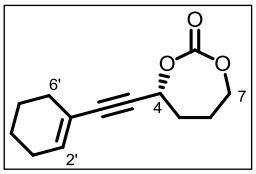


To a stirred suspension of diol **(*R*)-2.56f** (214 mg, 1.12 mmol, 1 eq.), pyridine (0.54 mL, 6.72 mmol, 6 eq.), Et_3N (0.94 mL, 6.72 mmol, 6 eq.) and powdered 4Å molecular sieves (200 mg) in anhydrous CH_2Cl_2 (10 mL) at −78 °C under argon was added a solution of triphosgene (166 mg, 0.56 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (2 mL). The reaction was stirred at −78 °C for 2 hours and quenched with sat. aq. NH_4Cl (10 mL). The mixture was allowed to warm to RT, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2 EtOAc/pet. ether→EtOAc) to

leave pure carbonate **(*R*)-2.06f** (54 mg, 0.249 mmol, 22%) as a viscous colourless oil.

R_f 0.40 (EtOAc); **$[\alpha]_D^{25}$** +74.8 (*c* = 1.67, $CHCl_3$); **IR** (thin film, cm^{-1}): 3016, 2970, 2236, 1745, 1476, 1366, 1184, 1055, 1017; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.65 (1H, dd, *J* = 2.0 and 0.5 Hz, H2'), 8.54 (1H, dd, *J* = 5.0 and 2.0 Hz, H6'), 7.72 (1H, dt, *J* = 8.0 and 2.0 Hz, H4'), 7.25 (1H, ddd, *J* = 8.0, 5.0 and 1.0 Hz, H5'), 5.27 (1H, dd, *J* = 5.0 and 4.0 Hz, H4), 4.29-4.17 (2H, m, H7), 2.28-2.13 (3H, m, H5 and 6), 2.02-1.89 (1H, m, H6); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ_C 153.3, 152.2, 149.4, 138.8, 123.0, 118.5, 86.5, 85.6, 70.6, 70.4, 33.4, 25.2; **HRMS** (ESI+): calc for $C_{12}H_{11}NO_3Na$ $[M+Na]^+$ 240.0631, found 240.0625.

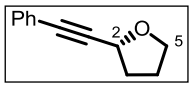
(*R*)-4-(cyclohex-1-en-1-ylethynyl)-1,3-dioxepan-2-one – (*R*)-2.06g



To a stirred suspension of diol **(*R*)-2.56g** (169 mg, 0.87 mmol, 1 eq.), pyridine (0.42 mL, 5.22 mmol, 6 eq.), Et_3N (0.73 mL, 5.22 mmol, 6 eq.) and powdered 4Å molecular sieves (200 mg) in anhydrous CH_2Cl_2 (8 mL) at −78 °C under argon was added a solution of triphosgene (129 mg, 0.43 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (2 mL). The reaction was stirred at −78 °C for 30 minutes and quenched with 1N aq. HCl (10 mL). The mixture was allowed to warm to RT, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N aq. HCl (1 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→1:2 EtOAc/pet. ether) to leave pure carbonate **(*R*)-2.06g** (72 mg, 0.33 mmol, 38%, 44% brsm) as a pale yellow solid.

m.p. 38-39 °C; **R_f** 0.41 (1:1 EtOAc/pet. ether); **$[\alpha]_D^{25}$** +49.1 (*c* = 0.88, $CHCl_3$); **IR** (thin film, cm^{-1}): 2929, 2220, 1751, 1436, 1392, 1239, 1202, 1162, 1054, 1013; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 6.17-6.13 (1H, m, H2'), 5.15 (1H, dd, *J* = 5.0 and 3.5 Hz, H4), 4.24-4.11 (2H, m, H7), 2.24-2.01 (7H, m, H5, 6, 3' and 6'), 1.92-1.84 (1H, m, H6), 1.64-1.51 (4H, m, H4' and 5'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 153.6, 137.0, 119.2, 91.2, 80.3, 71.1, 70.3, 33.6, 28.7, 25.5, 24.9, 22.0, 21.2; **HRMS** (ESI+): calc for $C_{13}H_{16}O_3Na$ $[M+Na]^+$ 243.0992, found 243.0992.

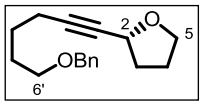
(*R*)-2-(phenylethynyl)tetrahydrofuran – (*R*)-2.61c[110]



To a degassed solution of cyclic carbonate **(*R*)-2.06c** (20.0 mg, 92.5 μmol, 1 eq.) and PPTS (2.3 mg, 10 mol%) in 1,4-dioxane (0.5 mL) under argon was added $Pd(PPh_3)_4$ (1.1 mg, 1 mol%). The reaction was heated to 50 °C for 12 minutes, and quenched *via* addition of pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent) and the solvent removed *in vacuo* to leave pure THF **(*R*)-2.61c** (15.9 mg, 92.3 μmol, 99%) as a pale yellow oil.

R_f 0.20 (1:9 Et_2O/pet. ether); **95% *ee*** (CHIRALPAK IA, 1.25 mL/min, 2% IPA/Hexane): t_R (*S*) = 6.84 min, t_R (*R*) = 7.45 min; $[\alpha]_D^{25}$ +9.0 (*c* = 0.40, CH_2Cl_2). All other spectroscopic data identical to **(±)-2.61c** prepared from cyclic carbonate **(±)-2.06c**.

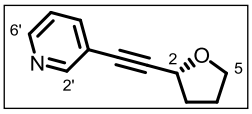
(*R*)-2-(6-(benzyloxy)hex-1-ynyl)tetrahydrofuran – (*R*)-2.61e



To a degassed solution of carbonate **(*R*)-2.06e** (27 mg, 89 μmol, 1 eq.) and PPTS (2.2 mg, 10 mol%) in 1,4-dioxane (0.75 mL) was added $Pd(PPh_3)_4$ (1.0 mg, 1 mol%). The reaction was heated to 50 °C for 25 minutes and quenched with pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent) and the solvent removed *in vacuo* to leave pure THF **(*R*)-2.61e** (22 mg, 85 μmol, 96%) as a colourless oil.

R_f 0.53 (EtOAc/pet. ether 1:3); **IR** (thin film, cm^{-1}): 2942, 2864, 2236, 1454, 1361, 1108, 1052, 737; **95% *ee*** (CHIRALPAK IB, 1.3 mL/min, 2% IPA/hexane): t_R (*S*): 6.20 min; t_R (*R*): 6.81 min; $[\alpha]_D^{25}$ +5.2 (*c* = 0.25, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.37-7.27 (5H, m, Ph), 4.56 (1H, ddt, *J* = 7.0, 5.5 and 2.0 Hz, H2), 4.50 (2H, s, PhCH_2O), 3.94 (1H, td, *J* = 8.0 and 6.0 Hz, H5), 3.78 (1H, td, *J* = 8.0 and 6.0 Hz, H5), 3.49 (2H, t, *J* = 6.5 Hz, H6'), 2.24 (2H, td, *J* = 7.0 and 2.0 Hz, H3'), 2.15-2.08 (1H, m, H3), 2.06-1.98 (1H, m, H4), 1.95-1.83 (2H, m, H3 and 4), 1.75-1.69 (2H, m, H5'), 1.64-1.58 (2H, m, H4'); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ_C 138.6, 128.3, 127.6, 127.5, 84.8, 80.2, 72.8, 69.8, 68.4, 67.6, 33.5, 28.9, 25.4, 25.3, 18.6; **HRMS** (ESI+): calc for $C_{17}H_{22}O_2Na$ $[M+Na]^+$ 281.1512, found 281.1514.

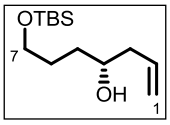
(*R*)-3-((tetrahydrofuran-2-yl)ethynyl)pyridine – (*R*)-2.61f



To a degassed solution of carbonate **(*R*)-2.06f** (20 mg, 92.1 μmol, 1 eq.) and PPTS (2.3 mg, 10 mol%) in 1,4-dioxane (0.92 mL) was added $Pd(PPh_3)_4$ (1.1 mg, 1 mol%). The reaction was heated to 100 °C and stirred for 10 minutes. The reaction was quenched with pet. ether (1 mL), filtered through a plug of silica gel (EtOAc), the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:2→1:1 EtOAc/pet. ether) to leave pure THF **(*R*)-2.61f** (12.7 mg, 73.3 μmol, 80%) as a pale yellow oil.

R_f 0.55 (EtOAc); **98% *ee*** (CHIRALPAK IC, 1.15 mL/min, 10% IPA/Hexane): t_R (*R*) = 18.79 min, t_R (*S*) = 23.23 min; $[\alpha]_D^{25}$ –12.1 (*c* = 0.39, $CHCl_3$); **IR** (thin film, cm^{-1}): 2981, 2873, 2231, 1584, 1476, 1408, 1338, 1187, 1050, 918, 807; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 8.67 (1H, d, *J* = 1.5 Hz, H2'), 8.53 (1H, dd, *J* = 5.0 and 1.5 Hz, H6'), 7.72 (1H, ddd, *J* = 8.0, 2.0 and 1.5 Hz, H4'), 7.24 (1H, dd, *J* = 8.0 and 5.0 Hz, H5'), 4.83 (1H, dd, *J* = 7.0 and 5.0 Hz, H2), 4.05-4.00 (1H, m, H5), 3.91-3.86 (1H, m, H5), 2.31-2.23 (1H, m, H3), 2.16-2.07 (2H, m, H3 and 4), 2.01-1.93 (1H, m, H4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 152.4, 148.7, 138.6, 122.9, 119.9, 92.6, 81.2, 68.4, 68.1, 33.3, 25.5; **HRMS** (ESI+): calc for $C_{11}H_{12}NO$ $[M+H]^+$ 174.0913, found 174.0910.

(*R*)-7-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-ol – (*R*)-3.68[155]

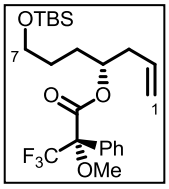


To a stirred solution of aldehyde **2.55** (800 mg, 3.96 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) at −20 °C under argon was added a solution of Leighton's reagent **(*R,R*)-3.64** (2.63 g, 4.75 mmol, 1.2 eq.) in anhydrous CH_2Cl_2 (6 mL). The resulting solution was transferred to the freezer and left to stand for 48 hours at −25 °C. The reaction was quenched with 1N aq. HCl solution (10 mL) and sat. aq. NH_4Cl (10 mL). The mixture was filtered and the solid recovered to return the free diamine **(*R,R*)-3.67** (1.66 g, 78%), after basifying with 1N NaOH and extraction into EtOAc. The filtrate was separated and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19→1:9 EtOAc/pet. ether) to leave pure alcohol **(*R*)-3.68** (457 mg, 1.87 mmol, 47%) as a colourless oil.

R_f 0.29 (1:9 EtOAc/pet. ether); **94% *ee*** (see below); $[\alpha]_D^{25}$ +3.9 (*c* = 1.24, $CHCl_3$) [lit.[155] +5.19 (*c* = 1.21, $CHCl_3$)]; **^{1}H NMR** (200 MHz, $CDCl_3$): δ_H 5.85 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2), 5.15-

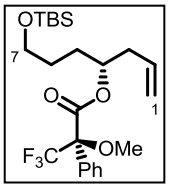
5.09 (2H, m, H1), 3.71-3.63 (3H, m, H4 and 7), 2.62 (1H, d, *J* = 4.0 Hz, O*H*), 2.32-2.17 (2H, m, H3), 1.70-1.43 (4H, m, H5 and 6), 0.91 (9H, s, Si*t-Bu*), 0.07 (6H, s, Si*Me*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_c 135.1, 117.6, 70.6, 63.5, 41.9, 34.0, 29.1, 25.9, 18.3, −5.4. Data consistent with literature.[155]

The enantiomeric excess of **(*R*)-3.68** was measured through the synthesis of the Mosher's ester derivatives **(*S,R*)-3.69** and **(*R,R*)-3.69** and the integration of diastereomeric peaks in their ^{19}F NMR spectra. This led to a complementary 96 : 4 *dr*, corresponding to 92% *ee* of **(*R*)-3.68**.



(*S*)-(*R*)-7-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate – (*S,R*)-3.69:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.57-7.51 (2H, m, Ph), 7.42-7.37 (3H, m, Ph), 5.72-5.59 (1H, m, H2), 5.21-5.15 (1H, m, H4), 5.06-5.00 (2H, m, H1), 3.61 (2H, td, *J* = 6.5 and 2.0 Hz, H7), 3.56-3.54 (3H, m, O*Me*), 2.37 (2H, t, *J* = 6.5 Hz, H3), 1.80-1.66 (2H, m, H5), 1.61-1.49 (2H, m, H6), 0.89 (9H, s, Si*t-Bu*), 0.04 (6H, s, Si*Me*$_2$); **^{19}F NMR** (377 MHz, $CDCl_3$): δ_F –71.28 (s, 4%), –71.36 (s, 96%).



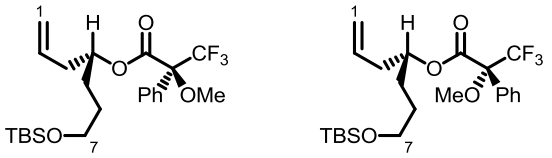
(*R*)-(*R*)-7-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-yl 3,3,3-trifluoro-2-methoxy-2-phenyl propanoate – (*R,R*)-3.69:

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.57-7.53 (2H, m, Ph), 7.45-7.35 (3H, m, Ph), 5.77 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2), 5.20 (1H, quintet, *J* = 6.0 Hz, H4), 5.15-5.09 (2H, m, H1), 3.56 (3H, s, O*Me*), 3.54 (2H, t, *J* = 6.0 Hz, H7), 2.44 (2H, t, *J* = 6.5 Hz, H3), 1.74-1.60 (2H, m, H5), 1.49-1.36 (2H, m, H6), 0.88 (9H, s, Si*t-Bu*), 0.02 (6H, s, Si*Me*$_2$); **^{19}F NMR** ($CDCl_3$, 377 MHz): δ_F −71.28 (s, 96%), −71.35 (s, 4%).

H	δ_H (*S,R*)-3.69	δ_H (*R,R*)-3.69	δ ($\delta_S - \delta_R$)
1	5.03	5.12	−0.09
2	5.66	5.77	−0.11
3	2.37	2.44	−0.07
4	5.18	5.20	−0.02
5	1.73	1.67	+0.06
6	1.55	1.42	+0.13
7	3.61	3.54	+0.07

Table 6.1

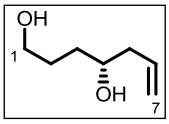
Relative shielding of the allyl group in **(*S,R*)-3.69** combined with relative shielding of the alkyl group in **(*R,R*)-3.69**, both by the phenyl group, suggests assignment of the alcohol as (*R*) when **(*R,S*)-3.69** and **(*R,R*)-3.69** are assumed to be in the conformations shown in *Figure 6.1*.[154]



(*S*,*R*)-3.69 **(*R*,*R*)-3.69**

Figure 6.1

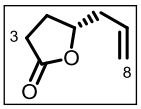
(*R*)-hept-6-ene-1,4-diol – (*R*)-3.62



To a stirred solution of alcohol **(*R*)-3.68** (380 mg, 1.55 mmol) in MeOH (10 mL) was added a catalytic amount of CSA. The reaction was stirred for 1 hour, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:2 EtOAc/pet. ether→EtOAc) to leave pure diol **(*R*)-3.62** (196 mg, 0.151 mmol, 97%) as a colourless oil.

R$_f$ 0.14 (1:1 EtOAc/pet. ether); $[\alpha]_D^{24}$ +17.8 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (250 MHz, $CDCl_3$): δ_H 5.92-5.74 (1H, m, H6), 5.19-5.09 (2H, m, H7), 3.76-3.60 (3H, m, H1 and 4), 2.81-2.41 (2H, m, 2 x O*H*), 2.36-2.13 (2H, m, H5), 1.77-1.45 (4H, m, H2 and 3); **^{13}C NMR** (63 MHz, $CDCl_3$): δ_C 134.9, 118.3, 70.7, 63.0, 42.2, 34.0, 29.3. Spectroscopic data consistent with (±) in the literature.[257]

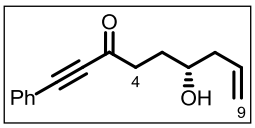
(*R*)-5-allyldihydrofuran-2(3*H*)-one – (*R*)-3.61[258]



To a stirred solution of diol **(*R*,*R*)-3.62** (184 mg, 1.41 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) was added TEMPO free radical (22 mg, 10 mol%) and BAIB (954 mg, 2.96 mmol, 2.1 eq.). The reaction was stirred overnight and quenched with sat. aq. $Na_2S_2O_3$ (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (25 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:1 Et_2O/pet. ether) to leave pure lactone **(*R*)-3.61** (156 mg, 1.24 mmol, 88%) as a colourless oil.

R$_f$ 0.60 (EtOAc); $[\alpha]_D^{25}$ −21.4 (*c* = 1.58, $CHCl_3$) [lit.[258] −17.22 (*c* = 1.0, $CHCl_3$)]; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.78 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H7), 5.20-5.14 (2H, m, H8), 4.56 (1H, *apt* quintet, *J* = 7.0 Hz, H5), 2.53 (2H, dd, *J* = 10.0 and 7.0 Hz, H3), 2.54-2.46 (1H, m, H6), 2.44-2.36 (1H, m, H6), 2.35-2.26 (1H, m, H4), 1.97-1.87 (1H, m, H4); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 177.1, 132.0, 119.0, 79.7, 39.4, 28.6, 27.0. Data consistent with literature.[258]

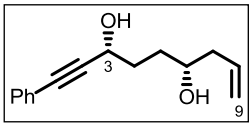
(*R*)-6-hydroxy-1-phenylnon-8-en-1-yn-3-one – (*R*)-3.70



To a stirred solution of phenyl acetylene (0.15 mL, 1.36 mmol, 1.1 eq.) in anhydrous THF (5 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 0.60 mL, 1.49 mmol, 1.2 eq.) dropwise. The resulting solution was allowed to warm to −30 °C and stirred for 30 minutes. The reaction was cooled to −78 °C and to it added $BF_3{\cdot}OEt_2$ (0.17 mL, 1.36 mmol, 1.1 eq.). After a further 10 minutes at −78 °C a solution of lactone **(*R*)-3.70** (156 mg, 1.24 mmol, 1 eq.) in anhydrous THF (1.5 mL) was added in one portion. The reaction was allowed to warm to RT and stirred for 2 hours. The reaction was quenched *via* addition of sat. aq. NH_4OH/NH_4Cl (1:2 v:v, 5 mL) and the mixture diluted with water (10 mL). The aqueous layer was extracted with Et_2O (4 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2→1:1 Et_2O/pet. ether) to leave pure hydroxy ketone **(*R*)-3.70** (210 mg, 0.92 mmol, 74%) as a colourless oil.

R_f 0.56 (Et_2O); **IR** (thin film, cm^{-1}): 3443, 2927, 2203, 1669, 1490, 1444, 1071, 920; $[\alpha]_D^{25}$ +9.4 (*c* = 1.01, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.58 (2H, dt, *J* = 7.5 and 1.5 Hz, Ph), 7.46 (1H, tt, *J* = 7.5 and 1.5 Hz, Ph), 7.39 (2H, tt, *J* = 7.5 and 1.5 Hz, Ph), 5.88-5.79 (1H, m, H8), 5.24-5.11 (2H, m, H9), 3.75-3.70 (1H, m, H6), 2.93-2.81 (2H, m, H4), 2.37-2.18 (2H, m, H7), 2.00-1.79 (3H, m, H5 and O*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): 187.9, 134.3, 133.0, 130.7, 128.6, 119.9, 118.6, 91.0, 87.8, 70.0, 42.1, 41.9, 30.6; **HRMS** (ESI+): calc for $C_{15}H_{16}O_2Na$ $[M+Na]^+$ 251.1043, found 251.1044.

(3*R*,6*R*)-1-phenylnon-8-en-1-yne-3,6-diol – (*R*,*R*)-3.71

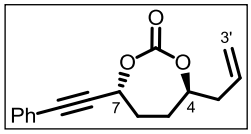


To a stirred solution of [RuCl((*R*,*R*)TsDPEN)(*p*-cymene)] **(*R*,*R*)-3.53·HCl** (1.9 mg, 1 mol%) and ketone **(*R*)-3.71** (69 mg, 0.302 mmol, 1 eq.) in IPA (1.5 ml) was added a solution of KOH (0.2 mg, 1.2 mol%) in IPA (0.1 mL). The reaction was stirred for 72 hours and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2→1:1 Et_2O/pet. ether) to leave pure diol **(*R*,*R*)-3.71** (51 mg, 0.221 mmol, 73%) as a pale yellow oil.

R_f 0.15 (1:1 Et_2O/pet. ether); **>95:5 *dr***; **IR** (thin film, cm^{-1}): 3356, 2929, 2229, 1641, 1490, 1443, 1029, 916, 757; $[\alpha]_D^{25}$ +19.0 (*c* = 0.58, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.45-7.40 (2H, m, Ph), 7.32-7.28 (3H, m, Ph), 5.88-5.78 (1H, m, H8), 5.17-5.11 (2H, m, H9), 4.65 (1H, t, *J* = 6.0 Hz,

H3), 3.79-3.73 (1H, m, H6), 3.36 (1H, bs, O*H*), 2.58 (1H, bs, O*H*), 2.35-2.17 (2H, m, H7), 2.00-1.93 (2H, m, H4), 1.87-1.77 (1H, m, H5), 1.69-1.60 (1H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 134.6, 131.7, 128.3, 128.3, 122.6, 118.2, 90.0, 84.8, 70.5, 62.8, 41.9, 34.2, 32.5; **HRMS** (ESI+): calc for $C_{15}H_{18}O_2Na$ $[M+Na]^+$ 253.1199, found 253.1203.

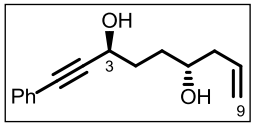
(4*R*,7*R*)-4-allyl-7-(phenylethynyl)-1,3-dioxepan-2-one – (*R*,*R*)-3.60



To a stirred solution of **(*R*,*R*)-3.71** (19 mg, 83 μmol, 1 eq.), Et_3N (70 μL, 0.498 mmol, 6 eq.), pyridine (40 μL, 0.498 mmol, 6 eq.) and powdered 4Å molecular sieves (50 mg) in anhydrous CH_2Cl_2 (1 mL) at −78 °C under argon was added a solution of triphosgene (12 mg, 41 μmol, 0.5 eq.) in anhydrous CH_2Cl_2 (0.5 mL) dropwise. The reaction was stirred for 30 minutes at −78 °C and quenched with sat. aq. $NaHCO_3$ solution (1 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with 1N aq. HCl (1 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (4:1→2:1 Et_2O/pet. ether) to leave pure carbonate **(*R*,*R*)-3.60** (14 mg, 55 μmol, 66%) as a pale yellow oil.

R_f 0.43 (1:1 Et_2O/pet. ether); **>99:1 *dr***; **IR** (thin film, cm^{-1}): 2925, 2235, 1759, 1644, 1492, 1443, 1211, 1056, 925, 758; $[\alpha]_D^{25}$ +49.6 (*c* = 0.25, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.47-7.43 (2H, m, Ph), 7.36-7.30 (3H, m, Ph), 5.89-5.79 (1H, m, H2'), 5.21-5.15 (3H, m, H3' and 7), 4.38 (1H, dtd, *J* = 10.5, 6.5 and 1.5 Hz, H4), 2.54 (1H, dtt, *J* = 14.5, 6.5 and 1.5 Hz, H1'), 2.41 (1H, dtt, 14.5, 6.5 and 1.5 Hz, H1'), 2.32 (1H, dtd, *J* = 15.5, 4.5 and 2.0 Hz, H6), 2.25-2.15 (1H, m, H6), 2.08 (1H, dtd, *J* = 15.0, 4.5 and 2.0 Hz, H5), 1.90-1.80 (1H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 153.0, 132.5, 131.8, 129.0, 128.4, 121.6, 118.8, 87.3, 84.5, 71.7, 39.7, 33.4, 31.1; **HRMS** (FI+): calc for $C_{16}H_{16}O_3$ $[M]^+$ 256.1099, found 256.1103.

(3*S*,6*R*)-1-phenylnon-8-en-1-yne-3,6-diol – (*S*,*R*)-3.71

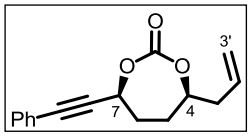


To a stirred solution of [RuCl((*S*,*S*)-TsDPEN)(p-cymene)] **(*S*,*S*)-3.53·HCl** (1.7 mg, 1 mol%) and ketone **(*R*)-3.70** (60 mg, 0.263 mmol, 1 eq.) in IPA (2.5 ml) was added a solution of KOH (0.2 mg, 1.2 mol%) in IPA (0.1 mL). The resulting solution was stirred

for 16 hours and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2 Et_2O/pet. ether→Et_2O) to leave pure diol **(*S*,*R*)-3.71** (18 mg, 78 μmol, 30%, 86% brsm) as a colourless oil.

R_f 0.15 (1:1 Et_2O/pet. ether); **>95:5 *dr***; **IR** (thin film, cm^{-1}): 3338, 2929, 2867, 2232, 1641, 1599, 1490, 1443, 1332, 1027, 916; $[\alpha]_D^{25}$ –10.0 (*c* = 0.34, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.47-7.41 (2H, m, Ph), 7.35-7.29 (3H, m, Ph), 5.89-5.80 (1H, m, H8), 5.19-5.14 (2H, m, H9), 4.70 (1H, t, *J* = 5.5 Hz, H3), 3.77-3.71 (1H, m, H6), 3.05 (1H, bs, O*H*), 2.38-2.32 (1H, m, H7), 2.28-2.10 (1H, m, H7), 2.12 (1H, bs, O*H*), 2.03-1.94 (2H, m, 4), 1.81-1.75 (2H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 134.5, 131.7, 128.3, 128.3, 122.6, 118.5, 89.9, 85.0, 70.6, 62.6, 42.1, 34.3, 32.2; **HRMS** (ESI+): calc for $C_{15}H_{18}O_2Na$ $[M+Na]^+$ 253.1199, found 253.1201.

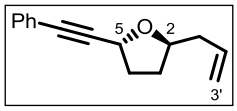
(4*R*,7*S*)-4-allyl-7-(phenylethynyl)-1,3-dioxepan-2-one – (*R*,*S*)-3.60



To a stirred solution of **(*S*,*R*)-3.71** (18 mg, 78 μmol, 1 eq.), triethylamine (65 μL, 0.468 mmol, 6 eq.), pyridine (38 μL, 0.468 mmol, 6 eq.) and powdered 4Å molecular sieves (50 mg) in anhydrous CH_2Cl_2 (1 mL) at −78 °C under argon was added a solution of triphosgene (11.5 mg, 39 μmol, 0.5 eq.) in anhydrous CH_2Cl_2 (0.5 mL) dropwise. The reaction was stirred for 30 minutes at −78 °C and quenched with sat. aq. $NaHCO_3$ (1 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with 1N aq. HCl, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (4:1→2:1 Et_2O/pet. ether) to leave pure carbonate **(*R*,*S*)-3.60** (8 mg, 31 μmol, 40%) as a pale yellow oil.

R_f 0.31 (1:1 Et_2O/pet. ether); **>99:1 *dr***; **IR** (thin film, cm^{-1}): 2918, 2850, 2232, 1753, 1643, 1490, 1443, 1367, 1202, 1041, 975; $[\alpha]_D^{25}$ –22.6 (*c* = 0.46, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.48-7.44 (2H, m, Ph), 7.39-7.31 (3H, m, Ph), 5.86 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2'), 5.37-5.34 (1H, m, H7), 5.20-5.15 (2H, m, H3'), 4.35-4.29 (1H, m, H4), 2.57 (1H, dt, *J* = 14.0 and 6.5 Hz, H1'), 2.42 (1H, dt, *J* = 14.0 and 6.5 Hz, H1'), 2.28-2.12 (3H, m, H6 and H5), 1.98-1.91 (1H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 152.8, 132.8, 131.9, 129.4, 128.3, 121.4, 118.7, 90.0, 82.5, 81.6, 70.2, 40.0, 32.5, 28.7; **HRMS** (ESI+): calc for $C_{16}H_{16}O_3Na$ $[M+Na]^+$ 279.0992, found 279.0990.

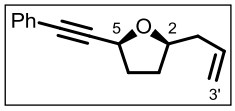
(2*R*,5*R*)-2-allyl-5-(phenylethynyl)tetrahydrofuran – (*R*,*R*)-3.72



To a degassed solution of carbonate **(*R*,*R*)-3.60** (13.0 mg, 50.7 μmol, 1 eq.) and PPTS (1.3 mg, 10 mol%) in 1,4-dioxane (0.5 mL) was added $Pd(PPh_3)_4$ (0.6 mg, 1 mol%). The reaction was heated to 100 °C for 10 minutes, cooled and quenched *via* addition of pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O) and the solvent removed *in vacuo* to leave pure THF **(*R*,*R*)-3.72** (9.7 mg, 45.6 μmol, 90%, 83 : 17 *dr*) as a colourless oil. The mixture was carefully chromatographed on silica gel (1:99→1:19 Et_2O/pet. ether) to leave pure *trans*-THF **(*R*,*R*)-3.72** as a colourless oil.

R_f 0.70 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ +54 (*c* = 0.10, $CHCl_3$); **IR** (thin film, cm^{-1}): 2932, 2249, 1643, 1599, 1490, 1444, 1052, 909; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph), 7.31-7.28 (3H, m, Ph), 5.84 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2'), 5.15-5.07 (2H, m, H3'), 4.92 (1H, dd, *J* = 7.0 and 5.5 Hz, H5), 4.24 (1H, *apt* quintet, *J* = 7.0 Hz, H2), 2.45-2.38 (1H, m, H1'), 2.33-2.26 (2H, m, H4 and 1'), 2.21-2.14 (1H, m, H3), 2.14-2.07 (1H, m, H4), 1.66-1.59 (1H, m, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 134.7, 131.9, 128.4, 128.3, 123.0, 117.3, 89.5, 84.6, 78.4, 68.7, 39.9, 33.7, 30.7; **HRMS** (ESI+): calc for $C_{15}H_{16}ONa$ $[M+Na]^+$ 235.1093, found 235.1092.

(2*R*,5*S*)-2-allyl-5-(phenylethynyl)tetrahydrofuran – (*R*,*S*)-3.72

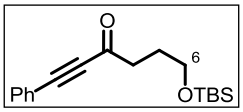


To a degassed solution of carbonate **(*R*,*S*)-3.60** (8.0 mg, 31.2 μmol, 1 eq.) and PPTS (0.8 mg, 10 mol%) in 1,4-dioxane (0.25 mL) was added $Pd(PPh_3)_4$ (0.4 mg, 1 mol%). The reaction was heated to 100 °C for 10 minutes, cooled and quenched *via* addition of pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O) and the solvent removed *in vacuo* to leave pure THF **(*R*,*S*)-3.72** (5.5 mg, 25.9 μmol, 83%, 77 : 23 *dr*) as a colourless oil. The mixture was carefully chromatographed on silica gel (1:99→1:19 Et_2O/pet. ether) to leave pure *cis*-THF **(*R*,*S*)-3.72** as a colourless oil.

R_f 0.66 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ +1.4 (*c* = 0.36, $CHCl_3$); **IR** (thin film, cm^{-1}): 2979, 2246, 1642, 1599, 1490, 1443, 1355, 1054, 912; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.32-7.29 (3H, m, Ph), 5.88 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2'), 5.16-5.07 (2H, m, H3'), 4.78 (1H, dd, *J* = 7.0 and 6.0 Hz, H5), 4.04-3.98 (1H, m, H2), 2.55-2.49 (1H, m, H1'), 2.40-2.33 (1H, m, H1'), 2.28-2.21 (1H, m, H4), 2.15-2.09 (1H, m, H4), 2.08-2.02 (1H, m, H3), 1.85-1.77 (1H, m, H3); **^{13}C NMR**

(125 MHz, $CDCl_3$): δ_C 134.9, 131.8, 128.4, 128.3, 123.0, 117.2, 89.5, 84.6, 79.7, 68.8, 40.5, 33.6, 30.8; **HRMS** (ESI+): calc for $C_{15}H_{16}ONa$ $[M+Na]^+$ 235.1093, found 235.1093.

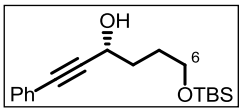
6-(*tert*-butyldimethylsilyloxy)-1-phenylhex-1-yn-3-one – 2.59c.1



To a stirred solution of hydroxy ketone **2.59c** (200 mg, 1.06 mmol, 1 eq.), imidazole (80 mg, 1.17 mmol, 1.1 eq.) and DMAP (1 crystal, cat.) in anhydrous CH_2Cl_2 (5 mL) at 0 °C was added TBSCl (176 mg, 1.17 mmol, 1.1 eq.) portionwise. The reaction was allowed to warm to RT and stirred for 1 hour. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1N aq. HCl (15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19→1:9 Et_2O/pet. ether) to leave pure silyloxy ketone **2.59c.1** (294 mg, 0.97 mmol, 92%) as a colourless oil.

R_f 0.56 (1:9 EtOAc/pet. ether); **IR** (thin film, cm^{-1}): 2930, 2857, 2203, 1673, 1490, 1361, 1257, 1100, 996, 836; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.58 (2H, d, *J* = 8.0 Hz, Ph), 7.46 (1H, t, *J* = 7.5 Hz, Ph), 7.39 (2H, t, *J* = 8.0 Hz, Ph), 3.69 (2H, t, *J* = 6.0 Hz, H6), 2.76 (2H, t, *J* = 7.0 Hz, H4), 1.96 (2H, quintet, *J* = 6.5 Hz, H5), 0.91 (9H, s, Si*t-Bu*), 0.07 (6H, s, Si*Me*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.0, 133.2, 130.8, 128.7, 102.2, 90.7, 88.0, 62.1, 42.3, 27.4, 26.1, 18.5, −5.2; **HRMS** (ESI+): calc for $C_{18}H_{26}O_2SiNa$ $[M+Na]^+$ 325.1594, found 325.1589.

(*R*)-6-(*tert*-butyldimethylsilyloxy)-1-phenylhex-1-yn-3-ol – (*R*)-3.75c

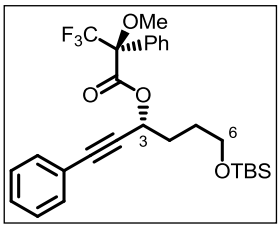


To a stirred solution of silyloxy ketone **2.59c.1** (151 mg, 0.50 mmol, 1 eq.) and [RuCl((*R*,*R*)-TsDPEN)(*p*-cymene)] **(*R*,*R*)-3.53·HCl** (3.4 mg, 1 mol%) in IPA (4.75 mL) under argon was added a solution of KOH in IPA (0.34 mg in 0.34 mL IPA, 1.2 mol%). The reaction was stirred for 2 hours and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:3 Et_2O/pet. ether) to leave pure alcohol **(*R*)-3.75c** (142 mg, 0.47 mmol, 94%) as a colourless oil.

R_f 0.40 (1:3 Et_2O/pet. ether); **97% *ee*** (CHIRALPAK IC, 1.25 mL/min, 2% IPA/Hexane): t_R (*R*) = 10.48 min, t_R (*S*) = 11.60 min; $[\alpha]_D^{25}$ +9.1 (*c* = 0.53, CH_2Cl_2); **IR** (thin film, cm^{-1}): 3386, 2954, 2858, 2228, 1599, 1491, 1462, 1255, 1098, 836; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph),

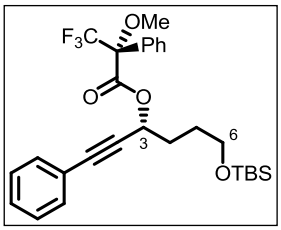
7.31-7.28 (3H, m, Ph), 4.69-4.64 (1H, m, H3), 3.77-3.67 (2H, m, H6), 3.47 (1H, bs, O*H*), 1.99-1.84 (3H, H4 and 5), 1.80-1.71 (1H, m, H5), 0.92 (9H, s, Si*t-Bu*), 0.09 (6H, s, Si*Me*$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.8, 128.3, 128.3, 123.0, 90.4, 84.7, 63.4, 62.6, 35.5, 28.7, 26.0, 18.4, −5.2, −5.3; **HRMS** (ESI+): calc for $C_{18}H_{28}O_2SiNa$ $[M+Na]^+$ 327.1751, found 327.1751.

Absolute configuration was determined by synthesis of the diastereomeric pair of Mosher esters, and comparison of their ^{1}H NMR spectra:



(*S*)-(*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-phenylhex-1-yn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate – (*S,R*)-3.75c.1

R$_f$ 0.56 (Et_2O/pet. ether 1:3); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ_H 7.57 (2H, d, *J* = 7.5 Hz, Ph), 7.43-7.30 (8H, m, Ph), 5.82 (1H, t, *J* = 7.0 Hz, H3), 3.69 (2H, t, *J* = 6.0 Hz, H6), 3.60 (3H, s, O*Me*), 2.06-2.01 (2H, m, H4), 1.81-1.69 (2H, m, H5), 0.90 (9H, s, Si*t-Bu*), 0.06 (6H, s, Si*Me*$_2$).



(*R*)-(*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-phenylhex-1-yn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate – (*R,R*)-3.75c.1

R$_f$ 0.60 (Et_2O/pet. ether 1:3); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ_H 7.60 (2H, d, *J* = 7.5 Hz, Ph), 7.45-7.31 (8H, m, Ph), 5.86 (1H, t, *J* = 7.0 Hz, H3), 3.63 (2H, t, *J* = 6.0 Hz, H6), 3.62 (3H, s, O*Me*), 2.00-1.95 (2H, m, H4), 1.72-1.59 (2H, m, H5), 0.89 (9H, s, Si*t-Bu*), 0.05 (6H, s, Si*Me*$_2$).

H	δ_H (*S,R*)-3.75c.1	δ_H (*R,R*)-3.75c.1	δ ($\delta_S - \delta_R$)
3	5.82	5.86	−0.04
4	2.03	1.98	+0.05
5	1.75	1.66	+0.09
6	3.69	3.63	+0.06

Table 6.2

Relative shielding of the alkyl protons in **(*R,R*)-3.75c.1** by the phenyl group suggests assignment of the alcohol as (*R*) when **(*S,R*)-3.75c.1** and **(*R,R*)-3.75c.1** are assumed to be in the conformations shown in *Figure 6.2*.[154]

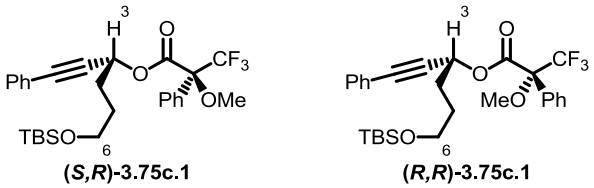
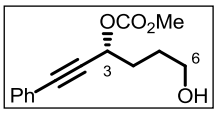


Figure 6.2

(*R*)-6-hydroxy-1-phenylhex-1-yn-3-yl methyl carbonate – (*R*)-3.76c

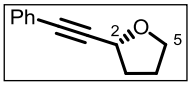


To a stirred solution of alcohol **(*R*)-3.75c** (1.85 g, 6.08 mmol, 1 eq.) and pyridine (2.95 mL, 36.48 mmol, 6 eq.) in anhydrous CH_2Cl_2 (80 mL) at 0 °C under argon was added methyl chloroformate (1.41 mL, 18.24 mmol, 3 eq.) dropwise. The reaction was stirred for 20 minutes and quenched *via* addition of sat. aq. $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with 1N aq. HCl (2 x 50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to leave crude siloxycarbonate (2.16 g) which was used in the next step without further purification.

The above crude silyoxycarbonate (2.16 g) was taken up in MeOH (100 mL) and to it added a catalytic amount of CSA. The resulting solution was stirred at RT for 1 hour and the solvent removed *in vacuo.* The crude product was purified by flash chromatography on silica gel to leave pure carbonate **(*R*)-3.76c** (1.30 g, 5.24 mmol, 86%, *2 steps*) as a viscous yellow oil.

R_f 0.50 (1:1 EtOAc/pet. ether); **IR** (thin film, cm^{-1}): 3379, 2957, 2236, 1751, 1491, 1443, 1267, 1070, 962; $[\alpha]_D^{26}$ +121.7 (*c* = 1.15, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ_H 7.48-7.42 (2H, m, Ph), 7.36-7.24 (3H, m, Ph), 5.53 (1H, t, *J* = 6.5 Hz, H3), 3.83 (3H, s, O*Me*), 3.74 (2H, t, *J* = 6.0 Hz, H6), 2.09-1.75 (4H, m, H4 and 5), 1.57 (1H, bs, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 155.0, 131.9, 128.7, 128.3, 122.0, 86.4, 85.5, 68.4, 62.2, 55.0, 31.4, 28.0; **HRMS** (ESI+): calc for $C_{14}H_{16}O_4Na$ $[M+Na]^+$ 271.0941, found 271.0946.

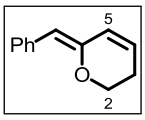
(*R*)-2-(phenylethynyl)tetrahydrofuran - (*R*)-2.61c[110]



A degassed solution of $Pd(OAc)_2$ (0.9 mg, 5 mol%) and dppf (4.5 mg, 10 mol%) in 1,4-dioxane (0.8 mL) was added to a vial fitted with a septum containing carbonate **(*R*)-3.76c** (20 mg, 81 μmol, 1 eq.) and $B(OH)_3$ (2.5 mg, 41 μmol, 1.1 eq.) under argon. The reaction was stirred and heated to 50 °C for 30 minutes, cooled and quenched *via* addition of pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O) and the solvent removed *in vacuo* to pure THF **(*R*)-2.61c** (13.8 mg, 80 μmol, 99%) as a colourless oil.

96% *ee* (CHIRALPAK IA, 1.25 mL/min, 2% IPA/Hexane): t_R (*S*) = 6.84 min, t_R (*R*) = 7.45 min. All spectroscopic data identical to **(*R*)-2.61c** prepared previously from cyclic carbonate **(*R*)-2.06c**.

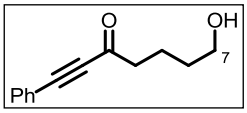
(*Z*)-6-benzylidene-3,6-dihydro-2*H*-pyran – 3.86[69]



Isolated from the reaction of carbonate **(*R*)-2.76c** with bidentate ligands in the absence of $B(OH)_3$.

R_f 0.25 (1:9 Et_2O/pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.66-7.63 (2H, m, Ph), 7.31-7.27 (2H, m, Ph), 7.15-7.11 (1H, m, Ph), 6.11 (1H, dt, *J* = 10.0 and 1.5 Hz, H5), 6.01 (1H, dt, *J* = 10.0 and 4.0 Hz, H4), 5.34 (1H, s, PhC*H*), 4.20 (2H, t, *J* = 5.5 Hz, H2), 2.40-2.36 (2H, m, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 150.0, 136.3, 128.5, 128.1, 126.1, 125.8, 125.7, 107.9, 64.7, 24.7. Data consistent with literature.[69]

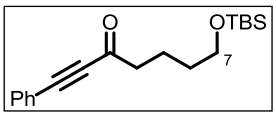
7-hydroxy-1-phenylhept-1-yn-3-one – 3.116.1c[146]



To a stirred solution of phenyl acetylene (1.15 mL, 10.5 mmol, 1.05 eq.) in anhydrous THF (50 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 4.40 mL, 11.0 mmol, 1.1 eq.) dropwise. The solution was stirred for 30 minutes and to it added $BF_3{\cdot}OEt_2$ (1.36 mL, 11.0 mmol, 1.1 eq.) dropwise. The solution was stirred for a further 5 minutes and to it added a δ-valerolatone **3.116** (0.93 mL, 10.0 mmol, 1 eq.) in one portion. The reaction was allowed to warm to RT and stirred for 1 hour. The reaction was quenched with sat. aq. NH_4Cl/NH_4OH (2:1 v:v, 50 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2→1:1 Et_2O/pet. ether) to leave pure ketone **3.116.1c** (1.95 g, 9.64 mmol, 96%) as a pale yellow oil.

R_f 0.38 (Et_2O); **IR** (thin film, cm^{-1}): 3400, 2940, 2203, 1668, 1489, 1444, 1285, 1058, 759; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.58 (2H, d, *J* = 7.5 Hz, Ph), 7.46 (1H, t, *J* = 7.5 Hz, Ph), 7.39 (2H, t, *J* = 7.5 Hz, Ph), 3.69 (2H, *apt* q, *J* = 6.0 Hz, H7), 2.74 (2H, t, *J* = 7.5 Hz, H4), 1.85 (2H, quintet, *J* = 7.5 Hz, H5), 1.69-1.61 (2H, m, H6), 1.51 (1H, bs, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 187.9, 133.0, 130.7, 128.6, 119.9, 90.9, 87.8, 62.3, 45.1, 31.9, 20.2; **HRMS** (ESI+): calc for $C_{13}H_{14}O_2Na$ $[M+Na]^+$ 225.0886, found 225.0887. Data consistent with literature.[146]

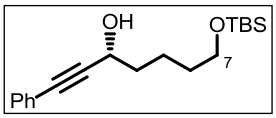
7-((*tert*-butyldimethylsilyl)oxy)-1-phenylhept-1-yn-3-one – 3.129[259]



To a stirred solution of ketone **3.129** (1.95 g, 9.64 mmol, 1 eq.), imidazole (788 mg, 11.57 mmol, 1.2 eq.) and DMAP (117 mg, 10 mol%) in anhydrous CH_2Cl_2 (50 mL) at 0 °C under argon was added TBSCl (1.60 g, 10.60 mmol, 1.1 eq.) portionwise. The reaction was allowed to warm to RT and stirred for 1 hour. The reaction was quenched with sat. aq. $NaHCO_3$ solution (50 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product passed through a short plug of silica gel (1:19→1:9 Et_2O/pet. ether) to leave pure silyloxy ketone **3.129** (2.78 g, 8.78 mmol, 91%) as pale yellow oil.

R_f 0.69 (Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.58 (2H, d, *J* = 7.5 Hz, Ph), 7.46 (1H, t, *J* = 7.5 Hz, Ph), 7.39 (2H, t, *J* = 7.5 Hz, Ph), 3.66 (2H, t, *J* = 6.0 Hz, H7), 2.71 (2H, t, *J* = 7.0 Hz, H4), 1.82 (2H, quintet, *J* = 7.0 Hz, H5), 1.60 (2H, quintet, *J* = 7.0 Hz, H6), 0.90 (9H, s, Si*t-Bu*), 0.06 (6H, s, Si*Me*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.2, 133.2, 130.8, 128.7, 120.2, 90.8, 88.0, 62.8, 45.4, 32.5, 26.1, 20.9, 18.5, −5.2. Data consistent with literature.[259]

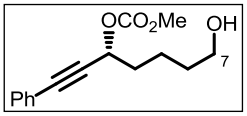
(*R*)-7-((*tert*-butyldimethylsilyl)oxy)-1-phenylhept-1-yn-3-ol – (*R*)-3.117c



A solution of ketone **3.129** (1.38 g, 4.36 mmol, 1 eq.) in IPA (22 mL) was degassed for 30 minutes. To it was added a solution of [Ru((*R*,*R*)-TsDPEN)(*p*-cymene)] **(*R*.*R*)-3.53** (52 mg, 2 mol%) in anhydrous CH_2Cl_2 (0.5 mL). The reaction was stirred for 1 hour, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:9→1:3 Et_2O/pet. ether) to leave pure alcohol **(*R*)-3.117c** (1.38 g, 4.33 mmol, 99%) as a pale yellow oil.

R_f 0.53 (1:1 Et_2O/pet. ether); **98% *ee*** (CHIRALPAK IC, 1.3 mL/min, 1% IPA/Hexane): t_R (*R*) = 11.00 min, t_R (*S*) = 12.04 min; **$[\alpha]_D^{25}$** −8.1 (*c* = 0.74, $CHCl_3$); **IR** (thin film, cm^{-1}): 3356, 2930, 2858, 2230, 1490, 1472, 1255, 1100, 836; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46-7.41 (2H, m, Ph), 7.33-7.27 (3H, m, Ph), 4.61 (1H, t, *J* = 7.0 Hz, H3), 3.65 (2H, t, *J* = 6.0 Hz, H7), 2.18 (1H, bs, O*H*), 1.88-1.79 (2H, m, H4), 1.65-1.54 (4H, m, H5 and 6), 1.40 (1H, bs, O*H*), 0.90 (9H, s, Si*t-Bu*), 0.06 (6H, s, Si*Me*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 131.7, 128.3, 128.2, 122.7, 90.2, 84.8, 63.0, 62.9, 37.6, 26.0, 21.6, 18.3, −5.3; **HRMS** (ESI+): calc for $C_{19}H_{30}O_2Si$ $[M+Na]^+$ 341.1907, found 341.1909.

(*R*)-7-hydroxy-1-phenylhept-1-yn-3-yl methyl carbonate – (*R*)-3.118c

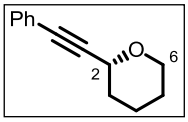


To a stirred solution of alcohol **(*R*)-3.117c** (1.18 g, 3.70 mmol, 1 eq.) and pyridine (2.39 mL, 29.6 mmol, 8 eq.) in anhydrous CH_2Cl_2 (40 mL) at 0 °C under argon was added methyl chloroformate (0.86 mL, 11.1 mmol, 3 eq.). The reaction was stirred for 15 minutes at 0 °C and quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with 1N aq. HCl (2 x 20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was used directly in the next step without further purification.

The above crude carbonate was taken up in MeOH (10 mL) and to it added a catalytic amount of CSA. The reaction was stirred for 1 hour, and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4 Et_2O/pet. ether→Et_2O) to leave pure carbonate **(*R*)-3.118c** (920 mg, 3.51 mmol, 95%, *2 steps*) as a colourless oil.

R_f 0.27 (2:1 Et_2O/pet. ether); **$[\alpha]_D^{25}$** +127.1 (*c* = 0.75, $CHCl_3$); **IR** (thin film, cm^{-1}): 3360, 2953, 2867, 2233, 1750, 1491, 1443, 1267, 946, 791; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.47-7.43 (2H, m, Ph), 7.36-7.28 (3H, m, Ph), 5.48 (1H, t, *J* = 6.5 Hz, H3), 3.83 (3H, s, O*Me*), 3.69 (2H, t, *J* = 6.0 Hz, H7), 2.01-1.90 (2H, m, H4), 1.71-1.58 (4H, m, H5 and 6), 1.47 (1H, bs, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 155.0, 131.9, 128.7, 128.2, 122.1, 86.3, 85.6, 68.6, 62.6, 55.0, 34.7, 32.2, 21.3; **HRMS** (ESI+): calc for $C_{15}H_{18}O_4Na$ $[M+Na]^+$ 285.1097, found 285.1096; **Elemental Analysis:** $C_{15}H_{18}O_4$ requires C, 68.68%; H, 6.92%; found C, 68.51%; H, 6.97%.

(*R*)-2-(phenylethynyl)tetrahydro-2*H*-pyran – (*R*)-3.119c[145]

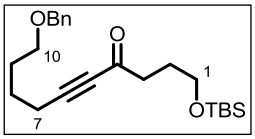


To a degassed solution of carbonate **(*R*)-3.118c** (20.0 mg, 76 μmol, 1 eq.) and $B(OH)_3$ (5.2 mg, 84 μmol, 1.1 eq.) in 1,4-dioxane (0.25 mL) was added a degassed solution of $Pd(OAc)_2$ (0.9 mg, 5 mol%) and dppf (4.2 mg, 10 mol%) in 1,4-dioxane (0.25 mL). The resulting solution was stirred at 100 °C for 15 minutes, quenched with pet. ether (1 ml) and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* to leave pure THP **(*R*)-3.119c** (14 mg, 75 μmol, 99%) as a colourless oil.

R_f 0.67 (1:1 Et_2O/pet. ether); **94% *ee*** (CHIRALPAK IA, 1.3 mL/min, 0.8% IPA/hexane): t_R (*S*) = 4.78 min, t_R (*R*) = 5.68 min; **$[\alpha]_D^{25}$** +1.6 (*c* = 1.15, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.48-7.44 (2H,

m, Ph), 7.33-7.29 (3H, m, Ph), 4.53-4.50 (1H, m, H2), 4.09-4.04 (1H, m, H6), 3.63-3.57 (1H, m, H6), 1.97-1.88 (2H, m, H4), 1.84-1.74 (1H, m, H3), 1.67-1.55 (3H, m, H3 and 5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.7, 128.3, 128.2, 122.7, 88.1, 85.2, 67.4, 66.6, 32.2, 25.6, 21.8. Spectroscopic data consistent with (±) in the literature.[145]

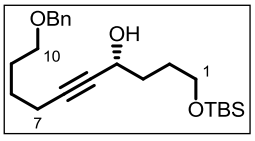
10-(benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)dec-5-yn-4-one – 2.59e.1



To a stirred solution of ketone **2.59e** (200 mg, 0.73 mmol, 1 eq.) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under argon was added imidazole (60 mg, 0.88 mmol, 1.2 eq.) and a catalytic amount of DMAP. To it was added TBSCl (121 mg, 0.80 mmol, 1.1 eq.) and the reaction stirred at 0 °C for 1 hour. The reaction was allowed to warm to RT and stirred for a further 2 hours. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N aq. HCl (1 x 30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave pure silyoxy ketone **2.59e.1** (221 mg, 0.57 mmol, 78%) as a colourless oil.

R_f 0.60 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2930, 2857, 2212, 1675, 1496, 1361, 1104, 837; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.38-7.27 (5H, m, Ph), 4.51 (2H, s, PhC*H*$_2$O), 3.63 (2H, t, *J* = 6.5 Hz, H1), 3.51 (2H, t, *J* = 6.0 Hz, H10), 2.62 (2H, t, *J* = 7.5 Hz, H3), 2.40 (2H, t, *J* = 6.5 Hz, H7), 1.87 (2H, *apt* quintet, *J* = 7.0 Hz, H2), 1.78-1.66 (4H, m, H8 and 9), 0.90 (9H, s, Si*t-Bu*), 0.05 (6H, s, Si*Me*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.2, 138.6, 128.5, 127.7, 127.7, 93.9, 81.2, 73.1, 69.6, 62.0, 42.2, 29.0, 27.3, 26.1, 24.8, 18.9, 18.4, −5.2; **HRMS** (ESI+): calc for $C_{23}H_{36}O_3SiNa$ $[M+Na]^+$ 411.2326, found 411.2315.

(*R*)-10-(benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)dec-5-yn-4-ol – (*R*)-3.75e

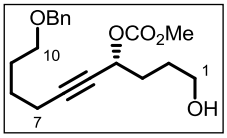


A stirred solution of ketone **3.75e** (210 mg, 0.54 mmol, 1 eq.) in IPA (2.7 mL) was degassed for 30 minutes. To it was added a solution of [Ru((*R,R*)-TsDPEN)(*p*-cymene)] **(*R,R*)-3.53** (6.5 mg, 2 mol%) in anhydrous CH_2Cl_2 (0.1 mL). The reaction was degassed for a further 15 minutes and stirred for 72 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (Et_2O/pet.

ether 1:14→2:1) to leave pure alcohol **(*R*)-3.75e** (148 mg, 0.38 mmol, 70%) as a colourless oil.

R_f 0.45 (1:1 Et_2O/pet. ether); **96% *ee*** (CHIRALPAK IC, 1.2 mL/min, 6% IPA/hexane): t_R (*R*) = 5.09 min; t_R (*S*) = 5.43 min); $[\alpha]_D^{25}$ +5.8 (*c* = 1.22, $CHCl_3$); **IR** (thin film, cm^{-1}): 3418, 2931, 2858, 2245, 1455, 1362, 1255, 1105, 910, 836; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.38-7.27 (5H, m, Ph), 4.51 (2H, s, PhC*H_2*O), 4.42-4.38 (1H, m, H4), 3.73-3.61 (2H, m, H1), 3.49 (2H, t, *J* = 6.5 Hz, H10), 3.00 (1H, d, *J* = 5.0 Hz, O*H*), 2.24 (2H, td, *J* = 7.0 and 2.0 Hz, H7), 1.82-1.57 (8H, m, H2, 3, 8 and 9), 0.91 (9H, s, Si*t-Bu*), 0.08 (6H, s, Si*Me_2*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 138.7, 128.5, 127.7, 127.6, 85.0, 81.7, 73.0, 70.0, 63.3, 62.5, 35.7, 29.0, 28.7, 26.0, 25.6, 18.7, 18.4, −5.2; **HRMS** (ESI+): calc for $C_{23}H_{38}O_3SiNa$ $[M+Na]^+$ 413.2482, found 413.2471.

(*R*)-10-(benzyloxy)-1-hydroxydec-5-yn-4-yl methyl carbonate – (*R*)-3.76e



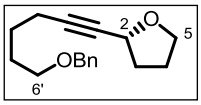
To a stirred solution of alcohol **(*R*)-3.75e** (145 mg, 0.37 mmol, 1 eq.) and pyridine (0.24 mL, 2.96 mmol, 8 eq.) in anhydrous CH_2Cl_2 (4 mL) at 0 °C under argon was added methyl chloroformate (86 μL, 1.11 mmol, 3 eq.). The reaction was stirred for 30 minutes at 0 °C and quenched with sat. aq. $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with 1N aq. HCl (1 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave the crude carbonate which was used directly in the next step without further purification.

The crude carbonate was taken up in MeOH (5 mL) and to it added a catalytic amount of CSA. The reaction was stirred for 1 hour and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave pure carbonate **(*R*)-3.76e** (113 mg, 0.34 mmol, 91%, *2 steps*) as a colourless oil.

R_f 0.22 (2:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ +55.1 (*c* = 1.12, $CHCl_3$); **IR** (thin film, cm^{-1}): 3420, 2952, 2867, 2243, 1750, 1444, 1265, 1106, 934, 792; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.37-7.27 (5H, m, Ph), 5.27 (1H, tt, *J* = 6.5 and 2.0 Hz, H4), 4.50 (2H, s, PhC*H_2*O), 3.79 (3H, s, O*Me*), 3.67 (2H, t, *J* = 6.5 Hz, H1), 3.49 (2H, t, *J* = 6.5 Hz, H10), 2.25 (2H, td, *J* = 7.0 and 2.0 Hz, H7), 1.91-1.85 (2H, m, H3), 1.77-1.67 (4H, m, H2 and 9), 1.64-1.58 (2H, m, H8), 1.56 (1H, bs, O*H*); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ_C 155.2, 138.6, 128.5, 127.8, 127.7, 87.3, 77.2, 73.0, 69.9, 68.6, 62.3, 55.0, 31.7, 28.9, 28.2, 25.3, 18.6;

HRMS (ESI+): calc for $C_{19}H_{26}O_5Na$ $[M+Na]^+$ 357.1672, found 357.1659.

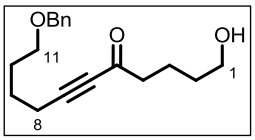
(*R*)-2-(6-(benzyloxy)hex-1-ynyl)tetrahydrofuran – (*R*)-2.61e



To a degassed solution of carbonate **(*R*)-3.76e** (20.0 mg, 60 μmol, 1 eq.) and $B(OH)_3$ (1.9 mg, 30 μmol, 0.5 eq.) in 1,4-dioxane (0.25 mL) was added a solution of $Pd(OAc)_2$ (0.7 mg, 5 mol%) and dppf (3.3 mg, 10 mol%) in degassed 1,4-dioxane (0.5 mL). The reaction was heated to 100 °C for 10 minutes, allowed to cool and quenched with pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent) and the solvent removed *in vacuo* to leave pure THF **(*R*)-2.61e** (15.5 mg, 60 μmol, 99%) as a colourless oil.

92% *ee* (CHIRALPAK IB, 1.3 mL/min, 2% IPA/hexane): t_R (*S*) = 6.20 min; t_R (*R*) = 6.81 min. All other spectroscopic data identical to **(*R*)-2.61e** prepared previously from cyclic carbonate **(*R*)-2.06e**.

11-(benzyloxy)-1-hydroxyundec-6-yn-5-one – 3.116.1e

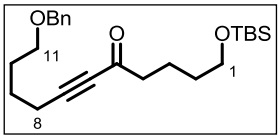


To a stirred solution of alkyne **3.48** (420 mg, 2.23 mmol, 1.1 eq.) in anhydrous THF (10 mL) at −78 °C was added *n*-butyllithium (2.5 M in hexanes, 0.97 mL, 2.43 mmol, 1.2 eq.) dropwise. The resulting solution was allowed to warm to −30 °C and stirred for 30 minutes. The solution was cooled to −78 °C and $BF_3{\cdot}OEt_2$ (0.28 mL, 2.23 mmol, 1.1 eq.) added dropwise. After a further 10 minutes at −78 °C, δ-valerolactone **3.116** (0.19 mL, 2.03 mmol, 1 eq.) was added in one portion. The reaction was allowed to warm to RT and stirred for 2 hours. The reaction was quenched with sat. aq. NH_4OH/NH_4Cl (1:2 v:v, 10 mL) and diluted with water (20 mL). The mixture was extracted with Et_2O (4 x 20 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave pure ketone **3.116.1e** (484 mg, 1.68 mmol, 83%) as a colourless oil.

R_f 0.38 (Et_2O); **IR** (thin film, cm^{-1}): 3425, 2939, 2867, 2211, 1671, 1455, 1362, 1162, 1107; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.38-7.27 (5H, m, Ph), 4.51 (2H, s, PhC*H*$_2$O), 3.66-3.60 (2H, m, H1), 3.50 (2H, t, *J* = 6.0 Hz, H11), 2.58 (2H, t, *J* = 7.5 Hz, H4), 2.40 (2H, t, *J* = 7.0 Hz, H8), 1.79-1.62 (7H, m, H3, 9, 10 and O*H*), 1.62-1.54 (2H, m, H2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.3, 138.5, 128.5, 127.7, 127.7, 94.3, 81.1, 73.1, 69.6, 62.4, 45.2, 32.0, 29.0, 24.7, 20.3, 18.9; **HRMS** (ESI+): calc for

$C_{18}H_{24}O_3Na$ $[M+Na]^+$ 311.1618, found 311.1618.

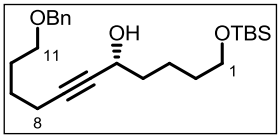
11-(benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)undec-6-yn-5-one – 3.116.2e



To a stirred solution of ketone **3.116.1e** (200 mg, 0.69 mmol, 1 eq.) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under argon was added imidazole (56 mg, 0.83 mmol, 1.2 eq.) and a catalytic amount of DMAP. To it was added TBSCl (115 mg, 0.76 mmol, 1.1 eq.) and the reaction stirred at 0 °C for 1 hour. The reaction was allowed to warm to RT and stirred for a further 2 hours. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N aq. HCl (1 x 30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave pure silyloxy ketone **3.116.2e** (245 mg, 0.61 mmol, 88%) as a colourless oil.

R_f 0.60 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2930, 2857, 2212, 1674, 1496, 1361, 1255, 1106, 837, 776; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.38-7.27 (5H, m, Ph), 4.51 (2H, s, PhCH_2O), 3.62 (2H, t, *J* = 6.0 Hz, H1), 3.50 (2H, t, *J* = 6.0 Hz, H11), 2.56 (2H, t, *J* = 7.5 Hz, H4), 2.40 (2H, t, *J* = 6.5 Hz, H8), 1.78-1.66 (6H, m, H3, 9 and 10), 1.57-1.50 (2H, m, H2), 0.90 (9H, s, Si*t-Bu*), 0.05 (6H, s, SiMe_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.2, 138.4, 128.4, 127.6, 127.6, 93.8, 81.0, 72.9, 69.5, 62.7, 45.2, 32.0, 28.9, 25.9, 24.6, 20.6, 18.7, 18.3, −5.3; **HRMS** (ESI+): calc for $C_{24}H_{38}O_3SiNa$ $[M+Na]^+$ 425.2482, found 425.2479.

(*R*)-11-(benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)undec-6-yn-5-ol – (*R*)-3.117e

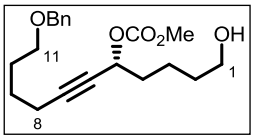


A solution of ketone **3.116.2e** (285 mg, 0.71 mmol, 1 eq.) in IPA (3.6 mL) was degassed for 30 minutes. To it was added a solution of [Ru((*R*,*R*)-TsDPEN)(*p*-cymene)] **(*R*,*R*)-3.53** (8.5 mg, 2 mol%) in anhydrous CH_2Cl_2 (0.1 mL). The reaction was degassed for a further 15 minutes and stirred for 72 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:14→2:1 Et_2O/pet. ether) to leave pure alcohol **(*R*)-3.117e** (188 mg, 0.46 mmol, 66%) as a yellow oil.

R_f 0.44 (1:1 Et_2O/pet. ether); **97% *ee*** (CHIRALPAK IC, 1.2 mL/min, 6% IPA/hexane): t_R (*R*):

4.95 min; t_R (*S*): 5.26 min; $[\alpha]_D^{25}$ −1.2 (*c* = 3.10, $CHCl_3$); **IR** (thin film, cm^{-1}): 3419, 2932, 2860, 2250, 1462, 1362, 1256, 1102, 909, 837; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.38-7.27 (5H, m, Ph), 4.51 (2H, s, PhC*H*$_2$O), 4.37-4.32 (1H, m, H5), 3.63 (2H, t, *J* = 6.5 Hz, H1), 3.50 (2H, t, *J* = 6.5 Hz, H11), 2.24 (2H, td, *J* = 7.0 and 2.0 Hz, H8), 1.93 (1H, bs, O*H*), 1.76-1.45 (10H, m, H2, 3, 4, 9 and 10), 0.91 (9H, s, Si*t-Bu*), 0.06 (6H, s, Si*Me*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 138.6, 128.5, 127.7, 127.7, 85.2, 81.7, 73.0, 69.9, 63.2, 62.8, 38.0, 32.5, 29.0, 26.1, 25.5, 21.7, 18.6, 18.5, −5.1; **HRMS** (ESI+): calc for $C_{24}H_{40}O_3SiNa$ $[M+Na]^+$ 427.2639, found 427.2630.

(*R*)-11-(benzyloxy)-1-hydroxyundec-6-yn-5-yl methyl carbonate – (*R*)-3.118e

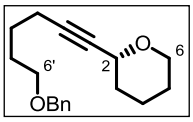


To a stirred solution of alcohol **(*R*)-3.117e** (185 mg, 0.46 mmol, 1 eq.) and pyridine (0.30 mL, 3.68 mmol, 8 eq.) in anhydrous CH_2Cl_2 (5 mL) at 0 °C under argon was added methyl chloroformate (0.11 mL, 1.37 mmol, 3 eq.). The reaction was stirred for 30 minutes at 0 °C and quenched with sat. aq. $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with 1N aq. HCl (1 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave the crude carbonate which was used directly in the next step without further purification.

The crude carbonate was taken up in MeOH (5 mL) and to it added a catalytic amount of CSA. The reaction was stirred for 1 hour and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave pure carbonate **(*R*)-3.118e** (149 mg, 0.43 mmol, 94%, *2 steps*) as a colourless oil.

R_f 0.22 (2:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ +57.4 (*c* = 0.98, $CHCl_3$); **IR** (thin film, cm^{-1}): 3418, 2940, 2865, 2242, 1749, 1443, 1265, 1076, 937, 792; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.38-7.26 (5H, m, Ph), 5.22 (1H, tt, *J* = 6.5 and 2.0 Hz, H5), 4.50 (2H, s, PhC*H*$_2$O), 3.79 (3H, s, O*Me*), 3.63 (2H, t, *J* = 6.5 Hz, H1), 3.49 (2H, t, *J* = 6.5 Hz, H11), 2.25 (2H, td, *J* = 7.0 and 2.0 Hz, H8), 1.88-1.77 (2H, m, H4), 1.77-1.67 (2H, m, H10), 1.65-1.50 (7H, m, H2, 3, 9 and O*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.2, 138.6, 128.5, 127.7, 127.7, 87.1, 77.3, 73.0, 69.9, 68.7, 62.6, 54.9, 35.0, 32.2, 28.9, 25.2, 21.4, 18.6; **HRMS** (ESI+): calc for $C_{20}H_{28}O_5Na$ $[M+Na]^+$ 371.1829, found 371.1818.

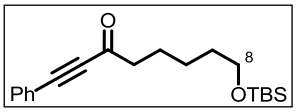
(*R*)-2-(6-(benzyloxy)hex-1-yn-1-yl)tetrahydro-2*H*-pyran – (*R*)-3.119e



To a degassed solution of carbonate **(*R*)-3.118e** (20.0 mg, 57.4 μmol, 1 eq.) and $B(OH)_3$ (1.8 mg, 28.7 μmol, 0.5 eq.) in 1,4-dioxane (0.15 mL) was added a solution of $Pd(OAc)_2$ (0.6 mg, 5 mol%) and dppf (3.2 mg, 10 mol%) in degassed 1,4-dioxane (0.45 mL). The reaction was heated to 100 °C for 10 minutes and quenched with pet. ether (1 mL). The reaction mixture was passed through a plug of silica gel (Et_2O) to leave pure THP **(*R*)-3.119e** (14.4 mg, 52.9 μmol, 92%) as a colourless oil.

R_f 0.42 (1:4 Et_2O/pet. ether); $[\alpha]_D^{25}$ +0.3 (*c* = 0.6, $CHCl_3$); **87% *ee*** (CHIRALPAK IA, 1.3 mL/min, 1% IPA/Hexane): t_R (*S*) = 5.00 min, t_R (*R*) = 6.09 min; **IR** (thin film, cm^{-1}): 2937, 2857, 2241, 1440, 1362, 1293, 1238, 1083, 1036; **^{1}H NMR** (500 MHz, $CDCl_3$): 7.37-7.27 (5H, m, Ph), 4.51 (2H, s, PhC*H*$_2$O), 4.25-4.21 (1H, m, H2), 3.98 (1H, ddd, *J* = 11.5, 5.5 and 3.5 Hz, H6), 3.53-3.48 (1H, m, H6), 3.50 (2H, t, *J* = 6.5 Hz, H6'), 2.27 (2H, td, *J* = 7.0 and 2.0 Hz, H3'), 1.88-1.78 (2H, m, H3 and H5), 1.77-1.70 (2H, m, H5'), 1.67-1.59 (3H, m, H3 and H4'), 1.59-1.49 (3H, m, H4 and H5); **^{13}C NMR** (125 MHz, $CDCl_3$): 138.6, 128.3, 127.6, 127.5, 85.4, 79.5, 72.9, 69.8, 67.3, 66.7, 32.5, 28.9, 25.7, 25.4, 22.0, 18.5; **HRMS** (ESI+): calc for $C_{18}H_{24}O_2Na$ $[M+Na]^+$ 295.1669, found 295.1664.

8-(*tert*-butyldimethylsilyloxy)-1-phenyloct-1-yn-3-one – 3.121



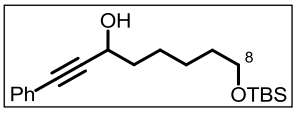
To a stirred solution of phenylacetylene (0.53 mL, 4.82 mmol, 1.1 eq.) in anhydrous THF (15 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 2.10 mL, 5.26 mmol, 1.2 eq.) dropwise. The reaction was allowed to warm to RT and stirred for 15 minutes. The solution was cooled to −78 °C and a solution of ε-caprolactone (500 mg, 4.38 mmol, 1 eq.) in anhydrous THF (5 mL) was added dropwise. The reaction was stirred for 2 hours at −78 °C and quenched by addition of sat. aq. $NaHCO_3$ (20 mL). The mixture was allowed to warm to RT and the THF removed *in vacuo*. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* and the product purified by flash chromatography (1:4→ 1:1 EtOAc/pet. ether) to leave the hydroxy ketone as a pale yellow oil (0.84 g, *ca.* 80% pure), which was used directly in the next step.

To a stirred solution of the above crude hydroxy ketone (0.84 g, 3.88 mmol, 1 eq.) in anhydrous CH_2Cl_2 (30 mL) at 0 °C under argon was added imidazole (317 mg, 4.66 mmol, 1.2 eq.) and a

catalytic amount of DMAP. To this solution was added TBSCl (644 mg, 4.27 mmol, 1.1 eq.) portionwise. The reaction was stirred at 0 °C for 30 minutes, allowed to warm to RT and stirred for a further 2 hours. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (20 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with 1N aq. HCl (2 x 50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:9 Et_2O/pet. ether) to leave pure silyloxy ketone **3.121** (845 mg, 2.56 mmol, 58%, *2 steps*) as a colourless oil.

R_f 0.74 (1:2 EtOAc/pet. ether); **IR** (thin film, cm^{-1}): 2931, 2858, 2204, 1673, 1490, 1444, 1226, 1101, 836; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.58 (2H, d, *J* = 7.5 Hz, Ph), 7.46 (1H, t, *J* = 7.5 Hz, Ph), 7.39 (2H, t, *J* = 7.5 Hz, Ph), 3.62 (2H, t, *J* = 6.5 Hz, H8), 2.68 (2H, t, *J* = 7.5 Hz, H4), 1.77 (2H, quintet, *J* = 7.5 Hz, H5), 1.61-1.54 (2H, m, H7), 1.46-1.39 (2H, m, H6), 0.90 (9H, s, Si*t-Bu*), 0.05 (6H, s, Si*Me_2*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.1, 133.0, 130.6, 128.6, 120.0, 90.6, 87.8, 62.9, 45.5, 32.5, 26.0, 25.3, 24.0, 18.3, −5.3; **HRMS** (ESI+): calc for $C_{20}H_{30}O_2SiNa$ $[M+Na]^+$ 353.1907, found 353.1907.

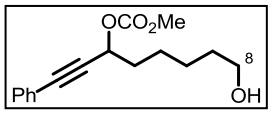
8-(*tert*-butyldimethylsilyloxy)-1-phenyloct-1-yn-3-ol – 3.121.1



To a stirred solution of siloxy ketone **3.121** (100 mg, 0.30 mmol, 1 eq.) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (5.7 mg, 0.15 mmol, 0.5 eq.). The reaction was stirred at 0 °C for 20 minutes, and quenched with water (5 mL). The MeOH was removed *in vacuo* and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure alcohol **3.121.1** (101 mg, 0.30 mmol, 99%) as a colourless oil.

R_f 0.13 (1:9 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3339, 2929, 2857, 2227, 1599, 1490, 1254, 1097, 1008, 834; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46-7.41 (2H, m, Ph), 7.33-7.29 (3H, m, Ph), 4.61 (1H, t, *J* = 7.0 Hz, H3), 3.63 (2H, t, *J* = 7.0 Hz, H8), 1.92 (1H, bs, O*H*), 1.86-1.76 (2H, m, H4), 1.61-1.50 (4H, m, H5 and 7), 1.46-1.37 (2H, m, H6), 0.90 (9H, s, Si*t-Bu*), 0.06 (6H, s, Si*Me_2*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 131.7, 128.3, 128.3, 122.6, 90.1, 84.8, 63.1, 62.9, 37.8, 32.7, 26.0, 25.5, 18.4, −5.3; **HRMS** (ESI+): calc for $C_{20}H_{32}O_2SiNa$ $[M+Na]^+$ 355.2064, found 355.2063.

8-hydroxy-1-phenyloct-1-yn-3-yl methyl carbonate – 3.122

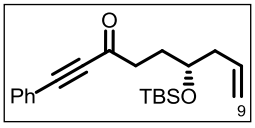


To a stirred solution of alcohol **3.121.1** (101 mg, 0.30 mmol, 1 eq.) and pyridine (0.19 mL, 2.40 mmol, 8 eq.) in anhydrous CH_2Cl_2 (5 mL) at 0 °C under argon was added methyl chloroformate (70 μL, 0.90 mmol, 3 eq.) dropwise. The reaction was stirred for 1 hour and quenched with sat. aq. $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1N aq. HCl (2 x 20 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to leave the crude silyoxycarbonate as a colourless oil that was used directly in the next step without further purification.

The above crude carbonate was taken up in MeOH (5 mL) and to it added a catalytic amount of CSA. The reaction was stirred for 1 hour and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2→2:1 Et_2O/pet. ether) to leave pure hydroxy carbonate **3.122** (74 mg, 0.268 mmol, 89%, *2 steps*) as a colourless oil.

R_f 0.43 (2:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3370, 2937, 2863, 2233, 1751, 1491, 1443, 1268, 1056, 946; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.47-7.43 (2H, m, Ph), 7.34-7.29 (3H, m, Ph), 5.47 (1H, t, *J* = 6.5 Hz, H3), 3.83 (3H, s, O*Me*), 3.67 (2H, t, *J* = 6.5 Hz, H8), 1.97-1.90 (2H, m, H4), 1.66-1.54 (4H, m, H5 and 7), 1.50-1.42 (2H, m, H6), 1.38 (1H, bs, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 155.1, 131.9, 128.7, 128.2, 122.1, 86.2, 85.7, 68.6, 62.8, 55.0, 34.9, 32.5, 25.3, 24.7; **HRMS** (ESI+): calc for $C_{16}H_{20}O_4Na$ $[M+Na]^+$ 299.1254, found 299.1250.

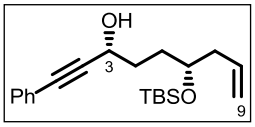
(*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-phenylnon-8-en-1-yn-3-one – (*R*)-3.125



To a stirred solution of hydroxy ketone **(*R*)-3.70** (210 mg, 0.92 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under argon was added imidazole (75 mg, 1.10 mmol, 1.2 eq.) and a catalytic amount of DMAP. TBSCl (153 mg, 1.01 mmol, 1.1 eq.) was added portionwise, the reaction stirred at 0 °C for 1 hour, allowed to warm to RT and stirred for 16 hours. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N aq. HCl solution (1 x 30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19→1:9 Et_2O/pet. ether) to leave pure silyloxy ketone **(*R*)-3.125** (209 mg, 0.61 mmol, 66%, 82% brsm) as a colourless oil.

R_f 0.53 (1:9 Et_2O/pet. ether); **$[\alpha]_D^{22}$** +16.3 (*c* = 0.38, $CHCl_3$); **IR** (thin film, cm^{-1}): 2930, 2858, 2204, 1668, 1490, 1444, 1257, 1072, 910; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.59-7.55 (2H, m, Ph), 7.49-7.43 (1H, m, Ph), 7.42-7.36 (2H, m, Ph), 5.88-5.75 (1H, m, H8), 5.12-5.04 (2H, m, H9), 3.85-3.77 (1H, m, H6), 2.74 (2H, t, *J* = 7.5 Hz, H4), 2.28-2.23 (2H, m, H7), 2.01-1.91 (1H, m, H5), 1.87-1.77 (1H, m, H5), 0.91 (9H, s, Si*t-Bu*), 0.08 (6H, s, Si*Me*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.1, 134.7, 133.1, 130.8, 128.7, 120.2, 117.4, 90.8, 88.0, 70.8, 41.9, 41.4, 30.7, 26.0, 18.2, −4.2, −4.5; **HRMS** (ESI+): calc for $C_{21}H_{30}O_2SiNa$ $[M+Na]^+$ 365.1907, found 365.1904.

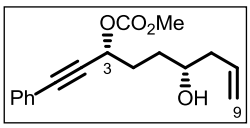
(3*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-phenylnon-8-en-1-yn-3-ol – (*R*,*R*)-3.125.1



To a stirred solution of silyloxy ketone **(*R*)-1.25** (105 mg, 0.307 mmol, 1 eq.) and [RuCl((*R*,*R*)-TsDPEN)(*p*-cymene)] **(*R*,*R*)-3.53·HCl** (2.0 mg, 1 mol%) in IPA (1.5 mL) was added a solution of KOH (0.2 mg, 1.2 mol%) in IPA (0.1 mL). The reaction was stirred for 16 hours and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19→1:2 Et_2O/pet. ether) to leave pure alcohol **(*R*,*R*)-3.125.1** (94 mg, 0.273 mmol, 89%) as a pale yellow oil.

R_f 0.24 (Et_2O/pet. ether 1:4); 95:5 ***dr***; **$[\alpha]_D^{25}$** +10.3 (*c* = 0.39, $CHCl_3$); **IR** (thin film, cm^{-1}): 3363, 2955, 2930, 2857, 2231, 1641, 1599, 1490, 1255, 1046, 913, 835; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46-7.41 (2H, m, Ph), 7.33-7.29 (3H, m, Ph), 5.81 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H8), 5.12-5.04 (2H, m, H9), 4.68-4.63 (1H, m, H3), 3.89-3.82 (1H, m, H6), 3.08 (1H, bs, O*H*), 2.30 (2H, t, *J* = 6.5 Hz, H7), 1.93-1.81 (3H, m, H4 and 5), 1.77-1.66 (1H, m, H5), 0.92 (9H, s, Si*t-Bu*), 0.11 (3H, s, Si*Me*), 0.10 (3H, s, Si*Me*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 135.0, 131.7, 128.3, 122.9, 117.2, 90.3, 84.9, 71.6, 62.7, 41.3, 32.9, 31.6, 26.0, 18.3, −4.4, −4.4; **HRMS** (ESI+): calc for $C_{21}H_{32}O_2SiNa$ $[M+Na]^+$ 367.2064, found 367.2059.

(3*R*,6*R*)-6-hydroxy-1-phenylnon-8-en-1-yn-3-yl methyl carbonate – (*R*,*R*)-3.126c



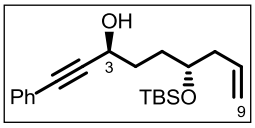
To a stirred solution of alcohol **(*R*,*R*)-3.125.1** (94 mg, 0.273 mmol, 1 eq.) and pyridine (0.18 mL, 2.18 mmol, 8 eq.) in anhydrous CH_2Cl_2 (3 mL) at 0 °C under argon was added methyl chloroformate (63 μL, 0.818 mmol, 3 eq.). The reaction was stirred for 20 minutes at 0 °C and quenched with sat. aq. $NaHCO_3$ (3 mL). The layers were separated and the

aqueous layer extracted with DCM (3 x 5 mL). The combined organic layers were washed with 1N aq. HCl (1 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was used in the next step without further purification.

The crude carbonate was taken up in MeOH (2 mL) and to it added a catalytic amount of CSA. The reaction was stirred at RT for 2 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to leave pure carbonate **(*R*,*R*)-3.126c** (68 mg, 0.236 mmol, 86%) as a colourless oil.

R_f 0.08 (1:3 Et_2O/pet. ether); **>95:5 *dr***; **$[\alpha]_D^{25}$** +109.1 (*c* = 0.46, $CHCl_3$); **IR** (thin film, cm^{-1}): 3419, 2958, 2931, 2234, 1750, 1641, 1491, 1443, 1267, 959, 792; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.34-7.27 (3H, m, Ph), 5.88-5.77 (1H, m, H8), 5.52 (1H, t, *J* = 6.5 Hz, H3), 5.17-5.11 (2H, m, H9), 3.81 (3H, s, O*Me*), 3.72 (1H, *apt* septet, *J* = 4.0 Hz, H6), 2.36-2.28 (1H, m, H7), 2.23-2.15 (1H, m, H7), 2.14-2.08 (1H, m, H4), 2.03-1.93 (1H, m, H4), 1.89 (1H, bs, O*H*), 1.80-1.62 (2H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 155.1, 134.5, 131.9, 128.8, 128.3, 122.1, 118.5, 86.4, 85.6, 70.1, 68.6, 55.0, 42.1, 31.9, 31.3; **HRMS** (ESI+): calc for $C_{17}H_{20}O_4Na$ $[M+Na]^+$ 311.1254, found 311.1248.

(3*S*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-phenylnon-8-en-1-yn-3-ol – (*S*,*R*)-3.125.1

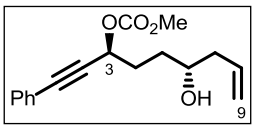


To a stirred solution of silyloxy ketone **(*R*)-3.125** (105 mg, 0.307 mmol, 1 eq.) and [RuCl((*S*,*S*)-TsDPEN)(*p*-cymene)] **(*S*,*S*)-3.53·HCl** (2.0 mg, 1 mol%) in IPA (1.5 mL) was added a solution of KOH (0.2 mg, 1.2 mol%) in IPA (0.1 mL). The reaction was stirred for 16 hours and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19→1:2 Et_2O/pet. ether) to leave pure alcohol **(*S*,*R*)-3.125.1** (70 mg, 0.203 mmol, 66%) as a pale yellow oil.

R_f 0.24 (1:4 Et_2O/pet. ether); 95:5 ***dr***; **$[\alpha]_D^{25}$** +7.5 (*c* = 0.60, $CHCl_3$); **IR** (thin film, cm^{-1}): 3357, 2955, 2930, 2857, 2231, 1641, 1599, 1490, 1255, 1052, 938, 836; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.45-7.42 (2H, m, Ph), 7.33-7.29 (3H, m, Ph), 5.81 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H8), 5.11-5.04 (2H, m, H9), 4.62 (1H, t, *J* = 6.5 Hz, H3), 3.82 (1H, *apt* quintet, *J* = 5.5 Hz, H6), 2.62 (1H, bs, O*H*), 2.29 (2H, t, *J* = 6.0 Hz, H7), 1.93-1.86 (2H, m, H4), 1.79-1.66 (2H, m, H5), 0.92 (9H, s, Si*t-Bu*), 0.10 (3H, s,

Si*Me*), 0.09 (3H, s, Si*Me*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 135.1, 131.8, 128.4, 128.4, 122.8, 117.2, 90.3, 84.8, 71.8, 63.2, 41.6, 33.6, 32.4, 26.0, 18.2, −4.3, −4.4; **HRMS** (ESI+): calc for $C_{21}H_{32}O_2SiNa$ $[M+Na]^+$ 367.2064, found 367.2059.

(3*S*,6*R*)-6-hydroxy-1-phenylnon-8-en-1-yn-3-yl methyl carbonate – (*S*,*R*)-3.126c

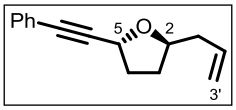


To a stirred solution of the above alcohol (70 mg, 0.203 mmol, 1 eq.) and pyridine (0.13 mL, 1.62 mmol, 8 eq.) in anhydrous CH_2Cl_2 (3 mL) at 0 °C under argon was added methyl chloroformate (47 μL, 0.609 mmol, 3 eq.). The reaction was stirred for 20 minutes at 0 °C and quenched with sat. aq. $NaHCO_3$ (3 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1N aq. HCl (1 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was used in the next step without further purification.

The crude carbonate was taken up in MeOH (2 mL) and to it added a catalytic amount of CSA. The reaction was stirred at RT for 2 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to leave pure carbonate **(*S*,*R*)-3.126c** (26 mg, 90 μmol, 44%) as a pale yellow oil.

R_f 0.08 (1:3 Et_2O/pet. ether); **>95:5 *dr***; $[\alpha]_D^{25}$ −90.7 (*c* = 1.23, $CHCl_3$); **IR** (thin film, cm^{-1}): 3419, 2957, 2933, 2234, 1750 (C=O), 1642, 1491, 1443, 1267, 954, 792; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.35-7.28 (3H, m, Ph), 5.89-5.77 (1H, m, H8), 5.51 (1H, t, *J* = 6.5 Hz, H3), 5.19-5.13 (2H, m, H9), 3.83 (3H, s, O*Me*), 3.73 (1H, *apt* septet, *J* = 4.0 Hz, H6), 2.37-2.29 (1H, m, H7), 2.24-2.15 (1H, m, H7), 2.15-2.08 (1H, m, H4), 2.05-1.95 (1H, m, H4), 1.81-1.63 (3H, m, H5 and O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 155.1, 134.5, 132.0, 128.9, 128.4, 122.2, 118.6, 86.5, 85.7, 70.2, 68.7, 55.1, 42.2, 32.1, 31.4; **HRMS** (ESI+): calc for $C_{17}H_{20}O_4Na$ $[M+Na]^+$ 311.1254, found 311.1249.

(2*R*,5*R*)-2-allyl-5-(phenylethynyl)tetrahydrofuran – (*R*,*R*)-3.72c

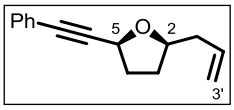


A degassed solution of $Pd(OAc)_2$ (0.8 mg, 5 mol%) and dppf (3.8 mg, 10 mol%) in 1,4-dioxane (0.7 mL) was added to a vial fitted with a septum containing carbonate **(*R*,*R*)-3.126c** (18.0 mg, 62 μmol, 1 eq.) and $B(OH)_3$ (4.2 mg, 69 μmol, 1.1 eq.) under argon.

The reaction was stirred and heated to 50 °C for 40 minutes, cooled and quenched *via* addition of pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O) and the solvent removed *in vacuo* to leave crude THF (11.0 mg, 93:7 *dr*) as a pale yellow oil. The crude product was purified by flash chromatography on silica gel (Et_2O/pet. ether 1:99→1:19) to leave pure *trans*-THF **(*R*,*R*)-3.72c** (10.0 mg, 47 μmol, 76%, single diastereomer) as a colourless oil.

All spectroscopic data identical to **(*R*)-3.72c** prepared previously from cyclic carbonate **(*R*,*R*)-3.60**.

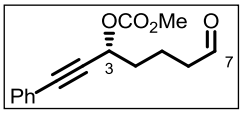
(2*R*,5*S*)-2-allyl-5-(phenylethynyl)tetrahydrofuran – (*R*,*S*)-3.72c



To a degassed solution of carbonate **(*S*,*R*)-3.126c** (18.0 mg, 62 μmol, 1 eq.) and $B(OH)_3$ (4.2 mg, 69 μmol, 1.1 eq.) in 1,4-dioxane (0.35 mL) was added a solution of $Pd(OAc)_2$ (0.8 mg, 5 mol%) and dppf (3.8 mg, 10 mol%) in degassed 1,4-dioxane (0.25 mL). The reaction was heated to 50 °C for 35 minutes, cooled and quenched *via* addition of pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O) and the solvent removed *in vacuo* to leave pure THF (12.3 mg, 96:4 *dr*) as a colourless oil. The mixture was chromatographed on silica gel (1:99→1:19 Et_2O/pet. ether) to leave pure *cis*-THF (12.0 mg, 57 μmol, 92%, single diastereomer) as a colourless oil.

All spectroscopic data identical to **(*R*,*S*)-3.72c** prepared previously from cyclic carbonate **(*R*,*S*)-3.60**.

(*R*)-methyl (7-oxo-1-phenylhept-1-yn-3-yl) carbonate – (*R*)-3.127

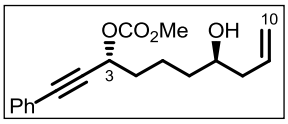


To a stirred solution of carbonate **3.118c** (100 mg, 0.38 mmol, 1 eq.), Et_3N (0.37 mL, 2.66 mmol, 7 eq.) and DMSO (0.26 mL, 3.61 mmol, 9.5 eq.) in anhydrous CH_2Cl_2 (5 mL) at 0 °C was added SO_3·pyridine complex (182 mg, 1.14 mmol, 3 eq.). The reaction was stirred at 0 °C for 30 minutes, allowed to warm to RT and stirred for a further 3 hours. The reaction was quenched with 1N aq. HCl (5 mL), the layers separated and the organic layer washed with 1N aq. HCl (5 mL) and sat. aq. $NaHCO_3$ solution (5 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2→1:1 Et_2O/pet. ether) to leave pure aldehyde **(*R*)-3.127** (69 mg, 0.27 mmol, 71%) as a viscous yellow oil.

R_f 0.30 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ +69.7 (*c* = 0.35, $CHCl_3$); **IR** (thin film, cm^{-1}): 2958, 2235, 1751,

1735, 1443, 1266, 942, 791, 759; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 9.81 (1H, t, *J* = 1.5 Hz, H7), 7.46-7.43 (2H, m, Ph), 7.36-7.29 (3H, m, Ph), 5.49 (1H, t, *J* = 6.5 Hz, H3), 3.84 (3H, s, O*Me*), 2.56 (2H, td, *J* = 7.0 and 1.5 Hz, H6), 2.02-1.87 (4H, m, H4 and 5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 201.6, 155.0, 131.9, 128.8, 128.3, 121.9, 86.6, 85.1, 68.1, 55.0, 43.1, 34.1, 17.6; **HRMS** (FI+): calc for $C_{15}H_{16}O_4$ $[M]^+$ 260.1049, found 260.1053.

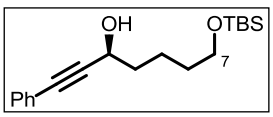
(3*R*,7*R*)-7-hydroxy-1-phenyldec-9-en-1-yn-3-yl methyl carbonate – (*R*,*R*)-3.128



To a stirred solution of aldehyde **(*R*)-3.127** (163 mg, 0.63 mmol, 1 eq.) in anhydrous CH_2Cl_2 (5 mL) at −20 °C under argon was added Leighton's reagent **(*R*,*R*)-3.64** (0.45 M in CH_2Cl_2, 1.67 mL, 0.75 mmol, 1.2 eq). The reaction was transferred to a freezer at −25 °C and allowed to stand for 48 hours. The reaction was quenched with 1N aq. HCl (5 mL) and sat. aq. NH_4Cl (5 mL). The reaction was filtered, the filtrate separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to leave pure allyl alcohol **(*R*,*R*)-3.128** (104 mg, 0.344 mmol, 55%) as a colourless oil.

R_f 0.29 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ +82.1 (*c* = 1.37, $CHCl_3$); **IR** (thin film, cm^{-1}): 3386, 2927, 2235, 1751, 1443, 1267, 1105, 791, 758; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.35-7.28 (3H, m, Ph), 5.87-5.78 (1H, m, H9), 5.48 (1H, t, *J* = 6.5 Hz, H3), 5.16-5.12 (2H, m, H10), 3.82 (3H, s, O*Me*), 3.71-3.65 (1H, m, H7), 2.32 (1H, ddt, *J* = 14.0, 6.5 and 1.0 Hz, H8), 2.16 (1H, dtt, *J* = 14.0, 8.0 and 1.0 Hz, H8), 2.01-1.88 (2H, m, H4), 1.76-1.51 (5H, m, H5, 6 and O*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 134.6, 131.9, 128.7, 128.2, 122.1, 118.3, 86.2, 85.6, 70.3, 68.5, 54.9, 41.9, 36.1, 34.8, 21.2; **HRMS** (ESI+): calc for $C_{18}H_{22}O_4Na$ $[M+Na]^+$ 325.1410, found 325.1397.

(*S*)-7-((*tert*-butyldimethylsilyl)oxy)-1-phenylhept-1-yn-3-ol – (*S*)-3.117c

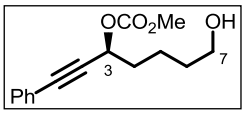


A solution of ketone **3.129** (1.38 g, 4.36 mmol, 1 eq.) in IPA (10 mL) was degassed for 30 minutes. Alongside this a solution of [RuCl((*S*,*S*)-TsDPEN)(*p*-cymene)] **(*S*,*S*)-3.53·HCl** (28 mg, 1 mol%) in IPA (10 mL) was degassed for 30 minutes. A solution of KOH (2.9 mg, 1.2 mol%) in degassed IPA (2 mL) was added to the catalyst solution and

the resulting mixture stirred until a yellow colour developed. The catalyst solution was transferred *via* syringe to the ketone solution and the reaction stirred at RT for 12 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave pure alcohol **(*S*)-3.117c** (1.325 g, 4.16 mmol, 95%) as a pale yellow oil.

R_f 0.30 (1:9 EtOAc/pet. ether); **97% *ee*** (CHIRALPAK IC, 1.3 mL/min, 1% IPA/hexane): t_R (*R*) = 10.05 min, t_R (*S*) = 10.97 min; $[\alpha]_D^{25}$ +7.6 (*c* = 1.06, $CHCl_3$) [**(*R*)-3.117c** −8.1 (c = 0.74, $CHCl_3$)]. All other spectroscopic data identical to **(*R*)-3.117c** prepared previously.

(*S*)-7-hydroxy-1-phenylhept-1-yn-3-yl methyl carbonate – (*S*)-3.118c

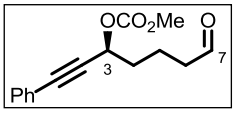


To a stirred solution alcohol **(*S*)-3.117c** (1.325 g, 4.16 mmol, 1 eq.) and pyridine (2.69 mL, 33.3 mmol, 8 eq.) in anhydrous CH_2Cl_2 (50 mL) at 0 °C under argon was added methyl chloroformate (0.96 mL, 12.5 mmol, 3 eq.). The resulting solution was stirred at 0 °C for 15 minutes and quenched with sat. aq. $NaHCO_3$ (25 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with 1N aq. HCl (2 x 25 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave the crude carbonate (1.54 g) as a yellow oil which was used directly without further purification.

The crude carbonate (1.54 g) was taken up in methanol (20 mL) and to it added a catalytic amount of CSA. The reaction was stirred at RT for 20 minutes and the solvent removed *in vacuo.* The crude product was purified by flash chromatography on silica gel (1:4 Et_2O/pet. ether→Et_2O) to leave pure carbonate **(*S*)-3.118c** (1.029g, 3.92 mmol, 94%, *2 steps*) as a colourless oil.

R_f 0.15 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ −125.6° (*c* = 1.05, $CHCl_3$) [**(*R*)-3.118c** +127.1 (*c* = 0.75, $CHCl_3$)]. All other spectroscopic data identical to **(*R*)-3.118c** prepared previously.

(*S*)-methyl (7-oxo-1-phenylhept-1-yn-3-yl) carbonate – (*S*)-3.127

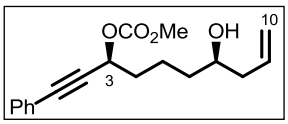


To a stirred suspension of carbonate **(*S*)-3.118c** (500 mg, 1.91 mmol, 1 eq.) and $NaHCO_3$ (152 mg, 1.81 mmol, 0.95 eq.) in CH_2Cl_2 (40 mL) was added Dess-Martin periodinane (889 mg, 2.10 mmol, 1.1 eq.). The reaction was stirred at RT for 15 minutes and quenched with sat. aq. $NaHCO_3$/$Na_2S_2O_3$ (1:1 v:v, 40 mL). The resulting biphasic mixture was stirred until the layers became clear, separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). The

combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2→1:1 Et_2O/pet. ether) to leave pure aldehyde **(*S*)-3.127** (386 mg, 1.48 mmol, 77%) as a pale yellow oil.

R_f 0.28 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ −83.2 (*c* = 0.68, $CHCl_3$) [**(*R*)-3.127** +69.7 (*c* = 0.35, $CHCl_3$)]. All other spectroscopic data identical to **(*R*)-3.127** prepared previously.

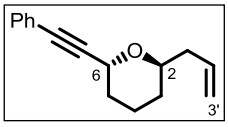
(3*S*,7*R*)-7-hydroxy-1-phenyldec-9-en-1-yn-3-yl methyl carbonate – (*S*,*R*)-3.128



To a stirred solution of aldehyde **(*S*)-3.127** (370 mg, 1.42 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) at −20 °C under argon was added Leighton's reagent **(*R*,*R*)-3.128** (0.45 M in CH_2Cl_2, 3.8 mL, 1.71 mmol, 1.2 eq.). The reaction was transferred to a freezer at −20 °C and allowed to stand for 48 hours. The reaction was quenched with 1N aq. HCl (10 mL) and sat. aq. NH_4Cl (10 mL). The reaction was filtered, the filtrate separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to leave pure carbonate **(*S*,*R*)-3.128** (294 mg, 0.972 mmol, 68%) as a colourless oil.

R_f 0.29 (1:1 Et_2O/pet. ether); **>95:5 *dr***; $[\alpha]_D^{25}$ −68.9 (*c* = 1.51, $CHCl_3$); **IR** (thin film, cm^{-1}): 3413, 2932, 2867, 2234, 1748, 1491, 1442, 918, 790; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.43 (2H, m, Ph), 7.34-7.28 (3H, m, Ph), 5.87-5.78 (1H, m, H9), 5.47 (1H, t, *J* = 6.5 Hz, H3), 5.16-5.12 (2H, m, H10), 3.82 (3H, s, O*Me*), 3.71-3.66 (1H, m, H7), 2.31 (1H, dddt, *J* = 14.0, 6.5, 4.5 and 1.0 Hz, H8), 2.25 (1H, bs, O*H*), 2.16 (1H, dtt, *J* = 14.0, 8.0 and 1.0 Hz, H8), 1.97-1.92 (2H, m, H4), 1.77-1.68 (1H, m, H5), 1.64-1.49 (3H, m, H5 and 6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 134.6, 131.8, 128.7, 128.2, 122.1, 118.3, 86.2, 85.6, 70.3, 68.5, 54.9, 41.9, 36.1, 34.8, 21.2; **HRMS** (ESI+): calc for $C_{18}H_{22}O_4Na$ $[M+Na]^+$ 325.1410, found 325.1398.

(2*R*,6*R*)-2-allyl-6-(phenylethynyl)tetrahydro-2*H*-pyran – (*R*,*R*)-3.130

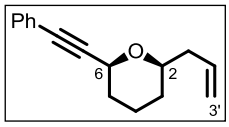


To a degassed solution of carbonate **(*R*,*R*)-3.128** (20.0 mg, 66.1 μmol, 1 eq.) and $B(OH)_3$ (4.5 mg, 72.7 μmol, 1.1 eq.) in 1,4-dioxane (0.20 mL) under argon was added a solution of $Pd(OAc)_2$ (0.7 mg, 5 mol%) and dppf (3.7 mg, 10 mol%) in degassed 1,4-dioxane

(0.45 mL). The reaction was heated to 100 °C and stirred for 30 minutes. The reaction was quenched *via* addition of pet. ether (1 mL) and filtered through a short plug of silica gel (Et_2O). The solvent was removed *in vacuo* and the mixture chromatographed on silica gel (1:19 Et_2O/pet. ether) to leave pure THP **(*R*,*R*)-3.130** (12.7 mg, 56.1 μmol, 85%) as a colourless oil.

R_f 0.53 (1:9 Et_2O/pet. ether); **90:10 *dr***; $[\alpha]_D^{25}$ +7.0 (*c* = 0.74, $CHCl_3$); **IR** (thin film, cm^{-1}): 2936, 2862, 2228, 1642, 1598, 1489, 1441, 1337, 1196, 1077, 1040, 914; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.49-7.45 (2H, m, Ph), 7.34-7.29 (3H, m, Ph), 5.86 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2'), 5.14-5.05 (2H, m, H3'), 4.99 (1H, d, *J* = 4.5 Hz, H6), 4.03 (1H, dtd, *J* = 11.0, 6.0 and 2.0 Hz, H2), 2.33 (1H, dtt, *J* = 14.5, 7.0 and 1.0 Hz, H1'), 2.25-2.19 (1H, m, H1'), 1.98 (1H, qt, *J* = 13.5 and 3.5 Hz, H4), 1.87 (1H, tdd, *J* = 13.0, 5.0 and 3.5 Hz, H5), 1.79-1.71 (2H, m, H4 and 5), 1.69-1.64 (1H, m, H3), 1.31 (1H, tdd, *J* = 13.0, 11.0 and 3.0 Hz, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 134.8, 131.7, 128.3, 128.2, 122.9, 116.7, 87.9, 86.4, 71.2, 65.7, 40.7, 31.0, 30.6, 19.4; **HRMS** (ESI+): calc for $C_{16}H_{18}ONa$ $[M+Na]^+$ 249.1250, found 249.1246.

(2*R*,6*S*)-2-allyl-6-(phenylethynyl)tetrahydro-2*H*-pyran – (*R*,*S*)-3.130

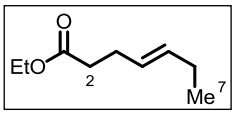


To a degassed solution of carbonate **(*S*,*R*)-3.128** (20.0 mg, 66.1 μmol, 1 eq.) and $B(OH)_3$ (4.5 mg, 72.7 μmol, 1.1 eq.) in 1,4-dioxane (0.4 mL) under argon was added a solution of $Pd(OAc)_2$ (0.7 mg, 5 mol%) and dppf (10 mol%) in degassed 1,4-dioxane (0.3 mL). The reaction was heated to 100 °C and stirred for 30 minutes. The reaction was quenched *via* addition of pet. ether (1 mL) and filtered through a short plug of silica gel (Et_2O). The solvent was removed *in vacuo* and purified by flash chromatography on silica gel (1:49 Et_2O/pet. ether) to leave pure THP **(*R*,*S*)-3.130** (6.8 mg, 30.0 μmol, 45%, 96% brsm) as a colourless oil.

R_f 0.53 (1:9 Et_2O/pet. ether); **95:5 *dr***; $[\alpha]_D^{25}$ –76.7 (*c* = 0.30, $CHCl_3$); **IR** (thin film, cm^{-1}): 2938, 2849, 2233, 1642, 1599, 1491, 1442, 1379, 1313, 1196, 1076, 1046, 914; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.47-7.44 (2H, m, Ph), 7.33-7.28 (3H, m, Ph), 5.87 (1H, dddd, *J* = 17.0, 10.0, 8.0 and 7.0 Hz, H2'), 5.12-5.04 (2H, m, H3'), 4.35 (1H, dd, *J* = 11.5 and 2.0 Hz, H6), 3.43 (1H, dtd, *J* = 11.0, 6.5 and 2.0 Hz, H2), 2.44 (1H, dtt, *J* = 14.0, 6.5 and 1.0 Hz, H1'), 2.24 (1H, dt, *J* = 14.0 and 7.0 Hz, H1'), 1.94-1.87 (2H, m, H4 and 5), 1.79-1.70 (1H, m, H5), 1.67-1.63 (1H, m, H3), 1.61-1.51 (1H, m, H4), 1.34-

1.25 (1H, m, H3); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ_C 134.7, 131.9, 128.2, 128.1, 116.9, 88.6, 84.2, 78.1, 68.8, 40.9, 32.6, 30.3, 23.4; **HRMS** (ESI+): calc for $C_{16}H_{18}O$ $[M+Na]^+$ 249.1250, found 249.1250.

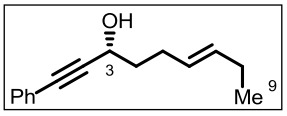
(*E*)-ethyl hept-4-enoate – 3.137[260]



A 100 mL flask containg a stirrer bar was charged with 1-pentene-3-ol **3.136** (2.0 g, 23.2 mmol, 1 eq.), trimethyl orthoacetate (29.8 mL, 0.163 mol, 7 eq.) and propionic acid (1.3 mL, 17.4 mmol, 0.75 eq.). The flask was fitted with distillation apparatus and the reaction heated to 125 °C for 3 hours until no more ethanol distilled off. The reaction was allowed to cool and the remaining volatiles removed *in vacuo*. The crude product was purified by distillation to leave ester **3.137** (800 mg, 5.12 mmol, 22%, *ca.* 90% pure) of sufficient purity to use in the next step.

b.p. 88 °C @ 20 mbar [lit.[261] 81-83 °C @ 10 torr]; **R_f** 0.75 (1:1 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.51 (1H, dt, *J* = 15.0 and 6.0 Hz, H5), 5.39 (1H, dt, *J* = 15.0 and 6.0 Hz, H4), 4.12 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 2.38-2.27 (4H, m, H2 and 3), 1.99 (2H, *apt* quintet, *J* = 7.0 Hz, H6), 1.25 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.95 (3H, t, *J* = 7.5 Hz, H7); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 173.3, 133.3, 126.9, 60.2, 34.4, 27.9, 25.5, 14.2, 13.8. Data consistent with literature.[260]

(*R*,*E*)-1-phenylnon-6-en-1-yn-3-ol – (*R*)-3.138



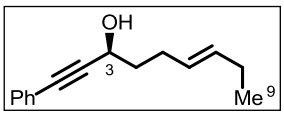
To a stirred solution of phenyl acetylene (74 μL, 0.68 mmol, 1.05 eq.) in anhydrous THF (1 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 0.28 mL, 0.70 mmol, 1.1 eq.) dropwise. The resulting solution was allowed to warm to −30 °C and stirred for 30 minutes. The solution was cooled to −78 °C and to it added $BF_3{\cdot}OEt_2$ (82 μL, 0.68 mmol, 1.05 eq.). The solution was stirred for a further 10 minutes and a solution of ester **3.137** (100 mg, 0.64 mmol, 1 eq.) in anhydrous THF (0.5 mL) was added in one portion. The reaction was allowed to warm to RT and stirred for 2 hours. The reaction was quenched with sat. aq. NH_4Cl/NH_4OH (2:1 v:v, 1.5 mL) and extracted with Et_2O (4 x 2 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was passed through a short plug of silica gel (Et_2O/pet. ether 1:19) to leave the ketone (82 mg, *ca.* 70% pure) as a pale yellow oil. This mixture was used in the next step without further purification.

To a stirred solution of the crude ketone (75 mg, *ca.* 0.27 mmol) and [RuCl((*R*,*R*)-TsDPEN)(*p*-

cymene)] **(*R*,*R*)-3.53·HCl** (1.7 mg, ca. 1 mol%) in IPA (0.5 mL) was added a solution of KOH (0.18 mg, 1.2 mol%) in IPA (0.1 mL). The resulting solution was stirred for 40 hours and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (19:1→4:1 Et_2O/pet. ether) to leave pure alcohol **(*R*)-3.138** (20 mg, 93 μmol, 15%, *2 steps*) as a pale yellow oil.

R_f 0.10 (1:9 Et_2O/pet. ether); $[\alpha]_D^{25}$ −29.6 (*c* = 1.86, $CHCl_3$); **97% *ee*** (CHIRALPAK IC, 1.2 mL/min, 2% IPA/hexane): t_R (*R*) = 8.80 min, t_R (*S*) = 9.46 min; **IR** (thin film, cm^{-1}): 3356, 2962, 2931, 2202, 1599, 1490, 1443, 1067, 967, 756; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.42 (2H, m, Ph), 7.33-7.30 (3H, m, Ph), 5.56 (1H, dtt, *J* = 15.5, 6.0 and 1.5 Hz, H7), 5.45 (1H, dtt, *J* = 15.5, 6.5 and 1.5 Hz, H6), 4.63 (1H, t, *J* = 6.5 Hz, H3), 2.28-2.22 (2H, m, H5), 2.06-1.99 (3H, m, H8 and O*H*), 1.93-1.83 (2H, m, H4), 0.98 (3H, t, *J* = 7.5 Hz, H9); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 133.4, 131.8, 128.5, 128.4, 128.0, 122.8, 90.1, 85.2, 62.7, 37.7, 28.4, 25.7, 14.0; **HRMS** (ESI+): calc for $C_{15}H_{18}ONa$ $[M+Na]^+$ 237.1250, found 237.1249.

(*S*,*E*)-1-phenylnon-6-en-1-yn-3-ol – (*S*)-3.138



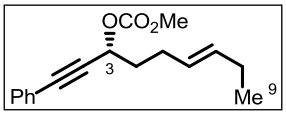
To a stirred solution of phenyl acetylene (0.28 mL, 2.56 mmol, 2 eq.) in anhydrous THF (5 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 1.08 mL, 2.69 mmol, 2.1 eq.). The solution was stirred at −78 °C for 30 minutes and to it added $BF_3{\cdot}OEt_2$ (0.35 mL, 2.82 mmol, 2.2 eq.). The solution was stirred for a further 10 minutes at −78 °C before ester **3.127** (200 mg, 1.28 mmol, 1 eq.) was added in one portion. The reaction was stirred at −78 °C for 1 hour, quenched with sat. aq. NH_4Cl/NH_4OH (2:1 v:v, 5 mL) and allowed to warm to RT. The reaction was diluted with Et_2O (10 mL), the layers separated and the aqueous layer extracted with Et_2O (4 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was passed through a short plug of silica gel (Et_2O/pet. ether 1:19→1:9) to leave impure ketone (158 mg) as yellow oil which was used directly in the next step.

A solution of the above ketone (158 mg) in IPA (2 mL) was degassed for 30 minutes. Alongside this a solution of [RuCl((*S*,*S*)-TsDPEN)(*p*-cymene)] **(*S*,*S*)-3.35·HCl** (4.7 mg, *ca.* 1 mol%) in IPA (1.6 mL) was degassed for 30 minutes. A solution of KOH (0.5 mg, *ca.* 1.2 mol%) in IPA (0.1 mL) was added to the catalyst solution and the resulting mixture stirred until a yellow colour developed. The catalyst solution was transferred *via* syringe to the ketone and the reaction stirred at RT for 16 hours. The

solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:14→1:4 Et_2O/pet. ether) to leave pure alcohol **(*S*)-3.138** (93 mg, 0.434 mmol, 34%, *2 steps*) as a colourless oil.

$[\alpha]_D^{25}$ +34.7 (*c* = 0.99, $CHCl_3$) [**(*R*)-3.138** −29.6 (*c* = 1.86, $CHCl_3$)]; **97% *ee*** (CHIRALPAK IC, 2% IPA/hexane, 1.3 mL/min): t_R (*R*) = 8.92 min, t_R (*S*) = 9.61 min. All other spectroscopic data identical to **(*R*)-3.138** prepared previously.

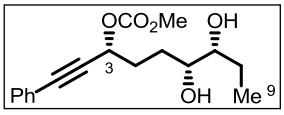
(*R*,*E*)-methyl (1-phenylnon-6-en-1-yn-3-yl) carbonate – (*R*)-3.138.1



To a stirred solution of **(*R*)-3.138** (20 mg, 93 μmol, 1 eq.) and pyridine (60 μL, 0.744 mmol, 8 eq.) in anhydrous CH_2Cl_2 (1 mL) at 0 °C under argon was added methyl chloroformate (22 μL, 0.280 mmol, 3 eq.). The reaction was stirred at 0 °C for 30 minutes and quenched with sat. aq. $NaHCO_3$ (1 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were washed with 1N aq. HCl (1 x 5 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure carbonate **(*R*)-3.138.1** (24 mg, 88 μmol, 95%) as a pale yellow oil.

$\mathbf{R_f}$ 0.40 (1:9 Et_2O/pet. ether); $[\alpha]_D^{25}$ +78.3 (*c* = 0.95, $CHCl_3$); **IR** (thin film, cm^{-1}): 2960, 2235, 1753, 1491, 1442, 1266, 948, 791, 758; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.47-7.44 (2H, m, Ph), 7.36-7.29 (3H, m, Ph), 5.55 (1H, dtt, *J* = 15.0, 6.5 and 1.5 Hz, H7), 5.47 (1H, t, *J* = 6.5 Hz, H3), 5.43 (1H, dtt, *J* = 15.0, 7.0 and 1.5 Hz, H6), 3.83 (3H, s, O*Me*), 2.24 (2H, q, *J* = 7.0 Hz, H5), 2.06-1.92 (4H, m, H4 and 8), 0.98 (3H, t, *J* = 7.5 Hz, H9); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.9, 133.5, 131.8, 128.6, 128.2, 126.9, 122.1, 86.2, 85.6, 68.1, 54.9, 34.7, 27.9, 25.5, 13.7; **HRMS** (ESI+): calc for $C_{17}H_{20}O_3Na$ $[M+Na]^+$ 295.1305, found 295.1301.

(3*R*,6*R*,7*R*)-6,7-dihydroxy-1-phenylnon-1-yn-3-yl methyl carbonate – (*R*,*R*,*R*)-3.134

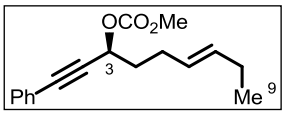


To a stirred solution of carbonate **(*R*)-3.138.1** (23 mg, 84 μmol, 1 eq.) and methanesulfonamide (8 mg, 84 μmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 1 mL) at 0 °C was added AD-mix-β (118 mg, 1.4 g/mmol). The reaction was kept at 0 °C and stirred vigorously for 64 hours. The reaction was quenched with careful addition of solid Na_2SO_3 (125 mg) and the resulting mixture diluted with EtOAc (2 mL) and water (2 mL). The layers were separated and

the aqueous layer extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with 1N aq. HCl (1 x 10 mL) and sat. aq. $NaHCO_3$ (1 x 10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave pure diol **(*R*,*R*,*R*)-3.134** (16 mg, 52 μmol, 62%) as a colourless oil.

R_f 0.15 (3:1 Et_2O/pet. ether); **>95:5 *dr***; $[\alpha]_D^{25}$ +107.6 (*c* = 0.59, $CHCl_3$); **IR** (thin film, cm^{-1}): 3385, 2961, 2934, 2233, 1751, 1491, 1443, 1267, 1071, 970; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.43 (2H, m, Ph), 7.35-7.29 (3H, m, Ph), 5.54 (1H, t, *J* = 6.0 Hz, H3), 3.83 (3H, s, O*Me*), 3.55-3.49 (1H, m, H6), 3.40-3.35 (1H, m, H7), 2.28 (1H, bs, O*H*), 2.20-2.12 (1H, m, H4), 2.08 (1H, bs, O*H*), 2.06-1.98 (1H, m, H4), 1.81-1.66 (2H, m, H5), 1.65-1.57 (1H, m, H8), 1.52-1.44 (1H, m, H8), 1.00 (3H, t, *J* = 7.5 Hz, H9); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 131.9, 128.7, 128.2, 122.0, 86.4, 85.4, 75.9, 73.4, 68.5, 55.0, 31.2, 28.8, 26.4, 9.9; **HRMS** (ESI+): calc for $C_{17}H_{22}O_5Na$ $[M+Na]^+$ 329.1359, found 329.1346.

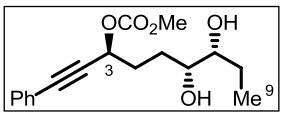
(*S*,*E*)-methyl (1-phenylnon-6-en-1-yn-3-yl) carbonate – (*S*)-3.138.1



To a stirred solution of alcohol **(*S*)-3.138** (93 mg, 0.434 mmol, 1 eq.) and pyridine (0.21 mL, 2.58 mmol, 6 eq.) in anhydrous CH_2Cl_2 (4 mL) at 0 °C under argon was added methyl chloroformate (0.10 mL, 1.30 mmol, 3 eq.). The reaction was allowed to warm to RT and stirred for 15 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1N aq. HCl (1 x 20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure carbonate **(*S*)-3.138.1** (106 mg, 0.389 mmol, 90%) as a pale yellow oil.

$[\alpha]_D^{25}$ −73.2 (*c* = 1.04, $CHCl_3$) [**(*R*)-3.138.1** +78.3 (*c* = 0.95, $CHCl_3$)]. All other spectroscopic data identical to **(*R*)-3.138.1** prepared previously.

(3*S*,6*R*,7*R*)-6,7-dihydroxy-1-phenylnon-1-yn-3-yl methyl carbonate – (*S*,*R*,*R*)-3.134

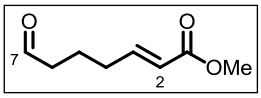


To a stirred solution of carbonate **(*S*)-3.138.1** (106 mg, 0.389 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 4 mL) was added AD-mix-β (545 mg, 1.4 g/mmol) and methanesulfonamide (37 mg, 0.389 mmol, 1 eq.). The resulting suspension was stirred vigorously at 0 °C for 5 days. The reaction was quenched with careful addition of solid Na_2SO_3 (600 mg). The

reaction was diluted with EtOAc (10 mL) and H_2O (10 mL), the layers separated and the aqueous layer extracted with EtOAc (5 x 10 mL). The combined organic layers were washed with 1N aq. HCl (5 x 10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→1:1 EtOAc/pet. ether) to leave pure diol **(*S,R,R*)-3.314** (110 mg, 0.359 mmol, 92%) as a colourless oil.

R_f 0.33 (1:1 EtOAc/pet. ether); **>95:5 *dr***; $[\alpha]_D^{25}$ −89.2 (*c* = 0.61, $CHCl_3$); **IR** (thin film, cm^{-1}): 3390, 2960, 2234, 1748, 1491, 1442, 1255, 1069, 948; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph), 7.34-7.27 (3H, m, Ph), 5.51 (1H, t, *J* = 6.5 Hz, H3), 3.82 (3H, s, O*Me*), 3.52-3.46 (1H, m, H6), 3.38-3.33 (1H, m, H7), 2.52 (2H, bs, 2 x O*H*), 2.18-2.09 (1H, m, H4), 2.06-1.97 (1H, m, H4), 1.81-1.72 (1H, m, H5), 1.72-1.64 (1H, m, H5), 1.62-1.54 (1H, m, H8), 1.50-1.41 (1H, m, H8), 0.98 (3H, t, *J* = 7.0 Hz, H9); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 131.8, 128.7, 128.2, 121.9, 86.4, 85.4, 75.8, 73.4, 68.5, 55.0, 31.2, 28.9, 26.3, 9.9; **HRMS** (ESI+): calc for $C_{17}H_{22}O_5Na$ $[M+Na]^+$ 329.1359, found 329.1348.

(*E*)-methyl 7-oxohept-2-enoate – (*E*)-3.142[262]

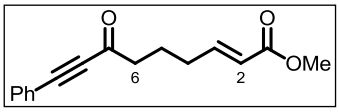


To a stirred solution of tetrahydro-2*H*-pyran-2-ol **3.139** (1.0 g, 9.79 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) under argon was added methyl 2-(triphenylphosphoranylidene)acetate **3.140** (3.93 g, 11.7 mmol, 1.2 eq.). The reaction was stirred at RT for 5 days and the solvent removed *in vacuo*. The resulting oil was triturated with EtOAc (2 x 10 mL), filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→1:1 EtOAc/pet. ether) to leave pure alcohol **3.141** (1.33 g, 8.41 mmol 86%, 87:13 *E*/*Z* by ^{1}H NMR spectroscopy) as a colourless oil which was used directly in the next step.

To a stirred suspension of alcohol **3.141** (1.31 g, 8.28 mmol, 1 eq.) and Celite® (2.14 g) in anhydrous CH_2Cl_2 (20 mL) was added PCC (2.14 g, 9.94 mmol, 1.2 eq.). The reaction was stirred for 2 hours, diluted with Et_2O (50 mL) and passed through a short plug of silica gel (Et_2O). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→1:2 Et_2O/pet. ether) to leave pure aldehyde **(*E*)-3.142** (841 mg, 5.38 mmol, 65%, >99:1 *E/Z* by ^{1}H NMR spectroscopy) as a pale yellow oil.

R_f 0.15 (1:3 Et_2O/pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 9.78 (1H, t, *J* = 1.5 Hz, H7), 6.93 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.85 (1H, dt, *J* = 15.5 and 1.5 Hz, H2), 3.73 (3H, s, O*Me*), 2.49 (2H, td, *J* = 7.0 and 1.5 Hz, H6), 2.26 (2H, qd, *J* = 7.0 and 1.5 Hz, H4), 1.81 (2H, quintet, *J* = 7.5 Hz, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 201.5, 166.8, 147.9, 121.8, 51.5, 42.9, 31.2, 20.3. Data consistent with literature.[262]

(*E*)-methyl 7-oxo-9-phenylnon-2-en-8-ynoate – 3.143



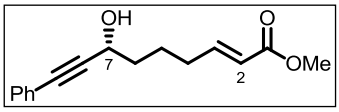
To a stirred solution of phenyl acetylene (0.61 mL, 5.55 mmol, 1.05 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 2.22 mL, 5.55 mmol, 1.05 eq.) dropwise. The resulting solution was stirred at −78 °C for 30 minutes before being transferred *via* cannula to a stirred solution of aldehyde **3.142** (825 mg, 5.28 mmol, 1 eq.) in anhydrous THF (10 mL) at −78 °C under argon. The reaction was stirred at −78 °C for 1 hour, quenched with sat. aq. NH_4Cl (10 mL) and allowed to warm to RT. The layers were separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by filtration through a short plug of silica gel (1:5 EtOAc/pet. ether) to leave pure alcohol **(±)-3.144** (1.138 g) as a pale yellow oil which was used directly in the next step.

To a stirred suspension of alcohol **(±)-3.144** (1.13 g, 4.37 mmol, 1 eq.) and $NaHCO_3$ (341 mg, 4.06 mmol, 0.95 eq.) in CH_2Cl_2 (90 mL) was added Dess-Martin periodinane (2.22 g, 5.24 mmol, 1.2 eq.). The reaction was stirred for 15 minutes and quenched with sat. aq. $NaHCO_3$/$Na_2S_2O_3$ (1:1 v:v, 90 mL). The biphasic mixture was stirred until the layers became clear, separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:5 EtOAc/pet. ether) to leave pure ketone **3.143** (913 mg, 3.56 mmol, 67% *2 steps*) as a colourless oil.

R_f 0.43 (1:3 EtOAc/pet. ether); **IR** (thin film, cm^{-1}): 2950, 2200, 1720, 1666, 1489, 1436, 1271, 1198, 1102, 1031; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.60-7.57 (2H, m, Ph), 7.49-7.45 (1H, m, Ph), 7.42-7.38 (2H, m, Ph), 6.97 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.88 (1H, dt, *J* = 15.5 and 1.5 Hz, H2), 3.74 (3H, s, O*Me*), 2.71 (2H, t, *J* = 7.5 Hz, H6), 2.30 (2H, *apt* q, *J* = 7.0 Hz, H4), 1.92 (2H, quintet, *J* = 7.5 Hz,

H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 187.0, 166.9, 147.9, 133.1, 128.6, 121.8, 119.8, 91.0, 87.7, 51.5, 44.4, 31.2, 22.3; **HRMS** (ESI+): calc for $C_{16}H_{16}O_3Na$ $[M+Na]^+$ 279.0992, found 279.0984.

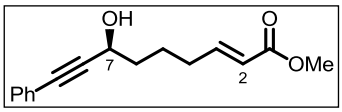
(*R*,*E*)-methyl 7-hydroxy-9-phenylnon-2-en-8-ynoate – (*R*)-3.144



A solution of ketone **3.143** (450 mg, 1.76 mmol, 1 eq.) in IPA (5 mL) was degassed for 30 minutes. Alongside this a solution of [RuCl((*R*,*R*)-TsDPEN)(*p*-cymene)] **(*R*,*R*)-3.53·HCl** (11.2 mg, 1 mol%) in IPA (3.25 mL) was degassed for 30 minutes. A solution of KOH (1.2 mg, 1.2 mol%) in degassed IPA (0.5 mL) was added to the catalyst solution and the resulting mixture stirred until a yellow colour developed. The catalyst solution was transferred *via* syringe to the ketone and the reaction stirred at RT for 5 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:9→1:2 EtOAc/pet. ether) to leave pure alcohol **(*R*)-3.144** (435 mg, 1.68 mmol, 95%) as a yellow oil.

R_f 0.42 (1:2 EtOAc/pet. ether); $[\alpha]_D^{25}$ −5.1 (*c* = 1.12, $CHCl_3$); **98% *ee*** (CHIRALPAK IB, 20% IPA/hexane, 1.15 mL/min): t_R (*R*) = 5.07 min, t_R (*S*) = 15.27 min; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph), 7.35-7.29 (3H, m, Ph), 6.99 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.87 (1H, dt, *J* = 15.5 and 1.5 Hz, H2), 4.64-4.60 (1H, m, H7), 3.73 (3H, s, O*Me*), 2.30 (2H, qd, *J* = 7.0 and 1.5 Hz, H4), 2.01 (1H, bs, O*H*), 1.88-1.78 (2H, m, H6), 1.76-1.69 (2H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 167.1, 148.9, 131.7, 128.5, 128.3, 122.4, 121.3, 89.7, 85.1, 62.6, 51.4, 37.1, 31.7, 23.6. Data consistent with (±) in the literature.[263]

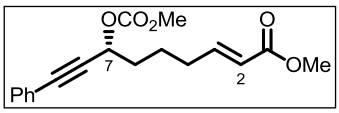
(*S*,*E*)-methyl 7-hydroxy-9-phenylnon-2-en-8-ynoate – (*S*)-3.144



A solution of ketone **3.143** (450 mg, 1.76 mmol, 1 eq.) in IPA (5 mL) was degassed for 30 minutes. Alongside this a solution of [RuCl((*S*,*S*)-TsDPEN)(*p*-cymene)] **(*S*,*S*)-3.53·HCl** (11.2 mg, 1 mol%) in IPA (3.25 mL) was degassed for 30 minutes. A solution of KOH (1.2 mg, 1.2 mol%) in degassed IPA (0.5 mL) was added to the catalyst solution and the resulting mixture stirred until a yellow colour developed. The catalyst solution was transferred *via* syringe to the ketone and the reaction stirred at RT for 3 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:9→1:2 EtOAc/pet. ether) to leave pure alcohol **(*S*)-3.144** (432 mg, 1.67 mmol, 95%) as a yellow oil.

R_f 0.42 (1:2 EtOAc/pet. ether); $[\alpha]_D^{25}$ +4.8 (*c* = 1.06, $CHCl_3$) [**(*R*)-3.144** −5.1 (*c* = 1.12, $CHCl_3$)]; **98% *ee*** (CHIRALPAK IB, 20% IPA/hexane, 1.15 mL/min): t_R (*R*) = 5.10 min, t_R (*S*) = 14.92 min. All other spectroscopic data identical to **(*R*)-3.144** prepared previously.

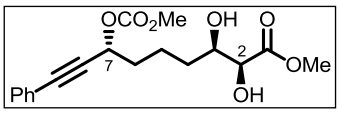
(*R*,*E*)-methyl 7-((methoxycarbonyl)oxy)-9-phenylnon-2-en-8-ynoate – (*R*)-3.144.1



To a stirred solution of alcohol **(*R*)-3.144** (430 mg, 1.66 mmol, 1 eq.) and pyridine (1.07 mL, 13.28 mmol, 8 eq.) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under argon was added methyl chloroformate (0.39 mL, 4.99 mmol, 3 eq.). The reaction was stirred for 15 minutes and quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N aq. HCl (2 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure carbonate **(*R*)-3.144.1** (490 mg, 1.55 mmol, 93%) as a yellow oil.

R_f 0.20 (1:4 Et_2O/pet. ether); $[\alpha]_D^{25}$ +96.5 (*c* = 1.00, $CHCl_3$); **IR** (thin film, cm^{-1}): 2954, 2236, 1750, 1722, 1658, 1491, 1441, 1264, 983; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.36-7.28 (3H, m, Ph), 6.96 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.86 (1H, d, *J* = 15.5 Hz, H2), 5.48 (1H, t, *J* = 7.5 Hz, H7), 3.82 (3H, s, OCO_2*Me*), 3.73 (3H, s, CO_2*Me*), 2.33-2.26 (2H, m, H4), 1.97-1.90 (2H, m, H6), 1.77-1.68 (2H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 166.9, 154.9, 148.3, 131.8, 128.7, 128.2, 121.9, 121.5, 86.4, 85.3, 68.2, 54.9, 51.4, 34.2, 31.5, 23.3; **HRMS** (ESI+): calc for $C_{18}H_{20}O_5Na$ $[M+Na]^+$ 339.1203, found 339.1194.

(2*S*,3*R*,7*R*)-methyl 2,3-dihydroxy-7-((methoxycarbonyl)oxy)-9-phenylnon-8-ynoate – (*S*,*R*,*R*)-3.135

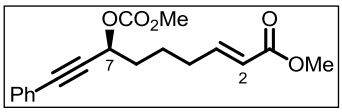


To a stirred solution of carbonate **(*R*)-3.144.1** (490 mg, 1.55 mmol, 1 eq.) and methanesulfonamide (147 mg, 1.55 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 15.5 mL) at 0 °C was added AD-mix-β (2.17 g, 1.4 g/mmol). The reaction was stirred at 0 °C for 5 days and quenched *via careful* addition of solid Na_2SO_3 (2.3 g). The mixture was diluted with EtOAc (15 mL) and water (15 mL), the layers separated and the aqueous layer was extracted with EtOAc (4 x 15 mL). The combined organic layers were washed with 1N aq. HCl (5 x 15 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→2:1 EtOAc/pet. ether) to leave pure diol **(*S*,*R*,*R*)-3.135** (450 mg,

1.28 mmol, 83%) as a colourless oil.

R_f 0.18 (1:1 EtOAc/pet. ether); **>95:5 *dr***; $[\alpha]_D^{25}$ +66.8 (*c* = 1.13, $CHCl_3$); **IR** (thin film, cm^{-1}): 3482, 2955, 2235, 1755, 1491, 1443, 1265, 1127, 948; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.35-7.28 (3H, m, Ph), 5.48 (1H, t, *J* = 6.5 Hz, H7), 4.11 (1H, dd, *J* = 5.5 and 2.0 Hz, H2), 3.95-3.89 (1H, m, H3), 3.83 (3H, s, O*Me*), 3.82 (3H, s, O*Me*), 3.14 (1H, d, *J* = 5.5 Hz, O*H*), 2.11 (1H, d, *J* = 9.0 Hz, O*H*), 2.03-2.00 (2H, m, H6), 1.79-1.59 (4H, m, H4 and 5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 173.9, 155.0, 131.9, 128.7, 128.2, 122.0, 86.3, 85.5, 73.1, 68.4, 55.0, 52.8, 34.6, 33.1, 21.2; **HRMS** (ESI+): calc for $C_{18}H_{22}O_7Na$ $[M+Na]^+$ 373.1258, found 373.1242.

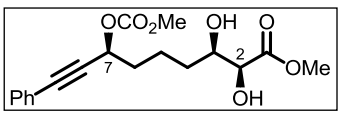
(*S*,*E*)-methyl 7-((methoxycarbonyl)oxy)-9-phenylnon-2-en-8-ynoate – (*S*)-3.144.1



To a stirred solution of alcohol **(*S*)-3.144** (412 mg, 1.59 mmol, 1 eq.) and pyridine (1.03 mL, 12.72 mmol, 8 eq.) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under argon was added methyl chloroformate (0.37 mL, 4.78 mmol, 3 eq.). The reaction was stirred for 15 minutes and quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N aq. HCl (2 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure carbonate **(*S*)-3.144.1** (503 mg, 1.59 mmol, 99%) as a yellow oil.

R_f 0.20 (1:4 Et_2O/pet. ether); $[\alpha]_D^{25}$ −90.2 (*c* = 1.60, $CHCl_3$) [**(*R*)-3.144.1** +96.5 (*c* = 1.00, $CHCl_3$)]. All other spectroscopic data identical to **(*R*)-3.144.1** prepared previously.

(2*S*,3*R*,7*S*)-methyl 2,3-dihydroxy-7-((methoxycarbonyl)oxy)-9-phenylnon-8-ynoate – (*S*,*R*,*S*)-3.135

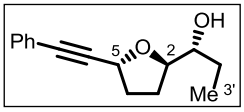


To a stirred solution of carbonate **(*S*)-3.144.1** (503 mg, 1.59 mmol, 1 eq.) and methanesulfonamide (151 mg, 1.59 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 16 mL) at 0 °C was added AD-mix-β (2.23 g, 1.4 g/mmol). The reaction was stirred at 0 °C for 5 days and quenched *via careful* addition of solid Na_2SO_3 (2.4 g). The mixture was diluted with EtOAc (15 mL) and water (15 mL), the layers separated and the aqueous layer extracted with EtOAc (4 x 15 mL). The combined organic layers were washed with 1N aq. HCl (5 x 15 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→2:1 EtOAc/pet. ether) to leave pure diol **(*S*,*R*,*S*)-3.135** (490 mg,

1.40 mmol, 88%) as a colourless oil.

R_f 0.18 (1:1 EtOAc/pet. ether); **$[\alpha]_D^{25}$** −58.8 (*c* = 1.02, $CHCl_3$); **IR** (thin film, cm^{-1}): 3480, 2955, 2233, 1745, 1491, 1443, 1265, 1127, 947; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.43 (2H, m, Ph), 7.35-7.29 (3H, m, Ph), 5.49 (1H, t, *J* = 6.5 Hz, H7), 4.12 (1H, dd, *J* = 5.0 and 2.0 Hz, H2), 3.95-3.90 (1H, m, H3), 3.84 (3H, s, O*Me*), 3.83 (3H, s, O*Me*), 3.08 (1H, d, *J* = 5.0 Hz, O*H*), 2.00 (1H, d, *J* = 9.0 Hz, O*H*), 1.99-1.95 (2H, m, H6), 1.81-1.58 (4H, m, H4 and 5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 173.9, 155.0, 131.9, 128.7, 128.2, 122.0, 86.3, 85.5, 73.0, 72.1, 68.4, 55.0, 52.9, 34.6, 33.2, 21.3; **HRMS** (ESI+): calc for $C_{18}H_{22}O_7Na$ $[M+Na]^+$ 373.1258, found 373.1242.

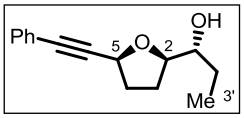
(*R*)-1-((2*R*,5*R*)-5-(Phenylethynyl)tetrahydrofuran-2-yl)propan-1-ol – (*R,R,R*)-3.145



To a degassed solution of carbonate **(*R,R,R*)-3.134** (16 mg, 52 μmol, 1 eq.) and $B(OH)_3$ (1.6 mg, 26 μmol, 0.5 eq.) in 1,4-dioxane (0.2 mL) was added a solution of $Pd(OAc)_2$ (0.6 mg, 5 mol%) and dppf (2.9 mg, 10 mol%) in degassed 1,4-dioxane (0.3 mL). The reaction was heated to 50 °C and stirred for 30 minutes. The reaction was quenched *via* addition of pet. ether (1 mL) and the reaction mixture passed through a short plug of silica gel (Et_2O). The solvent was removed *in vacuo* to leave the pure THF (12.0 mg, 52 μmol, 99%, 95:5 *dr*) as mixture of diastereomers. The mixture was chromatographed on silica gel (Et_2O/pet. ether 1:4→1:2) to leave pure *trans*-THF **(*R,R,R*)-3.145** (10.5 mg, 46 μmol, 88%, single diastereomer) as a colourless oil.

R_f 0.33 (1:2 Et_2O/pet. ether); **$[\alpha]_D^{25}$** +39.7 (*c* = 0.70, $CHCl_3$); **IR** (thin film, cm^{-1}): 3444, 2964, 2876, 2229, 1599, 1490, 1443, 1060, 757; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.33-7.28 (3H, m, Ph), 4.90 (1H, t, *J* = 6.0 Hz, H5), 4.07 (1H, *apt* q, *J* = 6.5 Hz, H2), 3.41-3.36 (1H, m, H1'), 2.35-2.27 (1H, m, H4), 2.23 (1H, d, *J* = 5.0 Hz, O*H*), 2.19-2.09 (2H, m, H3 and 4), 1.80-1.72 (1H, m, H3), 1.59-1.44 (2H, m, H2'), 1.02 (3H, t, *J* = 7.5 Hz, H3'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.7, 128.4, 128.2, 122.6, 88.5, 84.8, 81.9, 75.3, 68.9, 34.0, 27.9, 26.6, 10.1; **HRMS** (ESI+): calc for $C_{15}H_{18}O_2Na$ $[M+Na]^+$ 253.1199, found 253.1190.

(*R*)-1-((2*R*,5*S*)-5-(Phenylethynyl)tetrahydrofuran-2-yl)propan-1-ol – (*R,R,S*)-3.145

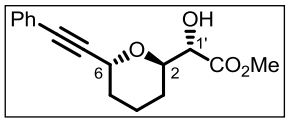


To a degassed solution of carbonate **(*S,R,R*)-3.134** (20.0 mg, 65 μmol, 1 eq.) and $B(OH)_3$ (2.0 mg, 33 μmol, 0.5 eq.) in 1,4-dioxane (0.20 mL) was added a

solution of $Pd(OAc)_2$ (0.7 mg, 5 mol%) and dppf (3.6 mg, 10 mol%) in degassed 1,4-dioxane (0.45 mL). The reaction was heated to 50 °C and stirred for 30 minutes. The reaction quenched *via* addition of pet. ether (1 mL), filtered through a short plug of silica gel (Et_2O) and the solvent removed *in vacuo* to leave a crude mixture of THF diastereomers (95:5 ***dr***, 13.4 mg, 89%) as a colourless oil. The mixture was chromatographed on silica gel (1:9→1:2 Et_2O/pet. ether) to leave pure *cis*-THF **(*R*,*R*,*S*)-3.145** (12.3 mg, 53 μmol, 82%) as a colourless oil.

R_f 0.24 (1:2 Et_2O/pet. ether); $[\alpha]_D^{25}$ −13.0 (*c* = 0.44, $CHCl_3$); **IR** (thin film, cm^{-1}): 3460, 2964, 2876, 2230, 1491, 1339, 1062, 1024, 971; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph), 7.34-7.28 (3H, m, Ph), 4.87 (1H, dd, *J* = 7.5 and 4.5 Hz, H5), 3.90 (1H, td, *J* = 7.5 and 6.0 Hz, H2), 3.52-3.46 (1H, m, H1'), 2.40 (1H, d, *J* = 5.5 Hz, O*H*), 2.30-2.22 (1H, m, H4), 2.19-2.12 (1H, m, H4), 2.06-1.95 (2H, m, H3), 1.58-1.43 (2H, m, H2'), 1.03 (3H, t, *J* = 7.5 Hz, H3'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.7, 128.4, 128.3, 122.5, 89.1, 85.0, 83.1, 75.2, 68.9, 33.9, 27.7, 26.9, 10.2; **HRMS** (ESI+): calc for $C_{15}H_{18}O_2Na$ $[M+Na]^+$ 253.1199, found 253.1194.

(*S*)-methyl 2-hydroxy-2-((2*R*,6*R*)-6-(phenylethynyl)tetrahydro-2*H*-pyran-2-yl)acetate – (*S*,*R*,*R*)-3.146

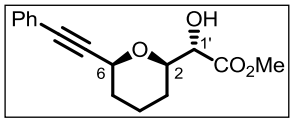


To a vial containing a solution of carbonate **(*S*,*R*,*R*)-3.135** (50 mg, 0.143 mmol, 1 eq.) and $B(OH)_3$ (4.4 mg, 71 μmol, 0.5 eq.) in degassed 1,4-dioxane (0.3 mL) was added a solution of $Pd(OAc)_2$ (1.6 mg, 5 mol%) and dppf (7.9 mg, 10 mol%) in degassed 1,4-dioxane (1.1 mL). The reaction was stirred and heated to 100 °C for 10 minutes. The reaction was allowed to cool and quenched with pet. ether (3 mL). The reaction mixture was passed through a plug of silica gel (Et_2O) and the solvent removed *in vacuo* to leave the crude product as a pale yellow oil (97:3 *dr*). The crude product was purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave pure *trans*-THP **(*S*,*R*,*R*)-3.146** (32 mg, 0.117 mmol, 82%) as a colourless oil.

R_f 0.19 (1:4 Et_2O/pet. ether); $[\alpha]_D^{25}$ +118.2 (*c* = 0.88, $CHCl_3$); **IR** (thin film, cm^{-1}): 3496, 2949, 2864, 2228, 1746, 1490, 1442, 1276, 1198, 1127, 1036, 935; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H, m, Ph), 7.35-7.32 (3H, m, Ph), 4.98 (1H, d, *J* = 5.0 Hz, H6), 4.35 (1H, dt, *J* = 11.5 and 2.5 Hz, H2), 4.12 (1H, dd, *J* = 8.0 and 2.5 Hz, H1'), 3.82 (3H, s, O*Me*), 2.89 (1H, d, *J* = 8.0 Hz, O*H*), 2.09-

1.97 (1H, m, H4), 1.91-1.72 (4H, m, H3, 4 and 5), 1.64-1.59 (1H, m, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 173.3, 131.6, 128.3, 128.3, 122.8, 87.0, 86.9, 73.6, 72.7, 66.1, 52.5, 29.9, 26.6, 19.2; **HRMS** (ESI+): calc for $C_{16}H_{18}O_4Na$ $[M+Na]^+$ 297.1097, found 297.1093.

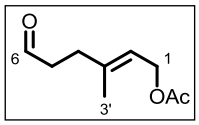
(*S*)-methyl 2-hydroxy-2-((2*R*,6*S*)-6-(phenylethynyl)tetrahydro-2*H*-pyran-2-yl)acetate – (*S,R,S*)-3.146



To a vial containing a solution of carbonate **(*S,R,S*)-3.135** (50 mg, 0.143 mmol, 1 eq.) and $B(OH)_3$ (4.4 mg, 71 μmol, 0.5 eq.) in degassed 1,4-dioxane (0.3 mL) was added a solution of $Pd(OAc)_2$ (1.6 mg, 5 mol%) and dppf (7.9 mg, 10 mol%) in degassed 1,4-dioxane (1.1 mL). The reaction was stirred and heated to 100 °C for 10 minutes. The reaction was allowed to cool and quenched with pet. ether (3 mL). The reaction mixture was passed through a plug of silica gel (Et_2O) and the solvent removed *in vacuo* to leave the crude product as a pale yellow oil (96:4 *dr*). The crude product was purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave pure *cis*-THP **(*S,R,S*)-3.146** (30 mg, 0.109 mmol, 76%) as a colourless oil.

R_f 0.18 (1:4 Et_2O/pet. ether); $[\alpha]_D^{25}$ −20.5 (*c* = 1.22, $CHCl_3$); **IR** (thin film, cm^{-1}): 3501, 2949, 2860, 2230, 1743, 1492, 1442, 1276, 1167, 1075, 1032; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.42 (2H, m, Ph), 7.32-7.28 (3H, m, Ph), 4.35 (1H, dd, *J* = 11.5 and 2.5 Hz, H6), 4.10 (1H, dd, *J* = 8.0 and 3.0 Hz, H1'), 3.83 (3H, s, O*Me*), 3.78 (1H, ddd, *J* = 11.5, 3.0 and 2.0 Hz, H2); 2.98 (1H, d, *J* = 8.0 Hz, O*H*), 2.01-1.94 (1H, m, H4), 1.93-1.88 (1H, m, H5), 1.81-1.69 (2H, m, H3 and 5), 1.67-1.55 (2H, m, H3 and 4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 172.8, 131.8, 128.4, 128.2, 122.6, 88.1, 84.5, 78.5, 73.7, 69.1, 52.6, 32.2, 26.3, 23.0; **HRMS** (ESI+): calc for $C_{16}H_{18}O_4Na$ $[M+Na]^+$ 297.1097, found 297.1092.

(*E*)-3-methyl-6-oxohex-2-en-1-yl acetate – 3.150[173]



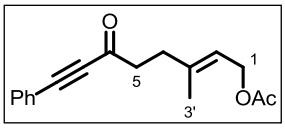
To a stirred suspension of geraniol **3.148** (2.0 g, 12.97 mmol, 1 eq.) and DMAP (158 mg, 1.297 mmol, 0.1 eq.) at 0 °C under argon was added Ac_2O (2.45 mL, 25.93 mmol, 2 eq.) and pyridine (2.10 mL, 25.93 mmol, 2 eq.) dropwise. The reaction was allowed to warm to RT and stirred for 30 minutes. The reaction was quenched *via* dropwise addition of 6N aq. HCl (5 mL) at 0 °C. The reaction was extracted with Et_2O (3 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo* to leave geraniol acetate **3.149** (2.54 g, 99%) as a

colourless oil which was used without further purification.

Ozone was bubbled through a solution of **3.149** (7.68 g, 39.1 mmol, 1 eq.) in CH_2Cl_2/pyridine (25:1 v:v, 260 mL) cooled to −78 °C. The reaction was monitored closely by TLC (9:1 pet. ether/EtOAc) for disappearance of the starting material (2 hr) before the solution was sparged with oxygen for 10 minutes to remove excess ozone. SMe_2 (8.62 mL, 0.117 mol, 3 eq.) was added with stirring and the reaction allowed to warm to RT overnight under a gentle stream of nitrogen to evaporate the solvent and excess SMe_2. The resulting crude residue was diluted with water (30 mL) and extracted with EtOAc (5 x 30 mL). The combined organic layers were washed sequentially with 1N aq. HCl (1 x 100 mL) and sat. aq. $NaHCO_3$ (1 x 100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→1:2 Et_2O/pet. ether) to leave pure aldehyde **3.150** (2.62 g, 40%) as a pale yellow oil.

R_f 0.18 (1:3 Et_2O/pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 9.78 (1H, t, *J* = 1.5 Hz, H6), 5.38-5.34 (1H, m, H2), 4.58 (2H, d, *J* = 7.0 Hz, H1), 2.58 (2H, td, *J* = 7.5 and 2.0 Hz, H5), 2.38 (2H, t, *J* = 7.5 Hz, H4), 2.05 (3H, s, C(O)*Me*), 1.72 (3H, s, H3'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 201.7, 171.0, 140.0, 119.3, 61.1, 41.7, 31.4, 21.0, 16.6. Data consistent with literature.[173]

(*E*)-3-methyl-6-oxo-8-phenyloct-2-en-7-yn-1-yl acetate – 3.151



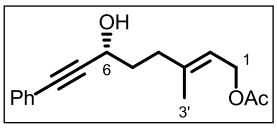
To a stirred solution of phenyl acetylene (0.65 mL, 5.88 mmol, 1 eq.) in anhydrous THF (10 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 2.35 mL, 5.88 mmol, 1 eq.) dropwise. The solution was stirred for 30 minutes before being transferred dropwise *via* cannula to a solution of aldehyde **3.150** (1.0 g, 5.88 mmol, 1 eq.) in anhydrous THF (10 mL) at −78 °C under argon. The reaction was stirred for 1 hour, quenched with sat. aq. $NaHCO_3$ solution (20 mL) and allowed to warm to RT. The reaction was diluted with Et_2O (20 mL), the layers separated and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→1:1 Et_2O/pet. ether) to leave propargylic alcohol **(±)-3.152** (1.272 g) as a colourless oil which was used directly in the next step.

To a stirred solution of **(±)-3.152** (1.272 g, 4.67 mmol, 1 eq.) in CH_2Cl_2 (140 mL) was added Dess-Martin periodinane (2.38 g, 5.60 mmol, 1.2 eq.). The reaction was stirred for 15 minutes and quenched

with a mixture of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ (1:1 v:v, 100 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→1:2 Et_2O/pet. ether) to leave pure ketone **3.151** (1.089 g, 4.03 mmol, 69%, *2 steps*) as a pale yellow oil.

R_f 0.49 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2938, 2202, 1734, 1667, 1489, 1443, 1366, 1229, 1089, 1023; **^{1}H NMR** (250 MHz, $CDCl_3$): δ_H 7.60-7.55 (2H, m, Ph), 7.50-7.35 (3H, m, Ph), 5.45-5.36 (1H, m, H2), 4.59 (2H, d, *J* = 7.0 Hz, H1), 2.86-2.77 (2H, m, H5), 2.52-2.43 (2H, m, H4), 2.04 (3H, s, C(O)*Me*), 1.75 (3H, s, H3'); **^{13}C NMR** (63 MHz, $CDCl_3$): δ_C 186.9, 171.0, 139.9, 133.0, 130.7, 128.6, 119.8, 119.3, 91.0, 87.6, 61.1, 43.5, 33.3, 21.0, 16.6; **HRMS** (ESI+): calc for $C_{17}H_{18}O_3Na$ $[M+Na]^+$ 293.1148, found 293.1150.

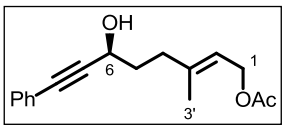
(*R*,*E*)-6-hydroxy-3-methyl-8-phenyloct-2-en-7-yn-1-yl acetate – (*R*)-3.152



A solution of ketone **3.151** (215 mg, 0.79 mmol, 1 eq.) in IPA (2 mL) was degassed for 30 minutes. Alongside this, a solution of [RuCl((*R*,*R*)-TsDPEN)(*p*-cymene)] **(*R*,*R*)-3.53·HCl** (5 mg, 1 mol%) in IPA (2 mL) was degassed for 30 minutes and to it added a solution of KOH (0.53 mg, 1.2 mol%) in IPA (0.1 mL). The catalyst solution was stirred until a yellow colour developed, and transferred *via* syringe to the ketone solution. The reaction was stirred under argon for 24 hours and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to leave pure alcohol **(*R*)-3.152** (190 mg, 0.70 mmol, 89%) as a pale yellow oil.

R_f 0.09 (1:2 Et_2O/pet. ether); **$[\alpha]_D^{25}$** −23.0 (*c* = 1.79, $CHCl_3$); **98% *ee*** (CHIRALPAK IC, 7% IPA/hexane 1.25 mL/min): t_R (*S*) = 16.48 min, t_R (*R*) = 17.19 min; **IR** (thin film, cm^{-1}): 3413, 2948, 2229, 1735, 1490, 1443, 1382, 1231, 1067, 951; **^{1}H NMR** (250 MHz, $CDCl_3$): δ_H 7.47-7.39 (2H, m, Ph), 7.35-7.29 (3H, m, Ph), 5.34 (1H, t, *J* = 7.0 Hz, H2), 4.65-4.55 (3H, m, H1 and 6), 2.30 (2H, t, *J* = 7.5 Hz, H4), 2.10 (1H, bs, O*H*), 2.06 (3H, s, C(O)*Me*), 1.99-1.89 (2H, m, H5), 1.76 (3H, s, H3'); **^{13}C NMR** (63 MHz, $CDCl_3$): δ_C 171.1, 141.3, 131.6, 128.4, 128.3, 122.5, 119.0, 89.7, 85.1, 62.4, 61.3, 35.6, 35.0, 21.0, 16.5; **HRMS** (ESI+): calc for $C_{17}H_{20}O_3Na$ $[M+Na]^+$ 295.1305, found 295.1303.

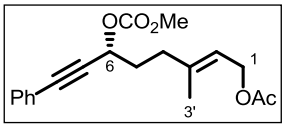
(*S*,*E*)-6-hydroxy-3-methyl-8-phenyloct-2-en-7-yn-1-yl acetate – (*S*)-3.152



A solution of ketone **3.151** (500 mg, 1.85 mmol, 1 eq.) in IPA (4.5 mL) was degassed for 30 minutes. Alongside this, a solution of [RuCl((*S*,*S*)-TsDPEN)(*p*-cymene)] **(*S*,*S*)-3.53·HCl** (11.8 mg, 1 mol%) in IPA (4.5 mL) was degassed for 30 minutes and to it added a solution of KOH (1.2 mg, 1.2 mol%) in IPA (0.1 mL). The catalyst solution was stirred until a yellow colour developed, and transferred *via* syringe to the ketone solution. The reaction was stirred under argon for 2 hours and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to leave pure alcohol **(*S*)-3.152** (470 mg, 1.73 mmol, 94%) as a pale yellow oil.

$[\alpha]_D^{25}$ +24.8 (*c* = 1.03, $CHCl_3$) [**(*R*)-3.152** −23.0 (*c* = 1.79, $CHCl_3$)]; **98% *ee*** (CHIRALPAK IC, 7.5% IPA/hexane, 1.3 mL/min): t_R (*S*) = 14.39 min, t_R (*R*) = 14.92 min. All other spectroscopic data identical to **(*R*)-3.152** prepared previously.

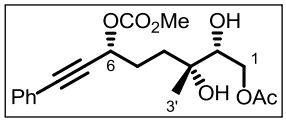
(*R*,*E*)-6-((methoxycarbonyl)oxy)-3-methyl-8-phenyloct-2-en-7-yn-1-yl acetate – (*R*)-3.152.1



To a stirred solution of alcohol **(*R*)-3.152** (190 mg, 0.70 mmol, 1 eq.) and pyridine (0.34 mL, 4.19 mmol, 6 eq.) in anhydrous CH_2Cl_2 (5 mL) at 0 °C under argon was added methyl chloroformate (0.16 mL, 2.10 mmol, 3 eq.). The reaction was allowed to warm to RT and stirred for 15 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N aq. HCl (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure carbonate **(*R*)-3.152.1** (217 mg, 0.657 mmol, 94%) as a yellow oil.

R_f 0.19 (1:2 Et_2O/pet. ether); $[\alpha]_D^{25}$ +60.6 (*c* = 1.24, $CHCl_3$); **IR** (thin film, cm^{-1}): 2958, 2233, 1738, 1731, 1491, 1442, 1258, 1230, 1023, 948; **^{1}H NMR** (250 MHz, $CDCl_3$): δ_H 7.48-7.40 (2H, m, Ph), 7.36-7.28 (3H, m, Ph), 5.44 (1H, t, *J* = 6.5 Hz, H6), 5.44-5.37 (1H, m, H2), 4.59 (2H, d, *J* = 7.0 Hz, H1), 3.82 (3H, s, O*Me*), 2.33-2.24 (2H, m, H4), 2.11-1.99 (2H, m, H5), 2.05 (3H, s, C(O)*Me*), 1.75 (3H, s, H3'); **^{13}C NMR** (63 MHz, $CDCl_3$): δ_C 171.0, 154.9, 140.3, 131.8, 128.7, 128.2, 122.0, 119.3, 86.4, 85.4, 68.1, 61.1, 54.9, 34.6, 32.8, 21.0, 16.4; **HRMS** (ESI+): calc for $C_{19}H_{22}O_5Na$ $[M+Na]^+$ 353.1359, found 353.1350.

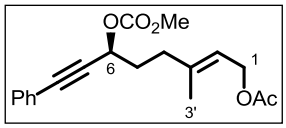
(2*R*,3*R*,6*R*)-2,3-dihydroxy-6-((methoxycarbonyl)oxy)-3-methyl-8-phenyloct-7-yn-1-yl acetate – (*R*,*R*,*R*)-3.147



To a stirred solution of carbonate **(*R*)-3.152.1** (216 mg, 0.654 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 6.5 mL) at 0 °C was added AD-mix-β (916 mg, 1.4 g/mmol) and methanesulfonamide (62 mg, 0.654 mmol, 1 eq.). The reaction was stirred at 0 °C for 64 hours and quenched *via* careful addition of solid Na_2SO_3 (1 g). The reaction was diluted with water (10 mL) and EtOAc (10 mL), the layers separated and the aqueous layer extracted with EtOAc (5 x 10 mL). The combined organic layers were washed with 1N aq. HCl (5 x 25 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4 Et_2O/pet. ether→Et_2O) to leave pure diol **(*R*,*R*,*R*)-3.147** (45 mg, 0.123 mmol, 19%, 31% brsm) as a pale yellow oil.

R_f 0.23 (Et_2O); **>95:5 *dr***; $[\alpha]_D^{25}$ +93.4 (*c* = 1.04, $CHCl_3$); **IR** (thin film, cm^{-1}): 3467, 2961, 2234, 1746, 1491, 1443, 1265, 1071, 948; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.43 (2H, m, Ph), 7.35-7.29 (3H, m, Ph), 5.50 (1H, t, *J* = 6.5 Hz, H6), 4.30 (1H, dd, *J* = 11.5 and 3.0 Hz, H1), 4.09 (1H, dd, *J* = 11.5 and 8.5 Hz, H1), 3.83 (3H, s, O*Me*), 3.72 (1H, dd, *J* = 8.5 and 3.0 Hz, H2), 2.72 (1H, bs, O*H*), 2.28 (1H, bs, O*H*), 2.10 (3H, s, C(O)*Me*), 2.08-1.99 (2H, m, H5), 1.86-1.72 (2H, m, H4), 1.20 (3H, s, H3'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 171.3, 155.0, 131.9, 128.8, 128.3, 121.9, 86.5, 74.6, 72.9, 68.7, 65.7, 55.0, 34.0, 29.1, 21.7, 20.9; **HRMS** (ESI+): calc for $C_{19}H_{24}O_7Na$ $[M+Na]^+$ 387.1414, found 387.1408.

(*S*,*E*)-6-((methoxycarbonyl)oxy)-3-methyl-8-phenyloct-2-en-7-yn-1-yl acetate – (*S*)-3.152.1

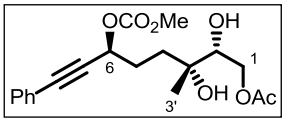


To a stirred solution of alcohol **(*S*)-3.152** (460 mg, 1.69 mmol, 1 eq.) and pyridine (0.82 mL, 10.14 mmol, 6 eq.) in anhydrous CH_2Cl_2 (15 mL) at 0 °C under argon was added methyl chloroformate (0.39 mL, 5.07 mmol, 3 eq.). The reaction was allowed to warm to RT and stirred for 15 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with 1N aq. HCl (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure carbonate **(*S*)-3.152.1** (498 mg, 1.51 mmol, 89%) as a pale yellow oil.

$[\alpha]_D^{25}$ −63.8 (*c* = 1.68, $CHCl_3$) [**(*R*)-3.152.1** +60.6 (*c* = 1.24, $CHCl_3$)]. All other spectroscopic data

identical to **(*R*)-3.152.1** prepared previously.

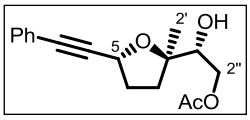
(2*R*,3*R*,6*S*)-2,3-dihydroxy-6-((methoxycarbonyl)oxy)-3-methyl-8-phenyloct-7-yn-1-yl acetate – (*R*,*R*,*S*)-3.147



To a stirred solution of carbonate **(*S*)-3.152.1** (480 mg, 1.45 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 14.5 mL) at 0 °C was added AD-mix-β (2.03 g, 1.4 g/mmol) and methanesulfonamide (138 mg, 1.45 mmol, 1 eq.). The reaction was stirred at 0 °C for 6 days, and quenched *via careful* addition of solid Na_2SO_3 (2.2 g). The reaction was diluted with water (15 mL) and EtOAc (15 mL), the layers separated and the aqueous layer extracted with EtOAc (5 x 15 mL). The combined organic layers were washed with 1N aq. HCl (5 x 25 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3 Et_2O/pet. ether→Et_2O) to leave pure diol **(*R*,*R*,*S*)-3.147** (363 mg, 0.98 mmol, 68%, 84% brsm) as a colourless oil.

R_f 0.24 (Et_2O); **>95:5 *dr***; $[\alpha]_D^{25}$ −55.9 (*c* = 0.82, $CHCl_3$); **IR** (thin film, cm^{-1}): 3480, 2961, 2252, 1740, 1443, 1262, 1031, 909; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46-7.42 (2H m, Ph), 7.35-7.28 (3H, m, Ph), 5.49 (1H, t, *J* = 6.5 Hz, H6), 4.30 (1H, dd, *J* = 11.5 and 2.5 Hz, H1), 4.07 (1H, dd, *J* = 11.5 and 8.5 Hz, H1), 3.89 (1H, s, O*Me*), 3.71 (1H, dd, *J* = 8.5 and 2.5 Hz, H2), 2.84 (1H, bs, O*H*), 2.41 (1H, bs, O*H*), 2.10 (3H, s, C(O)*Me*), 2.08-2.01 (2H, m, H5), 1.81-1.75 (2H, m, H4), 1.19 (3H, s, H3'); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 171.3, 154.9, 131.8, 128.7, 128.2, 121.9, 86.4, 85.4, 74.6, 72.9, 68.7, 65.6, 55.0, 34.0, 29.1, 21.6, 20.9; **HRMS** (ESI+): calc for $C_{19}H_{24}O_7Na$ $[M+Na]^+$ 387.1414, found 387.1404.

(*R*)-2-hydroxy-2-((2*R*,5*R*)-2-methyl-5-(phenylethynyl)tetrahydrofuran-2-yl)ethyl acetate – (*R*,*R*,*R*)-3.153

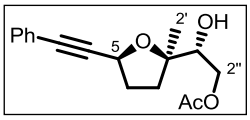


To a degassed solution of carbonate **(*R*,*R*,*R*)-3.147** (20.0 mg, 55 μmol, 1 eq.) and $B(OH)_3$ (1.7 mg, 27 μmol, 0.5 eq.) in 1,4-dioxane (0.25 mL) under argon was added a solution of $Pd(OAc)_2$ (0.6 mg, 5 mol%) and dppf (3.0 mg, 10 mol%) in degassed 1,4-dioxane (0.30 mL). The reaction was heated to 50 °C for 30 minutes and quenched *via* addition of pet. ether (1 mL). The reaction mixture was passed through a plug of silica gel (Et_2O) and the solvent removed *in vacuo* to leave a crude mixture of THF diastereomers (96:4 *dr*, 14.1 mg, 90%). The product was purified by flash chromatography on silica gel (1:4→1:1 Et_2O/pet. ether) to leave pure

trans-THF **(*R*,*R*,*R*)-3.153** (11.8 mg, 41 μmol, 75%) as a colourless oil.

R_f 0.50 (Et_2O); $[\alpha]_D^{25}$ +59.4 (*c* = 0.16, $CHCl_3$); **IR** (thin film, cm^{-1}): 3468, 2976, 2231, 1738, 1491, 1444, 1369, 1238, 1036; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.41 (2H, m, Ph), 7.34-7.29 (3H, m, Ph), 4.87 (1H, t, *J* = 6.5 Hz, H5), 4.26 (1H, dd, *J* = 11.5 and 3.0 Hz, H2''), 4.03 (1H, dd, *J* = 11.5 and 8.5 Hz, H2''), 3.73 (1H, ddd, *J* = 8.5, 4.0 and 3.0 Hz, H1''), 2.59 (1H, d, *J* = 4.0 Hz, O*H*), 2.37-2.30 (1H, m, H4), 2.26-2.16 (1H, m, H4), 2.14-2.06 (1H, m, H3), 2.12 (3H, s, C(O)*Me*), 1.97-1.91 (1H, m, H3), 1.55 (3H, s, H2'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 171.3, 131.7, 128.4, 128.2, 122.6, 88.6, 84.9, 84.8, 75.1, 69.1, 65.5, 34.6, 34.1, 22.5, 21.0; **HRMS** (ESI+): calc for $C_{17}H_{20}O_4Na$ $[M+Na]^+$ 311.1254, found 311.1248.

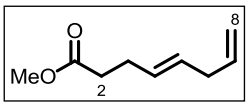
(*R*)-2-hydroxy-2-((2*R*,5*S*)-2-methyl-5-(phenylethynyl)tetrahydrofuran-2-yl)ethyl acetate – (*R*,*R*,*S*)-3.153



To a degassed solution of carbonate **(*R*,*R*,*S*)-3.147** (20.0 mg, 55 μmol, 1 eq.) and $B(OH)_3$ (1.7 mg, 27 μmol, 0.5 eq.) in 1,4-dioxane (0.15 mL) under argon was added a solution of $Pd(OAc)_2$ (0.6 mg, 5 mol%) and dppf (3.0 mg, 10 mol%) in degassed 1,4-dioxane (0.40 mL). The reaction was heated to 50 °C for 30 minutes, and quenched *via* addition of pet. ether (1 mL). The reaction mixture was filtered through a plug of silica gel (Et_2O) and the solvent removed *in vacuo* to leave a crude mixture of THF diastereomers (97:3 ***dr***, 14.0 mg, 89%) as a colourless oil. The product was purified by flash chromatography on silica gel (1:4→1:1 Et_2O/pet. ether) to leave pure *cis*-THF **(*R*,*R*,*S*)-3.153** (12.8 mg, 44 μmol, 80%) as a colourless oil.

R_f 0.19 (1:2 Et_2O/pet. ether); $[\alpha]_D^{25}$ +25.2 (*c* = 0.85, $CHCl_3$); **IR** (thin film, cm^{-1}): 3469, 2972, 2227, 1737, 1491, 1444, 1369, 1236, 1084, 1032; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.30 (2H, m, Ph), 7.34-7.29 (3H, m, Ph), 4.96 (1H, dd, *J* = 7.0 and 4.5 Hz, H5), 4.29 (1H, dd, *J* = 11.5 and 3.0 Hz, H2''), 4.04 (1H, dd, *J* = 11.5 and 8.5 Hz, H2''), 3.89 (1H, ddd, *J* = 8.5, 5.0 and 3.0 Hz, H1''), 2.70 (1H, d, *J* = 5.0 Hz, O*H*), 2.39-2.28 (2H, m, H3 and 4), 2.21-2.15 (1H, m, H4), 2.11 (3H, s, C(O)*Me*), 1.82-1.75 (1H, m, H3), 1.22 (3H, s, H2'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 171.2, 131.7, 128.5, 128.3, 122.4, 88.9, 85.2, 85.1, 75.0, 69.0, 65.6, 34.1, 33.6, 21.8, 21.0; **HRMS** (ESI+): calc for $C_{17}H_{20}O_4Na$ $[M+Na]^+$ 311.1254, found 311.1243.

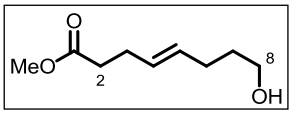
(*E*)-methyl octa-4,7-dienoate – 3.160[264]



To a stirred solution of hexa-1,5-dien-3-ol **3.159** (1.05 g, 10.7 mmol, 1 eq.) in anhydrous *m*-xylene (30 mL) was added trimethyl orthoacetate (8.17 mL, 64.2 mmol, 6 eq.) and propionic acid (40 μL, 5 mol%). The reaction was heated to 135 °C for 20 hours, and the solvent removed *in vacuo*. Water (10 mL) and EtOAc (10 mL) were added, the layers separated and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19 Et_2O/pet. ether) to leave pure skipped diene (1.17 g, 7.59 mmol, 71%) as a pale orange oil.

R_f 0.42 (1:9 Et_2O/pet. ether); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 5.80 (1H, dtt, *J* = 17.0, 10.5 and 6.5 Hz, H7), 5.52-5.42 (2H, m, H4 and 5), 5.04-4.97 (2H, m, H8), 3.67 (3H, s, O*Me*), 2.75-2.72 (2H, m, H6), 2.31-2.41 (4H, m, H2 and 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 173.6, 137.0, 129.3, 129.0, 115.0, 51.5, 36.6, 34.0, 27.8. Data consistent with literature.[264]

(*E*)-methyl 8-hydroxyoct-4-enoate – 3.161

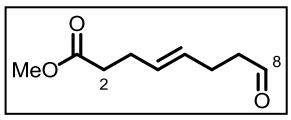


To a stirred solution of diene **3.160** (890 mg, 5.77 mmol, 1 eq.) in anhydrous THF (10 mL) at 0 °C under argon was added 9-BBN (0.5 M in THF, 23.0 mL, 11.5 mmol, 2 eq.) dropwise. The reaction was allowed to warm to RT and stirred for 16 hours. Aqueous phosphate buffer (pH 7, 10 mL) was added and the reaction cooled to 0 °C. A solution of H_2O_2 (30% wt. in H_2O, 3.27 mL, 5 eq.) was added dropwise. The resultant solution was allowed to warm to RT and stirred for a further 2 hours. The reaction was diluted with water (10 mL) and the THF removed *in vacuo*. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were washed sequentially 1N aq. HCl (1 x 50 mL) and sat. aq. $NaHCO_3$ (1 x 50 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→2:1 Et_2O/pet. ether) to leave pure alcohol **3.161** (762 mg, 4.42 mmol, 77%) as a colourless oil.

R_f 0.14 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3385, 2936, 2863, 1739, 1439, 1363, 1173, 1059, 971; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 5.52-5.42 (2H, m, H4 and 5), 3.67 (3H, s, O*Me*), 3.67-3.62 (2H, m, H8), 2.40-2.36 (2H, m, H2), 2.34-2.29 (2H, m, H3), 2.08 (2H, q, *J* = 7.0 Hz, H6), 1.63 (2H, *apt*

quintet, *J* = 7.0 Hz, H7), 1.32 (1H, t, *J* = 5.0 Hz, O*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 173.6, 130.9, 128.7, 62.4, 51.5, 34.0, 32.2, 28.8, 27.8; **HRMS** (ESI+): calc for $C_9H_{16}O_3Na$ $[M+Na]^+$ 195.0992, found 195.0991.

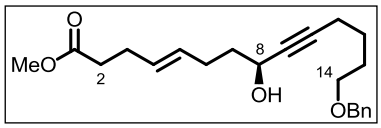
(*E*)-methyl 8-oxooct-4-enoate – 3.162



To a stirred solution of the above alcohol (820 mg, 4.76 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) was added Celite® (1.54 g) and PCC (1.54 g, 7.14 mmol, 1.5 eq.). The reaction was stirred for 2 hours, the reaction mixture passed through a short plug of silica gel (1:1 Et_2O/pet. ether) and the solvent removed *in vacuo* to leave pure aldehyde **3.162** (616 mg, 3.62 mmol, 76%) as a colourless oil.

R_f 0.31 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2953, 2923, 1737, 1731, 1601, 1438, 1255, 1158, 972; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 9.74 (1H, t, *J* = 1.5 Hz, H8), 5.50-5.42 (2H, m, H4 and 5), 3.65 (3H, s, O*Me*), 2.48 (2H, td, *J* = 7.0 and 1.5 Hz, H7), 2.37-2.27 (6H, m, H2, 3 and 6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 202.0, 173.4, 129.5, 129.2, 51.5, 43.3, 33.8, 27.7, 25.0; **HRMS** (FI+): calc for $C_9H_{14}O_3$ $[M]^+$ 170.0943, found 170.0936.

(*S*,*E*)-methyl 14-(benzyloxy)-8-hydroxytetradec-4-en-9-ynoate – (*S*)-3.163

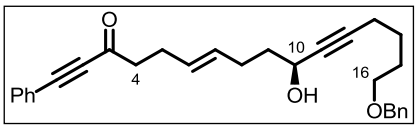


To a flask charged with $Zn(OTf)_2$ (3.42 g, 9.40 mmol, 2.0 eq.) and (−)-*N*-methylephedrine (1.77 g, 9.87 mmol, 2.1 eq.) was added wet toluene (9.4 mL) and Et_3N (1.38 mL, 9.87 mmol, 2.1 eq.). The resulting suspension was stirred vigorously at RT for 2 hours and to it added alkyne **3.48** (1.86 g, 9.87 mmol, 2.1 eq.) in one portion. The resulting mixture was stirred for a further 15 minutes and to it added a solution of aldehyde **3.162** (800 mg, 4.70 mmol, 1 eq.) in toluene (11.8 mL) over *ca.* 16 hours *via* syringe pump. The reaction was stirred for a further 2 hours and quenched with sat. aq. NH_4Cl (25 mL). The mixture was diluted with Et_2O (20 mL), the layers separated and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→2:1 Et_2O/pet. ether) to leave pure alcohol **(*S*)-3.163** (928 mg, 2.59 mmol, 55%) as a colourless oil.

R_f 0.24 (1:1 Et_2O/pet. ether); **89% *ee*** (CHIRALPAK IB, 1.3 mL/min, 5% IPA/hexane): t_R (*R*) =

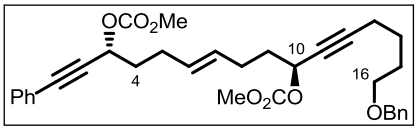
11.14 min, t_R (*S*) = 11.65 min; $[\alpha]_D^{25}$ +7.0 (*c* = 1.04, $CHCl_3$, for 92% ***ee***); **IR** (thin film, cm^{-1}): 3436, 2943, 2858, 2243, 1736, 1437, 1362, 1171, 1094, 969, 912; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.36-7.23 (5H, m, Ph), 5.51-5.42 (2H, m, H4 and 5), 4.50 (2H, s, PhC*H*$_2$O), 4.35-4.30 (1H, m, H8), 3.66 (3H, s, O*Me*), 3.48 (2H, t, *J* = 6.5 Hz, H14), 2.39-2.34 (2H, m, H2), 2.33-2.28 (2H, m, H3), 2.23 (2H, td, *J* = 7.0 and 1.5 Hz, H11), 2.17-2.11 (2H, m, H6), 2.10-2.04 (1H, m, O*H*), 1.76-1.66 (4H, m, H9 and 13), 1.63-1.57 (2H, m, H12); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 173.6, 138.4, 130.5, 128.8, 128.3, 127.5, 127.4, 85.1, 81.3, 72.8, 69.7, 61.9, 51.4, 37.6, 33.9, 28.8, 28.2, 27.8, 25.3, 18.4; **HRMS** (ESI+): calc for $C_{22}H_{30}O_4Na$ $[M+Na]^+$ 381.2036, found 381.2036.

(*S*,*E*)-16-(benzyloxy)-10-hydroxy-1-phenylhexadeca-6-en-1,11-diyn-3-one – (*S*)-3.167



To a stirred solution of phenyl acetylene (1.13 mL, 10.30 mmol, 4 eq.) in anhydrous THF (50 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 4.21 mL, 10.50 mmol, 4.1 eq.). The resulting solution was stirred for 30 minutes at −78 °C and to it added $BF_3{\cdot}OEt_2$ (1.33 mL, 10.80 mmol, 4.2 eq.). The resulting solution was stirred for 10 minutes at −78 °C and to it added a solution of ester **(*S*)-3.163** (920 mg, 2.57 mmol, 1 eq.) in anhydrous THF (10 mL) in one portion. The reaction was stirred and allowed to warm to RT and stirred for 48 hours. The reaction was quenched with sat. aq. NH_4OH/NH_4Cl (1:2 v:v, 50 mL) and the THF removed *in vacuo*. The resulting mixture was diluted with Et_2O (50 mL), the layers separated and the aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and the crude product purified by flash chromatography on silica gel (1:4→1:1 Et_2O/pet. ether) to leave the ketone **(*S*)-3.167** (1.014 g) as a mixture with ester **(*S*)-3.163**. This crude mixture was divided in half and submitted to either hand of Noyori transfer hydrogenation, described below.

(3*R*,10*S*,*E*)-16-(benzyloxy)-1-phenylhexadeca-6-en-1,11-diyne-3,10-diyl dimethyl dicarbonate – (*R*,*S*)-3.169



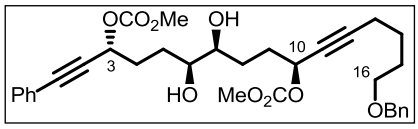
A solution of impure ketone **(*S*)-3.167** (500 mg) in IPA (6 mL) was degassed for 15 minutes. To it was added a solution of [Ru((*R*,*R*)-TsDPEN)(*p*-cymene)] **(*R*,*R*)-3.53** (14.6 mg, *ca.* 2 mol%) in anhydrous CH_2Cl_2 (0.2 mL). The reaction was degassed for a further 15 minutes and stirred under argon for 20 hours. The solvent

was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→2:1 Et_2O/pet. ether) to leave pure diol **(*R*,*S*)-3.168** (267 mg, 0.69 mmol, 48%, *2 steps*, 93:7 *dr*, >99% *ee*) as a yellow oil which was used directly in the next step without further characterisation.

To a stirred solution of diol **(*R*,*S*)-3.168** (260 mg, 0.604 mmol, 1 eq.) and pyridine (0.78 mL, 9.66 mmol, 16 eq.) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under argon was added methyl chloroformate (0.28 mL, 3.62 mmol, 6 eq.). The reaction was stirred for 30 minutes at 0 °C and quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with 1N aq. HCl (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave pure *bis*-carbonate **(*R*,*S*)-3.169** (298 mg, 0.545 mmol, 90%) as a colourless oil.

R_f 0.18 (1:2 Et_2O/pet. ether); **$[\alpha]_D^{25}$** +12.5 (*c* = 0.34, $CHCl_3$); **IR** (thin film, cm^{-1}): 2953, 2855, 2238, 1750, 1491, 1442, 1262, 1106, 941; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.47-7.43 (2H, m, Ph), 7.37-7.27 (8H, m, Ph), 5.52-5.44 (2H, m, H6 and 7), 5.46 (1H, t, *J* = 6.5 Hz, H3), 5.21 (1H, tt, *J* = 6.5 and 1.5 Hz, H10), 4.50 (2H, s, PhC*H*$_2$O), 3.83 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 3.49 (2H, t, *J* = 6.0 Hz, H16), 2.25 (2H, td, *J* = 7.0 and 1.5 Hz, H13), 2.26-2.21 (2H, m, H5), 2.19-2.14 (2H, m, H8), 2.03-1.92 (2H, m, H4), 1.91-1.78 (2H, m, H9), 1.74-1.68 (2H, m, H15), 1.65-1.59 (2H, m, H14); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 155.0, 138.5, 131.9, 129.8, 129.5, 128.7, 128.3, 128.2, 127.6, 127.5, 122.1, 87.1, 86.3, 85.6, 76.8, 72.8, 69.7, 68.1 (C3 and 10), 54.9, 54.8, 34.8, 34.6, 28.8, 28.0 (C5 and 8), 25.2, 18.5; **HRMS** (ESI+): calc for $C_{33}H_{38}O_7Na$ $[M+Na]^+$ 569.2510, found 569.2504.

(3*R*,6*S*,7*S*,10*S*)-16-(benzyloxy)-6,7-dihydroxy-1-phenylhexadeca-1,11-diyne-3,10-diyl dimethyl dicarbonate - (*R*,*S*,*S*,*S*)-3.170

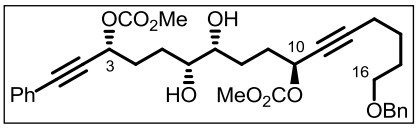


To a stirred solution of *bis*-carbonate **(*R*,*S*)-3.169** (145 mg, 0.265 mmol, 1 eq.) and methanesulfonamide (25 mg, 0.265 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 2.7 mL) at 0 °C was added AD-mix-α (371 mg, 1.4 g/mmol). The resultant suspension was stirred vigorously for 48 hours at 0 °C and quenched with addition of solid Na_2SO_3 (400 mg). The mixture was diluted with EtOAc (5 mL) and water (5 mL), the layers separated and the aqueous layer extracted with EtOAc (5 x 5 mL). The combined organic layers

were washed with 1N aq. HCl (5 x 5 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→2:1 EtOAc/pet. ether) to leave pure diol **(*R*,*S*,*S*,*S*)-3.170** (131 mg, 2.26 mmol, 85%, 94:6 *dr*) as a colourless oil.

R_f 0.17 (1:2 EtOAc/pet. ether); $[\alpha]_D^{25}$ +6.8 (*c* = 0.97, $CHCl_3$); **IR** (thin film, cm^{-1}): 3432, 2954, 2863, 2236, 1749, 1491, 1443, 1262, 942; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.42 (2H, m, Ph), 7.37-7.26 (8H, m, Ph), 5.50 (1H, t, *J* = 6.5 Hz, H3), 5.28 (1H, tt, *J* = 6.0 and 2.0 Hz, H10), 4.50 (2H, s, PhC*H*$_2$O), 3.82 (3H, s, O*Me*), 3.78 (3H, s, O*Me*), 3.48 (2H, t, *J* = 6.5 Hz, H16), 3.49-3.43 (2H, m, H6 and 7), 2.48 (1H, bs, O*H*), 2.38 (1H, bs, O*H*), 2.23 (2H, td, *J* = 7.0 and 2.0 Hz, H13), 2.15-2.07 (1H, m, H4), 2.04-1.95 (2H, m, H4 and 9), 1.92-1.84 (1H, m, H9), 1.79-1.56 (8H, m, H5, 8, 14 and 15); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 154.9, 138.3, 131.8, 128.7, 128.3, 128.2, 127.6, 127.5, 121.9, 87.3, 86.4, 85.4, 77.0, 73.7, 73.7, 72.8, 69.7, 68.5, 68.4, 55.0, 54.8, 31.2, 31.2, 28.9, 28.8, 28.7, 25.0, 18.4; **HRMS** (ESI+): calc for $C_{33}H_{40}O_9Na$ $[M+Na]^+$ 603.2565, found 603.2652.

(3*R*,6*R*,7*R*,10*S*)-16-(benzyloxy)-6,7-dihydroxy-1-phenylhexadeca-1,11-diyne-3,10-diyl dimethyl dicarbonate - (*R*,*R*,*R*,*S*)-3.170

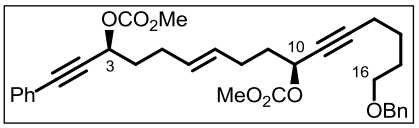


To a stirred solution of *bis*-carbonate **(*R*,*S*)-3.169** (145 mg, 0.265 mmol, 1 eq.) and methanesulfonamide (25 mg, 0.265 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 2.7 mL) at 0 °C was added AD-mix-β (371 mg, 1.4 g/mmol). The resultant suspension was stirred vigorously for 48 hours at 0 °C and quenched with addition of solid Na_2SO_3 (400 mg). The mixture was diluted with EtOAc (5 mL) and water (5 mL), the layers separated and the aqueous layer extracted with EtOAc (5 x 5 mL). The combined organic layers were washed with 1N aq. HCl (5 x 5 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (EtOAc/pet. ether 1:4→2:1) to leave pure diol **(*R*,*R*,*R*,*S*)-3.170** (124 mg, 0.214 mmol, 81%, 93:7 *dr*) as a colourless oil.

R_f 0.17 (1:2 EtOAc/pet. ether); $[\alpha]_D^{25}$ +23.0 (*c* = 0.77, $CHCl_3$); **IR** (thin film, cm^{-1}): 3449, 2954, 2864, 2237, 1749, 1443, 1354, 1264, 1105, 941; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.43 (2H, m, Ph), 7.37-7.27 (8H, m, Ph), 5.53 (1H, t, *J* = 6.5 Hz, H3), 5.27 (1H, tt, *J* = 6.5 and 2.0 Hz, H10), 4.50 (2H, s, PhC*H*$_2$O), 3.83 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 3.48 (2H, t, *J* = 6.5 Hz, H16), 3.49-3.44 (2H, m, H6 and 7), 2.30 (2H, d, *J* = 5.5 Hz, 2 x O*H*), 2.24 (2H, td, *J* = 7.0 and 2.0 Hz, H13), 2.17-2.09 (1H, m,

H4), 2.05-1.95 (2H, m, H4 and 9), 1.94-1.86 (1H, m, H9), 1.79-1.56 (8H, m, H5, 8, 14 and 15); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 155.0, 138.4, 131.9, 128.8, 128.4, 128.3, 127.7, 127.6, 122.0, 87.4, 86.5, 85.4, 77.2, 73.8, 73.7, 72.9, 69.8, 68.4 (C3 and 10), 55.0, 54.9, 31.3, 31.2, 29.0, 28.8, 28.8, 25.1, 18.5; **HRMS** (ESI+): calc for $C_{33}H_{40}O_9Na$ $[M+Na]^+$ 603.2565, found 603.2565.

(3*S*,10*S*,*E*)-16-(benzyloxy)-1-phenylhexadeca-6-en-1,11-diyne-3,10-diyl dimethyl dicarbonate – (*S*,*S*)-3.169



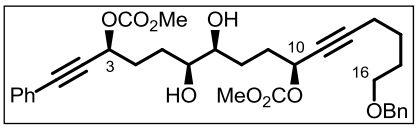
A solution of impure ketone **(*S*)-3.167** (500 mg) in IPA (6 mL) was degassed for 15 minutes. To it was added a solution of [Ru((*S*,*S*)-TsDPEN)(*p*-cymene)] **(*S*,*S*)-3.53** (14.6 mg, *ca.* 2 mol%) in anhydrous CH_2Cl_2 (0.2 mL). The reaction was degassed for a further 15 minutes and stirred under argon for 20 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→2:1 Et_2O/pet. ether) to leave pure diol **(*S*,*S*)-3.168** (250 mg, 0.581 mmol, 45%, *2 steps*, 94:6 *dr*, >99% *ee*) as a pale yellow oil which was used directly in the next step without further characetrisation.

To a stirred solution of diol **(*S*,*S*)-3.168** (250 mg, 0.581 mmol, 1 eq.) and pyridine (0.75 mL, 9.30 mmol, 16 eq.) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under argon was added methyl chloroformate (0.27 mL, 3.48 mmol, 6 eq.). The reaction was stirred for 30 minutes at 0 °C and quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with 1N aq. HCl (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave pure *bis*-carbonate **(*S*,*S*)-3.169** (297 mg, 0.543 mmol, 93%) as a colourless oil.

R_f 0.18 (1:2 Et_2O/pet. ether); **$[\alpha]_D^{25}$** −49.8 (*c* = 0.41, $CHCl_3$); **IR** (thin film, cm^{-1}): 2953, 2854, 2236, 1750, 1491, 1442, 1262, 1106, 1028, 942; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.47-7.43 (2H, m, Ph), 7.37-7.27 (8H, m, Ph), 5.52-5.44 (2H, m, H6 and 7), 5.46 (1H, t, *J* = 6.5 Hz, H3), 5.21 (1H, tt, *J* = 6.5 and 1.5 Hz, H10), 4.50 (2H, s, PhC*H*$_2$O), 3.83 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 3.49 (2H, t, *J* = 6.0 Hz, H16), 2.25 (2H, td, *J* = 7.0 and 1.5 Hz, H13), 2.26-2.21 (2H, m, H5), 2.19-2.14 (2H, m, H8), 2.03-1.92 (2H, m, H4), 1.91-1.78 (2H, m, H9), 1.74-1.68 (2H, m, H15), 1.65-1.59 (2H, m, H14); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 155.0, 138.5, 131.9, 129.8, 129.5, 128.7, 128.3, 128.2, 127.6, 127.5,

122.1, 87.1, 86.3, 85.6, 76.8, 72.8, 69.7, 68.1 (C3 and 10), 54.9, 54.8, 34.8, 34.6, 28.8, 28.0 (C5 and 8), 25.2, 18.5; **HRMS** (ESI+): calc for $C_{33}H_{38}O_7Na$ $[M+Na]^+$ 569.2510, found 569.2510.

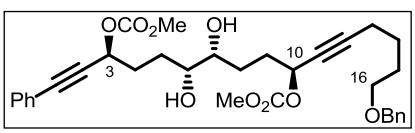
(3*S*,6*S*,7*S*,10*S*)-16-(benzyloxy)-6,7-dihydroxy-1-phenylhexadeca-1,11-diyne-3,10-diyl dimethyl dicarbonate - (*S*,*S*,*S*,*S*)-3.170



To a stirred solution of *bis*-carbonate **(*S*,*S*)-3.169** (145 mg, 0.265 mmol, 1 eq.) and methanesulfonamide (25 mg, 0.265 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 2.7 mL) at 0 °C was added AD-mix-α (371 mg, 1.4 g/mmol). The resultant suspension was stirred vigorously for 48 hours at 0 °C and quenched with addition of solid Na_2SO_3 (400 mg). The mixture was diluted with EtOAc (5 mL) and water (5 mL), the layers separated and the aqueous layer extracted with EtOAc (5 x 5 mL). The combined organic layers were washed with 1N aq. HCl (5 x 5 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→2:1 EtOAc/pet. ether) to leave pure diol **(*S*,*S*,*S*,*S*)-3.170** (115 mg, 0.198 mmol, 75%, 92:8 *dr*) as a colourless oil.

R_f 0.15 (1:2 EtOAc/pet. ether); $[\alpha]_D^{25}$ –84.6 (*c* = 0.96, $CHCl_3$); **IR** (thin film, cm^{-1}): 3428, 2954, 2863, 2235, 1748, 1491, 1443, 1262, 940; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.43 (2H, m, Ph), 7.37-7.27 (8H, m, Ph), 5.53 (1H, t, *J* = 6.5 Hz, H3), 5.29 (1H, tt, *J* = 6.5 and, 2.0 Hz, H10), 4.50 (2H, s, PhC*H*$_2$O), 3.82 (3H, s, O*Me*), 3.78 (3H, s, O*Me*), 3.48 (2H, t, *J* = 6.5 Hz, H16), 3.49-3.44 (2H, m, H6 and 7), 2.36 (1H, d, *J* = 5.5 Hz, O*H*), 2.28 (1H, d, *J* = 5.5 Hz, O*H*), 2.24 (2H, td, *J* = 7.0 and 2.0 Hz, H13), 2.16-2.09 (1H, m, H4), 2.05-1.94 (2H, m, H4 and 9), 1.92-1.85 (1H, m, H9), 1.78-1.63 (6H, m, H5, 8 and 15), 1.63-1.56 (2H, m, H14); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0 (2x*C*=O), 138.4, 131.9, 128.7, 128.4, 128.2, 127.6, 127.6, 122.0, 87.3, 86.4, 85.4, 77.0, 73.7, 73.6, 72.9, 69.7, 68.4 (C3 and 10), 55.0, 54.8, 31.2, 31.2, 28.9, 28.8, 28.7, 25.0, 18.5; **HRMS** (ESI+): calc for $C_{33}H_{40}O_9Na$ $[M+Na]^+$ 603.2565, found 603.2566.

(3*S*,6*R*,7*R*,10*S*)-16-(benzyloxy)-6,7-dihydroxy-1-phenylhexadeca-1,11-diyne-3,10-diyl dimethyl dicarbonate - (*S*,*R*,*R*,*S*)-3.170

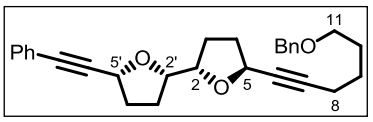


To a stirred solution of *bis*-carbonate **(*S*,*S*)-3.169** (145 mg, 0.265 mmol, 1 eq.) and methanesulfonamide (25 mg, 0.265 mmol, 1 eq.) in *t*-BuOH/H_2O (1:1 v:v, 2.7 mL) at 0 °C was added AD-mix-β (371 mg,

1.4 g/mmol). The resultant suspension was stirred vigorously for 48 hours at 0 °C and quenched with addition of solid Na_2SO_3 (400 mg). The mixture was diluted with EtOAc (5 mL) and water (5 mL), the layers separated and the aqueous layer extracted with EtOAc (5 x 5 mL). The combined organic layers were washed with 1N aq. HCl (5 x 5 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→2:1 EtOAc/pet. ether) to leave pure diol **(*S*,*R*,*R*,*S*)-3.170** (124 mg, 0.214 mmol, 81%, 93:7 *dr*) as a colourless oil.

R_f 0.15 (1:2 EtOAc/pet. ether); $[\alpha]_D^{25}$ –57.8 (*c* = 1.10, $CHCl_3$); **IR** (thin film, cm^{-1}): 3425, 2954, 2863, 2237, 1749, 1491, 1443, 1263, 944; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.43 (2H, m, Ph), 7.37-7.26 (8H, m, Ph), 5.51 (1H, t, *J* = 6.5 Hz, H3), 5.26 (1H, tt, *J* = 6.5 and 2.0 Hz, H10), 4.50 (2H, s, PhC*H*$_2$O), 3.82 (3H, s, O*Me*), 3.78 (3H, s, O*Me*), 3.48 (2H, t, *J* = 6.5 Hz, H16), 3.49-3.43 (2H, m, H6 and 7), 2.40 (1H, d, *J* = 5.0 Hz, O*H*), 2.37 (1H, d, *J* = 5.0 Hz, O*H*), 2.23 (2H, td, *J* = 7.0 and 2.0 Hz, H13), 2.16-2.08 (1H, m, H4), 2.04-1.96 (2H, m, H4 and 9), 1.93-1.86 (1H, m, H9), 1.79-1.56 (8H, m, H5, 8, 14 and 15); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0 (2x*C*=O), 138.4, 131.8, 128.7, 128.3, 128.2, 127.6, 127.5, 121.9, 87.3, 86.4, 85.4, 76.8, 73.7, 73.7, 72.9, 69.7, 68.5, 68.4, 55.0, 54.8, 31.3, 31.2, 28.9, 28.9, 28.7, 25.0, 18.4; **HRMS** (ESI+): calc for $C_{33}H_{40}O_9Na$ $[M+Na]^+$ 603.2565, found 603.2650.

(2*S*,2'*S*,5*S*,5'*R*)-5-(6-(benzyloxy)hex-1-yn-1-yl)-5'-(phenylethynyl)octahydro-2,2'-bifuran – (*S*,*S*,*S*,*R*)-3.171

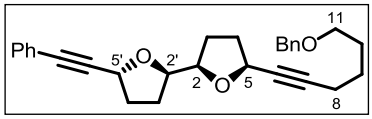


To a degassed solution of diol **(*R*,*S*,*S*,*S*)-3.170** (20.0 mg, 34.4 μmol, 1 eq.) and $B(OH)_3$ (1.1 mg, 17.2 μmol, 0.5 eq.) in 1,4-dioxane (0.15 mL) under argon was added a solution of $Pd(OAc)_2$ (0.4 mg, 5 mol%) and dppf (1.9 mg, 10 mol%) in degassed 1,4-dioxane (0.2 mL). The reaction was stirred and heated to 75 °C for 16 hours. The reaction was quenched with pet. ether (1 mL) and filtered through a short plug of silica gel (Et_2O). The crude product was purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave pure bifuran **(*S*,*S*,*S*,*R*)-3.171** (10.7 mg, 25.0 μmol, 73%) as a colourless oil.

R_f 0.17 (1:4 Et_2O/pet. ether); **>95:5 *dr***; $[\alpha]_D^{25}$ –2.7 (*c* = 0.15, $CHCl_3$); **IR** (thin film, cm^{-1}): 2942, 2865, 2236, 1599, 1491, 1454, 1443, 1357, 1104, 1045; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph), 7.37-7.32 (4H, m, Ph), 7.31-7.27 (4H, m, Ph), 4.81 (1H, *apt* t, *J* = 6.5 Hz, H5'), 4.78 (1H, tt, *J* = 6.5 and 2.0 Hz, H5), 4.50 (2H, s, PhC*H*$_2$O), 4.20 (1H, td, *J* = 7.0 and 5.0 Hz, H2), 3.93 (1H, td, *J* = 7.0

and 5.0 Hz, H2'), 3.48 (2H, t, *J* = 6.5 Hz, H11), 2.28-2.16 (3H, m, H4 and 4'), 2.20 (2H, td, *J* = 7.0 and 2.0 Hz, H8), 2.15-2.08 (1H, m, H3), 2.06-1.89 (3H, m, H3' and 4'), 1.85-1.78 (1H, m, H3), 1.73-1.67 (2H, m, H10), 1.62-1.57 (2H, m, H9); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 138.6, 131.7, 128.3, 128.2, 127.6, 127.5, 123.0, 89.3, 84.7, 84.3, 82.2, 80.6, 80.3, 72.8, 69.8, 69.2, 69.1, 33.8, 33.6, 28.9, 27.9, 27.8, 25.3, 18.6; **HRMS** (ESI+): calc for $C_{29}H_{32}O_3Na$ [M+Na$^+$] 451.2244, found 451.2245.

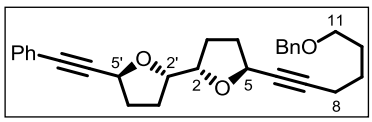
(2*R*,2'*R*,5*S*,5'*R*)-5-(6-(benzyloxy)hex-1-yn-1-yl)-5'-(phenylethynyl)octahydro-2,2'-bifuran – (*R*,*R*,*S*,*R*)-3.171



To a degassed solution of diol **(*R*,*R*,*S*,*R*)-3.170** (20.0 mg, 34.4 μmol, 1 eq.) and $B(OH)_3$ (1.1 mg, 17.2 μmol, 0.5 eq.) in 1,4-dioxane (0.15 mL) under argon was added a solution of $Pd(OAc)_2$ (0.4 mg, 5 mol%) and dppf (1.9 mg, 10 mol%) in degassed 1,4-dioxane (0.2 mL). The reaction was stirred and heated to 75 °C for 16 hours. The reaction was quenched with pet. ether (1 mL) and filtered through a short plug of silica gel (Et_2O). The crude product was purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave pure bifuran **(*R*,*R*,*S*,*R*)-3.171** (12.2 mg, 28.5 μmol, 82%) as a colourless oil.

R_f 0.21 (1:4 Et_2O/pet. ether); **>95:5 *dr***; **$[\alpha]_D^{25}$** +10.0 (*c* = 0.17, $CHCl_3$); **IR** (thin film, cm^{-1}): 2943, 2865, 2235, 1599, 1491, 1454, 1443, 1357, 1104, 1045; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.44-7.40 (2H, m, Ph), 7.36-7.31 (4H, m, Ph), 7.31-7.26 (4H, m, Ph), 4.99 (1H, t, *J* = 6.5 Hz, H5'), 4.57 (1H, tt, *J* = 6.5 and 2.0 Hz, H5), 4.48 (2H, s, PhC*H*$_2$O), 4.23 (1H, td, *J* = 7.0 and 5.0 Hz, H2'), 3.88 (1H, td, *J* = 7.0 and 5.0 Hz, H2), 3.48 (2H, t, *J* = 6.5 Hz, H11), 2.37-2.30 (1H, m, H4'), 2.24 (2H, td, *J* = 7.0 and 2.0 Hz, H8), 2.20-1.98 (4H, m, H3', 4 and 4'), 1.96-1.91 (2H, m, H3), 1.87-1.79 (1H, m, H3'), 1.75-1.69 (2H, m, H10), 1.64-1.58 (2H, m, H9); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 138.6, 131.7, 128.3, 128.2, 128.1, 127.6, 127.5, 122.9, 89.2, 84.8, 84.3, 81.9, 80.9, 80.3, 72.8, 69.8, 69.2, 69.1, 33.7, 33.7, 28.9, 27.8, 27.8, 25.3, 18.6; **HRMS** (ESI+): calc for $C_{29}H_{32}O_3Na$ [M+Na]$^+$ 451.2244, found 451.2235.

(2*S*,2'*S*,5*S*,5'*S*)-5-(6-(benzyloxy)hex-1-yn-1-yl)-5'-(phenylethynyl)octahydro-2,2'-bifuran – (*S*,*S*,*S*,*S*)-3.171

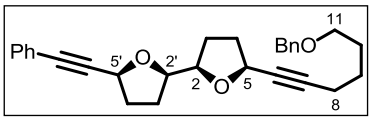


To a degassed solution of diol **(*S*,*S*,*S*,*S*)-3.170** (20.0 mg, 34.4 μmol, 1 eq.) and $B(OH)_3$ (1.1 mg, 17.2 μmol, 0.5 eq.) in 1,4-dioxane (0.15 mL) under argon was added a solution of $Pd(OAc)_2$ (0.4 mg, 5 mol%) and dppf (1.9 mg,

10 mol%) in degassed 1,4-dioxane (0.2 mL). The reaction was stirred and heated to 75 °C for 16 hours. The reaction was quenched with pet. ether (1 mL) and filtered through a short plug of silica gel (Et_2O). The crude product was purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave pure bifuran **(*S,S,S,S*)-3.171** (10.4 mg, 24.3 μmol, 71%) as a colourless oil.

R_f 0.16 (1:4 Et_2O/pet. ether); **>95:5 *dr***; **$[\alpha]_D^{25}$** –69.1 (*c* = 0.43, $CHCl_3$); **IR** (thin film, cm^{-1}): 2945, 2865, 2230, 1599, 1491, 1454, 1359, 1334, 1104, 1048, 952; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph), 7.36-7.33 (4H, m, Ph), 7.31-7.28 (4H, m, Ph), 4.90 (1H, t, *J* = 6.5 Hz, H5'), 4.68 (1H, tt, *J* = 6.5 and 2.0 Hz, H5), 4.51 (2H, s, PhCH_2O), 4.16-4.08 (2H, m, H2 and 2'), 3.50 (2H, t, *J* = 6.5 Hz, H11), 2.36-2.30 (1H, m, H4'), 2.24 (2H, td, *J* = 7.0 and 2.0 Hz, H8), 2.25-2.19 (1H, m, H4), 2.17-2.03 (3H, m, H3, 3' and H4'), 1.96-1.85 (3H, m, H3, 3' and H4), 1.75-1.69 (2H, m, H10), 1.64-1.58 (2H, m, H9); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 138.6, 131.7, 128.4, 128.2, 128.2, 127.6, 127.5, 122.9, 89.1, 84.9, 84.4, 80.8, 80.5, 80.2, 72.9, 69.8, 69.2, 69.1, 34.0, 33.8, 28.9, 27.9, 27.9, 25.3, 18.6; **HRMS** (ESI+): calc for $C_{29}H_{32}O_3Na$ $[M+Na]^+$ 451.2244, found 451.2235.

(2*R*,2'*R*,5*S*,5'*S*)-5-(6-(Benzyloxy)hex-1-yn-1-yl)-5'-(phenylethynyl)octahydro-2,2'-bifuran – (*R,R,S,S*)-3.171

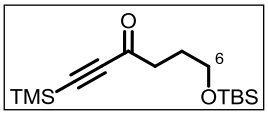


To a degassed solution of diol **(*S,R,R,S*)-3.170** (20.0 mg, 34.4 μmol, 1 eq.) and $B(OH)_3$ (1.1 mg, 17.2 μmol, 0.5 eq.) in 1,4-dioxane (0.15 mL) under argon was added a solution of $Pd(OAc)_2$ (0.4 mg, 5 mol%) and dppf (1.9 mg, 10 mol%) in degassed 1,4-dioxane (0.2 mL). The reaction was stirred and heated to 75 °C for 16 hours. The reaction was quenched with pet. ether (1 mL) and filtered through a short plug of silica gel (Et_2O). The crude product was purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave pure bifuran **(*R,R,S,S*)-3.171** (12.0 mg, 28.0 μmol, 81%) as a colourless oil.

R_f 0.27 (1:9 Et_2O/pet. ether); **>95:5 *dr***; **$[\alpha]_D^{25}$** –40.9 (*c* = 1.17, $CHCl_3$); **IR** (thin film, cm^{-1}): 2942, 2865, 2237, 1599, 1491, 1454, 1358, 1105, 1044; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.43-7.40 (2H, m, Ph), 7.37-7.33 (4H, m, Ph), 7.31-7.27 (4H, m, Ph), 4.83 (1H, dd, *J* = 7.0 and 5.0 Hz, H5'), 4.59 (1H, ddt, *J* = 7.0, 5.5 and 2.0 Hz, H5), 4.50 (2H, s, PhCH_2O), 4.06-3.97 (2H, m, H2 and 2'), 3.48 (2H, t, *J* = 6.5 Hz, H11), 2.28-2.19 (1H, m, H4'), 2.20 (2H, td, *J* = 7.0 and 2.0 Hz, H8), 2.16-2.09 (2H, m, H4 and 4'), 2.05-1.94 (3H, m, H3, 3' and 4), 1.87-1.75 (2H, m, H3 and 3'), 1.73-1.67 (2H, m, H10), 1.61-1.55

(2H, m, H9); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 138.6, 131.6, 128.3, 128.1, 128.1, 127.6, 127.5, 123.0, 89.4, 84.8, 84.4, 82.7, 82.4, 80.4, 72.8, 69.8, 69.1, 69.0, 33.6, 33.5, 28.9, 27.6, 27.5, 25.3, 18.6; **HRMS** (ESI+): calc for $C_{29}H_{32}O_3Na$ $[M+Na]^+$ 451.2244, found 451.2237.

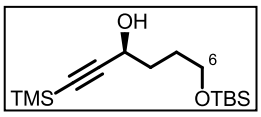
6-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)hex-1-yn-3-one – 2.59b.1[256]



To a stirred solution of ketone **2.59b** (2.16 g, 11.7 mmol, 1 eq.), imidazole (953 mg, 14.0 mmol, 1.2 eq.) and DMAP (208 mg, 10 mol%) in anhydrous CH_2Cl_2 (75 mL) at 0 °C under argon was added TBSCl (1.94 g, 12.9 mmol, 1.1 eq.). The reaction was stirred at 0 °C for 1 hour, allowed to warm to RT and stirred for a further 1 hour. The reaction was quenched with sat. aq. $NaHCO_3$ solution (50 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with 1N aq. HCl (50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:9 Et_2O/pet. ether) to leave pure silyloxy ketone **2.59b.1** (3.13 g, 10.5 mmol, 90%) as a colourless oil.

R_f 0.67 (1:4 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.64 (2H, t, *J* = 6.0 Hz, H6), 2.64 (2H, t, *J* = 7.0 Hz, H4), 1.88 (2H, *apt* quintet, *J* = 6.5 Hz, H5), 0.90 (9H, s, Si*t-Bu*), 0.25 (9H, s, Si*Me*$_3$), 0.05 (6H, s, Si*Me*$_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ_C 187.7, 102.0, 97.6, 61.8, 41.9, 27.0, 25.9, 18.3, −0.8, −5.4. Data consistent with literature.[256]

(*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)hex-1-yn-3-ol – (*S*)-3.75b[265]

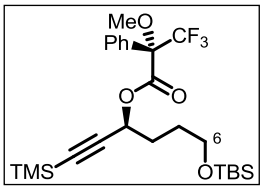


A solution of ketone **2.59b.1** (3.12 g, 10.45 mmol, 1 eq.) in IPA (52 mL) was bubble degassed with argon for 20 minutes. To it was added a solution of [Ru((*S*,*S*)-TsDPEN)(*p*-cymene)] **(*S*,*S*)-3.53** (62.6 mg, 1 mol%) in anhydrous CH_2Cl_2 (1 mL). The resulting solution was bubble degassed with argon for a further 10 minutes and stirred for 20 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave pure alcohol **(*S*)-3.75b** (2.93 g, 9.74 mmol, 93%) as a colourless oil.

R_f 0.22 (1:9 Et_2O/pet. ether); **98% *ee*** (see below); **$[\alpha]_D^{25}$** −9.4 (*c* = 1.00, $CHCl_3$); **IR** (thin film, cm^{-1}): 3418, 2957, 2858, 2172, 1472, 1251, 1099, 840; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 4.43 (1H, td, *J* = 6.5

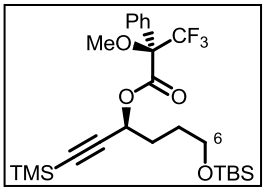
and 6.0 Hz, H3), 3.74-3.64 (2H, m, H6), 3.22 (1H, d, *J* = 6.0 Hz, O*H*), 1.89-1.77 (3H, m, H4 and 5), 1.73-1.64 (1H, m, H4), 0.92 (9H, s, Si*t-Bu*), 0.17 (9H, s, Si*Me*$_3$), 0.09 (3H, s, Si*Me*), 0.09 (3H, s, Si*Me*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 107.0, 89.1, 63.4, 62.7, 35.5, 28.7, 26.1, 18.5, 0.1, −5.2, −5.2; **HRMS** (ESI+): calc for $C_{15}H_{32}O_2Si_2Na$ $[M+Na]^+$ 323.1833, found 323.1828.

Enantiomeric excess was determined by preparation of the Mosher's ester derivatives **(*S,S*)-3.75b.1** and **(*R,S*)-3.75b.1** and integration of their ^{19}F NMR spectra. This indicated a complementary 99:1 *dr*, corresponding to 98% *ee*. **^{19}F NMR** (377 MHz, $CDCl_3$): δ_F −71.5 (s, 99.2%), −71.9 (s, 0.8%).



(*S*)-(*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)hex-1-yn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate – (*S,S*)-3.75b.1

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.59-7.54 (2H, m, Ph), 7.43-7.37 (3H, m, Ph), 5.61 (1H, t, *J* = 6.5 Hz, H3), 3.61-3.58 (5H, m, H6 and O*Me*), 1.89-1.83 (2H, m, H4), 1.65-1.52 (2H, m, H5), 0.89 (9H, s, Si*t-Bu*), 0.18 (9H, s, Si*Me*$_3$), 0.04 (6H, s, Si*Me*$_2$); **^{19}F NMR** ($CDCl_3$, 377 MHz): δ_F −71.5 (s, 99%), −71.9 (s, 1%).



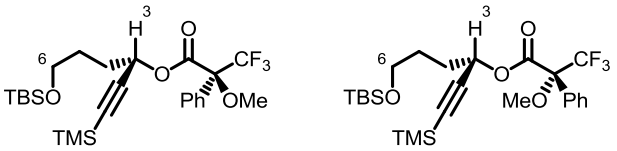
(*R*)-(*S*)-6-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)hex-1-yn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate - (*R,S*)-3.75b.1

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.56-7.53 (2H, m, Ph), 7.43-7.35 (3H, m, Ph), 5.57 (1H, t, *J* = 6.5 Hz, H3), 3.65 (2H, t, *J* = 6.0 Hz, H6), 3.56 (3H, s, O*Me*), 1.95-1.89 (2H, m, H4), 1.72-1.64 (2H, m, H5), 0.89 (9H, s, Si*t-Bu*), 0.16 (9H, s, Si*Me*$_3$), 0.05 (6H, s, Si*Me*$_2$); **^{19}F NMR** ($CDCl_3$, 377 MHz): δ_F −71.5 (s, 1%), −71.9 (s, 99%).

H	**δ_H (*S,S*)-3.75b.1**	**δ_H (*R,S*)-3.75b.1**	**δ ($\delta_S - \delta_R$)**
3	5.62	5.57	+0.05
4	1.86	1.92	−0.06
5	1.59	1.68	−0.09
6	3.60	3.65	−0.05

Table 6.3

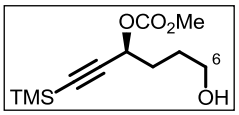
Relative shielding of the alkyl protons in **(*S,S*)-3.75b.1** by the phenyl group suggests assignment of the alcohol as (*S*) when **(*S,S*)-3.75c.1** and **(*R,S*)-3.75c.1** are assumed to be in the conformations shown in *Figure 6.3*.[154]



(*S*,*S*)-3.75c.1 **(*R*,*S*)-3.75c.1**

Figure 6.3

(*S*)-6-hydroxy-1-(trimethylsilyl)hex-1-yn-3-yl methyl carbonate - (*S*)-3.76b

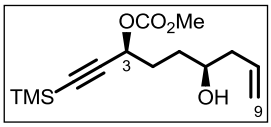


To a stirred solution of alcohol **(*S*)-3.75b** (2.90 g, 9.65 mmol, 1 eq.) and pyridine (6.24 mL, 77.2 mmol, 8 eq.) in anhydrous CH_2Cl_2 (100 mL) at 0 °C under argon was added methyl chloroformate (2.24 mL, 28.9 mmol, 3 eq.). The reaction was stirred for 1 hour and quenched with sat. aq. $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with 1N aq. HCl (2 x 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave the crude carbonate which was used directly in the next step without further purification.

The above crude carbonate was taken up in MeOH (100 mL) and to it added a catalytic amount of CSA. The reaction was stirred for 30 minutes and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2→2:1 Et_2O/pet. ether) to leave pure carbonate **(*S*)-3.76b** (2.31 g, 9.45 mmol, 98%, *2 steps*) as a colourless oil.

R_f 0.06 (1:9 Et_2O/pet. ether); $[\alpha]_D^{25}$ –98.6 (*c* = 1.13, $CHCl_3$); **IR** (thin film, cm^{-1}): 3375, 2960, 2180, 1754, 1444, 1267, 1056, 972, 846; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.29 (1H, t, *J* = 6.5 Hz, H3), 3.80 (3H, s, O*Me*), 3.72-3.63 (2H, m, H6), 1.94-1.87 (2H, m, H4), 1.78-1.70 (2H, m, H5), 1.48 (1H, bs, O*H*), 0.17 (9H, s, Si*Me*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 155.0, 101.6, 91.9, 68.3, 62.3, 55.1, 31.5, 28.1, −0.1; **HRMS** (ESI+): calc for $C_{11}H_{20}O_4SiNa$ $[M+Na]^+$ 267.1023, found 267.1021.

(3*S*,6*S*)-6-hydroxy-1-(trimethylsilyl)non-8-en-1-yn-3-yl methyl carbonate - (*S*,*S*)-3.126b



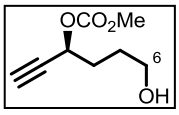
To a stirred solution of carbonate **(*S*)-3.76b** (500 mg, 2.05 mmol, 1 eq.), Et_3N (2.00 mL, 14.4 mmol, 7 eq.) and DMSO (1.38 mL, 19.5 mmol, 9.5 eq.) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under argon was added SO_3·pyridine complex (977 mg, 6.14 mmol, 3 eq.) portionwise. The reaction was stirred at 0 °C for 30 minutes, allowed to warm to RT and stirred for a further 1.5 hours. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL). The combined organic

layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:3→1:2 Et_2O/pet. ether) to leave pure aldehyde (445 mg, 1.84 mmol, 90%) as a colourless oil which was used directly in the next step without further characterisation.

To a vigorously stirred solution of the above aldehyde (440 mg, 1.82 mmol, 1 eq.) in anhydrous CH_2Cl_2 (12 mL) at 0 °C under argon was added a solution of Leighton's reagent **(*S*,*S*)-3.64** (0.38 M in CH_2Cl_2, 5.70 mL, 2.18 mmol, 1.2 eq.) and $Sc(OTf)_3$ (45 mg, 5 mol%). The reaction was stirred at 0 °C for 1.5 hours and the solvent removed *in vacuo*. Et_2O (20 mL) and 1N aq. HCl (20 mL) were added and the resulting biphasic mixture stirred for 30 minutes. The precipitate was filtered off, the layers separated and the aqueous layer extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to leave pure carboante **(*S*,*S*)-3.126b** (413 mg, 1.45 mmol, 80%) as a colourless oil.

R_f 0.25 (1:1 Et_2O/pet. ether); **>95:5 *dr***; $[\alpha]_D^{25}$ –75.3 (*c* = 1.00, $CHCl_3$); **IR** (thin film, cm^{-1}): 3429, 2959, 2180, 1750, 1642, 1443, 1260, 966, 841; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 5.85-5.76 (1H, m, H8), 5.27 (1H, t, *J* = 6.5 Hz, H3), 5.16-5.11 (2H, m, H9), 3.79 (3H, s, O*Me*), 3.72-3.66 (1H, m, H6), 2.32-2.26 (1H, m, H7), 2.17 (1H, dt, *J* = 14.0 and 8.0 Hz, H7), 2.04-1.96 (1H, m, H4), 1.90-1.82 (1H, m, H4), 1.75 (1H, bs, O*H*), 1.70-1.54 (2H, m, H5), 0.16 (9H, s, SiMe_3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.8, 134.3, 118.4, 101.5, 91.6, 69.9, 68.3, 54.9, 41.9, 31.7, 31.1, −0.3; **HRMS** (ESI+): calc for $C_{14}H_{24}O_4SiNa$ $[M+Na]^+$ 307.1336, found 307.1346.

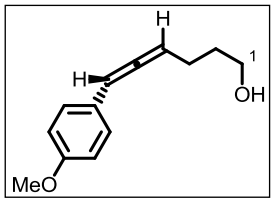
(*S*)-6-hydroxyhex-1-yn-3-yl methyl carbonate – (*S*)-3.76a



To a stirred solution of carbonate **(*S*)-3.76b** (200 mg, 0.818 mmol, 1 eq.) in THF (4 mL) at 0 °C was added TBAF (1M in THF, 0.78 mL, 0.78 mmol, 0.95 eq.). The reaction was stirred for 30 mins and diluted with water (5 mL) and Et_2O (5 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave pure carbonate **(*S*)-3.76a** (126 mg, 0.732 mmol, 89%) as a colourless oil.

R_f 0.14 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ −81.1 (*c* = 0.56, $CHCl_3$); **IR** (thin film, cm^{-1}): 3289, 3016, 2970, 2123, 1742, 1443, 1366, 1258, 955; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 5.27 (1H, td, *J* = 6.5 and 2.0 Hz, H3), 3.81 (3H, s, O*Me*), 3.72-3.68 (2H, m, H6), 2.54 (1H, d, *J* = 2.0 Hz, H1), 1.96-1.91 (2H, m, H4), 1.79-1.73 (2H, m, H5), 1.54 (1H, bs, O*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.9, 80.2, 74.7, 67.6, 62.0, 55.0, 31.0, 27.8; **HRMS** (ESI+): calc for $C_6H_{12}O_4Na$ $[M+Na]^+$ 195.0628, found 195.0632.

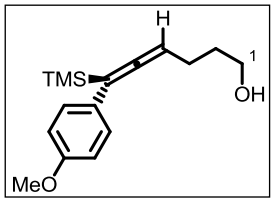
(*R*)-6-(4-methoxyphenyl)hexa-4,5-dien-1-ol - (*R*)-(−)-3.177a



A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*S*)-3.76a** (17.2 mg, 0.10 mmol, 1 eq.), 4-methoxylphenyl boronic acid (18.2 mg, 0.12 mmol, 1.2 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(PPh_3)_4$ (5.8 mg, 5 mol%) in degassed 1,4-dioxane (1 mL). The reaction was stirred and heated to 100 °C for 10 minutes. The reaction was allowed to cool and quenched with pet. ether (1 mL). The resulting mixture was passed through a short plug of silica gel (Et_2O eluent) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:1 Et_2O/pet. ether) to leave pure allene **(*R*)-(−)-3.177a** (9.0 mg, 44 μmol, 44%) as a colourless oil.

R_f 0.17 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ −99.6 (*c* = 0.57, $CHCl_3$); **IR** (thin film, cm^{-1}): 3343, 2935, 2837, 1947, 1739, 1607, 1510, 1301, 1245, 1172, 1034, 834; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.21 (2H, dt, *J* = 9.0 and 2.5 Hz, Ar*H*), 6.85 (2H, dt, *J* = 9.0 and 2.5 Hz, Ar*H*), 6.13 (1H, dt, *J* = 6.5 and 3.0 Hz, H6), 5.59 (1H, *apt* q, *J* = 6.5 Hz, H4), 3.81 (3H, s, O*Me*), 3.74-3.70 (2H, m, H1), 2.25-2.19 (2H, m, H3), 1.80-1.74 (2H, m, H2), 1.30 (1H, bs, O*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 204.5, 158.6, 127.6, 127.1, 114.1, 94.5, 94.3, 62.3, 55.3, 31.9, 25.1; **HRMS** (ESI+): calc for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227.1043, found 227.1051.

(*S*)-6-(4-methoxyphenyl)-6-(trimethylsilyl)hexa-4,5-dien-1-ol – (*S*)-(−)-3.177b

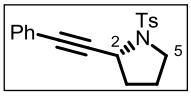


A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*S*)-3.76b** (24.4 mg, 0.10 mmol, 1 eq.), 4-methoxylphenyl boronic acid (18.2 mg, 0.12 mmol, 1.2 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(PPh_3)_4$ (5.8 mg, 5 mol%) in

degassed 1,4-dioxane (1 mL). The reaction was stirred and heated to 100 °C for 10 minutes. The reaction was allowed to cool and quenched with pet. ether (1 mL). The resulting mixture was passed through a short plug of silica gel (Et_2O eluent) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:1 Et_2O/pet. ether) to leave pure TMS-allene **(*S*)-()-3.177b** (9.0 mg, 33 μmol, 33%) as a colourless oil.

R_f 0.27 (1:1 Et_2O/pet. ether); **$[\alpha]_D^{25}$** −68.4 (*c* = 0.58, $CHCl_3$); **IR** (thin film, cm^{-1}): 3332, 2954, 1925, 1739, 1606, 1507, 1288, 1245, 1176, 1037, 837; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.23 (2H, dt, *J* = 9.0 and 2.5 Hz, Ar*H*), 6.85 (2H, dt, *J* = 9.0 and 2.5 Hz, Ar*H*), 5.17 (1H, t, *J* = 6.5 Hz, H4), 3.80 (3H, s, O*Me*), 3.73-3.69 (2H, m, H1), 2.19-2.14 (2H, m, H3), 1.77-1.70 (2H, m, H2), 1.28 (1H, bs, O*H*), 0.23 (9H, s, Si*Me*$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 207.7, 158.0, 129.9, 128.5, 113.9, 99.9, 86.5, 62.5, 55.3, 32.5, 24.6, −0.3; **HRMS** (ESI+): calc for $C_{16}H_{24}O_2SiNa$ $[M+Na]^+$ 299.1438, found 299.1440; **Elemental Analysis:** $C_{16}H_{24}O_2Si$ requires C, 69.51%; H, 8.75%; found C, 69.64%; H, 8.43%.

(*R*)-2-(phenylethynyl)-1-tosylpyrrolidine – (*R*)-4.36c

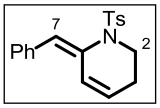


A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*)-4.33c** (10.0 mg, 24.9 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(dba)_2$ (0.7 mg, 5 mol%) and DPEphos (1.3 mg, 10 mol%) in degassed 1,4-dioxane (0.25 mL). The reaction was heated to 60 °C for 45 minutes, allowed to cool and quenched with pet. ether (0.5 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent), the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave pure pyrrolidine **(*R*)-4.36c** (6.2 mg, 19.2 μmol, 77%) as a white solid.

m.p. 122-123 °C; **R_f** 0.30 (1:2 Et_2O/pet. ether); **97% *ee*** (CHIRALPAK IC, 1.1 mL/min, 20% IPA/0.1% EDA/Hexane): t_R (*R*) = 32.76 min, t_R (*S*) = 34.88 min; **$[\alpha]_D^{20}$** +103.6 (*c* = 0.36, $CHCl_3$); **IR** (thin film, cm^{-1}): 2957, 2855, 2193, 1597, 1490, 1446, 1335, 1153, 1091, 1009; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.82 (2H, dt, *J* = 8.0 and 2.0 Hz, Ts*H*), 7.31-7.20 (7H, m, Ph and Ts*H*), 4.79 (1H, dd, *J* = 6.5 and 3.0 Hz, H2), 3.51-3.46 (1H, m, H5), 3.42-3.37 (1H, m, H5), 2.36 (3H, s, Ts*Me*), 2.14-2.04 (3H, m, H3 and 4), 1.98-1.91 (1H, m, H4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.2, 135.8,

131.6, 129.4, 128.2, 128.1, 127.7, 122.6, 87.5, 84.1, 50.9, 47.1, 34.1, 24.3, 21.4; **HRMS** (ESI+): calc for $C_{19}H_{19}NO_2SNa$ $[M+Na]^+$ 348.1029, found 348.1016; **Elemental Analysis**: $C_{19}H_{19}NO_2S$ requires C, 70.12%; H, 5.88%; N, 4.30%; found C, 69.99%; H, 5.80%; N, 4.20%.

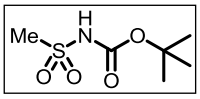
(*E*)-6-benzylidene-1-tosyl-1,2,3,6-tetrahydropyridine – 4.37c



A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*)-4.33c** (10.0 mg, 24.9 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(dba)_2$ (0.7 mg, 5 mol%) and dppe (1.0 mg, 10 mol%) in degassed 1,4-dioxane (0.25 mL). The reaction was heated to 60 °C for 30 minutes, allowed to cool and quenched with pet. ether (0.5 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent), the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave pure enamide **4.37c** (4.9 mg, 15.0 μmol, 60%) as a pale yellow oil.

R_f 0.40 (1:2 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3053, 2929, 1598, 1493, 1446, 1342, 1162, 1086, 978, 870; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.72 (2H, dt, *J* = 8.5 and 2.0 Hz, Ts*H*), 7.37-7.33 (2H, m, Ph), 7.28-7.26 (3H, m, Ph), 7.24 (2H, dt, *J* = 8.5 and 2.0 Hz, Ts*H*), 6.93 (1H, bs, H7), 6.43 (1H, dt, *J* = 10.5 and 2.0 Hz, H5), 5.68 (1H, dtd, *J* = 10.5, 4.0 and 2.0 Hz, H4), 3.88 (2H, t, *J* = 6.0 Hz, H2), 2.41 (3H, s, Ts*Me*), 2.03-1.99 (2H, m, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.4, 137.7, 135.7, 132.5, 129.4, 129.3, 128.4, 128.3, 127.4, 127.1, 125.9, 122.2, 44.5, 23.6, 21.6; **HRMS** (ESI+): calc for $C_{19}H_{19}NO_2SNa$ $[M+Na]^+$ 348.1029, found 348.1024.

tert-butyl methylsulfonylcarbamate – 4.58[266]

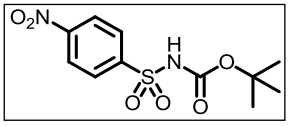


To a stirred suspension of methanesulfonamide (1.0 g, 10.5 mmol, 1 eq.) in anhydrous CH_2Cl_2 (12 mL) was added Et_3N (1.61 mL, 11.6 mmol, 1.1 eq.) and DMAP (128 mg, 10 mol%). To this was added a solution of Boc_2O (2.64 g, 12.1 mmol, 1.15 eq.) in anhydrous CH_2Cl_2 (20 mL) dropwise over 5 minutes. The reaction was stirred for 16 hours and the solvent removed *in vacuo*. The residue was taken up in EtOAc (50 mL) and washed with 1N aq. HCl (40 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue triturated with hot hexane

(~20 mL). The solid was filtered and washed with further portions of cold hexane. The solid was dried *in vacuo* to leave pure sulfonylcarbamate **4.58** (1.79 g, 9.17 mmol, 87%) as an off-white solid.

m.p. 109-110 °C [lit.[266] 108-109 °C]; $\mathbf{R_f}$ 0.26 (1:1 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.46 (1H, bs, N*H*), 3.27 (3H, s, *Me*), 1.52 (9H, s, *t*-Bu); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 149.8, 84.4, 41.2, 27.9. Data consistent with literature.[266]

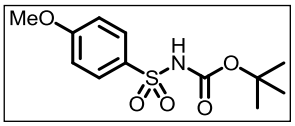
tert-butyl (4-nitrophenyl)sulfonylcarbamate – 4.59[141]



To a stirred suspension of 4-nitrobenzenesulfonamide (1.0 g, 4.95 mmol, 1 eq.) in anhydrous CH_2Cl_2 (6 mL) was added Et_3N (0.76 mL, 5.45 mmol, 1.1 eq.) and DMAP (60 mg, 10 mol%). To this was added a solution of Boc_2O (1.24 g, 5.69 mmol, 1.15 eq.) in anhydrous CH_2Cl_2 (10 mL) dropwise over 5 minutes. The reaction was stirred for 16 hours and the solvent removed *in vacuo*. The residue was taken up in EtOAc (30 mL) and washed with 1N aq. HCl (25 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue triturated with hot hexane (~20 mL). The solid was filtered and washed with further portions of cold hexane. The solid was dried *in vacuo* to leave pure sulfonylcarbamate **4.59** (996 mg, 3.29 mmol, 67%) as an off-white solid.

m.p. 143.5-144.5 °C; $\mathbf{R_f}$ 0.32 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3218, 2973, 1743, 1528, 1432, 1351, 1245, 1141, 1086, 919; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 8.41 (2H, dt, *J* = 9.0 and 2.5 Hz, Ar*H*), 8.25 (2H, dt, *J* = 9.0 and 2.5 Hz, Ar*H*), 7.55 (1H, bs, N*H*), 1.42 (9H, s, *t*-Bu); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 150.7, 148.6, 144.2, 129.7, 124.1, 85.1, 27.8; **HRMS** (ESI−): calc for $C_{11}H_{13}N_2O_6S$ $[M-H]^-$ 301.0500, found 301.0493.

tert-butyl (4-methoxyphenyl)sulfonylcarbamate – 4.60[267]

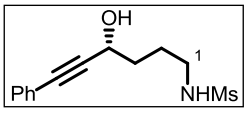


To a stirred solution of *p*-methoxybenzenesulfonamide (1.0 g, 5.34 mmol, 1 eq.) in anhydrous CH_2Cl_2 (6 mL) was added Et_3N (0.82 mL, 5.88 mmol, 1.1 eq.) and DMAP (65 mg, 10 mol%). To the resulting suspension was added a solution of Boc_2O (1.34 g, 6.14 mmol, 1.15 eq.) in anhydrous CH_2Cl_2 (10 mL) dropwise. The reaction was stirred overnight, the solvent removed *in vacuo* and the residue taken up in EtOAc (20 mL). The organic layer was washed with 1N aq. HCl (20 mL) and the aqueous layer back extracted with EtOAc (2 x

10 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the residue triturated with hot hexane. The resulting solid was filtered, washed with further portions of cold hexane and dried *in vacuo* to leave pure sulfonylcarbamate **4.60** (1.31 g, 4.56 mmol, 85%) as an orange solid.

m.p. 112-114 °C [lit.[267] 108-110 °C]; $\mathbf{R_f}$ 0.27 (1:1 Et_2O/pet. ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.96 (2H, d, *J* = 9.0 Hz), 7.38 (1H, bs, N*H*), 7.00 (2H, d, *J* = 9.0 Hz), 3.89 (3H, s, O*Me*), 1.40 (9H, s, *t*-Bu); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 163.7, 149.1, 130.5, 130.3, 114.0, 83.9, 55.7, 27.9. Data consistent with literature.[267]

(*R*)-*N*-(4-hydroxy-6-phenylhex-5-yn-1-yl)methanesulfonamide – (*R*)-4.61c



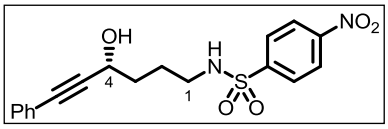
To a stirred solution of carbonate **(*R*)-3.76c** (100 mg, 0.403 mmol, 1 eq.), PPh_3 (137 mg, 0.524 mmol, 1.3 eq.) and *tert*-butyl methylsulfonylcarbamate (86 mg, 0.443 mmol, 1.1 eq.) in anhydrous THF (4 mL) under argon was added DIAD (95 μL, 0.484 mmol, 1.2 eq.) dropwise. The reaction was stirred for 1.5 hours and quenched with sat. aq. $NaHCO_3$ (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel ($CHCl_3$→99:1 $CHCl_3$/acetone) to leave pure Boc-sulfonamide (159 mg, 0.374 mmol, 93%) as a colourless oil which was used directly without further characterisation.

The above Boc-sulfonamide (155 mg, 0.364 mmol, 1 eq.) was taken up in MeOH (5 mL) and to it added K_2CO_3 (500 mg). The resulting suspension was stirred and heated to reflux for 1.5 hours. The mixture was allowed to cool and quenched with 1N aq. HCl (10 ml). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 EtOAc/pet. ether→EtOAc) to leave pure sulfonamide **(*R*)-4.61c** (94 mg, 0.352 mmol, 97%) as a white solid.

m.p. 67-69 °C; $\mathbf{R_f}$ 0.44 (EtOAc); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +28.8 (*c* = 0.16, $CHCl_3$, for 93% *ee*); **IR** (thin film, cm^{-1}): 3417, 3167, 2947, 2857, 2226, 1305, 1138, 1074, 1030, 984; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.45-7.41 (2H, m, Ph), 7.39-7.30 (3H, m, Ph), 4.70 (1H, t, *J* = 5.5 Hz, H4), 4.51 (1H, bs, N*H*), 3.25 (2H, *apt* q, *J* = 6.5 Hz, H1), 2.97 (3H, s, SO_2*Me*), 2.06 (1H, bs, O*H*), 1.93-1.83 (4H, m, H2 and 3); **^{13}C NMR**

(125 MHz, $CDCl_3$): δ_C 131.7, 128.6, 128.4, 122.2, 89.2, 85.5, 62.3, 43.0, 40.4, 34.3, 25.9; **HRMS** (ESI+): calc for $C_{13}H_{17}NO_3SNa$ $[M+Na]^+$ 290.0821, found 290.0816.

(*R*)-*N*-(4-hydroxy-6-phenylhex-5-yn-1-yl)-4-nitrobenzenesulfonamide - (*R*)-4.62c

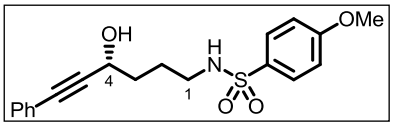


To a stirred solution of carbonate **(*R*)-3.76c** (100 mg, 0.403 mmol, 1 eq.), *tert*-butyl (4-nitrophenyl)sulfonyl carbamate (128 mg, 0.423 mmol, 1.05 eq.) and PPh_3 (127 mg, 0.484 mmol, 1.2 eq.) in anhydrous THF (4 mL) under argon was added DIAD (87 μL, 0.443 mmol, 1.1 eq.). The reaction was stirred for 1 hour and quenched with sat. aq. $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:2 Et_2O/pet. ether) to leave pure Boc-sulfonamide (184 mg) which was used in the next step without further characterisation.

The above Boc-sulfonamide was taken up in methanol (5 mL) and to it added K_2CO_3 (500 mg). The reaction was heated to 70 °C for 1 hour, allowed to cool and quenched with 1N aq. HCl (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2 Et_2O/pet. ether→Et_2O) to leave pure sulfonamide **(*R*)-4.62c** (104 mg, 0.278 mmol, 69% *2 steps*) as a white solid.

m.p. 111.5-112.5 °C; $\mathbf{R_f}$ 0.20 (2:1 Et_2O/pet. ether); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +6.3 (*c* = 0.38, acetone, for 93% *ee*); **IR** (thin film, cm^{-1}): 3463, 3181, 2949, 2891, 2228, 1528, 1400, 1296, 1243, 1151, 1051, 925; **^{1}H NMR** (500 MHz, acetone-d_6): δ_H 8.42 (2H, d, *J* = 9.0 Hz, 4-Ns*H*), 8.14 (2H, d, *J* = 9.0 Hz, 4-Ns*H*), 7.39-7.33 (5H, m, Ph), 4.55-4.52 (1H, m, H4), 3.11-3.07 (2H, m, H1), 1.78-1.73 (4H, m, H2 and 3); **^{13}C NMR** (125 MHz, acetone-d_6): δ_C 150.9, 147.8, 132.2, 129.3, 129.2, 129.1, 125.2, 124.0, 92.1, 84.3, 62.0, 43.8, 35.8, 26.4; **HRMS** (ESI−): calc for $C_{18}H_{17}N_2O_5S$ $[M-H]^-$ 373.0864, found 373.0858.

(*R*)-*N*-(4-hydroxy-6-phenylhex-5-yn-1-yl)-4-methoxybenzenesulfonamide – (*R*)-4.63c



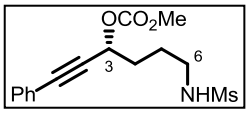
To a stirred solution of carbonate **(*R*)-3.76c** (100 mg, 0.403 mmol, 1 eq.), PPh_3 (137 mg, 0.524 mmol, 1.3 eq.) and *tert*-butyl (4-methoxyphenyl)sulfonylcarbamate (127 mg, 0.443 mmol, 1.1 eq.) in anhydrous THF (4 mL) under

argon was added DIAD (95 μL, 0.484 mmol, 1.2 eq.) dropwise. The reaction was stirred for 1.5 hours and quenched with sat. aq. $NaHCO_3$ (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was passed through a short plug of silica gel ($CHCl_3$) to leave the Boc-sulfonamide (contaminated with PPh_3) which was used directly in the next step without further purification.

The above Boc-sulfonamide was taken up in MeOH (5 mL) and to it added K_2CO_3 (500 mg). The resulting suspension was stirred and heated to reflux for 3 hours. The mixture was allowed to cool and quenched with 1N aq. HCl (10 ml). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3 EtOAc/pet. ether→EtOAc) to leave pure sulfonamide **(*R*)-4.63c** (124 mg, 0.354 mmol, 86%, *2 steps*) as a white solid.

m.p. 136-137 °C; $\mathbf{R_f}$ 0.27 (1:1 EtOAc/pet. ether); $[\alpha]_D^{25}$ +4.3 (*c* = 0.28, $CHCl_3$); **IR** (thin film, cm^{-1}): 3455, 3223, 2949, 2895, 2231, 1594, 1578, 1490, 1439, 1295, 1255, 1144, 1049, 817; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.80 (2H, d, *J* = 9.0 Hz, *p*-OMeAr*H*), 7.43-7.39 (2H, m, Ph), 7.35-7.30 (3H, m, Ph), 6.97 (2H, d, *J* = 9.0 Hz, *p*-OMeAr*H*), 4.61 (1H, t, *J* = 6.0 Hz, H4), 4.55 (1H, t, *J* = 5.5 Hz, N*H*), 3.86 (3H, s, O*Me*), 3.05 (2H, *apt* t, *J* = 6.5 Hz, H1), 1.96 (1H, bs, O*H*), 1.84-1.79 (2H, m, H3), 1.77-1.71 (2H, m, H2); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 162.8, 131.7, 131.5, 129.2, 128.6, 128.3, 122.3, 114.2, 89.2, 85.4, 62.3, 55.6, 42.9, 34.5, 25.4; **HRMS** (ESI+): calc for $C_{19}H_{21}NO_4SNa$ $[M+Na]^+$ 382.1083, found 382.1084.

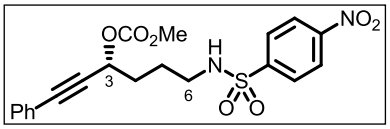
(*R*)-methyl (6-(methylsulfonamido)-1-phenylhex-1-yn-3-yl) carbonate – (*R*)-4.55c



To a stirred solution of sulfonamide **(*R*)-4.61c** (90 mg, 0.337 mmol, 1 eq.) and pyridine (73 μL, 0.674 mmol, 2 eq.) in anhydrous CH_2Cl_2 (3.4 mL) at 0 °C under argon was added methyl chloroformate (39 μL, 0.506 mmol, 1.5 eq.). The reaction was allowed to warm to RT and stirred for 3 hours. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), the layers separated and the aqueous layers extracted with CH_2Cl_2 (2 x 5 ml). The combined organic layers were washed with 1N aq. HCl (1 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:4→1:1 EtOAc/pet. ether) to leave pure carbonate **(*R*)-4.55c** (80 mg, 0.246 mmol, 73%, 87% brsm) as a colourless oil.

R_f 0.23 (1:1 EtOAc/pet. ether); **$[\alpha]_D^{25}$** +79.3 (*c* = 0.81, $CHCl_3$, for 93% *ee*); **IR** (thin film, cm^{-1}): 3293, 2958, 2234, 1750, 1491, 1443, 1319, 1265, 1151, 1075, 976; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.43 (2H, m, Ph), 7.36-7.29 (3H, m, Ph), 5.52 (1H t, *J* = 6.0 Hz, H3), 4.43 (1H, bs, N*H*), 3.83 (3H, s, O*Me*), 3.24 (2H, *apt* q, *J* = 6.5 Hz, H6), 2.97 (3H, s, SO_2*Me*), 2.03-1.98 (2H, m, H4), 1.89-1.82 (2H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.9, 131.9, 128.9, 128.3, 121.8, 86.8, 84.9, 67.9, 55.1, 42.7, 40.4, 31.8, 25.6; **HRMS** (ESI+) calc for $C_{15}H_{19}NO_5SNa$ $[M+Na]^+$ 348.0876, found 348.0874; **Elemental Analysis:** $C_{15}H_{19}NO_5S$ requires C, 55.37%; H, 5.89%; N, 4.30%; found C, 55.45%; H, 5.90%; N, 4.19%.

(*R*)-methyl (6-(4-nitrophenylsulfonamido)-1-phenylhex-1-yn-3-yl) carbonate - (*R*)-4.56c

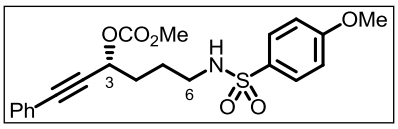


To a stirred suspension of sulfonamide **(*R*)-4.62c** (88 mg, 0.235 mmol, 1 eq.) in anhydrous CH_2Cl_2 (5 mL) under argon was added pyridine (38 μL, 0.47 mmol, 2 eq.). The mixture was stirred for 15 minutes to allow dissolution of the solid sulfonamide, then cooled to 0 °C and to it added methyl chloroformate (23 μL, 0.294 mmol, 1.25 eq.). The reaction was stirred for 1 hour at 0 °C and quenched with sat. aq. $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the residue azeotroped with toluene (2 x 5 mL). The crude product was purified by flash chromatography on silica gel (1:1→2:1 Et_2O/pet. ether) to leave pure carbonate **(*R*)-4.56c** (62 mg, 0.139 mmol, 59%, 93% brsm) as a white solid.

m.p. 115-116 °C; **R_f** 0.14 (1:1 Et_2O/pet. ether); **$[\alpha]_D^{25}$** +59.7 (*c* = 1.10, $CHCl_3$, for 93% *ee*); **IR** (thin film, cm^{-1}): 3276, 2957, 2235, 1757, 1741, 1533, 1443, 1350, 1267, 1161, 832; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 8.32 (2H, d, *J* = 9.0 Hz, 4-Ns*H*), 8.04 (2H, d, *J* = 4-Ns*H*), 7.41-7.38 (2H, m, Ph), 7.37-7.29 (3H, m, Ph), 5.44 (1H, t, *J* = 6.0 Hz, H3), 4.96 (1H, t, *J* = 6.0 Hz, N*H*), 3.81 (3H, s, O*Me*), 3.13 (2H, *apt* q, *J* = 6.5 Hz, H6), 1.94-1.89 (2H, m, H4), 1.80-1.73 (2H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.8, 150.0, 145.9, 131.8, 129.0, 128.3, 128.2, 124.4, 121.6, 86.8, 84.7, 67.7, 55.1, 42.8, 31.6, 25.1; **HRMS** (ESI+): calc for $C_{20}H_{20}N_2O_7SNa$ $[M+Na]^+$ 455.0883, found 455.0891; **Elemental Analysis:** $C_{20}H_{20}N_2O_7S$ requires C, 55.55%; H, 4.66%; N, 6.48%; found C, 55.41%; H, 4.55%; N,

6.56%.

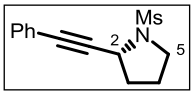
(*R*)-6-(4-methoxyphenylsulfonamido)-1-phenylhex-1-yn-3-yl methyl carbonate – (*R*)-4.57c



To a stirred solution of sulfonamide **(*R*)-4.63c** (120 mg, 0.333 mmol, 1 eq.) and pyridine (73 μL, 0.666 mmol, 2 eq.) in anhydrous CH_2Cl_2 (3.4 mL) at 0 °C under argon was added methyl chloroformate (39 μL, 0.500 mmol, 1.5 eq.). The reaction was allowed to warm to RT and stirred for 3 hours. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), the layers separated and the aqueous layers extracted with CH_2Cl_2 (2 x 5 ml). The combined organic layers were washed with 1N aq. HCl (1 x 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:1 EtOAc/pet. ether) to leave pure carbonate **(*R*)-4.57c** (91 mg, 0.218 mmol, 65%, 81% brsm) as a colourless oil.

R_f 0.39 (1:1 EtOAc/pet. ether); $[\alpha]_D^{25}$ +47.3 (*c* = 1.09, $CHCl_3$, for 93% *ee*); **IR** (thin film, cm^{-1}): 3286, 2957, 2234, 1749, 1597, 1498, 1442, 1325, 1259, 1153, 1095, 1026; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.80 (2H, d, *J* = 9.0 Hz, *p*-OMeAr*H*), 7.43-7.40 (2H, m, Ph), 7.35-7.28 (3H, m, Ph), 6.96 (2H, d, *J* = 9.0 Hz, *p*-OMeAr*H*), 5.42 (1H, t, *J* = 6.0 Hz, H3), 4.59 (1H, bs, N*H*), 3.84 (3H, s, ArO*Me*), 3.81 (3H, s, OCO_2*Me*), 3.02 (2H, *apt* q, *J* = 6.5 Hz, H6), 1.93-1.88 (2H, m, H4), 1.76-1.70 (2H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 162.9, 154.8, 131.9, 131.4, 129.2, 128.8, 128.3, 121.8, 114.2, 86.6, 85.0, 67.9, 55.5, 55.0, 42.6, 31.8, 25.1; **HRMS** (ESI+) calc for $C_{21}H_{23}NO_6SNa$ $[M+Na]^+$ 440.1138, found 440.1134; **Elemental Analysis:** $C_{21}H_{23}NO_6S$ requires C, 60.42%; H, 5.55%; N, 3.36%; found C, 60.39%; H, 5.48%; N, 3.46%.

(*R*)-1-(methylsulfonyl)-2-(phenylethynyl)pyrrolidine – (*R*)-4.64c

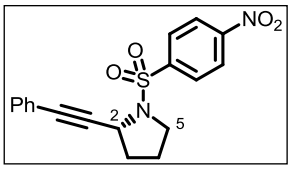


A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*)-4.55c** (10.0 mg, 30.7 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(dba)_2$ (0.9 mg, 5 mol%) and DPEphos (1.7 mg, 10 mol%) in degassed toluene (0.30 mL). The reaction was stirred and heated to 100 °C for 15 minutes. The reaction was allowed to cool and quenched with pet. ether (0.5 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent), the solvent removed *in vacuo* and

the crude product purified by flash chromatography on silica gel (1:9→1:1 Et_2O/pet. ether) to leave pure pyrrolidine **(*R*)-4.64c** (5.2 mg, 20.9 μmol, 72%) as a colourless oil.

R_f 0.13 (1:2 Et_2O/pet. ether); **$[\alpha]_D^{20}$** +108.2 (*c* = 0.39, $CHCl_3$); **IR** (thin film, cm^{-1}): 2983, 2879, 2231, 1490, 1444, 1333, 1194, 1149, 1072, 1019; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.43-7.39 (2H, m, Ph), 7.36-7.30 (3H, m, Ph), 4.81 (1H, dd, *J* = 7.0 and 2.5 Hz, H2), 3.57 (1H, dt, *J* = 9.5 and 7.5 Hz, H5), 3.44-3.39 (1H, m, H5), 3.05 (3H, s, SO_2*Me*), 2.33-2.26 (1H, m, H3), 2.25-2.15 (2H, m, H3 and 4), 2.13-2.06 (1H, m, H4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.6, 128.7, 128.4, 122.2, 87.4, 84.8, 50.6, 46.9, 38.2, 34.1, 24.5; **HRMS** (ESI+) calc for $C_{13}H_{15}NO_2SNa$ $[M+Na]^+$ 272.0716, found 272.0716; **Elemental Analysis:** $C_{13}H_{15}NO_2S$ requires C, 62.62%; H, 6.06%; N, 5.62%; found C, 62.74%; H, 6.18%; N, 5.73%.

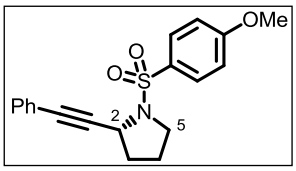
(*R*)-1-((4-nitrophenyl)sulfonyl)-2-(phenylethynyl)pyrrolidine – (*R*)-4.65c



A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*)-4.56c** (10.0 mg, 23.1 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(dba)_2$ (0.7 mg, 5 mol%) and DPEphos (1.3 mg, 10 mol%) in degassed toluene (0.25 mL). The resulting solution was stirred and heated to 100 °C for 15 minutes. The reaction was allowed to cool and quenched with pet. ether (0.5 mL). The mixture was passed through a short plug of silica gel (Et_2O eluent) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave pure pyrrolidine **(*R*)-4.65c** (4.5 mg, 12.6 μmol, 55%) as a white solid.

m.p. 122-123 °C; **R_f** 0.22 (1:2 Et_2O/pet. ether); **$[\alpha]_D^{25}$** +75.4 (*c* = 0.13, $CHCl_3$); **IR** (thin film, cm^{-1}): 2961, 2925, 2229, 1526, 1343, 1157, 1100, 1012, 853; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 8.20 (2H, d, *J* = 9.0 Hz, 4-Ns*H*), 8.11 (2H, d, *J* = 9.0 Hz, 4-Ns*H*), 7.33-7.30 (1H, m, Ph), 7.28-7.24 (2H, m, Ph), 7.13-7.11 (2H, m, Ph), 4.90 (1H, dd, *J* = 7.5 and 2.5 Hz, H2), 3.66-3.61 (1H, m, H5), 3.41-3.36 (1H, m, H5), 2.29-2.20 (1H, m, H3), 2.19-2.04 (3H, m, H3 and 4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 149.8, 144.9, 131.3, 128.8, 128.3, 123.9, 121.8, 86.5, 85.2, 51.1, 47.2, 34.1, 24.4; **HRMS** (ESI+): calc for $C_{18}H_{16}N_2O_4SNa$ $[M+Na]^+$ 379.0723, found 379.0739; **Elemental Analysis:** $C_{18}H_{16}N_2O_4S$ requires C, 60.66%, H, 4.53%; N, 7.86%; found C, 60.50%; H, 4.59%; N, 7.76%.

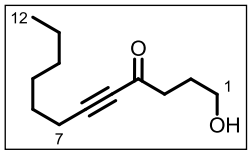
(*R*)-1-((4-methoxyphenyl)sulfonyl)-2-(phenylethynyl)pyrrolidine – (*R*)-4.66c



A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*)-4.57c** (10.0 mg, 24.0 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(dba)_2$ (0.7 mg, 5 mol%) and DPEphos (1.3 mg, 10 mol%) in degassed toluene (0.25 mL). The reaction was stirred and heated to 100 °C for 15 minutes. The reaction was allowed to cool and quenched with pet. ether (0.5 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent), the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:9→1:1 Et_2O/pet. ether) to leave pure pyrrolidine **(*R*)-4.66c** (6.0 mg, 17.6 μmol, 73%) as a white solid.

m.p. 142-143 °C; $\mathbf{R_f}$ 0.17 (1:2 Et_2O/pet. ether); $[\alpha]_D^{20}$ +113.0 (*c* = 0.33, $CHCl_3$); **IR** (thin film, cm^{-1}): 2976, 2877, 2237, 1596, 1578, 1497, 1343, 1260, 1155, 1095, 1022; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.87 (2H, d, *J* = 9.0 Hz, *p*-OMeAr*H*), 7.32-7.21 (5H, m, Ph), 6.88 (2H, d, *J* = 9.0 Hz, *p*-OMeAr*H*), 4.78 (1H, dd, *J* = 7.0 and 2.5 Hz, H2), 3.77 (3H, s, O*Me*), 3.48 (1H, dt, *J* = 9.5 and 7.5 Hz, H5), 3.40-3.35 (1H, m, H5), 2.14-2.04 (3H, m, H3 and 4), 1.99-1.92 (1H, m, H4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 162.7, 131.6, 130.4, 129.8, 128.2, 128.1, 122.6, 113.9, 87.6, 84.2, 55.4, 50.9, 47.0, 34.1, 24.3; **HRMS** (ESI+) calc for $C_{19}H_{19}NO_3SNa$ $[M+Na]^+$ 364.0978, found 364.0966; **Elemental Analysis:** $C_{19}H_{19}NO_3S$ requires C, 66.84%; H, 5.61%; N, 4.10%; found C, 66.90%; H, 5.71%; N, 4.21%.

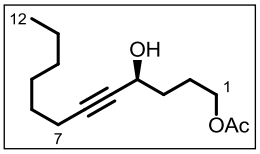
1-hydroxydodec-5-yn-4-one – 2.59d[109]



To a stirred solution of 1-octyne (1.80 mL, 12.20 mmol, 1.05 eq.) in anhydrous THF (60 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 5.11 mL, 12.78 mmol, 1.1 eq.) dropwise. The reaction was stirred for 30 minutes and to it added $BF_3{\cdot}OEt_2$ (1.58 mL, 12.78 mmol, 1.1 eq.) dropwise. The reaction was stirred for a further 10 minutes, and to it added γ-butyrolactone **2.57** (0.89 mL, 11.62 mmol, 1 eq.) in one portion. The reaction was allowed to warm to RT and stirred for 2 hours. The reaction was quenched with sat. aq. NH_4Cl/NH_4OH (2:1 v:v, 60 mL) and the THF removed *in vacuo*. The aqueous layer was extracted with Et_2O (3 x 50 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→2:1 Et_2O/pet. ether) to leave pure ketone **2.59d** (1.82 g, 9.27 mmol, 80%) as a pale yellow oil.

R_f 0.29 (1:1 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 3402, 2930, 2860, 2210, 1739, 1670, 1367, 1231, 1161, 1056; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.70-3.64 (2H, m, H1), 2.68 (2H, t, *J* = 7.0 Hz, H3), 2.36 (2H, t, *J* = 7.0 Hz, H7), 1.91 (2H, *apt* quintet, *J* = 6.5 Hz, H2), 1.72 (1H, bs, O*H*), 1.57 (2H, *apt* quintet, *J* = 7.0 Hz, H8), 1.44-1.36 (2H, m, H9), 1.35-1.25 (4H, m, H10 and 11), 0.89 (3H, t, *J* = 7.0 Hz, H12); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 188.1, 95.0, 80.8, 61.9, 42.2, 31.2, 28.5, 27.6, 26.7, 22.4, 18.9, 14.0; **HRMS** (ESI+): calc for $C_{12}H_{20}O_2Na$ $[M+Na]^+$ 219.1356, found 219.1359. Data consistent with literature.[109]

(*S*)-4-hydroxydodec-5-yn-1-yl acetate – (*S*)-4.73d



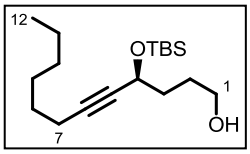
To a stirred solution of ketone **2.59d** (1.80 g, 9.17 mmol, 1 eq.), pyridine (1.48 mL, 18.34 mmol, 2 eq.) and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (20 mL) at 0 °C under argon was added Ac_2O (1.30 mL, 13.76 mmol, 1.5 eq.). The reaction was allowed to warm to RT and stirred for 2 hours. The solvent was removed *in vacuo* and the residue azeotroped with toluene (3 x 10 mL). The crude product was passed through a short plug of silica gel (1:9→1:2 Et_2O/pet. ether) to leave ynone-acetate **4.72d** (2.19 g, 9.17 mmol, 99%) as a colourless oil which was used without further characterisation.

A solution of ynone-acetate **4.72d** (1.82 g, 7.64 mmol, 1 eq.) in IPA (38 mL) was degassed for 30 minutes and to it added a solution of [Ru((*S*,*S*)-TsDPEN)(*p*-cymene)] **(*S*,*S*)-3.53** (69 mg, 1.5 mol%) in anhydrous CH_2Cl_2 (0.6 mL). The reaction was degassed for a further 10 minutes and stirred for 2 hours. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→1:1 Et_2O/pet. ether) to leave pure hydroxy-acetate **(*S*)-4.73d** (1.71 g, 7.11 mmol, 93%) as a pale yellow oil.

R_f 0.15 (1:3 Et_2O/pet. ether); **97% *ee*** (see below); $[\alpha]_D^{25}$ −3.8 (*c* = 1.24, $CHCl_3$); **IR** (thin film, cm^{-1}): 3432, 2956, 2931, 2859, 2236, 1740, 1331, 1242, 1036; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 4.45-4.37 (1H, m, H4), 4.12 (2H, t, *J* = 6.0 Hz, H1), 2.21 (2H, td, *J* = 7.0 and 2.0 Hz, H7), 2.06 (3H, s, C(O)*Me*), 1.93-1.86 (1H, m, O*H*), 1.86-1.70 (4H, m, H2 and 3), 1.56-1.45 (2H, m, H8), 1.44-1.24 (6H, m, H9, 10 and 11), 0.90 (3H, t, *J* = 7.0 Hz, H12); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 171.1, 86.0, 80.7, 64.1, 62.2, 34.5, 31.3, 28.6, 28.5, 24.5, 22.5, 20.9, 18.6, 14.0; **HRMS** (ESI+): calc for $C_{14}H_{24}O_3Na$ $[M+Na]^+$ 263.1618, found 263.1620.

Enantiomeric excess was determined by derivitisation with benzoyl chloride and comparison of the HPLC trace to a racemic sample. **97% *ee*** (CHIRALPAK IB, 1.3 mL/min, 0.8% IPA/Hexane) t_R (*R*): 5.93 min, t_R (*S*): 6.30 min.

(*S*)-4-((*tert*-butyldimethylsilyl)oxy)dodec-5-yn-1-ol – (*S*)-4.74d

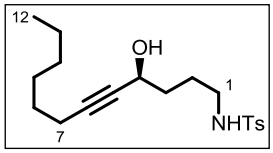


To a stirred solution of hydroxy-acetate **(*S*)-4.73d** (1.69 g, 7.03 mmol, 1 eq.), imidazole (574 mg, 8.44 mmol, 1.2 eq.) and DMAP (86 mg, 10 mol%) in anhydrous CH_2Cl_2 (35 mL) at 0 °C under argon was added TBSCl (1.17 g, 7.73 mmol, 1.1 eq.). The reaction was allowed to warm to RT and stirred for 16 hours. The reaction was quenched with sat. aq. $NaHCO_3$ (35 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with 1N aq. HCl (1 x 25 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was passed through a short plug of silica gel (1:19 Et_2O/pet. ether) to leave pure silyloxy-acetate (2.40 g, 6.76 mmol, 96%) as a colourless oil which was used without further characterisation.

To a stirred solution of the above silyloxy-acetate (2.39 g, 6.74 mmol, 1 eq.) in MeOH (27 mL) was added K_2CO_3 (2.79 g, 20.22 mmol, 3 eq.). The reaction was stirred for 30 minutes and quenched with 50% sat. aq. NH_4Cl (30 mL). The mixture was diluted with CH_2Cl_2 (20 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave pure silyloxy alcohol **(*S*)-4.74d** (2.11 g, 6.74 mmol, 99%) as a colourless oil.

R_f 0.27 (1:3 Et_2O/pet. ether); $[\alpha]_D^{25}$ −42.8 (*c* = 0.98, $CHCl_3$); **IR** (thin film, cm^{-1}): 3346, 2954, 2929, 2857, 2239, 1471, 1252, 1098, 1059, 836; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 4.45 (1H, m, H4), 3.72-3.62 (2H, m, H1), 2.19 (2H, td, *J* = 7.0 and 2.0 Hz, H7), 1.91 (1H, bs, O*H*), 1.80-1.69 (4H, m, H2 and 3), 1.52-1.46 (2H, m, H8), 1.41-1.34 (2H, m, H9), 1.34-1.26 (4H, m, H10 and 11), 0.91 (9H, s, Si*t-Bu*), 0.89 (3H, t, *J* = 7.0 Hz, H12), 0.14 (3H, s, Si*Me*), 0.12 (3H, s, Si*Me*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 85.2, 81.2, 63.0, 62.7, 35.4, 31.3, 28.6, 28.5, 28.5, 22.6, 18.7, 18.2, 14.0, −4.5, −5.0; **HRMS** (ESI+) calc for $C_{18}H_{36}O_2SiNa$ $[M+Na]^+$ 335.2377, found 335.2370.

(*S*)-*N*-(4-hydroxydodec-5-yn-1-yl)-4-methylbenzenesulfonamide – (*S*)-4.75d



To a stirred solution of silyloxy alcohol **(*S*)-4.74d** (500 mg, 1.60 mmol, 1 eq.), *tert*-butyl *p*-tosylcarbamate (564 mg, 1.3 mmol, 1.3 eq.) and PPh_3 (839 mg, 3.20 mmol, 2 eq.) in anhydrous THF (16 mL) at 0 °C under argon was added DIAD (0.47 mL, 2.40 mmol, 1.5 eq.) dropwise. The reaction was allowed to warm to RT and stirred for 1.5 hours. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and diluted with CH_2Cl_2 (15 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:9 Et_2O/pet. ether) to leave pure Boc-tosylamide (843 mg, 1.49 mmol, 93%) as a colourless oil which was used without further characterisation.

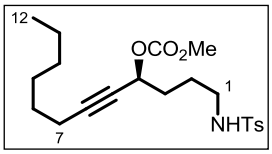
To a stirred solution of the above Boc-tosylamide (833 mg, 1.47 mmol, 1 eq.) in anhydrous THF (7.4 mL) was added TBAF (1 M in THF, 1.62 mL, 1.62 mmol, 1.1 eq.) dropwise. The reaction was stirred for 2 hours and quenched with water (10 mL). The resulting mixture was diluted with CH_2Cl_2 (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave the crude alcohol which was used directly in the next step without further purification.

The crude residue from the previous step was taken up in methanol (25 mL) and to it added K_2CO_3 (2.5 g, 10 % wt.). The resulting suspension was heated to reflux for 1 hour, allowed to cool and quenched with 1N aq. HCl (25 mL). The mixture was diluted with CH_2Cl_2 (20 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:1→2:1 Et_2O/pet. ether) to leave pure amido-alcohol **(*S*)-4.75d** (476 mg, 1.35 mmol, 92%, *2 steps*) as a colourless oil.

R_f 0.23 (2:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ −10.6 (*c* = 1.0, $CHCl_3$); **IR** (neat, cm^{-1}): 3472, 3280, 2930, 2859, 2239, 1599, 1430, 1324, 1157, 1093, 814; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.75 (2H, dt, *J* = 8.0 and 2.0 Hz, Ts*H*), 7.31 (2H, dt, *J* = 8.0 and 2.0 Hz, Ts*H*), 4.81 (1H, bs, N*H*), 4.37-4.32 (1H, m, H4), 3.02-2.96 (2H, m, H1), 2.43 (3H, s, Ts*Me*), 2.17 (2H, td, *J* = 7.0 and 2.0 Hz, H7), 1.95 (1H, bs, O*H*), 1.70-

1.63 (4H, m, H2 and 3), 1.52-1.44 (2H, m, H8), 1.39-1.24 (6H, m, H9, 10 and 11), 0.89 (3H, t, *J* = 7.0 Hz, H12); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 143.3, 136.9, 129.7, 86.2, 80.5, 62.0, 42.9, 34.8, 31.3, 28.5, 28.5, 25.3, 22.5, 21.5, 18.6, 14.0; **HRMS** (ESI+) calc for $C_{19}H_{29}NO_3SNa$ $[M+Na]^+$ 374.1760, found 374.1761.

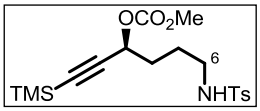
(*S*)-methyl (1-(4-methylphenylsulfonamido)dodec-5-yn-4-yl) carbonate – (*S*)-4.33d



To a stirred solution of amido-alcohol **(*S*)-4.75d** (470 mg, 1.34 mmol, 1 eq.) and pyridine (0.33 mL, 4.02 mmol, 3 eq.) in anhydrous CH_2Cl_2 (13.4 mL) at 0 °C under argon was added methyl chloroformate (0.21 mL, 2.67 mmol, 2 eq.) dropwise. The reaction was stirred for 30 minutes, quenched with sat. aq. $NaHCO_3$ (15 mL) and allowed to warm to RT. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the residue azeotroped with toluene (2 x 5 mL). The crude product was purified by flash chromatography on silica gel (1:2→1:1 Et_2O/pet. ether) to leave pure carbonate **(*S*)-4.33d** (548 mg, 1.34 mmol, 99%) as a colourless oil.

R_f 0.19 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ −45.4 (*c* = 0.83, $CHCl_3$); **IR** (neat, cm^{-1}): 3286, 2932, 2859, 2241, 1751, 1599, 1442, 1328, 1264, 1160, 1094, 939; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.75 (2H, dt, *J* = 8.0 and 2.0 Hz, Ts*H*), 7.31 (2H, dt, *J* = 8.0 and 2.0 Hz, Ts*H*), 5.18 (1H, tt, *J* = 6.0 and 2.0 Hz, H4), 4.43 (1H, t, *J* = 6.5 Hz, N*H*), 3.79 (3H, s, O*Me*), 2.99 (2H, *apt* q, *J* = 6.5 Hz, H1), 2.44 (3H, s, Ts*Me*), 2.18 (2H, td, *J* = 7.5 and 2.0 Hz, H7), 1.80-1.75 (2H, m, H3), 1.69-1.62 (2H, m, H2), 1.48 (2H, *apt* quintet, *J* = 7.5 Hz, H8), 1.37-1.23 (6H, m, H9, 10 and 11), 0.89 (3H, t, *J* = 7.0 Hz, H12); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.9, 143.4, 136.9, 129.7, 127.1, 88.0, 76.2, 67.9, 54.9, 42.7, 32.0, 31.2, 28.5, 28.3, 25.1, 22.5, 21.5, 18.6, 14.0; **HRMS** (ESI+) calc for $C_{21}H_{31}NO_5SNa$ $[M+Na]^+$ 432.1815, found 432.1819; **Elemental Analysis:** $C_{21}H_{31}NO_5S$ requires C, 61.59%; H, 7.63%; N, 3.42%; found C, 61.71%; H, 7.52%; N, 3.48%.

(*S*)-methyl (6-(4-methylphenylsulfonamido)-1-(trimethylsilyl)hex-1-yn-3-yl) carbonate – (*S*)-4.33b

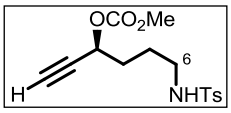


To a stirred solution carbonate **(*S*)-3.76b** (500 mg, 2.05 mmol, 1 eq.) in anhydrous THF (20 mL) under argon was added *tert*-butyl tosylcarbamate (721 mg, 2.66 mmol, 1.3 eq.) and PPh_3 (1.08 g, 4.10 mmol, 2 eq.). The resulting solution was cooled to 0 °C and DIAD (0.61 mL, 3.08 mmol, 1.5 eq.) was added dropwise. The reaction was allowed to warm to RT, stirred for 1 hour and quenched with sat. aq. $NaHCO_3$ (20 mL). The reaction mixture was diluted with water (10 mL) and Et_2O (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9→1:2 Et_2O/pet. ether) to leave pure Boc-tosylamide (1.022 g, 2.05 mmol, 99%) as a viscous colourless oil which was used directly in the next step without further characterisation.

To a stirred solution of the above Boc-tosylamide (950 mg, 1.91 mmol, 1 eq.) in anhydrous CH_2Cl_2 (19 mL) at 0 °C under argon was added TFA (1.9 mL). The reaction was allowed to warm to RT and stirred for 16 hours. The reaction was cooled to 0 °C and quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to leave pure carbonate **(*S*)-4.33b** (703 mg, 1.77 mmol, 93%) as a viscous colourless oil.

R_f 0.27 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ −51.0 (*c* = 1.25, $CHCl_3$); **IR** (thin film, cm^{-1}): 3284, 2959, 2179, 1751, 1599, 1442, 1327, 1262, 1159, 1094, 844; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.74 (2H, dt, *J* = 8.0 and 2.0 Hz, Ts*H*), 7.31 (2H, dt, *J* = 8.0 and 2.0 Hz, Ts*H*), 5.19 (1H, t, *J* = 6.0 Hz, H3), 4.66 (1H, t, *J* = 6.5 Hz, N*H*), 3.79 (3H, s, O*Me*), 2.98 (2H, *apt* q, *J* = 6.5 Hz, H6), 2.43 (3H, s, Ar*Me*), 1.82-1.77 (2H, m, H4), 1.68-1.61 (2H, m, H5), 0.15 (9H, s, SiMe_3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 152.7, 143.4, 136.8, 129.7, 127.0, 100.9, 92.0, 67.7, 55.0, 42.6, 31.7, 25.0, 21.5, −0.4; **HRMS** (ESI+): calc for $C_{18}H_{27}NO_5SSiNa$ $[M+Na]^+$ 420.1271, found 420.1268; **Elemental Analysis:** $C_{18}H_{27}NO_5SSi$ requires C, 54.38%; H, 6.85%; N, 3.52%; found C, 54.41%; H, 6.94%; N, 3.60%.

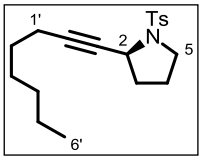
(*S*)-methyl (6-(4-methylphenylsulfonamido)hex-1-yn-3-yl) carbonate – (*S*)-4.33a



To a stirred solution of carbonate **(*S*)-4.33b** (110 mg, 0.277 mmol, 1 eq.) in THF (1.8 mL) at 0 °C was added TBAF (1M in THF, 0.26 mL, 0.263 mmol, 0.95 eq.). The reaction was stirred for 1 hour, quenched with water (2 mL) and allowed to warm to RT. The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was passed through a short plug of silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave pure tosylamide **(*S*)-4.33a** (86 mg, 0.264 mmol, 95%) as a viscous colourless oil.

R_f 0.14 (1:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ −24.4 (*c* = 1.33, $CHCl_3$); **IR** (thin film, cm^{-1}): 3283, 2958, 2873, 2123, 1749, 1598, 1442, 1324, 1305, 1157, 1019; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.75 (2H, dt, *J* = 8.5 and 2.0 Hz, Ts*H*), 7.31 (2H, dt, *J* = 8.5 and 2.0 Hz, Ts*H*), 5.17 (1H, td, *J* = 6.5 and 2.0 Hz, H3), 4.70 (1H, t, *J* = 6.0 Hz, N*H*), 3.80 (3H, s, O*Me*), 2.99 (2H, *apt* q, *J* = 6.5 Hz, H6), 2.50 (1H, d, *J* = 2.0 Hz, H1), 2.43 (3H, s, Ts*Me*), 1.85-1.80 (2H, m, H4), 1.70-1.64 (2H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.7, 143.5, 136.8, 129.7, 127.0, 79.8, 75.0, 67.0, 55.0, 42.5, 31.4, 24.9, 21.5; **HRMS** (ESI+): calc for $C_{15}H_{19}NO_5SNa$ $[M+Na]^+$ 348.0876, found 348.0872.

(*S*)-2-(oct-1-yn-1-yl)-1-tosylpyrrolidine – (*S*)-4.36d

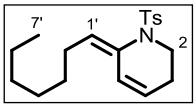


A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*S*)-4.33d** (50.0 mg, 0.122 mmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(dba)_2$ (3.5 mg, 5 mol%) and DPEphos (6.5 mg, 10 mol%) in degassed 1,4-dioxane (1.25 mL). The reaction was stirred and heated to 100 °C for 15 minutes. The reaction was allowed to cool, diluted with pet. ether (1 mL) and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave pure pyrrolidine **(*S*)-4.36d** (33 mg, 99 μmol, 81%) as a pale yellow solid.

m.p. 42-43 °C; **R_f** 0.40 (1:4 Et_2O/pet. ether); **96% *ee*** (CHIRALPAK IA, 1.25 mL/min, 5% IPA/0.1% EDA/Hexane) t_R (*S*): 7.26 min, t_R (*R*): 10.08 min; $[\alpha]_D^{25}$ −94.7 (*c* = 0.67, $CHCl_3$); **IR** (thin film, cm^{-1}): 2930, 2859, 2238, 1739, 1598, 1495, 1346, 1160, 1096, 1007, 815; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.78 (2H, dt, *J* = 8.0 and 2.0 Hz, Ts*H*), 7.29 (2H, dt, *J* = 8.0 and 2.0 Hz, Ts*H*), 4.55-4.52 (1H, m, H2),

3.38 (1H, dt, *J* = 9.5 and 7.5 Hz, H5), 3.32 (1H, ddd, *J* = 9.5, 7.5 and 4.0 Hz, H5), 2.43 (3H, s, Ts*Me*), 2.07-1.82 (6H, m, H3, 4 and 1'), 1.40-1.33 (2H, m, H2'), 1.32-1.20 (6H, m, H3', 4' and 5'), 0.89 (3H, t, *J* = 7.0 Hz, H6'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.0, 135.8, 129.2, 127.8, 84.7, 78.5, 50.7, 47.0, 34.3, 31.3, 28.5, 28.4, 24.3, 22.5, 21.5, 18.7, 14.0; **HRMS** (ESI+): calc for $C_{19}H_{27}NO_2SNa$ $[M+Na]^+$ 356.1655, found 356.1662; **Elemental Analysis:** $C_{19}H_{27}NO_2S$ requires C, 68.43%; H, 8.16%; N, 4.20%; found C, 68.58%; H, 8.05%; N, 4.01%.

(*E*)-6-heptylidene-1-tosyl-1,2,3,6-tetrahydropyridine – 4.37d



A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*)-4.33d** (50.0 mg, 0.122 mmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(dba)_2$ (3.5 mg, 5 mol%) and dppe (4.8 mg, 10 mol%) in degassed 1,4-dioxane (1.25 mL). The reaction was heated to 60 °C for 30 minutes, allowed to cool and diluted with pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent), the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave pure enamide **4.37d** (25 mg, 75 μmol, 61%) as a pale yellow oil.

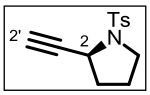
R_f 0.30 (1:4 Et_2O/pet. ether); **>95:5 *E/Z***; **IR** (thin film, cm^{-1}): 2927, 2856, 1739, 1598, 1454, 1343, 1127, 1093, 975, 814; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.65 (2H, dt, *J* = 8.0 and 2.0 Hz, Ts*H*), 7.21 (2H, d, *J* = 8.5 Hz, Ts*H*), 6.23-6.20 (1H, m, H5), 5.83 (1H, t, *J* = 8.0 Hz, H1'), 5.58 (1H, dtd, *J* = 10.0, 4.0 and 2.0 Hz, H4), 3.76 (2H, t, *J* = 6.0 Hz, H2), 2.40 (3H, s, Ts*Me*), 2.17 (2H, *apt* q, *J* = 7.5 Hz, H2'), 1.95-1.91 (2H, m, H3), 1.46-1.39 (2H, m, H3'), 1.36-1.25 (6H, m, H4', 5' and 6'), 0.90 (3H, t, *J* = 7.0 Hz, H7'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.1, 138.0, 130.8, 129.2, 128.2, 127.4, 126.2, 121.0, 44.4, 31.7, 29.5, 28.9, 26.8, 23.6, 22.6, 21.5, 14.1; **HRMS** (ESI+): calc for $C_{19}H_{27}NO_2SNa$ $[M+Na]^+$ 356.1655, found 356.1657.

(*S*)-2-ethynyl-1-tosylpyrrolidine and 6-methylene-1-tosyl-1,2,3,6-tetrahydropyridine – (*S*)-3.46a and 3.47a

A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*S*)-4.33b** (20.0 mg, 50.3 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(OAc)_2$ (0.6 mg, 5 mol%) and DPEphos (2.7 mg, 10 mol%) in degassed 1,4-dioxane (0.5 mL). The

reaction was heated to 100 °C for 15 minutes, allowed to cool and quenched with pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent) and the solvent removed *in vacuo* to leave the products as a *ca*. 35 : 30 : 35 ratio (**(*S*)-4.36b : (*S*)-4.36a : 4.37a**), by ^{1}H NMR spectroscopy. The crude mixture was taken up in THF (1 mL) and to it added TBAF (1.0 M in THF, 50 µL, 50 µmol, 1 eq.). The reaction was stirred for 30 minutes, the solvent removed *in vacuo* and the residue purified directly by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave an inseparable 53 : 47 mixture (by ^{1}H NMR spectroscopy) of pyrrolidine **(*S*)-3.46a** and enamide **3.47a** (6.0 mg, 24.1 µmol, 48%) as a colourless oil.

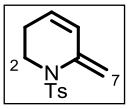
R_f 0.25 (1:4 Et_2O/pet. ether); **HMRS** (ESI+): calc for $C_{13}H_{15}NO_2SNa$ $[M+Na]^+$ 272.0716, found 272.0716.



(*S*)-2-ethynyl-1-tosylpyrrolidine – (*S*)-3.46a

98% *ee* (see below); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.79 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.31 (2H, d, *J* = 8.5 Hz, Ts*H*), 4.51 (1H, ddd, *J* = 7.0, 4.5 and 2.0 Hz, H2), 3.39 (1H, ddd, *J* = 9.5, 7.5 and 4.0 Hz, H5), 3.34 (1H, dt, *J* = 9.5 and 7.5 Hz, H5), 2.43 (3H, s, Ts*Me*), 2.26 (1H, d, *J* = 2.0 Hz, H2'), 2.10-1.93 (3H, m, H3 and 4), 1.89-1.82 (1H, m, H4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.4, 135.3, 129.5, 127.7, 82.6, 72.0, 50.1, 47.4, 33.9, 24.4, 21.5.

Enantiomeric excess was determined through conversion to pyrrolidine **(*S*)-4.36c** using PhI, $PdCl_2(PPh_2)_2$ (5 mol%) and CuI (10 mol%) in *i*-Pr_2NH / THF (1 : 2). **(*S*)-4.36c** was examined by chiral HPLC. (CHIRALPAK IC, 1.1 mL/min, 20% IPA/0.1% EDA/Hexane): t_R (*R*) = 28.62 min; t_R (*S*) = 30.03 min.



6-methylene-1-tosyl-1,2,3,6-tetrahydropyridine – 4.37a

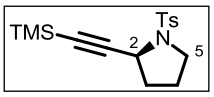
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.70 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.26 (2H, d, *J* = 8.5 Hz, Ts*H*), 8.54 (1H, dt, *J* = 10.0 and 2.0 Hz, H5), 5.72 (1H, dt, *J* = 10.0 and 4.0 Hz, H4), 5.34 (1H, bs, H7), 4.76 (1H, bs, H7), 3.80 (2H, t, *J* = 6.0 Hz, H2), 2.10-2.01 (2H, m, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.5, 138.5, 137.4, 129.5, 127.2, 127.0, 126.4, 107.2, 44.1, 23.8, 21.5.

(*S*)-1-tosyl-2-((trimethylsilyl)ethynyl)pyrrolidine and 6-methylene-1-tosyl-1,2,3,6-tetrahydropyridine – (*S*)-4.36b and 4.37a

A vial containing a stirrer bar was charged with carbonate **(*S*)-4.33b** (20.0 mg, 50.3 µmol, 1 eq.) and

placed under an argon atmosphere. To it was added a solution of $Pd(OAc)_2$ (0.6 mg, 5 mol%) and dppe (2.0 mg, 10 mol%) in degassed 1,4-dioxane (0.5 mL). The reaction was heated to 100 °C for 15 minutes, allowed to cool and quenched with pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent), the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave an inseparable 57 : 43 mixture of pyrrolidine **(*S*)-3.46b** and enamide **4.37a** (11.0 mg, 38.2 μmol, 76% estimated by ^{1}H NMR spectroscopy) as a colourless oil.

R_f 0.25 (1:4 Et_2O/pet. ether).



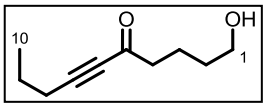
(*S*)-1-tosyl-2-((trimethylsilyl)ethynyl)pyrrolidine – (*S*)-4.36b

98% *ee* (see below); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.80 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.29 (2H, d, *J* = 8.0 Hz, Ts*H*), 4.59 (1H, dd, *J* = 7.0 and 3.5 Hz, H2), 3.42 (1H, dt, *J* = 9.5 and 7.0 Hz, H5), 3.34-3.29 (1H, m, H5), 2.07-1.98 (3H, m, H3 and 4), 1.92-1.85 (1H, m, H4), 0.08 (9H, s, Si*Me*$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.1, 137.4, 129.4, 127.6, 104.1, 88.3, 50.9, 47.1, 34.2, 24.4, 21.5, −0.3; **HRMS** (ESI+): calc for $C_{16}H_{23}NO_2SSiNa$ $[M+Na]^+$ 344.1111, found 344.1103.

Enantiomeric excess for **(*S*)-4.36b** was determined as for **(*S*)-4.36a**, after removal of the silyl group with TBAF in THF. **(*S*)-3.46c** (CHIRALPAK IC, 1.1 mL/min, 20% IPA/0.1% EDA/Hexane): t_R (*R*) = 28.58 min, t_R (*S*) = 30.09 min.

Spectroscopic data for **4.37a** identical to that prepared previously.

1-hydroxydec-6-yn-5-one – 3.116.1h[268]

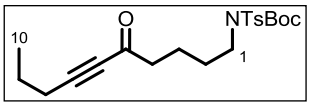


To a stirred solution of 1-pentyne (1.17 mL, 11.9 mmol, 1.1 eq.) in anhydrous THF (40 mL) at −78 °C under argon was added *n*-butyllithium (2.5 M in hexanes, 5.20 mL, 13.0 mmol, 1.2 eq.) dropwise. The resulting solution was stirred for 30 minutes at −78 °C and to it added $BF_3{\cdot}OEt_2$ (1.60 mL, 13.0 mmol, 1.2 eq.) dropwise. The solution was stirred for a further 5 minutes at −78 °C and to it added δ-valerolactone **3.116** (1.00 mL, 10.8 mmol, 1 eq.) in one portion. The reaction was allowed to warm to RT and stirred for 2 hours. The reaction was quenched with sat. aq. NH_4Cl/NH_4OH (2:1 v:v, 40 mL), the layers separated and the aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave ketone **3.116.1h** (1.81 g, 10.8 mmol, 99%) as a pale yellow oil of sufficient purity to

use in the next step.

R_f 0.54 (Et_2O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 3.67-3.63 (2H, m, H1), 2.59 (2H, t, 7.0 Hz, H4), 2.35 (2H, t, *J* = 7.0 Hz, H8), 1.76 (2H, *apt* quintet, *J* = 7.5 Hz, H2), 1.65-1.56 (5H, m, H3, 9 and O*H*), 1.02 (3H, t, *J* = 7.0 Hz, H10); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 188.2, 94.4, 80.9, 62.3, 45.1, 31.9, 21.2, 20.9, 20.1, 13.5. Data consistent with literature.[268]

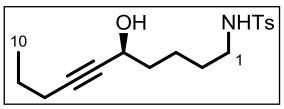
tert-butyl (5-oxodec-6-yn-1-yl)(tosyl)carbamate – 4.76h



To a stirred solution of ketone **3.116.1h** (100 mg, 0.594 mmol, 1 eq.) and *tert*-butyl tosylcarbamate (177 mg, 0.654 mmol, 1.1 eq.) in anhydrous THF (6 mL) under argon was added DIAD (0.14 mL, 0.713 mmol, 1.2 eq.), followed immediately by PPh_3 (203 mg, 0.772 mmol, 1.3 eq.) in one portion. The reaction was stirred at RT for 1 hour and quenched with sat. aq. $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:5→1:2 Et_2O/pet. ether) to leave pure ketone **4.76h** (204 mg, 0.484 mmol, 81%) as a colourless oil.

R_f 0.25 (1:3 Et_2O/pet. ether); **IR** (thin film, cm^{-1}): 2967, 2211, 1724, 1671, 1456, 1352, 1287, 1153, 1087, 999; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.77 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.30 (2H, d, *J* = 8.0 Hz, Ts*H*), 3.83 (2H, t, *J* = 7.0 Hz, H1), 2.61 (2H, t, *J* = 7.0 Hz, H4), 2.44 (3H, s, Ts*Me*), 2.35 (2H, t, *J* = 7.0 Hz, H8), 1.83-1.69 (4H, m, H2 and 3), 1.62 (2H, *apt* sextet, *J* = 7.0 Hz, H9), 1.33 (9H, s, CO_2t-*Bu*), 1.02 (3H, t, *J* = 7.5 Hz, H10); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 187.7, 150.9, 144.1, 137.4, 129.2, 127.8, 94.5, 84.2, 80.9, 46.6, 44.9, 29.4, 27.8, 21.6, 21.2, 21.1, 20.9, 13.5; **HRMS** (ESI+): calc for $C_{22}H_{31}NO_5SNa$ $[M+Na]^+$ 444.1815, found 444.1819.

(*S*)-*N*-(5-hydroxydec-6-yn-1-yl)-4-methylbenzenesulfonamide – (*S*)-4.76h.2



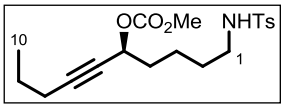
A solution of ketone **4.76h** (93 mg, 0.221 mmol, 1 eq.) was dissolved in IPA (1.1 mL) and degassed for 20 minutes. A solution of [Ru((*S*,*S*)-TsDPEN)(*p*-cymene)] **(*S*,*S*)-3.53** (2.6 mg, 2 mol%) in anhydrous CH_2Cl_2 (0.1 mL) was added and the reaction mixture degassed for a further 10 minutes. The reaction was stirred for a further 16 hours, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:3→1:1

Et_2O/pet. ether) to leave pure alcohol (68 mg, 0.161 mmol, 73%) as a colourless oil which was used directly in the next step without further characterisation. Enantiomeric excess was determined through chiral HPLC analysis at this stage, and found to be 96% *ee*. (CHIRALPAK IB, 1.3 mL/min, 10% IPA/Hexane): t_R (*R*): 6.00 min, t_R (*S*): 6.54 min.

The above alcohol was taken up in MeOH (2.5 mL) and to it added K_2CO_3 (250 mg). The resulting suspension was stirred and heated to 80 °C for 2 hours. The reaction was allowed to cool and quenched with 1N aq. HCl (2.5 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1 Et_2O/pet. ether→Et_2O) to leave pure sulfonamide **(*S*)-4.76h.1** (52 mg, 0.161 mmol, 99%) as a colourless oil.

R_f 0.17 (2:1 Et_2O/pet. ether); **96% *ee*** (see above); $[\alpha]_D^{20}$ −2.9 (*c* = 0.86, $CHCl_3$); **IR** (thin film, cm^{-1}): 3479, 3280, 2934, 2869, 2238, 1598, 1456, 1322, 1155, 1092, 1020; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.73 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.28 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.10 (1H, bs, N*H*), 4.31-4.25 (1H, m, H5), 2.93-2.87 (2H, m, H1), 2.40 (3H, s, Ts*Me*), 2.31 (1H, bs, O*H*), 2.16-2.10 (2H, m, H8), 1.64-1.53 (2H, m, H4), 1.52-1.36 (6H, m, H2, 3 and 9), 0.94 (3H, t, *J* = 7.0 Hz, H10); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 143.2, 136.8, 129.6, 127.0, 85.3, 81.1, 62.1, 42.9, 37.3, 29.0, 22.0, 22.0, 21.4, 20.5, 13.4; **HRMS** (ESI+): calc for $C_{17}H_{25}NO_3SNa$ $[M+Na]^+$ 346.1447, found 346.1449.

(*S*)-methyl (1-(4-methylphenylsulfonamido)dec-6-yn-5-yl) carbonate – (*S*)-4.44h

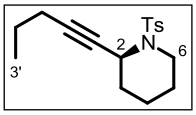


To a stirred solution of sulfonamide **(*S*)-4.76h.1** (49 mg, 0.151 mmol, 1 eq.) and pyridine (37 μL, 0.453 mmol, 3 eq.) in anhydrous CH_2Cl_2 (1.5 mL) at 0 °C under argon was added methyl chloroformate (23 μL, mmol, 2 eq.). The reaction was stirred at 0 °C for 30 minutes and quenched with sat. aq. $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with 1N aq. HCl (1 x 5 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to leave pure carbonate **(*S*)-4.44h** (57 mg, 0.149 mmol, 99%) as a colourless oil.

R_f 0.27 (1:1 Et_2O/pet. ether); $[\alpha]_D^{20}$ −46.3 (*c* = 1.02, $CHCl_3$); **IR** (thin film, cm^{-1}): 3286, 2959, 2871,

2241, 1748, 1599, 1442, 1325, 1258, 1157, 1093, 937; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.73 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.29 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.13 (1H, t, *J* = 6.5 Hz, H5), 4.89 (1H, t, *J* = 6.0 Hz, N*H*), 3.74 (3H, s, O*Me*), 2.90 (2H, *apt* q, *J* = 6.5 Hz, H1), 2.41 (3H, s, Ts*Me*), 2.15 (2H, td, *J* = 7.0 and 1.5 Hz, H8), 1.74-1.64 (2H, m, H4), 1.54-1.37 (6H, m, H2, 3 and 9), 0.93 (3H, t, *J* = 7.5 Hz, H10); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 154.9, 143.3, 136.8, 129.6, 127.0, 87.3, 76.7, 68.2, 54.7, 42.8, 34.4, 28.9, 21.9, 21.7, 21.4, 20.5, 13.3; **HRMS** (ESI+): calc for $C_{19}H_{27}NO_5SNa$ $[M+Na]^+$ 404.1502, found 404.1497; **Elemental Analysis:** $C_{19}H_{27}NO_5S$ requires C, 59.82%; H, 7.13%; N, 3.67%; found C, 59.72%; H, 7.07%; N, 3.76%.

(*S*)-2-(pent-1-yn-1-yl)-1-tosylpiperidine – (*S*)-4.45h



A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*S*)-4.44h** (20.0 mg, 48.1 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(OAc)_2$ (0.6 mg, 5 mol%) and DPEphos (2.8 mg, 10 mol%) in degassed 1,4-dioxane (0.5 mL). The reaction was heated to 100 °C for 15 minutes, allowed to cool and quenched with pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent), the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:9→1:4 Et_2O/pet. ether) to leave an inseparable mixture of piperidine **(*S*)-4.45h** and at least four additional unidentified compounds (11.6 mg, *ca.* 45% yield **(*S*)-4.45h** estimated) as a colourless oil.

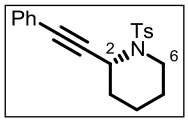
R_f 0.41 (1:2 Et_2O/pet. ether); **96% *ee*** (CHIRALPAK IC, 1.25 mL/min, 10% IPA/hexane): t_R (*S*) = 32.95 min; t_R (*R*) = 38.54 min; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.70 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.27 (2H, d, *J* = 8.0 Hz, Ts*H*), 4.84 (1H, bs, H2), 3.69-3.64 (1H, m, H5), 2.82-2.76 (1H, m, H5), 2,41 (3H, s, Ts*Me*), 1.86-1.58 (8H, m, H3, 4, 5 and 1'), 1.25-1.20 (2H, m, H2'), 0.79 (3H, t, *J* = 7.5 Hz, H3'); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 142.9, 135.3, 129.0, 128.1, 87.0, 75.1, 46.4, 42.0, 31.8, 25.3, 21.8, 21.4, 20.4, 19.3, 13.4; **HRMS** (ESI+): calc for $C_{17}H_{23}NO_2SNa$ $[M+Na]^+$ 328.1342, found 328.1336.

Repeating the reaction with dppe (2.1 mg, 10 mol%) replacing DPEphos resulted in the isolation of an inseparable mixture of a trace of piperidine **(*S*)-4.45h** alongside at least three additional unidentified compounds that made up the majority of the sample (9.2 mg).

(*R*)-2-(phenylethynyl)-1-tosylpiperidine and (*E*)-7-benzylidene-1-tosyl-2,3,4,7-tetrahydro-1*H*-azepine – (*R*)-4.45c and 4.46c

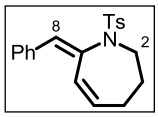
A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*)-4.44c** (20.0 mg, 48.1 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(OAc)_2$ (0.5 mg, 5 mol%) and DPEphos (2.6 mg, 10 mol%) in degassed 1,4-dioxane (0.5 mL). The reaction was heated to 100 °C for 15 minutes, allowed to cool and quenched with pet. ether (1 mL). The reaction mixture was passed through a short plug of silica gel (Et_2O eluent), the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel to leave an inseparable 80:20 (by ^{1}H NMR spectroscopy) mixture of piperidines **(*R*)-4.45c** and enamide **4.46c** (10.0 mg, 29.5 μmol, 61%) as a colourless oil. Enamide **4.46c** was present as an 85:15 mixture of *E/Z* isomers (by ^{1}H NMR spectroscopy).

R$_f$ 0.25 (1:4 Et_2O/pet. ether); **HRMS** (ESI+): calc for $C_{20}H_{21}NO_2SNa$ $[M+Na]^+$ 362.1185, found 362.1172.



(*R*)-2-(phenylethynyl)-1-tosylpiperidine – (*R*)-4.45c

98% *ee* (CHIRALPAK IC, 1.1 mL/min, 20% IPA/0.1% EDA/Hexane): t_R (*S*) = 30.24 min; t_R (*R*) = 36.66 min; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.73 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.28-7.19 (5H, m, Ph and Ts*H*), 6.99-6.97 (2H, m, Ph), 5.06 (1H, t, *J* = 3.0 Hz, H2), 3.79-3.74 (1H, m, H6), 2.88 (1H, td, *J* = 12.0 and 3.0 Hz, H6), 2.28 (3H, s, Ts*Me*), 1.93-1.85 (2H, m, H3), 1.76-1.64 (4H, m, H4 and 5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.2, 135.0, 131.4, 129.2, 128.1, 128.0, 128.0, 122.3, 86.8, 84.3, 46.8, 42.3, 31.6, 25.3, 21.3, 19.4.



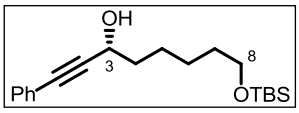
(*E*)-7-benzylidene-1-tosyl-2,3,4,7-tetrahydro-1*H*-azepine – 4.46c

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.75 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.34-7.31 (2H, m, Ph), 7.28-7.18 (5H, m, Ph and Ts*H*), 6.56 (1H, s, H8), 6.27 (1H, dq, *J* = 11.0 and 1.0 Hz, H6), 5.74 (1H, dtd, *J* = 11.0, 5.5 and 1.0 Hz, H5), 3.73 (2H, t, *J* = 6.5 Hz, H2), 2.43 (3H, s, Ts*Me*), 2.13-2.10 (2H, m, H4), 2.00-1.95 (2H, m, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.0, 138.2, 135.7, 135.0, 133.9, 131.1, 129.4, 129.3, 128.2, 127.6, 127.5, 126.7, 49.7, 27.1, 26.9, 21.5.

Repeating the reaction with dppe (1.9 mg, 10 mol%) replacing DPEphos resulted in a 19 : 81 mixture of **(*R*)-4.45c** and **4.46c** (11.0 mg, 32.4 μmol, 67%). Spectroscopic data for **(*R*)-4.45c** and **4.46c** were

identical, and **4.46c** was present as >95:5 *E/Z*.

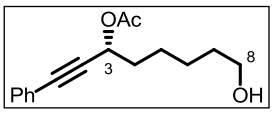
(*R*)-8-((*tert*-butyldimethylsilyl)oxy)-1-phenyloct-1-yn-3-ol – (*R*)-3.121.1



A solution of ketone **3.121** (230 mg, 0.695 mmol, 1 eq.) in IPA (3.5 mL) was degassed for 20 minutes. To it was added a solution of [Ru((*R,R*)-TsDPEN)(*p*-cymene)] **(*R,R*)-3.53** (8.3 mg, 2 mol%) in anhydrous CH_2Cl_2 (0.2 mL). The reaction was degassed for a further 10 minutes and stirred for 1 hour. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:9 Et_2O/pet. ether) to leave pure alcohol **(*R*)-3.121.1** (225 mg, 0.676 mmol, 97%) as a colourless oil.

97% *ee* (CHIRALPAK IB, 1.2 mL/min, 10% IPA/hexane): t_R (*R*) = 4.05 min, t_R (*S*) = 12.22 min; $[\alpha]_D^{25}$ −8.1 (*c* = 0.36, $CHCl_3$). All other spectroscopic data identical to *racemic* **3.121.1** prepared previously.

(*R*)-8-hydroxy-1-phenyloct-1-yn-3-yl acetate – (*R*)-4.79c



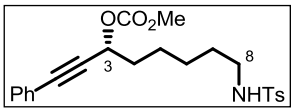
To a stirred solution of alcohol **(*R*)-3.121.1** (222 mg, 0.668 mmol, 1 eq.), pyridine (0.11 mL, 1.34 mmol, 2 eq.) and DMAP (8 mg, 67 μmol, 0.1 eq.) in anhydrous CH_2Cl_2 (7.0 mL) at 0 °C under argon was added Ac_2O (95 μL, 1.00 mmol, 1.5 eq.). The reaction was allowed to warm to RT and stirred for 2 hours. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with 1N aq. HCl (10 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue azeotroped with toluene (2 x 5 mL) to leave pure silyloxy acetate (225 mg, 0.601 mmol, 90%) as a colourless oil which was used without further characterisation.

To a stirred solution of the above silyloxy acetate (190 mg, 0.507 mmol, 1 eq.) in anhydrous THF (5 mL) was added TBAF (1M in THF, 0.56 mL, 0.56 mmol, 1.1 eq.) dropwise. The reaction was stirred for 16 hours and quenched with water (5 mL). The mixture was diluted with CH_2Cl_2 (5 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:2→2:1 Et_2O/pet. ether) to leave pure acetate **(*R*)-4.79c** (119 mg,

0.457 mmol, 90%) as a colourless oil.

R_f 0.47 (Et_2O); **$[\alpha]_D^{25}$** +92.0 (*c* = 0.66, $CHCl_3$); **IR** (thin film, cm^{-1}): 3397, 2936, 2863, 2232, 1742, 1491, 1443, 1372, 1230, 1020; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.46-7.43 (2H, m, Ph), 7.34-7.29 (3H, m, Ph), 5.61 (1H, t, *J* = 6.5 Hz, H3), 3.67 (2H, *apt* q, *J* = 6.0 Hz, H8), 2.12 (3H, s, C(O)*Me*), 1.90-1.85 (2H, m, H4), 1.65-1.58 (2H, m, H7), 1.58-1.52 (2H, m, H5), 1.49-1.42 (2H, m, H6), 1.30 (1H, t, *J* = 5.5 Hz, O*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 170.1, 131.9, 128.6, 128.2, 122.3, 86.5, 85.3, 64.4, 62.8, 34.8, 32.5, 25.3, 24.8, 21.1; **HRMS** (ESI+): calc for $C_{16}H_{20}O_3Na$ $[M+Na]^+$ 283.1305, found 283.1294.

(*R*)-methyl (8-(4-methylphenylsulfonamido)-1-phenyloct-1-yn-3-yl) carbonate – (*R*)-4.80c



To a stirred solution of acetate **(*R*)-4.79c** (143 mg, 0.549 mmol, 1 eq.), *tert*-butyl tosylcarbamate (194 mg, 0.714 mmol, 1.3 eq.) and PPh_3 (288 mg, 1.10 mmol, 2 eq.) in anhydrous THF (5 mL) under argon was added DIAD (0.16 mL, 0.824 mmol, 1.5 eq.) dropwise. The reaction was stirred for 1 hour and quenched with sat. aq. $NaHCO_3$ (5 mL). The mixture was diluted with CH_2Cl_2 (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was passed through a short plug of silica gel (Et_2O/pet. ether 1:9→1:2) and used directly in the next step without further purification.

The above residue was taken up in MeOH (5 mL) and to it added K_2CO_3 (500 mg). The reaction was heated to reflux and stirred for 4 hours. The reaction was allowed to cool, quenched with 1N aq. HCl (5 mL) and diluted with CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product passed through a short plug of silica gel (1:2→2:1 Et_2O/pet. ether) and used directly in the next step without further chaacterisation.

To a stirred solution of the above alcohol (102 mg, 0.275 mmol, 1 eq.) and pyridine (44 μL, 0.550 mmol, 2 eq.) in anhydrous CH_2Cl_2 (2.75 mL) at 0 °C under argon was added methyl chloroformate (32 μL, 0.413 mmol, 1.5 eq.). The reaction was stirred at 0 °C for 1 hour and quenched with sat. aq. $NaHCO_3$ (3 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2

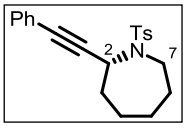
(2 x 5 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:2→2:1 Et_2O/pet. ether) to leave pure carbonate **(*R*)-4.80c** (91 mg, 0.212 mmol, 39%, *3 steps*) as a colourless oil.

R_f (Et_2O/pet. ether); **$[\alpha]_D^{20}$** +55.2 (*c* = 0.88, $CHCl_3$); **IR** (thin film, cm^{-1}): 3287, 2940, 2864, 2234, 1748, 1491, 1442, 1334, 1262, 1156, 1071, 942; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.45-7.42 (2H, m, Ph), 7.35-7.29 (5H, m, Ph and Ts*H*), 5.42 (1H, t, *J* = 6.5 Hz, H3), 4.55 (1H, t, *J* = 6.0 Hz, N*H*), 3.82 (3H, s, O*Me*), 2.94 (2H, *apt* q, *J* = 7.0 Hz, H8), 2.42 (3H, s, Ts*Me*), 1.89-1.79 (2H, m, H4), 1.52-1.44 (4H, m, H5 and 7), 1.37-1.30 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 143.3, 136.9, 131.8, 129.7, 128.7, 128.2, 127.0, 122.0, 86.2, 85.5, 68.4, 54.9, 43.0, 34.6, 29.4, 26.0, 24.4, 21.5; **HRMS** (ESI+): calc for $C_{23}H_{27}NO_5SNa$ $[M+Na]^+$ 452.1502, found 452.1496; **Elemental Analysis:** $C_{23}H_{27}NO_5S$ requires C, 64.31%; H, 6.34%; N, 3.26%; found C, 64.23%; H, 6.24%; N, 3.35%.

(*R*)-2-(phenylethynyl)-1-tosylazepane and (6*Z*)-8-benzylidene-1-tosyl-1,2,3,4,5,8-hexahydroazocine – (*R*)-4.81c and 4.82c

A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*)-4.80c** (20.0 mg, 46.6 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(OAc)_2$ (0.5 mg, 5 mol%) and DPEphos (2.5 mg, 10 mol%) in degassed 1,4-dioxane (0.5 mL). The reaction was stirred and heated to 100 °C for 15 minutes. The reaction was allowed to cool, quenched with pet. ether (0.5 mL) and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave a 75:25 mixture (by ^{1}H NMR spectroscopy) of pyrrolidine **(*S*,*R*)-4.81c** and enamide **(*R*)-4.82c** (4.3 mg, 12.1 μmol, 26%) as a colourless oil. Enamide **(*R*)-4.82c** was tentatively identified as a 3:2 mixture of geometrical isomers, although full assignment was complicated by overlapping signals in the ^{1}H and ^{13}C NMR spectra.

R_f 0.37 (1:2 Et_2O/pet. ether); **HRMS** (ESI+): calc for $C_{21}H_{23}NO_2SNa$ $[M+Na]^+$ 376.1342, found 376.1335.

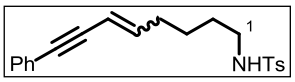


(*R*)-2-(phenylethynyl)-1-tosylazepane – (*R*)-4.81c

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.80 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.28-7.22 (5H, m, Ph

and Ts*H*), 7.10-7.07 (2H, m, Ph), 5.09 (1H, t, *J* = 7.0 Hz, H2), 3.67 (1H, dt, *J* = 14.5 and 4.5 Hz, H7), 3.07 (1H, ddd, *J* = 14.5, 10.5 and 3.0 Hz, H7), 2.35 (3H, s, Ts*Me*), 2.29-2.22 (1H, m, H3), 1.93-1.67 (6H, m, H3, 4, 5 and 6), 1.55-1.49 (1H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.0, 136.8, 131.4, 129.3, 128.2, 128.1, 127.5, 122.5, 86.8, 84.9, 49.1, 44.3, 36.8, 29.3, 27.9, 23.9, 21.4.

4-methyl-*N*-(8-phenyloct-5-en-7-yn-1-yl)benzenesulfonamide – 4.83



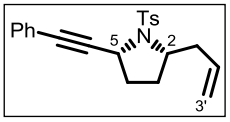
A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*)-4.80c** (20.0 mg, 46.6 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(OAc)_2$ (0.5 mg, 5 mol%) and dppe (1.9 mg, 10 mol%) in degassed 1,4-dioxane (0.5 mL). The reaction was stirred and heated to 100 °C for 15 minutes. The reaction was allowed to cool, quenched with pet. ether (0.5 mL) and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:9→1:2 Et_2O/pet. ether) to leave enyne **4.83** (12.8 mg, 38.9 μmol, 78%) as a colourless oil.

R_f 0.10 (1:2 Et_2O/pet. ether); **52:48 *E/Z***; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.76 (2H, d, *J* = 8.0 Hz, *E*-Ts*H*), 7.73 (2H, d, *J* = 8.0 Hz, *Z*-Ts*H*), 7.44-7.41 (2H, m, Ph), 7.34-7.27 (5H, m, Ph and Ts*H*), 6.14 (1H, dt, *J* = 16.0 and 7.0 Hz, *E*-H5), 5.88 (1H, dt, *J* = 10.5 and 7.0 Hz, *Z*-H5), 5.68 (1H, dt, *J* = 10.5 and 1.5 Hz, *Z*-H6), 5.65 (1H, dt, *J* = 16.0 and 1.5 Hz, *E*-H6), 4.45-4.40 (1H, m, N*H*), 3.00-2.94 (2H, m, H1), 2.44 (3H, s, *E*-Ts*Me*), 2.41 (3H, s, *Z*-Ts*Me*), 2.36 (2H, qd, *J* = 7.0 and 1.5 Hz, *Z*-H4), 2.12 (2H, qd, *J* = 7.0 and 1.5 Hz, *E*-H4), 1.56-1.39 (H4, m, H2 and 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.8, 143.4, 143.3, 142.9, 136.9, 131.4, 131.4, 129.7, 129.7, 128.3, 128.3, 128.1, 128.0, 127.1, 127.1, 123.4, 110.2, 109.8, 93.7, 88.2, 88.0, 86.1, 43.0, 42.9, 32.4, 29.6, 29.0, 29.0, 25.7, 25.6, 21.5, 21.5; **HRMS** (ESI+): calc for $C_{21}H_{23}NO_2SNa$ $[M+Na]^+$ 376.1342, found 376.1328.

(2*S*,5*R*)-2-allyl-5-(phenylethynyl)-1-tosylpyrrolidine and (*R*,*E*)-2-allyl-6-benzylidene-1-tosyl-1,2,3,6-tetrahydropyridine - (*S*,*R*)-4.48c and (*R*)-4.49c

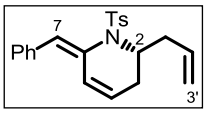
A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*S*,*R*)-4.47c** (20.0 mg, 45.3 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(OAc)_2$ (0.5 mg, 5 mol%) and DPEphos (2.4 mg, 10 mol%) in degassed 1,4-dioxane (0.45 mL). The reaction was stirred and heated to 100 °C for 15 minutes. The reaction was allowed to cool, quenched

with pet. ether (0.5 mL) and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave a 73:27 mixture (by ^1H NMR spectroscopy) of pyrrolidine **(*S*,*R*)-4.48c** and enamide **(*R*)-4.49c** (14.2 mg, 38.9 μmol, 86%) as a white solid. Careful chromatographic separation on silica gel (1:19→1:4 Et_2O/pet. ether) allowed isolation of pure samples of **(*S*,*R*)-4.48c** and **(*R*)-4.49c** for characterisation.



(2*S*,5*R*)-2-allyl-5-(phenylethynyl)-1-tosylpyrrolidine – (*S*,*R*)-4.48c

White solid. **m.p.** 138-139 °C; $\mathbf{R_f}$ 0.25 (1:4 Et_2O/pet. ether); **95:5 *dr***; $[\alpha]_D^{20}$ +104.2° (*c* = 0.34, $CHCl_3$); **IR** (thin film, cm^{-1}): 3068, 2977, 2234, 1641, 1598, 1491, 1444, 1349, 1160, 1093; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.82 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.35-7.28 (7H, m, Ph and Ts*H*), 5.82 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2'), 5.12-5.05 (2H, m, H3'), 4.74 (1H, dd, *J* = 7.0 and 4.0 Hz, H5), 3.94-3.88 (1H, m, H2), 2.68-2.62 (1H, m, H1'), 2.46-2.39 (1H, m, H1'), 2.41 (3H, s, Ts*Me*), 2.03-1.98 (1H, m, H4), 1.96-1.79 (3H, m, H3 and 4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.4, 136.4, 134.4, 131.6, 129.6, 128.2, 128.2, 127.5, 122.8, 117.7, 88.7, 83.6, 60.5, 52.2, 40.6, 32.9, 29.9, 21.5; **HRMS** (ESI+): calc for $C_{22}H_{23}NO_2SNa$ $[M+Na]^+$ 388.1342, found 388.1330.

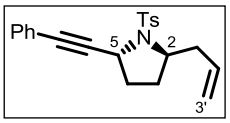


(*R*,*E*)-2-allyl-6-benzylidene-1-tosyl-1,2,3,6-tetrahydropyridine – (*R*)-4.49c

Colourless oil. $\mathbf{R_f}$ 0.28 (1:4 Et_2O/pet. ether); $[\alpha]_D^{20}$ +171.3 (*c* = 0.40, $CHCl_3$); **IR** (thin film, cm^{-1}): 3057, 2920, 1737, 1641, 1598, 1492, 1445, 1345, 1165; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.69 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.38-7.34 (2H, m, Ph), 7.30-7.25 (3H, m, Ph), 7.22 (2H, d, *J* = 8.5 Hz, Ts*H*), 6.91 (1H, bs, H7), 6.45 (1H, dd, *J* = 10.0 and 3.0 Hz, H5), 5.86 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2'), 5.54-5.49 (1H, m, H4), 5.11-5.04 (2H, m, H3'), 4.48 (1H, q, *J* = 7.5 Hz, H2), 2.46-2.39 (1H, m, H1'), 2.40 (3H, s, Ts*Me*), 2.19-2.10 (2H, m, H3 and 1'), 1.89 (1H, dd, *J* = 18.5 and 6.0 Hz, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.3, 137.6, 135.7, 134.6, 129.8, 129.3 (2xC), 128.8, 128.3, 127.4, 127.2, 125.9, 121.8, 117.6, 52.2, 37.8, 26.8, 21.5; **HRMS** (ESI+): calc for $C_{22}H_{23}NO_2SNa$ $[M+Na]^+$ 388.1342, found 388.1332.

Repeating the reaction with dppe (1.8 mg, 10 mol%) replacing DPEphos resulted in a 40:60 mixture of **(*S*,*R*)-4.48c** and **(*R*)-4.49c** (13.8 mg, 37.8 μmol, 83%). Spectroscopic data for **(*S*,*R*)-4.48c** and **(*R*)-4.49c** were identical, and **(*S*,*R*)-4.48c** was present as 98:2 *dr*.

(2*R*,5*R*)-2-allyl-5-(phenylethynyl)-1-tosylpyrrolidine – (*R*,*R*)-4.48c

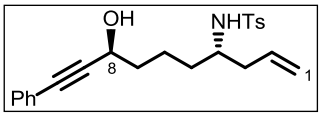


A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*,*R*)-4.47c** (20.0 mg, 45.3 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(OAc)_2$ (0.5 mg, 5 mol%) and DPEphos (2.4 mg, 10 mol%) in degassed 1,4-dioxane (0.45 mL). The reaction was stirred and heated to 100 °C for 15 minutes. The reaction was allowed to cool, quenched with pet. ether (0.5 mL) and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave pure pyrrolidine **(*R*,*R*)-4.47c** (12.6 mg, 34.5 μmol, 76%) as a white solid.

m.p. 69-70 °C; $\mathbf{R_f}$ 0.32 (1:4 Et_2O/pet. ether); **>99:1 *dr***; $[\alpha]_D^{20}$ +37.2 (*c* = 0.83, $CHCl_3$); **IR** (thin film, cm^{-1}): ; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.83 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.31-7.24 (3H, m, Ph), 7.12-7.09 (4H, m, Ph and Ts*H*), 5.82 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2'), 5.15-5.08 (2H, m, H3'), 4.91 (1H, d, *J* = 6.5 Hz, H5), 3.77-3.72 (1H, m, H2), 2.85-2.79 (1H, m, H1'), 2.43-2.36 (1H, m, H1'), 2.28 (3H, s, Ts*Me*), 2.25-2.16 (2H, m, H3 and 4), 1.98-1.87 (2H, m, H3 and 4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 142.9, 136.5, 134.7, 131.5, 129.0, 128.2, 128.1, 128.0, 122.5, 117.7, 87.1, 84.9, 58.5, 52.5, 40.1, 31.7, 29.1, 21.4; **HRMS** (ESI+): calc for $C_{22}H_{23}NO_2SNa$ $[M+Na]^+$ 388.1342, found 388.1330.

Repeating the reaction with dppe (1.8 mg, 10 mol%) replacing DPEphos resulted in an inseparable 65:35 mixture of **(*R*,*R*)-4.48c** and **(*S*)-4.49c** (11.8 mg, 32.3 μmol, 71%). Spectroscopic data for **(*R*,*R*)-4.48c** was identical, and was present as 95:5 *dr*. The spectroscopic data for **(*S*)-4.49c** was identical to **(*R*)-4.49c** prepared previously.

***N*-((4*S*,8*S*)-8-hydroxy-10-phenyldec-1-en-9-yn-4-yl)-4-methylbenzenesulfonamide – (*S*,*S*)-4.84c**



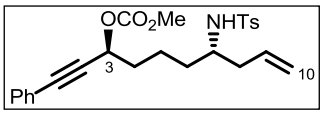
To a stirred solution of carbonate **(*S*,*R*)-3.128** (130 mg, 0.430 mmol, 1 eq.), *tert*-butyl tosylcarbamate (134 mg, 0.494 mmol, 1.15 eq.) and PPh_3 (158 mg, 0.602 mmol, 1.4 eq.) in anhydrous THF (4.5 mL) under argon was added DIAD (0.11 mL, 0.538 mmol, 1.25 eq.). The reaction was stirred for 16 hours and quenched with sat. aq. $NaHCO_3$ (5 mL). The reaction mixture was diluted with CH_2Cl_2 (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and

the solvent removed *in vacuo*. The crude product was passed through a short plug of silica gel (1:9→1:1 Et_2O/pet. ether) to leave the Boc-sulfonamide which was used directly in the next step without further purification.

The above crude Boc-sulfonamide was taken up in MeOH (2.5 mL) and to it added K_2CO_3 (250 mg). The mixture was heated to 75 °C and stirred for 72 hours. The reaction was allowed to cool to RT and quenched with 1N aq. HCl (2.5 mL). The reaction mixture was diluted with CH_2Cl_2 (5 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1→1:2 Et_2O/pet. ether) to leave pure sulfonamide **(*S*,*S*)-4.84c** (39 mg, 98 μmol, 23% *2 steps*) as a viscous colourless oil.

R_f 0.10 (1:1 Et_2O/pet. ether); **>95:5 *dr***; **$[\alpha]_D^{20}$** +8.9 (*c* = 0.62, $CHCl_3$); **IR** (thin film, cm^{-1}): 3475, 3277, 2927, 2236, 1641, 1598, 1490, 1443, 1323, 1156, 1092, 918; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.76 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.44-7.41 (2H, m, Ph), 7.33-7.29 (3H, m, Ph), 7.27 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.55 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2), 5.01 (1H, d, *J* = 10.0 Hz, H1), 4.95 (1H, d, *J* = 17.0 Hz, H1), 4.69 (1H, bs, N*H*), 4.51 (1H, t, *J* = 6.5 Hz, H8), 3.34-3.27 (1H, m, H4), 2.40 (3H, s, Ts*Me*), 2.21 (1H, bs, O*H*), 2.11 (2H, t, *J* = 6.5 Hz, H3), 1.74-1.64 (2H, m, H7), 1.53-1.41 (4H, m, H5 and 6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.3, 138.0, 133.1, 131.6, 129.6, 128.4, 128.3, 127.1, 122.5, 118.9, 89.9, 84.8, 62.5, 53.1, 39.1, 37.3, 34.0, 21.5, 21.0; **HRMS** (ESI+): calc for $C_{23}H_{27}NO_3SNa$ $[M+Na]^+$ 420.1604, found 420.1588.

methyl ((3*S*,7*S*)-7-(4-methylphenylsulfonamido)-1-phenyldec-9-en-1-yn-3-yl) carbonate – (*S*,*S*)-4.85c

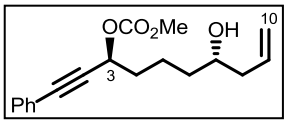


To a stirred solution of alcohol **(*S*,*S*)-4.84c** (35 mg, 88.0 μmol, 1 eq.) and pyridine (36 μL, 0.440 mmol, 5 eq.) in anhydrous CH_2Cl_2 (1 mL) at 0 °C under argon was added methyl chloroformate (17 μL, 0.220 mmol, 2.5 eq.). The reaction was allowed to warm to RT and stirred for 30 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (1 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with 1N aq. HCl (2 x 10 mL), dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to

leave pure carbonate **(*S*,*S*)-4.85c** (31 mg, 68.0 μmol, 77%) as a colourless oil.

R_f 0.22 (1:1 Et_2O/pet. ether); **>95:5 *dr***; $[\alpha]_D^{20}$ −40.3 (*c* = 1.18, $CHCl_3$); **IR** (thin film, cm^{-1}): 3286, 2955, 2866, 2234, 1750, 1641, 1599, 1491, 1442, 1324, 1265, 1158, 1093, 995; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.75 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.45-7.42 (2H, m, Ph), 7.36-7.29 (3H, m, Ph), 7.28 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.55 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H9), 5.36 (1H, t, *J* = 6.5 Hz, H3), 5.03 (1H, d, *J* = 10.0 Hz, H10), 4.97 (1H, d, *J* = 17.0 Hz, H10), 4.53 (1H, d, *J* = 8.0 Hz, N*H*), 3.83 (3H, s, O*Me*), 3.33-3.28 (1H, m, H7), 2.40 (3H, s, Ts*Me*), 2.12 (2H, t, *J* = 7.0 Hz, H8), 1.83-1.74 (2H, m, H4), 1.55-1.38 (4H, m, H5 and 6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 143.3, 138.0, 133.0, 131.8, 129.6, 128.7, 128.2, 127.0, 122.0, 119.0, 86.3, 85.4, 68.2, 55.0, 53.0, 39.0, 34.4, 33.9, 21.4, 20.8; **HRMS** (ESI+): calc for $C_{25}H_{29}NO_5SNa$ $[M+Na]^+$ 478.1659, found 478.1643.

(3*S*,7*S*)-7-hydroxy-1-phenyldec-9-en-1-yn-3-yl methyl carbonate – (*S*,*S*)-3.128



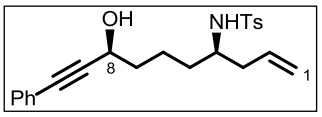
To a stirred solution of carbonate **(*S*)-3.118c** (500 mg, 1.91 mmol, 1 eq.), DMSO (1.29 mL, 18.15 mmol, 9.5 eq.) and Et_3N (1.86 mL, 13.37 mmol, 7 eq.) in anhydrous CH_2Cl_2 (19 mL) under argon was added SO_3·pyridine complex (910 mg, 5.72 mmol, 3 eq.) in one portion. The reaction was stirred for 90 minutes and quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:5→1:2 Et_2O/pet. ether) to leave, after azeotropic removal of residual pyridine (toluene, 2 x 5 mL), pure aldehyde **(*S*)-3.127** (423 mg, 1.63 mmol, 85%) as a pale yellow oil which was used directly in the next step.

To a stirred solution of aldehyde **(*S*)-3.127** (415 mg, 1.59 mmol, 1 eq.) in anhydrous CH_2Cl_2 (14 mL) at −20 °C under argon was added a solution of Leighton's reagent **(*S*,*S*)-3.64** (0.38 M in CH_2Cl_2, 5.03 mL, 1.91 mmol, 1.2 eq.). The reaction was transferred to a −25 °C freezer and allowed to stand for 60 hours. The solvent was removed *in vacuo* and the crude residue diluted with Et_2O (20 mL) and 1N aq. HCl (20 mL). The resultant biphasic mixture was stirred vigorously for 15 minutes and filtered. The filtrate was separated and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:4→1:1 Et_2O/pet. ether) to leave pure carbonate **(*S*,*S*)-3.128**

(244 mg, 0.81 mmol, 51%) as a pale yellow oil.

$[\alpha]_D^{20}$ −82.6 (*c* = 0.76, $CHCl_3$) [(*R,R*) $[\alpha]_D^{25}$ +82.1 (*c* = 1.37, $CHCl_3$)]. All other spectroscopic data identical to **(*R,R*)-3.128** prepared previously.

N-((4*R*,8*S*)-8-hydroxy-10-phenyldec-1-en-9-yn-4-yl)-4-methylbenzenesulfonamide – (*R,S*)-4.84c



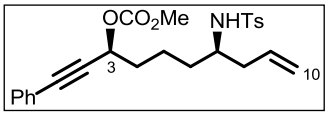
To a stirred solution of carbonate **(*S,S*)-3.128** (230 mg, 0.761 mmol, 1 eq.), *tert*-butyl tosylcarbamate (268 mg, 0.989 mmol, 1.3 eq.) and PPh_3 (399 mg, 1.52 mmol, 2 eq.) in anhydrous THF (8 mL) under argon was added DIAD (0.22 mL, 1.14 mmol, 1.5 eq.). The reaction was stirred for 16 hours, quenched with sat. aq. $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product passed through a short plug of silica gel (1:9→1:1 Et_2O/pet. ether) to leave the Boc-sulfonamide which was used directly in the next step without further purification.

The above crude Boc-sulfonamide was taken up in MeOH (5 mL) and to it added K_2CO_3 (500 mg). The reaction was stirred and heated to 75 °C for 72 hours. The reaction was allowed to cool, quenched with 1N aq. HCl (5 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:2 Et_2O/pet. ether→Et_2O) to leave pure sulfonamide **(*R,S*)-4.84c** (169 mg, 0.425 mmol, 56%, *2 steps*) as a viscous colourless oil.

R_f 0.10 (1:1 Et_2O/pet. ether); **>95:5 *dr***; $[\alpha]_D^{20}$ −4.7 (*c* = 0.73, $CHCl_3$); **IR** (thin film, cm^{-1}): 3468, 3279, 2927, 2865, 2232, 1641, 1598, 1573, 1490, 1443, 1323, 1155, 1092, 918; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.76 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.45-7.42 (2H, m, Ph), 7.34-7.31 (3H, m, Ph), 7.28 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.55 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2), 5.03 (1H, d, *J* = 10.0 Hz, H1), 4.97 (1H, d, *J* = 17.0 Hz, H1), 4.50 (1H, t, *J* = 6.5 Hz, H8), 4.41 (1H, d, *J* = 8.5 Hz, N*H*), 3.35-3.28 (1H, m, H4), 2.41 (3H, s, Ts*Me*), 2.12 (2H, t, *J* = 6.5 Hz, H3), 1.85 (1H, bs, O*H*), 1.73-1.64 (2H, m, H7), 1.56-1.40 (4H, m, H5 and 6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.3, 138.0, 133.1, 131.7, 129.6, 128.4, 128.3, 127.1, 122.5, 119.1, 89.8, 85.0, 62.6, 53.1, 39.0, 37.3, 34.1, 21.5, 21.0; **HRMS** (ESI+): calc for

$C_{23}H_{27}NO_3SNa$ $[M+Na]^+$ 420.1604, found 420.1603.

methyl ((3*S*,7*R*)-7-(4-methylphenylsulfonamido)-1-phenyldec-9-en-1-yn-3-yl) carbonate – (*S*,*R*)-4.85c



To a stirred solution of alcohol **(*R*,*S*)-4.84c** (167 mg, 0.42 mmol, 1 eq.) and pyridine (0.17 mL, 2.10 mmol, 5 eq.) in anhydrous CH_2Cl_2 (4 mL) at 0 °C under argon was added methyl chloroformate (81 μL, 1.05 mmol, 2.5 eq.). The reaction was allowed to warm to RT and stirred for 30 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1N aq. HCl (2 x 10 mL), dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:3→1:1 Et_2O/pet. ether) to leave pure carbonate **(*S*,*R*)-4.85c** (175 mg, 0.384 mmol, 91%) as a colourless oil.

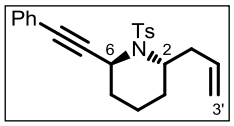
R_f 0.21 (1:1 Et_2O/pet. ether); **>95:5 *dr***; $[\alpha]_D^{20}$ −44.3 (*c* = 0.94, $CHCl_3$); **IR** (thin film, cm^{-1}): 3285, 2955, 2867, 2232, 1750, 1641, 1599, 1491, 1443, 1324, 1266, 1159, 1093, 950; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.76 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.45-7.42 (2H, m, Ph), 7.35-7.29 (3H, m, Ph), 727 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.56 (1H, ddt, *J* = 17.0, 10.0 and 7.0 Hz, H9), 5.31 (1H, t, *J* = 6.5 Hz, H3), 5.02 (1H, d, *J* = 10.0 Hz, H10), 4.97 (1H, d, *J* = 17.0 Hz, H10), 4.65 (1H, d, *J* = 8.0 Hz, N*H*), 3.82 (3H, s, O*Me*), 3.32-3.25 (1H, m, H7), 2.40 (3H, s, Ts*Me*), 2.13 (2H, t, *J* = 6.5 Hz, H8), 1.82-1.70 (2H, m, H4), 1.54-1.34 (4H, m, H5 and 6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.9, 143.3, 137.9, 133.0, 131.8, 129.6, 128.7, 128.2, 127.0, 122.0, 118.9, 86.2, 85.4, 68.2, 54.9, 52.9, 39.0, 34.4, 33.8, 21.4, 20.8; **HRMS** (ESI+): calc for $C_{25}H_{29}NO_5SNa$ $[M+Na]^+$ 478.1659, found 478.1648.

(2*S*,6*S*)-2-allyl-6-(phenylethynyl)-1-tosylpiperidine and (*S*,*E*)-2-allyl-7-benzylidene-1-tosyl-2,3,4,7-tetrahydro-1*H*-azepine – (*S*,*S*)-4.86c and (*S*)-4.87c

A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*S*,*S*)-4.85c** (15.0 mg, 32.9 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of $Pd(OAc)_2$ (0.4 mg, 5 mol%) and DPEphos (1.8 mg, 10 mol%) in degassed 1,4-dioxane (0.35 mL). The reaction was stirred and heated to 100 °C for 15 minutes. The reaction was allowed to cool, quenched with pet. ether (0.5 mL) and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4

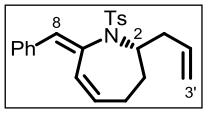
Et_2O/pet. ether) to leave an inseparable 77:23 mixture (by ^1H NMR spectroscopy) of piperidine **(*S*,*S*)-4.86c** and enamide **(*S*)-4.87c** (8.5 mg, 22.4 μmol, 68%) as a colourless oil.

R_f 0.32 (1:4 Et_2O/pet. ether); **HRMS** (ESI+): calc for $C_{23}H_{25}NO_2SNa$ $[M+Na]^+$ 402.1498, found 402.1492.



(2*S*,6*S*)-2-allyl-6-(phenylethynyl)-1-tosylpiperidine – (*S*,*S*)-4.86c

94:6 *dr*; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.82 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.38-7.19 (7H, m, Ph and Ts*H*), 5.73-5.64 (1H, m, H2'), 5.25 (1H, t, *J* = 4.0 Hz, H6), 5.08-5.02 (2H, m, H3'), 3.76-3.70 (1H, m, H2), 2.74-2.68 (1H, m, H1'), 2.49-2.40 (1H, m, H1'), 2.35 (3H, s, Ts*Me*), 2.02-1.95 (2H, m, H5), 1.92-1.83 (2H, m, H3 and 4), 1.78-1.72 (1H, m, H4), 1.57-1.51 (1H, m, H3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 142.8, 139.0, 135.2, 131.6, 129.3, 128.3, 128.1, 127.4, 122.6, 117.5, 86.9, 86.2, 55.4, 48.2, 38.3, 31.2, 28.8, 21.4, 18.8.



(*S*,*E*)-2-allyl-7-benzylidene-1-tosyl-2,3,4,7-tetrahydro-1H-azepine – (*S*)-4.87c

^{1}H NMR (500 MHz, $CDCl_3$, *E* isomer): δ_H 7.73 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.38-7.27 (5H, m, Ph), 7.22 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.57 (1H, bs, H8), 6.24 (1H, dd, *J* = 11.0 and 3.0 Hz, H6), 5.82 (ddt, *J* = 17.0, 10.0 and 7.0 Hz, H2'), 5.67-5.62 (1H, m, H5), 5.08-5.01 (2H, m, H3'), 4.25-4.18 (1H, m, H2), 2.48 (1H, dt, *J* = 14.0 and 7.0 Hz, H1'), 2.41 (3H, s, Ts*Me*), 2.27 (1H, dt, *J* = 14.0 and 7.0 Hz, H1'), 2.11 (1H, dt, *J* = 18.5 and 6.5 Hz, H4), 1.98 (1H, dt, *J* = 14.5 and 5.0 Hz, H3), 1.78-1.71 (1H, m, H4), 1.63-1.58 (1H, m, H3); **^{13}C NMR** (125 MHz, $CDCl_3$, *E* isomer): δ_C 142.9, 138.1, 136.9, 135.4, 135.1, 131.6, 129.5, 128.9, 128.2, 127.9, 127.9, 127.4, 126.7, 117.2, 60.1, 40.3, 33.1, 27.2, 21.5.

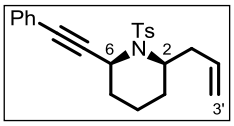
Repeating the reaction with dppe (1.3 mg, 10 mol%) replacing DPEphos resulted in an inseparable 18:82 mixture of **(*S*,*S*)-4.86c** and **(*S*)-4.87c** (8.0 mg, 21.1 μmol, 84%). Spectroscopic data for **(*S*,*S*)-4.86c** and **(*S*)-4.87c** were identical to the above. **(*S*,*S*)-4.86c** was present as >90:10 *dr*, and **(*S*)-4.49c** was present as 95:5 *E*/*Z*.

(2*R*,6*S*)-2-allyl-6-(phenylethynyl)-1-tosylpiperidine and (*R*,*E*)-2-allyl-7-benzylidene-1-tosyl-2,3,4,7-tetrahydro-1*H*-azepine – (*R*,*S*)-4.86c and (*R*)-4.87c

A vial containing a stirrer bar and fitted with a rubber septum was charged with carbonate **(*R*,*S*)-4.85c** (20.0 mg, 43.9 μmol, 1 eq.) and placed under an argon atmosphere. To it was added a solution of

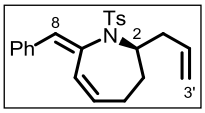
$Pd(OAc)_2$ (0.5 mg, 5 mol%) and DPEphos (2.4 mg, 10 mol%) in degassed 1,4-dioxane (0.45 mL). The reaction was stirred and heated to 100 °C for 15 minutes. The reaction was allowed to cool, quenched with pet. ether (0.5 mL) and passed through a short plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (1:19→1:4 Et_2O/pet. ether) to leave an inseparable 85:15 mixture (by ^1H NMR spectroscopy) of piperidine **(*R*,*S*)-4.86c** and enamide **(*R*)-4.87c** (10.0 mg, 26.3 μmol, 60%) as a colourless oil.

R_f 0.32 (1:4 Et_2O/pet. ether); **HRMS** (ESI+): calc for $C_{23}H_{25}NO_2SNa$ $[M+Na]^+$ 402.1498, found 402.1483.



(2*R*,6*S*)-2-allyl-6-(phenylethynyl)-1-tosylpiperidine – (*R*,*S*)-4.86c

97:3 *dr*; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.81 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.31-7.25 (7H, m, Ph and Ts*H*), 5.73-5.64 (1H, m, H2'), 5.25-5.22 (1H, m, H6), 5.02-4.97 (2H, m, H3'), 4.15 (1H, dt, *J* = 10.0 and 5.0 Hz, H2), 2.69 (1H, ddd, *J* = 14.0, 10.5 and 8.5 Hz, H1'), 2.47-2.39 (1H, m, H1'), 2.40 (3H, s, Ts*Me*), 1.99 (1H, qt, *J* = 13.5 and 3.5 Hz, H4), 1.94-1.89 (1H, m, H5), 1.76-1.71 (1H, m, H3), 1.68 (1H, ddd, *J* = 13.0, 5.5 and 4.0 Hz, H5), 1.57-1.44 (2H, m, H3 and 4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.1, 138.2, 135.9, 131.3, 129.5, 128.2 (2xC), 127.4, 122.8, 117.2, 89.1, 84.0, 53.1, 43.8, 36.0, 31.3, 26.6, 21.5, 18.7.



(*R*,*E*)-2-allyl-7-benzylidene-1-tosyl-2,3,4,7-tetrahydro-1*H*-azepine – (*R*)-4.87c

ca. **75:25 *E*/*Z***. Spectroscopic data identical to **(*S*)-4.87c** prepared previously.

Repeating the reaction with dppe (1.8 mg, 10 mol%) replacing DPEphos resulted in an inseparable 13:87 mixture of **(*R*,*S*)-4.86c** and **(*R*)-4.87c** (2.2 mg, 5.7 μmol, 13%). Spectroscopic data for **(*R*,*S*)-4.86c** and **(*R*)-4.87c** were identical to the above. **(*R*,*S*)-4.86c** was present as >90:10 *dr*, and **(*R*)-4.49c** was present as 88:12 *E*/*Z*.

Chapter 7. Bibliography

1. "The Nobel Prize in Chemistry 2010", *Nobelprize.org*, 18 Jun 2012, http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/index.html
2. C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.
3. R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320-2322.
4. S. Baba, E.-i. Negishi, *J. Am. Chem. Soc.* **1976**, *98*, 6729-6731.
5. A. O. King, N. Okukado, E.-i. Negishi, *J. Chem. Soc., Chem. Commun.* **1977**, 683-684.
6. N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437-3440.
7. J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger, H. Kojer, *Angew. Chem.* **1959**, *71*, 176-182.
8. J. Smidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier, A. Sabel, *Angew. Chem. Int. Ed. Eng.* **1962**, *1*, 80-88.
9. J. Tsuji, H. Takahashi, *J. Am. Chem. Soc.* **1965**, *87*, 3275-3276.
10. S. Cacchi, M. Felici, B. Pietroni, *Tetrahedron Lett.* **1984**, *25*, 3137-3140.
11. J. Tsuji, M. Morikawa, J. Kiji, *Tetrahedron Lett.* **1963**, *4*, 1437-1440.
12. J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, *6*, 4387-4388.
13. E.-i. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis, Vol. 1 and 2*, John Wiley & Sons, New York, **2003**.
14. T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147-1169.
15. J. Tsuji, *Palladium Reagents and Catalysis: New Perspectives for the 21st Century*, 2nd ed., John Wiley & Sons, Chichester, **2004**.
16. J. Tsuji, T. Mandai, *J. Organomet. Chem.* **1993**, *451*, 15-21.
17. N. A. Krause, S. K. Hashmi, *Modern Allene Chemistry, Vol. 1*, Whiley-VCH, Weinheim, **2004**.
18. J. Tsuji, H. Watanabe, I. Minami, I. Shimizu, *J. Am. Chem. Soc.* **1985**, *107*, 2196-2198.
19. T. Jeffery-Luong, G. Linstrumelle, *Tetrahedron Lett.* **1980**, *21*, 5019-5020.
20. J. H. van't Hoff, *La Chemie dans l'Espace*, P.M. Bazendijk, Rotterdam, **1875**.
21. C. J. Elsevier, P. M. Stehouwer, H. Westmijze, P. Vermeer, *J. Org. Chem.* **1983**, *48*, 1103-1105.
22. G. Lowe, *Chem. Commun.* **1965**, 411-413.
23. J. H. Brewster, in *Topics in Stereochemistry, Vol. 2*, John Wiley & Sons, **1967**, pp. 1-72.
24. C. J. Elsevier, H. Kleijn, J. Boersma, P. Vermeer, *Organometallics* **1986**, *5*, 716-720.
25. E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1984**, *25*, 3059-3062.
26. C. J. Elsevier, P. Vermeer, *J. Org. Chem.* **1985**, *50*, 3042-3045.
27. W. L. Parker, M. L. Rathnum, V. Seiner, W. H. Trejo, P. A. Principe, R. B. Sykes, *J. Antibiot.* **1984**, *37*, 431-440.
28. P. H. Dixneuf, T. Guyot, M. D. Ness, S. M. Roberts, *Chem. Commun.* **1997**, 2083-2084.
29. T. Konno, M. Tanikawa, T. Ishihara, H. Yamanaka, *Chem. Lett.* **2000**, *29*, 1360-1361.
30. G. A. Molander, E. M. Sommers, S. R. Baker, *J. Org. Chem.* **2006**, *71*, 1563-1568.
31. R. Riveiros, D. Rodríguez, J. Pérez Sestelo, L. A. Sarandeses, *Org. Lett.* **2006**, *8*, 1403-1406.
32. M. Kalek, J. Stawinski, *Adv. Synth. Catal.* **2011**, *353*, 1741-1755.
33. A. P. Boisselle, N. A. Meinhardt, *J. Org. Chem.* **1962**, *27*, 1828-1833.
34. M. Yoshida, T. Okada, K. Shishido, *Tetrahedron* **2007**, *63*, 6996-7002.
35. M. Yoshida, H. Ueda, M. Ihara, *Tetrahedron Lett.* **2005**, *46*, 6705-6708.
36. M. Yoshida, M. Hayashi, K. Shishido, *Org. Lett.* **2007**, *9*, 1643-1646.
37. B. n. Vaz, R. Pereira, M. n. Pérez, R. Álvarez, A. R. de Lera, *J. Org. Chem.* **2008**, *73*, 6534-6541.
38. J. L. Alonso-Gómez, P. Schanen, P. Rivera-Fuentes, P. Seiler, F. Diederich, *Chem-Eur. J.* **2008**, *14*, 10564-10568.
39. Y. Zhang, Y. Wu, *Org. Biomol. Chem.* **2010**, *8*, 4744-4752.
40. Y.-J. Jian, Y. Wu, *Org. Biomol. Chem.* **2010**, *8*, 811-821.
41. Y.-J. Jian, Y. Wu, *Org. Biomol. Chem.* **2010**, *8*, 1905-1909.
42. Y.-J. Jian, C.-J. Tang, Y. Wu, *J. Org. Chem.* **2007**, *72*, 4851-4855.

43. C.-J. Tang, Y. Wu, *Helv. Chim. Acta.* **2004**, *87*, 667-673.
44. C.-J. Tang, Y. Wu, *Tetrahedron* **2007**, *63*, 4887-4906.
45. T. Kato, K. Ishigami, K. Akasaka, H. Watanabe, *Tetrahedron* **2009**, *65*, 6953-6958.
46. M. Yoshida, M. Al-Amin, K. Shishido, *Synthesis* **2008**, 1099-1105.
47. E. M. Woerly, A. H. Cherney, E. K. Davis, M. D. Burke, *J. Am. Chem. Soc.* **2010**, *132*, 6941-6943.
48. K. Mikami, A. Yoshida, *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 858-860.
49. S. Ogoshi, T. Nishida, T. Shinagawa, H. Kurosawa, *J. Am. Chem. Soc.* **2001**, *123*, 7164-7165.
50. A. Horváth, J.-E. Bäckvall, *Chem. Commun.* **2004**, 964-965.
51. C. P. Casey, J. R. Nash, C. S. Yi, A. D. Selmeczy, S. Chung, D. R. Powell, R. K. Hayashi, *J. Am. Chem. Soc.* **1998**, *120*, 722-733.
52. K. Tsutsumi, S. Ogoshi, S. Nishiguchi, H. Kurosawa, *J. Am. Chem. Soc.* **1998**, *120*, 1938-1939.
53. S. Ogoshi, K. Tsutsumi, H. Kurosawa, *J. Organomet. Chem.* **1995**, *493*, C19-C21.
54. K. Tsutsumi, T. Kawase, K. Kakiuchi, S. Ogoshi, Y. Okada, H. Kurosawa, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687-2692.
55. A. Mayr, M. F. Asaro, T. J. Glines, *J. Am. Chem. Soc.* **1987**, *109*, 2215-2216.
56. K. Nakatsu, T.-a. Mitsudo, H. Nakanishi, Y. Watanabe, Y. Takegami, *Chem. Lett.* **1977**, *6*, 1447-1448.
57. R. P. Hughes, M. E. King, D. J. Robinson, J. M. Spotts, *J. Am. Chem. Soc.* **1989**, *111*, 8919-8920.
58. J. C. Calabrese, D. C. Roe, D. L. Thorn, T. H. Tulip, *Organometallics* **1984**, *3*, 1223-1230.
59. R. J. McKinney, T. H. Tulip, D. L. Thorn, T. S. Coolbaugh, F. N. Tebbe, *J. Am. Chem. Soc.* **1981**, *103*, 5584-5586.
60. C. Amatore, S. Bensalem, S. Ghalem, A. Jutand, *J. Organomet. Chem.* **2004**, *689*, 4642-4646.
61. D. Zargarian, H. Alper, *Organometallics* **1993**, *12*, 712-724.
62. A. Krasovskiy, B. H. Lipshutz, *Org. Lett.* **2011**, *13*, 3818-3821.
63. G.-P. Lu, K. R. Voigtritter, C. Cai, B. H. Lipshutz, *J. Org. Chem.* **2012**, *77*, 3700-3703.
64. G.-P. Lu, K. R. Voigtritter, C. Cai, B. H. Lipshutz, *Chem. Commun.* **2012**, *48*, 8661-8663.
65. J.-R. Labrosse, P. Lhoste, F. Delbecq, D. Sinou, *Eur. J. Org. Chem.* **2003**, *2003*, 2813-2822.
66. C.-C. Su, J.-T. Chen, G.-H. Lee, Y. Wang, *J. Am. Chem. Soc.* **1994**, *116*, 4999-5000.
67. J. Tsuji, T. Mandai, *Angew. Chem. Int. Ed. Eng.* **1996**, *34*, 2589-2612.
68. I. Minami, M. Yuhara, H. Watanabe, J. Tsuji, *J. Organomet. Chem.* **1987**, *334*, 225-242.
69. C. Fournier-Nguefack, P. Lhoste, D. Sinou, *Synlett* **1996**, 553-554.
70. H. Ohno, A. Okano, S. Kosaka, K. Tsukamoto, M. Ohata, K. Ishihara, H. Maeda, T. Tanaka, N. Fujii, *Org. Lett.* **2008**, *10*, 1171-1174.
71. S. Inuki, Y. Yoshimitsu, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2010**, *75*, 3831-3842.
72. Y. Kozawa, M. Mori, *Tetrahedron Lett.* **2002**, *43*, 1499-1502.
73. Y. Kozawa, M. Mori, *J. Org. Chem.* **2003**, *68*, 8068-8074.
74. A. Hoffmann-Röder, N. Krause, *Angew. Chem. Int. Ed.* **2004**, *43*, 1196-1216.
75. M. Yoshida, T. Gotou, M. Ihara, *Tetrahedron Lett.* **2004**, *45*, 5573-5575.
76. J. P. Parrish, Y. C. Jung, R. J. Floyd, K. W. Jung, *Tetrahedron Lett.* **2002**, *43*, 7899-7902.
77. A. Padwa, K. E. Krumpe, L. W. Terry, M. W. Wannamaker, *J. Org. Chem.* **1989**, *54*, 1635-1642.
78. E. Wenkert, M. H. Leftin, E. L. Michelotti, *J. Org. Chem.* **1985**, *50*, 1122-1124.
79. M. Csékei, Z. Novák, A. Kotschy, *Tetrahedron* **2008**, *64*, 975-982.
80. R. G. Carlson, W. W. Cox, *J. Org. Chem.* **1977**, *42*, 2382-2386.
81. Z.-X. Wang, G.-A. Cao, Y. Shi, *J. Org. Chem.* **1999**, *64*, 7646-7650.
82. Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806-9807.
83. A. L. Baumstark, C. J. McCloskey, *Tetrahedron Lett.* **1987**, *28*, 3311-3314.
84. A. L. Baumstark, P. C. Vasquez, *J. Org. Chem.* **1988**, *53*, 3437-3439.
85. R. D. Bach, J. L. Andres, A. L. Owensby, H. B. Schlegel, J. J. W. McDouall, *J. Am. Chem. Soc.* **1992**, *114*, 7207-7217.
86. Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.
87. J. Kang, G. J. Lim, S. K. Yoon, M. Y. Kim, *J. Org. Chem.* **1995**, *60*, 564-577.

88. Y. Saito, T. A. Zevaco, L. A. Agrofoglio, *Tetrahedron* **2002**, *58*, 9593-9603.
89. F. Andersson, B. Samuelsson, *Carbohyd. Res.* **1984**, *129*, C1-C3.
90. E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroeder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968-1970.
91. H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483-2547.
92. M. Schroeder, *Chem. Rev.* **1980**, *80*, 187-213.
93. K.-S. Jeong, P. Sjö, K. B. Sharpless, *Tetrahedron Lett.* **1992**, *33*, 3833-3836.
94. K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, *J. Org. Chem.* **1992**, *57*, 2768-2771.
95. M. H. Junttila, O. O. E. Hormi, *J. Org. Chem.* **2009**, *74*, 3038-3047.
96. R. M. Burk, M. B. Roof, *Tetrahedron Lett.* **1993**, *34*, 395-398.
97. E. A. Anderson, J. E. P. Davidson, J. R. Harrison, P. T. O'Sullivan, J. W. Burton, I. Collins, A. B. Holmes, *Tetrahedron* **2002**, *58*, 1943-1971.
98. A. Fürstner, M. Méndez, *Angew. Chem. Int. Ed.* **2003**, *42*, 5355-5357.
99. J. A. Marshall, K. G. Pinney, *J. Org. Chem.* **1993**, *58*, 7180-7184.
100. K. Matos, J. A. Soderquist, *J. Org. Chem.* **1998**, *63*, 461-470.
101. M. Yoshida, T. Murao, K. Sugimoto, M. Ihara, *Synlett* **2007**, 575-578.
102. C. Amatore, A. Jutand, G. Le Duc, *Chem-Eur. J.* **2011**, *17*, 2492-2503.
103. B. P. Carrow, J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 2116-2119.
104. P. G. McDougal, J. G. Rico, Y. I. Oh, B. D. Condon, *J. Org. Chem.* **1986**, *51*, 3388-3390.
105. J. R. Parikh, W. v. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.
106. P. J. Kocienski, *Protecting Groups*, 3rd ed., Georg Thieme Verlag, Stuttgart, **2005**.
107. E. Álvaro, M. C. de la Torre, M. A. Sierra, *Chem-Eur. J.* **2006**, *12*, 6403-6411.
108. H. Kim, J. B. Baker, S.-U. Lee, Y. Park, K. L. Bolduc, H.-B. Park, M. G. Dickens, D.-S. Lee, Y. Kim, S. H. Kim, J. Hong, *J. Am. Chem. Soc.* **2009**, *131*, 3192-3194.
109. C. Wedler, H. Schick, *J. Prakt. Chem.-Chem. Ztg.* **1993**, *335*, 410-414.
110. A. R. Katritzky, S. Rachwal, B. Rachwal, *J. Chem. Soc., Perkin Trans. 1* **1990**, 1717-1725.
111. K. Tsutsumi, K. Fujimoto, T. Yabukami, T. Kawase, T. Morimoto, K. Kakiuchi, *Eur. J. Org. Chem.* **2004**, *2004*, 504-510.
112. M. W. Baize, P. W. Blosser, V. Plantevin, D. G. Schimpff, J. C. Gallucci, A. Wojcicki, *Organometallics* **1996**, *15*, 164-173.
113. S. Bäurle, S. Hoppen, U. Koert, *Angew. Chem. Int. Ed.* **1999**, *38*, 1263-1266.
114. Y. Wu, Y.-P. Sun, *Org. Lett.* **2006**, *8*, 2831-2834.
115. B. Schmidt, F. Hölter, A. Kelling, U. Schilde, *J. Org. Chem.* **2011**, *76*, 3357-3365.
116. A. V. Malkov, O. Kysilka, M. Edgar, A. Kadlčíková, M. Kotora, P. Kočovský, *Chem-Eur. J.* **2011**, *17*, 7162-7166.
117. J. i. Uenishi, Y. Fujikura, N. Kawai, *Org. Lett.* **2011**, *13*, 2350-2353.
118. K. Hotta, X. Chen, R. S. Paton, A. Minami, H. Li, K. Swaminathan, I. I. Mathews, K. Watanabe, H. Oikawa, K. N. Houk, C.-Y. Kim, *Nature* **2012**, *483*, 355-358.
119. O. Kubo, K. Yahata, T. Maegawa, H. Fujioka, *Chem. Commun.* **2011**, *47*, 9197-9199.
120. K. Lee, H. Kim, J. Hong, *Eur. J. Org. Chem.* **2012**, *2012*, 1025-1032.
121. J. Muzart, *Tetrahedron* **2005**, *61*, 5955-6008.
122. D. D. Díaz, J. M. Betancort, V. S. Martín, *Synlett* **2007**, 343-359.
123. K. M. Nicholas, *Acc. Chem. Res.* **1987**, *20*, 207-214.
124. J. Palazón, V. S. Martín, *Tetrahedron Lett.* **1995**, *36*, 3549-3552.
125. F. R. P. Crisóstomo, T. Martín, V. S. Martín, *Org. Lett.* **2004**, *6*, 565-568.
126. D. D. Díaz, M. A. Ramírez, J. P. Ceñal, J. R. Saad, C. E. Tonn, V. S. Martín, *Chirality* **2003**, *15*, 148-155.
127. M. Lin, L. Hao, X.-t. Liu, Q.-z. Chen, F. Wu, P. Yan, S.-x. Xu, X.-l. Chen, J.-j. Wen, Z.-p. Zhan, *Synlett* **2011**, 665-670.
128. D. E. Chavez, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2001**, *40*, 3667-3670.
129. A. G. Dossetter, T. F. Jamison, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **1999**, *38*, 2398-2400.
130. J. Zeng, S. Vedachalam, S. Xiang, X.-W. Liu, *Org. Lett.* **2011**, *13*, 42-45.
131. S. R. Mothe, P. Kothandaraman, W. Rao, P. W. H. Chan, *J. Org. Chem.* **2011**, *76*, 2521-2531.
132. L. Liu, P. E. Floreancig, *Angew. Chem. Int. Ed.* **2010**, *49*, 3069-3072.
133. J. K. D. Brabander, B. Liu, M. Qian, *Org. Lett.* **2008**, *10*, 2533-2536.

134. C. J. Dutton, B. J. Banks, C. B. Cooper, *Nat. Prod. Rep.* **1995**, *12*, 165-181.
135. K.-S. Yeung, I. Paterson, *Chem. Rev.* **2005**, *105*, 4237-4313.
136. T. Nakata, *Chem. Rev.* **2005**, *105*, 4314-4347.
137. B. I. Morinaka, C. K. Skepper, T. F. Molinski, *Org. Lett.* **2007**, *9*, 1975-1978.
138. S. M. Lee, K. H. Bae, H. J. Sohn, *Tetrahedron Lett.* **2009**, *50*, 416-418.
139. B. M. Trost, Z. T. Ball, T. Jöge, *J. Am. Chem. Soc.* **2002**, *124*, 7922-7923.
140. H. Lindlar, *Helv. Chim. Acta.* **1952**, *35*, 446-450.
141. B. M. Trost, M. R. Machacek, B. D. Faulk, *J. Am. Chem. Soc.* **2006**, *128*, 6745-6754.
142. A. Aponick, B. Biannic, *Org. Lett.* **2011**, *13*, 1330-1333.
143. Y. K. Chung, G. C. Fu, *Angew. Chem. Int. Ed.* **2009**, *48*, 2225-2227.
144. Z. Zhang, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2007**, *46*, 283-285.
145. J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 4486-4487.
146. J. Doubský, L. Streinz, L. Lešetický, B. Koutek, *Synlett* **2003**, 937-942.
147. K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739.
148. G. T. Giuffredi, S. Purser, M. Sawicki, A. L. Thompson, V. Gouverneur, *Tetrahedron-Asymmetr.* **2009**, *20*, 910-920.
149. Toyo Kasei Kogyo Company Limited, **European Patent:** EP2112136 A1, **2009**
150. K. Kubota, J. L. Leighton, *Angew. Chem. Int. Ed.* **2003**, *42*, 946-948.
151. D. A. Nicewicz, A. D. Satterfield, D. C. Schmitt, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 17281-17283.
152. J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543-2549.
153. D. E. Ward, C. K. Rhee, *Tetrahedron Lett.* **1991**, *32*, 7165-7166.
154. T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451-2458.
155. H. Takahata, M. Kubota, T. Momose, *Tetrahedron-Asymmetr.* **1997**, *8*, 2801-2810.
156. A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974-6977.
157. I. Paterson, M. Tudge, *Tetrahedron* **2003**, *59*, 6833-6849.
158. C. Darcel, S. Bartsch, C. Bruneau, P. H. Dixneuf, *Synlett* **1994**, 457-458.
159. H. Ohmiya, M. Yang, Y. Yamauchi, Y. Ohtsuka, M. Sawamura, *Org. Lett.* **2010**, *12*, 1796-1799.
160. Y. Takahashi, T. Ito, S. Sakai, Y. Ishii, *J. Chem. Soc. Chem. Comm.* **1970**, 1065-1066.
161. J. Yin, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 6043-6048.
162. F. Ozawa, A. Kubo, T. Hayashi, *Chem. Lett.* **1992**, *21*, 2177-2180.
163. P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741-2770.
164. J. O. C. Jiménez-Halla, M. Kalek, J. Stawinski, F. Himo, *Chem-Eur. J.* **2012**, *18*, 12424-12436.
165. M. Kalek, T. Johansson, M. Jezowska, J. Stawinski, *Org. Lett.* **2010**, *12*, 4702-4704.
166. R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc., Trans.* **1915**, *107*, 1080-1106.
167. D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155-4156.
168. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *92*, 741-743.
169. M. Yamaguchi, K. Shibato, S. Fujiwara, I. Hirao, *Synthesis* **1986**, 421-422.
170. G. Wittig, G. Geissler, *Liebigs Ann. Chem.* **1953**, *580*, 44-57.
171. D. Craig, N. J. Geach, C. J. Pearson, A. M. Z. Slawin, A. J. P. White, D. J. Williams, *Tetrahedron* **1995**, *51*, 6071-6098.
172. E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, *16*, 2647-2650.
173. J. E. Zakarian, Y. El-Azizi, S. K. Collins, *Org. Lett.* **2008**, *10*, 2927-2930.
174. A. Bermejo, B. Figadere, M.-C. Zafra-Polo, I. Barrachina, E. Estornell, D. Cortes, *Nat. Prod. Rep.* **2005**, *22*, 269-303.
175. W.-C. Liu, D. S. Slusarchyk, G. Astle, W. H. Trejo, W. E. Brown, E. Meyers, *J. Antibiotics* **1978**, *31*, 815-819.
176. R. S. Dhillon, *Hydroboration and Organic Synthesis: 9-Borabicyclo[3.3.1]nonane (9-BBN)*, Springer, New York, **2007**.
177. D. Boyall, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2002**, *4*, 2605-2606.

178. N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688.
179. J. W. Bode, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 3611-3612.
180. S. G. Smith, R. S. Paton, J. W. Burton, J. M. Goodman, *J. Org. Chem.* **2008**, *73*, 4053-4062.
181. H. M. Sheldrake, C. Jamieson, S. I. Pascu, J. W. Burton, *Org. Biomol. Chem.* **2009**, *7*, 238-252.
182. H. Kim, S. Ho, J. L. Leighton, *J. Am. Chem. Soc.* **2011**, *133*, 6517-6520.
183. J. P. Michael, *Nat. Prod. Rep.* **2004**, *21*, 625-649.
184. T. H. Jones, A. Laddago, A. W. Don, M. S. Blum, *J. Nat. Prod.* **1990**, *53*, 375-381.
185. T. Kondo, T. Nekado, I. Sugimoto, K. Ochi, S. Takai, A. Kinoshita, Y. Tajima, S. Yamamoto, K. Kawabata, H. Nakai, M. Toda, *Bioorgan. Med. Chem.* **2007**, *15*, 2631-2650.
186. L. Schjelderup, O. Harbitz, P. Groth, A. J. Aasen, *Acta Chem. Scand. B* **1987**, *41*, 356-361.
187. M.-h. Kim, Y. Park, B.-S. Jeong, H.-g. Park, S.-s. Jew, *Org. Lett.* **2010**, *12*, 2826-2829.
188. A. Catassi, D. Servent, L. Paleari, A. Cesario, P. Russo, *Mutat. Res.-Rev. Mutat.* **2008**, *659*, 221-231.
189. A. Stoll, A. Hofmann, *Helv. Chim. Acta.* **1943**, *26*, 1570-1601.
190. S. Laschat, T. Dickner, *Synthesis* **2000**, 1781-1813.
191. C. Kibayashi, *Chem. Pharm. Bull.* **2005**, *53*, 1375-1386.
192. M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. D. VanDuyne, J. Clardy, *J. Am. Chem. Soc.* **1990**, *112*, 3715-3716.
193. J. Davies, H. Wang, T. Taylor, K. Warabi, X.-H. Huang, R. J. Andersen, *Org. Lett.* **2005**, *7*, 5233-5236.
194. R. W. Shaw, T. Gallagher, *J. Chem. Soc., Perkin Trans. 1* **1994**, 3549-3555.
195. I. W. Davies, R. W. Shaw, R. Wisedale, T. Gallagher, *J. Chem. Soc., Perkin Trans. 1* **1994**, 3557-3561.
196. C. Mukai, Y.-i. Sugimoto, K. Miyazawa, S. Yamaguchi, M. Hanaoka, *J. Org. Chem.* **1998**, *63*, 6281-6287.
197. D. Davis, P. Schwarz, T. Hernandez, M. Mitchell, B. Warnock, A. D. Elbein, *Plant Physiol.* **1984**, *76*, 972-975.
198. J. N. s. Hernández, M. A. Ramírez, M. a. L. Rodríguez, V. c. S. Martín, *Org. Lett.* **2008**, *10*, 2349-2352.
199. C. P. Allen, T. Benkovics, A. K. Turek, T. P. Yoon, *J. Am. Chem. Soc.* **2009**, *131*, 12560-12561.
200. J. Han, B. Xu, G. B. Hammond, *J. Am. Chem. Soc.* **2009**, *132*, 916-917.
201. X.-Y. Liu, C.-M. Che, *Angew. Chem. Int. Ed.* **2008**, *47*, 3805-3810.
202. R. Grigg, V. Sridharan, M. Thornton-Pett, J. Wang, J. Xu, J. Zhang, *Tetrahedron* **2002**, *58*, 2627-2640.
203. H. Ohno, K. Ando, H. Hamaguchi, Y. Takeoka, T. Tanaka, *J. Am. Chem. Soc.* **2002**, *124*, 15255-15266.
204. H. Hamaguchi, S. Kosaka, H. Ohno, N. Fujii, T. Tanaka, *Chem-Eur. J.* **2007**, *13*, 1692-1708.
205. A. S. Jones, *Cascade Reactions Involving Allenylpalladium Intermediates*, Part II Thesis, University of Oxford (Oxford, United Kingdom) **2011**.
206. M. Kollmar, H. Steinhagen, J. P. Janssen, B. Goldfuss, S. A. Malinovskaya, J. Vázquez, F. Rominger, G. Helmchen, *Chem-Eur. J.* **2002**, *8*, 3103-3114.
207. C. E. Housecroft, B. A. M. Shaykh, A. L. Rheingold, B. S. Haggerty, *Inorg. Chem.* **1991**, *30*, 125-130.
208. J. R. Henry, L. R. Marcin, M. C. McIntosh, P. M. Scola, G. Davis Harris Jr, S. M. Weinreb, *Tetrahedron Lett.* **1989**, *30*, 5709-5712.
209. B. R. Neustadt, *Tetrahedron Lett.* **1994**, *35*, 379-380.
210. T. M. Harris, C. M. Harris, J. E. Hill, F. S. Ungemach, H. P. Broquist, B. M. Wickwire, *J. Org. Chem.* **1987**, *52*, 3094-3098.
211. M. P. Heitz, L. E. Overman, *J. Org. Chem.* **1989**, *54*, 2591-2596.
212. K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490-4527.
213. S. P. Panchgalle, H. B. Bidwai, S. P. Chavan, U. R. Kalkote, *Tetrahedron-Asymmetr.* **2010**, *21*, 2399-2401.
214. J.-y. Ueda, M. Takagi, S.-y. Kazuo, *J. Nat. Prod.* **2009**, *72*, 2181-2183.
215. M. J. Cornwell, *Palladium-catalysed Cascade Cyclisations of Propargylic Electrophiles*, Part

II Thesis, University of Oxford (Oxford, United Kingdom), **2012**.
216. W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*, 5th ed., Butterworth-Heinemann, Burlington, **2003**.
217. W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.
218. E. J. Prisbe, J. Smejkal, J. P. H. Verheyden, J. G. Moffatt, *J. Org. Chem.* **1976**, *41*, 1836-1846.
219. K. Lee, Y.-H. Kim, S. B. Han, H. Kang, S. Park, W. S. Seo, J. T. Park, B. Kim, S. Chang, *J. Am. Chem. Soc.* **2003**, *125*, 6844-6845.
220. G. T. Giuffredi, S. Purser, M. Sawicki, A. L. Thompson, V. Gouverneur, *Tetrahedron-Asymmetr.* **2009**, *20*, 910-920.
221. J. E. D. Kirkham, T. D. L. Courtney, V. Lee, J. E. Baldwin, *Tetrahedron* **2005**, *61*, 7219-7232.
222. K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 285-288.
223. G. J. Meuzelaar, M. C. A. van Vliet, L. Maat, R. A. Sheldon, *Eur. J. Org. Chem.* **1999**, 2315-2321.
224. A. Brethon, J. J. E. Moreau, M. Wong Chi Man, *Tetrahedron-Asymmetr.* **2004**, *15*, 495-502.
225. D. M. Fisher, R. R. Fenton, J. R. Aldrich-Wright, *Chem. Commun.* **2008**, 5613-5615.
226. C. A. Brown, S. Krishnamurthy, *J. Org. Chem.* **1978**, *43*, 2731-2732.
227. J. A. Soderquist, A. Negron, *Org. Syn.* **1998**, *Col. Vol. 9*, 95.
228. M. A. Henderson, C. H. Heathcock, *J. Org. Chem.* **1988**, *53*, 4736-4745.
229. J. Tsuji, T. Sugiura, I. Minami, *Synthesis* **1987**, 603-606.
230. H. Yamabe, A. Mizuno, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2005**, *127*, 3248-3249.
231. J.-R. Labrosse, P. Lhoste, D. Sinou, *J. Org. Chem.* **2001**, *66*, 6634-6642.
232. Y. Masuyama, J. P. Takahara, K. Hashimoto, Y. Kurusu, *J. Chem. Soc., Chem. Commun.* **1993**, 1219-1220.
233. P. I. Dem'yanov, I. M. Styrkov, D. P. Krut'ko, M. V. Vener, V. S. Petrosyan, *J. Organomet. Chem.* **1992**, *438*, 265-288.
234. J. Zhao, Y. Liu, S. Ma, *Org. Lett.* **2008**, *10*, 1521-1523.
235. M. Ishikura, Y. Matsuzaki, I. Agata, N. Katagiri, *Tetrahedron* **1998**, *54*, 13929-13942.
236. N. Sakai, R. Kanada, M. Hirasawa, T. Konakahara, *Tetrahedron* **2005**, *61*, 9298-9304.
237. A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron* **1985**, *41*, 5121-5131.
238. R. Hässig, D. Seebach, H. Siegel, *Chem. Ber.* **1984**, *117*, 1877-1884.
239. A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, L. M. Parisi, *J. Organomet. Chem.* **2003**, *687*, 562-566.
240. A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron* **1991**, *47*, 1677-1696.
241. J. H. Babler, V. P. Liptak, N. Phan, *J. Org. Chem.* **1996**, *61*, 416-417.
242. Y. Ma, C. Song, W. Jiang, Q. Wu, Y. Wang, X. Liu, M. B. Andrus, *Org. Lett.* **2003**, *5*, 3317-3319.
243. C. Battistini, P. Crotti, F. Macchia, *J. Org. Chem.* **1981**, *46*, 434-438.
244. S. J. Hayes, D. W. Knight, M. D. Menzies, M. O'Halloran, W.-F. Tan, *Tetrahedron Lett.* **2007**, *48*, 7709-7712.
245. C. Deutsch, A. Hoffmann-Röder, A. Domke, N. Krause, *Synlett* **2007**, 737-740.
246. A. B. Smith, R. J. Fox, J. A. Vanecko, *Org. Lett.* **2005**, *7*, 3099-3102.
247. A. Jenmalm, W. Berts, Y.-L. Li, K. Luthman, I. Csoeregh, U. Hacksell, *J. Org. Chem.* **1994**, *59*, 1139-1148.
248. M. S. Shepard, E. M. Carreira, *J. Am. Chem. Soc.* **1997**, *119*, 2597-2605.
249. J. W. Herndon, J. Zhu, D. Sampedro, *Tetrahedron* **2000**, *56*, 4985-4993.
250. A. H. F. Lee, A. S. C. Chan, T. Li, *Tetrahedron* **2003**, *59*, 833-839.
251. A. B. Holmes, A. B. Tabor, R. Baker, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3301-3306.
252. T. Saito, Y. Nishimoto, M. Yasuda, A. Baba, *J. Org. Chem.* **2006**, *71*, 8516-8522.
253. M. Takagi, H. Takikawa, K. Mori, *Biosci. Biotechnol. Biochem.* **2001**, *65*, 2065-2069.
254. F. R. P. Crisóstomo, R. Carrillo, T. Martín, V. S. Martín, *Tetrahedron Lett.* **2005**, *46*, 2829-2832.
255. H. Ogura, H. Takahashi, T. Itoh, *J. Org. Chem.* **1972**, *37*, 72-75.
256. E. C. McLaughlin, M. P. Doyle, *J. Org. Chem.* **2008**, *73*, 4317-4319.
257. T. Nishikawa, H. Shinokubo, K. Oshima, *Tetrahedron* **2003**, *59*, 9661-9668.
258. V. Mamane, A. B. García, J. D. Umarye, T. Lessmann, S. Sommer, H. Waldmann,

Tetrahedron **2007**, *63*, 5754-5767.
259. A. Fusano, T. Fukuyama, S. Nishitani, T. Inouye, I. Ryu, *Org. Lett.* **2010**, *12*, 2410-2413.
260. J. Izquierdo, S. Rodríguez, F. V. González, *Org. Lett.* **2011**, *13*, 3856-3859.
261. V. N. Odinokov, R. R. Vakhidov, R. N. Shakhmaev, V. V. Zorin, *Chem. Nat. Compd.* **1996**, *32*, 912-914.
262. P. J. Chua, B. Tan, L. Yang, X. Zeng, D. Zhu, G. Zhong, *Chem. Commun.* **2010**, *46*, 7611-7613.
263. K. L. Salazar, K. M. Nicholas, *Tetrahedron* **2000**, *56*, 2211-2224.
264. L. Emmanuvel, D. A. Kamble, A. Sudalai, *Tetrahedron-Asymmetr.* **2009**, *20*, 84-88.
265. M. Takimoto, M. Kawamura, M. Mori, *Synthesis* **2004**, 791-795.
266. J. Vannada, E. M. Bennett, D. J. Wilson, H. I. Boshoff, C. E. Barry, C. C. Aldrich, *Org. Lett.* **2006**, *8*, 4707-4710.
267. W. H. Daly, C. W. Heurtevant, *Org. Mass. Spectrom.* **1970**, *4*, 165-174.
268. B. M. Trost, D. B. Horne, M. J. Woltering, *Chem-Eur. J.* **2006**, *12*, 6607-6620.

Appendix

Reactions of Allenylpalladium Intermediates in Organic Synthesis

A thesis submitted to the
Board of the Faculty of Physical Sciences
in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

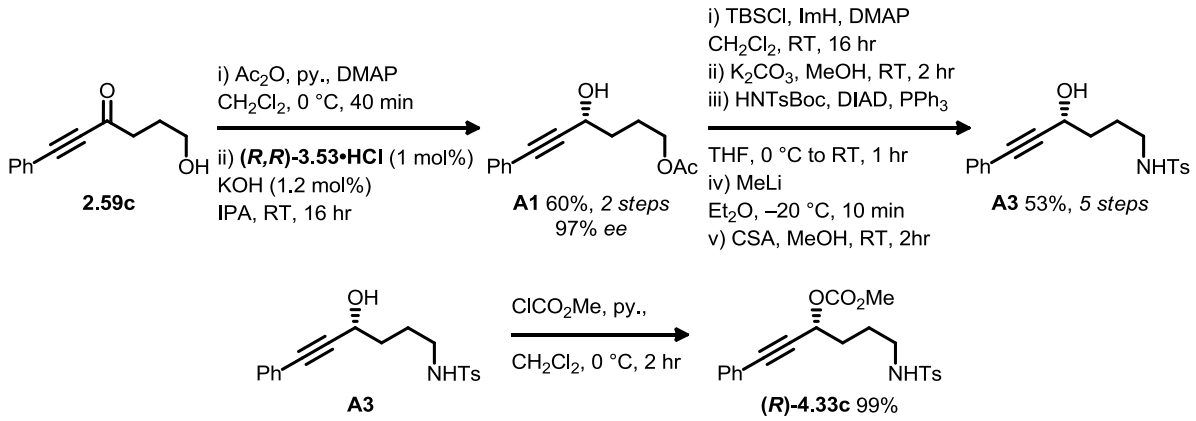
David S. B. Daniels

Pembroke College, University of Oxford, Trinity 2012



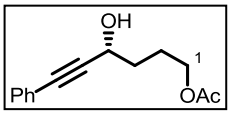
Aditional Experimental for compounds synthesised by Alison Jones[1]

Synthesis of **(*R*)-4.33c** (*Scheme A1*).



Scheme A1

(*R*)-4-hydroxy-6-phenylhex-5-yn-1-yl acetate – A1



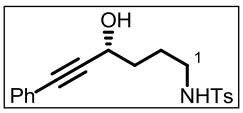
To a stirred solution of keto alcohol (3.85 g, 20.5 mmol, 1 eq.) in anhydrous CH_2Cl_2 (40 mL) at 0 ºC under argon was added pyridine (3.31 mL, 40.9 mmol, 2 eq.), DMAP (229 mg, 2.05 mmol, 10 mol%) and acetic anhydride (2.90 mL, 30.7 mmol, 1.5 eq.). The reaction was stirred for 40 minutes and quenched with sat. aq. $NaHCO_3$ (40 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with 1N aq. HCl solution (40 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield crude acetate as an orange oil, which was used in the next step without further purification.

To a stirred solution of keto-acetate (3.0 g, 13.0 mmol, 1 eq.) and [RuCl((*R*,*R*)-TsDPEN)(*p*-cymene)] **(*R*,*R*)-3.53·HCl** (82.8 mg, 1 mol%) in IPA (45 mL) was added a solution of KOH (8.8 mg, 1.2 mol%) in IPA (15 mL). The reaction was stirred overnight and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (4:1→1:1 pet. ether/Et_2O) to yield pure alcohol **A1** (2.90 g, 12.3 mmol, 60%, *2 steps*) as a yellow oil.

R_f 0.27 (2:1 Et_2O/pet. ether); **97% *ee*** (CHIRALPAK IC, 1.25 mL/min, 10% IPA/Hexane): t_R (*R*) 13.1 min, t_R (*S*) = 19.9 min); $[\alpha]_D^{25}$ +0.8 (*c* = 1.07, $CHCl_3$); **IR** (thin film, cm^{-1}): 3415, 2958, 2958, 2230, 1736, 1718, 1490, 1443, 1366, 1336, 1245, 1041; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.52-7.39 (2H, m, Ph), 7.38-7.29 (3H, m, Ph), 4.70-4.60 (1H, m, H4), 4.21-4.10 (2H, m, H1), 2.07 (3H, s, C(O)*Me*), 2.05 (1H, bs, O*H*), 1.95-1.83 (4H, m, H2 and 3); **^{13}C NMR** (125 MHz, $CDCl_3$,): δ_C 171.2,

131.7, 128.5, 128.3, 122.4, 89.5, 85.2, 64.1, 62.4, 34.2, 24.5, 21.0; **HRMS** (ESI+): calc for $C_{14}H_{16}O_3Na$ $[M+Na]^+$ 255.0992, found 255.0986.

(*R*)-*N*-(4-hydroxy-6-phenylhex-5-yn-1-yl)-4-methylbenzenesulfonamide – A3



To a solution of hydroxy acetate **A1** (1.0 g, 4.31 mmol, 1eq.) in anhydrous CH_2Cl_2 (20 mL) was added DMAP (48 mg, 10 mol%), imidazole (352 mg, 5.17 mmol, 1.2 eq.) and TBSCl (714 mg, 4.74 mmol, 1.1 eq.). The mixture was stirred overnight and quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were washed with 1N aq. HCl (40 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (19:1→9:1 pet. ether/Et_2O) to yield pure TBS-acetate (1.40 g, 4.05 mmol, 94%) as a colourless oil which was used directly in the next step.

To a solution of TBS-acetate (1.75 g, 5.04 mmol, 1 eq.) in MeOH (20 mL) was added K_2CO_3 (2.09 g, 15.1 mmol, 3 eq.). The reaction was stirred for two hours and quenched with 1 N aq. HCl (20 mL). The layers were separated, the aqueous layers extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers washed with sat. aq. $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to leave the crude TBS-alcohol **A2**, which was used in the next step without further purification.

To a stirred solution of TBS-alcohol (1.50 g, 4.93 mmol, 1 eq.), triphenylphosphine (2.59 g, 9.86 mmol, 2 eq.) and NHTsBoc (1.74 g, 6.40 mmol, 1.3 eq,) in anhydrous THF (50 mL) at 0 °C under argon was added DIAD (1.46 mL, 7.40 mmol, 1.5 eq.) drop-wise. The reaction was stirred for one hour and quenched with sat. aq. $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (5 x 40 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (19:1→9:1 pet. ether/Et_2O) to yield pure TBS-Boc-sulfonamide (1.77 g, 3.17 mmol, 64%) as a colourless oil.

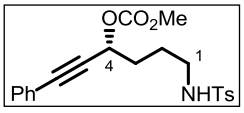
To a stirred solution of the above TBS-Boc-sulfonamide (1.10 g, 1.97 mmol, 1 eq.) in anhydrous Et_2O (20 mL) at −20 ºC under argon was added MeLi (2 M in DME, 2.98 mL, 5.91 mmol, 3 eq.) dropwise. The reaction was stirred for 10 minutes and quenched with water (10 mL). The layers were separated,

the aqueous layer extracted with Et_2O (3 x 10 mL) and the combined organic layers dried over $MgSO_4$ The solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel (1:1→1:2 pet. ether/EtOAc) to yield pure TBS-sulfonamide as a colourless oil (867 mg, 1.89 mmol, 96%) which was used directly in the next step.

To a stirred solution the above TBS-sulfonamide (867 mg, 1.89 mmol, 1 eq.) in MeOH (20 mL) at 0 ºC was added CSA (220 mg, 1.89 mmol, 1 eq.). The reaction was stirred for two hours and quenched with sat. aq. $NaHCO_3$ (2 mL). The mixture was passed through a short plug of celite and the solvent removed *in vacuo* to yield crude hydroxyl amine. The product was purified using flash chromatography on silica gel (1:1 EtOAc/pet. ether) to yield pure amino-alcohol **A3** (594 mg, 1.74 mmol, 92%) as a pale yellow solid.

R_f 0.23 (2:1 Et_2O/pet. ether); **$[\alpha]_D^{25}$** +13.9 (*c* = 0.96, $CHCl_3$); **IR** (thin film, cm^{-1}): 3458, 3283, 2927, 2869, 2229, 1598, 1572, 1490, 1443, 1323, 1158, 1092; **m.p.** 89-90 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.46-7.36 (2H, m, Ph), 7.36-7.22 (5H, m, Ph and Ts*H*), 5.23-5.08 (1H, m, H4), 4.59 (1H, q, *J* = 5.5 Hz, N*H*), 3.01 (2H, q, *J* = 6.5 Hz, H1), 2.61 (1H, d, *J* = 5.5 Hz, O*H*), 2.38 (3H, s, Ts*Me*), 1.86-1.76 (2H, m, H2), 1.76-1.66 (2H, m, H3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 143.3, 136.8, 131.6, 129.6, 128.4, 128.2, 127.0, 122.4, 89.5, 85.1, 62.2, 42.8, 34.5, 25.2, 21.4; **HRMS** (ESI+): calc for $C_{19}H_{21}NO_3SNa$ $[M+Na]^+$ 366.1134, found 366.1126.

(*R*)-methyl (6-(4-methylphenylsulfonamido)-1-phenylhex-1-yn-3-yl) carbonate – (*R*)-4.33c

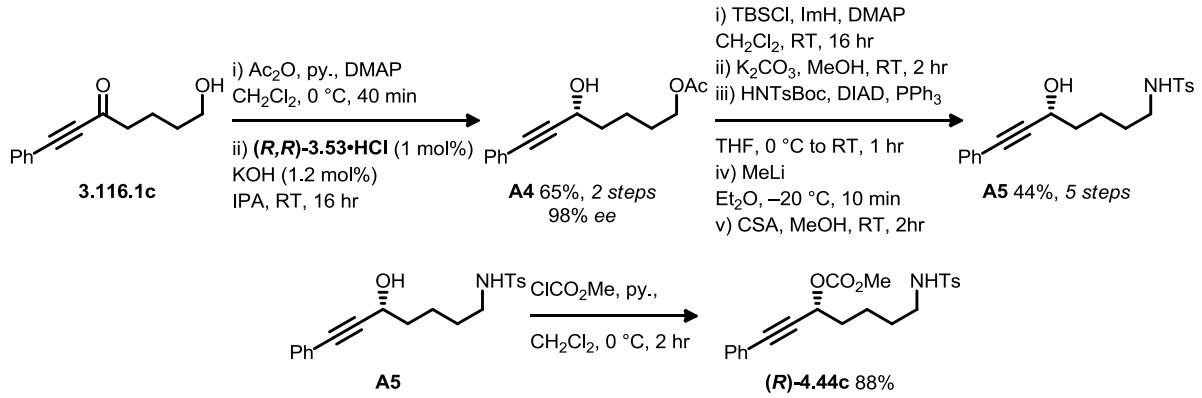


To a stirred solution of alcohol **A3** (148 mg, 0.431 mmol, 1 eq.) and pyridine (0.10 mL, 1.29 mmol, 3 eq.) in anhydrous CH_2Cl_2 (4.5 mL) at 0 °C under argon was added methyl chloroformate (67 µL, 0.826 mmol, 2 eq.). The reaction was stirred for 2 hours and quenched with sat. aq. $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed *in vacuo* and the residue azeotroped with toluene (2 x 5 mL). The crude product was purified by flash chromatography on silica gel (1:1→2:1 Et_2O/pet. ether) to leave pure **(*R*)-4.33c** (172 mg, 0.428 mmol, 99%) as a colourless oil.

R_f 0.14 (1:1 Et_2O/pet. ether); **$[\alpha]_D^{25}$** +67.4 (*c* = 0.46, $CHCl_3$); **IR** (thin film, cm^{-1}): 3288, 2957, 2239, 1751, 1598, 1491, 1443, 1326, 1266, 1159, 1094; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.75 (2H, d, 8.5

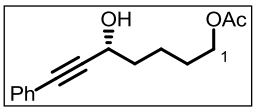
Hz, Ts*H*), 7.44-7.41 (2H, m, Ph), 7.36-7.28 (5H, m, Ph and Ts*H*), 5.33 (1H, t, *J* = 6.0 Hz, H4), 4.45 (1H, t, *J* = 6.0 Hz, N*H*), 3.82 (3H, s, O*Me*), 3.04 (2H, *apt* q, *J* = 6.5 Hz, H1), 2.41 (3H, s, Ts*Me*), 1.94-1.89 (2H, m, H3), 1.77-1.71 (2H, m, H2); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.8, 143.5, 136.9, 131.9, 129.7, 128.9, 128.3, 127.1, 121.8, 86.7, 84.9, 67.9, 55.0, 42.7, 31.8, 25.2, 21.5; **HRMS** (ESI+): calc for $C_{21}H_{23}NO_5SNa$ $[M+Na]^+$ 424.1189, found 424.1186; **Elemental Analysis**: $C_{21}H_{23}NO_5S$ requires C, 62.82%; H, 5.77%; N, 3.49%; found C, 62.73%; H, 5.66%; N, 3.60%.

Synthesis of **(*R*)-4.44c** (*Scheme A2*).



Scheme A2

(*R*)-5-hydroxy-7-phenylhept-6-yn-1-yl acetate – A4



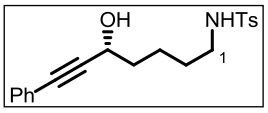
To a stirred solution of keto-alcohol **3.116.1c** (600 mg, 3.31 mmol, 1 eq.) in anhydrous CH_2Cl_2 (20 mL) at 0 ºC under argon was added pyridine (0.54 mL, 6.63 mmol, 2 eq.), DMAP (37 mg, 10 mol%), and acetic anhydride (0.47 mL, 4.97 mmol, 1.5 eq.). The reaction was left to stir for 40 minutes and the reaction quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with 1N aq. HCl (40 mL) and dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude mixture was azeotroped with toluene (2 x 5 mL) to leave pure keto-acetate (722 mg, 2.95 mmol, 89%) as a yellow oil which was used directly in the next step.

To a stirred solution of keto-acetate (720 mg, 2.95 mmol, 1 eq.) and [RuCl((*R*,*R*)-TsDPEN)(*p*-cymene)] **(*R*,*R*)-3.53·HCl** (11 mg, 1 mol%) in IPA (15 mL) was added a solution of KOH (2 mg, 1.2 mol%) in IPA (0.5 mL). The reaction was stirred overnight and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (4:1→1:1 pet. ether/Et_2O) to leave pure alcohol **A4** (528 mg, 2.15 mmol, 73%) as a yellow oil.

R_f 0.44 (1:1 pet. ether/Et_2O); **99% *ee*** (CHIRALPAK IC, 1.25 mL/min, 10% IPA/Hexane): t_R (*R*) =

15.9 min, t_R (*S*) = 17.5 min; $[\alpha]_D^{25}$ 2.93 (*c* = 1.03, $CHCl_3$); **IR** (thin film, cm^{-1}): 3427, 2948, 2867, 2221, 1736, 1719, 1490, 1443, 1391, 1366, 1243, 1030; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.45-7.35 (2H, m, Ph), 7.34-7.23 (3H, m, Ph), 4.59 (1H, t, *J* = 6.5 Hz, H5), 4.07 (2H, td, *J* = 6.5 and 2.0 Hz, H1), 2.32 (1H, bs, O*H*), 2.02 (3H, s, C(O)*Me*), 1.89-1.74 (2H, m, H4), 1.74-1.63 (2H, m, H2), 1.63-1.49 (2H, m, H3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 171.2, 131.6, 128.4, 128.2, 122.5, 89.9, 84.9, 64.3, 62.6, 37.3, 28.2, 21.6, 20.9; **HRMS** (ESI+): calc for $C_{15}H_{18}O_3Na$ $[M+Na]^+$ 269.1148, found 269.1148.

(*R*)-*N*-(5-hydroxy-7-phenylhept-6-yn-1-yl)-4-methylbenzenesulfonamide – A5



To a solution of hydroxy-acetate **A4** (624 mg, 2.53 mmol, 1 eq.) in anhydrous CH_2Cl_2 (15 mL) was added DMAP (28 mg, 10 mol%), imidazole (207 mg, 3.04 mmol, 1.2 eq.) and TBSCl (420 mg, 2.79 mmol, 1.1 eq.). The mixture was stirred overnight and quenched using sat. aq. $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with 1N aq. HCl (30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (19:1→9:1 pet. ether/Et_2O) to yield pure TBS-acetate as a colourless oil (739 mg, 2.05 mmol, 81%) which was used directly in the next step.

To a stirred solution of TBS-acetate (739 mg, 2.05 mmol, 1 eq.) in MeOH (7 mL) was added K_2CO_3 (851 mg, 6.16 mmol, 3 eq.). The reaction was stirred for 3 hours and quenched with 1 N aq. HCl (7 mL). The layers were separated, the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* to yield the TBS-alcohol (616 mg, 1.93 mmol, 94%) as a colourless oil which was used in the next step without further purification.

To a stirred solution of TBS-alcohol (300 mg, 0.942 mmol, 1 eq.), triphenylphosphine (494 mg, 1.88 mmol, 2 eq.) and NHTsBoc (332 mg, 1.22 mmol, 1.3 eq,) in anhydrous THF (15 mL) at 0 °C under argon was added DIAD (0.28 mL, 1.41 mmol, 1.5 eq.) dropwise. The reaction was stirred for 2 hours and quenched with sat. aq. $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (5 x 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (19:1→9:1 pet. ether/Et_2O) to yield pure Boc-sulfonamide as a yellow oil (421 mg, 0.735 mmol, 78%)

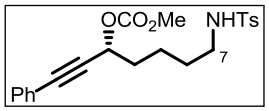
which was used directly in the next step.

To a stirred solution of the above Boc-sulfonamide (1.42 g, 2.48 mmol, 1 eq.) in anhydrous Et_2O (25 mL) at −20 ºC under argon was added MeLi (2 M in DME, 3.72 mL, 7.45 mmol, 3eq.) dropwise. The reaction was stirred for 10 minutes and quenched with water (10 mL). The layers were separated, the aqueous layer extracted with Et_2O (3 x 10 mL) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (9:1→1:1 pet. ether/EtOAc) to yield pure TBS-sulfonamide as a colourless oil (1.00 g, 2.11 mmol, 85%) which was used directly in the next step.

To a stirred solution of the above TBS-sulfonamide (1.00 g, 2.12 mmol, 1 eq.) in MeOH (20 mL) at 0 ºC was added CSA (492 mg, 2.12 mmol, 1 eq.). The reaction was stirred for 2 hours and quenched with sat. aq. $NaHCO_3$ (2 mL). The mixture was passed through a short plug of celite and the solvent removed *in vacuo* to yield crude hydroxyl amine. The product was purified by flash chromatography on silica gel (2:1→1:1 pet. ether/EtOAc) to leave pure amino alcohol **A5** (657 mg, 1.84 mmol, 87%) as a yellow oil.

R$_f$ 0.28 (2:1 Et_2O/pet. ether); $[\alpha]_D^{25}$ +3.05 (*c* = 1.05, $CHCl_3$); **IR** (thin film, cm^{-1}): 3456, 3283, 2943, 2865, 2202, 1598, 1490, 1443, 1322, 1155, 1093; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.46-7.38 (2H, m, Ph), 7.35-7.28 (5H, m, Ph and Ts*H*), 4.56 (1H, t, *J* = 6.5 Hz, H5), 4.51 (1H, t, *J* = 6.0 Hz, N*H*), 2.98 (2H, q, *J* = 6.5 Hz, H1), 2.43 (3H, s, Ts*Me*), 1.99 (1H, bs, O*H*), 1.80-1.68 (2H, m, H4), 1.59-1.43 (4H, m, H2 and 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 143.4, 136.9, 131.7, 129.7, 128.5, 128.3, 127.1, 122.4, 89.7, 85.1, 62.6, 43.0, 37.0, 29.2, 22.1, 21.5; **HRMS** (ESI+): calc for $C_{20}H_{23}NO_3SNa$ $[M+Na]^+$ 380.1291, found 380.1285.

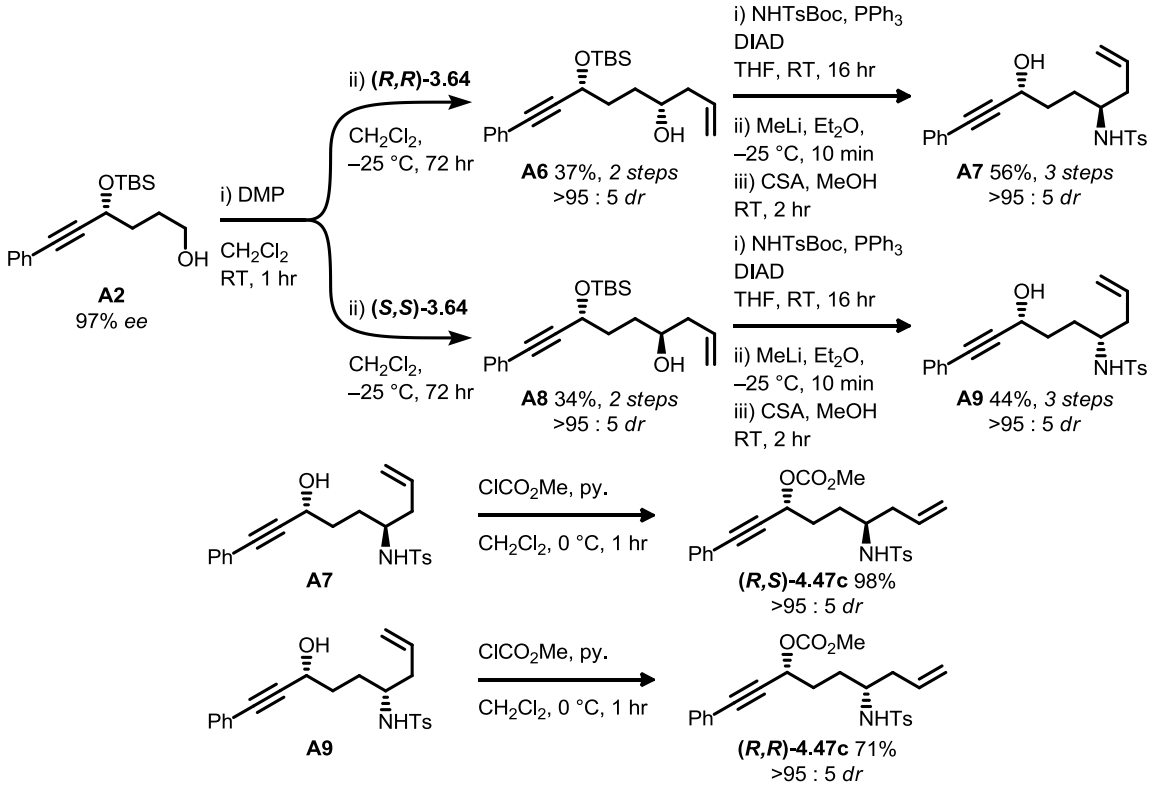
(*R*)-methyl (7-(4-methylphenylsulfonamido)-1-phenylhept-1-yn-3-yl) carbonate – (*R*)-4.44c



To a stirred solution of amino alcohol **A5** (650 mg, 1.82 mmol, 1 eq.) in anhydrous CH_2Cl_2 (20 mL) at 0 ºC under argon was added pyridine (0.44 mL, 5.46 mmol, 3 eq.) and methyl chloroformate (0.28 mL, 3.64 mmol, 2 eq.). The reaction was allowed to warm to room temperature, stirred for one hour and quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated, the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic layers washed with 1N aq. HCl (2 x 20 mL). The organic layer was dried over $MgSO_4$ and the solvent

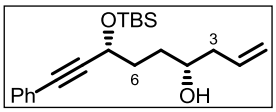
removed *in vacuo*. The crude product was purified by column chromatography on silica gel (1:1→2:1 EtOAc/pet. ether) to leave pure carbonate **(*R*)-4.44c** (663 mg, 1.60 mmol, 88%) as a pale yellow solid. **R_f** 0.69 (2:1 EtOAc/pet. ether); $[\alpha]_D^{25}$ +72.0 (*c* = 0.99, $CHCl_3$); **IR** (thin film, cm^{-1}): 3287, 2955, 2867, 2234, 1750, 1598, 1491, 1443, 1326, 1266, 1159, 1094; **m.p.** 73-75 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.46-7.40 (2H, m, Ph), 7.38-7.28 (5H, m, Ph and Ts*H*), 5.41 (1H, t, *J* = 6.5 Hz, H3), 4.43 (1H, t, *J* = 6.5 Hz, N*H*), 3.83 (3H, s, O*Me*), 2.97 (2H, q, *J* = 6.5 Hz, H7), 2.43 (3H, s, Ts*Me*), 1.92-1.79 (2H, m, H4), 1.59-1.42 (4H, m, H5 and 6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 155.0, 143.4, 136.9, 131.9, 129.7, 128.8, 128.3, 127.1, 121.9, 86.4, 85.3, 68.2, 55.0, 42.9, 34.3, 29.1, 22.0, 21.5; **HRMS** (ESI+): calc for $C_{22}H_{25}NO_5S$ $[M+Na]^+$ 438.1346, found 438.1330.

Synthesis of **(*R,S*)-4.47c** and **(*R,R*)-4.47c** (*Scheme A3*).



Scheme A3

(4*R*,7*R*)-7-((*tert*-butyldimethylsilyl)oxy)-9-phenylnon-1-en-8-yn-4-ol – A6

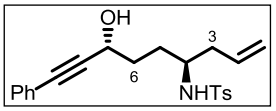


To a stirred solution of silyloxy alcohol **A2** (1.70 g, 5.58 mmol, 1 eq.) in CH_2Cl_2 (110 mL) was added DMP (2.84 g, 6.69 mmol, 1.2 eq.). The reaction was stirred for 1 hour and quenched with sat. aq. $NaHCO_3/Na_2S_2O_3$ (1:1 v:v, 110 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash

chromatography on silica gel (2:1 pet. ether/Et_2O) to yield pure aldehyde (1.58 g, 5.22 mmol, 94%) as a yellow oil.

To a solution of the above aldehyde (1.58 g, 5.22 mmol, 1 eq.) in anhydrous CH_2Cl_2 (35 mL) at −20 °C under argon was added a solution of Leighton's reagent **(*R*,*R*)-3.64** (2.93 g, 5.58 mmol, 1.05 eq.) in anhydrous CH_2Cl_2 (5 mL). The reaction was allowed to stand in the freezer at −20 ºC for 72 hours and quenched with 50% sat. aq. NH_4Cl (2 mL). The solvent was removed *in vacuo*, passed through a short plug of silica gel (4:1 pet. ether/EtOAc) and purified by flash chromatography on silica gel (9:1→4:1 pet. ether/Et_2O→1:1:0.1 pet. ether/Et_2O/NEt_3) to yield pure allylic alcohol **A6** (676 mg, 2.04 mmol, 39%) as a yellow oil. $\mathbf{R_f}$ 0.39 (1:1 pet. ether/Et_2O); **>95:5 *dr***; $[\alpha]_D^{25}$ +48.8 (*c* = 0.99, $CHCl_3$); **IR** (thin film, cm^{-1}): 3386, 3079, 2954, 2929, 2896, 2857, 2233, 1490, 1472, 1463, 1361, 1341, 1254, 1084; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.48-7.37 (2H, m, Ph), 7.36-7.24 (3H, m, Ph), 5.86 (1H, ddt, *J* = 17.0, 10.0 and 7.5 Hz, H2), 5.22-5.08 (2H, m, H1), 4.66 (1H, t, *J* = 6.0 Hz, H7), 3.82-3.70 (1H, m, H4), 2.39-2.28 (1H, m, H3), 2.28-2.16 (1H, m, H3), 2.01 (1H, bs, O*H*), 1.99-1.82 (2H, m, H6), 1.82-1.72 (1H, m, H5), 1.72-1.60 (1H, m, H5), 0.95 (9H, s, Si^t*Bu*), 0.21 (3H, s, Si*Me*), 0.18 (3H, s, Si*Me*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 134.8, 131.5, 128.2, 128.1, 123.0, 118.0, 90.6, 84.5, 70.2, 63.3, 41.9, 34.5, 32.2, 25.8, 18.2, −4.4, −5.0; **HRMS** (ESI+): calc for $C_{21}H_{32}O_2SiNa$ $[M+Na]^+$ 367.2064, found 367.2053.

N-((4*S*,7*R*)-7-hydroxy-9-phenylnon-1-en-8-yn-4-yl)-4-methylbenzenesulfonamide – A7



To a stirred solution of TBS-alcohol **A6** (609 mg, 1.77 mmol, 1 eq.), triphenylphosphine (929 mg, 3.54 mmol, 2 eq.) and NHTsBoc (623 mg, 2.30 mmol, 1.3 eq.) in anhydrous THF (20 mL) under argon was added DIAD (0.52 mL, 2.66 mmol, 1.5 eq.) dropwise. The reaction was stirred overnight and quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (19:1→9:1 pet. ether/Et_2O) to yield pure TBS-Boc-sulfonamide (725 mg, 1.22 mmol 69%) as a pale yellow oil.

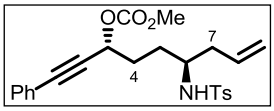
To a stirred solution of the above TBS-Boc-sulfonamide (785 mg, 1.31 mmol, 1 eq.) in anhydrous Et_2O (15 mL) at −20 ºC under argon was added MeLi (2 M in DME, 1.97 mL, 3.93 mmol, 3 eq.)

dropwise. The reaction was stirred for 10 minutes and quenched with water (10 mL). The layers were separated, the aqueous layer extracted with Et_2O (3 x 10 mL) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:1→1:2 pet. ether/EtOAc) to leave pure TBS-sulfonamide (620 mg, 1.25 mmol, 95%) as a colourless oil.

To a stirred solution of the above TBS-sulfonamide (620 mg, 1.25 mmol, 1 eq.) in MeOH (15 mL) at RT was added CSA (290 mg, 1.25 mmol, 1 eq.). The reaction was stirred for 2 hours and quenched with sat. aq. $NaHCO_3$ (2 mL). The mixture was passed through a short plug of Celite® and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (9:1 pet. ether/Et_2O→Et_2O) to yield pure amino-alcohol **A7** (406 mg, 1.06 mmol, 85%) as a white solid.

R_f 0.22 (1:1 pet. ether/Et_2O); $[\alpha]_D^{25}$ +17.8 (*c* = 0.98, $CHCl_3$); **IR** (thin film, cm^{-1}): 3462, 3280, 2926, 2866, 2233, 1641, 1598, 1490, 1443, 1322, 1157, 1092, 1031; **m.p.** 103 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.76 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.47-7.38 (2H, m, Ph), 7.38-7.27 (5H, m, Ph and Ts*H*), 5.56 (1H, ddt, *J* = 17.0, 10.0 and 7.5 Hz, H2), 5.01 (1H, dd, *J* = 10.0 and 1.5 Hz, H1), 4.97 (1H, dd, *J* = 17.0 and 1.5 Hz, H1), 4.60 (1H, d, *J* = 8.0 Hz, N*H*), 4.55 (1H, q, *J* = 5.5 Hz, H7), 3.44-3.31 (1H, m, H4), 2.40 (3H, s, Ts*Me*), 2.21-2.02 (3H, m, H3 and O*H*), 1.86-1.69 (3H, m, H5 and 6), 1.67-1.54 (1H, m, H5), **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 143.4, 138.0, 133.0, 131.7, 129.6, 128.5, 128.3, 127.1, 122.4, 119.2, 89.5, 85.2, 62.6, 53.0, 39.3, 33.5, 30.2, 21.5; **HRMS** (ESI+): calc for $C_{22}H_{25}NO_2SNa$ $[M+Na]^+$ 406.1447, found 406.1435.

methyl ((3*R*,6*S*)-6-(4-methylphenylsulfonamido)-1-phenylnon-8-en-1-yn-3-yl) carbonate – (*R,S*)-4.47c

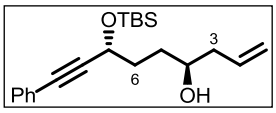


To a stirred solution of amino-alcohol **A7** (400 mg, 1.04 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) at 0 ºC under argon was added pyridine (0.25 mL, 3.13 mmol, 3 eq.) and methyl chloroformate (0.16 mL, 2.08 mmol, 2 eq.). The reaction was allowed to warm to room temperature, stirred for 1 hour and quenched with sat. aq. $NaHCO_3$ (10 mL). The layers were separated, the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic layers washed with 1N aq. HCl (2 x 20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The product was purified by flash chromatography on silica gel (3:1→1:1 pet. ether/EtOAc) to yield pure carbonate **(*R,S*)-4.47c** (450 mg, 1.02 mmol, 98%) as a colourless oil.

R_f 0.69 (1:1 pet. ether/EtOAc); $[\alpha]_D^{25}$ +76.5 (*c* = 1.00, $CHCl_3$); **IR** (thin film, cm^{-1}): 2957, 2861, 2233,

1751, 1642, 1599, 1492, 1443, 1325, 1305, 1160; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.81-7.71 (2H, m, Ts*H*), 7.47-7.38 (2H, m, Ph), 7.38-7.22 (5H, m, Ph and Ts*H*), 5.55 (1H, ddt, *J* = 17.0, 10.0 and 7.5 Hz, H8), 5.39 (1H, t, *J* = 6.0 Hz, H5), 5.05 (1H, dt, *J* = 10.0 and 1.0 Hz, H9), 4.97 (1H, dd, *J* = 17.0 and 1.5 Hz, H9), 4.41 (1H, d, *J* = 8.5 Hz, N*H*), 3.83 (3H, s, O*Me*), 3.40-3.34 (1H, m, H6), 2.40 (3H, s, Ts*Me*), 2.20-2.02 (2H, m, H7), 1.98-1.88 (1H, m, H4), 1.88-1.68 (2H, m, H4 and 5), 1.64-1.53 (1H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 154.9, 143.4, 138.0, 132.7, 131.9, 129.7, 128.8, 128.3, 127.1, 121.9, 119.5, 86.5, 85.2, 68.1, 55.0, 52.9, 39.2, 31.0, 29.9, 21.5; **HRMS** (ESI+): calc for $C_{24}H_{27}NO_5SNa$ $[M+Na]^+$ 464.1502, found 464.1486.

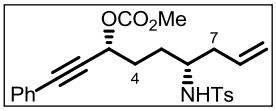
(4*S*,7*R*)-7-((*tert*-butyldimethylsilyl)oxy)-9-phenylnon-1-en-8-yn-4-ol – A8



TBS-alcohol **A8** (386 mg, 34%, *2 steps*) was prepared in identical fashion to **A6** from TBS-alcohol **A2**.

R_f 0.47 (pet. ether/Et_2O 1:1); **>95:5 *dr***; **$[\alpha]_D^{25}$** +42.5 (*c* = 1.04, $CHCl_3$); **IR** (neat, cm^{-1}): 3398, 3078, 2955, 2929, 2886, 2857, 2223, 1641, 1599, 1490, 1342, 1253, 1072; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.47-7.37 (2H, m, Ph), 7.34-7.28 (3H, m, Ph), 5.86 (1H, ddt, *J* = 17.5, 9.5 and 7.5 Hz, H2), 5.19-5.12 (2H, m, H1), 4.66 (1H, t, *J* = 6.0 Hz, H7), 3.72 (1H, septet, *J* = 4.0 Hz, H4), 2.37-2.28 (1H, m, H3), 2.28-2.17 (1H, m, H3), 2.07 (1H, bs, O*H*), 1.98-1.82 (2H, m, H6), 1.82-1.72 (1H, m, H5), 1.72-1.62 (1H, m, H5), 0.95 (9H, s, Si^t*Bu*), 0.20 (3H, s, Si*Me*), 0.18 (3H, s, Si*Me*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 134.9, 131.5, 128.2, 128.2, 123.0, 118.0, 90.5, 84.5, 70.6, 63.5, 42.0, 35.0, 32.5, 25.8, 18.3, −4.4, −5.0; **HRMS** (ESI+): calc for $C_{21}H_{32}O_2SiNa$ $[M+Na]^+$ 367.2064, found 367.2053.

methyl ((3*R*,6*R*)-6-(4-methylphenylsulfonamido)-1-phenylnon-8-en-1-yn-3-yl) carbonate – (*R*,*R*)-4.47c



Carbonate **(*R*,*R*)-4.47c** was prepared in identical fashion to **(*R*,*S*)-4.47c** in four steps from TBS-alcohol **A8** (133 mg, 31%, *4 steps*).

R_f 0.69 (1:1 pet. ether/EtOAc); **$[\alpha]_D^{25}$** +41.2 (*c* = 0.99, $CHCl_3$); **IR** (thin film, cm^{-1}): 3283, 3065, 2957, 2858, 2238, 1751, 1599, 1491, 1443, 1326, 1266, 1160, 1093; **^{1}H NMR** (500 MHz, $CDCl_3$): 7.76 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.49-7.40 (2H, m, Ph), 7.38-7.22 (5H, m, Ph and Ts*H*), 5.55 (1H, ddt, *J* = 17.0, 10.0 and 7.5 Hz, H8), 5.39 (1H, t, *J* = 6.5 Hz, H3), 5.05 (1H, d, *J* = 10.0 Hz, H9), 4.98 (1H, dd, *J* = 17.0 and 1.5 Hz, H9), 4.38 (1H, d, *J* = 8.5 Hz, N*H*), 3.83 (3H, s, O*Me*), 3.45-3.30 (1H, m, H6), 2.40 (3H, s, Ts*Me*), 2.19-2.05 (2H, m, H7), 2.00-1.87 (1H, m, H4), 1.82 (1H, m, H4), 1.78-1.66 (1H, m,

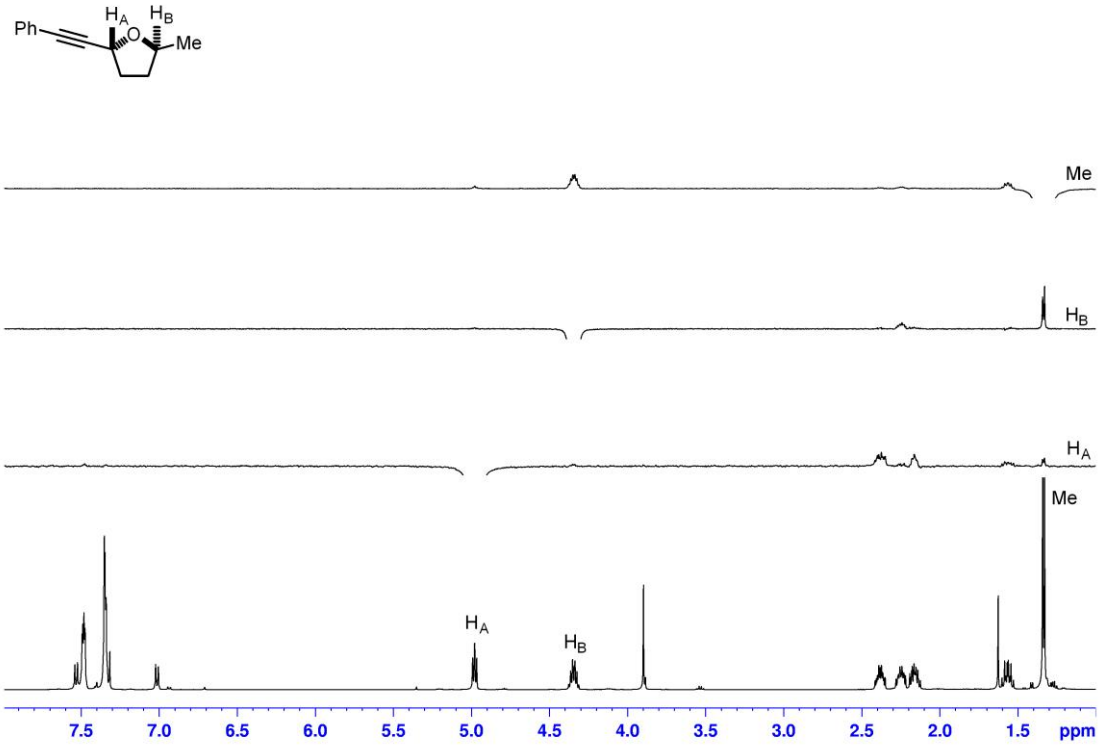
H5), 1.65-1.53 (1H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 154.9, 143.5, 137.9, 132.6, 131.9, 129.7, 128.8, 128.3, 127.1, 121.9, 119.5, 86.5, 85.2, 68.1, 55.0, 52.8, 39.2, 31.0, 29.9, 21.5; **HRMS** (ESI+): calc for $C_{24}H_{27}NO_5SNa$ $[M+Na]^+$ 464.1502, found 464.1500.

Appendix Bibliography

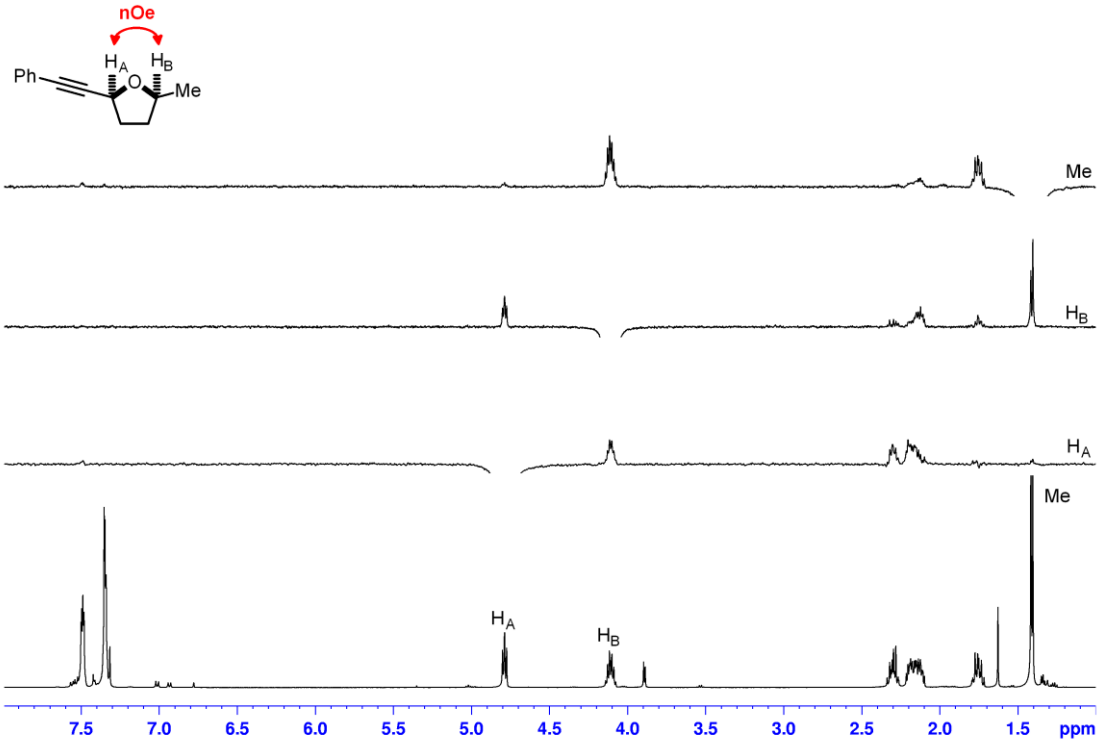
1. A. S. Jones, *Cascade Reactions Involving Allenylpalladium Intermediates*, Part II Thesis, University of Oxford (Oxford, United Kingdom) 2011.

1D nOe Spectra

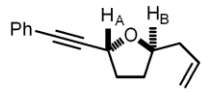
trans-(±)-3.40

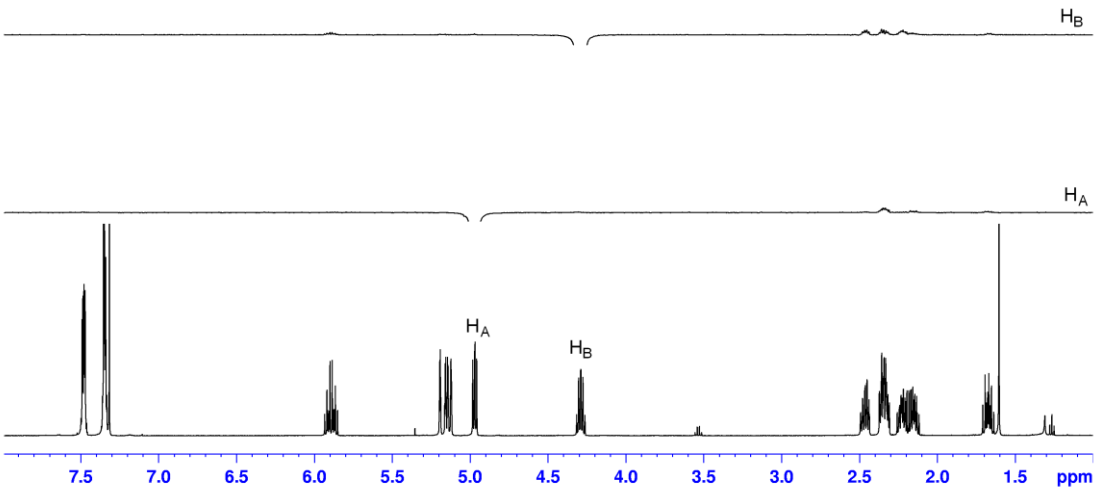


cis-(±)-3.40



(*R*,*R*)-3.72c





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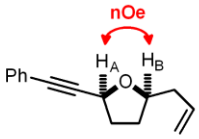

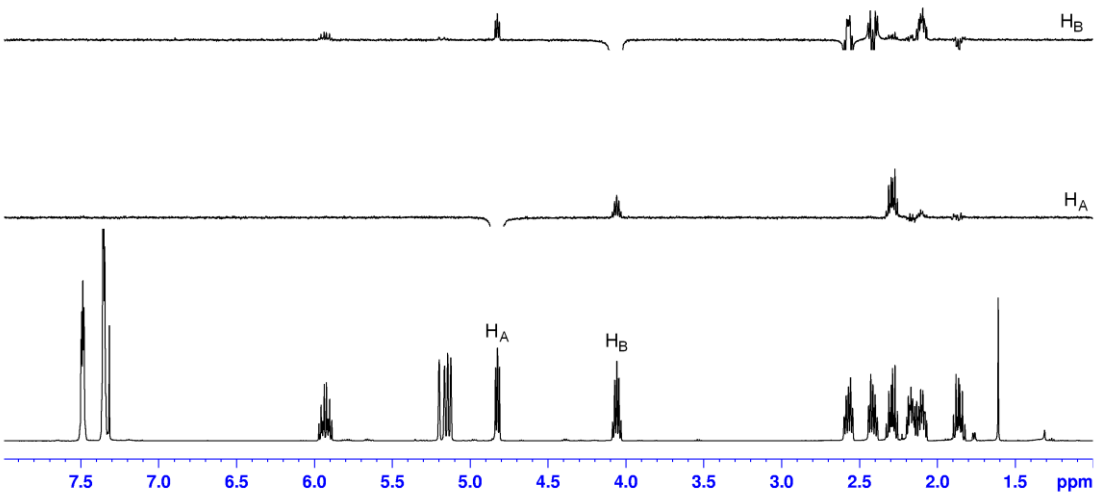

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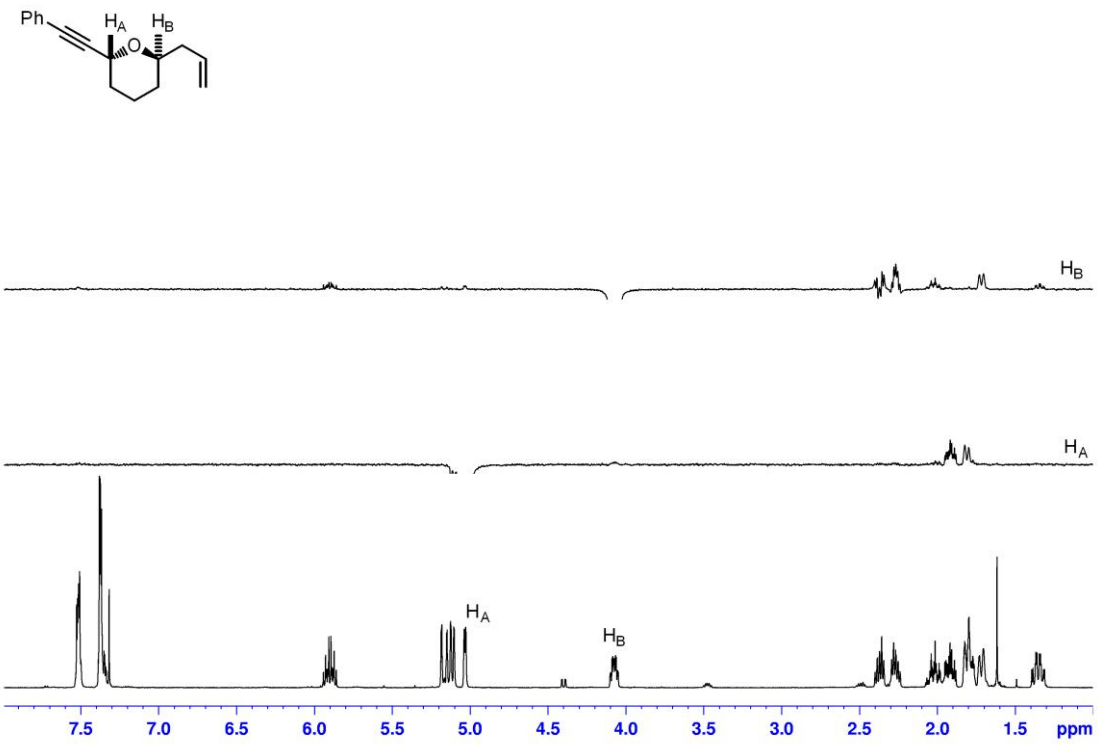

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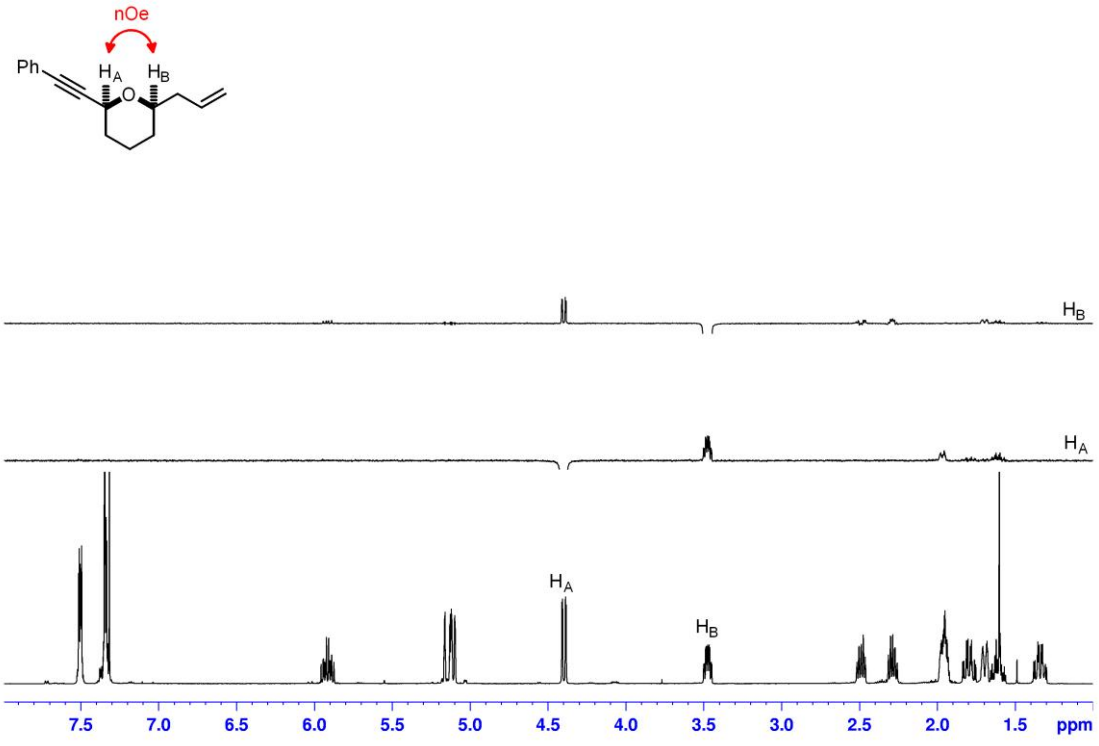

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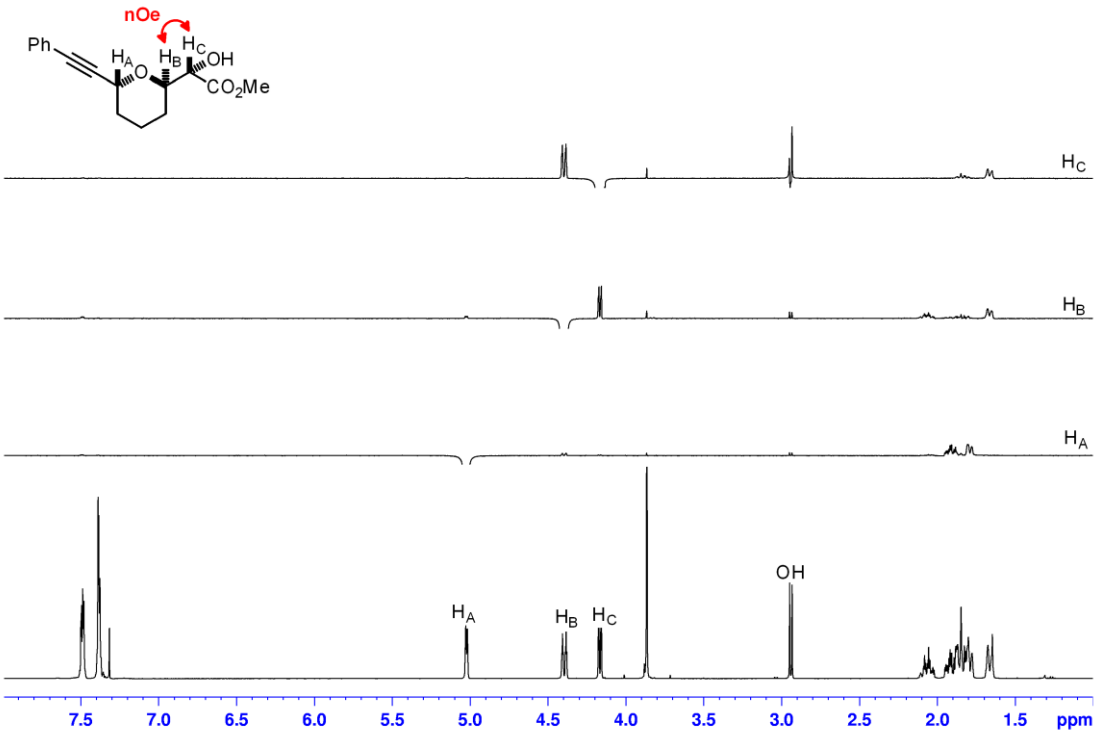

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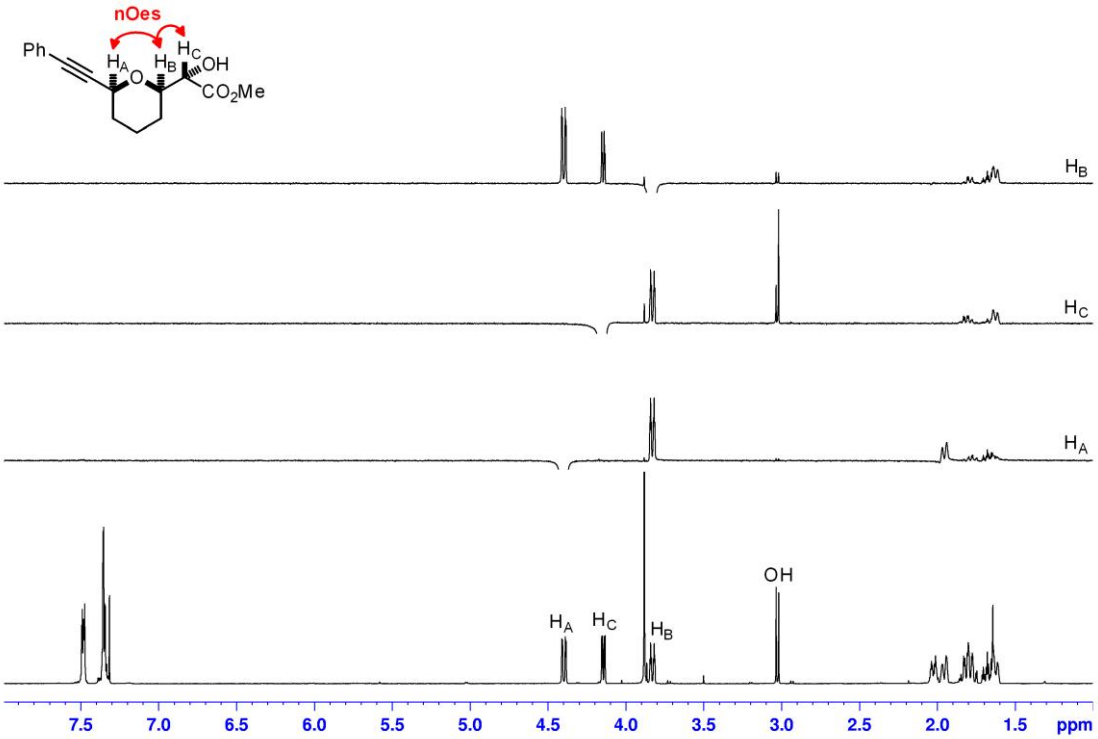

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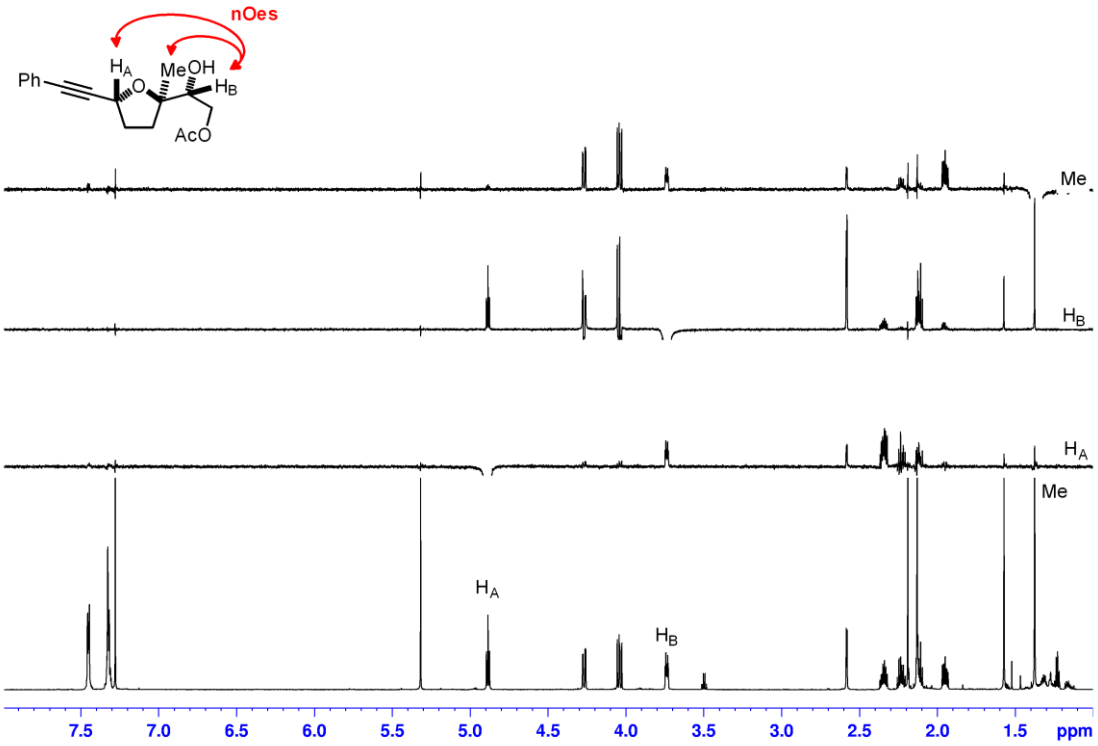

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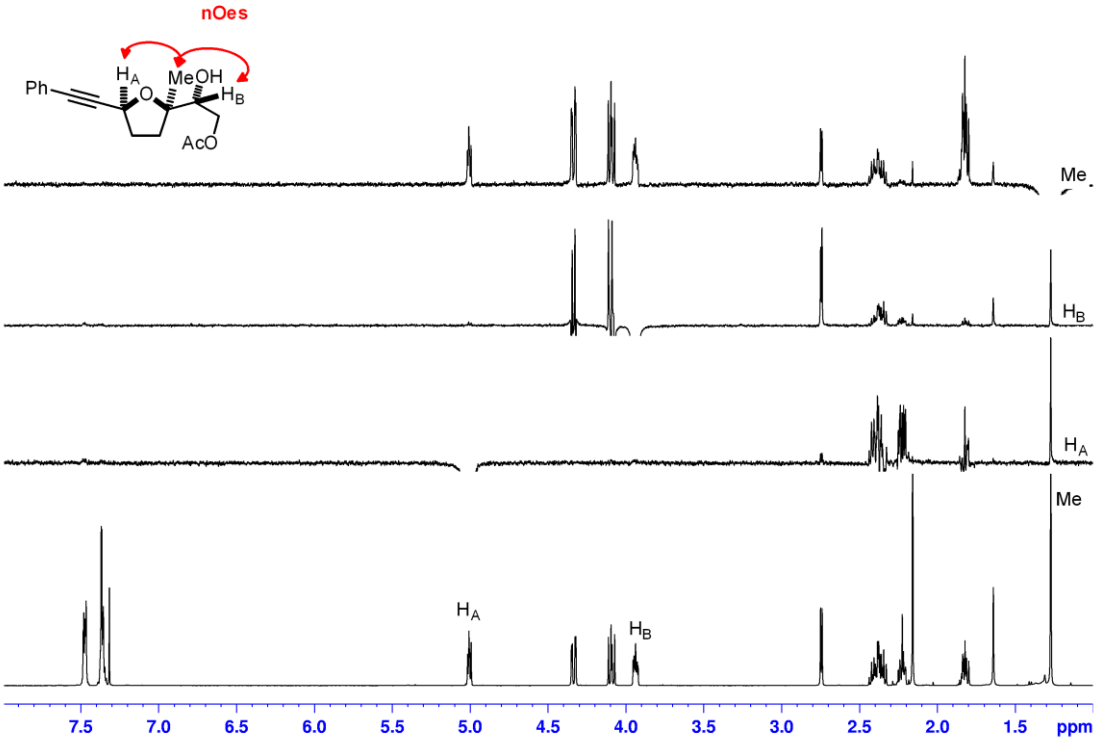
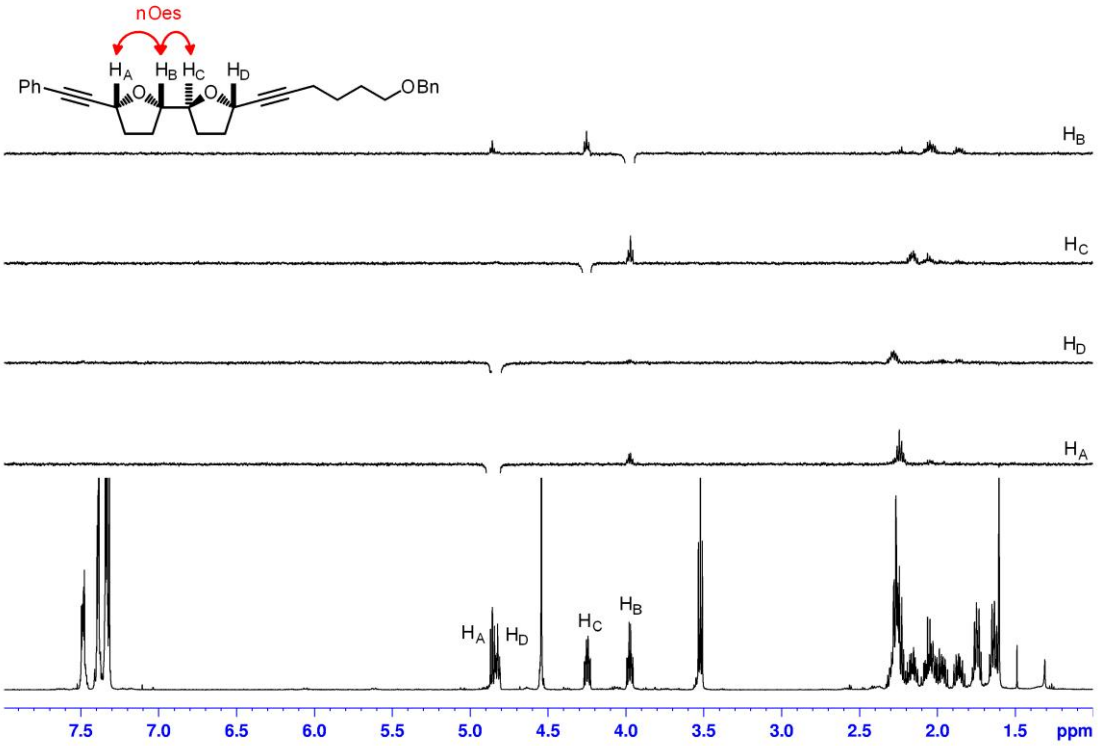


(*S*,*S*,*S*,*R*)-3.171



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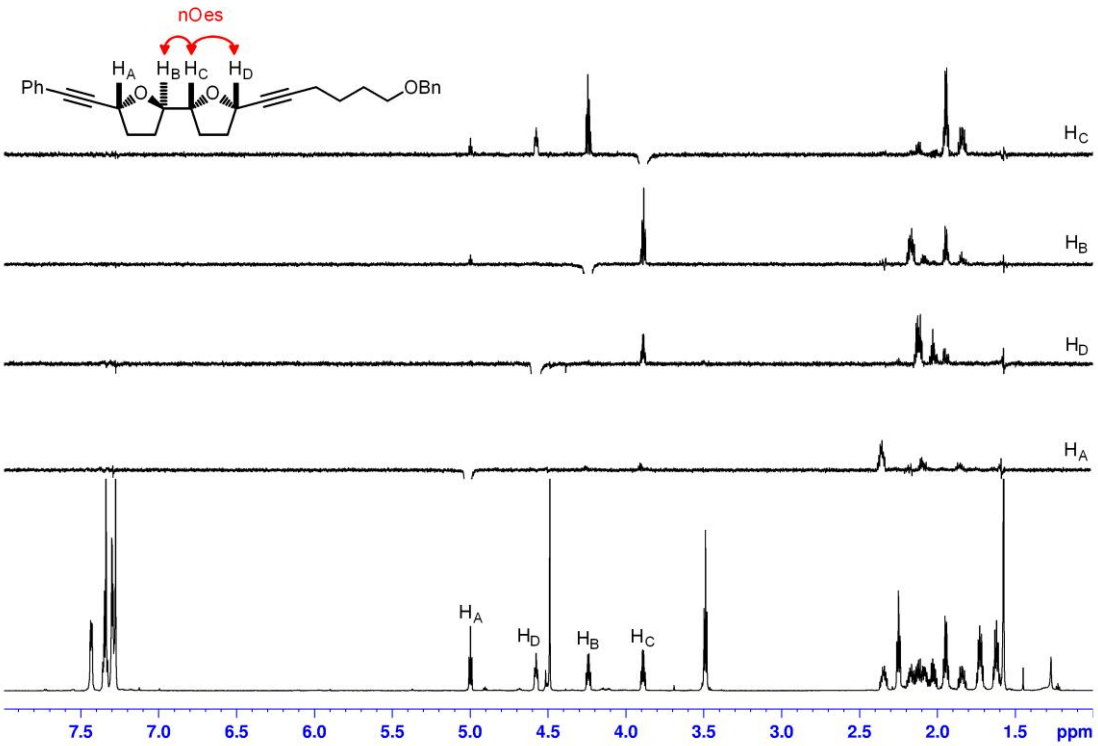

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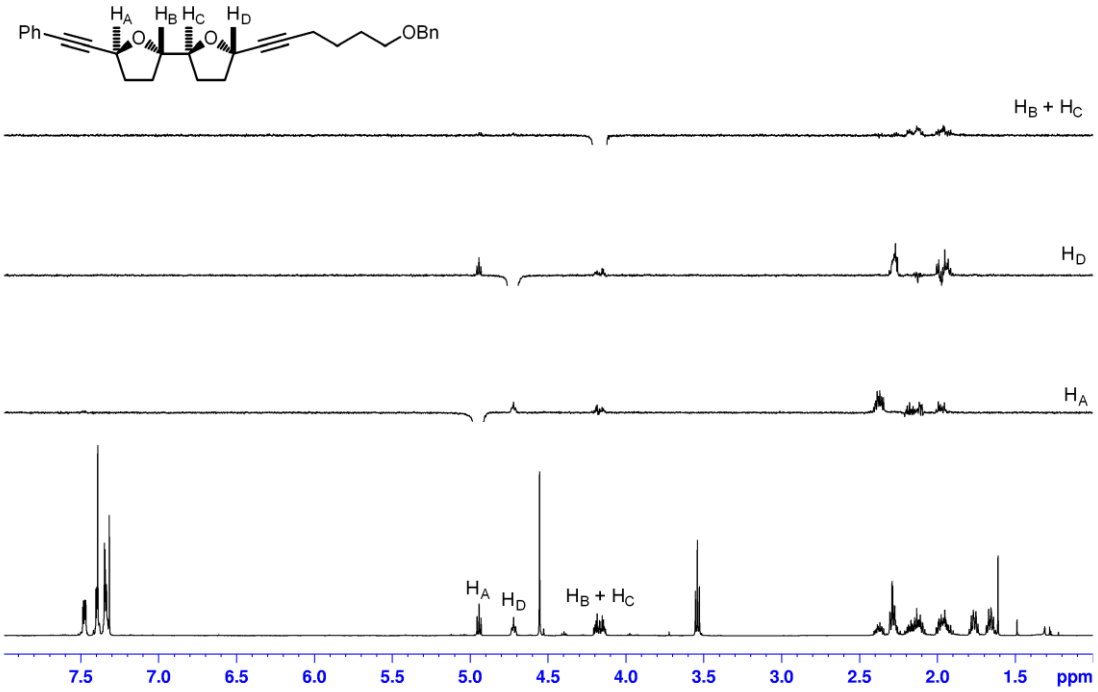
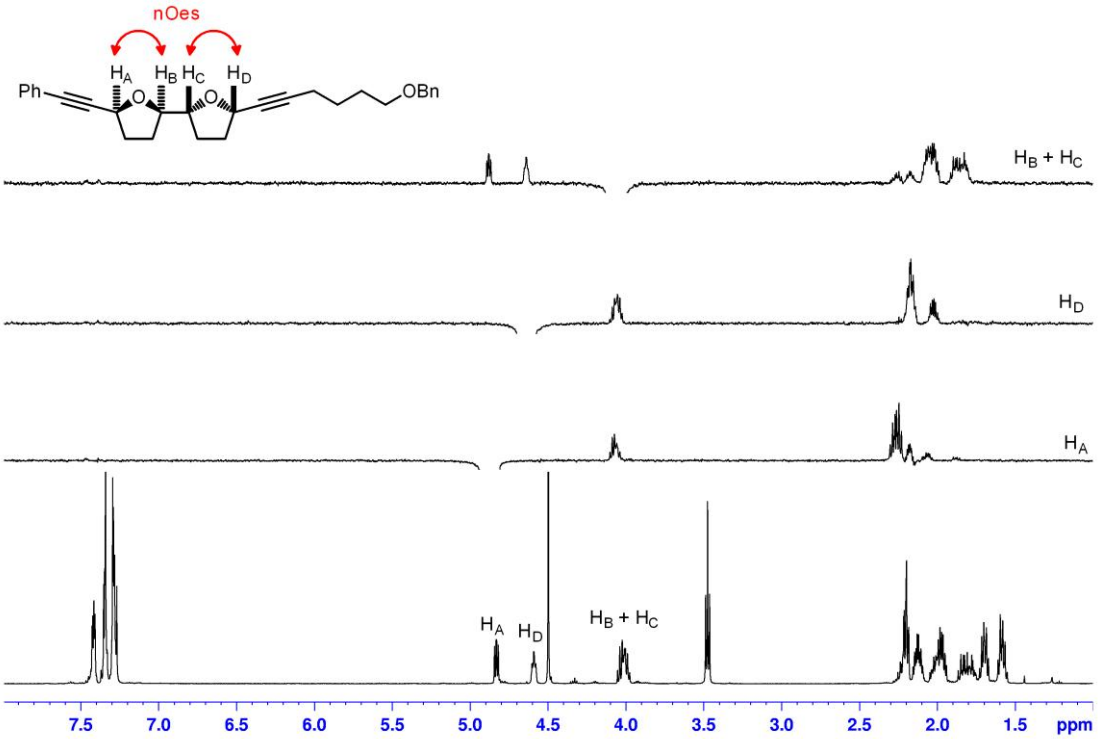
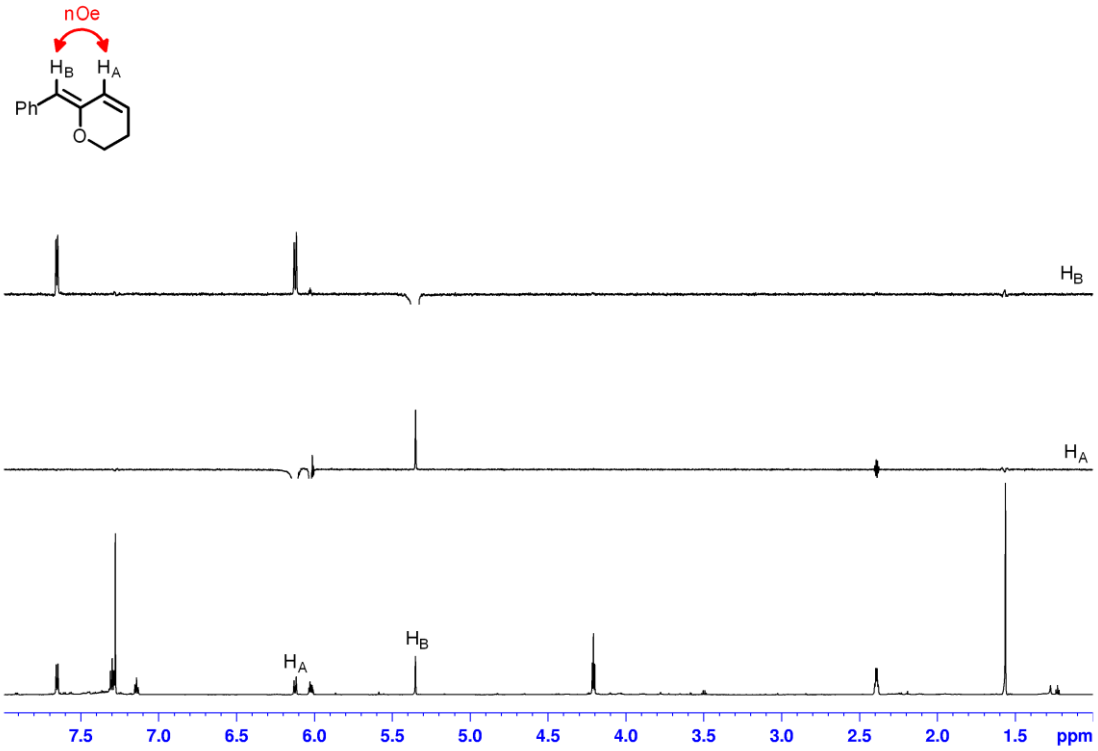


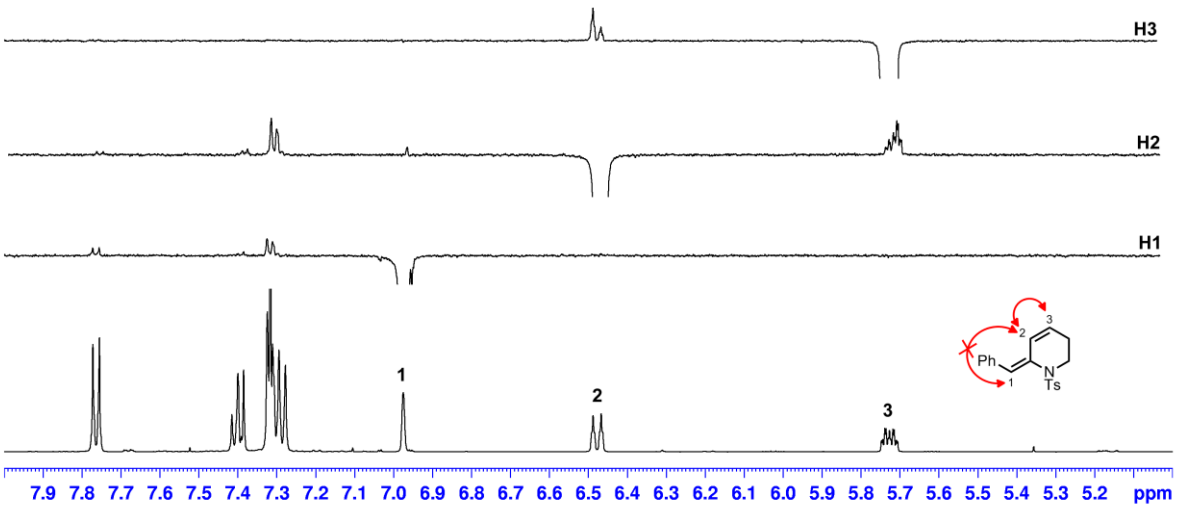
(*R*,*R*,*S*,*S*)-3.171



3.86



4.37c - ***Reproduced from ref 1 (above).***



X-Ray data for *anti*-2.33a, *trans*-(±)-3.39, (*R*)-4.36c, (*S*,*R*)-4.48c and (*R*,*R*)-4.48c is presented below.

Table 1. Crystal data and structure refinement for DIA0026.

Identification code	DIA0026	
Empirical formula	C15 H18 O2	
Formula weight	230.31	
Temperature	150 K	
Wavelength	0.68890 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 9.162(8) Å	α= 90°.
	b = 5.217(4) Å	β= 107.641(10)°.
	c = 13.759(12) Å	γ = 90°.
Volume	626.7(9) $Å^3$	
Z	2	
Density (calculated)	1.220 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	248	
Crystal size	0.020 x 0.020 x 0.010 mm^3	
Theta range for data collection	1.505 to 31.639°.	
Index ranges	-9<=h<=13, -7<=k<=7, -20<=l<=19	
Reflections collected	7888	
Independent reflections	2301 [R(int) = 0.070]	
Completeness to theta = 25.311°	97.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.45	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1463 / 1 / 154	
Goodness-of-fit on F^2	1.0239	
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1207	
R indices (all data)	R1 = 0.0478, wR2 = 0.1212	
Largest diff. peak and hole	0.25 and -0.29 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DIA0026. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	408(2)	8714(4)	487(1)	30
C(2)	2000(2)	8643(5)	1026(2)	27
C(3)	2975(3)	8232(5)	308(2)	30
C(4)	4681(3)	8265(5)	902(2)	31
C(5)	5075(3)	6236(5)	1736(2)	31
C(6)	4097(3)	6525(6)	2454(2)	33
C(7)	2402(2)	6656(5)	1868(2)	27
C(8)	1381(3)	5118(5)	2042(2)	29
C(9)	361(3)	3501(5)	2168(2)	28
C(10)	-564(2)	3731(5)	2878(2)	25
C(11)	-353(3)	5682(5)	3591(2)	28
C(12)	-1238(3)	5820(5)	4255(2)	28
C(13)	-2354(2)	3984(5)	4203(2)	28
O(14)	-3308(2)	3965(4)	4804(1)	36
C(15)	-3203(3)	6054(6)	5479(2)	41
C(16)	-2558(3)	1996(5)	3504(2)	30
C(17)	-1671(3)	1862(5)	2848(2)	28

Table 3. Bond lengths [Å] and angles [°] for DIA0026.

O(1)-C(2)	1.422(3)	C(16)-H(161)	0.921
O(1)-H(11)	0.825	C(17)-H(171)	0.938
C(2)-C(3)	1.535(3)		
C(2)-C(7)	1.515(3)	C(2)-O(1)-H(11)	113.9
C(2)-H(21)	0.984	O(1)-C(2)-C(3)	111.95(17)
C(3)-C(4)	1.529(3)	O(1)-C(2)-C(7)	112.93(19)
C(3)-H(31)	0.978	C(3)-C(2)-C(7)	110.03(19)
C(3)-H(32)	0.990	O(1)-C(2)-H(21)	106.9
C(4)-C(5)	1.522(3)	C(3)-C(2)-H(21)	106.8
C(4)-H(41)	0.970	C(7)-C(2)-H(21)	107.9
C(4)-H(42)	0.982	C(2)-C(3)-C(4)	110.8(2)
C(5)-C(6)	1.529(3)	C(2)-C(3)-H(31)	109.2
C(5)-H(51)	0.978	C(4)-C(3)-H(31)	110.6
C(5)-H(52)	0.993	C(2)-C(3)-H(32)	106.2
C(6)-C(7)	1.519(3)	C(4)-C(3)-H(32)	112.1
C(6)-H(61)	0.988	H(31)-C(3)-H(32)	107.9
C(6)-H(62)	0.997	C(3)-C(4)-C(5)	111.4(2)
C(7)-C(8)	1.308(4)	C(3)-C(4)-H(41)	106.1
C(8)-C(9)	1.309(4)	C(5)-C(4)-H(41)	108.2
C(9)-C(10)	1.480(3)	C(3)-C(4)-H(42)	111.1
C(9)-H(91)	0.940	C(5)-C(4)-H(42)	110.0
C(10)-C(11)	1.385(3)	H(41)-C(4)-H(42)	109.9
C(10)-C(17)	1.398(3)	C(4)-C(5)-C(6)	111.6(2)
C(11)-C(12)	1.395(3)	C(4)-C(5)-H(51)	109.2
C(11)-H(111)	0.951	C(6)-C(5)-H(51)	108.8
C(12)-C(13)	1.387(3)	C(4)-C(5)-H(52)	108.5
C(12)-H(121)	0.936	C(6)-C(5)-H(52)	108.9
C(13)-O(14)	1.374(3)	H(51)-C(5)-H(52)	110.0
C(13)-C(16)	1.388(4)	C(5)-C(6)-C(7)	111.5(2)
O(14)-C(15)	1.416(4)	C(5)-C(6)-H(61)	108.1
C(15)-H(151)	0.969	C(7)-C(6)-H(61)	107.8
C(15)-H(153)	0.965	C(5)-C(6)-H(62)	112.2
C(15)-H(152)	0.971	C(7)-C(6)-H(62)	109.5
C(16)-C(17)	1.387(3)	H(61)-C(6)-H(62)	107.6

C(6)-C(7)-C(2)	114.2(2)	C(12)-C(13)-O(14)	124.6(2)
C(6)-C(7)-C(8)	123.2(2)	C(12)-C(13)-C(16)	119.6(2)
C(2)-C(7)-C(8)	122.5(2)	O(14)-C(13)-C(16)	115.8(2)
C(7)-C(8)-C(9)	176.6(2)	C(13)-O(14)-C(15)	117.4(2)
C(8)-C(9)-C(10)	127.6(2)	O(14)-C(15)-H(151)	109.1
C(8)-C(9)-H(91)	116.5	O(14)-C(15)-H(153)	109.6
C(10)-C(9)-H(91)	115.9	H(151)-C(15)-H(153)	110.2
C(9)-C(10)-C(11)	122.8(2)	O(14)-C(15)-H(152)	110.7
C(9)-C(10)-C(17)	118.6(2)	H(151)-C(15)-H(152)	108.2
C(11)-C(10)-C(17)	118.56(19)	H(153)-C(15)-H(152)	109.0
C(10)-C(11)-C(12)	121.1(2)	C(13)-C(16)-C(17)	120.4(2)
C(10)-C(11)-H(111)	120.0	C(13)-C(16)-H(161)	119.3
C(12)-C(11)-H(111)	118.9	C(17)-C(16)-H(161)	120.3
C(11)-C(12)-C(13)	119.8(2)	C(10)-C(17)-C(16)	120.5(2)
C(11)-C(12)-H(121)	120.1	C(10)-C(17)-H(171)	120.1
C(13)-C(12)-H(121)	120.1	C(16)-C(17)-H(171)	119.4

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for DIA0026. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	28(1)	28(1)	33(1)	1(1)	7(1)	2(1)
C(2)	27(1)	24(1)	30(1)	-2(1)	10(1)	2(1)
C(3)	34(1)	31(1)	30(1)	6(1)	15(1)	3(1)
C(4)	32(1)	29(1)	37(1)	5(1)	19(1)	1(1)
C(5)	29(1)	28(1)	39(1)	3(1)	13(1)	1(1)
C(6)	28(1)	42(1)	29(1)	4(1)	7(1)	-2(1)
C(7)	29(1)	28(1)	26(1)	-4(1)	12(1)	0(1)
C(8)	30(1)	31(1)	26(1)	0(1)	10(1)	5(1)
C(9)	30(1)	26(1)	28(1)	2(1)	12(1)	3(1)
C(10)	26(1)	24(1)	27(1)	4(1)	10(1)	3(1)
C(11)	28(1)	26(1)	33(1)	2(1)	12(1)	-2(1)
C(12)	30(1)	26(1)	30(1)	-2(1)	11(1)	0(1)
C(13)	24(1)	33(1)	28(1)	8(1)	9(1)	4(1)
O(14)	33(1)	43(1)	38(1)	-3(1)	19(1)	-6(1)
C(15)	44(1)	47(2)	42(1)	-1(1)	27(1)	3(1)
C(16)	26(1)	29(1)	37(1)	5(1)	12(1)	-5(1)
C(17)	30(1)	24(1)	30(1)	-2(1)	9(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DIA0026.

	x	y	z	U(eq)
H(21)	2274	10339	1342	31
H(31)	2734	9567	-216	36
H(32)	2650	6566	-34	36
H(41)	4882	9936	1224	37
H(42)	5311	8025	445	37
H(51)	6154	6399	2132	38
H(52)	4883	4521	1409	39
H(61)	4383	8153	2832	40
H(62)	4280	5116	2966	39
H(91)	179	2034	1753	34
H(111)	403	6961	3631	34
H(121)	-1067	7126	4742	34
H(151)	-4018	5925	5790	62
H(153)	-2220	6027	5996	61
H(152)	-3317	7670	5114	62
H(161)	-3291	769	3479	37
H(171)	-1820	502	2382	34
H(11)	72	7363	193	46

Table 6. Hydrogen bonds for DIA0026 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(9)-H(91)...O(1)#1	0.940	2.509	3.413(3)	161.42(7)
O(1)-H(11)...O(1)#2	0.825	2.108	2.925(3)	170.58(8)

Symmetry transformations used to generate equivalent atoms:

#1 x,y-1,z #2 -x,y-1/2,-z

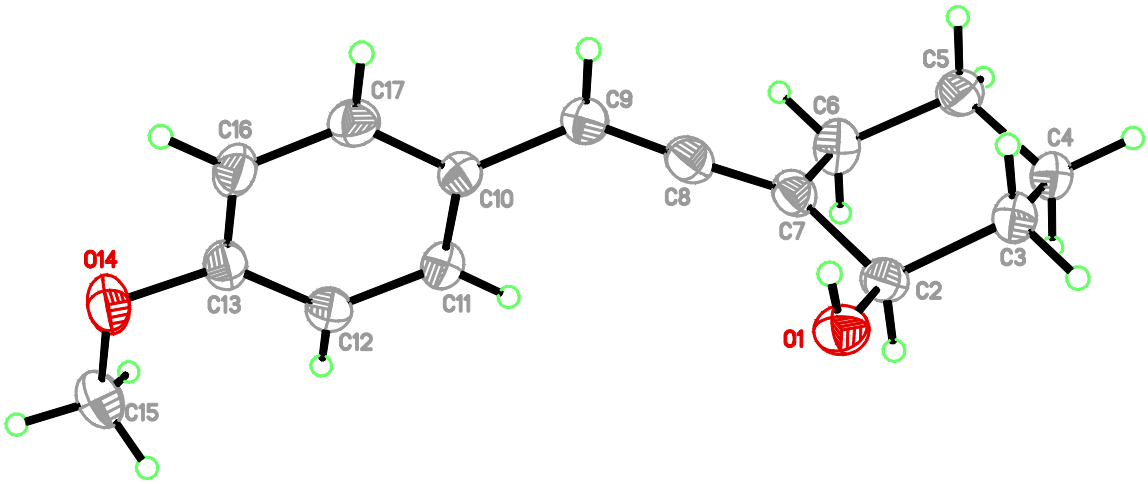


Table 1. Crystal data and structure refinement for 6134.

Identification code	6134	
Empirical formula	C14 H14 O3	
Formula weight	230.26	
Temperature	150 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 1 2/c 1	
Unit cell dimensions	a = 13.7825(4) Å	α= 90°.
	b = 12.4218(4) Å	β= 104.7742(16)°.
	c = 14.5247(5) Å	γ = 90°.
Volume	2404.47(13) $Å^3$	
Z	8	
Density (calculated)	1.272 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	976	
Crystal size	0.230 x 0.100 x 0.040 mm^3	
Theta range for data collection	5.156 to 27.450°.	
Index ranges	-17<=h<=17, -16<=k<=16, -18<=l<=18	
Reflections collected	12130	
Independent reflections	2718 [R(int) = 0.050]	
Completeness to theta = 26.352°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.95	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2717 / 0 / 154	
Goodness-of-fit on F^2	0.9489	
Final R indices [I>2sigma(I)]	R1 = 0.0423, wR2 = 0.0879	
R indices (all data)	R1 = 0.0728, wR2 = 0.1140	
Largest diff. peak and hole	0.39 and -0.46 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6134. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4734(1)	6020(1)	3497(1)	31
C(2)	4755(1)	4985(1)	3755(1)	28
O(3)	5597(1)	4605(1)	4350(1)	29
C(4)	6560(1)	4744(1)	4083(1)	28
C(5)	7169(1)	3767(2)	4493(1)	37
C(6)	7042(1)	5797(1)	4467(1)	32
C(7)	6457(1)	6773(2)	3995(1)	33
C(8)	5387(1)	6807(1)	4113(1)	28
C(9)	4920(1)	7854(2)	3825(1)	32
C(10)	4609(1)	8739(2)	3587(1)	32
C(11)	4244(1)	9808(1)	3317(1)	28
C(12)	4794(1)	10702(2)	3750(1)	33
C(13)	4444(1)	11736(2)	3494(1)	35
C(14)	3542(2)	11887(2)	2811(1)	35
C(15)	2995(1)	11001(2)	2382(1)	33
C(16)	3342(1)	9965(2)	2627(1)	32
O(17)	4032(1)	4423(1)	3467(1)	40

Table 3. Bond lengths [Å] and angles [°] for 6134.

O(1)-C(2)	1.337(2)	O(1)-C(2)-O(3)	118.17(15)
O(1)-C(8)	1.468(2)	O(1)-C(2)-O(17)	120.29(15)
C(2)-O(3)	1.344(2)	O(3)-C(2)-O(17)	121.53(16)
C(2)-O(17)	1.201(2)	C(2)-O(3)-C(4)	118.22(13)
O(3)-C(4)	1.4844(19)	O(3)-C(4)-C(5)	104.34(14)
C(4)-C(5)	1.510(2)	O(3)-C(4)-C(6)	110.07(13)
C(4)-C(6)	1.509(2)	C(5)-C(4)-C(6)	113.76(14)
C(4)-H(41)	1.017	O(3)-C(4)-H(41)	107.7
C(5)-H(52)	0.982	C(5)-C(4)-H(41)	111.1
C(5)-H(51)	0.976	C(6)-C(4)-H(41)	109.5
C(5)-H(53)	0.988	C(4)-C(5)-H(52)	110.3
C(6)-C(7)	1.519(2)	C(4)-C(5)-H(51)	108.7
C(6)-H(62)	0.988	H(52)-C(5)-H(51)	110.7
C(6)-H(61)	0.990	C(4)-C(5)-H(53)	108.4
C(7)-C(8)	1.529(2)	H(52)-C(5)-H(53)	110.2
C(7)-H(71)	0.994	H(51)-C(5)-H(53)	108.6
C(7)-H(72)	1.008	C(4)-C(6)-C(7)	113.03(14)
C(8)-C(9)	1.463(2)	C(4)-C(6)-H(62)	107.5
C(8)-H(81)	1.019	C(7)-C(6)-H(62)	109.4
C(9)-C(10)	1.198(3)	C(4)-C(6)-H(61)	107.0
C(10)-C(11)	1.439(2)	C(7)-C(6)-H(61)	109.0
C(11)-C(12)	1.400(2)	H(62)-C(6)-H(61)	111.0
C(11)-C(16)	1.397(2)	C(6)-C(7)-C(8)	112.82(15)
C(12)-C(13)	1.388(3)	C(6)-C(7)-H(71)	109.7
C(12)-H(121)	0.979	C(8)-C(7)-H(71)	105.9
C(13)-C(14)	1.390(3)	C(6)-C(7)-H(72)	109.7
C(13)-H(131)	0.972	C(8)-C(7)-H(72)	106.7
C(14)-C(15)	1.389(3)	H(71)-C(7)-H(72)	111.9
C(14)-H(141)	0.980	C(7)-C(8)-O(1)	111.86(14)
C(15)-C(16)	1.387(3)	C(7)-C(8)-C(9)	111.06(15)
C(15)-H(151)	0.971	O(1)-C(8)-C(9)	105.15(14)
C(16)-H(161)	0.966	C(7)-C(8)-H(81)	109.4
		O(1)-C(8)-H(81)	108.3
C(2)-O(1)-C(8)	120.24(13)	C(9)-C(8)-H(81)	111.0

C(8)-C(9)-C(10)	174.96(19)	C(14)-C(13)-H(131)	119.4
C(9)-C(10)-C(11)	179.06(19)	C(13)-C(14)-C(15)	119.76(17)
C(10)-C(11)-C(12)	119.88(16)	C(13)-C(14)-H(141)	119.9
C(10)-C(11)-C(16)	120.69(16)	C(15)-C(14)-H(141)	120.3
C(12)-C(11)-C(16)	119.42(16)	C(14)-C(15)-C(16)	120.50(17)
C(11)-C(12)-C(13)	120.13(16)	C(14)-C(15)-H(151)	119.8
C(11)-C(12)-H(121)	119.7	C(16)-C(15)-H(151)	119.7
C(13)-C(12)-H(121)	120.2	C(11)-C(16)-C(15)	120.00(16)
C(12)-C(13)-C(14)	120.17(17)	C(11)-C(16)-H(161)	119.8
C(12)-C(13)-H(131)	120.4	C(15)-C(16)-H(161)	120.2

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 6134. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	26(1)	31(1)	33(1)	5(1)	2(1)	0(1)
C(2)	28(1)	30(1)	25(1)	2(1)	4(1)	2(1)
O(3)	24(1)	34(1)	29(1)	6(1)	7(1)	4(1)
C(4)	23(1)	33(1)	30(1)	3(1)	9(1)	4(1)
C(5)	33(1)	35(1)	42(1)	5(1)	10(1)	10(1)
C(6)	25(1)	35(1)	34(1)	1(1)	4(1)	3(1)
C(7)	29(1)	30(1)	39(1)	2(1)	7(1)	-1(1)
C(8)	29(1)	26(1)	28(1)	0(1)	5(1)	1(1)
C(9)	33(1)	32(1)	33(1)	3(1)	12(1)	3(1)
C(10)	31(1)	34(1)	32(1)	3(1)	10(1)	2(1)
C(11)	28(1)	26(1)	32(1)	2(1)	12(1)	2(1)
C(12)	30(1)	34(1)	35(1)	1(1)	8(1)	0(1)
C(13)	38(1)	30(1)	37(1)	-3(1)	13(1)	-4(1)
C(14)	41(1)	29(1)	39(1)	5(1)	17(1)	5(1)
C(15)	29(1)	36(1)	34(1)	6(1)	8(1)	5(1)
C(16)	30(1)	32(1)	34(1)	0(1)	9(1)	-1(1)
O(17)	34(1)	34(1)	45(1)	-1(1)	-2(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 6134.

	x	y	z	U(eq)
H(41)	6404	4748	3359	34
H(52)	7812	3767	4319	56
H(51)	7277	3775	5183	56
H(53)	6779	3116	4238	56
H(62)	7722	5809	4359	41
H(61)	7076	5812	5156	40
H(71)	6788	7442	4296	40
H(72)	6400	6755	3289	41
H(81)	5397	6638	4802	33
H(121)	5432	10595	4225	40
H(131)	4827	12359	3787	44
H(141)	3288	12617	2647	43
H(151)	2357	11106	1919	40
H(161)	2952	9351	2338	40

Table 6. Hydrogen bonds for 6134 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(41)...O(17)#1	1.02	2.60	3.606(3)	171
C(8)-H(81)...O(3)#2	1.02	2.58	3.382(3)	136

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y,-z+1/2 #2 -x+1,-y+1,-z+1

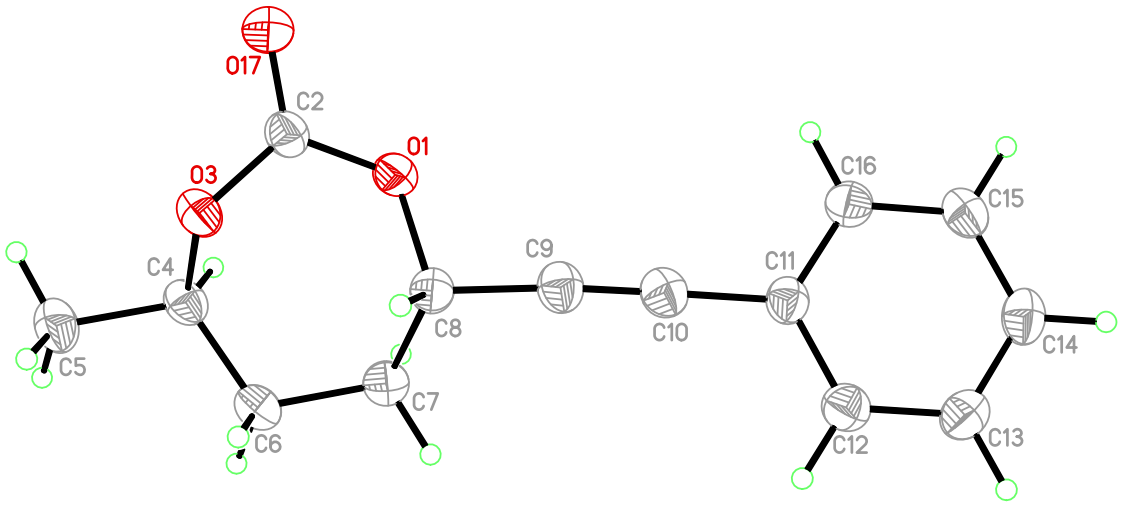


Table 1. Crystal data and structure refinement for 6315.

Identification code	6315	
Empirical formula	C19 H19 N1 O2 S1	
Formula weight	325.43	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.7310(1) Å	α= 90°.
	b = 10.8357(1) Å	β= 90°.
	c = 19.5005(1) Å	γ = 90°.
Volume	1633.57(3) $Å^3$	
Z	4	
Density (calculated)	1.323 Mg/m^3	
Absorption coefficient	1.829 mm^{-1}	
F(000)	688	
Crystal size	0.450 x 0.200 x 0.200 mm^3	
Theta range for data collection	4.535 to 75.815°.	
Index ranges	-9<=h<=9, 0<=k<=13, 0<=l<=24	
Reflections collected	3398	
Independent reflections	3398 [R(int) = 0.021]	
Completeness to theta = 75.815°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.69 and 0.57	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3398 / 0 / 210	
Goodness-of-fit on F^2	1.0130	
Final R indices [I>2sigma(I)]	R1 = 0.0222, wR2 = 0.0618	
R indices (all data)	R1 = 0.0222, wR2 = 0.0618	
Absolute structure parameter	0.007(10)	
Extinction coefficient	227.233	
Largest diff. peak and hole	0.36 and -0.32 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6315. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	-1383	7237	2868	24
O(2)	-2270	6293	2491	30
O(3)	-2158	8434	2941	32
N(4)	475	7436	2488	27
C(5)	1342	6335	2172	28
C(6)	3273	6529	2335	35
C(7)	3278	7315	2969	40
C(8)	1785	8214	2839	33
C(9)	1015	6270	1433	32
C(10)	893	6220	822	32
C(11)	848	6187	85	27
C(12)	-48	5264	-266	33
C(13)	-19	5234	-975	37
C(14)	887	6116	-1343	37
C(15)	1758	7042	-1000	36
C(16)	1744	7083	-289	31
C(17)	-994	6678	3704	25
C(18)	-508	5449	3801	29
C(19)	-232	5016	4460	30
C(20)	-442	5776	5030	29
C(21)	-915	7003	4920	35
C(22)	-1184	7460	4264	32
C(23)	-213	5275	5743	38

Table 3. Bond lengths [Å] and angles [°] for 6315.

S(1)-O(2)	1.435	C(19)-C(20)	1.393
S(1)-O(3)	1.435	C(19)-H(191)	0.976
S(1)-N(4)	1.630	C(20)-C(21)	1.395
S(1)-C(17)	1.766	C(20)-C(23)	1.504
N(4)-C(5)	1.501	C(21)-C(22)	1.387
N(4)-C(8)	1.485	C(21)-H(211)	0.943
C(5)-C(6)	1.540	C(22)-H(221)	0.987
C(5)-C(9)	1.465	C(23)-H(231)	0.938
C(5)-H(51)	0.968	C(23)-H(232)	0.954
C(6)-C(7)	1.502	C(23)-H(233)	0.958
C(6)-H(61)	0.975		
C(6)-H(62)	0.953	O(2)-S(1)-O(3)	119.712
C(7)-C(8)	1.531	O(2)-S(1)-N(4)	106.445
C(7)-H(71)	1.003	O(3)-S(1)-N(4)	107.075
C(7)-H(72)	1.005	O(2)-S(1)-C(17)	108.044
C(8)-H(81)	0.956	O(3)-S(1)-C(17)	106.806
C(8)-H(82)	0.944	N(4)-S(1)-C(17)	108.350
C(9)-C(10)	1.197	S(1)-N(4)-C(5)	118.345
C(10)-C(11)	1.437	S(1)-N(4)-C(8)	117.835
C(11)-C(12)	1.396	C(5)-N(4)-C(8)	109.592
C(11)-C(16)	1.399	N(4)-C(5)-C(6)	103.880
C(12)-C(13)	1.384	N(4)-C(5)-C(9)	111.381
C(12)-H(121)	0.962	C(6)-C(5)-C(9)	112.122
C(13)-C(14)	1.385	N(4)-C(5)-H(51)	108.9
C(13)-H(131)	0.953	C(6)-C(5)-H(51)	110.7
C(14)-C(15)	1.382	C(9)-C(5)-H(51)	109.7
C(14)-H(141)	0.965	C(5)-C(6)-C(7)	104.456
C(15)-C(16)	1.386	C(5)-C(6)-H(61)	110.3
C(15)-H(151)	0.941	C(7)-C(6)-H(61)	113.9
C(16)-H(161)	0.955	C(5)-C(6)-H(62)	107.7
C(17)-C(18)	1.397	C(7)-C(6)-H(62)	111.1
C(17)-C(22)	1.390	H(61)-C(6)-H(62)	109.1
C(18)-C(19)	1.386	C(6)-C(7)-C(8)	102.876
C(18)-H(181)	1.019	C(6)-C(7)-H(71)	113.5

C(8)-C(7)-H(71)	109.7	C(11)-C(16)-C(15)	120.216
C(6)-C(7)-H(72)	110.4	C(11)-C(16)-H(161)	118.4
C(8)-C(7)-H(72)	106.9	C(15)-C(16)-H(161)	121.4
H(71)-C(7)-H(72)	112.7	S(1)-C(17)-C(18)	119.829
C(7)-C(8)-N(4)	103.301	S(1)-C(17)-C(22)	119.919
C(7)-C(8)-H(81)	113.2	C(18)-C(17)-C(22)	120.250
N(4)-C(8)-H(81)	110.1	C(17)-C(18)-C(19)	119.279
C(7)-C(8)-H(82)	109.1	C(17)-C(18)-H(181)	121.3
N(4)-C(8)-H(82)	106.3	C(19)-C(18)-H(181)	119.4
H(81)-C(8)-H(82)	114.1	C(18)-C(19)-C(20)	121.500
C(5)-C(9)-C(10)	174.543	C(18)-C(19)-H(191)	119.4
C(9)-C(10)-C(11)	176.674	C(20)-C(19)-H(191)	119.0
C(10)-C(11)-C(12)	121.332	C(19)-C(20)-C(21)	118.103
C(10)-C(11)-C(16)	119.500	C(19)-C(20)-C(23)	120.672
C(12)-C(11)-C(16)	119.158	C(21)-C(20)-C(23)	121.202
C(11)-C(12)-C(13)	119.964	C(20)-C(21)-C(22)	121.438
C(11)-C(12)-H(121)	119.4	C(20)-C(21)-H(211)	122.0
C(13)-C(12)-H(121)	120.5	C(22)-C(21)-H(211)	116.5
C(12)-C(13)-C(14)	120.598	C(17)-C(22)-C(21)	119.419
C(12)-C(13)-H(131)	119.7	C(17)-C(22)-H(221)	118.5
C(14)-C(13)-H(131)	119.7	C(21)-C(22)-H(221)	122.1
C(13)-C(14)-C(15)	119.794	C(20)-C(23)-H(231)	110.1
C(13)-C(14)-H(141)	121.5	C(20)-C(23)-H(232)	112.6
C(15)-C(14)-H(141)	118.7	H(231)-C(23)-H(232)	108.8
C(14)-C(15)-C(16)	120.260	C(20)-C(23)-H(233)	109.5
C(14)-C(15)-H(151)	120.6	H(231)-C(23)-H(233)	104.9
C(16)-C(15)-H(151)	119.2	H(232)-C(23)-H(233)	110.6

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 6315. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	26	20	26	0	-2	2
O(2)	30	28	33	-3	-5	-2
O(3)	36	24	35	0	-3	9
N(4)	29	21	29	-1	1	-1
C(5)	32	23	29	2	3	2
C(6)	29	37	40	4	1	3
C(7)	36	40	42	-1	-5	-4
C(8)	35	24	41	1	-3	-7
C(9)	31	30	34	-1	5	2
C(10)	32	30	33	0	5	5
C(11)	26	27	29	-1	3	5
C(12)	30	28	41	-1	4	-1
C(13)	35	37	39	-10	-3	2
C(14)	41	40	29	-2	0	10
C(15)	40	33	36	5	8	3
C(16)	32	26	35	-3	3	0
C(17)	26	23	26	0	1	0
C(18)	32	25	30	0	3	3
C(19)	32	26	33	5	4	4
C(20)	26	33	28	2	0	-3
C(21)	47	30	28	-5	1	-2
C(22)	42	24	31	-2	1	2
C(23)	44	41	29	4	-2	-1

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 6315.

	x	y	z	U(eq)
H(51)	913	5595	2392	34
H(61)	3850	5735	2391	45
H(62)	3777	6955	1957	43
H(71)	3056	6839	3401	48
H(72)	4366	7822	2992	47
H(81)	1312	8552	3251	40
H(82)	2140	8812	2516	43
H(121)	-631	4629	-11	38
H(131)	-665	4620	-1213	46
H(141)	921	6106	-1838	43
H(151)	2359	7656	-1244	45
H(161)	2347	7712	-43	35
H(181)	-357	4864	3396	34
H(191)	67	4150	4530	37
H(211)	-1074	7563	5285	44
H(221)	-1515	8326	4180	39
H(231)	-1294	5099	5938	60
H(232)	393	5830	6037	58
H(233)	369	4494	5722	59

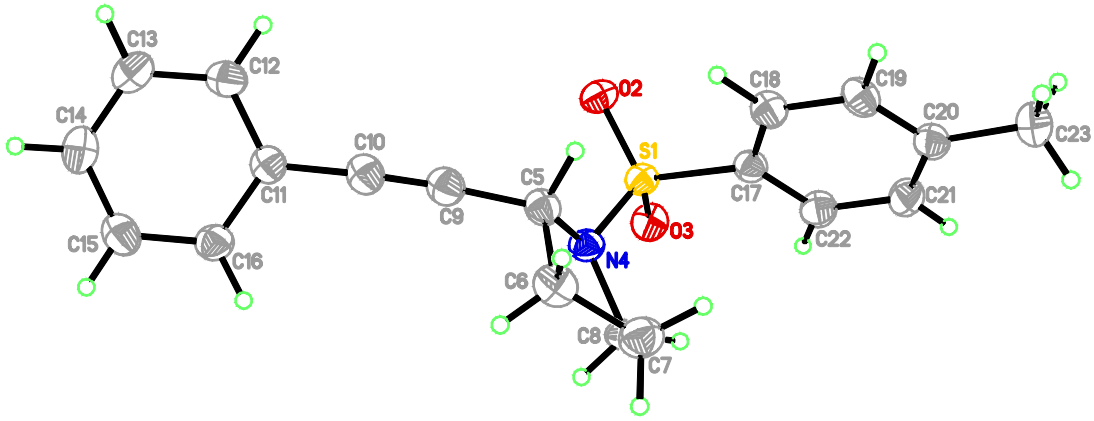


Table 1. Crystal data and structure refinement for 6363.

Identification code	6363	
Empirical formula	C22 H23 N1 O2 S1	
Formula weight	365.50	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.57410(10) Å	α= 90°.
	b = 10.85650(10) Å	β= 90°.
	c = 23.48000(10) Å	γ = 90°.
Volume	1930.72(3) $Å^3$	
Z	4	
Density (calculated)	1.257 Mg/m^3	
Absorption coefficient	1.604 mm^{-1}	
F(000)	776	
Crystal size	0.210 x 0.120 x 0.070 mm^3	
Theta range for data collection	3.765 to 76.847°.	
Index ranges	-8<=h<=9, -13<=k<=13, -29<=l<=29	
Reflections collected	59199	
Independent reflections	4069 [R(int) = 0.027]	
Completeness to theta = 76.847°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.89 and 0.65	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4069 / 0 / 237	
Goodness-of-fit on F^2	0.9975	
Final R indices [I>2sigma(I)]	R1 = 0.0225, wR2 = 0.0623	
R indices (all data)	R1 = 0.0229, wR2 = 0.0625	
Absolute structure parameter	0.000(10)	
Extinction coefficient	29(4)	
Largest diff. peak and hole	0.30 and -0.42 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6363. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	67(1)	5823(1)	2646(1)	20
O(2)	-579(1)	4628(1)	2803(1)	25
O(3)	-1034(1)	6883(1)	2723(1)	26
N(4)	1846(1)	6053(1)	3024(1)	21
C(5)	2791(2)	7251(1)	2949(1)	25
C(6)	3041(2)	7810(1)	3514(1)	27
C(7)	3227(2)	8207(1)	3984(1)	29
C(8)	3308(2)	8663(1)	4559(1)	26
C(9)	2308(2)	9693(1)	4713(1)	29
C(10)	2322(2)	10110(1)	5269(1)	34
C(11)	3334(2)	9516(1)	5678(1)	36
C(12)	4331(2)	8499(1)	5529(1)	37
C(13)	4324(2)	8067(1)	4973(1)	33
C(14)	4524(2)	6869(1)	2665(1)	34
C(15)	4953(2)	5654(1)	2955(1)	39
C(16)	3161(2)	5025(1)	3065(1)	24
C(17)	3056(2)	4424(1)	3652(1)	29
C(18)	4306(2)	3359(1)	3703(1)	30
C(19)	3847(2)	2241(1)	3847(1)	41
C(20)	715(2)	5773(1)	1924(1)	21
C(21)	1296(2)	4673(1)	1684(1)	25
C(22)	1918(2)	4678(1)	1127(1)	28
C(23)	1935(2)	5750(1)	805(1)	28
C(24)	1315(2)	6835(1)	1052(1)	28
C(25)	719(2)	6861(1)	1611(1)	25
C(26)	2594(2)	5742(2)	199(1)	40

Table 3. Bond lengths [Å] and angles [°] for 6363.

S(1)-O(2)	1.4350(8)	C(18)-H(181)	0.960
S(1)-O(3)	1.4318(8)	C(19)-H(191)	0.958
S(1)-N(4)	1.6330(10)	C(19)-H(192)	0.946
S(1)-C(20)	1.7649(11)	C(20)-C(21)	1.3913(16)
N(4)-C(5)	1.4944(14)	C(20)-C(25)	1.3918(15)
N(4)-C(16)	1.4986(14)	C(21)-C(22)	1.3908(17)
C(5)-C(6)	1.4709(17)	C(21)-H(211)	0.942
C(5)-C(14)	1.5299(17)	C(22)-C(23)	1.3885(18)
C(5)-H(51)	0.989	C(22)-H(221)	0.946
C(6)-C(7)	1.1928(19)	C(23)-C(24)	1.3943(18)
C(7)-C(8)	1.4391(17)	C(23)-C(26)	1.5058(17)
C(8)-C(9)	1.3981(17)	C(24)-C(25)	1.3880(17)
C(8)-C(13)	1.3984(17)	C(24)-H(241)	0.971
C(9)-C(10)	1.3821(19)	C(25)-H(251)	0.934
C(9)-H(91)	0.927	C(26)-H(261)	0.939
C(10)-C(11)	1.388(2)	C(26)-H(262)	0.973
C(10)-H(101)	0.944	C(26)-H(263)	0.963
C(11)-C(12)	1.382(2)		
C(11)-H(111)	0.930	O(2)-S(1)-O(3)	119.73(5)
C(12)-C(13)	1.3872(19)	O(2)-S(1)-N(4)	106.26(5)
C(12)-H(121)	0.947	O(3)-S(1)-N(4)	106.82(5)
C(13)-H(131)	0.959	O(2)-S(1)-C(20)	108.23(5)
C(14)-C(15)	1.5186(19)	O(3)-S(1)-C(20)	107.94(5)
C(14)-H(141)	1.017	N(4)-S(1)-C(20)	107.27(5)
C(14)-H(142)	0.969	S(1)-N(4)-C(5)	117.68(7)
C(15)-C(16)	1.5413(18)	S(1)-N(4)-C(16)	118.02(7)
C(15)-H(151)	0.964	C(5)-N(4)-C(16)	109.72(9)
C(15)-H(152)	1.005	N(4)-C(5)-C(6)	108.36(9)
C(16)-C(17)	1.5273(15)	N(4)-C(5)-C(14)	103.06(9)
C(16)-H(161)	0.984	C(6)-C(5)-C(14)	113.24(11)
C(17)-C(18)	1.4992(17)	N(4)-C(5)-H(51)	110.7
C(17)-H(171)	0.990	C(6)-C(5)-H(51)	109.7
C(17)-H(172)	0.970	C(14)-C(5)-H(51)	111.6
C(18)-C(19)	1.307(2)	C(5)-C(6)-C(7)	176.73(13)

C(6)-C(7)-C(8)	175.46(14)	C(17)-C(16)-H(161)	108.8
C(7)-C(8)-C(9)	119.66(11)	C(16)-C(17)-C(18)	111.62(10)
C(7)-C(8)-C(13)	121.09(12)	C(16)-C(17)-H(171)	109.9
C(9)-C(8)-C(13)	119.21(12)	C(18)-C(17)-H(171)	110.2
C(8)-C(9)-C(10)	120.21(12)	C(16)-C(17)-H(172)	107.3
C(8)-C(9)-H(91)	118.8	C(18)-C(17)-H(172)	109.5
C(10)-C(9)-H(91)	120.9	H(171)-C(17)-H(172)	108.2
C(9)-C(10)-C(11)	120.32(13)	C(17)-C(18)-C(19)	124.68(13)
C(9)-C(10)-H(101)	118.4	C(17)-C(18)-H(181)	117.2
C(11)-C(10)-H(101)	121.3	C(19)-C(18)-H(181)	118.1
C(10)-C(11)-C(12)	119.86(13)	C(18)-C(19)-H(191)	122.6
C(10)-C(11)-H(111)	119.1	C(18)-C(19)-H(192)	122.0
C(12)-C(11)-H(111)	121.0	H(191)-C(19)-H(192)	115.4
C(11)-C(12)-C(13)	120.42(13)	S(1)-C(20)-C(21)	120.21(9)
C(11)-C(12)-H(121)	120.0	S(1)-C(20)-C(25)	118.81(9)
C(13)-C(12)-H(121)	119.6	C(21)-C(20)-C(25)	120.90(10)
C(8)-C(13)-C(12)	119.98(12)	C(20)-C(21)-C(22)	118.98(11)
C(8)-C(13)-H(131)	120.1	C(20)-C(21)-H(211)	120.8
C(12)-C(13)-H(131)	119.9	C(22)-C(21)-H(211)	120.2
C(5)-C(14)-C(15)	102.94(10)	C(21)-C(22)-C(23)	121.32(11)
C(5)-C(14)-H(141)	108.7	C(21)-C(22)-H(221)	118.2
C(15)-C(14)-H(141)	109.8	C(23)-C(22)-H(221)	120.5
C(5)-C(14)-H(142)	112.2	C(22)-C(23)-C(24)	118.50(11)
C(15)-C(14)-H(142)	112.6	C(22)-C(23)-C(26)	120.86(12)
H(141)-C(14)-H(142)	110.2	C(24)-C(23)-C(26)	120.64(12)
C(14)-C(15)-C(16)	105.76(10)	C(23)-C(24)-C(25)	121.39(11)
C(14)-C(15)-H(151)	111.7	C(23)-C(24)-H(241)	119.9
C(16)-C(15)-H(151)	108.2	C(25)-C(24)-H(241)	118.8
C(14)-C(15)-H(152)	110.9	C(20)-C(25)-C(24)	118.90(11)
C(16)-C(15)-H(152)	109.7	C(20)-C(25)-H(251)	120.4
H(151)-C(15)-H(152)	110.4	C(24)-C(25)-H(251)	120.7
C(15)-C(16)-N(4)	104.15(9)	C(23)-C(26)-H(261)	112.3
C(15)-C(16)-C(17)	112.76(11)	C(23)-C(26)-H(262)	111.2
N(4)-C(16)-C(17)	110.02(9)	H(261)-C(26)-H(262)	107.8
C(15)-C(16)-H(161)	111.6	C(23)-C(26)-H(263)	110.7
N(4)-C(16)-H(161)	109.4	H(261)-C(26)-H(263)	107.2

H(262)-C(26)-H(263) 107.4

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 6363. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	18(1)	18(1)	22(1)	0(1)	1(1)	0(1)
O(2)	25(1)	21(1)	29(1)	2(1)	3(1)	-3(1)
O(3)	23(1)	23(1)	33(1)	-3(1)	2(1)	3(1)
N(4)	21(1)	22(1)	20(1)	0(1)	-1(1)	0(1)
C(5)	26(1)	26(1)	24(1)	1(1)	0(1)	-6(1)
C(6)	25(1)	27(1)	30(1)	-1(1)	-3(1)	-4(1)
C(7)	26(1)	26(1)	33(1)	-1(1)	-3(1)	-4(1)
C(8)	25(1)	25(1)	28(1)	-1(1)	-3(1)	-6(1)
C(9)	26(1)	28(1)	33(1)	1(1)	-5(1)	-2(1)
C(10)	29(1)	33(1)	39(1)	-9(1)	1(1)	-1(1)
C(11)	35(1)	44(1)	28(1)	-5(1)	0(1)	-9(1)
C(12)	38(1)	41(1)	32(1)	7(1)	-10(1)	-3(1)
C(13)	33(1)	29(1)	36(1)	1(1)	-6(1)	2(1)
C(14)	28(1)	39(1)	35(1)	3(1)	7(1)	-6(1)
C(15)	24(1)	46(1)	47(1)	8(1)	7(1)	3(1)
C(16)	22(1)	28(1)	23(1)	2(1)	1(1)	4(1)
C(17)	34(1)	32(1)	22(1)	3(1)	1(1)	6(1)
C(18)	29(1)	37(1)	25(1)	2(1)	-4(1)	4(1)
C(19)	34(1)	39(1)	51(1)	13(1)	-4(1)	8(1)
C(20)	21(1)	21(1)	21(1)	-1(1)	-2(1)	0(1)
C(21)	28(1)	21(1)	26(1)	-1(1)	-4(1)	0(1)
C(22)	31(1)	28(1)	26(1)	-6(1)	-3(1)	3(1)
C(23)	22(1)	38(1)	22(1)	-1(1)	-3(1)	-1(1)
C(24)	28(1)	28(1)	26(1)	5(1)	-4(1)	-3(1)
C(25)	27(1)	20(1)	26(1)	0(1)	-3(1)	0(1)
C(26)	39(1)	57(1)	23(1)	0(1)	1(1)	6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 6363.

	x	y	z	U(eq)
H(51)	2101	7814	2705	30
H(91)	1615	10072	4439	33
H(101)	1621	10801	5362	40
H(111)	3330	9812	6050	42
H(121)	5031	8096	5807	43
H(131)	5021	7362	4873	38
H(141)	4298	6726	2243	41
H(142)	5445	7478	2716	41
H(151)	5642	5124	2712	46
H(152)	5579	5796	3326	47
H(161)	2896	4401	2774	26
H(171)	1832	4151	3729	35
H(172)	3365	5048	3931	35
H(181)	5527	3514	3619	36
H(191)	2652	2019	3933	50
H(192)	4673	1588	3863	48
H(211)	1254	3932	1893	29
H(221)	2340	3929	972	34
H(241)	1294	7591	832	31
H(251)	315	7594	1773	28
H(261)	2201	6430	-8	59
H(262)	2206	5006	-1	60
H(263)	3865	5752	190	59

Table 6. Hydrogen bonds for 6363 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(5)-H(51)...O(2)#1	0.989	2.573	3.5473(18)	168.23
C(21)-H(211)...O(3)#2	0.942	2.407	3.3400(18)	170.54
C(25)-H(251)...O(2)#1	0.934	2.430	3.3062(18)	156.17

Symmetry transformations used to generate equivalent atoms:

#1 -x,y+1/2,-z+1/2 #2 -x,y-1/2,-z+1/2

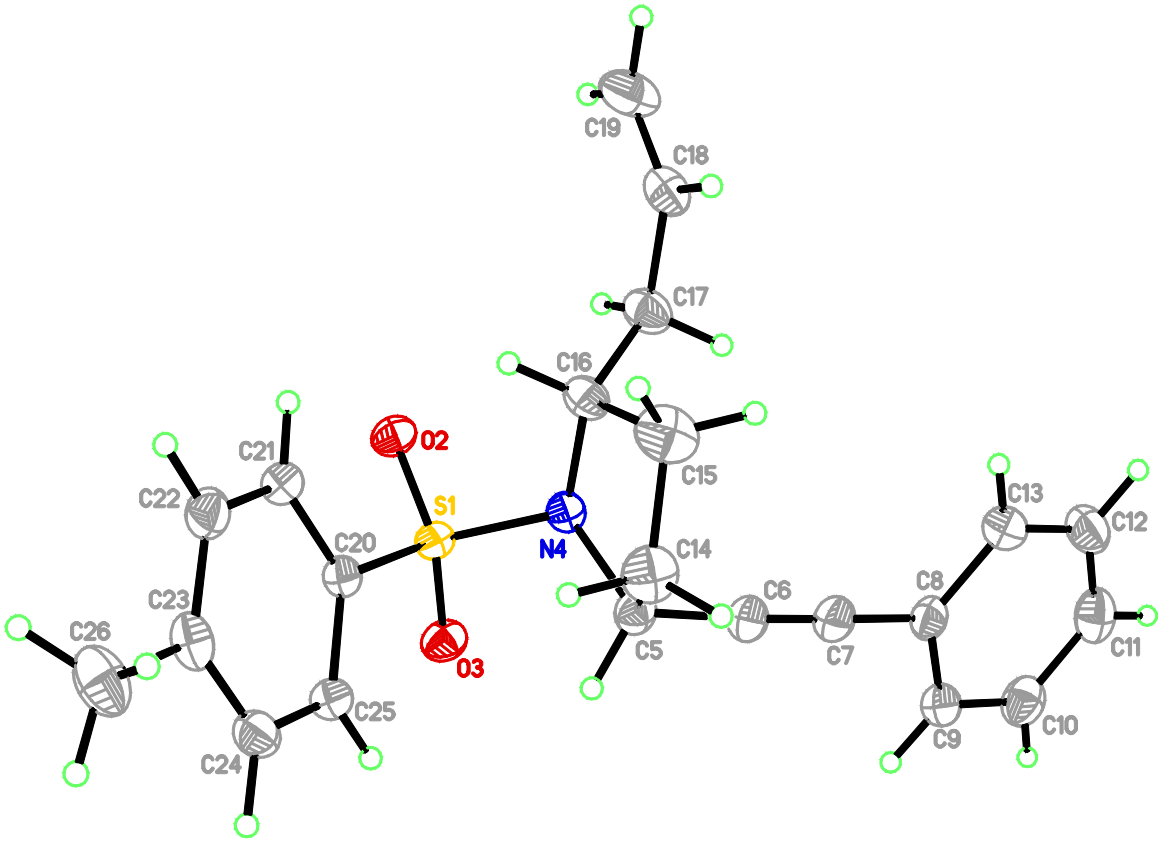


Table 1. Crystal data and structure refinement for 6367.

Identification code	6367	
Empirical formula	C22 H23 N1 O2 S1	
Formula weight	365.50	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.7355(1) Å	α= 90°.
	b = 10.5550(1) Å	β= 90°.
	c = 23.3632(2) Å	γ = 90°.
Volume	1907.56(3) $Å^3$	
Z	4	
Density (calculated)	1.273 Mg/m^3	
Absorption coefficient	1.624 mm^{-1}	
F(000)	776	
Crystal size	0.400 x 0.200 x 0.050 mm^3	
Theta range for data collection	3.784 to 76.849°.	
Index ranges	-9<=h<=9, -13<=k<=13, -27<=l<=29	
Reflections collected	15873	
Independent reflections	3989 [R(int) = 0.020]	
Completeness to theta = 75.312°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.92 and 0.60	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3973 / 270 / 300	
Goodness-of-fit on F^2	1.0072	
Final R indices [I>2sigma(I)]	R1 = 0.0269, wR2 = 0.0719	
R indices (all data)	R1 = 0.0271, wR2 = 0.0723	
Absolute structure parameter	-0.002(12)	
Largest diff. peak and hole	0.19 and -0.35 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6367. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	9078(1)	5772(1)	4138(1)	29
O(2)	9363(2)	4672(1)	4479(1)	50
O(3)	10188(1)	6849(1)	4200(1)	44
C(4)	9173(2)	5323(1)	3409(1)	29
C(5)	8199(2)	4310(1)	3207(1)	34
C(6)	8193(2)	4052(1)	2625(1)	35
C(7)	9156(2)	4773(1)	2242(1)	32
C(8)	10158(2)	5752(1)	2456(1)	36
C(9)	10162(2)	6039(1)	3034(1)	35
C(10)	9112(3)	4513(1)	1608(1)	45
N(11)	7152(1)	6264(1)	4280(1)	32
C(12)	6262(4)	7393(3)	4068(2)	32
C(13)	4481(4)	7216(4)	4330(1)	34
C(14)	4151(3)	5805(4)	4268(1)	34
C(15)	5874(3)	5204(2)	4441(1)	37
C(16)	5937(5)	4919(3)	5096(1)	30
C(17)	4949(5)	3697(3)	5242(1)	39
C(18)	3371(7)	3637(4)	5423(2)	56
C(112)	6749(4)	7575(4)	4044(2)	35
C(113)	4990(5)	7811(4)	4302(1)	49
C(114)	4104(3)	6544(5)	4253(1)	50
C(115)	5562(3)	5555(3)	4428(1)	39
C(116)	5511(4)	5254(4)	5051(1)	32
C(117)	4030(3)	4422(3)	5191(1)	41
C(118)	4138(6)	3262(4)	5397(2)	53
C(19)	6403(2)	7504(2)	3421(1)	45
C(20)	6245(2)	7445(1)	2912(1)	38
C(21)	6061(2)	7283(1)	2305(1)	33
C(22)	6991(2)	8023(1)	1919(1)	40
C(23)	6815(2)	7832(2)	1334(1)	47
C(24)	5713(2)	6909(2)	1132(1)	49

C(25)	4776(2)	6175(2)	1513(1)	50
C(26)	4958(2)	6352(2)	2097(1)	41

Table 3. Bond lengths [Å] and angles [°] for 6367.

S(1)-O(2)	1.4259(11)	C(16)-H(161)	0.973
S(1)-O(3)	1.4319(11)	C(16)-H(162)	0.971
S(1)-C(4)	1.7676(13)	C(17)-C(18)	1.293(5)
S(1)-N(11)	1.6123(10)	C(17)-H(171)	0.962
C(4)-C(5)	1.3905(18)	C(18)-H(181)	0.948
C(4)-C(9)	1.3876(18)	C(18)-H(182)	0.931
C(5)-C(6)	1.3886(18)	C(112)-C(113)	1.509(3)
C(5)-H(51)	0.956	C(112)-C(19)	1.483(4)
C(6)-C(7)	1.390(2)	C(112)-H(1121)	0.988
C(6)-H(61)	0.943	C(113)-C(114)	1.508(4)
C(7)-C(8)	1.385(2)	C(113)-H(1131)	0.970
C(7)-C(10)	1.5076(18)	C(113)-H(1132)	0.957
C(8)-C(9)	1.384(2)	C(114)-C(115)	1.589(3)
C(8)-H(81)	0.944	C(114)-H(1141)	0.983
C(9)-H(91)	0.941	C(114)-H(1142)	0.969
C(10)-H(101)	0.939	C(115)-C(116)	1.491(4)
C(10)-H(102)	0.973	C(115)-H(1151)	0.972
C(10)-H(103)	0.959	C(116)-C(117)	1.481(4)
N(11)-C(12)	1.462(3)	C(116)-H(1161)	0.981
N(11)-C(15)	1.539(3)	C(116)-H(1162)	0.988
N(11)-C(112)	1.522(3)	C(117)-C(118)	1.318(5)
N(11)-C(115)	1.480(3)	C(117)-H(1171)	0.962
C(12)-C(13)	1.519(3)	C(118)-H(1181)	0.940
C(12)-C(19)	1.520(4)	C(118)-H(1182)	0.933
C(12)-H(121)	0.976	C(19)-C(20)	1.197(2)
C(13)-C(14)	1.517(3)	C(19)-C(20)	1.197(2)
C(13)-H(131)	0.970	C(20)-C(21)	1.4365(19)
C(13)-H(132)	0.974	C(21)-C(22)	1.393(2)
C(14)-C(15)	1.531(3)	C(21)-C(26)	1.388(2)
C(14)-H(141)	0.953	C(22)-C(23)	1.388(2)
C(14)-H(142)	0.994	C(22)-H(221)	0.950
C(15)-C(16)	1.559(4)	C(23)-C(24)	1.378(3)
C(15)-H(151)	0.982	C(23)-H(231)	0.942
C(16)-C(17)	1.538(5)	C(24)-C(25)	1.385(3)

C(24)-H(241)	0.972	S(1)-N(11)-C(15)	114.20(11)
C(25)-C(26)	1.385(2)	C(12)-N(11)-C(15)	111.91(7)
C(25)-H(251)	0.932	S(1)-N(11)-C(112)	114.03(13)
C(26)-H(261)	0.956	S(1)-N(11)-C(115)	130.78(13)
		C(112)-N(11)-C(115)	111.97(7)
O(2)-S(1)-O(3)	119.77(7)	N(11)-C(12)-C(13)	100.98(7)
O(2)-S(1)-C(4)	108.21(6)	N(11)-C(12)-C(19)	111.5(3)
O(3)-S(1)-C(4)	106.64(6)	C(13)-C(12)-C(19)	118.3(2)
O(2)-S(1)-N(11)	106.87(7)	N(11)-C(12)-H(121)	106.5
O(3)-S(1)-N(11)	106.15(7)	C(13)-C(12)-H(121)	111.7
C(4)-S(1)-N(11)	108.85(6)	C(19)-C(12)-H(121)	107.3
S(1)-C(4)-C(5)	120.70(10)	C(12)-C(13)-C(14)	103.58(7)
S(1)-C(4)-C(9)	119.01(10)	C(12)-C(13)-H(131)	108.2
C(5)-C(4)-C(9)	120.20(12)	C(14)-C(13)-H(131)	112.1
C(4)-C(5)-C(6)	119.04(12)	C(12)-C(13)-H(132)	108.5
C(4)-C(5)-H(51)	120.2	C(14)-C(13)-H(132)	112.9
C(6)-C(5)-H(51)	120.8	H(131)-C(13)-H(132)	111.1
C(5)-C(6)-C(7)	121.41(13)	C(13)-C(14)-C(15)	103.60(7)
C(5)-C(6)-H(61)	119.3	C(13)-C(14)-H(141)	110.3
C(7)-C(6)-H(61)	119.3	C(15)-C(14)-H(141)	112.7
C(6)-C(7)-C(8)	118.46(12)	C(13)-C(14)-H(142)	112.2
C(6)-C(7)-C(10)	121.35(13)	C(15)-C(14)-H(142)	109.1
C(8)-C(7)-C(10)	120.19(13)	H(141)-C(14)-H(142)	108.9
C(7)-C(8)-C(9)	121.12(13)	N(11)-C(15)-C(14)	101.13(6)
C(7)-C(8)-H(81)	119.5	N(11)-C(15)-C(16)	111.12(9)
C(9)-C(8)-H(81)	119.3	C(14)-C(15)-C(16)	111.48(10)
C(4)-C(9)-C(8)	119.73(13)	N(11)-C(15)-H(151)	112.1
C(4)-C(9)-H(91)	119.8	C(14)-C(15)-H(151)	109.4
C(8)-C(9)-H(91)	120.5	C(16)-C(15)-H(151)	111.2
C(7)-C(10)-H(101)	112.5	C(15)-C(16)-C(17)	111.32(9)
C(7)-C(10)-H(102)	109.1	C(15)-C(16)-H(161)	108.3
H(101)-C(10)-H(102)	107.6	C(17)-C(16)-H(161)	111.8
C(7)-C(10)-H(103)	108.7	C(15)-C(16)-H(162)	109.1
H(101)-C(10)-H(103)	112.7	C(17)-C(16)-H(162)	108.0
H(102)-C(10)-H(103)	105.9	H(161)-C(16)-H(162)	108.2
S(1)-N(11)-C(12)	128.85(13)	C(16)-C(17)-C(18)	125.63(10)

C(16)-C(17)-H(171)	117.0	C(117)-C(116)-H(1161)	110.4
C(18)-C(17)-H(171)	117.4	C(115)-C(116)-H(1162)	107.7
C(17)-C(18)-H(181)	120.4	C(117)-C(116)-H(1162)	109.0
C(17)-C(18)-H(182)	117.7	H(1161)-C(116)-H(1162)	107.9
H(181)-C(18)-H(182)	121.9	C(116)-C(117)-C(118)	125.61(10)
N(11)-C(112)-C(113)	100.97(7)	C(116)-C(117)-H(1171)	117.9
N(11)-C(112)-C(19)	110.2(3)	C(118)-C(117)-H(1171)	116.5
C(113)-C(112)-C(19)	103.8(2)	C(117)-C(118)-H(1181)	120.1
N(11)-C(112)-H(1121)	112.1	C(117)-C(118)-H(1182)	121.9
C(113)-C(112)-H(1121)	114.9	H(1181)-C(118)-H(1182)	118.1
C(19)-C(112)-H(1121)	113.9	C(12)-C(19)-C(20)	167.6(2)
C(112)-C(113)-C(114)	103.48(7)	C(112)-C(19)-C(20)	175.4(2)
C(112)-C(113)-H(1131)	113.2	C(19)-C(20)-C(21)	176.15(16)
C(114)-C(113)-H(1131)	109.6	C(20)-C(21)-C(22)	121.39(14)
C(112)-C(113)-H(1132)	111.6	C(20)-C(21)-C(26)	119.38(13)
C(114)-C(113)-H(1132)	108.3	C(22)-C(21)-C(26)	119.21(13)
H(1131)-C(113)-H(1132)	110.3	C(21)-C(22)-C(23)	120.28(15)
C(113)-C(114)-C(115)	103.93(7)	C(21)-C(22)-H(221)	120.1
C(113)-C(114)-H(1141)	113.6	C(23)-C(22)-H(221)	119.6
C(115)-C(114)-H(1141)	109.3	C(22)-C(23)-C(24)	120.10(15)
C(113)-C(114)-H(1142)	111.7	C(22)-C(23)-H(231)	118.9
C(115)-C(114)-H(1142)	110.4	C(24)-C(23)-H(231)	121.0
H(1141)-C(114)-H(1142)	107.8	C(23)-C(24)-C(25)	119.92(15)
C(114)-C(115)-N(11)	101.41(6)	C(23)-C(24)-H(241)	119.2
C(114)-C(115)-C(116)	111.81(10)	C(25)-C(24)-H(241)	120.9
N(11)-C(115)-C(116)	110.95(9)	C(24)-C(25)-C(26)	120.32(16)
C(114)-C(115)-H(1151)	110.4	C(24)-C(25)-H(251)	121.1
N(11)-C(115)-H(1151)	110.9	C(26)-C(25)-H(251)	118.5
C(116)-C(115)-H(1151)	111.0	C(21)-C(26)-C(25)	120.17(14)
C(115)-C(116)-C(117)	111.27(9)	C(21)-C(26)-H(261)	120.0
C(115)-C(116)-H(1161)	110.5	C(25)-C(26)-H(261)	119.9

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 6367. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	25(1)	36(1)	26(1)	-2(1)	-1(1)	3(1)
O(2)	67(1)	49(1)	36(1)	6(1)	-7(1)	20(1)
O(3)	35(1)	60(1)	38(1)	-15(1)	3(1)	-15(1)
C(4)	26(1)	31(1)	28(1)	-3(1)	3(1)	4(1)
C(5)	35(1)	30(1)	36(1)	-3(1)	7(1)	-2(1)
C(6)	36(1)	30(1)	37(1)	-7(1)	2(1)	0(1)
C(7)	35(1)	29(1)	31(1)	-3(1)	1(1)	10(1)
C(8)	39(1)	35(1)	34(1)	-1(1)	9(1)	0(1)
C(9)	33(1)	35(1)	37(1)	-5(1)	6(1)	-5(1)
C(10)	62(1)	41(1)	31(1)	-4(1)	0(1)	9(1)
N(11)	25(1)	48(1)	24(1)	-1(1)	2(1)	4(1)
C(12)	20(2)	45(2)	32(2)	-7(1)	-9(1)	7(1)
C(13)	18(2)	53(2)	30(1)	-6(2)	2(1)	2(1)
C(14)	25(1)	50(2)	27(1)	-2(1)	3(1)	1(1)
C(15)	24(2)	59(2)	28(2)	-9(1)	4(1)	-2(2)
C(16)	30(2)	42(2)	18(1)	0(1)	1(1)	-1(2)
C(17)	50(2)	36(2)	29(1)	1(1)	3(1)	0(2)
C(18)	58(3)	50(2)	60(2)	3(2)	24(2)	-13(2)
C(112)	22(2)	57(2)	26(2)	-8(1)	-1(1)	18(1)
C(113)	38(2)	77(3)	31(1)	2(2)	6(1)	22(2)
C(114)	24(1)	92(3)	33(2)	6(2)	2(1)	4(2)
C(115)	20(1)	73(2)	22(1)	-14(1)	5(1)	-8(1)
C(116)	28(2)	38(2)	31(2)	-2(1)	0(1)	0(1)
C(117)	43(2)	44(2)	36(1)	-6(1)	11(1)	-6(2)
C(118)	62(3)	46(2)	51(2)	0(2)	12(2)	-13(2)
C(19)	52(1)	47(1)	34(1)	-3(1)	-7(1)	21(1)
C(20)	39(1)	40(1)	35(1)	1(1)	-3(1)	13(1)
C(21)	32(1)	37(1)	30(1)	4(1)	-1(1)	11(1)
C(22)	39(1)	43(1)	40(1)	7(1)	-2(1)	3(1)
C(23)	48(1)	57(1)	37(1)	13(1)	6(1)	8(1)
C(24)	58(1)	61(1)	29(1)	-1(1)	-2(1)	16(1)

C(25)	56(1)	52(1)	44(1)	-6(1)	-7(1)	-1(1)
C(26)	43(1)	43(1)	38(1)	4(1)	2(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 6367.

	x	y	z	U(eq)
H(51)	7517	3818	3466	42
H(61)	7512	3378	2485	42
H(81)	10820	6250	2202	45
H(91)	10822	6721	3174	42
H(101)	9048	5259	1390	69
H(102)	10166	4072	1498	69
H(103)	8184	3938	1529	68
H(121)	6862	8120	4232	37
H(131)	4532	7476	4727	41
H(132)	3658	7731	4116	41
H(141)	3219	5551	4509	41
H(142)	3879	5563	3867	41
H(151)	6063	4431	4216	43
H(161)	5471	5649	5299	37
H(162)	7133	4807	5212	35
H(171)	5553	2910	5185	45
H(181)	2740	4388	5499	68
H(182)	2883	2837	5468	67
H(1121)	7643	8202	4150	42
H(1131)	5039	8065	4701	58
H(1132)	4345	8416	4084	58
H(1141)	3110	6448	4512	60
H(1142)	3708	6382	3867	61
H(1151)	5463	4790	4198	45
H(1161)	5461	6035	5278	39
H(1162)	6597	4810	5148	38
H(1171)	2884	4742	5122	49
H(1181)	5227	2894	5463	64
H(1182)	3157	2781	5478	64
H(221)	7726	8679	2055	50

H(231)	7471	8333	1081	58
H(241)	5594	6792	721	59
H(251)	4025	5546	1384	62
H(261)	4316	5836	2358	51

Table 6. Hydrogen bonds for 6367 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(113)-H(1131)...O(3)#1	0.970	2.571	3.520(3)	165.97
C(14)-H(1141)...O(3)#2	1.197	2.411	3.261(3)	125.9
C(114)-H(1141)...O(3)#2	0.983	2.411	3.049(3)	122.04
C(116)-H(1161)...O(3)#1	0.981	2.554	3.533(3)	175.21

Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+3/2,-z+1 #2 x-1,y,z

