Development of novel catalytic asymmetric diborylation methodologies

ALBA PUJOL-SANTIAGO

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A thesis submitted in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

At the Department of Chemistry, Durham University, UK

Submitted by

Alba Pujol Santiago

Under the supervision of

Professor Andrew Whiting

2017

Declaration

The work described in this thesis was carried out in the Department of Chemistry at Durham University (UK) between October 2013 and January 2017, under the supervision of Prof. Andrew Whiting. Research was conducted at the Universitat Rovira i Virgili from November 2014 to January 2015, under the supervision of Prof. M. Elena Fernández. The material contained has not been previously submitted for a degree at this or any other university. The research reported within this thesis has been conducted by the author unless indicated otherwise.

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Alba Pujol Santiago

2017

Abstract

This thesis describes the study of the β-borylation reaction on different types of electron deficient substrates as well as the application of the methodologies herein developed into the synthesis of a key intermediate for cholesterol-lowering drug Atorvastatin.

Within the frame of the use of organoboron compounds in organic synthesis, the literature review presented in the first section after a brief introduction on organoboranes is focused on the different strategies for their synthesis *via* boron addition, specially the β-borylation reaction. Different aspects of the reaction are covered; enantioselective version, the different methodologies reported for the activation of the diborane reagents or organic electron deficient substrates.

Within the study of the β-borylation reaction on α,β-unsaturated aldehydes *via* the *in situ* generated amine-derived aldimine intermediates, and the further application of these synthetically attractive compounds, the relevant challenge of handling β-boryl aldehydes was met. It was confirmed that this type of compound was indeed unstable especially under chromatographic purification conditions, leading to de-borylation. In addition, mechanistic studies were carried out in order to achieve a better understanding of the whole process, but it was not possible to clarify it and avoid the undesired side-process. Hence, the establishment of an efficient derivatisation methodology was required. The solution consisted of a mild, efficient derivatisation process involving an *in situ* copper(II) sulfate-based imine hydrolysis followed by Wittig trapping of the resulting aldehyde.

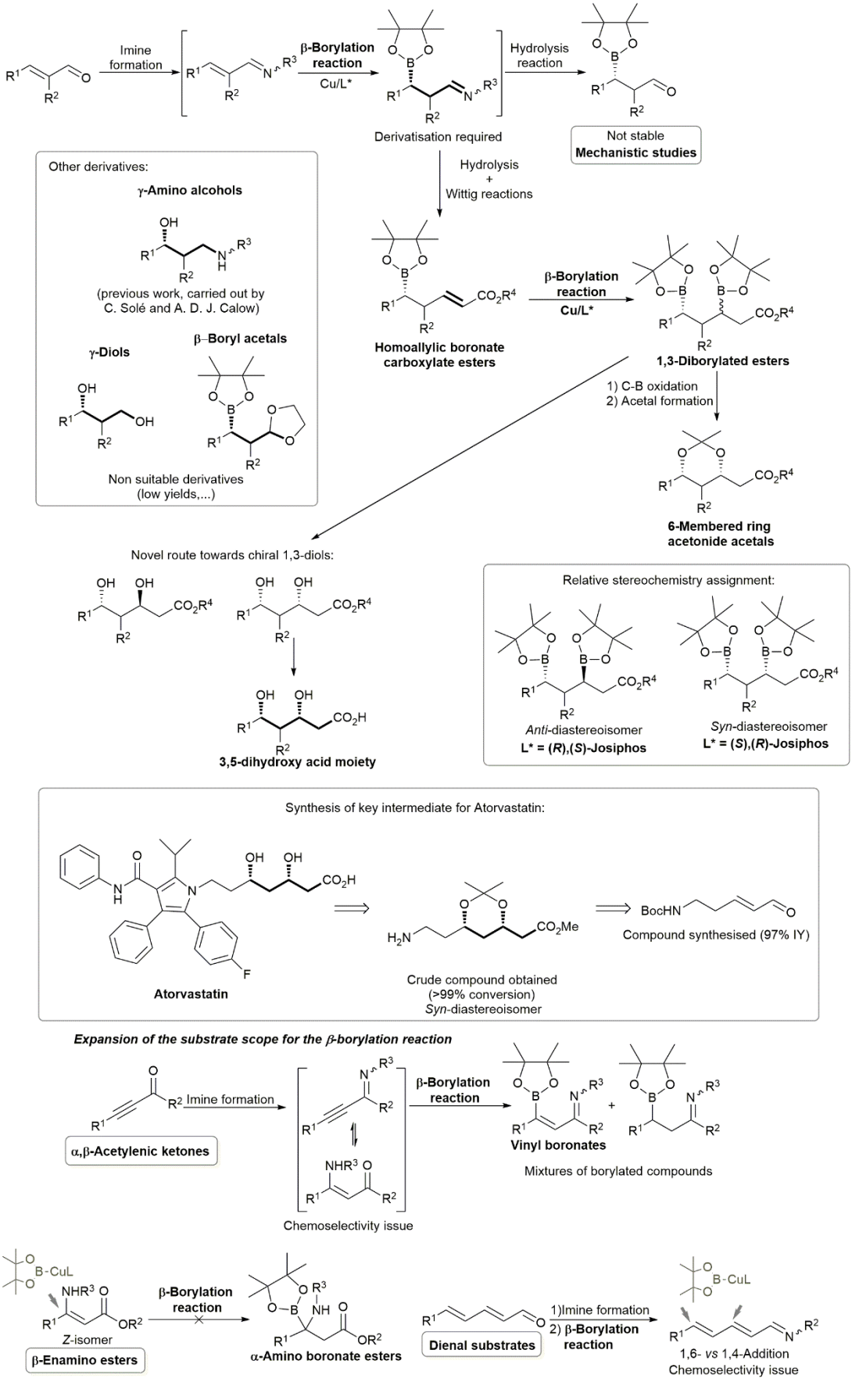
Further exploitation of homoallylic boronate carboxylate esters as substrates for a second borylation reaction, led to obtaining versatile 1,3-diborylated esters. A novel methodology was developed which allowed the control of the asymmetry induced in the new stereogenic centre created for a range of substrates, due to the presence of the two boryl units which could subsequently be transformed into other functionalities leading to building blocks for the synthesis of multi-functional, chiral compounds. Therefore, the two boryl units were then examined for transformation into functionalities which would allow unambiguous

stereochemical assignment of the two borylation reactions. Specifically, an oxidation/acetal formation sequence was examined showing that 6-membered ring acetonide acetals were ideal compounds for this purpose. Beside aiding the stereochemical analysis, it was confirmed that this dual asymmetric borylation methodology was useful for the synthesis of 3,5-dihydroxy acids (or esters analogous) side-chain present in many natural products or drugs, such as statin-type drugs.

Complementarily, and with the aim of expanding the type of substrates for the β-borylation reaction, structurally varied compounds were examined. Firstly, substrates presenting an additional unsaturation were evaluated under the imine formation/β-borylation reaction sequence conditions paying special attention to the 1,4- *vs* 1,6-addition selectivity, were examined as a possible alternative for the synthesis of diborylated compounds in a direct manner. This was followed by the study of different unsaturation, and in particular, an alkyne instead of an alkene, *i.e.* α,β-acetylenic carbonyl compounds, which were envisioned as ideal platforms for the synthesis of vinyl boronates. As well as a brief study on the β-borylation reaction on β-enamino ester substrates which could *a priori* give rise to valuable α-amino boronate compounds, is reported.

The following graphical abstract summarises the different projects contained in this thesis.

β-Borylation reaction on α,β-unsaturated aldehydes via aldimine intermediates



Expansion of the substrate scope for the β-borylation reaction

Contents

Publication list

Peer-reviewed publications produced from this thesis:

- ***'One-pot catalytic asymmetric borylation of unsaturated aldehyde-imines; functionalization to homoallylic boronate carboxylate ester derivatives'*** A. Pujol, A. D. J. Calow, A. S. Batsanov and A. Whiting, *Org. Biomol. Chem.*, 2015, **13**, 5122-5130

- ***'A double diastereoeselective approach to chiral syn- and anti-1,3-diol analogues through a double catalytic asymmetric borylation approach'*** A.Pujol and A. Whiting, *manuscript accepted in J. Org. Chem.*

- ***'Development and application of dual asymmetric borylation strategies: total synthesis of Atorvastatin'*** A. Pujol and A. Whiting, *manuscript in preparation*.

Acknowledgements

No és facil resumir en unes linies l'agraïment que sento envers les persones que han estat sempre al meu costat tant en l'aspecte personal com en el professional i que de una manera o altra formen part d'aquesta tesis.

In first place, I would like to thank to my supervisor Prof. Andy Whiting for giving me the great opportunity of carrying out my doctoral studies on this project, but specially thank him for having always time for a good advice when things had not worked out as planned. I also would like to have a special mention for Prof. M. Elena Fernández for introducing me into the fascinating world of the boron chemistry as well as for her confidence on me and constant help and support; gràcies Elena, sense tu aquesta tesis no hauria estat possible.

I would like to express my gratitude to the different services within the department for making our life easier with their support. Especially the staff in the NMR service for being always willing to help. I would also like to thank Dr. Aileen Congreve for her indefatigable help with the preparative HPLC experiments and Dr. Andrei S. Batsanov for all his work on the crystal structures. Many thanks to Ramón Guerrero for all his help in the NMR service back in Tarragona. Thank you to Durham University and Universitat Rovira i Virgili for letting me use their facilities during my PhD.

During these three years I had the chance to work with many people both in Durham and Tarragona, sharing many experiences not just in the lab, I will try to don't miss anyone. To my "mates" in England, first thank you to Dr. Adam D. J. Calow not only for offering me his inestimable help through my first months in the lab and making easier my move to UK, but also for always being a good friend. To the other members of the AW group that I had the pleasure to work with; Dr. Garr-Layy Zhou, Dr. Farhana Ferdousi, Dr. Hesham Raffat Shawky Haffez, Dr. Ludovic Eberlin, Kate Madden, David Chisholm, Sergey Arkhipenko, Dr. Alexander Gehre, Dr. Mona Al Batal, Dr. Wade Leu, Yihao Du (Eric). Without forgetting the

numerous students that had worked with us during their master's degree or other shorts stages, especially Tom Barber.

Als companys de Tarragona; en especial a la Dr. Cristina Solé gràcies per la seva ajuda al inici d'aquest projecte, i també a la Dr. Jessica Cid per ensenyar-me a treballar en un laboratori de recerca (en especial per la seva infinita paciencia) durant la meva primera estada al lab. Als altres membres del grup del bor: Dr. Gerard Palau, Dr. Xavier Sanz, Dr. Enrico La Cascia, Dr. Ana Belen Cuenca, Marc Garcia and Nuria Miralles, gràcies a tots!

No puc acabar aquests agraïments sense esmentar a la meva familia, en especial als meus pares i germana Imma, que sense ells al meu costat no hauria arrivat fins a aquí. Gràcies per haver-me recolçat al llarg dels meus estudis, us estimo. Al Sergi, que també formes part de la familia, sobretot gràcies per la teva paciencia amb els meus problemes amb la informàtica.

And finally I would like to thank Jonathan Purdie for being beside me during the last years, sharing with me good and not so good moments, it wouldn't had been the same without you.

Abbreviations

General

Å	Angström (s)
Ac	Acetyl
acac	Acetylacetonate
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	Tert-butyloxycarbonyl group
bpy	2,2'-Bipyridyl
^{t}Bu	Tert-butyl
^{o}C	Degrees Celsius
ca	Aproximately
$CHCl_3$	Chloroform
Cod	*Cis,cis*-1,5-cyclooctadiene
COSY	Correlation spectroscopy
Cy	Cyclopentyl
δ	Chemical shift (NMR)
d	Doublet
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	Dichloromethane
d.e.	Diastereomeric excess
DFT	Density Functional Theory
DIBAL-H	Diisobutylaluminium hydride
d.r.	Diastereomeric ratio
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
E	Enantiomer
e.e.	Enantiomeric excess
e.g.	*Exempli gratia* (for example)
Eqn	Equation
equiv.	Equivalents
e.r.	Enantiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl

et al.	*et altri*
EWG	Electron withdrawing group
FT-IR	Fourier transform infrared spectroscopy
g	Gram (s)
h	Hour (s)
HMQC	Heteronuclear multiple quantum correlation
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single quantum correlation
HRMS	High resolution mass spectroscopy
Hz	Hertz
i.e.	Id est (in other words)
IR	Infra-red spectroscopy
IY	Isolated Yield
J	Coupling constant (NMR spectroscopy)
K	Kelvin (s) (absolute temperature)
LRMS	Low ressonance mass spectra
LTQ-FT	Linear triple quadrupol fourier transform
m	Multiplet (NMR); milli; medium (IR)
m	Meta-position (in a phenyl ring)
M+	Molecular ion peak (Mass spectroscopy)
MCPBA	Meta-chloroperbenzoic acid
Me	Methyl
min.	Minute (s)
Mol	Mole (s)
MS	Molecular Sieves; Mass spectroscopy
M_T	Transition metal
m/z	mass to charge ratio (Mass spectroscopy)
NHC	N-heterocyclic carbene
NMR	Nuclear Magnetic Ressonance
NOESY	Nuclear Overhauser Effect Spectroscopy (NMR)
Nu	Nucleophile
o	Ortho-position (in a phenyl ring)
p	Para-position (in a phenyl ring)
Ph	Phenyl
ppm	Part (s) per million
PPTS	Pyridinium p-toluenesulfonate

^{i}Pr	Isopropyl
q	Quartet
®	Copyright registered
ReactIR	*in situ* IR spectroscopy
R_f	Retention factor (TLC)
RT	Room temperature
s	Singlet; small (IR)
sat.	Saturated
t	Triplet
TBME	Tertiarybutylmethyl ether
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TM	Trade mark
TMS	Trimethylsylil
TMSCl	Chlorotrimethylsilane
TQD	Triple Quadrupol Detector
t_R	Retention time (HPLC)
UV	Ultra violet
vis	Visible
v/v	Volume to volume ratio

Diborane reagents

B_2pin_2	Bis(pinacolato)diboron
B_2cat_2	Bis(catecholato)diboron
BpinBdan	2-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-naphtho[1,8]-de [1,3,2] diazaborinine
B_2neop_2	Bis(neopentylglycol)diboron
PDIPA	Pinacolato diisopropanolaminato diboron

Phosphine ligands

Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
PBu_3	Tributylphosphine
PCy_3	Tricyclohexylphosphine
Ph_3P	Triphenylphosphine
Ph_3PO (TPPO)	Triphenylphosphine oxide
(*R*),(*S*)-Josiphos	*(R)*-1-[(S_P)-2- (Diphenylphosphino) [Ferrocenyl]ethyldicyclohexyl phosphine
(*R*),(*S*)-Mandyphos	(S_P,S'_P)-1,1′-Bis(dicyclohexylphosphino)-2,2′-bis[(*R*)-α-(dimethylamino)benzyl]ferrocene
(*R*)-DTBM-Segphos	(*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
(*R*)-(+)-MeO-Biphep	(*R*)-(-)-2,2'-Bis[di(3,5-di-t-butyl-4-methoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl
(*R*),(*S*)-ppfa	(*R*)-(-)-N,N-dimethyl-1-(2-diphenylphosphino)ferrocenylethylamine
(*R*),(*S*)-Taniaphos	*(R)-(S)*-1-[(*S*)-α-(Dimethylamino)-2-(diphenylphosphino) benzyl]- 2-diphenylphosphinoferrocene
(*R*),(*R*)-Walphos	(*R*)-(*S*)-1-{(R_P)-2-[2-(Diphenylphosphino) phenyl] ferrocenyl}-ethyldiphenylphosphine
(*R*)-Binap	(*R*)-2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
(*R*)-Tol-Binap	(*R*)-(+)-2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
(*R*)-DM-Binap	(*R*)-1,1′-Binaphthalene-2,2′-diyl)bis[bis(3,5-dimethylphenyl)phosphine]
(*R*)-DM-Segphos	(*R*)-(+)-5,5′−Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole
(*R*)-^{i}Pr-DuPhos	(+)-1,2-Bis[(2R,5R)-2,5-diisopropylphospholano]benzene
(*S*)-DM-Binap	(*S*)-1,1′-Binaphthalene-2,2′-diyl)bis[bis(3,5-dimethylphenyl)phosphine]
(*S*),(*R*)-Josiphos	(*S*)-1-[(R_P)-2- (Diphenylphosphino) [Ferrocenyl]ethyldicyclohexyl phosphine
(*S*),(*R*)-Mandyphos	(R_P,R'_P)-1,1′-Bis(dicyclohexylphosphino)-2,2′-bis[(S)-α-(dimethylamino)benzyl]ferrocene
(*R*,*R*)-Me-DuPhos	(2*R*,2’*R*,5*R*,5′*R*)-2,2′,5,5′-Tetramethyl-1,1′-(o-phenylene)diphospholane
(*S*,*S*)-Me-DuPhos	(2*S*,2’*S*,5*S*,5′*S*)-2,2′,5,5′-Tetramethyl-1,1′-(o-phenylene)diphospholane

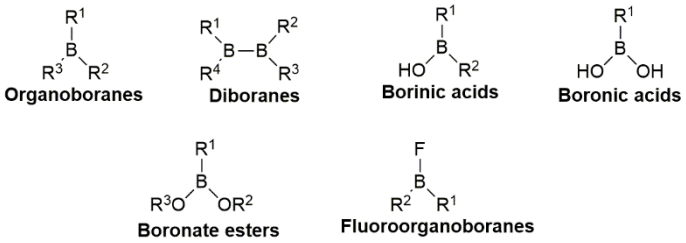
(*S*,*S*)-Dipamp	(1*S*,2*S*)-(+)-Bis[(2-methoxyphenyl)phenylphosphino]ethane
(*R*,*R*)-Dipamp	(1*R*,2*R*)-(+)-Bis[(2-methoxyphenyl)phenylphosphino]ethane
(*R*,*R*)-Quinox P	(*R*,*R*)-2,3-Bis(*tert*-butylmethylphosphino)quinoxaline

Als meus pares i germana

Literature review

1.1. Organoboron compounds: an introduction to boron chemistry

The term organoboron compound is used to define those compounds that contain at least one C-B bond, these are classified according to the number of boron atoms present per molecule, the nature of the bonding and the nature and number of bonds formed by boron with other atoms that are not carbon, *e.g.* organoboranes, diboranes, borinic and boronic acids, boronate esters or fluoroorganoboranes, amongst others.[1]

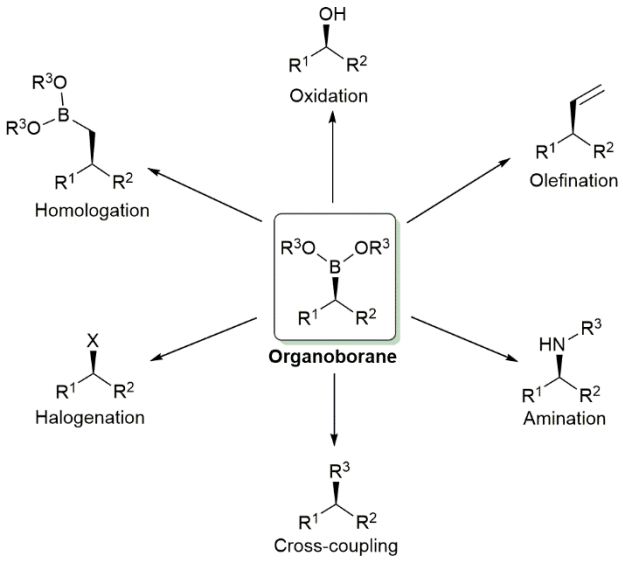


The existence of these compounds had been known for over a century, but it was not until the discovery of the hydroboration reaction by H. C. Brown[2] in 1956 that organoboranes began to be considered as an interesting group of compounds. As a result there was a considerable and rapid expansion of the range of reactions leading to organoboron compounds since they possess extraordinary electronic and physicochemical properties, as well as structural features. Hence, this discovery can be considered a breakthrough in boron chemistry and for that, Brown was awarded the Nobel Prize in 1979 jointly with Georg Wittig for their "*development of the use of boron- and phosphorus-containing compounds, respectively, into important reagents in organic synthesis*".[3]

The chemistry involving these types of compounds has been studied and developed comprehensively during the last decades, achieving several innovative improvements and becoming a very important field in contemporary chemistry in which many research lines are focused. In order to understand the interest that this area has aroused and, consequently, the growth that it has experienced, it is necessary to have a look at what makes these compounds exceptional, *i.e.* the boron atom. This element occupies a strategic position in the periodic table; allocated in the 13th group between metals and non-metals and it is classified as a

metalloid or semimetal and, therefore depending on the reaction conditions, it can behave as a metal or a non-metal. In addition, it is found in the same period as carbon, which means that it has a similar electronic configuration and, consequently, shares some structural and bonding features which explains the relevance of organoboron compounds in organic and medicinal chemistry.[4]

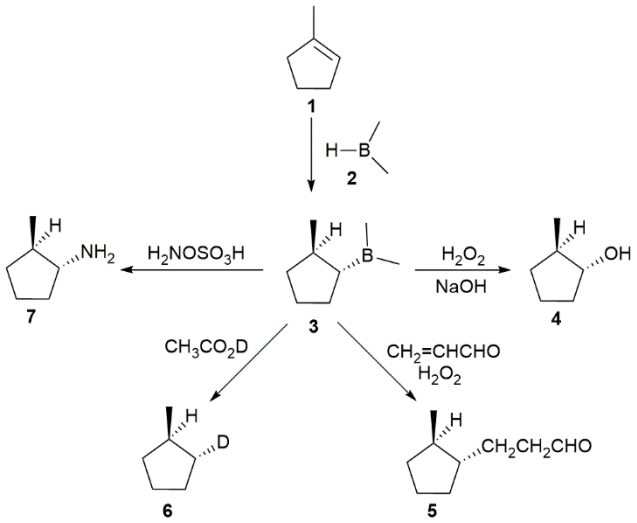
It is due to this set of exceptional features that makes organoboranes suitable for applications in several areas of chemistry and, indeed, their role as intermediates in organic synthesis has been extensively documented.[5-7] Compounds with a C-B bond are highly versatile since this bond allows the facile introduction of other functional groups in the molecule, *i.e.* it is relatively easy to exchange the boron atom for many other functional groups leading into the formation of new C-C[8,9] or C-heteroatom bonds,[10-12] as summarised in Scheme 1.



Scheme 1 General overview of the functional groups that can be introduced in a structure from organoboron compounds.[13]

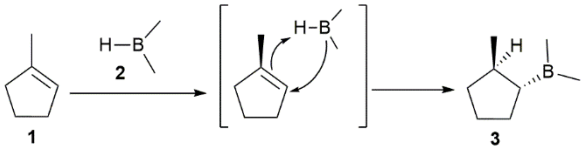
However, it is remarkable that the most widely used type of intermediates in synthesis are the boronate esters which in addition to this versatility, are easily accessible, and stable to air and water,[14] and hence, the range of reactions in which they can be used is considerably

wider in comparison with other organometallic reagents, *e.g.* Grignard reagents.[13] They also have low toxicity. It is for all these reasons that these compounds have such relevance in organic chemistry, especially in the synthesis of chiral molecules.[15,16] Their application in enantioselective synthesis has grown in recent times since the work carried out by Brown and co-workers[17-19] during the 1970s-1990s when their exceptional control of the induction of asymmetry in different functionalisations of the organoboranes, *e.g. via* hydroboration was highlighted, as displayed in Scheme 2.



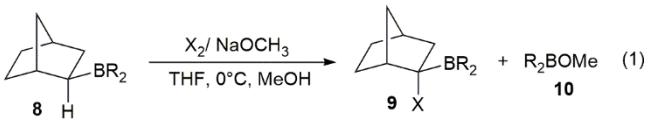
Scheme 2 Functionalisation of the organoborane that proceed with retention of configuration.

The most relevant conclusion that emerged from these studies was that complete retention of configuration occurred for the majority of transformations performed, *i.e.* the new functionality replacing the boryl moiety occupied exactly the same place on carbon. Especially for those cases where the new functionality included an oxygen, hydrogen or nitrogen atom, as well as a carbon atom. The selectivity observed in such reactions was determined by the first step; *i.e.* the hydroboration reaction. As shown in Scheme 3, the addition of dimethyl borane **2** to the double bond occured in a *syn*-manner and with an *anti*-Markovnikov orientation; the stereochemistry observed was hence determined mainly by the steric requirements of the substituents present on the double bond.[20]



Scheme 3 Reaction mechanism corresponding to the hydroboration reaction of an alkene.

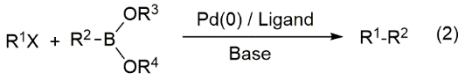
Although the retention of configuration is the predominant trend, there are also a few examples in which an inversion of configuration had been observed,[21,22] *e.g.* the case of the halogenation of tri-*exo*-norbornylborane **8** in the presence of methalonic sodium methoxide [Eqn. (1)].



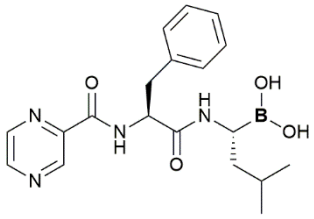
In this case, the stereochemistry observed in the final product was controlled by the reagent used in the electrophilic substitution of the boryl moiety.

The discovery of the contribution of organoboranes in the synthesis of chiral molecules gave rise to a new array of reactions that are very relevant today, especially for the synthesis of alcohols or amines.[23,24]

In addition to their role as reaction intermediates, the participation of organoboranes in metal-catalysed processes is notable and it has been exhaustively developed in recent times. This chemistry is based in cross-coupling reactions that are mediated by transition metals, and in which C-C, C-O or C-N bonds are formed.[25] Nowadays, the range of transition metals used in these type of processes is considerably wide, including the Suzuki-Miyaura cross-coupling [Eqn. (2)][26] (the first reaction studied), as well as other transition metal catalysts in different transformations, including Rh and Ni.[27,28]

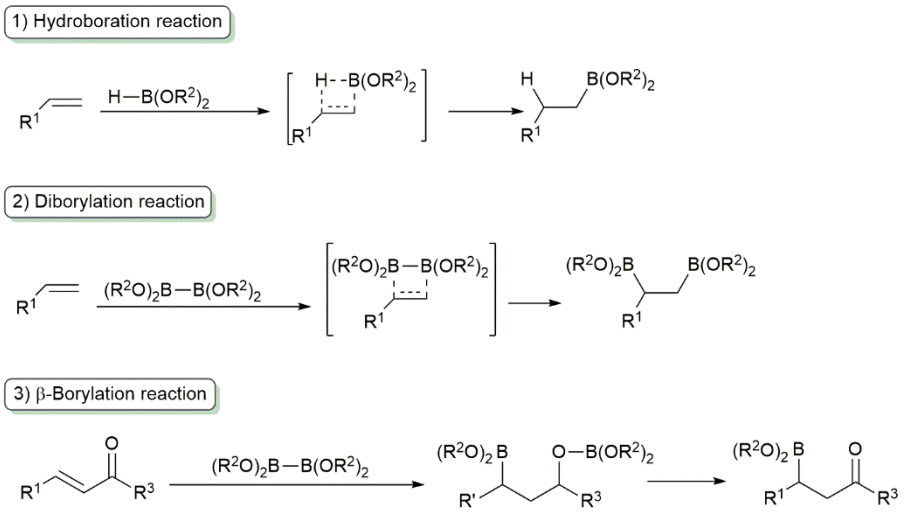


The progress made in these areas has had many impacts in other areas, such as medicinal chemistry, where organoboron compounds have become key compounds in synthetic routes for obtaining many medicines.[29] Although initially considered merely as intermediates or simple bearers of boron, it was also found that many boranes possess biological activity and have subsequently found use as drugs in certain therapeutic areas. The role played by these compounds in clinical applications is mainly as agents for boron neutron capture which is used in the treatment of cancer, *e.g.* bortezomib, the first clinically tested and commercially approved boron-containing drug.[30] Boron containing compounds have also found use as enzyme inhibitors.[31]



Bortezomib

Despite the interest aroused by these compounds in medicine their appearance in natural products is infrequent,[32] though research has focused on routes that provide these types of compounds. The introduction of boron into bioactive compounds has been based mainly on the innovation and improvement of the traditional methodologies, including transmetallation reactions of trialkylborates or haloboranes using Grignard or lithium reagents, as well as the addition of boron reagents to C=C bonds.[33,34] The main innovations in these strategies consists of the improvement of the chemo-, regio- and stereo-selectivity obtained through the development of applicable catalytic systems.[35] Additionally, due to some limitations presented by transmetallation reactions (mainly in terms of functional group tolerance)[36] the addition of boron reagents has become much used and developed. These methods can be divided in three main groups: 1) hydroboration;[37] 2) diborylation;[38] and 3) β-borylation,[39] depending on the nature of the substrate as well as the borating agent employed, as displayed in Scheme 4.

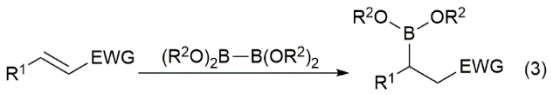


Scheme 4 General overview of the boron addition strategies for the synthesis of organoboranes.

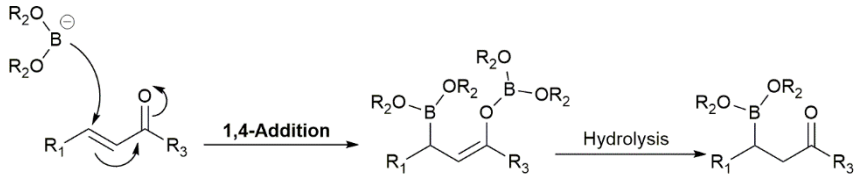
1.2. Boron conjugated addition or β-borylation reaction

1.2.1. General overview

Within the different boron additions to C-C multiple bond for the synthesis of organoboranes, the β-borylation reaction stands out and is one of the most useful and recently developed methods. It involves the conjugate addition of a boryl unit from a diborane reagent to an electron deficient substrate, *e.g.* an α,β-unsaturated carbonyl compound [Eqn. (3)].[40]

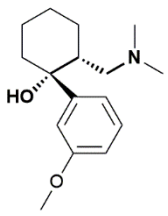


It is thought that the mechanism through which this transformation occurs consists of a 1,4-addition (Michael-type) of a boryl moiety to the C=C bond of the electron deficient substrate, followed by an α-protonation step and leading to the β-boryl compound,[39] as outlined in Scheme 5.



Scheme 5 General overview of the mechanism corresponding to the β-borylation reaction on an α, β-unsaturated carbonyl compound.

Although the resulting product of the reaction is a β-boryl compound, this transformation proceeds *via* a diborylation reaction, which means that it is not an effective process in terms of atom economy since just one of the boryl units is incorporated into the final product. However, it is one of the best ways to access β-boryl carbonyl compounds,[41] which after further derivatisation can lead to molecules with more than one functionality in the 1,3-positions respectively. 1,3-Difunctional compounds are of great utility as building blocks in the pharmaceutical industry, such as γ-amino alcohols[42] or β-amino acids,[43] *e.g.* Tramadol and Bestatin, respectively.

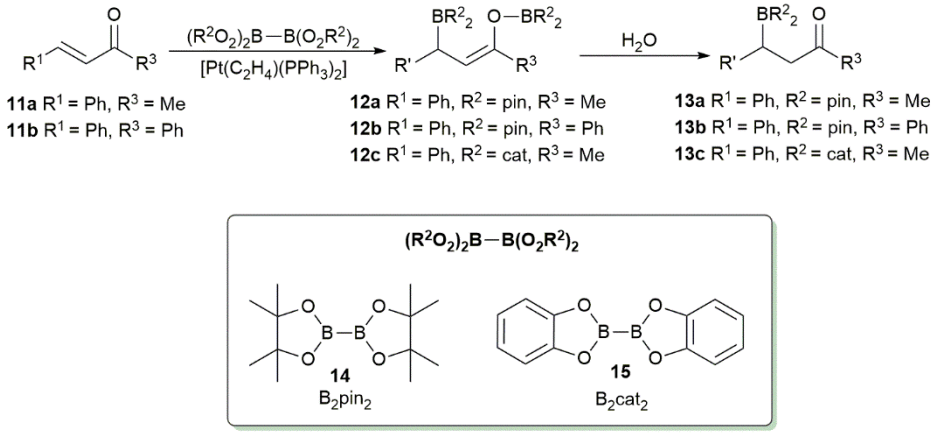

Tramadol


Bestatin

1.2.2. Origin and early examples

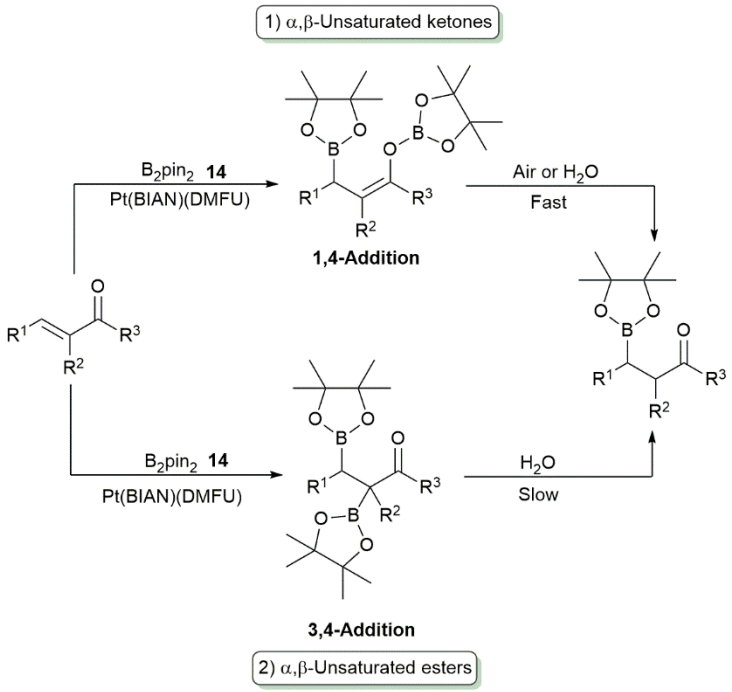
Although the hydroboration reaction was an important milestone in this field, it was observed that some types of substrates were not suitable for direct B-H addition reactions. Specifically, conjugated systems containing a carbonyl group were a particular challenge due to the hydroborating reagent reacting with the carbonyl group *via* reductive processes. In order to avoid this undesired side-process, and hence increase the array of organoboron compounds synthesised, alternative methodologies for boryl introduction

were required. The first example in which a diboron reagent was added to an electron deficient substrate was reported in 1997 by Marder *et al.*[44] and it consisted of a platinum-catalysed conjugate addition of boron to α,β-unsaturated ketones. Mechanistic details of this reaction were proposed involving the corresponding boron enolate after the 1,4-addition of the boryl unit, as outlined in Scheme 6.



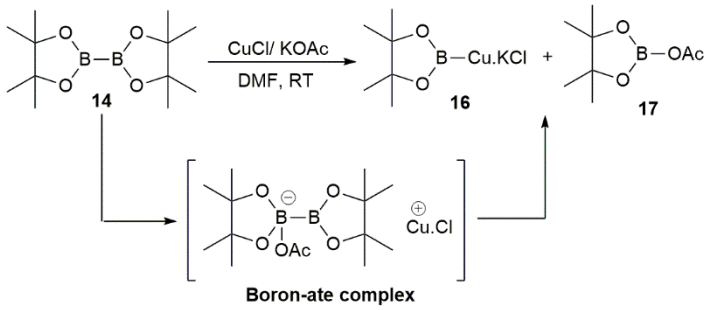
Scheme 6 β-Borylation reaction on α,β-unsaturated ketones catalysed by Pt(0).

Furthermore, Marder and co-workers also developed the addition of B_2pin_2 **14** to different types of α,β-unsaturated carbonyl compound, aided by platinum-based catalysts.[45] Interestingly, it was observed that the resulting β-borylated carbonyl compound was generated in two different ways depending on the nature of the R^3 group: 1) 1,4-addition for the case of ketones; and 2) 3,4-addition for the esters (see Scheme 7). In this case, the resulting β-borylated product was isolated and characterised; this being one of the only two examples in the literature.[44,45]



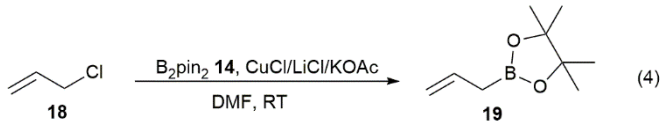
Scheme 7 β-Borylation reaction on α,β-unsaturated ketones and esters and hydrolysis of the primary diboration products.

Based on the conjugate addition of disilanes to activated olefins,[46] Hosomi *et al.* postulated an alternative catalytic system for the β-borylation reaction of α,β-unsaturated ketones composed of a copper(I) salt and phosphine ligands.[47] It was found that the phosphine ligands played a crucial role in the activation of the diborane, since in their absence no reaction took place and no consumption of the diborane reagent was detected. Hence, it was concluded that the generation of the nucleophilic boryl moiety did not take place *via* an oxidative addition, as established before in the case of Pt catalysis.[44] In the following years, copper catalysis achieved major relevance and some mechanistic details were postulated, especially concerning the generation of the active boryl moiety. It was in 2001 that Miyaura[48] demonstrated that boryl-copper species such **16** were generated *in situ* in the presence of a base, providing the nucleophilic source of boron through the equilibrium dissociation of a boron ate-complex, as outlined in Scheme 8.



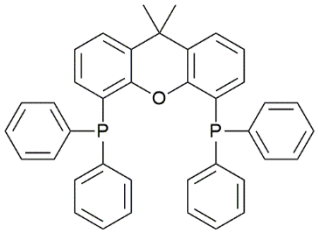
Scheme 8 Reaction of the formation of the nucleophilic boryl-copper moiety **16** from B_2pin_2 **14** in the presence of CuCl and KOAc.

The formation of the copper-boryl species was confirmed by the reaction between allyl chloride **18** and B_2pin_2 **14** in the presence of CuCl, LiCl and KOAc, to give the resulting allyl boronate **19** [Eqn. (4)].

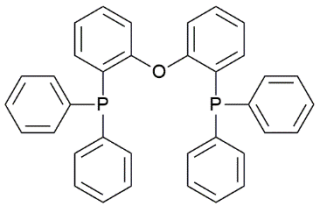


(4)

Although these pioneering examples were influential in this area, the protocols described herein highlight some disadvantages, mainly in terms of catalyst loadings (10-110 mol%). For example, in the methodology reported by Miyaura,[48] the amount of Cu(I) source was equimolar with respect to the amount of B_2pin_2, **14** which severely limited its applicability. However, copper catalysis was envisioned as a more viable option in comparison with other more expensive metals, *e.g.* Pt or Rh, hence, much interest has been generated in this area in the last few years and many innovative improvements had been achieved. The work of Yun *et al.* in 2006 postulated an efficient copper-diphosphine mediated β-borylation methodology for α,β-unsaturated carbonyl compounds in the presence of alcohols.[49] It is based on work previously published by that group in which catalytic copper(I) complexes with xanthene-phosphorus-based ligands were reported. Both Xantphos **P1** and DPEphos **P2** provided good conversions in the conjugate reduction of α,β-unsaturated nitriles.[50]



P1
Xantphos



P2
DPEphos

It was observed that the use of this type of bidentate ligand improved the nucleophilicity of the active copper-boryl species, increasing their catalytic activity so that the catalyst amount required could be considerably reduced. Additionally, it was confirmed that the addition of an alcohol could improve the reaction yield and at the same time accelerate the rate of the reaction, as reported by Buchwald in 2003.[51] This was applied to the copper mediated conjugated reduction of α,β-unsaturated lactones, lactams and esters, since the cuprate intermediate is protonated in the presence of a small molecule of alcohol. Based on this, optimal conditions for this transformation were established using (*E*)-ethyl crotonate **20a** [Eqn. (5)] as model substrate, as summarised in Table 1.[49]

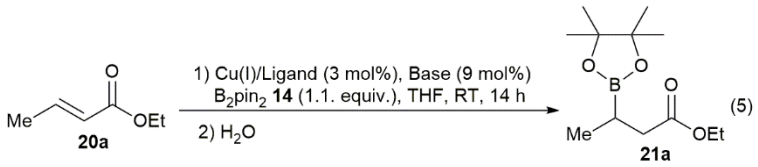


Table 1 Optimisation of the reaction conditions for the catalytic addition of B_2pin_2 **14** to (*E*)-ethyl crotonate **20a**.

Entry	$Cu^{(I)}$ source	Ligand	Base	Additive (equiv.)	Conv. [a]- **21a** (%)
1	Cu(OAc)	**P2**	-	-	26
2	CuCl	**P1**	NaO^{t}Bu	-	30
3	CuCl	**P2**	NaO^{t}Bu	-	48
4	CuCl	**P2**	NaO^{t}Bu	^{t}BuOH (2)	82
5	CuCl	**P2**	NaO^{t}Bu	MeOH (2)	>98
6	CuCl	PBu_3 **P3**	NaO^{t}Bu	MeOH (2)	85
7	CuCl	PCy_3 **P4**	NaO^{t}Bu	MeOH (2)	82
8	CuCl	-	NaO^{t}Bu	MeOH (2)	84

[a]Determined by GC analysis.

It was confirmed that the use of the catalytic system composed by CuCl and **P2** in the presence of a strong base (NaO^{t}Bu) and the addition of a sterically non-hindered alcohol additive (MeOH) enhanced the borylation reaction, leading to higher conversions (entry 5, Table 1). The optimal conditions were applied to a range of different α,β-unsaturated carbonyl compounds as displayed in Figure 1.

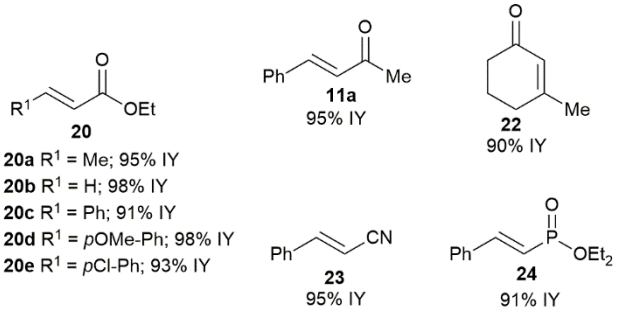
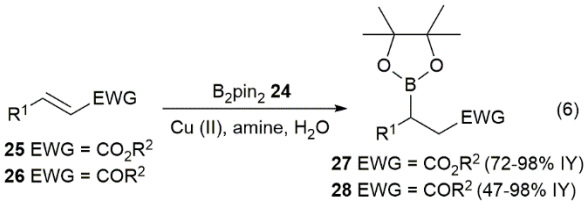
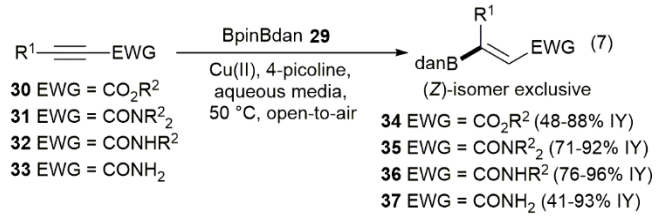


Figure 1 Substate scope evaluated under the optimised conditions.

For all the cases studied, the β-boryl ester was obtained in isolated yields over 90%, which was not significantly affected by the substituent on C_β. Moreover, it was demonstrated that this methodology was more efficient than the one reported previously by Hosomi[47] for α,β-unsaturated ketones and it was observed that this methodology could be also applied to other types of substrate, such as nitriles and phosphoranes.[49] In summary, this protocol represented progress in the area of copper-catalysed conjugated addition of diborane, resulting in higher yields with a lower catalyst loading in comparison with the systems employed until that date.[47,48] However, copper catalysis was not limited to only Cu(I) and a few years later Santos and coworkers[52] reported a very innovative methodology based on Cu(II). A surprising aspect of the protocol relied on water being used as the solvent for these reactions. In this study, the β-borylation of α,β-unsaturated esters and ketones was examined assisted by Cu(II)-amine complexes [Eqn. (6)]. It was demonstrated that Cu(II) shows good catalytic activity for this transformation, *i.e.* excellent yields of the resulting organoboranes were reported (up to 98%).

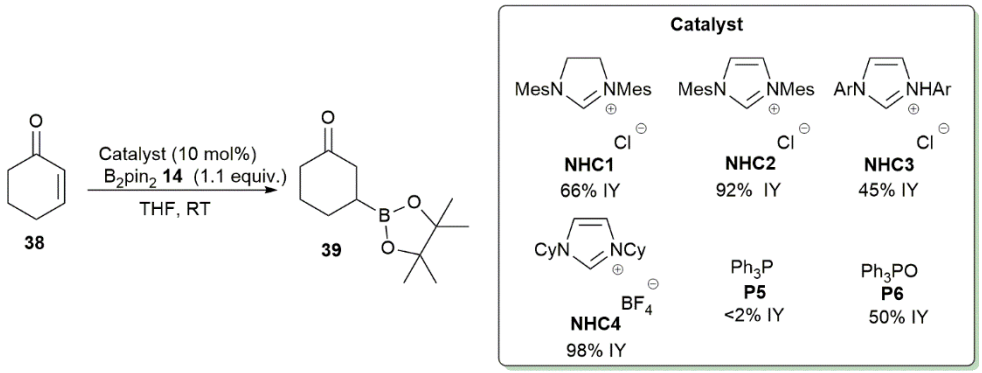


The main advantage presented by this methodology when reported was that it was possible to carry out these reactions in air. In 2016, this methodology was further expanded to the conjugated addition of BpinBdan **29** to α,β-acetylenic esters and amides [Eqn. (7)].[53]



With these examples, the β-borylation reaction was clarified from a catalytic point of view and a wide array of synthetic possibilities were opened up, with control of chemo- and regio- selectivity involving Pt,[44,45] Pd[54] and Cu[49] catalysis. As a consequence the scope of transition metals applicable to the catalytic system was expanded, including systems based on Rh[55] or Ni.[56]

In the following years, and based on the initial observations of organometallic catalytic processes, a new catalytic trend appeared involving organocatalysis. This novel trend consisted of dispensing with the metal and instead the catalysis was carried out by organic molecules of low molecular weight, *i.e.* metal-free catalytic systems. In 2009, Hoveyda *et al.* reported a novel organocatalytic system based on NHCs. In this case, a Lewis acid-Lewis base interaction took place between the diborane reagent and the NHC, generating the nucleophilic boryl unit. This innovative catalytic system was evaluated for the β-borylation reaction of α,β-unsaturated ketones.[57] Moreover, the role played by the phosphine ligands used in organometallic catalysis had aroused mechanistic doubts because these compounds were also catalytically active species even in the absence of the metal. Hence, in this study, as well as NHCs, some phosphines were also evaluated for their ability to catalyse additions of boron to cyclohexanone **38**, as displayed in Scheme 9.



Scheme 9 NHC and phosphine scope evaluated for the β-borylation reaction of cyclohexanone **38**.

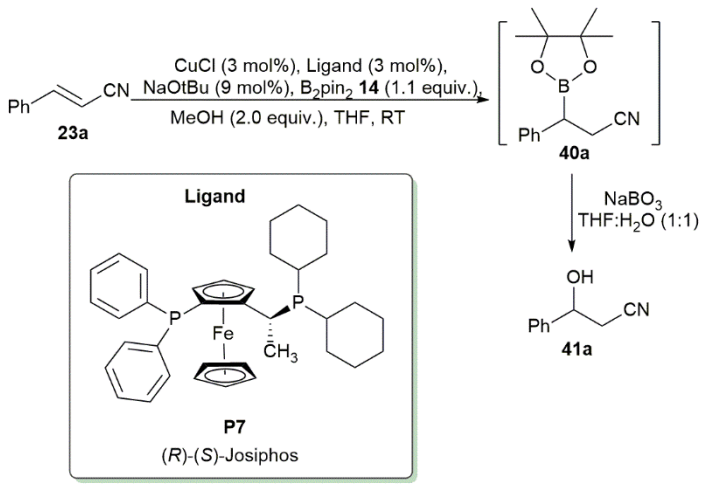
It was concluded that NHCs are suitable species for catalysing this transformation, leading to borylated compounds in yields comparable to those obtained using metallic catalytic complexes. Due to the promising results obtained, this methodology was tested on different types of substrates such as α,β-unsaturated esters giving excellent yields. With respect to the role played by the phosphine, it is remarkable that the phosphine oxide **P6** also provided a moderate yield of borylated product; a fact that coincides with previous observations by Hosomi.[47] With these results in hand, the possibility of the development of a phosphine assisted metal-free β-boration reaction was investigated by Fernández *et al.*[58] who developed a methodology using MeOH as protonating agent and a base that facilitates the heterolytic cleavage of the diborane reagent. For phosphorus compounds, it was found that a tertiary phosphine, preferably **P5** was required and the possibility of performing an enantioselective version of the transformation under organocatalytic conditions was also reported.

1.2.3. Synthesis of chiral organoboranes: an enantioselective approach

Today, enantiomerically pure molecules are widely employed in organic synthesis for application in medicines. The desired effect of such compounds is often provided by one of the stereoisomers rather than both, and indeed, some stereoisomers can even be harmful. So research for effective methodologies to synthesise enantiopure

molecules has achieved increasing interest.[59] In the majority of cases, these methods have limitations regarding the structural types that can be used. For this reason, boron-mediated pathways offer an attractive alternative.[60] During the last few years many research groups have focused their efforts on the development of an asymmetric version of the boryl addition strategy.

It was relatively recently that the stereoselective options provided by the use of stereogenic C-B bond resulting from a conjugated addition started to be explored, although since the first examples, the potential of this transformation for enantioselective applications is becoming clearer. Initially, it was thought that the diborane reagent was key for asymmetric induction.[44,61] Yun and co-workers initiated a detailed study of the β-borylation reaction from an enantioselective perspective by asymmetric induction *via* the catalytic system.[49] Specifically, it was suggested that the modification of the metallic catalyst centre with chiral ligands could induce asymmetry in the borylation, as previously observed for the hydroboration of prochiral alkenes giving e.e.s over 95%.[62,63] Based on this, the conjugate addition of the boryl moiety to cinnamonitrile **23a** was carried out using a system composed of a Cu(I) catalyst and disphosphine ligand, *e.g. (R),(S)*-Josiphos **P7**. The induction of asymmetry was evaluated after the oxidation of the resulting β-boryl nitrile **40a**, as outlined in Scheme 10. The corresponding β-hydroxy nitrile **41a** was obtained with the expected retention of configuration in over 80% e.e.[49] This result confirmed that Josiphos-type ligands are ideal for related asymmetric processes, as observed previously for the asymmetric reduction of acrylonitriles.[50]



Scheme 10 β-Borylation and subsequent oxidation of cinnamonitrile **23a** using **P7** as chiral ligand.

This example confirmed the potential of this reaction for enantioselective applications, as well as the phosphine ligand having a key role for the induction of asymmetry. The next step consisted of improving the e.e. by finding the most suitable chiral ligand.[64] With that objective, a series of bidentate phosphine ligands and P,N-ligands were tested for the reaction displayed in Scheme 10. Figure 2 summarises the ligands tested, along with the e.e.s observed for the β-hydroxy nitrile **41a**.

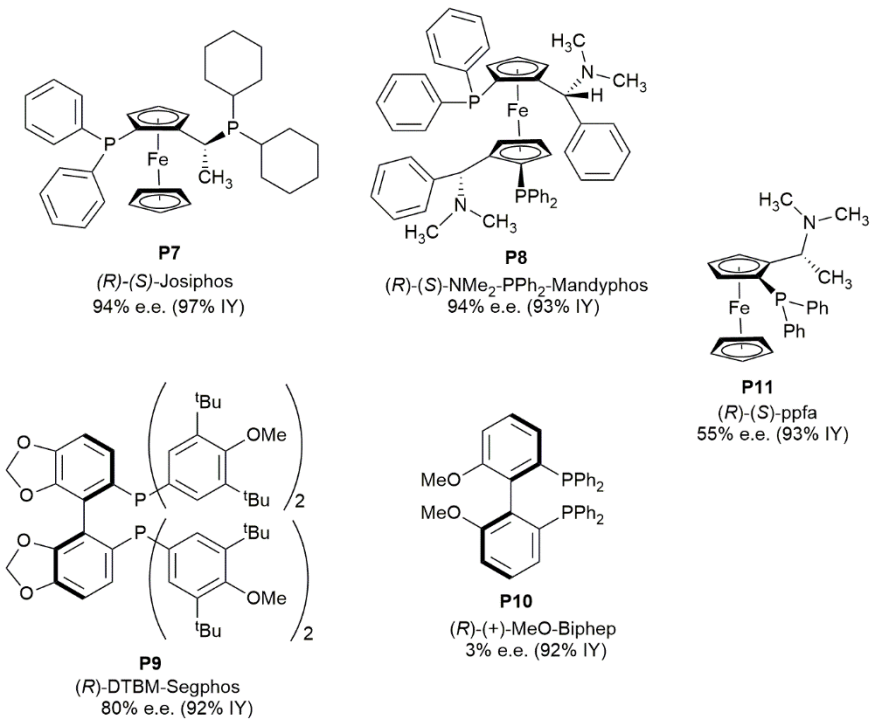
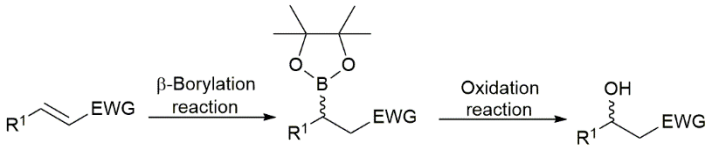


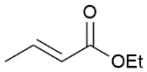
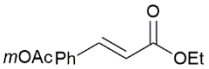
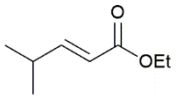
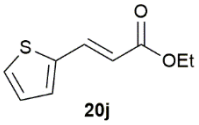
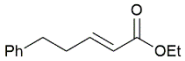
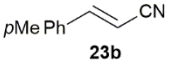
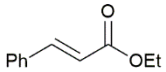
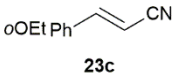
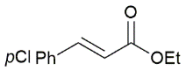
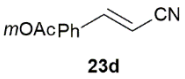
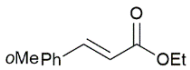
Figure 2 Scope of ligands tested for the β-borylation reaction of cinnamonitrile **23a**.

This study concluded that the ligands which provide the most promising enantioselectivity were **P7** and **P8**. Based on these results, the sequence of β-borylation/oxidation was performed under different sets of conditions on a series of α,β-unsaturated esters and nitriles. In general, in all the cases studied, the borylated product was obtained in good yield, as well as high levels of enantioselectivity for the corresponding β-hydroxy compounds (Scheme 11). Table 2 reports the results obtained.



Scheme 11 β-Borylation/oxidation reactions on α,β-unsaturated esters and nitriles.

Table 2 Asymmetric β-borylation/oxidation of α,β-unsaturated esters and nitriles.

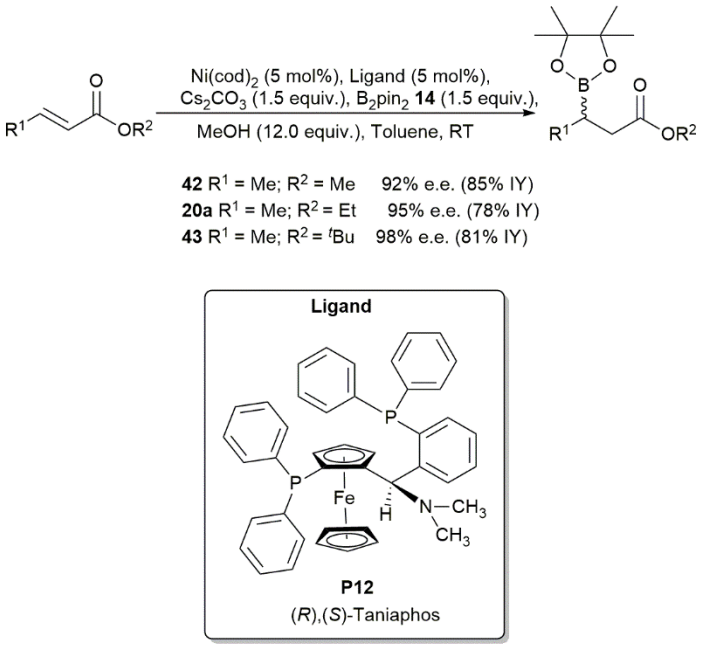
Entry	Substrate	Yield[a] (%)	e.e.[b] (%)	Entry	Substrate	Yield[a] (%)	e.e.[b] (%)
1	 **20a**	94[c]	90 *(R)*	8 9	 **20i**	95[c] 89[d]	87 84
2	 **20f**	92[c]	91 *(S)*	10	 **20j**	93[c]	82
3	 **20g**	97[c]	89	11	 **23b**	94[c]	90 *(S)*
4 5	 **20c**	93[c] 94[d]	90 *(S)* 87 *(S)*	12	 **23c**	90[c]	92
6	 **20e**	90[c]	91 *(S)*	13	 **23d**	94[d]	91
7	 **20h**	87[c]	88				

[a]Isolated yield of β-borylation product. [b]e.e. measured on the oxidation product. [c]CuCl (2 mol%), NaO^{t}Bu (3 mol%), **P7** (4 mol%), B_2pin_2 **14** (1.1 equiv.), MeOH (2 equiv.), THF, RT. [d]CuCl (3 mol%), NaO^{t}Bu (3 mol%), **P8** (3 mol%), B_2pin_2 **14** (1.1 equiv.), MeOH (2 equiv.), THF, RT.

The most relevant result to emerge from this study was the effect that the EWG had on the asymmetric induction, with higher e.e.s resulting in the case of nitriles, *e.g.* for cinnamonitrile **23a** and its ester analogue substrate **20c** (entry 5, Table 2), which afforded the corresponding β-hydroxyl compounds in 94% e.e. (Figure 2) and 87% e.e. (entry 5, Table 2), respectively. With respect to the possible influence of the substituent at C_β, there was no significant difference in the e.e.s. In conclusion, this approach represented the first effective asymmetric protocol to access functionalised chiral organoboron compounds under mild conditions. In the following years, the research developed by this group focused on expanding

the range of substrates that can be tolerated by this methodology, specifically looking at α,β-unsaturated ketones[65] and amides.[66] Interestingly, although the β-borylation of α,β-unsaturated amides had been reported previously[67] using a Ni(0) catalyst, it was found that in the case of the copper-mediated methodology this could not be effectively applied into this type of substrate, due to the fact that amides are poor Michael acceptors and hence providing conversions lower than 23%.[66]

With all these results in hand, it was suggested that the boryl moiety had no effect on the asymmetric induction in the β-borylation reaction. This aspect was later investigated by Fernández *et al.*, who explored the nickel-mediated boron conjugated addition of α,β-unsaturated esters.[68] It consisted of the application of a previously optimised set of reaction conditions for the B_2pin_2 addition in the presence of a Ni(0) complex modified with *(R),(S)*-Taniaphos ligand **P12** (see Scheme 12).



Scheme 12 Ni-catalysed β-borylation reaction of α,β-unsaturated esters.

It was observed that the ester moiety influenced the enantioselectivity of the process, with the bulkiest structure being the most efficient. Additionally, in the same paper was reported the first example of a palladium-mediated β-borylation of α,β-unsaturated carbonyl

esters which present analogous results to the Ni-catalysed methodology. Interestingly, in this case, it was also found that the ester moiety played an important role, following the same trend as described above. This aspect was also studied by Nishiyama,[69] although the trend observed in this case was the opposite of that reported by Fernández.[68] In this case, the asymmetry was proposed to be induced through a metallic complex formed by rhodium and a chiral bisoxazolinylphenyl ligand as shown in Figure 3.

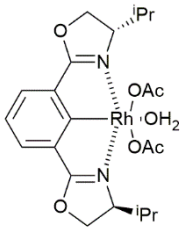
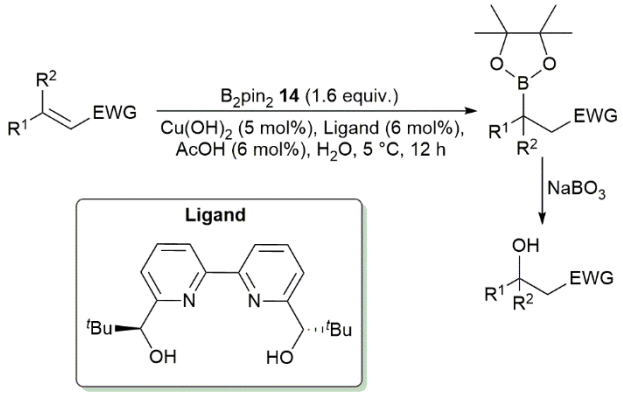


Figure 3 Structure corresponding to the rhodium catalytic complex developed by Nishiyama.[69]

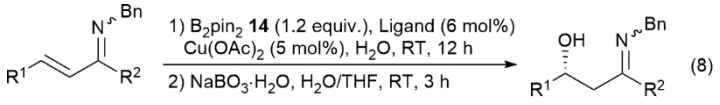
Another interesting aspect of this study was that with the use of this catalytic complex, the substrate scope could be expanded further, including even some α,β-unsaturated amides which were successfully β-borylated with excellent e.e.s, *i.e.* up to 97%, with good yields, unlike those reported by Yun.[66]

Later, in 2012 work based on Cu(II) catalysis in aqueous media was simultaneously reported by Santos *et al*.,[52] and an enantioselective version by Kobayashi and co-workers.[70] In this case, B_2pin_2 **14** was added into a wide range of α,β-unsaturated carbonyl compounds and nitriles in the presence of $Cu(OH)_2$ and chiral bipyridine ligands in water (Scheme 13). Once again, it was demonstrated that the reaction could be carried out effectively under non-anhydrous conditions (yields 73-99%) and, at the same time, good to excellent induction of asymmetry could be achieved (e.r.s up to 95.5:0.5).



Scheme 13 General overview of the β-borylation reaction and oxidation sequence of α,β-unsaturated carbonyl compounds under aqueous conditions.

Based on this, the substrate scope suitable for this transformation was expanded, with the publication of new methodology by the same group, consisting of the borylation of α,β-unsaturated ketimines [Eqn. (8)].[71] Surprisingly, no decomposition of the imine substrates was claimed, with the corresponding β-hydroxy ketimines being isolated in good yields and e.e.s. Table 3 summarises the most relevant results extracted from this study.



(8)

Table 3 Substrate scope for the asymmetric Cu(II)-catalysed β-borylation reaction/ oxidation of α,β-unsaturated imines in water.

Entry	R^1	R^2	Yield (%)	e.e. (%)
1	Ph	Me	83	>99
2	Ph	Ph	91	>99
3	*p*MePh	Ph	83	>99
4	Ph	*p*MePh	93	>99
5	*p*MePh	Me	85	>99
6	*p*ClPh	Ph	81	80

Although the great majority of the asymmetric methodologies reported are based on transition metal catalysis, organocatalytic methodologies had been shown to be effective from an asymmetric perspective. Fernández and coworkers[58] developed an innovative and effective protocol in which the chirality was induced by phosphine ligands. In this particular case,

diphosphine ligands containing a ferrocene backbone were used as catalytic species based on previous work developed by the same group, where it was observed that this type of ligand could substantially improve the results.[72,73] In this study, the β-borylation of ethyl crotonate **20a** was optimised and subsequently this system was evaluated in terms of induction of asymmetry. A series of mono- and diphosphine ligands were screened, confirming that in those cases in which the ligand contained a ferrocene group, the enantioselectivity was considerably higher. Interestingly, it was found that diphosphines were more effective than monophosphine ligands in terms of enantioselectivity. Figure 4 shows the different ferrocene-based diphosphine ligands studied along with the corresponding conversion and their respective e.e.s.

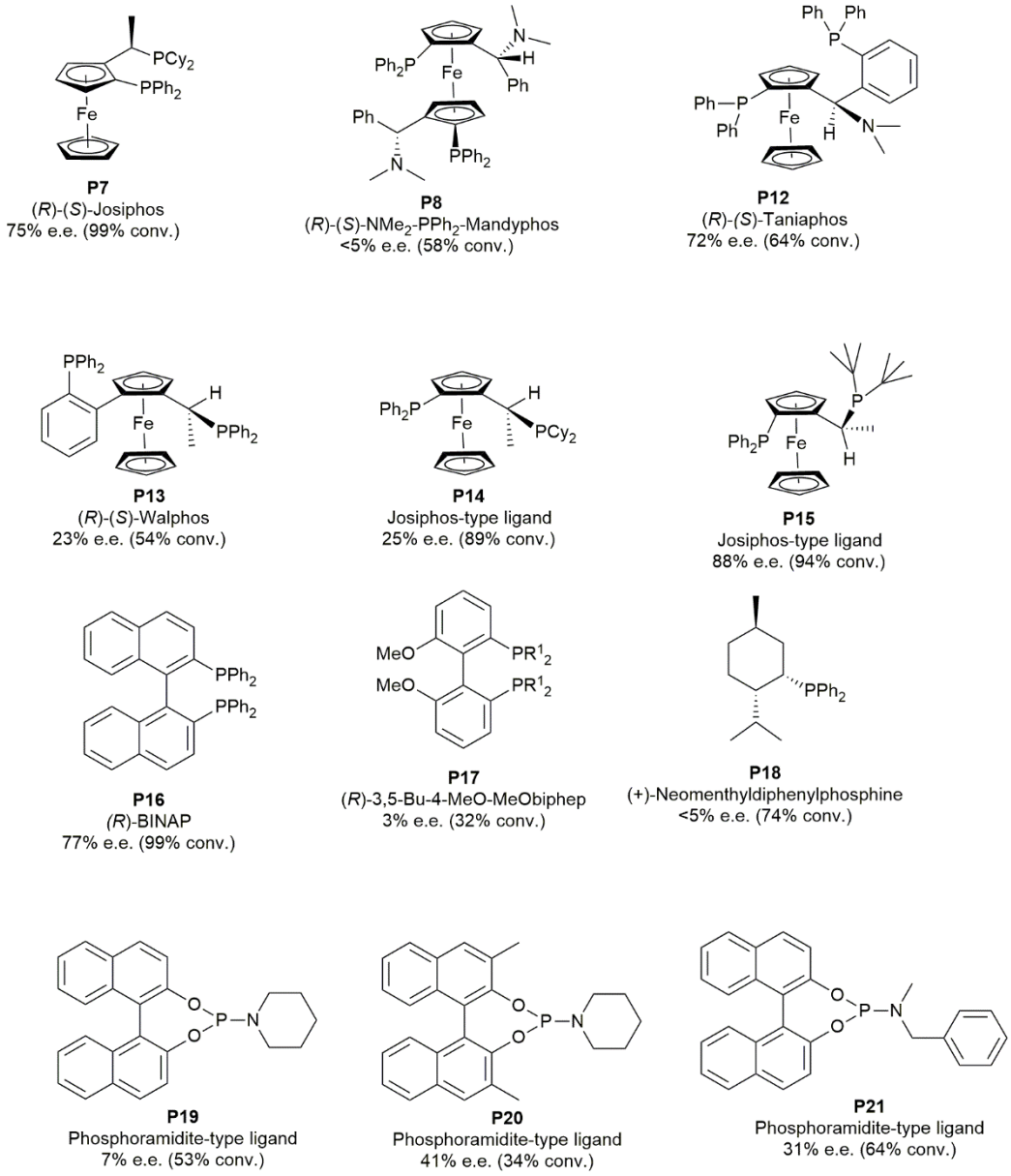
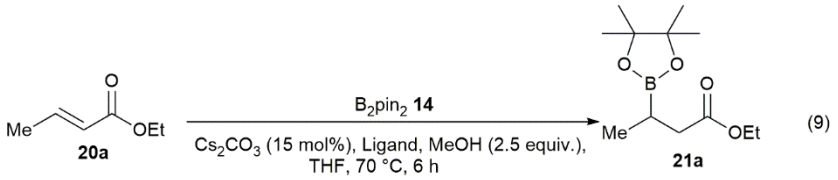


Figure 4 Scope of ligands tested under organocatalytic conditions for an enantioselective methodology postulated by Fernández and co-workers.

Among the types of ligands tested, it was observed that **P12** provided results comparable to those catalysed by $Ni(cod)_2$ (Scheme 12).[68] Also, it was observed that the Josiphos-type ligands **P7**, **P14** and **P15** provided diverse results, depending on the nature of the substituents on the phosphorous donor atoms, with **P15** being the most effective (25% e.e., 72% e.e. and 88% e.e., respectively). Surprisingly, it was observed that in the absence of a metal, the inorganic base played a key role. The role of the base was also examined and it was

found that Cs_2CO_3 provided better results in comparison with NaO^tBu and CsF. Additionally, the same reaction [Eqn. (9)] was performed using metal catalysts modified with **P15**, giving moderate asymmetry in the cases of Cu(I) and Ni(II), as summarised in Table 4.



(9)

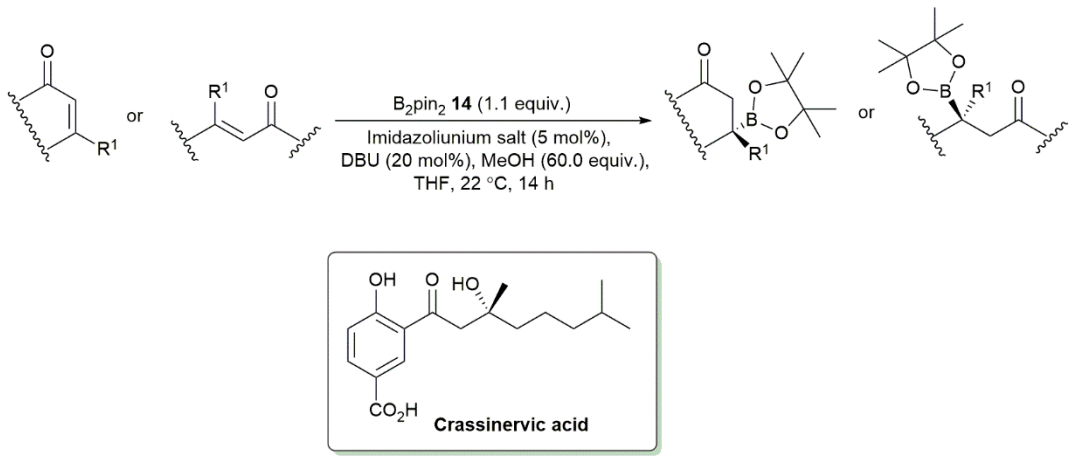
Table 4 Comparison of the induction of asymmetry in the β-borylation of ethyl crotonate under organocatalytic, Cu or Ni catalysis.

Entry	M_T catalyst	Conv. **21a**[b] (%)	e.e.[c] (%)
1	-	94	88 (*S*)
2	CuCl[a]	97	54 (*S*)
3	$NiCl_2$[a]	78	58 (*S*)

[a]Cu and Ni salt (4 mol%). [b]Determined by GC and confirmed by ^{1}H NMR. [c]Determined by HPLC on the β-boryl ester **21a**.

These results indicated that the mechanism of the transition-metal catalysis and the organocatalysis must be substantially different. In summary, these results established the first examples of enantioselection in boron-mediated synthesis in the absence of transition metals or chiral borylated reagents.

Hoveyda also demonstrated that using a chiral NHC in the presence of MeOH and a base, such as DBU, resulted in the synthesis of enantioselectively enriched organoboranes on α,β-unsaturated ketones, esters, aldehydes and Weinreb amides.[74] This methodology was successfully applied to a wide range of examples, and later on, the same group reported the use of this catalytic system for the formation of borylated quaternary carbon stereocentres with excellent asymmetric inductions and good to excellent yields. Moreover, this methodology was applied to the synthesis of crassinervic acid; a natural product with antifungal properties[75] (see Scheme 14).



Scheme 14 General overview of the synthesis of quaternary carbon stereocenters *via* a metal-free β-borylation protocol.

In the following years, Fernández and co-workers extensively explored the field examining a wide range of substrates upon which it was possible to perform the conjugate addition of boron in the absence of a transition metal. Beside the more conventional α,β-unsaturated carbonyl compounds,[71-73] other novel protocols were reported, *e.g.* borylative ring-opening of vinyl epoxides and aziridines,[76] and additions to propargylic and allylic alcohols.[77]

Once the reaction had been described from a catalytic perspective, some other aspects of the reaction required a better understanding. In the next two sections, the β-borylation reaction is examined from the points of view of the diboron reagents and the organic substrates on which the boryl can be added.

1.3. Generation of the nucleophilic boryl moiety: activation of the diborane reagent

1.3.1. General overview

Diboron compounds are widely used as sources of nucleophilic boryl units, which are essential in the β-borylation reaction.[78] Diboranes are attractive reagents in organic synthesis

due to the fact that they contain trivalent boron atoms, which makes them Lewis acids. As shown in Figure 5, this atom has a *p*-orbital perpendicular to the molecule plane, and as a consequence, it presents a vacant orbital that is susceptible to attack by a pair of electrons, *i.e.* strong σ-donor/ π-acceptor. This electronic feature derived their electrophilic reactivity.[79]

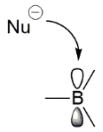


Figure 5 Representation of a nucleophilic attack into a trivalent boron atom.

It had been observed that boron reagents can also interact with electron deficient substrates, through acting as a nucleophile, which further increases their versatility. The existence of stable boryl anions was confirmed by Yamashita and Nozaki in 2006.[80] The explanation for this phenomenon lies with the hybridisation of the boron atom, which depends on the number of bonds attached to it. Hence, if a boron atom is coordinated by three bonds, its hybridisation is sp^2 and is planar trigonal in geometry and its compounds are neutral and isoelectronic to carbenes. As a consequence, they react as electrophiles. Conversely, if the boron compound reacts with an anion, the boron atom gains an extra bond changing its hybridisation to sp^3, becomes negatively charged and is tetravalent and tetrahedral.[36] Figure 6 shows the two different hybridisations that boron atoms can present.

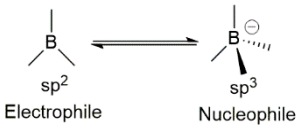
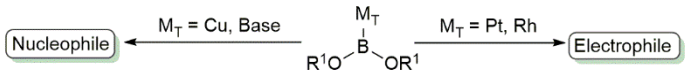


Figure 6 Possible hybridisation presented by boron atoms and its relation to their reactivity.

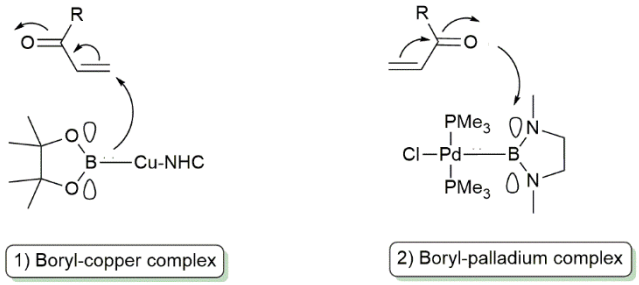
Besides the number of bonds, it is also necessary to take into account the nature of the substituents on the boryl moiety, because these have a significant impact upon the electronic properties of the boron centre. It is, therefore, possible to tune the reactivity of this moiety, *i.e.*

if the substituents are electron rich then the reactivity of the boryl can be switched from electrophilic to nucleophilic.[81] Scheme 15 highlights the change in the reactivity of a trivalent boron compound depending on the substituents.



Scheme 15 Change in the behaviour of the borated compound depending on the nature of the substituents.

Hence, every boryl moiety has distinctive structural and electronic properties, and Carbó and Fernández[82] have developed a 'tendency' map based on the correlation between the structure of the boryl unit and the reactivity of trivalent boron containing moieties. This involved a multidisciplinary study between experiment and theory, in which several types of boryl units coordinated to diverse atom types were examined by taking into consideration the charge, as well as the *p*/*s* population ratio on the boron atom. In general, it was observed that the most nucleophilic moieties were that in which the boron atom presents a higher *p* contribution, due to the fact that *p* orbitals are higher in energy than the *s*. Interestingly, an attractive and relevant aspect of the behaviour of boryl moieties was also confirmed, *i.e.* that the reactivity presented can be switched for the same boryl unit depending on the transition metal to which it is attached. With the aim of clarifying this point, in Scheme 16 are displayed two examples based on the β-borylation of an α,β-unsaturated ketone. One case shows the presence of a copper boryl[47,48] and the other, a palladium boryl system.[83]



Scheme 16 Mechanism corresponding to the β-borylation reaction of α,β-unsaturated ketones in the presence of: 1) a boryl-copper complex modified with *N*-heterocyclic carbenes; and 2) a boryl-palladium complex modified with phosphines.

As shown in Scheme 16, the reactivity of the boryl-metal species relative to an α,β-unsaturated carbonyl compound is reversed in the case of the copper boryl moiety, where the electron density is allocated in the B atom. This is supported by theoretical studies carried out by Marder and coworkers.[84] However, in the case mediated by Pd, the bond is polarized towards the metal centre providing an electrophilic B which can then be attacked by the substrate. Specifically, in the β-borylation reaction, the borated reagents are diboranes, *i.e.* B-B systems, which are homonuclear compounds and therefore, a new covalent bond requires cleavage along with the fact that they are trivalent atoms (electron deficient). However, when working with electron deficient organic molecules as substrates, the target is to obtain a nucleophilic boryl moiety, so that this can react with the Michael acceptor. Therefore, activation of the diborane is required in order to get the desired reactivity, either by the *in situ* generation of the boryl-metal catalytic species or by the generation of an extra bond to one of the two trivalent boron atoms.

It is worth noting that not all diborane reagents require catalytic activation. It has been demonstrated that diboron tetrahalide compounds, *e.g.* B_2Cl_4, can be added to an alkene in the absence of a catalyst.[85] However, these compounds are not stable so it is not such a useful system in more routine synthesis. Although diborane reagent research has not been as exhaustive as that into different transition metal catalytic systems,[86] it has been concluded that tetra-alkoxy diboron reagents, *i.e.* diboronyl esters, are the most appropriate due to their

relative ease of preparation, as well as high stability.[13] Beside the most commonly used reagent being B_2pin_2 **14**,[44] B_2cat_2 **15** [44] and B_2neop_2 **44**[87] have also been widely employed (see Figure 7).

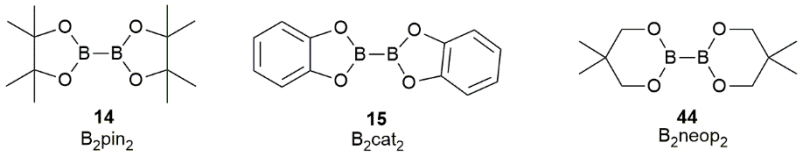
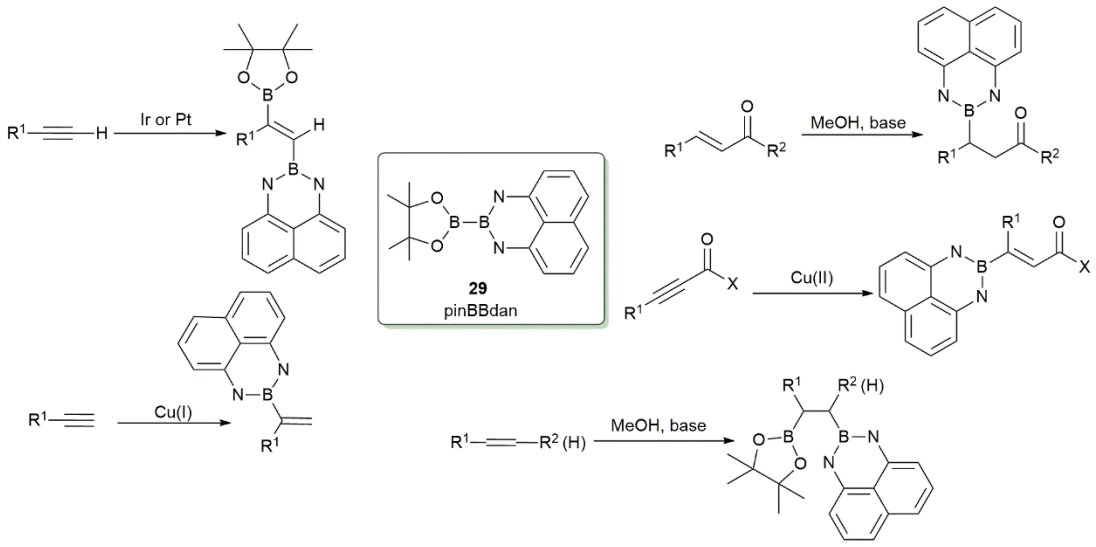


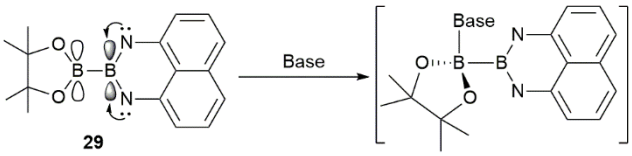
Figure 7 Most widely used diborane reagents for the β-borylation reaction.

Even though symmetric diboranes are the most broadly used, in the last few years diborane reagents with different boron protecting groups, have emerged as attractive alternatives, since they expand the synthetic options in terms of functionalisation of the organoborane due to the different reactivity exhibited by each boryl unit. Several methodologies have been reported using the mixed diboron reagent BpinBdan **29**, and its activation *via* organometallic catalysis[53,88,89] or organocatalysis,[90-92] as summarised in Scheme 17.



Scheme 17 Overview of different borylation methodologies using BpinBdan as diborane reagent.

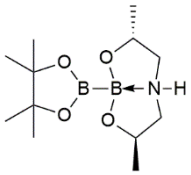
Interestingly, amongst all the different examples in the literature, it has been observed that under β-borylation conditions, the Bdan moiety is the boryl unit transferred to the resulting organoborane. The explanation as to this selectivity relies on the fact that the Bpin moiety is available for the formation of the acid-base adduct, hence the Bdan moiety gets transferred. This anionic adduct is less favoured in the case of the Bdan unit due to the fact that the B centre is prevented from nucleophilic attack due to π-donation of the lone pair of the N atoms, as displayed in Figure 8.



29

Figure 8 Activation of the unsymmetrical diborane BpinBdan.

Moreover, Santos *et al.*[93] disclosed the synthesis, characterisation and reactivity of a novel unsymmetric, internally activated, mixed diboron reagent, PDIPA diboron **45**.



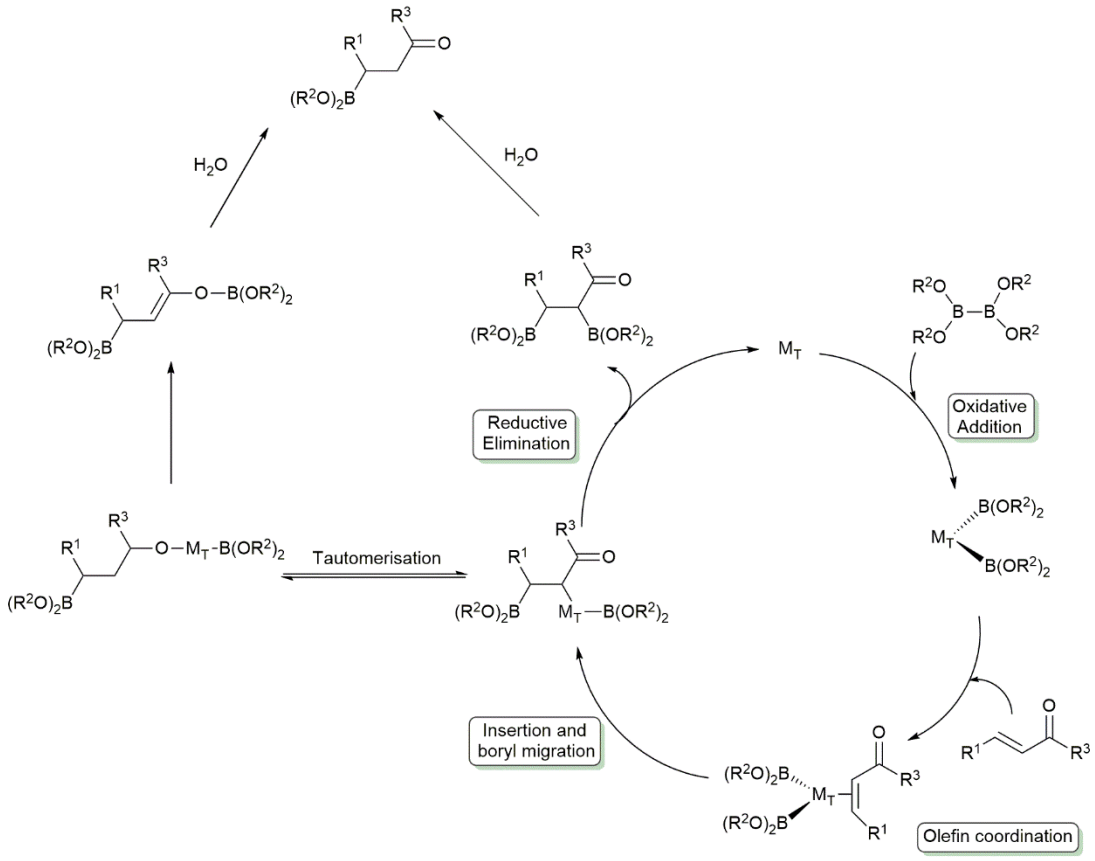
45
PDIPA

The most attractive feature of this compound is that it consists of an sp^2-sp^3 system due to the presence of the amino group which provides an intramolecular interaction with one of the B atoms, facilitating the B-B bond cleavage. In other words, this reagent is intrinsically activated, however, symmetric diboron compounds are still the most broadly used due to their relative ease of preparation and stability, as well as their commercial availability, and despite the inconvenience of catalytic activation being required for the cleavage of the stable B-B bond which has a bond energy of 104 kcal/mol.[94] This crucial step has been studied in detail

over the years, either from an organometallic or organocatalytic perspective, becoming the main focus of recent research developed in the β-borylation reaction.

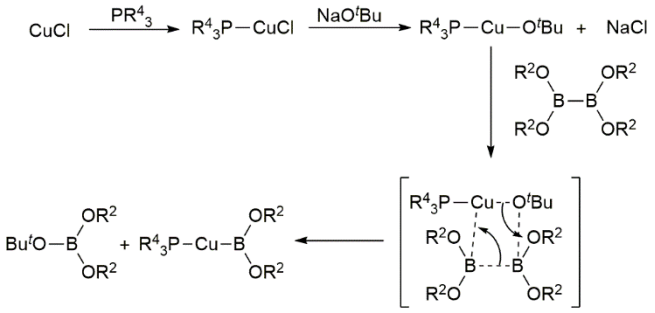
1.3.2. Organometallic activation strategies

It was observed that in diboronyl esters, B-B bond cleavage could be assisted by transition metals providing milder and controllable reaction conditions and this discovery marked an important landmark in the β-borylation reaction, as well as in other types of reactions. Although for all borylation methodologies, the first step is formation of a boryl-metal species, depending on the metal employed, this crucial step can take place *via* two different ways: 1) an oxidative addition of the B-B bond into the metal center; or 2) a σ-bond metathesis reaction between the diborane and the metallic complex.[36] Looking at the work performed since the late '90s, it had been observed that in the case of using Pt[44] or Rh,[27] the diboron reagent can be oxidatively added into the metallic catalyst, and subsequently, the nucleophilic boryl unit generated is introduced into the catalytic cycle. This involves an insertion of the boryl unit into the substrate *via* oxidative addition and coordination to the metallic center, followed by the subsequent migration of the boryl unit onto C_β. Depending on the nature of R^1 and R^2, this can then react *via* two different routes: 1) a direct reductive elimination which leads to the 3,4-diborylated product; or 2) a tautomerisation and reductive elimination to give the 1,4-diborylated compound. From these diborylated compounds and with an aqueous workup, the β-boryl carbonyl compound is obtained (see Scheme 18).



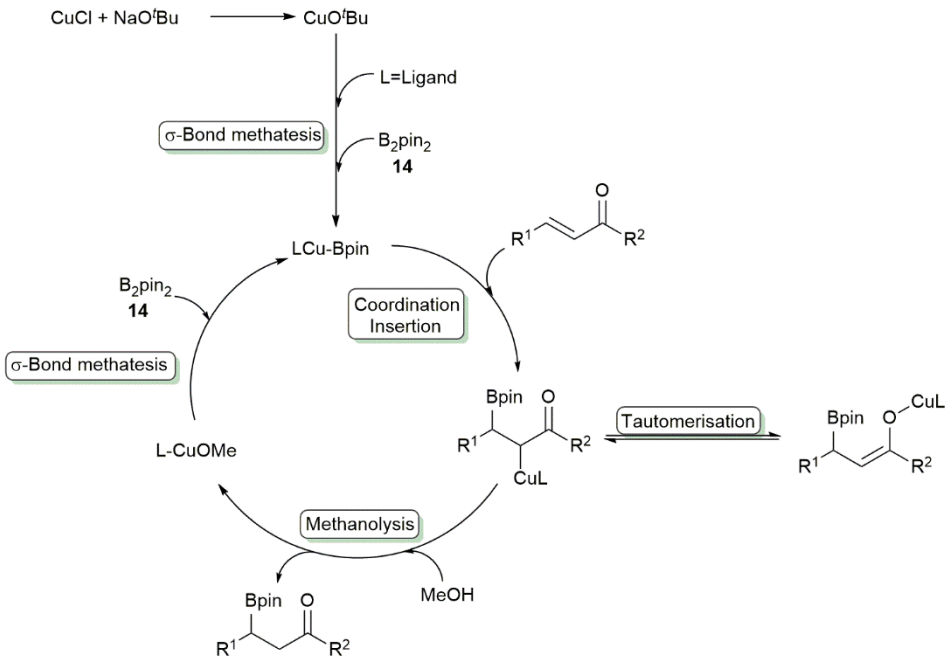
Scheme 18 Catalytic cycle for β-borylation *via* an oxidative addition for the activation of diborane.

However, in the case of working with a metal that presents a lower energy *d*-orbital, the activation takes place without a change in the formal oxidation state, *i.e.* it does not involve an oxidative addition. Instead, a σ-bond metathesis occurs involving the transition metal complex formed *in situ* and the diborane reagent. Examples of transition metals that undergo this concerted mechanism are copper[47-49] and nickel.[68] Scheme 19 outlines the proposed mechanism through which the generation of the boryl moiety takes place.[84]



Scheme 19 Mechanism for formation of the boryl moiety *via* σ-bond metathesis in Cu(I) catalysis.

Once the nucleophilic reagent is generated, it is introduced into a catalytic cycle; a plausible proposal was reported by Yun *et al.*[49] In this case, the copper-boryl catalytic species undergoes a coordination-insertion with the α,β-unsaturated carbonyl compound generating the boryl-copper enolate, which after protonation (methanolysis step) leads into the target β-borylated compound at the same time that the catalytic species is regenerated (Scheme 20).



Scheme 20 Mechanism for the Cu(I)-catalysed β-borylation reaction proposed by Yun *et al.*

Later on, several mechanistic studies consisting of DFT investigations were carried out by Marder and co-workers, which helped to understand the LCu-Bpin catalytic species formation. It was confirmed that initially, a LCu-alkoxide precursor is generated which in the presence of the diborane, the hybridisation of one of the B moieties changes from sp^2 to sp^3 leading to a preactivated sp^2-sp^3 diborane system. This then reacts *via* a σ-bond metathesis affording the desired LCu-Bpin intermediate.[95]

A relevant aspect in this mechanism is the use of ligands to form the copper-boryl catalytic species, hence, the most common ligands used are phosphines. Therefore, the stereoelectronic properties, and consequently, the metal-phosphine bonding, has been examined.[96] The main advantage that these type of ligands present is that they are excellent electron donors, so that the bond between the ligand and the metal center is stabilised. It is important to note the σ-donor/π-acceptor synergism presented by the M_T-phosphine complexes,[97] represented in Figure 9, is key to tuning metal electronic effects.

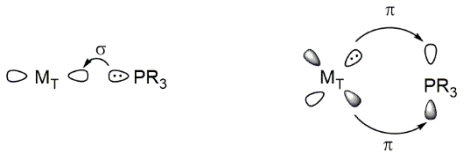


Figure 9 Orbtital representation of transition metal-phosphine bonding.

Another remarkable feature of these compounds is that they can be synthesised with a wide range of possibilities with respect to the R substituents, *i.e.* with control of steric effects.[98] As discussed in previous sections, phosphine ligands can also create an asymmetric environment around the metallic center so that chirality can be induced into the process. Chiral P,P-ligands, including Binap **P16**, which were developed by Noyori and Takaya[99] three decades ago, and, since then, many ligands containing the biaryl backbone have been developed as well as other types of chiral phosphorus-derived ligands. Figure 10 shows examples of the most common biaryl-based, diphosphine ligands.

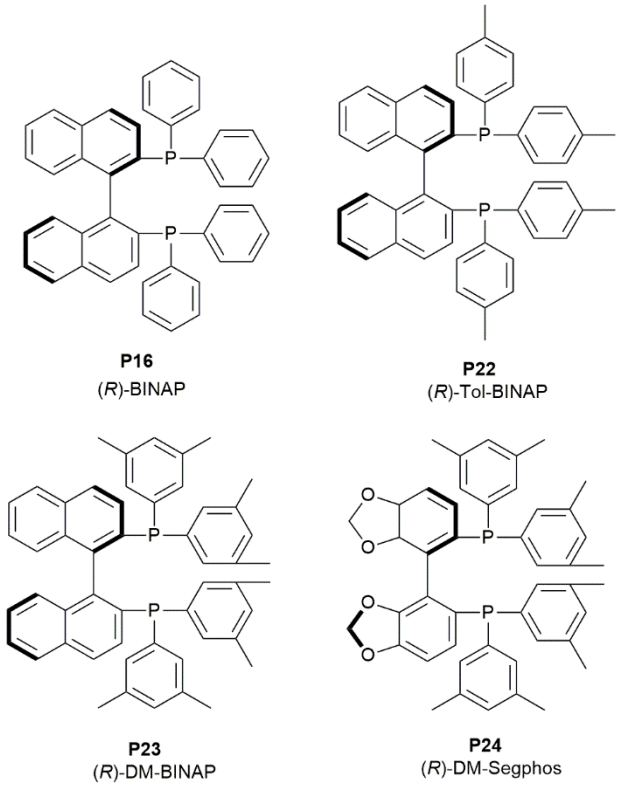
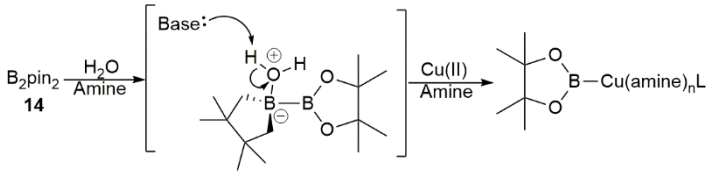


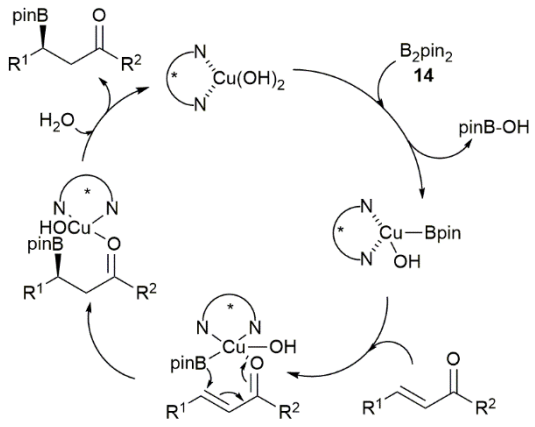
Figure 10 Examples of biaryl-based chiral diphosphine ligands.

Regarding the activation of the diboranes *via* copper-based catalysts, several studies involving Cu(II) catalytic systems in aqueous media have been reported since 2012, together with postulated mechanistic insights. Santos *et al*.[52] carried out several NMR studies in order to clarify the role played by the amine base. It was confirmed that the presence of the base gives rise to stable complexes with the metallic centre, *i.e.* pinB-Cu(amine)$_n$L and at the same time this acts as a Bronsted base activating a nucleophilic molecule of water promoting the quaternisation of one of the B atoms leading to an sp^2-sp^3 diborane and generating pinB-OH as by-product (see Scheme 21).



Scheme 21 Proposed mechanism of activation of diborane by amine-Cu(II) in aqueous media.

This mechanistic proposal also fit in with the catalytic cycle proposed by Kobayashi for the case of the enantioselective β-borylation of α,β-unsaturated carbonyl compounds in water.[70] In this case, it was postulated that a complex formed by $Cu(OH)_2$ and the chiral diamino ligand reacts with the diborane, eliminating pinB-OH. Subsequently, the metallic complex interacts with the α,β-unsaturated substrate, where the addition of the boryl takes place by a six-membered, cyclic transition-state leading to the corresponding copper enolate. This enolate subsequently undergoes protonolysis, generating the target β-boryl carbonyl compound and regenerating the catalytically active species. Scheme 22 displays this catalytic cycle.



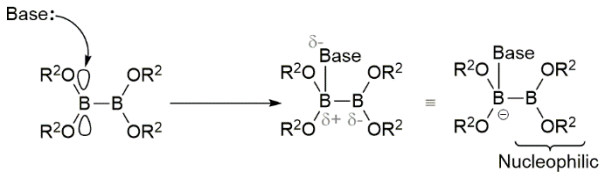
Scheme 22 Proposed catalytic cycle for Cu(II)-amine catalysed β-borylation of α,β-unsaturated carbonyl compounds in aqueous media.

In summary, it was observed that the organometallic activation of diboranes presents a wide diversity of mechanistic insights, depending not only on the transition metal in which the catalytic system is based on, but also the conditions under which the reaction is run.

1.3.3. Organocatalytic activation strategies

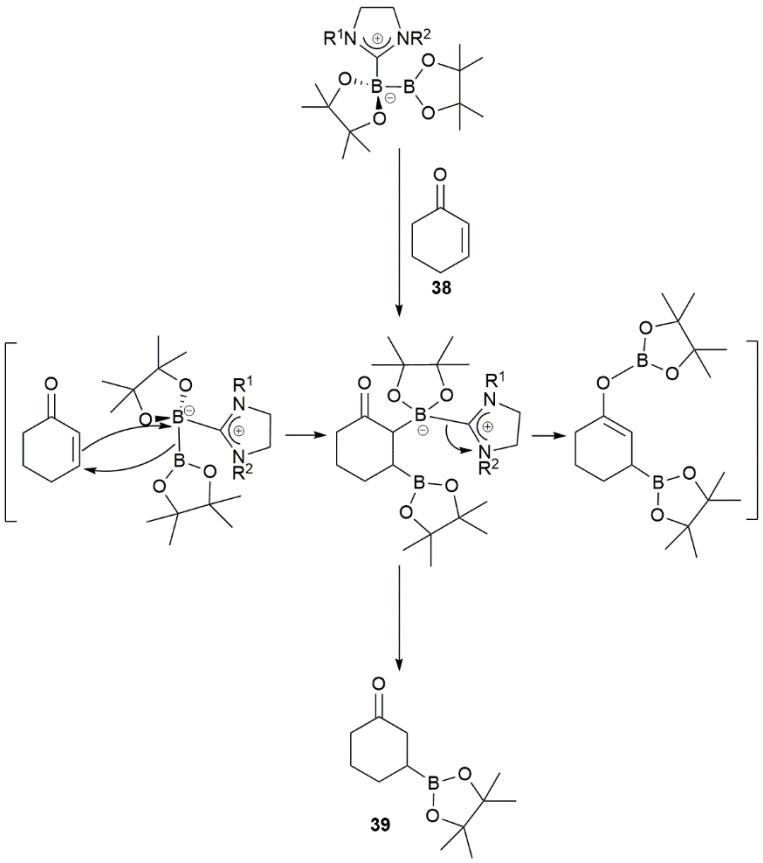
Unlike the conventional organometallic catalytic pathway, in organocatalysis the activation of the diborane reagents is caused by low molecular weight organic molecules. The advantages are mainly environmental, with ready availability of the catalysts due to their low price. In recent years, a great expansion in this field has occurred. Although there is evidence of transformations using organocatalysis previously, it was not until the '90s that there was a considerable expansion in the use of such catalysts.[100] The possibility of performing borylation reactions in the absence of a metal was considered since in 2009 when Marder *et al.*[95] reported a study in which the objective consisted on the addition of boron into aryl halides mediated by copper. Surprisingly, it was found that when a blank reaction was carried out, *i.e.* in the absence of the transition metal, the target borylated product was formed in a small amount. Hence, it was concluded that under these reaction conditions, the key nucleophilic boryl moiety was generated; probably by the formation of an acid-base adduct between the diborane and the alkoxide base. With this discovery, the addition of diborane reagents to electron deficient organic substrates without using transition metals, started to be considered as a suitable catalytic option which was widely explored in the following years.

The organocatalytic strategy for the activation of diboranes is based on the use of an electron donating reagent, *e.g.* amine, NHC or alkoxide.[81] Hence, an acid-base adduct is generated between the B sp^2 centre and the basic reagent, generating a nucleophilic boryl unit, as displayed in Scheme 23. The electron donating reagent coordinates to one of the two boron atoms giving electron density to this atom, and as consequence of this, electronic reorganisation occurs, resulting in the B-B bond polarisation, and generating an sp^3-sp^2 diborane system. Hence, one of the B atoms can attack the electrophilic substrate as a nucleophile.[101]



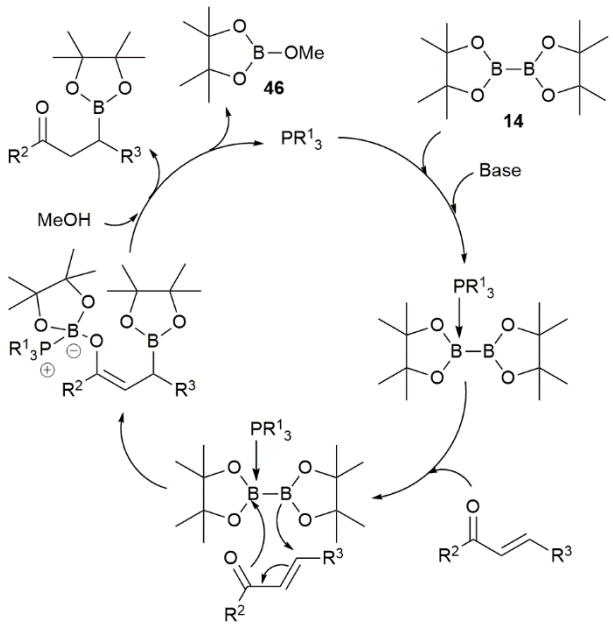
Scheme 23 Generation of a nucleophilic boryl from diborane under organocatalytic conditions.

This novel strategy was first reported by Hoveyda and coworkers[57] who studied the role played by readily available NHCs in the activation of diboranes and subsequent conjugate addition to cyclic and acyclic α,β-unsaturated ketones and esters. In this study, the initial hypothesis regarding the mechanism of this transformation was confirmed by DFT calculations and NMR studies. Scheme 24 outlines the mechanism for the NHC-catalysed β-borylation reaction of enones. Later on, theoretical and experimental evidence regarding the neutral B_2pin_2-NHC adduct was presented by Lin and Marder.[102]



Scheme 24 NHC-catalysed β-borylation reaction of enones.

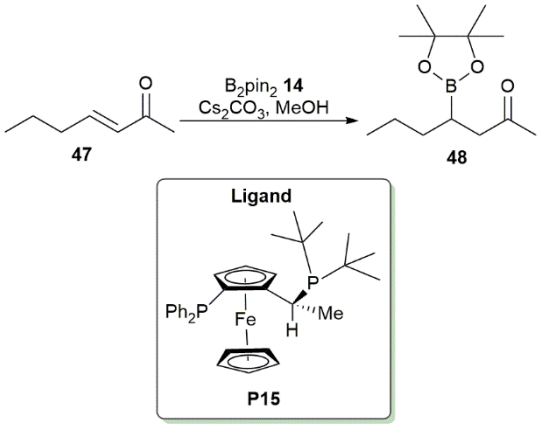
As highlighted in previous sections, Fernández *et al.* also contributed to this area of organocatalysis by the postulation of several methodologies along with mechanistic studies. In 2010, the catalytic cycle corresponding to the phosphine-mediated conjugated addition of boron to α,β-unsaturated ketones and esters was suggested, as displayed in Scheme 25.[58]



Scheme 25 Proposed mechanism for the phosphine-catalysed β-borylation reaction of α,β-unsaturated carbonyl compounds.

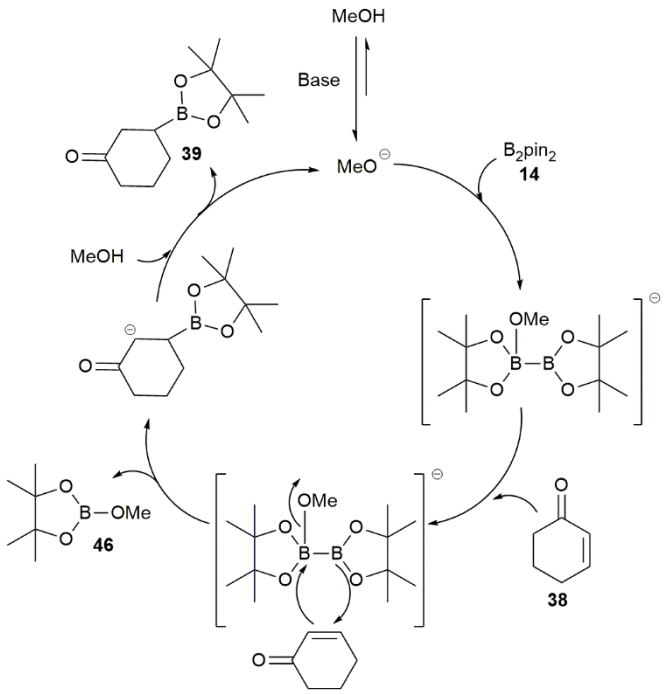
It was suggested that the polarisation of the B-B bond takes place as consequence of the direct interaction between the phosphine ligand and the empty *p*-orbital of one of the boron atoms, generating the nucleophilic boryl unit. Although several ^{11}B and ^{31}P NMR studies were carried out, the interaction P-B could not be confirmed, however, when base and MeOH were added to a mixture of PMe_3 and B_2pin_2 at 70 °C, the ^{11}B NMR spectrum showed two new signals at δ -9.2 ppm and 39.4 ppm, which likely correspond to an sp^2-sp^3 diborane system. At the same time, the ^{31}P NMR spectrum showed a signal that did not correspond to the free phosphine (δ -10.5 ppm compared to the original signal at δ -61.9 ppm). They concluded that this represents the first example of a phosphine-assisted, metal-free, asymmetric approach of the β-borylation reaction. In this case the enantiodifferentiation of the two faces of the

saturated C-C bond was proposed to be caused by the direct interaction of the chiral auxiliary. Scheme 26 shows the β-borylation reaction of 3-hepten-2-one **47** under these conditions.



Scheme 26 Example of a metal-free enantioselective β-borylation of α,β-unsaturated carbonyl compounds.

It was also confirmed that the presence of a base along with an alcohol additive is crucial for the organocatalytic version of the β-borylation reaction, however, mechanistic details remain unclear. Hence in 2012, Fernández, in collaboration with Bo,[103] reported an interesting experimental and theoretical study focused on the function of the base and the alcohol in this transformation. It was postulated that a novel catalytic cycle for the β-borylation reaction of activated olefins occurs, mediated by MeOH and a base, as outlined in Scheme 27.



Scheme 27 Methoxide-catalysed B_2pin_2 **14** conjugate addition to cyclic α,β-unsaturated ketone **38**.

This mechanism consists of the formation of an alkoxide and subsequent formation of an acid-base adduct with the diborane. Then, the sp^2 B atom adds to the activated olefin by heterolytic cleavage of the B-B bond and simultaneous formation of the new C-B bond. After protonation of the anionic intermediate, the product is obtained and the methoxide initiator is regenerated so that the cycle can start again. The basis of this methodology comes from the same group in which a Lewis base-catalysed diboration method was proposed which opened a wide range of possibilities for organoborane synthesis on an industrial scale.[40]

1.4. Organic electron deficient substrates: addition to α,β-unsaturated carbonyl compounds

1.4.1. General overview

Another important aspect to take into account regarding the β-borylation reaction is the nature of the substrate where the boryl moiety adds to, *i.e.* the Michael acceptor. In general, it consists of an activated olefin, being an α,β-unsaturated carbonyl compound. The carbonyl

functionality being conjugated to the alkene fragment provides special properties, *i.e.* the carbonyl group withdraws electrons and the β-position becomes electron deficient. Hence, the olefin is activated towards nucleophilic reagents. See Figure 11.

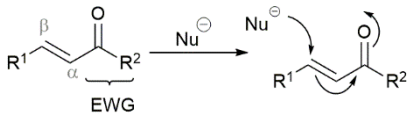


Figure 11 General structure of an α,β-unsaturated carbonyl compound.

Although it had been observed that these structures provide an excellent scenario for the conjugate addition of boron, it is also necessary to take into account that depending on the nature of the EWG, competitive 1,2-addition can take place. This is due to the fact that another electrophilic position is susceptible to be attacked by a nucleophile, *i.e.* the carbonyl group. This is especially relevant to the chemoselectivity issue which occurs with α,β-unsaturated aldehydes (see Section 1.4.2).

It has been demonstrated that depending on the reaction conditions, some EWGs are more appropriate than others. Figure 12 presents a summary of the different methodologies reported in Section 1.2, focused on the type of EWG group on the α,β-unsaturated carbonyl compound.[36]

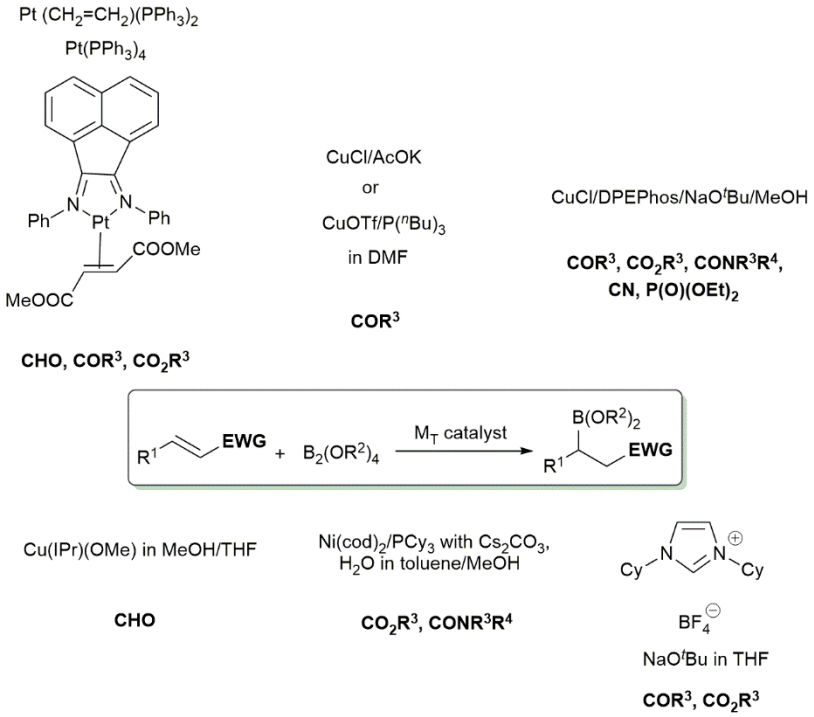


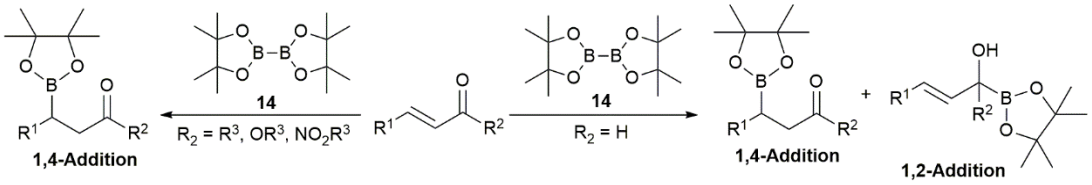
Figure 12 Different methodologies for the catalytic β-borylation reaction of α,β-unsaturated carbonyl compounds depending on the EWG.

Among the extensive research carried out to understand this reaction, many types of substrates have been studied. It has been demonstrated that several type of electron deficient compounds are tolerated, such as esters,[64] ketones[50] and amides.[66] Esters and ketones are the main type of substrates in the majority of the studies carried out and consequently their reactivity towards the β-borylation reaction is now well known and understood. It is also interesting to mention that few examples of borylated amides have been reported. In summary, for the majority of cases, exclusive 1,4-addition was observed, hence, no chemoselectivity issues were reported. However, among the list of substrates, aldehydes give rise to complex reactivity, as discussed in the following section.

1.4.2. α,β-Unsaturated aldehydes: challenging substrates

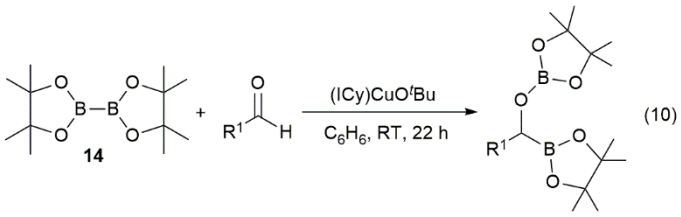
α,β-Unsaturated aldehydes requires especial mention due to the fact that borylation at C_β can result in efficient reactions, giving rise to complex reactivity in comparison with other

α,β-unsaturated carbonyl compounds. This is because in enals, both electrophilic carbons can be attacked by the nucleophilic boryl moiety. Conversion towards the desired 1,4-borylated aldehydes was not complete selectively because of competing 1,2-addition as displayed in Scheme 28.



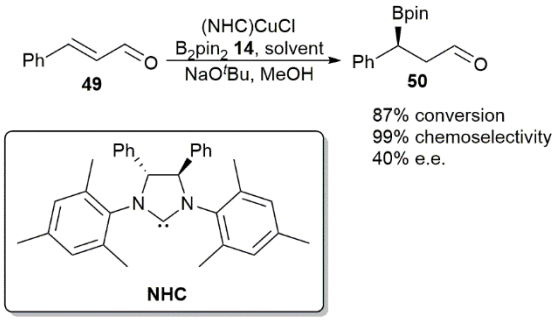
Scheme 28 Comparison of the reactivity under borylation conditions depending on the nature of the EWG.

As a consequence of the difficulty of this transformation being chemoselective, along with the instability of the resulting borylated products, not many methodologies involving these substrates have been reported. In the early 2000s, only a few examples had been reported using Rh[55] and Pt[104] catalysed protocols. However, later on Sadighi *et al.*[105] reported that the analogous diboration reaction [Eqn. (10)] can be successfully carried out with good conversion (yields up to 97%), providing a basis for the boron conjugated addition to aldehydes, and partly dealing with some of the issues associated with such substrates.



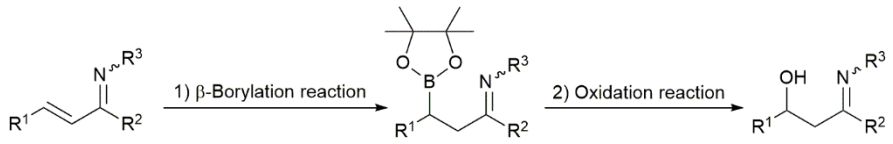
Fernández and co-workers needed to understand the reactivity of these substrates also, and hence, initiated exhaustive research in order to explore and develop new methodologies for the conjugate addition of boron to α,β-unsaturated aldehydes in the presence of copper-based catalysts. In 2009, this group proposed a selective strategy for the synthesis of β-boryl aldehydes under mild conditions mediated by NHC-Cu complexes.[106] The main aspect of this

methodology was the observation that the chemoselectivity could be controlled by the use of (NHC)CuOR catalyst. Specifically, the reaction was performed in the presence of IPrCuOR and base, providing excellent selectivity towards 1,4-addition (over 80%). Complementarily, that strategy was studied from an asymmetric point of view with α,β-unsaturated aldehydes, with the β-borylation reaction of cinnamaldehyde **49** used as a model substrate (see Scheme 29), from which to obtain enantioenriched β-boryl aldehyde **50**.[107]



Scheme 29 First enantioselective synthesis of β-boryl cinnamaldehyde derivative **50**.

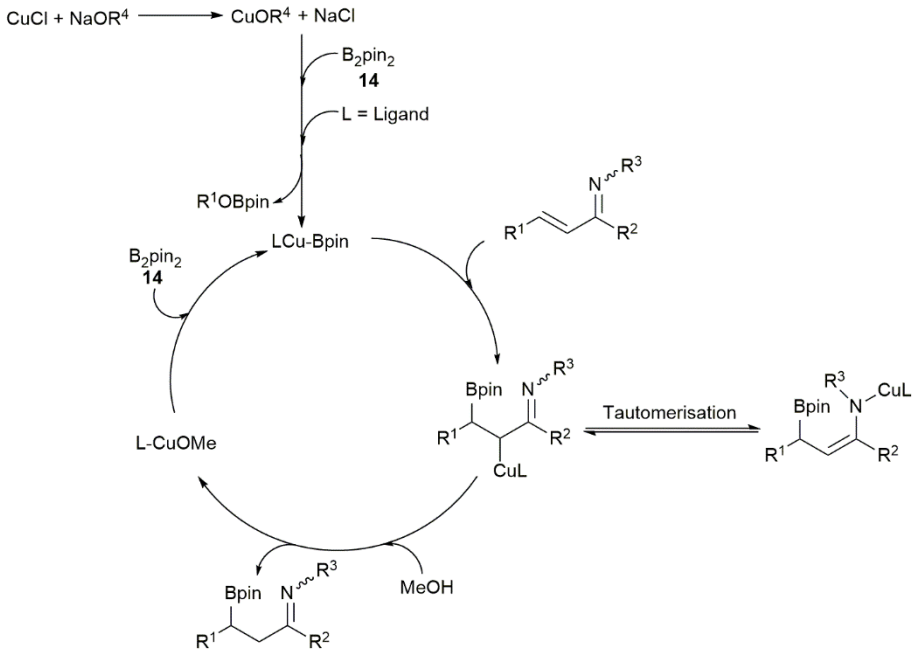
With the aim of controlling the chemoselectivity for the boryl conjugate addition, the application of a novel type of substrate had been reported recently. α,β-Unsaturated imines, whose chemistry is under-explored were examined by Fernández and Solé,[108] who in 2009 reported the β-borylation/oxidation of 1-azadienes (Scheme 30).



Scheme 30 Synthesis of β-iminoalcohols from α,β-unsaturated imines *via* a β-borylation/oxidation sequence.

The main objective of this study was the influence that the R^1 substituent on the imino group on the stabilisation of the anionic intermediates generated during the borylation process. With that aim, a series of ketimines and oximes were prepared and subsequently borylated

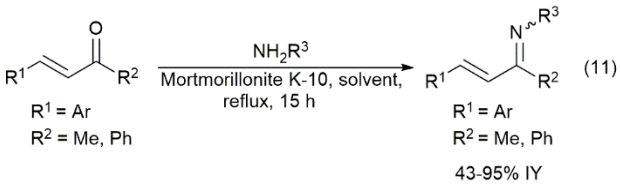
under different copper-phosphine catalysis conditions. Surprisingly, it was found that the presence of an alcohol additive was not necessary for the acceleration of the reaction, which suggested that an enamine analogous to that of the copper-enolate intermediate would result in a faster protonolysis step in comparison with the conventional copper-enolate formed with other substrates such as ketones or esters. Moreover, it was also found that the base had a beneficial effect in terms of conversion of the borylated product. Scheme 31 shows the proposed catalytic cycle for the β-borylation reaction involving α,β-unsaturated ketimines.



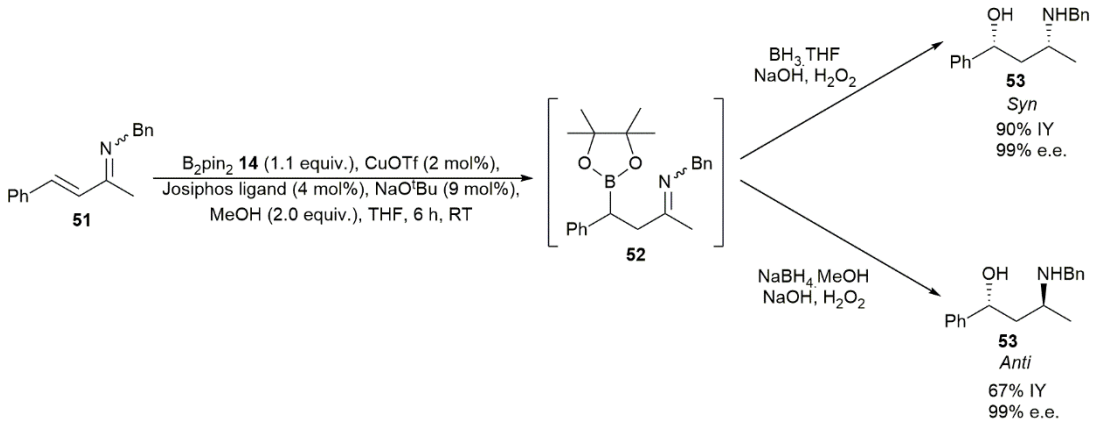
Scheme 31 Plausible mechanism corresponding to the Cu-PR_3 mediated β-borylation of α,β-unsaturated ketimines.

An efficient route towards β-iminoalcohols was developed, and based on this, in 2011 Fernández in collaboration with the Whiting group, disclosed a one-pot, three-step methodology towards the synthesis of chiral 1,3-aminoalcohols from α,β-unsaturated ketimines consisting of a β-borylation/reduction/oxidation sequence.[109,110] In first place, the α,β-unsaturated ketimines were generated from the condensation between the α,β-unsaturated ketone and an amine in the presence of a dehydrating agent [Eqn. (11)]. A series of different

ketones and amines were evaluated, with the target compounds being obtained in moderate to excellent yields.



The prochiral nature of the ketimines made them interesting substrates to carry out the borylation step in an enantioselective manner. Different chiral phosphine ligands were screened; a Josiphos-type ligand in combination with a Cu(I) salt resulting in excellent asymmetric induction in the formation of the new C-B stereogenic centre (e.e. > 99%). The electronic and steric properties of the R^3 substituent on the imino group was found to be important for complete chemoselectivity towards the 1,4-addition product, with a bulky group (*e.g.* aryl) being required. Moreover, optimisation of the reduction and oxidation steps allowed the *syn*- or *anti*-diastereoisomers to be obtained for the final γ-amino alcohol **53**, with exceptional control, depending on the reaction conditions, as displayed in Scheme 32.



Scheme 32 Example of the enantioselective synthesis of both *syn*-and *anti*-γ-aminoalcohols *via* a β-borylation/reduction/oxidation sequence from α,β-unsaturated ketimines.

It is also worth mentioning that the β-boryl imino intermediates in the ^{11}B NMR spectrum showed a signal at δ 22 ppm, which differs considerably to the one observed for the case of the analogous ketones (δ 37.2 ppm). The difference in chemical shift was attributed to the loss of planarity at the sp^2 B atom due to an intramolecular B-N interaction. This observation helped to explain the relative stereoselectivity observed, especially towards the *syn*-diastereoisomer, since the cyclic B-N chelated form of the β-boryl ketimine **52** would reveal the *Re*-face of the imine as less hindered, resulting in the corresponding *syn*-diastereoisomer **53** to be formed (see Figure 13).[109]

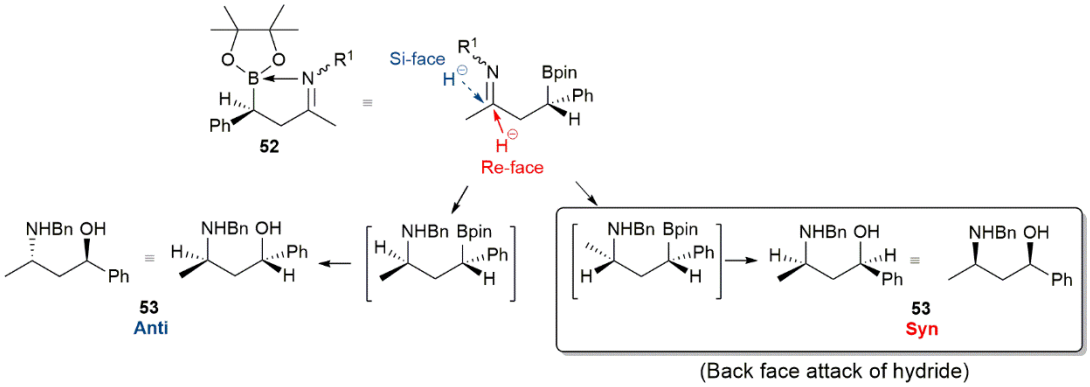


Figure 13 Relative stereocontrol towards the *syn*-diastereoisomer due to B-N intramolecular interaction.

However, the use of MeOH as solvent resulted in reversal in stereoselectivity. In this case, the ^{11}B NMR spectrum showed an additional signal at δ 18.9 ppm, which would suggest that MeOH forms an adduct with the β-boryl ketimine,[111] disabling the weak intramolecular B-N interaction and resulting in the linear form of **52**, which undergoes acyclic stereoselection under the reducing conditions, resulting in the *anti*-diastereoisomer.[110]

The highly effective use of these ketimine substrates, generated *in situ* led to the idea that this approach would be ideal for obtaining β-boryl aldehydes, with the potential for avoiding the chemoselectivity drawbacks due to 1,2-addition, through reducing the electrophilicity of the aldehyde carbon by imine formation. Particularly by using a bulky R^3

group on the imine (see Figure 14), it showed that maximal chemoselectivity could be exercised.

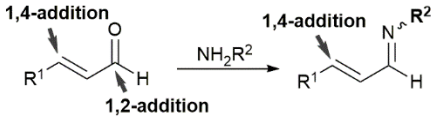
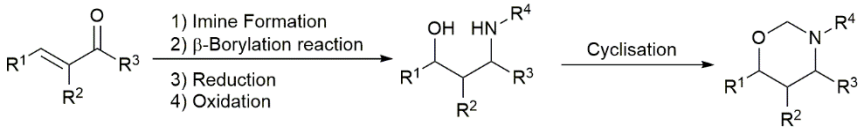


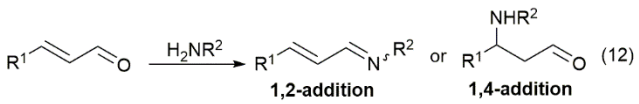
Figure 14 Comparison of the electrophilic positions available between an α,β-unsaturated aldehyde and its analogous aldimine.

This principle was successfully applied into a range of α,β-unsaturated aldehydes and ketones, defining an efficient four or five-step, one-pot methodology for the synthesis of γ-amino alcohols and 1,3-oxazines, respectively.[112] Scheme 33 outlines these methodologies.



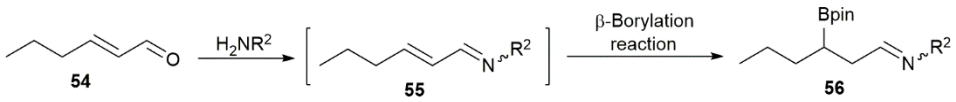
Scheme 33 Synthesis of γ-amino alcohols and 1,3-oxazines from α,β-unsaturated carbonyl compounds *via* a one-pot methodology.

Special attention was focused on the first step of this process, *i.e.* the imine formation. The reactivity of enals with amines was studied in detail by monitoring the process by *in situ* IR spectroscopy (ReactIR). Using this approach, it was possible to determine the time required for completion, as well as the chemoselectivity, *i.e.* formation of the condensation product (1,2-addition) or Michael addition (1,4-addition) of the amine to the conjugated aldehyde [Eqn. (12)].



From this study, it was observed that imine formation was relatively fast for the majority of substrates, and the reaction was complete within 3 h. In terms of the chemoselectivity, the desired 1,4-addition product was obtained for nearly all cases studied, with the exception of methyl vinyl ketone. One year later, an asymmetric application of this methodology was reported by the same group,[113] and an interesting aspect of this study was the evaluation of the influence of the steric hindrance on the C=N bond towards the chemoselectivity obtained for the β-borylation step. Hence, 2-hexenal **54** was transformed into the corresponding aldimine using different amines and subsequently borylated, as shown in Table 5.

Table 5 Scope of amine evaluated for the imine formation of 2-hexenal **54**.

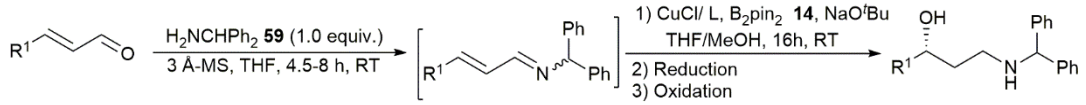


Entry	Ligand	Amine	Conv. (%)[a]	β-Borylated **56** (%)
1	PPh_3	-	99	63
2	PPh_3	NH_2CH_2Ph **57**	99	99
3	PPh_3	NH_2CH_2*p*-C_6H_4OMe **58**	99	99
4	PPh_3	$NH_2CH_2Ph_2$ **59**	99	99
5	PPh_3	$NH_2C_4H_9$ **60**	99	75

A 0.25 mmol scale reaction: 2.0 mmol (1:1, amine/enal) were stirred in THF (8.0 mL) and 3 Å-MS (2.0 g) for 16 h, after which a 1.0 mL aliquot was transferred to a Schlenk tube (under Ar) containing Cu(I) salt (3 mol %), PPh_3 **P5** (6 mol %), NaO^tBu (9 mol %), and B_2pin_2 (1.1 equiv). After 5 mins, MeOH (2.5 equiv) was added to the solution and the reaction was stirred for 6 h. [a]Determined by ^1H NMR.

It was confirmed that, as expected, bulkier substituents on the imino group gave rise to the desired 1,4-addition (entries 2-4, Table 5), with benzhydrylamine **59** being the most suitable in order to ensure the desired chemoselectivity. The asymmetric borylation step was studied using a wide range of chiral diphosphine ligands, with (*R*)-DM-Binap **P23** providing the highest e.e.s for these type of substrates. Hence, an enantioselective synthesis of γ-amino

alcohols was successfully developed giving good to excellent asymmetric induction (80-97% e.e.) and yields (42-90%), as displayed in Scheme 34.

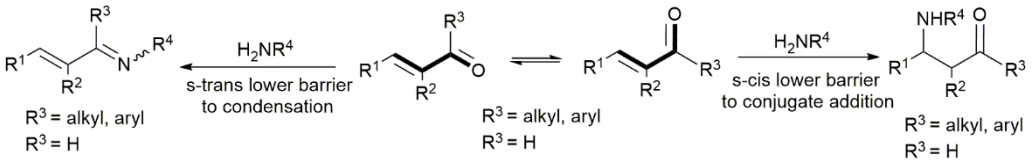


Scheme 34 General overview of the synthesis of γ-amino alcohols from enals *via* the corresponding amine-derived aldimine.

This study demonstrated that the *in situ* generation of the aldimines allows the chemoselective borylation of α,β-unsaturated aldehydes, which can be subsequently used for the synthesis of γ-amino alcohols or other synthetically interesting targets.

In summary, the use of α,β-unsaturated imines as substrates provided an ideal solution to the limitations of chemoselectivity presented by α,β-unsaturated aldehydes, and a better understanding of their formation was developed. In 2014, Fernández, Whiting and Carbó[114] reported a study in which experimental and theoretical investigations were combined in order to understand the formation of the α,β-unsaturated imine substrates. The main objective of the study was to elucidate which factors promote the selectivity observed for the case of the addition of an amine into an α,β-unsaturated carbonyl compound, *i.e.* 1,2-addition (imine) *vs* 1,4-addition (enamine). It is well-known that in the presence of a primary amine, enals and enones undergo either 1,2- or 1,4-addition, with or without a dehydrating agent (3 Å MS in this case). However, *in situ* ReactIR monitoring of several examples suggested that the condensation product was kinetically preferred for all enals and the majority of enones. This result was not consistent with the literature where imines were reported as kinetic control products due to the reversibility of the process, *i.e.* by its facile hydrolysis, whilst the conjugated addition corresponds to the thermodynamically controlled product.[115] Moreover, the DFT calculations performed attributed the chemoselectivity to conformational and electronic effects on the electron deficient substrate; kinetic products (imines) are favoured

for s-*trans* conformations of the substrates, and s-*cis* conformations favour thermodynamic products (enamines), as summarised in Scheme 35.



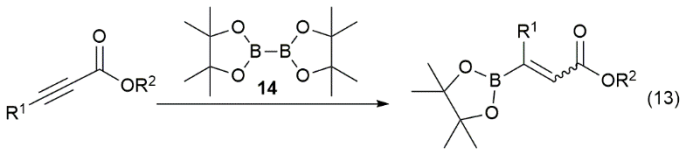
Scheme 35 Influence of the conformational effects in the selectivity obtained for the addition of amine into an α,β-unsaturated system.

1.4.3. α,β-Acetylenic carbonyl compounds: towards vinyl boronates

In order to extend the range of synthetic possibilities, new substrates have been considered, such as α,β-acetylenic carbonyl compounds which might lead to synthetically interesting products including vinyl boronates. Vinyl boron compounds are attractive reagents for organic synthesis because they can be utilised in many transformations, such as cross-coupling reactions,[26,116] widely applied in natural product total synthesis,[26] and other applications due to their facile transformation to a wide range of functional groups.[117,118]

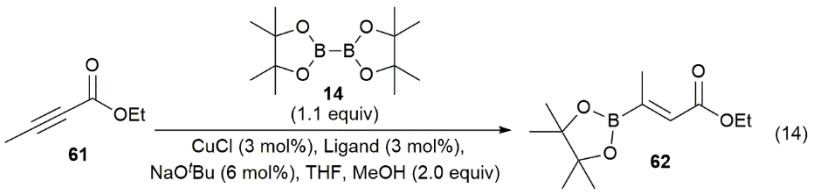
Although β-boryl acrylates can be obtained by hydroborylation of propyolic acid esters, the analogous ketones and aldehydes require a multistep sequence.[119] Hence, a general and efficient alternative methodology was required and the adaptation of the conjugated addition of a boryl moiety (β-borylation reaction) was proposed as a suitable option for this purpose. Therefore, as well as in the analogous case of the α,β-unsaturated carbonyl compounds, the development of β-borylation protocols has aroused much interest, especially for those cases assisted by organometallic catalysis. In particular, copper-catalysed strategies have achieved a significant relevance since the first examples reported in 2000,[47,48] with many methodologies and useful practical applications for the direct synthesis of alkenylboranes in a high regio- and stereo-selectivity.

In addition to these areas of the copper-assisted boryl conjugated additions, the use of acetylenic substrates has also been developed by Yun *et al*. who in 2008 expanded their research [Eqn. (13)] by the application of a previously stablished protocol for α,β-unsaturated carbonyl compounds.[119]



(13)

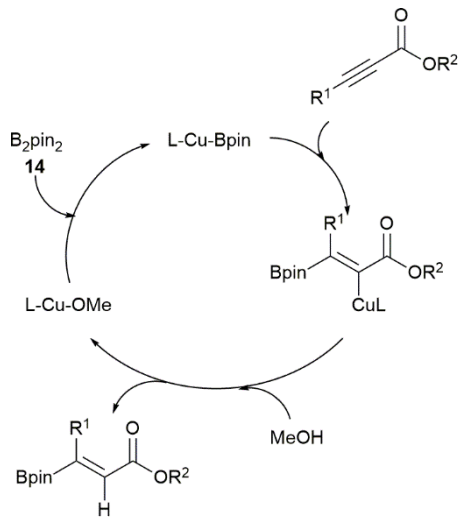
In this work, a preliminary screening of different sets of conditions using ethyl 2-butynoate **61** as model substrate allowed many key aspects of the reaction to be elucidated. In first place, it was observed that the alcohol additive played a crucial role in the catalytic cycle (this was observed also in the case of α,β-unsaturated carbonyl compounds), moreover, it was also observed that the exclusive *syn*-addition product was obtained, *i.e.* (Z)-**62** [Eqn. (14)].



(14)

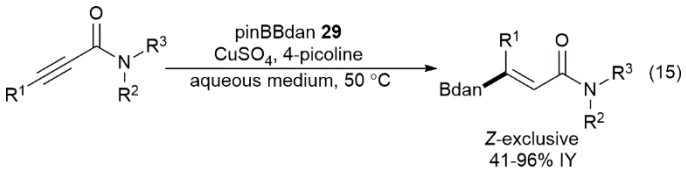
Complementarily, this methodology was tested on a range of α,β-acetylenic esters confirming the high stereo-selectivity with the majority of the cases studied giving the *Z*-isomer (s*yn*-addition) exclusively. Furthermore, it was corroborated that this methodology required an electron withdrawing group (EWG) in the substrate to be effective, *i.e.* with aliphatic substrates such as 1-octyne, boryl addition was not observed. From a mechanistic point of view, this study allowed the elucidation of a plausible catalytic cycle based on the formation of the well-known nucleophilic boryl-copper species, as reported by Miyaura *et al*.[48] Scheme 36 displays the proposed catalytic cycle in which the phosphine-copper-boryl complex adds into the C-C triple bond of the substrate leading into the copper enolate, which through a protonolysis reaction (in the presence of the alcohol additive, MeOH) gives rise to

the protonated product and the active catalyst is regenerated with the copper-alkoxide resulting from the protonolysis step.



Scheme 36 Catalytic cycle proposed for the β-borylation reaction of activated alkynes.

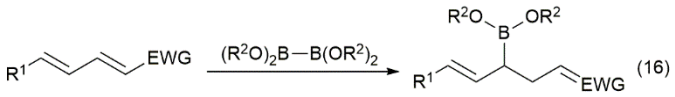
Recent work by Santos and co-workers[52] has reported the development of a novel Cu(II)-catalysed system in aqueous media for the stereoselective synthesis of (*Z*)-β-boryl-α,β-unsaturated esters with yields up to 98%. Moreover, in 2016 this methodology was expanded by its application on a wider range of substrates, including the successful use of primary and secondary amides [Eqn. (15)].[53]



With all these examples, it had been demonstrated that the conjugated addition of a boryl unit into α,β-acetylenic carbonyl compounds provides a useful synthetic approach towards vinyl boronate containing molecules.

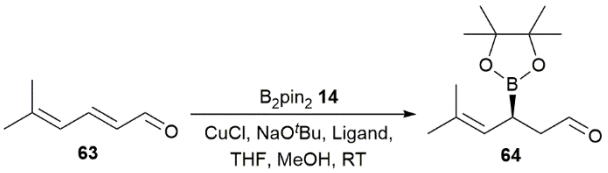
1.4.4. α,β,γ,δ-Unsaturated carbonyl compounds

Although the utility of dienyl substrates as ideal platforms for nucleophile addition has been demonstrated,[120] in comparison with α,β-unsaturated carbonyl compounds, its diene analogues have not been as intensively exploited in boryl additions. It was envisioned that the derivatisation of the resulting organoboranes could lead into interesting building blocks, such as secondary allylic alcohols [Eqn. (16)].[121]



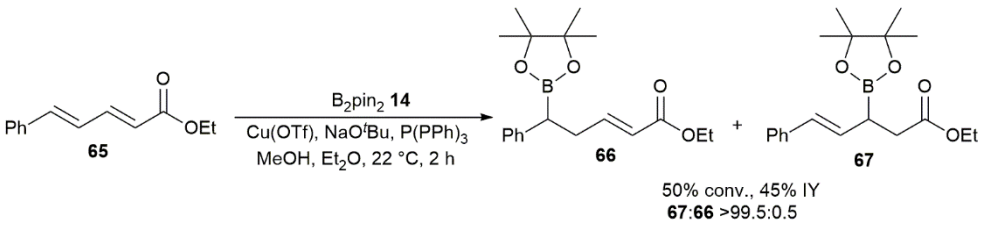
(16)

The main drawback associated with these substrates results from the regioselectivity of the boryl addition, *i.e.* difficulty of control the regioselectivity with 1,6- 1,4- and 1,2-additions all being possible. It was in 2009, when Yun and co-workers, in one of their early papers on the asymmetric copper-catalysed β-borylation of enones, included an interesting example which consisted in an extended version of the α,β-unsaturated ketone.[65] In this case, the β-borylated product **63** was obtained in excellent e.e. and high yield [Eqn. (17)].



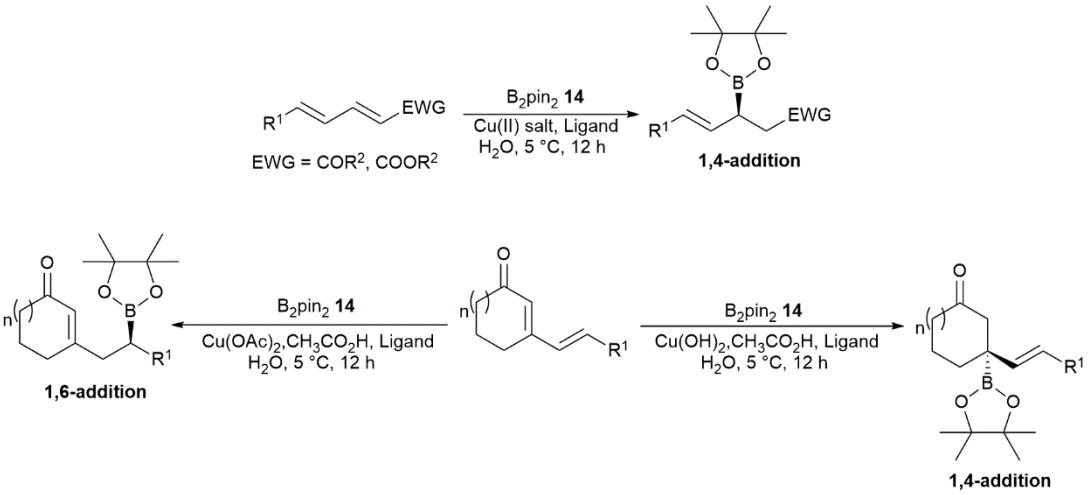
(17))

This example showed that the application of this type of chemistry to such substrates to give conjugate addition boron products was possible, expanding the range of synthetic options provided by this reaction. Based on this, Ibrahem and Córdova carried out further work,[122] confirming the selectivity observed in the first example; *i.e.* that the 1,4-addition **67** predominated over the 1,6-addition **66**, as displayed in Scheme 37.



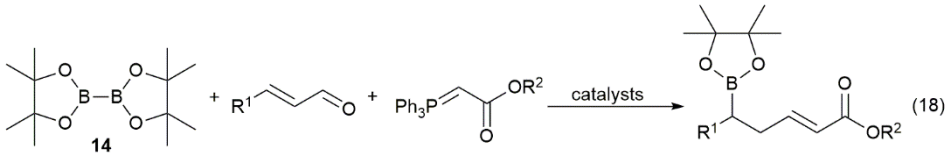
Scheme 37 Example of the conjugate addition of boron into a dienoate.

Soon after this, Kobayashi *et al.*[70] reported an interesting β-borylation of different α,β-unsaturated carbonyl compounds, catalysed by chiral copper complexes in an aqueous medium which was extended to its application on a diene system. As previously reported in the literature, the 1,4-addition product predominated (98:2 ratio). In subsequent work by this group,[123] a series of α,β,γ,δ-unsaturated dienones and dienoesters in the presence of different Cu(II) salts were also studied. Interestingly, it was found that the 1,4-addition product was exclusively obtained independently of the Cu(II) source used in the case of acyclic substrates. Conversely, for the case of cyclic dienones, either 1,4- or 1,6-addition products were obtained, depending on the conditions employed, as summarised in Scheme 38.

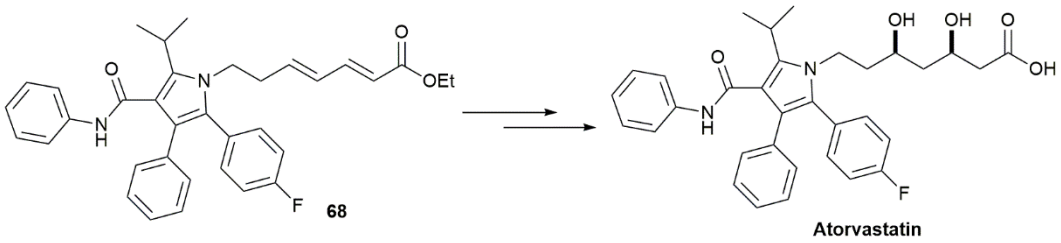


Scheme 38 Addition of B_2pin_2 **14** into a cyclic diene ketone.

The development of a stereo- and enantio-selective methodology was required and, hence, Córdova's group focused their efforts in the synthesis of homoallylboronates *via* a one-pot catalytic asymmetric β-borylation reaction/Wittig reaction sequence [Eqn. (18)]. Achieving good selectivity and yields towards the desired 1,6-addition product using copper-catalysis,[122] as well as an alternative metal-free methodology.[124] This sequence will be discussed further in Section 2.2 in the context of the borane derivatives.



Recently Lam and coworkers[125] reported an efficient enantioselective methodology for the 1,6-borylation of α,β,γ,δ-unsaturated ketones and esters. It has been demonstrated that the reaction can be chemoselective towards the 1,6-position also in the absence of a substituent in C_β, *i.e.* without a group blocking the 1,4-position. It was also observed that for those cases in which a large group was in this position, the preference for the 1,6-addition over the 1,4 decreased, being sensitive to steric hindrance. Additionally, it was demonstrated that from the organoboron compound obtained by this strategy, the product could be a precursor for the synthesis of drugs, for example, for the cholesterol–lowering drug known as atorvastatin (see Scheme 39).



Scheme 39 General approach to the synthesis of lowering-cholesterol drug Atorvastatin from the corresponding dienoate.

1.5. Summary

The study of organoborane chemistry encompasses many research lines with the reason being the presence of a boron atom which provides exceptional chemical features. Among the wide range of applications for which these compounds are suitable, their use as intermediates in asymmetric synthesis is perhaps considered the most valuable tool. Consequently, a great part of research in this area is focused on the preparation of these key compounds, mainly by the addition of boron reagents into C=C bonds.

Regarding boryl addition strategies available for their synthesis, recently a novel strategy consisting of conjugate additions of diboron reagents to electron deficient organic substrates had been developed; the β-boration reaction. The need for the establishment of methodologies that allows the addition of boryl moieties to α,β-unsaturated carbonyl systems occurred due to the fact that it was not possible to carry out this transformation through other methodologies.

Since the first example reported in the latest 1990s, many alternative methodologies have been reported and subsequently improved, involving different types of metal catalysis as well as organocatalytic versions. An enantioselective version has aroused much interest and consequently has been exhaustively explored leading to the development of many catalytic systems, so that the *a priori* envisioned asymmetric potential of the reaction has been demonstrated.

The requirement of a catalytic system is a preliminary activation step of the diborane reagents employed in the reaction, in order to switch its reactivity from an initial electrophilic trivalent boryl unit into a nucleophilic tetravalent unit, and particularly employed on symmetric diboranes and specially B_2pin_2 **14**, and B_2cat_2 **15**. With regard to the substrate where the boryl moiety is added, ketones, esters and amides are the most common types of organic molecules used. In the remarkable case of the analogous α,β-unsaturated aldehydes, these represent a challenge and until

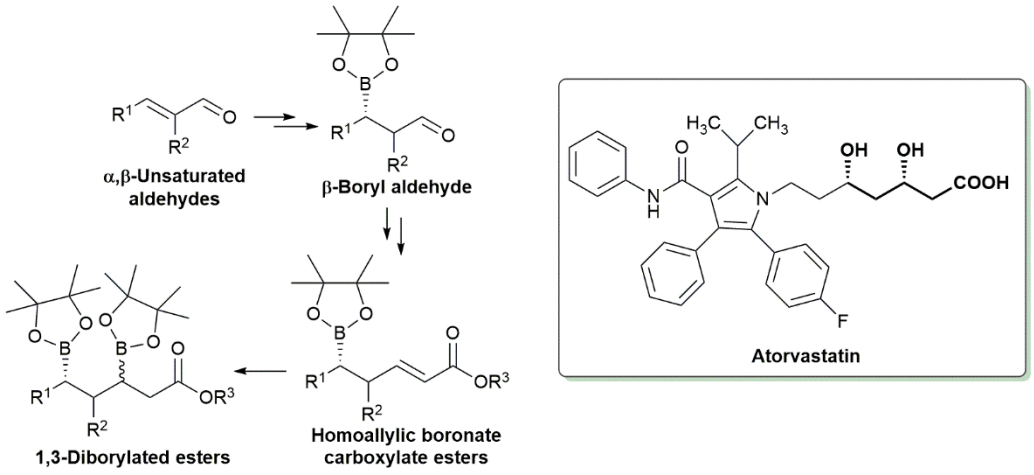
recently have not been well studied due to the chemoselectivity and stability issues. With the aim to solve these drawbacks, in the last five years, methodologies mediated by amine-derived imines have been developed through which the chemoselectivity problem can be avoided, as well as the subsequent derivatisation of the borated carbonylic species. This type of compound can provide an excellent platform for the synthesis of molecules containing more than one functionality in 1,3-position respectively, *e.g.* γ-amino alcohols, γ-diols, homoallylboronates, etc.

Results and discussion

2.0. Research general aim

Establishing new catalytic enantioselective approaches towards chiral molecules is an important goal in synthetic organic chemistry, and organoboranes stand out as an ideal tool for this purpose. Therefore, the development of new methodologies for the synthesis of chiral C-B bond containing compounds is the focus of much research in recent times.

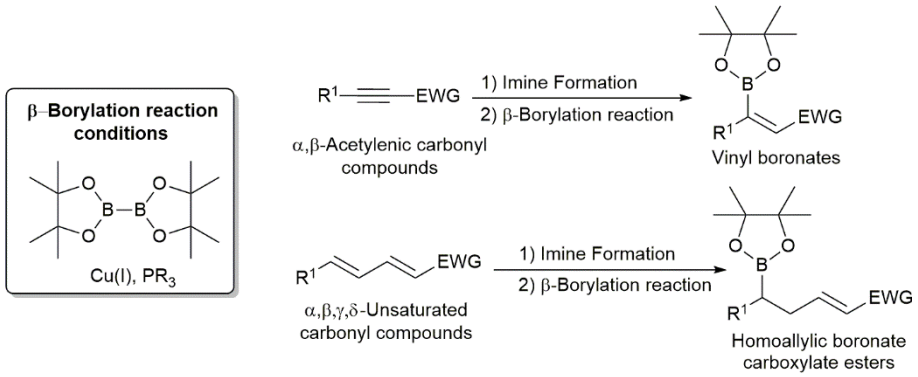
The objective of this project is to study the β-borylation reaction of α,β-unsaturated aldehyde-derived imines, formed *in situ*, *via* a one-pot methodology, as a route to β-boryl aldehydes. Furthermore, these compounds can be derivatised into the corresponding homoallylboronates using an *in situ* imine hydrolysis-Wittig olefination protocol. The resulting homoallylic boronate esters can also provide an opportunity to introduce a second boryl unit in a stereoselective manner yielding versatile diborylated esters, which opens up synthetic possibilities leading to key building blocks, such as chiral 1,3-diols, present in certain pharmaceuticals, *e.g.* Atorvastatin (Scheme 40).



Scheme 40 Stereoselective synthesis of diborylated esters from α,β-unsaturated aldehydes *via* the corresponding homoallylic boronate carboxylate esters.

Additionally, the methodology developed herein was applied on other types of substrates, *i.e.* α,β-acetylenic carbonyl compounds or α,β,γ,δ-unsaturated carbonyl

compounds with the aim of developing alternative routes towards vinyl boronates or homoallylboronates, respectively (Scheme 41).



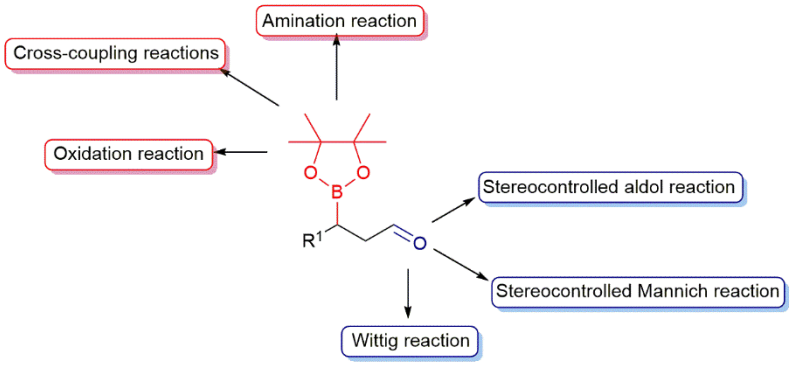
Scheme 41 Novel routes towards vinyl boronates and homoallylic boronate carboxylate esters explored.

2.1. β-Borylation reaction on α,β-unsaturated aldehydes *via* amine-derived imine intermediates

2.1.1. Background

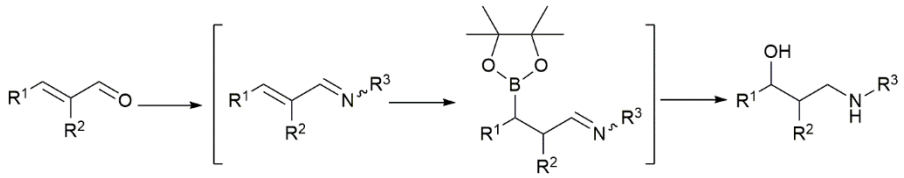
Despite the major success in the area of the β-borylation reactions, the introduction of a boryl unit into α,β-unsaturated aldehydes still represents a substantial challenge because the desired 1,4-boryl addition can be competitive with 1,2-addition.[105] Moreover, current procedures for the catalytic asymmetric synthesis of β-boryl aldehydes suffers from a number of further problems, including variable enantiomeric excesses (generally low to moderate), and the reactions require high catalyst and base loadings to produce even moderate yields.[122]

For all these reasons, the literature regarding the synthesis and isolation of this type of substrate is limited, however, β-boryl aldehydes could provide an ideal platform for the synthesis of many interesting targets due to the wide range of synthetic applications that they provide. Scheme 42 presents a summary of some different synthetic applications of β-boryl aldehydes.



Scheme 42 Synthetic possibilities provided by β-boryl aldehydes.

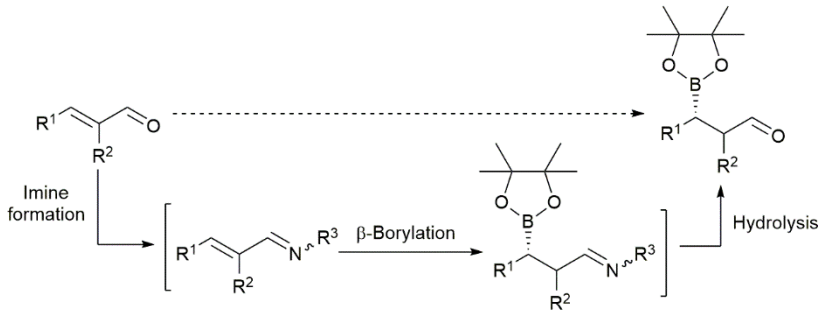
The use of α,β-unsaturated aldimines as substrates was developed by our group as an ideal alternative since one major advantage of this methodology should be that one could potentially overcome the major issue of regiocontrol in the borylation reaction on α,β-unsaturated aldehydes. Indeed, the formation of *N*-sterically hindered α,β-unsaturated aldimines can be used to promote a completely regioselective C_β-boryl-addition, resulting in the formation of β-boryl aldimines which can be readily transformed into γ-amino alcohols[113,126] as previously reported by our group in collaboration with Fernández (Scheme 43).[109,110,112,114]



Scheme 43 Synthesis of γ-amino alcohols from α,β-unsaturated aldehydes *via* the corresponding aldimines.

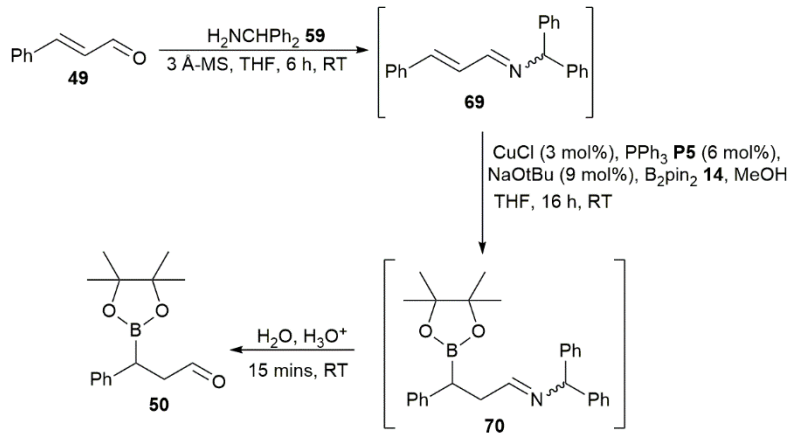
2.1.2. Developing a Cu(I)-phosphine mediated methodology for the β-borylation reaction of α,β-unsaturated aldehydes *via* amine-derived imine intermediates

The β-borylation reaction of α,β-unsaturated aldehyde-derived imines, formed *in situ*, has been studied using a one-pot methodology as a route towards β-boryl aldehydes, as shown in Scheme 44.



Scheme 44 β-Borylation reaction on *in situ* generated α,β-unsaturated aldimines leading into β-boryl aldehydes.

In order to explore the conjugate addition of B_2pin_2 **14** to enals *via* the corresponding aldimine, cinnamaldehyde **49** was chosen as the model substrate for developing optimal reaction conditions for the overall process as outlined in Scheme 45.



Scheme 45 Synthetic pathway proposed for the synthesis of β-boryl aldehyde **50** from cinnamaldehyde **49**.

Hence, after imine formation (to give **69**), catalytic borylation (*via* **70**) and hydrolysis using aqueous HCl, compound **50** was obtained in a crude form with high mass recovery and there was a notable absence of any starting aldehyde **49**. However, after attempts to purify the crude β-boryl aldehyde **50**, mixtures of the desired product **50** along with the starting aldehyde **49** were obtained (up to 17% of α,β-unsaturated aldehyde **49**) , graphically demonstrating the instability of β-boryl aldehydes of this type and their facile capability to re-eliminate the boryl unit, leading back to the starting unsaturated aldehyde. Figure 15 presents a comparison between the ^{1}H NMR spectra of the reaction crude product **50** and the mixture of **49** and its β-borylated analogous **50** resulting after purification, respectively.

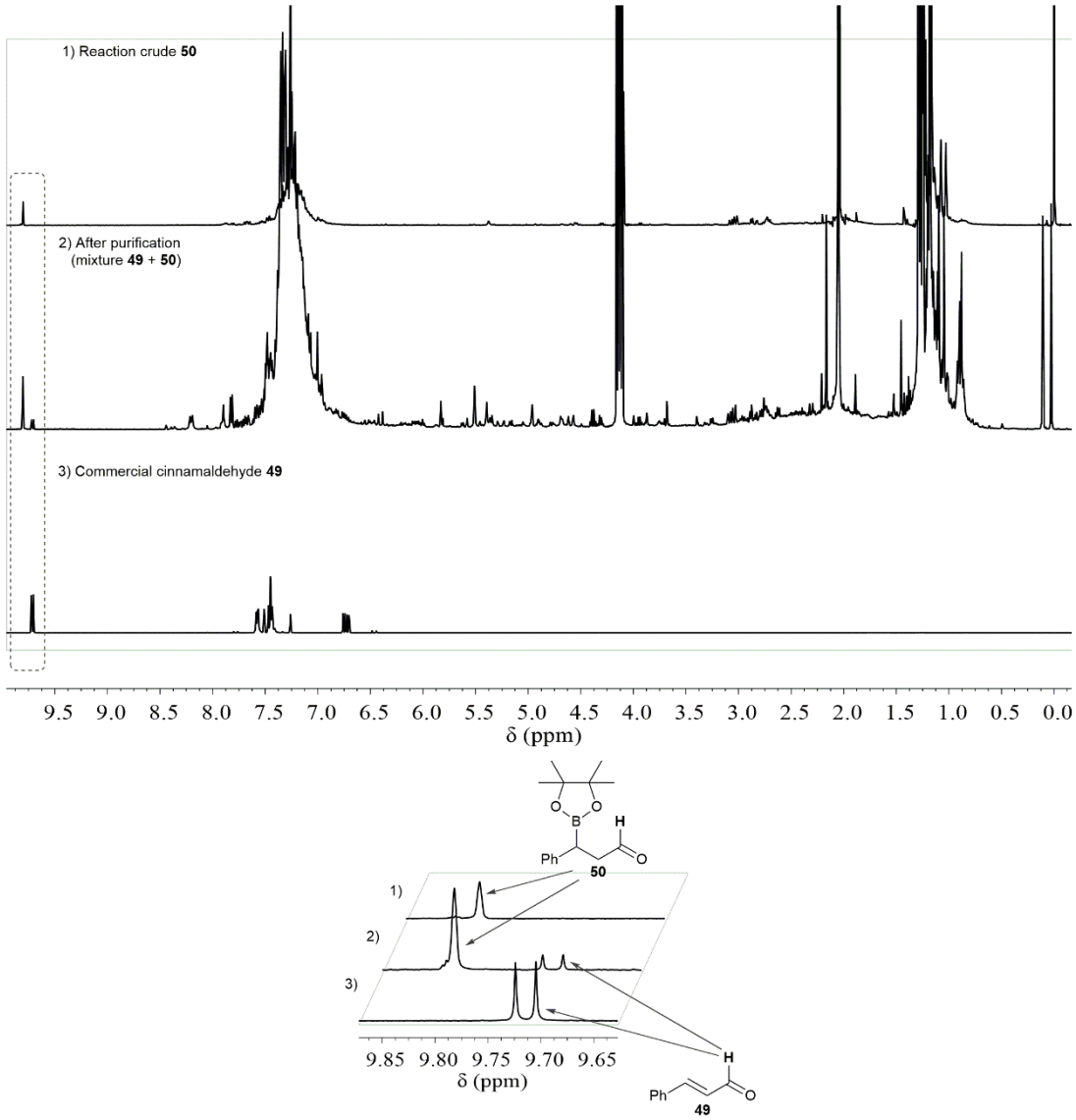
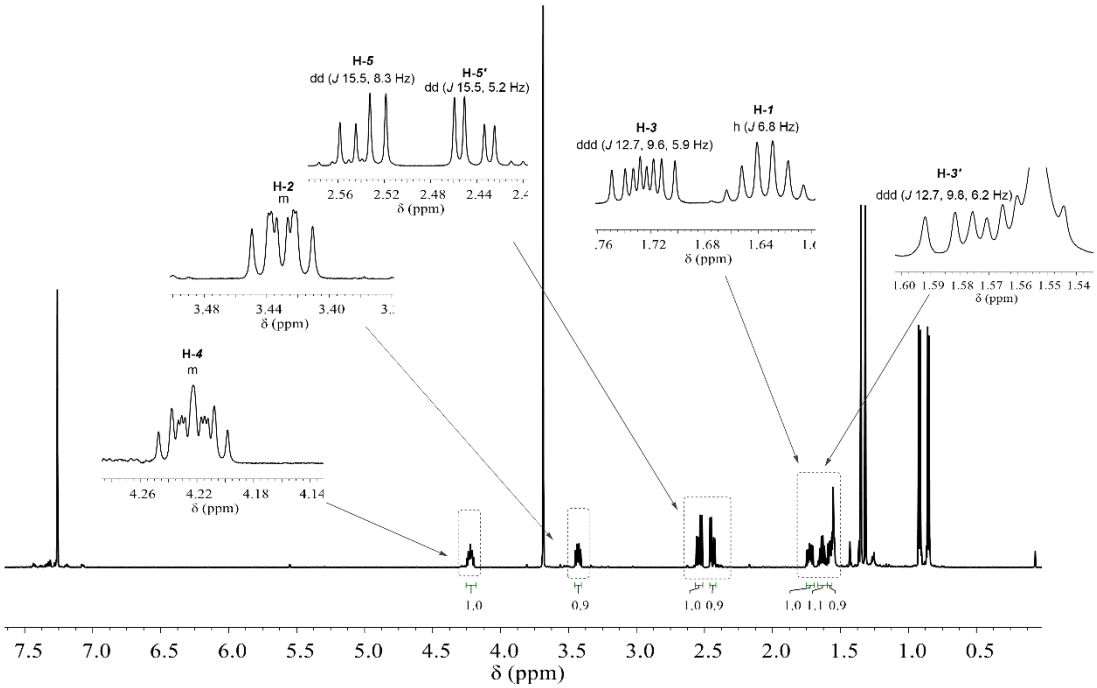


Figure 15 ^{1}H NMR spectrum corresponding to: 1) hydrolysis reaction crude mixture of **50**; 2) mixture of **49** and **50** resulting after the purification; and 3) starting α,β-unsaturated aldehyde **49**.

In order to examine possible means by which to avoid the instability problem associated with **50** upon purification, the sequence shown in Scheme 45 was repeated with *p*-methoxycinnamaldehyde **71** as starting material to see if the electron donating group on the benzene might reduce the instability of the benzylic boryl product, *i.e.* **72**. However, the β-boryl aldehyde **72** was again obtained in high mass recovery in crude form, yet during the purification process using either alumina or silica gel chromatography, only starting α,β-

unsaturated aldehyde **71** was obtained. Additionally, attempting to apply this methodology to a non-benzylic, and more substituted system such as tiglic aldehyde **73** surprisingly prevented the borylation reaction completely under the conditions outlined in Scheme 45. The use of a more reactive catalytic system (*i.e.* $CuCl/PBu_3$ **P3** as described in previous work[112]) gave the target β-boryl aldehyde **74** (starting from **73**). However, it was not possible to isolate the product in a pure form without decomposition back to the starting tiglic aldehyde **73**. Scheme 46 displays a summary of the different substrates examined.



Scheme 46 Application of the imine formation/β-borylation/hydrolysis sequence to *p*-methoxycinnamaldehyde **71** and tiglic aldehyde **73.** [a]Conversion calculated in comparison to the starting α,β-unsaturated aldehydes **71** or **73**.

These results clearly corroborated literature reports that β-boryl aldehydes are potentially unstable compared to β-boryl ketones and esters.[44,45] However, in exceptional circumstances, β-boryl aldehydes containing highly hindered boronate esters have been isolated.[127-129]

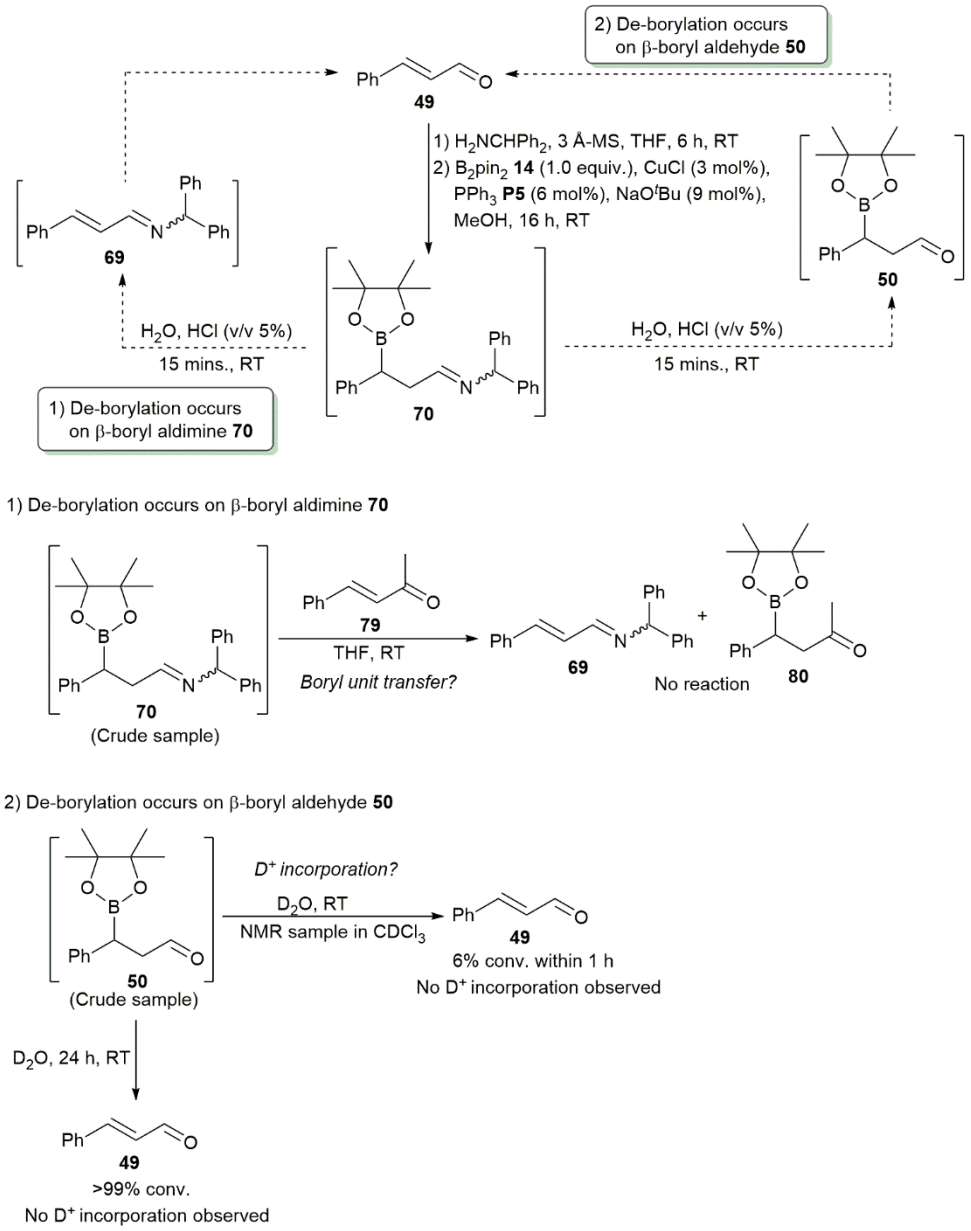
At present, the mechanism by which this de-borylation occurs is not clear (Section 2.1.3 presents different mechanistic studies performed in order to clarify this process); however, and more importantly, this result highlighted that this approach was incapable of providing clean β-boryl aldehyde on which to perform further studies.

2.1.3. Mechanistic studies: understanding the de-borylation process

As consequence of the study of the copper(I)-phosphine catalysed β-borylation reaction and due to the finding of the instability issue that resulted from this, it was necessary to obtain a better understanding of the de-borylation process in order to find a suitable solution for its prevention. With that aim, studies were performed on the β-boryl cinnamaldehyde-derivative **50** as described below:

- Loss of boryl moiety takes place on the β-boryl aldimine **70** or on the β-boryl aldehyde **50**?
- ^{1}H NMR study on the β-boryl cinnamaldehyde-derivative **50** in the presence of D_2O
- Effect of silica gel on the de-borylation process

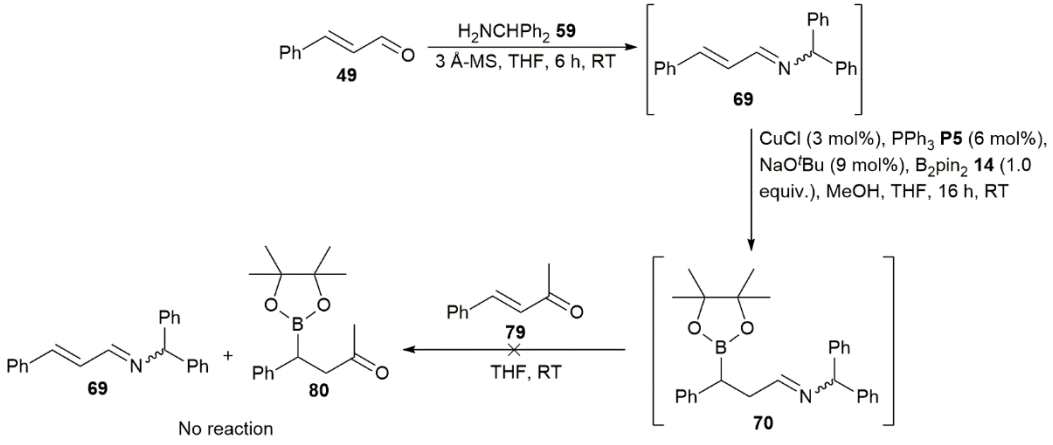
Scheme 47 displays a general overview of the experiments conforming the mechanistic study carried out in order to clarify the de-borylation process observed during the synthesis of β-boryl aldehydes.



Scheme 47 Mechanistic studies carried out for a better understanding of the de-borylation process.

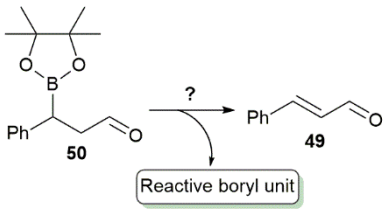
Previous observations indicated the occurrence of an elimination reaction of the boryl moiety, particularly during column purification and perhaps due to the known instability reported for this type of compounds.[121] Although it was likely that the undesired reaction took place on compound **50**, it was considered necessary to confirm, in the first place, that it was actually the aldehyde that was unstable, and not the β-boryl aldimine **70** (Option 1, Scheme 47).

A test was carried out on the borylated imine intermediate consisting of the addition of a stoichiometric amount of benzylideneacetone **79** to the reaction mixture containing the intermediate boryl aldimine **70** to see if a boryl transfer occurred between these two species leading to the borylated ketone **80**, as displayed in Scheme 48.



Scheme 48 Test reactions carried out to determine if boryl loss takes place on β-boryl aldimine **70**.

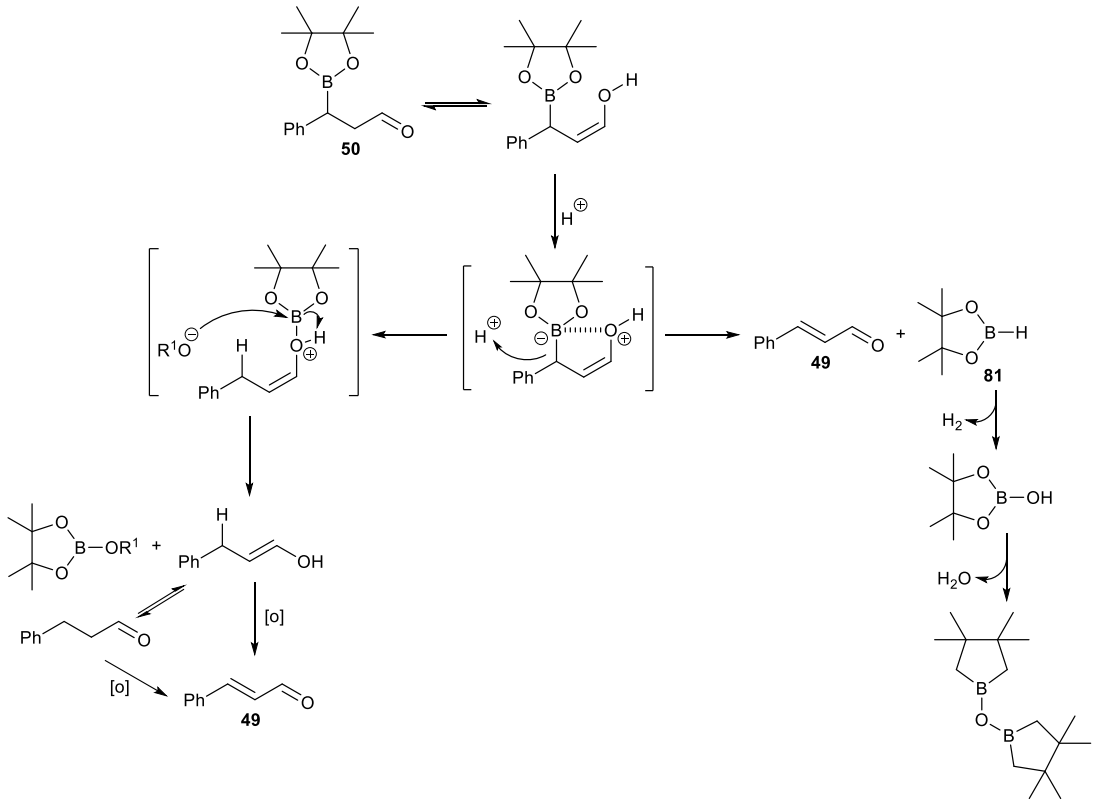
The reaction mixture was analysed by ^{1}H NMR after 4, 7 and 24 h. No boryl transfer occurred to give compound **80**, which indicated that the borylated aldimine **70** does not eliminate a reactive boryl unit that can re-add to another enone substrate. Once it was then confirmed that the boron loss took place on the β-boryl aldehyde **50**, the study of the loss of boron from a mechanistic point of view was focused on this compound (Scheme 49).



Scheme 49 De-borylation process on the borylated cinnamaldehyde derivative **50**.

A plausible suggested mechanism through which this undesired process could take place could be due the aldehyde-enol tautomerisation equilibrium on the β-boryl aldehyde **50**.

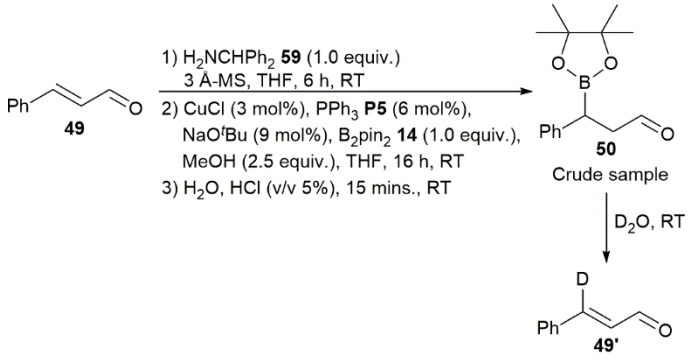
Based on this, it was envisioned that in the case of the β-boryl enolate form an intramolecular B-O interaction could occur and under acidic reaction conditions (HCl used for the hydrolysis step or silica gel during the purification process), a de-borylative process would be promoted *via* an oxidation reaction, although this oxidative process seems unlikely. Another possibility would be that from the same intermediate, the protodeborylation process lead into the starting α,β-unsaturated aldehyde **49** along with pinacol boronate **81**, which in turn would lead into the B-O-B compound through the corresponding B-OH compound, as summarised in Scheme 50).



Scheme 50 Proposed mechanism for the de-borylation of β-boryl aldehyde **50** under acidic reaction conditions.

With a view to further understanding the mechanism through which the boryl elimination took place, a sample of crude **50** was treated with D_2O to see if water was sufficient to trigger boryl elimination (Option 2, Scheme 47). The study was carried out through the

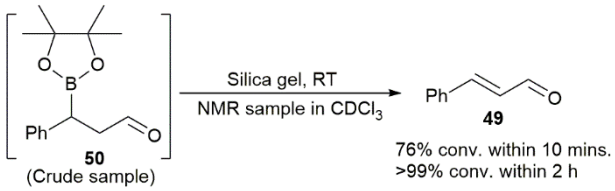
observation of the evolution of a sample of **50** over time by ^{1}H NMR spectroscopy, as displayed in Scheme 51.



Scheme 51 D_2O test reaction carried out on a crude sample of β-boryl aldehyde **50.**

The use of deuterium oxide would allow the identification of the position at which protonation occurred, confirming the mechanism suggested (Scheme 50). From this study emerged the conclusion that in the presence of water, cinnamaldehyde **49** was obtained and its proportion with respect the β-boryl aldehyde **50** increased with time, *i.e.* up to 6% of **49** detected within 1 h, achieving complete conversion when the mixture was stirred overnight in an additional test, confirming the high instability of this type of compound. However, no deuterated cinnamaldehyde **49** was observed in the reaction mixture, *i.e.* no incorporation of deuterium. These observations suggested that the mechanism by which the β-borylation reaction is reversed does not involve enolate intermediates which would be expected to deuterate, and thus disproving this initial hypothesis regarding the de-borylation mechanism.

Moreover, it was also interesting to test the effect silica gel had on this undesired side-process. For that reason, another crude sample of **50** was treated with silica gel and the resulting mixture was analysed by ^{1}H NMR spectroscopy, as outlined in Scheme 52. After 10 minutes of the addition of silica gel, 76% conversion towards cinnamaldehyde **49** was observed, *i.e.* de-borylated product. After 2 h, this proportion increased up to >99%. Therefore, it was concluded that the major boryl unit loss took place upon exposure to silica gel although it was not clear what mechanism was operating.

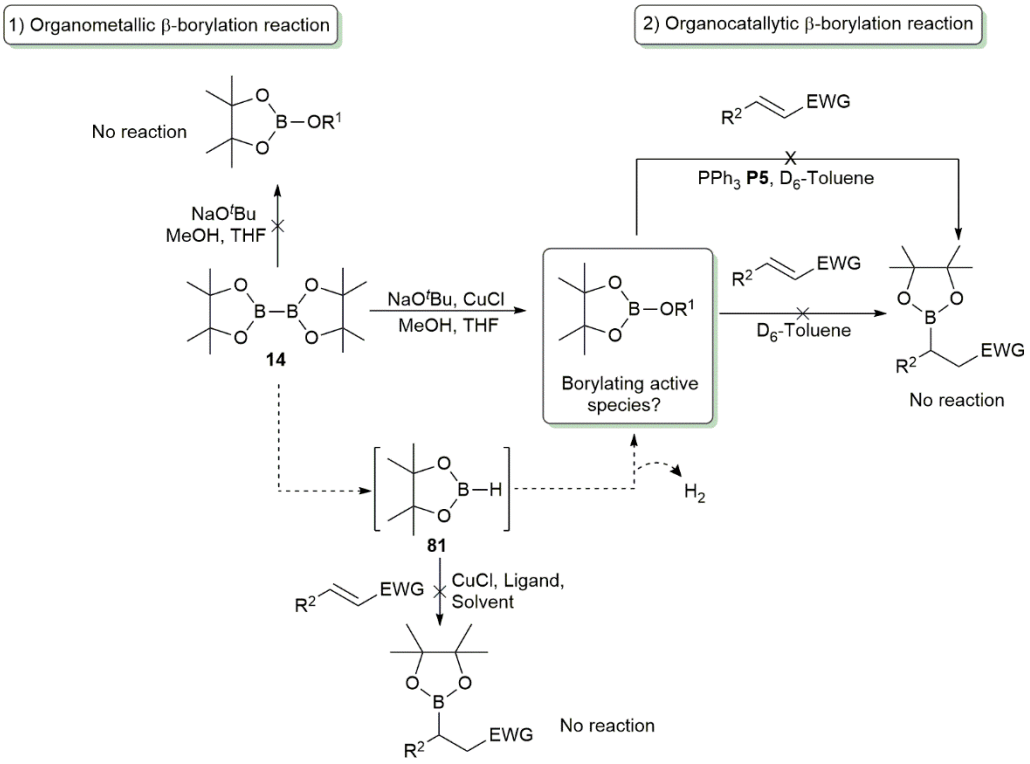


Scheme 52 ^{1}H NMR spectroscopy experiment carried out on β-boryl aldehyde **50** in order to evaluate the effect of the silica gel on the de-borylation process.

In order to achieve a better understanding of this whole process, it was necessary to carry out mechanistic studies regarding the conjugate addition of the boryl unit. Specifically, the activation of the diborane reagent (*i.e.* generation of the nucleophilic boryl unit), which confirms a key aspect of the β-borylation reaction and had raised major questions regarding its mechanistic details. Herein, are reported two main studies regarding mechanistic insights of the catalytic activation of B_2pin_2 **14** from both organometallic and organocatalytic points of view:

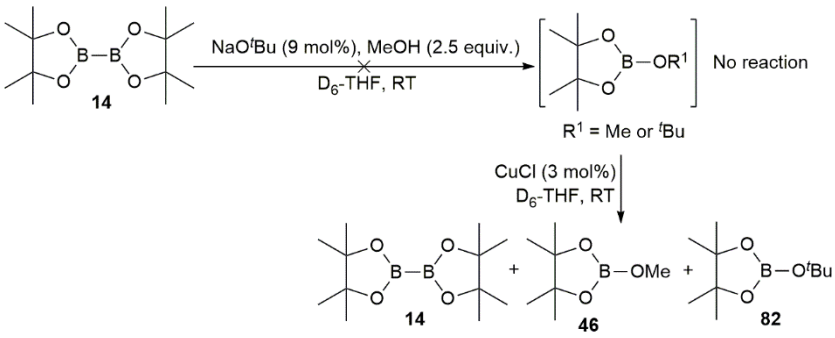
- Species involved in the catalytic cycle of the organometallic catalysed β-borylation on α,β-unsaturated aldehydes?
- Organocatalytic β-borylation reaction: role of the phosphine ligands in the catalytic cycle?

Scheme 53 displays a general overview of the different studies carried out herein.



Scheme 53 Mechanistic studies carried out for the clarification of the borylating active species for: 1) organometallic β-borylation reaction; and 2) organocatalytic β-borylation reaction.

Initially, the formation of the nucleophilic boryl moiety was analysed by a ^{11}B NMR spectroscopy study consisting of the successive addition of different key reagents (Scheme 54).



Scheme 54 Reaction examined by ^{11}B NMR spectroscopy for the study regarding the formation of the nucleophilic boryl species.

Firstly, the diborane B_2pin_2 **14** (0.25 mmol), the base NaO^tBu (9 mol%) and the alcohol MeOH (2.5 equiv.) were mixed in D_8-THF. The ^{11}B NMR spectrum showed one signal at δ 30.7 ppm corresponding to the diborane reagent **14**. Subsequently, a catalytic amount of CuCl was added and the mixture was stirred for 10 minutes, after this time the ^{11}B NMR spectrum showed three signals: δ 30.7 ppm; 22.1 ppm (5% relative to B_2pin_2 **14**); and 18.5 ppm (2% relative to B_2pin_2 **14**) which literally indicates the formation of alkoxide-boryl complexes,[103] along with remaining diborane **14**. After stirring the reaction for 2 h, the reaction mixture was analysed again. This time the diborane **14** was completely consumed (no signal at δ 30.7 ppm) and at the same time, that the signal attributed to compound **46** increased considerably (from 10% to 44%). Interestingly, it was observed that instead of one signal at δ 18.5 ppm, there were two overlapping peaks at δ 19.1 and 18.5 ppm (12% and 11% relative to the BpinOMe **46**, respectively). The reaction mixture was analysed again after 4 h, when no further differences in the composition of the mixture were observed in comparison to that observed after 2 h. However, when the reaction was stirred for a further 20 h, the peaks at δ 19.2 ppm showed a small overlapping peak (δ 19.8 ppm) and the intensity of the peak at 18.5 ppm had decreased, *i.e.* from 10% to 4%, respectively, and due to BpinOMe **46**. Figure 16 summarises the different results obtained for the ^{11}B NMR spectrum from this study.

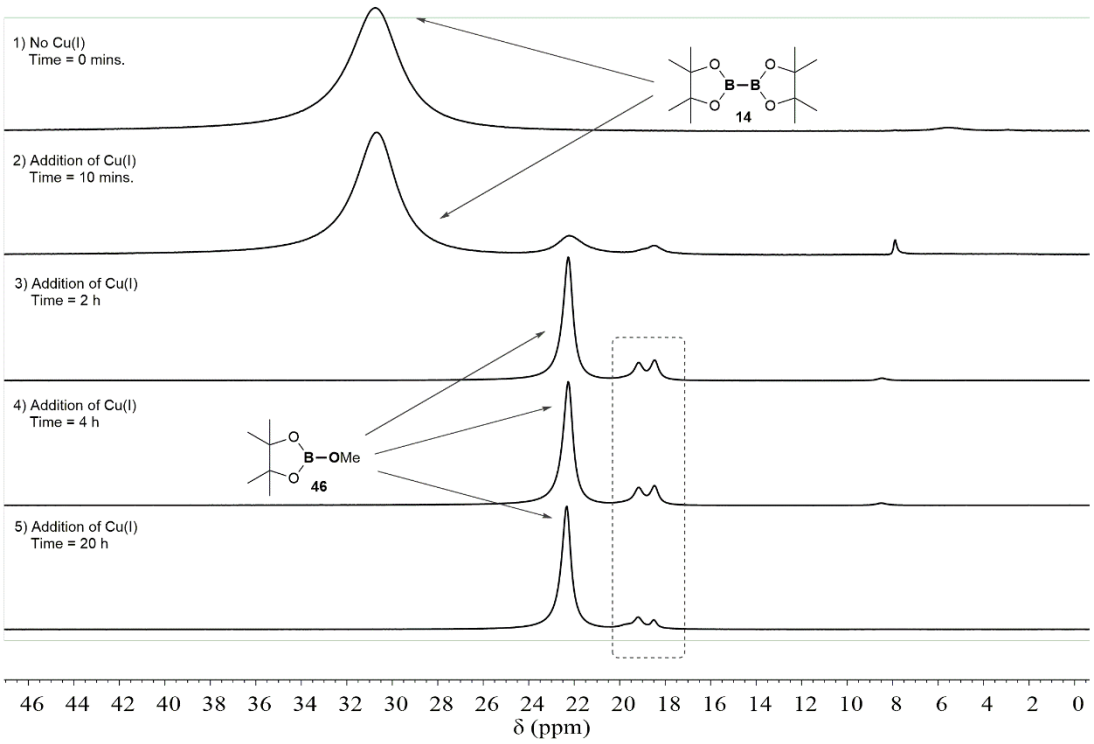
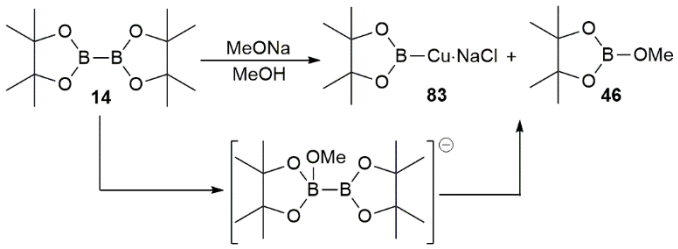


Figure 16 Evolution of the ^{11}B NMR spectrum along time obtained for the study of the formation of boryl species for a model system.

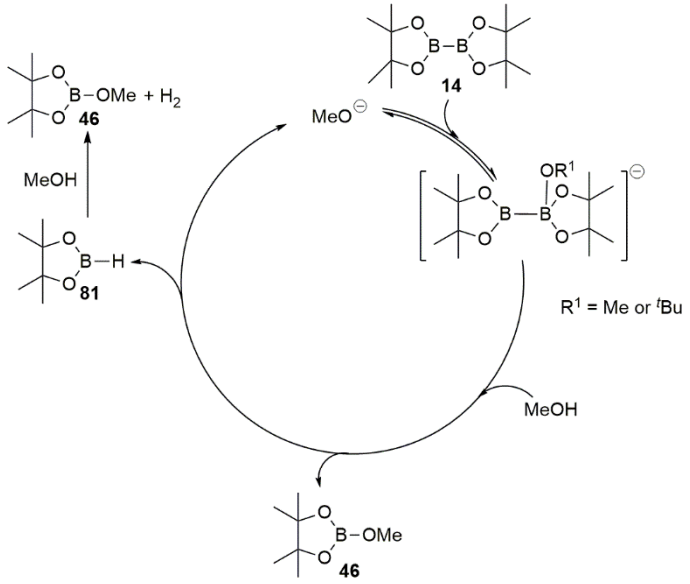
With these results in hand, the formation of alkoxide-boryl species was confirmed in the presence of the copper catalyst, as suggested by Miyaura and co-workers[48] (see Scheme 55).



Scheme 55 Formation of the nucleophilic boryl-copper moiety from B_2pin_2 **14** in the presence of CuCl and NaO^{t}Bu in MeOH.

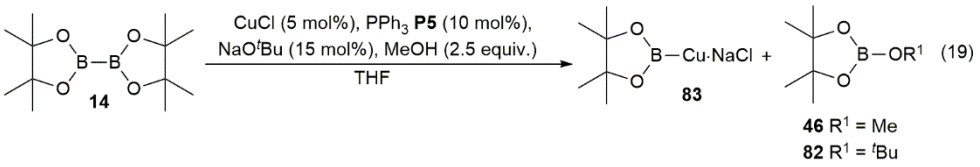
Another aspect that aroused much interest in this procedure was the role of the protonating agent, *i.e.* the alcohol additive. The fact that an exothermic reaction takes place

when the MeOH is added into the reaction mixture is particularly noteworthy. Based on these observations, Scheme 56 displays a plausible catalytic cycle for the activation of the diborane reagent in the presence of stoichiometric base, and providing a borane species (B-H) *in situ*. However, the actual catalytic reaction was sub-stoichiometric.



Scheme 56 Mechanism proposed for the activation of the B_2pin_2 **14**.

Hence, a model reaction was carried out using diborane **14**, phosphine ligand **P5**, copper(I) salt, base and the alcohol [Eqn. (19)].



The reaction was monitored by ReactIR, following the temperature change during the reaction as well as the loss of **14,** along with the signal that was attributed to the R^1O-Bpin product. Figure 17 shows the graphical output obtained from these ReactIR experiments.

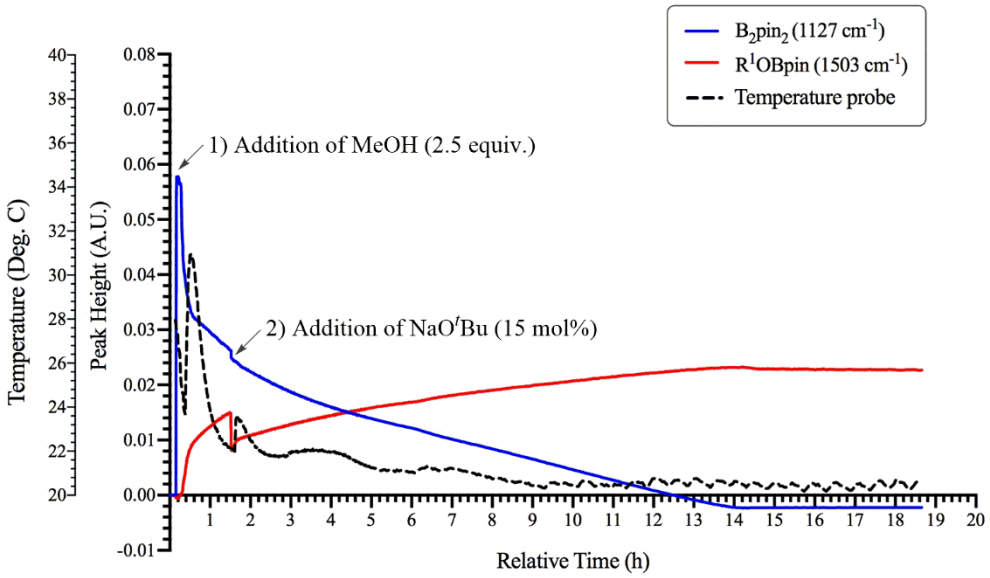


Figure 17 Graphical output obtained from the ReactIR of the monitoring of the formation of boryl-alkoxide species.

When MeOH was added, the amount of B_2pin_2 **14** decreased considerably and at the same time, the temperature increased. After 1.5 hours of reaction, an additional 15 mol% of NaO^tBu was added, and another increase in temperature was observed. The reaction reached completion in less than 14 h and the ^{11}B NMR spectrum showed that alkoxy-boryl species (BpinB-OR^1, R^1= Me or ^{t}Bu) were quantitatively formed, *i.e.* observed as a single peak at δ 22 ppm.

Although this study confirmed that alkoxide-boron compounds are formed, it was not possible to determine if it is the base (NaO^tBu) or the alcohol additive (MeOH) that formed the alkoxyde-boron compound. The data from this study (Figure 17) suggests the formation of other boron-containing species, most likely the alkoxide-boryl species, *i.e.* BpinB-OMe and BpinB-O^tBu, since a decrease of the intensity of the signal associated to the diborane reagent **14** was observed when MeOH (point 1, Figure 17) and additional base (point 2, Figure 17) were added. However, it was observed that the consumption of the diborane **14** did not take place at the same rate; *i.e.* when MeOH was added (2.5 equiv.) the decrease was in greater

proportion in comparison to when NaO^{t}Bu (15 mol%) was added. This difference could be associated to the stoichiometry in which these reagents were added (2.5 equiv. *vs.* 15 mol%). This result correlates with those observed in a previous study regarding the evolution of the boron-containing species during this process (see pages 80 and 81) in which case it was observed that the corresponding Bpin-OMe was obtained in a higher proportion than the analogous Bpin-O^{t}Bu. Interestingly, in both cases, along with the increase of the temperature, an effervescence was also observed, which indicates the potential generation of H_2 which in turn suggests the formation of the borane **81** (see Scheme 56).

Therefore, in order to clarify this aspect, the experiment was repeated but in this new attempt, the composition of the system was modified as follows: MeOH was added to a solution of B_2pin_2 **14** in THF. No reaction was observed after 3 h stirring the mixture. Hence, NaO^{t}Bu was sequentially added (point 1, figure 18), whereupon rapid loss of the B_2pin_2 **14** was observed along with an increase of the temperature, as shown in Figure 18.

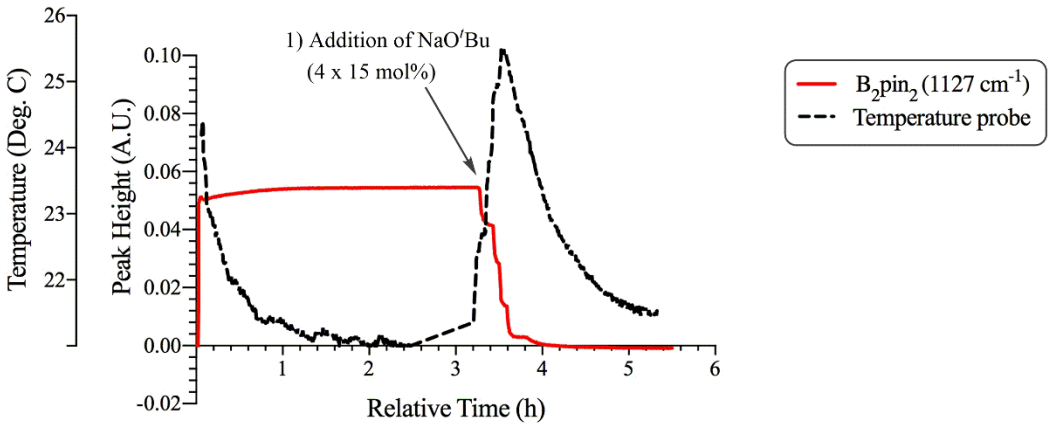
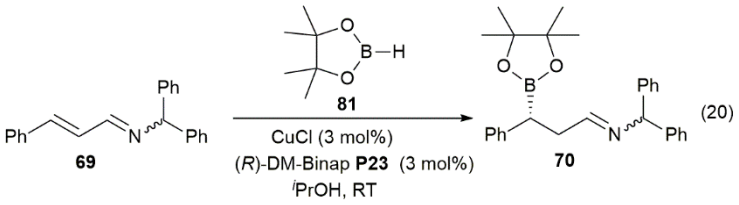


Figure 18 Graphical output obtained from the ReactIR for the sequentially addition of NaO^{t}Bu.

Interestingly, the ^{11}B NMR spectrum of this crude reaction mixture showed the presence of several different peaks at δ 31, 22, 5 and 1 ppm, which correspond to B_2pin_2 **14**, alkoxide-boron complex and boron-ate complexes (R^1 = Me and R^1 = ^{t}Bu), respectively. This

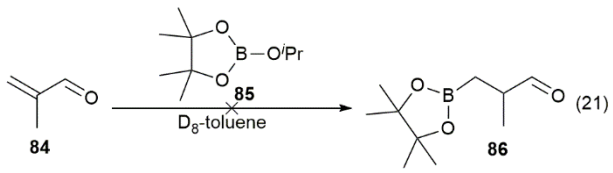
increase in temperature, along with the effervescence observed, suggests that indeed, a borane (B-H) (*i.e.* pinacolborane **81**) could be formed *in situ*. This would then react slowly with more MeOH (excess in the mixture) to give Bpin-OMe and H_2, and hence, the observation of effervescence. These observations suggest that the resulting borane would in fact be pinacolborane **81**, which might then borylate the electron deficient substrate. Although pinacolborane **81** has been widely used in hydroborylations,[130-131] it was envisioned that in the presence of the rest of the reagents, it could also give rise to the nucleophilic boron complexes required for the β-borylation reaction to result. Therefore, a borylation model reaction was carried out using pinacolborane **81** instead of B_2pin_2 **14** [Eqn. (20)]. This consisted of the *in situ* generation of the α,β-unsaturated aldimine derived from cinnamaldehyde **69** and its subsequent β-borylation reaction in ^{i}PrOH as solvent. Interestingly, when the solution containing **69** was added to the borylation reagents mixture, effervescence was observed. After 30 minutes, the ^{1}H NMR spectrum did not show borylation of the substrate, however, the ^{11}B NMR spectrum showed a signal at δ 22.5 ppm corresponding to the alkoxyde-boron complex, suggesting the expected alcohol reaction of pinacolborane **81** to give Bpin-OMe **46** and H_2, but more importantly, showing that no active borylating species were being generated.



Moreover, after a further 3 h of reaction, no evidence of borylation of the substrate was observed. The ^{11}B NMR spectrum showed only the peak previously observed, split as two peaks, indicating the generation of novel types of boron-ate complexes. Although the initial hypothesis regarding the generation of the borane intermediate was confirmed, the experiments carried out did not provide enough evidence to postulate an alternative mechanism for this transformation under these reaction conditions.

Following the discussion regarding the species that provides the nucleophilic boryl unit (proposed to be compound **46**), two NMR experiments were carried out in order to examine the role played by the alkoxide-boryl species in the absence of metal. In this case, the role of the phosphine ligands might be highlighted in the metal-free version of the conjugated addition of boron, since it is well-known that these ligands can catalyse this process, with many examples to corroborate this fact.[47,57,58]

With that purpose, a model reaction was carried out consisting of methacrolein **84** as electron deficient substrate, isopropyl pinacol borate **85** as borylating agent and PPh_3 **P5**. In the first place, an equimolar mixture of **84** and **85** was dissolved in D_8-toluene [Eqn. (21)]. The reaction mixture was analysed by ^{1}H, ^{11}B and ^{13}C NMR spectroscopy, with no difference being observed in comparison to the respective spectra of each of the components of the mixture. It was concluded that no reaction took place in the absence of the phosphine.



Hence, after 24 h, **P5** was added to the mixture (1:1:1) but as observed previously, NMR spectra did not show any shift in the signals, which would indicate the occurrence of some interaction between these compounds. A second reaction consisted of an equimolar mixture of the three components (*i.e.* **84**, **85** and **P5**). As in the previous case, no shift in the ^{1}H, ^{11}B, ^{13}C or ^{31}P NMR signals was observed, and hence, no interaction could be confirmed by this type of phosphine mediated reaction.

Although this study did not provide any evidence that could clarify the role of the phosphine ligands in the organocatalytic β-borylation reaction, these results indicated that the alkoxide-boryl compound was not the active borylating agent, *i.e.* in the absence of the other components of the borylation mixture such as diborane reagent, alcohol and base the β-borylation reaction did not take place. More exhaustive studies should be performed regarding this transformation in order to obtain evidence that might help to understand it further.

2.1.4. Instability of the β-boryl aldehydes: further derivatisation required

Initial studies showed that β-boryl aldehydes readily showed loss of the boryl unit, especially during the purification process. With these results in hand, the instability of these compounds in comparison with ketones or esters, was confirmed. In order to circumvent their instability, the prolonged presence of the aldehyde functionality needed to be avoided, so that further derivatisation into more stable and more easily handleable compounds could be achieved.

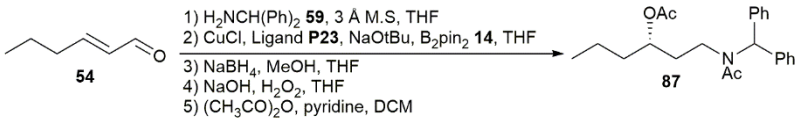
Therefore, alternative solutions were examined for the synthesis of different potential derivatives, to enable:

- Extension of previous work based on the exploration of β-boryl aldehydes as a platform for the synthesis of γ-amino alcohols.
- Exploration of the synthesis of γ-diols from β-boryl aldehydes.
- Evaluation of the deprotection of the β-boryl aldimine followed by the formation of the corresponding β-boryl acetal.

In the first place, an extension of a study based on the catalytic synthesis of γ-amino alcohols from α,β-unsaturated aldehydes *via* the corresponding amine-derived imine was examined. This consisted of an asymmetric approach over a four step, one-pot methodology, as established in previous work (see work developed by C. Solé and A. D. J. Calow).[108-110,112,113,126] The main objective was to optimise the reaction conditions for aldehyde substrates that did not show good e.e.s previously (*i.e*. 2-hexenal **54**, 87% e.e. and 59% IY)[113] and then apply the products for further derivatisations and synthetic applications.

As reported by Yun and co-workers in 2006,[49] the presence of an alcohol additive is key for an efficient borylation reaction. Hence, the effect that the protonating agent could have on the e.e. was analysed by the evaluation of a range of structurally different alcohols, as reported in Table 6.

Table 6 Study of the effect of the alcohol additive in the enantioselective β-borylation reaction of 2-hexenal **54**.



Entry	Alcohol	pKa	Conv. (%)[a]	IY(%)[b]	e.e. (%)[c]
1	MeOH	15.5	91	9	86 (*R*)
2	^{i}PrOH	16.5	99	8	89 (*R*)
3	^{t}BuOH	17	96	14	85 (*R*)
4	Phenol	9.95	97	18	82 (*R*)

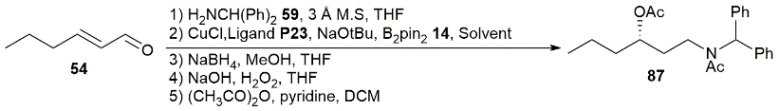
Reaction conditions: 1) 2-hexenal **54**:benzhydylamine **59** (1:1) was stirred in THF and 3 Å M.S. for 3h at RT. 2) An aliquot of *in situ* formed imine was transferred to a Schlenk-tube (under argon) containing CuCl (3mol%), (*R*)-DM-Binap **P23**, NaO^{t}Bu (9 mol%), B_2pin_2 **14** (1.1 equiv.). After 5 min alcohol (2.5 equiv.) was added to the solution and the reaction was stirred foir 16 h at RT. 3) $NaBH_4$ was added, followed by the drop-wise addition of MeOH. The mixture was stirred for 3h at RT, followed by the removal of solvent under reduced pressure. 4) THF was added to the resulting residue, followed by NaOH (w/v 20%) and H_2O_2 (w/v 35%), and the solution was heated to reflux for 1 h. 5) The resulting white solid was dissolved in DCM and $(CH_3CO)_2O$ and pyridine were added. The mixture was stirred for 16 h at RT. [a]Determined by ^{1}H NMR spectroscopy on a sample of pure amino alcohol before acetylation by comparison of the ^{1}H signal corresponding to the starting aldehyde **54** and the analogous imine derivative. [b]Determined on the N/O-diacetate derivative **87**. [c]Determined by HPLC on the N/O-diacetate derivative **87**.

It was envisioned that both the pKa and the steric hindrance of the alcohol could have an impact on the e.e. observed. Although the e.e.s provided by the different alcohols tested did not differ significantly (within ± 1% error), there was a small but direct correlation between the acidity of the alcohol and the e.e. The alcohols with the lowest pKa value, *i.e.* alcohols reported in entries 3 and 4, Table 6 (the more acidic) gave the lowest e.e.s, while the alcohols with higher pKas gave higher e.e.s, although the differences were not major. Regarding the possible effect of the structure of the alcohol, it was observed that although ^{t}BuOH has the highest pKa, it is also more sterically hindered than ^{i}PrOH, and therefore,

providing slightly lower e.e. Hence, it was concluded that the most appropriate alcohol for this purpose was in fact ^{i}PrOH in which the pKa and the steric effects produce the highest e.e.s.

A study of the effect of solvent polarity was also carried out by a set of reactions using different solvents with the same alcohol as additive, *i.e.* methanol (see Table 7). It is remarkable that the use of TBME, the reaction did not take place. With the other cases, good results in terms of conversion were obtained, together with some differences in the e.e, also being observed.

Table 7 Study of the effect of the solvent polarity in the enantioselective β-borylation reaction of 2-hexenal **54**.



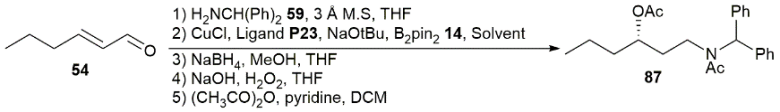
Entry	Solvent	Conv. (%)[a]	IY(%)[b]	e.e. (%)[c]
1	THF	91	9	86 (*R*)
2	Toluene	96	63	81(*R*)
3	TBME	-	-	-
4	DMF	95	44	78(*R*)

Reaction conditions: 1) 2-hexenal **54**:benzhydylamine **59** (1:1) was stirred in THF and 3 Å M.S. for 3h at RT. 2) An aliquot of *in situ* formed imine was transferred to a Schlenk-tube (under argon) containing CuCl (3mol%), (*R*)-DM-Binap **P23**, NaO^{t}Bu (9 mol%), B_2pin_2 **14** (1.1 equiv.). After 5 min MeOH (2.5 equiv.) was added to the solution and the reaction was stirred for 16 h at RT. 3) $NaBH_4$ was added, followed by the drop-wise addition of MeOH. The mixture was stirred for 3h at RT, followed by the removal of solvent under reduced pressure. 4) THF was added to the resulting residue, followed by NaOH (w/v 20%) and H_2O_2 (w/v 35%), and the solution was heated to reflux for 1 h. 5) The resulting white solid was dissolved in DCM and $(CH_3CO)_2O$ and pyridine were added. The mixture was stirred for 16 h at RT. [a]Determined by ^{1}H NMR spectroscopy on a sample of pure amino alcohol before acetylation by comparison of the ^{1}H signal corresponding to the starting aldehyde **54** and the analogous imine derivative. [b]Determined on the N/O-diacetate derivative **87**. [c]Determined by HPLC on the N/O-diacetate derivative **87**.

With the exception of TBME (entry 3, Table 7), where reaction did not take place, it was observed that all the solvents studied provided good conversions, however, the e.e.s. differed. It was concluded that the polarity of the solvent does not influence the induction of asymmetry in the borylation step, *i.e.* the more polar solvents, THF and DMF, showed the highest and the lowest e.e.s, respectively. It appeared that the most optimal conditions were obtained when using THF as solvent, with ^{i}PrOH as protonating agent.

Moreover, the possibility of using an alcohol as solvent and additive at the same time was considered. With that purpose, MeOH and ^{i}PrOH were evaluated as reaction media for the transformation of 2-hexenal **54** into the corresponding γ-amino alcohol (Table 8).

Table 8 Comparison of MeOH and ^{i}PrOH as reaction media for the synthesis of the γ-amino alcohol.



Entry	Reaction medium	Conv. (%)	IY (%)	e.e. (%)
1	MeOH	96	23	78 (*R*)
2	^{i}PrOH	75	36	89 (*R*)

Reaction conditions: 1) 2-hexenal **54**:benzhydylamine **59** (1:1) was stirred in THF and 3 Å M.S. for 3h at RT. 2) An aliquot of *in situ* formed imine was transferred to a Schlenk-tube (under argon) containing CuCl (3mol%), (*R*)-DM-Binap **P23**, NaO^{t}Bu (9 mol%), B_2pin_2 **14** (1.1 equiv.). After 5 min MeOH (2.5 equiv.) was added to the solution and the reaction was stirred for 16 h at RT. 3) $NaBH_4$ was added, followed by the drop-wise addition of MeOH. The mixture was stirred for 3h at RT, followed by the removal of solvent under reduced pressure. 4) THF was added to the resulting residue, followed by NaOH (w/v 20%) and H_2O_2 (w/v 35%), and the solution was heated to reflux for 1 h. 5) The resulting white solid was dissolved in DCM and $(CH_3CO)_2O$ and pyridine were added. The mixture was stirred for 16 h at RT. [a]Determined by ^{1}H NMR spectroscopy on a sample of pure amino alcohol before acetylation by comparison of the ^{1}H signal corresponding to the starting aldehyde **54** and the analogous imine derivative. [b]Determined on the N/O-diacetate derivative **87**. [c]Determined by HPLC on the N/O-diacetate derivative **87**.

For the reaction in ^{i}PrOH, the imine formation step was also monitored by *in situ* IR spectroscopy (ReactIR) which enabled us to follow the conversion of the enal into the imine over time. Surprisingly, it was found that complete conversion of the aldehyde **54** to the corresponding amine-derived aldimine **88** was achieved within 1 h. Previously, it was reported that in THF, the reaction took 6 h.[113] Figure 19 presents the graphical output obtained from the ReactIR monitoring of this transformation.

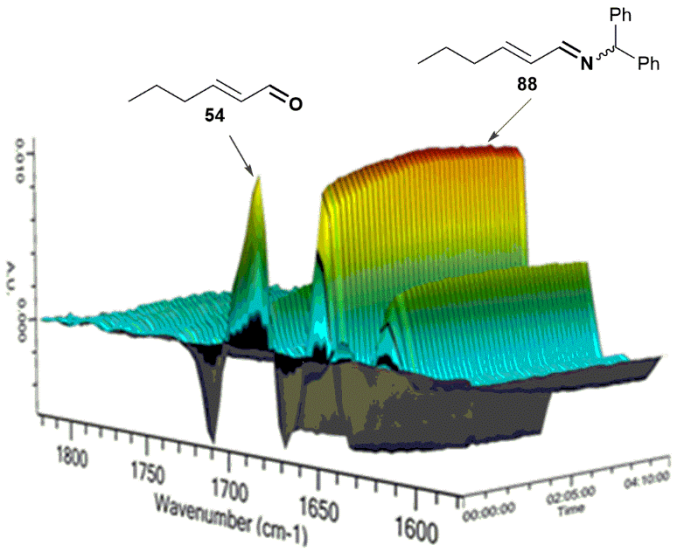


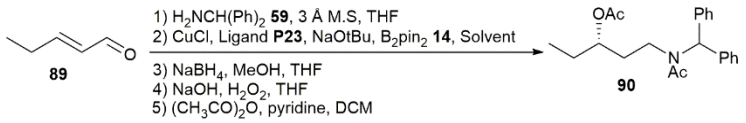
Figure 19 Graphical output obtained from the ReactIR for the formation of α,β-unsaturated aldimine **88**.

Based on this, ^{i}PrOH was revealed as a better alternative to the conventional THF/MeOH system due to a faster reaction for imine formation step and higher e.e.s in the final N/O-diacetate **87**. In order to complete this study, an additional chiral diphosphine ligand was tested in this solvent, *i.e.* (*R*)-^{i}Pr-DuPhos **P25**. This ligand had previously provided excellent results, comparable to (*R*)-DM-Binap **P23**, in terms of e.e.[113] However, the N/O-diacetate **87** was obtained in only 10% e.e. and hence, it was concluded that this ligand was not suitable for use in this solvent system.

The next target consisted of testing these reaction conditions on other substrates, *i.e.* 2-pentenal **89** which presented the lowest e.e. in previous work[113] (76% e.e.). Surprisingly, it

was observed that performing the reaction in ^{i}PrOH improved the e.e. considerably although a detrimental effect on the yield was observed (Table 9).

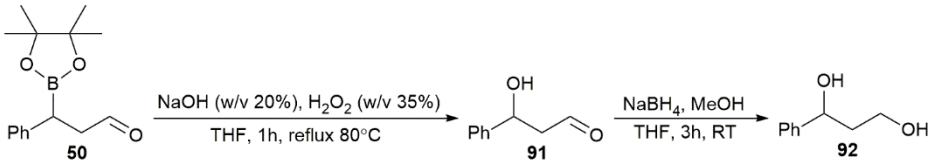
Table 9 Comparison of MeOH and ^{i}PrOH as reaction media for the synthesis of the γ-amino alcohol.



Entry	Reaction medium	Conv. (%)	IY (%)	e.e. (%)
1	THF/MeOH	95	65	76 (*R*)
2	^{i}PrOH	96	23	87 (*R*)

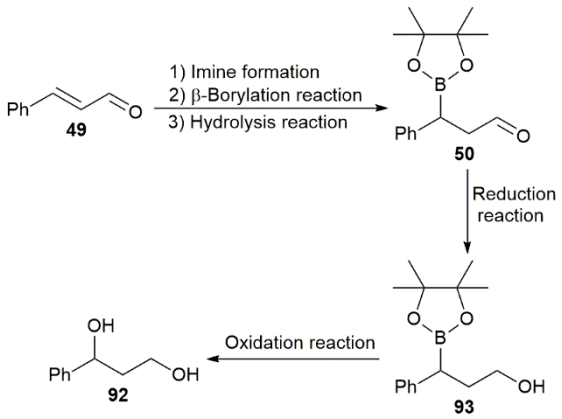
Reaction conditions: 1) 2-pentenal **89**:benzhydylamine **59** (1:1) was stirred in THF and 3 Å M.S. for 3h at RT. 2) An aliquot of *in situ* formed imine was transferred to a Schlenk-tube (under argon) containing CuCl (3mol%), (*R*)-DM-Binap **P23**, NaO^{t}Bu (9 mol%), B_2pin_2 **14** (1.1 equiv.). After 5 min MeOH (2.5 equiv.) was added to the solution and the reaction was stirred foir 16 h at RT. 3) $NaBH_4$ was added, followed by the drop-wise addition of MeOH. The mixture was stirred for 3h at RT, followed by the removal of solvent under reduced pressure. 4) THF was added to the resulting residue, followed by NaOH (w/v 20%) and H_2O_2 (w/v 35%), and the solution was heated to reflux for 1 h. 5) The resulting white solid was dissolved in DCM and $(CH_3CO)_2O$ and pyridine were added. The mixture was stirred for 16 h at RT. [a]Determined by ^{1}H NMR spectroscopy on a sample of pure amino alcohol before acetylation by comparison of the ^{1}H signal corresponding to the starting aldehyde **89** and the analogous imine derivative. [b]Determined on the N/O-diacetate derivative **90**. [c]Determined by HPLC on the N/O-diacetate derivative **90**.

Moreover, the *in situ* derivatisation of β-boryl aldehydes into the corresponding 1,3-diols was studied by the proposed synthetic route using cinnamaldehyde **49** as a model substrate (Scheme 57).



Scheme 57 Proposed synthetic pathway for the synthesis of γ-diol **92** from β-boryl aldehyde **50** *via* the corresponding β-hydroxy aldehyde **91**.

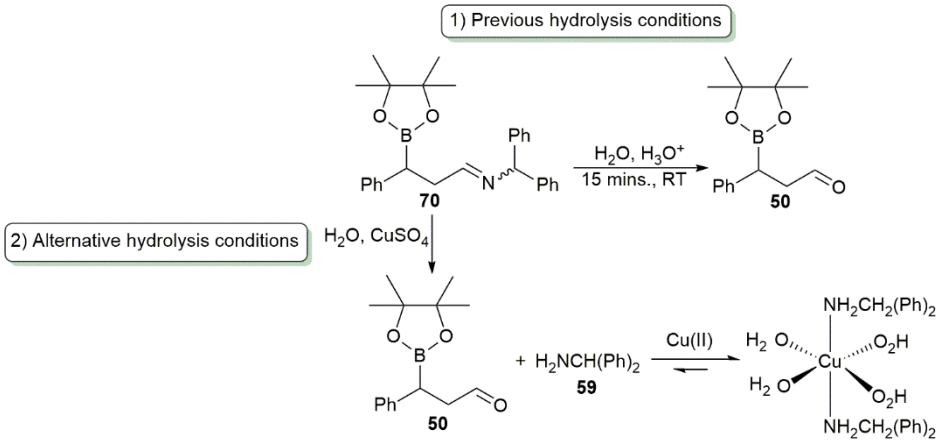
The formation of the intermediate β-hydroxy aldehyde **91** was confirmed by ^{1}H NMR spectroscopy; however, it was not possible to isolate this compound in a pure form by SiO_2 column chromatography. Again, the sensitivity of the aldehyde functionality was demonstrated. In this case, it was suspected that the cause may involve a deprotonation of the aldehyde due to the remaining base (from the β-borylation step), forming the enolate and this could react with other aldehydes leading to competitive aldol condensations. A possible solution, in order to avoid this side-reaction, was to transform the aldehyde group rapidly, *e.g.* to reduce the aldehyde leading to a β-boryl alcohol **93** followed, by subsequent oxidation of the boryl unit. Based on this, a one-pot, five-step synthetic route was proposed for the synthesis of 1,3-diol **92** from α,β-unsaturated aldehyde **50** was proposed (Scheme 58).



Scheme 58 One-pot, five-step methodology proposed for the synthesis of 1,3-diol **92** from α,β-unsaturated aldehyde **49**.

Following the synthetic route proposed in Scheme 58, the target 1,3-diol **92** was successfully obtained and isolated in an overall yield of 38%. The low yield obtained was

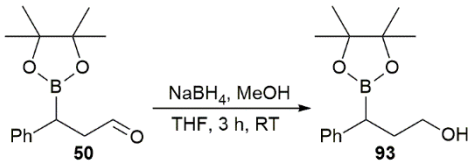
attributed to possible loss of product in the last steps; *i.e.* hydrolysis, reduction and oxidation reactions. Regarding the hydrolysis step, an alternative procedure was found to be more suitable, consisting of the substitution of the HCl by $CuSO_4$. Hence, in the reaction medium, the free benzhydrylamine **59** resulting from the hydrolysis of the β-boryl aldimine **70** could be trapped by Cu(II) ions. It is well-known that the first row transition metals (Lewis acids) tend to form coordination complexes in the presence of ligands (Lewis bases), *e.g.* Cu(II) and benzhydrylamine **59**, respectively (Scheme 59).[132]



Scheme 59 Comparison between the hydrolysis reaction of the β-boryl aldimine **70** under acidic conditions and assisted by $CuSO_4$.

Regarding the reduction reaction, different amounts of reducing agent as well as other alcohols were tested (Table 10).

Table 10 Optimisation of the conditions for the reduction of β-boryl aldehyde **50** to the corresponding β-boryl alcohol **93**.

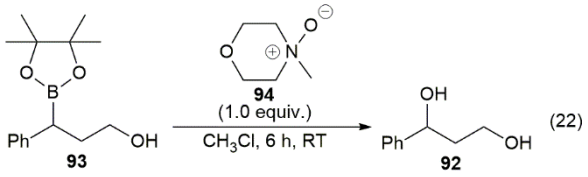


Entry	Reducing agent (equiv.)	Alcohol (mL)	IY [a](%)
1	$NaBH_4$ (3.0 equiv.)	MeOH (2.0)	40
2	$NaBH_4$ (6.0 equiv.)	MeOH (4.0)	38
3	$NaBH_4$ (3.0 equiv.)	EtOH (2.0)	34

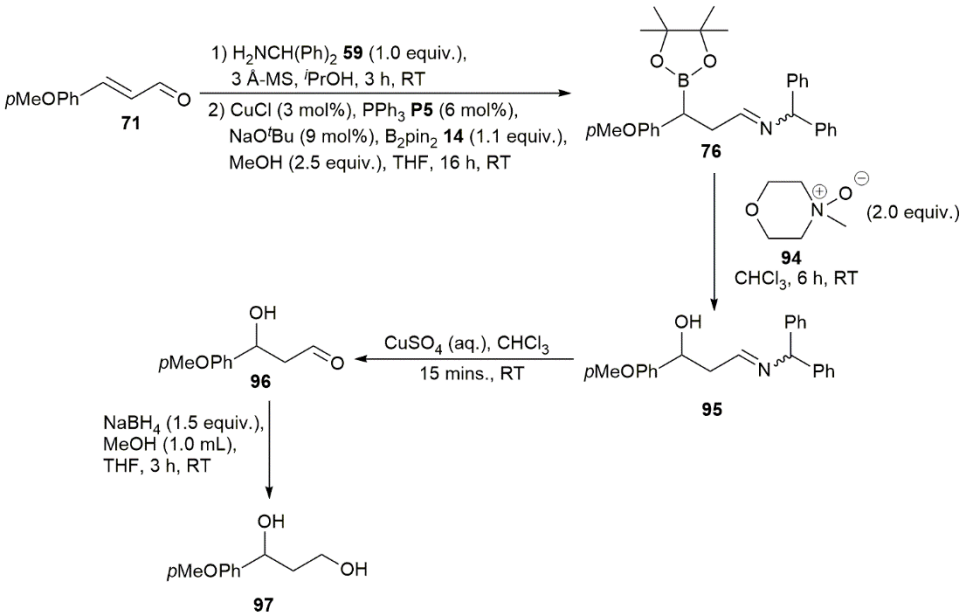
Reaction conditions: $NaBH_4$ was added into a solution of crude β-boryl aldehyde **50** in THF, followed by the drop-wise addition of MeOH. The mixture was stirred for 3h at RT, followed by the removal of solvent under reduced pressure. [a]IY determined on the final diol **92**.

It was concluded that increasing the amount of reducing agent did not have a positive impact on the isolated yield; *i.e.* from 3.0 equiv. to 6.0 equiv., the yield varied by only 2% (entries 1 and 2, Table 10). Additionally, it was corroborated that the most suitable alcohol for this transformation was methanol which provided better results than ethanol (entries 2 and 3, Table 10).

Finally, in order to complete this study, the oxidation step was also optimised using the standard substrate cinnamaldehyde **49**, since it was envisioned that the aqueous conditions required for the work-up procedure in the conventional C-B oxidation methodology (*i.e.* $NaOH/H_2O_2$) could lead to a loss of product due to the high solubility of diols in aqueous media. Hence, alternative methodologies based on the use of trialkylamine *N*-oxides as oxidizing agent,[133] *e.g.* trimethylamine *N*-oxide, had been demonstrated to be an ideal alternative to the traditional methodology of hydrogen peroxide and hydroxide. In this case, the *N*-oxide chosen was 4-methylmorpholine *N*-oxide **94** [Eqn. (22)].



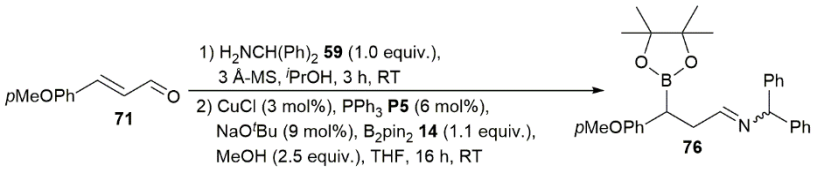
Initial attempts showed that the use of 2.0 equiv. of 4-MMNO **94** gave an efficient reaction resulting in the target diol being obtained in good yield. Although these steps were improved, it was not possible to obtain an excellent yield of the final diol, probably due to the instability associated with the intermediate β-boryl aldehyde **50**. Hence, the reaction conditions developed were tested further on a different substrate. In this case, the methodology was tested on *p*-methoxycinnamaldehyde **71** (discussed in previous sections), with the presence of the electron donating group providing additional stability perhaps preventing the boryl elimination and subsequently facilitating the development of the synthetic sequence to access the corresponding 1,3-diol. Hence, based on the better understanding of the reaction provided by previous studies, and avoiding the aldehyde presence until the last step of the sequence or using *N*-oxide reagents for the C-B oxidation, a new synthetic pathway was proposed (Scheme 60).



Scheme 60 Proposed synthetic pathway for the synthesis of γ-diol **97** from α,β-unsaturated aldehyde **71**.

In this case, after the imine formation and subsequent β-borylation reaction, the resulting β-boryl aldimine **76** was obtained as a crude product which underwent an oxidation reaction using 4-MMNO **94** leading to the corresponding β-hydroxy aldimine **95**. After imine hydrolysis and oxidation of the resulting aldehyde, the target 1,3-diol **97** would be obtained in >99% conversion. Surprisingly, it was observed that metallic copper was deposited after the β-borylation step. Because of this observation, this crucial step aroused much interest and an optimisation of the reaction conditions was carried out based on the role of the Cu(I) catalyst (Table 11).

Table 11 Study of the influence of the copper(I) source in the formation of the β-boryl aldimine **76**.



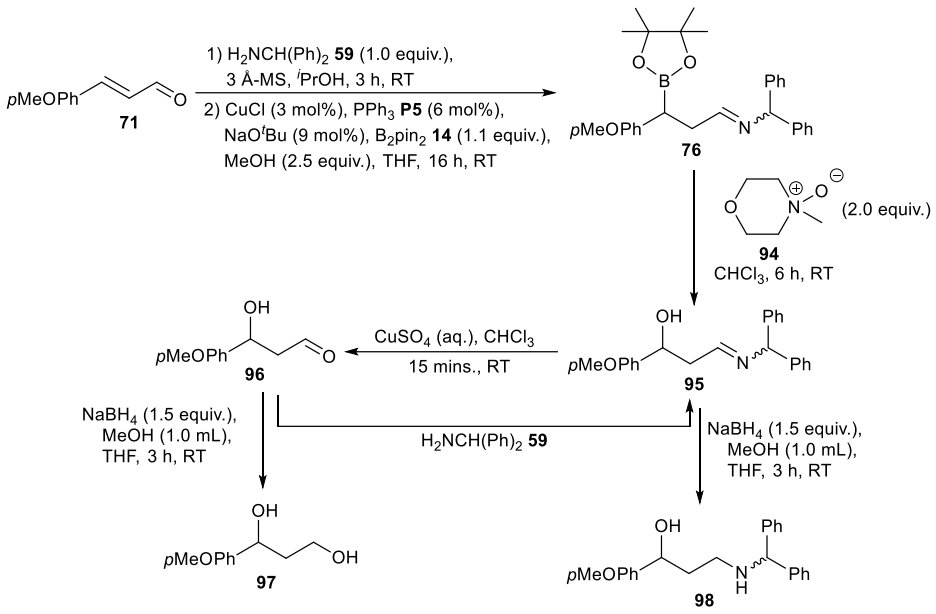
Entry	Copper source (mol%)	Solvent	Conv.-**76**[a] (%)
1	CuCl (3)	^{i}PrOH	99
2	CuCl (3)	THF	97
3	CuCl (0.3)	^{i}PrOH	99
4	Cu bronze	^{i}PrOH	79
5	-	^{i}PrOH	87

Reaction conditions: 1) *p*-Methoxycinnamaldehyde **71**:benzhydylamine **59** (1:1) was stirred in THF and 3 Å M.S. for 3h at RT. 2) An aliquot of *in situ* formed imine was transferred to a Schlenk-tube (under argon) containing CuCl (3mol%), PPh_3 **P5** (6 mol%), NaO^{t}Bu (9 mol%), B_2pin_2 **14** (1.1 equiv.). After 5 min MeOH (2.5 equiv.) was added to the solution and the reaction was stirred for 16 h at RT. [a]Determined by crude ^{1}H NMR spectroscopy.

This study confirmed that the conditions previously developed for 2-hexenal **54**, *i.e.* the use of ^{i}PrOH and CuCl (entry 1, Table 11) were also suitable in the case of the enal **71**, giving high conversions to compound **76**. It is worth mentioning that the solvent used did not make a remarkable difference in terms of conversion towards **76** (entries 1 and 2, Table 11), while the advantage of ^{i}PrOH as solvent for the first step was observed due to complete imine

formation in half the time compared with THF. It was also interesting to see that the amount of Cu(I) could be considerably reduced without having major repercussions on the effectiveness of the reaction in terms of conversion (entries 1 and 3, Table 11). However, changing the copper from Cu(I) in CuCl to Cu(0) in copper bronze, the conversion was decreased (see entries 1 and 4, Table 11). Indeed, the absence of copper in the boryl addition step did not make any difference in terms of conversion (entries 1, 3 and 5, Table 11).

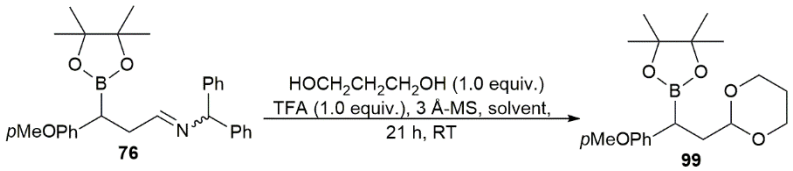
In the next two steps of the synthetic sequence (Scheme 60), some improvements were applied based on the results obtained in the preceding section, such as doubling the amount of 4-methylmorpholine *N*-oxide **94** so that the β-hydroxyl aldimine **95** was obtained. Afterwards, a hydrolysis reaction employing an aqueous solution of $CuSO_4$, followed by a reduction reaction, were performed in order to obtain the 1,3-diol **97**. However, the target compound **97** was not obtained and instead the analogous γ-amino alcohol **98** was obtained. A suitable explanation for this unexpected reactivity could be due to the fact that during the hydrolysis step, the β-hydroxy aldehyde **96** is being formed and benzhydrylamine **59** is released into the reaction medium. Although there is $CuSO_4$ in the reaction medium in order to trap the benzhydrylamine **59** by complexation, remaining benzhydrylamine **59** could give rise to a condensation reaction with the aldehyde **96** regenerating the initial aldimine **76**, which under reduction conditions could lead to compound **98** (Scheme 61).



Scheme 61 Overview of the undesired side-process that explains the formation of the γ-amino alcohol **98**.

As a consequence, a new protocol for the hydrolysis reaction was established, consisting of an aqueous workup after the hydrolysis process including a washing with an aqueous saturated $CuSO_4$ solution in order to completely remove all the amine present in the reaction mixture. Although 1,3-diol **97** was finally synthesised *via* the improved route described in Scheme 61, it was isolated in 17% yield. Therefore, it was concluded that diols are not the most appropriate derivatives due to their high solubility in water and consequently low effectiveness of the protocol through which they are synthesised. Hence, an alternative strategy was considered; the protection of the imine functionality using an acetal group. Therefore, with the aim of obtaining the corresponding β-boryl acetal, a series of reaction conditions were tested using β-boryl aldimine **76** as model substrate in order to determine the most suitable reaction conditions for this transformation (Table 12).

Table 12 Reaction conditions tested for the optimisation of the transformation of β-boryl aldimine **76** to the corresponding β-boryl acetal **99**.

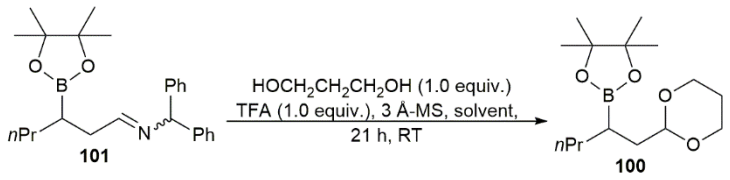


Entry	Solvent	3 Å-MS (g)	Conv.-**99**[a] (%)
1	THF	0.5	93
2	THF	0	68
3	Toluene	0.5	97
4	Toluene	0	87
5	TBME	0.5	91
6	TBME	0	81

Reaction conditions: The solid residue of the β-boryl aldimine **76** was redissolved in the solvent, and pinacol (1.0 equiv.), TFA (1.0 equiv.) and 3 Å MS were added. The reaction mixture was stirred at RT during 21 h. [a]Determined by crude ^{1}H NMR.

From this study emerges the conclusion that the polarity of the solvent was inversely proportional to the effectiveness of the reaction, since the less polar solvent (toluene) provided better conversions towards the acetal (see entries 3 and 4, Table 12). Also it was observed that the presence of molecular sieves in the reaction media is required to get a considerable conversion. Therefore, it was concluded that the most appropriate reaction conditions are the ones described in entry 3 of Table 12, so that reaction was reproduced on larger scale. However, it was not possible to isolate the target β-boryl acetal **99** which was obtained in 87% conversion, and instead of this, the compound that was obtained was *p*-methoxycinnamaldehyde **71**. Moreover, in order to corroborate the results obtained here, a structurally different substrate; 2-hexenal **54**, was also examined under the same conditions for the formation of the corresponding β-boryl acetal **100** (Table 13).

Table 13 Reaction conditions tested for the optimisation of the transformation of β-boryl aldimine **101** to the corresponding β-boryl acetal **100**.



Entry	Solvent	3 Å-MS (g)	Conv.-**100**[a] (%)
1	THF	0.5	93
2	THF	0	96
3	Toluene	0.5	94
4	Toluene	0	96
5	TBME	0.5	95
6	TBME	0	97

Reaction conditions: The solid residue of the β-boryl aldimine **101** was redissolved in the solvent, and pinacol (1.0 equiv.), TFA (1.0 equiv.) and 3 Å MS were added. The reaction mixture was stirred at RT during 21 h. [a]Determined by crude ^{1}H NMR (β-boryl acetal **100** was not stable for purification).

Although in this case no correlation between the polarity of the solvent and the effectiveness of the reaction was observed, it was concluded that the presence of molecular sieves was required for a good conversion as observed in the previous case. Unfortunately, it was not possible to obtain a clean sample of either β-boryl acetals due to decomposition of the compound during the purification step. With this study, it was concluded that the protection of the imine functionality by an acetal group was not a viable option in the case studied herein.

2.1.5. Summary of the study of the β-borylation reaction on amine-derived α,β-unsaturated aldimines

In summary, the significant challenges of working with α,β-unsaturated aldehydes were met in terms of controlling the competitive 1,2- *vs*. 1,4-addition, which were dealt with by the *in situ* derivatisation into the corresponding α,β-unsaturated aldimines. Additionally, and more importantly, the even greater challenge of handling β-boryl aldehydes was circumvented after confirming that β-boryl aldehydes are indeed unstable especially under chromatographic

purification conditions, leading to de-borylation. This undesired side-process was examined from a mechanistic point of view and it was confirmed that the loss of the boryl unit occurred in the β-boryl aldehyde and not in the aldimine intermediate. Moreover, the boron containing species involved in the catalytic cycle for the β-borylation reaction were examined.

Regarding the derivatives studied and with respect to the optimisation of the experimental conditions for the enantioselective transformation of 2-hexenal **54** into the corresponding γ-amino alcohol, it was observed that the e.e. could be improved with the use of CuCl and (*R*)-DM-Binap **P23** and in THF/^{i}PrOH as solvent and additive, respectively. As well as the effectiveness of ^{i}PrOH as solvent, it was revealed that the e.e. provided in that case was comparable to the obtained when using THF/MeOH, presenting the advantage that the imine formation step was faster (complete in 3 h).

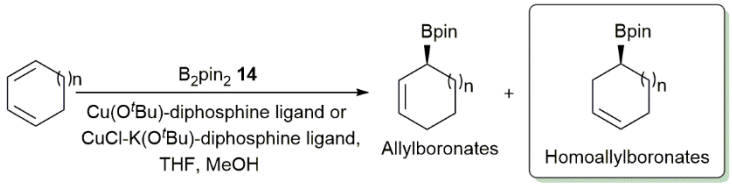
1,3-Diols and β-boryl acetals were found unsuitable derivatives, since the yields provided were very low due to the high solubility in aqueous media presented by these compounds, although improvements were implemented in the synthetic strategy this problem was not solved.

2.2. Functionalisation of the β-boryl aldehydes: synthesis of homoallylic boronate carboxylate ester derivatives

2.2.1 Background

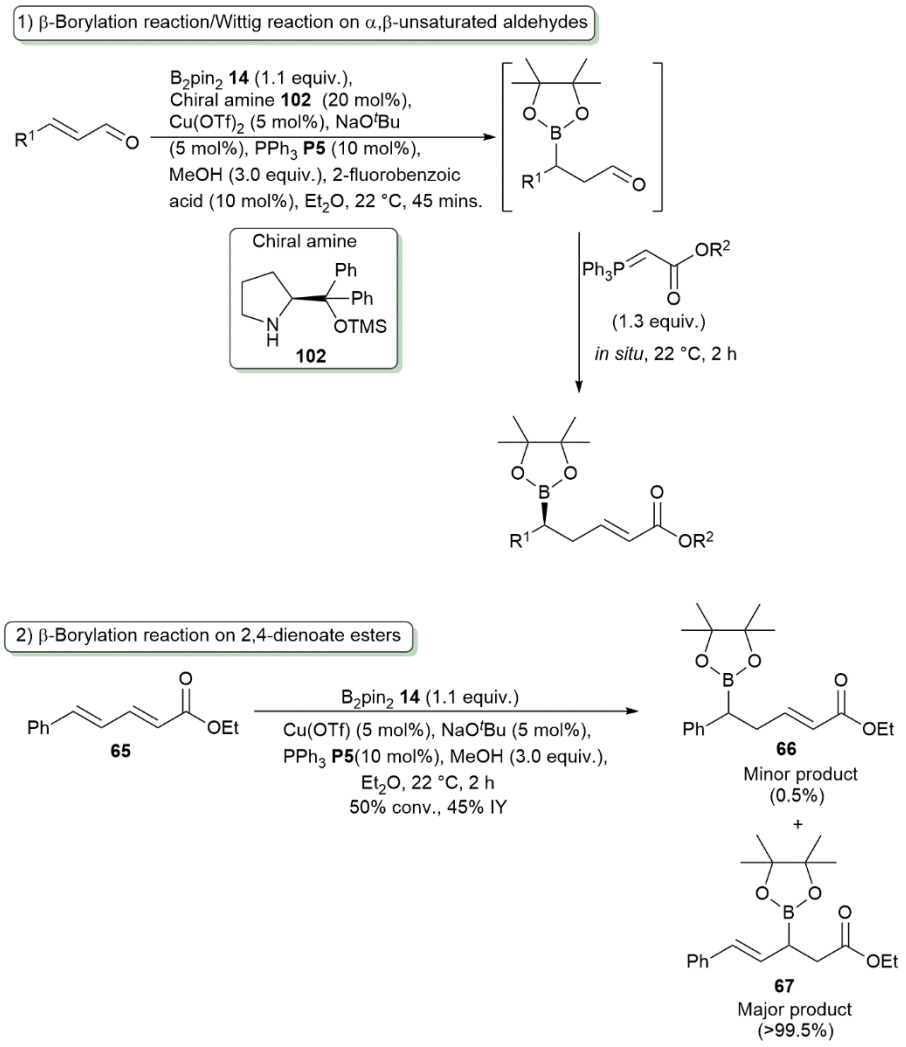
Amongst the broad spectrum of organoboron compounds, homoallylic boronate carboxylate esters are attractive synthetic targets due to the presence of the alkene moiety along with the boryl unit, which allows further derivatisation processes to be readily accomplished leading to key building blocks for accessing multifunctional chiral compounds.[124] In 2010, Ito and co-workers reported novel methodology to access chiral cyclic homoallylic boronates consisting on the Cu(I)-catalysed addition of B_2pin_2 **14** to 1,3-dienes.[134] However, in all the cases studied, this methodology showed a lack of regioselectivity and

mixtures of borylated compounds resulted from both 1,2- and 1,4-addition, *i.e.* allylic- and homoallylic compounds (Scheme 62).



Scheme 62 Copper(I) mediated addition of B_2pin_2 **14** to 1,3-cyclohexadiene substrates.

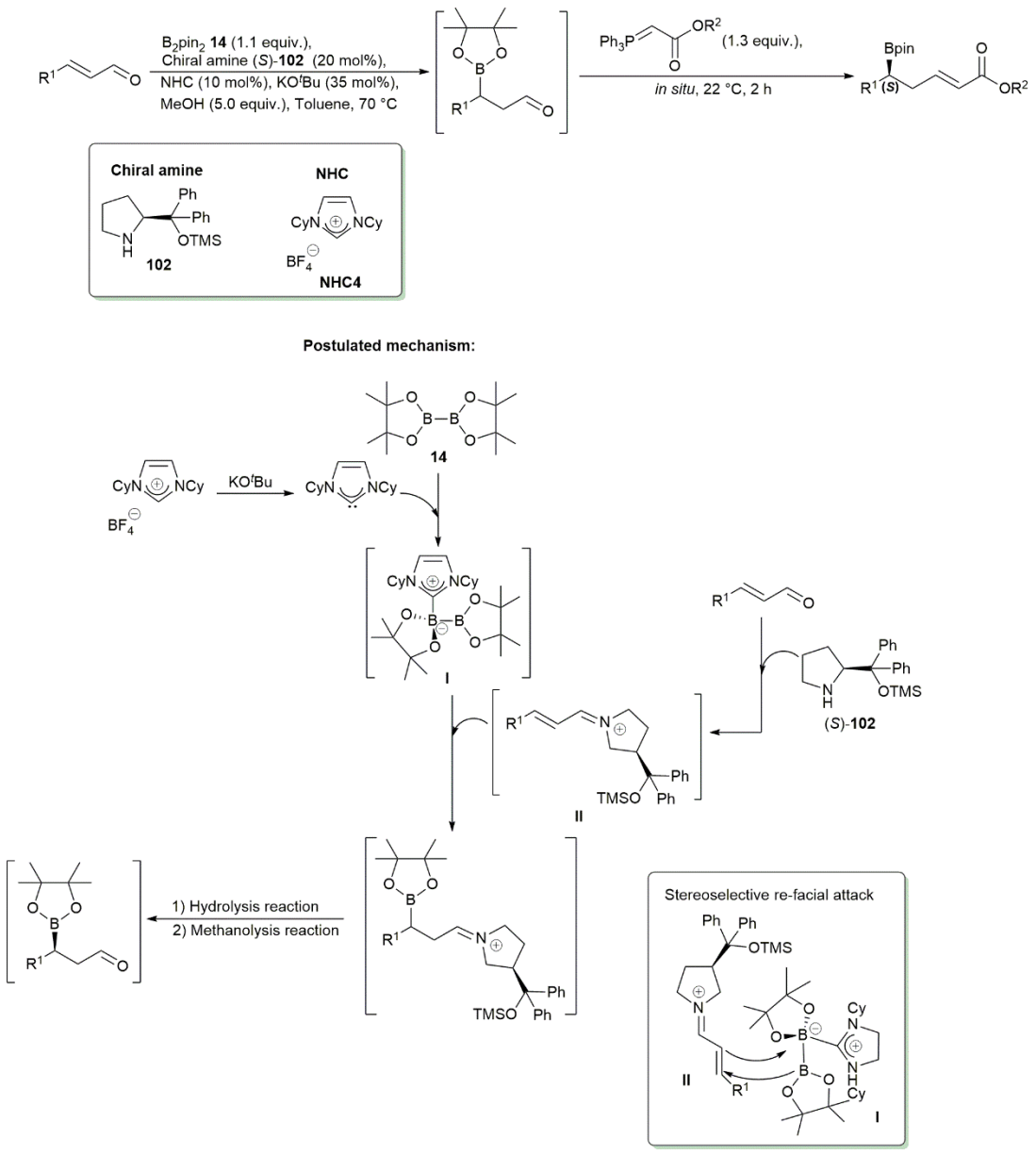
Based on this, different parameters for the reaction were examined, *e.g.* the chiral diphosphine ligand or the substituents on the diene substrate, conditions for the exclusive synthesis of the target homoallylic boronate were not found. Hence, the development of efficient methodologies towards these key compounds was required; Córdova *et al*. reported an alternative strategy consisting on a β-borylation/Wittig reactions sequence on α,β-unsaturated aldehydes (option 1, Scheme 63). Although the initial aim was to study the conjugated addition of B_2pin_2 **14** into 2,4-dienoate ester, such as compound **65**, due to chemoselectivity drawbacks, this approach proved not suitable (option 2, Scheme 63).[122]



Scheme 63 Different approaches towards homoallylboronates reported by Córdova *et al.*[122]

Later on, in 2012, the same group reported a metal-free version of this methodology.[124] In this case, the activation of the diborane reagent was mediated by an NHC and a plausible mechanism for the transformation was proposed which involved the *in situ* formation of the iminium species **I** from the reaction between the α,β-unsaturated aldehyde and the chiral amine co-catalyst **102**, *i.e.* ensuring a chemoselective borylation of the substrate. Moreover, it was found that the iminium intermediate **I** allowed the control on the stereoselectivity observed in the final homoallylic boronate carboxylate ester; in the case of using (*S*)-**102**, the (*S*)-homoallylic boronate carboxylate ester was the product obtained. A suitable explanation for

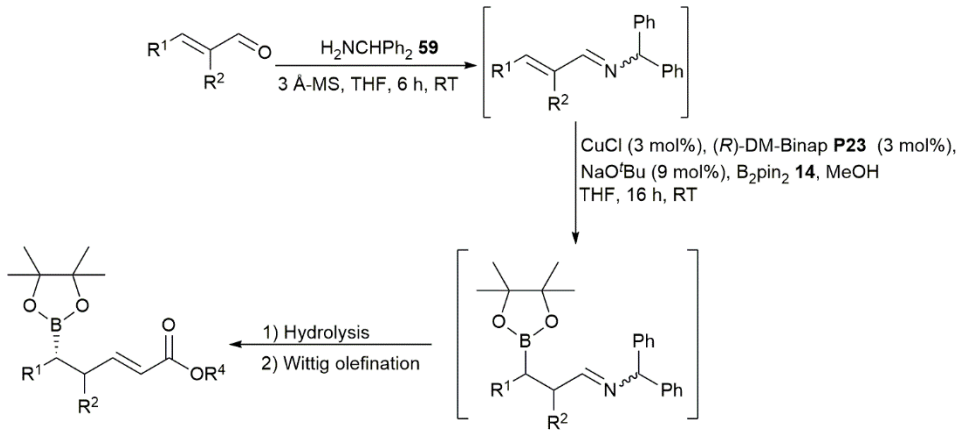
this observation relied on the attack of the boron-ate complex **I**, to the iminium intermediate **II** by the less hindered face. Scheme 64 summarises the mechanism proposed.



Scheme 64 Iminium-mediated mechanism suggested by Córdova *et al*. for the metal-free version of the β-borylation/Wittig sequence.

Although this strategy demonstrated that it was possible to access homoallylboronates *via* organoboron compounds, some drawbacks were associated to these methodologies; such as high catalyst loading [*i.e.* 5 mol% Cu(I) and 20 mol% chiral secondary

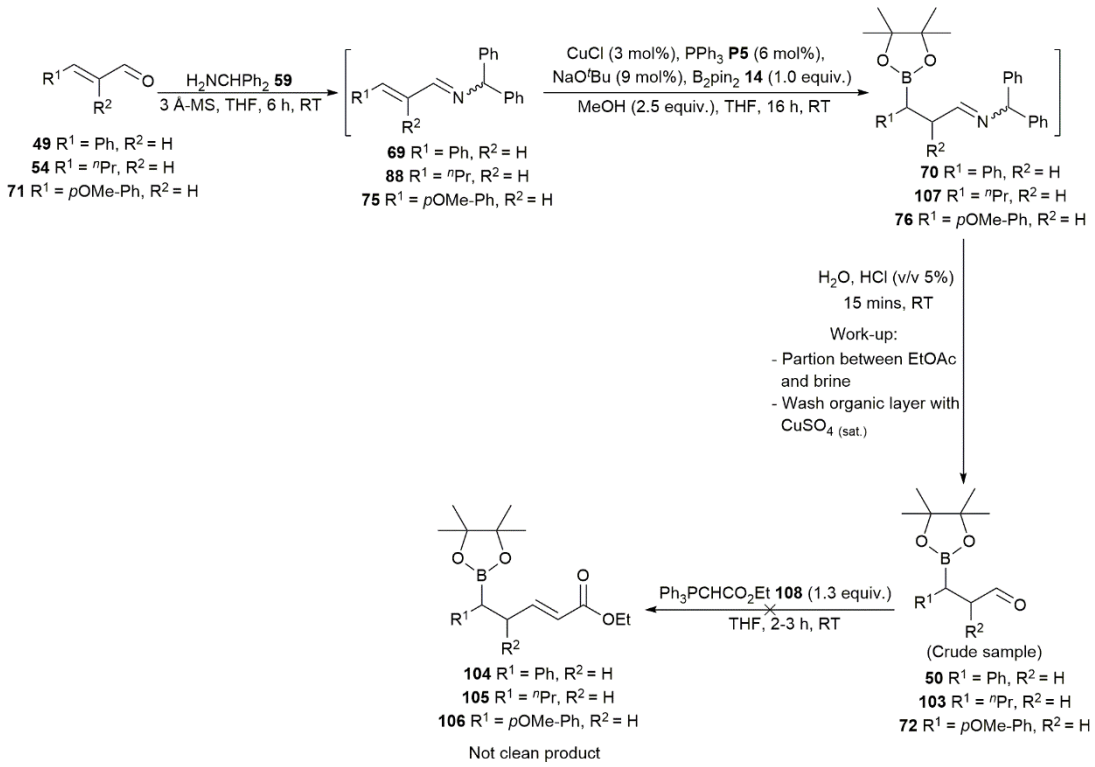
amine] and variable enantioselectivity (*i.e.* from 0-95% e.e.). Therefore, the development of a reliable, general, efficient, low catalyst loading [typically 3 mol% Cu(I)-chiral bis-phosphine][113] and highly enantioselective methodology towards β-boryl aldehydes would make such species more amenable for use in synthesis. Based on this, it was envisioned that an *in situ* trapping of the β-boryl aldehyde by a Wittig olefination could be a potential solution to the problematic isolation associated to these type of compounds, and at the same time, synthetically interesting homoallylboronates could be obtained. Hence, we aimed to develop a new process for the one-pot, formation of β-boryl aldehydes and *in situ* derivatisation into chiral homoallylboronates (Scheme 65).



Scheme 65 Proposed route towards chiral homoallylboronate esters from α,β-unsaturated aldehydes *via* the corresponding amine-derived aldimine intermediates.

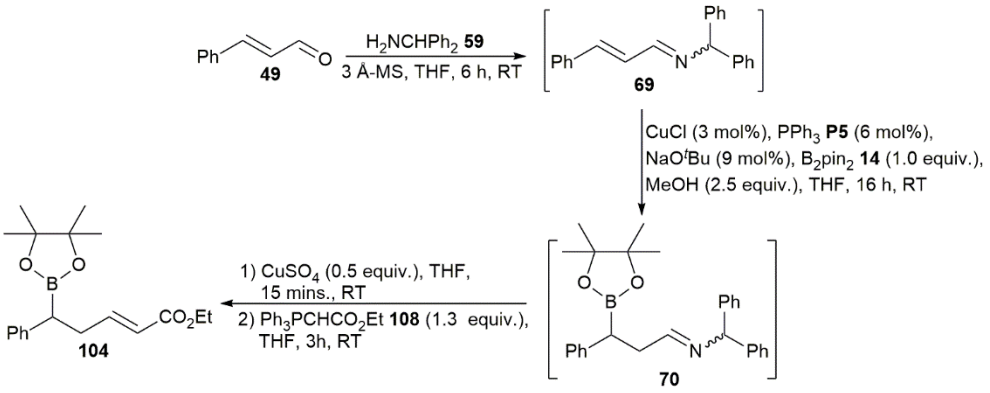
2.2.2. Developing a one-pot, four step methodology towards chiral homoallylic boronate carboxylate ester derivatives from α,β-unsaturated aldehydes

Initially, Wittig reactions were attempted using β-boryl aldehydes **50**, **72** and **103** (all formed *via* the acid hydrolysis conditions). However, β-boryl aldehydes were not cleanly converted to the corresponding homoallylic boronates **104**, **105** and **106** and only complex mixtures of products resulted. Seemingly, the instability of the β-boryl aldehydes precludes the direct derivatisation of these systems under the Wittig reaction conditions (Scheme 66).



Scheme 66 Synthetic pathway for the synthesis of homoallylboronates tested on α,β-unsaturated aldehydes **49**, **54** and **71**.

Hence, an alternative *in situ*, one-pot methodology was examined to see if it was possible to generate the β-boryl aldehyde and immediately trap through a Wittig reaction, which required the use of a stabilised phosphorane to withstand the conditions required to hydrolyse the imine function. To that end, and to test if that was feasible, unsaturated aldehyde **49** was chosen as a model substrate, as outlined in Scheme 67, for examination of the *in situ* imine hydrolysis-olefination reaction without isolation of the β-boryl aldehyde **50** intermediate.



Scheme 67 One-pot, four-step methodology proposed for the synthesis of the homoallylboronate ester **104** from α,β-unsaturated aldehyde **49**.

Target homoallylboronate **104** was successfully synthesised with high overall conversion by the proposed one-pot, four-step sequence. However, the presence of starting enal **50** was detected in the product after purification, and for that reason, an optimisation of the conditions for the chromatographic purification was required (Table 14).

Table 14 Optimisation of the conditions for the chromatographic purification of homoallylboronate **104**.

Entry	Column support	Ratio (Petroleum ether:EtOAc)	Yield (%)
1	Silica gel	20:1	35
2	Silica gel	2:1[a]	60
3	Silica gel	3:2[a]	64
4	Silica gel	13:1[a]	55
5	Alumina	1:1[a]	77
6	Alumina	2:1[a]	36
7	Florisil	2:1[a]	88
8	Florisil	Gradient[a,b]	71

[a]Mixture of solvents used as eluent was cooled down to 0 °C;

[b]Eluent as gradient 9:1; 5:1; 1:1; 0:1.

As shown in Table 14, the first attempts to purify compound **104** (obtained in over 95% conversion in all cases) provided only a low yield (35%) using silica gel under standard room temperature conditions, along with a considerable proportion of starting unsaturated aldehyde **49** (entry 1, Table 14). Cooling the solvent and changing its polarity gave increased isolated yields (entries 2–4, Table 14), again using silica gel, however, the highest yield was

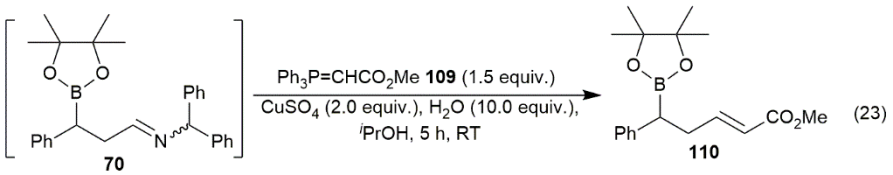
still only 64%. It was noted though that using either alumina or Florisil (entries 5–8, Table 14) gave no decomposition of the homoallylic boronate **104**, and high yields could be obtained, *i.e.* up to 88%. However, the product obtained was not as clean as when using silica gel (*i.e.* other impurities such as remaining reagents from previous steps were still present). At this point, it was clear that purification of the homoallylic boronates was possible, however, it was felt that the yields obtained needed to be optimised further to reduce the presence of starting unsaturated aldehyde **49**, *i.e.* by ensuring the complete hydrolysis of the intermediate imine **70** and a fast, efficient Wittig reaction to trap the intermediate β-boryl aldehyde **50**. Each of these steps were further screened for different conditions, as reported in Table 15.

Table 15 Reaction conditions screened for the hydrolysis and Wittig reactions.

Entry	$CuSO_4$ (equiv)	Ylide (equiv)	Time (h)	Temperature (◦C)	Presence of **49**[a]
1	0.5	Ph_3PCHCO_2Et **108** (1.3)	3	RT	Yes
2	1.0	Ph_3PCHCO_2Et **108** (1.3)	4	40	Yes
3	1.0	Ph_3PCHCO_2Et **108** (1.5)	8	RT	Yes
4	Excess (sat.)	Ph_3PCHCO_2Me **109** (1.1)	4	RT	Yes
5	2.0	Ph_3PCHCO_2Me **109** (1.5)	5	RT	No
6	2.0	Ph_3PCHCO_2Me **109** (1.5)	5	40	Yes

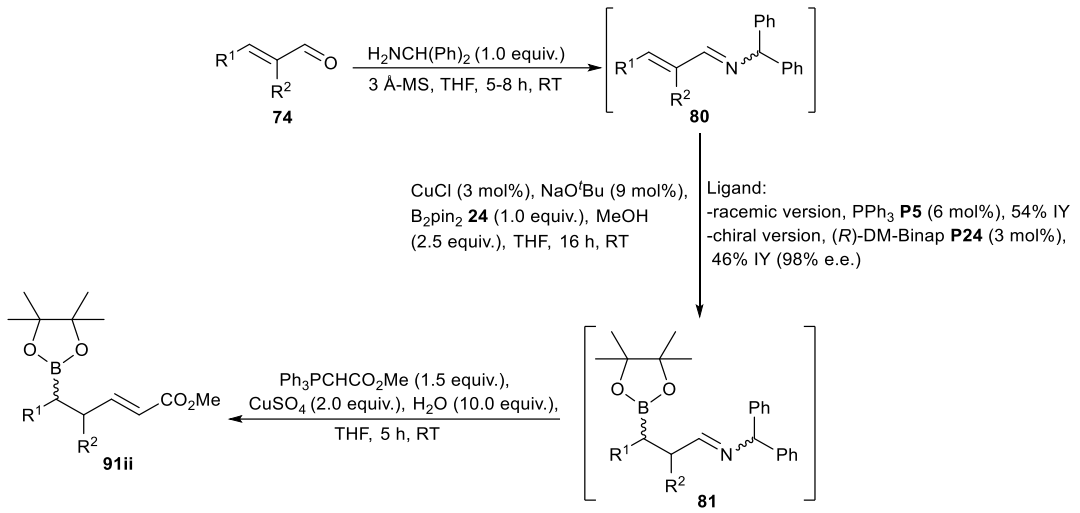
[a]Residual **49** was observed by ^1H NMR on the reaction crude mixture.

It was observed that using 2.0 equivalents of copper(II) sulfate gave complete β-boryl imine **70** hydrolysis and efficient Wittig trapping occurred with 1.5 equivalents of ylide **109** instead of **108**, and hence, transformation into **110** (entry 5, Table 15). In this case, there was no starting unsaturated aldehyde **49** remaining in the crude reaction mixture [Eqn. (23)].



(23)

Hence, these reaction conditions defined an asymmetric synthetic pathway using (*R*)-DM-Binap **P23** as the chiral diphosphine ligand (which was found to be the most appropriate ligand for the enantioselective conversion of α,β-unsaturated aldimines to the corresponding β-boryl imines in a previous work)[113] was established, as outlined in Scheme 68.

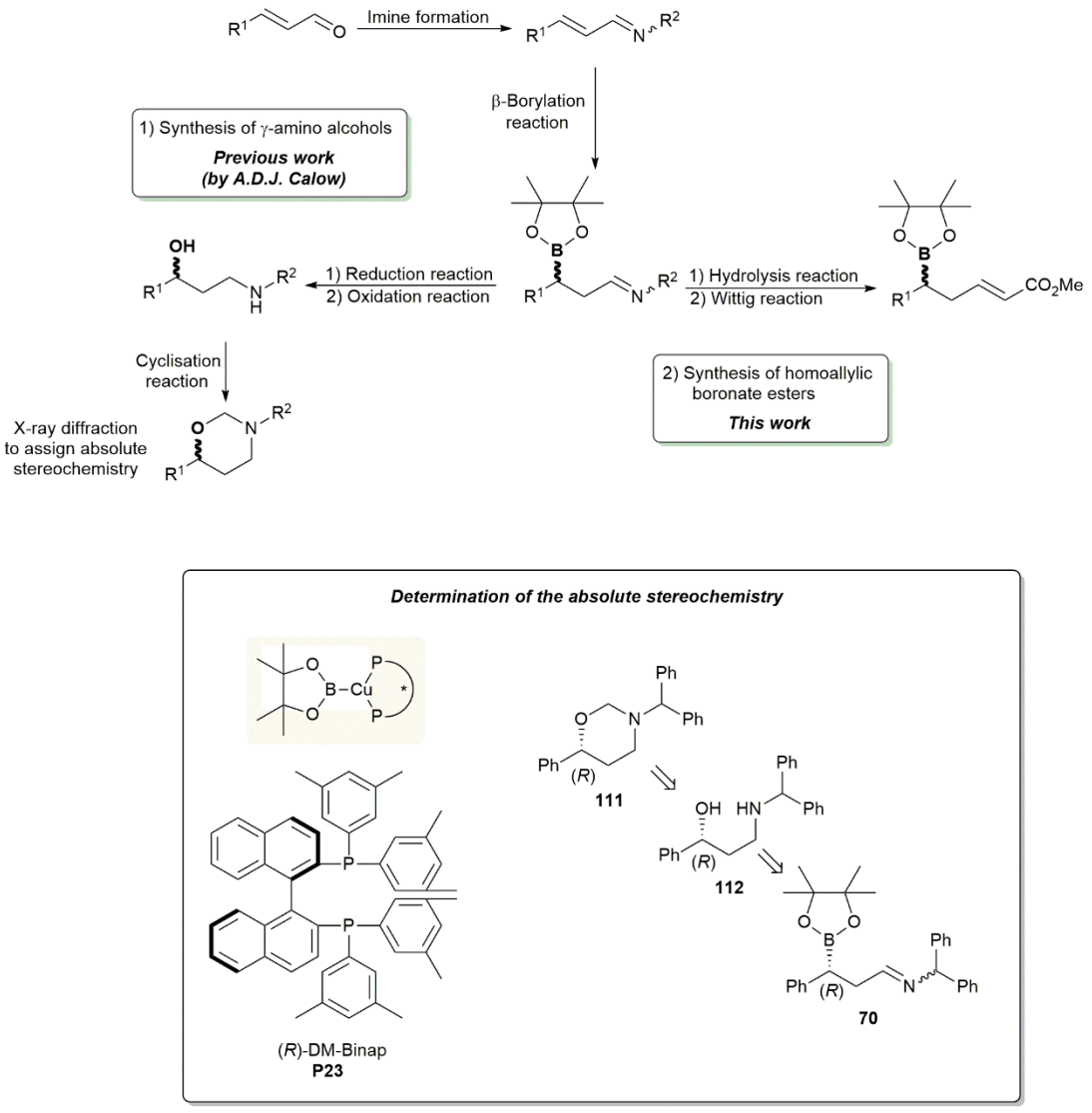


Scheme 68 Enantioselective pathway proposed for the synthesis of homoallylic boronate carboxylate ester derivatives from α,β-unsaturated aldehydes.

By the application of the proposed route to the model substrate, cinnamaldehyde **49**, homoallylic boronate carboxylate ester **110** was obtained in a 54% IY, overall for the four-step sequence for the racemic version, and 46% IY overall with an e.e. of 98% for its chiral version, confirming the suitability of this approach.

2.2.2.1. Stereochemical analysis (work carried out by previous PhD student A. D. J. Calow, 2012)

This study corroborated again that a catalytic system composed by CuCl and (*R*)-DM-Binap **P23** provides an effective asymmetric induction reaction for the conjugated addition of a boryl unit into α,β-unsaturated aldimines. However, the formation of the enantiomer was also required in order to enable determination of the absolute stereochemistry of the products of these reactions, particularly of the homoallylic boronate ester derivatives which were assumed to be consistent with the previous work developed in our group as employed for the synthesis of γ-amino alcohols[113] (option 1, Scheme 69).



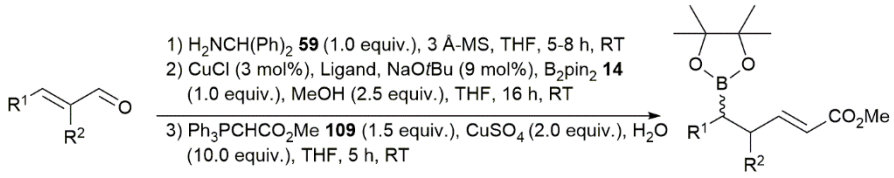
Scheme 69 Determination of the absolute stereochemistry for the creation of the stereogenic centre resulting from the β-borylation reaction on the α,β-unsaturated aldimine.

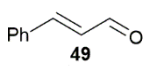
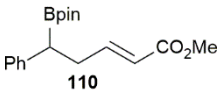
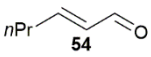
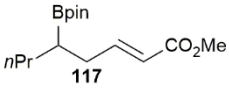
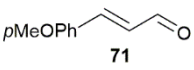
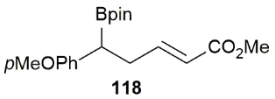
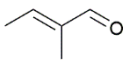
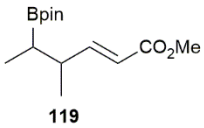
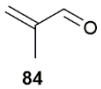
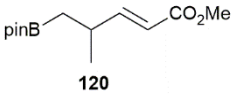
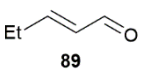
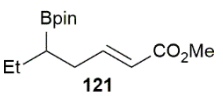
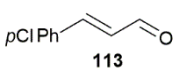
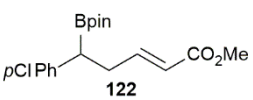
In this case, 1,3-oxazine derivatives were envisioned as the possible structures on which to perform the stereochemical analysis.[135] Specifically, the cinnamaldehyde-derived oxazine **111** was chosen as model substrate for that aim. The cyclisation of the γ-amino alcohol **112** led to the formation of a white solid, *i.e.* the corresponding oxazine **111**, which was suitable for the X-ray analysis.[136] From this study, it was concluded that the use of the (*R*)-enantiomer of the ligand, *i.e.* **P23**, lead into the formation an (*R*)-configuration of the stereocentre.

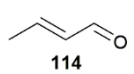
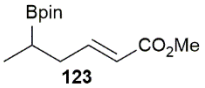
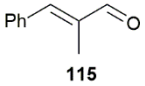
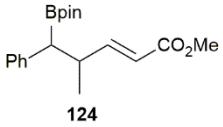
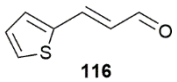
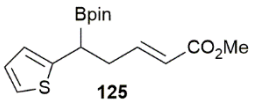
2.2.3. Study of the effect of the C_β-substituent: Substrate scope

With the methodology optimised for the model substrate, the next step consisted of the confirmation of the efficiency of the process by its application on a wide-range of α,β-unsaturated aldehydes. Additionally, this substrate scope would allow the study of the effect that the substituent in C_β had on the e.e. Table 16 summarises the different enals evaluated for this purpose.

Table 16 Substrate scope examined for the enantioselective synthesis of homoallylic boronate carboxylate esters from α,β-unsaturated aldehydes.



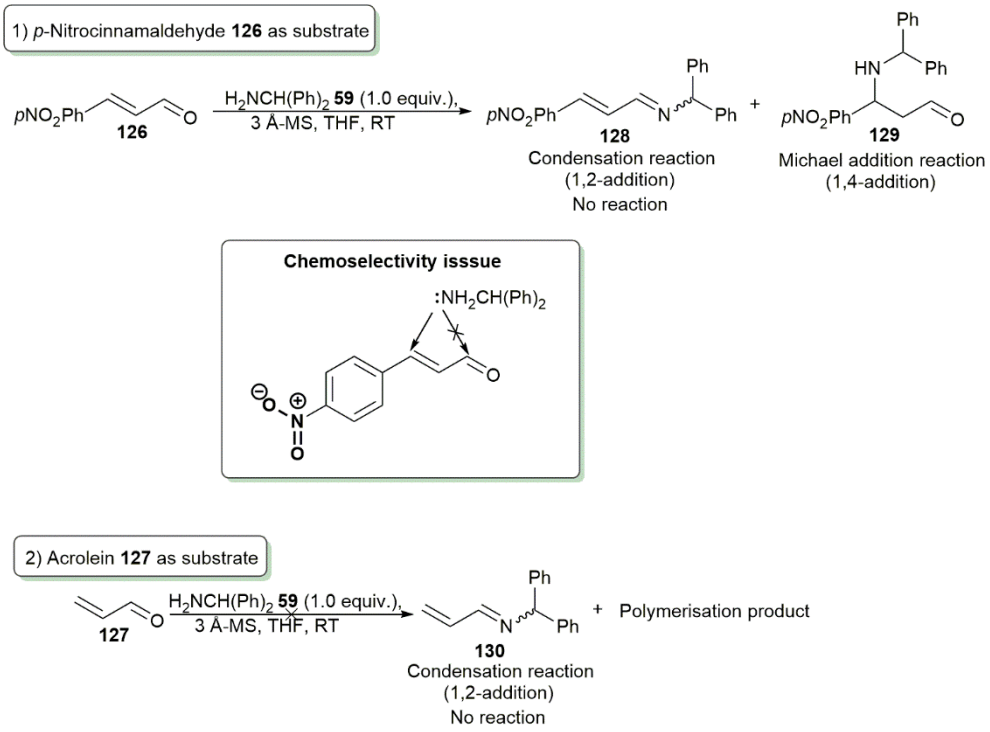
Entry	α,β-Unsaturated aldehyde	Homoallylic boronate ester	Ligand	IY (%)	e.e (%)[a,b]
1	 **49**	 **110**	PPh_3 **P5**	54	-
2			(*R*)-DM-Binap **P23**	46	98 (*R*)
3	 **54**	 **117**	PPh_3 **P5**	74	-
4			(*R*)-DM-Binap **P23**	45	91 (*R*)
5	 **71**	 **118**	PPh_3 **P5**	27	-
6			(*R*)-DM-Binap **P23**	40	87 (*R*)
7	 **73**	 **119**	PPh_3 **P5**	60[c]	-
8			(*R*)-DM-Binap **P24**	20	[-][d]
9	 **84**	 **120**	PPh_3 **P5**	36	-
10			(*R*)-DM-Binap **P23**	-	-
11	 **89**	 **121**	PPh_3 **P5**	54	-
12			(*R*)-DM-Binap **P23**	70	73 (*R*)
13	 **113**	 **122**	PPh_3 **P5**	54	-
14			(*R*)-DM-Binap **P23**	38	98 (*R*)
			PPh_3 **P5**	34	-

15 16	 **114**	 **123**	(*R*)-DM-Binap **P23**	65	80 (*R*)
17 18	 **115**	 **124**	PPh_3 **P5** (*R*)-DM-Binap **P23**	29[e] 19[e]	- [-][d]
19[f] 20[f]	 **116**	 **125**	PPh_3 **P5** (*R*)-DM-Binap **P23**	- -	- -

Reaction conditions: 1) Enal:benzhydylamine **59** (1:1) was stirred in THF and 3 Å M.S. for 5-8 h at RT; 2) An aliquot of *in situ* formed imine was transferred to a Schlenk-tube (under Ar) containing CuCl (3 mol%), Ligand, NaO^{t}Bu (9 mol%), B_2pin_2 **14** (1.0 equiv.). After 5 min MeOH (2.5 equiv.) was added to the solution and the reaction was stirred for 16 h at RT; 3) The resulting β-boryl imine was transferred into a round bottom flask, then methyl(triphenylphosphoranylidene)acetate **109** (2.0 g, 1.5 equiv) was added, after 5 minutes $CuSO_4$ (1.3 g, 2.0 g) was added along with H_2O (0.7 mL, 10.0 equiv). The mixture was stirred for 5 h at RT. [a]Absolute stereochemistry as shown in Scheme 69 where relevant and on the basis of previous reports.[113] [b]Measured by chiral HPLC. [c]Obtained as an 1:4 mixture of *syn*-:*anti*-diastereoisomers, determined by ^{1}H NMR spectroscopy. [d]Not determined. [e]Conversion only and with a 50 °C reaction temperature. [f]Substrate synthesised by A. D. J. Calow;[135] β-Borylation proved efficient (measured by NMR), but subsequent transformation *via* Wittig chemistry failed to form the resulting compound.

It was observed that this methodology also worked well on a wider range of α,β-unsaturated aldehydes to derive the corresponding homo allylic boronates with e.e.s varying from 73 to >98%. The isolated yields, considering the number of steps in this one-pot protocol, were moderate to good (up to 74% after 3 steps). Despite the successful application of this methodology to a range of substrates, as outlined in Table 16, not all substrates were suitable for the borylation reaction, *i.e. p*-nitrocinnamaldehyde **126** was found to be unsuitable for imine formation resulting only in Michael addition products, *i.e.* the enamine analogue, rather than imine formation (option 1, Scheme 70). A suitable explanation for this observation could be the fact that in the case of being a *p*-nitro substituted phenyl ring, the β-position would be considerably more electrophilic (more activated) towards a nucleophilic attack (*i.e.* the 1,4-addition would be promoted over the 1,2-addition). In addition, acrolein **127** was also unsuitable, since attempts to use it as a starting material resulted only in polymerisation

products (option 2, Scheme 70). However, and perhaps surprisingly, methacrolein **84** did undergo the imine formation, borylation and hydrolysis and Wittig trapping (entry 9, Table 16) to give the corresponding homoallylic boronate carboxylate ester.



Scheme 70 Unsuitable substrates evaluated for this methodology.

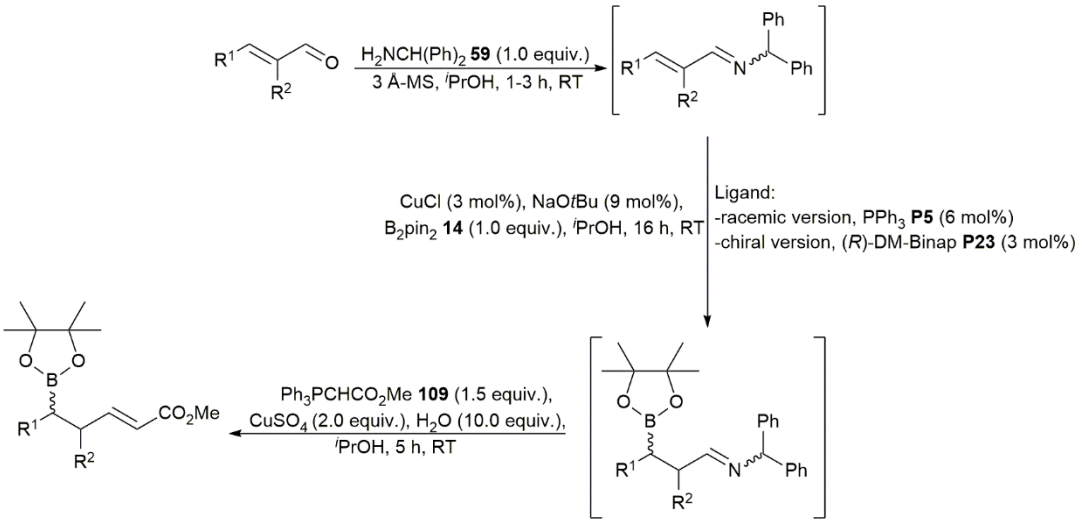
The impact of the different unsaturated aldehyde substituents on the overall process is interesting to note. The highest e.e.s were obtained for those cases in which R^1 substituent corresponds to an aryl function (entries 2, 6 and 14, Table 16). With alkyl substituents, there was evidence of steric effects operating, and hence, a R^1 being a propyl function (entry 4, Table 16) gave higher e.e. than the corresponding ethyl or methyl groups (entries 12 and 16, Table 16 respectively). The influence of a substituent R^2 in the starting unsaturated aldehyde was also interesting and gave mixed results. Hence, tiglic aldehyde **73** (entry 8, Table 16) and α-methyl-cinnamaldehyde **115** (entry 18, Table 16) provided the corresponding imines smoothly. However, there was a significant effect of the R^2 methyl groups in both cases, with the boryl conjugate addition step being slower, and especially when the chiral diphosphine

ligand **P23** was used. This was reflected in slower reactions, and low yields, in both cases and in fact, for the α-methyl-cinnamaldehyde substrate **115**, the β-borylation did not take place at room temperature and the reaction needed to be performed at 50 °C. Because of this, the efficiency of the asymmetric step was not determined, however, the diastereocontrol was the same for both the achiral and chiral phosphines, *i.e.* a 1:4 mixture of *syn:anti*-diastereoisomers (entry 18, Table 16). For the tiglic aldehyde **73** (entry 8, Table 16), homoallylic boronate **119** was obtained in 20% isolated yield as a mixture of diastereoisomers which were not readily separable by chiral HPLC using several different HPLC columns (including OD, OJ-H, AS and AD and a range solvent elution systems). However, the relative stereochemistry from the racemic reaction (PPh_3 **P5** as ligand) was assigned, and was in agreement with previous reports, *i.e.* as a 1:4 mixture of *syn*:*anti*-diastereoisomers.

2.2.4. Refinement of the methodology: study of an alternative reaction medium (THF/MeOH *vs.* ^{i}PrOH)

This methodology represents an effective enantioselective protocol providing good to excellent e.e.s in the asymmetric variant. However, the lower enantiomeric excesses obtained from hexenal **54** and pentenal **89**, *i.e.* homoallylic boronate esters **117** and **121**, respectively (entries 4 and 12, Table 16) prompted us to further examine possible methods of improving the asymmetric induction. Considering the key role of methanol as the protonating additive in the catalytic cycle corresponding of the β-borylation step as originally developed by Yun *et al.*,[49] and based on the results obtained from the study of the effect of an alcohol additive in the enantioselective β-borylation reaction on α,β-unsaturated aldimines (see Section 2.1)**,** we decided to examine the use of an alcohol as both the reaction medium and protonating agent. Hence, a more hindered alcohol might improve the enantioselectivity (as previously also observed for the study of the effect alcohol additive in the enantioselective β-borylation reaction of 2-hexenal **54** (see Section 2.1) while maintaining a solvent polarity similar to THF

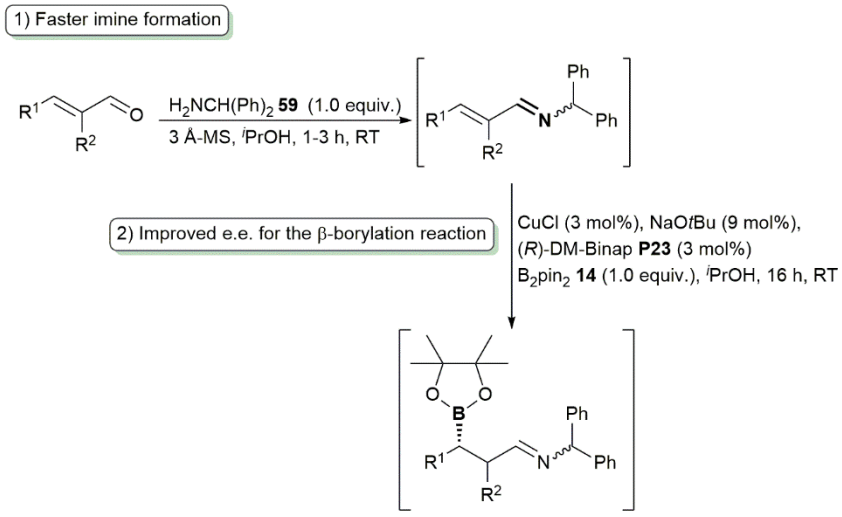
for solubility purposes. Therefore, ^{i}PrOH was employed in place of THF as sole solvent for the entire reaction sequence, from imine formation to imine hydrolysis/Wittig trapping (Scheme 71), with no methanol addition.



Scheme 71 Enantioselective pathway proposed for the synthesis of homoallylic boronate carboxylate ester derivatives from α,β-unsaturated aldehydes, using ^{i}PrOH as reaction medium.

This solvent change had an impact on the output of the sequence in two aspects in comparison to the conventional system (Scheme 72):

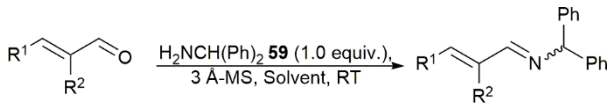
- Faster imine formation reaction was observed (study of the process by an *in situ* IR spectroscopy, ReactIR, monitoring).
- Improved asymmetric induction was observed for the β-borylation reaction step, *i.e.* higher e.e. values were obtained for the homoallylic boronate carboxylate ester derivatives.

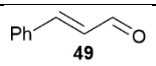
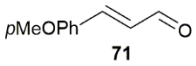
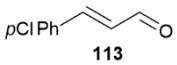
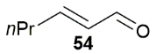
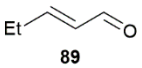
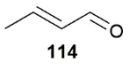
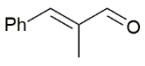
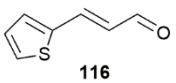


Scheme 72 Beneficial effects of the use of ^{i}PrOH as solvent instead of THF/MeOH.

Regarding the rate of the imine formation reaction, *in situ* IR spectroscopy monitoring of the reaction (ReactIR) showed faster imine formation reaction in comparison with the conventional system (THF), see Table 17. Moreover, it is worth mentioning, that for those cases in which the C_{β}-substituent was an aryl group (entries 1,5-6, Table 17), the aldimine crystallised in a suitable form for X-ray crystallographic analysis (see Figure 20).

Table 17 Comparison of the imine formation reaction time between ^{i}PrOH and THF.



Entry	Substrate	Reaction time (h)[a,b]	
		^{i}PrOH	THF
1	 **49**	2.5	4.5[c]
2	 **71**	-[d]	5[c]
3	 **113**	-[d]	8[c]
2	 **54**	1	7[c]
3	 **89**	1	8[c]
4	 **114**	1	5[c]
5	 **115**	2	[-][e]
6	 **116**	2	< 9[c]

Reaction conditions: Enal:benzhydrylamine **59** (1:1) was stirred in ^{i}PrOH and 3 Å M.S. for 1-3 h at RT. [a]Determined by *in situ* IR spectroscopy (ReactIR). [b]Consumption of the aldehyde signal (υ 1740-1720 cm^{-1}). [c]Work carried out by A.D.J. Calow, 2012. [d]Not monitored by ReactIR due to solubility issues, assumed reaction time comparable to cinnamaldehyde **49**. [e]Not determined.

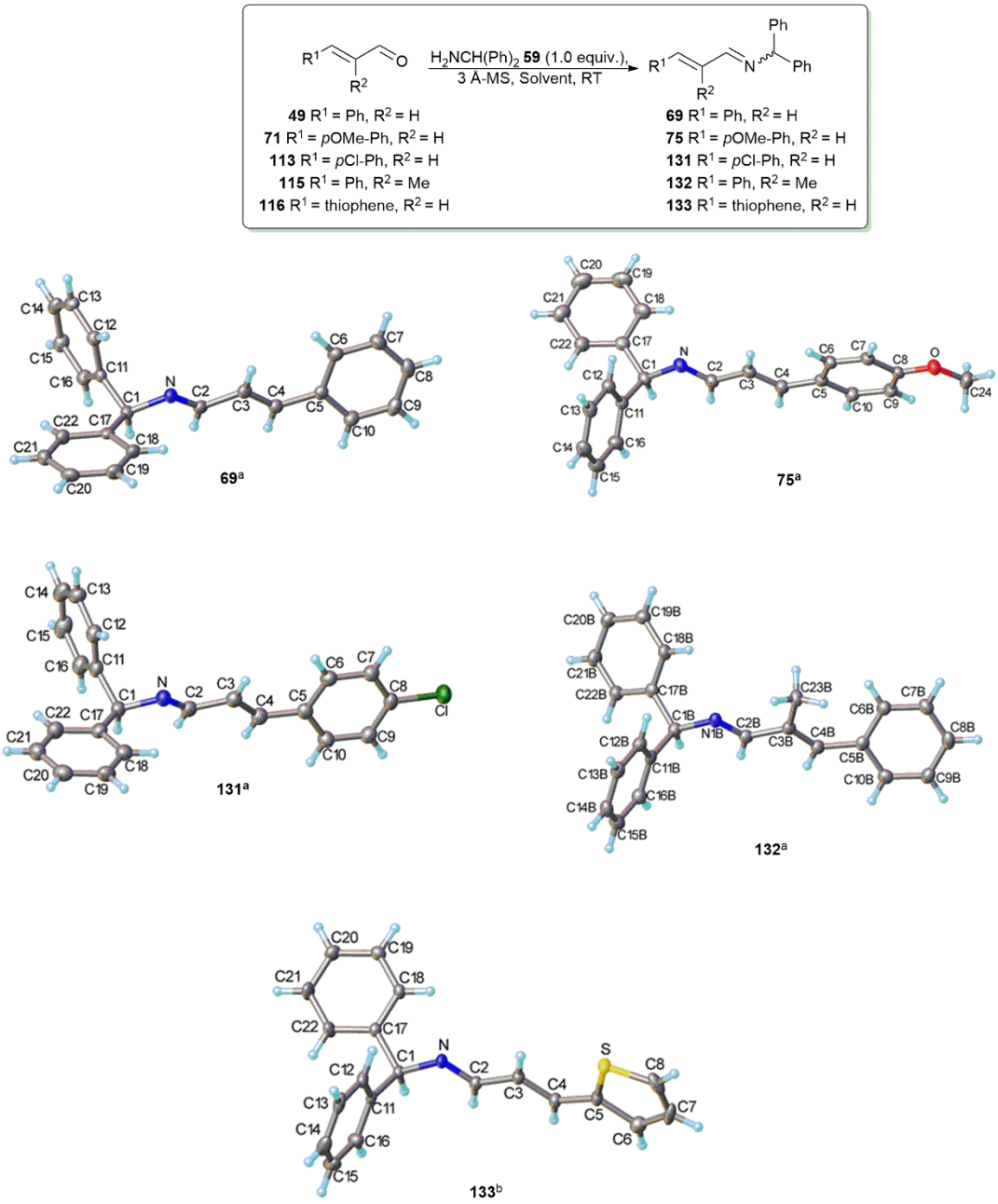
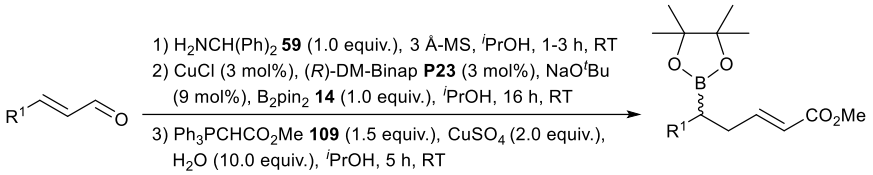


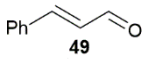
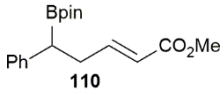
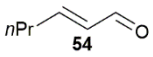
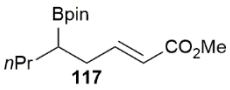
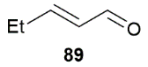
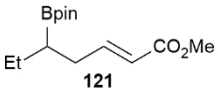
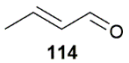
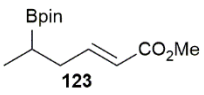
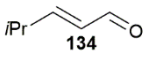
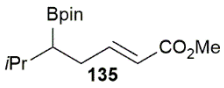
Figure 20 X-ray molecular structures of compounds **69**, **75**, **131**, **132** and **133** at 120 K. [a]Atomic displacement ellipsoids are drawn at 50% probability level. [b]The thiophene ring is disordered between two opposite orientations in 4:1 ratio (minor atom positions are primed).

The use of ^{i}PrOH resulted in favourable effects, not only in terms of a faster imine formation reaction, which was a clear improvement, but also in terms of induction of asymmetry in the addition of the boryl unit. Indeed, it was demonstrated that the use of an alcohol was crucial for this process being possible to optimise the e.e., and Table 18

summarises the selected substrates evaluated for the transformation into the corresponding homoallylic boronate carboxylate ester derivatives under this novel reaction medium.

Table 18 Enantioselective synthesis of homoallylic boronate carboxylate ester derivatives from α,β-unsaturated aldehydes in ^{i}PrOH.



Entry	α,β-Unsaturated aldehyde	Homoallylic boronate ester	IY (%)	e.e. (%)[a,b]
1	 **49**	 **110**	66	99
2	 **54**	 **117**	50	96
3	 **89**	 **121**	65	83
4	 **114**	 **123**	37	82
5	 **134**	 **135**	59	60

Reaction conditions: 1) Enal:benzhydrylamine **59** (1:1) was stirred in ^{i}PrOH and 3 Å M.S. for 1-3 h at RT; 2) An aliquot of *in situ* formed imine was transferred to a Schlenk-tube (under Ar) containing CuCl (3 mol%), (*R*)-DM-Binap **P23** (3 mol%), NaO^{t}Bu (9 mol%), B_2pin_2 **14** (1.0 equiv.) and the reaction was stirred for 16 h at RT; 3) The resulting β-boryl imine was transferred into a round bottom flask, then methyl(triphenylphosphoranylidene)acetate **109** (2.0 g, 1.5 equiv) was added, after 5 minutes $CuSO_4$ (1.3 g, 2.0 g) was added along with H_2O (0.7 mL, 10.0 equiv). The mixture was stirred for 5 h at RT. [a]Absolute stereochemistry as shown in Scheme 69 where relevant and on the basis of previous reports.[113] [b]Measured by chiral HPLC.

In fact, both hexenal and pentenal-derived products and showed e.e.s of 96% and 83%, respectively (entries 2 and 3, Table 18), and even crotonaldehyde **115** could be employed

effectively in this asymmetric process to give the corresponding homoallylic boronate in 82% e.e. (entry 4, Table 18). Furthermore, in order to complete the substrate scope, the steric effects on the C_β-substituent an additional substrate were examined; 4-methyl-2-pentenal **134** being obtained the corresponding homoallylic boronate ester **135** in a good isolated yield and 60% e.e. In this case, it is worth mentioning that although it was a more hindered substrate, the imine formation was complete within 2 h, comparable to the linear alkyl aldehyde substrates. Hence, it was concluded that the steric hindrance did not have an impact on the imine formation rate; on the other hand, the induction of asymmetry in this case was poor with a low e.e. This might be affected by the steric hindrance of the isopropyl group.

2.2.4.1. Role of the alcohol additive in the catalytic cycle for the β-borylation reaction?

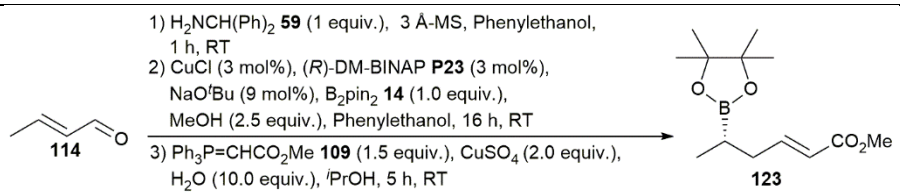
With the aim of clarifying the mechanistic details regarding the role of the alcohol and in order to understand the improvements observed from the use of ^{i}PrOH as reaction medium, additional experiments were carried out. Specifically, this consisted of the synthesis of the homoallylic boronate derivative using both enantiomers of a chiral alcohol as solvent. For this purpose, 1-phenylethanol was chosen due to its commercial availability and similarity to ^{i}PrOH (*i.e.* secondary alcohol).

(*R*)-1-Phenylethanol

(*S*)-1-Phenylethanol

Regarding the substrate, reactions were carried out on crotonaldehyde **114** which provided a low e.e. in previous studies (see entry 16, Table 16, Section 2.2.3) and therefore, would allow the visualisation of an improvement or deterioration of the asymmetric induction value, *i.e.* through double diastereoselection effects. Table 19 shows the results obtained from this set of experiments.

Table 19 Evaluation of the role of the alcohol in the asymmetry induction for the synthesis of homoallylic boronate **123**.

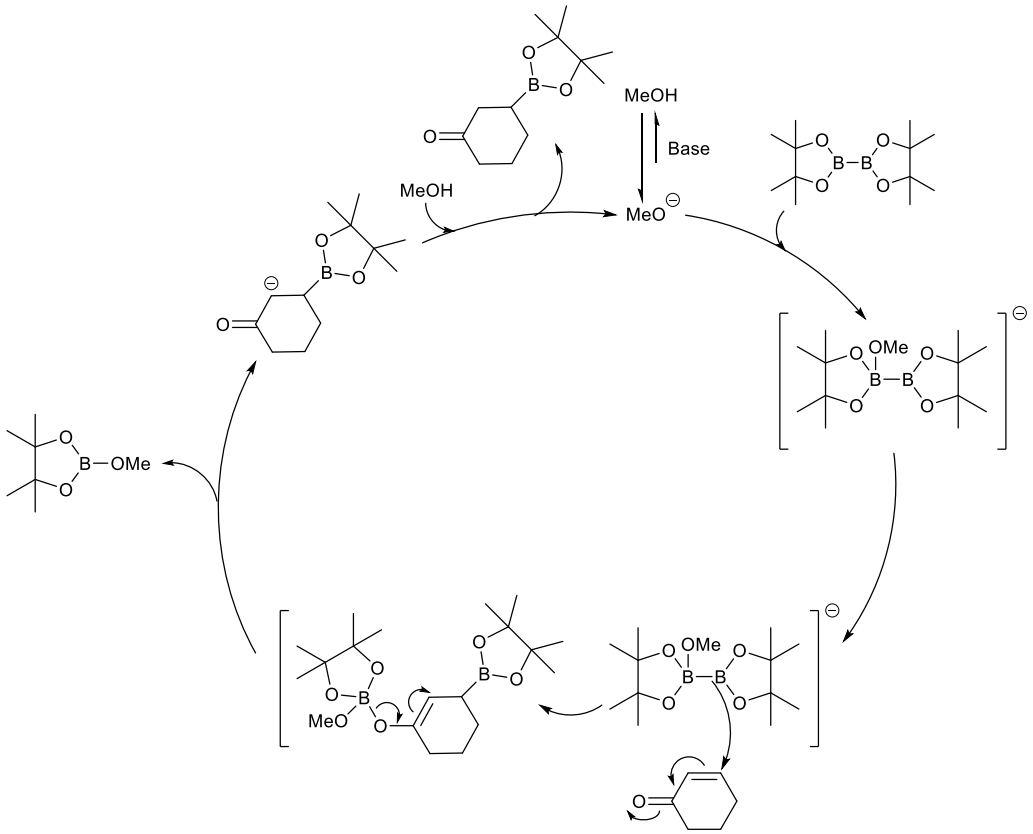


Entry	Solvent	IY (%)	e.e (%)[a]
1	^{i}PrOH	37	82
2	*(R)*-1-Phenylethanol	35	82
3	*(S)*-1-Phenylethanol	45	84

Reaction conditions: 1) Crotonaldehyde **114**:benzhydrylamine **59** (1:1) was stirred in solvent and 3 Å M.S. for 1h at RT; 2) An aliquot of *in situ* formed imine was transferred to a Schlenk-tube (under argon) containing CuCl (3 mol%), (*R*)-DM-Binap **P23** (3 mol%), NaO^{t}Bu (9 mol%), B_2pin_2 **14** (1.0 equiv.) and the reaction was stirred for 16 h at RT; 3) The resulting β-boryl imine was transferred into a round bottom flask, then methyl(triphenylphosphoranylidene)acetate **109** (2.0 g, 1.5 equiv) was added, after 5 minutes $CuSO_4$ (1.3 g, 2.0 g) was added along with H_2O (0.7 mL, 10.0 equiv). The mixture was stirred for 5 h at RT. [a]Absolute stereochemistry as shown in Scheme 69 where relevant and on the basis of previous reports.[113] [b]Measured by chiral HPLC.

No significant difference in the e.e. was observed for each of the enantiomers (entries 2 and 3, Table 19), with the difference in values being attributed to experimental ± error. This strongly suggested that here was no important role for the solvent (usually ^{i}PrOH or MeOH in the THF/MeOH conditions) during the enantio-determining step of the reaction. Hence, it was concluded that the boryl-alkoxide system is presumably not associated with the copper boryl system during the addition step; a result that would be consistent with the mechanism suggested by Fernández and co-workers[103] for the methoxy-catalysed β-borylation of α,β-unsaturated ketones (Scheme 73). This mechanism consists of the formation of an alkoxide and acid-base adduct with B_2pin_2 **14**. Then the sp^2 B atom adds to the activated olefin by heterolytic cleavage of the B-B bond and simultaneous formation of the new C-B bond. After the protonation of the anionic intermediate, the product is obtained and the methoxide initiator is regenerated and the cycle can start again. The basis of this methodology, the same group

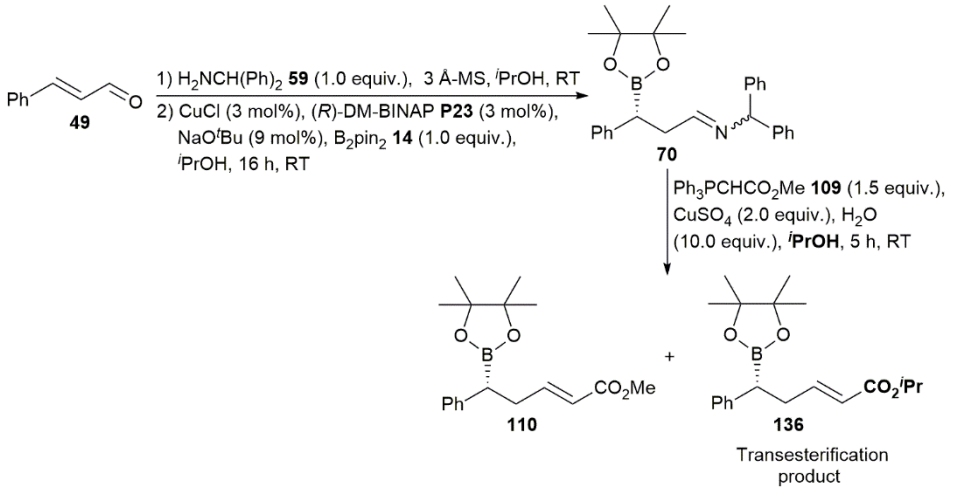
postulated a Lewis base catalysed diboration mechanism which opens up a wide-range of possibilities for organoborane synthesis on an industrial scale.[58]



Scheme 73 Methoxide-catalysed B_2pin_2 **14** conjugated addition to α,β-unsaturated ketones.

2.2.5. Homoallylic boronate esters as a useful synthetic intermediates: scaling up their synthesis

Although the methodology established herein resulted in an efficient transformation of α,β-unsaturated aldehydes into homoallylic boronate esters, a larger scale synthesis was found to be challenging, presumably due to mass transfer issues, *i.e.* the presence of a larger amount of $CuSO_4$, results in more dense reaction medium dificulting the process, hence larger it was not possible to work in a scale higher than 2.0 mmol without significant loss of yield. It is worth noting that when ^{i}PrOH was used as reaction medium, undesired transesterification side-process under the hydrolysis/Wittig reaction conditions were obtained, resulting in a mixture of homoallylic boronate esters **110** and **136** (Scheme 74)**.**



Scheme 74 Transesterification process observed for the synthesis of homoallylic boronate carboxylate ester derivatives associated to the use of ^{i}PrOH as reaction medium.

Hence, optimisation was required, both in terms of the rate of addition of the β-boryl aldimine into the hydrolysis/Wittig reaction mixture and the solvent used for the process. As with previous cases, the optimisation of the reaction was carried out on cinnamaldehyde **49** model substrate.

Firstly, the rate of addition of a solution of the boryl imine **70** to a solution of copper(II) sulfate and ylide was examined. Table 20 summarises the results obtained.

Table 20 Effect of the rate of addition of boryl imine **70** to the hydrolysis/Wittig reaction.

Entry	Addition rate	IY[a] (%)
1	1 mL/ 30 min[b]	32
2	1 mL/ 15 min[b]	54
3	1 mL/ 10 min[c]	61
4	N/A[d]	22

Reaction conditions: 1) Cinnamaldehyde **49**:benzhydrylamine **59** (1:1) was stirred in ^{i}PrOH and 3 Å-MS for 2.5 h at RT; 2) An aliquot of *in situ* formed imine **69** was transferred to a Schlenk-tube (under Ar) containing CuCl (3 mol%), (*R*)-DM-Binap **P23** (3 mol%), NaO^{t}Bu (9 mol%), B_2pin_2 **14** (1.0 equiv.) and the reaction was stirred for 16 h at RT; 3) The ^{i}PrOH was removed under reduced pressure and the solid residue of the β-boryl imine was redissolved in THF. This solution was then drop-wise added into a round bottom flask containing methyl(triphenylphosphoranylidene)acetate **109** (2.0 g, 1.5 equiv), $CuSO_4$ (1.3 g, 2.0 g) and H_2O (0.7 mL, 10.0 equiv). The mixture was stirred for 5 h at RT. [a]Isolated yield of pure homoallylic boronate carboxylate ester **110**. [b]Addition in batches of 1 mL. [c]Dropwise addition *via* syringe pump. [d]Comparative batch reaction (direct addition of Wittig reagent and copper salt directly to **70**).

It was observed that compared to the standard batch reaction (entry 4, Table 20), the slow addition of the aldimine **70** into the stirring hydrolysis/Wittig reactions mixtures (entries 2-4, Table 20) resulted in higher yields of the target homoallylboronate **110**, *i.e.* from 22% up to 61%. It is worth noting that for slower addition reactions, cleaner products were obtained.

Having optimised the addition rate of the boryl imine **70** to the hydrolysis-Wittig reaction mixture, in order to access the homoallylic boronate carboxylate ester **110**, the issue of the trans-esterification was examined by employing different solvents for the imine hydrolysis-Wittig step, as summarised in Table 21.

Table 21 Solvent optimisation for the imine hydrolysis-Wittig step converting imine **70** to homoallyl boronate **110** (see Scheme 74).

Entry	Reaction solvent	β-Boryl aldimine solvent[a]	Presence of **136**[b]	Yield of **110**[c] (%)
1	^{i}PrOH	^{i}PrOH	Yes	20
2	MeOH	^{i}PrOH	Yes	17
3	MeOH	MeOH	No	12
4	THF	THF	No	89

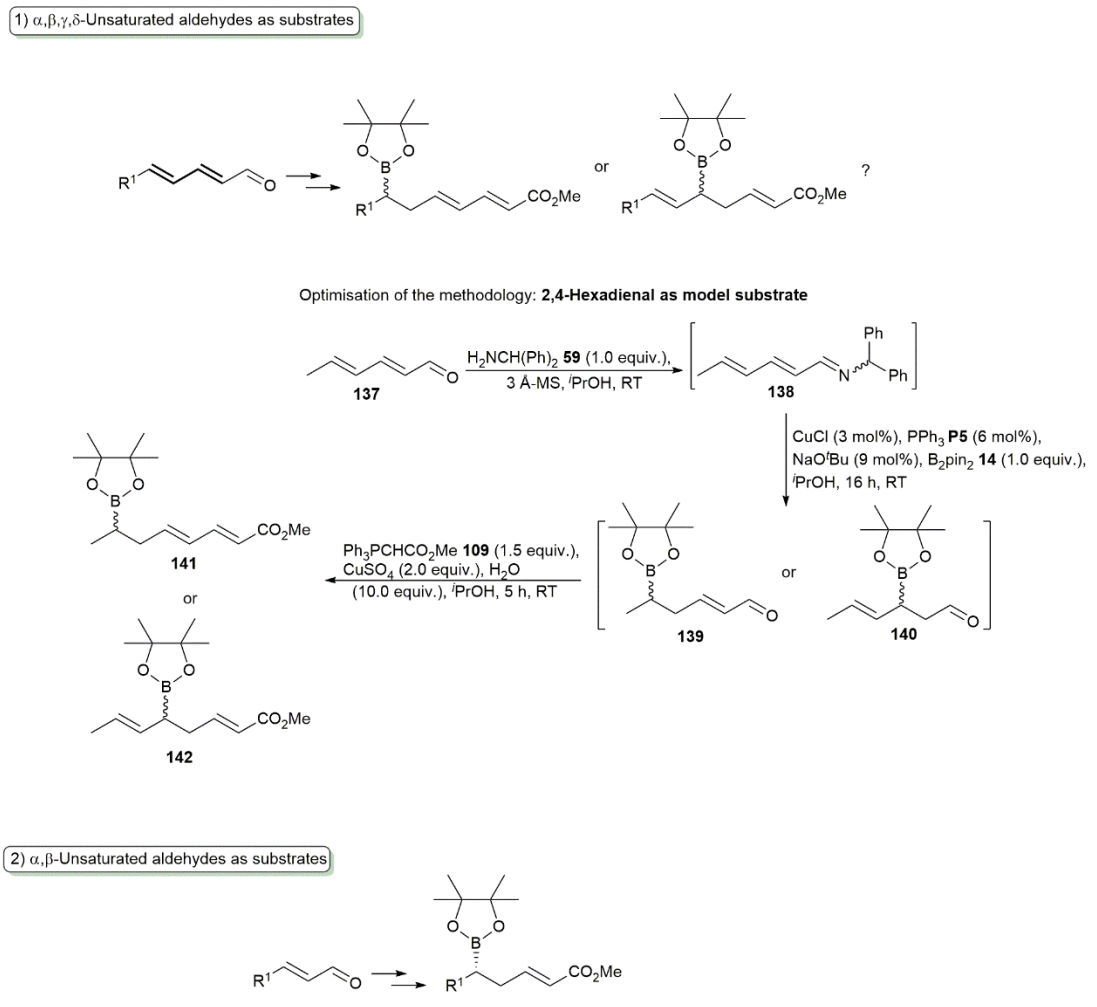
Reaction conditions: 1) Cinnamaldehyde **49**:benzhydrylamine **59** (1:1) was stirred in ^{i}PrOH and 3 Å M.S. for 2.5 h at RT; 2) An aliquot of *in situ* formed imine **69** was transferred to a Schlenk-tube (under Ar) containing CuCl (3 mol%), (*R*)-DM-Binap **P23** (3 mol%), NaO^{t}Bu (9 mol%), B_2pin_2 **14** (1.0 equiv.) and the reaction was stirred for 16 h at RT; 3) The ^{i}PrOH was removed under reduced pressure and the solid residue of the β-boryl imine **70** was redissolved in THF, followed by the addition into a round bottom flask containing methyl(triphenylphosphoranylidene)acetate **109** (2.0 g, 1.5 equiv), $CuSO_4$ (1.3 g, 2.0 g) and H_2O (0.7 mL, 10.0 equiv). The mixture was stirred for 5 h at RT. [a]Solid residue of the crude β-boryl aldimine **70** was redisolved in the stated solvent. [b]Trans-esterification product **136** observed by ^{1}H NMR (crude product). [c]Isolated yield of pure homoallylboronate **110**.

From the results shown in Table 21, it became apparent that the use of an alcohol solvent for the imine hydrolysis-Wittig step either to solvate the copper salt-Wittig reagent, or the aldimine, was not ideal either due to the esterification or due to diminished yields. Hence, after the boryl imine formation step, the use of THF (entry 4, Table 21) emerged as the best option for this transformation leading to good yields on the desired product **110** with complete suppression of the transesterification.

2.2.6. Application of the methodology to dienal systems

Once the methodology for the β-borylation on α,β-aldimine substrates was established, we were then interested in expanding the substrate scope of this protocol starting

by examining its efficiency in α,β,γ,δ-unsaturated carbonyl compounds. These type of substrates were considered interesting mainly due to the presence of the diene moiety which provides novel synthetic moieties at the same time that the functional group is the same which will allow a direct comparison with its α,β-unsaturated analogous (Scheme 75).



Scheme 75 Comparative study between α,β,γ,δ-unsaturated aldehydes and α,β-unsaturated aldehydes.

With that aim, 2,4-hexadienal **137** was chosen as model substrate and the methodology previously established was tested (option 1, Scheme 75). Firstly, the imine formation step was approached; in this case the *in situ* IR (ReactIR) technique was used for a better understanding of the reaction. Figure 21 displays the graphical output obtained in this

case, where it can be observed that the reaction rate was comparable to that obtained for the alkyl-substituted enals, *i.e.* being completed within 3 h.

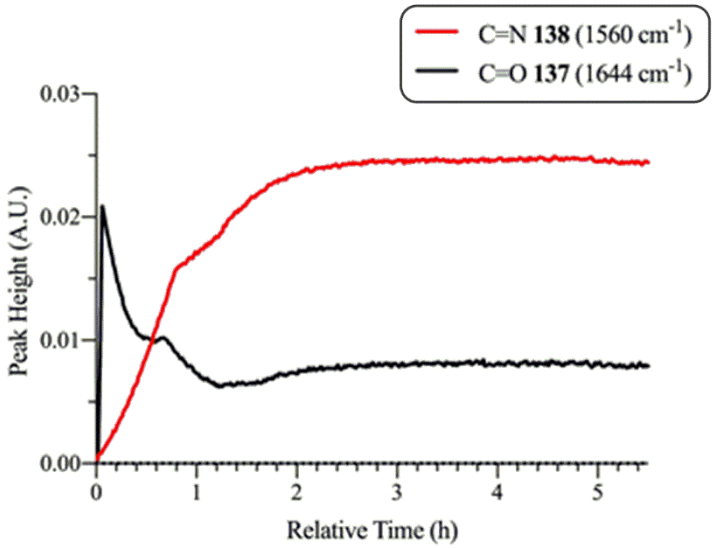


Figure 21 Graphical output corresponding to the ReactIR monitoring of the imine formation for the case of α,β,γ,δ-unsaturated aldehyde **137**.

The formation of the corresponding imine **138** was corroborated by crude ^{1}H NMR spectroscopy, which could not be purified due to the stability issues associated to this type of compound (Figure 22).

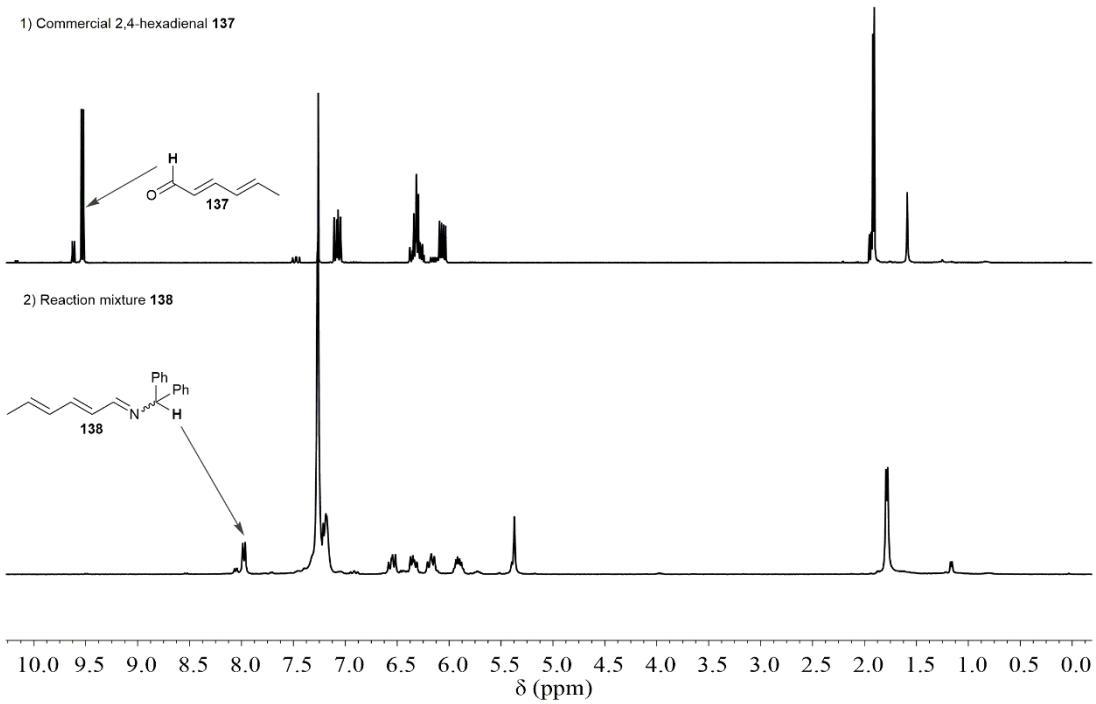


Figure 22 ^{1}H NMR spectra corresponding to: 1) commercial 2,4-hexadienal **137**; and 2) crude reaction mixture of the imine formation reaction containing α,β,γ,δ-unsaturated aldimine **138**.

Moreover, the conjugate addition of a boryl moiety was evaluated, and as envisioned, the expected chemoselectivity issue was observed.[122] In this case, the use of 1.0 equivalents of the diborane reagent **14** lead to a complex mixture of compounds which was presumably composed of the δ-boryl compound **139** along with its β-boryl analogous **140**. Hence, in order to be able to isolate the individual compounds present in this mixture, and hence clarify the outcome of the reaction, the hydrolysis/Wittig reactions sequence was applied. Surprisingly, instead of simplifying the spectrum and facilitating the isolation task, the derivatisation made the mixture more complex and it was not possible to separate the different components by silica gel chromatography. It was concluded that further optimisation of the methodology and purification was required before further application could be achieved.

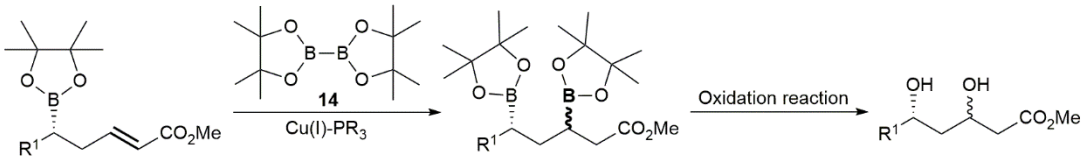
2.2.7. Summary of the enantioselective synthesis of homoallylic boronate esters from α,β-unsaturated aldehydes

In summary, an efficient one-pot methodology for the synthesis of chiral homoallylic boronates was developed (e.e.s up to 99%). During this work, the significant challenge of working with α,β-unsaturated aldehydes was met in terms of controlling the competitive 1,2-*vs.* 1,4-addition. Additionally, and more importantly, the even greater challenge of handling β-boryl aldehydes was circumvented by the development of a mild, efficient derivatisation process involving an *in situ* copper(II) sulfate-based imine hydrolysis followed by Wittig trapping of the resulting aldehyde. Additionally, the use of ^{i}PrOH as a reaction medium for all steps in the one-pot sequence resulted in faster reactions and higher e.e.s when compared to previous attempts using THF. The further exploitation of the chiral homoallylic boronates as platforms in synthetic chemistry is reported in following sections.

2.3. Exploitation of homoallylic boronate carboxylate ester derivatives as substrates for the β-borylation reaction: an ideal platform for the synthesis of versatile diborylated esters

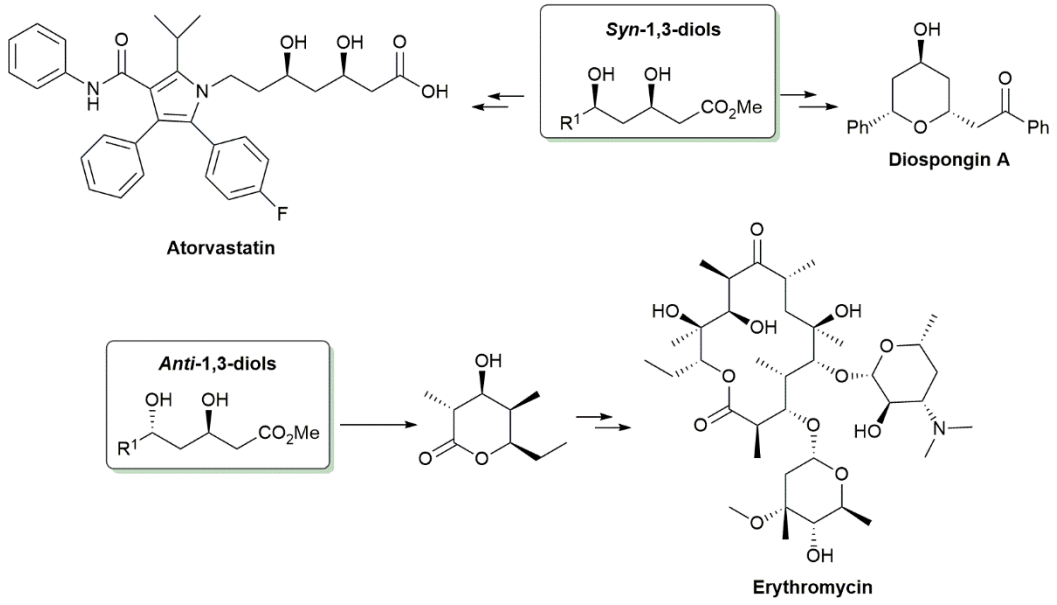
2.3.1 Background

Following on the synthesis of homoallylic boronate esters, we considered that the presence of the alkene moiety in the homoallylic boronate carboxylate esters offered the ideal opportunity for the introduction of a second boryl moiety, and hence, creating an additional C-B bond and second stereogenic centre. In turn, this opens up further synthetic possibilities for applications in asymmetric synthesis through diborylated ester derivatives, for example, to access chiral 1,3-diols (Scheme 76).



Scheme 76 Proposed pathway for the β-borylation reaction on homoallylic boronate esters and their application as intermediates for the synthesis of chiral 1,3-diols.

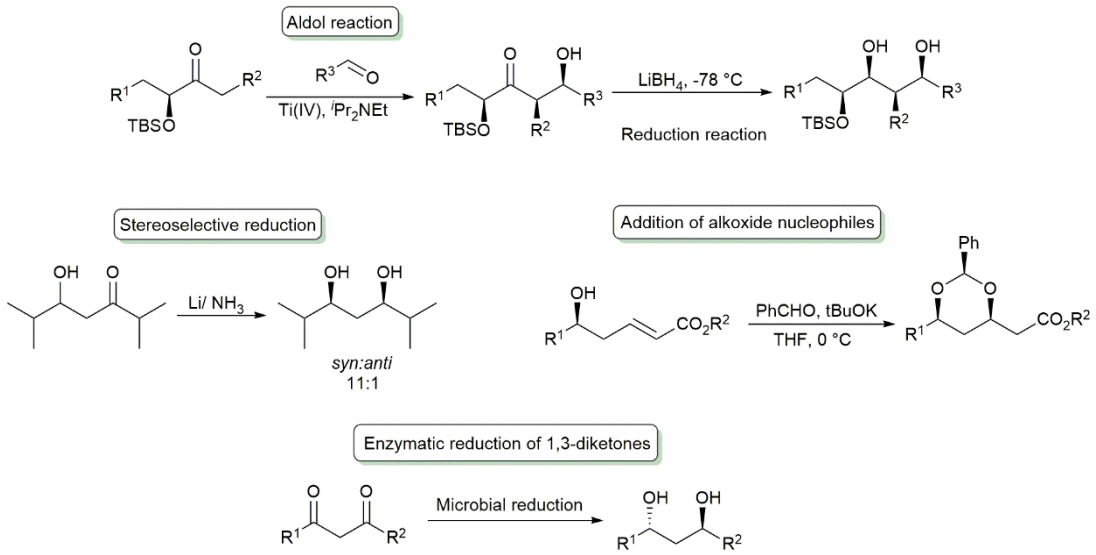
The development of effective synthetic strategies towards 1,3-diols, and more importantly, the stereochemistry control on their synthesis encompasses a very relevant area of the contemporary synthesis of natural products. This type of moiety is found in many intermediates for the synthesis of important pharmaceuticals (*e.g.* diospongin A[137] or erythromycin[138]) or also can give rise to 3,5-dihydroxy acid moieties, fragment widely present in many drugs such as statins[139] (see Scheme 77).



Scheme 77 Selected examples of compounds with biological interest containing a *syn*- or *anti*-1,3-diol moiety.

Regarding the stereoselectivity, it still represents a substantial challenge nowadays since only a few building blocks are used for the synthesis of a wide spectrum of structurally diverse compounds. Hence, small changes in well-known synthetic procedures result in a decrease in the yield or even loss of enantioselectivity.[140] Therefore, the need for alternative

routes has enhanced research in this area, and enantioselective synthesis of these key building blocks has been addressed from many perspectives, *e.g.* aldol reactions,[141] stereoselective reductions,[142] addition of alkoxide nucleophiles,[143] or even biocatalytic methods such as enzymatic reduction of 1,3-diketones,[144] amongst others (Scheme 78).

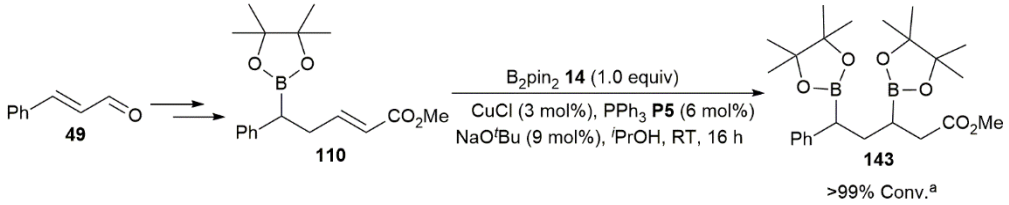


Scheme 78 Most common strategies to access chiral 1,3-diols.

Hence, in this study, homoallylic boronate esters were evaluated for their applicability as substrates for further asymmetric copper(I)-catalysed β-borylation and examining the stereochemical control effects involved in accessing the 1,3-diborylated compounds. Moreover, methods were developed to provide both relative and absolute stereocontrol at each new asymmetric stereocentre using the copper(I) phosphine ligands to effect stereocontrol. The two boryl units were then examined for transformation into functionalities which would allow unambiguous stereochemical assignment of the two borylation reactions.

2.3.2. β-Borylation reaction on homoallylic boronate carboxylate esters: optimisation of a Cu(I)-phosphine catalysed methodology

As with previous studies, the substrate chosen as the model compound was used again in this case, *i.e.* the homoallylic boronate ester **110** derived from cinnamaldehyde **49**, as displayed in Scheme 79.



Scheme 79 β-Borylation reaction of the homoallylic boronate carboxylate ester derivative **110**. [a]Convesion determined by crude ^{1}H NMR spectroscopy by consumption of starting α,β-unsaturated aldehyde **49**.

Initial attempts performed on a previously synthesised racemic version of homoallylic boronate ester **110** and under racemic standard β-borylation conditions gave rise to the corresponding diborylated ester **143**. Although substrate **110** was consumed in a conversion >99% (crude ^{1}H NMR), the presence of an additional product (*i.e.* compound **144**) was also detected. It was attributed to a non-desired transesterification side-process due to the presence of the methyl ester and the use of an alcohol in a large excess (^{i}PrOH as solvent), which would be promoted under this borylation reaction conditions, *i.e.* due to the presence of NaO^{t}Bu in the reaction medium (Figure 23).

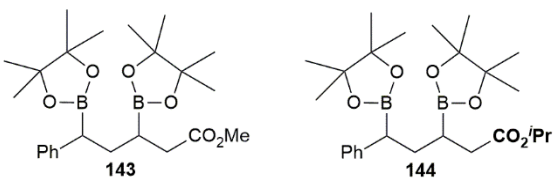
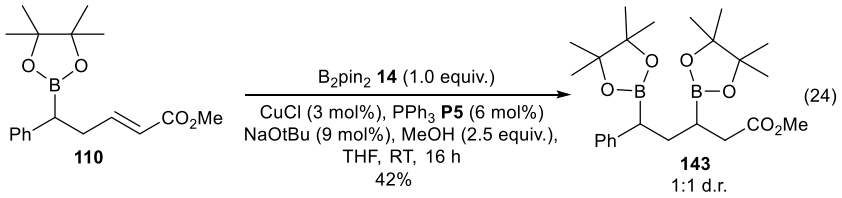


Figure 23 Structures corresponding to the different diborylated esters **143** and **144**.

After several separation attempts, it was concluded that the great similarity between compounds **143** and **144** made it very difficult to carry out clean separation. Therefore, the next goal consisted of avoiding that side reaction by using a different solvent for the β-borylation reaction of the homoallylic boronate substrate **110**. Specifically, the conventional solvent/additive system of THF/MeOH was employed again for that step [Eqn. (24)]. By this modification, the transesterification problem was successfully tackled and the target diborylated ester **143** was obtained as a 1:1 clean mixture of diastereoisomers in a 42% isolated yield.

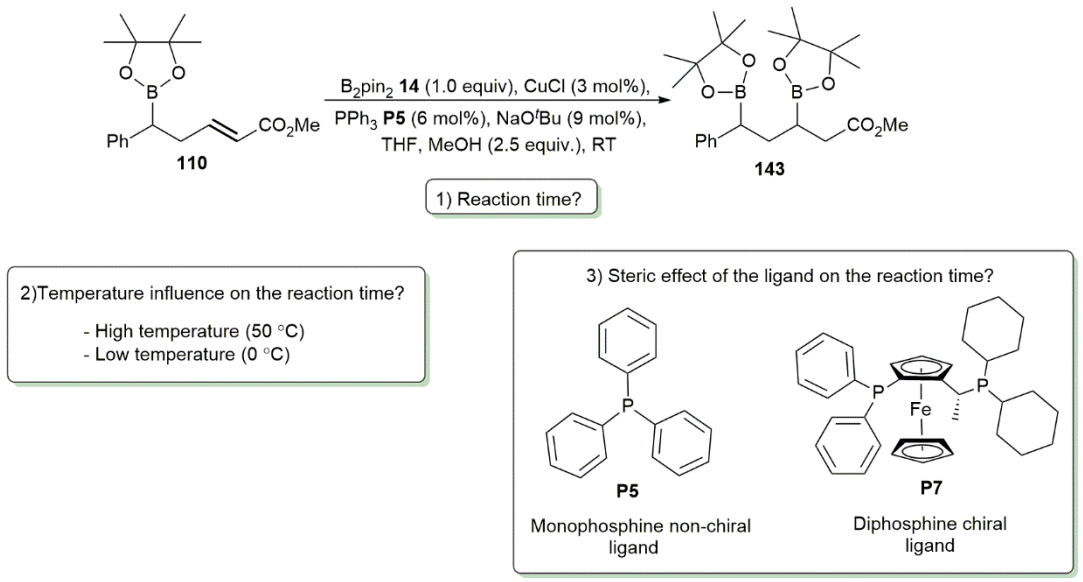


(24)

Although it was demonstrated that homoallylic boronate esters can be suitable substrates for the addition of a second boryl unit leading into versatile diborylated esters, it was considered necessary to develop a better understanding of the process. With that purpose, and based on the fact that the carbonyl functionality undergoes modification, *i.e.* from α,β-unsaturated ester functionality (homoallylic boronate ester) to a saturated ester (diborylated ester), allowing the monitoring of the process by *in situ* IR spectroscopy (ReactIR), providing an opportunity to know more details about the reaction by the optimisation of different parameters of the reaction for the model system (cinnamaldehyde-derived homoallylic boronate ester **110** as substrate);

- Time necessary for the complete borylation of the substrate (option 1, Scheme 80).
- Influence of the temperature on the reaction rate (option 2, Scheme 80).
- Steric effects of the copper-phosphine-boryl species on the reaction rate: comparison between monophosphine and diphosphine ligands (option 3, Scheme 80).

Scheme 80 displays a general overview of the experiments herein reported in order to optimise this process.



Scheme 80 ReactIR studies carried out for the optimisation of the β-borylation reaction on the model substrate **110**.

Therefore, using the model racemic system the reaction was followed, initially over time at room temperature (option 1, Scheme 80), as shown in Figure 24.

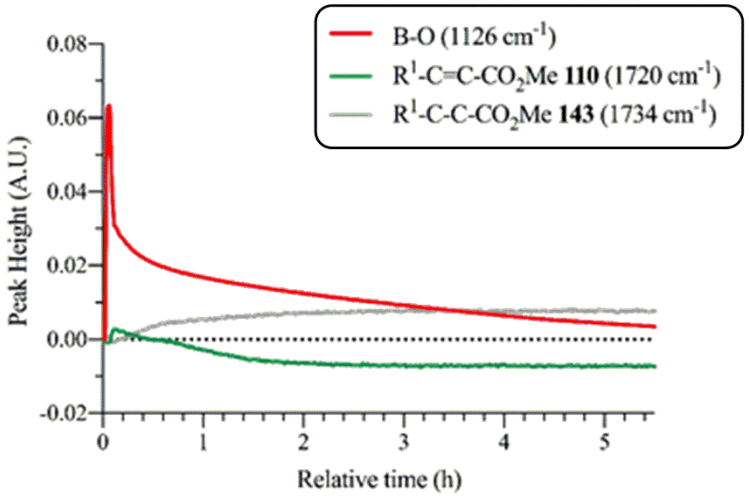


Figure 24 Graphical output corresponding to the ReactIR study of the β-borylation reaction on homoallylic boronate ester **110** at RT.

It was observed that the signal corresponding to the B-O stretch (1126 cm^{-1}) decreased considerably initially, decreasing smoothly along with the consumption of the α,β-unsaturated ester **110** (1720 cm^{-1}) and formation of the product **143** (1734 cm^{-1}) over 3 h. From this reaction, the pure product was obtained in a 47% yield; a result which was comparable to that previously reported for the first attempt in the case of the 16 h reaction (42% IY), and showing that longer reaction times were not required for this transformation.

The reaction temperature was also examined at both higher (50 °C) and lower temperatures (0 °C), respectively (option 2, Scheme 80). As was observed in the case of working at room temperature, an initial decrease in the B_2pin_2 **14** concentration took place. However, there was no other obvious influence of temperature on the reaction time (see Figures 25 and 26).

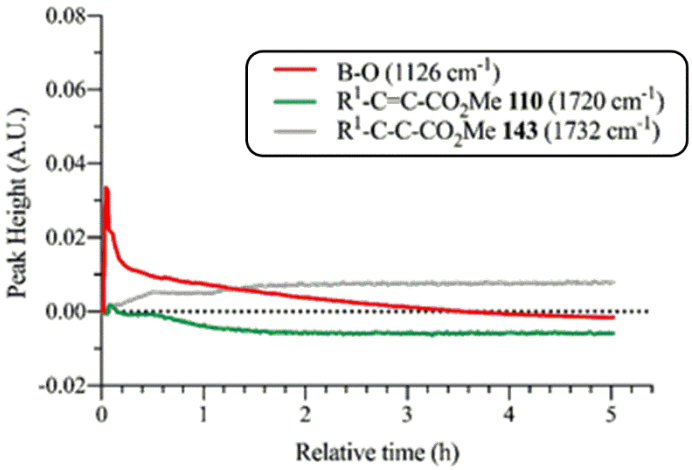


Figure 25 Graphical output corresponding to the ReactIR study of the β-borylation reaction on homoallylic boronate ester **110** at 50 °C.

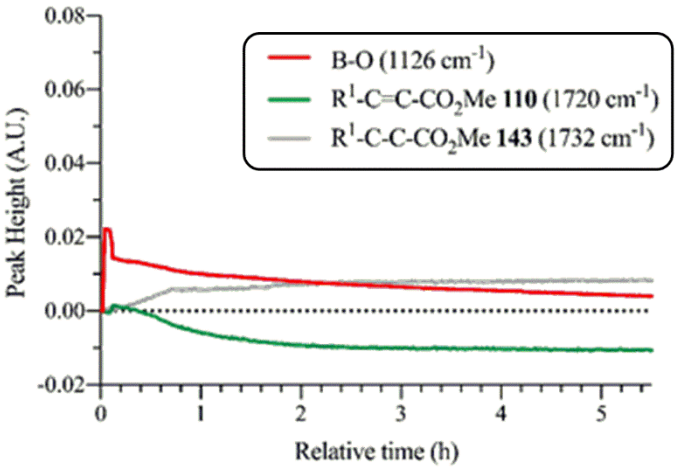


Figure 26 Graphical output corresponding to the ReactIR study of the β-borylation reaction on homoallylic boronate ester **110** at 0 °C.

Next, the phosphine ligand effect was examined, and hence, a diphosphine ligand was compared with the standard triphenylphosphine **P5** with that purpose, (*R*),(*S*)-Josiphos **P7** was applied as both a chiral and diphosphine ligand (option 3, Scheme 80). The results are shown in Figure 27.

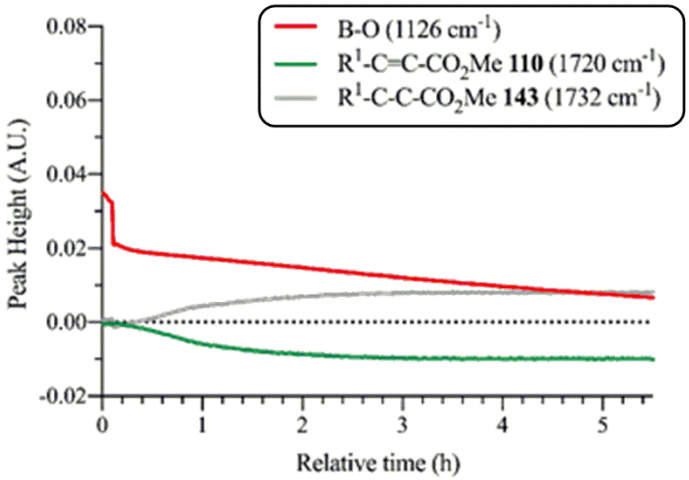


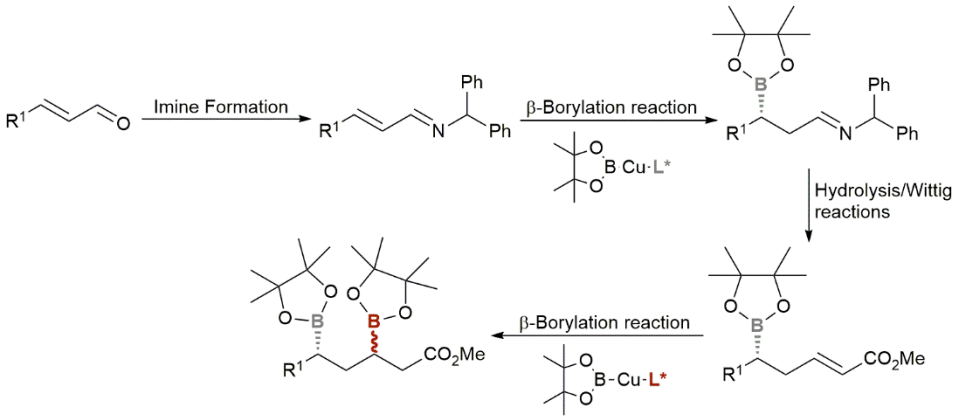
Figure 27 Graphical output corresponding to the ReactIR study of the β-borylation reaction on homoallylic boronate ester **110** using (*R*),(*S*)-Josiphos **P7** ligand, replacing PPh_3 **P5**.

By comparing Figures 24 and 27, it was clear that the presence of a more bulky and bidentate *(R),(S)*-Josiphos **P7** ligand did not have a significant influence on the reaction time.

With these results in hand, it was confirmed that homoallylic boronate carboxylate esters are suitable substrates for the β-borylation reaction allowing the access to diborylated esters and potentially open up a wide-range of synthetic possibilities.

2.3.3. Creation of a new stereocentre: induction of asymmetry in the new C-B bond

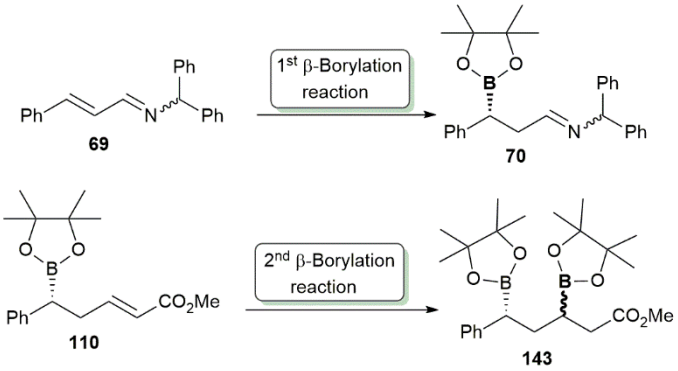
Once it was confirmed that the conjugate addition of boron on homoallylic boronate carboxylate esters was possible being, as expected, a stereocontrolled reaction; *i.e.* resulting in mixtures of diastereoisomers for the target diborylated esters (1:1 for the racemic version using PPh_3 **P5** as ligand). As reported in the literature,[63,64] the modification of the copper-boryl moiety with a chiral ligand allows the enantioselective generation of a C-B bond. Therefore, the possibility of controlling the new stereocentre by the use of a chiral ligand in this new step was envisioned (Scheme 81).



Scheme 81 Origin of the asymmetry induction during the synthesis of the diborylated esters from α,β-unsaturated aldehydes.

In order to study the effect of a chiral diphosphine ligands on the diastereoselectivity, a set of reactions were carried out on the model system using both enantiomers of DM-Binap **P23** and **P26** as ligand, varying the enantiomer of the ligand depending on the borylation step

(Scheme 82), *i.e.* previously, the (*R*)-enantiomer of this ligand (**P23**) was used in the β-borylation on α,β-unsaturated aldehydes, providing the highest e.e.s.[113] Table 22 shows the results obtained.



Scheme 82 β-Borylation on α,β-unsaturated aldimine **69** (1st borylation) and the borylation on homoallylboronate ester **110** (2nd borylation).

Table 22 Evaluation of the diastereoisomers ratio depending on the enantiomer of the chiral ligand.

Entry	Ligand		d.r.[a]	IY[b] (%)	Conv. (%)[c]
	1st Borylation	2nd Borylation			
1	*(R)*-DM-Binap **P23**	*(R)*-DM-Binap **P23**	4:1	35	>99
2	*(R)*-DM-Binap **P23**	*(S)*-DM-Binap **P26**	1:1.7	35	>99
3	*(S)*-DM-Binap **P26**	*(S)*-DM-Binap **P26**	4:1	50	>99
4	*(S)*-DM-Binap **P26**	*(R)*-DM-Binap **P23**	1:1.7	30	>99

[a]Diastereoisomeric ratio of **143** determined by ^{1}H NMR. [b]Isolated yield on 1,3-diborylated ester **143**. [c]Determined by ^{1}H NMR on pure 1,3-diborylated ester **143**.

These results confirmed the stereocontrol for the new stereocenter, as a function of the enantiomer of the chiral ligand used, *i.e.* that double diastereocontrol was operating. Although the enantioselective potential of this reaction had been demonstrated, it was envisioned that the induction of asymmetry in the creation of the novel C-B could be improved, particularly by the use of a most appropriate ligand, since in this case, the electron deficient substrate is an ester rather than an aldimine (1st borylation).

Regarding this type of substrates, in 2008 when Yun *et al.*[64] reported a study based on copper-mediated β-borylation of α,β-unsaturated esters and nitriles which showed the use of (*R*),(*S*)-Josiphos **P7** and (*R*),(*S*)-NMe_2- PPh_2-Mandyphos **P8** ligands in the catalytic system,

which provided excellent yields and >90% e.e. Hence, these ligands were also tested for the β-borylation on the homoallylic boronate ester **110** (2nd β-borylation reaction), as previously both enantiomers of each ligand were tested amongst other diphosphine ligands structurally different, as summarised in Table 23.

Table 23 Evaluation of the effect of the enantiomer of the chiral diphosphine ligand in the diastereoisomer ratio in the 1,3-diborylated ester **143**.

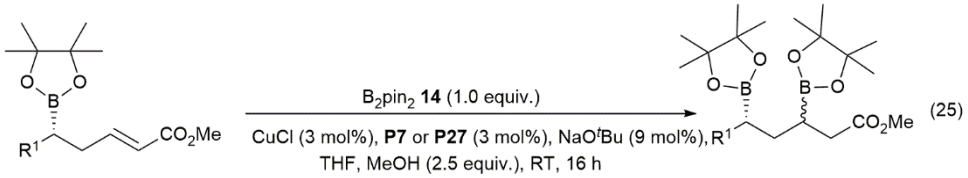
Entry	Ligand[a]	d.r.[b]	IY (%)[c]	Conv. (%)[d]
1	*(R),(S)*-Josiphos **P7**	6:1	50	>99
2	*(S),(R)*-Josiphos **P27**	1:6	30	>99
3	*(R),(S)*-NMe_2-PPh_2-Mandyphos **P8**	3:1	44	>99
4	*(S),(R)*-NMe_2-PPh_2-Mandyphos **P28**	3:1	24	>99
5	*(R,R)*-Me-DuPhos **P29**	1.85:1	42	>99
6	*(S,S)*-Me-DuPhos **P30**	1.4:1	35	>99
7	*(S,S)*-Dipamp **P31**	2.45:1	32	>99
8	*(R,R)*-Dipamp **P32**	2:1	41	>99

[a]Chiral ligand used for the β-borylation reaction on homoallylic boronate esters (2nd borylation), (R)-DM-Binap used as chiral ligand for the 1st borylation. [b]Determined by ^{1}H NMR on the diborylated ester pure sample. [c]Determined on the pure 1,3-diborylated ester **143**. [d]Determined by ^{1}H NMR on pure 1,3-diborylated ester **143**.

It was corroborated that the ferrocene-based ligands (entries 1-4, Table 23) provide good asymmetric induction for the introduction of a boryl unit into an α,β-unsaturated ester. It is remarkable the Josiphos-type ligands **P7** and **P27** (entries 1 and 2, Table 23) presented both an excellent diastereoisomer ratio, as well as giving clear matched and missmatched effects. Complementarily, less bulky ligands were tested (entries 5-8, Table 23) in which cases, no matching/mismatching effects were observed and poor asymmetric induction in the novel C-B bond also resulted, demonstrating that the steric hindrance of the ligand does have an impact on the diastereoselectivity of the reaction and reversing the substrate stereocontrol becomes difficult with the use of much more hindered ligands.

2.3.4. Evaluation of the influence of the C_β-substituent in the addition of a second boryl unit: substrate scope

In order to evaluate the influence that the C_β-substituent in the homoallylic boronate ester substrate could have on the diastereoselectivity of the reaction, a screening of different substrates was performed [Eqn. (25)].

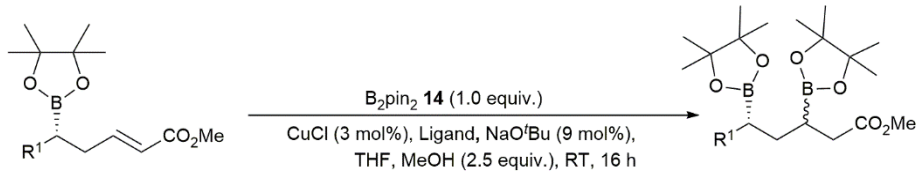


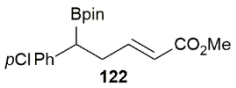
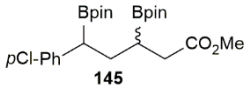
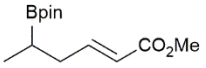
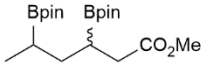
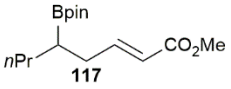
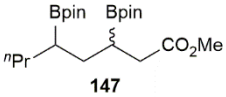
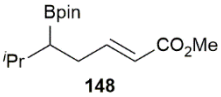
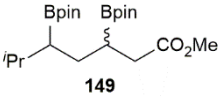
Moreover, it was envisioned that the rate of the reaction for the addition of the 2nd boryl unit could vary as function of the C_β-substituent. Therefore, reactions with the different substrates were monitored by ReactIR. Table 24 summarises the results obtained examining different substrates, using **P7** and **P27** as diphosphine chiral ligands. The new methodology worked successfully when applied to the linear substrates; compounds **123** and **117** (entries 4-9, Table 24) providing good isolated yields, whilst the aryl substitued substrates resulted in moderate yields (entries 1-3, Table 24). Moreover, when the aryl substituent was *p*-substituted with an electron donating group by resonance, but electron withdrawing by inductive effects, *e.g.* a *p*-chloro substitutent; compound **122** (entries 1-3, Table 24), the target diborylated ester was obtained in very low yields. Moreover, it was observed that the use of a more electron donating groups such as OMe in the same position did not have a beneficial effect on the reaction, and in fact, it was not possible to obtain a clean sample of the corresponding diborylated ester. On the other hand, regarding the induction of asymmetry on the new C-B bond created followed an inverse trend, *i.e.* higher d.r. values were observed for the aryl substituted substrates. Within the substrate scope, it was observed that the methodology developed for the β-borylation of the homoallylic boronate esters provided the target diborylated compounds in better yields, as well as cleaner products, for those substrates

containing an alkylic substituent in the C_β position. Therefore, 4-methyl-2-pentenal-derived homoallylic boronate ester **148** was examined.

The reaction was carried out under racemic conditions and monitored by ReactIR. As observed before with linear substrates, the reaction was completed in 2 h with the 1,3-diborylated ester **149** being obtained as a 1:1 mixture of diastereoisomers in 60% IY (entry 10, Table 24). As with the other substrates evaluated, the β-borylation reaction on the homoallylboronate was also carried out under chiral conditions using both enantiomers of Josiphos ligand, *i.e.* (*R*),(*S*)-Josiphos **P7** and (*S*),(*R*)-Josiphos **P27** (entries 11 and 12, Table 24). In both cases, the diborylated ester **149** was obtained in good yield (72% and 69%, respectively), regarding the induction of asymmetry in the new C-B bond created; the diastereoisomeric ratio obtained was 1:11 and 7:1, respectively. It is worth noting that the NMR samples had been run in a 700 MHz NMR machine using D_8-toluene as solvent, and as with other linear substrates previously analysed, improved resolution was obtained by operating at higher frequency resulting in a more accurate integration of the peaks of interest these samples. Table 24 summarises the results obtained the substrate scope herein studied.

Table 24 Substrate scope for the 2nd β-borylation reaction



Entry	Substrate	1,3-Diborylated ester	Reaction time (h)[a]	d.r.[b,c] (Ligand)	Conv. (%)[d] [IY, %]
1	 **122**	 **145**	6	1:1 (**P5**)	88 [20]
2			6	8:1 (**P7**)	89 [19]
3			6	1:5 (**P27**)	89 [18]
4	 **123**	 **146**	4	1:1[e] (**P5**)	96 [51]
5			4	1:1.38[e] (**P7**)	>99[52]
6			4	1:1.38[e] (**P27**)	>99[42]
7	 **117**	 **147**	4	1:1[e] (**P5**)	>99[78]
8			4	1:2.5[e] (**P7**)	>99[73]
9			4	1.5:1[e] (**P27**)	>99[70]
10	 **148**	 **149**	2	1:1[e] (**P5**)	>99[60]
11			2	1:11[e] (**P7**)	>99[72]
12			2	7:1[e] (**P27**)	>99[69]

[a]Reaction followed by *in situ* ReactIR. [b]Chiral ligand used for the β-borylation reaction on homoallylic boronate esters (2nd borylation), (R)-DM-Binap used as chiral ligand for the 1st borylation. [c]Determined by pure 1,3-diborylated ester ^{1}H NMR. [d]Determined by crude 1,3-diborylated ester ^{1}H NMR. [e]Determined by 700 MHz ^{1}H NMR using D_8-toluene as solvent.

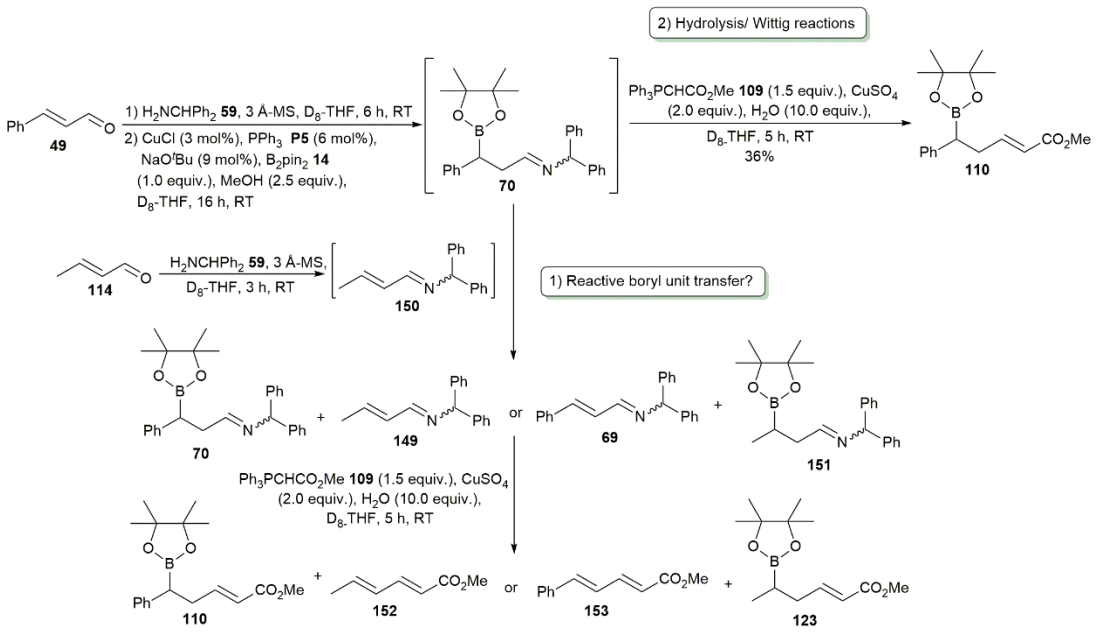
2.3.4.1. Methodology not efficient for aryl-substituted substrates: de-borylation process?

In the study on the effect of the C_β-substituent on the addition of a second boryl unit to the homoallylboronates, it was observed that the aryl substituted substrates led to poor yields of the diborylated ester. These substrates were especially challenging when phenyl substituent was *p*-substituted, such as those involving a *p*-chlorocinnamaldehyde-derived homoallylboronate **122**, where only 20% isolated yield (entries 1-3, Table 24) could be achieved. Indeed, in the case of its *p*-methoxy analogue, it was not possible to isolate a clean product, which was attributed to a possible stability problem within the homoallylboronate, resulting in a de-borylation process. Based on previous work on the synthesis of β-boryl

aldehydes, the loss of the boryl unit was observed (see Section 2.1) and a related process might be possible with the homoallylboronate substrates. It is also worth mentioning that there may be a possible contribution from the remaining Cu(II) from previous steps in the synthetic sequence (*i.e.* $CuSO_4$ used in the hydrolysis/Wittig reactions) to the de-borylation process. Hence, the crude reaction mixtures were washed with a 10% NH_3 solution in order to complex and remove the Cu(II) from the media.[132] As a result of this, cleaner crude products were obtained, although the isolated yields of the corresponding final diborylated esters was not improved.

With the aim of clarifying this, a mechanistic study was performed on the model reaction on a small scale, *i.e.* by using cinnamaldehyde **49** as starting α,β-unsaturated aldehyde and performing the reaction in D_8-THF. In this case, the β-boryl aldimine **70** was synthesised following the imine formation/β-borylation one-pot methodology, as previously described, and a portion of this crude compound was then examined further for the possible loss of Bpin unit by the introduction of an activated olefin; *i.e.* a different α,β-unsaturated aldimine, specifically that derived from crotonaldehyde **150** which would behave as a Michael acceptor in the case of that a reactive boryl unit transfer took place leading into the β-boryl aldimine **151** (option 1, Scheme 83). The rest of the β-boryl aldimine **70** crude reaction mixture was also examined for the hydrolysis/Wittig reactions sequence to corroborate that the sequence was reproducible (option 2, Scheme 83).

Scheme 83 outlines the mechanistic study carried out to examine the stability of the homoallylic boronate carboxylate ester derivatives.



Scheme 83 Mechanistic study carried out in order to determine if a de-borylation process takes place in the homoallylic boronate ester **110**.

Firstly, the reaction mixture composed of the crude β-boryl aldimine **70** along with preformed α,β-unsaturated aldimine **150** was analysed by ^{1}H and ^{11}B NMR after 6 h. No major changes in the composition of the mixture were observed, and after 3 days, the same result occurred. Furthermore, in order to be able to isolate the different compounds present, the resulting crude reaction mixture was subjected to a hydrolysis/ Wittig reaction sequence. However, this reaction resulted in a complex mixture and it was not possible to clarify its composition (option 1, Scheme 83).

On the other hand, the other half of the crude reaction mixture of the β-boryl aldimine **70** underwent the hydrolysis/Wittig sequence giving rise to the target homoallylboronate ester **110** in 36% IY (option 2, Scheme 83). This result that is slightly lower in comparison to that which was previously observed,[145] which could be associated with the small scale on which the reaction was performed (0.25 mmol) resulting in material loss, especially during the purification process.

In conclusion, a boryl unit transfer was not observed, although the complexity of the resulting mixture from this study prevented the isolation of the different compounds obtained and it was not possible to confirm their structure.

2.3.5. Determination of the relative stereochemistry: identification of the diastereoisomers

Once it was confirmed that the conjugate addition of boron to the homoallylic boronate carboxylate esters was possible, and being as expected in terms of a stereocontrolled reaction; *i.e.* resulting in mixtures of diastereoisomers for the target diborylated esters (1:1 for the racemic version using PPh_3 **P5** as ligand), it was necessary to complete the optimisation of the methodology. Hence, the identification and separation of the diastereoisomers of **143** (Figure 28) as the test substrate was next examined.

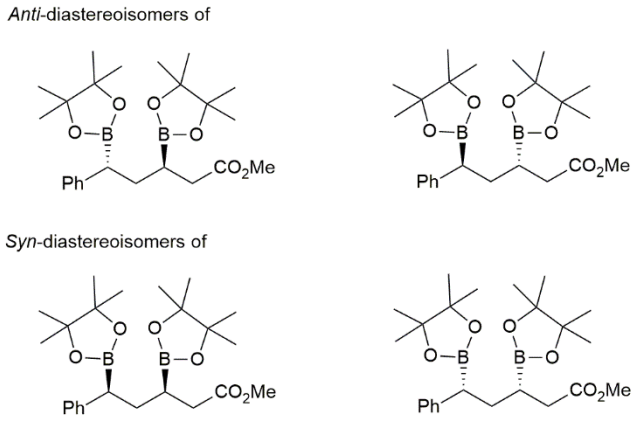
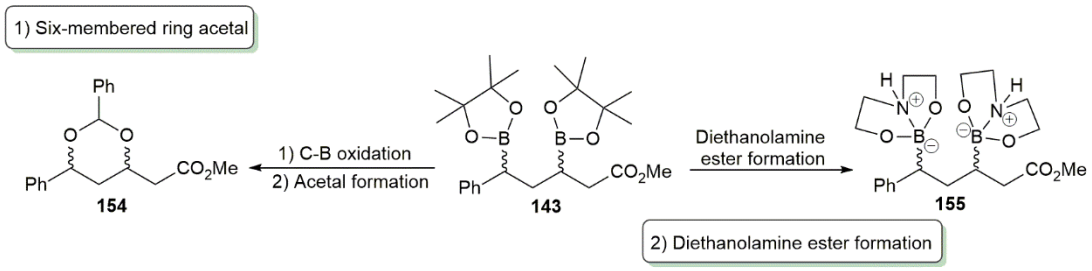


Figure 28 Possible diastereoisomers corresponding to diborylated ester **143**.

Compound **143** was examined for its transformation into derivatives that might allow the determination of the relative and absolute stereochemistry. With that purpose, two strategies were examined;

- Transformation of **143** into the corresponding six-membered ring acetal **154** and subsequent ^{1}H NMR analysis of the locked cyclic structure (strategy 1, Scheme 84)
- Formation of the corresponding diethanolamine-boron complex **155** and the corresponding X-ray diffraction studies on the crystalline solid (strategy 2, Scheme 84).

Scheme 84 outlines a general overview of the synthetic pathways herein evaluated.

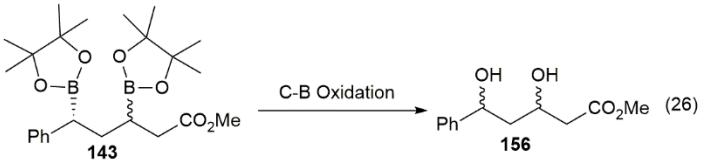


Scheme 84 Synthetic pathways studied to obtain cyclic structures that allow the determination of the relative stereochemistry.

Firstly, strategy 1, involving a six-membered ring acetal **154** formation was examined. The synthetic pathway to transform the diborylated ester **143** into the corresponding acetal **154** consisted of double B-C bond oxidation, leading to the 1,3-diol intermediate **156**, followed by acetal incorporation.

Within this strategy, the oxidation step constitutes an interesting step mainly in terms of optimisation; in this case, rather than use standard oxidation conditions for the transformation of **143** to **156**, *i.e.* sodium hydroxide/hydrogen peroxide, we decided to avoid such aqueous conditions due to the high solubility of diols and the likelihood of not being able to easily extract the product from the oxidation. Hence, non-aqueous conditions were tested using trialkylamine *N*-oxides, which have been widely demonstrated to oxidise the B-C bond in a range of systems [Eqn. (26)].[133] Application of 4-methylmorpholine-*N*-oxide **94** (4-

MMNO) to access the 1,3-diol intermediate **156** from **143** did result in formation of the diol, however, after purification by silica gel chromatography, it was not possible to obtain the desired 1,3-diol **156** product cleanly. It was because the oxidation reaction required high loadings of the oxidising agent (8.0 equiv.) and hence, the residual oxidant and amine were not easily separated from the product. Therefore, to optimise this procedure further and avoid this issue, the use of an alternative trialkylamine *N*-oxides was examined. In this case, trimethylamine *N*-oxide **157** (TMANO)[146] proved to be superior. The different *N*-oxide conditions examined are summarised in Table 25.



(26)

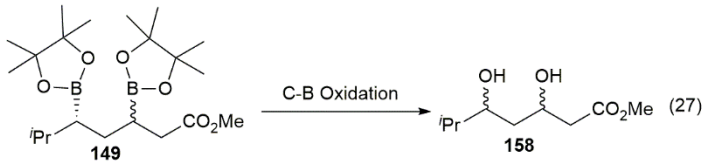
Table 25 Screening oxidation conditions to obtain 1,3-diol **156** from the diborylated ester **143**.

Entry	*N*-Oxide (equiv.)	Reaction time (h)	Temp. (°C)	Isolated yield[a] (%)
1	4-MMNO **94** (2)	6	RT	52 [b,d]
2	4-MMNO **94** (4)	16	RT	23[b,d]
3	TMANO **157** (2)	6	RT	26[b,d]
4	TMANO **157** (2)	3	50	60[c,d]

[a]Isolated yield of pure diol **156**. [b]For full conversion (>90%) longer reaction times (up to 32 h) as well as addition of extra oxidising agent (2 or 4 equiv.) were required. [c]Reaction stirred for an additional 3 h to ensure full completion. [d]Different samples of compound **143** were used to test the different sets of oxidation conditions. The d.r. of each sample was the same after oxidation.

It was found that the most suitable *N*-oxide was TMANO since it required a lower loading than 4-MMNO **94**. Indeed, this could be used to provide shorter reaction times by running the reaction at 50 °C (entry 4, Table 25). Under these conditions, the racemic diboronate **143** could be successfully transformed into the target diol **156** in a 60% yield. However, when this methodology was tested on a structurally different substrate, *i.e.* isopropyl substituted analogous diborylated ester **149** [Eqn. (27)], it was found that the reaction was not as effective as it was for the model substrate **143** and longer reaction times as well as larger

amounts of TMANO **157** (up to 48 h and 8.0 equivalents, respectively) were required. Therefore, this transformation needed to be optimised further and alternative oxidation conditions were tested for that purpose (Table 26).



(27)

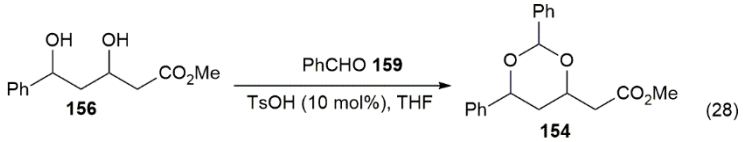
Table 26 Screening conditions for the oxidation of diborylated ester **149**.

Entry	Oxidant reagent (equiv.)	Solvent	Conv.-**158**[a] (%)
1	$NaBO_3.4H_2O$ (6.0)	THF/H_2O	>99
2	Oxone (6.0)	MeOH	0
3	MCPBA (6.0)	DCM	>99

Reaction conditions: For a 0.2 mmol reaction scale, stirred at RT during 2h, monitorisation by TLC. [a]Determined by crude ^{1}H NMR.

As expected, $NaBO_3.4H_2O$ (entry 1, Table 26) was found to be an ideal reagent for the oxidation of C-B bonds as it has been widely reported in the literature.[147,148] The reaction using MCPBA gave complete conversion to the desired diol **158**, however, the reaction was not as clean as with sodium perborate, whilst the use of Oxone did not yield into the desired 1,3-diol **158**. Although its efficiency as an oxidising agent had been widely demonstrated,[149] it was found to not be suitable for this type of system. Hence, it was concluded that sodium perborate conditions were optimal for this transformation.

With the oxidation step optimised, the acetal formation was exhaustively studied in order to determine the optimal conditions for this transformation [Eqn. (28)]. Benzaldehyde **159**[150] was chosen in first place and the different parameters of the reaction were modified. Table 27 summarises the conditions screened for the synthesis of acetal **154** from diol **156**.



(28)

Table 27 Conditions for the synthesis of acetal **154** from the diol **156**.

Entry	PhCHO **159** (equiv.)	3 Å-MS	Temp. (°C)	Reaction Time (h)	Conv.[a,b] (%)
1	1.1	No	0	1.5	-
2	2.5	No	RT	1.5	24
3	1.1	Yes	RT	1.5	20
4	1.1	No	50	1.5	25
5	1.1	No	RT	1.5	-[c]
6	2.5	Yes	50	1.5	50
7	2.5	Yes	50	1.5	-[c]
8	1.5[c]	Yes[d]	50	6	>99

[a]Determined by crude ^{1}H NMR on the acetal **154**. [b]Different samples of compound **156** were used to test the different sets of oxidation conditions. The d.r. of each sample was the same after oxidation. [c]Toluene was used as solvent. [d]$PhCH(OMe)_2$ **160** used instead of PhCHO **159**, using 4 Å M.S.

Using benzaldehyde **159**, it was observed that the reaction was difficult to follow and estimate the conversion of the 1,3-diol to the target acetal. The reaction was not clean enough to follow easily, especially with the excess benzaldehyde **159**. Although reaction did take place, the product was not easily isolated in a pure form, and hence, benzaldehyde dimethyl acetal was examined; the target acetal **154** was successfully obtained using optimised conditions (entry 8, Table 27), when non-chiral conditions were used for the β-borylation reactions in previous steps, *i.e.* starting from a racemic diborylated ester. Interestingly, the 6-membered ring acetal was obtained as one major isomer in 40% IY and ^{1}H NMR spectroscopy readily aided the identification of this diastereisomer by examination of the ring coupling constants, it was observed a *trans*-diaxial coupling constant, typically *J* 9-12 Hz, between *H-1* and *H-2'* (*J* 11.3 Hz) and a cis-^{3}J coupling, *J* 3-6 Hz, between *H-1* and *H-2* which clearly showed that both the phenyl and carboxylate groups were orientated in an equatorial position (Scheme 85). Figure 29 shows the ^{1}H NMR spectrum corresponding to the acetal **154** obtained from the racemic version of the reaction after purification being highlighted the crucial signals for the relative stereochemistry assignment.

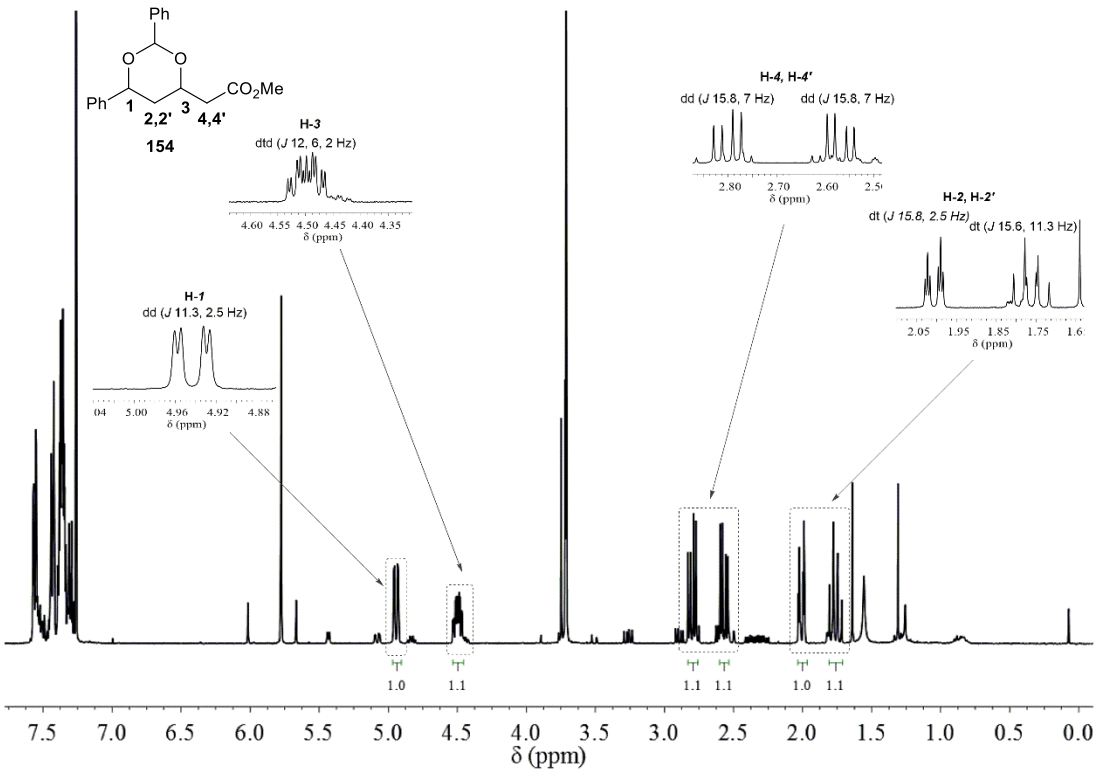
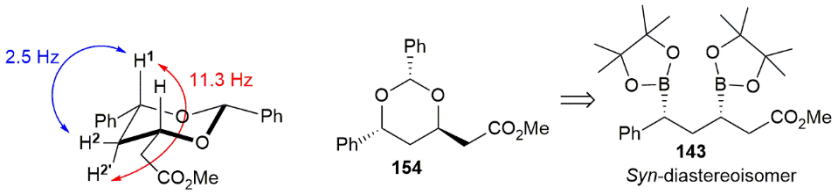


Figure 29 ^{1}H NMR spectral analysis for the determination of the relative stereochemistry of the major diastereoisomer obtained for the racemic version of the synthesis of six-membered ring acetal **154**.

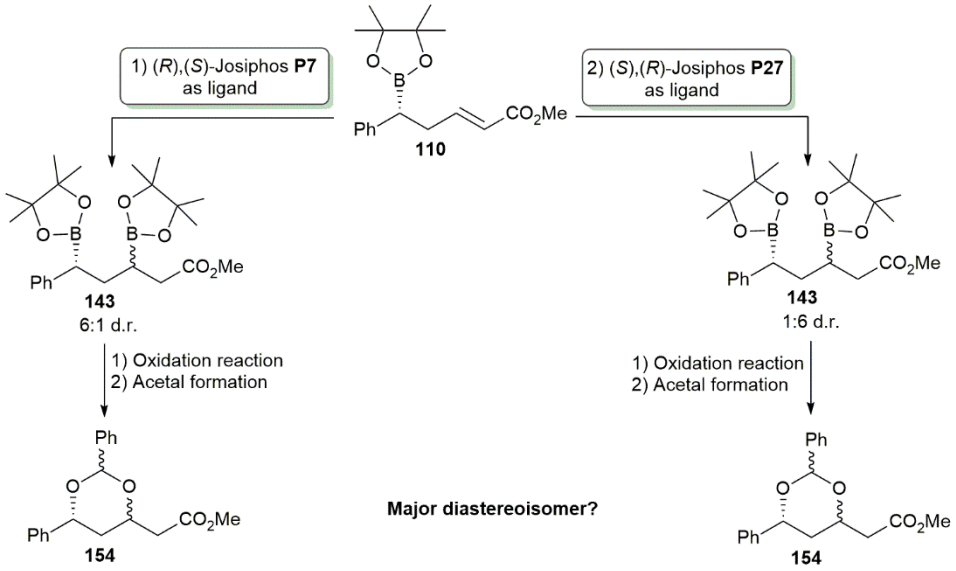
With these results in hand, it was concluded that the major diastereoisomer of **154** was derived from the 1,3-*syn*-stereoisomer of the 1,3-diol **156**, and hence, the diboronate **143** was also *syn* (Scheme 85).



Scheme 85 *J* coupling values observed for the major diastereoisomer obtained from the racemic version of the reaction corresponding to the *syn*-diastereoisomer.

In this case, it was concluded that the formation of both diastereoisomers did take place as a 1:1 mixture, however, the diastereoisomers differ in terms of their behaviour during the column chromatography, *i.e.* one of the diastereoisomers interacts more with the silica gel (remaining retained for longer on the column), whilst the other was easier to extract from the column, fact that would be corroborated by the IY being only 40%.

Moreover, our aim consisted of separating and identifying the diastereoisomers for those cases in which a chiral diphosphine ligand was used, *e.g.* (*R*),(*S*)-Josiphos **P7** and (*S*),(*R*)-Josiphos **P27**. With that purpose, the diborylated ester **143**, obtained as a mixture of diastereoisomers in each case, underwent oxidation and acetal formation sequence, as summarised in Scheme 86.

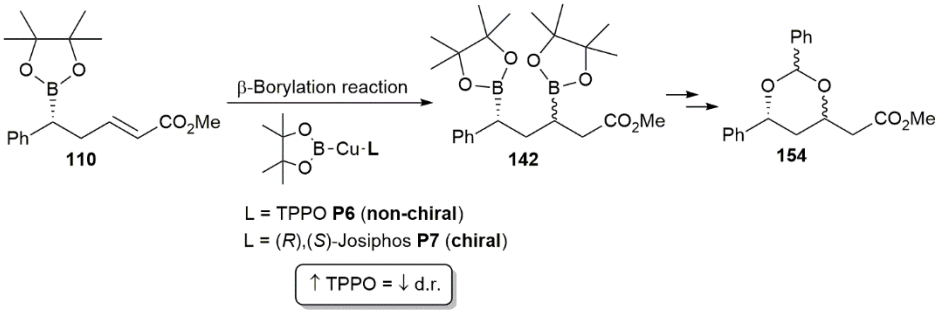


Scheme 86 Examination of chiral six-membered ring acetals to determine the relative stereochemistry on the 2nd β-borylation depending on the enantiomer of the chiral diphosphine ligand used for the phenyl substituted model system.

Firstly, the diborylated ester resulting from the β-borylation reaction using (*R*),(*S*)-Josiphos **P7** as ligand (option 1, Scheme 86), was subjected to the oxidation and acetal formation reaction conditions, as previously described, giving rise to the target acetal **154**. In this case, the acetal was obtained in good conversion (*i.e.* >99%) as a 4:1 mixture of diastereoisomers. It is worth mentioning that although this ratio was previously reported as 6:1 (see Section 2.3.3), for this specific reaction it was found that the corresponding diborylated ester was isolated as a 4:1 mixture of diastereoisomers; a ratio that matches with the one observed for 1,3-diol. The diastereoisomeric ratio can vary slightly from one reaction to another due to two main causes:

- The measured ratio results from the integration in the ^{1}H NMR spectrum which has associated error.

- During the experimental procedure, some purity issues of the commercial ylide, *i.e.* methyl (triphenylphosphoranylidene)acetate **109** were encountered (some traces of triphenylphosphine oxide, TPPO **P6** were detected) which varied with the batch of reagent used. It was concluded that for those cases containing a high proportion of this contaminant, that it perhaps participates detrimentally in the borylation reaction and has a negative effect on the diastereoselectivity of the reaction (Scheme 87).



Scheme 87 Effect of the proportion of TPPO **P6** on the variation on the d.r. observed for the diborylated esters.

Following on the determination of the relative stereochemistry for this model system, the six-membered ring acetal **154** was purified by silica gel column chromatography and it was possible to separate the diastereoisomers (4:1 d.r.). As a result of this purification process, a fraction containing one of the diastereoisomers (only a minor proportion of the other diastereoisomer was detected, approximately 5%) was obtained (spectrum 1, Figure 30) along with a second mixed fraction (spectrum 2, Figure 30). These fractions represent 15 and 55% IYs, respectively.

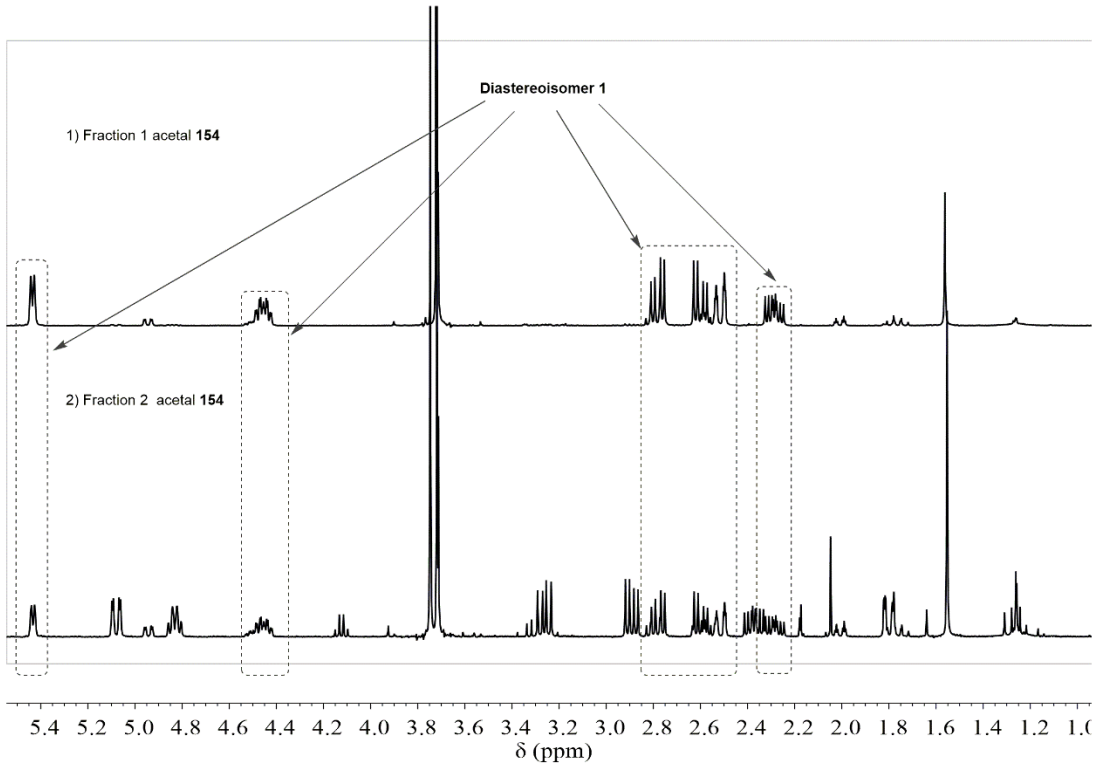


Figure 30 ^{1}H NMR spectra corresponding to; 1) fraction 1 (pure diastereoisomer) and 2) fraction 2 (mixed fraction) of acetal **154** highlighting the key signals for the relative stereochemistry assignment.

Firstly, the analysis of the *J* coupling constants was performed on the fraction that contained a single diastereoisomer (spectrum 1, Figure 30) to determine the relative stereochemistry for this diastereoisomer, and hence, by subsequent comparison and subtraction of the spectrum for the mixed fraction (spectrum 2, Figure 30), the major diastereoisomer could be identified. Figure 31 displays the structural analysis carried out on the major diastereoisomer for compound **154**.

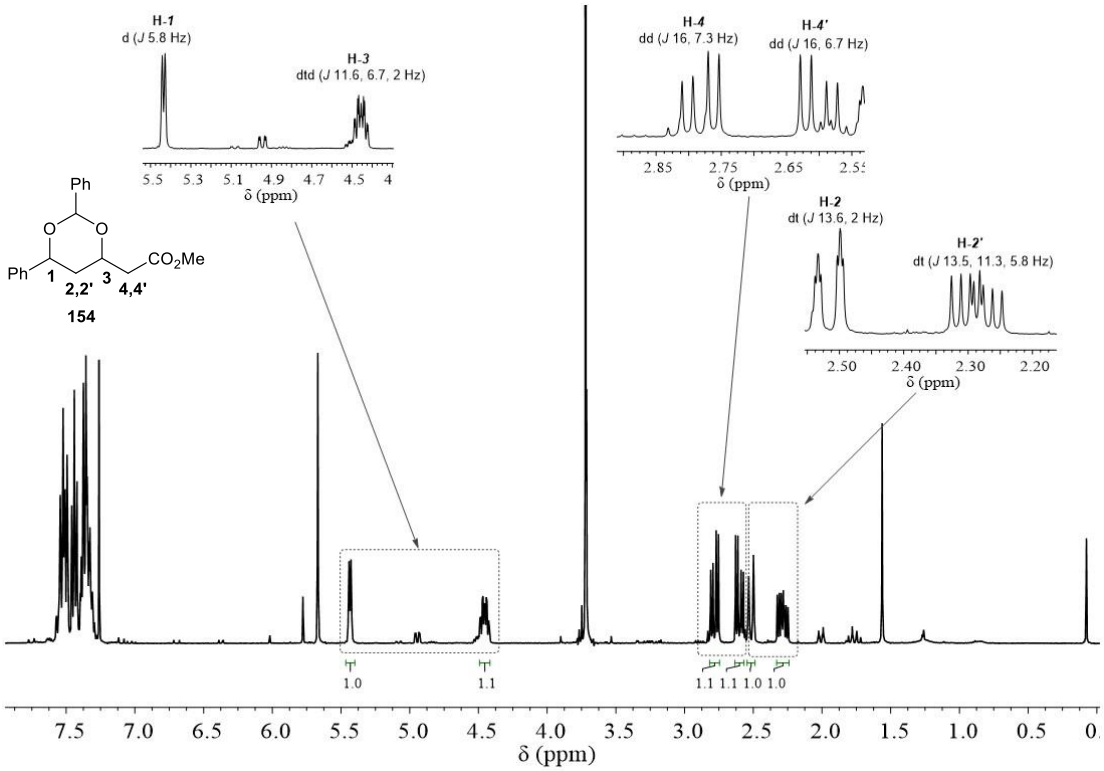
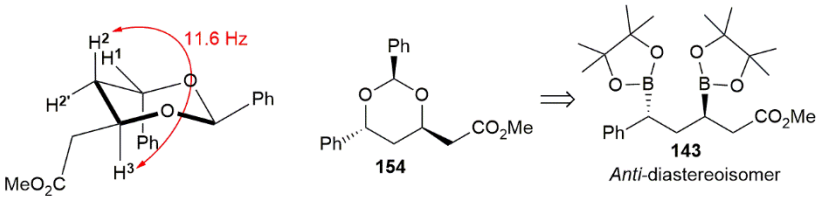


Figure 31 ^{1}H NMR analysis performed on fraction 1 of acetal **154** in order to determine the relative stereochemistry.

With these results in hand, it was concluded that the relative stereochemistry of the acetal present in the first fraction corresponded to the *anti*-diastereoisomer, as displayed in Scheme 88.



Scheme 88 *J* couplings for the *anti*-configuration of the 6-membered ring acetal **154**.

Surprisingly, when the other fraction was analysed, instead of the expected *syn*-diastereoisomer, what was observed was a different diastereoisomer of **143** (Figure 32).

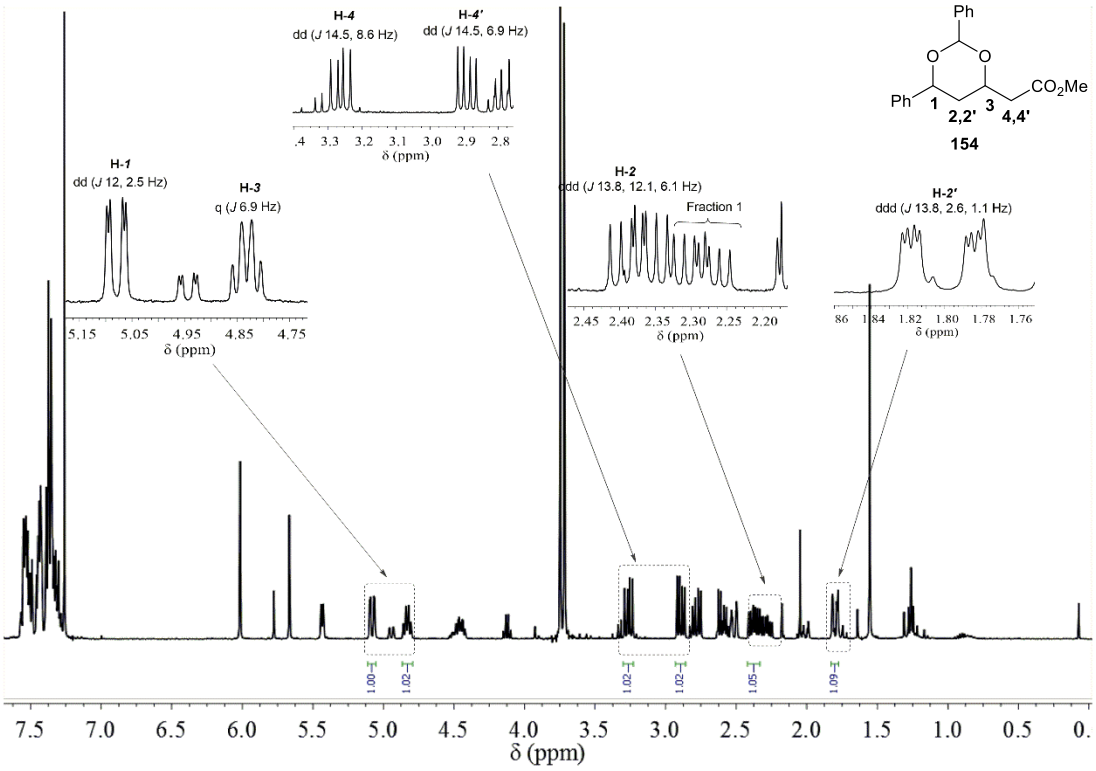
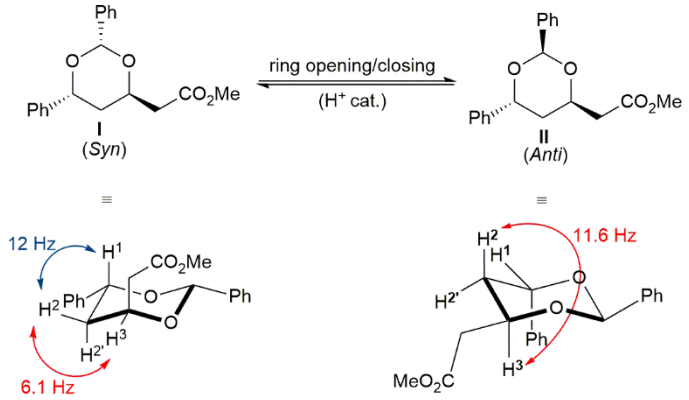


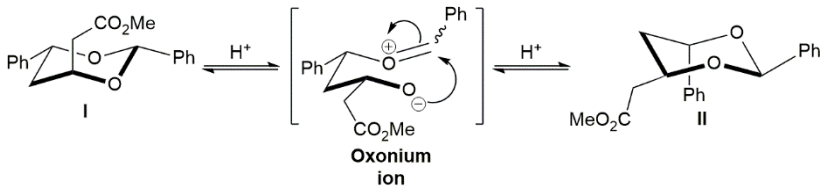
Figure 32 ^{1}H NMR analysis of fraction 2 of acetal **154** in order to determine the relative stereochemistry.

These different diastereoisomeric acetals are produced and may interconvert under the formation conditions in equilibrium when formed, most likely preferably as diastereosiomers **I** and **II** due to minimisation of the 1,3-diaxial interactions of the bulky phenyl groups (Scheme 89).



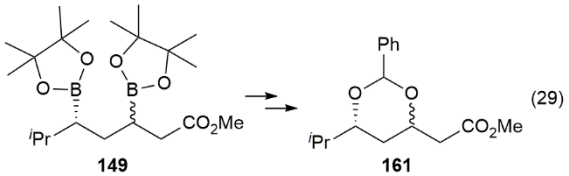
Scheme 89 Configurational enantiomers for the 6-membered ring phenyl-substituted acetal **154**.

The interconversion between these diastereoisomers can take place due to ring opening/ring closing of the acetal in the presence of catalytic amounts of acid during their formation. In this case the benzylidene acetal position changes as results of the opening of this group and generation of the oxonium ion which subsequently closes, as outlined in Scheme 90. Hence, a thermodynamic ratio of acetal configurations is expected. Indeed, subsequent re-examination of the crude ^{1}H NMR showed a 1:1 ratio of acetals **I** and **II**.



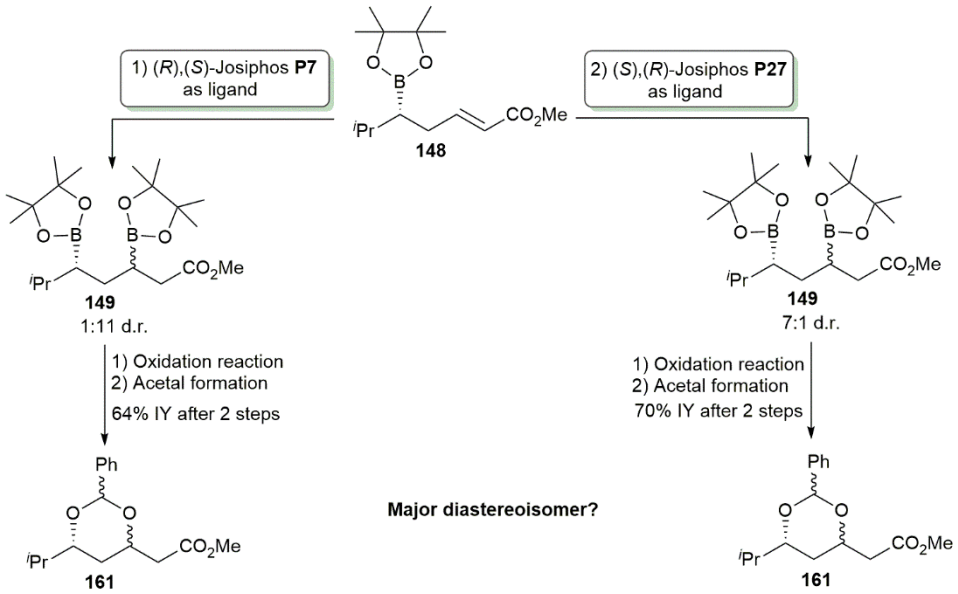
Scheme 90 Possible explanation of the presence of different conformational isomers for the case of the structural analysis of the 6-membered ring acetal **154**.

It was concluded that in addition to this substrate, it was appropriate to study systems with different substituents to two phenyl groups, hence, a non-aryl substituted substrate, *e.g.* the derived from the isopropyl substituted system **149** [Eqn. (29)] was examined. This substrate was chosen due to the fact that when the introduction of the second boryl unit was evaluated in previous sections, an excellent diastereoselectivity was observed (up to 1:11 and 7:1, for (*R*),(*S*)-Josiphos **P7** and (*S*),(*R*)-Josiphos **P27**, respectively), hence, it was envisioned as an ideal substrate for this purpose.



With that purpose, the 6-membered ring acetal **161** was synthesised *via* the oxidation/acetal formation sequence previously described. At this stage, it was interesting to note that the oxidation reaction was found to require longer times for completion, in comparison to the model system (*i.e.* Ph-substituted), for either TMANO or $NaBO_3.4H_2O$ conditions. A suitable explanation for this might be the steric hindrance associated with the

isopropyl group on C_β. Furthermore, the target chiral acetals **161** were successfully obtained in good yields, as summarised in Scheme 91.



Scheme 91 Examination of chiral 6-membered ring acetals in order to determine the relative stereochemistry on the 2nd β-borylation depending on the enantiomer of the chiral diphosphine ligand used for the isopropyl substituted substrate.

Although it was possible to purify the acetals, they were obtained as a mixture of diastereoisomers in both cases due to co-elution during the column chromatography. Therefore, preparative HPLC was considered an ideal option to obtain a clean sample that allow us to identify the diastereoisomers, and hence, determine the relative stereochemistry of the diborylated esters for each case, depending on the chiral diphosphine ligand. With that aim, the reaction was carried out and resulted in the highest diastereoselectivity, *i.e.* when using (*R*),(*S*)-Josiphos **P7** the diborylated ester was obtained as an 1:11 mixture of diastereoisomers and which was purified by preparative HPLC. From this purification process, it was possible to obtain a clean sample of the major component which allowed the structural analysis to be undertaken and comparison with the mixed fraction, the analysis could be completed. Figure 33 summarises the ^{1}H NMR data extracted from the analysis of the different fractions obtained for the 6-membered ring acetal **161**.

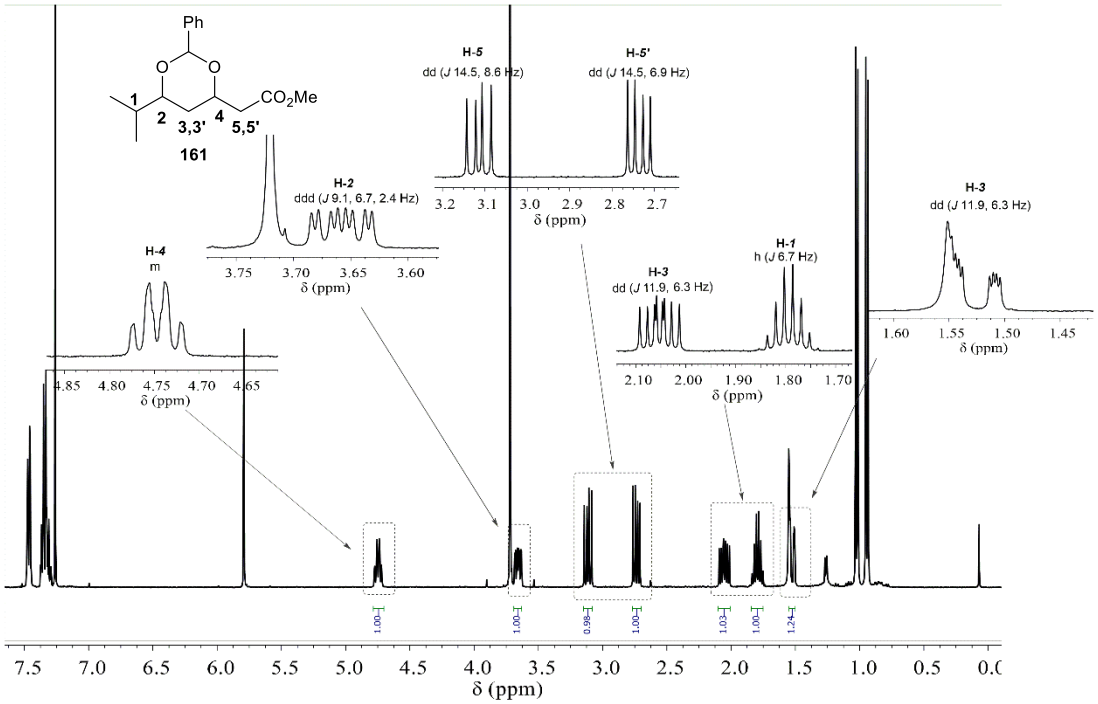


Figure 33 ^{1}H NMR analysis of the diastereomerically pure sample of acetal **161** in order to determine the relative stereochemistry.

Based on this results, it was determined that the diastereoisomer present in this fraction corresponded to the *anti*-diastereoisomer of acetal **161**, hence, the spectrum of the mixed fraction was also analysed (Figure 34).

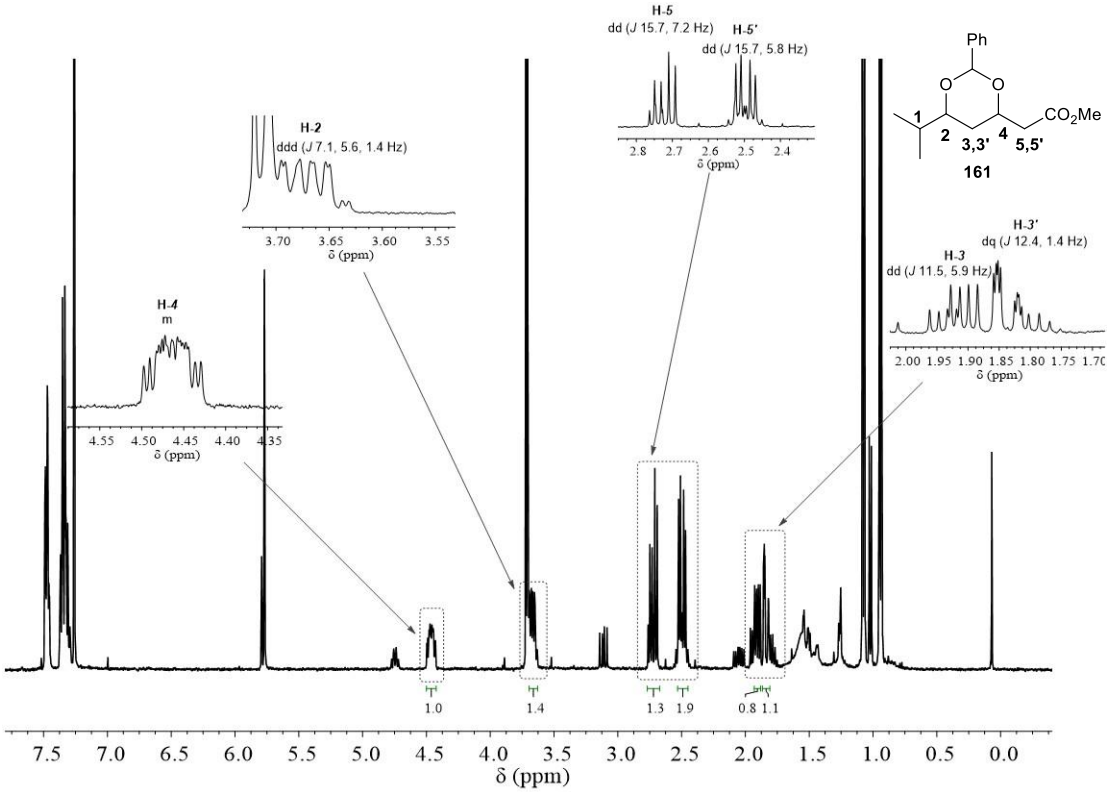


Figure 34 ^{1}H NMR analysis performed on a mixed sample of acetal **161** in order to determine the relative stereochemistry.

In this case, as previously observed for the case of the phenyl substituted analogous **154**, what seemed to be two different diastereoisomers, corresponds to the two different acetal diastereosiomers of the same diol, *i.e.* the *anti*-diastereosiomer.

Hence, it was confirmed that the use of phenyl substituted acetals did not aid the assignment of the relative stereochemistry since the presence of this group gave rise to different acetals diastereoisomers making this assignment more complex. With the aim of sorting out this downside, alternative substituents on the acetal group had to be considered; and the use of acetonide substituted acetals had been widely reported for the protection of 1,2- and 1,3-diols.[151-154] More relevant in this case, however, is the fact that the ^{13}C NMR analysis of these compounds provides an excellent tool for the determination of the relative stereochemistry of this type of system.[136,155,156] The [^{13}C] acetonide method developed by Rychnovsky *et al.* in the 90's stands out here.[157,158] This method is based on the different chemical shifts presented for the methyl groups of the acetonide functionality depending on

their relative orientation, *i.e.* for the case of the *anti*-diastereoisomer, a twist-boat conformation is adopted, which means that both methyl groups have a very similar chemical environment resulting in very similar chemical shifts; typically around 25 ppm (option 1, Figure 35). However, for the case of the *syn*-diastereosiomer, one of the methyl groups is in an axial position whilst the other is equatorial, resulting in the chair conformation adopted by this diastereosiomer. Therefore, the chemical shifts of these groups differ considerably by approximately 20 ppm and 30 ppm, respectively (option 2, Figure 35). Figure 35 displays a graphical representation of the different conformations adopted by acetonide 6-membered ring acetals depending on their relative stereochemistry.

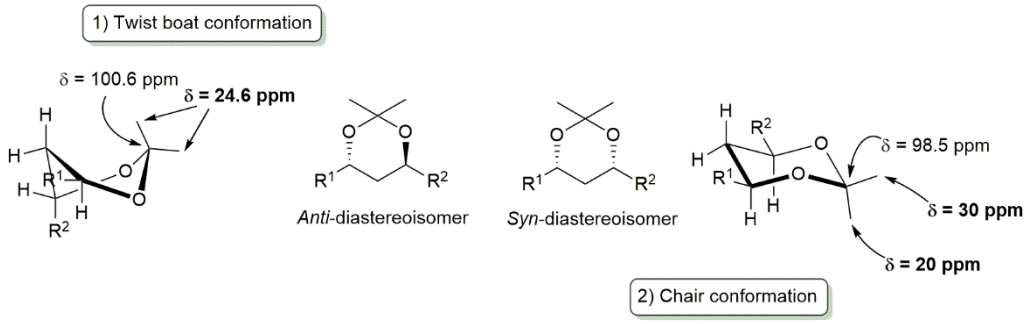
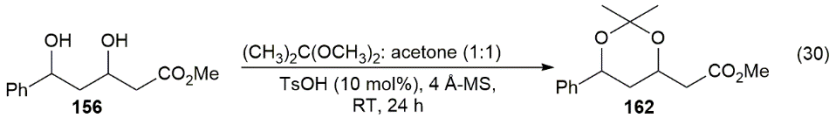


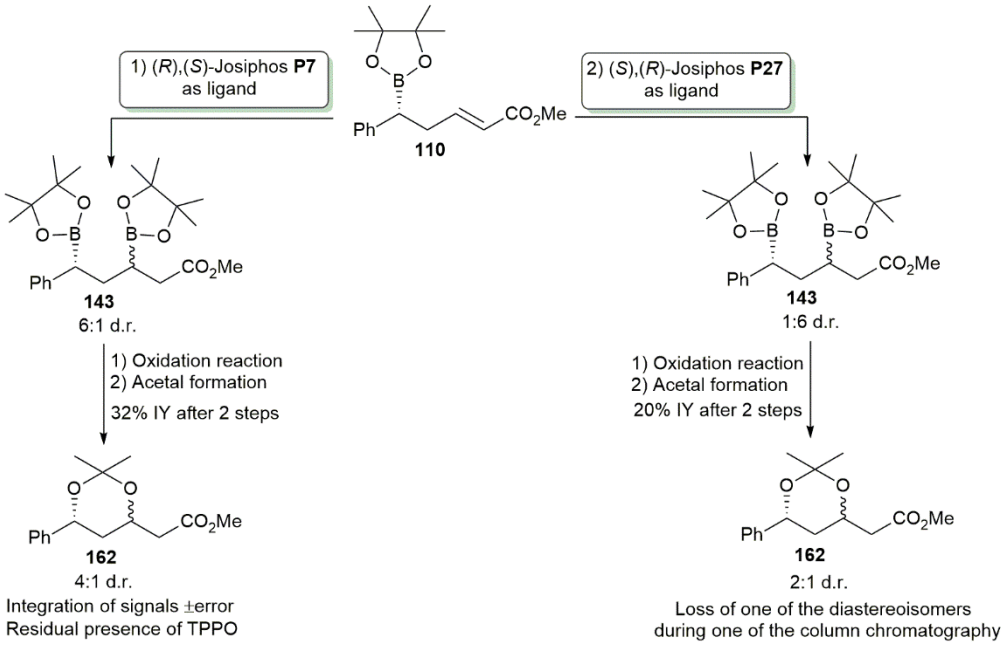
Figure 35 ^{13}C NMR analysis for the determination of relative stereochemistry in acetonide acetal protected 1,3-diols according to the [^{13}C] acetonide method.[158]

Since its establishment, this method has proved efficient for the assignment of configurations not only for diols, but also for polyols or polyene macrolides. Based on this, the synthesis of the acetonide acetal **162** was approached [Eqn. (30)].



Hence, 1,3-diols **156** synthesised using either (*R*),(*S*)-Josiphos **P7** or (*S*),(*R*)-Josiphos **P27** as chiral diphosphine ligand were examined, successfully obtaining the target chiral 6-membered ring acetals **162** in moderate isolated yields (32% and 20%, respectively). In terms

of diastereoselectivity, in both cases, the acetal was obtained as a mixture of diastereoisomers (4:1 and 2:1, respectively). This case, a low level of matching/mismatching effects between both the enantiomers of the chiral ligand in contrast to what had been previously observed for this substrate *i.e.* β-borylation of homoallylic boronate ester **110** (see Section 2.3.3). For the case of using (*R*),(*S*)-Josiphos **P7** as ligand, gave a d.r. that was slightly lower compared to the one observed for the precursor diborylated ester **143** previously (see entry 1, Table 23), likely associated with the ±error in the integration of the ^{1}H NMR signals and possible remaining TPPO contaminant (see Scheme 87). In contrast, the d.r. calculated for the same compound generated from the reaction using the opposite enantiomer (*i.e.* ligand **P27**) was not the expected; instead of 1:6, a d.r. of 2:1 was observed. This result suggested that a loss of one of the diastereoisomers was taking place, possibly during the purification process due to the different behaviour of the different diastereoisomers on silica gel or at some stage during the oxidation/acetal formation sequence. With these results in hand, we then moved on to examine the same procedure but as a one-pot methodology, *i.e.* avoiding the column chromatography purifications between each step. Scheme 92 summarises the results of this one-pot approach.



Scheme 92 Synthesis of the chiral acetonide-substituted 6-membered ring acetals for model substrate **162**.

The suppression of the purification processes in between the different steps led to the target acetals in consistent d.r. according to those obtained previously for the precursor diborylated esters; 6:1 (23% IY) and 1:4 (12% IY), respectively. Moreover, we were interested in assigning the relative stereochemistry; hence, the separation of the diastereoisomers was required in order to study the *J* coupling constants of ^{1}H NMR, and the ^{13}C NMR shifts of the acetonide to complete the structural analysis assignment. Unfortunately, the separation of the diastereoisomers was not possible by column chromatography due to co-elution of the diastereoisomers, hence separation by preparative chiral HPLC was considered. This technique provided satisfactory separation of the diastereoisomers providing clean NMR spectra for the major diastereoisomer in each case. Figures 36 presents the *J* coupling constant analysis carried out for the case of using (*R*),(*S*)-Josiphos **P7** as chiral ligand for the 2nd β-borylation reaction in the synthesis of the precursor diborylated ester **143**.

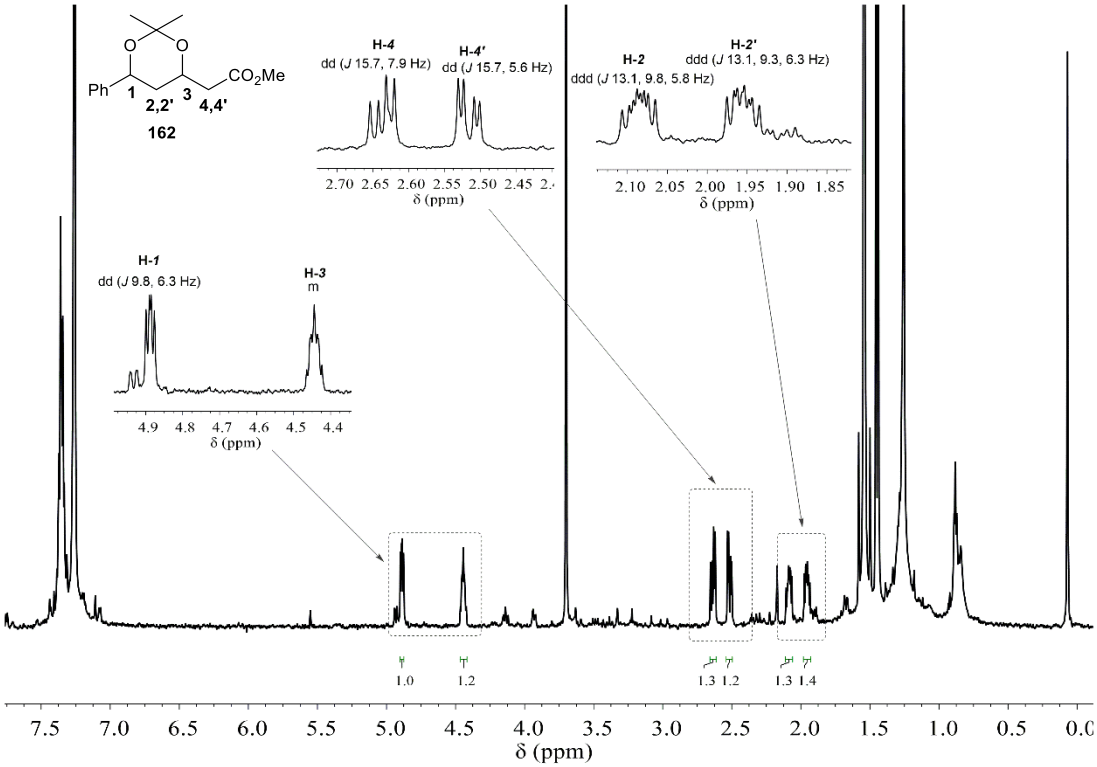


Figure 36 ^{1}H NMR analysis performed on a diastereomerically pure sample of acetal **162** to determine the relative stereochemistry when (*R*),(*S*)-Josiphos **P7** was used as chiral diphosphine ligand for the introduction of the 2nd boryl unit in the synthesis of the precursor diborylated ester **143**.

For the assignment of the relative stereochemistry it was crucial to analyse the signals corresponding to H-*2* and H-*2'* (δ 2.10-1.95 ppm) which in this case appeared as ddd in both cases with two different types of ^{3}J couplings in each case; *i.e.* 9.8 and 5.8 Hz for H-*2*, and 9.3 and 6.3 Hz for H-*2'*, beside the expected geminal coupling between both protons (13.1 Hz). Figure 37 presents a detailed analysis of the couplings for H-*2*.

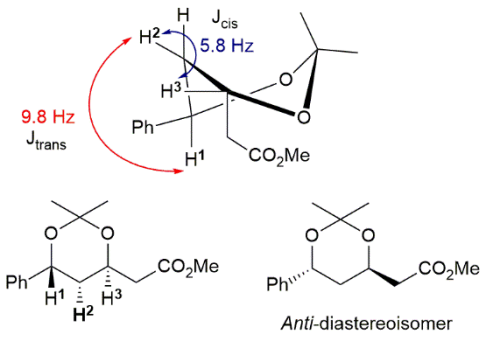


Figure 37 *J* coupling constants analysis developed on the *anti*-diastereoisomer of 6-membered ring acetal **162**.

As outlined in Figure 37, the analysis of the *J* coupling constants showed that this proton had a large *J* coupling (9.8 Hz) to H-*1* indicating that these protons can be allocated in a *trans*-diaxial position with respect to each other, whilst the other ^{3}J coupling of H-*2* corresponds to a *cis*-coupling and relates it to H-*3* (9.8 Hz). The analysis of these signals indicates that the 6-membered ring acetal **162** is in a chair-like (twisted boat) conformation which would correspond to the *anti*-diastereoisomer.[159] Furthermore, in order to confirm this observation, the NOESY spectrum was analysed in which a *trans*-ring coupling between H-*1* and one of the methyl groups from the acetonide functionality (signal at δ 1.42 ppm) as well as between H-*3* and the other methyl group on the acetonide (signal at δ 1.45 ppm), as outlined in Figure 38.

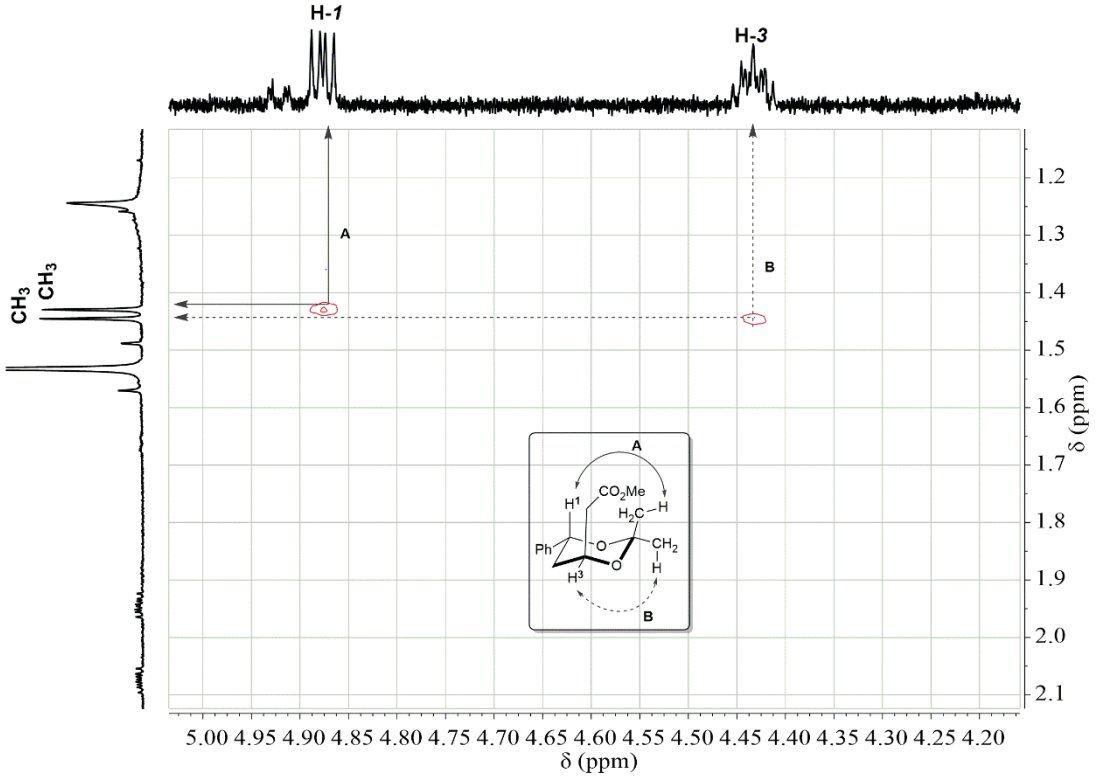


Figure 38 NOESY spectrum corresponding to the *anti*-diastereoisomer of the acetonide acetal **162**.

In order to complete this study, the same analysis was carried out on another sample of chiral acetal, however, in this case the chiral diphosphine ligand employed for the 2nd β-borylation reaction was (*S*),(*R*)-Josiphos **P27** (see Figure 39).

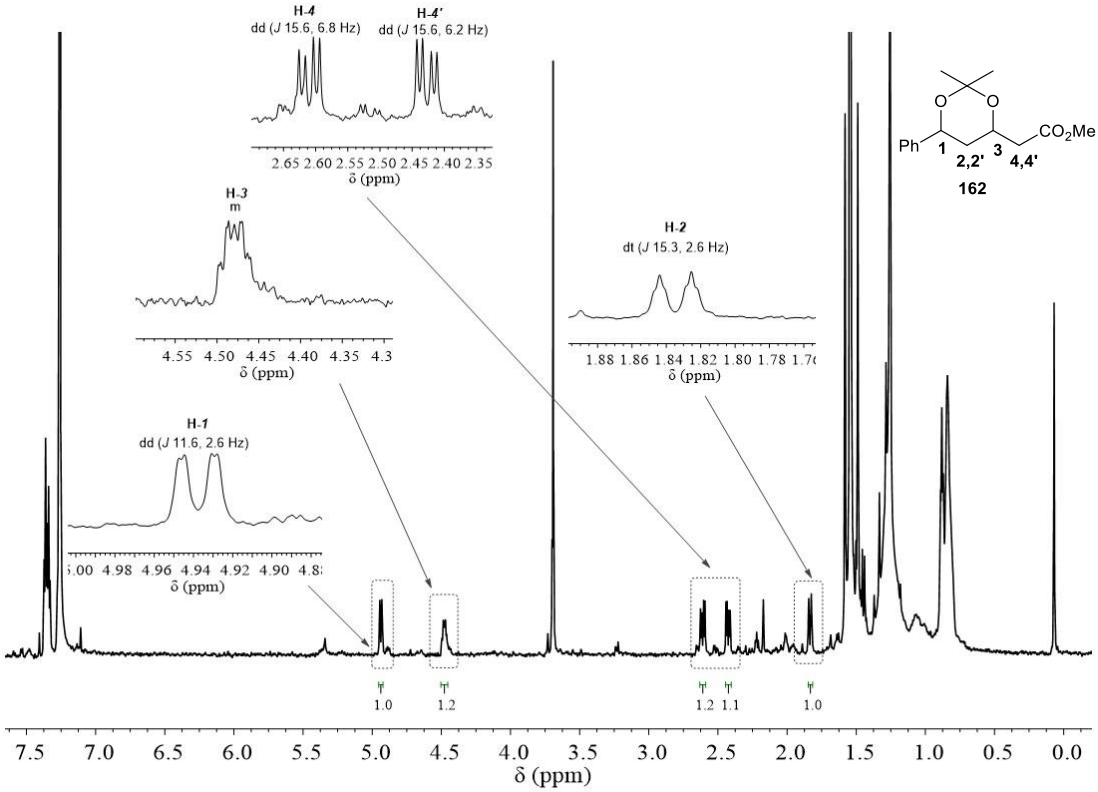


Figure 39 ^{1}H NMR analysis performed on a diastereomerically pure sample of acetal **162** to determine the relative stereochemistry when (*S*),(*R*)-Josiphos **P27** was used as chiral diphosphine ligand for the introduction of the 2nd boryl unit in the synthesis of the precursor diborylated ester **143**.

The most relevant feature of this spectrum, in comparison with the previous one, is the multiplicity observed for H-*2* which unlike the spectrum shown in Figure 36, though in this case the multiplicity of the signal corresponding to this proton corresponds to a dt (instead of a ddd). This would indicate that in this case the diastereoisomer obtained corresponds to the *syn*-diastereoisomer. In which case, the 6-membered ring adopts a chair-like conformation meaning that H-*2* couples with H-*1* (giving a doublet with a small *J* value of 2.6 Hz) as well as with H-*4* and H-*4'* (giving a triplet with a large *J* value of 15.4 Hz) resulting in the observed dt. Figure 40 presents a graphical representation of this conformational analysis.

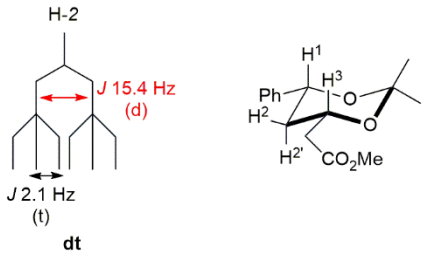


Figure 40 Conformational analysis of the *syn*-diastereoisomer of acetal **162**.

At this point, it is also worth mentioning that a second double triplet was expected (which would correspond to H-*2'*) which could not be observed in the ^{1}H NMR spectrum (Figure 39) because it appeared in the same region where larger signals were observed (δ 1.6-1.4 ppm). However, it was identified by the 2D spectrum (COSY), as displayed in Figure 41.

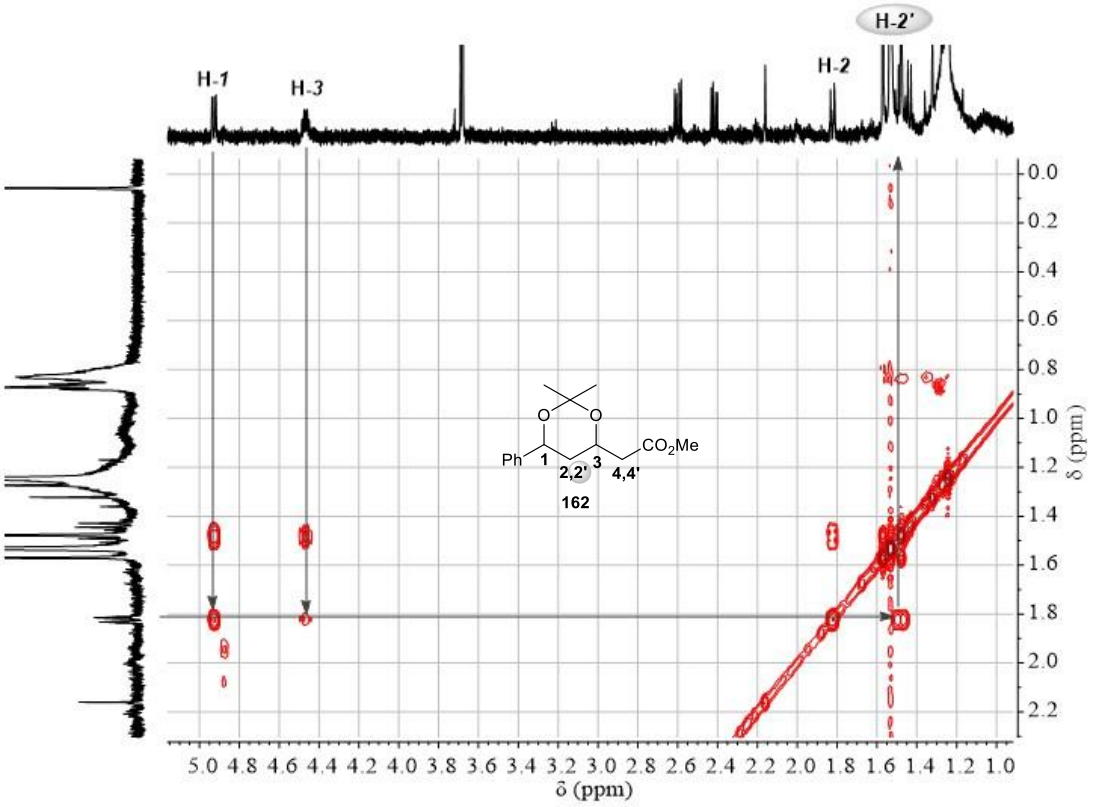


Figure 41 2D NMR spectrum COSY corresponding to acetal **162** used to aid the identification of H-2'.

Additionally, these samples were also analysed by the [^{13}C] acetonide method being confirmed the relative stereochemistry; when using (*R*),(*S*)-Josiphos **P7** as the ligand, the ^{13}C NMR spectrum presented two signals at 24.9 ppm and 24.6 ppm corresponding to the methyl

groups of the acetonide functionality (Spectrum 1, Figure 42), which means that in this case, these groups are in a very similar chemical environment, indicating conformational flexibility, perhaps between chair-like and twist-boat-like conformations due to the *anti*-diastereoisomer conformation. For the opposite enantiomer, ligand **P27**, the ^{13}C NMR spectrum presented two distinct signals; at δ 30.53 ppm corresponding to the equatorial orientated methyl group and at δ 20.10 ppm for the axial methyl group (Spectrum 2, Figure 42). Hence this is an indication of the *syn*-diastereoisomer. In Figure 42 is displayed a comparison between the ^{13}C NMR spectra for each diastereoisomer.

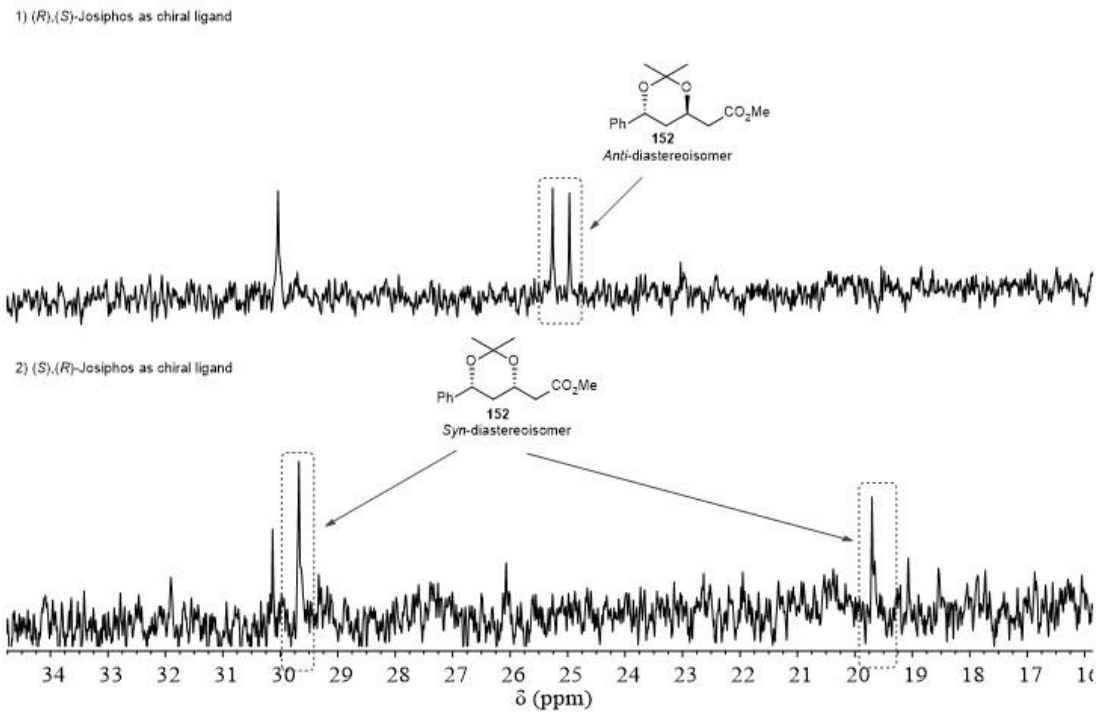
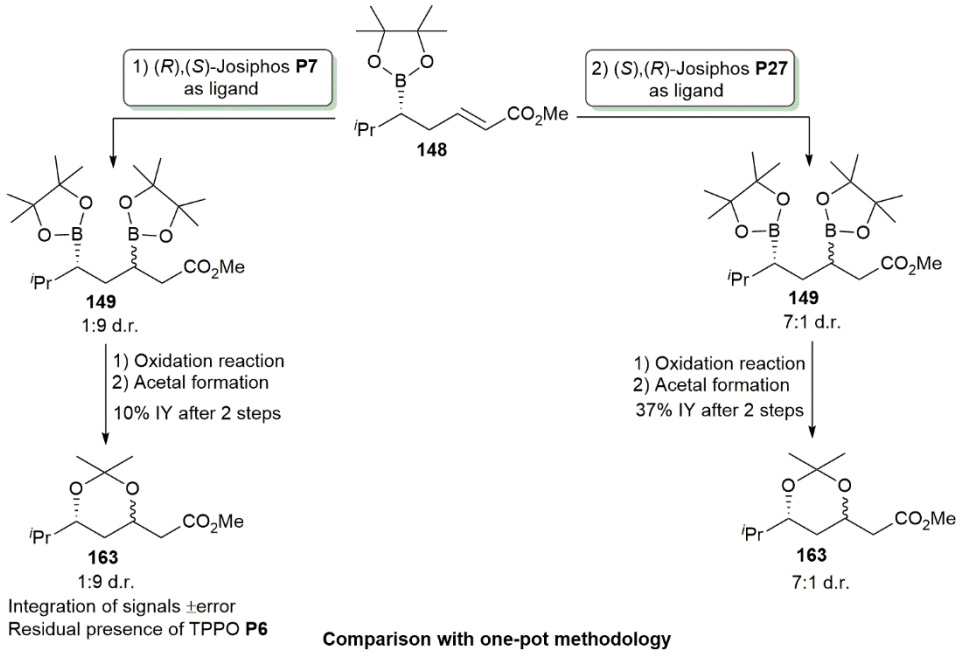


Figure 42 Comparison of the ^{13}C MMR spectra corresponding to the *anti*- and *syn*-diastereoisomers of compound **162**.

As previously reported, once the relative stereochemistry was elucidated for the model system we then wanted to corroborate these results by the study of an additional substrate; *e.g.* isopropyl substituted analogous. Scheme 93 displays the results obtained for the chiral acetals in this case.



Scheme 93 Synthesis of the chiral acetonide-substituted 6-membered ring acetal **163**.

In this case, although the efficiency of the reaction differed depending upon the enantiomer of the chiral ligand used for the β-borylation reaction on the homoallylic boronate ester **148**; *i.e.* from a low yield in the final acetal for the case of **P7** (10%) to a moderate yield for its opposite enantiomer (37%), a matching/mismatching effect was observed. The low yield could be associated to the poor effectivity presented by the C-B oxidation reaction for these systems as previously reported. Nevertheless, the pure acetals (obtained as mixture of diastereoisomers after column chromatography) were further purified by preparative HPLC, being possible to develop the study of the *J* coupling constants and the [^{13}C] acetonide method on samples containing exclusively the major diastereoisomer for each case. Figures 43 and 44 display the ^{1}H NMR spectra along with the corresponding *J* coupling analysis for each case.

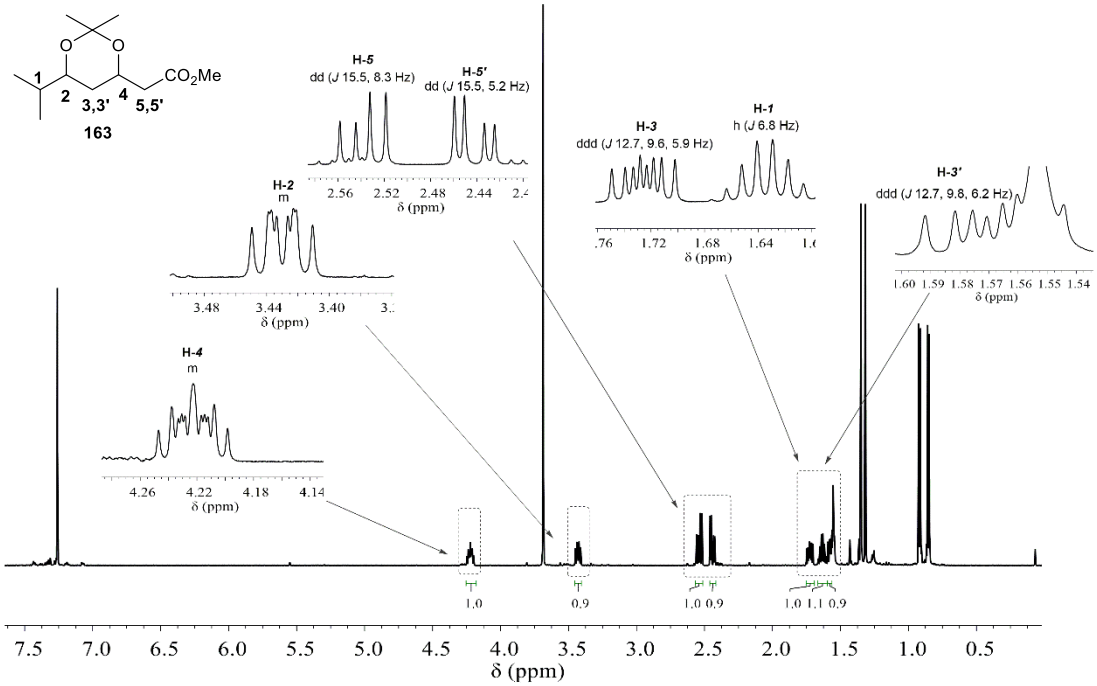


Figure 43 ^{1}H NMR analysis performed on a diastereomerically pure sample of acetal **163** to determine the relative stereochemistry when (*R*),(*S*)-Josiphos **P7** was used as chiral diphosphine ligand for the introduction of the 2nd boryl unit in the synthesis of the precursor diborylated ester **148**.

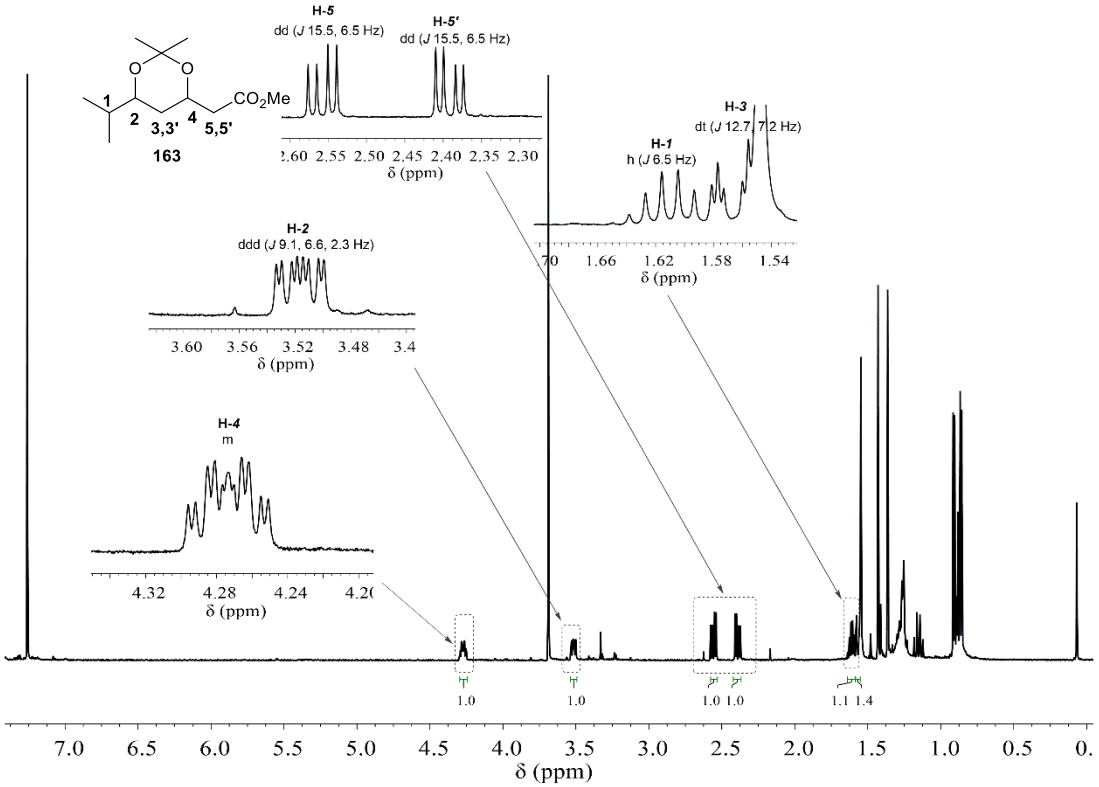


Figure 44 [1]H NMR analysis performed on a diastereomerically pure sample of acetal **163** to determine the relative stereochemistry when (*S*),(*R*)-Josiphos **P27** was used as chiral diphosphine ligand for the introduction of the 2[nd] boryl unit in the synthesis of the precursor diborylated ester **148**.

According to the [[13]C] acetonide method, the use of (*R*),(*S*)-Josiphos ligand **P7** led to the *anti*-diastereoisomer; methyl groups at δ 24.9 ppm and 24.5 ppm, *i.e.* similar chemical environment (Spectrum 1, Figure 45), whilst the use of (*S*),(*R*)-Josiphos **P27** lead into the *syn*-diastereoisomer (Spectrum 2, Figure 45); one methyl in equatorial position (δ 30.0 ppm) and the other methyl in the axial position (δ 19.6 ppm). Figure 45 displays the relevant spectra.

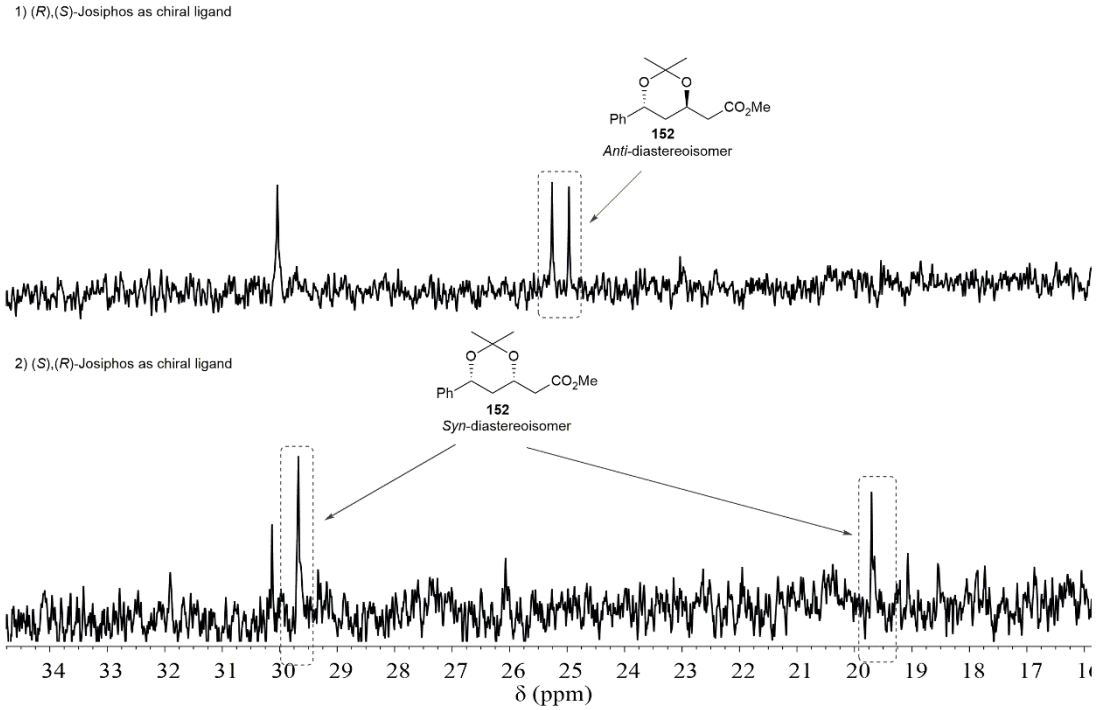


Figure 45 Comparison of the ^{13}C MMR spectra corresponding to the *anti*- and *syn*-diastereoisomers of compound **163**.

Hence, it was concluded that the nucleophilic boryl unit adds into the homoallylic boronate ester substrate either from the same face were the first boryl unit is already allocated or from its opposite face upon the enantiomer of the diphosphine ligand used for the generation of this reactive boryl unit, as displayed in Figure 46.

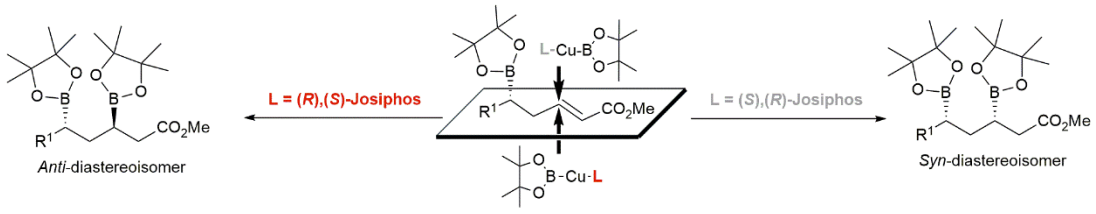
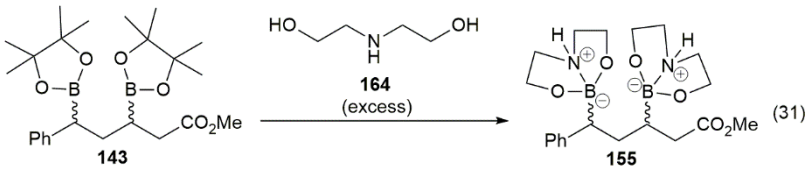


Figure 46 Stereoselectivity observed upon the addition of the 2nd boryl unit into chiral homoallylic boronate esters based on the enantiomer of the chiral diphosphine ligand used.

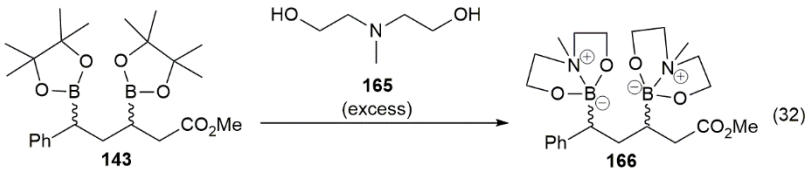
Complimentarily, another strategy for determining the relative stereochemistry was approached; the synthesis of the diethanolamino-boron complex **155**, with the hope that X-ray crystallography would be useful to confirm the stereochemistry. After years of research and

with several studies,[159] the facility for forming coordinating bonds with its neighbouring elements, *e.g.* N or O, exhibited by acidic tricoordinated sp^2 boron atoms has been demonstrated. Taking into account this interesting property, it was envisioned that the reaction of the diborylated ester **143** with diethanolamine **164**[160] could afford the formation of the bicyclic structure stabilised by the B-N interaction [Eqn. (31)].



(31)

The diborylated ester **143** was treated with diethanolamine **164** (6.0 equiv), which after azeotropic removal of the pinacol with toluene and extraction of the remaining excess of **164** to give a semi-crystalline material. Further attempts to crystallise from diethyl ether-DCM resulted in an amorphous solid not suitable for X-ray diffraction. Alternative methodologies, such as distillation in a Kugelrohr for the removal of pinacol as well as the diethanolamine **164** in excess were examined. It was not possible to obtain the desired complex due to possible decomposition processes associated to the distillation. Moreover, *N*-substituted diethanolamine (*e.g.* N-methyldiethanolamine **165**)[161] was also evaluated for the B-N complex formation [Eqn. (32)], being not possible to obtain compound **166**.



(32)

2.3.6. Summary of the application of homoallylic boronate esters as substrates for the β-borylation reaction

In summary, homoallylic boronate carboxylate ester derivatives were confirmed as ideal substrates for the the β-borylation reaction. Diborylated ester were successfully obtained. Additionally, the stereocontrol for the new stereocentres was a function of the enantiomer of the chiral ligand used, *i.e.* double diastereocontrol. However, not all the chiral ligands tested presented matching/mismatching effect between the two enantiomers. Regarding the effect that the substituent in C_β could have on the asymmetry induced *via* the 2nd β-borylation reaction, it was observed that alkyl substitued substrates provided lower diastereoselectivity with not always matching/missmatching effect, whilst aryl substituted provided higher diastereoselectivity.

2.4. Application of dual asymmetric borylation strategies: synthesis of Atorvastatin

2.4.1. Background

Atorvastatin is a synthetic lipid-lowering drug classified as a statin[162] (Figure 47), employed as an inhibitor of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase which plays a crucial role in cholesterol biosynthesis, reducing the levels of low density lipoprotein or LDL (bad cholesterol) and triglycerides in the blood. It is prescribed to prevent cardiovascular complications such as stroke or heart attack in people with Type II diabetes, coronary disease or other risk factors.[163] Although some of the statins are of natural origin (Type I, Figure 47) being derived from fungal metabolites, systems such as Lovastatin, Simvastatin, other statins which possess a fluorophenyl group, instead of the butyril present in Type I, are synthetic compounds (Type II, Figure 47); *e.g.* Atorvastatin or Fluvastatin, amongst others.[164] Within the group of the statins, Atorvastatin stands out due to its high efficiency towards the reduction of LDL cholesterol,[165] becoming the best-selling drug in pharmaceutical history exceeding US $125 billion since its approval.[166]

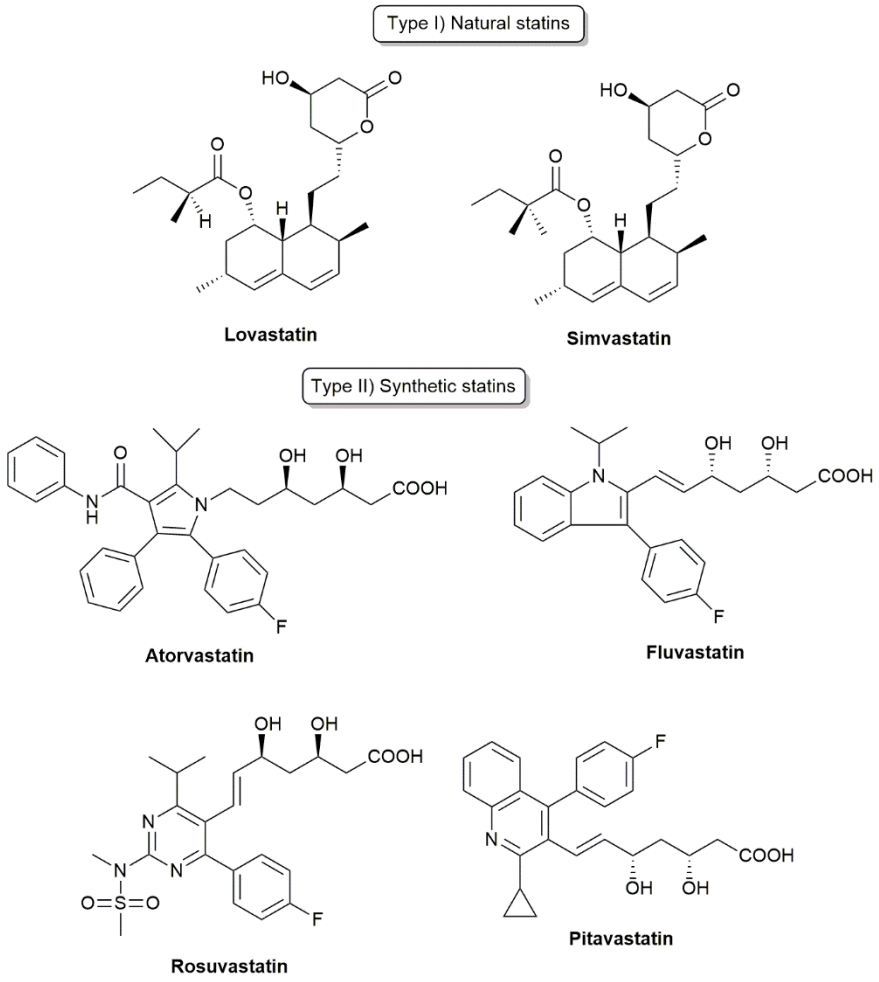
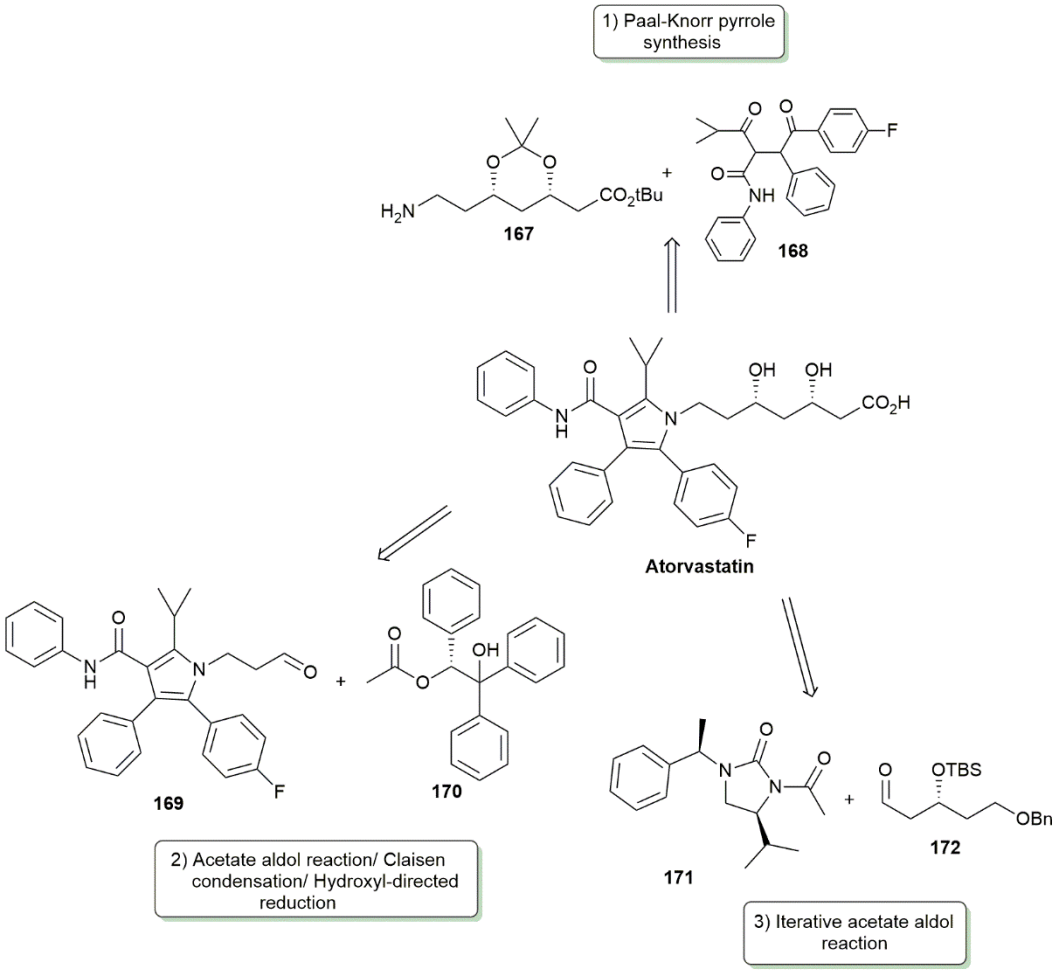


Figure 47 Structures of some relevant statin-type drugs.

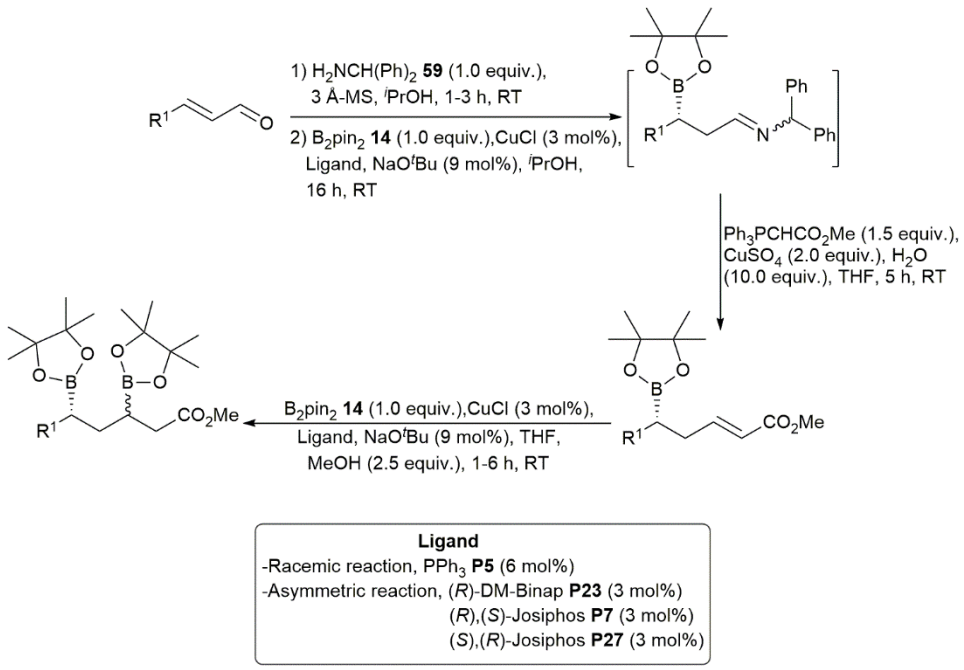
Atorvastatin was first synthesised as a racemic mixture and subsequent enantiomer separation in 1985 by Bruce Roth of Parke-Davis-Warner-Lambert Company.[167-170] It was not until 1996 when it was commercialised as the calcium salt and sold under the trade name of Lipitor® by Pfizer. Since then, many synthetic approaches towards its synthesis have been developed including a diverse range of chemical or biocatalytic transformations,[162,171-172] focused on its enantioselective version. Scheme 94 summarises the most relevant approaches towards the synthesis of Atorvastatin disclosed in recent years.



Scheme 94 Selected examples of the different synthetic approaches towards Atorvastatin reported in recent years.

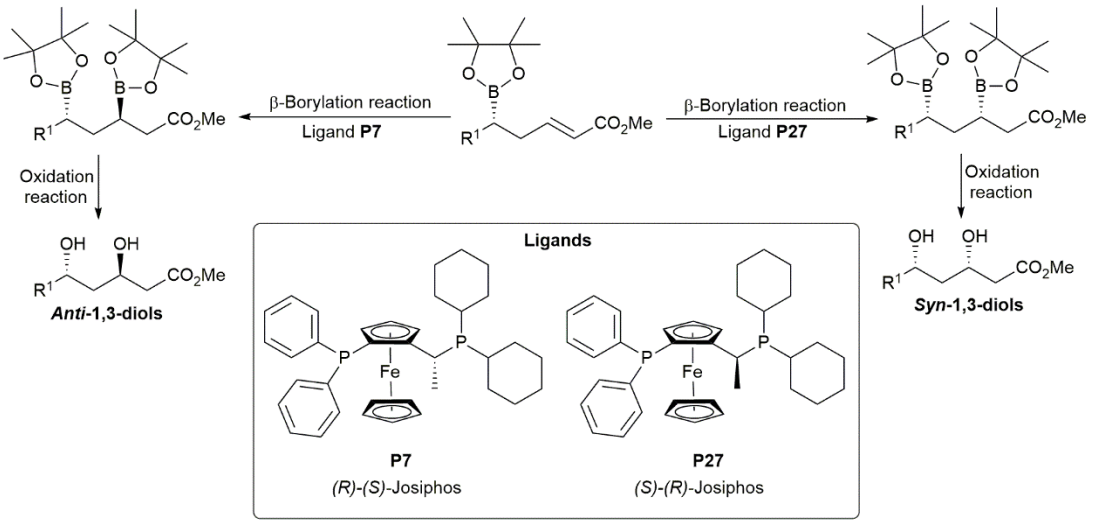
New methodologies for the synthesis of enantiopure molecules has achieved increasing interest,[59] and the use of organoboron compounds in particular has emerged as an ideal platform for chiral synthesis.[60]

Based on this, it was envisioned that the previously developed dual asymmetric borylation methodology for the synthesis of 3,5-dihydroxy esters starting from α,β-unsaturated aldehydes *via* the corresponding homoallylic boronate esters, could be applied for the synthesis of this drug, as outlined in Scheme 95.



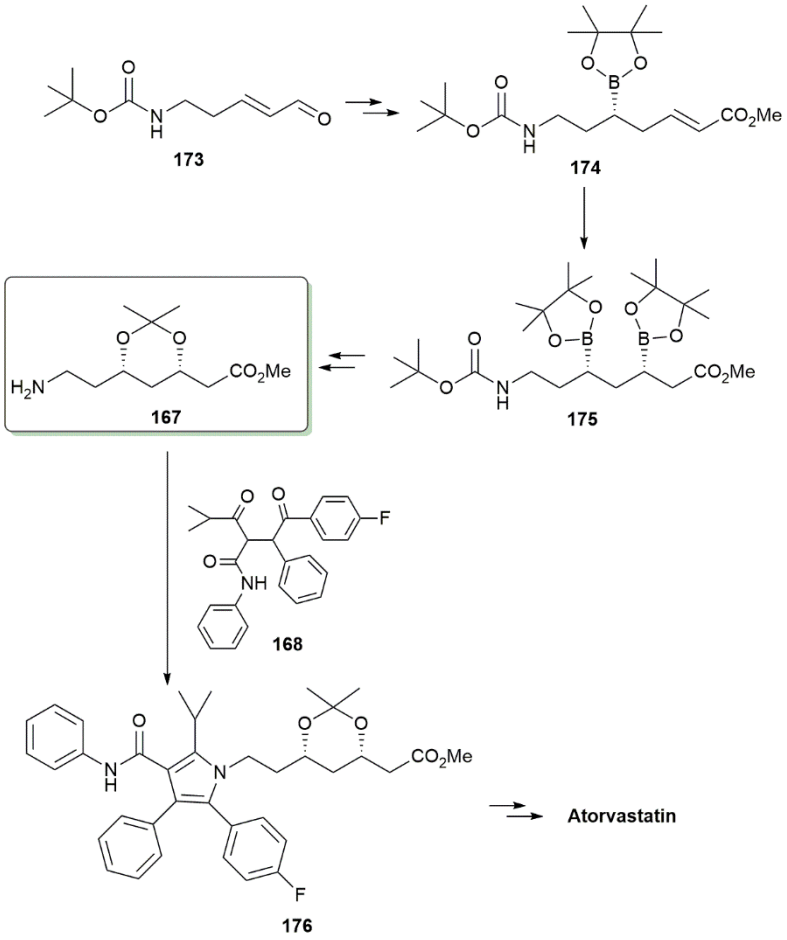
Scheme 95 Enantioselective route for the synthesis of 3,5-diborylated esters from α,β-unsaturated aldehydes *via* the corresponding homoallylic boronate carboxylate esters.

Additionally we demonstrated in Section 2.3, that this methodology was an excellent tool for the enantioselective synthesis of 1,3-*anti*- and 1,3-*syn*-diols (Scheme 96).



Scheme 96 Enantioselective synthesis of chiral 1,3-diols *via* the asymmetric β-borylation reaction on homoallylic boronate ester derivatives.

Hence, with this methodology it would be possible to access the key intermediate amino acetal compound **167**, which after subsequent Paal-Knorr synthesis with the commercially available 1,4-diketone **168** would lead into the desired precursor of this pharmaceutical, as outlined in Scheme 97.

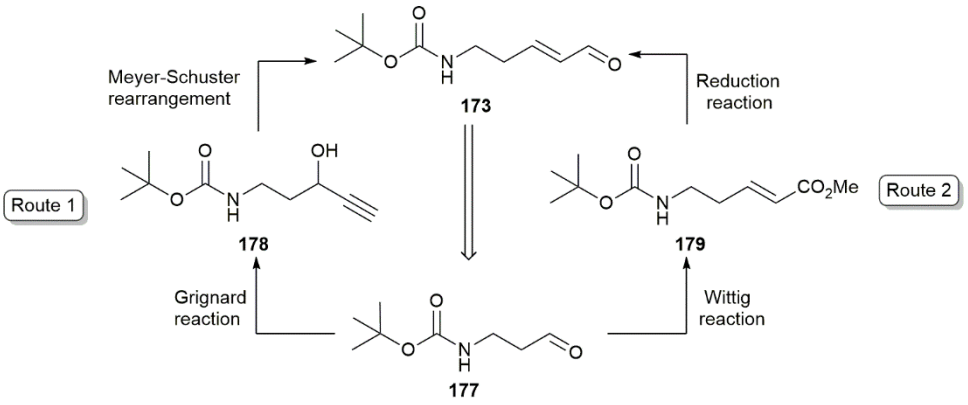


Scheme 97 Retrosynthetic analysis corresponding to the synthesis of Atorvastatin *via* the Paal-Knorr approach involving the amino acetal ester **167**.

2.4.2. Development of a methodology for the synthesis of the starting α,β-unsaturated aldehyde

In order to be able to apply the previously developed dual asymmetric methodology towards the synthesis of the key diborylated ester intermediate, a procedure towards the starting α,β-unsaturated aldehyde **173** was required due to the commercial unavailability of this reagent. With that purpose, an initial retrosynthetic analysis was carried out which

identified aldehyde **177** as a good starting point for the synthesis of the desired α,β-unsaturated aldehyde **173** *via* either a Grignard reaction/Meyer Schuster rearrangement sequence (Route 1, Scheme 98) or a Wittig reaction/ reduction sequence (Route 2, Scheme 98).

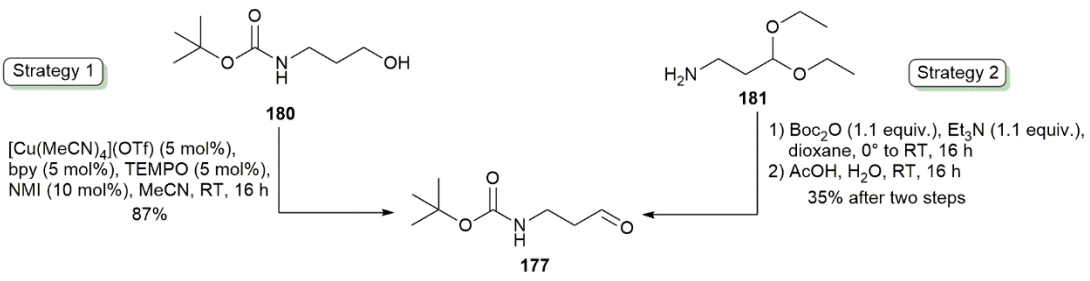


Scheme 98 Strategies proposed for the synthesis of the α,β-unsaturated aldehyde **173**.

Hence, initially 3-(Boc-amino)-1-propylcarbamate **177** synthesis was approached *via* two different procedures, involving;

- Cu(I)-TEMPO mediated oxidation of 3-(Boc-amino)-1-propanal **180** (strategy 1, Scheme 99).[173,174]
- Boc-protection of the amino group followed by hydrolysis the of 1-amino-3,3-diethoxypropane **181** (strategy 2, Scheme 99).[175]

Scheme 99 summarises the different approaches evaluated for the synthesis of compound **177**.

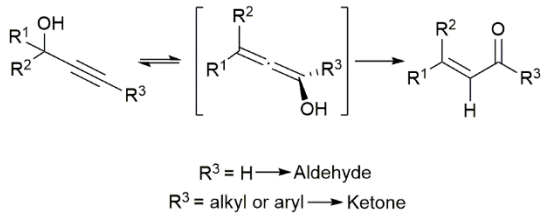


Scheme 99 Synthetic strategies studied for the synthesis of 3-(Boc-amino)-1-propylcarbamate **177**.

It was concluded that the oxidation methodology was more effective for this particular case, leading to higher isolated yields of the resulting aldehyde (up to 87%), whilst the second strategy resulted in poor yield possibly associated with some loss of product during the workup process in between the steps. With the key starting material obtained, the study of its transformation into the target enal **173** was examined. In this case, two different routes were exhaustively studied;

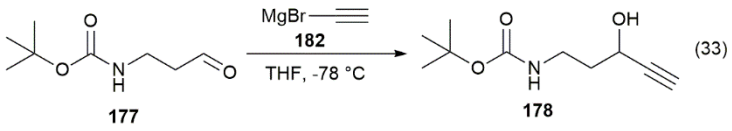
- Grignard reaction on the aldehyde leading into the propargylic alcohol and subsequent Meyer-Schuster rearrangement (strategy 1, Scheme 98).
- Wittig reaction on the aldehyde leading into the α,β-unsaturated ester and subsequent reduction of this functionality (strategy 2, Scheme 98).

Regarding strategy 1, the use of propargylic alcohols as precursors for α,β-unsaturated aldehydes or ketones by the Meyer Schuster rearrangement has been widely reported.[176-180] This popularity is due to the fact that it allows access to synthetically valuable compounds in a very atom economic manner since it consists of a rearrangement.[179] In terms of mechanistic insights, this transformation occurs *via* a formal 1,3-shift followed by a tautomerisation, therefore, the substituents present on the alkyne moiety determine the type of α,β-unsaturated carbonyl compound resulting from this, *i.e.* α,β-unsaturated ketone or aldehyde (Scheme 100).



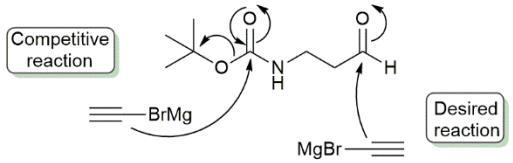
Scheme 100 Mechanism corresponding to the Meyer Schuster rearrangement for the synthesis of α,β-unsaturated carbonyl compounds from propargylic alcohols.

Hence, we envisioned that the conversion of 3-(Boc-amino)-1-propylcarbamate **177** into the corresponding propargylic alcohol **178** and subsequent rearrangement could provide the desired α,β-unsaturated aldehyde **173**. Therefore, a study of the first part of the sequence, the Grignard reaction to form the propargylic alcohol **178**, was initiated. In this case the use of ethynyl bromide **182** as a Grignard reagent [Eqn. (33)] was examined.[181]



(33)

From the first attempt of the reaction, it was observed that after 16 h, the crude ^{1}H NMR spectrum was very complex and the presence of the desired propargylic product was not detected. It was concluded that the presence of the carbamate could, perhaps, be preventing the desired reaction giving rise to a competitive nucleophilic attack of the Grignard reagent into the carbonyl position (Scheme 101), promoted by the large amounts of ethynylmagnesium present (3.5 equiv.) as well as long reaction times (up to 16 h).

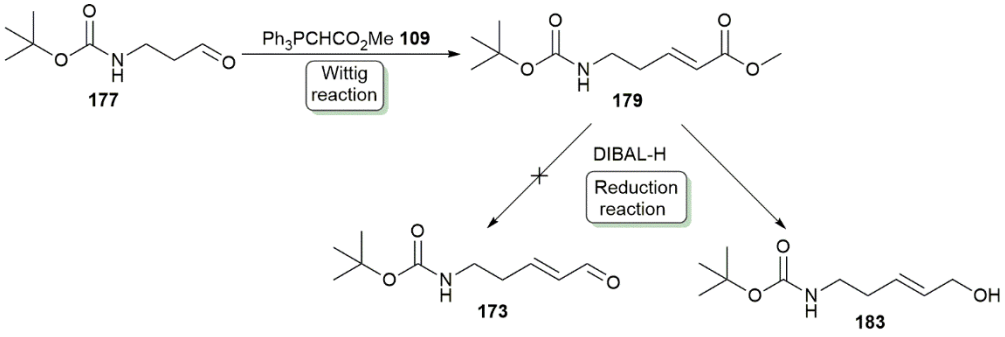


Scheme 101 Desired addition of the Grignard reagent into the aldehyde functionality (desired reaction) *vs.* the possible addition on the carbamate group (competitive reaction).

Hence, an optimisation of the methodology was carried out starting with a reduction of the amount of ethynyl magnesium bromide **182** used. The reaction was then repeated using 2.0 and 1.0 equivalents of this reagent; as results of this, the crude spectra simplified and the Boc-protecting group was observed to stay intact. However, the desired product was not formed in either of the cases studied. It was concluded that although the side-reaction seemed to had been prevented, by reducing the amount of Grignard reagent, the resulting propargylic

alcohol **178** was too unstable to be obtained, probably undergoing some type of decomposition during the work-up process. Furthermore, the reaction was repeated using 1.0 equiv. of compound **182** but the reaction time was shorter in this case; the reaction was left stirring for only 1 h. The resulting ^{1}H NMR spectrum showed a complex mixture of compounds amongst which the presence of the starting 3-(Boc-amino)-1-propylcarbamate **177** was detected. It was concluded that this approach was not viable due to the impossibility of synthesising the key terminal propargylic alcohol **178**, hence, a new route towards the desired enal **173** needed to be developed.

This new approach consisted on the synthesis of the corresponding α,β-unsaturated ester **179** *via* a Wittig olefination on the previously synthesised 3-(Boc-amino)-1-propylcarbamate **177**[182] and subsequent reduction of the ester functionality into the aldehyde **173** (strategy 2, Scheme 98).[183] Within this sequence, the reduction using DIBAL-H was found to be a challenging step, since although it was tested under different conditions for both the reaction and the workup procedure, it was not possible to stop the reaction at the aldehyde step, and instead the product obtained was the analogous alcohol **183** (Scheme 102).



Scheme 102 Wittig reaction/reduction reaction sequence proposed for the synthesis of α,β-unsaturated aldehyde **173**.

Hence, at this stage it was concluded that an optimisation process was required in order to find a better set of conditions to obtain the aldehyde **173** instead of the analogous **183**. Table 28 summarises the different reaction conditions screened for that purpose.

Table 28 Screening of the conditions for the reduction of the α,β-unsaturated ester **179**.

Entry	DIBAL-H (equiv.)	Reaction medium	Temp. (°C)	Reaction time (h)	Work-up conditions	Product (%)		
						173	**179**	**183**
1	1.0	THF	-78	16	A	0	62	38
2	1.0[a]	THF	-78	16	A	2	55	43
3	1.0	Toluene	-78	0.5	A	<2	53	46
4	1.0	Toluene	-78	0.5	B	<2	59	40
5	1.8	DCM	-78	0.5[b]	C	0	0	<99

[a]DIBAL-H solution in toluene added using a syringe pump (0.25 mL/h). [b]Reaction monitored by *in situ* IR spectroscopy (ReactIR). Work up conditions: A) $KNaC_4H_4O_6{\cdot}4H_2O_{(sat.)}$ and stirred during 1 h at RT; B) HCl (v/v 5%) and stirred during 1 h at RT; C) Mixture of EtOAc and $KNaC_4H_4O_6{\cdot}4H_2O_{(sat.)}$ and stirred during 1 h at RT.

It was found that in all the sets of conditions evaluated, a mixture of starting α,β-unsaturated ester **179** and its analogous alcohol **183** was obtained instead of the desired α,β-unsaturated aldehyde **173**, varying in the relative proportions depending on the conditions used. In order to complete this study, the reaction was monitored by ReactIR (Entry 5, Table 28), which was envisioned as an ideal technique to show when all the starting material had been consumed (*i.e.* coordinated into the aluminium centre), and hence, the ideal time to quench the reaction and avoiding the formation of the alcohol. Figure 48 shows the graphical output obtained from the ReactIR study carried out in this case.

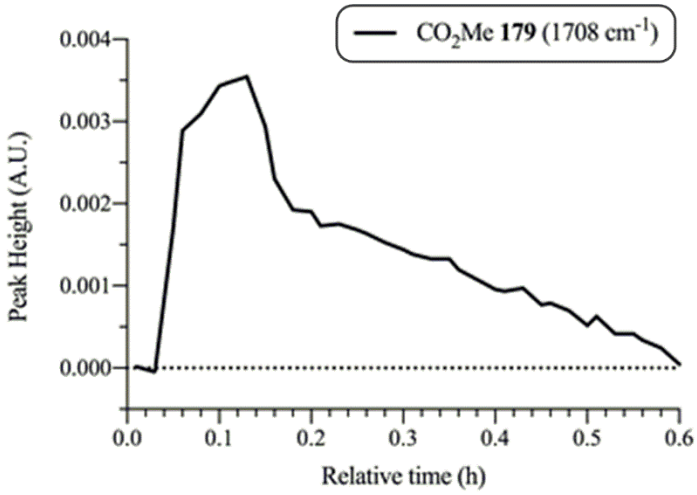
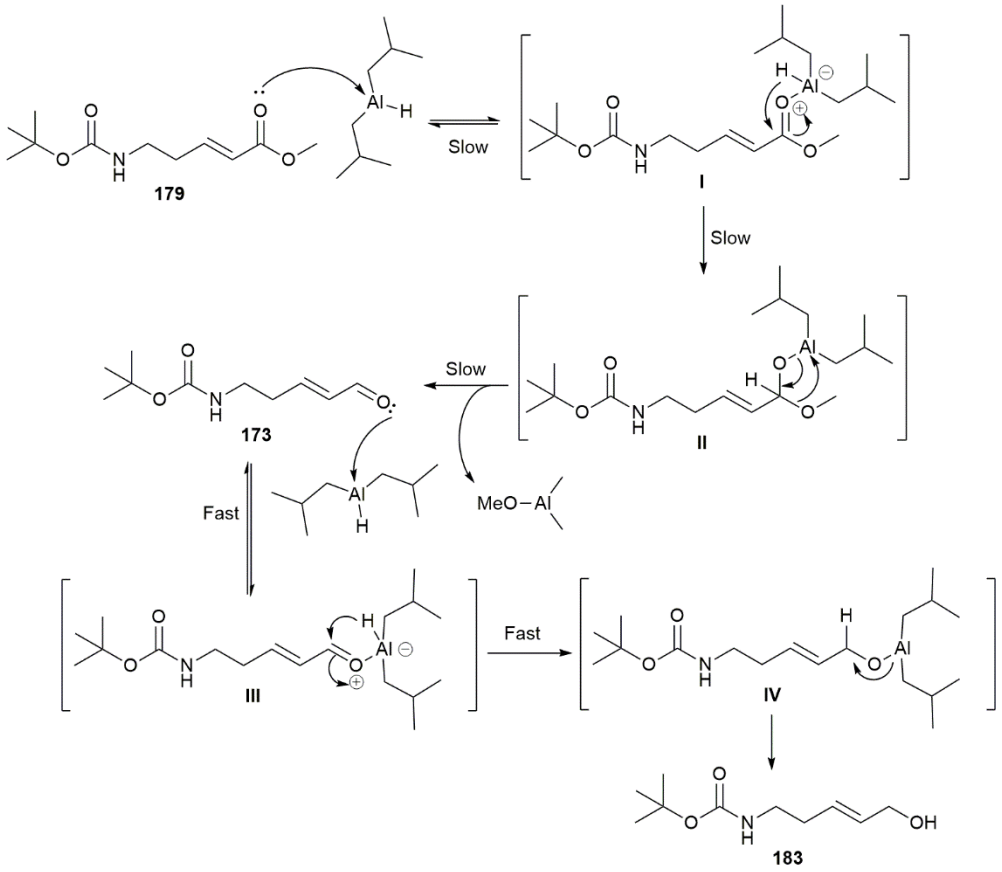


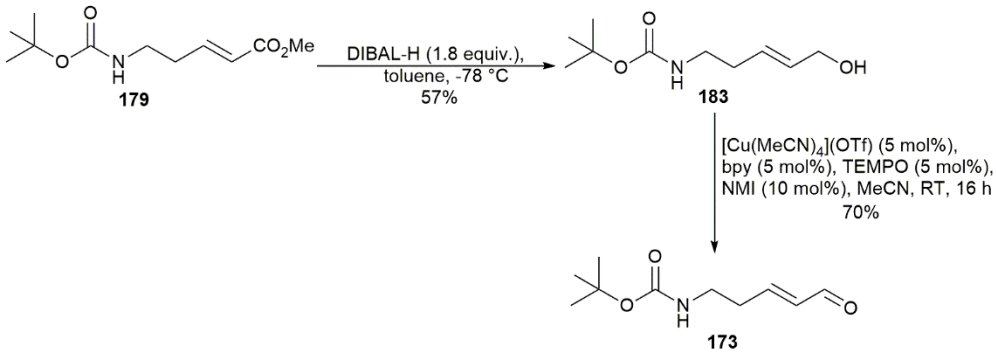
Figure 48 ReactIR study of the reduction using DIBAL-H of α,β-unsaturated ester **179**.

As observed in the ReactIR graphical output, all the ester functionality (signal at υ 1708 cm^{-1}) was coordinated into the DIBAL-H within 0.6 h, giving rise to tetrahedral intermediate **II** which would then lead to the formation of the aldehyde. However, aldehydes are compounds that reduce easily in the presence of such a reducing agent. Therefore, at this stage remaining ester **179** and generated aldehyde **173** compete, but the aldehyde would react faster with the aluminium hydride due to its higher electrophilicity, giving rise to the tetrahedral intermediate **III** and then to the alcohol **183** (Scheme 103).[184]



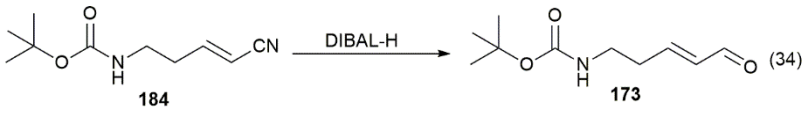
Scheme 103 Mechanism through which the reduction of the α,β-unsaturated ester **179** into the corresponding alcohol **183** takes place.

Hence, due to the difficulties on stopping the reaction at the aldehyde oxidation state, the possibility of adding an extra step to the sequence consisting on the oxidation of the alcohol was considered. In this case, the α,β-unsaturated alcohol **183** was obtained in >99% conversion using an excess of the reducing reagent (entry 5, Table 28). After purification, this compound was then subjected to the Cu(I)-tempo oxidation conditions[173,174] used for the first step of the sequence to successfully obtain the desired α,β-unsaturated aldehyde **173** in 70% isolated yield (Scheme 104).

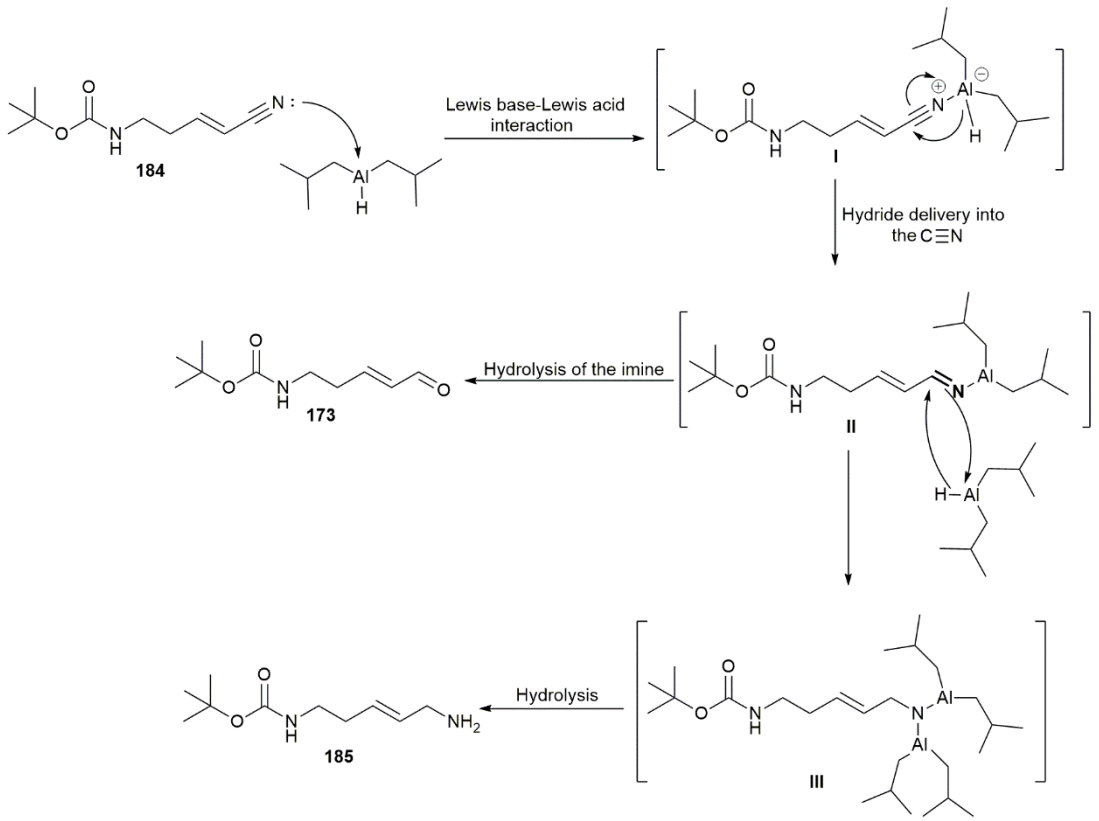


Scheme 104 α,β-Unsaturated ester **179** reduction and subsequent oxidation of the resulting alcohol **183** yielding α,β-unsaturated aldehyde **173**.

Additionally, the possibility of evaluating a slightly different functionality for the DIBAL-H reduction instead of the ester was examined, such a nitrile, which can be more effective in the reduction,[185] allowing the direct formation of the desired α,β-unsaturated aldehyde **173** [Eqn. (34)].



α,β-Unsaturated nitrile **184** was obtained by a Wittig olefination on 3-(Boc-amino)-1-propylcarbamate **177** with (triphenylphosphoranylidene)acetonitrile **185** in a good yield (63%), which was then examined for its transformation into the aldehyde **173**. Hence, screening reduction reaction conditions was performed (Table 29). A similar drawback to the one described previously was found; in this case mixtures of amine and starting nitrile were obtained. Having a look to the mechanism through which this transformation takes place, see Scheme 105, the formation of the imine intermediate is an ideal way to follow the reaction by *in situ* IR spectroscopy (ReactIR).



Scheme 105 DIBAL-H reduction of the α,β-unsaturated nitrile **185** to the corresponding α,β-unsaturated aldehyde **173**.

Hence, the complete formation of the key imino aluminium intermediate would be followed spectroscopically and which then would be subjected to hydrolysis to yield the enal **173**. Although it was possible to determine that the imine intermediate **II** (signal at υ 1655 cm^{-1}) was completely formed after 1.5 h, the crude reaction mixture obtained containing aldehyde and imine showing that the hydrolysis was not complete (entry 2, Table 29). Hence, the reaction was repeated and monitored again by IR and the hydrolysis step left to proceed longer, however, the same result as in the previous case was obtained (entry 3, Table 29). Moreover, it was found that performing the reaction at higher temperature (*i.e.* -42 ºC), as well as the use of a mixture of acetic acid and H_2O for the hydrolysis step, yielded the target α,β-unsaturated aldehyde **173** in better proportions in comparison with previous attempts (entries 5 and 6, Table 29). However, a clean product was still not possible to obtain in this

case because of the presence of an excess of reducing agent which gave some of the analogous amine **185** due to over reduction. Table 29 summarises the different conditions tested.

Table 29 Screening on the conditions for the reduction of the α,β-unsaturated nitrile **176**.

Entry	DIBAL-H (equiv.)	Reaction medium	Temp. (ºC)	Reaction time (h)	Work-up conditions	Product (%)		
						173	**185**	**184**
1	1.0	DCM	-78	1	A	7	40	53
2	1.0	DCM	-78	1.5[a]	A[b]	6	42	52
3	1.0	DCM	-78	2[a]	A[c]	11	44	45
4	1.0	DCM	-78	2	B	26	74	0
5	1.5	DCM	-42	15 mins.	C	30	34	36
6	1.5	DCM	-42	2	C[d]	29	32	39

[a]Reaction monitored by *in situ* IR spectroscopy (ReactIR).[b] After addition of the EtOAc and $KNaC_4H_4O_6{\cdot}4H_2O_{(sat.)}$ the solution was stirred at 0°C during 30 mins. [c] After addition of the EtOAc and $KNaC_4H_4O_6{\cdot}4H_2O_{(sat.)}$ the solution was stirred at RT during 10 mins. [d] After addition of the 1:1 mixture of AcOH:H_2O stirred during 30 mins. at RT. Work up conditions: A) Mixture of EtOAc and $KNaC_4H_4O_6{\cdot}4H_2O_{(sat.)}$ and stirred during 1 h at RT; B) Mixture of EtOAc and $NH_4Cl_{(sat.)}$ and stirred during 1 h at RT; C) 1:1 mixture of AcOH:H_2O and stirred during 1 h at RT.

From the studies described above, it was concluded that the most effective procedure for the reduction of the α,β-unsaturated ester **179** to the corresponding aldehyde **173** was the reduction/oxidation sequence (Scheme 104).

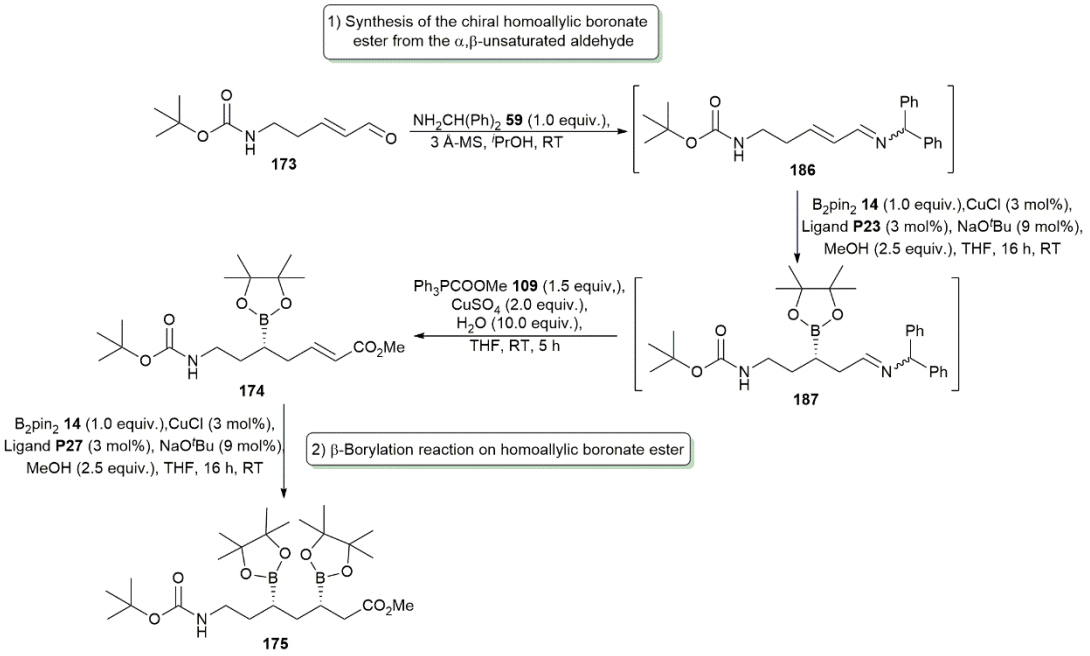
2.4.3. Application of the dual asymmetric borylation strategies: towards the versatile diborylated ester

A plausible synthetic pathway towards the versatile diborylated ester **175** was proposed *via* the dual asymmetric borylation methodologies previously established which encompasses;

- One-pot four-step functionalisation of β-boryl aldimines into homoallylic boronate esters (part 1, Scheme 106).

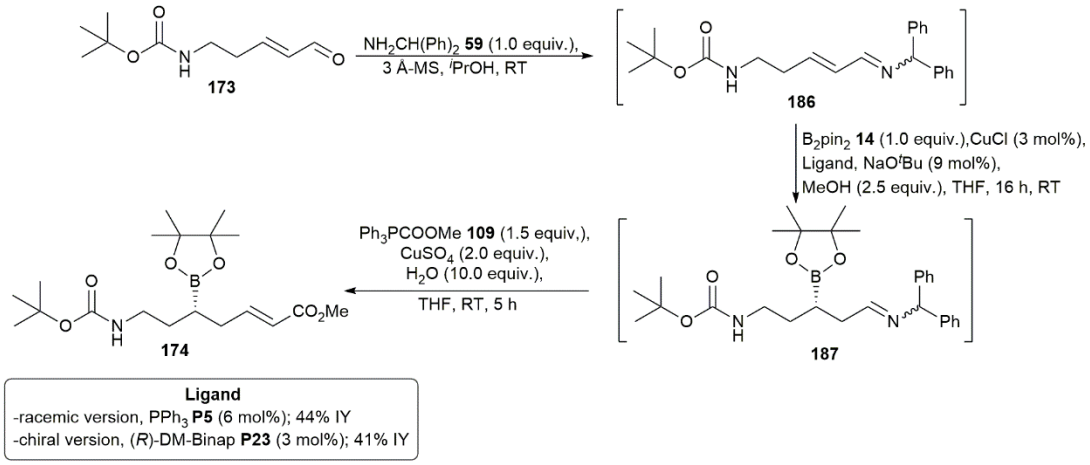
- Conjugated addition of a second boryl unit into the previously synthesised homoallylic boronate ester leading into the desired diborylated ester (part 2, Scheme 106).

  Scheme 106 displays the synthetic methodology herein proposed.



Scheme 106 Proposed synthetic pathway for the synthesis of the diborylated ester **175** *via* the corresponding homoallylic boronate **174**.

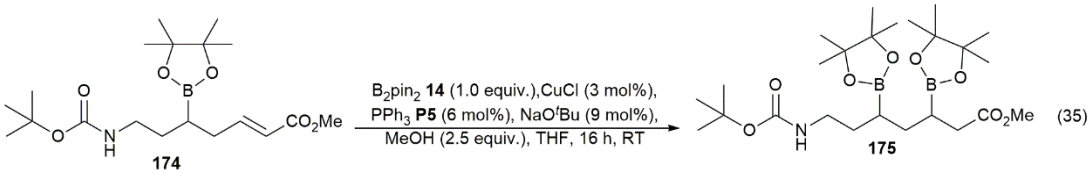
The first step of this sequence, *i.e.* the imination of 3-(Boc-amino)-1-propylcarbamate **173**, was monitored by *in situ* IR spectroscopy (ReactIR), and as expected, the use of ^{i}PrOH as solvent lead into a relatively fast reaction, under 2 h. Subsequently, the β-borylation reaction was successfully carried out with conversions >99% using a Cu(I)-based catalytic system modified with a racemic or chiral phosphine ligand (PPh_3 **P5** or (*R*)-DM-Binap **P23**, respectively). Subsequently, the resulting β-boryl aldimine **187** was trapped *via* the hydrolysis/Wittig olefination sequence leading into the target homoallylboronate **174** in moderate yields (44% and 41% IY for the racemic and chiral versions, respectively) (Scheme 107).



Scheme 107 Synthetic pathway for the synthesis of homoallylic boronate ester **174**.

In this case, as reported previously for the different homoallylic boronate esters (see Section 2.2), the induction of asymmetry during the β-borylation reaction was evaluated on the homoallylic boronate ester **174**. However, for this specific substrate it was not possible to obtain the right conditions for enantiomeric resolution on the racemic standard by HPLC analysis. This was attributed to the presence of the carbamate functionality which seems to have a relevant influence in the chiral separation. Further work on this stage will be done in due course, involving the use of other eluents or different columns.

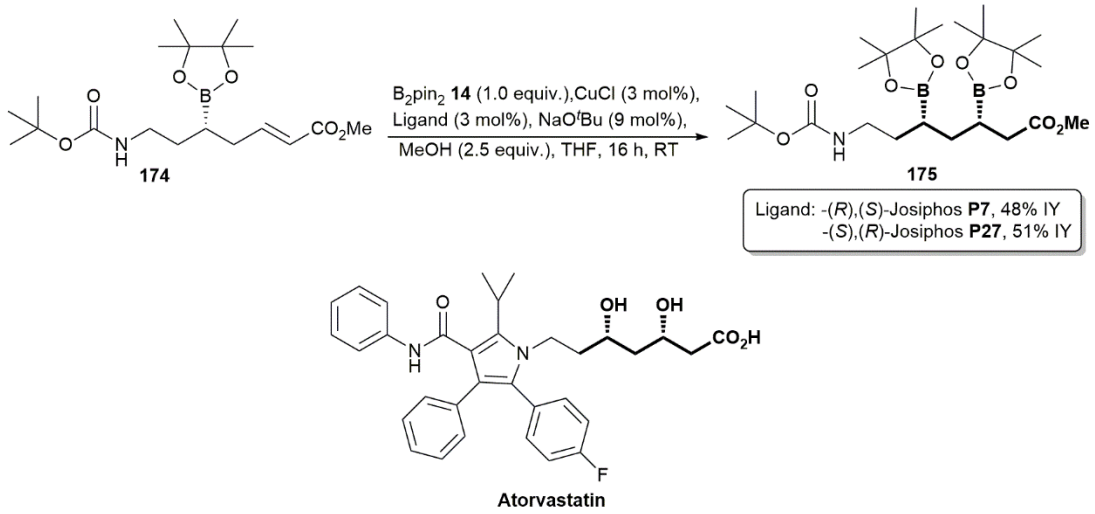
Nevertheless, with the homoallylic boronate ester **174** synthesised, the next step consisted of testing the conjugate addition of a second boryl unit leading into the desired diborylated ester **175** [Eqn. (35)].



The conjugate addition of the second boryl unit was monitored by ReactIR and was found to go to completion in 1 h. This result matched that previously observed when the effect of the C_β-substituent in this process was studied; for alkyl substituted substrates (*e.g.* Me, Et

or ^{i}Pr) faster reactions were observed, *i.e.* typically (2-4 h) whilst aryl-substituted compounds (*e.g.* Ph or *p*Cl-Ph) needed longer times (up to 6 h), see Section 2.3. The target diborylated ester **175** was obtained as a 1:1 mixture of diastereosiomers in a 46% yield when the non-chiral ligand (*i.e.* PPh_3 **P5**) was used in the catalytic system.

Moreover, at this stage, the relative stereochemistry of the stereocentres generated was crucial since in Atorvastatin, the diol groups are in a *syn*-relative orientation, meaning that the desired diastereoisomer for the diborylated ester in this case should also be the *syn* (Scheme 108).



Scheme 108 Required stereocontrol during the 2nd β-borylation reaction in order to achieve the right diastereoisomer for the synthesis of Atorvastatin.

Therefore, the control of the stereochemistry was required and from the previous study (see Section 2.3), it was known that the stereocontrol of the 2nd β-borylation reaction was a function of the enantiomer of the catalyst ligand used, *i.e.* (*R*),(*S*)-Josiphos **P7** gave rise to the *anti*-diastereoisomer mainly, whilst the use of (*S*),(*R*)-Josiphos **P27** lead into the *syn*-diastereoisomer. Hence, the β-borylation reaction of the homoallylic boronate ester **174** was exhaustively studied from an enantioselective point of view.

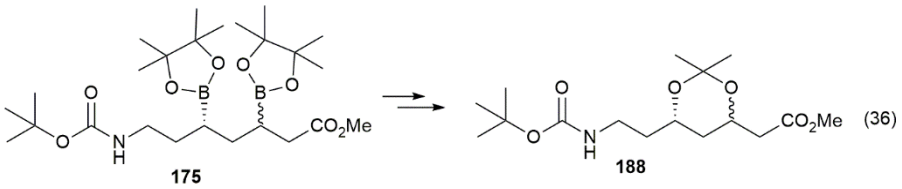
In addition, regarding the asymmetric version of the reaction, it was found that using a matching/mismatching effect between the enantiomers of the ligand and the first chiral centre, a 1:6 d.r. for the (*R*),(*S*)-Josiphos ligand **P7** and 2.5:1 for the case of using (*S*),(*R*)-Josiphos **P27** could be obtained. The yields in both cases were moderate, as observed before for the racemic version (*i.e.* 48% and 51%, respectively). This was corroborated using the methodology previously developed, showing that it was a viable methodology for a structurally different substrate such as the homoallylic boronate ester **174**.

2.4.4. Developing a methodology towards the key amino acetal building block

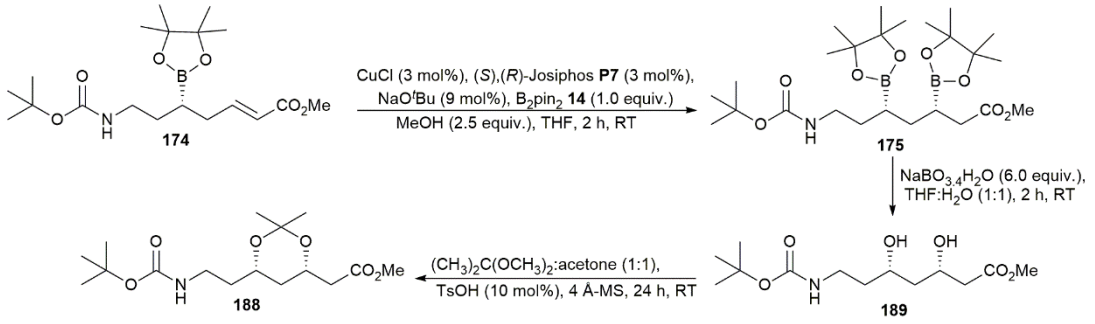
Once it was proved that the dual asymmetric methodology for the synthesis of diborylated esters was also suitable for this substrate, with good levels of diastereoselectivity being obtained, the next goal consisted on the synthesis of the 6-membered ring acetonide acetal **181** for the following reasons;

- Assignment of the relative stereochemistry, *i.e.* confirmation that the (*S*),(*R*)-Josiphos **P27** ligand give the *syn*-diastereoisomer as established for the model systems.
- Protection of the diol moiety for further steps in the synthesis such as Paal-Knorr synthesis for the construction of the tetrasubstituted pyrrole.

Hence, the derivatisation of the diborylated ester **175** into the corresponding 6-membered ring acetonide acetal **188** was examined with that purpose [Eqn. (36)].

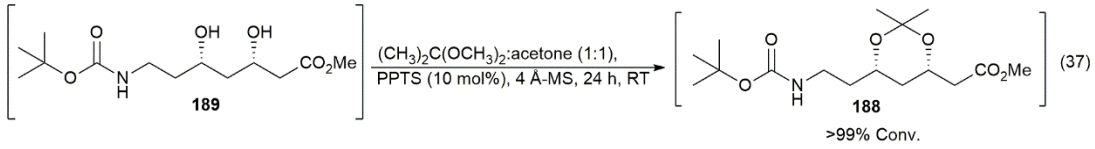


With that purpose, the C-B oxidation/acetal formation sequence previously established was also evaluated for this case (Scheme 109).



Scheme 109 Synthetic pathway previously developed for the synthesis of 6-membered ring acetonide acetal **188** from homoallylic boronate carboxylate ester **174**.

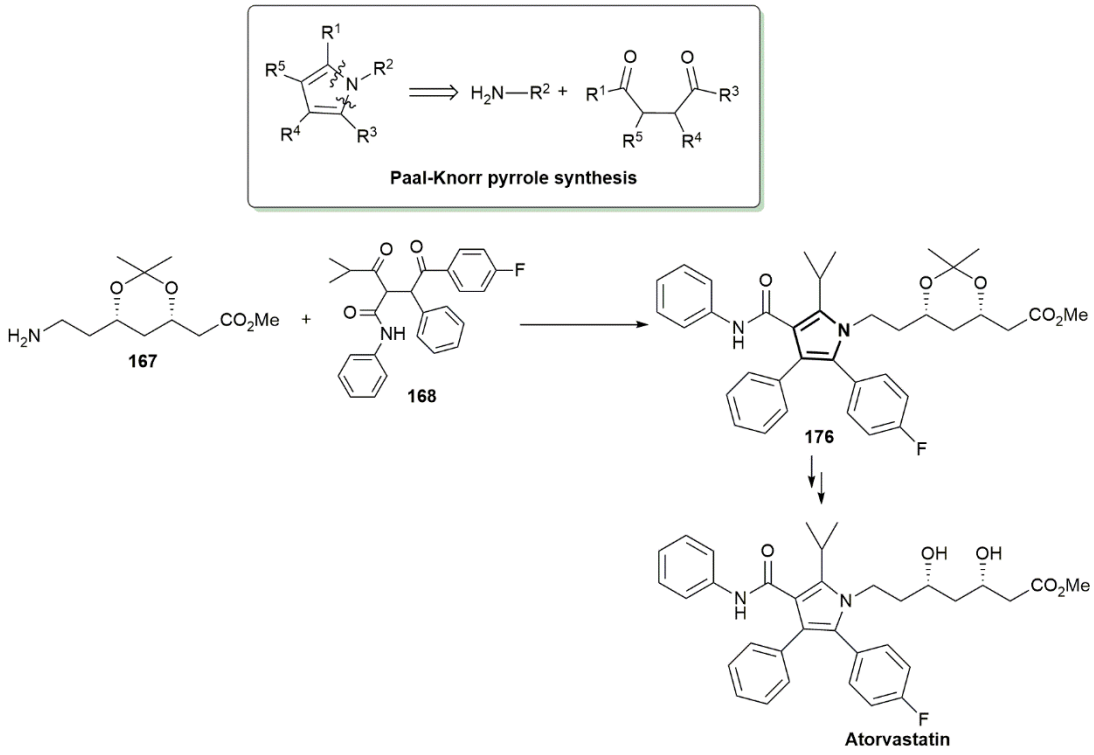
The application of these conditions on the *N*-Boc-protected diborylated ester **174** successfully gave the corresponding 1,3-diol, although when the acetal formation step was attempted, a complex ^{1}H NMR spectrum was obtained for the crude reaction mixture which suggested that some undesired side-reaction was taking place, *i.e.* the de-protection of the *N*-Boc-amino protecting group, catalysed by the acid present in the reaction mixture (TsOH), of which there are a few examples in the literature for removing this protecting group.[186,187] In order to solve this drawback, the reaction was then tested using pyridinium *p*-toluensulfonate (PPTS) instead of *p*-toluensulfonic acid (TsOH) since it has lower acidity, *i.e.* pKa (PPTS) = 5.2 *vs* pKa (TsOH) = -0.6. This modification gave rise to the successful synthesis of the *N*-Boc-protected amino acetonide acetal ester **188** (<99% conversion), [Eqn. (37)].



2.4.5. Synthesis of Atorvastatin: evaluation of the amino acetal as substrate for the Paal-Knorr synthesis of pyrroles

Once the synthesis of the key intermediate amino acetal **188** was achieved, the next step of the synthesis of Atorvastatin consisted of the synthesis of the tetrasubstituted pyrrole ring. Due to the natural occurrence of this moiety, in many natural products and medicines,

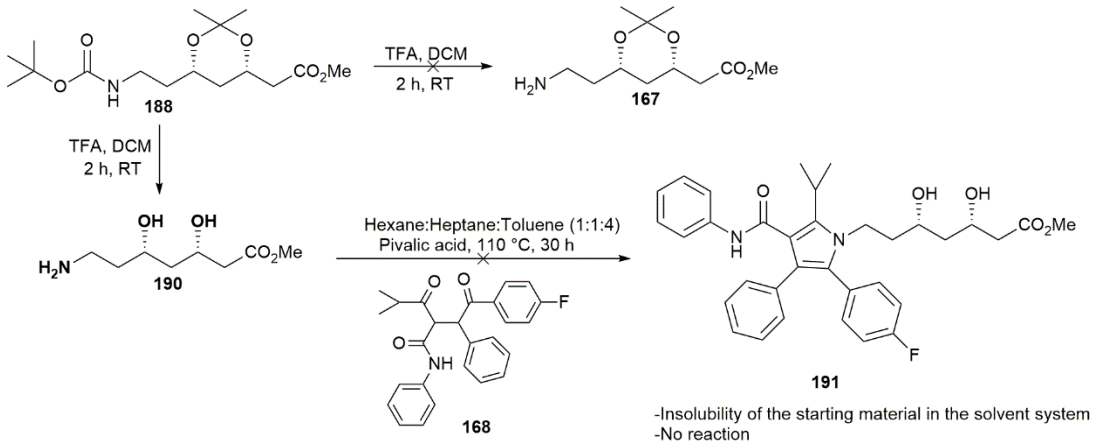
research involving its synthesis has been widely developed during recent decades.[188] Within the myriad of reactions available for the construction of these synthetically useful heterocycles, the Paal-Knorr synthesis stands out, consisting of the condensation of a 1,4-dicarbonyl compound with an amine[189] (Scheme 110).



Scheme 110 Application of the Paal-Knorr reaction for the synthesis of the tetrasubstituted pyrrole ring of Atorvastatin.

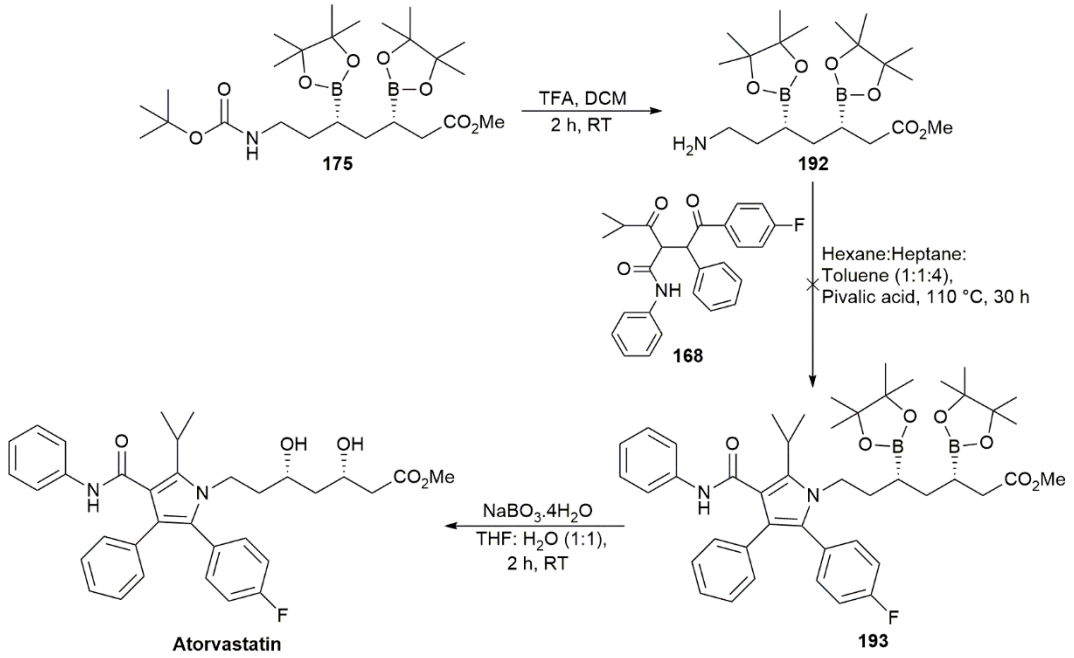
Although the *N*-Boc-protected amino acetal **167** building block synthesis could be achieved, in order to be able to perform the pyrrole synthesis on this compound, deprotection of the amino group was required, which turned out to be a challenging stage. The difficulty of this step was the fact that under the conditions normally used for the carbamate deprotection (TFA), the acetonide acetal moiety was removed as well, resulting into the formation of the amino diol compound **190**. Although the final compound, Atorvastatin, contains this moiety as the diol and this route would allow direct access to this target compound, it is preferable to remove the acetonide acetal protecting group once the pyrrole ring has been formed. This

would avoid the presence of the diol whilst other transformations are performed, and reduce possible complications, as summarised in Scheme 111.



Scheme 111 *N*-Boc deprotection and Paal-Knorr synthesis sequence for the synthesis of Atorvastatin.

Hence, alternative ways to perform this step were required, involving the deprotection of the *N*-Boc-amino group at the diborylated ester stage, followed by the synthesis of the pyrrole fragment and completed with the C-B oxidations, as outlined in Scheme 112.



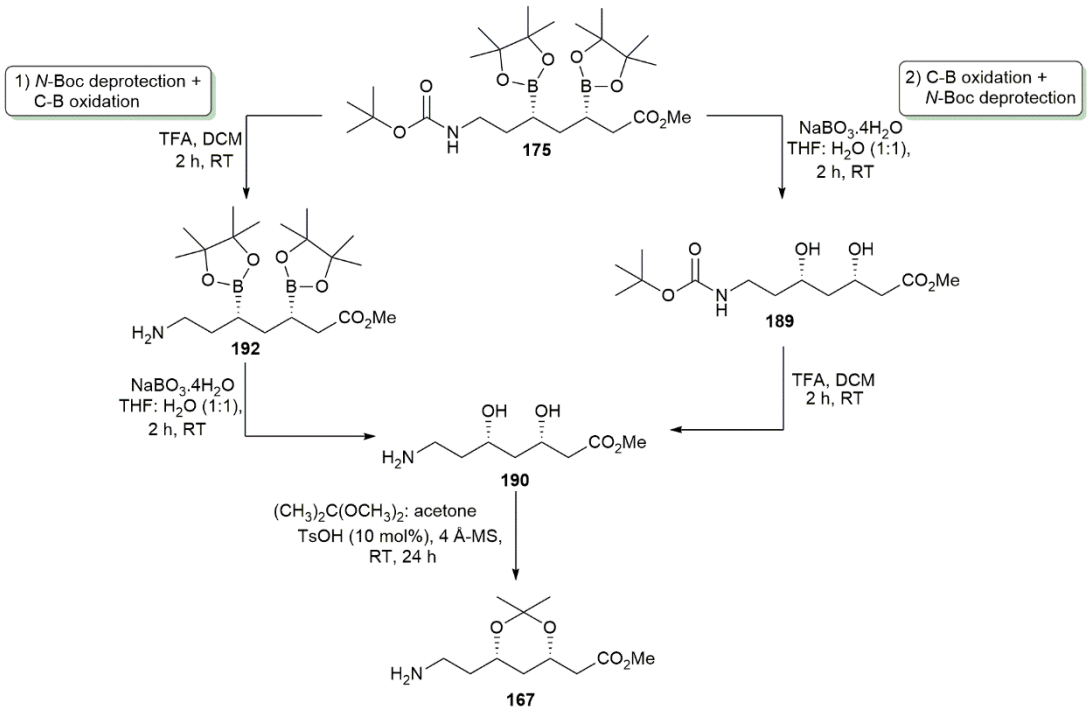
Scheme 112 Synthetic pathway proposed for the synthesis of Atorvastatin from the diborylated ester analogous **175**.

Regarding the first step of the sequence, the deprotection of the amino group of **175** proceeded with no detrimental effect of the acid on the boryl groups (*i.e.* the pinacol units on the boryl groups can be deprotected in the presence of acid leading into the corresponding boronic acids). However, when the Paal-Knorr synthesis was attempted on amine **192**, the desired pyrrole diborylated ester **193** was not obtained. This was attributed to possible side-processes as result from the presence of acid and heat. Hence, the initial synthesis of the amino acetal intermediate was examined again but this time the synthesis proposed was approached *via* two different routes differing only in the order in which the different steps take place:

- *N*-Boc deprotection of the diborylated ester **175** and subsequent C-B oxidation leading into the desired amino diol ester **189** which could readily be converted into the target 6-membered ring acetonide acetal **167** (strategy 1, Scheme 113).

- After the double C-B oxidation of the diborylated ester **175**, the *N*-Boc amino group was deprotected, followed by the acetonide acetal protection of the diol moiety (strategy 2, Scheme 113).

Scheme 113 outlines the two different routes proposed.

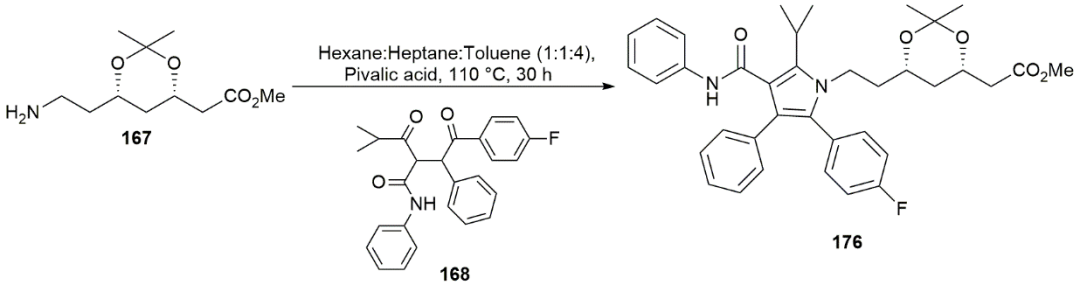


Scheme 113 Alternative synthetic pathways proposed for the synthesis of the amino acetal ester **167**.

Based on this, a sample of pure diborylated ester **175** was tested under strategy 1 and 2 in a small scale (0.5 mmol) being ontained the crude amino diol **190** in good conversions (>90%) for both cases. Therefore, it was concluded that the order in which the *N*-Boc deprotection/C-B oxidation are performed does not have an impact on the synthesis of compound **190**. However, the main drawback associated to these routes was found in the purification step of the resulting amino diol **190** which as expected, was complicated due to the high polarity of this type of compounds. Hence, the synthesis of the 6-membered ring acetal derivative **167** was performed on the crude sample of **190**, herein it is worth mentioning

that since the amino group was not protected at this stage, for the acetal formation TsOH could be used as the acid catalyst. And as in the previous step, the crude compound **167** was obtained in excellent conversion, however it was not possible to isolate although the diol functionality was herein protected, the presence of a free primary amine still represents a challenge in terms of purification.

In order to complete this study, crude amino acetonide acetal ester **167** was subjected to the literature conditions for the synthesis of the Atorvastatin[190] using the Paal-Knorr reaction (Scheme 114).



Scheme 114 Application of the amino acetal ester intermediate **167** into a Paal-Knorr reaction to synthesise Atorvastatin precursor **176**.

A small scale, one-pot procedure, was tested reacting **167** with dione **168**, and evidence for the formation of the acetal **176** was obtained both by LRMS and HRMS. After deprotection of the acetonide acetal moiety and subsequent saponification, formation of the sodium salt of the Atorvastatin was further evidenced by LRMS and HRMS. Due to the fact that a small-scale reaction was carried out along with the fact that several steps needed to be carried out in an one-pot manner difficulting the purification process, it was not possible to obtain a clean sample of the final Atorvastatin. However, it was demonstrated that the acetal **176** was an ideal precursor for the synthesis of Atorvastatin, being only required optimisation especially in terms of scaling-up the process.

2.4.6. Determination of the relative stereochemistry

As mentioned before, the control of the stereochemistry is crucial for the synthesis of pharmaceuticals, and although the diastereoisomers resulting from the β-borylation reaction on homoallylic boronate esters were identified from the model study (see Section 2.3), an exhaustive study in this particular reaction was also required here.

Hence, the assignment of the relative stereochemistry was performed on the crude 6-membered ring acetonide acetal in its Boc-deprotected form, *i.e.* compound **167**. In this case the *syn*-diastereoisomer was expected to be the major diastereoisomer since (*S*),(*R*)-Josiphos **P27** was used as ligand for the 2nd β-borylation reaction step (see Section 2.3). It is worth noting that the ^{1}H NMR analysis were carried out on a crude sample of the amino acetonide acetal **167** due to difficulties during the purification process associated to the presence of the free primary amine. Despite that, in the ^{1}H NMR spectrum, the key signals to assign the stereochemistry were clear allowing the *J* coupling analysis to be carried out, as shown in Figure 49.

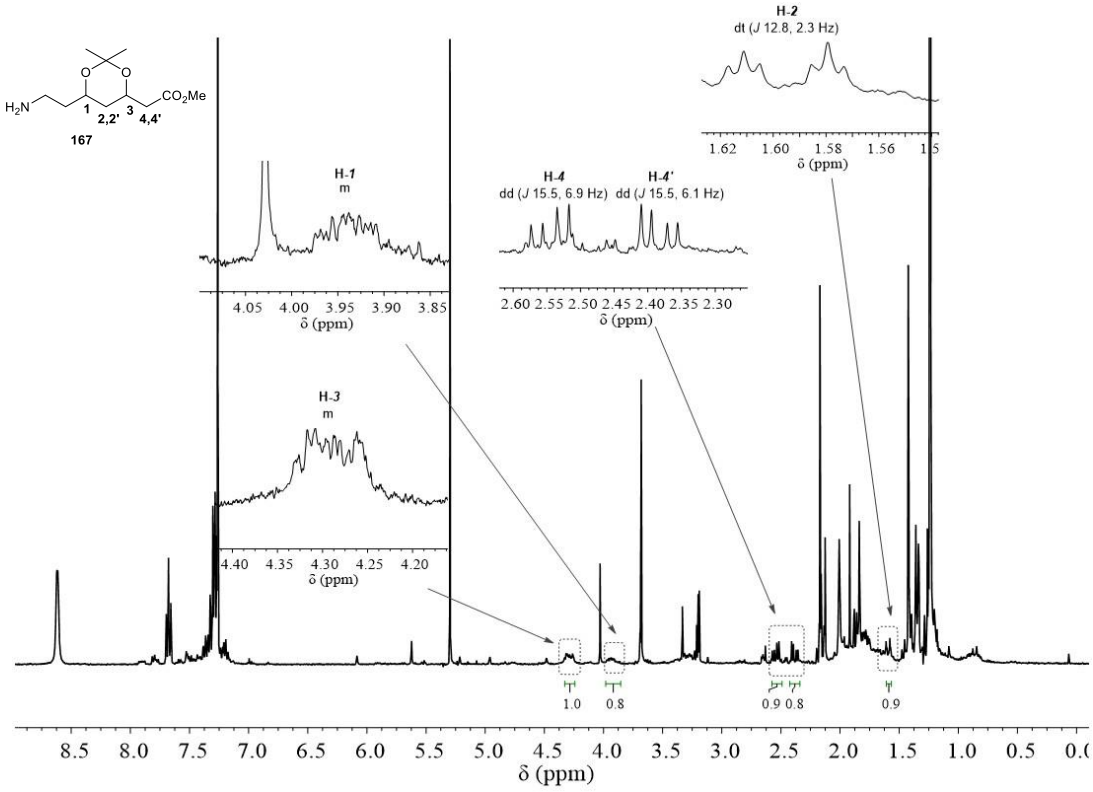


Figure 49 ^{1}H NMR analysis performed on a crude sample of acetal **167** in order to determine the relative stereochemistry when (*S*),(*R*)-Josiphos **P27** was used as chiral diphosphine ligand for the introduction of the 2nd boryl unit in the synthesis of the precursor diborylated ester **175**.

As in previous cases, the multiplicity of H-*2* (or H-*2'*) was key for the relative stereochemistry assignment, *i.e*. it is a dt which indicates that this proton is coupling with H-*1* resulting in a doublet with a large *J* coupling (12.8 Hz) which would correspond to a vicinal coupling (or ^{3}J) and to H-*4*/H-*4'* resulting in a triplet with a small *J* coupling (2.3 Hz) corresponding to a long range coupling (or ^{4}J), respectively. Hence, the conformation adopted by this 6-membered ring is a chair (Figure 50).

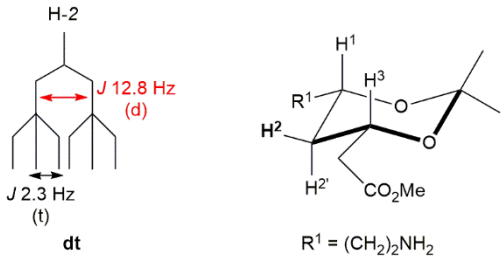


Figure 50 Conformational analysis of acetonide acetal **167**.

With these results in hand and based on the model systems (see Section 2.3), it was confirmed that the major stereoisomer obtained in this case was the desired *syn*-diastereoisomer of **167**.

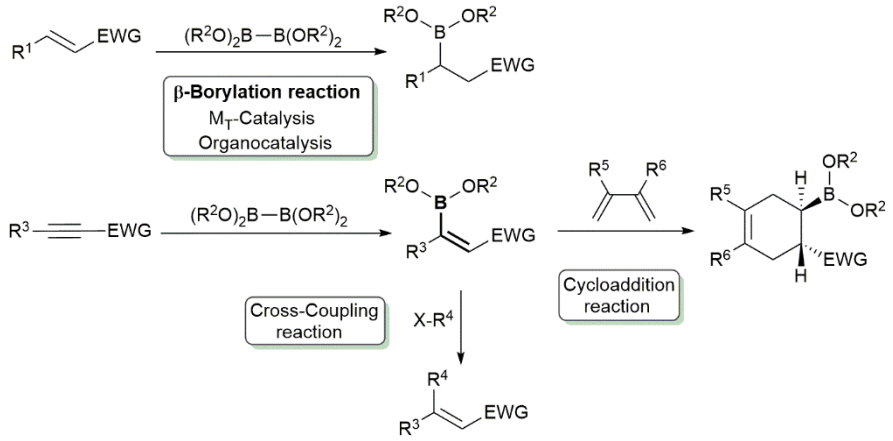
2.4.7. Summary of the application of the dual asymmetric diborylation strategies into the synthesis of Atorvastatin intermediates

In conclusion, the dual asymmetric borylation methodology developed was an efficient enantioselective alternative for accessing the key amino acetal intermediate for the synthesis of cholesterol-lowering drug Atorvastatin. Although further optimisation for the total synthesis of this pharmaceutical was required, the control of the stereochemistry for the synthesis of the amino acetal opened up many synthetic possibilities not only for the synthesis of Atorvastatin, but also for other statin analogous, *e.g.* Fluvastatin or Pitavastatin. Given the right substituents in the starting α,β-unsaturated aldehyde, the synthesis of the chiral homoallylic boronate ester and subsequent addition of a second boryl unit into this substrate and further derivatisation, can give rise to the relevant 3,5-dihydroxy acid side-chain characteristic of this type of drug in a stereocontrolled manner.

2.5. β-Borylation reaction on α,β-acetylenic carbonyl compounds: towards vinyl boronates

2.5.1. Background

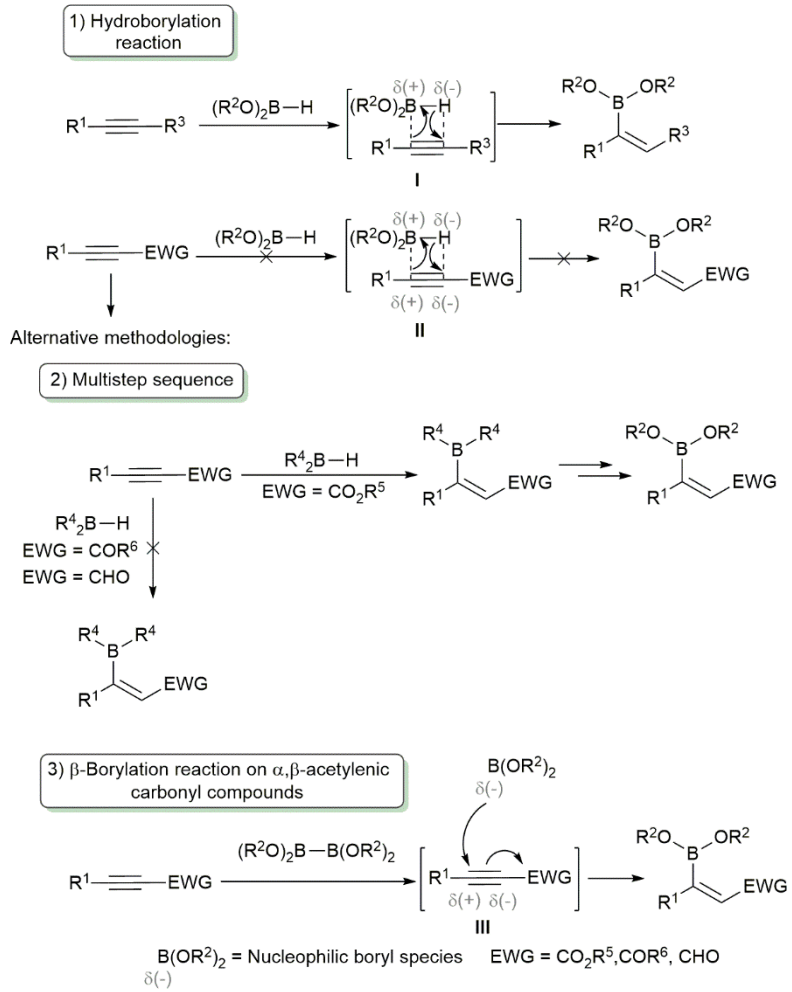
Since the conjugate addition of diborane reagents is a well-established strategy, novel applications for this useful transformation were sought. Alkyne-containing electron deficient substrates, *e.g.* acetylenic carbonyl compounds, have aroused much interest due to the fact that their β-borylation reaction allows the direct access to vinyl boronates.[119] These compounds are valued intermediates in organic synthesis due to the versatility of the boryl unit which allows many transformations to be carried out,[8-12] including cross-coupling reactions.[191] On the other hand, the presence of the alkene moiety makes them ideal platforms for several organic transformations, such as cycloaddition reactions[192] (Scheme 115).



Scheme 115 Comparison between α,β-acetylenic carbonyl compounds and its unsaturated analogous as substrates for the β-borylation reaction and application of the resulting vinyl boronate esters.

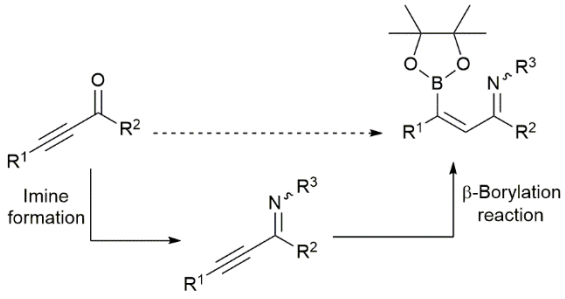
Although the synthesis of vinyl boronates have been exhaustively exploited,[193,194] alkynyl substrates conjugated to an electron withdrawing group are not generally suitable substrates (option 1, Scheme 116). Indeed, less efficient routes are required, such as multistep reactions (option 2, Scheme 116). In order to overcome these drawbacks, the adaptation of the

conjugate addition of a boryl moiety (β-borylation reaction) could be a suitable option (option 3, Scheme 116).



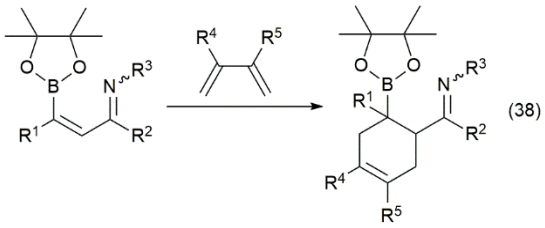
Scheme 116 General overview of the synthesis of vinyl boronate esters.

Hence, following on our research on the development of borylation methodologies on imine substrates, our aim was to study the copper(I)-phosphine mediated β-borylation reaction of α,β-acetylenic carbonylic compounds *via* the corresponding amine-derived imine intermediates. This methodology would provide an alternative route towards vinyl boronates, as outlined in Scheme 117. In this case, it is worth noting that the substrates evaluated were α,β-acetylenic ketones, *via* the corresponding ketimine, which unlike their aldehyde counterparts, are more stable and hence, making them better substrates for such a process.



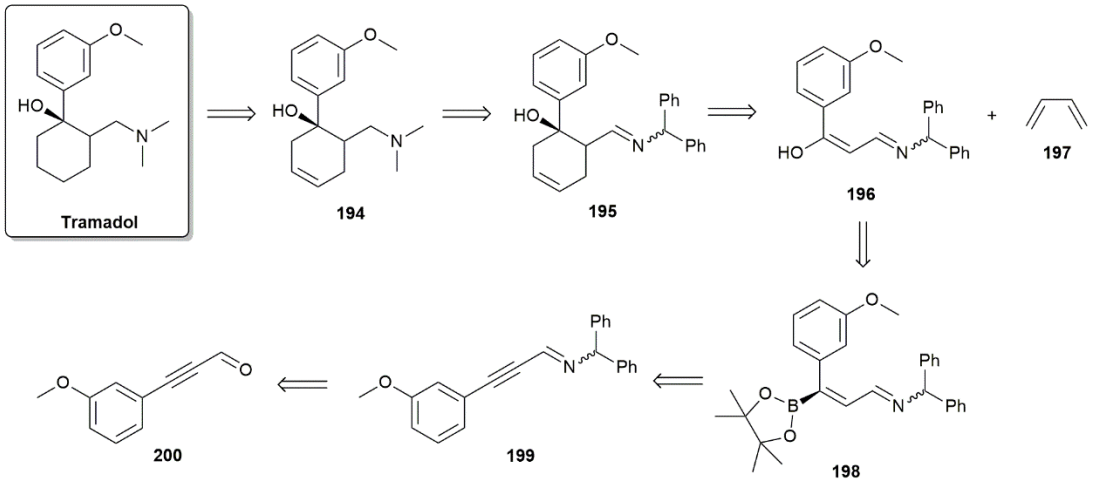
Scheme 117 β-Borylation of α,β-acetylenic ketones through the corresponding amine-derived ketimine intermediates.

It was envisioned that once a methodology for the synthesis of vinyl boronate compounds had been stablished, these compounds could be evaluated for their use as dienophiles in Diels-Alder reactions [Eqn. (38)].



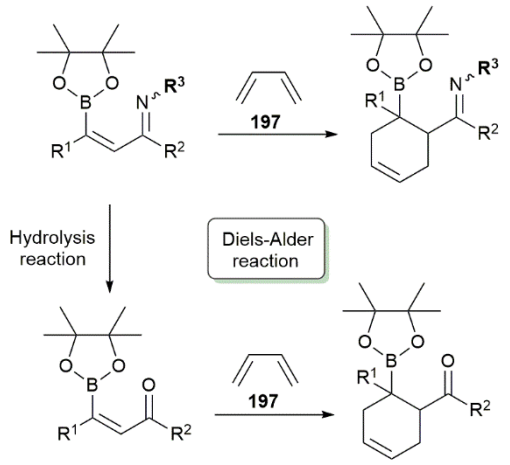
(38)

The establishment of an efficient methodology for this purpose would be attractive since it had been envisioned as a possible route towards more complex targets, such as the pain killer Tramadol, as outlined in Scheme 118.



Scheme 118 Retrosynthetic analysis of Tramadol starting from the corresponding α,β-acetylenic aldehyde **200** involving the vinyl boronate synthesis and subsequent Diels-Alder reaction.

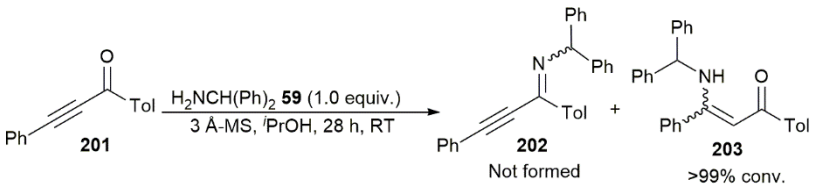
Beside the development of an efficient synthesis towards vinyl boronates with control of the stereochemistry, it would also be interesting to study the effect of the steric hindrance of the R^3-group on the imine functionality for the cycloaddition step, in comparison with its aldehyde or ketone analogues, as in Scheme 119.



Scheme 119 Comparison between the α,β-acetylenic imines and its analogous carbonylic compounds for the Diels-Alder reaction.

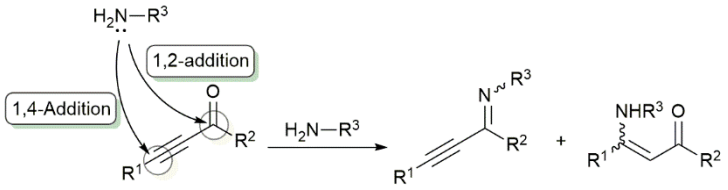
2.5.2. Synthesis of α,β-acetylenic ketimines and evaluation as substrates for the β-borylation reaction

The synthesis of α,β-acetylenic ketimines was approached by application of the methodology postulated in previous work, developed in our group for the analogous case of the α,β-unsaturated aldimines,[113,145] using 1-(4-methylphenyl)-3-phenyl-2-propyn-1-one **201** as model substrate, as displayed in Scheme 120.



Scheme 120 Application of the standard conditions for the imine formation on electron deficient olefins into α,β-acetylenic carbonyl compounds.

Even though these reaction conditions had been proved efficient for the imination of keto-olefins and their aldehyde anaogues previously, in this new approach, a chemoselectivity issue was observed, *i.e.* the nucleophilic addition of a primary amine resulted in a competitive 1,4-addition (conjugate addition) giving rise to an enamine instead of the desired ketimine (Scheme 121).



Scheme 121 Chemoselectivity issue associated to the imination of α,β-acetylenic ketones.

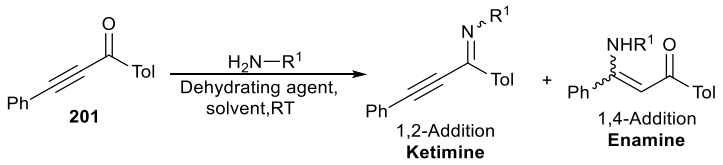
In 2014, our group in collaboration with Fernández and Carbó examined imine formation on enals and unsaturated ketones from an analytical and theoretical perspective.[114] It was concluded that the kinetic product (*i.e*. the condensation product) was predominant for

all enals studied and the majority of the ketones. Two possible explanations for this chemoselectivity issue were disclosed;

- The kinetically preferred product for some ketones is the 1,4-addition product.
- The 1,2-addition product is formed, but in the presence of water (generated as consequence of the condensation reaction) this product hydrolyses back to the starting ketone rapidly, releasing the amine into the medium which immediately reacts with the alkene moiety resulting into a formal 1,4-addition reaction.

In the case of α,β-acetylenic ketones, with the aim of determining if in this case the 1,4-addition product was kinetically favoured or it is just a consequence of a side-reaction, different sets of conditions were evaluated as summarised in Table 30.

Table 30 Reaction conditions screened for the establishment of the methodology for the synthesis of α,β-acetylenic ketimine **201**.



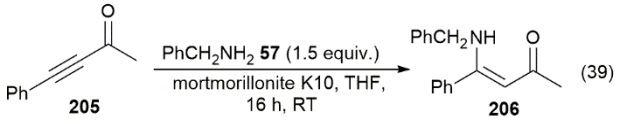
Entry	Amine	Dehydrating agent	Solvent	Reaction time (h)	Selectivity [a,b]
1	Benzylamine **57** (1.0 equiv.)	3Å-MS (0.5 g)	THF	6	1,4
2	Benzylamine **57** (1.0 equiv.)	3Å-MS (0.5 g)	^{i}PrOH	6	1,4
3	Benzylamine **57** (1.5 equiv.)	3Å-MS (0.5 g)	Toluene	16	1,4
4	Benzhydrylamine **59** (1.5 equiv.)	3Å-MS (0.5 g)	^{i}PrOH	4	1,4
5	Benzylamine **57** (1.0 equiv.)	Mortmorillonite K10 (25 mg)	THF	16	1,2
6	Benzylamine **57** (1.5 equiv.)	Mortmorillonite K10 (25 mg)	Toluene	16	1,2
7	Benzhydrylamine **59** (1.5 equiv.)	Mortmorillonite K10 (25 mg)	Toluene	24	1,4
8	Aniline **204** (1.5 equiv.)	Mortmorillonite K10 (25 mg)	Toluene	24	1,2
9	Butylamine **60** (1.5 equiv.)	Mortmorillonite K10 (25 mg)	Toluene	24	1,2
10	Benzylamine **57** (2.0 equiv.)	Mortmorillonite K10 (125 mg)	THF	24	1,4

Reaction conditions: α,β-Acetylenic ketone **201**:amine (1:1) was stirred in solvent and dehydrating agent at RT. [a]Determined by ^{1}H NMR spectroscopy on the reaction crude mixture. [b]Conversions >90% for the main product.

With these results in hand, it was not clear whether the ketimine or the enamine was the kinetically favoured product since for the same substrate both products were obtained, depending upon the reaction conditions used. However, conjugate addition chemoselectivity was corroborated for the majority of the cases studied. Interestingly, it was found that the use of mortmorillonite K10 as dehydrating agent, along with an excess of the amine and longer reaction times gave the desired α,β-acetylenic ketimine (entries 5-6 and 8-9, Table 30). Even though the use of mortmorillonite K10 as catalyst in some processes involving condensation reactions have been reported,[195] the fact that these results were a better alternative to molecular sieves was surprising since its main application in organic synthesis is to act as a solid acid.[196] Furthermore, toluene was revealed as the best solvent option (Entry 6, Table 30) unlike THF

or ^{i}PrOH, both of which were established as suitable solvents for the analogous cases of the α,β-unsaturated aldehydes (see Section 2.1).[113,148] Moreover, it was considered that the structure of the substrate **201** might not be ideal because it could favour the conjugate addition due to the presence of the aryl substituents on both sides, *i.e.* R^1 = phenyl and R^2 = *p*-tolyl groups. Specifically, the R^2 group being a phenyl ring might help reduce carbonyl reactivity (1,2-addition) and hence, aid conjugate (1,4-addition).

Therefore, the presence of aliphatic R^2 groups were evaluated as substrates, *i.e.* through 4-phenyl-3-butyn-2-one **205**. It is worth remarking that the commercial availability of these compounds also limited the scope of accessible substrates. For this substrate, the reaction was performed under the optimised conditions that gave rise to the desired corresponding imine (entry 6, Table 30) but surprisingly afforded the conjugate addition product (enamine), compound **206** [Eqn. (39)]. Hence, it was concluded that the C_α-substituent was not the dominant factor on the chemoselectivity of the process.



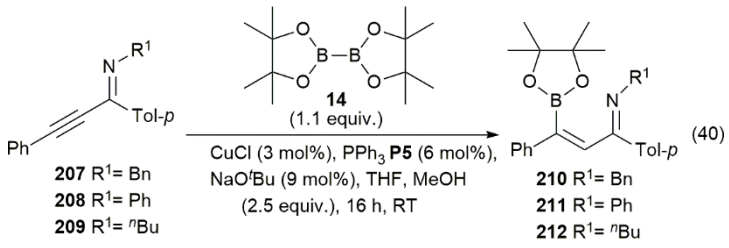
(39)

Although at this stage a general methodology for the synthesis of α,β-unsaturated ketimines was not established, efforts were then focused on the isolation and characterisation of the ketimine products obtained for certain cases (using α,β-acetylenic ketone **201**). Even though it is well known that this type of compounds can be challenging to handle since the condensation reaction can be easily reversed by hydrolysis, it was presumed that the presence of the substituent in the α-position could provide additional stability preventing this undesired side-process. Unfortunately, standard purification methods, such as column chromatography, were unsuccessful leading to hydrolysis of the imine yielding the starting α,β-acetylenic ketone **201**.

As an alternative purification technique, crystallisation of the resulting ketimine was examined in the case of compound **201**. Indeed, the desired imine structure provides the

possibility to be purified by crystallisation techniques. Hence, the imine **202** was recovered from the reaction as a crude solid and subjected to crystallisation conditions. Unfortunately, it was not possible to obtain crystal structures suitable for X-ray diffraction analysis.

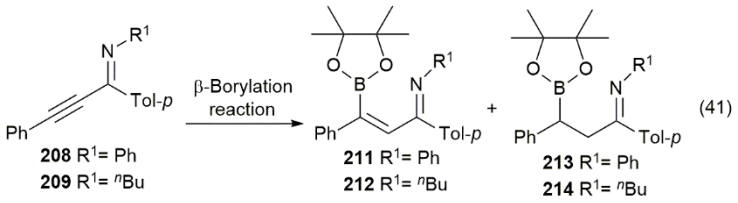
It was concluded that the synthesis of these compounds, and especially their isolation, represented a challenge. Even so, evaluation of this novel type of substrates for borylation in order to explore their applicability for further elaboration was examined under standard racemic Cu(I)-PR_3 β-borylation reaction conditions [Eqn. (40)].



(40)

The alkenyl boronate **210** was obtained in a >99% conversion (determined by crude ^{1}H NMR spectroscopy) and the reaction product was purified by crystallisation. Unfortunately, it was not possible to perform X-ray diffraction analysis due to decomposition of the product.

Surprisingly, in the cases of both **208** and **209**, a mixture of products was observed composed of the desired vinyl boronate products **211** and **212** respectively, and their hydrogenated analogues **213** and **214** [Eqn. (41)]; a fact that suggested that the reaction time was too long promoting the formation of the side-products.

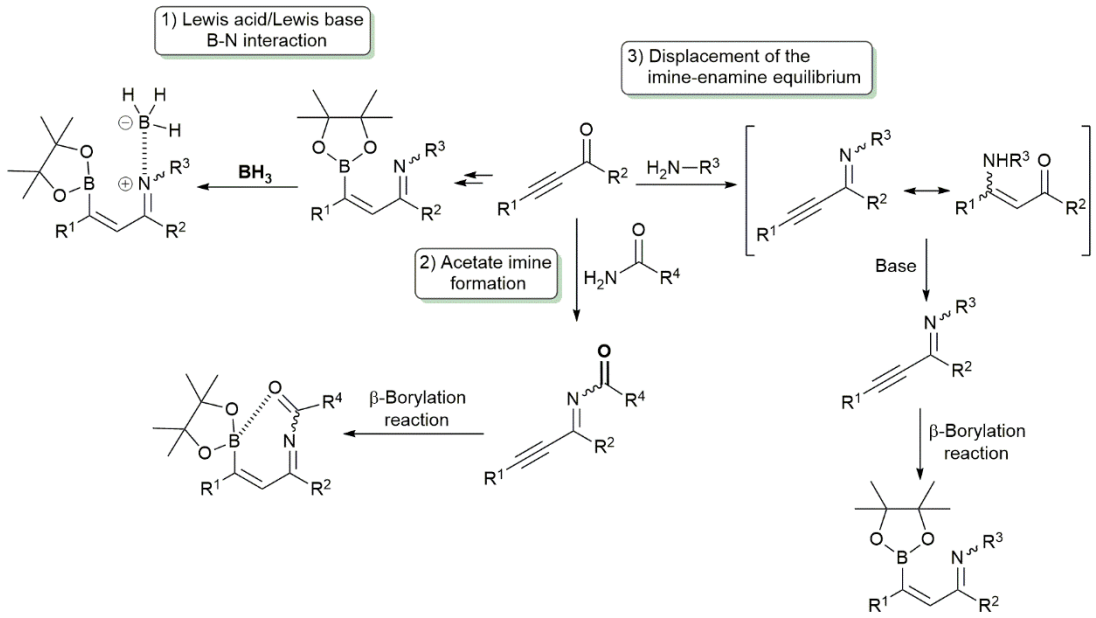


(41)

From this study, two major drawbacks were identified:

- In the case of the β-boryl aldimine, it could not be purified due to its intrinsic instability towards hydrolysis on the column.
- The existence of an imine-enamine equilibrium might add difficulties to the borylation process.

Hence, accessing stable analogues was carried out through two different strategies based on intermolecular and intramolecular interactions, as summarised in Scheme 122.



Scheme 122 Strategies examined for the stabilisation of β-boryl ketimines.

The different strategies evaluated consisted of:

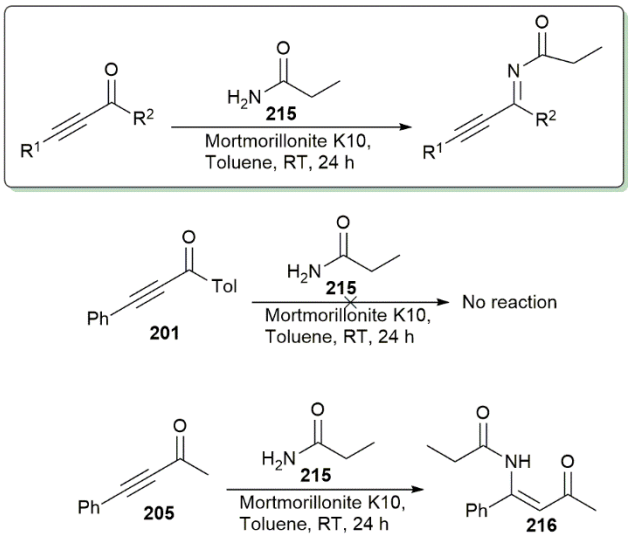
- Intermolecular stabilisation of the vinyl boronate ketimine by the addition of borane to the solution (strategy 1, Scheme 122).
- Substitute the amine for an amide for the imination process to obtain *N*-acetate analogues of the α,β-unsaturated ketimines which could provide additional stability in the subsequent borylation steps due to the intrinsic B-O interaction present in compound (strategy 2, Scheme 122).

- Prevent the formation of the enamine form by the addition of a base into the medium in order to reverse the imine-enamine equilibrium existent (strategy 3, Scheme 122).

Ito *et al.*[197] reported accessing stable *N*-substituted (boryl)(silyl)iminomethanes by the use of BH_3 in order to form a borane-imine complex, which allows its purification by column chromatography. In this case, borane was used as Lewis acid, *i.e.* the empty *p*-orbital on B is attacked by the lone pair of electrons belonging to the N atom of the imine making it less reactive, and therefore, less prone to suffer hydrolysis through complexation (strategy 1, Scheme 122). Based on this, a crude mixture of vinyl boronate ketimine **210** was tested for the formation of this complex, unfortunately, the formation of the complex was not observed (analysed by ^{11}B NMR). It was concluded that this strategy was not suitable for this purpose due to the fact that in the β-borylated form of the ketimine substrates they could already be present in a chelated form between the N atom and the B from the boryl group.

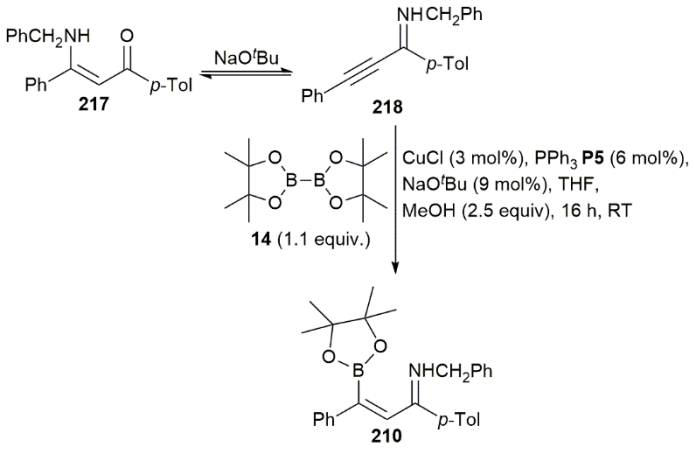
Additionally, it was also envisioned that the stabilisation could be carried out in an intramolecular manner by the substituent located on the amino function, such as an acetate group; *i.e.* the use of an amide instead of an amine to form the ketimine.[198] Once the imine substrate was borylated, this intramolecular interaction between the B and the O corresponding to the amide carbonyl group could indeed stabilise this compound (strategy 2, Scheme 122).

With that aim, the reaction was tested using propanamide **215**. However, the crude ^1H NMR spectra did not show formation of the α,β-acetylenic ketimines, being only observed starting ketone for the case of compound **201**, and the enamine form (compound **216**) for the case of compound **205** (Scheme 123).



Scheme 123 Synthesis of α,β-acetylenic ketimines using propanamide.

Moreover, the fact that the imine and the enamine forms exist in equilibrium provides, *a priori*, the chance to displace it towards the desired form.[199] It was envisioned that the addition of a base might assist the displacement of the equilibrium towards the imine (strategy 3, Scheme 122). Hence, for a case in which the 1,4-addition took place, an equimolar amount of NaO^{t}Bu was added in order to displace the equilibrium towards the imine **218**. Subsequently, this substrate would undergo β-borylation, as outlined in Scheme 124.



Scheme 124 Transformation of the β-enamine **217** into the corresponding vinyl boronate ketimine **210**.

This approach was unsuccessful since it was not possible to obtain the target vinyl boronate ketimine **210**, and indeed, there was no evidence of the reversion of the tautomeric equilibrium.

2.5.3. Developing a one-pot methodology towards vinyl boronates from α,β-acetylenic ketones *via* amine-derived ketimine intermediates

Due to the lack of the desired results discussed above, further studies using *in situ* monitoring techniques (ReactIR), were required in order to establish a one-pot methodology involving the imine formation and subsequent β-borylation reaction. With that purpose, α,β-acetylenic ketone **205** was reacted with an equimolar amount of benzhydrylamine **59** in the presence of 3 Å M.S. It is worth noting that this new attempt was carried out with the dehydrating agent being activated at a higher temperature (220 ºC). Regarding the reaction medium, the reaction was first tested in THF but it was found that the reaction was considerably slower in comparison with the α,β-unsaturated aldehydes analogues (typically between 3-8 h), taking up to 72 h for completion of the reaction. Based on the knowledge acquired from previous studies, the use of ^{i}PrOH was likely to result in beneficial effects on the reaction, and indeed, in this case the time required for the completion of imine formation was 28 h, demonstrating that the use of an alcohol as solvent has a positive effect on this step. The selectivity of the process was exclusively in favour of the desired 1,2-product (ketimine **219**); from the graphical output from the ReactIR it can be observed that a clear decrease in the signal at υ 1680 cm^{-1} corresponding to the C=O stretch from the ketone substrate occurred and a simultaneous appearance of a signal at υ 1620 cm^{-1}. Although it has been previously reported that the presence of molecular sieves did not have an impact in the chemoselectivity;[114] for this particular case, it seemed to be critical since in the case of alkyne substrates, the imine and the enamine are in equilibrium and the removal of the water is key

for the displacement of the equilibrium towards the imine form. Figure 51 present the graphical output from the ReactIR study for the imine formation in THF.

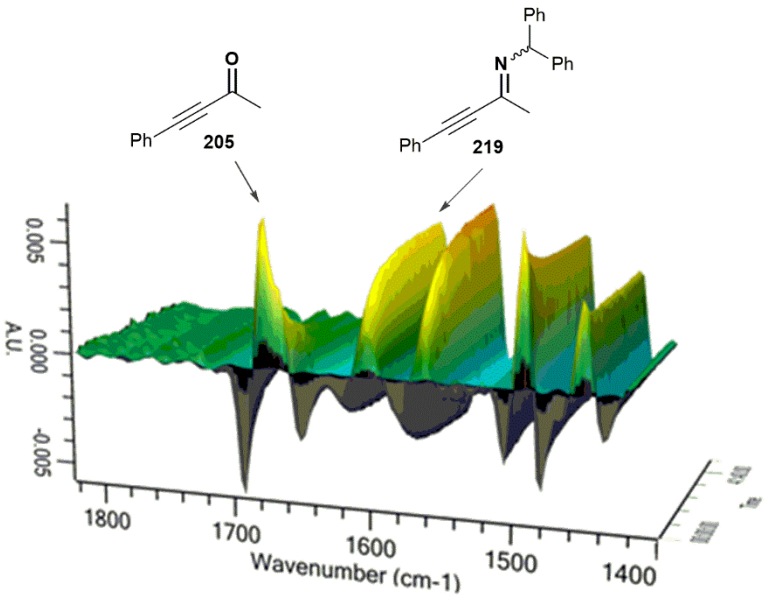
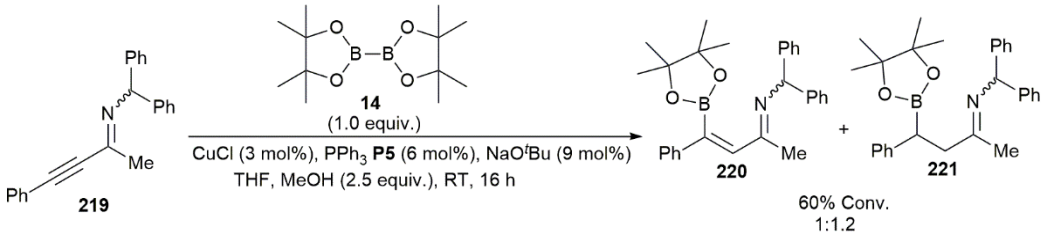


Figure 51 Graphical output obtained from the ReactIR for the formation of α,β-acetylenic ketimine **219**.

With this initial step sorted out, the *in situ* generated α,β-acetylenic ketimine **219** was tested for the β-borylation reaction under the CuCl/PPh_3 standard reaction conditions. In this case, the crude reaction showed the presence of two different products in a 45:55 ratio (61% conversion) which corresponded to the vinyl boronate (compound **220**) and its hydrogenated analogue (compound **221**), as outlined in Scheme 125.



Scheme 125 Application of standard Cu(I)/PR_3 β-borylation reaction conditions on the *in situ* generated α,β-acetylenic ketimine substrate **219**.

Hence, efforts were focused on the control of the formation of the desired vinyl boronate **220** over the hydrogenated analogue **221**, by evaluation of different sets of reaction conditions as summarised in Table 31.

Table 31 Optimisation of the methodology for the β-borylation reaction on α,β-acetylenic ketimine **219**.

Entry	Cu^I (mol%)	Ligand (mol%)	Base (mol%)	Borane reagent (equiv.)	Solvent	Time (h)	Ratio[a]		Conv.[a] (%)
							220	**221**	
1	CuCl (3)	PPh_3 **P5** (6)	NaO^tBu (9)	B_2pin_2 (1)	THF[b,c]	24	45	55	61
2	CuCl (3)	PPh_3 **P5** (6)	NaO^tBu (9)	B_2pin_2 (2)	THF[b,c]	24	6	94	70
3	CuCl (3)	PPh_3 **P5** (6)	NaO^tBu (9)	B_2pin_2[e] (0.5)	^{i}PrOH[c]	16	67	33	45
4	CuCl (3)	PPh_3 **P5** (6)	NaO^tBu (9)	B_2pin_2[e] (0.9)	^{i}PrOH[c]	16	28	72	73
5	CuCl (3)	Xantphos **P1** (3)	NaO^tBu (6)	B_2pin_2 (1.1)	THF[b,c]	6	38	62	67
6	CuCl (3)	Xantphos **P1** (3)	NaO^tBu (6)	B_2pin_2 (2)	THF[b,c]	24	44	56	75
7	-	PPh_3 **P5** (4)	Cs_2CO_3 (15)	B_2pin_2 (1)	THF[a,d]	6	38	62	66
8	-	PPh_3 **P5** (4)	Cs_2CO_3 (15)	B_2pin_2 (1)	^{i}PrOH[c,d]	6	29	71	66
9	-	PPh_3 **P5** (4)	Cs_2CO_3 (15)	B_2pin_2 (1)	^{i}PrOH[c,d]	24	16	84	91
10	CuCl (3)	PPh_3 **P5** (6)	NaO^tBu (9)	HBpin (1)	THF[b,c]	6	-[f]	-[f]	43
11	-	-	-	HBpin (1)	THF[b,c]	6	-[g]	-[g]	-[g]

[a]Determined by crude ^{1}H NMR. [b]MeOH(2.5 equiv.) as alcohol additive. [c]Reaction perfomed at RT. [d]Reaction performed at 70 ºC. [e]Slow addition: 10 mol% every 10 mins. [f]None of **220** or **221** products were obtained, instead hydroboration/protodeborylation product obtained. [g]No product obtained.

It was observed that the amount of diborane reagent did have an impact on which of the two products was the predominant. For 1.0 equivalents of B_2pin_2 **14**, compounds **220** and **221** were obtained in similar proportions (entry 1, Table 31), whilst when the amount of diborane reagent was doubled, compound **221** was predominantly obtained (entry 2, Table 31). However, for relatively low amounts of B_2pin_2 **14** (up to 0.5 equiv.), along with a slow addition of this diborane, it was possible to reverse this trend, to obtain a higher proportion the vinyl boronate **220** (entry 3, Table 31). At this point, it was concluded that this type of substrate present complex reactivity under the borylation conditions, *i.e.* the fact that the

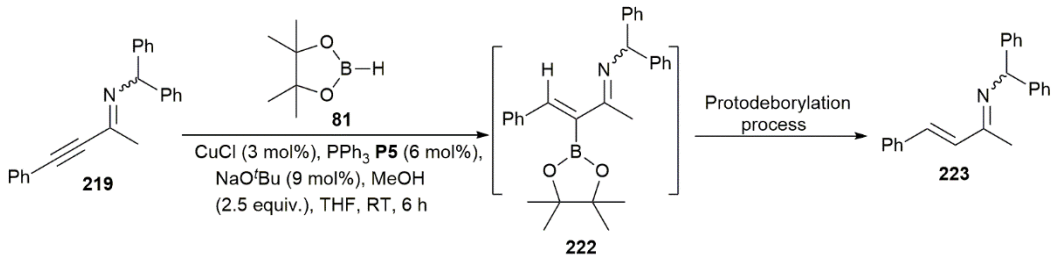
unsaturation is an alkyne, rather than an alkene, seemed to give rise to undesired side-processes, as well as low conversions. Hence, the use of different catalytic systems were examined as possible solutions.

In 2008, Yun *et al.*[119] postulated a copper catalysed method for the β-borylation of α,β-acetylenic esters through which β-borylated-α,β-ethylenic esters were synthesised. In this case, the catalytic system used was also Cu(I) based although the phosphine ligand was a diphosphine (Xantphos **P1**). It is worth noting that the production of what was identified for the authors as a "protodeboronated product" was also observed for other diphosphine ligands examined (*e.g.* DPEphos **P2**) within the phosphine ligand screening reported. Even so, the optimised conditions (Entry 5, Table 31) were tested on the ketimine **219** giving a mixture of products, as well as a low conversion value. It was then considered that perhaps due to the greater steric hindrance from the benzhydryl group on the imine functionality (in comparison to the ethyl ester studied in the original report[119]), the reaction might require longer times in order to reach full conversion. Hence, the reaction was repeated but the reaction time was extended up to 24 h and a minor increase in the conversion from 67% to 75% was observed, with no significant change regarding the product ratio (within the error associated with the ^{1}H NMR integration).

It was concluded that the use of an organometallic catalyst was not the best option for these substrates because of promoting undesired side-processes. Hence, the dispensation of the use of the transition metal was envisioned as a possible solution for obtaining better control of the whole process. Therefore, the organocatalytic protocol postulated by Fernández and co-workers[58] was applied (entry 7, Table 31). Interestingly, the organocatalytic conditions did not make a major difference in comparison to the organometallic version; being obtained mixtures of compounds **220** and **221** in similar ratios and low conversions (entries 1 and 5, Table 31). Additionally, the comparison between the conventional solvent/alcohol additive reaction medium and the use of only an alcohol was examined by using sole ^{i}PrOH as reaction medium. However, this did not make any difference either in terms of products ratio or conversion

(entries 7 and 8, Table 31) as previously observed for the organometallic case (entries 1-2 and 3-4, Table 31). In this case, the reaction was not complete within 6 h (only 66% conversion), hence, the reaction was repeated using a longer reaction time which achieved completion, however, the proportion of the side-product **221** was higher (entry 9, Table 31).

It was concluded that α,β-acetylenic ketimine substrates were not readily applicable to the β-borylation reaction and in order to obtain any borylated derivatives, different techniques were required. Based on this, pinacolborane **81** was evaluated as a possible borylating reagent in order to achieve better control of the selectivity of the reaction. Interestingly, in the case of performing the reaction under standard copper (I)-phosphine catalysis conditions (entry 10, Table 31) neither the desired vinyl boronate compound **220** nor the hydrogenated analogue **221** were obtained. Instead, a product containing an alkene moiety was obtained which suggests that borylation of the alkyne with HBpin **81** may be possible (*i.e. via* an hydroborylation reaction) introducing the boron containing unit in C_α and leading to compound **218**, which would then be prone to suffer protodeborylation resulting in the α,β-unsaturated ketimine **219** (Scheme 126).



Scheme 126 β-Borylation of α,β-acetylenic ketimine **219** using HBpin **81** as boron source.

However, when the same reaction was carried out without the presence of the catalyst system (entry 11, Table 31), no product was obtained. This would indicate that in the presence of the catalytic system, some reactive boryl species was generated leading to the addition of these species to the substrate in a concerted manner, rather than a conjugate addition (as

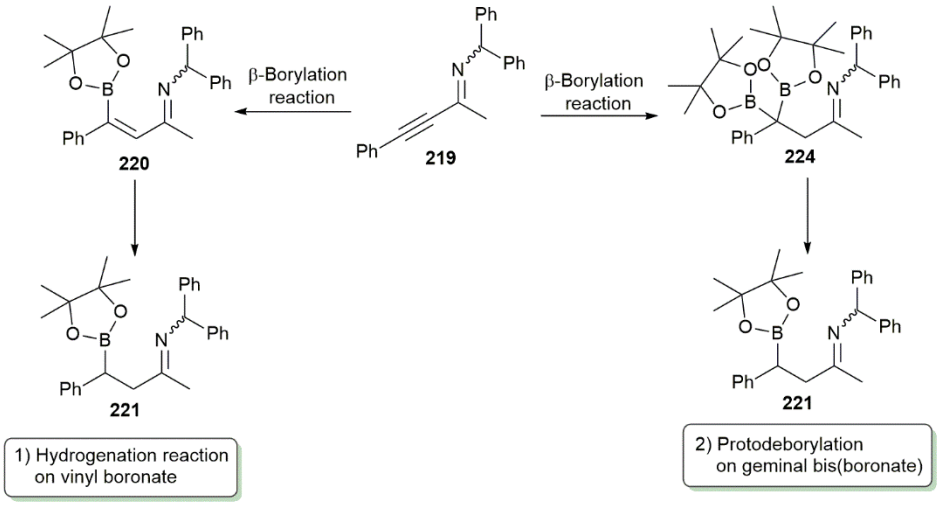
previously observed in the mechanistic studies section that pinacolborane **81** does not β-borylate electron deficient olefins, see Section 2.1.3) leading into an α-boryl product (compound **222**).

2.5.4. Unexpected reactivity for the β-borylation reaction: origin of the hydrogenated product?

After screening several different sets of conditions for the borylation reaction, and having not found a suitable methodology for an efficient synthesis of the target vinyl boronates, it was concluded that a better understanding of the formation of the side-products would be necessary. Two different possible routes towards its formation were considered;

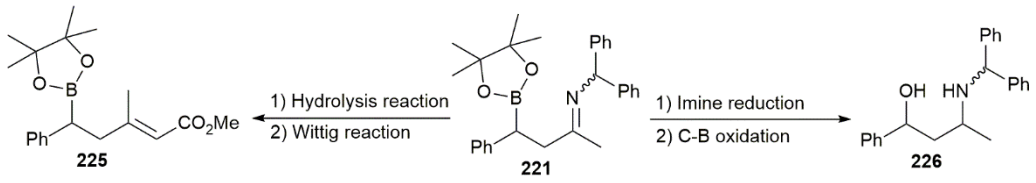
- Hydrogenation of the initially formed vinyl boronate **220** (option 1, Scheme 127).
- Protodeborylation process on a geminal bis(boronate) compound **224** (option 2, Scheme 127).

Scheme 127 summarises the two proposed different possible routes towards compound **221**.



Scheme 127 Proposed routes for the formation of hydrogenated boryl compound **221**.

Firstly, the possibility that what was taking place in the reaction mixture was the monoborylation of the acetylenic ketimine leading to the desired vinyl boronate **220** was considered, which in the presence of base, for example, undergoes a hydrogenation process leading to compound **221** (option 1, Scheme 127). Hence, in order to determine if the presence of a strong base (*i.e.* NaO^{t}Bu) was effecting the hydrogenation of the vinyl boronate, the same reaction was performed using Cs_2CO_3 instead. Additionally, the reaction was also tested using a base-free protocol.[200] In both cases, the outcome of the reaction was the same; *i.e.* a not complex mixture where the presence of the hydrogenated product **221** was detected. Due to the impossibility of purification, further derivatisation protocols were evaluated, such as the application of the hydrolysis/Wittig reactions sequence previously developed,[148] or the reduction of the imine functionality and subsequent oxidation of the boryl unit giving rise to the amino alcohol analogue[113] (Scheme 128).

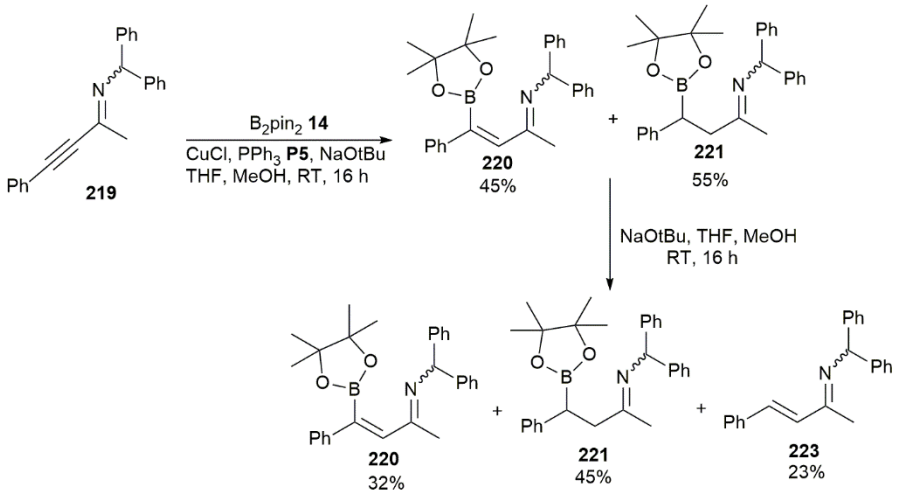


Scheme 128 Derivatisation strategies studied for boronate **225**.

Unfortunately, the application of the derivatisation protocols previously successfully applied to the case of the α,β-unsaturated aldehydes or ketones, were not suitable for this particular case. It was concluded that the slight structural variation on the substrate was having an impact and was leading to complex mixtures where no clear product could be identified.

Due to the lack of isolated products that could prove the hydrogenation on the vinyl boronate compound **220**, a sample of the crude mixture after the β-borylation reaction (filtered through Celite in order to remove the remaining borylation reagents) was subjected to conditions similar to the ones in the reaction mixture, *i.e.* in a solution containing the NaO^{t}Bu. The initial composition of the reaction crude product was 45% and 55% for compounds **220**

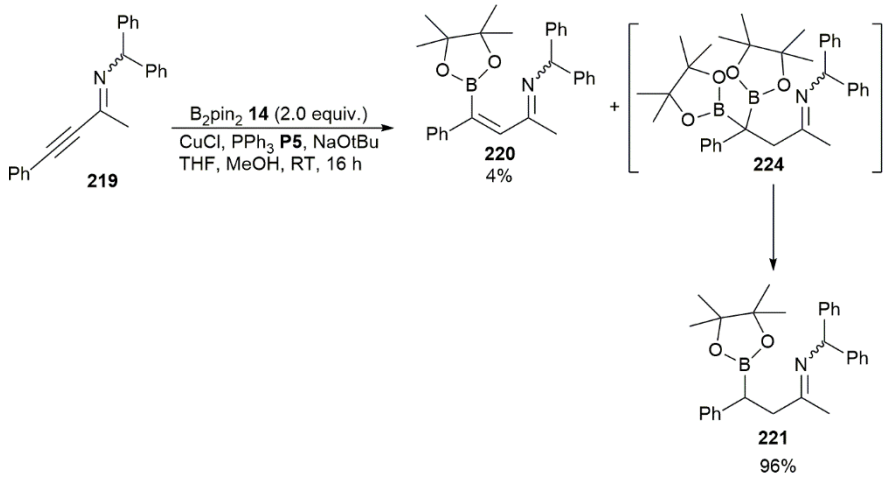
and **221**, respectively. This mixture was then introduced into a THF solution containing NaO^{t}Bu in a catalytic amount (9 mol%) and MeOH (2.5 equiv.). After 16 h at RT, the presence of a third compound was identified as the analogous α,β-unsaturated ketimine **223** was observed, as outlined in Scheme 129.



Scheme 129 Effect of the base in the borylation reaction.

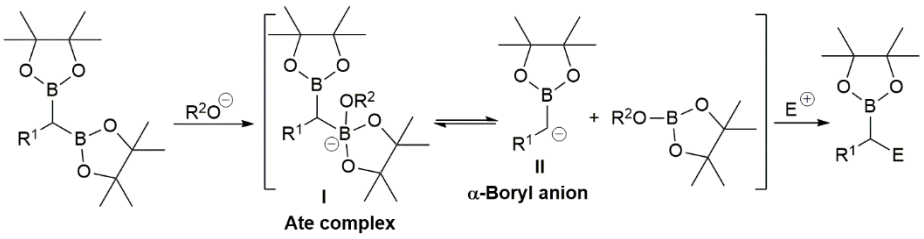
The analysis of the resulting crude mixture indicated that long exposure of these compounds to a strong base has a detrimental effect, whilst the proportions between the vinyl compound **220** and the hydrogenated analogous **221** were almost comparable to the previously observed, it also was found that protodeborylation was occurring.

On the other hand, the possibility of a geminal bis(boronate) compound **224** and subsequent loss of one of the boryl units resulting in compound **221** (option 2, Scheme 127) can be considered. Interestingly, it was observed that when 2.0 equivalents of B_2pin_2 **14** were used (entry 2, Table 31), compound **221** was almost exclusively obtained (96% in comparison to the vinyl boronate **220**), Scheme 130.



Scheme 130 Reaction sequence giving 'hydrogenated' product by protodeborylation of geminal bis(boronate) compound **224**.

This result suggests that the formation of a bis(borylated) product **224** could indeed take place and result in what appeared to be a hydrogenated derivative of the vinyl boronate species **221**. Hence, the effect of the base could be to cause loss of the boryl fragment, a process which was reported by Morken and coworkers,[201] *i.e.* 1,1-bis(pinacolboronate) esters undergo a diborylation process assisted by metal alkoxides leading into α-boryl anions **II**, *i.e.* boron stabilised carbanions which can be then alkylated leading into synthetically useful organoborane compounds (Scheme 131).



Scheme 131 Deborylative alkylation of geminal bis(boronate) compounds reported by Morken *et al.*[201]

In this work, the use of NaO^{t}Bu in THF was effective for this purpose, therefore, it would indicate that in order to confirm that this was the process that was taking place, the

reaction using 2.0 equivalents of B_2pin_2 **14** would need to be carried out using the base and solvent that provided lower conversions for the alkylation reaction (entry 2, Table 32).[201] Hence, a study on the effect of different bases was carried as summarised in Table 32.

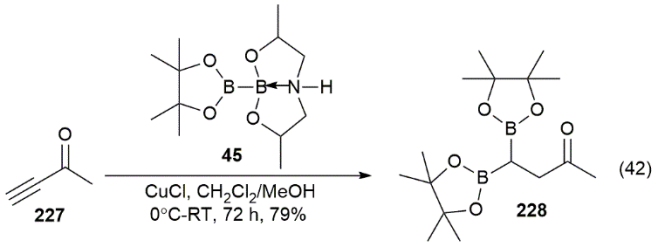
Table 32 Screening of bases in order to avoid possible deborylative process in the geminal bis (pinacolate) **224**.

Entry	Base (mol%)	Ratio[a]			Conversion (%)[a]
		220	**221**	**224**	
1	NaO^tBu (9)	6	94	-	70
2	LiO^tBu (9)	21	79	-	73
3	Cs_2CO_3 (9)	62	38	-[b]	71
4	-[c]	76	24	-[b]	63

[a]Determined by crude ^{1}H NMR. [b]Another product observed in the mixture; α,β-unsat. ketimine **223**. [c]Cu_2O instead of CuCl. [d]Reactions performed using 2.0 equivalents of B_2pin_2 **14**.

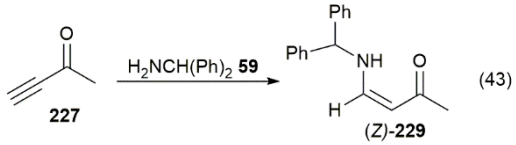
In all cases studied, the presence of the geminal bis(pinacolboronate) compound **224** was detected as well as the hydrogenated monoborylated compound **221**, which was produced in reduced amounts where the base used was not an alkoxide base or in the absence of base (entries 3 and 4, Table 32). This would indicate that compound **221** could originate as a result of the hydrogenation of the vinyl boronate **220**. Interestingly, for those cases in which the major product was the vinyl boronate **220**, the presence of another compound was detected which could correspond to the analogous α,β-unsaturated ketimine **223**.

Another aspect to take into account was the fact that the geminal bis(boronate) group would be located in a benzylic position, which could make it more prone to undergo this undesired process. Therefore, the reaction was tested on an analogous terminal alkyne lacking the phenyl group, specifically 3-butyn-2-one **227**. The products from the use of an α,β-acetylenic carbonyl compounds as substrates for the β-borylation reactions have been reported by Santos and co-workers,[202] derived from a copper catalysed methodology using a preactivated sp^2-sp^3 hybridised mixed diboron reagent, in which the α,β-acetylenic ketone **227** underwent double borylation leading to the β,β-diborylated product **228** [Eqn. (42)].



(42)

In our reaction, the imine formation was evaluated on this new substrate by monitoring by ReactIR. It was observed that the signal corresponding to the C=O stretch from the ketone functionality (υ 1694 cm^{-1}) was completely consumed in 1 h resulting in a relatively fast reaction (1 h *vs* 28 h for substrate **205** when a phenyl substituent is allocated in C_β). However, according to crude ^{1}H NMR spectroscopy, the product generated was the enamine **229** rather than the desired ketimine [Eqn. (43)].



(43)

Figure 52 shows the ^{1}H NMR spectrum corresponding to the crude reaction mixture of β-enamine ketone **229**. From the analysis of the spectrum, it was observed that the signal corresponding to the NH group (H-*2*), herein observed as a broad singlet at δ 10.5 ppm, indicates that the *cis*- orientation between the enamine and the ketone groups, most likely due to the hydrogen bonding. It is confirmed by the higher chemical shift of H-*2*. Hence, compound 229 is obtained as the (*Z*)-isomer.

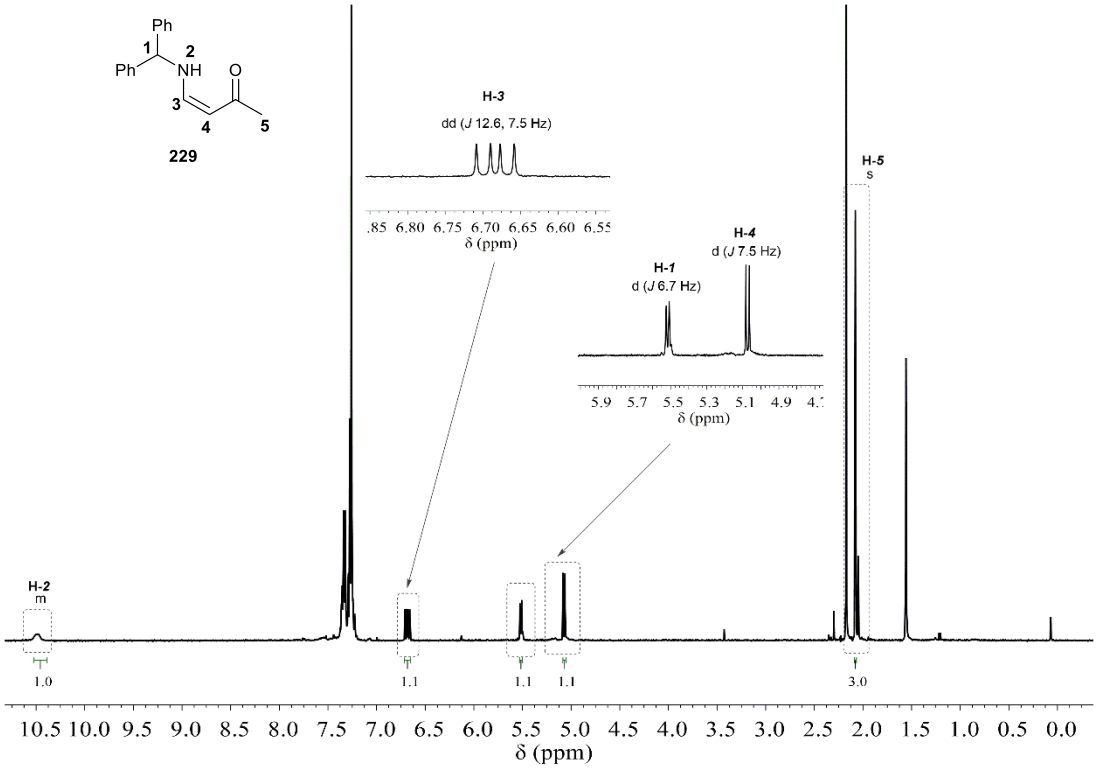
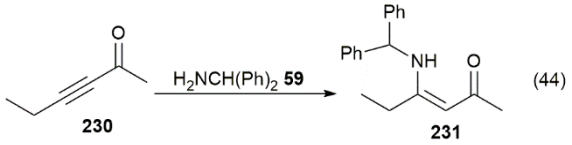


Figure 52 ^{1}H NMR spectrum of the crude reaction mixture containing β-enamino ketone **229**.

It was concluded that although the reaction conditions used were the appropriate for the imination reaction, the terminal position of the alkyne moiety was promoting the 1,4-addition over the desired 1,2-addition. Hence, another substrate was evaluated, an α,β-acetylenic ketone with an alkynic C_{β}-substituent, *i.e.* 3-hexyn-2-one **230**. The formation of the amine-derived ketimine was again monitored by ReactIR and a C-N bond containing product was formed (peak at υ 1603 cm^{-1}), however, by crude ^{1}H NMR spectroscopy, only the 1,4-addition product could be observed, *i.e.* the corresponding enamine was formed [Eqn. (44)].



(44)

2.5.5. β-Borylation reaction on α,β-acetylenic ketone substrates: a comparative study

Due to the difficulties of purifying the products resulting from the ketimine borylations, it was envisioned that precursor ketones might result in more stable products facilitating the purification. Hence, a comparative study with the α,β-acetylenic ketones **205** was approached [Eqn. (45)].

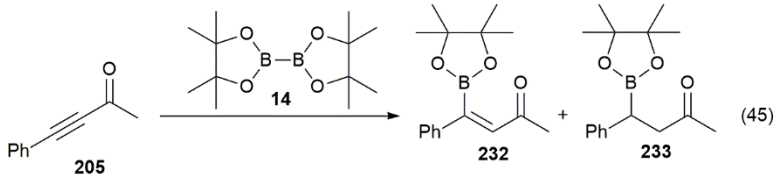


Table 33 summarises the results obtained from the study of the β-borylation reaction on α,β-acetylenic ketone **205**.

Table 33 Optimisation of the methodology for the β-borylation reaction on α,β-acetylenic ketone **205**.

Entry	Cu^{I} (mol%)	Ligand (mol%)	Base (mol%)	Borane reagent (equiv.)	Solvent	Time (h)	Ratio[a]		Conv.[a] (%)
							232	**233**	
1	CuCl (3)	Xantphos **P1** (3)	NaO^tBu (6)	B_2pin_2 (1.1)	THF[b,c]	6	-[e]	-[e]	-[e]
2	CuCl (3)	PPh_3 **P5** (6)	NaO^tBu (9)	B_2pin_2 (1)	^{i}PrOH[c]	24	21	79	90
3	CuCl (3)	PPh_3 **P5** (6)	NaO^tBu (9)	B_2pin_2 (2)	^{i}PrOH[c]	24	0	100	>99
4	-	PPh_3 **P5** (4)	Cs_2CO_3 (15)	B_2pin_2 (1)	^{i}PrOH[d]	6	4	96	>99
5	CuCl (3)	PPh_3 **P5** (6)	NaO^tBu (9)	HBpin (1)	THF[b,c]	6	-[f]	-[f]	10
6	-	-	-	HBpin (1)	THF[b,c]	6	-[e]	-[e]	-[e]

[a]Determined by crude ^{1}H NMR spectroscopy. [b]MeOH(2.5 equiv.) as alcohol additive. [c]Reaction perfomed at RT. [d]Reaction performed at 70 ºC.[e] No product obtained. [f]None of **232** or **233** products were obtained, instead hydroboration/protodeborylation product obtained.

As in the case of the amine-derived ketimine **219**, the α,β-acetylenic ketone **205** was evaluated under the conditions postulated by Yun's group[119] (entry 1, Table 33), where a complex mixture of organoboron compounds was obtained and any attempts to purify them resulted successful. This was corroborated by Yun and co-workers in later work[203] in which

compound **205** (along with others), Figure 53, were reported as unsuitable for the copper-catalysed β-borylation reaction.

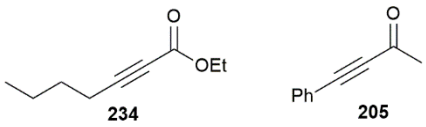
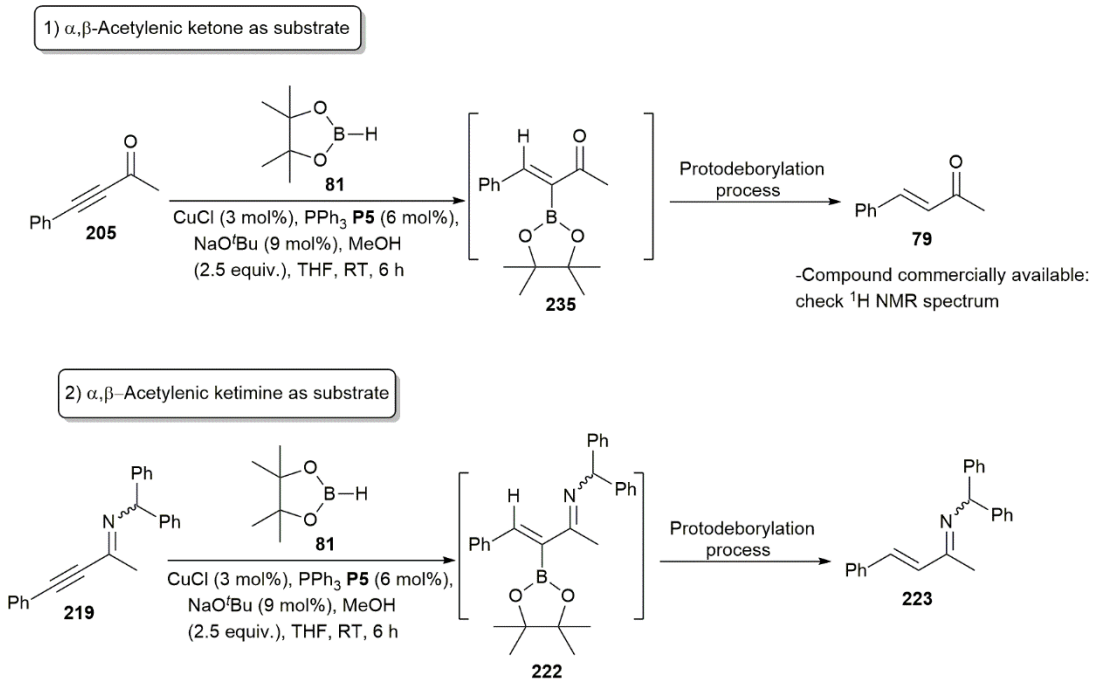


Figure 53 Examples of other substrates reported as unsuitable for the copper-catalysed β-borylation reaction.

Regarding the other β-borylation reaction sets of conditions (entries 2-4, Table 33), in any of the cases studied the vinyl boronate **232** could be exclusively obtained either with organometallic catalysis or organocatalysis. In the case of using pinacolborane **81**, neither the vinyl boronate **232** nor the hydrogenated analogue **233** were obtained, and instead what was observed in the crude reaction mixture was benzylideneacetone **79** (option 1, Scheme 132). This result would be comparable to the one observed previously for the case of the ketimine analogues, although in this case α,β-unsaturated ketone **79** was observed instead of the α,β-unsaturated ketimine **223** (option 2, Scheme 132).



Scheme 132 Comparison between the α,β-acetylenic ketone and the α,β-acetylenic ketimine under borylation conditions using HBpin **81**.

In this case it was possible to confirm that benzylideneacetone **79** was present in the crude reaction mixture from a comparison between the ^{1}H NMR spectrum of the pure benzylideneacetone **79** (commercially available, spectrum 1 in Figure 54) and the ^{1}H NMR spectrum resulting of the crude reaction mixture (spectrum 2 in Figure 54).

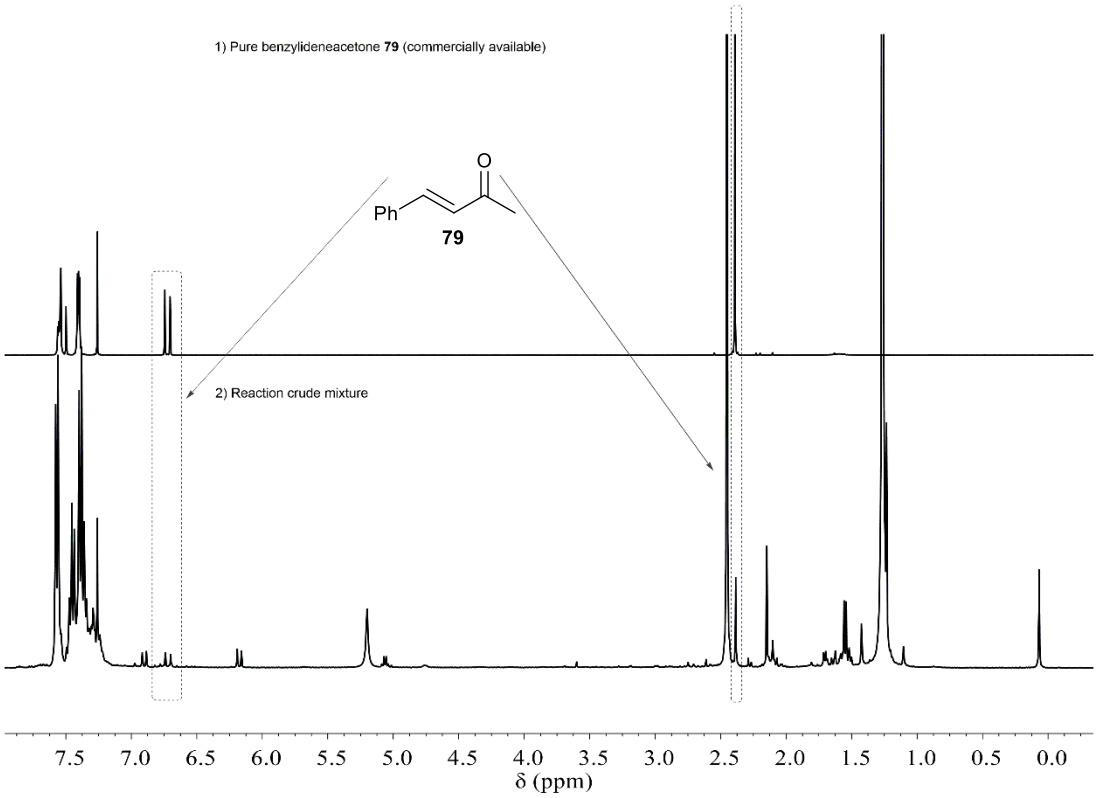
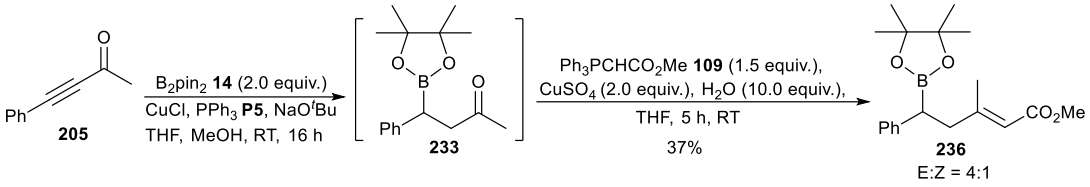


Figure 54 Comparison between the ^{1}H NMR spectra of benzylideneacetone **79** and the crude reaction mixture from the β-borylation of α,β-acetylenic ketone **205** with HBpin **81**.

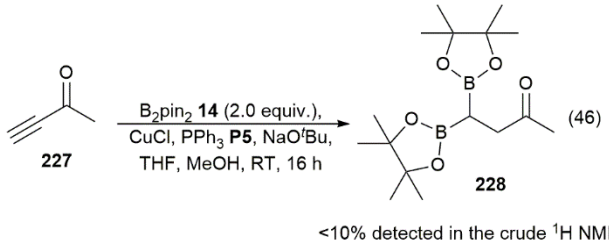
Furthermore, it was also confirmed that the use of HBpin **81**, in the absence of the catalytic system, did not result in the formation of any new products and only the starting α,β-acetylenic ketone **205** was recovered.

As well as in the case of the ketimines, it was not possible to obtain a clean product when the α,β-acetylenic ketone **205** was used as substrate. Therefore, a Wittig reaction was carried out, to obtain the desired α,β-unsaturated ester **236**, in this case, the borylation reaction was performed using 2.0 equivalents of B_2pin_2 **14**, in order to ensure the formation of a single product (entry 3, Table 33) which would simplify the process especially in terms of purification. Hence, the target homoallylic boronate ester analogue was obtained in a 37% isolated yield, as a 4:1 ratio of E:Z stereoisomers, as expected for a stabilised ylide (Scheme 133).

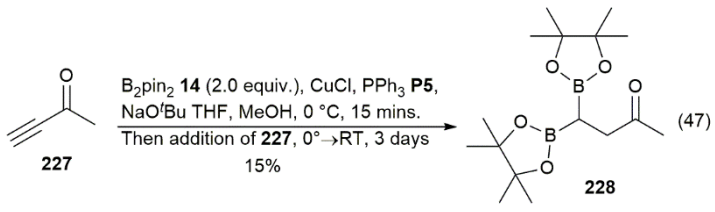


Scheme 133 Hydrolysis/Wittig reactions sequence application into the β-boryl ketone **233**.

In order to complete this study, the synthesis of geminal bis(pinacolboronate) compounds from the borylation on α,β-acetylenic ketones was also examined, hence other substrates were studied, specifically those substrates with no substituent at the C_β, *i.e.* 3-butyn-2-one **227**. Firstly, organometallic conditions using 2.0 equivalents of B_2pin_2 **14** were employed, however, the crude ^1H NMR spectrum was complex, and only a small proportion looked to be the target compound **228** [Eqn. (46)].



The reaction was repeated using the methodology developed by Santos and co-workers[202] but using our catalytic system (the literature reports using activated diborane reagent PDIPA **45**). In our case, the precatalyst mixture (CuCl, PPh_3 **P5**, NaO^{t}Bu) was stirred at 0°C and the substrate was added at this temperature, then the reaction mixture was allowed to warm to RT and was stirred for 3 days. The *bis*-pinacolboronate **228** was obtained in a 15% IY [Eqn. (47)]. The low yield obtained was associated with the fact that in our conditions a catalytic amount of base was used unlike the literature.



2.5.6. Summary of the development of a methodology for the β-borylation reaction on α,β-acetylenic carbonyl compounds

In summary, the reaction conditions for the imination of α,β-unsaturated aldehydes previously developed were successfully applied into the α,β-acetylenic ketones being possible to sort out the chemoselectivity issue found when working with this type of substrates. It is also remarkable that the use of ^{i}PrOH in substitution of the THF/MeOH system resulted in beneficial effects leading to faster reactions.

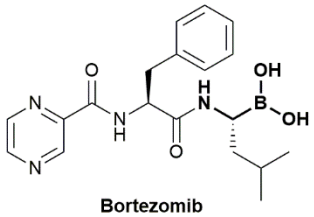
Regarding the β-borylation step, this was a challenging thing to accomplish in either the imine or ketone series, form leading to complex mixtures of compounds composed by the desired vinyl boronates along with hydrogenated analogues. Due to the difficulties of purification, especially for ketimines, it was not possible to isolate and characterise the resulting borylated products **220** and **221**. However, for the case of the ketone, the resulting mixture from the β-borylation reaction was successfully derivatised into the corresponding unsaturated ester **236** after a Wittig olefination.

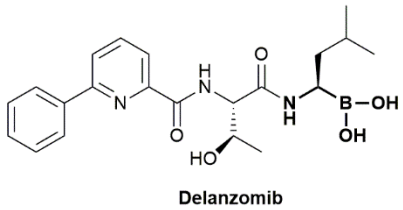
2.6. β-Enamino esters: a platform for α-amino boronate compounds

2.6.1. Background

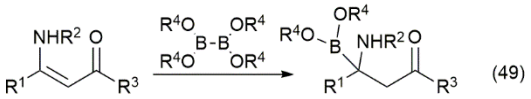
α-Amino boronates have emerged as interesting compounds within the organoboron chemistry field. Besides their key role as synthetic organic intermediates,[204] their application in medicinal chemistry is well documented, in part due to their easy transformation into the corresponding α-amino boronic acid compounds [Eqn. (48)] which are building blocks for anticancer drugs, such as *e.g.* Bortezomib or Delanzomib.

(48)

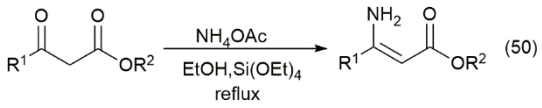




In the last three decades, much research has contributed to the development of catalytic methodologies towards α-amino boronic acids from an asymmetric point of view.[205-208] Hence, it was considered that β-enamino carbonylic compounds could be interesting substrates for borylation, leading to the desired α-amino boronates [Eqn. (49)].

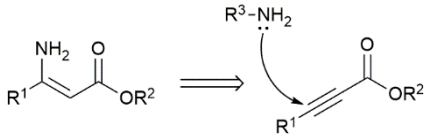

(49)

It is worthwhile mentioning regarding this type of β-enamino esters and β-enaminones substrates, that they could be valuable for use in different areas of organic synthesis, such as for the synthesis of *N*-containing compounds,[209,210] natural products or therapeutic agents.[211] Hence, the development of methodologies for their synthesis has been an active area in organic chemistry recently. A protocol based on the direct condensation of 1,3-dicarbonylic compounds with amines was reported by Zhang and co-workers[212] in 2005. This work emerged from the need for a general method for the synthesis of compounds containing a free β-amino group [Eqn. (50)] from a β-keto ester.


(50)

Such conjugated enamino-substituted compounds can also be obtained using an aryl or alkylamine in the presence of acetic acid instead of ammonium acetate. A range of substrates were examined under these conditions to obtain a series of β-enamino esters and β-enaminones and this protocol provided good yields of the *Z*-isomers of the β-enamino esters in the majority of cases studied, with no by-products (amides by amide-ester exchange) produced.

Later, novel methodologies towards β-enamino esters had been reported based on a retrosynthetic approach which suggested that these compounds could result from a conjugate addition (Michael addition) of an amino group into an α,β-unsaturated C-C multiple bond (Scheme 134).



Scheme 134 Retrosynthetic analysis of β-enamino esters *via* the conjugate addition of an amine into a multiple C-C bond.

With regard to this reactivity, an interesting type of amino-containing reagents have aroused much interest recently, *i.e.* aminoboranes. Corresponding to the general formula $(R^1O)_2B\text{-}NR^2_2$ (which have been known since 1963[213]), their application in organic synthesis has been widely explored.[214,215] Furthermore, these compounds were envisioned as ideal reagents to allow the addition of an amino group to the C_β due to the nucleophilic character of the amino moiety, which can also be assisted by Lewis acid-base interactions between the aminoboranes and the alkoxide generated *in situ*,[214] as has been observed previously for B-B[103] or B-Si[215] systems activation under organocatalytic conditions (Figure 55).

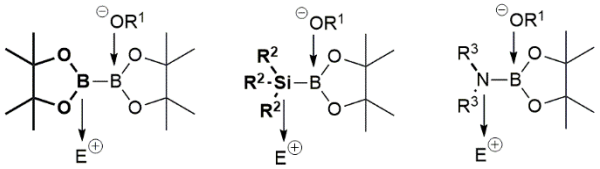
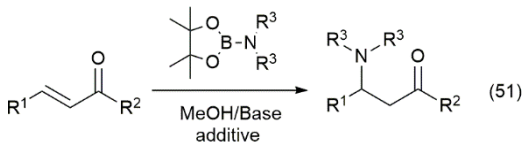


Figure 55 *In situ* generation of nucleophilic moieties through Lewis acid-base adducts between borane reagents and alkoxides.

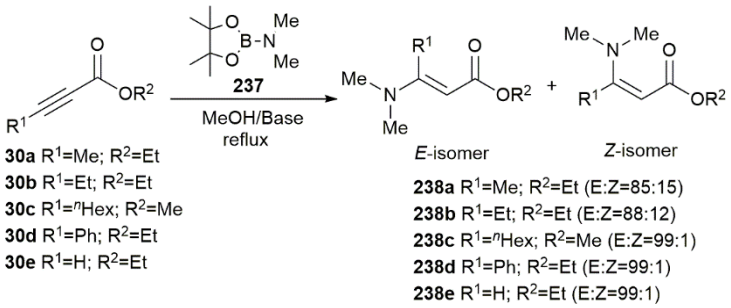
This type of amination strategy was shown to be highly effective for the synthesis of β-enamino ketones and esters.[216] Indeed, Fernández *et al.*[214] demonstrated the benefits of the

use of an alcohol to activate the B-N reagent towards a nucleophilic attack to electron deficient substrates [Eqn. (51)].



(51)

The efficiency of this protocol was proved by its application on a series of α,β-acetylenic esters, resulting in good conversions. In addition, the *E*-isomer was produced preferentially in all cases studied (Scheme 135). In addition, the stereoselectivity observed was attributed to the bulkiness of the alkoxide-aminoborane adduct which in the case of a substrate with a bulky R^1-substituent, the amino addition gave rise exclusively to the *E*-isomer, *e.g.* $R^1 = {}^n$Hex (**30c**) or Ph (**30d**).

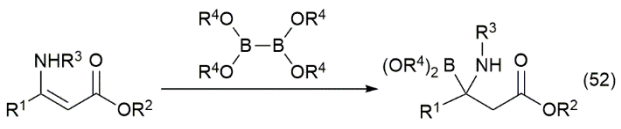


30a R^1=Me; R^2=Et
30b R^1=Et; R^2=Et
30c R^1=^{n}Hex; R^2=Me
30d R^1=Ph; R^2=Et
30e R^1=H; R^2=Et

238a R^1=Me; R^2=Et (E:Z=85:15)
238b R^1=Et; R^2=Et (E:Z=88:12)
238c R^1=^{n}Hex; R^2=Me (E:Z=99:1)
238d R^1=Ph; R^2=Et (E:Z=99:1)
238e R^1=H; R^2=Et (E:Z=99:1)

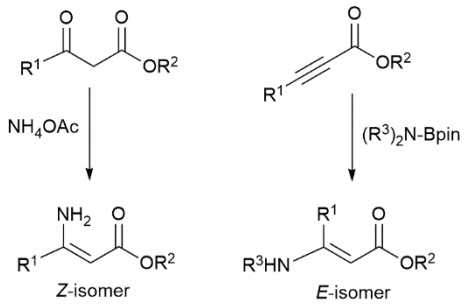
Scheme 135 β-Amination of a scope of α,β-acetylenic esters **30a-e** with dimethylamino-pinacolborane **237**.

Based on this, we initiated a study of different approaches to access β-enamino esters, which could then be exposed to β-borylation giving rise to α-amino boronates [Eqn. (52)].



(52)

In this case, the synthesis of the enamine substrates was carried out using two approaches, taking into account the geometric isomerism presented for this type of structure, as displayed in Scheme 136.

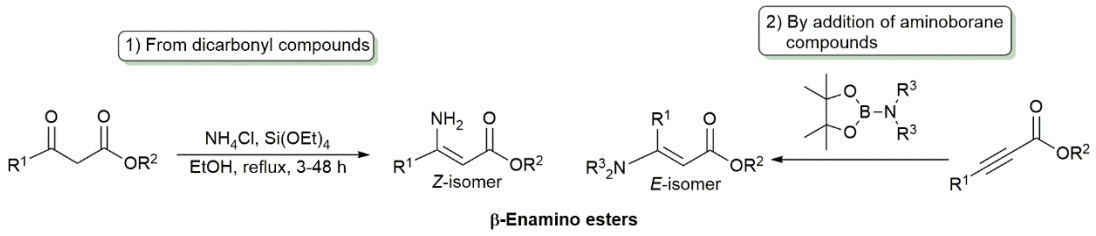


Scheme 136 Strategies for the synthesis of the β-enamino esters.

With the aim of preparing the corresponding α-amino boronate, the β-borylation reaction of the *Z*-isomer of the β-enamino ester was examined under different sets of conditions in order to establish the most suitable for this purpose.

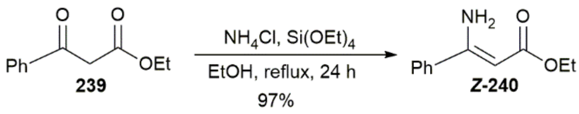
2.6.2. Synthesis of the β-enamino ester substrates

The synthesis of β-enamino esters was approached from the two different perspectives, depending on the isomer of interest, as outlined in Scheme 137.



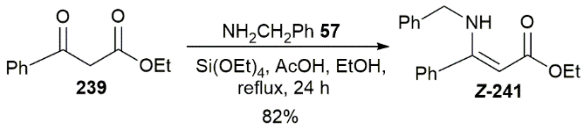
Scheme 137 Synthetic routes proposed for the formation of β-enamino esters.

Firstly, the synthesis of the *Z*-isomer of β-enamino ester (strategy 1, Scheme 137) was approached by the use of ethyl benzoylacetate **239**,[212] resulting in the synthesis of the target β-enamine ester **240** in excellent isolated yield (97%) [Eqn. (53)].



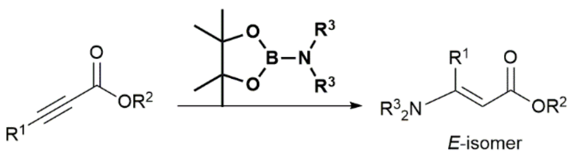
(53)

Interestingly, this protocol could be also applied to the synthesis of β-enamino compounds containing a substituted amino group, from the reaction between dicarbonyl compounds and aryl amines.[212] Hence, using this approach, an analogous compound which contained a benzyl group attached to the amino group, **241** was obtained. The synthesis of the amino-substitued analogue was carried out with the object of testing if the presence of an R^3-substituent in the amino group could have an effect on the subsequent introduction of the boryl unit. Hence, compound **241** was obtained in 82% isolated yield [Eqn. (54)].



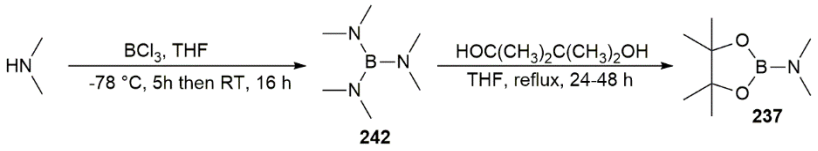
(54)

Regarding the synthesis of the *E*-isomer of the β-enamino ester **240** (strategy 2, Scheme 137), the synthesis of the aminoborane reagent was required, which could then be reacted with the α, β-acetylenic ester [Eqn. (55)].[214]



(55)

Hence, the synthesis of dimethylamino-pinacolborane reagent **237** was approached from tris-(dimethylamino)-borane **242**, in turn from the reaction of dimethyl amine with trichloroborane (Scheme 138).[214]

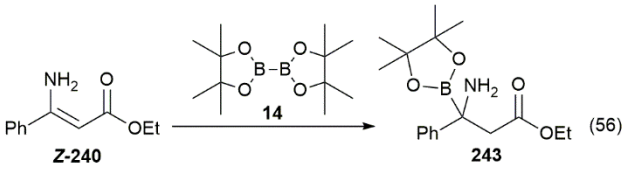


Scheme 138 Synthetic pathway for the synthesis of dimethylamino-pinacolborane **237**.

After several attempts, compound **237** was not obtained. The difficulty of this process derived from: 1) the difficulty of handling dimethylamine (high volatility); and 2) use of Kügelrohr techniques to remove excess pinacol leading to decomposition of the final product **236**. Therefore, the synthesis of *E*-isomer of the target β-enamino ester **240** was not achieved.

2.6.3. Study of the β-borylation reaction on β-enamino esters as a novel route towards α-amino boronate compounds

Once the β-enamino ester **240** (*Z*-isomer) was synthesised, testing this model substrate *Z*-**240** towards β-borylation was undertaken [Eqn. (56)]. Table 34 summarises the different sets of reaction conditions studied in order to optimise the reaction.



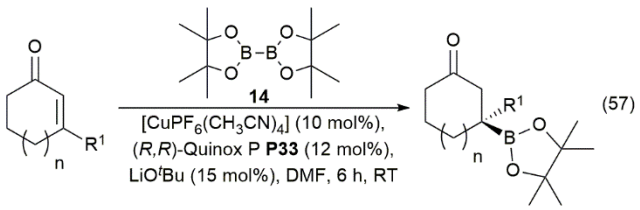
(56)

Table 34 Reaction conditions screened for the β-borylation of the β-enamino ester *Z*-**240**.

Entry	Catalyst (mol%)	Ligand (mol%)	Base (mol%)	Solvent	Reaction time (h)	Ratio[a]	
						240	**243**
1	CuCl (3)	PCy_3 **P4** (9)	Cs_2CO_3 (9)	THF[b,c]	16	>99	-
2	CuCl (3)	PCy_3 **P4** (9)	Cs_2CO_3 (9)	THF[b,d]	24	>99	-
3	CuCl (5)	Quinox P **P33** (5)	NaO^{t}Bu (10)	THF[b,c]	24	>99	-
4	$CuPF_6(CH_3CN)_4$ (5)	Quinox P **P33** (10)	LiO^{t}Bu (10)	DMSO[c]	24	>99	-
5	CuCl (5)	Quinox P **P33** (5)	NaO^{t}Bu (10)	THF[b,e]	24	>99	-
6	$CuPF_6(CH_3CN)_4$ (5)	Quinox P **P33** (10)	LiO^{t}Bu (10)	DMSO[e]	24	>99	-
7	-	-	Cs_2CO_3 (9)	THF[b,e]	24	>99	-
8	-	PPh_3 **P5** (9)	Cs_2CO_3 (9)	THF[b,e]	24	>99	-
9	$Fe(acac)_2$ (0.01 mmol)	PPh_3 **P5** (9)	Cs_2CO_3 (9)	THF[b,e]	24	>99	-
10	-	-	NaO^{t}Bu (9)	THF[b,e]	24	>99	-

[a]Determined by crude ^{1}H NMR spectroscopy. [b]MeOH (2.5 equiv.) as alcohol additive. [c]Reaction perfomed at RT. [d]Reaction performed at 50 ºC. [e]Reaction performed at 70 ºC.

When organometallic catalysis was evaluated for the β-borylation of β-enamino ester **240** using CuCl a more nucleophilic phosphine ligand was used; PCy_3 **P4** (entries 1-2, Table 34) being found more effective in comparison to PPh_3 **P5** when working with sterically hindered substrates such as tiglic aldehydes (see section 2.1). However, in this case it was not possible to add the boryl unit into the substrate **240**, and even with an increase in reaction temperature (50 ºC) resulting in non-beneficial effect being obtained a similar crude mixture as the case of working at RT. A diphosphine ligand was also examined under Cu(I) catalysis; Quinox P **P33** (entry 3 and 4, Table 34) which had been widely used for β-borylations.[217] In this case no better results were obtained in comparison to the previous case either, as well as the increase of the reaction temperature did not result beneficial. Due to the difficulties encountered being not possible to borylate this substrate, alternative catalytic systems were evaluated. Specifically, the methodology reported by Shibasaki and co-workers[218,219] in which $[CuPF_6(CH_3CN)_4]$ and Quinox P **P33** ligand were used along with LiO^{t}Bu as base for the borylation of β-substituted cyclic α,β-unsaturated ketones [Eqn. (57)].



An interesting aspect of this methodology is that unlike the majority of methodologies postulated, in this case it was found that protic additives (alcohol additive, *e.g.* MeOH or ^{i}PrOH) were not required. The success of the methodology was explained by the fact that under these conditions, when the copper alkoxyde catalytically active species (CuOtBu) are generated it also formed $LiPF_6$ which in turn it was found to accelerate the turnover catalytic limiting step.[219]

Hence, these reaction conditions were examined on the enamine system (entry 5, Table 34) being not obtained the desired α-amino boronate **243**, in this case an increase of the reaction temperature was also tested (entry 6, Table 34), however, again it was found that even working at 70 ºC it was not possible to obtain compound **243**.

In order to complete this study, organocatalytic β-borylation protocols were also evaluated. Firstly, β-enamino ester **240** was examined under the metal-free methodology postulated by Fernández *et al.*[58] (entries 7 and 8, Table 34) resulting unsuccessful either in the presence or the absence of a phosphine ligand. Moreover, the use of an iron catalyst (entry 9, Table 34) was examined to see if it would promote nucleophilic attack of the boryl moiety, which was also no effective. Additionally, the base is an essential factor in the absence of a metal catalyst for the activation of the diborane reagent, and although the use of a carbonate base (*e.g.* Cs_2CO_3) had been proved effective for this type of systems, it was considered that the use of an alkoxyde base, could perhaps improve the reaction (entry 10, Table 34). Unfortunately, the type of base used did not have an impact on the efficiency of the reaction.

In summary, compound **243** was not obtained in any of the cases studied. A feasible explanation could be that electronic effects in these substrate structures, *i.e*. the effect of the

lone pair of electrons belonging to *N*-atom (Figure 56) which is delocalised, giving rise to resonance structures that prevent the nuceophilic attack of the boryl moiety.

Figure 56 Delocalisation of the enamino *N*-atom.

With the aim of avoiding these drawbacks, the previously synthesised substrate *Z*-**241** was also used in the borylation conditions (Table 35) since it was envisioned that the presence of the benzyl group on the amino function could inhibit the delocalisation of this lone pair [Eqn. (58)].

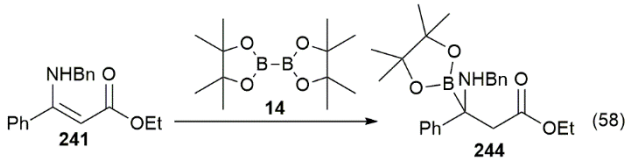


Table 35 Reaction conditions screened for the β-borylation of the β-enamino ester **241**.

Entry	Catalyst (mol%)	Ligand (mol%)	Base (mol%)	Solvent	Reaction time (h)	Ratio[a]	
						241	**244**
1	CuCl (3)	PCy_3 **P4** (9)	Cs_2CO_3 (9)	THF[b,c]	16	>99	-
2	CuCl (5)	Quinox P **P33** (5)	NaO^tBu (10)	THF[b,c]	24	>99	-
3	$Fe(acac)_2$ (0.01 mmol)	PPh_3 **P5** (9)	Cs_2CO_3 (9)	THF[b,c]	24	>99	-

[a]Determined by crude ^{1}H NMR. [b]MeOH (2.5 equiv.) as alcohol additive. [c]Reaction performed at 70 ºC.

Although in this case the reaction conditions screening was not as wide as in the previous case, organometallic catalytic conditions were tested (entries 1 and 2, Table 35) being found that the use of a diphosphine ligand (*i.e.* Quinox P **P33**) did not improve the borylation. Regarding the organocatalytic conditions attempted, the phosphine mediated β-borylation protocol was tested adding a catalytic amount of iron catalyst in order to enhance the conjugate

addition of the boryl unit (entry 3, Table 35), however target α-amino boronate **244** was not obtained.

These results showed that having a substituted amino group does not favour the β-borylation reaction for this type of substrates being not found any sets of conditions that yield compound **244**.

2.6.4. Summary of the study of β-enamino esters as substrates for the β-borylation reaction

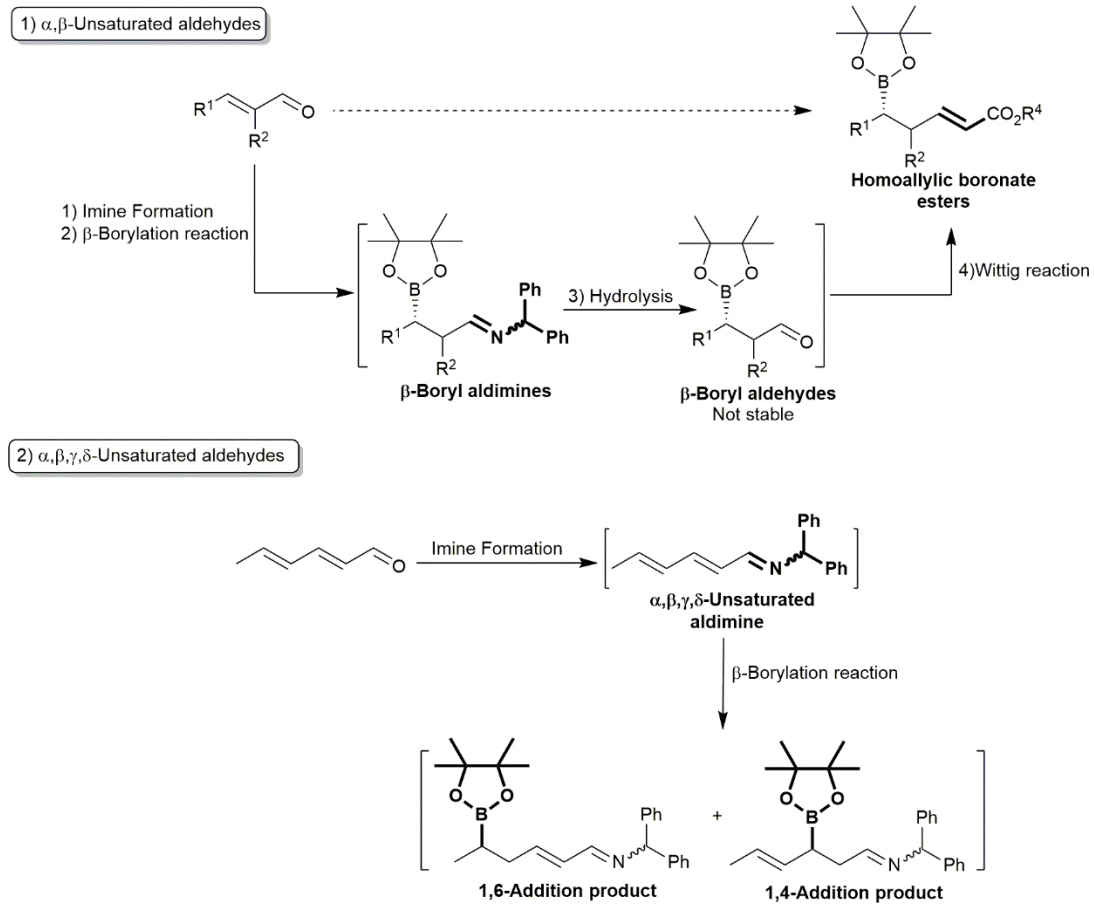
Within the synthesis of the β-enamino esters, it was only possible to obtain the *Z*-isomer which was found to be an unsuitable substrate for the β-borylation reaction even under different organometallic or organocatalytic conditions.

Another aspect herein studied was the possible effect that the presence of a substituent on the amino group could have promoting the conjugate addition of a boryl unit, being found that this substituent does not have a beneficial impact in terms of electronic effects for that purpose.

2.7. Concluding remarks

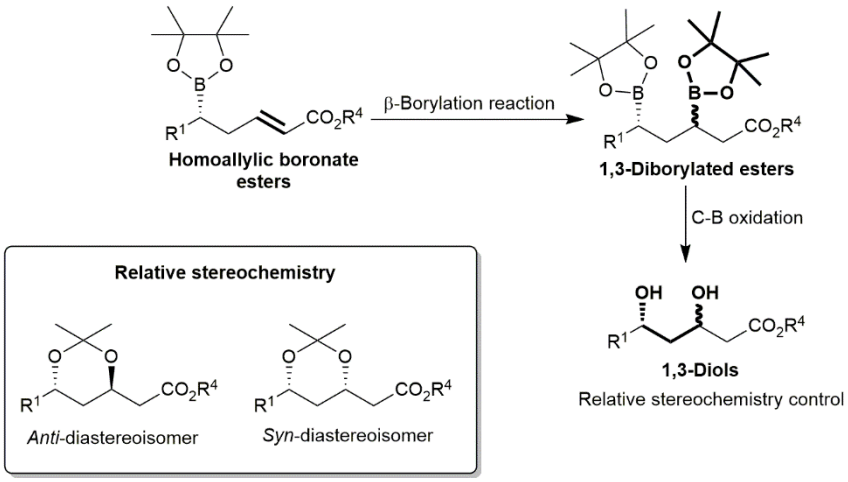
An efficient enantioselective one-pot methodology for the synthesis of homoallylic boronate carboxylate esters has been developed as a result of the need for a derivatisation route of β-boryl aldehydes. It has been confirmed that β-boryl aldehydes are unstable especially under chromatographic purification conditions, leading to de-borylation. Although mechanistic studies were carried out in order to achieve a better understanding of this process, especially in order to prevent it, it has not been possible to clarify the precise details of this process. Complementarily, the use of ^{i}PrOH as reaction medium, instead of the conventional solvent/alcohol additive system (*i.e.* THF/MeOH) was shown to be a better alternative resulting in faster imine formation and a considerable improvement of the induction of asymmetry in the formation of the C-B bond (option 1, Scheme 139).

Furthermore, this methodology was directly applied into analogous dienal substrates, and although the imine formation was possible, the addition of the boryl unit turned out to be substantially more complex than the cases previously studied (see option 2, Scheme 139). The complexity of this step stems from the fact that in this case, more than one unsaturated site is present leading into competitive 1,4- *vs.* 1,6-addition resulting in complex mixtures which due to the difficulty of the purification of this type of compound was not possible to isolate the products.



Scheme 139 General overview of; 1) the one-pot, four steps methodology for the functionalization of β-boryl aldehydes to homoallylic boronate carboxylate ester derivatives; 2) application of the imine formation/ β-borylation reaction sequence to the analogous dienal systems.

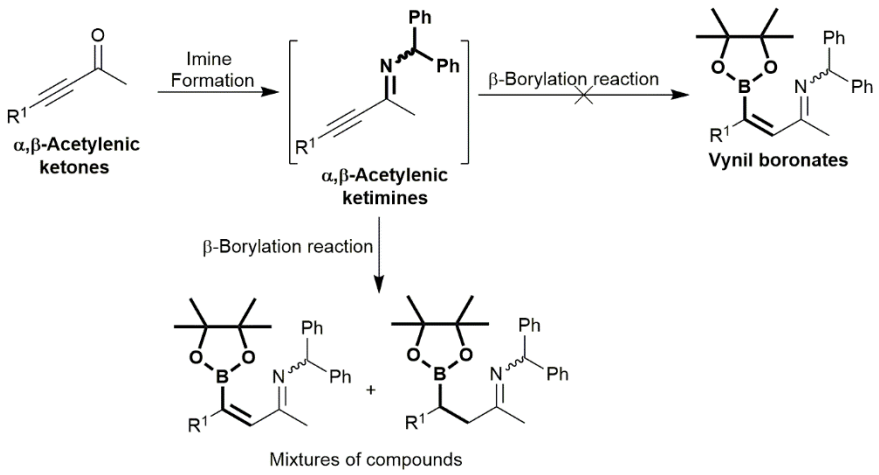
Moreover, homoallylic boronate carboxylate esters were confirmed as ideal solutions to the stability issues and they opened up a wide range of synthetic possibilities mainly due to the presence of the alkene moiety which could, indeed, be evaluated for the addition of a second boryl unit. Based on this, a novel strategy for the synthesis of 1,3-diborylated esters was approached confirming such systems as ideal substrates for the β-borylation reaction. Additionally, the stereocontrol for the new stereocentre was examined as function of the enantiomer of the chiral ligand used, *i.e.* double diastereocontrol. However, not all the chiral ligands tested presented matching/mismatching effects between the two enantiomers. Regarding the effect that the substituent in C_β could have on the asymmetry induced *via* the 2nd β-borylation reaction, it was observed that alkyl substituted substrates provided lower diastereoselectivity without always matching/mismatching effects, whilst aryl substituted systems provided higher diastereoselectivity. The transformation of the resulting diborylated esters into the 6-membered ring acetonide acetals aided the separation and identification of the different diastereoisomers herein obtained, as outlined in Scheme 140.



Scheme 140 Summary of the application of homoallylic boronate carboxylate esters as substrates for the β-borylation reaction leading into chiral 1,3-diols.

Complementarily, by extrapolation of the methodology into readily synthesised *tert*-butyl (*E*)-(5-oxopent-3-en-1-yl)carbamate **173**, allowed access to a key intermediate in the synthesis of Atorvastatin; the *syn*-amino acetonide acetal ester analogous, which provided a basis for the synthesis of the 3,5-dihydroxy acid side-chain of Atorvastatin.

Although the use of substrates containing an alkyne as an unsaturated function, instead of an alkene, seemed to be an ideal platform for the synthesis of vinyl boronates by the direct application of the imine formation/β-borylation reaction sequence, a chemoselectivity issue was observed for the synthesis of the α,β-acetylenic imines, *i.e.* in the majority of the cases studied the 1,4-addition product (or β-enamino ketone) was obtained and the use of activated dehydrating agent (M.S. preferably) was critical for the production of the desired chemoselectivity. With this first step sorted out and due to the impossibility of purifying this type of compounds, a synthetic strategy had to be proposed in a one-pot multistep methodology. Regarding the introduction of the boryl unit, this step appeared to be rather challenging, leading to mixtures composed of the desired vinyl boronate along with its hydrogenated analogous in varying ratios based upon the borylation conditions used, as displayed in Scheme 141. The study of the origin of this undesired side-product did not lead to conclusive results, it seemed that either a base-trigged reduction of the alkene or a proto-deborylation of the initially generated geminal bis (boronate) compound due to the C_β benzylic position could promote the proto-deborylation process. In order to obtain clean products that would, perhaps, help with understanding these undesired processes, a parallel study was also developed based on the use of the α,β-acetylenic ketone substrates. As expected, this led to some isolated products, however, did not aid a clearer interpretation of the results obtained.

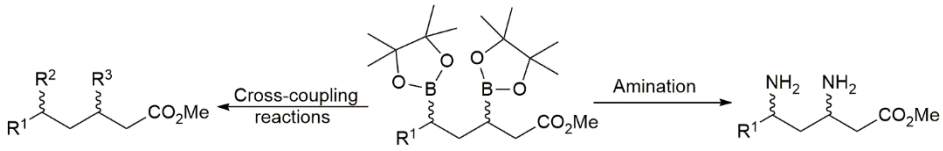


Scheme 141 General overview of the synthesis of vynil boronates from α,β-acetylenic ketones *via* the corresponding α,β-acetylenic amine-derived ketimine intermediate.

Within the synthesis of the β-enamino esters, it was only possible to obtain the *Z*-isomer which was found to be an unsuitable substrate for the β-borylation reaction even under different organometallic or organocatalytic conditions.

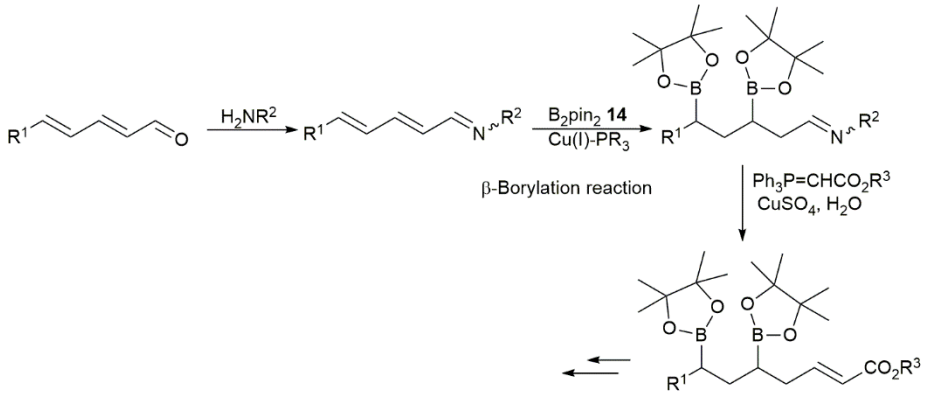
2.8. Future work

In the course of this thesis, several challenges have been met, mainly regarding chemoselectivity issues during the borylation process and lack of stability of the resulting products. For the case of the α,β-unsaturated aldehydes, it was possible to sort out efficient methodology towards chiral 1,3-diborylated esters which exploration under amination conditions or even cross-coupling reactions could lead to interesting compounds (Scheme 142). This methodology also proved to be efficient for the synthesis of a key intermediates for the synthesis of Atorvastatin, although further optimisation of the last few steps for the total synthesis of this statin drug are required.



Scheme 142 Possible further applications of 1,3-diborylated esters.

Although the application of the homoallylic boronate carboxylate esters borylation was demonstrated, the corresponding development of the borylation of dienal systems, could still be an ideal option for the synthesis of multifunctional poly-borylated compounds *via* an iterative process. Such a methodology for the β-borylation could be as shown in Scheme 143.



Scheme 143 Application of the methodology for the synthesis of diborylated esters on diene systems.

In spite of this, the analogous α,β-acetylenic carbonyl compounds still represents a challenge due to the difficulty of obtaining clean products along with instability of the products generated. A more exhaustive study would be required, focused on different derivatisation routes that allow the removal of the problematic functionality (*i.e.* ketimine) at the same time as providing better discrimination between the different products (*i.e.* vinyl boronate and its hydrogenated analogous). A wider substrate scope could facilitate the search for better reaction conditions, however, the commercial availability of this type of substrate is limited. It would therefore be worth synthesising a few examples, including analogous α,β-

acetylenic aldehydes. Furthermore, for the case of the terminal alkyne-containing substrate, it could be interesting to optimise the synthesis of the geminal bis (boronate) compounds since they could provide an alternative route towards these synthetically interesting compounds.

Experimental section

3.1. General experimental

All the reactions herein reported were performed under air unless specified otherwise. The reagents were purchased directly from standard chemical suppliers and used as received from the supplier without further purification. All solvents were also used as received from the supplier, except THF, MeOH and ^{i}PrOH which were stored over a dehydrating agent and deoxygenated before use. Molecular Sieves, 3 Å 1-2 mm beads and 4 Å 1-2 mm beads, were supplied from Alfa Aesar and stored at 220 ºC (>48 h), Mortmorillonite K10 powder, 250 m^2/g, was supplied from Sigma Aldrich and stored at 80 ºC (>48 h) and heated (150 ºC) under vacuum before use. The purification of the crude reaction mixtures was performed using medium-pressure column chromatography, which was carried out using different supports as supplied from Sigma Aldrich; Silica gel (230-400 mesh, 40-63 µm, 60 Å); activated magnesium silicate FLORISIL® (100-200 mesh, 289 $m^2 \cdot g^{-1}$); and all were monitored by TLC analysis using POLYGRAM® SIL G/UV254 (40 x 80 mm) plates or aluminium oxide TLC-PET foil plates (40 x 80 mm) with a 254 nm fluorescent indicator. In all cases, the TLC plates were visualised under a UV lamp operating at short (254 nm) and long (365 nm) wavelength ranges. Visualisation was aided by dipping the plates into an alkaline potassium permanganate solution or a *p*-anisaldehyde solution.

Deuterated chloroform ($CDCl_3$) was used as solvent for routine NMR measurements, unless stated otherwise. ^{1}H NMR spectra were recorded on a Bruker Advance-400 at 400 MHz or a Varian VNMRS-700 at 700 MHz, operating at ambient probe temperature unless specified elsewhere. Coupling constants (*J*) are given in Hz, and the multiplicity of the NMR signals is described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). ^{13}C NMR spectra were recorded on a Bruker Advance-400 at 100.6 MHz or a Varian VNMRS-700 at 176 MHz, operating at ambient probe temperature unless specified elsewhere. ^{1}H NMR and ^{13}C NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane, references to the chemical shifts of residual solvent resonances. ^{11}B NMR spectra were recorded on a Varian Brüker

Advance-400 operating at a frequency of 128 MHz and the chemical shifts are reported in ppm (δ) relative to $BF_3(CH_3)_2O$.

Mass spectra for liquid chromatography mass spectrometry (LCMS) were obtained using a Waters (UK) TQD mass spectrometer (low resolution ESI+, electrospray in positive ion mode, ES+) unless stated elsewhere. Accurate mass spectrometry was obtained on a Finnigan LTQ-FT.

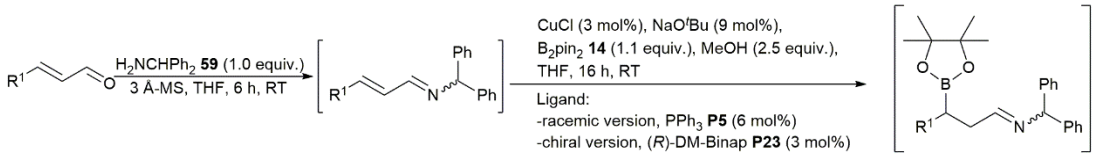
IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer with an ATR attachment.

HPLC analysis were carried out on an Agilent 1100 series instrument, fitted with a Perkin Elmer series 200 degasser on chiral columns: OJ-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.60 mm); and OD-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.60 mm); were used to achieve chiral resolution. Mixtures of hexane and ^{i}PrOH were used as eluent, unless otherwise stated. To prepare the samples, the solid residue (1.0 mg) was dissolved in a mixture of hexane and ^{i}PrOH in proportions 20:1. Preparative scale HPLC separations were carried out on a PerkinElmer Series 200 HPLC system equipped with a UV-Vis detector operating at 254 nm. Reversed-phase purifications used a Waters Sunfire C18 column (100 x 19mm, 5µm) with a gradient elution using a CH_3CN/H_2O mobile phase. Chiral purification was achieved using a YMC-Actus CHIRAL ART Amylose-SA column (250 x 10mm, 5µm) fitted with a guard cartridge (20 x 10mm, 5µm), using mixtures of hexane: EtOH: DCM as the mobile phase.

In some cases the reaction was monitored by *in situ* IR spectroscopy using a Metler-Toledo ReactIR 4000 equipped with an MCT detector (ConcIRT, window 1900–900 cm^{-1}; Advanced setting, Laser WN 7901–415 cm^{-1}; Apodization Happ General; Probe, Prob A DiComp (Diamond) connected *via* K6 Conduit (16 mm probe); Sampling 4000–6500 at 8 cm^{-1} resolution; Scan option auto select, gain 2×.

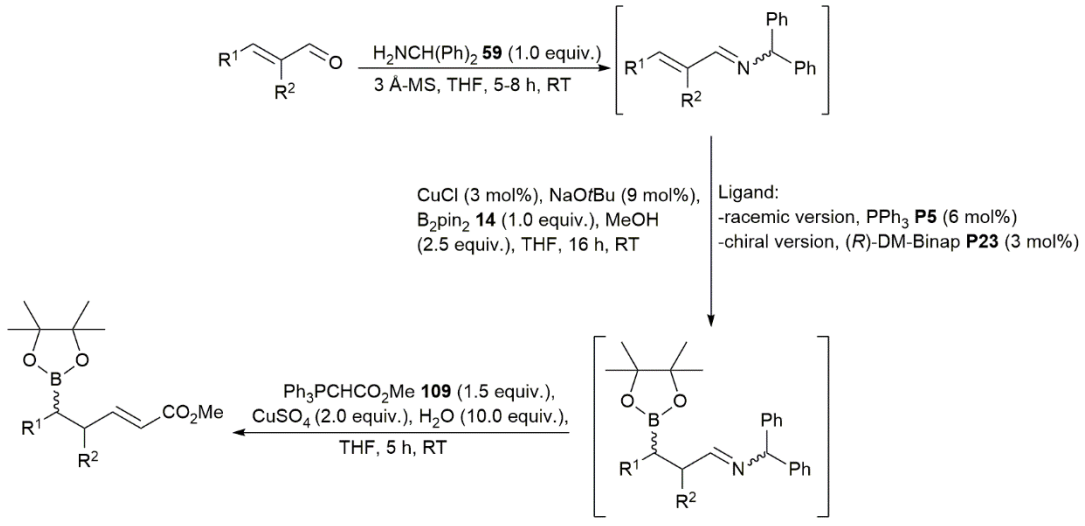
3.2. General experimental procedures

3.2.1. General procedure for the synthesis of β-boryl aldimines from α,β-unsaturated aldehydes (reported in Section 2.1.2)



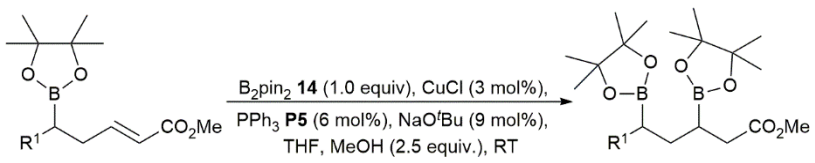
To a stirred solution of THF (8 mL) with oven-dried 3 Å M.S. (2.0 g) was added an α,β-unsaturated aldehyde (2.0 mmol) and benzhydylamine **59** (345.0 µL, 2.0 mmol, 1.0 equiv.) and the reaction mixture stirred at RT. After 6h, an aliquot of the *in situ* formed α,β-unsaturated imine (2.0 mL, 0.5 mmol) was transferred to a Schlenk-tube (under Ar) containing CuCl (1.50 mg, 0.015 mmol, 3 mol%), PPh_3 **P5** (6.3 mg, 0.015 mmol, 6 mol%) or (*R*)-DM-Binap **P23** (11.0 mg, 0.015 mmol, 3 mol%), NaO^{t}Bu (4.3 mg, 0.045 mmol, 9 mol%) and B_2pin_2 **14** (140 mg, 0.55 mmol, 1.1 equiv.). After 5 min, MeOH (51.0 µL, 1.25 mmol, 2.5 equiv.) was added to the solution and the reaction was stirred for 16 h at RT.

3.2.2. General procedure for the optimised synthesis of homoallylic boronate carboxylate esters from α,β-unsaturated aldehydes (reported in Section 2.2.2)



To a round bottom flask containing THF (8 mL) and oven-dried 3 Å-MS (2.0 g) was added an α,β-unsaturated aldehyde (2.0 mmol) and benzhydylamine **59** (345.0 µL, 2.0 mmol, 1.0 equiv.) and the reaction mixture stirred at RT. After 5-8 h, an aliquot of the *in situ* formed α,β-unsaturated imine (2.0 mL, 0.5 mmol) was transferred to a Schlenk-tube (under Ar) containing CuCl (1.50 mg, 0.015 mmol, 3 mol%), PPh_3 **P5** (6.3 mg, 0.015 mmol, 6 mol%) or (*R*)-DM-Binap **P23** (11.0 mg, 0.015 mmol, 3 mol%), NaO^tBu (4.3 mg, 0.045 mmol, 9 mol%) and B_2pin_2 **14** (127.3 mg, 0.5 mmol, 1.1 equiv.). After 5 min, MeOH (51.0 µL, 1.25 mmol, 2.5 equiv.) was added to the solution, after 5 minutes stirring the mixture, MeOH (40 µL, 2.5 equiv.) was added. After 16 h, the resulting β-boryl aldimine was transferred to a round bottom flask, then methyl(triphenylphosphoranylidene)acetate **109** (2.0 g, 1.5 equiv) was added, and after 5 minutes $CuSO_4$ (1.3 g, 2.0 g) was added along with H_2O (0.7 mL, 10.0 equiv). The mixture was stirred for 5 h at RT. The resulting solution was partioned between EtOAc (200 mL) and brine (20 mL). The aqueous layer was extracted further with EtOAc (3 x 50 mL EtOAc). The combined organic phase was separated and washed with $CuSO_4$ (sat.) (3 x 20 mL $CuSO_4$), and dried over $MgSO_4$. After filtration, the organic layer was removed *in vacuo* to yield the crude homoallylic boronate ester, was purified by SiO_2 chromatography using as hexane: EtOAc (20:1 and 10:1) as eluent.

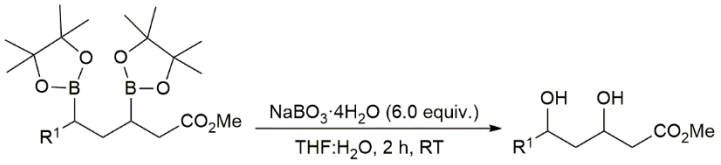
3.2.3. General procedure for the synthesis of 1,3-diborylated esters *via* the β-borylation reaction on homoallylic boronate carboxylate esters (reported in Section 2.3.2)



The solid residue of homoallylic boronate carboxylate ester (synthesised following the general procedure for the optimised synthesis of homoallylic boronate carboxylate esters from α,β-unsaturated aldehydes, as reported in Section 3.2.2) was dissolved in THF (10 mL)

and this solution transferred to a Schlenk tube (under Ar) containing CuCl (7.4 mg, 0.075 mmol, 3 mol%), PPh_3 **P5** (40 mg, 0.15 mmol, 6 mol%) or **P7-P8**, **P27-P32** (0.075 mmol, 3 mol%) and B_2pin_2 **14** (1.3 g, 2.5 mmol, 1.0 equiv.) after 5 minutes MeOH (0.25 mL, 6.3 mmol, 2.5 equiv.) was added and the mixture was stirred for 10 minutes followed by NaO^tBu (21.6 mg, 0.23 mmol, 9 mol%). The reaction mixture was stirred at RT for 2-6 h and the resulting solution partitioned between EtOAc (250 mL) and brine (25 mL). The aqueous layer was extracted further with EtOAc (3 x 50 mL EtOAc) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The reaction crude mixture was purified by SiO_2 chromatography using petroleum ether:EtOAc (5:1 and 3:1) as eluent.

3.2.4. General procedure for the oxidation of 1,3-diborylated esters (reported in Section 2.3.5)



The diborylated ester (2.0 mmol) was dissolved in a mixture of THF:H_2O (1:1 by volume, 20 mL), followed by the addition of $NaBO_3.4H_2O$ (1.85 g, 12.0 mmol, 6.0 equiv.). The reaction mixture was stirred at RT for 2 h, the solvent was removed *in vacuo*, and the remaining white solid re-dissolved in EtOAc (50 mL) and filtered leading into the crude 1,3-diol.

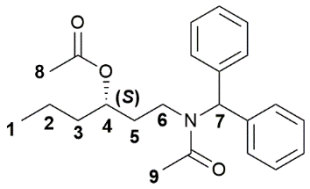
3.3. Specific experimental procedures and characterisation

3.3.1. Synthesis of N/O-diacetates

An aliquot of crude β-boryl aldimine synthesised following the general procedure described in Section 3.2.1 (2.0 mL, 0.5 mmol) was transferred to a round bottom flask. $NaBH_4$ (28.5 mg, 0.75 mmol, 1.5 equiv.) was added, followed by the drop-wise addition of MeOH

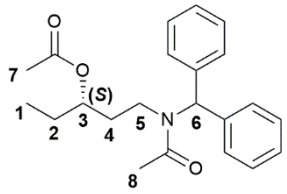
(0.5 mL). The mixture was stirred for 3 h at RT, followed by the removal of solvent *in vacuo*. THF (1.5 mL) was added to the resulting residue, followed by NaOH (300 µL, w/v 20%) and H_2O_2 (130 µL, w/v 35%), and the solution was heated to reflux for 1 h. After cooling, the resulting solution was partioned between EtOAc (50 mL) and brine (5 mL). The aqueous layer was extracted further with EtOAc (3 x 10 mL EtOAc) and the combined organic phase was dried over $MgSO_4$. After filtration, the organic phase was removed *in vacuo* to yield the crude γ-amino alcohol. To a stirring solution of γ-amino alcohol in DCM (1.5 mL), acetic anhydride (50 µL) and pyridine (50 µL) were added and the resulting mixture stirred for 16 h at RT. The resulting solution was then washed with HCl (3 x 10 mL HCl, v/v 5%) and then H_2O (3 x 10 mL H_2O). The aqueous layer was extracted further with EtOAc (3 x 20 mL EtOAc). The combined organic phase was dried over $MgSO_4$ and after filtration, the organic phase was removed *in vacuo* to yield the crude N/O-diacetate. Purification by SiO_2 chromatography using a mixture of hexane : EtOAc (2 : 1) as eluent gave the pure product.

(*S*)-1-[*N*-(Diphenylmethyl)acetamido]hexan-3-yl acetate **87**



Compound **87** was obtained following the general procedure for the synthesis of N/O-diacetates a colorless oil was obtained (60.0 mg, 36%; 86% e.e.): ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) major rotamer δ 7.41-7.08 (m, 10H, *Ph*), 6.21 (s, 1H, H-*7*), 4.54-4.48 (m, 1H, H-*4*), 3.44-3.22 (m, 2H, H-*2*), 2.08 (s, 3H, H-*8*), 2.04 (s, 3H, H-*9*), 1.24-1.11 (m, 2H, H-*3*/*5*), 1.11-1.01 (m, 2H, H-*5*/*3*), 0.88-0.86 (m, 2H, H-*6*), 0.78 (t, *J* 7.2 Hz, 3H, H-*1*); Enantiomeric excess was determined by chiral HPLC using an AS-H-CHIRALCEL column (250 x 4.6 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ˚C, 1.0 mL/min, 210 nm, hexane : IPA (90 : 10). t_R (*S*) = 12.3 min; t_R (*R*) = 14.7 min. All spectroscopic and analytical data were identical to those reported in the literature.[113]

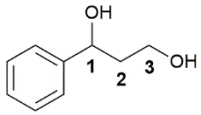
(*S*)-1-[N-(Diphenylmethyl)acetamido] pentan-3-yl acetate **90**



Compound **90** was obtained following the general procedure for the synthesis of the N/O-diacetates to give a colorless oil (40.0 mg, 21%; 76% e.e.): ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) major rotamer δ 7.24 - 7.12 (m, 10H, *Ph*), 6.21 (s, 1H, H-*6*), 4.43 (m, 1H, H-*3*), 3.33 (m, 2H, H-*2*), 2.04 (s, 3H, H-*8*), 1.92 (s, 3H, H-*7*), 1.16 (m, 2H, H-*4*), 0.86 (t, *J* 2.14 Hz, 2H, H-*5*), 0.52 (t, *J* 7.0 Hz, 3H, H-*1*). Enantiomeric excess was determined by chiral HPLC using an AS-H-CHIRALCEL column (250 x 4.6 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ̊C, 1.0 mL/min, 210 nm, hexane : IPA (90 : 10). t_R (*S*) = 13.2 min; t_R (*R*) = 17.2 min. All spectroscopic and analytical data were identical to those reported in the literature.[113]

3.3.2. Synthesis of 1,3-diols

1-Phenylpropane-1,3-diol **92**

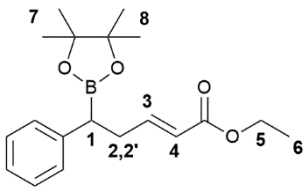


An aliquot of crude β-boryl aldimine synthesised following the general procedure described in Section 3.2.1 (8.0 mL, 2.0 mmol) was transferred to a round bottom flask and H_2O (20 mL) was added. The reaction mixture was stirred at RT. After 1h, $CuSO_{4\ (sat.)}$ (20 mL) was added and the mixture stirred for a further 20 minutes at RT. The resulting solution was partioned between EtOAc (200 mL) and brine (20 mL). The aqueous layer was extracted further with EtOAc (3 x 20 mL). The combined organic phase washed with $CuSO_{4\ (sat.)}$ (3 x 20 mL $CuSO_4$) and H_2O (3 x 20 mL H_2O). The organic phase was separated, dried over $MgSO_4$, filtered and the organic phase was removed *in vacuo*. The solid residue corresponding

to the β-boryl alcohol was dissolved in THF (15 mL) followed by the addition of NaOH (1.20 mL, w/v 20%) and H_2O_2 (520 µL, w/v 35%). The solution was stirred with heating at reflux for 1 h. After cooling, the resulting solution was partitioned between EtOAc (200 mL) and brine (20 mL). The aqueous layer was extracted further with EtOAc (3 x 20 mL EtOAc), and the combined organic phase was separated and dried over $MgSO_4$. After removal of the solvent *in vacuo* the crude product was purified by SiO_2 chromatography using a mixture of petroleum ether : EtOAc (gradient elution) as eluent leading to pure compound **92** as a colorless oil (121.4 mg, 40%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.24 (m, 5H, *Ph*), 4.98 (dd, *J* 8.8, 3.8 Hz, 1H, H-*1*), 3.88 (m, 2H, H-*2*), 2.10-1.90 (m, 2H, H-*3*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 128.5, 127.6, 125.6, 74.4 (*C*HOH), 61.5 (*C*H_2OH), 40.5. LRMS (ESI+) *m/z* $[M+H]^+$ 172.8 (100%), 150.9 (92%), 104.9 (50%). HRMS (ESI+) *m/z* calculated $C_9H_{12}O_2Na$ $[M+Na]^+$ 175.0735, found 175.0725. All spectroscopic and analytical data were identical to those reported in the literature.[220]

3.3.3. Synthesis of homoallylic boronate carboxylate esters

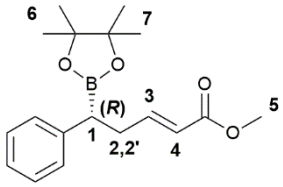
Ethyl (*E*)-5-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate **104**



An aliquot of crude racemic β-boryl aldimine synthesised following the general procedure described in Section 3.2.1 (4.0 mL, 1.0 mmol) was transferred to a round bottom flask, followed by the addition of $CuSO_4$ (80.0 mg, 0.5 mmol, 0.5 equiv.) and H_2O (5 mL). The reaction mixture was stirred for 15 mins at RT. (Carbethoxymethylene)triphenylphosphorane **108** (453 mg, 1.3 mmol, 1.3 equiv.) was added and the reaction mixture stirred for further 3 h at RT. The resulting solution was partitioned between EtOAc (100 mL) and brine (10 mL). The aqueous layer was extracted further with

EtOAc (3 x 10 mL EtOAc). The combined organic phase was separated and dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by a SiO_2 chromatography using a cold mixture of petroleum ether:EtOAc (2 : 1) as eluent leading to pure **104** as a yellow oil (906 mg, 55%): IR (neat) ν_{max} 2978 (m), 1718 (m), 1653 (s), 1365 (m), 1326 (m), 1265 (m), 1167 (s), 1140 (m), 1030 (s), 966 (s), 849 (s), 696 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.12 (m, 5H, *Ph*), 6.96 (dt, *J* 15.7, 6.9 Hz, 1H, H-*3*), 5.82 (dt, *J* 15.6, 1.4 Hz, 1H, H-*4*), 4.15 (q, *J* 7.1 Hz, 2H, H-*5*), 2.73 (m, 1H, H-*1*), 2.53 (m, 1H, H-*2/2'*), 2.46 (m, 1H, H-*2/2'*), 1.26 (t, *J* 7.1 Hz, 3H, H-*6*), 1.21 (s, 6H, H-*7*), 1.18 (s, 6H, H-*8*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (*C*OOR), 148.3, 141.6 (*C*H=CH-COOR), 128.6, 128.3, 125.4, 121.9 (CH=*C*H-COOR), 83.6, 60.0 (O-*C*$H_2$$CH_3$), 35.1, 24.5 (*C*-CH=C), 21.4, 14.2 (H_3*C*-C-O); ^{11}B NMR (128 MHz, $CDCl_3$) δ 32.7; LRMS (ESI+) *m/z* $[M+H]^+$ 354.1 (100%), 329.9 (23%), 317 (21%), 313.9 (8%). All spectroscopic and analytical data were identical to those reported in the literature.[122]

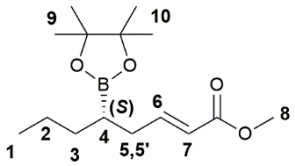
(*R*)-Methyl (*E*)-5-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate **110**



Compound **110** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.2) obtained as a yellow oil (680.0 mg, 54%; 98% e.e.) with an R_f 0.25: IR (neat) ν_{max} 2980 (m), 1720 (l), 1656 (m), 1438 (m), 1370 (l), 1328 (l), 1270 (l), 1194 (m), 1140 (l), 1032 (s), 966 (m), 848 (l), 752 (l), 700 (l); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.14 (m, 5H, *Ph*), 7.02 – 6.94 (m, 1H, H-*3*), 5.86 – 5.82 (d, *J* 16 Hz, 1H, H-*4*), 3.71 (s, 3H, H-*5*), 2.82 – 2.72 (m, 1H, H-*1*), 2.62 – 2.54 (m, 1H, H-*2/2'*), 2.51 – 2.47 (m, 1H, H-*2'/2*), 1.23 (s, 6H, H-*6*), 1.20 (s, 6H, H-*7*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0 (*C*OOR), 148.2, 141.7 (*C*H=CH-COOR), 128.8, 128.3, 125.7, 121.8 (CH=*C*H-COOR), 83.6, 51.7, 35, 24.9 (*C*-CH=C); ^{11}B (128 MHz, $CDCl_3$) δ 32.7; LRMS (ESI

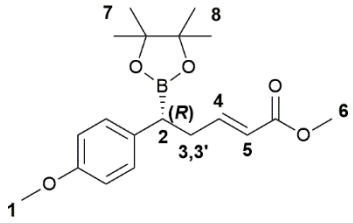
+) *m/z* $[M+H]^+$ 318.3 (100%), 317.7 (21%), 317.8 (33%); HRMS (ESI+) *m/z* calculated $C_{18}H_{26}{}^{10}BO_4$ $[M+H]^+$ 316.1960, found 316.1953; Enantiomeric excess was determined by HPLC using an OJ-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ºC, 0.2 mL/min, 210 nm, hexane:^{i}PrOH (99 : 1), t_R (*R*)= 41.9 min; t_R (*S*) = 45.8 min. All spectroscopic and analytical data were identical to those reported in the literature.[122]

(*S*)-Methyl (*E*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-2-enoate **117**



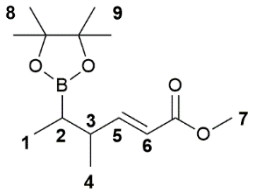
Compound **117** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.2) obtained as a yellow oil (832.0 mg, 74%; 91% e.e.) with a R_f 0.33: IR (neat) ν_{max} 2934 (m), 1722 (l), 1656 (s), 1434 (s), 1386 (m), 1316 (l), 1262 (m), 1140 (l), 1046 (s), 982 (m), 860 (m), 752 (l), 696 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 - 6.95 (m, 1H, H-*6*), 5.86 – 5.82 (d, *J* 16.0 Hz, 1H, H-*7*), 3.73 (s, 3H, H-*8*), 2.83 – 2.66 (m, 1H, H-*5/5'*), 2.38 – 2.21 (m, 1H, H-*5'/5*), 2.38 – 2.21 (m, 1H, H-*4*), 1.61 (s, 6H, H-*9*), 1.35 (s, 6H, H-*10*), 0.92 – 0.89 (t, *J* 7.2, 3H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1 (*C*OOR), 149.8, 121.2 (CH=*C*H-COOR), 83.2, 51.3, 33.7, 33.0, 24.8 (*C*-CH=C), 22.0, 14.30; ^{11}B (128 MHz, $CDCl_3$) δ 33.9; LRMS (ESI +) *m/z* $[M+H]^+$ 283.2 (100%), 282.1 (12%), 284.5 (10%); HRMS (ESI+) *m/z* calculated $C_{15}H_{28}{}^{10}BO_4$ $[M+H]^+$ 282.2117, found 282.2130; Enantiomeric excess was determined by HPLC using an OD-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ºC, 0.7 mL/min, 210 nm, hexane :^{i}PrOH (99.5 : 0.5), t_R (*S*) = 8.7 min; t_R (*R*) = 11.1 min.

(*R*)-Methyl (*E*)-5-(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate **118**



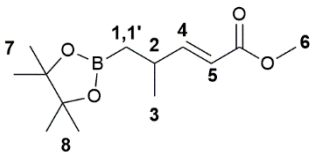
Compound **118** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.2) obtained as a yellow oil (367.0 mg, 53%, 87% e.e.): IR (neat) ν_{max} 2984 (m), 2886 (s), 1722 (l), 1658 (m), 1650 (m), 1630 (s), 1510 (l), 1442 (m), 1368 (m), 1328 (m), 1248 (l), 1180 (m), 1140 (l), 1124 (s), 1042 (m), 1016 (s), 970 (m), 852 (m), 850 (m), 760 (m), 744 (m), 710 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.14 (m, H, *Ph*), 6.85 – 6.81 (dt, *J* 8.0, 1H, H-*4*), 5.82 (d, *J* 15.0, 1H, H-*5*), 3.80 (s, 3H, H-*1*), 3.71 (s, 3H, H-*6*), 2.69 (m, 1H, H-*2*), 2.54 (m, 1H, H-*3/3'*), 2.43 (m, 1H, H-*3'/3*), 1.22 (s, 6H, H-*7/8*), 1.20 (s, 6H, H-*8/7*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0 (*C*OOR), 157.6, 148.9 (*C*H=CH-COOR), 133.5, 129.1, 121.4 (CH=*C*H-COOR), 113.9, 83.5, 55.1, 51.3, 35.3, 24.6, 24.5; ^{11}B (128 MHz, $CDCl_3$) δ 32.6; LRMS (ESI +) *m/z* $[M+H]^+$ 368.9 (100%), 364.0 (37%), 347.1 (35.5%), 363.5 (12%); HRMS (ESI+) *m/z* calculated $C_{19}H_{27}{}^{10}BO_5$ $[M+H]^+$ 346.2066 found 346.2066; Enantiomeric excess was determined by HPLC using an OJ-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ºC, 0.8 mL/min, 210 nm, hexane : ^{i}PrOH (97 : 3), t_R (*R*) = 12.6 min; t_R (*S*) = 14.7 min.

Methyl (*E*)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-2-enoate, **119**



Compound **119** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.2) obtained as a yellow oil (161 mg, 60%): IR (neat) ν_{max} 2986 (m), 2904 (S), 2336 (l), 2370 (l), 1726 (l), 1704 (m), 1466 (m), 1464 (m), 1382 (l), 1380 (l), 1320 (l), 1308 (m), 1240 (m), 1144 (l), 1032 (m), 1030 (m), 954 (s), 848 (m), 750 (s), 704 (m), 670 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 – 6.83 (m, 1H, H-*5*), 5.80 (d, *J* 16.0 Hz, 1H, H-*6*), 3.74 (s, 3H, H-*7*), 1.58 (s, 1H, H-*3*), 1.26 (s, 6H, H-*8*), 1.25 (s, 6H, H-*9*), 1.09 (dd, *J* 6.8, 2.6 Hz, 3H, H-*4*), 0.93 (d, *J* 7.3 Hz, 3H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.2 (*C*OOR), 154.9 (*C*H=CH-COOR), 128.3, 127.2, 119.7 (CH=*C*H-COOR), 83.1, 51.2, 39.2, 24.8 (C-CH=C), 19.0, 13.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.8; LRMS (ESI+) *m/z* 269.2 (100%), 237.1 (95%), 291.2 (66%); [M+H] HRMS (ESI+) *m/z* calculated $C_{14}H_{25}{}^{10}BO_4$ $[M+H]^+$ 268.1960 found 268.1982.

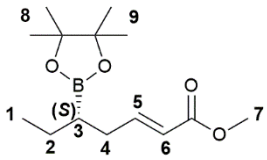
Methyl (*E*)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate **120**



Compound **120** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.2) obtained as a yellow oil (181 mg, 36%): IR (neat) ν_{max} 2980 (m), 2944 (s), 2910 (s), 1724 (l), 1658 (m), 1440 (m), 1368 (l), 1324 9 (l), 1274 (l), 1202 (m), 1200 (s), 1140 (l), 1014 (s), 986 (s), 970 (m), 940 (s), 888 (s), 848 (l), 834 (s), 762 (s), 716 (s), 706 (s); ^{1}H NMR (400 MHz,

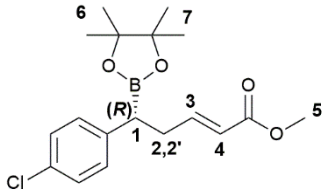
$CDCl_3$) δ 7.03 – 6.93 (m, 1H, H-*4*), 5.80 (m, 1H, H-*5*), 3.74 (s, 3H, H-*6*), 2.65 – 2.57 (m, 1H, H-*2*), 1.26 (s, 6H, H-*7*), 1.24 (s, 6H, H-*8*), 1.11 – 1.10 (m, 3H, H-*3*), 0.95 (d, *J* 6.7Hz, 1H, H-*1/1'*), 0.89 (m, 1H, H-*1/1'*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (*C*OOR), 157.5, 156.1, 118.0 (CH=*C*H-COOR), 116.5, 83.2, 83.0, 51.3, 32.5, 29.0, 24.8 (*C*-CH=C), 22.3, 21.4; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.1; LRMS (ESI +) *m/z* $[M+H]^+$ 277.1 (100%), 255.1 (62%), 253.9 (10%); HRMS (ESI+) *m/z* calculated $C_{13}H_{24}BO_4$ $[M+H]^+$ 254.1804 found 254.1814.

(*S*)-Methyl (*E*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-2-enoate **121**



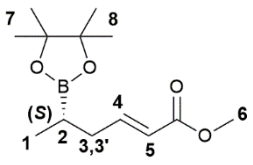
Compound **121** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.2) obtained as a yellow oil (746 mg, 70%; 73% e.e.) with a R_f 0.1: IR (neat) ν_{max} 2980 (l), 2982 (l), 2914 (m), 1726 (l), 1656 (m), 1440 (m), 1388 (l), 1322 (l), 1266 (l), 1200 (s), 1138 (l), 1048 (s), 974 (m), 846 (m), 760 (m), 744 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 – 6.91 (dt, *J* 15.6, 7.2 Hz, 1H, H-*5*), 5.84 – 5.88 (dt, *J* 15.6, 1.5 Hz, 1H, H-*6*), 3.70 (s, 3H, H-*7*), 2.36 – 2.18 (m, 2H, H-*2*), 1.50 – 1.36 (m, 2H, H-*4*), 1.26 – 1.18 (s, 12H, H-*8+9*), 1.12 (m, 1H, H-*3*), 0.93 – 0.86 (t, *J* 7.4 Hz, 3H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5 (*C*OOR), 150.1, 121.5 (CH=*C*H-COOR), 83.5, 51.7, 33.8, 25.1 (*C*-CH=C), 24.0, 13.7; ^{11}B (128 MHz, $CDCl_3$) δ 34.1; LRMS (ESI +) *m/z* $[M+H]^+$ 269.2 (74%), 290.8 (60%), 237.1 (54%); HRMS (ESI+) *m/z* calculated $C_{14}H_{26}{}^{10}BO_4$ $[M+H]^+$ 269.1924 found 269.1933; Enantiomeric excess was determined by HPLC using an OD-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ºC, 0.40 mL/min, 210 nm, hexane:^{i}PrOH (98 : 2), t_R (*S*) = 12.8 min; t_R (*R*) = 14.9 min.

(*R*)-Methyl (*E*)-5-(4-chlorophenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate **122**



Compound **122** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.2) obtained as a yellow oil (377 mg, 54%; 98% e.e.): IR (neat) ν_{max} 2982 (m), 2970 (s), 1722 (l), 1658 (m), 1492 (l), 1438 (m), 1372 (m), 1332 (m), 1274 (m), 1202 (m), 1200 (m), 1142 (l), 1092 (m), 1012 (m), 970 (m), 844 (m), 842 (m), 796 (s), 702 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.11 (m, 4H, *Ph*), 7.03 – 6.89 (m, 1H, H-*3*), 5.84 – 5.79 (dt, *J* 16.0, 1.4 Hz, 1H, H-*4*), 3.71 (s, 3H, H-*5*), 2.79 – 2.68 (m, 1H, H-*1*), 2.59 – 2.49 (m, 1H, H-*2/2'*), 2.48 – 2.44 (m, 1H, H-*2/2'*), 1.22 (s, 6H, H-*6*), 1.20 (s, 6H, H-*7*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 148.1, 147.7, 140.1, 131.1, 129.5, 128.4, 127.5, 121.7, 83.7, 51.1, 34.8, 33.6, 33.3, 30.2, 24.5; ^{11}B NMR (128 MHz, $CDCl_3$) δ 32.7; LRMS (ESI +) *m/z* $[M+H]^+$ 373.5 (100%), 351.1 (91%), 372.6 (80%), 375.1 (75%); HRMS (ESI+) *m/z* calculated $C_{18}H_{25}{}^{10}BO_4{}^{35}Cl$ $[M]^+$ 350.1571 found 350.1573; Enantiomeric excess was determined by HPLC using an OD-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ºC, 0.8 mL/min, 210 nm, hexane:^{i}PrOH (99 : 1), t_R (*S*) = 10.7 min; t_R (*R*) = 13.0 min.

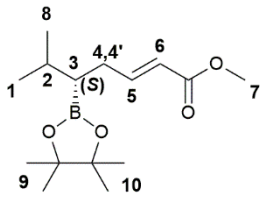
(*S*)-Methyl (*E*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-2-enoate **123**



Compound **123** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.2) obtained as a yellow oil

(662 mg, 65%; 80% e.e.) with a R_f 0.1: IR (neat) ν_{max} 2976 (s), 1720 (l), 1654 (s), 1458 (s), 1436 (s), 1368 (m), 1316 (m), 1266 (m), 1158 (s), 1142 (l), 1038 (s), 966 (m), 850 (m), 706 (m), 670 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.93 (dt, *J* 15.6, 7.2 Hz, 1H, H-*4*), 5.85 – 5.79 (dt, *J* 15.6, 1.5 Hz, 1H, H-*5*), 3.72 (s, 3H, H-*6*), 2.40 – 2.31 (m, 1H, H-*3/3'*), 2.22 -2.13 (m, 1H, H-*3'/3*), 1.23 (s, 12H, H-*7+8*), 1.01 – 0.95 (d, *J* 7.4, 3H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5(*C*OOR), 150.0, 121.7 (CH=*C*H-COOR), 83.6, 51.7, 35.9, 25.1 (*C*-CH=C), 15.5; ^{11}B (128 MHz, $CDCl_3$) δ 33.9; LRMS (ESI +) *m/z* $[M+]^+$ 236.2 (58%), 235.6 (40%), 254.2 (25%); HRMS (ESI+) *m/z* calculated $C_{13}H_{24}{}^{10}BO_4$ $[M+H]^+$ 254.1804 found 254.1817; Enantiomeric excess was determined by HPLC using an OD-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ºC, 1.0 mL/min, 210 nm, hexane:^{i}PrOH (98 : 2), t_R (*S*) = 5.3 min; t_R (*R*) = 5.9 min.

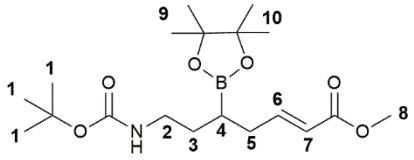
(*S*)-Methyl (*E*)-6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-2-enoate **148**



Compound **148** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.2) obtained as a yellow oil (395 mg, 60%; 60% e.e.): R_f 0.1; IR (neat) ν_{max} (cm^{-1}) 2955 (m), 1724 (l), 1655 (s), 1436 (s), 1379 (m), 1318 (m), 1268 (m), 1196 (m), 1142 (l), 1043 (s), 971 (m), 849 (m), 700 (m), 578 (s); ^{1}H NMR (400 MHz, D_8-toluene) δ 7.02-6.94 (dt, *J* 14.48, 7.2 Hz, 1H, H-*5*), 5.85-5.80 (dt, *J* 15.61, 1.48 Hz, 1H, H-*6*), 3.71 (s, 3H, H-*7*), 2.37-2.23 (m, 2H, H-*4*), 1.78-1.70 (m, 1H, H-*3*), 1.23 (s, 12H, H-*9+10*), 1.07-1.00 (m, 1H, H-*2*), 0.96-0.94 (d, *J* 6.78 Hz, 3H, H-*1/8*), 0.93-0.91 (d, *J* 6.76 Hz, 3H, H-*8/1*); ^{13}C NMR (101 MHz, D_8-toluene) δ 175.3 (*C*OOR), 158.9, 146.5, 138.1, 137.9, 137.6, 137.2, 137.2, 136.9, 136.9, 136.7, 136.7, 134.4, 134.1, 133.9, 130.6, 92.1, 59.7, 41.4, 38.9, 33.9, 33.8, 31.5, 30.4, 30.0, 29.8, 29.6, 29.4, 29.2, 29.1, 28.8;

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.53; LRMS (ESI+) *m/z* $[M + Na]^+$ 305.2 (100%); HRMS (ESI+): *m/z* calculated $C_{15}H_{28}{}^{10}BO_4$ [M+H] 282.2117, found 282.2117; Enantiomeric excess was determined by HPLC using an OJ-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ºC, 0.2 mL/min, 254 nm, hexane:^{i}PrOH (99 : 1), t_R (*S*) = 21.4 min; t_R (*R*) = 22.1 min.

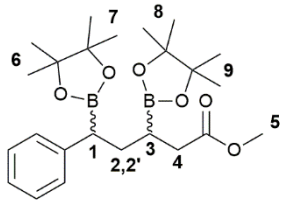
Methyl (*R*,*E*)-7-((tert-butoxycarbonyl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-2-enoate **174**



Compound **174** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.2) obtained as a yellow oil (208 mg, 36 %) with an R_f 0.18: IR (neat) υ_{max} 2978 (m), 1712 (l), 1450 (s), 1366 (l), 1321 (m), 1244 (l), 1165 (l), 1142 (l), 1044 (m), 982 (s), 915 (m), 852 (m), 731 (l), 700 (l), 646 (s), 542 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dt, *J* 15.7, 7.3 Hz, 1H, H-*6*), 5.83 (d, *J* 15.6 Hz, 1H, H-*7*), 3.71 (s, 3H, H-*8*), 3.17-3.12 (m, 2H, H-*2*), 2.39-2.22 (m, 2H, H-*5*), 1.42 (s, 9H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$) 149.0 (*C*OOR), 121.8 (CH=*C*H-COOR), 83.7, 77.5, 77.2, 76.8, 60.5, 51.5, 28.6, 24.9 (*C*-CH=C); ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7; LRMS (ESI+) m/z $[M]^+$ 383.2 (100%); HRMS (ESI+) calculated $C_{19}H_{35}{}^{10}BNO_6$ $[M+H]^+$ 383.2594, found 383.2615.

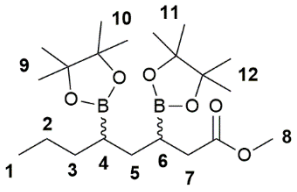
3.3.4. Synthesis of 1,3-diborylated esters

Methyl 5-phenyl-3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate **143**



Compound **143** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.3) obtained as a yellow oil (103 mg, 47%) with an R_f 0.61: IR (neat) ν_{max} 3025 (s), 2978 (m), 2929 (s), 1734 (l), 1601 (s), 1493 (s), 1481 (s), 1452 (m), 1436 (m), 1379 (l), 1371 (l), 1315 (m), 1271 (m), 1214 (m), 1198 (m), 1166 (m), 1140 (l), 1109 (s), 1032 (s), 1005 (s), 967 (m), 863 (m), 850 (m), 767 (s), 737 (s), 701 (m), 671 (s), 520 (s); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers further analysis was required for the determination of the major diastereoisomer, see Section 2.3.5 for further discussion), major isomer: δ 7.24–7.08 (m, 5H, *Ph*), 3.61 (s, 3H, H-*5)*, 2.50–2.41 (m, 1H, H-*2/2'*), 2.41–2.36 (m, 1H, H-*2'/2*), 2.07–1.98 (m, 1H, H-*1*), 1.88–1.80 (m, 2H, H-*4*), 1.71–1.63 (m, 1H, H-*3*), 1.24 (s, 12H, H-*6/7*), 1.18 (s, 12H, H-*8/9*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (*C*OOR), 142.6, 128.6, 128.3, 124.9, 82.6, 51.3, 36.1, 35.7, 32.5, 32.2, 25.0; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2; LRMS (ESI+) *m/z* $[M+H]^+$ 445.0 (99%), 466.0 (40%), 465.6 (18%); HRMS (ESI+): *m/z* calculated $C_{24}H_{39}{}^{10}B_2O_6$ $[M+H]^+$ 443.3005, found 443.2998.

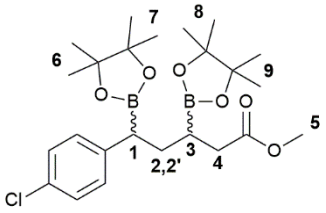
Methyl 3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octanoate **147**



Compound **147** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.3) obtained as a yellow oil (318 mg, 78%) with an R_f 0.71: IR (neat) ν_{max} 2977 (m), 1737 (l), 1379 (l), 1371 (l), 1313 (l), 1249 (s), 1197 (m), 1165 (m), 1140 (l), 967 (m), 861 (l), 670 (m), 578 (s); ^{1}H NMR (700 MHz, D_8-toluene) (mixture of diastereoisomers further analysis was required for the determination of the major diastereoisomer, see Section 2.3.5 for further discussion), major isomer: δ 3.74 (s, 3H, H-*8*), 2.74–2.71 (m, 1H, H-*6*), 2.68 – 2.61 (m, 1H, H-*7/7'*), 2.12–2.06 (m, 1H, H-*7'/7*), 1.83–1.89 (m, 1H, H-*5'/5*), 1.82 – 1.77 (m, 1H, H-*5/5'*), 1.76–1.68 (m, 2H, H-*3*), 1.66–1.62 (m, 2H, H-*2*), 1.48-1.43 (m, 1H, H-*4*), 1.24 (s, 6H, H-*9/10*), 1.23 (s, 6H, H-*10/9*), 1.17 (s, 6H, H-*11/12*), 1.15 (s, 6H, H-*12/11*), 1.09–1.06 (dd, *J* 14.0, 7.0 Hz, 3H, H-*1*); ^{13}C NMR (101 MHz, D_8-toluene) δ 184.2 (*C*OOR), 183.0 (*C*OOR), 147.5, 93.0, 92.8, 92.7, 60.8, 46.7, 45.5, 44.7, 44.3, 43.2, 42.2, 33.0, 32.7, 24.8, 24.7; ^{11}B NMR (128 MHz, D_8-toluene) δ 33.86 ppm. LRMS (ESI+): *m/z* $[M + Na]^+$ 433.9 (96%), $[M]^+$ 410.0 (88%); HRMS (ESI+) *m/z* calculated $C_{21}H_{40}{}^{10}B_2O_6$ $[M + H]^+$ 409.3162, found 409.3170.

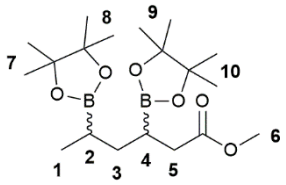
Methyl 5-(4-chlorophenyl)-3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate

145



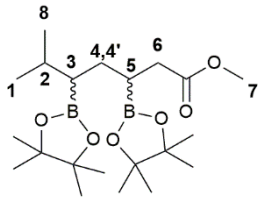
Compound **145** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.3) obtained as a yellow oil (93 mg, 20%) with an R_f 0.68: IR (neat) ν_{max} 2978 (s), 1735 (l), 1662 (s), 1598 (s), 1490 (m), 1472 (s), 1447 (m), 1436 (m), 1411 (m), 1379 (m), 1371 (m), 1358 (m), 1318 (m), 1271 (s), 1213 (m), 1166 (m), 1139 (l), 1109 (s), 1014 (m), 967 (m), 861 (m), 851 (m), 731 (s), 703 (m), 637 (m), 639 (m); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers further analysis was required for the determination of the major diastereoisomer, see Section 2.3.5 for further discussion), major isomer: δ 7.21 -7.10 (m, 4H, *Ph*), 3.61 (s, 3H, H-*5*), 2.49–2.40 (m, 1H, H-*4/4'*), 2.40–2.34 (m, 1H, H-*4'/4*), 2.02-1.94 (m, 1H, H-*1*), 1.84–1.77 (m, 2H, H-*2*), 1.69–1.60 (m, 1H, H-*3*), 1.24 (s, 6H, H-*6/7*), 1.22 (s, 6H, H-*7/6*), 1.21 (s, 6H, H-*8/9*), 1.18 (s, 6H, H-*9/8*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (*C*OOR), 141.4, 130.0, 129.7, 128.4, 83.5, 83.1, 51.3, 35.9, 35.0, 32.8, 32.5, 24.8, 24.6; ^{11}B NMR (128 MHz, $CDCl_3$): δ 33.1. LRMS (ESI+): *m/z* $[M+Na]^+$ 501.6 (100%), 480.8 (60%); HRMS (ESI+) *m/z* calculated $C_{24}H_{37}{}^{10}B_2{}^{35}ClO_6$ $[M+H]^+$ 477.2616, found 477.2603.

Methyl 3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanoate **146**



Compound **146** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.3) obtained as a yellow oil (97 mg, 51%) with an R_f 0.6: IR (neat) ν_{max} 2977 (m), 1737 (l), 1461 (s), 1379 (l), 1371 (l), 1312 (l), 1267 (m), 1214 (m), 1165 (m), 1140 (l), 1111 (s), 1007 (m), 967 (m), 861 (l), 670 (m), 578 (s); ^{1}H NMR (700 MHz, D_8-toluene) (mixture of diastereoisomers further analysis was required for the determination of the major diastereoisomer, see Section 2.3.5 for further discussion), major isomer: δ 3.46 (s, 3H, H-*6*), 2.18–2.12 (m, 1H, H-*5/5'*), 2.10–2.06 (m, 1H, H-*5'/5*), 2.02–1.95 (m, 1H, H-*4)*, 1.67–1.61 (m, 1H, H-*2*), 1.40–1.34 (m, 2H, H-*3*), 1.30 (d, *J* 8.4, 3H, H-*1*), 1.16 (s, 12H, H-*7+8*), 1.14 (s, 12H, H-*9+10*); ^{13}C NMR (101 MHz, D_8-toluene) δ 184.5 (*C*OOR), 183.6 (*C*OOR), 147.5, 93.0, 92.6, 60.8, 46.5, 46.3, 45.7, 44.8, 44.5, 44.1, 41.1, 40.0, 35.0, 34.8, 28.1, 26.4, 26, 24.9; ^{11}B NMR (128 MHz, D_8-toluene): δ 34.09 ppm; LRMS (ESI+) *m/z* $[M + Na]^+$ 405.3 (100%); HRMS (ESI+) *m/z* calculated $C_{19}H_{37}{}^{10}B_2O_6$ $[M + H]^+$ 381.2849, found 381.2842.

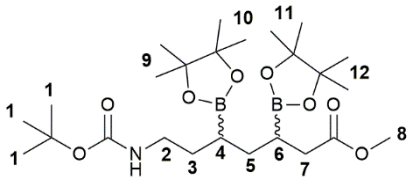
Methyl 6-methyl-3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptanoate **149**



Compound **149** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.3) obtained as a yellow oil

(245 mg, 60%) with an R_f 0.75; IR (neat) ν_{max} 2977 (m), 1737 (l), 1436 (s), 1379 (s), 1371 (s), 1311 (s), 1269 (m),1212 (m), 1197 (m), 1165 (m), 1140 (s), 1111 (m), 1005 (l), 971 (m), 863 (s), 849 (m), 670 (m); ^{1}H NMR (700 MHz, D_8-toluene) (mixture of diastereoisomers further analysis was required for the determination of the major diastereoisomer, see Section 2.3.5 for further discussion), major isomer: δ 3.48 (s, 3H, H-*7*), 2.78–2.74 (m, 1H, H-*6/6'*), 2.65 – 2.61 (m, 1H, H-*6'/6*), 2.09–2.12 (m, 1H, H-*4*), 1.86–1.81 (m, 1H, H-*5*), 1.40–1.36 (m, 1H, H-*2*), 1.34–1.31 (m, 2H, H-*4*), 1.24 (s, 12H, H-*9/10*), 1.19 (s, 12H, H-*11/12*), 1.16 (s, 6H, H-*1+8*); ^{13}C NMR (176 MHz, D_8-toluene) δ 178.7, 178.5 (*C*OOR), 87.6, 87.5, 87.4, 87.3, 55.3, 41.8, 39.7, 35.7, 35.3, 34.64, 34.4, 29.6, 29.5, 29.5, 29.5, 29.4, 27.6, 27.4, 26.2, 26.1; ^{11}B NMR (128 MHz, D_8-toluene): δ 33.4 ppm; LRMS (ESI+) *m/z* $[M + Na]^+$ 433.8 (100%); HRMS (ESI+) *m/z* calculated $C_{21}H_{40}{}^{10}B_2O_6$ $[M + H]^+$ 409.3162, found 411.3071.

Methyl-7-((tert-butoxycarbonyl)amino)-3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptanoate, **175**



Compound **175** was obtained following the general procedure for the synthesis of homoallylic boronate carboxylate esters (reported in Section 3.2.3) obtained as a yellow oil (125 mg, 46 %): IR (neat) υ_{max} 2977 (m), 1714 (l), 1509 (l), 1370 (l), 1315 (l), 1165 (m), 1245 (s), 1140 (l), 968 (s), 860 (m), 697 (s), 670 (s), 579 (s), 542 (m); ^{1}H NMR (400 MHz, D_8-toluene) (mixture of diastereoisomers further analysis was required for the determination of the major diastereoisomer, see Section 2.3.5 for further discussion), major isomer: δ 4.52 (s, 1H, N*H*), 3.35 (s, 3H, H-*8*), 3.2 (m, 2H, H-*2*), 2.5 (m, 2H, H-*3*), 1.87 (m, 1H, H-*5*), 1.68-1.54 (m, 5H, H-*5+6+7*), 1.43 (s, 9H, H-*1*), 1.11 (s, 12H, H-*9+10*), 1.03 (s, 12H, H-*11+12*); ^{13}C NMR (101 MHz, D_8-toluene) δ 183.5 (*C*OOR), 165.3, 147.1, 138.7, 138.5, 138.3, 137.9,

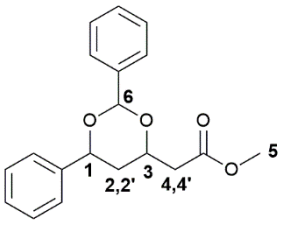
137.8, 137.6, 137.6, 137.4, 137.4, 135.0, 134.8, 134.5, 92.8, 60.5, 46.3, 45.3, 38.24, 34.56, 34.5, 34.5, 30.6, 30.5, 30.3, 30.1, 29.9, 29.7, 29.5; ^{11}B NMR (128 MHz, D_8-toluene): δ 33.5 ppm; LRMS (ESI+): *m/z* $[M + Na]^+$ 534.7 (100%); HRMS (ESI+) *m/z* calculated $C_{25}H_{48}{}^{10}B_2NO_8$ $[M + H]^+$ 510.3639, found 510.3643.

3.3.5. Synthesis of 6-membered ring acetals

Procedure a) Synthesis of phenyl substituted 6-membered ring acetals

The solid residue of 1,3-diol synthesised following the general procedure for the oxidation of diborylated esters, Section 3.2.4 (0.9 mmol) was dissolved in toluene (15 mL), benzaldehyde dimethyl acetal (195 µL, 1.3 mmol, 1.5 equiv.) was added along with TsOH (17.4 mg, 0.087 mmol, 10 mol%). After stirring for 10 minutes, 4 Å-Molecular Sieves (1.5 g) were added and mixture heated for 6 h at 50 °C. The molecular sieves were removed by filtration and the solvent removed *in vacuo*, to give a crude product that was purified by SiO_2 chromatography using a mixture of petroleum ether:EtOAc (5:1, 3:1 and 0:1) as eluent which gave the pure phenyl-substituted six-membered ring acetal.

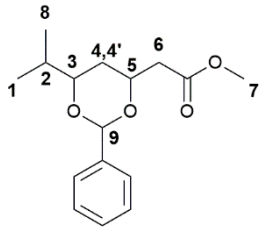
Methyl 2-(2,6-diphenyl-1,3-dioxan-4-yl)acetate **154**



Compound **154** was obtained following the general procedure for the synthesis of phenyl-substituted six-membered ring acetals obtained as a yellow oil (68 mg, 70%) with an R_f 0.5: IR (neat) ν_{max} 2951 (m), 1733 (l), 1495 (s), 1451 (m), 1436 (m), 1339 (s), 1312 (s), 1205 (m), 1161 (l), 1104 (l), 1009 (l), 905 (s), 855 (s), 752 (l), 696 (l), 609 (m), 538 (m); major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.31 (m, 10 H, *Ph*), 5.67 (s, 1H, H-*6*), 5.44 (d,

J 5.8 Hz, 1H, H-*1*), 4.45 (dtd, *J* 11.6, 6.7, 2.0 Hz, 1H, H-*3*), 3.71 (s, 3H, H-*5*), 2.78 (dd, *J* 16.0, 7.3 Hz, 1H, H-*4/4'*), 2.60 (dd, *J* 16, 6.7 Hz, 1H, H-*4'/4*), 2.52 (dt, *J* 13.6, 2.0 Hz, 1H, H-*2/2'*), 2.30 (ddd, *J* 13.5, 11.3, 5.8 Hz, 1H, H-*2'/2*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 141.4, 138.4, 128.9, 128.6, 128.4, 127.9, 126.4, 125.9, 100.9, 78.7, 73.5, 51.8, 40.7, 38.7; LRMS (ESI+) *m/z* $[M + Na]^+$ 335.2 (100%); HRMS (ESI+) *m/z* calculated $C_{19}H_{20}O_4Na$ $[M + Na]^+$ 335.1259, found 335.1267.

Methyl 2-(6-isopropyl-2-phenyl-1,3-dioxan-4-yl) acetate **161**

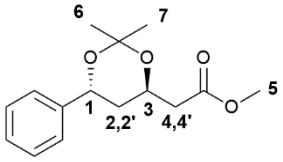


Compound **161** was obtained following the general procedure for the synthesis of phenyl-substituted six-membered ring acetals obtained as a yellow oil as a mixture of diastereosiomers (45 mg, 64%), enantiomers separated by HPLC (Sunfire C18 column, 250 x 10 mm, 5 µm; H_2O: CH_3CN gradient 90:10, 4.4 mL.min^{-1}, 254 nm) t_R = 17.4 min., t_R = 17.9 min.: IR (Et_2O film) ν_{max} 2958 (m), 1737 (l), 1452 (s), 1436 (m), 1384 (m), 1398 (s), 1362 (s), 1302 (m), 1255 (s), 1192 (m), 1170 (m), 1105 (l), 1070 (s), 1027 (m), 986 (m), 900 (s), 862 (s), 698 (l), 653 (s); major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) 7.48 – 7.31 (m, 5H, *Ph*), 5.80 (s, 1H, H-*9*), 4.75 (m, 1H, H-*5*), 3.66 (ddd, *J* 9.1, 6.7, 2.4 Hz, 1H, H-*3*), 3.12 (dd, *J* 14.5, 8.6 Hz, 1H, H-*6/6'*), 2.73 (dd, *J* 14.5, 6.9 Hz, 1H, H-*6'/6*), 2.07 (dd, *J* 11.9, 6.3 Hz, 1H, H-*4/4'*), 2.03 (dd, *J* 11.9, 6.3 Hz, 1H, H-*4'/4*), 1.80 (h, *J* 6.7 Hz, 1H, H-*2*), 1.02 (d, *J* 6.7 Hz, 3H, H-*1/8*), 0.94 (d, *J* 6.7 Hz, 3H, H-*8/1*); LRMS (ESI+): *m/z* $[M + Na]^+$ 301.8 (100%); HRMS (ESI+): *m/z* calculated $C_{16}H_{22}O_4Na$ $[M + Na]^+$ 301.1416, found 301.1423.

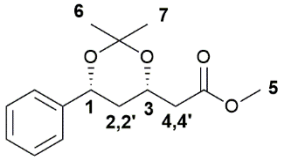
Procedure b) Synthesis of acetonide substituted six-membered ring acetals

The solid residue of 1,3-diol synthesised following the general procedure for the oxidation of diborylated esters, Section 3.2.4 (2.0 mmol) This compound was then re-dissolved in a mixture of acetone:2,2'-dimethoxypropane (1:1 by volume, 100 mL), followed by the addition of TsOH (45 mg, 0.2 mmol, 10 mol%). This mixture was stirred at RT during 10 minutes, then 4 Å-MS (2.0 g) were added and the reaction mixture was stirred for a further 24 h. After filtration, the solvent was removed *in vacuo* to give the crude acetal which was purified by SiO_2 chromatography using a mixture of petroleum ether:EtOAc (5:1, 3:1 and 2:1) as eluent to give the pure acetonide-substituted six-membered ring acetal.

Methyl 2-(2,2-dimethyl-6-phenyl-1,3-dioxan-4-yl)acetate **162**



Anti-diastereoisomer

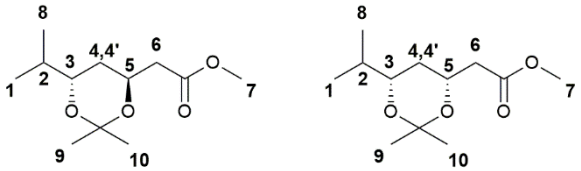


Syn-diastereoisomer

Compound **162** was obtained following the general procedure for the synthesis of acetonide-substituted six-membered ring acetals obtained as a yellow oil (109 mg, 23%), enantiomers separated by HPLC (chiral ART amylose-SA column, 250 x 10 mm, 5 µm; Hexane: EtOH: DCM, 97: 2: 1; 4.4 mL.min^{-1}, 254 nm) t_R (*anti*-diastereoisomer) = 6.9 min; t_R (*syn*-diastereoisomer) = 7.2 min; with an R_f 0.72: IR (neat) ν_{max} (cm^{-1}) 2988 (s), 1739 (l), 1661 (s), 1494 (s), 1437 (m), 1379 (m), 1317 (s), 1275 (s), 1223 (m), 1165 (l), 1073 (m), 1000 (s), 956 (s), 905 (s), 843 (s), 752 (s), 697 (l), 604 (s), 543 (m), 401 (s), 362 (m); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers), *Anti*-diastereoisomer δ 7.38 – 7.33 (m, 5H, *Ph*), 4.89 (dd, *J* 9.8, 6.3 Hz, 1H, H-*1*), 4.44 (m, 1H, H-*3*), 3.70 (s, 3H, H-*5*), 2.64 (dd, *J* 15.7, 7.9 Hz, 1H, H-*4/4'*), 2.52 (dd, *J* 15.7, 5.6 Hz, 1H, H-*4/4'*), 2.08 (ddd, *J* 13.1, 9.8, 5.8 Hz, 1H, H-*2/2'*), 1.95 (ddd, *J* 13.1, 9.3, 6.3 Hz, 1H, H-*2'/2*), 1.45 (s, 3H, H-*6/7*), 1.44 (s, 3H, H-*7/6*); *Syn*-diastereoisomer: δ 7.39 – 7.33 (m, 5H, *Ph*), 4.94 (dd, *J* 11.6, 2.6 Hz, 1H, H-*1*), 4.48 (m, 1H, H-*3*), 3.69 (s, 3H, H-*5*), 2.61 (dd, *J* 15.6, 6.8 Hz, 1H, H-*4/4'*), 2.43 (dd, *J* 15.6, 6.2 Hz, 1H, H-

4'/4), 1.83 (dt, *J* 15.3, 2.6 Hz, 1H, H-*2/2'*), 1.58 (s, 3H, H-*6/7*), 1.49 (s, 3H, H-*7/6*); ^{13}C NMR (101 MHz, $CDCl_3$) (mixture of diastereoisomers), *Anti*-diastereoisomer: δ 171.6 (*C*OOR), 128.8, 128.8, 128.6, 127.8, 126.4, 126.3, 101.5, 77.5, 77.3, 77.2, 68.8, 64.0, 52.0, 40.9, 39.7, 30.0, 25.3, 24.9, 23.0, 1.4; *Syn*-diastereoisomer: δ 171.67 (*C*OOR), 128.8, 128.0, 126.3, 99.7, 77.5, 77.3, 77.2, 71.6, 66.5, 52.0, 41.5, 39.2, 30.5, 30.0, 20.0, 14.5; LRMS (ESI+) *m/z* $[M+Na]^+$ 287.2 (100%); HRMS (ESI+): *m/z* calculated $C_{15}H_{20}O_4Na$ $[M+Na]^+$ 287.1259, found 287.1263.

Methyl 2-(6-isopropyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate **163**

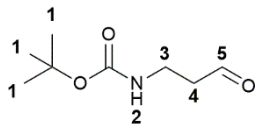


Compound **163** was obtained as a yellow oil (169 mg, 32%); enantiomers separated by HPLC (chiral ART amylose-SA column, 250 x 10 mm, 5 µm; Hexane: EtOH: DCM, 95: 4: 1; 4.4 $mL.min^{-1}$, 254 nm) R_T (*anti*-diastereoisomer) = 6.7 min; R_T (*syn*-diastereoisomer) = 6.8 min; with an R_f 0.6: IR (neat) ν_{max} (cm^{-1}); 2956 (m), 1741 (l), 1663 (s), 1437 (m), 1378 (l), 1316 (s), 1257 (m), 1202 (l), 1168 (l), 1145 (l), 1072 (l), 1096 (m), 998 (m), 975 (m), 932 (s), 839 (l), 703 (l), 639 (s), 544 (m), 472 (s), 400 (m), 370 (s), 354 (l); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers), *Anti*-diastereoisomer 4.25-4.20 (m, 1H, H-*5*), 3.67 (s, 3H, H-*7*), 3.42 (m, 1H, H-*3*), 2.54 (dd, *J* 15.5, 8.26 Hz, 1H, H-*6/6'*), 2.44 (dd, *J* 15.5, 5.2 Hz, 1H, H-*6'/6*), 1.74 (dd, *J* 9.6, 5.9 Hz, 1H, H-*4/4'*), 1.71 (dd, *J* 9.6, 5.9 Hz, 1H, H-*4'/4*), 1.64 (h, *J* 6.8 Hz, 1H, H-*2*), 1.34 (s, 3H, H-*9/10*), 1.31 (s, 3H, H-*10/9*), 0.92 (d, *J* 6.7 Hz, 3H, H-*1/8*), 0.85 (d, *J* 6.7 Hz, 3H, H-*8/1*); *Syn*-diastereoisomer 4.30-4.25 (m, 1H, H-*5*), 3.69 (s, 3H, H-*7*), 3.51 (ddd, *J* 9.1, 6.6, 2.3 Hz, 1H, H-*3*), 2.56 (dd, *J* 15.5, 6.5 Hz, 1H, H-*6/6'*), 2.39 (dd, *J* 15.5, 6.5 Hz, 1H, H-*6'/6*), 1.61 (h, *J* 6.5 Hz, 1H, H-*3*), 1.43 (s, 3H, H-*9/10*), 1.36 (s, 3H, H-*10/9*), 0.91

(d, *J* 6.7 Hz, 3H, H-*1/8*), 0.86 (d, *J* 6.7 Hz, 3H, H-*8/1*); ^{13}C NMR (101 MHz, $CDCl_3$) (mixture of diastereoisomers), *Anti*-diastereoisomer δ 171.8 (*C*OOR), 129.1, 128.7, 128.7, 128.3, 128.1, 127.9, 127.0, 100.9, 98.9, 77.6, 77.4, 77.2, 74.1, 71.9, 70.2, 66.4, 64.0, 51.9, 41.8, 41.0, 36.2, 33.7, 33.3, 33.2, 30.5, 24.9, 24.5, 20.1, 19.0, 18.7, 18.0, 17.9; *Syn*-diastereoisomer δ 171.9 (*C*OOR), 98.9, 77.6, 77.4, 77.2, 74.1, 66.4, 51.9, 41.8, 33.7, 33.3, 31.9, 30.5, 30.1, 23.3, 23.0, 20.1, 18.7, 18.0, 14.5, 1.4; LRMS (ESI+) *m/z* $[M + Na]^+$ 253.1 (100%); HRMS (ESI+): *m/z* calculated $C_{12}H_{22}O_4Na$ $[M+Na]^+$ 253.1416, found 253.1425.

3.3.6. Synthesis of α,β-unsaturated aldehyde

3-(Boc-amino)-1-propylcarbamate **177**



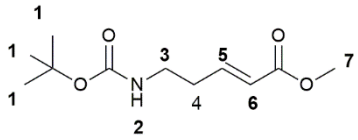
Procedure a) Cu(I)-Tempo mediated oxidation of 3-(Boc-amino)-1-propanol

A stirred solution of 3-(Boc-amino)-1-propanol (340.3 µL, 2.0 mmol) in CH_3CN (4 mL), was treated with $[Cu(CH_3CN)_4](OTf)$ (38 mg, 0.1 mmol, 0.05 equiv.), 2,2'-bipirydyl (16 mg, 0.1 mmol, 0.05 equiv.), TEMPO (16 mg, 0.1 mmol, 0.05 equiv.), and *N*-methyl imidazole (16 µL, 0.1 mmol, 0.05 equiv.). After each addition, CH_3CN (2 mL) was added to rinse the walls of the flask. The flask was equipped with a balloon of air and the mixture was stirred for 16 h at RT. The resulting solution was partioned between EtOAc (200 mL) and brine (200 mL), the aqueous layer was extracted further with EtOAc (3 x 50 mL EtOAc), and the combined organic extracts washed with brine (100 mL), dried over $MgSO_4$, filtered and solvent removed *in vacuo* to yield a pale pink oil. Purification by SiO_2 chromatography using a mixture of hexane:EtOAc (2:1) as eluent gave compound **177** as a colorless oil (340 mg, 98%).

Procedure 2) Boc-protection and subsequent hydrolysis of 1-amino-3,3-methoxypropane

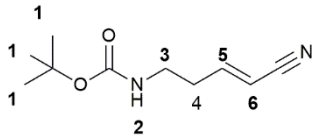
A solution of *tert*-butyloxycarbonyl (24.0 g, 0.11 mol, 1.1 equiv.) in dioxane (80 mL) was added drop-wise to a stirring solution of 1-amino-3,3-methoxypropane (16.2 mL, 0.10 mol) and Et_3N (15.3 mL, 0.11 mol, 1.1 equiv.) in dioxane (10 mL) at 0 °C over 2 h. The solution was allowed to warm to RT and stirred for a further 16 h. The resulting solution was concentrated *in vacuo* and the residual oil was dissolved in H_2O (40.0 mL), acidified with HCl (v/v 3%) to pH 1 and extracted with EtOAc (3 x 100 mL EtOAc). The combined organic extract was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residual oil was dissolved in a mixture of H_2O (12 mL) and acetic acid (48 mL) and stirred for 16 h at RT. The resulting solution was neutralised with $NaHCO_{3\,(sat)}$ and extracted with EtOAc (3 x 100 mL EtOAc). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, the solvent removed *in vacuo* to yield a colourless oil. Purification by silica gel chromatography using a mixture of hexane:EtOAc (2:1) as eluent gave compound as a colourless oil (5.7 g, 32%) R_f 0.21; IR (neat) υ_{max} 3363 (br), 2977 (s), 1686 (l), 1513 (m), 1454 (s), 1391 (m), 1365 (l), 1272 (m), 1249 (m), 1162 (l), 1040 (s), 1001 (s), 850 (m), 780 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H, H-*5*), 4.88 (br,s, 1H, H-*2*), 3.44-3.39 (q, 2H, H-*3*), 2.72-2.69 (t, *J* 5.73 Hz, 2H, H-*4*), 1.42 (s, 9H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (*C*HO), 156.0, 79.6, 76.8, 44.5, 34.2, 28.6, 28.5, 28.4; LRMS (ESI+) *m/z* $[M+Na]^+$ 196 (100%); HRMS (ESI+) *m/z* calculated $C_8H_{14}NO_3$ $[M-H]^+$ 172.0974, found 172.0977. All spectroscopic and analytical data were identical to those reported in the literature.[175]

Methyl (*E*)-5-((tert-butoxycarbonyl)amino) pent-2-enoate **179**



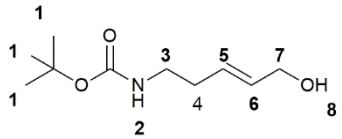
A stirred solution of 3-(Boc-amino)-1-propylcarbamate **177** (0.80 mg, 4.6 mmol) in DCM (16 mL) at 0 °C was treated with methyl (triphenylphosphoranylidene) acetate (1.58 g, 4.73 mmol, 1.03 equiv.) for 4 h. The solution was warmed to RT and stirred for a further 16 h. The resulting solution was dissolved in cold Et_2O (150 mL) and the solvent partially removed *in vacuo* until PPh_3=O precipitated. After filtration and evaporation of remaining solvent *in vacuo*, a crude colorless oil was obtained. Purification by SiO_2 chromatography using a mixture of petroleum ether:EtOAc (4:1) as eluent gave compound **179** as a colourless oil (1.31 g, 73%) R_f 0.16: IR (neat) υ_{max} 3363 (br,m), 2977 (s), 2951 (s), 1691 (l), 1658 (m), 1516 (l), 1436 (m), 1392 (s), 1365 (m), 1315 (s), 1269 (l), 1248 (l), 1216 (m), 1164 (l), 1112 (s), 1040 (m), 975 (m), 854 (s), 824 (s), 781 (s), 758 (s), 719 (s), 611 (s), 461 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dt, *J* 15.6, 7.1 Hz, 1H, H-*5*), 5.88 (dt, *J* 15.7, 1.5 Hz, 1H, H-*6*), 4.56 (br s, 1H, H-*2*), 3.73 (s, 3H, H-*7*), 3.26 (q, *J* 6.2 Hz, 2H, H-*3*), 2.40 (q, 6.6 Hz, 2H, H-*4*), 1.43 (s, 9H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1 (*C*OOR), 156.2, 146.1, 123.5, 77.8, 77.7, 77.5, 77.2, 52.0, 39.5, 33.3, 28.9, 28.8; LRMS (ESI+) *m/z* $[M+Na]^+$ 252.1 (90%); HRMS (ESI+) calculated $C_{11}H_{19}NO_4Na$ $[M+Na]^+$ 252.1212 found 252.1217. All spectroscopic and analytical data were identical to those reported in the literature.[182]

tert-Butyl (*E*)-(4-cyanobut-3-en-1-yl)carbamate **184**



To a stirred solution of 3-(Boc-amino)-1-propylcarbamate (563 mg, 3.20 mmol) in DCM (12.5 mL) at 0 °C was added (triphenylphosphoranylidene)acetonitrile (960 mg, 3.30 mmol, 1.03 equiv.). After 4 h, the solution was warmed to RT and stirred for a further 16 h. The resulting solution was dissolved in cold Et_2O (100 mL) and partially evaporated *in vacuo* until PPh_3=O precipitated. After filtration and evaporation *in vacuo* a crude colorless oil was obtained. Purification by SiO_2 chromatography using a mixture of petroleum ether:EtOAc (4:1) as eluent gave the product as a colourless oil (395 mg, 63%) R_f 0.09; IR (neat) υ_{max} 3357 (br, m), 2978 (m), 2934 (s), 2224 (m), 1687 (l), 1634 (s), 1514 (l), 1454 (s), 1392 (m), 1366 (l), 1271 (m), 1249 (l), 1164 (l), 1041 (s), 967 (m), 859 (m), 780 (m), 756 (s), 559 (s), 461 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71-6.67 (dt, *J* 16.3, 7.2 Hz, 1H, H-*5*), 5.40 (dt, *J* 16.3, 1.6 Hz, 1H, H-*6*), 4.57 (br s, 1H, H-*2*), 3.26 (q, *J* 6.4 Hz, 2H, H-*3*), 2.43 (q, *J* 6.6 Hz, 2H, H-*4*), 1.44 (s, 9H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9, 156.3, 156.2, 152.8, 152.1, 117.5, 116.1, 102.2, 101.9, 80.1, 77.8, 77.7, 77.5, 77.2, 62.4, 44.7, 39.3, 39.0, 34.5, 33.4, 28.8, 28.7, 28.5, 21.3; LRMS (ESI+) *m/z* $[M+Na]^+$ 219.1 (78%), $[M+H]^+$ 197.1 (21%); HRMS (ESI+) calculated $C_{10}H_{17}N_2O_2$ $[M]^+$ 197.1290 found 197.1304.

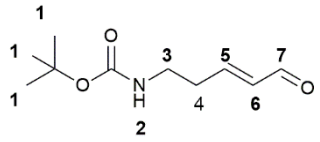
tert-Butyl (*E*)-(5-hydroxypent-3-en-1-yl)carbamate **183**



A stirred solution of methyl (*E*)-5-((*tert*-butoxycarbonyl)amino)-pent-2-enoate (464 mg, 2.02 mmol) in THF (22 mL) under Ar at -78 °C was treated drop-wise with DIBAL-H (1M solution in toluene, 6.06 mL, 6.06 mmol, 3.0 equiv.). After 2 h, the reaction was quenched

by the addition of saturated aqueous solution of NH_4Cl (60 mL), allowed to warm to RT and stirred for a further 1 h.The resulting solution was extracted with EtOAc (3 x 50 mL EtOAc), the combined organic phase was dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* yielding to a crude colourless oil. Purification by SiO_2 chromatography using a mixture of hexane:EtOAc (4:1) as eluent gave the product as a colorless oil (320 mg, 79%). IR (neat) υ_{max} 3346 (br, l), 2977 (m), 2932 (m), 1685 (l), 1518 9l), 1453 (s), 1392 (m), 1365 (m), 1275 (m), 1249 (m), 1166 (l), 1087 (s), 1009 (m), 968 (m), 865 (s), 780 (s), 757 (s), 607 (s), 463 (s), 432 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75-5.60 (m, 2H, H-*7*), 4.56 (br s, 1H, H-*2*), 4.10 (dd, *J* 5.2, 0.9, 2H), 3.18 (q, *J* 6.1, 2H, H-*3*), 2.23 (q, *J* 6.3, 2H, H-*4*), 1.44 (s, 9H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.0, 77.8, 77.5, 77.2, 64.0 ($\underline{C}H_2OH$), 33.3, 28.9; LRMS (ESI+) *m/z* $[M+Na]^+$ 224.1 (100%); HRMS (ESI+) calculated $C_{10}H_{19}NO_3Na$ $[M+Na]^+$ 224.1263 found 224.1264. All spectroscopic and analytical data were identical to those reported in the literature.[221]

<u>*tert*-Butyl (*E*)-(5-oxopent-3-en-1-yl)carbamate **173**</u>

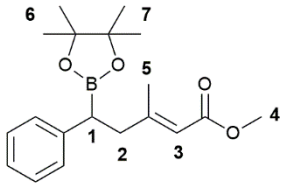


To a stirred solution of *tert*-butyl (*E*)-(5-hydroxypent-3-en-1-yl)carbamate (624 mg, 3.10 mmol) in CH_3CN (7 mL) was added $[Cu(CH_3CN)_4](OTf)$ (59 mg, 0.15 mmol, 0.05 equiv.), 2,2'-bipirydyl (24.8 mg, 0.15 mmol, 0.05 equiv.), TEMPO (24.5 mg, 0.15 mmol, 0.05 equiv.) and *N*-methyl imidazole (24.5 µL, 0.15 mmol, 0.05 equiv.). After each addition, CH_3CN (3.5 mL) was added to rinse the walls of the flask. The flask was equipped with a balloon of air and the mixture was stirred at RT. After 16 h, the resulting solution was partioned between EtOAc (155 mL) and brine (155 mL), the aqueous layer was extracted further with EtOAc (3 x 50 mL EtOAc), the combined organic extract was washed with brine (75.0 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield a pale pink

oil. Purification by SiO_2 chromatography using a mixture of hexane:EtOAc (2:1) as eluent gave the product as a colorless oil (493 mg, 80%): IR (neat) υ_{max}; 3356 (br, m), 2977 (br, m), 1683 (l), 1516 (m), 1453 (s), 1391 (s), 1365 (m), 1249 (l), 1165 (l), 1092 (m), 1012 (s), 971 (m), 859 (s), 780 (s), 556 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* 7.8 Hz, 1H, H-*7*), 6.82 (dt, *J* 15.7, 6.9 Hz, 1H, H-*5*), 6.16 (ddt, *J* 15.7, 7.8, 1.5 Hz, 1H, H-*6*), 4.62 (br s, 1H, H-*2*), 3.33 (q, *J* 6.5 Hz, 2H, H-*3*), 2.54 (qd, *J* 6.8, 1.5 Hz, 2H, H-*4*), 1.43 (s, 9H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5 (*C*HO), 155.6, 154.4, 134.3, 79.5, 77.2, 76.8, 76.5, 38.6, 33.4, 28.2, 27.9; LRMS (ESI+) *m/z* $[M+Na]^+$ 222.1 (40%); HRMS (ESI+) calculated $C_{10}H_{17}NO_3Na$ $[M+Na]^+$ 222.1106 found 222.1115.

3.3.7. Synthesis of β-boryl unsaturated ester

Methyl (*E*)-3-methyl-5-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)pent-2-enoate **236**

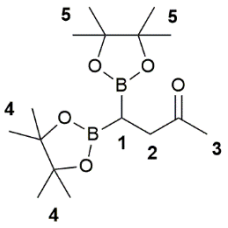


To a stirred suspension of CuCl (12.0 mg, 0.12 mmol, 3 mol%), PPh_3 **P5** (64.0 mg, 0.24 mmol, 6 mol%), NaO^{t}Bu (34.0 mg, 0.36 mmol, 9 mol%) and B_2pin_2 **14** (2.0 g, 4.0 mmol, 1.0 equiv.) in THF (8 mL) under Ar was added 4-phenyl-3-butyn-2-one (436.8 µL, 4.0 mmol) followed after 5 min, by MeOH (400.0 µL, 10.0 mmol, 2.5 equiv.).The mixture was stirred for 16 h at RT and then partioned between EtOAc (350 mL) and brine (35 mL). The aqueous layer was extracted further with EtOAc (3 x 50 mL EtOAc), the combined organic extract was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*, yielding to the crude β-boryl ketone as a yellow oil. An aliquot of crude β-boryl ketone in THF (8.0 mL, 2.0 mmol) was treated with methyl(triphenylphosphoranylidene)acetate **109** (1.0 g, 3.0 mmol, 1.5 equiv). The reaction mixture was stirred for 5 h at RT. The resulting solution was

partitioned between EtOAc (200 mL) and brine (10 mL), the aqueous layer was extracted further with EtOAc (3 x 20 mL EtOAc). The combined organic extract was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by SiO_2 chromatography using a mixture of hexane:EtOAc (2:1) as eluent gave the product as a colorless oil (330.0 mg, 37%): IR (neat) υ_{max} 2979 (br, m), 1721 (l), 1451 (l), 1372 (m), 1331 (m), 1272 (s), 1218 (m), 1145 (l), 1009 (s), 981 (l), 911 (l), 850 (l), 729 (l), 698 (l), 672 (l), 648 (s), 577 (s), 542 (s), 387 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 5H, *Ph*), 5.67 (q, *J* 1.2 Hz, 1H, H-*3*), 3.65 (s, 3H, H-*4*), 2.77-2.71 (m, 1H, H-*2/2'*), 2.66-2.60 (m, 1H, H-*2'/2*), 2.52-2.47 (m, 1H, H-*1*), 2.16 (s, 3H, H-*5*), 1.19 (s, 6H, H-*6/7*), 1.16 (s, 6H, H-*7/6*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.0, 128.6, 128.6, 127.1, 83.1, 77.2, 76.8, 76.5, 24.4; LRMS (ESI+) *m/z* $[M+Na]^+$ 353.2 (100%); HRMS (ESI+) calculated $C_{19}H_{28}BO_4$ $[M+H]^+$ 330.2117 found 330.2116.

3.3.8. Synthesis of geminal *bis*(boronate) compounds

4,4-*Bis*(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one **228**



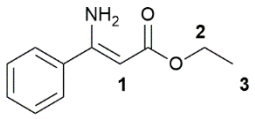
To a stirred suspension of CuCl (1.5 mg, 0.015 mmol, 3 mol%), PPh_3 (8 mg, 0.03 mmol, 6 mol%) and NaO^{t}Bu (4.32 mg, 0.045 mmol, 9 mol%) in THF (0.25 mL) under Ar, was added B_2pin_2 **14** (250 mg, 1.0 mmol, 2.0 equiv.) after 5 mins, followed by THF (1.75 mL) for rinsing. The reaction mixture was stirred at RT for 10 mins, cooled to 0 ºC, followed by the addition of 3-butyn-2-one (40 µL, 0.5 mmol) and MeOH (250 µL, 1.25 mmol, 2.5 equiv.). The reaction mixture was then allowed to warm up to RT and stirred for 3 days. The crude mixture was filtered through Celite, and the solvent removed *in vacuo* leading to a crude yellow oil. Purification by SiO_2 chromatography using a mixture of petroleum ether:EtOAc

(2:1) as eluent gave the product as a colorless oil (25.0 mg, 15%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (d, *J* 7.8 Hz, 2H, H-*2*), 2.10 (s, 3H, H-*3*), 1.23 (s, 12H, H-*4/5*), 1.21 (s, 12H, H-*5/4*), 0.97 (t, *J* 8.1 Hz, 1H, H-*1*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (*C*OR), 83.6, 77.8, 77.5, 77.2, 41.1, 29.6, 25.2, 25.0; ^{11}B NMR (128 MHz, $CDCl_3$): δ 33.8 ppm; LRMS (ESI+) *m/z* $[M+Na]^+$ 374.4 (100%); HRMS (ESI+) calculated $C_{16}H_{30}{}^{10}B_2O_5$ $[M+H]^+$ 323.2430 found 323.2442. All spectroscopic and analytical data were identical to those reported in the literature.[202]

3.3.9. Synthesis of β-enamino esters

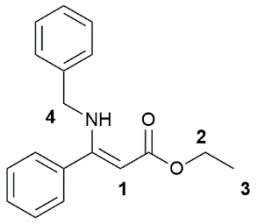
To a stirred solution of ethyl benzoylacetate (173.0 µL, 1.0 mmol) and tetraethyl orthosilicate (447.0 µL, 2.0 mmol, 2.0 equiv.) in absolute ethanol (5 mL) was added ammonium acetate (308.3 mg, 4.0 mmol, 4.0 equiv.) or benzylamine (262.4 µL, 2.4 equiv., 2.4 equiv.) and acetic acid (137.4 µL, 2.4 mmol, 2.4 equiv.). The reaction mixture was heated to reflux for 24 h. After cooling, the resulting solution was concentrated *in vacuo* to give the crude compound as yellow oil.

(*Z*)-3-Amino-3-phenyl-acrylic acid ethyl ester **240**



Compound was obtained following the general procedure for the synthesis of β-enamino esters to give a colorless oil (371 mg, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.37 (m, 5H, *Ph*), 4.95 (s, 1H, H-*1*), 4.19 – 4.13 (q, *J* 7.1 Hz, 2H, H-*2*), 1.29 (t, *J* 7.1 Hz, 3H, H-*3*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.1 (*C*OOR), 160.5, 137.7, 130.2, 128.5, 126.0, 85.0, 58.8 (H_3C-*C*H_2-O), 14.6 (H_3*C*-CH_2-O). All spectroscopic and analytical properties were identical to those reported in the literature.[212]

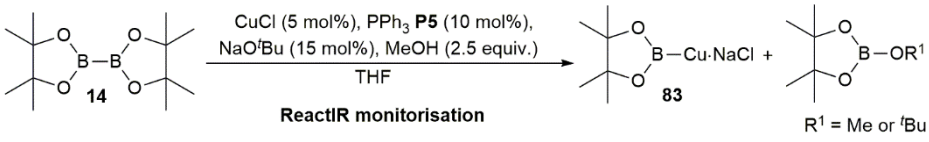
(*Z*)-Ethyl (*Z*)-3-(benzylamino)-3-phenylacrylate **241**



Compound was obtained following the general procedure for the synthesis of β-enamino esters to give a colorless solid (460 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.16 (m, 10H, *Ph*), 4.67 (s, 1H, H-*1*), 4.14 (q, *J* 7.1 Hz, 2H, H-*2*), 3.85 (m, 2H, H-*4*), 1.25 (t, *J* 7.1 Hz, 3H, H-*3*). All spectroscopic and analytical properties were identical to those reported in the literature.[212]

3.4. *In situ* IR spectroscopy monitored experimental procedures

3.4.1. Experimental procedure for the mechanistic study on the formation of nucleophilic boryl moieties under organometallic catalysis (reported in Section 2.1.3)



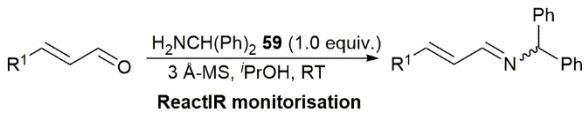
A stirred solution of CuCl (495.2 mg, 0.5 mmol, 5 mol%), PPh_3 (262.2 mg, 1.0 mmol, 10 mol%) and B_2pin_2 **14** (2.5394 g, 10.0 mmol, 1.0 equiv.) in THF (40.0 mL) under Ar was monitored by *in situ* IR spectroscopy. Once the B-O stretch signal (υ 1127 cm^{-1}) achieved maximum intensity (5 minutes after the addition), MeOH (1.012 mL, 25 mmol, 2.5 equiv.) was added. After 1.5 h, NaO^{t}Bu (144.1 mg, 1.5 mmol, 15 mol%) was added. The reaction mixture was stirred at for further 19 h at RT.

3.4.2. Experimental procedure for the mechanistic study on the formation of nucleophilic boryl moieties under organocatalytic conditions (reported in Section 2.1.3)

A stirred solution of B_2pin_2 **14** (2.5394 g, 10.0 mmol, 1.0 equiv.) in THF (40.0 mL) under Ar was monitored by *in situ* IR spectroscopy. Once the B-O stretch signal (υ 1127 cm^{-1}) achieved maximum intensity (5 minutes after the addition), MeOH (1.012 mL, 25 mmol, 2.5 equiv.) was added. After 3 h, NaO^{t}Bu (144.1 mg, 1.5 mmol, 15 mol%) was added sequentially (4 x NaO^{t}Bu). The reaction mixture was stirred at for further 5.5 h at RT.

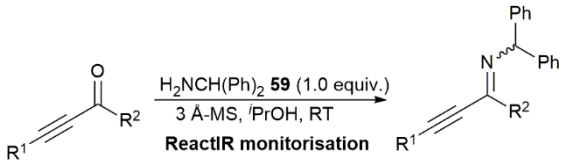
3.4.3. General procedure for the monitoring of the imine formation

Procedure a) Synthesis of α,β-unsaturated aldimines (reported in Section 2.2.4)



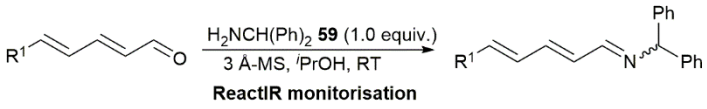
A stirred mixture of ^{i}PrOH (2.0 mL), 3 Å-MS (0.5 g) and α,β-unsaturated aldehyde (0.5 mmol) was monitored by *in situ* IR spectroscopy. When C=O peak (typically υ 1740-1720 cm^{-1}) reached its maximum intensity, benzhydrylamine **59** (0.5 mmol, 1.0 equiv.) was added. The completion of the reaction was observed by the signal corresponding to the C=N functionality (υ 1690-1640 cm^{-1}) was maximal. For the cases in which the $C_β$-substituent was an aryl group, a white solid precipitate was observed. An aliquot (ca. 1.0 mL, 0.025 mmol) of crude reaction mixture was filtered through a cotton wool, followed by the addition of toluene (2.0 mL). The resulting mixture was slowly evaporated yielding to crystals suitable for X-ray diffraction analysis.

Procedure b) Synthesis of α,β-acetylenic ketimines (reported in Section 2.5.3)



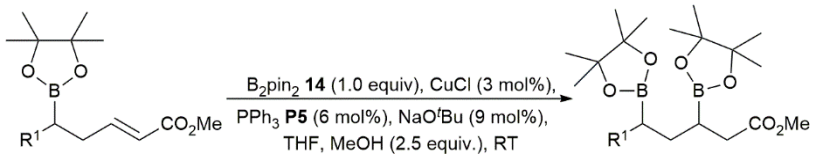
A stirred mixture of ^{i}PrOH (2.0 mL), 3 Å-MS (0.5 g) and α,β-acetylenic ketone (0.5 mmol) was monitored by *in situ* IR spectroscopy. When C=O peak (typically υ 1740-1720 cm^{-1}) reached its maximum intensity, benzhydrylamine **59** (0.5 mmol, 1.0 equiv.) was added. The completion of the reaction was observed by the signal corresponding to the C=N functionality (υ 1690-1640 cm^{-1}) was maximal.

Procedure c) Synthesis of diene imines (reported in Section 2.2.6)



A stirred mixture of ^{i}PrOH (10.0 mL), 3 Å-MS (2.5 g) and dienal (2.5 mmol) was monitored by *in situ* IR spectroscopy. When C=O peak (typically υ 1740-1720 cm^{-1}) reached its maximum intensity, benzhydrylamine **59** (0.5 mmol, 1.0 equiv.) was added. The completion of the reaction was observed by the signal corresponding to the C=N functionality (υ 1690-1640 cm^{-1}) was maximal.

3.4.4. General procedure for the optimization on the 2nd β-borylation reaction on homoallylic boronate carboxylate esters (reported in Section 2.3.2)



Procedure a) Determination of the reaction time

A stirred solution of CuCl (2.96 mg, 0.03 mmol, 3 mol%), PPh_3 (15.72 mg, 0.06 mmol, 6 mol%), NaO^tBu (8.64 mg, 0.09 mmol, 9 mol%) and B_2pin_2 **14** (253.7 mg, 1.0 mmol, 1.0 equiv.) in THF (2.0 mL) under Ar was monitored by *in situ* IR spectroscopy. Once the B-O stretch signal (υ 1127 cm^{-1}) achieved maximum intensity (5 minutes after the addition), an aliquot of homoallylic boronate ester synthesised following the general procedure reported in Section 3.2.3 (4.0 mL, 1.0 mmol) was added into the reaction mixture, the mixture stirred at RT. After 5 mins, (102.0 μL, 2.5 mmol, 2.5 equiv.) was added and the reaction mixture was stirred at RT following the change on the C=O stretch peak which varied from 1720 cm^{-1} (CH_2=CH-$COOR^1$) to 1734 cm^{-1} (CH_2-CH_2-$COOR^1$).

Procedure b) Study of the effect of the temperature in the reaction rate

A stirred solution of CuCl (2.96 mg, 0.03 mmol, 3 mol%), PPh_3 (15.72 mg, 0.06 mmol, 6 mol%), NaO^tBu (8.64 mg, 0.09 mmol, 9 mol%) and B_2pin_2 **14** (253.7 mg, 1.0 mmol, 1.0 equiv.) in THF (2.0 mL) under Ar was monitored by *in situ* IR spectroscopy. Once the B-O stretch signal (υ 1127 cm^{-1}) achieved maximum intensity (5 minutes after the addition), an aliquot of homoallylic boronate ester synthesised following the general procedure reported in Section 3.2.3 (4.0 mL, 1.0 mmol) was added into the reaction mixture, the mixture stirred at 0 ºC (low temperature) or 50 ºC (high temperature). After 5 mins, (102.0 μL, 2.5 mmol, 2.5 equiv.) was added and the reaction mixture was stirred at 0 ºC (low temperature) or 50 ºC (high temperature) following the change on the C=O stretch peak which varied from 1720 cm^{-1} (CH_2=CH-$COOR^1$) to 1734 cm^{-1} (CH_2-CH_2-$COOR^1$).

Procedure c) Study of the effect of the steric hindrance of the boryl-copper-ligand system in the reaction rate

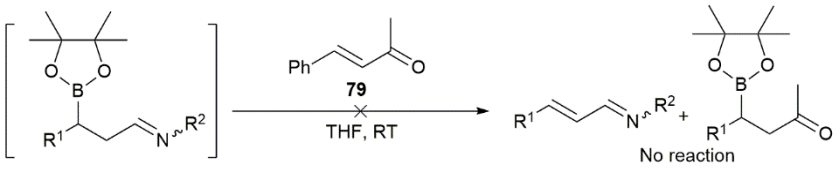
A stirred solution of CuCl (2.96 mg, 0.03 mmol, 3 mol%), (*R*),(*S*)-Josiphos **P7** (19.4 mg, 0.03 mmol, 3 mol%), NaO^{t}Bu (8.64 mg, 0.09 mmol, 9 mol%) and B_2pin_2 **14** (253.7 mg, 1.0 mmol, 1.0 equiv.) in THF (2.0 mL) under Ar was monitored by *in situ* IR spectroscopy. Once the B-O stretch signal (υ 1127 cm^{-1}) achieved maximum intensity (5 minutes after the addition), an aliquot of homoallylic boronate ester synthesised following the general procedure reported in Section 3.2.3 (4.0 mL, 1.0 mmol) was added into the reaction mixture, the mixture stirred at RT. After 5 mins, (102.0 µL, 2.5 mmol, 2.5 equiv.) was added and the reaction mixture was stirred RT following the change on the C=O stretch peak which varied from 1720 cm^{-1} (CH_2=CH-COOR^1) to 1734 cm^{-1} (CH_2-CH_2-COOR^1).

3.5. NMR spectroscopy monitored experimental procedures

3.5.1. Experimental procedures for the mechanistic studies on the de-borylation process

(reported in Section 2.1.3)

Test of the reactive boryl unit in the β-boryl aldimine with benzylideneacetone



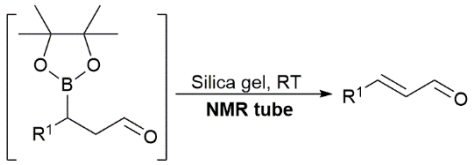
A stirred solution of crude *in situ* generated β-boryl aldimine in THF (2 mL, 0.5 mmol), synthesised following general procedure reported in Section 3.2.1, benzylideneacetone **75** (0.5 mmol, 1.0 equiv.), was added and the mixture was stirred at RT for 24 h. The crude mixture was dried *in vacuo*, the solid residue was dissolve in $CDCl_3$ and the sample was analysed by ^{1}H NMR spectroscopy after 4, 7 and 24 h.

Mechanistic studies on the β-boryl aldehyde

1) Protonation (deuteration) at β-position triggers boryl loss?

A crude sample of β-boryl aldehyde was added to an NMR tube (Norell® Standard Series™ 5 mm x 178 mm NMR tubes) and some drops of D_2O were added, ^1H NMR spectrum were subsequently recorded every 10 minutes over 1 h with intermittent shaking of the NMR tube in order to aid mixing.

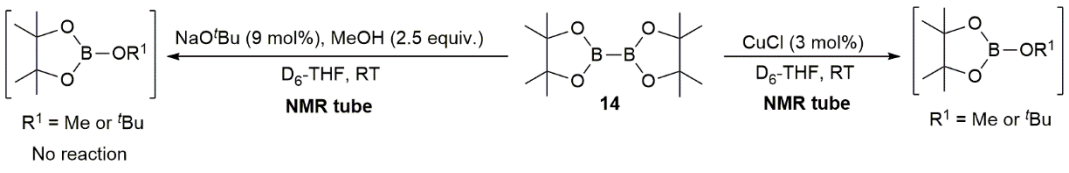
2) Effect of silica gel in the de-borylation process?



A crude sample of β-boryl aldehyde was added to an NMR tube (Norell® Standard Series™ 5 mm x 178 mm NMR tubes) and silica gel (ca. 1 mg) was added, ^1H NMR spectrum were subsequently recorded every 10 minutes over 1 h with intermittent shaking of the NMR tube in order to aid mixing.

3.5.2. Procedure for the mechanistic studies on the catalytic activation of the diborane reagent (reported in Section 2.1.3)

NMR study on the formation of the nucleophilic boryl unit



In an NMR tube (Norell® Standard Series™ 5 mm x 178 mm NMR tubes) containing D_6-THF (0.7 mL) was added B_2pin_2 **14** (63.5 mg, 0.25 mmol) followed by the addition of MeO^{t}Bu (2.2 mg, 0.022 mmol, 9 mol%) and MeOH (25.3 µL, 0.625 mmol, 2.5 equiv.). After 5 minutes, the first ^{11}B NMR spectrum was recorded. Then CuCl (0.75 mg, 0.075 mmol, 3 mol%) was added and ^{11}B NMR spectra were sequentially recorded over time with intermittent shaking of the NMR tube in order to aid mixing.

NMR study on the role of the phosphine ligands in the organocatalytic cycle

To an NMR tube (Norell® Standard Series™ 5 mm x 178 mm NMR tubes) containing D_8-Toluene (0.7 mL) an equimolar mixture of methacrolein (20.6 µL, 0.25 mmol), isopropyl pinacol borate **85** (50.5 µL, 0.25 mmol, 1.0 equiv.) was added. After 5 minutes, the ^{1}H, ^{11}B and ^{13}C NMR spectra was recorded. Then PPh_3 **P5** (65.5 mg, 0.25 mmol, 1.0 equiv.) was added followed by the recording of the ^{1}H, ^{11}B, ^{13}C and ^{31}P NMR spectra were recorded.

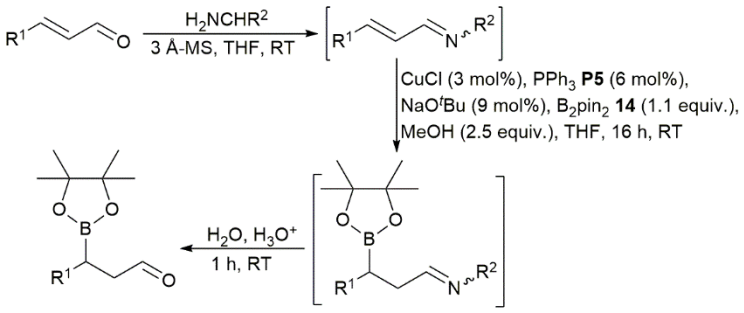
3.5.3. Procedure for the mechanistic studies on the de-borylation process on the aryl-substituted diborylated esters (reported in Section 2.3.4.1)

A stirred solution of β-boryl aldimine derived from cinnamaldehyde was synthesised following the general procedure reported in Section 3.2.1 (0.25 mmol) using D_6-THF (0.7 mL) was added an aliquot of α,β-unsaturated aldimine derived from crotonaldehyde in D_6-THF, synthesised following the general procedure for the synthesis of aldimines reported in Section 3.2.1 (1.0 mL, 0.25 mmol), reaction mixture was stirred at RT. The ^{1}H and ^{11}B NMR spectrum were recorded after 6 h and 3 days. After 3 days, the resulting reaction mixture was subjected to the hydrolysis/Wittig reactions sequence following the general experimental procedute reported in Section 3.2.2.

3.6. Other experimental procedures (no isolated products)

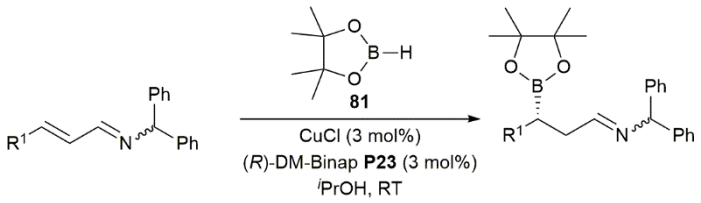
3.6.1. General procedure for the Cu(I)-phosphine mediated methodology for the β-borylation reaction of α,β-unsaturated aldehydes *via* amine-derived imine intermediates

(reported in Section 2.1.2)



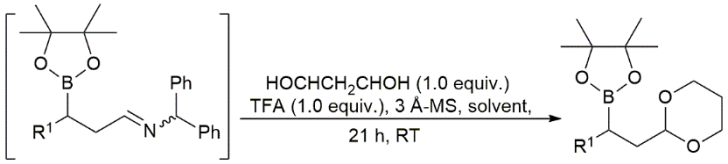
A stirred solution of THF (8 mL) with oven-dried 3 Å-MS (2.0 g) was added an α,β-unsaturated aldehyde (0.5 mmol) and benzhydylamine (86.3 µL, 0.5 mmol, 1.0 equiv.) and the reaction mixture stirred at RT. After 6h, an aliquot of the *in situ* formed α,β-unsaturated imine (2.0 mL, 0.5 mmol) was transferred to a Schlenk-tube (under Ar) containing CuCl (1.5 mg, 0.015 mmol, 3 mol%), PPh_3 **P5** (6.3 mg, 0.015 mmol, 6 mol%) or (*R*)-DM-Binap **P23** (11.0 mg, 0.015 mmol, 3 mol%), NaO^tBu (4.3 mg, 0.045 mmol, 9 mol%) and B_2pin_2 **14** (140 mg, 0.55 mmol, 1.1 equiv.). After 5 min, MeOH (51.0 µL, 1.25 mmol, 2.5 equiv.) was added to the solution and the reaction was stirred for 16 h at RT. The solution containing the β-boryl aldimine was transferred into a round bottom flask, then H_2O (5.0 mL) was added into the solution. The reaction mixture was stirred during 1 h at room temperature. The resulting solution was partitioned between EtOAc (60 mL) and brine (10 mL). The organic layer was washed with HCl (3 x 10 mL, v/v 5%) and neutralised with H_2O (3 × 10 mL). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield a crude product.

3.6.2. General procedure for the Copper(I)-phosphine catalysed β-borylation of α,β-unsaturated aldimines with pinacolborane (reported in Section 2.1.3)



A stirred solution of ^{i}PrOH (12 mL) with oven-dried 3 Å-MS (3.0 g) was added an α,β-unsaturated aldehyde (3.0 mmol) and benzhydylamine (518.0 µL, 3.0 mmol, 1.0 equiv.) and the reaction mixture stirred at RT. After 3h, an aliquot of the *in situ* formed α,β-unsaturated imine (8.0 mL, 2.0 mmol) was transferred to a Schlenk-tube (under Ar) containing CuCl (6.0 mg, 0.06 mmol, 3 mol%), (*R*)-DM-Binap (44.0 mg, 0.12 mmol, 6 mol%), NaO^{t}Bu (4.3 mg, 0.045 mmol, 9 mol%) and H-Bpin (290.0 µL, 2.2 mmol, 1.1 equiv.), the reaction was stirred for 16 h at RT.

3.6.3. General procedure for the acetal protection of β-boryl aldimines (reported in Section 2.1.4)



A stirred solution of β-boryl aldimine (0.5 mmol) in toluene (2 mL) with oven-dried 3 Å M.S. (0.5 g), pinacol (60.0 mg, 0.5 mmol, 1.0 equiv.) and TFA (38.3 µL, 0.5 mmol, 1.0 equiv.) were added. The reaction mixture was stirred at RT during 21 h.

3.6.4. General procedure for the optimised large scale synthesis of homoallylic boronate carboxylate esters (reported in Section 2.2.5)

To a stirred solution of methyl (triphenylphosphoranylidene)acetate (2.5 g, 7.5 mmol, 1.5 equiv.) in THF (20 mL), after 5 mins $CuSO_4$ (1.6 g, 10.0 mmol, 2.0 equiv.) and H_2O (0.9

mL, 50.0 mmol, 10.0 equiv.) were added. An aliquot of β-boryl aldimine (5.0 mmol) synthesised following the general procedure reported in Section 3.2.1 dissolved in THF (20.0 mL), was added by syringe pump (6.0 mL/h) over 4 h. The reaction mixture was stirred at RT for an additional hour. The resulting solution was partioned between EtOAc (350 mL) and brine (35 mL). The aqueous layer was extracted further with EtOAc (3 x 50 mL EtOAc). The combined organic phases were separated, washed with a saturated solution of $CuSO_4$ (3 x 35 mL $CuSO_4$), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The reaction crude was purified by a SiO_2 chromatography using a mixture of hexane:methanol (20:1 and 10:1) as eluent to give pure homoallylic boronate ester.

3.6.5. General procedure for the application of the synthesis of homoallylic boronate carboxylate esters into dienal systems (reported in Section 2.2.6)

To a round bottom flask containing THF (10 mL) and oven-dried 3 Å-MS (2.5 g) was added a dienal (2.5 mmol) and benzhydylamine (431.3 µL, 2.5 mmol, 1.0 equiv.) and the reaction mixture stirred at RT. After 4 h, an aliquot of the *in situ* formed α,β-unsaturated imine (8.0 mL, 2.0 mmol) was transferred to a Schlenk-tube (under Ar) containing CuCl (1.50 mg, 0.015 mmol, 3 mol%), PPh_3 **P5** (6.3 mg, 0.015 mmol, 6 mol%), NaO^tBu (4.3 mg, 0.045 mmol, 9 mol%) and B_2pin_2 **14** (127.3 mg, 0.5 mmol, 1.1 equiv.). After 5 min, MeOH (51.0 µL, 1.25 mmol, 2.5 equiv.) was added to the solution, after 5 minutes stirring the mixture, MeOH (40 µL, 2.5 equiv.) was added. After 16 h, the resulting β-boryl aldimine was transferred to a round bottom flask, then methyl(triphenylphosphoranylidene)acetate **109** (2.0 g, 1.5 equiv) was added, and after 5 minutes $CuSO_4$ (1.3 g, 2.0 g) was added along with H_2O (0.7 mL, 10.0 equiv). The mixture was stirred for 5 h at RT. The resulting solution was partioned between EtOAc (250 mL) and brine (25 mL). The aqueous layer was extracted further with EtOAc (3 x 25 mL EtOAc). The combined organic phase was separated and washed with $CuSO_{4\,(sat.)}$ (3 x 25 mL $CuSO_4$), and dried over $MgSO_4$. After filtration, the organic layer was removed *in vacuo.*

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Appendix: Crystallographic data

All crystallographic data was acquired by Dr. Andrei S. Batsanov at Durham University (2013-2016).

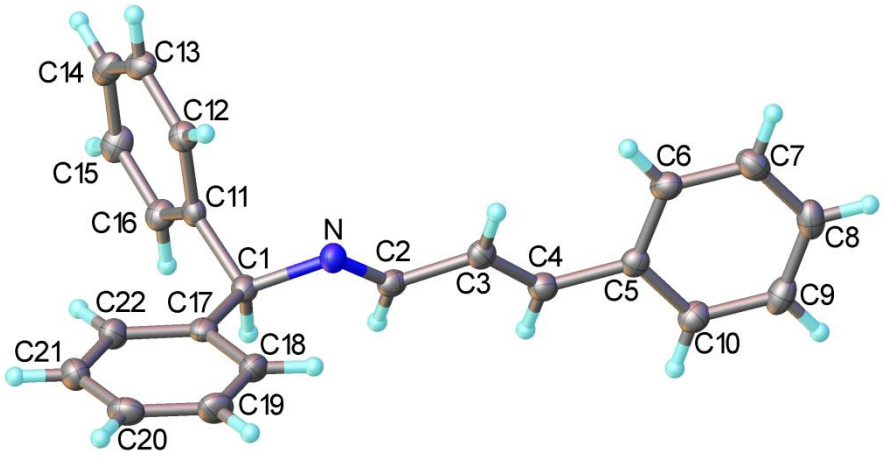

Figure A1 X-ray molecular structure of compound **69** at 120 K. Here and below, atomic displacement ellipsoids are drawn at 50% probability level.

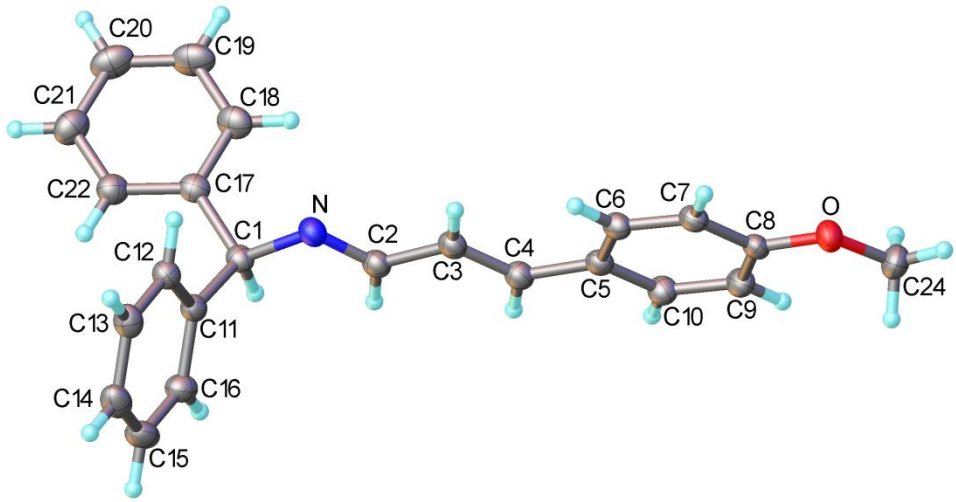

Figure A2 X-ray molecular structure of compound **75** at 120 K.

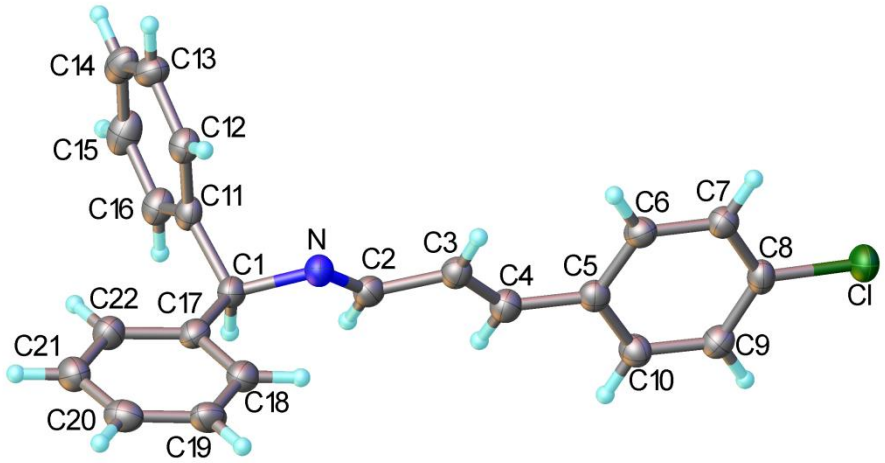

Figure A3 X-ray molecular structure of compound **131** at 120 K.

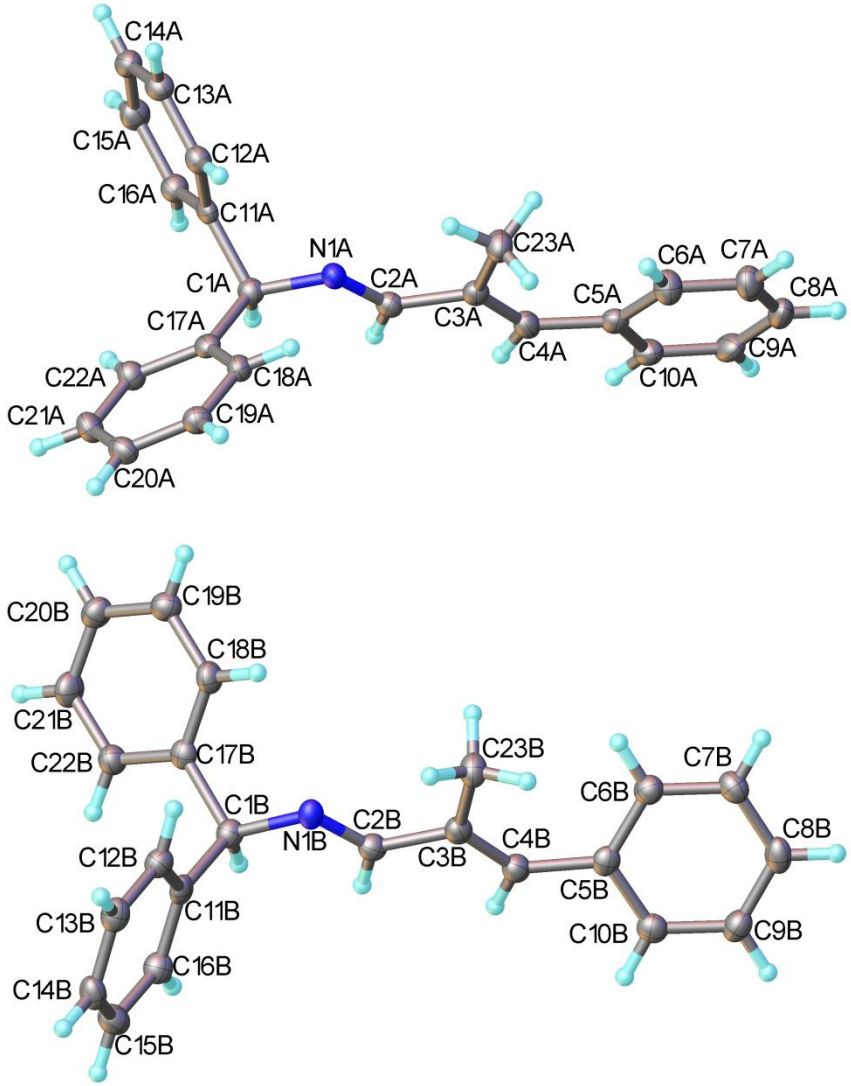

Figure A4 Two independent molecules in the crystal structure of compound **132** at 120 K.

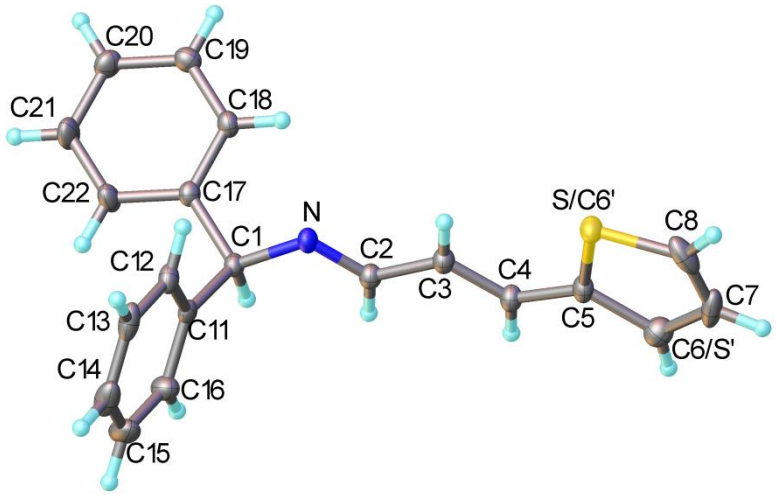

Figure A5 X-ray molecular structure of **133** at 120 K; the thiophene ring is disordered between two opposite orientations in 4:1 ratio (minor atom positions are primed)

Experimental

X-ray quality single crystals of **69**, **75**, **131-133** were grown by slow evaporation of toluene solutions. Experiments for **69** and **75** were carried out on an Agilent Technologies Xcalibur κ-diffractometer with a Sapphire3 CCD area detector, using an Enhance (Mo) X-ray source with a graphite monochromator; for **131-133** on a Bruker D8 Venture 3-circle diffractometer with a PHOTON 100 CMOS area detector, using Incoatec IμS Cu- or Mo-microsources (microfocus sealed X-ray tubes) with focusing mirrors. Crystals were cooled to 120 K using Cryostream 700 (Oxford Cryosystems) open-flow N_2 gas cryostats. The structures were solved by direct methods using SHELXS software,[X1] and refined by full-matrix least squares using SHELXL[X2] and OLEX2 software.[X3]

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Table A1 Crystal data and experimental details.

Compound	**69**	**75**	**131**	**132**	**133**
CCDC	1040392	1040393	1040394	1040395	1040594
Formula	$C_{22}H_{19}N$	$C_{23}H_{21}NO$	$C_{22}H_{18}ClN$	$C_{23}H_{21}N$	$C_{20}H_{17}NS$
$D_{calc.}$/ g cm^{-3}	1.192	1.216	1.297	1.199	1.239
μ/mm^{-1}	0.069	0.074	1.977	0.069	0.195
Formula Weight	297.38	327.41	331.82	311.41	303.40
Colour	colourless	colourless	colourless	colourless	orange
Shape	prism	lathe	prism	prism	irregular
Size/mm^3	0.40×0.10×0.08	0.77×0.27×0.10	0.70×0.07×0.04	0.22×0.18×0.11	0.52×0.36×0.17
T/K	120	120	120	120	120
Crystal System	monoclinic	triclinic	triclinic	triclinic	triclinic
Space Group	$P2_1/c$ (no. 14)	$P\bar{1}$ (no. 2)	$P\bar{1}$ (no. 2)	$P\bar{1}$ (no. 2)	$P\bar{1}$ (no. 2)
a/Å	5.4941(2)	6.1174(4)	5.6806(5)	6.1195(5)	6.04042(15)
b/Å	24.8448(10)	11.8050(4)	12.4099(9)	8.1503(7)	11.6602(3)
c/Å	12.4135(5)	12.9211(4)	12.5191(9)	34.905(3)	12.1628(2)
α/°	90	89.082(3)	89.497(4)	93.937(3)	99.352(2)
β/°	102.044(4)	80.227(5)	79.611(4)	93.167(3)	98.908(2)
γ/°	90	76.501(5)	78.354(4)	95.383(3)	101.371(2)
V/Å^3	1657.15(12)	893.89(8)	849.85(12)	1725.8(3)	813.07(3)
Z	4	2	2	4	2
Z'	1	1	1	2	1
Wavelength/Å	0.71073	0.71073	1.54184	0.71073	0.71073
Radiation type	Mo*K*□	Mo*K*□	Cu*K*□	Mo*K*□	Mo*K*□
θ_{max}/°	27.864	32.306	73.674	24.998	30.352
Measured Refl.	11019	29862	5801	18314	12662
Independent Refl.	3426	5955	3006	6066	4269
Reflections with *I*>2(*I*)	2917	4775	2399	4453	3829
R_{int}	0.029	0.046	0.062	0.077	0.029
Parameters	208	227	217	437	199
Δρ max/min, e/Å^3	0.22, -0.20	0.41, -0.22	0.48, -0.47	0.41, -0.26	0.48, -0.33

Goodness of fit	1.059	1.020	1.026	1.016	1.055
wR_2 (all data)	0.0961	0.1452	0.2178	0.1784	0.1085
wR_2 [I>2(I)]	0.0903	0.1310	0.2033	0.1598	0.1033
R_1 (all data)	0.0495	0.0662	0.0918	0.0868	0.0468
R_1 [I>2(I)]	0.0397	0.0512	0.0788	0.0644	0.0415