Development of Electron-Deficient Alkene Asymmetric Hydroboration Methodologies

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Development of Electron-Deficient Alkene Asymmetric Hydroboration Methodologies

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

MASTER OF SCIENCE

At the Department of Chemistry, Durham University, UK

Submitted by

Jing-Biao Chen

Under the supervision of

Professor Andrew Whiting

2017－2018

Declaration

The experimental work and review writing of this thesis was accomplished by Jing-Biao Chen (author) under the supervision of Prof. Andrew Whiting. The research was carried out between October 2017 and August 2018 in the Department of Chemistry, Durham University (United Kingdom). The description and experimental data in this thesis has not been submitted for another degree at any university. Unless specially indicated, the research mentioned in this thesis is conducted by the author under Prof. Andrew Whiting's supervision.

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Jing-Biao Chen

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2018

Abstract

In this thesis, the investigation of reaction optimisations and enantioselectivity explorations for the novel total synthesis route of cholesterol-lowering drug atorvastatin was demonstrated.

Firstly, an updated literature review selected the key achievements in copper-catalysed electron deficient alkene enantioselective hydroboration methodologies, mechanism investigations and synthetic applications over recent years. Based on the previous investigations, a copper-catalysed enantioselective borylation method was employed in the synthesis route to atorvastatin utilising the hydroboration of electron-deficient alkenes to successfully constructed chiral *cis*-1,3-diol as the key functional moiety of atorvastatin. A streamlined, one-pot synthetic process generating an intermediate homoallylic boronate carboxylate ester was successfully demonstrated for the total synthesis of atorvastatin. Moreover, the enantioselective excess determination of an intermediate homoallylic boronate carboxylate ester was explored. The separation conditions of the enantiomers were also optimised using HPLC analysis.

Contents

Publication list

- ***'Development and application of dual asymmetric borylation strategies: total synthesis of atorvastatin'*** Santiago, A. P.; Chen, J.-B. and Whiting, A. *manuscript in preparation*
- ***'Recent Advances in Copper-Catalysed Asymmetric Hydroboration of Electron-Deficient Alkenes: Methodologies and Mechanism'*** Chen, J.-B. And Whiting, A. *Synthesis*, **2018**, *50*, 3843-3861.

Acknowledgements

First of all, I would like to express my big debt of gratitude to my supervisor, Prof. Andy Whiting. Sincerely thanks to him, not only for the excellent opportunity of carrying me on my postgraduate study, but also introducing his fascinating research of boron chemistry to me. His kind encouragement and helpful advice throughout the period of my study is indispensable to my research work. I did learn a lot from him in both academia and life-attitude under his guidance. I would also like to thank Prof. Patrick G. Steel who provided me lots of help as my co-supervisor.

Then I would like to thank staff that provided excellent services and advice of experimental or analysing supports in the Department of Chemistry. All of this research work in the department is based on their efforts. It is necessary to give my sincere appreciation to my academic colleagues, NMR service, MS analysis, store service, security team and other staff who provided me the a great research environment. I would also like to express my special thanks to Dr Aileen Congreve who offered me very helpful advice on HPLC analysis. Dr Elizabeth Grayson and Dr AnnMarie C. O'Donoghue also helped with my academic studies.

In this year, I have enjoyed an excellent experience on my research project and enjoyed life in Durham. Looking back at the period of study in Durham, I felt well supported as a candidate an MSc degree candidate in Chemistry, and had the chance to improve my academic skills and enjoy my research. After expressing my appreciation to my supervisors and departmental staff, special thanks go to members in AW group. Firstly, my gratitude to

Yi-Hao Du (Eric) who provided me with lots of help with my language problems at the beginning. It was important for me to understand how everything worked in the laboratory and to get familiar with study in UK. He made my first move to UK much easier and became my best friend. The same appreciation to Dr. Alba Pujol Santiago for her help with my research project, the total synthesis of atorvastatin. She started the synthesis with a great synthetic route design and provided important experimental details from her PhD. With great cooperation with her, I continued her work and explored the synthetic process in this thesis. Thanks to her continuing email communications with me. It was a great pleasure to work with all of the other members in AW group. They were Melinda Morelli, Anna Wu, David R. Chisholm, Diego D. J. Perera-Solis, Emily Wan, Galina Badalova, Tania Chakraborti, etc. I would not forget the help they have given, as well as the good days working with them.

Moreover, I would like to thank all of my friends in UK or from China, especially my roommates who shared college life in St Cuthbert’s Society. Another thanks to my family members. My parents, Qiu-Wang Chen and Dong-Ying Zhao and my dear sister, Fen Chen, who's encouragement always made me stronger facing new challenges. Great thanks to them for their indispensable support to me, both in financial and mental terms.

Finally, thanks to Durham University and all the other people I did not mention but helped me during this year. I would not be so happy with my studies without their help!

Abbreviations and Chemical formulae

General

Å	Angström (s)
Ac	Acetyl
AFIR	Artificial force induced reaction
aq.	Aqueous
Ar	Aryl
A.U.	Absorbance unit
BArF	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	Benzyl
Boc	Tert-butyloxycarbonyl
bpy	2,2'-Bipyridyl
^{t}Bu	Tert-butyl
Bz	Benzoyl
°C	Degrees Celsius
cal	Calorie
$CHCl_3$	Chloroform
conv.	Conversion
Cy	Cyclohexyl
18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
δ	Chemical shift (NMR)

d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DFT	Density Functional Theory
DIBAL-H	Diisobutylaluminium hydride
d.r.	Diastereomeric ratio
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
E	Electrophile
EDG	Electron donating group
e.e.	Enantiomeric excess
e.g.	*Exempli gratia* (for example)
Eqn	Equation
e.r.	Enantiomeric ratio
eq.	Equivalents
Et	Ethyl
et al.	*et alia*
etc.	*et cetera*
eV	Electronvolt
EWG	Electron withdrawing group
g	Gram (s)
ΔG	Gibbs free energy (change)

GC	Gas chromatography
h	Hour (s)
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
Hz	Hertz
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPA	*i*-Propanol
IPr (**L19**)	1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
IR	Infra-red spectroscopy
J	Coupling constant (NMR spectroscopy)
k	kilo
K	Kelvin (s) (absolute temperature)
L	Ligands
L*	Chiral ligands
LG	Leaving group
m	Multiplet (NMR); milli; medium (IR)
m	Meta-position (in a aryl ring)
M	Moler
M+	Molecular ion peak (Mass spectrometry)
*m*CPBA	Meta-chloroperbenzoic acid
Me	Methyl

Mol	Mole (s)
MS	Molecular Sieves; Mass spectrometry
m/z	mass to charge ratio (Mass spectrometry)
[Ni]	Nickle complexes
NHC	N-Heterocyclic Carbene
NMI	N-Methylimidazole
NMP	1-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Ressonance
Nu (Nuc)	Nucleophile
o	Ortho-position (in a aryl ring)
p	Para-position (in a aryl ring)
Pa	Pascal
Ph	Phenyl
PMB	*p*-Methoxybenzyl
ppm	Part (s) per million
^{i}Pr	Isopropyl
q	Quartet
Quant.	Quantitative
®	Copyright registered
rac	racemic
ReactIR	*in situ* IR spectroscopy
rr	Regioselectivity ratio

RT (rt)	Room temperature
s	Singlet
sat.	Saturated
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
t	Triplet
TBAF	Tetra-n-butylammonium fluoride
TBME	Tert-butyl methyl ether
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMANO	Trimethylamine N-oxide
TMP	2,2,6,6-Tetramethylpiperidinyl
TMS	Trimethylsilyl
TMSCl	Chlorotrimethylsilane
TPPO	Triphenylphosphine oxide
Ts	*p*-Toluenesulfonyl
TS	Tkatchenko-Scheffler
UV	Ultra violet
X	Halide

Borane reagents

B_2cat_2	Bis(catecholato)diboron
B_2nep_2	Bis(neopentyl glycolato)diboron
B_2pin_2	Bis(pinacolato)diboron
Bpin	Pinacolatoboron
(-)-$IpcBH_2$	(-)-Isopinocampheylborane
9-BBN	9-Borabicyclo[3.3.1]nonane

Phosphine ligands

L1a (*R*)-DM-Binap	(*R*)-1,1′-Binaphthalene-2,2′-diyl)bis[bis(3,5-dimethylphenyl)phosphine]
L1b (*R*)-Binap	(*R*)-2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
L1c (*R*)-*p*-Me-Binap	(*R*)-(+)-2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
L2a (*R*),(*S*)-Josiphos	(*R*)-1-[(S_P)-2- (Diphenylphosphino) [Ferrocenyl]ethyldicyclohexyl phosphine
L2b (*S*),(*R*)-Josiphos	(*S*)-1-[(R_P)-2- (Diphenylphosphino) [Ferrocenyl]ethyldicyclohexyl phosphine
L5a (*S*)-DTBM-Segphos	(*S*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
L5b (*R*)-DTBM-Segphos	(*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole

L5c (*S*)-Segphos	(*S*)-(+)-5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
L6a (*S*)-MeO-Biphep	(*S*)-2,2'-Bis[di(3,5-di-t-butyl-4-methoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl
L7 (R,S_p)-Josiphos	(*R*)-1-[(S_P)-2- (Dicyclohexylphosphino) [Ferrocenyl]ethyldiphenyl phosphine
L8 (*R*,*R*)-Quinox P	(*R*,*R*)-2,3-Bis(*tert*-butylmethylphosphino)quinoxaline
L12 (*R*,*R*)-Ph-BPE	1,2-Bis[(2*R*,5*R*)-2,5-diphenylphospholano]ethane
L14 (*R*,*R*)-PTBP-BDPP	((2*R*,4*R*)-pentane-2,4-diyl)bis(bis(4-(tert-butyl)phenyl)phosphane
dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
L15a Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
L15b Cy-Xantphos	4,5-Bis(dicyclohexylphosphino)-9,9-dimethylxanthene
L18 dCybe	1,2-Bis(dicyclohexylphosphino)ethane

Literature review

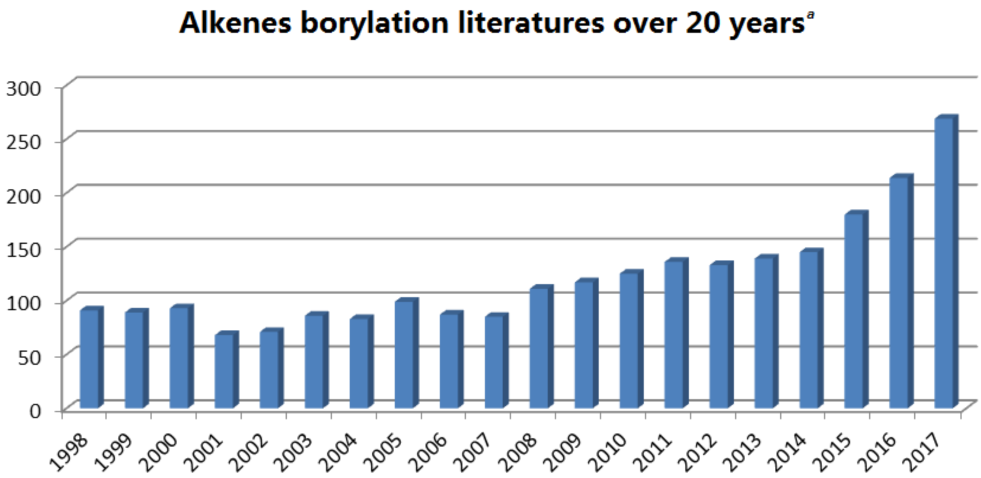
1.1. Introduction to hydroboration of electron deficient alkenes

In recent decades, enantioenriched borylated compounds have become very important in the field of organoboron chemistry.[1] Considering their extensive applications as synthetic intermediates for chiral pharmaceuticals and biologically active molecules,[2] numerous methodologies and mechanistic investigations have been focused on catalytic asymmetric borylation, followed by further transformations. Rather than enantioselective transformations of racemic borylated compounds,[3] direct chirality introduction as part of the borylation step, has shown its benefits.[4c,10c] With high yields and toleration of a wide range of substrates, as well as being viable for difunctionalization or cascade transformations with high stereoselectivity control, such enantioenriched organoboron intermediates provide flexibility and applicability in subsequent synthetic strategies.[4,7,8] Consequently, it is highly desirable to develop novel catalytic asymmetric borylation methods and to carry out relevant mechanistic studies.

Asymmetric catalytic borylation has gained much research interest in the last twenty years. Several excellent reviews have covered the various contributions and key points of this research topic, including C-H or C-X (X = leaving group) substituting borylation[5,6] and unsaturated bond borylation[7-10] as two of the main borylation methods. With focus on generating new carbon-boron chiral centers, asymmetric hydroboration of alkenes is the main strategies employed.[9,10] In 2012, Whiting *et al.* reviewed catalytic conjugate β-boration methodologies of electron deficient alkenes, including discussion of key mechanistic aspects.[10c] Another important review was published in 2016 by Marder *et al.* containing a detailed introduction of the structural and synthetic applications of diboron compounds.[4j] One year later, discussing asymmetric synthetic methods of secondary and tertiary boronic esters, Aggarwal *et al.* surveyed asymmetric borylation methods covering the period up until the end of 2016 and comprehensively including alkene borylation methods.[4k] However, with the rapid growth of literature in this area (Figure 1), there have been numerous additional contributions to alkene borylation methods. Furthermore, literature on copper-catalysed borylation and including mechanistic discussions have been appearing regularly.[4h,9h,9i]

This thesis updates the previous important contributions reviews by reporting on copper-catalysed asymmetric hydroboration methodologies of electron deficient alkenes including mechanistic proposals disclosed since 2017. Moreover, a review of enantioenriched borylated compoundsrelating to their use for producing chiral 1,3-diols for application in medicinal chemistry.[11]

Figure 1 Number of publications on alkenes borylation (Web of Science Core Collection)



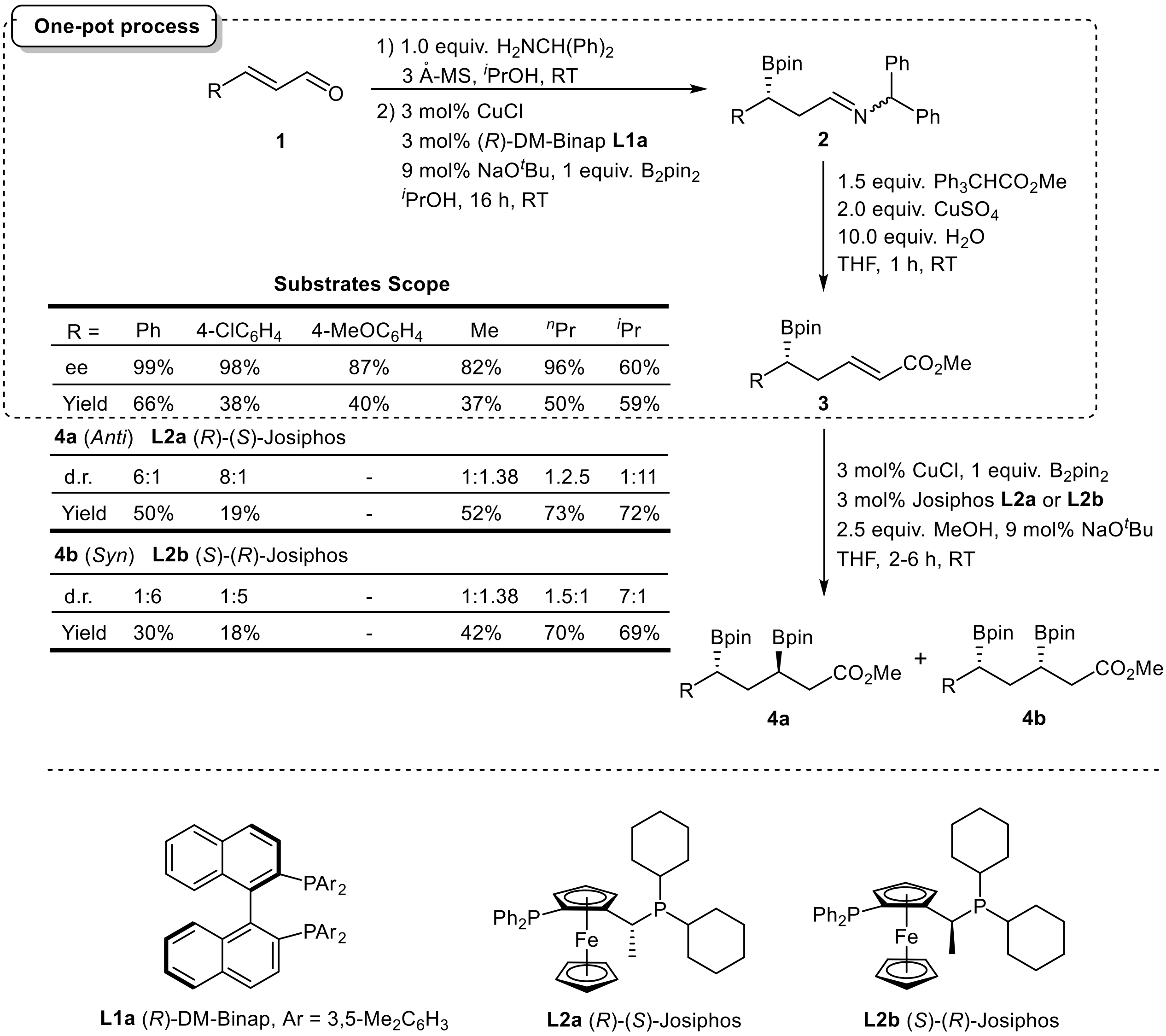
[a] Search criteria: "Topic: (borylation or boration or *boration or hydroboration) AND Topic: (alkene or alkenes or olefin or olefins or unsaturated or double bonds)"

1.2. Methodologies for the copper-catalysed hydroboration

The copper-catalysed system is the most frequently employed system in catalytic hydroboration of electron deficient alkenes.[9,10] Due to many excellent contributions to this field, numerous methodologies have been developed providing good substrate scope, high yields and excellent enantioselectivities. To date, the classic Brown hydroboration[9a] has been included in expansion of catalytic asymmetric borylation, through further functionalizations, such as by utilising cascade transformations and bifunctional additions of unsaturated bonds.[8] Achievements focusing on the synthesis of highly enantioenriched secondary and tertiary organoboron compounds were well-documented in 2017.[4k] Consequently, recent advances in asymmetric borylative conjugate addition to alkenes are highlighted in this section.

1.2.1. α,β-Unsaturated ketones and imines

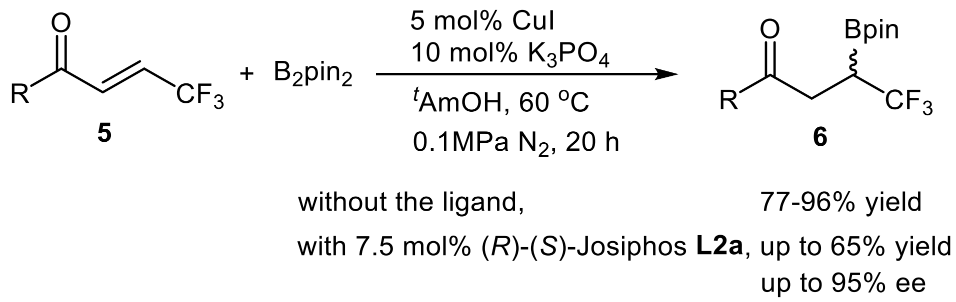
In 2017, based on a series of previous investigations,[12b-l] Whiting *et al.* realised a consecutive copper-catalysed asymmetric hydroboration of α,β-unsaturated aldehydes **1** *via* a one-pot imine formation/borylation/hydrolysis/Wittig trapping procedure, followed by a second hydroboration of the resultant homoallylic boronate carboxylate esters **3** (Scheme 1). They achieved good yields, high ees and demonstrated effective double diastereocontrol, providing a streamlined preparation of both chiral *syn*- and *anti*-1,3-diboronates **4a** and **4b**. Further details of stereoselective catalytic hydroboration reactions and further transformations were also investigated.[12a]



R =	Ph	4-ClC_6H_4	4-$MeOC_6H_4$	Me	^{n}Pr	^{i}Pr
ee	99%	98%	87%	82%	96%	60%
Yield	66%	38%	40%	37%	50%	59%
4a (*Anti*) **L2a** (*R*)-(*S*)-Josiphos						
d.r.	6:1	8:1	-	1:1.38	1.2.5	1:11
Yield	50%	19%	-	52%	73%	72%
4b (*Syn*) **L2b** (*S*)-(*R*)-Josiphos						
d.r.	1:6	1:5	-	1:1.38	1.5:1	7:1
Yield	30%	18%	-	42%	70%	69%

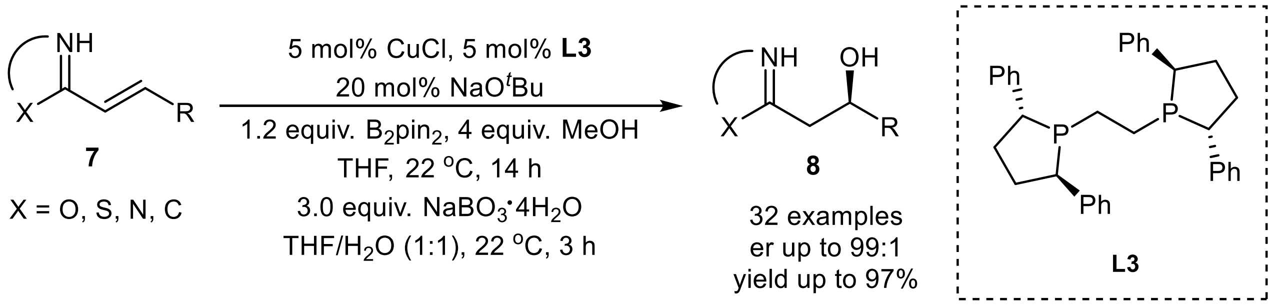
Scheme 1 Consecutive copper-catalysed asymmetric hydroborations producing 1,3- diboronates

In the same year, Yu *et al.* reported an enantioselective hydroboration method for the synthesis of CF_3 containing molecules, using an asymmetric hydroboration of β-trifluoromethyl-α,β-unsaturated ketones **5**, that employed CuI and (*R*)-(*S*)-Josiphos **L2a** (up to 65% yield and 95% ee) (Scheme 2).[13]



Scheme 2 Hydroboration of β-trifluoromethyl-α,β-unsaturated ketones

Meng *et al.* accomplished a Cu-complex catalysed enantioselective, one-pot transformations of *N*-heteroaryl-substituted alkenes **7** with an hydroboration/oxidative workup providing products **8** in up to 97% yield and 99:1 enantiomeric ratio (Scheme 3).[14] Moreover, this work showed a remarkably broad scope in the *N*-heteroaryl moiety as the unique electron-withdraw group.



Scheme 3 Enantioselective catalytic hydroboration/oxidation of *N*-heteroaryl-substituted alkenes

1.2.2. α,β-Unsaturated esters and cyanides

In 2017, Crévisy, Baslé and Mauduit reported a new procedure for the synthesis of NHC ligands **L4a** and **L4b**, which were applied in the copper catalysed asymmetric hydroboration reaction of α,β-unsaturated ester **9** to give 60-76% yields of chiral secondary alcohol **10** after oxidation, and with up to 87:13 er (Scheme 4).[15]

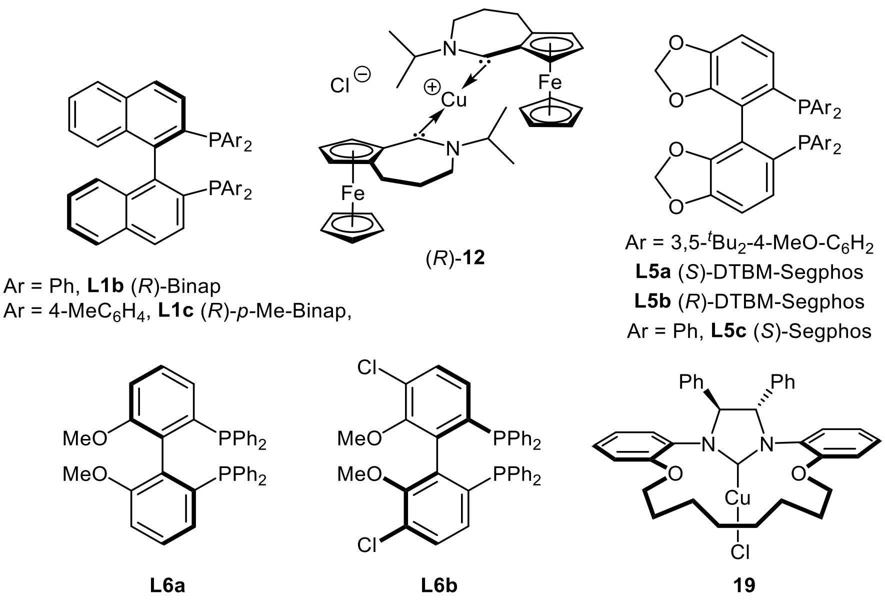
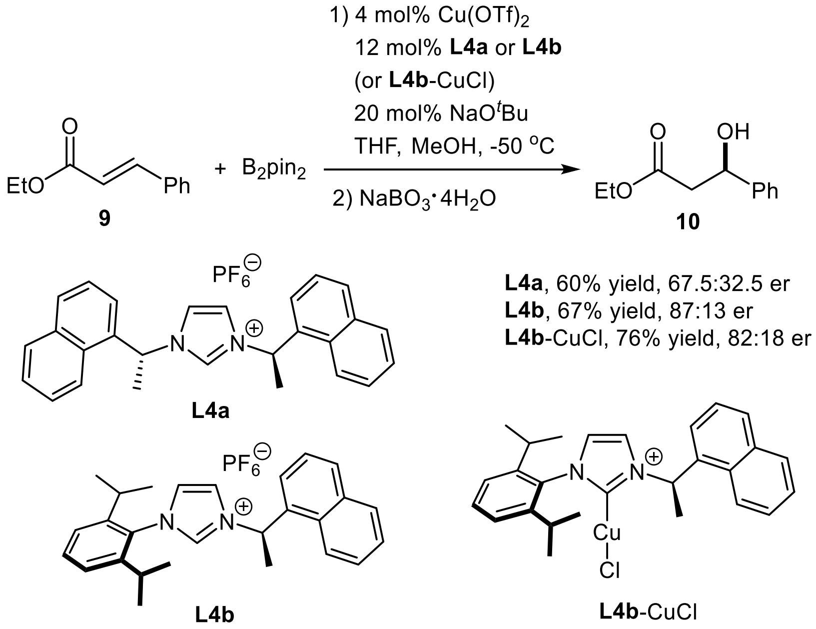
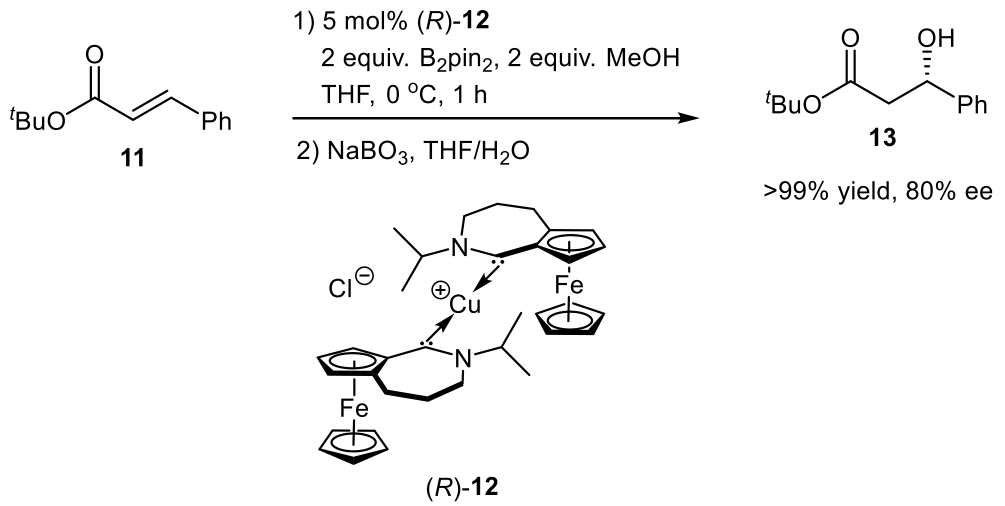


Figure 2 Ligands and catalysts employed in hydroboration reactions



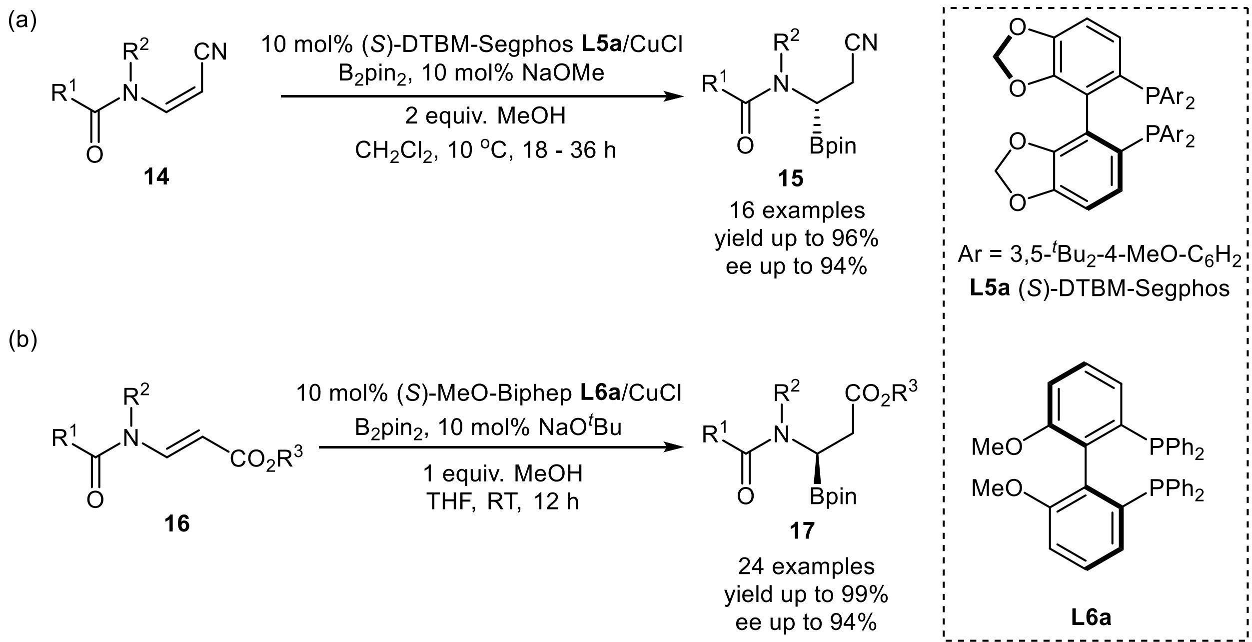
Scheme 4 Catalytic application of Cu-NHC in asymmetric hydroboration of alkenes

Published at the same time, involving a novel planar chiral cyclic (amino)(ferrocenyl) carbene ligand with copper ((*R*)-**12**, Figure 2), Yoshida *et al.* described its catalytic application in enantioselective hydroboration. Combined with oxidation, β-hydroxyl ester **13** was produced with >99% yield and in 80% *ee* (Scheme 5).[16] The structures of the ligands and catalysts used in the hydroboration reactions shown in Scheme 5-8 are given in Figure 2.



Scheme 5 Catalyst 12 employed in asymmetric hydroboration reaction

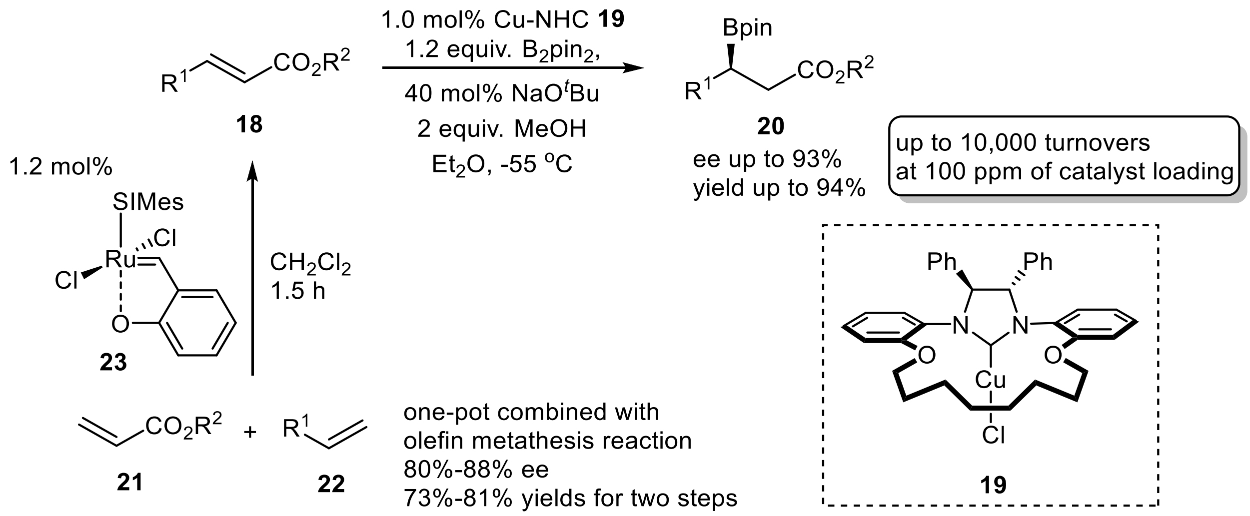
Specifically tolerating both *Z-β*-amidoacrylonitriles **14** and ethyl *E-β*-amidoacrylates **16** (Scheme 6), Xu *et al.* demonstrated an attractive methodology involving mild conditions for the asymmetric hydroboration reaction employing (*S*)-DTBM-Segphos **L5a** (up to 96% yield, up to 94% ee) and (*S*)-MeO-Biphep **L6a** (up to 99% yield, up to 94% ee) (Figure 2).[17]



Scheme 6 Chiral α-amino boronate esters prepared *via* hydroboration

In 2018, Jana and Grela employed a well-defined chiral NHC-copper complex **19** (Figure 2) in the highly enantioselective hydroboration reaction of α,β-unsaturated esters **18** (up to 94% yield, up to 93% ee).

Interestingly, up to 10,000 turnovers at 100 ppm of catalyst loading was obtained from catalyst activity investigations. In addition, a one-pot metathesis/borylation method was reported where starting materials were assembled *in situ*, resulting in 73%-81% overall yields and with 80%-88% *ee* (Scheme 7).[18]



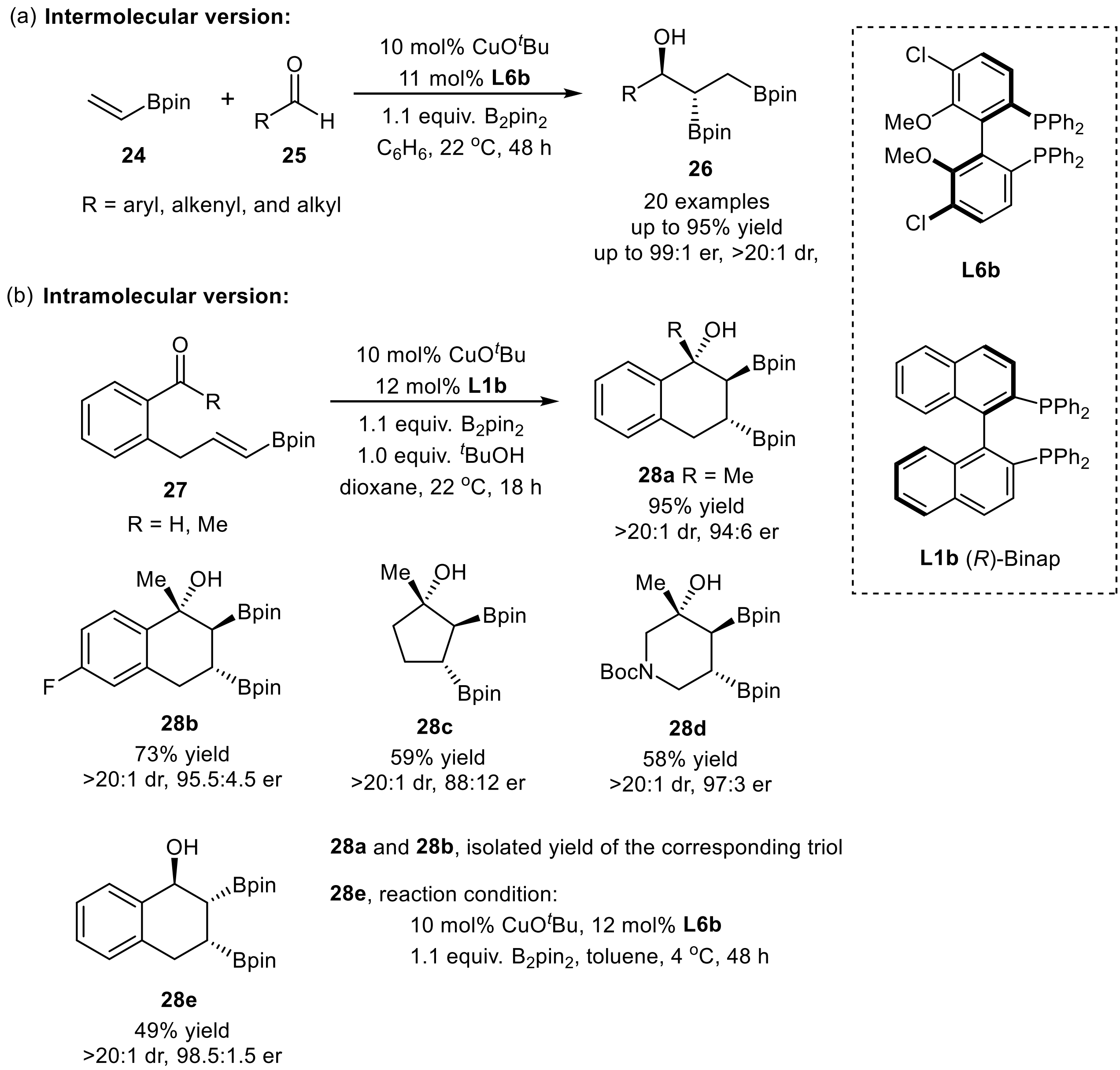
Scheme 7 One-pot metathesis/borylation reaction of α,β-unsaturated esters

In addition to carboxylate esters, it is noteworthy that by utilising vinyl-B(pin) **24**, Meek *et al.* demonstrated a multicomponent enantioselective cascade borylcupration/1,2-addition reaction. This resulted in up to 95% yield and 99:1 er and >20:1 dr from 20 examples of aryl, alkenyl, and alkyl aldehydes **25** (Scheme 8a). Moreover, good results were obtained in the intramolecular version with a wide range of products **28** (49-95% yields, >20:1 dr, up to 98.5:1.5 er) (Scheme 8b).[19]

1.2.3. Aryl alkenes and alkyl alkenes

Although without the activation of electron withdrawing groups, aryl alkenes and alkyl alkenes were subjected to borylative addition using a copper catalytic system. Employing mild condition for the catalytic enantioselective hydroboration of aryl alkenes (up to 47% yield and 99% ee, dr > 99:1 for the hydroboration products **30**), Hou *et al.* realised a cascade kinetic resolution of racemic 2-substituted 1,2-dihydroquinolines **29a**. Up to 48% yield and up to 99.9% *ee* of enantiomer **29b** was obtained (Scheme 9a).[20a] Also, in 2018, Hou and Zhang developed this reaction further by application for the asymmetric synthesis of medicinal intermediates, (+)-sumanirole **34** and (*S*)-903 **36** *via* optimizing the catalytic enantioselective hydroboration of 1,2-dihydroquinolines **31** (up to 94% yield and 98% ee) (Scheme 9b).[20b]

The structures of the ligands and catalysts used in the hydroboration reactions shown in Schemes 9-15 are given in Figure 3.



Scheme 8 Catalytic borylcupration/1,2-addition reactions of vinyl-B(pin)

In 2017, Liao *et al.* reported an enantioselective aminoboration of styrenes **37** with oxidative workup generating valuable β-hydroxylalkylamines **39** *via* catalysis with copper and chiral sulfoxide-phosphine ligand **L9a**. Although reaction limitations appeared when normal non-terminal alkenes were used, i.e., no reaction, 22 substrates were reported, giving up to 83% yield with up to 95% *ee* (Scheme 10). A gram scale reaction of substrate **37a** was also achieved providing 92% isolated yield with 90% ee.[21]

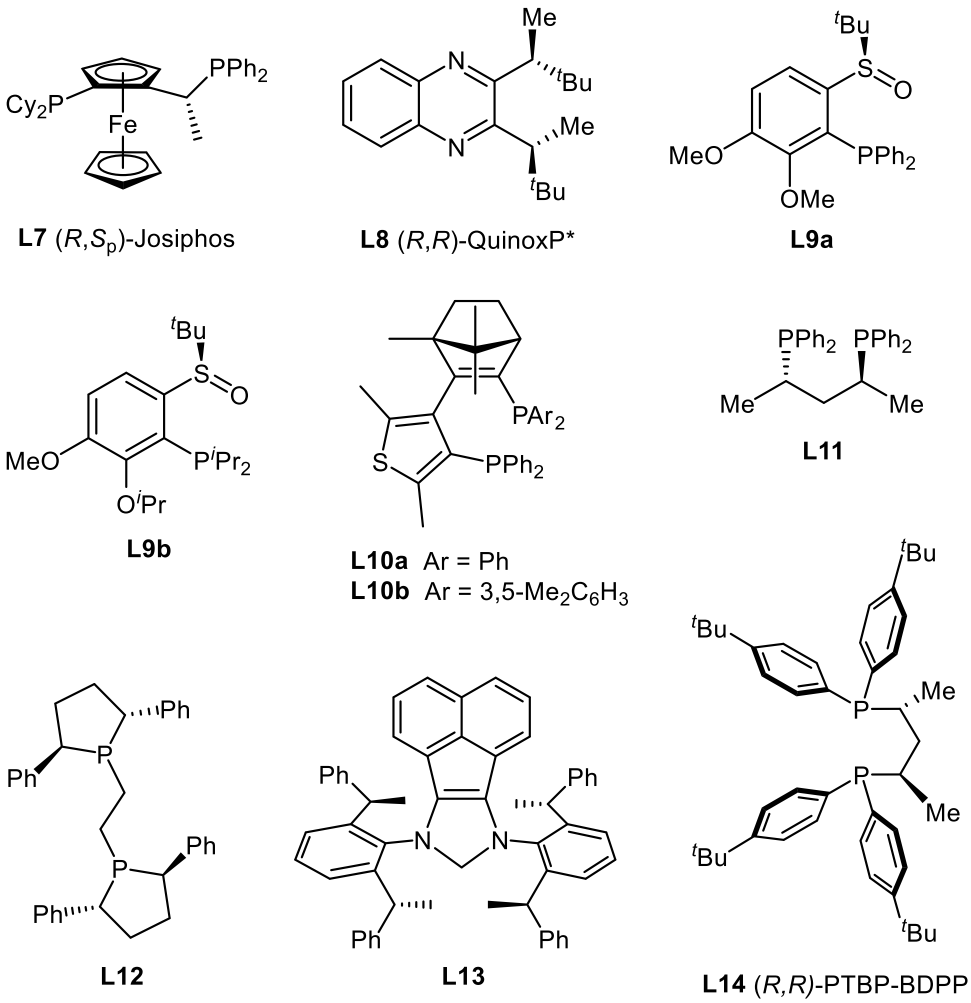
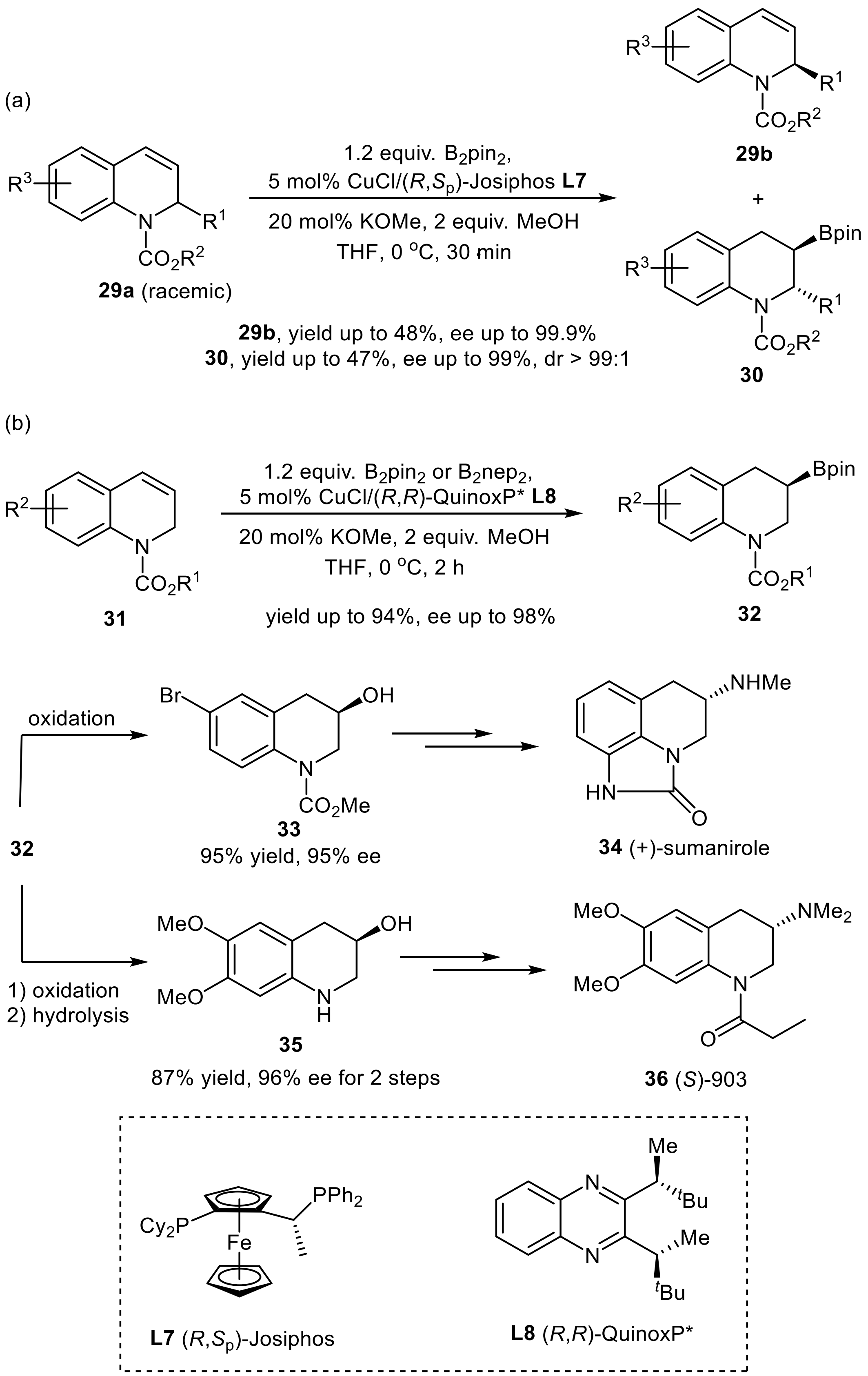
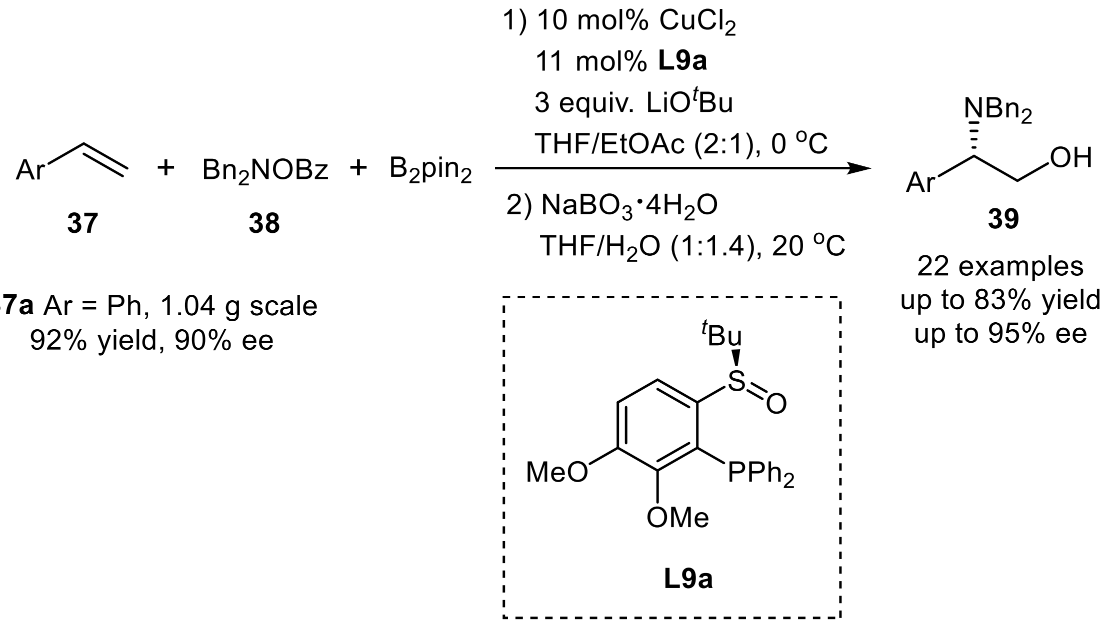


Figure 3 Ligands and catalysts employed in hydroboration reactions

Further literature has demonstrated the utility of the asymmetric borylative difunctionalization of aryl alkenes for applications in synthesis. With a detailed mechanistic study, Hoveyda *et al.* reported upon on the expanded reaction scope and improved enantioselectivities for the catalytic allylboration of aryl alkenes **37**, improving upon previous work (Scheme 10).[22a-c] A model reaction was used for optimizing conditions to achieve 14-84% yields with 2-96% ee (Scheme 11, one-catalyst conditions). The development of a novel Cu/Pd two-catalyst system was revealed having both broader scope (Scheme 11, two-catalyst conditions).[22c] Moreover, transformation of **42f** was performed in the 4 steps synthesis of intermediate **43** in 42% overall yield with 89:11 dr, which was able to combine a total synthesis of (-)-heliespirone C **44a** and (-)-heliespirone A **44b**.[22d,22e]



Scheme 9 Kinetic resolution *via* asymmetric copper-catalysed borylation

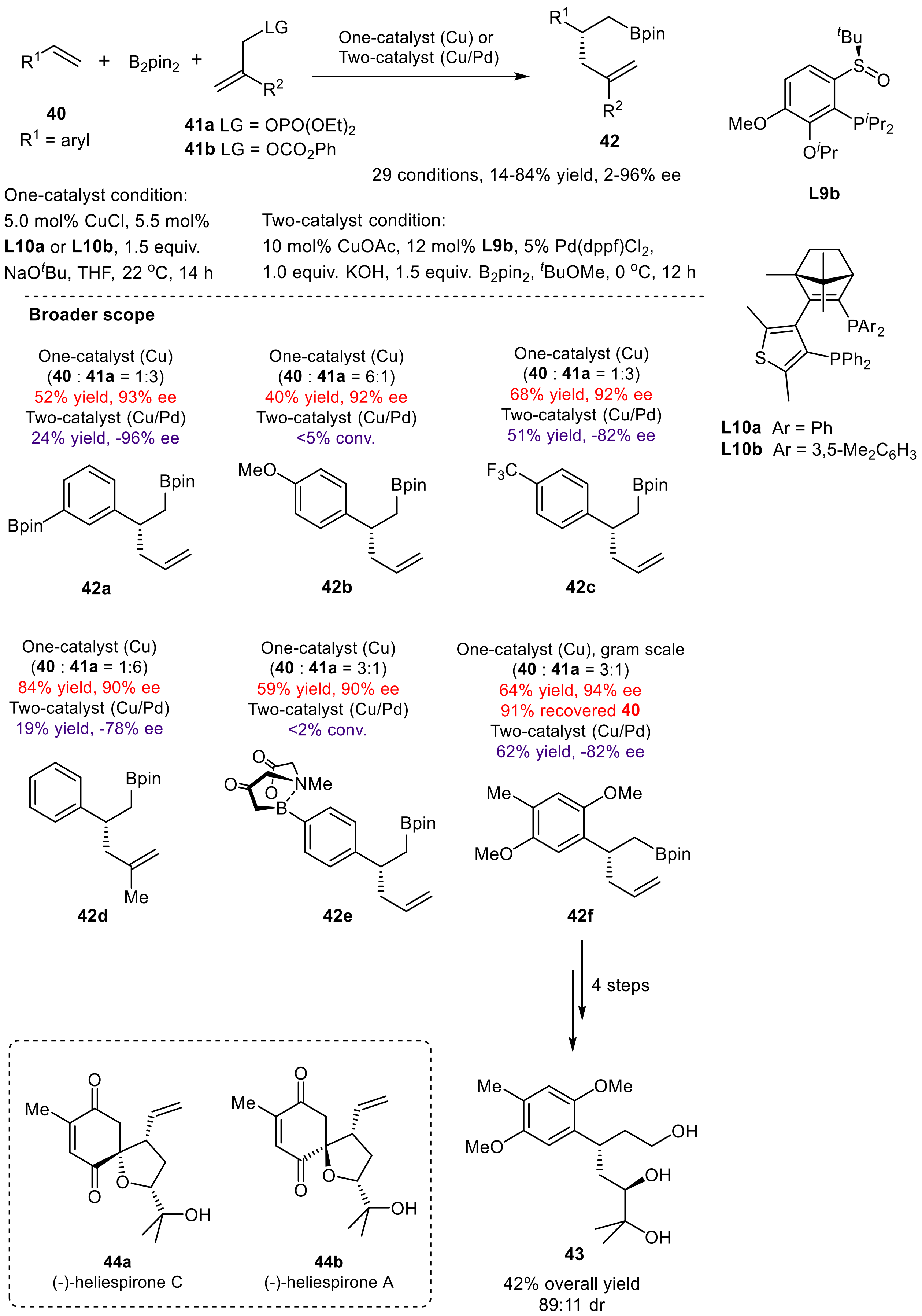


Scheme 10 Copper/chiral sulfoxide-phosphine catalysed enantioselective aminoboration of styrenes

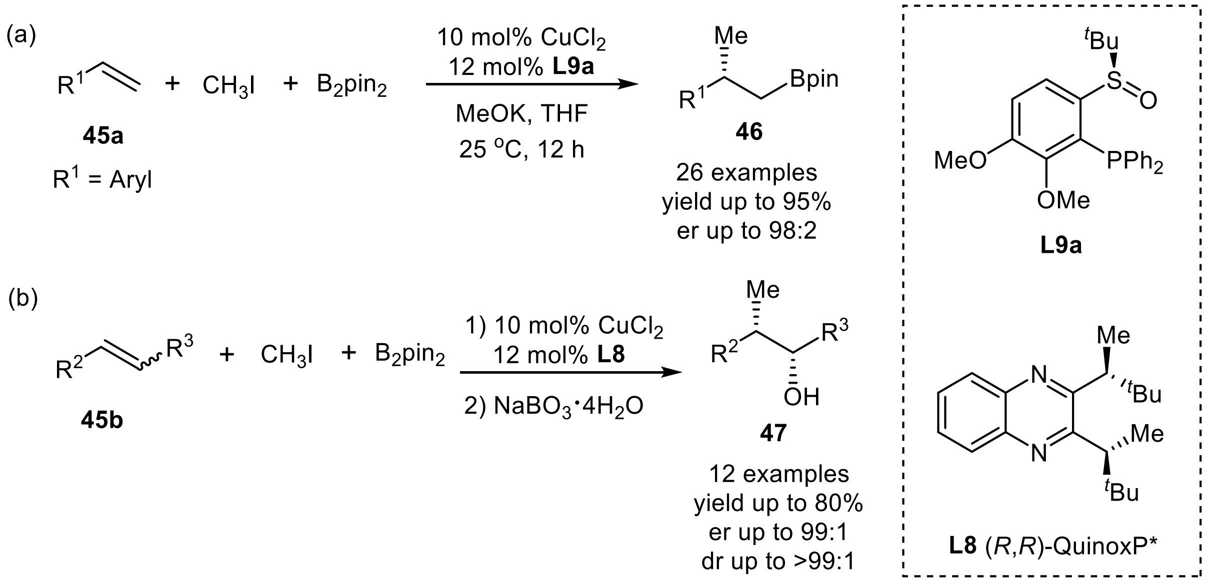
1,1-Disubstitued alkenes are challenging substrates due to the high steric demand of the double bonds. However, it is considered a good challenge to develop effective asymmetric functionalization reactions of 1,1-disubstitued alkenes as the chiral products are valuable for the synthesis of bioactive molecules.[24a] Xiong *et al.* developed mild conditions for the copper catalysed 1,1-diaryl alkenes **48a** and α-alkyl styrenes **48b** hydroboration reaction affording up to 98% yield with up to 98:2 er. A gram-scale synthesis was performed in 94% yield with 97:3 er requiring lower catalyst loading. In addition, transformation of **49a** was described *via* intermediate **50**, applied to the synthesis of (*R*)-tolterodine **51** (Scheme 13a).[24b]

At the same time, Wen *et al.* accomplished a similar copper-catalysed hydroboration utilising (*R*,*R*)-Ph-BPE **L12** as the optimized chiral phosphine ligand. Up to 98% yield and 99:1 enantiomeric ratio of the borylation product **53** was obtained, which was also applied to a gram-scale oxidation process for the synthesis of (S)-ketoprofen **55** (Scheme 13b).[24c]

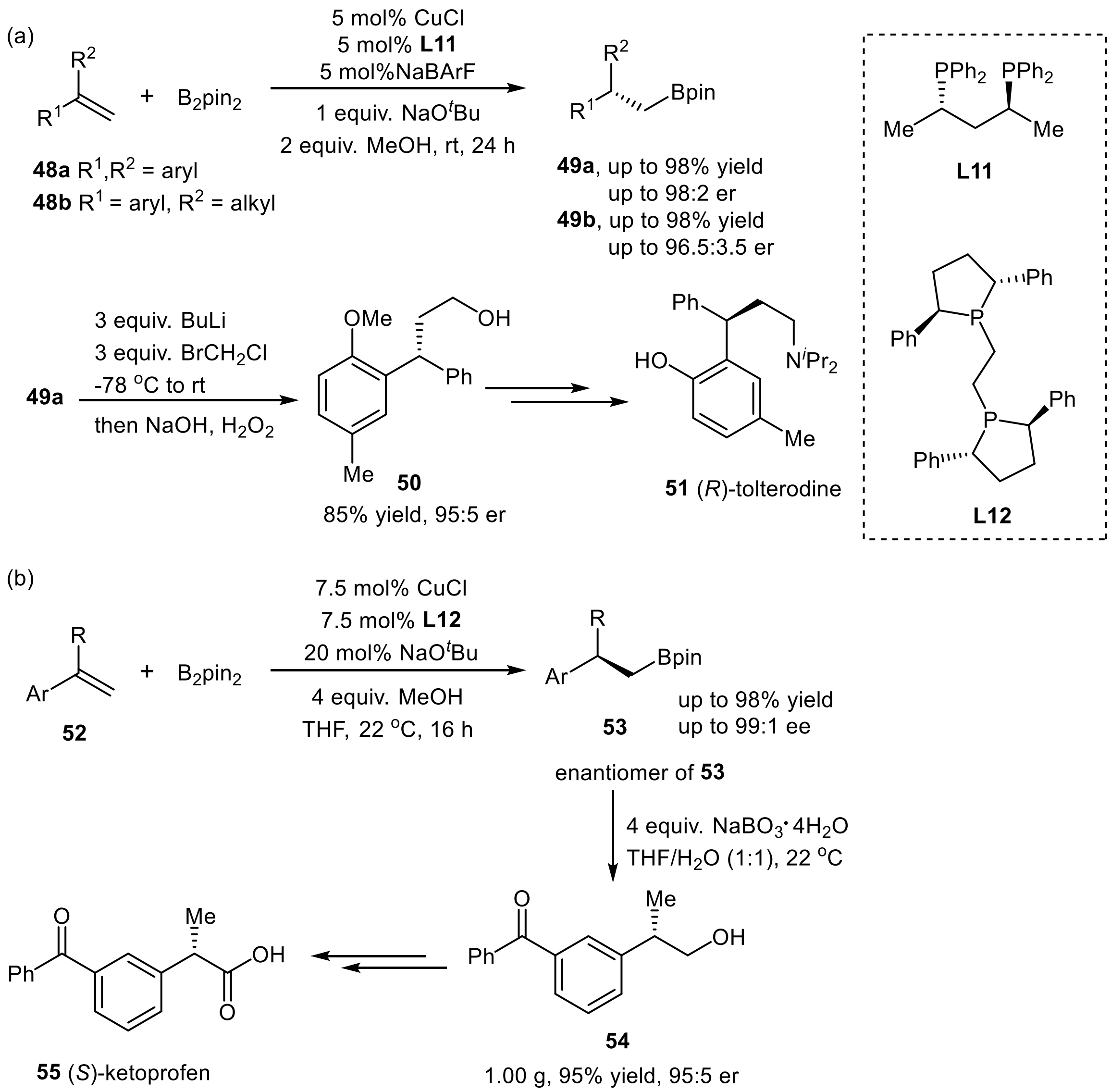
Compared to aryl alkenes, aliphatic alkenes are less activated substrates for copper catalysed borylation reactions. Nevertheless, Hong and Shi realised the enantioselective Markovnikov hydroboration of unactivated terminal alkenes **56** utilising NHC(**L13**)/copper catalyst. B_2dmpd$_2$ **57** was selected to be the favoured borylation reagent, generating enantioenriched secondary boronic esters **58** in up to 85% yield (29 examples, 86-98% ee, up to 96:4 regioselectivity ratio (rr)) (Scheme 14).[25]



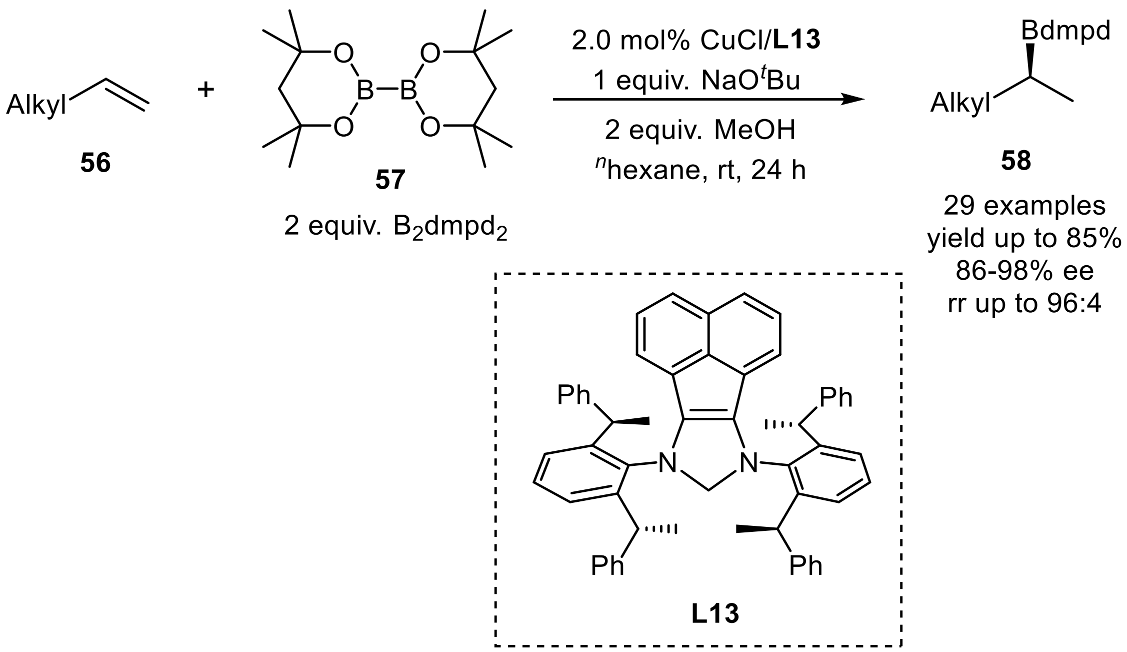
Scheme 11 Asymmetric allylboration of aryl alkenes and its application on total synthesis



Scheme 12 Copper catalysed asymmetric methylboration of alkenes

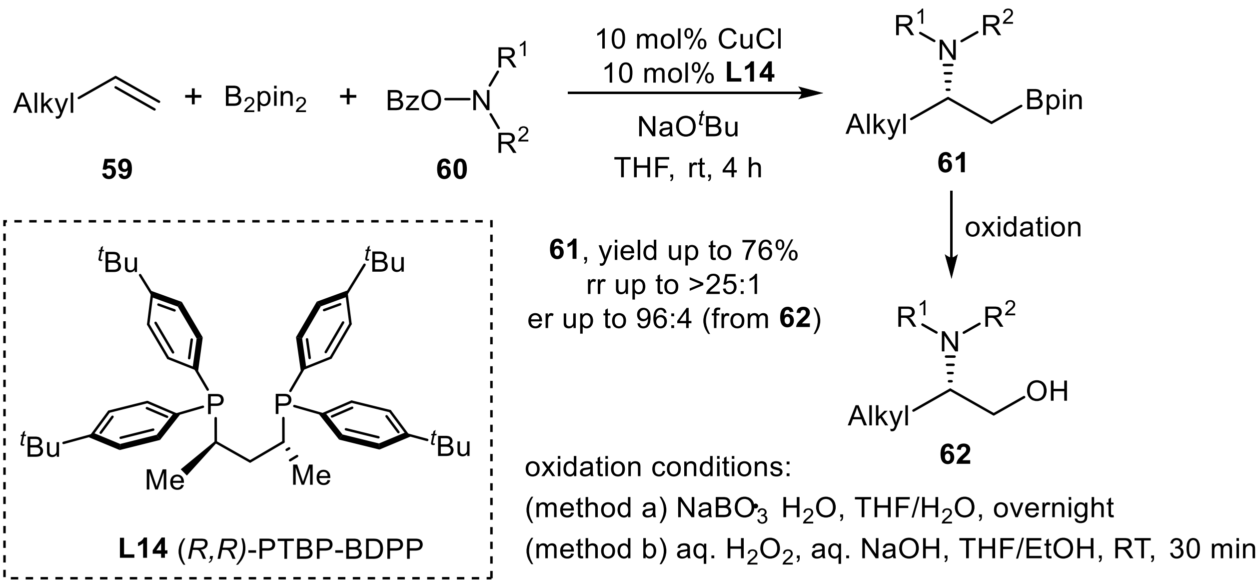


Scheme 13 Asymmetric hydroboration of 1,1-disubstitued alkenes and its application



Scheme 14 Markovnikov hydroboration of unactivated terminal alkenes

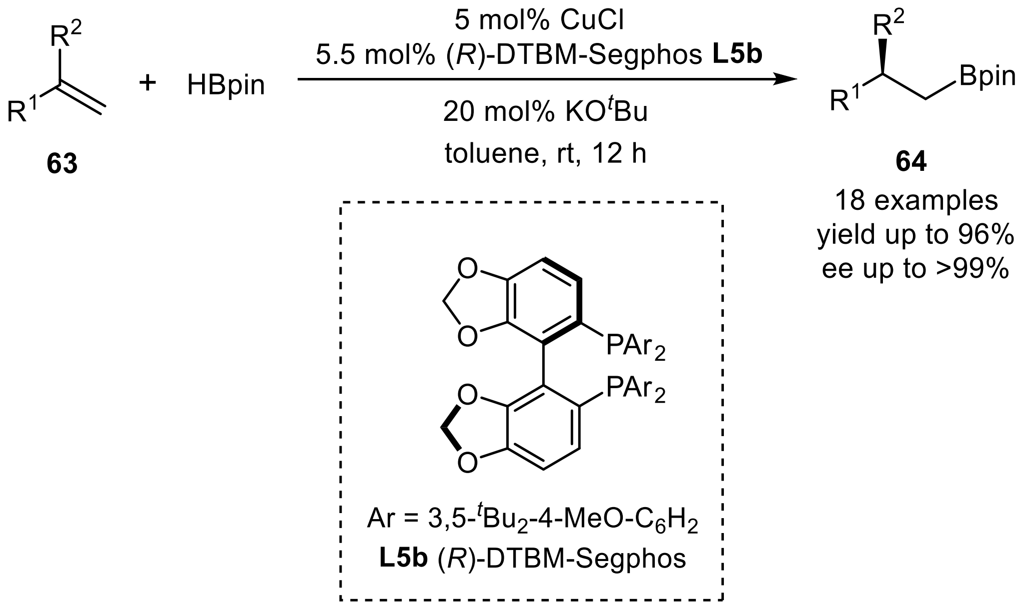
In 2018, the regiocontrolled asymmetric aminoboration of unactivated terminal alkenes **59** was developed by Hirano and Miura. Using a copper catalyst and (*R*,*R*)-PTBP-BDPP **L14** ligand successfully gave up to 76% yield of the favoured borylated regioisomer **61** with up to >25:1 rr (up to 96:4 er of oxidation product **62**) (Scheme 15).[26]



Scheme 15 Copper catalysed regio- and enantioselective aminoboration of terminal alkenes

Another challenging goal of asymmetric hydroboration of aliphatic 1,1-disubstituted alkenes was realised by Yun *et al.* employing HBpin with Cu/(*R*)-DTBM-Segphos **L5b** in high yields with up to 99% ees.

The functional group compatibility indicated the enantio-discrimination of the two alkyl groups affected in the catalytic hydrobortion process. Moreover, excellent results, 96% yield with >99% *ee* was obtained with 1 mol% catalyst loading for gram-scale synthesis of compound **64** in this reaction (Scheme 16).[27]



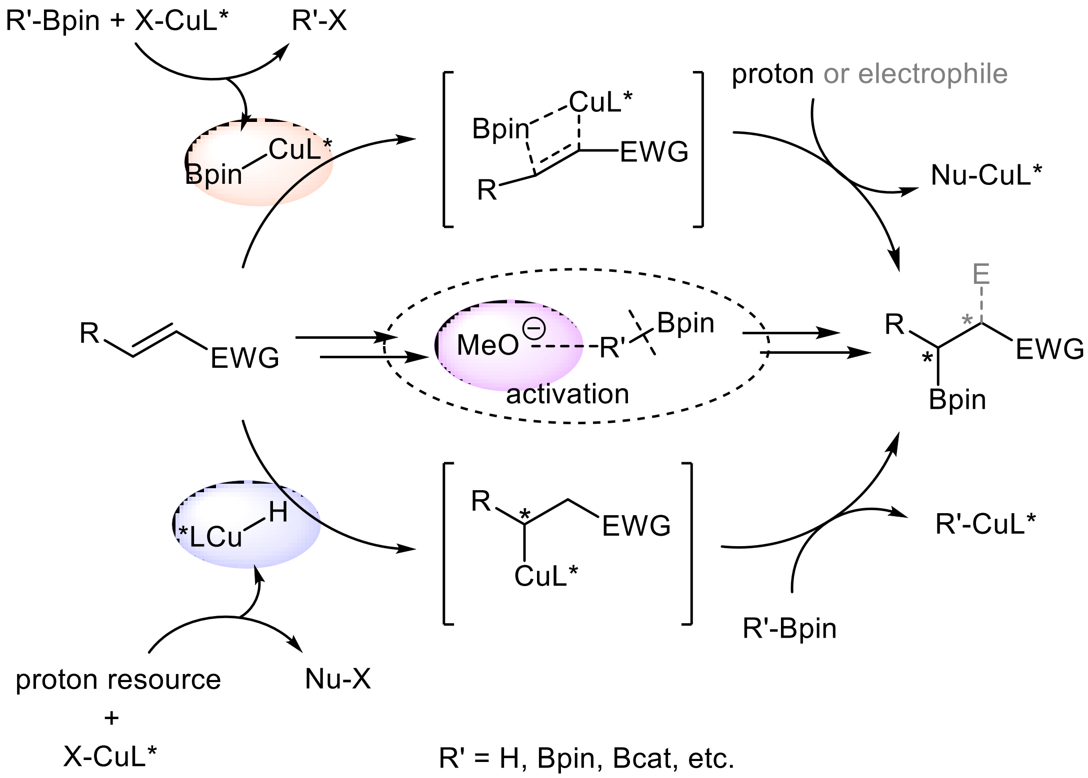
Scheme 16 Asymmetric hydroboration of aliphatic 1,1-disubstituted alkenes

1.3. Mechanistic investigations of the copper-catalysed hydroboration

While methodologies for copper catalysed asymmetric hydroboration have undergone significant development in recent years, the proposed mechanism is still a matter of discussion. To date, there are two principal mechanistic proposals supported by various experimental evidence or thermodynamic data (Scheme 17).[4h,9h,9i] Copper-Bpin (or copper-BX_2) and copper-hydride as key intermediates have been the focus of most discussions. Interestingly, neither of these species has been fully confirmed or ruled out. In addition, the methoxy anion has been suggested to play an important role in the activation of the borylation agent,[45] which might result in a direct hydroboration of alkenes *via* a single electron transfer mechanism. We now consider recent literature that provides new evidence and alternative mechanistic proposals.

1.3.1. Cu-BX_2 intermediate

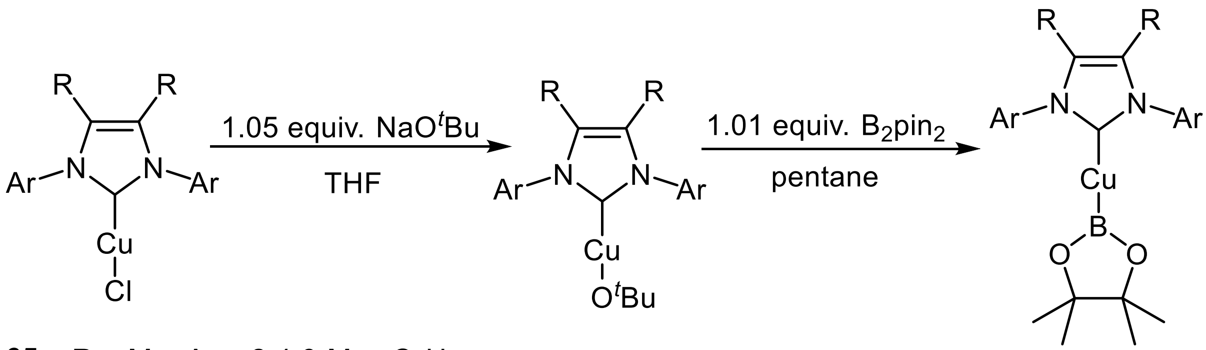
Since the Brown hydroboration[9] was expanded into the copper catalytic system, the copper-boron species has been recognized as the key borylation intermediate in most mechanism proposals.[28] Among the mechanistic discussions of the copper-catalysed hydroboration procedure of alkenes, there have been many experimental analysis and calculation methods employed in recent years. The copper-boron intermediate proposal has gained wide support in the methodology publications. Hence, recent advances have been in the form of supporting literature that consider the copper-boron species as the key intermediate of copper catalysed hydroboration or borylative difunctionalization of alkenes and are thus considered here.



Scheme 17 Summarized main procedure of possible mechanism of copper catalysed borylative addition to alkenes

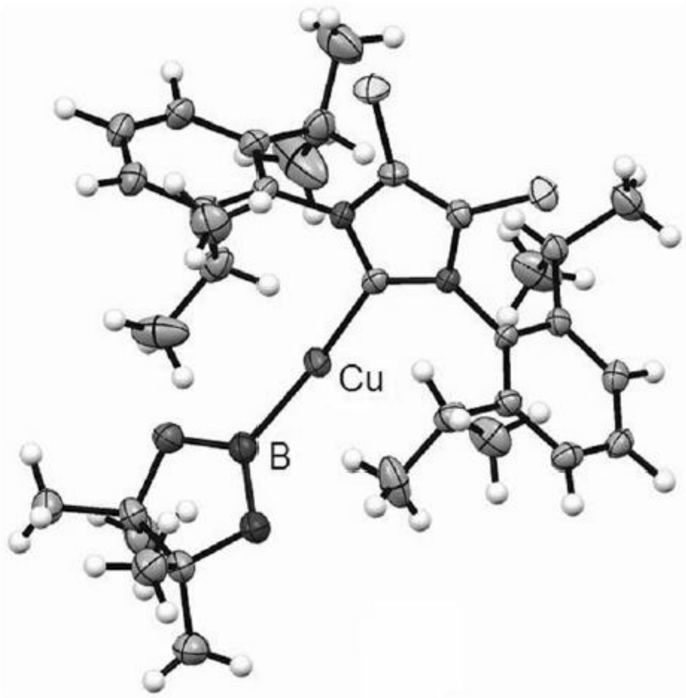
1.3.1.1. Experimental analysis

Firstly, it is noteworthy that according to Tsuji *et al.*'s work, the copper-boron species were possible to be prepared with good yields of the copper-boron complexes **67a** and **67b** (62% yield for **66a**, 74% yield for **67a**; quant. yield for **66b**, 65% yield for **67b**) (Scheme 18), and whose structure was determined by X-ray crystallography (Figure 4).[29]



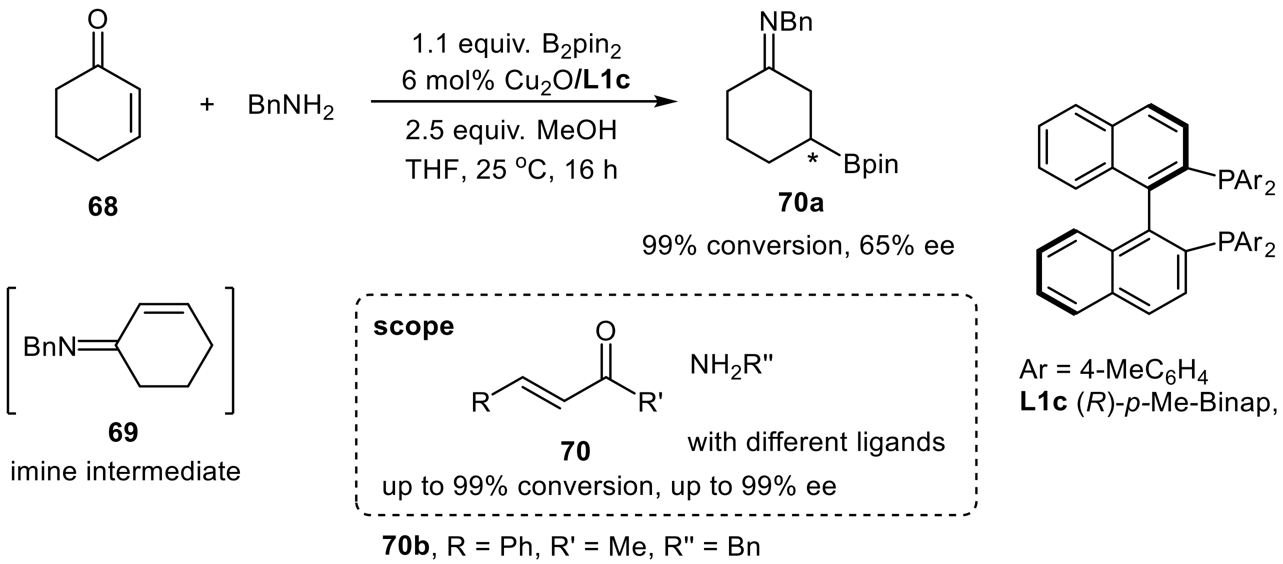
Scheme 18 Synthesis of copper-Bpin species

Figure 4 Crystal structure of Cu-Bpin compound **67b**[a]



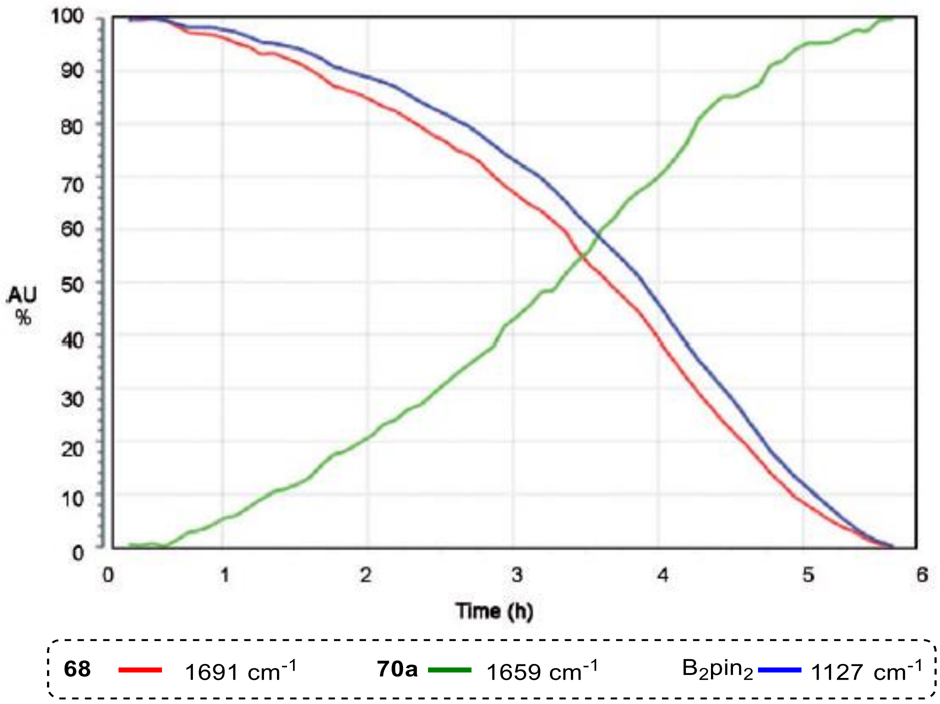
[a] The X-ray crystallography result is produced by the reference 29.

In situ IR spectroscopy experiments (ReactIR), is one of the most useful tools utilised in investigations of reaction process. In 2013, Whiting and Fernández *et al.* reported an asymmetric borylation reaction *via* a copper catalysed system (Scheme 19). A reaction profile was revealed by ReactIR showing Cu_2O to be a clean and efficient catalyst for the *in situ* formation of imine **69** followed by catalytic borylation resulting in a rapid pseudo-first-order reaction for product **70** for which the relevant decrease of B_2pin_2 (Figure 5) was observed. Interestingly, with the addition of an additional base, the B_2pin_2 vanished more rapidly, followed by a slower but full conversion of the unsaturated imine to the borylated product **70b** (Figure 6), the rate of which increased with increasing base. This demonstrated that the rate of the borylation reaction of **70b** with B_2pin_2 was not dependent upon base being present (reaction proceeds with no base); but speeds up substantially upon base addition.[30]



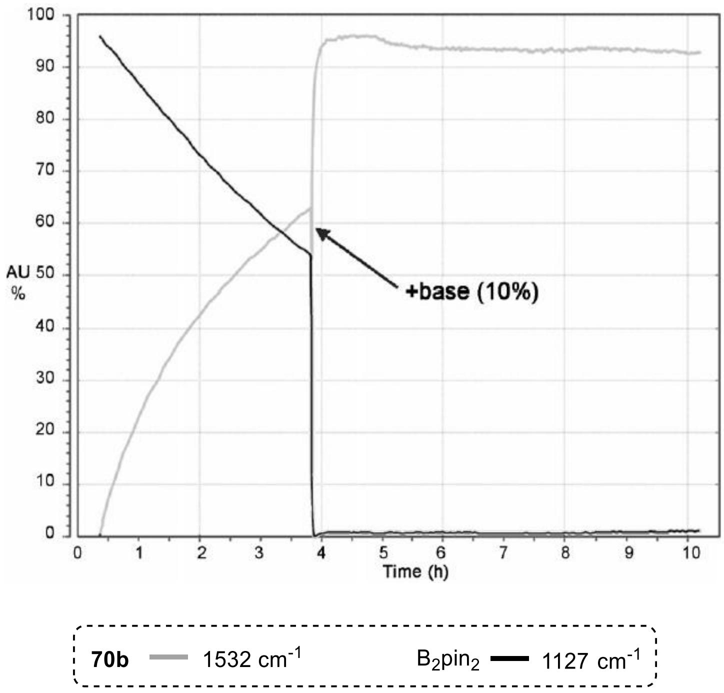
Scheme 19 Copper catalysed asymmetric borylation reaction of *in situ* formed α,β-unsaturated imines

Figure 5 ReactIR showing a rapid pseudo-first-order reaction of copper-catalysed borylation[a]



[a] The ReactIR result is produced by the reference 30.

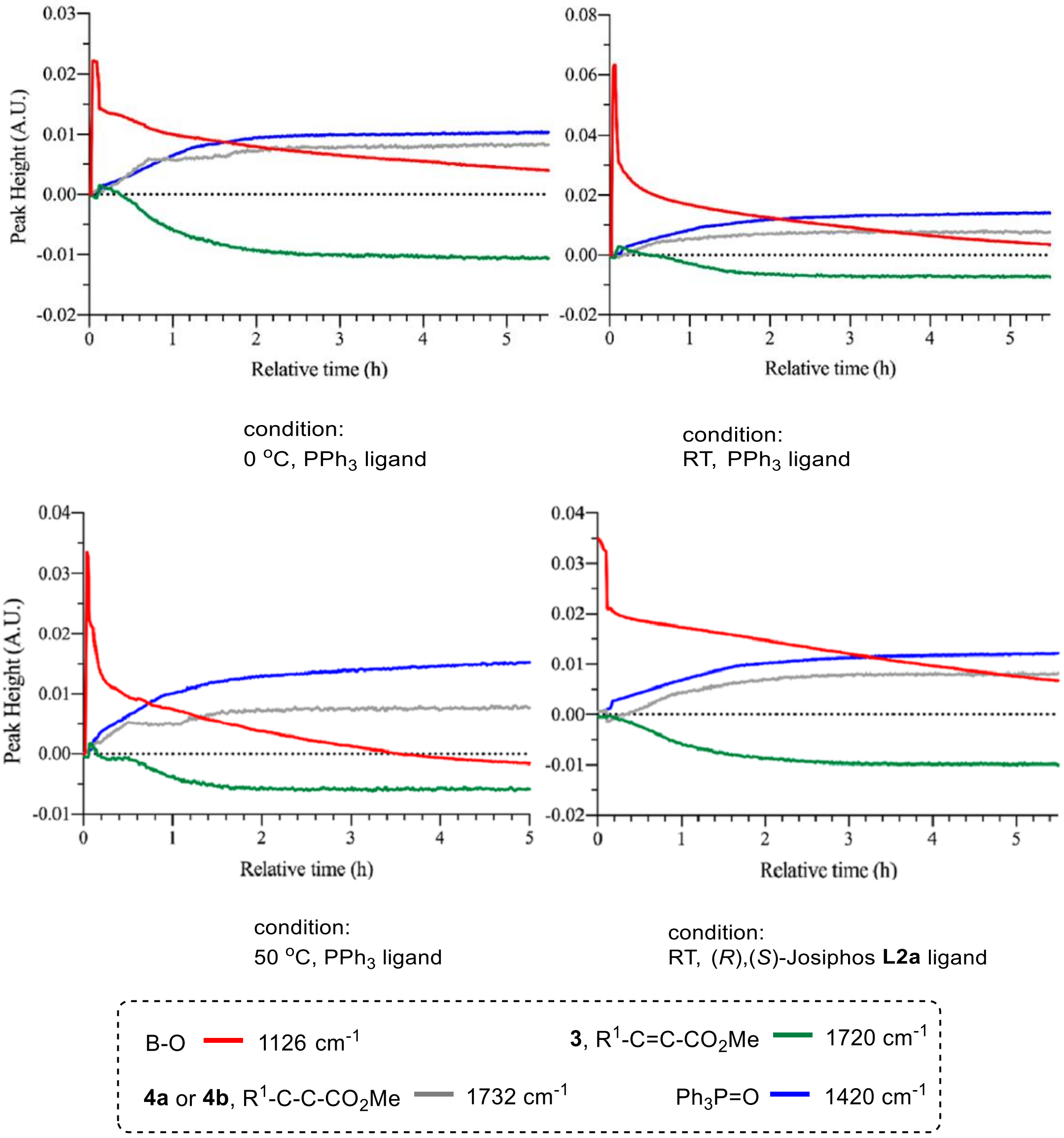
Figure 6 ReactIR showing the base effect to the borylation reaction producing **70b**[a]



[a] The ReactIR result is produced by the reference 30.

In 2017, the same group developed an updated catalytic asymmetric hydroboration method (Scheme 1).[12a] In order to better understand the mechanism of the second catalytic hydroboration of the homoallylic boronate esters **3**, ReactIR was again utilised to observe the key stretches of the components in the reaction system (Figure 7). Whilst a smooth decrease of the substrate **3** and a corresponding increase of the diborylated product **4a** or **4b** and by-product TPPO (triphenylphosphine oxide) was observed, a rapid consumption of the B-B bond occurred and was replaced by the appearance of a new B-O bond. This analysis suggested that nearly half of the B_2pin_2 (Scheme 1) was rapidly transformed in the first few minutes upon mixing of the reagents. The increase of the reaction temperature slightly speeded up the B-O bond loss. Comparing to PPh_3 ligand, chiral ligand **L2a** resulted more B-O remained after the rapid B-O bond decrease (Figure 7). Although there was no mechanistic explanation was given, it was still a valuable clue for further investigation and likely that the Cu-Bpin intermediates proposed in the literature may not fit with these observations.[28] The proposed copper species, Cu-Bpin, cannot play its claimed role because the decrease in B_2pin_2 concentration is quite different from the smooth conversion from the starting material to product.

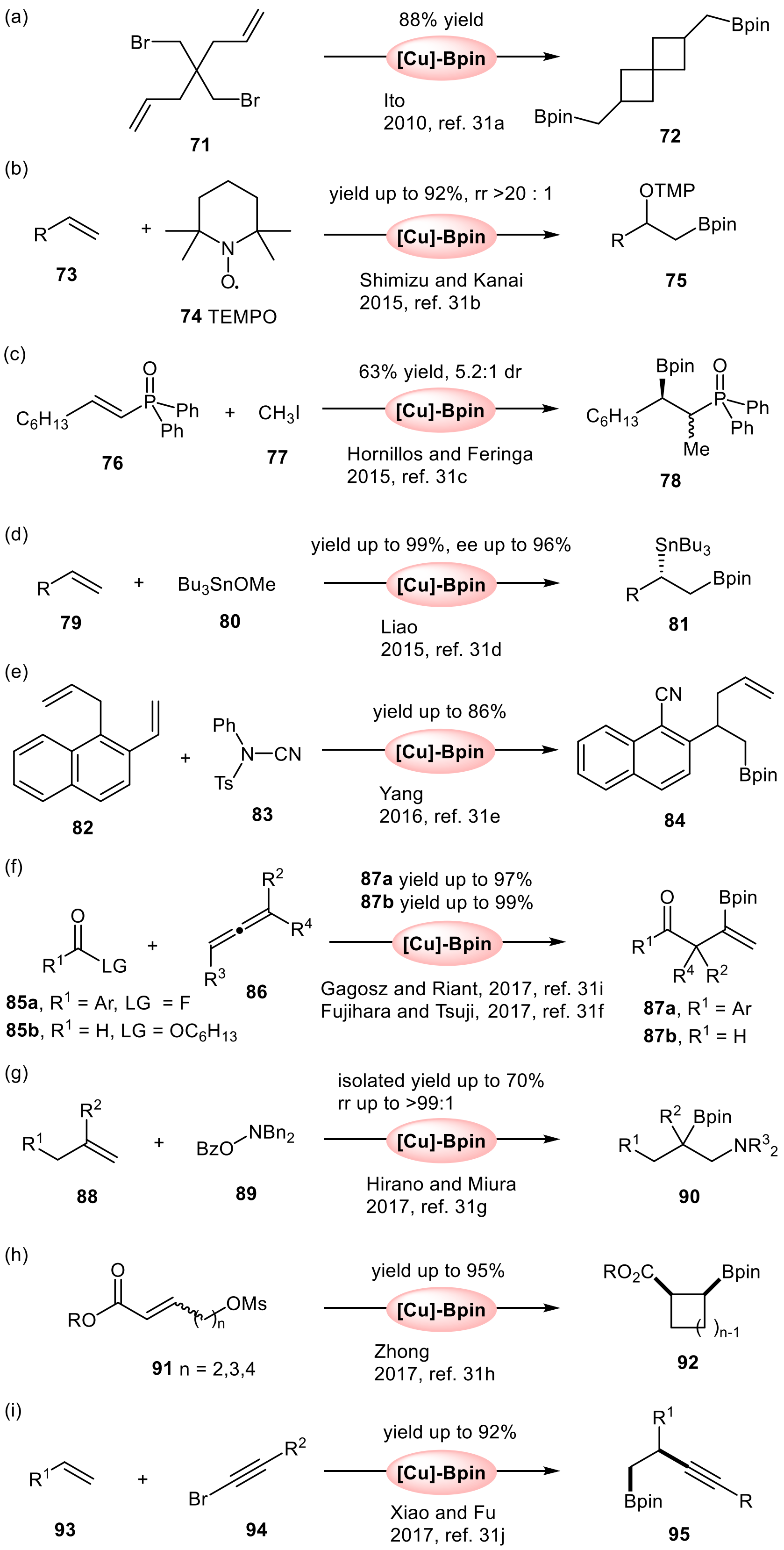
Figure 7 ReactIR indicating unexpected B_2pin_2 loss in the hydroboration reaction of homoallylic boronate esters[a]



[a] The ReactIR result is produced by the reference 28.

1.3.1.2. Borylative difunctionalization methodologies

Despite these analytical techniques, borylative difunctionalization of alkenes was also suggested through a copper-boron intermediate mechanism.[31] After addition to alkenes with a Cu-Bpin species, the copper-carbon bond is easily broken and able to cascade with further transformations for the bifunctionalizations. In comparation, the copper hydride intermediate only gives a hydroboration product and is therefore ruled out for such borylative bifunctionalization reactions. (Scheme 17).[31] Unless there were suitable directing groups present for a second copper-catalysis functionalization, the proposed mechanism involving simply a Cu-H addition was unable to achieve catalytic difunctionalization of alkenes. Thus, most recently, the copper-catalysed borylative difunctionalization reaction of alkenes has been proposed to employ borocupration as the key step in a proposed mechanism.[31] Selected catalytic borylative difunctionalization approaches of alkenes involving copper-Bpin intermediates are highlighted in Scheme 20.

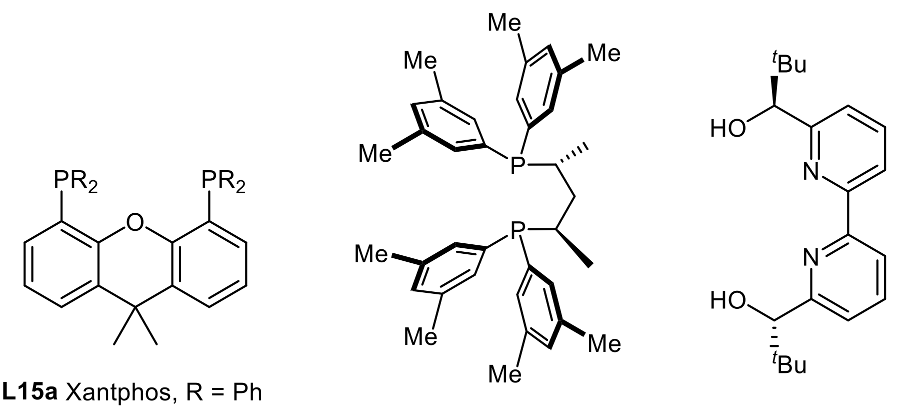


Scheme 20 Summarized recent methodologies of copper catalysed borylative difunctionalization

1.3.1.3. Density functional theory

Density functional theory (DFT) has gained acceptance as a tool for the exploration of organic reaction mechanisms. Among the publications involving copper catalysed hydroboration of alkenes in recent years, there has been a series of reports employing DFT calculations to support Cu-Bpin intermediates, seemingly generally recognized as a key and active species of alkene borylation.[32]

In 2013, Ito *et al.* reported B3PW91/cc-cVDZ level DFT calculations describing the copper-boron addition step to ethylene (Figure 8).[31a] Although a radical process is still under discussion,[33a] the Cu-pin addition mechanism for different ligands was compared *via* activation free energy and HOMO potential energy of the alkene. Combined with further investigations, Cu-pin was shown to have a strong ligand influence on the regioselectivity of the reaction, an explanation was proposed on the bases of DFT calculations (Figure 9).[31a,33b] The structures of the ligands used in the copper-catalysed borylations of alkenes are shown in Figure 9 and Schemes 22 and 23 are given in Figure 10.



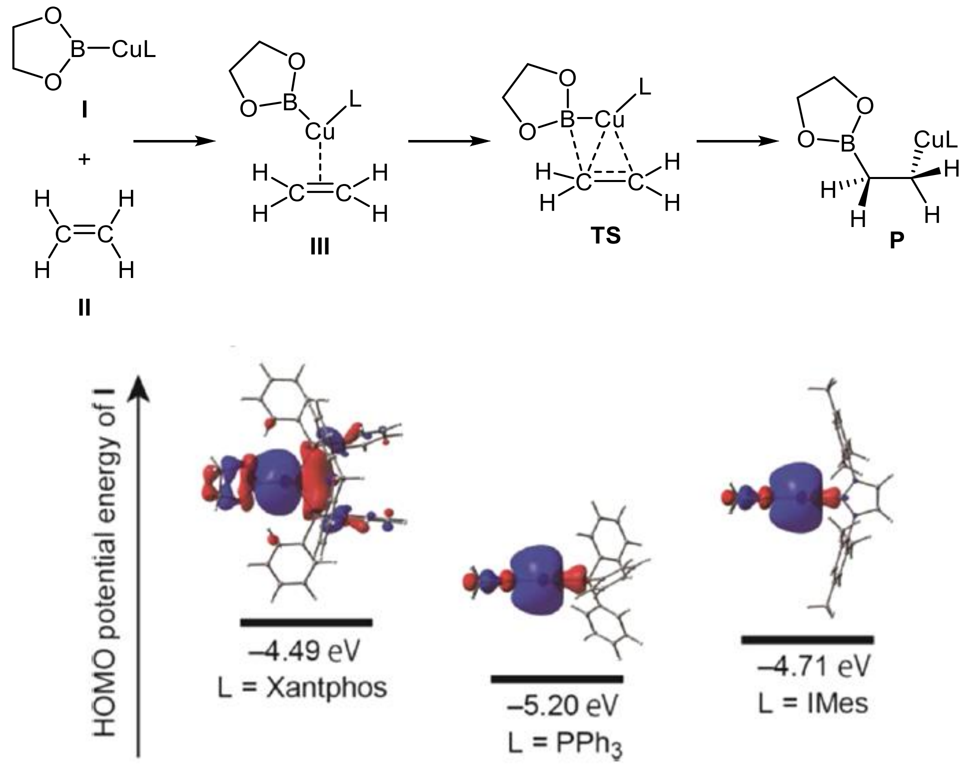
L15a Xantphos, R = Ph
L15b Cy-Xantphos, R = Cy

(*R*,*R*)-**L16**

L17

Figure 10 Ligands employed in copper-catalysed borylation of alkenes

Figure 8 DFT calculations (B3PW91/cc-cVDZ) of borocupration addition of ethylene[a]



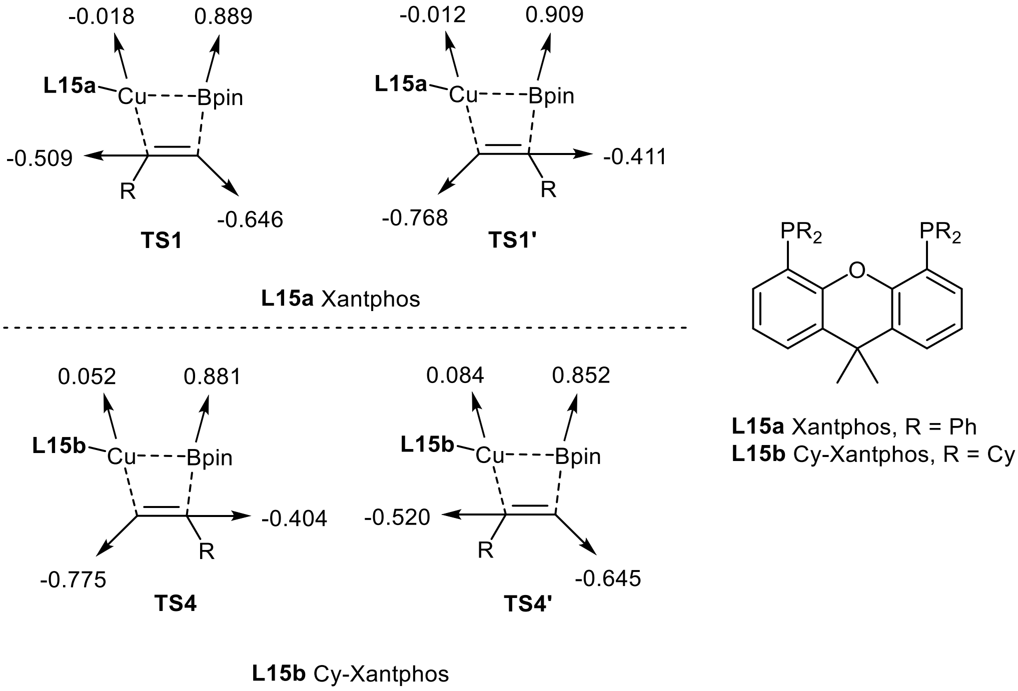
Ligand	ΔG (298 K, 1.0 atm, gas phase),[b] kcal mol^{-1}			
	I + II	III	TS	P
Xantphos(**L15a**)	0	7.1 (-6.5)	17.6 (2.1)	-11.4 (-24.9)
PPh_3	0	3.5 (-10.4)	19.0 (3.6)	-16.2 (-30.5)
IMes	0	7.3 (-8.1)	18.9 (3.0)	-14.2 (-30.1)

[a] The DFT result is produced by the reference 31a.

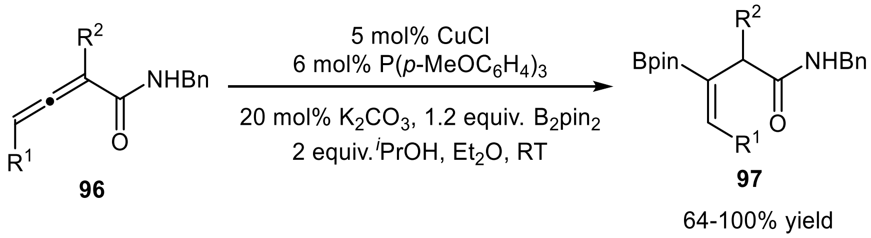
[b] Electronic energies are shown in parentheses.

In 2013, Ma *et al.* utilised energy profile calculation to clarify the copper-boron addition mechanism in the regio- and stereoselective catalytic hydroboration of 2,3-allenamides **96** (64-100% yield) (Figure 11, Scheme 21).[34a] A further breakthrough was accomplished by Hoveyda *et al.* on the allylative borylation of unactivated allenes in 2014, with a DFT calculated stereochemical model and applied the work in natural product synthesis.[34b]

Figure 9 Transition states showing ligand influence on regioselectivity of Cu-Bpin addition to alkenes[a]



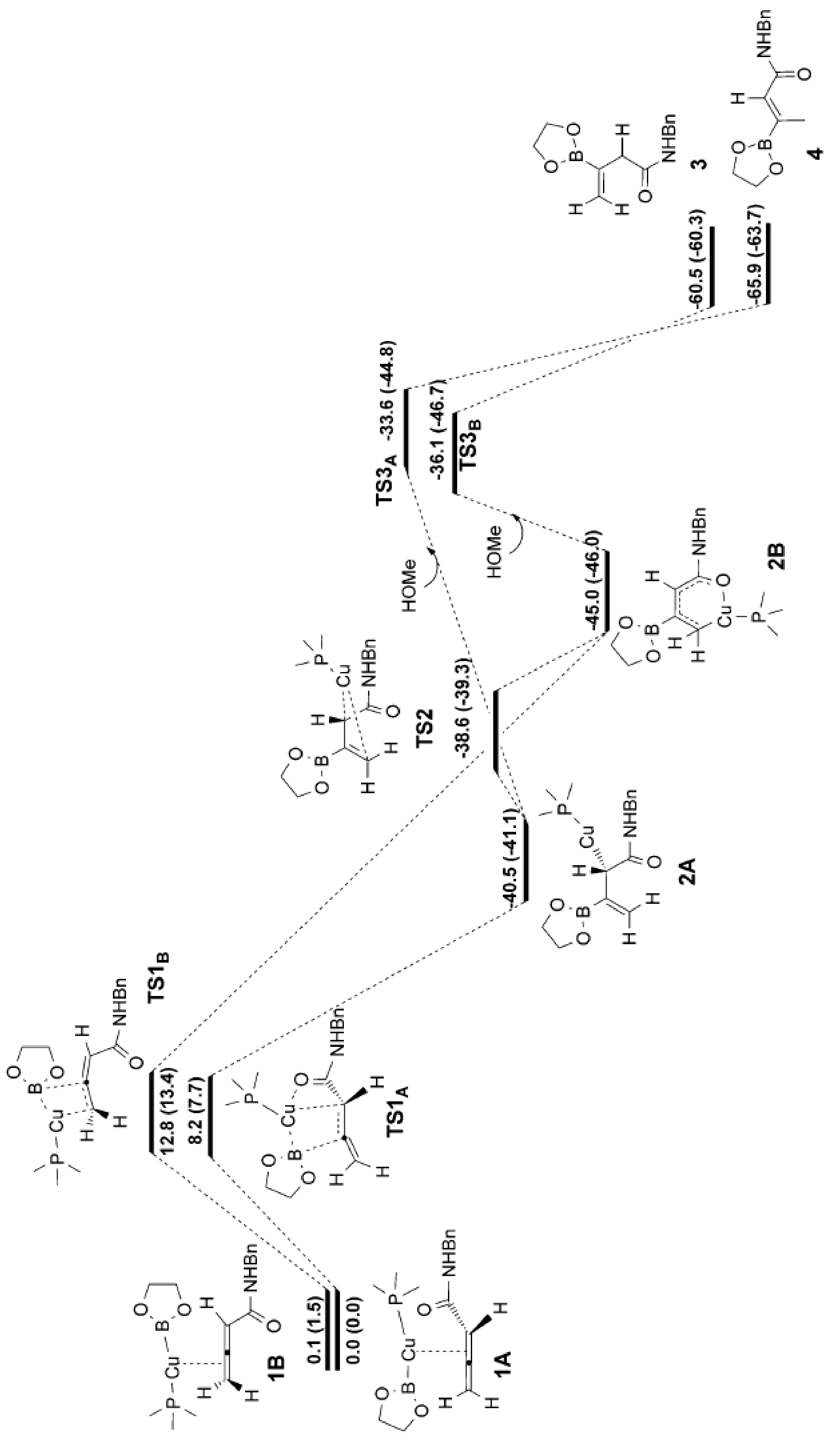
[a] The calculation result is produced by the reference 31b.



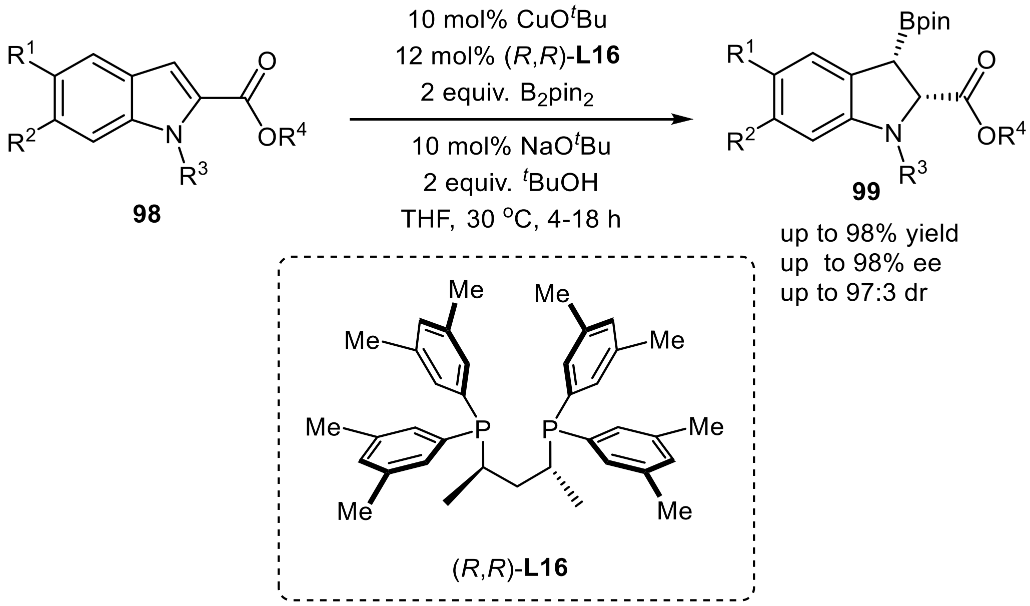
Scheme 21 Copper-catalysed regioselective hydroboration of 2,3-allenamides

Indole dearomative borylation is recognized as an important method of indole functionalization,[35a] as well as dearomatization in general.[9k] In 2015, Ito *et al.* realised the asymmetric dearomative hydroboration of indole-2-carboxylates **98** (Scheme 22) and suggested that the mechanism proceeds *via* a 3,4-addition of Cu-Bpin based on DFT calculations (Figure 12). The low Free Energy (-12.8 kcal/mol) showed the intermediate **IV** stable transferred by Cu-Bpin mechanism. [35b] Further related DFT studies on additional examples of hydroboration keep reported by same group.[35c,35d]

Figure 11 Energy profiles calculation of copper catalysed regioselective hydroboration of 2,3-allenamides *via* Cu-Bpin addition[a]

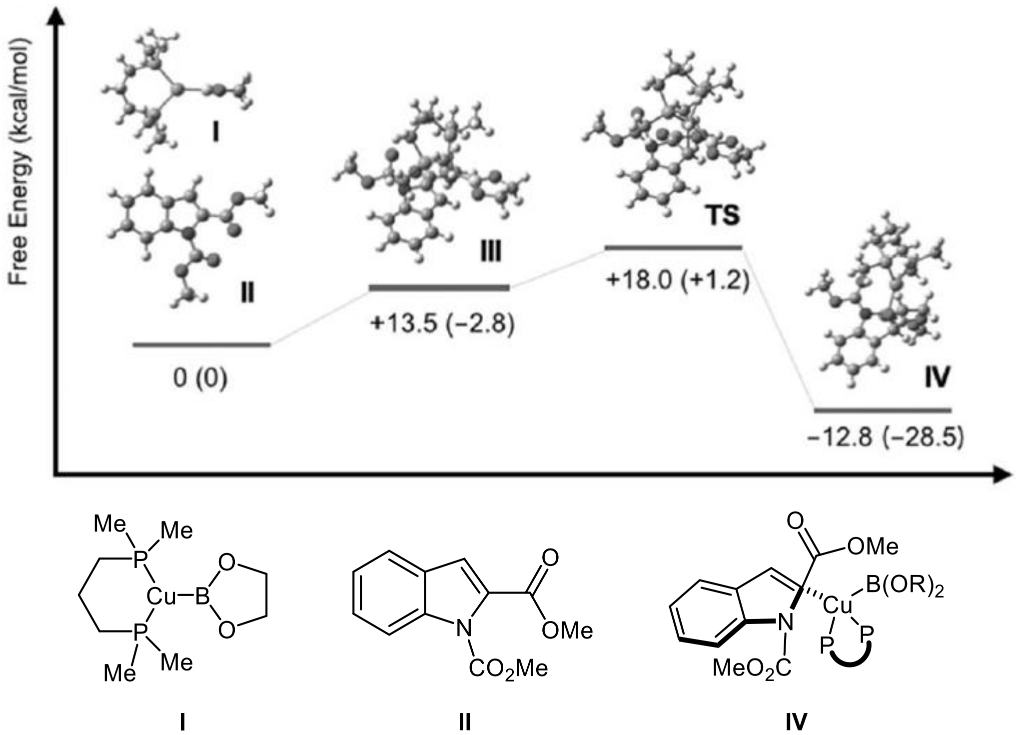


[a] The DFT result is produced by the reference 34a.



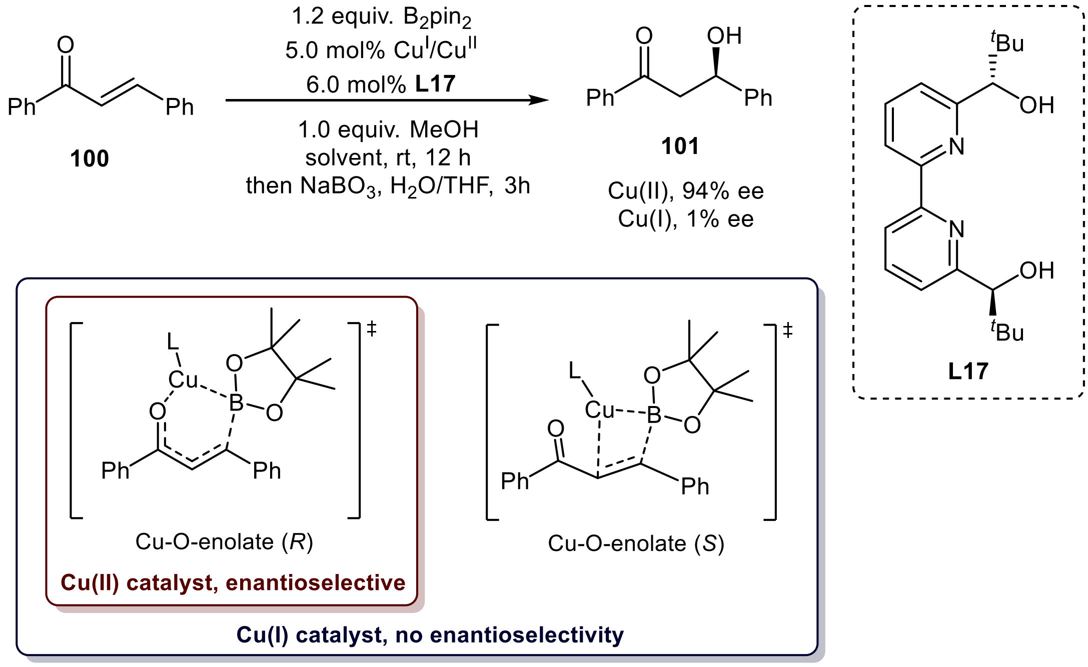
Scheme 22 Asymmetric copper-catalysed dearomative hydroboration of indoles

Figure 12 DFT calculation on Cu-Bpin dearomative insertion step[a]



[a] The DFT result is produced by the reference 36b.

In 2017, Kobayashi and Morokuma *et al.* published a detailed mechanistic study using both DFT and AFIR (artificial force induced reaction) methods for the enantioselective hydroboration of chalcones **100** which proceeds *via* a Cu^{I}/Cu^{II} catalysed conjugated addition reaction (Scheme 23).[36b] The reaction was reported by Zhu previously, who proposed the oxidation state of copper caused the stark contrast in enantioselectivities.[36a]

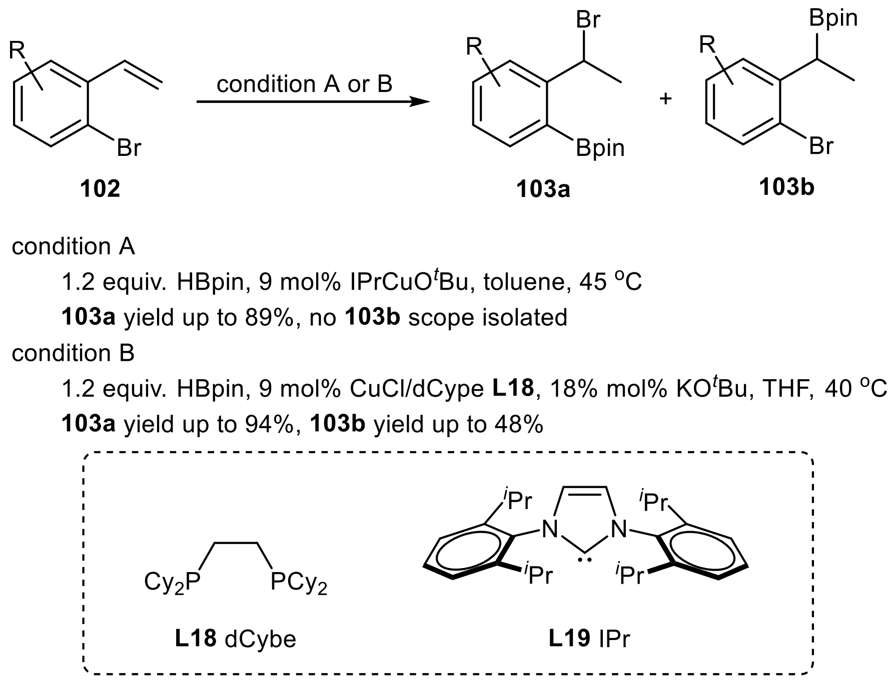


Scheme 23 Thermodynamical calculation model explaining Cu^{I}/Cu^{II} catalytic enantioselectivity difference on chalcones Cu-Bpin borylation

1.3.2. A Cu-H intermediate

Despite the mechanistic proposal with the Cu-BX_2 intermediate, the copper-catalysed hydroboration of alkenes was argued to occur by another mechanism with Cu-H as the proposed species. Although it was not suggested in the majority of mechanistic studies, hydrocupration has been comprehensively studied, especially in recent years.[37,38]

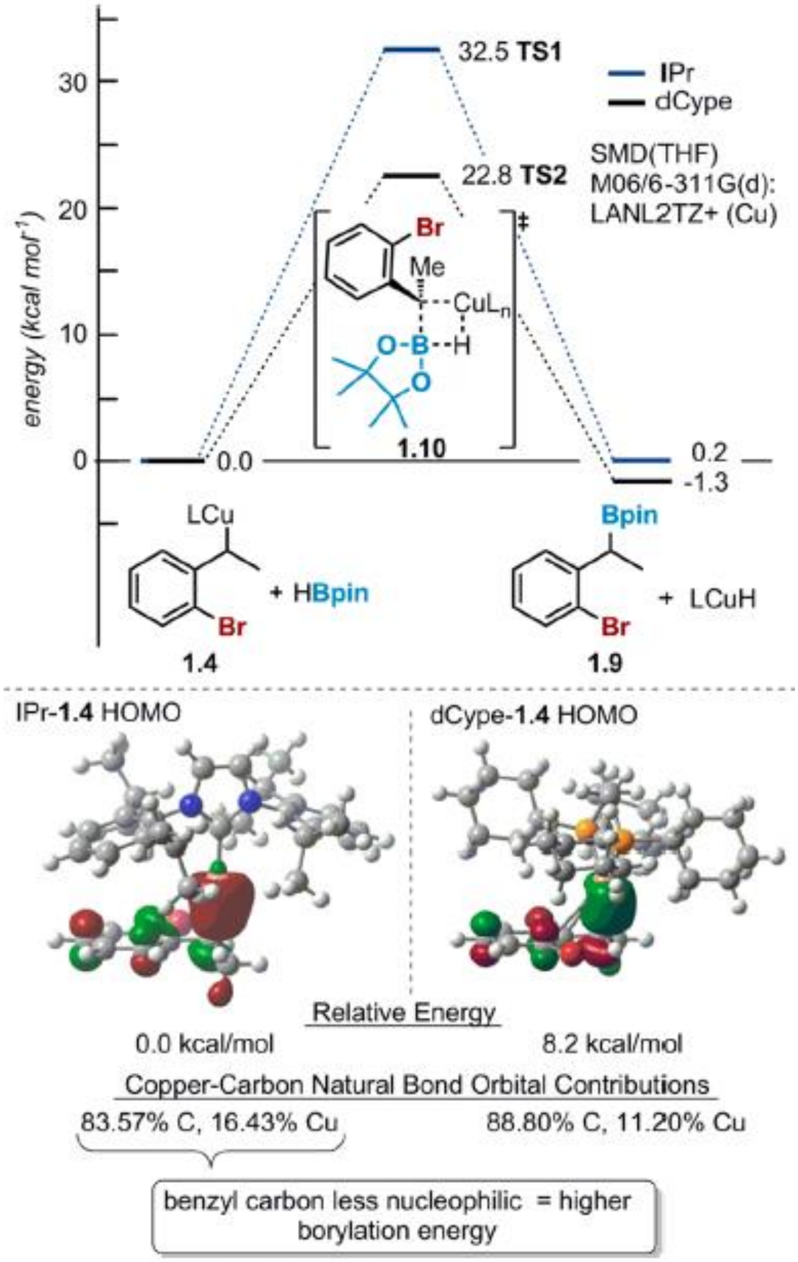
Following Yun and Lee's experimental and theoretical study on the hydrocupration/borylation mechanism of styrene in 2010,[38] there has been little additional work on the mechanism involving Cu-H intermediates. A more recent example published in 2015 by Schomaker *et al.* described an HCu-ligand (**L18** or **L19**) species which promoted competing borylative 1,3-halogen migration or hydroboration (Scheme 24). The hydroboration reaction was examined using DFT calculations also by the same group to reveal the borylation intermediate energy comparison between **L18** dCybe or **L19** IPr conditions (Figure 13).[39]



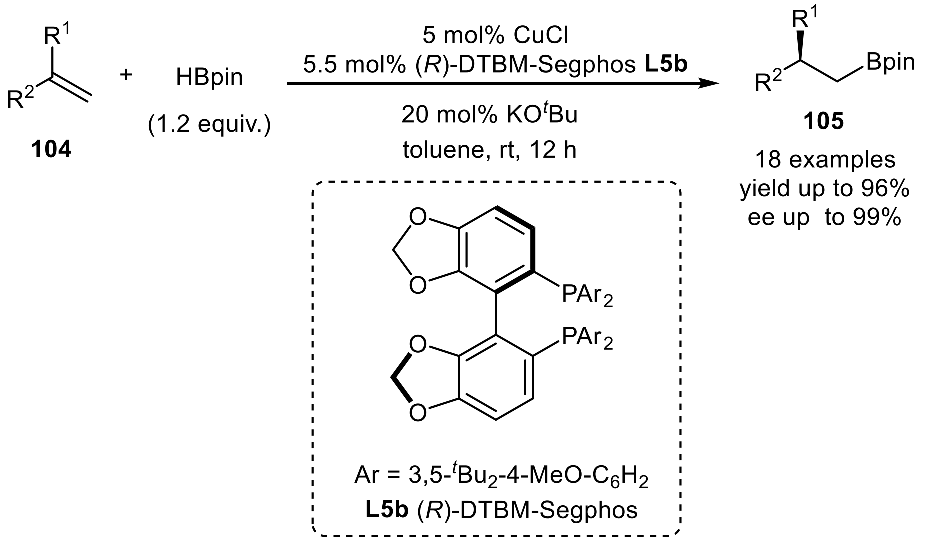
Scheme 24 Copper catalysed competing borylative 1,3-halogen migration or hydroboration of 2-bromostyrenes

A breakthrough came in 2017, when investigations of both the methodology and mechanism of the copper-catalysed asymmetric hydroboration of aliphatic alkenes and aryl alkenes was simultaneously accomplished by both Yun *et al.*[40] and Hartwig *et al.*[41] Yun *et al.* reacted aliphatic 1,1-disubstitued alkenes **104** resulting in up to 96% yield and 99% *ee* employing a Cu/**L5b** (*R*)-DTBM-Segphos catalyst system (Scheme 25). A gram-scale synthesis gave 96% yield with >99% ee, tolerating as low as 1 mol% catalyst loading (1.46 g borylated product generated). Moreover, a brief mechanism study was reported, giving rate orders of reaction components with relevant reaction profiles (alkenes zero, HBpin first, and Cu-catalyst first order respectively) as well as DFT calculations based on stereochemical models of the catalytic hydroboration of **104a** to clarify the enantioselectivities (Figure 14).[40]

Figure 13 DFT calculation study on dCybe or IPr ligand influence to hydroboration of 2-bromostyrenes[a]

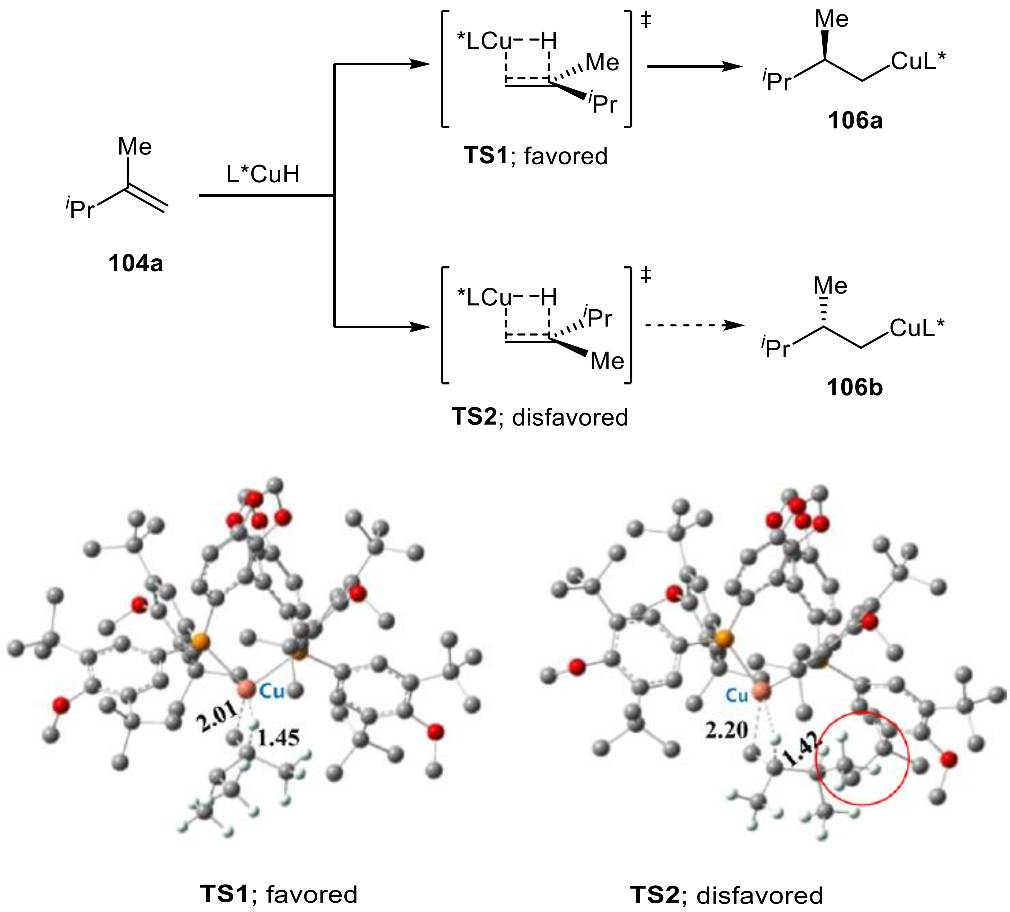


[a] The DFT result is produced by the reference 39.



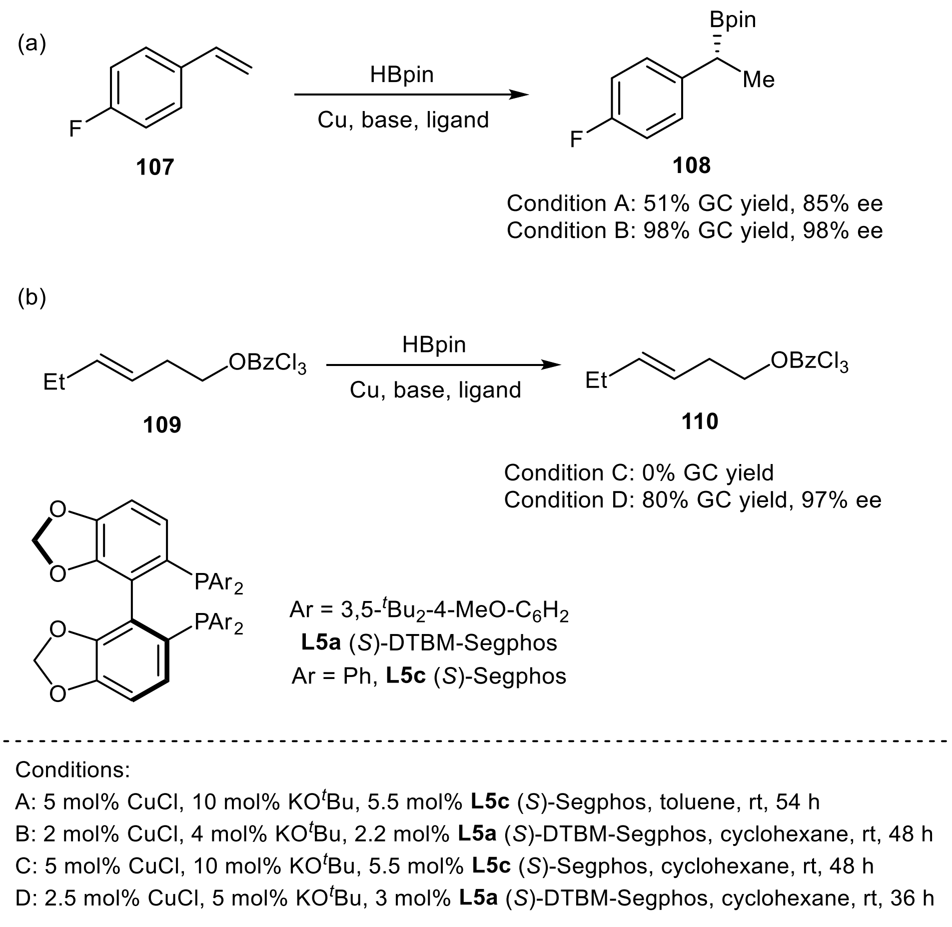
Scheme 25 Copper catalysed enantioselective hydroboration of 1,1-disubstituted aliphatic alkenes

Figure 14 DFT calculation model as the stereochemical clarification of enantioselectivity of alkenes hydroboration[a]

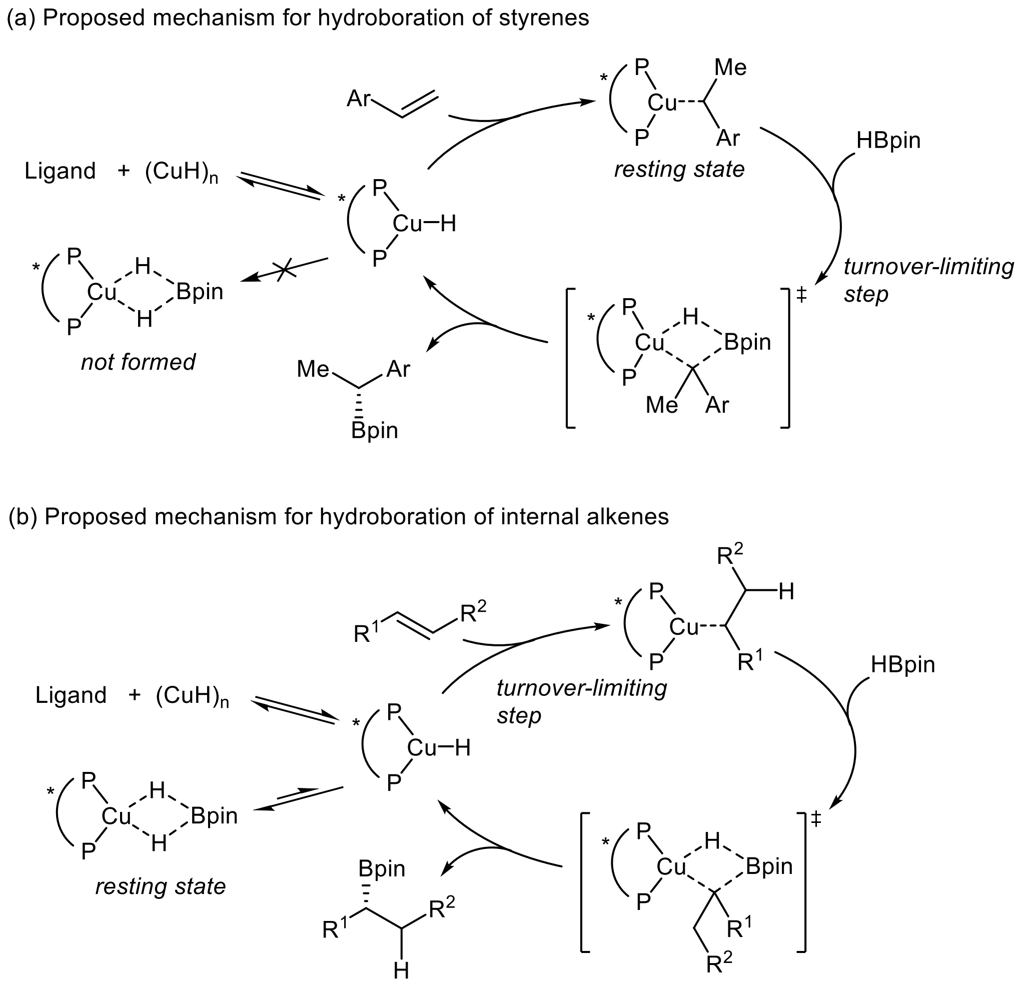


[a] The DFT result is produced by the reference 40.

More detailed mechanistic investigations were accomplished by Hartwig *et al.* employing a model hydroboration reaction of styrenes **107** and internal aliphatic alkenes **109** (Scheme 26). A series of active copper(I) species with ligands were structurally characterized and evaluated. Certain mechanistic details including turn-over limiting steps, resting states and reversible steps, were supported with more evidence and illuminated the substrates scope (Scheme 27).[41] Further investigations into the copper-catalysed hydroamination reactions by Lambrecht, Buchwald and Liu *et al.* also described the hydrocupration process. These studies provided additional support to the understanding of the proposed Cu-H addition mechanism to alkenes.[42]



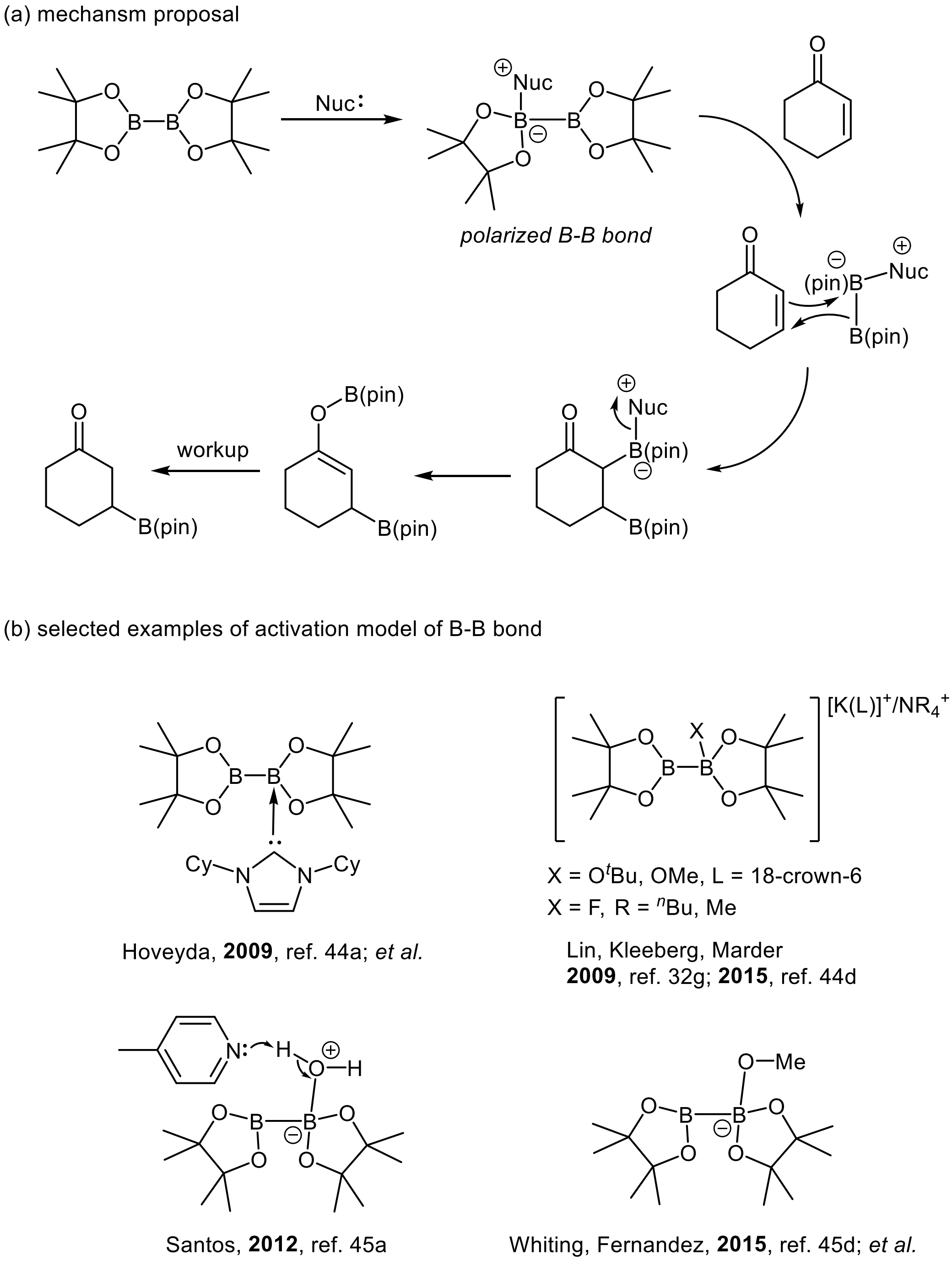
Scheme 26 Model reactions employed in mechanism study of catalysed hydroboration of alkenes



Scheme 27 Proposed mechanism for hydroboration of styrenes or internal alkenes

1.3.3. Other mechanistic proposals

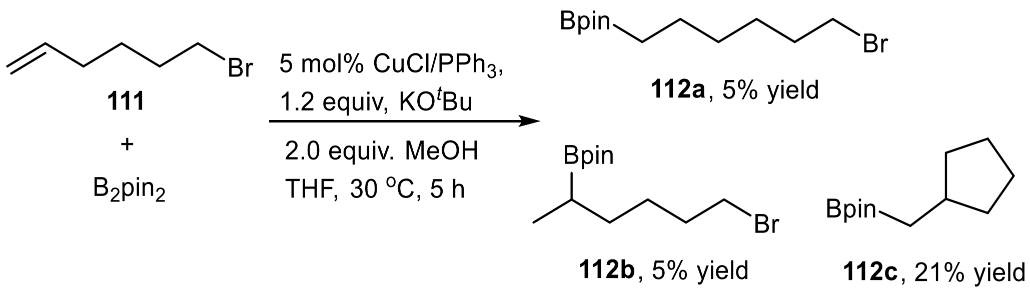
Despite the two main mechanistic proposals of copper catalysed hydroboration of alkenes *via* borocupration or hydrocupration addition being most frequently reported, there are, other potential models of borylation reactions. For instance, an uncatalysed background reaction has been proven to occur when employing alkyl boron compounds or boron hydrides (9-BBN, BH_3, $B(alkyl)_3$, and $HB(C_6F_5)_2$, etc.).[43] Recently, there have been numerous reports demonstrating relevant direct hydroborations utilising these borylation reagents. These have been applied to cascade reactions, including consecutive second-step copper catalysed reactions.[43] It is therefore important to consider the background reactions and their influence on the copper-catalysed hydroboration when similar alkyl boron compounds are employed.



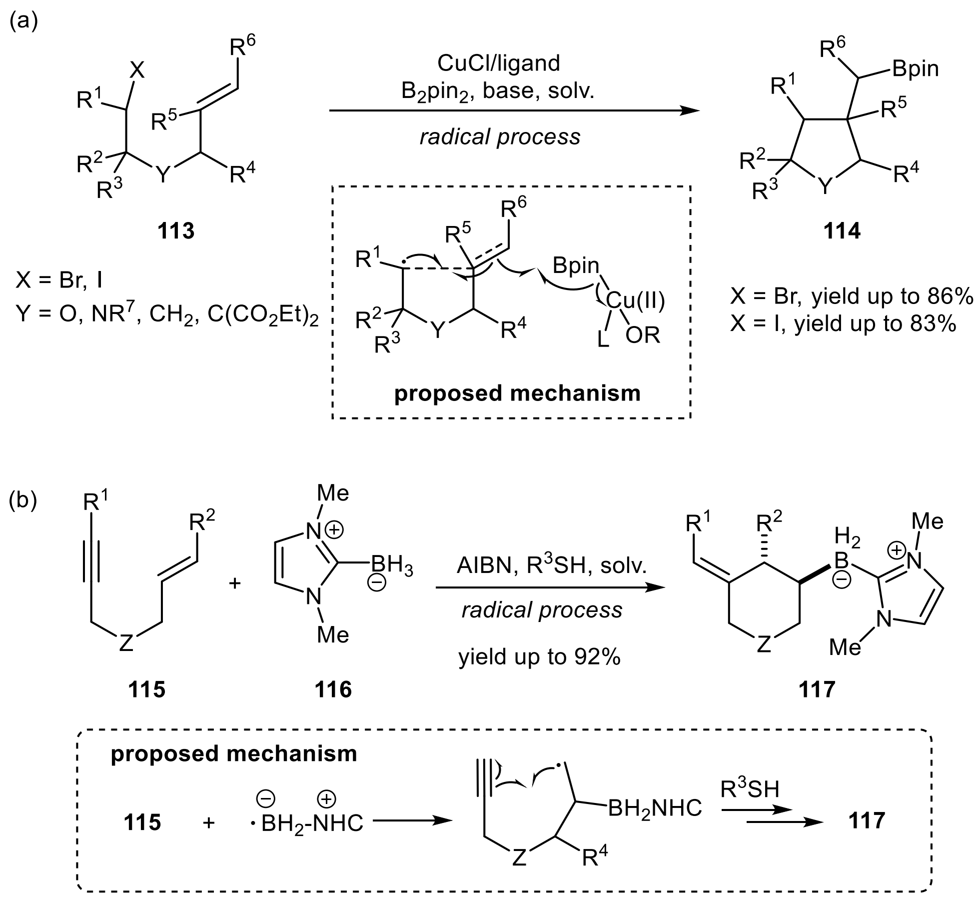
Scheme 28 Proposed mechanism of nucleophile activation of B_2pin_2 for metal-free hydroboration reaction

Metal-free activation methods of borylation reagents were utilised as a good strategy for achieving hydroboration of alkenes. Significantly, *N*-heterocyclic carbenes (NHC)[44] and alkoxide (or hydroxide) anions[45] were employed for the activation of diboron compounds. Since the NHC and anion play an important role in the copper-catalysed hydroboration system, the possibility of promoting the borylation mechanism is worthy of mention. Based on Hoveyda's mechanistic proposal of Lewis base catalysis (Scheme 28a),[44a] relevant characterization, mechanistic and methodological studies were developed (Scheme 28b).[44-45]

In addition, as mentioned in relation to DFT investigations of B-pin addition mechanism revealed by Steel, Marder and Liu *et al.* in 2012,[33a] and Ito *et al.* in 2013,[31a] a radical process has been suggested in the copper-catalysed hydroboration of alkene **111** with PPh_3 ligand (proposed to be the key effect) based on mechanistic studies[31a] (Scheme 29). In 2017, further methodologies for intramolecular borylative cascade coupling alkylation of haloalkenes **113**[46a,46b] and enynes **115**[46c] were also accomplished via a proposed radical mechanism (Scheme 30).[46d]



Scheme 29 Copper catalysed hydroboration influenced by PPh_3 ligand to process a radical related mechanism proposal



Scheme 30 Radical process proposed intramolecular borylative cascade coupling alkylation of alkenes

1.4. Synthetic application: Chiral 1,3-diols

The 1,3-diol is recognized as a key moiety of numerous bioactive molecules.[11] A series of drug molecules containing chiral 1,3-diols or derived therefrom, for example, diospongin A **118**,[47] atorvastatin **119** (within the statin class, the 3,5-dihydroxy acid fragment is frequently present),[48] and erythromycin **120**,[49] have all played an important role in disease treatment (Figure 15).[12a] Thus, efficient methods of synthesis of highly enantioenriched 1,3-diol have gained wide interest in the synthetic chemistry community. In 2006, Müller *et al.* summarized a series of stereoselective synthesis methods.[11d] In addition, Tortosa *et al.*

published an account article about 1,4-diols synthesis in 2013.[11g] Among these, asymmetric borylation/oxidation methods have been developed with various applications, especially for such polyol synthesis.

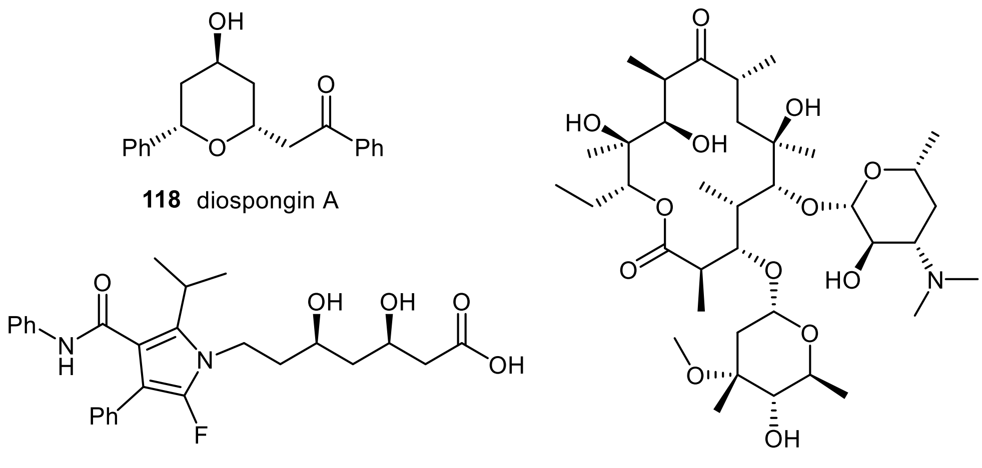
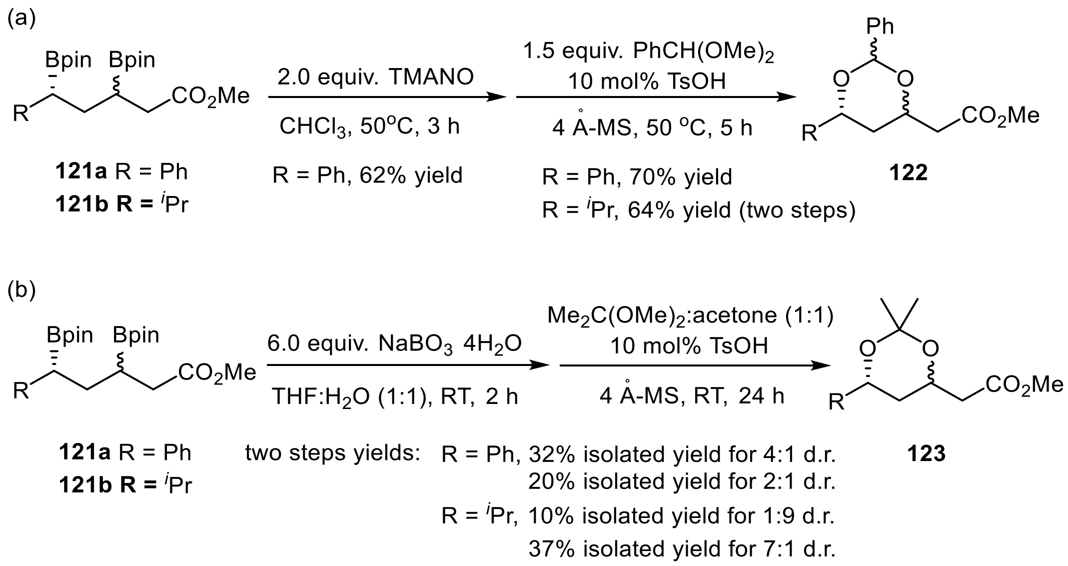


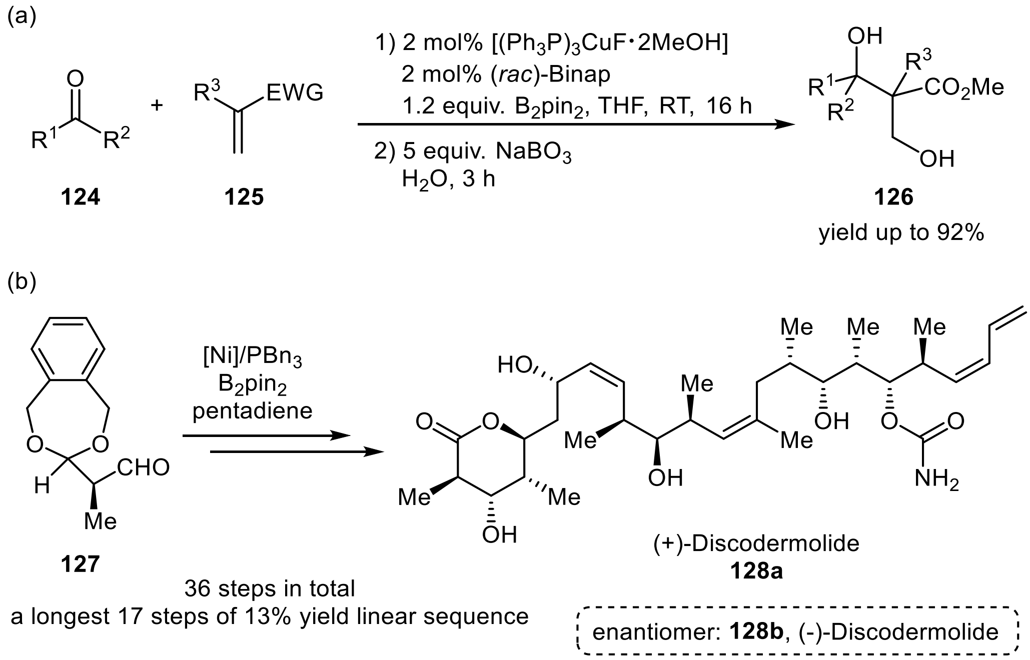
Figure 15 Bioactive molecules with 1,3-diol moiety

Essentially derived from the classic Brown hydroboration/oxidation reaction,[9] the enantioselective version of catalytic asymmetric hydroboration with a subsequent stereoselective oxidation, is one of the most powerful methods forming enantioenriched secondary or tertiary alcohols. By utilising the copper-catalysed double hydroboration strategy of electron deficient alkenes (Scheme 1), an effective streamlined method was achieved by Whiting *et al.* in 2017.[12a] Inspired by the results of a series of related papers,[12b-l] 1,3-diborylated esters **121a** and **121b** were produced and stereochemical control examined, followed by oxidation and 1,3-diol protection (Scheme 31).



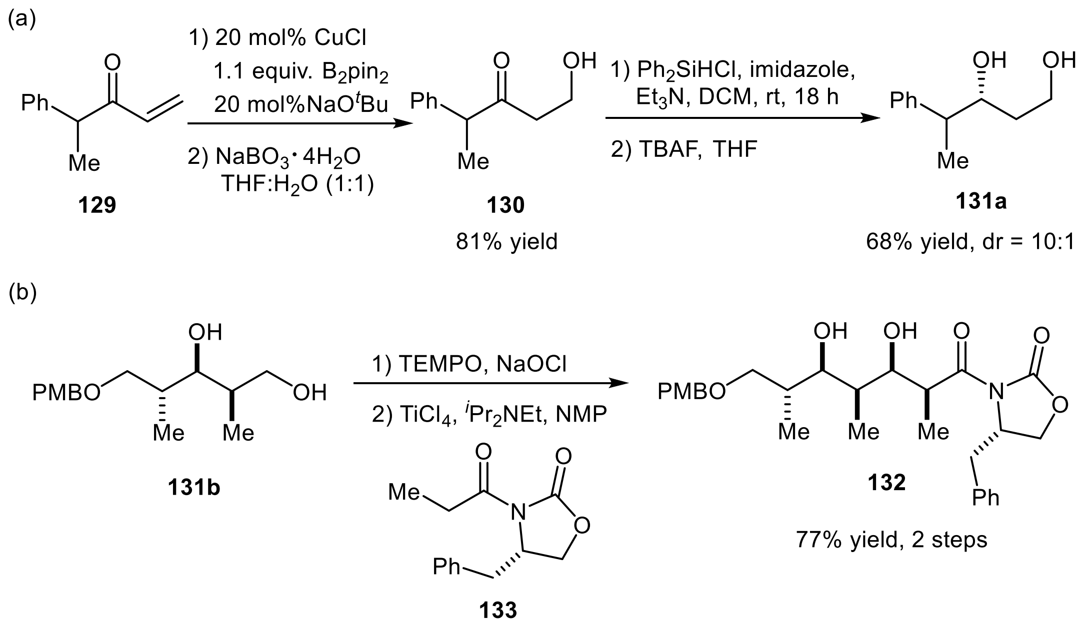
Scheme 31 Oxidation/1,3-diol protection process of 1,3-diborylated esters

Further to Hoveyda *et al.*'s[44a] and Kanai and Shibasaki *et al.*'s work,[50a] Riant *et al.* described the Cu/Binap catalysised cascade borylation/aldol reaction. 1,3-Diols **126** were obtained in up to 92% yield after oxidation (Scheme 32a).[50b] Employing nickel-catalysis by Morken *et al.* in 2014, this reaction was involved in the tandem borylation/aldol reaction, as a part of the total synthesis of (+)-discodermolide **128a** (36 steps in total) (Scheme 32b).[50c,50d]



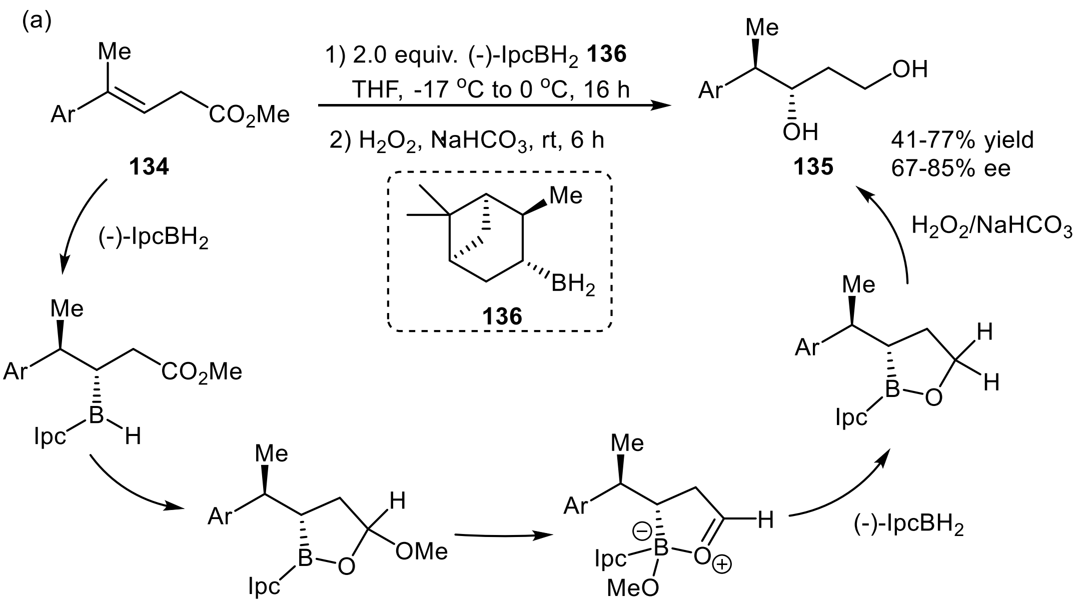
Scheme 32 Tandem borylation/aldol reaction of alkenes utilised in 1,3-diol synthetic applications

In 2013, O'Neil *et al.* reported a streamlined stereoselective synthesis route to 1,3-diols. Copper-catalysed hydroboration/oxidation of α,β-unsaturated ketone **129** gave an 81% yield. An intramolecular carbonyl hydrosilylation of β-hydroxy ketone **130** was then performed to generate the 1,3-diol **131a** in 68% yield with up to >10:1 dr *via* a cooperative Lewis-base activation process (Scheme 33a). With this preparation method in hand, a diastereoselective synthesis of polyketide fragments, (-)-discodermolide **128b** (Scheme 32b) were developed. Further oxidation/Evans *syn*-aldol reactions were then employed (Scheme 33b).[51]



Scheme 33 Copper-catalysed hydroboration/oxidation with intramolecular carbonyl hydrosilylation and its synthetic application

Borylation/reduction strategies were employed to afford 1,3-diols[12k,52] in 2013 by Bull *et al.*, utilising the chiral borylation reagent, (-)-IpcBH_2 **136**, for the cascade hydroboration/reduction reaction. Tolerating different aryl groups, chiral 1,3-diols **135** were obtained 41-77% yields and 67-85% ees after H_2O_2 based oxidation. Interestingly, the ester group was reduced by excess (-)-IpcBH_2 **136** according to the proposed mechanism (Scheme 34).[53]



Scheme 34 Chiral 1,3-diol synthesis *via* one-pot hydroboration/reduction reaction

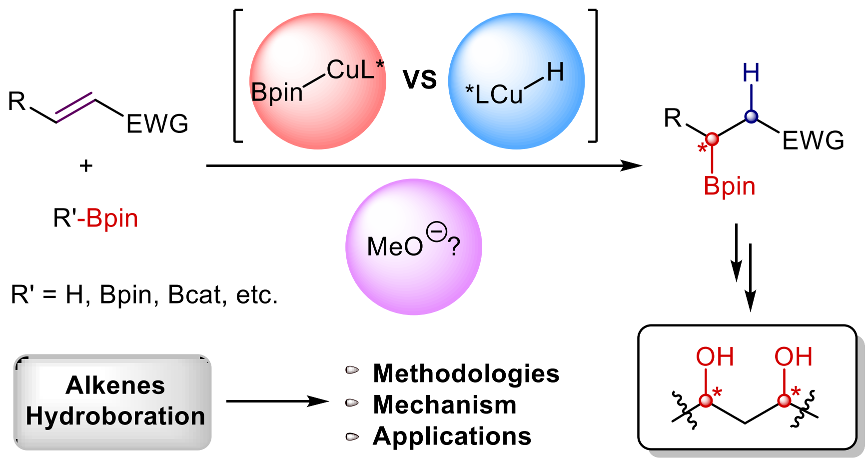
1.5. Summary and outlook

In summary, advances in the copper-catalysed asymmetric hydroboration of electron deficient alkenes have occurred, with development of new methodology, mechanistic investigations and synthetic applications. After Aggarwal's excellent review,[4k] a number of developments highlighted a series of tandem synthetic strategies or difunctionalization transformations. Thus, it is not surprising that further methodology developed. These studies have focused on wider scope for the copper-catalysed borylation, tolerating tertiary carbon centers, applications in complex substrate skeletons, and combined cascade reactions of relevant unactivated alkenes with high regio-, stereo- and enantioselectivities. In terms of mechanistic investigations, various experimental insights and DFT calculations have been reported to support mechanistic proposals. These updated the general proposed mechanism reviewed in 2012.[10c] Numerous investigations have suggested mechanisms employing Cu-Bpin intermediates as key species, as well as several other examples of Cu-H addition to alkenes utilising HBpin as borylation reagents. Moreover, other reports have demonstrated metal-free activations systems and radical procedures. Hence, the borylation mechanism has been under heated debate and no fully convincing evidence has appeared to date. Finally, many applications of asymmetric borylation chemistry in total synthesis have been developed, including strategies for the preparation of chiral 1,3-diols. The total synthesis of bioactive molecules containing 1,3-diol, or derived moieties, has indisputably benefited from the catalytic asymmetric borylation and subsequent product transformation methods.

Results and discussion

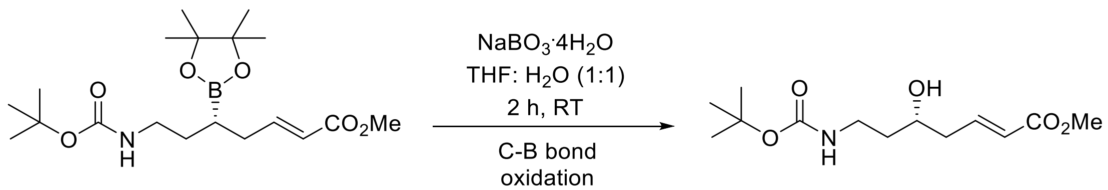
2.1. Research aims

The evolution of methodologies and mechanistic studies for the copper-catalysed enantioselective hydroboration of electron deficient alkenes has gained much attention.[54] It is important to investigate novel borylation reaction methods aiming at mild, cheap and green conditions with excellent substrate scope, but also understanding the relevant mechanisms.[7-10] To date, the activation model in this reaction is still under discussion, as reviewed in the first section of this dissertation. Bpin-Cu, Cu-H and base anions have each been supported separately by different evidence as being the key species in the hydroboration reactions of alkenes (Scheme 35).[54] Following the previous investigations on the asymmetric borylation reaction of alkenes,[3] further applications in the total synthesis of bioactive molecules is of value for validating the use of such procedures.[2] Among these, utilising the borylation strategy as a tool to construct enantioenriched natural products containing 1,3-diol moieties that have been an attractive topic in recent years (Scheme 35).[11, 12, 50-53]



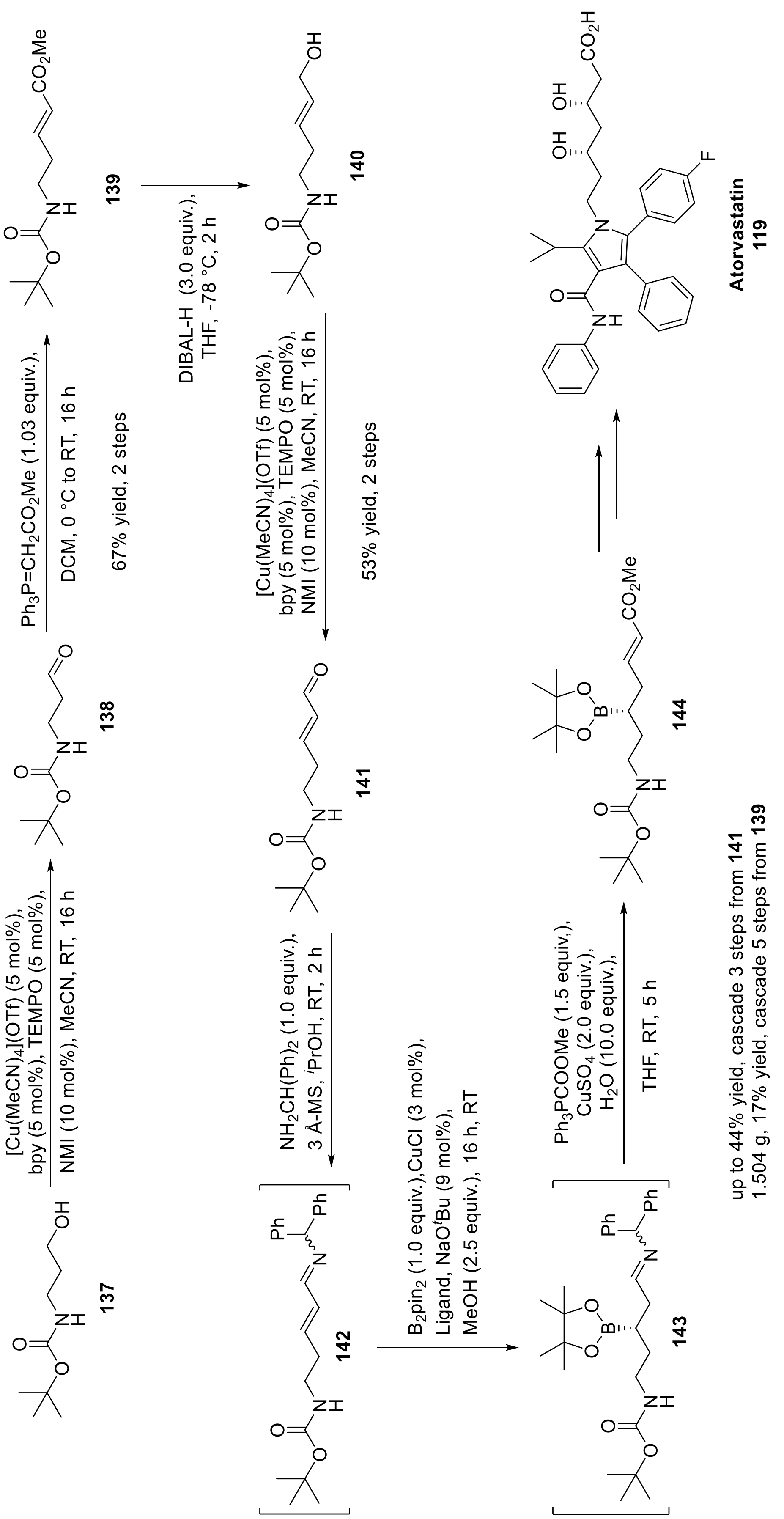
Scheme 35 The methodologies, mechanism and applications of alkenes hydroboration

This research aimed to develop an asymmetric borylation strategy for the total synthesis of atorvastatin **119** (Scheme 36). Previous research in the Whiting group demonstrated a series of methodology developments and mechanism investigations on the copper-catalysed asymmetric borylation of electron-efficient alkenes, especially involving a streamlined, one-pot process for the catalytic hydroboration of α,β-unsaturated imines, as well as their further transformations and stereochemical investigations (Scheme 1 and Scheme 31).[12] Based on the previous synthetic procedures involving the cascade imine formation/borylation/hydrolysis/Wittig trapping method with a second hydroboration reaction,[12a] previous preliminary investigations in our group started to develop a dual asymmetric borylation strategy for the total synthesis of atorvastatin.[55] However, the work was only conducted on small scales and no operationally streamlined synthesis process had been developed to allow completion of the synthesis. The aim therefore was to continue this work, and this thesis is an update that examines optimisation and completion of the total synthesis. Further reaction conditions and the development of optimised reaction processes to be efficient and with high stereochemical control was also carried out. This project therefore involved the first nine steps in the total synthesis of atorvastatin **119** and then aimed at completing the total synthesis (Scheme 36). Moreover, a key part of this project was the control of the enantioselectivity in the first copper-catalysed borylation of α,β-unsaturated imine **142**, which would require major studies to be carried out, especially HPLC method development to investigate the levels of stereochemical control in each key stereochemical step of the total synthesis. To date, suitable and effective HPLC conditions to analyse homoallylboronate carboxylate boronate ester **144** had not been reported, and hence, the *ee* value of the corresponding allyl alcohol **145** after a further oxidation of C-B bond of **144**[55], had not been determined (Scheme 37). Thus, this project aimed to examine and solve issues related to estimating the ee, and whether any potential racemisation during the oxidation step in the previous work might be occurring, and to develop a more detailed and robust HPLC analytical method to determine the exact *ee* of the borylated product **144**.



144 **145**

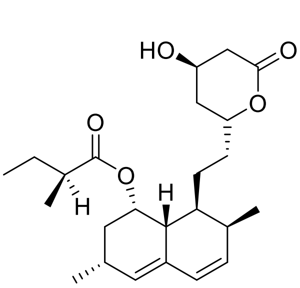
Scheme 37 Oxidation of C-B bond of homoallylboronate carboxylate boronate ester **144**



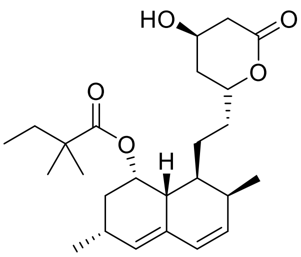
Scheme 36 The first nine steps on the total synthesis of atorvastatin

2.2. Background

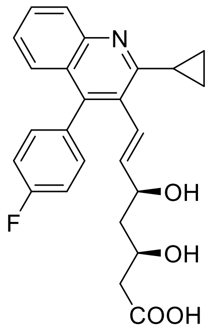
Atorvastatin **119** is one of the most important lipid-lowering prescription drugs for the treatment of cardiovascular disease.[56a,56b] The Statin class (Figure 16) has achieved over $125 billion sales and become one of the bestselling medicines in pharmaceutical history.[56c] As a HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitor, it is generally used to control cholesterol levels in the blood lowering unfavourable LDL-C cholesterol and raising favourable HDL-C cholesterol. It is prescribed for reducing the risks of heart attack, stroke, and other types of heart disease. It is used in heart surgery for certain types of heart condition and in high blood pressure regulation.[56d]



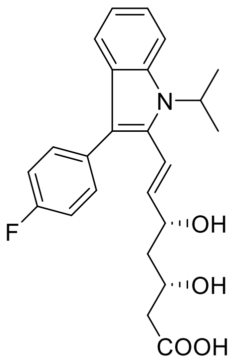
146
lovastatin



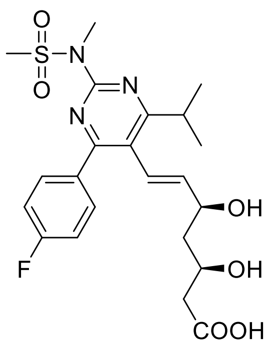
147
simvastatin



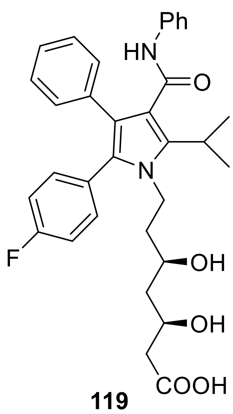
148
pitavastatin



149
fluvastatin



150
rosuvastatin



119
atorvastatin

Figure 16 The statin class

Due to its importance in medicine, the total synthesis of atorvastatin has gained much research interest in synthetic chemistry. The first racemic total synthesis and enantiomeric separation of atorvastatin was realised by Parke-Davis-Warner-Lambert.[57] Produced as the calcium salt with the trade name Lipitor®, atorvastatin was sold by Pfizer in 1996.[56d,58] In the following years, numerous synthetic investigations have focused on novel enantioselective approaches to atorvastatin using a variety of synthetic strategies.[56a,58] Interestingly, the key chiral 1,3-dihydroxy group requires a synthetic step yielding a 1,3-diol with highly *cis*-stereoselective control and high enantioselectivity (Figure 16). Hence, developing a strategy for the efficient construction of the chiral 1,3-diol intermediate is key for the total synthesis of atorvastatin (Scheme 31-34).

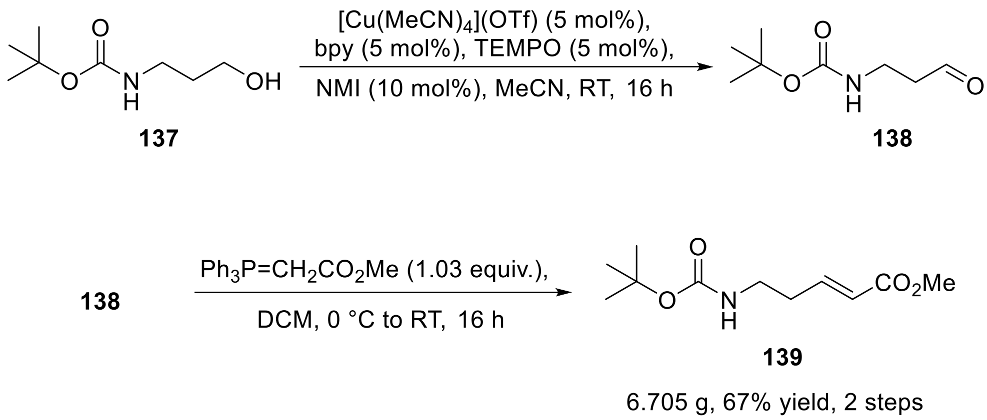
2.3. Synthesis optimisations

In order to access the chiral 1,3-diol moiety which would allow the total synthesis of atorvastatin, the synthesis of relevant precursors was investigated with the aim of optimising reaction efficiencies, by modifying reaction conditions and work-up methods. The overall aim was to access atorvastatin in good yield and on a practical scale (big scales to ensure the synthesis efficiency to reach out the final product atorvastatin **119**), substantially improving upon the previous small scale synthesis examined by Santiago.[55]

Based on the previous work of our group,[55] an efficient method for the preparation of the intermediate homoallylic boronate ester **144** (Scheme 36) was employed. Although initial attempts at this reaction met a series of problems, good yields were achieved on a practical scale.

2.3.1. Combined oxidation/Wittig reaction from alcohol 137

Firstly, employing a copper-catalysed oxidation method with TEMPO, aldehyde **138** had previously been reported to be formed in up to 87% yield from alcohol **137** (Scheme 38).[55] The aldehyde **138** was found to be volatile *in vacuo*, decreasing the isolated yield to 46% and 42% (Table 1, entry 1 and 2). In order to avoid isolation of the aldehyde, a one-pot synthesis was developed, i.e. through crude aldehyde **138** being used in reaction with the methyl acetic ester ylide (Scheme 37) obtaining a 27% isolated yield of **139** (Table 1, entry 3). Further attempts were made to increase the yields of **139** and to optimisation of the reaction work-up. The addition of $ZnCl_2$[59] was developed to remove the Wittig reaction by-product, triphenylphosphine oxide TPPO, since later investigations revealed that this compound caused issues in the later stages of the synthetic route, i.e. during the transformation of the β-borylated imine **143** transforming to homoallylboronate carboxylate boronate ester **144**.



Scheme 38 The oxidation and Wittig reaction generating α,β-unsaturated ester **139**

In addition, it is worth mentioning that when this reaction of compound **137** was carried out on a large scale (Table 1, entry 3), the yield was improved if air was kept running through the reaction (an air line and needle was employed for pumping the air, rather than using an air balloon) with 72 hours. Due to the volatile characteristics for the product **139**, the product was dried *in vacuo* to remove the solvent for only 2 hours. However, ^{1}H-NMR spectra confirmed that a clean product with the isolated yield 67% over the two steps was obtained. Interestingly, if the oxidation was run for an even longer reaction time, the yield was reduced.

Table 1 Optimization of oxidation/Wittig reaction generating α,β-unsaturated ester **139**

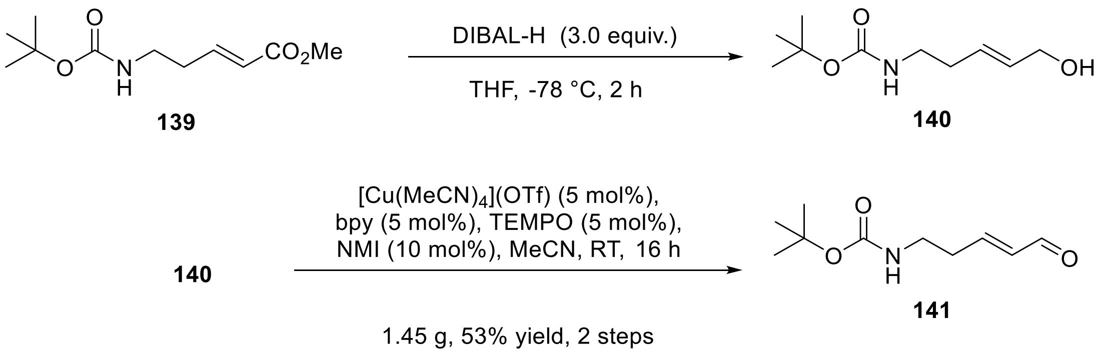
Entry	Previous work in AW group	1	2	3	4
Yields of step 1	87%	46%	42%	crude	crude
Yields of step 2	73%	63%[a]	65%[b]	27%	67%
Product **139** output	1.31 g	0.783 g	3.15 g	6.20 g	6.70 g
Comments	The volatile **138** purification decreased isolated yield			Yields for two steps	

[a] Solvent escaped during overnight open reaction system.
[b] With $ZnCl_2$/IPA work-up for TPPO removal.

2.3.2. Combined reduction/oxidation for α,β-unsaturated aldehyde 144

With the α,β-unsaturated ester **139** in hand, it was then utilised for the reduction/oxidation strategy. The previous investigation from our group revealed that the direct reduction of the α,β-unsaturated ester **139** generated the unsaturated alcohol **140** and aldehyde **141** at the same time. It was not possible to control the ratio of the main product to by-product, nor separate them effectively.[55] Following the DIBAL-H reduction method (Scheme 39), the DIBAL-H reduction product **140** was found to contain a by-product with an ^{i}Bu group still present, as detected in the ^{1}H-NMR spectrum after purification (entry 1, Table 2). Therefore, a DIBAL-H reduction/TEMPO oxidation reaction was employed in a one-pot synthesis to obtain, in 53% isolated yield over the two steps, the product **141** (entry 2, Table 2). This compound was also found the volatile *in vacuo*, so a cold-finger rotary evaporator was required to diminish the losses upon drying *in vacuo*.

In the reduction of **139** to **140**, it was found that keeping the reaction system under argon when the saturated NH_4Cl solution was added to quench the reaction was important (entry 3. Table 2). It presumably prevents the possible competing oxidation (or other competing reactions) *via* air. These reaction conditions for the conversion of **139** to **140** resulted in reducing the amount of the unknown by-product. Also, an additional amount of 5% HCl helped the reaction work-up, with easier layer separation during the extraction. Due to the larger reaction scale, only 2 equivalents of DIBAL-H was utilised, preventing too much of the reducing reagent being used and making work up easier.



Scheme 39 The DIBAL-H reduction/copper-TEMPO oxidation of α,β-unsaturated ester **139**

Table 2 Optimization of DIBAL-H reduction/copper-TEMPO oxidation reactions

Entry	Previous work in AW group	1	2	3[d]	4[e]
Yields of step 1	57%	<93% [a]	crude	crude	crude
Yields of step 2	70%	65%	53%[b]	crude	23% [b]
Product **141** output	0.493 g	0.406 g	1.45 g	<2.76 g [c]	1.39 g

[a] Including impurity with ^{i}Bu group.
[b] Yields for two steps.
[c] Including solvents without clearly removed, the crude product was employed for a 5 steps yield.
[d] 2.0 eq. DIBAL-H.
[e] 2.1 eq. DIBAL-H, longer reaction time, **139** observed as by-product.

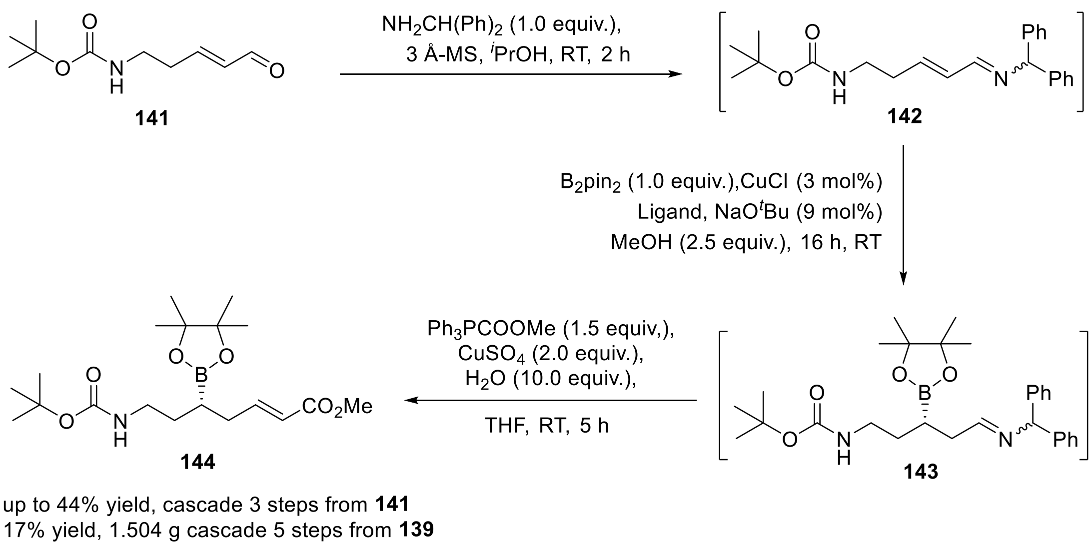
Following the reduction step, the oxidation was then carried out and due to the scale, the reaction was allowed to run for 72 hours equipped with air balloon (entry 3, Table 2). In order to minimise product **141** loss through evaporation, evaporation of the solvent after purification was carried out by opening the reaction for 5 days. However, solvent still remained in the product, and the yield was artificially high (estimated 101% yield). Hence, the next step was carried out without purification at this stage. In this case, a 17% isolated yield over 5 steps for product **144** was obtained after the one-pot imine formation/borylation/hydrolysis/Wittig reaction sequence (entry 3, Table 2).

The reaction yield in entry 4 was reduced if the oxidation step was run for 9 days (Table 2). Long oxidation reaction times resulted in the α,β-unsaturated aldehyde **141** being re-oxidized to the α,β-unsaturated ester **139**. Therefore, the α,β-unsaturated aldehyde **141** was obtained only 23% isolated yield.

2.3.3. Optimisations of imine formation/borylation/hydrolysis/Wittig reaction

The Whiting group has been focusing research on the catalytic enantioselective hydroboration reactions for several years and in 2017,[12a,55] the methodology for the enantioselective cascade imine formation/borylation/hydrolysis/Wittig reaction[12a] was developed and employed for the total synthesis of atorvastatin[55] and was explored for constructing chiral 1,3-diol moieties.

In this investigation, the previous attempts at the 1st borylation reaction after imine formation, was optimised[55] by changing the reaction conditions, including using IPA as the solvent for the imine formation/borylation steps (Scheme 40). This provided the proton that was necessary for the borylation in the proposed mechanism (the exact mechanism is still not confirmed as discussed in the literature review section), rather than additional water, the hydrolysis of the C-B bond might cause racemisation of the catalytic borylation reaction. Longer reaction times for the Wittig reaction also provided an opportunity for the optimisation of the reaction. Unfortunately, when the reaction was scaled-up, the isolated yield was reduced (entry 4 and 5, Table 3). As a result, only 27% isolated yield of product **143** was obtained in the entry 4. It is worth mentioning that on larger reaction scale synthesis using a combined 5 steps gave 17% isolated yield of the product homoallylic boronate ester **144** (entry 5, Table 3). Because 1.504 g of product was obtained, the intermediate was suitable for the following steps in the total synthesis of atorvastatin.



Scheme 40 One-pot synthesis of homoallylic boronate ester **144** *via* imine formation/borylation/hydrolysis/Wittig reaction

Table 3 Optimization of one-pot imine formation/borylation/hydrolysis/Wittig reaction

Entry	Previous work[a]	1	2	3	4[b]	5
TPPO removal methods	CuSO4 (sat.) wash after extraction	Dissolved in Et_2O	-$MgCl_2$. (2.0 eq.)	$ZnCl_2$. (3.0 eq.)	$ZnCl_2$. (3.0 eq.)	$ZnCl_2$. (2.5 eq.)
Yields in 3 steps	41%	-	-	44%	27%	17%[c]
Product **139** output		Mass	Mass	0.085 g	0.353 g	1.50 g

[a] 44% yield racemic (6 mol% PPh_3 as ligand).
[b] Racemic sample obtained from TLC separation.
[c] 5 steps yield from **139**.

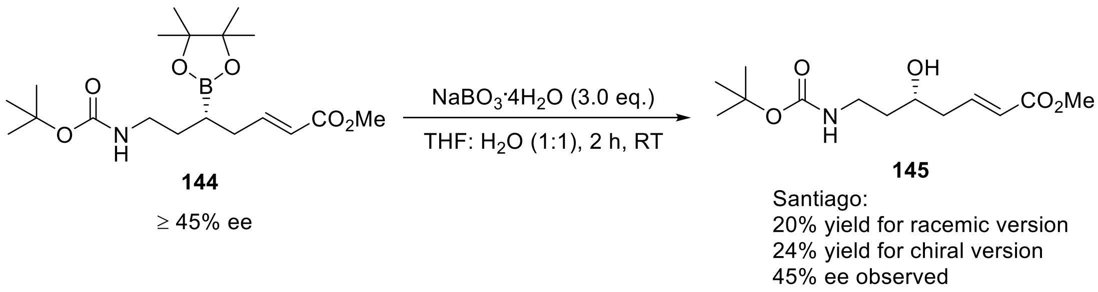
Moreover, under the Santiago conditions from previous work of our group (entry 3), the E/Z isomer ratio observed was poor according to ^{1}H-NMR analysis (88:12). When IPA was employed as the solvent under the optimised reaction condition, the Z/E isomer ratio improved according to ^{1}H-NMR (>95:5). However, when analysed by HPLC was carried out, the chromatograms suggested that both the Z/E isomers were present, complicating the determination of enantiomer ratio of the borylated product.

Interestingly, before the enantioselective synthesis of the homoallylic boronate ester **144** was explored, HPLC analysis problems needed to be solved.[55] Also, the by-product, TPPO from the Wittig reaction, needed to be removed from the product. The presence of TPPO in the product, even in trace amounts, caused detection problems for the HPLC analysis due to its high UV absorbance. In the HPLC chromatogram, the TPPO peak proved problematic, overlapping with the Z/E isomers of the alkene; this is a commonly encountered problem in reactions such as the classic Corey−Fuchs and Mitsunobu reaction.[59a] According to the work of Lukin and Weix, different TPPO removal methods were previously tried after the borylation reaction. They suggested a TPPO removal method with $MgCl_2$ additive[59b] and

Et_2O solvent,[55] both this failed in this case (entry 1 and 2, Table 3). A $ZnCl_2$ additive with ^{i}PrOH solvent work-up process[59a] was employed and found to be efficient for TPPO removal and 44% isolated yield with 85 mg of product **144** on a 0.5 mmol scale was obtained, revealing the utility of this approach (entry 3, Table 3). This new process not only helped with generating a purer isolated product with less TPPO interfering with the HPLC analysis, but this also provided pure compounds that could be used in subsequent steps in the following total synthesis. Since the $ZnCl_2$/^{i}PrOH method was employed, the various reaction sequence attempts showed the products to be absence of TPPO by TLC and ^{1}H-NMR analysis.

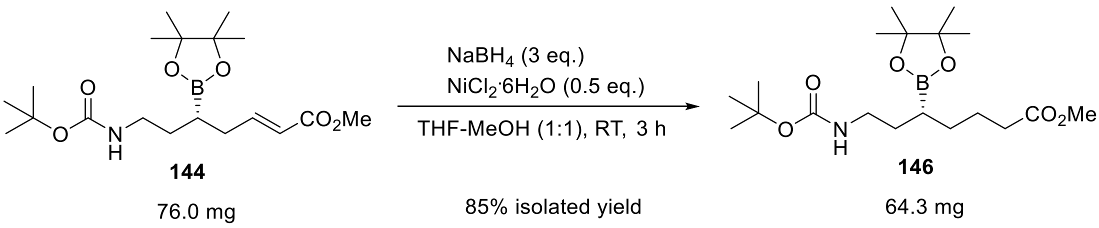
2.4. Enantioselectivity of the borylation reaction

The enantioselectivity of the copper-catalysed hydroboration in the cascade imine formation/borylation/hydrolysis/Wittig reaction is worthy of investigation.[12] As described in the literature review section, the one-pot imine formation/borylation/hydrolysis/Wittig reaction of α,β-unsaturated aldehyde **1** was initially reported by Santiago and Whiting in 2017. It has a broad scope generating the homoallylic boronate carboxylate esters **3** with high enantioselectivity *via* their methodology involving imine formation (Scheme 1).[12a] For these all these products, HPLC analysis was successful for *ee* determination (60-99% ee). However, when trying to develop methods for measuring the *ee* value of the homoallylic boronate ester **144** in the work for total synthesis of atorvastatin, the previous investigations in our group failed to optimise separation conditions for the HPLC analysis. The presence of the Boc-NH moiety substitution possibly makes a big difference, making analysis more challenging compared to previous products. Thus, a C-B bond oxidation transfer was employed to the corresponding alcohol **145** to indicate the original *ee* value of homoallylic boronate ester **144**. This approach gave a 20% yield for the racemic product and a 24% yield for chiral version in the reduction of **144** to **145** (Scheme 41); a 45% *ee* of the alcohol **145** was revealed. However, the *ee* of **145** was lower than the general *ee* value of this type of product previously observed (typically higher than 82% ee) (Scheme 1).[12a] Although in some publications, high *ee*s were obtained after the oxidation of the chiral C-B bonds,[48b] preventing racemisation during the C-B oxidation was observed to be necessary. Nevertheless, previous work did confirm that the enantioselectivity of homoallylic boronate ester **144** in the borylation reaction was no less than 45%.



Scheme 41 C-B bond oxidation of borylated **144** for its enantioselectivity investigation

To solve the problem of measuring the *ee* of the homoallylic boronate ester **144** *via* HPLC analysis, when trying to explore the correct conditions for the separation of two enantiomers, the key was to determine whether the chiral sample and racemic sample had simular retention times but different integral areas, showing they had been successfully separated. At the same time, the Z/E isomers and trace TPPO impurity were also interfering factors. Nevertheless, the first samples showed two peaks with the same retention times in the racemic and chiral samples (they did not have the same integration area in the racemic sample) which suggested these could be Z/E alkene isomers. To investigate the Z/E-isomers, the homoallylic boronate ester **144** was hydrogenated[60] in 85% yield (Scheme 42). Unfortunately, the product **146** had a weak absorption in the UV region due to the double bond being hydrogenated and failed to be suitable for HPLC analysis.



Scheme 42 Hydrogenation of homoallylic boronate ester **144**

Since we failed on the strategy of simplifying the diffculties associated with the Z/E isomers from the product **144** conditions for HPLC analysis of compound **144** were instead investigated using both chiral and racemic material. Previous work had involved CJ-H, OD and AD columns; while AS-H and IA columns had not been examined. We therefore investigated a wide range of sepearation conditions of homoallylic boronate ester **144** enantiomers *via* HPLC analysis, using AS-H and IA columns. The details are shown in experimental section. The result was partial separation, and further work needs to be carried out in order to have a satisfactory analytic method for the ee determination.

2.5. Conclusions

In summary, a dual enantioseletive hydroboration strategy was applied as the key steps on the total synthesis of cholesterol-lowering drug atorvastatin **119**. Previous work had investigated the synthesis route *via* a series of reactions with the relevant optimisation on small scale. In this work, further optimisations of the reactions were developed within the first nine steps, obtaining the key intermediate homoallylboronate carboxylate boronate ester **144** in good overall yield (11.3% isolated yield in 8 steps). The complex purification requirement within some of the steps was simplified by combining steps into one-pot synthesis strategies. Up to 116 mmol scale was realised in good yields with condition optimisations of the reactions. A good intermediate preparation of compound **144** was realised even up to 1.504 g all in a one pot synthesis. Moreover, a novel method was studied to enable TPPO removal from the Wittig reaction, which was beneficial to the HPLC analysis of compound **144** as well as the following steps in the total synthesis. The attempted exploration of the enantioselectivity of the copper-catalysed hydroboration of α,β-unsaturated imines **142** was demonstrated with AS-H column and IA column with several primary results on the optimisation of HPLC analysis.

Hence, with the streamlined synthesis route in hand, the complication of the total synthesis of atorvastatin can be tackled. In addition, with optimisations of HPLC analysis conditions determined to separate the enantiomers of boronate **144**, the enantioselectivity of the copper-catalysed hydroboration of the α,β-unsaturated imines **142** was nearly revealed. Further investigations on both the streamlined total synthesis and the enantioselectivity analysis and completion of the total synthesis can be the next goal.

Experimental section

3.1. General experimental

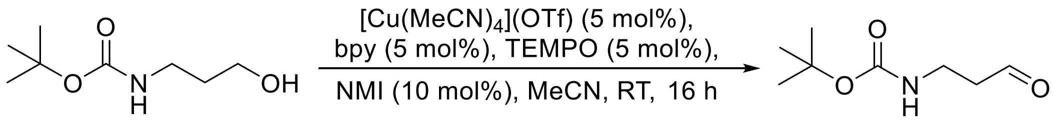
All the reactions herein reported were performed under air unless specified otherwise. The reagents were purchased directly from standard chemical suppliers and used as received from the supplier without further purification. All solvents were also used as received from the supplier, except THF which was stored over dehydrating agent, molecular sieves. Molecular Sieves, 3 Å 1-2 mm beads were supplied from Alfa Aesar and stored at 220 ^{0}C (> 48 h). 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); and all were monitored by TLC analysis using POLYGRAM® SIL G/UV254 (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.

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, 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). ^{1}H NMR shifts are reported in ppm (δ) relative to tetramethylsilane, and referenced to the chemical shifts of residual solvent resonances.

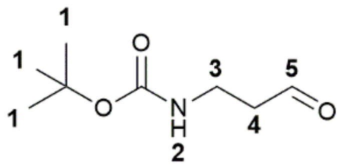
HPLC analyses were carried out on an Agilent 1100 series instrument, fitted with a Perkin Elmer series 200 degasser on chiral column: AS-H-CHIRALCEL column (250 x 4.60 mm) and CHIRALPAK-IA column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.60 mm); were used to achieve chiral resolution. Mixtures of hexane and ^{i}PrOH, EtOH 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 or hexane only.

3.2. Synthesis of enoate 139 from 3-(Boc-amino)-1-propanol 137

<u>3-(Boc-amino)-1-propylcarbamate **138**</u>



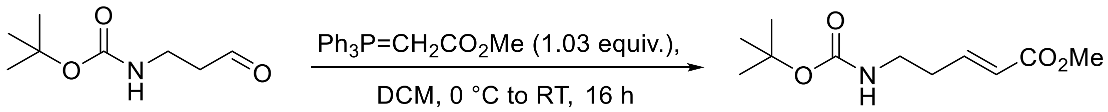
137 **138**



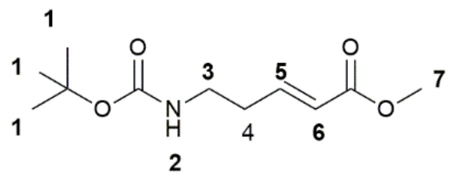
A stirred solution of 3-(Boc-amino)-1-propanol **137** (2.04 g, 11.6 mmol) in CH_3CN (20.0 mL), was treated with [Cu(CH_3CN)$_4$](OTf) (0.220 g, 0.580 mmol), 2,2'-bipirydyl (0.0920 g, 0.580 mmol), TEMPO (0.0920 g, 0.580 mmol), and *N*-methyl imidazole (0.0920 mL, 0.580 mmol). Then CH_3CN (15.0 mL) was 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 portioned between EtOAc (40.0 mL) and brine (70.0 mL), the aqueous layer was extracted further with EtOAc (3 x 50.0 mL), and the combined organic extracts dried over anhydrous

$MgSO_4$, filtered and concentrated. A crude pale pink oil was obtained. Purification by SiO_2 chromatography using a mixture of hexane:EtOAc (2:1) as eluent gave product **138** as colourless oil (0.931 g, 46% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H, H-*5*), 4.88 (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*); All spectroscopic and analytical data were identical to those reported in the literature.[55]

<u>Methyl (*E*)-5-((tert-butoxycarbonyl)amino) pent-2-enoate **139**</u>

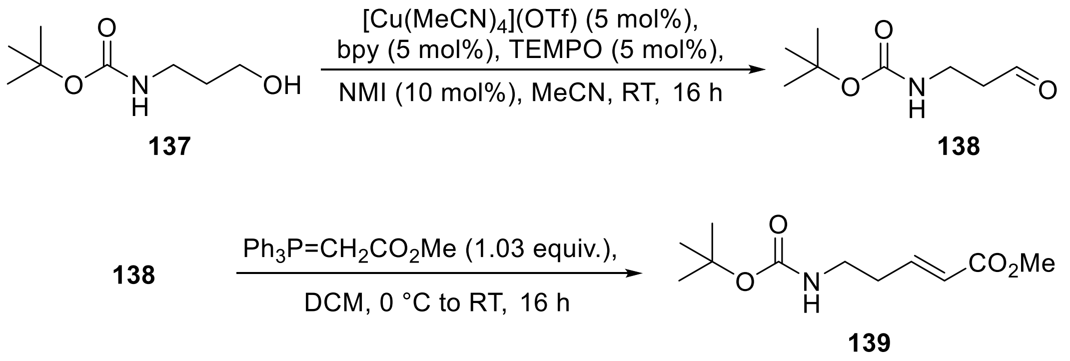


138 **139**



A stirred solution of 3-(Boc-amino)-1-propylcarbamate **138** (4.23 g, 21.0 mmol) in DCM (50.0 mL) at 0 ℃ was treated with methyl (triphenylphosphoranylidene) acetate (8.37 g, 21.3 mmol) and additional of 20.0 mL DCM to rinse the walls of the flask, kept 0 ℃ for 1 h. The solution was warmed to RT and stirred for a further 16 h. After evaporation of the remaining solvent *in vacuo*, a crude colourless oil was obtained. Purification by SiO_2 chromatography using a mixture of petroleum ether:EtOAc (2:1) as eluent gave compound **139** as colourless oil (3.15 g, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89-6.96 (dt, *J* 15.7, 7.1 Hz, 1H, H-*5*), 5.88-5.93 (dt, *J* 15.7, 1.5 Hz, 1H, H-*6*), 4.60 (s, 1H, H-*2*), 3.76 (s, 3H, H-*7*), 3.29 (q, *J* 6.6 Hz, 2H, H-*3*), 2.42 (m, 2H, H-*4*), 1.43 (s, 9H, H-*1*); All spectroscopic and analytical data were identical to those reported in the literature.[55]

<u>Combined oxidation/Wittig reaction from alcohol **137** to ester **139**</u>

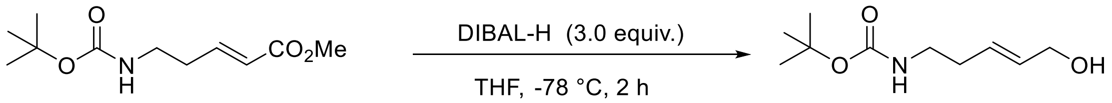


A stirred solution of 3-(Boc-amino)-1-propanol **137** (10.2 g, 58.1 mmol) in CH_3CN (100 mL), was treated with [Cu(CH_3CN)$_4$](OTf) (1.10 g, 2.91 mmol), 2,2'-bipirydyl (0.460 g, 2.91 mmol), TEMPO (0.460 g, 2.91 mmol), and *N*-methyl imidazole (0.46 mL, 5.81 mmol). Then CH_3CN (40 mL) was added to rinse the walls of the flask. The flask was opened to air with a perforated cover (equipped with a balloon of air when less scale) and the mixture was stirred for 72 h at RT. The resulting solution was portioned between DCM (100 mL) and brine (70 mL), the aqueous layer was extracted further with DCM (3 x 60 mL), and the combined organic extracts dried over anhydrous $MgSO_4$, filtered and concentrated. The solvent was partly removed *in vacuo* and re-addition of DCM (3 x 60 mL) to yield a colourless crude oil product **138** (<58.1 mmol), dissolved in 60 mL DCM solution. The solution was treated at 0 ℃ with methyl (triphenylphosphoranylidene) acetate (22.8 g, 58.1 mmol) and additional of 20 mL DCM to rinse the walls of the flask, kept 0 ℃ for 1 h. The solution was warmed to RT and stirred for a further 16 h. After evaporation of the remaining solvent *in vacuo*, a crude colourless oil was obtained. Purification by SiO_2 chromatography using a mixture of petroleum ether:EtOAc (2:1) as eluent gave compound **139** as colourless oil (6.71 g, 67% for two steps).

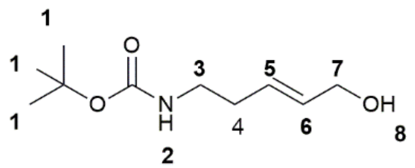
All spectroscopic and analytical data were identical to those reported in the separated synthesis procedure of product **138** in this thesis.

3.3. Synthesis of α,β-unsaturated aldehyde 139 to carbamate 141

Tert-butyl (*E*)-(5-hydroxypent-3-en-1-yl)carbamate **140**

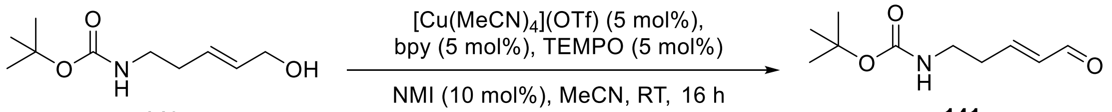


139 **140**

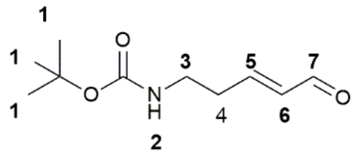


A stirred solution of methyl (*E*)-5-((*tert*-butoxycarbonyl)amino)-pent-2-enoate **139** (0.783 g, 3.42 mmol) in THF (37.0 mL) under Ar at -78 °C was treated drop-wise with DIBAL-H (1M solution in toluene, 10.2 mL, 10.2 mmol). After 2 h, the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (102.0 mL) under Ar, allowed to warm to RT and stirred for a further 1 h. The resulting solution was extracted with EtOAc (4 x 80 mL) and 5% HCl (aq.) (3.0 mL), the combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by SiO_2 chromatography using a mixture of hexane:EtOAc (2:1) as eluent gave. a colourless oil product **140** was obtained (<0.643 g, <93% yield, with trace impurity indicated by H^1 NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78-5.60 (m, 2H, H-*7*), 4.60 (br s, 1H, H-*2*), 4.13 (d, *J* 5.2, 0.9, 2H), 3.21 (q, *J* 6.6, 2H, H-*3*), 2.26 (qd, *J* 6.7, 1.1 H, H-*4*), 1.44 (s, 9H, H-*1*); except impurity peak of ^{i}Bu group, all other spectroscopic and analytical data were identical to those reported in the literature.[55]

<u>*Tert*-butyl (*E*)-(5-oxopent-3-en-1-yl)carbamate **141**</u>

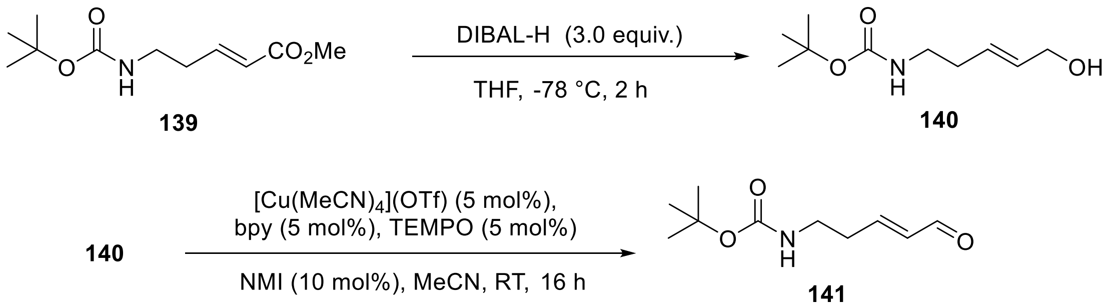


140 **141**



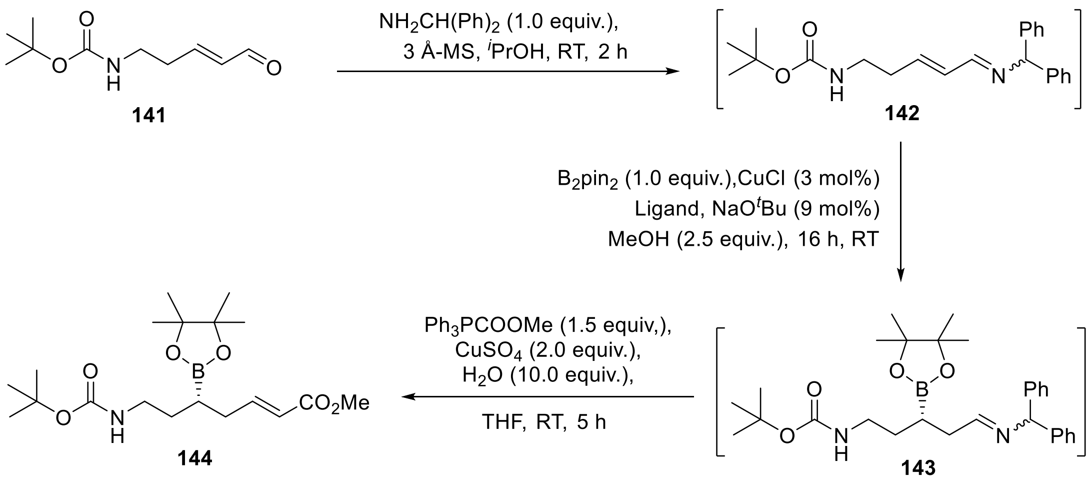
To a stirred solution of *tert*-butyl (*E*)-(5-hydroxypent-3-en-1-yl)carbamate **140** (0.630 g, 3.13 mmol) in CH_3CN (6.00 mL) was added [Cu(CH_3CN)$_4$](OTf) (0.596 g, 0.151 mmol), 2,2'-bipirydyl (0.0250 g, 0.151 mmol), TEMPO (0.0250 g, 0.151 mmol) and *N*-methyl imidazole (0.0250 mL, 0.300 mmol). Then CH_3CN (4.50 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 (25 mL) and brine (40 mL), the aqueous layer was extracted further with EtOAc (3 x 30 mL), the combined organic extract was dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo* to yield a crude yellow oil. Purification by SiO_2 chromatography using a mixture of hexane:EtOAc (2:1) as eluent gave compound_*tert*-butyl (*E*)-(5-oxopent-3-en-1-yl)carbamate **141** as yellow oil (0.406 g, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54-9.56 (d, *J* 7.8 Hz, 1H, H-*7*), 6.80-6.87 (dt, *J* 15.7, 7.1 Hz, 1H, H-*5*), 6.15-6.22 (m, 1H, H-*6*), 4.62 (s, 1H, H-*2*), 3.34-3.38 (q, *J* 6.6 Hz, 2H, H-*3*), 2.54-2.60 (m, 2H, H-*4*), 1.46 (s, 9H, H-*1*); All spectroscopic and analytical data were identical to those reported in the literature.[55]

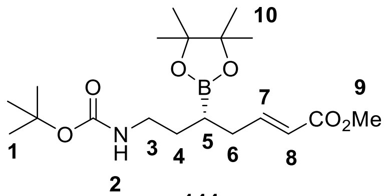
Combined DIBAL-reduction/Cu-TEMPO oxidation of α,β-unsaturated aldehyde 139



A stirred solution of methyl (*E*)-5-((*tert*-butoxycarbonyl)amino)-pent-2-enoate **139** (3.15 g, 13.7 mmol) in THF (130 mL) under Ar at -78 ℃ was treated drop-wise with DIBAL-H (1M solution in toluene, 41.1 mL, 31.1 mmol). After 2 h, the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (95 mL) under Ar, allowed to warm to RT and stirred for a further 1 h. The resulting solution was extracted with EtOAc (4 x 100 mL) and 5% HCl (aq.) (3 mL), the combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. The solvent was partly removed *in vacuo* and re-addition of MeCN (3 x 60 mL) to yield a colourless crude oil product **140** (< 13.7 mmol), dissolved in 20 mL MeCN solution. The stirred solution was added [Cu(CH_3CN)$_4$](OTf) (0.240 g, 0.680 mmol), 2,2'-bipirydyl (0.100 g, 0.680 mmol), TEMPO (0.100 g, 0.680 mmol) and *N*-methyl imidazole (0.100 mL, 1.37 mmol). Then CH_3CN (15 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 (50 mL) and brine (50 mL), the aqueous layer was extracted further with EtOAc (3 x 40 mL), the combined organic extract was dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo* to yield a yellow oil. Purification by SiO_2 chromatography using a mixture of hexane:EtOAc (2:1) as eluent gave compound *tert*-butyl (*E*)-(5-oxopent-3-en-1-yl)carbamate **141** as yellow oil (1.45 g, 53% yield for 2 steps). All spectroscopic and analytical data were identical to those reported in the separated synthesis procedure of product **141** in this thesis.

3.4. The synthesis of homoallylboronate carboxylate boronate ester



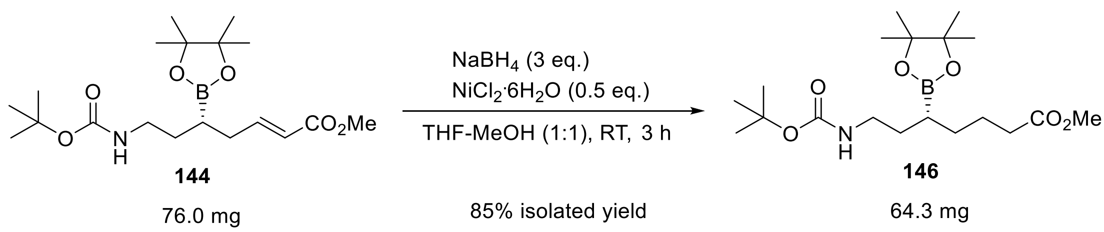


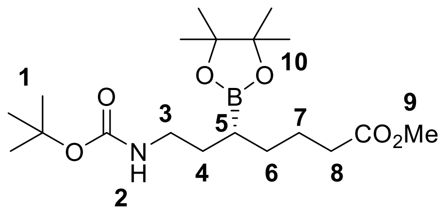
144

To a round bottom flask containing IPA (14 mL) and oven-dried 3 Å-MS (3.40 g) was added α,β-unsaturated aldehyde **141** (0.688 g, 3.43 mmol) and benzhydrylamine (0.590 mL, 3.43 mmol) and the reaction mixture stirred at RT. After 2 h, an aliquot of the *in situ* formed α,β-unsaturated imine was transferred to a Schlenk-tube (under Ar) containing CuCl (10.2 mg, 0.102 mmol), PPh_3 (53.5 mg, 0.204 mmol) or (*R*)-DM-Binap (74.8 mg, 0.102 mmol), NaO^{t}Bu (29.2 mg, 0.306 mmol) and B_2pin_2 (0.871 g, 3.43 mmol). After 16 h, the resulting β-boryl aldimine was transferred to a round bottom flask, the IPA solvent was removed and replaced by dry THF (27 mL), then methyltriphenylphosphoranylideneacetate (1.72 g, 5.15 mmol) was added, and after 5 minutes $CuSO_4$ 1.10 g, 6.86 mmol) added along with H_2O (0.620 mL, 34.3

mmol). The mixture was stirred for 5 h at RT. The resulting solution was partioned between EtOAc (40 mL) and brine (40 mL). The aqueous layer was extracted further with EtOAc (3 x 40 mL). The combined organic phase was separated and dried over anhydrous $MgSO_4$, filtered and the solvent removed. $ZnCl_2$ (204 mg, 1.50 mmol) and IPA (15 mL) was added and the mixture stirred at RT for 21 hr. After filtration, the solvent was removed *in vacuo*. Purification by SiO_2 chromatography using a mixture of hexane:EtOAc (10:1) as eluent gave compound homoallylic boronate carboxylate ester **144** as yellow oil (353 mg, 27% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92-7.00 (dt, *J* 15.5, 7.2 Hz, 1H, H-*7*), 5.82-5.89 (dt, *J* 15.6, 1.5 Hz, 1H, H-*8*), 4.76 (s, 1H, H-*2*), 3.73 (s, 3H, H-*9*), 3.16-3.18 (d, *J* 6.7 Hz, 2H, H-*3*), 2.39-2.24 (m, 2H, H-*6*), 1.56-1.64 (m, 2H, H-*4*), 1.45 (s, 9H, H-*1*), 1.26 (s, 12H, H-*10*), 1.15-1.20 (m, 1H, H-*5*) ; All other spectroscopic and analytical data were identical to those reported in the literature.[55]

3.5. Hydrogenation of homoallylboronate carboxylate boronate ester





145

To a dry Schlenk tube containing $NaBH_4$ (11.1 mg, 0.589 mmol), $NiCl_2 \cdot 6H_2O$ (11.7 mg, 0.0980 mmol) and filled with argon, 2.50 mL MeOH-THF (1:1) solution of homoallylboronate carboxylate boronate ester **144** was added under argen. The mixture was stirred for 3 h at room temperature. After removal of solvent, the product was purified by SiO_2 chromatography using as hexane: EtOAc (2:1) as eluent gave compound **145** as colorless oil (64.3 mg, 85% isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (s, 1H, H-*2*), 4.29 – 4.22 (m, 2H, H-*3*), 3.77 – 3.71 (m, 2H, H-*6*), 3.68 (s, 3H, H-*9*), 3.63 – 3.56 (m, 2H), 3.49 (t, J = 6.7 Hz, 2H, H-*3*), 3.15 (s, 3H), 2.32 (t, J = 7.5 Hz, 2H, H-*7*), 2.11 (s, 2H), 1.70 – 1.54 (m, 6H), 1.45 (s, 9H, H-*1*), 1.27 (s, 12H, H-*10*), 1.01 (m, 1H, H-*5*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.3, 77.3, 77.0, 76.7, 63.6, 51.4, 34.2, 30.5, 28.4, 24.8, 24.3, 19.2, 13.9; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.

3.6. HPLC analysis of the ee of compound 144

The optimized results with 1.2 ml/min flow rate (hexane:IPA = 90:10) employing the AS-H column are summerised in Figure 18 and 19. Similar peaks were observed both in the racemic and chiral versions (from product **144** of entry 3, Table 3). Hence, only Z/E isomers were observed partly seperated, rather than the enantiomers. Although the racemic version shown a new peak seperating from 27.2 min retention time, the optimisation of conditions failed to realise further sepearation.

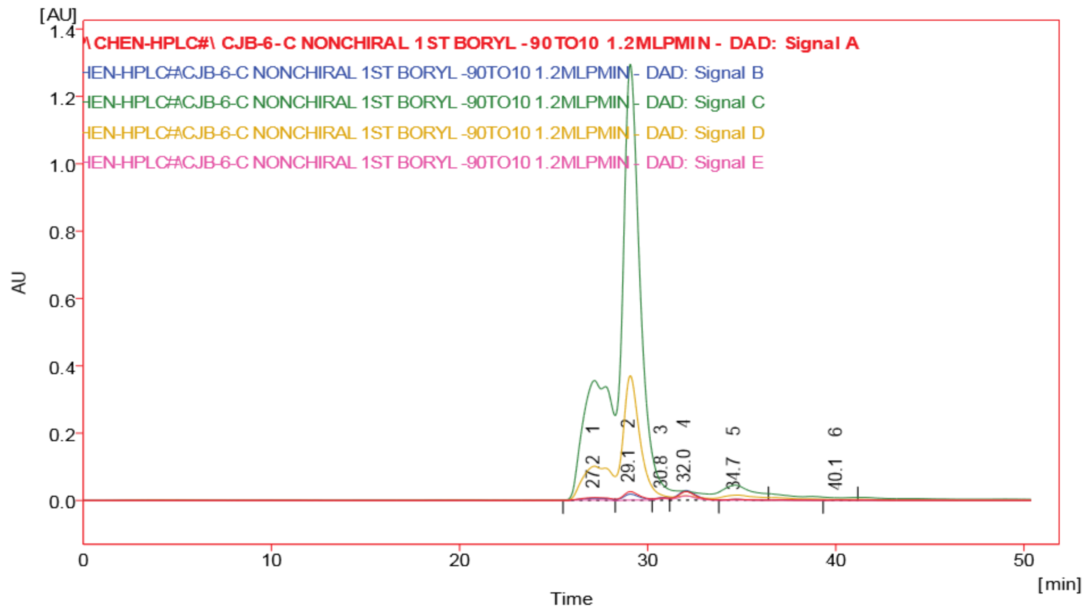


Figure 18 HPLC analysis of racemic version of compound **144** with 1.2 ml/min flow rate (hexane:IPA = 90:10) employing the AS-H column

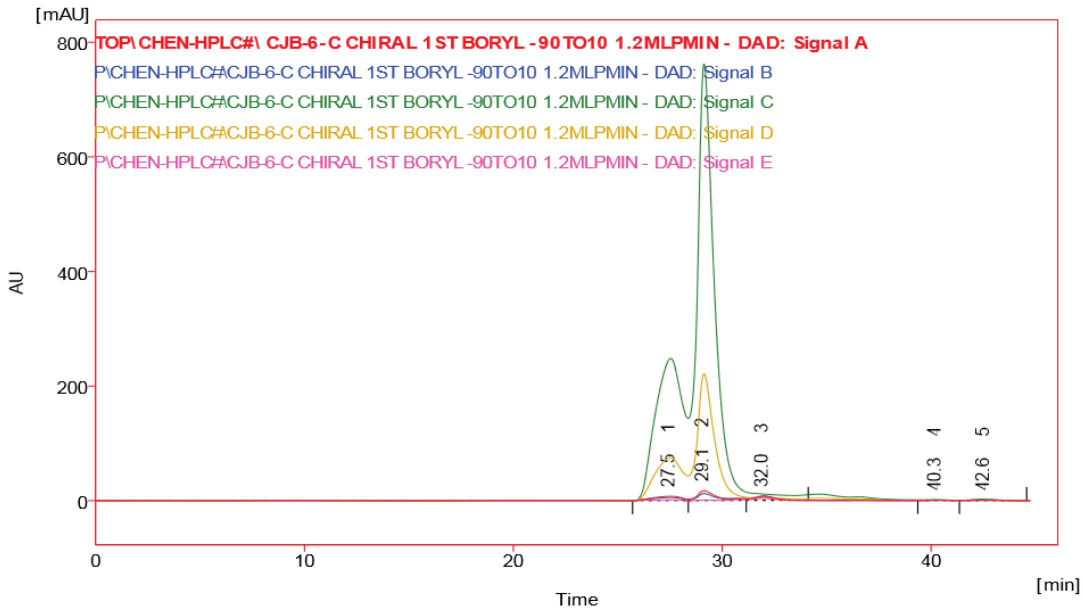
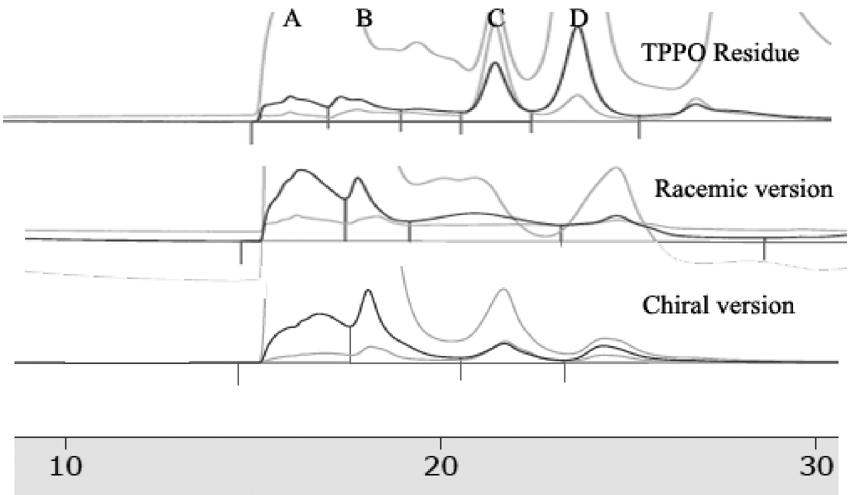


Figure 19 HPLC analysis of chiral version of compound **144** with 1.2 ml/min flow rate (hexane:IPA = 90:10) employing the AS-H column

Further optimisations based on the previous conditions (hexane: IPA =75:25, 0.8 ml/min in IA column) were investigated for the homoallylic boronate ester **144** from entey 5, Table 3 (higher purity, as indicated by the ^{1}H-NMR analysis). And comparing with two of the samples (Figure 18) Improved seperation was observed, however further work was required to be sure which peak is which. Hence, a completely TPPO removal method is required to access effective HPLC analysis of the homoallylic boronate ester **144** product of the catalytic borylation reaction, as well as to obtain a better Z/E selectivity in this synthesis.

Figure 20 Study on the effect of TPPO residue to the separations of the enantiomers **144**[a]



[a] Condition: IA column, Hexane: IPA (75:25), 0.8 ml/min

References

[1] (a) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*, 201. (b) Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51. (c) *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2011**. (d) Suzuki, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6723. (e) Kaur, P.; Khatik, G. L.; Nayak, S. K. *Curr. Org. Synth.* **2017**, *14*, 665.

[2] Applications in pharmaceuticals and bioactive molecules: (a) Woodward, R. B.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Ward, D. E.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3213. (b) Flores-Parra, A.; Contreras, R. *Coord. Chem. Rev.* **2000**, *196*, 85. (c) Yang, W.; Gao, X.; Wang, B. *Med. Res. Rev.* **2003**, *23*, 346. (d) Tobert, J. A. *Nat. Rev. Drug Discovery* **2003**, *3*, 178. (e) Petasis, N. A. *Aust. J. Chem.* **2007**, *60*, 795. (f) Kumar, R. N.; Meshram, H. M. *Tetrahedron Lett.* **2011**, *52*, 1003. (g) Smoum, R.; Rubinstein, A.; Dembitsky, V. M.; Srebnik, M. *Chem. Rev.* **2012**, 112, 4156.

[3] For selected reviews on borylation and its transformations: (a) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392. (b) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704. (c) Hall, D. G.; Lee, J. C. H.; Ding, J. *Pure Appl. Chem.* **2012**, *84*, 2263. (d) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412. (e) Leonori, D.; Aggarwal, V. K. *Acc. Chem. Res.* **2014**, *47*, 3174. (f) Xu, L.; Zhang, S.; Li, P. *Chem. Soc. Rev.* **2015**, *44*, 8848. (g) Leonori, D.; Aggarwal, V. K. *Angew. Chem . Int. Ed.* **2015**, *54*, 1082. (h) Lee, A.-L. *Org. Biomol. Chem.* **2016**, *14*, 5357. (i) Chatterjee, N.; Goswami, A. *Adv. Synth. Catal.* **2017**, *359*, 358. (j) Scharnagl, F. K.; Bose, S. K.; Marder, T. B. *Org. Biomol. Chem.* **2017**, *15*, 1738. (k) Yang, J.-M.; Li, Z.-Q.; Zhu, S.-F. *Chin. J. Org. Chem.* **2017**, *37*, 2481. (l) Armstrong, R. J.; Aggarwal V. K. *Synthesis* **2017**, *49*, 3323. (m) Willemse, T.; Schepens, W.; van Vlijmen, H. W. T.; Maes, B. U. W.; Ballet, S. *Catalysts* **2017**, *7*, 74. (n) Nallagonda, R.; Padala, K.; Masarwa, A. *Org. Biomol. Chem.* **2018**, *16*, 1050.

[4] For selected reviews relevant to the topic of borylation: (a) Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, *3*, 271. (b) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (c) Dang, L.; Lin, Z.; Marder, T. B. *Chem. Commun.* **2009**, 3987. (d) Cid, J.; Gulyás, H.; Carbó, J. J.; Fernández, E. *Chem. Soc. Rev.* **2012**, *41*, 3558. (e) Yun, J. *Asian J. Org. Chem.* **2013**, *2*, 1016. (f) Westcott, S. A.; Fernández, E. *Adv. Het. Chem.* **2015**, *63*, 39.

(g) Hensel, A.; Oestreich, M. *Top. Organomet. Chem.* **2015**, *58*, 135. (h) Tsuji, Y.; Fujihara, T. *Chem. Rec.* **2016**, *16*, 2294. (i) Yoshida, H. *Chem. Rec.* **2016**, *16*, 419. (j) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091. (k) Collins, B. S. L.; Wilson, C. M.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 11700. (l) Lawson, J. R.; Melen, R. L. *Inorg. Chem.* **2017**, *56*, 8627. (m) Lawson, J. R.; Melen, R. L. *Organomet. Chem*. **2017**, *41*, 1. (n) Fujihara, T.; Tsuji, Y. *Synthesis*, **2018**, *50*, 1737. (o) Verma, P. K.; Shegavi, M. L.; Bose, S. K.; Geetharani, K. *Org. Biomol. Chem.* **2018**, *16*, 857. (p) Yan, G.; Huang, D.; Wu, X. *Adv. Synth. Catal.* **2018**, *360*, 1040.

[5] For selected reviews on C-H borylation: (a) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2003**, *680*, 3. (b) Ishiyama, T.; Miyaura, N. *Pure Appl. Chem.* **2006**, *78*, 1369. (c) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (d) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (e) Hartwig, J. F. *Acc. Chem. Res.* ***2*012**, *45*, 864. (f) Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229. (g) Shinokubo, H. *Proc. Jpn. Acad., Ser. B* **2014**, *90*, 1. (h) Geier, S. J.; Westcott, S. A. *Rev. Inorg. Chem.* **2015**, *35*, 69. (i) Xu, L.; Wang, G.; Zhang, S.; Wang, H.; Wang, L.; Liu, L.; Jiao, J.; Li, P. *Tetrahedron* **2017**, *73*, 7123.

[6] For selected reviews on C-X borylation: (a) Murata, M. *Heterocycles* **2012**, *85*, 1795. (b) Chow, W. K.; Yuen, O. Y.; Choy, P. Y.; So, C. M.; Lau, C. P.; Wong, W. T.; Kwong, F. Y. *RSC Advances* **2013**, *3*, 12518. (c) Kubota, K.; Iwamoto, H.; Ito, H. *Org. Biomol. Chem.* **2017**, *15*, 285.

[7] For selected reviews on diboration: (a) Marder, T. B.; Norman, N. C. *Top. Catal.* **1998**, *5*, 63. (b) Dembitsky, V. M.; Ali, H. A.; Srebnik, M. *Appl. Organometal. Chem.* **2003**, *17*, 327. (c) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320. (d) Bonet, A.; Sole, C.; Gulyás, H.; Fernández, E. *Org. Biomol. Chem.* **2012**, *10*, 6621. (e) Zhao, F.; Jia, X.; Li, P.; Zhao, J.; Zhou, Y.; Wang, J.; Liu, H. *Org. Chem. Front.* **2017**, *4*, 2235.

[8] For selected reviews on borylative bifunctionalization: (a) Suginome, M.; Ito, Y. *J. Organomet. Chem.* **2003**, *680*, 43. (b) Oestreich, M.; Hartmann, E.; Mewald, M. *Chem. Rev.* **2013**, *113*, 402. (c) Buñuel, E.; Cárdenas, D. J. *Eur. J. Org. Chem.* **2016**, 5446. (d) Cuenca, A. B.; Shishido, R.; Ito, H.; Fernández, E. *Chem. Soc. Rev.* **2017**, *46*, 415.

[9] For selected literatures on Brown hydroboration: (a) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486. (b) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287. (c) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957. (d) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695. (e) Carroll, A.-M.; O'QSullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609; (f) Vogels, C. M.; Westcott, S. A. *Curr. Org. Chem.* **2005**, *9*, 687. (g) Huang, S.; Xie, Y.; Wu, S.; Jia, M.; Wang, J.; Xu, W.; Fang, H. *Curr. Org. Synth.* **2013**, *10*, 683. (h) Fujihara, T.; Semba, K.; Terao, J.; Tsuji, Y. *Catal. Sci. Technol.* **2014**, *4*, 1699. (i) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Tetrahedron* **2015**, *71*, 2183. (j) Liu, Q.; Tian, B.; Tian, P.; Tong, X.; Lin, G.-Q. *Chin. J. Org. Chem.* **2015**, *35*, 1. (k) Ito, H. *Pure Appl. Chem.* **2018**, *90*, 703.

[10] For selected reviews on alkenes hydroboration: (a) Lillo, V.; Bonet, A.; Fernández, E. *Dalton Trans.* **2009**, 2899. (b) Thomas, S. P.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 1896; (c) Calow, A. D. J.; Whiting, A. *Org. Biomol. Chem.* **2012**, *10*, 5485. (d) Stavber, G.; Časar, Z. *ChemCatChem* **2014**, *6*, 2162. (e) Liu, Y.; Zhang, W. *Chin. J. Org. Chem.* **2016**, *36*, 2249. (f) Chen, J.; Lu, Z. *Org. Chem. Front.* **2018**, *5*, 260.

[11] For selected reviews on 1,3-diol synthesis and relevant strategies: (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1. (b) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I.; *Acc. Chem. Res.* **1998**, *31*, 9. (c) Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M. *Eur. J. Org. Chem.* **2005**, 2867. (d) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557. (e) Bonet, A.; Sole, C.; Gulyás, H.; Fernández, E. *Curr. Org. Chem.* **2010**, *14*, 2531. (f) Paterson, I.; Dalby, S. M.; Maltas, P. *Isr. J. Chem.* **2011**, *51*, 406. (g) Alfaro, R.; Parra, A.; Alemán, J.; Tortosa, M. *Synlett* **2013**, *24*, 804. (h) Barreiro, E. M.; Adrio,

L. A.; Hii, K. K.; Brazier, J. B. *Eur. J. Org. Chem.* **2013**, 1027. (i) Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176.

[12] (a) Pujol, A.; Whiting, A. *J. Org. Chem.* **2017**, *82*, 7265. (b) Ibrahem, I.; Breistein, P.; Córdova, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 12036. (c) Solé, C.; Tatla, A.; Mata, J. A.; Whiting, A.; Gulyás, H.; Fernández, E. *Chem. Eur. J.* **2011**, *17*, 14248. (d) Solé, C.; Whiting, A.; Gulyás, H.; Fernández, E. *Adv. Synth. Catal.* **2011**, *353*, 376. (e) Ibrahem, I.; Breistein, P.; Córdova, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 12036. (f) Calow, A. D. J.; Batsanov, A. S.; Fernández, E.; Solé, C.; Whiting, A. *Chem. Commun.* **2012**, *48*, 11401. (g) Kitanosono, T.; Xu, P.; Kobayashi, S. *Chem. Commun.* **2013**, *49*, 8184. (h) Calow, A. D. J.; Batsanov, A. S.; Pujol, A.; Solé, C.; Fernández, E.; Whiting, A. *Org. Lett.* **2013**, *15*, 4810. (i) Calow, A. D. J.; Fernández, E.; Whiting, A. *Org. Biomol. Chem.* **2014**, *12*, 6121. (j) Kitanosono, T.; Xu, P.; Isshiki, S.; Zhu, L.; Kobayashi, S. *Chem. Commun.* **2014**, *50*, 9336. (k) He, Z.-T.; Zhao, Y.-S.; Tian, P.; Wang, C.-C.; Dong, H.-Q.; Lin, G.-Q. *Org. Lett.* **2014**, *16*, 1426. (l) Pujol, A.; Calow, A. D. J.; Batsanov, A. S.; Whiting, A. *Org. Biomol. Chem.* **2015**, *13*, 5122.

[13] Jiang, Q.; Guo, T.; Yu, Z. *J. Org. Chem.* **2017**, *82*, 1951.

[14] Wen, L.; Yue, Z.; Zhang, H.; Chong, Q.; Meng, F. *Org. Lett.* **2017**, *19*, 6610.

[15] Tarrieu, R.; Dumas, A.; Thongpaen, J.; Vives, T.; Roisnel, T.; Dorcet, V.; Crévisy, C.; Baslé, O.; Mauduit, M. *J. Org. Chem.* **2017**, *82*, 1880.

[16] Yasue, R.; Miyauchi, M.; Yoshida, K. *Adv. Synth. Catal.* **2017**, *359*, 255.

[17] Chen, L.; Zou, X.; Zhao, H.; Xu, S. *Org. Lett.* **2017**, *19*, 3676.

[18] Jana, A.; Trzybiński, D.; Woźniak, K.; Grela, K. *Chem. Eur. J.* **2018**, *24*, 891.

[19] Green, J. C.; Joannou, M. V.; Murray, S. A.; Zanghi, J. M.; Meek, S. J. *ACS Catal.* **2017**, *7*, 4441.

[20] (a) Kong, D.; Han, S.; Wang, R.; Li, M.; Zi, G.; Hou, G. *Chem. Sci.* **2017**, *8*, 4558. (b) Kong, D.; Han, S.; Zi, G.; Hou, G.; Zhang, J. *J. Org. Chem.* **2018**, *83*, 1924.

[21] Zhang, Y.; Wang, M.; Cao, P.; Liao, J. *Acta Chim. Sinica* **2017**, *75*, 794.

[22] (a) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160. (b) Jia, T.; Cao, P.; Wang, B.; Lou, Y.; Yin, X.; Wang, M.; Liao, J. *J. Am. Chem. Soc.* **2015**, *137*, 13760. (c) Lee, J.; Radomkit, S.; Torker, S.; del Pozo, J.; Hoveyda, A. H. *Nat. Chem.* **2017**, *10*, 99. (d) Huang, C.; Liu, B. *Chem. Commun*. **2010**, *46*, 5280. (e) Bai, W.-J.; Green, J. C.; Pettus, T. R. R. *J. Org. Chem.* **2012**, *77*, 379.

[23] Chen, B.; Cao, P.; Liao, Y.; Wang, M.; Liao, J. *Org. Lett.* **2018**, *20*, 1346.

[24] (a) Corberán, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079. (b) Wang, Z.; He, X.; Zhang, R.; Zhang, G.; Xu, G.; Zhang, Q.; Xiong, T.; Zhang, Q. *Org. Lett.* **2017**, *19*, 3067. (c) Wen, L.; Cheng, F.; Li, H.; Zhang, S.; Hong, X.; Meng, F. *Asian J. Org. Chem.* **2018**, *7*, 103.

[25] Cai, Y.; Yang, X.-T.; Zhang, S.-Q.; Li, F.; Li, Y.-Q.; Ruan, L.-X.; Hong, X.; Shi, S.-L. *Angew. Chem. Int. Ed.* **2018**, *57*, 1376.

[26] Kato, K.; Hirano, K.; Miura, M. *Chem. Eur. J.* **2018**, *24*, 5775.

[27] Jang, W. J.; Song, S. M.; Moon, J. H.; Lee, J. Y.; Yun, J. *J. Am. Chem. Soc.* **2017**, *139*, 13660.

[28] For selected examples of methodologies proposing "Cu-BX_2" as borylation intermediates: (a) Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226. (b) Zhao, L.; Ma, Y.; Duan, W.; He, F.; Chen, J.; Song, C. *Org. Lett.* **2012**, *14*, 5780. (c) Kitanosono, T.; Kobayashi, S. *Asian J. Org. Chem.* **2013**, *2*, 961. (d) Tian, B.; Liu, Q.; Tong, X.; Tian, P.; Lin, G.-Q. *Org. Chem. Front.* **2014**, *1*, 1116. (e) Lee, H.; Lee, B. Y.; Yun, J. *Org. Lett.* **2015**, *17*, 764. (f) Wen, Y.; Xie, J.; Deng, C.; Li, C. *J. Org. Chem.* **2015**, *80*, 4142. (g) Iwamoto, H.; Kubota, K.; Ito, H. *Chem. Commun.* **2016**, *52*, 5916. (h) Kerchner, H. A.; Montgomery, J. *Org. Lett.* **2016**, *18*, 5760. (i) Mazzacano, T. J.; Leon, N. J.; Waldhart, G. W.; Mankad, N. P. *Dalton Trans.* **2017**, *46*, 5518. (j) Kuang, Z.; Li, B.; Song, Q. *Chem. Commun.* **2018**, *54*, 34.

[29] (a) Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2013**, *19*, 7125. (b) Kitanosono, T.; Xu, P.; Kobayashi, S. *Chem. Asian J.* **2014**, *9*, 179.

[30] Calow, A. D. J.; Solé, C.; Whiting, A.; Fernández, E. *ChemCatChem* **2013**, *5*, 2233.

[31] For selected recent works on coppe-catalysed borylative difunctionalization: (a) Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2013**, *135*, 2635. (b) Itoh, T.; Matsueda, T.; Shimizu, Y.; Kanai, M. *Chem. Eur. J.* **2015**, *21*, 15955. (c) Hornillos, V.; Vila, C.; Otten, E.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 7867. (d) Jia, T.; Cao, P.; Wang, D.; Lou, Y.; Liao, J. *Chem. Eur. J.* **2015**, *21*, 4918. (e) Yang, Y. *Angew. Chem.* **2016**, *128*, 353. (f) Fujihara, T.; Sawada, A.; Yamaguchi, T.; Tani, Y.; Terao, J.; Tsuji, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 1539. (g) Kato, K.; Hirano, K.; Miura, M. *J. Org. Chem.* **2017**, *82*, 10418. (h) Zuo, Y.-J.; Chang, X.-T.; Hao, Z.-M.; Zhong, C.-M. *Org. Biomol. Chem.* **2017**, *15*, 6323. (i) Boreux, A.; Indukuri, K.; Gagosz, F.; Riant, O. *ACS Catal.* **2017**, *7*, 8200. (j) Gong, T.-J.; Yu, S.-H.; Li, K.; Su, W.; Lu, X.; Xiao, B.; Fu, Y. *Chem. Asian J.* **2017**, *12*, 2884.

[32] For selected relevant literatures on DFT study of catalytic borylation of alkenes: (a) Zhao, H.; Lin, Z.; Marder, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 15637. (b) Lam, K. C.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 3149. (c) Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 2824. (d) Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 1178. (e) Zhao, H.; Dang, L.; Marder, T. B.; Lin, Z. *J. Am. Chem. Soc.* **2008**, *130*, 5586. (f) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 4443. (g) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 5350. (h) Tan, D.-H.; Lin, E.; Ji, W.-W.; Zeng, Y.-F.; Fan, W.-X.; Li, Q.; Gao, H.; Wang, H. *Adv. Synth. Catal.* **2018**, *360*, 1032.

[33] (a) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528. (b) Xu, Z.-Y.; Jiang, Y.-Y.; Su, W.; Yu, H.-Z.; Fu, Y. *Chem. Eur. J.* **2016**, *22*, 14611.

[34] Yuan, W.; Zhang, X.; Yu, Y.; Ma, S. *Chem. Eur. J.* **2013**, *19*, 7193. (b) Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367.

[35] Chen, J.-B.; Jia, Y.-X. *Org. Biomol. Chem.* **2017**, *15*, 3550. (b) Kubota, K.; Hayama, K.; Iwamoto, H.; Ito, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 8809. (c) Kubota, K.;

Watanabe, Y.; Ito, H. *Adv. Synth. Catal.* **2016**, *358*, 2379. (d) Kubota, K.; Jin, M.; Ito, H. *Organometallics* **2016**, *35*, 1376

[36] Zhu, L.; Kitanosono, T.; Xu, P.; Kobayashi, S. *Chem. Commun.* **2015**, *51*, 11685. (b) Isegawa, M.; Sameera, W. M. C.; Sharma, A. K.; Kitanosono, T.; Kato, M.; Kobayashi, S.; Morokuma, K. *ACS Catal.* **2017**, *7*, 5370.

[37] For selected recent methodological and mechanical investigations on hydrocupration of alkenes: (a) Gribble, M. W.; Pirnot, M. T.; Bandar, J. S.; Liu, R. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 2192. (b) Liang, T.; Jiang, L.; Gan, M.; Su, X.; Li, Z. *Chin. J. Org. Chem.* **2017**, *37*, 3096. (c) Zhou, Y.; Bandar, J. S.; Liu, R. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018**, *140*, 606. (d) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62. (e) Kim, H.; Yun, J. *Adv. Synth. Catal.* **2010**, *352*, 1881.

[38] Won, J.; Noh, D.; Yun, J.; Lee, J. Y. *J. Phys. Chem. A* **2010**, *114*, 12112.

[39] Schmid, S. C.; Hoveln, R. V.; Rigoli, J. W.; Schomaker, J. M. *Organometallics* **2015**, *34*, 4164.

[40] Jang, W. J.; Song, S. M.; Moon, J. H.; Lee, J. Y.; Yun, J. *J. Am. Chem. Soc.* **2017**, *139*, 13660.

[41] Xi, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2017**, *139*, 12758.

[42] Lu, G.; Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D. S.; Buchwald, S. L.; Liu, P. *J. Am. Chem. Soc.* **2017**, *139*, 16548.

[43] For selected examples on background reaction of alkene hydroboration: (a) Mömming, C. M.; Frömel, S.; Kehr, G.; Fröhlich, R.; Grimme, S.; Erker, G. *J. Am. Chem. Soc.* **2009**, *131*, 12280. (b) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *J. Am. Chem. Soc.* **2012**, *134*, 6571. (c) Bailey, J. O.; Singleton, D. A. J. *Am. Chem. Soc.* **2017**, *139*, 15710. (d) Jin, S.; Nguyen, V. T.; Dang, H. T.; Nguyen, D. P.; Arman, H. D.; Larionov, O. V. *J. Am. Chem. Soc.* **2017**, *139*, 11365. (e) Juhl, M.; Laursen, S. L. R.; Huang, Y.; Nielsen, D. U.; Daasbjerg, K.; Skrydstrup, T. *ACS Catal.* **2017**, *7*, 1392. (f) Rarig, R.-A. F.; Nelson, J. M.; Vedejs, E. *J. Org. Chem.* **2017**, *82*, 12757. (g) Nagashima, Y.; Sasaki, K.; Suto, T.; Sato, T.; Chida, N. *Chem.*

Asian J. **2018**, *13*, 1024. (h) Sanzone, J. R.; Hu, C. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **2017**, *139*, 8404. (i) Meyer, D.; Renaud, P. *Angew. Chem. Int. Ed.* **2017**, *56*, 10858.

[44] For selected examples on NHC activation of diboron compounds: (a) Lee, K.-S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253. (b) Wen, K.; Chen, J.; Gao, F.; Bhadury, P. S.; Fan, E.; Sun, Z. *Org. Biomol. Chem.* **2013**, *11*, 6350. (c) Palau-Lluch, G.; Sanz, X.; La Cascia, E.; Civit, M. G.; Miralles, N.; Cuenca, A. B.; Fernández, E. *Pure Appl. Chem.* **2015**, *87*, 181. (d) Pietsch, S.; Neeve, E. C.; Apperley, D. C.; Bertermann, R.; Mo, F.; Qiu, D.; Cheung, M. S.; Dang, L.; Wang, J.; Radius, U.; Lin, Z.; Kleeberg C.; Marder, T. B. *Chem. Eur. J.* **2015**, *21*, 7082. (e) Eichhorn, A. F.; Kuehn, L.; Marder, T. B.; Radius, U. *Chem. Commun.* **2017**, *53*, 11694. (f) Eck, M.; Würtemberger-Pietsch, S.; Eichhorn, A.; Berthel, J. H. J.; Bertermann, R.; Paul, U. S. D.; Schneider, H.; Friedrich, A.; Kleeberg, C.; Radius, U.; Marder, T. B. *Dalton Trans.* **2017**, *46*, 3661.

[45] For selected examples on alkoxide or hydroxide base anion catalysed alkene hydroboration: (a) Thorpe, S. B.; Calderone, J. A.; Santos, W. L. *Org. Lett.* **2012**, *14*, 1918. (b) Sanz, X.; Lee, G. M.; Pubill-Ulldemolins, C.; Bonet, A.; Gulyás, H.; Westcott, S. A.; Bo, C.; Fernández, E. *Org. Biomol. Chem.* **2013**, *11*, 7004. (c) Cid, J.; Carbó, J. J.; Fernández, E. *Chem. Eur. J.* **2014**, *20*, 3616. (d) La Cascia, E.; Sanz, X.; Bo, C.; Whiting, A.; Fernández, E.; *Org. Biomol. Chem.* **2015**, *13*, 1328. (e) Yang, K.; Song, Q. *Green Chem.* **2016**, *18*, 932. (f) Wu, Y.; Shan, C.; Ying, J.; Su, J.; Zhu, J.; Liu, L. L.; Zhao, Y. *Green Chem.* **2017**, *19*, 4169. (g) Yamamoto, E.; Shishido, R.; Seki, T.; Ito, H. *Organometallics* **2017**, *36*, 3019. (h) Deng, C. M.; Ma, Y. F.; Wen, Y. M. *ChemistrySelect* **2018**, *3*, 1202. (i) Huang, X.; Hu, J.; Wu, M.; Wang, J.; Peng, Y.; Song, G. *Green Chem.* **2018**, *20*, 255. (j) Yan, L.; Meng, Y.; Haeffner, F.; Leon, R. M.; Crockett, M. P.; Morken, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 3663.

[46] For selected examples on radical mechanism of borylation of alkenes: (a) Iwamoto, H.; Akiyama, S.; Hayama, K.; Ito, H. *Org. Lett.* **2017**, *19*, 2614. (b) Cui, J.; Wang, H.; Song, J.; Chi, X.; Meng, L.; Liu, Q.; Zhang, D.; Dong, Y.; Liu, H. *Org. Biomol.*

Chem. **2017**, *15*, 8508. (c) Ren, S.-C.; Zhang, F.-L.; Qi, J.; Huang, Y.-S.; Xu, A.-Q.; Yan, H.-Y.; Wang, Y.-F. *J. Am. Chem. Soc.* **2017**, *139*, 6050. (d) Zhang, L.; Jiao, L. *Chem. Sci.* **2018**, *9*, 2711.

[47] Kumar, R. N.; Meshram, H. M. *Tetrahedron Lett.* **2011**, *52*, 1003.

[48] (a) Tobert, J. A. *Nat. Rev. Drug Discovery* **2003**, *3*, 178. (b) Luo, Y.; Roy, I. D.; Madec, A. G. E.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 4186.

[49] Woodward, R. B.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Ward, D. E.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3213.

[50] (a) Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Soc. Chem.* **2009**, *131*, 11664. (b) Welle, A.; Cirriez, V.; Riant, O. *Tetrahedron* **2012**, *68*, 3435. (c) Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 7576. (d) Yu, Z.; Ely, R. J.; Morken, J. P. *Angew. Chem.* **2014**, *126*, 9786.

[51] Medina, C.; Carter, K. P.; Miller, M.; Clark, T. B.; O'Neil, G. W. *J. Org. Chem.* **2013**, *78*, 9093.

[52] (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Yadav, J. S.; Hossain, Sk. S.; Madhu, M.; Mohapatra, D. K. *J. Org. Chem.* **2009**, *74*, 8822. (c) Yadav, J. S.; Rajender, V.; Rao, Y. G. *Org. Lett.* **2010**, *12*, 348. (d) Yadav, J. S.; Rao, K. V. R.; Ravindar, K.; Reddy, B. V. S. *Eur. J. Org. Chem.* **2011**, 58.

[53] Fordred, P. S.; Bull, S. D. *Tetrahedron Lett.* **2013**, *54*, 27.

[54] Chen, J.-B.; Whiting, A. *Synthesis* **2018**, *50*, 3843.

[55] Development of novel catalytic asymmetric diborylation methodologies: A. P. Santiago, Department of Chemistry, Durham University, Durham DH1 3LE, UK.

[56] (a) Yang, W.; Gao, X.; Wang, B. *Medicinal Research Reviews* **2003**, *23*, 364. (b) Tobert, J. A. *Nat. Rev. Drug Discovery* **2003**, *3*, 178. (c) J. J. Li and E. J. Corey, *Drug discovery: practices, processes and perspectives*, ed Jon Wiley & Sons, New Jersey, 2013. (d) Cholesterol Treatment, Lipitor® (atorvastatin calcium) safety information, www.lipitor.com, (accessed August2018)

[57] (a) Roth, B. D.; Ortwine, D. F.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 21. (b) Roth, B. D.; Blankley,

C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W. *J. Med. Chem.* **1991**, *34*, 357. (c) Brower, P. L.; Butler, D. E.; Deering,C. F.; Le, T. V.; Millar, A.; Nanninga, T. N.; Roth, B. D. *Tetrahedron Lett.* **1992**, *33*, 2279. (d) Baumann, K. L.; Butler, D. E.; Deering, C. F.; Mennen, K. E.; Millar, A.; Nanninga, T. N.; Palmer, C. W.; Roth, B. D. *Tetrahedron Lett.* **1992**, *33*, 2283.

[58] (a) Goyal, S.; Patel, B.; Sharma, R.; Chouhan, M.; Kumar, K.; Gangar, M. *Tetrahedron Lett.* **2015**, *56*, 5409. (b) Dias, L. C.; Vieira, A. S.; Barreiro, E. J. *Org. Biomol. Chem.* **2016**, *14*, 2291.

[59] (a) Batesky, D. C.; Goldfogel, M. J.; Weix, D. J. *J. Org. Chem.* **2017**, *82*, 9931. (b) Lukin, K.; Kishore, V.; Gordon, T. *Org. Process Res. Dev.* **2013**, *17*, 666.

[60] (*a*) Chen, S.-S.; Wu, M.-S.; Han, Z.-Y. *Angew. Chem. Int. Ed.*, **2017**, *56*, 6641. (*b*) Hoshi, M.; Kaneko, O.; Nakajima, M.; Arai, S.; Nishida, A. *Org. Lett.*, **2014**, *16*, 768. (*c*) Lopez, J. A. V.; Petitbois, J. G.; Vairappan, C. S.; Umezawa, T.; Matsuda, F.; Okino, T. *Org. Lett.*, **2017**, *19*, 4231. (*d*) Paladuguac, S.; Mainkarbc, P. S.; Chandrasekhar, S. *Tetrahedron Lett.*, **2017**, *58*, 2784. (*e*) Hoshiya, N.; Noda, K.; Mihara, Y.; Kawai, N.; Uenishi, J. *J. Org. Chem.*, **2015**, *80*, 77.