Asymmetric allylation of carbonyl compounds: Kinetic resolution of *sec*-Allylboronates and Total synthesis of natural products

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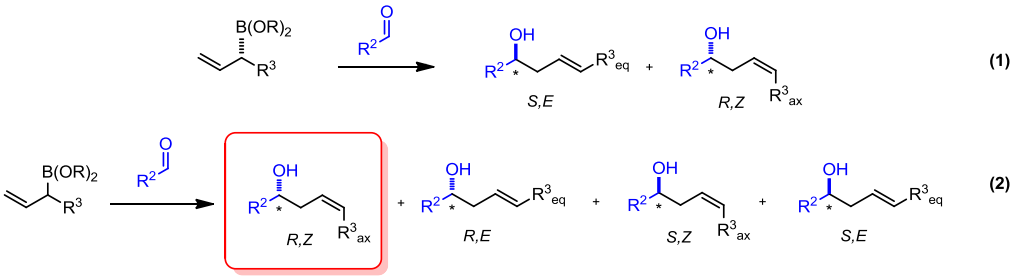
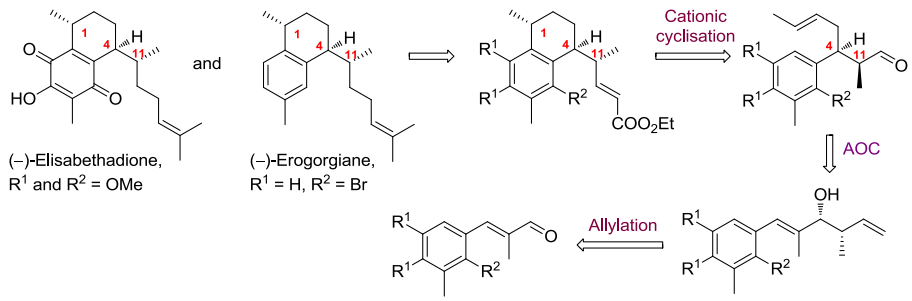
Dedicated to mum, dad and brother, my most beloved

Abstract

Asymmetric allylation of aldehydes with stoichiometric allylmetal reagents has evolved into an efficient and well established methodology for the synthesis of enantiomerically enriched homoallylic alcohols. The use of enantioenriched secondary allylboronates gives rise to a mixture of *E/Z* homoallylic alcohols with the opposite configuration at the stereogenic centre (reaction **1**). The first part of this thesis presents a novel and conceptually different solution to attain high stereoselectivity in the allylation of aldehydes with secondary allylboronates. The method revolves around an efficient kinetic resolution of chiral racemic allylboronates (reaction **2**). Catalysis by a chiral Brønsted acid ensures a face- and *Z*-selective allylation of aldehydes. This asymmetric allylation has proved successful over a wide range of aldehydes with different electronic and steric properties. The methodology provides a shortcut to enantio- and diastereomerically enriched homoallylic alcohols finding a wide use in pharmaceutical and fine chemicals development.



The second part of the present thesis describes the asymmetric total synthesis of two bioactive metabolites of the *Pseudopterogorgiane elisabethae* family, (–)-elisabethadione and (–)-erogorgiane. Three key reactions steps to introduce the stereogenic centres in the natural product scaffold include asymmetric allylation, oxy-Cope rearrangement and cationic cyclisation.



Acknowledgments

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I would also like to thank Loughborough University and the Department of Chemistry who provided me with funding, without which the chemistry here onward could not have been accomplished. It is also worth thanking all the members of the staff as well as all technicians whom I have taken up time from to solve issues I encountered along my way. Thank you all for your time and patience.

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And last but not the least I would very much like to thank my family for bringing me up in such a way that one day, back in 2010, allowed me to start this arduous but amazing journey towards my doctorate in philosophy in a foreign country. Thank you so much for your efforts on understanding me.

Abbreviations

(HR)MS	(High Resolution) Mass Spectrometry
(prep-)HPLC	(preparative) High Performace Liquid Chromatrography
°C	degrees Celsius
18-C-6	18-Crown-6
9-BBN	9-Borabicyclo[3.3.1]-nonane
Å	Angstroms
Ac	Acetate
AcOH/HOAc	Acetic acid
AIBN	Azobis(isobutyronitrile)
AOC	Anionic Oxy-Cope
$B_2(pin)_2$	Bis(pinacolato) diboron
BAIB	Bis(acetoxyl)iodobenzene
BH_3•DMS	borane dimethylsulfide
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINAPO	2-diphenylphosphino-2'-diphenylphosphinyl-1,1'-binaphthalene
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	tert-butoxycarbonyl
Bpin	boron pinacolato ester
brsm	based on recovered starting material
Bz	Benzoate
BzOH	benzoic acid
c	Concentration
CAN	cerium amonium nitrate
cat.	Catalyst
CbCl	*N*,*N*-diisopropylcarbamoyl chloride
conv	Conversion
CuTC	Copper(I)-thiophene-2-carboxylate
d	doublet
d.r.	diastereomeric ratio

DCM	Dichloromethane
DFT	Density functional theory
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	(4-dimethylamino)pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
EA	ethyl acetate
ee	enantiomeric excess
ent	enantiomer
Epin	tetraethylethylenegycol
eq.	Equivalents
ESI	electrospray ionization
Et	Ethyl
HB	Hünig Base
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
***i*Pr**	Isopropyl
K	Kelvin
kcal	kilocalories
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LP	light petroleum
mCPBA	m-chloroperbenzoic acid
MeCN	acetonitrile
min	minute
M	molar
MS	Molecular sieves
MsOH	methanesulfonic acid

MVK	methylvinyl ketone
NBS	N-bromosuccinimide
NLE	non-linear effects
nm	nanometres
NMR	Nuclear Magnetic Ressonance
nPr	propyl
ox.	oxidation
PCC	Pyridinium chlorochromate
PE	pseudoephedrine
PG	protecting group
Piv	pivaloyl
PMA	phosphomolybdic acid
PPA	polyphosphoric acid
ppm	part per million
Py	pyridine
q	quartet
quint.	quintet
r.t.	room temperature
rac	racemic
s	singlet
sec	secondary
sept.	septuplet
sex.	sextet
S_N2	bimolecular nucleophilic substitution
SPINOL	1,1'-spirobiindane-7,7'-diol
t	triplet
T/temp.	temperature
***t*-AmOH**	tertiary butyl carbinol (2,2-dimethylpropan-1-ol)
TBAF	tetra-n-butylammonium fluoride
TBAI	tetra-n-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
tert	tertiary

Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Tol	toluene
TPPA	triphenyl phosphoramide
TS	transition state
TsOH	*p*-toluenesulfonic acid

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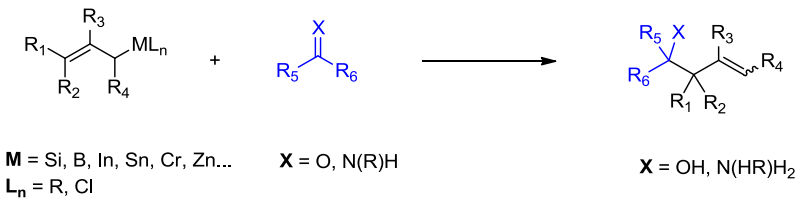
1. Introduction

Chirality is a phenomenon characteristic to all living organisms. As a consequence, different behaviour of enantiomers in the chiral environment of the human body may have contrasting biological effects. Therefore, in the last two decades pharmaceutical and agrochemical industries underwent a so-called chiral switch, whereby all the new molecular entities have to be tested as single enantiomers, which, in turn, placed a demand for the efficient methods for their production. In the modern organic methodology, asymmetric catalysis remains the preferred way of introducing new stereogenic centres into the molecule. However, there are many instances where asymmetric methodology is either inadequate or the methods are not practical, therefore alternative techniques based on resolution of racemic mixtures, including chemocatalytic kinetic resolution and related enzymatic methods still hold their value. Furthermore, resolution protocols are becoming an invaluable tool for upgrading enantiopurity of compounds obtained in asymmetric catalytic processes by removing the undesired minor enantiomer. To address the rising demand for an efficient chiral technology, the development of new single-step reactions where a new C-C bond and a new stereogenic centre is formed with high stereoselectivity is of vital importance for the achievements of the challenges that we, as a scientific community, face regarding enantioselective synthesis of novel and complex molecules.

1.1. Addition of allylmetal reagents to carbonyl compounds.

Amid the possible methods to construct a new covalent bond, one of the most popular is the creation of a new C-C bond *via* the addition of organometallic reagents to carbonyl compounds or related imines leading to alcohols or amines, respectively. This transformation has been widely studied due to its important practical outcome; the reaction often generates a new stereogenic centre in the molecule. Particularly interesting is the addition of carbon nucleophiles to non-symmetrical ketones or ketimines since it leads to a new quaternary stereogenic centre, which is a challenging moiety to synthesise. One of the most important classes of these transformations is the addition of allylmetal reagents (Scheme 1).



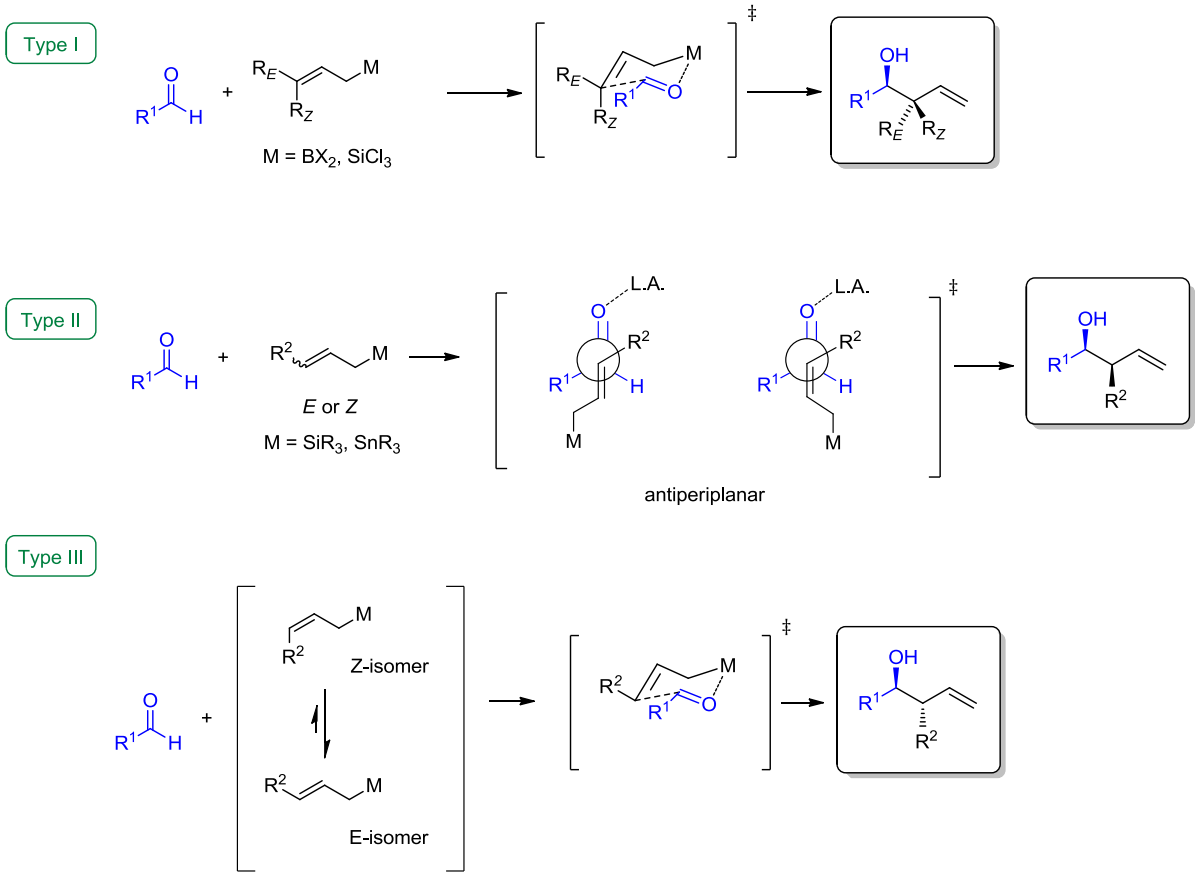
Scheme 1

The interest in the resulting homoallylic systems stems from the possibility of further functionalisation of the molecule. The asymmetric version of these transformations is remarkably valuable since it produces chiral homoallylic alcohols or amines, which are important building blocks in organic synthesis, particularly in the total synthesis of natural and bioactive compounds.

From the structural point of view, all the allylmetal reagents share some common features. They all contain at least one transferable allylic group and a variable number of alkyl (R) or heteroatom-containing (L) groups on the metal to complete the valence shell. Nevertheless, the allylmetal reagents differ from each other by the mechanism of allyl transfer and, hence, the stereochemical outcome.

In the early 80s, Denmark proposed a classification system for allylating reagents depending on the stereochemistry of the final homoallylic compound.[1] Allylboron and allyltrihalosilane reagents are classified as Type I (Scheme 2, M = B, Si). The relative stereochemistry of the final homoallylic compound depends on the geometry of the allylmetal reagent used, i.e. *E*-allylmetal reagents give raise to *anti* homoallylic products, while *Z*-allylmetal reagents afford the respective *syn* product. Such a good transfer of stereochemical information is due to the highly organised transition state. There is a strong experimental and theoretical evidence that the reaction occurs though a Zimmerman-Traxler chair-like transition state with an internal activation of carbonyl oxygen by the metalloid atom. In contrast, allyl trialkylsilanes and stannanes are classified as Type II reagents (Scheme 2, M= Si, Sn). Regardless of the stereochemistry of the starting allylmetal system, these reagents produce predominantly *syn* homoallylic products. Such stereoselectivity is caused by the open transition state mechanism where the carbonyl oxygen is activated externally. Allyltrialkyltin reagents can also proceed through a six-membered transition state with internal activation; however, high temperatures are required in order to achieve the desired product.[2] There is a third type, which can be exemplified by allylchromium reagents. They provide the same diastereomeric

outcome of the final homoallylic product regardless of the geometrical selectivity of the original allylmetal system (Scheme 2, Type III). The convergent diastereoselectivity is explained by a rapid isomerization between *Z* and *E* isomer through secondary allylic organometallic species prior to the carbonyl addition. Provided that a more stable *E* isomer predominates over *Z*, the formation of *anti* homoallylic product points to a cyclic six-membered transition state similar to Type I reagents.



Scheme 2

The research projects presented in this thesis involve allylboron and allyltrichlorosilane reagents. Therefore, due to the broadness of the field of asymmetric allylation of carbonyl compounds, the literature review will be focused only on Type I allylmetal reagents.

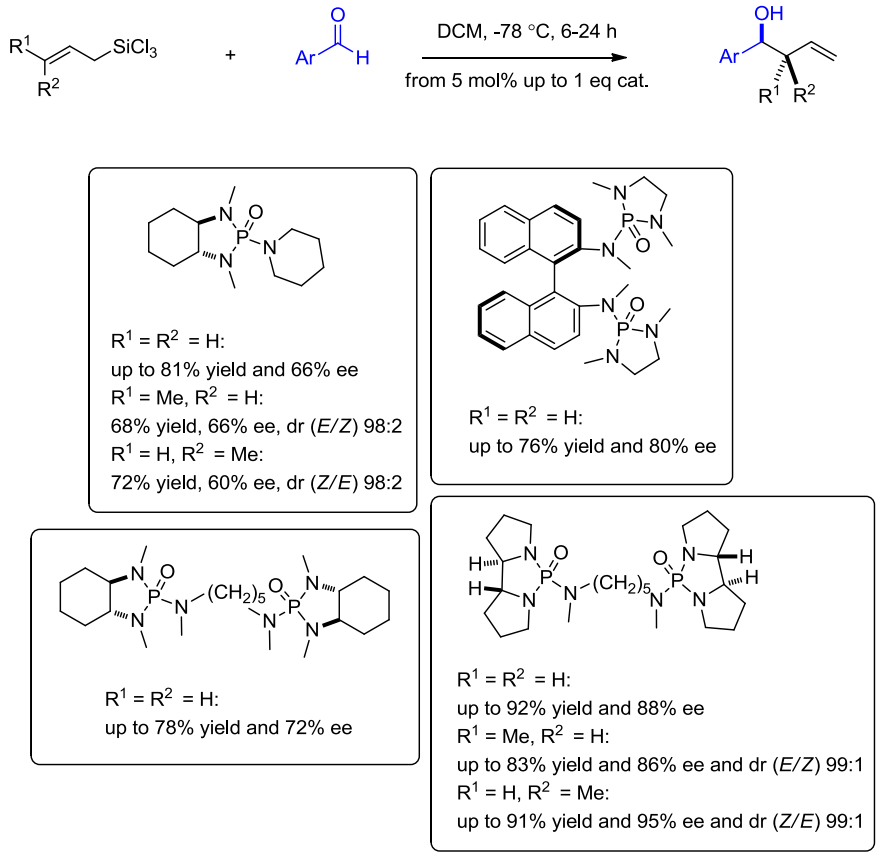
1.1.1. Allyltrichlorosilanes as allylating reagents.

Aldehydes as electrophiles.

Pioneering the field in the late 1980s, Sakurai reported a highly diastereoselective allylation of aldehydes with allyltrifluorosilanes in the presence of stoichiometric amounts of

CsF.[3] A few years later, Kobayashi showed that allyl- and crotyltrichlorosilanes successfully reacted with aldehydes using DMF as a solvent.[4] Since then, allyltrichlorosilanes became one of the most common reagents for the allylation of carbonyl compounds. Enantioselective versions of these reactions have been widely studied by a number of research groups using chiral Lewis-basic promoters such as chiral phosphoramides and phosphonamides, chiral phosphine oxides, chiral sulfoxides, and chiral *N*-oxides.

Denmark and co-workers extensively studied phosphoramides as Lewis base promoters for the allylation of aldehydes. First, they established that the use of achiral Lewis bases such as DMF, MPA or TPPA in substoichiometric amounts promoted the allylation of aromatic aldehydes with allyltrichlorosilane.[5] Further investigations led to the development of a series of chiral mono and diphosphoramides (Scheme 3).[6,7]



Scheme 3

They also reported excellent stereoselectivity in the crotylation of benzaldehyde. As shown in Scheme 3, geometrically enriched *E* or *Z* crotylsilane, gave rise to *anti* or *syn* homoallylic alcohols, respectively.. The high level of stereospecificity clearly suggests the

formation of a siliconate complex and the reaction proceeding *via* a chair-like transition state. The nature of the transition state and the origins of the excellent stereoselectivity were analysed in detail by Denmark *et. al.*[6] Two reaction pathways were suggested, one involving a pentacoordinated Si (trigonal bipyramidal) with a single phosphoramide bound to the silicon; and the second involving a hexacoordinated Si atom (octahedral) having two phosphoramides completing the silicon valence shell (Figure 1).

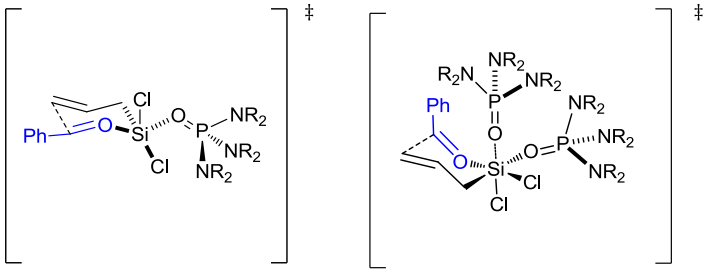
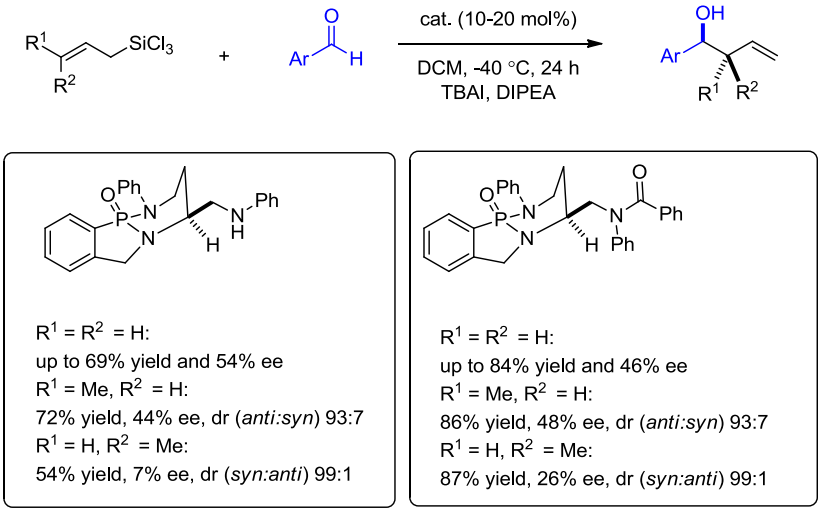


Figure 1

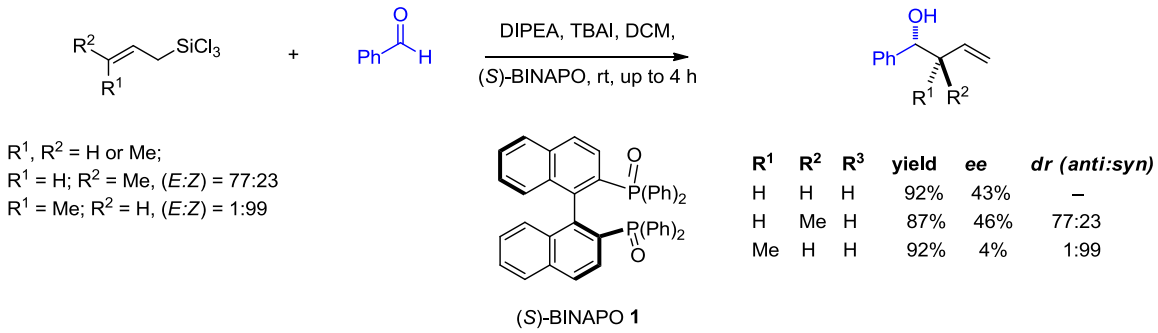
Kinetic data together with NLE probe led to the conclusion that more than one chiral phosphoramide molecule is present in the stereochemistry determining step. Kinetic studies revealed the reaction order of 1.77 in the chiral promoter, which could be due to the two competing pathways involving one or two phosphoramides running concurrently.[6] The fact that the two competing mechanisms were in operation would explain the observed modest-to-good enantioselectivities since the pentacoordinate TS **A** would be less enantioselective due to the reduced influence of a single chiral promoter

Following Denmark's attempt at using phosphoramides as Lewis base promoters for allylation reactions, Yasumasa Hamada reported the synthesis of a novel chiral phosphonamide and its application to Lewis base-catalysed asymmetric allylation of aldehydes.[8] It was found that TBAI accelerated the reaction. The presence of ammonium salts in solution favoured the dissociation of a chloride, which is advantageous for the reactivity.[9] However, the reaction occurred in modest yields and enantioselectivities. They also reported on the addition of *E* and *Z*-crotyltrichlorosilane with benzaldehyde achieving excellent diastereoselectivity (Scheme 4).



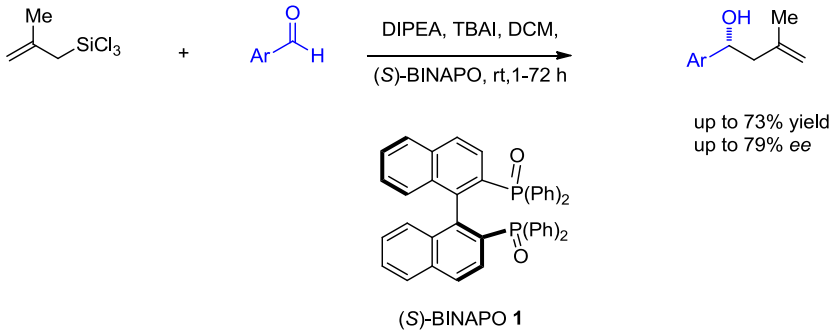
Scheme 4

The first enantioselective allylation of aromatic aldehydes with allyltrichlorosilanes catalysed by chiral phosphine oxide was reported by Nakajima.[10] BINAPO **1**, which can be readily obtained from the known chiral diphosphine BINAP, was employed as a catalyst. The results obtained with BINAPO were modest in terms of enantioselectivities and were dependent on the substitution pattern of the aromatic aldehyde. The excellent stereoselectivity achieved in the crotylation experiments supported the proposed Zimmermann-Traxler chair-like transition state (Scheme 5).



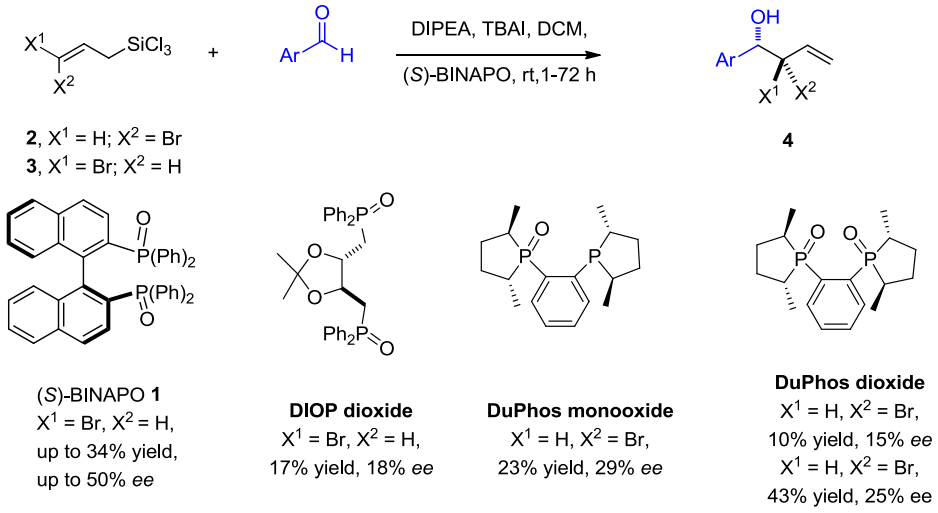
Scheme 5

Methallylation of various aldehydes using **1** was more successful (Scheme 6).[11] A decrease of enantioselectivity was observed when electron-rich or sterically hindered aldehydes were employed.



Scheme 6

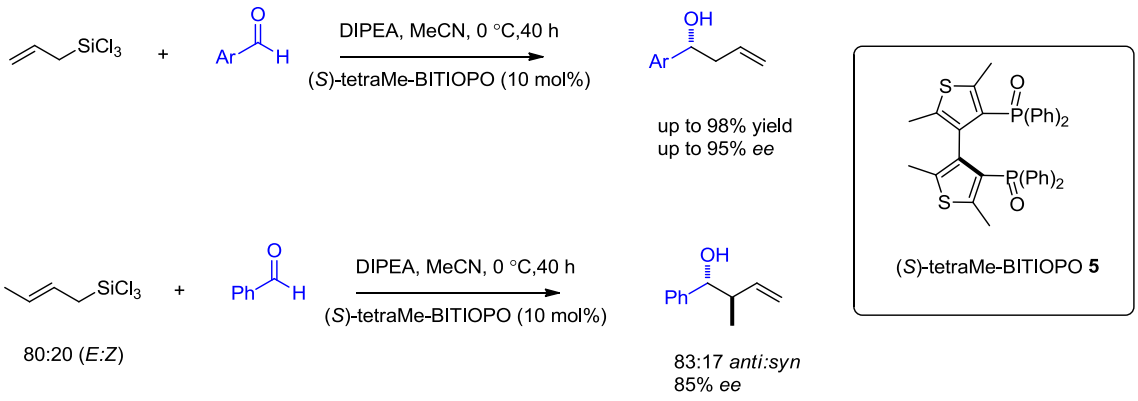
Malkov and Kocovsky reported on the efficiency of **1** for the unreactive γ-halosubstituted allyltrichlorosilanes.[12] The nucleophilicity of the γ-carbon in the allylating reagents **2** and **3** is decreased due to the electron-withdrawing effect of the bromine substituent. Therefore, an increased reactivity on the chiral catalyst is needed to allow for the synthesis of halohydrins **4** (Scheme 8). Other mono and diphosphine oxides shown in Scheme 7 were tested in the reaction but gave lower chemical yield and enantioselectivities.



Scheme 7

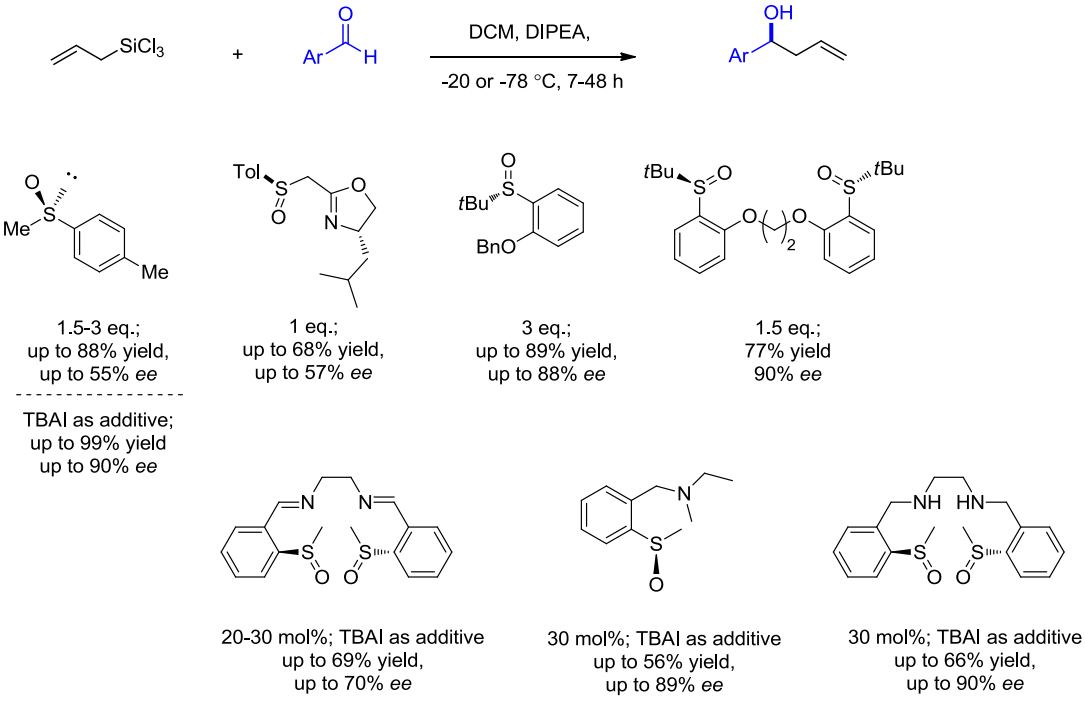
Benaglia and co-workers[13] developed a highly reactive chiral phosphine oxide based on electron-rich heteroaromatic rings such as 3-thienyl (**5**, Scheme 8). With this novel scaffold, both chemical yield and enantioselectivity in the addition of allyltrichlorosilane to different aromatic aldehydes were improved significantly. Notably, the 3-thiophenyl scaffold exhibited higher reactivity. Chiral phosphine oxide **5** also produced excellent stereoselectivity in the

crotylation experiments supporting formation of a chair-like six-membered transition state in the course of the reaction.



Scheme 8

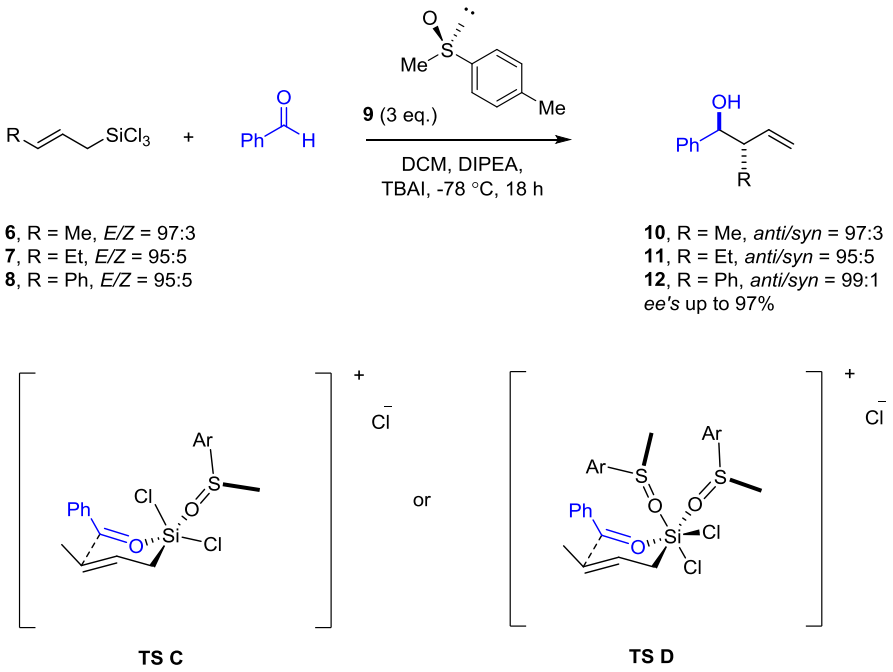
Several research groups investigated the use of chiral sulfoxides as chiral promoters in the allylation of aldehydes with allyltrichlorosilanes (Scheme 9).[14–19]



Scheme 9

In general, this type of Lewis base commonly required stoichiometric loading to promote the reaction. They exhibited moderate to good yields and enantioselectivities. The use of tetrabutylammonium salts seemed to improve slightly the enantioselectivity, whereas the use of stoichiometric loading enhanced the chemical yield.[19] However, these chiral promoters are

rarely recovered because sulfoxides can be reduced or decomposed during the reaction.[15] This family of chiral Lewis bases showed excellent diastereoselectivity when geometrically enriched homologues of *E*-crotyltrichlorosilane **6-8** were employed to afford the respective *anti* homoallylic alcohol **10-12**, supporting a closed chair-like transition state (Scheme 10).

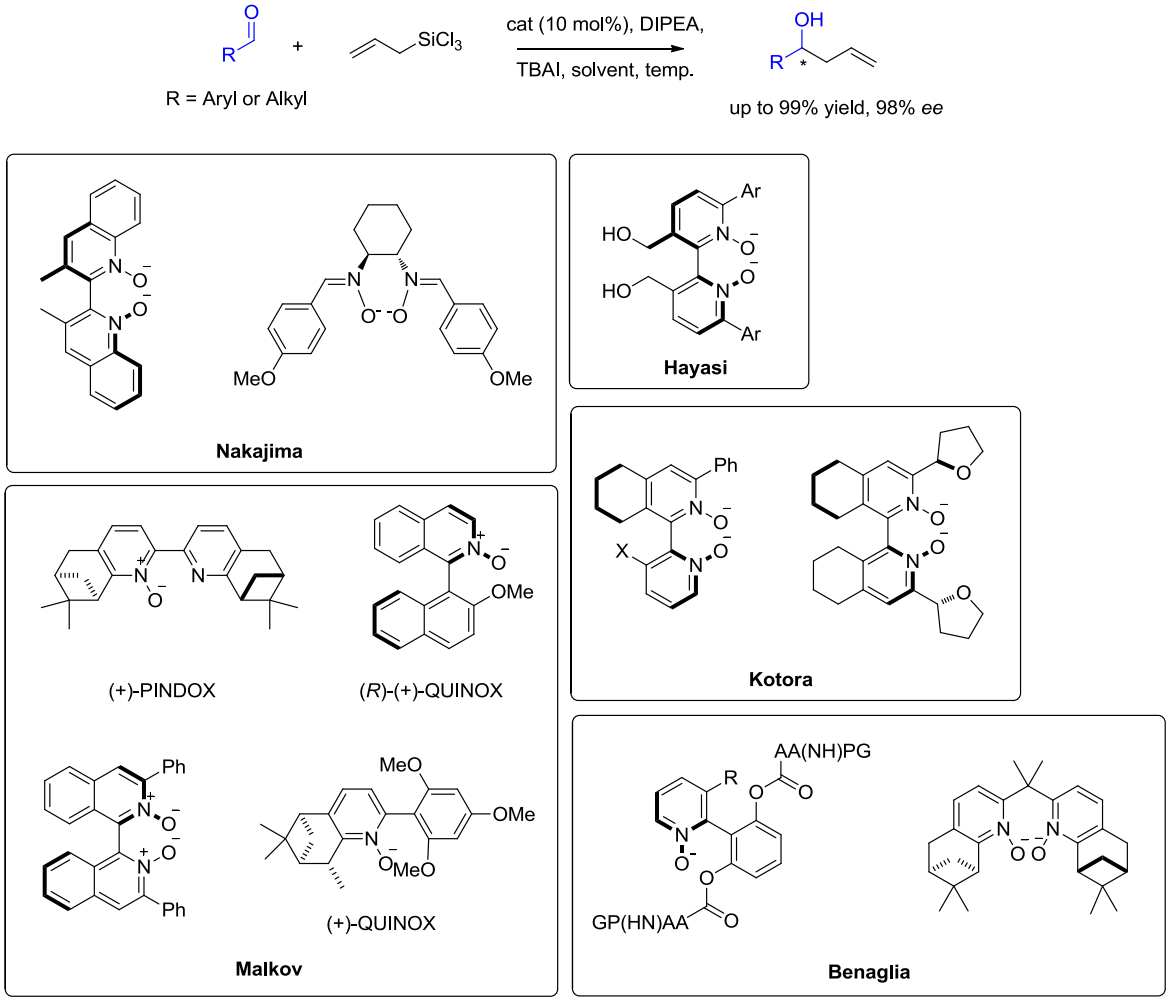


Scheme 10

A positive NLE observed in the asymmetric allylation of aldehydes using chiral sulfoxide **9** as a promoter is in agreement with a chair-like transition state involving coordination of two molecules of sulfoxide to the silicon atom and, consequently, the formation of a hexacoordinate Si intermediate in the stereoselectivity determining step (**TS D**, Scheme 10).[19]

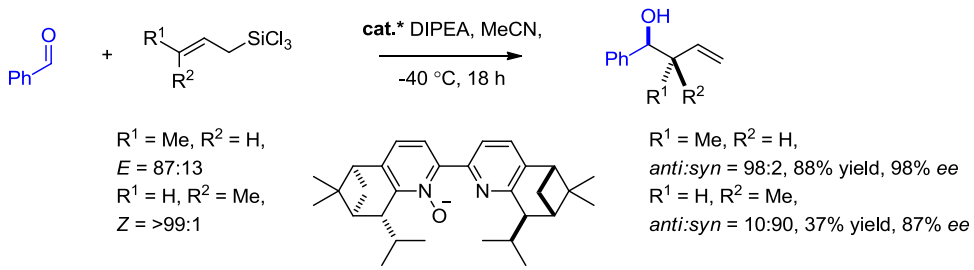
Another large family of chiral Lewis base promoters widely employed for the Sakurai-Hosomi-type reaction are the mono and bis-pyridine *N*-oxides. There are a vast number of examples reporting on the capability of such chiral Lewis bases as catalysts for the asymmetric addition of allyltrichlorosilane to aldehydes. *N*-Oxides are not only the most reactive Lewis bases due to their electronic nature but also are usually able to induce good to excellent enantioselectivity. Since Nakajima[20] reported that axially chiral bypyridine *N,N'*-bisoxides are effective for such a transformation, different architectures have been synthesised and assessed on the addition of allyltrichlorosilanes to aldehydes. Scheme 11 presents the most efficient *N*-

oxide catalysts introduced by Nakajima,[20,21] Hayashi,[22] Malkov,[23–25] Kotora[26,27] and Benaglia.[28,29]



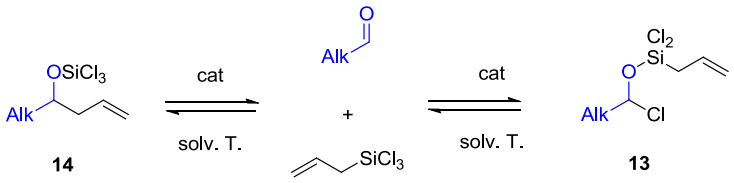
Scheme 11

DIPEA was used as scavenger of adventitious HCl trace that could block the catalyst by protonation. In some cases, TBAI was additionally used to enhance the rate of the reaction, possibly by stabilising the ion-paired hexacoordinate reactive complexes. The commonly used solvents were DCM, MeCN and THF and temperatures could vary from room temperature down to −78 °C. Crotylation experiments were also carried out to confirm the high diastereoselectivity of the reaction, occurring through a closed, chair-like transition state (Scheme 12).[23]



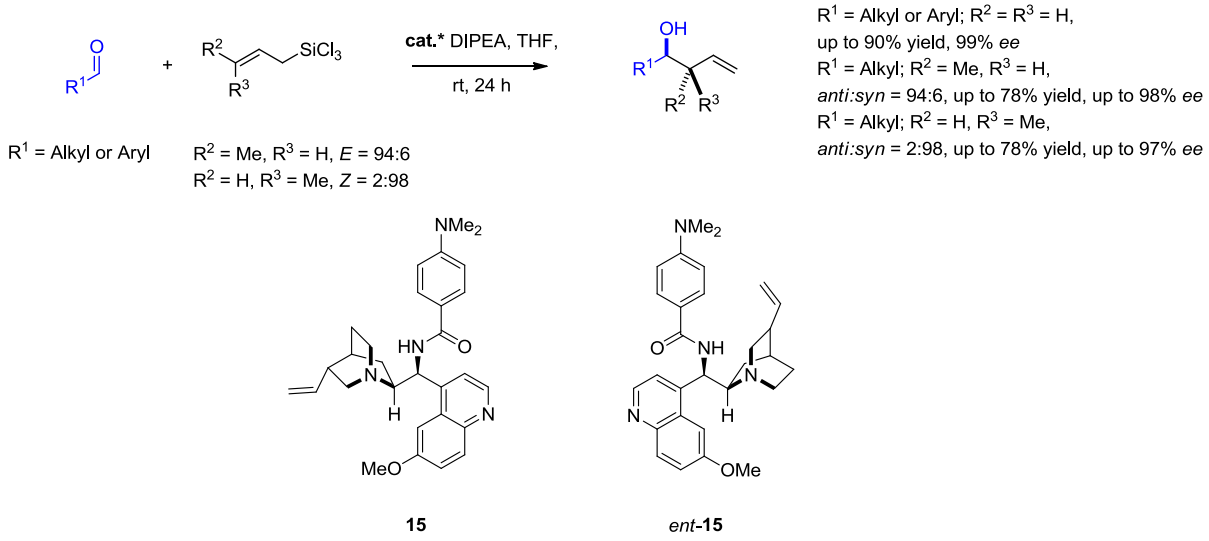
Scheme 12

Up to this point, the major challenge in the use of allyltrichlorosilanes was the lack of suitable methods for the allylation of aliphatic aldehydes which in contrast with the aromatic aldehydes mostly formed α-chloro silyl ether **13**, thus preventing allylation (Scheme 13).



Scheme 13

The equilibrium between the aliphatic aldehyde and silyl ether **13** is shifted to the right and appears to be slow at low temperatures leading to very low conversions, whereas at higher temperatures enantioselectivity in the formation of **14** dropped dramatically.[23] This problem was resolved with the introduction of novel amides derived from cinchona alkaloids, as reported by Zhao and co-workers.[30] They designed a highly efficient catalyst **15** for the allylation of aliphatic aldehydes. This novel cinchona derivative acts as bidentate Lewis base catalyst with the chelation taking place via the amide group and the quinuclidine nitrogen. The resulting homoallylic alcohols were obtained in high enantioselectivities. Also, excellent diastereomeric ratios were achieved using geometrically enriched *E* or *Z*-crotyltrichlorosilanes (Scheme 14).



Scheme 14

The practical importance of the novel catalytic system resides in 1) the possibility to obtain high enantioselectivity at ambient temperature; 2) the ability of scaling up the reaction with recovery of the catalyst in almost quantitative yields while preserving the high level of stereoselectivity. Screening of the electronic properties of the aryl group of the amide moiety revealed that it acts as a Lewis base rather than an H-bond donor. Replacement of the strongly donating dimethylamino substituent for the highly withdrawing nitro group resulted in a low conversion (35%) compared to that of the dimethylamino analogue (88%), although the level of enantioselectivity was comparable (81% *ee* and 96% *ee*, respectively). Zhao *et al.* also performed kinetic studies showing first-order dependence in the catalyst supporting its bidentate character; a possible transition state **E** was suggested (Figure 2).

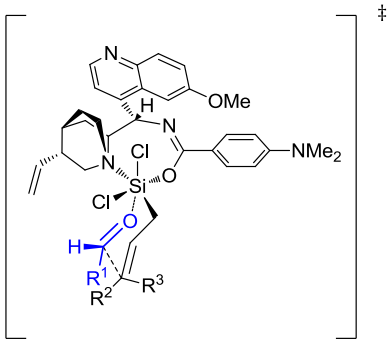
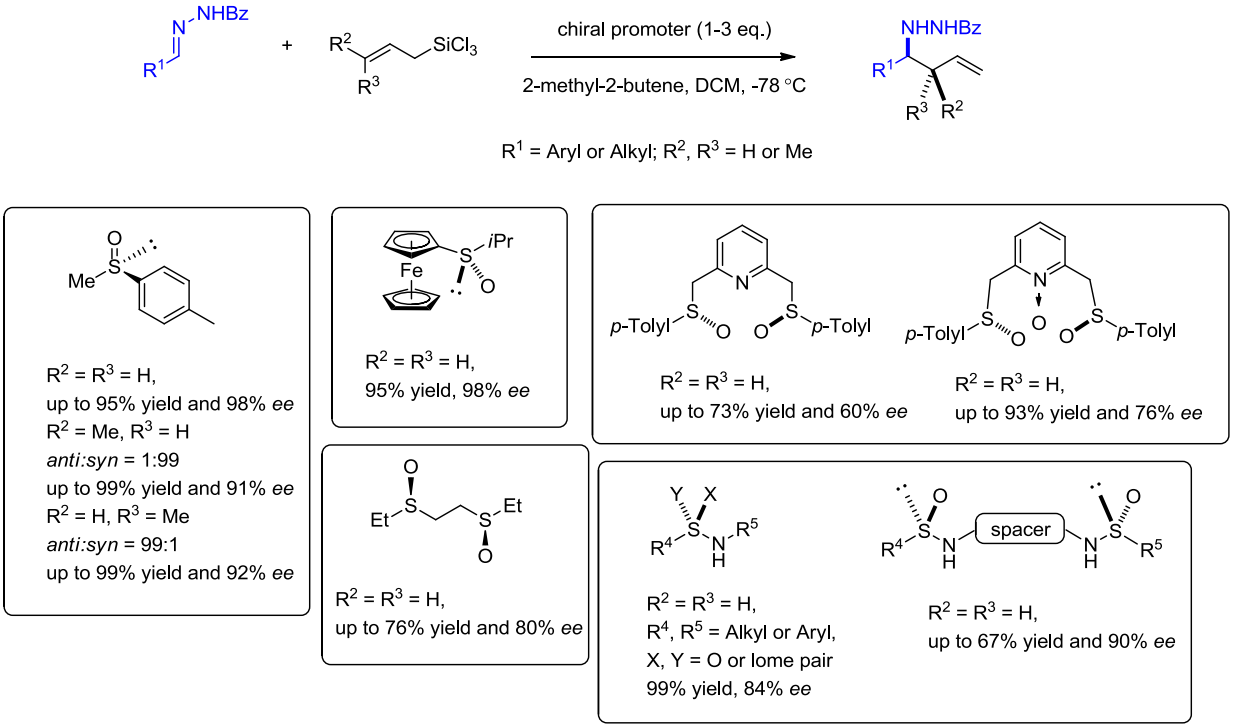


Figure 2

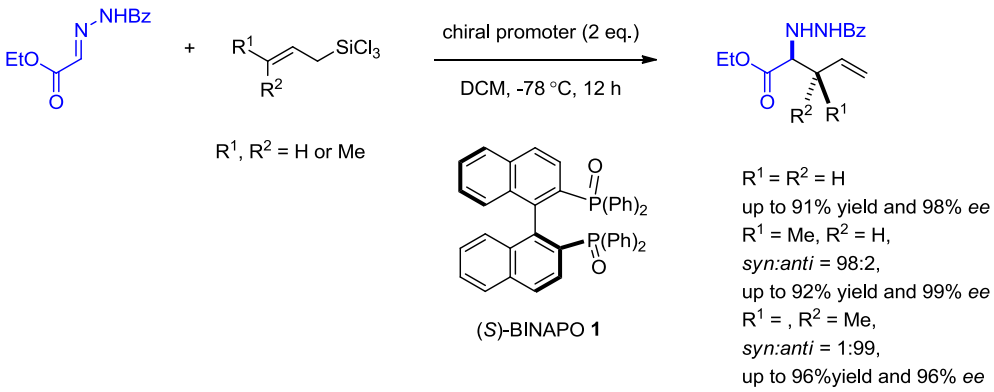
Imines and imine derivatives as electrophiles.

Apart from the enantiopure homoallylic alcohols, enantiopure homoallylic amines represent another class of useful building blocks, particularly for the synthesis of nitrogen-containing biologically active compounds. There are several reports on the allylation of imines and hydrazones with allyltrichlorosilanes that mainly focused on the use of chiral sulfoxides as the activators.[31–34] The main drawback of these chiral promoters is the need for stoichiometric or even higher loadings to achieve practical results. 2-Methyl-2-butene is commonly used as a proton scavenger. Crotylation experiments showed high levels of diastereoselectivity indicating closed transition state (Scheme 15). Closely related, enantioenriched mono- and bis-sulfinamides, also proved successful in the asymmetric allylation of hydrazones producing good to excellent yields and enantioselectivities (Scheme 15).[35,36]



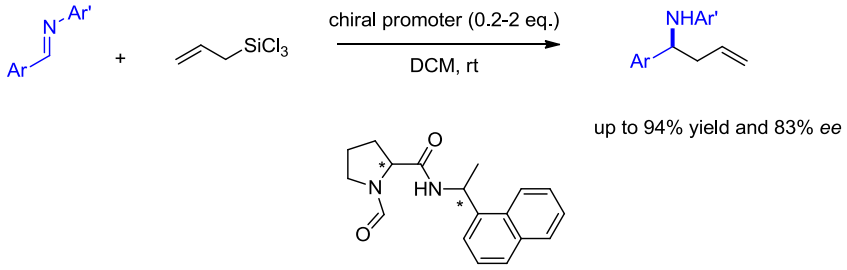
Scheme 15

Chiral phosphine oxides, such as (*S*)-BINAPO **1**, also showed ability to promote the asymmetric allylation and crotylation of α-hydrazono esters, achieving excellent enantio- and diastereoselectivites (Scheme 16).[37]



Scheme 16

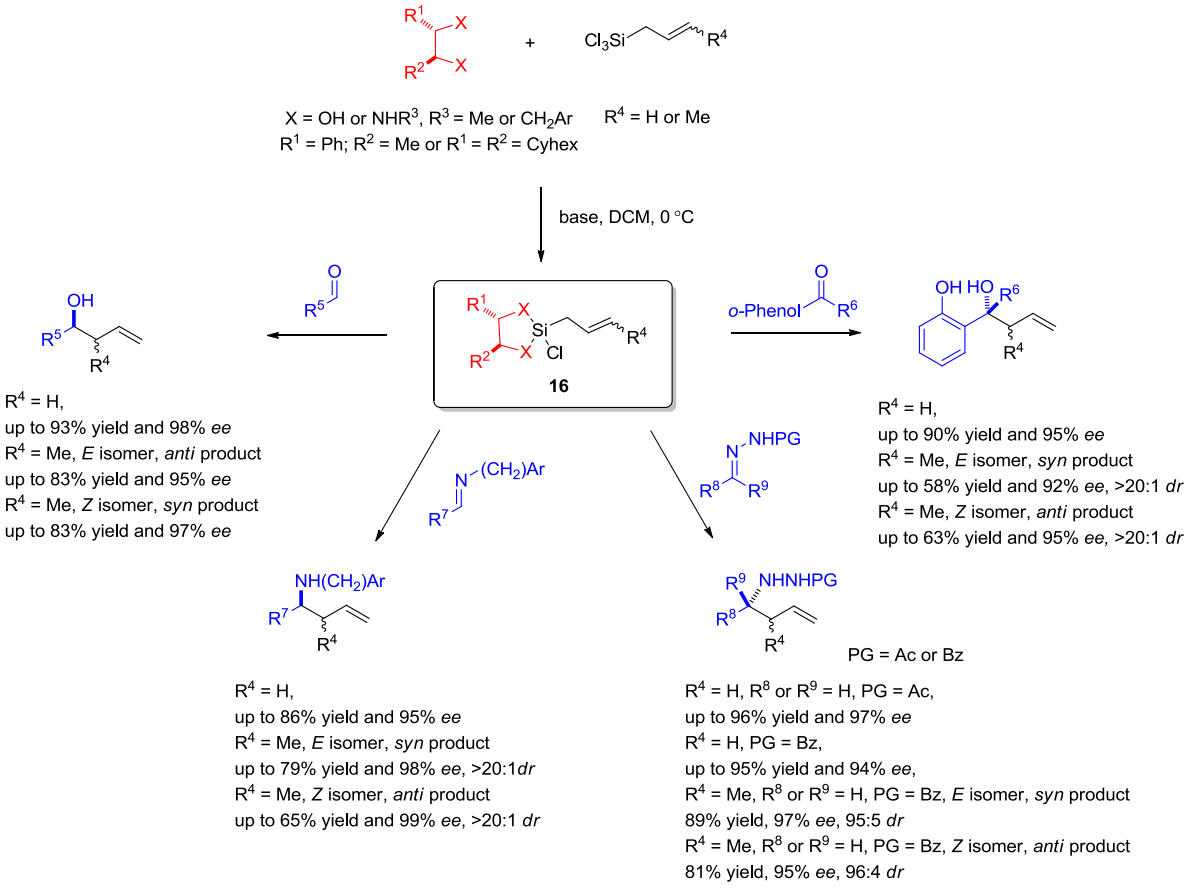
Highly enantiopure homoallylic amines were also obtained by the asymmetric allylation of *N*-aryl aldimines promoted by chiral formamides derived from D- and L-proline (Scheme 17).[38] It is worth noting that high loading of chiral promoter was needed to achieve excellent levels of stereoselectivity.



Scheme 17

Allylsilanes with Chiral Auxilliary

In the previous sections, the addition of achiral allyltricholosilanes to carbonyl compounds was promoted by chiral Lewis bases. However, there is also a methodology developed principally by Leighton and co-workers[39] where the reaction is taking place between carbonyl compounds or derivatives and allylsilanes bearing a chiral auxiliary that lead to homoallylic alcohols or amines in excellent yields (up to 96%) and stereoselectivities (up to 99% *ee* and 99:1 *dr*) in the absence of catalysts. This novel family of allylsilane reagents **16** features a constrained five-membered ring which increases the Lewis acidity of the silicon centre, making it more active. These chiral reagents are easily prepared from the corresponding allyltrichlorosilanes and various 1,2-diols, 1,2-amino alcohols or 1,2-diamines (Scheme 18).



Scheme 18

Leighton's group fine-tuned these chiral reagents to accommodate a wide range of carbonyl compounds. The addition to aldehydes was rather straightforward and did not require much tuning. However, it was found that electron-withdrawing groups in their chiral scaffold further increased Lewis acidity of the silicon centre, thus improving the efficiency of the reaction.[40] In the case of aldimines (ketimines) and hydrazones, for the allylation to proceed the substrate should contain a nucleophilic atom in the proximity of the heterocarbonyl group capable of chelating the Si atom (TS F and H, Figure 3) creating a tight chiral environment thus improving the selectivity.[41–43] Allylation of ketones required both the activated auxiliary and a chelating group near the carbonyl to achieve excellent yields and stereoselectivities (TS G, Figure 3).[44]

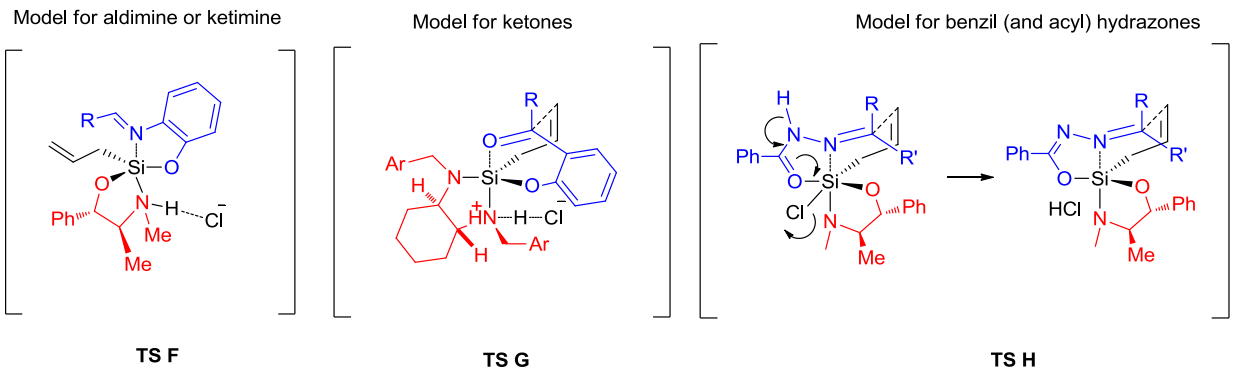


Figure 3

1.1.2. Allylboron reagents

Allylboron reagents present advantages over the allyltrichlorosilane analogues. They are stable to chromatography, easier to handle and not moisture sensitive. However as for their analogues, they can be manipulated at room temperature and stored at –20 °C under inert atmosphere for extended periods of time. Since Mikhailov and Bubnov, back in 1964, first discovered the formation of homoallylic alcohol in the reaction of triallylborane with aldehydes, use of allylboron reagents for the synthesis of homoallylic alcohols has evolved into a major synthetic methodology. Dialkyl allylboranes are still used as allylation reagents, however allylboronic esters became the most commonly used reagents. Their reactivity can be tuned by varying both the boronate residues and the nature of the α and/or γ substituent in the allyl group. The stereoselectivity of the final product can therefore be controlled as the reaction proceeds through a highly organised six-membered chair-like transition state.

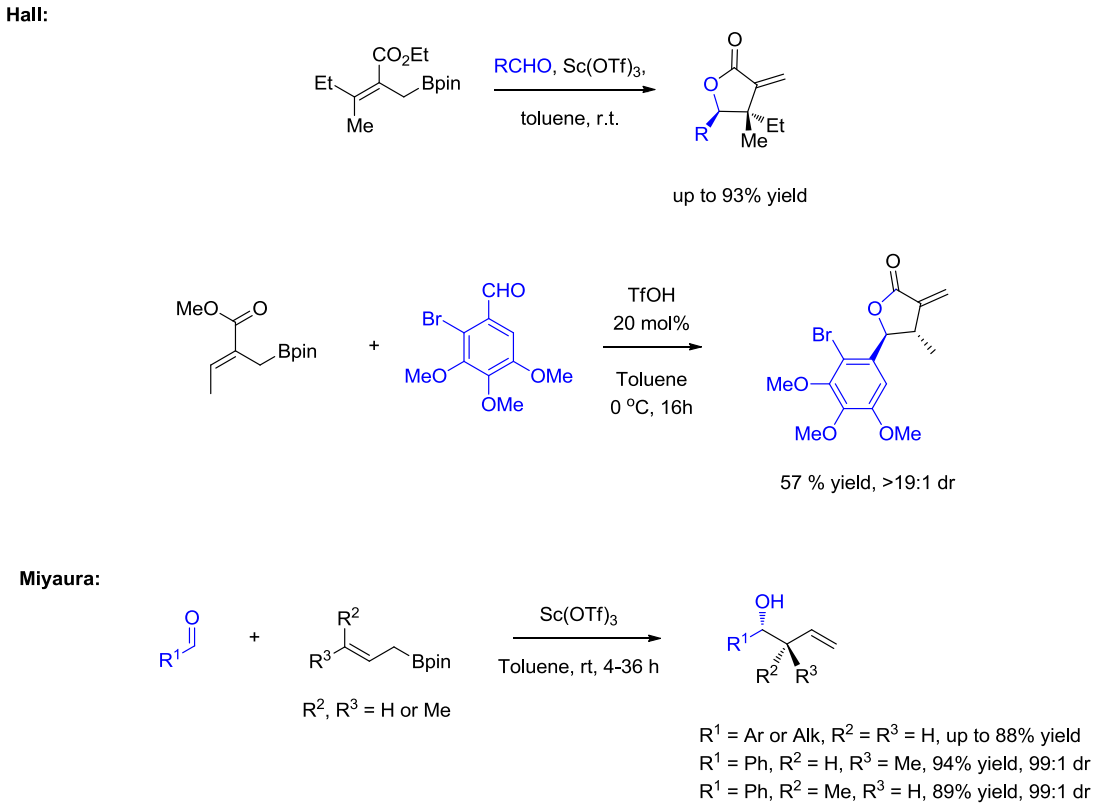
1.1.2.1. External chiral induction.

This section will describe methodologies where the chirality is introduced by an external chiral catalyst. Lewis and Brønsted acid catalysis as well as metal based catalysis using allylboronic acid esters as substrates will be discussed.

Lewis and Brønsted acid catalysed asymmetric allylation

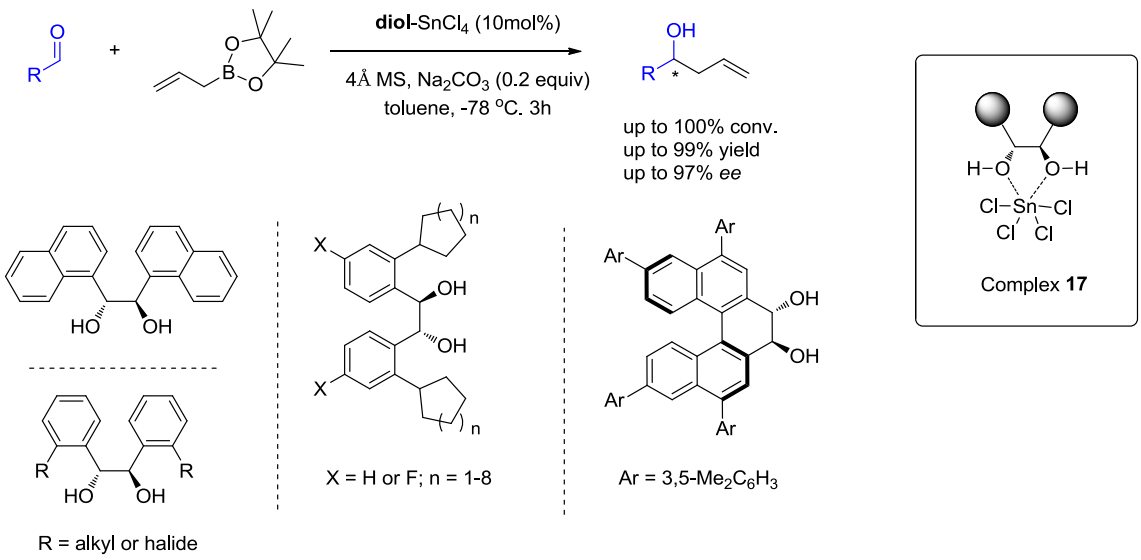
Despite a widespread utility of Lewis acid catalysis, its application in the addition of allylboronates to carbonyl compounds is fairly recent. Hall and co-workers employed Lewis acid catalysis in an attempt to overcome the sluggish reaction between electron-deficient, highly substituted allylboronates and aldehydes in the synthesis of *α*-butyrolactones (Scheme 19).[45] They also developed Brønsted acid catalysis to tackle allylation of electron-rich

aldehydes to furnish α-butyrolactones (Scheme 19).[46] Miyaura and co-workers reported on the Lewis acid catalysed allylation and crotylation of aldehydes with excellent yields but moderate to low diastereoselectivities.[47]



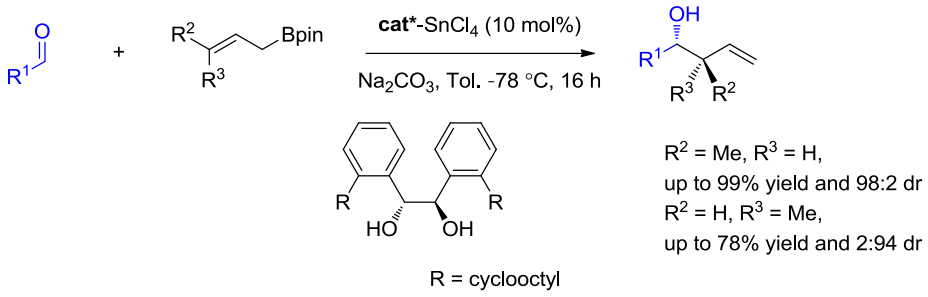
Scheme 19

Asymmetric allylation of aldehydes using simple allylboronate derived from pinacol was also developed by Hall and co-workers.[48–50] The catalysts made of C_2-symmetrical chiral diols and $SnCl_4$ led to a high level of asymmetric induction (Scheme 20). A wide range of chiral diol scaffolds shown in Scheme 20 were tested, all of them delivering an excellent level of enantioselectivity.



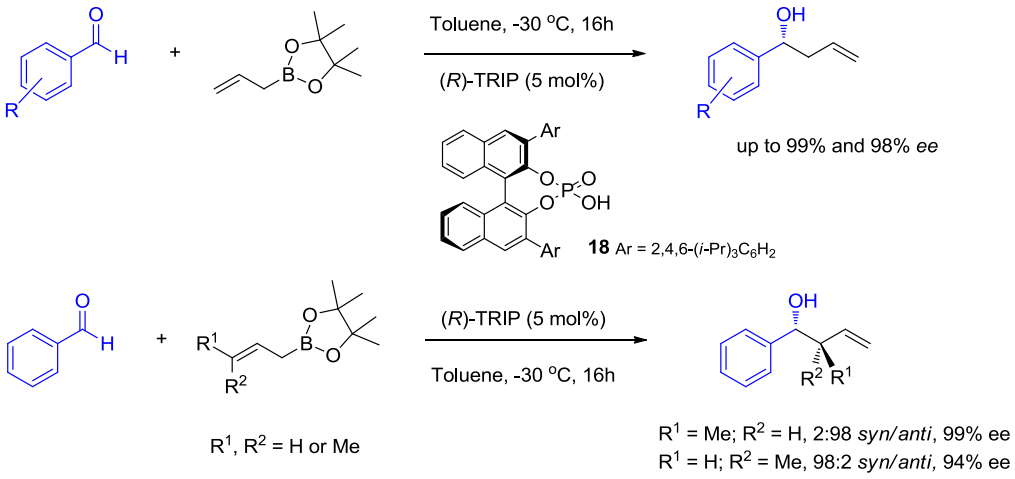
Scheme 20

In this catalytic system, coordination of $SnCl_4$ to the oxygens of the chiral diol generates a rigid, highly dissymmetrical complex **17**, which restricts the directional orientation of the hydroxylic protons and enhances their Brønsted acidity. The crucial importance of the free hydroxyl groups in such a complex was demonstrated by the use of methoxy protected diol in the presence of $SnCl_4$ under the same reaction conditions. The reaction proceeded in less than 10% conversion producing a racemic mixture of the homoallylic alcohol. Molecular sieves and Na_2CO_3 were added as scavengers of traces of moisture and HCl during the complex formation. Slower reaction rates were observed when the hydroxylic protons were sterically hindered by the bulky neighbouring *ortho*-substituents, *e.g.* *t*-butyl or trimethylsilyl group. In general, alkyl nonpolar substituents worked best. Crotylation experiments proved the excellent diastereoselectivity of the reaction characteristic to the Type I allylmetal reagents, thus *anti* homoallylic alcohol was obtained from *E* crotylboronate while *syn* alcohol resulted from the *Z* isomer. In both cases good to excellent diastereoselectivities were attained, however the *syn* homoallylic alcohols were produced in lower yield (Scheme 21).[51]



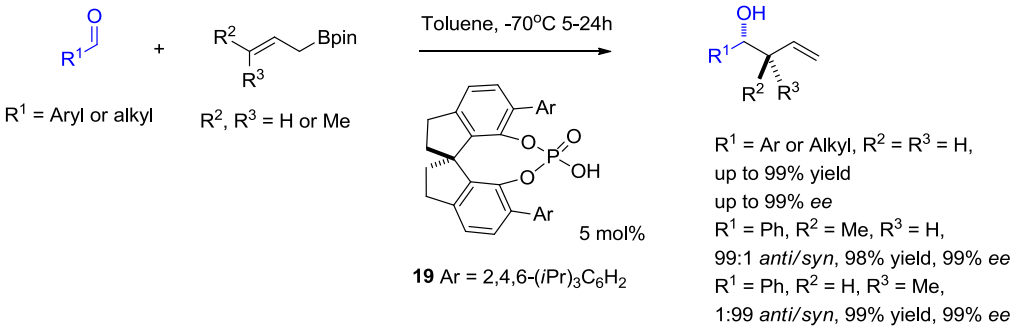
Scheme 21

Antilla and co-workers expanded the use of chiral phosphoric acids to the asymmetric allylation of aldehydes. The well-known binaphthyl-derived phosphoric acid (*R*)-TRIP (**18**) was employed as Brønsted acid catalyst yielding the corresponding homoallylic alcohols in excellent yields and enantioselectivities. High enantio and diastereoselectivities were also achieved in the crotylation studies (Scheme 22).[52]



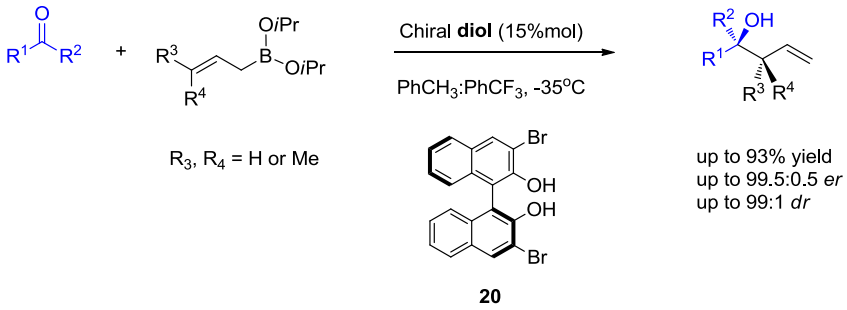
Scheme 22

Hu and co-workers reported on the development of novel spirocyclic C_2-symmetric chiral Brønsted acid catalysts (**19**, SPINOL) and its application in the asymmetric allylation of aldehydes.[53] High yields and enantioselectivities were achieved for a wide range of aromatic and aliphatic aldehydes, including α,β-unsaturated and propargylic aldehydes. High diastereoselectivity was also achieved in the crotylation of benzaldehyde (Scheme 23).



Scheme 23

Quaternary chiral homoallylic alcohols are valuable building blocks for natural products synthesis. They can be obtained by allylation of ketones; however, this process has been less investigated due to the lower reactivity of ketones. To fill this gap, Schaus and co-workers developed the first enantioselective allylation of ketones promoted by BINOL derivatives to afford chiral tertiary homoallylic alcohols.[54,55] After screening a wide range of chiral diols, 3,3'-dibromo-BINOL **20** emerged as the best catalyst delivering high yield and stereoselectivities (Scheme 24).



Scheme 24

^{1}H NMR and kinetic studies identified the mechanism that involves transesterification of one of the isopropoxy group by the chiral diol and hydrogen bonding to the second alkoxyl group as depicted in Figure 4.

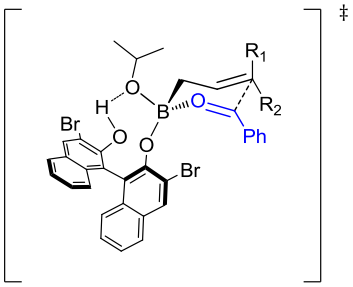
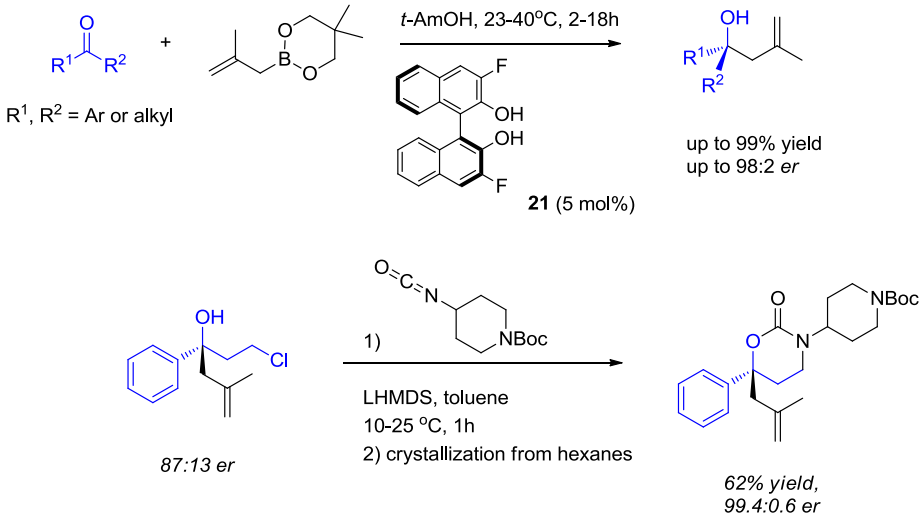


Figure 4

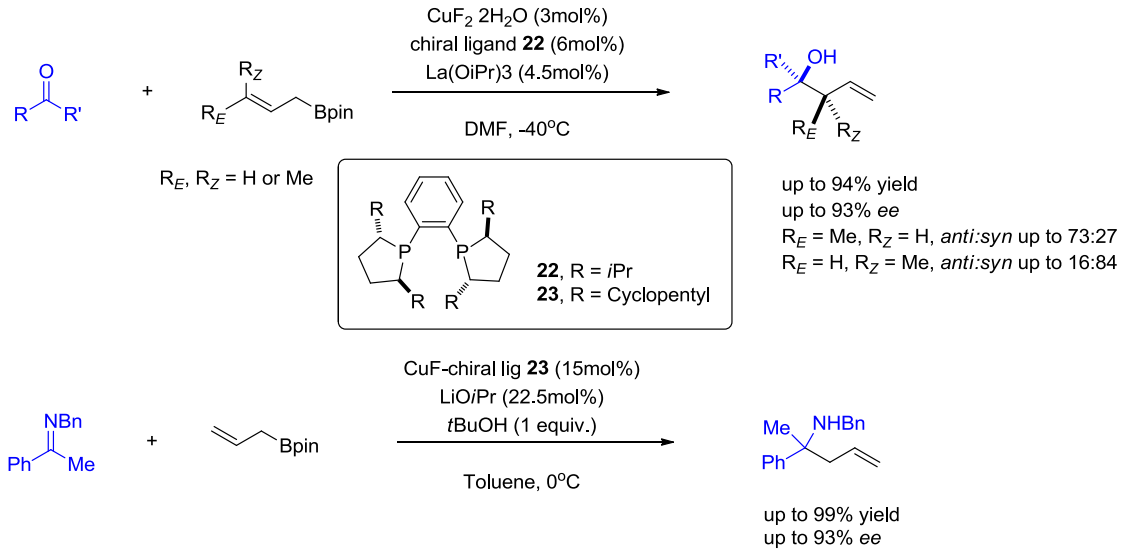
Methallylation of ketones to afford β-substituted tertiary homoallylic alcohols was also studied under conditions of chiral Brønsted acid catalysis. However, in this case, a stronger Brønsted acid **21** was needed to achieve the target compounds in good to excellent enantioselectivities and high yields.[56] This novel approach was used in the large scale synthesis of enantiopure biologically active compounds. The enantiopurity of the final product was upgraded by recrystallisation from hexanes (Scheme 25).



Scheme 25

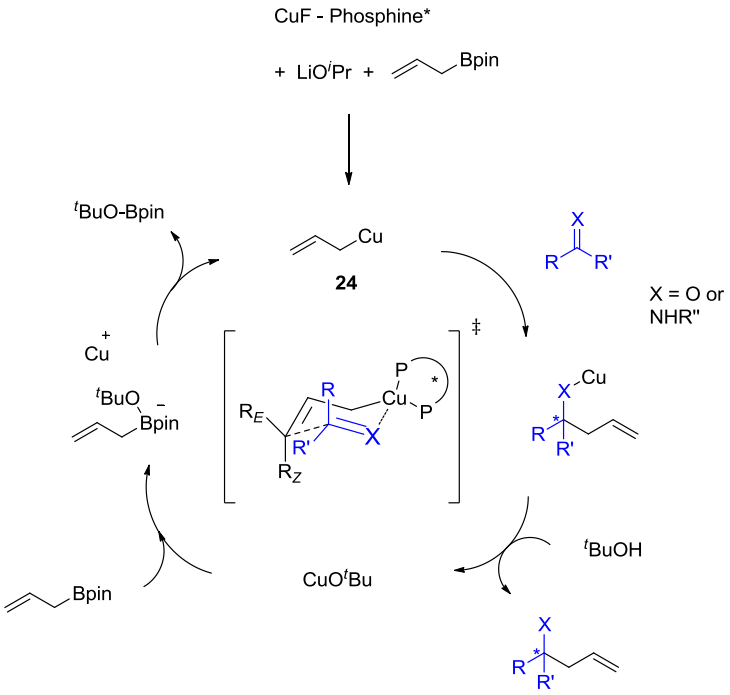
Metal catalysed asymmetric allylations

The stereoselective addition of allylboron reagents to carbonyl compounds and their imine derivatives has also been studied in the presence of metal salts and chiral ligands. Shibasaki and co-workers developed the first catalytic enantioselective methodology using ketones and ketimines (Scheme 26).[57–59] Highly enantio- and diastereoselective allylations were achieved using Cu-phosphine chiral complexes.



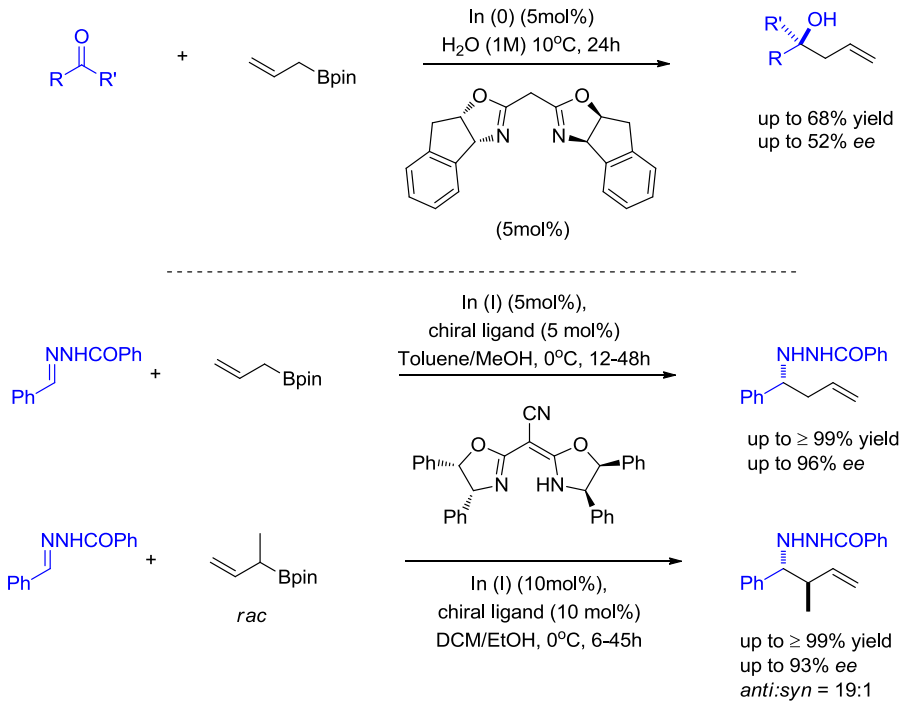
Scheme 26

The reaction mechanism involves a B-to-Cu transmetalation forming the active allylcopper reagent **24**, which is accelerated by the co-catalyst ($La(OiPr)_3$ for ketones or LiO*i*Pr for ketimines). Addition to the corresponding carbonyl compound occurs through a Zimmerman-Traxler chairlike transition state and further dissociation/protonation releases the homoallylic target product (Scheme 27).



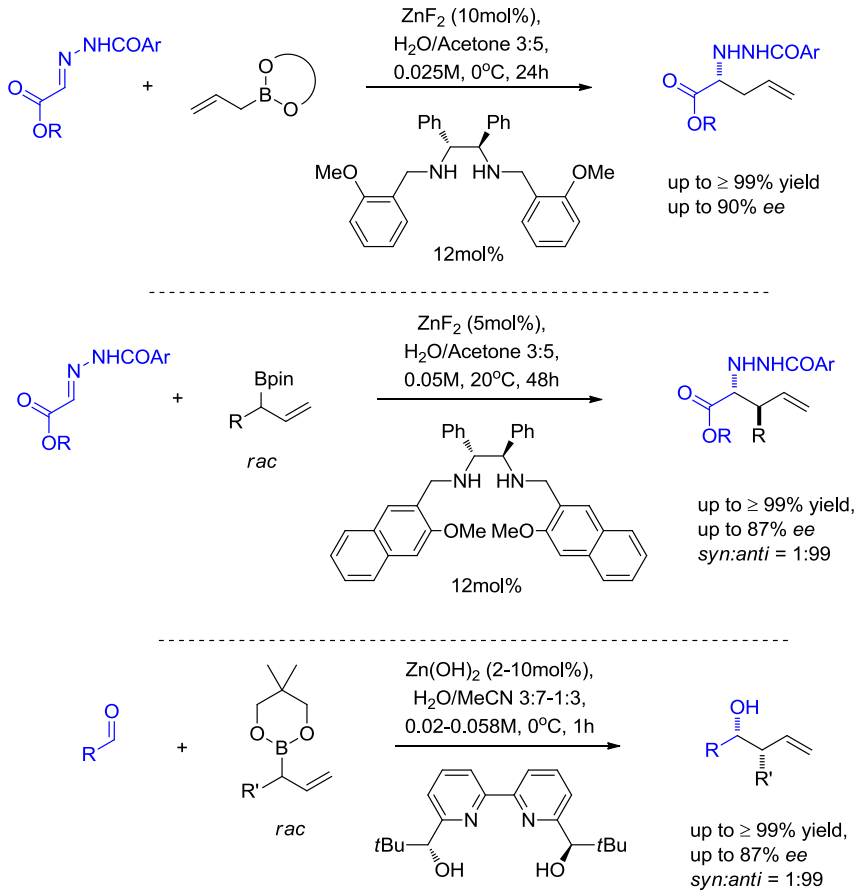
Scheme 27

Kobayashi reported greener methods employing In[60,61] and Zn[62,63] to catalyse asymmetric addition of allylboronates to ketones and ketimines. In-catalysed reactions were carried out in the presence of catalytic amounts of chiral ligands providing good to excellent enantioselectivities (Scheme 28)



Scheme 28

Zn mediated additions also proved high yielding and proceded highly stereoselectivity. Catalytic amounts of ZnF_2 in the presence of chiral heterocyclic ligands afforded the target homoallylic product in excellent selectivity. Addition of α-methylallylboronate to α-hydrazonoesters and aldehydes also proved highly diastereoselective giving the *anti* and *syn* isomers, respectively (Scheme 29).



Scheme 29

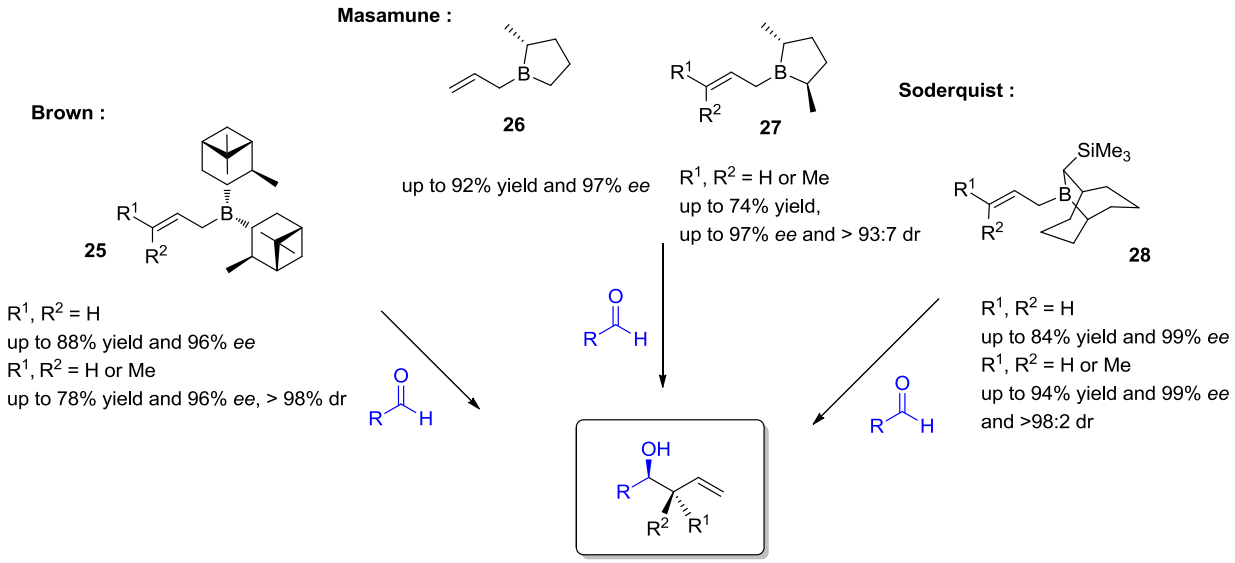
1.1.2.2. Allyllboron reagents with chiral group on boron.

Since Hoffmann reported the first asymmetric addition of allylboron reagents to carbonyl compounds using camphor-derived auxiliaries, the contribution to the field has been growing over the years. The most important contribution to the field came from the group of Corey,[64] Roush,[65] Brown,[66] Masamune[67,68] and Soderquist[69,70] separately. More recent is the contribution of Aggarwal, which will also be mentioned.

Allylboranes chiral auxiliares

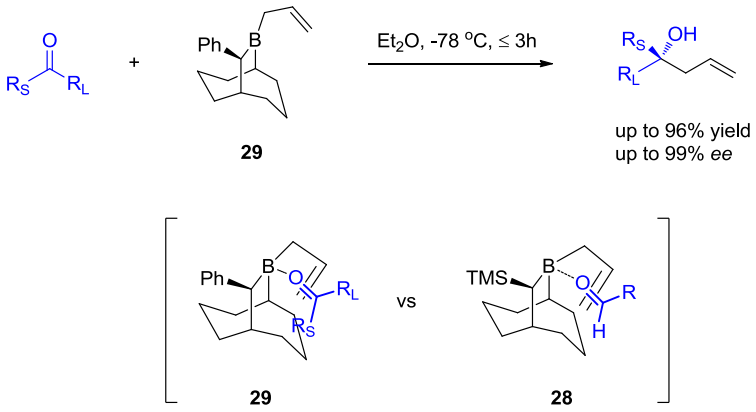
Allyldialkylboranes are known to be significantly more reactive than their boronic ester counterparts. Moreover, the lack of a heteroatom spacer allows the chirality to be closer to the boron centre, which generally enhances the selectivity. Since the late 80s, several research groups carried out detailed investigation into the asymmetric allylation of carbonyl compounds using enantiopure allylboranes. Brown developed *B*-allyl and *B*-crotyl diisopinecampheylboranes **25**, which upon addition to aldehydes yielded the corresponding homoallylic alcohol in excellent yields, enantio- and diastereoselectivities.[71] Masamune and

co-workers introduced chiral monosubstituted allylborolanes **26** and disubstituted crotylborolanes **27**, which on the addition to aldehydes showed excellent transfer of stereochemical information.[67,68] Soderquist and co-workers expanded the field to 10-TMS-9-borabicyclo[3.3.2]decanes (10-TMS-9-BBD, **28**) as allylating reagents,[70,72] which also afforded the target homoallylic alcohols in high yields, enantio- and diastereoselectivities (Scheme 30).



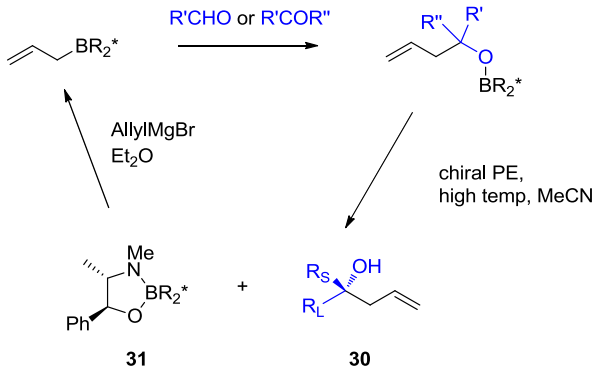
Scheme 30

Soderquist took a step further to develop a modified 10-Ph-9-BBD **29**, which served as a more reactive allylating reagent for methyl ketones, in contrast to its counterpart 10-TMS-9-BBD.[69] 10-Trimethylsilyl derivative was too bulky to accommodate groups bigger than hydrogen, while 10-phenyl presented less steric hindrance and hence was capable of hosting bulkier groups (Scheme 31).



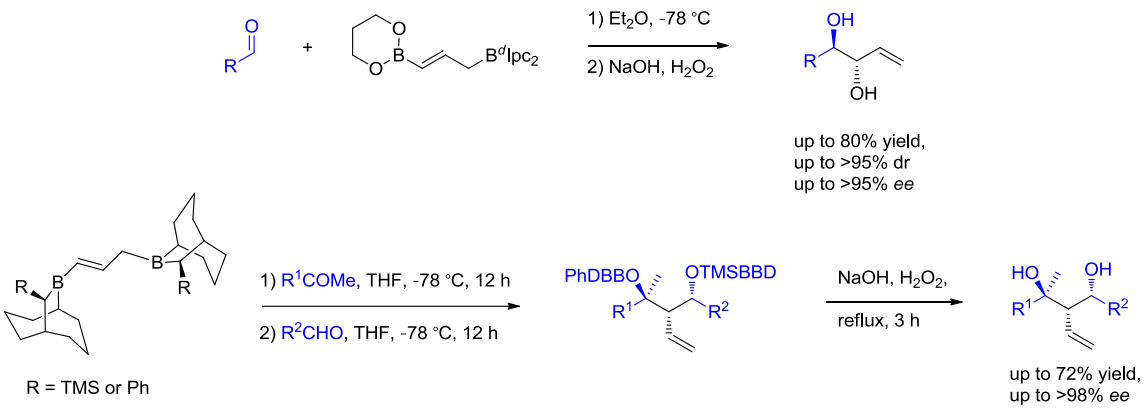
Scheme 31

Despite the fact that a chiral auxiliary is employed, the methodologies developed by Masamune and Soderquist allowed recovery of the chiral moiety. Refluxing the boron intermediate in MeCN in the presence of enantiopure pseudoephedrine resulted in the transterification yielding the corresponding homoallylic alcohol **30** and borane complex **31** as a crystalline solid (Scheme 32), which can be recycled.



Scheme 32

Valuable building blocks, such as 1,2- and 1,3-diols, were synthesised by Brown[66] and Soderquist,[73] respectively, using allyl vinyl diboron reagents. A single asymmetric allylation followed by oxidative workup afforded 1,2-diols, while a sequential double allylboration of ketones and aldehydes gave rise to 1,3-diols. In both cases, the products were obtained in moderate to good yields and excellent enantioselectivities (Scheme 33).



Scheme 33

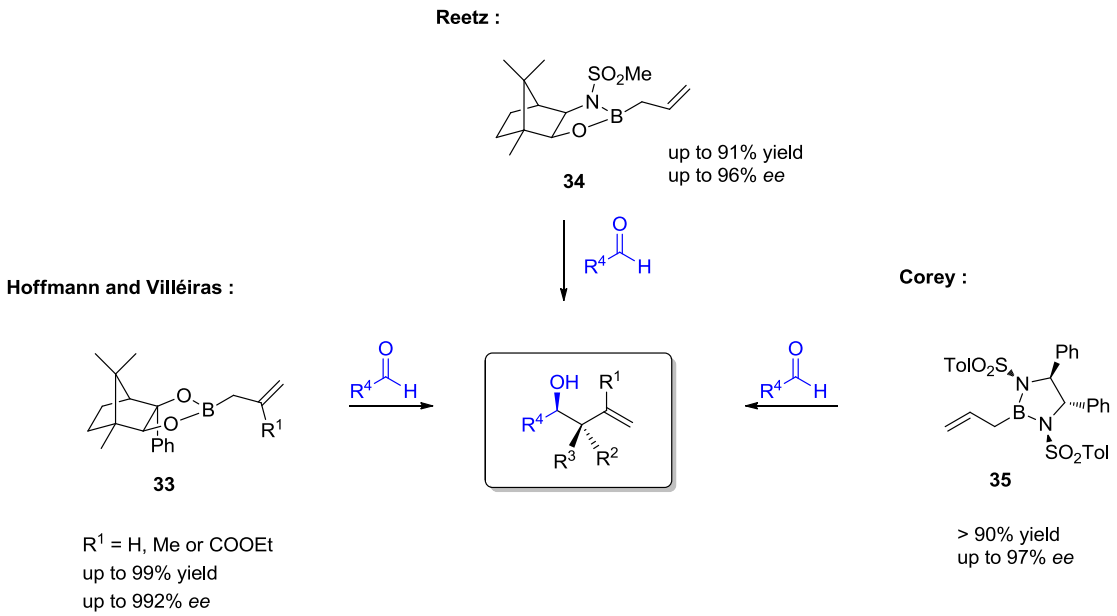
Jäkle and co-workers reported the use of ferrocene-based planar chiral bimetallic complexes as allylation reagents. This novel reagent gave no significant asymmetric induction in the allylation of aldehydes. At the same time, when ketones were used as substrates, the respective tertiary homoallylic alcohols were obtained in up to 80% *ee* in DCM within 30 minutes at room temperature (Scheme 34).[74]

Scheme 34

NMR spectroscopic analysis of the intermediate obtained upon reaction of the chiral ferrocene derivative **32** with acetophenone showed an ^{11}B NMR signal shift to 48.9 ppm (initially being 71 ppm) while the ^{119}Sn NMR signal remained at -14.4 ppm (initially being -14.3 ppm). These studies confirmed the allyl transfer occurred from the boron rather than the tin centre.

Allylboronate chiral auxiliaries

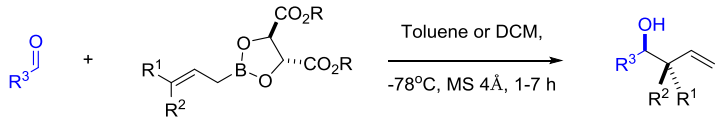
Since the late 70s, when they were pioneered by Hoffman, chiral allyl boronic esters and amides have been widely studied by different research groups. Several architectures were explored as chiral auxiliaries, such as camphor derivatives **33** and **34**[75–77] and bis-sulfonamides **35** (Scheme 35).[64]



Scheme 35

Extensive investigations have been carried out by Roush[78,79] using chiral esters and amide analogues. After initial studies on the addition of achiral allylboronates to chiral aldehydes revealing substrate control of the stereoselectivity, the group then studied the allylation of achiral and chiral aldehydes using chiral auxiliaries on the dioxaborolanes (**36**-**40**), as illustrated in Scheme 36.[80]

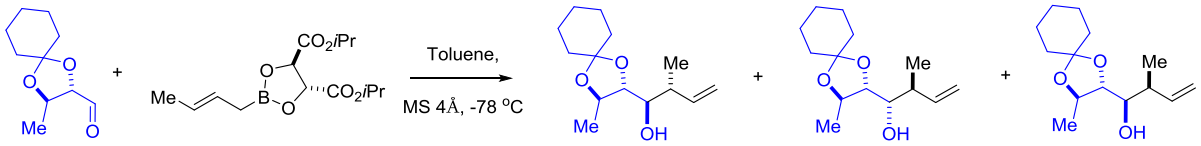
Single asymmetric allylation:



R^1, R^2 = Me or H
36, R = (+) or (-)-DIPT,
37, R = (-)-2,3-butandiol
38, R = (-)-2,4-pentandiol

R^1 = Me, R^2 = H,
97% yield, *anti:syn* = >99:1 dr, 87% *ee*
R^1 = H, R^2 = Me,
> 99% yield, *anti:syn* = >1:99 dr, 88% *ee*
R^1 = R^2 = H,
up to 95% yield, up to 87% *ee*

Double asymmetric allylation:

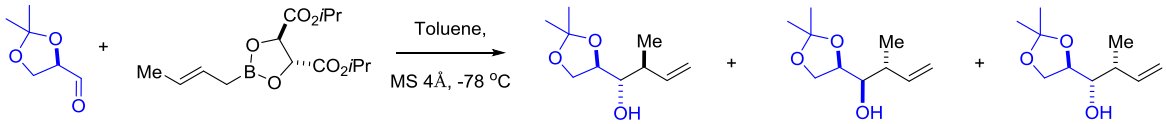


39, (-)-DIPT
40, (+)-DIPT

anti,anti *syn,anti* *anti,syn*

(+)-DIPT,
80% yield, *anti,anti*: 88:4:8 dr

(-)-DIPT,
88% yield, *anti,syn*: 4:93:3 dr



39, (-)-DIPT
40, (+)-DIPT

anti,anti *syn,anti* *anti,syn*

(-)-DIPT,
87% yield, *anti,anti*: 87:9:4 dr

(+)-DIPT,
85% yield, *anti,syn*: 2:96:2 dr

Scheme 36

The high level of stereoselectivity was attributed to the repulsive electronic interactions between the lone pairs of the aldehydic oxygen and the neighbouring ester oxygen within the associative six-membered transition state (Figure 5a). Hence by changing the enantiomer of the chiral auxiliary, the stereochemistry of the final homoallylic alcohol was inverted. Further studies to probe this hypothesis led to the development of a conformationally more rigid cyclic *N,N'*-dibenzyl-*N,N'*-ethylenetartramide allylboronate derivative **41**, which improved stereoselectivity up to 99.7:0.3 e.r. and 98:2 d.r. in the reactions with chiral aldehydes (Figure 5b).[81]

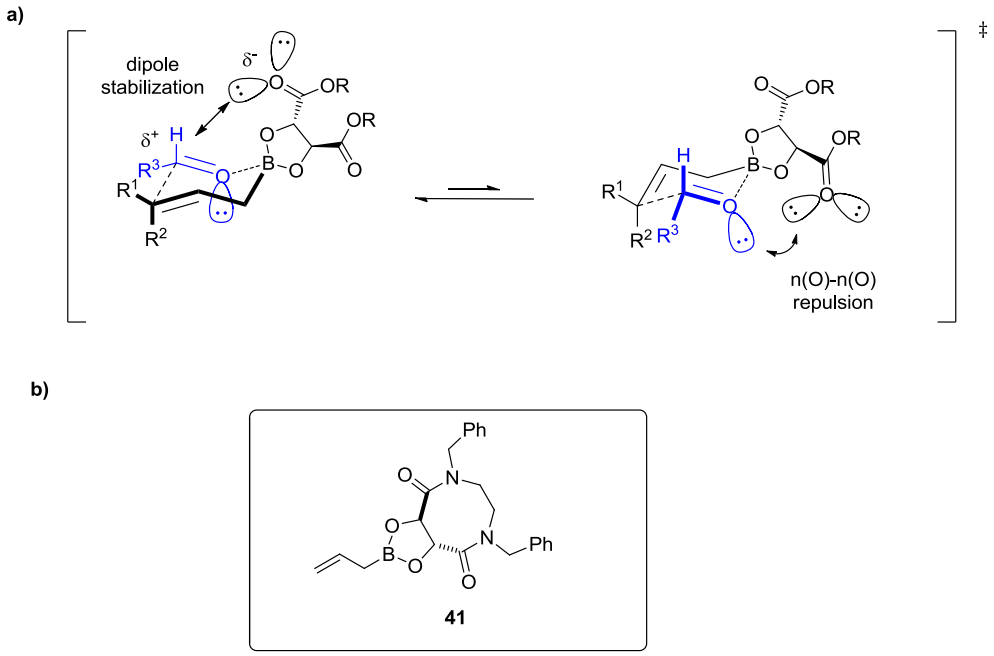
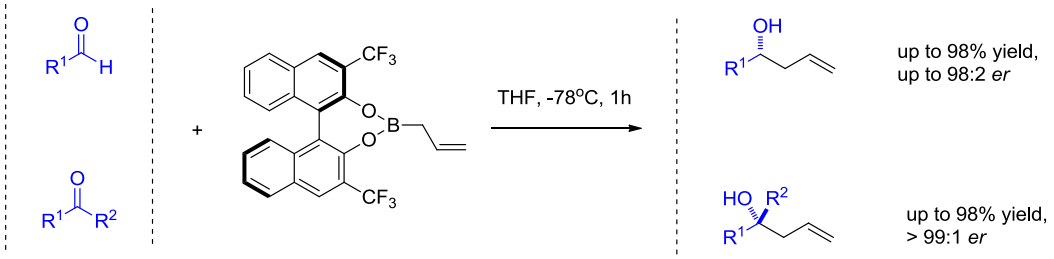


Figure 5

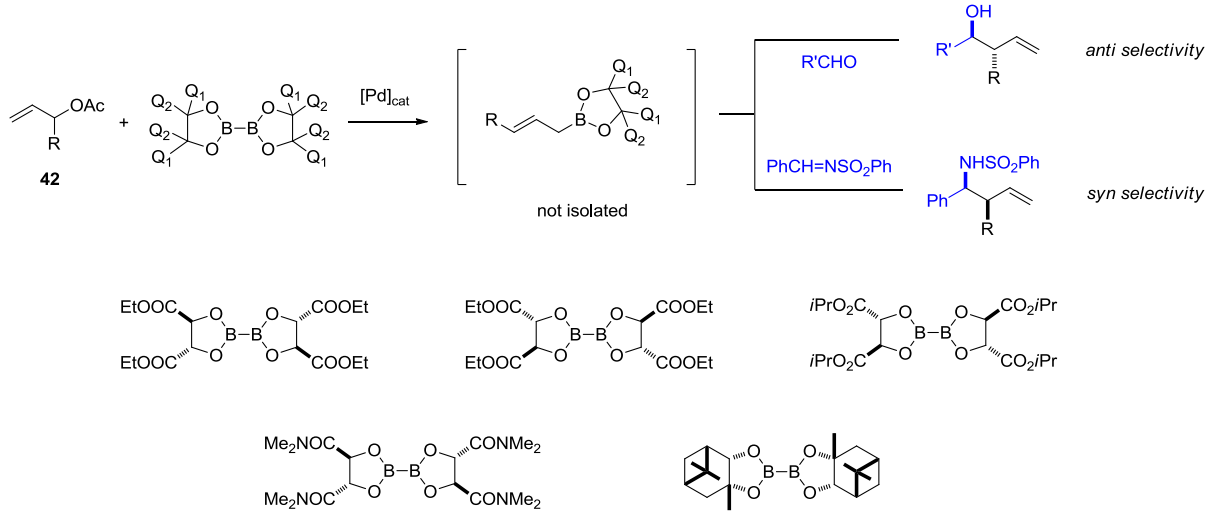
This methodology that has been known since the late 80s, recently was adapted to continuous flow systems. Ley and co-workers[82] described the addition of chiral crotylboronates to both achiral and chiral aldehydes using their developed flow technology. The reactions produced high levels of stereoselectivity, up to 20:1 d.r. and 16:1 d.r. for achiral and chiral aldehydes respectively.

After Kaufmann reported the first example of chiral boron BINOL scaffolds for a wide range of asymmetric allyl transfer reactions.[83] Chong introduced a more reactive BINOL derivative for the asymmetric allylation methodology.[84] A highly electrophilic BINOL derivative bearing electron-withdrawing CF_3 groups proved more reactive towards carbonyl compounds. The allylation of both aldehydes and ketones led to the corresponding secondary and tertiary homoallylic alcohols in high yields and excellent enantiomeric ratios (Scheme 37).



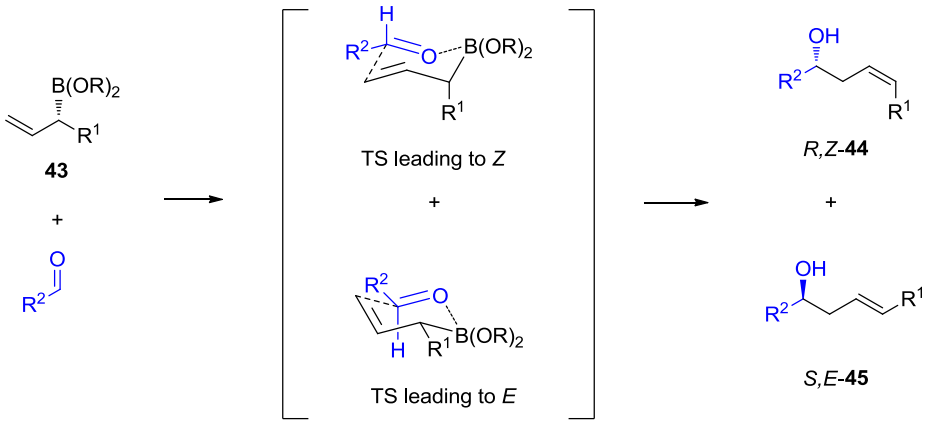
Scheme 37

Further studies on the asymmetric allylation of carbonyl compounds and their derivatives were reported by Szabó and co-workers.[85] They developed a one-pot allylic substitution of allyl acetates **42** catalyzed by Pd(0) using diboron compounds derived from chiral diols followed by *in situ* allylation of aldehydes or sulfonylimines (Scheme 38). In this one-pot synthesis of chiral homoallylic alcohols and amines, the allylation proceeded through the well-established six-membered transition state yielding high level of diastereoselectivity (> 99% d.r.) in most examples. However, only moderate enantioselectivities (up to 53% *ee*) were achieved for the homoallylic products.



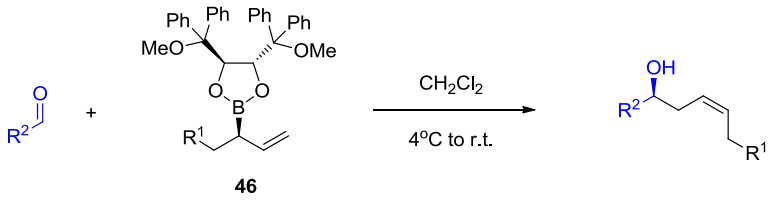
Scheme 38

In a special area of asymmetric allylation of aldehydes using chiral secondary allylboronates extensive work was carried out by Pietruszka and co-workers.[86] Due to the close chair like transition state mechanism, secondary allylboronates **43** give raise to *E* or *Z* linear homoallylic alcohols **44-45**. Furthermore, the use of enantiopure α-substituted allylboron reagents yields a mixture of geometrical isomers with opposite stereochemistry at the new chiral centre (Scheme 39).



Scheme 39

The control of the geometrical selectivity can be achieved by tuning the electronic and steric properties of the allylating reagent. Pietruszka's group focused on the synthesis of *Z*-homoallylic alcohols by increasing the bulk of the chiral boronic ester moiety and modifying the electronic properties of the α-substituent. Thus, by using enantiopure secondary allylboronates **46** with bulky diol moieties the corresponding homoallylic alcohols were obtained in good to excellent yields and high level of stereoselectivity (Scheme 40). This methodology was employed in the synthesis of different analogues of the dihydro-α-pyrone class of natural products.[87]



R^1 = COOEt:
R^2 = Ph, 91% yield, 95% *ee*
R^2 = CH_2CH_2Ph, 67% yield, 98% *ee*

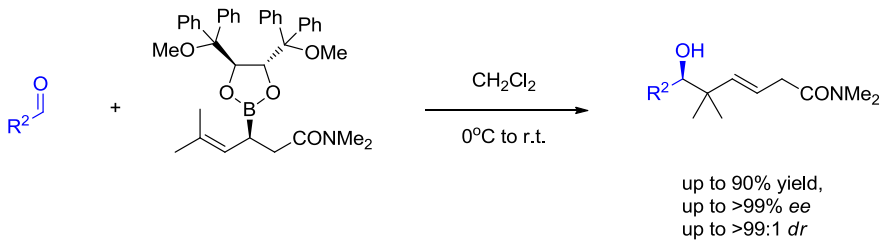
R^1 = $CONMe_2$:
R^2 = Ph, 79% yield, 94% *ee*
R^2 = CH_2CH_2Ph, 65% yield, >99% *ee*

R^1 = CH_2OTBS:
R^2 = Ph, 80% yield, >95% *ee*
R^2 = CH_2CH_2Ph, 52% yield, 99% *ee*

R^1 = Me:
R^2 = Ph, 83% yield, >99% *ee*
R^2 = CH_2CH_2Ph, 91% yield, >95% *ee*

Scheme 40

Recently, Pietruszka and co-workers used the same boronate fragment in the synthesis of *E*-homoallylic alcohols. A range of highly substituted *E*-homoallylic alcohols were obtained in high enantio- and diastereoselectivities (Scheme 41).[88]



Scheme 41

The apparent inversion in the geometrical selectivity results from the steric interactions in the six-membered chair-like transition state (Figure 6). The transition state leading to *Z* isomer presents $A^{1,3}$ interactions between the substituents in the α– and γ-positions (**TS*Z***). The TS leading to *E* isomer (**TS*E***) is free from destabilising $A^{1,3}$ interactions but presented disfavoured interactions between the amide and the chiral diol moiety, however, the pseudoequatorial position of the former minimised the interactions with the aldehydic side chain, thus overall favouring this reaction pathway (Figure 6).

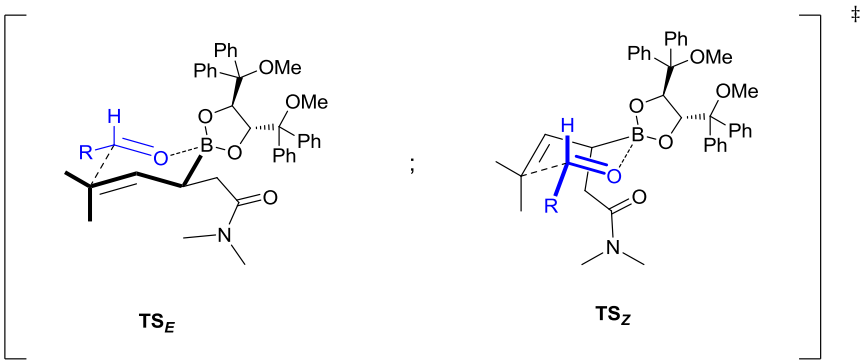
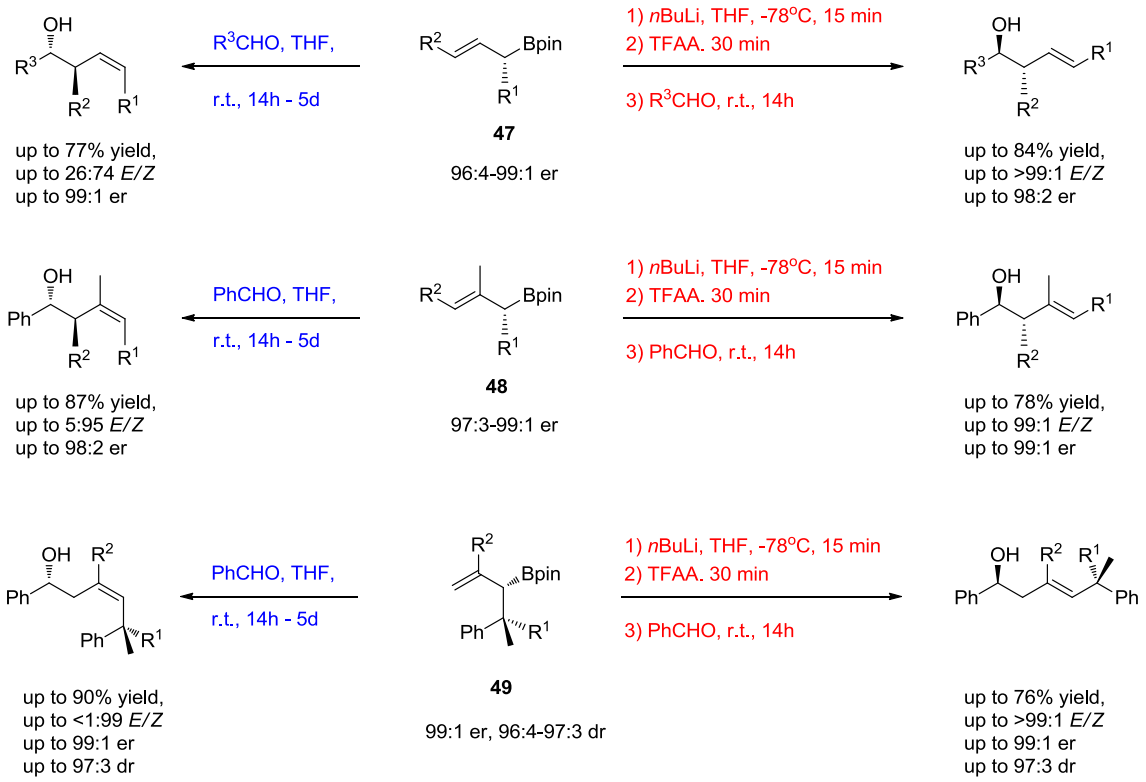


Figure 6

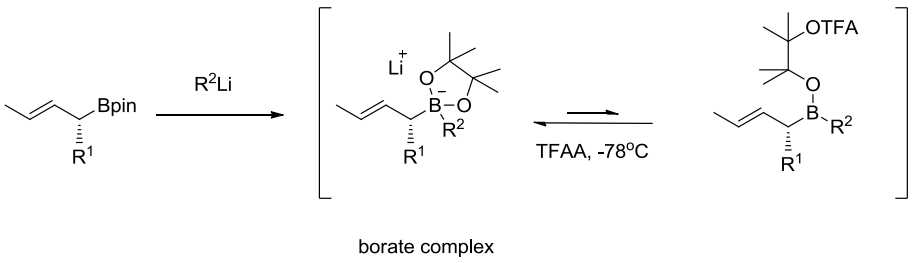
Lewis base catalysed asymmetric allylation

Aggarwal recently reported the use of Lewis bases to promote the asymmetric allylation of aldehydes via the in situ generated borinic esters, which have an intermediate reactivity between borolanes and dioxaborolanes.[89] They investigated the allylation reaction using chiral *α*-substituted crotyl and methallyl boronic esters resulting in the corresponding homoallylic alcohols with excellent stereoselectivity (Scheme 42).



Scheme 42

When the chiral α-substituted allylboron reagents **47**-**49** were reacted at room temperature with aldehydes without further activation, *Z*-isomers were formed. However, in the presence of a Lewis base, a borate complex is formed in the equilibrium with a ring opened form (Scheme 41), which subsequently is trapped with trifluoroacetic anhydride (TFAA) stabilising the borinic intermediate at lower temperatures. This prevents 1,3-borotropic shift to occur, allowing for the allylation reaction to proceed through the well-known chair-like transition state with an excellent *E* selectivity.



Scheme 43

1.2. Addition of allylic halides

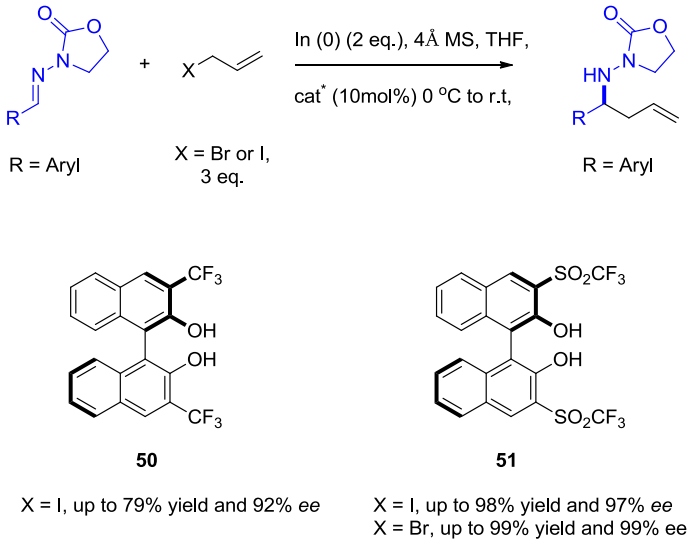
The catalytic asymmetric addition of allyl fragments to different types of carbonyl compounds proved to be a powerful methodology for to achieve enantiomerically enriched homoallylic alcohols or amines. The previous sections have been focused on the organometallic reagents. However, there are also catalytic asymmetric allylation procedures employing allyl halides as precursors to the organometallic reagents. In the next section, these strategies will be discussed briefly.

1.2.1. Indium mediated allylations

Despite the fact that indium (In) has been known since the 19th century, it was not until the early 90s when it was introduced to organic synthesis to mediate organic reactions. In-promoted reactions became attractive due to low air- and moisture sensitivity of the organoindium intermediates, their significantly lower toxicity and higher tolerance to a wide range of functional groups. For the formation of a new C-C bond *via* transfer of an allyl fragment to carbonyl or heterocarbonyl compounds, allylindium reagents can successfully compete with their Si, B and Sn analogues. In the case of the base-sensitive imine derivatives, allylindium reagents are promising as they have low basicity.

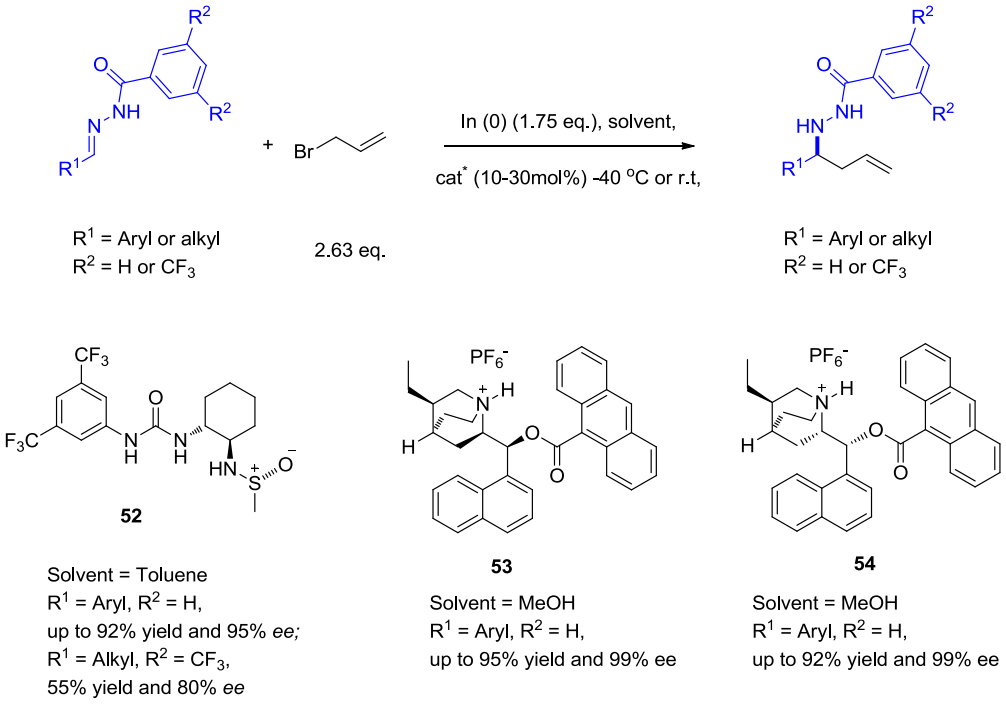
Several asymmetric procedures were reported in the literature where allylindium reagents were used either with the substrates decorated with chiral auxiliaries,[90] or in combination with stoichiometric chiral promoters.[91,92]

There are also a few examples of asymmetric addition of allyl halides mediated by In under Barbier-type conditions in the presence of catalytic quantities of chiral controllers. Cook and co-workers[93] developed the first catalytic asymmetric addition of allylindium reagents to hydrazones employing 3,3'-disubstituted BINOL derivatives **50**. They found that acidity of the hydroxyl protons has a strong effect on the overall outcome of the reaction. The second generation of structurally similar chiral BINOL derivatives **51** with a strong electron-withdrawing substituent in the 3,3'-positions gave the products in better isolated yield and higher enantioselectivity (Scheme 44).[94]



Scheme 44

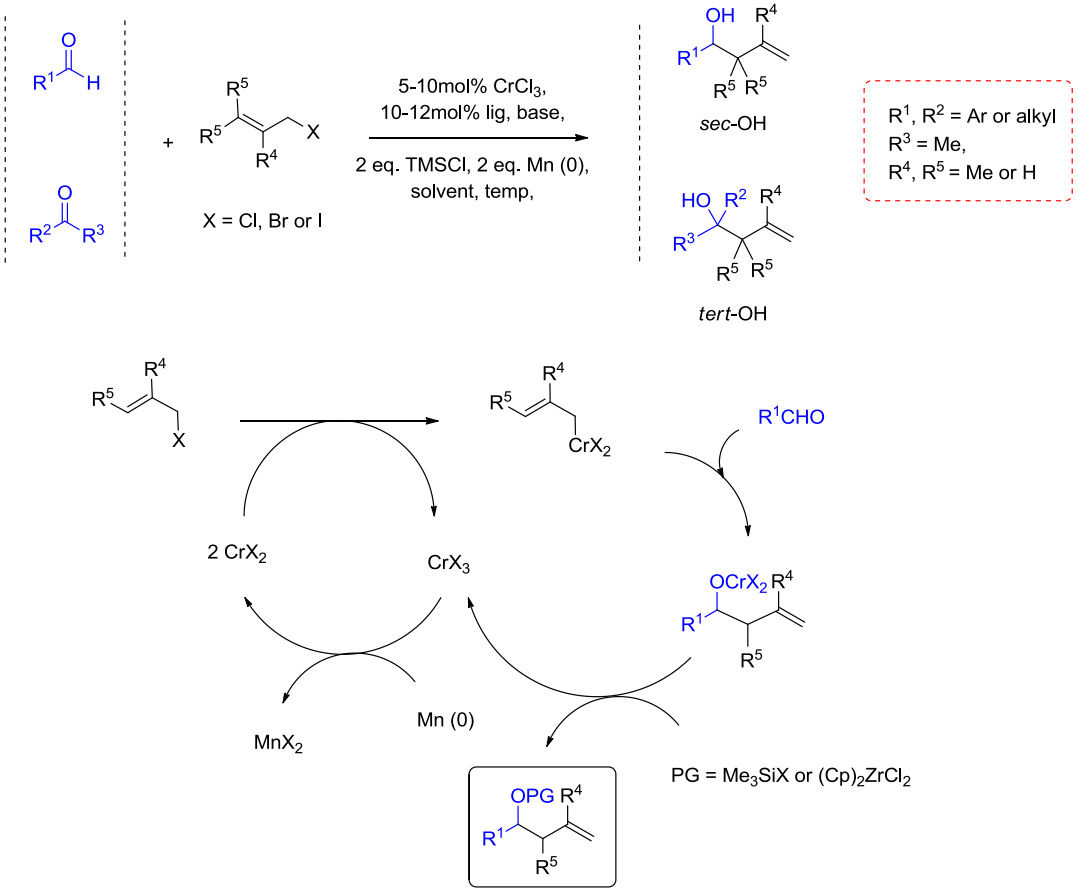
Jacobsen and co-workers exploited the potential of chiral ureas and thioureas as promoter for the catalytic asymmetric allylation of acylhydrazones. They developed a new sulfinamide-urea catalyst **52** that afforded the target chiral homoallylic hydrazines in good to excellent yields and enantioselectivities (Scheme 38). This new chiral promoter also worked well in the crotylation of the imine derivatives with both *E* and *Z* crotyl bromide, however, poor diastereoselectivity was observed.[95] A similar level of selectivity was achieved when cinchona alkaloid derivatives **53** and **54** were used as chiral promoters.[96] It was assumed that low basicity of the allylindium reagents permitted the use of protonated chiral amines as chiral promoters providing high to excellent yields and enantioselecivities (Scheme 45).



Scheme 45

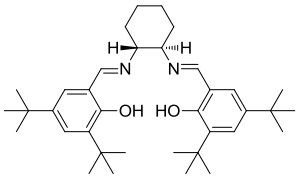
1.2.2. Chromium mediated allylations

The reaction of organochromium compounds was pioneered by Nozaki and Hiyama in the late 70s using stoichiometric amounts of Cr (III) and $LiAlH_4$ as reducing agent. The subsequent addition to carbonyl compounds led to homoallylic alcohols in good to excellent yield.[97] Kishi and co-workers found that Ni salts had a catalytic effect on the formation of the C-Cr bond, improving the efficiency of such transformations.[98] However it was not till the mid-90s when the use of catalytic amounts of Cr source was realised by Fürstner and co-workers (Scheme 46).[99] They introduced two reagents in the reaction system: nontoxic, commercially available manganese powder as stoichiometric reducing agent to recycle Cr(II) species and TMSCl assisting in the dissociation of Cr-O bond. The new improved reaction conditions had beneficial effect on the scope, chemo- and diastereoselectivity in the addition of allylchromium species to carbonyl compounds.

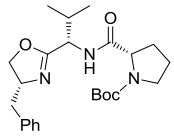


Scheme 46

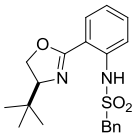
Although Kishi introduced a chiral bipyridine derivative as ligand for the allylation of carbonyl compounds mediated by Cr, the procedure required stoichiometric amounts of metal source.[100] Cozzi and co-workers developed chiral ligands. Enantiopure salen-type of ligands promoted the Barbier-type reaction with good enantioselectivities but moderate yields.[101] Since then, a wide range of chiral ligands has been explored and tested in the addition of allylic, methallylic and crotyl halide mediated by Cr. Figure 7 presents a selection of ligands reported to date capable of performing the addition in a good level of enantio- and/or diastereoselectivity. The yield and selectivities correspond to the target secondary or tertiary homoallylic alcohol.[102–105]



sec-OH, R^4 = R^5 = H,
up to 67% yield and 89% *ee*

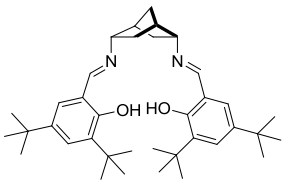


sec-OH, R^4 = H or Me; R^5 = H,
up to 98% yield and 94% *ee*
sec-OH, R^4 = H, R^5 = Me, *E-isomer,*
88% yield,
2.3:1 *anti:syn*, 91% *ee*, 95% *ee*

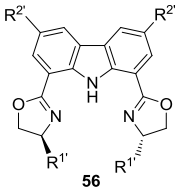


55

sec-OH, R^4 = H or Me; R^5 = H,
up to 86% yield and 93% *ee*

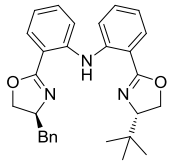


sec-OH, R^4 = H or Me; R^5 = H,
up to 78% yield and 92% *ee*

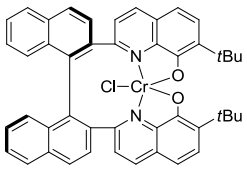


56

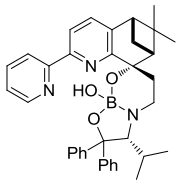
sec-OH, R^4 = H or Me; R^5 = H,
up to 98% yield and 96% *ee*
$R^{1'}$ = Ph or *i*Pr, $R^{2'}$ = Ph or H



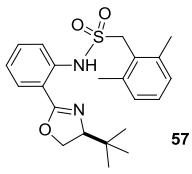
sec-OH, R^4 = R^5 = H,
up to 98% yield and 91% *ee*
sec-OH, R^4 = H, R^5 = Me, *E-isomer,*
up to 86% yield,
77:23 *anti:syn*, 82% *ee*, 90% *ee*



sec-OH, R^4 = R^5 = H,
up to 95% yield and 99% *ee*
sec-OH, R^4 = H, R^5 = Me, *E-isomer,*
up to 88% yield,
up to 10.3:1 *anti:syn*, 90% *ee*, 87% *ee*

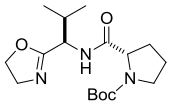


tert-OH, R^1 = Ar, R^2 = Alk, R^4 = R^5 = H,
up to 87% yield and 97% *ee*



57

sec-OH, R^1 = Alk, R^4 = R^5 = H,
up to 88% yield and 99% *ee*
sec-OH, R^1 = Alk, R^4 = H, R^5 = 2xMe,
up to 79% yield, 98% *ee*,
sec-OH, R^1 = Alk, R^4 = Me, R^5 = H,
up to 85% yield, 99% *ee*
sec-OH, R^1 = Alk, R^4 = halo, R^5 = H,
up to 85% yield, 99% *ee*



tert-OH, R^1 = Ar, R^2 = Alk, R^4 = R^5 = H,
up to 95% yield and 93% *ee*
tert-OH, R^4 = H, R^5 = Me, *E-isomer,*
69% yield,
3.8:1 *anti:syn*, 88% *ee*, 70% *ee*
sec-OH, R^4 = Me; R^5 = H,
73% yield, 91% *ee*

Figure 7

It is clear that many types of chiral architectures have been developed. It is worth mentioning bis-oxazoline ligands **56**. Both the isolated yield and the absolute configuration of the final homoallylic alcohol depended on the presence or absence of substituents in the oxazoline ring.[106–108] Kishi and co-workers also developed the sulfonamide-base scaffold which induced high levels of enantioselecectivity. With their first generation of chiral sulfonamides **55**, they introduced the use of a second metallic species which enhanced the rate of formation of the chromium-bromide complex.[109] The second generation of sulfonamides **57** presented the advantage of being easily recovered. Their crystallinity makes them rather convenient for large scale processes.[110]

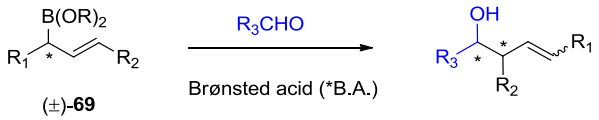
As seen in this chapter, allylation of carbonyl compounds has been a well-known methodology to achieve chiral homoallylic alcohols, amines and their derivatives for more than two decades. Due to the excellent control of the stereoselectivity, the product of the γ-allylation, resulting in branched products, has a defined stereochemistry, *E*-allylreagents give exclusively *anti* homoallylic adducts and *Z*-allylreagents give *syn* homoallylic adducts,

whereas α-allylation, resulting in linear products, does not happen. Excellent stereoselectivities are achieved using chiral auxiliaries or chiral catalytic systems as well as excellent yields for the target molecule. However, to achieve α-products, i.e. linear homoallylic adducts, secondary allylboron reagents are required. When enantiopure secondary allyl reagents are used, a mixture of *E:Z* homoallylic adducts are obtained, each of which has opposite absolute configuration.

2. KINETIC RESOLUTION

2.1. Aims and objectives

The aim of the present project is to establish a new and efficient methodology for kinetic resolution of chiral racemic α-substituted allylboronates (±)-**69** in the addition to aldehydes employing chiral Brønsted acid catalysis (Scheme 47).



Scheme 47

To achieve these aims, two converging objectives were set up 1) to develop a practical method for the synthesis of secondary allylboronates; 2) to develop chiral Brønsted acids capable of an efficient kinetic resolution of α-substituted allylboronates (±)-**69**.

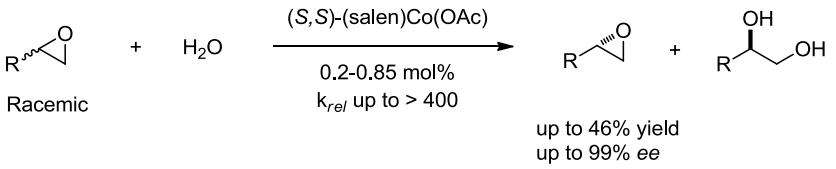
As the intended outcome of this project, it is hoped to develop a practical catalytic strategy allowing for the synthesis of highly enantio- and geometrically enriched homoallylic alcohols representing valuable building blocks for use in pharmaceutical and fine chemicals development.

2.2. Results and discussion

2.2.1 Brief overview of kinetic resolution methodologies.

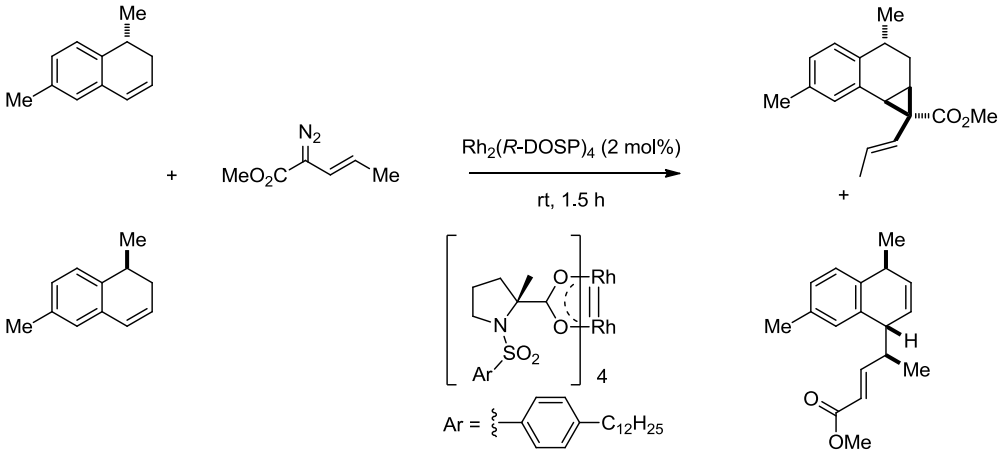
In modern synthesis, asymmetric catalysis remains the preferred method of introducing new stereogenic centres into the molecule and is the most widely used among total synthesis strategies. However, there are many instances where asymmetric methodology is either inadequate or the methods are not practical; therefore alternative techniques based on resolution of racemic mixtures still hold their value. In fact, resolution methods together with chiral pool processes take almost a 50% share of the industrial chiral technology. Desirable characteristics of all catalytic asymmetric reactions, such as high yield, short reaction times, scalability, low catalyst loading, inexpensive catalyst, minimal generation of waste, reproducibility, broad substrate scope and functional group compatibility are also important considerations in kinetic resolution

Kinetic resolution methods are used to resolve a racemic mixture of two enantiomers (*R*,*S*) aided by a chiral reagent or by the combination of an achiral reagent and a chiral catalyst in substoichiometric loading. The latter methods represent an advantage since they do not need stoichiometrical chiral reagents, hence being more economical. There are different methods to carry out kinetic resolution. In a classical kinetic resolution (CKR) one enantiomer of a racemic mixture is derivatised much faster than another, so ideally at 50% conversion, both the product and the starting substrate could be obtained in enantiomerically pure form. However, this is not always the case, and special care has to be taken in order to stop the reaction at the appropriate conversion values, so that the product or the substrate can be obtained in satisfactory enantiomeric excess (*ee*). In this case, while the more reactive enantiomer is being converted into the final product, the enantiopurity of the less reactive enantiomer increases (Scheme 48).



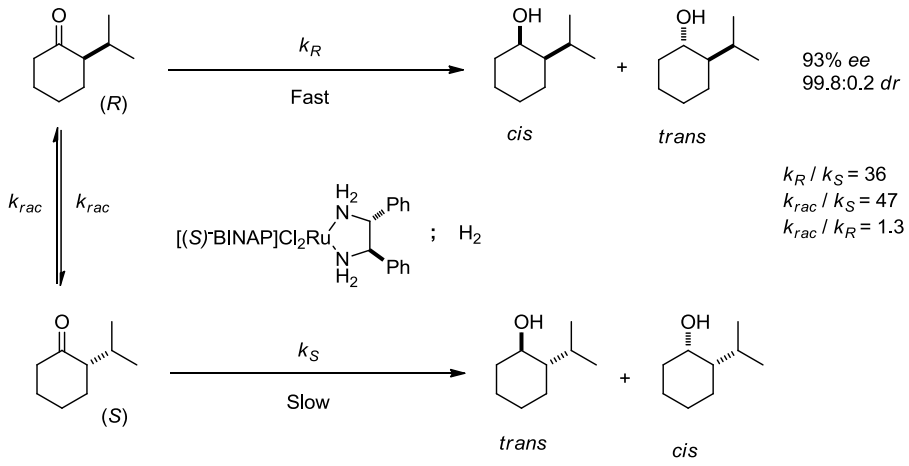
Scheme 48

A slightly different method is the parallel kinetic resolution (PKR) where both enantiomers react independently with similar reaction rate affording enantiomers of different final products (Scheme 49). Due to both enantiomers following different reaction pathways, the *ee* values are independent of each other, therefore both of them can be optimised separately.[111]



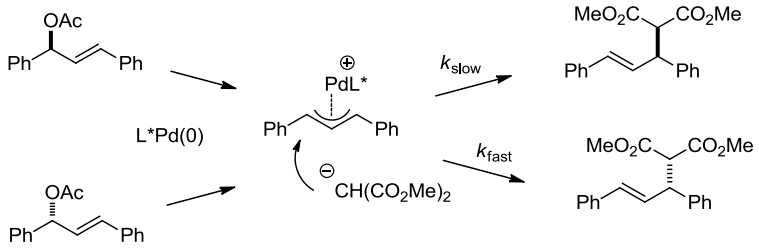
Scheme 49

A drawback of the strategies so far described is the low yield achieved for the target molecule. Since the reaction starts from a racemic mixture, the yield will not be higher than 50% based on the racemic mixture. To overcome this issue, many elegant processes have been designed that can transform both enantiomers of a racemic starting mixture into a single enantiopure product. Dynamic kinetic resolution (DKR), dynamic kinetic asymmetric transformation (DYKAT) or enantioconvergent processes (ECP) serve as the examples. The DKR couples a kinetic resolution with a rapid *in situ* racemization of the chiral substrate through an achiral intermediate or transition state. As the faster reacting enantiomer of the substrate is converted into the product in a stereoselective manner, the less reactive enantiomer is converted into the more reactive one through the racemization process (Scheme 50).[112]



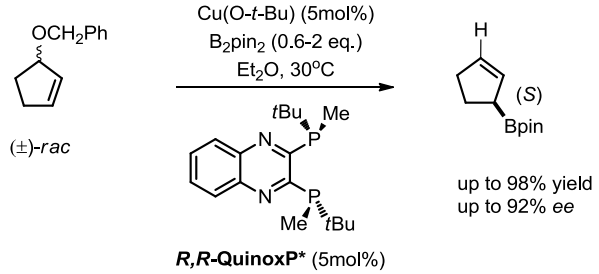
Scheme 50

In DYKAT strategies, both enantiomers of the mixture form a single intermediate losing the stereogenic centre, which then undergoes desymmetrization or epimerization in the course of the final product formation (Scheme 51).



Scheme 51

In the ECP, each enantiomer of the racemic mixture is converted into the same enantiomer of the product through different pathways (Scheme 52).[113] One pathway involves retention of the configuration of the stereogenic centre while the other involves inversion.



Scheme 52

Overall, the efficiency of a kinetic resolution is given by the relative rates of reaction of the substrate enantiomers (S_R and S_S) with the chiral catalyst (Cat_R) to generate the products

(P_R and P_S). Another descriptive parameter of the efficiency is the selectivity factor, *s*, which is related to the $\Delta\Delta G^{\ddagger}$, the free energy difference between the selectivity-determining diastereomeric transition states. These two parameters are used interchangeably (Figure 8).

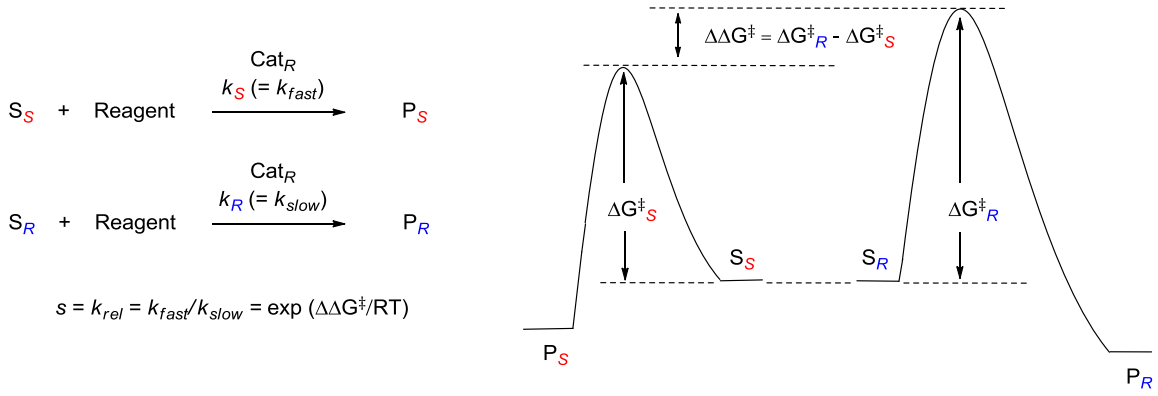


Figure 8

2.2.2 Brief overview of the synthesis of chiral α-substituted allylboronates

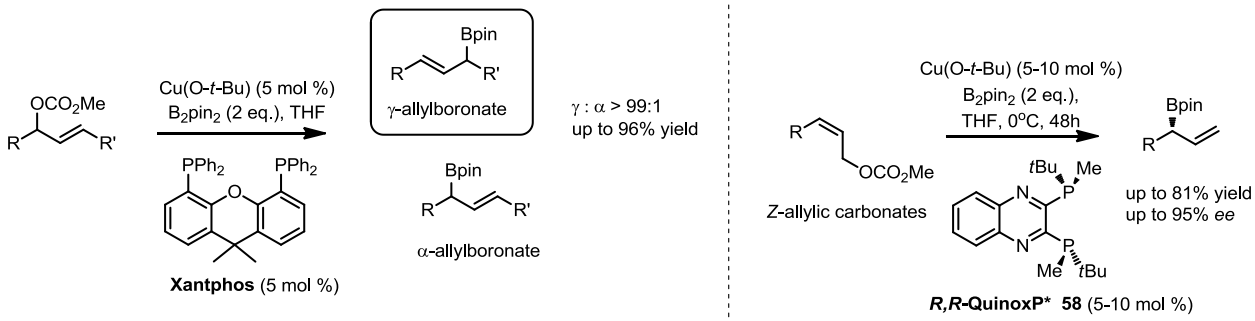
Organoboron compounds have attracted considerable attention in organic synthesis because C-B bonds can be converted into C-O, C-N, or C-C bonds in a stereospecific manner. Moreover, the presence of the allylic moiety makes α-substituted allylboron reagents appealing for total synthesis strategies. Chiral allylboron compounds are very versatile reagents for the synthesis of allylic alcohols, amines or new C-C bond formation. It can be achieved either via direct reaction of the C-B bond or by allyl transfer to carbonyl compounds. In fact, allylboronic ester derivatives are the most versatile and commonly used reagents for the allylation due to their relative stability to air and moisture, low toxicity and relatively low cost.

Methodologies for the synthesis of chiral α-substituted allylboronate reagents include both metal-free and metal-catalysed processes. It expands from the use of stoichiometric chiral auxiliary reagents to the application of catalytic methods including asymmetric hetero [4+2] cycloaddition mediated by Cr (III) catalyst;[114] 1,4-silaboration;[115] enantioselective Pd-catalysed diboration of allenes developed by Morken[116] and asymmetric allylic substitution of 3-chloropropenboronates using Grignard reagent.[117,118] Nucleophilic substitution of allylic carbonates with diboron compounds also played an important role as it provides an access to functionalised enantioenriched allylboronic esters. Owing to the similarities of the final products in all the methodologies listed above, this brief overview will be focused mainly on

Cu(I) catalysed S_N2' reactions developed by groups of Ito,[119,120] Hoveyda,[121] McQuade[122] and also Hall[117] independently. The use of metal-free chemistry developed by Pietruszka and Aggarwal towards the synthesis of chiral α-substituted allylboronate reagents will be explored separately.

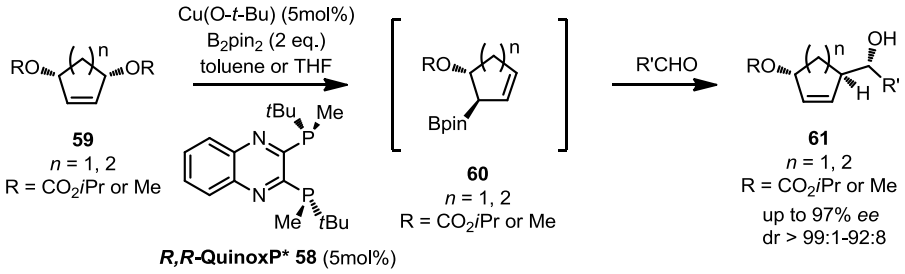
2.2.2.1 Metal catalysed synthesis of chiral α-substituted allylboronates

The γ-selective and stereospecific nucleophilic substitution of allyl carbonates was reported by Ito and co-workers using a catalytic system Cu(I)/achiral phosphine-type ligand (Xantphos) to afford the corresponding allylboronates in excellent yield and regioselectivity.[119] A few years later, the same group developed an enantioselective version of the reaction producing chiral α-substituted allylboronate reagents (Scheme 53).[120] They employed *R,R*-QuinoxP* ligand **58** to induce chirality into the final product. The corresponding allylboronates were obtained in good yields and excellent enantioselectivities.



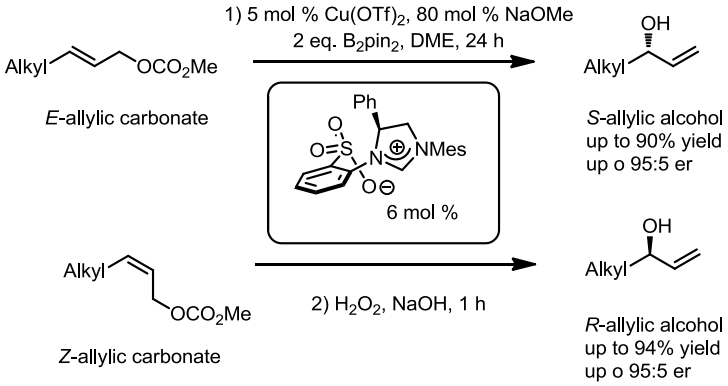
Scheme 53

Using this catalytic procedure, they also developed desymmetrisation of *meso* carbonates **59** to synthesise chiral α-substituted allylboronates **60**.[123] Although isolation of the corresponding chiral allylboronates proved difficult, the high stereoselectivity of the formation of the allylboron compounds was proven by one-pot allylation of various aromatic aldehydes to afford the corresponding homoallylic alcohols **61** with a high enantio- and diastereoselectivity (Scheme 54).



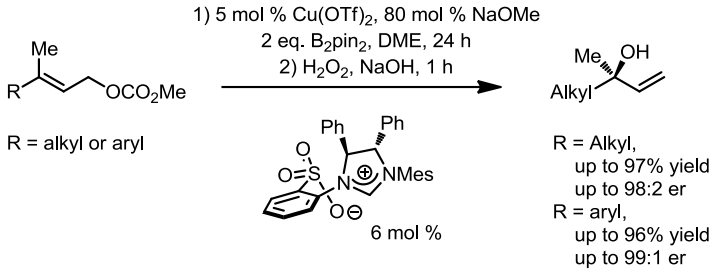
Scheme 54

The main drawback of the Ito's protocol for the synthesis of enantiopure acyclic α-substituted allylboronates was the dependency on the substrate structure; the reaction proceeded with a high level of selectivity only with *Z*-carbonates, whereas the use of *E*-isomers resulted in a drop in enantioselectivity from 94% to 44%, even though the yield improved (from 77% to 94%). In a further development, Hoveyda and co-workers broadened the scope of this reaction by using complexes of Cu(II) with bidentate N-heterocyclic carbene (NHC) as catalysts.[124] The allylboron compounds were not isolated but oxidised *in situ* to afford the corresponding secondary allylic alcohols in a stereospecific manner in excellent yields and enantiopurity (Scheme 55).



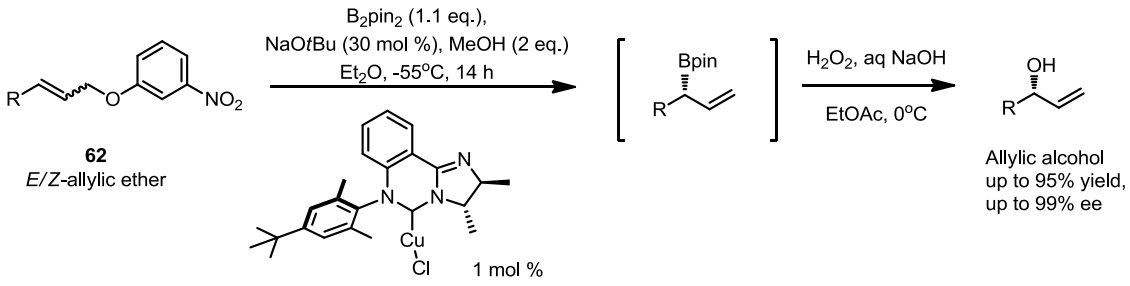
Scheme 55

With a slight modification to the bidentate NHC ligand, the reaction could also be applied to the synthesis of tertiary allylic alcohols in a high enantioselectivity and excellent yields (Scheme 56).



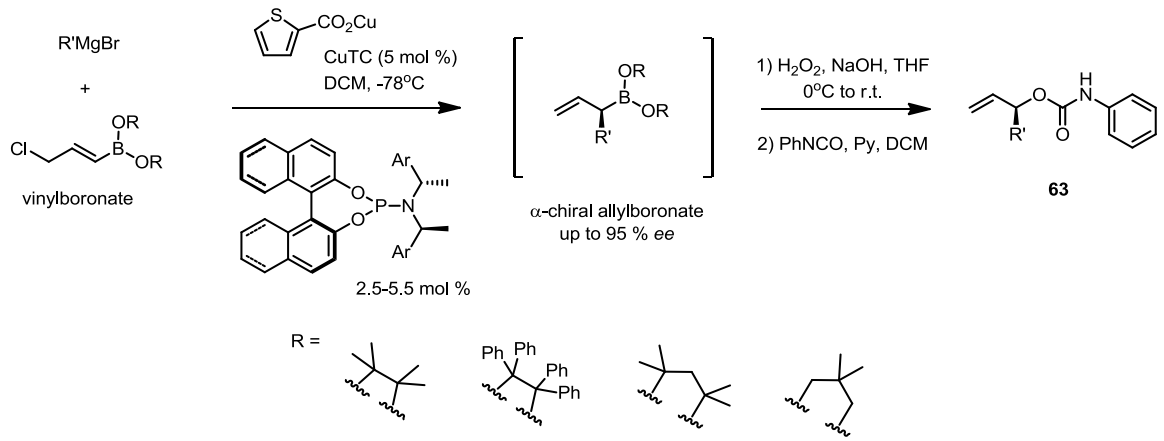
Scheme 56

Similar investigation was carried out by McQuade.[122] His group described a stereoconvergent process using a complex of Cu(I) with six-membered NHC ligand as catalyst for the nucleophilic substitution of allylic aryl ethers **62** (Scheme 57). Advantages of this methodology included lower loadings of B_2pin_2 (1.1 eq.) and catalyst (1 mol %) still providing high yield. Again, the excellent enantioselectivity of the reaction was established by oxidising the resulting boronates to the corresponding allylic alcohols.



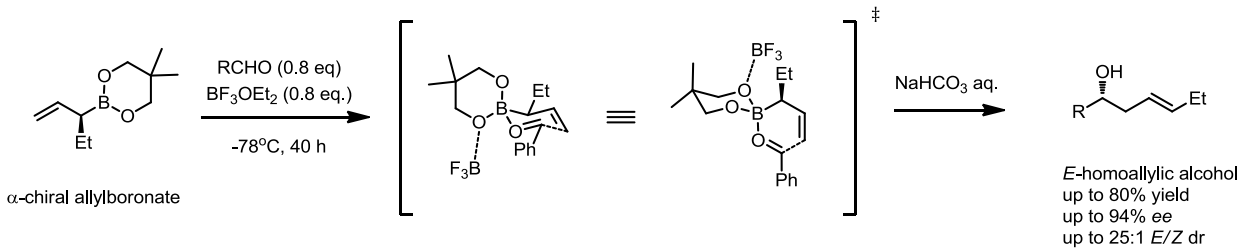
Scheme 57

In line with allylic substitution catalysed by Cu(I) chiral complexes, Hall reported the alkylation of 3-chloropropenylboronates affording chiral α-substituted allylboronates.[117] Due to the instability of this family of organoboron compounds on silica gel, the enantioselectivity of the allylboronate was determined, in this case, on the isocyanate derivative **63**. Screening of chiral phosphoramidate ligands and different boronic acid groups was carried out to optimise the reaction conditions (Scheme 58).



Scheme 58

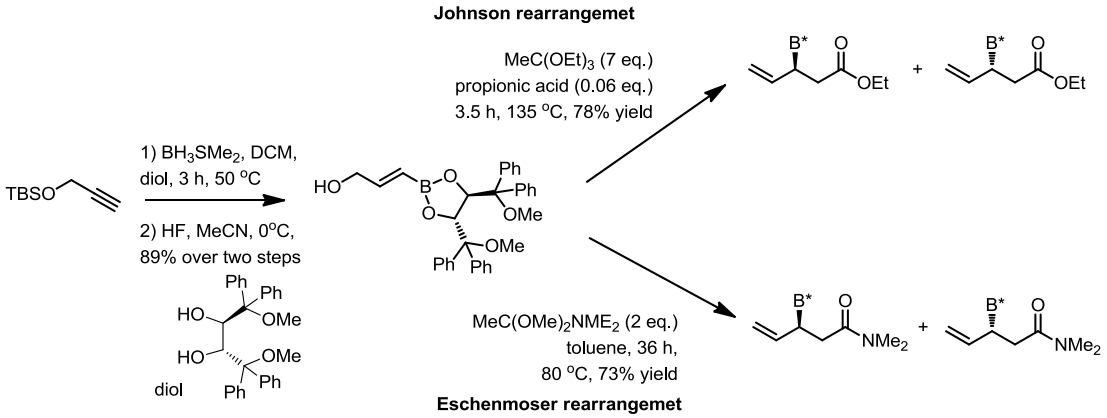
Subsequently, they developed a one-pot procedure for the stereoselective allylation of aldehydes based on the synthesis of chiral α-substituted allylboronate presented above. The excellent chirality transfer in the allylation reaction produced the target homoallylic alcohols in excellent overall selectivity (Scheme 59).



Scheme 59

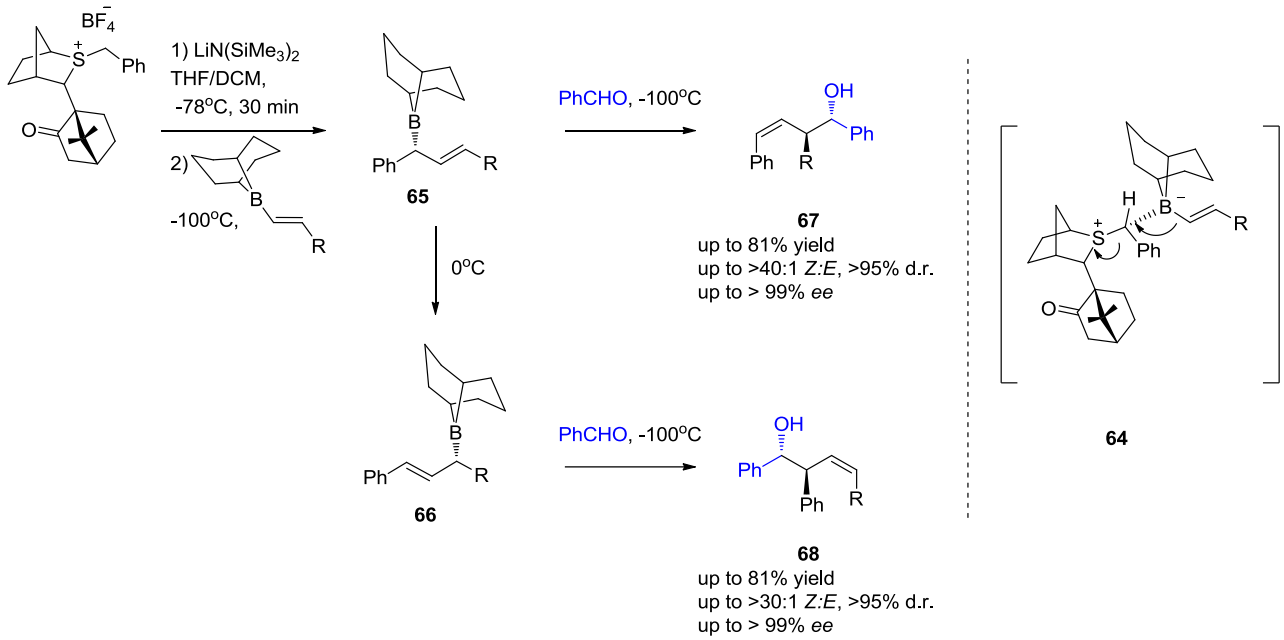
2.2.2.2 Metal free synthesis of α-substituted chiral allylboronates

The use of chiral secondary allylboronates modified by chiral boronic esters was extensively studied by Pietruszka and co-workers.[86] They focused on the synthesis of enantiopure *Z*-homoallylic alcohols which proved to be a challenge. Since the allylation with allylboronates proceeds through a well-defined transition state (Scheme 39), *Z*-selectivity would be enhanced by increasing the bulk of the boronic ester and/or the use of an electron-withdrawing group. They synthesised enantiopure secondary allylboronates from readily available propargyl alcohols through [3,3]-sigmatropic rearrangement using a chiral boronic ester group (Scheme 60).



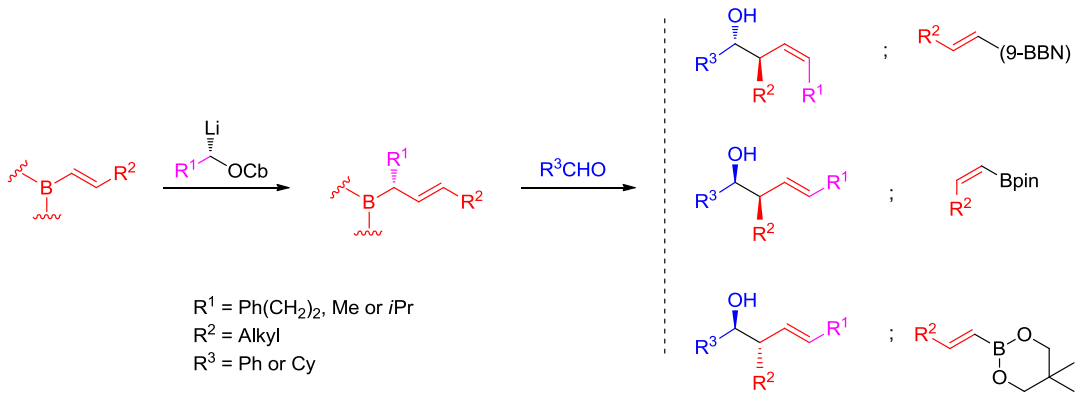
Scheme 60

Another interesting approach to chiral α-substituted allylboron reagents was reported by Aggarwal and co-workers.[125] The target optically active boranes were obtained upon reacting chiral sulfur ylides with vinyl boranes at low temperature (Scheme 60). The absolute stereochemistry of the allylborane is determined by the sulfur ylide configuration (**64**, Scheme 61). The subsequent stereospefic 1,2-migration of the vinyl group yielded the corresponding allylborane. The kinetic allylborane **65** can undergo a 1,3-borotropic rearrangement to its isomer **66**. Both allylboranes proved excellent allylating reagents yielding structural isomeric homoallylic alcohols **67** and **68** upon addition to benzaldehyde (Scheme 61).



Scheme 61

A more recent work published by Aggarwal and co-workers described the synthesis of highly diastereomerically enriched homoallylic alcohols where stereoselectivity was controlled by choosing the appropriate reaction conditions.[126] They developed elegant strategies for the synthesis of α-substituted allylboron reagents *via* lithiated carbamates focusing on minimizing both the $A^{1,3}$ strains and the steric hindrance between the equatorial substituent and the boron moiety in the transition state. Thus, by tuning the non-vinyl substituents on the boron atom and the geometry of the vinyl group, a selection of homoallylic alcohols with different relative stereochemistry were obtained in >95:5 e.r. and >98:2 d.r. in all cases (Scheme 62).

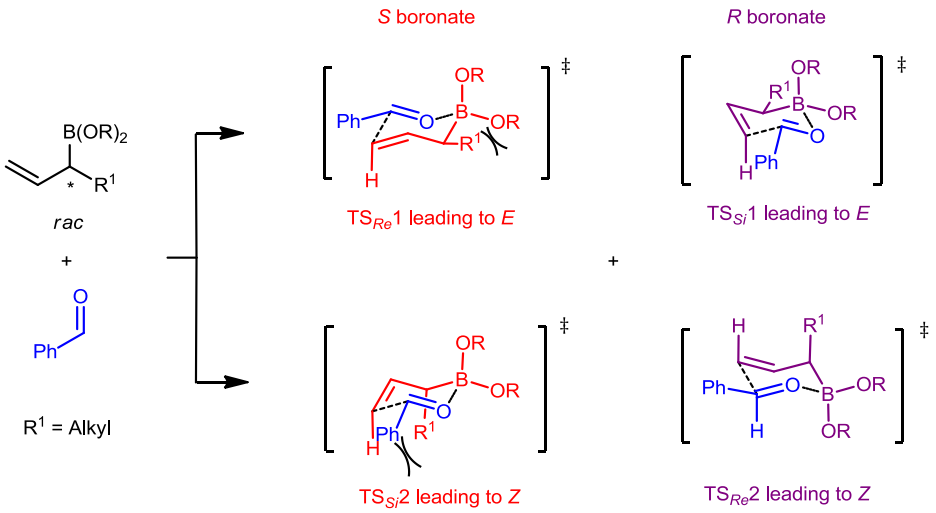


Scheme 62

2.2.3 Kinetic resolution of secondary allylboronates. Theoretical studies

2.2.3.1 Theoretical modelling of the reaction

It has been demonstrated that addition of enantiomerically enriched α-substituted allylboronates to achiral aldehydes proceeds with a near perfect transfer of chirality, so-called substrate controlled allylation. The addition produces a mixture of geometrical isomers of opposite stereochemistry at the carbinol centre (Scheme 39). However, if a racemic mixture of α-substituted allylboronate is used instead four stereoisomeric transition states are possible, leading to a mixture of four stereoisomeric homoallylic alcohols (Scheme 63).



Scheme 63

In order to perform a kinetic resolution, three essential factors have to be taken into account: 1) the enantiofacial selectivity in the addition of the allylic group to aldehyde; 2) selective recognition/differentiation of the enantiomers of the allylboronate and 3) the structure of the boronic ester. Chiral Brønsted acid catalyst was chosen as external controller to address the first issue, whereas the second will rely on the pseudo axial/equatorial preference of the α-alkyl group, which can be analysed in terms of steric effects. In both **TS1** and **TS2**, unfavourable steric interactions are present. The non-bonding 1,2-interactions between the pseudo-equatorial α-alkyl and the boronic ester in $\mathbf{TS_{Re}1}$ (or $\mathbf{TS_{Si}1}$, Scheme 63) have a detrimental effect, whereas in $\mathbf{TS_{Si}2}$ (or $\mathbf{TS_{Re}2}$, Scheme 63) it is the unfavourable $A^{1,3}$ strain between the pseudo-axial α-alkyl and the pseudo-axial olefinic hydrogen. Therefore, when bulky boronic esters are used, *Z* homoallylic alcohols are expected to modestly predominate

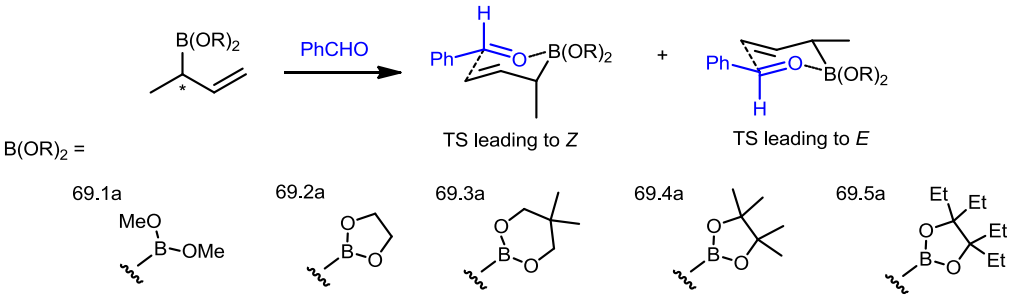
among the final reaction products. Hence, the larger the ester group, the more preference for *Z*-homoallylic alcohol.

To increase the geometrical selectivity, preference for a certain transition state can be enhanced by changing either the boronic ester fragment or the α-alkyl substituent. In this respect, the reaction was modelled using quantum chemical computations to assist and facilitate the bench chemistry. DFT level calculations were accomplished to elucidate the influence of the steric size of the cyclic boronate moiety on the *E/Z* ratio of the resulting homoallylic alcohols. The initial calculations were performed at B3LYP/6-311+g(d,p) level of theory. Solvation of the system was taken into account using the implicit polarisable continuum model using toluene as the reaction solvent; while the intrinsic reaction coordinates (IRC) analysis was performed to unambiguously assign the transition states of the reaction pathway. Theoretically predicted diastereomeric ratios were calculated from the corresponding relative free Gibbs energies using Arrhenius approximation,

$$\frac{k(Z)}{k(E)} = exp^{\left(\frac{\Delta G\ddagger(Z) - \Delta G\ddagger(E)}{RT}\right)}$$

where **ΔG‡** values are expressed in kcal mol^{-1}; **R** is the ideal gas constant expressed in kcal K^{-1} mol^{-1} (1.98 10^{-3} kcal K^{-1} mol^{-1}), **T** is the temperature expressed in Kelvin (298 K). First, the non-catalysed reaction was modelled in order to obtain optimised structures.

The first case study was the addition of α-methyl substituted allylboronates with a range of different boronic esters moieties to benzaldehyde under non-catalysed conditions (Scheme 64). The results in Table 1 show that the bulkier the boronic ester moiety is the more preferred the pathway leading to the formation of *Z* isomer. This outcome agrees with the rational explanation of the increased steric interactions between the pseudo-equatorial *α*-alkyl and the boronic ester residue in **TS$_{Si}$1** (or **TS$_{Re}$1**, Scheme 63). These data follow the same trend of the experimental results reported by Hoffmann in 1980.[127]



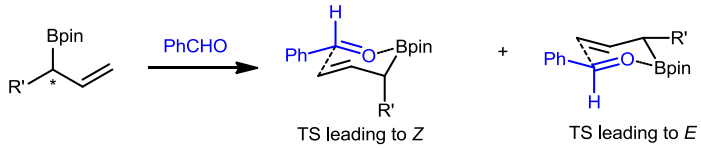
Scheme 64

Table 1. Activation energies (**ΔG)** for both transition states.

	TS_69.1a	**TS_69.2a**	**TS_69.3a**	**TS_69.4a**	**TS_69.5a**
ΔG_Z[a]	26.91	30.2	26.14	32.18	35.7
ΔG_E[a]	24.17	29.56	26.29	32.89	37.41
d.r.[b] **(*Z*:*E*)**	1:88	1:3	1:1	3:1	18:1
d.r.[c] **(*Z*:*E*)**	24:76	49:51	n.r.[d]	69:31	n.r.[d]

[a] Values given in kcal/mol; [b] predicted; [c] values reported by Hoffmann: [d] not reported

Investigation of the influence of different α-substituents was carried out with boronic acid pinacol ester **69.4a** taking into account the ease of synthesis[128] of the respective allylboronates **69.4b-d** (scheme 65).



69.4b : R' = CH_2CH_3
69.4c : R' = $CH(CH_3)_2$
69.4d : R' = $CH_2CH_2CH_3$

Scheme 65

Table 2. Activation energies (**ΔG)** for the isomeric transition states.

	TS_69.4b	**TS_69.4c**	**TS_69.4d**
ΔG*Z*a	29.57	31.79	30.51
ΔG*E*a	30.17	32.41	32.24
d.r.[b] (Z:E)	3:1	3:1	19:1
d.r.[c] (*Z*:*E*)	n.r.[d]	79:21	n.r. [d]

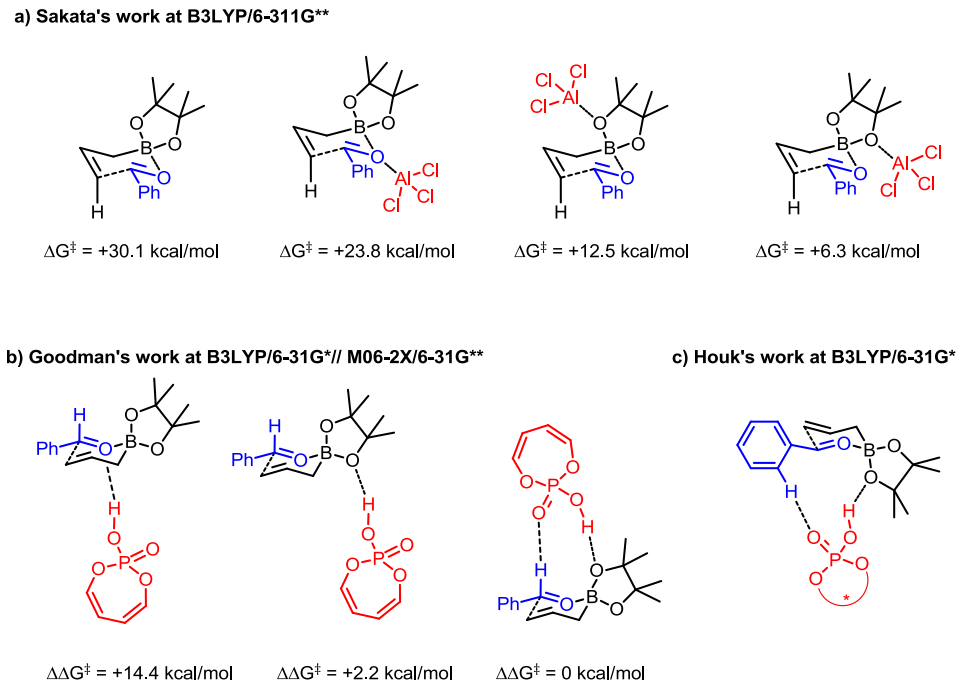
[a] Values given in kcal/mol; [b] predicted; [c] values reported by Hoffmann; [d] not reported

Computational data (Table 2) revealed the same tendency as described for the boronic ester group: the larger the α-substituent, the higher the preference for the Z isomer. The $A^{1,3}$ strain between the pseudo-axial α-alkyl group and the pseudo-axial olefinic proton is less disfavoured over the 1,2-interaction between the pseudo-equatorial α-alkyl group and the boronic ester. This difference grows with increase in size of the α-group.

2.2.3.2Computational insight into the reaction mechanism.

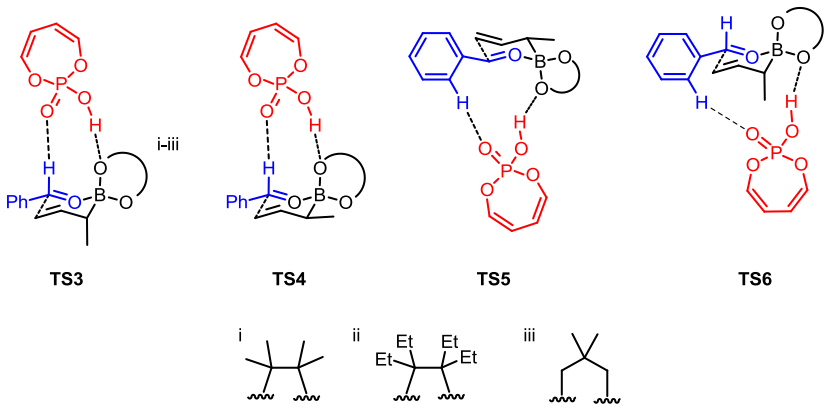
In the Brønsted acid catalysed allylation of aldehydes with allylboronates, protonation can take place at either of the oxygen atoms of the boronate fragment, as well as at the carbonyl oxygen of the aldehyde. Theoretical studies published by Sakata and Fujimoto revealed that Lewis acid catalysis of the reaction occurs through coordination on the pseudo-equatorial oxygen of the boronate (scheme 66a).[129] On the other hand computational investigation on the asymmetric allylboration of aldehydes catalysed by Brønsted acids, recently published by Goodman and co-workers,[130] revealed that a double activation mode is preferred over the classical single-point coordination (scheme 66b). They claimed the stabilisation will arise from the H-bonding interaction between the phosphoryl oxygen and the

formyl hydrogen of the aldehyde. Moreover, Houk, in collaboration with Antilla,[131] reported the existence of H-bonding interactions between the phosphoryl oxygen and the *ortho* aromatic proton of the aldehyde, which also plays an important role in the reaction pathway (scheme 66c).



Scheme 66

Since the present work relies on the chiral Brønsted acid catalysis, both Houk's and Goodman's findings were adopted to investigate how the additional interactions between the phosphoryl oxygen of the catalyst and the formyl hydrogen of the aldehyde (**TS3** and **TS4**, Scheme 67) or the *ortho*-hydrogen of the aromatic group (**TS5** and **TS6**, Scheme 67) will influence the selectivity of the kinetic resolution of racemic secondary allylboronates. DFT calculations of the catalytic system were carried out at a high level of theory (TPSSh/cc-pVTZ) using the implicit polarisable continuum model to implement solvation in toluene. In order to save computational time and resources, the BINOL-derived chiral phosphoric acid was initially mimicked as its butadiene analogue. The computations were performed on three different boronic ester groups, i) pinacol; ii) tetraethylethylengycol and iii) 2,2-dimethyl-1,3-propandiol (scheme 67), all *sec*-butenyl derivatives (α-methyl allylboronates).



Scheme 67

Table 3

ΔG‡ (kcal/mol)[a]	TS3 (*Z*)	TS4 (*E*)	TS5 (*E*)	TS6 (*Z*)
i	15.4	15.7	16.4	16.4
ii	18.1	20.5	20.4	20.4
iii	12.9	11.9	12.8	14.4

[a] Predicted values calculated at 233 K

The calculations summarised in Table 3 revealed a general trend: in all three boronic esters, the two-point activation mode described by Goodman is generally more favoured for both transition states, leading to *Z* and *E*-isomer compared to the Houk mode. Also, a clear trend emerged showing that the larger the steric bulk of the boronate, the higher the preference for the formation of *Z*-isomer (ii > i > iii), mirroring the results of the non-catalysed studies. It is worth noting that 2.4 kcal/mol difference between **TS3-ii** and **TS4-ii** predicted a highly enhanced ~100:1 *Z/E* ratio for the tetraethylethylenglycol (Epin) derivative, whereas 2,2-dimethyl-1,3-propandiol (iii) should favour *E*-isomer.

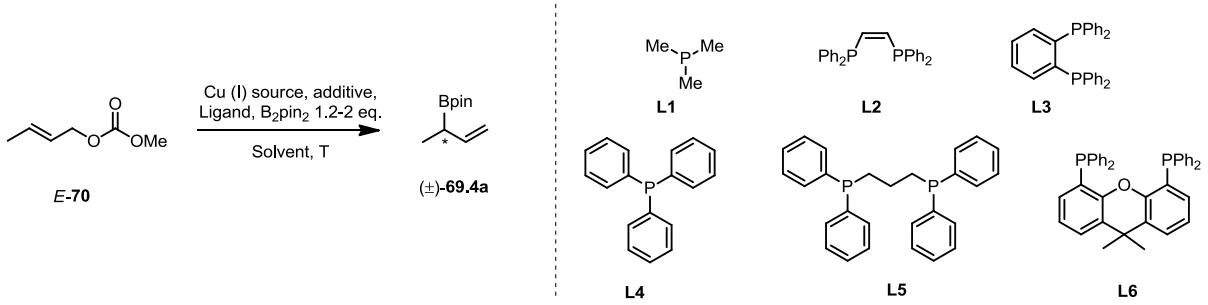
2.2.4 Experimental studies.

2.2.4.1 Synthesis of α-substituted allylboronic esters.

Taking into account the outcome of the theoretical calculations performed on the allylboration of aldehydes, synthesis of different allylboronates was carried out. Several methods were examined to find the most practical, reliable and applicable to a wide substrate scope.

The synthesis of racemic secondary allylboronate **69.4a** was first tackled *via* a catalytic nucleophilic substitution of the methyl carbonate derivative of crotyl alcohol (**70**) using Cu-phosphine complex and bis(pinacolato)diboron (B_2pin_2). The reaction was examined by varying both Cu sources and ligands. The Table 4 summarises the screened reaction conditions.

Table 4



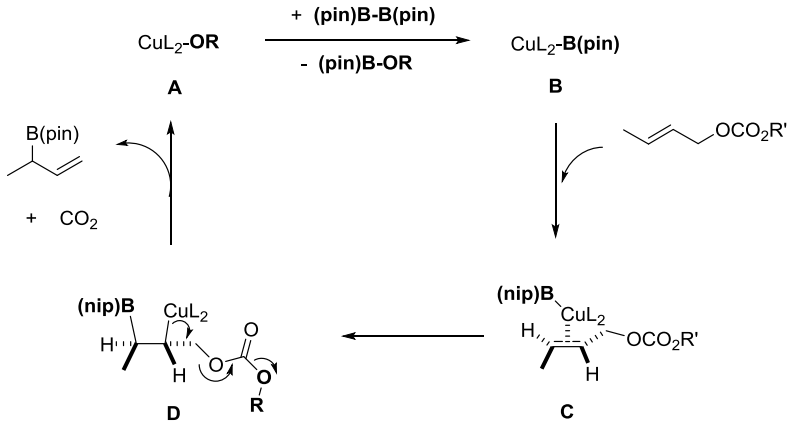
Entry	Cu(I) salt	Ligand	Solvent	Additive	T	Conversion[a]
1	CuCl (5%)	L4 (5%)	THF	None	r.t.	0
2	CuCl (15%)	L1 (10%)	THF	KO^{t}Bu (10%)	r.t.	0
3	CuCl (20%)	L2 (5%)	THF	KO^{t}Bu (20%)	30 °C	100
4	CuCl (10%)	L3 (5%)	Et_2O	KO^{t}Bu (10%)	30 °C	<10
5	CuI (20%)	L5 (20%)	THF	KO^{t}Bu (100%)	r.t.	100 (6)[b]
6[c]	CuI (5%)	L6 (5%)	THF	KO^{t}Bu (20%)	r.t.	30

[a] analysed by the 1H NMR of the reaction mixture; [b] isolated yield in parenthesis; [c] carbonate added after 1h stirring.

The reaction was carried out using a 1:1 or 2:1 Cu/ligand ration (for bidentate and monodentate ligands, respectively). Potassium *tert*-butoxide emerged as an optimal additional base to form the Cu complex, after screening several other alkoxide additives such as sodium methoxide and sodium *tert*-butoxide. Several types of phosphine ligand were screened, mainly the bidentate ligands with a different tether length (entries 5 and 6). Also, a more rigid 1,2-bis(diphenylphosphino)benzene phosphine was synthesised following the literature procedure[132] and tested in the nucleophilic substitution (entry 4).

The proposed[120] reaction mechanism suggests that initial addition of the diboron reagent across the Cu-OR bond forms the intermediate **B**, which subsequently gives a Cu-

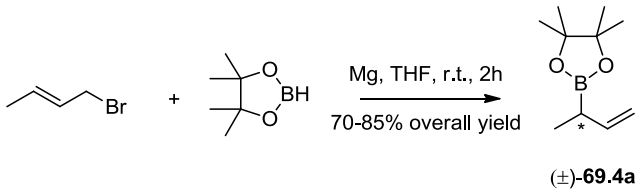
alkene π-complex **C** prior to the addition across the double bond forming β-borylalkylcopper intermediate **D**. This intermediate eliminates CO_2, which is the major driving force of the reaction, releasing the target allylboronate and regenerates the starting copper alkoxide complex **A** (Scheme 68).



Scheme 68

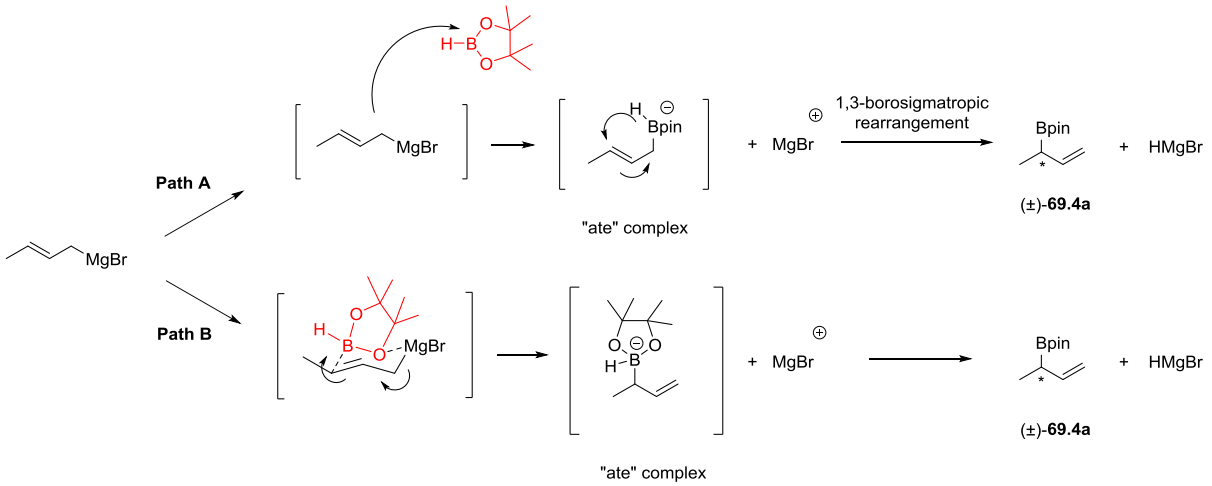
The results shown in Table 4 indicate that despite considerable efforts, suitable reaction conditions could not be found to form secondary boronate (±)-**69.4a** in satisfactory yields. Although all the necessary precautions were taken while performing the above reaction, the lack of success could be explained by two main factors: 1) the instability of the target allylboronate under acidic conditions, including silica gel that was used to purify the crude product; and 2) adventitious traces of air and moisture in the reaction media that could inhibit the activity of the highly air- and moisture sensitive catalyst species. Therefore, attention turned to other processes.

Following the recent report in the literature,[128] the focus now shifted to the addition of boranes to the corresponding allyl bromides under Barbier type conditions. For the synthesis of (±)-**69.4a**, technical grade crotyl bromide was added to a solution of commercially available pinacolborane in dry THF in the presence of Mg turnings at room temperature (Scheme 69). After a period of two hours, the reaction gave rise to the target compound, which was distilled under reduced pressure and obtained as pure colorless oil.



Scheme 69

Scheme 70 presents two possible routes for the reaction, both of them initiated by the formation of the corresponding Grignard reagent. Path **A** relies on the nucleophilic attack of the aliphatic carbanion onto the borane forming a primary "ate" complex with a subsequent suprafacial 1,3-borotropic rearrangement yielding the target product and HMgBr. This mechanism was originally proposed by Singaram and co-workers.[128] However, in an alternative route, a possible coordination of Lewis acidic Mg to the Lewis basic oxygen of the borane can be envisioned. This might facilitate the allylic addition of the Grignard reagent to the boron atom through a six-membered transition state delivering the secondary "ate" complex. Hydride elimination affords the target allylboronate along with HMrBr (Path **B**).

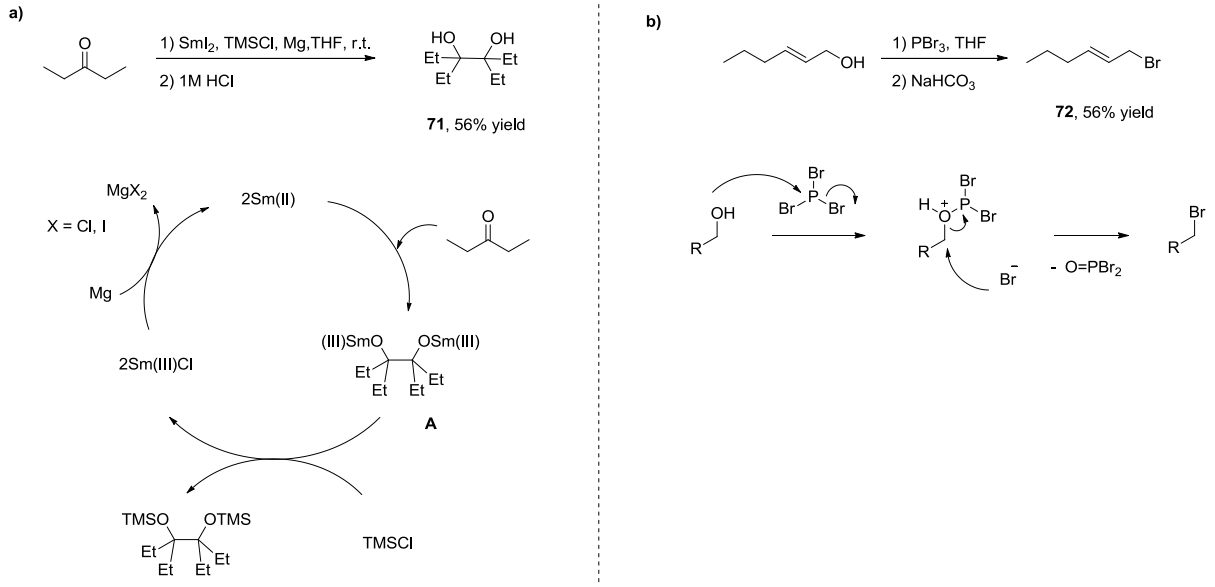


Scheme 70

Compared to the metal-catalysed S_N2' reaction, the main advantage of this synthesis of allylboronates is its applicability to a wide range of allyl bromides and boranes. To obtain a set of α-substituted allylboronates, synthesis of 1-bromohex-2-ene and tetraethylethylene glycol, that were not commercially available, was carried out following literature protocols.

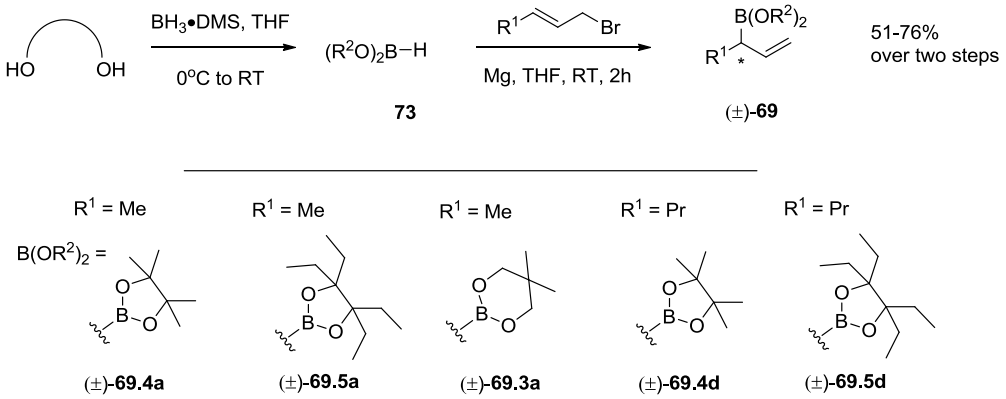
The bulky diol tetraethylethylene glycol **71** was synthesised by pinacol coupling of 3-pentanone in the presence of catalytic amounts of SmI_2.[133] In the catalytic cycle (Scheme 71a),

the initially formed Sm(III) alkoxide **A** was converted by TMSCl into the silyl enol ether releasing $SmClI_2$, which was reduced by Mg turnings to Sm(II). Deprotection of the silyl enol ether under acidic conditions yielded the corresponding diol (Scheme 71a). The longer alkyl chain analogue, 1-bromohex-2-ene **72**, was synthesised from the corresponding alcohol by treatment with PBr_3 in THF through a typical S_N2 mechanism (Scheme 71b).[134]



Scheme 71

Once all the precursors were ready, a set of 5 different allylboronates could be synthesised following the one-pot reaction sequence shown in Scheme 72. Treatment of the corresponding diol with BH_3•DMS in THF delivered the target borane.[135] The borane **73** was reacted with the appropriate allyl bromide under Barbier-type conditions to produce the final allylboronates (±)-**69** in moderate to good yields.

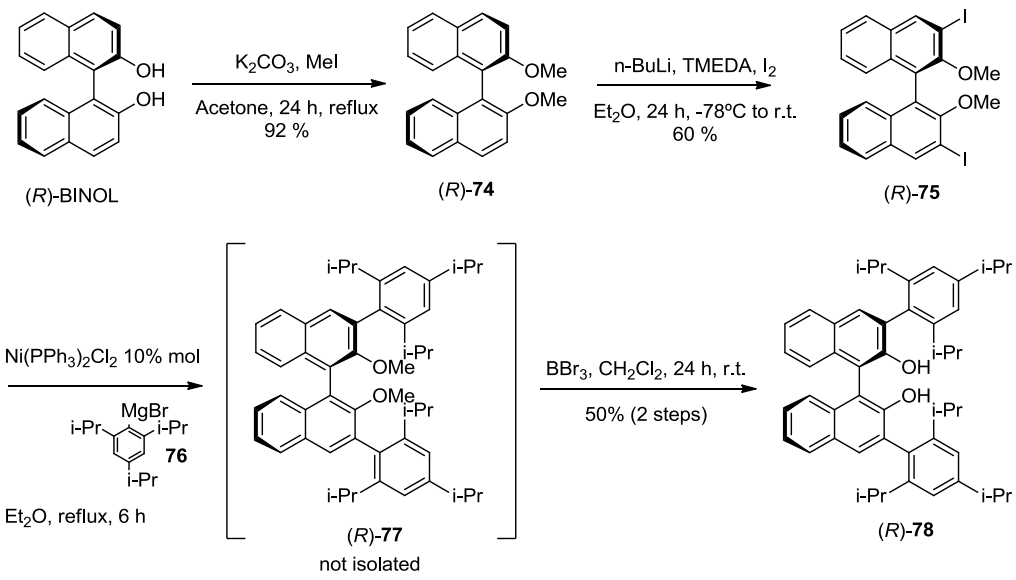


Scheme 72

2.2.4.2 Synthesis of chiral Brønsted acids BINOL-derivatives.

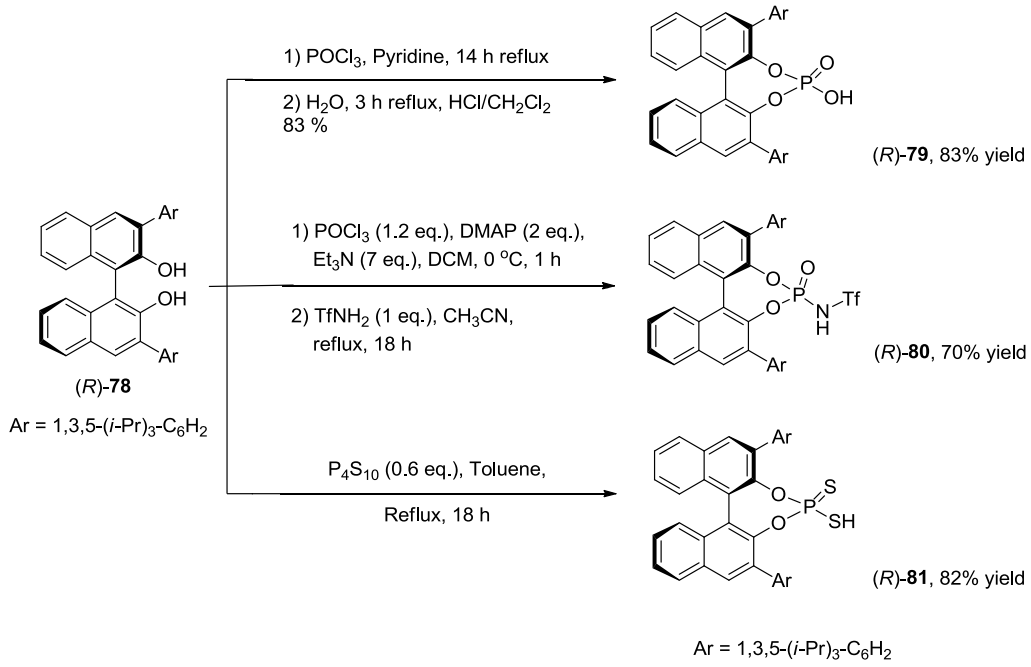
In their pioneering work Terada[136] and Akiyama,[137] independently reported on the use of BINOL-derived phosphoric acids as efficient chiral Brønsted acid catalysts. Since then this area of organocatalysis experienced an explosive development and a vast number of stereoselective reactions have been carried out under chiral Brønsted acids catalysis, including the earlier mentioned allylboration of aldehydes by Antilla and Hu.[52,53] Therefore for kinetic resolution of racemic secondary allylboronates in the allylation of carbonyl compounds, chiral Brønsted acid catalysis, specifically the BINOL-derived phosphoric acid (*R*)-TRIP, was chosen. Due to the high cost of the commercial reagent, the catalysts were synthesised in laboratory.

The synthesis was accomplished in a 23% overall yield following the procedure published by List.[138] However, a slight variation in the functionalization of the 3,3'-positions was needed to improve the yield in this step (Scheme 73). (*R*)-BINOL was protected by methylation upon treatment with potassium carbonate and methyl iodide in refluxing acetone yielding compound (*R*)-**74** in 92% yield. Iodination in 3,3' position yielded precursor (*R*)-**75** (60%), which was submitted to the Ni-catalysed Kumada coupling with (2,4,6-triisopropylphenyl)magnesium bromide **76** leading to compound (*R*)-**77**. Cleavage of the protecting group using BBr_3 led to compound (*R*)-**78** which was obtained in 50% yield over two steps.



Scheme 73

Synthesis of (*R*)-TRIP **79** was completed by treating diol (*R*)-**78** with phosphoryl oxychloride in refluxing pyridine for 14 h followed by subsequent hydrolysis by refluxing in water for 3 h (Scheme 74). Two other chiral Brønsted acids were synthesised alongside (*R*)-TRIP **79** to test their activity in the kinetic resolution. (*R*)-*N*-Triflyl phosphoramide **80** was obtained upon treatment of the phosphorylated chiral binaphthol (*R*)-**78** with trifluoromethansulfonamide in CH_3CN under reflux for 18 h in 70% yield after purification (Scheme 74).[139] (*R*)-Thio-TRIP was prepared by treating (*R*)-**78** with P_4S_{10} in toluene under reflux for 24 h in 82% yield (Scheme 74).[140]

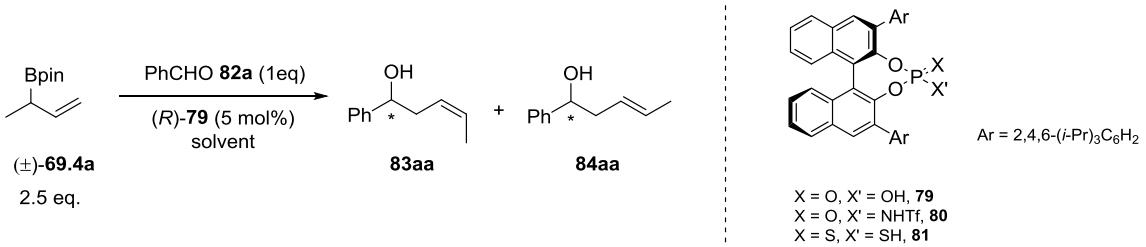


Scheme 74

The last two chiral acids (*R*)-**80** and (*R*)-**81** are stronger acids compared to the oxo-analogue (*R*)-**79**. The presence of the strongly electron-withdrawing *N*-trifluoromethanesulfonyl group in (*R*)-**80** enhances acidity of the N-H bond. In the case of the phosphorodithionic acid (*R*)-**81**, the higher acidity can be explained by a possible delocalisation of the negative charge onto the vacant *d* orbitals of the sulfur atom, which is not possible in the case of the phosphoric acid (*R*)-**79**.

2.2.4.3 Optimisation of the reaction conditions

Addition of allylboronate (±)-**69.4a** to benzaldehyde was chosen as the model reaction. First, optimisation of the reaction conditions for the kinetic resolution included testing the set of the three different Brønsted acids at 5 mol% loading, anhydrous solvents at concentration of 0.23M and the reaction temperature. The allylboronate (±)-**69.4a** was used in 2.5-fold excess (Scheme 75).



Scheme 75

Optimisation of solvent, temperature and chiral catalyst.

The preliminary results of the first steps towards the optimised reaction conditions are summarised in Table 5.

Table 5

Entry[a]	Brønsted acid	Svt.	T, °C	Reaction time	d.r. (*83aa:84aa*)[b]	*ee* (*83aa:84aa*)[c]
1	(*R*)-**79**	Tol	r.t	18 h	67:33	60:91
2	(*R*)-**79**	Tol	–30	18 h	75:25	91:97
3	(*R*)-**79**	Tol	–78	18 h	75:25	66:92
4	(*R*)-**79**	THF	–78	18 h	67:33	3:10
5	(*R*)-**79**	DCM	–78	18 h	71:29	44:71
6[d]	(*R*)-**79**	Tol	–30	72 h	ND	91:97
7	(*R*)-**80**	Tol	–30	1 h	86:14	54:64
8	(*R*)-**81**	Tol	–30	18 h	67:33	0:2

[a] full conversion based on benzaldehyde was observed in all case otherwise stated; [b] d.r. (%) was taken from ^{1}H NMR of the crude reaction mixture; [c] ee (%) were determined by chiral HPLC; [d] recrystallised (*R*)-TRIP was used

Initially the reaction was carried out at room temperature using (*R*)-**79** in toluene as a solvent. The alcohols *Z*-**83aa** and *E*-**84aa** were obtained in 60% and 91% enantioselectivity, respectively, with diastereomeric ratio of 67:33 (entry 1), close to that predicted by calculations (3:1, Table 1). Seeking to boost the efficiency of the process, the next reaction was performed at –30 °C. The reaction reached full conversion in 18 h, bringing improvement in enantioselectivity for the *Z* isomer and a slight increase in diastereoselectivity (entry 2). At –78

°C the reaction was also completed in 18 h but, rather surprisingly, *ee* of the *Z* isomer dropped to the level achieved at room temperature, while the d.r. was maintained at 75:25 (entry 3). The influence of the solvent was studied next by increasing the polarity of the reaction media. THF and DCM were used at −78 °C, but both provided lower enantioselectivities, especially THF (entries 4 and 5). These results are in agreement with the findings of Antilla,[52] who reported a drop in enantioselectivity as the polarity of the solvent increased.

Next, the inconsistencies in the stereoselectivities obtained at −30 °C and −78 °C were investigated. From the energetic point of view and according to transition state theory, the lower the temperature of the reaction, the slower it will proceed. Thus, running the reaction in toluene at −30 °C, further control experiments were carried out in order to 1) shed light on the apparent inconsistency and 2) exclude the possibility of any artefact being responsible for the high enantioselectivity and ensure the reproducibility of the reaction. Unfortunately, all the attempts failed to deliver consistent and reproducible results giving a wide variation in the enantioselectivities and the reaction times. Luckily, the geometrical selectivity was kept at the same level. Careful analysis of the experimental data led to the conclusion that the observed irreproducibility might be caused by 1) an early quench of the reaction whereby the uncatalysed reaction may take place during the work-up; 2) traces of HCl remaining in the (*R*)-**79** after the synthesis competing with the chiral catalyst. The unconsumed benzaldehyde could react during the work-up procedure in an uncatalysed fashion, thus lowering the enantioselectivity. Monitoring the reaction by TLC gives only a qualitative assessment of the reaction course as both reagents, aldehyde and allylboronate, can react on silica, so based on the TLC data, the reaction might be stopped at different conversion stages. Hydrochloric acid may also play a detrimental role in the catalysed reaction. It is reasonable to assume that HCl would accelerate the background reaction thus also decreasing the level of enantioselectivity. It is worth noting that in the initial optimisation trials, a non-purified batch of (*R*)-TRIP **79** (a pale brown solid) was employed. However, in the protocol by List,[138] recrystallization of the final product was recommended to remove impurities that may influence the catalytic activity of (*R*)-**79**. In the ^{1}H NMR spectrum ($CDCl_3$) of the crude product, significant differences in the signals corresponding to the isopropyl CH groups were observed (Figure 9, **A** and **B**, respectively).

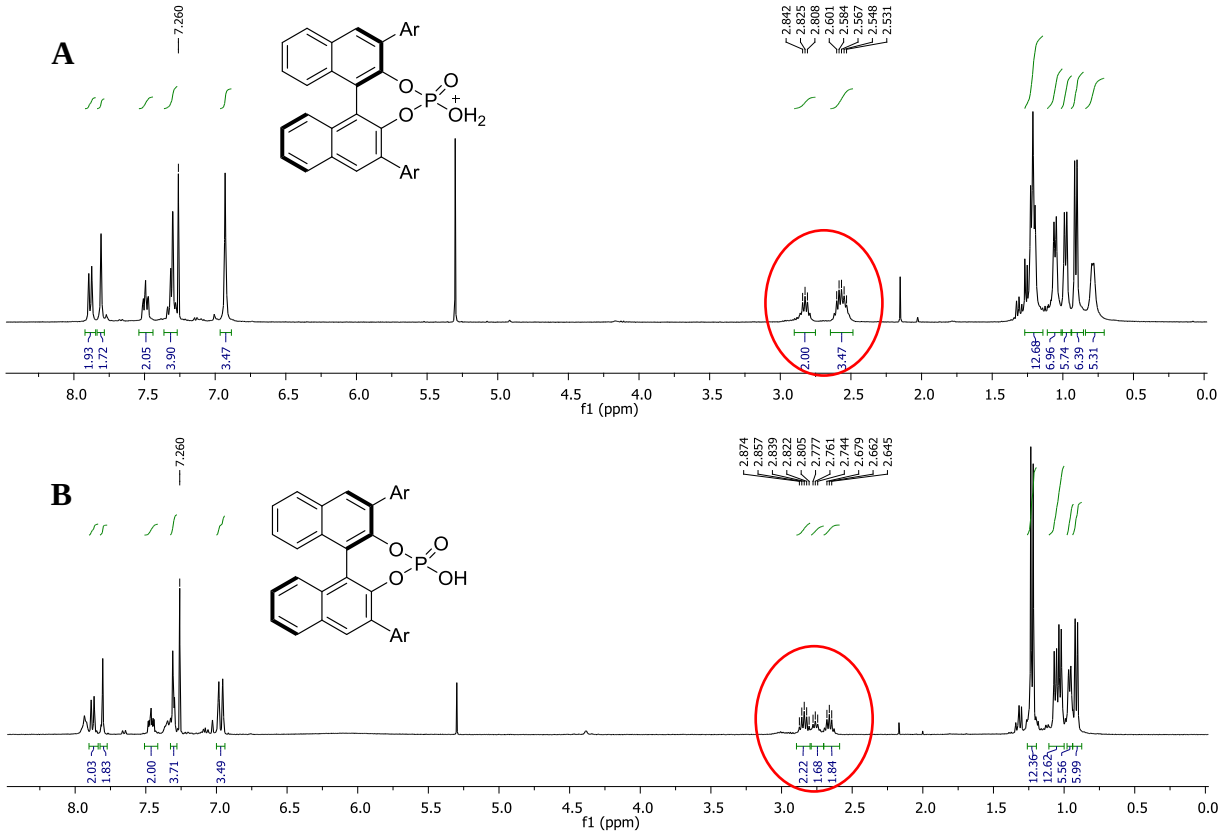


Figure 9

Only two signals (4H and 2H) were observed for the phosphate salt (**A**) and three separate signals (2H each) for the free acid (**B**). Prompted by these results, recrystallisation of the crude chiral phosphoric acid (*R*)-**79** from acetonitrile was carried out. The ^{1}H NMR spectrum of the purified product exhibited a clear difference in the isopropyl CH groups signals compared to the non-recrystallised sample (Figure 9 **B**).

The kinetic resolution of allylboronate (±)-**69.4a** in the reaction with benzaldehyde was performed with a pure batch of (*R*)-TRIP **79** at –30 °C in toluene as a solvent. Under these conditions, a high enantioselectivity was reproduced for both *Z* and *E* homoallylic alcohol; however, 72 h were needed to complete the reaction (entry 6).

The catalytic activity of the chiral (*R*)-*N*-triflyl phosphoramide **80** and the analogue phosphorodithionic acid (*R*)-**81** were also tested in the model reaction under the same conditions. Chiral Brønsted acid (*R*)-**80** reacted faster than (*R*)-**79** but gave only modest enantioselectivities (entry 7), whereas in the case of dithionic acid (*R*)-**81** both geometrical isomers of homoallylic alcohol were obtained as racemates. The reason for the latter

phenomenon might be due to the stronger acidity of (*R*)-**81**, so that it forms a loose ion pair thus preventing creation of a tight chiral environment around the transition state.

Electing the best additive

Preliminary results indicated that the presence of an acidic additive in the reaction mixture could be beneficial for the reaction rate. Hence, next efforts were focused on the search for an adequate additive, which would increase the reaction rate without compromising the overall selectivity. Various Brønsted acid additives at different catalytic loadings were investigated (Table 6).

Table 6

Entry[a]	Additive	T, °C	Reaction time	d.r. (*Z:E*)[b]	*ee* (*Z:E*)[c]
1	H_3PO_4 (2.5 mol %)	–30	18 h	67:33	85:88
2	AcOH (2.5 mol %)	–30	18 h	75:25	85:88
3	TFA (2.5 mol %)	–30	18 h	72:28	80:79
4	AcOH (1 mol %)	–30	18 h	75:25	89:91
5	TFA (1 mol %)	–30	18 h	65:35	85:87
6	AcOH (1 mol %)	–78	72 h	80:20	96:98

[a] reactions were carried out in toluene and full conversion was observed in all case otherwise stated; [b] d.r. (%) was taken from ^{1}H NMR of the crude reaction mixture; [c] *ee* (%) were determined by chiral HPLC

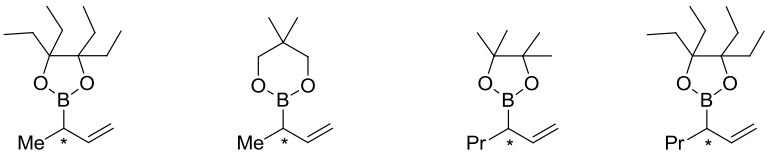
The acids selected were orthophosphoric, acetic and trifluoroacetic acids, having lower, similar and higher dissociation constant, respectively, compared to the chiral BINOL-derived phosphoric acid. They were used as aliquots of a 1M stock solution in toluene. The reaction was initially carried out at a 2.5 mol% loading of the additive at −30 °C in toluene. All three acids succeeded in accelerating the reaction from 72 h to 18 h while maintaining the geometrical selectivity within the theoretically calculated values. However, a loss in enantioselectivity occurred for all of them, with the sharpest fall observed for trifluoroacetic acid (entry 3). Both orthophosphoric acid and acetic acid gave identical enantio- and geometrical selectivity (entries 1 and 2), however orthophosphoric acid was ruled out of further investigation due to its poor solubility in toluene. Therefore, acetic acid alongside trifluoroacetic acid was taken for further optimisation. Lowering the catalytic loading from 2.5

to 1 mol% resulted in a modest increase in enantioselectivity in both cases (up to 6% *ee*, entries 4 and 5); the highest overall selectivity was achieved with acetic acid (entry 4). Finally, the reaction was carried out with 1mol% loading of acetic acid at −78 °C to yield a 4:1 mixture of *Z:E* homoallylic alcohols with greatly improved selectivity of 96 and 98% *ee*, respectively (entry 6), though the reaction required longer time for completion (72 h). The optimal reaction conditions included 2.5 equivalents of allylboronate (±)-**69.4a**, 1 equivalent of benzaldehyde at 0.23M final concentration in toluene, 5 mol% of (*R*)-TRIP and 1 mol% of acetic acid.

Tuning the allylboronate architecture

The theoretical conclusions (see Table 3) were tested by submitting the set of different racemic allylboronic acid esters to the model allylation of benzaldehyde under the optimal reaction conditions identified in the previous section, at –42 °C. This temperature represents the lowest temperature that could be maintained by the laboratory cryocoolers.

Table 7



(±)-**69.5a** (±)-**69.3a** (±)-**69.4d** (±)-**69.5d**

Entry[a]	Allylboronate	Additive	T, °C	Reaction time	d.r. (*Z:E*)[b]	*ee* (*Z:E*)[c]
1	**(±)-69.5a**	AcOH (1 mol %)	–42	48 h	>95:5	98 (*Z*)
2	**(±)-69.5a**	Benzoic Ac. (1 mol %)	–42	18 h	>97:3	97 (*Z*)
3	**(±)-69.3a**	Benzoic Ac. (1 mol%)	–42	72[d] h	40:60	41:40
4	**(±)-69.4d**	Benzoic Ac. (1 mol%)	–42	18 h	67:33	60:72
5	**(±)-69.5d**	Benzoic Ac. (1 mol%)	–42	18 h	98:2	94 (*Z*)

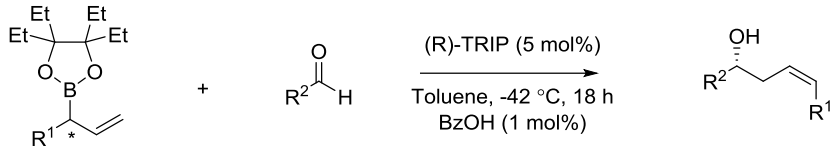
[a] reactions were carried out in toluene and full conversion was observed in all case; [b] d.r. (%) was taken from ^{1}H NMR of the crude reaction mixture; [c] ee (%) were determined by chiral HPLC; [d] 4.0 equivalents of **(±)-69.4d** were used.

In an excellent agreement with the computational data, tetraethyl analogue (±)-**69.5a** showed far superior *Z*-selectivity than the parent pinacolboronate (±)-**69.4a** (entry 1, Table 7 vs entry 6, Table 6). Importantly, the *Z*-homoallylic alcohol **83** was obtained in 98% ee. However, the reaction seemed to be slower, probably due to the increased steric bulk of the boronic ester moiety. Replacing acetic acid with benzoic acid at the same loading of 1 mol% appeared to circumvent the issue while improving the *Z*-selectivity on the target homoallylic alcohol (>97:3, entry 2). With the least sterically hindered boronate (±)-**69.3a**, the *Z*/*E* ratio of the products started to switch in favour of the *E*-isomer, as predicted computationally, and was accompanied by a significant drop in enantioselectivity (entry 3). Moreover, the superior selectivity shown by the tetraethylethyleneglycol group extends to the propyl homologue (±)-**69.5d**, producing a virtually geometrically pure *Z*-**83** with high enantioselectivity, whereas the parent boronate (±)-**69.4d** gave geometrical selectivity similar to the α-Me analogue (±)-**69.4a** (cf entries 4 and 5).

2.2.4.4Scope and limitations of the reaction

After establishing the optimal conditions and fine-tuning the structure of the boronate unit, the scope and applicability of the reaction was investigated. Boronates (±)-**69.5a** and (±)-**69.5d** were employed in the allylation of a range of aromatic and aliphatic aldehydes (Table 8).

Table 8



2.5 eq.
(±)-**69.5a**, R^1 = Me
(±)-**69.5d**, R^1 = *n*Pr

1 eq.
82a-k

83a, R^1 = Me
83d, R^1 = *n*Pr

Entry[a]	(±)-69.5	82, R^2	83	Yield	*d.r.* (*Z:E*)[b]	*ee* (*Z*)[c]
1	**69.5a**	**82a**, Ph	**83aa**	96%	>25:1	97%
2	**69.5a**	**82b**, PhCH=CH	**83ab**	84%	>25:1	97%
3	**69.5a**	**82c**, $PhCH_2CH_2$	**83ac**[d]	81%	>25:1	91%
4	**69.5a**	**82d**, 4-$MeOC_6H_4$	**83ad**	70%	>25:1	98%
5	**69.5a**	**82e**, 4-FC_6H_4	**83ae**	80%	>25:1	85%
6	**69.5a**	**82f**, 4-ClC_6H_4	**83af**	81%	>25:1	99%
7	**69.5a**	**82g**, 2-naphthyl	**83ag**	78%	>25:1	98%
8	**69.5a**	**82h**, 2-MeC_6H_4	**83ah**	75%	>25:1	91%
9	**69.5a**	**82i**, 2-thienyl	**83ai**	78%	>25:1	99%
10	**69.5a**	**82j**, 4-$CF_3C_6H_4$	**83aj**	80%	>25:1	96%
11	**69.5a**	**82k**, *c*-C_6H_{11}	**83ak**	72%	>25:1	88%
12	**69.5d**	**82a**, Ph	**83da**	90%	>25:1	94%
13	**69.5d**	**82b**, PhCH=CH	**83db**	97%	>25:1	93%
14	**69.5d**	**82c**, $PhCH_2CH_2$	**83dc**[d]	80%	13:1	87%

[a] reactions were carried out in toluene and full conversion based on the aldehyde was observed in all case; [b] d.r. was taken from ^{1}H NMR spectra of the crude reaction mixture; [c] *ee* were determined by chiral HPLC; [d] the product was *S*-configured as a result of the change in the priorities of the substituents in Cahn-Ingold-Prelog system.

The results shown in Table 8 clearly demonstrate that the kinetic resolution methodology can be successfully applied to a wide range of aldehydes. The target homoallylic alcohols were obtained in a high to excellent enantioselectivities (up to 99% *ee*,), regardless of the electronic nature of the substituents. Furthermore, the geometrical selectivity was also kept at a high level of >25:1, in favour of *Z*-isomer **83**. The use of the more sterically demanding allylboronate (±)-**69.5d** yielded the corresponding homoallylic alcohol **83** with a slight drop in enatntioselectivity compared to its analogue **69.5a** (cf entries 12 and 13 vs 1 and 2) while maintaining the high geometrical selectivity. A drop in d.r. was observed in the case of 3-phenylpropionaldehyde, which showed a 13:1 *Z*/*E* ratio when a more hindered allylboronate **69.5d** was used (entry 14).

In conclusion, a highly efficient protocol for the kinetic resolution of chiral secondary allylboronates has been developed in the frame of asymmetric allylation of aldehydes catalysed by the chiral phosphoric acid (*R*)-TRIP. The success of this resolution method depends on the contribution of the two major factors: 1) the enantiofacial selectivity in the C-C bonds formation and 2) kinetic preference towards the axially orientated α-alkyl substituent of the secondary allylboronate in the transition state. Quantum chemical calculations identified the tetraethylethylene glycol boronate scaffold as optimal to favour *Z*-selective reaction pathway. A wide range of *Z*-homoallylic alcohols were obtained with high geometrical and enantiomeric purity.[141] Further investigations to elucidate the mechanism of the enantio- and stereodifferentiation are in progess.

3 TOTAL SYNTHESIS

3.1. Introduction

(+)-Elisabethadione **85** and (+)-erogorgiaene **86** (Figure 10) are members of the family of marine diterpenes isolated from the West Indian sea whip *Pseudopterogorgia elizabethae*. These marine soft corals are found in warm nutrient rich reefs and shallows of the Bahamas, Florida Keys and West Indian region. *P. Elisabethae* first came to light in 1982 when routine screening showed the presence of cytotoxic metabolites with antimicrobial activity. Since then a whole host of gorgonian corals have been sampled and extracted. The isolation of a wide family of metabolites has been achieved and they are collectively known as Pseudopterosins **87** which general structure is shown in Figure 10. Pseudopterosins are a family of diterpene pentosides sharing a hexahydro-1*H*-phenalene core skeleton with more than 26 variants of the core structure and diversity on the level of aromatic functionalisation.

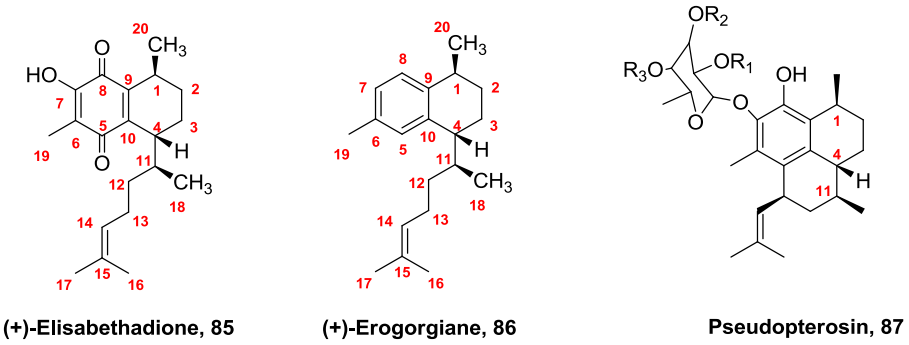
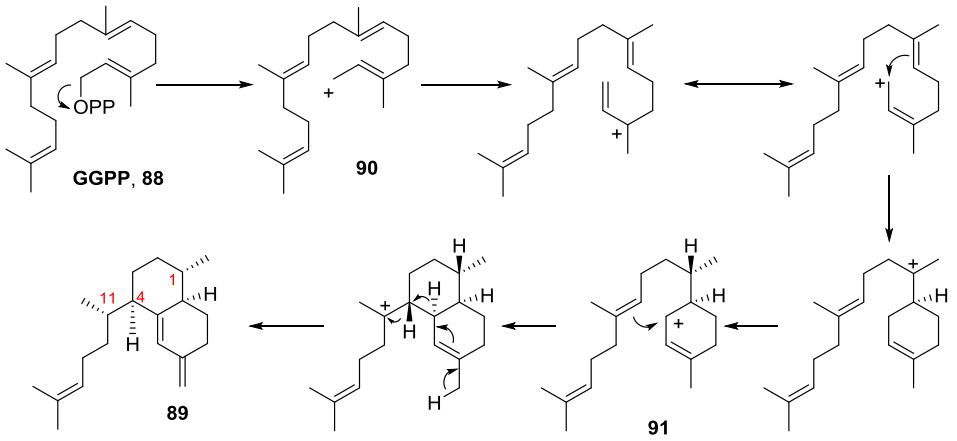


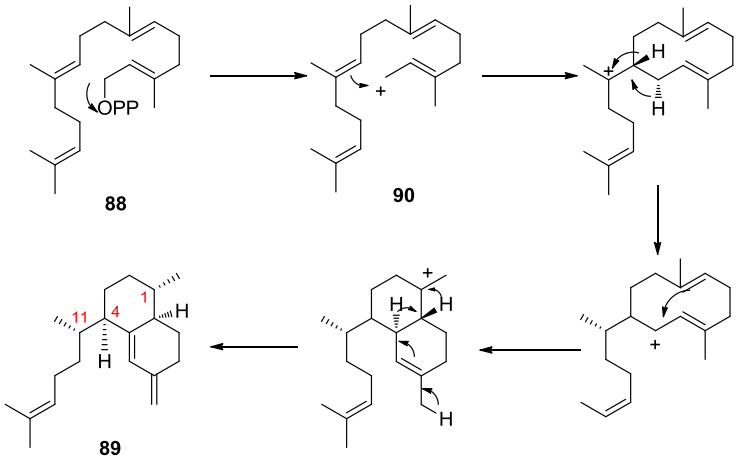
Figure 10

Recent research into the biosynthetic pathway of pseudopterosins has been conducted by the Kerr research group.[142] They have shown a possible mechanism for the formation of key intermediates in the biosynthesis of pseudopterosins. Compound **89** has been synthesised from geranylgeranyl diphosphate (GGPP) **88**. It is postulated that cyclisation can occur through 2 routes. In the first (Scheme 76), allylic cation **90** derived from initial loss of the pyrophosphate group from GGPP **88** initiates a ring closure. Allylic carbocation **90** undergoes a ring closure to generate a six membered ring. A second hydride shifts affords the corresponding allylic carbocation **91**, which facilitates the second ring closure. Finally, proton abstraction at vinyl methyl followed by hydrogen shift gives rise to bicyclic triene elisabethatriene **89**.



Scheme 76

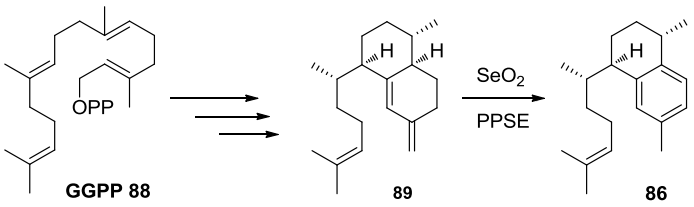
An alternative mechanism is shown in Scheme 77, in which intermediate **90** leads to a ten-membered ring. Hydride migration then leads to the bicyclic ring system, which undergoes proton abstraction at the vinyl methyl followed by hydrogen shift to afford **89**.[143]



Scheme 77

The significance of intermediate **89** comes from extensive isolation and extractions of the crude natural product, which was doped with radiolabeled ^{3}H-GGPP and ^{14}C-xylose by adsorbing the radiolabeled compounds onto food particles for ingestion via the filter feeding gorgonian.[142] This allowed the determination of intermediates in the biosynthetic pathway and allows the attempt of a biomimetic synthesis in the laboratory from the commercially available GGPP. The next transformation from elisabethatriene **89** to erogorgiane **86** proceeded via a

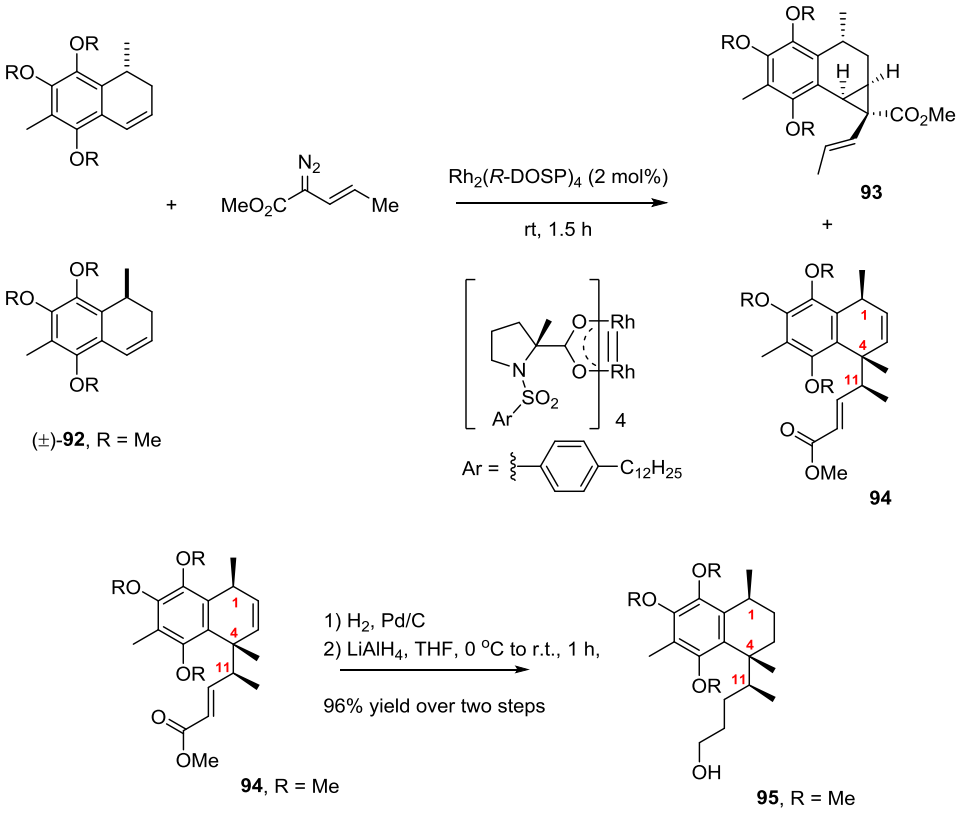
dehydrogenation and aromatization process using selenium dioxide in the presence of trimethylsilyl polyphosphate (PPSE) (Scheme 78).[144]



Scheme 78

3.1.1. Synthetic methodologies towards (+)-Elisabethadione

Despite the fact that (+)-elisabethadione **85** exhibits high levels of biological activity, only one total synthesis has been accomplished so far by Davies and co-workers where the stereocontrolled formation of the three key stereogenic centres is achieved in a single step through the combined C-H activation/Cope rearrangement sequence. The racemic poly hydroxylated compound **92** was resolved to yield the cyclopropane **93** and the desired intermediate **94**. The latter was first hydrogenated followed by ester reduction to yield the alcohol **95** (Scheme 79).[145]



Scheme 79

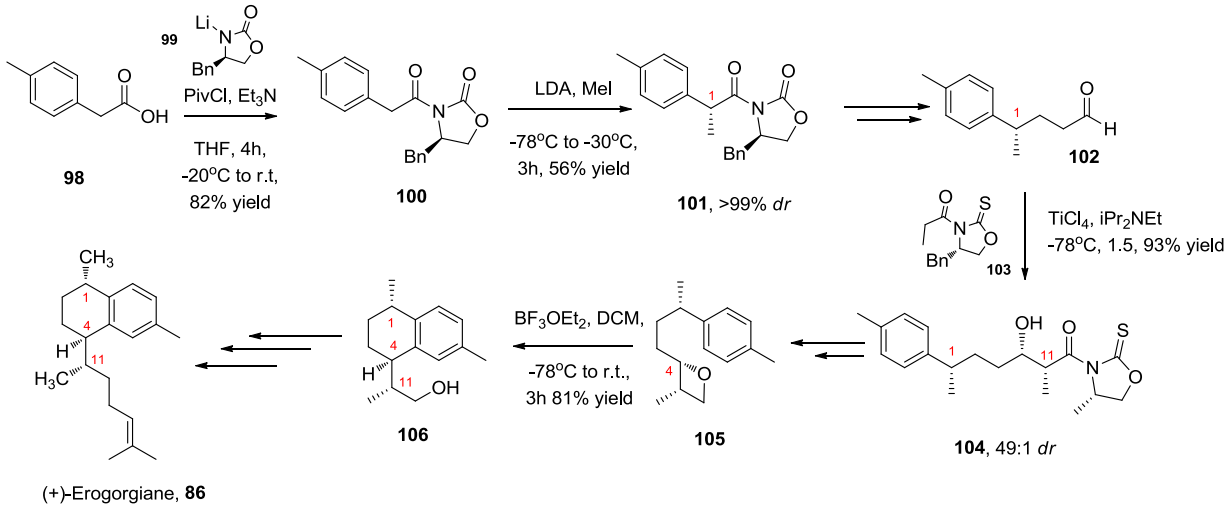
After resetting the aldehyde functionality upon oxidation with PCC, a chain extension was accomplished through Wittig olefination. Further deprotection of the hydroxyl functionalities revealed the quinone scaffold thus furnishing (+)-elisabethadione **85** (Scheme 80).

Scheme 80

3.1.2. Synthetic methodologies towards (+)-Erogorgiane

Biological evaluation of (+)-erogorgiane **86** has revealed its high activity against *Mycobacterium tuberculosis* $H_{37}Rv$ (96% inhibition at concentration of 12.5 μg/mL), an aetiological agent that causes tuberculosis. However, the natural sources of it are scarce, and that encouraged the scientific community to develop stereoselective synthetic routes towards this potent natural product. Even though its structure is not very complex, the major challenge associated with its synthesis resides in the introduction of three stereogenic centres on the diterpene backbone lacking functional groups, which neighbour the chirality. To date, there are four total syntheses and two formal syntheses of (+)-erogorgiane **86** published in the literature.

Yadav and co-workers reported the total synthesis of (+)-erogorgiane in a 16-step sequence in an overall yield of 8.2% using the aldol chemistry approach.[146] The use of Evans chiral auxiliary, Crimmins aldol protocol with chiral oxazolidin-2-thione and an intramolecular Friedel-Crafts reaction *via* an oxetane established the three stereocentres C1, C11 and C4 respectively, present in the natural product (Scheme 81).

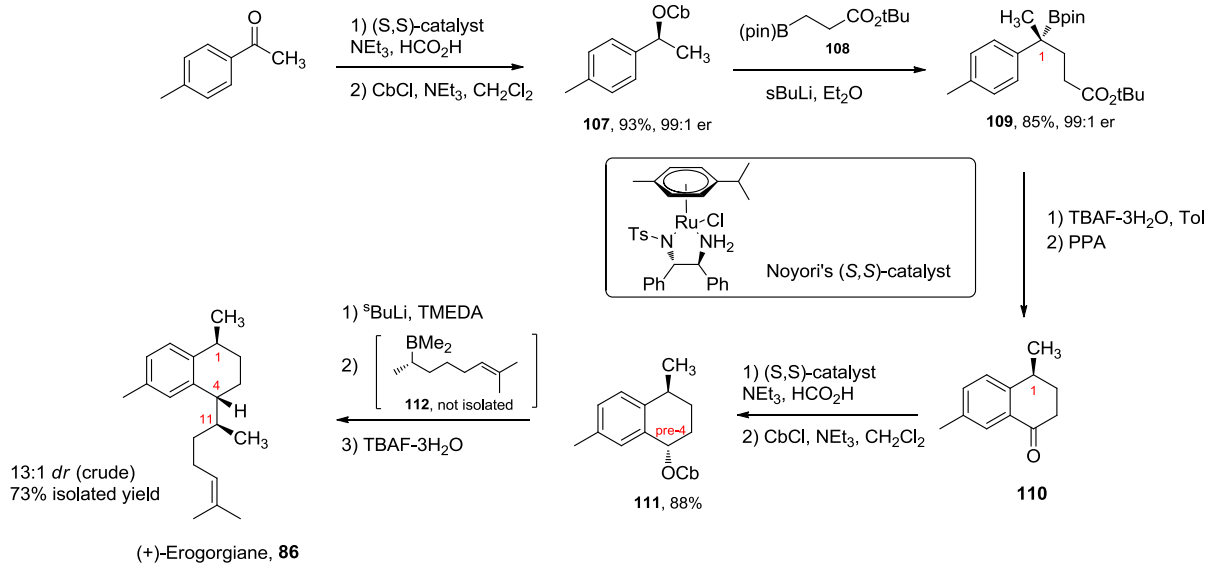


Scheme 81

The benzylic stereogenic centre C1 was established by means of alkylation using the Evans chiral auxiliary **99** with complete control over the diastereoselectivity (>99% *dr*). Crimmins protocol afforded the *non*-Evans aldol product **104** in a highly diastereoselective manner introducing the next stereocentre C11. After three further steps the derived oxetane **105** was obtained, which after treatment with Lewis acid led to the intramolecular Friedel-Crafts

alkylation product **106** installing the third chiral centre C4. The target diterpene (+)-**86** was synthesised within three more steps.

More recently, Aggarwal and co-workers accomplished the total synthesis of (+)-erogorgiane in 8 steps with an overall yield of 44%.[147] They used their own developed methodology of lithiation/borylation-protodeboronation as key steps to install the stereogenic centres C1, C4 and C11 (Scheme 82).

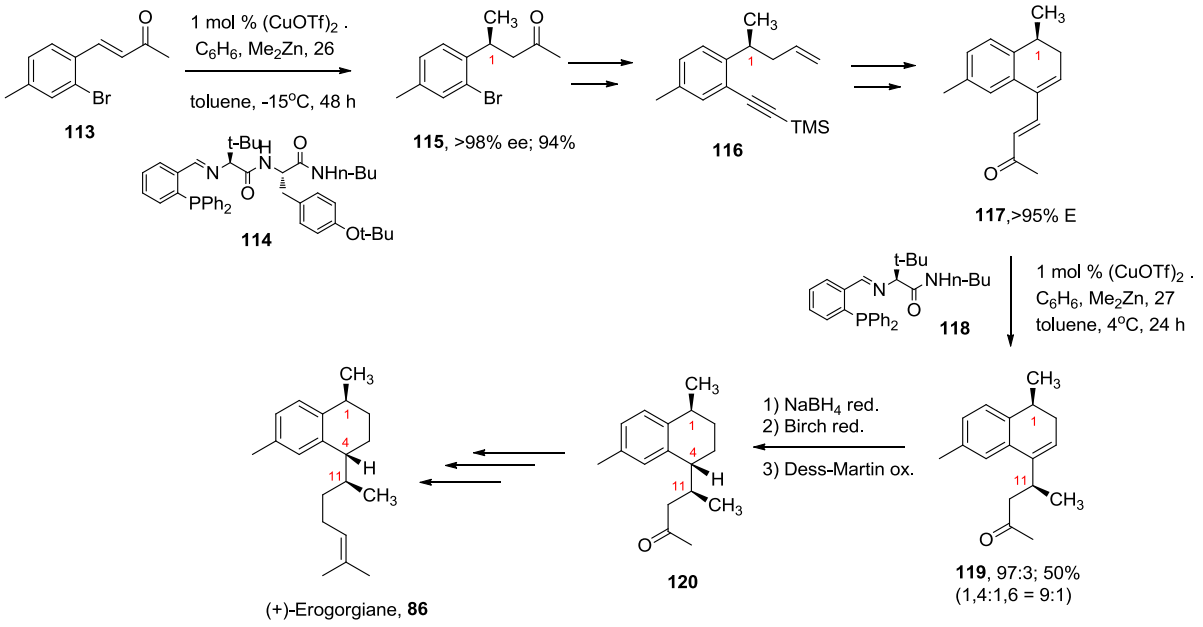


Scheme 82

Asymmetric reduction of *p*-methylacetophenone with Noyori's catalyst and subsequent carbamoylation, afforded the precursor **107** for the first lithiation-borylation sequence upon which the chiral centre C1 was introduced using boronic acid pinacol ester **108**. A second reduction/carbamoylation sequence allowed for the preparation of the *trans* carbamate **111**. The use of the borane **112**, prepared *in situ*, established the adequate stereochemistry at this centre through a second lithiation-borylation-protodeboronation affording the final natural product in a 73% yield and 13:1 diastereomeric mixture. The synthesis of the C4-epimer carbamates **111** together with the opposite enantiomer of the borane **112** allowed the preparation of each of the remaining diastereomers of (+)-erogorgiane.

Hoveyda and co-workers reported the first asymmetric total synthesis of (+)-erogorgiane.[148] The key steps to install the stereogenic centres involved Cu-catalyzed

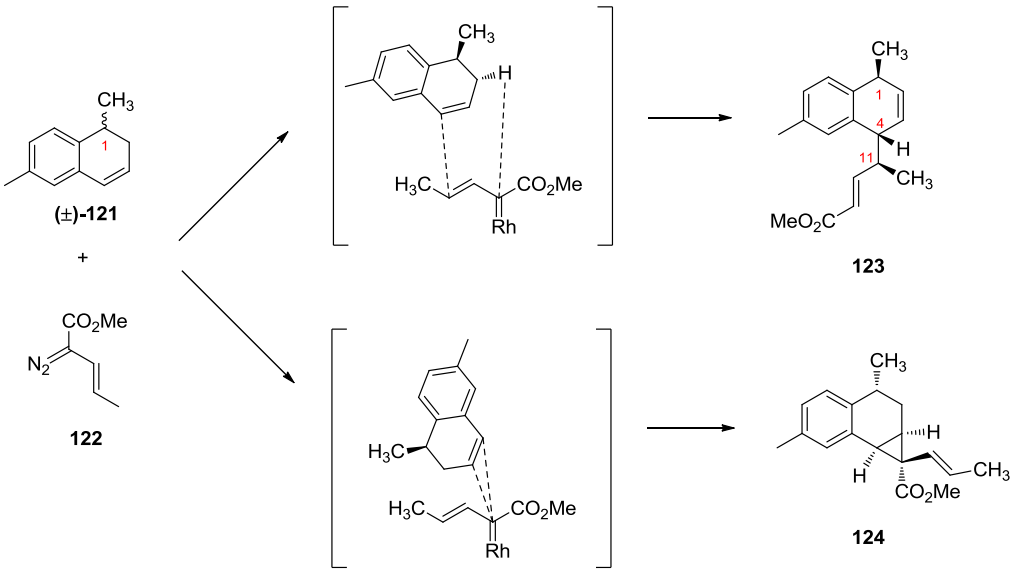
alkylation of α,β-unsaturated ketones and Birch reduction (Li/NH_3) (Scheme 83). The synthesis was achieved in 18 high yielding steps and high stereoselectivity.



Scheme 83

The use of the less hindered phosphine ligand **118** introduced C11 in a higher regioselectivity (1,4 *vs* 1,6 alkylation) in the conjugate addition to the unsaturated ketone **117** (9:1 in favour of 1,4 addition *vs* 1.5:1 in the case of the bulkier dipeptide ligand **114**).

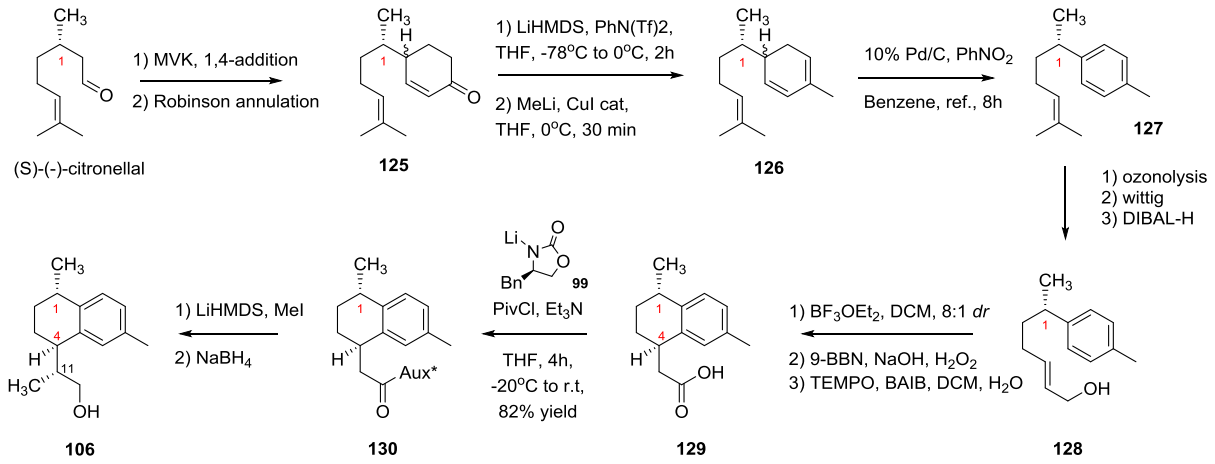
A shorter asymmetric total synthesis of (+)-erogorgiane was reported by Davies *et al.*[111] By means of an elegant enantiodifferentiation in the C-H activation/Cope rearrangement sequence, C4 and C11 stereogenic centres were introduced in a one-pot operation (Scheme 84).



Scheme 84

Due to the fact that C1 stereogenic centre is resolved in the course of the parallel kinetic resolution process that operates in the cascade C-H activation/Cope rearrangement, the racemic dihydronaphthalene (±)-**121** could be used. The reaction gave a 1:1 mixture of the C-H activation/Cope rearrangement product **123** and the cyclopropane **124**, both of 98% *ee*. The synthesis of (+)-erogorgiane was completed in four further steps involving hydrogenation of the two double bonds over Pd/C (10 mol%), reduction of the ester to the alcohol using $LiAlH_4$, oxidation to the aldehyde with PCC and final alkenylation as reported for (+)-elisabethadione.[145]

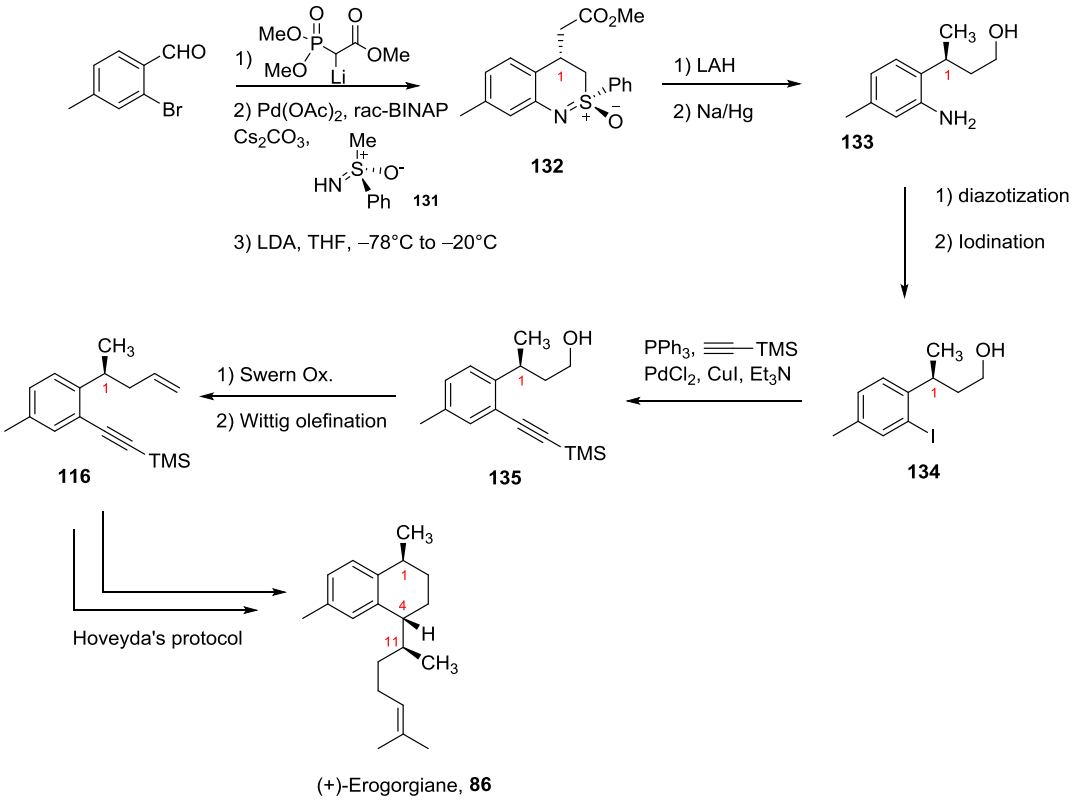
Yadav reported a protecting group free formal total synthesis of (+)-erogorgiane starting from commercially available (*S*)-(-)-citronellal (Scheme 85).[149]



Scheme 85

The formal total synthesis is composed of 12 steps and an overall yield of 14.2%. This novel sequence had the advantage of employing (*S*)-(-)-citronellal as the starting material that already contains one out of the three required chiral centres. The stereogenic centre C4 was introduced before C11 *via* intramolecular Friedel-Crafts cyclisation in the presence of Lewis acid and at a later stage, C11 was successfully installed using the previously reported lithiated Evans benzyloxazolidinone chiral auxiliary **99**.

Harmata and co-workers also developed a formal total synthesis of (+)-erogorgiane *via* benzothiazines using stoichiometric amounts of the chiral sulfonimide **131** to set the benzylic stereogenic centre at C1 (Scheme 86).[150]



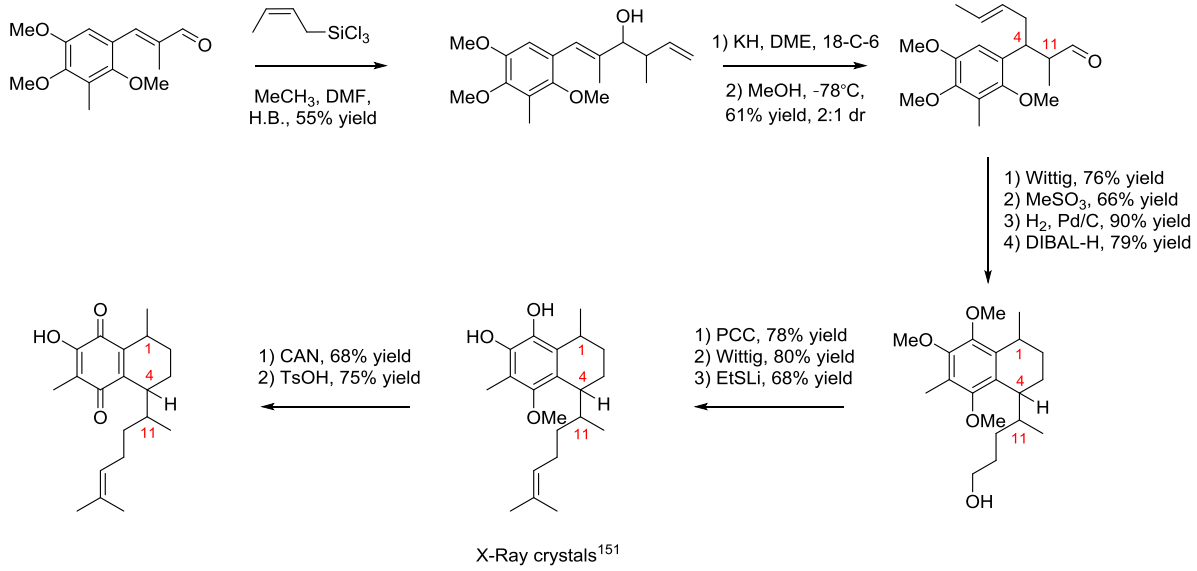
Scheme 86

Synthesis of compound **116** represented a formal total synthesis of (+)-erogorgiane since this intermediate was featured in the synthetic sequence reported by Hoveyda.[148]

3.2. Aims and objectives

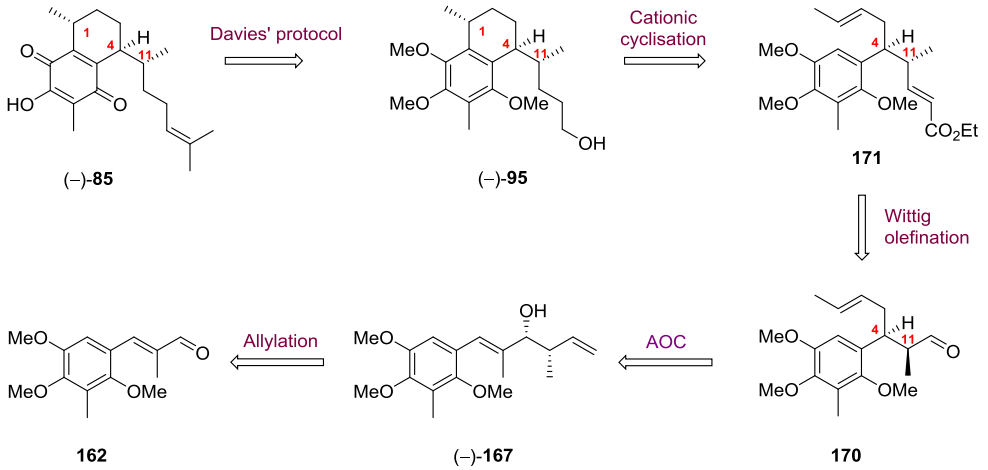
The aim of this project was to develop a practical scalable method for the asymmetric allylation of highly substituted cinnamaldehydes to be used in the asymmetric total synthesis of (–)-elisabethadione **85** and (–)-erogorgiane **86**, the marine natural products of the pseudopterogorgia secondary metabolite family.

The strategy for the racemic total synthesis of (±)-elisabethadione was developed in the Malkov group by Paul O'Hora during his PhD project (Scheme 87).[151]



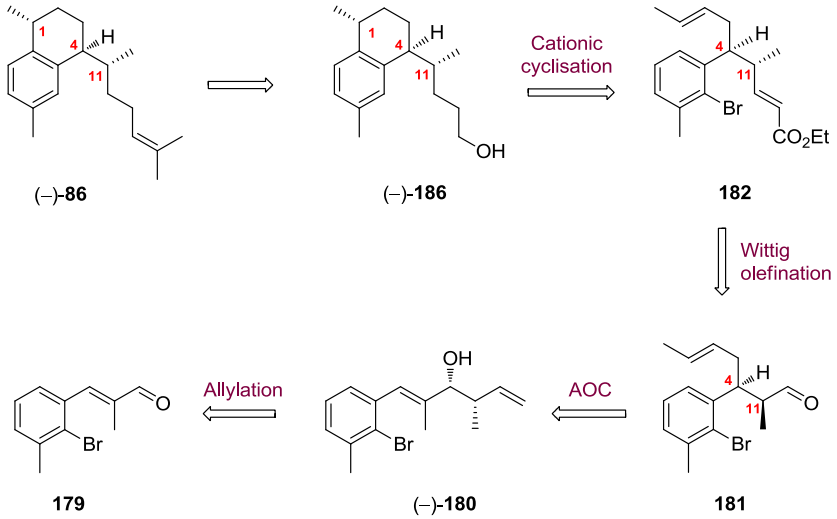
Scheme 87

The retrosynthetic analysis is shown in Scheme 88. The advanced intermediate alcohol **95** was featured in the synthesis of (+)-elisabethadione reported by Davies and co-workers[145] and may, therefore, represent a formal total synthesis of (–)-**85**. The synthetic strategy is built around the three key steps for the construction of the stereogenic centres C1, C4 and C11. It involves asymmetric allylation of the suitably functionalised cinammyl aldehyde **162**; anionic oxy-Cope rearrangement (AOC) of the resulting enantiopure homoallylic alcohol **167** (C1 and C11) and cationic cyclisation of the *trans*-alkene **171** (C4).



Scheme 88

The same strategy will be applied to the total synthesis of (–)-erogorgiane (Scheme 89). A detailed investigation of the AOC would be conducted to improve the diastereoselectivity obtained in the previous studies. In this instance, to circumvent the problem of regioselectivity in the cationic cyclisation step, the *ortho* position to the methyl group in the aromatic ring is blocked by bromine, which will be removed at a later stage in the synthesis.



Scheme 89

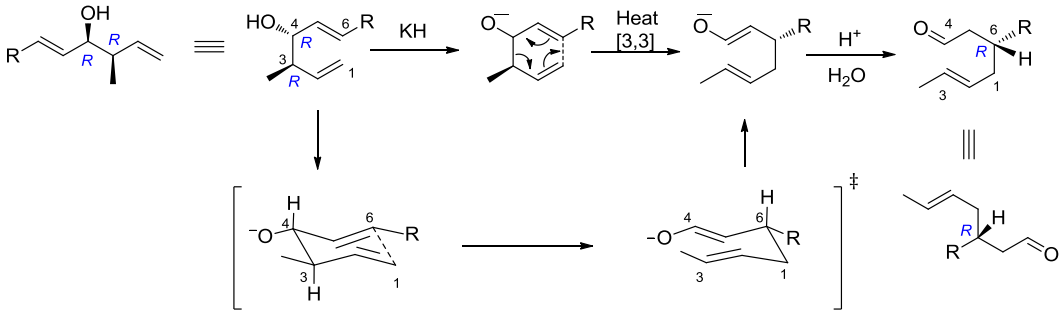
3.3. Results and discussion

Despite the fact that both marine diterpenes (−)-**85** and (−)-**86** share the key reactions for the installation of the stereogenic centres, the precursor cinnamyl aldehydes for the asymmetric allylation step are different and prepared by different synthetic sequences. Therefore, the total synthesis of each natural product will be described separately.

The advantage of the proposed synthetic route over those already described in the literature is that a single asymmetric transformation, a Lewis base catalysed allylation of a cinnamaldehyde, is employed to introduce chirality into the molecule, which efficiently controls the formation of the required stereocentres by two subsequent stereoselective transformations: anionic oxy-Cope rearrangement and cationic cyclisation. This synthesis does not use any alternative directing/controlling groups such as chiral auxiliaries. It does not require costly protecting groups or resolution techniques. To get a better insight into the stereochemistry of the oxy-Cope rearrangement and the cationic cyclisation, a brief overview of those transformations will be presented below. Asymmetric allylation was already been extensively discussed in chapter 1.

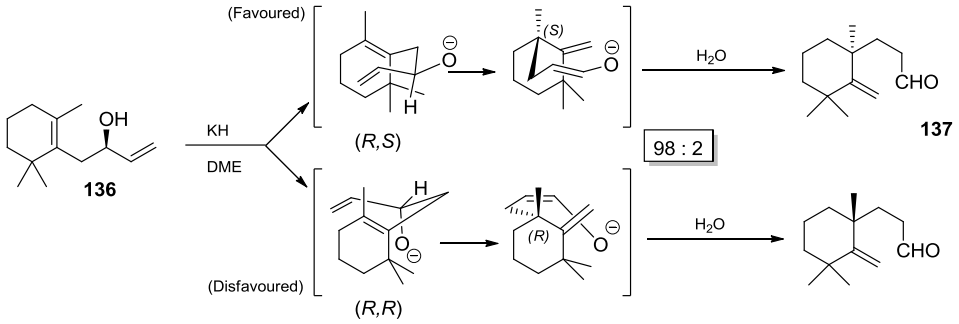
3.3.1. Anionic oxy-Cope rearrangement

The well-known anionic oxy-Cope (AOC) rearrangement is a [3,3]-sigmatropic rearrangement. It is generally accepted that it proceeds through a chair-like transition state, whereby the oxyanionic bond sits in the pseudoequatorial position. Theoretical and experimental studies on isotope effects showed the AOC is characterised by a highly dissociative transition state where the C3 – C4 bond is extensively dissociated with only a small degree of bond formation between C1 and C6 (Scheme 90).[152] Numerous investigations were reported, in which chair-like transition state was found to have both pseudoequatorial and pseudoaxial orientations of the oxyanionic bond. Further examples have also shown that the pseudoaxial oxyanionic bond and boat like transition states are possible in a structurally enforced transition state.[153,154] It should be noted that the structure of the molecule plays an important role in the rearrangements because the steric effects of substituents can severely retard the rate of reaction or indeed stop it altogether.



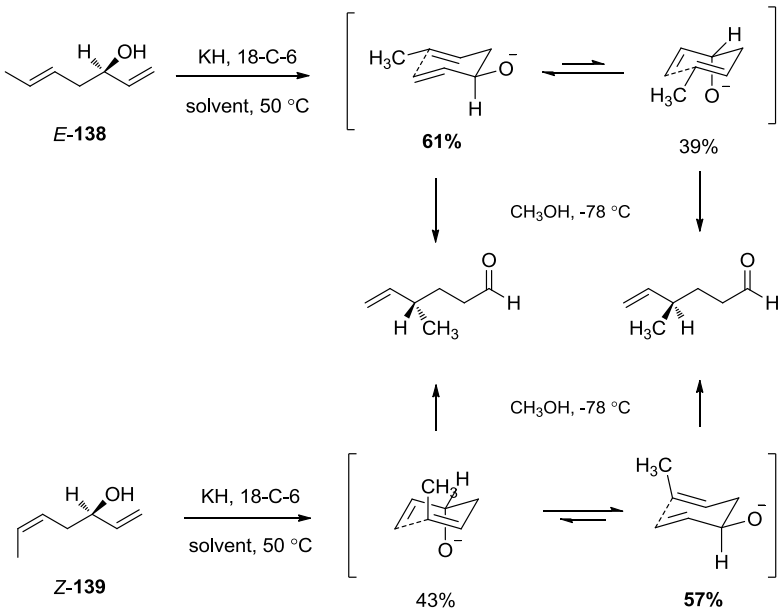
Scheme 90

One of the main advantages of the AOC is its ability to translate chirality from the reactant to the product. Transfer of chiral information may proceed in a highly selective process, as Lee and co-workers[155] showed in their route to the synthesis of (+)-dihydromayurone. Allylic alcohol **136**, with a single stereogenic centre, was converted into the corresponding aldehyde **137** (Scheme 91). The single stereogenic centre at the carbinol carbon was successfully transferred into the product in a highly stereoselective manner. The efficiency of the chirality transfer had its origins in the preferred pseudoequatorial position of the oxyanionic bond in the chair-like transition state during the rearrangement.



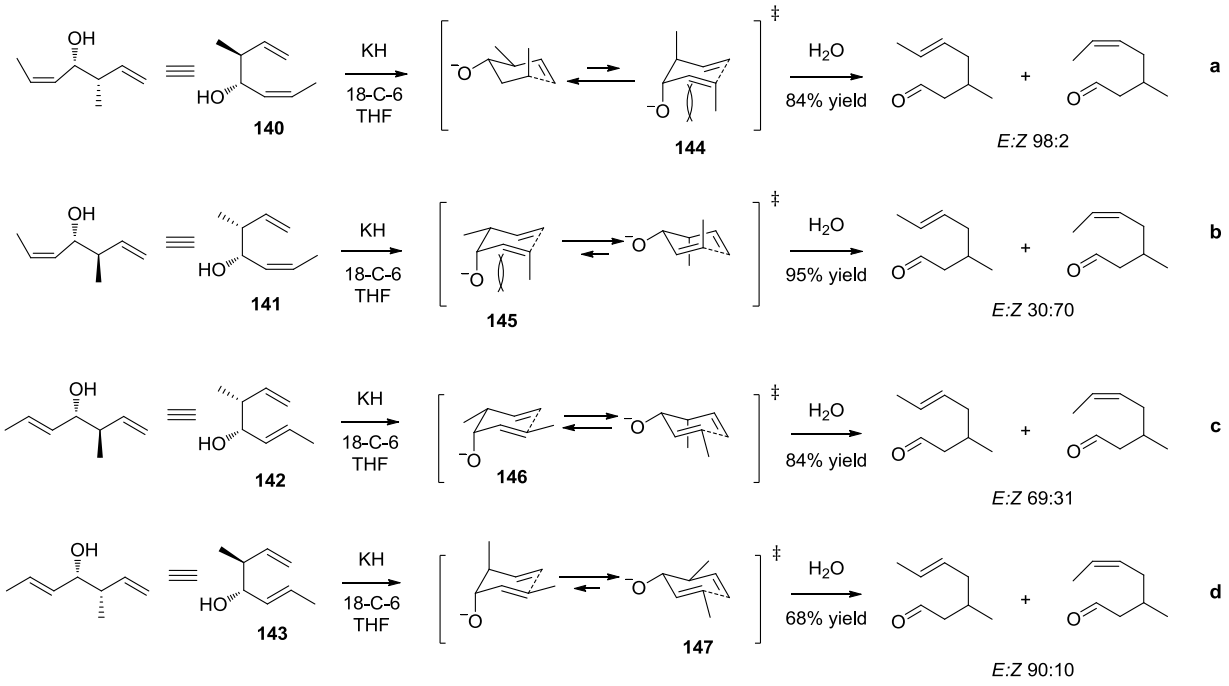
Scheme 91

Further research on the AOC rearrangement by Paquette and co-workers[156,157] demonstrated that pure *E*-**138** and *Z*-**139** underwent [3,3]-sigmatropic rearrangement with a slight preference for the pseudoequatorial orientation of the oxyanion (61% and 57%, respectively, Scheme 92).



Scheme 92

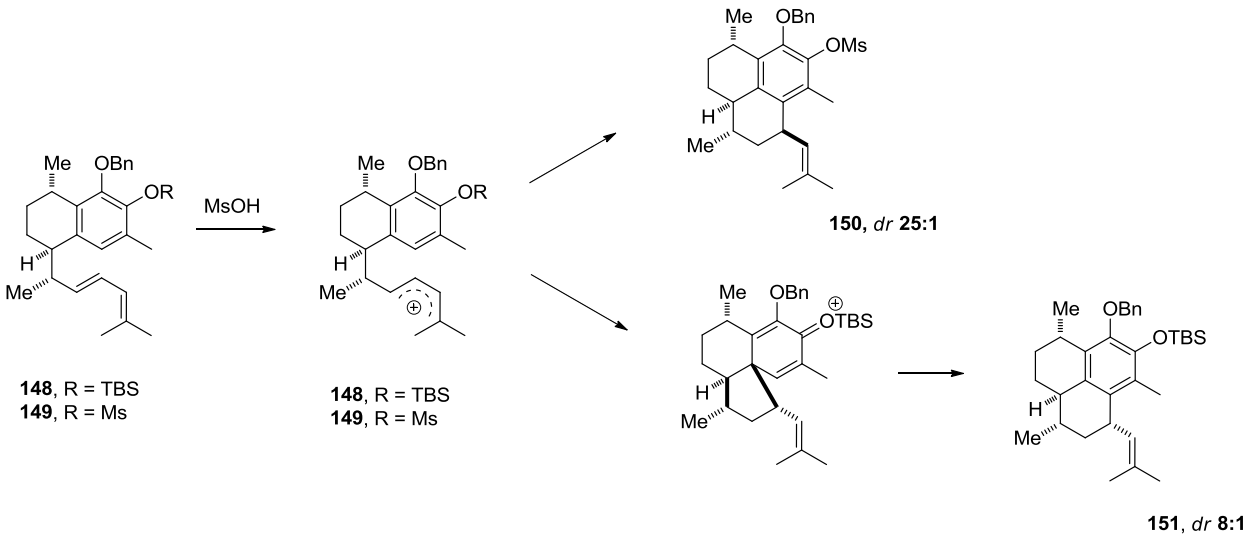
Nakai improved the diastereoselectivity by placing an alkyl substituent in the α-carbon to that bearing the hydroxyl group.[158] This is shown in the examples of alcohols **140-143** (Scheme 93). In the first two examples the pseudoaxial position of the oxyanion induces $A^{1,3}$ interactions disfavours reaction pathways involving **144** and **145** (reactions **a** and **b**). When dienol **142** is used (reaction **c**), the alkoxide and methyl groups adopt pseudoaxial or pseudoequatorial positions with no $A^{1,3}$ interactions. The 69:31 diastereoselectivity of *E/Z* aldehydes shows the rearrangement proceeds with a slight preference through transition state **146**. The use of alcohol **143** also avoids any $A^{1,3}$ interactions and favours the pseudoequatorial orientation of the oxyanion bond leading to a 90:10 diastereoselectivity through the chair-like transition state **147** (reaction **d**).



Scheme 93

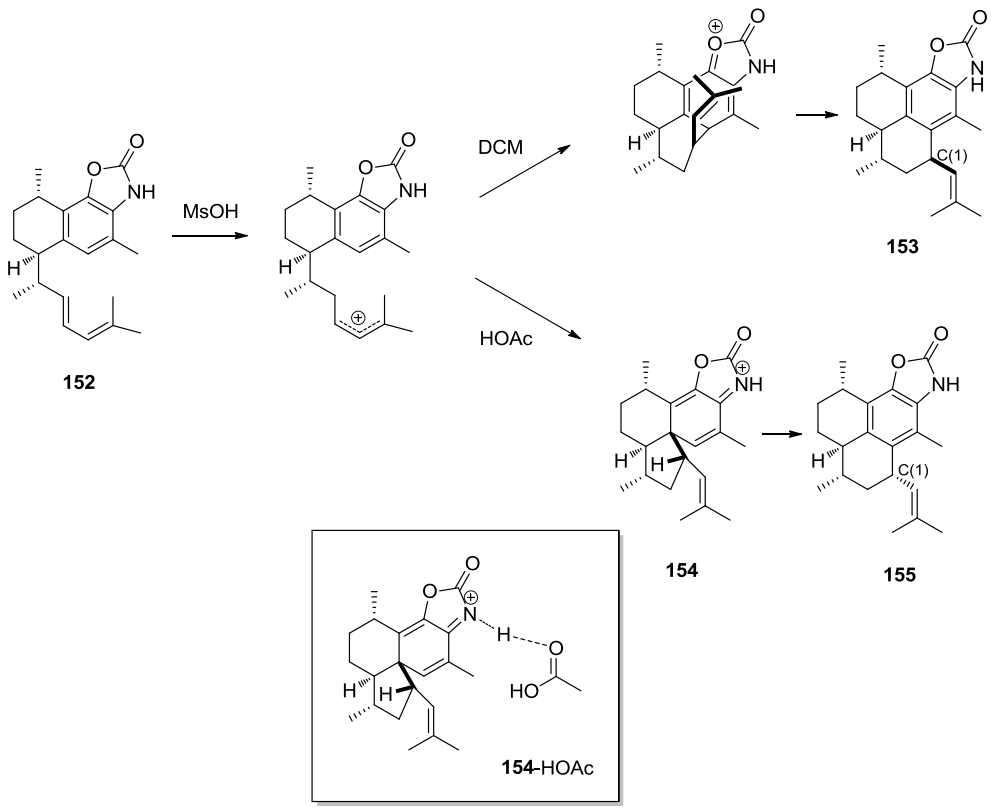
3.3.2. Cationic cyclisation

The topic of cationic cyclisation in the synthesis of natural products has been little mentioned in the literature over the past 25 years, mainly due to the lack of control over the stereoselectivity during the reaction. However, Corey and co-workers in the late 90s disclosed the influence of the electronic properties of the arene substituents in the cationic cyclisation of **148** and **149** catalysed by methanesulfonic acid.[159] Working towards the total synthesis of pseudopterosins, they observed that TBS and Ms protecting groups on phenolic oxygen yielded opposite stereoselectivity in the formation of the new chiral centre during the cationic ring closure (Scheme 94).



Scheme 94

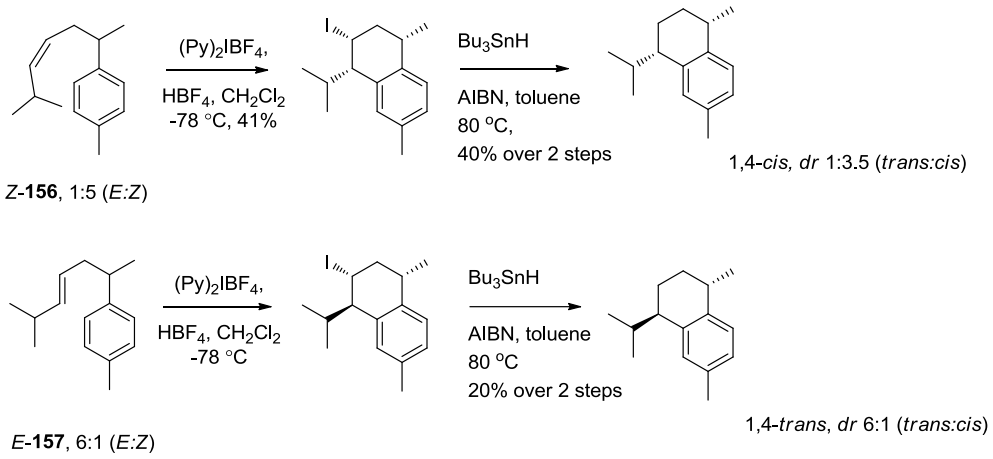
After the initial protonation of the diene **148** (or **149**), the presence of the electron withdrawing group MsO could favour the direct cyclisation of the allylic cation onto the arene ring to give **150**. However, the alternative cyclisation to form a 5-membered ring followed by a 1,2-rearrangement with ring expansion 5 $\rightarrow$ 6, could explain the opposite stereochemistry on the new chiral centre when TBSO group was used (**151**). They found a similar stereochemical dichotomy during the synthesis of the diastereoisomers of pseudopteroxazoles (Scheme 95).[160]



Scheme 95

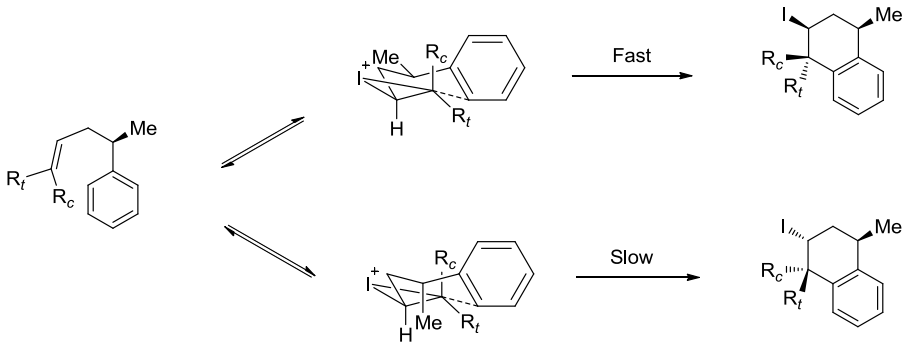
In this case the solvent played an important role during the mechanism. When the reaction was performed in acetic acid using methanesulfonic acid as catalyst, the preferred reaction pathway was likely to proceed *via* the 5-member ring closure followed by 1,2-rearrangement with ring expansion (**152** → **155**). The higher electron donating ability of the carbamate NH-group compared to the carbamate oxygen combined with the solvation stabilisation of the transition state favoured this pathway. However, when DCM was used as solvent, the direct 6-membered ring closure was favoured as the reaction pathway (**152** → **153**).

Casey and co-workers investigated cationic cyclisation for their synthesis of tetralins.[161] Following literature precedent, they initiated the reaction by addition of an electrophile (I^+) followed by electrophilic attack onto the arene. They studied the 6-*exo* and 6-*endo* modes of addition. The 6-*exo* cationic cyclisation showed limited reaction scope. However, 6-*endo* proved to proceed stereoselectively, allowing to access different stereochemistry in the tetralins depending on the geometry of the starting alkene, *i.e.* 1,4-*cis* tetralins were obtained from *Z*-alkenes, whereas 1,4-*trans* tetralins were prepared from *E*-alkenes (Scheme 96).



Scheme 96

In order to explain the diastereoselectivity, they postulated a reversible formation of the iodonium intermediate and a faster cyclisation occurring when the benzylic methyl occupies a pseudoequatorial position in the six-membered transition state (Scheme 97).



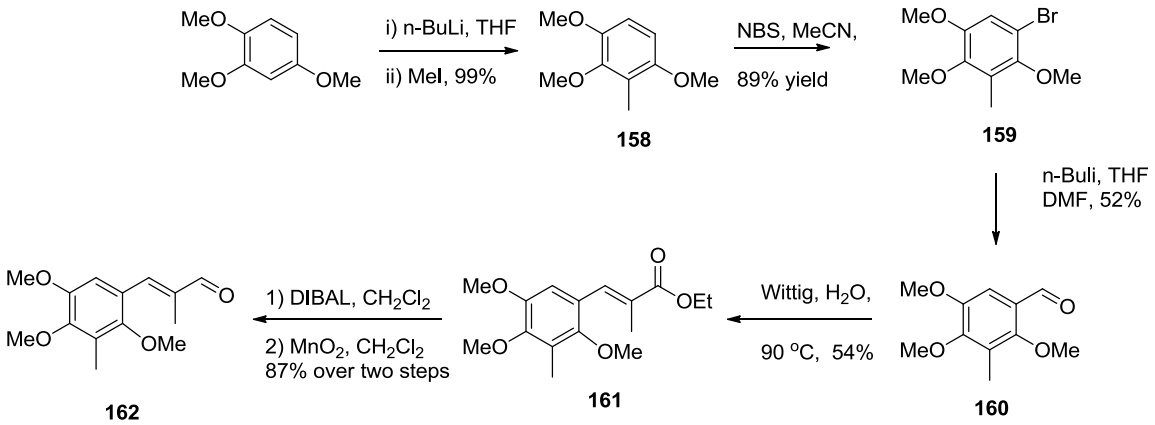
Scheme 97

From this brief overview on the key synthetic steps, it can be concluded that a *E,syn* homoallylic alcohol will be required to achieve a reliable transfer of the stereochemical information from the homoallylic alcohol in the AOC rearrangement (to set up C4), additionally, the *trans* alkene configuration is a prerequisite for setting up the correct stereochemistry at C1 in the subsequent cationic cyclisation.

3.3.3. Total Synthesis of (–)-Elisabethadione

The asymmetric synthesis of elisabethadione started by producing the starting cinnamaldehyde **162** (Scheme 98). This sequence was initiated by alkylation of the commercially available 1,2,4-trimethoxybenzene at the C-3 position yielding compound **158**

quantitatively. In the next step, selective halogenation at C-5 was performed using the method optimised by the former researcher to afford compound **159** in 89% yield.[151] Lithium/bromine exchange followed by addition of DMF, after hydrolysis, provided the required aromatic aldehyde **160** in a 52% yield.

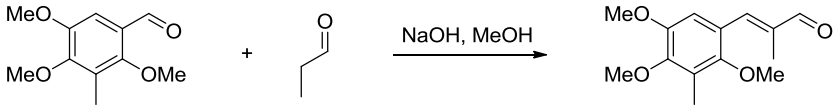


Scheme 98

Wittig alkenylation of aldehyde **160** with (carbethoxyethylidene)triphenylphosphorane in aqueous media needed to be repeated three times to achieve full conversion. Unfortunately, due to the purification process after each cycle, the corresponding ester **161** was obtained in a rather moderate yield (54%). The reduction-oxidation sequence of the α,β-unsaturated ester **161** furnished the respective cinnamaldehyde **162** which is required for the asymmetric allylation step.

To streamline the route to aldehyde **162**, a direct aldol condensation between aldehyde **160** and propanal using sodium hydroxide as a base was also investigated. Optimisation of the reaction conditions are summarised in Table 9. The reaction was performed by adding a solution of propanal in MeOH to a solution of substituted benzaldehyde and base in MeOH.

Table 9. Direct aldol condensation towards **162**



160 **162**

Entry	ArCHO (eq.)	EtCHO (eq.)	NaOH 2M (eq.)	Temp.	τ (h)	Conversion
1	1	2	0.8[a]	r.t.	2	60%
2	1	2	0.8[a]	r.t.	18	70%
3	1	1	1	50 °C	2	80%
4[b]	1	1	1.1	50 °C	18	45%
5	1	1.5	1.1	50 °C	18	60%
6	1	2.5	2.5	50 °C	5	>90%

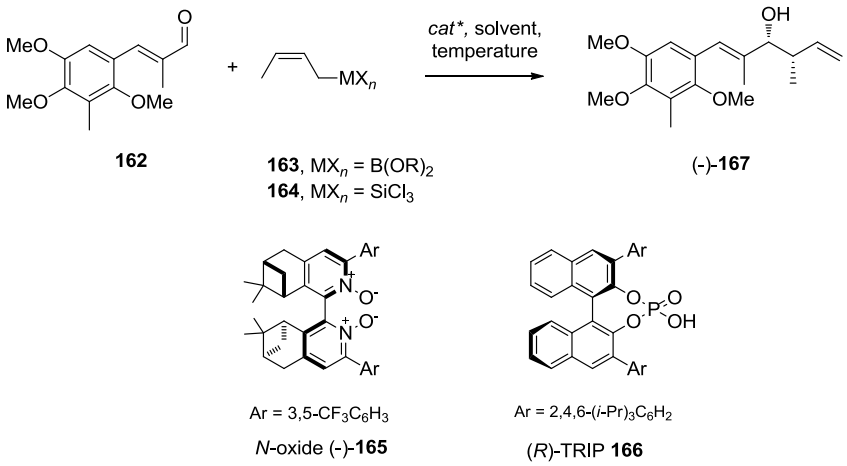
[a] NaOH 1M was used; [b] the base was added dropwise to a solution of aldehydes in MeOH

The reaction was initially carried out with one equivalent of the substituted benzaldehyde **160** and two equivalents of propanal in the presence of substoichiometric amounts of 1M NaOH. After the reaction was stirred at room temperature for two hours, the conversion of **160** to the corresponding cinnamaldehyde **162** reached 60% (entry 1). Extended period of time under the same reaction conditions did not deliver significant improvements (entry 2). The use of an equimolar mixture of aldehydes and 2M NaOH at 50 °C, stirring for two hours, improved conversion to the target aldehyde to 80% (entry 3). To examine the influence of the order of addition, an equimolar mixture of the corresponding aldehydes was prepared in MeOH. A slight excess of 2M NaOH was added to the reaction mixture at room temperature followed by stirring at 50 °C (entry 4). The low conversion obtained confirmed that an excess of base was needed in the reaction mixture prior to the addition of propanal to accelerate the reaction. In order to improve the conversion, 1.5 eq. of propanal and 1.1 eq. of 2M NaOH were employed carrying out the reaction at 50 °C. Conversion to the desired cinnamaldehyde **162** reached 60%, significantly lower than previously (cf entry 5 with entry 3). Next, the amounts of both propanal and 2M NaOH were increased in order to cut the reaction time to 5 hours. The new conditions resulted in *ca.* 90% conversion of **160** to **162** (entry 6), the isolated compound was suitable for use in the allylation protocol, as it was illustrated by a racemic variant of addition of *Z*-crotyltrichlorosilane **164** to aldehyde **162** in

DMF. Due to time restrictions, the aldol condensation was not optimised further. However, it is clear that the synthesis of the cinnamaldehyde precursor can be obtained in fewer steps using the direct aldol addition reaction

Retrosynthetic analysis of **86** and **87** (Schemes 88 and 89) and the literature overview clearly demonstrate that to achieve efficient transfer of chirality in the AOC rearrangement and install correct relative stereochemistry at C1 and C4, enantioenriched *syn*-homoallylic alcohol **167** is required. To meet this requirement, asymmetric 1,2-addition of *Z*-crotylmetal reagents to aldehyde **162** were attempted. It became apparent during the development of the racemic version of the synthesis[151] that the reactivity of the cinnamaldehyde **162** is considerably reduced due to the electron-rich nature of the aromatic ring, which complicated the search for an efficient chiral catalyst. The main task in this project was to find a catalytic system and optimise the reaction conditions that would allow (a) to circumvent the poor reactivity problem of the aldehyde and (b) to achieve the desired level of enantioselectivity. The results of this investigation are presented in Table 10.

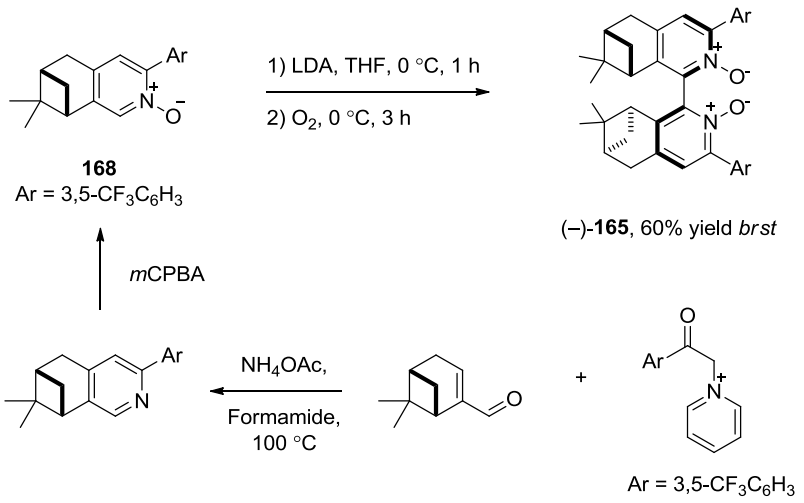
Table 10. Asymmetric allylation of cinammyl aldehyde **162**



Entry	AllylM	Solvent	Temp.	Reaction scale	Catalyst[a]	Yield	*ee*
1	**163**	Toluene	–30 °C	0.5 mmol	(*R*)-TRIP	78%	90%
2	**163**	Toluene	–30 °C	5.0 mmol	(*R*)-TRIP	65%	40%
3	**164**	EtCN	–60 °C	0.5 mmol	Bis-*N*-oxide	85%	97%
4	**164**	EtCN	–60 °C	5.0 mmol	Bis-*N*-oxide	82%	94%

[a] TRIP 10 mol%; *N*-oxide 2 mol%

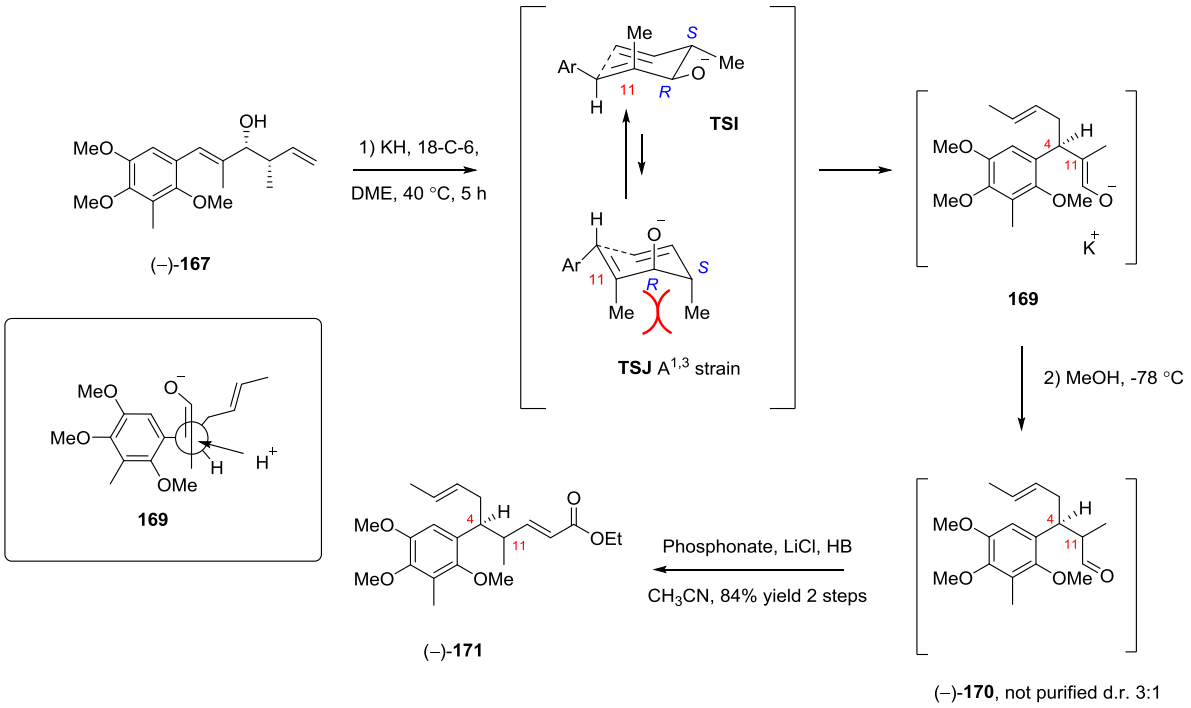
With the experience gained in the project of the Brønsted acid catalysed addition of allylboronates to aldehydes (see Chapter 2), the attention was first focused on the allylation of **162** employing commercially available *Z*-crotylboronic acid pinacol ester **163** using 10 mol% of (*R*)-TRIP as the catalyst. When the reaction was performed at 0.5 mmol scale, the desired homoallylic alcohol **167** was obtained in good yield and excellent enantioselectivity (entry 1). However, an attempt to carry out the reaction at a larger scale (5 mmol) under the same conditions led to a sluggish reaction and was accompanied by a substantial drop in enantioselectivity (entry 2). Taking into consideration the relatively high cost of the *Z*-crotylboronate **163** (SigmaAldrich, 1 g at £96), the attention shifted to the Lewis base catalysed addition of allyltrichlorosilanes to aldehydes, where Malkov's group has accumulated a considerable experience. In a parallel project in the group, a new bis-*N*-oxide **165** was developed, which exhibited a very high reactivity in model allylation reactions, exceeding reactivity of the existing Lewis bases.[24,25] It is worth noting that the chiral catalyst **165** was synthesised by an oxidative coupling of the corresponding isoquinoline-*N*-oxide **168** yielding a single diastereoisomer of **165** (Scheme 99). The absolute configuration of the catalyst is not known but it is assumed to be as shown in Table 10 by comparison with literature results.[162]



Scheme 99

The asymmetric allylation of **162** with *Z*-crotyltrichlorosilane **164** catalysed by the chiral bis-*N*-oxide **165** (2 mol%) at 0.5 mmol scale afforded the enantioenriched *syn*-homoallylic alcohol **167** in 85% yield and 97% *ee* (entry 3). Importantly, applying the same reaction conditions to a large scale synthesis (5 mmol) retained excellent yield and enantioselectivity (entry 4).

With the single stereoisomer of the homoallylic alcohol (–)-**167** in hand, next the anionic oxy-Cope rearrangement was performed. Treatment of (–)-**167** with KH and 18-crown-6 in DME at 40 °C for 5 h led to a full conversion producing enolate **169**. After brief optimisation of the quenching conditions, the best results were achieved when the mixture was first cooled to −78 °C followed by a quick addition of MeOH. In this way, aldehyde **170** was obtained, according to the ^{1}H NMR spectrum of the crude product, as a 3:1 mixture of diastereoisomers at C11, an improvement over the original procedure developed by the former researcher. It is worth noting the excellent transfer of chirality during the AOC rearrangement to form the C4 stereocentre, as evidenced by the stereochemical course of the subsequent steps and X-ray analysis of one of the advanced intermediates (compound **97**, *vide infra*, page 112[151]). The origin of the observed high stereoselectivity in the AOC rearrangement is in the presence of the α-methyl substituent in the cinnamyl fragment in **167**; of the two possible chair-like transition structures **I** and **J**, the TS **J** is clearly disfavoured due to the $A^{1,3}$ clash (Scheme 100). In order to visualise how the protonation of the enolate **169** occurs, a Felkin Ahn model along the bond C-11/C-4 can be used (Scheme 100). The proton is more likely to approach the less hindered face of the enolate, namely pro-*Re* face. The approach from the pro-*Si* face will be disfavour due to the presence of the *ortho*-methoxy group.

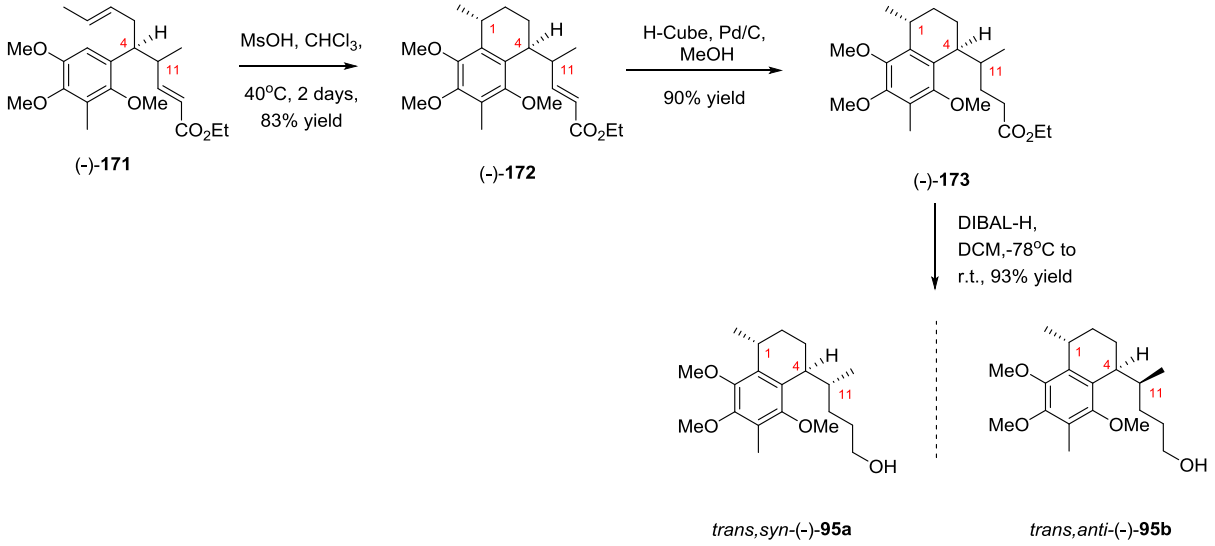


Scheme 100

To minimise manipulation of the oxidation prone aldehyde and to avoid epimerisation of C11, crude **170** was subjected to Wittig-Horner-Emmons olefination conditions. The corresponding α,β-unsaturated ethyl ester **171** was obtained in 84% yield over two steps (Scheme 100).

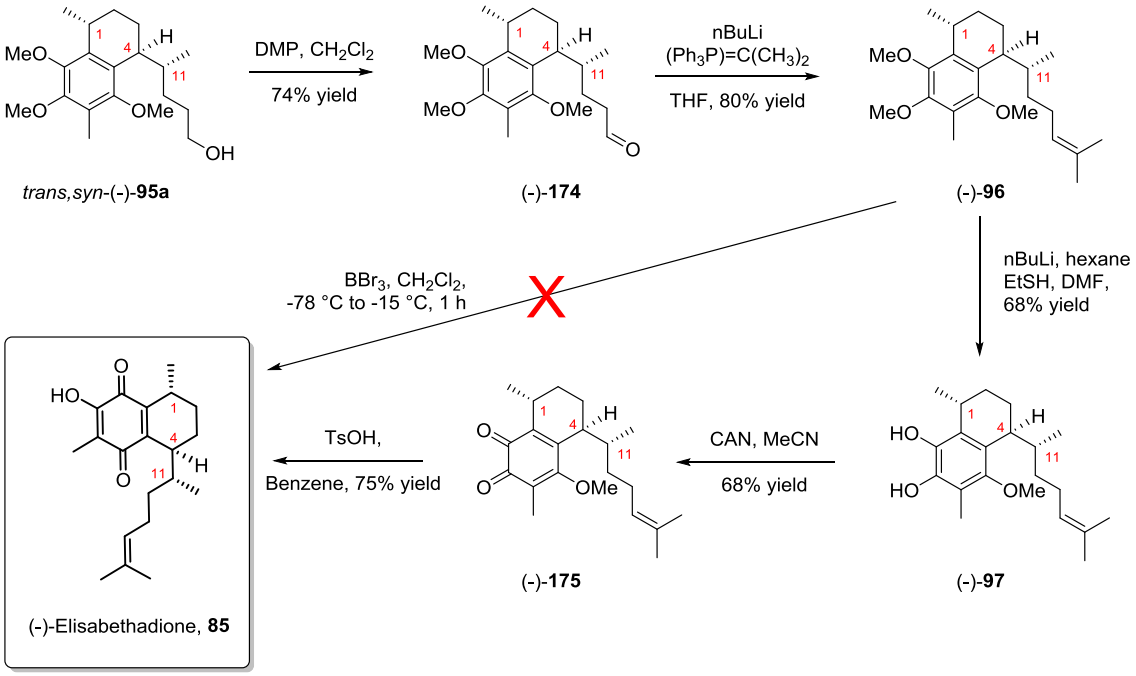
Diastereoisomers of ethyl ester **171** were not separable by conventional column chromatography, therefore the synthesis continued with the mixture. The final stereogenic centre C1 was installed through the cationic cyclisation of **171** upon treatment with methanesulfonic acid to afford the hexahydro-1*H*-phenalene derivative **172**. Importantly, the process proved to be highly stereoselective to form only trans cyclohexene ring (no other diastereoisomers were detectable by ^{1}H NMR spectroscopy). Next, continuous flow hydrogenation of **172** using an H-Cube furnished aliphatic ethyl ester **173** followed by its full reduction with DIBAL-H to afford primary alcohol **95** as a 2.7:1 mixture of C-11 isomers. At this stage, the isomers showed slightly different Rf values on TLC but gave a clear baseline separation on analytical HPLC column. Therefore, separation of 500 mg of the mixture was successfully accomplished using preparative HPLC to afford pure *trans,syn*-**95a** and *trans,anti*-**95b**, the latter slightly contaminated by other isomers (Scheme 101). The stereochemistry is defined in such a way that *trans* refers to the relative configuration of the methyl group at C1

and the alkyl chain at C4; while *syn* refers to the relative configuration of the hydrogen at C4 and the methyl at C11, according to the reported example (*vide supra Figure 10*).



Scheme 101

After isolation of the isomerically pure primary alcohol **95a**, the formal synthesis of elisabethadione was completed. The subsequent five steps to the actual natural product were accomplished following Davies' report (Scheme 102).[145]

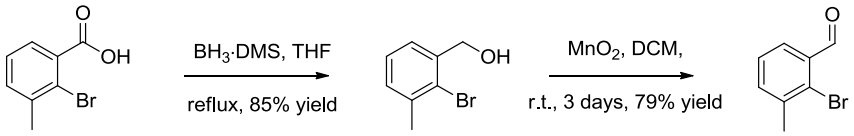


Scheme 102

Partial oxidation of the primary alcohol (–)-**95a** using DMP in CH_2Cl_2 yielded the corresponding aldehyde (–)-**174** in 74% yield. The subsequent alkenylation afforded (–)-**96** in 80% yield. In an attempt of create a shortcut to the (–)-elisabethadione **85**, a full deprotection of **96** using BBr_3 to the final natural product **85** was examined.[163] However, the reaction yielded an intractable deep-purple oil, similar to what was experienced by other researchers using similar compounds.[164] Therefore Davies' route was continued. Partial deprotection of **96** using lithium ethanethiolate yielded the corresponding aryl diol (–)-**97** in 68% yield. Importantly, in the racemic variant of the synthesis, compound **97**, obtained as a 2:1 mixture of isomers, gave crystals suitable X-ray crystallography analysis,[151] which confirmed the correct relative configuration of the major isomer and also showed that the two isomers differ only at C11. To complete the synthesis, (–)-**97** was oxidised to ortho-quinone (–)-**175** by CAN, followed by treatment with tosic acid in benzene to afford (–)-elisabethadione **85** (20% yield after 5 steps), the enantiomer of the target natural product. The synthesised compound exhibited optical rotation $[\alpha]_D^{25}$ = –267 (c = 0.16, $CHCl_3$), opposite in sign but similar in the absolute value to the compound reported by Davies ($[\alpha]_D^{25}$ = +278, c = 0.58, $CHCl_3$).[145]

3.3.4. Total synthesis of (–)-Erogorgiane

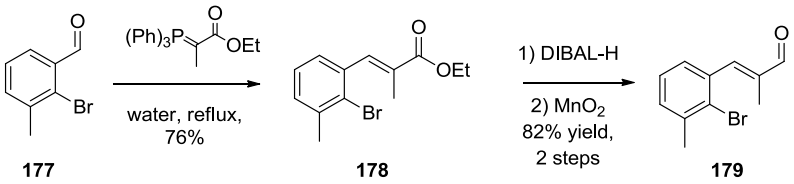
The total synthesis of (–)-erogorgiane started with the synthesis of the corresponding substituted cinnamaldehyde **179**. Reduction of commercial 2-bromo-3-methylbenzoic acid by borane dimethylsulfide complex yielded benzylic alcohol **176** in 85% yield. Subsequent oxidation using MnO_2 produced substituted benzaldehyde **177** in 79 % yield (Scheme 103).



176 **177**

Scheme 103

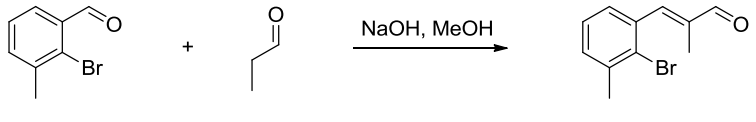
The aldehyde **177** was subjected to a Wittig olefination upon treatment with ethyl-2-(triphenylphosphoranylidene)propanoate in water under reflux to yield the α,β-unsaturated ester **178** in 76% yield. Reduction of the ester with DIBAL-H followed by oxidation of the alcohol with MnO_2 afforded aldehyde **179** in 82% yield over two steps (Scheme 104).



Scheme 104

Analogously to the (–)-elisabethadione route, synthesis of the precursor cinnamaldehyde **179** was also examined *via* the aldol condensation between benzaldehyde **177** and propanal using NaOH as base, as summarised in Table 11.

Table 11. Direct aldol condensation towards cinammyl aldehyde **179**



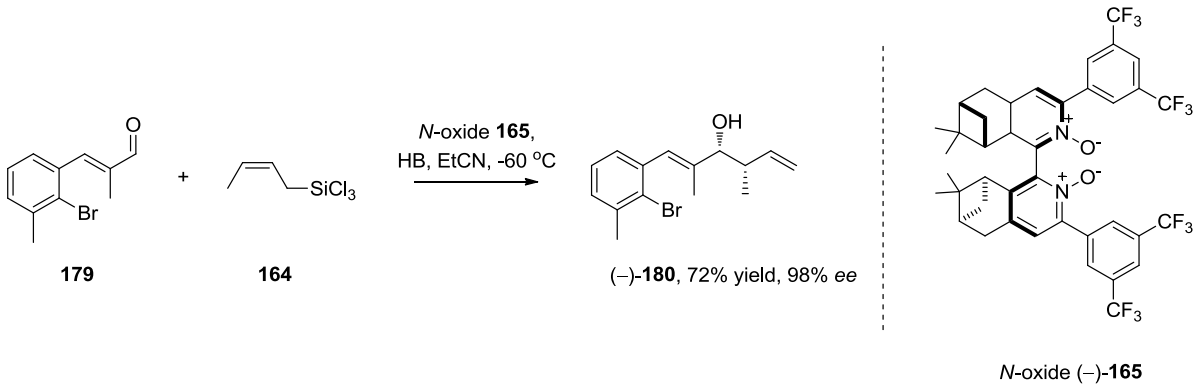
Entry	ArCHO (eq.)	EtCHO (eq.)	2M NaOH (eq.)	Temp.	τ (h)	Conversion
1	1	1	1[a]	r.t.	3	>99%[b]
2	1	1	1[a]	r.t.	18	60%
3	1	1.5	1	50 °C	18	90%[c]
4	1	1.5	1	50 °C	48	86%

[a] 1M NaOH was used; [b] compound **179** could not be separated from byproducts; [c] isolated yield 60%

The reaction was first attempted using an equimolar mixture of the substituted benzaldehyde **177**, propanal and 1M NaOH following the same procedure as in the (–)-elisabethadione synthesis. After stirring for 3 hours at room temperature, a full conversion was reached but the target cinnamaldehyde **179** was obtained together with other aldehydic byproducts, which could not be separated (entry 1). Dropwise addition of base to the solution of both aldehydes at room temperature and extending the reaction time gave 60% conversion (entry 2). Following the latter procedure, the conditions were further modified by using 1.5 eq. of propanal and a stronger concentration of base. After stirring the reaction at 50 °C for 18 hours, the target cinnamaldehyde **179** was obtained in 90% conversion and 60% isolated yield (entry 3). Longer reaction time using the same reaction conditions did not bring any

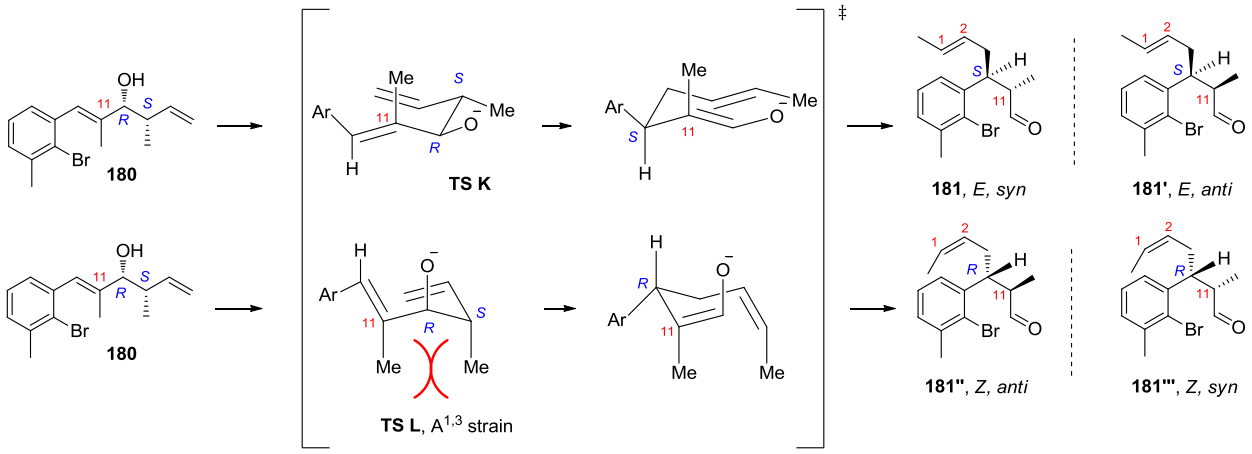
improvement, as entry 4 shows. These results demonstrated that direct aldol condensation methodology can be used as a shortcut in the synthesis of the precursor cinnamaldehyde **179**.

Having learnt from the synthesis of (–)-elisabethadione, asymmetric crotylation was carried out using allyltrichlorosilane methodology under the conditions of Lewis base catalysis. Addition of *cis*-crotyltrichlorosilane **164** to **179** in the presence of 2 mol% of the chiral bis-*N*-oxide **165** in propionitrile at −60 °C yielded the corresponding *syn*-homoallylic alcohol **180** in 72% yield and 98% *ee* (Scheme 105).



Scheme 105

Having successfully synthesised *syn* homoallylic alcohol **180**, the oxy-Cope rearrangement was carried out next. Due to the chair-like pathway, the AOC would occur stereoselectively: the presence of the methyl group at C11 favours the **TS K** where the oxyanionic bond occupies a pseudoequatorial position and which is free from any $A^{1,3}$ interactions between the substituents, unlike the **TS L**, where there is $A^{1,3}$ strain between the two methyl groups (Scheme 106).

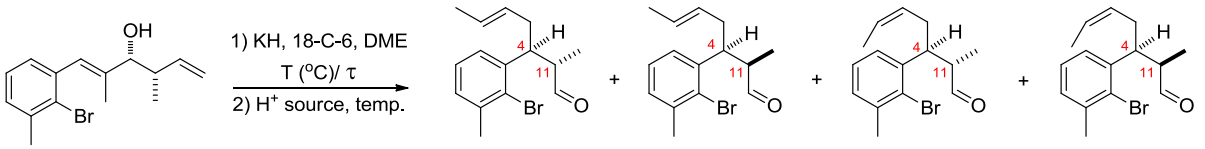


Scheme 106

The AOC controls the stereochemistry at C4. At the same time, the configuration at C11 is more difficult to control since it is created during the protonation of the enolate. It was hoped that the existing stereogenic centre at C4 and the appropriate choice of the proton source for quenching the reaction would favour formation of the correct diastereoisomer. Obviously, the desired overall stereochemistry to proceed with the total synthesis of (–)-erogorgiane **86** is represented by *E*,*syn*-**181**.

Taking into account the lack of success in the AOC of **180** by the former researcher, optimization of reaction conditions was first performed using racemic *syn*-homoallylic alcohol **180** (Table 12).

Table 12. AOC rearrangement optimization



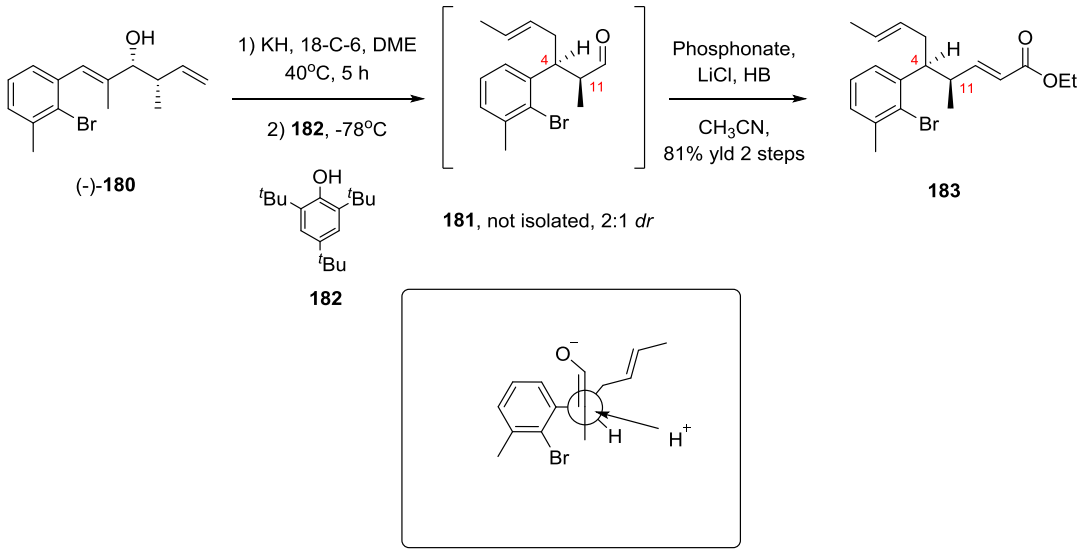
(±)-**180** (±)-**181**, *E, syn* (±)-**181'**, *E, anti* (±)-**181"**, *Z, syn* (±)-**181'"**, *Z, anti*

Entry	KH (eq.)	18-C-6 (eq.)	*T* (°C)/ τ (h)	H+ source	Conversion	*Dr* [a]
1	16	0.5	40/2	MeOH/r.t.	>99%	2.6:1:1.7:1.5
2	3	1	22/48	MeOH/r.t.	20%	1.7:1
3	3	1	40/18	MeOH/-78 °C	>99%	1.2:1
4	8[b]	1	22/18	MeOH/-78 °C	>99%	1.2:1
5	16	1	22/18	**182**[c]/-78 °C	>99%	2:1

[a] determined by ^{1}H NMR of the reaction crude; [b] KH was use neat weighted by mass difference; [c] **182** = 2,4,6-tri-*tert*-butylphenol

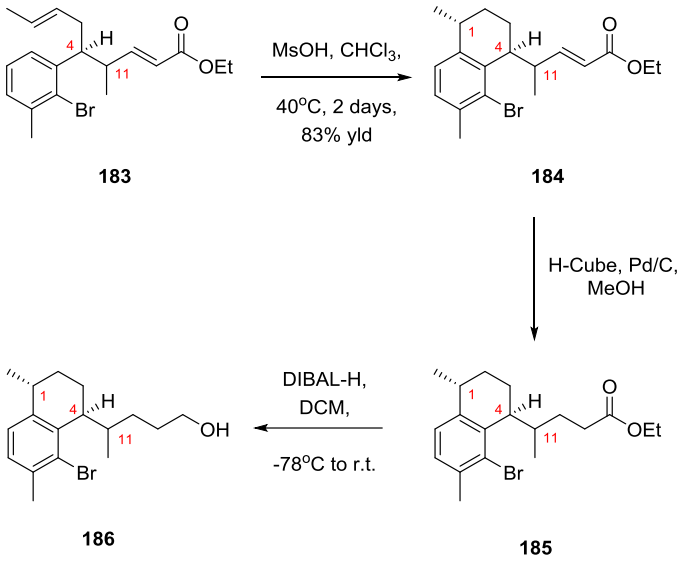
The use of 16 equivalents of KH 30% in mineral oil, 0.5 equivalents of 18-Crown-6 in DME at 40 °C gave a mixture of 4 diastereoisomers (entry 1). It was realised that the use of 18-crown-6 helped to capture the potassium cation into the complex so the ionic pair K-alkoxide was fully dissociated. Hence, at least one equivalent of the crown-ether would be needed. In addition to this increment, the use of only three equivalents of KH 30% in mineral oil at room temperature gratifyingly afforded a mixture of only two diastereoisomers in 1.7:1 ratio after methanolic quenching at room temperature. Although the major isomer was the desired one, the reaction only proceeded at 20% conversion after 48 h (entry 2). Full conversion and only two diastereoisomers were achieved when the reaction was performed at 40 °C using three equivalents of KH 30% in mineral oil and one equivalent of 18-Crown-6. The subsequent methanolic quenching at −78 °C produced a 1.2:1 diastereomeric ratio (entry 3). The use of 8 equivalents of neat KH, 1 equivalent of 18-crown-6 at room temperature was used next. However, after the subsequent methanolic quenching at low temperature the same diastereomeric ratio was achieved (entry 4). Finally, the reaction was performed at room temperature increasing the amount of KH to 16 equivalents affording only two diastereoisomers. Quenching the enolate at −78 °C with bulkier 2,4,6-*tert*-butylphenol (**182**) gave a mixture a 2:1 d.r. (entry 5).

Once the reaction conditions for the AOC rearrangement were optimised, enantiopure *syn*-homoallylic alcohol (–)-**180** was subjected to the [3,3]-sigmatropic rearrangement affording aldehyde (–)-**181**. Analogously with (–)-elisabethadione, a Felkin-Ahn model can help visualising how the protonation of the corresponding enolate occurs (Scheme 107). The protonation is also likely to happen at the pro-*Re* face of the enolate as it provides less steric hindrance compared to the pro-*Si* face. To avoid oxidation of the aldehyde functionality and epimerisation at C11, the crude product was submitted straight to the Wittig-Horner-Emmons olefination protocol to afford the α,β-unsaturated ethyl ester (–)-**183** in a two-step yield of 81% (Scheme 107). Mirroring the route towards (–)-**85**, the diastereoisomers of ethyl ester (–)-**183** were not separable by column chromatography, so the total synthesis was carried out with the mixture.



Scheme 107

To introduce the final stereogenic centre of the natural product scaffold, cationic cyclisation was carried out next. Treatment of the ester **183** with methanesulfonic acid in $CHCl_3$ at room temperature yielded the cyclisation product **184** after 2 days in 83% yield. It has to be noted that in this instance, *cis*-cyclohexene isomer was visible by ^1H NMR spectroscopy (ca. 5-8%). Continuous flow hydrogenation of the double bond employing an H-Cube furnished the aliphatic ester **185** and the subsequent reduction of the ethyl ester functionality produced primary alcohol **186** (Scheme 108).



Scheme 108

At this stage, attempts to debrominate the intermediate **186** were carried out. Following published procedure employing a similar substrate,[165,166] compound **186** was treated with $LiAlH_4$ in the presence of dry air that was purged into the reaction vessel through a column filled with KOH. Several attempts were performed but without much success, as evidenced by the ^1H NMR spectra of the crude reaction mixtures. A more detailed look at the ^1H NMR spectrum of the primary alcohol **186**, taking the chemical shift of the aromatic methyl group as a standard, revealed that the first flow hydrogenation protocol afforded a mixture of brominated alcohol **188** and the desired debrominated analogue **187** in an 85:15 ratio (Figure 11). The presence of **187** in this mixture was confirmed by high resolution mass spectrometry which contained two major peacks corresponding to the brominated alcohol **186** ($[M+^{107}Ag]^+$ requires 431.0134, found 431.0140) and debrominated **187** ($[M+^{109}Ag]^+$ requires 353.0984, found 353.1033).

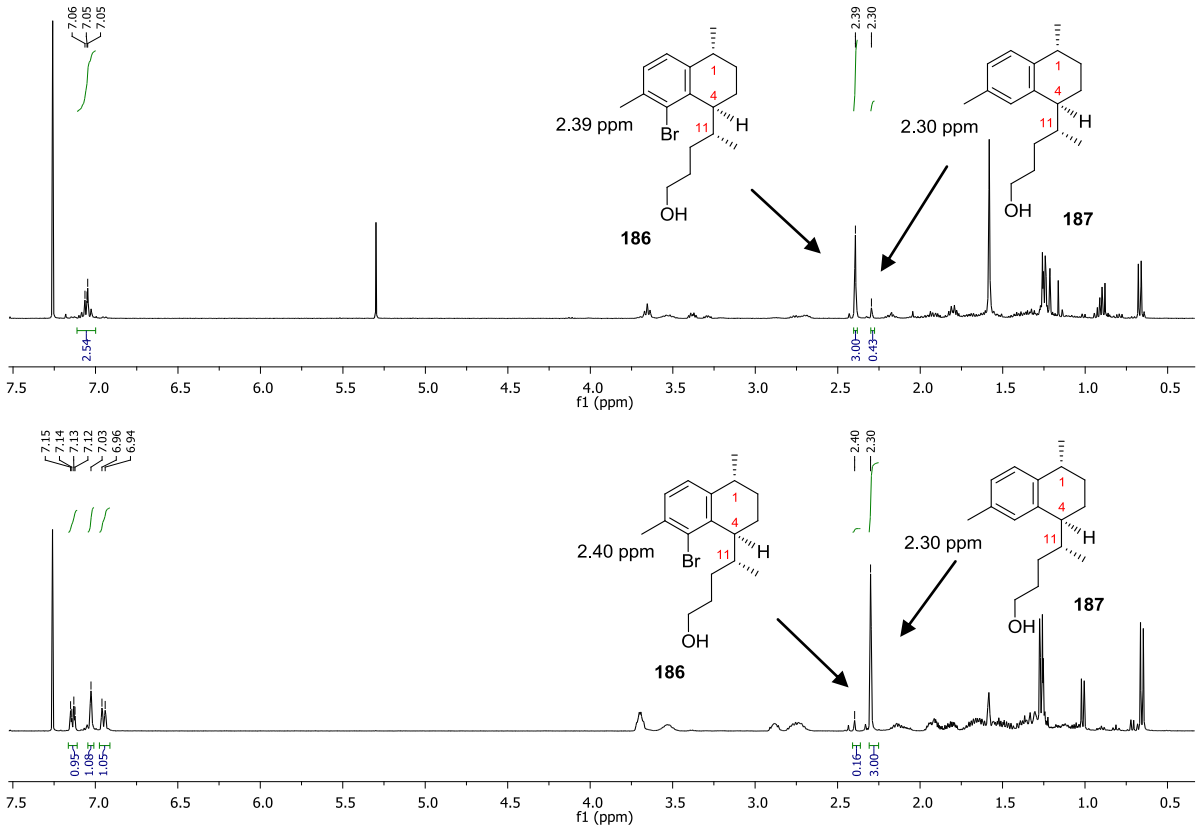
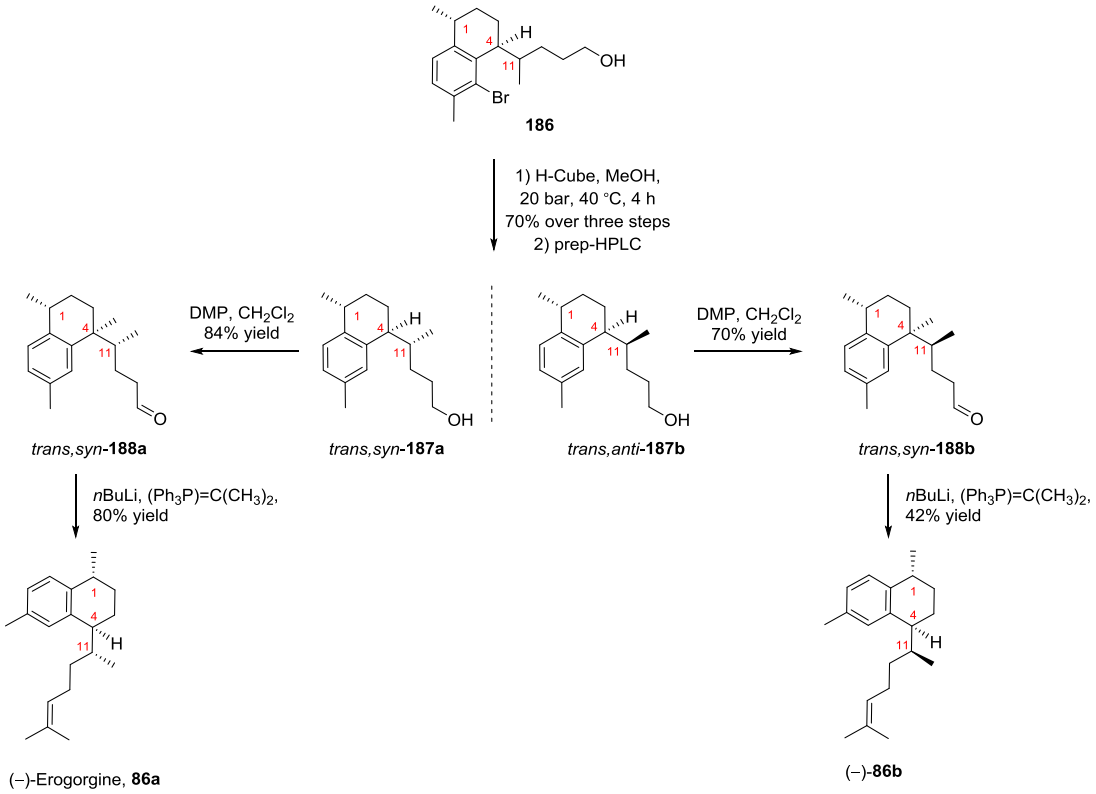


Figure 11

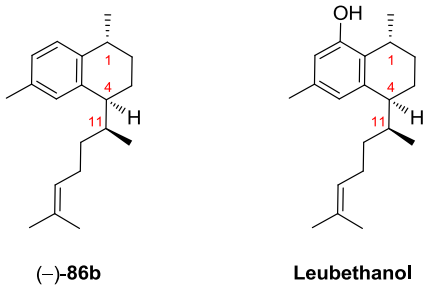
Encouraged by these results, the mixture of the primary alcohols was subjected to harsher conditions of the flow hydrogenation (20 bar, 40 °C) (Scheme 108). After 4 hours, the debrominated primary alcohol **187** was obtained in 70% yield over three steps (with *ca*. 5% of alcohol **186** remaining in the mixture, Figure 11). The mixture of the C11 isomers was separated by preparative HPLC to afford both C11-epimers. Dess-Martin periodinane oxidation of (–)-*trans,syn*-**187a** led to the aldehyde (–)-*trans,syn*-**188a** in 84% yield. The final chain elongation through a Wittig procedure afforded the enantiomer of the natural product (–)-erogorgiane in 80% yield exhibiting optical rotation $[\alpha]_D^{25}$ = –25.5 (c = 0.52, $CHCl_3$; $[\alpha]_D^{25}$ = +23.2, c = 0.75, $CHCl_3$;[146] $[\alpha]_D^{25}$ = +69.1, c = 0.77, DCM;[147] $[\alpha]_D^{25}$ = +40.6, c = 0.14, $CHCl_3$[148] $[\alpha]_D^{25}$ = +21.4 (c = 0.14, $CHCl_3$[111]). The stereochemistry is defined as shown previously for (–)-elisabethadione (Scheme 109, also *vide supra Scheme 101*).



Scheme 109

The asymmetric total synthesis of (–)-erogorgiane was accomplished in 12 steps with an overall yield of 14.2% based on the commercially available 2-bromo-3-methyl benzaldehyde **177**. Despite the fact that the synthesised isomer had optical rotation of opposite sign to those previously reported, (–)-**86a** is a natural product that has been isolated from a brown alga (*Dictyota dichotoma*) collected in Troista Bay of the Peter the Great Gulf, Sea of Japan, also exhibiting potent biological activity.[167]

Furthermore, the (–)-**86b** C11-epimer of (–)-erogorgiane derived from (–)-*trans,anti*-**187b** was also completed. It has the same absolute stereochemistry as the natural diterpene leubethanol (Figure 12) isolated from the root bark of *Leucophyllum frutescens*, an evergreen shrub in the figwort family, also known as cenizo, a medicinal plant of Mexican traditional medicine, which has long been used to treat lung complaints and specifically tuberculosis.[168] This hydroxylated analogue also exhibits potent biological activity against *Mycobacterium tuberculosis* H_{37}Rv.



(–)-**86b** Leubethanol

Figure 12

The asymmetric total synthesis of (–)-elisabethadione and (–)-erogorgiane has been accomplished in 2.1% and 14.2% yield, respectively. The methodology here presented benefits from the use of a single asymmetric step which in turn is the key step where the enantioselectivity is introduced. The stereochemistry of the homoallylic alcohol controls the installation of the three stereogenic centres in the backbone skeleton. The biological activity of these natural products is currently being tested. Preliminary studies carried out at Perm State University (Russia) have shown (–)-**86b** exhibits anti-inflammatory properties against carrageenan induced paw edema in mice with 23% at 25 μg/kg (voltaren exhibits 49% at 10 μg/kg).

4. EXPERIMENTAL

General Procedures

NMR spectra were recorded in $CDCl_3$, ^1H at 400 MHz and ^{13}C at 100.6 MHz with chloroform-d_1 (δ 7.26 ppm, ^1H; δ 77.0 ppm, ^{13}C) as internal standard unless otherwise indicated. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded in KBr disc unless otherwise indicated. The mass spectra were measured on a Thermo Exactive (Orbi), where the spectra was recorded in a positive or negative ion mode using electrospray ionization (ESI) from methanol or acetonitrile in the presence of $AgNO_3$ where specified. All reactions were performed under atmosphere of dry, oxygen-free nitrogen using oven-dried glassware. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum.

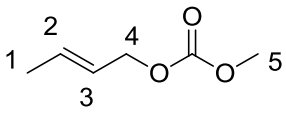
All chromatographic manipulations used silica gel as the absorbent. Reactions were monitored by thin layer chromatography (TLC) on aluminium backed plates with Merck Kiesel 60 F254 silica gel. TLCs were either visualized by UV radiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid or potassium permanganate aqueous solution, following by charring where appropriate. Purification by column chromatography was carried out using Merck Kiesel 60 H silica adsorbent.

All solvents and reagents for the reactions were of reagent grade and were dried and distilled under nitrogen immediately before use as follows: benzaldehyde from sodium hydroxide, toluene from calcium hydride and tetrahydrofuran was distilled under argon atmosphere from the sodium/benzophenone. Petroleum ether refers to the fraction boiling in the range 40-60 °C.

4.1. Synthesis of allylboronates

4.1.1. Synthesis of the precursors.

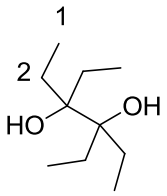
(E)-but-2-en-1-yl methyl carbonate (70)



70

A solution of crotyl alcohol (25 mmol, 2.13 mL, 1 eq.) and pyridine (110 mmol, 8.8 mL, 4.4 eq.) in DCM was placed in a 100 mL round bottom flask. The mixture was cooled at 0 °C and methylchloroformate (55 mmol, 4.25 mL, 2.2 eq.) was added dropwise to the solution while stirring. The resulting white suspension was allowed to stir for further 2 h at r.t. The mixture was diluted in 30 mL of water and extracted with light petroleum (3×50 mL). The organic phase was washed with 35 mL of brine and dried over Na_2SO_4. The solvent was remove in *vacuum* and the residue was purified by column chromatography on silica eluting with 90:10 mixture of light petroleum:ethyl acetate to yield the title compound as a colorless oil (1.17 g, 60%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 1.63 (dm, 3H, *J* = 4.8 Hz, 1-H); 3.66 (s, 3H, 5-H); 4.44 (dt, 2H, *J* = 6.4, 0.8 Hz, 4-H); 5.51 (m, 1H, 3-H); 5.74 (m, 1H, 2-H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 17.6 (*C*H_3), 54.4 (*C*H_3), 68.4 (*C*H_2), 124.6 (*C*H), 131.9 (*C*H), 155.6 (*C*). **IR:** 3028, 2959, 1749, 1443, 1379, 944, 793 cm^{-1}. **HRMS (ESI)** 153.0521 ($C_6H_{10}O_3Na$ ([M+Na]$^+$) requieres 153.0522).

3,4-diethylhexane-3,4-diol (71)

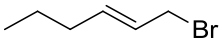


71

A round bottom flask was charged with magnesium turnings (14 g, 600 mmol, 8 eq) and flame dried under inert atmosphere. After vigorous stirring for 1 hour, a 0.1 M solution of SmI_2 in THF (75 mL, 7.5 mmol, 10 mol%) and TMSCl (4.7 mL, 37.5 mmol, 0.5 eq) were

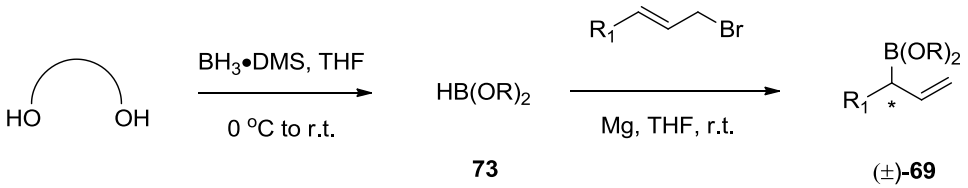
added at room temperature. Into the mixture was added dropwise a mixture of 3-pentanone (7.6 mL, 75 mmol, 1 eq) and TMSCl (9.5 mL, 75 mmol, 1 eq) at the rate to maintain the blue colour of SmI_2. After the reaction was completed, HCl 1M was added (ca 25 mL) and the organic compounds were extracted with diethyl ether (3x 75 mL). The organic layers were combined, dried over MgSO4 and concentrated *in vacuum* The title compound was obtained as a pale yellow oil by flash chromatography on SiO_2 (3.67 g, 56 % yield); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.93 (s, 2H, O*H*); 1.66-1.56 (qd, *J* = 15.6, 3.2 Hz, 8H, 2-H); 0.94 (t, *J* = 8 Hz, 12H, 1-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 78.8 (*C*), 27.3 (*C*H_2), 8.8 (*C*H_3); **IR:** υ 3454, 2968, 2882, 1462, 1383, 1265, 1125, 1039, 951, 916, 851 cm^{-1}; **HRMS (ESI)** 197.1511 ($C_{10}H_{22}O_2Na$ $[M+Na]^+$ requires 197.1512).

(E)-1-bromohex-2-ene (72)



PBr_3 (16.96 mmol, 1.6 mL, 0.4 eq.) was added at –10 °C to (*E*)-3-hex-2-en-1-ol (42.4 mmol, 5 mL, 1 eq.) in dry diethyl ether (95 mL). The reaction mixture was allowed to stir overnight while warming up to room temperature. The reaction was cooled in an ice bath and slowly quenched with water; it was washed with $NaHCO_3$ and extracted with DCM. The organic layers were combined and dried over Na_2SO_4. Flash column chromatography eluting with 100% petroleum ether afforded 5.4g of the target compound (56% yield); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.90 (t, *J* = 7.2 Hz, 3H); 1.41 (sept, *J* = 7.6 Hz, 2H); 2.04 (q, *J* = 7.2 Hz, 2H); 3.95 (d, *J* = 7.4 Hz, 2H); 5.65-5.81 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.6 (C*H*$_3$), 22.0 (C*H*$_2$), 33.7 (C*H*$_2$), 34.1 (C*H*$_2$), 126.5 (C*H*), 136.5 (C*H*); **IR:** υ 3032, 2960, 2930, 2873, 1660, 1463, 1436, 1379, 1203, 963, 592 cm^{-1}; **MS** was in agreement to the literature.[134]

4.1.2. General synthesis of allylboronates:



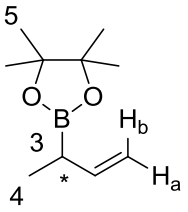
73 (±)-**69**

A flame dried round bottom flask was charged with a solution of the corresponding diol (1 eq.) in a freshly distilled THF. The solution was cooled at 0 °C with an ice bath and

BH_3•DMS (0.9 eq.) was added dropwise to the mixture. After the addition was completed the reaction was allowed to stir at this temperature for 30 minutes and then 90 minutes at room temperature. The corresponding borane **73** was used in the next step without further purification in solution at *ca* 1.3M in THF.

A flame-dried round bottom flask was charged with magnesium turnings (1.2 eq.). Freshly distilled THF was added to the flask followed by the previously prepared solution of borane with vigorous stirring (*ca* 0.8M in THF). The corresponding allylbromide (1 eq.) was added at room temperature to the solution and let stirred for 30 minutes. After this time a second equivalent of allylbromide was added to the reaction mixture and the solution was stirred for an additional 1.5 h. The reaction was quenched by dropwise addition of 0.1M HCl until the remaining magnesium turnings were fully consumed. The mixture was extracted with dichloromethane and the organic phase was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography using a gradient eluent system (100 hexane to 95/5, hexane/ethyl acetate) unless otherwise stated.

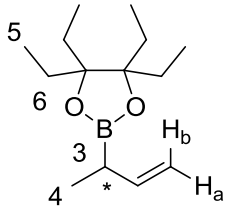
(±)-2-(But-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (69.4a).



(±)-**69.4a**

(±)-69.4a was purified using bulb-to-bulb distillation under reduced pressure (b.p = 100 ^oC, *p* = 4 mbar) was obtained as a colorless oil (997 mg, 72 % yield); **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 1.03 (d, *J* = 7.2 Hz, 3H, 4-H); 1.73 (s, 12H, 5-H); 1.83 (t, *J* = 7.2 Hz, 1H, 3-H); 4.89 (dt, *J* = 10.0, 1.6 Hz, 1H, CH_a=CH); 4.94 (dt, *J* = 17.2, 1.6 Hz, 1H, CH_b=CH) 5.87 (m, 1H, C*H*=CH_2); **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 14.1 (*C*H_3), 24.6 (*C*H_3), 24.7 (*C*H_3), 83.2 (*C*), 111.9 (*C*H_2), 140.9 (*C*H); **IR:** υ 3415, 3080, 2979, 2933, 2875, 1634, 1458, 1372, 1351, 1323, 1272, 1145, 983, 853 cm^{-1}. **MS** was in agreement with the literature.[120]

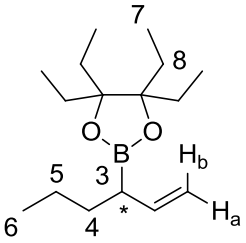
(±)-2-(But-3-en-2-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (69.5a).



(±)-**69.5a**

(±)-69.5a was obtained as a yellowish oil (668.4 mg, 76 % yield); **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 0.90 (t, *J* = 8.0 Hz, 12H, 5-H); 1.10 (d, *J* = 8.0 Hz, 3H, 4-H); 1.64 (m, 8H, 6-H); 1.91 (t, *J* = 8.0 Hz, 1H, 3-H); 4.89 (dt, *J* = 10.0, 1.6 Hz, 1H, CH_a=CH); 4.95 (dt, *J* = 17.2, 1.6 Hz, 1H, CH_b=CH); 5.97 (ddd, *J* = 17.2, 10.0, 6.8 Hz, 1H, C*H*=CH_2); **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 8.7 (*C*H_3), 8.8 (*C*H_3), 14.2 (*C*H_3), 26.2 (*C*H_2), 26.3 (*C*H_2), 88.1 (*C*), 111.5 (*C*H_2), 141.4 (*C*H); **IR:** υ 2973, 2947, 2884, 1635, 1458, 1384, 1351, 1307, 1289, 1195, 1114, 930 cm^{-1}; **HRMS (ESI)** 239.2175 ($C_{14}H_{27}BO_2Na$ $[M+Na]^+$ requires 239.2177).

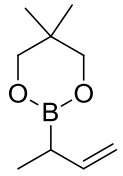
(±)-2-(Hex-1-en-3-yl)- 4,4,5,5-tetraethyl-1,3,2-dioxaborolane (69.5d).



(±)-**69.5d**

(±)-69.5d was obtained as colorless oil (2.1 g, 51 % yield); **^{1}H NMR (400 MHz, $CDCl_3$):** δ_H 0.89 (m, 15H, 6,7-H); 1.25-1.42 (m, 4H, 4,5-H); 1.60-1.66 (m, 8H, 8-H); 1.84 (q, *J* = 7.6 Hz, 1H, 3-H); 4.89 (ddd, *J* = 10.0, 2.0, 0.8 Hz, 1H, CH_{1a}=CH); 4.95 (ddd, *J* = 17.2, 2, 1.2 Hz, CH_{1b}=CH); 5.74-5.83 (m, 1H, C*H*=CH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 8.7 (*C*H_3), 8.8 (*C*H_3), 14.1 (*C*H_3), 22.0 (*C*H_2), 26.1 (*C*H_2), 26.2 (*C*H_2), 32.5 (*C*H_2), 88.1 (*C*), 112.9 (*C*H_2), 140.2 (*C*H); **IR:** υ 2957, 2884, 1632, 1460, 1384, 1366, 1349, 1306, 1289, 1253, 1114, 1043, 995, 974, 919 cm^{-1}; **HRMS (ESI)** 372.1490 ($C_{16}H_{31}BO_2Ag$ $[M+Ag]^+$ requires 372.1499).

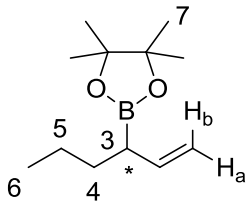
(±)-2-(But-3-en-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (69.3a).[63]



(±)-**69.3a**

(±)-69.3a was purified using bulb-to-bulb distillation under reduced pressure (b.p = 100 °C, *p* = 4 mbar) was obtained as a colorless oil (1.3 g, 57% yield). $_1$H NMR (400 MHz, $CDCl_3$): 0.88 (s, 6H, 6-H); 0.99 (d, *J* = 7.2 Hz, 3H, 1-H); 1.72-1.77 (m, 1H, 2-H); 3.53 (s, 4H, 5-H); 4.09-4.89 (m, 2H, 4-H); 5.86-5.94 (m, 1H, 3-H).

(±)-2-(hex-1-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (69.4d).

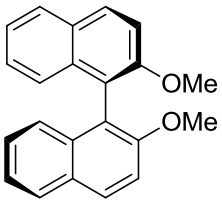


(±)-**69.4d**

(±)-69.4d was obtained as colorless oil (1.9 g, 55% yield); **^{1}H NMR (400 MHz, $CDCl_3$):** δ_C 0.81 (t, *J* = 7.2 Hz, 3H, 6-H); 1.16 (s, 12H, 7-H); 1.23-1.34 (m, 4H, 4,5-H); 1.76 (q, *J* = 7.6 Hz, 1H, 3-H); 4.84 (ddd, *J* = 10, 2, 0.8 Hz, 1H, CH_a=CH); 4.89 (ddd, *J* = 17.2, 2, 1.2 Hz, 1H, CH_b=CH); 5.65-5.74 (m, 1H, C*H*=CH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ_C 13.9 (*C*H_3), 21.9 (*C*H_2), 24.4 (*C*H_3), 24.5 (*C*H_3), 32.3 (*C*H_2), 82.8 (*C*), 113.2 (*C*H_2), 139.5 (*C*) ; **IR:** υ 2978, 2928, 2872, 1632, 1465, 1371, 1321, 1270, 1144, 969, 848 cm^{-1}; **HRMS (ESI)** 317.0826 ($C_{14}H_{27}BO_2Ag$ $[M+Ag]^+$ requires 317.0837).

4.2. Synthesis of chiral phosphoric acids

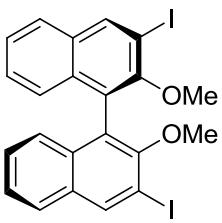
(R)-2,2'-dimethoxy-1,1'-binaphthyl (74).



(*R*)-**74**

A 100 mL three-necked round bottom flask was charged with (*R*)-BINOL (4 g, 14 mmol, 1 equiv.) and equipped with a magnetic stirrer bar, reflux condenser with N_2 inlet and an addition funnel. The flask was evacuated and back filled with N_2. Subsequently the vessel was charged with dried acetone (140 mL). Upon complete solution of the prior compound, K_2CO_3 (6.37 g, 46.2 mmol, 3.3 equiv.) was added followed by methyl iodide (3.5 mL, 56 mmol, 4 equiv.). The resulting mixture was heated to reflux for 24 h. The volatiles were removed under *vacuum*. The resulting mixture was redissolved in water (100 mL) and it was allowed to stir for 2 h. The resulting solid was collected in a funnel and dried under *vacuum* furnishing 4.09 g of the title compound **74** (92 %) as dim yellow solid. **m.p.:** 200-210 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 3.68 (s, 6H), 7.03 (d, *J* = 8 Hz, 2H), 7.13 (m, 2H), 7.23 (m, 2H), 7.37 (d, *J* = 9.2 Hz, 2H), 7.78 (d, *J* = 8 Hz, 2H), 7.89 (d, *J* = 9.2 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 56.9 (CH_3), 114.3 (*C*H), 119.6 (*C*), 123.5 (*C*H), 125.3 (*C*H), 126.3 (*C*H), 127.9 (*C*H), 129.2 (*C*), 129.4 (*C*H), 134.0 (*C*), 154.9 (*C*). **IR:** υ 3047, 3022, 2955, 2837, 1618, 1590, 1505, 1461, 1354, 1264, 1250, 1091, 1065, 811, 747 cm^{-1}. **HRMS (ESI)** was in agreement with the literature.[138]

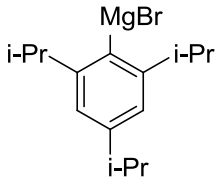
(R)-3,3'-diiodo-2,2'-dimethoxy-1,1'-binaphthyl (75).



(*R*)-**75**

A 250 three-necked round bottom flask was equipped with a magnetic stirrer bar, an addition funnel, an N_2 inlet and a glass stopper. The vessel was evacuated and backfilled with N_2 and charged with (*R*)-2,2'-dimethoxy-1,1'-binaphthyl (4.09 g, 13 mmol, 1 equiv.) in 100 mL of freshly distilled Et_2O. Freshly distilled TMEDA (6.2 mL, 41.68 mmol, 3.2 equiv.) was added followed by n-BuLi 2M in hexanes (23.4 mL, 46.8 mmol, 3.6 equiv.) dropwise via syringe at r.t. The mixture was allowed to stir for 4 h. I_2 (13.2 g, 52 mmol, 4 equiv.) in 100 mL of dry Et_2O was added dropwise *via* addition funnel at −78 °C. The resulting yellow-brownish reaction mixture was stirred overnight while being allowed to reach room temperature. The reaction was quenched with 150 mL saturated solution of Na_2SO_3 and stir for 1 h. The reaction mixture was extracted with Et_2O (3 x 150 mL). The organic layers were combined, washed with brine (150 mL) and dried over Na_2SO4. The solvents were removed in *vacuum* and the crude mixture was subjected to column chromatography (hexanes/ethyl acetate, 95:5) yielding (*R*)-**75** as pale yellow solid (4.42 g, 60%). **m.p.:** 160-170 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 3.34 (s, 6H), 6.99 (d, *J* = 8.5 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.72 (d, *J* = 8 Hz, 2H), 8.46 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 61.1 (*C*H_3), 92.3 (*C*), 125.4 (*C*), 125.7 (*C*H), 125.8 (*C*H), 126.9 (*C*H), 127.1 (*C*H), 132.2 (*C*), 133.8 (*C*), 139.9 (*C*H), 154.5 (*C*). **IR:** υ 3054, 2934, 2865, 1560, 1492, 1455, 1387, 1347, 1231, 1041, 1019, 967, 884, 748 cm^{-1}. **HRMS (ESI)** was in agreement with the literature.[138]

(2,4,6-triisopropylphenyl)magnesium bromide (76).

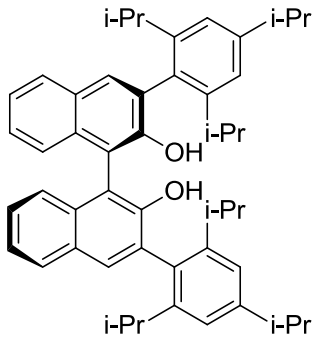


76

A 100-mL round bottom flask fitted with magnetic stirrer bar, a condenser and charged with Mg turnings (3.1 g, 128 mmol, 2 equiv., activated with 0.1 mL of 1,2-dibromoethane) was flamed dried under *vacuum* and was evacuated and filled with N_2 (three circles). The Mg was covered with anhydrous Et_2O (70 ml) and, subsequently, 2-bromo-1,3,5-triisopropylbenzene (18.12 g, 64 mmol, 1.0 equiv.) was added dropwise controlling the reflux. After the addition was completed, the rest of the Et_2O (10 ml) was added rinsing the walls of the condenser. The

resulting grey solution was placed in a pre-heated sand bath to be refluxed for 24 h. The resulting solution was used directly in the next step.

(1R,3R)-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol (78).

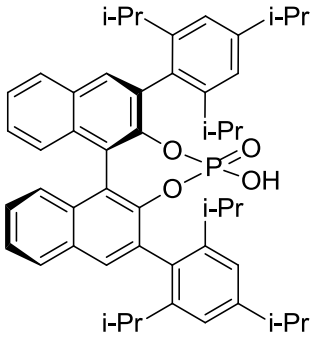


(*R*)-**78**

An flamed-dried 100 mL round bottom flask fitted with magnetic stirrer was charged with (*R*)-3,3'-diiodo-2,2'-dimethoxy-1,1'-binaphthyl (3.52 g, 6.23 mmol 1 equiv.) and $Ni(PPh_3)_2Cl_2$ (505 mg, 0.77 mmol, 0.12 equiv.). The flask was carefully evacuated and filled with N_2 (three circles). Et_2O (50 mL) was added followed by dropwise addition of the Grignard-solution **76** at room temperature. After the addition was complete, the resulting mixture was allowed to reflux for 6 h. The resulting brown solution was allowed to reach r.t. and then cooled to 0 °C with an ice bath. 1M HCl solution was added dropwise until no vigorous reaction occurred. The resulting mixture was extracted with Et_2O (3 x 50 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed in *vacuum*. The resulting yellowish solid crude **77** was used in the next step without further purification. The crude material was evacuated and backfilled with N_2 in a 250 mL round bottom flask fitted with a magnetic stirrer. Freshly distilled dichloromethane (25 mL) was added. The solution was cooled at 0 °C and BBr_3 (1M in DCM, 44 ml, 43.6 mmol, 7.0 equiv. based on (*R*)-3,3'-diiodo-2,2'-dimethoxy-1,1'-binaphthyl) was added dropwise. After complete addition, the resulting clear solution was allowed to stir for 24 h at room temperature. Subsequently, water (70 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL), the organic layers were combined, dried over MgSO4, and the solvents were removed in *vacuum.* Column chromatography (hexane/ethyl acetate 99:1) gave the title compound **78** as a dim yellow solid (1.62 g, 38 % over two steps). **m.p.:** 125-135 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 2.86-3.01 (sept., 2H), 3.03-3.10 (sept., 2H), 3.12-3.17

(sept., 2H), 7.32 (d, *J* = 6 Hz, 4H), 7.47-7.53 (m, 6H), 7.95 (s, 2H), 8.03 (d, *J* = 8Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 23.7 (*C*H_3), 23.9 (*C*H_3), 24.0 (*C*H_3), 24.0 (*C*H_3), 24.3 (*C*H_3), 24.3 (*C*H_3), 30.8 (*C*H), 30.9 (*C*H), 34.3 (*C*H), 113.1 (*C*), 121.2 (*C*H), 121.2 (*C*H), 123.8 (*C*H), 124.5 (*C*H), 126.6 (*C*H), 128.2 (*C*H), 130.7 (*C*H), 133.4 (*C*), 147.4 (*C*), 147.8 (*C*), 149.1 (*C*), 150.6 (*C*);
IR: υ 3523, 3057, 2960, 2868, 1604, 1497, 1455, 1422, 1383, 1361, 1317, 1263, 1147, 877, 74 8 cm^{-1}. **HRMS (ESI+)** was in agreement with the literature.[138]

(R)-TRIP (79).

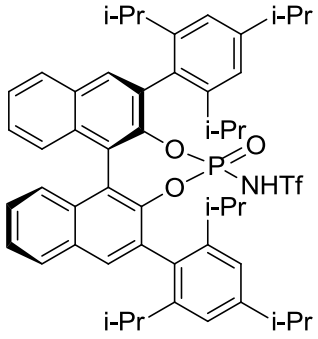


(*R*)-**79**

Chiral diol (*R*)-**78** (0.408 mmol, 281.7 mg, 1 eq.) was charged in a 50 mL two-necked round bottom flask fitted with a reflux condenser. The flask was evacuated and backfilled with N_2. Pyridine (1 mL) was added followed by $POCl_3$ (1.224 mmol, 0.114 mL, 3 eq.) and the reaction was allowed to reflux overnight. The reaction was allowed to reach room temperature, followed by the addition of 1.5 mL of water and the resulting mixture was heated to reflux for 3h. After the reaction reached r.t., 5 mL of DCM were added and the resulting organic layer was throughly washed with 1M HCl (3x5mL) until pH < 7. The combined organic layers were dried under $MgSO_4$ and volatile was removed in *vacuum*. (*R*)-TRIP (**79**) was obteined as a white-dim brownish solid after recrystalization from acetonitrile (255 mg, 83 %). **M.p.:** 190-200 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 0.94 (d, *J* = 6.8 Hz, 6H), 0.98 (d, *J* = 6.4 Hz, 6H), 1.05 (d, *J* = 6.8 Hz, 6H), 1.08 (d, *J* = 6.8 Hz, 6H), 1.25 (d, *J* = 6.8 Hz, 12H), 2.67-2.73 (m, 2H), 2.77-2.80 (m, 2H), 2.82-2.90 (m, 2H), 5.32 (s, 1H), 6.97 (m, 4H), 7.28-7.33 (m, 4H), 7.47-7.51 (m, 2H), 7.85 (s, 2H), 7.90 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 23.2 (*C*H_3), 23.4 (*C*H_3), 24.0 (*C*H_3), 24.1 (*C*H_3), 25.0 (*C*H_3), 26.3 (*C*H_3), 30.8 (*C*H), 34.2 (*C*H), 120.1 (*C*H), 121.0 (*C*H), 122.4 (*C*), 125.1 (*C*H), 125.9 (*C*H), 127.3 (*C*H), 128.1 (*C*H), 130.7 (*C*), 132.2 (*C*H),

132.6 (*C*), 147.4 (*C*), 147.8 (*C*), 148.0 (*C*). **IR:** υ 2959, 2928, 2865, 1607, 1465, 1411, 1361, 1241, 1080, 960 cm^{-1}. **HRMS (ESI)** was in agreement with the literature.[138]

(R)-(+)-[3,3'-Bis(2,4,6-triisopropyl)phenyl-1,1'-binaphthalen-2,2'-yl)-N-triflyl phosphoramide (80).[139]

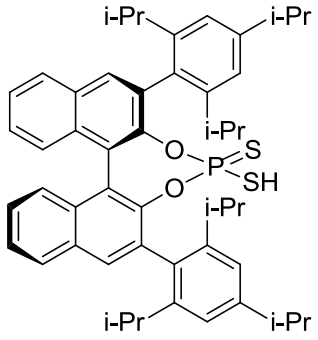


(*R*)-**80**

To a solution of (*R*)-**78** (350 mg, 0.5 mmol, 1 equiv.) in dichloromethane (3 mL), Et_3N (0.5 mL, 3.5 mmol, 7 equiv.), $POCl_3$ (56 µL, 0.6 mmol, 1.2 equiv.) and DMAP (122.2 mg, 1 mmol, 2 equiv.) were added at 0 °C. After the mixture was stirred for 1 hour at room temperature, CH_3CN (3 mL) was added at room temperature followed by $TfNH_2$ (149 mg, 1 mmol, 1 equiv.). Then the reaction was stirred at 100 °C for 12 hours. The reaction was quenched with H_2O (5 mL) and extracted with Et_2O (2x20 mL). The organic layers were combined, washed with sat. aq $NaHCO_3$ (30 mL) and 4N HCl (30 mL). The Resultant organic layer was dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude material was purified by column chromatography on silica gel (hexane:ethyl acetate, 75:25) yielding the target phosphoramide (*R*)-**80** as a pale yellow solid (310 mg, 70%). **M.p.:** 215-220 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 0.83(d, *J* = 6.8 Hz, 6H); 1.03 (t, *J* = 6.4Hz, 6H); 1.17 (m, 24H); 2.56 (sept., *J* = 6.8 Hz, 2H); 2.75 (quint., *J* = 6.8 Hz, 1H); 2.77-2.88 (m, 3H); 6.93-7.03 (m, 6H); 7.17 (m, 2H); 7.37 (quad., *J* = 6.4Hz, 2H); 7.77 (d, *J* = 14.4Hz, 2H); 7.80 (t, *J* = 8.8Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 22.6 (*C*H_3), 23.1 (*C*H_3), 23.3 (*C*H_3), 23.4 (*C*H_3), 23.8 (*C*H_3), 24.0 (*C*H_3), 24.1 (*C*H_3), 24.3 (*C*H_3), 25.0 (*C*H_3), 25.1 (*C*H_3), 26.3 (*C*H_3), 26.7 (*C*H_3), 30.6 (*C*H), 30.8 (*C*H), 30.9 (*C*H), 34.2 (*C*H), 34.5 (*C*H), 119.9 (*C*H), 120.3 (*C*H), 120.7 (*C*H), 121.1 (*C*), 121.4 (*C*), 121.6 (*C*H), 122.3 (*C*H), 125.5 (*C*H), 126.2 (*C*H), 126.3 (*C*H), 127.1 (*C*H), 127.2 (*C*H), 128.0 (*C*H), 128.3 (*C*H), 130.6 (*C*), 131.0 (*C*), 131.4 (*C*), 131.5 (*C*),

132.3 (*C*H), 132.5 (*C*H), 132.6 (*C*), 132.6 (*C*), 132.7 (*C*), 145.9 (*C*), 146.0 (*C*), 146.7 (*C*), 146.9 (*C*), 147.4 (*C*), 148.1 (*C*), 148.6 (*C*), **^{31}P NMR (162 MHz, CDCl$_3$)** δ_P 2.3. **^{19}F NMR (377 MHz, CDCl$_3$)** δ_F 82.3. **IR:** υ 3629, 3498, 2960, 2870, 1610, 1462, 1292, 1229, 1195, 1149, 1089, 975, 894, 750 cm^{-1}. **HRMS (ESI):** 928.3359, found 928.3334 ($C_{51}H_{56}O_5SF_3PNNa_2$), in agreement with literature.[139]

(R)-thio-TRIP (81).[140]

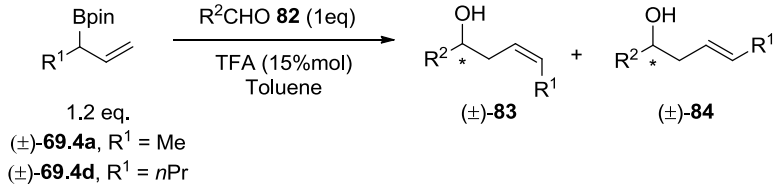


(*R*)-**81**

(*R*)-**78** (150 mg, 0.22 mmol, 1 equiv.) was charged in a 25 mL round bottom flask fitted with a magnetic stirrer. The vessel was flushed with N_2 and freshly distilled toluene (4 mL) was added. P_4S_{10} (29 mg, 0.13 mmol, 0.6 equiv.) in toluene was added to the solution. The mixture was allowed to reflux overnight. After the reaction was cooled at room temperature, the solvent was removed in *vacuum*. The target compound was obtained as a pale brown solid, 141.6 mg, 82% yield. **M.p.:** 242-245 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H 0.78 (d, *J* = 6.8 Hz,3H); 1.08 (m, 6H); 1.18 (m, 6H); 1.23 (d, *J* = 6.8 Hz, 3H); 2.67 (quint, *J* = 6.8 Hz, 1H); 2.82 (quint., *J* = 6.8 Hz, 1H); 3.05 (quint, *J* = 6.8 Hz, 1H); 6.94 (s, 1H); 7.02 (s, 1H); 7.07 (d, *J* = 8.4 Hz, 1H); 7.15 (t, *J* = 8.4 Hz, 1H); 7.36 (t, *J* = 7.6 Hz, 1H); 7.77 (s, 1H); 7.79 (d, *J* = 8 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ_C 23.6 (*C*H$_3$), 24.1 (*C*H$_3$), 25.0 (*C*H$_3$), 27.3 (*C*H), 30.8 (*C*H) 34.2 (*C*H) 120.1 (*C*H), 121.6 (*C*H), 123.5 (*C*), 125.0 (*C*H), 125.8 (*C*H), 127.3 (*C*H), 128.1 (*C*H), 130.6 (*C*), 132.1 (*C*H), 132.2 (*C*), 133.0 (*C*), 133.3 (*C*), 148.2 (*C*), 148.4 (*C*), 149.0 (*C*). **^{31}P NMR (162 MHz, CDCl$_3$)** δ_P 126.1. **IR:** υ 3400, 2960, 2932, 2869, 1605, 1460, 1407, 1149, 993, 963, 859, 832, 748, 701 cm^{-1}. **MS (ESI):** 829.3249, found 829.3234 ($C_{50}H_{56}O_2S_2PNa_2$).

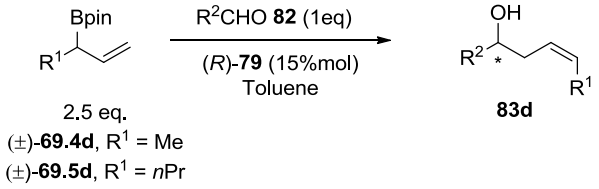
4.3 Kinetic resolution of racemic allylboronates. Allylation of aldehydes

4.3.1. General procedure for the synthesis of racemic homoallylic alcohols 83/84aa-83/84ak and 83/84da-83/84dc



A 10 mL round bottom flask was charged with allylboronate (±)-**69.4a** or (±)-**69.4d** (0.82 mmol, 1.2 eq.) in 1.5 mL of toluene. The corresponding aldehyde (0.68 mmol, 1 eq.) was added followed by trifluoroacetic acid (0.10 mmol, 7.6 μL, 15 mol%). The reaction mixture was allowed to stir at room temperature overnight. To the reaction mixture, 2 mL of a saturated solution of $NaHCO_3$ was added and stirred for further 30 minutes. The mixture was diluted with 10 mL of a saturated solution of $NaHCO_3$ and extracted with dichloromethane (3x15 mL). The organic layers were combined and dried over Na_2SO_4. Solvents were removed under reduced pressure. The crude mixture was purified by flash column chromatography on *sílica* with a gradient eluent system (100 hexane to 95:5, hexane/ethyl acetate) afforded the corresponding racemic homoallylic alcohols (±)-**83** and (±)-**84**.

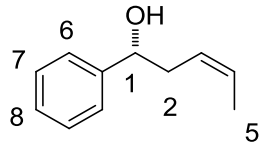
4.3.2. General procedure for the kinetic resolution of racemic allylboronates in the allylation of aldehydes.



A reaction tube was fitted with a stirring bar. The vessel was evacuated, backfilled with N_2 and then charged successively with a solution of (*R*)-TRIP (12.6 mg, 0.0168 mmol, 5 mol %) in 0.5 mL of dry toluene and a 0.5M stock solution of benzoic acid in toluene (6.7 μL, 0.0034 mmol, 1 mol%). The solution was cooled at –42 °C. Aldehyde (0.34 mmol, 1 equiv.) dissolved in 0.5 mL of dry toluene was added followed by a dropwise addition of a solution of

allylboronate (0.84 mmol, 2.5 equiv.) in 0.5 mL of dry toluene. After the reaction was complete, as evidenced by TLC, a saturated solution of $NaHCO_3$ (5 mL) was added, the mixture was stirred for 1 h and then the organic phase was extracted with ethyl acetate (3 × 15 mL). Organic layers were combined and dried over Na_2SO_4. Solvent was removed in *vacuum*. Flash chromatography on *sílica* with a gradient eluent system (100 hexane to 95:5, hexane/ethyl acetate) afforded the target homoallylic alcohol.

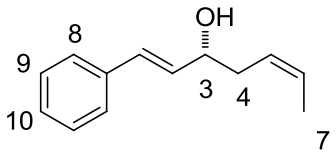
(R,Z)-(+)-1-Phenylpent-3-en-1-ol (83aa).



(+)-**83aa**

***R*-(+)-83aa** Colorless oil (52 mg, 96 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.28; $[\alpha]_D^{25}$ = + 60.0 (*c* = 2.5, $CHCl_3$; literature gives[169] **$[\alpha]_D^{25}$** = +70.3 (*c* = 1.0, $CHCl_3$, 98% ee); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H 1.58 (dt, *J* = 6.8, 0.8 Hz, 3H, 5-H); 1.97 (br s, 1H, O*H*); 2.43-2.48 (m, 1H, 2-H); 2.51-2.57 (m, 1H, 2'-H); 4.67-4.71 (m, 1H, 1-H); 5.34-5.45 (m, 1H, C*H*=CH); 5.57-5.68 (m, 1H, C*H*=CH); 7.28-7.22 (m, 1H, 8-H); 7.37-7.30 (m, 4H, 6,7-H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C 13.0 (*C*H_3), 36.9 (*C*H_2), 73.8 (*C*H-O), 125.6 (*C*H), 125.8 (*C*H), 127.4 (*C*H), 127.7 (*C*H), 128.4 (*C*H), 144.1 (*C*); **IR:** υ 3368, 3025, 2918, 1603, 1493, 1453, 1404, 1311, 1200, 1048, 912, 873, 758 cm^{-1}; **HRMS (ESI)** 185.0939 ($C_{11}H_{14}ONa$ $[M+Na]^+$ requires 185.0937); Chiral HPLC (Dynmax-60Å+Chiralpak IB-3 columns in series, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 225 nm) showed 98% ee (t_R = 27.5 min (major), t_S = 28.6 min (minor)).

(R,1E,5Z)-(+)-1-phenylhepta-1,5-dien-3-ol (83ab).

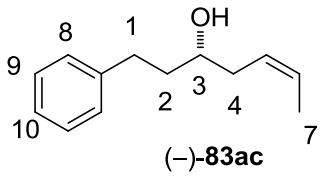


(+)-**83ab**

***R*-(+)-83ab** was obtained as colorless oil (53 mg, 84 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.25; **$[\alpha]_D^{25}$** = +17.9 (*c* = 0.78, $CHCl_3$, 83% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.67 (dt, *J* = 6.8, 0.8 Hz, 3H, 7-H); 2.40-2.46 (m, 2H, 4-H); 4.32-4.37 (m, 1H, 3-H); 5.46-5.51

(m, 1H, C*H*=CH); 5.66-5.70 (m, 1H, C*H*=CH); 6.26 (dd, *J* = 16.0, 6.4 Hz, 1H, C*H*=CH); 6.61 (d, *J* = 16.0 Hz, 1H, C*H*=CH); 7.24-7.30 (m, 1H, 10-H); 7.32 (t, *J* = 7.2 Hz, 2H, 9-H); 7.38-7.40 (m, 2H, 8-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.1 (*C*H_3), 35.0 (*C*H_2), 72.3 (*C*H-O), 125.2 (*C*H), 126.4 (*C*H), 127.6 (*C*H), 127.7 (*C*H), 128.5 (*C*H), 130.2 (*C*H), 131.7 (*C*H), 136.7 (*C*); **IR:** υ 3375, 3024, 2926, 1656, 1599, 1494, 1449, 1031, 966, 916, 748 cm^{-1}; HRMS (ESI) 211.1093 ($C_{13}H_{16}ONa$ $[M+Na]^+$ requires 211.1093); chiral HPLC (ChiralPak IB-3 column, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 225 nm) showed 97% ee (t_R = 30.2 min (major), t_S = 62.6 min (minor)).

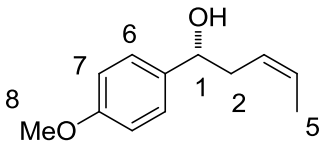
(S,Z)-(–)-1-phenylhept-5-en-3-ol (83ac).



(–)-**83ac**

***S*-(-)-83ac** was obtained as colorless oil (52 mg, 81 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.25; **$[\alpha]_D^{25}$** = – 17.7 (*c* = 0.61, $CHCl_3$, 91% ee; literature gives[169,170] **$[\alpha]_D^{25}$** = – 21.2 (*c* = 1.0, CH_2Cl_2); **$[\alpha]_D^{25}$** = – 12.2 (*c* = 1.0, $CHCl_3$): **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.75 (dt, *J* = 6.8, 0.8 Hz, 3H, 7-H); 1.87-1.93 (m, 2H, 1-H); 2.34-2.39 (2, 2H, 2-H); 2.76-2.83 (m, 1H, 4-H); 2.89-2.96 (m, 1H, 4'-H); 3.76-3.78 (m, 1H, 3-H); 5.50-5.57 (m, 1H, C*H*=CH); 5.73-5.81 (m, 1H, C*H*=CH); 7.27-7.32 (m, 3H, 9,10-H); 7.36-7.41 (m, 2H, 8-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.0 (*C*H_3), 32.1 (*C*H_2), 35.0 (*C*H_2), 38.4 (*C*H_2), 70.7 (*C*H-O), 125.7 (*C*H), 125.8 (*C*H), 127.5 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 142.1 (*C*); **IR:** υ 3368, 3062, 3025, 2934, 2860, 1603, 1496, 1454, 1404, 1048, 933, 862, 747 cm^{-1}; chiral HPLC (ChiralPak IB-3, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 220 nm) showed 91% ee (t_S = 18.3 min (major), t_R = 29.4 min (minor)).

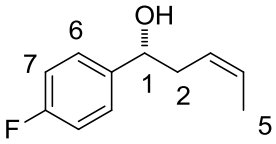
(R,Z)-(+)-1-(4-methoxyphenyl)pent-3-en-1-ol (83ad).



(+)**-83ad**

***R*-(+)-83ad** was obtained as colorless oil (45 mg, 70 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.28; **$[\alpha]_D^{25}$** = +52.2 (*c* = 0.72, $CHCl_3$, 98% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.61 (dt, *J* = 6.8, 0.8 Hz, 3H, 5-H); 2.04 (br s, 1H, OH); 2.40-2.47 (m, 1H, 2-H); 2.53-2.61 (m, 1H, 2'-H); 3.80 (s, 3H, 8-H); 4.64-4.67 (m, 1H, 1-H); 5.37-5.43 (m, 1H, C*H*=CH); 5.58-5.66 (m, 1H, C*H*=CH); 6.88 (dt, *J* = 8.8, 2.8 Hz, 2H, 7-H); 7.29 (dt, *J* = 8.8, 2.8 Hz, 2H, 6-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.0 (*C*H_3), 36.8 (*C*H_2), 55.2 (*C*H_3), 73.4 (*C*H-O), 113.7 (*C*H), 125.8 (*C*H), 127.1 (*C*H), 127.4 (*C*H), 136.2 (*C*), 158.9 (*C*); IR: υ 3397, 3016, 2928, 2836, 1612, 1512, 1460, 1247, 1174, 1036, 831 cm^{-1}; **HRMS (ESI)** 215.1038 ($C_{12}H_{16}O_2Na$ $[M+Na]^+$ requires 215.1043); Chiral HPLC (ChiralPak IB-3 column, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 220 nm) showed 98% ee (t_R = 24.4 min (major), t_S = 26.9 min (minor)).

(R,Z)-(+)-1-(4-fluorophenyl)pent-3-en-1-ol (83ae).

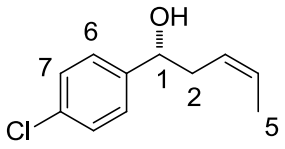


(+)**-83ae**

***R*-(+)-83ae** was obtained as colorless oil (48 mg, 80 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.28; **$[\alpha]_D^{25}$ =** +35.2 (*c* = 1.34, $CHCl_3$, 57% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.57 (dt, *J* = 6.8, 0.8 Hz, 3H, 5-H); 1.96 (d, *J* = 2.8 Hz, 1H, OH); 2.39-2.44 (m, 1H, 2-H); 2.49-2.54 (m, 1H, 2'-H); 4.68 (ddd, *J* = 8.0, 5.2, 2.8 Hz, 1H, 1-H); 5.36-5.39 (m, 1H, C*H*=CH), 5.61-5.65 (m, 1H, C*H*=CH); 7.00 (t, *J* = 8.4 Hz, 2H, 7-H), 7.31 (dd, *J* = 8.4, 5.2 Hz, 2H, 6-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.0 (*C*H_3), 37.0 (*C*H_2), 73.2 (*C*H-O), 115.1 (d, $^2J_{C\text{-}F}$ = 21 Hz, *C*H), 125.3 (*C*H), 127.4 (d, $^3J_{C\text{-}F}$ = 8 Hz, *C*H), 128.0 (*C*H), 139.7 (d, $^4J_{C\text{-}F}$ = 4 Hz, *C*), 162.1 (d, *J* = 244 Hz, *C*-F); **IR:** υ 3375, 3020, 2921, 1605, 1510, 1439, 1371, 1223, 1156, 1048, 968, 874, 835 cm^{-1}; **HRMS (ESI)** 163.0917 ($C_{11}H_{12}F$ $[M\text{-}OH]^+$ requires 163.0929); chiral HPLC

(two Chiralpak IB-3 columns in series, hexane/2-propanol = 98:2, 0.7 mL/min, UV detection at 220 nm) showed 85% ee (t_S = 32.8 min (minor), t_R = 33.9 min (major)).

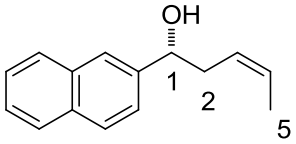
(R,Z)- (+)-1-(4-chlorophenyl)pent-3-en-1-ol (83af).



(+)-**83af**

***R*-(+)-83af** was obtained as colorless oil (53 mg, 81 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.29; $[\alpha]_D^{25}$ = +65.8 (*c* = 0.98, $CHCl_3$, 98% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.59 (dt, *J* = 6.8, 0.8 Hz, 3H, 5-H); 2.02 (br s, 1H, OH); 2.40-2.47 (m, 1H, 2-H); 2.50-2.58 (m, 1H, 2'-H); 4.70 (br t, *J* = 6.4 Hz, 1H,1-H); 5.36-5.43 (m, 1H, C*H*=CH); 5.62-5.69 (m, 1H, C*H*=CH); 7.29 - 7.32 (m, 4H, 6,7-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.0 (*C*H_3), 37.0 (*C*H_2), 73.1 (*C*H-O), 125.1 (*C*H), 127.2 (*C*H) 128.1 (*C*H), 128.4 (*C*H), 133.1 (*C*), 142.5 (*C*); **IR:** υ 3366, 3020, 2920, 1491, 1406, 1091, 1049, 1013, 829, 784 cm^{-1}; **HRMS (ESI)** 219.0547 ($C_{11}H_{13}ClONa$ $[M+Na]^+$ requires 219.0567); Chiral HPLC (ChiralPak IB-3 column, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 220 nm) showed 98% ee (t_S = 16.5 min (minor), t_R = 17.2 min (major)).

(R,Z)-(+)-1-(naphthalen-2-yl)pent-3-en-1-ol (83ag).

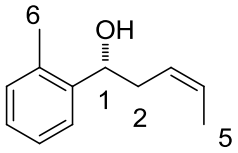


(+)-**83ag**

***R*-(+)-83ag** was obtained as colorless oil (56 mg, 78 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.28; $[\alpha]_D^{25}$ = +61.6 (c = 0.73, $CHCl_3$, 98% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.63 (d, *J* = 6.8 Hz, 3H, 5-H); 2.12 (d, *J* = 2.8 Hz, 1H, OH); 2.54-2.61 (m, 1H, 2-H); 2.63-2.71 (m, 1H, 2'-H); 4.88-4.92 (m, 1H, 1-H); 5.42-5.49 (m, 1H, C*H*=CH); 5.62-5.70 (m, 1H, C*H*=CH); 7.46-7.52 (m, 3H, Ar-H); 7.82-7.85 (m, 4H, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.0 (*C*H_3), 36.8 (*C*H_2), 73.9 (*C*H-O), 124.0 (*C*H), 124.5 (*C*H), 125.5 (*C*H), 125.7 (*C*H), 126.1 (*C*H), 127.7 (*C*H), 127.8 (*C*H), 127.9 (*C*H), 128.2 (*C*H), 132.9 (*C*), 133.2 (*C*), 141.4 (*C*); **IR:** υ

3370, 3018, 2916, 1601, 1508, 1437, 1368, 1318, 1270, 1123, 896, 856, 819, 747 cm^{-1}; **HRMS (ESI)** 235.1089 ($C_{15}H_{16}ONa$ $[M+Na]^+$ requires 235.1093); Chiral HPLC (Dynmax-60Å+ChiralPak IB-3 columns in series, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 220 nm) showed 98% ee (t_S = 49.2 min (minor), t_R = 53.2 min (major)).

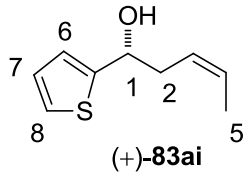
(R,Z)-(+)-1-(o-tolyl)pent-3-en-1-ol (83ah).



(+)**-83ah**

***R*-(+)-83ah** was obtained as colorless oil (44 mg, 75 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.28; **$[\alpha]_D^{25}$ =** +80.3 (*c* = 1.2, $CHCl_3$, 91% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.63 (dt, *J* = 6.8, 0.8 Hz, 3H, 5-H); 1.94 (d, *J* = 3.1 Hz, 1H, OH); 2.35 (s, 3H, 6-H); 2.46-2.53 (m, 2H, 2-H); 4.96 (ddd, *J* = 8.0, 4.7, 3.0 Hz, 1H, 1-H); 5.47-5.50 (m, 1H, C*H*=CH); 5.65-5.69 (m, 1H, C*H*=CH); 7.13-7.24 (m, 3H, Ar-H); 7.52 (dd, *J* = 7.7, 1.0 Hz, 1H, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.0 (*C*H_3), 19.1 (*C*H_3), 35.7 (*C*H_2), 70.2 (*C*H-O) 125.2 (*C*H), 125.9 (*C*H), 126.2 (*C*H), 127.2 (*C*H), 127.6 (*C*H), 130.3 (*C*H), 134.4 (*C*H), 142.2 (*C*H); **IR:** υ 3367, 3021, 2922, 1656, 1605, 1488, 1461, 1404, 1309, 1286, 1179, 1046, 874, 757, 726, 702 cm^{-1}; **HRMS (ESI)** 177.1273 ($C_{12}H_{17}O$ $[M+H]^+$ requires 177.1274); Chiral HPLC (Dynmax-60Å+Chiralpak IB-3 columns in series, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 220 nm) showed 91% ee (t_S = 24.9 min (minor), t_R = 26.2 min (major)).

(R,Z)-(+)-1-(thiophen-2-yl)pent-3-en-1-ol (83ai).

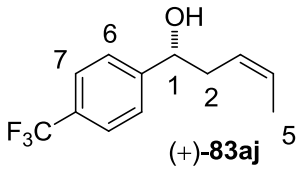


(+)**-83ai**

***R*-(+)-83ai** was obtained as colorless oil (44 mg, 78 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.26; **$[\alpha]_D^{25}$ =** +40.3 (*c* = 1.3, $CHCl_3$, 99% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.65 (dt, *J* = 6.8, 0.8 Hz, 3H, 5-H); 2.12 (d, *J* = 4.0 Hz, 1H, OH); 2.53-2.75 (m, 2H, 2-H); 4.96-5.00 (m, 1H, 1-H); 5.39-5.49 (m, 1H, C*H*=CH); 5.61-5.73 (m, 1H, C*H*=CH); 6.96-7.00 (m, 2H,

6,7-H); 7.21-7.29 (m, 1H, 8-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.1 (*C*H_3), 36.9 (*C*H_2), 69.8 (*C*H-O), 123.7 (*C*H), 124.5 (*C*H), 125.1 (*C*H), 126.6 (*C*H), 128.0 (*C*H), 148.0 (*C*); **IR:** υ 3374, 3018, 2921, 1995, 1656, 1439, 1404, 1314, 1229, 1035, 851 cm^{-1}; HRMS (ESI) 191.0501 ($C_9H_{12}OSNa$ $[M+Na]^+$ requires 191.0501); Chiral HPLC (two ChiralPak IB-3 columns in series, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 220 nm) showed 99% ee (t_S = 40.6 min (minor), t_R = 41.7 min (major)).

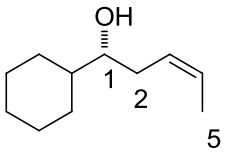
(R,Z)-(+)-1-(4-(trifluoromethyl)phenyl)pent-3-en-1-ol (83aj).



(+)-**83aj**

***R*-(+)-83aj** was obtained as colorless oil (62 mg, 80 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.29; **$[\alpha]_D^{25}$ =** +56.7 (*c* = 1.0, $CHCl_3$, 96% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.57 (dt, *J* = 6.8, 0.8 Hz, 3H, 5-H); 2.08 (d, *J* = 2.8 Hz, 1H, OH); 2.41-2.56 (m, 2H, 2-H); 4.74-4.78 (m, 1H, 1-H); 5.34-5.41 (m, 1H, C*H*=CH); 5.62-5.68 (m, 1H, C*H*=CH); 7.46 (d, *J* = 8.0 Hz, 2H); 7.58 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 12.3 (*C*H_3), 37.0 (*C*H_2), 73.1 (*C*H-O), 125.3 (*C*H), 125.3 (*C*H), 126.1 (*C*H), 128.5 (*C*H), 147.9 (*C*); **IR:** υ 3367, 3022, 2923, 1922, 1657, 1620, 1418, 1327, 1165, 1126, 1016, 875. 842, 704, 608 cm^{-1}; **HRMS (ESI)** 336.9953 ($C_{12}H_{13}F_3OAg$ $[M+Ag]^+$ requires 336.9964); Chiral HPLC (ChiralpaK IC-3 column, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 220 nm) showed 96% ee (t_R = 9.6 min (major), t_S = 10.6 min (minor)).

(S,Z)-(+)-1-cyclohexylpent-3-en-1-ol (83ak).

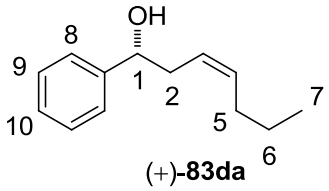


(+)-**83ak**

S*-(+)-83aj** was obtained as colorless oil (41 mg, 72 % yield). TLC (8.5:1.5 LP:EA, PMA): 0.28; **$[\alpha]_D^{25}$ =** +11.1 (*c* = 0.94, $CHCl_3$, 87% ee; literature gives $[\alpha]_D^{25}$ = –2.5, *c* = 1.0, CH_2Cl_2 for ***R isomer); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.03-1.09 (m, 2H); 1.15-1.25 (m, 3H); 1.36-1.37 (m, 1H); 1.63-1.65 (m, 6H), 1.74-1.77 (m, 2H); 1.84-1.89 (m, 1H); 2.21-2.24 (m, 2H,

2-H); 3.37 (q, *J* = 6.0 Hz, 1H, 1-H); 5.41-5.48 (m, 1H, C*H*=CH); 5.61-5.69 (m, 1H, C*H*=CH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.0 (*C*H_3), 26.1 (*C*H_2), 26.3 (*C*H_2), 26.5 (*C*H_2), 28.1 (*C*H_2), 29.2 (*C*H_2), 31.8 (*C*H_2), 43.1 (*C*H), 75.5 (*C*H-O) 126.6 (*C*H) 127.3 (*C*H); **IR:** υ 3389, 2924, 2852, 1449, 1038 cm^{-1}; **HRMS (ESI)** 275.0552 ($C_{11}H_{20}OAg$ $[M+Ag]^+$ requires 275.0560); **^{19}F NMR** of the corresponding Mosher ester showed 87% ee (δ_S = 90.83 ppm and δ_R = 90.98 ppm).

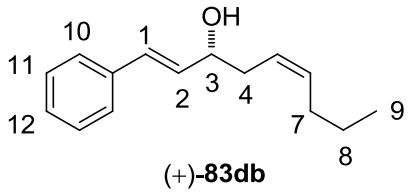
(R,Z)-(+)-1-phenylhept-3-en-1-ol (83da).



(+)**-83da**

***R*-(+)-83da** was obtained as colorless oil (51 mg, 90 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.28; **$[\alpha]_D^{25}$ =** +40.5 (*c* = 0.84, $CHCl_3$, 94% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.88 (t, *J* = 7.2 Hz, 3H, 7-H); 1.31-1.37 (m, 2H, 6-H); 1.98-2.05 (m, 3H, 5-H, OH); 2.45-2.51 (m, 1H, 2-H); 2.53-2.61 (m, 1H, 2'-H); 4.68-4.72 (m, 1H, 1-H); 5.37-5.44 (m, 1H, C*H*=CH); 5.53-5.60 (m, 1H, C*H*=CH); 7.28-7.30 (m, 1H, 10-H); 7.33-7.38 (m, 4H, 8,9-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.7 (*C*H_3), 22.6 (*C*H_2), 29.4 (*C*H_2), 37.3 (*C*H_2), 73.8 (*C*H-O), 124.7 (*C*H), 125.8 (*C*H), 127.4 (*C*H), 128.3 (*C*H), 133.6 (*C*H) 144.0 (*C*); **IR:** υ 3365, 3063, 3012, 2958, 2929, 2871, 1493, 1453, 1404, 1377, 1310, 1200, 1049, 910, 876, 758, 700 cm^{-1}; **HRMS (ESI)** 297.0394 ($C_{14}H_{21}O_2Ag$ $[M+Ag]^+$ requires 297.0403); Chiral HPLC (Chiralpak IB-3 column, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 220 nm) showed 94% ee (t_R = 14.8 min (major), t_S = 16.7 min (minor)).

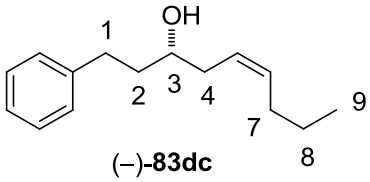
(R,1E,5Z)-(+)-1-phenylnona-1,5-dien-3-ol (83db).



(+)-**83db**

***R*-(+)-83db** was obtained as colorless oil (64 mg, 97 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.28; **$[\alpha]_D^{25}$ =** +18.0 (*c* = 1.6, $CHCl_3$, 94% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.83 (t, *J* = 7.2 Hz, 3H, 9-H); 1.32 (sex, *J* = 7.2 Hz, 2H, 8-H); 1.98 (q, *J* = 7.2 Hz, 2H, 7-H); 2.29-2.39 (m, 2H, 4-H); 4.25 (q, *J* = 6.4 Hz, 1H, 3-H); 5.34-5.41 (m, 1H, C*H*=CH); 5.48-5.55 (m, 1H, C*H*=CH); 6.18 (dd, *J* = 15.6, 6.4 Hz, 1H, 2-H); 6.53 (d, *J* = 15.6 Hz, 1H, 1-H); 7.24 (t, *J* = 7.2, 1H, 12-H); 7.32 (t, *J* = 7.2 Hz, 2H, 11-H); 7.39 (d, *J* = 7.2 Hz, 2H, 10-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.7 (*C*H_3), 22.7 (*C*H_2), 29.4 (*C*H_2), 35.4 (*C*H_2), 72.3 (*C*H-O), 125.4 (*C*H), 126.4 (*C*H), 127.5 (*C*H), 128.5 (*C*H), 130.2 (*C*H), 131.7 (*C*H), 133.5 (*C*H), 136.6 (*C*); **IR:** υ 3350, 3060, 3024, 2958, 2870, 1599, 1494, 1449, 1377, 1263, 1129, 1091, 1070, 1029, 966, 873, 748, 692 cm^{-1}**; HRMS (ESI)** 323.0550 ($C_{15}H_{20}OAg$ $[M+Ag]^+$ requires 323.0560); Chiral HPLC (Chiralpak IB-3 column, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 220 nm) showed 94% ee (t_R = 24.2 min (major), t_S = 45.1 min (minor)).

(S,Z)-(–)-1-phenylnon-5-en-3-ol (83dc).



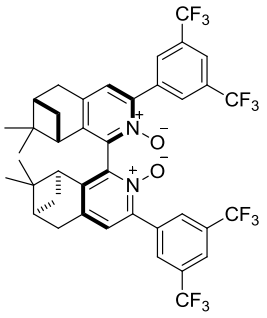
(–)-**83dc**

***S*-(-)-83dc** was obtained as colorless oil (52 mg, 80 % yield). TLC (8.5:1.5 LP:EA, UV, PMA): 0.28; **$[\alpha]_D^{25}$ =** –5.8 (*c* = 1.1, $CHCl_3$, 84% ee); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.91 (t, *J* = 7.6 Hz, 3H, 9-H); 1.39 (sex, *J* = 7.6, 2H, 8-H); 1.63 (s, 1H, OH); 1.77-1.83 (m, 2H, 7-H); 2.02-2.07 (m, 2H, 1-H); 2.24-2.28 (m, 2H, 2-H); 2.65-2.73 (m, 1H, 4-H); 2.78-2.86 (m, 1H, 4'-H); 3.62-3.68 (m, 1H, 3-H); 5.38-5.44 (m, 1H, C*H*=CH); 5.55-5.62 (m, 1H, C*H*=CH); 7.17-7.23 (m, 3H, 11,12-H); 7.27-7.31 (m, 2H, 10-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.8 (*C*H_3), 22.8 (*C*H_2), 29.4 (*C*H_2), 32.1 (*C*H_2), 35.4 (*C*H_2), 38.4 (*C*H_2), 70.7 (*C*H-O), 124.9 (*C*H), 125.7 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 133.5 (*C*H), 142.1 (*C*); **IR:** υ 3362, 3062, 3025, 2929, 2867,

1603, 1496, 1454, 1403, 1377, 1052, 927, 872, 746, 699 cm^{-1}; **HRMS (ESI)** 325.076 ($C_{11}H_{13}OAg$ $[M+Ag]^+$ requires 325.0716); Chiral HPLC (Chiralpak IB-3 column, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 220 nm) showed 84% ee (t_R = 15.7 min (major), t_S = 24.6 min (minor)).

4.4. Synthesis of bis-N-oxide 165

(–)-Bis-N-oxide 165

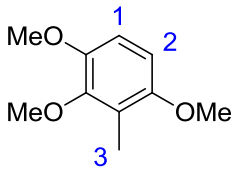


(–)-**165**

To a solution of freshly distilled diisopropylamine (84.6 μL, 0.6 mmol, 1.2 eq.) in THF (10 mL), 1.6M *n*BuLi in hexanes (0.312 mL, 0.5 mmol, 1 eq.) was added dropwise under inert atmosphere at 0 °C and the reaction was stirred for 1 hour. Isoquinoline-*N*-oxide **168** (200 mg, 0.5 mmol, 1 eq.) in THF (5 mL) was added dropwise at 0 °C, the solution gradually turned purple. The mixture was stirred for further 30 minutes after which time inert atmosphere was replaced by O_2 atmosphere. The solution was let to stir for 3 hours while turning dark brown in colour. The reaction was quenched with saturated solution of $NaHCO_3$ (20 mL) and extracted with DCM (3×35 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica using gradient eluent up to 20:80 petroleum ether/ethyl acetate afforded in order of elution the target compound (–)-**165** (63 mg, 30%, or 60% yield based on recovered starting material) and the starting isoquinoline–*N*-oxide **168** (95 mg, 47%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.85 (s, 3H); 1.2 (s, 1H); 1.34 (s, 3H); 2.32-2.38 (m, 2H); 2.62-2.67 (m, 1H); 3.08 (m, 2H); 7.33 (s, 1H); 7.89 (s, 1H); 8.38 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 21.2 (*C*H_3), 25.9 (*C*H_3), 30.5 (*C*H_2), 32.3 (*C*H_2), 39.4 (*C*), 39.8 (*C*H), 44.2 (*C*H), 122.7 (*C*H), 123.2 (q, $^2J_{C\text{-}F}$ = 271 Hz, *C*), 126.3 (*C*H), 129.7 (*C*H), 131.4 (q $^3J_{C\text{-}F}$ = 132 z, *C*), 133.6 (*C*), 135.2 (*C*), 139.3 (*C*), 143.2 (*C*), 146.3 (*C*); **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F 99.2; **IR**: υ 3386, 2956, 2927, 2873, 1622, 1459, 1427, 1397, 1366, 1341, 1279, 1256, 1179, 1135, 1009, 992, 900, 880, 845, 703, 681 cm^{-1}; **HRMS (ESI)** 801.2342 ($C_{40}H_{33}N_2O_2F_{12}$ $[M–H]^-$ requires 801.2356). **$[\alpha]_D^{25}$** = –51.2 (*c* = 0.26, $CHCl_3$).

4.5. Synthesis of (–)-Elisabethadione.

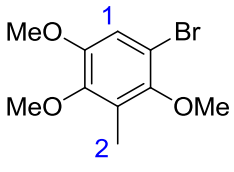
1,2,4-Trimethoxy-3-methylbenzene (158)



158

2.5 M *n*-BuLi in hexane (23 mL, 57 mmol, 1.2 eq.) was added to a solution of 1,2,4-trimethoxybenzene (9 mL, 47.4 mmol, 1 eq.) in freshly distilled THF (35 mL) at 0 °C. The reaction was stirred at room temperature for 1 h before being cooled to −78 °C. Then, MeI (4 mL, 64 mmol, 1.3 eq.) was added and the reaction stirred for a further 1 h. The reaction was quenched with saturated NH_4Cl (15 mL) and extracted with ether (3 x 40 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography on silica (eluting with 4% ethyl acetate in petroleum ether) gave the title compound **158** as a yellow oil (8.5 g, 99 %); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 2.15 (s, 3H, 3-H), 3.78 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 6.53 (d, J = 8.8 Hz, 1H, 1-H), 6.69 (d, J = 8.8 Hz, 1H, 2-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 8.9 (*C*H$_3$), 55.9 (*C*H$_3$), 56.2 (*C*H$_3$), 60.3 (*C*H$_3$), 105.2 (*C*), 109.3 (*C*H), 121.2 (*C*), 147.2 (*C*), 148.1 (*C*), 152.5 (*C*); **IR** (neat) 2938.9, 1489.0, 1257.4, 1115.2, 717.6 cm^{-1}; **HRMS (ESI)** 205.0833 ($C_{10}H_{14}O_3Na$ $[M+Na]^+$ requires 205.0835).

1-Bromo-2,4,5-trimethoxy-3-methylbenzene (159)

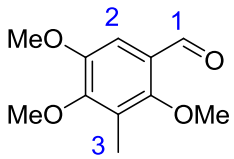


159

To a solution of **158** (8.5 g, 46.9 mmol, 1 eq.) in acetonitrile (110 mL) *N*-bromosuccinimide (10.8 g, 60.8 mmol, 1.3 eq.) was added and the reaction mixture was stirred at room temperature for 1 h before being concentrated in *vacuo*. The solution was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 75mL). The combined organic layers were,

dried over Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography on silica (eluting with 4% ethyl acetate in petroleum ether) gave the title compound **159** as a yellow oil (10.9 g, 89 %); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 2.24 (s, 3H, 2-H), 3.74 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 6.92 (s, 1H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 10.1 (*C*H_3), 56.1 (*C*H_3), 60.2 (*C*H_3), 60.4 (*C*H_3), 110.7 (*C*), 113.4 (*C*H), 127.1 (*C*), 147.2 (*C*), 149.3 (*C*), 149.7 (*C*); **IR** (neat) 2936.8, 1481.3, 1237.6, 1089.2, 1007.9, 778.1 cm^{-1}; **HRMS (ESI)** 282.9936, and 284.9916 ($C_{10}H_{13}O_3{}^{79}BrNa$ and $C_{10}H_{13}O_3{}^{81}BrNa$ $[M+Na]^+$ require 282.9940 and 285.9920).

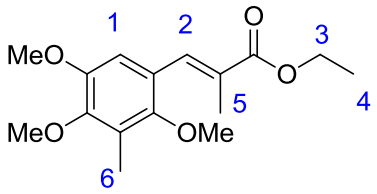
2,4,5-Trimethoxy-3-methylbenzaldehyde (160)



160

2.5 M *n*-BuLi in hexane (25 mL, 62.8 mmol,1.5 eq.) was added to a solution of **159** (10.9 g, 41.8 mmol, 1 eq.) in freshly distilled THF (60 mL) at −78 °C. The mixture was stirred at −78 °C for 30 min before DMF (6.5 mL, 83.6 mmol, 2 eq.) was added. The reaction was stirred for a further 10 min and then warmed to 0 °C for 1 h. The reaction was diluted with water and extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography on silica (eluting with 4% ethyl acetate in petroleum ether) gave the title compound **160** a pale yellow solid (4.6 g, 52 %); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 2.23 (s, 3H, 3-H), 3.84 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 7.23 (s, 1H, 2-H), 10.31 (s, 1H, 1-H),; **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 8.7 (*C*H_3), 55.4 (*C*H_3), 59.9 (*C*H_3), 63.2 (*C*H_3), 106.7 (*C*H), 124.2 (*C*), 125.7 (*C*), 149.3 (*C*), 153.5 (*C*), 157.0 (*C*), 188.6 (*C*); **IR** (neat) 2940.2, 1682.3, 1481.9, 1389.8, 1087.8 cm^{-1}; **HRMS (ESI)** 233.0784 ($C_{11}H_{14}O_4Na$ $[M+Na]^+$ requires 233.0784).

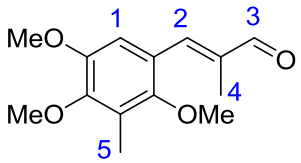
(E)-Methyl 2-methyl-3-(2,4,5-trimethoxy-3-methylphenyl)acrylate (161)



161

(Carbethoxyethylidene)triphenylphosphorane (10.3 g, 28.6 mmol, 1.5 eq.) was added to a solution of **160** (4.0 g, 19.1 mmol, 1 eq.) in water (17 mL) and the solution was heated to 90 °C for 2 days. Then the reaction was cooled, poured onto saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo* to give the title compound **161** as a light yellow oil (3.0 g, 54 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 1.29 (t, *J* = 7.2 Hz, 3H, 4-H), 1.98 (s, 3H, 5-H), 2.17 (s, 3H, 6-H), 3.58 (s, 3H), 3.77 (s, 6H), 4.20 (q, *J* = 14.0, 7.2 Hz, 2H, 3-H), 6.64 (s, 1H, 1-H), 7.72 (s, 1H, 2-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 9.4 (*C*H_3), 14.3 (*C*H_3), 14.3 (*C*H_3), 56.0 (*C*H_2), 60.3 (*C*H_3), 60.7 (*C*H_3), 61.3 (*C*H_3), 110.8, 124.3 (*C*), 125.7 (*C*), 128.5 (*C*), 134.8, 148.7 (*C*), 151.7 (*C*), 168.6 (*C*); **IR** (neat) 2935.4, 1706.7, 1484.8, 1251.6, 1089.5, 754.4 cm^{-1}; **HRMS (ESI)** 317.1359 ($C_{16}H_{22}O_5Na$ $[M+Na]^+$ requires 317.1356).

(E)-2-Methyl-3-(2,4,5-trimethoxy-3-methylphenyl)acrylaldehyde (162)



162

Reduction-oxidation protocol:

1M DIBAL in hexane (30.6 mL, 30.6 mmol, 3 eq.) was added dropwise to a solution of **161** (3.0 g, 10.2 mmol, 1 eq.) in freshly distilled DCM (150 mL) and 4Å molecular sieves at –78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was carefully quenched with MeOH (10 mL), 5M HCl (15 mL) and extracted with DCM (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in

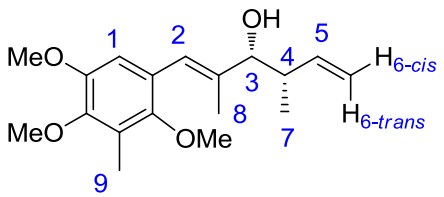
vacuo to give the title compound as light yellow oil which was used in the next step without purification.

MnO_2 (3.1 g, 35.8 mmol) was added to a solution of the above crude product in DCM (250 mL) and stirred at room temperature for 24 h. The reaction was filtered through a pad of celite and concentrated in *vacuo*. Purification by column chromatography on silica (eluting with 10% ethyl acetate in petroleum ether) gave the title compound **162** as a dim-yellow solid (2.23 g, 87 % over two steps).

Aldol condensation protocol:

Aldehyde **160** (100 mg, 0.47 mmol, 1 eq.) was dissolved in MeOH (1 mL). A 2M solution of NaOH (0.47 mL, 0.94 mmol, 2 eq.) was added to the solution. Propanal (84.7 μL, 1.2 mmol, 2.5 eq.) in MeOH (1 mL) was added dropwise to the mixture at room temperature. The reaction was allowed to stir at 50 °C for 5 h before being quenched with NH_4Cl. The mixture was washed with NH_4Cl until neutral pH and extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield the corresponding cinnamaldehyde **162** (76 mg, 65% yield). **Mp** = 77.9-85.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 2.05 (s, 3H, 4-H), 2.22 (s, 3H, 5-H), 3.67 (s, 3H), 3.84 (s, 6H), 6.90 (s, 1H, 1-H), 7.51 (s, 1H, 2-H), 9.60 (s, 1H, 3-H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 9.4 (*C*H_3), 11.1 (*C*H_3), 56.0 (*C*H_3), 60.4 (*C*H_3), 61.7 (*C*H_3), 110.6 (*C*H), 123.5 (*C*), 126.0 (*C*), 137.8 (*C*), 145.1 (*C*H), 148.9 (*C*), 149.7 (*C*), 152.3 (*C*), 195.6 (*C*H); **IR** (neat) 2934.9, 1662.0, 1614.7, 1455.6, 1235.4, 1084.5, 999.0, 835.8 cm^{-1}; **HRMS (ESI)** 273.1097 ($C_{14}H_{18}O_4Na$ $[M+Na]^+$ requires 273.1093).

(–)-(3S,4R,E)-2,4-Dimethyl-1-(2,4,5-trimethoxy-3-methylphenyl)hexa-1,5-dien-3-ol (167)

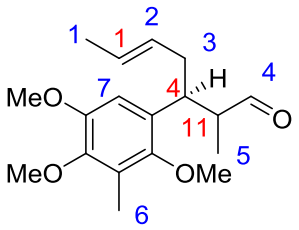


(–)-**167**

A 100 mL round bottom flask fitted with a magnetic stirring bar was flame-dried under *vacuo*, evacuated and backfilled with N_2. The flask was charged with dry propionitrile (25 mL)

and successively with a solution of bis-*N*-oxide **165** (80.4 mg, 0.1 mmol, 2 mol%), aldehyde **162** (1.12 g, 4.48 mmol, 1 eq.) and Hünig's base (1.5 mL, 8.9 mmol, 2 eq.) in 1 mL of dry propionitrile each. The mixture was cooled to –60 °C using a cryocooler and a solution of *Z*-crotyltrichlorosilane **164** (1.4 g, 7.3 mmol, 1.7 eq.) in 1 mL of dried propionitrile was added dropwise. The reaction mixture was stirred at this temperature for 2 days. Then, it was quenched with a saturated solution of $NaHCO_3$ (10 mL), washed with 20 mL of $NaHCO_3$ and extracted with DCM (3 x 60 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in *vacuo*. Flash chromatography on *silica* with a gradient eluent system (100% hexane to 95:5, hexane/ethyl acetate) afforded the target homoallylic alcohol (–)-**167** as colorless oil (1.3 g, 82 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 1.12 (d, *J* = 6.4 Hz, 3H, 7-H), 1.80 (s, 3H, 8-H), 2.20 (s, 3H, 9-H), 2.52 (quint, *J* = 7.2 Hz, 1H, 4-H), 3.61 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 4.03 (d, *J* = 6.8 Hz, 1H, 3-H), 5.03 (dm, *J* = 10.4 Hz, 2H, 6-cis-H), 5.10 (dt, *J* = 17.2, 1.6 Hz, 1H, 6-trans-H), 5.81 (m, 1H, 5-H), 6.53 (s, 1H, 1-H), 6.62 (s, 1H, 2-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 9.3 (*C*H_3), 13.9 (*C*H_3), 15.0 (*C*H_3), 41.5 (*C*H), 56.0 (*C*H_3), 60.1 (*C*H_3), 60.7 (*C*H_3), 81.0 (*C*H), 111.2 (*C*H), 114.4 (*C*H_2), 122.5 (*C*H), 125.3 (*C*), 125.9 (*C*), 139.1 (*C*), 140.9 (*C*H), 146.8 (*C*), 148.5 (*C*), 150.7 (*C*); **IR** (neat) 3447.4, 2959.5, 1484.9, 1228.2, 1088.8, 1011.8 cm^{-1}; **HRMS (ESI)** 329.1723 ($C_{18}H_{26}O_4Na$ $[M+Na]^+$ requires 329.1715). **Chiral HPLC** (Chiralpak IA-3, hexane/2-propanol = 95:5, 1 mL/min, UV detection at 225 nm) showed 94% ee (t_R = 12.28 min (minor), t_S = 18.14 min (major)). **$[\alpha]_D^{25}$** = –108.17 (*c* = 0.83, $CHCl_3$, 84% *ee*).

(2R,3R,E)-2-Methyl-3-(2,4,5-trimethoxy-3-methylphenyl)hept-5-enal (170)

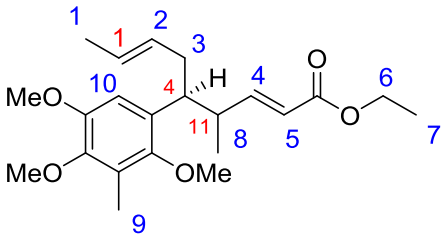


170

A 30 % suspension of KH in mineral oil (1.9 g, 48.4 mmol, 15 eq.) was washed with anhydrous DME (3 x 5 mL). Anhydrous DME (10 mL) was added to the KH. Alcohol (–)-**167** (990 mg, 3.23 mmol, 1 eq.) and 18-crown-6 (853 mg, 3.23 mmol, 1 eq.) were successively added to the solution, which was then heated for 5 h at 40 °C. The solution was cooled to –78

°C and quenched with MeOH (4 mL). The mixture was poured into a saturated solution of NH_4Cl (20 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. Compound **170** (d.r. 3:1 at C-11) was obtained as yellow oil and was used immediately in the next step. **Major isomer** (taken as a mixture): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 1.08 (d, *J* = 7.2Hz, 3H, 5-H); 1.56 (d, *J* = 7.6Hz, 3H, 1-H); 2.02 (s, 3H, 6-H); 2.34-2.37 (m, 3H, 3,11-H); 3.41-3.48 (m, 1H, 4-H); 3.67 (s, 3H); 3.78 (s, 3H); 3.80 (s, 3H); 5.21-5.29 (m, 1H, 2-H); 5.39-5.48 (m, 1H, 1-H); 6.52 (s, 1H, 7-H); 9.56 (d, *J* = 2Hz, 1H, 4-H). **Minor isomer** (taken as a mixture): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.85 (d, *J* = 6.8Hz, 3H, 5-H); 1.57 (d, *J* = 5.2Hz, 3H, 1-H); 2.02 (s, 3H, 6-H); 2.53-2.61 (m, 3H, 3,11-H); 3.41-3.48 (m, 1H, 4-H); 3.67 (s, 3H); 3.79 (s, 3H); 3.81 (s, 3H); 5.21-5.29 (m, 1H, 2-H); 5.39-5.48 (m, 1H, 1-H); 6.47 (s, 1H, 7-H); 9.87 (d, *J* = 3.2Hz, 1H, 4-H).

(2E,4S,5R,7E)-Ethyl 4-methyl-5-(2,4,5-trimethoxy-3-methylphenyl)nona-2,7-dienoate (171)

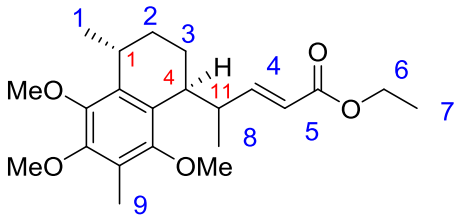


171

LiCl (260 mg, 6 mmol, 1.2 eq.) was weighted in a 50 mL flame-dried round bottom flask. The flask was evacuated and backfilled with N_2. Dry CH_3CN (15 mL) was added followed by a solution of Hünig's base (1.1 mL, 6 mmol, 1.2 eq.) and triethyl phosphonoacetate (1.2 mL, 6 mmol, 1.2 eq.) in 2 mL of dry CH_3CN each. After stirring the mixture for 5 min, the crude product from the previous step (**170**, ~3.23 mmol, 1 eq.) in 2 mL of anhydrous CH_3CN was added dropwise. The reaction mixture was stirred overnight. Then, the mixture was quenched with a saturated solution of NH_4Cl (20 mL) and extracted with DCM (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude mixture was purified by flash column chromatography on silica eluting with a gradient system (100% petroleum ether up to 5:1 petroleum ether and ethyl acetate) to yield the target compound **171** (a 3:1 mixture of isomers at C11) as a colorless oil (812 mg, 84% yield over two steps). **Major isomer** (taken as a mixture): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.98 (d, *J* = 6.8Hz, 3H, 8-H); 1.25 (t, *J* = 6.8Hz, 3H, 7-H); 1.57 (dd, *J* = 6.4, 1.2Hz, 3H, 1-H); 2.20 (s, 3H, 9-H); 2.30-2.43 (m, 2H, 3-H); 2.60-2.65

(m, 1H, 11-H); 3.14-3.19 (m, 1H, 4-H); 3.61 (s, 3H); 3.78 (s, 3H); 3.79 (s, 3H); 4.15 (qd, *J* = 6.8, 2 Hz, 2H, 6-H); 5.24-5.35 (m, 1H, 2-H); 5.39-5.46 (m, 1H, 1-H); 5.70 (dd, *J* = 15.6, 1.2 Hz, 1H, 5-H); 6.42 (s, 1H, 10-H); 6.91 (dd, *J* = 16, 7.6 Hz, 1H, 4-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 9.8 (*C*H_3), 14.2 (*C*H_3), 16.6 (*C*H_3), 17.9 (*C*H_3), 35.4 (*C*H_2), 40.5 (*C*H), 42.4 (*C*H), 55.8 (*C*H_3), 60.1 (*C*H_3), 60.2 (*C*H_2), 60.9 (*C*H_3), 109.1 (*C*H), 120.6 (*C*H), 124.9 (*C*), 126.9 (*C*H), 129.2 (*C*H), 129.7 (*C*), 146.0 (*C*), 148.7 (*C*), 151.0 (*C*), 152.7 (*C*H), 166.7 (*C*). **IR** (neat) 2935.8, 1722.6, 1487.4, 1236.1, 1087.2 cm^{-1}. **Minor isomer** (taken as a mixture): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.86 (d, *J* = 6.4 Hz, 3H, 8-H); 1.30 (t, *J* = 7.2 Hz, 3H, 7-H); 1.52 (dd, *J* = 6, 1.2 Hz, 3H, 1-H); 2.21 (s, 3H, 9-H); 2.30-2.43 (m, 2H, 3,11-H); 2.96-3.02 (m, 1H, 4-H); 3.61 (s, 3H); 3.79 (s, 3H); 3.81 (s, 3H); 4.20 (q, *J* = 7.2 Hz, 2H, 6-H); 5.12-5.20 (m, 1H, 2-H); 5.24-5.35 (m, 1H, 1-H); 5.83 (d, *J* = 16 Hz, 1H, 5-H); 6.47 (s, 1H, 10-H); 6.96 (m, 1H, 4-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 9.9 (*C*H_3), 14.3 (*C*H_3), 16.6 (*C*H_3), 17.8 (*C*H_3), 36.6 (*C*H_2), 40.5 (*C*H), 42.8 (*C*H), 56.0 (*C*H_3), 60.1 (*C*H_3), 60.2 (*C*H_2), 60.9 (*C*H_3), 108.1 (*C*H), 121.0 (*C*H), 124.9 (*C*), 126.6 (*C*H), 129.1 (*C*H), 130.8 (*C*), 146.0 (*C*), 149.2 (*C*), 151.2 (*C*), 153.5 (*C*H), 166.7 (*C*). **IR** (neat) 2935.8, 1722.6, 1487.4, 1236.1, 1087.2 cm^{-1}.

(S,E)-Ethyl-4-((1R,4S)-5,6,8-trimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pent-2-enoate (172)

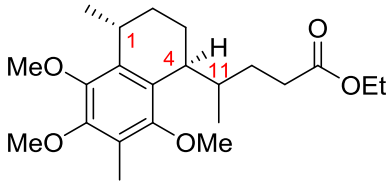


172

Methanesulphonic acid (0.42 mL, 6.48 mmol, 3 eq.) was added to a solution of **171** (812 mg, 2.16 mmol, 1 eq.) in $CHCl_3$ (15 mL) and the reaction stirred at 40 °C for 7 hours. The reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. Filtration of the crude reaction mixture through a pad of silica gel gave the title compound **172** (*ca.* 2.7:1 mixture of isomers at C11 epimer) as a light yellow oil (683.2 mg, 84 % yield). The compound was used in the next step without further purification. **Major isomer** (taken as a mixture): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.92 (d, *J* = 6.8 Hz, 3H, 8-H); 1.12 (d, *J* = 6.8 Hz, 3H, 1-H); 1.27

(t, *J* = 7.2 Hz, 3H, 7-H); 1.46-1.56 (m, 2H, 2/3-H); 1.69-1.82 (m, 2H, 2/3-H); 2.14 (s, 3H, 9-H); 2.92-2.96 (m, 1H, 11-H); 3.02 (t_{br}, *J* = 4.8 Hz, 1H, 4-H); 3.11-3.17 (m, 1H, 1-H); 3.65 (s, 3H); 3.78 (s, 3H); 3.84 (s, 3H); 4.15 (q, *J* = 7.2 Hz, 2H, 6-H); 5.63 (dd, *J* = 15.6, 1.2 Hz, 1H, 5-H); 7.07 (dd, *J* = 15.6, 6.8 Hz, 1H, 4-H). **Minor isomer** (taken as a mixture): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.88 (d, *J* = 6.8 Hz, 3H, 8-H); 1.11 (d, *J* = 6.4 Hz, 3H, 1-H); 1.23 (t, *J* = 7.2 Hz, 3H, 7-H); 1.46-1.56 (m, 2H, 2/3-H); 1.69-1.82 (m, 2H, 2/3-H); 2.17 (s, 3H, 9-H); 2.83-2.85 (m, 1H, 11-H); 2.92-2.96 (m, 1H, 4-H); 3.11-3.17 (m, 1H, 1-H); 3.66 (s, 3H); 3.80 (s, 3H); 3.82 (s, 3H); 4.11-4.15 (m, 2H, 6-H); 5.54 (dd, *J* = 16, 1.6 Hz, 1H, 5-H); 6.84 (dd, *J* = 15.6, 7.2 Hz, 1H, 4-H).

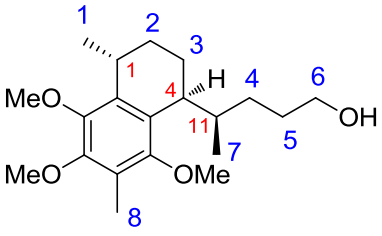
(S)-Ethyl-4-((1R,4S)-5,6,8-trimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentanoate (173)



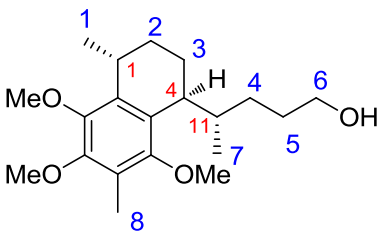
173

A solution of **172** (683.2 mg, 1.81 mmol, 1 eq.) in MeOH (15 mL) was circulated for 3 hours through an H-Cube (set at 2.0 mL/min, Full hydrogen mode, r.t.) equipped with a cartridge containing catalyst Pd/C 10%. The resulting solution was concentrated in *vacuo* to give product **173** as a colourless oil (622.3 mg, 91 %), which was used in the next step without further purification.

(S)-4-((1R,4S)-5,6,8-trimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentan-1-ol (95)



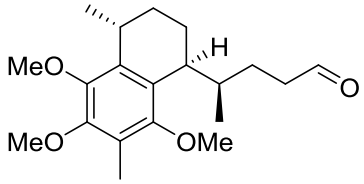
trans,syn-**95a**



trans,anti-**95b**

DIBAL, 1M in hexanes (3.2 mL, 3.2 mmol, 2 eq.), was added to a solution of **173** (622.5 mg, 1.6 mmol, 1 eq.) in anhydrous CH_2Cl_2 (5 mL) at −78 °C. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with MeOH (5 mL), 5M HCl (5 mL) and extracted with CH_2Cl_2 (3x15 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography on silica eluting with 7:3 petroleum ether/ethyl acetate gave the title compound **95** as colourless oil in a 2.7:1 mixture of diastereoisomers (500 mg, 93%). The diastereoisomers were separated by preparative HPLC (Dynmax-60Å, hexane/2-propanol = 98:2, 5 mL/min, UV detection at 220 nm). *Trans,syn*-**95a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.73 (d, *J* = 7.2 Hz, 3H, 7-H) , 1.13 (d, *J* = 7.2 Hz, 3H, 1-H), 1.31-1.38 (m, 2H), 1.44-1.47 (m, 1H, 2-H), 1.51-1.68 (m, 3H), 1.78-1.80 (m, 2H, 3-H), 1.91-2.03 (m, 2H, 2,11-H), 2.17 (s, 3H, 8-H), 2.83-2.86 (m, 1H, 4-H), 3.15 (quint, *J* = 6.8 Hz, 1H, 1-H), 3.63 (m, 5H, 6,CH_3O-H), 3.80 (s, 3H), 3.84 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 9.4 (*C*H_3), 18.1 (*C*H_3), 18.6 (*C*H_2), 23.2 (*C*H_3), 26.4, 27.0, 30.6, 31.2 (*C*H_2), 35.4 (*C*H), 37.4 (*C*H), 59.9 (*C*H_3), 60.2 (*C*H_3), 60.5 (*C*H_3), 63.4 (*C*H_2), 76.7, 122.2 (*C*), 128.6 (*C*), 134.8 (*C*), 147.1 (*C*), 152.8 (*C*),; **IR** (neat) 3370.9, 2930.5, 1457.9, 1403.5, 1069.0 cm^{-1}; **HRMS (ESI)** 359.2189 ($C_{20}H_{32}O_4$ $[M+Na]^+$ requires 359.2193). **$[\alpha]_D^{25}$** = –7.05 (*c* = 2, $CHCl_3$; $[\alpha]_D^{25}$ = +6.4 (*c* = 1.4, CHCl3)[145]). *Trans,anti*-**95b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.78 (d, *J* = 6.8 Hz, 3H, 7-H), 1.14 (d, *J* = 6.8 Hz, 3H, 1-H), 1.31-1.38 (m, 3H), 1.44-1.60 (m, 3H), 1.75-1.94 (m, 4H), 2.10 (s, 3H, 8-H), 2.76-2.80 (m, 1H, 4-H), 3.12 (quint, J = 6.8 Hz, 1H, 1-H), 3.50-3.54 (m, 2H, 6-H), 3.62 (s, 3H), 3.79 (s, 3H),3.82 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 9.5 (*C*H_3), 18.5 (*C*H_3), 20.2 (*C*H_2), 23.1 (*C*H_3), 26.4 (*C*H_2), 27.2 (*C*H), 31.1 (*C*H_2), 31.3 (*C*H_2), 37.2 (*C*H), 37.9 (*C*H_2), 59.9 (*C*H_3), 60.1 (*C*H_3), 60.5 (*C*H_3), 63.3 (*C*H_2), 122.1 (*C*), 128.4 (*C*), 134.5 (*C*), 147.2 (*C*), 149.5 (*C*), 153.0 (*C*); **IR** (neat) 3370.9, 2930.5, 1457.9, 1403.5, 1069.0 cm^{-1}. **HRMS (ESI)** 359.2189 ($C_{20}H_{32}O_4$ $[M+Na]^+$ requires 359.2193).

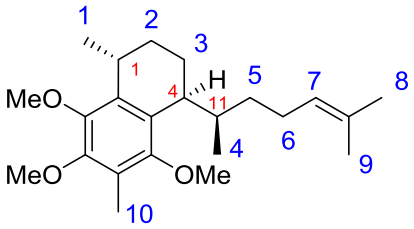
(–)-4-((1R,4S)-5,6,8-trimethoxy-1,4,7-trimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentane (174)



trans,syn-**174**

Dess-Martin periodinane (396 mg, 0.935 mmol, 1.5 eq.) was weighted in a 25 mL flame-dried round bottom flask. The vessel was evacuated and backfilled with N_2 before being charged with alcohol *trans,syn*-**95** (205.3 mg, 0.61 mmol, 1 eq.) in 6 mL of DCM. The reaction was allowed to stir at room temperature for 2 hours. The crude mixture was filtrated through a pad of silica and the crude *trans,syn*-**174** was subjected to the next step without further purification (151.1 mg, 74% yield).

(–)-(1R,4S)-5,6,8-trimethoxy-1,4,7-trimethyl-1-(6-methylhept-5-en-2-yl)-1,2,3,4-tetrahydronaphthalene (96a)

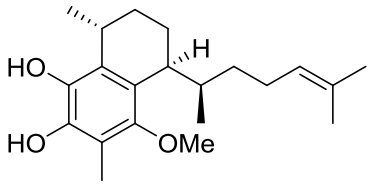


(–)-*trans,syn*-**96**

n-BuLi, 2M solution in hexane (2.00 mL, 4.0 mmol), was added dropwise to a solution of isopropyltriphenylphosphonium iodide (1.85 g, 4.3 mmol) in anhydrous THF (15 mL) at 0 °C under N_2. The mixture was stirred for 1 hour before *trans,syn*-**174** (1.3 mmol) in THF (15 mL) was added. The solution was allowed to stir at the same temperature for 30 minutes before warming to room temperature and heating at reflux for a further 2 hrs. After cooling, the reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with ether (3x50 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification by column chromatography on silica gel (eluting with 2 % ethyl acetate in petroleum ether) gave the title compound as a colourless oil (–)-**96** (72 mg, 60 % yield over to

steps); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.72 (d, *J* = 7.2 Hz, 3H, 4-H); 1.15 (d, *J* = 6.8 Hz, 3H, 1-H); 1.26-1.35 (m, 2H); 1.45 (dm, *J* = 13.2 Hz, 1H); 1.60 (s, 3H, 8/9-H); 1.69 (s, 3H, 8/9-H); 1.78-1.81 (m, 2H); 1.94-2.08 (m, 4H); 2.18 (s, 3H, 10-H); 2.88 (m, 1H, 1/4-H); 3.16 (quint, *J* = 6 Hz, 1H, 1/4-H); 3.65 (s, 3H); 3.81 (s, 3H); 3.85 (s, 3H); 5.14 (tt, *J* = 6.8, 1.6 Hz, 1H, 7-H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 9.4 (*C*H_3), 17.6 (*C*H_3), 18.2 (*C*H_3), 18.5 (*C*H_2), 23.1 (*C*H_3), 25.7 (*C*H_3), 26.4 (*C*H_2), 26.6 (*C*H_2), 27.0 (*C*H), 35.6 (*C*H), 35.7 (*C*H_2), 37.5 (*C*H), 59.8 (*C*H_3), 60.1 (*C*H_3), 60.4 (*C*H_3), 122.2 (*C*), 125.2 (*C*H), 128.6 (*C*), 136.8 (*C*), 134.8 (*C*), 146.9 (*C*), 149.4 (*C*),152.9 (*C*); **IR** (neat) 2930.5, 2867.6, 1460.7, 1406.4, 1074.7 cm^{-1}; **HRMS (ESI)** 383.2549 ($C_{23}H_{36}O_3$ $[M+Na]^+$ requires 383.2557). $[\alpha]_D^{25}$ = –9.65 (*c* = 0.58, $CHCl_3$; $[\alpha]_D^{25}$ = +6.4 (*c* = 1.0, CHCl3)[145])

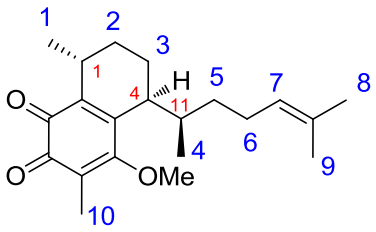
(–)-(5R,8S)-4-methoxy-3,8-dimethyl-5-((S)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalene-1,2-diol (97)



(–)-*trans,syn*-**97**

To a solution of ethanethiol (2.2 mL, 29.4 mmol, 145 eq.) in anhydrous hexane (15 mL) at 0 °C under N_2 was added *n*-BuLi 2M in hexane (4.6 mL, 7.3 mmol, 36 eq.) and the reaction stirred at room temperature for 30 minutes. The mixture was concentrated in *vacuo* to give a white powder. The white powder and (–)-*tran,syn*-**96** (72 mg, 0.2 mmol, 1 eq.) were dissolved in anhydrous DMF (13 mL) and the reaction was refluxed for 3 hrs. After cooling the reaction was acidified with 5 % HCl and extracted with ether (3x20 mL). The organic layer were combined, dried over Na_2SO_4 and concentrated in *vacuo*. The crude mixture was filtrated through a short pad of silica and used in the next step without further purification.

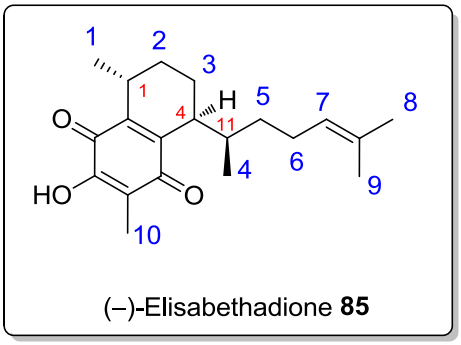
(–)-(5S,8R)-4-methoxy-3,8-dimethyl-5-((R)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalene-1,2-dione (175)



(–)-*trans,syn*-**175**

A solution of cerium ammonium nitrate (237 mg, 0.43 mmol, 3 eq.) in water (5 mL) was added to a solution of diol (–)-*trans,syn*-**97** (48 mg, 0.14 mmol, 1 eq.) in MeCN (5 mL) at 0 °C. The reaction was stirred for 20 minutes before water (10 mL) was added. The mixture was extracted with DCM (3x20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the title compound as an orange-red oil (–)-*trans,syn*-**175** (33 mg, 50% yield over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.84 (d, *J* = 7.2 Hz, 3H, 4-H); 1.07 (d, *J* = 7.2 Hz, 3H, 1-H); 1.22-1.43 (m, 6H); 1.61 (s, 3H); 1.67-1.81 (m, 5H); 1.96 (s, 3H, 10-H); 1.96-2.04 (m, 1H); 2.64 (m, 1H, 1/4-H); 2.88 (quint, *J* = 6.4 Hz, 1H, 1/4-H); 3.91 (s, 3H, OCH_3); 5.10 (t, *J* = 7.6 Hz, 1H, 7-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 9.7 (CH_3), 17.4 (CH_3), 17.7 (CH_3), 18.5 (CH_2), 21.3 (CH_3), 25.7 (CH_3), 25.8 (CH_2), 26.2 (CH_2), 26.3 (*C*H), 35.6 (CH_2), 36.4 (*C*H), 37.2 (*C*H), 61.2 (CH_3), 119.6 (*C*), 124.4 (*C*H), 131.6 (*C*), 140.3 (*C*), 150.6 (*C*), 167.7 (*C*), 179.4 (*C*), 181.1 (*C*); **IR** (neat) 2963.1, 1656.8, 1454.1, 1575.3, 1377.4, 1235.7 cm^{-1}; **HRMS (ESI)** 353.2087 ($C_{21}H_{30}O_3$ $[M+Na]^+$ requires 353.1714).

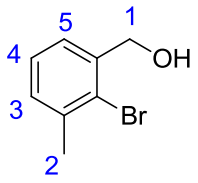
(–)-(5R,8S)-2-hydroxy-3,8-dimethyl-5-(6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalene-1,4-dione. (–)-Elisabethadione (85)



4-Methylbenzenesulphonic acid (38 mg, 0.2 mmol, 2 eq.) was added to a solution of (–)-*trans,syn*-**175** (33 mg, 0.1 mmol, 1 eq.) in anhydrous benzene (8 mL) at rt. The reaction was stirred for 2 hours before being diluted with ether (20 mL). The solution was washed with water (15 mL) and extracted with ether (3×20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography on silica gel (eluting with 1 % ethyl acetate in hexane) gave the target (–)-elisabethadione as a yellow oil (22 mg, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.83 (d, *J* = 6.8 Hz, 3H, 4-H); 1.12 (d, *J* = 7.2 Hz, 3H, 1-H); 1.23-1.33 (m, 3H); 1.44-1.48 (m, 1H); 1.60 (s, 3H, 8/9-H); 1.68 (s, 3H, 8/9-H); 1.75-1.86 (m, 3H); 1.93 (s, 3H, 10-H); 1.97-2.04 (m, 2H); 2.88 (m, 1H, 1/4-H); 2.94 (m, 1H, 1/4-H); 5.12 (t, *J* = 6.4 Hz, 1H, 7-H); 6.97 (s, 1H, OH). **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 8.2 (CH_3), 17.6 (CH_3), 17.7 (CH_3), 18.1 (CH_2), 20.8 (CH_3), 25.7 (*C*H), 26.0 (CH_2), 26.1 (*C*H), 26.3 (CH_2), 35.7 (*C*H), 36.0 (CH_2), 36.9 (CH_3), 116.8 (*C*), 124.5 (*C*H), 131.3 (*C*), 143.1 (*C*), 148.2 (*C*), 150.6 (*C*), 182.9 (*C*), 187.9 (*C*); **IR** (neat) 3391.5, 2933.4, 1638.4, 1336.2, 1234.6, 1155.1 cm^{-1}; **HRMS (ESI)** 316.1986 ($C_{20}H_{28}O_3$ $[M]^+$ requires 316.2033). **$[\alpha]_D^{25}$** = –267 (*c* = 0.16, $CHCl_3$; $[\alpha]_D^{25}$ = +278, c = 0.58, $CHCl_3$[145]).

4.6. Synthesis of (–)-Erogorgiane

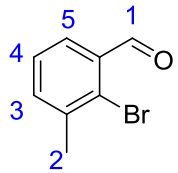
(2-bromo-3-methylphenyl)Methanol (176)



176

2-Bromo-3-methyl benzoic acid (3.55 g, 15.5 mmol, 1 eq.) was placed in a 500 mL RBF fitted with a stirring bar, evacuated and backfilled with N_2. DCM (200 mL) was added into the vessel and the solution was cooled at –78 °C. DIBAL-H, 1M in hexanes, (58.9 mL, 58.9 mmol, 3.8 eq.) was added dropwise *via* syringe pump. The reaction was stirred for two further hours while allowed to warm at room temperature. The reaction was quenched with MeOH (10 mL) and HCl 5M (10 mL), washed with water and extracted with DCM (2x80 mL). The compound **176** was obtained as a white solid (2.65 g, 85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 2.78 (s_{broad}, 1H, OH); 2.46 (s, 3H, 2-H); 4.78 (s, 2H, 1-H); 7.21-7.34 (m, 3H, 3/4/5-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 23.3 (*C*H_3), 65.6 (*C*H_2), 125.1 (*C*), 126.7 (*C*H), 127.1 (*C*H), 129.9 (*C*H), 138.4 (*C*), 140.0 (*C*). **IR**: υ 3304, 2918, 1644, 1452, 1435, 1409, 1352, 1376, 1242, 1167, 1069, 1056, 1027, 1003, 988, 900, 769 cm^{-1}, **HRMS (ESI)** 310.8851 ($C_8H_9O^{81}Br^{109}Ag$ $[M+Ag]^+$ requires 310.8858).

2-Bromo-3-methylbenzaldehyde (177)

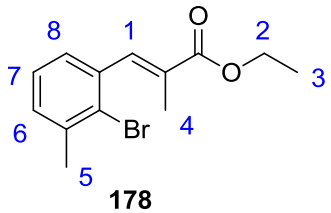


177

MnO_2 (11.4 g, 132 mmol, 10 eq.) was added to a solution of compound **176** (2.65 g, 13.2 mmol, 1 eq.) in DCM (50 mL) and stirred at room temperature for three days. The reaction was filtered through a pad of Celite and concentrated in *vacuo*. Purification by column chromatography on silica gel (eluting with 85:15 petroleum ether/ethyl acetate) gave the *title compound* **177** as a white solid (2.1 g, 80%); **Mp** = 77.9-85.2 °C; **^{1}H NMR** (400 MHz,

$CDCl_3$): δ_H 2.47 (s, 3H, 2-H); 7.31 (t, *J* = 7.6 Hz, 1H, 4-H); 7.46 (ddd, *J* = 7.6, 2, 0.8 Hz, 1H, 5-H); 7.73 (dm, *J* = 7.6 Hz, 1H, 3-H); 10.44 (d, *J* = 0.8 Hz, 1H, 1-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 22.8 (*C*H_3), 127.3 (*C*H), 127.4 (*C*H), 129.6 (*C*), 133.9 (*C*), 136.2 (*C*H), 139.6 (*C*), 192.7 (*C*H). **IR**: υ 3065, 2950, 2922, 2868, 2735, 1952, 1889, 1721, 1697, 1678, 1573, 1452, 1416, 1374, 1265, 1241, 1168, 1105, 1031, 1006, 912, 781, 701 cm^{-1}.

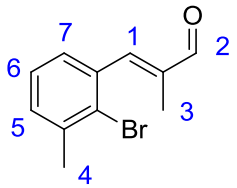
(E)-Ethyl-3-(2-bromo-3-methylphenyl)-2-methylacrylate (178)



178

(Carbethoxyethylidene)triphenylphosphorane (5.73 g, 15.8 mmol, 1.5 eq.) was added to a solution of benzaldehyde **177** (2.10 g, 10.55 mmol, 1 eq.) in water (10 mL) and the solution heated to 90 °C for two days. The reaction was cooled and poured onto saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2x70 mL). The organic layer was dried over Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the target compound **178** as colorless oil (2.29 g, 76 %); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 1.36 (t, *J* = 7.2 Hz, 3H, 3-H); 1.95 (d, *J* = 1.2 Hz, 3H, 4-H); 2.43 (s, 3H, 5-H); 4.29 (q, *J* = 7.2 Hz, 2H, 2-H); 7.09 (dd, *J* = 6.8, 2.4 Hz, 1H, 8-H); 7.19-7.21 (m, 2H, 7/6-H); 7.73 (d, *J* = 1.2 Hz, 1H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 13.8 (*C*H_3), 14.2 (*C*H_3), 23.5 (*C*H_3), 60.8 (*C*H_2), 126.4 (*C*), 126.5 (*C*H), 129.7 (*C*), 130.2 (*C*H), 136.8 (*C*), 138.7 (*C*), 138.9 (*C*H), 168.1 (*C*); **IR**: υ 3427, 3068, 3048, 2980, 2958, 2927, 2905, 1711, 1640, 1586, 1572, 1464, 1446, 1400, 1366, 1346, 1273, 1232, 1171, 1115, 1028, 935, 870, 800, 771, 746, 729 cm^{-1}, **HRMS (ESI)** 305.0147 and 307.0126 ($C_{13}H_{15}O_2{}^{79}BrNa$ and $C_{13}H_{15}O_2{}^{81}BrNa$ $[M+Na]^+$ requires 305.0148 and 307.0127).

(E)-3-(2-bromo-3-methylphenyl)-2-methylacrylaldehyde (179)



179

Reduction-oxidation protocol:

DIBAL-H 1M in hexane (28.3 mL, 28.3 mmol, 3.5 eq.) was added to a solution of **178** (2.3 g, 8.1 mmol) in anhydrous CH_2Cl_2 (100 mL) with 4Å molecular sieves at −78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH (15 mL) followed by dropwise addition of 5M HCl (25 mL) and extracted with CH_2Cl_2 (2x75 mL). The organic layers were combined and dried over Na_2SO_4 and concentrated in *vacuo*. The crude mixture was used in the next step without further purification.

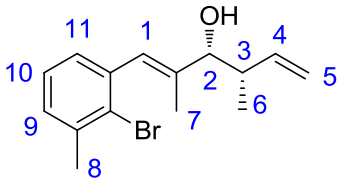
MnO_2 (2.2 g, 25 mmol, 3 eq.) was added to a solution of the previous crude in CH_2Cl_2 (100 mL) and stirred at room temperature for three days. The reaction was filtered through a pad of Celite and concentrated in *vacuo*. Purification by flash column chromatography on silica gel (eluting with 10 % ethyl acetate/petroleum ether) gave the *title compound* **179** as yellow oil (1.59 g, 82% over two steps).

Direct aldol condendensation:

To a solution of aldehyde **177** (100 mg, 0.5 mmol, 1 eq.) and propanal (54 μL, 0.75 mmol, 1.5 eq.) in MeOH (2 mL), a 2M solution of NaOH (0.25 mL, 0.5 mmol, 1 eq.) was added dropwise at room temperature. The reaction was allowed to stir at 50 °C overnight before being quenched with NH_4Cl. The mixture was washed with NH_4Cl until neutral pH and extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield the corresponding cinnamaldehyde **179** (72 mg, 60% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 1.92 (s, 3H, 3-H); 2.47 (s, 3H, 4-H); 7.20-7.22 (m, 1H, 5/6/7-H); 7.25-7.27 (m, 2H, 5/6/7-H); 7.50 (s, 1H, 1-H); 9.69 (s, 1H, 2-H) **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 10.7 (*C*H_3), 23.6 (*C*H_3), 126.6 (*C*), 126.7 (*C*H), 127.8 (*C*H), 131.2 (*C*H), 135.5 (*C*), 139.1 (*C*), 139.5 (*C*), 149.1 (*C*H), 195.3 (*C*H); **IR**: υ 3049, 2954, 2922, 2819, 2710, 1686, 1629,

1572, 1445, 14411, 1385, 1355, 1264, 1186, 1027, 1005, 935, 866, 834, 789, 771, 723, 681 cm^{-1}; **HRMS (ESI)** 239.0054 and 241.0034 ($C_{11}H_{11}{}^{79}BrO$ and $C_{11}H_{11}{}^{81}BrO$ $[M+H]^+$ requires 239.0066 and 241.0046).

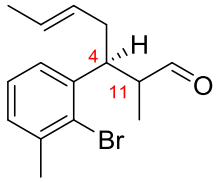
(–)-(3S,4R,E)-1-(2-bromo-3-methylphenyl)-2,4-dimethlhexa-1,5-dien-3-ol (180)



(–)-**180**

A 100mL round bottom flask fitted with a magnetic stirring bar was flame-dried, evacuated and backfilled with N_2. The flask was charged with 30 mL of dry propionitrile and successively with a solution of bis-*N*-oxide (–)-**165** (80.4 mg, 0.1 mmol, 2 mol%), aldehyde **179** (1.25 g, 5.2 mmol, 1 eq.) and Hünig's base (1.8 mL, 10.3 mmol, 2 eq.) in 1 mL of dry propionitrile each. The solution was cooled at –60 °C and a solution of *Z*-crotyltrichlorosilane **164** (1.7 g, 8.9 mmol, 1.7 eq.) in 1 mL of dry propionitrile was added dropwise to the reaction mixture. The reaction was stirred at this temperature for two days. After that time, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL), washed with 20 mL of $NaHCO_3$ and extracted with DCM (3 x 60 mL). Combined organic layers were dried over Na_2SO_4 and solvent was removed in *vacuo*. Flash chromatography on *silica* with a gradient eluent system (100% hexane to 95:5, hexane/ethyl acetate) afforded the target homoallylic alcohol (–)-**180** as a colourless oil (1.10 g, 72 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 1.13 (d,*J* = 6.8 Hz, 3H, 6-H); 1.70 (s, 3H, 7-H); 1.73 (s_{broad}, 1H, O*H*); 2.43 (s, 3H, 8-H); 2.53 (q, *J* = 6.8 Hz, 1H, 3-H); 4.08 (d, *J* = 6.4 Hz, 1H, 2-H); 5.06-5.15 (m, 2H, 5-H); 5.83-5.91 (m, 1H, 4-H); 6.53 (s, 1H, 1-H); 7.04-7.06 (m, 1H, H_{Ar}); 7.11-7.17 (m, 2H, H_{Ar}); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 13.9 (*C*H_3), 14.4 (*C*H_3), 23.7 (*C*H_3), 41.4 (*C*H), 80.0 (*C*H), 114.7 (*C*H_2), 126.3 (*C*H), 126.7 (*C*), 127.1 (*C*H), 128.2 (*C*H), 128.9 (*C*H), 138.3 (*C*), 138.3 (*C*), 139.5 (*C*), 140.9 (*C*H); **IR**: υ 3412, 3069, 2975, 2923, 2870, 1640, 1586, 1463, 1449, 1401, 1379, 1228, 1107, 1024, 913, 791, 767, 725 cm^{-1}; **HRMS (ESI)** 400.9666 and 402.9651 ($C_{15}H_{19}{}^{79}BrO$ and $C_{15}H_{19}{}^{81}BrO$ $[M+Ag]^+$ requires 400.9665 and 402.9644).; **Chiral HPLC** (Chiralpak IA-3, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 225 nm) showed 98% ee (t_R = 19.3 min (major), t_S = 20.8 min (minor)). **$[\alpha]_D^{25}$** = –27 (*c* = 6.5, $CHCl_3$).

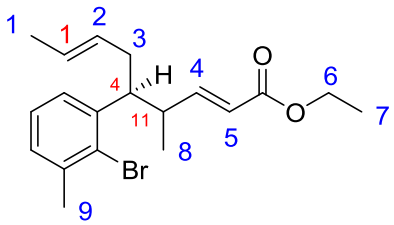
(3R,E)-3-(2-bromo-3-methylphenyl)-2,3-dimethylhept-5-enal (181)



181

A 30 % suspension of KH in mineral oil (2.2 g, 55.5 mmol, 15 eq.) was washed with anhydrous DME (3 x 10 mL). Anhydrous DME (45 mL) was added to the KH. Alcohol **180** (1.10 g, 3.7 mmol, 1 eq.) and 18-crown-6 (0.97 g, 3.7 mmol, 1 eq.) were successively added to the solution and the mixture was stirred for two days at room temperature. The solution was cooled to −78 °C and quenched with a 1M solution of 2,4,6-tri-tert-butylphenol in dry DME (7eq). The solution was poured into a saturated solution of NH_4Cl (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. Compound **181** (d.r. 2:1 at C-11) was obtained as a yellow oil and was used in the next step without purification.

(2E,5R,7E)-ethyl 5-(2-bromo-3-methylphenyl)-4,5-dimethylnona-2,7-dienoate (183)

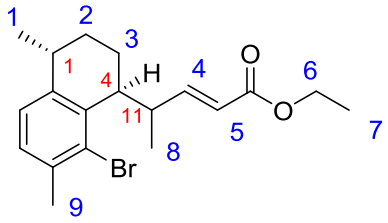


183

LiCl (186.5 mg, 4.44 mmol, 1.2 eq.) was weighted in a 50 mL flame-dried round bottom flask. The flask was evacuated and backfilled with N_2. Dried CH_3CN (10 mL) was added followed by a solution of Hünig's base (0.8 mL, 4.44 mmol, 1.2 eq.) and triethyl phosphonoacetate (0.9 mL, 4.44 mmol, 1.2 eq.) in 2 mL of dry CH_3CN each. After stirring the mixture for 5 minutes, the crude aldehyde **181** (3.7 mmol, 1 eq.) in 2 mL of anhydrous CH_3CN was added dropwise. The reaction was stirred overnight at room temperature before quenching with a saturated solution of NH_4Cl (20 mL). The mixture was extracted with DCM (3x50 mL), the organic phases dried over Na_2SO_4 and the solvents removed under reduced pressure. The crude mixture was purified by flash column chromatography on *silica* eluting with a gradient

system (100% petroleum ether to 5:1 petroleum ether/ethyl acetate) to yield the target compound **183** (d.r. 2:1) as a colorless oil (1.1 g, 81% yield over two steps). **Major isomer** (taken as a mixture): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 1.01 (d, *J* = 6.8Hz, 3H, 1-H); 1.27 (t, *J* = 6.8 Hz, 3H, 7-H); 1.53 (d, 6.4Hz, 3H, 8-H); 2.37-3.33 (m, 2H, 3-H); 2.43 (s, 3H, 9-H); 2.68-2.71 (m, 1H, 4/11-H); 3.49-3.53 (m, 1H, 4/11-H); 4.14-4.23 (m, 2H, 6-H); 5.11-5.41 (m, 2H, 1/2-H); 5.74 (d, *J* = 15.6Hz, 1H, 5-H); 6.92-7.01 (m, 2H, Ar/4-H); 7.06-7.17 (m, 2H, Ar/4-H). **Minor isomer** (taken as a mixture): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.91 (d, *J* = 6.4Hz, 3H, 1-H); 1.31 (t, *J* = 7.2 Hz, 3H, 7-H); 1.49 (d, *J* = 6.4Hz, 3H, 8-H); 2.37-3.33 (m, 2H, 3-H); 2.44 (s, 3H, 9-H); 2.49-2.53 (m, 1H, 4/11-H); 3.38-3.41 (m, 1H, 4/11-H); 4.14-4.23 (m, 2H, 6-H); 5.11-5.41 (m, 2H, 1/2-H); 5.82 (d, *J* = 14.8Hz, 1H, 5-H); 6.92-7.01 (m, 2H, Ar/4-H); 7.06-7.17 (m, 2H, Ar/4-H).

(E)-ethyl-4-((1R,4S)-8-bromo-1,4,7-trimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pent-2-enoate (184)

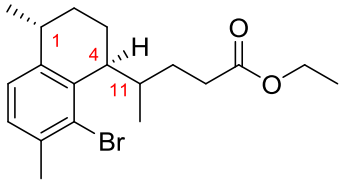


184

Methanesulfonic acid (0.37 mL, 5.7 mmol, 3 eq.) was added to a solution of **183** (693 mg, 1.9 mmol, 1 eq.) in $CHCl_3$ (3 mL) and the reaction mixture was stirred at 40 °C for two days. The reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography on *silica* (eluting with 95:5 petroleum ether/ethyl acetate) gave the title compound **184** as a pale yellow oil (570 mg, 83% yield); **Major isomer** (taken as a mixture): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.89 (d, *J* = 6.8Hz, 3H, 8-H); 1.21-1.31 (m, 6H, 7,1-H); 1.74-1.95 (m, 4H, 2,3-H); 2.38 (s, 3H, 9-H); 2.74-2.79 (m, 1H, 11-H); 3.04-3.09 (m, 1H, 4-H); 3.49-3.53 (m, 1H, 1-H); 4.12-4.4.21 (m, 2H, 6-H); 5.74 (dd, *J* = 16, 1.6Hz, 1H, 5-H); 7.06-7.12 (m, 3H, 4,Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 14.2 (*C*H_3), 14.2 (*C*H_3), 16.9 (*C*H_3), 21.5 (*C*H_2), 22.3 (*C*H), 24.2 (*C*H_3), 29.2 (*C*H_2), 32.2 (*C*H), 39.6 (*C*H), 41.7 (*C*H), 60.1 (*C*H_2), 120.0 (*C*H), 125.4 (*C*H), 128.2 (*C*H), 136.1 (*C*), 137.8 (*C*), 143.4 (*C*), 153.3 (*C*H), 166.8 (*C*). **Minor isomer** (taken as a mixture): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.90 (d,

J = 6.8Hz, 3H, 8-H); 1.15 (d, *J* = 7.2Hz, 3H, 1-H); 1.21-1.31 (m, 3H, 7-H); 1.74-1.95 (m, 4H, 2,3-H); 2.41 (s, 3H, 9-H); 2.74-2.79 (m, 1H, 11-H); 2.97-3.00 (m, 1H, 4-H); 3.40-3.44 (m,1H, 1-H); 4.12-4.21 (m, 2H, 6-H); 5.64 (dd, *J* = 15.6, 1.6Hz, 1H, 5-H), 6.79 (dd, *J* = 15.6, 6.4Hz, 1H, 4-H); 7.06-7.07 (m, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 14.2 (*C*H_3), 14.3 (*C*H_3), 16.9 (*C*H_3), 21.1 (*C*H_2), 22.6 (*C*H), 24.2 (*C*H_3), 28.5 (*C*H_2), 31.8 (*C*H), 40.0 (*C*H), 42.7 (*C*H), 60.0 (*C*H_2), 120.0 (*C*H), 125.7 (*C*H), 128.4 (*C*H), 136.0 (*C*), 138.1 (*C*), 143.1 (*C*), 152.6 (*C*H), 166.6 (*C*).

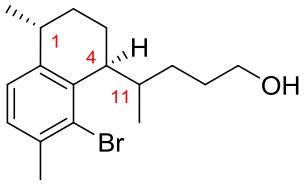
Ethyl 4-((1R,4S)-8-bromo-1,4,7-trimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentanoate (185)



185

A solution of compound **184** (557 mg, 1.52 mmol, 1 eq.) in MeOH (35 mL) was circulated for three hours through an H-Cube in-flow reactor (set at 2.0 mL/min, Full hydrogen mode, rt) equipped with a cartridge containing catalyst Pd/C 10%. The resulting solution was concentrated in *vacuo* to give crude **185** as a colourless oil (407 mg, 72 %), which was subjected to the next step without further purification.

4-((1R,4S)-8-bromo-1,4,7-trimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentan-1-ol (186)

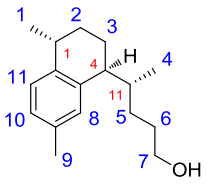


186

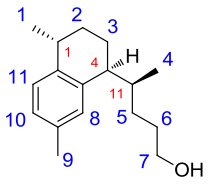
DIBAL, 1M in hexanes (2.2 mL, 2.2 mmol), was added to a solution of **185** (370 mg, 1 mmol) in anhydrous CH_2Cl_2 (20 mL) at −78 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with MeOH (10 mL), 5M HCl (15 mL) and extracted with CH_2Cl_2 (3x30 mL). The organic layer were combined, dried over Na_2SO_4 and concentrated in *vacuo*. The crude reaction mixture was filtered through a pad of

silica and after removal of solvent in *vacuo* gave **186** as colourless oil. The material was subjected to the next step without further purification.

(–)-4-((1R,4S)-1,4,7-trimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentan-1-ol (187)



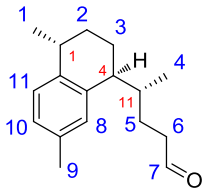
trans,syn-**187a**



trans,anti-**187b**

A solution of compound **186** (336 mg, 1.03 mmol, 1 eq.) in MeOH (15 mL) was circulated for 5 hrs through an H-Cube flow reactor (2.0 mL/min, 20 bar, 40 °C) equipped with a cartridge containing catalyst Pd/C 10%. The reaction solution was concentrated *in vacuo* to give product **187** (d.r. 2:1) as a colourless oil (234 mg, 92 %). The diastereomers were separated by preparative HPLC (Dynmax-60Å, hexane/2-propanol = 98:2, 5 mL/min, UV detection at 220 nm). (–)-*Trans,syn*-**187a**, major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.65 (d, *J* = 5.2Hz, 3H, 4-H); 1.26 (d, *J* = 5.6Hz, 3H, 1-H); 1.31-1.38 (m, 3H); 1.61-1.70 (m, 3H); 1.78-1.84 (m, 1H); 1.90-1.95 (m, 1H); 2.13-2.16 (m, 1H, 11-H); 2.30 (s, 3H, 9-H); 2.71-2.75 (m, 1H, 4-H); 2.87-2.91 (m, 1H, 1-H); 3.70 (t, *J* = 5.2Hz, 2H, 7-H); 6.95 (d, *J* = 6.4Hz, 1H, 10-H); 7.03 (s, 1H, 8-H); 7.14 (d, *J* = 6Hz, 1H, 11-H) ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 14.5 (*C*H_3), 21.1 (*C*H_3), 21.5 (*C*H_2), 21.8 (*C*H_3), 31.1 (*C*H_2), 31.6 (*C*H_2), 32.8 (*C*H), 37.1 (*C*H), 41.6 (*C*H), 63.4 (*C*H_2), 126.0 (*C*H), 126.4 (*C*H), 128.0 (*C*H), 134.7 (*C*), 139.6 (*C*), 140.3 (*C*); **IR** (neat) 3343, 2928, 2869, 1497, 1455, 1376, 1058, 812 cm^{-1}; **HRMS** (ESI) 353.1037 ($C_{17}H_{26}O^{107}Ag$ $[M]^+$ required 353.1029). **$[\alpha]_D^{25}$** = –54.5 (*c* = 1.02, $CHCl_3$; $[\alpha]_D^{25}$ = +36.5, c = 0.81, $CHCl_3$[111]). (–)-*Trans,anti*-**187b**, minor isomer: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 1.03 (d, *J* = 6.8Hz, 3H, 4-H); 1.28 (d, *J* = 6.8Hz, 3H, 1-H); 1.33-1.39 (m, 2H); 1.47 (s_{broad}, 1H, OH); 1.55-1.60 (m, 3H); 1.89-1.94 (m, 2H); 2.08-2.13 (m, 1H, 11-H); 2.32 (s, 3H, 9-H); 2.75-2.81 (m, 2H, 1,4-H); 3.48-3.56 (m, 2H, 7-H); 6.96 (d, *J* = 8Hz, 1H, 10-H); 7.04 (s, 1H, 8-H); 7.15 (d, *J* = 8Hz, 1H, 11-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 140.3 (*C*), 139.6 (*C*), 134.6 (*C*), 128.2 (*C*H), 126.8 (*C*H), 126.2 (*C*H), 63.1 (*C*H_2), 43.7 (*C*H), 36.9 (*C*H), 32.7 (*C*H), 31.2 (*C*H_2), 31.1 (*C*H_2), 27.3 (*C*H_2), 22.2 (*C*H_2), 22.1 (*C*H_3), 21.1 (*C*H_3), 18.2 (*C*H_3); **IR** (neat) 3343, 2928, 2869, 1497, 1455, 1376, 1058, 812 cm^{-1}; **HRMS** (ESI) 353.1037 ($C_{17}H_{26}O^{107}Ag$ $[M]^+$ required 353.1029). **$[\alpha]_D^{25}$** = –32.9 (*c* = 0.413, $CHCl_3$).

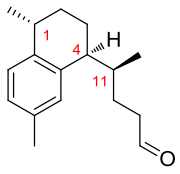
(–)-4-((1R,4S)-1,4,7-trimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentanal (188a)



trans,syn-**188a**

Dess-Martin periodinane (1.5 eq.) was weighted in a 25 mL flame-dried round bottom flask. The vessel was evacuated and backfilled with N_2 before being charged with alcohol *trans,syn*-**187a** (1 eq.) in 5 mL of DCM. The reaction was allowed to stir at room temperature for 2 hours. The solvent was partially removed in *vacuum* and the crude mixture was directly purified on a silica gel column chromatography (95:5, petroleum ether: ethyl acetate). *Trans,syn*-**188a**, pale yellow oil (85.6 mg, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.67 (d, *J* = 6.8 Hz, 3H, 4-H); 1.27 (d, *J* = 6.8 Hz, 3H, 1-H); 1.28-1.37 (m, 1H); 1.57-1.83 (m, 4H); 1.90-1.95 (m, 1H); 2.11-2.14 (m, 1H); 2.29 (s, 3H, 9-H); 2.49-2.55 (m, 2H); 2.70-2.76 (m, 1H); 2.84-2.89 (m, 1H); 6.94-7.00 (m, 2H, 8,10-H); 7.14 (d, *J* = 8 Hz, 1H, 11-H); 9.83 (s, 1H, 7-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 14.4 (*C*H_3), 21.2 (*C*H_3/*C*H), 21.6 (*C*H_3/*C*H), 21.9 (*C*H), 27.3 (*C*H_2), 31.6 (*C*H_2), 32.8 (*C*H), 37.0 (*C*H), 41.8 (*C*H), 42.5 (*C*H_2), 126.4 (*C*H), 126.7 (*C*H), 128.1 (*C*H), 134.9 (*C*), 139.2 (*C*), 140.4 (*C*), 202.8 (*C*H); **IR** (neat) 2956, 2928, 2871, 2716, 1725, 1612, 1497, 1456, 1411, 1377, 1321, 1043, 814 cm^{-1}; **$[\alpha]_D^{25}$** = –25.3 (*c* = 0.3, $CHCl_3$).

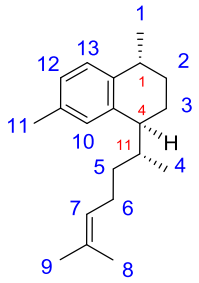
(S)-4-((1S,4R)-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)pentanal (188b)



trans,anti-**188b**

Dess-Martin periodinane (1.5 eq.) was weighted in a 25 mL flame-dried round bottom flask. The vessel was evacuated and backfilled with N_2 before being charged with alcohol *trans,syn*-**187a** (1 eq.) in 5 mL of DCM. The reaction was allowed to stir at room temperature for 2 hours. The solvent was partially removed in *vacuum*. *Trans,syn*-**188b** was obtained as a pale yellow oil which was not purified but subjected to the subsequent alkenylation reaction.

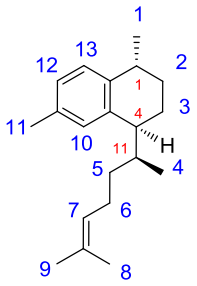
(–)-(1R,4S)-1,4,7-trimethyl-1-(6-methylhept-5-en-2-yl)-1,2,3,4-tetrahydronaphthalene. (–)-Erogorgiaene (86a)



(–)-Erogorgiane, **86a**

n-BuLi, 1.6M solution in hexane (0.5 mL, 0.81 mmol, 3 eq.), was added dropwise to a solution of isopropyltriphenylphosphonium iodide (385.2 mg, 0.89 mmol) in anhydrous THF (3 mL) at 0 °C under N_2. The mixture was stirred for one hour before aldehyde (–)-*trans,syn*-**188a** (65 mg, 1.3 mmol) in THF (15 mL) was added. The solution was allowed to stir at the same temperature for 30 minutes before warming to room temperature and heating at reflux for a further 2 hrs. After cooling, the reaction mixture was quenched with saturated NH_4Cl (5 mL) and extracted with DCM (3x20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography on *silica* (10:1 petroleum ether/ethyl acetate) gave (–)-erogorgiaene **86a** as a colourless oil (58 mg, 80 %); (–)-Erogorgiane **86a**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 0.66 (d, *J* = 6.8 Hz, 3H, 4-H); 1.29 (d, *J* = 6.8 Hz, 3H, 1-H); 1.32-1.41 (m, 2H); 1.45-1.57 (m, 2H); 1.67 (s, 3H, 8/9-H); 1.75 (s, 3H, 8/9-H); 1.80-1.87 (m, 1H); 1.91-1.97 (m, 1H); 2.04-2.19 (m, 3H); 2.33 (s, 3H, 11-H); 2.72-2.76 (m, 1H, 1/4-H); 2.88-2.93 (m, 1H, 1/4-H); 5.20 (tm, *J* = 6.8 Hz, 1H, 7-H); 6.97 (d, *J* = 8 Hz, 1H, 12-H); 7.05 (s, 1H, 10-H); 7.16 (d, *J* = 8 Hz, 1H, 13-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 14.5 (*C*H_3), 17.7 (*C*H_3), 21.1 (*C*H_3), 21.5 (*C*H_2), 21.8 (*C*H_3), 25.7 (*C*H_3), 26.3 (*C*H_2), 31.8 (*C*H_2), 32.8 (*C*H), 35.2 (*C*H_2), 36.9 (*C*H), 41.4 (*C*H), 124.9 (*C*H), 126.0 (*C*H), 126.4 (*C*H), 128.1 (*C*H), 131.2 (*C*), 134.7 (*C*), 139.9 (*C*), 140.4 (*C*); **IR** (neat) 2959, 2924, 2853, 1613, 1497, 1452, 1376, 1320, 1109, 1039, 983, 881, 811 cm^{-1}; **HRMS (ESI)** 377.1390 and 379.1386 ($C_{20}H_{30}{}^{107}Ag$ $[M+Ag]^+$ requires 377.1393 and $C_{20}H_{30}{}^{109}Ag$ $[M+Ag]^+$ requires 379.1390). **$[\alpha]_D^{25}$** = –25.5 (*c* = 0.52, $CHCl_3$; $[\alpha]_D^{25}$ = +23.2, c = 0.75, $CHCl_3$;[146] $[\alpha]_D^{25}$ = +69.1, c = 0.77, DCM;[147] $[\alpha]_D^{25}$ = +40.6, c = 0.14, $CHCl_3$[148]; $[\alpha]_D^{25}$ = +21.4; c = 0.14, $CHCl_3$[111]).

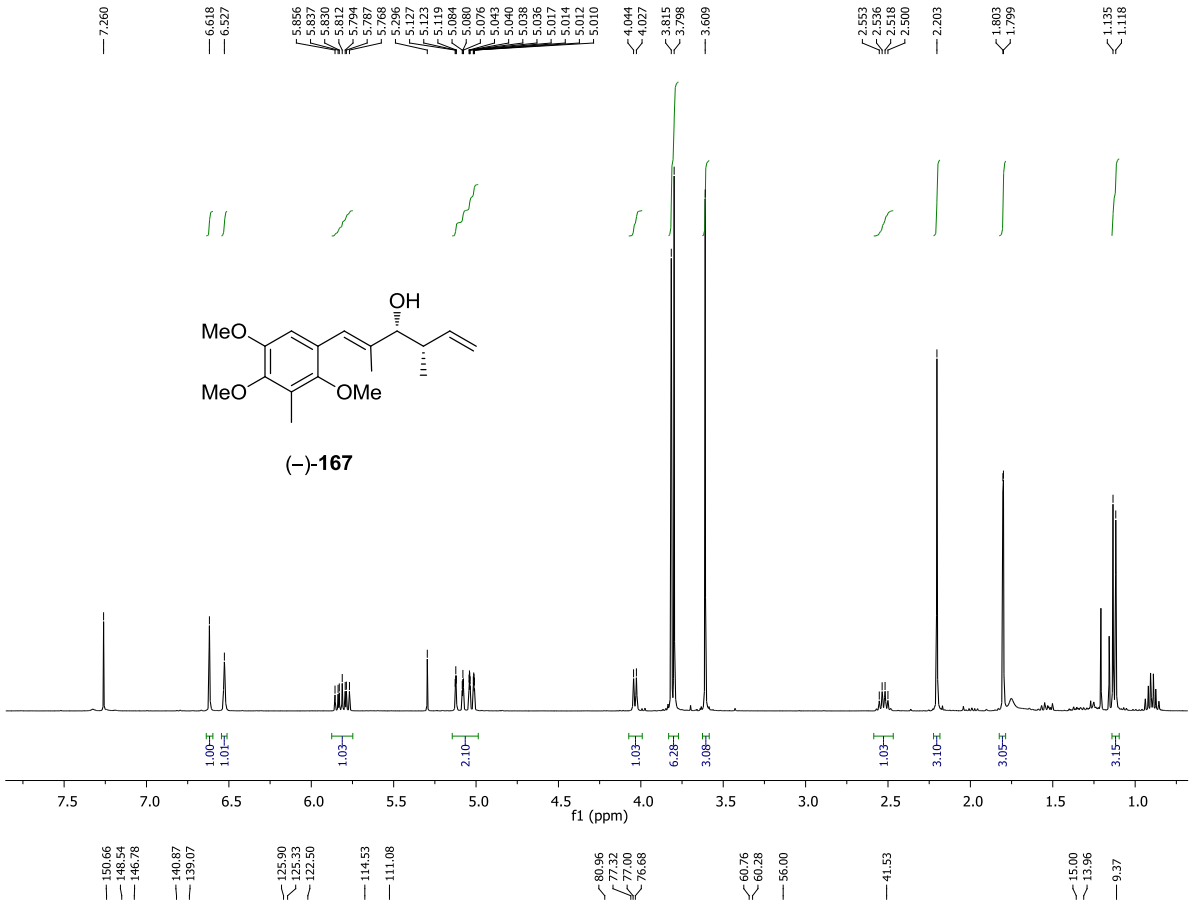
(–)-(1R,4S)-1,6-dimethyl-4-((S)-6-methylhept-5-en-2-yl)-1,2,3,4-tetrahydronaphthalene (86b)



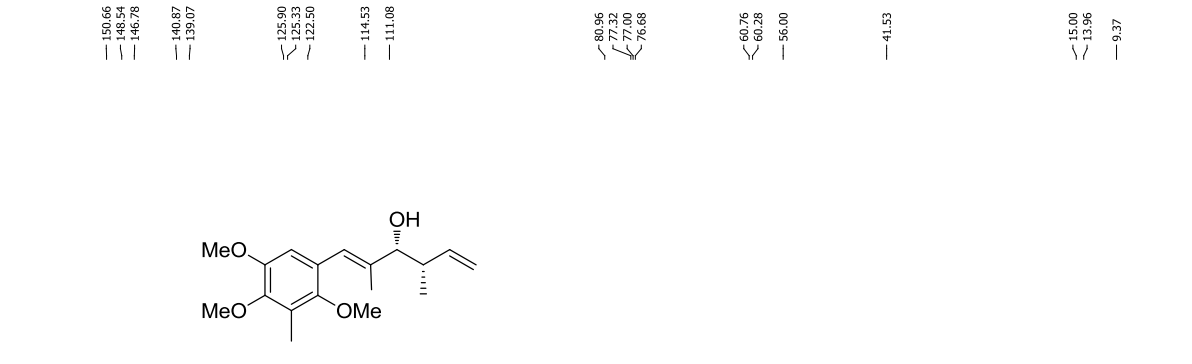
(–)-86b

(–)-**86b** C-11 epimer was obtained similarly to (–)-**86a** as a pale yellow oil (15 mg, 30% yield over two steps): **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 1.00 (d, *J* = 6.8 Hz, 3H, 1-H); 1.23-1.27 (m, 7H); 1.55 (s, 3H, 8/9-H); 1.66 (s, 3H, 8/9-H); 1.80-2.00 (m, 4H); 2.07-2.12 (m, 2H); 2.30 (s, 3H); 2.73-2.77 (m, 2H, 1,4-H); 4.98 (t, *J* = 7.4 Hz, 1H, 7-H); 6.94 (m, 1H, 12-H); 7.03 (s, 1H, 10-H); 7.13 (d, *J* = 8 Hz, 1H, 13-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 17.6 (*C*H_3), 18.1 (*C*H_3), 21.1 (*C*H_3), 22.2 (*C*H_3), 22.4 (*C*H_2), 25.7 (*C*H_3), 26.3 (*C*H_2), 31.4 (*C*H_2), 31.5 (*C*H_2), 32.7 (*C*H), 36.2 (*C*H), 43.8 (*C*H), 125.0 (*C*H), 126.1 (*C*H), 126.7 (*C*H), 128.4 (*C*H), 131.2 (*C*), 134.5 (*C*), 139.7 (*C*), 140.2 (*C*). **IR** (neat) 2959, 2924, 2853, 1613, 1497, 1452, 1376, 1320, 1109, 1039, 983, 881, 811 cm^{-1}; **HRMS (ESI)** 377.1390 and 379.1386 ($C_{20}H_{30}{}^{107}Ag\,[M+Ag]^+$ requires 377.1393 and $C_{20}H_{30}{}^{109}Ag\,[M+Ag]^+$ requires 379.1390). **$[\alpha]_D^{25}$** = –25.3 (*c* = 0.3, $CHCl_3$; $[\alpha]_D^{25}$ = +55.2, c = 0.83, DCM[147])

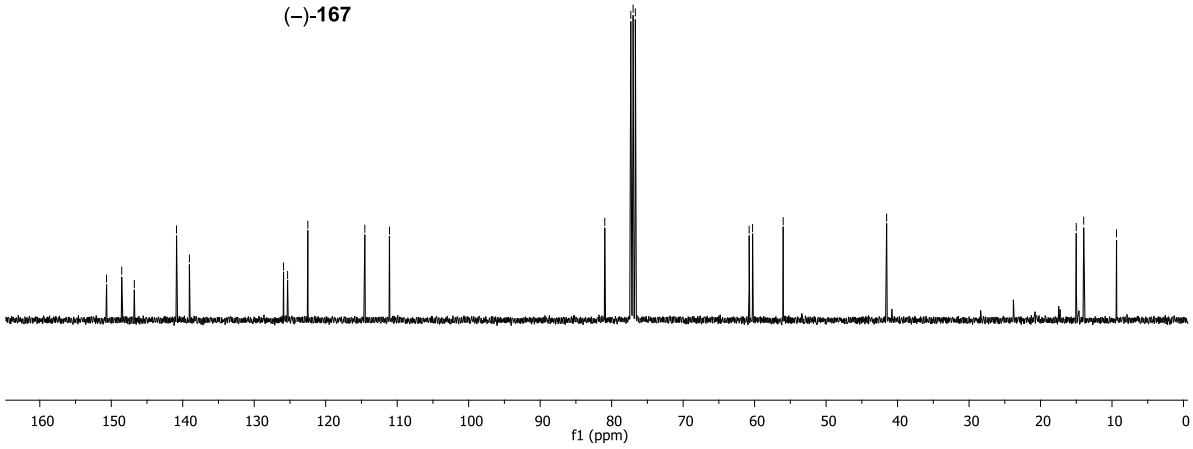
4.7. NMR spectra and HPLC traces

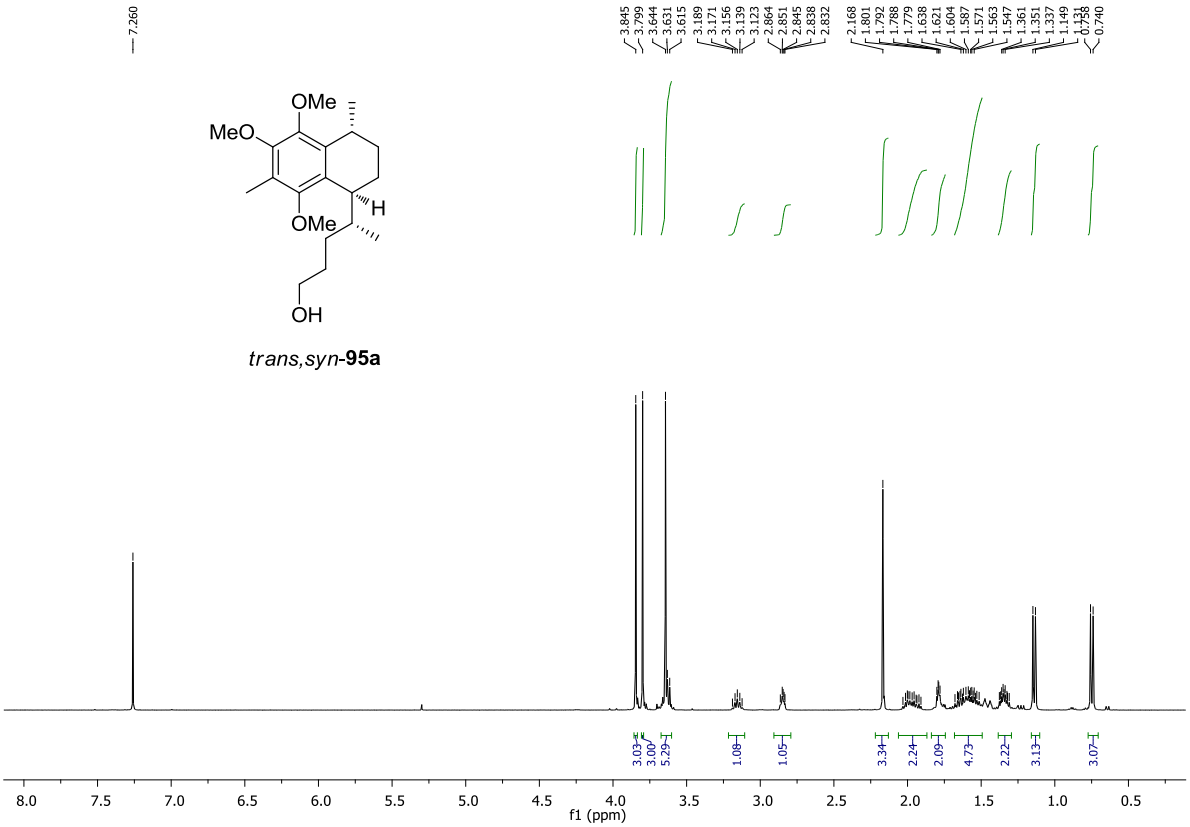


(–)-**167**

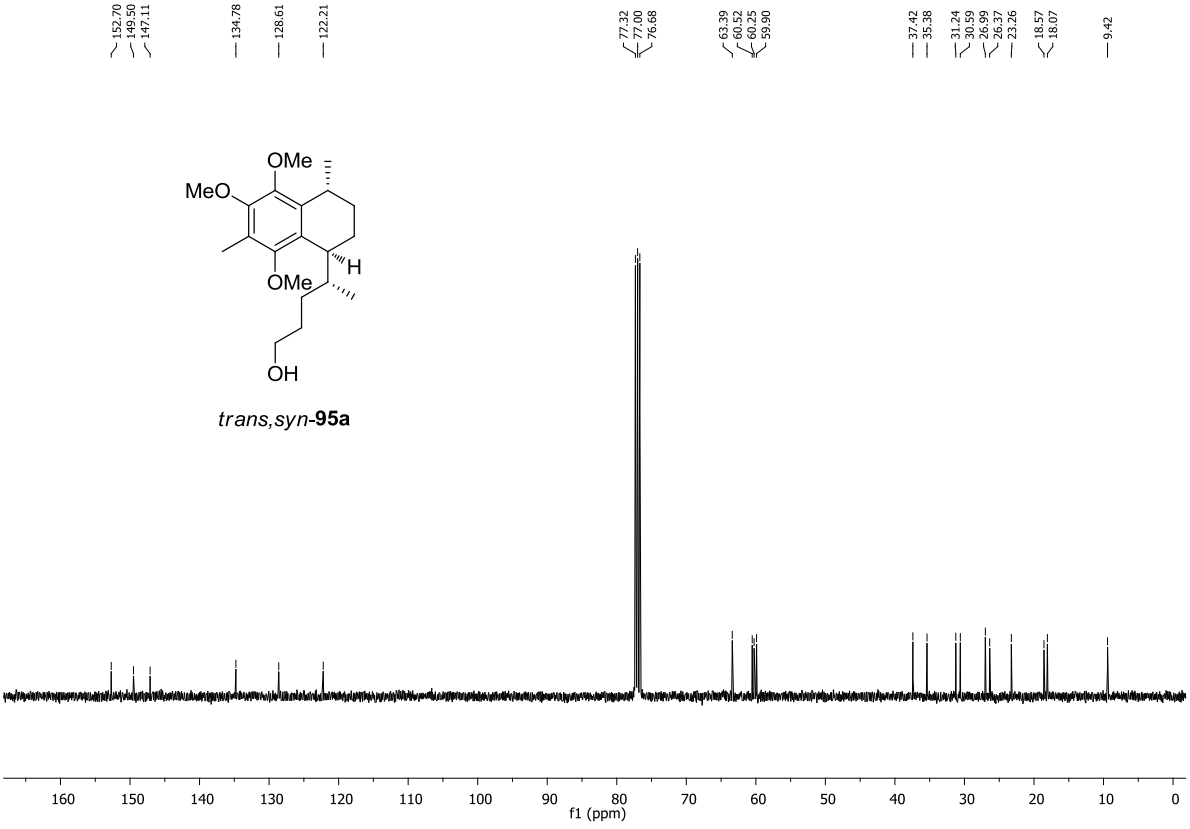


(–)-**167**

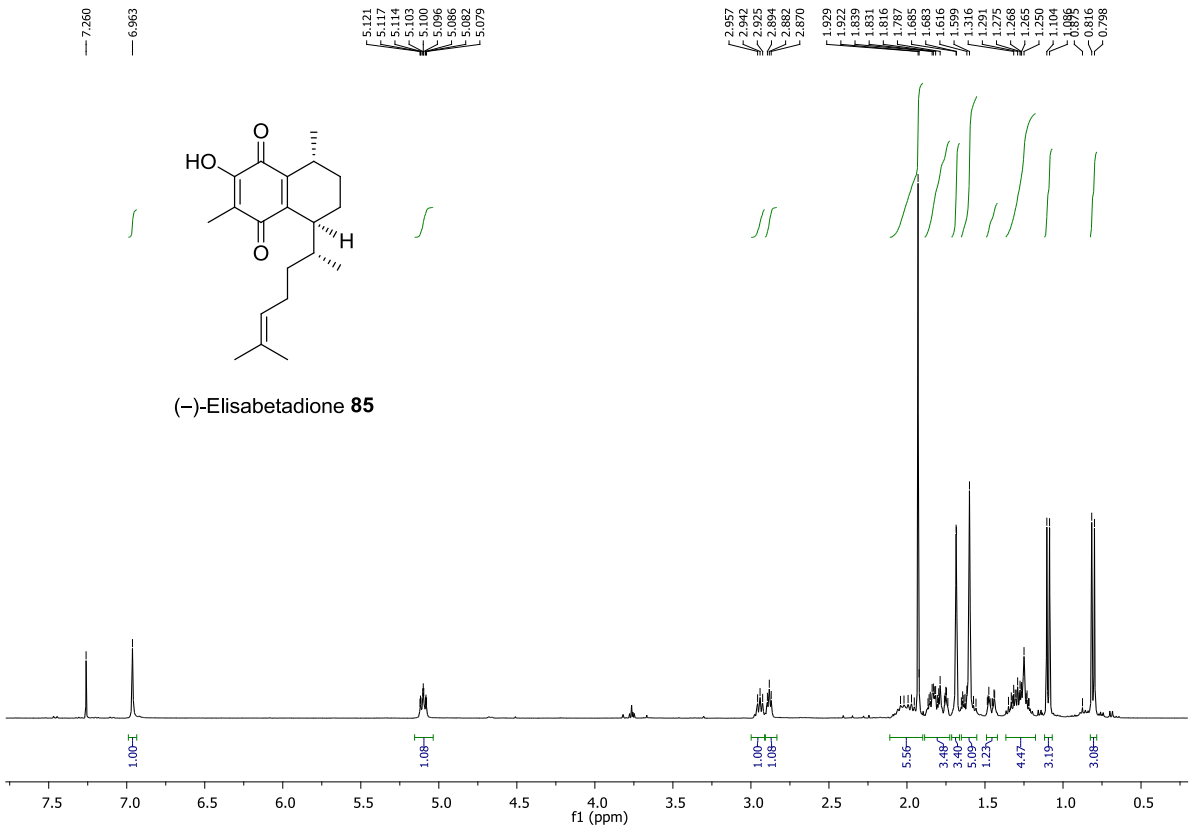




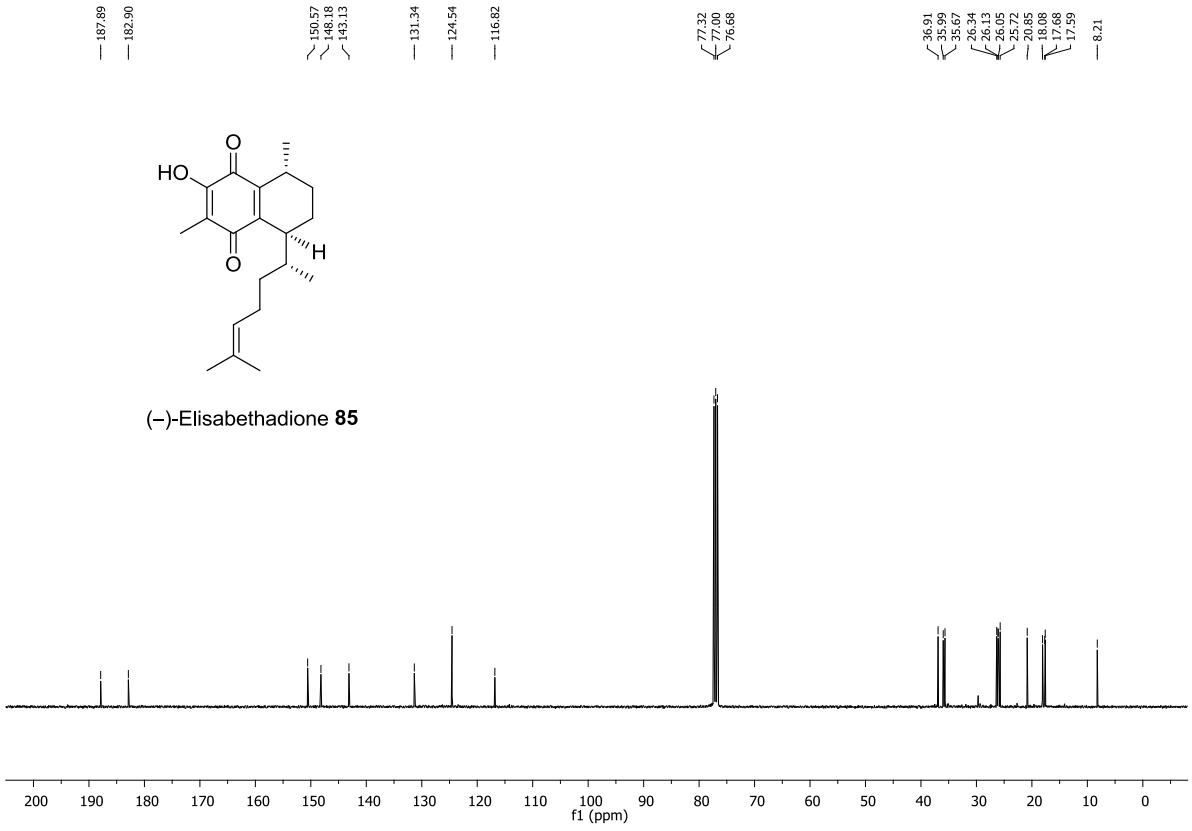
trans,syn-**95a**



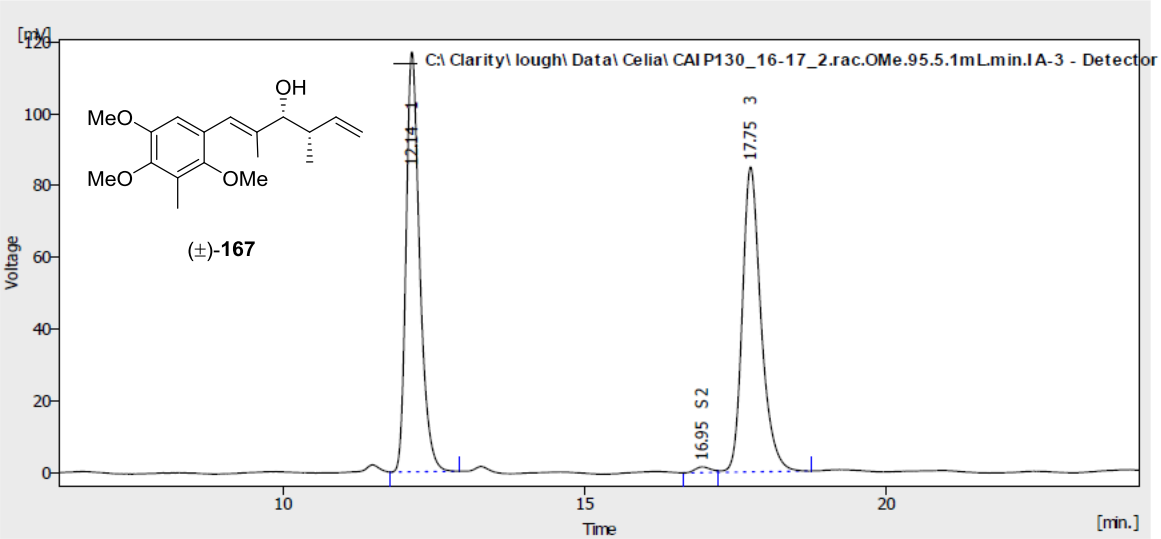
trans,syn-**95a**



(–)-Elisabetadione **85**

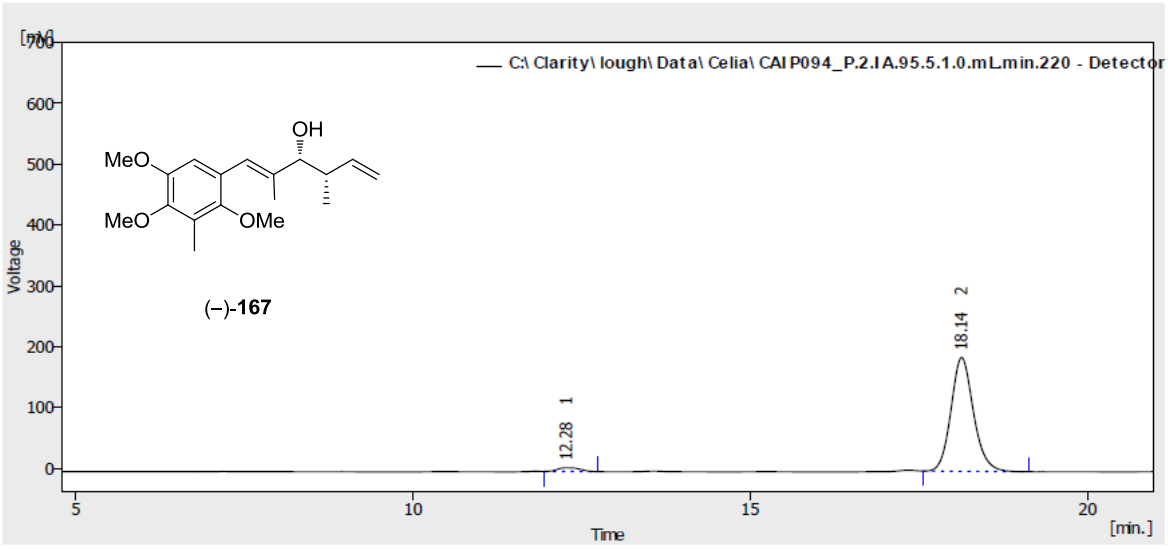


(–)-Elisabethadione **85**



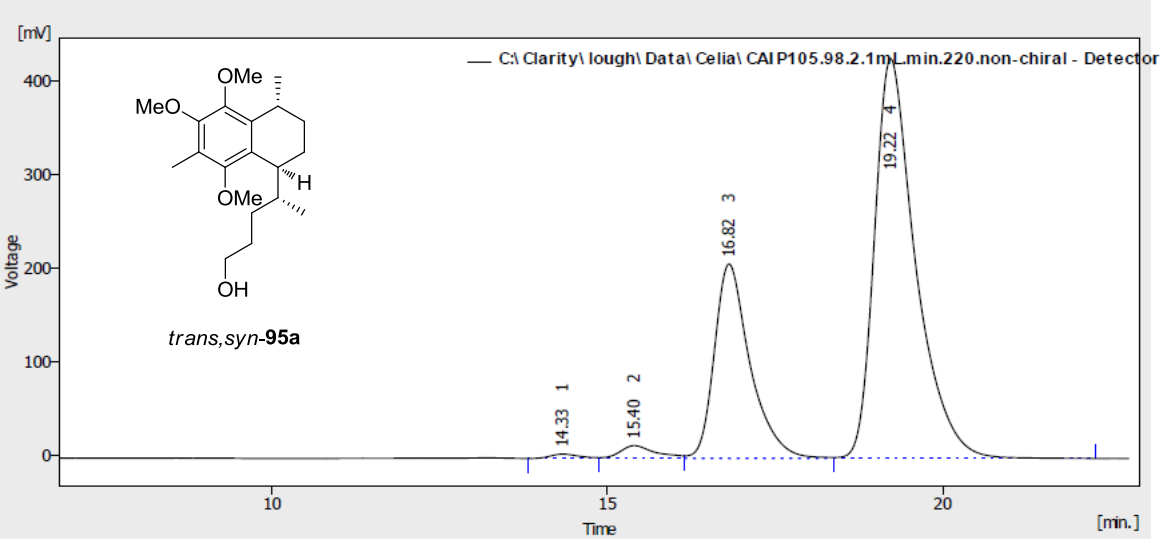
Result Table (Uncal - C:|Clarity|lough|Data|Celia|CAIP130_16-17_2.rac.OMe.95.5.1mL.min.IA-3 - Detector 2)

	Reten. Time [min]	Start Time [min]	End Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	12.136	11.780	12.916	1832.375	116.807	50.1	57.9	0.24
3	17.748	17.200	18.764	1826.062	84.816	49.9	42.1	0.32
	Total	Total	Total	3658.437	201.622	100.0	100.0	



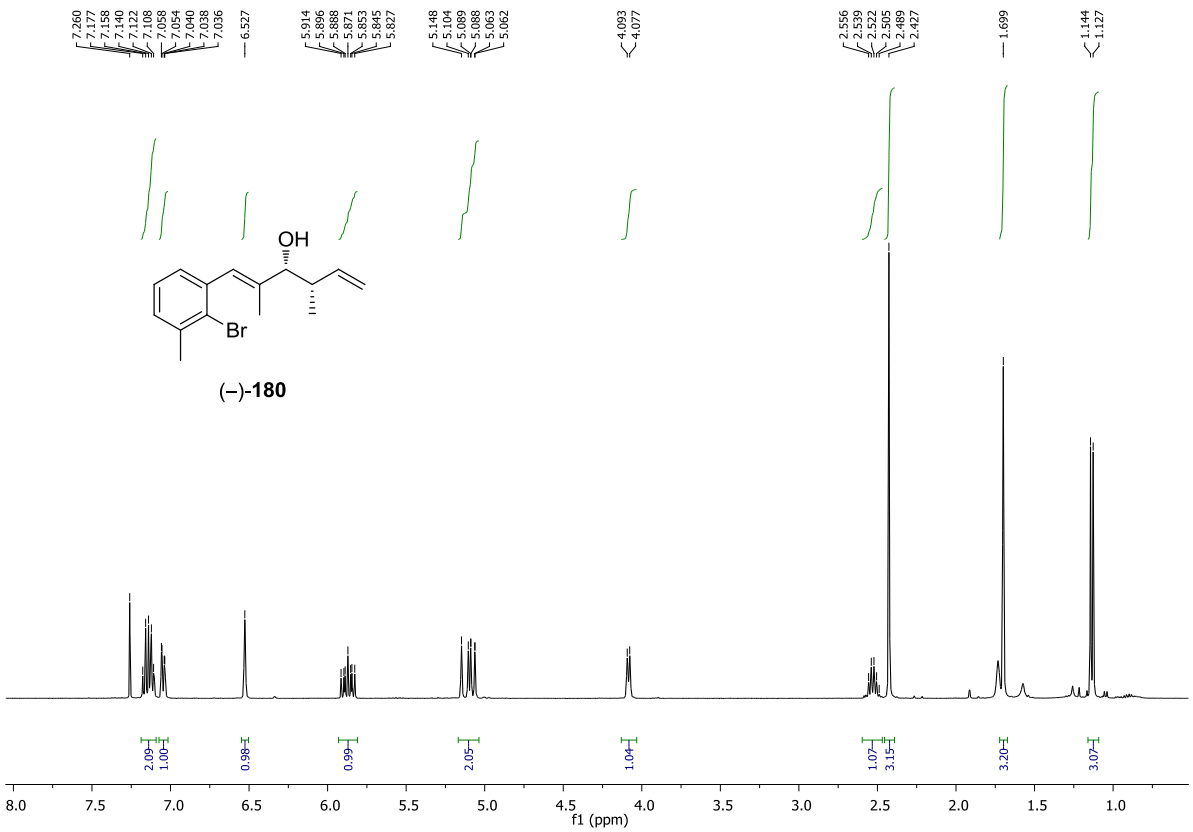
Result Table (Uncal - C:|Clarity|lough|Data|Celia|CAIP094_P.2.IA.95.5.1.0.mL.min.220 - Detector 2)

	Reten. Time [min]	Start Time [min]	End Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	12.276	11.952	12.732	145.209	6.187	3.2	3.2	0.39
2	18.136	17.572	19.128	4340.266	186.999	96.8	96.8	0.36
	Total	Total	Total	4485.475	193.187	100.0	100.0	

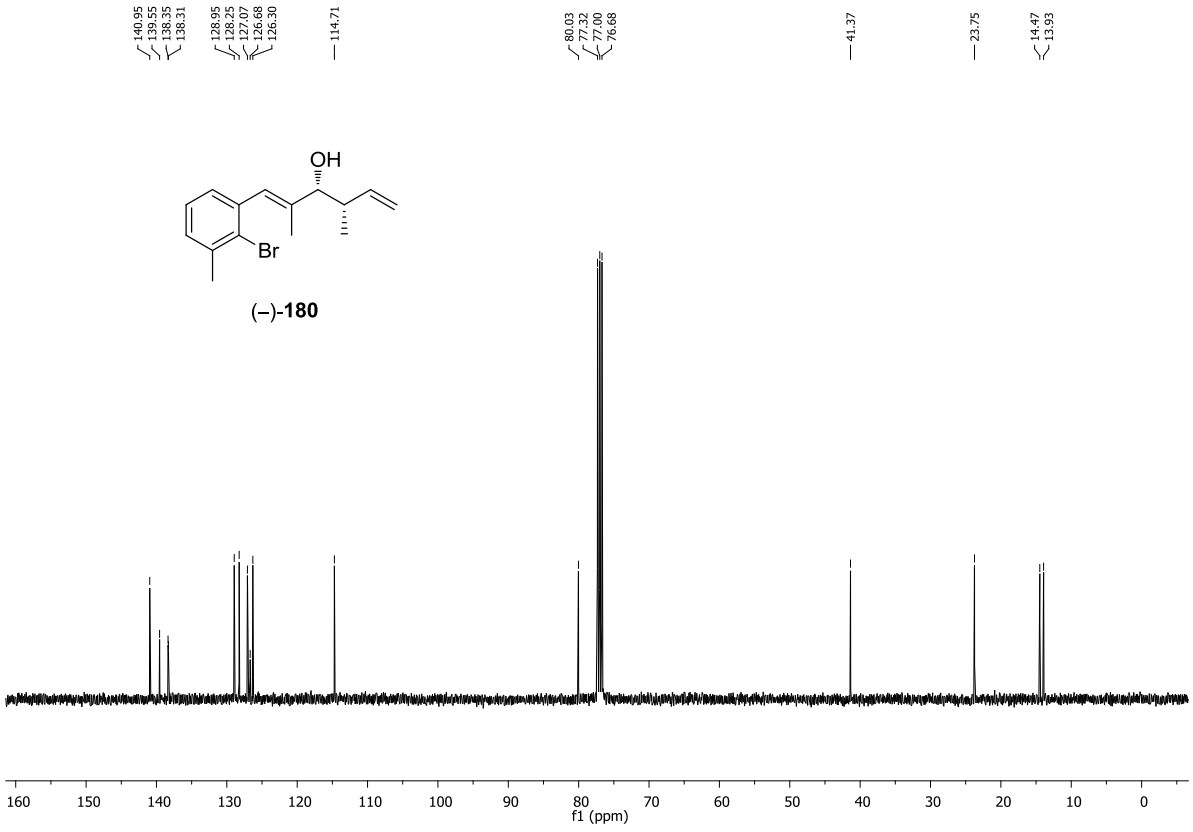


Result Table (Uncal - C:|Clarity|lough|Data|Celia|CAIP105.98.2.1mL.min.220.non-chiral - Detector 2)

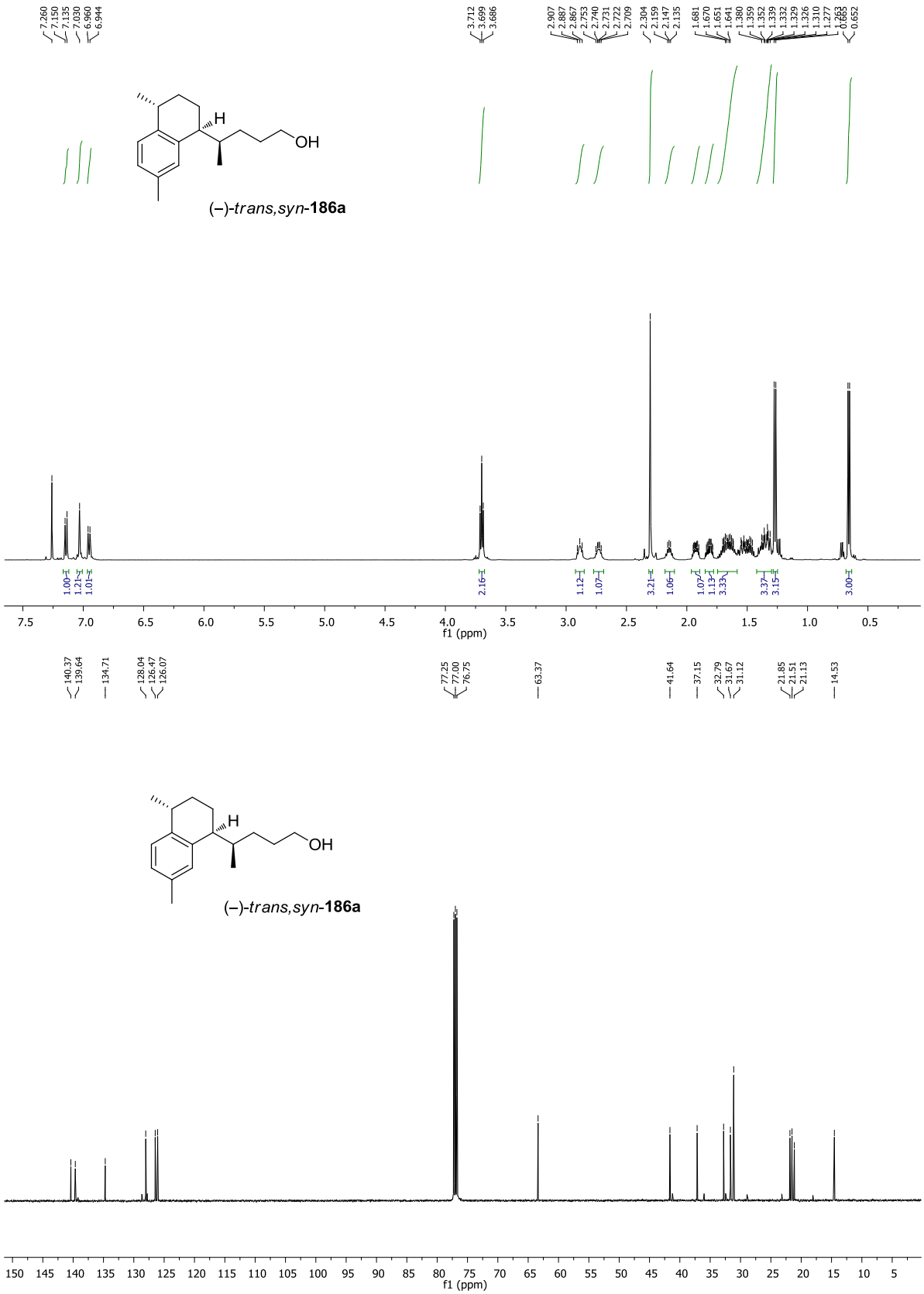
	Reten. Time [min]	Start Time [min]	End Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	14.332	13.812	14.872	136.500	4.628	0.5	0.7	0.46
2	15.400	14.872	16.152	502.750	13.667	1.9	2.1	0.52
3	16.816	16.152	18.372	7670.928	207.137	29.0	31.8	0.54
4	19.224	18.372	22.284	18148.196	426.098	68.6	65.4	0.62
	Total	Total	Total	26458.374	651.529	100.0	100.0	

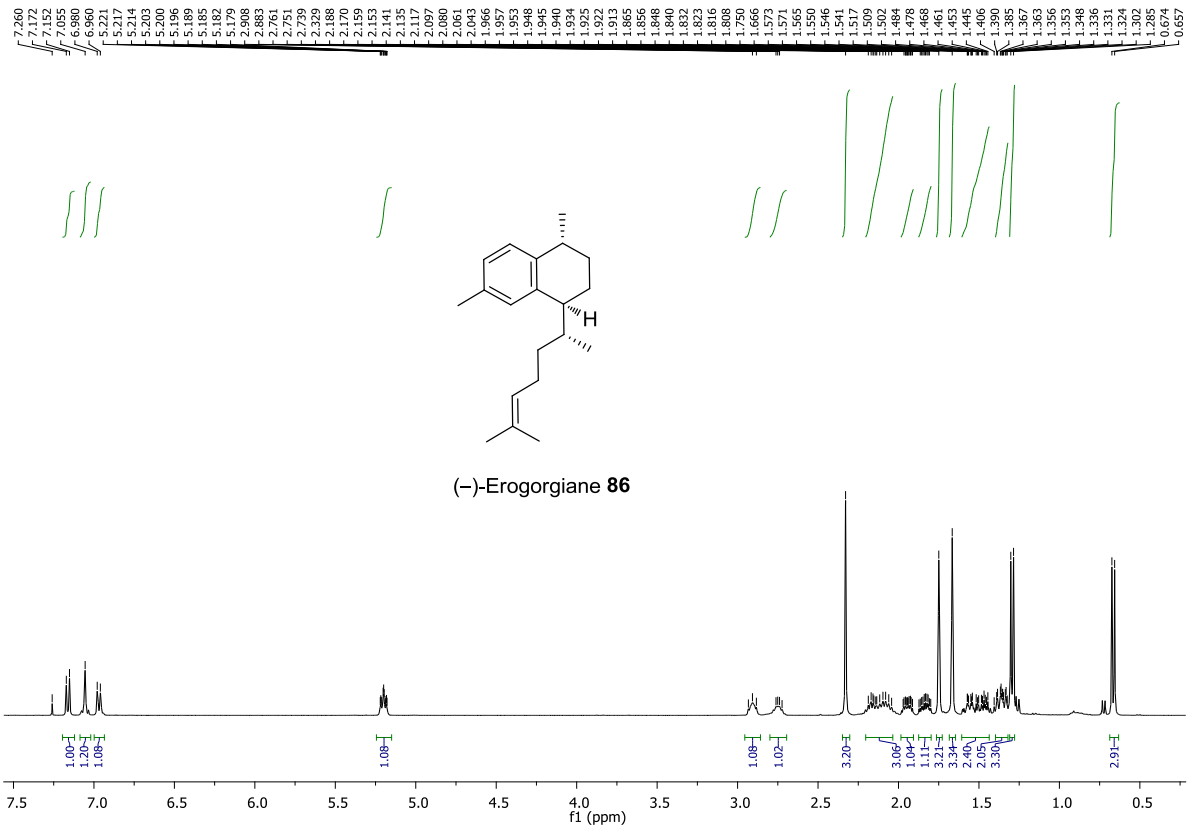

7.260
7.177
7.158
7.140
7.122
7.108
7.058
7.054
7.040
7.038
7.036
6.527
5.914
5.896
5.888
5.871
5.853
5.845
5.827
5.148
5.104
5.089
5.088
5.063
5.062
4.093
4.077
2.556
2.539
2.522
2.505
2.489
2.427
1.699
1.144
1.127
OH
Br
2.09
1.00
0.98
0.99
2.05
1.04
1.07
3.15
3.20
3.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

(–)-**180**

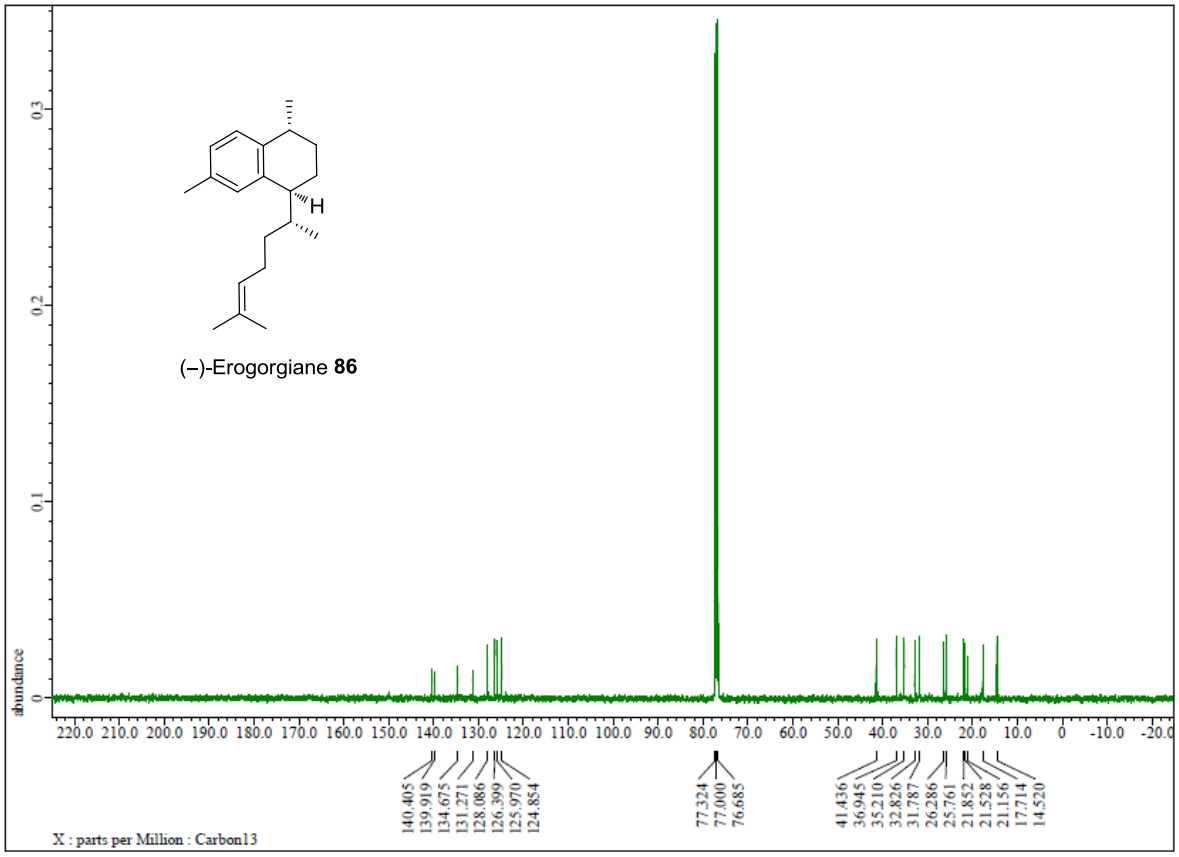

140.95
139.55
138.35
138.31
128.95
128.25
127.07
126.68
126.30
114.71
80.03
77.32
77.00
76.68
41.37
23.75
14.47
13.93
OH
Br
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(–)-**180**

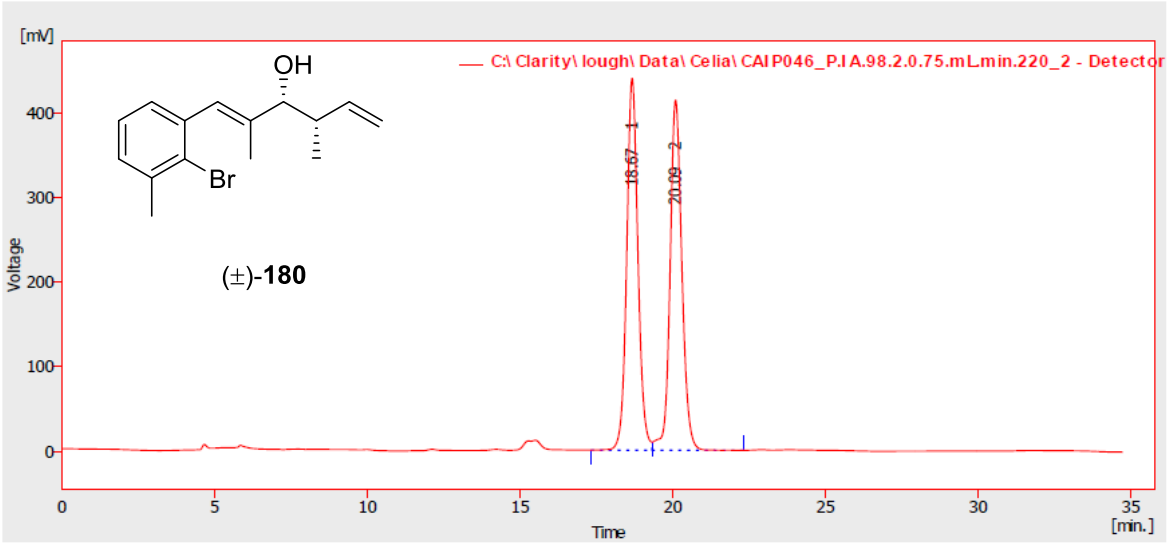

7.260
7.150
7.135
7.030
6.960
6.944
3.712
3.699
3.686
2.907
2.887
2.867
2.753
2.740
2.731
2.722
2.709
2.304
2.159
2.147
2.135
1.681
1.670
1.651
1.641
1.380
1.359
1.352
1.339
1.332
1.329
1.326
1.310
1.277
0.652
H
OH
(–)-trans,syn-186a
1.00
1.21
1.01
2.16
1.12
1.07
3.21
1.06
1.07
1.13
3.33
3.37
3.15
3.00
f1 (ppm)
140.37
139.64
134.71
128.04
126.47
126.07
77.25
77.00
76.75
63.37
41.64
37.15
32.79
31.67
31.12
21.85
21.51
21.13
14.53
H
OH
(–)-trans,syn-186a
f1 (ppm)



(–)-Erogorgiane **86**

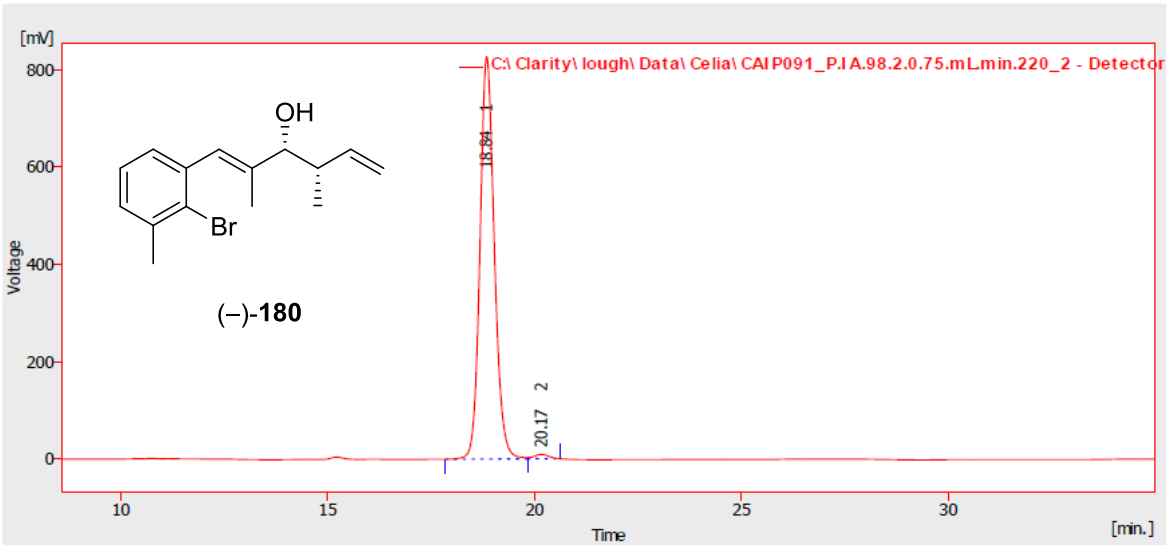


(–)-Erogorgiane **86**



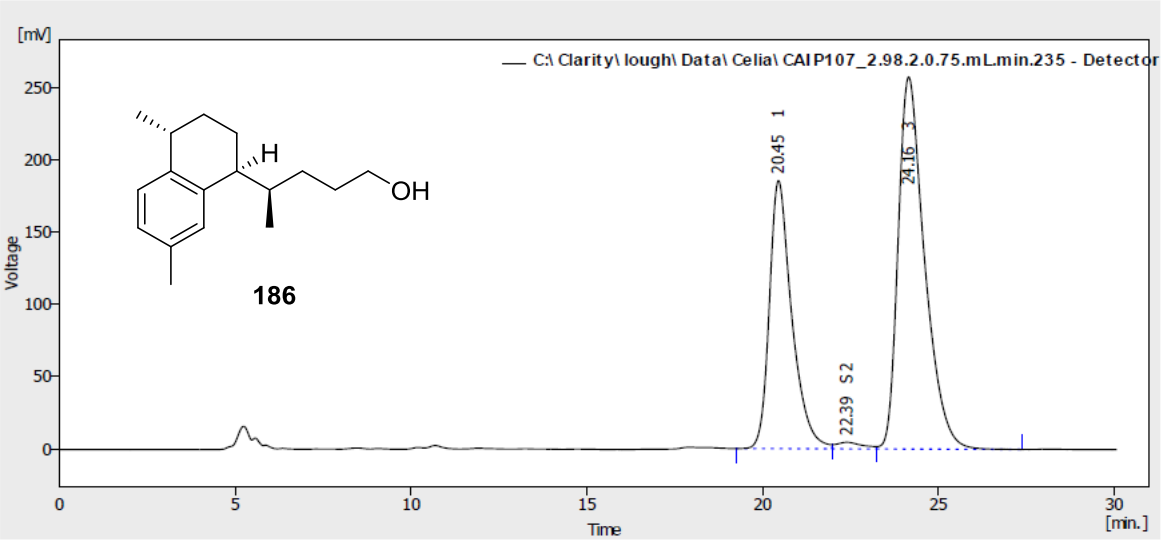
Result Table (Uncal - C:|Clarity|lough|Data|Celia|CAIP046_P.IA.98.2.0.75.mL.min.220_2 - Detector 2)

	Reten. Time [min]	Start Time [min]	End Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	18.668	17.332	19.320	11258.321	439.942	50.2	51.5	0.38
2	20.092	19.320	22.312	11164.013	414.229	49.8	48.5	0.40
	Total	Total	Total	22422.333	854.171	100.0	100.0	



Result Table (Uncal - C:|Clarity|lough|Data|Celia|CAIP091_P.IA.98.2.0.75.mL.min.220_2 - Detector 2)

	Reten. Time [min]	Start Time [min]	End Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	18.840	17.848	19.824	19969.924	826.839	98.9	98.9	0.37
2	20.172	19.824	20.628	229.831	9.242	1.1	1.1	0.39
	Total	Total	Total	20199.755	836.082	100.0	100.0	



Result Table (Uncal - C:|Clarity|lough|Data|Celia|CAIP107_2.98.2.0.75.mL.min.235 - Detector 2)

	Reten. Time [min]	Start Time [min]	End Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	20.452	19.240	21.972	8251.583	185.643	38.0	41.9	0.66
3	24.156	23.240	27.372	13485.032	257.706	62.0	58.1	0.79
	Total	Total	Total	21736.615	443.350	100.0	100.0	

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